

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/US2018/031945	International filing date (day/month/year) 10.05.2018	Priority date (day/month/year) 11.05.2017
International Patent Classification (IPC) or both national classification and IPC INV. C07D409/12 C07D495/04 A61P35/00 A61K31/4365		
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 Weisbrod, Thomas 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>1-12</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-12</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-12</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

1 Reference is made to the following documents.

D1 WO 2016/144844 A1, 15 September 2016.

D2 WO 2016/144849 A1, 15 September 2016.

2 Novelty and inventive step

D1 discloses bicyclic 10-membered (hetero)aryl compounds and D2 relates to thienopyrazines as inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK-4). The present claims are novel over D1 on account of the thieno ring in the compounds (I). Furthermore, the present claims are novel over D2 on account of the substituents -O-R1, R3, and -C(O)NH2 in the compounds (I).

The application describes the synthesis of certain compounds (I) and shows that they inhibit IRAK-4 (cf. pages 56-57, table 2). In view of one of D1 or D2, the problem to be solved is the provision of further IRAK-4 inhibitors. The compounds of D1 are bicyclic 10-membered (hetero)aryl derivatives, whereas the present compounds are 9-membered thieno(hetero)aryl derivatives. Furthermore, the present compounds differ from those of D2 through all peripheral substituents. No document hints or suggests to modify the compounds of D1 or D2 such as to arrive at the present compounds (I), whilst maintaining the desired activity. Hence, the present claims appear to comply with the criterion of inventive step.

Re Item VII

Certain defects in the international application

It would appear that D1 and D2 are not cited in the description (Rule 5.1(a)(ii) PCT).

Re Item VIII

Certain observations on the international application

The claims are directed to compounds (I) and prodrugs thereof. Thus, the claims encompass also compounds of a desired function (i.e. being prodrugs) having structures and formulae different from those compounds represented by formula (I). The claims, however, do not give a specific technical guidance which structures and formulae would in fact have the desired function in the context of the present application. Hence, the claims are not clearly defined, contrary to Article 6 PCT. This objection may be overcome by deleting the term prodrug from the claims and the description.

The reference to solvates in the description as part of the invention (page 16) is not reflected in the claims. This inconsistency between description and claims renders the claims unclear (Article 6 PCT).