

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

## PCT

### 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/IB2020/057815

International filing date (day/month/year)  
20.08.2020

Priority date (day/month/year)  
20.08.2019

International Patent Classification (IPC) or both national classification and IPC  
INV. C07D487/04 A61P35/00 A61K31/4985

Applicant  
OTSUKA PHARMACEUTICAL CO., LTD.

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:



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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**

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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:

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**Box No. II Priority**

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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 43bis.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 43bis.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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**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**

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1. Statement

|                               |             |                    |
|-------------------------------|-------------|--------------------|
| Novelty (N)                   | Yes: Claims | <u>1-35</u>        |
|                               | No: Claims  |                    |
| Inventive step (IS)           | Yes: Claims | <u>23</u>          |
|                               | No: Claims  | <u>1-22, 24-35</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-35</u>        |
|                               | No: Claims  |                    |

2. Citations and explanations

see separate sheet

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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**Box No. VII Certain defects in the international application**

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The following defects in the form or contents of the international application have been noted:

see separate sheet

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

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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

**Re Item V**

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

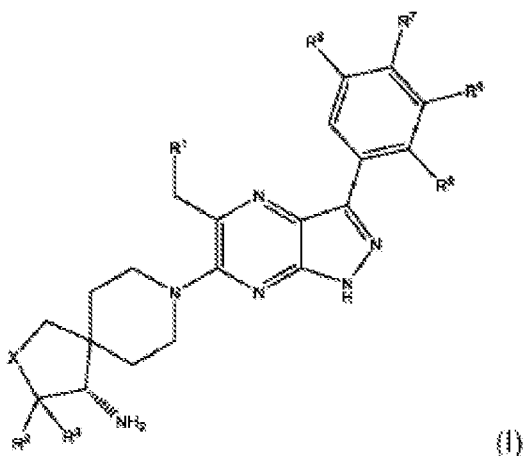
Reference is made to the following documents:

- D3 WO 2017/211303 A1 (JACOBIO PHARMACEUTICALS CO LTD [CN]) 14 December 2017 (2017-12-14)
- D4 WO 2018/057884 A1 (RELAY THERAPEUTICS INC [US]; DE SHAW RES LLC [US]) 29 March 2018 (2018-03-29)

Although claim 31 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/ composition. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claim 31 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

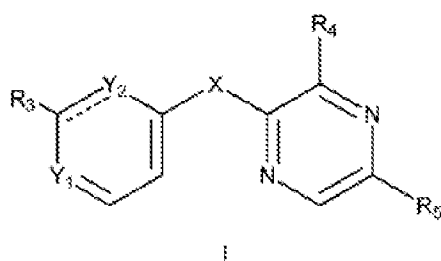
Claimed are compounds of formula (I), these compounds are used in the treatment of cancer and are SHP2 inhibitors.



1 **Novelty (Article 33(2) PCT):**

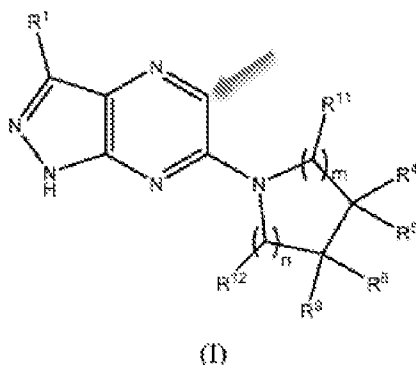
**D3:**

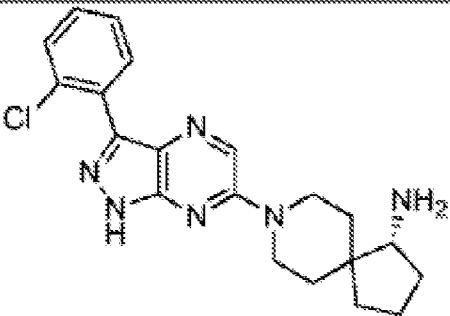
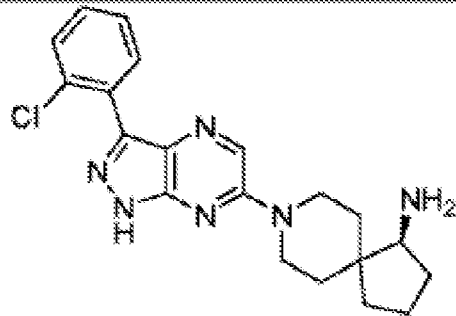
The compounds of D3 differ from the presently claimed compounds in that they do not comprise a pyrazolopyrazin moiety. Instead, these compounds comprise a central pyrazine moiety. Furthermore, the substitution pattern on the pyrazine ring differs from that of the claimed compounds. The pyrazine also is linked to the phenyl substituent via a sulfide linker. The claimed compounds do not comprise such a linker.



**D4:**

The compounds of D4 differ from the claimed compounds in that the pyrazolopyrazin moiety does not comprise a substituent in the 5-position of this ring. Compounds 16 and 35 of D4 are structurally very close to the claimed compounds, but also do not comprise a substituent -methylene-R1 and in addition do also not comprise a substituent R8.



|    |                                                                                   |   |
|----|-----------------------------------------------------------------------------------|---|
| 16 |  | A |
| 35 |  | A |

The subject-matter of claims 1-23 therefore is considered novel over the prior art.

Since the compounds of formula (I) are novel, the remainder of the claims 24-35, which also relate to these compounds, can also be considered novel.

