

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2014229-0028	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2023/012521	International filing date (<i>day/month/year</i>) 7 February 2023 (07-02-2023)	(Earliest) Priority Date (<i>day/month/year</i>) 8 February 2022 (08-02-2022)
Applicant THERAS, INC.		

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 12 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:

COMPOUNDS HAVING A T-STRUCTURE FORMED BY AT LEAST FOUR CYCLES FOR USE IN THE TREATMENT OF CANCER AND OTHER INDICATIONS

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

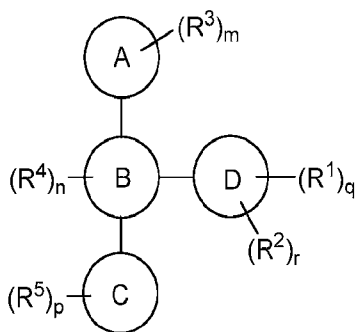
- ☐ the text is approved as submitted by the applicant
☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

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

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ 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

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Provided herein are compounds and compositions thereof that may be capable of disrupting, interrupting, and/or preventing an interaction between a small GTPase protein and a PI3K protein (e.g., PI3Ka). The present disclosure also provides methods of treating cancers and other indications with such compounds or compositions thereof.



I

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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.: **32-34 (completely); 1-30, 35-213 (partially)**
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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:

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 an 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.:

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.

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A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07D401/04	C07D401/14
	C07D495/04	C07D498/04
	A61K31/437	A61K31/4375
	C07D471/04	C07D471/10
	C07D513/04	C07D519/00
	A61K31/472	A61K31/4985
	C07D487/04	A61K31/519
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) C07D A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MA JUN-RUI ET AL: "Efficient approach to 2-hydroxy-2,3-dihydrofuran derivatives and its application for the synthesis of novel 4-(1H-pyrazol-4-yl)pyridazines", ORGANIC & BIOMOLECULAR CHEMISTRY, vol. 13, no. 17, 1 January 2015 (2015-01-01), pages 4976-4980, XP093044181, ISSN: 1477-0520, DOI: 10.1039/C5OB00163C Retrieved from the Internet: URL:https://pubs.rsc.org/en/content/articlepdf/2015/ob/c5ob00163c?page=search> compounds 4a-k	1-3, 21-25, 37, 38
X	WO 2010/011772 A2 (VERTEX PHARMA [US]; JIMENEZ JUAN-MIGUEL [GB]; STUDLEY JOHN [GB]) 28 January 2010 (2010-01-28) compounds 49, 50	1-3, 14, 16, 21-25, 40
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☒	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 2 June 2023		Date of mailing of the international search report 13/06/2023
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Sotoca Usina, E

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COOKE GARETH ET AL: "Substituted pyridazines as ligands in homoleptic (fac and mer) and heteroleptic Ru(ii) complexes", DALTON TRANSACTIONS, vol. 40, no. 32, 1 January 2011 (2011-01-01), page 8206, XP093044346, Cambridge ISSN: 1477-9226, DOI: 10.1039/c1dt10340g compounds 1a, 1b, 2a, 2b, 5a, 3a, 4a, 3b, 4b -----	1, 14, 26, 38
X	AZIZIAN J. ET AL: "Synthesis of Trisubstituted 1,2,4-Triazines in Presence of NaHSO₄/SiO₂", ASIAN JOURNAL OF CHEMISTRY, vol. 23, no. 3, 1 January 2011 (2011-01-01), pages 980-982, XP93044357, pages 981-982; table 1; compounds 6a, 6b, 6c, 6e, 6f, 7b, 8a, 8b -----	1-3, 23, 25
X	VARUGHESE SUNIL ET AL: "Pyridazines in Crystal Engineering. A Systematic Evaluation of the Role of Isomerism and Steric Factors in Determining Crystal Packing and Nano/Microcrystal Morphologies", CRYSTAL GROWTH & DESIGN, vol. 10, no. 6, 4 May 2010 (2010-05-04), pages 2571-2580, XP93044361, US ISSN: 1528-7483, DOI: 10.1021/cg9015383 compounds 1a, 1b, 1c -----	1-3, 21-26
X	US 6 509 469 B1 (SHINTOU TAICHI [JP] ET AL) 21 January 2003 (2003-01-21) Column 13 Compound B-6 Column 19-20 Table 2 Ex 15 - triazine + pyridine derivative ----- -/--	1-3, 14, 21-23, 25, 38, 42, 57

