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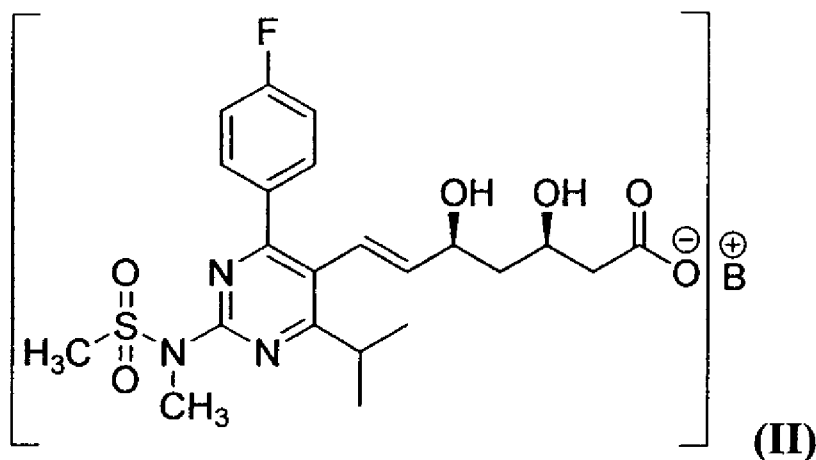
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(54) **Title:** SALTS OF ROSUVASTATIN

(57) **Abstract:** The present invention relates to pharmaceutically acceptable salts of rosuvastatin of Formula (II), (II) wherein B is an organic amine selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine and process for the preparation thereof.

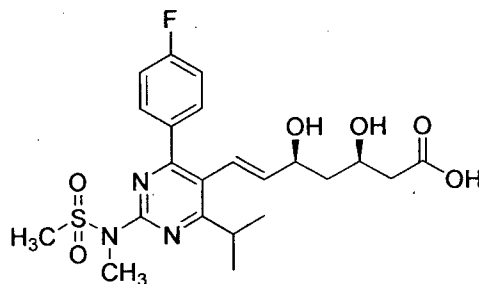


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SALTS OF ROSUVASTATIN**FIELD OF THE INVENTION**

The present invention relates to novel salts of (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl-sulphonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-

5 (E)-6-heptene carboxylic acid (rosuvastatin) of Formula (I),



(I)

and its hydrates. The invention includes processes for the preparation of novel salts. The invention also relates to pharmaceutical compositions that include the novel salts

10 and use of the compositions for the treatment of hypercholesterolemia, hyperlipoproteinemia, atherosclerosis and dementia.

BACKGROUND OF THE INVENTION

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of

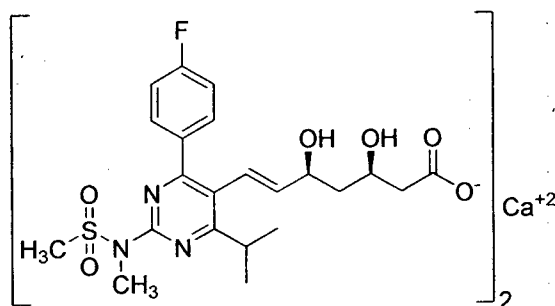
15 common general knowledge in the field.

(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl-sulphonyl-amino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptene-carboxylic acid of the Formula (I) is known as rosuvastatin and marketed as hemi-calcium salt under the brand name Crestor®.

20 U.S. Patent No. RE 37314 (Reissue of U.S. Patent No. 5,260,440) discloses rosuvastatin and its alkali and alkaline earth metal salts. The patent specifically discloses the sodium salt and calcium salt of rosuvastatin and process for their preparation. These compounds are HMG-CoA reductase inhibitors and useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

25 The compound, (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl-sulphonyl-amino)-pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptene-carboxylic acid hemi-calcium salt (rosuvastatin calcium) is a HMG-CoA reductase inhibitor. It can

lower LDL-cholesterol and triglycerides more effectively than the first generation drugs. Rosuvastatin Calcium has the following structure being shown by formula:



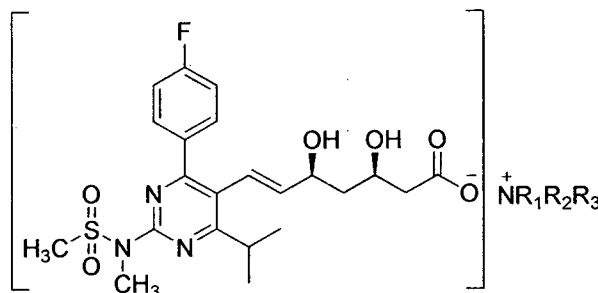
5 Rosuvastatin Calcium is marketed under the trade name of CRESTOR for treatment of a mammal such as a human. According to the maker of CRESTOR, it is administered in a daily dose of from about 5 mg to about 40 mg. For patients requiring less aggressive LDL-C reductions or who have pre-disposing factors for myopathy, the 5 mg dose is recommended, while 10 mg dose is recommended for the average patient,
 10 20 mg dose for patients with marked hyper-cholesterolemia and aggressive lipid targets (>192 mg/dL), and the 40 mg dose for patients who have not been responsive to lower doses. International (PCT) publication WO 2003/032995 further discloses a method of preventing dementia by administering to a patient rosuvastatin.

U.S. Patent Application No. 2006/0014766 A1 discloses a various crystalline
 15 salt of the rosuvastatin, wherein the salt is an ammonium (NH_4^+), methylammonium (CH_3NH_3^+), ethylammonium ($\text{CH}_3\text{CH}_2\text{NH}_3^+$), diethanolammonium [$(\text{HOCH}_2\text{CH}_2)_2\text{NH}_2^+$], tris(hydroxymethyl)methyl ammonium [$(\text{HOCH}_2)_3\text{CNH}_3^+$], benzylammonium ($\text{C}_6\text{H}_5\text{CH}_2\text{NH}_3^+$), 4-methoxybenzyl ammonium ($4\text{-CH}_3\text{O-C}_6\text{H}_5\text{CH}_2\text{NH}_3^+$), Lithium (Li^+) or magnesium (Mg^{2+}) salts characterized by their X-ray
 20 diffraction patterns and 2-theta values.

U.S. Patent Application No. 2005/0131066 A1 discloses the isopropyl ammonium salt and cyclohexyl ammonium salt of rosuvastatin characterized by their X-ray diffraction patterns and 2-theta values as an intermediate in the process for purification of rosuvastatin calcium.

25 International PCT Publication, WO 2005/077916 A1 discloses the amine salts of rosuvastatin of formula below as or solvate, hydrate, crystalline or amorphous form thereof, in which amine residue has a formula $\text{NR}_1\text{R}_2\text{R}_3$ wherein R_1 , R_2 and R_3 are defined therein with the proviso that the amine is not ammonia, methylamine,

ethylamine, diethanolamine, tris(hydroxymethyl)-methylamine, benzylamine, or 4-methoxybenzylamine. The patent application specifically discloses cyclohexyl ammonium salt, diisopropyl ammonium salt, isopropyl ammonium salt, dicyclohexyl ammonium salt, (S)-(+)- α -methylbenzyl ammonium salt.



International PCT Publication, WO 2005/028450 A1 discloses tris (hydroxymethyl)- methylammonium salt of rosuvastatin.

Various other salts of rosuvastatin are disclosed in International PCT Publications, WO 2005/077917 A1, 2006/136407 A1, 2007/119085 A1, 2007/125547 A2, 2007/086082 A2, 2008/038132A1, and 2010/00081861 A1.

Solubility and stability are important characteristic of a salt form that can affect its suitability for use as a drug. Where aqueous solubility is low, i.e. less than 10 mg/ml, the dissolution rate at in vivo administration can be rate limiting in the absorption process leading to poor bioavailability. Therefore, poorly soluble drug substance requires special efforts in formulation development to achieve desired results. The stability of drug product is important parameter for its pharmaceutical use.

Although rosuvastatin calcium provides good pharmaceutical activity, it would be beneficial to find other forms of rosuvastatin; in particular, rosuvastatin salts having advantageous properties for pharmaceutical use.

SUMMARY OF THE INVENTION

In one general aspect, there are provided novel pharmaceutically acceptable salts of rosuvastatin. In particular, there are provided lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine salts of rosuvastatin.

In another general aspect there are provided processes for the preparation of novel pharmaceutically acceptable salts of rosuvastatin.

The invention may provide novel salts in crystalline or amorphous forms.

The invention may provide pharmaceutically acceptable salts of rosuvastatin, which show better purity and physiochemical properties. The novel salts of rosuvastatin

may have high purity with respect to related impurities and may have improved physiochemical properties like melting point, solubility and improved stability under various stress conditions.

The invention may provide stable pharmaceutically acceptable salts of
5 rosuvastatin.

In general, the pharmaceutically acceptable salts of rosuvastatin may have purity greater than 99% by area percentage of HPLC.

In another general aspect there are provided pharmaceutical compositions that include a therapeutically effective amount of the pharmaceutically acceptable salts of
10 rosuvastatin; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect, there are provided pharmaceutical compositions that include a therapeutically effective amount of the pharmaceutically acceptable salts of rosuvastatin substantially free of one or more of its corresponding impurities as
15 measured by HPLC.

In another general aspect, there are provided pharmaceutical compositions that include a therapeutically effective amount of the pharmaceutically acceptable salts of rosuvastatin substantially free of residual solvents.

In another general aspect there are provided chemically stable pharmaceutically
20 acceptable salts of rosuvastatin, which contains less than about 0.1% (wt/wt) 5-oxo impurity, lactone impurity, diastereomer impurity, *cis*-isomer impurity upon exposure to a relative humidity of 75% at 40°C for a period of at least about three months and are substantially free from residual solvents.

In another general aspect there are provided chemically stable pharmaceutically
25 acceptable salts of rosuvastatin, which contains less than about 0.1% (wt/wt) 5-oxo impurity, lactone impurity, diastereomer impurity, *cis*-isomer impurity upon exposure to a relative humidity of 60% at 25°C for a period of at least about three months and are substantially free from residual solvents.

BRIEF DESCRIPTION OF THE DRAWINGS

30 **FIG. 1** is an X-ray powder diffractogram (XRD) of the crystalline rosuvastatin lysine.
FIG. 2 is an X-ray powder diffractogram (XRD) of the amorphous rosuvastatin lysine.
FIG. 3 is an X-ray powder diffractogram (XRD) of the crystalline rosuvastatin ethanolamine.

FIG. 4 is a differential scanning calorimetry graph of crystalline rosuvastatin ethanolamine.

FIG. 5 is an X-ray powder diffractogram (XRD) of the crystalline rosuvastatin arginine.

5 **FIG. 6** is a differential scanning calorimetry graph of crystalline rosuvastatin arginine.

DESCRIPTION OF THE INVENTION

The inventors have found novel pharmaceutically acceptable salts of rosuvastatin, in particular, the salts of organic amine selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

10 The novel salts are characterized in their crystalline forms or amorphous forms.

The inventors also have developed a process for the preparation of novel pharmaceutically acceptable salts of rosuvastatin, by providing solution of rosuvastatin salt in one or more solvent to obtain solution; and obtaining pharmaceutically acceptable salts of rosuvastatin by the removal of solvent.

