

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/US2015/065940

International filing date (day/month/year)
16.12.2015

Priority date (day/month/year)
22.12.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D513/04 A61K31/506 ADD. A61P35/00

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:



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this opinion

see form
PCT/ISA/210

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2015/065940

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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2015/065940

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>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-19</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

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

1 Reference is made to the following documents:

- D1 US 2003/064982 A1 (DAVIES ROBERT [US] ET AL) 3 April 2003
- D2 WO 2013/130976 A1 (ARRAY BIOPHARMA INC [US]) 6 September 2013
cited in the application
- D3 WO 2007/053776 A1 (SGX PHARMACEUTICALS INC [US]) 10 May 2007

2 Method for treatment of the human or animal body by therapy

Claims 9 to 13 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 also depend 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 in a first or further medical treatment.

3 Novelty

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 19 is considered to be new over the prior art D1 to D3 in the sense of Article 33(2) PCT for the following reasons:

D1 to D3 refer also to 2-aminopyrimidine derivatives useful for treating cancer.

The compounds of D1 to D3 differ from the compounds of present claim 1 in the nature of the substitution of position 4 which is not a thieno[2,3-c]pyrrol-4-one cycle as required by present formula (I).

4 Inventive step

The present application addresses the problem of providing ERK inhibitors useful for treating cancer.

4.1 Closest State of the Art and Difference

D1 is considered to represent the closest prior art, since it refers also to 2-pyrrazolylamino-pyrimidine derivatives as ERK inhibitors.

The structural distinguishing feature of the compounds of present claim 1 is to be seen in the thieno[2,3-c]pyrrol-4-one moiety of position 4 instead of a cycle D for the compounds of D1 (see especially claim 2, definition of cycle D, e.g. thienyl).

4.2 Technical effect and objective problem

There is no comparative data in the present application showing that this distinguishing feature is responsible for an unexpected effect over the compounds of D1, thus the objective technical problem solved by the subject-matter of claim 1 should be seen in the provision of a further cyclic substitution at position 4 of the pyrimidine ring in order to provide alternative ERK inhibitors.

In view of the examples and the biological data given for the compound of example 1 in tables 3 and 4 it is credible that the distinguishing feature solve the above-mentioned problem.

4.3 Obviousness of the solution

There is no technical link in D2 nor in D3 which would have incited the skilled worker to consider a thieno[2,3-c]pyrrol-4-one cycle of present formula (I) as an alternative substitution for position 4 of the pyrimidine ring of the compounds of D1 if he was looking for alternative ERK inhibitors.

The subject-matter of claims 1 to 19 involves thus an inventive step.