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(54) Title: PROCESSES FOR THE PREPARATION OF LOPINAVIR AND ITS INTERMEDIATE - (S)-TETRAHYDRO-ALPHA-(1-METHYLETHYL)-2-OXO-1(2H)-PYRIMIDINEACETIC ACID

(57) Abstract: The invention relates to processes for the preparation of (S)-tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid or a salt thereof, and to use of this compound as intermediate for the preparation of compounds with antiviral activity. The invention also relates to a process for the preparation of lopinavir, and pharmaceutical compositions that include the lopinavir.



WO 2006/100552 A1

**PROCESSES FOR THE PREPARATION OF LOPINAVIR AND ITS
INTERMEDIATE - (S)-TETRAHYDRO- α -(1-METHYLETHYL)-2-OXO-1(2H)-
PYRIMIDINEACETIC ACID**

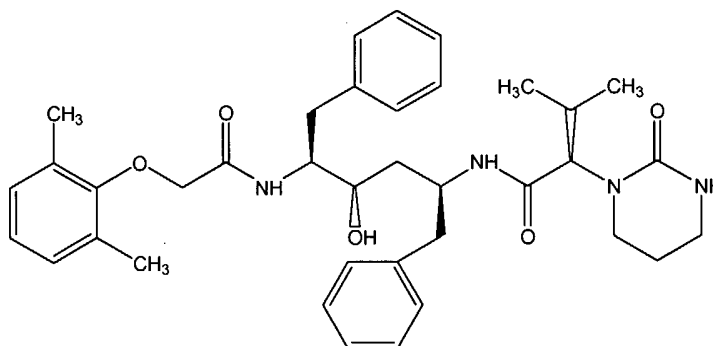
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Field of the Invention

The field of the invention relates to processes for the preparation of (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid or a salt thereof, and to use of this compound as an intermediate for the preparation of compounds with antiviral activity. The invention also relates to a process for the preparation of lopinavir, and pharmaceutical
10 compositions that include the lopinavir.

Background of the Invention

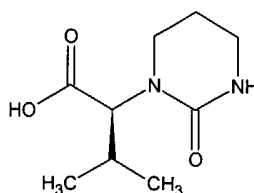
Chemically, lopinavir is [1S-[1R*,(R*),3R*,4R*]]-N-[4-[[[(2,6-dimethyl-
phenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro- α -(1-
methylethyl)-2-oxo-1(2H)-pyrimidineacetamide having the structural Formula I. It is
15 indicated in combination with other antiretroviral agents for the treatment of HIV-
infection.



Formula I

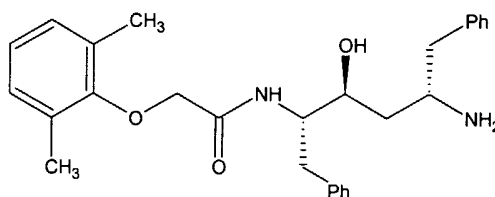
(S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II
20 is a useful intermediate in the preparation of lopinavir of Formula I.

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**Formula II**

U.S. Patent No. 5,914,332 discloses a process for the preparation of (S)-tetrahydro-
 α-(1-methylethyl)-2-oxo-1(2H)-pyrimidine acetic acid by reacting L-valine with
 5 acrylonitrile and methyl chloroformate, followed by isolating the N-(2-cyanoethyl)-N-(methoxycarbonyl)-L-valine intermediate which is then hydrogenated over Raney-nickel in the presence of alkaline earth metal hydroxide to get the required intermediate. The overall yield obtained is about 25%.

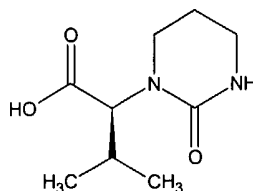
The intermediate of formula II thus obtained is reacted with N-[(1S,2S,4S)-4-
 10 amino-1-benzyl-2-hydroxy-5-phenylpentyl]-2-(2,6-dimethylphenoxy)acetamide of formula III, to get lopinavir of formula I.

**Formula III**

International (PCT) Publication No. WO 03/101971 discloses another method for
 15 the preparation of compound of Formula II. L-valine is reacted with acrylonitrile to isolate N-(2-cyanoethyl)-L-valine which on treatment with methylchloroformate, followed by catalytic hydrogenation on Rhodium-charcoal, provides N-(3-aminopropyl)-N-(methoxycarbonyl)-L-valine, which then is cyclized in the presence of alkaline earth metal hydroxide to afford the title compound. The overall yield obtained is about 38%.

