REDACTED VERSION – PUBLICLY FILED

EXHIBIT A

REDACTED VERSION – PUBLICLY FILED

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY LTD. and TAP PHARMACEUTICAL PRODUCTS INC., Plaintiffs and Counterclaim-Defendants, v. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES LTD., Defendants and Counterclaim-Plaintiffs.	Civil Action No.: 1:06-cv-0033-SLR

TEVA PHARMACEUTICALS USA, INC.'S AND TEVA PHARMACEUTICAL INDUSTRIES LTD.'S AMENDED ANSWER, DEFENSES, AND COUNTERCLAIMS TO AMENDED COMPLAINT

Defendants and Counterclaim-Plaintiffs, Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") (collectively "Teva"), respond to the numbered paragraphs of the Amended Complaint filed by Plaintiffs and Counterclaim-Defendants, Takeda Pharmaceutical Company Ltd. and TAP Pharmaceutical Products Inc., (collectively "Plaintiffs") as follows:

ANSWER

THE PARTIES

1. Teva states that it lacks knowledge or information sufficient to form a belief as to the truth of the allegations set forth in Paragraph 1 of the Amended Complaint, and therefore, Teva denies the allegations of Paragraph 1.

2. Teva states that it lacks knowledge or information sufficient to form a belief as to the truth of the allegations set forth in Paragraph 2 of the Amended Complaint, and therefore, Teva denies the allegations of Paragraph 2.

3. Teva admits the allegations in Paragraph 3 of the Amended Complaint.

4. Teva admits Teva Ltd. is an Israeli corporation having a principal place of business located at 5 Basel St., Petach Tikva 49131, Israel. Teva further admits Teva Ltd. manufactures pharmaceutical products. Except as expressly admitted above, Teva denies the allegations in Paragraph 4 of the Amended Complaint.

5. Teva admits the allegations in Paragraph 5 of the Amended Complaint.

6. Teva denies the allegations in Paragraph 6 of the Amended Complaint.

7. Teva admits only that Teva USA conducts business in North America. Except as expressly admitted above, Teva denies the allegations in Paragraph 7 of the Amended Complaint.

JURISDICTION AND VENUE

8. Teva admits only that this action purports to arise under the patent laws of the United States and that this Court has subject matter jurisdiction. Teva denies any and all remaining allegations in Paragraph 8 of the Amended Complaint including denying that it has infringed any valid and enforceable claim of any of Plaintiffs' patents-in-suit.

9. Teva admits only that Teva USA is subject to personal jurisdiction in this District, Teva USA is incorporated in Delaware, and Teva USA conducts business within the District of Delaware. Except as expressly admitted above, Teva denies the allegations in Paragraph 9 of the Amended Complaint.

10. Teva admits only that Teva USA conducts business within the District of Delaware. Except as expressly admitted above, Teva denies the allegations in Paragraph 10 of the Amended Complaint.

11. Teva denies the allegations in Paragraph 11 of the Amended Complaint.

12. Teva denies the allegations in Paragraph 12 of the Amended Complaint.

13. Teva denies the allegations in Paragraph 13 of the Amended Complaint.

14. Teva denies the allegations in Paragraph 14 of the Amended Complaint.

15. Teva admits only that Teva Ltd. is subject to personal jurisdiction in this District for purposes of this action, Teva USA is incorporated in Delaware, and Teva USA conducts business in the District of Delaware. Except as expressly admitted above, Teva denies the allegations in Paragraph 15 of the Amended Complaint.

16. Teva admits the allegations in Paragraph 16 of the Amended Complaint.

FACTS PERTINENT TO ALL CLAIMS FOR RELIEF

17. In response to the allegations of Paragraph 17 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 17 and therefore denies them.

18. Upon information and belief, Teva admits the term of the '098 patent without adjustment has expired. Except as expressly admitted above, Teva denies the allegations in Paragraph 18 of the Amended Complaint.

19. In response to the allegations of Paragraph 19 of the Amended Complaint, Teva states that the certificate extending the patent term of the '098 patent speaks for itself and Teva is

without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 19 and therefore denies them.

20. In response to the allegations of Paragraph 20 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 20 and therefore denies them.

21. In response to the allegations of Paragraph 21 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 21 and therefore denies them.

22. In response to the allegations of Paragraph 22 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 22 and therefore denies them.

23. In response to the allegations of Paragraph 23 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 23 and therefore denies them.

24. Upon information and belief, Teva admits that the FDA approved NDA No. 20-406 for lansoprazole delayed release capsules, 15 and 30 mg, on May 10, 1995. Except as expressly admitted above, Teva is without knowledge or information sufficient to form a belief as to the truth of any remaining allegations contained in Paragraph 24 and therefore denies them.

25. Teva admits the allegations in Paragraph 25 of the Amended Complaint.

26. Teva admits only that Teva Ltd. offers a broad range of generic pharmaceutical products. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 26 of the Amended Complaint.

27. Teva admits only that Teva USA manufactures, markets, and sells pharmaceutical products within the United States generally and the State of Delaware specifically. Except as expressly admitted above, Teva denies the allegations of Paragraph 27 of the Amended Complaint.

28. Teva denies the allegations in Paragraph 28 of the Amended Complaint as stated.

29. Teva admits only that Teva USA filed ANDA No. 77-255 for lansoprazole delayed release capsules with the FDA, Teva Ltd. was aware of the patents-in-suit when Teva USA filed ANDA No. 77-255, and Teva Ltd. was aware of commercial information relating to lansoprazole when Teva USA filed ANDA No. 77-255. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 29 of the Amended Complaint.

30. Teva admits only that Teva USA filed ANDA No. 77-255 for lansoprazole delayed release capsules with the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 30 of the Amended Complaint.

31. Teva admits only that Teva USA submitted to the FDA an amendment to ANDA No. 77-255 that included a Paragraph IV certification. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 31 of the Amended Complaint.

32. Upon information and belief, Teva admits the allegations of Paragraph 32 of the Amended Complaint.

33. Teva admits only that Teva USA filed ANDA No. 77-255 for lansoprazole delayed release capsules with the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 33 of the Amended Complaint.

34. Teva admits only that Teva Ltd. was aware of the patents-in-suit when Teva USA filed ANDA No. 77-255 and the Paragraph IV certification with the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 34 of the Amended Complaint.

35. Upon information and belief, Teva admits the allegations of Paragraph 35 of the Amended Complaint.

36. Teva admits only that Teva USA continues to seek approval of ANDA No. 77-255 from the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 36 of the Amended Complaint.

FIRST CLAIM FOR RELIEF

37. Teva incorporates by reference as if stated fully herein its responses to Paragraphs 1 through 36 of the Amended Complaint.

38. Teva denies the allegations in Paragraph 38 of the Amended Complaint.

39. Teva denies the allegations in Paragraph 39 of the Amended Complaint.

40. Teva admits only that Teva USA was aware of the existence of the '098 patent prior to amending ANDA No. 77-255. Except as expressly admitted above, Teva denies the allegations of Paragraph 40 of the Amended Complaint.

41. Teva denies the allegations in Paragraph 41 of the Amended Complaint.

42. Teva admits that its Paragraph IV certification does not assert that claims 1, 2, 5, 6, 8, and 10 of the '098 patent are not infringed. Teva further admits that its Paragraph IV certification asserts that these claims are invalid. Except as expressly admitted, Teva denies the allegations set forth in Paragraph 42 of the Amended Complaint.

43. Teva denies the allegations in Paragraph 43 of the Amended Complaint.

44. Teva denies the allegations in Paragraph 44 of the Amended Complaint.

SECOND CLAIM FOR RELIEF

45. Teva incorporates by reference as if stated fully herein its responses to Paragraphs 1 through 44 of the Amended Complaint.

46. Teva denies the allegations in Paragraph 46 of the Amended Complaint.

47. Teva denies the allegations in Paragraph 47 of the Amended Complaint.

48. Teva denies the allegations in Paragraph 48 of the Amended Complaint.

49. Teva denies the allegations in Paragraph 49 of the Amended Complaint.

50. Teva denies the allegations in Paragraph 50 of the Amended Complaint.

THIRD CLAIM FOR RELIEF

51. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 50 of the Amended Complaint.

52. Teva denies the allegations in Paragraph 52 of the Amended Complaint.

53. Teva denies the allegations in Paragraph 53 of the Amended Complaint.

54. Teva denies the allegations in Paragraph 54 of the Amended Complaint.

55. Teva denies the allegations in Paragraph 55 of the Amended Complaint.

56. Teva denies the allegations in Paragraph 56 of the Amended Complaint.

57. Teva denies the allegations in Paragraph 57 of the Amended Complaint.

FOURTH CLAIM FOR RELIEF

58. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 57 of the Amended Complaint.

59. Teva denies the allegations in Paragraph 59 of the Amended Complaint.

60. Teva denies the allegations in Paragraph 60 of the Amended Complaint.

61. Teva denies the allegations in Paragraph 61 of the Amended Complaint.

62. Teva denies the allegations in Paragraph 62 of the Amended Complaint.

63. Teva denies the allegations in Paragraph 63 of the Amended Complaint.

FIFTH CLAIM FOR RELIEF

64. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 63 of the Amended Complaint.

65. Teva denies the allegations in Paragraph 65 of the Amended Complaint.

66. Teva denies the allegations in Paragraph 66 of the Amended Complaint.

67. Teva denies the allegations in Paragraph 67 of the Amended Complaint.

68. Teva denies the allegations in Paragraph 68 of the Amended Complaint.

69. Teva denies the allegations in Paragraph 69 of the Amended Complaint.

70. Teva denies the allegations in Paragraph 70 of the Amended Complaint.

SIXTH CLAIM FOR RELIEF

71. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 70 of the Amended Complaint.

