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(71) Applicant: **MYLAN LABORATORIES LIMITED** [IN/IN]; Plot No. 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(72) Inventors: **GORE, Vinayak**; Mylan Laboratories Limited, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **SHUKLA, Vinay Kumar**; Mylan Laboratories Limited, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **SHINDE, Dhananjay**; Mylan Laboratories Limited, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **PRAKASH, Bansode**; Mylan Laboratories Limited, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(74) Agent: **NAIR, Manisha Singh**; Lex Orbis, Intellectual Property Practice, 709/710, Tolstoy House, 15 - 17, Tolstoy Marg, New Delhi 110 001 (IN).

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Declarations under Rule 4.17:

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

[Continued on next page]

(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF POMALIDOMIDE AND ITS PURIFICATION

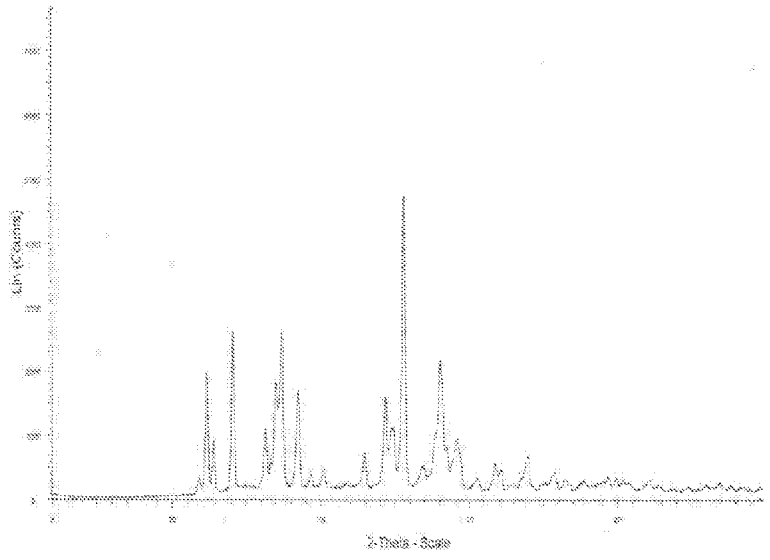

Fig.1

(57) Abstract: Methods of synthesizing pomalidomide are disclosed. Further, methods of purifying pomalidomide from a reaction mixture are also disclosed.

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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

"IMPROVED PROCESS FOR THE PREPARATION OF POMALIDOMIDE AND ITS PURIFICATION"

CROSS-REFERENCE TO RELATED APPLICATIONS

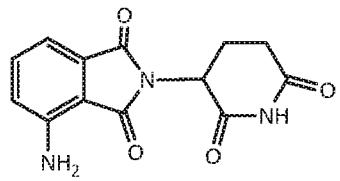
This application claims priority from Indian patent applications 5409/CHE/2013 filed on Nov. 25, 2013 and 424/CHE/2014 filed on Jan. 30, 2014, the contents of which are incorporated by reference in their entirety.

FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of pomalidomide and its purification.

BACKGROUND OF THE INVENTION:

Pomalidomide is chemically known as (RS)-4-amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione and structurally represented as below:



Pomalidomide is an immunomodulatory antineoplastic agent. Pomalidomide is marketed with the brand name POMALYST®. It is indicated for the treatment of relapsed and refractory multiple myeloma.

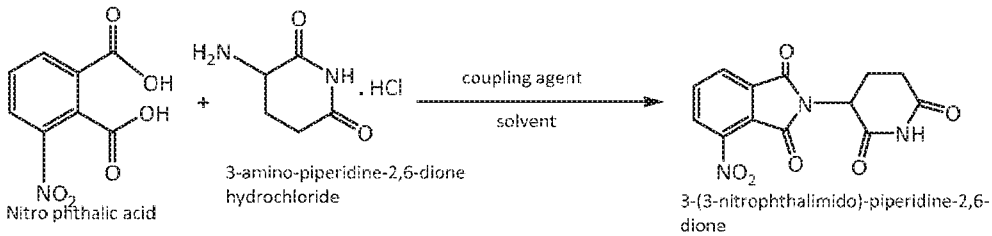
Several references disclose methods for the preparation and purification of pomalidomide. For example, U.S. Pat. Nos. 5,635,517; 6,335,349; and 7,994,327 (which are all hereby incorporated by reference) disclose processes for the preparation of pomalidomide. Additionally, Chinese Pat. No. 103288797 (which is hereby incorporated by reference) also discloses a process for the purification of pomalidomide.

