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Declarations under Rule 4.17:

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- 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:** PROCESS FOR THE PREPARATION OF FOSAMPRENAVIR CALCIUM AND INTERMEDIATE USED IN ITS PREPARATION

(57) **Abstract:** The present invention provides a novel intermediate, Calcium (3S) tetrahydro - 3 - furanyl (1S,2R)-3- [[(4- nitro -phenyl) - sulfonyl] (isobutyl) amino] - 1 -benzyl - 2 -phosphonoxy) propyl- carbamate (V) and a process for its preparation comprising reacting (3 S) tetrahydro - 3 - furanyl (1S,2R)-3 - [[(4 -nitrophenyl) sulfonyl] (isobutyl) amino] - 1 -benzyl - 2 - (hydroxy) propyl carbamate (II) with a phosphorylating agent to obtain (3S) tetrahydro- 3 - furanyl (1S,2R)-3- [[(4- nitrophenyl) sulfonyl] (isobutyl) amino] - 1 -benzyl - 2 - (phosphonoxy) propyl carbamate (III); optionally converting compound (III) to its sodium salt (IV); adding calcium ions to compound (III) or compound (IV); and optionally purifying the resultant compound (V). The present invention also provides a process for the preparation of fosamprenavir calcium comprising reacting a compound (V) with a reducing agent.



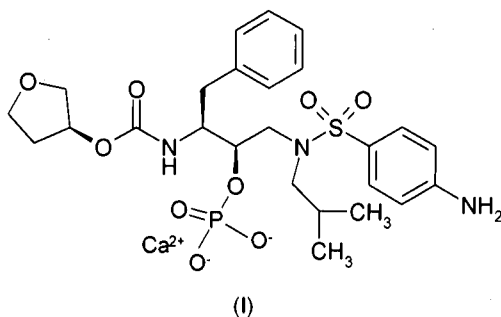
PROCESS FOR THE PREPARATION OF FOSAMPRENAVIR CALCIUM AND INTERMEDIATE USED IN ITS PREPARATION

FIELD OF INVENTION

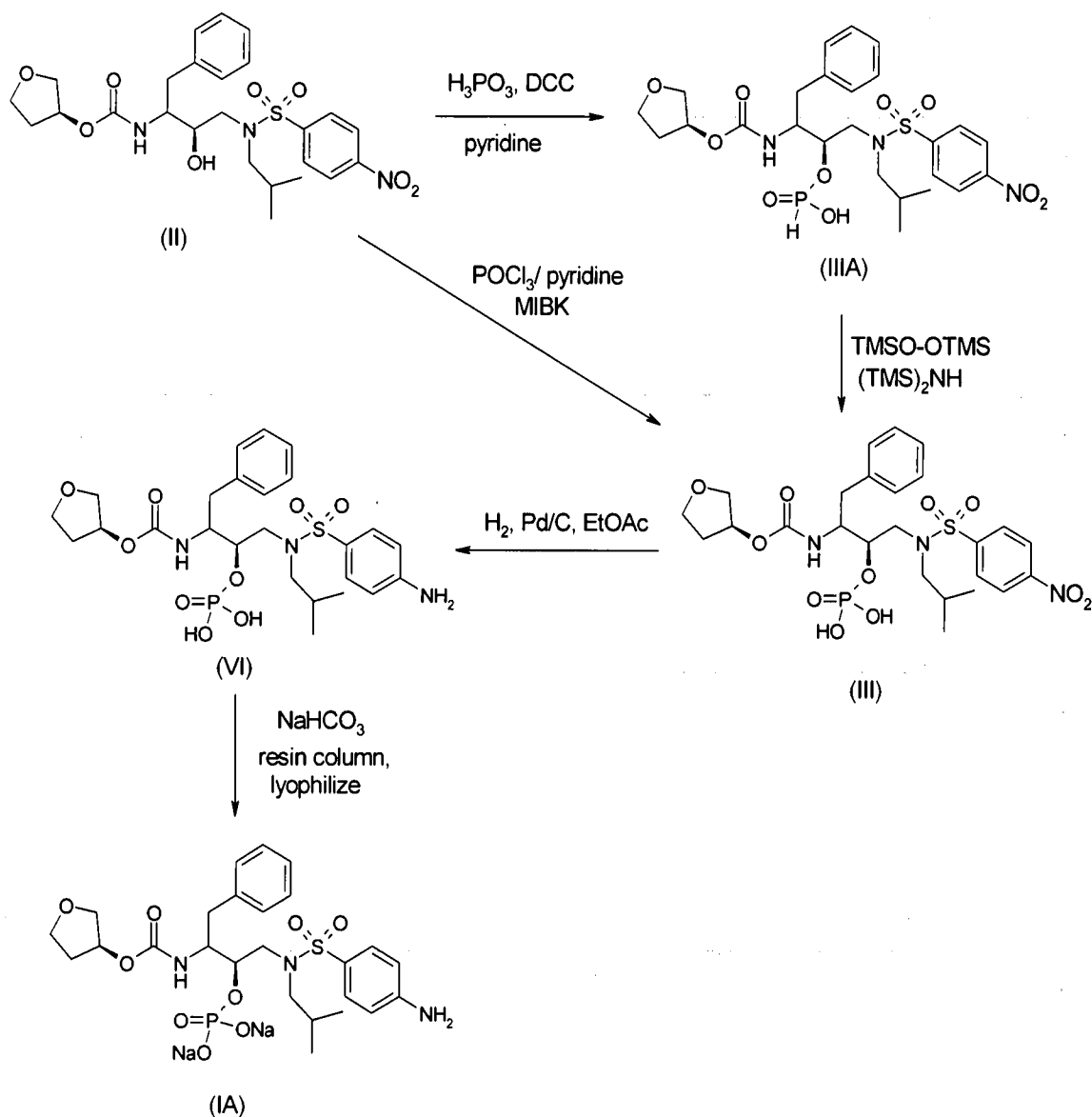
The present invention relates to a novel process for preparation of fosamprenavir calcium (I) and novel intermediate calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitro-phenyl)-sulfonyl] (isobutyl) amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V)