72. Teva denies the allegations in Paragraph 72 of the Amended Complaint.

73. Teva denies the allegations in Paragraph 73 of the Amended Complaint.

74. Teva denies the allegations in Paragraph 74 of the Amended Complaint.

75. Teva denies the allegations in Paragraph 75 of the Amended Complaint.

76. Teva denies the allegations in Paragraph 76 of the Amended Complaint.

SEVENTH CLAIM FOR RELIEF

77. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 76 of the Amended Complaint.

78. Teva denies the allegations in Paragraph 78 of the Amended Complaint.

79. Teva denies the allegations in Paragraph 79 of the Amended Complaint.

80. Teva denies the allegations in Paragraph 80 of the Amended Complaint.

81. Teva denies the allegations in Paragraph 81 of the Amended Complaint.

82. Teva denies the allegations in Paragraph 82 of the Amended Complaint.

83. Teva denies the allegations in Paragraph 83 of the Amended Complaint.

EIGHTH CLAIM FOR RELIEF

84. Teva incorporates by reference as if stated fully herein its responses to Paragraphs 1 through 83 of the Amended Complaint.

85. Teva denies the allegations in Paragraph 85 of the Amended Complaint.

86. Teva denies the allegations in Paragraph 86 of the Amended Complaint.

87. Teva denies the allegations in Paragraph 87 of the Amended Complaint.

88. Teva denies the allegations in Paragraph 88 of the Amended Complaint.

89. Teva denies the allegations in Paragraph 89 of the Amended Complaint.

NINTH CLAIM FOR RELIEF

90. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 89 of the Amended Complaint.

91. Teva denies the allegations in Paragraph 91 of the Amended Complaint.

92. Teva denies the allegations in Paragraph 92 of the Amended Complaint.

93. Teva denies the allegations in Paragraph 93 of the Amended Complaint.

94. Teva denies the allegations in Paragraph 94 of the Amended Complaint.

95. Teva denies the allegations in Paragraph 95 of the Amended Complaint.

96. Teva denies the allegations in Paragraph 96 of the Amended Complaint.

TENTH CLAIM FOR RELIEF

97. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 96 of the Amended Complaint.

98. Teva denies the allegations in Paragraph 98 of the Amended Complaint.

99. Teva denies the allegations in Paragraph 99 of the Amended Complaint.

100. Teva denies the allegations in Paragraph 100 of the Amended Complaint.

101. Teva denies the allegations in Paragraph 101 of the Amended Complaint.

102. Teva denies the allegations in Paragraph 102 of the Amended Complaint.

103. To the extent any allegation in any paragraph of Plaintiffs' Amended Complaint is not specifically admitted or otherwise responded to, it is hereby denied.

DEFENSES

FIRST DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 4,628,098 ("the '098 patent").

SECOND DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,026,560 ("the '560 patent").

THIRD DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,045,321 ("the '321 patent").

FOURTH DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,093,132 ("the '132 patent").

FIFTH DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,433,959 ("the '959 patent").

SIXTH DEFENSE

Upon information and belief, the claims of the '098 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

SEVENTH DEFENSE

Upon information and belief, the claims of the '560 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

EIGTH DEFENSE

Upon information and belief, the claims of the '321 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

NINTH DEFENSE

Upon information and belief, the claims of the '132 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

TENTH DEFENSE

Upon information and belief, the claims of the '959 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

ELEVENTH DEFENSE

As set forth in greater detail in paragraphs 28-34 of the Counterclaim below, which paragraphs are incorporated herein by reference, the claims of the '098 patent are unenforceable as procured through inequitable conduct before the United States Patent and Trademark Office ("PTO").

In violation of Takeda's duty of candor to the PTO under 37 C.F.R. § 1.56, Takeda intentionally misled the PTO concerning the effectiveness of the alleged invention during prosecution of patent application no. 06/760,568 ("the '568 application"), the application that led to the issuance of the '098 patent. More particularly, to support patentability of the '568 application, Takeda asserted that the alleged invention exhibited superior anti-ulcer activity, up to 20 times more effective, over "known" prior art compounds. (See, e.g., '098 patent, col. 6, ll. 5-36.)

Having chosen to assert efficacy data as a basis for patentability, any efficacy data that was not cumulative of and that refuted or was inconsistent with the submitted data became material to patentability and would have been considered important by a reasonable examiner in deciding whether or not to allow the application to issue as a patent. Takeda had a duty under 37 C.F.R. § 1.56 to disclose all such data in its possession to the PTO during the prosecution of the of the application that led to the '098 patent. Takeda, however, chose not to disclose the material test data or reports thereof or to correct the misrepresentations in its patent application. Takeda did so with the intent to deceive the PTO concerning the patentability of the application, and therefore is guilty of inequitable conduct rendering the '098 patent unenforceable.

TWELFTH DEFENSE

As set forth in greater detail in paragraphs 28-42 of the Counterclaims below, which paragraphs are incorporated herein by reference, the patent term extension for the '098 patent is unenforceable.

On July 6, 1995, Takeda filed for a patent term extension for the '098 patent pursuant to 35 U.S.C. §§ 155-156. On January 6, 1997, the PTO awarded Takeda a patent term extension of 1381 days extending the term of the patent to May 10, 2009. Without that patent term extension, the '098 patent would be expired and would not be part of this action.

At the time it sought the patent term extension, Takeda knew that the '098 patent was invalid and unenforceable due to its inequitable conduct before the PTO during prosecution. Takeda knew that it misrepresented the efficacy data in the table at Column 6 comparing the claimed invention to prior art compounds and that it withheld test results that made clear that the claimed invention did not show the superior efficacy that was the basis for Takeda's claim of patentability.

Moreover, Takeda continued to test the efficacy of the claimed invention against prior art compounds after issuance of the '098 patent. The results of those efficacy tests further confirmed to Takeda that the claimed invention was not superior to the prior art compounds as represented to the PTO. Despite knowing that it misrepresented the efficacy data and that it failed to disclose material efficacy test results, Takeda continued to pursue the patent term extension through the PTO.

Takeda's failures to disclose its misrepresentations to the PTO and the underlying efficacy test results, both during and after prosecution, were material to Takeda's entitlement to the extension under 37 C.F.R. § 1.765 because there is a substantial likelihood the PTO would have considered such adverse information important in considering whether to grant the extension. Takeda knew that the patent was invalid and unenforceable upon filing for and during prosecution of the patent term extension. The patent term extension granted for the '098 patent therefore is unenforceable.

COUNTERCLAIMS

Defendants Teva hereby counterclaim against Plaintiffs, and in support thereof, allege as follows:

1. The Plaintiffs have filed an Amended Complaint against Teva seeking, *inter alia*, a judgment that Teva infringed the claims of the '098 patent, the '560 patent, the '321 patent, the '132 patent, and the '959 patent (collectively "the patents-in-suit") by Teva USA filing ANDA No. 77-255 and a Paragraph IV certification. As a result of the filing of the Amended Complaint, an immediate and justiciable controversy exists between the Plaintiffs and Teva regarding the alleged infringement and validity of the patents-in-suit.

2. The following counterclaims arise under the patent laws of the United States, 35 U.S.C. § 1, *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

3. This Court has personal jurisdiction over the Plaintiffs because, *inter alia*, the Plaintiffs have submitted to the jurisdiction of this Court by filing Plaintiffs' Amended Complaint.

4. Subject matter jurisdiction in this Court is proper under, *inter alia*, 28 U.S.C. §§ 1331 and 1338.

5. Venue is proper in this Court because, *inter alia*, the Plaintiffs have submitted to the jurisdiction of this Court and selected this venue by filing their Complaint with this Court.

COUNT ONE
(Non-infringement of the '098 Patent)

6. Teva incorporates by reference all allegations contained in Paragraphs 1 through 5 of its Counterclaims.

7. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '098 patent.

COUNT TWO
(Non-infringement of the '560 Patent)

8. Teva incorporates by reference all allegations contained in Paragraphs 1 through 7 of its Counterclaims.

9. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '560 patent.

COUNT THREE
(Non-infringement of the '321 Patent)

10. Teva incorporates by reference all allegations contained in Paragraphs 1 through 9 of its Counterclaims.

11. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '321 patent.

COUNT FOUR
(Non-infringement of the '132 Patent)

12. Teva incorporates by reference all allegations contained in Paragraphs 1 through 11 of its Counterclaims.

13. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '132 patent.

COUNT FIVE
(Non-infringement of the '959 Patent)

14. Teva incorporates by reference all allegations contained in Paragraphs 1 through 13 of its Counterclaims.

15. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '959 patent.

COUNT SIX
(Declaration of Invalidity of the '098 Patent)

16. Teva incorporates by reference the allegations contained in paragraphs 1-15 of its Counterclaims.

17. The claims of the '098 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT SEVEN
(Declaration of Invalidity of the '560 Patent)

18. Teva incorporates by reference the allegations contained in paragraphs 1-17 of its Counterclaims.

19. The claims of the '560 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT EIGHT
(Declaration of Invalidity of the '321 Patent)

20. Teva incorporates by reference the allegations contained in paragraphs 1-19 of its Counterclaims.

21. The claims of the '321 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT NINE
(Declaration of Invalidity of the '132 Patent)

22. Teva incorporates by reference the allegations contained in paragraphs 1-21 of its Counterclaims.

23. The claims of the '132 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT TEN
(Declaration of Invalidity of the '959 Patent)

24. Teva incorporates by reference the allegations contained in paragraphs 1-23 of its Counterclaims.

25. The claims of the '959 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT ELEVEN
(Declaration of Award of Attorneys' Fees, Costs, and Expenses)

26. Teva incorporates by reference the allegations contained in paragraphs 1-25 of its Counterclaims.

27. This action is an exceptional case under 35 U.S.C. § 285, and Teva is entitled to reimbursement of attorneys' fees, costs, and expenses from Plaintiffs.

COUNT TWELVE
(Declaration of Unenforceability of the '098 Patent Due to Inequitable Conduct)

28. Teva incorporates by reference the allegations contained in paragraphs 1-27 of its Counterclaims.

29. In violation of Takeda's duty of candor to the PTO under 37 C.F.R. § 1.56, Takeda intentionally misled the PTO concerning the effectiveness of the alleged invention during prosecution of patent application no. 06/760,568 ("the '568 application"), the application that led to the issuance of the '098 patent. More particularly, to support patentability of the '568 application, Takeda represented to the PTO in the application that led to the '098 patent that prior art compounds' "gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents." (*See* '098 patent, Col. 1, ln. 14-16.)

30. Takeda further asserted that the alleged invention exhibited superior anti-ulcer activity, up to 20 times more effective, over "known" prior art compounds and summarized

results of unidentified test data in the table located in Column 6 of the '098 patent. (See, e.g., '098 patent, col. 6, ll. 5-36.)

31. Takeda's internal documents and test results, including monthly status reports and test data reports, dated prior to issuance of the '098 patent show that Takeda knew that the claimed invention was not superior to certain prior art compounds and certainly not 20 times superior to competitive anti-ulcer prior art compounds.

32. Having chosen to assert efficacy data as a basis for patentability, any efficacy data that was not cumulative of and that refuted or was inconsistent with the submitted data became material to patentability and would have been considered important by a reasonable examiner in deciding whether or not to allow the application to issue as a patent. Takeda had a duty under 37 C.F.R. § 1.56 to disclose all such data in its possession to the PTO during the prosecution of the of the application that led to the '098 patent. Takeda, however, chose not to disclose the material test data or reports thereof or to correct the misrepresentations in its patent application. Takeda did so with the intent to deceive the PTO concerning the patentability of the application, and therefore is guilty of inequitable conduct rendering the '098 patent unenforceable.

33. The efficacy of the claimed invention relative to prior art compounds is material to patentability. Takeda had a duty to disclose the test data or results thereof demonstrating efficacy data contrary to the representations made during prosecution to the PTO pursuant to 37 C.F.R. § 1.56 but failed to disclose any test data or reports thereof.

34. Takeda intentionally misrepresented the efficacy of the claimed invention to the PTO during prosecution to support patentability and intentionally did not disclose to the PTO contemporaneous test results material to patentability with the intent to deceive the PTO.

35. For at least the foregoing reasons, the '098 patent is unenforceable.

COUNT THIRTEEN
(Declaration of Unenforceability of the Patent Term Extension for the '098 Patent)

36. Teva incorporates by reference the allegations contained in paragraphs 1-35 of its Counterclaims.

37. The '098 patent issued on December 9, 1986. On July 6, 1995, Takeda applied for a Patent Term Extension pursuant to 35 U.S.C. §§ 155-156. On January 6, 1997, the PTO awarded Takeda a Patent Term Extension of 1381 days extending the term of the patent to May 10, 2009.

38. At the time it sought the patent term extension, Takeda knew that the '098 patent was invalid and unenforceable due to its inequitable conduct before the PTO during prosecution. As described in detail in paragraphs 28-35, Takeda misrepresented the efficacy of the claimed invention over prior art compounds and withheld material test data and reports demonstrating the lack of superior efficacy represented by Takeda to the PTO. Takeda knew that the '098 patent therefore was invalid and unenforceable.

39. After issuance of the '098 patent, Takeda continued to test the efficacy of the claimed invention against prior art compounds. Takeda's test results further confirmed to Takeda that the claimed invention does not have the superior efficacy as represented in the table at Column 6 of the '098 patent.

40. Despite knowing that it misrepresented the efficacy data and that it failed to disclose material efficacy test results, Takeda continued to pursue the patent term extension through the PTO.

41. Takeda's failures to disclose its misrepresentations to the PTO and the underlying efficacy test results, both during and after prosecution, were material to Takeda's entitlement to the extension under 37 C.F.R. § 1.765 because there is a substantial likelihood the PTO would have considered such adverse information important in considering whether to grant the extension. Takeda knew that the patent was invalid and unenforceable upon filing for and during prosecution of the patent term extension.

42. For at least the foregoing reasons, the patent term extension granted for the '098 patent is unenforceable.

PRAYER FOR RELIEF

WHEREFORE, Teva respectfully requests that this Court enter a Judgment and Order:

(a) dismissing the Amended Complaint, and each and every claim for relief contained therein, with prejudice;

(b) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '098 patent;

(c) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '560 patent;

(d) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '321 patent;

(e) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '132 patent;

(f) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '959 patent;

(g) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '098 patent;

(h) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '560 patent;

(i) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '321 patent;

(j) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '132 patent;

(k) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '959 patent;

(l) declaring all claims of the '098 patent invalid;

(m) declaring all claims of the '560 patent invalid;

(n) declaring all claims of the '321 patent invalid;

(o) declaring all claims of the '132 patent invalid;

(p) declaring all claims of the '959 patent invalid;

(q) declaring all claims of the '098 patent are unenforceable;

(r) declaring the patent term extension of the '098 patent is unenforceable;

(s) declaring this an exceptional case under 35 U.S.C. § 285 and awarding Teva its attorneys' fees, costs, and expenses; and

(t) granting Teva such other and further relief as this Court deems just and proper.

Respectfully submitted this ___ day of March, 2007.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

TAKEDA PHARMACEUTICAL COMPANY LTD. and TAP PHARMACEUTICAL PRODUCTS INC., Plaintiffs and Counterclaim-Defendants, v. TEVA PHARMACEUTICALS USA, INC., and TEVA PHARMACEUTICAL INDUSTRIES LTD., Defendants and Counterclaim-Plaintiffs.	Civil Action No.: 1:06-cv-0033-SLR

TEVA PHARMACEUTICALS USA, INC.'S AND TEVA PHARMACEUTICAL INDUSTRIES LTD.'S AMENDED ANSWER, DEFENSES, AND COUNTERCLAIMS TO AMENDED COMPLAINT

Defendants and Counterclaim-Plaintiffs, Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") (collectively "Teva"), respond to the numbered paragraphs of the Amended Complaint filed by Plaintiffs and Counterclaim-Defendants, Takeda Pharmaceutical Company Ltd. and TAP Pharmaceutical Products Inc., (collectively "Plaintiffs") as follows:

ANSWER

THE PARTIES

1. Teva states that it lacks knowledge or information sufficient to form a belief as to the truth of the allegations set forth in Paragraph 1 of the Amended Complaint, and therefore, Teva denies the allegations of Paragraph 1.

2. Teva states that it lacks knowledge or information sufficient to form a belief as to the truth of the allegations set forth in Paragraph 2 of the Amended Complaint, and therefore, Teva denies the allegations of Paragraph 2.

3. Teva admits the allegations in Paragraph 3 of the Amended Complaint.

4. Teva admits Teva Ltd. is an Israeli corporation having a principal place of business located at 5 Basel St., Petach Tikva 49131, Israel. Teva further admits Teva Ltd. manufactures pharmaceutical products. Except as expressly admitted above, Teva denies the allegations in Paragraph 4 of the Amended Complaint.

5. Teva admits the allegations in Paragraph 5 of the Amended Complaint.

6. Teva denies the allegations in Paragraph 6 of the Amended Complaint.

7. Teva admits only that Teva USA conducts business in North America. Except as expressly admitted above, Teva denies the allegations in Paragraph 7 of the Amended Complaint.

JURISDICTION AND VENUE

8. Teva admits only that this action purports to arise under the patent laws of the United States and that this Court has subject matter jurisdiction. Teva denies any and all remaining allegations in Paragraph 8 of the Amended Complaint including denying that it has infringed any valid and enforceable claim of any of Plaintiffs' patents-in-suit.

9. Teva admits only that Teva USA is subject to personal jurisdiction in this District, Teva USA is incorporated in Delaware, and Teva USA conducts business within the District of Delaware. Except as expressly admitted above, Teva denies the allegations in Paragraph 9 of the Amended Complaint.

10. Teva admits only that Teva USA conducts business within the District of Delaware. Except as expressly admitted above, Teva denies the allegations in Paragraph 10 of the Amended Complaint.

11. Teva denies the allegations in Paragraph 11 of the Amended Complaint.

12. Teva denies the allegations in Paragraph 12 of the Amended Complaint.

13. Teva denies the allegations in Paragraph 13 of the Amended Complaint.

14. Teva denies the allegations in Paragraph 14 of the Amended Complaint.

15. Teva admits only that Teva Ltd. is subject to personal jurisdiction in this District for purposes of this action, Teva USA is incorporated in Delaware, and Teva USA conducts business in the District of Delaware. Except as expressly admitted above, Teva denies the allegations in Paragraph 15 of the Amended Complaint.

16. Teva admits the allegations in Paragraph 16 of the Amended Complaint.

FACTS PERTINENT TO ALL CLAIMS FOR RELIEF

17. In response to the allegations of Paragraph 17 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 17 and therefore denies them.

18. Upon information and belief, Teva admits the term of the '098 patent without adjustment has expired. Except as expressly admitted above, Teva denies the allegations in Paragraph 18 of the Amended Complaint.

19. In response to the allegations of Paragraph 19 of the Amended Complaint, Teva states that the certificate extending the patent term of the '098 patent speaks for itself and Teva is

without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 19 and therefore denies them.

20. In response to the allegations of Paragraph 20 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 20 and therefore denies them.

21. In response to the allegations of Paragraph 21 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 21 and therefore denies them.

22. In response to the allegations of Paragraph 22 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 22 and therefore denies them.

23. In response to the allegations of Paragraph 23 of the Amended Complaint, Teva states that the referenced patent speaks for itself and Teva is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in Paragraph 23 and therefore denies them.

24. Upon information and belief, Teva admits that the FDA approved NDA No. 20-406 for lansoprazole delayed release capsules, 15 and 30 mg, on May 10, 1995. Except as expressly admitted above, Teva is without knowledge or information sufficient to form a belief as to the truth of any remaining allegations contained in Paragraph 24 and therefore denies them.

