

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/US2023/069331	International filing date (day/month/year) 29.06.2023	Priority date (day/month/year) 30.06.2022
International Patent Classification (IPC) or both national classification and IPC INV. C07D401/14 C07D405/14 C07D413/14 C07D417/14 C07D471/04 C07D491/048 C07D491/052 C07D491/08 C07D491/107 C07D498/08 A61P35/00 A61K31/4709 A61K31/517 A61K31/5377 A61K31/4545 A61K31/498		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

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 usually 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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Papathoma, Sofia Telephone No. -0
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Box No. I Basis of the 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

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

1. Statement

Novelty (N)	Yes: Claims	<u>8, 22-88, 92</u>
	No: Claims	<u>1-7, 9-21, 89-91, 93-95</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-95</u>
Industrial applicability (IA)	Yes: Claims	<u>1-95</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

This Written Opinion is based on the following application documents:

Description, Pages:

1-434 as originally filed

Claims, Numbers:

1-95 as originally filed

The present application relates to compounds of Formula (I) that reduce WEE1 kinase protein levels.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2018/102725 A1 (ARVINAS INC [US]) 7 June 2018 (2018-06-07)
- D2 CN 113 292 536 A (SICHUAN HAISCO PHARMACEUTICAL CO LTD) 24 August 2021 (2021-08-24)
- D3 WO 2021/077010 A1 (ARVINAS OPERATIONS INC [US]) 22 April 2021 (2021-04-22)
- D4 WO 2018/071606 A1 (ARVINAS INC [US]) 19 April 2018 (2018-04-19)
- D5 WO 2022/019597 A1 (UBIX THERAPEUTICS CO LTD) 27 January 2022 (2022-01-27); & EP 4 186 904 A1 (UBIX THERAPEUTICS INC [KR]) 31 May 2023 (2023-05-31)
- D6 US 2022/047709 A1 (GRAY NATHANAEL S [US] ET AL) 17 February 2022 (2022-02-17)
- D7 VAKILI-SAMIANI SAJJAD ET AL: "Cell cycle involvement in cancer therapy; WEE1 kinase, a potential target as therapeutic strategy", MUTATION RESEARCH, ELSEVIER, AMSTERDAM, NL, vol. 824, 1 January 2022 (2022-01-01), XP087060686, ISSN: 0027-5107, DOI: 10.1016/J.MRFMMM.2022.111776 [retrieved on 2022-02-19]

D8 YIN LINA ET AL: "Chimera induced protein degradation: PROTACs and beyond",
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, ELSEVIER,
AMSTERDAM, NL,
vol. 206, 19 July 2020 (2020-07-19), XP086299069,
ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2020.112494
[retrieved on 2020-07-19]

Claims 87-91 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

1) Article 33(2) PCT

Document D1 relates to estrogen receptor degraders. It discloses in Figure 6 (sheets 179/248 and 182/248) examples 533 and 540 that are prejudicial to the novelty of claims 1-3, 5-7, 10, 11 and 13-21. Further D1 discloses the use of the therein disclosed and claimed compounds for the treatment of cancer, such as e.g. breast cancer or melanoma, and therefore the disclosure of document D1 is also prejudicial to the novelty of claims 89-91 and 93-95.

Document D2 relates to Bcr-Abl or PARP degraders. It discloses on page 84 compounds (If) and (Ig) that are prejudicial to the novelty of claims 1-4, 7, 9 and 12-21. Further D2 discloses the use of the therein disclosed and claimed compounds for the treatment of cancer, such as e.g. breast cancer, and therefore the disclosure of document D2 is also prejudicial to the novelty of claims 89, 90, 93 and 94.

Document D3 relates to bifunctional compounds useful as modulators of B-cell lymphoma 6 protein. It discloses compound 177 on page 636 that is prejudicial to the novelty of claims 1-4, 7, 10 and 12-21. Further D3 discloses the use of the therein disclosed and claimed compounds for the treatment of cancer, such as e.g. breast cancer or melanoma, and therefore the disclosure of document D3 is also prejudicial to the novelty of claims 89-91 and 93-95.

