

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)

MAR 18 2021

Applicant's or agent's file reference
BPX-04625

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 20/54922

International filing date (day/month/year)

09 October 2020 (09.10.2020)

Priority date (day/month/year)

09 October 2019 (09.10.2019)

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

IPC - C07D 307/80; C07D 307/81; A61K 31/343 (2020.01)

CPC - A61K 31/343; A61P 21/02; A61P 25/00; A61P 25/08

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

08 December 2020

Authorized officer

Lee Young

PCT Help Desk

Telephone No. 571-272-4300

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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 43bis.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 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:

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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. 4-5, 9-10, 14, 18-19, 21-32

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. 4-5, 9-10, 14, 18-19, 21-32 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. 4-5, 9-10, 14, 18-19, 21-32

- ☐ 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, 6-8, 11-13, 15-17, and 20, directed to a compound of Formula (I)-(IV). The compound of Formula (I) will be searched to the extent that the compound encompasses the first species wherein A is the first moiety depicted for A in claim 1 (2-phenyl butyric acid); B is the first moiety depicted for B in claim 1 (4-fluorobenzofuran); -J-K- is the first moiety depicted for -J-K- depicted in claim 1 (-CH₂-O-); and C is the first moiety depicted for C in claim 1 (fluorobenzylamine). It is believed that claims 1 and 3 read on this first named invention, and thus these claims will be searched without fee. Applicant is invited to elect additional method(s) wherein each additional method elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected method. 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 A is the first moiety depicted for A in claim 1; B is the first moiety in the last row on p. 306 depicted for B in claim 1 (3-fluoro benzofuran); -J-K- is the first moiety depicted for -J-K- depicted in claim 1; and C is the first moiety depicted for C in claim 1 (i.e., claims 1, 3, 6, and 8).

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 of Formula (I), which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound of the formula C-B-J-K-A depicted in claims 1, 6, 11, and 15, wherein A is a substituted phenylacetic acid moiety; B is a heterocycle comprising a benzene ring fused to a furan or pyrrole ring; -J-K- is a linking moiety between the A and B moieties comprising at least one N or O heteroatom and at least one carbon; and C is an aryl or heteroaryl amine.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is obvious over WO 2019/057946 A1 to GENENTECH, Inc. (hereinafter GENENTECH). GENENTECH teaches the compound of Formula (I) wherein A is a substituted phenyl acetic acid moiety; B is a heterocycle comprising a benzene ring fused to a pyrrole ring; -J-K- is a linking moiety between the A and B moieties comprising one carbon and one O heteroatom; and C is an aryl amine (p. 3 ln 14; p.4 ln 9-10 and p. 5 ln 1; p.7 ln 1 and p. 7 ln 5-8- compound of formula (III-A) wherein Ar1 is the third moiety depicted in ln 1 of p.5; Ar2 is the last moiety depicted in ln 5 of p.7; R1 is C6 aryl, which is interpreted as including phenyl; and R2 is H), but does not teach the specific example/embodiment of this compound. Based on GENENTECH's teachings it would have been obvious to one of ordinary skill in the art to identify the specific compound by routine experimentation.

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature, that would otherwise unify the inventions of Group I+.

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 and 3

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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 and 3	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1 and 3	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1 and 3	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1 and 3 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, WO 2019/057946 A1 (GENENTECH, Inc., hereinafter GENENTECH) teaches the analogous compound to the compound of Formula (I) wherein ring A is 2-phenyl propionic acid; ring B is benzoxazole; -J-K- is the first moiety depicted for -J-K- depicted in claim 1 (-CH₂-O-) and C is the first moiety depicted for C in claim 1 (fluorobenzylamine) (p. 3 ln 13; p. 5 ln 1; p. 7 ln 5; p. 7 ln 6- compound of Formula (I-A) wherein Ar 1 is the third moiety depicted in ln 1 on p.5; Ar2 is the second moiety in ln 5 on p. 7; and R1 is H). However GENENTECH does not teach the compound wherein B is a benzofuran moiety (no N atom present) with 4-fluoro substitution. Further, GENENTECH does not teach the compound wherein A is a 2-phenyl butyric acid moiety (ethyl branch instead of methyl branch).

US 2011/0212940 A1 (BURLI et al., hereinafter BURLI) teaches the benzofuran compound analogous to the compound of Formula (I) (paras [0039]-[0043]- compound of formula (II) wherein A is aryl, which is interpreted as including phenyl; Z2 is O, which is interpreted as including Z2 in the 5-position of the benzofuran ring; R1 is aryl with 1 substituent, which is interpreted as including 2-phenyl butyric acid). However, BURLI does not teach the compound with the J portion of -J-K- linking moiety -CH₂-O-. Further BURLI does not teach the compound with 4-fluoro substitution on the benzofuran ring. Finally, BURLI does not teach ring C attached to the 7-position of ring B wherein ring C is fluorobenzyl amine.

Further, there is no motivation to combine these references.

As to claim 3, this claim is depending from claim 1 and therefore, meets the criteria set out under PCT Article 33 (2)-(3).

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