25. Teva admits the allegations in Paragraph 25 of the Amended Complaint.

26. Teva admits only that Teva Ltd. offers a broad range of generic pharmaceutical products. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 26 of the Amended Complaint.

27. Teva admits only that Teva USA manufactures, markets, and sells pharmaceutical products within the United States generally and the State of Delaware specifically. Except as expressly admitted above, Teva denies the allegations of Paragraph 27 of the Amended Complaint.

28. Teva denies the allegations in Paragraph 28 of the Amended Complaint as stated.

29. Teva admits only that Teva USA filed ANDA No. 77-255 for lansoprazole delayed release capsules with the FDA, Teva Ltd. was aware of the patents-in-suit when Teva USA filed ANDA No. 77-255, and Teva Ltd. was aware of commercial information relating to lansoprazole when Teva USA filed ANDA No. 77-255. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 29 of the Amended Complaint.

30. Teva admits only that Teva USA filed ANDA No. 77-255 for lansoprazole delayed release capsules with the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 30 of the Amended Complaint.

31. Teva admits only that Teva USA submitted to the FDA an amendment to ANDA No. 77-255 that included a Paragraph IV certification. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 31 of the Amended Complaint.

32. Upon information and belief, Teva admits the allegations of Paragraph 32 of the Amended Complaint.

33. Teva admits only that Teva USA filed ANDA No. 77-255 for lansoprazole delayed release capsules with the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 33 of the Amended Complaint.

34. Teva admits only that Teva Ltd. was aware of the patents-in-suit when Teva USA filed ANDA No. 77-255 and the Paragraph IV certification with the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 34 of the Amended Complaint.

35. Upon information and belief, Teva admits the allegations of Paragraph 35 of the Amended Complaint.

36. Teva admits only that Teva USA continues to seek approval of ANDA No. 77-255 from the FDA. Except as expressly admitted above, Teva denies the allegations set forth in Paragraph 36 of the Amended Complaint.

FIRST CLAIM FOR RELIEF

37. Teva incorporates by reference as if stated fully herein its responses to Paragraphs 1 through 36 of the Amended Complaint.

38. Teva denies the allegations in Paragraph 38 of the Amended Complaint.

39. Teva denies the allegations in Paragraph 39 of the Amended Complaint.

40. Teva admits only that Teva USA was aware of the existence of the '098 patent prior to amending ANDA No. 77-255. Except as expressly admitted above, Teva denies the allegations of Paragraph 40 of the Amended Complaint.

41. Teva denies the allegations in Paragraph 41 of the Amended Complaint.

42. Teva admits that its Paragraph IV certification does not assert that claims 1, 2, 5, 6, 8, and 10 of the '098 patent are not infringed. Teva further admits that its Paragraph IV certification asserts that these claims are invalid. Except as expressly admitted, Teva denies the allegations set forth in Paragraph 42 of the Amended Complaint.

43. Teva denies the allegations in Paragraph 43 of the Amended Complaint.

44. Teva denies the allegations in Paragraph 44 of the Amended Complaint.

SECOND CLAIM FOR RELIEF

45. Teva incorporates by reference as if stated fully herein its responses to Paragraphs 1 through 44 of the Amended Complaint.

46. Teva denies the allegations in Paragraph 46 of the Amended Complaint.

47. Teva denies the allegations in Paragraph 47 of the Amended Complaint.

48. Teva denies the allegations in Paragraph 48 of the Amended Complaint.

49. Teva denies the allegations in Paragraph 49 of the Amended Complaint.

50. Teva denies the allegations in Paragraph 50 of the Amended Complaint.

THIRD CLAIM FOR RELIEF

51. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 50 of the Amended Complaint.

52. Teva denies the allegations in Paragraph 52 of the Amended Complaint.

53. Teva denies the allegations in Paragraph 53 of the Amended Complaint.

54. Teva denies the allegations in Paragraph 54 of the Amended Complaint.

55. Teva denies the allegations in Paragraph 55 of the Amended Complaint.

56. Teva denies the allegations in Paragraph 56 of the Amended Complaint.

57. Teva denies the allegations in Paragraph 57 of the Amended Complaint.

FOURTH CLAIM FOR RELIEF

58. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 57 of the Amended Complaint.

59. Teva denies the allegations in Paragraph 59 of the Amended Complaint.

60. Teva denies the allegations in Paragraph 60 of the Amended Complaint.

61. Teva denies the allegations in Paragraph 61 of the Amended Complaint.

62. Teva denies the allegations in Paragraph 62 of the Amended Complaint.

63. Teva denies the allegations in Paragraph 63 of the Amended Complaint.

FIFTH CLAIM FOR RELIEF

64. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 63 of the Amended Complaint.

65. Teva denies the allegations in Paragraph 65 of the Amended Complaint.

66. Teva denies the allegations in Paragraph 66 of the Amended Complaint.

67. Teva denies the allegations in Paragraph 67 of the Amended Complaint.

68. Teva denies the allegations in Paragraph 68 of the Amended Complaint.

69. Teva denies the allegations in Paragraph 69 of the Amended Complaint.

70. Teva denies the allegations in Paragraph 70 of the Amended Complaint.

SIXTH CLAIM FOR RELIEF

71. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 70 of the Amended Complaint.

72. Teva denies the allegations in Paragraph 72 of the Amended Complaint.

73. Teva denies the allegations in Paragraph 73 of the Amended Complaint.

74. Teva denies the allegations in Paragraph 74 of the Amended Complaint.

75. Teva denies the allegations in Paragraph 75 of the Amended Complaint.

76. Teva denies the allegations in Paragraph 76 of the Amended Complaint.

SEVENTH CLAIM FOR RELIEF

77. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 76 of the Amended Complaint.

78. Teva denies the allegations in Paragraph 78 of the Amended Complaint.

79. Teva denies the allegations in Paragraph 79 of the Amended Complaint.

80. Teva denies the allegations in Paragraph 80 of the Amended Complaint.

81. Teva denies the allegations in Paragraph 81 of the Amended Complaint.

82. Teva denies the allegations in Paragraph 82 of the Amended Complaint.

83. Teva denies the allegations in Paragraph 83 of the Amended Complaint.

EIGHTH CLAIM FOR RELIEF

84. Teva incorporates by reference as if stated fully herein its responses to Paragraphs 1 through 83 of the Amended Complaint.

85. Teva denies the allegations in Paragraph 85 of the Amended Complaint.

86. Teva denies the allegations in Paragraph 86 of the Amended Complaint.

87. Teva denies the allegations in Paragraph 87 of the Amended Complaint.

88. Teva denies the allegations in Paragraph 88 of the Amended Complaint.

89. Teva denies the allegations in Paragraph 89 of the Amended Complaint.

NINTH CLAIM FOR RELIEF

90. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 89 of the Amended Complaint.

91. Teva denies the allegations in Paragraph 91 of the Amended Complaint.

92. Teva denies the allegations in Paragraph 92 of the Amended Complaint.

93. Teva denies the allegations in Paragraph 93 of the Amended Complaint.

94. Teva denies the allegations in Paragraph 94 of the Amended Complaint.

95. Teva denies the allegations in Paragraph 95 of the Amended Complaint.

96. Teva denies the allegations in Paragraph 96 of the Amended Complaint.

TENTH CLAIM FOR RELIEF

97. Teva incorporates by reference as if fully stated herein its responses to Paragraphs 1 through 96 of the Amended Complaint.

98. Teva denies the allegations in Paragraph 98 of the Amended Complaint.

99. Teva denies the allegations in Paragraph 99 of the Amended Complaint.

100. Teva denies the allegations in Paragraph 100 of the Amended Complaint.

101. Teva denies the allegations in Paragraph 101 of the Amended Complaint.

102. Teva denies the allegations in Paragraph 102 of the Amended Complaint.

103. To the extent any allegation in any paragraph of Plaintiffs' Amended Complaint is not specifically admitted or otherwise responded to, it is hereby denied.

DEFENSES

FIRST DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 4,628,098 ("the '098 patent").

SECOND DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,026,560 ("the '560 patent").

THIRD DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,045,321 ("the '321 patent").

FOURTH DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,093,132 ("the '132 patent").

FIFTH DEFENSE

Teva has not infringed, is not infringing and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of U.S. Patent No. 5,433,959 ("the '959 patent").

SIXTH DEFENSE

Upon information and belief, the claims of the '098 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

SEVENTH DEFENSE

Upon information and belief, the claims of the '560 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

EIGTH DEFENSE

Upon information and belief, the claims of the '321 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

NINTH DEFENSE

Upon information and belief, the claims of the '132 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

TENTH DEFENSE

Upon information and belief, the claims of the '959 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103, and/or 112.

ELEVENTH DEFENSE

As set forth in greater detail in paragraphs 28-34 of the Counterclaim below, which paragraphs are incorporated herein by reference, the claims of the '098 patent are unenforceable as procured through inequitable conduct before the United States Patent and Trademark Office ("PTO").

In violation of Takeda's duty of candor to the PTO under 37 C.F.R. § 1.56, Takeda intentionally misled the PTO concerning the effectiveness of the alleged invention during prosecution of patent application no. 06/760,568 ("the '568 application"), the application that led to the issuance of the '098 patent. More particularly, to support patentability of the '568 application, Takeda asserted that the alleged invention exhibited superior anti-ulcer activity, up to 20 times more effective, over "known" prior art compounds. (See, e.g., '098 patent, col. 6, ll. 5-36.)

