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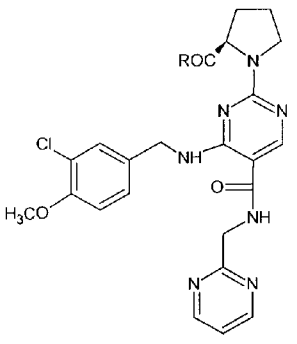
(54) **Title**: A PROCESS FOR THE PREPARATION OF AVANAFIL AND ITS NOVEL INTERMEDIATES



Formula (II)

(57) **Abstract**: The present invention relates to a novel compound of Formula (II), and its use in preparation of Avanafil, [Formula should be inserted here] wherein R is -OH, -CI or -OR^1 and R^1 is C_1 to C_3 alkyl group.

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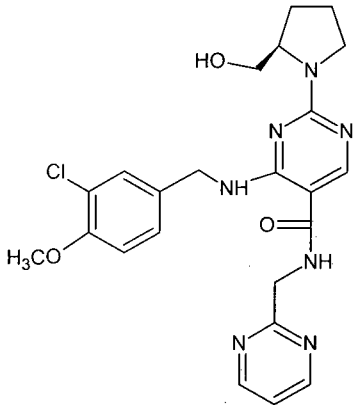
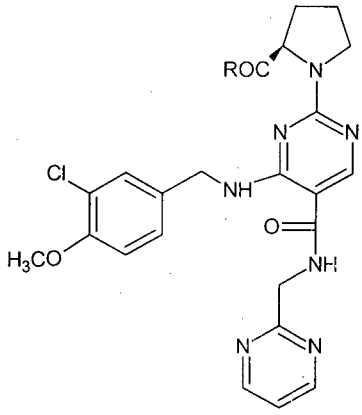
Technical field of the invention

The present invention mainly relates to the compound of Formula (II), wherein the compound of Formula (II) is used in preparation of Avanafil of Formula (I).



Formula (I)



Formula (II)

wherein R is -OH, -Cl or $-OR^1$ and R^1 is C_1 to C_3 alkyl group

The present invention further relates to a process for preparation of the compound of Formula (II).

Furthermore, the present invention relates to a process for preparation of Avanafil of Formula (I) substantially free from impurities by using compound Formula (II).

Background of the invention

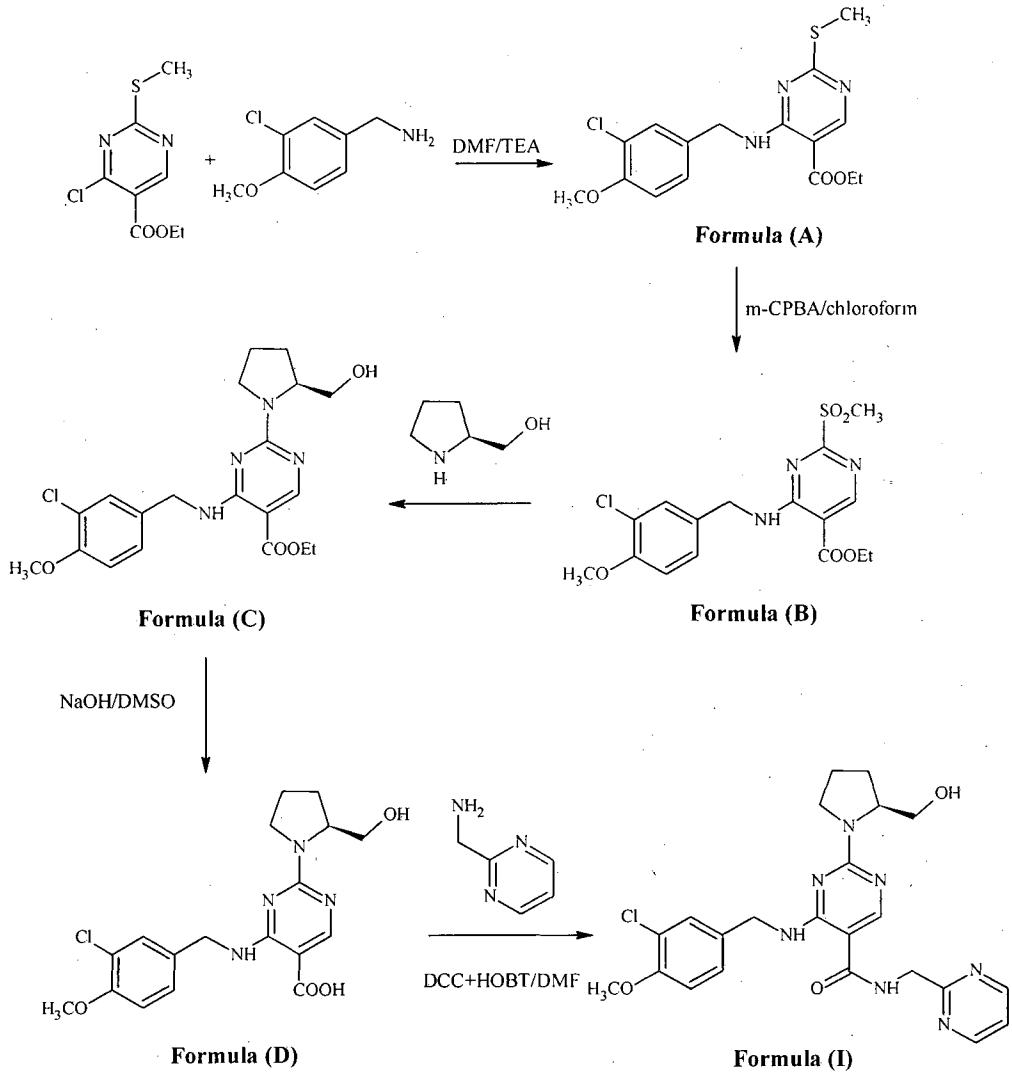
Avanafil is chemically known as 4-[(3-Chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide.

Avanafil is a FDA approved drug used for treatment of erectile dysfunction. It belongs to a group of medicines called phosphodiesterase 5 (PDE5) inhibitors and is said to exert a more rapid effect compared to other PDE5 inhibitors.

