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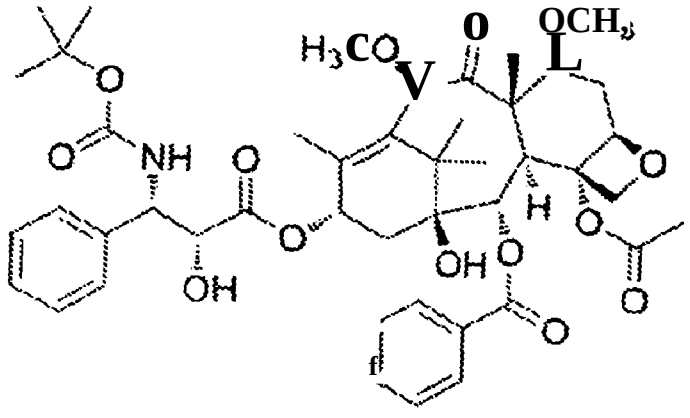
(54) Title: CRYSTALLINE FORM OF CABAZITAXEL AND PROCESS FOR PREPARING THE SAME



(I)

(57) Abstract: The present invention relates to a novel crystalline ethyl acetate solvate form of cabazitaxel or 4a-acetoxy-2a-benzoyloxy-5β,20-epoxy-1 β-hydroxy-7β,10β-dimethoxy-9-oxo-l 1-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate and process for preparing the same.

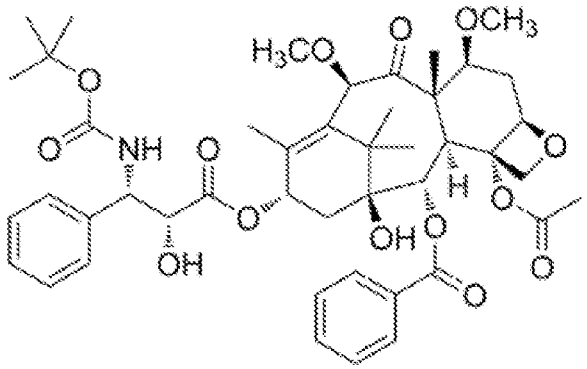
WO 2013/088335 A1

CRYSTALLINE FORM OF CABAZITAXEL AND PROCESS FOR PREPARING THE SAME

The present invention relates to a novel crystalline form of cabazitaxel or 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo-11-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

The invention also relates to the process for the preparation of said novel crystalline form, pharmaceutical compositions and medicament comprising it, and its therapeutic use in the prevention and/or treatment of cancers, more particularly prostate cancer.

The 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo-1 l-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, which has the following structure of formula (I):



(I)

exhibits notable anticancer properties and is particularly interesting for preventing and/or treating prostate cancers. Prostate cancer affects a large proportion of the male population worldwide, it is the most frequently occurring cancer in men after lung cancer.

The use of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo-11-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in the treatment of prostate cancer is known and described in WO 201 1/051894.

The process for the preparation of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P, 10P-dimethoxy-9-oxo-11-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3 -phenylpropionate is described more particularly in WO 96/30355.

Finally, crystalline acetone solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate is known and described in WO 2005/028462.

Crystalline ethanol solvates, anhydrous and hydrated forms of this compound are also known and described in WO 2009/1 15655.

The present invention is concerned with the obtaining of a new active crystalline form of such a compound.

Indeed, it is known that the identification of new crystalline forms of active principle useful for preventing and/or treating cancers may be particularly interesting.

It is also known that the ability of a substance to exist in more than one crystal form is defined as polymorphism and its different crystal forms are called polymorphs.

In general, polymorphism is due to the ability of a compound to change its molecular conformation or to form different inter- and/or intra-molecular interactions, particularly hydrogen bonds, which is reflected in different atom arrangements in the crystal lattice of different polymorphs. Thus, polymorphs of a compound can differ notably from each other by different energies in their crystal lattices and, therefore, generally have specific physical properties in the solid state such as crystal morphology, density, melting point, colour, chemical and physical stability, hygroscopy, solubility, dissolution rate, granular properties...

