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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

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(54) **Title**: AN IMPROVED PROCESS FOR THE PREPARATION OF AMLODIPINE FREE BASE AND ACID ADDITION SALTS THEREOF

(57) **Abstract**: Disclosed herein is an improved process for preparation of Amlodipine free base and acid addition salts thereof in good yield by deprotecting Phthaloyl Amlodipine using total concentration of 25% aqueous monomethyl amine in the reaction mixture and Amlodipine free base thus obtained is treated with suitable acids in aqueous medium to yield corresponding Amlodipine salts.

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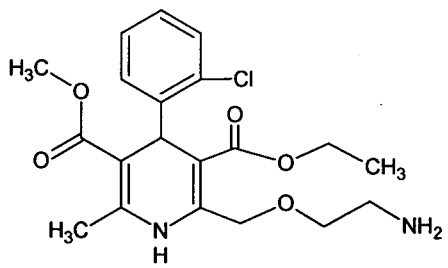
"AN IMPROVED PROCESS FOR THE PREPARATION OF AMLODIPINE FREE BASE AND ACID ADDITION SALTS THEREOF"

Technical field

The present invention relates to an improved process for preparation of Amlodipine free base and acid addition salts thereof preferably Amlodipine Besilate. Amlodipine free base in the present invention is prepared in good yield by deprotection of Phthaloyl Amlodipine using a total concentration of 25% aqueous monomethyl amine in reaction mixture. Amlodipine free base thus formed is treated with suitable acids in aqueous medium to form corresponding Amlodipine salts.

Background and prior art

Amlodipine is a long-acting calcium channel blocker used as an anti-hypertensive and in the treatment of angina. Like other calcium channel blockers, Amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina it increases blood flow to the heart muscle. It also dilates coronary arteries, increasing blood flow to the heart. Its chemical name is (RS)-3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. The molecular structure of Amlodipine is represented as follows:



Formula 2

In the pharmaceutical preparations, Amlodipine is used as a salt with pharmacologically acceptable acids wherein Amlodipine Besilate is used as most preferred salt.

US4572909 discloses Amlodipine as Amlodipine maleate in the treatment of ischaemic heart diseases and hypertension. Amlodipine free base is prepared by deprotection of Phthaloyl Amlodipine either by using methylamine in ethanol at room temperature or hydrazine hydrate in ethanol at reflux temperature or potassium hydroxide at room temperature. Methylamine used for the deprotection is 33% ethanolic methyl amine. Amlodipine free base is treated with maleic acid to give Amlodipine maleate, wherein the reaction was carried out in methylated spirit. Equivalent patent US4879303 was issued directed to the Besilate salt of Amlodipine. The Besilate salt is stated to provide certain advantages over the known salts including Amlodipine maleate.

WO 2002053135 discloses deprotection of Phthaloyl Amlodipine using 40% aqueous methylamine solution at temperature from ambient to 60 °C, and further extraction of resulting aqueous reaction mixture with water immiscible organic solvent like toluene, gives better yield then direct isolation of the free base of Amlodipine, however methylamine used in the reaction is in excess.

US 6784297 discloses hydrolysis of Phthaloyl Amlodipine using 40% monomethyl amine in protic solvent at 20 ° to 50° C to form Amlodipine base. Protic solvent includes ethanol, denatured spirit, methanol, isopropanol, chloroform or dioxane. Amlodipine base was treated with benzene sulfonic acid to form Amlodipine Besilate which was purified by dissolving it in an organic solvent at about 30°C and about 70° C and precipitating it by addition of an insoluble solvent preferably isopropyl alcohol.

US 5389654 describes a process for preparaing Amlodipine monobenzene sulfonate by reacting Amlodipine with benzene sulfonic acid in methanol at temperature of 20° C to reflux.

US 6608206 discloses a process for S (-) Amlodipine salts such as benzenesulphonic acid, oxalic acid, maleic acid, succinic acid and p-toluene sulfonic acid. The reaction is carried out in the presence of an organic solvent at room temperature. The acid to Amlodipine ratio is 1:1 and the water to organic solvent ratio is 5:1 to 8:1.

WO 2005023769 discloses a process for the preparation of salts of Amlodipine by the deprotection of Phthaloyl Amlodipine and converting free base thus obtained to a salt without isolating the free base. Phthaloyl Amlodipine is deprotected by using either 40% aq. monomethyl amine in water immisible solvent or 20% methanolic monomethyl amine followed by treatment of the organic phase with suitable organic acid to form Amlodipine salts.