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.

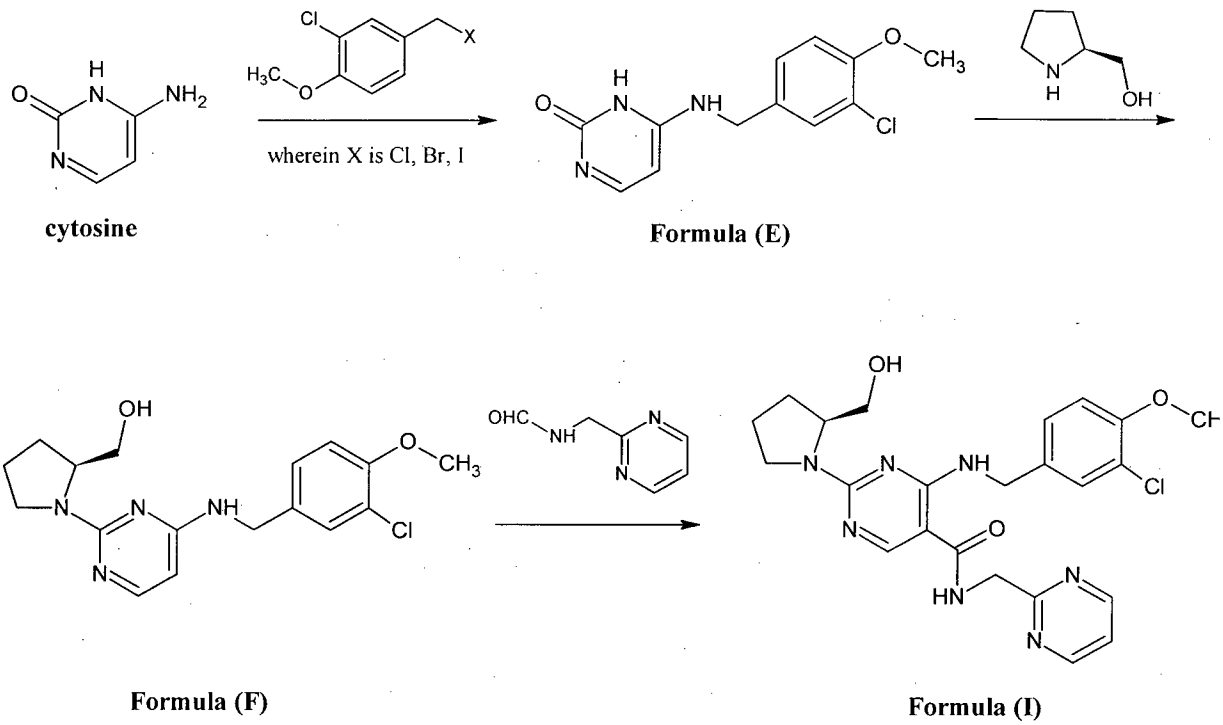
A process for preparation of Avanafil was first disclosed in US 6,797,709 (depicted in Scheme I), wherein 4-chloro-5-ethoxycarbonyl-2-methylthio-pyrimidine is coupled with 3-chloro-4-methoxybenzylamine in presence of triethylamine to provide compound of Formula (A), which on oxidization provides a sulfonyl compound of Formula (B). Said compound of Formula (B) is reacted with L-prolinol and exert compound of Formula (C). The resulting compound of Formula (C) undergoes column chromatographic purification and crystallization, while further subjected to hydrolysis to obtain compound of Formula (D). The compound of Formula (D) is coupled with 2-aminomethylpyrimidine to obtain Avanafil of Formula (I). The final product obtained is purified by column chromatography. The need to purify the intermediate compound of Formula (C) and final product, by column chromatography makes this process cumbersome, time consuming and unviable for large scale production thereby contributing to main disadvantages of the process.

Scheme I



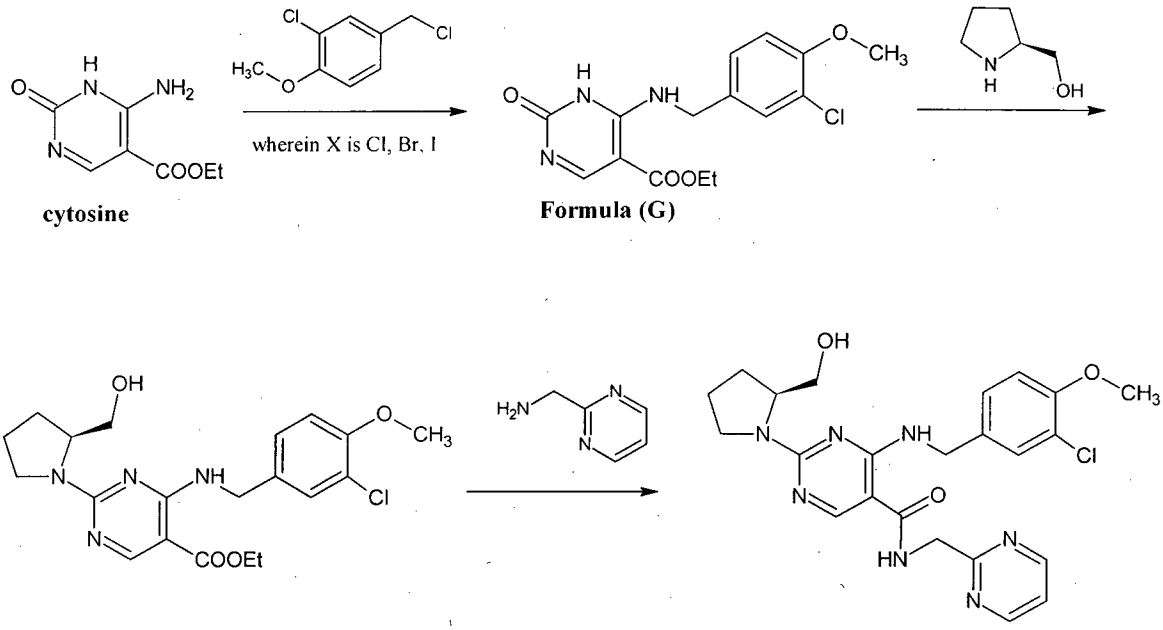
CN 103254179, discloses a process for preparation of Avanafi, wherein 3-chloro-4-methoxybenzylhalide is coupled with cytosine to result compound of Formula (E), later on condensation with L-prolinol yields 4-[(3-chloro-4-methoxy benzyl)amino-2-(2-hydroxymethyl)-1-pyrrolinyl]pyrimidine of Formula (F). The compound of Formula (F) is then condensed with N-(2-pyrimidylmethyl)formamide to obtain Avanafil of Formula (I). Process is depicted in Scheme II