BACKGROUND OF THE INVENTION

Fosamprenavir calcium has HIV aspartyl protease inhibitory activity and is particularly well suited for inhibiting HIV-1 and HIV-2 viruses; it is chemically known as calcium (3S) tetrahydro-3-furanyl(1S,2R)-3-[[[(4-aminophenyl) sulfonyl] (isobutyl) amino]-1-benzyl-2-(phosphonooxy)propyl carbamate and represented by formula I.



The patent US 6 436 989 is product patent for fosamprenavir and its pharmaceutically acceptable salts. It provides process for preparation of fosamprenavir sodium salt (IA) from compound (II) as depicted in Scheme 1. However, this patent does not provide enabling process for preparation of fosamprenavir calcium (I).

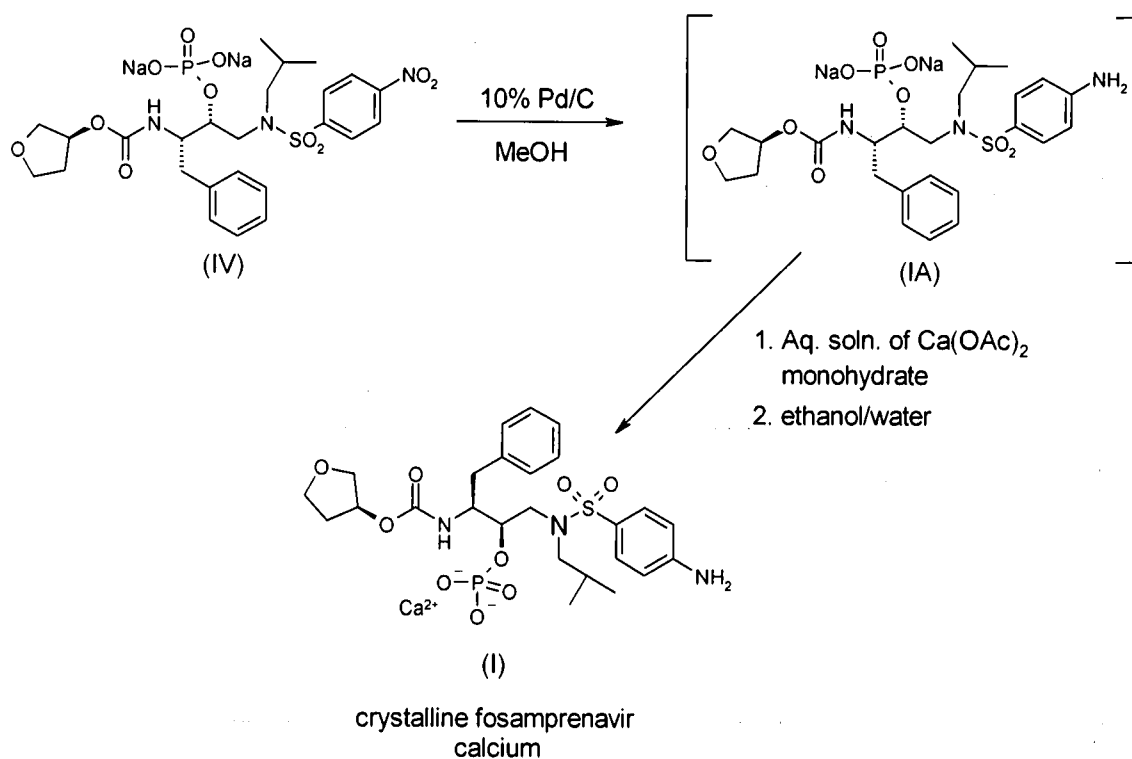


Scheme 1: Process for preparation of fosamprenavir sodium (IA) as given in US 6 436

989.

