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/220 (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/IB2021/057281

International filing date (day/month/year)
06.08.2021

Priority date (day/month/year)
03.09.2020

International Patent Classification (IPC) or both national classification and IPC
INV. C07D207/267 C07D403/12 C07D403/14 A61P31/14 C07D401/12 C07D497/04 A61K31/4015 A61K31/4025

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/220

Authorized Officer
Schuemacher, Anne
Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)
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 1-30
   No: Claims

   Inventive step (IS)  
   Yes: Claims 2-16
   No: Claims 1, 17-30

   Industrial applicability (IA)  
   Yes: Claims 1-30
   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. 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
Re Item V

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

1. Claims 19-30 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 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 ZHAI YANGYANG ET AL: "Cyanohydrin as an Anchoring Group for Potent and Selective Inhibitors of Enterovirus 71 3C Protease", JOURNAL OF MEDICINAL CHEMISTRY, vol. 58, no. 23, 10 December 2015 , p. 9414-9420, XP055841288, ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.5b01013, Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/acs.jmedchem.5b01013

D2 WANG YAXIN ET AL: "Inhibition of enterovirus 71 replication by an [alpha]-hydroxy-nitrile derivative NK-1.9k", ANTIVIRAL RESEARCH, vol. 141, 5 January 2017 (2017-01-05), pages 91-100, XP029949620, ISSN: 0166-3542, DOI: 10.1016/J.ANTIVIRAL.2017.01.002


3. The present application is directed to compounds of formula I" characterized by a N-[1-cyano-2-(2-oxopyrrolidin-3-yl)ethyl]carboxamide moiety as antiviral agents for the treatment of coronavirus such as CoVid-19.

D1, D2 and D4 are related to the same technical filed; however the compounds of D1 and D2 (compound 8 in table 1 of D1 and compound 1 in Table 1 of D2) differ only from the compounds I" claimed because of the para-fluoro-benzyl group not encompassed into the present definition of R1. The anti-coronavirus compound of D4 differ mainly form those of formula I" on account of the missing cyano group.

Thus, the compounds of claim 1 being novel, the subject-matter of claims 1-30 is considered to be novel. The requirements of Art.33(2) PCT are considered to be met.
4. D4 could be considered to represent the closest prior art document. The compounds of claims 10-13 of D4 are the structurally closest to example 4 of present application differing only on account of the replacement of the 2-oxo-ethanol group by a cyano group.

As this difference does not result in any additional technical effect, the objective technical problem to be solved by the present application may be seen in the provision of alternative compounds to those disclosed in D4.

D2 suggests to modify this specific position in the antivirus agents (see table 1 of D2) and cyano derivative in table 1 of D2 seems to be exhibit to a certain extend an enzyme inhibitory activity. Thus, the skilled person would be prompted to modify the compounds of D4 by replacing the 2-oxo-ethyl-X group by a cyano moiety and expect to obtain further compounds active against coronavirus.

The compounds of formula I” current claim 1 appears therefore obviously derivable from the teaching of D4 combined with D2. Thus the subject-matter of claim 1 and of the claims dependent thereon is not considered to meet the requirements of Art.33(3) PCT.

However the specific compounds of current claims 2-16, characterized by the pyrrolidine or piperidine ring formed by R1 and R2 taken together with the nitrogen and the carbon atoms to which they are attached, have a structure which is not suggested in any documents D1, D2 or D4.

It was shown in the present application that said compounds provide the desired activity.

Thus, an inventive step under Art.33(3) PCT can be recognized for the subject-matter of claims 2-16 and of the claims dependent thereon based on their unexpected antiviral activity.

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**Re Item VI**

**Certain documents cited**

**Certain published documents**

<table>
<thead>
<tr>
<th>Application No</th>
<th>Publication date</th>
<th>Filing date</th>
<th>Priority date (valid claim)</th>
</tr>
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<tbody>
<tr>
<td>XP055847761</td>
<td>10.05.2021</td>
<td></td>
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</tbody>
</table>
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.

This document discloses PF-07321332 a potent anti-coronavirus agent.

**Re Item VII**

**Certain defects in the international application**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D2 and D4 is not mentioned in the description, nor is this document identified therein.