

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/EP2019/050180	International filing date (day/month/year) 04.01.2019	Priority date (day/month/year) 05.01.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07D471/04 A61K31/437 A61P25/28		
Applicant AC IMMUNE SA		

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 Baston, Eckhard 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 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>1-36</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-36</u>
Industrial applicability (IA)	Yes: Claims	<u>1-36</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Item V

1) Reference is made to the following documents:

- D1 WO 2017/009454 A1 (AC IMMUNE SA [CH]; PIRAMAL IMAGING SA [CH]) 19 January 2017 (2017-01-19)
- D2 WO 2011/128455 A1 (AC IMMUNE SA [CH]; KROTH HEIKO [CH]; HAMEL COTINICA [CH]; BENDERITTER) 20 October 2011 (2011-10-20)
- D3 WO 2010/080253 A1 (MERCK PATENT GMBH [DE]; JONES CHRISTOPHER CHARLES VICTOR [US]; HUCK BA) 15 July 2010 (2010-07-15)
- D4 WO 2011/084439 A1 (SANOFI SA [FR]; GROSS ALEXANDRE [US]; LI RONGHUA [US]; MAJID TAHIR NAD) 14 July 2011 (2011-07-14)
- D5 EP 3 118 202 A1 (AC IMMUNE SA [CH]; PIRAMAL IMAGING SA [CH]) 18 January 2017 (2017-01-18)

2) The present application is directed to 1,3,4,5-tetrahydro-2H-pyrido[4,3-b] indole derivatives which act as TAU (Tubulin associated unit) disaggregation effectors and which are considered suitable for the treatment of various diseases like Alzheimer`s disease and various others.

3) Claim 1 is directed to compounds in general characterised by a proviso and claim 9 is directed to a second medical use of the compounds without proviso "in the treatment, alleviation or prevention of a disorder or abnormality associated with Tau protein aggregates".

4)a) A claim must contain sufficient disclosure of the solution to the problem. In the present case the person skilled in the art is left with an undue burden, when he has to assess every known compound and every conceivable future compound for a TAU protein disaggregation property to see if it falls within the scope of the claims.

Effectively, the applicant is attempting to patent what has not yet been invented and the fact that the applicant can test for the inhibitory property used to define the compounds does not necessarily confer sufficiency on the claim.

Moreover the application lacks support, since the skilled person is not enabled to carry out the invention over the whole of the claimed area. It is required to define the invention in technical terms; however, a TAU protein disaggregation property is only a formulation of a problem, which does not contain technical pointers (=chemical formulae) to the solution.

The functional definitions present in claims 9-12, 14-18 and 24-28 have to be replaced by well defined pathological conditions (Art. 6 PCT).

Similar considerations apply to claims 29-36 which define mixtures based on expressions like "biologically active compound" and other functional definitions.

4)b) Claims 11 and 19-23 relate to a subject-matter considered by this Authority to be covered by the provision 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 recognize 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 in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 11 and 19-23 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compounds.

5) The claimed subject-matter appears to be novel, since no document of the prior art reveals compounds as defined in claims 1 and 9. The proviso present in claim 1 "provided that when Y is N and Y¹, Y² and Y³ are CZ, B is N-alkyl or O") excludes compounds for which B is NH and appears to remove a generic overlap with D3. In case that further prior art known to the applicant underlies this proviso it should be communicated.

The requirements of Art. 33(2) PCT appear of being met.

6) The problem to be solved may be seen in the provision of further compounds which act as TAU (Tubulin associated unit) disaggregation effectors and which are considered suitable for the treatment of various diseases like Alzheimer`s disease. The closest prior art may be represented by document D1 or D5 which address the same problem. The compounds disclosed in these document differ at least in that the basic heterocycle is aromatic, whereas in the present case the ring which incorporates Q is saturated. The claimed subject-matter may be regarded non-obvious.

However, the last step of the problem solution approach requires to verify if the problem has actually been solved. The description reveals examples and test data for compounds where groups A, B, Q and Y were varied. However, Y¹-Y³ are unchangeably carbon in all examples, whereas the scope of protection is extended to nitrogen bearing analogs.

The problem posed is not considered of having been credibly solved over the whole scope claimed.

The requirements of Art. 33(3) PCT are not met.