

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

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Date of mailing
(day/month/year)

SEP 01 2022

Applicant's or agent's file reference
BPX-04925

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 22/24805

International filing date (day/month/year)

14 April 2022 (14.04.2022)

Priority date (day/month/year)

14 April 2021 (14.04.2021)

International Patent Classification (IPC) or both national classification and IPC

IPC - C07D 231/14; C07D 401/04; C07D 401/12 (2022.01)

CPC - A61K 31/415; A61K 31/4155; A61P 1/02; A61P 1/04

Applicant **BIOCRIST PHARMACEUTICALS, INC.**

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 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/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

4 August 2022

Authorized officer

Kari Rodriguez

PCT Help Desk

Telephone No. 571-272-4300

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Box No. 1 Basis of this 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 43*bis*.1(b)).
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 13*ter*.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 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.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:

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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. 4,14-22,26-35,40,54-69,73-81,86-102,104-111,116-118,122-126,128-136,140

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

Claims 4, 14-22, 26-35, 40, 54-69, 73-81, 86-102, 104-111, 116-118, 122-126, 128-136 and 140 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ 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 said claims Nos. see above

☐ 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 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
- ☐ paid additional fees under protest and, where applicable, the protest fee.
- ☐ paid additional fees under protest but the applicable protest fee was not paid.
- ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I: Claims 1-3, 5-13, 23-25 and 36, directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Group II: Claims 37-39, 41-53, 70-72 and 82, directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof.

Group III: Claims 83-85, 103 and 112, directed to a compound of formula (III), or a pharmaceutically acceptable salt thereof.

Group IV: Claims 113-115, 119-121 and 127, directed to a compound of formula (IV), or a pharmaceutically acceptable salt thereof.

Group V: Claims 137-139 and 141-145, directed to a method of treating or preventing a disease or condition characterized by aberrant kallikrein activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof; wherein the compound is selected from the group consisting of the formulas indicated in claim 137.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features

Group I requires a compound of formula (I), or a pharmaceutically acceptable salt thereof, which is not required by Groups II-V.

Group II requires a compound of formula (II), or a pharmaceutically acceptable salt thereof, which is not required by Groups I or III-V.

Group III requires a compound of formula (III), or a pharmaceutically acceptable salt thereof, which is not required by Groups I-II or IV-V.

Group IV requires a compound of formula (IV), or a pharmaceutically acceptable salt thereof, which is not required by Groups I-III or V.

Group V requires a method of treating or preventing a disease or condition characterized by aberrant kallikrein activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, which is not required by Groups I-IV.

Shared Common Features

The only feature shared by Groups I-V that would otherwise unify the groups is a compound having the core structure of formula (I) (excepting the amidine moiety). However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is anticipated by the article entitled "Structure-Activity Relationship Studies of Indole-Based Compounds as Small Molecule HIV-1 Fusion Inhibitors Targeting Glycoprotein 41" by Zhou et al. (hereinafter 'Zhou').

--continued in first Supplemental Box--

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-3,5-13,23-25,36

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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

1. Statement

Novelty (N)	Claims	1-3,5-13,23-25,36	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-3,5-13,23-25,36	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-3,5-13,23-25,36	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-3, 5-13, 23-25 and 36 meet the criteria set out under PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the claimed invention.

Regarding claim 1, the article entitled "Structure-Activity Relationship Studies of Indole-Based Compounds as Small Molecule HIV-1 Fusion Inhibitors Targeting Glycoprotein 41" by Zhou et al. (hereinafter 'Zhou') teaches an analog of formula (I) wherein ring A is arylene; ring B is heteroarylene; ring A is fused to ring B at two and only two adjacent positions; ring C is heteroaryl; ring D is aryl; J represents -CH₂-; K represents a bond; LD represents a bond; R1 represents unsubstituted alkyl; m, n, p and q are each 0 (pg 5271, Scheme 1, formula 5), but Zhou does not teach the amidine moiety attached to ring C, thus Zhou also does not teach wherein Rx is selected from the list of substituents in the instant claim.

US 2010/0256365 A1 to Ibrahim et al. (hereinafter 'Ibrahim') teaches an analog of formula (I) wherein ring A is heteroarylene; ring B is heteroarylene; ring A is fused to ring B at two and only two adjacent positions; ring C is heteroaryl; ring D is aryl; J represents -CH₂-; K represents a bond; RD is halo; R1 represents unsubstituted alkyl; m, n and q are 0; and p is 2 (para [1236], [2,4-Difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-ylmethyl)-phenyl]-carbamic acid methyl ester (P-0257); see also pg 169, Table, formula P-0257), but Ibrahim does not teach wherein LD is selected from the list of groups in the instant claim. Ibrahim also does not teach the amidine moiety attached to ring C, thus Zhou also does not teach wherein Rx is selected from the list of substituents in the instant claim.

The article entitled "Cell-active carbazole derivatives as inhibitors of the zika virus protease" by Rassias et al. (hereinafter 'Rassias') teaches an analog of formula (I) wherein ring A is arylene; ring B is arylene; ring A is fused to ring B at two and only two adjacent positions; ring C is aryl; Rx is H; and m, n and q are 0 (pg 539, Fig. 3a, formula 16), but Rassias does not teach J, K, ring D, LD or the ester functionality, thus Rassias does not teach R1 or p. Therefore the prior art does not teach or fairly suggest the claimed invention.

Regarding claims 2-3, 5-13, 23-25 and 36, these claims are dependent on claim 1, thus these claims also meet the criteria set out under PCT Article 33(2)-(3).

Claims 1-3, 5-13, 23-25 and 36 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--Box IV - Lack of Unity--

Zhou teaches a compound having the core structure of formula (I) wherein ring A is arylene; ring B is heteroarylene; ring A is fused to ring B; ring C is heteroaryl; ring D is aryl; J represents -CH₂-; K represents a bond; LD represents a bond; R₁ represents unsubstituted alkyl; m, n, p and q are each 0 (pg 5271, Scheme 1, formula 5).

As the technical features were known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups. Groups I-V therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

*Item 4 (contd): Claims 4, 14-22, 26-35, 40, 54-69, 73-81, 86-102, 104-111, 116-118, 122-126, 128-136 and 140 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).