15 In general, the solution of rosuvastatin salts may be obtained by dissolving rosuvastatin acid or its alkaline salt in one or more solvent and treating with suitable organic amine as disclosed herein above in one or more of suitable solvent. The solution may be obtained by heating the rosuvastatin salt in a solvent. The resultant solution may be clarified to remove foreign particulate matter or treated with charcoal
20 to remove coloring and other related impurities. The solution so obtained may be concentrated to reduce the amount of solvent. The solution may be concentrated by removing the solvent completely to get a residue.

Alternatively, such a solution may be obtained directly from a reaction in which rosuvastatin salt is formed. The solvent may be removed by a technique which
25 includes, for example, filtration, filtration under vacuum, decantation, centrifugation, distillation and distillation under vacuum.

The inventors have found chemically stable pharmaceutically acceptable salts of rosuvastatin, which contains less than about 0.1% (wt/wt) 5-oxo impurity, lactone impurity, diastereomer impurity or *cis*-isomer impurity and are substantially free from
30 residual solvents after storage for 3 months at 40°C and a relative humidity of 75% or at 25°C and a relative humidity of 60%.

All ranges recited herein include the endpoints, including those that recite a range “between” two values. Terms such as “about”, “general”, “substantially” and the like are to be construed as modifying a term or value such that it is not an absolute.

Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those skill in the art. This includes, at the very least, a degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

5 Thus, the advantage of the present invention is to provide at least chemically stable pharmaceutically acceptable salts of rosuvastatin which doesn't degrade to impurities.

When a molecule or other material is identified herein as "substantially free", it generally means, unless specified otherwise, that the material is about 99% pure or
10 more. In general, this refers to purity with regard to unwanted residual solvents, reaction byproducts, impurities and unreacted starting materials.

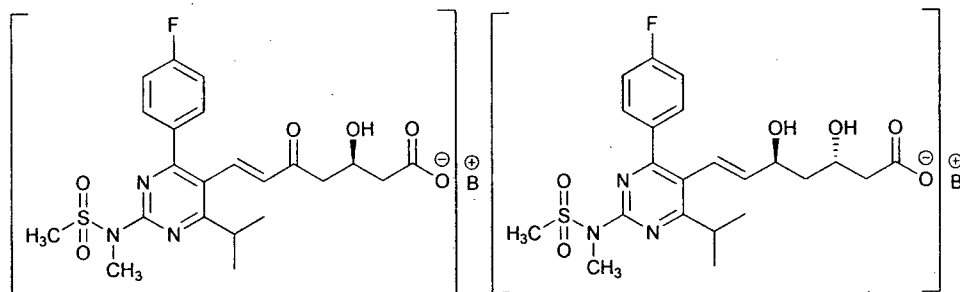
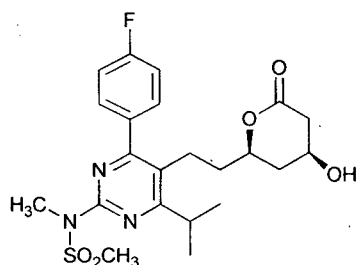
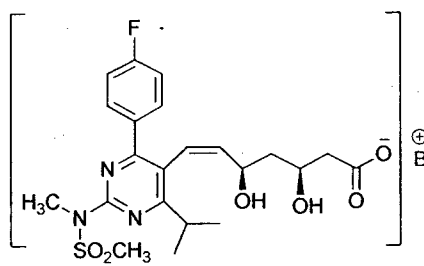
As used herein, the term "chemically stable" pharmaceutically acceptable salts of rosuvastatin includes either: rosuvastatin salts that after exposure to a relative humidity of 75% at 40°C or 60% at 25°C, for a period of at least three months contains
15 less than about 0.15% wt/wt, in particular less than about 0.1% wt/wt of 5-oxo impurity, lactone impurity, diastereomer impurity or *cis*-isomer impurity or substantially free from residual solvents.

As used herein, the term "crystallinity" includes crystalline nature of pharmaceutically acceptable salts of rosuvastatin. In particular, the crystalline
20 rosuvastatin salts may have % crystallinity from about 30% to 100%. In particular, the crystalline rosuvastatin salts are having atleast about 30% crystallinity to 100% crystallinity.

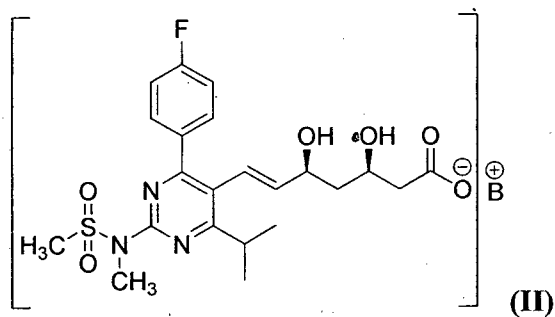
As used herein, the term "obtaining" may include filtration, filtration under vacuum, centrifugation, and decantation to isolate product. The product obtained may
25 be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a hot air oven, tray drier, dried under vacuum and/or in a Fluid Bed Drier.

"Suitable solvent" means a single or a combination of two or more solvents. As used herein, the term "contacting" includes mixing, adding, slurrying, stirring, or a
30 combination thereof.

The chemical structures of impurities 5-oxo impurity, diastereomer impurity, lactone impurity, *cis*-isomer impurity are:

**5-oxo Impurity****Diastereomer Impurity****Lactone Impurity****cis-Impurity**

- 5 In one general aspect, the invention provides novel salts of rosuvastatin of Formula (II)



where in B is organic amine selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

- 10 In another general aspect, the invention provides crystalline or amorphous form of pharmaceutically acceptable salts of rosuvastatin of Formula (II).

In another general aspect, there is provided a rosuvastatin lysine. In particular, the rosuvastatin lysine may be in an isolated form.

- 15 In another general aspect, the invention provides rosuvastatin lysine in the crystalline form. In further aspect, there is provided rosuvastatin lysine in an amorphous form.

In general, the rosuvastatin lysine obtained by the process of the present invention is anhydrous. The anhydrous rosuvastatin lysine may contain water content less than about 1% wt/wt. In particular, the water content is less than about 0.5% wt/wt.

In another general aspect, the present invention provides rosuvastatin lysine having at least about 50% crystallinity. In particular, the crystallinity of rosuvastatin lysine may be from about 50% to 100%, more particularly from about 60% to 100%.

In another general aspect, the present invention provides a crystalline rosuvastatin lysine characterized by X-ray powder diffraction pattern having peaks at about 5.5°, 9.3°, 10.9°, 14.0°, 15.2°, 17.6°, 20.1°, 21.5° and 22.6° (2 θ).

The present invention provides a crystalline rosuvastatin lysine characterized by X-ray diffraction substantially as depicted in FIG. 1.

In another general aspect, the invention provides crystalline rosuvastatin lysine having particle size distributions, wherein the 10th volume percentile particle size (D_{10}) is less than about 50 μ m, the 50th volume percentile particle size (D_{50}) is less than about 250 μ m, or the 90th volume percentile particle size (D_{90}) is less than about 500 μ m, or any combination thereof.

In another general aspect, the present invention provides a process for preparing a crystalline rosuvastatin lysine, the process comprising:

- (a) contacting rosuvastatin or its alkali or alkaline salt with lysine in one or more suitable solvent to obtain rosuvastatin lysine solution; and
- (b) obtaining the crystalline rosuvastatin lysine from the solution thereof by removal of solvents.

In general, the rosuvastatin or its alkali or alkaline salt comprises of rosuvastatin acid or rosuvastatin alkali or alkaline salt selected from sodium, potassium, lithium, barium, magnesium, calcium, strontium, and zinc. In particular, rosuvastatin alkali or alkaline salts may be converted to rosuvastatin acid before contacting with lysine.

In general, the reaction may be carried out in one or more of suitable solvents. The solvent system is particularly selected so as to facilitate the salt formation reaction and to allow subsequent separation of the resulting material. Advantageously, both rosuvastatin and the lysine are dissolvable, at least partly, in the solvent system, at least at elevated temperatures. In the process, a mixture, slurry, or solution of rosuvastatin or its alkali or alkaline salt and a solvent may be contacted with lysine or conversely, a mixture or solution of lysine and a solvent may be contacted with rosuvastatin or its alkali or alkaline salt.

In general, the lysine may be DL-lysine or its anhydrous or hydrate form. In particular, DL-lysine is monohydrate.

In further embodiments of the process, both may be combined with a solvent system prior to being contacted together, whereby the solvent system used for lysine
5 may be identical with or different from the solvent system used for the rosuvastatin or its alkali or alkaline salt. The solvent system can be comprised of a single solvent or a mixture of solvents. When two or more solvents are used, a two phase reaction scheme may be used wherein the rosuvastatin or its alkali or alkaline salt and lysine are primarily reacted in one phase and the resulting rosuvastatin lysine is primarily present
10 in the other phase due to, inter alia, solubility differences, etc. Suitable solvent comprises one or more of C₁-C₆ alcohols; esters; ketones; hydrocarbons; halogenated hydrocarbons and polar aprotic solvents.

In general, a suitable solvent comprises one or more of water, a C₁-C₆ alcohols like methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, tert-butanol and
15 the like; esters like ethyl acetate, isopropyl acetate, butyl acetate, iso-butyl acetate and the like; ketones like acetone, methyl ethyl ketone, methyl tert-butyl ketone and the like; ethers like tetrahydrofuran, diethyl ether, diisopropyl ether, dioxane and the like; hydrocarbons like toluene, xylene, hexane, cyclohexane, heptanes and the like; halogenated hydrocarbons like methylene dichloride, ethylene dichloride, chloroform,
20 chlorobenzene and the like; polar aprotic solvents like acetonitrile, dimethylformamide, N-methyl pyrrolidone, dimethyl acetamide, dimethylsulfoxide and the like. In particular, the solvent comprises a mixture of ethyl acetate and ethanol.

In general, the temperature of contact of rosuvastatin or its alkali or alkaline salt and lysine in the solvent system is from ambient to the boiling point of the solvent
25 system, with elevated temperatures, but generally less than the boiling point, being preferred. It is not required that a complete solution is formed in this step, i.e. slurry or two phase solution are also possible, though a single solution is generally preferred.

The embodiment of the process further comprises addition of one or more of suitable anti-solvent before the isolation of crystalline rosuvastatin lysine. The suitable
30 anti-solvent may be selected from diethyl ether, diisopropyl ether, methyl tert-butyl ether and the like.