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHAO Z ET AL: "Broadening the scope of 1,2,4-triazine synthesis by the application of microwave technology", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM , NL, vol. 44, no. 6, 3 February 2003 (2003-02-03), pages 1123-1127, XP004736108, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(02)02845-9 Compound 3 Page 1124 Table 1 - entries 1-7 Page 1125 Table 2 - entries 1-2 -----	1-3, 21-23, 25,26, 37,38, 42,57, 58,69
X	HANS NEUNHOEFFER ET AL: "Cycloaddition Reactions with Azabenzenes, XVIII. Synthesis of [2]Pyridines", HETEROCYCLES, JAPAN INSTITUTE OF HETEROCYCLIC CHEMISTRY, JP, vol. 35, no. 2, 1 January 1993 (1993-01-01), pages 1089-1101, XP009181046, ISSN: 0385-5414, DOI: 10.3987/COM-92-S(T)109 Compounds 3a, 3m, 3n, 4a, 4m, 4n, 5a, 5m, 5n, 6a, 6m, 6n, -----	1-3,14, 16, 21-31, 37,38, 68,69
X	MOSEEV TIMOFEY D ET AL: "Direct CH/CLi coupling of 1,2,4-triazines with C6F5Li followed by aza-Diels-Alder reaction as a pot, atom, and step economy (PASE) approach towards novel fluorinated 2,2'-bipyridine fluorophores", JOURNAL OF FLUORINE CHEMISTRY, ELSEVIER, NL, vol. 224, 26 May 2019 (2019-05-26), pages 89-99, XP085736043, ISSN: 0022-1139, DOI: 10.1016/J.JFLUCHEM.2019.05.008 [retrieved on 2019-05-26] compounds 5h, 5i, 5j -----	1-3,14, 15,21, 25,30, 31,38, 68,69
X	PALACIOS FRANCISCO: "FULL PAPER Cycloaddition Reactions of Neutral 2-Azadienes with Enamines ? Regiospecific Synthesis of Highly Substituted Dihydropyridines and Pyridines", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2001, no. 11, 1 January 2001 (2001-01-01), pages 2115-2122, XP093050967, compounds 7a, 7b, 7c ----- -/--	1-3,14, 15,21, 25,30, 31,38, 68,69

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YOLANDA FERNÁNDEZ SAINZ ET AL: "Improved Methodologies for the Preparation of Highly Substituted Pyridines", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 70, no. 24, 1 November 2005 (2005-11-01), pages 10086-10095, XP055355205, ISSN: 0022-3263, DOI: 10.1021/jo0518304 compound 5b -----	1, 14, 26, 30, 31, 38
X	NOGUCHI TEPPEI ET AL: "Rhodium-catalyzed Synthesis of 1-Arylisoquinoline Derivatives through Annulative Coupling of 3-Aryl-1,2-benzisoxazoles and Alkynes", CHEMISTRY LETTERS, vol. 46, no. 10, 5 October 2017 (2017-10-05), pages 1512-1514, XP093050973, JP ISSN: 0366-7022, DOI: 10.1246/cl.170618 Refer to Supporting Information	1-4, 14, 21-23, 29-31, 37, 42, 68, 69
X	& Noguchi Teppei ET AL: "Rhodium-catalyzed Synthesis of 1-Arylisoquinoline Derivatives through Annulative Coupling of 3-Aryl-1,2-benzisoxazoles and Alkynes Electronic Supporting Information", Chemistry Letters, 24 June 2017 (2017-06-24), pages S1-s37, XP93051030, Retrieved from the Internet: URL:https://www.journal.csj.jp/doi/suppl/10.1246/cl.170618?role=tab [retrieved on 2023-06-01] Compound 3ga -----	1-4, 14, 21-23, 29-31, 37, 42, 68, 69
X	WANG CHANG-SHENG ET AL: "Robust Cobalt Catalyst for Nitrile/Alkyne [2+2+2] Cycloaddition: Synthesis of Polyarylpiperidines and Their Mechanochemical Cyclodehydrogenation to Nitrogen-Containing Polyaromatics**", ANGEWANDTE CHEMIE INTERNATIONAL EDITION, vol. 60, no. 17, 12 March 2021 (2021-03-12), pages 9627-9634, XP093050993, Hoboken, USA ISSN: 1433-7851, DOI: 10.1002/anie.202017220 Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full/10.1002/anie.202017220> compound 5 ----- -/--	1-3, 14, 21, 25, 30, 31, 37, 68, 69

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/071264 A1 (INTELLIKINE LLC [US]; JESSEN KATAYOUN [US] ET AL.) 16 May 2013 (2013-05-16) Pi3Ka; claims 1-48 -----	1-31, 35-213
X	WO 2005/070431 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT] ET AL.) 4 August 2005 (2005-08-04) Pi3Ka; claims 1-13 -----	1-31, 35-213

