Novel Process for the Preparation of Pravastatin and its Pharmaceutically Acceptable Salts

**Abstract:** Novel Process for the preparation of Pravastatin and its pharmaceutically acceptable salts compound of formula-1 via novel triphenyl phosphonium bromide salt compound of formula-3 or tributyl phosphonium bromide salt compound of formula-7 by employing Wittig reagents. Formula (I): Wherein M is H, Na⁺, K⁺, Mg²⁺, Ca²⁺.

**Title:** NOVEL PROCESS FOR THE PREPARATION OF PRAVASTATIN AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS

**Formula (I):**

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
Novel Process for the preparation of Pitavastatin and its pharmaceutically acceptable salts

Related Applications

This application claims the benefit of Indian patent application number 867/CHE/2006 filed on May 17, 2006, which is incorporated herein by reference.

Field of the Invention

The present invention relates to a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salts, preferably pitavastatin calcium which is chemically known as (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid calcium salt having the following formula- 1

![Formula-1](image)

Wherein M is H, Na+, K+, Mg2+, Ca2+.

Pitavastatin is a synthetic lipid-lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMG-CoA Reductase inhibitor). This enzyme catalyzes the conversions of HMG-CoA to mevalonate, inhibitors are commonly referred to as "statins". Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease. Pitavastatin is used in the treatment of hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type Ha and lib).
The compound of the present invention inhibits the HMG-CoA reductase, which plays a main role in the synthesis of cholesterol, and subsequently they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

**Background of the Invention**

US Patent 5856336 claimed quinoline type mevalonolactones, specifically pitavastatin. The disclosed process using an expensive reagent like sodium hydride, n-butyl lithium and borane derivates, reagents that are difficult to use on a commercial scale.


Our co-pending international application PCT/IN07/000172 describes the process for the preparation of statins free of Z-isomer via julia-olefination.

Accordingly, there remains a need for a novel process for the preparation of quinoline derivatives such as pitavastatin that reduces the problems of the prior art on a commercial scale in a convenient and cost efficient manner.

**Brief description of the Invention**

In accordance with the present invention, a novel process is provided for the preparation of quinoline derivatives such as pitavastatin (HMG-CoA) inhibitors, more specifically, the present invention provides a novel process for the preparation of pitavastatin using Wittig reagents.
The first aspect of the present invention is to provide a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salt compound of formula-1, preferably calcium salt compound of general formula-1, which is chemically known as (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid calcium salt

![Formula-1](image)

Wherein M is H, Na⁺, K⁺, Mg₂⁺, Ca²⁺.

A novel process is provided for the preparation of pitavastatin and its pharmaceutically acceptable salts compound of a general formula-1 via Wittig reaction, which comprises of the following steps

a) Reacting the quinoline-bromo compound of formula-2 with Wittig reagent in a suitable solvent to provide novel bromide salt compound of formula-3,

b) Reacting the novel bromide salt compound of formula-3 with an aldehyde compound of formula-4 in presence of an alkali or alkaline earth metal bases in a suitable polar aprotic solvent to provide an olefin compound of formula-5,

c) The olefinic compound of formula-5 may be used to form a dihydroxy acid by subjecting olefin compound of formula-5 to acidic conditions to remove the acetonide and form diol compound, which upon treating with a base such as an alkali metal hydroxide to form the corresponding alkali metal salt then further treating with an organic amine base to form corresponding organic amine salt compound of formula-6,

d) Converting the organic amine salt compound of formula-6 into its pharmaceutically acceptable salts of the general formula-1 by treating the organic amine compound of general formula-6 with an alkali base followed by treating with corresponding alkali or alkaline earth metal salts in a suitable solvent.
The second aspect of the invention is to provide a novel process for the preparation of calcium salt of statins specifically pitavastatin which comprises of the following steps,

a) Converting the organic amine salt compound of formula-6 into its corresponding alkali salt by treating with an alkali base,

b) Setting the reaction mixture pH to 8.0 to 9.2 by expelling the organic amine followed by extraction or by extracting the organic amine with a suitable solvent or by adding an acid,

c) Adding the aqueous phase of the reaction mixture to a calcium source in a suitable solvent to give free flow calcium salt compound of formula-1.

