

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

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/US2020/057496

International filing date (day/month/year)
27.10.2020

Priority date (day/month/year)
28.10.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 C07D498/04 A61K31/522 A61P35/00

Applicant
MERCK SHARP & DOHME CORP.

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. 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 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:

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>1-32</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-32</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-32</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

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

Box No. VII Certain defects in the international application

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

see separate sheet

re item V:

1. Prior art

Reference is made to the following documents:

- D1 WO 2020/050890 A2 (AMGEN INC [US]) 12 March 2020 (2020-03-12)
- D2 WO 2020/259513 A1 (GUANGDONG NEWOPP BIOPHARMACEUTICALS CO LTD [CN]) 30 December 2020 (2020-12-30)
- D3 WO 2018/119183 A2 (AMGEN INC [US]) 28 June 2018 (2018-06-28)
- D4 WO 2018/217651 A1 (AMGEN INC [US]) 29 November 2018 (2018-11-29)

2. Novelty

The claimed 4-piperazinyl-1,7-bis(hetero)aryl-pyridopyrimidin-2-one derivatives differ structurally considerably from those according to documents D3 and D4, i.e. by the fact that the two (hetero)aryl residues are connected by heteroalkylene chain to build a macrocyclic heterocyclic ring including the pyridopyrimidinone moiety, whereas this cannot be the case according to documents D3 and D4. Therefore the subject matter of present claims 1 to 32 is considered to be novel with regard to the cited prior art according to Art. 33 (2) PCT.

3. Inventive step

The compounds as disclosed in documents D3 and D4 as well as the claimed compounds are inhibitors of the KRAS G12C mutant and thus are useful in the treatment of oncogenic related disorders like cancer. Therefore, documents D3 and D4 are considered to represent the closest prior art. As already set out under item 2, above, the structural difference between the claimed macrocyclic 4-piperazinyl-1,7-bis(hetero)aryl-pyridopyrimidin-2-one derivatives wherein the two (hetero)aryl rings in position 1 and 7 are connected via a heteroalkylene chain and the 4-piperazinyl-1,7-bis(hetero)aryl-pyridopyrimidin-2-one derivatives as disclosed in documents D3 and D4 is significant.

Thus, with respect to this closest prior art the problem underlying the present application is to be seen in the provision of further inhibitors of the KRAS G12C mutant. This problem has apparently been solved as can be seen from the description by the

provision of experimental section concerning biological assays. The solution of this problem is considered to involve an inventive step since the structure of the closest prior art compounds in document D3 and D4 are so completely different as set out above. Therefore, the subject matter of claims 1 to 33 is considered to fulfil the requirement of Art. 33(3) PCT.

4. Industrial applicability

Claims 23 to 25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. 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.

re item VI:

The Applicant is informed, that if documents D1 and D2 were to enter the european phase, these documents would be highly relevant for novelty and also for the consideration of inventive of any subject matter enetitled to the filing date only.

re item VII:

Claim 23 is defined in functional terms that are not considered to be clear in the sense of Art. 6 PCT. The therapeutic application is defined by means of a mechanism of action which does not allow for a practical application in the treatment of a specific pathological condition (disease). The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application or by showing that means are available which would allow the skilled person to recognise which additional conditions would fall within the functional definition.