Having chosen to assert efficacy data as a basis for patentability, any efficacy data that was not cumulative of and that refuted or was inconsistent with the submitted data became material to patentability and would have been considered important by a reasonable examiner in deciding whether or not to allow the application to issue as a patent. Takeda had a duty under 37 C.F.R. § 1.56 to disclose all such data in its possession to the PTO during the prosecution of the of the application that led to the '098 patent. Takeda, however, chose not to disclose the material test data or reports thereof or to correct the misrepresentations in its patent application. Takeda did so with the intent to deceive the PTO concerning the patentability of the application, and therefore is guilty of inequitable conduct rendering the '098 patent unenforceable.

TWELFTH DEFENSE

As set forth in greater detail in paragraphs 28-42 of the Counterclaims below, which paragraphs are incorporated herein by reference, the patent term extension for the '098 patent is unenforceable.

On July 6, 1995, Takeda filed for a patent term extension for the '098 patent pursuant to 35 U.S.C. §§ 155-156. On January 6, 1997, the PTO awarded Takeda a patent term extension of 1381 days extending the term of the patent to May 10, 2009. Without that patent term extension, the '098 patent would be expired and would not be part of this action.

At the time it sought the patent term extension, Takeda knew that the '098 patent was invalid and unenforceable due to its inequitable conduct before the PTO during prosecution. Takeda knew that it misrepresented the efficacy data in the table at Column 6 comparing the claimed invention to prior art compounds and that it withheld test results that made clear that the claimed invention did not show the superior efficacy that was the basis for Takeda's claim of patentability.

Moreover, Takeda continued to test the efficacy of the claimed invention against prior art compounds after issuance of the '098 patent. The results of those efficacy tests further confirmed to Takeda that the claimed invention was not superior to the prior art compounds as represented to the PTO. Despite knowing that it misrepresented the efficacy data and that it failed to disclose material efficacy test results, Takeda continued to pursue the patent term extension through the PTO.

Takeda's failures to disclose its misrepresentations to the PTO and the underlying efficacy test results, both during and after prosecution, were material to Takeda's entitlement to the extension under 37 C.F.R. § 1.765 because there is a substantial likelihood the PTO would have considered such adverse information important in considering whether to grant the extension. Takeda knew that the patent was invalid and unenforceable upon filing for and during prosecution of the patent term extension. The patent term extension granted for the '098 patent therefore is unenforceable.

COUNTERCLAIMS

Defendants Teva hereby counterclaim against Plaintiffs, and in support thereof, allege as follows:

1. The Plaintiffs have filed an Amended Complaint against Teva seeking, *inter alia*, a judgment that Teva infringed the claims of the '098 patent, the '560 patent, the '321 patent, the '132 patent, and the '959 patent (collectively "the patents-in-suit") by Teva USA filing ANDA No. 77-255 and a Paragraph IV certification. As a result of the filing of the Amended Complaint, an immediate and justiciable controversy exists between the Plaintiffs and Teva regarding the alleged infringement and validity of the patents-in-suit.

2. The following counterclaims arise under the patent laws of the United States, 35 U.S.C. § 1, *et seq.* and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

3. This Court has personal jurisdiction over the Plaintiffs because, *inter alia*, the Plaintiffs have submitted to the jurisdiction of this Court by filing Plaintiffs' Amended Complaint.

4. Subject matter jurisdiction in this Court is proper under, *inter alia*, 28 U.S.C. §§ 1331 and 1338.

5. Venue is proper in this Court because, *inter alia*, the Plaintiffs have submitted to the jurisdiction of this Court and selected this venue by filing their Complaint with this Court.

COUNT ONE
(Non-infringement of the '098 Patent)

6. Teva incorporates by reference all allegations contained in Paragraphs 1 through 5 of its Counterclaims.

7. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '098 patent.

COUNT TWO
(Non-infringement of the '560 Patent)

8. Teva incorporates by reference all allegations contained in Paragraphs 1 through 7 of its Counterclaims.

9. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '560 patent.

COUNT THREE
(Non-infringement of the '321 Patent)

10. Teva incorporates by reference all allegations contained in Paragraphs 1 through 9 of its Counterclaims.

11. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '321 patent.

COUNT FOUR
(Non-infringement of the '132 Patent)

12. Teva incorporates by reference all allegations contained in Paragraphs 1 through 11 of its Counterclaims.

13. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '132 patent.

COUNT FIVE
(Non-infringement of the '959 Patent)

14. Teva incorporates by reference all allegations contained in Paragraphs 1 through 13 of its Counterclaims.

15. Teva has not infringed, is not infringing, and will not infringe, literally or under the Doctrine of Equivalents, any valid and enforceable claim of the '959 patent.

COUNT SIX
(Declaration of Invalidity of the '098 Patent)

16. Teva incorporates by reference the allegations contained in paragraphs 1-15 of its Counterclaims.

17. The claims of the '098 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT SEVEN
(Declaration of Invalidity of the '560 Patent)

18. Teva incorporates by reference the allegations contained in paragraphs 1-17 of its Counterclaims.

19. The claims of the '560 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT EIGHT
(Declaration of Invalidity of the '321 Patent)

20. Teva incorporates by reference the allegations contained in paragraphs 1-19 of its Counterclaims.

21. The claims of the '321 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT NINE
(Declaration of Invalidity of the '132 Patent)

22. Teva incorporates by reference the allegations contained in paragraphs 1-21 of its Counterclaims.

23. The claims of the '132 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT TEN
(Declaration of Invalidity of the '959 Patent)

24. Teva incorporates by reference the allegations contained in paragraphs 1-23 of its Counterclaims.

25. The claims of the '959 patent are invalid for failure to comply with requirements of the patent laws of the United States, including, without limitation, 35 U.S.C. §§ 101, 102, 103 and/or 112.

COUNT ELEVEN
(Declaration of Award of Attorneys' Fees, Costs, and Expenses)

26. Teva incorporates by reference the allegations contained in paragraphs 1-25 of its Counterclaims.

27. This action is an exceptional case under 35 U.S.C. § 285, and Teva is entitled to reimbursement of attorneys' fees, costs, and expenses from Plaintiffs.

COUNT TWELVE
(Declaration of Unenforceability of the '098 Patent Due to Inequitable Conduct)

28. Teva incorporates by reference the allegations contained in paragraphs 1-27 of its Counterclaims.

29. In violation of Takeda's duty of candor to the PTO under 37 C.F.R. § 1.56, Takeda intentionally misled the PTO concerning the effectiveness of the alleged invention during prosecution of patent application no. 06/760,568 ("the '568 application"), the application that led to the issuance of the '098 patent. More particularly, to support patentability of the '568 application, Takeda represented to the PTO in the application that led to the '098 patent that prior art compounds' "gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents." (*See* '098 patent, Col. 1, ln. 14-16.)

30. Takeda further asserted that the alleged invention exhibited superior anti-ulcer activity, up to 20 times more effective, over "known" prior art compounds and summarized

results of unidentified test data in the table located in Column 6 of the '098 patent. (See, e.g., '098 patent, col. 6, ll. 5-36.)

31. Takeda's internal documents and test results, including monthly status reports and test data reports, dated prior to issuance of the '098 patent show that Takeda knew that the claimed invention was not superior to certain prior art compounds and certainly not 20 times superior to competitive anti-ulcer prior art compounds.

32. Having chosen to assert efficacy data as a basis for patentability, any efficacy data that was not cumulative of and that refuted or was inconsistent with the submitted data became material to patentability and would have been considered important by a reasonable examiner in deciding whether or not to allow the application to issue as a patent. Takeda had a duty under 37 C.F.R. § 1.56 to disclose all such data in its possession to the PTO during the prosecution of the of the application that led to the '098 patent. Takeda, however, chose not to disclose the material test data or reports thereof or to correct the misrepresentations in its patent application. Takeda did so with the intent to deceive the PTO concerning the patentability of the application, and therefore is guilty of inequitable conduct rendering the '098 patent unenforceable.

33. The efficacy of the claimed invention relative to prior art compounds is material to patentability. Takeda had a duty to disclose the test data or results thereof demonstrating efficacy data contrary to the representations made during prosecution to the PTO pursuant to 37 C.F.R. § 1.56 but failed to disclose any test data or reports thereof.

34. Takeda intentionally misrepresented the efficacy of the claimed invention to the PTO during prosecution to support patentability and intentionally did not disclose to the PTO contemporaneous test results material to patentability with the intent to deceive the PTO.

35. For at least the foregoing reasons, the '098 patent is unenforceable.

COUNT THIRTEEN
(Declaration of Unenforceability of the Patent Term Extension for the '098 Patent)

36. Teva incorporates by reference the allegations contained in paragraphs 1-35 of its Counterclaims.

37. The '098 patent issued on December 9, 1986. On July 6, 1995, Takeda applied for a Patent Term Extension pursuant to 35 U.S.C. §§ 155-156. On January 6, 1997, the PTO awarded Takeda a Patent Term Extension of 1381 days extending the term of the patent to May 10, 2009.

38. At the time it sought the patent term extension, Takeda knew that the '098 patent was invalid and unenforceable due to its inequitable conduct before the PTO during prosecution. As described in detail in paragraphs 28-35, Takeda misrepresented the efficacy of the claimed invention over prior art compounds and withheld material test data and reports demonstrating the lack of superior efficacy represented by Takeda to the PTO. Takeda knew that the '098 patent therefore was invalid and unenforceable.

39. After issuance of the '098 patent, Takeda continued to test the efficacy of the claimed invention against prior art compounds. Takeda's test results further confirmed to Takeda that the claimed invention does not have the superior efficacy as represented in the table at Column 6 of the '098 patent.

40. Despite knowing that it misrepresented the efficacy data and that it failed to disclose material efficacy test results, Takeda continued to pursue the patent term extension through the PTO.

41. Takeda's failures to disclose its misrepresentations to the PTO and the underlying efficacy test results, both during and after prosecution, were material to Takeda's entitlement to the extension under 37 C.F.R. § 1.765 because there is a substantial likelihood the PTO would have considered such adverse information important in considering whether to grant the extension. Takeda knew that the patent was invalid and unenforceable upon filing for and during prosecution of the patent term extension.