Scheme II



CN 103254180 describes an alternate process for preparation of Avanafil of Formula (I), wherein a substitution reaction on 6-amino-1,2-dihydropyrimidine-2-keto-5-carboxylic acid, ethyl ester and 3-chloro-4-methoxybenzylchloride provides 6-(3-chloro-4-methoxybenzylamino)-1,2-dihydropyrimidine-2-keto-5-carboxylic acid, ethyl ester of Formula (G) which on condensation with L-prolinol generates 6-(3-chloro-4-methoxybenzylamino)-1,2-dihydropyrimidine-2-keto-5-carboxylic acid ethyl ester of Formula (H). The compound of Formula (H) is then hydrolysed and coupled with N-(2-pyrimidylmethyl)formamide to obtain Avanafil of Formula (I). Process is depicted in Scheme III

Scheme III

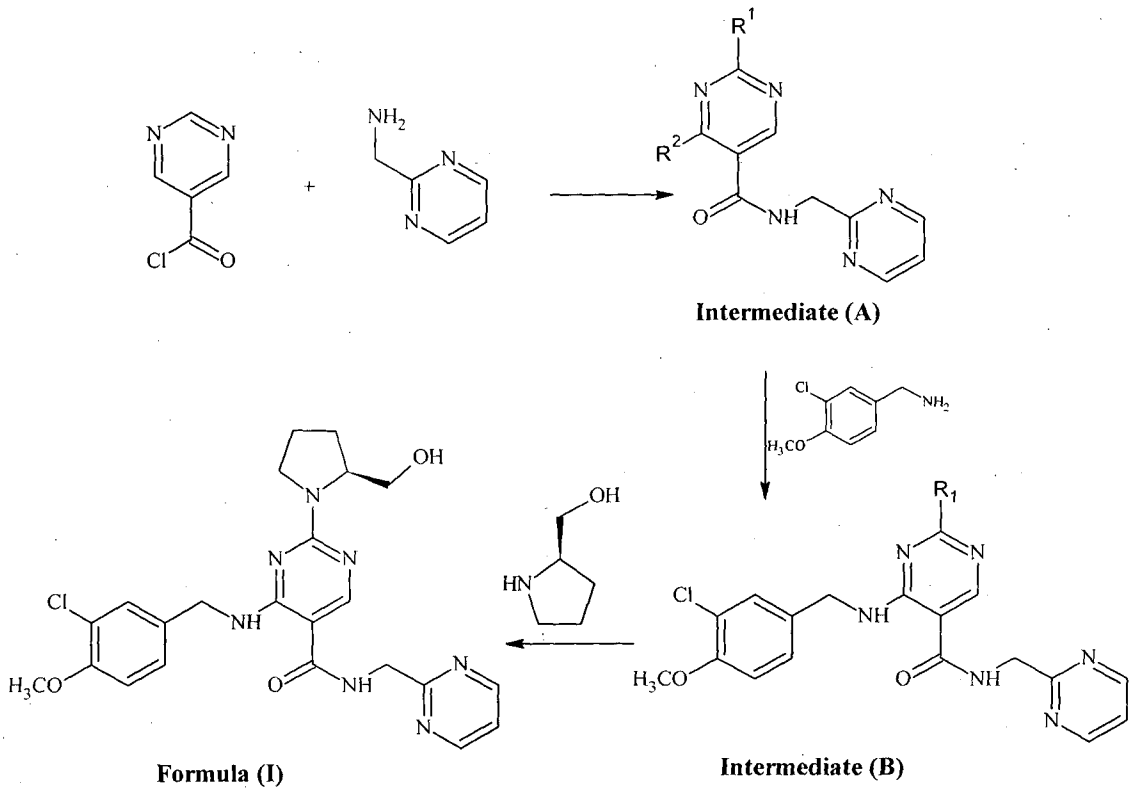


In all the prior art discussed above, chiral compound L-prolinol is coupled in molecule in earlier steps of synthesis. This approach seems to be less feasible for large scale production; the insertion of L-prolinol in early stage may need to exert number of purifications for intermediates. Further the main shortcoming in such process is that the chirality of molecule is disturbed by inserting L-prolinol in early stages because there are number of operations in line in process to obtain the target compound.

CN 103483323, discloses a synthetic method for preparation of avanafil, wherein amidation of pyrimidine-5-carbonyl chlorides with 2-(aminomethyl)pyrimidine at temperature ranging from -10 to 5°C resulted an amide (intermediates A); which underwent condensation with 3-chloro-4-methoxybenzylamine at the temperature ranging from 0 -3°C to give 4-[(3-chloro-4-methoxybenzyl)amino]-5-

pyrimidinecarboxamides (intermediates B), which further on condensation with L-prolinol gave avanafil. The disadvantage of this process is the need to maintain the reaction temperature in range of -10 to 5°C which adds up to cost of process and makes the process complicated. The process is depicted in Scheme IV.

Scheme IV



wherein, R^1 & R^2 are independently, hydrogen, halogen, alkoxy, alkoxyalkyl, cyno group, amino group

Hence, to overcome shortcomings of prior art the inventors of present invention have skillfully designed a process with novel intermediate which concomitantly result Avanafil compound of Formula (I), substantially free from impurities. Further this invention encompass L-proline in last stage of molecule in order to avoid the number of purifications of intermediate which relent the economic significances by taking into account yield of each stage.