WO 2006003672 discloses purification process of Phthaloyl Amlodipine. Phthaloyl Amlodipine is purified by dissolving it in chlorinated solvents like methylene chloride, ethylene chloride, chloroform and tetrachloroethane, followed by removal of insoluble matter. Hydrocarbon was added to the filtrate under stirring at temperature 30° to 50° C, to precipitate Phthaloyl Amlodipine, which is further suspended in ethanolic methylamine at reflux temperature to form Amlodipine base.

US20070260065 discloses deprotection of Phthaloyl Amlodipine with 40% aq. methylamine at 30°C to form Amlodipine base which is then treated with benzene sulfonic acid in an organic solvent to give Amlodipine Besilate.

Journal of Medicinal Chemistry, 1986, Vol. 29, No. 9, 1696-1702 describes series of dihydropyridines substituted at the 2-position by basic side chains and their potencies as calcium antagonists. This article further describes deprotection of Phthaloyl Amlodipine with 33 % aq. methyl amine, and then extraction with toluene.

US 6518288 disclose process for preparation of Amlodipine hemifumarate and crystalline salts thereof. Amlodipine fumarate was prepared by contacting Amlodipine as free base or its acid addition salts other than fumarate, with fumaric acid or its ammonium salts in a suitable solvent. Preferred solvents used for the reaction includes ethanol, isopropanol, ethyl acetate and toluene.

None of the aforementioned prior art reveals the deprotection of Phthaloyl Amlodipine to obtain Amlodipine free base in aqueous medium using 25% aqueous monomethyl amine. Most of the prior arts disclose preparation of Amlodipine free base from Phthaloyl Amlodipine using either 33 to 40% alcoholic methylamine or 40% aqueous methylamine.

Thus the prior art uses very large excess of methylamine for the deprotection of Phthaloyl Amlodipine, and it further involves a step of extraction with an organic solvent to isolate the Amlodipine free base which adds to the overall cost to the process. The free base is further converted to Amlodipine salts, which is again isolated by extraction process.

In the present invention, it has been surprisingly found that the deprotection of Phthaloyl Amlodipine can be carried in aqueous medium i.e. without use of any organic solvent, using lower concentration/ molar quantity of monomethyl amine, which gives high yield Amlodipine free base in a short period of time compared to that of prior art processes. The present invention also provides a process for preparation of acid addition salts of Amlodipine preferably Amlodipine Besilate, from the Amlodipine free base in aqueous medium, which makes the process environment friendly. The process further involves direct precipitation and isolation of Amlodipine free base as well as Amlodipine Besilate from the reaction medium, while reducing the step of solvent extraction of the products as mentioned in both cases, thus making the process highly cost-effective for industrial scale preparation.

Object of the invention

The main objective of the present invention is to provide a cost effective process for preparation of Amlodipine free base by deprotecting Phthaloyl Amlodipine in good yield using a total concentration of 25% aqueous monomethyl amine in reaction mixture, and subsequent preparation of Amlodipine Besilate from the free base in aqueous medium.

Further objective of the present invention is to provide a process for deprotection of Phthaloyl Amlodipine using lower concentration and molar quantity of monomethyl amine in aqueous medium.

Another objective of the present invention is to provide a process for preparation of Amlodipine Besilate in aqueous medium via precipitation, and its purification process using organic solvents.

Yet another objective of the present invention is to provide a cost effective and environment friendly process for preparation of Amlodipine Besilate, and to provide a high-yield and high-purity product.

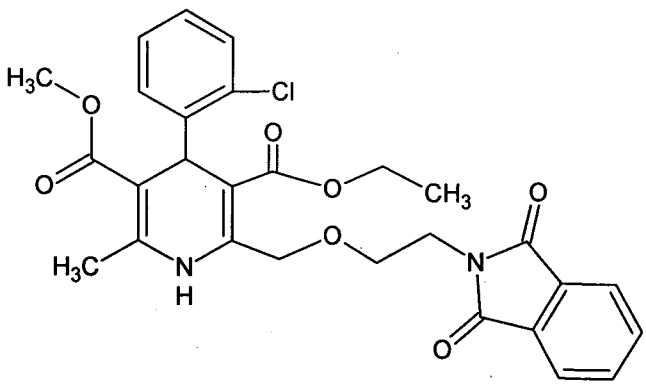
Summary of the invention

In accordance with the above objectives, the present invention discloses an improved process for preparation of Amlodipine free base and acid addition salts thereof preferably Amlodipine Besilate. Amlodipine free base in the present invention is prepared by deprotection of Phthaloyl Amlodipine using a total concentration of 25% aqueous monomethyl amine in reaction mixture, and Amlodipine free base thus formed is treated with suitable acids in aqueous medium to form corresponding salts, which are then purified by treating with organic solvents.