Summary of the Invention

In one general aspect there is provided a process for preparing (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II, or a salt thereof,

**Formula II**

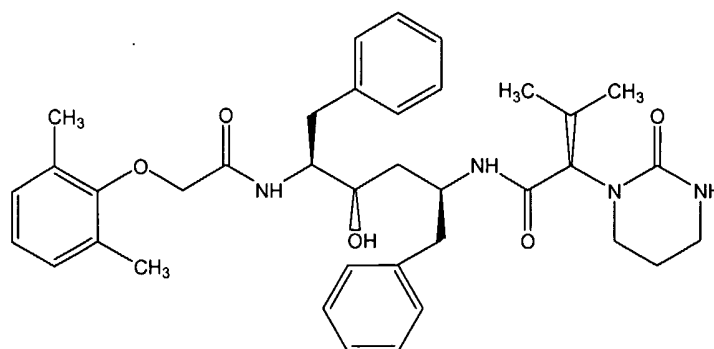
The process includes:

- a) reacting L-valine with acrylonitrile and alkyl chloroformate to form N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine;
- b) hydrogenating the product of step a) in the presence of a hydrogenating catalyst and a base; and
- c) cyclizing the product of step b) to get the (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II, or a salt thereof, wherein all the process steps are carried out *in situ*.

The process may include further drying of the product obtained. The process may include further converting the product obtained into lopinavir. The lopinavir may be made into a finished dosage form with one or more pharmaceutically acceptable excipients and administered to a patient in need of an anti-viral therapy.

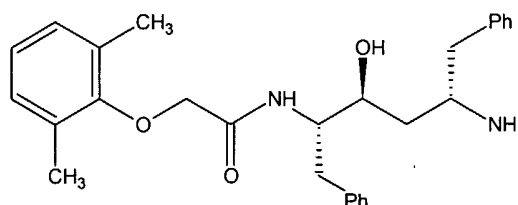
In another general aspect there is provided a process for the preparation of lopinavir of Formula I, or a pharmaceutically acceptable salt, ester or a prodrug thereof,

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**Formula I**

The process includes:

- a) reacting L-valine with acrylonitrile and alkyl chloroformate to form N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine;
- b) hydrogenating the product of step a) in the presence of a hydrogenating catalyst and a base;
- c) cyclizing the product of step b) to get (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II or salt thereof; and
- d) reacting the compound of Formula II with a compound of Formula III,

**Formula III**

to get lopinavir of Formula I, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the process steps a), b) and c) are carried out *in situ*.

In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of lopinavir; and one or more pharmaceutically acceptable carriers, excipients or diluents. The resulting pharmaceutical composition or dosage form may be administered to a patient in need of an anti-viral therapy.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

5 The inventors have developed an efficient process for the preparation of (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II. The process involves reacting L-valine with acrylonitrile and alkyl chloroformate to form N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine; hydrogenating in the presence of a hydrogenating catalyst and a base; and cyclizing to get the (S)-tetrahydro- α -(1-
10 methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II or salt thereof, wherein all the process steps are carried out *in situ*.

 In general, L-valine may be added to water or an organic solvent and an alkali metal salt or an alkaline earth metal salt, or a mixture thereof, at a temperature of from about 0°C to about 60°C for about 0 to 1.5 hours. The reaction mixture may be stirred at a
15 temperature from about 0°C to about 60°C to get a clear solution. Acrylonitrile may be added to the clear solution at a temperature of from about 0°C to about 10°C for about 0 to 1.5 hours. The resulting reaction mixture may be stirred at a temperature of from about 0°C to about 10 °C for about 2 to 10 hours and water may be added at the same temperature.

20 The organic solvent, alkali metal salt, or alkaline earth metal salts which can be used in the reaction are known to a person of ordinary skill in the art. Any organic solvents can be used which are inert and do not change under the reaction conditions. Examples of alkali metal salts include salts of lithium, sodium, or potassium. Examples of alkaline earth metal salts include those of magnesium, calcium or barium.

25 Examples of alkyl groups of alkylchloroformate include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, and the like.

 The alkylchloroformate may be added at a temperature from about 0°C to about 60°C, for example from about 20°C to about 40°C. During the addition of alkylchloroformate, the pH of the mixture may be maintained at about 8 to 12 with an
30 addition of an alkali metal salt or an alkaline earth metal salt over a period of 0.5 to 2

hours. The reaction mixture may be stirred at a temperature from about 0°C to about 60°C for about 2 to 30 hours at pH 8 to 12.

