

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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6th,Business Development Area,Daxing, Beijing

HUHuiping

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

11 July 2018

Applicant's or agent's file reference

3000BCPCT

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/IB2018/051973

International filing date (day/month/year)

23 March 2018

Priority date (day/month/year)

23 March 2017

International Patent Classification (IPC) or both national classification and IPC

C07D 241/18(2006.01)i; C07D 241/20(2006.01)i; C07D 401/14(2006.01)i; C07D 401/04(2006.01)i;
C07D 491/107(2006.01)i; C07D 498/10(2006.01)i; C07D 471/10(2006.01)i; A61K 31/497(2006.01)i;
A61P 35/00(2006.01)i; A61P 35/02(2006.01)i

Applicant

JACOBIO PHARMACEUTICALS CO.,LTD. et al

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 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/

**STATE INTELLECTUAL
PROPERTY OFFICE OF THE
P.R.CHINA
China 6, Xitucheng Rd., Jimen Bridge,
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Date of completion of this opinion

28 June 2018

Authorized officer

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/IB2018/051973

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 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. II

Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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INTERNATIONAL SEARCHING AUTHORITY**

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. See claims listed below

because:

- ☒ the said international application, or the said claims Nos. 131-134 relate to the following subject matter which does not require an international search (*specify*):

[1] Claims 131-134 relate to a method for treating diseases mediated by SHP2, which belong to a method for the treatment of the human/animal body (Rule 39.1(iv) PCT).

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☒ no international search report has been established for said claims Nos. 131-134

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

- ☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
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International application No.

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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	1-130	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-130	NO
Industrial applicability (IA)	Claims	1-130	YES
	Claims	None	NO

2. Citations and explanations :

[1] The statement and explanations have been carried out on the basis of the subject matter of claims 1-81, 117-130 that could reasonably be expected to be claimed (see Box VIII).

[2] 1. Prior Arts

[3] The following document is mentioned in the written opinion:

[4] D1 :WO 2016203406A1 (NOVARTIS AG) 22 Dec.2016(22.12.2016)

[5] **2.1 Novelty**

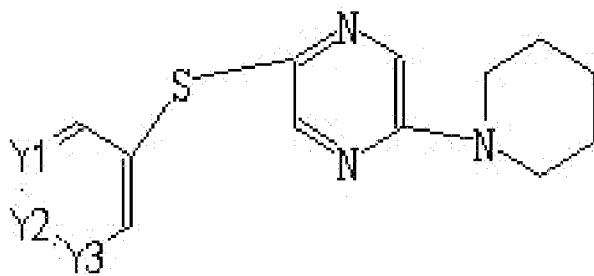
[6] Claim 1 relates to compounds of formula I or pharmaceutically acceptable salt thereof. D1 is the closest prior art. D1 (see examples and claims 4, 7 and 11) discloses some compounds. The difference between the claimed compounds in claim 1 and compounds disclosed in D1 lies in A, i. e. A is a 3-10 membered ring in claim 1 and A is absent in D1. So claim 1 is considered to be new in accordance with Article 33(2) PCT.

[7] Dependent claims 2-116 and 127-130 further define the compounds according to the foregoing claims. Claims 117-118 relate to the composition comprising the compounds in claims 1-116. Claims 119-126 relate to the use of compounds in claims 1-116 or the composition in claims 117-118. The subject matter of claims 2-130 is not disclosed in D1. Therefore, claims 2-130 are considered to be new in accordance with Article 33(2) PCT.

[8] **2.2 Inventive Step**

[9] D1 is the closest prior art. D1 (see claims 4, 7 and 11) discloses some compounds such as the forth compound in claim 4, which is similar in structure to those compounds in claim 1 and has the same uses. The difference between the claimed compounds in claim 1 and compounds disclosed in D1 lies in A, i. e. A is a 3-10 membered ring in claim 1 and A is absent in D1. The problem underlying the present invention therefore is the provision of further new compounds with the activity of SHP2 compared with the compound disclosed in D1. D1 (see claim 1) discloses the formula I, wherein R5 and R5b may be NH₂ et al. or R5a and R5b combine to form a cycloalkyl. The structure is the core structure of formula I in D1 as follows:

[10]



. There is an indication which would lead the skilled person to modify the compound of D1 by changing the substitution pattern in order to solve the above technical problem. Thus, based on the compounds disclosed in D1, it is obvious to a skilled person to arrive at the solutions of claim 1 by adjustment A group and easily expect a same or similar action to the compounds in D1. Claim 1 is not inventive according to Article 33(3) PCT.

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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**

- [11] Dependent claims 2-116 and 127-130 further define the compounds according to the foregoing claims. Claims 117-118 relate to the composition comprising the compounds in claims 1-116. Claims 119-126 relate to the use of compounds in claims 1-116 or the composition in claims 117-118. D1 (see claims 4-14) discloses the similar compounds, composition and the same use. So based on that claim 1 is not inventive, Claims 2-130 are not inventive according to Article 33(3) PCT.
- [12] **2.3 Industrial applicability**
- [13] Because the subject matter of claims 1-130 can be made or used in industry, claims 1-130 meet the criteria set out in Article 33(4) PCT.

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:

- [1] Claim 128 quotes "the use according to according to claim 127", whereas the subject matter of claim 127 is "at least one compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1-116, pharmaceutical composition of as defined in claim 117 or 118". Thus claim 128 is unclear and does not meet the requirement of Article 6 PCT. At the same reason, Claims 129 and 130 are unclear and do not meet the requirement of Article 6 PCT. The written opinion has been made under the reasonable presumption that Claims 128 quotes "the compound or pharmaceutically acceptable salt thereof, pharmaceutical composition according to claim 127", Claims 129 quotes "the compound or pharmaceutically acceptable salt thereof, pharmaceutical composition according to claims 127 or 128" and Claims 130 quotes "the compound or pharmaceutically acceptable salt thereof, pharmaceutical composition according to claims 127-129".
- [2] The subject matter of claims 1-81, 117-130 relates respectively to A which is absent, wherein the definition of A renders said claims to cover a very large number of different kinds of compounds. But the description only provides preparation, characterization and experiment of the use of some compounds, which belong to the scope of compounds claimed in dependent claim 116, i. e. only A is a 3-10 membered ring claimed in the said claims have been described sufficiently in the description and thus are supported by the description. The said broadly generalized claims could not be supported by the description and the description does not set forth the invention sufficiently. The present application does not meet the requirements of PCT Article 5 and PCT Article 6. This written opinion has been established on the basis of subject matter anticipated reasonably, i. e. the compounds in claims 1-81, 117-130 are limited to the scope of compounds that A is a 3-10 membered ring, not absent.