

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/EP2015/080221

International filing date (day/month/year)
17.12.2015

Priority date (day/month/year)
19.12.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/12 A61K31/423 A61K31/4439 A61K31/501 A61K31/506 A61P25/00 A61P31/00 A61P1/00

Applicant
GLAXOSMITHKLINE INTELLECTUAL PROPERTY...

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 <i>bis</i> .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:



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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. 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:

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>1-19</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-19</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-19</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

Item V.

Claims 16 and 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(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. Nevertheless, the present written opinion deals with the subject-matter of current claims 16 and 17.

1. Reference

Reference is made to the following documents:

D1: WO 2010/017132

D2: Ind. J. Chem. B, 2013, 52B(1), 160-163

D3: WO 2010/011302

D4: WO 2008/142134

2. Novelty

The isoxazole derivatives disclosed in document D1 differ from the compounds of formula (I) of current claim 1 through the fact that they are not condensed with a benzene ring.

Compound 1c of document D2, i.e. the precursor of compound 3c, differs from the compounds of formula (I) of current claim 1 through the nature of the substituent at position 6 of the benzisoxazole ring (i.e. a methyl group instead of group -OCHR¹R²).

The KMO inhibitors disclosed in document D3, and in particular the second compound depicted on page 75, differ from the compounds of formula (I) of current claim 1 *inter alia* through the absence of benzisoxazole ring.

Document D4 discloses benzisoxazole derivatives that differ from the compounds of formula (I) of current claim 1 *inter alia* through the absence of substituents at positions 5 and 6 of the benzisoxazole ring.

In fact, no compounds falling within formula (I) of current claim 1 could be retrieved from the available prior art.

The present application appears to be novel in the sense of Article 33(2) PCT.

3. Inventive Step

Document D1, which could be regarded as the closest prior art to the present application, discloses isoxazole derivatives inhibitors of KMO useful for the treatment of *inter alia* Huntington's disease. As previously mentioned, the present application differs from D1 through the nature of the core ring structure, i.e. a benzisoxazole ring as opposed to an isoxazole ring.

The problem to be solved by the present application could therefore be regarded as the provision of alternative isoxazole derivatives useful for the treatment of Huntington's disease.

The biological data provided on page 106 seem to indicate that at least some the compounds according to formula (I) actually solve the aforementioned technical problem. In addition, nothing in the prior art would have prompted the person skilled in the art to modify the isoxazole derivatives of D1 in such a way to arrive at the benzo [d]isoxazole compounds of formula (I) of the present application.

The present application appears to involve an inventive step in the sense of Article 33 (3) PCT.

Item VI.

With reference to the following document marked with the letter P in the International Search Report:

D5: WO 2015/091647

Document D5 discloses 2-oxobenzo[d]oxazole derivatives useful in the treatment of disorders mediated by KMO that could be relevant at a later stage if the present application does not enjoy the priority date.

Item VIII.

Current claims 12, 14 and 16 refers to "*a condition or a disorder mediated by KMO*". There is, however, no universal and exhaustive list of which diseases fall within said functional definition of the pathology. This has the effect that the person skilled in the art cannot decide clearly the scope of current claims 12, 14 and 16 and the present application, therefore, does not meet the requirements of Article 6 PCT. This objection could be overcome by introducing into the claims a list of specific pathological conditions and diseases associated with KMO, which is in fact already the subject-matter of current claims 13, 15 and 17.

In order to fulfil the requirements of Rule 6.4(a) PCT, claims 5, 6, 7 and 8 should be made dependent on claim 1 at least.

Finally, the central ring of formula (I) of the present application is sometimes called benzo[d]isoxazole (e.g. in current claim 5). A possible synonym is 1,2-benzisoxazole. However, in other passages of the present application (e.g. in current claim 6), it is named 1,2-benzoxazole, without the infix -iso-, while benzoxazole usually refers to the compounds in which the nitrogen and oxygen atoms are in position 1,3. The somewhat untraditional naming of the compounds of current claim 6 renders it unclear.