A suitable organic solvent may be added to the reaction mixture and it may be cooled to about 0°C to about 40°C. The pH of the mixture may be adjusted to about 0 to 4 by addition of a mineral acid. The organic layer may be separated and concentrated under reduced pressure to give N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine as oil.

The term suitable solvent includes any solvent which is immiscible or partially miscible with water. Examples of such solvents include chlorinated hydrocarbons such as methylene dichloride, chloroform, and dichloroethane; esters such as ethyl acetate and isopropyl acetate; ketones such as methylisobutylketone; hydrocarbons such as benzene, toluene and hexane; and mixtures thereof.

The term mineral acid includes, but is not limited to, hydrochloric acid, sulphuric acid, nitric acid, perchloric acid, hydroiodic acid, and hydrobromic acid.

N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine may be dissolved in an organic solvent followed by the addition of a hydrogenating catalyst and a base.

The hydrogenation catalysts are the customary hydrogenation catalysts known in organic chemistry, such as transition metal compounds. Examples of transition metal compounds include palladium compounds such as palladium/carbon and palladium hydroxide, platinum compounds such as platinum oxide and platinum/carbon, ruthenium compounds such as ruthenium oxide, rhodium compounds such as rhodium/carbon and nickel compounds such as Raney nickel.

Examples of bases which can be used in the hydrogenation reaction include, but are not limited to, pyridine, ammonia, hydroxylamine, methylamine, and the like.

The hydrogenation reaction may be carried out at normal pressure, or at elevated pressure depending on the choice of a catalyst. In general, it may be carried out at a hydrogen pressure in the range from about 1 kg/cm² to about 10 kg/cm², for example at a hydrogen pressure in the range from about 2 kg/cm² to about 6 kg/cm².

The hydrogenation temperature may be varied depending on the choice of a catalyst and/or pressure employed. For example, the hydrogenation may be carried out at a temperature range from about 20°C to about 120°C, or at a temperature range from about

30°C to about 80°C. In particular, it may be carried out at a temperature range from about 35°C to about 65°C.

After completion of the hydrogenation reaction, the catalyst may be filtered off and washed with a solvent. The filtrate may be concentrated under vacuum. The volume may
5 be reduced to between about half of the original volume and about one-fourth of volume. Water may be added to the reduced filtrate residue and hydroxide of an alkali metal or an alkaline earth metal may be added at a temperature of from about 0°C to about 60°C. The mixture may be heated up to a reflux temperature for about 5 hours to about 12 hours till the reaction is complete. The reaction mixture may be cooled to a temperature of from
10 about 0°C to about 40°C. It may be acidified with a mineral acid to a pH of less than 2. Sodium chloride may be added to the above mixture followed by the addition of a suitable organic solvent. The mixture may be stirred at a temperature of from about 0°C to about 60°C for about 1 to 60 minutes. The organic layer may be separated and the aqueous layer may be extracted with organic solvent. The organic layers may be combined and
15 evaporated under reduced pressure to get a solid. The solid may be suspended in organic solvent and the suspension stirred at a temperature of from about 10°C to about 100°C. The reaction mixture may be partially concentrated under reduced pressure. A further quantity of the same or a different organic solvent may be added into the above mixture and the suspended mixture may be stirred at a temperature of from about 10°C to about
20 100°C. It may be cooled down to about 5°C, stirred at the temperature of about 5 to 15°C for 5 to 18 hours and then at about 0°C for about 1 to 5 hours. The white solid then should be filtered, washed and dried.

The mineral acid which may be used includes hydrochloric acid, sulphuric acid, nitric acid, perchloric acid, hydroiodic acid, hydrobromic acid.

25 The organic solvents which can be used in these reactions are known to a person of ordinary skills in art. Suitable solvents are inert organic solvents which do not react under the reaction conditions. Examples of such solvents include alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl ketone; esters such as ethylacetate and isopropylacetate; chlorinated hydrocarbons such as
30 methylene chloride, ethylene dichloride and carbon tetrachloride; nitriles such as acetonitrile and benzonitrile; dipolar aprotic solvents such as dimethylsulfoxide and

dimethylformamide; alkyl ethers such as diethylether, diisopropylether and dimethoxyethane; cyclic ethers such as dioxane and tetrahydrofuran, and mixtures thereof.

