

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: WEN LI
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WASHINGTON, DC 20001-4413

RECEIVED

FEB 10 2016

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

05 FEB 2016

Applicant's or agent's file reference

10275-79-304

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/US 15/54316

International filing date
(day/month/year)

06 October 2015 (06.10.2015)

Applicant MILLER, MARK THOMAS

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

How? Directly to the International Bureau of WIPO preferably through ePCT or on paper to, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:**

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90bis.1 and 90bis.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45bis.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

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

Authorized officer

Lee W. Young

PCT Helpdesk: 571-272-4300
Telephone No. PCT OSP: 571-272-7774

REC'D PAO

FEB 12 2016

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 10275-79-304	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 15/54316	International filing date (<i>day/month/year</i>) 06 October 2015 (06.10.2015)	(Earliest) Priority Date (<i>day/month/year</i>) 06 October 2014 (06.10.2014)
Applicant MILLER, MARK THOMAS		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/54316

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-29, 33-55, 59-83, 87-111, 115-141, 143-185
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

--See attached extra sheet--

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-3, 142
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/54316

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A01N 41/06; A61K 31/18 (2016.01) CPC - A61K 31/18; A01N 41/06; C07C 311/29 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8): A01N 41/06; A61K 31/18 (2016.01) CPC: A61K 31/18; A01N 41/06; C07C 311/29 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 514/601; 514/595 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase; Keyword limited: cystic fibrosis; cfr; sulfonamide; acetyl; indol; pharmaceutical; pyrazol; cfr corrector; cyclopropyl ; cyclobutyl; cyclopentyl; cyclohexyl.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/071247 A1 (DANA FARBER CANCER INSTITUTE) 08 May 2014 (08.05.2014), entire document, especially: Compound 60, pg 206; Compound 190, pg 231.	1-2
X	PubChem-58132855 Create Date: 19 August 2012 (19.08.2012), entire document, especially: pg 3, Fig.	1-3
X	PubChem-44419393 Create Date: 19 November 2009 (19.11.2009), entire document, especially: pg 3, Fig.	142
A	PubChem-2545578 Create Date: 16 July 2005 (16.07.2005), entire document, especially: pg 3, Fig.	1-3
A	PubChem-49774135 Create Date: 02 December 2010 (02.12.2010), entire document, especially: pg 3, Fig.	1-3
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 22 January 2016		Date of mailing of the international search report 05 FEB 2016
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		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 15/54316

--Box III - Lack of Unity of Invention--

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.

Group I+: Claims 1-3, 30-32, 56-58, 84-86, 112-114 and 142 directed to a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compound of Formula (I) will be searched to the extent that it encompasses the first species of claim 1 formula I, wherein Ring A is a C6-C10 aryl ring; Ring B is a C3-C10 cycloalkyl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR; Z is NR; R1 is halo; R2 is halo; R3 is halo; R4 is H; R is H; n, o, p and q are 0; provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A.

It is believed that claims 1, 2 (in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1.

Applicant is invited to elect additional compounds of Formula (I), 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.

An exemplary election would be a compound of claim 1, wherein Ring A is a C3-C14 heteroaryl ring; Ring B is a C3-C10 cycloalkyl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR; Z is NR; R1 is halo; R2 is halo; R3 is halo; R4 is azide; R is H; n, o, p and q are 0; provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A (i.e. claims 1, 2 (in part), 3 (in part), 30-32, 56-58, 84-86, 142).

The groups 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 having the core structure of Formula (I).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by PubChem-CID-18680993 (hereinafter 'PubChem-993').

Regarding claim 1, PubChem-993 teaches a compound of Formula (I): wherein Ring A is a C3-C14 heteroaryl ring; Ring B is a C6-C10 aryl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR and R is H; Z is NR and R is H; R1 is not present (n = 0); R2 is not present (p = 0); R3 is C6-C10 aryl (q = 1); provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A (pg 3, Fig).

Regarding claim 142, with compound 71 selected from Table 1: PubChem-993 teaches a compound that is highly similar to compound 71 (pg 3, Fig), but PubChem-993 does not teach wherein methyl substituents are at the 4 and 6 positions of the N-benzyl moiety, and the methyl substituent at the 4 position is replaced by a phenyl group (pg 3, Fig) and PubChem-993 does not teach 3-amino substitution on the phenylsulfonyl carboxamide moiety. However, it would have been obvious to a person having ordinary skill in the art to synthesize the 3-amino substituted phenylsulfonyl moiety with 2,4,6-trimethyl substituted benzyl by routine experimentation in order to alter the physicochemical properties of the resulting compound.

