

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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/EP2020/081476

International filing date (day/month/year)
09.11.2020

Priority date (day/month/year)
15.11.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D213/75 C07D213/73

Applicant
KANDY THERAPEUTICS 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 43bis.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 66.1bis(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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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>1-7, 9, 12, 13</u>
	No: Claims	<u>8, 10, 11</u>
Inventive step (IS)	Yes: Claims	<u>1-7, 9</u>
	No: Claims	<u>8, 10-13</u>
Industrial applicability (IA)	Yes: Claims	<u>1-13</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2006/013050 A1 (HOFFMANN LA ROCHE [CH]; SCHNIDER PATRICK [CH]) 9 February 2006 (2006-02-09)cited in the application
- D2 WO 02/16324 A1 (HOFFMANN LA ROCHE [CH]) 28 February 2002 (2002-02-28)cited in the application
- D3 WO 2007/028654 A1 (SMITHKLINE BEECHAM CORP [US]; ALVARO GIUSEPPE [IT] ET AL.) 15 March 2007 (2007-03-15)cited in the application

Novelty (Art. 33 (1) and (2) PCT) :

The process of claim 1 is novel due to the fact that the preparation of the intermediate compound (III) as disclosed in step i) for the preparation of compound (IX) has not been reported before.

Claims 1-7 consequently fulfills the requirements of Art. 33(2) PCT.

The subject-matter of claims 8 and 10 cannot be considered novel because it relates to compounds (IX) and (A) which are known compounds. A product is not rendered novel merely by the fact that it is produced by means of a novel process. Organic compounds such as present compounds (IX) and (A) cannot be distinguished by their preparation processes.

Similarly the subject-matter of present 11 is not novel either. The reference to the preparation process being not considered as a limiting feature, it relates to compound A for use in the treatment of sex hormone diseases which is already known as acknowledged in the application on page 1 lines 15-18 (reference is made to WO2016184829).

The subject-matter of claim 12 appears novel since the compound (V) is disclosed in Document D3 as free form and not as one of the salts listed in present claim 12.

The compound of claim 13 is considered as a novel selection from the general family Ia disclosed in Document D2 (claim 18).

The subject-matter of present claims 1-7, 9, 12 and 13 comply with the requirements of Art. 33(2) PCT.

Inventive Step (Art. 33 (1) and (3) PCT) :

Process claims 1-7, 9:

Document D1 and Document D2 disclose processes for the preparation of compound (IX) which differs from that presently claimed mainly in the nature of the intermediate which is reacted with the boronic acid derivative indicated in claim 1.

In Document D1, the methyl amine referred to as intermediate 2 is used (see scheme 1 page 13) whereas a trihalo-substituted derivative (XVII) is reported in Document D2 (see scheme 5 page 19).

The technical problem raised is the provision of an alternative process for the preparation of the intermediate compound (IX) which is useful in the preparation of the pharmaceutically active compound A.

The process of claim 1 differs from those of the art in the use and preparation of intermediate (III) from compound (I). Examples 1-5 provided in the description show that the problem raised has been solved.

Starting from Document D1 or Document D2, the skilled person would have had no hint to use the starting material (I) with the boronic acid defined in claim 1 so as to arrive at present compound (III) and then to the desired final intermediate compound (IX).

Present claim 1 as well as all dependant claims thereof (1-7, 9) comply with the requirements of Art. 33(3) PCT.

Compounds claims 12 and 13 :

Document D3 reports a preparation process of compound A (example 34) from compound (IX) (see Description 24, reference being made to WO2005/002577).

Document D3 is considered as the closest prior art for the subject-matter of present claims 14 and 15 because it reports also the free salt of compound (V) for use in the preparation of an analog of present compound (IX) differing only in that it has a

cyclopropyl instead of a dimethyl methylene linker in the final intermediate. The analog of (VII) is methylated to lead to the analog of (XI) (see description 1 and description 2 on page 39-40).

The technical problem raised by these two claims is seen in the provision of further intermediate compounds useful for the preparation of compound (XI).

Starting from Document D3 and wishing to solve the problem raised, the skilled person would have expected that salts of compound (V) as well as non-methylated intermediate (VII) will be suitable intermediates to prepare the desired compound (XI). Present compound (VII) moreover falls within the generic family Ia of Document D2 which encompasses both compounds (VII) and (XI). Although the preparation of the specific compound (XI) is prepared in different ways in Document D2 and D3, analogy processes are clearly disclosed therein providing a hint to the skilled person searching for alternative novel intermediates. It is furthermore noted that claims directed to intermediates have to be inventive per se. The present intermediates do not possess any new structural element arising from the distinguishing element of the process claim 1 over the art (which is step i). They can not benefit from the inventiveness of the process of claim 1 because they are prepared at a later stage and do thus not share any special technical feature with it. Even if they would be inventive (which they are not), they would not be unitary with the subject-matter of claim 1.

The requirements of Art. 33(3) PCT are not complied with for claims 12-13.