

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/EP2020/081097

International filing date (day/month/year)
05.11.2020

Priority date (day/month/year)
06.11.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/14 C07D417/14 A61K31/454 A61P9/00 A61P11/00 A61P25/00

Applicant
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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

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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>1-16</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-16</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-16</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

Reference is made to the following documents:

- D1 WO 2015/091415 A1
- D2 WO 2015/091420 A1 (cited in the application)
- D3 WO 2008/060568 A2

Re Item V.

V.1. Patentability

Claims 7, 15 and 16 relate to subject-matter considered by this Authority to be covered by the provision 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 or claims to a method of medical treatment, but may allow claims to a compound or composition **for use** in a first or further medical treatment.

V.2. Novelty

The claimed subject-matter fulfils the requirements of Article 33(2) PCT because the compounds of formula (I) are novel.

The claimed compounds are novel over D1 and D2 at least due to the 5-membered heteroaryl containing X, Y and Z.

The claimed compounds are novel over D3 due to present R6.

V.3. Inventive step

D1 is the closest prior art to the claimed subject-matter. It discloses as ADRA2C inhibitors bipiperidines which can be linked to an aromatic moiety-amide group via a phenyl-carbonyl group (D1, claim 1, page 161-table 1, examples 43, 45, 50, 53, 54, 56, 70-98, 104, 105). The claimed compounds differ from the compounds of D1 in that the phenyl-carbonyl group is replaced by a 5-membered heteroaryl.

The technical problem underlying the present application is the provision of alternative compounds for the treatment of ADRA2C-mediated diseases (breathing difficulties, dysphagia, vascular disorders and disorders of the nervous system).

In view of the biological data provided in the description (pages 251-255), it can be assumed that this problem has been solved for the compounds as disclosed in the claims. D2 discloses further bipiperidines as ADRA2C inhibitors but they are also missing the present 5-membered heteroaryl (6-membered heteroaryl-carbonyl group instead). D3 is directed to the treatment of CGRP-mediated diseases (headache, inflammation, neurogenic vasodilation, thermal injury, shock or hot flashes) and there is a certain overlap with ADRA2C-mediated diseases. D3 discloses piperidines which can have a succession of rings similar to the claimed compounds but they contain a ring different from present R6 and only 5 of the 112 examples of D3 contain a 5-membered heteroaryl as well as a further aromatic moiety (D3, examples 76-80). Even combining the teaching of the prior art, the skilled person would not arrive at the present compounds. Therefore, it is considered that the present application involves an inventive step (Article 33(3) PCT).

Re Item VII.

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII.

VIII.1. Claims 9-12, the terms "including", "such as" or "in particular" have no limiting effect on the scope of a claim (Guidelines II, 5.40). Therefore, some of said claims have the same scope. This is contrary to the requirements of conciseness set forth in Article 6 PCT.

VIII.2. Page 16, it should not be mentioned that prodrugs are part of the invention because they are not and cannot be included in the scope of the claims (Article 6 PCT).