

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/EP2016/074008	International filing date (day/month/year) 07.10.2016	Priority date (day/month/year) 09.10.2015
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International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/22 C07D487/22 A61K31/438 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 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 Gutke, Hans-Jürgen Telephone No. +49 89 2399-0	
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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:
 - ☐ 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>1-23, 25</u>
	No: Claims	<u>24</u>
Inventive step (IS)	Yes: Claims	<u>15</u>
	No: Claims	<u>1-14, 16-25</u>
Industrial applicability (IA)	Yes: Claims	<u>1-25</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

1 Claims 19, 20 and 25 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.

2 Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D1 WO 2012/038307 A1 (HOFFMANN LA ROCHE [CH]; CHU XIN-JIE [US]; DING QINGJIE [US]; JIANG NAN) 29 March 2012 (2012-03-29)

3 Novelty

3.1 D1 discloses spirocyclic compounds and their use as inhibitors of MDM2 for the treatment of cancer (cf. D1, claims 1 and 11). The compounds of D1 differ from the present compounds with regard to the number of additionally fused ortho-fused rings, since in the present compounds there are two additional fused rings and also with regard to the position of one nitrogen in the spirocyclic ring system. D1 is therefore not relevant for novelty.

3.2 The compounds of D1 are relevant for novelty of present claim 24 (cf. item clarity") since the compounds of D1 are known for a medical use according to claim 24.

4 Inventive Step

4.1 D1 is regarded as closest prior art. The objective problem is seen in the provision of alternative compounds which are inhibitors of MDM2 for the treatment of cancer.

- 4.2 The applicant provides the compounds of formula I. For a number of specific compounds the applicant describes their inhibitory activity on MDM2 (cf. pages 333-334). However, the tested compounds belong to a small subgenus of the compounds of formula I, .e. only compounds wherein R1 = alkyl, R2 = phenyl, ring A = phenyl, E = N, D and F = carbon, n = 1 or 2, W, X and Y = carbon. Only for the generalisation of the successfully tested compounds the solution of the problem is at present acknowledged. At present only the compounds of present claim 15 appear to solve the problem as stated above.
- 4.3 It is considered that the structural modifications underlying the present solution of the problem namely the two additional fused rings and also the position of one nitrogen in the spirocyclic ring system, is not suggested by D1 and therefore not obvious. The requirements of inventive step do not appear to be fully met for claims 1-8 and 12-15.

Item VIII

- 5 The therapeutic application of present claim 19 is functionally defined (through the inhibition of the interaction of two proteins). This renders the claim unclear.
- 6 In claim 24 the feature "prepared for being administered .." is not regarded as limiting feature. Claim 24 therefore relates only to the medical use of all possible compounds. Cf. item "novelty".
- 7 Independent claim 15 should be made dependent on claim 1 (conciseness).