The inventors also have developed a process for the preparation of lopinavir of Formula I or a pharmaceutically acceptable salt, ester or a prodrug thereof. The process involves reacting L-valine with acrylonitrile and alkyl chloroformate to form N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine; hydrogenating in presence of hydrogenating catalyst and a base; cyclizing to get the (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II or salt thereof; and reacting the compound of Formula II with a compound of Formula III to get lopinavir of Formula I or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein all the process steps for the preparation of the compound of Formula II are carried out *in situ*.

(S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II obtained in the first aspect of the invention is converted into an acid chloride (for example, the acid chloride prepared by reaction of the carboxylic acid with thionyl chloride), and dissolved in dimethyl formamide. To this, a stirred solution of a compound of formula III and imidazole in ethyl acetate at 0°C is added to obtain lopinavir.

As may be seen from the examples that follow, by using or following the processes of the present invention the (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H) - pyrimidineacetic acid may be obtained in an overall yield of about 65%, i.e., in a yield higher than that obtained by working according to the process described in U.S. Patent No. 5,914,332 and PCT application WO 03/101971.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and should not be construed in a manner that limits the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: N-(2-cyanoethyl)-N-(2-methoxycarbonyl)-L-valine

L-valine (50 g) was added portion wise into a mixture of water (100 ml) and potassium hydroxide (28 g) at 20-25°C during 15-20 minutes. The reaction mixture was stirred at 20-

25°C for 30 minutes to get a clear solution which is cooled to about 0°C. Acrylonitrile (24.5 g) was added to the clear solution at 0 to +5°C over about 20 minutes. The resulting reaction mixture was stirred at 0 to +5°C for 5 hours and then water (125 ml) was added at this temperature. Methylchloroformate (79.5 g) was added slowly to the resultant mass at 5 20-25°C while maintaining the pH of the mixture from about 9.5 to 10.5 by addition of 30% sodium hydroxide over a period of 1 hour. The mixture was stirred at 20-25°C for 15 hours at pH 9.5–10.5. Methylene chloride (120 ml) was added into the mixture and it was cooled to 10°C. Concentrated hydrochloric acid (100 ml) was added to adjust its pH to 1.0-1.5. The organic layer was separated and the aqueous layer was extracted with 10 methylene chloride (2 X 120 ml). The combined organic layer was concentrated under reduced pressure to provide the title compound as a thick oil.

Yield: 83 g

Example 2: (S)-Tetrahydro- α -(1-methylethyl)-2-oxo-1(2h)-pyrimidineacetic acid

15 N-(2-cyanoethyl)-N-(2-methoxycarbonyl)-L-valine (20.5 g) was dissolved in methanol (70 ml) followed by addition of Raney-Nickel (50% wet, 16 g) and aqueous ammonia (70 ml). The mixture was hydrogenated under pressure 4 kg/cm² at 50°C for about 4-5 hours till completion of reaction. After cooling the reaction mixture to room temperature, the catalyst was filtered and washed with methanol (80 ml). The combined filtrate was 20 concentrated under vacuum to 1/4th of initial volume at a temperature not exceeding 50°C to obtain a residue. Water (100 ml) was added to the residue followed by addition of sodium hydroxide (6.6 g) at 20-25°C. The mixture was refluxed for 7-8 hours till reaction completion. The reaction mixture was cooled to 10-15°C and then acidified with concentrated hydrochloric acid (about 17 ml) to pH less than 1.5. Sodium chloride (40 g) 25 was added into the above mixture followed by addition of methylene chloride (80 ml). The mixture was stirred at 20-25°C for 10-15 minutes. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 80 ml). The combined organic layers were evaporated completely under reduced pressure to get an off white solid. Ethyl acetate (80 ml) was added to the solid so obtained, and the mass was stirred at 50-55°C for 30 25-30 minutes. The reaction mass was concentrated under reduced pressure until three-

fourths of the initial volume at a temperature not exceeding 45°C and isopropanol (2 ml) was added into the resultant mass. The mixture was stirred at 50-55°C for 3-4 hours and then cooled to 5°C, and further stirred at 5-10°C for 12 hours and then at 0°C for 3 hours. The white solid so obtained was filtered and washed with ethylacetate (10 ml) at room temperature. The solid was dried at 45-50°C under vacuum for 12 hours to get the title compound.

Yield: 14.1 g

Example 3: (2S, 3S, 5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-[2s-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1, 6-diphenylhexane

Step 1: Preparation of 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl chloride.

