Process for preparing rosuvastatin calcium having purity greater than 93.65% substantially free of impurities determined by area percentage of HPLC at RRT 1.26, 1.31, 1.41, 1.56, 1.71 & 3.99.
PROCESS FOR PREPARING ROSUVASTATIN CALCIUM

FIELD OF THE INVENTION

The present invention relates to improved process for preparing Rosuvastatin Calcium, which is chemically known as hemi calcium salt of (E)-7-[4-(4-flurophenyl)-6-isopropyl-2- [methyl (methylsulfonyl) amino] pyrimidin-5-yl](3R, 5S)-3, 5-dihydroxy-6-heptenoic acid of formula (I). Rosuvastatin calcium is a HMG CoA reductase inhibitor and useful for the treatment hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

BACKGROUND OF THE INVENTION:

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

US Patent No. RE 37314 (Reissue of US 5260440) discloses Rosuvastatin that is chemically known as (E)-7-[4-(4-flurophenyl)-6-isopropyl-2-[methyl(methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxy-6-heptenoic acid and its salts, which are HMG CoA reductase inhibitors and useful in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

Recently available statins include lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin and atorvastatin. Lovastatin (disclosed in U.S. Pat. No. 4321938) and simvastatin (disclosed in U.S. Pat. No. 4444784) are administered in the lactone form. After absorption, the lactone ring is opened in the liver by chemical or enzymatic hydrolysis, and the active hydroxy acid is generated. Pravastatin (disclosed in U.S. Pat. No. 4346227), Fluvastatin (disclosed in U.S. Pat. No. 4739073) and cerivastatin (disclosed in U.S. Pat No. 5006530 and 5177080) are administered as the...
sodium salt, are entirely synthetic compounds that are in part structurally distinct from
the fungal derivatives of this class that contain a \( \text{hβkαhydronaphthalβnβ} \) ring. Atorvastatin and two new 'superstates' i.e. rosuvastatin and pitavastatin are administered as calcium salts.

Rosuvastatin Calcium (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methyl sulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxy-6-heptenoic acid and its salts is a HMG-CoA reductase inhibitor, a superstatin developed by Shionogi for the treatment of hyperlipidaemia (Ann Rep, Shionogi, 1996, Direct Communication, Shionogi 8 Feb. 1999 and 25 Feb. 2000). It can lower LDL-cholesterol and triglycerides more effectively than the first generation drugs. Rosuvastatin calcium has the following structure being shown by formula (I)

![Rosuvastatin calcium structure](image)

Rosuvastatin calcium is marketed under the trade name of CRESTOR for treatment of a mammal such as a human. Accordingly CRESTOR 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, 20 mg dose for patients with marked hypercholesterolemia and aggressive lipid targets (>192 mg/dL), and the 40 mg dose for patients who have not been responsive to lower doses. WO 03/032995 further discloses a method of preventing dementia by administering to a patient rosuvastatin.

U.S. Pat. No. 5,260,440 discloses the process to produce rosuvastatin salt. The process of U.S. Pat. No. 5,260,440 starts with the methyl ester of rosuvastatin, known an (methyl-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino) pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (methyl rosuvastatin)). The process for preparation of the intermediates disclosed in the '440 patent is incorporated herein by reference.
In the '440 patent, rosuvastatin sodium is prepared from its methyl ester according to Example 1 (6) by adding sodium hydroxide to a solution of the methyl ester in ethanol, followed inter alia by distillation, followed by addition of ether to the residue obtained from distillation. When preparing a salt of rosuvastatin, the present applicants found that diethyl ether may not be used in production; after distillation of the solvent, the present applicants obtained a viscous oil that hardly precipitates in diethyl ether.

Preparation of Rosuvastatin calcium is disclosed in WO/ 04/052867, WO 00/49041 and WO 03/097614. The processes disclosed in these publications are of general nature.

