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PROCESS FOR PREPARATION OF ROSUVASTATIN CALCIUM

(57) Abstract:
Disclosed is the process for the preparation of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I), which is the intermediate of rosuvastatin calcium. Purification of substantially pure acetone protected tert-butyl ester of rosuvastatin (II) and its use for the preparation of substantially pure amorphous rosuvastatin calcium are also disclosed.
PROCESS FOR PREPARATION OF ROSUVASTATIN CALCIUM

FIELD OF INVENTION

The present application relates to a process for the preparation of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I)

![Chemical Structure](image)

which is an intermediate in the synthesis of rosuvastatin.

The present application also relates to a process for the preparation of substantially pure acetonide protected tert-butyl ester of rosuvastatin (II)

![Chemical Structure](image)

and its use for the preparation of substantially pure amorphous rosuvastatin calcium.

INTRODUCTION

Rosuvastatin calcium (XVII) is a well known HMG-CoA reductase inhibitor which is used for the treatment of hypercholesterolemia.
Hirai et al. U.S. Patent No. USRE 37, 314 E1 discloses rosuvastatin and its pharmaceutically acceptable salts. The patent teaches a process for the preparation of pyrimidine aldehyde of formula (I) and also a process for preparing rosuvastatin using pyrimidine aldehyde of formula (I).

Huang et al. WO 2008/151510 A1 discloses a process for the preparation of pyrimidine aldehyde of formula (I) as shown in Scheme 1.

Scheme 1: Preparation of pyrimidine aldehyde (XVII) as disclosed in WO 2008/151510 A1

Taylor et al. U.S. Patent No. 6,844,437 B1 discloses a process for the preparation of rosuvastatin calcium as outlined in Scheme 2. In this method, the diphenyl phosphine oxide is coupled with an aldehyde in presence of a base to provide the acetonide protected tert-butyl ester. The acetonide protecting group is then cleaved in an acidic medium and the tert-butyl group is cleaved in a basic medium and the resulting sodium salt is treated with methylamine to obtain a methyl ammonium salt of rosuvastatin. Rosuvastatin calcium is prepared from the methyl ammonium salt via its sodium salt.
Scheme 2: Preparation of rosuvastatin calcium (XVII) as disclosed in U.S. Patent No. 6,844,437 B1

Marine et al. PCT Publication No. WO07/125547A2 discloses a process for the preparation of rosuvastatin as shown in Scheme 3. The process involves Julia-Kocienski olefination reaction between a pyrimidine sulfone and a chiral aldehyde to provide acetonide protected tert-butyl ester of rosuvastatin of formula (II). First the acetonide group of compound of formula (II) is hydrolyzed by acid and then the ester group is hydrolyzed with base to provide rosuvastatin acid which is then treated with tert-butylamine to provide tert-butylamine salt of rosuvastatin. Tert-butyl amine salt of rosuvastatin is first treated with sodium hydroxide followed by calcium acetate to provide rosuvastatin calcium (XVII).
SUMMARY

One aspect of the present application relates to a process for preparation of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I) as shown in scheme 4.

Another aspect of the present application relates to the use of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I), for preparing rosuvastatin.
Yet another aspect of the present application relates to purification of acetonide protected tert-butyl ester of rosuvastatin (II).

Still another aspect of the present application relates to substantially pure compound of formula (II) free from any impurity, specifically free from the impurity at RRT $1.07 \pm 0.02$ designated as Impurity A.

Another aspect of the present application relates to crystalline acetOnide protected tert-butyl ester of rosuvastatin (II) having an XRPD pattern with peaks at $2\theta = 6.80, 7.60, 11.24, 15.24, 19.14$ and $21.42 \pm 0.2^\circ$.

Still another aspect of the present application relates to a process for the preparation of substantially pure amorphous rosuvastatin calcium using substantially pure compound of formula (II) as an intermediate.
Yet another aspect of the present application relates to a process for the preparation of substantially pure amorphous rosuvastatin calcium comprising:

a) removal of dihydroxy protecting group of pure acetonide protected tert-butyl ester of rosuvastatin (II) prepared by a process of claim 11 in an acidic medium;

b) hydrolyzing the tert-butyl ester group of the product of step a) in a basic medium;

c) converting the product of step b) to tert-butyl amine salt of rosuvastatin;

e) optionally purifying tert-butyl amine salt of rosuvastatin;

f) treating tert-butyl amine salt of rosuvastatin with alkali metal hydroxide and

g) treating the product of step f) with an aqueous solution of calcium chloride.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Fig. 1 shows the PXRD of acetonide protected tert-butyl ester of rosuvastatin of formula (II).

**DETAILED DESCRIPTION**

In accordance with the present application, a process is provided for preparing 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I), which may be used as an intermediate for preparing rosuvastatin.

In one aspect, the present application provides a process comprising dehydration and halogenation, in any order or simultaneously, of the hydroxy pyrimidine compound of formula (VII) to give halogenated compound of formula (VIII):
wherein \( X \) is halogen and selected from a group of chloro, bromo and iodo.

