

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/US2019/048788

International filing date (day/month/year)
29.08.2019

Priority date (day/month/year)
04.09.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4439 C07D213/00 A61P3/10 A61P9/04

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 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 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>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-17</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-17</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

The patentability of claims 7-10 is inter alia dependent upon their formulation as well as upon national and regional patent laws and no unifying criteria is provided in this field by the PCT. The assessment of their respective subject matter will be carried out based on the alleged effects of the compounds searched in the International Search Report.

1. Cited Documents

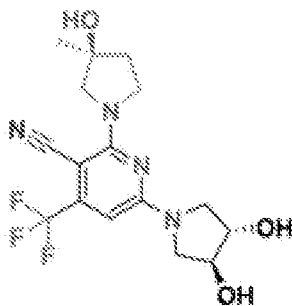
The following documents (**D**) are referred to in this Opinion; the numbering will be adhered to in the rest of the procedure:

- D1 KIM HUARD ET AL: "Discovery of Fragment-Derived Small Molecules for in Vivo Inhibition of Ketohexokinase (KHK)",
JOURNAL OF MEDICINAL CHEMISTRY,
vol. 60, no. 18, 11 September 2017 (2017-09-11), pages 7835-7849, XP055643458
- D2 MARYANOFF BRUCE E ET AL: "Inhibitors of Ketohexokinase: Discovery of Pyrimidinopyrimidines with Specific Substitution that Complements the ATP-Binding Site",
ACS MEDICINAL CHEMISTRY LETTERS, AMERICAN CHEMICAL SOCIETY, US,
vol. 2, no. 7, 14 July 2011 (2011-07-14), pages 538-543, XP008178354

Unless otherwise indicated reference is hereafter made to the passages cited in the International Search Report.

2. The prior art

D1 discloses inhibitors of KHK with a similar pharmacophore as presently claimed.



However, to arrive at the claimed compounds of formula (I) several selections have to be made.

D2 describes inhibitors of ketohexokinase being structurally different to the claimed ones.

3. Novelty (Article 33(2) PCT)

The subject matter of present claims 1-17 appears to meet the requirements of Article 33(2) PCT in view of the cited prior art at hand because no document discloses KHK inhibitors of general formula (I) or their use in the treatment of diabetes type II, heart failure, diabetic kidney disease or non-alcoholic steatohepatitis.

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

The subject matter of claims 1-17 of the present patent application appears to meet the requirements of Article 33(3) PCT because there is no teaching in the prior art as how to modify the compounds disclosed in **D1** to arrive at the claimed compounds of formula (I). A person skilled in the art would thus have no pointer when starting from **D1** as closest prior art which part of the molecule had to be modified to get the claimed compounds. Additionally, the patent application provides *in vitro* as well as *in vivo* data, which are considered as a contribution over the prior art.

5. Industrial applicability (Article 33(4) PCT)

The subject matter of claims 1-17 is industrially applicable.