

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

02 AUG 2019

Applicant's or agent's file reference
BPX-04125

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 19/26054

International filing date (day/month/year)

05 April 2019 (05.04.2019)

Priority date (day/month/year)

06 April 2018 (06.04.2018)

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

IPC(8) - A61K 9/50 (2019.01)

CPC - A61K 31/343; A61K 31/381; A61K 31/404

Applicant BIOCRYST 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

15 July 2019

Authorized officer

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

**WRITTEN OPINION OF THE
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Box No. I 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(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 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. 5-42, 49-66, 68-79

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. 5-42, 49-66, 68-79 are so unclear that no meaningful opinion could be formed (*specify*):

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. 5-42, 49-66, 68-79

☐ 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 1-4, 43-48 and 67, directed to a compound of claim 1, Formula I. The compound of claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of formula I wherein ring A is aryl; B is aryl; C is aryl; R1 is NH2; n is 0; m is 0; p is 0; J is C(O); K is C(O); L is a bond; U is N; V is N; the stereochemical configuration at any chiral center is R, S. It is believed that claims 1-4 and 43 reads on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional compounds of claim 1 wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of formula I wherein ring A is aryl; B is heteroaryl; C is aryl; R1 is CH2COOH; n is 0; m is 0; p is 0; J is C(O); K is NH; L is CH2; U is CR3; R3 is H; V is CH; the stereochemical configuration at any chiral center is R, S (i.e., claims 1-4, 43-48 and 67).

The group of inventions listed above 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+ includes the technical feature of a unique compound having the following formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Group I+ share the technical feature of a compound having the following formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over a document entitled Pubchem CID 14528241 (hereinafter Pubchem-241) in view of US 3,377,387 A to Bachman et al. (hereinafter Bachman). Pubchem-241 discloses a compound of formula I wherein A is aryl; B is aryl; C is aryl; n is 0; m is 0; p is 0; J is C(O); K is NH; L is a bond; U is N; V is N (pg. 2, compound listed), but does not disclose wherein R1 is NH2 or wherein L is bound to an NH2. However, Pubchem-241 further discloses a compound wherein R1 is NO2 and wherein L is bound to an NO2. Additionally, Bachman discloses wherein nitro (NO2) groups are prepared from amine (NH2) groups (col 1, ln 10-15; col 2, ln 9-13). It would have been obvious to one with skill in the art to prepare the compound disclosed by Pubchem-231, comprising two nitro groups, from the corresponding di-amine compound (ie wherein R1 is NH2 and wherein L is bound to an NH2), as disclosed by Bachman, as a routine method for synthesis of nitro functional groups.

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Group I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

--continued on supplemental page--

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. 1-4 and 43-44

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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)	Claims	1-4, 43-44	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-4, 43-44	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-4, 43-44	YES
	Claims	NONE	NO

2. Citations and explanations:

Group I+ (1st elected invention):

Claims 1-4 and 43 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the subject matter claimed.

Regarding Claim 1, WO 2017/136395 A1 to BIOCRYST PHARMACEUTICALS, INC. (hereinafter Biocryst) discloses compounds (pg. 24 - 55) useful in treating a disease characterized by an aberrant complement system activity (pg. 56, ln 10-15) but does not disclose a compound of formula I wherein ring A is aryl; B is aryl; C is aryl; R1 is NH2; n is 0; m is 0; p is 0; J is C(O); K is C(O); L is a bond; U is N; V is N.

A document entitled "An insight into the therapeutic potential of quinazoline derivatives as anticancer agents" to Shagufta et al. (hereinafter Shagufta) discloses a compound similar to a compound of formula I wherein U is N; V is N and B is aryl and C is aryl (pg. 872, Fig. 1: Gefitinib), but does not disclose a compound wherein ring A is aryl; R1 is NH2; n is 0; m is 0; p is 0; J is C(O); K is C(O); L is a bond or wherein ring C is bound directly to the heteroaryl ring.

US 9,056,874 B2 to Adams et al. (hereinafter Adams) discloses compounds (col 4, ln 5-15) which are complement pathway modulators (col 1, ln 5-11), but does not disclose a compound of formula I wherein ring A is aryl; B is aryl; C is aryl; R1 is NH2; n is 0; m is 0; p is 0; J is C(O); K is C(O); L is a bond; U is N; V is N.

Regarding Claims 2-4 and 43, these are dependent claims depending from claim 1 and therefore, meet the criteria set forth in PCT Article 33(2) and 33(3).

Group I+ (2nd elected invention):

Claims 1-4 and 43-44 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the subject matter claimed.

Biocryst discloses compounds (pg. 24 - 55) useful in treating a disease characterized by an aberrant complement system activity (pg. 56, ln 10-15) but does not disclose a compound of formula I wherein ring A is aryl; B is heteroaryl; C is heteroaryl; R1 is CH2COOH; n is 1; m is 0; p is 0; J is CH2; K is O; L is CH2; U is CR3; R3 is H; V is CH.

Adams discloses compounds (col 4, ln 5-15) which are complement pathway modulators (col 1, ln 5-11), wherein B is heteroaryl and U is CR3; R3 is H; V is CH (col 4, ln 5-15), but does not disclose a compound of formula I wherein B is heteroaryl; R1 is CH2COOH; n is 1; m is 0; p is 0; J is CH2; K is O; L is CH2.

US 7,442,808 B2 to Ge et al. (hereinafter Ge) discloses a compound similar to a compound of formula I wherein ring A is aryl and ring B is heteroaryl and J is CH2; K is O; U is CR3; R3 is H; V is CH, m is 0 (col 50, ln 30-50: 2nd compound listed), but does not disclose a compound wherein C is heteroaryl; R1 is CH2COOH; n is 1 or p is 0.

Regarding Claims 2-4 and 43-44, these are dependent claims depending from claim 1 and therefore, meet the criteria set forth in PCT Article 33(2) and 33(3).

Claims 1-4 and 43-44 have industrial applicability as defined by PCT Article 33(4) because the subject matter could be made or used in industry.

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Supplemental Box

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

Continuation of:
--continued from Box No. IV--

Item 4 (contd.): Claims 5-42, 49-66, 68-79 have been found to be unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Note: Regarding suggested claims of 1st elected invention listed in LOU response; the first elected invention of group I+ reads on claims 1-4 and 43, as claim 44 does not include a compound wherein J is C(O); K is C(O); and the compound of formula II in claim 45, does not include wherein RT3 and RT2 taken together with the intervening atoms, form an aryl ring.