

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/GB2020/053357	International filing date (day/month/year) 23.12.2020	Priority date (day/month/year) 23.12.2019
International Patent Classification (IPC) or both national classification and IPC INV. C07D271/06 A61K31/4245 A61P19/02 A61P29/00		
Applicant SITRYX THERAPEUTICS LIMITED		

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:  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 Gettins, Marc 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. 58

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. are so unclear that no meaningful opinion could be formed (*specify*):

☐ 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. 58

☐ 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>1-56, 59-69</u>
	No: Claims	<u>57</u>
Inventive step (IS)	Yes: Claims	<u>1-56, 59-69</u>
	No: Claims	<u>57</u>
Industrial applicability (IA)	Yes: Claims	<u>1-57, 59-69</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 III

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

- 1 In the compound claim 58 X is a "leaving group". It is impossible to know what the exact scope of a leaving group is in a compound claim and the definition leads to a lack of clarity (Art. 6 PCT). The Applicant should either define the said term in the light of the current application or else delete claim 58. Given the huge scope of the claim it is not possible to search claim 58 in its current form. It is noted for instance that in its current form claim 58 could encompass compounds (III). If X is defined a search of claim 58 may become possible.

Re Item V

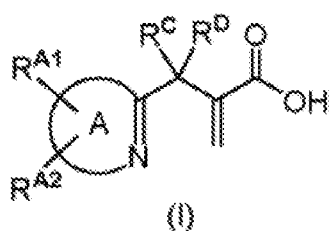
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 2 Relevant prior art is provided by:
- D1 AMRENDRA K. ROY ET AL: "Highly Substituted Isoxazoles: The Baylis-Hillman Reaction of Substituted 4-Isoxazolecarbaldehydes and Attempted Cyclization to Isoxazole-Annulated Derivatives.",
CHEMINFORM, vol. 34, no. 47, 25 November 2003 (2003-11-25), page 1356, XP055693022, DE
ISSN: 0931-7597, DOI: 10.1002/chin.200347112
- D2 AMRENDRA K. ROY ET AL: "Facile Baylis-Hillman Reaction of Substituted 3-Isoxazolecarbaldehydes: The Impact of a Proximal Heteroatom Within a Heterocycle on the Acceleration of the Reaction",
SYNTHESIS, no. 15, 1 January 2003 (2003-01-01), pages 2325-2330, XP055693028, STUTTGART, DE.
ISSN: 0039-7881, DOI: 10.1055/s-2003-41072

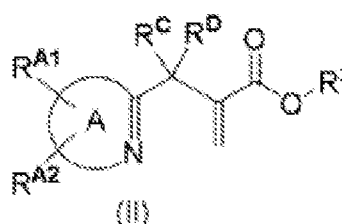
- D3 HAOPENG SUN ET AL: "Recent progress in the development of small molecule Nrf2 modulators: a patent review (2012-2016)", EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 27, no. 7, 10 May 2017 (2017-05-10), pages 763-785, XP055547200, ISSN: 1354-3776, DOI: 10.1080/13543776.2017.1325464
- D4 BAGAVANT G. ET AL.: INDIAN J. PHARM. SCI., vol. 56, 1994, pages 80-85, XP009512377,
- D5 JOACHIMIAK LUKASZ ET AL: "Synthesis and Biological Evaluation of Imidazole-Bearing [alpha]-Phosphonocarboxylates as Inhibitors of Rab Geranylgeranyl Transferase (RGGT)", CHEMMEDCHEM, vol. 13, no. 8, 23 April 2018 (2018-04-23), pages 842-851, XP055779219, DE ISSN: 1860-7179, DOI: 10.1002/cmdc.201700791
Retrieved from the Internet: URL: <https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fcmdc.201700791>
- D6 HAAS DIANA ET AL: "Regioselective Functionalization of the Oxazole Scaffold Using TMP-Bases of Mg and Zn", ORGANIC LETTERS, vol. 15, no. 24, 20 December 2013 (2013-12-20), pages 6162-6165, XP055779270, US
ISSN: 1523-7060, DOI: 10.1021/ol403019c
- D7 WO 95/11235

- 2.1 The Applicant should explain the reason for the proviso found in claim 1. If it is intended to exclude some unacknowledged prior art known to the Applicant the said prior art should be cited (Rule 5.1 (a) (ii) PCT).

