

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.
PCT/EP2018/071039

International filing date (day/month/year)
02.08.2018

Priority date (day/month/year)
04.08.2017

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/5395 C07D413/10 C07D417/10 C07D491/107 C07D273/04 A61P35/00

Applicant
BAYER AKTIENGESELLSCHAFT

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 notified 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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>1-20, 22-495</u>
	No: Claims	<u>21</u>
Inventive step (IS)	Yes: Claims	<u>1-20, 22-495</u>
	No: Claims	<u>21</u>
Industrial applicability (IA)	Yes: Claims	<u>1-495</u>
	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

- 1 Claims 19 and 20 relates to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. 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 in a first or further medical treatment.
- 2 Reference is made to the following documents:
 - D1 WO 2014/164704 A2 (BROAD INST INC [US]; DANA FARBER CANCER INST INC [US]) 9 October 2014 (2014-10-09)
 - D2 WO 2017/027854 A1 (BROAD INST INC [US]; DANA-FARBER CANCER INST INC [US]; BAYER PHARMA AG) 16 February 2017 (2017-02-16)
 - D3 WO 02/072103 A1 (MERCK PATENT GMBH [DE]; SUTTER ARNE [DE]; EHRING THOMAS [DE]; WELGE TH) 19 September 2002 (2002-09-19)
 - D4 DE 199 29 787 A1 (BAYER AG [DE]) 4 January 2001 (2001-01-04)
 - D5 EP 0 080 296 A1 (ICI PLC [GB]) 1 June 1983 (1983-06-01)
 - D6 US 4 158 094 A (NIZNIK GEORGE E [US]) 12 June 1979 (1979-06-12)
 - D7 EP 2 281 822 A1 (SERVIER LAB [FR]) 9 February 2011 (2011-02-09)
- 3 The current application discloses dihydrooxadiazone derivatives and their use for the treatment of cancer. The compounds of the current application differ from those of D1 and D2 through the inclusion of the oxygen in the ring. They differ from those of D3 through the absence of a substituent on the nitrogen and they differ from those of D4 through the choice of substituent in position R3. The subject-matter of claims 1-20 is therefore novel in the sense of Art. 33(2) PCT.

D5-D7 all discloses individual compounds falling within the scope of claim 21 (D54, Compound where R7 is H, R4 is fluoro and R5 is H, page 14; D6, 5-(p-bromophenyl)-3,6-dihydro-1,3,4-oxadiazin-2-one, page 1, column 1, line 62 - line 63; D7, 5-(4-Chloro-phényl)-3,6-dihydro-[1,3,4]oxadiazin-2-one, page 31, paragraph 150 - paragraph 151). The subject-matter of claim 21 is therefore not novel in the sense of Art. 33(2) PCT.

None of these documents mention the use of said compounds in the synthesis of the compounds of claims 1-7. The subject-matter of claim 22 is therefore novel in the sense of Art. 33(3) PCT.

- 4 Document D1 is considered the most relevant prior art and discloses similar compounds with the same activity. The problem to be solved by the current application is considered to be the provision of alternative compounds for the treatment of cancer. The addition of an oxygen atom in the ring would not have been obvious to the person skilled in the art. D3 and D4 disclose similar compounds containing a dihydrooxadiazone moiety, however, these compounds are for the treatment of cardiovascular disorders or anemia. The data provided in table 6 (pages 451-456) demonstrates that the compounds tested display the desired activity. Claim 1 would appear to represent a reasonable generalisation of said compounds. It is therefore possible to acknowledge an inventive step in the sense of Art. 33(3) PCT.

Re Item VII

Certain defects in the international application

- 1 The proviso in claim 1 serves to exclude a specific compound disclosed in D4. This should be made clear in the description and the relevant prior art should be cited (Rule 5.1(a)(ii) PCT). The same holds true for the compounds of D5 disclaimed in claim 21.

Re Item VIII

Certain observations on the international application

- 1 Claims 14-18 should be reformulated as purpose limited compound claims ("A compound according to for use...").