

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2015/048807	International filing date (day/month/year) 08.09.2015	Priority date (day/month/year) 16.09.2014
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International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/542 C07D513/04 C07K16/18 A61K39/395

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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Lechner, Oskar Telephone No. +49 89 2399-0
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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 43*bis*.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 13*ter*.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 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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>1-21</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-21</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-21</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

item V

1 Reference is made to the following documents:

Reference is made to the following documents:

D1 WO 2012/021469 A1 (LILLY CO ELI [US]; LU JIRONG [US]; TANG YING [US]; DEMATTOS RONALD BRA) 16 February 2012 (2012-02-16); & CN 103 068 848 A (LILLY CO ELI) 24 April 2013 (2013-04-24)

D2 WO 2012/098213 A1 (EISAI R&D MAN CO LTD [JP]; HALL ADRIAN [GB]; FARTHING CHRISTOPHER NEIL) 26 July 2012 (2012-07-26)

D3 US 2009/209755 A1 (SUZUKI YUICHI [JP] ET AL) 20 August 2009 (2009-08-20) cited in the application ; -& JP 4 520533 B2 4 August 2010 (2010-08-04)

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

2 Novelty (Art. 33(2) PCT)

The subject matter of **claims 1-21** is novel.

3 Inventive step (Art. 33(3) PCT)

D1 may be considered to represent the closest prior art. As already indicated in the description of the present application, **D1** discloses anti-N3pGlu Abeta Ab B12L and R17L used in the treatment of Alzheimer's disease (claims 1-13).

D2 discloses BACE1 inhibitors with a similar structure to "the BACE1 inhibitor" as claimed (c.f. p 159, Tab 5).

3.1 medical use claims 1-9, 16-21

The subject matter of **claims 1, 16** differs from the closest prior art in that it claims a combination therapy of anti-N3pGlu Abeta Ab plus N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d] [1,3]thiazin-7a(4H)-yl]-4-fluorophenyl]-5-methoxy-pyrazine-2-carboxamide (= "the BACE1 inhibitor").

Example 4 discloses the synthesis of "the BACE1 inhibitor" as claimed. Example 10 discloses the IC50 of "the BACE1 inhibitor" for inhibiting BACE1.

Thus, the technical problem resides in the provision of a combination therapy for treating Alzheimer.

None of the full prior art documents discloses "the BACE1 inhibitor" structure. In addition, the application provides evidence that "the BACE1 inhibitor" is able to inhibit BACE1 (Tab 3, p 66) and to inhibit Abeta production in whole cells (Tab 5, p 69).

Consequently the subject matter of **claims 1-9, 16-21** as well as compound **claims 10-15**. Can be considered to involve an inventive step.

4 **further remarks**

4.1

The meaning of the terms used in a claim must be clear for the person skilled in the art from the wording of the claim alone. This requirement serves the overriding purpose of legal certainty. It has to be ensured that the public is not left in any doubt as to which subject matter is covered by a particular claim and which is not.

B12L, R17L as used e.g. in **claims 11, 12, 17, 18** are considered to be unclear in-house designations. In order to render the claimed subject matter clear this in house designations should be replaced by the corresponding SeqIDs.

4.2

Abbreviations used within the claims (e.g N3pGlu Abeta) should be spelled out at first occurrence, and then introduced by placing the abbreviation in parentheses after the term being abbreviated, e.g. RPE (**Art. 6 PCT, PCTGL 5.31**).

item VI

Should the priority claim be found to be not valid, **D4** would become full prior art.

D4 claims N-[3-[(4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4a,5,6,7-tetrahydropyrrolo[3,4-d] [1,3]thiazin-7a(4H)-yl]-4-fluoro-phenyl]-5-methoxy-pyrazine-2-carboxamide used for use in treating Alzheimer. Identical effects for said compounds as those disclosed in the present application are provided.