

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 12296-WO-PCT	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2015/040254	International filing date (<i>day/month/year</i>) 14 July 2015 (14.07.2015)	Priority date (<i>day/month/year</i>) 15 July 2014 (15.07.2014)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																								
2.	This REPORT consists of a total of 6 sheets, including this cover sheet.																								
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																									
3.	This report contains indications relating to the following items: <table style="width: 100%;"> <tr> <td style="width: 5%; text-align: center;">☒</td> <td style="width: 25%;">Box No. I</td> <td style="width: 70%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;">☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;">☐</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	☒	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
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 5px;">Date of issuance of this report 17 January 2017 (17.01.2017)</td> </tr> <tr> <td style="padding: 10px; text-align: center;"> Authorized officer Yukari Nakamura </td> </tr> <tr> <td style="padding: 5px;">e-mail: pt07.pct@wipo.int</td> </tr> </table>	Date of issuance of this report 17 January 2017 (17.01.2017)	Authorized officer Yukari Nakamura	e-mail: pt07.pct@wipo.int
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e-mail: pt07.pct@wipo.int				

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/US2015/040254	International filing date (day/month/year) 14.07.2015	Priority date (day/month/year) 15.07.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D403/12 C07D413/14 C07D403/08 C07D237/32 C07D417/12 C07D417/14 C07D471/04 C07D513/04 C07D519/00 A61K31/502 A61P9/00		
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 Grassi, Damian 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>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>2-4, 6-14</u>
	No: Claims	<u>1, 5, 15-19</u>
Industrial applicability (IA)	Yes: Claims	<u>1-19</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D1 EP 2 025 676 (2009-02-18)

D2 US 2010/056518

Re Item V

1 The subject-matter of the present claims is new (Article 33(2) PCT).

2 The subject-matter of present claims 1 and 5 does not involve an inventive step (Article 33(3) PCT).

The closest prior art is represented by D1 relating to Rho kinase inhibitors.

The presently claimed group of compounds differs from the disclosure of claim 1 of document D1 in the bicyclic ring system containing ring B and in the position of the spiro-carbocycle (A).

The technical problem underlying the present application is seen in the provision of alternative Rho kinase inhibitors.

In all examples disclosed in the present application, ring A is a 2,6-disubstituted spiro[3.3]heptane ring system. Therefore, it appears that such a ring system is essential to the activity of the compounds. Due to the fact that claims 1 and 5 are not restricted to such compounds but e.g. also allow for 1,1-disubstituted spiro[2.6]nonane ring systems, it appears that not virtually all claimed compounds have the desired activity. Therefore, claims 1 and 5 do not involve an inventive step.

2.1 In view of the test data disclosed on pages 113-128, the technical problem appears to be solved by the compounds of claims 2-4 and 6-14.

D2 discloses further Rho kinase inhibitors containing a isoquinolone group complying with the present bicyclic ring system containing ring B.

However, the combination of the documents D1 and D2 does not appear to prompt the skilled person to the presently claimed group of compounds wherein the ring system containing B is directly linked to the spiro group.

Therefore, the subject-matter of claims 2-4 and 6-14 involves an inventive step.

- 2.2 The claims 15-19 relating to compositions containing the compounds of claim 1 or to the use thereof would only involve an inventive step if claim 1 fulfilled this requirement.

REMARKS

- 3 Present claim 1 refers to an optional substitution if R^1 is an alkyl group. However, the claim does not allow for R^1 being an alkyl group.
- 4 Present claim 2 refers to a group R^2 . However, formula (II) of claim 2 does not appear to contain a group R^2 .
- 5 When a claim is directed to a further therapeutic application of a medicament and the condition to be treated is defined in functional terms, e.g. any condition "associated with aberrant Rho kinase activity", the claim can be regarded as clear only if instructions, in the form of experimental tests or any testable criteria, are available from the patent documents or from the common general knowledge allowing the skilled person to recognise which conditions fall within the functional definition and accordingly within the scope of the claim.
- As these conditions do not appear to be fulfilled by the present application, claim 17 is not clear.
- 6 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.