WO2005068435 discloses a method of preparation of the amorphous hemi-calcium salt of Rosuvastatin by a one-pot manufacturing process from the Rosuvastatin ester or lactone intermediate. The invention describes use of alkali metal hydroxides for the purpose of the hydrolysis of Rosuvastatin ester or lactone intermediate in a suitable solvent system, which is subjected to the treatment of Calcium acetate or Calcium hydroxide to afford amorphous hemi-calcium salt of Rosuvastatin without isolating any intermediate alkali metal salt of Rosuvastatin.

WO2004/014872 disclosed an improved process for manufacturing rosuvastatin calcium salt, according to this patent application, various ammonium salts of Rosuvastatin is subjected to the treatment of inorganic bases containing alkali metal cations. The in-situ obtained Rosuvastatin alkali metal salt is converted to its corresponding calcium salt by means of reacting Rosuvastatin alkali metal salt with calcium chloride dihydrate.

US 2005/0080134 A1 discloses the process for preparation of rosuvastatin calcium from C_1 to C_4 alkyl ester of rosuvastatin with a base in presence of a C_1 to C_4 alcohol. The patent applications also disclose the process for preparation of rosuvastatin calcium by use of phase transfer catalyst. The process mainly concern with the hydrolysis of ester with alkali. The process includes the absence of impurities at different RRT's when compared with those of CRESTOR tablets when measured with area percentage of HPLC as the scope of invention.

US 2005/0187234 A1 discloses various degraded products of rosuvastatin. These degraded products of rosuvastatin are prepared by using the technique of irradiation with visible light and separating them by column chromatography or TLC.
These degraded products are independently disclosed as the scope of the present invention and considered as the reference standards.

WO 2005/040134 A1 discloses the amorphous rosuvastatin calcium having purity of more than 99% with diastereoisomeric impurity less than 0.5% by HPLC. The process for preparation of amorphous rosuvastatin calcium, from a solution of rosuvastatin calcium in one or more organic solvents, recovering the amorphous form of rosuvastatin calcium by removal of solvent i.e. either by distillation, distillation under vacuum, evaporation, spray drying, freeze-drying, lyophilization, filtration, filtration under vacuum, decantation, and centrifugation is also the scope of present invention.

In all the prior art purpose of the invention is related to the isolation of Rosuvastatin calcium salt that involves in-situ formation of various alkali metal salts of Rosuvastatin, which are not isolated. Moreover the various prior art process teaches the deprotection by the inorganic acid. However, it may produce higher level of impurities.

Therefore, there is a need to have simple process, that allows for preparation of highly pure rosuvastatin calcium in a facile manner on an industrial scale, which yields rosuvastatin by deprotection of hydroxy protecting group and in high purity.

The inventors of the present invention has found that the use of organic acid in deprotection step would alleviates the hitherto problems associated with prior art for preparing Rosuvastatin salts as described above.

**Object of Invention:**

The main object of the present invention is to provide a process for preparation of Rosuvastatin and its pharmaceutically acceptable salts.

It is an object of the present invention to provide a process for preparing rosuvastatin Calcium that yields highly pure rosuvastatin calcium with single individual impurity less than 0.1% by area percentage of HPLC

Further object of the present invention is to provide a process for preparing rosuvastatin by using organic acid in deprotection.

**BRIEF DESCRIPTION OF FIGURES:**

A preferred embodiment of the invention will now be described, by way of example only, with reference to the accompanying figures in which:

**FIG.1:** It represents X-ray diffraction of amorphous rosuvastatin calcium

**FIG.2:** It repcrbcn1b HPLC chromatogram of solid rosuvastatin calcium

**DETAILED DESCRIPTION:**
According to the present invention, there is provided an improved process for the preparation of Rosuvastatin diol ester of formula (Ia), which comprises

![Chemical Structure](image)

a) reacting tert-butyl (E)-6-(2-[(4-fluorophenyl)-6-isopropyl][methyl(methylsulfonyl) amino]pyrimidin-5-yl) vinyl]- (4R, 6S)-2,2-dimethyl[1,3] dioxan-4yl) acetate of formula (II)

![Chemical Structure](image)

with organic acid in polar solvent selected from C1 to C4 alcoholic solvent to obtain a solution;
b) gradually cooling the solution to first temperature and slowly to second temperature;
c) addition of a base to adjust the pH;
d) isolating the Rosuvastatin diol ester of formula (Ia).

