

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/EP2015/057546

International filing date (day/month/year)
08.04.2015

Priority date (day/month/year)
11.04.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D498/14 A61K31/529 A61P35/00

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>1-27</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-27</u>
Industrial applicability (IA)	Yes: Claims	<u>1-27</u>
	No: Claims	

2. Citations and explanations

see separate sheet

1 **Re Item V**

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

1.1 Reference is made to the following documents:

D1 US 2004/209895 A1 (LUECKING ULRICH [DE] ET AL) 21
October 2004 (2004-10-21)

D2 WO 2013/037896 A1 (BAYER IP GMBH [DE]; LUECKING
ULRICH [DE]; KOSEMUND DIRK [DE]; SCHOLZ A) 21 March
2013 (2013-03-21)

1.2 The present application relates to macrocyclic compounds (formula (I)) useful in the treatment of cancer, inflammatory and cardiovascular diseases in view of their activity CDK (selectively for CDK9) as well as two linear compounds (i.e. compounds of formula (7) and (26)) used as intermediates in the process for preparing the macrocyclic compounds.

1.3 **Novelty**

The current compounds differ from the compounds disclosed in D1 in that the formula of D1 does not comprise compounds in which B-X-A may represent the residue phenylene-O-L-O-phenylene/pyridinylenes as shown in the compounds of the present application. The compounds disclosed in D2 are not macrocyclic and differ from the intermediates of the current application, since they do not carry the group phenylene-O-L-O-phenylene/pyridinylenes as shown in the intermediates of the present application. The macrocyclic compounds disclosed in D3 also do not carry a group phenylene-O-L-O-phenylene/pyridinylenes and, in addition, they carry an indole in the place of a phenylene. Novelty is thus acknowledged.

1.4 **Inventive step**

The problem underlying the present application appears to reside in the provision of compounds which are antiproliferative agents active on the CDK. In the application, see pp 55-56, the macrocyclic compounds of the current application are said to show a surprisingly higher potency in CDK9 inhibitory activity as compared to the CDK9 inhibitors of the prior art.

1.5 D1 to D3 disclose compounds with the same qualitative activity. D1, which is considered to represent the closest state of the art, discloses macrocyclic compounds which inhibit i.a. CDK9 (see [0159]). A comparison of the structures indicates that the essential part of the molecule appears to be the pyrimidine/pyridine-NH-phenyl/pyridine substituted by a sulfinyl/sulfonyl group;

D1 and D3 teach that such a structure may be linked to form a macrocyclic structure. The nature of the link may vary in length and may incorporate a further ring (see e.g. D1, pp. 47-48).

In view of the fact that the current compounds are seen as derived from obvious structural modifications of the compounds disclosed in the closest prior art D1, the provision of the current compounds for the alleged use as alternative to the ones disclosed in D1 is not considered to involve an inventive step. However, if the Applicant were able to provide evidence of the superior potency of the current compounds compared to the prior art as implied already in the application, inventive step could be acknowledged. It is pointed out that the evidence should show for a representative group of the claimed compounds since the problem should be shown to be solved over the whole ambit of claim 1.