(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 February 2022 (10.02.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/032073 A3

(51) International Patent Classification:
C12N 15/63 (2006.01)

(21) International Application Number:
PCT/US2021/044911

(22) International Filing Date:
06 August 2021 (06.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

63/062,943	07 August 2020 (07.08.2020)	US
63/119,915	01 December 2020 (01.12.2020)	US
63/186,846	11 May 2021 (11.05.2021)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
31 March 2022 (31.03.2022)

(54) Title: TRPML MODULATORS

(57) Abstract: The present invention provides compounds, pharmaceutically acceptable compositions thereof, and methods of using the same.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/44911

A. CLASSIFICATION OF SUBJECT MATTER
IPC - C12N 15/63 (2022.01)
CPC - C12N 15/63; C12N 15/635; C12N 2830/52

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.
A	PubChem-SID-320109121, Modify Date: 3 June 2019 (03.06.2019), especially: pg 2, figure, this is a purchasable chemical.	1-3,8,37
A	WO 2020/022084 A1 (MITSUBISHI GAS CHEMICAL COMPANY) 30 January 2020 (30.01.2020), especially: pg 13, para 4, 2,3-dihydro-1H-pyrrolo [1,2-a] benzimidazole.	1-3,8,37
A	YE et al. "Pyrrole- and Dihydropyrrole-Fused Neonicotinoids: Design, Synthesis, and Insecticidal Evaluation", J. Agric. Food Chem. 2013. 61, pp 312-319, especially: pg 313, Scheme 1, Target molecule 7.	1-3,8,37

☐ 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
16 January 2022	FEB 28 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/44911

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.: 4-7, 9-14, 17-26, 28-31 and 40-54
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)

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.:
1-3,8,37

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 1-3, 8, 15-16, 27 and 32-39 directed to a compound of formula I or a pharmaceutically acceptable salt thereof. The compound of formula I will be searched to the extent that it encompasses the first species of claim 1, wherein Y1 is N and Y2 is C; L is unsubstituted -C0 alkyleneyl-S(O)2-; A is C3 cycloaliphatic; B is a fused 5-membered aryl; R1 is C1 aliphatic; m is 0; n is 0; p is 0; and q is 1. It is believed that claims 1-3, 8 and 37 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of formula I, 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 claim 1, wherein Y1 is C and Y2 is N; L is unsubstituted -C0 alkyleneyl-S(O)2-; A is C3 cycloaliphatic; B is a fused 5-membered aryl; R1 is C1 aliphatic; m is 0; n is 0; p is 0; and q is 1 (i.e. claims 1-3, 8 and 37).

The groups 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:

Group I+ includes the technical feature of a unique compound of formula I, 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 having the structure of formula I.

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by the document entitled PubChem-SID-320109121 (hereinafter 'PubChem-121').

PubChem-121 teaches a compound of formula I wherein Y1 and Y2 are C; L is -C(O)-C0 alkylenyl; A is C5 cycloaliphatic; B is a fused C6 aryl; R1 is C1 aliphatic; n is 0; m is 0; p is 0; and q is 1 (pg 2, figure, this is a purchasable chemical).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 4-7, 9-14, 17-26, 28-31 and 40-54 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are therefore, not included in the above analysis.

Claim 1 lacks clarity regarding fused ring B and Y1 and Y2. B is defined as "a fused optionally substituted C5-C6 aryl or optionally substituted 5- to 6-membered heteroaryl comprising 1 to 3 heteroatoms selected from N, O, and S" and Y1 and Y2 are defined as "each of Y1 and Y2 is independently selected from N and C. However, C5 unsaturated ring is not aryl, so if Y1 and Y2 are C, the ring is not aromatic. Furthermore, if B is an unsaturated ring, and one of Y1 and Y2 is N, the ring is aryl, but both Y1 and Y2 cannot be N simultaneously because it will exceed valency for one of the N atoms. Also if B is 6-membered aryl, neither Y1 or Y2 can be N because it exceeds valency. Therefore, for the purposes of completing this ISR, only the subset of possibilities which meet the requirements of valency were considered.