Wherein M is Ca$^{2+}$

Advantages of the present invention

- The present invention is more economical process on commercial scale because of the use of inexpensive raw materials, such as triphenyl phosphine and alkali/alkaline earth metal bases like carbonate bases.
- Easier and more economical production because of the reaction conditions are simple, like normal temperatures, and using cheaper Wittig reagent instead of Wittig-Horner type reagent and/or pyrophoric n-butyl lithium.
- The present invention provides high yields and highest purity of pitavastatin and its intermediates
- The present invention provides free flow solid of pitavastatin calcium
Detailed description of the Invention

In accordance with the present invention, a novel process is provided for the preparation of quinoline derivatives such as pitavastatin and its pharmaceutically acceptable salts, useful as HMG-CoA inhibitor, more specifically, the present invention provides a novel process for the preparation of Pitavastatin calcium using Wittig reagents.

The first aspect of the present invention is to provide a novel process for the preparation of pitavastatin and its pharmaceutically acceptable salt compound of formula-1, preferably calcium salt, which is chemically known as (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid calcium salt,

Wherein M is H, Na⁺, Mg²⁺, Ca²⁺.

A novel process is provided for the preparation of pitavastatin and its pharmaceutically acceptable salt compound of formula-1 via Wittig reaction, which comprises of the following steps

a) Reacting 3-(bromomethyl)-2-cyclopropyl-4(4'-fluorophenyl) quinoline compound of formula-2,
with wittig reagent like triphenyl phosphine, tributyl phosphine, preferably triphenyl phosphine in a suitable solvent selected from non-polar solvents like toluene, o-xylene, chlorobenzene preferably toluene at a temperature ranging from 80 to 140°C, preferably at 100-110°C to provide a novel triphenyl [2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium bromide salt compound of formula-3,

![Image](image-url)

**Formula-3**

b) Reacting the novel triphenyl[2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium] bromide salt compound of formula-3 with an aldehyde compound of formula-4,

![Image](image-url)

**Formula-4**

in presence of an alkali or alkaline earth metal bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, and cesium carbonate preferably potassium carbonate in a suitable polar aprotic solvent like dimethylformamide, dimethylsulfoxide, dimethylacetamide or mixtures thereof, preferably dimethylsulfoxide at a temperature ranging from 40-80°C preferably at 60-70°C to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-[1,3]-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5,
c) (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5 may be used to form a dihydroxy acid HMG CoA reductase inhibitor by subjecting (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5 to acidic conditions such as using hydrochloric acid, acetic acid, sulfuric acid to remove the acetonide and form diol compound, which upon treating with an alkali base such as sodium hydroxide to form the corresponding sodium salt then further treating with an organic amine base like methyl amine, dicyclohexyl amine, tertiary butyl amine, n-butyl amine and (+/-)-sec-butyl amine to form corresponding organic amine salt compound of general formula-6,

d) Converting the corresponding organic amine salt compound of general formula-6 into its pharmaceutically acceptable salt compound of general formula-1 by treating
the organic amine compound of general formula-6 with an alkali base followed by treating with corresponding alkali or alkaline earth metal salts in a suitable solvent.

\[
\text{Formula-1}
\]

Wherein \(M\) is \(\text{H, Na}^+, \text{K}^+, \text{Mg}^{2+}, \text{Ca}^{2+}\).

The second aspect of the invention is to provide a novel process for the preparation of calcium salt of pitavastatin, which comprises of the following steps.

a) Converting the organic amine salt compound of general formula-6 into its sodium salt by treating with sodium hydroxide,

b) Setting the reaction mixture pH to 8.0 to 9.2 by expelling the organic amine followed by extracting the reaction mixture with a suitable solvent such as ester solvents like ethyl acetate, methyl acetate, tertiary butyl acetate or by extracting the organic amine with a suitable solvent like ester solvents such as ethyl acetate, methyl acetate, tertiary butyl acetate, preferably tertiary butyl acetate to remove organic amine or by adding an acid like hydrochloric acid or acetic acid to set the pH of the reaction mixture to 8.0 to 9.2, preferably 8.5 to 9.2, more preferably 9.0 to 9.2.

c) Adding the aqueous phase of the reaction mixture to a calcium source like calcium chloride or calcium acetate in a suitable solvent like water at a temperature ranging from 25-50°C, preferably at 35-45°C, more preferably at 40-45°C to give free flow calcium salt compound of formula-1.
Wherein $M$ is $Ca^{2+}$

Following three options which are useful to remove the organic amine and to set the pH of the reaction mixture.

