

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/US2023/079720

International filing date (day/month/year)
15.11.2023

Priority date (day/month/year)
16.11.2022

International Patent Classification (IPC) or both national classification and IPC
INV. A61P3/00 C07D405/06 C07D405/14 A61K31/435

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 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:



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

Koch, Kristian

Telephone No. -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 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
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>1-33</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-33</u>
Industrial applicability (IA)	Yes: Claims	<u>1-33</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

1. Claims 19-23 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. Nevertheless, the present written opinion deals with the subject-matter of claim 19-23.

2. Reference is made to the following documents:

D1 WO 2021/081207 A1 (GILEAD SCIENCES INC [US]) 29 April 2021
(2021-04-29)cited in the application

D2 WO 2022/225941 A1 (GILEAD SCIENCES INC [US]) 27 October 2022
(2022-10-27)cited in the application

3. Novelty

D1 discloses compounds of formulae (I-A-1), (Ib), and (Ic) and examples such as example 345 (page 520), example 831 (page 693) and example 852 (page 707) having activity as GLP-1R modulators for the treatment of type 2 diabetes. The examples of D1 differ from the compounds of present generic formula on account of the combination of present groups R3 and R4. The compounds of the generic formulae of claim 1 may be considered to form a novel selection from the general disclosure of D1, wherein the combination of the benzimidazole ring with the specific lists of substituents R3, R4, and R5 establishes novelty over D1.

D2 discloses compounds of formula (I) and examples such as 143, 149, and 154 (table 2) having activity as GLP-1R modulators for the treatment of type 2 diabetes. The examples of D2 differ from compounds of the present generic formulae of claim 1 at last on account of the present group R3. The compounds of the generic formulae of claim 1 may be considered to form a novel selection from the general disclosure of D2, wherein the combination of the benzimidazole ring with the specific lists of substituents R3 and R4 establishes novelty over D1.

Thus, the subject-matter of claims 1-33 appears to be novel and fulfils the requirements of Article 33(2) PCT.

4. Inventive step

The current application is directed to compounds of formula (I) which are GLP-1R modulators and can be used for the treatment of diabetes 2, obesity, and hyperglycemia.

D1 discloses compounds for the same purpose and a generic overlap exists between the present generic formula and formula (I-A-1) of D1 when in D1 e.g. R1 = heteroaryl, Y = O, A = heteroaryl substituted with Z1a = halogen, B = aryl substituted with R4 = halogen, V = -C(R6b)(R6c)- wherein R6b = R6b = hydrogen, R2 = alkyl substituted with Z1 = heterocyclyl, R3 = -C(O)OR3a wherein R3a = hydrogen, X1 = X2 = X3 = carbon wherein X1 is substituted with R8 = -O(C1-9alkyl).

Thus, the objective technical problem to be solved is the provision of compounds having improved activity as modulators of GLP-1R for the treatment of diabetes 2, obesity, and hyperglycemia.

A solution to this problem can only be shown by empirical comparative data between compounds of the current application and the closest prior art. There are, however, no comparative data or any other relevant information supporting one or more improved effect(s) associated with compounds of formula (I) of the current application over D1.

In order to show any such improvement and unexpected effect vis-à-vis the said prior art any comparative test must be performed using compounds with the maximum structural similarity, i.e. at least as close as example 345 (see page 520) and example 831 (see page 693) of D1 compared to present example 2 (see page 31).

The initial technical problem is not solved and it must be reformulated into a less ambitious problem, namely the mere provision of alternative compounds having activity as modulators of GLP-1R for the treatment of diabetes 2, obesity, and hyperglycemia.

The skilled person knows that compounds of D1 have the wanted activity and must just select some of these compounds to solve the problem. An arbitrary selection from a group of equally suitable candidates cannot be viewed as involving an inventive step.

Thus, the subject-matter of claims 1-33 does not involve an inventive step and fails to fulfil the requirements of Article 33(3) PCT.