As Formula (I) 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+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 4-29, 33-55, 59-83, 87-111, 115-141 and 143-185 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

NOTE: From applicants elected compounds, claims 6,7,9-12, 15-21, 24, 27,33,34,36-39, 40-46, 48, 51, 59-72, 75, 78, 87-100, 103, 106, 110, 111, 115-128, 131,134,139 and 143-153 are determined unsearchable (see original LOU draft). Additional elected compound of formula I was searched to the extent that it encompasses the second species of claim 1 formula I, wherein Ring A is a C3-C14 hetero aryl ring; Ring B is a C3-C10 cycloalkyl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR; Z is NR; R1 is halo; R2 is halo; R3 is halo; R4 is H; R is H; n, o, p and q are 0; provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A. Claims 1-3 and 142 fall under this additional elected species and opinion have been provided for these claims.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

To: WEN LI
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP
901 NEW YORK AVENUE NW
WASHINGTON, DC 20001-4413

Date of mailing
(day/month/year)

05 FEB 2016

Applicant's or agent's file reference
10275-79-304

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 15/54316

International filing date (day/month/year)

06 October 2015 (06.10.2015)

Priority date (day/month/year)

06 October 2014 (06.10.2014)

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

IPC(8) - A01N 41/06; A61K 31/18 (2016.01)

CPC - A61K 31/18; A01N 41/06; C07C 311/29

Applicant MILLER, MARK THOMAS

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 43*bis*.1(a)(i) with regard to novelty, inventive step or 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 66.1 *bis*(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
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Facsimile No. 571-273-8300

Date of completion of this opinion

22 January 2016

Authorized officer:

Lee W. Young

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

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 15/54316

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(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:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 15/54316

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. 4-29, 33-55, 59-83, 87-111, 115-141, 143-185

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 4-29, 33-55, 59-83, 87-111, 115-141, and 143-185 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. 4-29, 33-55, 59-83, 87-111, 115-141, 143-185

- ☐ 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.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 15/54316

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:

--See 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, 142

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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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	1-3, 142	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-3, 142	NO
Industrial applicability (IA)	Claims	1-3, 142	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2 lack an inventive step under PCT Article 33(3) as being obvious over WO 2014/071247 A1 to Bradner et al. ('Bradner').

Regarding claim 1, Bradner teaches a compound of formula very similar to formula I, wherein Ring A is a C6 aryl ring; Ring B is a C3 cycloalkyl ring; Ring C is a C4-heteroaryl ring; W is O; X is O; Y is CRR, o is 0; Z is NR, R is H; R1 is halo, n is 0; R2 is halo, p is 0; R3 is C1 alkyl, q is 2; S--X bond is a double bond and Z--S bond is a single bond (Compound 190, pg 231), but not wherein Ring C is a C6-C10 aryl ring, and not wherein R3 is halo and q is 0. However, Bradner further teaches a different compound wherein Ring C is a C6 aryl ring (Compound 60, pg 206), and it would have been obvious to a person having ordinary skill in the art to prepare the compound of formula I wherein Ring C is an unsubstituted C6 aryl ring by routine experimentation to identify the most active compound.

Regarding claim 2, Bradner teaches the compound of claim 1 (see above discussion), wherein ring A is phenyl (Compound 190, pg 231).

Claims 1-3 lack an inventive step under PCT Article 33(3) as being obvious over the document PubChem-58132855 ('PubChem-855').

Regarding claim 1, PubChem-855 teaches a compound of formula very similar to formula I, wherein Ring A is a C8 heteroaryl ring; Ring B is a C3 cycloalkyl ring; Ring C is a C5 heteroaryl ring; W is O; X is O; Y is CRR, o is 0; Z is NR, R is H; R1 is ethyl and neopentyl; n is 2; R2 is halo, p is 0; two R3 groups taken together form a =O group, q is 2; S--X bond is a double bond and Z--S bond is a single bond (pg 3, Fig), but not wherein Ring C is a C6-C10 aryl ring, and not wherein R1 and R3 are halo, and n and q are 0. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound of formula I wherein Ring C is an unsubstituted C6 aryl ring by routine experimentation to identify the most active compound.

