

**PATENT COOPERATION TREATY**

**PCT**

**INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY**

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference CHL-PCT0779	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. PCT/IB2018/056732	International filing date ( <i>day/month/year</i> ) 04 September 2018 (04.09.2018)	Priority date ( <i>day/month/year</i> ) 05 September 2017 (05.09.2017)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant CADILA HEALTHCARE LIMITED			

<p>1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).</p> <p>2. This REPORT consists of a total of 10 sheets, including this cover sheet.</p> <p>In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.</p>																								
<p>3. This report contains indications relating to the following items:</p> <table> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> <p>4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).</p>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<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 Article 35(2) with regard to novelty, inventive step or 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 checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
<input checked="" type="checkbox"/>	Box No. I	Basis of the report																						
<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 Article 35(2) with regard to novelty, inventive step or 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 checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application																						

	Date of issuance of this report 10 March 2020 (10.03.2020)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer  Cécile Chatel
Facsimile No. +41 22 338 82 70	e-mail: ro.ib@wipo.int

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43*bis*.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/IB2018/056732

International filing date (day/month/year)  
04.09.2018

Priority date (day/month/year)  
05.09.2017

International Patent Classification (IPC) or both national classification and IPC  
INV. C07D401/14 C07D213/73 A61P33/06 A61K31/506

Applicant  
CADILA HEALTHCARE LIMITED

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually 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 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:

 European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0  
Fax: +49 89 2399 - 4465


Date of completion of this opinion

see form  
PCT/ISA/210

Authorized Officer

Dunet, Guillaume

Telephone No. +49 89 2399-0



---

**Box No. I Basis of the 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 43bis.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 13ter.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 13ter.1(a)).
    - on paper or in the form of an image file (Rule 13ter.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:

---

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

---

1. Statement

Novelty (N)	Yes: Claims	<u>2-6, 8, 9, 14, 15, 29, 30, 34, 35</u>
	No: Claims	<u>1, 7, 10-13, 16-28, 31-33, 36, 37</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-37</u>
Industrial applicability (IA)	Yes: Claims	<u>1-37</u>
	No: Claims	

2. Citations and explanations

see separate sheet

---

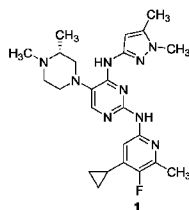
**Box No. VIII Certain observations on the international application**

---

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The present application is directed towards a triaminopyrimidine compound of formula 1, solids forms thereof, a process for preparing it, the intermediates involved, as well as processes for preparing said intermediates.



Item V:

Reference is made to the following documents:

- D1 WO 2015/165660 A1 (MEDICINES FOR MALARIA VENTURE MMV [CH]) 5 November 2015 (2015-11-05) cited in the application
- D2 SHAHUL HAMEED P. ET AL: "Triaminopyrimidine is a fast-killing and long-acting antimalarial clinical candidate", NATURE COMMUNICATIONS, vol. 6, no. 1, 31 March 2015 (2015-03-31), XP055478762, DOI: 10.1038/ncomms7715
- D3 MONICA A FITZGERALD ET AL: "Ni-Catalyzed C-H Functionalization in the Formation of a Complex Heterocycle: Synthesis of the Potent JAK2 Inhibitor BMS-911543", JOURNAL OF ORGANIC CHEMISTRY, vol. 80, no. 12, 7 April 2015 (2015-04-07), pages 6001-6011, XP055516661, ISSN: 0022-3263, DOI: 10.1021/acs.joc.5b00572
- D4 CAIRA ED - MONTCHAMP JEAN-LUC: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP008166276, ISSN: 0340-1022

**Preliminary remark:** when a compound is disclosed in a document, it is interpreted as being disclosed at all levels of purity.

## 1. Novelty

1.1. D1 discloses in its example 13 the triaminopyrimidine compound 1 that is obtained as a pure solid and it is also indicated in this document that such a compound is potentially useful for treating malaria. In addition, compound 5 is also disclosed (HCl salt of intermediate V on page 34 of D1). Compound 5b is also implicitly disclosed since intermediate V (in its HCl salt form) is further reacted under basic condition, i.e. the free base will be formed in situ (see for example the preparation of Intermediate Xa performed in the presence of 2 equiv. sodium tert-butoxide). Likewise, free base 2 and its use as intermediate in the preparation of compound 1, is also implicitly disclosed in example 13 of D1 since the HCl salt of compound 2 (obtained in example 2 of D1 is contacted with 2.5 equiv. of DIPEA, i.e. the free base will be formed in situ).

The preparation of compound 5 from compound 3a via intermediates 4a and 2a is also disclosed (see pages 33-34); however, D1 does not mention a crystallisation step at the end of the process.

The preparation of compound 1 from compounds 9 and 10 via intermediates 8, 7, 4 and 2 is also disclosed (see the scheme on page 27, and the preparation of intermediates II, III, IVa, as well as example 2 and 13).

Therefore, D1 seems to be relevant for the novelty of claims 1, 7, 10-13, 21-28, 31-33, 36 and 37 (Art. 33(2) PCT).

1.2. D2 discloses, as in D1, compound 1 (as a solid), its preparation from compounds 9 and 10 via intermediates 8, 7, 4 and 2 \*see Figure 1 on page 2 and the experimental parts on pages 7-8), and its use as a potential anti-malarial agent (see the passages cited in the SR)

Therefore, D2 seems to be relevant for the novelty of claims 1, 12, 13, 21-28, 31-33, 36 and 37 (Art. 33(2) PCT).

