

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/EP2019/066414	International filing date (day/month/year) 20.06.2019	Priority date (day/month/year) 21.06.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07D413/14 C07D333/66 C07D333/68 C07D333/78 C07D409/04 C07D409/06 C07D409/12 C07D409/14 C07D413/04 C07D413/12 C07D417/12 C07D487/04 C07D495/04 C07D495/10 C07D498/10 A61P37/08		
Applicant UCB BIOPHARMA SPRL		

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 Papathoma, Sofia 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. 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 43bis.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 43bis.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:

see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 1-7, 9-23(all partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☒ the claims, or said claims Nos. 1-7, 9-23(all partially) are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a) or (b).
- ☒ See Supplemental Box for further details

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>8, 24-39(completely); 4, 5, 12, 17, 19-22(partially)</u>
	No: Claims	<u>40-45(completely); 1-3, 6, 7, 9-11, 13-16, 18, 23(partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>8, 24-45(completely); 1-7, 9-23(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>8, 24-45(completely); 1-7, 9-23(partially)</u>
	No: Claims	

2. Citations and explanations

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

The Written Opinion is based on the **following application documents**

Description, Pages

1-695 as originally filed

Claims, Numbers

1-45 as originally filed

The present application relates to compounds of formula (I) useful for the treatment of disorders caused by IgE.

Re Item II

Priority

Close inspection of the priority document has shown that the priority is not validly claimed over the whole claimed scope. In particular, present set of claims contains additional claims in relation to the priority document and the description additional examples also reflected in the additional claims. Furthermore, present claim 1 defines the claimed compounds of formula (I) in a more broad manner than the respective claim 1 of the priority document.

In view of the above, it is considered that the priority claim is not valid over the whole scope claimed.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of claims 1-7, 9-19 and 23 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search of the whole scope of claims 1-7, 9-19 and 23 could not be carried out.

The search was therefore limited to compounds according to present claim 8 and according to present claim 24 -covering also the subgroups of claims 25-39-, which corresponds to the majority of the examples given in the description of the present application, covered also by claims 20-22.

All subject-matter going beyond the combination of features defined in claims 8 and 24-39 was searched partially, and documents D1-D12 and D16 cited in the search report are only a limited example of the prior art that is prejudicial to the novelty of said subject-matter.

Re Item V

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

Reference is made to the following documents:

- D1 WO 2005/033102 A2 (AMPHORA DISCOVERY CORP [US]; HODGE CARL NICHOLAS [US]; JANZEN WILLIAM) 14 April 2005 (2005-04-14)
- D2 WO 01/98290 A2 (PHARMACIA & UPJOHN SPA [IT]; FANCELLI DANIELE [IT]; PEVARELLO PAOLO [I]) 27 December 2001 (2001-12-27)
- D3 A P Mkrtchyan ET AL: "-SUBSTITUTED TETRA- HYDROBENZO[b] THIENO[2,3-d]PYRIMIDIN-4-ONES AND THEIR ANTICONVULSANT ACTIVITY",
Helv. Chim. Acta. J. Am. Chem. Soc. J. Am. Chem. Soc, 1 January 1963 (1963-01-01), pages 2658-2666, XP055498334,
Retrieved from the Internet:
URL:<https://link.springer.com/content/pdf/10.1007/BF00763695.pdf>
[retrieved on 2018-08-09]
- D4 WO 2005/044008 A2 (SYNGENTA PARTICIPATIONS AG [CH]; SYNGENTA LTD [GB]; SELLES PATRICE [CH] 19 May 2005 (2005-05-19)
- D5 SHIKHAR GUPTA ET AL: "Discovery of dual binding site acetylcholinesterase inhibitors identified by pharmacophore modeling and sequential virtual screening techniques",
BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL,
vol. 21, no. 4, 28 December 2010 (2010-12-28), pages 1105-1112,

XP028138651,
ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2010.12.131
[retrieved on 2011-01-01]

