

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/US2022/080565

International filing date (day/month/year)
29.11.2022

Priority date (day/month/year)
30.11.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C07D401/04 C07D491/08 C07D491/18 A61P35/00 A61K31/439

Applicant
KURA ONCOLOGY, 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 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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>1-77</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-77</u>
Industrial applicability (IA)	Yes: Claims	<u>1-77</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

Re Item V

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

1 The present application is directed to macrocyclic compounds which are inhibitors of farnesyltransferase (FTase) and therefore are useful in methods of treating cancer dependent on a farnesylated protein.

2 Present claims 69-77 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 recognize as patentable claims to a method of medical treatment by administering a compound or composition, but may allow claims to a product, in particular a compound or composition for use in a first or further medical treatment.

3 Reference is made to the following documents cited in the International Search Report:

D1 WO 97/21701 A1 (JANSSEN PHARMACEUTICA) 19 June 1997

D2 JAMES M. KRAUS ET AL: "Second Generation Analogues of the Cancer Drug Clinical Candidate Tipifarnib for Anti-Chagas Disease Drug Discovery", JOURNAL OF MEDICINAL CHEMISTRY, vol. 53, no. 10, 27 May 2010, pages 3887-3898, XP055056989

D3 EDWARD M. DRIGGERS ET AL: "The exploration of macrocycles for drug discovery - an underexploited structural class", NATURE REVIEWS DRUG DISCOVERY, vol. 7, no. 7, 1 July 2008, pages 608-624, XP055151640

D3a & DINSMORE CHRISTOPHER J. ET AL: "Conformational Restriction of Flexible Ligands Guided by the Transferred NOE Experiment: Potent Macrocyclic Inhibitors of Farnesyltransferase", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 123, no. 9, 8 February 2001, pages 2107-2108, XP093021516

3.1 Present claims 1-77 are all directed to compounds of the scope of formula (I) which are not known from the prior art: The structurally most related prior art compounds may be found in D1 (compounds 1-164 of tables 1-8) or D2 (compounds 1-33 of tables 1-4) which all lack the linker Y of the presently claimed compounds. The structures disclosed in D3 and D3a are not closely related.

Present claims 1-77 are novel in the sense of Art. 33(2) PCT by consequence.

3.2 The prior art documents D1 and D2 show the structurally most related inhibitors of FTase including tipifarnib and related compounds. They may both serve as closest prior art.

Starting from D1 or D2, the present technical problem can be seen in providing alternative inhibitors FTase as agents for treating cancer.

The solution resides in the macrocyclic compounds of formula (I). Their structural design is based on the closest prior art pharmacophore provided by tipifarnib and its analogs which can be found in the present moiety Z - CR6R7- bicyclus - W, but wherein the ring moieties Z and W are linked via group Y to form a macrocyclus as structural contribution over said prior art compounds.

However, document D3 indicates in its text and figures 1-7 that it is desirable strategy to restrict an inhibitor's conformation to arrive at macrocyclic variants of known inhibitors which may even improve their pharmacological activity or pharmacokinetic property and reviews various examples of macrocyclic derivatives of known pharmaceutically active non-macrocyclic agents. It even refers to the disclosure of D3a (scheme 1, table 1) with regard to the FTase inhibitor 24 (= compound 10 of D3a) which represents a macrocyclic derivative of non-macrocyclic compounds 23 and 25 (= compounds 9 and 11 of D3a) as it links the former terminal (het)aryl rings with an aliphatic methylene (CH₂) linker.

Therefore, it appears that it is obvious for the skilled person aware of such a strategy in drug design to arrive at the presently claimed compounds by introducing an aliphatic group to link the two terminal (het)aryl rings.

Therefore, present claims 1-77 are not inventive in the sense of Article 33(3) PCT in view of the teaching of D1 or D2 in combination with the teaching of D3 or D3a.

Furthermore it is also noted that, in order to fulfil the requirements of Art. 33(3) PCT, all alternatives of a claim should solve the technical problem underlying the claimed invention. In the present case, the number of alternative compounds falling within the scope of the present claims 1-60 and 63-77 is such that it is unlikely that all of them possess the type and level of activity required to achieve the technical effect essential for the solution of the problem: the definitions given in said present claims for all the Markush groups by far exceed the structural features shown by the examples as follows:

- 1) A3, A6 = CH or N
- 2) A4, A5 = CH
- 3) R6 = 1-Me-imidazol-5-yl, 1-Me-1,3,4-triazol-2-yl or 3-Me-1,2,4-triazolyl
- 4) R7 = H, OH, NH₂, N(H)AlkX or Hcy
- 5) Z = Ph or Py
- 6) W = Ph, and
- 7) Y = CH₂-CH₂, O-(CH₂)_{1,2} or (CH₂)_{1,2}-O

In other words, the scope of the current compound claims 1-60 and 62-77 is not a plausible generalisation of the active tested examples and these claims thus embrace speculative matter, which cannot be accepted as a credible solution to the above stated technical problem. Therefore, the skilled man would not have been able to predict if all compounds falling within the above definitions would actually be active as alleged. Hence, the subject-matter of the current claims 1-60 and 62-77 does not comply with the requirement of inventive step for this reason, too.

Re Item VII

Certain defects in the international application

The requirements of Rule 5.1(a)(ii) PCT are not met since the most relevant background art D1 and/or D2 has not been identified in the description.

Re Item VIII

Certain observations on the international application

Present claims 61 and 62 are directed to compounds which are only given by their compound number as only defined in the present description. Therefore, these claims do not meet the requirements of Rule 6.2(a) PCT according to which claims shall not rely on references to the description or drawings in specifying the technical features of the invention.