The present disclosure provides an improved process for the preparation of pomalidomide with a purity greater than about 99%. The process also results in a high yield, is simple, cost effective, and feasible for large scale production.

SUMMARY OF THE INVENTION:

A first aspect of the present disclosure provides a process for the preparation of pomalidomide that may include the steps of:

a) reacting nitro phthalic acid with 3-amino-piperidine-2,6-dione or its salt in the presence of a coupling agent and a suitable solvent to obtain 3-(3-nitrophthalimido)-piperidine-2,6-dione,

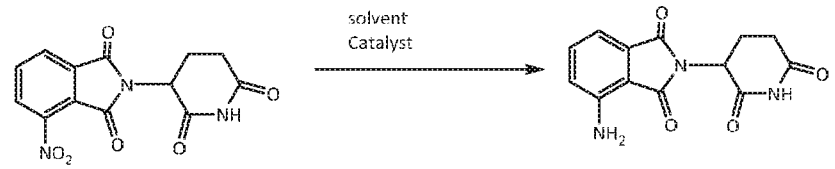


Nitro phthalic acid

3-amino-piperidine-2,6-dione hydrochloride

3-(3-nitrophthalimido)-piperidine-2,6-dione

b) reducing 3-(3-nitrophthalimido)-piperidine-2,6-dione in the presence of a solvent and catalyst to obtain pomalidomide.



3-(3-nitrophthalimido)-piperidine -2,6-dione

Pomalidomide

In one embodiment, the present disclosure provides a process for the purification of pomalidomide that may include the steps of:

a) dissolving pomalidomide in a sulfoxide compound solvent,

b) adding a second solvent,

c) adding an anti-solvent, and

d) isolating substantially pure pomalidomide.

Another aspect of the present disclosure provides a process for the preparation of thalidomide comprising the steps of reacting phthalic acid with 3-amino-piperidine-2,6-dione or its salt to give 2-(2,6-dioxopiperidin-3-yl)-isoindole-1,3-dione, commonly known as thalidomide.

BRIEF DESCRITION OF THE DRAWING:

Further aspects of the present disclosure together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying drawing figures wherein:

Figure 1 is an X-ray powder diffractogram of pomalidomide prepared and purified according to the present disclosure.

DETAILED DESCRIPTION OF THE INVENTION:

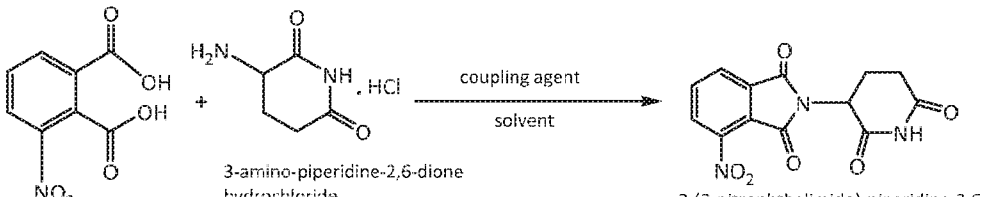
It is to be understood that the description of the present invention has been simplified to illustrate elements that are relevant for a clear understanding of the invention, while eliminating, for purposes of clarity, other elements that may be well known.

The present invention encompasses novel synthetic schemes for the synthesis of pomalidomide and thalidomide. These schemes provide an improved, efficient method for the synthesis of pomalidomide at a high yield and purity.

More specifically, the present disclosure relates to an improved process for the preparation of pomalidomide.

In one embodiment, the present disclosure provides a process for the preparation of pomalidomide that may include the following steps:

a) reacting nitro-substituted phthalic acid with 3-amino-piperidine-2,6-dione or its salt in the presence of a coupling agent and a solvent to obtain 3-(3-nitrophthalimido)-piperidine-2,6-dione,

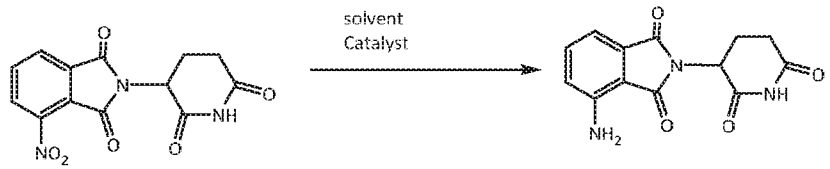


Nitro phthalic acid

3-amino-piperidine-2,6-dione hydrochloride

3-(3-nitrophthalimido)-piperidine-2,6-dione

b) reducing 3-(3-nitrophthalimido)-piperidine-2,6-dione in the presence of a solvent and catalyst to obtain pomalidomide.



