IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., PFIZER PHARMACEUTICALS, LLC, PFIZER LIMITED, C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT LTD.,	)	
Plaintiffs,	)	
v.	)	
RANBAXY LABORATORIES LIMITED, and RANBAXY INC.,	)	
Defendants.	)	
	)	C.A. No. 07-138 (JJF)
RANBAXY LABORATORIES LIMITED, and RANBAXY INC.,	)	
Counterclaimants,	)	
v.	)	
PFIZER INC., PFIZER PHARMACEUTICALS, LLC, PFIZER LIMITED, C.P. PHARMACEUTICALS INTERNATIONAL C.V., PFIZER IRELAND PHARMACEUTICALS, WARNER-LAMBERT COMPANY, WARNER-LAMBERT COMPANY, LLC and WARNER-LAMBERT EXPORT LTD.,	)	
Counterdefendants,	)	

ANSWER AND COUNTERCLAIMS OF DEFENDANTS RANBAXY LABORATORIES LIMITED AND RANBAXY INC.

Defendants Ranbaxy Laboratories Limited and Ranbaxy Inc. (collectively, "Ranbaxy"), hereby answer the Complaint of Plaintiffs Pfizer Inc., Pfizer Pharmaceuticals, LLC, Pfizer Limited, C.P. Pharmaceuticals International C.V., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export Ltd. (collectively, "Pfizer"), as follows:

1. Ranbaxy admits that this action concerns U.S. Patent Nos. 4,681,893 (the "'893 patent") and 6,455,574 (the "'574 patent"). Ranbaxy admits that Exhibits A and B purport to be copies of the '893 and '574 patents, respectively. Ranbaxy denies any and all other allegations in paragraph 1 of the Complaint.

2. Ranbaxy admits the allegations in paragraph 2 of the Complaint.

3. Ranbaxy admits that the PTO issued the '574 patent on Sept. 24, 2002. Ranbaxy admits that the '574 patent is entitled "Therapeutic Combination." Ranbaxy admits that the '574 patent identifies Jan Buch as inventor and Pfizer Inc. as assignee. Ranbaxy denies any and all remaining allegations in paragraph 3 of the Complaint.

PARTIES, JURISDICTION AND VENUE[1]

4. Ranbaxy admits that Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware and has corporate offices at 235 East 42nd Street, New York, New York, 10017. Ranbaxy lacks sufficient information to respond to the remaining allegations in paragraph 4 of the Complaint, and therefore denies those allegations.

[1] For the Court's convenience, Ranbaxy has incorporated the "Headings" that appear in the Complaint. It should be understood, however, that Ranbaxy does not necessarily agree with the characterizations of such Headings, and does not waive any right to object to those characterizations.

5. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 5 of the Complaint, and therefore denies those allegations.

6. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 6 of the Complaint, and therefore denies those allegations.

7. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 7 of the Complaint, and therefore denies those allegations.

8. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 8 of the Complaint, and therefore denies those allegations.

9. Ranbaxy admits that Warner-Lambert Co. is a corporation formerly organized under the laws of the State of Delaware with offices for service of process at 235 East 42nd Street, New York, New York, 10017. Ranbaxy lacks sufficient information to respond to the remaining allegations in paragraph 9 of the Complaint, and therefore denies those allegations.

10. Ranbaxy admits the allegations in paragraph 10 of the Complaint.

11. Ranbaxy admits the allegations in paragraph 11 of the Complaint.

12. Ranbaxy admits that Pfizer Ireland Pharmaceuticals is a partnership, organized and existing under the laws of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. Ranbaxy admits that Pfizer Ireland Pharmaceuticals is a wholly owned subsidiary of Pfizer Inc. Ranbaxy lacks sufficient information to respond to the remaining allegations in paragraph 12 of the Complaint, and therefore denies those allegations.

13. Ranbaxy admits the allegations in paragraph 13 of the Complaint.

14. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 14 of the Complaint, and therefore denies those allegations.

15. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 15 of the Complaint, and therefore denies those allegations.

16. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 16 of the Complaint, and therefore denies those allegations.

17. Ranbaxy admits that the '893 patent is identified pursuant to 21 U.S.C. § 355(b)(1) in connection with Caduet. Ranbaxy denies any and all remaining allegations in paragraph 17 of the Complaint.

18. Ranbaxy admits that the '574 patent is identified pursuant to 21 U.S.C. § 355(b)(1) in connection with Caduet. Ranbaxy denies any and all remaining allegations in paragraph 18 of the Complaint.

19. Ranbaxy admits the allegations in paragraph 19 of the Complaint.

20. Ranbaxy denies the allegations in paragraph 20 of the Complaint.

21. Ranbaxy admits that Ranbaxy Laboratories Limited is a corporation organized and existing under the laws of India, having its principal place of business in Gurgaon (Haryana), India. Ranbaxy denies any and all remaining allegations in paragraph 21 of the Complaint.

22. Ranbaxy admits the allegations in paragraph 22 of the Complaint.

23. Paragraph 23 of the Complaint states legal conclusions to which no response is required. To the extent a response is required, Ranbaxy admits that this action arises under the Patent Laws of the United States, Title 35, and that this Court has

jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

24. Paragraph 24 of the Complaint states legal conclusions to which no response is required. To the extent a response is required, Ranbaxy admits that it is subject to personal jurisdiction in this District for this action.

25. Paragraph 25 of the Complaint states legal conclusions to which no response is required. To the extent a response is required, Ranbaxy admits that venue is proper in this District for this action.

THE PRIOR INFRINGEMENT LITIGATION AGAINST RANBAXY

26. Ranbaxy admits the allegations in paragraph 26 of the Complaint.

27. Ranbaxy admits that Pfizer Inc. received a letter dated January 23, 2003, from Ranbaxy Pharmaceuticals Inc., which notified Pfizer Inc. that Ranbaxy Laboratories Limited had filed an Abbreviated New Drug Application ("ANDA"), ANDA No. 76-477, seeking approval from the FDA to engage in the commercial manufacture, use, and sale of a product containing atorvastatin calcium as the active ingredient prior to the expiration of the '893 patent term extension. Ranbaxy denies any and all remaining allegations in paragraph 27 of the Complaint.

28. Ranbaxy admits the allegations in paragraph 28 of the Complaint.

29. Ranbaxy admits the allegations in paragraph 29 of the Complaint.

30. Ranbaxy admits the allegations in paragraph 30 of the Complaint.

31. Ranbaxy admits that, in response to Pfizer's Complaints, Ranbaxy filed Answers, amended Answers and several Counterclaims. Ranbaxy denies any and all remaining allegations in paragraph 31 of the Complaint.

32. Ranbaxy admits that its Answers, amended Answers and Counterclaims averred that Ranbaxy did not infringe the '893 patent. Ranbaxy denies any and all remaining allegations in paragraph 32 of the Complaint.

33. Ranbaxy admits that its Answers, amended Answers and Counterclaims also challenged the validity of the patent term extension granted by the PTO for the '893 patent. Ranbaxy denies any and all remaining allegations in paragraph 33 of the Complaint.

34. Ranbaxy denies the allegations in paragraph 34 of the Complaint.

35. Ranbaxy admits the allegations in paragraph 35 of the Complaint.

36. Ranbaxy admits the allegations in paragraph 36 of the Complaint.

37. Ranbaxy admits that prior to trial in the Lipitor® Litigation, Ranbaxy was aware of the first examination report in the EP 247 633 prosecution, the citation of EP 179 559 in that report, and Warner-Lambert's written response to that report. Ranbaxy denies any and all remaining allegations in paragraph 37 of the Complaint.

38. Ranbaxy admits the allegations in paragraph 38 of the Complaint.

39. Ranbaxy admits the allegations in paragraph 39 of the Complaint.

40. Ranbaxy admits that the cover page of EP 179 559 was produced in discovery as document number P0267818 in the Lipitor Litigation. Ranbaxy denies any and all remaining allegations in paragraph 40 of the Complaint.

41. Ranbaxy admits the allegations in paragraph 41 of the Complaint.

42. Ranbaxy admits that by its opinion dated December 16, 2005 in the Lipitor Litigation, the District Court concluded that Ranbaxy had not proven the '893

patent to be invalid under 35 U.S.C. § 112. Ranbaxy denies any and all remaining allegations in paragraph 42 of the Complaint.

43. Ranbaxy admits the allegations in paragraph 43 of the Complaint.

44. Ranbaxy admits the allegations in paragraph 44 of the Complaint.

45. Ranbaxy admits that the District Court held that Ranbaxy had not proven the '893 patent term extension to be invalid. Ranbaxy denies any and all remaining allegations in paragraph 45 of the Complaint.

46. Ranbaxy admits the allegations in paragraph 46 of the Complaint.

47. Ranbaxy admits that the Federal Circuit affirmed the District Court's decision that the '893 patent was infringed. Ranbaxy denies any and all remaining allegations in paragraph 47 of the Complaint.

48. Ranbaxy admits that the Federal Circuit affirmed the District Court's decision that Ranbaxy had not proven the '893 patent term extension to be invalid. Ranbaxy denies any and all remaining allegations in paragraph 48 of the Complaint.

