

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/US2020/038617

International filing date (day/month/year)
19.06.2020

Priority date (day/month/year)
28.06.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4439 C07D405/14 A61P3/10

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>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-19</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

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

Claims 8-11 relate to a subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT.

Claims 17-19 are expressed in the so-called Swiss-type format.

The patentability of claims 8-11 and 17-19 can be dependent upon their formulation. 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.

Patentability, in particular novelty and inventive step, of claims 8-11 and 17-19 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

Reference is made to the following document:

D1 WO 2018/109607 A1 (PFIZER [US]) 21 June 2018 (2018-06-21) cited in the application

For what concerns the most important passages of the above-mentioned documents, please see citations in the international search report, unless otherwise stated.

Novelty

D1 discloses benzimidazole-based compounds of Formula I which are GLP-1 receptor agonists useful in treatment and/or prevention of cardiometabolic and associated diseases, such as Type II diabetes mellitus and hyperglycemia.

The compounds of D1 differ from the present claimed compounds on the account of the ring between the pyridine and the methylene-benzimidazole-substituted group, i.e. a six membered saturated N-heterocycle ring versus a phenyl ring.

Therefore, claims 1-19 are novel.

Inventive step

D1 discloses compounds which are structurally related to the claimed compounds for the same use and with the same mechanism of action.

As indicated above, the compounds of D1 differ from the present claimed compounds on the account of the ring between the pyridine and the methylene-benzimidazole-substituted group, i.e. a six membered saturated N-heterocycle ring versus a phenyl ring.

The present application provides *in vitro* data which show that six compounds which fall within the claimed Markus formula, *inter alia* the compounds defined in present claims 4, 5 are agonists of the human GLP-1R receptor. Furthermore, experimental evidence are provided which demonstrate the capability of three of these compounds to lower the concentration of blood glucose in mice expressing the human GLP-1R.

Therefore, the problem to be solved is seen in the provision of further GLP-1 receptor agonists, which are useful in the treatment of Type II diabetes mellitus and hyperglycemia.

There is no hint in the prior art that the structural modification of the compounds of D1 in order to arrive at the claimed compounds would have led to compounds retaining the same activity.

Therefore, an inventive step is acknowledge for the subject-matter of claims 1-19.