

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/US2018/041573	International filing date (day/month/year) 11.07.2018	Priority date (day/month/year) 12.07.2017
International Patent Classification (IPC) or both national classification and IPC INV. C07D403/12 C07D231/20 C07D231/22 C07D231/56 C07D401/04 C07D417/12 C07D417/14 C07D491/04 C07D495/04 C07D519/00 A61P21/00 A61P9/00 A61P29/00 A61P35/00 A61P37/00 A61K31/427 A61K31/437		
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 Brandstetter, T 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:

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>1-17</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-17</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-17</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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

- 1 Reference is made to the following documents:
- D1 WO 2016/010950 A1 (2016-01-21), cited in the application
 - D2 WO 2010/032875 A2 (2010-03-25)
 - D3 WO 2017/123860 A1 (2017-07-20)

Re Item V

- 2 Novelty (Article 33(2) PCT)
- 2.1 The application is interpreted as referring to compounds of formula I (claim 1), compositions comprising them (claim 13) and their medical use (claims 14 and 15) in the treatment of cardiovascular disorders, inflammatory disease, oncologic disorders, autoimmune disorders etc. (claim 16). The compounds are alleged to work via inhibition of ROCK.
- 2.2 Compounds of formula I have not been disclosed in the prior art and the subject-matter of claim 1 is therefore new. All other claims are dependent on claim 1 or refer to said new compounds and their subject-matter is new by consequence.
- 3 Inventive step (Article 33(3) PCT)
- 3.1 D1 represents the closest prior art and discloses spirocyclic compounds of formula I and II (claims 1 and 2, examples), their activity as inhibitors of ROCK (page 4, lines 21-23) and their medical use in the treatment of cardiovascular disorders, inflammatory disease, oncologic disorders, autoimmune disorders etc. (claim 18). The presently claimed compounds differ from the compounds of D1 at least due to their primary amide (instead of a cyclic lactam in D1) and the oxygen atom between the spirocyclic moiety and the heterocyclic moiety.
- 3.2 The problem to be solved can therefore be seen in the provision of further compounds with ROCK inhibitory activity for medical use. As a solution the present application provides compounds of formula I. The application contains data (page 51-56), which show that the example compounds exhibit the desired activity, i.e. the problem has been solved.
- 3.3 To arrive at the presently claimed compounds starting from the compounds exemplified in D1, at least two structural modifications have to be performed (removal of the ring atom M and substitution of the carbon atom between M and ring B by an oxygen atom or introduction of an oxygen between the

spirocyclic moiety and the heterocyclic moiety and introduction of an amide (instead of R¹⁰ of D1 which can only be H or alkyl) in ortho position of the connection to the spirocyclic system). Nothing in D1 or D2 or a combination thereof would prompt the skilled person to these modifications. It is noted that a carboxamide moiety on a heterocycle has been specifically proposed as structural feature of ROCK inhibitors in the compounds of D2. However D2 would lead the skilled person away from the presently claimed compounds, as ring A cannot be a six-membered monocyclic residue such as the pyridine in the compounds of D2. The solution is hence not obvious. Claim 1 represents a reasonable generalisation of the examples and the breadth of the claims therefore seems to be acceptable. Inventive step can thus be acknowledged to compounds of claim 1 and subject-matter referring to them.

4 Industrial Applicability

Claims 1-17 are considered to be industrially applicable, they fulfil the requirements of Article 33(4) PCT.

Re Item VI

- 5 The presently claimed compounds differ from the compounds of D3 at least due to their ring A which cannot be a 6-membered monocycle. D3 would however be relevant for the evaluation of inventive step if the claimed priority was not valid.

Re Item VIII

- 6 Claim 15 is considered by this Authority not to meet the requirements of Article 6 PCT for the following reasons. The therapeutic application is functionally defined by a mechanism of action which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by introducing into the claim a list of pathological conditions (diseases) cited in the application.
- 7 The statements in line 10 of page 6, line 15 of page 9, line 14 of page 12, line 26 of page 15, line 9 of page 17, line 19 of page 18, line 10 of page 20, line 10 of page 21, line 12 of page 22, lines 10 and 23 of page 23, line 6 of page 25 and lines 12-15 of page 44 indicate that the present application encompasses prodrugs of the compounds of the invention. This is in contradiction with the claims, thus rendering unclear the scope for which protection is claimed. Additionally, the term "prodrug" is unclear by itself, since it relies on a functional definition and does not provide the skilled

person with the necessary teaching for assessing what subject-matter is actually comprised therein. By using the term "prodrug" it is also attempted to define the invention by a result to be achieved which is not allowable.

- 8 The statement from line 30 of page 42 to line 2 of page 43 indicates that the present application encompasses N-oxides of the compounds of the invention. This is in contradiction with the claims, thus rendering unclear the scope for which protection is claimed.
- 9 The vague and imprecise statements in lines 11-12 on page 25 and lines 24-25 on page 34 of the description imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.
- 10 Several passages in the description (lines 10-13 of page 1, lines 9-25 of page 5, etc.) present the invention as a method of therapeutic treatment, which considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.