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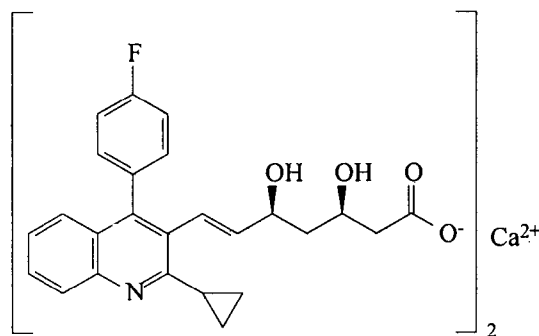
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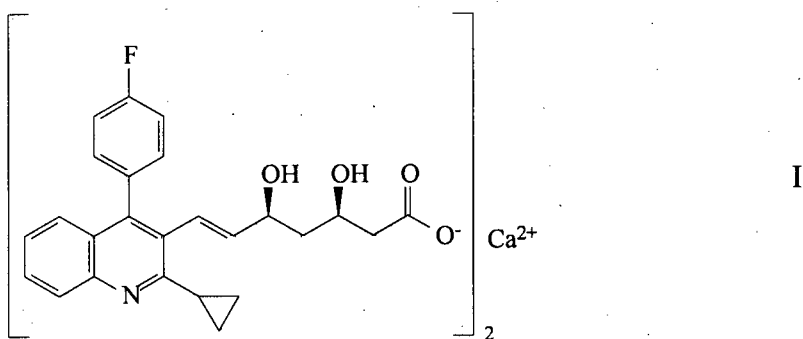
I

(57) Abstract: The present invention relates to a novel process for preparing Pitavastatin calcium salt of formula (I).

PROCESS FOR PREPARING QUINOLINE DERIVATIVE

FIELD OF THE INVENTION

The present invention relates to a novel process for preparing Pitavastatin calcium salt of formula I.

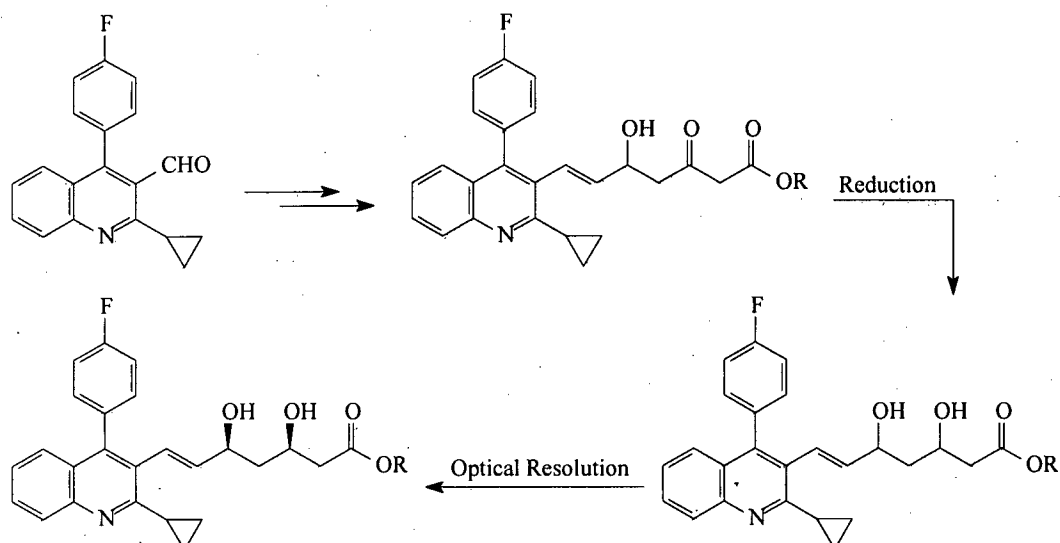


BACKGROUND OF THE INVENTION

Pitavastatin calcium, chemically known as (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid calcium (2:1) salt, is a synthetic lipid lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase).

Pitavastatin is being marketed under the brand name Livalo[®], as an oral tablet in 1 MG, 2 MG and 4 MG strengths. Pitavastatin calcium is used to lower the lipid levels including cholesterol in blood and can be used for the prevention or treatment of hyperlipidemia and arteriosclerosis.

Pitavastatin was disclosed for the first time in US patents US 4,761,419, US 5,011,930 and US 5,753,675. The process disclosed in these patents for the preparation of Pitavastatin is as shown below:

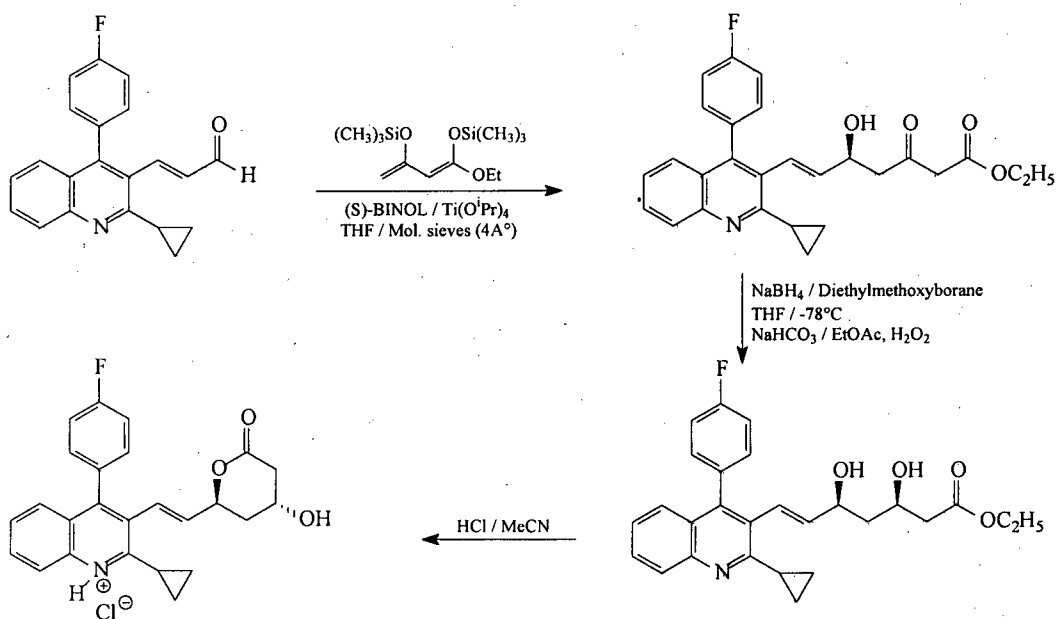


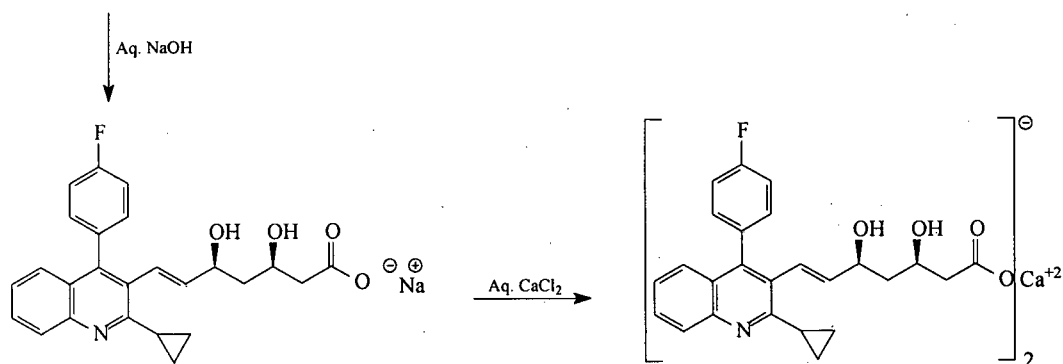
wherein R is hydrogen or protecting group.

US 5,284,953 discloses a process for the preparation of Pitavastatin calcium, which employs optically active α -methylbenzylamine as a resolving agent.

The above processes are economically not viable, as resolution is carried out in final stage.

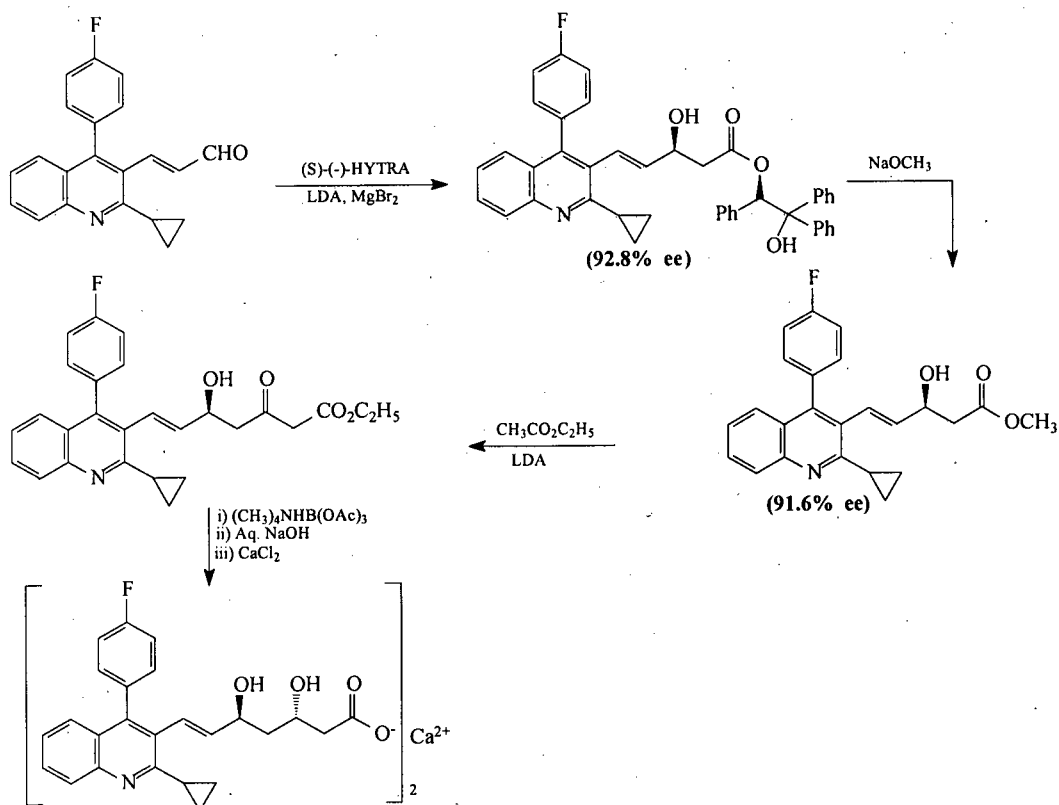
US 6,835,838 B2 discloses a process for the preparation of Pitavastatin calcium, which is as shown below:





