

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/IB2020/050009

International filing date (day/month/year)
02.01.2020

Priority date (day/month/year)
03.01.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/14 A61P35/00 A61K31/495 A61K31/4709

Applicant
ARRAY BIOPHARMA INC.

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

Sáez Díaz, R

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>1-49</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-49</u>
Industrial applicability (IA)	Yes: Claims	<u>1-49</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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

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

- 1 The present application relates to quinoline derivatives of formula (II) as TAM und MET inhibitors and their use in the treatment of cancer.
- 2 Claim 39-48 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.
- 3 Reference is made to the following documents:

D1	WO 2007/033196 A1
D2	WO 2007/146824 A2
- 4 No prior art document discloses quinoline derivatives of the present formula (II). The structurally closest compound is a MET kinase inhibitor and can be found in document D2 (example 6, claims 1-15). This compound shows however a phenoxy instead of a pyridinoxy moiety attached to the quinoline and a different substituent on the oxodihydropyridine ring (5-benzyl instead of 5-phenyl).

Document D1 discloses quinoline derivatives of formula (I) as c-Met inhibitors (claims 1-83). It is noted that the presently claimed compounds of general formula (I) represent a novel selection from D1, because they are generally but not specifically disclosed therein. The structurally closest compound of D1 is example 82. However, this prior art compound bear a phenoxy instead of a pyridinoxy moiety attached to the quinoline and 2-oxodihydropyridine instead of 4-oxodihydropyridine ring attached to the amide moiety.

Therefore, at present the subject-matter of claims 1-49 is novel and meets the requirements of Article 33(2) PCT.
- 5 Document D1 is considered to be the closest prior art to the subject-matter of claims 1-49 as it discloses quinoline derivatives of formula (I) as c-Met kinase inhibitors for use in the treatment of cancer (claims 1-83, example 82).

However, the compounds of the present application are covered by the general formula (I) of D1 according to claim 1. The presently claimed compounds as solution to the problem of providing alternative quinoline derivatives as c-Met kinase receptor antagonists for use in the treatment of cancer is obvious since said compounds are already disclosed in D1 although not explicitly described. The mere choice of specific compounds within a group of compounds known for the same pharmacological activity cannot be considered inventive, unless said compounds present unexpected effects or properties over the closest prior art, in this case for example an improved c-Met inhibitory activity over D1. Since no such effects or properties are indicated and supported in the application, the subject-matter of claims 1-49 does not involve an inventive step within the meaning of Article 33(3) PCT.

In order to show any of such improved or unexpected properties vis-à-vis the prior art comparative tests must be performed using compounds with the maximum structural similarity. This is necessary to show that the unexpected effect indeed originates from the distinguishing feature. In the present case, example 82 of D1 should be selected.

Re Item VII

Certain defects in the international application

- 1 Claim 1 comprises all the features of claims 2 and 3. Therefore claims 2 and 3 should be formulated as claims dependent on claim 1 (Rule 6.4 PCT).