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**Published:**
— *with international search report (Art. 21(3))*

(54) Title: NICOTINAMIDE- AND BENZAMIDE-BASED COMPOUNDS, CONJUGATES, AND COMPOSITIONS AS INHIBITORS OF TRANSLATIONAL- AND TRANSCRIPTIONAL-RELATED KINASES

(57) Abstract: Compounds comprising nicotinamide or benzamide linked to a bicyclic heterocycle such as an alkynyl imidazo-[1.2-*b*]-pyridazine, substituted with one or more ring moieties, as well as conjugates and compositions comprising the same. Methods for treatment of kinase-associated diseases and disorders are also provided.

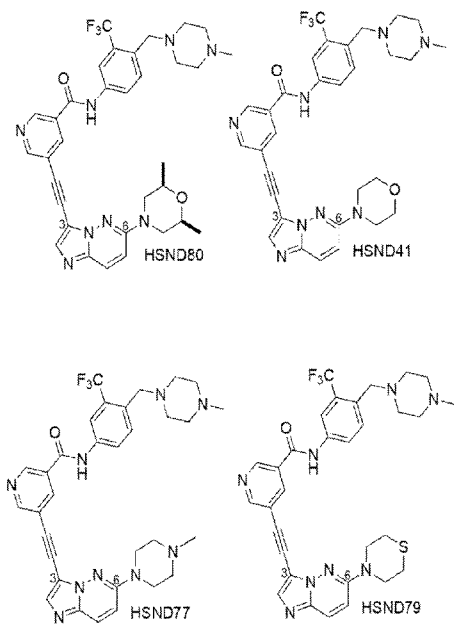


*FIG. 2*

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*[Continued on next page]*

**(88) Date of publication of the international search report:**
18 April 2024 (18.04.2024)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/65476

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/395, A61K 31/166, A61K 31/167 (2023.01)
ADD. A61K 31/33 (2023.01)

CPC - INV. A61K 31/395, A61K 31/166, A61K 31/167
ADD. A61K 31/33

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
See Search History document

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. |
|---|---|---|
| | First Invention | |
| A | WO 2018/035072 A1 (Purdue Research Foundation), 22 February 2018 (22.02.2018), entire document, especially para[0006], [0138]; page 220, compound HSL44 | 1, 3-4, 8, 15-18 |
| A | WO 2013/170770 A1 (Wan et al.), 21 November 2013 (21.11.2013), entire document, especially page 6, para 5; page 7, para 1-6; page 11; page 14, compounds listed | 1, 3-4, 8, 15-18 |
| A | US 2015/0105377 A1 (ARIAD Pharmaceuticals, Inc.), 16 April 2015 (16.04.2015), entire document, especially para[0008], [0013], [0046] | 1, 3-4, 8, 15-18 |
| A | US 2022/0089599 A1 (Purdue Research Foundation), 24 March 2022 (24.03.2022), entire document, especially para[0114]; page 12, compound 27 | 1, 3-4, 8, 15-18 |
| A | "Pubchem CID 153545325", Create date: 13 August 2020 (13.08.2020), entire document, especially page 2, compound listed | 1, 3-4, 8, 15-18 |
| A | Larocque, E. A. et al., "Alkynylnicotinamide-based compounds as ABL1 inhibitors with potent activities against drug-resistant CML harboring ABL1(T315I) mutant kinase", 20 June 2018 (20.06.2018), Chem. Med. Chem., Volume 13, Issue 12, Pages 1-9, entire document, especially Figures 2-3, 6 | 1, 3-4, 8, 15-18 |

☒ 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
"D" document cited by the applicant in the international application
"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 | Date of mailing of the international search report |
|---|---|
| 08 December 2023 | JAN 31 2024 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Kari Rodriquez<br>Telephone No. PCT Helpdesk: 571-272-4300 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/65476