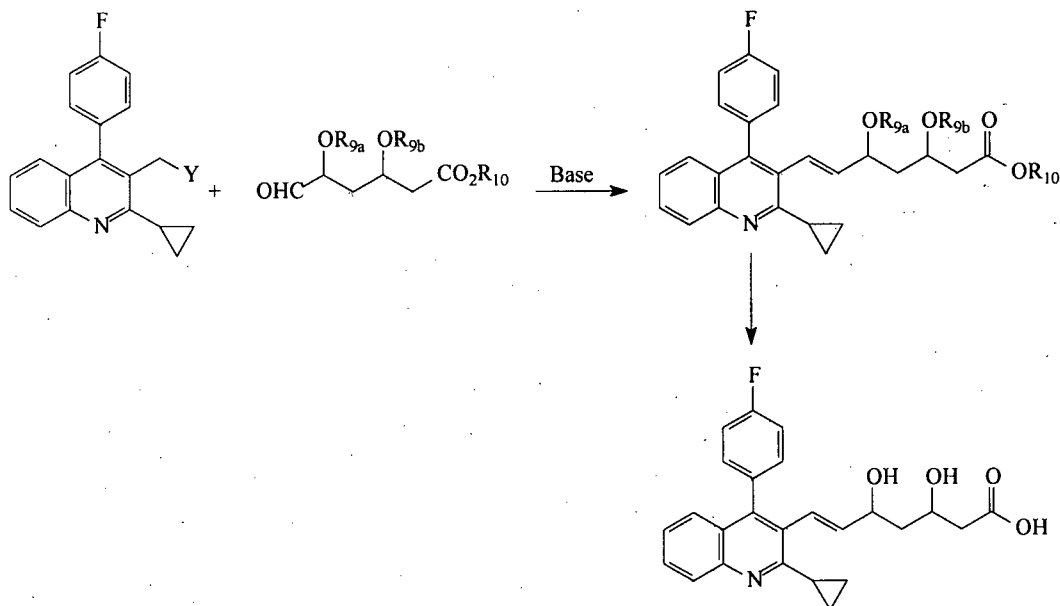
However, it has been observed that the above process of lactonization results in ~10-15% of unreacted Pitavastatin ethyl ester and therefore results in low yield. Further, ~10% of Pitavastatin acid results during the above lactonization process and therefore does not produce a single product which is required to keep adequate control for an intermediate through specifications to have consistently better quality of the finished product.

Bioorganic & Medicinal Chemistry Letters (1999), 9(20), 2977-2982 discloses a process for the preparation of pitavastatin epimers, which is as shown below:



The above process gives Pitavastatin calcium of less chiral purity.

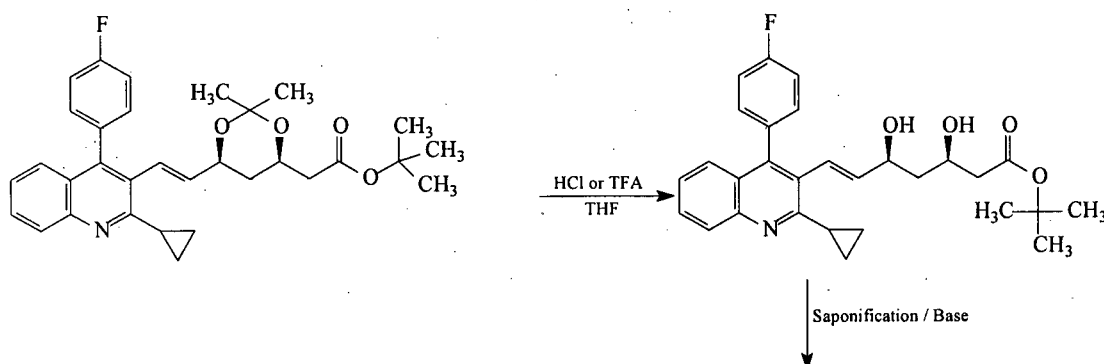
WO 1995/11898 A1 discloses a process for the preparation of Pitavastatin, which is as shown below:

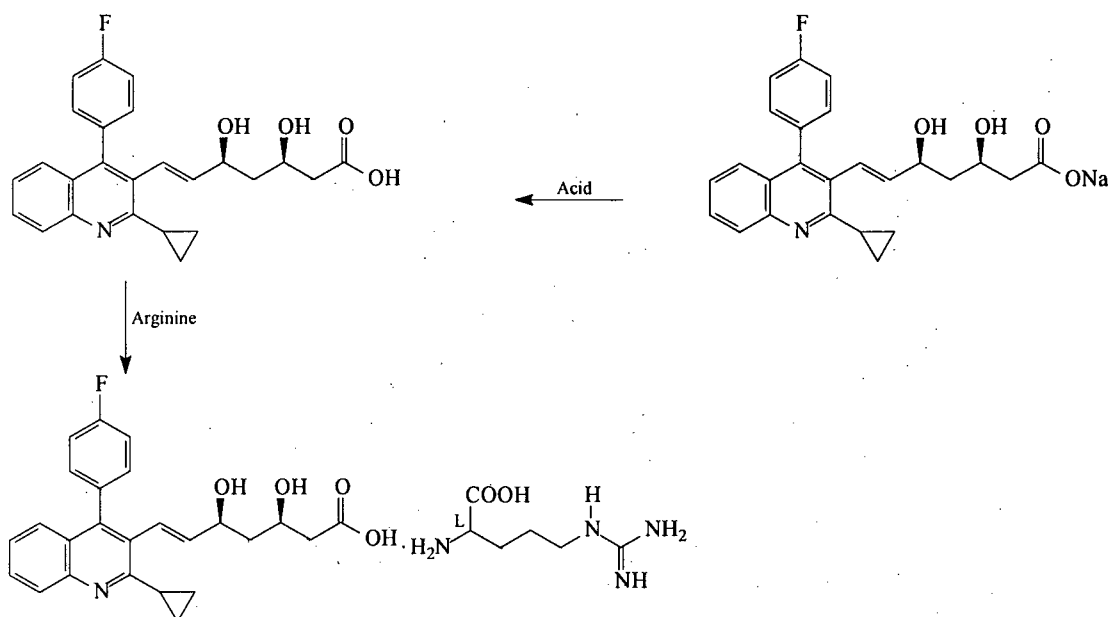


wherein Y represents P⁺R₁₁R₁₂R₁₃Hal⁻ or P(W)R₁₄R₁₅; R_{9a}, R_{9b} and R₁₀ are protecting groups each of R₁₁, R₁₂, R₁₃, R₁₄ and R₁₅ which are independent of one another, is optionally substituted alkyl or optionally substituted aryl group; R₁₄ and R₁₅ together form a 5- or 6-membered ring; Hal is chlorine, bromine or iodine; and W is O or S.

The above process results in 2-5% of Cis isomer of Pitavastatin which requires further purification and therefore results poor yield.

US 6,875,867 B2 discloses a process for the preparation of Pitavastatin arginine salt, which is as shown below:





During the above process Trifluoroacetic acid or hydrochloric acid is used to break the acetonide and the Pitavastatin ester formed is converted *in situ* to its corresponding alkali salt by treating with base, such as sodium hydroxide.

It is known that Pitavastatin is enantiomerically pure compound having two chiral centers in side chain of the molecule. All four isomers of Pitavastatin can be separated by HPLC and the Pitavastatin is (3*R*, 5*S*)-isomer.

The process shown above carries out diastereomeric purification of Pitavastatin calcium through its lactone hydrochloride intermediate or forming different salts of Pitavastatin like arginine salt, which makes the process economically unviable.

Further, it is well understood from the prior art that crystallization of Pitavastatin esters to remove diastereomers is practically a difficult process because of their lesser solubility in most of the organic solvents as compared to the required (3*R*, 5*S*)-isomer.

As mentioned above, though there are number of processes available in the art, there is a continuing need to identify alternative process for the manufacture of Pitavastatin and its pharmaceutically acceptable salts, such processes may, for example, when compared to previously known processes, be more convenient to use, be more suitable for large scale manufacture, give the product in a better yield, use intermediates which are more easily isolated, require less complex purification techniques, use less expensive reagents and/or be more environment friendly.

We have now found a process for preparing (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt of formula I, which is industrially feasible. Further, the present inventors have found that the formation of unwanted diastereomer can be reduced by making Pitavastatin alkyl ester as organic acid salt, which is industrially feasible.

OBJECTIVE OF THE INVENTION

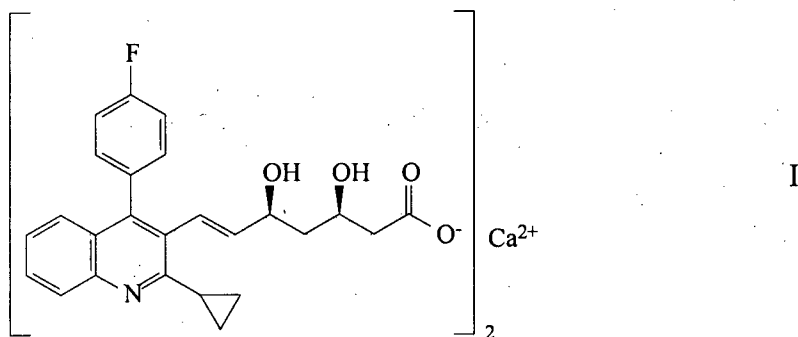
The objective of the present invention is to provide a novel process for preparing (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinoliny]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt with high yield and high purity, which is simple, industrially applicable and economically viable.

Another objective of the present invention is to provide a novel process for preparing (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinoliny]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt from novel intermediates.

Yet another objective of the present invention is to provide a process for preparing (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinoliny]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt, containing least amount of diastereomeric impurity.

