

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/IB2024/053239

International filing date (day/month/year)
03.04.2024

Priority date (day/month/year)
06.04.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07D231/56 C07D403/10 C07D405/04 C07D409/10 C07D417/10 C07D471/04 A61P37/00 A61P29/00
A61P1/00 A61K31/416

Applicant
PFIZER INC.

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

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 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.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. 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 43*bis*.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 43*bis*.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>1-26</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-26</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-26</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

1. Claims 21-25 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/ 67.1(iv) PCT. For the assessment of the present claims 21-25 on the question whether it is patentable, no unified criteria exist in the PCT Contracting States. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a known compound for first or further medical treatment.

2. Reference is made to the following documents:

- D1 WO 2020/142547 A1 (UNIV LELAND STANFORD JUNIOR [US]) 9 July 2020 (2020-07-09)
- D2 JOUNGMOK KIM ET AL: "AMPK activators: mechanisms of action and physiological activities",
EXPERIMENTAL & MOLECULAR MEDICINE, vol. 48, 1 January 2016,
pages e224-1, XP055723561,
DOI: 10.1038/emm.2016.16

3. The present application is directed to indole or indazole derivatives of formula (I) as defined in current claim 1. These compounds are AMPK activators useful in the treatment of inflammatory, autoimmune and gastrointestinal disorders.

D1 and D2 are related to the same technical field of AMPK activators:

D2 is a review disclosing AMPK activators which have a structure completely different from for the claimed indole or indazole compounds.

Claim 23 of D1 discloses indole derivatives as AMPK activators, however their ring A is a heteroaryl ring instead of present R4-para substituted phenyl ring and their indole ring is not substituted in the 3-position with a propionic acid moiety.

Since the compounds of claim 1 are novel over D1-D2, the subject-matter of claims 2-26 comprising the novel compounds is also considered to be novel.

The requirements of Art.33(2) PCT appear to be met for claims 1-26.

4. The present application is directed to indole or indazole derivatives of formula (I) as defined in current claim 1. These compounds are AMPK activators useful in the treatment of inflammatory, autoimmune and gastrointestinal disorders.

D1, related to the same technical field of AMPK activators, is considered to represent the closest prior art document.

Due to the structural differences re the active compounds in D1 (the missing propionic acid moiety, the missing R4-para-substituted phenyl ring) it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing further novel compounds acting as AMPK activators, would have been unambiguously led to prepare the compounds of the present application.

The proposed solution in current claim 1 is therefore not considered to be obviously derivable from the prior art.

It was shown in Table 2 of the present application that a representative set of illustrative compounds of formula (I) indeed provides the desired activity.

Thus, an inventive step according to Art.33(3) PCT can be recognized for the subject-matter of claims 1-26 based on the surprising AMPK activator activity of the compounds (I) as defined in claim 1.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date (day/month/ year)	Filing date (day/month/ year)	Priority date(valid claim) (day/month/year)
WO 2023/147312 A1	03-08-2023	24-01-23	25-01-2022

This document is also related to indole compounds as AMPK activators, however they differ from those claimed mainly on account of the absence of the propionic acid moiety.

This intermediate document is not taken into account in this written opinion accompanying the International search report. It should nevertheless be noticed that the extensive examination of this document, on the question whether it constitutes prior art or not, will depend essentially on the analysis of the claimed priority rights of the present application and will only be performed in the regional European proceedings to come.

Re Item VIII

Certain observations on the international application

There is a discrepancy between the claims and the description since it is stated in the description, p.5, I.13-15, p.26, I.20 and p.23, I.24 that prodrugs are included within the scope of the invention. The same objection is raised for the statement on p.24, I.25, wherein metabolites are indicated to be encompassed within the invention.

The embodiments disclosed in p.97-104 are claim-like clauses may lead to unclarity as to the actual scope of protection.

Prior art documents were acknowledged on p.105, I.3-7 by the expression "incorporated herein by reference". It is vague and ambiguous which technical features are referred to. Furthermore, it should be noted that this kind of reference contravenes the basic requirement of each application that the invention must be comprehensible from the specification by itself.

The vague and imprecise statement in the description on page 104, I.35-p.105, I.2 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.