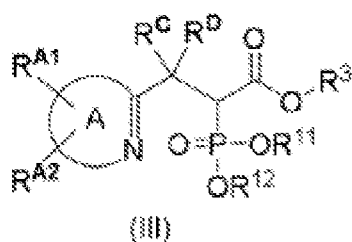
- 3 The current application has seven independent compound claims directed to:



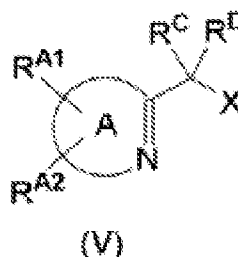
claim 1



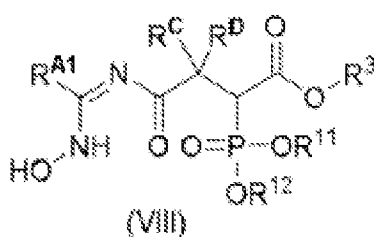
claim 56



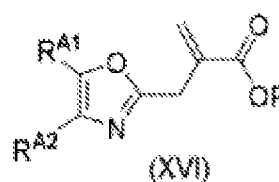
claim 57



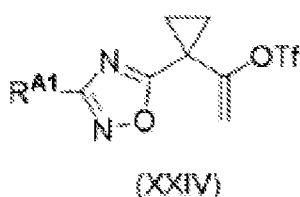
claim 58



claim 59



claim 60



claim 61

With so many independent claims the question of unity arises. Compounds (I)-(III) are all structurally close end products with the same activity, which can be interconverted (see claim 62) and are unitary. Compounds (V) can be used to make (III) (see Scheme 1 on page 36), compounds (VIII) are used to make (III) (see scheme 3 on page 37), compounds (XVI) are converted directly to claim 1 (see claim 63), (XXIV) is used to make (I) (see scheme 6 on page 39). The intermediates (V), (VIII), (XVI) and (XXIV) are therefore also unitary.

- 3.1 It is unclear why claim 40-41 directed to compounds (I) are independent since they appear to fall within the scope of claim 1. These claims should therefore be rewritten as a dependent claims (Rule 6.4 (a) PCT).

- 4 Compounds (III) appear to lack novelty in the light of D5 (see compounds 10g-10i in scheme 2 on page 844). The current application is novel vis-à-vis D1, compounds 13b and 13c (scheme 2) on account of the attachment point on the A ring on a ring carbon atom adjacent to a ring nitrogen atom. The current application is novel vis-à-vis D2 (compounds 16a-16c) on account of the proviso. Novelty vis-à-vis D3 (see e.g. page 778) is due to the acrylic acid group and the current application differs from D4 on account of the heteroaryl A ring. Compounds (XVI) are novel vis-à-vis 4k in D6 on account of the R^{A1} group. Compounds (III) are novel vis-à-vis D7, example 6 in that the A ring of the current application cannot have 4 substituents.
- 5 The current application addresses the problem of providing further compounds for use as NRF2 modulators. In the light of Table 2 it appears that the given problem has been solved. The closest prior art is taken to be D3. Given the significant structural differences between the current application and D3 the skilled person would not have been able to predict that the compounds of the current application would have the requisite qualitative activity. Accordingly an inventive step can be acknowledged for the novel end products and for the intermediates used to make them.

Re Item VIII

Certain observations on the international application

- 1 In compound claim 60 the group P is a carboxy protecting group. The scope of this is unclear in a compound claim. The examination has been limited to the specific possibility defined in claim 60 that P is p-methoxybenzyl.
- 2 The scope of the invention is said to include all isomers (page 47, line 1). This would also include structural isomers. This would mean that the present claim 1 relates to an extremely large number of possible compounds. Support and disclosure within the meaning of Articles 6 and 5 PCT are to be found, however, for only a very small proportion of the compounds. Non-compliance with the substantive provisions is such that a meaningful search of the whole claimed subject-matter of the claim could not be carried out. The Applicant should make it clear on page 47 that isomers only encompasses stereoisomers.

- 3 All "incorporated by reference" passages (see e.g. page 317) should be deleted.
- 4 The prior art documents D1-D3, D5-D7 should be cited (Rule 5.1 (a) (ii) PCT).