The embodiment of the process includes isolation or recovery of crystalline rosuvastatin lysine from the salt forming reaction by any convenient means. For example, the rosuvastatin lysine can be precipitated out of a solution or reaction

mixture. The precipitation may be spontaneous depending upon the solvent system used and the conditions. Alternatively, the precipitation can be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated. The precipitation may also be facilitated by reducing the volume of the solution/solvent
5 or by adding a contra solvent, i.e. a liquid miscible with the solvent in which the rosuvastatin lysine is less soluble. Seed crystals of rosuvastatin lysine may also be added to help induce precipitation. The crystalline rosuvastatin lysine can be isolated by conventional methods such as filtration or centrifugation, optionally washed and dried, preferably under diminished pressure.

10 In another general aspect, the invention provides an amorphous rosuvastatin lysine characterized by X-ray powder diffraction substantially as depicted in FIG.2.

The present invention provides amorphous rosuvastatin lysine having crystallinity less than about 30%. In particular, the amorphous rosuvastatin lysine having crystallinity less than about 20%, more particularly less than about 10%, still
15 more particularly less than about 5% and most particular not in detectable amount.

In another general aspect, the invention provides a process for the preparation of amorphous rosuvastatin lysine, the process comprising:

- (a) providing a solution of rosuvastatin lysine in one or more suitable solvents; and
- (b) obtaining the amorphous rosuvastatin lysine from the solution thereof by the
20 removal of solvents.

In general, the removal of solvent comprises one or more of suitable techniques like solvent evaporation, distillation, distillation under vacuum, rotational distillation device, spray drying, agitated thin film drying, freeze drying (lyophilization), and the like. In particular, rotational distillation like rotary evaporator or spray drying may be
25 used.

In general, the suitable solvent comprises one or more of methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, tert-butanol, ethyl acetate, isopropyl acetate, butyl acetate, iso-butyl acetate, acetone, methyl ethyl ketone, methyl tert-butyl ketone, toluene, xylene, hexane, cyclohexane, heptanes, methylene dichloride, ethylene
30 dichloride, chloroform, chlorobenzene, acetonitrile, dimethylformamide, N-methyl pyrrolidone, dimethylacetamide, dimethylsulfoxide and the like.

The embodiment of the process further includes addition of one or more of suitable anti-solvent selected from diethyl ether, diisopropyl ether, methyl tert-butyl ether and the like.

In its preferred aspect, the process embodiments include providing rosuvastatin acid solution in ethyl acetate and ethanol mixture, which may be treated with DL-lysine monohydrate at about 5°C to 10°C for sufficient time for salt formation. The product may be isolated by filtration upon salt formation followed by treating the wet-cake with
5 suitable anti-solvent like ethers selected from one or more of diethyl ether, diisopropyl ether, methyl tert-butyl ether and the like. Particularly, methyl tert-butyl ether to precipitate amorphous rosuvastatin lysine.

In general, the process of obtaining the amorphous rosuvastatin lysine as disclosed herein above leads to formation of the solid amorphous form of rosuvastatin
10 lysine.

Alternatively, the amorphous solid form of the rosuvastatin lysine may be obtained by spray drying or freeze drying of a solution containing the rosuvastatin lysine.

In general, the process for preparing an amorphous rosuvastatin lysine
15 comprises treating rosuvastatin lysine with a solvent under heating to obtain clear solution followed by removal of the solvent by any of the known methods disclosed herein above to obtain residue or partial removal of the solvent to obtain slurry or suspension of the rosuvastatin lysine. The obtained slurry or suspension or residue may be treated with one or more of suitable anti-solvents to precipitate the amorphous
20 rosuvastatin lysine. The amorphous rosuvastatin lysine may be isolated by the known method discloses herein above.

In general, the reaction mass may be heated in the range of about 40-90°C, particularly at about 40-45°C to obtain a clear solution. The distillation of solvent may be performed under vacuum on rota evaporator. The residue may be treated with one or
25 more of suitable anti-solvent selected from diethyl ether, diisopropyl ether, methyl tert-butyl ether and the like. In particular, methyl tert-butyl ether may be used to obtain amorphous rosuvastatin lysine.

In another general aspect, there is provided a rosuvastatin ethanolamine. In particular, the rosuvastatin ethanolamine may be in isolated form.

30 In another general aspect, the invention provides rosuvastatin ethanolamine in crystalline form. In general, the rosuvastatin ethanolamine obtained by the process of the present invention is anhydrous. The anhydrous rosuvastatin ethanolamine may contain water content less than about 1% wt/wt. In particular, the water content is less than about 0.5% wt/wt.

In another general aspect, the present invention provides rosuvastatin ethanolamine having at least about 70% crystallinity. In particular, the crystallinity of rosuvastatin ethanolamine may be from about 70% to 100%, more particularly from about 80% to 100%.

5 In another general aspect, the present invention provides a crystalline rosuvastatin ethanolamine salt characterized by X-ray powder diffraction pattern having peaks at about 10.9°, 16.6°, 18.3°, 18.9°, 19.6°, 20.8° and 23.1° (2θ).

The present invention provides a crystalline rosuvastatin ethanolamine characterized by X-ray diffraction substantially as depicted in FIG. 3. The crystalline
10 rosuvastatin ethanolamine is further characterized by differential scanning calorimetry having endothermic peak at about 134°C or differential scanning calorimetry substantially as depicted in FIG.4.

In another general aspect, the invention provides crystalline rosuvastatin ethanolamine having particle size distributions wherein the 10th volume percentile
15 particle size (D₁₀) is less than about 50 μm, the 50th volume percentile particle size (D₅₀) is less than about 250 μm, or the 90th volume percentile particle size (D₉₀) is less than about 500 μm, or any combination thereof.

In another general aspect, the present invention provides a process for preparing crystalline rosuvastatin ethanolamine, the process comprising:

- 20 (a) contacting rosuvastatin or its alkali or alkaline salt with monoethanolamine in one or more suitable solvents to obtain rosuvastatin ethanolamine solution; and
(b) obtaining the crystalline rosuvastatin ethanolamine from the solution thereof by removal of solvents.

In general, the rosuvastatin or its alkali or alkaline salt comprises of rosuvastatin
25 acid or rosuvastatin alkali or alkaline salt selected from sodium, potassium, lithium, barium, magnesium, calcium, strontium, and zinc. In particular, rosuvastatin alkali or alkaline salts may be converted to rosuvastatin acid before contacting with ethanolamine.

In general, the reaction may be carried out in one or more of suitable solvents.
30 The solvent system is particularly selected so as to facilitate the salt formation reaction and to allow subsequent separation of the resulting material. Advantageously, both rosuvastatin and the ethanolamine are dissolvable, at least partly, in the solvent system, at least at elevated temperatures. In the process, a mixture, slurry, or solution of rosuvastatin or its alkali or alkaline salt and a solvent may be contacted with

ethanolamine or conversely, a mixture or solution of ethanolamine and a solvent may be contacted with rosuvastatin or its alkali or alkaline salt.

In general, the ethanolamine may be monoethanolamine or its anhydrous or hydrate form. In particular, it may be monoethanolamine.

5 In further embodiments of the process, both may be combined with a solvent system prior to being contacted together, whereby the solvent system used for ethanolamine may be identical with or different from the solvent system used for the rosuvastatin or its alkali or alkaline salt. The solvent system can be comprised of a single solvent or a mixture of solvents. When two or more solvents are used, a two
10 phase reaction scheme may be used wherein the rosuvastatin or its alkali or alkaline salt and ethanolamine are primarily reacted in one phase and the resulting rosuvastatin ethanolamine is primarily present in the other phase due to, inter alia, solubility differences, etc. Suitable solvent comprises one or more of C₁-C₆ alcohols; esters; ketones; hydrocarbons; halogenated hydrocarbons and polar aprotic solvents.

15 In general, suitable solvent comprises one or more of water, methanol, ethanol, isopropanol, propanol, butanol, isobutanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dimethylsulfoxide, methylene dichloride, chlorobenzene, acetonitrile and the like.

In general, the temperature of contact of rosuvastatin or its alkali or alkaline salt
20 and ethanolamine in the solvent system is from ambient to the boiling point of the solvent system, with elevated temperatures, but generally less than the boiling point, being preferred. It is not required that a complete solution is formed in this step, i.e. slurry or two phase solution are also possible, though a single solution is generally preferred.

25 The embodiment of the process further comprises addition of one or more of suitable anti-solvent before the isolation of the crystalline rosuvastatin ethanolamine. The suitable anti-solvent may be selected from ethyl acetate, isopropyl acetate, n-butyl acetate, toluene, xylene, ethylbenzene, n-heptane, n-hexane, cyclohexane, diisopropyl ether, diethyl ether, methyl tert-butyl ether, dioxane and the like. In particular, methyl
30 tert-butyl ether may be used for isolation of crystalline rosuvastatin ethanolamine.

The embodiment of the process includes isolation or recovery of crystalline rosuvastatin ethanolamine from the salt forming reaction by any convenient means. For example, the rosuvastatin ethanolamine can be precipitated out of a solution or reaction mixture. The precipitation may be spontaneous depending upon the solvent system used

and the conditions. Alternatively, precipitation can be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated. The precipitation may also be facilitated by reducing the volume of the solution/solvent or by adding a contra solvent, i.e. a liquid miscible with the solvent in which the
5 rosuvastatin ethanolamine is less soluble. Seed crystals of rosuvastatin ethanolamine may also be added to help induce precipitation. The crystalline rosuvastatin ethanolamine may be isolated by conventional methods such as filtration or centrifugation, optionally washed and dried, preferably under diminished pressure.

Alternatively, rosuvastatin ethanolamine can be isolated by evaporating the
10 solvent and collecting residue. Such a method generally leads to an oil or solid amorphous form of rosuvastatin ethanolamine. Similarly, an amorphous solid form of the rosuvastatin ethanolamine may be recovered by spray drying a solution containing the rosuvastatin ethanolamine.

In the preferred embodiment, rosuvastatin is dissolved in acetonitrile and treated
15 with mono ethanolamine to obtain crystalline rosuvastatin ethanolamine. Particularly, rosuvastatin solution in acetonitrile may be obtained, which may be treated with mono ethanolamine at about -10 to 10°C for sufficient time for salt formation. The solvent may be removed by evaporation and reaction mass may be treated with ester solvent to precipitate crystalline rosuvastatin ethanolamine salt. The ester solvent comprises one
20 or more of ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate and the like. In particular, ethyl acetate may be used.

In another general aspect, there is provided a rosuvastatin arginine. In particular, the rosuvastatin arginine may be in isolated form.

In another general aspect, the invention provides rosuvastatin arginine in
25 crystalline form. In general, the rosuvastatin arginine obtained by the process of the present invention is anhydrous. The anhydrous rosuvastatin arginine may contain water content less than about 1% wt/wt. In particular, the water content is less than about 0.5% wt/wt.

In another general aspect, the present invention provides rosuvastatin arginine
30 having atleast about 30% crystallinity. In particular, the crystallinity of rosuvastatin arginine may be from about 30% to 100%, more particularly from about 35% to 100%.

In another general aspect, the present invention provides a crystalline rosuvastatin arginine characterized by X-ray powder diffraction pattern having peaks at about 17.7°, 18.8°, 20.2°, 21.1°, 23.7°, 26.0°, 26.3°, 26.7°, 31.7°, 32.2°, 33.9° (2 θ).