- 5 A stable crystalline Form I of fosamprenavir calcium is disclosed in US 6 514 953, Form I of fosamprenavir calcium is obtained by crystallization from a mixture of ethanol and water. This patent mentions that Form I has good pharmaceutical properties making it suitable for formulation into tablets.

US 6 514 953 provides process for preparation of crystalline fosamprenavir calcium (I) as depicted in Scheme 2, wherein compound (IV) is subjected to catalytic reduction to obtain fosamprenavir sodium (IA) which is treated in situ with calcium acetate to form the resultant compound (I).



Scheme 2: Process for preparation of fosamprenavir Calcium (I) as given in US 6 514 953

10 PCT application WO 2010/134045 provides amorphous fosamprenavir calcium. The application mentions that amorphous fosamprenavir calcium has appreciable solubility over the relevant physiological pH range; the solubility of amorphous is superior to that of crystalline form and the amorphous fosamprenavir calcium is essentially non-hygroscopic, stable on storage, reproducible and suitable for developing pharmaceutical dosage form.

WO 2010/134045 further provides process for preparation of amorphous form, wherein crystalline fosamprenavir calcium, as prepared by example of US 6 514 953, is converted to amorphous fosamprenavir calcium by utilizing thin film dryer or spray dryer processes or isolating amorphous fosamprenavir calcium from a mixture of solvent and an anti-solvent.

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PCT application WO 2011/001383 provides crystalline Form II of fosamprenavir calcium and process for preparation of the same. Fosamprenavir calcium, as prepared by example of US 6 514 953, is converted to crystalline Form II by dissolving fosamprenavir calcium in a water miscible organic solvent comprising a propanol, treating the solution with water and isolating Form II from the mixture.

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Prior art articles Drugs of the Future (2001), 26(3), 224-231 and Chinese Journal of pharmaceuticals (2006), 37(11), 723-726 provides process for preparation of fosamprenavir calcium (I) wherein, fosamprenavir (III) as prepared according to the process of scheme 1, is treated with calcium acetate to give the resultant compound.

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The above mentioned methods of preparation of fosamprenvir calcium suffer from many drawbacks such as:

- i) Costly reagents like DCC, TMSO-OTMS are utilized;
- 20 ii) these sensitive reagents require anhydrous reaction conditions and inert atmosphere;
- iii) multi step processes;
- iv) economically less preferred.

Since not many alternative efficient processes are available for synthesis of fosamprenavir calcium, a need arises to develop such a process. The present invention provides a novel process for preparation of fosamprenavir calcium suitable for large scale manufacture.

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DESCRIPTION OF DRAWING

Figure 1: X-ray powder diffraction pattern of compound (V).

SUMMARY OF THE INVENTION

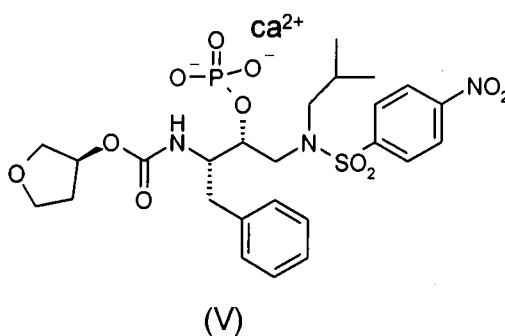
The present invention provides novel intermediate Calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitro-phenyl)-sulfonyl] (isobutyl) amino]-1-benzyl-2-phosphonooxy) propyl-carbamate (V) and process for its preparation comprising, reacting (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitrophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(hydroxy)propyl carbamate (II) with a phosphorylating agent to obtain (3S) tetrahydro-3-furanyl(1S,2R)-3-[[[(4-nitrophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy) propyl carbamate (III); optionally converting compound (III) to its sodium salt (IV); adding calcium ions to compound (III) or compound (IV); and optionally purifying the resultant compound (V).

The present invention provides process for preparation of fosamprenavir calcium comprising, reacting a compound (V) with a reducing agent.

The present invention provides process for preparation of amorphous fosamprenavir calcium comprising reacting compound (V) with a reducing agent and conversion to amorphous form.

