

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/EP2024/055766

International filing date (day/month/year)
06.03.2024

Priority date (day/month/year)
13.03.2023

International Patent Classification (IPC) or both national classification and IPC
INV. A61P9/10 A61P13/12 A61P25/28 A61P31/00 A61P35/00 C07D401/04 C07D401/14 C07D471/04
C07D487/04 A61K31/4545 A61K31/519 A61K31/501

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
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Brandstetter, T
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 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.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. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

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. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

1 Reference is made to the following documents:

- D1 M. Jimenez-Sanchez et al., Nature Chemical Biology, 11 (5), 2015, pages 347-354, XP055479437
& M. Jimenez-Sanchez et al., "Supplementary information: Nature Chemical Biology, 11 (5), 2015, cited in the application, XP093067541
- D2 WO 2018/178384 A1 (2018-10-04), cited in the application
- D3 WO 2022/086920 A1 (2022-04-28), cited in the application
- D4 WO 2024/020517 A1 (2024-01-25)

Re Item II

2 The claimed priority appears to be valid.

Re Item V

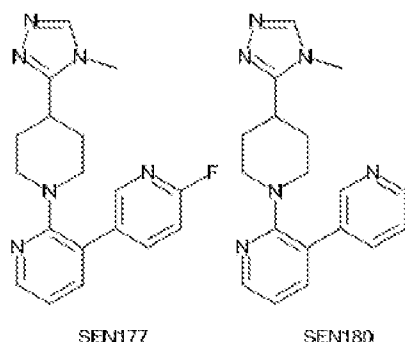
3 Claim 15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

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 use in a first or further medical treatment. Authorities other than the EPO, for example the USPTO might accept such claims as patentable.

4 Novelty (Article 33(2) PCT)

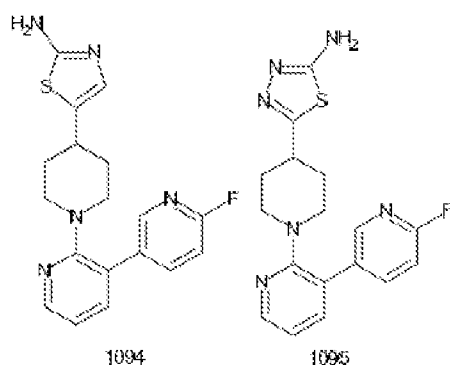
4.1 The present application is interpreted as referring to compounds of formula I (claim 1), compositions comprising them (claims 10-12) and their medical use (claim 14) in the treatment of cancer, fibrotic diseases, etc. (claims 15-16).

4.2 D1 discloses the human glutaminyl cyclase (hQC) inhibitors SEN177 and SEN180 (structures depicted below). SEN177 is disclosed therein (Fig 11a of supplementary information) as having a IC_{50} on isolated hQC of 53 nM and on isolated QPCTL of 13 nM. SEN180 is disclosed therein (Fig 11a of supplementary information) as having a IC_{50} on hQC of 170 nM and on QPCTL of 58 nM. The compounds of claim 1 carry a central cyanophenyl group instead of the pyridine in SEN177 and SEN180.

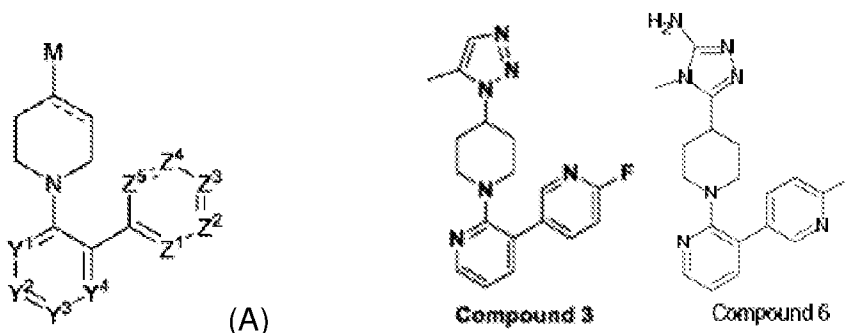


- 4.3 D2 discloses QPCTL inhibitors of the general formula A-B-D-E, wherein A can be 4-methyl-1,2,4-triazol-3-yl, B can be heterocyclyl and E can be heteroaryl (claim 1), which shall include examples 1094 and 1095 (Formula (XIIa) on page 123 and table on page 125). Formula (A) of claim 1 of D2 seems to need correction, since not all the specific compounds of D2 seem to fall within its scope (ring D in claim 1 of D2 cannot be pyridine [but heteroaryl-amino instead]).

D2 does not disclose any biological data for examples 1094 or 1095. The presently claimed compounds seem to differ from - or at least be a novel selection of - the compounds of D2 due to their cyanophenyl-moiety.



- 4.4 D3 discloses QPCTL inhibitors of the general formula (A), which include compounds 3 and 6. M in Formula (A) cannot be unsubstituted 4-methyl-1,2,4-triazol-3-yl- as required in present claim 1.



- 4.5 Novelty over D1-D3 can therefore be acknowledged.

- 5 Inventive step (Article 33(3) PCT)
- 5.1 Any of D1-D3 can be regarded as representing the closest prior art.
- 5.2 The application contains data (tables 2 and 3 on pages 43-44), which show that the example compounds exhibit significantly higher inhibitory activity on QPCTL and QPCT than most of the structurally closest related compounds of the prior art (SEN177 and SEN180 of D1, compounds 1094 and 1095 of D2 and compound 3 of D3) and similarly high activity as compound 6 of D3.
- 5.3 The problem to be solved can therefore be seen in the provision/selection of compounds with high inhibitory activity on QPCTL and QPCT which could be useful in the treatment of diseases such as cancer, fibrotic diseases, neurodegenerative diseases, atherosclerosis, infectious diseases or chronic kidney diseases.
- 5.4 As a solution, the present application provides compounds of formula I according to claim 1. In view of the data discussed in paragraph 5.2 above, the problem can be regarded as being solved.
- 5.5 Nothing in D1-D3 indicated the high activity of the presently claimed compounds, i.e. the solution is not obvious. The most active compound of the prior art (compound 6 of D3) leads the skilled person away from the presently claimed compounds. Inventive step can therefore be acknowledged for the compounds of claim 1 and subject-matter referring to them.
- 6 Industrial Applicability
- Claims 1-16 are considered to be industrially applicable, they fulfil the requirements of Article 33(4) PCT.

Re Item VI

- 7 D4 discloses compounds 24, 25, 26, 27, 30, 33, 38, 39, 53, 56, 57, 59, 66-71, 76, 77, 94, 100, 130, the top left compound on page 65, the compounds in the 4th row of page 66, the compound top right in the schemes in paragraphs [00419], [00432] and [00447], the starting materials in paragraphs [00467] and [00477], and the second compounds in schemes in paragraphs [00522] and [00613], which fall within the scope of at least claims 1-6 and 9. Compositions comprising them and their medical use in the treatment of cancer, etc. has also been disclosed in D4. D4 could therefore become relevant for novelty of at least claims 1-6 and 9-16.