The present invention provides a crystalline rosuvastatin arginine characterized by X-ray diffraction substantially as depicted in FIG. 5. The crystalline rosuvastatin arginine is further characterized by differential scanning calorimetry having endothermic peak at about 139°C or differential scanning calorimetry substantially as depicted in FIG.6.

In another general aspect, the invention provides crystalline rosuvastatin arginine having particle size distributions wherein the 10th volume percentile particle size (D_{10}) is less than about 50 μm , the 50th volume percentile particle size (D_{50}) is less than about 250 μm , or the 90th volume percentile particle size (D_{90}) is less than about 500 μm , or any combination thereof.

In another general aspect, the present invention provides a process for preparing crystalline rosuvastatin arginine, the process comprising:

- (a) contacting rosuvastatin or its alkali or alkaline salt with arginine in one or more suitable solvents to obtain rosuvastatin arginine; and
- (b) obtaining the crystalline rosuvastatin arginine from the solution by the removal of the solvents.

In general, the rosuvastatin or its alkali or alkaline salt comprises of rosuvastatin acid or rosuvastatin alkali or alkaline salt selected from sodium, potassium, lithium, barium, magnesium, calcium, strontium, and zinc. In particular, rosuvastatin alkali or alkaline salts may be converted to rosuvastatin acid before contacting with arginine.

In general, the reaction may be carried out in one or more of suitable solvents. The solvent system is particularly selected so as to facilitate the salt formation reaction and to allow subsequent separation of the resulting material. Advantageously, both rosuvastatin and the arginine are dissolvable, at least partly, in the solvent system, at least at elevated temperatures. In the process, a mixture, slurry, or solution of rosuvastatin or its alkali or alkaline salt and a solvent may be contacted with arginine or conversely, a mixture or solution of arginine and a solvent may be contacted with rosuvastatin or its alkali or alkaline salt.

In general, the arginine may be L-arginine or its anhydrous or hydrate form. In particular, arginine may be L-arginine.

In further embodiments of the process, both may be combined with a solvent system prior to being contacted together, whereby the solvent system used for arginine may be identical with or different from the solvent system used for the rosuvastatin or its alkali or alkaline salt. The solvent system can be comprised of a single solvent or a

mixture of solvents. When two or more solvents are used, a two phase reaction scheme may be used wherein the rosuvastatin or its alkali or alkaline salt and arginine are primarily reacted in one phase and the resulting rosuvastatin arginine is primarily present in the other phase due to, inter alia, solubility differences, etc. Suitable solvent
5 comprises one or more of C₁-C₆ alcohols; esters; ketones; hydrocarbons; halogenated hydrocarbons and polar aprotic solvents.

In general, suitable solvent comprises one or more of water, methanol, ethanol, isopropanol, propanol, butanol, isobutanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, dimethylformamide, dimethylacetamide, N-methylpyrrolidone,
10 dimethylsulfoxide, methylene dichloride, chlorobenzene, acetonitrile and the like.

The embodiment of the process includes addition of one or more of suitable anti-solvent selected from diethyl ether, diisopropyl ether, methyl tert-butyl ether and the like.

The reaction is preferably carried out in suitable solvent. The solvent system is
15 preferably selected so as to facilitate the salt reaction and to allow subsequent separation of the resulting rosuvastatin arginine. Advantageously, both rosuvastatin and the arginine are dissolvable, at least partly, in the solvent system, at least at elevated temperatures. In the process, a mixture, slurry, or solution of rosuvastatin and a solvent may be contacted with arginine or conversely, a mixture or solution of arginine and a
20 solvent may be contacted with rosuvastatin. In another embodiment, both may be combined with a solvent system prior to being contacted together, whereby the solvent system used for arginine may be identical with or different from the solvent system used for the rosuvastatin. The solvent system can be comprised of a single solvent or a mixture of solvents. When two or more solvents are used, a two phase reaction scheme
25 may be used wherein the rosuvastatin and arginine are primarily reacted in one phase and the resulting rosuvastatin arginine is primarily present in the other phase due to, inter alia, solubility differences, etc. Suitable solvents include water, a lower alcohol (C₁-C₆) such as methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, tert-butanol; ester such as ethyl acetate, isopropyl acetate, butyl acetate, iso-butyl acetate;
30 ketone such as acetone, methyl ethyl ketone, methyl tert-butyl ketone; ether such as tetrahydrofuran, di ethyl ether, diisopropyl ether, dioxane; chlorinated solvent like methylene dichloride, ethylene dichloride, chloroform, chlorobenzene, hydrocarbon solvents like toluene, xylene, hexane, cyclohexane, heptanes; polar solvents like

acetonitrile, dimethylformamide, N-methyl pyrrolidone, dimethylacetamide, dimethyl sulfoxide and the like.

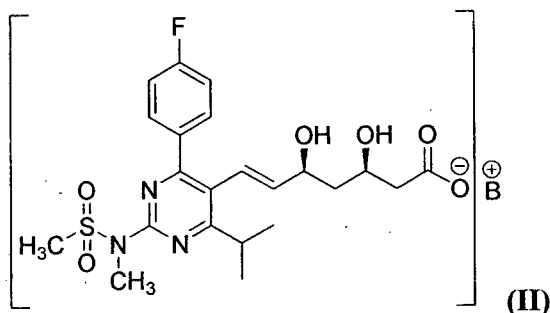
The temperature of contact of rosuvastatin and arginine in the solvent system is from ambient to the boiling point of the solvent system, with elevated temperatures, but
5 generally less than the boiling point, being preferred. It is not required that a complete solution is formed in this step, i.e. slurry or two phase solution are also possible, though a single solution is generally preferred.

The rosuvastatin arginine can be isolated or recovered from the salt forming reaction by any convenient means. For example, the rosuvastatin arginine can be
10 precipitated out of a solution or reaction mixture. The precipitation may be spontaneous depending upon the solvent system used and the conditions. Alternatively, the precipitation can be induced by reducing the temperature of the solvent, especially if the initial temperature at contact is elevated. The precipitation may also be facilitated by reducing the volume of the solution/solvent or by adding a contra solvent, i.e. a
15 liquid miscible with the solvent in which the rosuvastatin arginine is less soluble. Seed crystals of rosuvastatin arginine may also be added to help induce precipitation. The crystalline rosuvastatin arginine may be isolated by conventional methods such as filtration or centrifugation, optionally washed and dried, preferably under diminished pressure.

20 Alternatively, rosuvastatin arginine may be isolated by evaporating the solvent and collecting residue. Such a method generally leads to an oil or solid amorphous form of rosuvastatin arginine. Similarly, an amorphous solid form of the rosuvastatin arginine may be recovered by spray drying a solution containing the rosuvastatin arginine.

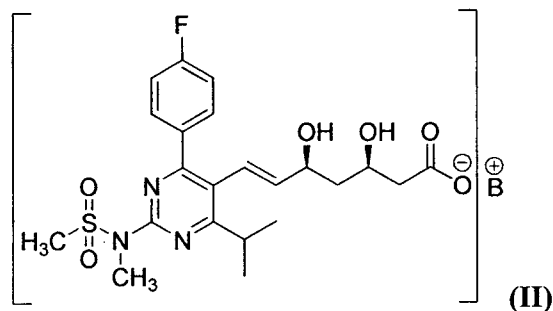
25 In the preferred embodiment, rosuvastatin may be dissolved in ethyl acetate and may be treated with arginine solution in ethanol and water followed by removal of solvent and treatment with diisopropyl ether to obtain rosuvastatin arginine.

In another general aspect, the invention provides chemically stable pharmaceutically acceptable salts of rosuvastatin of Formula (II),



wherein B is lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine, or ethylenediamine, which contains less than about 0.1% (wt/wt) 5-oxo impurity, lactone impurity, diastereomer impurity or cis-isomer impurity upon exposure to a relative humidity of 75% at 40°C for a period of about three months and are substantially free from residual solvents.

In another general aspect, the invention provides chemically stable pharmaceutically acceptable salts of rosuvastatin of Formula (II),



wherein B is lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine, or ethylenediamine, which contains less than about 0.1% (wt/wt) 5-oxo impurity, lactone impurity, diastereomer impurity or cis-isomer impurity upon exposure to a relative humidity of 60% at 25°C for a period of about three months and are substantially free from residual solvents.

In another general aspect, the invention provides pharmaceutically acceptable salts of rosuvastatin having purity greater than about 99% by area percentage of HPLC, wherein pharmaceutically acceptable salts selected from of lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

In another general aspect, the invention provides pharmaceutically acceptable salts of rosuvastatin substantially free from one or more of its impurities by area percentage of HPLC, wherein pharmaceutically acceptable salts is selected from lysine,

arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

The invention also encompasses pharmaceutical compositions comprising the pharmaceutically acceptable salts of rosuvastatin of Formula (II) of the invention. As
5 used herein, the term "pharmaceutical compositions" or "pharmaceutical formulations" includes tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

In another general aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of amorphous rosuvastatin lysine and
10 one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of crystalline rosuvastatin ethanolamine and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of crystalline rosuvastatin arginine and
15 one or more pharmaceutically acceptable carriers, excipients or diluents.

In another general aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of pharmaceutically acceptable salts of rosuvastatin, and one or more pharmaceutically acceptable carriers, excipients or
20 diluents, wherein pharmaceutically acceptable salts is selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

In another general aspect, the invention provides use of pharmaceutically acceptable salts of rosuvastatin for the treatment of hypercholesterolemia, hyperlipoproteinemia, atherosclerosis and dementia by administering to a patient a
25 therapeutically effective amount of pharmaceutically acceptable salts of rosuvastatin, wherein pharmaceutically acceptable salts is selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

Pharmaceutical compositions containing the rosuvastatin salts of the invention may be prepared by using diluents or excipients such as fillers, bulking agents, binders, wetting agents, disintegrating agents, surface active agents, and lubricants. Various
30 modes of administration of the pharmaceutical compositions of the invention can be selected depending on the therapeutic purpose, for example tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

Any excipient commonly known and used widely in the art can be used in the pharmaceutical composition.

Carriers used include, but are not limited to, lactose, white sugar, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, salicylic acid, and the like. Binders used include, but are not limited to, water, ethanol, propanol, simple syrup, glucose solutions, starch solutions, gelatin solutions, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate, polyvinyl pyrrolidone, and the like.

Disintegrating agents used include, but are not limited to, dried starch, sodium alginate, agar powder, laminaria powder, sodium hydrogen carbonate, calcium carbonate, fatty acid esters of polyoxyethylene sorbitan, sodium laurylsulfate, monoglyceride of stearic acid, starch, lactose, and the like.

Disintegration inhibitors used include, but are not limited to, white sugar, stearin, coconut butter, hydrogenated oils, and the like. Absorption accelerators used include, but are not limited to, quaternary ammonium base, sodium laurylsulfate, and the like.