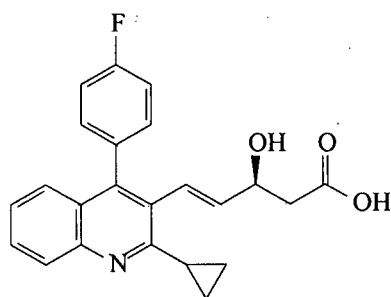
SUMMARY OF THE INVENTION

Present invention provides a novel process for preparing (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinoliny]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt of formula I,



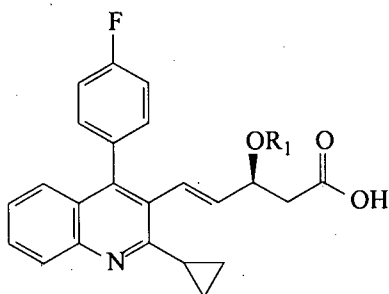
which comprises:

- a) protecting the compound of formula II with a suitable hydroxy protecting group,



II

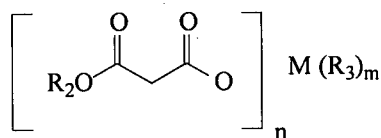
in an organic solvent to obtain a compound of formula III,



III

wherein R₁ represents a hydroxy protecting group;

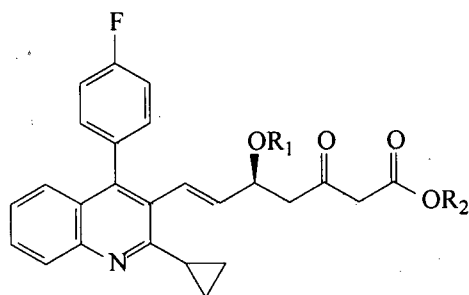
- b) activating the acid group of the compound of formula III with an acid activator, followed by treating the resulting intermediate with a metal complex of formula IV,



IV

wherein R₂ represents C₁₋₄ straight chain or branched chain alkyl, aryl, substituted aryl, aralkyl; M represents Mg, Zn, Ca or Cu; n represents an integer selected from 1-2; R₃ represents alkyl or alkoxy; m represents an integer selected from 0 or 1

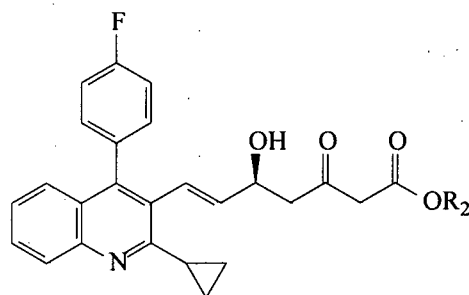
in an organic solvent to obtain a compound of formula V,



V

wherein R₁ and R₂ are same as defined above;

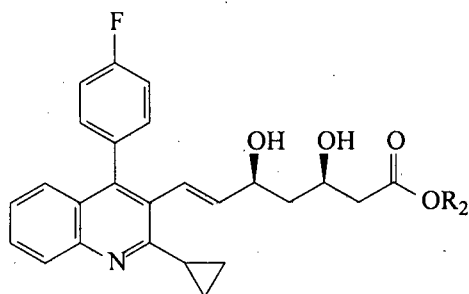
- c) deprotecting the compound of formula V with a suitable reagent in an organic solvent, water or mixture thereof to obtain compound of formula VI,



VI

wherein R_2 is same as defined above;

d) reducing the compound of formula VI to obtain a compound of formula VII,



VII

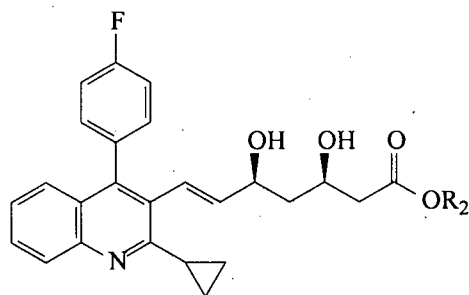
wherein R_2 is same as defined above;

e) hydrolyzing the compound of formula VII; and

f) treating the compound obtained in step (e) with calcium ion source to give Pitavastatin calcium of Formula I.

The present invention also provides a process for preparing (3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt of formula I, which comprises,

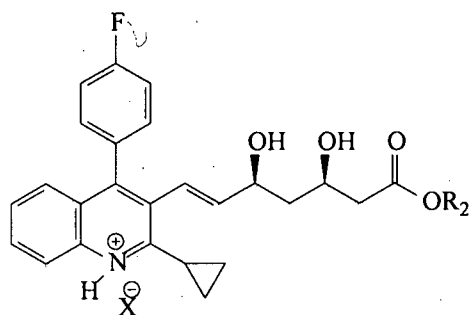
a) reacting Pitavastatin ester of formula VII,



VII

wherein R_2 is same as defined above

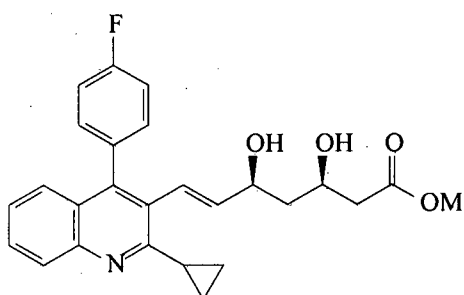
with an organic acid in the presence of inert solvent to obtain organic acid salt of Pitavastatin ester of formula VIII,



VIII

wherein wherein R_2 is same as defined above and X represents monobasic or dibasic acid;

- b) optionally, purifying compound of formula VIII using organic solvent;
- c) treating compound of formula VIII with aqueous inorganic base to obtain pure Pitavastatin ester of formula VII;
- d) hydrolyzing the compound of formula VII with strong base to obtain the corresponding alkali metal salt of compound of formula IX,



IX

wherein M represents Na, K, Li;

- e) treating compound of formula IX with a calcium source to obtain Pitavastatin calcium of formula I; and
- f) isolating the Pitavastatin calcium of formula I.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, present invention provides a process to prepare pitavastatin calcium comprising protecting (3*S*,4*E*)-5-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3-hydroxypentenoic acid of formula II with a suitable hydroxy protecting group selected from tertiarybutyldimethylsilyl, dihydropyran, trimethylsilyl, methoxymethyl, more preferably tert-butyldimethylsilyl in the presence of an organic solvent selected from toluene, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, N-methylpyrrolidinone, sulfolane or mixtures thereof with or without acid or base catalysts at a temperature ranging from 0 to 50°C; preferably at 0-30°C. The acid catalyst is selected from pyridinium p-toluene

sulfonate, p-toluene sulfonic acid, acetic acid, etc. and base catalyst is selected from triethylamine, pyridine, imidazole, etc. Optionally, during the silylation reaction a suitable additive is added to accelerate the reaction, which is selected from sodium iodide, potassium iodide, lithium iodide etc.

(3*S*,4*E*)-5-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3-(protected hydroxy)pentenoic acid of formula III is treated with acid activator like 1,1-carbonylimidazole, methyl chloroformate, ethyl chloroformate, phenyl chloroformate, 4-methoxyphenylchloroformate, 2,4-dinitrophenyl chloroformate, 4-trifluoromethylchloroformate, 4-nitrophenylchloroformate, etc.; more preferably with 1,1-carbonylimidazole in the presence or absence of organic base which is selected from triethylamine, pyridine, etc. The resulting activated imidazolimide intermediate is subsequently treated with metal complex of alkyl malonate selected from magnesium, zinc, calcium or copper complex.

Magnesium complex of monoalkyl malonate is prepared by treating 2 moles of malonic acid mono alkyl ester with 1 mole of magnesium ethoxide in the presence of an organic solvent selected from tetrahydrofuran, N,N-dimethylformamide, methylene chloride, acetonitrile or mixture thereof and the reaction is conducted at a temperature between 0-100°C, preferably at ambient temperature.

Zinc complex of monoalkyl malonate is prepared by using different methods known in the art, such as process I or II.

Process I:

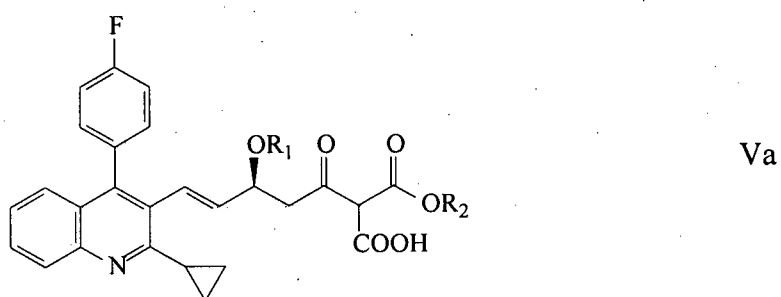
Zinc complex is prepared by reacting dialkyl zinc with 2 moles of lower alcohol, preferably ethanol in an inert solvent selected from tetrahydrofuran, toluene, hexane, methyl tert-butyl ether, isopropyl ether or mixture thereof, at -10°C to 40°C. 1-5 mole of monoalkyl malonate, preferably 2 to 3 mole are added to this reaction mixture and stirred for 1-15 h, preferably for 1-3 h.

Process II:

Zinc complex is prepared by reacting zinc oxide with 1 to 5 moles of monoalkyl malonate in an inert solvent selected from tetrahydrofuran, toluene, hexane, methyl

tert-butyl ether, isopropyl ether or mixture thereof, at ambient temperature for 2h to 6h. The water formed during the course of reaction is co-distilled with an inert solvent such as toluene.

The metal complex of formula IV is reacted with acid activated compound of formula III in an inert solvent such as tetrahydrofuran, acetonitrile, toluene, methyl tert-butyl ether, isopropyl ether or mixtures thereof at 0°C to 40°C, preferably at 10°C to 25°C for 8h to 24h, preferably 10h to 24h to yield (5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-5-(protectedhydroxy)-3-oxo-6-heptenoate of formula V. During the work-up of this reaction, a compound of formula Va, which is generated *in situ* gets decarboxylated giving directly ketoester of formula V.



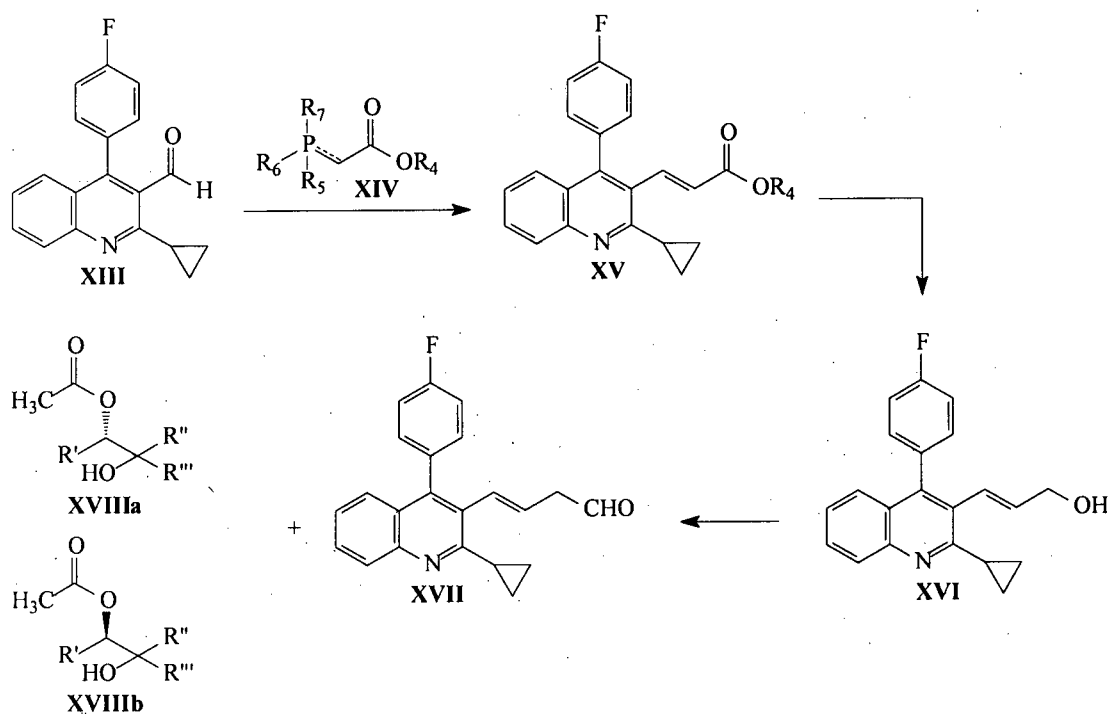
(5*S*,6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-5-(protectedhydroxy) -3-oxo-6-heptenoate of formula V is deprotected using acids having a general formula HX, wherein X represents halogen, or MX wherein X represent halogen and M is a cation derived from inorganic metal like Na⁺, K⁺, Li⁺, etc., organic ammonium salt like N⁺(R)₄ wherein R represents C₁-C₄ alkyl, straight or branched chain alkyl, sulphonic acid, organic acids selected from *p*-toluenesulfonic acid, methanesulfonic acid, trifluoromethanesulfonic acid, formic acid, trifluoroacetic acid, acetic acid in an aqueous solvent or in an organic solvent selected from tetrahydrofuran, acetonitrile, methanol, ethanol, dichloromethane, ethylene dichloride, toluene, xylene or mixtures thereof at room temperature to yield (5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-5-hydroxy-3-oxo-6-heptenoate of formula VI.