DETAILED DESCRIPTION OF THE INVENTION

In the most preferred embodiment, the present invention provides compound, calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitro-phenyl)-sulfonyl] (isobutyl) amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V)



and process for preparation of compound (V) comprising:

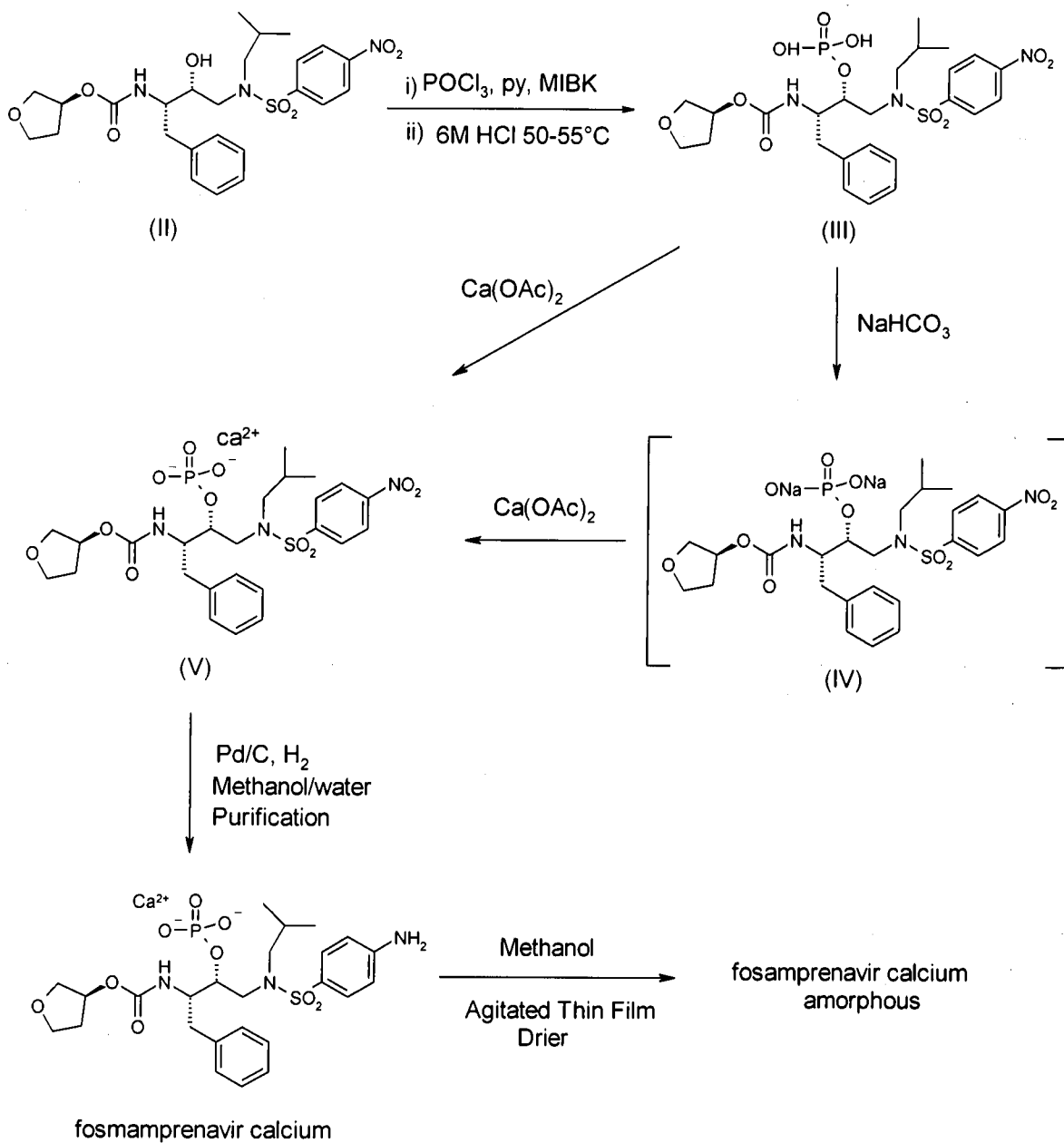
- a) reacting compound (II) with a phosphorylating agent to obtain compound (III);
- b) optionally converting compound (III) to its sodium salt (IV);
- 5 c) adding source of calcium ions to the compound (III) or sodium salt (IV); and
- d) optionally purifying the compound (V).

In a second embodiment, the present invention provides process for preparation of fosamprenavir calcium comprising:

- 10 a) reacting compound (II) with a phosphorylating agent to obtain compound (III);
- b) optionally converting compound (III) to its sodium salt (IV);
- c) adding source of calcium ions to compound (III) or sodium salt (IV);
- d) optionally purifying compound (V); and
- e) reducing compound (V) with a reducing agent.

15

The process for preparation of fosamprenavir calcium (I) of present invention is as depicted in scheme 3.



