

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/US2020/063272

International filing date (day/month/year)
04.12.2020

Priority date (day/month/year)
11.12.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61P35/00 C07D487/04 C07D498/04 A61K31/553

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:



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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>1-29</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-29</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-29</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 Rule 39 PCT

Claims 18 to 25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39(1)(iv) and Rule 67(1)(iv) PCT.

For the assessment of the present claims 18 to 25 on the question whether they are patentable, 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 patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first or further use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, and even if no opinion should be formulated with respect to the subject-matter of these claims (Article 34(4)(a)(I) PCT), this authority has decided to carry out and base the search and present opinion on the alleged effects of the compounds and/or compositions.

Reference is made to the following documents:

- D1 WO 2020/178282 A1 (ASTRAZENECA AB [SE]) 10 September 2020
(2020-09-10)cited in the application
- D2 WO 2018/206539 A1 (ASTRAZENECA AB [SE]) 15 November 2018
(2018-11-15)cited in the application
- D3 WO 2019/215203 A1 (ASTRAZENECA AB [SE]) 14 November 2019
(2019-11-14)
- D4 US 2009/318412 A1 (MATSUMOTO TAKAHIRO [JP] ET AL) 24 December
2009 (2009-12-24)

V.2 Novelty

D2 discloses compounds mainly differing from those presently claimed because of the pyrimidine ring fused to the benzoxazepine or benzodiazepine ring of D1 (present R₃

cannot form a ring together with any other adjacent substituent).

The same reasoning applies for D3's compounds.

D4 discloses compounds of a general formula (I') (claim 3) which overlaps with the present general formula. However, as D4 does not disclose any preferred subgroups or specific compounds wherein the A' ring has a cyclic substituent corresponding to the present benzothiazole or benzothiophene group (always substituted by NH₂) and at the same time the R1' group corresponds to the present C(O)CH=CHR₇ group, the present compounds may be considered to form a novel selection from the very general disclosure of D4.

D1 is an intermediate document and discloses compounds which never carry the distinguishing present -NH₂ substituted benzothiazole or benzothiophene element.

The requirements of novelty are fulfilled.

V.3 Inventive step

D2 (and/or D3) discloses compounds useful in the treatment of disorders mediated by Ras G12C mutations such as cancer (claims 10, 16). D4 relates to 5HT_{2C} receptor activators for use in the treatment of stress urinary incontinence, obesity, pelvic organ prolapse, and the like.

The technical problem underlying the present claims is that of providing compounds useful in the treatment of disorders mediated by Ras G12C mutations such as cancer. It can be seen from present tables 25 to 37 that this technical problem is solved by representative compounds of the present claims. D2 is taken as the closest prior art.

No incentive has been found in the prior art to remove the essential fused pyrimidine ring from the compounds of D2 in the expectation that the activity would be maintained. This modification along with the presence of a different bicyclic substituent (benzothiazole or benzothiophene group according to claim 1) would not be obvious without an incentive from the prior art.

The requirements of inventive step are fulfilled.

Re Item VI

Certain documents cited

The content of the PCT application D1 may be considered by the EPO authority, when entering the regional phase before the EPO, as comprised in the state of the art relevant to the question of novelty. D1 was published between the present priority and filing dates. This document discloses compounds for use in the treatment of disorders mediated by Ras G12C mutations differing from those presently claimed as stated above under novelty.

Re Item VIII

Certain observations on the international application

See remark above according to Rule 39 PCT.