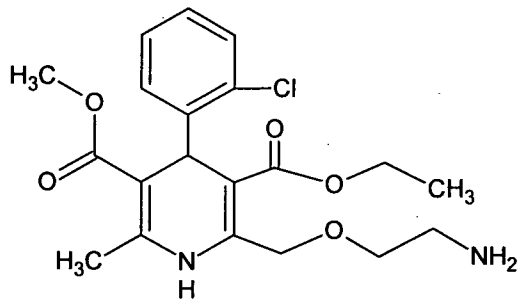
Detailed description of the invention:

Preparation of Amlodipine free base from Phthaloyl Amlodipine as per the existing art, requires high concentration and very high molar quantity of monomethyl amine, and a large quantity of solvent(s) in reaction mixture, and also preparation of Amlodipine salts from free base additionally requires organic solvents, in order to achieve overall process efficiency. It is therefore necessary to develop improved process, which is more efficient and environment friendly.

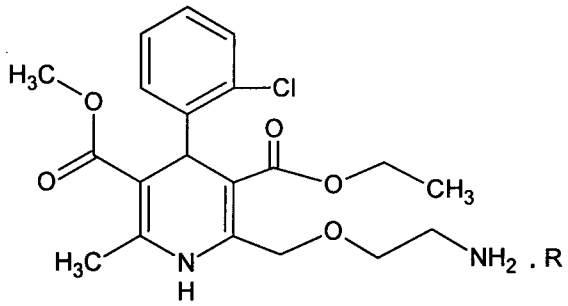
Accordingly, the present invention provides a process for the preparation of Amlodipine free base of Formula 2 by deprotection of Phthaloyl Amlodipine of Formula 1 using aqueous monomethyl amine with a total concentration of 25%,in the reaction mixture and subsequently preparation of Amlodipine acid addition salts of Formula 3 by reacting Amlodipine free base with suitable acids in aqueous medium.



Formula 1



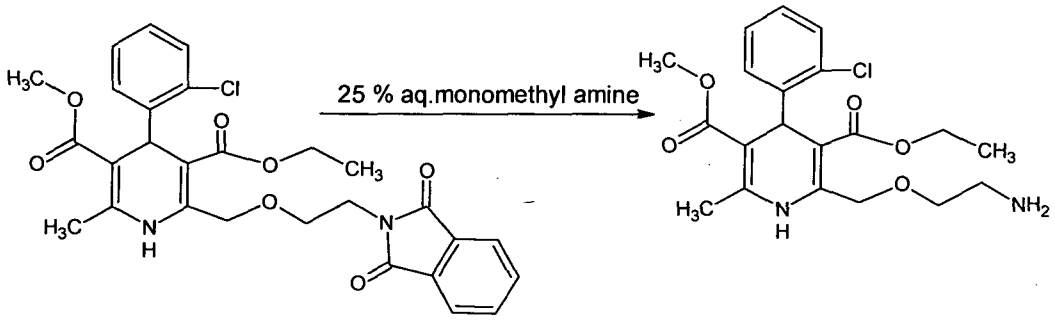
Formula 2



Formula 3

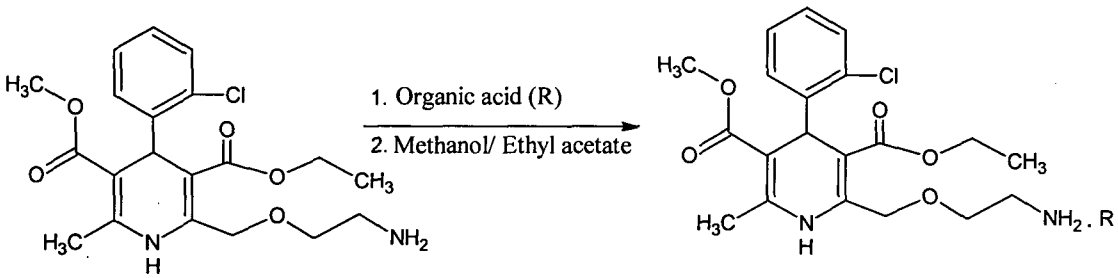
Wherein R is Benzenesulfonic acid

To illustrate the process of the invention, the detailed description is provided herein below as depicted in the following Scheme.