49. Ranbaxy admits the allegations in paragraph 49 of the Complaint.

50. Ranbaxy admits the allegations in paragraph 50 of the Complaint.

51. Ranbaxy admits that the District Court's Final Judgment Order entered judgment "in favor of plaintiffs Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export, Ltd. (collectively 'Pfizer') and against defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated (collectively 'Ranbaxy') on Pfizer's claims that Ranbaxy has infringed claims 1-4, and 8-9 of United States Patent No. 4,681,893 (the

''893 Patent'). . . ." Ranbaxy denies any and all remaining allegations in paragraph 51 of the Complaint.

52. Ranbaxy admits the allegations in paragraph 52 of the Complaint.

53. Ranbaxy admits the allegations in paragraph 53 of the Complaint.

54. Ranbaxy denies the allegations in paragraph 54 of the Complaint.

55. Ranbaxy denies the allegations in paragraph 55 of the Complaint.

FIRST CLAIM FOR RELIEF
INFRINGEMENT OF THE '893 PATENT

56. Ranbaxy repeats and realleges its responses to the allegations in paragraphs 1 through 55 of the Complaint as though fully set forth herein.

57. Ranbaxy admits the allegations in paragraph 57 of the Complaint.

58. Ranbaxy admits the allegations in paragraph 58 of the Complaint.

59. Ranbaxy admits the allegations in paragraph 59 of the Complaint.

60. Ranbaxy admits the allegations in paragraph 60 of the Complaint.

61. Ranbaxy admits the allegations in paragraph 61 of the Complaint.

62. Ranbaxy admits the allegations in paragraph 62 of the Complaint.

63. Ranbaxy denies the allegations in paragraph 63 of the Complaint.

64. Ranbaxy admits the allegations in paragraph 64 of the Complaint.

65. Ranbaxy denies the allegations in paragraph 65 of the Complaint.

66. Ranbaxy denies the allegations in paragraph 66 of the Complaint.

67. Ranbaxy denies the allegations in paragraph 67 of the Complaint.

68. Ranbaxy denies the allegations in paragraph 68 of the Complaint.

69. Ranbaxy denies the allegations in paragraph 69 of the Complaint.

SECOND CLAIM FOR RELIEF
INFRINGEMENT OF THE '574 PATENT

70. Ranbaxy repeats and realleges its responses to the allegations in paragraphs 1 through 69 of the Complaint as though fully set forth herein.

71. Ranbaxy admits the allegations in paragraph 71 of the Complaint.

72. Ranbaxy lacks sufficient information to respond to the allegations in paragraph 72 of the Complaint, and therefore denies those allegations.

73. Ranbaxy denies the allegations in paragraph 73 of the Complaint.

74. Ranbaxy denies the allegations in paragraph 74 of the Complaint.

75. Ranbaxy denies the allegations in paragraph 75 of the Complaint.

76. Ranbaxy denies the allegations in paragraph 76 of the Complaint.

AFFIRMATIVE DEFENSES

Ranbaxy sets forth the following affirmative and other defenses. Ranbaxy does not intend hereby to assume the burden of proof with respect to those matters on which, pursuant to law, Pfizer bears the burden.

First Affirmative Defense

(Noninfringement of the '574 patent)

77. Ranbaxy does not infringe any valid and enforceable claim of the '574 patent.

Second Affirmative Defense

(Invalidity of the '574 patent)

78. The '574 patent is invalid for failure to satisfy the provisions of one or more of Sections 101, 102, 103 and/or 112 of Title 35 of the United States Code.

Third Affirmative Defense

(Invalidity of the '893 patent/patent term extension)

79. The '893 patent/patent term extension is invalid for failure to satisfy the provisions of Section 103 of Title 35 of the United States Code.

80. The patent term extension of the '893 patent is invalid for failure to satisfy the provisions of one or more of Sections 156 and 282 of Title 35 of the United States Code, and/or 37 C.F.R. § 1.765.

RANBAXY'S COUNTERCLAIMS

Defendants/Counterclaimants Ranbaxy Laboratories Limited and Ranbaxy Inc. (collectively, "Ranbaxy") bring the following Counterclaims against Plaintiffs Pfizer Inc., Pfizer Pharmaceuticals, LLC, Pfizer Limited, C.P. Pharmaceuticals International C.V., Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export Ltd. (collectively, "Pfizer"), for declaratory judgment that U.S. Patent Nos. 4,681,893 (the "'893 patent"), 5,273,995 (the "'995 patent") and 6,455,574 (the "'574 patent"), and the '893 patent term extension, are invalid and/or not infringed by the amlodipine besylate/atorvastatin calcium product in Ranbaxy's Abbreviated New Drug Application ("ANDA").

PARTIES, JURISDICTION AND VENUE

81. These counterclaims seek a declaratory judgment pursuant to 28 U.S.C. §§ 2201 and 2202, and the Patent Laws of the United States.

82. Counterclaimant Ranbaxy Laboratories Limited is a corporation organized and existing under the laws of India, having its principal place of business in Gurgaon (Haryana), India. Counterclaimant Ranbaxy Inc. is a corporation organized and existing

under the laws of Delaware, having its principal place of business at 600 College Road East, Princeton, New Jersey.

83. On information and belief, Counterdefendant Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware and has corporate offices at 235 East 42nd Street, New York, New York, 10017.

84. On information and belief, Counterdefendant Pfizer Pharmaceuticals, LLC is a limited liability company organized and existing under the laws of the State of Delaware, with corporate offices at 235 East 42nd Street, New York, New York, 10017.

85. On information and belief, Counterdefendant Pfizer Limited is a company incorporated under the laws of England with offices at Ramsgate Road, Sandwich, Kent, England CT13 9NJ. On information and belief, Pfizer Limited is a wholly owned subsidiary of Counterdefendant Pfizer Inc.

86. On information and belief, Counterdefendant C.P. Pharmaceuticals International C.V. is a limited partnership (commanditaire vennootschap) organized under the laws of the Netherlands, having its registered seat in Rotterdam, and registered at the trade register held by the Chamber of Commerce in Rotterdam, the Netherlands, under number 24280998. On information and belief, C.P. Pharmaceuticals International C.V. is a wholly owned subsidiary of Counterdefendant Pfizer Inc.

87. On information and belief, Counterdefendant Pfizer Ireland Pharmaceuticals is a partnership, organized and existing under the laws of Ireland, with registered offices at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland. On information and belief, Pfizer Ireland Pharmaceuticals is a wholly owned subsidiary of

Counterdefendant Pfizer Inc., and was formerly Counterdefendant Warner-Lambert Export, Ltd.

88. On information and belief, Counterdefendant Warner-Lambert Export, Ltd. is a corporation formerly organized the laws of Ireland with a registered office located at Pottery Road, Dun Laoghaire, Co. Dublin, Ireland.

89. On information and belief, Counterdefendant Warner-Lambert Company is a corporation formerly organized under the laws of the State of Delaware with offices for service of process at 235 East 42nd Street, New York, New York, 10017. On information and belief, Warner-Lambert Company is a wholly owned subsidiary of Counterdefendant Pfizer Inc., and was converted into Counterdefendant Warner-Lambert Company, LLC.

90. On information and belief, Counterdefendant Warner-Lambert Company, LLC, is a Delaware limited liability company with offices located at 235 East 42nd Street, New York, New York, 10017.

91. This is an action based upon an actual controversy between Ranbaxy and Pfizer concerning the invalidity and/or noninfringement of the '893, '995 and '574 patents and the '893 patent term extension, and Ranbaxy's right to continue to seek approval of its ANDA for a product containing amlodipine besylate/atorvastatin calcium, and upon approval by the FDA, to manufacture, import, use, market, sell and offer to sell its amlodipine besylate/atorvastatin calcium ANDA product in the United States.

92. This Court has jurisdiction over these counterclaims pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 2202 and 35 U.S.C. § 271(e)(2).

93. Venue is proper under 28 U.S.C. §§ 1391 and 1400, and by Pfizer's choice of forum.

94. Ranbaxy has submitted, and is continuing to seek FDA approval of, an ANDA directed to a product containing amlodipine besylate/atorvastatin calcium, a generic version of Pfizer's Caduet® product. Ranbaxy's ANDA seeks approval for Ranbaxy to engage in the commercial manufacture, use and sale of a product containing amlodipine besylate/atorvastatin calcium, which Pfizer alleges infringes the '893 and '574 patents.

95. On information and belief, Warner-Lambert Company owns the '995 patent, issued on December 28, 1993, entitled "[R-(R*R*)]-2-(4-Fluorophenyl)-β,δ-Dihydroxy-5-(1-Methylethyl-3-Phenyl-4-[(Phenylamino) Carbonyl]-1H-Pyrrole-1-Heptanoic Acid, Its Lactone Form And Salts Thereof." Dr. Bruce D. Roth is the named inventor on the '995 patent. A copy of the '995 patent is attached hereto as Ex. A.

96. In consolidated Civil Action No. 03-209-JJF, adjudicated in the U.S. District Court for the District of Delaware (referred to as the "Lipitor Litigation" in Pfizer's Complaint), Counterdefendants Pfizer Inc., Pfizer Ireland Pharmaceuticals, Warner-Lambert Co., Warner-Lambert Co., LLC and Warner-Lambert Export, Ltd., previously sued Ranbaxy for infringement of Claims 1, 2, 6, 11 and 12 of the '995 patent based on Counterclaimant Ranbaxy Laboratories Limited's submission of ANDA No. 46-477 seeking FDA approval to engage in the commercial manufacture, use or sale of a drug product containing atorvastatin calcium.