Wetting agents used include, but are not limited to, glycerin, starch, and the like. Adsorbing agents used include, but are not limited to, starch, lactose, kaolin, bentonite, colloidal salicylic acid, and the like. Lubricants used include, but are not limited to, purified talc, stearates, boric acid powder, polyethylene glycol, and the like.

Tablets can be further coated with commonly known coating materials such as sugar coated tablets, gelatin film coated tablets, tablets coated with enteric coatings, tablets coated with films, double layered tablets, and multi-layered tablets.

When shaping the pharmaceutical composition into pill form, any commonly known excipient used in the art can be used. For example, carriers include, but are not limited to, lactose, starch, coconut butter, hardened vegetable oils, kaolin, talc, and the like. Binders used include, but are not limited to, gum arabic powder, tragacanth gum powder, gelatin, ethanol, and the like. Disintegrating agents used include, but are not limited to, agar, laminaria, and the like.

For the purpose of shaping the pharmaceutical composition in the form of suppositories, any commonly known excipient used in the art can be used. For example, excipients include, but are not limited to, polyethylene glycols, coconut butter, higher alcohols, esters of higher alcohols, gelatin, and semi-synthesized glycerides.

When preparing injectable pharmaceutical compositions, solutions and suspensions are sterilized and are preferably made isotonic to blood. Injection preparations may use carriers commonly known in the art. For example, carriers for injectable preparations include, but are not limited to, water, ethyl alcohol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, and fatty acid esters of polyoxyethylene sorbitan. One of ordinary skill in the art can easily determine with little or no experimentation the amount of sodium chloride, glucose, or glycerin necessary to make the injectable preparation isotonic.

Additional ingredients, such as dissolving agents, buffer agents, and analgesic agents may be added. If necessary, coloring agents, preservatives, perfumes, seasoning agents, sweetening agents, and other medicines may also be added to the desired preparations.

The amount of rosuvastatin salt contained in a pharmaceutical composition should be sufficient to treat, ameliorate, or reduce the symptoms of hypercholesterolemia, hyperlipoproteinemia, atherosclerosis and dementia. Particularly, rosuvastatin is present in an amount of about 1 % to about 60% by weight, and more preferably from about 1 % to about 35% by weight of the dose.

The pharmaceutical compositions of the invention may be administered in a variety of methods depending on the age, sex, and symptoms of the patient. For example, tablets, pills, solutions, suspensions, emulsions, granules and capsules may be orally administered. Injection preparations may be administered individually or mixed with injection transfusions such as glucose solutions and amino acid solutions intravenously.

In general, the starting material used for the preparation of pharmaceutically acceptable salts may be rosuvastatin condensed. The rosuvastatin condensed is compound of Formula (III) as shown herein after, which may be obtained by the known process of the prior arts like WO 00/49014 A1. Alternatively, the rosuvastatin condensed may be prepared by our own international (PCT) publication 2011/104725 A2, which is incorporated herein in its entirety.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification.

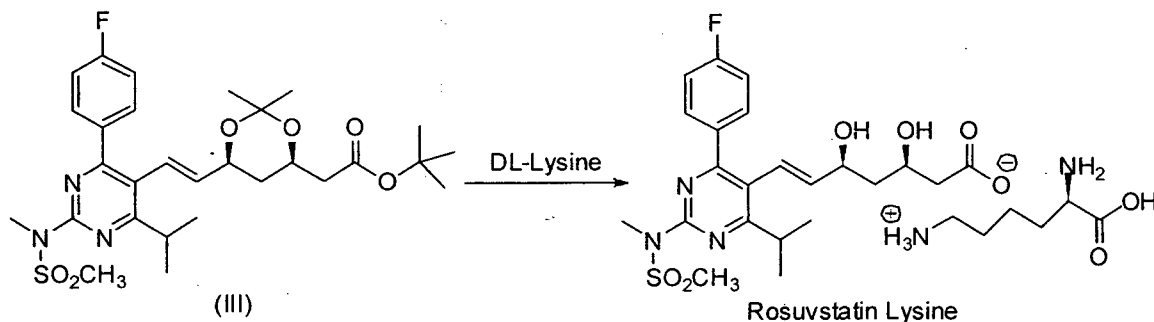
The novel salts and process for its preparation described in the present invention is demonstrated in examples illustrated below. These examples are provided as

illustration only and therefore should not be construed as limitation of the scope of invention.

Examples:

Example-1: Preparation of crystalline rosuvastatin lysine:

5



Rosuvastatin condensed compound (III) (100 gm) was hydrolyzed in 2.5 L methanol with dilute hydrochloric acid solution at 25°C followed by hydrolysis with sodium hydroxide solution at 30°C and adjusting the pH from about 7.5 to 8.5. The reaction mixture was distilled to remove 50% methanol and extracted with toluene (500 mL). The separated aqueous phase was treated with dilute hydrochloric acid to adjust the pH 3.5 to 4.0 to obtain rosuvastatin acid solution. The rosuvastatin acid solution was extracted with ethyl acetate (500 mL). Ethanol (200 mL) was added to the rosuvastatin acid solution in ethyl acetate followed by addition of DL-lysine monohydrate (27 g) at 5°C. The reaction mixture was maintained for 5 hours and precipitated rosuvastatin lysine was filtered. The wet-cake was slurried with methyl tert-butyl ether (500 mL) and filtered. The product thus obtained was washed and dried to obtain 85 g crystalline salt of rosuvastatin lysine having XRD pattern as depicted in FIG. 1.

The clear solution of rosuvastatin as the starting for preparation of rosuvastatin ethanolamine and rosuvastatin arginine may also be prepared by the process of example-1 starting from rosuvastatin condensed compound of Formula (III).

Example-2: Preparation of amorphous rosuvastatin lysine

Rosuvastatin lysine (6.0 g) and add methanol (120 mL) was heated at 40-45°C till obtain clear solution obtained. Solution was filtered through hyflow bed. From the filtrate methanol was distilled out under vacuum on rota evaporator. Further, MTBE (20 mL) was added and distilled out under vacuum up to dryness. Product was dried at

60 to 65°C under vacuum to afford the title compound as amorphous rosuvastatin lysine having XRD pattern as depicted in FIG. 2.

Example-3: Preparation of rosuvastatin ethanolamine

To a clear solution of rosuvastatin (11.6 gm) in 50 ml of acetonitrile was cooled
5 to 0 to 10°C, added monoethanol amine (1.5ml) to obtain the pH in the range of 8 to 9
and stirred for about 1 hour. The acetonitrile was removed under vacuum and ethyl
acetate was added to the reaction mass under stirring, obtained crystalline rosuvastatin
ethanolamine. The precipitates were filtered and dried. (Yield: 9.4gm). The X-ray
powder diffraction (FIG.3) and DSC (FIG.4).

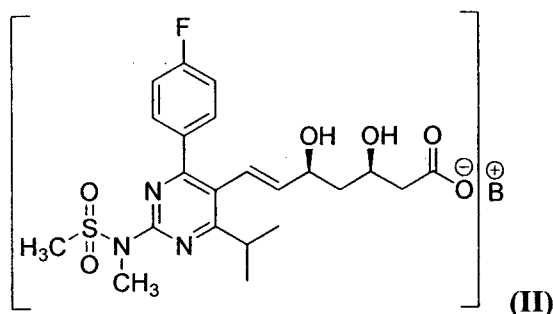
10 **Example-4: Preparation of rosuvastatin arginine:**

To a clear solution of rosuvastatin (25 gm) in 450 ml of ethyl acetate at 25°C,
was added L-arginine (8.6 gm) solution in mixture of ethanol (86 mL) and water (43
mL). The reaction mixture was stirred for 30 min and solvent distilled completely under
vacuum below 45°C. The residue was dissolved in ethylacetate (137 mL), ethanol (96
15 mL) and water (44 mL) mixture at 50°C to 55°C. The reaction mixture was stirred for
about 30 min and water (12 mL) was added to obtain clear solution at 55°C.
Ethylacetate (524 mL) was added and cooled to 25°C. The reaction mixture was
maintained. The solution was distilled under vacuum completely and residue was
treated with ethylacetate (100 mL) and heated to 55°C. The reaction mixture was
20 cooled to room temperature and treated with diisopropyl ether (200 mL) and stirred till
precipitation. The product thus obtained was filtered and washed and dried to obtain 18
g crystalline salt of rosuvastatin arginine having purity of 98.95% and melting point
130°C. The X-ray powder diffraction (FIG.5) and DSC (FIG.6).

While the present invention has been described in terms of its specific
25 embodiments, certain modifications and equivalents will be apparent to those skilled in
the art and are intended to be included within the scope of the present invention.

We Claim:

1. Pharmaceutically acceptable salts of rosuvastatin of Formula (II),



wherein B is an organic amine selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

2. The pharmaceutically acceptable salts as claimed in claim 1, which are crystalline.
3. The pharmaceutically acceptable salts as claimed in claim 1, which are amorphous.
4. Rosuvastatin lysine.
5. An isolated rosuvastatin lysine.
6. The rosuvastatin lysine as claimed in claim 4, which is crystalline.
7. The rosuvastatin lysine as claimed in claim 4, which is amorphous.
8. Rosuvastatin lysine having at least about 50% crystallinity.
9. Crystalline rosuvastatin lysine characterized by one or both of X-ray powder diffraction having characteristic peaks at about 5.5°, 9.3°, 10.9°, 14.0°, 15.2°, 17.6°, 20.1°, 21.5° and 22.6° (2θ), or X-ray powder diffraction substantially as depicted in FIG.1.
10. The amorphous rosuvastatin lysine as claimed in claim 7 characterized by X-ray powder diffraction substantially as depicted in FIG.2.
11. Crystalline rosuvastatin lysine having particle size distributions, wherein the 10th volume percentile particle size (D₁₀) is less than about 50 μm, the 50th volume percentile particle size (D₅₀) is less than about 250 μm, or the 90th volume percentile particle size (D₉₀) is less than about 500 μm, or any combination thereof.
12. A process for the preparation of crystalline rosuvastatin lysine, the process comprising:
 - (a) contacting rosuvastatin or its alkali or alkaline salt with lysine in one or more suitable solvents to obtain rosuvastatin lysine solution; and
 - (b) obtaining the crystalline rosuvastatin lysine from the solution thereof by the removal of the solvents.

