

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: RAYMOND F. HORVATH
HAUKAAS FORTIUS PLLC
5100 EDEN AVENUE
SUITE 303
EDINA, MN 55436

PCT

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)

28 OCT 2019

Applicant's or agent's file reference
500.091WO1

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US2019/040058

International filing date
(day/month/year) 01 July 2019

Applicant **THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS**

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

Authorized officer

Blaine R. Copenheaver

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

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 500.091WO1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2019/040058	International filing date (<i>day/month/year</i>) 01 July 2019	(Earliest) Priority Date (<i>day/month/year</i>) 03 July 2018
Applicant THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS		

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. 4B

☒ 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/US2019/040058

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.:
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 extra sheet(s).

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.:
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.:
1-5, 17-19, 21, 22, 24-27

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/US2019/040058

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/34; A61K 31/343; C07D 307/78; C07D 307/82; C07D 307/83 (2019.01)

CPC - A61K 31/34; A61K 31/343; C07D 307/78; C07D 307/82; C07D 307/83 (2019.08)

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 514/468; 514/469 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014/113820 A1 (SHAPIRO et al) 24 July 2014 (24.07.2014) entire document	1-5, 17-19, 21, 22, 24-27
A	US 2007/0299102 A1 (FELDING et al) 27 December 2007 (27.12.2007) entire document	1-5, 17-19, 21, 22, 24-27
A	PUBCHEM, Substance Record for SID 50779888, Available Date: 05 September 2008 [retrieved on 2 October 2019]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/50779888 >. entire document	1-5, 17-19, 21, 22, 24-27

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* 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

03 October 2019

Date of mailing of the international search report

28 OCT 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/040058

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-5, 17-19, 21, 22, and 24-27 have been analyzed subject to the restriction that the claims read on a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently H; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O.

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 examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-27 are drawn to compounds of Formula I or a salt or solvate thereof, compositions thereof, pharmaceutical compositions thereof, methods of treating a cancer thereof, and use of the compound for the treatment of an ER α positive disease in a subject in need thereof.

The first invention of Group I+ is restricted based on the proviso when present, -ORB and -ORC are not both -OH; and is restricted to a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently H; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O; compositions thereof; pharmaceutical compositions thereof; methods of treating a cancer thereof; and use of the compound for the treatment of an ER α positive disease in a subject in need thereof. It is believed that claims 1-5, 17-19, 21, 22, and 24-27 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently halo; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O; compositions thereof; pharmaceutical compositions thereof; methods of treating a cancer; and use of the compound for the treatment of an ER α positive disease in a subject in need thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/examined.

The inventions listed in Groups I+ 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:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, G1, G2, A1, A2, A3, A4, X, and Z and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of Formula I or a salt or solvate thereof; a composition comprising the compound and a second drug; a pharmaceutical composition comprising the compound in combination with a pharmaceutically acceptable diluent, carrier, excipient, or buffer; a method of treating a cancer comprising administering to an ER α positive cancer subject in need thereof a therapeutically effective amount of the compound, thereby treating the cancer in the subject; and a use of the compound for the treatment of an ER α positive disease in a subject in need thereof, wherein a therapeutically effective amount of the compound is administered to the subject thereby treating the cancer in the subject, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2014/113820 A1 to Shapiro et al.

WO 2014/113820 A1 to Shapiro et al. teach a compound having the core structure of Formula I (Claim 1, ...BHPI...; Fig. 2, BHPI, see shown structure); a composition (Paras. [0247] and [0248], The pharmaceutical compositions...) comprising the compound (Paras. [0247], [0248], and [0251], ... a composition of Formula A ...) and a second drug (Paras. [0247] and [0248], ... compounds may be combined with any drug, in one preferred embodiment, an effective compound is combined with the anticancer drug paclitaxel or with other taxanes.); a pharmaceutical composition (Paras. [0247] and [0248], The pharmaceutical compositions ...) comprising the compound (Paras. [0247], [0248], and [0251], ... a composition of Formula A ...) in combination with a pharmaceutically acceptable carrier (Para. [030], ... a pharmaceutical formulation comprises one or more excipients, carriers ...); a method of treating a cancer (Abstract, A method of treating ER α positive cancer ...; Claims 1, 2, and 9) comprising administering to an ER α positive cancer subject in need thereof a therapeutically effective amount of the compound (Para. [025], ... a method of treating cancer comprising administering to a patient in need thereof an effective amount of BHPI, ...; Claims 1, 2, and 9), thereby treating the cancer in the subject (Para. [025]); and a use of the compound for the treatment of an ER α positive disease in a subject in need thereof (Abstract, A method of treating ER α positive cancer ...; Claims 1, 2, and 9), wherein a therapeutically effective amount of the compound is administered to the subject thereby treating the cancer in the subject (Para. [025], ... a method of treating cancer comprising administering to a patient in need thereof an effective amount of BHPI, ...; Claims 1, 2, and 9).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: RAYMOND F. HORVATH
HAUKAAS FORTIUS PLLC
5100 EDEN AVENUE
SUITE 303
EDINA, MN 55436