Regarding claim 2, PubChem-855 teaches the compound of claim 1 (see above discussion), wherein ring A is indole (pg 3, Fig).

Regarding claim 3, PubChem-855 teaches the compound of claim 1 (see above discussion), wherein ring A is the first formula in the second row selected from the group of formulas listed in the instant claim: indolyl (pg 3, Fig).

Claim 142 lacks an inventive step under PCT Article 33(3) as being obvious over the document PubChem-44419393 ('PubChem-393').

Regarding claim 142, PubChem-393 teaches a compound very similar to compound 264 from pg 279 in Table 1 (pg 3, Fig), but PubChem-393 teaches 3-trifluoromethylbenzyl substituent on the nitrogen of the indole moiety instead of the 1,3,5-trimethylbenzyl substituent of the claimed compound. However, it would have been obvious to a person having ordinary skill in the art to prepare the compound with a trimethylbenzyl group on the indole nitrogen by routine experimentation in order to identify the most active compound.

Claims 1-3 and 142 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 15/54316

Supplemental Box

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

Continuation of:

--Box IV - Lack of Unity of Invention--

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.

Group I+: Claims 1-3, 30-32, 56-58, 84-86, 112-114 and 142 directed to a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compound of Formula (I) will be searched to the extent that it encompasses the first species of claim 1 formula I, wherein Ring A is a C6-C10 aryl ring; Ring B is a C3-C10 cycloalkyl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR; Z is NR; R1 is halo; R2 is halo; R3 is halo; R4 is H; R is H; n, o, p and q are 0; provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A.

It is believed that claims 1, 2 (in part) encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1.

Applicant is invited to elect additional compounds of Formula (I), 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.

An exemplary election would be a compound of claim 1, wherein Ring A is a C3-C14 heteroaryl ring; Ring B is a C3-C10 cycloalkyl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR; Z is NR; R1 is halo; R2 is halo; R3 is halo; R4 is azide; R is H; n, o, p and q are 0; provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A (i.e. claims 1, 2 (in part), 3 (in part), 30-32, 56-58, 84-86, 142).

The groups 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 having the core structure of Formula (I).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by PubChem-CID-18680993 (hereinafter 'PubChem-993').

Regarding claim 1, PubChem-993 teaches a compound of Formula (I): wherein Ring A is a C3-C14 heteroaryl ring; Ring B is a C6-C10 aryl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR and R is H; Z is NR and R is H; R1 is not present (n = 0); R2 is not present (p = 0); R3 is C6-C10 aryl (q = 1); provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A (pg 3, Fig).

Regarding claim 142, with compound 71 selected from Table 1: PubChem-993 teaches a compound that is highly similar to compound 71 (pg 3, Fig), but PubChem-993 does not teach wherein methyl substituents are at the 4 and 6 positions of the N-benzyl moiety, and the methyl substituent at the 4 position is replaced by a phenyl group (pg 3, Fig) and PubChem-993 does not teach 3-amino substitution on the phenylsulfonyl carboxamide moiety. However, it would have been obvious to a person having ordinary skill in the art to synthesize the 3-amino substituted phenylsulfonyl moiety with 2,4,6-trimethyl substituted benzyl by routine experimentation in order to alter the physicochemical properties of the resulting compound.

As Formula (I) 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+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 4-29, 33-55, 59-83, 87-111, 115-141 and 143-185 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

NOTE:

From applicants elected compounds, claims 6,7,9-12, 15-21, 24, 27,33,34,36-39, 40-46, 48, 51, 59-72, 75, 78, 87-100, 103, 106, 110, 111, 115-128, 131,134,139 and 143-153 are determined unsearchable (see original LOU draft). Additional elected compound of formula I was searched to the extent that it encompasses the second species of claim 1 formula I, wherein Ring A is a C3-C14 hetero aryl ring; Ring B is a C3-C10 cycloalkyl ring; Ring C is a C6-C10 aryl ring; W is O; X is O; Y is CRR; Z is NR; R1 is halo; R2 is halo; R3 is halo; R4 is H; R is H; n, o, p and q are 0; provided that the moieties containing ring B and ring C are substituted at adjacent positions on ring A. Claims 1-3 and 142 fall under this additional elected species and opinion have been provided for these claims.