

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

28.09.2020

Applicant's or agent's file reference
REAT.P0103WO

IMPORTANT NOTIFICATION

International application No.
PCT/US2019/037543

International filing date (day/month/year)
17.06.2019

Priority date (day/month/year)
15.06.2018

Applicant
Reata Pharmaceuticals, Inc.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REAT.P0103WO	FOR FURTHER ACTION See Form PCT/PEA/416	
International application No. PCT/US2019/037543	International filing date (day/month/year) 17.06.2019	Priority date (day/month/year) 15.06.2018
International Patent Classification (IPC) or national classification and IPC INV. C07D401/14		
Applicant Reata Pharmaceuticals, Inc.		
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>60</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).		
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) with regard to novelty, inventive step or 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		
Date of submission of the demand 15.04.2020	Date of completion of this report 28.09.2020	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Gavrilu, Daniela Telephone No. +49 89 2399-8274 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2019/037543

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-365 as originally filed

Claims, Numbers

1-165 filed with the letter of

11-08-2020

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2019/037543

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 06.05.2020 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-165</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-165</u>
Industrial applicability (IA)	Yes: Claims	<u>1-165</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

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 Reference is made to the following documents:

- D1 WO 2016/130927 A1
- D2 HUERTA CARLOS ET AL: "Characterization of novel small-molecule NRF2 activators: Structural and biochemical validation of stereospecific KEAP1 binding", BIOCHIMICA ET BIOPHYSICA ACTA (BBA) - GENERAL SUBJECTS, ELSEVIER, AMSTERDAM, NL, vol. 1860, no. 11, 27 July 2016 (2016-07-27), pages 2537-2552, XP029708201, ISSN: 0304-4165, DOI: 10.1016/J.BBAGEN.2016.07.026
- D3 WO 2015/112792 A1
- D4 WO 2012/083306 A2

2 Independent claims:

- compounds claims (claim 1 and 131)
- their pharmaceutical compositions (claim 132)
- their pharmaceutical uses (claim 140)

3 For the assessment of the present claims 140-165 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.

4 Amendments (Article 19 PCT)

The amendments from claim 1 filed with the letter of 15.04.2020 relate to the deletion of the possibility that R2 and R2' form together an alkanediyl or alkenediyl group, the deletion of the possibilities that R4, R5 are hydrogen or alkyl and R6 is hydrogen and limitation of R2' to hydrogen. The dependent claims were amended to be in line with the limitation from claim 1.

The amendments from the current set of claims appear to comply with the requirements of Article 19 PCT.

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

With the letter of 15.04.2020, the Applicant argued that due to the limitations from claim 1, in particular due to the fact that R4 and R5 cannot be anymore alkyl, the novelty over D2 was re-established. The ISA agrees with this point of view. Further, the Applicant considered that the present claimed compounds are novel over D1 and D3-D4 compounds due to a different stereochemistry. With the letter of 11.08.2020, the Applicant further argued that the present specific stereochemistry for R3 substituent in combination with the specific stereochemistry for the opposed hydrogen can be seen as a selection in two lists (selection from the potential two positions for R3 and the two positions for H). On account of the argumentation provided with the letter of 11.08.2020 under Article 33(2) PCT, the ISA reconsidered its position and is of the opinion that the present claimed subject-matter appears to fulfill the requirements of Article 33(1) and (2) PCT.

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

The present compounds, are to be seen as a novel selection from the general structures disclosed in D1, D3-D4. The documents D1 to D4 disclose compounds having anti-inflammatory activity and which activate the NRF2 (the same activation is disclosed also for the present compounds). Such a selection can only be regarded as inventive if the compounds of formula (I) present unexpected effects or properties in relation to the rest of compounds disclosed in the prior art.

With the letter of 15.04.2020, the Applicant argued that the present compounds selectively inhibit IL-17 pathway, "which is a promising therapeutic property not shared by all even most other previously reported anti-inflammatory agents".

The present application discloses in table 1 data regarding the inhibitory activity of the present compounds re the IL17, RORgamma and NRF2 ARE. From the data provided in this table it can be seen that a selectivity for the IL17 over the NRF2 ARE is not necessarily present for all of the claimed compounds (see e.g. the data reported for compounds T9, T11). The same could be concluded regarding the selectivity of the present compounds for RORgamma over NRF2 ARE (see the data provided for compounds T98, T99, T111, T173 and T174). In addition, compounds T52 and T91 are not active for any of the 3 pathways mentioned above. The compounds disclosed in D1, D3 and D4 are indicated to act through a NRF2 pathway.

With the letter of 11.08.2020, the Applicant deleted the compounds T9, T11, T52 and T91 from the claimed subject-matter and argued that the IL17 pathway disclosed for the present compounds is linked to specific inflammatory conditions while these conditions are not necessarily linked also to the mechanism disclosed in D1, D3-D4.

The ISA is still of the opinion that deleting from the claimed scope of the examples disclosed in the specification as not presenting a specificity/activity for the IL17 does not overcome the objections raised under Article 33(3) PCT. These examples which are still encompassed by the scope of claim 1 and do not show the indicated IL17 specificity makes questionable if the claimed effect is shared by all the alternatives covered by the claimed breadth. Since the NRF2 pathway disclosed for D1, D3-D4 compounds is also disclosed in the present application, a potential selectivity for the IL17 could be considered as an inventive feature as long as it is connected to a specific structural element which would not have been obvious for the skilled person in view of D1, D3-D4 disclosure. This appears not to be the case since from the data provided in table 1 it is not clear which is the common element connected to a selectivity for IL17 over NRF2 activity (the present compounds possess at least the same NRF2 activity as shown for the compounds disclosed in table 1). In addition, the data disclosed in table 1 cannot support the breadth of claims 1 which covers compounds wherein the dashed bond could be double or simple, index n could 0, 1 or 2 and the definitions for R1 to R6 cover a huge variation of potential substituents. In other words, the scope of the claimed subject-matter is not considered as a fair generalisation over the specific embodiments exemplified and tested in the description.

The requirements of Article 33(1) and (3) PCT appear not to be fulfilled.

Re Item VIII

Certain observations on the international application

- 1 Current claim 131 appears to claim specific compounds which fall under the scope of claim 1. Thus, in order to fulfill the requirements of Article 6 PCT claim 131 should be dependent on claim 1.
- 2 Several of dependent claims (see e.g. claims 2 to 10) repeat definitions for substituents which are the same as the ones provided in claim 1 (see e.g. the definition of R2'=H (claim 1) which is repeated in several of the dependent claims). In order to be concise all the definitions which are redundant should be deleted.