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010011772 A2	28-01-2010	AR 074171 A1 AU 2009274027 A1 BR PI0916295 A2 CA 2731432 A1 CN 102159574 A EP 2318408 A2 JP 5931976 B2 JP 2011529066 A JP 2014208710 A KR 20110033299 A TW 201018680 A WO 2010011772 A2	29-12-2010 28-01-2010 24-09-2019 28-01-2010 17-08-2011 11-05-2011 08-06-2016 01-12-2011 06-11-2014 30-03-2011 16-05-2010 28-01-2010
US 6509469 B1	21-01-2003	AU 1310101 A CN 1402708 A DE 60017795 T2 EP 1243579 A1 JP 4603648 B2 JP 2001158773 A US 6509469 B1 WO 0140186 A1	12-06-2001 12-03-2003 23-06-2005 25-09-2002 22-12-2010 12-06-2001 21-01-2003 07-06-2001
WO 2022199662 A1	29-09-2022	NONE	
WO 2012122383 A2	13-09-2012	AU 2012225382 A1 CA 2829558 A1 CN 103501610 A EP 2683243 A2 JP 2014511395 A US 2012258967 A1 WO 2012122383 A2	10-10-2013 13-09-2012 08-01-2014 15-01-2014 15-05-2014 11-10-2012 13-09-2012
WO 2013071264 A1	16-05-2013	CA 2855666 A1 CN 104204804 A EP 2776837 A1 HK 1202333 A1 JP 6126615 B2 JP 2014533284 A US 2015030588 A1 WO 2013071264 A1	16-05-2013 10-12-2014 17-09-2014 25-09-2015 10-05-2017 11-12-2014 29-01-2015 16-05-2013
WO 2005070431 A1	04-08-2005	AR 049769 A1 AU 2005205915 A1 BR PI0507071 A CA 2552885 A1 CN 1909908 A EC SP066718 A EP 1708710 A1 JP 2007519662 A KR 20070009546 A MA 28400 B1 PE 20051089 A1 RU 2006130003 A TN SN06226 A1 TW 200528103 A WO 2005070431 A1	06-09-2006 04-08-2005 19-06-2007 04-08-2005 07-02-2007 31-10-2006 11-10-2006 19-07-2007 18-01-2007 02-01-2007 25-01-2006 10-04-2008 03-12-2007 01-09-2005 04-08-2005

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 32-34 (completely); 1-30, 35-213 (partially)

The present application contains 213 claims. There are so many dependent claims, and they are drafted in such a way that the claims as a whole are not in compliance with the provisions of clarity and conciseness of Article 6 PCT, as they create a smoke screen in front of the skilled reader when assessing what should be the subject-matter to search,. The non-compliance with the substantive provisions is to such an extent, that the search would be performed taking into consideration the non-compliance in determining the extent of the search (PCT Guidelines 9.19).

The present claims relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the compounds claimed, see the examples. From all possible B cycles, only thieno[3,2-c]pyridine, furo[3,2-c]pyridine, 6,7-dihydro-5H[2]pyrindine and [1,3]-thiazolo[4,5-c]pyridine have been exemplified, and the particular linking points to rings A, C and D at clearly defined points ring A at C-7 (for thienopyridine), ring C at C-4 (for thienopyridine) and ring D at C-6 (for thienopyridine). Furthermore, the atom at ring position 5 (for thienopyridine) is always a N and the atoms at ring positions 4, 6 and 7 (for thienopyridine) are always C.

Furthermore, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

D1 discloses compounds 4a-k which are seen as novelty hindering for at least claims 1-3, 21-25, 37, 38 under Article 33(2) PCT.

D2 discloses compounds 49 and 50 which are seen as novelty hindering for at least claims 1-3, 14, 16, 21-25, 32, 33, 40 under Article 33(2) PCT.

D3 discloses compounds 1a, 1b, 2a, 2b, 5a, 3a, 4a, 3b, 4b which are seen as novelty hindering for at least claims 1, 14, 26, 32, 38 under Article 33(2) PCT.

D4 discloses on pages 981-982 table 1 compounds 6a, 6b, 6c, 6e, 6f, 7b, 8a, 8b which are novelty hindering for at least claims 1-3, 23, 25 under Article 33(2) PCT.

D5 discloses compounds 1a, 1b, 1c which are seen as novelty hindering for at least claims 1-3, 23, 25 under Article 33(2) PCT.

D6 discloses in column 13 compound B-6, in columns 19-20 table 2 examples 15 - triazine + pyridine derivative which are seen as novelty hindering for at least claims 1-3, 14, 21-23, 25, 32, 33, 38, 42, 57 under Article 33(2) PCT.

D7 discloses in page 1123 compound 3, in page 1124 Table 1 - entries 1-7 and in page 1125 Table 2 - entries 1-2 which are seen as novelty hindering for claims

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1-3, 21-23, 25, 26, 37, 38, 42, 57, 58, 69 under Article 33(2) PCT.

The applicant was therefore invited to file a statement indicating the subject-matter to be searched within the time limit indicated in the present communication.

The applicant answered with date of 24.05.2023, as a main request, she requests the search to be carried out on the scope of claim 30 and as an auxiliary request, the search to be carried out in the scope of claim 31.

The search has been restricted to the subject-matter indicated by the applicant in her reply of 24.05.2023 auxiliary request, that is the scope of claim 31 filed in reply to the invitation.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) PCT declaration be overcome.