Document D4 discloses structurally close related compounds as androgen receptor degraders. It discloses in particular compounds 105, 106, 117, 128, 130, 155, 156, 178, 190, 204, 216, 235, 237, 240, 245, 309, 334, 337, 338, 542, 579, 580, 584, 586, 597, 600, 601, 619, 620, 621-623 and 625 that differ from the presently claimed compounds in that they have an azetidiny or piperidinyl ring in place of the presently claimed pyrrolidinyl ring moiety. The disclosure of document D4 is therefore not prejudicial to the novelty of the claimed compounds and of the subject-matter relating to them.

Document D5 discloses structurally close related compounds as androgen receptor degraders. It discloses in particular examples 146, 148, 163 and 167 that differ from the presently claimed compounds in that they have a piperidinyl ring in place of the presently claimed pyrrolidinyl ring moiety. The disclosure of document D5 is therefore not prejudicial to the novelty of the claimed compounds and of the subject-matter relating to them.

Document D6 discloses WEE1 kinase degraders. The compounds disclosed therein differ from the presently claimed compounds in that they lack a pyrrolidinyl moiety. The disclosure of document D6 is therefore not prejudicial to the novelty of the claimed compounds and of the subject-matter relating to them.

Document D7 discloses on page 5 WEE1 inhibitors, among those the known in the art ZNL-02-096. Said WEE1 kinase degrader lacks a pyrrolidinyl bridging moiety. The disclosure of document D7 is therefore not prejudicial to the novelty of the claimed compounds and of the subject-matter relating to them.

Document D8 discloses a WEE1 kinase degrader (see Table 2, last compound) as well as other PROTAC degraders that lack the pyrrolidinyl bridging moiety as presently claimed. The disclosure of document D8 is therefore not prejudicial to the novelty of the claimed compounds and of the subject-matter relating to them.

Summarizing the above, claims 1-7, 9-21, 89-91 and 93-95 do not fulfil the requirements of novelty under Article 33(2) PCT and only claims 8, 22-88 and 92 are acknowledged as novel.

2) Article 33(3) PCT

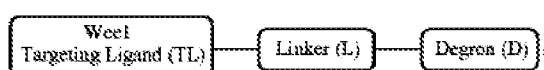
Although assessment of inventive step should normally be restricted to that of claims 8, 22-88 and 92 reference is made to the inventiveness of the claimed subject-matter in its entirety.

Documents D6-D8 disclose WEE1 kinase degraders and can be equally regarded to represent the closest prior art.

In view of the closest prior art the technical problem underlying the present application is seen in the provision of a further WEE1 kinase degraders.

As a solution are claimed the compounds of present Formula (I) and of the sub-Formulae (Ia), (II), (IIa), (III), (IIIa) and (IIIb).

According to document D6 WEE1 kinase degraders have the structural features/ moieties:



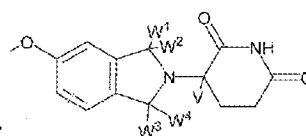
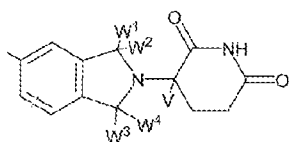
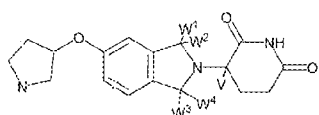
(The same sequence of structural features is also present in other types of degraders, see Figure 1 of D8: Warhead - Linker - Binding Moiety)

D6, as well as D7 and D8, disclose conjugates of the clinical candidate inhibitor AZD1775 to pomalidomide.

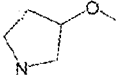
Thus for the WEE1 kinase degrader of the -closest- prior art the WEE1 targeting ligand (warhead) is the clinical candidate AZD1775, the linker is a propylene group and the degron (binding moiety) is pomalidomide or its equivalent with an -O-bridging moiety.

