

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/US2018/058104

International filing date (day/month/year)
30.10.2018

Priority date (day/month/year)
06.11.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/14 C07D403/14 A61P25/00 A61P37/00 A61P19/02 A61K31/506

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 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:



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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. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

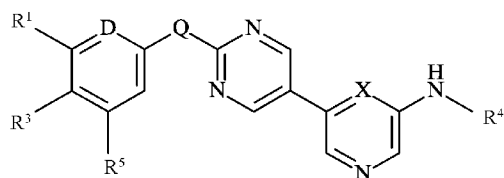
1. Statement

Novelty (N)	Yes: Claims	<u>1-27</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-27</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-27</u>
	No: Claims	

2. Citations and explanations

see separate sheet

The present application is directed towards compounds of formula I as BTK inhibitors and their use in therapy.



Formula I

Item V:

Reference is made to the following documents:

- D1 WO 2012/170976 A2 (MERCK PATENT GMBH [DE]; HODOUS BRIAN L [US]; LIU-BUJALSKI LESLEY [US];) 13 December 2012 (2012-12-13)cited in the application
- D2 WO 2014/093230 A2 (MERCK PATENT GMBH [DE]; LIU-BUJALSKI LESLEY [US]; JOHNSON THERESA L [U] 19 June 2014 (2014-06-19)
- D3 US 2015/152068 A1 (ANGST DANIELA [CH] ET AL) 4 June 2015 (2015-06-04)
- D4 ZOU YI ET AL: "Structure-based discovery of novel 4,5,6-trisubstituted pyrimidines as potent covalent Bruton's tyrosine kinase inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 26, no. 13, 7 May 2016 (2016-05-07), pages 3052-3059, XP029568924, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2016.05.014
- D5 GB 2 516 303 A (REDX PHARMA LTD [GB]) 21 January 2015 (2015-01-21)
- D6 WO 2017/059280 A1 (UNIV NORTH CAROLINA CHAPEL HILL [US]) 6 April 2017 (2017-04-06)

Preliminary note: Claims 15-19 and 25-27, which are directed towards methods of treatment by therapy, are considered to fall under the provision of Rules 39.1(iv) PCT and 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 15-19 and 25-27 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

1. Novelty

1.1. D1-D5 disclose structurally close compounds as BTK inhibitors and their use in therapy (see the passages cited in the SR). However, the compounds of D1-D2 differ in the nature and substitution pattern of the tricyclic core comprising a pyrimidine moiety.

1.2. D6 discloses compounds having a tricyclic core (the one comprising a pyrimidine moiety) similar to the one of the compounds of the invention as tyrosine kinase inhibitors and their use in therapy (see the passages cited in the SR). However, the compounds of D6 do not possess a "NH-R⁴" moiety as defined in the present invention, display a different substitution pattern on the tricyclic core, and this document is not directed towards BTK inhibitors.

1.3. Claims 1-27 thus seem to be novel (Art. 33(3) PCT).

2. Inventive step

2.1. D1 (or any of D2-D5) can be seen as the closest prior art. The compounds of the invention differ from those of the prior art in their structure, in particular in the tricyclic core comprising a pyrimidine moiety. In the absence of any demonstrated advantage / technical effect over the compounds of the prior art (no comparative data at hand), the problem to be solved is thus seen as the provision of **further BTK inhibitors** potentially useful in therapy.

2.2. The data given Tables 1 and 2 demonstrate that the underlying technical problem is solved in a credible manner by the compounds of the invention.

2.3. Although compounds having a "pyrimidine-pyrimidine-O-phenyl" core linked to a "R⁴" moiety are already known from D1 (see e.g. compound A170 on pages 144-145), there is no suggestion in the prior art that would prompt the skilled person looking for alternative BTK inhibitors to arrive at the presently claimed compounds. Indeed, the pyrimidine ring attached to the "NH-R⁴" moiety in D1 is structurally different to the one encompassed in the prior art (position the the C and N atoms), has a different substitution pattern, and D1 does not suggest to modify that ring of the core (it is not a variable). The skilled person is thus taught in D1 to "fix" that position.

Similarly, documents D2-D6 do not give any hint towards the compounds of the invention either: indeed, D2-D5 also disclose compounds having a different tricyclic core and the compounds of D6, although having a core structure similar to the one of the present compounds, have a different substitution pattern, lack the "N-R⁴" moiety and more importantly are not BTK inhibitors.

Therefore, the skilled person looking for alternative BTK inhibitors would have no pointer that would prompt him to arrive at the compounds of the invention. An inventive step is thus acknowledged (Art. 33(3) PCT).