

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/US2019/038889	International filing date (day/month/year) 25.06.2019	Priority date (day/month/year) 27.06.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07D487/04 C07D491/04 C07D495/04 C07D519/00 A61P25/00 A61P25/14 A61P25/28 A61K31/4985 A61K31/5025		
Applicant PTC THERAPEUTICS, 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:  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 Brandstetter, T Telephone No. +49 89 2399-0	
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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:
 - ☐ 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 13*ter*.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 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.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 43*bis*.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 43*bis*.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>2, 6-17</u>
	No: Claims	<u>1, 3-5</u>
Inventive step (IS)	Yes: Claims	<u>6, 7, 17</u>
	No: Claims	<u>1-5, 8-16</u>
Industrial applicability (IA)	Yes: Claims	<u>1-17</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

- 1 Reference is made to the following documents:
- D1 WO 2018/081091 A1 (2018-05-03)
 - D2 WO 2017/023987 A1 (2017-02-09)
 - D3 Abdul Khader, K. K. et al., Tetrahedron Lett., 55 (10), 2014 , pages 1778-1783
 - D4 Ingo Knepper et al., Tetrahedron, 67 (29), 2011), pages 5293-5303
 - D5 Mariusz Mojzych et al., Bioorg. Med. Chem. Lett., 22 (23), 2014, pages 6616-6624
 - D6 US 2014/121197 A1 (2014-05-01)
 - D7 WO 2007/133756 A2 (2007-11-22)
 - D8 EP 2 841 428 A1 (2015-03-04)
 - D9 WO 2017/210134 A1 (2017-12-07)
 - D10 WO 2017/100726 A1 (2017-06-15), cited in the application
 - D11 WO 2018/218133 A1 (2018-11-29)

Re Item V

- 2 Claims 8-11 and 14-15 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 recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.
- Authorities other than the EPO, for example the USPTO might accept such claims as patentable.
- 3 Novelty (Article 33(2) PCT)
- 3.1 The application is interpreted as referring to compounds of formula I (claim 19, specific compounds (claim 6), their medical use in the treatment of Huntington's disease (claims 8, 10, 14, 16 and 17) and their use in a preparation process (claim 12).

- 3.2 D1 discloses compounds of formula I and salts thereof (claim 1) and their medical use (claim 16). Specific compounds falling at least within the scope of present claim 1 have also been disclosed in D1 (claim 14, examples 18-28, compounds 65-118 in table on page 110, ff).
- D2 (5-(1-methyl-1*H*-pyrazol-4-yl)-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[3,4-*b*]pyridine on page 147) D3 (compound 3k), D4 (compound 14, page 6618), D5 (compounds 13b, 16c, 16d) disclose compounds which fall within the scope of claims 1, 4, and/or 5.
- D6 discloses compounds (claim 4) and their medical use (claim 19). The compounds of D6 and the compounds of present claim 1 exhibit a certain overlap. A specific compound falling within this overlapping area and within the scope of claims 1, 3 and 5 has also been disclosed in D6 (example 73).
- D7 discloses compounds and salts thereof (claim 3) and their medical use (claim 5). Some of the compounds of D7 fall within the scope of claims 1, 3 and 5 (table I: compounds 8, 27, 82, 98, 183, 185, 190, 203, 229, 239, 265, 348, 384, 403, 517 and 556).
- D8 discloses compounds of formula I (claim 1) and their medical use (claim 24). The compounds of D8 and the compounds of present claim 1 exhibit a certain overlap. Specific compounds falling within this overlapping area and within the scope of claims 1, 3 and 5 have also been disclosed in D8 (claim 17: compounds 82, 83, 141, 145, 151, 155, 171, etc). It is noted that these compounds are compounds of present formula I wherein R² is substituted with R⁵, R⁵ is C₁₋₆alkyl-amino wherein C₁₋₆alkyl in turn is substituted (cf. definition of C₁₋₆alkyl on page 69, lines 1-3).
- D9 discloses compounds (claim 1) and their medical use (claim 35). The compounds of D9 and the compounds of present claim 1 exhibit a certain overlap. Specific compounds falling within this overlapping area and within the scope of claims 1 and 5 have also been disclosed in D9 (last compound on page 154 and all compounds on page 155).
- At least the subject-matter of claims 1 and 3-5 is therefore not new.
- 4 Inventive step (Article 33(3) PCT)
- 4.1 The claims contain open-ended definitions such as alkyl, aryl, heterocyclyl, heteroaryl etc. which embrace virtually any imaginable substituents on said alkyl, heterocyclyl, aryl, heteroaryl etc. groups (see in particular definitions on pages 68-74). By this authority, it is considered inherently unlikely that

