

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/EP2022/083954	International filing date (day/month/year) 30.11.2022	Priority date (day/month/year) 01.12.2021
International Patent Classification (IPC) or both national classification and IPC INV. C07D498/10 A61K31/513 A61K31/519 A61K31/551 A61K31/553 A61P35/00		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

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 P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Beyss-Kahana, Ellen Telephone No. +31 70 340-0
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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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
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>1-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-18</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-18</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

Reference is made to the following documents:

- D1 WO 2020/028706 A1 (ARAXES PHARMA LLC [US]) 6 February 2020 (2020-02-06)
- D2 WO 2021/118877 A1 (LILLY CO ELI [US]) 17 June 2021 (2021-06-17)
- D3 ABBAS NERMEEN S ET AL: "Abbas and Ahmed: New Approaches for the Synthesis and Cytotoxicity New Approaches for the Synthesis and Cytotoxicity of Thiazoles Derived from Cyclohexanone", ACTA CHIM. SLOV, vol. 61, 1 January 2014 (2014-01-01), pages 835-843, XP093023897,

1. Novelty

D1 (claims; examples), D2 (claims; examples), D3 (scheme 2;abstract) disclose compounds similar to formula (I) as RAS inhibitors for use for treating cancer. The distinguishing feature is the spiro-condensed bicyclic thiophene moiety.

2. Inventive Step

The present application addresses the problem of providing further inhibitors of G12C mutant RAS family proteins for use for treating proliferative diseases (page 3).

D1 is considered to represent the closest prior art, since it solves the same problem (page 3).

The compounds of present claim 1 differ from the compounds of D1 in the presence of the spiro condensed annulated amino-cyano-thiophene moiety.

The application as filed does not contain any evidence that this distinguishing feature is responsible for a technical advantage with respect to D1.

Consequently the objective problem underlying the present application equals the subjective problem.

The claimed solution to the above mentioned objective problem is the introduction of a spiro condensed annulated amino-cyano-thiophene moiety into the compounds as known from D1.

It is considered that the prior art documents would not have directed the skilled person towards the present compounds. There is no hint or suggestion from the prior art that would have incited him to introduce into the known compounds the said structural modification if the above mentioned problem should be solved.

Re Item VIII

Certain observations on the international application

Claims 2, 3 comprise all the features of claim 1 and are therefore not appropriately formulated as claims dependent on the latter (Rule 6.4 PCT).