

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2019/039135

International filing date (day/month/year)
26.06.2019

Priority date (day/month/year)
27.06.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 A61P35/00 A61K31/496

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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>1-16</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-16</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-16</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 Claims 14-16 relate to a 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 a first or further medical treatment.

2 Reference is made to the following documents.

D1 US 2005/124604 A1, 9 June 2005.

D2 US 2008/139551 A1, 12 June 2008.

D3 US 2005/266510 A1, 1 December 2005.

D4 WO 2017/177037 A1, 12 October 2017.

3 Novelty

D1-D2 disclose inter alia 1,5-naphthyridines as inhibitors of macrophage migration inhibitory factor and tumor necrose factor alpha inhibitors, respectively. The present claims are novel over D1 on account of R4, which does not include a carbonyl group adjacent to the piperidine ring nitrogen, and the additional group R5. The present compounds (I) overlap with the compounds of D2 (cf. paragraphs 43 and 45, last formula) but embodiments of the present formula (I) are not specifically disclosed in D2. Hence, the present claims are a novel selection of D2 with the 1,5-naphthyridine core and its substituents as novel technical features.

D3-D4 disclose inhibitors of diacetyl glycerol kinase alpha (DGK α) and/or zeta (DGK ζ), which are structurally remote from the present compounds (I) (cf. D3, paragraphs 54-57; D4, abstract). The most similar compound of D3 and D4 is

represented by R59499 (D3, paragraph 56; D4, abstract). The present claims are novel over D3-D4, because they relate to 1,5-naphthyridines rather than to the thioxo-quinazolinone R59499.

4 Inventive step

The application describes the synthesis of certain compounds (I) and shows that about 1400 tested examples inhibit DGK α and/or DGK ζ (cf. page 946-989, table 1; page 989, lines 4-6). Accordingly, they are potentially useful in the indication of claims 14-15. Starting from one of D3 or D4 the problem to be solved is the provision of further inhibitors of DGK α and/or DGK ζ . The present compounds (I) are not obvious to the skilled artisan, because they are structurally unrelated to the compounds of D3-D4 and none of the cited documents hints or suggests to modify the compounds of D3 or D4 such as to arrive at the present compounds (I), whilst maintaining the desired activity. It would thus appear that the present claims comply with the criterion of inventive step.

Re Item VII

Certain defects in the international application

It would appear that D3 and D4 are not cited in the description (Rule 5.1(a)(ii) PCT).

Re Item VIII

Certain observations on the international application

Claim 16 does not comply with Article 6 PCT, because 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. This objection may be overcome by introducing in the claims a list of pathological conditions cited in the application.