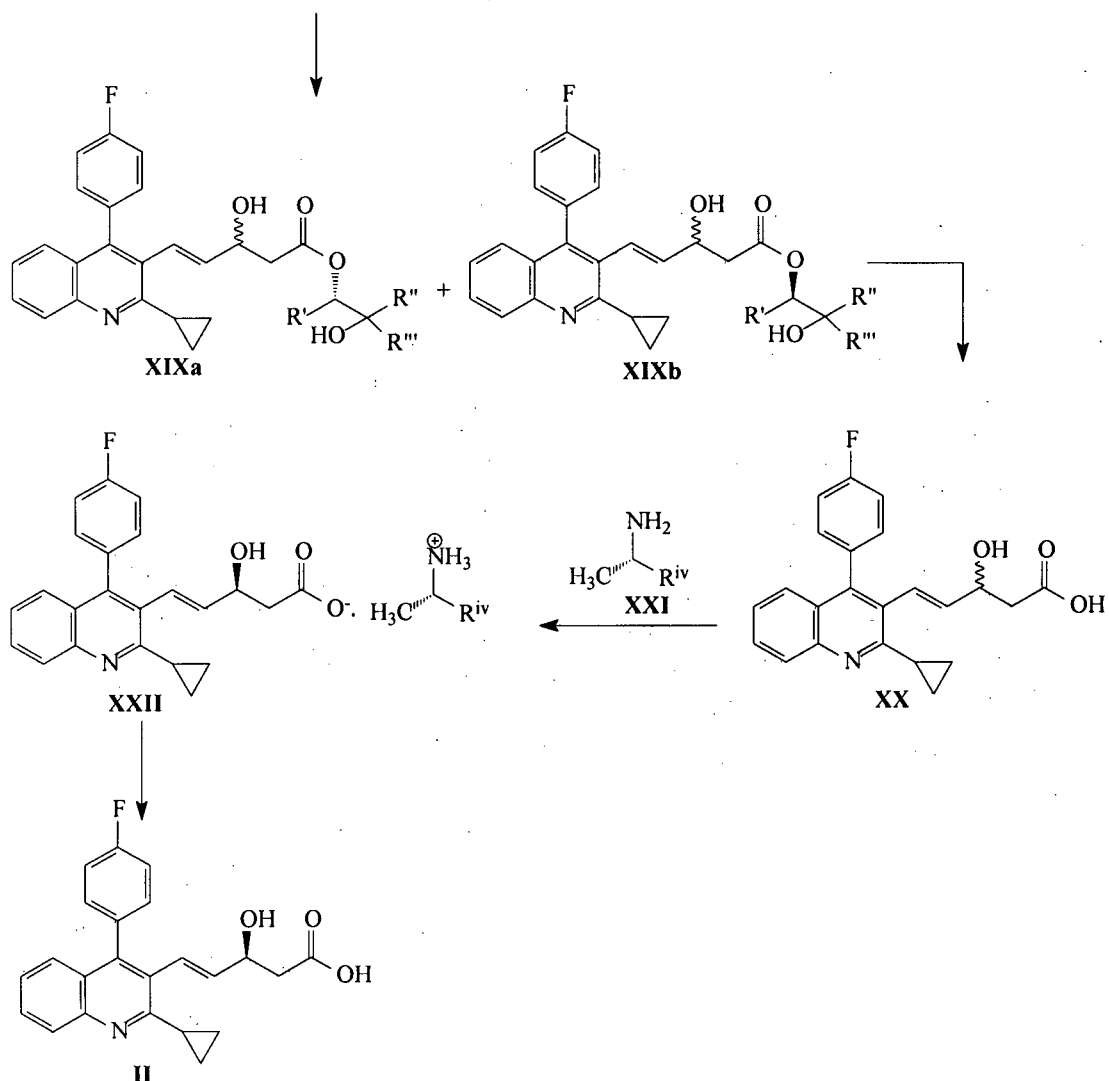
(5*S*,6*E*)-7-[2-Cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-5-hydroxy-3-oxo-6-heptenoate of formula VI is stereoselectively reduced with metal borohydride selected from sodium borohydride, more preferably sodium borohydride in the presence of chelating agents like trialkylborane or boronates selected from dialkylalkoxyborane

such as diethylmethoxyborane, diethylethoxyborane, dimethylmethoxyborane, more preferably with diethylmethoxyborane, in a mixture of inert solvent selected from tetrahydrofuran, a lower alkanol, more preferably methanol and C₁₋₄ alkyl ester like methyl acetate, ethyl acetate, propyl acetate, more preferably ethyl acetate at -78°C to -0°C . After completion of the reaction, excess sodium borohydride is destroyed by adding acetic acid and resulting (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoate of formula VII is isolated by extracting into an organic solvent. The organic layer is concentrated under reduced pressure to give crude compound, which is purified by crystallization or is used as such for hydrolysis.

Saponification of (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3,5-dihydroxy-6-heptenoate of formula VII is carried out using a base, selected from alkali or alkali earth metal hydroxide selected from group sodium hydroxide, potassium hydroxide, calcium hydroxide, lithium hydroxide; preferably using sodium hydroxide. The sodium salt of Pitavastatin thus obtained can be optionally isolated or the solution containing Pitavastatin sodium is treated with a calcium ion source such as calcium chloride, calcium acetate, etc. to yield Pitavastatin calcium.

(3*S*,4*E*)-5-[2-Cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3-hydroxypentenoic acid of formula II is prepared by following the prior-art process, which is as shown below:





wherein R₇ selected from (=O), C₁₋₄ alkyl, aralkyl, phenyl, substituted phenyl, R₆ and R₅ are selected from OR₈, C₁₋₄ alkyl, aralkyl, phenyl, substituted phenyl; R₄ and R₈ are selected from C₁₋₄ alkyl, aralkyl, phenyl, substituted phenyl; “----” represents an optional bond with a provision that when R₇ is =O, “----” is not a bond and when R₇ represents C₁₋₄ alkyl, phenyl, substituted phenyl, then “----” is a bond; R’, R”, R”’ and R^{iv} are selected from alkyl, aralkyl, cycloalkyl, aryl, heterocyclic reissue.

2-Cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxaldehyde of formula XIII is reacted with a phosphorous compound of formula XIV optionally in the presence of a base such as organic base selected from sodium methoxide, lithium diisopropylamide, n-butyllithium, lithium hexamethyldisilazane, sodium hexamethyldisilazane, etc. or inorganic base selected from sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, a solvent selected from

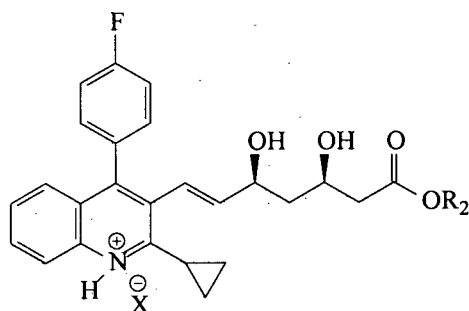
acetonitrile, dichloromethane, tetrahydrofuran, methanol, ethanol, isopropyl alcohol and mixture thereof, at a temperature ranging from 20-90°C, preferably at 40-80°C for 1-8 h to yield (2*E*)-3-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]acrylate of formula XV, which is reduced using a reducing agent such as diisobutylaluminium hydride (DIBAL), Vitride, Lithium aluminium hydride (LAH), etc. in an organic solvent selected from toluene, tetrahydrofuran, at 35°C to -80°C, preferably at -78°C to yield (2*E*)-3-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]propen-1-ol of formula XVI.

(2*E*)-3-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]propen-1-ol of formula XVI is oxidized using an oxidizing agent such as pyridinium dicromate (PDC), Pyridinium chlorocromate (PCC), manganese dioxide (MnO₂), and tetrapropylammoniumperrutheniate (TPAP), sodium hypochlorite (NaOCl) / TEMPO, N-methylmorpholine-N-oxide (MNO) and the like, at a temperature ranging from 0-100°C preferably at 0-25°C to yield (2*E*)-3-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-2-propenal of formula XVII, which is condensed with a compound of formula XVIIIa or XVIIIb in presence of base selected from *n*-butyllithium, lithium hexamethyldisilazane, sodium hexamethyldisilazane, lithium diisopropylamine, etc. more preferably lithium hexamethyldisilazane in an organic solvent selected from tetrahydrofuran, ether, hydrocarbon solvents such as heptane, hexane or mixture thereof, preferably tetrahydrofuran and hexane and the reaction is carried out at a temperature ranging from -78°C to 25°C.

After completion the reaction is quenched with 5N hydrochloric acid and extracted with an organic solvent to give a diastereomeric mixture of compounds of formula XIXa or XIXb and is hydrolyzed to its corresponding acid, (4*E*)-5-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3-hydroxypentenoic acid of formula XX, which is then resolved using optically pure precipitating agents, for example (+) or (-) phenylalkylamine or substituted phenylalkylamine, preferably (R)-1-phenylethylamine is a suitable organic solvent selected from acetonitrile, tetrahydrofuran, ethyl acetate, methanol, ethanol, isopropyl alcohol or a mixture of organic solvent and water to obtain enantiomerically pure (3*S*,4*E*)-5-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3-hydroxypentenoic acid, (R)- α -methylbenzylamine salt of formula XXII, which then converted to the free acid

(3*S*,4*E*)-5-[2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl]-3-hydroxypentenoic acid of formula II by treating with dilute inorganic acid, such as aqueous hydrochloric acid.

In another embodiment, present invention relates to novel organic acid salts of Pitavastatin alkyl ester of formula VIII.



VIII

wherein R_2 is same as defined above.

