

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

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/US2015/055421	International filing date (day/month/year) 14.10.2015	Priority date (day/month/year) 15.10.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D405/14 C07D413/14 C07D405/04 C07D417/14 A61P13/12 A61P9/12 A61P9/10 A61K31/43		
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

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 Seelmann, Marielle 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. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1, 2, 4(all partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1, 2, 4(all partially) are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a) or (b).

☒ See Supplemental Box for further details

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>3, 5-14(completely); 1, 2, 4(partially)</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>3, 5-14(completely); 1, 2, 4(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>3, 5-14(completely); 1, 2, 4(partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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 III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Compounds of claim 2 for which X = O and R4 = CH₂-SO₂-C₁₋₃alkyl do not fall under formula I of claim 1, even though claim 2 is dependent thereof. This discrepancy of scope between claims 1-2 leads to doubts about the exact extent of protection sought. This needs to be clarified (Art. 6 PCT).

The same problem exists in present claim 4 as well (Art. 6 PCT).

Re Item V

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

1 Medical uses

Claims 11-13 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.

Patentability, in particular novelty and inventive step, of claims 11-13 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 Article 33 PCT

D1 US 2010 029 2225

D2 WO 2014 055 595

D3 S. Lucas et al., J. Med. Chem., 51, 8077-8087 (2008)

D4 WO 2010 042 477

2.1 Novelty (Art. 33(2) PCT)

Known aldosterone inhibitors are structurally characterized by a pyridine linked to benzofurane or benzodioxole in D1 (compounds 59-60 and 81), an indole system in D2 (formula I in claim 1) or benzodioxane in D3 (compound 8).

Benzodioxane derivatives wherein an 1,3-diazaring is attached directly to the 1,4-dioxanring is known from D4.

None of these compounds do fall under present formula I of claim 1 of the present application. Novelty prevails for the different claimed subject-matters.

2.2 Inventive step (Art.33(3) PCT)

The closest structurally known aldosterone inhibitor is the compound 8 of D3 (see scheme 1 therein). It does not fall under present formula I, since R1 = H and the pyridine moiety is directly attached to the benzene instead of the dioxane ring. The present posed technical problem is the provision of an alternative. The proposed solution are the compounds of formula I (see claim 1), preferably the compounds under present claim 8. Examples 1-16 provide the synthesis of compounds covering the claimed scope, followed by their chiral separation and pharmaceutical tests (see table 5).

The teaching of D3 leads away to the presence of a dioxane ring, since decrease in inhibition is registered by the introduction of heteroatoms into the saturated ring (see D3, page 8079, left-hand column). Presence of a pyridine or a benzodioxane rings is known from the skilled person to keep the pharmaceutical activity for the treatment of cardiac failure (see D1, D3, D4). There is no hint from the prior art knowledge to come to the proposed structural combination. An inventive step is accordingly acknowledged for the proposed solution.

Re Item VII

Certain defects in the international application

The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT, since D3 is not indicated therein.

Re Item VIII

Certain observations on the international application

The vague and imprecise terms "etc" and "and the like" should be removed from the description in each of their occurrence (Article 6 PCT).

The use of "prodrug" in the description implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them. This term as such should be removed from the description, since it defines the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.