

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/IB2022/061495

International filing date (day/month/year)
28.11.2022

Priority date (day/month/year)
01.12.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C07D333/70 C07D307/85 C07D409/04 A61K31/381 A61K31/343 A61K31/352 A61P3/10 A61P9/04
A61P13/12 A61P1/16

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 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:



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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. V Reasoned statement under Rule 43*bis*.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>1-32</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-32</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-32</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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 under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are cited in the present International Search Report:

- D1 SHIH-CHIA TSO ET AL: "Benzothiophene Carboxylate Derivatives as NoAllosteric Inhibitors of Branched-chain alpha-Ketoacid Dehydrogenase Kinase", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 289, no. 30, 3 June 2014 (2014-06-03), pages 20583-20593, XP055719590, US; ISSN: 0021-9258, DOI: 10.1074/jbc.M114.569251

The present claims 14 to 21 relate to and/or encompass methods of medical treatment and/or medical or diagnostic uses, which are 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 does not recognise as patentable, claims directed to methods of medical treatment or medical uses, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

With entry into the regional phase before the EPO the present claims 14 to 21 must be deleted or rephrased into an allowable form (e.g. "*The compound of claim 1 for use in a method of treatment of ...*").

Novelty (Article 33(2) PCT)

The present compounds differ from the compounds in D1 in the substituent A (page 20587, figure 1, compounds BT2 and BT2F), i.e. in the phenyl or fused phenyl substituent at 3-position of the benzothiophene.

The claimed matter is novel.

Inventive Step (Article 33(3) PCT)

D1 discloses halo-substituted benzothiophene-2-carboxylic acid derivatives as allosteric inhibitors of branched-chain alpha-ketoacid dehydrogenase kinase for the treatment of e.g. diabetes (page 20587 to page 20590, figures 1 to 5, compounds BT2 and BT2F).

D1 is the closest prior art.

The problem of the invention was the provision of new branched-chain alpha keto acid dehydrogenase kinase inhibitors for the treatment of e.g. diabetes, kidney disease, NASH and heart failure.

The present description discloses the synthesis and characterisation of exemplary compounds as well as pharmacological data thereof (e.g. page 87 to page 202; examples 1 to 159; tables 1 to 3 and 4a to 4c; figures 1/3 to 3/3).

The problem seems to have been solved over the whole of the claimed scope.

D1 does not disclose or suggest any benzothiophene-2-carboxylic acid derivatives substituted at 3-position by a phenyl group or a fused phenyl group.

The claimed matter is based on an inventive step.

Re Item VII

Certain defects in the international application

Description

Some parts of the description refer to methods of medical treatment or medical uses as part of the claimed invention (e.g. page 4, line 1; page 5, line 9; page 9, line 12 to page 10, line 20; page 35, line 2).

Some parts of the description refer to structurally undefined "*prodrugs*" as part of the claimed invention (e.g. page 7, line 27; page 12, lines 34 and 36; page 15, line 26).

Some parts of the description refer to structurally undefined "*metabolites*" as part of the claimed invention (e.g. page 15, line 25).

The description contains irrelevant expressions, like e.g.:

- "... *incorporated by reference* ..." (e.g. page 52, line 30; page 53, line 1; page 202, line 4),
- "*It is to be understood that this invention is not limited to specific synthetic methods of making that may of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.*" (e.g. page 6, lines 11 to 14) or
- "*Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application for all purposes.*"

It will be apparent to those skilled in the art that various modifications and variations can be made without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims." (e.g. page 202, lines 3 to 11).

With entry into the regional phase before the EPO this deficiencies should be fixed by deleting said references to methods of medical treatment, "*prodrugs*" and "*metabolites*", and irrelevant expressions.

Re Item VIII

Certain observations on the international application

Lack of Clarity (Article 6 PCT)

The present claim 1 seems to be fully encompassed by the present claim 2.

With entry into the regional phase before the EPO the present claim 2 should be made the new claim 1 and the present claim 1 should be made the new claim 2 containing a reference to new claim 1.

Claims 8 to 13, 30 and 32 lack a reference to claims 1 and 2.

With entry into the regional phase before the EPO the lacking reference should be included into these claims.