

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/US2022/018644

International filing date (day/month/year)
03.03.2022

Priority date (day/month/year)
04.03.2021

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

Applicant
ELI LILLY AND COMPANY

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:



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

Bedel, Christian

Telephone No. +49 89 2399-0



Box No. 1 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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2022/018644

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>1-67</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-67</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-67</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 Preliminary remark

The subject-matter of claims 56-60 concerns a method of treatment and is therefore 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.

Patentability, in particular novelty and inventive step, of claims 56-60 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 Reference is made to the following documents:

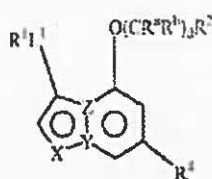
- D1 WO 2020/131627 A1 (ARRAY BIOPHARMA INC [US]) 25 June 2020 (2020-06-25)
- D2 WO 2010/017047 A1 (MERCK & CO INC [US]; BANYU PHARMA CO LTD [JP] ET AL.) 11 February 2010 (2010-02-11)
- D3 WO 2016/191172 A1 (PRINCIPIA BIOPHARMA INC [US]) 1 December 2016 (2016-12-01)
- D4 WO 2016/134320 A1 (INCYTE CORP [US]) 25 August 2016 (2016-08-25)
- D5 MARTIN JAMES S ET AL: "Characterising covalent warhead reactivity",
BIOORGANIC,
vol. 27, no. 10 , pages 2066-2074, XP085664299,
ISSN: 0968-0896, DOI: 10.1016/J.BMC.2019.04.002

3 Novelty (Art. 33(2) PCT)

3.1 Application

Claim 1 is novel on account of the presence of a cyano group on the left end opposite to the pyrazolopyridine (position of W in D1). Therefore D1, does even not overlap with presently claimed subject-matter.

- 3.3 D2 discloses the pyrazolo- or imidazolo-pyridine pharmacophore (V), substituted with a heteroaryl group on the pyridine part and further substituted on the "4"- position of the pyrazol part (see examples and tables). D2 reports an inhibition activity on inter alia FGFR3, however no precise examples or tests are provided.



(V)

- 3.4 D3-D4 disclose FGFR inhibitors structurally remote from the present compounds and from those of D1.
- 3.5 D5 is a general teaching about "targeted covalent inhibition". Therefore claim 1 could be considered as novel.

4 Inventive step (Art. 33(3) PCT)

The closest prior art is D1.

There is no comparative data vis-à-vis the compounds of D1 and the present compounds, therefore the technical problem can be construed as the provision of further FGFR3 specific inhibitors and their potential use in the treatment of related diseases, inter alia cancer.

The compounds of D1 have been developed according to the targeted covalent inhibition principle wherein a pharmacophore is attached via a linker to a suitable terminal group that forms a covalent bond with a cysteine in a kinase insert domain of FGFR3 protein.

The present application appears to be based on the same principle although it is not explicitly expressed in the description. The presently claimed compounds differ nevertheless from the ones of D1 essentially by this terminal group wherein a cyano group linked to the nitrogen atom of an N-containing heterocycle is used, instead of acrylamide groups or derivatives thereof in D1.

The numerous tests provided prove that said compounds have the intended effect. It appears also credible that said effect is demonstrated on the whole claimed scope.

D1 only encompasses compounds with a terminal acrylamide group or derivative thereof.

D2 discloses the pyrazolo-pyridine pharmacophore.

D3 encompasses a cyano group but within a cyano acrylamide group and with a different pharmacophore, albeit showing FGFR inhibition.

D4 discloses FGFR inhibitors with a cyano terminal group for some of the examples but none directly connected to the N-atom of N-containing heterocycle. Furthermore, D4 also concerns a different pharmacophore and does not show any specific enhanced inhibition on FGFR3.

To sum up, there is no suggestion to be found in the prior art D1-D5 that pyrazolo- or imidazolo-pyridine pharmacophore linked to a terminal cyano group-N-substituted N-containing heterocycle could retained the specific FGFR3 inhibition action already shown in D1.

Therefore an inventive step should be acknowledged for the subject-matter of claim 1 as well as for the rest of the claims 2-67, by consequence.

- 5 Claims 2-67 are dependent on, or directly refer to independent claim 1 whose subject-matter is considered as being new and inventive, as discussed above, and as such said claims also meet the requirements of the PCT with respect to novelty and inventive step.

Re Item VII

Certain defects in the international application

- 1 The closest prior art D1 and D2 should be cited and briefly commented.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO/ISA)

General information

For all international applications, the competent International Searching Authority (ISA) will establish an international search report (ISR) accompanied by a written opinion of the International Searching Authority (WO/ISA). The WO/ISA may be responded to by

- filing informal comments with the International Bureau of WIPO (IB) (where no demand for international preliminary examination (demand) is filed)
- filing amendments under Art. 19 PCT (this can be done whether or not a demand is filed)
- filing amendments under Art. 34 PCT and/or formal observations in response to objections raised in the WO/ISA (where a demand is actually filed)

This document explains these possibilities.

Filing informal comments

After receipt of the ISR and WO/ISA, the applicant may file informal comments on the WO/ISA, directly with the IB (see International Search and Preliminary Examination Guidelines 2.15). These will be communicated to the designated/elected Offices, together with the International Preliminary Report on Patentability (IPRP) at 30 months from the priority date.

Amending claims under Art. 19 PCT

The applicant may file amended claims under Art. 19 PCT, directly with the IB by the later of the following dates:

- 2 months from the date of mailing of the ISR and the WO/ISA
- 16 months from the priority date

However, any such amendment received by the IB after the expiration of the applicable time limit shall be considered to have been received on time by the IB, if it reaches it before the technical preparations for international publication have been completed (the 15th day prior to the date of publication, see PCT Applicant's Guide, International Phase, 9.013).

For further information, please see Rule 46 PCT as well as form PCT/ISA/220.

Please also note that, when filing amended claims under Art. 19 PCT, such amendments shall be accompanied by a letter identifying the amendments made and also the basis for the amendments in the application as originally filed (Rule 46.5(b) PCT). Where a demand is filed, failure to comply with this requirement may result in the amendments being ignored in the International Preliminary Examination Report (IPER), see Rule 70.2(c-bis) PCT.

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