> Setting the reaction mixture pH 8.0 to 9.2 by expelling the reaction mixture to remove the traces of organic amine and finally extracting the reaction mixture with suitable solvent to remove the final traces of organic amine

> Or simply extracting the reaction mixture with suitable solvent to remove the complete traces of organic amine and to set the pH of the reaction mixture 8.0 to 9.2.

> Or by adding an acid like acetic acid, hydrochloric acid to the reaction mixture to set the pH 8.0 to 9.2

The addition is carried out at a temperature of between 25 and approximately 50°C, preferably 35-43°C, more preferably between 35 and 45°C, and most preferably at 45°C.

The aqueous phase of the reaction mixture is added at a temperature of between 40 to 45°C over a period of 15 to 45 minutes, the mixture is held at a temperature of between 40-45°C over period of at least 30 minutes.
Particle size of the pitavastatin calcium salt before micronisation is below 200µD (v, 0.9) and below 50µD (v, 0.5), after micronisation the particle size is below 40µD (v, 0.9) and below 20µD (v, 0.5).

The starting material compound of formula-2 process described in US Patents 6627636 and US 5763675.

Particle size of Pitavastatin calcium analyzed using dry powder method by laser technique and the instrument is MALVERN.

The pitavastatin calcium sample is being packed in a white bag with nitrogen or vaccumised nitrogen, the first container being disposed in to a second black bag with nitrogen or vaccumised nitrogen and one oxygen buster sachet, and the second container being disposed in to a third triple laminated aluminum bag with nitrogen or vacuumised nitrogen with one oxygen buster sachet.
The present invention schematically represented by the following scheme.

[Chemical structures and reactions as shown in the image]
The processes described in the present invention were demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Example 1:

**Preparation of Triphenyl[2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl)-phosphonium] bromide compound of formula-3**

Added a solution of 16.1 grams of triphenyl phosphine in 50 ml of toluene to 15 grams of 3-(bromomethyl)-2-(1-cyclopropyl)-4-(4'-fluorophenyl)quinoline compound of formula-2. Heated the reaction mixture to 110°C. Stirred the reaction mixture for 60 minutes at 110°C. Cooled the reaction mixture to 25-35°C. Filtered the solid and washed with hexanes to get the title compound.

Yield: 20 grams
M.R: 218 - 225°C (decomposed)

Example-2:

**Preparation of Tributyl [2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl)-phosphonium] bromide compound of formula-3**

Added a solution of 20 grams of tributyl phosphine in 60 ml of toluene to 15 grams of 3-(bromomethyl)-2-(1-cyclopropyl)-4-(4'-fluorophenyl)quinoline compound of formula-2. Heated the reaction mixture to 110°C. Stirred the reaction mixture for 60 minutes at 110°C. Cooled the reaction mixture to 25-35°C. Filtered the solid and washed with hexanes to get the title compound.

Yield: 19.2 grams
Example -3:

**Preparation of (4R, 6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5**

Added a solution of 2.7 grams tert-butyl-2-((4R,6S)-6-formul-2,2-dimethyl-1,3-dioxan-4-yl)acetate compound of formula-4 in 46 ml of dimethylsulfoxide to a mixture of 5 grams of triphenyl[2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium]bromide compound of formula-3 and 2.88 grams of potassium carbonate. Heated the reaction mixture to 70°C. Stirred the reaction mixture for 3 hours at 70°C. Quenched the reaction mixture with water. Extracted the reaction mixture with toluene. Concentrated the organic phase and isolated the title compound using hexanes.