Object of the invention

1. The main object of the invention is to provide a novel compound of Formula (II).

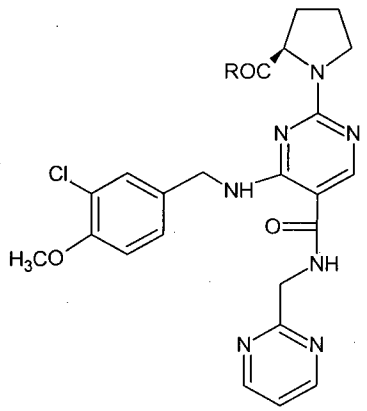
2. Another object of present invention is to provide a process for preparation of a novel compound of Formula (II).

3. Yet another object of present invention is to provide a process for preparation of Avanafil of Formula (I), in high yield and purity using a novel compound of Formula (II).

4. Yet another object of the present invention to provide simple, economic and industrially scalable process for the preparation of Avanafil o Formula (I).

Summary of the invention

According to an aspect of present invention, there is provided a novel compound of Formula (II).



Formula (II)

wherein R is -OH, -Cl or $-OR^1$ and R^1 is C_1 to C_3 alkyl group

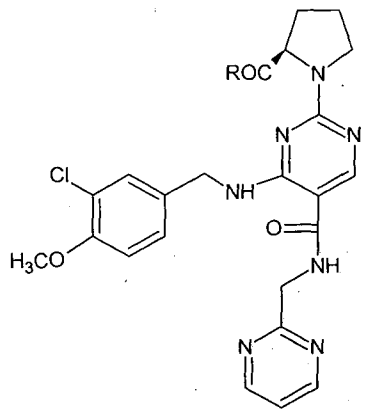
According to another aspect of present invention, there is provided a process for preparation of a novel compound of Formula (II), by oxidizing an intermediate of Formula (III), with a strong oxidizing agent in a polar aprotic solvent to give compound of Formula (IV), followed by reacting the compound of Formula (IV) with L-proline in presence of a base to obtain compound of Formula (II), which may further undergoes either esterification or chlorination.

According to another aspect of present invention, there is provide a process for preparation of Avanafil of Formula (I), by reduction of a compound of Formula (II) using reducing agent in suitable polar solvent.

According to yet another aspect of present invention, Avanafil of Formula (I) is obtained in high purity and yield.

Detailed Description of the Invention

The present invention mainly relates to a novel compound of Formula (II)



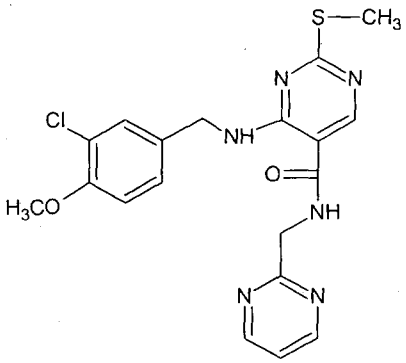
Formula (II)

wherein R is -OH, -Cl or $-OR^1$ and R^1 is C_1 to C_3 alkyl group

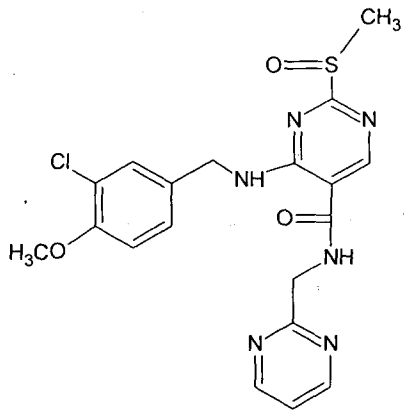
The compound of Formula (II), in the present invention is used for preparation of Avanafil of Formula (I).

The present invention further relates to a process for preparation of compound of Formula (II), comprising:

i) oxidizing a compound of Formula (III), with an suitable oxidizing agent in a polar solvent to form compound of Formula (IV);



Formula (III)



Formula (IV)

ii) reacting compound of Formula (IV) with L-proline in suitable solvent in presence of base to obtain a reaction mixture

iii) washing the reaction mixture of step ii) with a carbonate solution and separating an organic layer

iv) evaporating the organic layer and stripping the thus formed residue with acetone to obtain compound of Formula (II)

According to an embodiment of the present invention, the oxidizing agent used in step i), is selected from m-chloroperoxybenzoic acid, benzoyl peroxide, peracetic acid, monoperoxyphthalate, hydrogen peroxide, mangnesium dioxide and dinitrogen tetraoxide, but preferably m-chloroperoxybenzoic acid is used.

The molar ratio of the oxidizing agent used in step i) with respect to compound of Formula (III) is in range of 1 to 2.

The polar solvent used in step i), is selected from methylene dichloride, acetone, tetrahydrofuran, dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile are used in step i), but preferably methylene dichlorideis used.

The volume of polar solvent used with respect to compound of Formula (III) is in range of 15 to 25 volumes.

According to an embodiment of the present invention, in step i) compound of Formula (IV) is optionally, isolated.

According to another embodiment of the present invention, a compound of Formula (IV) is in-situ reacted in step ii).

According to another embodiment of the present invention, the molar ratio of L-proline used in step ii), with respect to compound of Formula (III) is in range of 0.5 to 1.5

The base used in step ii), of the process is selected from an organic base like triethylamine, N,N-diisopropylethylamine, N-methyl morpholine, pyridine or an inorganic base like sodium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, sodium hydroxide but preferably triethylamine is used.

The molar ratio of base used in step ii), with respect to compound of Formula (III) is in range of 0.5 to 1.5.

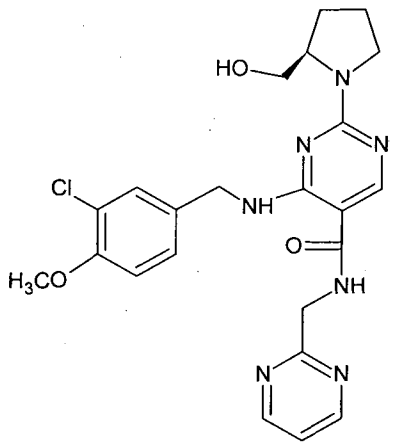
The solvent used in step ii), is selected from ethyl acetate, methylene dichloride, ethylene dichloride, acetone, methanol, ethanol, propanol but preferably methylene dichloride.

