PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2020/031747	07.05.2020	13.05.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D409/06 A61P35/00

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Seelmann, Marielle Telephone No. +49 89 2399-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2020/031747

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 43*bis*.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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	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

D1: WO 2015 103 509

D2: WO 2015 103 508

1 Novelty

ROR gamma agonists are already known from the prior art (D1 or D2) for the treatment of cancer and differ structurally by the presence of an additional substituted methylene group between the phenylmethylenoxy and phenylpyrrolidinebenzensulfonyl moieties.

The compounds presently claimed are consequently not disclosed in D1-D2.

Novelty prevails for the different claimed subject-matters.

2 Inventive step

Either D1 or D2 could represent the closest prior art document, since they are both directed to the treatment of the same diseases using the same mechanism of action. They also disclose compounds differing from present Formula (I), in both cases, solely due to the presence of A = -C(CF3)R- between Ph-CH2O and Ph, i.e. Ph-CH2O-**A**-Ph-. There is no comparative example to sustain any particular effect relating to this structural difference.

The objective technical problem is accordingly the provision of alternative compounds.

The proposed solution are the compounds of present formula (I).

Such compounds were prepared and tested in the present application (see examples 1-47 and activity in table on pages 60-61). This corresponds to the scope of present claim 5. There is quite a fluctuation in the results: a factor of 60 for the inhibitory capacity of the proposed compounds. The best ones correspond to compounds of formula (I) with A-Ra = N-C(O)-thiolane-1,1-dione.

If the applicant sustained the the alleged effect can be generalized in view of the examples provided, then for the same reasons the proposed solution is considered obvious in light of the teachings of D1 and D2. The reasons are that even though all examples in these documents are characterized by the presence of an additional methylene moiety: -C(CF3)-, the possibility of having only PhCH2O as R1 is given in D1 (claims 1-5 for r = 0). Alternatively if the skilled person could not anticipate that the proposed compounds are active versus those of D1 or D2 by the sole structural difference of one methylene group, then far more remote structural modifications falling under present claim 1, cannot be accepted without the submission of further experimental results, since they are not considered as isosteric modifications. Such modifications concern essentially the parameter ARa.

The scope of protection should represent a fair generalization of what has been shown.

The requirements of Articles 33(3) PCT are therefore not considered met for the subject-matters of present claims 1-7 and 10.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 or D2 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

The present claims in light of the description relate i.a. to compounds defined by reference to a desirable property, namely that they are "prodrugs". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. This term should therefore be removed from the description in each of its occurrence.

The expression "incorporated by reference" should be removed as well.

The paragraph on page 20, lines 19-26 should be removed, since it is directed to the "spirit and scope" of the present application.

Further subject-matters are claimed in the description to be part of the present invention, even though not mentioned as claims (see reference to page 24, lines 1-3).

In view of the description, the term heterocycle seems to include "heteroaryl", whereas cycloalkyl does not include aryl (see pages 25-26)