In other words, polymorphic forms of the same compound can exhibit different behaviors in terms of formulation, therapeutic activity and chemical and physical stability.

Unexpectedly, the inventors have discovered that the 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate can exist in a crystalline ethyl acetate solvate form.

Thus, the present invention provides a novel crystalline ethyl acetate solvate form of the 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo-1 l-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Advantageously, this novel crystalline ethyl acetate solvate form of the cabazitaxel is obtained in higher purity than the acetone solvate form, as illustrated in the examples.

Further, this new crystalline ethyl acetate solvate form of the cabazitaxel may be stored for a long time without the need for specific conditions to prevent a premature vaporization of the solvent ethyl acetate contrary to the prior crystalline forms having solvent like acetone or ethanol.

This slower desolvatation over time compared to the crystalline ethanol solvate form and crystalline acetone solvate form is also an advantage for the handling.

In particular, the crystalline ethyl acetate solvate form has the following characteristics: X-Ray Powder Diffraction (XRPD) pattern having the peaks at 8.7, 10.1, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta.

More particularly, said crystalline ethyl acetate solvate form has the following characteristics: X-Ray Powder Diffraction (XRPD) pattern having the peaks at 7.5, 7.9, 8.7, 10.1, 10.2, 12.6, 12.9, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta.

More particularly, the novel crystalline ethyl acetate solvate form of the 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate having the above defined characteristics, is defined as form A.

Another aspect of the present invention is the process for the preparation of said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P, 10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Thus, the present invention is directed to a particular process for preparing said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P, 10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, said process comprising at least the following steps:

- having the 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in solution in an organic solvent (for example acetone or methylene chloride) at room temperature;
- making a change of solvent to ethyl acetate at atmospheric or under reduced pressure;
- maintaining the so-formed solution in ethyl acetate on continued stirring, and

- recovering said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Said process is particularly advantageous over those disclosed in the prior art since it provides a crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3 S)-3-tert-butoxy carbonylamino-2-hydroxy-3-phenylpropionate in good yields and with good chemical purity.

The present invention also relates to said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo-l 1-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate as a medicament.

In a further aspect, the present invention provides said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3 S)-3 -tert-butoxycarbonylamino-2-hydroxy-3 -phenylpropionate for its use for preventing and/or treating cancers.

Crystalline ethyl acetate solvate form of cabazitaxel

In a preferred aspect, the invention provides a crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo-l 1-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate as herein defined substantially free of impurities.

By *"substantially free"*, it is meant that the crystalline ethyl acetate solvate form comprises less than 2% of impurities, preferably less than 1.5% of impurities, and more preferably less than 0.9% of impurities.

In a another preferred embodiment, said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, has a X-Ray Powder Diffraction (XRPD) diagram exhibiting characteristic lines located at 8.7, 10.1, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta.

More particularly said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-

tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate, has a X-Ray Powder Diffraction (XRPD) diagram exhibiting characteristic lines located at 7.5, 7.9, 8.7, 10.1, 10.2, 12.6, 12.9, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta (see Figure 1).

More particularly the novel crystalline ethyl acetate solvate form of the 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-l P-hydroxy-7P,10P-dimethoxy-9-oxo-ll-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate having the above defined characteristics is defined as form A. ± 0.2 degrees 2-theta.

The ethyl acetate content was determined by Gas Chromatography (GC). The obtained value is of about 9.5% m/m, an ethyl acetate mole per cabazitaxel mole.

Process for preparing crystalline ethyl acetate solvate form of cabazitaxel

As stated previously, another aspect of the present invention is the process for the preparation of the crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3 S)-3-tert-butoxy carbonylamino-2-hydroxy-3-phenylpropionate.

Said process for preparing the crystalline ethyl acetate solvate form may comprise the following steps:

- having the 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in solution in an organic solvent (for example acetone or methylene chloride) at room temperature;
- making a change of solvent to ethyl acetate at atmospheric or under reduced pressure;
- maintaining the so-formed solution in ethyl acetate on continued stirring, and
- recovering said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

Regarding the step 1, the solution may be prepared by dissolving crude 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in six volumes of acetone at room temperature.