The carbonate solution used in step iii) is selected from sodium carbonate or potassium carbonate.

According to yet another embodiment of present invention, the compound Formula (II) obtained in step iv), in isolated form or in-situ, is subjected to esterification by using C_1 to C_3 alcohol in presence of an acid. The alcohol used is selected from methanol, ethanol, n-propanol and *iso*-propanol, but preferably ethanol is used.

Alternatively, the compound of Formula (II) obtained in step iv), in isolated form or in-situ, is chlorinated using a chlorinating agent in a solvent like methylene dichloride or ethylene dichloride. The chlorinating agent used is selected from phosphoryl chloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, but preferably thionyl chloride is used.

The present invention relates to a process for the preparation of Avanafil of Formula (I), in high yields and purity.



Formula (I)

According to yet another embodiment of present invention, compound Formula (II), either in isolated form or in-situ, undergoes reduction to obtain compound of Formula (I).

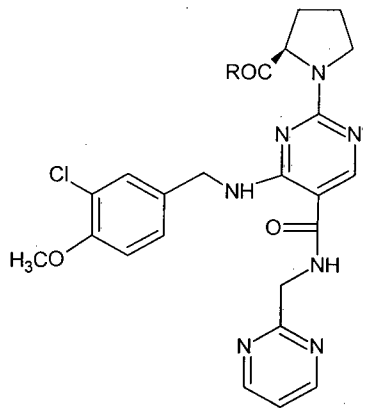
According to an embodiment of the present invention, a process for the preparation of Avanafil of Formula (I), by using compound of Formula (II), comprising;

a) reducing compound of Formula (II), by using a suitable reducing agent in a polar solvent to obtain crude Avanafil of Formula (I);
b) purifying the crude Avanafil of Formula (I) in methanol.

According to yet another embodiment of present invention, the reducing agent used in step (a), is selected from sodium borohydride, vitride, iodine, Fe powder, lithium aluminium hydride, copper sulfate, lithium bromide, iodine, bromine, sulfuric acid, methanesulfonic acid or mixture thereof.

According to yet another embodiment of present invention, the solvent used in step (a) is polar solvent independently selected from, methanol, ethanol, propanol, iso-propanol, ethyl acetate, tetrahydrofuran but preferably ethanol or tetrahydrofuran is used.

The inventors of present invention skillfully designed the synthesis of Avanafil of Formula (I) from a novel compound of Formula (II).

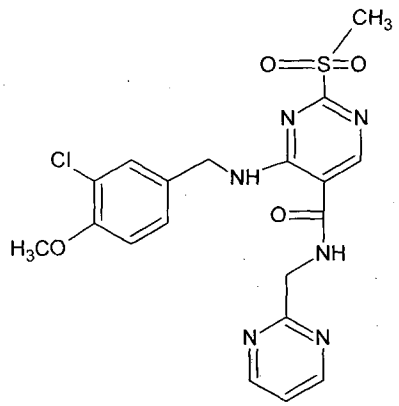


Formula (II)

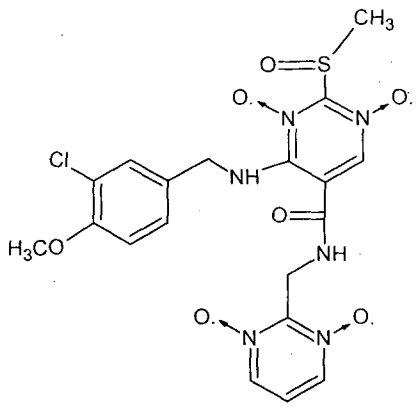
wherein R is -OH, -Cl or $-OR^1$ and R^1 is C_1 to C_3 alkyl group

The objective of preparing compound of Formula (II) is that it undergoes the reduction reaction to form Avanafil, substantially free from the impurities like

compound of Formula (a) and compound of Formula (b), without the constraint of further extensive purification.



Formula (a)



Formula (b)

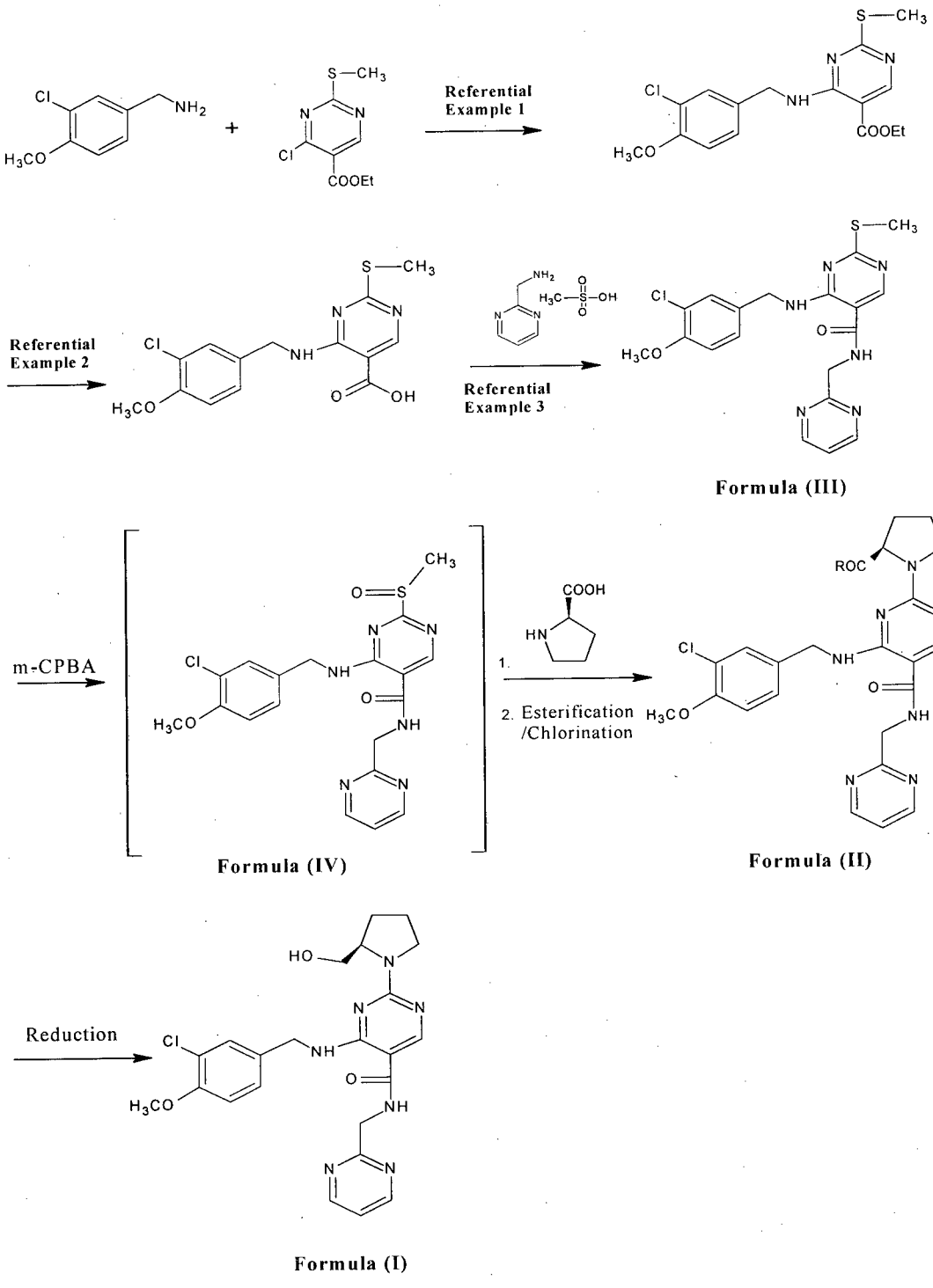
The compound of Formula (III), used as starting material in present invention, is prepared by the methods known in prior arts.