In another aspect, the present application provides a process further comprising preparation of hydroxy pyrimidine compound of formula (VII) by oxidation of dihydropyrimidine ketone of formula (VI) in a suitable solvent.

\[
\text{(VI) \xrightarrow{\text{Oxidation}}} \text{(VII)}
\]

In yet another aspect, the present application provides a process further comprising the preparation of dihydropyrimidine ketone of formula (VI) by amidation of the compound of formula (III) followed by condensation with 4-fluorobenzaldehyde in presence of urea and metal salt in suitable solvent.

\[
\text{(III) \xrightarrow{\text{Amidation}}} \text{(IV) \xrightarrow{\text{Metal salt}}} \text{(V) \xrightarrow{}} \text{(VI)}
\]

wherein \( R \) is \( \text{C1-C6 alkyl, C6-C14 aryl, or C6-C14 (aryl)alkyl.} \)

In still another aspect, the present application provides a process further comprising reaction of halogenated compound of formula (VIII) with N-methylmethanesulfonamide in presence of a base and in a suitable solvent to give 2-(N-methyl-methanesulfonyl amino)pyridine compound of formula (IX).

\[
\text{(VIII) \xrightarrow{\text{NHMe}}} \text{(IX)}
\]
In another aspect, the present application provides a process further comprising reduction of the 2-(N-methyl-methanesulfonyl amino)pyridine compound of formula (IX) by reaction with a reducing agent in a suitable solvent to give 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I).

\[
\begin{align*}
&\text{(IX)} \quad \text{Reduction} \quad \text{(I)} \\
\end{align*}
\]

In still another aspect, the present application provides a process for the preparation of the compound of Formula (I) comprising:

a) amidation of compound of formula (III)

\[
\text{(III)}
\]

followed by condensation with 4-flurobenzaldehyde in presence of urea and metal salt in suitable solvent to give dihydropyrimidine ketone of formula (VI)

\[
\begin{align*}
&\text{(III)} \quad \text{Amidation} \quad \text{(IV)} \\
&\text{(V)} \\
&\text{(VI)}
\end{align*}
\]

wherein \( R \) is \( \text{C}_1-\text{C}_6 \)alkyl, \( \text{C}_6 \)aryl, or \( \text{C}_6\text{-C}_{14} \) (aryl)alkyl;

b) oxidation of dihydropyrimidine ketone of formula (VI) in a suitable solvent to give hydroxy pyrimidine compound of formula (VII)
c) dehydration and halogenation, in any order or simultaneously, of the hydroxy pyrimidine compound of formula (VII) to give halogenated compound of formula (VIII)

\[
\text{(VII)} \xrightarrow{\text{Dehydration}} \begin{bmatrix} \text{CN} & \text{CN} \\ \text{OH} & \text{H} \end{bmatrix} \xrightarrow{\text{Halogenation}} \begin{bmatrix} \text{CN} & \text{CN} \\ \text{X} & \text{H} \end{bmatrix}
\]

wherein X is halogen and selected from a group of chloro, bromo and iodo;

d) reaction of halogenated compound of formula (VIII) with N-methyl-methanesulfonamide in presence of a base and in a suitable solvent to give 2-(N-methyl-methanesulfonyl amino)pyridine compound of formula (IX)

\[
\text{(VIII)} \xrightarrow{\text{NHMeSO}_{2}\text{Me}} \begin{bmatrix} \text{CN} & \text{CN} \\ \text{N} & \text{Me} \end{bmatrix}
\]

and
e) reduction of the 2-(N-methyl-methanesulfonyl amino)pyridine compound of formula (IX) by reacting with a reducing agent in a suitable solvent to give 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I)
Suitable amidation agents which can be used in step a) for amidation include but are not limited to ammonia solution. The temperature at which the amidation of step a) is carried out is between about 5 °C and about 40 °C. In one embodiment, the temperature is between about 10 °C and about 30 °C. Suitable metal salts used for condensation of fluorobenzaldehyde (V) and the amidated compound (IV) include, but are not limited to cuprous chloride, aluminum chloride, or tin chloride.

Suitable organic solvents for condensation of step a) include alcohol solvents like methanol or isopropyl alcohol; ketone solvents such as acetone; aromatic hydrocarbon solvents like toluene or xylene; dimethyl sulfoxide; ethers like THF or 1,4-dioxane; chlorinated hydrocarbon solvents, such as chloroform, ethylene dichloride, carbon tetrachloride, or methylene chloride; or mixtures thereof. The temperature at which the condensation reaction between compound of formula (IV) and fluorobenzaldehyde (V) is carried out is between about 30 °C and about 70 °C. In one embodiment, the temperature is between about 35 °C and about 65 °C.

Suitable oxidizing agents which can be used in step b) include, but are not limited to, organic peroxides like tert-butyl hydroperoxide, hydrogen peroxide, benzoyl peroxide, benzyl peroxide, m-chloro-perbenzoic acid, oxone®, and the like. Suitable solvents which can be used for the reaction step b) include, but are not limited to halogenated solvents such as chloroform, ethylene dichloride, carbon tetrachloride, dichloromethane or the like; alcohol solvents such as methanol, ethanol, 2-propanol, 1-butanol, or 2-butanol; nitrile solvents such as acetonitrile or propionitrile; ketone solvents like acetone; aromatic hydrocarbon solvents like toluene or xylene; dimethyl sulfoxide; dimethyl sulfoxide; or mixtures
thereof. Suitable temperature at which step b) can be carried out is in the range from about 0 °C to about 30 °C.

