

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/US2020/063357

International filing date (day/month/year)
04.12.2020

Priority date (day/month/year)
10.12.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K51/04 A61K101/02 C07D257/08

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 <i>bis</i> .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. 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 43bis.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 43bis.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>1-9</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-9</u>
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

Re Item V

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

V.1. Subject-Matter under Rule 39.1(iv) PCT

The imaging methods of claims 8 and 9 comprise steps of introducing compounds into a mammal; this introducing may encompass methods which qualify as surgical, such as injections. Claims 8 and 9 thus relate to subject-matter considered by this Authority to be covered by the provisions of R. 39.1(iv) PCT, namely to methods for treatment of the human or animal body by surgery. No unified criteria exist in the PCT contracting states about whether such methods are patentable. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable a method for medical treatment or the use of a substance or composition in medical treatment. In the practice of the EPO, an example for an allowable claim wording would be: "a method of pretargeted imaging wherein a detectable quantity of the compound... has been introduced into a mammal, the method comprising detecting said compound...".

V.2. Documents

Reference is made to the following documents:

- D1 Outi Keinänen ET AL, ACS MEDICINAL CHEMISTRY LETTERS, vol. 7, no. 1
 (2015-12-10), pages 62-66, XP055718702
- D2 WO 2017/059397 A1 (2017-04-06)

V.3. Novelty (Art. 33(2) PCT) and Inventive Step (Art. 33(3) PCT)

V.3.1. The presently claimed subject-matter is novel.

D2 discloses compound [¹⁸F]-5 which carries a 4-methyl substituent on a tetrazine ring; the compound can undergo a cycloaddition with a TCO-moiety in the construction of biomolecule conjugates which are suitable for PET imaging (see Ex. 1 on p. 121-124, par. 346-350 and Fig. 4A and 4B). The compounds according to the present claims differ therefrom in that the tetrazine ring is unsubstituted in the 4-position.

V.3.2. The presently claimed subject-matter does not comprise an inventive step over D1 in combination with D2.

D1 explains that ^{18}F -labelled tetrazines can be reacted with TCO moieties in vivo in pretargeted imaging methods (see the abstract and the paragraph bridging p. 62 and 63). As the presently claimed compounds are not shown to be distinguished over the one of D1 by any specific technical effect, the objectively solved problem is the provision of alternative labelled tetrazine compounds for use in pretargeted imaging. As comp. $[^{18}\text{F}]$ -5 according to D2 is an ^{18}F -labelled tetrazine and furthermore is disclosed as a precursor for conjugates undergoing PET imaging, it was obvious that this compound could also be used in pretargeted imaging methods as described in D1. It was further evident that the slight modification of removing the methyl substituent of the tetrazine ring would not impede the desired functionality, so that the skilled person would have expected the presently claimed compounds as suitable solutions to the above problem.

With respect to present claims 3-5 and 9, an objection of lack of inventive step is also given due to the circumstance that the compounds as defined in these claims contain fluorine in general and thus do not show radioactivity in all embodiments. The claims thus cover compounds which are not suitable for PET imaging; the provision of such compounds must be regarded as a non-functional arbitrary modification of the prior art.

The additional features of claims 6 and 7 cannot contribute to the acknowledgement of an inventive step, because they merely refer to well-known characteristics of pharmaceutical compositions.

Re Item VI

Certain documents cited

Application No	Publication date	Filing date	Priority date
WO 2021/034924 A1	25/02/2021	19/08/2020	20/08/2019

Re Item VIII

Certain observations on the international application

The present application contains two independent claims 5 and 6 concerning compositions and two independent claims 8 and 9 concerning methods of pretargeted imaging. Furthermore, claims 5 and 6 as well as claims 8 and 9 overlap in their respective scopes. The application thus does not meet the clarity and conciseness requirements of Art. 6 PCT. If the application should enter the regional phase before the EPO, a corresponding objection under R. 43(2) EPC is to be expected.