## 2 Inventive Step (Article 33(3) PCT):

2.1 Both D3 and D4 discloses compounds which are modulators of SHP2.

The compounds of D4 are structurally closer to the claimed compounds and can therefore be regarded as the closest prior art.

As there are no comparative tests disclosed in the present application, a technical effect cannot be attributed to the difference between the compounds of D4 and the presently claimed ones. The technical effect therefore has to be seen in the provision of further compounds which can be used to treat cancer. In particular, further compounds which are SHP2 inhibitors.

D4 does not provide any hint that the pyrazolopyrazine ring should have another substituent in position 5 of the ring. Since D3 does not disclose compounds containing a pyrazolopyrazine ring, D3 would not lead to the claimed compounds in combination with D4. From D4 in combination with D3 then the skilled person would not have arrived at the claimed subject-matter without using inventive skill.

The claims are however not considered inventive over the entire scope of the claims. The present application comprises 25 individual examples, which have been tested for SHP2 inhibitory activity. The compounds defined in present claim 1 can however be structurally very different from the exemplified compounds. Ring A, which can be formed from R6 and R7, is defined as three different types of rings (i-iii) of which only few have been synthesized and tested. Not only can these rings A contain further heteroatoms in addition to nitrogen, they also can be further substituted. Let's have a look at how such substitutions can look like, to illustrate how different such compounds are when compared with the tested compounds. Ring A can be substituted with R10, which can be a five- or six-membered heterocyclic group, which is optionally substituted with a five- to six-membered unsaturated heterocyclic group, containing from 1-4 heteroatoms and which can be optionally substituted with a four- to six-membered saturated heterocyclic group, which can be again optionally substituted with a four- to six-membered saturated heterocyclic group, optionally substituted with a C1-4 alkyl group.

Such a compound contains 4 additional heterocyclic groups in a chain, each of them optionally being also further substituted and cannot be considered to be *structurally closely related*. Having in mind that in the medicament field small structural changes often give rise to substantial and unexpected changes in activity, a generalization of experimental results for compounds with quite different structures does not appear to be justified.

Inventive step with respect to whether the technical problem has been solved over the entire scope of the claim, has to be assessed on the basis of the same knowledge and considerations as is done when comparing an invention with the disclosure of the prior art. If we suppose that the skilled person would not have expected that compounds which differ by only a methyl or hydroxymethylene group from the disclosed compounds retain the same activity, then the same should also be assumed for compounds for which Ring A as defined in claim 1 is substantially different from this group as defined in the examples.

For compounds which cannot be considered close structural analogues of the tested compounds, the technical problem can only be formulated in a less ambitious way, e.g. the provision of chemical compounds. The solution of this problem is considered to be part of the routine work carried out by the skilled organic chemist and lacks an inventive activity.

The subject-matter of claims 1-22 therefore lacks an inventive step.

Claims 24, 25, 34 and 35 cannot be considered inventive by analogy, as they encompass combinations, compositions and prepare the compounds which lack an inventive step.

The subject-matter of claims 26-33 is considered to lack enablement, as it has not been shown that the compounds can be sued to treat cancer/are SHP2 inhibitors (Article 5 PCT).

2.2 The subject-matter of claim 23 is considered inventive.

## **Re Item VI**

### **Certain documents cited**

Certain published documents

| Application No<br>Patent No | Publication date<br>(day/month/<br>year) | Filing date<br>(day/month/<br>year) | Priority date ( <i>valid claim</i> )<br>(day/month/year) |
|-----------------------------|------------------------------------------|-------------------------------------|----------------------------------------------------------|
| WO2019/183364               | 26/09/19                                 | 21/03/19                            | 21/03/18                                                 |
| WO2019/213318               | 07/11/19                                 | 01/05/19                            | 02/05/18<br>30/11/18                                     |

## **Re Item VII**

### **Certain defects in the international application**

- 3      Claims 18 (reference to the tables), 28, 30, 31 and 34 ("as defined hereinbefore") contain a reference to the description and/or 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.

**Re Item VIII**

**Certain observations on the international application**

- 4      Claim 35 contains a reference to claim 38 although the application does only contain 35 claims in total. This reference thus does not make sense (Article 6 PCT).
- Furthermore, there is a reference to a compound of "formula (X)" in claim 35, but no such formula is shown in this claim or any other claim.
- 5      The description suggests that a large number of compounds are encompassed in the invention which are defined only by reference to a desired functional activity (compound being a "Prodrug", see page 53 and 60 of the present description). This functional term does not give a specific technical guidance for the selection of the suitable derivatives, without proven general knowledge, to show which derivatives are suitable "prodrugs" in the particular case of the current problem and thus could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants.
- The description does not provide support and disclosure within the meaning of Article 6 PCT and, in addition, does not appear to be sufficiently disclosed under Art. 5 PCT for any of such compounds having the desired function and there is no general common knowledge of this kind available to the skilled person. In such a situation, the invention cannot be carried out over the whole claimed area without imposing an undue burden, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims.
- The same objection also applies to the disclosure of "esters" and "complexes" on pages 53 and 58 of the present description, *mutatis mutandis*.

- 6      The claims contain features, which seem to be mere illustrations of the claimed embodiments. Such illustrations render the subject-matter of the claims unclear, as it cannot be clearly determined whether these features should be considered as preferred embodiments or limiting technical features. Such features should be either formulated as separate, dependent claims, or clearly formulated as preferred embodiments (Article 6 PCT). The expressions objected to are "e.g.", "such as" and "for example".
- 7      Claim 27 does not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating SHP2), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).