- D6 HUNG THE DANG ET AL: "Syntheses and biological evaluation of 2-amino-3-acyl-tetrahydrobenzothiophene derivatives; antibacterial agents with antivirulence activity",
ORGANIC & BIOMOLECULAR CHEMISTRY,
vol. 12, no. 12, 1 January 2014 (2014-01-01), pages 1942-1956,
XP055498237,
ISSN: 1477-0520, DOI: 10.1039/C3OB42478B
- D7 WO 2009/079373 A2 (UNIV CALIFORNIA [US]; VERKMAN ALAN S [US];
DE LA FUENTE GONZALEZ RICAR) 25 June 2009 (2009-06-25)
- D8 US 2015/045327 A1 (VAN DER PLAS STEVEN EMIEL [BE] ET AL) 12
February 2015 (2015-02-12)
- D9 WO 2005/023818 A2 (AXXIMA PHARMACEUTICALS AG [DE]; KOUL
ANIL [BE]; KLEBL BERT [DE]; MUELL) 17 March 2005 (2005-03-17)
- D10 JP 2001 151780 A (NIKKEN CHEMICALS CO LTD) 5 June 2001
(2001-06-05)
- D11 US 2009/018114 A1 (CARROLL WILLIAM A [US] ET AL) 15 January 2009
(2009-01-15)
- D12 STEVEN E. VAN DER PLAS ET AL: "Discovery of N -(3-Carbamoyl-5,5,7,7-tetramethyl-5,7-dihydro-4 H -thieno[2,3- c]pyran-2-yl)-l
H -pyrazole-5-carboxamide (GLPG1837), a Novel Potentiator Which Can
Open Class III Mutant Cystic Fibrosis Transmembrane Conductance
Regulator (CFTR) Channels to a High Extent",
JOURNAL OF MEDICINAL CHEMISTRY,
vol. 61, no. 4, 17 November 2017 (2017-11-17), pages 1425-1435,
XP055498730,
ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.7b01288
- D13 WO 01/47874 A1 (SMITHKLINE BEECHAM PLC [GB]; BRUTON
GORDON [GB]; FALLER ANDREW [GB]; O) 5 July 2001 (2001-07-05)

- D14 EP 0 317 295 A2 (KISSEI PHARMACEUTICAL [JP]) 24 May 1989
(1989-05-24)
- D15 WO 01/17516 A2 (NOVO NORDISK AS [DK]; ONTOGEN CORP [US]) 15
March 2001 (2001-03-15)
- D16 ANDERSEN H S ET AL: "Discovery and SAR of a Novel Selective and
Orally Bioavailable Nonpeptide Classical Competitive Inhibitor Class of
Protein-Tyrosine Phosphatase 1B",
JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL
SOCIETY, US,
vol. 45, 1 January 2002 (2002-01-01), pages 4443-4459, XP002318790,
ISSN: 0022-2623, DOI: 10.1021/JM0209026

Claim 45 relates 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.

1) Article 33(2) PCT

Documents D1-D12 and D16 are prejudicial to the novelty of claims 1-3, 6, 7, 9-11, 13-16, 18, 23 and 40-45 (see passages cited in the search report).

Documents D13 and D14 relate to compounds useful for the treatment of conditions associated with excess production of soluble CD23 (the low affinity IgE receptor FcεRII, Blast 2)) such as autoimmune disease, inflammation and allergy and to 4H-quinolizin-4-one compounds useful for the treatment of diseases associated with IgE such as allergic bronchial asthma, atopic dermatitis and hyper-sensitivity, respectively.

The compounds disclosed therein, however, do not fall under the structural definition of the claimed entities according to claim 1. The disclosure of D13 and D14 is therefore not prejudicial to the novelty of the claimed subject-matter.

Document D15 relates to structurally close related compounds that inhibit CD45. *"...an IgE-mediated degranulation was demonstrated in wild type but not CD45-deficient T cells from mice. These data suggest that CD45 inhibitors could also play a role in the*

symptomatic or therapeutic treatment of allergic disorders, such as asthma, allergic rhinitis, food allergies, eczema, urticaria and anaphylaxis." The compounds explicitly disclosed therein, however, are characterised by a -COOH group as R¹ substituent, i.e. by a group that is not covered by the definition of the R¹ substituent in the presently claimed entities. The disclosure of D15 is therefore not prejudicial to the novelty of the claimed subject-matter.