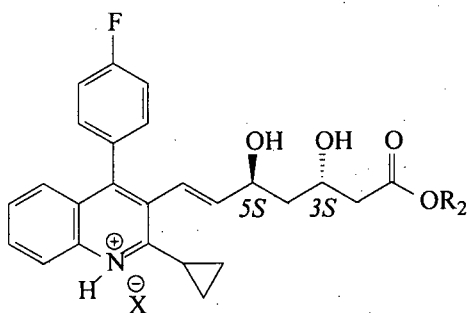
The organic acid salt of Pitavastatin ester is selected from trifluoroacetic acid, trifluoromethane sulfonic acid, acetic acid, methanesulfonic acid, perchloric acid, periodic acid, oxalic acid, mandelic acid, malic acid, tartaric acid, camphorsulfonic acid, benzenesulfonic acid, p-toluenebenzene sulphonic acid, 4-nitrobenzene sulfonic acid, etc.

The process to prepare organic acid salt of Pitavastatin ester of formula VIII according to present invention comprises reacting Pitavastatin ester of formula VII in an organic solvent selected from C_1 - C_5 alcohol such as methanol, ethanol, butanol; C_3 - C_8 esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate; C_3 - C_8 ketones such as methyl ethyl ketone, methyl isobutyl ketone, acetone; C_6 - C_{10} aromatic hydrocarbons such as toluene; ethers such as tetrahydrofuran, methyl ethyl ether; acetonitrile and mixture thereof, with an organic acid, selected from monobasic, dibasic, or tribasic acid, such as trifluoroacetic acid, trifluoromethane sulfonic acid, acetic acid, methanesulfonic acid, perchloric acid, periodic acid, oxalic acid, mandelic acid, malic acid, tartaric acid, camphorsulfonic acid, benzenesulfonic acid, p-toluenebenzene sulphonic acid, 4-nitrobenzene sulfonic acid; preferably trifluoroacetic acid at temperature below 15°C , preferably at 0 - 5°C , for 15 min to 2 hr, preferably 15-20 min. Non-polar solvent selected from hexane, heptane,

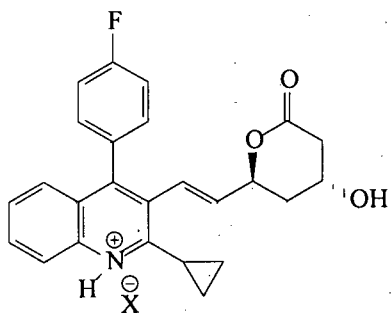
cyclohexane, ethers such as diisopropyl ether, etc. is added and isolated the organic acid salt of Pitavastatin ester of formula VIII.

The organic acid salt of formula VIII is prepared using organic acid and ester compound of VII in molar ratio within the range from 1.25:1 to 0.8 :1; preferably 1.1:1.

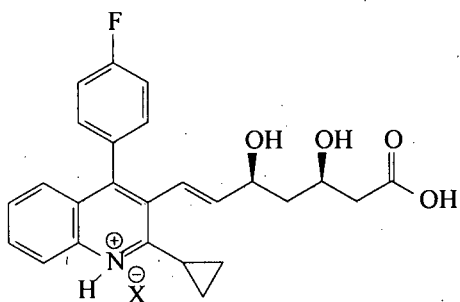
In another aspect, the present invention provides Pitavastatin ethyl ester organic acid salt of formula VIII, containing less than ~0.3% of its anti-isomer of formula VIII(a) and least amount of Pitavastatin lactone salt of formula X or less than 0.5% corresponding Pitavastatin acid salt of formula XI.



VIII(a)



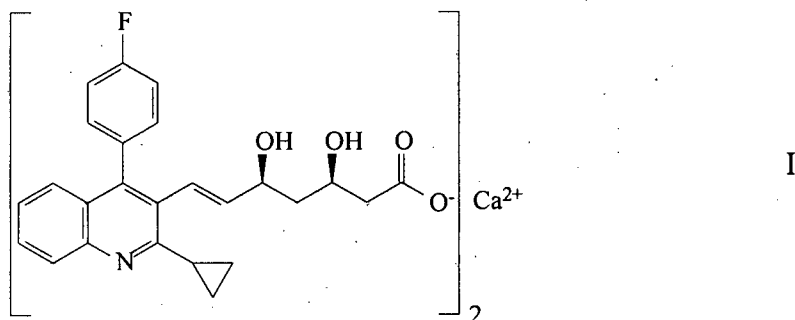
X



XI

wherein X represents monobasic or dibasic acid

In yet another embodiment of the present invention, the process for preparing (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid, calcium (2:1) salt of formula I,



which comprises, reacting Pitavastatin ester in an organic solvent selected from C₁-C₅ alcohol such as methanol, ethanol, butanol; C₃-C₈ esters such as ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate; C₃-C₈ ketones such as methyl ethyl ketone, methyl isobutyl ketone, acetone; C₆-C₁₀ aromatic hydrocarbons such as toluene; ethers such as tetrahydrofuran, methyl ethyl ether; acetonitrile and mixture thereof, with an organic acid, selected from monobasic, dibasic, or tribasic acid, such as trifluoroacetic acid, trifluoromethane sulfonic acid, acetic acid, methanesulfonic acid, perchloric acid, periodic acid, oxalic acid, mandelic acid, malic acid, tartaric acid, camphorsulfonic acid, benzenesulfonic acid, p-toluenebenzene sulphonic acid, 4-nitrobenzene sulfonic acid; preferably trifluoroacetic acid at temperature below 15°C, preferably at 0-5°C, for 15 min to 2 hr, preferably 15-20 min. Non-polar solvent selected from hexane, heptane, cyclohexane, ethers such as diisopropyl ether etc. is added and isolated the organic acid salt of Pitavastatin ester of formula VIII. The obtained organic acid salt of Pitavastatin ester of formula VIII is optionally purified using organic solvent or from a mixture of solvent selected from ethanol, methanol, isopropyl alcohol, methyl tert-butyl alcohol, ethyl acetate, isopropyl acetate, tetrahydrofuran, toluene, acetonitrile, water, hexanes, heptane, pentane, cyclohexane etc. Inorganic base selected from sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, lithium hydroxide, lithium bicarbonate, lithium carbonate; in the presence of an organic solvent selected from-ethyl acetate, isopropyl acetate, toluene, tetrahydrofuran, acetonitrile and water is added to obtain Pitavastatin ester free from acid and then treated with aqueous alkali selected from sodium bicarbonate,

potassium bicarbonate, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, lithium hydroxide, lithium bicarbonate, lithium carbonate, etc. to obtain Pitavastatin alkali salt of formula IX, which *in situ* converted to Pitavastatin calcium of formula I by treating with a source of calcium ions selected from calcium chloride, calcium acetate, calcium carbonate.

The invention is illustrated with the following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

EXAMPLE 1

PREPARATION OF METHYL (2E)-3-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3YL]ACRYLATE

Mixture of 2-Cyclopropyl-4-(4-fluorophenyl)quinoline-3-carboxaldehyde (50 g, 0.171 mole) and methyl(triphenylphosphoranylidene)acetate (68.86 g, 0.205 mole) was suspended in isopropyl alcohol (250 ml) at 25-30°C. The contents were heated to 78-82°C during which a clear solution was obtained. The completion of the reaction was confirmed by TLC. After completion of the reaction, the temperature was subsequently lowered to 25-30°C during which product was precipitated out. The product was cooled to 0-5°C, filtered, washed with precooled isopropyl alcohol and dried at 40-45°C under reduced pressure (~20 mm Hg) till water content is < 0.3%.

Yield: 58.0 g (97%).

¹H NMR (CDCl₃, 300 MHz): δ 1.06-1.09 (m, 2H), 1.38-1.40 (m, 2H), 2.37-2.39 (m, 1H), 3.73 (s, 3H), 6.04 (d, J = 16.2 Hz, 1H), 7.19-7.25 (m, 4H), 7.33-7.36 (m, 2H), 7.63-7.66 (m, 1H), 7.78 (d, J = 16.2 Hz, 1H), 7.96 (d, J = 8.7 Hz, 1H).

EXAMPLE 2

PREPARATION OF (2E)-3-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-2-PROPENAL

Methyl (2E)-3-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]acrylate (50 g, 0.144 mole) was dissolved in toluene (600 ml) at 25-30°C. It was cooled to -50 to -60°C under nitrogen atmosphere. Diisobutylaluminium hydride (82 g, ~25% w/w solution in toluene) was added slowly in ~ 2 h by keeping the temperature of the reaction mass between -50°C and -60°C. The completion of the reaction was confirmed by TLC

and thereafter, water (300 ml) was added to the above reaction mass slowly in ~30 min at -50°C and temperature was raised to 25-30°C. The precipitated inorganic salt was filtered through hyflow. From the filtrate, toluene layer was separated and the aqueous layer was extracted with toluene (300 ml). The combined toluene layer was washed with water. Thereafter the toluene layer was partially concentrated to control the water content below 0.1% w/w. Manganese dioxide (100 g) was added to the above partially distilled toluene layer and stirred at 25-30°C for ~24 h. Thereafter the reaction mass was filtered and the residue was washed with preheated toluene (2 × 150 ml). The filtrate was concentrated at 35-45°C. The crude mass obtained was crystallized from hexanes (250 ml) and dried at 40-45°C till the loss on drying is less than 3% w/w.

Yield: 45 g (99.80%).

¹H NMR (CDCl₃, 300 MHz): δ 1.08-1.34 (m, 2H), 1.42-1.61 (m, 2H), 2.33-2.36 (m, 1H), 6.56-6.49 (m, 1H), 7.22-7.27 (m, 4H), 7.27-7.37 (m, 2H), 7.56 (d, J = 15.6 Hz, 7.66-7.97 (m, 1H), 7.99 (d, J = 6 Hz, 1H), 9.50, (d, J = 7.8 Hz, 1H).

EXAMPLE 3

PREPARATION OF (1S)-2-HYDROXY-1,2,2-TRIPHENYLETHYL (3S,4E)(3R,4E)-5-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3-HYDROXY-4-PENTENOATE

Hexamethyldisilazane (73.31 g, 0.454 mole) was added to n-butyl lithium (272 ml, ~15% w/w solution in hexanes) at 0-5°C over a period of ~15 min and thereafter temperature was raised to 20-30°C and stirred for 30 min. The above contents were diluted with tetrahydrofuran (450 ml) and the reaction mass was cooled to -35°C. A slurry of (2S)-2-acetoxy-1,1,2-triphenylethanol (83.78 g, 0.252 mole) in tetrahydrofuran (400 ml) was added to the above reaction mass. Thereafter, the temperature of the reaction mass was increased to -15°C and stirred for 1 h at this temperature. Subsequently, the temperature was lowered to -75°C and a solution of (2E)-3-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-2-propenal (45 g, 0.142 mole) in tetrahydrofuran (200 ml) was added slowly over a period of 1 h keeping the temperature between -75°C to -80°C. After addition, stirring was continued for 15 min and progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was quenched by adding ~5N hydrochloric acid (500 ml).

