

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/US2020/046116

International filing date (day/month/year)
13.08.2020

Priority date (day/month/year)
14.08.2019

International Patent Classification (IPC) or both national classification and IPC

INV. C07D207/08 C07D207/09 C07D213/61 C07D213/62 C07D213/70 C07D213/74 C07D231/20 C07D401/04
C07D401/14 C07D513/22

Applicant

VERTEX PHARMACEUTICALS INCORPORATED

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 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. 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 43bis.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 43bis.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>1-36</u>
	No: Claims	<u>37</u>
Inventive step (IS)	Yes: Claims	<u>1-36</u>
	No: Claims	<u>37</u>
Industrial applicability (IA)	Yes: Claims	<u>1-37</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

Re Item V

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

- 1 The present application relates to a process for the preparation of compound I. Compound I is a modulator of cystic fibrosis transmembrane conductance regulator (CFTR) and as such useful in the treatment of cystic fibrosis.
- 2 Reference is made to the following documents:
- D1 NEWKOME G.R. ET AL: "Nicotinic Acid Crown Ethers. Synthesis, Reactions, and Complexation of Nicotinonitrile macrocycles", JOURNAL OF ORGANIC CHEMISTRY, vol. 44, no. 15, 1 January 1979, pages 2639-2697, XP55732460,
- D2 REWCASTLE G W ET AL: "TYROSINE KINASE INHIBITORS. 10. ISOMERIC 4-Ú(3-BROMOPHENYL)AMINO3?4 PYRIDOÚD3?4-PYRIMIDINES ARE POTENT ATP BINDING SITE INHIBITORS OF THETYROSINE KINASE FUNCTION OF THE EPIDERMAL GROWTH FACTOR RECEPTOR", JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, no. 9, 26 April 1996, pages 1823-1835, XP000671261
- D3 ARTEM YU. CHEREPAKHA ET AL: "Hetaryl Bromides Bearing the SO₂F Group - Versatile Substrates for Palladium-Catalyzed C-C Coupling Reactions", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2018, no. 47, 19 December 2018, pages 6682-6692, XP0055733124
- D4 NISHIDA HARUYUKI ET AL: "Exploration of pyrrole derivatives to find an effective potassium-competitive acid blocker with moderately long-lasting suppression of gastric acid secretion", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 25, no. 13, 27 April 2017, pages 3447-3460, XP085037327
- D5 PRASHANTHA GUNAGA ET AL: "Selective I Kur Inhibitors for the Potential Treatment of Atrial Fibrillation: Optimization of the Phenyl Quinazoline Series Leading to Clinical Candidate 5-[5-Phenyl-4-

(pyridin-2-ylmethylamino)quinazolin-2-yl]pyridine-3-sulfonamide",
JOURNAL OF MEDICINAL CHEMISTRY, vol. 60, no. 9, 28 April
2017, pages 3795-3803, XP055733118

D6 WO 2019/195739 A1 (ABELA ALEXANDER RUSSELL ET AL) 10
October 2019

D7 WO 2019/200246 A1 (ABELA ALEXANDER RUSSELL ET AL) 17
October 2019

D8 US 2018/162839 A1

D9 WO 2019/161078 A1 (VERTEX PHARMA [US]) 22 August 2019

D10 WO 2020/102346 A1 (VERTEX PHARMA [US]) 22 May 2020

Documents D6, D7, D9 and D10 were published after the priority date. In the
presumption the priority is valid these documents are not regarded as prior art.

3 Novelty

Document D1 discloses a compound of formula VII.

Document D2 discloses a compound of formula VII.

Document D3 discloses a compound of formula V.

Document D4 discloses a compound of formula V.

Document D5 discloses a compound of formula V.

It is noted that document D6 discloses a compound of formula VII.

It is noted that document D7 discloses a compound of formula VII.

Document D8 discloses modulators of cystic fibrosis transmembrane
conductance regulator differing from compound I in that they do not have a
macrocyclic structure.

It is noted that document D9 discloses the synthesis of compound I by closing
the bond between the pyrrolidine ring and the pyridine ring as the last step.

It is noted that document D10 discloses the synthesis of compound I by closing
the bond between the pyrrolidine ring and the pyridine ring as the last step.

Compound I is not disclosed in the cited prior art. A method for the preparation
of compound I is novel by consequence.

Claims 1-36 therefore fulfil the requirements of Art 33(2) PCT.

Compounds of formula V and VII are disclosed in documents D1-D5. Claim 37 therefore does not fulfil the requirements of Art 33(2) PCT.

4 Inventive step

Starting from document D8 the problem to be solved by the present application may be regarded to be the provision of a further modulator of CFTR. The solution of the applicant resides in compound I. The applicant shows in paragraph [0009] that compound I is indeed a modulator of CFTR. As the structural modifications have not been made obvious by the cited prior art the solution of the applicant may be regarded to involve an inventive step. A method for the preparation of compound I is inventive by consequence. Claims 1-36 therefore fulfil the requirements of Art 33(3) PCT.

Re Item VI

Certain documents cited

WO 2019/195739 A1

WO 2019/200246 A1

WO 2019/161078 A1

WO 2020/102346 A1