Thionyl chloride (1.56 g) was added to a cooled (0°C) and stirred suspension of 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoic acid, (2.1 g) in tetrahydrofuran (42 ml), at 0 to +5°C over 5 minutes. The reaction mixture was warmed to room temperature (20-25°C) and stirred for 1.5 hours. The solution became homogeneous on warming to room temperature. The reaction mixture was concentrated to dryness under reduced pressure. The excess thionyl chloride was further removed azeotropically with heptane (2 X 20 ml). The residue was dissolved in dimethyl formamide (15 ml) at 35-40°C, and cooled to room temperature.

Step 2: (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-[2s-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoyl]amino-1,6-diphenylhexane

Imidazole (2.1 g) in ethyl acetate (50 ml) was added to a stirred solution of N-[(1S,2S,4S)-4-amino-1-benzyl-2-hydroxy-5-phenylpentyl]-2-(2,6-dimethylphenoxy)acetamide (4.2 g), at room temperature (20-25°C). The mixture was cooled to 0°C. To the cold reaction mixture, the suspension of acid chloride in dimethyl formamide (obtained from Step 1 of Example 3) was slowly added at 0 to 5°C during 30 minutes. The reaction mixture was stirred at 0 to 5°C for next 30 minutes, and then warmed to room temperature (20-25°C) and stirred at room temperature (20-25°C) for 12 hours. The reaction mixture was again

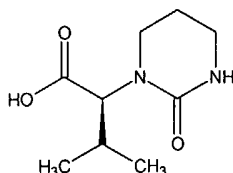
cooled to 10°C and quenched with aqueous hydrochloric acid (100 ml, 0.2N) at 10-15°C. Ethyl acetate (50 ml) was added into the mixture and stirred at room temperature (20 to 25°C) for 30 minutes. The layers were separated and the organic layer was washed with aqueous sodium bicarbonate (50 ml, 5% w/v) followed by washing with water (2 X 50
5 ml). The solvent was evaporated under reduced pressure to get crude material as an off-white solid. The solid so obtained was dissolved in ethyl acetate (28 ml) at 45-50°C and then heptane (28 ml) was slowly added at 50-45°C. The resulting clear solution was slowly allowed to cool to room temperature and stirred at room temperature for 12 hours. A white solid, precipitated out from the solution was filtered and washed with 1:1 mixture
10 of ethyl acetate and heptane (5 ml). It was dried under vacuum at 50-60°C for 12 hours to get the title compound as a white solid.

Yield: 3.5 g

While the present invention has been described in terms of its specific
15 embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention. For example, the compounds described herein can be formulated into dosage forms that are suitable for administering to patients in need of the compound for treating a medical condition for which the compound is indicated, approved, or otherwise beneficial. Specifically, the
20 lopinavir made according to the above processes can be formulated into a tablet, capsule, injectable solution, etc. along with one or more pharmaceutically acceptable excipients and administered to a patient in need of an anti-viral treatment.

CLAIMS:

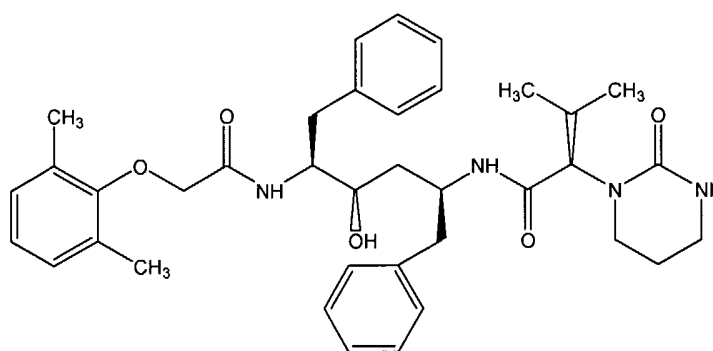
1. A process for the preparation of (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II,

**Formula II**

the process comprising:

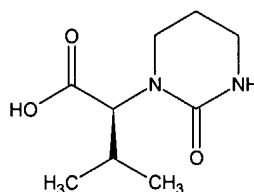
- a) reacting L-valine with acrylonitrile and alkyl chloroformate to form N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine;
 - b) hydrogenating the product of step a) in the presence of a hydrogenating catalyst and a base; and
 - c) cyclizing the product of step b) to get (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II, or a salt thereof, wherein all the process steps are carried out *in situ*.
2. The process according to claim 1, wherein the alkyl group of alkyl chloroformate is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or n-pentyl.
3. The process according to claim 1, wherein the hydrogenating catalyst comprises one or more of palladium on carbon, palladium acetate, palladium chloride, Raney nickel, platinum oxide, platinum chloride, ruthenium and rhodium.
4. The process according to claim 3, wherein the hydrogenating catalyst is Raney nickel.
5. The process according to claim 1, wherein the base comprises one or more of pyridine, ammonia, hydroxylamine, and methylamine.
6. The process according to claim 5, wherein the base is methanolic ammonia or aqueous ammonia.