**Yield:** 13 gram
**M.R:** 105 - 116°C

Example-4:

**Preparation of pitavastatin methyl amine compound of formula-6a**

A mixture of 7.2 grams of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-5 and 216 ml of acetonitrile was cooled to 23-28°C. Added 45.36 ml of 4.75% aqueous hydrochloric acid to the reaction mixture. Stirred the reaction mixture for 2 hours at 23-28°C. Added 21.6 ml of 10% sodium hydroxide solution to the reaction mixture. Stirred the reaction mixture for 2 hours 30 minutes at 25-35°C. Distilled the solvent completely. Quenched the reaction mixture with water and filtered through hyflow. Washed the reaction mixture tertiary butyl acetate and expelled the aqueous phase. Added sodium chloride solution followed by acetonitrile. Cooled the reaction mixture to 0-10°C. Adjusted the pH of the reaction mixture to 4.5 with 10% hydrochloric acid. Stirred the reaction mixture for 1 hour. Separated the organic and aqueous phases. Cooled the organic phase to 0-10°C. Added 2.38 ml of methyl amine to the reaction mixture. Stirred the reaction mixture for 30 minutes at 25-35°C. Distilled the
solvent completely under reduced pressure and isolated the title compound using acetonitrile as a solvent.

Yield: 2.7 gram
M.R: 136 - 143°C

Example-5:

**Preparation of pravastatin tertiary butyl amine compound of formula-6b**

A mixture of 7.2 grams of \((4R,6S)-(E)-6-[2-(2-cyclopropyl-4-fluorophenyl)quinoline-3-yl]-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-5 and 216 ml of acetonitrile was cooled to 23-28°C. Added 45.36 ml of 4.75% aqueous hydrochloric acid to the reaction mixture. Stirred the reaction mixture for 2 hours at 23-28°C. Added 21.6 ml of 10% sodium hydroxide solution to the reaction mixture. Stirred the reaction mixture for 2 hours 30 minutes at 25-35°C. Distilled the solvent completely. Quenched the reaction mixture with water and filtered through hyflow. Washed the reaction mixture tertiary butyl acetate and expelled the aqueous phase. Added sodium chloride solution followed by acetonitrile. Cooled the reaction mixture to 0-10°C. Adjusted the pH of the reaction mixture to 4.5 with 10% hydrochloric acid. Stirred the reaction mixture for 1 hour. Separated the organic and aqueous phases. Cooled the organic phase to 0-10°C. Added 2.38 ml of tertiary butyl amine to the reaction mixture. Stirred the reaction mixture for 30 minutes at 25-35°C. Distilled the solvent completely under reduced pressure and isolated the title compound using acetonitrile as a solvent.

Yield: 2.4 grams

Example-6:

**Preparation of pravastatin n-butyl amine compound of formula-6c:**

A mixture of 7.2 grams of \((4R,6S)-(E)-6-[2-(2-cyclopropyl-4-fluorophenyl)quinoline-3-yl]-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-5 and 216 ml of acetonitrile was cooled to 23-28°C. Added 45.36 ml of 4.75% aqueous hydrochloric acid to the reaction mixture. Stirred the
reaction mixture for 2 hours at 23-28°C. Added 21.6 ml of 10% sodium hydroxide solution to the reaction mixture. Stirred the reaction mixture for 2 hours 30 minutes at 25-35°C. Distilled the solvent completely. Quenched the reaction mixture with water and filtered through hyflow. Washed the reaction mixture tertiary butyl acetate and expelled the aqueous phase. Added sodium chloride solution followed by acetonitrile. Cooled the reaction mixture to 0-10°C. Adjusted the pH of the reaction mixture to 4.5 with 10% hydrochloric acid. Stirred the reaction mixture for 1 hour. Separated the organic and aqueous phases. Cooled the organic phase to 0-10°C. Added 2.38 ml of n-butyl amine to the reaction mixture. Stirred the reaction mixture for 30 minutes at 25-35°C. Distilled the solvent completely under reduced pressure and isolated the title compound using acetonitrile as a solvent.