3-(3-nitrophthalimido)-piperidine-2,6-dione

Pomalidomide

According to the present disclosure, nitrophthalic acid with 3-amino-piperidine-2,6-dione or its salt is converted to 3-(3-nitrophthalimido)-piperidine-2,6-dione in the presence of a coupling agent and a solvent per step (a) above. The reaction may be performed at about 25°C to about 80°C for about 5 to 18 hours. Within the context of the present disclosure, the coupling agent may include, as examples, 1,1-carbonyldiimadazole, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), dimethylaminopyridine, and mixtures thereof. One of skill in the art will readily recognize additional compounds that may be useful in activating the carboxylic acid groups of nitrophthalic acid so that 3-amino-piperidine-2,6-dione hydrochloride may react and create the pyrrolidine ring to couple together nitrophthalic acid and the 3-amino-piperidine-2,6-dione. The solvent may include, as examples, nitriles (such as acetonitrile and propionitrile), acid amides (such as N,N-

dimethylformamide and dimethylacetamide), and cyclic ethers (such as tetrahydrofuran and 1,4-dioxane). Again, one of skill in the art will recognize other solvents that may be suitable for use in this reaction.

According to the present disclosure, 3-(3-nitrophthalimido)-piperidine-2,6-dione is then reacted at ambient temperature for about 5 – 6 hours in the presence of a solvent and catalyst to obtain pomalidomide, per step (b) above. Within the context of the present disclosure, the catalyst may be, for example, palladium on carbon, Raney nickel or reducing agents such as iron-hydrochloric acid, zinc-acetic acid, zinc ammonium chloride, bubbled hydrogen (per Example 3 below), and sodium dithionite. One skilled in the art may recognize a variety of other compounds that may be useful reducing agents for use in this step of the reaction disclosed herein. The solvent used in this particular step of the process may be, for example, an acid amide (such as N,N-dimethylformamide and N,N-dimethyl acetamide), dimethyl sulfoxide, a nitrile (such as acetonitrile or propionitrile), or aliphatic alcohols (such as methanol, isopropanol and mixtures thereof). Again, one skilled in the art may recognize a variety of other solvents that may be useful in performing this reaction.

Another aspect of the present disclosure provides a process for the preparation of thalidomide, wherein phthalic acid is reacted with 3-amino-piperidine-2,6-dione or its salt in the presence of a coupling agent and solvent to give 2-(2,6-dioxopiperidin-3-yl)-isoindole-1,3-dione (thalidomide). Within the context of this disclosure, the coupling agents may include, as examples, 1,1-carbonyldiimadazole, dicyclohexylcarbodiimide, diisopropylcarbodiimide, 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), dimethylaminopyridine, and mixtures thereof. One of skill in the art will readily recognize additional compounds that may be useful in activating the carboxylic acid groups of nitrophthalic acid so that 3-amino-piperidine-2,6-dione hydrochloride may react and create the pyrrolidine ring to couple together phthalic acid and the 3-amino-piperidine-2,6-dione. The solvent may include, as examples, nitriles (such as acetonitrile and propionitrile), acid amides (such as N,N-dimethylformamide and dimethyl

acetamide), and cyclic ethers (such as tetrahydrofuran and 1,4-dioxane). Again, one of skill in the art will recognize other solvents that may be suitable for use in this reaction.

Another aspect of the present disclosure is to provide a process for the purification of pomalidomide which may include the following steps:

a) dissolving pomalidomide in an organic solvent or mixture of solvents,
b) adding an anti-solvent, and
c) isolating substantially pure pomalidomide.

According to the present disclosure, pomalidomide is dissolved in an organic solvent. Within the context of the current invention, the organic solvent used in step (a) is used may include, for example, dimethyl sulfoxide, diethyl sulfoxide, di-n-propyl sulfoxide, di-or tetra-n-butyl sulfone sulfoxide, acetone, methyl isobutyl ketone, or mixtures thereof.

