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14 CV 2759

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Kowa Company, Ltd.,
Kowa Pharmaceuticals America, Inc., and
Nissan Chemical Industries, Ltd.,

Plaintiffs,

v.

Orient Pharma Co., Ltd.,

Defendant.

Civil Action No. _____

COMPLAINT

Plaintiffs, Kowa Company, Ltd. ("KCL"), Kowa Pharmaceuticals America, Inc. ("KPA")(collectively, "Kowa"), and Nissan Chemical Industries, Ltd. ("NCI") by their undersigned counsel, for their Complaint against defendant Orient Pharma Co., Ltd. ("Orient"), allege as follows:

Jurisdiction and Venue

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code and arising under 35 U.S.C. §§ 271(e)(2), 271(b), 271(c), and 281-283. Subject matter jurisdiction is proper under 28 U.S.C. §§ 1331 and 1338(a). Venue is proper under 28 U.S.C. §§ 1391 (c)(3) and 1400(b). Personal jurisdiction over the defendant in New York and this district is proper under N.Y. C.P.L.R. §§ 301 and 302(a) and/or Fed. R. Civ. P. 4(k)(2).

Parties

2. KCL is a Japanese corporation having its corporate headquarters and principal place of business in Aichi, Japan. KPA is a wholly owned U.S. subsidiary of KCL. KPA has its corporate headquarters and principal place of business in Montgomery, Alabama and is organized under the laws of Delaware.

3. NCI is a Japanese corporation having its corporate headquarters and principal place of business in Tokyo, Japan.

4. KCL and NCI are engaged in the business of research, developing, manufacturing, and marketing of a broad spectrum of innovative pharmaceutical products, including Livalo®.

5. Upon information and belief, Orient is a corporation organized and existing under the laws of Taiwan having a place of business in Taipei, Taiwan. Upon information and belief, Orient filed Abbreviated New Drug Application ("ANDA") No. 20-5932.

6. Upon information and belief, Orient intends to transact business in the Southern District of New York, at least by making and shipping into this Judicial District, or by using, offering to sell or selling or by causing others to use, offer to sell or sell, pharmaceutical products into this Judicial District.

7. Upon information and belief, Orient will derive substantial revenue from interstate and/or international commerce, including substantial revenue from goods used or consumed or services rendered in the State of New York and the Southern District of New York. By filing its ANDA, Orient has committed, and unless enjoined, will continue to commit a tortious act without the state of New York, that Orient expects or should reasonably expect to have consequences in the State of New York including in this Judicial District.

The New Drug Application

8. KPA sells drug products containing pitavastatin calcium (the "pitavastatin drug product") under the trade name Livalo® in the United States pursuant to the United States Food and Drug Administration's approval of a New Drug Application ("NDA") held by KCL (NDA No. 22-363).

9. Livalo® is approved for use as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

10. The approval letter for Livalo®, with approved labeling, was issued by the FDA on August 3, 2009.

11. Certain amendments to the approved labeling for Livalo® have subsequently been approved.

The Patents in Suit

12. United States Patent No. 5,856,336 ("the '336 patent"), entitled "Quinoline Type Mevalonolactones," a true and correct copy of which is appended hereto as **Exhibit A**, was duly issued on January 5, 1999 to inventors Yoshihiro Fujikawa, Mikio Suzuki, Hiroshi Iwasaki, Mitsuaki Sakashita, and Masaki Kitahara, and assigned to plaintiff NCI. The '336 patent claims,

inter alia, the pitavastatin drug product, and a method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the pitavastatin drug product.

13. Plaintiff NCI has been and still is the owner through assignment of the '336 patent, which expires on December 25, 2020 pursuant to a patent-term extension. KCL is NCI's licensee for the '336 patent and KPA holds a license from KCL for the '336 patent.

14. United States Patent No. 6,465,477 ("the '477 patent"), entitled "Stable Pharmaceutical Composition," a true and correct copy of which is appended hereto as **Exhibit B**, was duly issued on October 15, 2002 to inventors Toyojiro Muramatsu, Katsumi Mashita, Yasuo Shinoda, Hironori Sassa, Hiroyuki Kawashima, Yoshio Tanizawa, and Hideatsu Takeuchi, and jointly assigned to plaintiffs KCL and NCI. The '477 patent claims, inter alia, pharmaceutical compositions containing pitavastatin salts.

15. Plaintiffs KCL and NCI have been and still are the owners through assignment of the '477 patent, which expires on December 20, 2016. KPA holds a license from KCL for the '477 patent.

16. United States Patent No. 8,557,993 ("the '993 patent"), entitled "Crystalline Forms of Pitavastatin Calcium," a true and correct copy of which is appended hereto as **Exhibit C**, was duly issued on October 15, 2013 to inventors Paul Adriaan Van Der Schaaf, Fritz Blatter, Martin Szelagiewicz, and Kai-Uwe Schoening, and ultimately was assigned to plaintiff NCI. The '993 patent claims, inter alia, crystalline polymorphs or the amorphous form of pitavastatin or processes for preparing the same.

17. Plaintiff NCI has been and still is the owner through assignment of the '993 patent, which expires on February 2, 2024. KCL is NCI's licensee for the '993 patent and KPA holds a license from KCL for the '993 patent.

18. In accordance with its license, KPA sells the pitavastatin drug product under the trade name Livalo® in the United States. Sales of Livalo® are made pursuant to approval by the FDA of NDA No. 22-363.

19. Plaintiff KCL manufactures the Livalo® drug products as sold by KPA.

20. Plaintiffs Kowa and NCI will be substantially and irreparably harmed by infringement of any of the '336, '477, or '993 patents (the "Livalo® patents"). There is no adequate remedy at law.

COUNT I

INFRINGEMENT OF THE '336 PATENT UNDER 35 U.S.C. § 271(e)(2)(A)

21. Plaintiffs repeat and incorporate herein by reference the allegations contained in each of the foregoing paragraphs.

22. Upon information and belief, defendant Orient filed an Abbreviated New Drug Application ("ANDA") with the Food and Drug Administration ("FDA") under 21 U.S.C. § 355(j) (ANDA No. 20-5932) seeking approval to market 1 mg, 2 mg, and 4 mg tablets comprising pitavastatin calcium.

23. By this ANDA filing, Orient has indicated that it intends to engage, and that there is substantial likelihood that it will engage, in the commercial manufacture, importation, use, offer for sale, and/or sale, or inducement thereof, of Plaintiffs' patented pitavastatin drug product immediately or imminently upon receiving FDA approval to do so. Also by its ANDA filing, Orient has indicated that its drug product is bioequivalent to Plaintiffs' pitavastatin drug product.

24. By its ANDA filing, Orient seeks to obtain approval to commercially manufacture, use, import, offer for sale, and/or sell, alleged generic equivalents of Plaintiffs' Livalo® pitavastatin drug product prior to the expiration date of the '336 patent.

25. By a letter dated March 20, 2014 (the "Notice Letter"), Orient informed Kowa and NCI that Orient had filed a certification to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I). On or about March 21, 2014, KPA received the Notice Letter. On or about March 24, 2014, KCL and NCI received the Notice Letter.

26. The Notice Letter, purporting to be Orient's Notification Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), asserts that in Orient's opinion, the '336 patent purportedly is "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, sale or importation of the drug products described in Orient's ANDA."

27. Orient's filing of ANDA No. 20-5932 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, importation, offer for sale and/or sale, or inducement thereof, of its proposed pitavastatin drug product before the expiration of the '336 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

28. Orient's manufacture, use, importation, offer for sale, and/or sale, or inducement thereof, of its proposed pitavastatin drug product will directly infringe or induce infringement of at least one claim of the '336 patent under 35 U.S.C. § 271(e)(2)(A).

29. Upon information and belief, Orient's proposed label for its pitavastatin drug product will include the treatment of at least one of hyperlipidemia, hyperlipoproteinemia, and atherosclerosis.

30. Unless Orient is enjoined from infringing and inducing the infringement of the '336 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT II

INFRINGEMENT OF THE METHOD CLAIM OF THE '336 PATENT UNDER 35 U.S.C. § 271(b)

31. Plaintiffs repeat and incorporate herein by reference the allegations contained in each of the foregoing paragraphs.

32. Upon information and belief, approval of ANDA 20-5932 is substantially likely to result in the commercial manufacture, use, importation, offer for sale, and/or sale, or inducement thereof, of a pitavastatin drug product which is marketed and sold for use in a method claimed in one or more claims of the '336 patent, immediately or imminently upon approval of the ANDA, and prior to the expiration of the '336 patent.

33. Upon information and belief, Orient's proposed label for its pitavastatin drug product will include the treatment of at least one of hyperlipidemia, hyperlipoproteinemia or atherosclerosis.

34. Upon information and belief, Orient is aware or reasonably should be aware, of the widespread use of pitavastatin as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia. The beneficial effects of pitavastatin as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia would be readily apparent to customers of Orient (e.g., including, without limitation, physicians, pharmacists, pharmacy

benefits management companies, health care providers who establish drug formularies for their insurers and/or patients). Orient will be marketing its pitavastatin drug product with specific intent to actively induce, aid and abet infringement of the '336 patent. Orient knows or reasonably should know that its proposed conduct will induce infringement of the '336 patent.

35. Unless Orient is enjoined from infringing and inducing the infringement of the '336 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT III

INFRINGEMENT OF THE METHOD CLAIM OF THE '336 PATENT UNDER 35 U.S.C. § 271(c)

36. Plaintiffs repeat and incorporate herein by reference the allegations contained in each of the foregoing paragraphs.

37. Upon information and belief, Orient's proposed pitavastatin drug product comprises pitavastatin calcium as referenced in the claims of the '336 patent.

38. Upon information and belief, Orient's proposed pitavastatin drug product will be especially made for use in a manner that is an infringement of the '336 patent.

39. Upon information and belief, Orient knows that Orient's proposed pitavastatin drug product will be especially made for use in a manner that is an infringement of the '336 patent.

40. Upon information and belief, sale of Orient's proposed pitavastatin drug product will result in direct infringement of the '336 patent.

41. Upon information and belief, Orient's proposed pitavastatin drug product is not a staple article or commodity of commerce which is suitable for a substantial noninfringing use.

42. Upon information and belief, Orient knows that Orient's proposed pitavastatin drug product is not a staple article or commodity of commerce which is suitable for substantial noninfringing use.

43. Upon information and belief, approval of ANDA 20-5932 is substantially likely to result in the commercial use, manufacture, offer for sale and/or sale (or the inducement thereof or contribution thereto) of a drug product which is especially made, adapted, marketed, sold, and approved exclusively for use in a method claimed in the '336 patent, immediately or imminently upon approval of the ANDA.

44. Plaintiffs will be substantially and irreparably harmed if defendant is not enjoined from contributing to the infringement of the '336 patent. Plaintiffs have no adequate remedy at law.

COUNT IV

INFRINGEMENT OF THE '477 PATENT UNDER 35 U.S.C. § 271(e)(2)(A)

45. Plaintiffs repeat and incorporate herein by reference the allegations contained in each of the foregoing paragraphs.

46. Orient's Notice Letter, purporting to be Orient's Notice of Certification under 21 U.S.C.§ 355(j)(2)(B)(ii), indicates that Orient intends to manufacture, use, sell, or offer for sale, its proposed pitavastatin drug product prior to the expiration of the '477 patent.

47. The Notice Letter asserts that in Orient's opinion, the '477 patent purportedly is "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, sale or importation of the drug products described in Orient's ANDA."

48. Orient's filing of ANDA No. 20-5932 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, importation, offer for sale and/or sale, or the

inducement thereof, of its proposed pitavastatin drug product before the expiration of the '477 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

49. Orient's manufacture, use, importation, offer for sale, sale, and/or importation of its proposed pitavastatin drug product will directly infringe or induce infringement of at least one claim of the '477 patent under 35 U.S.C. § 271(e)(2)(A).

50. Unless Orient is enjoined from infringing the '477 patent, Plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

COUNT V

INFRINGEMENT OF THE '993 PATENT UNDER 35 U.S.C. § 271(e)(2)(A)

51. Plaintiffs repeat and incorporate herein by reference the allegations contained in each of the foregoing paragraphs.

52. Orient's Notice Letter, purporting to be Orient's Notice of Certification under 21 U.S.C.§ 355(j)(2)(B)(ii), indicates that Orient intends to manufacture, use, sell, or offer for sale, its proposed pitavastatin drug product prior to the expiration of the '993 patent.

53. The Notice Letter asserts that in Orient's opinion, the '993 patent purportedly is "invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, sale or importation of the drug products described in Orient's ANDA."

54. Orient's filing of ANDA No. 20-5932 for the purpose of obtaining FDA approval to engage in the commercial manufacture, use, importation, offer for sale and/or sale, or the inducement thereof, of its proposed pitavastatin drug product before the expiration of the '993 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

55. Orient's manufacture, use, importation, offer for sale, sale, and/or importation of its proposed pitavastatin drug product will directly infringe or induce infringement of at least one claim of the '993 patent under 35 U.S.C. § 271(e)(2)(A).

56. Unless Orient is enjoined from infringing the '993 patent, plaintiffs will suffer substantial and irreparable injury. Plaintiffs have no adequate remedy at law.

WHEREFORE, Plaintiffs request the following relief:

(a) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that making, using, selling, offering to sell and/or importing Orient's pitavastatin drug product for which it seeks FDA approval or any drug product containing pitavastatin will infringe at least one claim of one or more of the Livalo® patents;

(b) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that the making, using, offering for sale, selling and/or importing of Orient's pitavastatin drug product or any drug product containing pitavastatin, will induce the infringement at least one claim of one or more of the Livalo® patents;

(c) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. that the making, using, offering for sale, selling and/or importing of Orient's pitavastatin drug product or any drug product containing pitavastatin, will contribute to the infringement of at least one claim of one or more of the Livalo® patents;

(d) a declaratory judgment pursuant to 28 U.S.C. § 2201 et seq. and an order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any FDA approval for Orient to commercially make, use, sell, offer to sell or import its pitavastatin drug product or any drug product containing pitavastatin be no

earlier than the date following the expiration date of the last to expire of the Livalo® patents (as extended, if applicable);

(e) a permanent injunction restraining and enjoining against any infringement by defendant, its officers, agents, attorneys, employees, successors or assigns, or those acting in privity or concert with them, of the Livalo® patents, through the commercial manufacture, use, sale, offer for sale or importation into the United States of Orient's pitavastatin drug product or any drug product containing pitavastatin, and/or any inducement of or contribution to the same;

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

(g) Such further and other relief in favor of Plaintiffs and against defendant as this Court may deem just and proper.

Dated: New York, New York
April 17, 2014

Kowa Company, Ltd.,
Kowa Pharmaceuticals America, Inc., and
Nissan Chemical Industries, Ltd.

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EXHIBIT A

US005856336A

United States Patent [19]

Fujikawa et al.

[11] **Patent Number: 5,856,336**

[45] **Date of Patent: Jan. 5, 1999**

[54] **QUINOLINE TYPE MEVALONOLACTONES**

[75] Inventors: **Yoshihiro Fujikawa**; **Mikio Suzuki**; **Hiroshi Iwasaki**, all of Funabashi; **Mitsuaki Sakashita**; **Masaki Kitahara**, both of Shiraoka-machi, all of Japan

[73] Assignee: **Nissan Chemical Industries Ltd.**, Tokyo, Japan

[21] Appl. No.: **883,398**

[22] Filed: **May 15, 1992**

Related U.S. Application Data

[62] Division of Ser. No. 631,092, Dec. 19, 1990, which is a continuation of Ser. No. 233,752, Aug. 19, 1988.

[30] **Foreign Application Priority Data**

Aug. 20, 1987 [JP] Japan 62-207224
Jan. 26, 1988 [JP] Japan 63-15585
Aug. 3, 1988 [JP] Japan 63-193606

[51] **Int. Cl.**[6] **A61K 31/47**; C07D 215/12

[52] **U.S. Cl.** **514/311**; 546/173

[58] **Field of Search** 546/173; 514/311

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,753,675 5/1998 Wattanasin 514/311

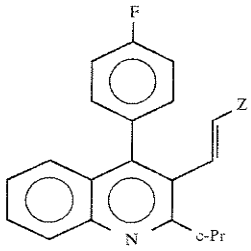
Primary Examiner—Laura L. Stockton

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

[57] **ABSTRACT**

A compound of the formula

[A]



Z=—CH(OH)—CH_2—CH(OH)—CH_2—COO.½Ca have HMG—CoA inhibiting effects, making them useful as inhibitors of cholesterol biosynthesis. The compound may be prepared as a pharmaceutical for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis.

2 Claims, No Drawings

QUINOLINE TYPE MEVALONOLACTONES

This is a division, of application Ser. No. 07/631,092, filed on Dec. 19, 1990, which is a continuation of 07/233,752, filed Aug. 19, 1988.

The present invention relates to novel mevalonolactones having a quinoline ring, processes for their production, pharmaceutical compositions containing them and their pharmaceutical uses particularly as anti-hyperlipidemic, hypolipoproteinemic and anti-atherosclerotic agents, and intermediates useful for their production and processes for the production of such intermediates.

Some fermentation metabolic products such as compactine, CS-514, Mevinolin or semi-synthetic derivatives or fully synthetic derivatives thereof are known to be inhibitors against HMG-CoA reductase which is a rate limiting enzyme for cholesterol biosynthesis. (A. Endo J. Med Chem., 28(4) 401 (1985))

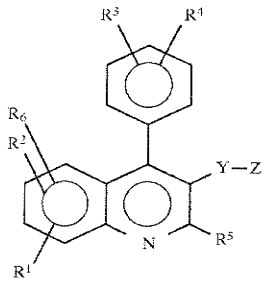
CS-514 and Mevinolin have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents, and they are considered to be effective for curing or preventing diseases of coronary artery sclerosis or atherosclerosis. (IXth Int. Symp. Drugs Affect. Lipid Metab., 1986, p30, p31, p66)

However, with respect to fully synthetic derivatives, particularly hetero aromatic derivatives of inhibitors against HMG-CoA reductase, limited information is disclosed in the following literatures:

WPI ACC NO. 84-158675, 86-028274, 86-098816, 86-332070, 87-124519, 87-220987, 88-07781, 88-008460, 88-091798 and 88-112505.

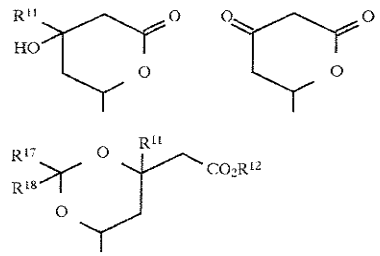
The present inventors have found that mevalonolactone derivatives having a quinoline ring, the corresponding dihydroxy carboxylic acids and salts and esters thereof have high inhibitory activities against cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme. The present invention has been accomplished on the basis of this discovery.

The novel mevalonolactone derivatives of the present invention are represented by the following formula I:

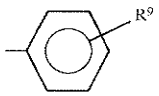


(I)

wherein R_1, R_2, R_3, R_4 and R^6 are independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, n-butoxy, i-butoxy, sec-butoxy, R^7R^8N- (wherein R^7 and R8 are independently hydrogen or C_{1-3} alkyl), trifluoromethyl, trifluoromethoxy, difluoromethoxy, fluoro, chloro, bromo, phenyl, phenoxy, benzyloxy, hydroxy, trimethylsilyloxy, diphenyl-t-butylsilyloxy, hydroxymethyl or $—O(CH_2)_iOR^{19}$ (wherein R^{19} is hydrogen or C_{1-3} alkyl, and l is 1, 2 or 3); or when located at the ortho position to each other, R^1 and R^2, or R^3 and R^4 together form —CH=CH—CH=CH—; or when located at the ortho position to each other, R^1 and R^2 together form $—OC(R^{15})(R^{16})O—$(wherein R^{15} and R^{16} are independently hydrogen or C_{1-3} alkyl); Y is $—CH_2—$, $—CH_2CH_2—$, —CH=CH—, $—CH_2—CH=CH—$ or $—CH=CH—CH_2—$; and Z is -Q-CH_2WCH_2-CO_2R^{12},



(wherein Q is —C(O)—, $—C(OR^{13})_2—$ or —CH(OH)—; W is —C(O)—, $—C(OR^{13})_2—$ or $—C(R^{11})(OH)—$; R^{11} is hydrogen or C_{1-3} alkyl; R^{12} is hydrogen or R^{14} (wherein R^{14} is physiologically hydrolyzable alkyl or M (wherein M is NH_4, sodium, potassium, ½ calcium or a hydrate of lower alkylamine, di-lower alkylamine or tri-lower alkylamine)); two R^{13} are independently primary or secondary C_{1-6} alkyl; or two R^{13} together form $—(CH_2)_2—$ or $—(CH_2)_3—$; R^{17} and R^{18} are independently hydrogen or C_{1-3} alkyl; and R^5 is hydrogen, C_{1-6} alkyl, C_{2-3} alkenyl, C_{3-6} cycloalkyl,



(wherein R^9 is hydrogen, C_{1-4} alkyl, C_{1-3} alkoxy, fluoro, chloro, bromo or trifluoromethyl), phenyl-$(CH_2)_m$— (wherein m is 1, 2 or 3), $—(CH_2)_nCH(CH_3)$-phenyl or phenyl-$(CH_2)_nCH(CH_3)$— (wherein n is 0, 1 or 2).

Various substituents in the formula I will be described in detail with reference to specific examples. However, it should be understood that the present invention is by no means restricted by such specific examples.

C_{1-6} alkyl for R^1, R^2, R^3, R^4, R^6 and R^9 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. C_{1-3} alkoxy for R^1, R^2, R^3, R^4 and R^6 includes, for example, methoxy, ethoxy, n-propoxy and i-propoxy.

C_{1-3} alkyl for R^{11} includes, for example, methyl, ethyl, n-propyl and i-propyl.

C_{1-3} alkyl for R^{13} includes, for example, methyl, ethyl, n-propyl and i-propyl.

Alkyl for R^{14} includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl and i-butyl.

M is a metal capable of forming a pharmaceutically acceptable salt, and it includes, for example, sodium and potassium.

CO_2M includes, for example, $—CO_2NH_4$ and $—CO_2H$. (primary to tertiary lower alkylamine such as trimethylamine).

C_{1-6} alkyl for R^5 includes, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

C_{3-6} cycloalkyl for R^5 includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

C_{2-3} alkenyl for R^5 includes, for example, vinyl and i-propenyl.

Phenyl-$(CH_2)_m$- for R^5 includes, for example, benzyl, β-phenylethyl and γ-phenylpropyl.

Phenyl-$(CH_2)_nCH(CH_3)$— for R^5 includes, for example, α-phenylethyl and α-benzylethyl.

C_{1-3} alkyl for R^7 and R^8 includes, for example, methyl, ethyl, n-propyl and i-propyl.

Further, these compoundsmay have at least one or two asymmetric carbon atoms and may have at least two to four

optical isomers. The compounds of the formula I include all of these optical isomers and all of the mixtures thereof.

Among compounds having carboxylic acid moieties falling outside the definition of $—CO_2R^{12}$ of the carboxylic acid moiety of substituent Z of the compounds of the present invention, those which undergo physiological hydrolysis, after intake, to produce the corresponding carboxylic acids (compounds wherein the $—CO_2R^{12}$ moiety is $—CO_2H$) are equivalent to the compounds of the present invention.

Now, preferred substituents of the compounds of the present invention will be described.

In the following preferred, more preferred still further perferred and most preferred examples, the numerals for the positions of the substituents indicate the positions on the quinoline ring. For example, N' shown by e.g. 1' or 2' indicates the position of the substituent on the phenyl substituted at the 4-position of the quinoline ring (the carbon connected to the quinoline ring is designated as 1'). The meanings of the respective substituents are the same as the above-mentioned meanings.

Preferred substituents for R^1, R^2 and R^6 are hydrogen, fluoro, chloro, bromo, C_{1-5} alkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, dimethylamino, hydroxy, hydroxymethyl, hydroxyethyl, trifluoromethyl, trifluoromethoxy, difluoromethoxy, phenoxy and benzyloxy.

Further, when R^6 is hydrogen, it is preferred that R^1 and R^2 together form methylenedioxy.

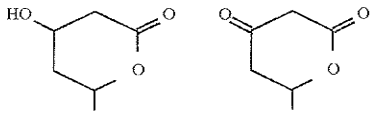
As preferred examples for R^3 and R^4, when R^4 is hydrogen, R^3 is hydrogen, 3'-fluoro, 3'-chloro, 3'-methyl, 4'-methyl, 4'-chloro and 4'-fluoro.

Other preferred combinations of R^3 and R^4 include 3'-methyl-4'-chloro, 3',5'-dichloro, 3',5'-difluoro, 3',5'-dimethyl and 3'-methyl-4'-fluoro.

Preferred examples for R^5 include primary and secondary C_{1-6} alkyl and C_{3-6} cycloalkyl.

Preferred examples for Y include $—CH_2—CH_2—$ and —CH=CH—.

Preferred examples for Z include



$—CH(OH)CH_2CH_2(OH)CH_2CO_2R^{12}$, $—CH(OH)CH_2C(O)CH_2CO_2R^{12}$ and $—CH(OH)CH_2C(OR^{13})_2CH_2CO_2R^{12}$.

Now, more preferred substituents of the compounds of the present invention will be described.

As more preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 5-fluoro, 6-fluoro, 7-fluoro, 8-fluoro, 5-chloro, 6-chloro, 7-chloro, 8-chloro, 5-bromo, 6-bromo, 7-bromo, 8-bromo, 5-methyl, 6-methyl, 7-methyl, 8-methyl, 5-methoxy, 6-methoxy, 7-methoxy, 8-methoxy, 5-trifluoromethyl, 6-trifluoromethyl, 7-trifluoromethyl, 8-trifluoromethyl, 6-trifluoromethoxy, 6-difluoromethoxy, 8-hydroxyethyl, 5-hydroxy, 6-hydroxy, 7-hydroxy, 8-hydroxy, 6-ethyl, 6-n-butyl and 7-dimethylamino.

When R^6 is hydrogen, R^1 and R^2 together represent 6-chloro-8-methyl, 6-bromo-7-methoxy, 6-methyl-7-chloro, 6-chloro-8-hydroxy, 5-methyl-2-hydroxy, 6-methoxy-7-chloro, 6-chloro-7-methoxy, 6-hydroxy-7-chloro, 6-chloro-7-hydroxy, 6-chloro-8-bromo, 5-chloro-6-hydroxy, 6-bromo-8-chloro, 6-bromo-8-hydroxy, 5-methyl-8-chloro, 7-hydroxy-8-chloro, 6-bromo-8-hydroxy, 6-methoxy-7-methyl, 6-chloro-8-bromo, 6-methyl-8-bromo, 6,7-difluoro, 6,8-difluoro, 6,7-methylenedioxy, 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo or 6,8-dibromo.