13. The process as claimed in claim 12, wherein the suitable solvent comprises one or more of C₁-C₆ alcohols, esters, ketones, hydrocarbons, halogenated hydrocarbons, polar aprotic solvents, or mixtures thereof.
14. The process as claimed in claim 13, wherein the suitable solvent comprises one or
5 more of methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, tert-butanol, ethyl acetate, isopropyl acetate, butyl acetate, iso-butyl acetate, acetone, methyl ethyl ketone, methyl tert-butyl ketone, toluene, xylene, hexane, cyclohexane, heptanes, methylene dichloride, ethylene dichloride, chloroform, chlorobenzene, acetonitrile, dimethyl- formamide, N-methyl pyrrolidone,
10 dimethylacetamide, and dimethylsulfoxide.
15. The process as claimed in claim 12, further comprising adding one or more suitable anti-solvents comprising diethyl ether, diisopropyl ether, methyl tert-butyl ether, and the like.
16. The process as claimed in claim 12, wherein the rosuvastatin or its alkali or alkaline
15 salts is present in a mixture of solvents comprising one or more of ethyl acetate, isopropyl acetate, butyl acetate, methanol, ethanol, isopropanol, butanol, or mixtures thereof.
17. A process for the preparation of amorphous rosuvastatin lysine, the process comprising:
- 20 (a) providing a solution of rosuvastatin lysine in one or more suitable solvents; and
(b) obtaining the amorphous rosuvastatin lysine from the solution thereof by the removal of the solvents.
18. The process as claimed in claim 17, wherein the removal of solvent comprises one or more of suitable techniques like solvent evaporation, distillation, distillation
25 under vacuum, rotational distillation device, spray drying, agitated thin film drying, freeze drying (lyophilization), and the like.
19. The process as claimed in claim 17, further comprising adding one or more suitable anti-solvents comprising diethyl ether, diisopropyl ether, methyl tert-butyl ether, and the like.
- 30 20. The process as claimed in claim 17, wherein the suitable solvent comprises one or more of methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, tert-butanol, ethyl acetate, isopropyl acetate, butyl acetate, iso-butyl acetate, acetone, methyl ethyl ketone, methyl tert-butyl ketone, toluene, xylene, hexane,

cyclohexane, heptanes, methylene dichloride, ethylene dichloride, chloroform, chlorobenzene, acetonitrile, dimethyl- formamide, N-methyl pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

21. Rosuvastatin ethanolamine.

5 22. An isolated rosuvastatin ethanolamine.

23. The rosuvastatin ethanolamine as claimed in claim 21, which is crystalline.

24. Rosuvastatin ethanolamine having at least 70% crystallinity.

25. Crystalline rosuvastatin ethanolamine characterized by one or both of X-ray powder diffraction having characteristic peaks at about 10.9°, 16.6°, 18.3°, 18.9°, 19.6°,
10 20.8° and 23.1° (2 θ), or X-ray powder diffraction substantially as depicted in FIG.3.

26. The crystalline rosuvastatin ethanolamine as claimed in claim 25, characterized by one or both of differential scanning calorimetry having endothermic peak at about 134°C or a differential scanning calorimetry substantially as depicted in FIG.4.

27. Crystalline rosuvastatin ethanolamine having particle size distributions wherein the
15 10th volume percentile particle size (D₁₀) is less than about 50 μ m, the 50th volume percentile particle size (D₅₀) is less than about 250 μ m, or the 90th volume percentile particle size (D₉₀) is less than about 500 μ m, or any combination thereof.

28. A process for the preparation of crystalline rosuvastatin ethanolamine, the process comprising:

20 (a) contacting rosuvastatin or its alkali or alkaline salt with monoethanolamine in one or more suitable solvents to obtain rosuvastatin ethanolamine solution; and
(b) obtaining the rosuvastatin ethanolamine from the solution thereof by the removal of the solvents.

29. The process as claimed in claim 28, further comprising adding one or more suitable
25 anti-solvents.

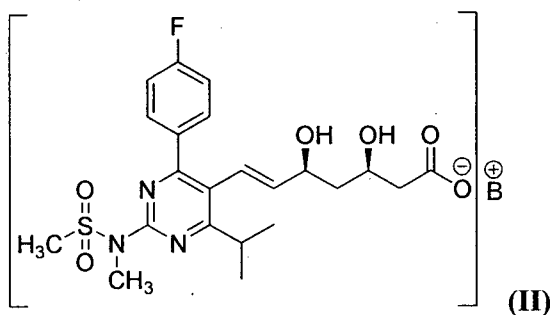
30. The process as claimed in claim 28, wherein the suitable solvent comprises one or more of water, methanol, ethanol, isopropanol, propanol, butanol, isobutanol, acetone, methyl ethyl ketone, methyl isobutyl ketone, dimethylformamide, dimethylacetamide, N-methylpyrrolidone, dimethylsulfoxide, methylene dichloride,
30 chlorobenzene, and acetonitrile.

31. The process as claimed in claim 28, wherein the removal of solvent comprises one or more of suitable techniques like solvent evaporation, distillation, distillation under vacuum, rotational distillation device, and the like.

32. The process as claimed in claim 29, wherein the suitable anti-solvent comprises one or more of ethyl acetate, isopropyl acetate, n-butyl acetate, toluene, xylene, ethylbenzene, n-heptane, n-hexane, cyclohexane, diisopropyl ether, diethyl ether, methyl tert-butyl ether, dioxane, and the like.
- 5 33. Rosuvastatin arginine.
34. An isolated rosuvastatin arginine.
35. The rosuvastatin arginine as claimed in claim 33, which is crystalline.
36. Rosuvastatin arginine having at least 30% crystallinity.
37. Crystalline rosuvastatin arginine characterized by one or both of X-ray powder
10 diffraction having characteristic peaks at about 17.7°, 18.8°, 20.2°, 21.1°, 23.7°, 26.0°, 26.3°, 26.7°, 31.7°, 32.2°, 33.9° (2 θ), or X-ray powder diffraction substantially as depicted in FIG.5.
38. The crystalline rosuvastatin arginine as claimed in claim 37, characterized by one or both of differential scanning calorimetry having endothermic peak at about 139°C
15 or a differential scanning calorimetry substantially as depicted in FIG.6.
39. Crystalline rosuvastatin arginine having particle size distributions wherein the 10th volume percentile particle size (D₁₀) is less than about 50 μ m, the 50th volume percentile particle size (D₅₀) is less than about 250 μ m, or the 90th volume percentile particle size (D₉₀) is less than about 500 μ m, or any combination thereof.
- 20 40. A process for the preparation of crystalline rosuvastatin arginine, the process comprising:
- (a) contacting rosuvastatin or its alkali or alkaline salts with arginine in one or more suitable solvents to obtain rosuvastatin arginine solution; and
- (b) obtaining the rosuvastatin arginine from the solution thereof by the removal of the
25 solvents.
41. The process as claimed in claim 40, wherein the suitable solvent comprises one or more of C₁-C₆ alcohols; esters; ketones; hydrocarbons; halogenated hydrocarbons and polar aprotic solvents.
42. The process as claimed in claim 41, wherein the suitable solvent comprises one or
30 more of methanol, ethanol, isopropanol, n-propanol, n-butanol, iso-butanol, tert-butanol, ethyl acetate, isopropyl acetate, butyl acetate, iso-butyl acetate, acetone, methyl ethyl ketone, methyl tert-butyl ketone, toluene, xylene, hexane, cyclohexane, heptanes, methylene dichloride, ethylene dichloride, chloroform,

chlorobenzene, acetonitrile, dimethyl- formamide, N-methyl pyrrolidone, dimethylacetamide, and dimethylsulfoxide.

43. The process as claimed in claim 40, further comprising adding one or more suitable anti-solvents selected from diethyl ether, diisopropyl ether, methyl tert-butyl ether, and the like.
44. The process as claimed in claim 40, wherein the rosuvastatin or its alkali or alkaline salts is present in a mixture of solvents comprising one or more of water, ethyl acetate, isopropyl acetate, butyl acetate, methanol, ethanol, isopropanol, butanol, or mixtures thereof.
45. Chemically stable pharmaceutically acceptable salts of rosuvastatin of Formula (II),



wherein B is lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine, or ethylenediamine, which contains less than about 0.1% (wt/wt) of 5-oxo impurity, lactone impurity, diastereomer impurity or *cis*-isomer impurity upon exposure to a relative humidity of 75% at 40°C for a period of about three months and are substantially free from residual solvents.

46. Chemically stable pharmaceutically acceptable salts of rosuvastatin as claimed in claim 45, which contains less than about 0.1% (wt/wt) of 5-oxo impurity, lactone impurity, diastereomer impurity or *cis*-isomer impurity upon exposure to a relative humidity of 60% at 25°C for a period of about three months and are substantially free from residual solvents.

47. Pharmaceutically acceptable salts of rosuvastatin having purity greater than about 99% by area percentage of HPLC, wherein the pharmaceutically acceptable salts are selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.

48. A pharmaceutical composition comprising a therapeutically effective amount of crystalline rosuvastatin lysine and one or more pharmaceutically acceptable carriers, excipients or diluents.
- 5 49. A pharmaceutical composition comprising a therapeutically effective amount of amorphous rosuvastatin lysine and one or more pharmaceutically acceptable carriers, excipients or diluents.
50. A pharmaceutical composition comprising a therapeutically effective amount of crystalline rosuvastatin arginine and one or more pharmaceutically acceptable carriers, excipients or diluents.
- 10 51. A pharmaceutical composition comprising a therapeutically effective amount of crystalline rosuvastatin ethanolamine and one or more pharmaceutically acceptable carriers, excipients or diluents.
52. A pharmaceutical composition comprising a therapeutically effective amount of a pharmaceutically acceptable salt of rosuvastatin, and one or more pharmaceutically acceptable carriers, excipients or diluents, wherein the pharmaceutically acceptable salt is selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.
- 15 53. Use of pharmaceutically acceptable salts of rosuvastatin for the treatment of hypercholesterolemia, hyperlipoproteinemia, atherosclerosis and dementia by administering to a patient a therapeutically effective amount of pharmaceutically acceptable salts of rosuvastatin, wherein the pharmaceutically acceptable salts is selected from lysine, arginine, triethanol amine, ethanolamine, choline, epolamine, meglumine and ethylenediamine.
- 20

