

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/EP2023/080705

International filing date (day/month/year)
03.11.2023

Priority date (day/month/year)
09.11.2022

International Patent Classification (IPC) or both national classification and IPC
INV. C07D498/22 A61P31/12 A61P37/00 A61K31/529

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Sahagún Krause, H

Telephone No. -0



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>1-42</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-42</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-42</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

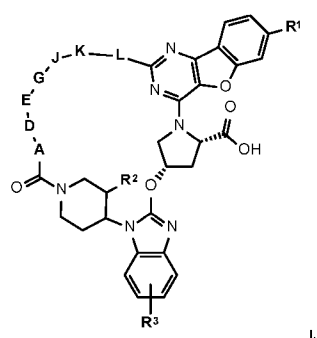
Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

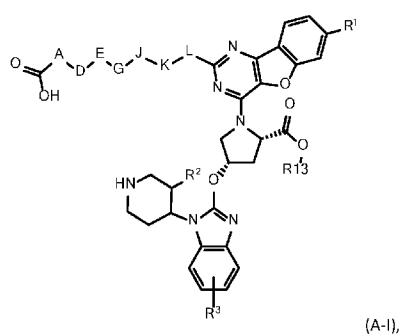
- D1 WO 2020/142729 A1 (BELLBROOK LABS [US]) 9 July 2020
(2020-07-09)cited in the application
- D2 WO 2022/174012 A1 (BELLBROOK LABS LLC [US]) 18 August 2022
(2022-08-18)cited in the application
- D3 WO 2020/210649 A1 (RIBOSCIENCE LLC [US]) 15 October 2020
(2020-10-15)

The present application relates to a compound of formula I

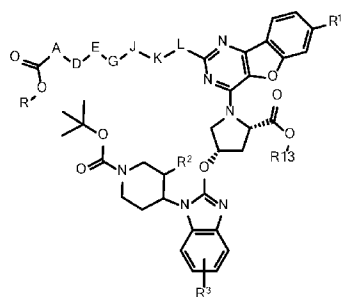


The compound of formula I are disclosed for use in the treatment of a disease that can be treated by the inhibition of cGAS.

Intermediate compounds to obtain a compound of formula I are also claimed in claim 31: formula (A-I)

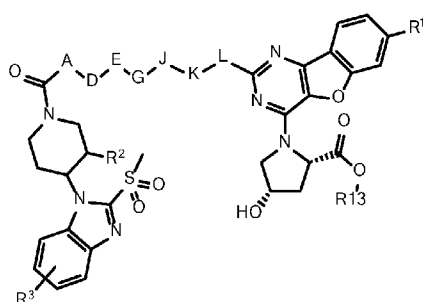


or formula (A-II),



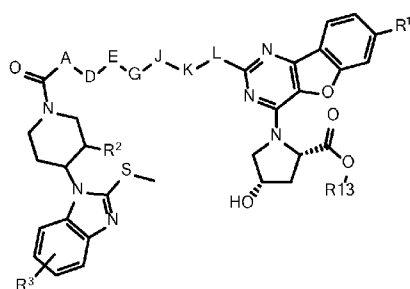
(A-II),

or formula (B-1)



(B-I),

or formula (B-II)



(B-II),

V-1. Novelty (Article 33(1) and (2) PCT):

The present compounds in formula I are novel over the cGAS inhibitors in D1-D2 at least on account of the linkage between the three membered heterocycle and the piperidine ring (see claim 1 in D1-D2 and closest compound 29 in D2).

Compounds in D3 are benzimidazole which are involved in the cGAS pathway lacking all other features of the present compounds (see claim 1 and [0006]-[0007]).

Also the intermediates in claim 31 are novel.

The present subject-matter can be considered novel in the sense of Article 33(2) PCT.

V-2. Inventive step (Article 33(1) and (3) PCT):

D1-D2, related to cGAS inhibitors, can be seen as the closest prior art to the present application.

The difference of the present compounds with those in the cited prior art is at least the presence of a linkage -A-D-E-G-J-K-L- between the three membered heterocycle and the piperidine ring. There is no effect linked to the cited difference and thus the problem underlying the present application can be seen in the provision of further cGAS inhibitors.

The solution are the present compounds as proven in the test results in Table 1 (pages 99-106).

The provision of the present macrocycles is not rendered obvious by the disclosure in D1-D4 nor appears to be obvious *per se*. D3 does also not offer any suggestion for the present solution.

For an intermediate taking part in a standard process for the preparation of an inventive product to be considered to be inventive, it must share with the latter the structural features that differentiate it from the prior art. Thus with regard to the intermediates in claim 31, they all appear to be necessary intermediates to prepare the present compounds sharing the differential feature with the final compounds and can equally be considered inventive.

The present subject-matter can thus be considered as involving an inventive step in the sense of Article 33(3) PCT.

V-3. Industrial applicability (Article 33(4) PCT):

Claims 1-42 fulfil the requirements of Article 33(4) PCT in respect to their industrial applicability.

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Item VIII

Certain observations on the international application

Claims 1-30 and 32-42 encompass a large number of compounds which are defined only by reference to a desired functional activity (compound being a "Prodrug"). This functional term does not give a specific technical guidance for the selection of the suitable derivatives, without proven general knowledge, to show which derivatives are

suitable "prodrugs" in the particular case of the current problem and thus could be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants.

The description does not provide support and disclosure within the meaning of Article 6 PCT for all possible prodrugs and, in addition, does not appear to be sufficiently disclosed under Art. 5 PCT for any of such compounds having the desired function and there is no general common knowledge of this kind available to the skilled person. In such a situation, the invention cannot be carried out over the whole claimed area without imposing an undue burden, even when simple in vivo or in vitro tests are available to determine whether or not a particular compound is covered by the claims.