When R^1, R^2 and R^6 are not hydrogen, they together represent 5,7-dimethoxy-8-hydroxy, 5,8-dichloro-6-hydroxy, 6,7,8-trimethoxy, 6,7,8-trimethyl, 6,7,8-trichloro, 5-fluoro-6,8-dibromo or 5-chloro-6,8-dibromo.

As more preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-methyl, 4'-chloro or 4'-fluoro. When both R^3 and R^4 are not hydrogen, they together represent 3',5'-dimethyl or 3'-methyl-4'-fluoro.

As more preferred examples for R^5, the above-mentioned preferred examples of R^5 may be mentioned.

As preferred examples for Y, $—CH_2—CH_2—$ and (E)——CH=CH—may be mentioned. As more preferred examples for Z, the above preferred examples for Z may be mentioned.

Now, still further preferred substituents of the compounds of the present invention will be described. As examples for R^1, R^2 and R^6 , when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl, 6-ethyl, 6-trifluoromethyl, 6-hydroxy, 6-methoxy, 6-chloro, 6-bromo, 6-n-butyl and 7-dimethylamino.

When only R^6 is hydrogen, R^1 and R^2 represent 6,8-dichloro, 5,8-dimethyl, 6,8-dimethyl, 6,7-dimethoxy, 6,7-diethoxy, 6,7-dibromo, 6,8-dibromo, 6,7-difluoro and 6,8-difluoro.

As still further preferred examples for R^3 and R^4, when R^3 is hydrogen, R^4 is hydrogen, 4'-chloro or 4'-fluoro, or R^3 and R^4 together represent 3'-methyl-4'-fluoro.

Still further preferred examples for R^5 include ethyl, n-propyl, i-propyl and cyclopropyl.

Still further preferred examples for Y include (E)——CH=CH—.

As still further preferred examples for Z, the above-mentioned preferred example for Z may be mentioned.

Now, the most preferred substituents for the compounds of the present invention will be described.

As the most preferred examples for R^1, R^2 and R^6, when both R^2 and R^6 are hydrogen, R^1 is hydrogen, 6-methyl or 6-chloro.

When only R^6 is hydrogen, R^1 and R^2 together represent, for example, 6,7-dimethoxy.

As the most preferred examples for R^3 and R^4, R^3 is hydrogen and R^4 is hydrogen, 4'-chloro or 4'-fluoro.

The most preferred examples for R^5 include i-propyl and cyclopropyl. The most preferred example for Y may be (E)——CH=CH—.

As the most preferred examples for Z, the above-mentioned preferred examples for Z may be mentioned.

Now, particularly preferred specific compounds of the present invention will be presented. The following compounds (a) to (z) are shown in the form of carboxylic acids. However, the present invention include not only the compounds in the form of carboxylic acids but also the corresponding lactones formed by the condensation of the carboxylic acids with hydroxy at the 5-position, and sodium salts and lower alkyl esters (such as methyl, ethyl, i-propyl and n-propyl esters) of the carboxylic acids, which can be physiologically hydrolyzed to the carboxylic acids.

(a) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(b) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(c) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(d) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(e) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(f) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(g) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(h) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(i) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(j) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(k) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(l) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-(1"-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(m) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(n) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(o) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(p) (E)-3,5-dihydroxy-7-[4'-(4"-chlorophenyl)-2'-cyclopropyl-6'7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(q) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid

(r) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

(s) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(t) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-(1"-methylethyl)-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(u) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-quinolin-3'-yl]-hept-6-enoic acid

(v) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-chloro-quinolin-3'-yl]-hept-6-enoic acid

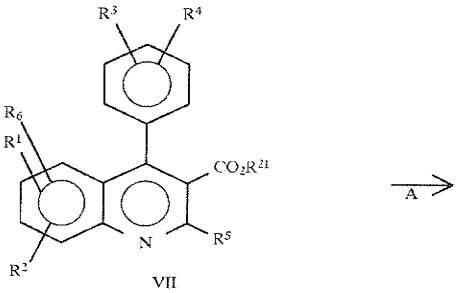
(w) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6'-methyl-quinolin-3'-yl]-hept-6-enoic acid

(x) (E)-3,5-dihydroxy-7-[4'-phenyl-2'-cyclopropyl-6',7'-dimethoxy-quinolin-3'-yl]-hept-6-enoic acid

(y) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

(z) (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-cyclopropyl-6'-methoxy-quinolin-3'-yl]-hept-6-enoic acid

The mevalonolactones of the formula I can be prepared by the following reaction scheme. The enal III can also be prepared by processes K, L and M.



VII

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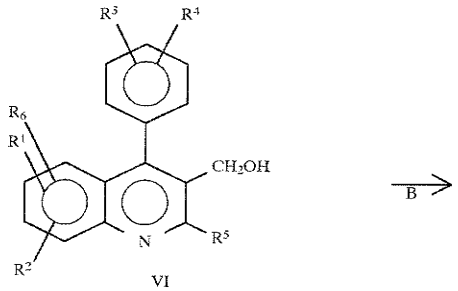

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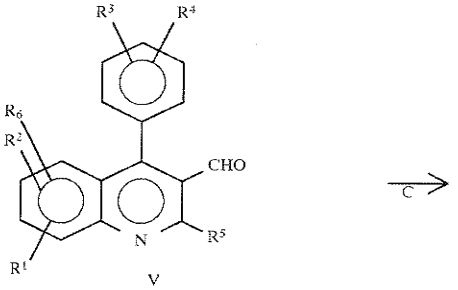

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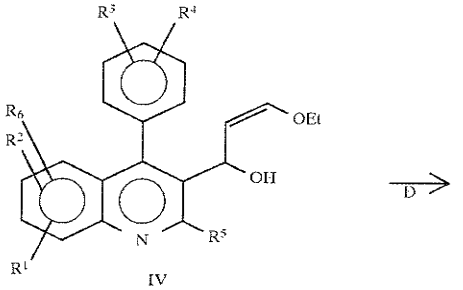

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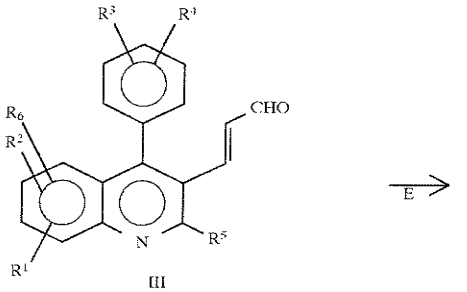

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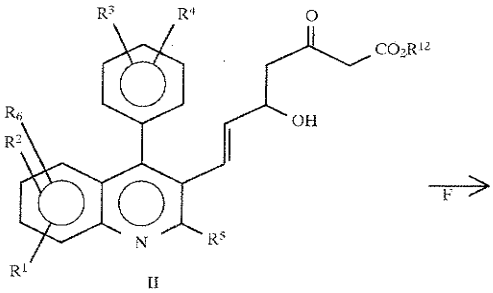

II

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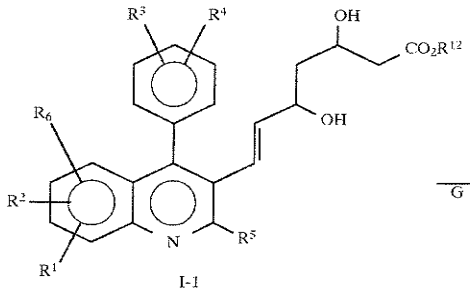
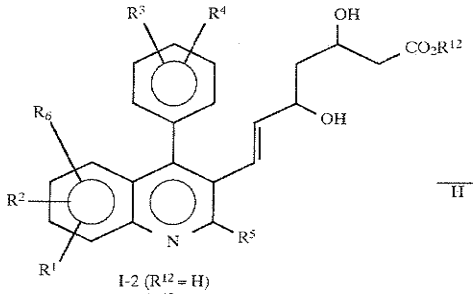
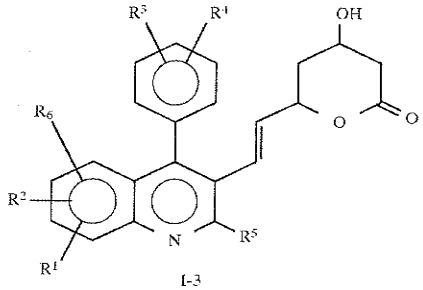


I-1



I-2 (R^{12} = H)
I-5 (R^{12} = Na)



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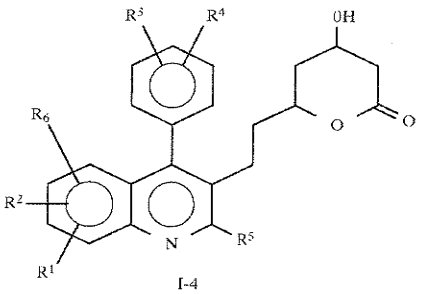
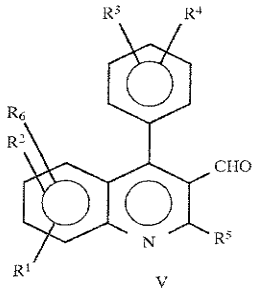


I-4



V

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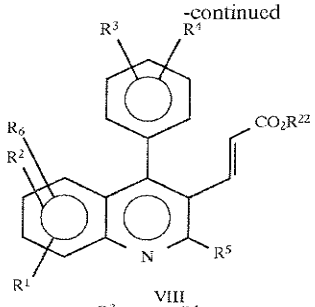

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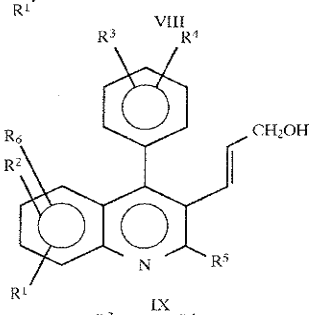
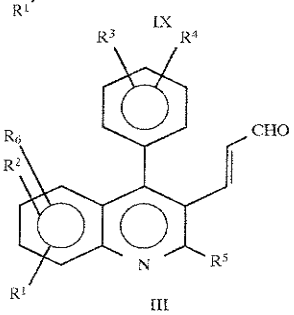


IX



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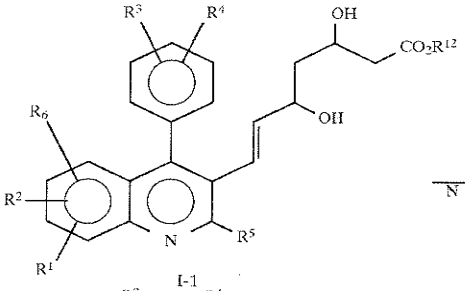
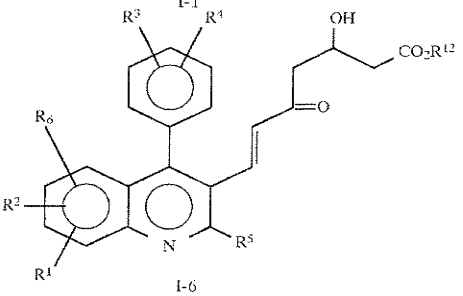


I-1



I-6

In the above reaction scheme, R^1, R^2, R^3, R^4, R^5, R^6 and R^{12} are as defined above with respect to the formula I, and

R^{21} and R^{22} independently represent C_{1-4} lower alkyl such as methyl, ethyl, n-propyl, i-propyl or n-butyl.

Step A represents a reduction reaction of the ester to a primary alcohol. Such reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminium hydride, in a solvent such as tetrahydrofuran or toluene at a temperature of from −20° to 20° C., preferably from −10° to 10° C.

Step B represents an oxidation reaction of the primary alcohol to an aldehyde, which can be conducted by using various oxidizing agents. Preferably, the reaction can be conducted by using pyridinium chlorochromate in methylene chloride at a temperature of from 0° to 25 ° C., or by using oxalyl chloride, dimethyl sulfoxide and a tertiary amine such as triethylamine (Swern oxidation), or by using a sulfur trioxide pyridine complex.

Step C represents a synthesis of a 3-ethoxy-1-hydroxy-2-propene derivative, which can be prepared by reacting a compound V to lithium compound which has been preliminarily formed by treating cis-1-ethoxy-2-(tri-n-butylstannyl) ethylene with butyl lithium in tetrahydrofuran.

As the reaction temperature, it is preferred to employ a low temperature at a level of from −60° to −78° C.

Step D represents a synthesis of an enal by acidic hydrolysis. As the acid catalyst, it is preferred to employ p-toluene sulfonic acid, hydrochloric acid or sulfuric acid, and the reaction may be conducted in a solvent mixture of water and tetrahydrofuran or ethanol at a temperature of from 10° to 25° C. The 3-ethoxy-1-hydroxy-2-propene derivative obtained in Step C can be used in Step D without purification i.e. by simply removing tetra-n-butyl tin formed simultaneously.

Step E represents a double anion condensation reaction between the enal III and an acetoacetate. Such condensation reaction is preferably conducted by using sodium hydride and n-butyl lithium as the base in tetrahydrofuran at a temperature of from −80° to 0° C., preferably from −30° to −10° C.

Step F represents a reduction reaction of the carbonyl group, which can be conudcted by using a metal hydride, preferably sodium borohydride in ethanol at a temperature of from −10° to 25° C., preferably from −10° to 5° C.

Further, the reduction reaction may be conducted by using zinc borohydride in dry ethyl ether or dry tetrahydrofuran at a temperature of −100° to 25° C., preferably from −80° to −50° C.

Step G is a step for hydrolyzing the ester. The hydrolysis can be conducted by using an equimolar amount of a base, preferably potassium hydroxide or sodium hydroxide, in a solvent mixture of water and methanol or ethanol at a temperature of from 10° to 25° C. The free acid hereby obtained may be converted to a salt with a suitable base.

Step H is a step for forming a mevalonolactone by the dehydration reaction of the free hydroxy acid I-2. The dehydration reaction can be conducted in benzene or toluene under reflux while removing the resulting water or by adding a suitable dehydrating agent such as molecular sieve.

Further, the dehydration reaction may be conducted in dry methylene chloride by using a lactone-forming agent such as carbodiimide, preferably a water soluble carbodiimide such as N-cyclohexyl-N'-[2'-(methylmorpholinium)ethyl] carbodiimide p-toluene sulfonate at a temperature of from 10° to 35 ° C., preferably from 20° to 25° C.

Step J represents a reaction for hydrogenating the double bond connecting the mevalonolactone moiety and the quinoline ring. This hydrogenation reaction can be conducted by using a catalytic amount of palladium-carbon or rhodium-carbon in a solvent such as methanol, ethanol, tetrahydrofuran or acetonitrile at a temperature of from 0° to 50° C., preferably from 10° to 25° C.

Step K represents a reaction for the synthesis of an α,β-unsaturated carboxylic acid ester, whereby a trans-form α,β-unsaturated carboxylic acid ester can be obtained by a so-called Horner-Wittig reaction by using an alkoxycarbonylmethyl phosphonate. The reaction is conducted by using sodium hydride or potassium t-butoxide as the base in dry tetrahydrofuran at a temperature of from −30° to 0° C., preferably from −20° to −15° C.

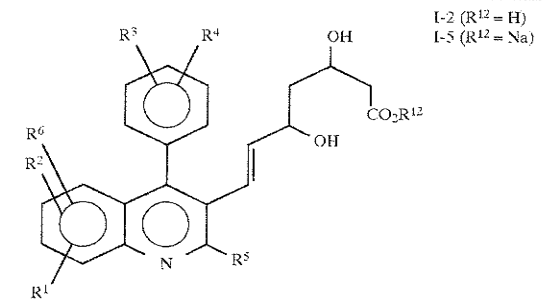
Step L represents a reduction reaction of the α,β-unsaturated carboxylic acid ester to an allyl alcohol. This reduction reaction can be conducted by using various metal hydrides, preferably diisobutylaluminiumhydride, in a solvent such as dry tetrahydrofuran or toluene at a temperature of from −10° to 10° C., preferably from −10° to 0° C.

Step M represents an oxidation reaction of the allyl alcohol to an enal. This oxidation reaction can be conducted by using various oxidizing agents, particularly active manganese dioxide, in a solvent such as tetrahydrofuran, acetone, ethyl ether or ethyl acetate at a temperatrue of from 0° to 100° C., preferably from 15° to 50° C.

Step N represents a reaction for the synthesis of an α,β-unsaturated ketone by the selective oxidation of the dihydroxy carboxylic acid ester. This reaction can be conducted by using activated manganese dioxide in a solvent such as ethyl ether, tetrahydrofuran, benzene or toluene at a temperature of from 20° to 80° C., preferably from 40° to 80° C.

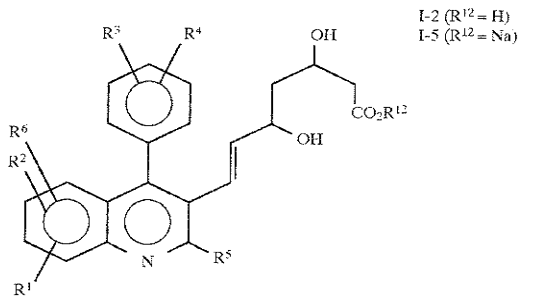
In addition to the compounds disclosed in Examples given hereinafter, compounds of the formulas I-2 and I-5 given in Table 1 can be prepared by the process of the present invention. In Table 1, i- means iso, sec- means secondary and c- means cyclo. Likewise, Me means methyl, Et means ethyl, Pr means propyl, Bu means butyl, Pent means pentyl, Hex means hexyl and Ph means phenyl.

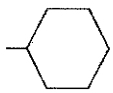
TABLE 1



R^1	R^2	R^3	R^4	R^5	R^6
6-OMe	H	H	H	i-Pr	H
6-OMe	H	4-F	H	i-Pr	H
6-Br	H	4-F	H	i-Pr	H
6-Me	8-Me	4-F	H	i-Pr	H
7-OMe	8-OMe	4-F	H	i-Pr	H
6-Br	H	2-F	H	i-Pr	H
6,7		4-F	H	i-Pr	H

TABLE 1-continued



R^1	R^2	R^3	R^4	R^5	R^6
H	H	4-F	H		H
H	H	4-Ph	H	i-Pr	H
H	H	4-$PhCH_2$	H	i-Pr	H
6-Cl	H	4-F	H	c-Pr	H
6-Cl	H	4-F	H	sec-Bu	H
6-OCH_2Ph	H	4-F	H	i-Pr	H
H	H	4-F	H	i-Bu	H
H	H	4-F	H	c-Pent	H
6-Cl	H	4-F	H	c-Pent	H
6-Me_2N	H	4-F	H	i-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-i-Pr	H	4-F	H	i-Pr	H
7-Me	H	4-F	H	c-Pr	H
6-OMe	H	4-F	H	c-Pr	H
6-Br	H	4-F	H	c-Pr	H
6-i-Pr	H	4-F	H	c-Pr	H
6-Cl	8-Cl	4-F	H	c-Pr	H
5-F	6-Br	4-F	H	i-Pr	8-Br
6-OMe	7-OMe	4-F	H	i-Pr	8-OMe
6-Me	7-Me	4-F	H	i-Pr	8-Me
6-Cl	7-Cl	4-F	H	i-Pr	8-Cl
H	H	4-F	H	c-Bu	H
H	H	4-F	H	c-Hex	H
6-OMe	7-OMe	H	H	i-Pr	H
6-OMe	7-OMe	4-Cl	H	i-Pr	H
6-OMe	7-OMe	H	H	c-Pr	H
6-OMe	7-OMe	4-Cl	H	c-Pr	H
6-OMe	7-OMe	4-F	H	c-Pr	H
6-Me	H	H	H	i-Pr	H
6-Me	H	4-Cl	H	i-Pr	H
6-Me	H	H	H	c-Pr	H
6-Me	H	4-Cl	H	c-Pr	H
6-Me	H	4-F	H	c-Pr	H
6-Cl	H	H	H	i-Pr	H
6-Cl	H	4-Cl	H	i-Pr	H
6-Cl	H	H	H	c-Pr	H
6-Cl	H	4-Cl	H	c-Pr	H
6-Cl	H	4-F	H	c-Pr	H
H	H	H	H	i-Pr	H
H	H	4-Cl	H	i-Pr	H
H	H	H	H	c-Pr	H
H	H	4-Cl	H	c-Pr	H
H	H	4-F	H	c-Pr	H

Further, pharmaceutically acceptable salts such as potassium salts or esters such as ethyl esters or methyl esters of these compounds can be prepared in the same manner.

The compounds of the present invention exhibit high inhibitory activities against the cholesterol biosynthesis wherein HMG-CoA reductase acts as a rate limiting enzyme, as shown by the test results given hereinafter, and thus are capable of suppressing or reducing the amount of cholesterol in blood as lipoprotein. Thus, the compounds of the present invention are useful as curing agents against hyperlipidemia, hyperlipoproteinemia and atherosclerosis.

They may be formulated into various suitable formulations depending upon the manner of the administration. The compounds of the present invention may be administered in the form of free acids or in the form of physiologically hydrolyzable and acceptable esters or lactones, or pharmaceutically acceptable salts.

The pharmaceutical composition of the present invention is preferably administered orally in the form of the compound of the present invention per se or in the form of powders, granules, tablets or capsules formulated by mixing the compound of the present invention with a suitable pharmaceutically acceptable carrier including a binder such as hydroxypropyl cellulose, syrup, gum arabic, gelatin, sorbitol, tragacanth gum, polyvinyl pyrrolidone or CMC-Ca, an excipient such as lactose, sugar, corn starch, calcium phosphate, sorbitol, glycine or crystal cellulose powder, a lubricant such as magnesium stearate, talk, polyethylene glycol or silica, and a disintegrator such as potato starch.

However, the pharmaceutical composition of the present invention is not limited to such oral administration and it is applicable for parenteral administration. For example, it may be administered in the form of e.g. a suppository formulated by using oily base material such as cacao butter, polyethylene glycol, lanolin or fatty acid triglyceride, a transdermal therapeutic base formulated by using liquid paraffin, white vaseline, a higher alcohol, Macrogol ointment, hydrophilic ointment or hydro-gel base material, an injection formulation formulated by using one or more materials selected from the group consisting of polyethylene glycol, hydro-gel base material, distilled water, distilled water for injection and excipient such as lactose or corn starch, or a formulation for administration through mucous membranes such as an ocular mucous membrane, a nasal mucous membrane and an oral mucous membrane.

Further, the compounds of the present invention may be combined with basic ion-exchange resins which are capable of binding bile acids and yet not being absorbed in gastrointestinal tract.

The daily dose of the compound of the formula I is from 0.05 to 500 mg, preferably from 0.5 to 50 mg for an adult. It is administered from once to three times per day. The dose may of course be varied depending upon the age, the weight or the condition of illness of the patient.

The compounds of the formulas II to VII are novel, and they are important intermediates for the preparation of the compounds of the formula I. Accordingly, the present invention relates also to the compounds of the formulas II to VII and the processes for their production.

Now, the present invention will be described in further detail with reference to Test Examples for the pharmacological activities of the compounds of the present invention, their Preparation Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by such specific Examples.

PHARMACOLOGICAL TEST EXAMPLES

Test A: Inhibition of cholesterol biosynthesis from acetate in vitro

Enzyme solution was prepared from liver of male Wistar rat billialy cannulated and discharged bile for over 24 hours. Liver was cut out at mid-dark and microsome and supernatant fraction which was precipitable with 40–80% of saturation of ammonium sulfate (sup fraction) were prepared from liver homogenate according to the modified method of Knauss et. al.; Kuroda, M., et. al., Biochim. Biophys. Acta, 489, 119 (1977). For assay of cholesterol biosynthesis, microsome (0.1 mg protein) and sup fraction (1.0 mg protein) were incubated for 2 hours at 37° C. in 200 μl of the

reaction mixture containing ATP; 1 mM, Glutathione; 6 mM, Glucose-1-phosphate; 10 mM, NAD; 0.25 mM, NADP; 0.25 mM, CoA; 0.04 mM and 0.2 mM [2-^{14}C]sodium acetate (0.2 μCi) with 4 μl of test compound solution dissolved in water or dimethyl sulfoxide. To stop reaction and saponify, 1 ml of 15% EtOH-KOH was added to the reactions and heated at 75° C. for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and incorporated ^{14}C radioactivity was counted. Inhibitory activity of compounds was indicated with IC50.

Test B: Inhibition of cholesterol biosynthesis in culture cells

Hep G2 cells at over 5th passage were seeded to 12 well plates and incubated with Dulbecco's modified Eagle (DME) medium containing 10% of fetal bovine serum (FBS) at 37° C., 5% CO_2 until cells were confluent for about 7 days. Cells were exposed to the DME medium containing 5% of lipoprotein deficient serum (LpDS) prepared by ultracentrifugation method for over 24 hours. Medium was changed to 0.5 ml of fresh 5% LpDS containing DME before assay and 10 μl of test compound solution dissolved in water or DMSO were added. 0.2 μCi of [2-^{14}C]sodium acetate (20 μl) was added at O hr(B-1) or 4 hrs(B-2) after addition of compounds. After 4 hrs further incubation with [2-^{14}C] sodium acetate, medium was removed and cells were washed with phosphate buffered saline(PBS) chilled at 4° C. Cells were scraped with rubber policeman and collected to tubes with PBS and digested with 0.2 ml of 0.5N KOH at 37° C. Aliquot of digestion was used for protein analysis and remaining was saponified with 1 ml of 15% EtOH-KOH at 75° C. for 1 hour. Nonsaponifiable lipids were extracted with petroleum ether and ^{14}C radioactivity was counted. Counts were revised by cell protein and indicated with DPM/mg protein. Inhibitory activity of compounds was indicated with IC50.

Test C: Inhibition of cholesterol biosynthesis in vivo

Male Sprague-Dawley rats weighing about 150 g were fed normal Purina chow diet and water ad libitum, and exposed to 12 hours light/12 hours dark lighting pattern (2:00 PM–2:00 AM dark) prior to use for in vivo inhibition test of cholesterol biosynthesis. Animals were separated groups consisting of five rats as to be average mean body weight in each groups. Test compounds at dosage of 0.02–0.2 mg/kg body weight (0.4 ml/100 g body weight), were dissolved in water or suspended or in 0.5% methyl cellulose and orally administered at 2–3 hours before mid-dark (8:00 PM), while cholesterol biosynthesis reaches to maximum in rats. As control, rats were orally administered only water or vehicle. At 90 minutes after sample administration, rats were injected intraperitoneally with 10 μCi of [2-^{14}C]sodium acetate at volume of 0.2 ml per one. 2 Hours later, blood samples were obtained and serum were separated immediately. Total lipids were extracted according to the method of Folch et al. and saponified with EtOH-KOH. Nonsaponifiable lipids were extracted with petroleum ether and radio activity incorporated into nonsaponifiable lipids was counted.

Inhibitory activity was indicated as percent decrease of counts in testing groups (DPM/2 ml serum/2 hours) from that in control group.

With respect to the compounds of the present invention, the inhibitory activities against the cholesterol biosynthesis in which HMG-CoA reductase serves as a rate limiting enzyme, were measured by the above Test A and B. The results are shown in Tables, 2, 2-2, 3 and 3-2. Further, the results of the measurements by Test C are also presented.

