

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/US2019/067717

International filing date (day/month/year)
20.12.2019

Priority date (day/month/year)
21.12.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07D513/04 C07C55/00 C07C55/10 C07C55/22

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>1-13</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-13</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-13</u>
	No: Claims	

2. Citations and explanations

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 2013/163279, 31 October 2013 cited in the application
- D2 A. V. YADAV ET AL.;
INDIAN JOURNAL OF PHARMACEUTICAL SCIENCE 2009, (2009-07-01),
pages 359-370, XP055398519

2. Novelty

D1 discloses the compound of formula (I) in its free form (example 36). D1 does not disclose co-crystals of the compounds of formula (I).

D2 does not disclose the compound of formula (I).

Novelty is acknowledged (Art. 33(2) PCT).

3. Inventive step

The present application is directed to co-crystals of the compound of formula (I) and their use for treating thromboembolic disorders.

D1 can be considered the closest prior art as it discloses the compound of formula (I) (example 36) for the same use.

The difference between D1 and the present application lies in the different solid form: a solid in D1 and a co-crystal in the present case.

This difference results in improved solubility and bioavailability of the present form compared to the form disclosed in D1.

Therefore the problem to be solved is seen in the provision of further solid forms of the compound of formula (I) with improved solubility and bioavailability.

This problem has been solved with the provision of the present co-crystals of the compound of formula (I) with succinic acid and citric acid which have the improved solubility and bioavailability as shown by the results shown in Figure 15 and 16 and in Tables 6 and 7 of the description.

It is considered that this solution involves an inventive step. It is known in the art that the formation of co-crystals is per se not predictable as discussed on p. 362 of D2. Besides, it could not have been expected that the co-crystal would have shown the improved solubility and bioavailability.

Re Item VIII

Certain observations on the international application

The crystal form claimed in claim 8 is only arbitrarily defined by means of the label Form N-1. However, no standard nomenclature for polymorphic crystal forms exists. It is therefore unclear which product is covered by the definition in claim 8 (Article 6 PCT). The crystal form should be defined by reproducible physicochemical parameters, for example by referring to the parameters of claim 6.