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(54) Title: PROTEIN-BINDING COMPOUNDS

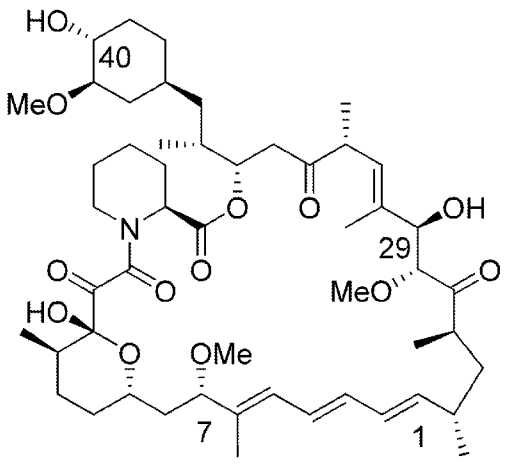

FIG. 1

(57) Abstract: The technology relates in part to compounds that bind to proteins. In certain examples, the compounds can bind to proteins that bind to rapamycin. In some examples, the compounds can bind to cellular proteins, and/or variant forms of cellular proteins, that bind to rapamycin and/or analogs of rapamycin. In certain examples, the compounds bind to and multimerize proteins that bind to rapamycin and/or analogs of rapamycin, such as for example, an FKBP12 protein (and/or variants threreof) and an mTOR polypeptide and/or region such as FRB, and/or variants thereof. Compounds provided include those having a structure of Formula A Formula A, where R^{20}, R^{21} and R^{22} moieties are described herein.

[Continued on next page]

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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:

— *of inventorship (Rule 4.17(iv))*

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:
22 May 2020 (22.05.2020)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/55067

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/436; C07D 498/18 (2020.01)

CPC - A61K 31/436; C07D 498/18

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.
Y	US 2009/0253732 A1 (GREGORY, MA et al.) 08 October 2009; paragraphs [0039]-[0041], [0043]-[0046], [0049]-[0050], [0052]	1-2, 6-7
Y	US 2009/0239855 A1 (GRAZIANI, El et al.) 24 September 2009; paragraphs [0030]-[0031]	1-2, 6-7
Y	US 2003/0170831 A1 (OKUHARA, M et al.) 11 September 2003; paragraph [0009]	1-2, 6-7
A	US 2016/0176893 A1 (ISOMERASE THERAPEUTICS LIMITED) 23 June 2016; entire document	1-2, 6-7

☐ 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
29 January 2020 (29.01.2020)	31 MAR 2020
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 Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US19/55067

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.: 5, 23-37, 43-144
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:

-***-Continued Within the Next 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.:
1-2, 6-7

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/55067

-***-Continued from Box No. III Observations where unity of invention is lacking -***-

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 examined, the appropriate additional examination fees must be paid. Groups I+, Claims 1-4, 6-22, 38-42; and a compound of Formula A, wherein R20 is hydrogen; R21 is hydrogen; and R22 is halogen (compound structure) are directed do compounds.

The compounds will be searched to the extent they encompass a compound of Formula A, wherein R20 is hydrogen; R21 is hydrogen; and R22 is halogen (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof (e.g. no optional or variable atoms, bonds, or substituents) for each, where available as an option within at least one searchable claim, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1-2 (in-part) and 6-7 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula A, wherein R20 is hydrogen; R21 is hydrogen; and R22 is halogen (compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the searchable 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/examined. An exemplary election would be a compound of Formula A, wherein R20 is -R23 wherein R23 is alkyl; R21 is hydrogen; and R22 is halogen (compound structure).