1.3. The preparation of compound 6 from a 2-butenitrile via halogenation and reaction with methyl hydrazine is known from D3 (see in particular Scheme 8 on page 6005). D3 thus seems to be relevant for the novelty of claims 16-20 (Art. 33(2) PCT).

1.4. D4 is concerned with polymorphism in pharmaceutically interesting compounds, but fails to disclose compounds 1, 2, 5 or 6.

1.5. As a consequence, only claims 2-6, 8, 9, 14, 15, 29, 30, 34 and 35 seem to be novel (Art. 33(2) PCT).

## 2. Inventive step

2.1. D1 is seen as the closest prior art. The crystalline forms of claims 2-6 differ from the solid compound disclosed in example 13 of D1 in their internal structure. In the absence of any demonstrated advantage / technical effect associated with the solid forms of the invention, the problem to be solved is seen as the provision of further solid forms of compound 1.

2.2. The biological activity of a compound depends primarily on its molecular structure. To reach its target, it will be at some point in solution (e.g. in body fluids) where all differences among solid forms / polymorphs disappear. The skilled person would thus expect that all solid forms / polymorphs of a given compound (here compound 1) possess, at least to some extent, the same activity (here an anti-malarial activity). From the common technical knowledge, it is known that the systematic investigation of a compound to determine whether it is prone to polymorphism is routine practice in the pharmaceutical industry. It is also known that most substances will reveal more than one polymorph if investigated for a sufficiently long time (see D4, the paragraph bridging pages 165-166). In addition, the methods to screen for polymorphs are well known in the art (see paragraph 3.1. of D4). The skilled person interested in the therapeutic application of compound 1 would thus routinely screen for solid forms / polymorphs. If such routine work yields another solid form / polymorph which does not display any substantiated unexpected property, then its provision is an obvious solution of the underlying technical problem, and no inventive step can be acknowledged for said further solid form / polymorph.

Consequently, none of the solid forms of claims 2-6, and their use in therapy, is seen as involving an inventive step (Art. 33(3) PCT).

2.3. Regarding the crystalline compounds 5 of claims 8 and 9, the problem to be solved can be seen as the provision of a further solid form of compound 5. Again, compound is known to be solid, it would thus be trivial for the skilled person looking for an alternative form of the known intermediate to consider trying to crystallise it by known methods (e.g. those described in D4). Consequently, none of the solid forms of claims 8 and 9 is seen as involving an inventive step (Art. 33(3) PCT).

2.4. For the same reasons, it would be an obvious alternative for the skilled person to envision trying to crystallise compound 5 at the end of an already known reaction sequence, i.e. the process of claim 14 is also considered to lack inventiveness (Art. 33(3) PCT).

2.5. Similarly, the process of claim 30 is not seen as inventive either insofar as it would be a trivial alternative for the skilled person looking for a further form of a compound known to be solid (as evidenced from the first step of example 13 in D1) to envision trying to crystallise it using standard methods (like those described in D4).

2.6. Finally, the features of claim 35 are not seen as involving an inventive step either in view of D4 since they correspond to the use of standard solvents for testing the presence of polymorph of a known substance, as already suggested in D4.

2.7. All in all, known of claims 1-37 is seen as involving an inventive step (Art. 33(3) PCT).

Item VIII:



3.1. claim 4: a) the claim contains a reference to the to the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here; b) the use of the term "substantially same", without any precise definition of its meaning, renders the exact scope of protection sought unclear (Art. 6 PCT).

3.2. claim 6: a) the claim contains a reference to the to the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here; b) the use of the term "substantially same", without any precise definition of its meaning, renders the exact scope of protection sought unclear (Art. 6 PCT).

3.3. Claim 11: the use of the term "substantially free", without any precise definition of its meaning, renders the exact scope of protection sought unclear (Art. 6 PCT).

3.4. Claim 21: the nature / structure of "compound 1" is missing, thus rendering the exact scope of protection sought unclear (Art. 6 PCT).

3.5. Claim 22: the use of the term "substantially free", without any precise definition of its meaning, renders the exact scope of protection sought unclear (Art. 6 PCT).

3.6. Claims 23-25: the nature / structure of "compound 1" is missing, thus rendering the exact scope of protection sought unclear (Art. 6 PCT).

3.7. Claim 30: the nature / structure of "free base compound 2" is missing, thus rendering the exact scope of protection sought unclear (Art. 6 PCT).

3.8. Claim 31: the nature / structure of "compound 1" and "compound 2" is missing, thus rendering the exact scope of protection sought unclear (Art. 6 PCT).

3.9. Claims 34-37: the nature / structure of "compound 1" is missing, thus rendering the exact scope of protection sought unclear (Art. 6 PCT).

3.10. Claim 36: the use of the term "substantially pure", without any precise definition of its meaning, renders the exact scope of protection sought unclear (Art. 6 PCT).

3.11. Claims 27 and 28: it is not clear to which step of the process of claim 25 the limitation of the nature of the base and acid applies to (Art. 6 PCT)..

3.12. Claim 30: it is not clear what has to be crystallised in order to obtain free base compound 2 (Art. 6 PCT).

3.13. Claim 34: it is not clear what has to be crystallised in order to obtain compound 1 (Art. 6 PCT).

3.14. Finally, the use of the term "about" throughout the claims, without a precise definition of its meaning, renders the exact scope of protection sought unclear (Art. 6 PCT).