7. The process according to claim 1, wherein the hydrogenation reaction is performed at a pressure of from about 2 kg/cm² to about 6 kg/cm².
8. The process according to claim 1, wherein the hydrogenation reaction is performed at a temperature of from about 35°C to about 65°C.
- 5 9. A process for the preparation of lopinavir of Formula I, or a pharmaceutically acceptable salt, ester or a prodrug thereof,

**Formula I**

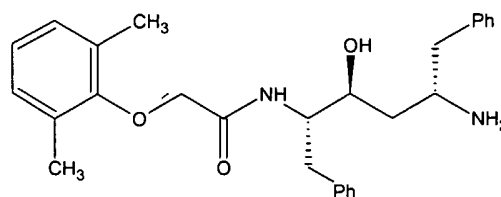
the process comprising:

- 10 a) reacting L-valine with acrylonitrile and alkyl chloroformate to form N-(2-cyanoethyl)-N-(2-alkoxycarbonyl)-L-valine;
- b) hydrogenating the product of step a) in the presence of a hydrogenating catalyst and a base;
- 15 c) cyclizing the product of step b) to get (S)-tetrahydro- α -(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetic acid of Formula II, or a salt thereof; and

**Formula II**

- d) reacting the compound of Formula II with a compound of Formula III,

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**Formula III**

to get lopinavir of Formula I, or a pharmaceutically acceptable salt, ester or a prodrug thereof, wherein the process steps a), b) and c) are carried out *in situ*.

10. The process according to claim 9, wherein the alkyl group of alkyl chloroformate is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl or n-pentyl.
11. The process according to claim 9, wherein the hydrogenating catalyst comprises one or more of palladium on carbon, palladium acetate, palladium chloride, Raney nickel, platinum oxide, platinum chloride, ruthenium and rhodium.
12. The process according to claim 11, wherein the hydrogenating catalyst is Raney nickel.
13. The process according to claim 10, wherein the base comprises one or more of pyridine, ammonia, hydroxylamine, and methylamine.
14. The process according to claim 13, wherein the base is methanolic ammonia or aqueous ammonia.
15. The process according to claim 9, wherein the hydrogenation reaction is performed at a pressure of from about 2 kg/cm² to about 6 kg/cm².
16. The process according to claim 9, wherein the hydrogenation reaction is performed at a temperature of from about 35°C to about 65°C.
17. The process of claim 9, further comprising forming the product into a finished dosage form.
18. The process of claim 17, further comprising administering the finished dosage form to a patient in need of an anti-viral therapy.

19. A pharmaceutical composition comprising a therapeutically effective amount of lopinavir, or a pharmaceutically acceptable salt, ester or a prodrug thereof obtained by the process of claim 9; and one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000413

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D239/10 A61K31/513 A61P31/18

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 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, 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
X	US 5 914 332 A (SHAM H L ET AL) 22 June 1999 (1999-06-22) cited in the application the whole document, particularly scheme IV, and examples 37 and 38 -----	1-19
A	WO 03/101971 A (CLARIANT LIFE SCIENCE MOLECULES (ITALIA) S.P.A.) 11 December 2003 (2003-12-11) cited in the application the whole document -----	1



Further documents are listed in the continuation of Box C



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

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

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

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

G document member of the same patent family

Date of the actual completion of the international search

30 August 2006

Date of mailing of the international search report

06/09/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Aillard, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/000413

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/000413

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5914332	A	22-06-1999	ZA	9610475 A	31-07-1997
WO 03101971	A	11-12-2003	AU	2003233012 A1	19-12-2003
			EP	1513819 A1	16-03-2005
			HU	0500258 A2	28-06-2005
			IT	MI20021168 A1	01-12-2003
			JP	2005533037 T	04-11-2005
			US	2005222184 A1	06-10-2005