The organic acid can be selected from the group comprising of oxalic acid, maleic acid, citric acid, acetic acid, preferably oxalic acid.

The deprotection can be performed in the polar solvent selected from C1 to C4 alcoholic solvent is methanol, ethanol, propanol, isopropanol and butanol or acetonitrile, preferably methanol.

The process as described herein as the preferred embodiment is carried out at a higher temperature of about 50°C to about 55°C, which is gradually cooled to about 40°C and further to about 20°C.
The addition of base like liquor ammonia is carried out preferably at lower temperature of 10°C to 20°C to adjust the pH of about less than 10, preferably of 8 to 9.

Thus, Rosuvastatin diol ester (Ia) obtained by deprotection reaction can be isolated and subsequently converted to its calcium salt or without isolating it can be converted to its calcium salt.

In preferred embodiments, there is provided a process of preparing amorphous rosuvastatin calcium substantially free of impurities comprising the steps of:

a) reacting tert-butyl (E)- (6- {2- [4- (4-fluorophenyl)-6-isopropy2- [methyl (methylsulfonyl) amino]pyrimidin-5-yl] vinyl} (4R, 6S)-2,2-dimethyl[1,3] dioxan-4yl) acetate of formula (II)

with organic acid in presence of Ci to C4 alcoholic solvent to obtain a solution;

b) addition of a base to adjust the pH to obtain

c) Isolating Rosuvastatin diol ester of formula (Ia);

d) treating said rosuvastatin diol ester of formula (Ia) with a base in Ci to C4 alcohol to obtain the solution;

e) addition of acid to adjust the pH;

f) addition of source of calcium ion to the solution to precipitate rosuvastatin calcium;

and
g) isolating amorphous rosuvastatin calcium substantially free from impurities.

The process as described herein, wherein the base in the step (b) is alkali hydroxides preferably sodium or potassium hydroxide is also within the scope of present invention.
The addition of acid like HCl in step (e) is carried out at lower temperature of about 100°C to 200°C thereby adjusting the pH of about less than 9, preferably of 7.5 to 8.5.

In preferred embodiments, Rosuvastatin obtained by deprotection reaction is treated with calcium chloride in presence of alkali metal hydroxide such as sodium hydroxide to give rosuvastatin calcium.

According to embodiment of the present invention, there is provided amorphous rosuvastatin calcium having purity greater than 99.65% and does not having detectable level of impurities when measured by area percentage of HPLC at RRT 1.26, 1.31, 1.41, 1.56, 1.71 and 3.99.

The present invention further provides a process for preparing amorphous rosuvastatin calcium substantially free of impurities comprising the steps of:

a) reacting a diol protected alkyl ester derivative of formula (II)

\[
\text{(II)}
\]

with organic acid in presence of C1 to C4 alcoholic solvent at higher temperature to obtain a solution;
b) gradually cooling the solution to first temperature and slowly to second temperature;
c) addition of a base to adjust the pH;
d) isolating the wet-cake of rosuvastatin diol ester of formula (Ia);
e) washing the wet-cake in water at 40°C-45°C and drying;
f) treating the dry rosuvastatin diol ester of formula (Ia) with a base in C1 to C4 alcohol solvent to obtain the solution;
g) cooling the solution to second temperature;
h) addition of acid to adjust the pH;
i) removing the traces of organic solvent;
j) addition of source of calcium ion to the solution to precipitate rosuvastatin calcium; and
isolating amorphous rosuvastatin calcium substantially free from impurities.

The process for preparing Rosuvastatin calcium (I) according to the present invention is depicted by below mentioned reaction scheme:

According to the present invention there is provided a calcium salt of the compound (E)-7-[4-(4-flurophenyl)-6-isopropyl-2-[methyl (methylsulfonyl) amino]pyrimidin-5-yl](3R, 5S)-3, 5-dihydroxy-6-heptenoic acid with high purity level (individual known/unknown impurity less than 0.1%).