TABLE 2

Inhibitory activities by Test A

Compound	I_{50} (molar concentration)
(Compounds of the present invention)	
I-13	1.25×10^{-7}
I-51	1.0×10^{-8}
I-52	7.1×10^{-8}
I-53	1.9×10^{-7}
(Reference compounds)	
Mevinolin	1.4×10^{-8}
CS-514	9.0×10^{-9}

In Table 2-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

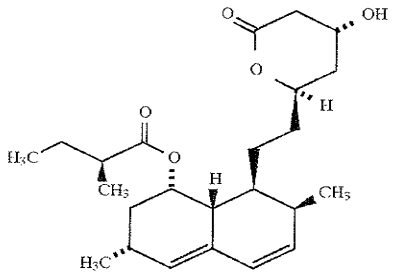
TABLE 2-2

Relative activities by Test A

Compound	Relative activities
(Compounds of the present invention)	
I-16	1.75
I-116	2.25
I-117	0.37
I-120	3.21
I-522	0.76

Structures of reference compounds:

(1) Mevinolin



(2) CS-514

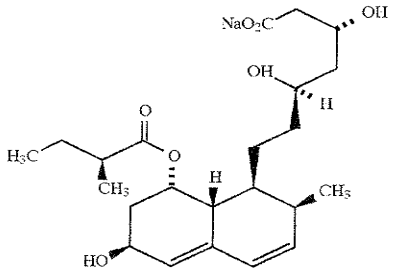


TABLE 3

Inhibitory activities by Test B-1

Compound	I_{50} (molar concentration)
(Compound of the present invention)	
I-51	1×10^{-7}
(Reference compound)	
CS-514	3.5×10^{-7}

In Table 3-2, the relative activities are shown based on the activities of CS-514 being evaluated to be 1.

TABLE 3-2

Relative activities by Test B-1

Compound	Relative activities
I-116	19.4
I-520	20.0
II-20	20.8

Results of the measurement of the inhibitory activities by Test C

The percent decrease of counts after the oral administration of 0.05 mg/kg of compound I-520 was 55% relative to the measured value of the control group. The percent decrease of counts after the oral administration of 10 mg/kg of CS-514 was 55% under the same condition. The compounds of the present invention exhibited activities superior to the reference compound such as CS-514 or Mevinolin in Test A, and exhibited activities superior to CS-514 in Tests B and C.

Test D: Acute toxicity

A 0.5% CMC suspension of a test compound was orally administered to ICR male mice (group of three mice). The acute toxicity was determined based on the mortality after seven days. With compound I-57, I-58, I-59, I-511, I-512, I-513, I-514, I-515, I-517 and I-523 of the present invention, the mortality was 0% even when they were orally administered in an amount of 1000 mg/kg.

Example 1

Ethyl (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoate (compound I-11) (prepared by steps of Example 1-a through Example I-q)

Example 1-a

Ethyl 4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinolin-3-yl-carboxylate (compound VII-1)

The synthesis was conducted in accordance with the method disclosed in J. Org. Chem., 2899 (1966).

6.45 g (0.03 mol) of 2-amino-4'-fluorobenzophenone, 5.53 g (0.035 mol) of ethyl isobutyrylacetate and 0.1 ml of conc. sulfuric acid were dissolved in 30 ml of glacial acetic acid, and the mixture was heated at 100° C. for about 10 hours. After confirming the substantial disappearance of 2-amino-4'-fluorobenzophenone by thin layer chromatography, the reaction solution was cooled to room temperature, and a mixture of 45 ml of conc. aqueous ammonia and 120 ml of water cooled with ice, was gradually added thereto. A separated oily substance was solidified when left to stand overnight in a refrigerator. This solid was recrystallized from a small amount of ethanol to obtain 6.47 g (55%) of white powder. Melting point: 68°–70.5° C.

Example 1-b

4-(4'-fluorophenyl)-3-hydroxymethyl-2-(1'-methylethyl)-quinoline (compound VI-1)

5.4 g (0.016 mol) of compound VII-1 was dissolved in dry toluene under a nitrogen atmosphere and cooled in ice bath to 0° C. To this solution, 40 ml of a 16 wt % diisobutylaluminium hydride-toluene solution was dropwise added, and the mixture was stirred at 0° C. for two hours. After confirming the complete disappearance of compound VII-1 by thin layer chromatography, a saturated ammonium chloride solution was added thereto at 0° C. to terminate the reaction. Ethyl ether was added to the reaction mixture, and the organic layer was separated. A gelled product was dissolved by an addition of an aqueous sodium hydroxide solution and extracted anew with ethyl ether. The ethyl ether extracts were put together, dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off. The residual oil underwent crystallization when left to stand. It was recrystallized from ethyl acetate-n-hexane to obtain 3.3 g of white crystals. Yield: 70%. Melting point: 136°–137° C.

Example 1-c

4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinolin-3-yl-carboxyaldehyde (compound V-1)

2.0 g (9.3 mmol) of pyridinium chlorochromate and 0.4 g of anhydrous sodium acetate was suspended in 10 ml of dry dichloromethane. To this suspension, a solution obtained by dissolving 1 g (3.4 mmol) of compound VI-1 in 10 ml of dry dichloromethane, was immediately added at room temerature. The mixture was stirred for one hour. Then, 100 ml of ethyl ether was added thereto, and the mixture was throughly mixed. The reaction mixture was filtered under suction through a silica gel layer. The filtrate was dried under reduced pressure. The residue was dissolved in the isopropyl ether, and insoluble substances were filtered off. The filtrate was again dried under reduced pressure, and the residue was recrystallized from diisopropyl ether to obtain 0.7 g (Yield: 70%) of slightly yellow prism crystals. Melting point: 124°–126° C.

Example 1-d

3-(3'-ethoxy-1'-hydroxy-2'-propenyl)-4-(4'-fluorophenyl)-2-(1'-methylethyl)-quinoline (compound IV-1)

1.13 g (3.13 mmol) of cis-1-ethoxy-2-(tri-n-butylstannyl) ethylene was dissolved in 8 ml of dry tetrahydrofuran, and the solution was cooled to −78° C. in a nitrogen stream. To this solution, 2 ml (3.2 mmol) of a 15 wt % n-butyllithium-n-hexane solution was dropwise added. The mixture was stirred for 45 minutes. Then, a solution prepared by dissolving 0.76 g (2.6 mmol) of compound V-1 in 10 ml of dry tetrahydrofuran was dropwise added thereto. The reaction mixture was stirred at −78° C. for two hours. Then, 2 ml of a saturated ammonium chloride solution was added thereto to terminate the reaction. The organic layer was extracted with diethyl ether, and the diethyl ether extract was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was separated with n-hexane and acetonitrile. The solvent was distilled off under reduced pressure from the acetonitrile layer, and an oily substance thereby obtained was purified by silica gel column chromatography (eluent: 2.5% methanol-chloroform) to obtain 0.91 g of the desired compound in a purified oily form.

H-MNR ($CDCl_3$) δ ppm: 1.1(t,3H,7Hz) 1.37(d,6H,J=7Hz) 3.7(m,1H); 3.7(q,2H,J=7Hz) 4.75(t,1H,7Hz) 5.7(m,1H) 5.95(m,1H) 7.05–8.2(m,8H)

Example 1-e

(E)-3-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]propenaldehyde (compound III-1)

0.91 g of compound IV-1 was dissolved in 20 ml of tetrahydrofuran, and 5 ml of water and 100 mg of p-toluenesulfonic acid were added thereto. The mixture was stirred at room temperature for 24 hours. The reaction solution was extracted with diethyl ether a few times. The extracts were washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent: chloroform) to obtain the desired product as white prism crystals. 0.4 g (50%). Melting point: 127°–128° C.

Example 1-f

Ethyl (E)-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-5-hydroxy-3-oxohepto-6-enoate (compound II-1)

50 mg of 60% sodium hydride was washed with dry petroleum ether and dried under a nitrogen stream, and then suspended in 5 ml of dry tetrahydrofuran. The suspension was cooled to −15° C. in a nitrogen atmosphere. Then, 120 mg (0.92 mmol) of ethyl acetoacetate was dropwise added thereto, and the mixture was stirred for 15 minutes. Then, 0.6 ml (0.92 mmol) of a 15 wt % n-butyllithium-n-hexane solution was dropwise added thereto, and the mixture was stirred for 30 minutes. Then, a solution prepared by dissolving 160 mg (0.5 mmol) of compound III-1 in dry tetrahydrofuran, was dropwise added thereto, and the mixture was stirred for one hour. To the reaction mixture, 1 ml of a saturated ammonium chloride aqueous solution was added at −15° C. Then, the mixture was extracted three times with diethyl ether. The diethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. The solution was evaporated to dryness under reduced pressure. The residue was recrystallized from diisopropyl ether to obtain 130 mg (yield: 59%) of white crystals. Melting point: 99°–101° C.

Example 1-g

Ethyl (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3 '-yl]-hept-6-cnoatc (compound I-11)

110 mg (0.245 mmol) of compound II-1 was dissolved in 5 ml of ethanol in a nitrogen atmosphere, and the solution was cooled 0° C. Then, 10 mg (0.263 mmol) of sodium borohydride was added, and the mixturer was stirred for one hour. Then, 1 ml of a 10% hydrochloric acid aqueous solution was added thereto, and the mixture was extracted three times with ethyl ether. The ethyl ether solution was washed with a saturated sodium chloride aqueous solution and dried over anhydrous magnesium sulfate. Then, the solution was evaporated to dryness under reduced pressure. The residual oil was purified by silica gel column chromatography (eluent: 5% methanol-chloroform) to obtain the desired product as a pure colorless oily substance. 70 mg (Yield: 64%)

H-NMR ($CDCl_3$) δ ppm: 1.30(t,3H,J=8Hz) 139(d,6H,J=8Hz) 1.4–1.8(m,2H); 2.42(d,2H,J=7Hz) 3.0–3.8 (m,2H) 3.50(m,1H) 3.9–4.6(m,2H) 4.20(q,2H,J=8Hz) 5.35(m,1H) 6.59(m,1H) 7.10–8.18(m,8H)

Example 2

Sodium salt of (E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3 '-yl]-hept-6-enoic acid (compound I-51)

60 mg (0.133 mmol) of compound I-11 was dissolved in 3 ml of ethanol. Then, 0.26 ml of a 0.5N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 5 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was freeze-dried to obtain 40 mg (67%) of hygroscopic white powder. Melting point: 207°–209° C. (decomposed).

Example 3

(E)-3,5-dihydroxy-7-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-yl]-hept-6-enoic acid (compound I-21)

110 mg (0.244 mmol) of compound I-11 was dissolved in 10 ml of ethanol. Then, 0.79 ml of a 0.5N sodium hydroxide aqueous solution was dropwise added thereto. The mixture was stirred at room temperature for further one hour, and ethanol was distilled off under reduced pressure. Then, 10 ml of water was added thereto, and the mixture was extracted with ethyl ether. The aqueous layer was weakly acidified (pH 4) with a dilute hydrochloric aqueous solution and extracted three times with ethyl ether. The ethyl ether layers were put together and dried over anhydrous magnesium sulfate. Then, the solvent was distilled off under reduced pressure to obtain 90 mg of slightly yellow oily substance.

H-NMR ($CDCl_3$) δ ppm: 1.36(d,6H,J=7Hz) 2.4(m,2H) 3.5(m,1H) 3.45(m,1H); 3.8–4.6(m,2H) 5.40(dd,1H,J_1=19Hz,J_2=8Hz) 6.55 (d,1H,J=19Hz) 7.0–8.3(m,8H)

Example 4

(E)-6-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-ylethenyl]-4-hydroxy-3,4, 5,6-tetrahydro-2H-pyran-2-one (compound I-31)

90 mg of compound I-21 was dissolved in 10 ml of dry toluene, and the solution refluxed under heating for 3 hours by means of a Dean Stark apparatus.

Toluene was distilled off under reduced pressure, and the residual solid was recrystallized from diisopropyl ether to obtain 40 mg of colorless prism crystals. Melting point: 182°–184 ° C.

By silica gel thin chromatography, the product gave two absorption spots close to each other attributable to the diastereomers. (Developping solvent: 3% methanol-chloroform)

These diasteromers were separated and isolated by silica gel thin layer chromatography. [Developping solvent: t-BuOMe/hexane/acetone=7/2/1 (v/v), Rf=0.6 and 0.7 (obtained weight ratio: 1/2)]

Rf=0.7: trans lactone

H-NMR ($CDCl_3$) δ ppm: 1.40(d,6H,J=7Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H); 4.20(m,1H) 5.15(m,1H) 5.37(dd, 1H,J_1=18Hz,J_2=7Hz) 6.68(d,1H, J=19Hz) 7.1–8.2(m,8H)

Rf=0.6: cis lactone

H-NMR ($CDCl_3$) δ ppm: 1.40(d,6H,J=7Hz) 1.6(m,2H) 2.65(m,2H) 3.48(m,1H); 4.20(m,1H) 4.65(m,1H) 5.40(dd, 1H,J_1=18Hz,J_2=7Hz) 6.66(m,1H) 7.0–8.2(m,8H)

Example 5

6-[4'-(4"-fluorophenyl)-2'-(1"-methylethyl)-quinolin-3'-ylethynyl]-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound I-41)

20 mg of a mixture of diastereomers of compound I-31 was dissolved in 5 ml of ethanol, and 10 mg of 5% palladium-carbon was added thereto. The mixture was stirred under a hydrogen atmosphere. After confirming the disappearance of the starting substance and the appearance of a new spot by thin layer chromatography, the palladium-carbon was filtered off, and ethanol was distilled off to obtain colorless oil.

This oil was purified by preparative thin layer chromatography to obtain 16 mg of the desired product as pure colorless oil.

MS(m/e): 408(M^++H), 407(M^+), 366, 292, 278

In the same manner as in Example 1-a, compounds VII-2 to VII-27 were prepared. The physical properties of these compounds are shown in Table 4. (In the Table, R^1, R^2, R^3, R^4, R^5 and R^{21} correspond to the substitients of compound VII.)

TABLE 4

(Compounds in this Table are compounds of the formula VII wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{21}	m.p. (°C.)
VII-2	H	H	4-F	H	CH_3	C_2H_5	121–122
VII-3	H	H	H	H	CH_3	C_2H_5	102–102.5
VII-4	H	H	H	H	i-Pr	C_2H_5	85–85.5
VII-5	6-Cl	H	H	H	CH_3	C_2H_5	100.5–101.5
VII-6	6-Cl	H	H	H	i-Pr	C_2H_5	105.5–106.5
VII-7	H	H	2-F	H	i-Pr	C_2H_5	101.0–102.0
VII-8	7-Me	H	H	H	i-Pr	C_2H_5	oil
VII-9	H	H	4-Cl	H	i-Pr	C_2H_5	134.0–136.5
VII-10	H	H	4-OMe	H	i-Pr	C_2H_5	88.0–89.0
VII-11	H	H	4-Me	H	i-Pr	C_2H_5	108.5–109.5
VII-12	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	101.0–103.0
VII-13	H	H	4-CF_3	H	i-Pr	C_2H_5	117.5–119.0
VII-14	H	H	3-Me	4-F	i-Pr	C_2H_5	oil
VII-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
VII-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	96.0–98.0
VII-17	H	H	4-F	H	C_2H_5	CH_3	139.0–139.5
VII-18	H	H	4-F	H	n-Pr	C_2H_5	oil
VII-19	6-Cl	H	4-F	H	i-Pr	C_2H_5	94.5–95.5
VII-20	H	H	4-F	H	c-Pr	CH_3	113.5–116.5
VII-21	H	H	4-OPh	H	i-Pr	C_2H_5	oil
VII-22	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	96.0–98.0
VII-23	6-Cl	H	H	H	Ph	C_2H_5	118.8–119.5
VII-24	6-Cl	H	H	H	c-Pr	CH_3	97.0–98.5
VII-25	H	H	4-F	H	sec-Bu	CH_3	oil
VII-26	6-Me	H	4-F	H	i-Pr	C_2H_5	109.0–111.0
VII-27	6-OMe	7-OMe	4-F	H	c-Pr	CH_3	153.0–153.5

VII-8

H-NMR (in $CDCl_3$) δ ppm: 0.92 (t,3H,J=7Hz), 1.41 (d,6H,J=6Hz); 2.47 (s,3H), 3.27 (Heptaplet,1H,J=6Hz) 3.96 (q,2H,J=7Hz), 7.0–7.8(m, 8H)

VII-14

H-NMR (in $CDCl_3$) δ ppm: 1.01 (t,3H,J=7Hz), 1.42 (d,6H,J=6Hz); 2.38 (s,3H,J=3Hz), 3.25(Heptaplet, 1H,J=6Hz) 4.04 (q,2H,J=7Hz), 6.9 –8.1(m,7Hz)

VII-15

H-NMR(in $CDCl_3$) δ ppm: 0.97(t,3H,J=7Hz), 1.43 (d,6H, J=6Hz); 2.29 (s,6H) 3.25 (Heptaplet, 1H,J=6Hz) 4.00 (q,2H, J=7Hz), 6.8–8.0(m,7H)

VII-18

H-NMR (in $CDCl_3$) δ ppm: 0.98 (t,3H,J=7Hz), 1.02 (t,3H,J=7Hz); 1.6–2.3(m,2H), 2.8–3.1(m,2H) 4.03 (q,2H,J= 7Hz), 6.9–8.1(m,8H)

VII 21

H-NMR (in $CDCl_3$) δ ppm: 1.03 (t,3H,J=7Hz), 1.41 (d,6H,J=6Hz); 3.25(Heptapet,1H,J=6Hz), 4.05(q,2H,J= 7Hz), 6.8–8.1(m, 13H)

VII-25

H-NMR (in $CDCl_3$) δ ppm: 0.97 (d,6H,J=6Hz), 2.0–2.6 (m,1H); 2.85 (d,2H,J=7Hz), 3.51(s,3H), 6.8–8.1 (m,8H)

In the same manner as in Example 1-b, compounds VI-2 to VI-27 were prepared. (In Table 5, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents in compound VI.)

TABLE 5

(Compounds in this Table are compounds of the formula VI wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
VI-2	H	H	p-F	H	CH_3	—
VI-3	H	H	H	H	CH_3	149–151
VI-4	H	H	H	H	i-Pr	130–130.5
VI-5	6-Cl	H	H	H	CH_3	139–141
VI-6	6-Cl	H	H	H	i-Pr	168–169
VI-7	H	H	2-F	H	i-Pr	140.5–142.0
VI-8	7-Me	H	H	H	i-Pr	155.0–157.0
VI-9	H	H	4-Cl	H	i-Pr	192.0–195.0
VI-10	H	H	4-OMe	H	i-Pr	186.0–188.5
VI-11	H	H	4-Me	H	i-Pr	161.0–164.0
VI-12	6-Cl	H	2-Cl	H	i-Pr	122.0–124.0
VI-13	H	H	4-CF_3	H	i-Pr	183.0–186.0
VI-14	H	H	3-Me	4-F	i-Pr	161.0–162.5
VI-15	H	H	3-Me	5-Me	i-Pr	137.0–138.0
VI-16	6-Me	7-OMe	4-F	H	i-Pr	164.0–165.0
VI-17	H	H	4-F	H	C_2H_5	141.5–143.5
VI-18	H	H	4-F	H	n-Pr	146.5–148.5
VI-19	6-Cl	H	4-F	H	i-Pr	171.0–172.0
VI-20	H	H	4-F	H	c-Pr	120–126
VI-21	H	H	4-OPh	H	i-Pr	153.0–154.0
VI-22	6-Cl	8-Cl	4-F	H	i-Pr	98.5–103
VI-23	6-Cl	H	H	H	Ph	171.5–172.5
VI-24	6-Cl	H	H	H	c-Pr	84.0–86.0
VI-25	H	H	4-F	H	sec-Bu	119.0–121.0
VI-26	6-Me	H	4-F	H	i-Pr	160.0–161.5
VI-27	6-OMe	7-OMe	4-F	H	c-Pr	162.0–163.0

In the same manner as in Example 1-c, compounds V-2 to V-27 were prepared. (In Table 6, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound of V.)

TABLE 6

(Compounds in this Table are compounds of the formula V wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
V-2	H	H	p-F	H	CH_3	125–128
V-3	H	H	H	H	CH_3	143–146
V-4	H	H	H	H	i-Pr	92–93
V-5	6-Cl	H	H	H	CH_3	220–222
V-6	6-Cl	H	H	H	i-Pr	140–140.5
V-7	H	H	2-F	H	i-Pr	121.5–124.0
V-8	7-Me	H	H	H	i-Pr	105.1–109.2
V-9	H	H	4-Cl	H	i-Pr	147.0–147.8
V-10	H	H	4-OMe	H	i-Pr	135.6–136.8
V-11	H	H	4-Me	H	i-Pr	119.4–120.4
V-12	6-Cl	H	2-Cl	H	i-Pr	105.8–106.9
V-13	H	H	4-CF_3	H	i-Pr	163.7–164.2
V-14	H	H	3-Me	4-F	i-Pr	161.1–108.1
V-15	H	H	3-Me	5-Me	i-Pr	120.8–122.3
V-16	6-OMe	7-OMe	4-F	H	i-Pr	164.4–165.2
V-17	H	H	4-F	H	C_2H_5	143.1–144.2
V-18	H	H	4-F	H	n-Pr	150.2–155.3
V-19	6-Cl	H	4-F	H	i-Pr	164.5–165.3
V-20	H	H	4-F	H	c-Pr	150.1–151.6
V-21	H	H	4-OPh	H	i-Pr	106.9–107.7
V-22	6-Cl	8-Cl	4-F	H	i-Pr	135.0–135.7
V-23	6-Cl	H	H	H	Ph	174.8–175.3
V-24	6-Cl	H	H	H	c-Pr	157.5–158.0
V-25	H	H	4-F	H	sec-Bu	125.0–126.5
V-26	6-Me	H	4-F	H	i-Pr	155.0–157.0
V-27	6-OMe	7-OMe	4-F	H	c-Pr	200.0–200.5

In the same manner as in Example 1-d, compounds IV-2 to IV-6 were prepared. (In Table 7, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound IV.)

TABLE 7

(Compounds in this Table are compounds of the formula IV wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
IV-2	H	H	4-F	H	CH_3	177–179
IV-3	H	H	H	H	CH_3	—
IV-4	H	H	H	H	i-Pr	—
IV-5	6-Cl	H	H	H	CH_3	—
IV-6	6-Cl	H	H	H	i-Pr	—

In the same manner as in Example 1-e, compounds III-2 to III-27 were prepared. (In Table 8, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound III.)

TABLE 8

(Compounds in this Table are compounds of the formula III wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	m.p. (°C.)
III-2	H	H	4-F	H	CH_3	194–196
III-3	H	H	H	H	CH_3	170–171.5
III-4	H	H	H	H	i-Pr	107–108.5
III-5	6-Cl	H	H	H	CH_3	192–194
III-6	6-Cl	H	H	H	i-Pr	125.5–127
III-7	H	H	2-F	H	i-Pr	80.1–80.2
III-8	7-Me	H	H	H	i-Pr	121.1–122.3
III-9	H	H	4-Cl	H	i-Pr	148.0–149.1
III-10	H	H	4-OMe	H	i-Pr	137.4–140.1
III-11	H	H	4-Me	H	i-Pr	111.6–113.1
III-12	6-Cl	H	2-Cl	H	i-Pr	83.8–84.5
III-13	H	H	4-CF_3	H	i-Pr	126.2–128.8
III-14	H	H	3-Me	4-F	i-Pr	124.8–126.4
III-15	H	H	3-Me	5-Me	i-Pr	117.6–120.3
III-16	6-OMe	7-OMe	4-F	H	i-Pr	147.8–150.9
III-17	H	H	4-F	H	C_2H_5	124.3–128.5
III-18	H	H	4-F	H	n-Pr	117.8–121.5
III-19	6-Cl	H	4-F	H	i-Pr	135.2–135.9
III-20	H	H	4-F	H	c-Pr	141.3–144.1
III-21	H	H	4-OPh	H	i-Pr	oil
III-22	6-Cl	8-Cl	4-F	H	i-Pr	117–122
III-23	6-Cl	H	H	H	Ph	142.8–144.3
III-24	6-Cl	H	H	H	c-Pr	161.0–161.5
III-25	H	H	4-F	H	sec-Bu	78.0–81.0
III-26	6-Me	H	4-F	H	i-Pr	137.0–137.5
III-27	6-OMe	7-OMe	4-F	H	c-Pr	189.5–191.0

III-22

H-NMR(in $CDCl_3$) δ ppm: 1.40(d6H,J=7Hz), 3.44 (Heptaplet,1H,J=7Hz); 5.93(dd,1H,J=8Hz,J=16Hz), 6.8–8.1 (m,14H) 9.34(d,1H,J=8Hz)

In the same manner as in Example 1-f, compounds II-2 to II-27 were prepared. (In Table 9, R^1, R^2, R^3, R^4 and R^5 correspond to the substituents of compound II.)

TABLE 9

(Compounds in this Table are compounds of the formula of II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
II-2	H	H	p-F	H	CH_3	C_2H_5	oil
II-3	H	H	H	H	CH_3	C_2H_5	105–106
II-4	H	H	H	H	i-Pr	C_2H_5	88.5–90.5
II-5	6-Cl	H	H	H	CH_3	C_2H_5	77–82
II-6	6-Cl	H	H	H	i-Pr	C_2H_5	96–98
II-7	H	H	2-F	H	i-Pr	C_2H_5	oil
II-8	7-Me	H	H	H	i-Pr	C_2H_5	68.5–74.0
II-9	H	H	4-Cl	H	i-Pr	C_2H_5	91.0–94.0

TABLE 9-continued

(Compounds in this Table are compounds of the formula of II wherein R^6 is hydrogen.)

Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
II-10	H	H	4-OMe	H	i-Pr	C_2H_5	78.0–78.5
II-11	H	H	4-OMe	H	i-Pr	C_2H_5	75.0–78.0
II-12	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	oil
II-13	H	H	4-CF_3	H	i-Pr	C_2H_5	78.0–83.0
II-14	H	H	3-Me	4-F	i-Pr	C_2H_5	66.0–71.0
II-15	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
II-16	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	83.0–90.0
II-17	H	H	4-F	H	C_2H_5	C_2H_5	94.0–97.0
II-18	H	H	4-F	H	n-Pr	C_2H_5	oil
II-19	6-Cl	H	4-F	H	i-Pr	C_2H_5	111.0–113.5
II-20	H	H	4-F	H	c-Pr	C_2H_5	91.0–93.0
II-21	H	H	4-OPh	H	i-Pr	C_2H_5	121.0–125.0
II-22	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	oil
II-23	6-Cl	H	H	H	Ph	C_2H_5	oil
II-24	6-Cl	H	H	H	c-Pr	C_2H_5	69.0–71.0
II-25	H	H	4-F	H	sec-Bu	C_2H_5	oil
II-26	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
II-27	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	oil

II-7

H-NMR(in $CDCl_3$) δ ppm: 1.21(t,3H,J=7Hz), 1.32(d,6H, J=6Hz); 2.2–2.4(m,2H), 2.5–2.7(m,1H) 3.28(s,1H), 3.34 (Heptaplet, 1H,J=6Hz) 4.08(q,2H,J=7Hz), 4.3–4.6(m,1H) 5.28(dd,1H,J=6Hz,J=15Hz), 6.53(dd,1H,J=1.5Hz,J=15Hz), 6.9–8.0(m,8H)

II-12

H-NMR(in $CDCl_3$) δ ppm: 1.25(t,3H,J=7Hz), 1.33(d,6H, J=6Hz); 2.2–2.4(m,2H), 2.5–2.8(m,1H); 3.32(s,2H), 3.38 (Heptaplet, 1H, J=6Hz); 4.13(q,2H,J=7Hz), 4.2–4.6(m,1H); 5.34(dd,1H,J=6Hz, J=15Hz), 6.53(dd,1H,J=1.5Hz,J=15Hz), 7.0–8.0(m,7H)

II-15

H-NMR (in $CDCl_3$) δ ppm: 1.23(t,3H,J=7Hz), 1.35(d,6H, J=6Hz); 2.2–2.4(m,2H), 2.31(s,6H); 2.6–2.8(m,1H), 3.32(s, 2H); 3.35(Heptaplet,1H,J=6Hz), 4.12(q,2H,J=7Hz); 4.3–4.7 (m,1H), 5.30(dd,1H,J=6Hz,J=16Hz); 6.51(dd,1H,J=1Hz,J= 16Hz), 6.7–8.0(m,7H)

II-18

H-NMR (in $CDCl_3$) δ ppm: 1.00 (t,3H,J=7Hz), 1.26(t, 3H,J=7Hz); 1.6–2.3(m,2H), 2.42 (d, 2H,J=6Hz); 2.6–3.2(m, 3H), 3.35(s,2H) 4.11(q,2H,J=7Hz), 4.3–4.7(m,1H) 5.27(dd, 1H,J=6Hz,J=16Hz) 6.46(dd,1H,J=1.5Hz,J=16Hz), 6.9–8.0 (m,8H)

II22

H-NMR(in $CDCl_3$) δ ppm: 1.26(t,3H,J=7Hz), 1.33(d,6H, J=6Hz); 2.43(d,2H,J=6Hz), 2.6–2.9(m,1H) 3.36(s, 2H), 3.44 (Heptaplet,1H,J=6Hz) 4.13(q,2H,J=7Hz), 4.3–4.7(m,1H) 5.30(dd,1H,J=6Hz,J=16Hz), 6.53(dd,1H,J=1.5Hz,J=16Hz), 7.0–7.6(m,6H)

II-23

H-NMR(in $CDCl_3$) δ ppm: 1.23(t,3H,J=7Hz), 2.21(d,2H, J=6Hz); 2.4–2.6(m,1H), 3.25(s,2H) 4.09(q,2H,J=7Hz), 4.1–4.4(m,1H) 5.08(dd,1H,J=6Hz,J=16Hz), 6.26(dd,1H,J= 1.5Hz,J=16Hz), 7.0–8.0 (m,13H)

II25

H-NMR(in $CDCl_3$) δ ppm: 0.96(d,6H,J=6Hz), 1.26(t,3H, J=7Hz), 1.8–2.4(m,1H), 2.43 (d,2H,J=6Hz), 2.6–2.9(m,1H), 2.88(d,2H,J=7Hz), 3.36(s,2H), 4.14(q,2H,J=7Hz), 4.3–4.7 (m,1H), 5.0–5.5(m,1H), 6.3–6.7(m,1H), 6.9–8.1(m,3H)

II-26

H-NMR(in $CDCl_3$) δ ppm: 1.25(t,3H, J=7Hz), 1.32(d,6H, J=6Hz), 2.32(s,3H), 2.39(d,2H, J=7Hz), 2.6–3.1(m,1H),

3.36(s,2H), 3.41(Heptaplet,1H,J=6Hz), 4.11(q,2H,J=7Hz), 4.3–4.7(m,1H), 5.0–5.5(m,1H), 6.3–6.7(m,1H), 6.8–7.9(m, 7H)

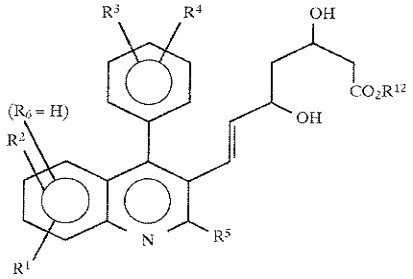
II-27

H-NMR (in $CDCl_3$) δ ppm: 0.8–1.5(m,4H), 1.26(t,3H,J= 7Hz), 2.0–2.9(m,4H), 3.42(s,2H), 3.71(s,3H), 4.00(s,3H), 4.20(q,2H,J=7Hz), 4.4–4.8(m,1H), 5.3–5.8(m,1H), 6.4–6.9 (m,1H), 6.58(s,1H), 7.0–7.5(m,5H)

In the same manner as in Example 1-g, compounds I-12 to I-127 were prepared.

TABLE 10

I-1



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.) Mass spectrum
I-12	H	H	4-F	H	CH_3	C_2H_5	oil
						M/e	423, 292 264, 249
I-13	H	H	H	H	CH_3	C_2H_5	92–105
I-14	H	H	H	H	i-Pr	C_2H_5	97–100
I-15	6-Cl	H	H	H	CH_3	C_2H_5	oil
I-16	6-Cl	H	H	H	i-Pr	C_2H_5	oil
I-17	H	H	2-F	H	i-Pr	C_2H_5	oil
I-18	7-Me	H	H	H	i-Pr	C_2H_5	oil
I-19	H	H	4-Cl	H	i-Pr	C_2H_5	98–104
I-110	H	H	4-OMe	H	i-Pr	C_2H_5	94–98
I-111	H	H	4-Me	H	i-Pr	C_2H_5	79–85
I-112	6-Cl	H	2-Cl	H	i-Pr	C_2H_5	oil
I-113	H	H	4-CF_3	H	i-Pr	C_2H_5	117–128
I-114	H	H	3-Me	4-F	i-Pr	C_2H_5	85–92
I-115	H	H	3-Me	5-Me	i-Pr	C_2H_5	oil
I-116	6-OMe	7-OMe	4-F	H	i-Pr	C_2H_5	gum
I-117	H	H	4-F	H	C_2H_5	C_2H_5	oil
I-118	H	H	4-F	H	n-Pr	C_2H_5	oil
I-119	6-Cl	H	4-F	H	i-Pr	C_2H_5	79–82
I-120	H	H	4-F	H	c-Pr	C_2H_5	100–104
I-121	H	H	4-OPh	H	i-Pr	C_2H_5	oil
I-222	6-Cl	8-Cl	4-F	H	i-Pr	C_2H_5	133–143
I-123	6-Cl	H	H	H	Ph	C_2H_5	gum
I-124	6-Cl	H	H	H	c-Pr	C_2H_5	oil
I-125	H	H	4-F	H	sec-Bu	C_2H_5	oil
I-126	6-Me	H	4-F	H	i-Pr	C_2H_5	oil
I-127	6-OMe	7-OMe	4-F	H	c-Pr	C_2H_5	gum

I-17

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.40(d,6H, J=6Hz); 1.4–1.7(m,2H), 2.3–2.5(m,2H) 2.9–3.2(m,1H), 3.49(Heptaplet,1H,J=6Hz) 3.5–3.8(m,1H), 3.9–4.5(m,2H) 4.20(q,2H,J=7Hz), 5.2–5.7(m,1H) 6.5–6.9(m,1H), 7.0–8.2 (m,8H)

I-18

H-NMR (in $CDCl_3$) δ ppm: 1.0–1.4(m,2H), 1.31(t,3H,J= 7Hz); 1.39(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.52(s,3H), 3.1–3.4 (m,1H) 3.48(Heptaplet,1H,J6Hz),3.5–3.8(m,1H) 3.8–4.1(m,1H), 4.20(q,2H,J=7Hz) 4.2–4.5(m,1H), 5.2–5.6 (m,1H) 6.4–6.8(m,1H), 7.0–8.0(m,8H)

I-19

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.38(d,6H, J=6Hz); 1.4–1.8(m,2H), 2.3–2.5(m,2H) 3.2–3.4(m,1H). 3.49(Heptaplet,1H,J=6Hz) 3.6–3.8(m,1H), 3.9–4.2(m,1H) 4.20(q,2H,J=7Hz), 4.3–4.5(m,1H) 5.2–5.5(m,1H), 6.5–6.8 (m,1H) 7.0–8.2(m,8H)

I-110

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.40(d,6H, J=6Hz); 1.5–1.6(m,2H), 2.3–2.5(m,2H) 2.8–3.0(m,1H), 3.4–3.6(m,1H) 3.52(Heptaplet,1H,J=6Hz), 3.88(s,3H) 3.9–4.1(m,1H), 4.20(q,2H,J=7Hz) 4.3–4.5(m,1H), 5.3–5.5 (m,1H) 6.5–6.7(m,1H), 6.9–8.1(m,8H)

H-NMR (in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.3–1.5(m, 2H); 1.39(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.43(s,3H), 2.8–3.0 (m,1H) 3.50(Heptaplet,1H,J=6Hz), 3.5–3.7(m,1H) 3.9–4.2 (m,1H), 4.19(q,2H,J=7Hz) 4.2–4.5(m,1H), 5.2–5.6(m,1H) 6.4–6.8(m,1H), 6.9–8.2(m,8H)

I-112

H-NMR (in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.3–1.6(m, 2H); 1.37(d,6H,J=6Hz), 2.3–2.5(m,2H) 2.9–3.2(m,1H), 3.47 (Heptaplet,1H ,J=6Hz) 3.5–3.8(m,1H), 3.9–4.1(m,1H) 4.19 (q,2H,J=7Hz), 4.2–4.5(m,1H) 5.3–5.7(m,1H), 6.5–6.8(m, 1H) 7.1–8.1(m,7H)

I-113

H-NMR(in $CDCl_3$) δ ppm: 1.0–1.3(m,2H), 1.30(t,3H,J= 7Hz); 1.40(d,6H,J=6Hz), 2.3–2.4(m,2H) 3.3–3.5(m,1H), 3.49 (Heptaplet,1H,J=6Hz) 3.6–3.7(m,1H), 3.9–4.1(m,1H) 4.18(q,2H,J=7Hz), 4.2–4.5(m,1H) 5.1–5.5(m,1H), 6.5–6.8 (m,1H) 7.2–8.2(m,8H)

I-114

H-NMR (in $CDCl_3$) δ ppm: 1.2–1.4(m,2H), 1.30(t,3H,J= 7Hz); 1.39(d,6H,J=6Hz), 2.32(bs,3H) 2.3–2.5(m,2H), 3.0–3.3(m,1H) 3.50(Heptaplet,1H,J=6Hz), 3.6–3.8(m,1H) 3.8–4.1(m,1H), 4.20(q,2H,J=7Hz) 4.3–4.6(m,1H), 5.2–5.6 (m,1H) 6.5–6.8(m,1H), 7.0–8.2(m,7H)

I-115

H-NMR (in $CDCl_3$) δ ppm: 1.1–1.4(m,2H), 1.30(t,3H,J= 7Hz); 1.40(d,6H,J=6Hz), 2.2–2.5(m,2H) 2.35(s,6H), 2.7–3.1(m,1H) 3.51(Heptaplet, 1H,J=6Hz), 3.6–3.7(m,1H) 3.8–4.1(m,1H), 4.20 (q,2H,J=7Hz) 4.2–4.6(m,1H), 5.2–5.6 (m,1H) 6.4–6.8(m,1H), 6.8–8.2(m,7H)

I-116

H-NMR (in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.37(d,6H, J=6Hz); 1.5–1.8(m,2H), 2.3–2.5(m,2H) 2.9–3.2(m,1H), 3.46 (Heptaplet,1H,J=6Hz) 3.6–3:8(m,1H), 3.75(s,3H) 3.9–4.1(m,1H), 4.07(s,3H) 4.20(q,2H,J=7Hz), 4.2–4.5(m, 1H) 5.1–5.5(m,1H), 6.4–6.8(m,2H) 7.1–7.5(m,5H)

I-117

H-NMR(in $CDCl_3$) δ ppm: 1.30(t,3H,J=7Hz), 1.37(t,3H, J=7Hz); 1.4–1.7 (m,2H), 2.2–2.6(m,2H) 2.8–3.2(m,3H), 3.6–3.9(m,1H) 3.9–4.7(m,4H), 5.2–5.7(m,1H) 6.3–6.7(m, 1H) 7.0–8.2(m,8H)

I-118

H-NMR (in $CDCl_3$) δ ppm: 1.01(t,3H,J=7Hz), 1.27(t,3H, J=7Hz); 1.4–2.1(m,4H), 2.3–2.6(m,2H); 2.8–3.3(m,3H), 3.6–3.3(m,1H); 3.9–4.1(m,1H), 4.18(q,2H,J=7Hz); 4.2–4.5 (m,1H), 5.2–5.6(m,1H); 6.4–6.7(m,1H), 7.0–8.1(m,8H);

I-119

H-NMR (in $CDCl_3$) δ ppm: 1.2–1.5(m,2H), 1.31(t,3H,J= 7Hz); 1.37(d,6H,J=7Hz), 2.3–2.6(m,2H); 3.0–3.4(m,1H), 3.49(Heptaplet,1H,J=6Hz); 3.6–3.8(m,1H), 3.8–4.2(m,1H); 4.20(q,2H,J=7Hz), 4.3–4.5(m,1H); 5.2–5.6(m,1H), 6.4–6.8 (m,1H); 7.0–8.1(m,7H);

I-120

H-NMR (in CDCl3) δ ppm: 0.8–1.8(m,6H), 1.30(t,3H,J= 7Hz); 2.1–2.6(m,3H), 2.9–3.3(m,1H); 3.4–3.7(m,1H), 3.8–4.6(m,2H); 4.20(q,2H,J=7Hz), 5.4–5.8(m,1H); 6.4–6.3 (m,1H), 6.8–8.0(m,8H);

I-121

H-NMR (in $CDCl_3$) δ ppm: 1.29(t,3H,J=7Hz), 1.39(d,6H, J=6Hz); 1.4–1.9(m,2H), 2.3–2.5(m,2H); 2.7–3.2(m,1H),

3.51(Heptaplet,1H,J=6Hz); 3.6–3.8(m,1H), 3.9–4.2(m,1H); 4.19(q,2H,J=7Hz), 4.3–4.6(m,1H); 5.2–5.6(m,1H), 6.4–6.8 (m,1H); 6.9–8.2(m,13H);

I-122

H-MNR (in $CDCl_3$) δ ppm: 1.1–1.8(m,2H), 1.31(t,3H,J=7Hz); 1.41(d,6H,J=6Hz), 2.3–2.5(m,2H); 2.9–3.4(m,1H), 3.50(Heptaplet,1H,J=6Hz); 3.6–3.8(m,1H), 3.9–4.5(m,2H); 4.20(q,2H,J=7Hz), 5.2–5.6(m,1H); 6.4–6.8 (m,1H), 7.1–7.3 (m,5H); 7.72(d,1H,J=6Hz);

I-123

H-NMR (in $CDCl_3$) δ ppm: 0.8–1.5(m,2H), 1.29(t,3H,J=7Hz); 2.2–2.4(m,2H), 2.6–2.9(m,1H); 3.2–3.6(m,1H), 3.7–4.3(m,2H); 4.17(q,2H,J=7Hz), 5.0–5.4(m,1H); 6.1–6.5 (m,1H), 7.0–8.2(m,13H);

I-124

H-NMR (in $CDCl_3$) δ ppm: 0.8–1.8(m,6H), 1.29(t,3H,J=7Hz), 2.2–2.6(m,3H), 2.8–3.2(m,1H), 3.3–3.7(m,1H), 3.9–4.5(m,2H), 4.19(q,2H,J=7Hz), 5.4–5.8(m,1H), 6.5–6.8 (m,1H), 7.1–8.0(m,8H),

I-125

NMR (in $CDCl_3$) δ ppm: 0.94(d,6H,J=6Hz), 1.0–1.7(m, 3H), 1.27(t,3H,J=7Hz), 1.9–2.5(m,3H), 2.90(d,2H,J=7Hz), 3.3–4.4(m,3H), 4.12(q,2H,J=7Hz), 5.0–5.5(m,1H), 6.2–6.7 (m,1H), 6.9–8.0(m,8H),

I-126

H-NMR (in $CDCl_3$) δ ppm: 1.0–1.6(m,3H), 1.21(t,3H,J=7Hz), 1.34(d,6H,J=6Hz), 2.34(s,3H), 2.37(d,2H,J=7Hz), 2.9–3.7(m,2H), 3.8–4.5(m,2H), 4.15(q,2H,J=7Hz), 5.0–5.5 (m,1H), 6.3–6.7(m,1H), 6.9–8.0(m,7H),

I-127

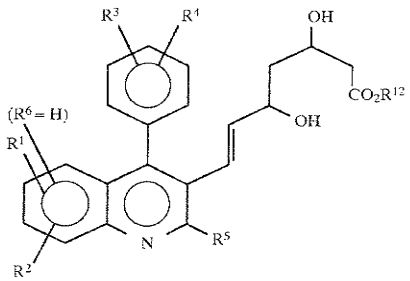
H-NMR (in $CDCl_3$) δ ppm: 0.8–1.9(m,8H), 1.29(t,3H,J=7Hz),

2.1–2.6(m,3H), 2.8–3.2(m,1H), 3.72(s,3H), 4.02(s,3H), 4.19(q,2H,J=7Hz), 4.3–4.6(m,1H), 5.4–5.8(m,1H), 6.4–6.8 (m,1H), 6.56(s,1H), 7.0–7.4(m,5H)

In the same manner as in Exmple 2, compounds I-52 to I-527 were prepared.

TABLE 11

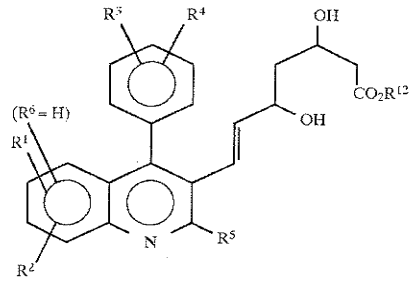
I-5 (R^{12} = Na)



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
I-52	H	H	4-F	H	CH_3	Na	138–142 (decomposed)
I-53	H	H	H	H	CH_3	Na	130–132 (decomposed)
I-54	H	H	H	H	i-Pr	Na	196–197 (decomposed)
I-55	6-Cl	H	H	H	CH_3	Na	211–215 (decomposed)
I-56	6-Cl	H	H	H	i-Pr	Na	195–198 (decomposed)
I-57	H	H	2-F	H	i-Pr	Na	193–201 (decomposed)
I-58	7-Me	H	H	H	i-Pr	Na	170–175 (decomposed)
I-59	H	H	4-Cl	H	i-Pr	Na	193–202 (decomposed)
I-510	H	H	4-OMe	H	i-Pr	Na	178–193 (decomposed)
I-511	H	H	4-Me	H	i-Pr	Na	187–200 (decomposed)
I-512	6-Cl	H	2-Cl	H	i-Pr	Na	203–209 (decomposed)
I-513	H	H	4-CF_3	H	i-Pr	Na	200–212 (decomposed)
I-514	H	H	3-Me	4-F	i-Pr	Na	195–200 (decomposed)
I-515	H	H	3-Me	5-Me	i-Pr	Na	192–197 (decomposed)
I-516	6-OMe	7-OMe	4-F	H	i-Pr	Na	239–245 (decomposed)
I-517	H	H	4-F	H	C_2H_5	Na	230–237 (decomposed)
I-518	H	H	4-F	H	n-Pr	Na	193–200 (decomposed)

TABLE 11-continued

I-5 (R^{12} = Na)



Compound	R^1	R^2	R^3	R^4	R^5	R^{12}	m.p. (°C.)
I-519	6-Cl	H	4-F	H	i-Pr	Na	193–198 (decomposed)
I-520	H	H	4-F	H	c-Pr	Na	197–199 (decomposed)
I-521	H	H	4-OPh	H	i-Pr	Na	180–189 (decomposed)
I-522	6-Cl	8-Cl	4-F	H	i-Pr	Na	183–187 (decomposed)
I-523	6-Cl	H	H	H	Ph	Na	190–196 (decomposed)
I-524	6-Cl	H	H	H	c-Pr	Na	204–210 (decomposed)
I-525	H	H	4-F	H	sec-Bu	Na	—
I-526	6-Me	H	4-F	H	i-Pr	Na	204–208 (decomposed)
I-527	6-OMe	7-OMe	4-F	H	c-Pr	Na	234–238 (decomposed)

I-57

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.2(m,2H), 1.37(d, 6H,J=7Hz); 1.6–2.1(m,2H), 3.48(Heptaplet,1H,J=6Hz); 3.7–4.3(m,4H), 5.3–5.6(m,1H); 6.4–6.7(m,1H), 7.1–8.1(m, 8H);

I-58

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.2(m,2H), 1.31(d, 6H,J=7Hz); 1.7–2.2(m,2H), 2.50(s,3H); 3.3–4.5(m,5H), 5.2–5.6(m,1H); 6.3–6.6(m,1H), 7.1–7.9(m,8H);

I-59

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.48(Heptaplet,1H,J=7Hz); 3.5–4.6(m,4H), 5.2–5.6(m,2H); 6.3–6.6(m,1H), 7.1–8.1(m, 8H);

I-510

H-NMR (in DMSO-d^6) δ ppm: 1.0–1.3(m,2H), 1.32(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.0–3.8(m,4H); 3.86(s,3H), 4.0–4.3(m,1H); 5.3–5.6(m,1H), 6.3–6.6(m,1H); 6.9–8.1(m, 8H);

I-511

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.7–2.1(m,2H), 2.41(s,3H); 3.2–4.3(m,5H), 5.3–5.6(m,1H); 6.3–6.6(m,1H), 7.0–8.3(m,8H);

I-512

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.1–3.8(m,3H); 3.48(Heptaplet, 1H,J=7Hz),3.9–4.2(m,1H); 5.3–5.7(m,1H), 6.3–6.7(m,1H); 7.0–8.1(m,7H);

I-513

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.3(m,2H), 1.34(d,6H, J=7Hz); 1.6–2.2(m,2H), 2.7–3.9(m,3H); 3.49(Heptaplet,1H, J=7Hz), 3.9–4.3(m,1H); 5.2–5.6(m,1H), 6.3–6.7(m,1H); 7.1–8.1(m,8H);

I-514

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2 H), 1.35(d, 6H,J=7Hz); 1.7–2.1(m,2H), 2.30(d,3H,J=2Hz); 3.0–3.8(m, 3H), 3.51(Heptaplet,1H,J=7Hz); 3.9–4.3(m,1H), 5.3–5.6(m, 1H); 6.3–6.6(m,1H), 6.9–8.1(m,7H);

II-515

H-NMR (in DMSO-d^6) δ ppm: 1.0–1.2(m,2H), 1.35(d, 6H,J=7Hz); 1.6–2.2(m,2H), 2.35(s,6H); 3.0–3.8(m,3H), 3.51(Heptaplet,1H,J=7Hz); 4.0–4.3(m,1H), 5.3–5.6(m,1H); 6.3–6.6(m,1H), 6.8–8.0(m,7H);

I-516

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.31(d, 6H,J=7Hz); 1.7–2.0(m,2H), 3.2–3.7(m,4H); 3.62(s,3H), 3.9–4.2(m,1H); 3.94(s,3H), 5.1–5.5(m,1H); 6.2–6.6(m,1H), 7.0–7.5(m,6H);

I-517

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.5(m,2H), 1.34(t,3H, J=7Hz); 1.6–2.2(m,2H), 2.7–3.4(m,4H); 3.6–4.3(m,2H), 5.2–5.7(m,1H); 6.1–6.6(m,1H), 6.9–8.1(m,8H);

I-518

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.3(m,2H), 1.01(t,3H, J=7Hz); 1.6–2.1(m,4H), 2.7–3.8(m,5H); 3.9–4.3(m,1H), 5.2–5.7(m,1H); 6.3–6.6(m,1H), 7.1–8.1(m,8H);

I-519

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.3(m,2H), 1.33(d, 6H,J=7Hz); 1.6–2.2(m,2H), 2.9–3.9(m,3H); 3.49(Heptaplet, 1H,J=7Hz), 4.0–4.3(m,1H); 5.3–5.6(m,1H), 6.3–6.6(m,1H); 7.2–8.1(m,7H);

I-520

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.5(m,6H), 1.7–2.2 (m,2H); 2.3–2.7(m,1H), 3.0–3.9(m,3H); 4.0–4.3(m,1H), 5.5–5.8(m,1H); 6.4–6.7(m,1H), 7.2–8.0(m,8H);

I-521

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.5(m,2H), 1.36(d, 6H,J=7Hz); 1.7–2.3(m,2H), 3.0–3.9(m,3H); 3.50(Heptaplet,

1H,J=6Hz), 4.0–4.3(m,1H); 5.2–5.6(m,1H) 6.4–6.7(m,1H); 7.0–8.1 (m,13H);

I-522

H-NMR (in DMSO-d^6) δ ppm: 0.8–1.3(m,2H), 1.37(d, 6H,J=7Hz); 1.6–2.2(m,2H), 3.1–3.9(m,3H); 3.51(Heptaplet, 1H,J=7Hz),4.0–4.3(m,1H); 5.3–5.7(m,1H), 6.3–6.7(m,1H); 7.1–8.0(m,6H);

I-523

H-NMR (in DMSO-d6) δ ppm: 0.8–1.4(m,2H), 1.6–2.1 (m,2H); 2.9–3.7(m,3H), 3.7–4.1(m,1H); 5.1–5.4(m,1H), 6.1–6.4(m,1H); 7.1–8.2(m,13H);

I-524

H-NMR (in DMSO-d6) δ ppm: 0.8–1.5(m,5H), 1.6–2.2 (m,2H); 2.3–2.7(m,2H), 3.0–3.8(m,3H); 3.9–4.3(m,1H), 5.4–5.8(m,1H); 6.3–6.6(m,1H), 7.0–8.0(m,8H);

I-525

H-NMR (in DMSO-d^6) δ ppm: 0.9–1.6(m,2H) 0.96(d,6H, J=6Hz); 1.7–2.6(m,3H), 2.89(d,2H,J=7Hz); 3.0–3.8(m,3H), 3.9–4.2(m,1H); 5.2–5.6(m,1H), 6.2–6.6(m,1H); 7.1–8.1(m, 8H);

I-526

H-NMR (in DMSO-d^6) δ ppm: 1.30(d,6H,J=7Hz), 1.7–2.0(m,2H), 2.34(s,3H), 2.4–2.6(m,1H), 3.0–3.3(m,2H), 3.3–3.8(m,3H); 3.9–4.2(m,1H), 5.2–5.6(m,1H); 6.3–6.6(m, 1H), 7.0–8.0(m,7H);

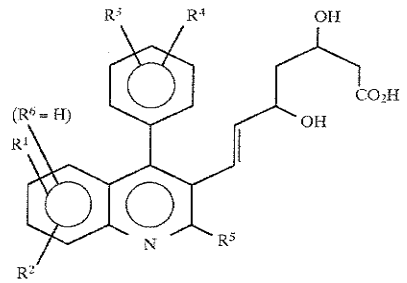
I-527

H-NMR (in DMSO-d^6) δ ppm: 0.7–1.5(m,5H), 1.8–2.2 (m,2H), 2.2–2.6(m,2H), 3.1–3.3(m,2H), 3.59(s,3H), 3.9–4.2 (m,2H), 3.91(s,3H), 5.4–5.7(m,1H), 6.3–6.6(m,1H), 6.52(s, 1H), 7.0–7.4(m,5H);

In the same manner as in Example 3, compounds I-22 to I-26 can be prepared.