Summarizing the above, claims 1-3, 6, 7, 9-11, 13-16, 18, 23 and 40-45 do not fulfil the requirements of novelty under Article 33(2) PCT and only claims 4, 5, 8, 12, 17, 19-22 and 24-39 can be acknowledged as novel (however, with respect to claims 4, 5, 12, 17 and 19-22 see Re Item III): i.e. said claims could not be searched completely) .

2) Article 33(3) PCT

*The assessment of inventive step is limited to claims 4, 5, 8, 12, 17, 19-22 and 24-39. However, as mentioned above, claims 4, 5, 12, 17 and 19-22 could not be searched completely.

The technical problem underlying the present application is the provision of compounds useful for the treatment of disorders caused by IgE.

Compounds useful for the treatment of conditions associated with IgE are known in the art, see e.g. documents D13 and D14.

The compounds according to claims 4, 5, 8, 12, 17, 19-22 and 24-39 differ from the compounds disclosed in documents D13 and D14 not only in their core structure but also in their type of substitution.

It is therefore considered that documents D13 and D14 could not have given a hint to the person skilled in the art towards the structural design of the compounds according to claims 4, 5, 8, 12, 17, 19-22 and 24-39.

On the other hand, document D15 discloses structurally close related compounds useful as CD45 inhibitors. D15 discloses the relationship between CD45 and IgE-mediated degranulation. In addition, the compounds disclosed therein differ from the claimed entities only in their corresponding R¹ substituent being -COOH while in the claimed entities -in their closest case- R¹ is -COOAlk. Therefore the structural modification the person skilled in the art would have to carry out in order to arrive to the presently claimed entities according to claims 4, 5, 8, 12 and 20 is considered as obvious and not to be based on an inventive step.

The structural features claimed in claims 17, 19, 21, 22 and 24-39 are, however, regarded not to be obvious in the light of D15 or the cited prior art in general and inventive step for the subject-matter of said claims could be in principle acknowledged.

However, before a positive opinion under Article 33(3) PCT for claims 17, 19, 21, 22 and 24-39 is given, it should be mentioned that the claimed entities are defined in a very broad manner, such that the claims cannot be considered to be a reasonable generalization of the examples given in the description: see e.g. the definition of X, Y, Z and W, their substitution, the definition / existence of groups up to a fourth row of substituents, the use of terms such as aryl, heteroaryl or heterocycle without further qualification.

The applicant is entitled to claim only obvious modifications of what was described (close related variations), since the claims should represent a reasonable generalisation of the examples given in the description: the technical features stated in the description/ examples as being essential must be the same as those used to define the invention in the claims. The reason for that is that the problem to be solved should be solved by the whole scope of the claimed subject matter (every compound falling within its scope) and not just by individual compounds- especially since the problem may be seen in the provision of compounds acting on a biological system (i.e. on a system depending upon very different parameters). If this were not the case, an invention could arbitrarily be broadened to any limit without consideration, whether the compounds are actually solving the problem underlying the invention (Article 33(3) PCT).

Therefore, it is considered that either further evidence is needed that the problem is solved over the whole breadth claimed or the claims need to be revised and reduced to those compounds that are actually disclosed, and obvious equivalents thereof.

Re Item VIII

Certain observations on the international application

a) The use of terms "aryl", "heteroaryl", "heterocycle" etc. throughout the claims without further qualification renders the claims obscure in scope. These terms are non-limitative and embrace an infinite number of possibilities not yet explored by the Applicant. Therefore it is not clear whether all compounds implied fall within the scope of the present claims and/or represent a solution of the problem underlying the present application. Consequently, for reasons of inventive step and clarity these terms should be limited to the specific meanings given in the description.

b) Claim 41 does not meet the requirements of Article 6 PCT for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating IgE), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease)).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.