

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.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/EP2019/058389	International filing date (day/month/year) 03.04.2019	Priority date (day/month/year) 10.04.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07D405/12 C07D249/12 A61P35/00 A61K31/4196		
Applicant BAYER 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 43*bis*.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 66.1*bis*(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 Hanisch, Inken 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. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

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>1-30</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-30</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-30</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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 II.

The current claims are considered to be entitled to the earliest priority date of 10.04.2018.

Re Item V.

Reference is made to the following documents:

- D2 JOURNAL OF MEDICINAL CHEMISTRY 2013, 56 (8), 3148-3167, DOI:
 10.1021/jm301848w
- D3 CN 103 006 645 A

Claims 20, 21 and 24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Novelty

None of D2 and D3 disclose the compounds of any of current formulae (I), (A9), (A7), (A6), (A5) or (A4). As a consequence, not only the respective product claims but also the preparation method of compounds of formula (I) and pharmaceutical compositions comprising the compounds of formula (I) as well as medical uses thereof are novel in the sense of Article 33(2) PCT.

Inventive Step

D2 and D3 both disclose various inhibitors of DHODH. The current application provides a crystal form of the compound of current formula (I) which according to the experimental data provided in D1 (see item VI. below; example 121 in table 3) is a DHODH inhibitor as well.

In the absence of any improved effect vis-à-vis D2 or D3 the current application is therefore considered to solve the problem of providing further DHODH inhibitors useful for the treatment of particularly cancer.

As the skilled person looking for a solution to the given problem had no incentive from the disclosure of the structurally remote known agents of D2 or D3 to chose the compound of current formula (I), an inventive step in the sense of Article 33(3) PCT may be acknowledged. The current preparation process towards the compound of formula (I) thus is considered to be non-obvious as well, the same as the currently claimed intermediate compounds of formulae (A9) and (A4)-(A7), all of which share the non-obvious 4-ethyl-5-substituted-1,2,4-triazolin-3-one ring with the inventive compound of formula (I).

Re Item VI.

Certain documents cited

Application No	Publication date	Filing date	Priority date
D1: WO 2018/077923 A1	03-05-2018	25-10-2017	27-10-2016

D1 has been filed prior to the current priority date of 10.04.2018 but published only in-between the said current priority date and the current filing date of 03.04.2019. As a consequence, D1 may only be taken into account for the assessment of novelty of current subject-matter entitled to the said current priority date. It is noted that D1 discloses the compound of current formula (I) in example 121, however, apparently no crystalline form thereof. The current preparation process, moreover, differs from all preparation schemes disclosed on pages 197f of D1 (from scheme 1 essentially on account of the intermediate protection of the hydroxymethylene group; from schemes 2-5 essentially on account of the order of adding the triazole group, the optically active reagent (xxx6) and finally the amine (xxx7)). The intermediate compounds of current formulae (A9) and (A4)-(A7) essentially differ from the disclosure of D1 on account of their 2-tetrahydropyranyloxymethyl group in 5-position of the triazole ring.

Re Item VIII.

According to particularly current pages 18-24 all current steps of the currently claimed preparation processes are considered to only work successfully in case certain crucial conditions are respected as disclosed on the said pages. These essential technical features are not yet apparent from current claims 1-16.

Furthermore, the scope of protection sought by current claim 17 is not clearly defined as the skilled person is left in doubt as to all properties/characteristics of the claimed crystalline form A of compound (I) in comparison to any potential further crystalline form thereof.

It is noted that inconsistencies exist between the text and the respective formulas disclosed on current pages 8f (e.g. line 15 "formula (A7)" vs. line 17 "(A7.1)" etc.).

It is further noted that D2 and D3 are not yet cited and briefly discussed.