The process for preparing rosuvastatin calcium according to present invention is simple, easy safe and yields Rosuvastatin Calcium with single individual impurity, less than 0.1%.

Although the invention has been described with reference to a specific example, it will be appreciated by those skilled in the art that the invention can be embodied in many other forms.

The Impurity Profile Determination of Rosuvastatin calcium comprised testing a sample using HPLC. Typically, the HPLC testing parameters included a column of Hypersil BDS C18 5 µm 4.6*250 mm (Part No. 28105-020 or equivalent column) at a temperature of 25°C and eluted with a two solvent system. A first reservoir, Reservoir A, contained 0.005 M ammonium formate dissolved in 1000 ml water, adjusted to pH 4.0 with H₃PO₄, and a second reservoir, Reservoir B, contained acetonitrile. The gradient was as follows: at the initial time, 40% Reservoir A and 60% Reservoir B; time 28.5 min 36% Reservoir A and 64% Reservoir B; and at time 43.0 min 36% Reservoir A and 64% Reservoir B, and at time 50 min 40% Reservoir A and 60%
Reservoir B. The system equilibrated further for 10 min and a flow rate of 1.0 ml/min. The detector was set for 245 nm. The sample volume was 10 µL and the diluent was acetonitrile: water 50:50. As commonly known by the skilled artisan, the mobile phase composition and flow rate may be varied in order to achieve the required system suitability.

The sample was prepared by weighing accurately about 10 mg of Rosuvastatin Ca sample in a 20 ml amber volumetric flask. Dissolving the sample with 10 ml of acetonitrile and diluting to the desired volume with water.

Thereafter, the freshly prepared sample was injected. The sample solutions were injected into the chromatograph and the chromatogram of sample was continued up to the end of the gradient. Thereafter, the areas for each peak in each solution was determined using a suitable integrator. The calculations were obtained using the following formula:

Impurity Profile Determination

\[
\%\text{ impurity} = \frac{\text{area impurity in sample}}{\text{Total area}} \times 100
\]

**Example-1:**

50.0 g of alkyl ester diol protected derivative of rosuvastatin of formula (II) was taken in 750 mL of methanol under stirring to prepare a solution. A solution was maintained at temperature of about 55 to 65°C, then the mixture of oxalic acid (12g) and water (250ml) is added slowly within 1hr time. After complete addition, solution was gradually cooled first at 25°C-35°C and then further at 10°C-20°C. 17 mL of Liq. ammonia was added to adjust the pH between 8-9 and solution was for 1 hr. The product was filtered and washed with 2*50mL MeOH-.tfcO (1:1). The above wet cake was taken in 500 mL water and heated to 40°C-45°C and stirred for 1 hr. further filter wash with hot water (Water temperature is 40-45°C). Dry the cake to get 42 g of Rosuvastatin diol ester.

**Example-2:**

40 g of Rosuvastatin diol ester as prepared in example-1 above was taken in 400 mL of methanol at 25°C to 35°C and cooled to 20°-25°C. The mixture of sodium hydroxide (3.6 g) and water (72 mL) solution was added to above solution within 30 minutes. After complete addition, the solution was stirred and further cooled to 10°-20°C. The pH was adjusted between 7.5-8.5 by IN HCl (17 mL). Remaining mixture was washed with toluene at 20° to 30°C. The aqueous layer was subjected to distillation
under vacuum to remove MeOH below 50°C till remaining volume becomes 130 mL. The volume was adjusted to 250 mL by adding water. The remaining mixture was passed through hydrobed and washed with water. A solution of 10.3 g calcium chloride in 40 mL water was added to the reaction mixture and the solution was filtered at 15°C to 20°C. The temperature was raised up to 25°C to 35°C and stirred for 1 hr. The product was filtered and washed with water. The product was dried at 50°C to 55°C to get 34.7 g of Rosuvastatin Calcium having individual impurity less than 0.1% HPLC Purity ≥ 99.65%.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art would appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications.