Most of the prior art employs L-prolinol as one of the raw material in process for preparation of Avanafil, however the availability and cost of L-prolinol is far above the ground as compared to L-proline. It was observed by the inventors of present invention that insertion of L-proline into the molecule after formation of compound of Formula (IV), not only exert the economic significance but also makes process simple and time efficient by avoiding need of multiple purification.

According to an aspect of present invention, Avanafil of Formula (I) is obtained in high purity and yield.

The invention will be specifically described below with reference to Examples but it should not be construed that the scope of the invention is limited thereto. Since the starting compound was produced by a modified method from that described in prior art, it will be described as Referential Example 1 to 3. Here synthesis routes of Referential Example 1 to 3 and Example 1 to 10 are illustrated below in Scheme (V).

Scheme (V)


Referential Example 1
Referential Example 2
Referential Example 3
Formula (III)
m-CPBA
Formula (IV)
1.
2. Esterification /Chlorination
Formula (II)
Reduction
Formula (I)

Referential Examples

Referential Example 1 – Preparation of ethyl 4-[(3-chloro-4-methoxybenzyl)amino]-2-(methyl sulfanyl)pyrimidine-5-carboxylate

To 600ml of methylene dichloride was added 100g of ethyl 4-chloro-2-(methylsulfanyl) pyrimidine-5-carboxylate and 91.2g of 3-chloro-4-methoxybenzylamine. The reaction mixture was stirred and 500ml of water, 48g of sodium carbonate and 1g of tetra-butylammonium bromide were added to it. The reaction mixture was then maintained overnight at 25-30°C. After completion of reaction, methylene dichloride layer was separated, washed with water and evaporated to obtain 145g of ethyl 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfanyl) pyrimidine-5-carboxylate having 95% of HPLC purity.

Above reaction can also be carried out using ammonia or triethylamine in same reaction conditions and parameters, in place of sodium carbonate.

Referential Example 2 – Preparation of 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfanyl) pyrimidine-5-carboxylic acid

To 600ml of methanol was added 100g of ethyl 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfanyl) pyrimidine-5-carboxylate (Referential Example 1) and an aqueous solution of sodium hydroxide (15g of NaOH in 140ml of water). The reaction mixture was heated to reflux temperature. After completion of reaction, the pH of mixture was adjusted to 1-2 using concentrated hydrochloric acid followed by stirring the mixture for 1 hour at 10-15°C. The solid product obtained was filtered, washed sequentially with water and methanol, and dried overnight at 70-75°C to get 87g of 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfanyl) pyrimidine-5-carboxylic acid.

Referential Example 3 – Preparation of 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfinyl)-N-(pyrimidin-2-ylmethyl) pyrimidine-5-carboxiamide of Formula (III)

To a mixture of 400ml of toluene and 0.5ml of dimethylformamide was added 50g of 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfanyl) pyrimidine-5-carboxylic acid (Referential Example 2) and 70g of thionyl chloride, and the reaction mixture was refluxed for 2.5 hours. After completion of reaction, solvent was distilled under vacuum and the residue was stripped with toluene to obtain yellow solid mass. The solid mass thus obtained, was cooled to 15-20°C followed by addition of 175ml of methylene dichloride, 36.1g of 2-amino methyl pyrimidine mesylate and 35.55g of triaethylamine. The reaction mixture was stirred overnight at 25-30°C. After completion of reaction, methylene dichloride was distilled out to get residue. The residue was washed sequentially with 2.5% sodium carbonate solution and water. The residue was then treated with methanol to obtain 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfinyl)-N-(pyrimidin-2-ylmethyl) pyrimidine-5-carboxiamide of Formula (III) having HPLC purity of more than 95% (yield: 80%)

Referential Example 4 - Preparation of 4-[(3-Chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide (Avanafil)

Step i)

To 200ml of dichloromethane was added 10g of 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfinyl)-N-(pyrimidin-2-ylmethyl) pyrimidine-5-carboxiamide and 6.5g of m-chloro per benzoic acid and the mixture was stirred for 1 hour at 25-30°C. After completion of reaction, the reaction mixture was washed with aqueous solution of sodium carbonate and water. The resulting dichloromethane layer comprising compound of Formula (IV) was taken to next step.

