

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/EP2015/080041	International filing date (day/month/year) 16.12.2015	Priority date (day/month/year) 18.12.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D213/84 C07D405/12 C07D213/56 C07D213/61 C07D213/64 C07D213/65 A61K31/4418 A61P1/00 A61P15/00 A61P29/00		
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 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 Kiernan, Andrea 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. 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>1-26</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>9-11, 15, 16</u>
	No: Claims	<u>1-8, 12-14, 17-26</u>
Industrial applicability (IA)	Yes: Claims	<u>1-26</u>
	No: Claims	

2. Citations and explanations

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 V

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

- D1 WO 2011/051165 A1
- D2 US 2011/034450 A1
- D3 XP55191514 (Korotkova, M. et al., Basic & Clinical Pharmacology & Toxicology, vol. 114, no. 1 (2013), p. 64-69)
- D4 XP55191557 (Xu, D. et al., J. of Pharmacology and Experimental Therapeutics, vol. 326, no. 3 (2008), p. 754-763)
- D5 XP026939427 (Mbalaviele, G. et al., Biochemical Pharmacology, vol. 79, no. 10 (2010), p. 1445-1454)
- D6 XP55191511 (Finetti, F. et al., PLoS ONE, vol. 7, no. 7 (2012), p. e40576)
- D7 XP025468966 (Aquino, M. et al., Bioorg. & Med. Chem., vol. 16, no. 19 (2008), p. 9056-9064)

The application relates to substituted pyridyl-cycloalkyl-carboxylic acids, to pharmaceutical compositions containing them, and their use for the treatment or prophylaxis of pain, or for the treatment or prophylaxis of pain syndromes (acute and chronic), inflammatory-induced pain, pelvic pain, cancer-associated pain, endometriosis-associated pain as well as endometriosis and adenomyosis as such, cancer as such, and proliferative diseases as such like endometriosis.

The compounds are described as microsomal prostaglandin E synthase-1 inhibitors.

Novelty

D1 and D2 disclose 3-phenylpropionic acid derivatives for the treatment of the same or similar diseases such as atherosclerosis and myocardial infarction which differ from the presently claimed compounds in the definition of the variable R⁵ in present Formula (I), i.e. they do not contain a pyridine ring directly connected to the second phenyl ring.

D3 and D4 disclose the compound MF63 (for structure see D4, page 757, Figure 2) which acts as a selective microsomal prostaglandin E synthase-1 inhibitors, i.e. acts via the same mechanism as the presently claimed compounds of Formula (I). The compound MF63 structurally differs considerably from the claimed compounds.

D5-D7 also disclose further microsomal prostaglandin E synthase-1 inhibitors. The compounds described therein also differ considerably from the presently claimed compounds; they do not contain a pyridine ring or a carboxylic acid functional group.

The subject-matter of claims 1-26 is thus novel over the available prior art (Article 33 (2) PCT).

Inventive Step

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-8, 12-14 and 17-26 does not involve an inventive step.

D1 and D2 disclose structurally very similar compounds for use in the treatment of diseases some of which overlap or are related to the diseases to be treated by the presently claimed compounds (for example atherosclerosis and myocardial infarction).

Example 115 on page 200 in D2, for example, differs from the presently claimed compounds only in the variable R⁵ of present formula (I), i.e. no substituted pyridine ring is present in the compounds of D2 (and similarly in the compounds of D1).

However, while the presently claimed compounds are described as inhibitors of microsomal prostaglandin E synthase 1, the compounds in D1 and D2 are said to act via a different mechanism of action (stimulation of soluble guanylate cyclase).

In order to make it credible that all compounds falling within the scope of present formula (I) show the desired activity and are thus able to solve the problem posed, the claimed compounds should share one or more common structural elements which differ from the compounds of the prior art and which can be said to be responsible for the difference in activity or mechanism (new technical teaching).

It is observed that in all the 215 examples in the present application, the moiety R⁵ represents a pyridine-3-yl ring, i.e. the pyridine ring is connected to the phenyl ring in the 3-position.

The scope of possible substituents on said pyridine ring in claim 1 is considered too broad in scope in comparison with the substituents in the examples and in view of the fact that this part of the molecule is the only part which could be responsible for the different activity of the claimed compounds.

The subject-matter of present claims 1-8, 12-14 and 17-26 is therefore not considered inventive in view of D1 and D2 (Article 33(3) PCT).

An inventive step can be acknowledged for the subject-matter as disclosed in present claims 9-11, 15 and 16 wherein the variable R⁵ is specified such that the problem can be considered credibly solved.

Industrial Applicability

Industrial applicability is acknowledged.

Re Item VIII

Certain observations on the international application

- 1 Claims 18 and 20-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of the present claims 18 and 20-22 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to compounds or compositions for use in a first or further medical treatment.

- 2 The expression "or an isomer thereof" in present claims 1, 17, 18, 19, 23, 24, 25 and 26 renders the scope of the claims unclear since the term isomer does not describe a limited and well-defined group of compounds (Article 6 PCT).

- 3 Claims 12, 15, 17, 18, 19, 20, 21, 22, 24, 25 and 26 contain further preferred features which define a second scope of protection within one claim ("particularly...", "such as....", "including...", "preferably...."). This renders the scope of the claims unclear (Article 6 PCT).

It could also be argued that these features are simply non-limiting for these claims. In this case, they are superfluous, and the requirement of conciseness is not met (Article 6 PCT).

Such further preferred features have to be deleted or formulated as separate dependent claims.

It is additionally mentioned that the parenthesis in some of these claims also render the scope of the claims unclear since it leaves the reader in doubt as to whether or not the subject-matter between parenthesis is meant to be limiting (Article 6 PCT).

- 4 The expression "or a mixture of the same" in claims 17-19 is confusing since it is not entirely clear to which feature(s) in the list it refers - a combination at least of some features in the list before said expression would not appear to make sense (Article 6 PCT).

- 5 Claim 23 is formulated as a compound for the manufacture of a medicament and is thus not properly formulated as a medical use claim. This renders the category and thus the scope of said claim unclear (Article 6 PCT).

- 6 According to the description page 19, lines 1-3, the invention also relates to metabolites and prodrugs. Said statement renders the scope of the claims unclear when used to interpret them (Article 6 PCT).

- 7 It appears that the Examples 158, 159, 160, 162, 163, 164, 165, 166 and 193 in the description and listed in present dependent claim 16 do not fall within the scope of formula (I) in claim 1 since the linker X does not fall within the definition in claim 1.

This renders the scope of the claims unclear (Article 6 PCT).

- 8 In various examples in the description, some compounds are named "stereoisomer 1/2/3/4" or "stereoisomeric mixture 1".

However, it is not clear what this means since both the structural formulae in the description and the compound names are identical, and it appears that the isomers had not been further identified or characterized.

The nature of these examples is thus unclear (Article 6 PCT).