Groups I+ share the technical features including: a compound having a structure of the following Formula A: as shown, wherein R20 is hydrogen, -R23 or -RF -R23; R21 is hydrogen, hydroxy, -RG-R24, -RG-R24-R25 or -RG-R24-R26-R25; R22 is halogen, -NR27R28 , -RH-R29-R30 or -RH-R29-R31-R30; RF, RG and RH each independently is -O-, -C(O)-, -O-C(O)-, -C(O)-O-, -S-, -S(O)n-, -O-S(O)n-, -S(O)n-O-, -NH-S(O)n-, -S(O)n-NH-, -NH-C(O)-, -C(O)-NH-, -NH-C(S)-, -C(S)NH-, -S-C(S)-, -C(S)-S-, or -C(S)-; n is 1 or 2; R23 independently is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl, which independently is optionally substituted by one or more substituents chosen from halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, perhaloalkyl, perhaloalkoxy, alkoxy, haloalkoxy, alkoxyalkyl, acyl, oxo, acyloxy, carboxyl, amido, cyano, amino, alkylamino, alkylaminoalkyl, thiol, alkylthio, alkylthioalkyl, haloalkylthio, perhaloalkylthio, nitro, aryl, arylalkyl, cycloalkylalkyl, heterocycle-alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, sulfonamide, alkylsulfonamido, alkylsilyloxy, alkylsulfinamido, arylsulfinamido, and arylsulfonamido; R24 is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, which independently is optionally substituted by one or more substituents chosen from halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, perhaloalkyl, perhaloalkoxy, alkoxy, haloalkoxy, alkoxyalkyl, acyl, oxo, acyloxy, carboxyl, amido, cyano, amino, alkylamino, alkylaminoalkyl, thiol, alkylthio, alkylthioalkyl, haloalkylthio, perhaloalkylthio, nitro, aryl, arylalkyl, cycloalkylalkyl, heterocycle-alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, sulfonamide, alkylsulfonamido and alkylsilyloxy; R29 is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, which independently is optionally substituted by one or more substituents chosen from halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, hydroxyalkyl, haloalkyl, perhaloalkyl, perhaloalkoxy, alkoxy, haloalkoxy, alkoxyalkyl, acyl, oxo, acyloxy, carboxyl, amido, cyano, amino, alkylamino, alkylaminoalkyl, thiol, alkylthio, alkylthioalkyl, haloalkylthio, perhaloalkylthio, nitro, aryl, arylalkyl, cycloalkylalkyl, heterocyclealkyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, sulfonamide, alkylsulfonamido and alkylsilyloxy; R25, R30 and R33 each independently is halogen, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, which independently is optionally substituted by one or more substituents chosen from halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, perhaloalkyl, perhaloalkoxy, alkoxy, haloalkoxy, alkoxyalkyl, acyl, oxo, acyloxy, carboxyl, amido, cyano, amino, alkylamino, alkylaminoalkyl, thiol, alkylthio, alkylthioalkyl, haloalkylthio, perhaloalkylthio, nitro, aryl, arylalkyl, cycloalkylalkyl, heterocycle-alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, sulfonamide, alkylsulfonamido and alkylsilyloxy; R26, R31 and R32 each independently is an alkyl, alkenyl or alkynyl linker or heteroalkyl linker, which independently is optionally substituted with one or more substituents chosen from hydroxy, halogen, acyl, oxo, acyloxy, carboxyl, amido, cyano, amino, alkylamino, alkylaminoalkyl, thiol, alkylthio, alkylthioalkyl, haloalkylthio, perhaloalkylthio and nitro; and R27 and R28 each independently is -R32-R33 , or hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, perhaloalkyl, alkoxy, cycloalkyl, aryl, heterocycloalkyl, heterocycle-alkyl or heteroaryl, which independently is optionally substituted with one or more substituents chosen from halogen, hydroxy, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, perhaloalkyl, perhaloalkoxy, alkoxy, haloalkoxy, alkoxyalkyl, acyl, oxo, acyloxy, carboxyl, amido, cyano, amino, alkylamino, alkylaminoalkyl, thiol, alkylthio, alkylthioalkyl, haloalkylthio, perhaloalkylthio, nitro, aryl, arylalkyl, cycloalkylalkyl, heterocycle-alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, heteroarylalkyl, alkylsulfonyl, sulfonamide, alkylsulfonamido, alkylsilyloxy, alkylsulfinamido, arylsulfinamido and arylsulfonamido, with the proviso that R27 and R28 are not both hydrogen when -RF is -O- and R23 is alkyl.

However, these shared technical features are previously disclosed by US 2009/0253723 A1 to Gregory, et al. (hereinafter 'Gregory'). Gregory discloses a compound having a structure similar to a structure of the following Formula A: as shown, wherein R20 is -RF-R23 wherein RF is -O- and R23 is alkyl; R21 is hydroxy; and R22 is halogen (compound of the shown formula (R21 is hydroxy) wherein X is CH2, R1 is =O, R3 is OMe, R5 and R6 are each hydrogen, R2 is OMe (R20 is -RF-R23 wherein RF is -O- and R23 is alkyl), R4 is structure C wherein R7 is OMe and R8 (R22) is halo; paragraphs [0039]-[0041], [0043]-[0046], [0049]-[0050], [0052]). Gregory does not provide a single concise embodiment with each of the selected moieties, from the list of possible moieties. However, provided that Gregory discloses the chosen substituents (Gregory; paragraphs [0039]-[0041], [0043]-[0046], [0049]-[0050], [0052]), it would have been obvious to one of ordinary skill in the art, at the time of the invention, to have modified the compound of Gregory, by narrowing the range of substituents so to as select the chosen substituents for Formula (I), for enhancing the compound's efficacy as a rapamycin-like compound useful in the induction or maintenance of immunosuppression, the stimulation of neuronal regeneration or the treatment of cancer, B-cell malignancies, fungal infections, transplantation rejection, graft vs. host disease, autoimmune disorders, diseases of inflammation vascular disease and fibrotic diseases, and in the regulation of wound healing (Gregory; abstract).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Gregory reference, unity of invention is lacking.