

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/US2015/047415

International filing date (day/month/year)
28.08.2015

Priority date (day/month/year)
04.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/14 A61K31/4439 A61P13/10

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 66.1 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.

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NOV 24 2015

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this opinion

see form
PCT/ISA/210

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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>1-9</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-9</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-9</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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

1 Reference is made to the following documents:

D1 WO 2014/159012

D2 EP 2 564 849

D3 WO 01/47905

D4 NICHOLS, P. J.; DEMATTEI, J. A; BARNETT, B. R.; LEFUR, N. A; CHUANG, T.; PISCOPIO, A. D.; KOCK, K.: "Preparation of pyrrolidine-based PDE4 inhibitors via enantioselective conjugate addition of alpha-substituted malonates to aromatic nitroalkenes", ORG. LETT., vol. 8, no. 7, 3 April 2006 (2006-04-03), pages 1495-1498, XP002747953

2 **Item VI**

D1, published on 2 October 2014, is not taken into consideration in the present Written Opinion. However, its content could become relevant after the entrance into the European Phase if the present priority were found invalid.

3 **Item V**

3.1 Claims 5-6 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 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.

3.2 **Article 33(2) PCT**

Present claims are directed to a crystalline form of the compound (2S)-3-[(3S, 4S)-3-[(1R)-1-hydroxyethyl]-4-(4-methoxy-3-[[1-(5-methylpyridin-2-yl)-azetidin-3-yl]oxy}phenyl)-3-methylpyrrolidin-1-yl]-3-oxopropane-1,2-diol.

The crystalline form of claim 2 has been characterized by an X-ray powder diffraction pattern using CuK α radiation.

None of the cited documents discloses this compound or a crystalline form thereof.

The subject-matter of present claims 1-9 can then be considered to meet the requirements of Article 33(2) PCT.

3.3 Article 33(3) PCT

D3, which can be considered to represent the closest state of the art, discloses general pyrrolidine derivatives useful as phosphodiesterase 4 inhibitors (PDE4) in the treatment of different diseases. Overactive bladder is however not mentioned.

The problem to be solved by the present application may be regarded as the provision of further PDE4 inhibitors useful in the treatment of overactive bladder.

The compounds of D3 comprise a pyrrolidine substituted with a phenyl ring, but none of these compounds possesses the specific structure of the compound of present claim 1.

The skilled person wishing to solve the mentioned technical problem would have therefore not arrived at the present subject-matter starting from D3.

The compounds of D2 have been found useful in the treatment of diseases accompanied by urinary pain, such as interstitial cystitis/bladder pain syndrome and chronic non-bacterial prostatitis/chronic pelvic pain syndrome.

Also D2 is silent as to a possible treatment of overactive bladder.

Further to that, the compounds of D2 possess a different chemical structure in comparison with present compounds.

Accordingly, also starting from the teaching of D2, the skilled person would have not arrived at the present subject-matter.

The Applicant has shown on pages 7 and 8 that the claimed compound is a PDE4 inhibitor and that it is active in the treatment of overactive bladder.

Thus, the subject-matter of present claims 1-9 can be considered to fulfil the requirements of Article 33(3) PCT.

4 Item VIII

Although claims 1-4 and 7-9 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

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