Scheme 3: Process for preparation of fosamprenavir calcium (I) of the present invention.

In a third embodiment, the present invention provides process for preparation of amorphous fosamprenavir calcium comprising:

- a) reacting compound (II) with a phosphorylating agent to obtain compound (III);

- b) optionally converting compound (III) to its sodium salt (IV);
- c) adding source of calcium ions to compound (III) or sodium salt (IV);
- d) optionally purifying compound (V);
- e) reducing compound (V) with a reducing agent; and
- 5 f) conversion to amorphous form.

Compound of formula (II) reacts with a phosphorylating agent in presence of an organic base and optionally in presence of a solvent.

- 10 The phosphorylating agent is selected from phosphorous oxychloride, phosphorous pentachloride, preferably phosphorous oxychloride.

The organic base is selected from pyridine, triethylamine, diisopropylethylamine, preferably pyridine.

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The solvent is selected from ketones like methyl ethyl ketone, methylisobutylketone, preferably methylisobutylketone; chlorinated solvents like dichloromethane, ethylene dichloride, carbon tetrachloride, chloroform, chlorobenzene.

- 20 Phosphorylation can be performed at a temperature range of -10 to 100°C, preferably 0 to 40°C, more preferably 10-20°C.

The phosphorylating agent phosphorous oxychloride may be employed in a range of 0.3 to 3.0 moles equivalent of compound (II), preferably 0.9 to 2.0 moles, more preferably 1.0 to
25 1.3 moles.

Compound of formula (III) can be converted to its sodium salt (IV) utilizing source of sodium ions selected from sodium bicarbonate, sodium carbonate.

The source of calcium ions is selected from calcium carbonate, calcium acetate, calcium chloride, calcium hydroxide, preferably calcium acetate.

The compound (V) is purified by slurry washing or crystallization, from a solvent selected from alcohol like methanol, ethanol, isopropanol; esters like ethylacetate; ketones like acetone; nitriles like acetonitrile; chlorinated solvents like dichloromethane, ethylene dichloride; ethers like tetrahydrofuran, diisopropyl ether; amides like dimethyl formamide; or mixture thereof; preferred solvent is methanol.

10 Compound (V) is treated with a suitable reducing agent in presence of an appropriate solvent.

Reducing agent is selected from alkali metals, transition metals and metal complexes or combination thereof; alkali metal hydrides selected from sodium borohydride or lithium aluminium hydride; transition metals selected from chromium, cobalt, iron, nickel, palladium, platinum, ruthenium, rhodium, titanium, zinc and their oxides which are optionally supported on active carbon; other reagents such as tin, iron and zinc hydrochlorides etc.

In accordance to the reducing reagent appropriate solvent is selected from an organic solvent, water or mixture thereof; organic solvent is selected from alcohols such as methanol, ethanol, isopropanol, butanol; ethers such as diisopropyl ether, tetrahydrofuran, dioxane, diglyme; acids such as acetic acid, propionic acid etc; or mixtures thereof.

The reduction is carried out preferably using palladium carbon in a mixture of alcohol and water.

The reduction is carried out at a temperature range of 10-60°C, preferably 20-40°C and at a pressure of 1-20 kg, preferably 5-10 kg.

Our earlier patent application 277/KOL/2010, dated March 19, 2010, filed at the Indian Patent Office describes three different methods for preparation of amorphous fosamprenavir calcium, wherein:

- i) fosamprenavir calcium was dissolved in ethanol and amorphous fosamprenavir calcium was precipitated by addition of diisopropyl ether;
- ii) solution of methanol and fosamprenavir calcium was prepared and concentrated to obtain the amorphous form;
- iii) fosamprenavir calcium crystalline form I was dried at 120°C for 20 hours to convert it to amorphous form.

Additionally amorphous fosamprenavir calcium can be prepared by subjecting a solution of alcohol and fosamprenavir calcium to an agitated thin film dryer and obtaining the amorphous form.

The manufacture of fosamprenavir calcium (I) by the process of present invention is simple and utilizes cheaper reagents; has less number of steps and suitable for commercial use.

The present invention is further illustrated by the following representative examples and does not limit the scope of the invention.