Yield: 2.5gram

Example-7:

**Preparation of pravastatin calcium compound of formula-1:**

A solution of 2 grams of pitavastatin methyl amine compound of formula-6a in 12 ml of water was cooled to 25-30°C. Added 2 ml of 8% aqueous sodium hydroxide solution at 25-30°C. Stirred the reaction mixture for 1 hour at 25-30°C. Washed the reaction mixture with tertiary butyl acetate and expelled the solvent completely under nitrogen atmosphere. Filtered the reaction mixture through filter paper. The aqueous phase of the reaction mixture was added to a solution of 0.4 grams of calcium chloride dihydrate in 2 ml of water in 15 minutes at 45°C. Stirred the reaction mixture for 30 minutes. Filtered the solid and washed with water to get the title compound.

Yield: 2.5gram

Example-8:

**Preparation of pitavastatin calcium compound of formula-1:**

A solution of 2 grams of pitavastatin tertiarybutyl amine compound of formula-6b in 12 ml of water was cooled to 25-30°C. Added 2 ml of 8% aqueous sodium hydroxide solution at 25-30°C. Stirred the reaction mixture for 1 hour at 25-30°C. Washed the reaction mixture with tertiary butyl acetate and expelled the solvent completely under
nitrogen atmosphere. Filtered the reaction mixture through filter paper. The aqueous phase of the reaction mixture was added to a solution of 0.4 grams of calcium chloride dihydrate in 2 ml of water in 15 minutes at 45°C. Stirred the reaction mixture for 30 minutes. Filtered the solid and washed with water to get the title compound.

Yield: 2.45 gram

Example-9:

Preparation of pitavastatin calcium compound of formula-1:

A solution of 2 grams of pitavastatin n-butyl amine compound of formula-6c in 12 ml of water was cooled to 25-30°C. Added 2 ml of 8% aqueous sodium hydroxide solution at 25-30°C. Stirred the reaction mixture for 1 hour at 25-30°C. Washed the reaction mixture with tertiary butyl acetate and expelled the solvent completely under nitrogen atmosphere. Filtered the reaction mixture through filter paper. The aqueous phase of the reaction mixture was added to a solution of 0.4 grams of calcium chloride dihydrate in 2 ml of water in 15 minutes at 45°C. Stirred the reaction mixture for 30 minutes. Filtered the solid and washed with water to get the title compound.

Yield: 2.35 gram
We Claim:

1. A Novel process for preparing Pitavastatin and its pharmaceutically acceptable salt compound of general formula-1,

Wherein M is H, Na⁺, K⁺, Mg⁺², Ca⁺²
which comprises of the following steps

a) Reacting 3-(bromomethyl)-2-cyclopropyl-4(4'-fluorophenyl) quinoline compound of formula-2,

with wittig reagent like triphenyl phosphine, tributyl phosphine, preferably triphenyl phosphine in a suitable solvent selected from non-polar solvents like toluene, o-xylene, chlorobenzene preferably toluene at a temperature ranging from 80 to 140°C, preferably at 100-110°C to provide a novel triphenyl[2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium] bromide salt compound of formula-3,
b) Reacting the novel triphenyl[2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium] bromide salt compound of formula-3 with an aldehyde compound of formula-4,

in presence of an alkali or alkaline earth metal bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, and cesium carbonate preferably potassium carbonate in a suitable polar aprotic solvent like dimethylformamide, dimethylsulfoxide, dimethylacetamide or mixtures thereof, preferably dimethylsulfoxide at a temperature ranging from 40-80°C preferably at 60-70°C to provide (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5,
c) (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5 may be used to form a dihydroxy acid HMG CoA reductase inhibitor by subjecting (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-5 to acidic conditions such as using hydrochloric acid, acetic acid, sulfuric acid to remove the acetonide and form diol compound, which upon treating with an alkali base such as sodium hydroxide to form the corresponding sodium salt then further treating with an organic amine base like methyl amine, dicyclohexyl amine, tertiary butyl amine, n-butyl amine, (+/-)-sec-butyl amine to form corresponding organic amine salt compound of formula-6,

\[
\begin{align*}
\text{Formula-6} & \\
\end{align*}
\]