The organic layer was separated and aqueous layer was extracted with ethyl acetate (250 ml). The combined organic layer was washed with water (250 ml) and evaporated to obtain the product as a solid residue.

Yield: 115 g.

EXAMPLE 4

PREPARATION OF (3*S*,4*E*)-5-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINO-LIN-3-YL]-3-HYDROXYPENTENOIC ACID, (R)- α -METHYLBENZYLAMINE SALT

(1*S*)-2-Hydroxy-1,2,2-triphenylethyl (3*S*,4*E*)(3*R*,4*E*)-5-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3-hydroxy-4-pentenoate (115 g, crude) was suspended in tetrahydrofuran (500 ml) and ~1M sodium hydroxide (520 ml) was added slowly to the above suspension. The reaction mass was stirred at 20-30°C for ~24 h. The completion of the reaction was confirmed by TLC. Thereafter, solvent was evaporated and water (500 ml) was added to it. The resulting aqueous layer was extracted with methylene chloride (2 x 250 ml) at 25-30°C. The pH of the resulting aqueous layer was lowered to 1.5 to 2 with aqueous hydrochloric acid and the product was extracted with methylene chloride (2 x 250 ml). The combined methylene chloride extracts was washed with water (250 ml) and solvent was evaporated. The residue obtained was dissolved in acetonitrile (600 ml) and (R)- α -Methylbenzyl amine (17.0 g) was added to it. The product precipitated was filtered, washed with acetonitrile (950 ml) and dried at 40-45°C under reduced pressure for 8 h.

Yield: 65 g (92.8%).

¹H NMR (300 MHz, DMSO-*d*⁶ + D₂O): δ 1.06-1.09 (m, 2H), 1.19 (brs, 1H), 1.46 (d, J = 6 Hz, 3H), 1.81-1.98 (m, 2H), 2.47-2.50 (m, 1H), 4.21-4.31 (m, 2H), 5.62 (dd, J = 12 Hz, 6 Hz, 1H), 6.49 (d = 15 Hz, 1H), 7.28-7.44 (m, 11H), 7.64-7.69 (m, 1H), 7.89 (d, J = 6Hz, 1H).

EXAMPLE 5

PREPARATION OF (2*S*,3*E*)-4-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-2-(*tert*-BUTYLDIMETHYLSILOXY)-1-CARBONYLIMIDAZOL-3-BUTENE

Part A: (3*S*,4*E*)-5-[2-Cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3-hydroxy pentenoic acid, (R)- α -methylbenzylamine salt (50 g) was suspended in a mixture of methylene chloride (150 ml) and water (150 ml) and cooled the suspension to 0-5°C. The contents were acidified with ~1N hydrochloric acid (~100 ml) to pH 2.0 – 2.5.

Thereafter, the temperature of the reaction mass was raised to 20-30°C and methylene chloride layer was separated. The aqueous layer was extracted with methylene chloride (150 ml) and the combined methylene chloride extracts was washed with water (250 ml). The washed methylene chloride layer was concentrated to obtain a viscous oily residue.

Part B: Anhydrous potassium iodide (41.66 g) was suspended in N,N-dimethylformamide (160 ml) at 25-30°C under nitrogen atmosphere. tert-butyldimethylsilyl chloride (37.65 g) was added to the above suspension and temperature was raised to 60-65°C. It was stirred for 45 min at 60-65°C and triethyl amine (30.42 g) was added to it slowly over a period of 30 min. The part A product was dissolved in N,N-dimethylformamide (100 ml) and added to the above reaction mass at 60-65°C. The reaction mass was stirred for 30 min and the completion of the reaction was confirmed by TLC. Thereafter it was quenched by pouring into pre-cooled water (1.0 Lt, 0-5°C). The temperature was raised to 20-30°C and the product was extracted with toluene (2 x 250 ml). The combined toluene extracts was washed with ~0.35% w/v aqueous hydrochloric acid (250 ml). Finally, it was washed with water (250 ml) and evaporated to obtain the product as an oily residue.

Part C: The Part B product was dissolved in methylene chloride at 25-30°C and cooled to 15-20°C. Carbonyldiimidazole (48.80 g) was dissolved in methylene chloride (500 ml) and added to the above reaction mass over a period of 15 min. at 15-20°C. The stirring was continued at this temperature for ~ 3h and the completion of the reaction was confirmed by TLC. Thereafter it was quenched by pouring into pre-cooled water (1.0 Lt, 2-5°C). The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (250 ml). The combined methylene chloride layer was washed with water (250 ml), with ~5% w/w aqueous citric acid solution and finally with water (250 ml). The methylene chloride layer was concentrated at 40-45°C under vacuum to obtain the product as an oily residue.

Yield: ~60 g.

EXAMPLE 6**PREPARATION OF ETHYL (5*S*,6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-5-(*tert*-BUTYLDIMETHYLSILYLOXY)-3-OXO-6-HEPTENOATE**

Under nitrogen atmosphere, zinc oxide (16.26 g) was suspended in toluene (300 ml) at 25-30°C. Mono-Ethyl malonate (79.5 g) in tetrahydrofuran (100 ml) was added to the above suspension in one lot and the mixture was stirred for 2 h at 25-30°C during which a clear solution was obtained. The solvents were evaporated and the concentrated mass was re-dissolved in toluene (250 ml). (2*S*,3*E*)-4-[2-Cyclopropyl-4-[4-fluorophenyl]quinoline-3-yl]-2-(*tert*-butyldimethylsilyloxy)-1-carbonylimidazol-2-butene (~60 g, - as obtained from example 4) was dissolved in tetrahydrofuran (250 ml) and added to the above zinc monoethyl malonate complex. The reaction mass was stirred for ~12 h and the completion of the reaction was confirmed by TLC. Thereafter water (1.0 Lt) was added to it. The organic layer was separated and the aqueous layer was extracted with toluene (250 ml). The combined organic layer was washed with water (250 ml) and evaporated to obtain the product as an oily mass.

Yield: ~55 g.

EXAMPLE 7**PREPARATION OF ETHYL (5*S*, 6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-5-HYDROXY-3-OXO-6-HEPTENOATE**

Ethyl (5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-5-(*tert*-butylsilyloxy)-3-oxo-6-heptenoate (~55g) was dissolved in acetonitrile (750 ml) and cooled the solution to -10°C. Hydrochloric acid (~35% w/w, 17 ml) was added slowly to it. The reaction mass was stirred at this temperature for ~ 4h and the completion of the reaction was confirmed by TLC. Thereafter pH of the reaction mass was raised to 7.5 to 7.0 by adding ~7% w/w aqueous sodium bicarbonate solution. The reaction mass was diluted with ethyl acetate (500 ml) and temperature of the reaction mass was raised to 15-20°C. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (250 ml) and the combined organic layer was washed with water. Solvent was evaporated to obtain a viscous residue which was re-dissolved in toluene (250 ml), washed with ~2% w/w aqueous potassium carbonate

solution (2 x 75 ml) and finally with water (75 ml). The toluene layer was concentrated under vacuum to obtain the product as viscous residue which was subsequently crystallized from ethyl acetate- hexane (2:8 ; v/v). The product was dried under vacuum at 40-45°C till the loss on drying is $\leq 0.5\%$ w/w.

Yield: 32.5 g (73%).

¹H NMR (CDCl₃, 300 MHz): δ 1.01-1.05 (m, 2H), 1.26-1.35 (m, 5H), 2.34-2.39 (m, 1H), 2.53-2.55 (m, 2H), 2.67-2.68 (m, 1H), 3.42 (s, 2H), 4.17-4.24 (q, J = 7.2 Hz, 2H), 4.59 (brs, 1H), 5.58 (dd, J = 16.2 Hz, 5.7 Hz, 1H), 6.67 (dd, J = 16.2 Hz, 1.2 Hz), 7.17-7.35 (m, 6H), 7.56-7.61 (m, 1H), 7.95 (d, J = 8.4 Hz, 1H).

EXAMPLE 8

PREPARATION OF ETHYL (3R,5S,6E)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOATE

Under nitrogen atmosphere, a mixture of tetrahydrofuran (900 ml), ethyl acetate (75 ml) and methanol (200 ml) was cooled to -80°C. Diethylmethoxyborane (50% w/w solution in tetrahydrofuran, 15.0 g) was added to the above mixture of solvents at -75°C to -80°C. Sodium borohydride (3.8 g) was added to the above reaction mass and thereafter a solution of ethyl (5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3-oxo-6-heptenoate (30 g) dissolved in a mixture of tetrahydrofuran (75 ml), ethyl acetate (45 ml) and methanol (30 ml) was added to the above reaction mass maintaining the temperature between -80°C to -75°C. The reaction mass was stirred at this temperature for ~ 5h and the completion of the reaction was confirmed by TLC. Thereafter, acetone (45 ml) was added to quench the reaction. Acetic acid (30 ml) was added to the reaction mass and temperature was raised to -30°C. Thereafter, water (750 ml) and ethyl acetate (750 ml) were added to it. ~20% w/w Sodium chloride solution (75 ml) was added to the above content to facilitate the separation of the layers. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (9500 ml). The combined organic extracts was washed with water (500 ml) followed by ~7% w/w aqueous sodium bicarbonate (500 ml). The ethyl acetate layer was concentrated under vacuum at 40-45°C to obtain the crude product. It was co-distilled with methanol (80 ml X 2) and finally with n-heptane (80 ml). The residue obtained after distillation was dissolved in ethyl acetate (50 ml) and ethanol (25 ml) at 20-30°C. n-Heptane (200 ml) was added to it for crystallization. The

product was filtered, washed with n-heptane (25 ml) at 0-5°C and dried at 40-45°C under vacuum for 8 h till the loss on drying is less than 0.5% w/w.

Yield: 25 g (83%).

¹H NMR (CDCl₃, 300 MHz): δ 1.01-1.05 (m, 2H), 1.27-1.43 (m, 7H), 1.44-1.61 (m, 1H), 2.38-2.44 (m, 2H), 4.11-4.21 (m, 3H), 4.22-4.32 (m, 1H), 5.60-5.65 (m, 1H), 6.63 (d, J = 15 Hz, 1H), 7.17-7.56 (m, 6H), 7.56-7.60 (m, 1H), 7.95 (d, J = 8 Hz, 1H).

EXAMPLE 9

PREPARATION OF (3*R*,5*S*,6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOIC ACID, CALCIUM SALT

Ethyl (3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl]-3,5-dihydroxy-6-heptenoate (25 g, 0.055 mole) was suspended in ethanol (125 ml) and cooled to 0-5°C. Sodium hydroxide (2.28 g, 97% w/w assay, 0.055 mole) in water (50 ml) was added to the above suspension at 0-5°C and stirred for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, solvent was evaporated and water (240 ml) was added to it. The resulted aqueous layer was extracted with methyl tert-butyl ether (2 x 50 ml). Carbon (1 g) was added to the aqueous layer and stirred for 30 min. It was filtered through hyflo and a solution of calcium chloride (4.5 g, dihydrate, 0.030 mole) in water (25 ml) was added to it. The Pitavastatin calcium, which precipitated out was filtered and washed with water (2 x 25 ml). The product was dried under vacuum at 40-45°C for 8 h.