EXAMPLES:

The X-ray diffraction pattern was measured using Philips PANalytical, X'Pertpro machine with following parameters:

Scan axis: Gonio

Step size: 0.0080°

Scan type: continuous

Divergence slit size: 0.2393°

Anode material: Cu

Radiation type" K-alpha 1

Scan: 2° from 3.49 to 39.99

Spinning: Yes

Measurement temperature: 25°C

5 **Example 1:** Preparation of Calcium (3S) tetrahydro-3-furanyl (1S, 2R)-3-[[[(4-nitro-phenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V)

Mixture of 100 g (0.1869 mol) (3S)-tetrahydro-3-furyl N-[(1S,2R)-1-benzyl-2-hydroxy-3-(N-isobutyl-4-nitrobenzene sulphonamido) propyl] carbamate (II) and 200 ml pyridine was
10 cooled to 0-10°C and 70 g (0.448 mol) of POCl₃ was added and stirred at 27°C for 4 hours. To the reaction mixture 400 ml methyl isobutyl ketone was added, cooled and 1:1 conc. HCl-water was added. Mixture was heated to 45-50°C for 1 hour and then cooled to 25-30°C. Organic layer was separated, washed with water and partially concentrated; to the concentrate was added a mixture of 31.5 g sodium bicarbonate in 315 ml water and stirred.
15 The aqueous layer was separated and mixed with 800 ml methanol. A solution of 33 g calcium acetate in 100 ml water was added to the mixture stirred and solid was filtered. The wet solid was stirred in 200 ml methanol at 5-10°C for 30 minutes and filtered. Solid was dried under reduced pressure to obtain compound (V); yield 86.1 g (70.4%). M/z: 616.20 (M+1, free acid); ¹H NMR (DMSO-d₆ + drop of DCl): 8.36 (2H), 8.08 (2H), 7.22 (5H), 4.88 (1H), 4.34 (1H), 4.04-4.02 (1H), 3.30-3.27 (1H), 3.68-3.53 (4H), 3.28-2.87 (4H), 2.57-2.54 (1H), 1.98-1.78 (3H), 0.78 (6H);
20 IR: 3381.82, 1687.82, 1605.86, 1531.81, 1350.42, 1313.09, 1161.69, 1108.55, 1088.30 cm⁻¹; X-ray powder diffraction pattern as depicted in Figure 1, which indicates amorphous material.

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Example 2: Preparation of Calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitro-phenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V) from (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitrophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy)propylcarbamate (III)

To the solution of 25 g (0.040 mol) (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[4-nitrophenyl)sulfonyl](isobutyl)amino]-1-benzyl-2-(phosphonooxy)propylcarbamate (III) in 250 ml methanol was added a solution of 7.86 g calcium acetate in 25 ml water. Mixture was stirred at 25-27°C for one hour. The solid was filtered and dried under reduced pressure to obtain compound (V).

Example 3: Preparation of fosamprenavir calcium (I)

To a mixture of 12 g (0.0183) calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[4-nitrophenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V) as obtained in example 1 or 2 and 240 ml methanol was added 1.2 g 10% Pd/C and stirred under a hydrogen pressure of 20 kg (~300 psi) at 25-40°C for 12 hours. The reaction mixture was filtered and partially concentrated. To the concentrate was added 60 ml water and stirred at 25-28°C for 1 hour. The solid was filtered and dried under reduced pressure to obtain crude fosamprenavir calcium (I).

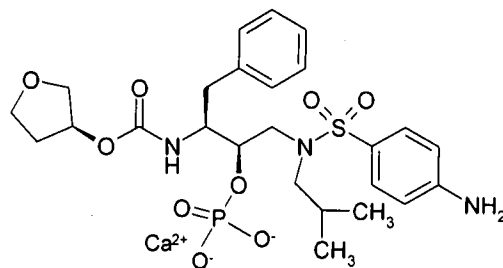
A mixture of 3.5 g crude fosamprenavir calcium (I) and 52.5 ml ethanol was heated at 72°C, the solution was filtered hot and the filtrate was maintained at 72°C and 14.45 ml water was added. The mixture was cooled at 25°C and stirred for 1 hour. The solid was filtered and dried under reduced pressure to obtain fosamprenavir calcium; yield 2.5 g (71%); HPLC purity: 98.49%.

Example 4: Preparation of amorphous fosamprenavir calcium (I)

A mixture of 2.0 g (0.0032 mol) fosamprenavir calcium of example 3 and 14 ml methanol was stirred at 25°C for 30 minutes, the resultant solution was filtered. The filtrate was concentrated under reduced pressure at 40°C to obtain a solid, which was dried under reduced pressure to give amorphous fosamprenavir calcium; yield 1.75 g (87.5%).