Table-1
Comparison of HPLC chromtogram of the present invention with that of CRESTOR Tablets (40 mg Lot)

<table>
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<tr>
<th>Samples</th>
<th>RRT 0.54</th>
<th>RRT 1.00</th>
<th>RRT 1.21</th>
<th>RRT 1.26</th>
<th>RRT 1.31</th>
<th>RRT 1.41</th>
<th>RRT 1.51</th>
<th>RRT 1.56</th>
<th>RRT 1.71</th>
<th>RRT 2.24</th>
<th>RRT 3.99</th>
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<tr>
<td>CRESTOR</td>
<td>0.04</td>
<td>99.45</td>
<td>ND</td>
<td>0.28</td>
<td>0.01</td>
<td>ND</td>
<td>0.01</td>
<td>0.06</td>
<td>ND</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Sample as prepared in</td>
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<td>Example-2</td>
<td>ND</td>
<td>99.82</td>
<td>0.03</td>
<td>ND</td>
<td>ND</td>
<td>0.02</td>
<td>0.08</td>
<td>ND</td>
<td>ND</td>
<td>0.03</td>
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We claims

1. Amorphous rosuvastatin calcium having purity greater than 99.65%, substantially free of impurities determined by area percentage of HPLC at RRT 1.26, 1.31, 1.41, 1.56, 1.71 & 3.99.

2. A process for preparing rosuvastatin diol ester of formula (Ia),

\[
\text{(Ia)}
\]

which comprises:

a) reacting tert-butyl (E)- (6- [2- [4- (4-fluorophenyl)-6-isopropyl-]methyl (methylsulfonyl) amino]pyrimidin-5-yl] vinyl)- (4R, 6S)-2,2-dimethyl[1,3]dioxan-4yl) acetate of formula (II)

\[
\text{(II)}
\]

with organic acid in polar solvent at elevated temperature to obtain a solution;

b) gradually cooling the solution to first temperature and slowly to second temperature;

c) addition of a base to adjust the pH; and

d) isolating the rosuvastatin diol ester of formula (Ia).

3. A process as claimed in claim 2, wherein the organic acid is oxalic acid, maleic acid, citric acid, acetic acid, preferably oxalic acid.

4. A process as claimed in claim 2 or 3, wherein the polar solvent is a C1 to C4 alcoholic solvent.

5. A process as claimed in claim 4 wherein said alcoholic solvent is methanol.
6. A process as claimed in any one of claims 2 to 6, wherein said elevated temperature is of 50°C to 55°C.

7. A process as claimed in any one of claims 2 to 6 wherein in step (b), the first temperature is 40°C to 42°C.

8. A process as claimed in any one of claims 2 to 7 wherein in step (b) the second temperature is 10°C to 20°C.

9. A process as claimed in any one of claims 2 to 8 wherein the addition of base is at second temperature.

10. A process as claimed in any one of claims 2 to 9 wherein the base is liquor ammonia.

11. A process as claimed in any one of claims 2 to 10 wherein the pH is of less than about 10, preferably of 8 to 9.

12. A process for preparing Rosuvastatin calcium, which comprises the steps of

a) reacting tert-butyl (E)-{(6-2-[4-(4-fluorophenyl)-6-isopropyl[methylsulfonyl]amino]pyrimidin-5-yl} vinyl)-(4R, 6S)-2,2-dimethyl[1,3]dioxan-4yl) acetate of formula (II) with organic acid in presence of C1 to C4 alcoholic solvent to obtain a solution; 

b) addition of a base to adjust the pH; 

c) isolating rosuvastatin diol ester of formula (Ia); 

d) treating the dry rosuvastatin diol ester of formula (Ia) with a base in C1 to C4 alcohol to obtain the solution; 

e) addition of acid to adjust the pH; 

f) addition of source of calcium ion to the solution to precipitate rosuvastatin calcium; and 