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | Second Invention | |
| X | WO 2018/035072 A1 (Purdue Research Foundation), 22 February 2018 (22.02.2018), entire document, especially para[0006], [0138]; page 220, compound HSL44 | 1-4, 8-9, 11, 15-18, 21, 34, 46 |
| A | US 2022/0089599 A1 (Purdue Research Foundation), 24 March 2022 (24.03.2022), entire document, especially para[0114]; page 12, compound 27 | 1-4, 8-9, 11, 15-18, 21, 34, 46 |
| A | "Pubchem CID 155927613", Create date: 07 July 2021 (07.07.2021), entire document, especially page 2, compound listed | 1-4, 8-9, 11, 15-18, 21, 34, 46 |
| A | WO 2013/170770 A1 (Wan et al.), 21 November 2013 (21.11.2013), entire document, especially page 6, para 5; page 7, para 1-6; page 11; page 14, compounds listed | 1-4, 8-9, 11, 15-18, 21, 34, 46 |
| A | US 2015/0105377 A1 (ARIAD Pharmaceuticals, Inc.), 16 April 2015 (16.04.2015), entire document, especially para[0008], [0013], [0046] | 1-4, 8-9, 11, 15-18, 21, 34, 46 |
| A | Wang et al., "Identification of nicotinamide aminonaphthyridine compounds as potent RET kinase inhibitors and antitumor activities against RET rearranged lung adeno-carcinoma", (2019), Bioorganic Chemistry, Vol. 90, 103052, Pages 1-15, entire document, especially pages 6-7, series A, B; page 15, graphical abstract | 1-4, 8-9, 11, 15-18, 21, 34, 46 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/65476

**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.: 13, 49-60
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 supplemental box----

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.:
1-4, 8-9, 11, 15-18, 21, 34, 46

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.

Box III: lack of unity

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-12 and 14-48 are directed to a compound having a structure of Formula (XX) as seen in instant claim 1. Claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of Formula (XX) wherein R4 is a nicotinamide; L is a linker comprising at least one atom wherein the linker is ethynyl as seen in instant claim 2; Z is a bicyclic heterocycle substituted with R3 wherein the bicyclic heterocycle is imidazo[1,2-b]pyridazine as listed in instant claim 2; R3 comprises one ring moiety wherein the moiety is Formula (II) as listed in instant claim 2 wherein each X is independently an alkyl, with the proviso that all X are not H, and Q is O (i.e., morpholine). It is believed that claims 1, 3-4, 8, and 15-18 read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of Formula (XX) wherein R4 is a benzamide; L is a linker comprising at least one atom wherein the linker is ethynyl as seen in instant claim 2; Z is a bicyclic heterocycle substituted with R3 wherein the bicyclic heterocycle is imidazo[1,2-b]pyridazine as listed in instant claim 2; R3 comprises one ring moiety wherein the moiety is Formula (II) as listed in instant claim 2 wherein each X is independently alkyl, with the proviso that all X are not H, and Q is O (i.e., morpholine) (i.e., claims 1, 3-4, 8, 15-18).

The group 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:

Each invention in Group I+ includes the technical feature of a unique compound of Formula (XX), 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 of Formula (XX).

These shared technical features, however, do not provide a contribution over the prior art as being anticipated by US 2022/0089599 A1 to Purdue Research Foundation (hereinafter 'Purdue'). Purdue teaches a compound having a structure of Formula (XX) as seen in instant claim 1 or a pharmaceutically acceptable salt thereof, wherein; R4 is a nicotinamide substituted with a fluoro in the ortho position relative to the nitrogen atom of the pyridine ring and with a phenyl group connected to the nitrogen of the carboxamide wherein the phenyl group is substituted with a trifluoromethyl group and an alkyl piperazine group; L is a linker comprising at least one atom (i.e., an ethynyl group); Z is a bicyclic heterocycle substituted with R3 (i.e., imidazo[1,2-b]pyridazine); R3 comprises one ring moiety (i.e., -NH-cyclopropane) (see Figure 5, compound 27).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Item 4 continued: Claims 13 and 49-60 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:
Claim 14 lacks clarity. R4 is defined as unsubstituted morpholine. However, based on claim 2, morpholine cannot be unsubstituted. For the purpose of this opinion, it will be interpreted that claim 14 corresponds to the compound of claim 1.

Claims 57-58 lacks clarity. They are method claims dependent upon claim 46, which is a compound claim. For the purposes of this opinion, it is interpreted that claim 57 is dependent upon claim 56.

The second paid invention erroneously included claims 13 and 36. Claim 13 is unsearchable because it is a dependent claim and are not drafted in accordance with the second and third sentences of Rule 6.4(a). Claim 36 should not be included because none of the listed compounds exactly matches the compound listed for the additional search (i.e., Compound HSND101 of claim 46).