Suitable dehydrating agents which can be used in step c) include but not limited to phosphorous pentoxide, sulfuric acid, calcium chloride, calcium carbonate and phosphorous oxychloride. Suitable halogenating agent which can be used in step c) include but not limited to phosphorous oxychloride, phosphorous trichloride, phosphorous bromide, hydrobromic acid, iodine and sodium iodide. In one embodiment, dehydration is performed first and then the dehydrated compound is subjected to halogenation. In another embodiment, halogenation is performed first and then the halogenated product is subjected to dehydration. In yet another embodiment, dehydration and halogenation is performed by using a single reagent like phosphorous oxychloride.

Suitable bases which can be used in step d) include but not limited to alkali carbonates like sodium carbonate, potassium carbonate, or lithium carbonate; alkali metal bicarbonate like sodium bicarbonate, potassium bicarbonate, or lithium bicarbonate; alkali hydroxide like sodium hydroxide, lithium hydroxide, or potassium hydroxide; alkali metal alkoxides like sodium methoxide, potassium tert-butoxide, or lithium methoxide; and amines like triethyl amine. Suitable solvents which can be used for the reaction step d) include, but are not limited to halogenated solvents such as chloroform, ethylene dichloride, carbon tetrachloride, dichloromethane or the like; alcohol solvents such as methanol, ethanol, 2-propanol, 1-butanol, or 2-butanol; nitrile solvents such as acetonitrile or propionitrile; ketone solvents like acetone; aromatic hydrocarbon solvents like toluene or xylene; dimethyl sulfone; dimethyl sulphoxide; ester solvents like ethyl acetate; amide solvents like dimethyl formamide; or mixtures thereof. Suitable temperature at which step d) can be carried out is in the range from about 25 °C to about 120 °C.

Suitable reducing agents which can be used in step e) include, but not limited to, diisobutyl aluminum hydride, Vitride® solution, or lithium aluminum hydride. Suitable solvents which can be used for the reaction step e) include, but are not limited to halogenated solvents such as chloroform, ethylene dichloride,
carbon tetrachloride, dichloromethane or the like; aromatic hydrocarbon solvents like toluene, xylene or benzene; or mixtures thereof. Suitable temperature at which step e) can be carried out is in the range of about 0 °C to about 70 °C. Isolation and purification of the intermediate of formula (I) described above can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, centrifugation, extraction, acid-base treatment, crystallization, conventional isolation and refining means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, phase-transfer chromatography, column chromatography, or by a combination of these procedures.

Another aspect of the present application provides use of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I) prepared according to the disclosure for preparing rosvastatin.

Yet another aspect of the present application provides a process for the preparation of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I) from amide intermediates of formula (VI) and (VII), thus providing a process which affords cost effective route which can be practiced on an industrial scale.

Still another aspect of the present application relates to purification of tert-butyl (E) (6-[2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl]vinyl]-4R,6S)-2,2-dimethyl[1,3]dioxin-4-yl)acetate (II) (hereinafter referred as acetonide protected tert-butyl ester of rosvastatin).

Acetonide protected tert-butyl ester of rosvastatin (II) may be prepared by following the process disclosed in the prior art references. Alternatively, compound of formula (I) obtained by the process of the present application may be subjected to appropriate reactions as disclosed in the prior art to obtain suitable intermediates for the preparation of acetonide protected tert-butyl ester of rosvastatin (II).

It has been observed that compound of formula (II) contains an impurity (hereinafter Impurity A) at RRT 1.07±0.2 upto a level of 1.0 %. Removal of the
Impurity A from the compound of formula (II) has become very difficult, and thus fails to prepare pure rosuvastatin calcium as the said impurity is carried forward to rosuvastatin calcium. Crystallization of acetonide protected tert-butyl ester (II) from methanol as reported in US6,844,437 B1 and WO05/54207A1 or from a mixture of toluene-hexane as reported in WO07/125547A2 or isopropanol as reported in WO05/54207A1 does not result substantially pure compound of formula (II). Hence, there is a need in the art to develop an effective purification method to produce substantially pure compound of formula (II).

It was observed that crystallization of the compound of formula (II) from a solvent selected from a group of n-butanol, sec-butanol, tert-butanol, ethanol and mixture thereof produces substantially pure compound of formula (II). A mixture of compound of formula (II) and n-butanol was heated from about 50 °C to about 90 °C for about 30 minutes to about 90 minutes. The solution was then cooled to about 60 °C to about 70 °C. Optionally, a seeding material was added and the temperature is maintained for about 45 minutes to about 75 minutes. The solution was again cooled from about 50 °C to about 60 °C and maintained for about 45 minutes to about 75 minutes. The solution was again cooled to 30 °C to about 40 °C and maintained for about 45 minutes to about 75 minutes. Next, the solution was cooled to about -5 °C to about 0 °C and the precipitated crystalline material is collected by filtration and washed with cold n-butanol and cold n-heptane to provide substantially pure compound of formula (II). Optionally, the compound of formula (II) is recrystallized in n-butanol using 1-2 times over input to achieve the desired purity.