97. Prior to trial in the Lipitor Litigation, Pfizer withdrew its assertion of infringement of Claims 1, 2, 11 and 12. Pfizer granted Ranbaxy a covenant not to sue on

all claims of the '995 patent other than Claim 6, *i.e.*, Claims 1-5 and 7-12, which the District Court entered as D.I. 255 on November 17, 2004. The covenant not to sue pertains to "the formulation currently described in ANDA No. 76-477 (as set forth in the documents provided to Pfizer during discovery in the [Lipitor Litigation])" and the atorvastatin calcium described in Ranbaxy Laboratories Limited's Drug Master File No. 16098.

98. In its December 16, 2005 decision in the Lipitor Litigation, the District Court held that Ranbaxy's atorvastatin calcium product, as described in ANDA No. 76-477, literally infringed Claim 6 of the '995 patent. The District Court also held that Ranbaxy had not proven that Claim 6 of the '995 patent was invalid for anticipation, obviousness, non-statutory double patenting or failure to comply with 35 U.S.C. § 112, ¶ 4. The District Court also held that Ranbaxy had not proven that the '995 patent was unenforceable for inequitable conduct.

99. On appeal from the District Court decision in the Lipitor Litigation, the United States Court of Appeals for the Federal Circuit (the "Federal Circuit"), in Appeal No. 06-1179 (the "Lipitor Appeal"), ruled that the only asserted claim of the '995 patent, Claim 6, was invalid for failure to comply with 35 U.S.C. § 112, ¶ 4. The Federal Circuit declined to review whether Claim 6 of the '995 patent was invalid on other grounds or whether the '995 patent is unenforceable, deeming those arguments moot in view of its ruling that Claim 6 was invalid.

100. After the Lipitor Appeal, Pfizer publicly stated that the Federal Circuit's decision invalidating Claim 6 of the '995 patent turned on a "technical defect." *See* Exs. B and C attached hereto. Pfizer further stated that, "[t]here is a process for correcting

such defects in the U.S. Patent and Trademark Office, and Pfizer plans to pursue that option." *See* Ex. B; *see also* Ex. C.

101. On January 16, 2007, Counterdefendant Warner-Lambert Co., LLC filed an application with the U.S. Patent and Trademark Office ("PTO") seeking reissue of the '995 patent to "correct" what it deemed a "technical defect" in the failure of various claims of the '995 patent, including Claim 6, to comply with 35 U.S.C. § 112, ¶ 4.

102. In addition to asserting the '995 patent against Ranbaxy in the Lipitor Litigation in the United States, Pfizer has also sued Ranbaxy on foreign counterparts to the '995 patent in several countries, including Australia, Canada and the United Kingdom.

103. Ranbaxy has undertaken substantial efforts in developing and seeking approval for its amlodipine besylate/atorvastatin calcium ANDA product.

104. Pfizer has sued Ranbaxy for alleged infringement of the '893 patent, and its term extension, and the '574 patent based on Ranbaxy's amlodipine besylate/atorvastatin calcium ANDA product. Ranbaxy is under reasonable apprehension that Pfizer will sue Ranbaxy for infringement of the '995 patent based on Ranbaxy's amlodipine besylate/atorvastatin calcium ANDA product given Pfizer's previous assertion of the '995 patent against Ranbaxy in the United States, Pfizer's ongoing efforts to reissue the '995 patent and Pfizer's prior and ongoing assertion of foreign counterparts to the '995 patent against Ranbaxy.

105. Ranbaxy's amlodipine besylate/atorvastatin calcium ANDA product does not infringe any valid and enforceable claims of the '893, '995 or '574 patents, or the '893 patent term extension. The claims of the '893, '995 and/or '574 patents, and the

'893 patent term extension, are invalid for failure to comply with one or more of the requirements of 35 U.S.C. §§ 102, 103, 112, 156, and/or 282, for double patenting and/or for unenforceability due to inequitable conduct.

106. In view of the foregoing, a conflict of asserted rights has arisen between Ranbaxy and Pfizer with respect to the infringement, validity and/or enforceability of the relevant claims of the '893, '995 and '574 patents and the '893 patent term extension, and as to Ranbaxy's right to obtain FDA approval to engage in the commercial manufacture, importation, use, offer for sale, and sale of its amlodipine besylate/atorvastatin calcium ANDA product. An actual controversy exists between Ranbaxy and Pfizer.

FIRST COUNTERCLAIM — DECLARATION OF INVALIDITY OF THE '893 PATENT/PATENT TERM EXTENSION

107. Ranbaxy repeats and realleges paragraphs 81-106 as if set forth specifically herein.

108. The claims of the '893 patent/patent term extension are invalid for failure to satisfy the provisions of Section 103 of Title 35 of the United States Code.

SECOND COUNTERCLAIM — DECLARATION OF INVALIDITY OF THE '893 PATENT TERM EXTENSION

109. Ranbaxy repeats and realleges paragraphs 81-108 as if set forth specifically herein.

110. The patent term extension of the '893 patent is invalid for failure to satisfy the provisions of one or more of Sections 156 and/or 282 of Title 35 of the United States Code, and/or 37 C.F.R § 1.765.

THIRD COUNTERCLAIM — DECLARATION OF NONINFRINGEMENT OF THE '574 PATENT

111. Ranbaxy repeats and realleges paragraphs 81-110 as if set forth specifically herein.

112. Ranbaxy does not infringe any valid and enforceable claim of the '574 patent.

FOURTH COUNTERCLAIM — DECLARATION OF INVALIDITY OF THE '574 PATENT

113. Ranbaxy repeats and realleges paragraphs 81-112 as if set forth specifically herein.

114. The '574 patent is invalid for failure to satisfy the provisions of one or more of Sections 101, 102, 103 and/or 112 of Title 35 of the United States Code.

FIFTH COUNTERCLAIM — DECLARATION OF NONINFRINGEMENT OF THE '995 PATENT

115. Ranbaxy repeats and realleges paragraphs 81-114 as if set forth specifically herein.

116. Ranbaxy does not infringe any valid and enforceable claim of the '995 patent.

SIXTH COUNTERCLAIM — DECLARATION OF INVALIDITY OF THE '995 PATENT

117. Ranbaxy repeats and realleges paragraphs 81-116 as if set forth specifically herein.

118. The '995 patent is invalid for failure to satisfy the provisions of one or more of Sections 101, 102, 103 and/or 112 of Title 35 of the United States Code, and/or for double patenting.

SEVENTH COUNTERCLAIM — DECLARATION OF UNENFORCEABILITY OF THE '995 PATENT

119. Ranbaxy repeats and realleges paragraphs 81-118 as if set forth specifically herein.

120. Pfizer filed U.S. Application No. 07/303,733 (the "'733 application") on February 1, 1989, which is more than five months prior to the '995 patent's earliest priority date. The '733 application issued as U.S. Patent No. 5,003,080 (the "'080 patent") on March 26, 1991, which is more than two years before the issue date of the '995 patent.

121. The '080 patent describes, *inter alia*, the enantiomer atorvastatin in lactone, acid and various salt forms, as well as methods for making these compounds.

122. The '080 patent names Dr. Bruce D. Roth as a co-inventor, and the '995 patent names Dr. Roth as the sole inventor. Ronald A. Daignault prosecuted the patent applications that led to both the '080 and '995 patents.

123. Although both were aware of the '733 application and the '080 patent, neither Dr. Roth nor Ronald Daignault disclosed them during prosecution of the application that led to the '995 patent.

124. The '080 patent and the '733 application were highl y material to the prosecution of the application that led to the '995 patent.

125. Upon information and belief, Ronald Daignault and/or Dr. Roth, with intent to deceive the PTO, withheld the highly material '080 patent and '733 application from the PTO during prosecution of the application that led to the '995 patent.

126. Ronald Daignault and/or Dr. Roth violated their duty of candor to the PTO under 37 C.F.R. § 1.56 by intentionally withholding the '080 patent and the '733 application from the PTO.

127. Based on Dr. Roth and/or Ronald Daignault's intentional withholding of this material information, the '995 patent is unenforceable.

EIGHTH COUNTERCLAIM — DECLARATION OF UNENFORCEABILITY OF THE '995 PATENT

128. Ranbaxy repeats and realleges paragraphs 81-127 as if set forth specifically herein.

129. The specification of the '995 patent alleges that "[i]t is now unexpectedly found that the enantiomer" atorvastatin acid "provides surprising inhibition of the biosynthesis of cholesterol." The specification alleges that "an ordinarily skilled artisan may not predict the unexpected and surprising inhibition of cholesterol biosynthesis of the present invention." The specification also contains data allegedly showing that the R-enantiomer, *i.e.*, atorvastatin, was ten times more active than the corresponding racemate when tested in the CSI screen disclosed in the '893 patent.

