

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/IB2015/059843	International filing date (day/month/year) 21.12.2015	Priority date (day/month/year) 23.12.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D487/04 A61K31/519 A61P35/00		
Applicant NOVARTIS AG		

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 Sahagún Krause, H 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>1-20</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-20</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-20</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

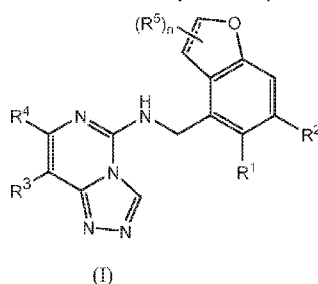
Re Item V

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

Reference is made to the following documents:

- D1 WO 03/044021 A2 (AMGEN INC [US]; CAI GUOLIN [US]; CHAU JENNIFER N [US]; DOMINGUEZ CELIA) 30 May 2003 (2003-05-30)
- D2 WO 2014/144747 A1 (EPIZYME INC [US]) 18 September 2014 (2014-09-18)

The present application discloses compounds of Formula (I) as inhibitors of the activity of polycomb repressive complex 2 (PCR2) through targeting the subunit EED (embryonic ectoderm development):



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

Compounds of formula (I) are novel over the compounds in D1 at least on account of the present R₄ group (see claim 1 in D1) and further over the exemplified compounds in D1 on account of the present oxygen containing bicycle (see Table 5).

they are also novel over the compounds in D2 at least on account of the present triazolo[4,3-c]pyrimidine (see claim 1 in D2).

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):

The compounds in D1 are disclosed as useful in the treatment of cancer through modulation of interleukin-1 and tumour necrosis factor- α . The compounds in D2 are disclosed as inhibitors of the activity of PCR2 through targeting the subunit EZH2.

D2 is therefore considered the closest prior art to the present compounds.

The difference between D2 and the present compounds is at least the present triazolo [4,3-c]pyrimidine bicycle and the aminomethyl linker.

The effect is that compounds are obtained that act as inhibitors of the activity of PCR2 through a different target, namely the subunit EED (see competition binding assay with EED-H3K27Me3 test results in Table 3, p. 150-171 and antiproliferative assay results in Table 4, p. 172).

The problem which the present application has to solve was thus the provision of compounds with activity as inhibitors of the activity of PCR2 through targeting the subunit EED.

The solution are the present compounds. This solution is not considered obvious since none of the prior art documents disclose or even suggest the use of similar compounds for targeting said subunit.

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

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

Claims 1-20 fulfill the requirements of Article 33(4) PCT in respect to their industrial applicability.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

Re Item VIII

Certain observations on the international application

Claim 13 contains references to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.