Phthaloyl Amlodipine

Amlodipine free base



Amlodipine free base

Amlodipine Salt

The starting material Phthaloyl Amlodipine of Formula 1 can be produced by general processes known in the art.

Accordingly, in one embodiment, the process of the present invention comprises deprotection of Phthaloyl Amlodipine using 40% monomethyl amine and further diluting the reaction mixture with water in order to give a final concentration of 25% aqueous monomethyl amine in the reaction mixture, followed by heating the reaction to 40 - 50°C for 4 - 5hrs to form Amlodipine free base. This solution is cooled and the precipitate is filtered under vacuum.

The inventiveness of the present invention is attributed to the use of 25% aqueous monomethyl amine in order to precipitate out the amlodipine free base from the reaction mass with good amount of yield and purity. Thus decreasing the total concentration of monomethyl amine not only increases the yield but also avoids the solvent extraction work up. The co-product water soluble phthalimide remains in aqueous phase.

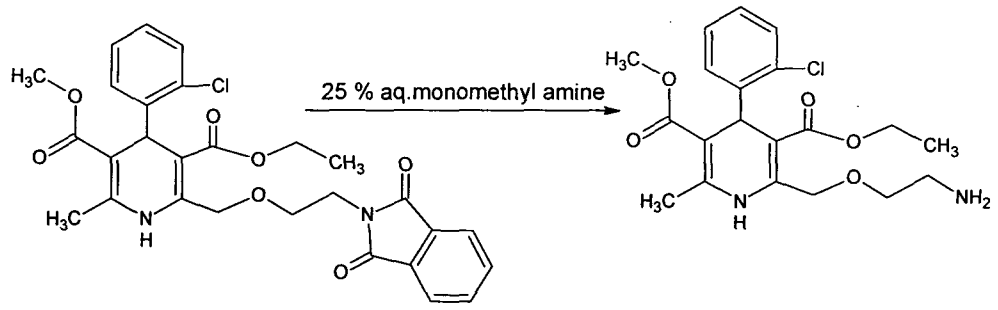
In another embodiment, the wet mass of Amlodipine free base was then treated with Benzenesulfonic acid (1.1M to 1.2M) in water at room temperature for 4 to 5 hrs. The resulting crude Amlodipine Besilate was then filtered and dried. Crude Amlodipine Besilate was further mixed with 4 volumes of methanol at 50 to 55°C under stirring. The resulting solution was cooled and filtered, followed by distillation of methanol under reduced pressure. The residual mass thus obtained was stirred with 4 volumes of ethyl acetate, and 50% of ethyl acetate was distilled out under reduced pressure. The resulting pure solid was filtered and washed with ethyl acetate and then dried.

The following examples are presented for illustrative purpose and not intended to limit the scope of this invention.

Examples of preparation of Amlodipine Besilate:

Example 1:

(A) Preparation of Amlodipine free base from Phthaloyl Amlodipine

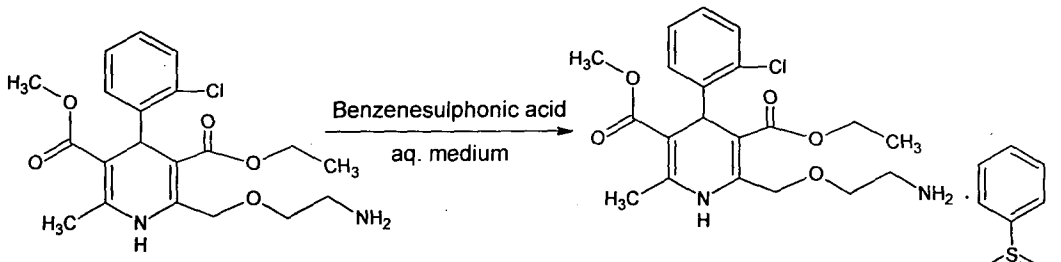


Phthaloyl Amlodipine Amlodipine free base

Charged 50 gm of Phthaloyl Amlodipine in 250 ml R.B.F. equipped with agitator, thermometer pocket, and water condenser. To this, added 125 ml 40% Monomethyl amine solution followed by 75 ml purified water at room temp and stirred well to get proper slurry. Heated the reaction mass upto 40 – 45 °C for 4.5 hrs under stirring and monitored the reaction by TLC for completion of reaction (i.e. for absence of Phthaloyl Amlodipine). After completion, the reaction mass was cooled to room temperature &

further chilled to 15-20°C for 1.0 hr. The precipitate thus obtained was filtered and washed with chilled purified water to get Amlodipine free base. (47.5 gm) wet with water content (~24%).