130. During prosecution of the '995 patent, the named inventor, Dr. Bruce D. Roth, executed a Declaration under 37 C.F.R. § 1.132 in support of the patentability of the application claims of the '995 patent (the "Roth Declaration"). The Roth Declaration was signed by Dr. Roth on February 25, 1991.

131. Dr. Roth declared, *inter alia*, that he tested the activities of atorvastatin calcium (referred to as "Compound I" in the Roth Declaration), the S-isomer calcium salt (referred to as "Compound II" in the Roth Declaration) and the racemic calcium salt using the CSI screen described in the '893 patent.

132. In paragraph 9 of the Roth Declaration, Dr. Roth set forth data that he alleged showed, *inter alia*, that Compound I has "at least ten-fold" greater activity in inhibiting cholesterol synthesis than the racemate. Dr. Roth declared in paragraph 10 that "the differences in the data of paragraph 9 among Compounds I, II and racemate shows the activity of Compound I is surprising and unexpected because if the Compound II is accepted as inactive, the activity of the Compound I would be expected to be only accepted as twice that of the racemic mixture[.]"

133. Upon information and belief, prior to executing the Roth Declaration, Dr. Roth was aware of the results of *in vivo* AICS tests, which showed that the cholesterol synthesis inhibiting activity of Compound I was only about twice that of the racemate. Furthermore, upon information and belief, prior to executing the Roth Declaration, Dr. Roth was aware of other CSI test results that showed that the cholesterol biosynthesis inhibiting activity of the R-enantiomer was substantially less than about ten-times that of the racemate. Indeed, Dr. Roth was aware of CSI test results that showed that the racemate was more active than the R-enantiomer. Such information as described in this paragraph would have been highly material to the PTO's determination of the patentability of the application claims of the '995 patent.

134. Upon information and belief, Dr. Roth, with intent to deceive the PTO, withheld the material results of the above-mentioned tests, including those showing only

about two-fold difference in activity between Compound I and the racemate. Dr. Roth violated his duty of candor to the PTO under 37 C.F.R. § 1.56 by intentionally withholding those results from the PTO.

135. Based on Dr. Roth's conduct in misrepresenting the comparative activity of the R-enantiomer and the racemate and intentionally withholding the above-mentioned material test results, including those showing only a two-fold difference in activity, the '995 patent is unenforceable.

DEMAND FOR JUDGMENT

WHEREFORE, Ranbaxy prays for the following relief:

A. That all claims against Ranbaxy be dismissed with prejudice and that all relief requested by Pfizer be denied;

B. That a judgment be entered declaring that Ranbaxy has not, and does not, infringe any valid claim of U.S. Patent Nos. 4,681,893, 5,273,995 and 6,455,574, that Ranbaxy has a lawful right to obtain FDA approval of its ANDA for its amlodipine besylate/atorvastatin calcium product, and further that Ranbaxy has a lawful right to manufacture, import, market, use, sell and/or offer to sell its amlodipine besylate/atorvastatin calcium ANDA product once approved by FDA;

C. That a judgment be entered declaring that the claims of U.S. Patent No. 4,681,893 are invalid;

D. That a judgment be entered declaring that the patent term extension of U.S. Patent No. 4,681,893 is invalid;

E. That a judgment be entered declaring that the claims of U.S. Patent No. 5,273,995 are invalid and unenforceable against Ranbaxy, their officers, agents, servants and employees;

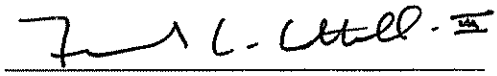
F. That a judgment be entered declaring that the claims of U.S. Patent No. 6,455,574 are invalid;

G. That Pfizer and its agents, representatives, attorneys and those persons in active concert or participation with them who received actual notice hereof, be preliminarily and permanently enjoined from threatening or initiating infringement litigation against Ranbaxy or any of its customers, dealers or suppliers, or any prospective sellers, dealers, distributors or customers of Ranbaxy, or charging any of them either orally or in writing with infringement of U.S. Patent Nos. 4,681,893, 5,273,995 or 6,455,574;

H. That a judgment be entered declaring this action is an exceptional case within the meaning of 35 U.S.C. § 285 and that Ranbaxy is entitled to recover its reasonable attorneys' fees upon prevailing in this action;

I. That Ranbaxy be awarded costs, attorneys' fees and other relief, both legal and equitable, to which they may be justly entitled; and

J. That Ranbaxy be awarded such other and further relief as is just and proper.



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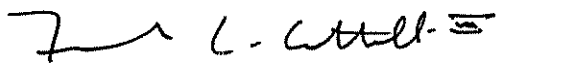
Dated: March 29, 2007

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on March 29, 2007, I caused to be served by hand delivery the foregoing document and electronically filed the same with the Clerk of Court using CM/ECF which will send notification of such filing(s) to the following:

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EXHIBIT A

US005273995A

United States Patent [19]

Roth

[11] Patent Number: 5,273,995

[45] Date of Patent: Dec. 28, 1993

[54] [R-(R*R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID, ITS LACTONE FORM AND SALTS THEREOF

[75] Inventor: Bruce D. Roth, Ann Arbor, Mich.

[73] Assignee: Warner-Lambert Company, Morris Plains, N.J.

[21] Appl. No.: 660,976

[22] Filed: Feb. 26, 1991

Related U.S. Application Data

[63] Continuation of Ser. No. 384,187, Jul. 21, 1989, abandoned.

[51] Int. Cl.[5] A61K 31/40; C07D 405/06

[52] U.S. Cl. 514/422; 514/423; 548/517; 548/537

[58] Field of Search 514/422, 423; 548/517, 548/537

[56] References Cited

U.S. PATENT DOCUMENTS

4,681,893 7/1987 Roth 514/223

OTHER PUBLICATIONS

J. Med. Chem. 1985, 28, 347–358—G. E. Stokker, et al "3–Hydroxy–3–Methylglutaryl–Coenzyme a Reductase . . . ".

Tetrahedron Letters, vol. 28, No. 13, pp. 1385–1388, 1987 "Synthesis of an HMG–COA Reductase Inhibitor, . . . "

Primary Examiner—Mary C. Lee
Assistant Examiner—Jacqueline Haley
Attorney, Agent, or Firm—Ronald A. Daignault

[57] ABSTRACT

[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; and pharmaceutically acceptable salts thereof.

12 Claims, No Drawings

[R-(R*R*)]-2-(4-FLUOROPHENYL)-β,δ-DIHYDROXY-5-(1-METHYLETHYL-3-PHENYL-4-[(PHENYLAMINO) CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID, ITS LACTONE FORM AND SALTS THEREOF

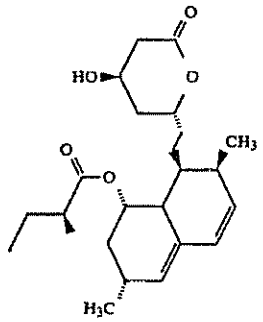
This is a continuation of U.S. application Ser. No. 07/384,187 filed Jul. 21, 1989, abandoned.

BACKGROUND OF THE INVENTION

Trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamides are among compounds of U.S. Pat. No. 4,681,893 having usefulness as inhibitors of cholesterol biosynthesis. The compounds therein broadly include 4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom.

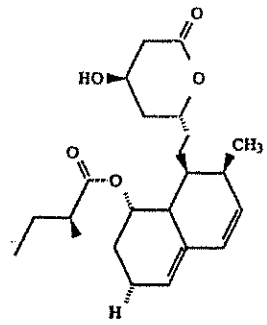
It is now unexpectedly found that the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; that is [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, provides surprising inhibition of the biosynthesis of cholesterol.

It is known that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) exists as the 3R-stereoisomer. Additionally, as shown in the study of a series of 5-substituted 3,5-dihydroxypentanoic acids by Stokker et al., in "3-Hydroxy-3-methylglutaryl-Coenzyme A Reductase Inhibitors. 1. Structural Modification of 5-Substituted 3,5-Dihydroxypentanoic acids and Their Lactone Derivatives," *J. Med. Chem.* 1985, 28, 347–358, essentially all of the biological activity resided in the trans diastereomer of (E)-6-[2-(2,4-dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyranone having a positive rotation. Further, the absolute configuration for the β-hydroxy-δ-lactone moiety common to mevinolin of the formula (1a)



1a

and compactin of the formula (1b)



1b

apparently is required for inhibition of HMG-CoA reductase. This is reported by Lynch et al. in "Synthesis of an HMB-CoA Reductase Inhibitor; A diastereoselective Aldol Approach in Tetrahedron Letters, Vol. 28, No. 13, pp. 1385–1388 (1987) as the 4R, 6R configuration.

However, an ordinarily skilled artisan may not predict the unexpected and surprising inhibition of cholesterol biosynthesis of the present invention in view of these disclosures.

SUMMARY OF THE INVENTION

Accordingly the present invention provides for compounds consisting of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-((1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid (compound of formula I), pharmaceutically acceptable salts thereof and (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (the lactone form of the heptanoic acid or compound of formula II).

The present invention also relates to a pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, its pharmaceutically acceptable salts or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide acid; and a pharmaceutically acceptable carrier. Further, the present invention is also a method of treating mammals, including humans, suffering from hypercholesterolemia by administering to such mammal a dosage form of the pharmaceutical composition described above.

