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[Continued on next page]

(54) Title: ANTIMICROBIAL POTENTIATORS

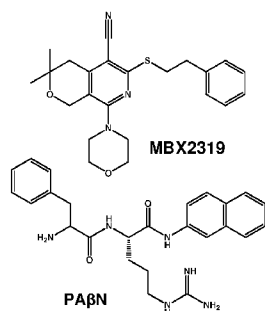
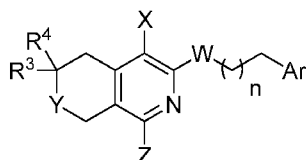


Fig. 1

(57) Abstract: Novel compounds are disclosed having the structure of Formula I. The compounds are potent bacterial efflux pump inhibitors (EPis). Such compounds are useful to potentiate the antimicrobial activity of antimicrobial compounds such as beta-lactam antibiotics and quinolone antibiotics against Gram-negative bacteria. These novel compounds are effective as antibiotic or antimicrobial potentiators. Structures of these compounds are distinctive from other reported efflux pump inhibitors and antibiotic potentiators. Also disclosed are methods for inhibiting bacterial efflux pumps with the novel compounds described herein. In another embodiment, the present invention discloses the use of these novel compounds for the inhibition of bacterial efflux pumps. In yet another embodiment, the present invention discloses the use of these novel compounds for treating or inhibiting bacterial infection.



FORMULA I



TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *of inventorship (Rule 4.17(iv))*

(88) Date of publication of the international search report:

19 November 2015

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/036712

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/436 (2014.01)

CPC - A61K 31/436 (2014.10)

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)

IPC(8) - A61K 31/165, 31/4015, 31/436; A61P 31/00, 31/04 (2014.01)

CPC - A61K 31/436 (2014.10) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

USPC - 424/423; 514/291, 302 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, PubChem, Google Scholar

Search terms used: bacterial efflux inhibitor EPI pump

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2012/0165276 A1 (GLINKA et al) 28 June 2012 (28.06.2012) entire document	1-7, 28-31
A	PUBCHEM, Compound Summary for CID 1289417, Create Date: 2005-07-11. [retrieved on 29 October 2014]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/1289417?from=summary >. entire document	1-7, 28-31
A	US 2008/0234256 A1 (MILLER et al) 25 September 2008 (25.09.2008) entire document	1-7, 28-31



Further documents are listed in the continuation of Box C.



* 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

30 October 2014

Date of mailing of the international search report

14 NOV 2014

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2014/036712

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.:
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.:
1-7, 28-31

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/US2014/036712

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 need to be paid.

Group I: Claims 1-7, and 28-31 are drawn to a compound having the structure of Formula I, or a pharmaceutically acceptable salt thereof and methods of use thereof.

Group II: Claims 8-27 are drawn to the use of a compound having the structure of Formula II, or a pharmaceutically acceptable salt thereof.

The inventions listed in Groups I and II 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:

The special technical features of Group I, a compound having the structure of Formula I, or a pharmaceutically acceptable salt thereof and methods of use thereof, are not present in Group II; and the special technical features of Group II, the use of a compound having the structure of Formula II, or a pharmaceutically acceptable salt thereof and a method of use thereof, are not present in Group I.

Groups I and II share the technical features of a bacterial efflux inhibiting compound having a bicyclic structure, use of a composition for treating bacterial infections, use of a compound having a bicyclic structure to treat a bacterial infection caused by antibacterial resistant strains of bacteria, use of a bicyclic compound for potentiating the antibacterial activity of a beta-lactam antibiotic or a quinolone antibiotic comprising administering or applying said antibiotic in combination with said compound, a method for treating a bacterial infection comprising administering a compound with a bicyclic structure and pharmaceutically acceptable carrier or excipient. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2012/0165276 A1 to Glinka et al. teach a bacterial efflux inhibitor compound with a bicyclic structure (Para. [0003]; Para. [0350], Structure 1, ...see shown structure...), use of a composition for treating bacterial infections (Para. [0015]; Paras. [0084]; [0085]), the use of a compound with a bicyclic structure to treat a bacterial infection caused by antibacterial resistant strains of bacteria (Paras. [0087] and [0088]; Para. [0003]; Para. [0350]); and the use of a compound with a bicyclic structure for potentiating the antibacterial activity of a beta-lactam antibiotic or a quinolone antibiotic comprising administering or applying said antibiotic in combination with said compound (Para. [0469]; Para. [0487]; Para. [0003]; Para. [0350]).

Further, US 2008/0234256 A1 to Miller et al. teach a core having a bicyclic structure (Para. [0004], ...see shown structure...; Paras. [0126]; [0136]); the use of a compound with a bicyclic structure to treat bacterial infections (Para. [0003], This invention is also a method of treating bacterial infections in mammals, particularly in humans.; Para. [0047]); a method for treating a bacterial infection comprising administering a compound with a bicyclic structure and pharmaceutically acceptable carrier or excipient (Para. [0108]; Para. [0109]).

The inventions listed in Groups I and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.