(B) Preparation of Amlodipine Besilate crude from Amlodipine free base.



Amlodipine free base

Amlodipine Besylate (crude)

Charged the wet cake of Amlodipine free base (47.5gm wet) in 250 ml RBF equipped with agitator, air condenser, & thermometer pocket and added 150 ml purified water in it & stirred to obtain proper slurry. A solution of 16.3 gm Benzenesulphonic acid in 50.0 ml purified water was added drop wise to reaction mixture at room temperature and the pH of the reaction mass was adjusted to attain a pH of 1-2. The reaction mass was stirred at room temperature for 4.5 hr and filtered the reaction mixture to obtain wet Amlodipine Besilate crude. The wet Amlodipine Besilate crude was dried at 60-65 °C in hot air oven for 8.0 hr and further cooled to room temperature to obtain dry Amlodipine Besilate crude (50.58 gm) with water content (1.21%).

(C) Purification of Amlodipine Besilate

Charged 50.58gm crude Amlodipine Besilate (1.21% water content) in 250 ml R.B.F. equipped with agitator, thermometer pocket, water condenser and added methanol 200 ml (4 volumes of crude Amlodipine Besilate) and stirred the reaction mass. Heated the reaction mass to 50 – 55 °C to get clear solution and filtered the clear reaction mass through sintered glass funnel. Collected all filtered mother liquor in 250 ml R.B.F. equipped with agitator, thermometer pocket, water condenser, distillation bend, and

distilled out methanol up to dryness under vacuum. Ethyl acetate 200 ml (4 times volume of crude Amlodipine Besilate) was added, stirred the reaction mass and distilled out 50% ethyl acetate under vacuum at 40 – 45°C. The reaction mass was cooled to room temp to get pure Amlodipine Besilate The amlodipine besilate thus obtained was filtered and washed with ethyl acetate. The product dried at 60 – 65 °C for 8 hrs in hot air oven to get pure Amlodipine Besilate, yield = 89.16 %, purity (HPLC) = 99.53 %.

Example 2:

(A) Preparation of Amlodipine free base from Phthaloyl Amlodipine

Charged 100 gm of Phthaloyl Amlodipine in 1000 ml R.B.F. equipped with agitator, thermometer pocket, water condenser. To this, added 250 ml 40% Monomethyl amine solution followed by 150 ml purified water at room temp and stirred well to get proper slurry. Heated the reaction mass upto 40 – 45 °C for 4.5 hrs under stirring and monitored the reaction by TLC for completion of reaction (i.e. for absence of Phthaloyl Amlodipine). After completion, the reaction mass was cooled to room temperature & further chilled to 15-20°C for 1.0 hr. The precipitate thus obtained was filtered and washed with chilled purified water to get Amlodipine free base. (97.8 gm) wet with water content (~22%).

(B) Preparation of Amlodipine Besilate crude from Amlodipine free base.

Charged the wet cake of Amlodipine free base (97.8gm wet) in 1000 ml RBF equipped with agitator, air condenser, & thermometer pocket and added 293.5.0 ml ml purified water in it & stirred to obtain proper slurry. A solution of 35.4 gm Benzenesulphonic acid in 100.0 ml purified water was added drop wise to reaction mixture at room temperature and the pH of the reaction mass was adjusted to attain a pH of 1-2. The reaction mass was stirred at room temperature for 4.0 hr and flittered the reaction mixture to obtain wet Amlodipine Besilate crude. The wet Amlodipine Besilate crude was dried at 60-65 °C in hot air oven for 8.0 hr and further cooled to room temperature to obtain dry Amlodipine Besilate crude (103.2 gm) with water content (1.84%).

(C) Purification of Amlodipine Besilate.