DETAILED DESCRIPTION OF THE INVENTION

The pharmaceutically acceptable salts of the invention are those generally derived by dissolving the free acid or the lactone; preferably the lactone, in aqueous or aqueous alcohol solvent or other suitable solvents with an appropriate base and isolating the salt by evaporating the solution or by reacting the free acid or lactone; preferably the lactone and base in an organic solvent in which the salt separates directly or can be obtained by concentration of the solution.

In practice, use of the salt form amounts to use of the acid or lactone form. Appropriate pharmaceutically acceptable salts within the scope of the invention are

those derived from bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, 1-deoxy-2-(methylamino)-D-glucitol, magnesium hydroxide, zinc hydroxide, aluminum hydroxide, ferrous or ferric hydroxide, ammonium hydroxide or organic amines such as N-methylglucamine, choline, arginine and the like. Preferably, the lithium, calcium, magnesium, aluminum and ferrous or ferric salts are prepared from the sodium or potassium salt by adding the appropriate reagent to a solution of the sodium or potassium salt, i.e., addition of calcium chloride to a solution of the sodium or potassium salt of the compound of the formula I will give the calcium salt thereof.

The free acid can be prepared by hydrolysis of the lactone form of formula II or by passing the salt

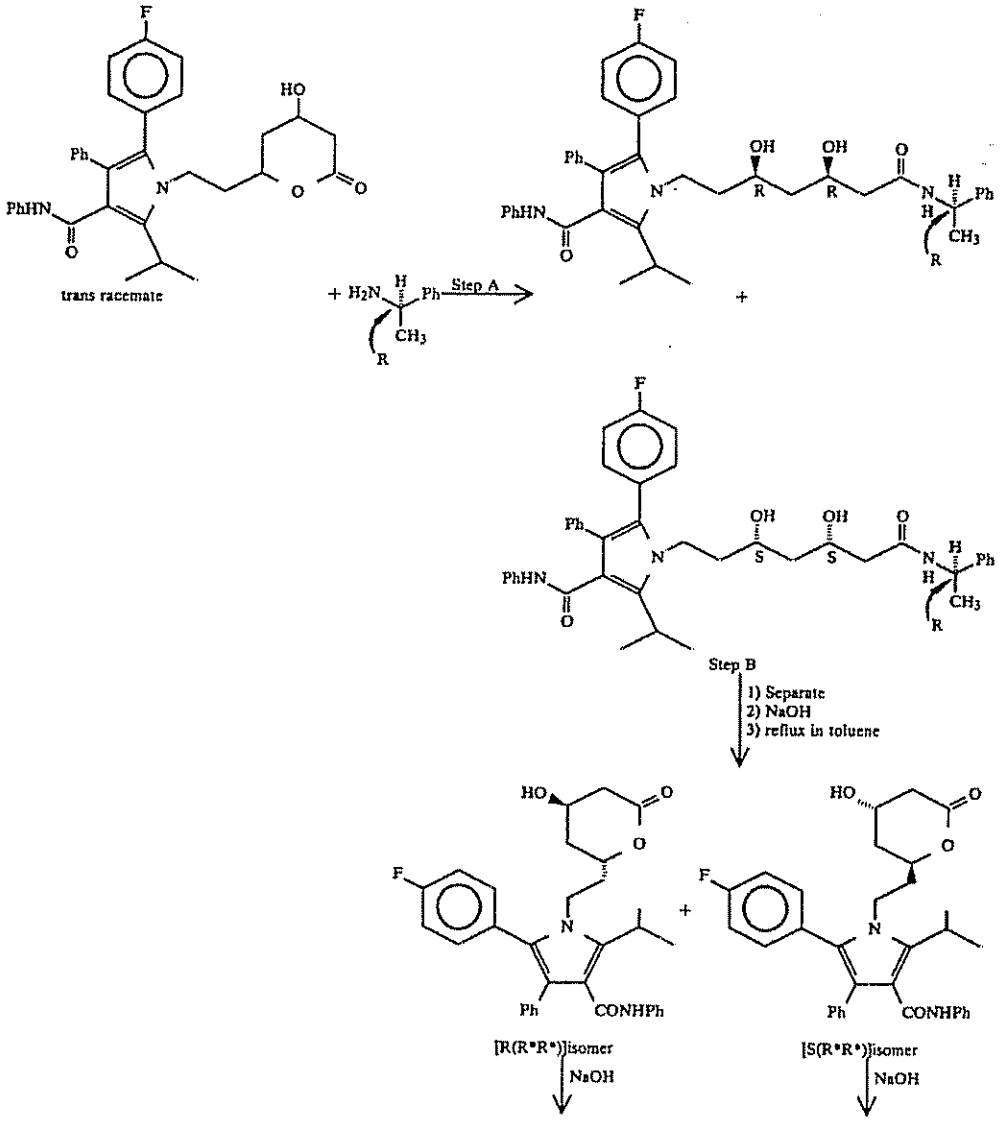
through a cationic exchange resin (H+resin) and evaporating the water.

The most preferred embodiment of the present invention is [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt.

Generally, the compounds I and II of the present invention can be prepared by (1) resolving the racemate, that is prepared by the processes described in U.S. Pat. No. 4,681,893 which is incorporated by reference therefor, or (2) synthesizing the desired chiral form beginning from starting materials which are known or readily prepared using processes analogous to those which are known.

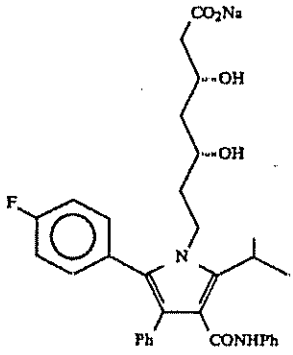
Specifically, resolution of the racemate may be accomplished as shown in Scheme I (where Ph is phenyl) as follows:

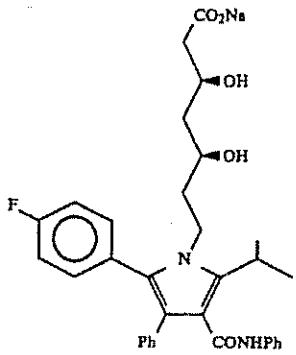
Scheme I



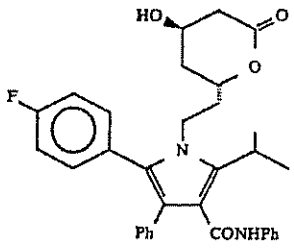
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Scheme 1





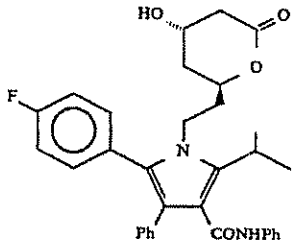
The "trans racemate" of Scheme 1 means a mixture of the following:



[R(R*R*)]isomer

and

-continued

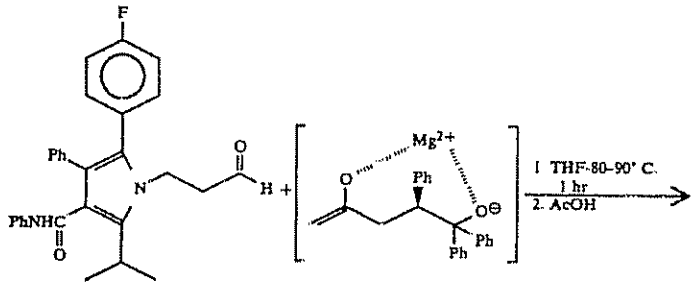


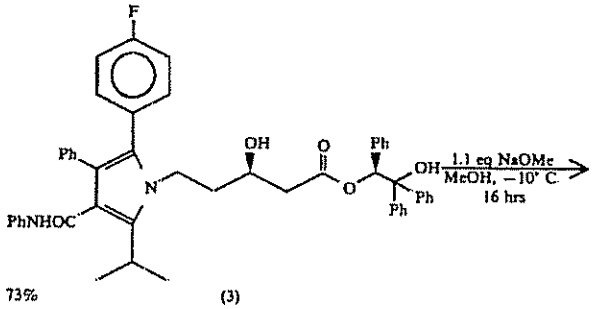
[S(R*R*)]isomer

The conditions of the Step 1 and 2 of Scheme 1 are generally as found in the Examples 6 and 7 hereinafter.

