

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/B2020/055992

International filing date (day/month/year)
24.06.2020

Priority date (day/month/year)
28.06.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D239/90 A61P35/00 C07D239/91 C07D401/12 C07D403/12 C07D405/04 C07D405/12 C07C271/28
A61K31/517

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 <i>bis</i> .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

Authorized Officer

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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. 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. 37

because:

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

☐ 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 the whole application or for said claims Nos. 37

☐ 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

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-36, 38

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>1-36, 38</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>8, 10-18, 38</u>
	No: Claims	<u>1-7, 9, 19-36</u>
Industrial applicability (IA)	Yes: Claims	<u>1-36, 38</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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:

see separate sheet

Re Item IV

Lack of unity of invention

The present claims are directed to compounds of formulae I-III, as well as to the synthetic intermediates of claims 35-38.

In order for a group of claims to fulfil the requirements of unity (Rule 13.1 PCT) a single general inventive concept must be present between the claimed inventions. Said general inventive concept finds its expression in one or more of the same or corresponding special technical features (Rule 13.2 PCT). Special technical features are those features that define the contribution that the claimed invention makes over the prior art. Thus features which do not provide a contribution over the prior art cannot be used to unify claimed inventions.

The compounds of formulae I-III are distinguished from the closest prior art, WO2012/118492, by the identity of the present R² substituent. Whilst a corresponding R² substituent is present on the synthetic intermediates of claims 35, 36 and 38, the synthetic intermediate of present claim 37 lacks said distinguishing feature. Claim 37 therefore lacks the special technical feature that is present in the remaining claims. For this reason claim 37 is not unitary with the remaining claims.

The present claims therefore are directed to the following two non-unitary inventions:

Invention 1: claims 1-36, 38;

Invention 2: claim 37.

As the applicant has not paid an extra fee for the 2nd invention, the present opinion is given for Invention 1 only.

Re Item V

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

Claims 21-34 are directed to therapeutic methods. 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 allows claims to a product for use in a first or further medical treatment.

Claims 36 and 38 are compound claims wherein the PG group is defined as an amine protecting group. Whilst such a term may be considered acceptable in the context of a process claim, wherein the conditions under which the protecting group should be stable, and those under which the protecting group should be removable are clear, a compound claim does not define such conditions. The skilled person is therefore not able to ascertain the scope of the term amine protecting group as used in claims 36 and 38. For this reason these claims lack clarity. The claims have only been searched and examined in so far as said group is as defined on p. 50, I. 21-22.

Reference is made to the following documents:

D1: WO2012/118492

D2: WENGLOWSKY STEVE ET AL: "Highly potent and selective 3-N-methylquinazoline-4(3H)-one based inhibitors of B-RafV600Ekinase", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 24, no. 8, 13 March 2014 (2014-03-13), pages 1923-1927, XP028841756, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2014.03.007

D3: WO 2019/060611 A1 (ABM THERAPEUTICS INC; CHEN CHEN [US]) 28 March 2019 (2019-03-28)

Novelty

The compounds of D1 (claim 1) have a Y group at the position corresponding to the C-R² group of present formulae I, II and III and of present claims 35 and 36, and at the position corresponding to the C-CH₃ group of the compounds of present claim 38. This Y group can be CR¹¹, wherein R¹¹ is hydrogen or halogen. The present R² or CH₃ group therefore establishes novelty over the disclosure of D1.

D2 also discloses compounds (10-25) differing from those presently claimed because they lack the present R² or CH₃ group. The compounds of D2 have a H at this position.

The compounds of D3 (claim 1) have a fused ring between the quinazoline 3- and 4-positions which is lacking in the present compounds.

The requirements of novelty are fulfilled.

Inventive step

The compounds of D1-D3 are inhibitors of BRAF (D1, [00204]-[00206]; D2 Tables 1-4; D3, claim 49).

The compounds of present formulae I-III have been shown to have BRAF kinase inhibitory activity (Table A, pp. 144-152). This includes both compounds wherein R² is methyl and wherein R² is ethynyl.

If the technical problem underlying the claims relating to compounds of formulae I-III were that of providing further BRAF inhibitors, the present solution to said problem, i.e. the replacement of the H or halogen atom of D1 or D2 by the present methyl, CD₃ or ethynyl group would be considered obvious, as D3 teaches in structurally similar compounds with the same activity that the corresponding position (X₁, which can be CR^a) that amongst others, H, halogen, alkyl and alkynyl groups are suitable substituents at this position.

It can be seen from a comparison of the data in Tables B2 and B3 (pp. 163-171) that inventive compound 10, differing from examples 34 and 37 of D1 solely in that it has an R² group that is methyl, whereas said examples have a corresponding group that is H or Cl, respectively, has lower efflux ratios. A lower efflux ratio is an indication of increased brain penetration.

Furthermore, it can be seen from a comparison of the data in Tables C1 and C2 (pp. 172-174) that inventive compound 10 has a higher free brain to free plasma ratio than examples 34 and 37 of D1. A higher free brain to free plasma ratio is an indication of increased ability to penetrate the blood brain barrier.

The fact that the replacement of a H or Cl substituent by a methyl substituent would lead to the above-mentioned improvements does not appear to be taught in D3. Therefore an inventive step may be recognised for the present compounds wherein R² is methyl or deuterated methyl.

However, there do not appear to be any data in the application showing that the replacement of a H or Cl substituent by an ethynyl group leads to an unexpected effect. Thus the compounds wherein R² is ethynyl are considered to be alternative BRAF inhibitors which are obvious based on the teaching of D1 or D2 combined with that of D3.

Furthermore, the methods of preparation, in the absence of an inventive final product, are obvious over the preparation methods of D1 (Schemes 11-15).

In view of the above, claims 1-7, 9, 19-34 are obvious over D1 combined with D3.

As the synthetic intermediates of claims 35 and 36 may be used to prepare final products wherein the R² group is ethynyl, these claims lack inventive step for the same reasons as those given above.

As the compounds of claim 38 are synthetic intermediates for preparing inventive final products having an R² group which is methyl, these intermediate compounds are considered inventive for the same reasons as those given above.

Thus, in summary, claims 1-7, 9 and 19-36 do not fulfil the requirements of inventive step whereas claims 8, 10-18 and 38 fulfil the requirements of inventive step.

Re Item VIII

Certain observations on the international application

Claim 12 comprises all the features of claim 10 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

Claims 14-17 comprise all the features of claim 13 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT).