

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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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/EP2015/067804

International filing date (day/month/year)
03.08.2015

Priority date (day/month/year)
04.08.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/04 A61K31/5377 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 43*bis*.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>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-15</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

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

1 Prior art

Reference is made to the following documents:

D1: WO 2011/163527

D2: WO 2010/073034

2 Novelty

The claimed compounds of formulae (I) and (Ib) and the intermediates claimed in claim 15 differ from the compounds disclosed in D1 and D2 in view of their 2-(morpholin-4-yl)-1,7-naphthyridine moiety.

3 Inventive step

3.1 The present application is directed to 2-(morpholin-4-yl)-1,7-naphthyridine derivatives of formulae (I) and (Ib) and use thereof as ATR kinase inhibitors in the treatment of cancer.

The closest prior art is represented by D1 or D2 which both disclose ATR kinase inhibitors.

The claimed compounds are structurally remote from those disclosed in D1 and D2 in view of their 2-(morpholin-4-yl)-1,7-naphthyridine moiety. The compounds disclosed in D1 are pyrrolopyrazine derivatives and those disclosed in D2 are pyrimidinyl indole derivatives.

The technical problem underlying the present invention is seen as the provision of further ATR kinase inhibitors for the treatment of cancer. The claimed compounds are solutions to said technical problem as shown in table 7 on pages 446-459.

There is no hint in the prior art that a 2-(morpholin-4-yl)-1,7-naphthyridine scaffold would be appropriate for preparing ATR kinase inhibitors. An inventive step is therefore acknowledged for the claimed compounds of formulae (I) and (Ib).

3.2 An inventive step is equally acknowledged for the intermediates claimed in claim 15 as said intermediates possess the distinguishing technical feature of the inventive end-products of formulae (I) and (Ib) i.e. the 2-(morpholin-4-yl)-1,7-naphthyridine moiety.