

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/EP2015/069739

International filing date (day/month/year)
28.08.2015

Priority date (day/month/year)
01.09.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 A61K31/5025 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

Authorized Officer

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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. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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>1-14, 17-21</u>
	No: Claims	<u>15, 16</u>
Inventive step (IS)	Yes: Claims	<u>1-14, 17-21</u>
	No: Claims	<u>15, 16</u>
Industrial applicability (IA)	Yes: Claims	<u>1-21</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

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 IV

Lack of unity of invention

The International Searching Authority found the following groups of inventions, which are not linked by a common inventive concept:

1. claims: 1-15, 17-21

A process for the preparation of a compound of formula (I) and the new intermediates of formula (IV) and (VI) of this process

2. claim: 16

A crystalline form of N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide

WO 2014/020041 A1 (D1) discloses the present title compound N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide as well as a process for its preparation.

D1 could be regarded as the closest prior art.

The problem of the present invention 1 was the provision of a new process for the preparation of a compound of formula (I) and new intermediates of this process.

This problem is solved by the process of the present claim 1 and by the new intermediates of formulae (IV) and (VI) of the present claims 17 and 19.

The problem of the present invention 2 was the provision of a new solid form of the present title compound N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide.

This problem could be solved by the crystalline form characterized by the x-ray diffractogram of the present figure 1 and by the peaks specified in the present claim 16.

The process of the present claim 1 is not a process for the crystallisation of the title compound, but a new process for its synthesis. It is also not limited to the present title compound but encompasses the generic compound group of formula (I). Process parameters specifying the crystallisation step are defined only the dependent claim 14.

Since the present title compound N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide as well as a process for its preparation is already known from D1, the present claim set falls apart into two different groups of inventions which are not linked by a common inventive concept.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are cited in the present International Search Report:

- D1 WO 2014/020041 A1 (BAYER PHARMA AG [DE]) 6 February 2014 (2014-02-06)
- D2 WO 2014/131739 A2 (BAYER PHARMA AG [DE]) 4 September 2014 (2014-09-04), P-document, cited in the application
- D3 WO 2014/198776 A1 (BAYER PHARMA AG [DE]) 18 December 2014 (2014-12-18), P-document

Novelty (Article 33(2) PCT)

The present title compound N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide is already known from D1.

The reference to the process of claim 13 (product-by-process) in the present claim 15 does not make the known compound novel.

The present title compound is obtained in D1 as a solid product. D1 does not disclose whether the solid product is amorphous or crystalline.

The present application does not disclose any comparative data which would prove the novelty of the claimed crystalline form of the present claim 16 over the solid form obtained in D1.

Therefore the present claims 15 and 16 lack novelty in view of D1.

The process of the present claim 1 differs from the process in D1 in the intermediates of formulae (IV) and (VI).

The process of claim 1 as well as the intermediates of formulae (IV) and (VI) of the present claims 17 and 19 are novel.

Inventive Step (Article 33(3) PCT)

D1 discloses the present title compound N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide as well as a process for its preparation.

D1 could be regarded as the closest prior art.

The problem of invention 1 was the provision of a new process for the preparation of a compound of formula (I) and new intermediates of this process.

This problem is solved by the process of the present claim 1 and by the new intermediates of formulae (IV) and (VI) of the present claims 17 and 19.

The present application discloses exemplary processes and intermediates thereof (e.g. pages 30 to 42, examples 1 to 13).

It is credible that the problem has been solved over the whole of the scope of invention 1.

The process of claim 1 differs substantially from the process in D1. In the present process the 6-phenoxy group is introduced first (process step (a), intermediate (IV)), then the 3-phenyl group (process step (c), intermediate (VI)) and finally the 8-alkylamino group. In D1 first the 8-alkylamino group is introduced, then the 3-phenyl group and then the 6-phenoxy group.

None of the present process steps (a) or (b) or of the present intermediates (ICVI or (VI)) are suggested by D1.

The scope of invention 1 corresponds to the contribution to the prior art.

The matter of the present invention 1 is based on an inventive step.

The problem of the present invention 2 was the provision of a new solid form of the present title compound N-cyclopropyl-4-{6-(2,3-difluor-4-methoxyphenoxy)-8-[(3,3,3-trifluoropropyl)amino]imidazo[1,2-b]pyridazin-3-yl}-2-methylbenzamide.

This problem could be solved by the crystalline form characterized by the x-ray diffractogram of the present figure 1 and by the peaks specified in the present claim 16.

So far it has not been proven that the claimed crystalline form is novel over the solid form disclosed in D1.

The provision of known compound in a crystalline form is also usually not regarded as an activity which would require an inventive step, but as a routine activity for a skilled person working in organic chemistry and/or drug development.

Therefore the matter of the present invention 2 lacks an inventive step.

Re Item VI

Certain documents cited

The two P-documents D2 and D3 have essentially the same relevant disclosure content as D1 with regard to the present inventions 1 and 2.

The claimed priority (01-09-2014, EP 14183029.9) is valid.

D2 and D3 could play a role in the assessment of novelty in the European phase.

Re Item VII

Certain defects in the international application

Description

The relevant prior art D1 and D3 has not been cited in the description.

With entry into the regional phase before the EPO:

- When filing amended claims the description has to be brought in line with the amended claim set at the same time.
- Those parts of the application which then do not refer any more to the claimed invention must be deleted.
- The relevant prior art D1 and D3 cited in the present search report must be cited in the description.
- A marked-up version wherein the amendments are visible as well as a readable, re-typed version (clean copy) as the print version must be filed at the same time, in order to avoid print errors (hand-amended pages are not allowed as the print version).
- The basis for the amendments in the application as originally filed must be indicated.

Re Item VIII

Certain observations on the international application

Lack of Clarity (Article 6 PCT)

Claim 15 is directed to a product-by-process of a low molecular, structurally well-defined compound and therefore not allowable.