According to the present disclosure, anti-solvent is then added to the pomalidomide/organic solvent solution. Within the context of the present specification, an anti-solvent is a fluid in which the product is insoluble, thus permitting more facile isolation of the product. For the present invention, useful anti-solvents may include alcohols, ethers, water, or mixtures thereof. Suitable alcohols include methanol, ethanol, n-propanol, isopropanol, and n-butanol. Suitable ethers include diethyl ether, tert-butyl methyl ether, and diisopropyl ether.

Another embodiment of the present disclosure is to provide another process for the purification of pomalidomide which may include the following steps:

a) dissolving pomalidomide in a sulfoxide compound solvent,
b) adding a second solvent,
c) adding an anti-solvent, and
d) isolating substantially pure pomalidomide.

According to the present invention, pomalidomide is dissolved in a sulfoxide compound solvent. This sulfoxide compound may include, for example, dimethyl sulfoxide, diethyl sulfoxide, di-n-propyl sulfoxide, or di- or tetra-n-butyl sulfone. Next, a second solvent is

added. Examples of a useful second solvent include acetone and methyl isobutyl ketone. Next, an anti-solvent may be added to precipitate substantially pure pomalidomide. Examples of suitable anti-solvents include alcohols such as methanol and ethanol, ethers, water, or mixtures thereof.

Within the context of the current invention, the final pomalidomide product prepared by the processes described herein may yield a product with a purity greater than about 99.7% as measured by HPLC. Individual identified chemical impurities in the final pomalidomide product may be present at quantities less than about 0.10%.

A crystalline form of pomalidomide, prepared and purified according to the processes disclosed in the present invention, may be characterized by powder X-ray diffraction (PXRD), and have a PXRD pattern as shown in Fig. 1 and having peaks at 12.1, 13.9, 17.1, 18.3, 24.2, 25.4, 27.9 ± 0.2 2θ.

The pomalidomide as synthesized and purified by the methods disclosed herein may be useful in generating pharmaceutical dosage forms suitable for administration to patients in need thereof. The dosage form may be an oral dosage form and in some embodiments, the oral dosage form may be a capsule. The capsule may include appropriate excipients including mannitol, pre-gelatinized starch, and sodium stearyl fumarate. Such formulations may be useful in the treatment of multiple myeloma. Formulations of pomalidomide are particularly useful for patients having multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within sixty days of completion of the last therapy.

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules, compositions and formulations according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive,

but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

Examples:

Example 1: Synthesis of 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-nitro-isoindoline-dione (3-nitrophthalidomide)

To the stirred mixture of 3-nitrophthalic acid (25.0 g or 0.12 mole) in acetonitrile (175 ml) was added 1,1-carbonyldiimidazole (CDI) (42.3 g or 0.26 mole) under nitrogen atmosphere at ambient temperature. To this mixture, 3-aminopiperidine 2,6-dione hydrochloride (19.5g or 0.12 mole) was added, and the reaction mixture was heated to 75 to 80 °C until the reaction was completed as monitored by TLC. After completion of the reaction, the solvent was distilled out under reduced pressure. Water (375 ml) was added to the reaction mass, and the reaction mass was slowly cooled at 0 to 5 °C while stirring. The isolated solid was filtered, washed with water, then by methanol, and suck dried. Finally the isolated solid was dried at 55 to 60 °C under vacuum until constant weight to obtain 3-nitrophthalidomide. Yield: 28.2 g, 78.5% (molar) (HPLC purity ~99.5%).

Example 2: Synthesis of 2-(2,6-dioxopiperidin-3-yl)-isoindole-1,3-dione (Thalidomide)

1,1-carbonyldiimidazole (21.5 g or 0.13 mole) was added to a stirred mixture of phthalic acid (10.0 g. or 0.06 mole) in acetonitrile (100 ml) maintained under nitrogen at ambient temperature. To this mixture, 3-aminopiperidine 2,6-dione hydrochloride (9.9 g or 0.06 mole) was added, and the reaction mixture was stirred at 25 to 30 °C until the reaction was completed as monitored by TLC. After completion of the reaction, the solvent was distilled out under reduced pressure. Water (100 ml) was added to the reaction mass and the reaction mass was slowly cooled at 0 to 5 °C while stirring. The isolated solid was filtered, washed with water, then by methanol, and suck dried.