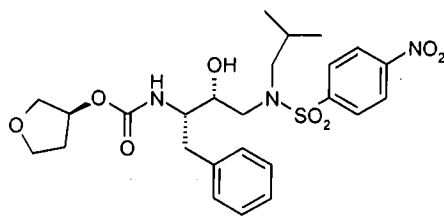
CLAIMS

- 5 1. A process for preparation of fosamprenavir calcium (I) comprising:

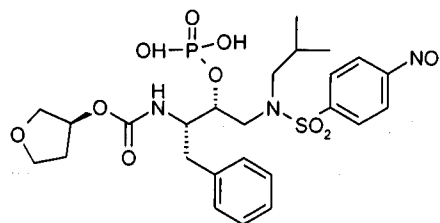


(I)

- a) reacting compound (II) with a phosphorylating agent to obtain compound (III);

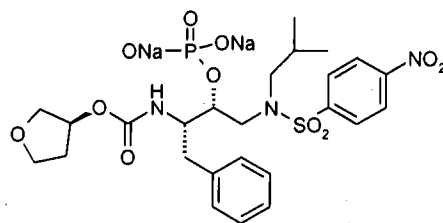


(II)



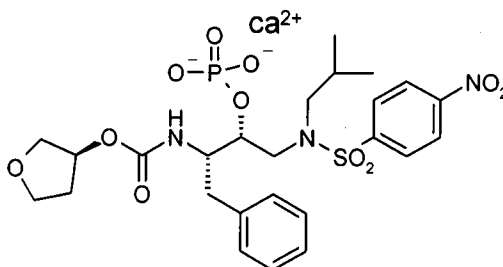
(III)

- b) optionally converting compound (III) to its sodium salt (IV);



(IV)

- c) adding source of calcium ions to compound (III) or sodium salt (IV);
d) optionally purifying compound (V); and



(V)

e) reducing compound (V) with a reducing agent.

2. A process for preparation of calcium (3S) tetrahydro-3-furanyl (1S,2R)-3-[[[(4-nitrophenyl)-sulfonyl] (isobutyl) amino]-1-benzyl-2-phosphonooxy]propyl-carbamate (V) comprising:

- reacting compound (II) with a phosphorylating agent to obtain compound (III);
- optionally converting compound (III) to its sodium salt (IV);
- adding source of calcium ions to the compound (III) or sodium salt (IV); and
- optionally purifying the compound (V).

3. A process according to claim 1 or 2, wherein compound (II) reacts with a phosphorylating agent in presence of an organic base and optionally in presence of a solvent.

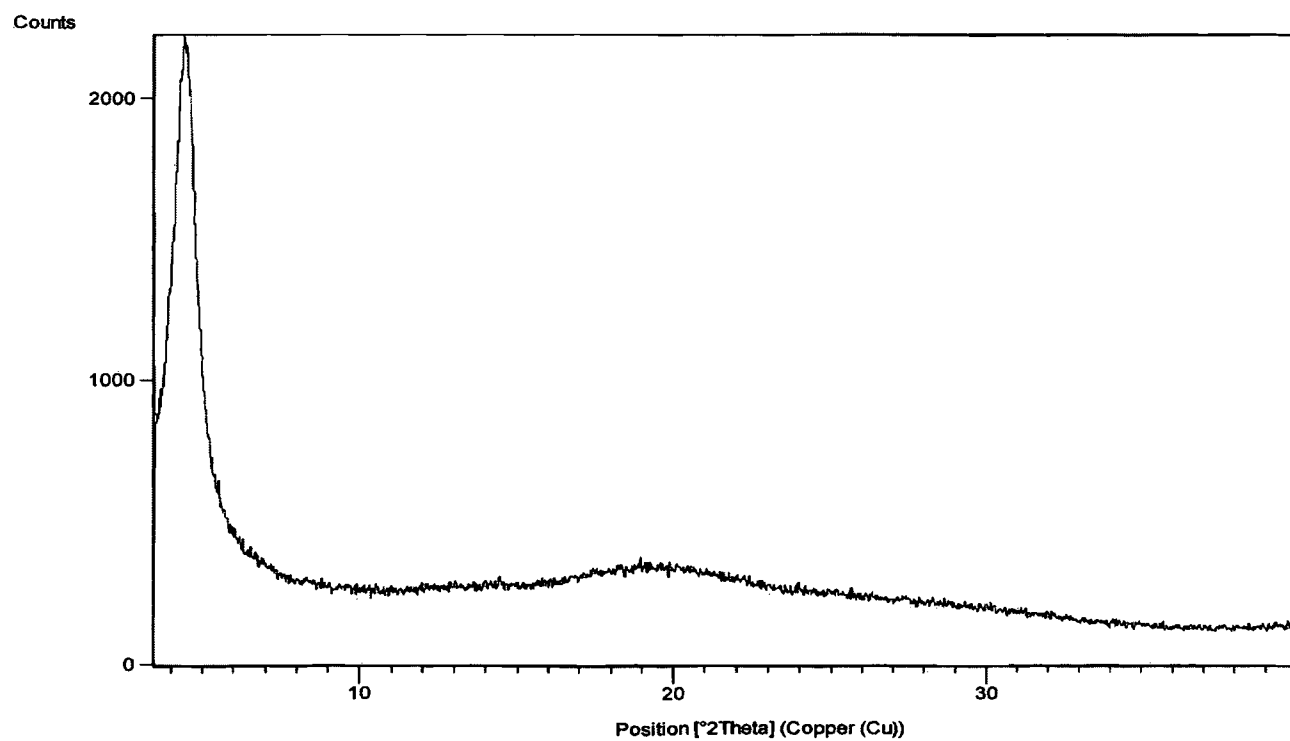
4. A process according to claim 3, wherein the phosphorylating agent is selected from phosphorous oxychloride, phosphorous pentachloride.

