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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

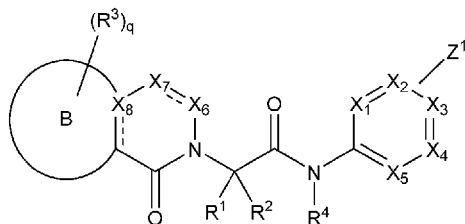
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01 May 2025 (01.05.2025)

(54) Title: TMEM175 AGONISTS, COMPOSITIONS, AND METHODS OF USE



Formula I

(57) Abstract: The present disclosure relates to compounds of the Formula I or a pharmaceutically acceptable salt thereof, wherein the variables are as defined herein. Also provided are compositions comprising said compounds and methods of use for treating certain diseases or disorders, including, for example, neurodegenerative diseases and lysosomal storage diseases.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/35781

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/395, A61K 31/4704, A61K 31/166, A61K 31/167 (2024.01)
ADD. A61K 31/33 (2024.01)

CPC - INV. A61K 31/395, A61K 31/4704, 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 documentDocumentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History documentElectronic 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	US 2021/0379052 A1 (Shenzhen Chipscreen Biosciences Co., Ltd.), 09 December 2021 (09.12.2021), entire document, especially para[0027]-[0043]	1
A	US 4,621,097 A (Butler et al.), 04 November 1986 (04.11.1986), entire document, especially col 1, ln 12-30	1
A	WO 2023/021278 A1 (Redx Pharma PLC), 23 February 2023 (23.02.2023), entire document, especially para[0007], [0079]	1
A	"Pubchem CID 9354358", Create date: 31 July 2006 (31.07.2006), entire document, especially page 2, compound listed	1
P/A	WO 2024/108155 A2 (Denali Therapeutics Inc.), 23 May 2024 (23.05.2024), entire document, especially page 13, ln 22-30; page 13-16; Table 1	1



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

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 24/35781

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.: 8-9, 12-46, 55-69, 71-77
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.:
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

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 1-7, 10-11, 47-54, and 70 are directed to a compound having the structure of Formula I as seen in instant claim 1, a compound having the structure of Formula II as seen in instant claim 2, or a compound having the structure of Formula III as seen in instant claim 47. Claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of Formula I or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein the dotted lines are each independently a single bond; Z1 is C1 alkyl; Ring B is a 5-membered carbocyclyl; X1 is absent; X2, X3, X4, and X5 are each independently CR5 wherein R5 is each independently H; X6 is absent; X7 is CH; X8 is C; R1 is H; R2 is C1 alkyl; R4 is H; q is 0. It is believed that claim 1 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 I or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein the dotted lines are each independently a single bond; Z1 is C1 alkyl; Ring B is a 5-membered carbocyclyl; X1 is absent; X2, X3, X4, and X5 are each independently CR5 wherein R5 is each independently H; X6 is absent; X7 is CH; X8 is C; R1 is H; R2 is C2 alkyl; R4 is H; q is 0 (i.e., claim 1).

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:

Each invention in Group I+ includes the technical feature of a unique compound of Formula I, Formula II, or Formula III, 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 I, a compound of Formula II, and a compound of Formula III.

These shared technical features, however, do not provide a contribution over the prior art as being anticipated by a document entitled "Pubchem CID 9354358" (hereinafter "Pubchem-358"). Pubchem-358 teaches a compound of Formula I as seen in instant claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Z1 is C1 alkyl; Ring B is phenyl; X1 is CR5 wherein R5 is H; X2, X3, X4, and X5 are each independently CR5 wherein the R5 on X2, X4, and X5 are each independently H and X3 is substituted with Z1; X6 is CH; X7 is CH; X8 is C; R1 is H; R2 is H; R4 is H; q is 0 (see page 2, compound listed).

Accordingly, the inventions listed as Groups I+ above lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature providing contribution over prior art.

RE: Item 4: Claims 8-9, 12-46, 55-69, and 71-77 have been held unsearchable because they are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Claim 1 lacks clarity. The dotted lines are not defined. For the purposes of this opinion, it is interpreted that the dotted lines represent a single bond or a double bond.

Claim 1 lacks clarity. Z1 is defined as C1-6 alkyl or C1-4alkylene-aryl, substituted with one or two halogen. However Example 240 on instant page 142 provides an example wherein Z1 is unsubstituted C2 alkyl. For the purposes of this opinion, it is interpreted that when Z1 is C1-6 alkyl or C1-4 alkylene-aryl, then Z1 is optionally substituted with one or two halogen.