Finally the isolated sold was dried at 55 to 60 °C under vacuum until constant weight to get thalidomide. Yield: 11.6 g, 75.2% (molar). Purity by HPLC 99.13%

Example 3: Synthesis of 4-amino-2-(2,6-dioxopiperidin-3-yl)-isoindoline-1,3-dione (Pomalidomide)

Catalyst palladium (10%) on carbon (0.5 g. or 5% w/w of substrate) was added to a stirred solution of 3-nitrophthalidomide (10 g or 0.033 mole) (Example 1) in N,N-dimethyl formamide (100 ml) maintained under nitrogen. Hydrogen gas was bubbled through the reaction mixture at atmospheric pressure. After completion of hydrogenation reaction, as monitored by TLC, hydrogen bubbling was stopped and the catalyst was separated by filtration of the reaction mixture on celite bed. The filtrate was distilled at 60 to 65 °C under reduced pressure until half of the solvent was removed. The solution was then cooled at ambient temperature and methanol (50 ml) was added while stirring. The solid obtained was filtered, washed with methanol (50 ml), and suck dried to obtain pomalidomide 8.2 g (90% molar yield) having HPLC purity > 99.0%.

Example 4: Pomalidomide Purification Process

In a reaction vessel, crude (RS) 4-amino-2-(2,6-dioxopiperidine-3-yl)isoindole-1,3-dione (pomalidomide, 10g) was dissolved in dimethylsulfoxide (40 ml) by heating at 60 to 65 °C. The solution was cooled to 25 to 30 °C. To this solution, acetone (40 ml) was added while stirring. After completion of acetone addition, the solution was stirred for 30 minutes and then methanol (40 ml) was added at slow rate while stirring at 25 to 30 °C. The resulting mixture was allowed to stir for one to two hours. The isolated solid was filtered, washed with a methanol-acetone mixture (1:1 v/v, 10 ml) and suck dried. Finally, the material was dried by vacuum at 55 to 60 °C to get pure pomalidomide (8 g, 80% yield) with HPLC purity greater than 99.7%. All known individual chemical impurities were present at quantities less than 0.10 %).

We Claim:

1. Process for the purification of pomalidomide, comprising the steps of:
   a) dissolving pomalidomide in an organic solvent,
   b) adding an anti-solvent, and
   c) isolating substantially pure pomalidomide.

2. The process according to claim 1, wherein the organic solvent is selected from the group consisting of dimethyl sulfoxide, diethyl sulfoxide, di-n-propyl sulfoxide, di- or tetra-n-butyl sulfone sulfoxide, acetone, methyl isobutyl ketone, and mixtures thereof.

3. The process according to claim 1, wherein the anti-solvent is selected from the group consisting of alcohol, ether, water, and mixtures thereof.

4. The process according to claim 3, wherein said alcohol is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, and n-butanol.

5. The process according to claim 3, wherein said ether is selected from the group consisting of diethyl ether, tert-butyl methyl ether, and diisopropyl ether.

6. The process according to claim 1, wherein said isolating step comprises filtering, drying, and evaporation.

7. A process for the synthesis of pomalidomide, comprising the steps of:
   a) reacting nitrophthalic acid with 3-amino-piperidine-2,6-dione or its salt in the presence of a coupling agent and a first solvent to obtain 3-(3-nitrophthalimido)-piperidine-2,6-dione; and
   b) reducing the 3-(3-nitrophthalimido)-piperidine-2,6-dione in the presence of a second solvent and a catalyst to obtain pomalidomide.

8. The process according to claim 7, wherein the coupling agent is selected from the group consisting of 1,1-carbonyldiimadazole, dicyclohexyl carbodiimide, diisopropyl carbodiimide, 2-chloro-4,6-dimethoxy-1,3,5-triazine(CDMT), and dimethyl aminopyridine.

9. The process of claim 7, wherein the first solvent is selected from the group consisting of acetonitrile, propionitrile, N,N-dimethylformamide, dimethyl acetamide, tetrahydrofuran, 1,4-dioxane, and mixtures thereof.

10. The process according to claim 7, wherein the catalyst is selected from the group consisting of palladium on carbon, Raney nickel, and a reducing agent.

11. The process of claim 10, wherein the reducing agent is selected from the group consisting of iron-hydrochloric acid, zinc-acetic acid, zinc ammonium chloride, bubbled hydrogen, and sodium dithionite.

12. The process of claim 7, wherein the second solvent is selected form the group consisting of N,N-dimethylformamide N,N-dimethyl acetamide, dimethyl sulfoxide, acetonitrile, propionitrile, methanol, isopropanol, and mixtures thereof.