42. For at least the foregoing reasons, the patent term extension granted for the '098 patent is unenforceable.

PRAYER FOR RELIEF

WHEREFORE, Teva respectfully requests that this Court enter a Judgment and Order:

(a) dismissing the Amended Complaint, and each and every claim for relief contained therein, with prejudice;

(b) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '098 patent;

(c) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '560 patent;

(d) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '321 patent;

(e) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '132 patent;

(f) declaring Teva USA has not infringed and is not infringing any valid and enforceable claim of the '959 patent;

(g) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '098 patent;

(h) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '560 patent;

(i) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '321 patent;

(j) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '132 patent;

(k) declaring Teva Ltd. has not infringed and is not infringing any valid and enforceable claim of the '959 patent;

(l) declaring all claims of the '098 patent invalid;

(m) declaring all claims of the '560 patent invalid;

(n) declaring all claims of the '321 patent invalid;

(o) declaring all claims of the '132 patent invalid;

(p) declaring all claims of the '959 patent invalid;

(q) declaring all claims of the '098 patent are unenforceable;

(r) declaring the patent term extension of the '098 patent is unenforceable;

(s) ~~(q)~~ declaring this an exceptional case under 35 U.S.C. § 285 and awarding Teva its attorneys' fees, costs, and expenses; and

(t) ~~(r)~~ granting Teva such other and further relief as this Court deems just and proper.

Respectfully submitted this ~~29th~~ ___ day of ~~June~~March, ~~2006~~2007.

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REDACTED VERSION – PUBLICLY FILED

REDACTED VERSION – PUBLICLY FILED

EXHIBIT C

REDACTED VERSION – PUBLICLY FILED

United States Patent [19]

Nohara et al.

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[45] **Date of Patent: Dec. 9, 1986**

[54] **2-[2-PYRIDYLMETHYLTHIO-(SULFINYL)-]BENZIMIDAZOLES**

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[4] **C07D 401/12**

[52] **U.S. Cl.** **546/271**

[58] **Field of Search** 546/271

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,045,563	8/1977	Berntsson et al.	546/271
4,255,431	3/1981	Junggren et al.	546/271
4,472,409	9/1984	Jenn-Bilfinger	546/271
4,575,554	3/1986	Sih	546/271

FOREIGN PATENT DOCUMENTS

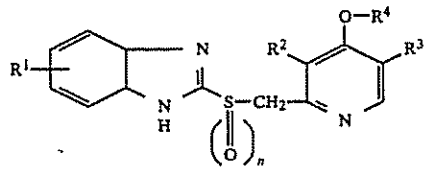
5129	10/1979	European Pat. Off. .
45200	2/1982	European Pat. Off. .
74341	3/1983	European Pat. Off. .
2134523A	8/1984	United Kingdom .

Primary Examiner—Jane T. Fan

Attorney, Agent, or Firm—Wegner & Bretschneider

[57] **ABSTRACT**

The compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof is novel, and useful for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis.

36 Claims, No Drawings

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2-[2-PYRIDYLMETHYLTHIO-(SULFINYL)]BENZIMIDAZOLES

This invention relates to pyridine derivatives useful as e.g. anti-ulcer agents and to a method of preparing them.

As the pyridine derivatives having anti-ulcer activity, those disclosed in U.S. Pat. No. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/79) and U.S. Pat. No. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/83) etc. have been known.

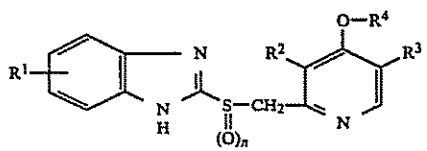
However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as being unstable and readily decomposed.

It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors, e.g. hydrochloric acid, pepsin, and defensive factors, e.g. mucus secretion and mucosal blood flow. Therefore, a medicine having both an action of inhibiting gastric acid secretion and an action of enhancing protection of gastric mucosa has been desired.

The present inventors diligently studied with the purpose of preparing an anti-ulcer agent having excellent actions of inhibiting gastric acid secretion, of protecting gastric mucosa and of antagonizing ulceration. They found that a certain type of pyridine derivatives meets the said purpose, and they conducted further study to accomplish the present invention.

The present invention relates to

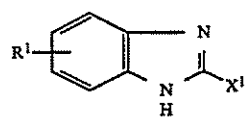
(1) pyridine derivatives of the formula (I)



(I)

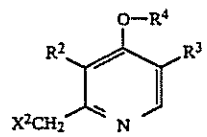
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(2) a method for preparing a compound (I) or its pharmacologically acceptable salt, which comprises allowing a compound of the formula (II)



(II)

wherein R^1 is of the same meaning as defined above, to react with a compound of the formula (III)



(III)

wherein R^2, R^3 and R^4 are of the same meaning as defined above, one of X^1 and X^2 is SH and the other is a leaving group and, when necessary, by subjecting the reaction product to oxidation.

In the above formulae, C_{2-5} fluorinated alkyl groups shown by R^4 are exemplified by 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl and 2,2,3,3,4,4,5,5-octafluoropentyl.

Examples of the leaving groups X^1 and X^2 in the above formulae are halogen, preferably chlorine, bromine or iodine, or a reactive esterified hydroxy group, e.g. an arylsulfonyloxy, for example, phenylsulfonyloxy or tosyloxy, or C_{1-4} alkylsulfonyloxy, for example, methanesulfonyloxy, or an organic phosphoryloxy, for example, diphenylphosphoryloxy, dibenzylphosphoryloxy or di-C_{1-4}alkylphosphoryloxy and the like.

R^1 may be located at 4- or 5-position, and preferably at 5-position.

A sulfide derivative (I) (n=0), among the object compounds of this invention, can be prepared by allowing a compound (II) to react with a compound (III). It is convenient to conduct this reaction in the presence of a base. The base is exemplified by alkali metal hydride e.g. sodium hydride and potassium hydride; alkali metal e.g. metallic sodium; sodium alcoholate e.g. sodium methoxide and sodium ethoxide; alkali metal carbonate e.g. potassium carbonate and sodium carbonate; and organic amines e.g. triethylamine. The solvent used for the reaction is exemplified by alcohols e.g. methanol and ethanol, as well as dimethylformamide. The amount of a base used for the reaction is usually in a little excess to the equivalent, but it may be in a large excess. Specifically, it is about 1–10 equivalents, more preferably about 1–equivalents. The reaction temperature ranges usually from about 0° C. to about the boiling point of the solvent then used, more preferably from about 20° C. to about 80° C. The reaction time ranges from about 0.2 to about 24 hours, more preferably from about 0.5 to about 2 hours.

A sulfinyl derivative (I) (n=1), which is also among the object compounds of this invention, can be prepared by subjecting a compound (I) (n=0) to oxidation. The oxidizing agent to be employed here is exemplified by peracid e.g. m-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid, or sodium bromite or sodium hypochlorite or hydrogen peroxide. The solvent used for the reaction is exemplified by halogenated hydrocarbon e.g. chloroform and dichloromethane, ethers e.g. tetrahydrofuran and dioxane, amides e.g. dimethylformamide, alcohols, e.g. methanol, ethanol, propanol, and t-butanol or water, and these solvents may used singly or in admixture. The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to the compound (I) (n=0). Specifically, it is about 1 to about 3 equivalents, more preferably about 1–1.5 equivalent. The reaction temperature ranges from that under ice-cooling to about the boiling point of the solvent then employed, usually from that under ice-cooling to room temperature, more preferably from about 0° C. to about 10° C. The reaction time usually ranges from about 0.1 to about 24 hours, more preferably from about 0.1 to about 4 hours.

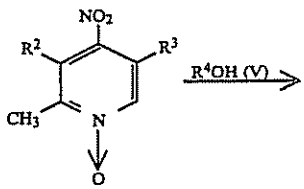
The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

The compound (I) of this invention may be led to pharmacologically acceptable salts thereof by per se conventional means, the salts being exemplified by hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate.

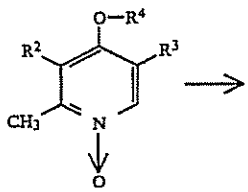
Among the compounds (I), those of n=0 give stable salts, while those of n=1 may exist as an aqueous solution though unstable.

The process of preparing the starting material (III) is described as follows.

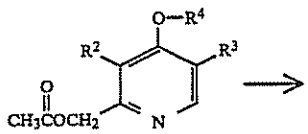
(Process 1)



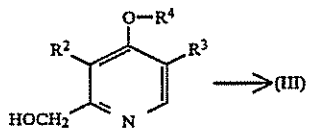
(IV)



(VI)



(VII)



(III)

(VIII)

A nitro compound of the formula (IV) [wherein R^2 and R^3 are of the same meaning as defined above] is allowed to react with an alcohol derivative R^4OH (V) [wherein R^4 is of the same meaning as defined above] in the presence of a base to give an alkoxy derivative of the formula (VI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The base is exemplified by alkali metal e.g. lithium, sodium and potassium; alkali metal hydride e.g. sodium hydride and potassium hydride; alcoholate e.g. potassium t-butoxide and sodium propoxide; alkali metal carbonate or hydrogen carbonate e.g. potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate; or alkali hydroxide e.g. sodium hydroxide and potassium hydroxide. The solvent used for the reaction is exemplified by, besides R^4OH itself, ethers such as tetrahydrofuran and dioxane as well as ketones such as acetone and methyl ethyl ketone, acetonitrile, dimethylformamide and hexamethylphosphoric acid triamide. The reaction temperature is suitably selected within the range from those under ice-cooling to those near the boiling point of the solvent used. The reaction time ranges usually from about 1 to about 48 hours.