The chiral synthesis is shown in Scheme 2 (where Ph is phenyl) as follows:

Scheme 2



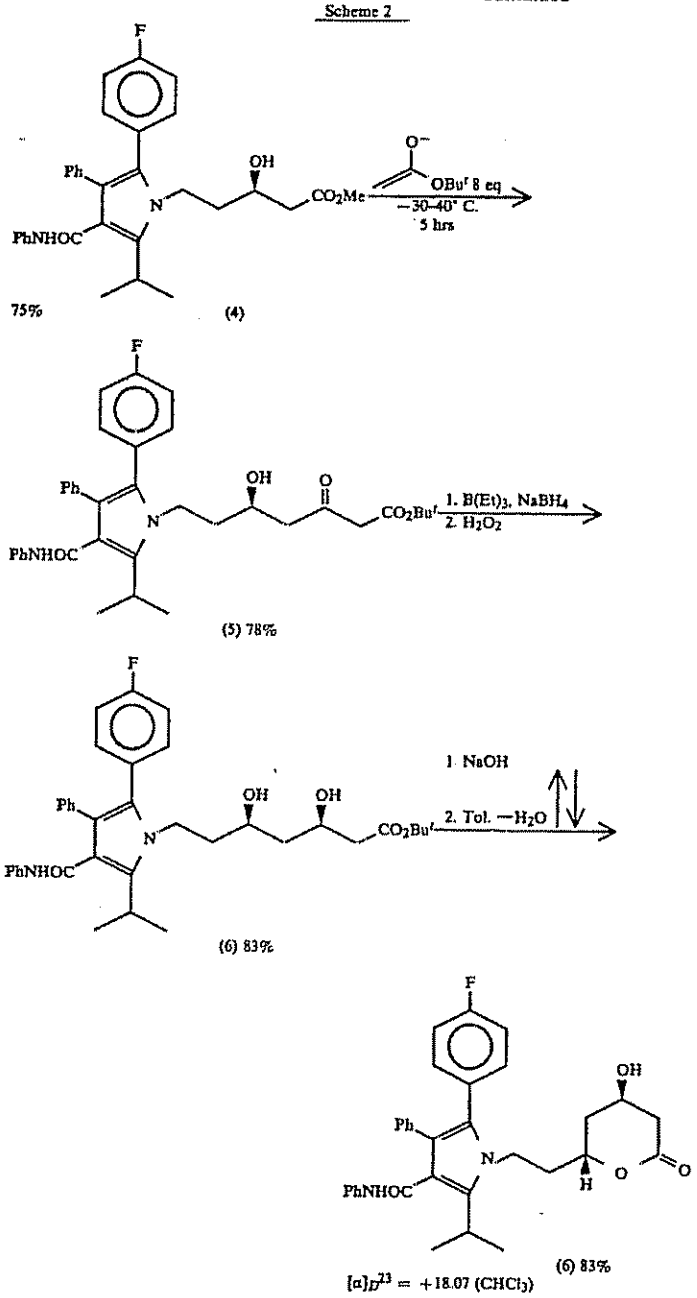


73%

(3)

-continued

Scheme 2



Generally, conditions for Scheme 2 are as shown in the Examples 1–5 hereinafter.

One of ordinary skill in the art would recognize variations in the Schemes 1 and 2 which are appropriate for the preparation of the compounds of the present invention.

The compounds according to present invention and especially according to the compound of the formula I inhibit the biosynthesis of cholesterol as found in the CSI screen that is disclosed in U.S. Pat. No. 4,681,893 which is now also incorporated by reference therefor. The CSI data of the compound I, its enantiomer the compound II and the racemate of these two compounds are as follows:

Compound	IC_{50} (micromoles/liter)
[R-(R*R*)] isomer	0.0044

-continued

Compound	IC_{50} (micromoles/liter)
[S-(R*R*)] isomer	0.44
Racemate	0.045

Accordingly, the present invention is the pharmaceutical composition prepared from the compound of the formula I or II or pharmaceutically acceptable salts thereof.

These compositions are prepared as described in U.S. Pat. No. 4,681,893 which is, therefore, again incorporated by reference here.

Likewise, the present invention is a method of use as hypolipidemic or hypocholesterolemic agents. The compounds of the present invention utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 10 to 500 mg per day which for a normal human adult of approximately 70 kg is a dosage of from 0.14 to 7.1 mg/kg of body weight per day. The dosages may be preferably from 0.5 to 1.0 mg/kg per day.

The dosage is preferably administered as a unit dosage form. The unit dosage form for oral or parenteral use may be varied or adjusted from 10 to 500 mg, preferably from 20 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other active therapeutic agents. Determinations of optimum dosages for a particular situation is within the skill of the art.

The compounds of the formula I and II and their pharmaceutically acceptable salts are in general equivalent for the activity of the utility as described herein.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are thus not to be read as limiting the scope of the invention.

EXAMPLE 1

285 ml 2.2M n-butyl lithium (in Hexane) is added dropwise to 92 ml diisopropylamine in 300 ml THF at 50°–60° C. in a 1000 ml 1 neck flask via dropping funnel and under nitrogen. The well stirred yellow solution is allowed to warm to about −20° C. Then it is cannulated into a suspension of 99 g S(+)-2-acetoxy-1,1,2-triphenylethanol in 500 ml absolute THF, kept in a 2L-3 neck flask at −70° C. When addition is complete, the reaction mixture is allowed to warm to −10° C. over a period of two hours. Meanwhile, a suspension of 0.63 mol $MgBr_2$ is prepared by dropping 564 ml (0.63 mol) of bromine into a suspension of 15.3 g of magnesium (0.63 mol) in 500 ml THF plus in 3 L. flask equipped with reflux condenser, and overhead stirrer. When this is completed, the $MgBr_2$ suspension is cooled to −78° C. and the enolate solution (dark brown) is cannulated into the suspension within 30 minutes. Stirring is continued for 60 minutes at −78° C. 150 g 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide in 800 ml THF absolute was added dropwise over 30 minutes; then stirred for 90 minutes at −78° C., then quenched with 200 ml AcOH at −78° C. This is removed to a cool bath, 500 ml of H_2O is added and the mixture concentrated in vacuo at 40°–50° C. 500 ml of 1:1 EtOAc/Heptane is added to the yellowish slurry and filtered. The filtrate is washed extensively with 0.5N HCl, then several times with H_2O and finally with EtOAc/Heptane (3:1) that was cooled with dry ice to −20° C. The light brown crystalline product (Example 1A) is dried in vacuum oven at 40° C. The yield is 194 g.

The product 1A is recrystallized from EtOAc at −10° C. to yield 100 g to yield product 1B and then recrystallized from acetone/pentane to yield 90 g to yield product 1C. The mother liquor is combined from the wash of the crude material and recrystallized from EtOAc/Hexane. 33 g of 1B shows the following: HPLC: 97.4:2.17 of the R,S to S,S isomers. 28.5 g of 1C shows the following: HPLC:95.7:3.7. The combined 1B and 1C is recrystallized from $CHCl_3$ MeOH 10:1; providing a product 1F having a yield of 48.7 g of white crystal.

The mother liquor of the first aqueous wash is crystallized (EtOAc/Heptane) to yield product 1D of 21.4 g; HPLC: 71.56:25.52.

The mother liquor of 1B and 1C is combined and recrystallized from $CHCl_3$/MeOH/Heptane to yield 55.7 g white crystals of product 1G.

1D is recrystallized from $CHCl_3$/MeOH to yield the product 1H.

All mother liquor is combined, concentrated then the residue is dissolved in hot $CHCl_3$/MeOH 10:1; put on a silica gel column; and eluted with EtOAc/Hexane 40:60. The material crystallized out on the column and the silica gel is extracted with $CHCl_3$/MeOH and concentrated. Recrystallization of the residue from $CHCl_3$/Heptane 3:1 yields 33.7 g of product 1I.

The mother liquor of 1I is recrystallized to yield 18.7 g of product 1K.

The mother liquor of 1K is crystallized to yield 6.3 g of product 1L.

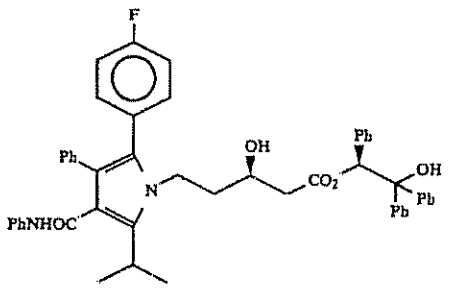
1I, 1K and 1L is combined and recrystallized from $CHCl_3$/Heptane to yield 48 g.

The combined mother liquor of 1I, 1K, and 1L is concentrated to yield 31 g of 1M.

The product 1F provides the following data.

Anal: 1F m.p. 229–230° C.	
Calc.	Found
C: 77.84	77.14
H: 6.02	6.45
N: 3.56	3.13

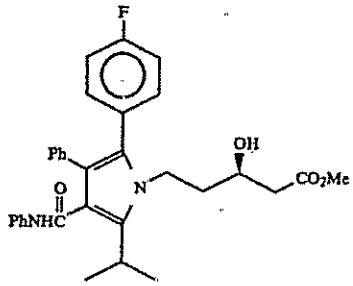
These data are consistent with the formula



EXAMPLE 2

162 g (0.206M) of the combined products 1F, 1G, 1H and 1L of Example 1 are suspended in 800 ml Methanol/THF (5:3). Cooled to 0° C. and added to 11.7 g

sodium methoxide. The mixture is stirred until everything is dissolved, then put in the freezer overnight. The reaction mixture is allowed to warm to room temperature, quenched with 15 ml HOAc, then concentrated in vacuo at 40° C. to obtain expected product as follows:



This product is added to 500 ml H_2O and extracted twice with EtOAc (300 ml). The combined extracts are washed with saturated $NaHCO_3$, brine, dried over anhydrous magnesium sulfate, filtered and the solvent evaporated. The residue is chromatographed on silica gel in EtOAc/Heptane (1:4) as eluent to yield 109 g colorless oil which is recrystallized from Et_2O/Heptane to yield:

73.9 g first crop; white crystals

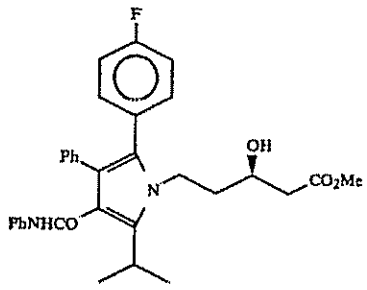
8.2 g second crop; white crystals.