TABLE 12

I-2

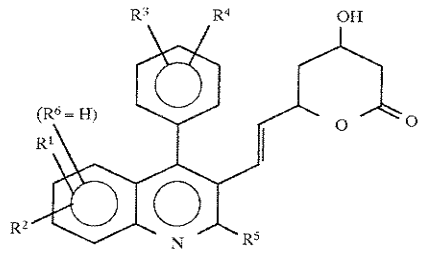


Compound	R^1	R^2	R^3	R^4	R^5
I-22	H	H	4-F	H	CH_3
I-23	H	H	H	H	CH_3
I-24	H	H	H	H	i-Pr
I-25	6-Cl	H	H	H	CH_3
I-26	6-Cl	H	H	H	i-Pr

In the same manner as in Example 4, compounds I-32 to I-36 can be prepared.

TABLE 13

I-3



Compound	R^1	R^2	R^3	R^4	R^5
I-32	H	H	4-F	H	CH_3
I-33	H	H	H	H	CH_3
I-34	H	H	H	H	i-Pr
I-35	6-Cl	H	H	H	CH_3
I-36	6-Cl	H	H	H	i-Pr

FORMULATION EXAMPLE 1

Tablets	
Compound I-51	1.0 g
Lactose	5.0 g
Crystal cellulose powder	8.0 g
Corn starch	3.0 g
Hydroxypropyl cellulose	1.0 g
CMC-Ca	1.5 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were mixed by a usual method and then tabletted to produce 100 tablets each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 2

Capsules	
Compound I-51	1.0 g
Lactose	3.5 g
Crystal cellulose powder	10.0 g
Magnesium stearate	0.5
Total	15.0 g

The above components were mix ed by a usual method and then packed in No. 4 gelatin capsules to obtain 100 capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 3

Soft capsules	
Compound I-51	1.00 g
PEG (polyethylene glycol) 400	3.89 g
Saturated fatty acid triglyceride	15.00 g
Peppermint oil	0.01 g
Polysorbate 80	0.10 g
Total	20.00 g

The above components were mixed and packed in No. 3 soft gelatin capsules by a usual method to obtain 100 soft capsules each containing 10 mg of the active ingredient.

FORMULATION EXAMPLE 4

Ointment	
Compound I-51	1.0 g (10.0 g)
Liquid paraffin	10.0 g (10.0 g)
Cetanol	20.0 g (20.0 g)
White vaseline	68.4 g (59.4 g)
Ethylparaben	0.1 g (0.1 g)
L-menthol	0.5 g (0.5 g)
Total	100.0 g

The above components were mixed by a usual method to obtain a 1% (10%) ointment.

FORMULATION EXAMPLE 5

Suppository	
Compound I-51	1.0 g
Witepsol H15*	46.9 g
Witepsol W35*	52.0 g
Polysorbate 80	0.1 g
Total	100.0 g

*Trademark for triglyceride compound

The above components were melt-mixed by a usual method and poured into suppository containers, followed by cooling for solidification to obtain 100 suppositories of 1 g each containing 10 mg of the active component.

FORMULATION EXAMPLE 6

Injection formulation	
Compound I-51	1 mg
Distilled water for injection formulation	5 ml

The formulation is prepared by dissolving the compound in the distilled water whenever it is required.

FORMULATION EXAMPLE 7

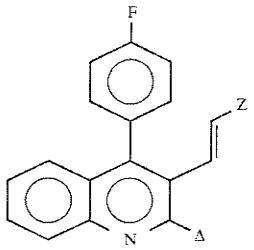
Granules	
Compound I-51	1.0 g
Lactose	6.0 g
Crystal cellulose powder	6.5 g
Corn starch	5.0 g
Hydroxypropyl cellulose	1.0 g
Magnesium stearate	0.5 g
Total	20.0 g

The above components were granulated by a usual method and packaged to obtain 100 packages each containing 200 mg of the granules so that each package contains 10 mg of the active ingredient.

We claim:

1. A compound of the formula,

[A]



Z=—CH(OH)—CH_2—CH(OH)—CH_2—COO.½Ca.

2. A method for reducing hyperlipidemia, hyperlipoproteinemia or atherosclerosis, which comprises administering an effective amount of the compound of formula A as defined in claim 1.

* * * * *

EXHIBIT B

US006465477B1

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

(10) **Patent No.: US 6,465,477 B1**
(45) **Date of Patent: Oct. 15, 2002**

(54) **STABLE PHARMACEUTICAL COMPOSITION**

(75) Inventors: **Toyojiro Muramatsu**, Shizuoka (JP); **Katsumi Mashita**, Fuji (JP); **Yasuo Shinoda**, Shizuoka (JP); **Hironori Sassa**, Numazu (JP); **Hiroyuki Kawashima**, Fuji (JP); **Yoshio Tanizawa**, Okayama (JP); **Hideatsu Takeuchi**, Fuji (JP)

(73) Assignees: **Kowa Company, Ltd.**, Aichi-Ken (JP); **Nissan Chemical Industries, Ltd.**, Tokyo (JP)

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

(21) Appl. No.: **09/436,789**

(22) Filed: **Nov. 8, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/894,279, filed on Aug. 18, 1997, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/435**; A61K 31/44; A61K 31/19

(52) **U.S. Cl.** **514/277**; 514/306; 514/569; 514/970

(58) **Field of Search** 514/256, 277, 514/306, 415, 569, 970

(56) **References Cited**

U.S. PATENT DOCUMENTS

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5,356,896 A * 10/1994 Kabidi et al. 514/256

* cited by examiner

Primary Examiner—Frederick Krass
Assistant Examiner—Donna Jagoe
(74) *Attorney, Agent, or Firm*—Peter F. Corless; Christine C. O'Day; Edwards & Angell, LLP

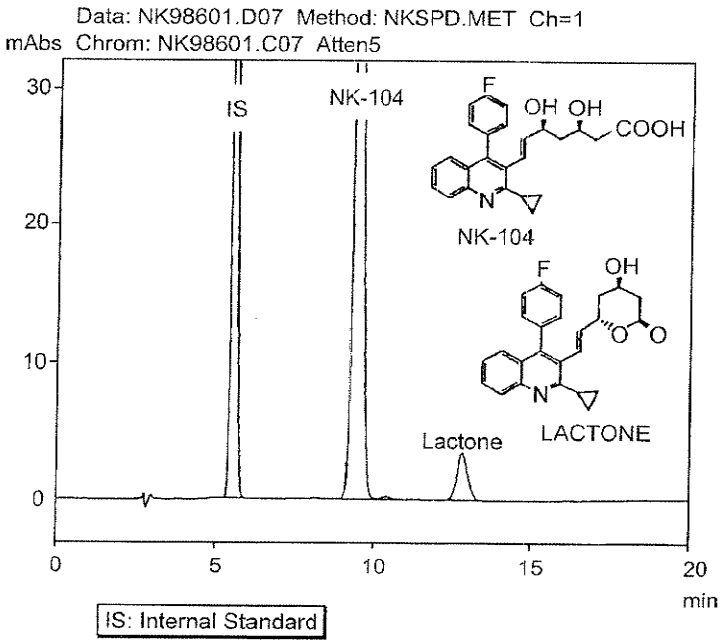
(57) **ABSTRACT**

Disclosed is a pharmaceutical composition comprising (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester, of which the aqueous solution or dispersion has pH of from 6.8 to 8. The composition has good time-dependent stability and has no change in its outward appearance even after having been stored long.

15 Claims, 2 Drawing Sheets

[NK-104]

After 2 days at 40°C(pH3)



[NK-104]

After 2 days at 40°C(pH3)

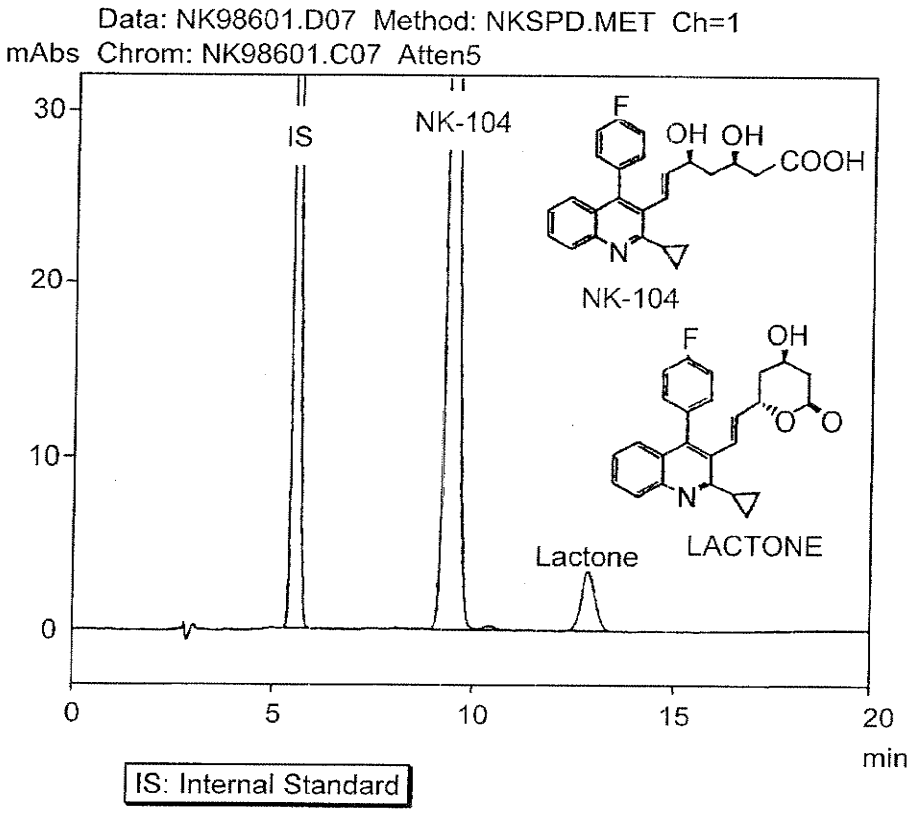


FIG. 1

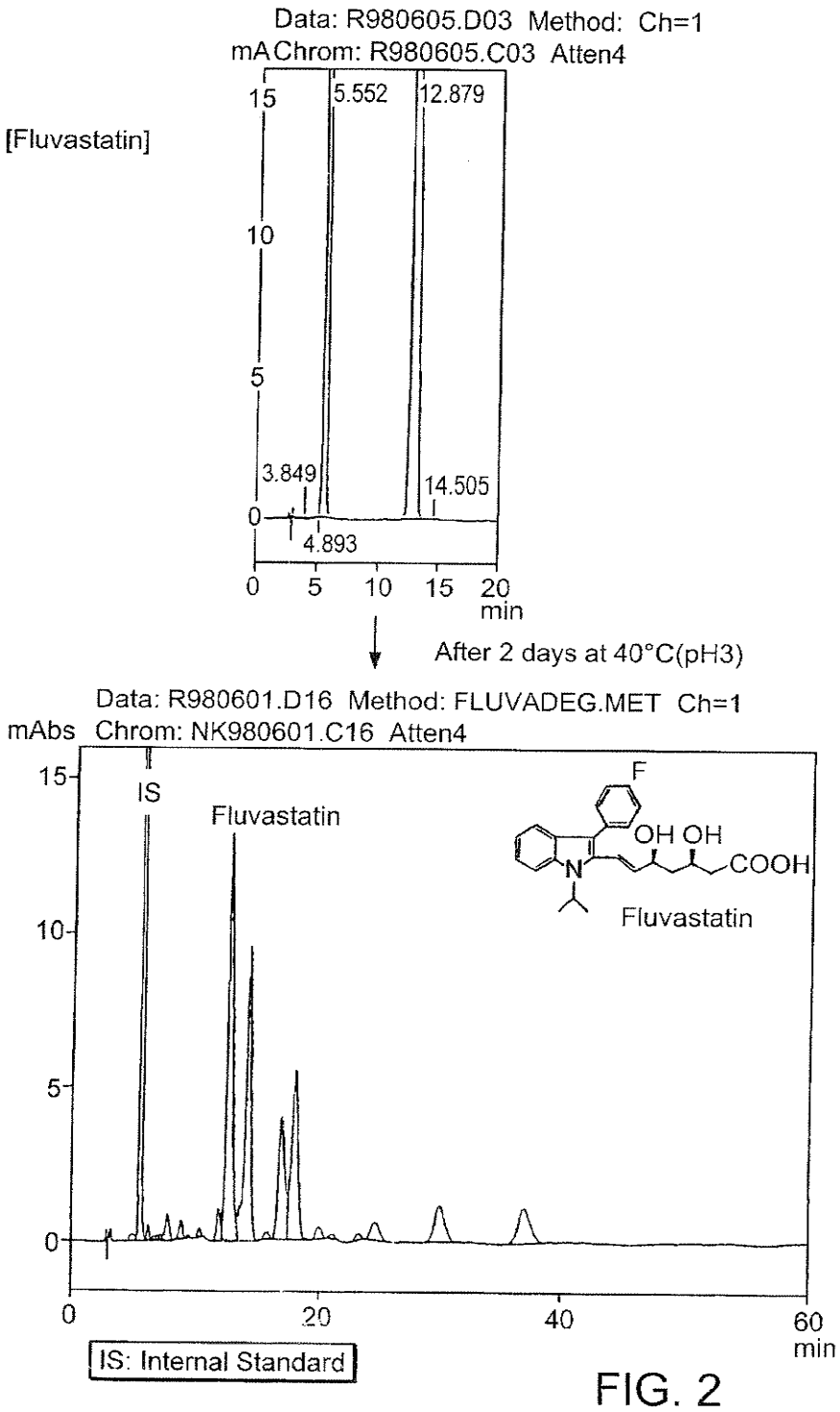

Data: R980605.D03 Method: Ch=1
mA Chrom: R980605.C03 Atten4
[Fluvastatin]
15
10
5
0
5.552
12.879
3.849
14.505
4.893
0 5 10 15 20
min
After 2 days at 40°C(pH3)
Data: R980601.D16 Method: FLUVADEG.MET Ch=1
mAbs Chrom: NK980601.C16 Atten4
15
10
5
0
IS
Fluvastatin
F
OH OH
N
COOH
Fluvastatin
0 20 40 60
min
IS: Internal Standard

FIG. 2

STABLE PHARMACEUTICAL COMPOSITION

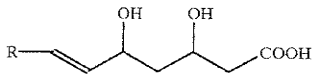
The present application is a continuation-in-part of U.S. application Ser. No. 08/894,279 filed Aug. 18, 1997, now abandoned.

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical composition with high stability and, more precisely, to a pharmaceutical composition comprising an HMG-CoA reductase inhibitor of which the stability varies depending on pH, especially (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester.

BACKGROUND OF THE INVENTION

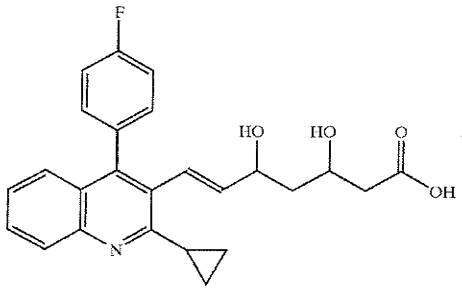
It is known that 7-substituted-3,5-dihydroxy-6-heptenoic acids of a general formula:



wherein R represents an organic group, have HMG-CoA reductase-inhibiting activity, and are useful as medicines for hyperlipemia and also as medicines for atherosclerosis (see U.S. Pat. Nos. 4,739,073, 5,001,255, 4,751,235, 4,804,679, EP-B-304,063).

However, these 7-substituted-3,5-dihydroxy-6-heptenoic acids are unstable at low pH, and require some particular means for formulating them into preparations. A means of formulating them along with an alkaline medium, such as calcium carbonate or sodium carbonate, into preparations with pH of 8 or higher (see U.S. Pat. No. 5,356,896), and a means of formulating them along with a basic agent, such as magnesium oxide or sodium hydroxide, into preparations with pH of 9 or higher (see EP-B-336,298) have been proposed.

(E)-3,5-dihydroxy-7-[4'-4 "-fluorophehyl-2 '-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid (hereinafter this may be referred to as NK-104) to be represented by a structural formula:



or its salt or ester is one of HMG-CoA reductase inhibitors that are represented by the above-mentioned general formula, and is known to be useful as a medicine for hyperlipemia and also as a medicine for atherosclerosis (see EP-B-304,063). NK-104 is also unstable at low pH, and many difficulties have been encountered in formulating it into preparations.

It has been reported that these HMG-CoA reductase inhibitors are formulated into preparations with pH 8 or higher, desirably pH 9 or higher, but unexpectedly, it has been found that NK-104 and its salts and esters are still unstable even within a high pH range.

Therefore, preparations comprising NK-104 or its salt or ester, if formulated in conventional manners, have low time-dependent stability, and are problematic in that their outward appearance changes with the lapse of time. Given the situation, the development of stable preparations comprising it is desired.

SUMMARY OF THE INVENTION

We the present inventors have variously studied in order to obtain stable pharmaceutical compositions comprising NK-104 and, as a result, have found unexpectedly that NK-104 is stable within a relatively low pH range. On the basis of this finding, we have completed the present invention.

Furthermore, we investigated decomposition products of NK-104 and fluvastatin in an aqueous solution of pH3. The decomposition product of NK-104 was found in small quantity and consisted only of the lactonized form of NK-104 (see FIG. **1**). On the other hand, decomposition products of fluvastatin were found in relatively large quantities consisting of more than one type of products which are believed to include an optical isomer and a lactonized form of fluvastatin (see FIG. **2**). These results showed that the decomposition pattern and stability of NK-104 and fluvastatin were different in the same pH.

In addition, we have further found that, if a basic substance is added to a pharmaceutical composition comprising NK-104 in such a manner that the aqueous solution or dispersion of the composition may have pH of from 6.8 to 8, the composition is stable.

An object of the present invention is to provide a pharmaceutical composition comprising NK-104, or its salt or ester, of which the aqueous solution or dispersion has pH of from 6.8 to less than 8, preferably has pH of from 6.8 to 7.8.

The active ingredient of the composition of the present invention is NK-104 to be represented by the above-mentioned structural formula. The configuration in this substance, NK-104 is not specifically defined herein. In addition, NK-104 may be in any form of its salts and esters. The salts include, for example, sodium salt, potassium salt and calcium salt. Preferred is calcium salt of NK-104.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** is a histogram of NK-104 decomposition products analyzed by HPLC.

FIG. **2** shows histograms of fluvastatin decomposition products analyzed by HPLC.

DETAILED DESCRIPTION OF THE INVENTION

The pH as referred to herein indicates the pH value to be determined in such a manner that a unit dose of a solid preparation comprising NK-104 or its salt or ester is sampled and dissolved or dispersed in from 1 to 10 ml of pure water, and the pH of the resulting aqueous solution or dispersion is measured.

A basic substance may be added to the pharmaceutical composition comprising NK-104 to control the pH of the composition, which may be any of antacids and pH regulators including, for example, antacids such as magnesium aluminometasilicate, magnesium aluminosilicate, magnesium aluminum silicate, magnesium aluminate, dry alumi-

num hydroxide, synthetic hydrotalcite, synthetic aluminum silicate, magnesium carbonate, precipitated calcium carbonate, magnesium oxide, aluminum hydroxide, and sodium hydrogencarbonate; and pH regulators such as L-arginine, sodium phosphate, disodium hydrogenphosphate, sodium dihydrogenphosphate, potassium phosphate, dipotassium hydrogenphosphate, potassium dihydrogenphosphate, disodium citrate, sodium succinate, ammonium chloride, and sodium benzoate. Of these, preferred are magnesium aluminometasilicate, magnesium aluminosilicate, and L-arginine.

Even more preferred are basic substances that may be added to the pharmaceutical composition comprising NK-104 to control the pH of the composition and that maintain the outward appearance and stability of said composition. These may be any of alkaline earth metal silicates including aluminum, and organic base compounds. For example, alkaline earth metal means magnesium, calcium, barium, etc. Preferred is magnesium. Particularly preferred alkaline earth metal silicates including aluminum are magnesium aluminometasilicate (NEUSILIN FH2), magnesium aluminosilicate (NEUSILIN A), and magnesium aluminum silicate (VEEGUM F). The preferred organic base is arginine. An even more preferred base is L-arginine.

The pharmaceutical composition of the present invention can be formulated into various forms of preparations, but preferred are peroral solid preparations. For example, the composition may be formulated into tablets, granules, powders, troches, capsules, chewables, film-coated preparations of these, and even sugar-coated preparations thereof.

Where the pharmaceutical composition of the present invention is formulated into such peroral solid preparations, any of vehicles (excipients), binders, disintegrators and lubricants can be added thereto, if desired. The preparations may be formulated from the composition along with any of these, in any ordinary manner.

The vehicles (excipients) include, for example, lactose, corn starch, denatured corn starch, mannitol, sorbitol, wood cellulose, fine crystalline cellulose and calcium carbonate, which can be used either singly or as combined.

The binders include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, and partial saponificates of these, which can be used either singly or as combined. Especially preferred is hydroxypropylmethyl cellulose.

The disintegrators include, for example, low substituted hydroxypropyl cellulose, carmellose, sodium carboxystarch, calcium carmellose, corn starch, partially-alphatized starch, sodium closcarmellose and clospovidone, which can be used either singly or as combined. Especially preferred is low substituted hydroxypropyl cellulose.

The lubricants includes, for example, magnesium stearate, stearic acid, palmitic acid, calcium stearate and talc, which can be used either singly or as combined.

The amounts of the ingredients constituting the composition of the present invention are not specifically defined. For example, the amount of NK-104 or its salt or ester may be from 0.01 to 40% by weight, preferably from 0.05 to 10% by weight, more preferably from 0.5 to 5% by weight; and the basic substance may be added to the composition in such an amount that is necessary for making the aqueous solution or dispersion of the composition have pH of from 6.8 to less than 8. Where the composition is formulated into peroral solid preparations, it is desirable that the vehicle is added thereto in an amount of from 30 to 95% by weight, the binder in an amount of from 1 to 20% by weight, the disintegrator in an amount of from 1 to 30% by weight, and the lubricant in an amount of from 0.5 to 10% by weight.

If further desired, any additional components, such as sweeteners, flavorings and colorants may also be added to the composition of the present invention.

The necessary amount of the basic substance to be added to the composition of the invention in order to make the aqueous solution or dispersion of the composition have pH of from 6.8 to less than 8 may be from about 1 to 6.5% by weight or so, if magnesium aluminometasilicate (NEUSILIN FH2) is used, from about 0.5 to 2% by weight or so, if magnesium aluminosilicate (NEUSILIN A) is used, from about 2 to 8% by weight or so, if magnesium aluminium silicate (VEEGAM F) is used, or from about 0.01 to 0.1% by weight or so, if L-arginine is used singly. As mentioned above, it is preferable that the basic substance is used singly. However, two or more such basic substances can be used in combination.

The composition of the present invention can be coated to give film-coated tablets or sugar-coated tablets. As the coating base, for example, usable are celluloses such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose; and also aminoalkyl methacrylate copolymer E, white sugar, and pullulan. As the plasticizer for the base, for example, usable are macrogol 6000, triethyl citrate, and triacetylpropylene glycol.

The pharmaceutical composition of the present invention can be produced according to any ordinary methods employable in producing peroral solid preparations. If stirring granulation is employed, this may be conducted as follows. First, NK-104, a basic substance, a vehicle, a binder and a disintegrator are mixed. Next, water is added to the resulting mixture, then granulated with stirring, dried and dressed to give dry granules. Further, the granules are mixed with a lubricant, and pelletized with a pelletizer into pellets. Also employable is fluidized bed granulation, which may be conducted as follows. First, NK-104, a basic substance, a vehicle and a disintegrator are mixed. Then, an aqueous solution of a binder is sprayed over the resulting mixture, using a fluidized bed granulator, to prepare granules. These granules are mixed with a lubricant, and then pelletized with a pelletizer into pellets.

Using ordinary coating devices, the pellets as produced according to the above-mentioned methods can be coated with a solution or suspension comprising a coating base and optionally a plasticizer and a colorant to give film-coated tablets or sugar-coated tablets.

BEST MODES OF CARRYING OUT THE INVENTION

Examples of the pharmaceutical composition of the present invention are mentioned below, which, however, are not intended to restrict the scope of the invention.

Example 1

Decomposition Products of NK-104 and Fluvastatine

Decomposition products of NK-104 were analyzed by HPLC after incubation for two days at 40° C. in aqueous solution of pH 3. NK-104 produced a single product, a lactonized form of NK-104 (see FIG. 1). The decomposition products of fluvastatin were also analyzed for comparison. Fluvastatin produced many types of products, which are believed to include an optical isomer of fluvastatin and a lactonized form of fluvastatin (see FIG. 2).

The conditions under which NK-104 and Fluvastatine decomposition products were analyzed are as follows:

HPLC system: Type LC-10 (Shimadz, Japan)

Column: DEVELOSIL ODS-HG-5 (NOMURA CHEM., Japan)

Mobil Phase: MeOH/0.02 mol/L phosphate buffer (pH 3)=7/3

Sample: NK-104 or fluvastatin/pH 3/40° C., 2 days

Detector: SPD-MLOAVP, UV 245 mm

NK-104 and fluvastatin have common α-δ-dihydroxy-ϵ-ene carboxylic acid chemical structure. However, NK-104 and fluvastatin differ in the types and amount of decomposition products. Namely, NK-104 provides a small quantity of one type of decomposition product while fluvastatin provides comparatively large quantities of different types of decomposition products (see FIGS. **1** and **2**). Such differences show that stability of each depends not only on the chemical structure of α-δ-dihydroxy-ϵ-ene carboxylic acid but also on the chemical structures that are unique to each.

In the following examples, the low substituted hydroxypropyl cellulose was commercially available as sold for a medicine additive and contains from 5–16% of —OC_3H_6OH group. Hydroxypropylmethyl cellulose 2910 contains 28–30% —OCH_3 and 7–12% —OC_3H_6—OH. Both low substituted hydroxypropyl cellulose and hydroxypropylmethyl cellulose 2910 as used in the examples are described in The Pharmacopoeia of Japan, 12th edition.

