

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/US2020/032832

International filing date (day/month/year)
14.05.2020

Priority date (day/month/year)
14.05.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D231/56 C07D487/04 C07D498/18 C07D513/04 A61P11/00 A61P1/16 A61K31/4162 A61K31/429

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 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

Gavriliu, Daniela
Telephone No. +49 89 2399-0



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:
 - ☐ 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>5, 6, 9-11, 13-54</u>
	No: Claims	<u>1-4, 7, 8, 12</u>
Inventive step (IS)	Yes: Claims	<u>5, 6, 9-11, 13-54</u>
	No: Claims	<u>1-4, 7, 8, 12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-54</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 Reference is made to the following documents:

- D1 MARIA LUISA SACCARELLO ET AL: "A New Synthesis of 1-Alkyl-3-aminoindoles", SYNTHESIS, vol. 1979, no. 09, 1 January 1979 (1979-01-01), pages 727-729, XP055674059, STUTTGART, DE. ISSN: 0039-7881, DOI: 10.1055/s-1979-28816
- D2 EP 0 465 398 A2 (LUNDBECK & CO AS H [DK]) 8 January 1992 (1992-01-08)
- D3 Thomas Balle ET AL: "Synthesis and structure-affinity relationship investigations of 5-aminomethyl and 5-carbamoyl analogues of the antipsychotic sertindole. A new class of selective .alpha.1 adrenoceptor antagonists", Bioorganic & Medicinal Chemistry (2003), 11(6), 1065-1078 CODEN: BMECEP; ISSN: 0968-0896, 1 January 2003 (2003-01-01), pages 1065-1078, XP055740784, Retrieved from the Internet: URL:10.1016/S0968-0896(02)00459-5 [retrieved on 2020-10-16]
- D4 WEN WANDONG ET AL: "Substituted indoles as selective protease activated receptor 4 (PAR-4) antagonists: Discovery and SAR of ML354", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM,NL, vol. 24, no. 19, 15 August 2014 (2014-08-15), pages 4708-4713, XP029064429, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2014.08.021
- D5 US 2016/083363 A1 (HAMM HEIDI E [US] ET AL) 24 March 2016 (2016-03-24)
- D6 JAYANTA GHORAI ET AL: "Cobalt(III)-Catalyzed Intramolecular Cross-Dehydrogenative C-H/X-H Coupling: Efficient Synthesis of Indoles and Benzofurans", CHEMISTRY - A EUROPEAN JOURNAL, vol. 22, no. 45, 30 September 2016 (2016-09-30), pages 16042-16046, XP055740819, DE ISSN: 0947-6539, DOI: 10.1002/chem.201604111

- D7 WO 2017/197240 A1 (UNIV MICHIGAN REGENTS [US]) 16 November 2017 (2017-11-16)
- D8 JAYANTA GHORAI ET AL: "Divergent Functionalization of N - Alkyl-2-alkenylanilines: Efficient Synthesis of Substituted Indoles and Quinolines", CHEMISTRY - AN ASIAN JOURNAL, vol. 13, no. 17, 10 June 2018 (2018-06-10), pages 2499-2504, XP055740833, ISSN: 1861-4728, DOI: 10.1002/asia.201800441
- D9 SAGER J. GOSAI ET AL: "Automated High-Content Live Animal Drug Screening Using C. elegans Expressing the Aggregation Prone Serpin [alpha]1-antitrypsin Z", PLOS ONE, vol. 5, no. 11, 12 November 2010 (2010-11-12), page e15460, XP055662681, DOI: 10.1371/journal.pone.0015460

- 2 For the assessment of the present claims 43-46 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

3 **Independent claims**

- compounds of formula (I)(claim 1)
- specific embodiments (claim 11)
- compounds of formula (I')(claim 12)
- specific crystalline and amorphous forms (claims 13-36)
- solid dispersions of compound 33 (claims 36-41)
- their pharmaceutical compositions (claim 42)
- their second medical use (claim 43)
- method of preparing of compound 33 (claim 47)
- specific intermediates (claim 53)

-spray- dried amorphous (claim 54)

4 Novelty (Article 33(1) and (2) PCT)

The compounds of current independent claims 1 and 12 do not fulfill the requirements of Article 33(2) PCT since documents D1-D8 disclose embodiments which are novelty destroying for the subject-matter claimed by these claims (see the citations given in the international search report).

The compounds claimed by current claims 5, 6, 9-11 as well their pharmaceutical compositions, solid forms and uses appear to fulfill the novelty requirements. The same applies for the specific intermediates of claim 53 (this could however be reconsidered at the regional phase in view of D10 disclosure).

5 Inventive step (Article 33(1) and (3) PCT)

D9 could be considered as being the closest prior art since it discloses compound SB206553 which is potentially useful to treat diseases connected to the modulation of alpha-1 antitrypsin. This compound differs from the ones claimed by current claim 5 mainly to the fact that it does not contain any substituent in the position corresponding to the present substituent R1 and from those of claims 6, 9-11 mainly on account of the specific definitions of Z1 to Z3.

In the absence of comparative data, the technical problem underlying the present application is to be seen in the provision of further tricyclic condensed pyrroles useful to treat diseases connected to the modulation of alpha-1 antitrypsin. The skilled person starting from D9 would not arrive in an obvious way at the present compounds claimed by claims 5, 6, 9-11 with the expectation to have the claimed activity as supported by the data provided in table 22 of the application. However, in view of the vary different definitions for the substituents Z1-Z3, X1, X2 and R1 to R3 provided in claims 5-6, it is not credible that all the alternatives covered by these claims would possess the claimed activity. The subject-matter of claim 9 appears to be a fair generalisation over the examples provided in the application. With respect to the subject-matter of current claim 53, an inventive step could be acknowledged only for the intermediates which contain the technical feature on which an inventive step was acknowledged for the end-compounds. This appears not to be the case for several of the intermediates claimed by claim 53.

Re Item VI

Certain documents cited

D10 WO 2020/081257 A1 (VERTEX PHARMA [US]) 23 April 2020
(2020-04-23)

D10 could become a very relevant document for assessing novelty and eventually inventive step (in the case of not entitlement to the claimed priority) in the regional phase.

Re Item VIII

Certain observations on the international application

1. The proviso for the definitions of Z1 to Z2 in combination with the definitions of a potential R3 appears to be unclear (the presence of R3 appears not to be possible in view of the definitions provided for the free valances)
2. Current claims 13 to 36 are not clear since the skilled person would not know what is meant by Form A to C.
3. Claims 13 to 35 directed to forms of compound 33 should be dependent on claim 11, since this compound is an embodiment covered by independent claim 11.