According to document D8 pomalidomide is amongst the most common CRBN binding moieties together with its equivalent with an -O-bridging moiety, lenalidomide or thalidomide (see Figure 1).

The presently claimed compounds have following moiety in common:



The CRBN moiety or is, however, as seen in document D8, shared by different degraders and is not specific to WEE1 kinase degraders.

The A-moiety together with the  or  moiety appears to represent the linker.

This results to the $-B(R''')_n$ moiety to correspond to the WEE1 targeting ligand (warhead). However, B is only defined as a cyclic group (cycloalkyl, heterocyclyl, aryl or heteroaryl group) and there are no further structural features that would justify a specificity of this targeting ligand / warhead to the WEE1 target protein (even if one were to take into account the definition of the B group as in claims 22, 39, 56, 60 and/or 75).

(see also in this respect that examples 533 and 540 that have the structural features presently claimed and that are prejudicial to the novelty of claims 1-3, 5-7, 10, 11 and 13-21 are disclosed in D1 as estrogen receptor degraders).

It is therefore considered that the presently claimed compounds do not solve the technical problem underlying the present application, at least not over the whole breadth claimed.

In this respect it is also stressed that an applicant is entitled to claim only obvious modifications of what was described (close related variations), since the claims should represent a reasonable generalisation of the examples given in the description: the technical features stated in the description/examples as being essential must be the same as those used to define the invention in the claims. The reason for that is that the problem to be solved should be solved by the whole scope of the claimed subject matter (every compound falling within its scope) and not just by individual compounds- especially since the problem may be seen in the provision of compounds acting on a biological system (i.e. on a system depending upon very different parameters). If this were not the case, an invention could arbitrarily be broadened to any limit without consideration, whether the compounds are actually solving the problem underlying the invention (Article 33(3) PCT).

Re Item VII

Certain defects in the international application

Claim 18 should be formulated as dependent on claim 17, claim 20 as dependent on claim 19, claim 36 as dependent on claim 35, claim 38 as dependent on claim 37, claim 51 as dependent on claim 50, claim 54 as dependent on claim 53, claim 57 as dependent on claim 54, claim 70 as dependent on claim 69, claim 72 as dependent on claim 71, claim 74 as dependent on claim 73, and claim 85 as dependent on the previous claims in order that the requirements of Rule 6.4(a) PCT are fulfilled.

Re Item VIII

Certain observations on the international application

- a) The wording "optionally substituted" used in claims 1, 5, 9, 10, 15, 16, 22, 24, 27, 33, 34, 39, 41, 44, 50, 53, 54, 60, 62, 65, 68, 75, 77, 80 and 81 is not acceptable under Article 6 PCT. This expression must be construed under its normal technical meaning, namely "substituted by absolutely anything" and thus this expression is unreasonably broad under the support aspect of Article 6 PCT.
- b) Further, terms such as "heterocyclyl", "aryl" and "heteroaryl" used in the claims (claims 1, 9, 10, 16, 22, 33, 34, 39, 50, 53, 54, 60, 68, 75 and 81) are objected under Article 6 PCT as such terms are considered to be non-limitative and embrace an infinite number of possibilities not yet explored by the applicant. Therefore it is not clear whether all compounds implied fall within the scope of the present claims and/or represent a solution of the problem underlying the present application. Consequently, for reasons of inventive step and clarity these terms should be limited to the specific meanings given in the description.
- c) According to Rule 6.2(a) PCT "Claims shall not, except where absolutely necessary, rely, in respect of the technical features of the invention, on references to the description or drawings. In particular, they shall not rely on such references as: "as described in part ... of the description," or "as illustrated in figure ... of the drawings."". Claim 86 referring to Table 2 of the description is therefore objected under Rule 6.2(a) PCT.
- d) Claims 87-88 and 92 are objected under Article 6 PCT. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of reducing WEE1 kinase protein levels), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.