The crystals provide the following data:

m.p. 125°–126° C., α_D^{20}=4.23° (1.17M, CH_3OH)

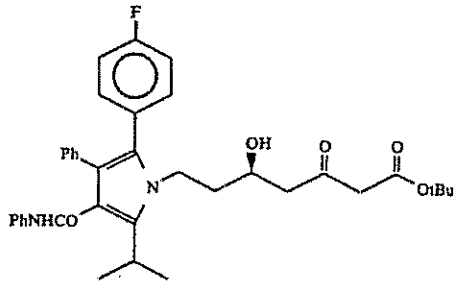
Calc.	Found
C: 72.76	72.51
H: 6.30	6.23
N: 5.30	5.06

These data are consistent with the formula



EXAMPLE 3

77 ml of diisopropylamine is dissolved in 250 ml THF in a 2000 ml three-neck flask equipped with thermometer and dropping funnel. The reaction mixture is kept under nitrogen. The mixture is cooled to −42° C. and added to 200 ml 2.2M of n-butyl lithium (in Hexane) dropwise over 20 minutes and stirred for 20 minutes before adding dropwise 62 ml of t-butylacetate, dissolved in 200 ml THF (over about 30 minutes). This mixture is stirred 30 minutes at −40° C., then 140 ml 2.2M of n-butyl lithium is added over 20 minutes. When addition is complete, 81 g of the product of Example 2 in 500 ml absolute THF is added as quickly as possible without allowing the temperature to rise above −40° C. Stirring is continued for four hours at −70° C. The reaction mixture is then quenched with 69 ml glacial acetic acid and allowed to warm to room temperature. The mixture is concentrated in vacuo and the residue is taken up in EtOAc, washed with water extensively, then saturated NH_4Cl, $NaHCO_3$ (saturated), and finally with brine. The organic layer is dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The NMR of the reaction is consistent with starting material plus product in about equal amounts plus some material on the baseline of the TLC. The material of the baseline of the TLC is separated from starting material and the product is extracted by acid/base extraction. The organic phase is dried and concentrated in vacuo to yield 73 g. The NMR and TLC are consistent with the formula



EXAMPLE 4

73 g crude product of Example 3 is dissolved in 500 ml absolute THF and 120 ml triethyl borane is added, followed by 0.7 g t-butylcarboxylic acid. The mixture is stirred under a dry atmosphere for 10 minutes, cooled to −78° C. and 70 ml methanol is added and followed by 4.5 g sodium borohydride. The mixture is again stirred at −78° C. for six hours. Then poured slowly into a 4:1:1 mixture of ice/30% H_2O_2/H_2O. This mixture is stirred overnight then allowed to warm to room temperature.

$CHCl_3$ (400 ml) is added and the mixture is partitioned. The water layer is extracted again with $CHCl_3$. The organic extracts are combined and washed extensively with H_2O until no peroxide could be found. The organic layer is dried over $MgSO_4$, filtered and the solvent is evaporated.

The residue is treated by flash chromatography on silica gel, i.e. EtOAc/Hexane 1:3 to yield 51 g.

The product is dissolved in THF/MeOH and added to 100 ml in NaOH, then stirred for four hours at room temperature. The solution is concentrated at room temperature to remove organic solvent, added to 100 ml H_2O, and extracted with Et_2O twice. The aqueous layer is acidified with 1N HCl and extracted with EtOAc three times. The combined organic layers are washed with H_2O. The organic layer is dried with anhydrous $MgSO_4$, filtered, and the solvent evaporated. The residue is taken up in 2 liters of toluene and heated to reflux using a Dean-Stark trap for 10 minutes.

The reaction mixture is allowed to cool to room temperature overnight. Reflux is repeated for 10 minutes and cooled for 24 hours.

The procedure above is repeated. The reaction is left at room temperature for the next 10 days, then concentrated to yield 51 g of colorless foam.

This product is dissolved in minimum $CHCl_3$ and chromatographed on silica gel eluting with EtOAc/-Heptane (50:50) to yield 23 g in pure material.

Chromatography on silica gel in $CHCl_3$/2-propanol (98.5:1.5) yields 13.2 g.

Calc.
C: 73.31
H: 6.15
N: 5.18

EXAMPLE 5

Preparation of 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H/-pyrrole-3-carboxamide

The product of Example 4 is recrystallized from EtOAc/Hexane. Fraction 1 yields 8.20 g of 4A. The mother liquor yields 4.60 g of 4B. HPLC of 4B shows 100% of the product to be the [R-(R*R*)] isomer. 4A is recrystallized to yield 4.81 g of 4C. 4B is chromatographed on silica gel in $CHCl_3$/2-propanol to yield 4.18 g colorless foam of 4D showing α_D^{23} +24.53° (0.53% in $CHCl_3$). 4C is recrystallized and the mother liquor of 4C is to yield 2.0 g HPLC which indicates 100% of the R-trans isomer 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

EXAMPLE 6

Preparation of diastereomeric α-methylbenzylamides

A solution of the racemate, trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, (30 g, 55.5 ml) in (R)-(+)-α-methylbenzylamine (575 ml, 4.45 mol, 98% Aldrich) is stirred overnight at room temperature.

The resulting solution is then diluted with ether (2 l) and then washed exhaustively with 2M HCl (4×500 ml), water (2×500 ml) and brine (2×500 ml). The organic extract is then dried over $MgSO_4$, filtered and concentrated in vacuo to yield 28.2 g of the diastereomeric α-methylbenzylamides as a white solid; m.p. 174.0°–177°. The α-methylbenzylamides are separated by dissolving 1.5 g of the mixture in 1.5 ml of 98:1.9:0.1 $CHCl_3$:CH_3OH:NH_4OH (1000 mg/ml) and injecting onto a preparative HPLC column (silica gel, 300 mm×41.4 mm I.D.) by gastight syringe and eluting with the above solvent mixture. Fractions are collected by UV monitor. Diastereomer 1 elutes at 41 minutes. Diastereomer 2 elutes at 49 minutes. Center cut fractions are collected. This procedure is repeated three times and the like fractions are combined and concentrated. Examination of each by analytical HPLC indicates that diastereomer 1 is 99.84% pure and diastereomer 2 is 96.53% pure. Each isomer is taken on separately to following Examples.

EXAMPLE 7

Preparation of 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

To an ethanolic solution (50M) of diastereomer 1 of Example 6, [3R-[3R*(R*),5R*]]-2-(4-fluorophenyl)-[β],[δ]-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-N-(1-phenylethyl-1H-pyrrole-1-heptanamide, (hydroxy centers are both R) (1 g, 1.5 mmol) is added 1N NaOH (3.0 ml, 3 mmol). The resulting solution is heated to reflux for 48 hours.

The solution is cooled to room temperature and concentrated in vacuo. The residue is resuspended in water and carefully acidified with 6N HCl. The resulting acidic solution is extracted with ethyl acetate. The organic extract is washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. This residue is redissolved in toluene (100 ml) and heated to reflux with azeotropic removal of water for three hours. This is cooled to room temperature and concentrated in vacuo to yield 1.2 g of a yellow semi-solid. Flash chromatography on silica gel eluting with 40% EtOAc/-Hexane gives 0.42 g of a white solid which still contains impurities. This is rechromatographed to give 0.1 g of essentially pure R,R, enantiomer, 2R-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, as a white foam. HPLC shows this material to be 94.6% chemically pure $[\alpha]_D^{23}$;0.51% in $CHCl_3$=25.5°. The peak at room temperature=53.46 minutes is tentatively assigned to an unknown diastereomer resulting from the 2% (S)-(−)-α-methylbenzylamine present in the Aldrich α-methylbenzylamine.

EXAMPLE 8

Preparation of 2S-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide-(S,S enantiomer of the compound prepared in Example 5

Carrying out the procedure described in Example 7 on diastereomer 2 afforded 0.6 g of a foamy solid which was flash chromatographed on silica gel. Elution with 50% EtOAc/Hexane gave 0.46 g of essentially pure S,S, enantiomer 2S-trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, as a white foam. HPLC showed this material to be 97.83% chemically pure. $[\alpha]_D^{23}$=0.51% in $CHCl_3$=−24.8°.

EXAMPLE 9

Hydrolysis of chemical lactone of formula II

To a room temperature, solution of the lactone in THF is added a solution of sodium hydroxide in water. The mixture is stirred for two hours HPLC:99.6% (product); 0.34 to (starting lactone). The mixture is diluted with 3 L water, extracted with ethyl acetate (2×1 L) and acidified to pH×4 by addition of 37 ml of 5N hydrochloric acid. The aqueous layer is extracted with 2×1.5 L portions of ethyl acetate. The combined ethyl acetate extracts are washed with 2×1 L of water, brine and dried, gave after filtration the ethyl acetate solution of the required face-acid. This solution is used directly in the fraction of the N-methylglucamine salt.