Another embodiment of the present application relates to substantially pure compound of formula (II). Substantially pure acetonide protected tert-butyl ester of rosuvastatin (II) means that the compound is free from any impurity and specifically free from the Impurity A. Substantially pure acetonide protected tert-butyl ester of rosuvastatin (II) means that the compound is having at least about 95 % purity by HPLC. Specifically, the compound of formula (II) is having at least 98 % purity by HPLC and more specifically the compound of formula (II) is having more than about 99 % purity by HPLC. Substantially pure acetonide protected tert-
butyl ester of rosuvastatin (II) does not contain more than about 5% of total impurities by HPLC, specifically less than about 2% of total impurities and more specifically less than about 1% of total impurities. Substantially pure acetonide protected tert-butyl ester of rosuvastatin (II) does not contain more than about 0.15% of the Impurity A and specifically less than about 0.05% of the Impurity A.

Although crystallization of acetonide protected tert-butyl ester of rosuvastatin (II) is known in the prior art from methanol, isopropanol and a mixture of toluene-hexane, the XRPD of the crystalline compound has not been reported. One embodiment of the present application relates to crystalline acetonide protected tert-butyl ester of rosuvastatin (II) obtained by crystallization from n-butanol. Another embodiment of the present application relates to the crystalline acetonide protected tert-butyl ester of rosuvastatin (II) having an X-Ray powder diffraction (XRPD) pattern substantially as shown in Fig. 1. Yet another embodiment of the present application relates to crystalline acetonide protected tert-butyl ester of rosuvastatin (II) having an XRPD pattern with one or more peaks present at 2-theta 6.80, 7.60, 11.24, 15.24, 19.14 and 21.42 ±0.2°. The crystalline acetonide protected tert-butyl ester of rosuvastatin (II) of the present application having an XRPD pattern with peaks at 2Θ = 5.76, 6.80, 7.60, 8.52, 11.24, 14.40, 15.24, 16.16, 17.66, 18.10, 19.14, 19.82, 20.16, 21.42 and 24.88 ±0.2°.

The acetonide protected tert-butyl ester of rosuvastatin (II) is treated in an acidic medium to remove the dihydroxy protecting acetonide group by following the process as disclosed in prior art references. Rosuvastatin has two diastereomers, namely (R, R)-isomer of rosuvastatin of formula (XIII) and (S, S)-isomer of rosuvastatin of formula (XIV). It was observed that diastereomeric impurity of rosuvastatin, specifically the (R, R)-isomer of rosuvastatin of formula (XIII) is generated during the deprotection of the acetonide group in acidic medium.

The inventors of the present application have tried different acids and different reaction conditions to restrict the generation of the diastereomeric impurity during the reaction since the removal of the diastereomeric impurity is found to be very difficult in final compound after the isolation. They have
surprisingly found that when trifluoroacetic acid (TFA) is employed for the removal of the dihydroxy protecting acetonide group, the generation of diastereomeric impurity of rosuvastatin, specifically the (R, R)-isomer of rosuvastatin of formula (XIII) is restricted considerably.

\[
\begin{align*}
\text{(XIII)} & \\
\text{(XIV)} & \\
\text{(XV)} &
\end{align*}
\]

The acetonide protected tert-butyl ester of rosuvastatin (II) is treated with TFA in an organic solvent at a temperature of from about 10 °C to about 60 °C for 30 minutes to 5 hours to obtain dihydroxy rosuvastatin ester of formula (XV) which may be subjected to next step of reaction, with or without isolation.

\[
\begin{align*}
\text{(XV)} &
\end{align*}
\]

Specifically, the organic solvent used for deprotection reaction is selected from a group of acetonitrile, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) and mixtures thereof. More specifically, the organic solvent is acetonitrile. After the deprotection reaction is completed, the reaction mixture is treated with an aqueous solution of an alkali metal hydroxide selected from a group of sodium hydroxide, potassium hydroxide and lithium hydroxide to hydrolyze the tert-butyl ester group. Specifically, the alkali metal hydroxide is sodium hydroxide. The aqueous solution of the reaction mixture containing rosuvastatin sodium is washed with an organic solvent, preferably for about 2-3
times. The organic solvent is selected from a group of esters, alcohols, hydrocarbons, ethers and a mixture thereof. Specifically, the organic solvent is a hydrocarbon solvent. More specifically, the hydrocarbon solvent is an aromatic hydrocarbon solvent and most specifically the aromatic hydrocarbon solvent is toluene.

The aqueous solution containing rosuvastatin sodium is mixed with an organic solvent. The organic solvent is selected from a group of esters, alcohols, hydrocarbons, ethers and a mixture thereof. Specifically, the organic solvent is ether solvent. More specifically, the ether solvent is selected from a group of diethyl ether, diisopropyl ether and methyl tert-butyl ether. Most specifically, the organic solvent is methyl tert-butyl ether (MTBE). To the above solution of water and organic solvent, sodium chloride is added and the reaction mass is cooled from a temperature of about 15 °C to about 30 °C. Specifically, the reaction mass is cooled to 20 °C. The pH of the mixture is adjusted from about pH 1 to about pH 5 by the addition of aqueous sodium bisulphate solution. Specifically, the pH of the reaction mass is adjusted from about pH 2 to about pH 4. The organic layer is separated from the reaction mass.

