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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/040612	01.07.2016	07.07.2015

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/14 C07D471/14 A61K31/55 A61P27/16 A61P35/00

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 notifed 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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Sáez Díaz, R Telephone No. +49 89 2399-0

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. 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	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Re Item V

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

1 The present application relates to 4,4,4-trifluoro-N-((2S)-1 -((9-methoxy-3,3 -dimethyl-5 -oxo-2,3,5,6-tetrahydro-1H-benzo[f]pyrrolo[1,2-a]azepin-6-yl)arnino)-1-oxopropan-2-yl)butanamide and N-((2S)-1 -((8,8-dimethyl-6-oxo-6, 8,9,10-tetrahydro-5H-pyrido[3,2-f]pyrrolo[1,2-a]azepin-5-yl)amino)-1-oxo-propan-2-yl)-4,4,4-trifluorobutanamide, pharmaceutically acceptable salts and compositions thereof as Notch pathway signaling inhibitors for use in the treatment of cancer, sensorineural hearing loss caused by auditory hair cell loss, and for inducing auditory hair cell generation.

2 Claims 4-7 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 Reference is made to the following documents:

D1 WO 2014/039781 A1

D2 US 2013/029972 A1

D3 CATERINA FATTORUSSO ET AL: "Specific Targeting Highly Conserved Residues in the HIV-1 Reverse Transcriptase Primer Grip Region. Design, Synthesis, and Biological Evaluation of Novel, Potent, and Broad Spectrum NNRTIs with Antiviral Activity", JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 23, 2005, pages 7153-7165, XP055064516

Document D1 has been cited by the applicant in the description (Rule 5.1(a)(ii) PCT).

4 No prior art document discloses the compounds of claims 1 and 2. It is noted that the tricyclic ring system of the compound of claim 2 is novel in the prior art.

The structurally closest compound is found in document D3 (compound 20a). This prior art compound differs, however, from the compounds presently claimed through the tricyclic ring system (for e.g. pyrrole ring instead of a

pyrrolidine ring condensed to the diazepine ring). Therefore, the subject-matter of claims 1-16 is novel and meets the requirements of Article 33(2) PCT.

Document D1 describes the tricyclic compounds LY-411575, RO4929097 and YO-01027 as Notch inhibitors for use in the treatment of hearing loss (figure 10a, claims 1-15). These compounds differ from the ones presently claimed mainly through the tricyclic ring system (two phenyl rings condensed to the diazepine ring instead of the present pyrrolidine ring and phenyl/pyridine rings) (figure 10a). Therefore, the subject-matter of claims 1-16 is novel over D1.

Document D2 sets forth compound 1 as a Notch inhibitor for use in the treatment of cancer. This compound differs from the presently claimed ones mainly through the tricyclic ring system (phenyl ring instead of pyrrolidine ring condensed to the diazepine ring). Therefore, the subject-matter of claims 1-16 is novel over D2.

5 Documents D1 and D2 are considered to be the closest prior art to the subject-matter of claims 1-16 as they disclose tricyclic Notch inhibitors for use in the treatment of hearing loss and cancer, respectively (D1: figure 10a, claims 1-15; D2: claims 1-9). The main difference between the example compounds of D1 and D2 and the presently claimed compounds resides in the tricyclic ring system. The problem to be solved by the present invention may therefore be regarded as the provision of alternative tricyclic derivatives as Notch inhibitors for use in the treatment of hearing loss and cancer. The applicant has shown on tables 1-8 that the compounds of the application are Notch inhibitors useful in the treatment of hearing loss. Starting from D1 and D2, it would not be obvious for the person skilled in the art wanting to solve the above-mentioned problem to introduce multiple structural modifications (which are not taught or suggested by the prior art related to Notch inhibitors) to arrive at the structural design of the presently claimed compounds, which is therefore based on inventive ingenuity. Therefore, the subject-matter of claims 1-16 involves an inventive step within the meaning of Article 33(3) PCT.

Re Item VII

Certain defects in the international application

6 Claims 4, 9 and 13 comprise all the features of claims 5, 10 and 14, which are therefore not appropriately formulated as independent claims (Rule 6.4 PCT).