25

30

FIG. 1

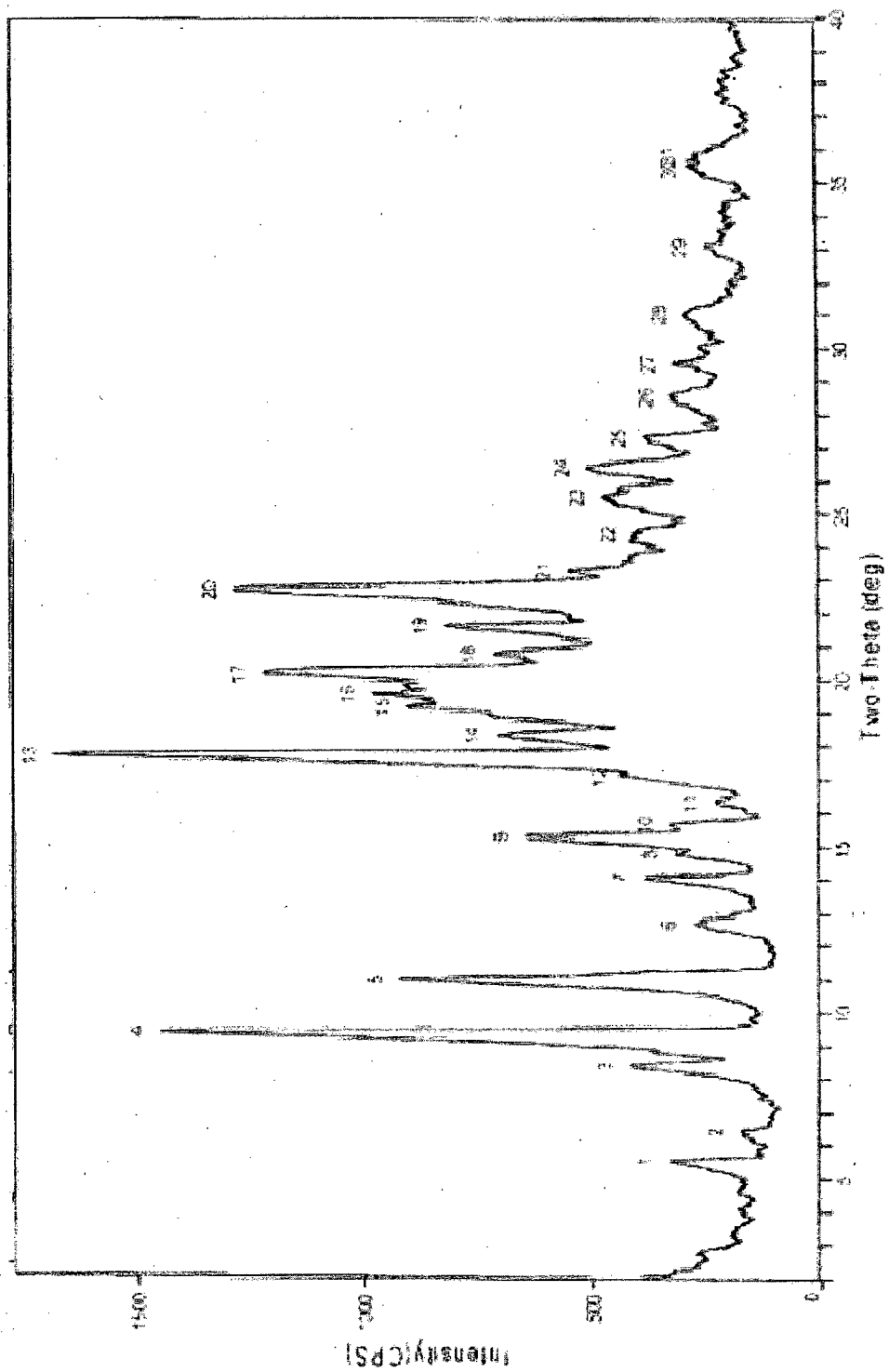


FIG. 2

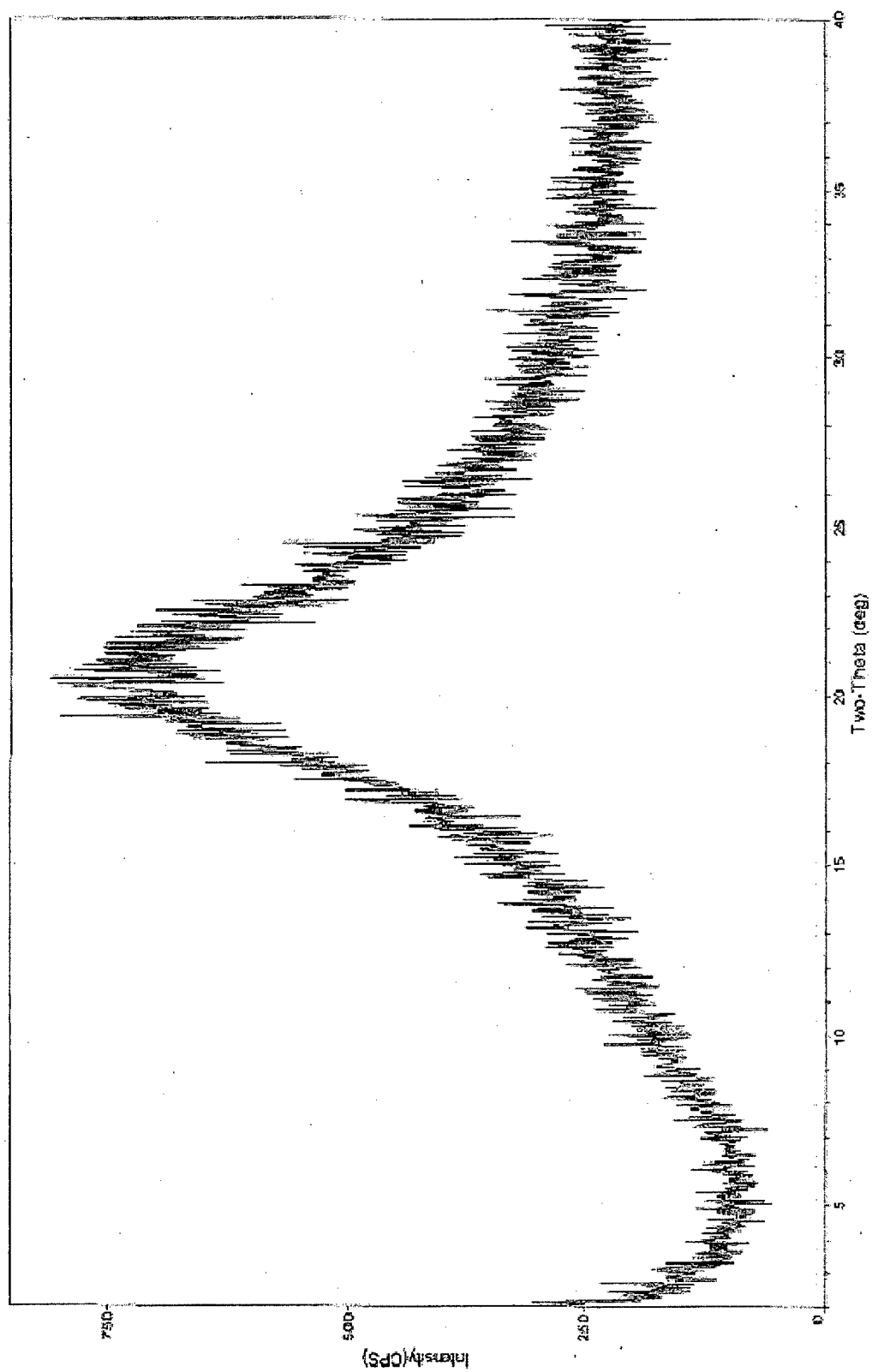


FIG. 3

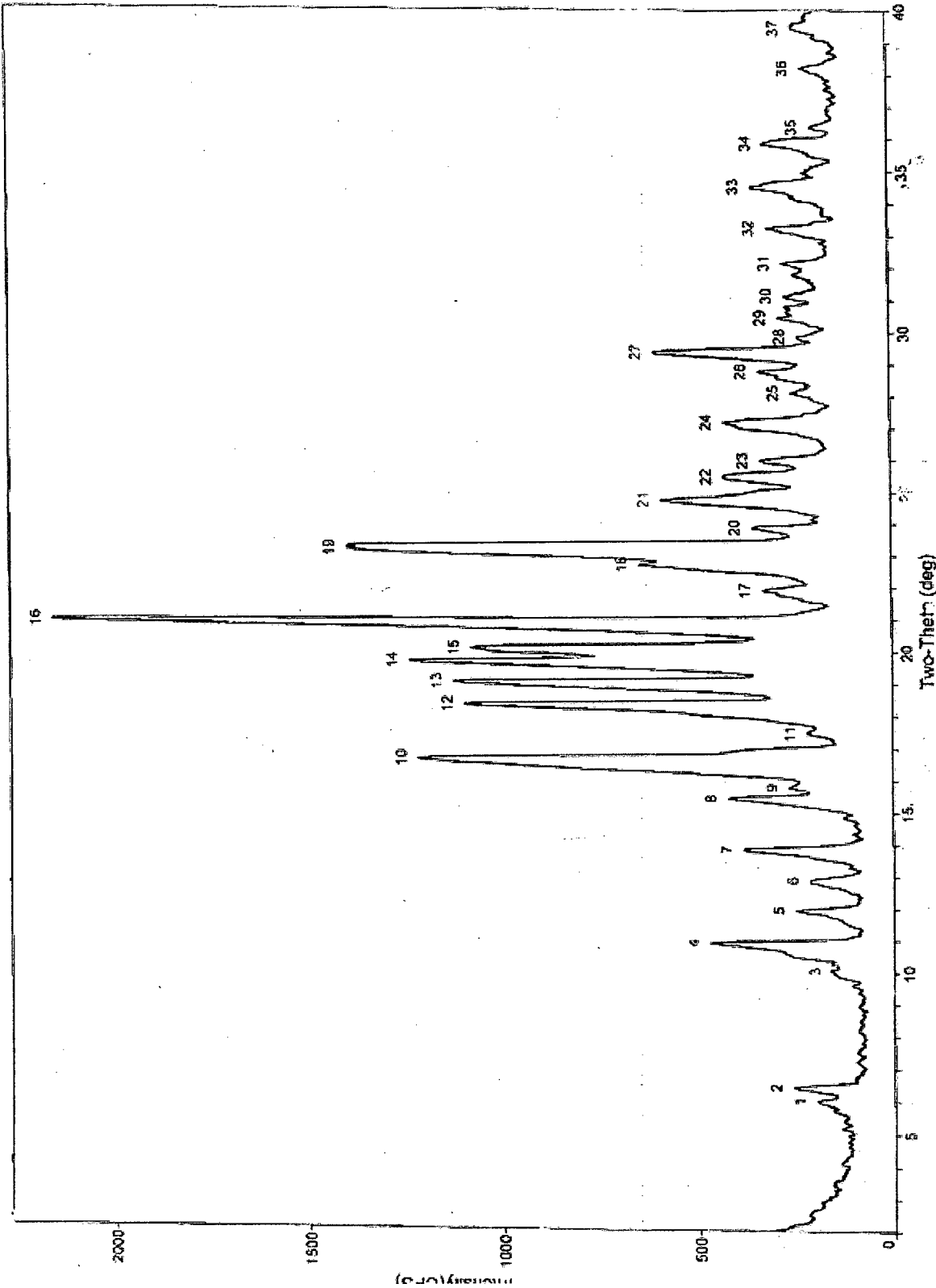


FIG. 4

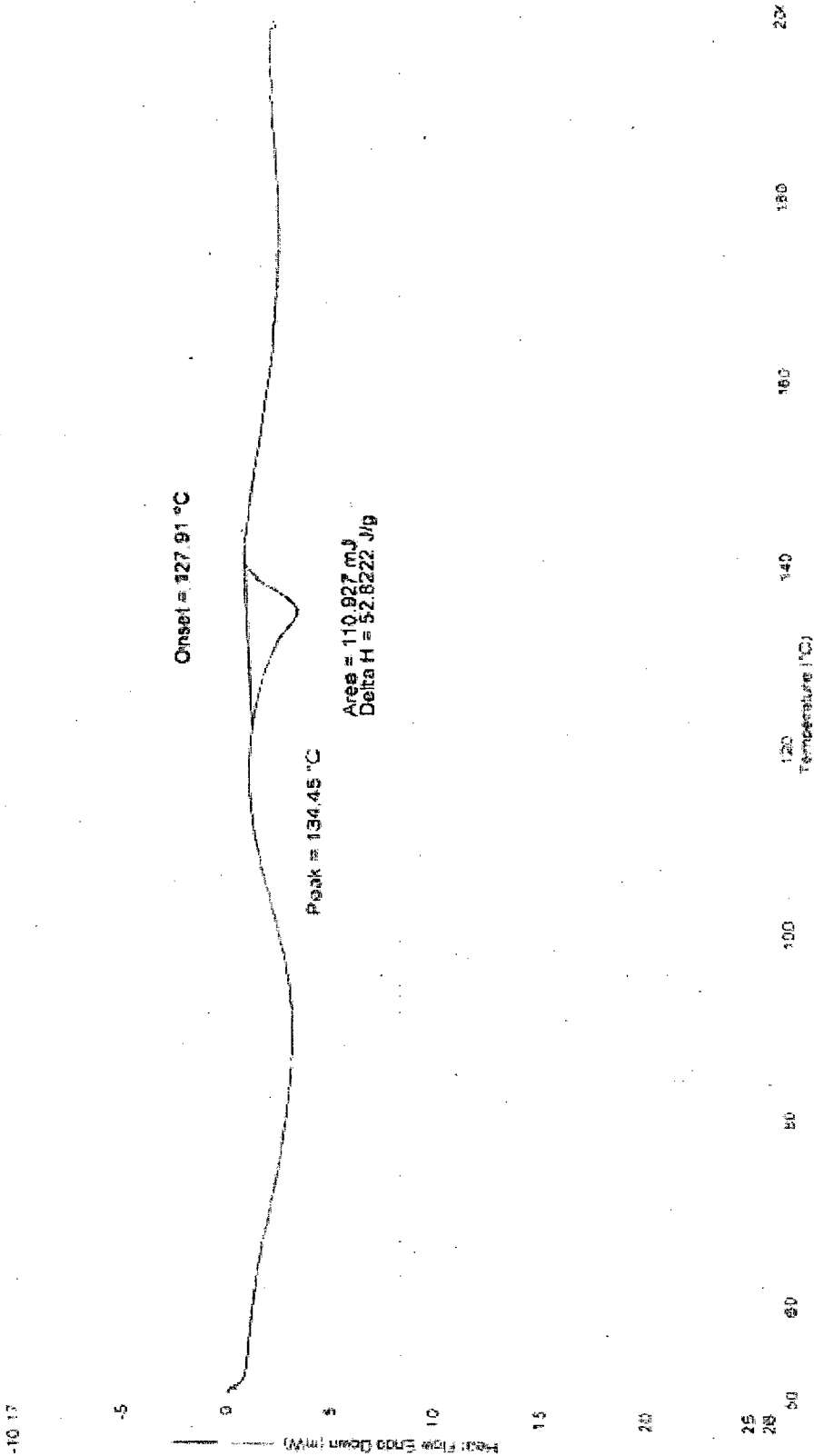


FIG. 5

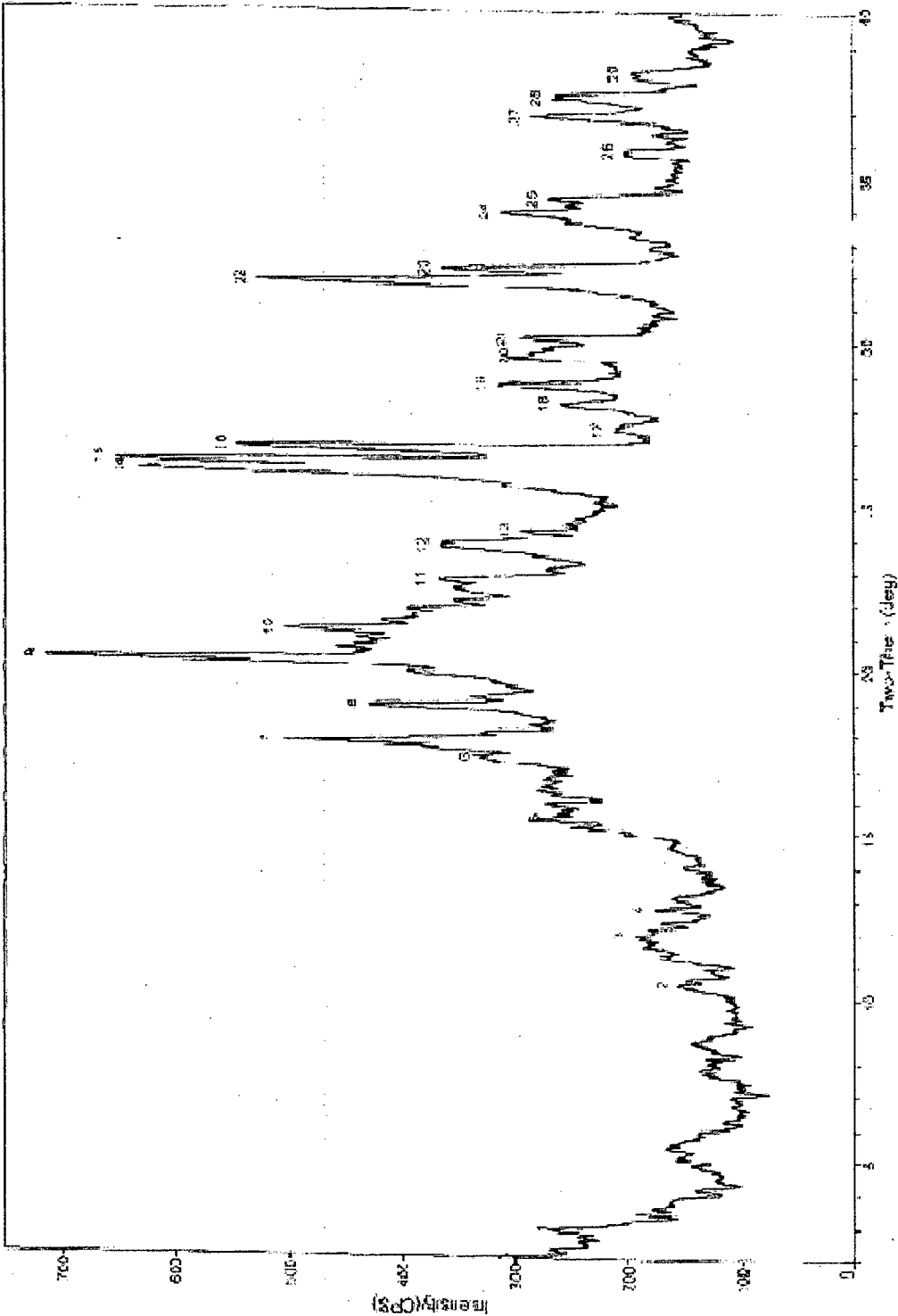
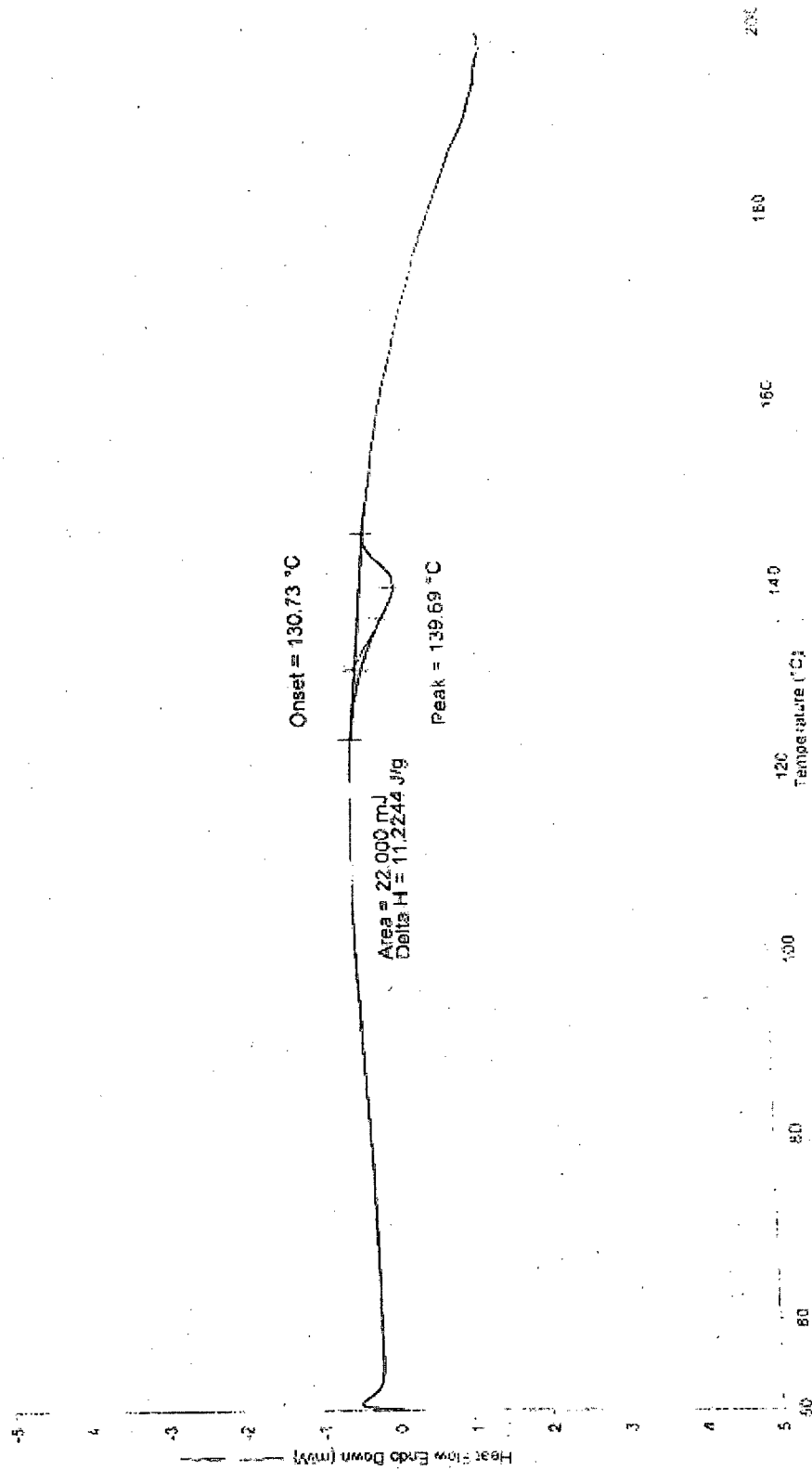


FIG. 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/000814

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/42 A61K31/505 A61P3/06
ADD.

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)
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 practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

21 March 2012

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/000814

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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