A solution of tert-butyl amine in an organic solvent selected from a group of esters, alcohols, hydrocarbons, ethers and a mixture thereof is added to the above organic solvent containing rosuvastatin acid at a temperature of about 15 °C to about 40 °C, specifically at a temperature of about 25 °C to about 35 °C. The reaction mixture is then stirred for a period of about 1 hour to 10 hours, specifically the reaction mixture is stirred for a period of about 2 hours to about 8 hours and more specifically the reaction mixture is stirred for a period of about 4 hours to about 6 hours. The reaction mixture is then cooled to a temperature of about 5 °C to about 25 °C, specifically to a temperature of about 15 °C to about 25 °C. The resulting solid is filtered and the wet cake is washed with an organic solvent. Optionally, the resulted tert-butyl amine salt of rosuvastatin (XVI) is purified by leaching in an organic solvent or from a mixture of organic solvents. The organic solvent is selected from a group of an ester solvent, an alcohol solvent, a hydrocarbon solvent, an ether solvent, a nitrile solvent and a mixture thereof.
Specifically, the solvent for the purification of tert-butyl amine salt of rosuvastatin (XVI) is a mixture of a nitrile solvent and an alcohol solvent. More specifically, the solvent for crystallization is a mixture of acetonitrile and IPA.

The tert-butyl amine salt of rosuvastatin (XVI) is suspended in water and an aqueous solution of an alkali metal hydroxide selected from a group of sodium hydroxide, lithium hydroxide and potassium hydroxide is added at a temperature of about 15 °C to about 40 °C, specifically from about 25 °C to about 35 °C and stirred for 30 minutes to 5 hours. Specifically, the alkali metal hydroxide is sodium hydroxide. After the reaction is completed, the reaction mass is heated to a temperature from about 40 °C to about 90 °C for 30 minutes to 3 hours under vacuum. Specifically, the reaction mass heated from about 40 °C to about 50 °C for 1 to 2 hours under vacuum. Then the reaction mass is diluted with water and filtered through a 0.2-0.4 micron filter. The reaction mass is cooled from about 15 °C to about 20 °C. An aqueous solution of calcium chloride is added slowly to the reaction mass maintaining the temperature from about 15 °C to about 20 °C for a period of about 15 to about 25 minutes. The isolated solid was filtered and the wet cake containing rosuvastatin calcium is stirred with water for a period of about 5 minutes to 30 minutes to ensure the removal of all inorganic salts. The solid is then filtered and dried under vacuum to provide substantially pure amorphous rosuvastatin calcium (XVII).

Substantially pure amorphous rosuvastatin calcium (XVII) means that the compound is having at least about 95 % purity by HPLC. Specifically, amorphous rosuvastatin calcium (XVII) is having at least about 98 % purity by HPLC and more specifically amorphous rosuvastatin calcium (XVII) is more than about 99 % pure by HPLC. Substantially pure amorphous rosuvastatin calcium (XVII) does not contain more than about 0.15 % of Impurity A and specifically less than about 0.05 % of Impurity A. Substantially pure amorphous rosuvastatin calcium (XVII) does not contain more than about 0.15 % of diastereomeric impurity and specifically less than about 0.05 % of diastereomeric impurity.
The substantially pure amorphous rosuvastatin calcium (XVII) of the present application may be subjected to micronization, milling to result the required particle size which is suitable for formulation.

Still another aspect of the present disclosure provides a pharmaceutical composition comprising rosuvastatin prepared according to the process of the present disclosure along with one or more pharmaceutically acceptable carriers, excipient, or diluents.

The pharmaceutical composition comprising rosuvastatin or its salts and its combination with a pharmaceutically acceptable carrier of this disclosure may further formulated as solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared by direct blending, dry granulation, or wet granulation or by extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present disclosure may further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that find use in the present disclosure include, but are not limited to: diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, pregelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch,
crospovidone, croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins, resins; release rate controlling agents such as hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, methyl cellulose, various grades of methyl methacrylates, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but are not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

Certain specific embodiments will be further explained in the following examples, which are being provided only for the purpose of illustration, and the scope of this application is not limited thereto.

EXAMPLES

EXAMPLE 1: Preparation of 3-oxo pentanamide (IV)

To a solution of methyl isobutyl acetate (III) (100g) in toluene (50 mL) under nitrogen was added dimethylaminopyridine (7.56 g) and the solution cooled to 0-5 °C. Aqueous ammonia solution (500 mL) was added to the reaction mass over a period of 30 to 45 minutes maintaining the temperature below 10 °C. The reaction mixture was maintained at 30-35 °C for 1 hour and stirred at room temperature for 15-20 hours. Reaction mass was concentrated on a rotary evaporator at bath temperature 60-70 °C to furnish the crude product. The crude product was purified by column chromatography using n-hexane and ethyl acetate as solvent to give the title compound.