Example 2

Herein produced were tablets each having the composition mentioned below.

Calcium Salt of NK-104	1.0 mg
Lactose	101.4
Low Substituted Hydroxypropyl Cellulose	12.0
Hydroxypropylmethyl Cellulose 2910	2.0
Magnesium Aluminometasilicate	2.4
Magnesium Stearate	1.2
Total (one tablet)	120.0

The components of the above-mentioned composition, except magnesium stearate, were mixed to prepare a homogeneous powdery mixture, to which was added a suitable amount of pure water. The resulting mixture was granulated with stirring, and pelletized to give pellets. Magnesium stearate was added to and mixed with these pellets, which were then tabletted into NK-104-containing tablets.

Example 3

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below.

Calcium Salt of NK-104	1.0 mg
Lactose	102.8
Low Substituted Hydroxypropyl Cellulose	12.0
Hydroxypropylmethyl Cellulose 2910	2.0
Dipotassium Hydrogenphosphate	1.0
Magnesium Stearate	1.2
Total (one tablet)	120.0

Example 4

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below.

Calcium Salt of NK-104	1.0 mg
Lactose	103.7
Low Substituted Hydroxypropyl Cellulose	12.0
Hydroxypropylmethyl Cellulose 2910	2.0
L-arginine	0.1
Magnesium Stearate	1.2
Total (one tablet)	120.0

Example 5

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below.

Calcium Salt of NK-104	1.0 mg
Lactose	103.2
Low Substituted Hydroxypropyl Cellulose	12.0
Hydroxypropylmethyl Cellulose 2910	2.0
Magnesium Aluminometasilicate	0.6
Magnesium Stearate	1.2
Total (one tablet)	120.0

TEST 1

The pH of a 5% suspension of tablets produced in any of Examples 2 to 5 (the suspension was prepared by suspending one tablet in 2.4 ml of pure water) was measured.

After having been stored at 60° C. for 2 weeks, the percentage retention of calcium salt of NK-104 in the tablets was measured according to HPLC. After having been stored at 60° C. for 3 days, the change in the outward appearance of the tablets was observed. The test results are shown in Table 1.

TABLE 1

	Example 2	Example 3	Example 4	Example 5
pH of 5% Suspension	7.8	7.7	7.5	7.1
Percentage Retention of Ca NK-104	97%	97%	93%	92%.
Change in Outward Appearance	No change	No change	No change	No change

Control Examples 1 to 3

In the same manner as in Example 2, herein produced were control tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5% suspension of each tablet, the percentage retention of Ca NK-104, and the change in the outward appearance of the tablets. The test results are shown in Table 2.

TABLE 2

	Control Example 1	Control Example 2	Control Example 3
Ca NK-104	1.0 mg	1.0 mg	1.0 mg
Lactose	103.8	98.8	98.8
Low Substituted Hydroxypropyl Cellulose	12.0	12.0	12.0

TABLE 2-continued

	Control Example 1	Control Example 2	Control Example 3
Hydroxypropyl Cellulose 2910	2.0	2.0	2.0
Sodium Ascorbate		5.0	
Ascorbic Acid			5.0
Magnesium Stearate	1.2		
Total (one tablet)	120.0	120.0	120.0
pH of 5% Suspension	6.6	6.3	3.3
Percentage Retention of Ca NK-104, after stored at 60° C. for 2 weeks	88%	77%	38%
Change in Outward Appearance, after stored at 60° C. for 3 days	No change	No change	No change

As in Tables 1 and 2 showing the test results, it is obvious that the percentage retention of Ca NK-104 in the 5% suspension of the composition having pH of 7 or higher is high, after having been stored at 60° C. for 2 weeks, while the same in the 5% suspension thereof having pH of lower than 6.6 becomes lower with the decrease in the pH value thereof.

Example 6 and Control Example 4

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5% suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 3.

TABLE 3

	Example 6	Control Example 4
Ca NK-104	1.0 mg	1.0 mg
Lactose	101.4	93.9
Low Substituted Hydroxypropyl Cellulose	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0
Magnesium Aluminometasilicate	2.4	9.9
Magnesium Stearate	1.2	1.2
Total (one tablet)	120.0	120.0
pH of 5% Suspension	7.8	8.3
Change in Outward Appearance, after stored at 60° C. for 3 days	No change	Changed to pale yellowish brown

Example 7 and Control Examples 5 and 6

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5% suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 4.

TABLE 4

	Example 7	Control Example 5	Control Example 6
Ca NK-104	1.0 mg	1.0 mg	1.0 mg
Lactose	103.7	95.8	93.9
Low Substituted Hydroxypropyl Cellulose	12.0	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	—	2.0
TC-5R	—	2.0	—
L-arginine	0.1	8.0	9.9
Magnesium Stearate	1.2	1.2	1.2
Total (one tablet)	120.0	120.0	120.0
pH of 5% Suspension	7.5	9.3	9.8
NK-104 remaining (%) after 2 weeks at 60° C.	93.4	66.0	—
Change in Outward Appearance, after 2 weeks at 60° C.	No change	Changed to brown	—
Change in Outward Appearance, after stored at 60° C. for 3 days	—	—	Changed to pale yellowish green

Example 8 and Control Example 7

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5% suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 5.

TABLE 5

	Example 8	Control Example 7
Ca NK-104	1.0 mg	1.0 mg
Lactose	101.8	93.9
Low Substituted Hydroxypropyl Cellulose	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0
Sodium Hydrogencarbonate	2.0	9.9
Magnesium Stearate	1.2	1.2
Total (one tablet)	120.0	120.0
pH of 5% Suspension	7.8.	9.8
Change in Outward Appearance, after stored at 60° C. for 3 days	No change	Changed to dark navy blue

Example 9 and Control Example 8

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below. These tablets were tested in the same manner as in Test 1, to determine the pH of the 5% suspension of each tablet, and the change in the outward appearance of the tablets. The test results are shown in Table 6.

TABLE 6

	Example 9	Control Example 8
Ca NK-104	1.0 mg	1.0 mg
Lactose	102.8	93.9
Low substituted Hydroxypropyl Cellulose	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0
Dipotassium Hydrogenphosphate	1.0	9.9
Magnesium Stearate	1.2	1.2
Total (one tablet)	120.0	120.0
pH of 5% Suspension	7.7	8.4
Change in Outward Appearance, after stored at 60° C. for 3 days	No change	Changed to orange

As is obvious from the test results in Tables 3 to 6, no change in the outward appearance of the tablets was found when the 5% suspensions of the tablets had pH of 8 or lower, even after having been stored at 60° C. for 3 days, but the outward appearance of the tablets changed when the 5% suspensions of the tablets had pH of higher than 8.

Example 10

Magnesium Aluminometasilicate

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below. The tablets were tested in the same manner as in Test 1 to determine the pH of the 5% suspension of each tablet, but the percentage retention of Ca NK-104 and the change in outward appearance of the tablets were observed one month after storing at 60° C. The test results are shown in Table 7.

TABLE 7

	1	2	3	4	5
Ca NK-104	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Lactose	101.4	100.8	91.8	53.8	0
Low substituted Hydroxypropyl Cellulose	12.0	12.0	12.0	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0	2.0	2.0	2.0
Magnesium Aluminometasilicate	2.4	3.0	12.0	50.0	103.8
Magnesium Stearate	1.2	1.2	1.2	1.2	1.2
Total (one tablet)	120.0	120.0	120.0	120.0	120.0
pH of 5% Suspension	7.8	8.1	8.4	9.0	9.3
NK-104 remaining rate (%) after 1 month at 60° C.	97.4	96.5	92.2	84.5	69.1
Change in Outward Appearance, after stored at 60° C. for 1 month	No change	Pale yellow	Pale yellow	Pale yellow	No change

Example 11

Magnesium Aluminosilicate

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below. The tablets were tested in the same manner as in Test 1 to determine the pH of the 5% suspension of each tablet, but the percentage retention of Ca NK-104 was observed at both 2 weeks and one month after storing at 60° C. and the change in outward appearance of the tablets was observed one month after storing at 60° C. The test results are shown in Table 8.

TABLE 8

	1	2	3	4	5
Ca NK-104	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Lactose	103.2	102.6	101.8	98.8	96.8
Low substituted Hydroxypropyl Cellulose	12.0	12.0	12.0	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0	2.0	2.0	2.0
Magnesium Aluminosilicate	0.6	1.2	2.0	5.0	7.0
Magnesium Stearate	1.2	1.2	1.2	1.2	1.2
Total (one tablet)	120.0	120.0	120.0	120.0	120.0
pH of 5% Suspension	6.8	7.8	8.1	8.4	8.7
NK-104 remaining rate (%) after two weeks at 60° C.	97.3	98.5	91.7	87.4	86.8
NK-104 remaining rate (%) after 1 month at 60° C.	97.5	93.5	87.2	80.7	79.1
Change in Outward Appearance, after stored at 60° C. for 1 month	No change	No change	No change	No change	No change

Example 12

Magnesium Aluminum XSilicate

In the same manner as in Example 2, herein produced were tablets each having the composition mentioned below.

The tablets were tested in the same manner as in Test 1 to determine the pH of the 5% suspension of each tablet, but the percentage retention of Ca NK-104 and the change in outward appearance of the tablets were observed one month after storing at 60° C. The test results are shown in Table 9.

TABLE 9

	1	2	3	4	5
Ca NK-104	1.0 mg	1.0 mg	1.0 mg	1.0 mg	1.0 mg
Lactose	100.2	99.4	97.8	91.8	43.8
Low substituted Hydroxypropyl Cellulose	12.0	12.0	12.0	12.0	12.0
Hydroxypropylmethyl Cellulose 2910	2.0	2.0	2.0	2.0	2.0
Magnesium Aluminum Silicate	3.6	4.4	6.0	12.0	60.0
Magnesium Stearate	1.2	1.2	1.2	1.2	1.2
Total (one tablet)	120.0	120.0	120.0	120.0	120.0
pH of 5% Suspension	7.5	8.2	8.7	9.1	9.7
NK-104 remaining rate (%) after 1 month at 60° C.	97.7	98.8	98.2	92.5	84.3
Change in Outward Appearance, after stored at 60° C. for 1 month	No change	No change	Pale yellow	Pale gray	Gray

INDUSTRIAL APPLICABILITY OF THE INVENTION

The pharmaceutical composition of the present invention has good time-dependent stability, with having no change in the outward appearance thereof even after having been stored long. Therefore, the composition is good in medical use, especially in the form of peroral solid preparations.

The pharmaceutical compositions of the present invention that contains NK-104 or salt or ester thereof are especially useful for treating a patient, particularly a human, that is suffering from or susceptible to hyperlipemia or atherosclerosis by administering the pharmaceutical composition to such patient.

Particularly preferred unit dosages have been described in the examples above. It will be appreciated the specifically preferred dosage amounts of a pharmaceutical composition of the invention used in a given therapy will vary according to various known factors such as the particular compositions formulated, the specific compound utilized, the mode of application, the particular site of administration, etc. Optimal administration rates for a given protocol of administration can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the foregoing guidelines.

The invention has been described in detail with reference to preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of this disclosure, may make modifications and improvements within the spirit and scope of the invention as set forth in the following claims.

What is claimed is:

1. A pharmaceutical composition comprising (E)-3,5-dihydroxy-7-[4'-4"-flurophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid, or its salt or ester, and a pharmaceutically acceptable carrier, of which an aqueous solution or dispersion of the pharmaceutical composition has pH of from 6.8 to 7.8.

2. The pharmaceutical composition as claimed in claim **1**, wherein the salt of (E)-3,5-dihydroxy-7-[4'-4"-fluorophenyl-2'-cyclopropyl-quinolin-3'-yl]-6-heptenoic acid is a calcium salt of the acid.

3. The pharmaceutical composition of claim **1** wherein the composition further comprises a basic substance.

4. The pharmaceutical composition of claim **3** wherein the basic substance is an organic base compound.

5. The pharmaceutical composition of claim **3** wherein the basic substance is an alkaline earth metal silicate.

6. The pharmaceutical composition of claim **5** wherein the basic substance is an aluminum compound.

7. The pharmaceutical composition of claim **5** wherein the alkaline earth metal silicate is a magnesium salt.

8. The pharmaceutical composition of claim **3** wherein the basic substance is one or more selected from magnesium aluminometasilicate, magnesium aluminosilicate and magnesium aluminum silicate.

9. The pharmaceutical composition of claim **3** wherein the basic substance is L-arginie.

10. The pharmaceutical composition of claim **3** wherein the composition further comprises at least one material selected from the group consisting of vehicles, disintegrators, binders and lubricants.

11. The pharmaceutical composition of claim **3** wherein the composition further comprises a peroral solid preparation.

12. The pharmaceutical composition of claim **3** wherein the composition further comprises a lactose vehicle.

13. The pharmaceutical composition of claim **3** wherein the composition further comprises hydroxypropyl cellulose with a low degree of substitution.

14. The pharmaceutical composition of claim **3** wherein the composition further comprises a binder of hydroxy propylmethyl cellulose.

15. The pharmaceutical composition of claim **1** wherein the composition further comprises at least one material selected from the group consisting of vehicles, disintegrators, binders and lubricants.

* * * * *

EXHIBIT C

US008557993B2

(12) **United States Patent**
Van der Schaaf et al.

(10) **Patent No.: US 8,557,993 B2**
(45) **Date of Patent: Oct. 15, 2013**

(54) **CRYSTALLINE FORMS OF PITAVASTATIN CALCIUM**

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

(21) Appl. No.: **13/664,498**

(22) Filed: **Oct. 31, 2012**

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Related U.S. Application Data

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(30) **Foreign Application Priority Data**

Feb. 12, 2003 (EP) 03405080

(51) **Int. Cl.**
C07D 215/38 (2006.01)

(52) **U.S. Cl.**
USPC **546/101**

(58) **Field of Classification Search**
USPC 546/101
See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to new crystalline forms of Pitavastatin hemicalcium salt, referred to hereinafter as polymorphic Forms A, B, C, D, E and F, as well as the amorphous form. Furthermore, the present invention is directed to processes for the preparation of these crystalline forms and the amorphous form and pharmaceutical compositions comprising these crystalline forms or the amorphous forms.

39 Claims, 9 Drawing Sheets

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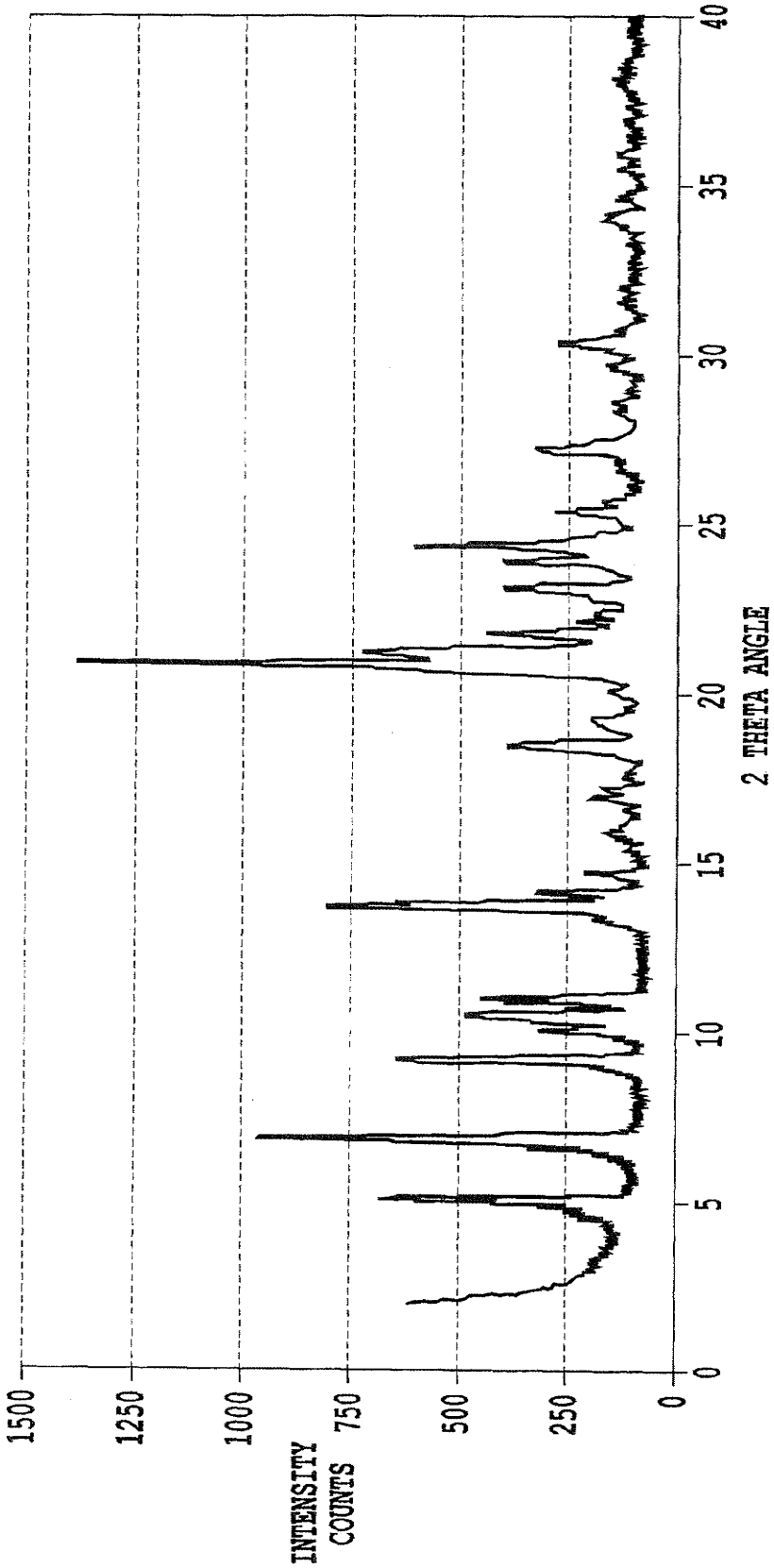
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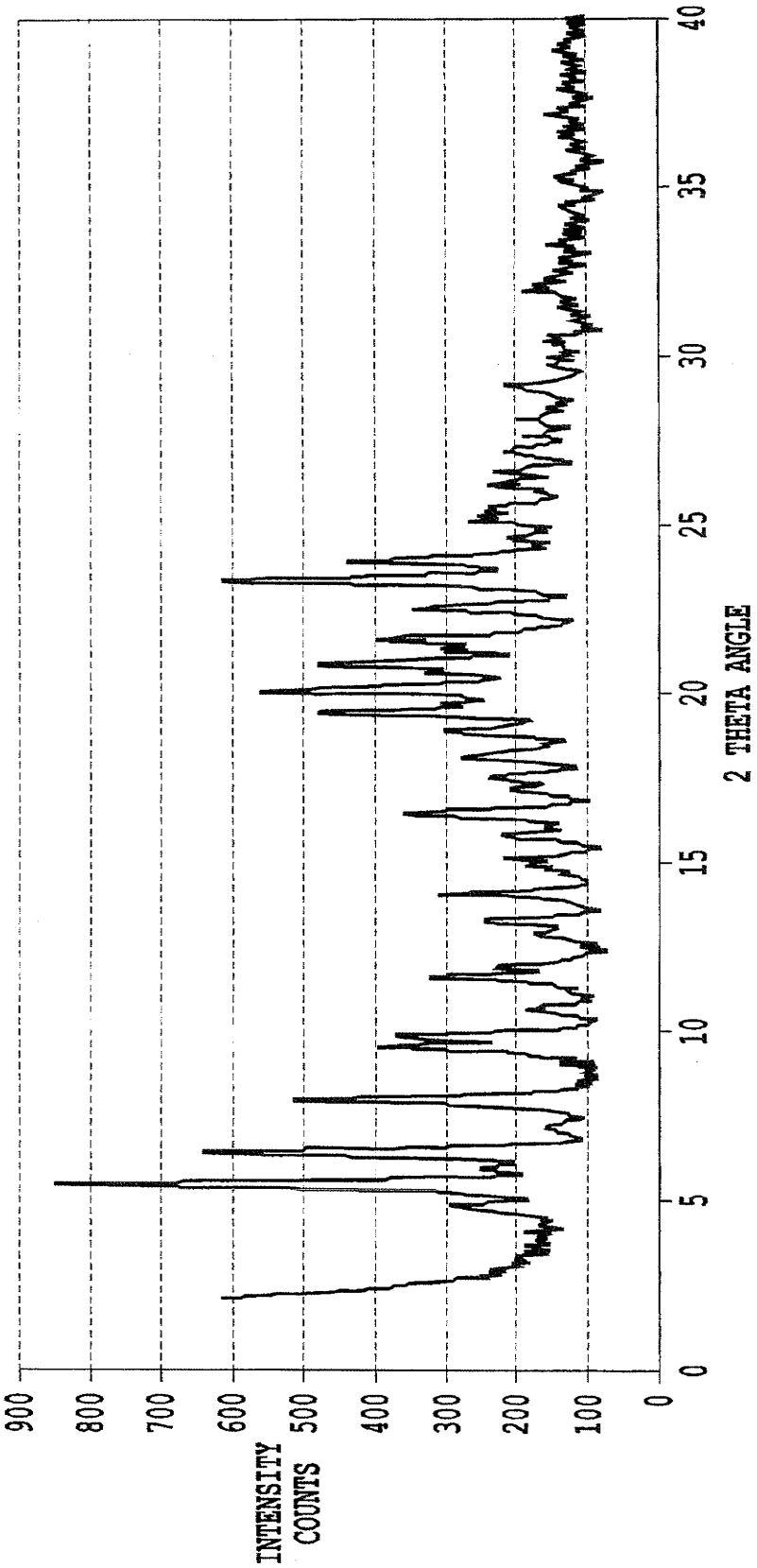
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Fig. 2

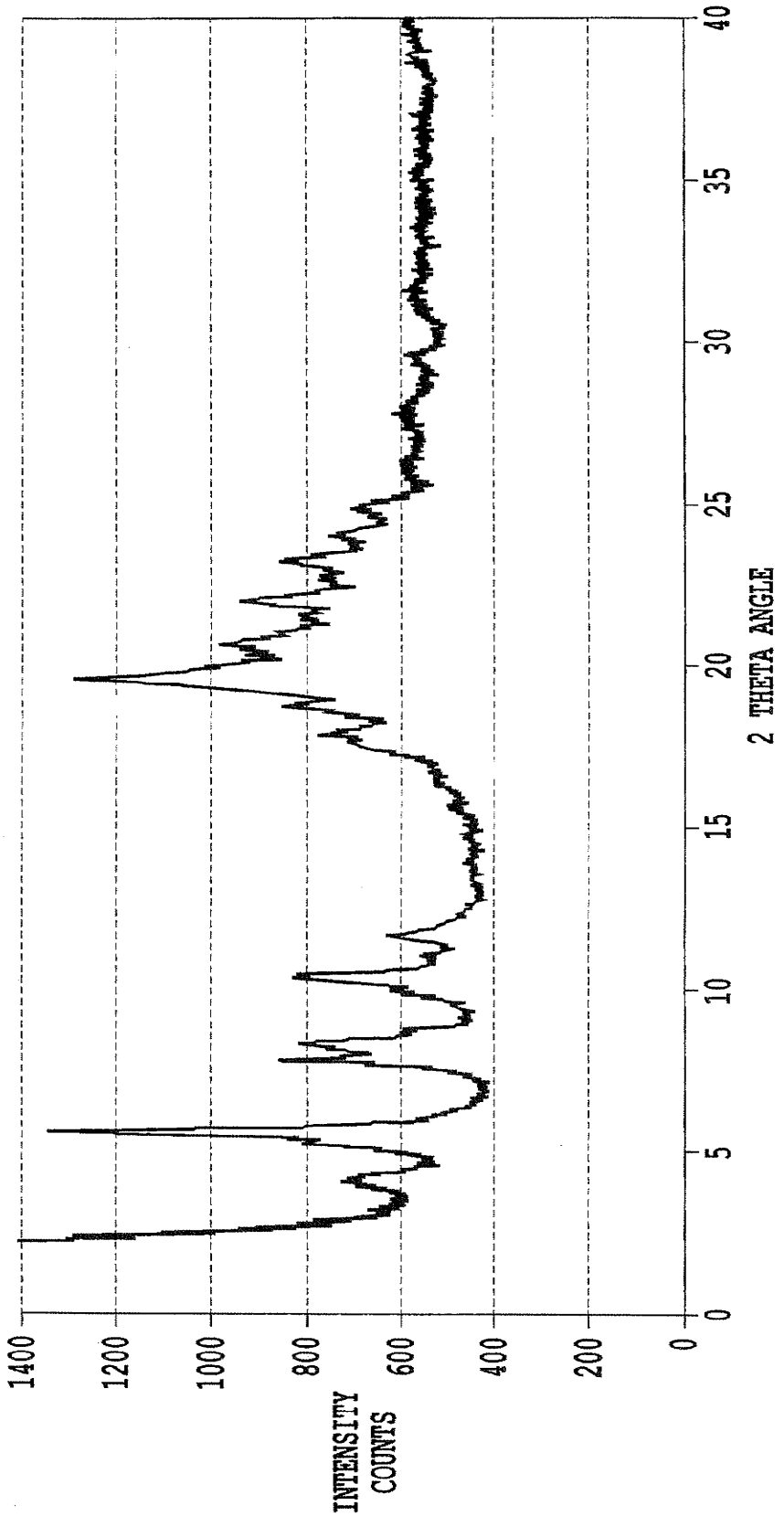
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Fig. 3A