substantially all compounds falling under a claim comprising an open-ended definition of a structural feature (here: substituted with any substituent) would exhibit a particular desired biological activity. The claims are therefore likely to embrace subject matter which will not represent any solution to the relevant problem underlying the present application. Merely as a solution to the problem of providing new compounds, the subject matter of such claims would seem obvious to the person skilled in the art. The objection could be overcome by specifying the substituents which may be optionally present as found in the description or by deleting/amending the definitions on pages 68-74).

4.2 D10 represents the closest prior art and discloses compounds for the treatment of Huntington's disease (claims 1-4). The presently claimed compounds differ from the compounds of D10 due to an additional ring fusion between the moieties X and W of formula I of claim 1 of D10 or between X and the adjacent pyrazine in formula Ia11, Ia15 or Ia18 of claim 4 of D10. The problem to be solved can therefore be seen in the provision of further compounds for the treatment of Huntington's disease. As a solution, the present application provides compounds of formula I of claim 1.

4.3 The skilled person would not necessarily expect that the compounds of claim 1 exhibit the desired pharmacological activity despite the additional ring closure. However, in order to fulfil the requirements of Article 33(3) PCT, according to the problem solution approach, all alternatives of a claim should solve the technical problem underlying the claimed invention. In the present case, the number of alternative compounds falling within the scope of the present claims is such that it is unlikely that all of them possess the type and level of activity required to achieve the technical effect essential for the solution of the problem.

The structural difference of some compounds according present claims 1-5 to the active compounds (see the examples) is by far larger than the difference of many other claimed compounds to the compounds of the prior art D10. If the skilled person was not able to generalise from D10 to the presently claimed compounds, then he cannot at the same time be able to generalise from the data presently on file to all claimed compounds.

Therefore, the subject-matter of claims 1-5 and 8-16 cannot be considered to involve an inventive step and does not meet the requirements of Article 33(3) PCT.

4.4 This objection could be overcome either by submitting data, which render it credible that all claimed compounds, in particular compounds wherein W⁴ and W⁵ are both N, compounds wherein W⁴ and W⁵ are both C-R^a, and/or

compounds wherein R² is other than phenyl or as defined in lines 22-25 of page 16 and/or compounds wherein R¹ is other than as defined in claim 3 solve the above problem or by restricting the claims.

5 Industrial Applicability

Claims 1-17 are considered to be industrially applicable, they fulfil the requirements of Article 33(4) PCT.

Re Item VI

- 6 D11 discloses compounds of formula II (claim 12) and their medical use (claim 35). The compounds of D11 and the compounds of present claim 1 exhibit a certain overlap. Specific compounds falling within this overlapping area and within the scope of claims 1 and 5 have also been disclosed in D11 (compounds 20-471 and 519-533). D11 could therefore become relevant for novelty, in particular if the priority was not valid.

Re Item VIII

- 7 It is noted that claims 12-13 in their present formulation are interpreted by this authority as non-medical use claims and the mentioned diseases are not considered to be limiting. The mentioning of the diseases is hence redundant and the claims therefore do not comply with the conciseness criterion of Article 6 PCT.
- 8 The term "about" used in claims 9, 11, 13 and 15 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.
- 9 The statements in the passage from line 5 of page 75 to line 15 of page 76 indicate and in the passage from line 24 to line 30 of page 87 indicate that the present application encompasses prodrugs and metabolites of the compounds of the invention. This is in contradiction with the claims, thus rendering unclear the scope for which protection is claimed. Additionally, the terms "prodrug" and "metabolite" are unclear by themselves, since they rely on a functional definition and do not provide the skilled person with the necessary teaching for assessing what subject-matter is actually comprised therein. By using the term "prodrug" it is also attempted to define the invention by a result to be achieved which is not allowable.

- 10 The vague and imprecise statements in lines 16 to 20 of page 103 and lines 1-4 of page 202 of the description imply 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.