Yield: 65 g (72%).

EXAMPLE 2: Preparation of 4-(4-fluorophenyl)-6-isopropyl-2-oxo-1, 2,3,4-tetrahydro-pyrimidine-5-carboxamide (VI)

To a solution of 3-oxopentanamide (26 g), urea (21.17g), 4-fluorobenzaldehyde (V) (25g), and cuprous chloride (0.2 g) in methanol (150 mL) at 30-35 °C was added concentrated sulfuric acid (2 mL) under nitrogen
atmosphere. The reaction mixture was refluxed at 65-70 °C for 15-18 hours. Reaction mass was cooled to 20-25 °C, water (250 mL) was slowly added to the reaction mass and stirred for one hour. The precipitated solid was collected by filtration, washed with water (100 mL), and dried to yield the desired compound. Yield: 32 g (58%)

Purity by HPLC: 93.3%.

EXAMPLE 3: Preparation of 4-(4-fluorophenyl)-2-hydroxy-6-isopropylpyrimidine-5-carboxamide (VII)

To a solution of 4-(4-fluorophenyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (VI) (5 g), potassium carbonate (0.24 g), and cupric chloride dihydrate (0.03 g) in dichloromethane (50 mL) at 25-30 °C was added 70% tert-butyl hydroperoxide (5 mL) under nitrogen atmosphere. The reaction mixture was maintained at 25-30 °C for 10-12 hours. Dichloromethane (50 mL) and methanol (10 mL) were added to the reaction mass and then maintained at 25-30 °C for 10-12 hours. The reaction mass was then cooled to 0-5 °C and sodium thiosulfate solution (10% w/v) was slowly added. Ammonium chloride solution (25% w/v) was slowly added to reaction mass at 0-5 °C and stirred for one hour. The precipitated solid was collected by filtration, washed with water (50 mL), and dried to the title compound. Yield: 3.8 g (76%).

EXAMPLE 4: Preparation of 2-chloro-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carbonitrile (VIII)

To a solution of 4-(4-fluorophenyl)-2-hydroxy-6-isopropylpyrimidine-5-carboxamide (VII) (1 g) in dichloromethane (10 mL) at 0-5 °C was added phosphorous oxychloride (10 mL) under nitrogen atmosphere. The reaction mixture was heated to 35 °C and maintained at that temperature for 15-18 hours. The reaction mass cooled to 0-5 °C and phosphorous oxychloride (5 mL) was slowly added under nitrogen atmosphere. The reaction mixture was heated to 100-105 °C and maintained at same temperature for 15-18 hours. The reaction mass was then cooled to 25-30 °C and the excess phosphorous oxychloride was completely evaporated. To the residue, water (5 mL) and ethyl acetate (5 mL) was
added at 0-5 °C. The organic layer was separated and washed twice with water (2 x 5 mL). The organic layer was washed with sodium chloride solution (10 % w/v), dried over sodium sulfate, and evaporated under vacuum to give 2-chloro-4-(4-fluorophenyl)-6-isopropyl pyrimidine-5-carbonitrile (VIII).

Yield: 0.4 g (40%)
Purity by HPLC: 88.4%.

**EXAMPLE 5:** Preparation of N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (IX)

To a solution of 2-chloro-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carbonitrile (VIII) (1 g) and potassium carbonate (1.73g) in toluene (12 mL) at 25-30°C was added N-methyl methane sulfonamide (0.47g) under nitrogen atmosphere and stirred for 5-10 minutes. The reaction mixture was heated to 110-115 °C and refluxed azeotropically. The azeotropic distillation was maintained at same temperature for 6-8 hours. The reaction mass was cooled to 25-30 °C, filtered, and collected the wet cake, washed with ethyl acetate (5 mL). Water (10 mL) was added to the filtrate and stirred for 30 minutes. Organic layer was separated and washed the aqueous layer with ethyl acetate (2 x 10 mL). The combined ethyl acetate layers were washed with water (10 mL), dried over sodium sulfate, and evaporated under vacuum. The mixture of ethyl acetate and n-hexane was added to residue which was then stirred for 30 minutes. The solid was collected by filtration, washed with 30 % ethyl acetate in n-hexane (2mL), and dried under vacuum for 14-16 hours at 60-65°C to afford the title compound.

Yield: 0.65 g (51.5%)
Purity by HPLC: 98.96%.

**EXAMPLE 6:** Preparation of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methlysulfonyl-amino)-5-formyl-pyrimidine (I)

To a solution of N-(5-cyano-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-N-methylmethanesulfonamide (IX) (60 g) in dichloromethane (480 mL) at 0-5 °C was added DIBAL-H (205.4 mL) under nitrogen atmosphere. The reaction mixture was maintained at same temperature for 2 hours. To the reaction mass cold dilute hydrochloric acid solution and stirred for 1-2 hours at 0-5 °C. Dichloromethane
(480 mL) was added to reaction mass. Slowly the temperature of the reaction mass was raised to 25-30 °C and the reaction mass was stirred at the same temperature for 8-10 hours. The organic layer was separated from the reaction mass and further extracted 2-3 times with dichloromethane. The combined organic layer was washed with water (600 mL) and stirred at 25-30 °C for one hour. The organic phase was separated and evaporated under vacuum completely. Isopropyl alcohol (60 mL) was added to the resultant residual mass and heated to a temperature of 60-70 °C for 2 hours. The reaction mixture was cooled to 5-10 °C, filtered the precipitated solid, washed with isopropyl alcohol (60 mL), and dried under vacuum for 12-15 hours at 60-70 °C to afford the desired compound (I).