The change of solvent to ethyl acetate can be made under reduced pressure or at atmospheric pressure depending of the boiling point of the solvent used, preferably at constant volume under reduced pressure (for example 80 mbar at about 14°C with acetone).

To maintain the so-formed solution in ethyl acetate in step 3, the slurry volume can be adjusted to 10 volumes by casting of ethyl acetate.

Finally, regarding the step 4, to obtain the crystalline ethyl acetate solvate form of cabazitaxel, the slurry may be filtered and the resulting cake washed with ethyl acetate. This cake may be dried under vacuum at 38°C for 15H.

As states previously, said process is particularly advantageous over those disclosed in the prior art since it provides a crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxy carbonyl amino-2-hydroxy-3-phenylpropionate in good yields and with good chemical purity.

By *"good yield"* in the present invention, it is meant that said ethyl acetate solvate form is obtained in a yield higher than or equal to 80%.

As used herein a *"good chemical purity"* is a purity which is higher than or equal to 99%.

Application

The present invention is also directed to a medicament comprising said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P, 10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxy carbonylamino-2-hydroxy-3 -phenylpropionate .

Thus, the present invention also relates to a pharmaceutical composition comprises said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxy carbonylamino-2-hydroxy-3-phenylpropionate and also at least one pharmaceutically acceptable excipient.

All components of the present compositions must be pharmaceutically acceptable.

As used herein, a *"pharmaceutically acceptable"* component is one that is suitable for use with humans and/or other animals without undue adverse side effects (such as toxicity, irritation and allergic response) commensurate with a reasonable benefit/risk ratio.

The compositions of the present invention are generally administered to patients, which include, but are not limited to, mammals, for example, humans, by conventional routes known in the art.

The present invention further relates to the use of the ethyl acetate solvate crystalline form according to the invention, as a medicament.

The present invention further relates to the use of the ethyl acetate solvate crystalline form according to the invention, as a medicament in the prevention and/or treatment of cancers.

For example, the cancer may be prostate cancer.

Brief description of the drawing

Figure 1: XRPD pattern (λ_{Cu} = 1.5406 A) of ethyl acetate solvate form of cabazitaxel.

The examples that follow describe the preparation of crystalline ethyl acetate solvate form of cabazitaxel and its purity. These examples are not limiting, and serve merely to illustrate the present invention.

Example 1: Preparation of crystalline ethyl acetate solvate form of cabazitaxel

The crude 4a-acetoxy-2a-benzoyloxy-5 P,20-epoxy-1P-hydroxy-7P,10β-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate has been dissolved in six volumes of acetone, at room temperature.

The change of solvent to ethyl acetate under reduced pressure and at constant volume has been made at 80 mbar and T = 14.4°C.

The slurry volume has been adjusted to 10 volumes by casting of ethyl acetate.

After two hours under continued stirring, the slurry has been filtered and the resulting cake washed with ethyl acetate.

Said cake has been dried under vacuum at 38°C for 15H.

Example 2 : Purity of the ethyl acetate solvate form of cabazitaxel

Cabazitaxel synthesized by the conventional process (crystallized as acetone solvate in acetone/water, see WO2005/028462) and enriched with impurities has been purified by formation of the ethyl acetate solvate form. Results are compared with the cabazitaxel purified by the conventional process.

The obtained results are summarized in the following table.

Impurities	***Starting cabazitaxel***	***Purified cabazitaxel with AcOEt crystallization treatment***	***Purified cabazitaxel with conventional process (crystallized in acetone/water)***
Total	**1.52 %**	**0.71 %**	**0.98 %**
p-anisaldéhyde	0.02 %	Undetected	Undetected
Impurity A	0.02 %	0.01 %	0.01 %
Impurity B	0.16 %	0.14 %	0.10 %
Impurity C	0.21 %	0.18 %	0.20 %
Impurity D	0.02 %	Undetected	Undetected
Impurity E	0.17 %	0.12 %	0.11 %
Impurities F+G	0.18 %	0.05 %	0.14 %
Impurity H	0.25 %	0.10 %	0.12 %
Impurity I	0.34 %	0.12 %	0.24 %
Impurity J	0.21 %	0.05 %	0.07 %

These results show that ethyl acetate treatment has a higher purifying power.

