

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: SINGH, MANISHA LEX ORBIS, 709/710, TOLSTOY HOUSE, 15-17, TOLSTOY MARG, NEW DELHI- 110001 INDIA
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Date of mailing (day/month/year) 23-02-2018
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Applicant's or agent's file reference 1134W0405	FOR FURTHER ACTION See paragraph 2 below
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International application No. PCT/IB2017/057251	International filing date (day/month/year) 20-11-2017	Priority date (day/month/year) 08-03-2017
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International Patent Classification (IPC) or both national classification and IPC C07D403/06 Version=2018.01

Applicant JUBILANT GENERICS LIMITED
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<p>1. This opinion contains indications relating to the following items:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Box No. I Basis of the opinion <input type="checkbox"/> Box No. II Priority <input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability <input type="checkbox"/> Box No. IV Lack of unity of invention <input checked="" type="checkbox"/> Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement <input type="checkbox"/> Box No. VI Certain documents cited <input type="checkbox"/> Box No. VII Certain defects in the international application <input type="checkbox"/> Box No. VIII Certain observations on the international application <p>2. FURTHER ACTION</p> <p>If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.</p> <p>If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.</p> <p>For further options, see Form PCT/ISA/220.</p>
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Name and mailing address of the ISA/ Indian Patent Office Plot No. 32, Sector 14, Dwarka, New Delhi-110075 Facsimile No.	Date of completion of this opinion 23-02-2018	Authorized officer B. Ramamuni Telephone No. +91-1125300200
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2017/057251

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - the international application in the language in which it was filed.
 - a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. forming part of the international application as filed:
 - in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
 - b. furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. furnished subsequent to the international filing date for the purposes of international search only:
 - in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-10</u>	YES
	Claims	_____	NO
Inventive step (IS)	Claims	_____	YES
	Claims	<u>1-10</u>	NO
Industrial applicability (IA)	Claims	<u>1-10</u>	YES
	Claims	_____	NO

2. Citations and explanations:

Reference is made to the following:-

D1: Chadwell et al. "Synthesis and characterization of group 10 metal complexes with a new trifunctional ether phosphine. The X-ray crystal structures of bis[bis(2-ethoxyethyl)benzylphosphine]dichloronickel(II) and bis[bis(2-ethoxyethyl)benzylphosphine]chlorophenylnickel(II)", Polyhedron Vol, 14, No. 8, pp. 1057-1065 & 10-APRIL-1995
D2: The article Proceedings of the International Symposium, 7th, Dresden, Germany, June 18-22, 2000
D3: US5045302A (GE HEALTHCARE LTD) & 03-09-1991
D4: WO2006/064175A1 (GENERAL ELECTRIC CO) & 22-06-2006

Novelty under Article 33(2) of PCT:-

The present application relates to an improved process for the preparation of tetrofosmin or acid addition salt thereof. The present invention also relates to the process for the preparation of disulfosalicylate salt of tetrofosmin.

D1 discloses the syntheses and characterizations of the new trifunctional ligand bis(2-ethoxyethyl) benzylphosphine (OPO; 1) and some new group 10 metal complexes are described. Reactions of this potentially hemilabile ligand with the nickel, palladium and platinum chlorides have been studied, resulting in isolation of the series, $MCl_2(OPO)_2$, where $M = Ni(2), Pd(3) \text{ or } Pt(4)$.
D2 discloses a process for the preparation of tetrofosmin.

None of the above cited documents disclose the same process steps as mentioned in the present application.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Continuation of Citation and Explanation(Box5)

So the present set of claims 1-10 is novel under Article 33(2) of PCT.

Inventive step under Article 33(3) of PCT:-

The problem to be solved with the present application is to provide a process for the preparation of tetrofosmin and its intermediates without using photolytic conditions.

The difference between the prior art and the present application lies in the preparation of tetrofosmin and its intermediates without using photolytic conditions.

D1 appears to be the closest prior art for the present application. It discloses the syntheses and characterizations of the new trifunctional ligand bis(2-ethoxyethyl) benzylphosphine (OPO; 1) and some new group 10 metal complexes. It further discloses process steps of a,b of claim 1 of the present application (pls see scheme 1, page no 1058). D1 does not disclose the other steps of the present application.

D2 discloses a process for the preparation of tetrofosmin. The remaining process steps c,d,e of the present application are disclosed in the document D2.

D3 discloses ^{99m}Tc -coordinating diphosphine ligands (L), wherein one preferred example thereof is the ether functionalized diphosphine ligand 1,2-bis[bis(2-ethoxy-ethyl)phosphino]ethane according to Formula 1, called tetrofosmin ("P53"), that forms a dimeric cationic technetium (V) dioxo phosphine complex, $[\text{TcO}_2\text{L}_2]$ with ^{99m}Tc , useful as myocardial imaging agent. It further teaches the synthesis of formula 4 of the present application with reagents AIBN i.e without using UV photolysis / photolytic conditions.

D4 discloses stabilised ^{99m}Tc radiopharmaceutical compositions of the ligand tetrofosmin, which include an ascorbic acid or ascorbate radioprotectant, in the absence of an antimicrobial preservative. It further discloses preparation of its salts such as tetrofosmin sulphosalicylate with ethanol /ethers. Similar process for the different salt preparation was claimed in the claims 8-10 of the present application. Preparation of different salt forms is obvious to a person skilled in the art with the

general knowledge along with routine laboratory skills.

So in view of the teachings mentioned in the above said documents D1-D4 it would have been obvious to a person skilled in the art can arrive at the present application.

So inventive step cannot be acknowledged for the subject matter of claims 1-10.

Industrial Applicability under Article 33(4) of PCT:-

The subject matter of claims 1-10 is industrially applicable under Article 33(4) of PCT.