

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/US2015/048788

International filing date (day/month/year)
08.09.2015

Priority date (day/month/year)
15.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D513/04 A61K31/547 A61P25/28

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.

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NOV 24 2015

ELI LILLY AND COMPANY
PATENT DIVISION

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Date of completion of 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>1-12</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-12</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

Re Item V

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

1 Reference to the following documents:

- D1 WO 2013/151832 A1 (LILLY CO ELI [US]) 10 October 2013 (2013-10-10)
- D2 WO 2012/098461 A1 (EISAI R&D MAN CO LTD [JP]; TAKAIHSI MAMORU [JP]; ISHIDA TASUKU [JP]) 26 July 2012 (2012-07-26)
- D3 US 2009/209755 A1 (SUZUKI YUICHI [JP] ET AL) 20 August 2009 (2009-08-20)

- 2 For the assessment of the present claims 7-8 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

3 Novelty (Article 33(1) and (2) PCT)

The present compound of formula (I) is novel over D1 compounds on account of pyrazine-2-carboxamide moiety, over D2 compounds on account of core-structure and of the substituent from position 7 and is a novel selection over the compounds of formula (I) as disclosed in D3 (see the embodiments of D3 which present the same core-structure as the present ones, but do not have the present substitution pattern from position 7-see e.g. examples 37, 46-48 83-88, 226-230). Thus, the present claimed subject-matter directed to compound of formula (I), its crystalline forms and uses appears to fulfill the requirements of Article 33(1) and (2) PCT.

4 Inventive step (Article 33(1) and (3) PCT)

The present application discloses a specific derivative of pyrrolo[3,4-d][1,3]thiazine useful to treat Alzheimer's diseases (BACE inhibitor). D1-D3 disclose all compounds having the same pharmacological use as the present ones. Considering the chemical structure of the present compound and the examples of D1 and D3 (as well as the general structures of D1 and D3), D1 appears to be the closest prior art document. Example 1 of D1 differs from the present compound only through the substitution in position 5 (pyrazide-carboxamide)-see example 1 of D1. In the absence of any data showing an improved/unexpected property for the present compound over example 1 of D1, the technical problem underlying the present application is to be seen in the provision of further pyrrolo[3,4-d][1,3]thiazine derivatives useful to treat Alzheimer's diseases. D2 discloses furo[3,4-d][1,3]thiazine derivative which presents the same substituent in position 7 as the present one. This specific substituent is also disclosed in D3 (see example 178), which moreover teaches the equivalence between pyrrolo[3,4-d][1,3]thiazine and furo[3,4-d][1,3]thiazine as core-structures. Thus, the skilled person starting from D1 and looking for a solution to solve the above-mentioned technical problem would modify in an obvious way the compounds of D1 by introducing the substituent as taught by D2.

An inventive step cannot be recognised as it is not yet shown by appropriate information, e.g. in form of experimental data, that the claimed compound (forms) have an unexpected property or improved activity over the structurally closest prior art compounds (D1-example 1), which is attributable to the distinguishing feature of the invention.

Re Item VI

Certain documents cited

D4 WO 2014/143579 A1 (LILLY CO ELI [US]) 18 September 2014
(2014-09-18)

It is pointed out that D4 could be a very relevant document in the regional phase.

Re Item VIII

Certain observations on the international application

Claims 4 and 5 make reference to Form 1 and Form 3 without any further indication what was meant by these terms. Thus, the requirements of clarity are considered as not being fulfilled.