Yield: 48.6 g (80.3%)
Purity by HPLC: 99.54%.

Example 7: Purification of tert-butyl (E) (6-[2-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl]vinyl](4R,6S)-2,2-dimethyl[1,3]dioxin-4-yl)acetate (II)

A mixture of acetonide protected tert-butyl ester of rosuvastatin (II) and n-Butanol (200 mL) was heated to 70-80 °C and maintained for a period of 45 minutes to 1 hour. The reaction mixture was then cooled to 60-65 °C and seeding material was added. The reaction mass was stirred at 60-65 °C for 1 hr and further cooled to 50-55 °C. The reaction mass is stirred 1 hr at 50-55 °C, and further cooled to 30-35 °C. The reaction mass was maintained for 1 hour at this temperature and then cooled to -5 to 0 °C. The crystalline precipitate was collected by filtration and washed with chilled n-Butanol (100 mL), heptane (150 mL) and dried to provide pure acetonide protected tert-butyl ester of rosuvastatin (II).

Purity by HPLC: 98.8 %

Example 8: Preparation of tert-butyl amine salt of rosuvastatin (XVI)

To a solution of acetonide protected tert-butyl ester of rosuvastatin (II) (25 g) a dilute solution of TFA in water (2.5 g in 25 mL water) was added at 30-40 °C. The reaction was stirred for 30 minutes to 1 hour and then water (25 mL) was added to it. The reaction mixture was again stirred for 3-4 hours at the same temperature. Then an aqueous solution of sodium hydroxide (3.46 g in 100 mL
water) was added and the reaction mixture was stirred for 1 hour. The reaction mixture was further diluted with water (200 mL) and washed with toluene (2 x 250 mL) and MTBE (125 mL). MTBE (250 mL) was further added to the aqueous layer. Then sodium chloride (6.25 g) was added to the reaction mixture. An aqueous solution of sodium bisulphate (15 g in 100 mL of water) was added to the reaction mass and the pH was adjusted to 2.4. The organic layer was separated. The aqueous layer was again extracted with MTBE (200 mL) and the combined organic layer was washed with sodium chloride solution (125 mL). A solution of tert-butyl amine (7.91 g) in MTBE (250 mL) was added to the reaction mixture and stirred for 2-6 hours. The reaction mixture was cooled to 15-20 °C and stirred at this temperature for 1 hour. The precipitated solid was isolated and dried. The solid was suspended in a mixture of acetonitrile (62.5 mL) and IPA (62.5 mL) and heated to a temperature of 50-55 °C for 1-3 hours. The reaction mixture was then cooled to 25-35 °C and stirred at this temperature for 2-6 hours. The reaction mixture was further cooled to 10-15 °C and stirred for 1 hour. The precipitated solid was filtered, washed with a mixture of acetonitrile and IPA and dried to provide the title compound.

Yield: 20.5 g (86 %)
Purity by HPLC: 99.82 %

**Example 9: Preparation of substantially pure amorphous rosvastatin calcium (XVII)**

To an aqueous solution of tert-butyl amine salt of rosvastatin (XVI) (25 g in 125 mL of water), a solution of sodium hydroxide (1.98 g) in water (50 mL) was added under nitrogen atmosphere and the reaction mixture was stirred for 1 hour. The reaction mass was heated to 40-45 °C and nitrogen gas was bubbled through the reaction mass under vacuum for 1-2 hrs and water (50 mL) was added to the reaction mass. The reaction mixture was then filtered through 0.2-0.4 micron filter and cooled to 15-20 °C. An aqueous solution of calcium chloride (2.75 g in 75 mL water) was added slowly to the reaction mixture for a period of 15-25 minutes and the reaction mixture was stirred for 15-45 minutes. The precipitated solid was filtered and washed with water. The wet cake was dried in vacuum oven below 50
°C for 6-10 hours. The dried material was sieved and charged into a reaction vessel and water (300 mL) was added to it. The reaction mixture was stirred for 15-45 minutes at 25-35 °C under nitrogen atmosphere. The solid was filtered and dried to provide the title compound.