\text{Organic amine}

d) Converting the corresponding organic amine salt compound of formula-6 into its pharmaceutically acceptable salt compound of general formula-1 by treating the organic amine compound of formula-6 with an alkali base followed by treating with corresponding alkali or alkaline earth metal salts in a suitable solvent,

\[
\begin{align*}
\text{Formula-1} & \\
\end{align*}
\]

Wherein \( M \) is \( H, Na^+, K^+, Mg^{+2}, Ca^{+2} \).
2. The process of claim Ia), wherein the Wittig reagent is triphenyl[-2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium] bromide salt compound of formula-3.

\[
\begin{align*}
\text{Formula-3} \\
\end{align*}
\]

3. The process of claim Ia), wherein the Wittig reagent is tributyl[-2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl]-phosphonium] bromide salt compound formula-7.

\[
\begin{align*}
\text{Formula-7} \\
\end{align*}
\]

4. The process of claim Ib), wherein the base is selected from the group consisting of alkali metal carbonates, alkali metal hydroxides and mixtures thereof, preferably alkali metal carbonates selected from sodium carbonate, potassium carbonate, magnesium carbonate and mixtures thereof, more preferably potassium carbonate.

5. The process of claim Ia), wherein the reaction is carried out at a temperature of about 80-120°C, preferably at a temperature of 100-110°C.
6. The process of claim Ib), wherein the reaction is carried out at a temperature of above 40-80°C, preferably at a temperature of 60-70°C.

7. The process of claim Ib), wherein the reaction is carried out in one or more polar aprotic solvents like dimethylformamide, dimethylsulfoxide, dimethylacetamide or mixtures thereof, preferably dimethyl sulfoxide.

8. The organic amine salt compound according to claim Ic) is (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid methyl amine salt compound of formula-6a.

![Formula-6a](image)

9. The organic amine salt compound according to claim Ic) is (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid tertiary butyl amine salt compound of formula-6b.

![Formula-6b](image)

10. The organic amine salt compound according to claim Ic) is (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid n-butyl amine salt compound of formula-6c.
11. The organic amine salt compound according to claim 1c) is (3R, 5S)-7-[(2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid (+/-)-sec-butyl amine salt compound of formula-6d.


![Formula-7](image)

15. A Novel process for the preparation of calcium salt of pitavastatin compound of formula-1,

![Formula-1](image)

Wherein M is Ca$^{2+}$

which comprises of the following steps,

a) Converting the organic amine salt compound of formula-6 into its sodium salt by treating with sodium hydroxide,

b) Setting the reaction mixture pH to 8.0 to 9.2 by expelling the organic amine followed by extracting the reaction mixture with a suitable solvent such as ester solvents like ethyl acetate, methyl acetate, tertiary butyl acetate or by extracting the organic amine with a suitable solvent like ester solvents ethyl acetate, methyl acetate, tertiary butyl acetate, preferably tertiary butyl acetate to remove organic amine or by adding an acid like hydrochloric acid or acetic acid to set the pH of the reaction mixture to 8.0 to 9.2, preferably 8.5 to 9.2, more preferably 9.0 to 9.2,
c) Adding the aqueous phase of the reaction mixture to a calcium source like calcium chloride or calcium acetate in a suitable solvent like water at a temperature ranging from 25-50°C, preferably at 35-45°C, more preferably at 40-45°C to give free flow calcium salt compound of formula-1.

16. The process according to claim 15 b), pH of the reaction mixture is 8.0 to 9.2, preferably 8.5 to 9.2, more preferably 9.0 to 9.2.

17. Addition of aqueous phase of the reaction mixture according to claim 15 c), wherein the addition is carried out at a temperature of between 25 and approximately 50°C, preferably 35-43°C, more preferably between 35 and 45°C, and most preferably at 45°C.

18. Addition of aqueous phase of the reaction mixture according to claim 15 c), wherein the aqueous phase of the reaction mixture is added at a temperature of between 40-45°C over a period of 15 to 45 minutes, the mixture is held at a temperature of between 40-45°C over period of at least 30 minutes.