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

28 OCT 2019

Applicant's or agent's file reference
500.091WO1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2019/040058

International filing date (day/month/year)

01 July 2019

Priority date (day/month/year)

03 July 2018

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

IPC(8) - A61K 31/34; A61K 31/343; C07D 307/78; C07D 307/82; C07D 307/83 (2019.01)

CPC - A61K 31/34; A61K 31/343; C07D 307/78; C07D 307/82; C07D 307/83 (2019.08)

Applicant THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS

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, VA 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

03 October 2019

Authorized officer

Blaine R. Copenheaver

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

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2019/040058

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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2019/040058

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. 1-5, 17-19, 21, 22, 24-27

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2019/040058

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	1-5, 17-19, 21, 22, 24-27	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-5, 17-19, 21, 22, 24-27	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-5, 17-19, 21, 22, 24-27	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5, 17-19, 21, 22, and 24-27 have been analyzed subject to the restriction that the claims read on a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently H; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O.

Claims 1-5, 17-19, 21, 22, and 24-27 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 1, the prior art of record, individually or in combination, does not teach or fairly suggest a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently H; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O.

Claims 2-5, 17-19, 21, 22, and 24-27 depend from claim 1, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 1.

Claims 1-5, 17-19, 21, 22, and 24-27 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2019/040058

Supplemental Box

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

Continuation of:

<Box No. 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. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-27 are drawn to compounds of Formula I or a salt or solvate thereof, compositions thereof, pharmaceutical compositions thereof, methods of treating a cancer thereof, and use of the compound for the treatment of an ER α positive disease in a subject in need thereof.

The first invention of Group I+ is restricted based on the proviso when present, -ORB and -ORC are not both -OH; and is restricted to a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently H; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O; compositions thereof; pharmaceutical compositions thereof; methods of treating a cancer thereof; and use of the compound for the treatment of an ER α positive disease in a subject in need thereof. It is believed that claims 1-5, 17-19, 21, 22, and 24-27 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula I or a salt or solvate thereof; wherein R1, R2, R3 and R4 are each independently halo; A1, A2, A3 and A4 are each independently H; G1 is halo; G2 is halo; and X and Z are each independently O; compositions thereof; pharmaceutical compositions thereof; methods of treating a cancer; and use of the compound for the treatment of an ER α positive disease in a subject in need thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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/examined.

The inventions listed in Groups I+ 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:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, G1, G2, A1, A2, A3, A4, X, and Z and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of Formula I or a salt or solvate thereof; a composition comprising the compound and a second drug; a pharmaceutical composition comprising the compound in combination with a pharmaceutically acceptable diluent, carrier, excipient, or buffer; a method of treating a cancer comprising administering to an ER α positive cancer subject in need thereof a therapeutically effective amount of the compound, thereby treating the cancer in the subject; and a use of the compound for the treatment of an ER α positive disease in a subject in need thereof, wherein a therapeutically effective amount of the compound is administered to the subject thereby treating the cancer in the subject, these shared technical features do not represent a contribution over the prior art as disclosed by WO 2014/113820 A1 to Shapiro et al.

WO 2014/113820 A1 to Shapiro et al. teach a compound having the core structure of Formula I (Claim 1, ...BHPI...; Fig. 2, BHPI, see shown structure); a composition (Paras. [0247] and [0248], The pharmaceutical compositions...) comprising the compound (Paras. [0247], [0248], and [0251], ... a composition of Formula A ...) and a second drug (Paras. [0247] and [0248], ... compounds may be combined with any drug, in one preferred embodiment, an effective compound is combined with the anticancer drug paclitaxel or with other taxanes.); a pharmaceutical composition (Paras. [0247] and [0248], The pharmaceutical compositions ...) comprising the compound (Paras. [0247], [0248], and [0251], ... a composition of Formula A ...) in combination with a pharmaceutically acceptable carrier (Para. [030], ... a pharmaceutical formulation comprises one or more excipients, carriers ...); a method of treating a cancer (Abstract, A method of treating ER α positive cancer ...; Claims 1, 2, and 9) comprising administering to an ER α positive cancer subject in need thereof a therapeutically effective amount of the compound (Para. [025], ... a method of treating cancer comprising administering to a patient in need thereof an effective amount of BHPI, ...; Claims 1, 2, and 9), thereby treating the cancer in the subject (Para. [025]); and a use of the compound for the treatment of an ER α positive disease in a subject in need thereof (Abstract, A method of treating ER α positive cancer ...; Claims 1, 2, and 9), wherein a therapeutically effective amount of the compound is administered to the subject thereby treating the cancer in the subject (Para. [025], ... a method of treating cancer comprising administering to a patient in need thereof an effective amount of BHPI, ...; Claims 1, 2, and 9).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.