5. A process according to claim 3, wherein the phosphorylating agent may be employed in a range of 0.3 to 3.0 moles equivalent of compound (II), preferably 0.9 to 2.0 moles, more preferably 1.0 to 1.3 moles.

6. A process according to claim 3, wherein phosphorylation can be performed at a temperature range of -10 to 100°C, preferably 0 to 40°C, more preferably 10-20°C.
7. A process according to claim 3, wherein the organic base is selected from pyridine,
5 triethylamine, diisopropylethylamine, preferably pyridine.
8. A process according to claim 3, wherein the solvent is selected from ketones like methyl ethyl ketone, methylisobutylketone, preferably methylisobutylketone; chlorinated solvents like dichloromethane, ethylene dichloride, carbon tetrachloride,
10 chloroform, chlorobenzene.
9. A process according to claim 1 or 2, wherein compound (III) can be converted to its sodium salt (IV) utilizing source of sodium ions selected from sodium bicarbonate, sodium carbonate.
15
10. A process according to claim 1 or 2, wherein the source of calcium ions is selected from calcium carbonate, calcium acetate, calcium chloride, calcium hydroxide, preferably calcium acetate.
- 20 11. A process according to claim 1 or 2, wherein compound (V) is purified either by slurry washing or crystallization, from a solvent selected from alcohol like methanol, ethanol, isopropanol; esters like ethylacetate; ketones like acetone; nitriles like acetonitrile; chlorinated solvents like dichloromethane, ethylene dichloride; ethers like tetrahydrofuran, diisopropyl ether; amides like dimethyl formamide; or mixture thereof;
25 preferred solvent is methanol.
12. A process according to claim 1, wherein compound (V) is treated with reducing agent in an appropriate solvent.

13. A process according to claim 12, wherein reducing agent is selected from alkali metals, transition metals and metal complexes or combination thereof; alkali metal hydrides selected from sodium borohydride or lithium aluminium hydride; transition metals selected from chromium, cobalt, iron, nickel, palladium, platinum, ruthenium, rhodium, titanium, zinc and their oxides which are optionally supported on active carbon; other reagents such as tin, iron and zinc hydrochlorides etc.
14. A process according to claim 13, wherein preferred reducing agent is palladium carbon.
15. A process according to claim 12, wherein appropriate solvent is selected from an organic solvent, water or mixture thereof; organic solvent is selected from alcohols such as methanol, ethanol, isopropanol, butanol; ethers such as diisopropyl ether, tetrahydrofuran, dioxane, diglyme; acids such as acetic acid, propionic acid etc; or mixtures thereof.
16. A process according to claim 15, wherein appropriate solvent is mixture of alcohol and water.
17. A process according to claim 12, wherein the reduction is carried out at a temperature range of 10-60°C, preferably 20-40°C and at a pressure of 1-20 kg, preferably 5-10 kg.
18. The compound calcium (3S) tetrahydro-3-furanyl (1S, 2R)-3-[[[(4-nitro-phenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V).
19. Amorphous calcium (3S) tetrahydro-3-furanyl (1S, 2R)-3-[[[(4-nitro-phenyl)-sulfonyl](isobutyl)amino]-1-benzyl-2-phosphonooxy)propyl-carbamate (V) characterized by an X-ray powder diffraction pattern as shown in figure 1.

1/1

**Figure 1**

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2011/000481

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07F9/655
 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)
 C07F

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2011/033469 A1 (RANBAXY LABORATORIES LIMITED) 24 March 2011 (2011-03-24) cited in the application the whole document	1-19
X	----- "Process for the preparation of Calcium (2R,3S)-1-(4-amino-N-isobutylphenylsulfonamido)-4-phenyl-3-(((S)-tetrahydrofuran-3-yloxy)carbonylamino)butan-2-yl phosphate", IP.COM JOURNAL, 21 June 2010 (2010-06-21), XP013138772, ISSN: 1533-0001 Retrieved from the Internet: URL:http://ip.com/IPCOM/000196928> the whole document -----	1-19



Further documents are listed in the continuation of Box C.



See patent family annex.

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

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

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011033469	A1	24-03-2011	NONE