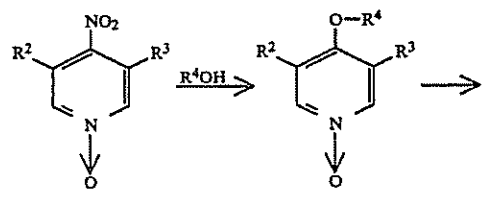
The thus-obtained compound (VI) is subjected to heating (about 80° to about 120° C.) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction time ranges usually from about 0.1 to about 10 hours.

Then, the compound (VII) is subjected to alkali-hydrolysis to give a 2-hydroxymethyl pyridine derivative of the formula (VIII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The alkali is exemplified by sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. The solvent used for the reaction is exemplified by methanol, ethanol and water. The reaction temperature ranges usually from about 20° C. to about 60° C. The reaction time is within the range of from about 0.1 to about 2 hours.

The compound (VIII) is further subjected to reaction with a chlorinating agent such as thionyl chloride, or an esterifying agent, e.g. an organic sulfonic acid chloride such as methanesulfonyl chloride or p-toluenesulfonyl chloride, or an organic phosphoric acid chloride such as diphenylphosphoryl chloride to give the compound (III). The amount of the chlorinating agent used for the reaction is usually in equivalent to a large excess relative to the compound (VIII). The solvent used for the reaction is exemplified by chloroform, dichloromethane and tetrachloroethane. The reaction temperature is usually within the range of from about 20° C. to about 80° C., and the reaction time is about 0.1 to about 2 hours.

The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic base e.g. sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The amount of a base used for the reaction is usually in equivalent to a little excess. The solvent used for the reaction is exemplified by chloroform, dichloromethane, carbon tetrachloride or acetonitrile. The reaction temperature ranges usually from that under ice-cooling to about the boiling point of the solvent then used. The raction time ranges usually from a few minutes to a few hours. It is usually preferable to use the thus-produced compound (III) immediately for the reaction with a compound (II).

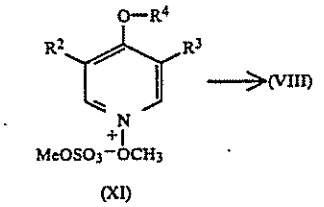
(Process 2)



(IX) (X)

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-continued



(XI)

By a reaction similar to the above-described process (I), a compound of the formula (IX) [wherein R^2 and R^3 are of the same meaning as defined above] is led to a compound of the formula (X) [wherein R^2, R^3 and R^4 are of the same meaning as defined above].

Then, the compound (X) is subjected to methylation with dimethyl sulfate to give a compound of the formula (XI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction can be conducted usually without solvent. The reaction temperature ranges from about 100° C. to about 120° C., and the reaction time is within the range of from about 0.1 to about 4 hours.

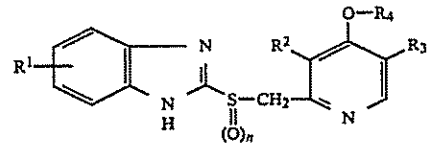
Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20° C. to about 80° C., and the reaction time ranges from about 0.5 to about 4 hours.

Pharmacological actions of the compounds of the present invention are described as follows.

As the models of gastrointestinal ulcers, restraint and water-immersion stress-induced ulcer, indomethacin-induced ulcer and ethanol-induced gastric mucosal lesions have been used. However, as a model mimicking human gastric ulcer, indomethacin-induced gastric antral ulcer was reported in "Gastroenterology" (Satoh et al. 81, p. 719, 1981), which is considered to be of value as an experimental model. Therefore, the following are data of anti-ulcer actions of the object compounds (I) and of some representable known compounds, on the ulcer model in the above-mentioned literature reference. Experimental Method:

Male Sprague-Dawley rats of 7-weeks old were fasted for 24 hours. These animals were administered test compounds into stomach by using a gastric tube. After 30 minutes, indomethacin, 30 mg/kg subcutaneously, was administered. During 30–90 minutes after the administration of indomethacin, these animals had free access to chow pellets (Japan Clea, CE-2). At 5 hours after the administration of indomethacin, 1 ml of 1% Evans blue was injected to the animals via the tail vein, followed by sacrificing these animals with carbon dioxide gas. The stomach was removed together with the lower part of esophagus and the duodenum. The esophagus was clipped, 10 ml of 1% formalin solution was instilled into the stomach from the duodenum, and then the duodenum was clipped. The whole stomach waa immersed in 1% formalin solution. About 15 minutes later, the stomachs were opened along the greater curvature. The area of the lesions which occurred in the gastric antral mucosa was measured under a dissecting microscope with a square-grid eye piece (x10). The sum total of the individual lesions in each animal was measured, and the average value per group was calculated. Based on the difference between the average value of each group and that of the control group, the inhibition rate was determined. The test compound and indomethacin were suspended in a 5% gum arabic solution, respectively and administered in a volume of 2 ml/kg.

Experimental Results:



R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	H	H	CH_2CF_3	1	2.4
H	CH_3	H	CH_2CF_3	1	<1.0
H	H	H	$CH_2CF_2CF_3$	1	1.3
H	CH_3	H	$CH_2CF_2CF_3$	1	<1.0
H	H	H	$CH_2CF_2CF_2H$	1	1.3
H	CH_3	H	$CH_2CF_2CF_2H$	1	<1.0
H	CH_3	H	$CH_2CF_2CF_3$	0	3.7
5-OCH_3	CH_3	CH_3	CH_3*1		21.0
5-CF_3	CH_3	H	CH_3*2		5.5

*1The compound disclosed in Example 23 of USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/1979)

*2The compound disclosed in Example 3 of USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/1983)

[a]Using 6 rats per group, each of the test compounds was administered in a dose of 1, 3, 10 and 30 mg/kg to determine ID_{50}.

As shown by the above data, the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5–20 times or more. Besides, the compound (I) of this invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucous membrane and preventing ulceration.

Regarding about the toxicity of the compound (I) of this invention, oral administration of the compound employed for the experiment of anti-ulceration (compound of R^1=H, R^2=CH_3, R^3=H, R^4=$CH_2CF_2CF_3$, n=1) to mice even in a dose of 2000 mg/kg caused no fatal effect; thus the compound (I) is low in toxicity.

As described in the foregoing, the compound (I) of this invention has an anti-ulcer action, a gastric acid secretion controlling action and a mucous membrane protecting action, furthermore is of low toxicity and is relatively stable as a chemical substance. The compound (I) of this invention can thus be used for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis in mammalian animals (e.g. mouse, rat, rabbit, dog, cat and man).

When the compound (I) of this invention is used as an anti-ulcer agent for the therapy of digestive ulcers in mammalian animals, it can be administered orally in a dosage form of capsules, tablets, granules, etc. by formulating with a pharmacologically acceptable carrier, excipient, diluent, etc. The daily dose is about 0.01–30 mg/kg, more preferably about 0.1–3 mg/kg.

Incidentally, the compound of this invention (I) (n=0) is useful as a starting material for preparing the compound (I) (n=1).

The processes of producing the starting compounds to be employed in the method of this invention as well as those of producing the compound (I) of this invention are specifically explained by the following Reference Examples and Working Examples.

REFERENCE EXAMPLE 1

In 2,2,3,3-tetrafluoropropanol (10 ml) was dissolved 2,3-dimethyl-4-nitropyridine-1-oxide (2 g). To the solution was added potassium t-butoxide (1.6 g) little by little at room temperature. The mixture was then heated at 80°–90° C. for 22 hours. The reaction solution was diluted with water, which was subjected to extraction with chloroform. The extract was dried on magnesium sulfate, and then concentrated. The concentrate was chromatographed on a column of silica gel (70 g). Elution was conducted with methanol-chloroform (1:10), and then subjected to recrystallization from ethyl acetate-hexane to yield 2.6 g of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 138°–139° C.

After the manner above, compounds (VI) were prepared from compounds (IV).

		Compound (VI)	
R^2	R^3	R^4	Melting point (°C.)
H	H	CH_2CF_3	148–150
CH_3	CH_3	CH_2CF_3	138–139

REFERENCE EXAMPLE 2

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethyl phosphoric acid triamide (2.07 g) was heated at 70°–80° C. for 4.5 days under stirring, then insolubles were filtered off. The filtrate was concentrated, to which was added water. The mixture was subjected to extraction with ethyl acetate. The extract solution was dried on magnesium sulfate, followed by removing the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from ethyl acetate-hexane to yield 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 148°–149° C.

By this process, compounds (VI) were prepared from starting compounds (IV).

		Compound (VI)	
R^2	R^3	R^4	Melting point (°C.)
CH_3	H	CH_2CF_3	131.0–131.5
H	CH_3	CH_2CF_3	153–154
H	H	$CH_2CF_2CF_3$	79–81
H	CH_3	$CH_2CF_2CF_3$	140–142
H	H	$CH_2CF_2CF_2H$	Oily
H	CH_3	$CH_2CF_2CF_2H$	143.5–144.5
CH_3	H	$CH_2CF_2CF_2H$	138–139

REFERENCE EXAMPLE 3

Concentrated sulfuric acid (two drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide (2.6 g) in acetic anhydride (8 ml). The mixture was stirred at 110° C. for 4 hours, which was then concentrated. The residue was dissolved in methanol (20 ml), to which was added sodium hydroxide (1.2 g) dissolved in water (5 ml). The mixture was stirred at room temperature for 30 minutes, which was concentrated. To the residue was added water, and the mixture was subjected to extraction with ethyl acetate. The extract was dried on magnesium sulfate, followed by removal of the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from isopropyl ether to yield 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine as yellow crystals, m.p. 67°–68° C.

By this process, compounds (VIII) were prepared from compounds (VI).