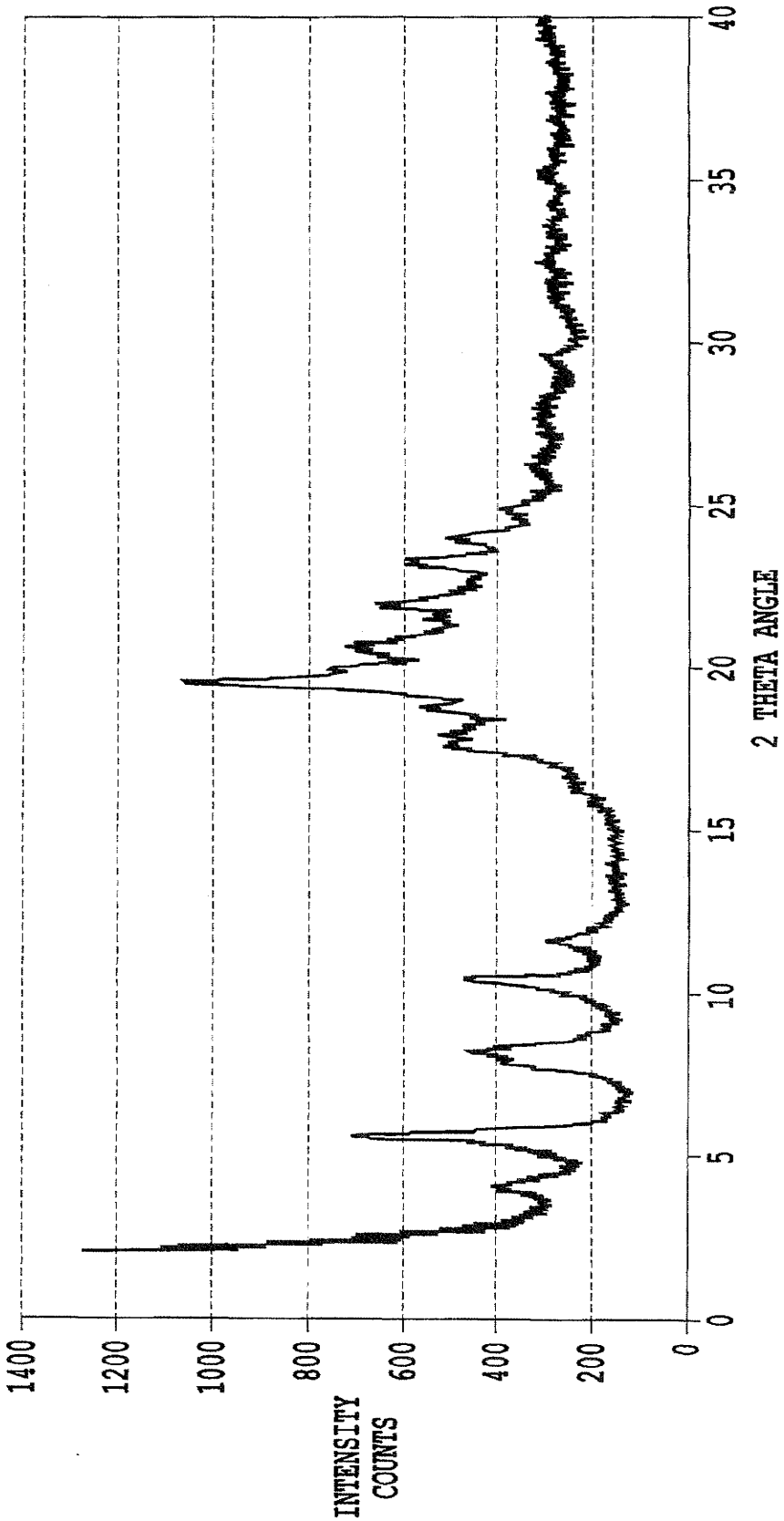
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Fig. 3B

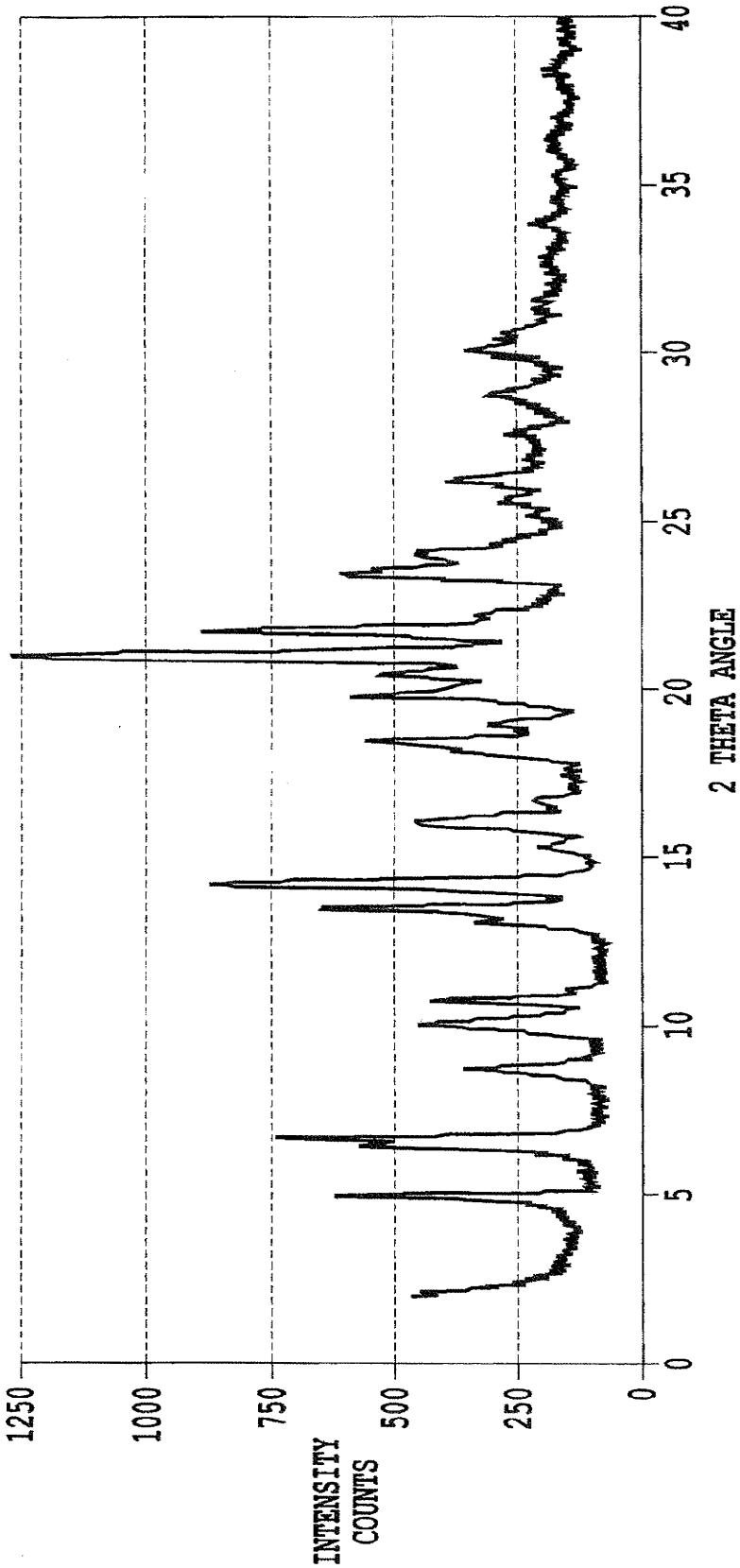
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Fig. 4

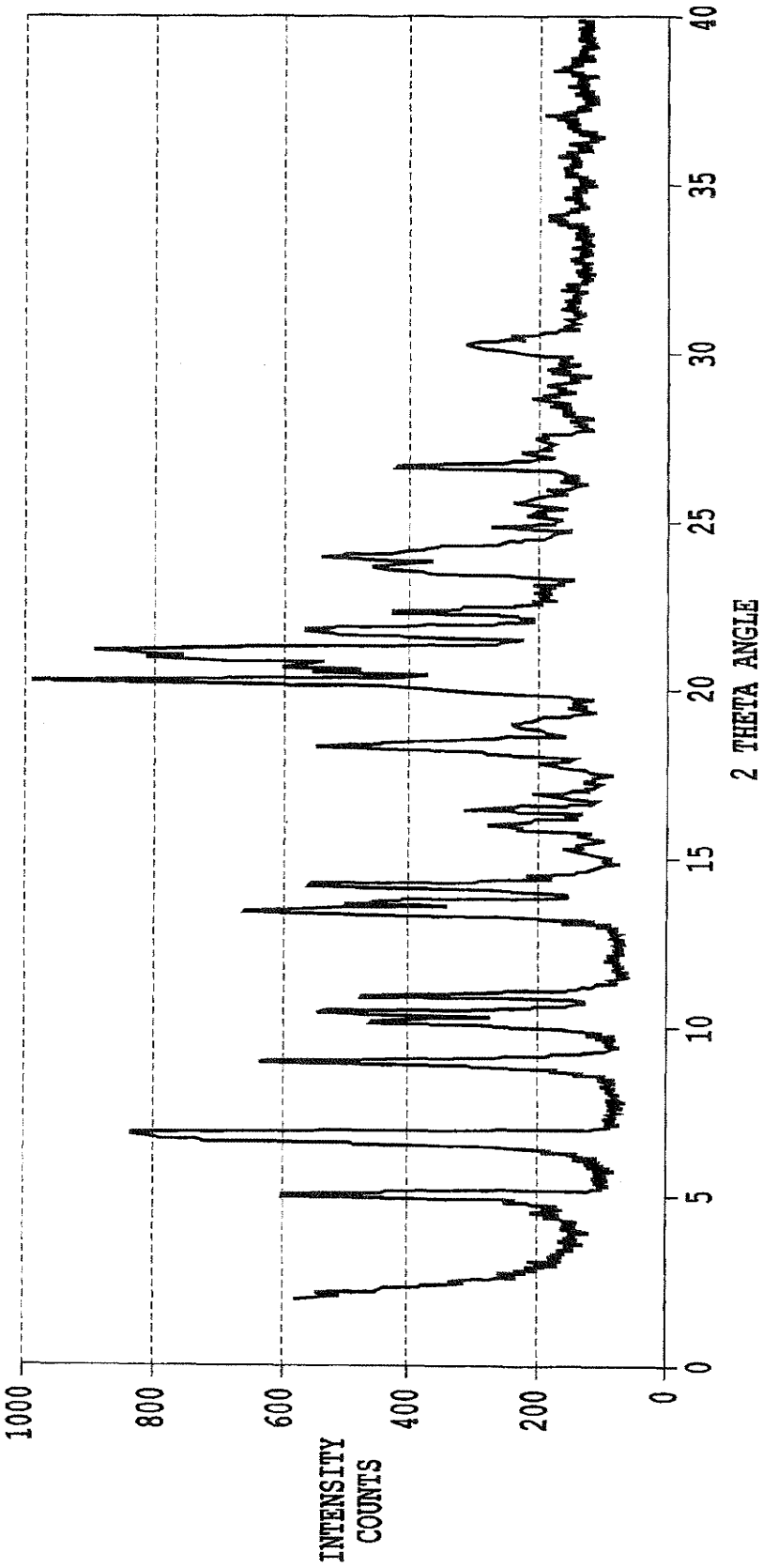
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Fig. 5

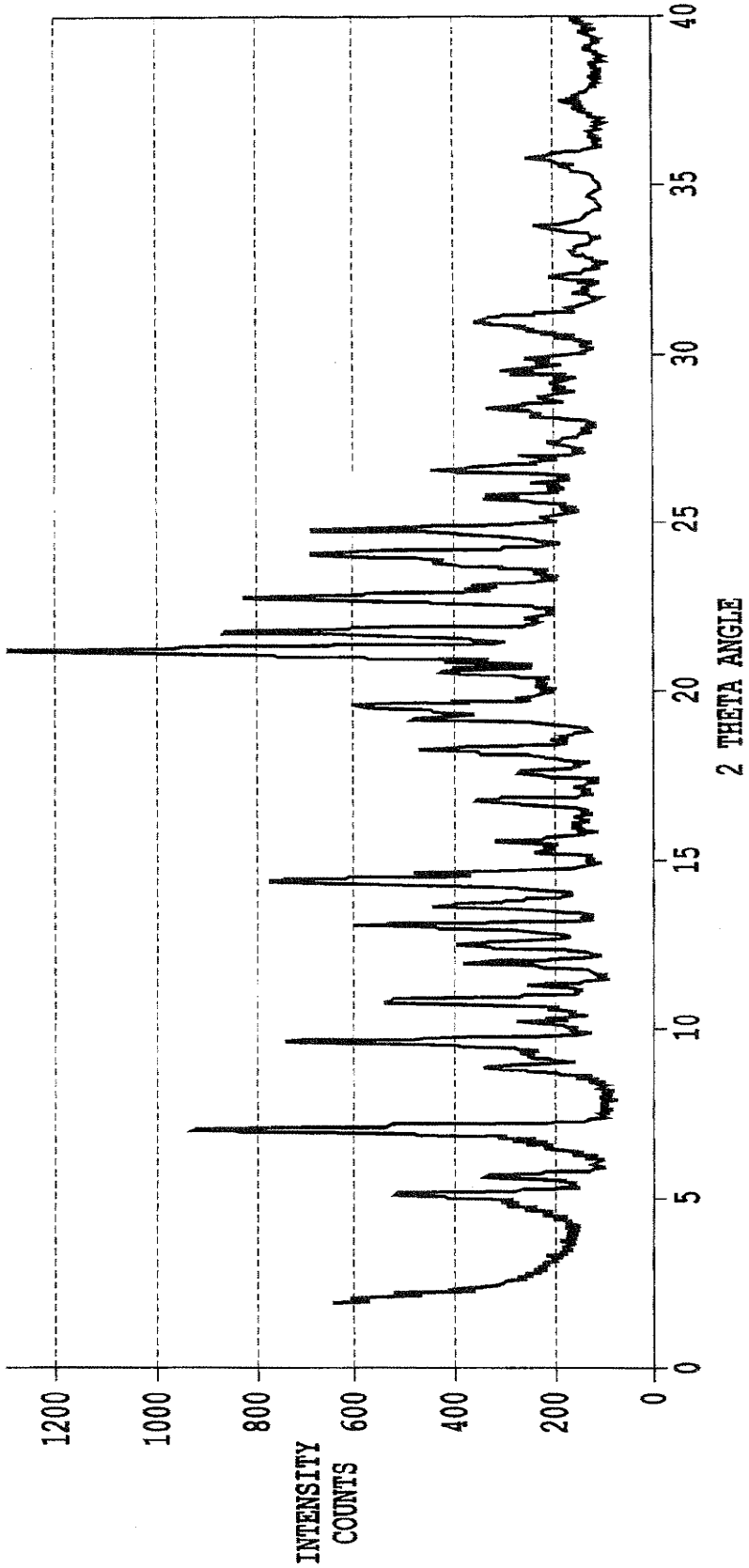
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Fig. 6

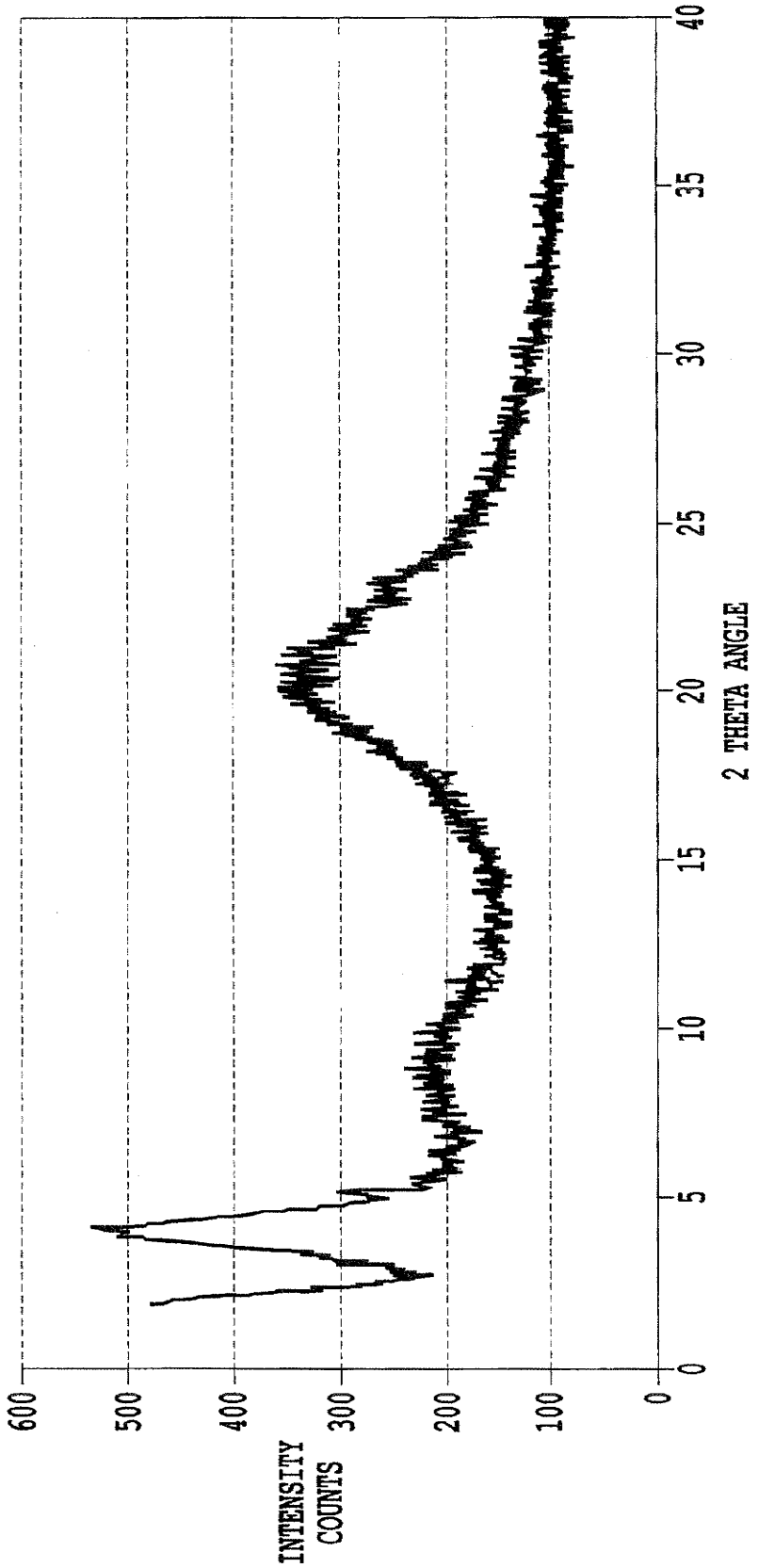
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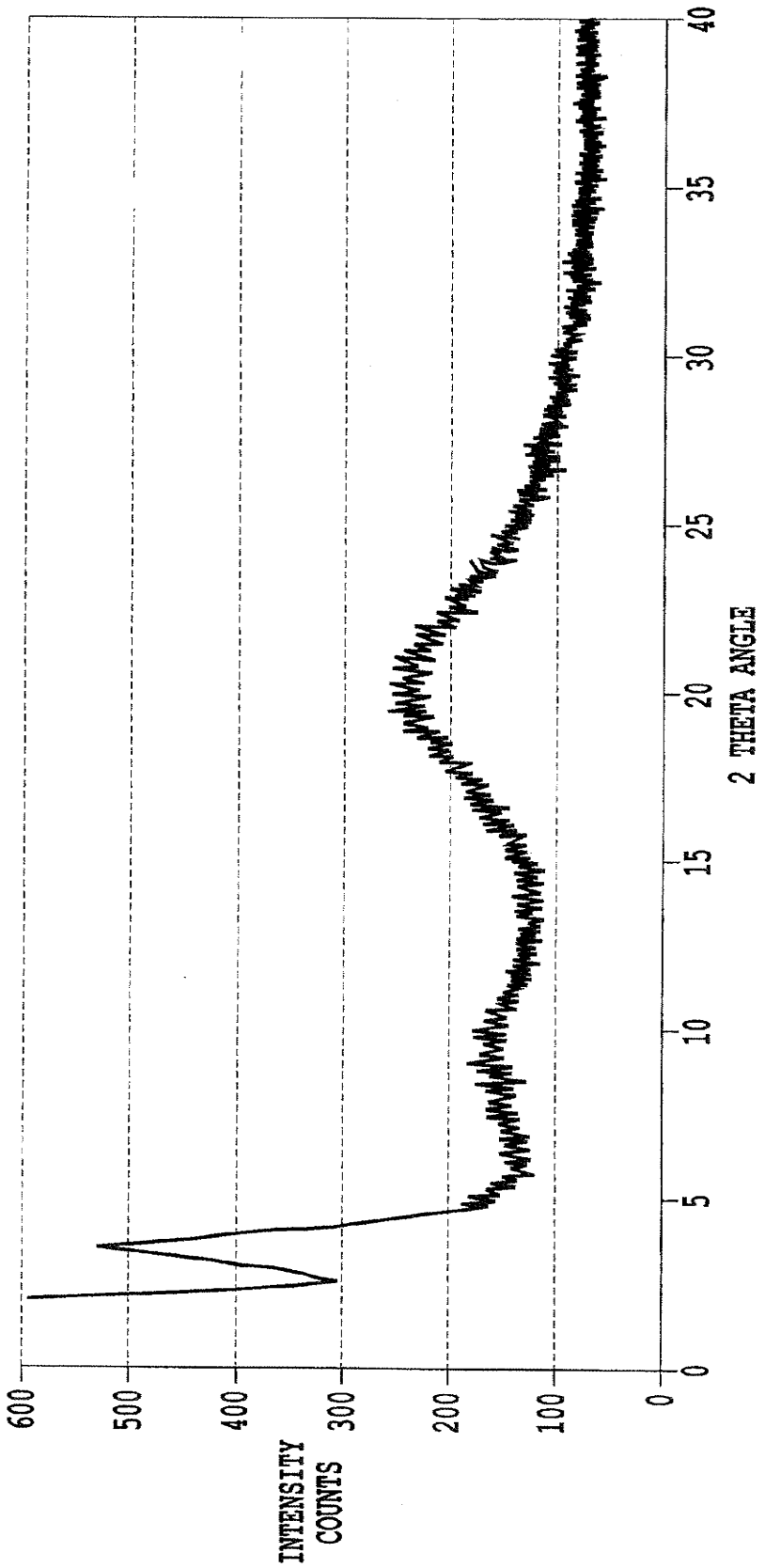
Fig. 7A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2 THETA ANGLE

Fig. 7B

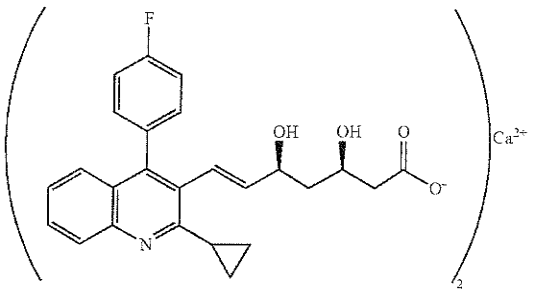
CRYSTALLINE FORMS OF PITAVASTATIN CALCIUM

CROSS REFERENCES TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/280,431, filed Oct. 25, 2011, which is a continuation of U.S. patent application Ser. No. 12/331,086, filed on Dec. 9, 2008, now abandoned; which is a continuation of U.S. patent application Ser. No. 10/544,752, filed on Aug. 8, 2005, now abandoned; which was a 371 of International Patent Application No. PCT/EP2004/050066, filed on Feb. 2, 2004, and claims priority to European Patent Application No. 03405080.7, filed on Feb. 12, 2003, all of which are incorporated herein by reference in their entireties.

The present invention is directed to new crystalline forms and the amorphous form of Pitavastatin calcium, processes for the preparation thereof and pharmaceutical compositions comprising these forms.

The present invention relates to new crystalline forms and the amorphous form of Pitavastatin calcium. Pitavastatin is also known by the names NK-104, Itavastatin and Nisvastatin. Pitavastatin calcium is known by the chemical name: (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt. Pitavastatin calcium has the following formula:



Pitavastatin calcium has recently been developed as a new chemically synthesized and powerful statin by Kowa Company Ltd, Japan. On the basis of reported data, the potency of Pitavastatin is dose-dependent and appears to be equivalent to that of Atorvastatin. This new statin is safe and well tolerated in the treatment of patients with hypercholesterolaemia. Significant interactions with a number of other commonly used drugs can be considered to be extremely low.

Processes for the preparation of Pitavastatin are described in EP-A-0304063 and EP-A-1099694 and in the publications by N. Miyachi et al. in Tetrahedron Letters (1993) vol. 34, pages 8267-8270 and by K. Takahashi et al. in Bull. Chem. Soc. Jpn. (1995) vol. 68.2649-2656. These publications describe the synthesis of Pitavastatin in great detail but do not describe the hemicalcium salt of Pitavastatin. The publications by L. A. Sorbera et al. in Drugs of the Future (1998) vol. 23, pages 847-859 and by M. Suzuki et al. in Bioorganic & Medicinal Chemistry Letters (1999) vol. 9, pages 2977-2982 describe Pitavastatin calcium, however, a precise procedure for its preparation is not given. A full synthetic procedure for the preparation of Pitavastatin calcium is described in EP-A-0520406. In the process described in this patent Pitavastatin calcium is obtained by precipitation from an aqueous solution as a white crystalline material with a melting point of 190-192 C. It is known that pharmaceutical substances can exhibit

polymorphism. Polymorphism is commonly defined as the ability of any substance to have two or more different crystal structures. Drug substances may also encapsulate solvent molecules when crystallized. These solvates or hydrates are referred to as pseudopolymorphs. It is also possible that the amorphous form is encountered. Different polymorphs, pseudopolymorphs or the amorphous form differ in their physical properties such as melting point, solubility etc. These can appreciably influence pharmaceutical properties such as dissolution rate and bioavailability. It is also economically desirable that the product is stable for extended periods of time without the need for specialized storage conditions. It is therefore important to evaluate polymorphism of drug substances. Furthermore, the discovery of new crystalline polymorphic forms of a drug enlarge the repertoire of materials that a formulation scientist has with which to design a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics. We now have surprisingly found novel crystalline forms of Pitavastatin calcium, herein designated as form A, B, C, D, E and F, and the amorphous form of Pitavastatin calcium.

Accordingly, the present invention is directed to the polymorphic Forms A, B, C, D, E and F, and the amorphous form of Pitavastatin calcium salt (2:1).

One object of the invention is a crystalline polymorph of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, herein designated as Form A, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 1 (vs=very strong intensity, s=strong intensity, m=medium intensity, w=weak intensity, vw=very weak intensity).

TABLE 1

d-spacings and 2θ angles for Form A.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
17.6	5.0	s
13.0	6.8	s
9.7	9.1	s
8.8	10.0	w
8.4	10.5	m
8.1	11.0	m
6.7	13.3	vw
6.5	13.7	s
6.3	14.0	w
6.0	14.7	w
5.57	15.9	vw
5.25	16.9	w
5.17	17.1	vw
4.82	18.4	m
4.64	19.1	w
4.27	20.8	vs
4.20	21.1	m
4.10	21.6	m
3.87	22.9	m
3.74	23.7	m
3.67	24.2	s
3.53	25.2	w
3.29	27.1	m
3.02	29.6	vw
2.95	30.2	w
2.63	34.0	w

Another object of the invention is a crystalline polymorph of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, herein designated as Form B, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 2.

TABLE 2

d-spacings and 2θ angles for Form B.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
19.0	4.6	w
16.6	5.3	vs
14.2	6.2	s
11.5	7.7	s
9.6	9.2	m
9.2	9.6	m
8.5	10.3	w
7.8	11.3	m
7.6	11.7	w
7.0	12.6	vw
6.8	13.0	w
6.4	13.9	m
6.0	14.7	vw
5.94	14.9	w
5.66	15.6	w
5.43	16.3	m
5.22	17.0	vw
5.10	17.4	vw
4.92	18.0	w
4.74	18.7	m
4.59	19.3	m
4.43	20.0	s
4.33	20.5	w
4.26	20.8	m
4.19	21.2	w, shoulder
4.13	21.5	m
3.97	22.4	m
3.83	23.2	s
3.73	23.6	m
3.64	24.4	vw
3.53	25.2	w, broad
3.42	26.0	w
3.37	26.4	vw
3.30	27.0	w
3.19	27.9	vw
3.09	28.9	w

Another object of the invention is a crystalline polymorph of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, herein designated as Form C, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 3.