13. The process according to claim 1, wherein the pomalidomide has a purity of greater than about 99.7%.

14. Pomalidomide prepared according to claim 1, having any individual known chemical impurity at a concentration of less than about 0.10 %.

15. A pharmaceutical composition, comprising pomalidomide synthesized by the process of claim 7.

16. The pharmaceutical composition of claim 15, wherein said pomalidomide is purified according the process of claim 1.

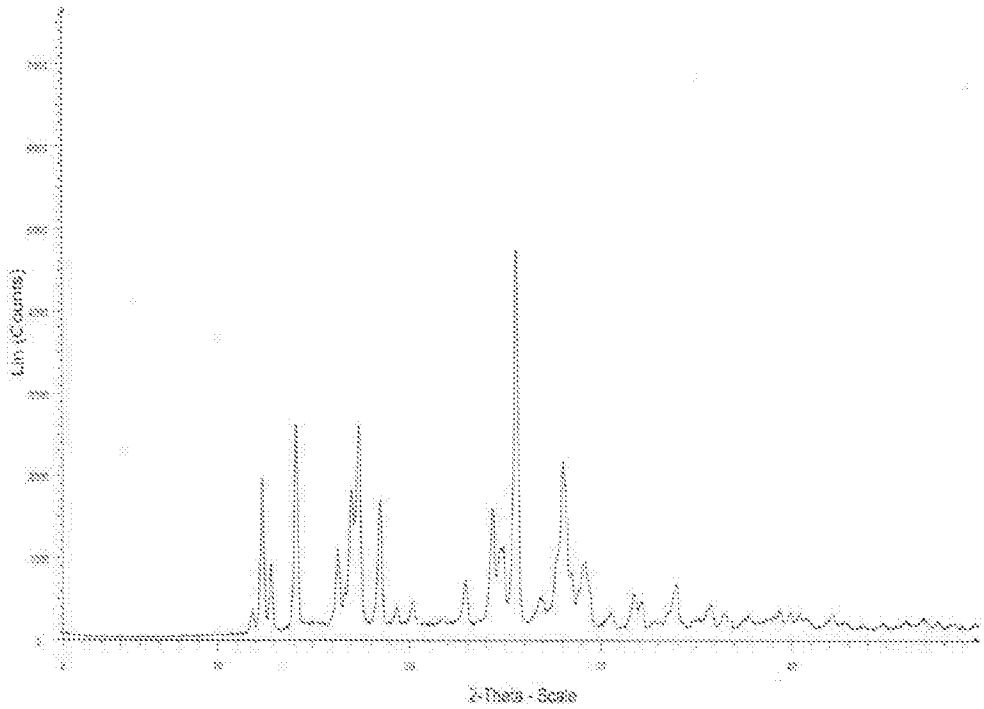


Fig.1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/066285

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04
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.
X	CN 103 288 797 A (NINGBO YINZHOU BAITEJIA PHARMACEUTICAL CO LTD) 11 September 2013 (2013-09-11) cited in the application paragraph [0044]; example 11 paragraph [0046]; example 12 reference example; paragraph [0049] -----	1-6
X	CN 103 275 062 A (NINGBO YINZHOU BAITEJIA MEDICAL SCIENCE & TECHNOLOGY CO LTD) 4 September 2013 (2013-09-04) examples 1-15 paragraphs [0024] - [0054] -----	1-6
A	WO 2013/126326 A1 (CELGENE CORP [US]) 29 August 2013 (2013-08-29) paragraph [0213] -----	1-6
	-/--	

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

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2015	18/03/2015

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	Samsam Bakhtiary, M

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/066285

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2014/170909 A2 (HETERO RESEARCH FOUNDATION [IN]; PARTHASARADHI REDDY BANDI [IN]; RATHN) 23 October 2014 (2014-10-23) examples 1-17 claims 1-9 -----	1-6

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/066285

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 103288797 A	11-09-2013	NONE	
CN 103275062 A	04-09-2013	NONE	
WO 2013126326 A1	29-08-2013	NONE	
WO 2014170909 A2	23-10-2014	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/066285

Box No. 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:

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 No. 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:

see additional sheet

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 fees, this Authority did not invite payment of additional fees.

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.:

1-6

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6

   Process for the purification of pomalidomide

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2. claims: 7-13

   Process for the synthesis of pomalidomide

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3. claims: 14-16

   Pomalidomide per se, pharmaceutical composition containing pomalidomide

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