Step ii)

To the dichloromethane layer obtained in step i), was added 2.57g of triethylamine followed by slow addition of 125ml solution of L-prolinol in dichloromethane (2.46g of L-prolinol in 125ml of dichlromethane). The reaction mixture was maintained overnight. After completion of reaction, the reaction mixture was washed with water followed by evaporation of dichloromethane to obtain an oily mass. The oily mass thus obtained was treated with methanol to yield 8g of Avanafil.

Examples

Example 1: Preparation of Compound of Formula (II) (wherein R is –OH)

Step i)

To 200ml of methylene dichloride was added 10g of 4-[(3-chloro-4-methoxybenzyl) amino]-2-(methyl sulfinyl)-N-(pyrimidin-2-ylmethyl) pyrimidine-5-carboxiamide of Formula (III) and 6.5g of m-chloro per benzoic acid and the mixture was stirred for 1 hour at 25-30°C. After completion of reaction, the reaction mixture was washed with aqueous solution of sodium carbonate and water. The resulting methylene dichloride layer comprising compound of Formula (IV) was taken to next step.

Step ii)

To the methylene dichloride layer comprising compound of Formula (IV) obtained in step i), was added 5g of triethylamine followed by slow addition of 125ml solution of L-proline in methylene dichloride (2.8g of L-proline in 125ml of methylene dichloride). The reaction mixture was maintained overnight. After completion of reaction, the reaction mixture was washed with water and 5% sodium carbonate solution, followed by evaporation of methylene dichloride to obtain an oily mass. The oily mass obtained was stripped with 50ml acetone to yield 9g of compound of Formula (II) having HPLC purity 98%.

Example 2: Preparation of Compound of Formula (II) (wherein R is $-OC_2H_5$)

To 100ml of ethanol was added 0.5ml of sulphuric acid and 10g of compound of Formula (II) obtained in example 1, and the reaction mixture was maintained at reflux temperature till completion of reaction. The reaction mixture was then cooled to 25-30°C and the pH of reaction mixture was adjusted to 7-8 using sodium carbonate. Filter the reaction mixture and collect filtrate containing product. The ethanol in filtrate is completely distilled out to isolate 10.45g of esterified compound of Formula (II).

Example 3: Preparation of Compound of Formula (II) (wherein R is –Cl)

To a mixture of 400ml of toluene and 0.5ml of dimethylformamide was added 50g of compound of Formula (II) obtained in example 1, and 70g of thionyl chloride. The reaction mixture was refluxed for 2.5 hours. After completion of reaction, solvent was distilled under vacuum and the residue was stripped with toluene to obtain 50.5g of oily carboxylic acid chloride compound of Formula (II).

Example 4: Preparation of Avanafil of Formula (I)

In an inert atmosphere, a solution of 30g of compound of Formula (II) obtained in example 1 or 2, in 150 ml of tetrahydrofuran was dropwise added to 180ml of suspension of 1.0M lithium aluminium hydride solution in tetrahydrofuran. The reaction mixture was refluxed for 5 hours. After completion of reaction, the mixture was cooled in ice-bath and saturated aqueous solution of sodium sulfate was added to decompose excess of lithium aluminium hydride. The mixture was then diluted with 200ml of methylene dichloride and thus formed organic layer was separated. The organic layer was washed with water (3 × 100 ml), dried over MgSO4 and concentrated to collect crude Avanafil of Formula (I) which was subjected to purification using methanol as solvent to yield 22.8g of Avanafil of Formula (I) having HPLC purity of 99.20%.

Example 5: Preparation of Avanafil of Formula (I)

To a mixture of 1.3g sodium borohydride, 1ml methanesulfonic acid and 50ml ethanol was added 10g of compound of Formula (II) obtained in example 1 or 2, and the mixture was stirred at 25-30°C for 5 hours. After completion of reaction, 100ml water was added and the mixture was extracted with 100ml methylene dichloride (50ml X 2). The methylene dichloride layer obtained was evaporated under reduced pressure to get an oily mass. The oily mass was stripped with ethyl acetate at 45-50°C. To the oily residue formed was added 50ml of ethyl acetate and the mixture was cooled to 0-5°C. The solid obtained was filtered, washed with ethyl acetate and dried to yield crude Avanafil of Formula (I) which was subjected to purification using methanol as solvent to yield 7g of Avanafil of Formula (I) having HPLC purity of 99%.

Example 6 to Example 8

The procedure is carried out as in example 5 except for instead of methanesulfonic acid other reducing agents are used in combination with sodium borohydride. The results are given in Table I

Table I

Example No.	**Reducing agent used in combination with $NaBH_4$**	**Yield in Percentage**	**HPLC purity in Percentage**
6	Iodine	71.02%	98.50%
7	Copper sulfate	71.90%	98.88%
8	Lithium bromide	72%	99.02%

Example 9: Preparation of Avanafil of Formula (I)

To 100ml of ethanol was added 0.5ml of sulphuric acid and 10g of compound of Formula (II) obtained in example 1, and the reaction mixture was maintained at reflux temperature till completion of reaction. The reaction mixture was then cooled to 25-30°C and the pH of reaction mixture was adjusted to 7-8 using sodium carbonate. Filter the reaction mixture and collect filterate containing product. To the filterate was added 1.2g of sodium borohydride and 2.6g of lithium bromide, and the mixture was stirred for 5 hours. After complete conversion of ester to final product, 100ml water was added and the mixture was extracted with 100ml methylene dichloride (50ml X 2). The methylene dichloride layer obtained was evaporated under reduced pressure to get an oily mass. The oily mass was stripped with 25ml ethyl acetate at 45-50°C. To the oily residue formed was added 50ml of ethyl acetate and the mixture was cooled to 0-5°C. The solid obtained was filtered, washed with ethyl acetate and dried to yield crude Avanafil of Formula (I) which was subjected to purification using methanol as solvent to yield 7.5g of Avanafil of Formula (I) having HPLC purity of 99%.

