

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/EP2015/075765

International filing date (day/month/year)
05.11.2015

Priority date (day/month/year)
07.11.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 C07D233/24 C07D295/088

Applicant
BAYER PHARMA 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 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

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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>1-9</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-9</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-9</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

Re Item V

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

1. The invention relates to an alternative process for preparing copanlisib (7) or its dihydrochloride salt (8) which involves a ring-closure reaction of a substituted imidazoliny-aniline derivative (5) obtained by reduction of the nitro group containing key-intermediate (4).

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

- D1 WO 2008/070150 A1 (BAYER PHARMACEUTICALS CORP [US];...) 12 June 2008
- D2 FUJIOKA ET AL: "One-pot synthesis of imidazolines from aldehydes: detailed study about solvents and substrates", TETRAHEDRON, 63, no. 3, 13 December 2006, pages 638-643, XP005802290

2. The specific intermediate compound (4) and its precursor (3) are not disclosed in the prior art. Structurally resembling compounds of D1 (see page 53) and D2 (see table 2) do not exhibit the combination of present ether and nitro groups. Since all claims refer at least to one of these novel products the novelty requirement of Art. 33 (2) PCT is met by the present claims.

3. D1 discloses on page 53 a synthesis route leading to present (7)/(8). The currently proposed process differs from the prior art in that the imidazoline group in present (4) is introduced at a rather early stage of the multi-step synthesis process where the amino group required in the ring-closure step (see present step A5) is present as a nitro precursor group. According to the information given on present page 10 the present process allows to use reagents which are not hazardous when compared to the ammonia/iodine system which is of severe safety concern in industrial manufacturing processes. Accordingly, the objective technical problem can be seen in the provision of an alternative method of preparing (7)/(8) which is viable and safe at an industrial scale.

As shown in the present examples, the problem has been solved by the use of the nitro-imidazoline compound (4) as the key-intermediate in the multi-step synthesis route leading to (7)/(8).

The skilled person does not find in D1 the incentive to modify the sequence of functional group interconversions. Nothing points to the advantages which arise from an earlier introduction of the imidazoline group (see the summary on page 10 of the present description). While the conversion of an aldehyde group to an imidazoline group per se is a functional group conversion described in the prior art (see for instance, Table 2 of D2) the skilled person would not have derived from the prior art disclosure its suitability for the particular synthesis problem under consideration. The imidazoline derivatives obtained according to D2 lack the substituents and the substitution pattern of the present intermediates (4) and (5). In particular, the prior art compounds lack the nitro and amino groups which are essential for the ring-closure reaction. The skilled person would therefore not have been tempted to modify the process of D1 by the method described in D2.

In view of the above, the consideration of the key-intermediate (4) in the synthesis of (7)/(8) would not have been obvious for the skilled person. Since (4) could not be made without its novel aldehyde precursor (3), also the compound (3) is considered to have involved an inventive step. Consequently, present claims 1 to 8 meet the requirement of Art. 33(3) PCT by virtue of their reference to present (4) and/or (3).

Re Item VIII

Certain observations on the international application

1. The process claims contain a number of features which are said to be optional or exemplary (see "optionally" or "such as"). Such features have no limiting effect on the scope of the claims and should have been placed in separate and dependent claims in order to comply with the requirement of Rule 6.4(a) to (c) PCT.
2. Contrary to the requirement of Rule 5.1(a)(ii) PCT the relevant prior art disclosed in D2 has not been mentioned in the description.