TABLE 3

d-spacings and 2θ angles for Form C.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
21.6	4.1	m
15.9	5.6	s
11.4	7.8	m
10.6	8.3	m
8.6	10.3	m
7.7	11.6	w
5.06	17.5	w
4.95	17.9	w
4.74	18.7	m
4.55	19.5	s
4.31	20.6	m
4.13	21.5	vw
4.06	21.9	m
3.84	23.1	m
3.71	24.0	w
3.58	24.8	w

Another object of the invention is a crystalline polymorph of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, herein designated as Form D, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 4.

TABLE 4

d-spacings and 2θ angles for Form D.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
17.5	5.0	m
13.5	6.5	m
13.0	6.8	s
10.1	8.7	m
8.8	10.0	m
8.6	10.2	m
8.2	10.8	m
6.8	13.1	w
6.55	13.5	m
6.20	14.3	s
5.78	15.3	vw
5.52	16.1	m
5.28	16.8	w
4.87	18.2	w
4.80	18.5	m
4.66	19.0	w
4.46	19.9	m
4.34	20.5	m
4.23	21.0	vs
4.09	21.7	s
3.99	22.3	w
3.80	23.4	m
3.70	24.0	m
3.47	25.6	w
3.40	26.2	m

Another object of the invention is a crystalline polymorph of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, herein designated as Form E, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 5.

TABLE 5

d-spacings and 2θ angles for Form E.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
20.0	4.4	vw
17.7	5.0	s
13.4	6.6	s
13.1	6.8	s
10.0	8.9	s
8.8	10.0	m
8.6	10.3	s
8.2	10.8	m
6.6	13.3	s
6.5	13.6	m
6.3	14.0	s
5.84	15.2	vw
5.56	15.9	w
5.39	16.4	w
5.24	16.9	vw
4.99	17.8	vw
4.84	18.3	m
4.69	18.9	w
4.39	20.2	vs
4.34	20.4	m
4.30	20.7	m
4.24	20.9	m
4.21	21.1	vs
4.12	21.6	m
4.08	21.7	m
3.99	22.3	m
3.77	23.5	m
3.73	23.8	m
3.69	24.1	w
3.60	24.7	vw
3.50	25.4	vw
3.35	26.6	m

TABLE 5-continued

d-spacings and 2θ angles for Form E.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
2.96	30.2	w
2.64	34.0	vw

Another object of the invention is a crystalline polymorph of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, herein designated as Form F, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 6.

TABLE 6

d-spacing and 2θ angles for Form F.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
17.2	5.1	m
15.8	5.6	w
12.6	7.0	s
10.0	8.8	m
9.2	9.6	s
8.7	10.2	w
8.1	10.9	m
7.8	11.3	w
7.4	11.9	m
7.1	12.5	m
6.8	13.0	s
6.5	13.7	m
6.2	14.4	s
8.04	14.7	m
5.79	15.3	vw
5.70	15.5	w
5.28	16.8	m
5.03	17.6	w
4.85	18.3	m
4.61	19.3	m
4.51	19.7	m
4.30	20.6	m
4.18	21.2	vs
4.08	21.8	s
3.90	22.8	s
3.84	23.1	w
3.74	23.8	w, shoulder
3.69	24.1	s
3.59	24.8	s
3.46	25.7	m
3.40	26.2	vw
3.35	26.6	m
3.31	26.9	w
3.14	28.4	w
3.02	29.5	w
3.00	29.8	vw
2.89	30.9	m

Small changes in the experimental details can cause small deviation in the d-values and 2θ of characteristic peaks in the X-ray powder diffraction patterns.

Another object of the invention is the amorphous form of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt which exhibits characteristic X-ray powder diffraction patterns as depicted in FIG. 7.

Powder X-ray diffraction is performed on a Philips 1710 powder X-ray diffractometer using Cu k (α1) radiation (1.54060 Å); 2θ angles are recorded with an experimental error of ±0.1-0.2°. A discussion of the theory of X-ray powder diffraction patterns can be found in "X-ray diffraction procedures" by H. P. Klug and L. E. Alexander, J. Wiley, New York (1974).

Furthermore, the present invention is directed to processes for the preparation of Form A, B, C, D, E and F, and the amorphous form of Pitavastatin calcium.

Form A can be generally prepared from Pitavastatin sodium upon reaction with $CaCl_2$ in an aqueous reaction medium. Alternatively, Form A of the invention may also be obtained in situ from the free acid ((3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid) or the corresponding lactone with $Ca(OH)_2$, advantageously also in an aqueous reaction medium. The aqueous reaction medium usually contains at least 80% b.w. of water; preferably it is water or water containing minor amounts of solvents and/or reactants from previous steps. Form A may contain up to 15% water, preferably about 3 to 12%. more preferably 9 to 11% of water.

Form B can be generally prepared by suspending form A in ethanol containing water as a co solvent. The amount of water is preferably about 1 to 50%.

Form C can be generally prepared by suspending form A in isopropanol containing water as a co solvent. The amount of water is preferably about 1 to 50%. especially 1 to 20% and more preferably about 5%. Form C can also be prepared from a mixture of isopropanol and a ketone solvent, containing water as a co solvent. Preferably, the ketone solvent is acetone, and the amount of ketone solvent are about 1 to 30%, more preferably about 10%. The amount of water is preferably about 1 to 20%, more preferably about 5%.

Form D can be generally prepared by suspending form A in absolute ethanol.

Form E can be generally prepared by suspending form A in 1,4-dioxane containing water as a co solvent. The amount of water is preferably about 1 to 50%.

Form F can be generally prepared by suspending form A in methanol containing water as a co solvent. The amount of water is preferably about 1 to 50%.

In the above mentioned processes small amounts of seeding crystals of the desired crystalline form may be added to the reaction mixture. Preferably small amounts are about 1 to 20 weight %, more preferably about 5 weight %. Seeding crystals may be added before or, where appropriate, after the step initiating the crystallization (e. g. cooling, addition of non-solvent etc. as described above). Addition before initiating the crystallization is of specific technical interest.

The amorphous form can be generally prepared by addition of a non-solvent to a concentrated solution of Pitavastatin calcium in an organic solvent. As non-solvent may be taken for example heptane or methyl tert-butyl ether, whereas examples for the organic solvent are 1,4-dioxane, tetrahydrofuran and ethyl methyl ketone. It is preferable that the non-solvent and solvent are miscible. The amorphous form can also be prepared by lyophilization of an aqueous solution of Pitavastatin calcium.

Preparations of polymorphic forms A, B, C, D, E, F as well as the amorphous form are usually done in substantially pure reaction systems, essentially consisting of the educt specified, preferably in substantially crystalline form, and solvents and/or non-solvents as given above.

Another object of the present invention are processes for the preparation of crystalline forms of Pitavastatin calcium essentially free of residual organic solvent.

Particularly, the present invention is related to processes for the preparation of crystalline forms of Pitavastatin calcium essentially free of residual organic solvent by exposing the crystalline form of Pitavastatin calcium to an atmosphere with a defined relative air humidity. More particularly, the present invention is directed to a process for the preparation of any crystalline form or amorphous form of Pitavastatin calcium which is essentially free of residual organic solvent.

These can, for example, be prepared by exposing the crystalline form or amorphous form to an atmosphere with a relative air humidity of 5 to 100%. Preferably, these are prepared by exposure to an inert gas stream with a defined relative air humidity to exchange residual organic solvent with water. In general, a relative air humidity of 5 to 100%, especially 40 to 80%, is used.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic Form A, B, C, D, E or F or the amorphous form of Pitavastatin calcium, and a pharmaceutical acceptable carrier.

These polymorphic forms may be used as single component or as mixtures with other crystalline forms or the amorphous form.

As to the novel polymorphic forms and amorphous form of Pitavastatin calcium it is preferred that these contain 25-100% by weight, especially 50-100% by weight, of at least one of the novel forms, based on the total amount of Pitavastatin calcium. Preferably, such an amount of the novel polymorphic forms or amorphous form of Pitavastatin calcium is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising at least one of the novel forms. In addition, the compositions that are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl, cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolat, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and losenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Pitavastatin calcium whereupon the properties that distinguish the solid forms of Pitavastatin calcium are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 0.5 to 100 mg of the novel Pitavastatin calcium forms or mixtures thereof with each other or other forms of Pitavastatin calcium. More usually, the combined weight of the

Pitavastatin calcium forms of a unit dosage are from 2.5 mg to 80 mg, for example 5, 10, 20 or 40 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius.

EXAMPLE 1

Preparation of Form A

4.15 gr of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid tert-butyl ester (Pitavastatin tert-butyl ester) was suspended in 52 ml of a mixture of methyl tert-butyl ether and methanol (10:3). To this mixture were added 2.17 ml of a 4M aqueous solution of NaOH, and the resulting yellowish solution was stirred for 2.5 hours at 50° C. The reaction mixture was cooled to room temperature followed by the addition of 50 ml water and stirring for an additional hour. The aqueous phase was separated and once extracted with 20 ml of methyl tert-butyl ether. To this aqueous solution were added a solution of 0.58 gr $CaCl_2$ in 80 ml of water over a period of 1 hour. The resulting suspension was stirred for about 16 hours at room temperature. The suspension was filtered and the obtained solid was dried at 40° C. and 50 mbar for about 16 hours. The obtained product is crystal Form A which is characterized by an X-ray powder diffraction pattern as shown in FIG. **1**. Further characterization of the obtained Form A by thermogravimetry coupled with FT-IR spectroscopy revealed a water content of about 10%. Differential scanning calorimetry revealed a melting point of 95° C.

EXAMPLE 2

Preparation of Form B

100 mg Pitavastatin calcium Form A was suspended in 2 ml water and stirred at room temperature for 30 min, followed by the addition of 2 ml of ethanol and additional stirring for 18 hours. The suspension was filtered and dried in air, yielding 36 mg of Form B. The obtained crystal Form B is characterized by an X-ray powder diffraction pattern as shown in FIG. **2**. Further characterization of the obtained Form B by thermogravimetry coupled with FT-IR spectroscopy revealed a water content of about 10%.

EXAMPLE 3

Preparation of Form C

62 mg Pitavastatin calcium Form A was suspended in 2 ml isopropanol containing 5% water. This suspension was heated to 60° C., which led to almost complete dissolution of Form A, and again cooled to room temperature. At this temperature the suspension was stirred for 66 hours. The resulting suspension was filtered, once washed with some isopropanol containing 5% water, and dried in air. The obtained crystal Form C is characterized by an X-ray powder diffraction pattern as shown in FIG. **3**. Further characterization of the obtained Form C by thermogravimetry coupled with FT-IR spectroscopy revealed that the sample contains about 6.3% isopropanol and a small amount of water.

EXAMPLE 4

Preparation of Form C

65 mg Pitavastatin calcium Form A was suspended in a mixture of 0.9 ml isopropanol, 0.1 ml acetone and 40 μl water. Stirring this suspension for about 1 hour led to nearly complete dissolution. Seeding with 4 mg of Form C (from example 3) and stirring for 2 hours led to the formation of a concentrated suspension. This suspension was diluted with the same amount of solvent mixture as above and stirred for an additional 40 hours. The suspension was filtered and the obtained solid was dried at 40° C. for about 10 min. Analysis by X-ray powder diffraction indicates the product to be crystal Form C as shown in FIG. **3**.

EXAMPLE 5

Preparation of Form D

60 mg of Pitavastatin calcium Form A was suspended in 1 ml absolute ethanol and stirred at room temperature for 20 hours. The resulting suspension was filtered and dried in air. The obtained crystal Form D is characterized by an X-ray powder diffraction pattern as shown in FIG. **4**.

EXAMPLE 6

Preparation of Form E

60 mg of Pitavastatin calcium Form A was suspended in a mixture of 1,4-dioxane and water (1:1), and stirred for 18 hours at room temperature. The resulting suspension was filtered and dried in air. The obtained crystal Form E is characterized by an X-ray powder diffraction pattern as shown in FIG. **5**.

EXAMPLE 7

Preparation of Form F

60 mg of Pitavastatin calcium Form A was suspended in 3 ml methanol containing 20% water, and stirred at 40° C. for 1 hour. The resulting suspension was slowly cooled to room temperature and stirring was continued for 4 hours. The suspension was heated again to 40° C., stirred for 30 min, slowly cooled to room temperature and stirred for an additionally 15 hours. The suspension was filtered and the obtained white solid dried in air. The obtained crystal Form F is characterized by an X-ray powder diffraction pattern as shown in FIG. **6**.

EXAMPLE 8

Preparation of the Amorphous Form

62 mg of Pitavastatin calcium Form A was dissolved in 0.3 ml 1,4-dioxane. To this stirred solution was slowly added 2.3 ml n-heptane at room temperature, and stirred for an additional 16 hours. The resulting suspension was filtered and dried in air. The obtained solid was amorphous as is shown by the X-ray diffraction pattern given in FIG. **7** (top).

EXAMPLE 9

Preparation of the Amorphous Form

60 mg of Pitavastatin calcium Form A was dissolved in 1.5 ml ethyl methyl ketone. To this solution was added in steps of 1 ml each 30 sec a total of 21 ml methyl tert-butyl ether. The resulting suspension was stirred at room temperature for about 16 hours. The suspension was filtered and the obtained solid was dried in air. An X-ray diffraction study on the product showed it to be amorphous, see FIG. **7** (bottom). Further characterization of the obtained product by thermogravimetry coupled with FT-IR spectroscopy revealed that the sample contained about 5.5% methyl tert-butyl ether. Differential scanning calorimetry showed the sample to have a glass transition temperature of about 68° C.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a characteristic X-ray powder diffraction pattern for Form A.

FIG. **2** is a characteristic X-ray powder diffraction pattern for Form B.

FIGS. **3**A and **3**B are two characteristic X-ray powder diffraction patterns for Form C.

FIG. **4** is a characteristic X-ray powder diffraction pattern for Form D.

FIG. **5** is a characteristic X-ray powder diffraction pattern for Form E.

FIG. **6** is a characteristic X-ray powder diffraction pattern for Form F.

FIGS. **7**A and **7**B are two characteristic X-ray powder diffraction patterns for the amorphous form.

The invention claimed is:

1. A crystalline polymorph A, B, C, D, E, F, or the amorphous form, of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenye)quinolin-3-yl]-3.5-dihydroxy-6(E)-heptenoic acid hemicalcium salt wherein

A) polymorph A exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (s), 6.8 (s), 9.1 (s), 10.0 (w), 10.5 (m), 11.0 (m), 13.3 (vw), 13.7 (s), 14.0 (w), 14.7 (w), 15.9 (vw), 16.9 (w), 17.1 (vw), 18.4 (m), 19.1 (w), 20.8 (vs), 21.1 (m), 21.6 (m), 22.9 (m), 23.7 (m), 24.2 (s), 25.2 (w), 27.1 (m), 29.6 (vw), 30.2 (w), 34.0 (w);

B) polymorph B exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.6 (w), 5.3 (vs), 6.2 (s), 7.7 (s), 9.2 (m), 9.6 (m), 10.3 (w), 11.3 (m), 11.7 (w), 12.6 (vw), 13.0 (w), 13.9 (m), 14.7 (vw), 14.9 (w), 15.6 (w), 16.3 (m), 17.0 (vw), 17.4 (vw), 18.0 (w), 18.7 (m), 19.3 (m), 20.0 (s), 20.5 (w), 20.8 (m), 21.2 (w, shoulder), 21.5 (m), 22.4 (m),

23.2 (s), 23.8 (m), 24.4 (vw), 25.2 (w, broad), 26.0 (w), 26.4 (vw), 27.0 (w), 27.9 (vw), 28.9 (w);

C) polymorph C exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.1 (m), 5.6 (s), 7.8 (m), 8.3 (m), 10.3 (m), 11.6 (w), 17.5 (w), 17.9 (w),18.7 (m), 19.5 (s), 20.6 (m), 21.5 (vw), 21.9 (m), 23.1 (m), 24.0 (w), 24.8 (w);

D) polymorph D exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (m), 6.5 (m), 6.8 (s), 8.7 (m), 10.0 (m), 10.2 (m), 10.8 (m), 13.1 (w), 13.5 (m), 14.3 (s), 15.3 (vw), 16.1 (m), 16.8 (w), 18.2 (w), 18.5 (m), 19.0 (w), 19.9 (m), 20.5 (m), 21.0 (vs), 21.7 (s), 22.3 (w), 23.4 (m), 24.0 (m), 25.6 (w), 26.2 (m);

E) polymorph E exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.4 (vw), 5.0 (s), 6.6 (s), 6.8 (s), 8.9 (s), 10.0 (m), 10.3 (s), 10.8 (m), 13.3 (s), 13.6 (m), 14.0 (s), 15.2 (vw), 15.9 (w), 16.4 (w), 16.9 (vw), 17.8 (vw), 18.3 (m), 18.9 (w), 20.2 (vs), 20.4 (m), 20.7 (m), 20.9 (m), 21.1 (vs), 21.6 (m), 21.7 (m), 22.3 (m), 23.5 (m), 23.8 (m), 24.1 (w), 24.7 (vw), 25.4 (vw), 26.6 (m), 30.2 (w), 34.0 (vw); and

F) polymorph F exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.1 (m), 5.6 (w), 7.0 (s), 8.8 (m), 9.6 (s), 10.2 (w), 10.9 (m), 11.3 (w), 11.9 (m), 12.5 (m), 13.0 (s), 13.7 (m), 14.4 (s), 14.7 (m), 15.3 (vw), 15.5 (w), 16.8 (m), 17.6 (w), 18.3 (m), 19.3 (m), 19.7 (m), 20.6 (m), 21.2 (vs), 21.8 (s), 22.8 (s), 23.1 (w), 23.8 (w, shoulder), 24.1 (s), 24.8 (s), 25.7 (m), 26.2 (vw), 26.6 (m), 26.9 (w), 28.4 (w), 29.5 (w), 29.8 (vw), 30.9 (m); wherein, for each of said polymorphs, (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

2. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph A; and

the process comprises reacting (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid sodium salt with $CaCl^2$ in an aqueous reaction medium.

3. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph B; and

the process comprises suspending the crystalline polymorph A in ethanol containing water as a cosolvent.

4. The process according to claim **3**, wherein the water is present in an amount of 1 to 50% by volume of the suspension of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

5. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph C; and

the process comprises suspending the crystalline polymorph A the process comprises suspending the crystalline polymorph A in isopropanol containing water as a cosolvent.

6. The process according to claim **5**, wherein the water is present in an amount of 1 to 50% by volume of the suspension of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

7. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph C; and

the process comprises suspending the crystalline polymorph A in a mixture of isopropanol and a ketone solvent, containing water as a cosolvent.

8. The process according to claim **7**, wherein the ketone solvent is acetone.

9. The process according to claim **7**, wherein the ketone solvent is present in an amount of 1 to 30% by volume of the suspension of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

10. The process according to claim **7**, wherein the water is present in an amount of 1 to 20% by volume of the suspension of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

11. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph D; and

the process comprises suspending the crystalline polymorph A in absolute ethanol.

12. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph E; and

the process comprises suspending the crystalline polymorph A in 1,4-dioxane containing water as a cosolvent.

13. The process according to claim **12**, wherein the water is present in the amount of 1 to 50% by volume of the suspension of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

14. A process for perparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph F; and

the process comprises suspending the crystalline polymorph A in methanol containing water as a cosolvent.

15. The process according to claim **14**, wherein the water is present in an amount of 1 to 50% by volume of the suspension of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

16. The process according to claim **2**, wherein (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt is isolated by filtration and dried in air or vacuum.

17. The process according to claim **2**, wherein seeding is carried out with crystals of the desired crystalline polymorph.

18. A process preparing the crystalline polymorph or amorphous form according claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the amorphous form; and

the process comprises adding a non-solvent to a solution of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt in an organic solvent.

19. The process according to claim **18**, wherein the non-solvent is selected from heptane and methyl tert-butyl ether.

20. The process according to claim **18**, wherein the organic solvent is selected from 1,4-dioxane, tetrahydrofuran and ethyl methyl ketone.

21. A process for preparing the crystalline polymorph or amorphous form according claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the amorphous form; and

the process comprises drying an aqueous solution of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt by lyophilization.

22. A pharmaceutical composition comprising an effective amount of the crystalline polymorph or amorphous form according to claim **1**, and a pharmaceutically acceptable carrier.

23. A crystalline polymorph A, B, C, D, E, F, or the amorphous form, of (3 R,5 S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3 -yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt of claim **1**, wherein polymorph A has an X-ray powder diffraction pattern substantially as depicted in FIG. **1**, polymorph B has an X-ray powder diffraction pattern substantially as depicted in FIG. **2**, polymorph C has an X-ray powder diffraction pattern substantially as depicted in FIGS. **3**A and **3**B, polymorph D has an X-ray powder diffraction pattern substantially as depicted in FIG. **4**, polymorph E has an X-ray powder diffraction pattern substantially as depicted in FIG. **5**, polymorph F has an X-ray powder diffraction pattern substantially as depicted in FIG. **6**, and

the amorphous form has an X-ray powder diffraction pattern substantially as depicted in FIGS. **7**A and **7**B.

24. A crystalline polymorph A of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (s), 6.8 (s), 9.1 (s), 10.0 (w), 10.5 (m), 11.0 (m), 13.3 (vw), 13.7 (s), 14.0 (w), 14.7 (w), 15.9 (vw), 16.9 (w), 17.1 (vw), 18.4 (m), 19.1 (w), 20.8 (vs), 21.1 (m), 21.6 (m), 22.9 (m), 23.7 (m), 24.2 (s), 25.2 (w), 27.1 (m), 29.6 (vw), 30.2 (w), and 34.0 (w), wherein (vs) stands for very strong intensity, (s) stands for strong intensity, (m) stands for medium intensity, (w) stands for weak intensity, and (vw) stands for very weak intensity.

25. A crystalline polymorph A of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIG. **1**.

26. A crystalline polymorph B of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.6 (w), 5.3 (vs), 6.2 (s), 7.7 (s), 9.2 (m), 9.6 (m), 10.3 (w), 11.3 (m), 11.7 (w), 12.6 (vw), 13.0 (w), 13.9 (m), 14.7 (vw), 14.9 (w), 15.6 (w), 16.3 (m), 17.0 (vw), 17.4 (vw), 18.0 (w), 18.7 (m), 19.3 (m), 20.0 (s), 20.5 (w), 20.8 (m), 21.2 (w, shoulder), 21.5 (m), 22.4 (m), 23.2 (s), 23.8 (m), 24.4 (vw), 25.2 (w, broad), 26.0 (w), 26.4 (vw), 27.0 (w), 27.9 (vw), and 28.9 (w), wherein (vs) stands for very strong intensity, (s) stands for strong intensity, (m) stands for medium intensity, (w) stands for weak intensity, and (vw) stands for very weak intensity.

27. A crystalline polymorph B of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIG. **2**.

28. A crystalline polymorph C of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.1 (m), 5.6 (s), 7.8 (m), 8.3 (m), 10.3 (m), 11.6 (w), 17.5 (w), 17.9 (w), 18.7 (m), 19.5 (s), 20.6 (m), 21.5 (vw), 21.9 (m), 23.1 (m), 24.0 (w), and 24.8 (w), wherein (vs) stands for very strong intensity, (s) stands for strong intensity, (m) stands for medium intensity, (w) stands for weak intensity, and (vw) stands for very weak intensity.

29. A crystalline polymorph C of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIGS. **3**A and **3**B.

30. A crystalline polymorph D of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (m), 6.5 (m), 6.8 (s), 8.7 (m), 10.0 (m), 10.2 (m), 10.8 (m), 13.1 (w), 13.5 (m), 14.3 (s), 15.3 (vw), 16.1 (m), 16.8 (w), 18.2 (w), 18.5 (m), 19.0 (w), 19.9 (m), 20.5 (m), 21.0 (vs), 21.7 (s), 22.3 (w), 23.4 (m), 24.0 (m), 25.6 (w), and 26.2 (m), wherein (vs) stands for very strong intensity, (s) stands for strong intensity, (m) stands for medium intensity, (w) stands for weak intensity, and (vw) stands for very weak intensity.

31. A crystalline polymorph D of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIG. **4**.

32. A crystalline polymorph E of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.4 (vw), 5.0 (s), 6.6 (s), 6.8 (s), 8.9 (s), 10.0 (m), 10.3 (s), 10.8 (m), 13.3 (s), 13.6 (m), 14.0 (s), 15.2 (vw), 15.9 (w), 16.4 (w), 16.9 (vw), 17.8 (vw), 18.3 (m), 18.9 (w), 20.2 (vs), 20.4 (m), 20.7 (m), 20.9 (m), 21.1 (vs), 21.6 (m), 21.7 (m), 22.3 (m), 23.5 (m), 23.8 (m), 24.1 (w), 24.7 (vw), 25.4 (vw), 26.6 (m), 30.2 (w), and 34.0 (vw), wherein (vs) stands for very strong intensity, (s) stands for strong intensity, (m) stands for medium intensity, (w) stands for weak intensity, and (vw) stands for very weak intensity.

33. A crystalline polymorph E of (3R,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIG. **5**.

34. A crystalline polymorph F of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.1 (m), 5.6 (w), 7.0 (s), 8.8 (m), 9.6 (s), 10.2 (w), 10.9 (m), 11.3 (w), 11.9 (m), 12.5 (m), 13.0 (s), 13.7 (m), 14.4 (s), 14.7 (m), 15.3 (vw), 15.5 (w), 16.8 (m), 17.6 (w), 18.3 (m), 19.3 (m), 19.7 (m), 20.6 (m), 21.2 (vs), 21.8 (s), 22.8 (s), 23.1 (w), 23.8 (w, shoulder), 24.1 (s), 24.8 (s), 25.7 (m), 26.2 (vw), 26.6 (m), 26.9 (w), 28.4 (w), 29.5 (w), 29.8 (vw), and 30.9 (m), wherein (vs) stands for very strong intensity, (s) stands for strong intensity, (m) stands for medium intensity, (w) stands for weak intensity, and (vw) stands for very weak intensity.

35. A crystalline polymorph F of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIG. **6**.

36. The amorphous form of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3.5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

37. The amorphous form of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt, having an X-ray powder diffraction pattern substantially as depicted in FIGS. **7**A and **7**B.

38. A process for preparing the crystalline polymorph or amorphous form according to claim **1**, wherein:

the crystalline polymorph or amorphous form being prepared is the crystalline polymorph F; and

the process comprises suspending the crystalline polymorph A in methanol containing water as a cosolvent.

39. The process according to claim **38**, wherein the water is present in an amount of 1 to 50% by volume of the suspension of (3R,5S)-7[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(E)-heptenoic acid hemicalcium salt.

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