More particularly, cabazitaxel treated with ethyl acetate has less impurities F+G and I.

Characterizations

Said crystalline ethyl acetate solvate form according to the invention was characterized by X-Ray Powder Diffraction (XRPD) and Gas Chromatography (GC) as shown below.

a) X-Ray Powder Diffraction (XRPD):

Experimental diagram is recorded at ambient conditions on a PANalytical X'Pert Pro MPD powder diffractometer using the Bragg-Brentano (vertical Θ-2Θ configuration) parafocusing geometry coupled with a X'Celerator detector. A sealed copper anode X-ray tube is used, running at 45 kV and 40 mA levels. An incident beam monochromator (Johansson type: a symmetrically cut curved germanium (111) crystal) produces pure Cu Kα1 radiation (λ = 1.54060 A). A thin layer of the product is deposited on a single-crystal silicon wafer, cut out according to Si (510) crystallographic orientation that, by systematic extinction, impedes any Bragg reflection. In order to bring more crystallites into the diffraction position and thus reduce the influence of particle statistics on the measurements, a sample spinner is used. The spinner rotation speed is set at 1 revolution per second. The angular range extends from 1.5 to 40° in 2Θ, with a 0.017° step size in 2Θ. A counting time of 500 seconds per step was used.

Figure 1 shows XRPD pattern obtained for ethyl acetate solvate form of cabazitaxel. Characteristic peaks at 7.5, 7.9, 8.7, 10.1, 10.2, 12.6, 12.9, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta are observed in the pattern of crystalline ethyl acetate solvate form of cabazitaxel.

b) Gas chromatography:

The content of ethyl acetate has been determined by Gas Chromatography (GC) on a Rtx®-200 column (fused silica).

The obtained value is of about 9.5% m/m, an ethyl acetate mole per cabazitaxel mole.

CLAIMS

1. Crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy- 1P-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

2. Crystalline form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7β,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3 S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate according to claim 1, characterized by X-Ray Powder Diffraction diagram exhibiting characteristic lines located at 8.7, 10.1, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta.

3. Crystalline form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7β,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3 S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate according to claim 1, characterized by X-Ray Powder Diffraction diagram exhibiting characteristic lines located at 7.5, 7.9, 8.7, 10.1, 10.2, 12.6, 12.9, 13.8, 14.1 and 14.8 ± 0.2 degrees 2-theta.

4. Medicament, characterized in that it comprises a crystalline form according to any one of claims 1 to 3.

5. Pharmaceutical composition, characterized in that it comprises a crystalline form according to any one of claims 1 to 3, and also at least one pharmaceutically acceptable excipient.

6. Crystalline form according to any one of claims 1 to 3, for its use as a medicament.

7. Crystalline form according to any one of claims 1 to 3 for use according to claim 6, wherein the medicament is for use in the prevention and/or treatment of cancers.

8. Crystalline form according to any one of claims 1 to 3 for use according to claim 7, wherein the cancer is prostate cancer.

9. Process for the preparation of the crystalline form according to any one of claims 1 to 3, characterized in that it comprises at least the following steps:

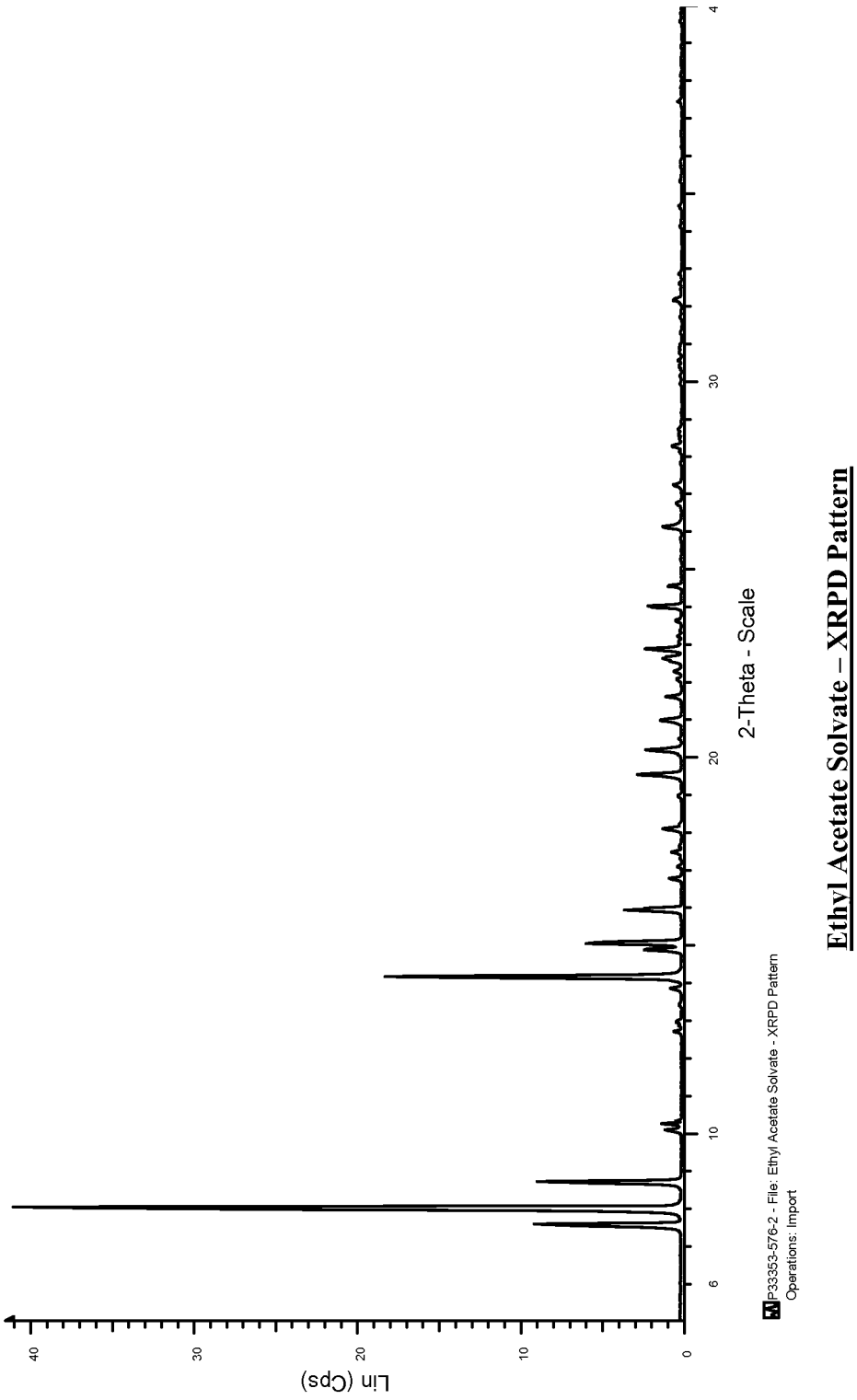
- having the 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-ip-hydroxy-7P,10P-dimethoxy-9-oxo- 11-taxen- 13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate in solution in an organic solvent at room temperature;

- making a change of solvent to ethyl acetate at atmospheric or under reduced pressure;

- maintaining the so-formed solution in ethyl acetate on continued stirring, and

- recovering said crystalline ethyl acetate solvate form of 4a-acetoxy-2a-benzoyloxy-5P,20-epoxy-l P-hydroxy-7P,10P-dimethoxy-9-oxo-ll-taxen-13a-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate.

FIGURE 1



Ethyl Acetate Solvate – XRPD Pattern

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/057170

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D305/14 A61K31/337 A61P35/00
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 , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/115655 A2 (AVENTIS PHARMA SA [FR] ; BILLOT PASCAL [FR] ; DUFRAIGNE MARIELLE [FR] ; E) 24 September 2009 (2009-09-24) cited in the application claim 8	1-9
A	WO 2005/028462 Al (AVENTIS PHARMA SA [FR]) 31 March 2005 (2005-03-31) cited in the application claim 1	1-9

☐ 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

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Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2013	14/03/2013

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	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/057170

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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