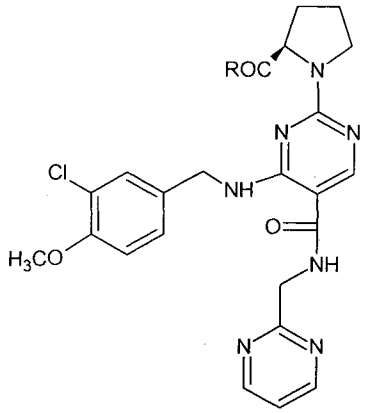
Example 10: Preparation of Avanafil of Formula (I) from Compound of Formula (II) (wherein R is –Cl)

To a mixture of 400ml of tetrahydrofuran and 50g of carboxylic acid chloride compound of Formula (II) obtained in example 3, was added 12g sodium borohydride at 0-5°C. After completion of reaction, water was added to reaction mixture to decompose excess of sodium borohydride present. The reaction mixture was then concentrated and a solution of 30g of potassium hydroxide in 200 ml of water was added. The mixture was heated to 60-70°C and maintained for 15-18 hours. The mixture was then cooled to 25-30°C and 500 ml of methylene dichloride was added. The organic layer thus formed, was separated and evaporated to yield crude Avanafil

of Formula (I) which was then subjected to purification using methanol as solvent to obtain 40g of Avanafil of Formula (I) having HPLC purity of 99.01%.

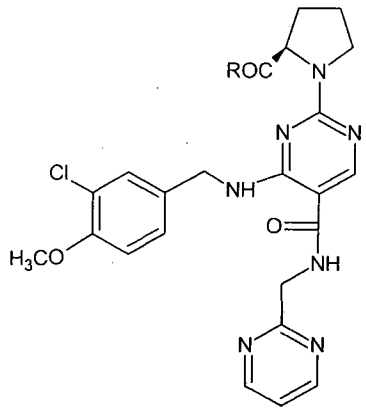
We Claim

1. A compound of Formula (II)



wherein R is -OH, -Cl or $-OR^1$ and R^1 is C_1 to C_3 alkyl group

2. A process for preparation of compound of Formula (II),

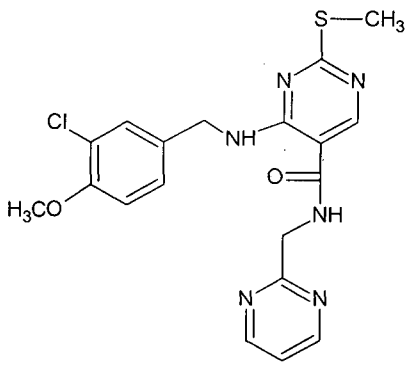


Formula (II)

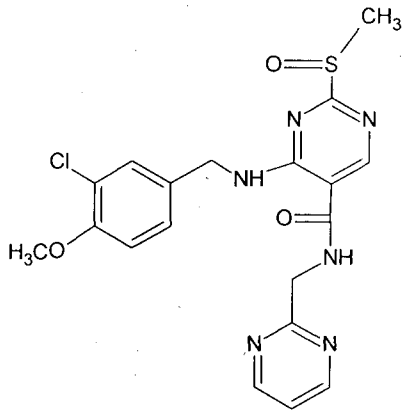
wherein R is -OH

comprising:

i) oxidizing compound of Formula (III) with m-chloroperoxybenzoic acid in methylene dichloride to form compound of Formula (IV)



Formula (III)



Formula (IV)

ii) in-situ reacting compound of Formula (IV) with L-proline in presence of triethylamine to obtain a reaction mixture

iii) washing the reaction mixture of step ii) with a carbonate solution and separating an organic layer

iv) evaporating the organic layer and stripping the thus formed oily mass with acetone to obtain compound of Formula (II)

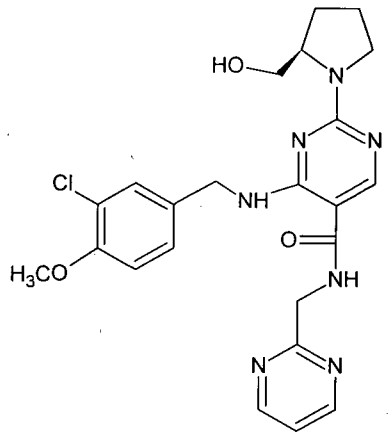
3. The process as claimed in claim 2, wherein compound of Formula (II) obtained in step iv) is subjected to esterification using a C_1 to C_3 alcohol in presence of an acid.

4. The process as claimed in claim 2, wherein compound of Formula (II) obtained in step iv) is subjected to chlorination using a chlorinating agent in a suitable solvent.

5. The process as claimed in claim 4, wherein the chlorinating agent is selected from phosphoryl chloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride, preferably thionyl chloride is used.

6. The process as claimed in claim 4, wherein the solvent is selected from methylene dichloride or ethylene dichloride.

7. A process for preparation of Avanafil of Formula (I),



Formula (I)

comprising:

a) reducing compound of Formula (II), by using a suitable reducing agent in a polar solvent to obtain crude Avanafil of Formula (I);

b) purifying the crude Avanafil of Formula (I) in methanol.

8. The process as claimed in claim 8, wherein the reducing agent used is selected from sodium borohydride, vitride, iodine, Fe powder, lithium aluminium hydride, copper sulfate, lithium bromide, iodine, bromine, sulfuric acid, methanesulfonic acid or mixture thereof.

9. The process as claimed in claim 8, wherein the polar solvent used in step a) is selected from methylene dichloride, ethyl acetate, acetone, methanol, ethanol, propanol, or a mixture thereof.

10. The process as claimed in claim 8, wherein solvent used in step a) is ethanol.

Dated this 3rd day of February 2015.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000066

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14
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 practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 7 273 868 B2 (YAMADA KOICHIRO [JP] ET AL) 25 September 2007 (2007-09-25) Reference Example 2; examples 304-348	1-10
A	ANGIOLINI M ET AL: "Solid-phase synthesis of pyrido[2,3-d]pyrimidin-7-ones", TETRAHEDRON LETTERS, PERGAMON, GB, vol. 46, no. 50, 12 December 2005 (2005-12-12), pages 8749-8752, XP027863124, ISSN: 0040-4039 [retrieved on 2005-12-12] Scheme 3; compound H7	1-10

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

☒ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 July 2015	03/08/2015

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/IN2015/000066

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