

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/US2019/045424	International filing date (day/month/year) 07.08.2019	Priority date (day/month/year) 08.08.2018
International Patent Classification (IPC) or both national classification and IPC INV. A61P35/00 C07D401/14 C07D403/14 C07D405/14 C07D409/14 C07D413/14 C07F9/00 A61K31/4184		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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 Sahagún Krause, H 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>1-24</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-24</u>
Industrial applicability (IA)	Yes: Claims	<u>1-24</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

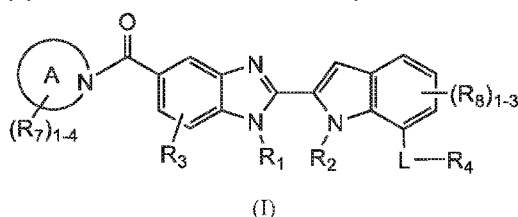
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2018/022897 A1 (PADLOCK THERAPEUTICS INC [US]) 1 February 2018 (2018-02-01)
- D2 WO 2017/100594 A1 (PADLOCK THERAPEUTICS INC [US]) 15 June 2017 (2017-06-15) cited in the application
- D3 WO 2016/185279 A1 (GLAXOSMITHKLINE IP DEV LTD [GB]) 24 November 2016 (2016-11-24)
- D4 WO 2014/015905 A1 (GLAXO GROUP LTD [GB]; ATKINSON STEPHEN JOHN [GB] ET AL.) 30 January 2014 (2014-01-30)

Claims 21-23 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 directed 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.

The present application discloses compounds of Formula (I):



V-1. Novelty (Article 33(1) and (2) PCT):

The present compounds are novel over the compounds in D1 on account of the present definition of -L-R4, which in D1 can only be H.

The present compounds are, furthermore, novel over the compounds in D2 (see claim 1) on account of the present provisos 1) and 2), in other words, they differ on account of the present -R₄ when L is absent and on account of the present -L-R₄ when -L- is NR_a. In general they differ on account of the present definition of -L-R₄ (see R₄ in claim 1 of D2).

They also differ from the compounds in D3 on account of the present definition of -L-R₄ (see R₅ in claim 1 of D3) and from those in D4 in that the indole ring does not have a further nitrogen atom (see definition of A-C in claim 1 of D4).

The present subject-matter can be considered novel in the sense of Article 33(2) PCT.

V-2. Inventive step (Article 33(1) and (3) PCT):

Compounds in D1-D4 are inhibitors of PAD4 (see abstract in D1-D4).

The present application differs from the compounds in the prior art on account of the definition of the group -L-R₄.

There is no special effect linked to this difference, and thus the problem underlying the present application is seen in the provision of further inhibitors of PAD4.

The present compounds solve the problem as proven in the test results in pages 217-224.

The problem is solved by introducing -L-R₄ groups which are quite different to each other, i.e. R₄ is selected from -C(=O)NR_aR_a, -(CR_dR_d)₁₋₇-R_{5a}, -(CR_dR_d)_r-aryl substituted with 1-5 R₅, -(CR_dR_d)_r-C₃₋₁₂ cycloalkyl substituted with 1-5 R_{5b}, -(CR_dR_d)_r-C₄₋₆cycloalkenyl substituted with 1-5 R_{5b}, and -(CR_dR_d)_r-heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NR₆, O, and S and substituted with 1-5 R₅; wherein R_{5a}, at each occurrence, is independently selected from CN, -C(=O)OR_b, -C(=O)NR_aR_a, -NR_aR_a, -NR_aC(=O)R_b, -NR_aC(=O)OR_b, -S(=O)_pR_c and -NR_aS(=O)_pR_c.

D1 discloses compounds with only -H in that position, D3, -H, C₁₋₆alkyl, -O C₁₋₆alkyl, -OH, -halo and -CN and D4 -H and C₁₋₆alkyl. D2, however, discloses i.a. -CH=CH-cyclopropyl, -CH=CH-phenyl, tetrahydropyran-4-yl, morpholine, -NH-(CH₂)₁₋₂-cyclopropyl, -NMe-(CH₂)₁₋₂-cyclopropyl and R which can be C1-6-aliphatic (also substituted, see [0013]). Therefore the skilled person knew that variation was accepted in a position according to the present -L-R₄, even a very general definition like substituted aliphatic gave compounds with the claimed activity. It appears that the present compounds are to be seen as a selection out of the compounds in D2 or so close to them that they can only be regarded as inventive if they present unexpected

effects or properties in relation to the rest of compounds. Since no such effects or properties are indicated and supported in the application, the subject-matter of the present claims does not involve an inventive step within the meaning of Article 33(3) PCT.

V-3. Industrial applicability (Article 33(4) PCT):

Claims 1-24 fulfill the requirements of Article 33(4) PCT in respect to their industrial applicability.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3-D4 is not mentioned in the description, nor are these documents identified therein.

The wording "...hereby incorporated by reference ...", as used on page 1 and [0032] [0041] of the present description, should be deleted (Rule 9.1(iv) PCT).

Re Item VIII

Certain observations on the international application

The "prodrugs" in [0042]-[0044] do not meet the requirements of Article 5 PCT in that the matter for which protection is sought is not well defined and it is an attempt to define the subject-matter in terms of the result to be achieved. It appears to be no concrete information in the description as to which derivatives of the presently claimed compounds would have suitable pharmacokinetic properties to release the active compound when administered in vivo. Furthermore, these compounds are not apparent from the claims and thus this inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear, Article 6 PCT.