g) isolating amorphous rosuvastatin calcium substantially free from impurities.
13. A process of preparing amorphous rosuvastatin calcium substantially free of impurities comprising the steps of:
   a) reacting a diol protected alkyl ester derivative of formula (II)
   \[
   \text{Formula (II)}
   \]
   with organic acid in presence of C$_1$ to C$_4$ alcoholic solvent at higher temperature to obtain a solution;
   b) gradually cooling the solution to first temperature and slowly to second temperature;
   c) addition of a base to adjust the pH;
   d) isolating the wet-cake of rosuvastatin diol ester of formula (Ia);
   e) washing the wet-cake in water at 40°C-45°C and drying;
   f) treating the dry rosuvastatin diol ester of formula (Ia) with a base in Ci to C$_4$ alcohol solvent to obtain the solution;
   g) cooling the solution to second temperature;
   h) addition of acid to adjust the pH;
   i) removing the traces of organic solvent;
   j) addition of source of calcium ion to the solution to precipitate rosuvastatin calcium; and
   k) isolating amorphous rosuvastatin calcium substantially free from impurities.

14. A process as claimed in claim 12 or 13, wherein said organic acid is oxalic acid, maleic acid, citric acid, acetic acid, preferably oxalic acid.

15. A process as claimed in claim 12 or 13, wherein the Ci to C$_4$ alcoholic solvent in step is methanol.

16. A process as claimed claim 12 or 13, wherein the higher temperature is of about 50°C to about 55°C.

17. A process of claim 11 or 12, wherein the first temperature is of about 40°C to about 42°C.
18. A process of claim 11 or 12, wherein the second temperature is of about 10°C to about 20°C.
19. A process of claim 11 or 12, wherein the base in step (c) is liquor ammonia.
20. A process of claim 11 or 12, wherein the pH in the step (c) is less than about 10, preferably of 8 to 9.
21. A process as claimed in claim 13, wherein the base in the step (f) is alkali hydroxides preferably sodium or potassium hydroxide.
22. A process as claimed in claim 12 or 13, wherein the acid is HCl.
23. A process as claimed in claim 13, wherein the pH in the step (h) is of about less than 9, preferably of 7.5 to 8.5.
24. A process as claimed in claim 12 or 13, wherein the source of calcium is calcium chloride.
25. A process as claimed in claim 2, 12 or 13, wherein the calcium salt contains less than or of about 0.35% total impurities as measured by area percentage HPLC.
26. A process as claimed in claim 25, wherein the impurities present in Rosuvastatin calcium are less than about 0.3% as measured by area percentage of HPLC.
27. Rosuvastatin calcium in solid state does not having detectable level of impurities when measured by HPLC at RRT 1.26, 1.31, 1.41, 1.56, 1.71 & 3.99.
28. Rosuvastatin calcium of claim 1, wherein the impurities are less than about 0.01% as measured by area percentage of HPLC.
29. Rosuvastatin calcium claim 1, wherein the single individual impurity at RRT 1.21 is of less than about 0.07%, preferably not detected by area percentage of HPLC.
30. Rosuvastatin calcium of claim 1, wherein the single individual impurity rosuvastatin lactone at RRT 1.41 is of or less than about 0.07%, preferably not detected by area percentage of HPLC.
31. A process of preparing rosuvastatin calcium substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.
Figure 2

Analytical Research, ZRC

Peaks = 161.249 °C
Onset = 160.083 °C

Area = 184.065 mJ
Delta H = 69.972 J/g
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION NO.**

PCT/IN2007/000083

**A. CLASSIFICATION OF SUBJECT MATTER**

**INV. C07D239/42**

**A. CLASSIFICATION OF SUBJECT MATTER**

According to International Patent Classification (IPC) and 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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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**Date of the actual completion of the international search**

26 July 2007

**Date of mailing of the international search report**

07/08/2007

**Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL 2280 HV RI(SWA) Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016**

**Authorized officer**

Fritz, Martin
**INTERNATIONAL SEARCH REPORT**
Information on patent family members

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Form PCT/ISA/2 (patent family annex) (April 2005)