

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/US2020/021883

International filing date (day/month/year)
10.03.2020

Priority date (day/month/year)
10.05.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D277/18 A61P29/00 A61K31/425

Applicant
CERSCI 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

Guspanová, Jana
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. 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>1-14, 22, 23</u>
	No: Claims	<u>15-21</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-23</u>
Industrial applicability (IA)	Yes: Claims	<u>1-23</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. Relevant prior art

The following documents D1-D2 are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1 US 9 102 636 B2 (MANNION JAMES C [US]; DAX SCOTT L [US] ET AL.) 11 August 2015 (2015-08-11), cited in the application
- D2 MINO R CAIRA ED - MONTCHAMP JEAN-LUC: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS",
TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE,
vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954,
ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5
[retrieved on 1999-02-26]

2. Novelty

The present application relates to a process for the preparation of Compound 1 which is acid addition salt with HCl comprising reacting L-penicillamine and 2-chlorobenzoxazole in the presence of a base to form zwitterionic intermediate (free base of Compound 1) and contacting it with an acid, to said compound per se defined by the amount of the impurities and to its pharmaceutical composition as well as to a crystalline form of Compound 1 defined by XRPD pattern.

D1 discloses Compound 2 in Table 1 in column 28 which is the free base corresponding to the present free base of Compound 1, as well as the process for the preparation of Compound 2 HCl salt in column 40 which corresponds with present Compound 1. The process of D1 comprises reacting L-penicillamine and 2-chlorobenzoxazole in MeOH/THF to form the free base which is further treated with concentrated HCl.

Compound 2 was tested in D1 for its use against pain (Experimental Examples). Compound 2 was administered intravenously, i.e. in a form of pharmaceutical composition (Biological examples in column 49). Compound 2 was prepared in D1 as a white solid. It is not characterized by its impurities and/or by its enantiomeric purity. Therefore, it cannot be distinguished from the present Compound 1 defined in claims 15-19. These claims are considered not novel. The same applies for claims 20 and 21 which relate to a pharmaceutical composition containing Compound 1 defined in claims

15-19. Novelty of claims 15-21 can only be acknowledged if it is shown by appropriate comparative data that differences between Compound 2 HCl and present Compound 1 do exist. The burden of proof lies with the applicant.

Crystalline Compound 1 of claims 22 and 23 can be considered novel on account of a higher degree of crystallinity in comparison with white solid disclosed in D1.

The present process of claim 1 differs from the process disclosed in D1 in column 40 solely in the presence of a second solvent. The intermediate compound of formula II is not considered to be a distinguishing technical feature since it is a zwitterionic form which is in equilibrium with the free base that is the intermediate compound in the preparation of Compound 2 in D1 (column 40).

The present application does not fulfill the requirements of Article 33(2) PCT because the subject-matter of present claims 15-21 is considered not novel.

3. Inventive step

The closest prior art is represented by D1 which discloses present Compound 1 as a white solid, its preparation process as well as its use in the treatment of pain as already stated under point 2. above.

The present process of claim 1 in its broadest sense differs from the process disclosed in D1 in column 40 solely in the presence of a second solvent. A technical effect originating from that difference is not demonstrated in the present application.

Therefore, the problem to be solved by the present invention is defined as a provision of an alternative process for the preparation of Compound 1.

A sole addition of a solvent to a reaction mixture is considered trivial and hence cannot be considered inventive. Therefore, claim 1 does not involve an inventive step.

Also dependent claims 5, 6 and 9-11 are considered not inventive because the features defined in these claims are known from D1 (MeOH/THF, HCl).

Claims 2-4, respectively, define the base used in the preparation process as metal hydroxide; LiOH, NaOH, KOH; or NaOH, respectively.

D2 discloses DIPEA as base in the process for the preparation of Compound 2.

However, NaOH is used in the preparation of Compound 26 in column 44 which is structurally very similar to Compound 2. The skilled person would see that NaOH can be used in the same type of reaction as an alternative and would use it in the preparation of Compound 2 without applying any inventive skills. Claims 2-4 are considered not inventive.

The features of claims 7 and 8 are considered trivial.

Conventional methods for the purification of low molecular organic reaction products, which could normally be successfully applied in purification steps are within the common general knowledge. Seeking a highest possible purity and identifying the impurities cannot be considered inventive. Hence, claims 12-14 are also considered not inventive.

Since claims 15-21 are not novel they are consequently not inventive.

According to the common general knowledge the systematic investigation of a compound on polymorphism is routine practice in the pharmaceutical industry (see e.g. D2). It is also known that most substances, when investigated for a sufficiently long time, will reveal more than one polymorph. Furthermore, the methods to screen for polymorphs and solvates are well known in the art.

Thus, the skilled person being interested in the therapeutic use of Compound 1 would routinely screen for polymorphs thereof. If such routine work yields another solid state form, e.g. the form of claim 22 in the present application or any other form, then its provision is an obvious solution of the problem of providing an alternative solid form of a known compound. Hence, in the absence of any substantiated unexpected effect of the claimed form of claim 22 in comparison with known solid form of Compound 2 HCl known from D1, no inventive step can be acknowledged for the subject-matter of claims 22 and 23.

The present application does not fulfill the requirements of Article 33(3) PCT.

Re Item VII

Certain defects in the international application

To fulfill the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 should be mentioned under background in the description.

It is noted that the formulation "incorporated herein by reference" used in the description might be objected during the regional phase.

Re Item VIII

Certain observations on the international application

Claims 1, 9 and 19 are not clear in view of the product in claim 1, Compound 1, which is acid addition salt with hydrochloric acid (HCl) while in the preparation process of Compound 1 any acid can be used. It appears that the essential feature "the use of hydrochloric acid" is missing in said claims.

The vague and imprecise statement in the description in the paragraph bridging pages 40 and 41 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 when used to interpret them.

The arbitrary names of impurities employed in claims 13-18 have no precise meaning as they are not internationally accepted as a standard descriptive terms, thereby rendering the definition of the subject-matter of these claims unclear.

The application does not meet the requirements of Article 6 PCT.