

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/IB2015/058978

International filing date (day/month/year)
19.11.2015

Priority date (day/month/year)
19.11.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C07D471/18 A61K31/551 A61P3/10 A61P9/00 A61P25/28

Applicant
GLAXOSMITHKLINE INTELLECTUAL PROPERTY (NO. 2...

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. 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>1-18</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>2, 7-18</u>
	No: Claims	<u>1, 3-6</u>
Industrial applicability (IA)	Yes: Claims	<u>1-18</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

Re Item V

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

1. Claims 12-16 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 recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a known compound for first or further medical treatment.

2. Reference is made to the following documents:

- D1 WO 2006/094210 A2 (SIRTRIS PHARMACEUTICALS(2006-09-08)
- D2 WO 2011/059839 A1 (SIRTRIS PHARMACEUTICALS INC [US]) 19 May 2011

3. The present application is directed to substituted bridged urea compounds as sirtuin modulators useful for the treatment of a wide variety of diseases which include diabetes, obesity, neurodegenerative diseases, cardiovascular disease, inflammation or cancer.

D1 and D2 are also related to sirtuin modulators: D1 discloses tetrahydroquinoxalinone compounds and D2 discloses 2,3-dihydropyrido[2, 3-b]pyrazine-4(1H)-carboxamide compounds but none of them discloses a bridged ring system.

Since the compounds of claim 1 are novel over D1 and D2, the subject-matter of claims 2-18 is also considered to be novel.

4. D2 can be considered to be the closest prior art.

The claimed compounds of formula (I) according to claim 1 differ from those disclosed in D2 mainly on account of the presence of a bridged ring system.

Since this difference does not result in any additional technical effect, the objective technical problem to be solved by the present application may be seen in the provision of further compounds useful for the treatment of the above listed diseases in view of their affinity for the sirtuin protein.

Due to the structural differences re the active compounds in D2, it cannot be said with any degree of accuracy that the skilled person, faced with the problem of providing further novel compounds with sirtuin modulator activity, would have been unambiguously led to prepare the compounds of the present application.

It was shown in Table 1 that the illustrative examples of the description indeed provide the desired activity.

However, it should be credible that this technical effect occurs over the whole range claimed. In this respect the question arises if substantially all compounds of claim 1 are really solution to the technical problem raised: whereas all the illustrative examples have $R_4 = -CONHR_bR_c$, $R_1 = -CONR_bR_c$, $m=1$, $n=2$ and $X_2=C$, claim 1 also includes a huge number of other compounds since R_4 can also be $=-H$, R_1 can vary from $-H$ to a $-N$ -substituted heterocyclyl, m and n could both vary from 1 to 3 and $X_2=N$. It is therefore doubtful that substantially all compounds of current claim 1 solve the above mentioned technical problem and claim 1 does not appear as a reasonable generalisation of the examples provided in the description. The same objection applies to the compounds (III) of claim 6.

Thus for the time being, claims 1 and 6 are not considered to fulfill the requirements of Art. 33(3) PCT taken in conjunction with Articles 5 and 6 PCT. If necessary, the claims have to be restricted to such compounds which illustrate respectable patentable effects. In this respect, it appears that the examples of the description represent a representative set of compounds as defined according to claims 2 and 7. An inventive step could therefore be recognized for the subject-matter of claims 2, 7 and 8-18 as far as they are dependent on claims 2 and 7.

Re Item VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (<i>valid claim</i>) (day/month/year)
WO2014186313	20.11.2014	13.05.2014	13.05.2013

This document discloses specific examples of compounds falling under the generic formula (I) according to current claim 1 and also for use as sirtuin modulators.

This intermediate document is not taken into account in this written opinion according to the Chap II PCT proceedings. It should nevertheless be noticed that the extensive examination of this document, on the question whether it constitutes prior art or not, will depend essentially on the analysis of the claimed priority rights of the present application and will only be performed in the regional European proceedings to come.

Re Item VIII

Certain observations on the international application

1. The radicals R1 to R4 and Ra to Rf can optionally be substituted with one or more substituents and among the list of possible substituents there is also -H (Art. 6 PCT).
2. The set of claims lacks of conciseness under Art.6 PCT since claim 5 discloses compounds of formula (II), however there is no difference between the scope of claim 1 and claim 5; thus, claim 5 is redundant and superfluous.
3. Claim 6 discloses preferred embodiments of claim 1 and should therefore be formulated as a dependent claim referring back to claim 1.
4. Claim 7 discloses preferred embodiments of claim 1 and should therefore be formulated as a dependent claim referring back to claim 1.
5. Claim 8 discloses preferred embodiments of claim 7 and should therefore be formulated as a dependent claim referring back to claim 7.
6. In claims 7 and 8, formulae (IV) and (V) have $m=1$ and $n=2$ so that their respective definitions are no longer necessary.
7. Claim 9 contains a reference to the description. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
8. The category of claim 18 is not clear.
9. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D2 is not mentioned in the description, nor is this document identified therein.