		Compound (VIII)	
R^2	R^3	R^4	Melting point (°C.)
H	H	CH_2CF_3	Oily
CH_3	H	CH_2CF_3	93.5–94.0
H	H	$CH_2CF_2CF_3$	Oily
CH_3	H	$CH_2CF_2CF_3$	Oily
H	CH_3	$CH_2CF_2CF_3$	87–89
H	H	$CH_2CF_2CF_2H$	88–89
H	CH_3	$CH_2CF_2CF_2H$	98–99
CH_3	H	$CH_2CF_2CF_2H$	67–68

REFERENCE EXAMPLE 4

To a solution of 3,5-dimethyl-4-nitropyridine-1-oxide (2.0 g) in 2,2,3,3,3-pentafluoropropanol (10 g) was added at 0° C. little by little potassium t-butoxide (2 g) over 15 minutes. The mixture was stirred at 60° C. for 18 hours. To the reaction mixture was added chloroform, which was subjected to filtration with celite. The filtrate was chromatographed on a column of silica gel (80 g), eluted with ethyl acetate-hexane (1:1), then with 20% methanol-ethyl acetate, and recrystallized from ether-hexane to yield 2.6 g of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as crystals, m.p. 89°–91° C.

By this process, compounds (X) were prepared from compounds (IX).

		Compound (X)	
R^2	R^3	R^4	Melting point (°C.)
CH_3	H	CH_2CF_3	82–94
CH_3	CH_3	CH_2CF_3	138–139

REFERENCE EXAMPLE 5

A mixture of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide (2.5 g) and dimethyl sulfate (1 ml) was heated at 120° C. for 30 minutes, to which was then added methanol (12.5 ml). To the mixture was added dropwise at 80° C. ammonium persulfate (4.3 g) dissolved in water (20 ml)-methanol (10 ml) over 30 minutes, which was stirred for further 30 minutes. The resultant solution was concentrated. To the residue was added ice, which was neutralized with sodium carbonate, followed by extraction with chloroform. The extract was dried on sodium sulfate, followed by removing the solvent by evaporation to give 2.2 g of 3,5-dimethyl-2-hydroxymethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as an oily substance.

By this process, compounds (VIII) were prepared from compounds (X).

		Compound (VIII)	
R^2	R^3	R^4	Melting point (°C.)
H	CH_3	CH_2CF_3	116–119
CH_3	CH_3	CH_2CF_3	62–63

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EXAMPLE 1

To a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) was added thionyl chloride (0.2 ml). The mixture was refluxed for 30 minutes, which was then concentrated. The residue was dissolved in methanol (5 ml). The solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml), which was refluxed for 30 minutes. From the resultant was removed methanol by evaporation. To the residue was added water, which was subjected to extraction with ethyl acetate. The extract was washed with a dilute sodium hydroxide solution, followed by drying on magnesium sulfate. From the resultant was removed the solvent by evaporation. The residue was then chromatographed on a column of silica gel (20 g), eluted with ethyl acetate-hexane (2:1), and then recrystallized from ethyl acetate-hexane to yield 370 mg of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.½ hydrate as colorless plates, m.p. 145°–146° C.

By this process, compounds (I) (n=0) were prepared by allowing compounds (II) to react with compounds (III).

Compound (I) (n = 0)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	H	H	CH_2CF_3	138–139
H	CH_3	H	CH_2CF_3	149–150
H	H	CH_3	CH_2CF_3	168–170
H	CH_3	CH_3	CH_2CF_3	151.5–152.0
H	H	H	$CH_2CF_2CF_3$	125–126
H	H	CH_3	$CH_2CF_2CF_3$	151–152
H	H	H	$CH_2CF_2CF_2H$	Oily*3
H	CH_3	H	$CH_2CF_2CF_2H$	134–135
H	H	CH_3	$CH_2CF_2CF_2H$	148–149
H	CH_3	CH_3	$CH_2CF_2CF_3$	158–160
*4 5-CF_3	CH_3	H	CH_2CF_3	92–93
5-OCH_3	CH_3	H	CH_2CF_3	159–160
5-OCH_3	H	H	CH_2CF_3	152–153

*3NMR spectrum ($CDCl_3$)δ: 4.35(S), 4.39 (t,t,J=1.5 and 12 Hz), 5.98 (1H,t,t,J=52.5 and 4 Hz), 6.81 (1H,d,d,J=2 and 6 Hz) 6.95 (1H,d,J=2Hz), 7.1–7.3 (2H,m), 7.4–7.7 (2H,m), 8.50 (1H,d,J=6 Hz)

*4½H_2O (crystal water)

EXAMPLE 2

To a solution of 2-[3-methyl-4-(2,2,3,3,3,-pentafluoropropoxy)pyrid-2-yl-methylthiobenzimidazole (2.2 g) in chloroform (20 ml) was added dropwise under ice-cooling over a period of 30 minutes m-chloroperbenzoic acid (1.3 g) dissolved in chloroform (15 ml). The solution was washed with a saturated aqueous solution of sodium hydrogen carbonate, then dried on magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (50 g), eluted with ethyl acetate, and then recrystallized from aceton-isopropyl ether to give 1.78 g of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropxy)pyrid-2-yl]methylsulfinylbenzimidazole as pale yellow prisms, m.p. 161°–163° C. (decomp.).

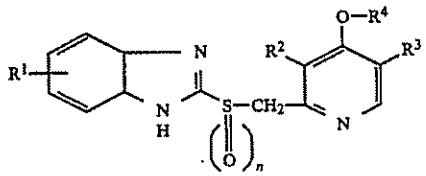
By this process, compounds (I) (n=1) were prepared from compounds (I) (n=0).

Compound (I) (n = 1)				
R^1	R^2	R^3	R^4	Melting point (°C.)
H	H	H	CH_2CF_3	176–177
H	CH_3	H	CH_2CF_3	178–182(d)
H	H	CH_3	CH_2CF_3	175–177(d)
H	CH_3	CH_3	CH_2CF_3	177–178(d)
H	H	H	$CH_2CF_2CF_3$	148–150(d)
H	H	CH_3	$CH_2CF_2CF_3$	145–148(d)
H	H	H	$CH_2CF_2CF_2H$	132–133
H	CH_3	H	$CH_2CF_2CF_2H$	147–148(d)
H	H	CH_3	$CH_2CF_2CF_2H$	136–139(d)
H	CH_3	CH_3	$CH_2CF_2CF_3$	157–159
5-CF_3	CH_3	H	CH_2CF_3	161–162(d)
5-OCH_3	CH_3	H	CH_2CF_3	140.5–142(d)
5-OCH_3	H	H	CH_2CF_3	162–163(d)

(Note) (d): decomposition

What we claim is:

1. A compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, and a pharmacologically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen.

3. A compound according to claim 1, wherein R^1 is methoxy.

4. A compound according to claim 1, wherein R^2 is hydrogen.

5. A compound according to claim 1, wherein R^2 is methyl.

6. A compound according to claim 1, wherein R^3 is hydrogen.

7. A compound according to claim 1, wherein R^3 is methyl.

8. A compound according to claim 1, wherein R^4 is a C_{2-3} fluorinated alkyl.

9. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

10. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

11. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

12. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

13. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

14. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-5-methyl-pyrid-2-yl]methylsulfinylbenzimidazole.

15. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

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16. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

17. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

18. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

19. A compound according to claim 1, wherein the compound is 2-[3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

20. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinyl-5-trifluoromethylbenzimidazole.

21. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinyl-5-methoxybenzimidazole.

22. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]-methylsulfinyl-5-methoxybenzimidazole.

23. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]-methylthiobenzimidazole.

24. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

25. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

26. A compound according to claim 1, wherein the compound is 2-[3,5-dimethyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthiobenzimidazole.

27. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

28. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

29. A compound according to claim 1, wherein the compound is 2-[4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

30. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

31. A compound according to claim 1, wherein the compound is 2-[5-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

32. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole.

33. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-5-methyl-pyrid-2-yl]methylthiobenzimidazole.

34. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl-methylthio-5-trifluoromethylbenzimidazole.

35. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl-methylthio-5-methoxybenzimidazole.

36. A compound according to claim 1, wherein the compound is 2-[4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylthio-5-methoxybenzimidazole.

* * * * *

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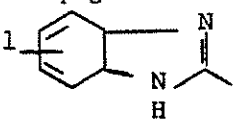
CERTIFICATE OF CORRECTION

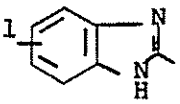
PATENT NO. : 4,628,098

DATED : December 9, 1986

INVENTOR(S) : Akira NOHARA 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:

In the Abstract delete ""

and insert ----.

In column 1, line 40, delete " (O)n" and insert ----.

In column 4, line 52, delete "raction" and insert --reaction--.

In column 6, line 10, delete " (O)n and insert ----.

In column 9, line 49, delete "pyrid-2-yl-methyl" and insert --pyrid-2-yl]methyl--.

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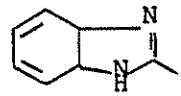
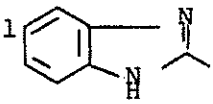
CERTIFICATE OF CORRECTION

PATENT NO. : 4,628,098

DATED : December 9, 1986

INVENTOR(S) : Akira NOHARA et al

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

In column 10, line 23, claim 1, delete "" and insert ----.

Signed and Sealed this

Twelfth Day of April, 1988

Attest:

DONALD J. QUIGG

Attesting Officer

Commissioner of Patents and Trademarks

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,628,098
ISSUED	:	December 9, 1986
INVENTOR(S)	:	Akira Nohara et al.
PATENT OWNER	:	Takeda Chemical Industries Ltd.

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1381 days

from the original expiration date of the patent, July 29, 2005, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the Patent and Trademark Office to be affixed this 6th day of January 1997.

Bruce A. Lehman
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

EXHIBIT D

[REDACTED]

EXHIBIT E

[REDACTED]

EXHIBIT F

[REDACTED]

EXHIBIT G

[REDACTED]

EXHIBIT H

[REDACTED]