The ethyl acetate extracts from the brine-water were concentrated to give 15.5 g of an off-white solid.

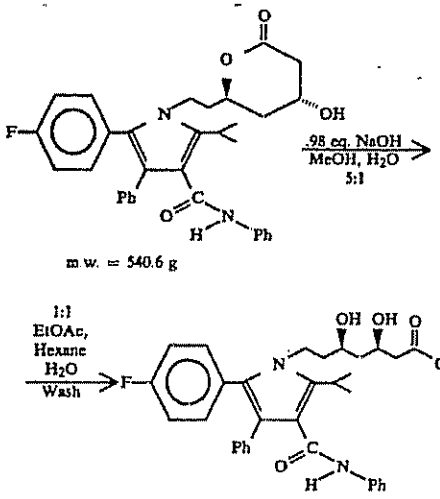
EXAMPLE 10

Calcium Salt from Sodium Salt and/or Lactone

Dissolve one mole lactone (540.6 g) in 5 L of MeOH; after dissolution add 1 L H_2O. While stirring, add one

equivalent NaOH and follow by HPLC until 2% or less lactone and methyl ester of the diolacid remains (cannot use an excess of NaOH, because $Ca(OH)_2$ will form an addition of $CaCl_2$). Charge NaOH as caustic (51.3 ml, 98 eq.) or as pellets (39.1 g, 0.98 eq.).

The above procedure is shown as follows:

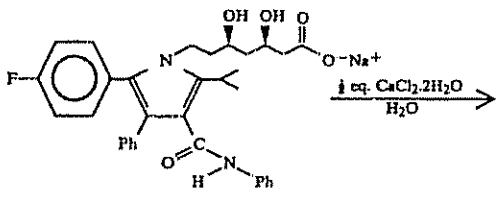


Upon completion of hydrolysis, add 10 L H_2O, then wash at least two times with a 1:1 mixture of EtOAc/-Hexane. Each wash should contain 10 L each of EtOAc/Hexane. If sodium salt is pure, add 15 L of MeOH. If it is impure and/or contains color, add 100 g of G-60 charcoal, stir for two hours and filter over supercel. Wash with 15 L MeOH. Perform a wt/vol % on the reaction mixture, by HPLC, to determine the exact amount of salt in solution.

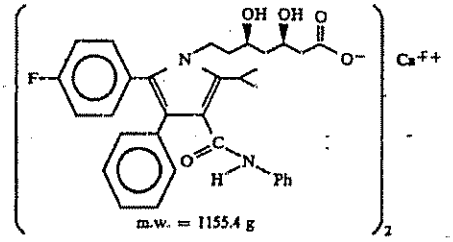
Dissolve 1 eq. or slight excess $CaCl_2.2H_2O$ (73.5 g) in 20 L H_2O. Heat both reaction mixture and $CaCl_2$ solution to 60° C. Add $CaCl_2$ solution slowly, with high agitation. After complete addition, cool slowly to 15° C. and filter. Wash filter cake with 5 L H_2O. Dry at 50° C. in vacuum oven.

Can be recrystallized by dissolving in 4 L of EtOAc (50° C.) filtering over supercel, washing with 1 L EtOAc, then charging 3 L of hexane to the 50° C. rxn solution.

The above procedure is shown as follows:



-continued



EXAMPLE 11

Treatment of Ethyl Acetate Solution of Free-acid of the Formula I with N-methylglucamine

To a solution of the free-acid of the formula I (0.106M) in ethyl acetate (3 L) is added a solution of N-methylglucamine (20.3 g, 0.106 m) in (1:1) water-acetone (120 ml, 120 ml) with vigorous stirring at room temperature. Stirring is continued for 16 hours and the hazy solution concentrated in vacuo to ~250 mp. Toluene (1 L) is added and the mixture concentrated to a white solid ~100 g. The solid is dissolved in 1670 ml acetone and filtered into a three-neck flask equipped with a mechanical stirrer and thermostat controlled thermometer The flask and filter is washed with 115 ml (1:1) water-acetone and the clear solution is cooled slowly. This provided a precipitate which is re-dissolved by heating back to 65° C. Addition of a further 20 ml of water followed by the washing gives a crystalline product which was isolated by filtration. The solids are washed with 1200 ml CH_3Cl and vacuum dried at 255° to give a white solid. Analysis of this material indicates that it contains 4% amine as well as 0.4% residual acetone and 0.67% water. Analytical results are noted as follows:

Melting point: 105°–155° C. (decomposition) Analysis Expected: C=63.73; H-6.95; N=5.57; F2=9.53. Analysis Found: C=62.10; H-6.89; N-5.34; F2. C=61.92; H-7.02; N=5.38; F2.

H_2O=0.47% (KF)

HPLC: MeOH, H_2O, THF (40; 550; 250)

Econosil: C18, 5 μ, 25 CM

256 nm: 1.0 ml/min.

6–81 min.: 98.76%

Opt. Ret.: $[\alpha]\cdot b = -10.33°$ (c=1.00, MeOH)

Residual Solvents: CH_2CH=0.26%

Titrations:

$HClO_4$ (0.1N)=203.8%

Bu_4NOH (0.1N)=98.5%

Other salts prepared in a manner analogous to those processes appropriately selected from Examples 10 and 11 above may be the potassium salt, hemimagnesium salt, hemizinc salt or the 1-deoxy-2-(methylamino)-D-glucitol complex of the compound of formula I.

I claim:

1. [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid or (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide; or pharmaceutically acceptable salts thereof.

2. A compound of claim 1 which is [R-(R*R*)]-2-(4-fluorophenyl)-β-δ-dihydroxy-5-(1-methylethyl)-3-phe-

nyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

3. A compound of claim 1 which is (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. The monosodium salt of the compound of claim 2.

5. The monopotassium salt of the compound of claim 2.

6. The hemicalcium salt of the compound of claim 2.

7. The N-methylglucamine salt of the compound of claim 2.

8. The hemimagnesium salt of the compound of claim 2.

9. The hemizinc salt of the compound of claim 2

10. The 1-deoxy-1-(methylamino)-D-glucitol mixture with the compound of claim 2.

11. A pharmaceutical composition for treating hypercholesterolemia comprising a hypocholesterolemic effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.

12. A method of inhibiting cholesterol synthesis in a human suffering from hypercholesterolemia comprising administering a compound of claim 1 in unit dosage form.

* * * * *

EXHIBIT B

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August 02, 2006 08:00 AM Eastern Daylight Time

U.S. Appeals Court Upholds Lipitor's Basic Patent With Exclusivity Maintained in U.S. Until March, 2010

Appeals Court Also Invalidates Second Patent on Technical Defect

Pfizer Pursuing Options For Further Review of Decision on Second Patent

NEW YORK--(BUSINESS WIRE)--Pfizer Inc said today that a panel of the Court of Appeals for the Federal Circuit has upheld the exclusivity of the main patent covering atorvastatin, the active ingredient in Lipitor, maintaining patent protection for Lipitor in the U.S. until March 2010.

The Appeals Court also ruled that a second patent (U.S. 5,273,995) at issue in the lawsuit covering the calcium salt of atorvastatin is invalid on technical grounds. That patent would have expired in June 2011.

The Appeals Court ruled in a lawsuit brought by Pfizer against the generic manufacturer Ranbaxy Ltd. The court held that Ranbaxy's generic atorvastatin product would infringe the company's basic patent (U.S. 4,681,893) broadly covering atorvastatin.

"While we are pleased that the court has affirmed that our basic patent is valid and infringed, we are disappointed in the decision on the '995 patent," said Peter Richardson, Pfizer's senior vice president, associate general counsel and chief of intellectual property. "The decision turned on a technical defect in the patent. There is a process for correcting such defects in the U.S. Patent and Trademark Office, and Pfizer plans to pursue that option."

In addition, either party may seek review of the decision by the full U.S. Court of Appeals for the Federal Circuit.

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EXHIBIT C

Archives: 2007 / **2006** / 2005 / 2004

Category: All

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October 23, 2006 08:00 AM Eastern Daylight Time

U.S. Appeals Court Denies Ranbaxy Petition for Rehearing Regarding Main Patent in Lipitor Case

Pfizer to Seek Correction of Technical Defect in Second Lipitor Patent

NEW YORK--(BUSINESS WIRE)--Pfizer Inc said today the Court of Appeals for the Federal Circuit has denied Ranbaxy's petition for rehearing of an August 2 decision upholding the exclusivity of the main patent covering atorvastatin, the active ingredient in Lipitor. That patent expires in March 2010.

"The court has declined to further review the August 2 decision," said Peter Richardson, Pfizer's senior vice president and associate general counsel. "As we noted in our response to the rehearing petition, the issues in this case were straightforward, the lower court's decision was consistent with prior law, and it raised no matters of exceptional importance requiring that they be revisited again."

Pfizer now plans to go back to the U.S. Patent office to seek to correct a technical defect in a second patent covering the calcium salt of atorvastatin. The second patent, expiring in June 2011, was ruled invalid by the court on technical grounds.

The company noted that Ranbaxy may seek review of the Court of Appeals decision by the U.S. Supreme Court.

Web site: http://www.pfizer.com/

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