

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/US2023/032282

International filing date (day/month/year)
08.09.2023

Priority date (day/month/year)
09.09.2022

International Patent Classification (IPC) or both national classification and IPC
INV. C07D405/04 C07D487/04 A61P11/00 A61K31/4162 A61P1/16

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:



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

Schuemacher, Anne

Telephone No. -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 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>1-24</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-24</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-24</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

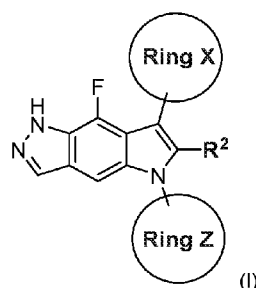
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Claims 15 and 22 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 15 and 22 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.

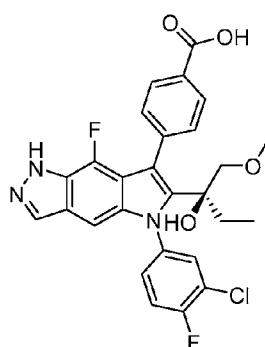
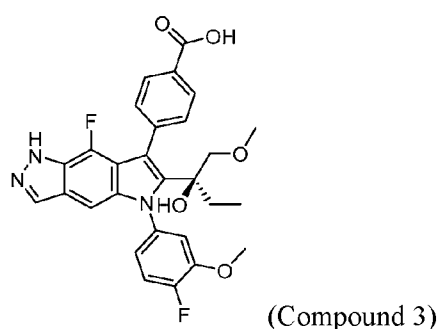
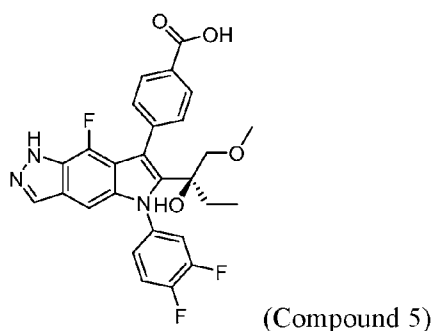
2. Reference is made to the following document:

D1 WO 2020/247160 A1 (VERTEX PHARMA [US]) 10 December 2020, cited in the application

3. The present application is directed to compounds of formula (I),



as well as to three specific compounds (compound 3, 4 and 5) in a crystalline form,



to the process for its preparation, to the pharmaceutical composition comprising the compounds (I), compounds 3, 4 and 5 and to their use as modulators of alpha-1 antitrypsin (ATT).

The compounds (I) and the compounds 3, 4 and 5 are characterized by the 8-Fluoro atom on the pyrrolo[2,3-f]indazole ring structure and the -OH present in the R2 group.

The presently claimed compounds (I) and compounds 3, 4 and 5 are encompassed within the generic disclosure (claim 1) of D1. However D1 does not disclose any example which falls under the scope of formula (I) of current claim 1. The new structural elements which distinguish the subject matter claimed from the prior art in the sense of a novel selection are the 8-Fluoro atom on the pyrrolo[2,3-f]indazole ring structure and the -OH present in the R2 group.

Thus, the subject-matter of claims 1-24 is considered to be novel over D1 (Art.33(2) PCT).

4. The subject-matter of claim 1 can be considered as a selection of a formula (I) from the compounds of formula (I) disclosed in document D1 for the same use. Such a selection can only be regarded as inventive if the presently claimed compounds present unexpected effects or properties in relation to the rest of compounds.

It was shown in [0326] of the present application that the claimed compounds 1-5 exhibit enhanced human exposure multiple value (EM) when compared to the structurally closest compounds of D2 differing only because of the 8-H atom on the pyrrolo[2,3-f]indazole ring.

Thus, the objective technical problem to be solved by the present application may be seen in the provision of improved ATT modulators.

The solution proposed in the present claims are compounds of formula (I) of claim 1, characterized by the 8-Fluoro atom on the pyrrolo[2,3-f]indazole ring structure and the -OH present in the R2 group .

Starting from D1, the skilled person would not be prompted to prepare the presently claimed compounds (I) with a reasonable expectation to get ATT modulators with enhanced EM.

it appears credible that the unexpected technical effect occurs over the whole claimed range of formula (I) as defined in claim 1.

Thus, an inventive step according to Art.33(3) PCT could be acknowledged for the subject-matter of claims 1-24 based on the surprising enhanced activity of the compounds (I) of claim 1, such as the specific compounds 3,4 and 5 of claims 16, 17 and 18.

Re Item VII

Certain defects in the international application

The statement in the description on page 233 [00441] 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.

Prior art documents were acknowledged on p.1 [0001] 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 embodiments disclosed in [00208] are claim-like clauses. This leads to a discrepancy between the claims and the description and as to the actual scope of protection (Art. 6PCT).

Re Item VIII

Certain observations on the international application

Claims 16-18 are formulated as independent claims. however they are directed to compounds 3, 4 and 5 which are preferred embodiments of the compounds of formula (I) as defined in claim 1. These claims 16-18 are therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

The relative term "substantially" employed in claims 16-22 has no well recognized meaning and renders unclear the meaning of the technical feature to which it refer, thereby rendering the subject matter for which protection is sought unclear (Art. 6 PCT).The fact that there is an explicit disclosure of the meaning of such term in [00181] of the description is not sufficient since the claims have to be clear in themselves.