Yield: 22 g (90%).

EXAMPLE 10

PREPARATION OF ETHYL (3*R*,5*S*,6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOATE

A solution of diethylmethoxyborane in tetrahydrofuran (8.95 g, 50% solution, 0.044 mole) was added to a cold mixture of tetrahydrofuran (300 ml), methanol (65 ml) and ethyl acetate (25 ml) at -75°C to -80°C. Sodium borohydride (1.36 gm, 0.033 mole) was added to the above solution in one lot and stirred for 5 min. at the same temperature. Thereafter, a solution of Ethyl (5*S*,6*E*)-3-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3-hydroxy-5-oxo-6-heptenoate (10 gm, 0.022 mole)

prepared in a mixture of tetrahydrofuran, (25 ml), methanol (10 ml) and ethyl acetate (5 ml) was added to the above reaction mixture, while maintaining the temperature at -75°C to -80°C. The reaction mass was further stirred at the same temperature till starting material content less than 0.1% monitored by qualitative HPLC. Thereafter, excess borohydride was quenched by adding acetone (15 ml) and thereafter acetic acid (10 ml) was added to it. The reaction mass was diluted with water and brought to 25-30°C. The product was extracted using ethyl acetate (2 x 250 ml) and the combined organic extract was washed with saturated sodium bicarbonate (250 ml) followed by with water (250 ml) and aqueous sodium chloride (250 ml). Solvents were removed and the crude Pitavastatin ethyl ester was co-distilled with ethyl acetate.

Yield: 10 gm.

Anti isomer (3*S*,5*S*-Isomer): 0.85%.

EXAMPLE 11

PREPARATION OF ETHYL (3*R*,5*S*,6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOATE, TRIFLUOROACETATE SALT [PITAVASATTIN ETHYL ESTER TRIFLUOROACETATE SALT]

The crude Pitavastatin ethyl ester (10 gm, 0.022), as obtained from example 10, was dissolved in ethyl acetate (50 ml) and cooled to 0-5°C. Trifluoacetic acid (1.89 ml, 0.024 mole) was added to the above solution maintaining the temperature below 5°C. The reaction mixture was stirred for 15 min. at 0-5°C and thereafter temperature was raised to 20-30°C. Heptane (10 ml) was added to it and stirred for 1 hr. The precipitated trifluoroacetate salt of Pitavastatin ethyl ester was isolated by filtration.

Yield: 6 gm.

Anti isomer (3*S*,5*S*-Isomer): 0.38%

EXAMPLE 12

PREPARATION OF ETHYL (3*R*,5*S*,6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOATE, TRIFLUOROACETATE SALT [PITAVASATTIN ETHYL ESTER TRIFLUOROACETATE SALT]

The crude Pitavastatin ethyl ester (10 gm, 0.022 mole, anti isomer: 0.85%), was dissolved in a mixture of ethyl acetate (25 ml) and ethanol (10 ml). It was cooled to 0-5°C. Trifluoroacetic acid (1.89 ml, 0.024 mole) was added to the above solution maintaining the temperature below 5°C. The reaction mixture was stirred for 15 min at 0-5°C and thereafter temperature was raised to 20-30°C. Heptane (150 ml) was added to it and stirred for 1 hr. The precipitated Pitavastatin ethyl ester trifluoroacetate salt was isolated by filtration.

Yield: 8.6 gm.

Anti isomer (3*S*,5*S*-Isomer): 0.60%.

¹H NMR (300 MHz, CDCl₃): δ 1.28 -1.39 (m, 7H), 1.69-1.71 (m, 2H), 2.42-2.45 (m, 2H), 2.52-2.55 (m, 1H), 4.15-4.22 (m, 3H), 4.40-4.43 (m, 1H), 5.63 (dd, J = 18, 6 Hz, 1H), 6.62 (d, J = 18 Hz, 1H), 7.24-7.49 (m, 4H), 7.52-7.56 (m, 2H), 7.81-7.83 (m, 1H), 8.46 (d, J= 9 Hz, 1H).

EXAMPLE 13

PREPARATION OF ETHYL (3*R*,5*S*,6*E*)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOATE, TRIFLUOROACETATE SALT [PITAVASATTIN ETHYL ESTER TRIFLUOROACETATE SALT]

The crude Pitavastatin ethyl ester (10 gm, 0.022 mole), as obtained from example 10, was dissolved in a mixture of ethyl acetate (25 ml) and ethanol (15 ml). It was cooled to 0-5°C. Trifluoroacetic acid (1.89 ml, 0.024 mole) was added to the above solution maintaining the temperature below 5°C. The reaction mixture was stirred for 15 min at 0-5°C and thereafter temperature was raised to 20-30°C. Heptane (150 ml) was added to it and stirred for 1 hr. The precipitated Pitavastatin ethyl ester trifluoroacetate salt was isolated by filtration.

Yield: 6.0 gm.

Anti isomer (3*S*,5*S*-Isomer): 0.50%.

¹H NMR (300 MHz, CDCl₃): δ 1.28 -1.39 (m, 7H), 1.69-1.71 (m, 2H), 2.42-2.45 (m, 2H), 2.52-2.55 (m, 1H), 4.15-4.22 (m, 3H), 4.40-4.43 (m, 1H), 5.63 (dd, J = 18, 6 Hz, 1H), 6.62 (d, J = 18 Hz, 1H), 7.24-7.49 (m, 4H), 7.52-7.56 (m, 2H), 7.81-7.83 (m, 1H), 8.46 (d, J= 9 Hz, 1H).

EXAMPLE 14**CRYSTALLIZATION OF PITAVASATTIN ETHYL ESTER, TRIFLUOROACETATE SALT**

The Pitavastatin ethyl ester, trifluoroacetate salt (10 gm, anti isomer: 0.51%) was dissolved in a mixture of ethyl acetate (25 ml) and ethanol (10ml). n-Heptane (150 ml) was added to it slowly over a period of 30 min. at 20-30°C. The product precipitated was further stirred for 2 hr and filtered.

Yield: 6.0 gm.

Anti isomer (3S,5S-Isomer): 0.31%

EXAMPLE 15**PREPARATION OF (3R,5S,6E)-7-[2-CYCLOPROPYL-4-(4-FLUOROPHENYL)-QUINOLIN-3-YL]-3,5-DIHYDROXY-6-HEPTENOIC ACID, CALCIUM SALT [PITAVASATATIN CALCIUM]**

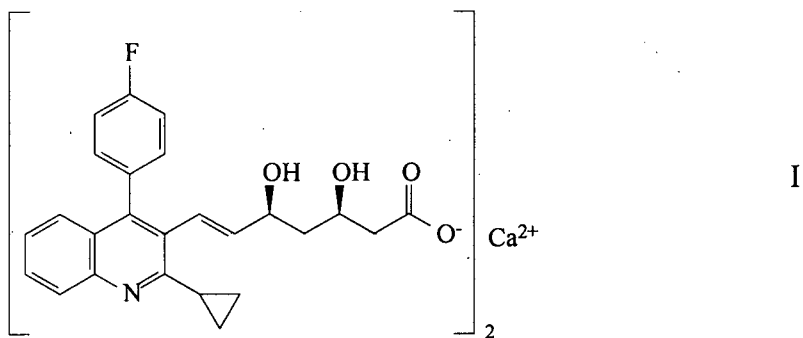
Pitavastatin ethyl ester, trifluoroacetate salt (6 gm, 0.010 mole, Anti isomer: 0.38%) was suspended in water (215 ml) and ethyl acetate (25 ml) and cooled to 0-5°C. The pH was adjusted to 7.5 with saturated NaHCO₃. The organic layer was separated and washed with water (25 ml). The ethyl acetate layer was concentrated to obtain Pitavastatin ethyl ester having anti content 0.38%. Obtained Pitavastatin ethyl ester was dissolved in ethanol (25 ml) and THF (2.5 ml) and cooled to 0-5°C. ~1N aq. NaOH (11 ml, 0.010 mole) was added to it over a period of 20 min and the hydrolysis of Pitavastatin ethyl ester was monitored by qualitative HPLC till the unhydrolyzed Pitavastatin ethyl ester was less than 0.1%. Thereafter, solvents were evaporated and water (100 ml) was added to it. The resulted solution was extracted once with MTBE (25 ml). The aqueous layer was concentrated partially to ensure complete removal of solvents. Thereafter, the temperature of the aqueous layer was raised to 40-45°C and aqueous Calcium chloride dihydrate solution (0.86 gm. 0.005 mole, dissolved in 25 ml of water) was added to it slowly over a period of 30 min, with slow stirring. The resulted Pitavastatin calcium was further stirred at 20-30°C and was filtered, washed with water (25 ml x 2). The product was dried under vacuum to remove the filtrate for 1 hr and further at 20-30°C till a moisture content of ~10% w/w.

Yield: 3.8 gm.

Anti isomer (3S,5S-Isomer): 0.36%

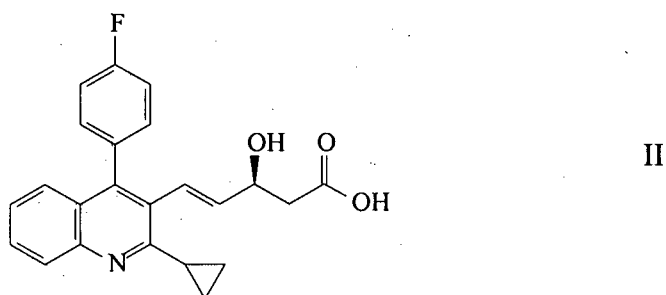
WE CLAIM

1. A process for the preparation of Pitavastatin calcium of formula I,

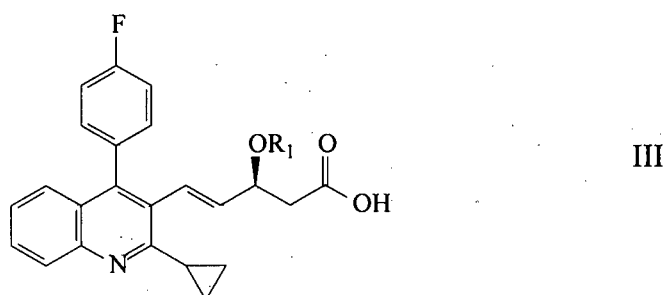


which comprises:

- a) protecting compound of formula II,

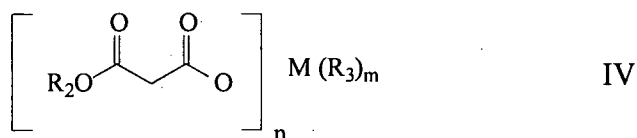


with a suitable hydroxy protecting group in an organic solvent to obtain a compound of formula III,



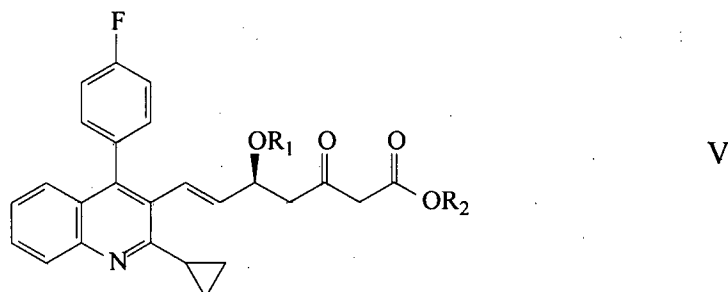
wherein R₁ represents a hydroxy protecting group;

- b) activating the acid group of the compound of formula III with an acid activator, followed by treating the resulting intermediate with a metal complex of formula IV,



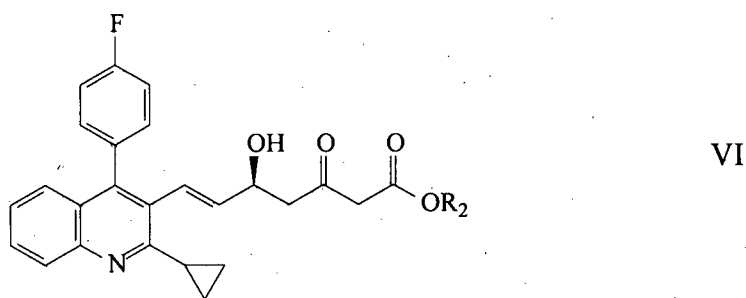
wherein R_2 represents C_{1-4} straight chain or branched chain alkyl, aryl, substituted aryl or aralkyl; M represents Mg, Zn, Ca or Cu; n represents an integer selected from 1-2; R_3 represents alkyl or alkoxy; m represents an integer selected from 0 or 1

in an organic solvent to obtain a compound of formula V,



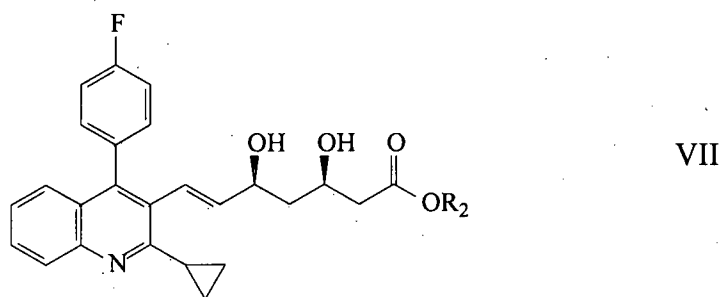
wherein R_1 and R_2 are same as defined above;

- c) deprotecting the compound of formula V with a suitable reagent in a solvent to obtain compound of formula VI,



wherein R_2 is same as defined above;

- d) reducing the compound of formula VI to obtain a compound of formula VII,

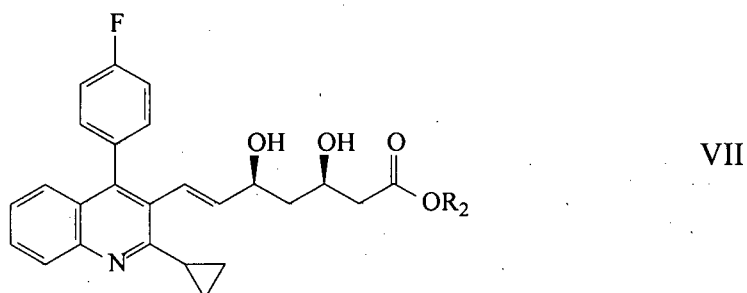


wherein R_2 is same as defined above;

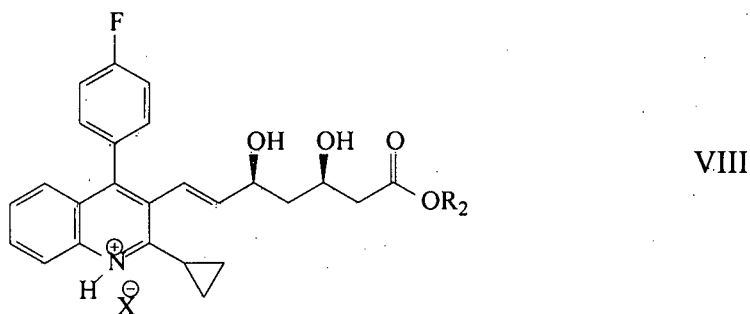
- e) hydrolyzing the compound of formula VII; and
 f) treating the compound obtained in step (e) with calcium salt to give the Pitavastatin calcium of formula I.

2. The process according to claim 1, wherein hydroxy protecting group is selected from the group consisting of tert-butyldimethylsilyl, dihydropyran, trimethylsilyl and methoxymethyl.
3. The process according to claim 1, wherein organic solvent used in step (a) is selected from the group consisting of toluene, N,N-dimethylformamide, dimethylsulfoxide, tetrahydrofuran, dichloromethane, N-methylpyrrolidinone, sulfolane and mixtures thereof.
4. The process according to claim 1, wherein acid activator is selected from the group consisting of 1,1-carbonylimidazole, methyl chloroformate, ethyl chloroformate, phenyl chloroformate, 4-methoxyphenylchloroformate, 2,4-dinitrophenyl chloroformate, 4-trifluoromethylchloroformate and 4-nitrophenylchloroformate.
5. The process according to claim 1, wherein step (b) is carried out in an organic solvent selected from the group consisting of tetrahydrofuran, acetonitrile, toluene, methyl tert-butyl ether, isopropyl ether and mixtures thereof.
6. The process according to claim 1, wherein compound of formula V is deprotected using suitable reagent selected from the group consisting of acids having a general formula HX, wherein X represents halogen; MX wherein X represent halogen and M is a cation derived from inorganic metals selected from Na⁺, K⁺, Li⁺; organic ammonium salts selected from N⁺(R)₄, wherein R represents C₁-C₄ alkyl, straight or branched chain alkyl; sulphonic acid and organic acid selected from p-toluenesulfonic acid, methanesulfonic acid, trifluoromethanesulfonic acid, formic acid, trifluoroacetic acid, acetic acid.
7. The process according to claim 1, wherein step (c) is carried out in solvent selected from an aqueous solvent or organic solvent selected from tetrahydrofuran, acetonitrile, methanol, ethanol, dichloromethane, ethylene dichloride, toluene, xylene or mixtures thereof.

8. The process according to claim 1, wherein compound of formula VI is reduced using metal borohydride.
9. The process according to claim 1, wherein compound of formula VII is hydrolysed using a base selected from alkali or alkali earth metal hydroxides.
10. The process according to claim 1, wherein calcium ion source is selected from the group consisting of calcium chloride and calcium acetate.
11. A process for the preparation of Pitavastatin calcium of formula I, comprising:
 - a) reacting compound of formula VII,

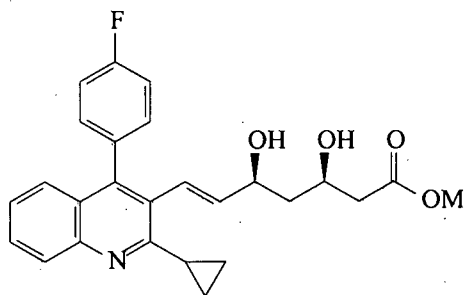


wherein R_2 represents C_{1-4} straight chain or branched chain alkyl, aryl, substituted aryl, aralkyl and X represents monobasic or dibasic acid with an organic acid in the presence of organic solvent to obtain organic acid salt of compound of formula VIII,



wherein R_2 is same as defined above;

- b) optionally, purifying compound of formula VIII using organic solvent;
- c) treating compound of formula VIII with aqueous inorganic base to obtain pure Pitavastatin ester of formula VII;
- d) hydrolyzing the compound of formula VII with a base to obtain the corresponding alkali metal salt of compound of formula IX,



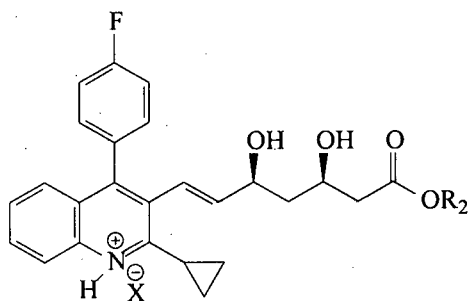
IX

wherein M represents Na, K, Li;

- e) treating compound of formula IX with a calcium source to obtain Pitavastatin calcium of formula I; and
 - f) isolating the Pitavastatin calcium of formula I.
12. The process according to claim 11, wherein organic acid is selected from monobasic, dibasic, or tribasic acid.
 13. The process according to claim 11 or 12, wherein acid is selected from the group consisting of trifluoroacetic acid, trifluoromethane sulfonic acid, acetic acid, methanesulfonic acid, perchloric acid, periodic acid, oxalic acid, mandelic acid, malic acid, tartaric acid, camphorsulfonic acid, benzenesulfonic acid, p-toluenebenzene sulphonic acid and 4-nitrobenzene sulfonic acid.
 14. The process according to claim 11, wherein step (a) is carried out in an organic solvent selected from the group consisting of C₁-C₅ alcohols, C₃-C₈ esters, C₃-C₈ ketones, C₆-C₁₀ aromatic hydrocarbons, ethers, acetonitrile and mixtures thereof.
 15. The process according to claim 11, wherein step (b) is carried out in organic solvent selected from the group consisting of ethanol, methanol, isopropyl alcohol, methyl tert-butyl alcohol, ethyl acetate, isopropyl acetate, tetrahydrofuran, toluene, acetonitrile, water, hexanes, heptane, pentane, cyclohexane and mixture thereof.
 16. The process according to claim 11, wherein step (c) is carried out using inorganic base selected from sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, lithium hydroxide, lithium bicarbonate or lithium carbonate.

17. The process according to claim 11, wherein step (d) is carried out using a base selected from sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, lithium hydroxide, lithium bicarbonate or lithium carbonate.

18. Organic acid salt of compound of formula VIII,



VIII

wherein R_2 represents C_{1-4} straight chain or branched chain alkyl, aryl, substituted aryl, aralkyl and X represents monobasic or dibasic acid.

19. The organic acid salt of compound of formula VIII according to claim 18, wherein acid is selected from the group consisting of trifluoroacetic acid, trifluoromethane sulfonic acid, acetic acid, methanesulfonic acid, perchloric acid, periodic acid, oxalic acid, mandelic acid, malic acid, tartaric acid, camphorsulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 4-nitrobenzene sulfonic acid.