Yield: 17.4 g (38 %)

Purity by HPLC: 99.77 %.
We claim:
1. A process for the preparation of 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I)

![Chemical Structure](image)

comprising

a) amidation of compound of formula (III) followed by condensation with 4-flurobenzaldehyde in presence of urea and metal salt in suitable solvent to give dihydropyrimidine ketone of formula (VI)

![Chemical Reactions](image)

wherein R is alkyl, aryl, arylalkyl;

b) oxidation of dihydropyrimidine ketone of formula (VI) in suitable solvent to give hydroxy pyrimidine compound of formula (VII)

![Chemical Reactions](image)
c) dehydration followed by halogenation of hydroxyl pyrimidine compound of formula (VII) to give halogenated compound of formula (VIII)

Wherein X is halogen and selected from a group of chloro, bromo and iodo;

d) reaction of halogenated compound of formula (VIII) with N-methylmethanesulfonylamide in presence of a base and suitable solvent to give 2-(N-methyl-methanesulfonyl amino)pyridine compound of formula (IX)

e) reaction of 2-(N-methyl-methanesulfonyl amino)pyridine of formula (IX) with suitable reducing agents in suitable solvent to give 4-(fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-formyl-pyrimidine of formula (I)

2. A Process for preparation of compound of formula (VII) comprising

a) amidation of compound of formula (III) followed by condensation with 4-flurobenzaldehyde in presence of urea and metal salt in suitable solvent to give dihydropyrimidine ketone of formula (VI)
wherein R is alkyl, aryl, arylalkyl

b) oxidation of dihydropyrimidine ketone of formula (VI) in suitable solvent to give hydroxy pyrimidine compound of formula (VII)

3. The process of claim 1 or claim 2, wherein R is methyl.
5. The process of claim 1, wherein the halogen used in step c) is chloro.
6. 4-(4-Fluorophenyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide of formula (VI)

7. 4-(4-Fluorophenyl)-2-hydroxy-6-isopropylpyrimidine-5-carboxamide of formula (VII)
8. Use of 4-(4-fluorophenyl)-6-isopropyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide of formula (VI) for preparation of substantially pure amorphous rosuvastatin calcium (XVII).

9. Use of 4-(4-fluorophenyl)-2-hydroxy-6-isopropylpyrimidine-5-carboxamide of formula (VII) for preparation of substantially pure amorphous rosuvastatin calcium (XVII).

10. A process for the purification of acetonide protected tert-butyl ester of rosuvastatin (II) comprising crystallization of compound (II) in a solvent selected from a group of ethanol, n-butanol, sec-butanol, tert-butanol and mixture thereof.

11. The process of claim 10, wherein the alcoholic solvent is n-butanol.

12. A process for the preparation of substantially pure amorphous rosuvastatin calcium comprising:
   a) removal of dihydroxy protecting group of pure acetonide protected tert-butyl ester of rosuvastatin (II) prepared by a process of claim 11 in an acidic medium;
   b) hydrolyzing the tert-butyl ester group of the product of step a) in a basic medium;
   c) converting the product of step b) to tert-butyl amine salt of rosuvastatin;
   e) optionally purifying tert-butyl amine salt of rosuvastatin;
   f) treating tert-butyl amine salt of rosuvastatin with alkali metal hydroxide and
   g) treating the product of step f) with an aqueous solution of calcium chloride.

13. A crystalline form of acetonide protected tert-butyl ester of rosuvastatin (II) having an X-ray powder diffraction pattern with one or more peaks at 2-theta 6.80, 7.60, 11.24, 15.24, 19.14 and 21.42 ±0.2°.

15. The crystalline form of acetonide protected tert-butyl ester of rosuvastatin (II) according to claim 13 or 14, characterized by XRPD pattern as depicted in Fig. 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Database: WPI, EPDOC, CNKI, CPRS, REG, CAPLUS, CASREACT
Search terms: rosvastatin, +statin+, 287714-41-4, 147098-20-2, 147118-37-4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search 09 Oct. 2012(09.10.2012)

Date of mailing of the international search report 08 Nov. 2012 (08.11.2012)

Name and mailing address of the ISA/CN
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jiemin Bridge, Haidian District, Beijing, China 100088
Facsimile No. 86-10-62019451

Authorized officer LI Xueying
Telephone No. (86-10)62084376

Form PCT/ISA /210 (second sheet) (July 2009)
**INTERNATIONAL SEARCH REPORT**

**Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

The 1st invention: claims 1-9, relating to the process for preparation of compound of formula I, process for preparing formula VII, intermediate compounds of formula (VI), (VII) used in the aforesaid processes and uses of the intermediate compounds;

The 2nd invention: claims 10-11, relating to the process for the purification of acetonide protected tert-butyl ester of rosuvastatin (II);

The 3rd invention: claim 12, relating to the process for the preparation of substantially pure amorphous rosuvastatin calcium;

The 4th invention: claims 13-15, relating to crystalline form of acetonide protected tert-butyl ester of rosuvastatin (II).

The compounds of rosuvastatin calcium, formula VIII, formula IX, formula I and formula II are known in this art (see WO2008151510A1, pages 1-2 of the description and claim 1; US6844437B1, column 1). Thus the four groups of inventions cannot be considered as involving one or more of the same or corresponding special technical feature within the meaning of Rule 13.2 PCT. Therefore the four groups of inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9

**Remark on protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA /210 (continuation of first sheet (2)) (July 2009)
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Form PCT/ISA/210 (patent family annex) (July 2009)
## INTERNATIONAL SEARCH REPORT

### Classification of Subject Matter

- C07D239/42(2006.01)i
- C07D239/22(2006.01)i
- C07D239/36(2006.01)i
- C07D405/06(2006.01)i