

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/EP2016/067477	International filing date (day/month/year) 22.07.2016	Priority date (day/month/year) 27.07.2015
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International Patent Classification (IPC) or both national classification and IPC
INV. C07D235/30 A61K31/4184 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:  European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Hoepfner, Wolfgang Telephone No. +49 30 25901-0	
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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>1-10</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-10</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-10</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

- D1 WO 2010/151441 A1 (WANG TONG [US]; GATELY STEPHEN [US]; TRANSLATIONAL GENOMICS RES INST []) 29 December 2010 (2010-12-29); cited in the application
- D2 WO 2013/046136 A1 (NOVARTIS AG [CH]; CHO YOUNG SHIN [US]; LEVELL JULIAN ROY [US]; TOURE B) 4 April 2013 (2013-04-04)

Re Item V

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

Novelty

The document D1 discloses 2-(phenylamino)-benzimidazole compounds and their use in the treatment of cancer from which the compounds of claim 1 mostly structurally differ in that the substituent at position 4 of the anilino moiety is trifluoromethoxy (see page 1, lines 9-15; page 1, line 24; page 17, line 14 - page 19, line 8; Examples; pages 33-35).

The document D2 discloses 3-pyrimidin-4-yl-oxazolidin-2-one compounds and their use in the treatment of cancer which are inhibitors of mutant IDH proteins (see page 1, lines 4-8; page 2, lines 10-12; page 2, Formula (I); page 30, line 16 - page 34, line 6; Examples; pages 280-301).

In view of this prior art, the subject-matter of independent claims 1, 4 and 5-7 and dependent claims 2, 3 and 8-10 is deemed novel by this Authority.

Inventive step

The *subjective* problem underlying the novel subject-matter may be regarded as the provision of effective medicaments for the treatment of tumours (see description, page 1).

Even, if document D2 addresses compounds which are likewise inhibitors of mutant IDH proteins, the document D1 which is likewise related to treatment of cancer (see D1, page 1) is deemed the closest prior art for this subject-matter, since its compounds come structurally closest to it.

The primary distinguishing features between the novel subject-matter and the subject-matter of D1 is to be seen in that the substituent at position 4 of the anilino moiety is trifluoromethoxy and in that the said imidazole compound is used as 1:4 adduct with fumaric acid.

The experimental data on file (see description, pages 15-23) give rise to the assumption that the novel subject-matter may be useful in the treatment of tumours.

However, since it is not possible to determine by direct comparison to the data provided by D1 (see D1, pages 33-35), if the said distinguishing feature gives rise to technical advantages over D1, the *objective* problem underlying the novel subject-matter can merely be regarded as the provision of *further* medicaments for the treatment of tumours.

The claimed solution to this very general problem was the selection and modification of suitable candidate compounds from D1 and their combination with fumaric acid in order to arrive at the novel composition of claim 1.

However, since this solution was not derivable from the prior art on file, either read alone or in combination; and since it is deemed surprising that of all things this particular solution would give rise to useful medicaments; the presence of inventive step for the novel subject-matter can be acknowledged by this Authority.