Charged 103.2 gm crude Amlodipine Besilate (1.84% water content) in 1000 ml R.B.F. equipped with agitator, thermometer pocket, water condenser and added methanol 413.0 ml (4 volumes of crude Amlodipine Besilate) and stirred the reaction mass. Heated the reaction mass to 50 – 55 °C to get clear solution and filtered the clear reaction mass through sintered glass funnel. Collected all filtered mother liquor in 1000 ml R.B.F. equipped with agitator, thermometer pocket, water condenser, distillation bend, and distilled out methanol up to dryness under vacuum. Ethyl acetate 413.0 ml (4 times volume of crude Amlodipine Besilate) was added, stirred the reaction mass and distilled out 50% ethyl acetate under vacuum at 40 – 45°C. The reaction mass was cooled to room temp to get pure Amlodipine Besilate The amlodipine besilate thus obtained was filtered and washed with ethyl acetate. The product dried at 60 – 65 °C for 8 hrs in hot air oven to get pure Amlodipine Besilate, yield = 89.82 %, purity (HPLC) = 99.65 %.

We claim,

1. An improved process for preparation of Amlodipine free base and acid addition salts thereof characterized by deprotecting Phthaloyl Amlodipine using a total concentration of 25% aqueous monomethyl amine in reaction mixture to precipitate Amlodipine free base.

2. The improved process for preparation of Amlodipine free base and acid addition salts thereof according to claim 1 comprising following steps
    a. deprotecting Phthaloyl Amlodipine using a total concentration of 25% aqueous monomethyl amine in reaction mixture to precipitate Amlodipine free base;
    b. treating Amlodipine free base with suitable acids in aqueous medium to obtain corresponding salts; and
    c. purifying the Amlodipine salts.

3. The process for the preparation of Amlodipine free base as claimed in claim 1, wherein the molar quantity of monomethyl amine is 25% in total reaction mass.

4. The process for the preparation of Amlodipine free base as claimed in claim 1, wherein the deprotection is carried out in water.

5. The process for the preparation of Amlodipine acid addition salts as claimed in claims 1 and 2, where in acid addition salt of Amlodipine is Amlodipine Besilate.

6. The process for the preparation of Amlodipine acid addition salts as claimed in claims 1 and 2, wherein suitable acid is Benzenesulfonic acid in the ratio of about 1.0M to about 1.5M, preferably about 1.1M to about 1.2M.

7. The process for the preparation of Amlodipine acid addition salts as claimed in any one of the preceding claim, wherein the reaction is carried out in water and the salt is isolated by precipitation.

8. The purification process of Amlodipine acid addition salts as claimed in claim 2, comprising a step of stirring crude Amlodipine acid addition salt with methanol at 50° to 55°C, filtering it, evaporating methanol under reduced pressure followed by stirring the resulting residual mass with ethyl acetate at room temperature.

9. The purification process as claimed in claim 8, wherein the 50% of ethyl acetate is distilled out prior to filtering the product followed by washings with ethyl acetate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2010/000296

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/82 C07D401/12
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, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2004/044218 A1 (PUROHIT ARUN KUMAR [IN] ET AL) 4 March 2004 (2004-03-04) cited in the application column 3 - column 4 examples 1,5	8,9 1-7
Y A	WO 2005/023769 A1 (CIPLA LTD [IN]; KANKAN RAJENDRA NARAYANRAO [IN]; SRINIVAS PATHI L [IN]) 17 March 2005 (2005-03-17) cited in the application claims 1-8 example 1	1-3,5-7 4,8,9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2011	26/01/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lécaillon, Jennifer

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2010/000296

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/260065 A1 (BOLUGODDU VIJAYABHASKAR [IN] ET AL) 8 November 2007 (2007-11-08) cited in the application	4,6
A	claim 9 page 2 - column 2 page 5 - column 1 examples 6,7	1-3,5, 7-9
Y	JP 2007 015978 A (SAGAMI KASEI KOGYO KK) 25 January 2007 (2007-01-25)	1-3,5-7
A	paragraph [[0029]]	4,8,9
A	WO 2007/096724 A1 (ORCHID CHEMICALS & PHARM LTD [IN]; SIRIPRAGADA MAHENDER RAO [IN]; SANT) 30 August 2007 (2007-08-30) examples 1-3	1-9

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2010/000296

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004044218 A1	04-03-2004	NONE	
WO 2005023769 A1	17-03-2005	NONE	
US 2007260065 A1	08-11-2007	NONE	
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