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- with sequence listing part of description (Rule 5.2(a))

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(54) Title: SMALL MOLECULE RNASE INHIBITORS AND METHODS OF USE

(57) Abstract: Small molecule inhibitors of bacterial ribonuclease (e.g., RnpA) and methods for their synthesis and use are described herein. The methods of using the compounds include treating and preventing microbial infections and inhibiting bacterial ribonuclease. Also described herein are methods of identifying compounds for treating or preventing a microbial infection.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/22662

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 31/497; C07D 403/00 (2012.01)
 USPC - 514/253.01
 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 31/497; C07D 403/00 (2012.01)
 USPC: 514/253.01

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 IPC(8): C07D 403/00 (2012.01)
 USPC: 544/364

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST, PGPB, USPT, EPAB, JPAB, SureChem, PubChem, Dialog
 RNase inhibitor, bacterial ribonuclease inhibitor, drug resistant Staphylococcus aureus, biofilm-associated Staphylococcus aureus infection, RnpA inhibitor, Staphylococcus aureus RNase P is RnpA , pyrrole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2004/0180889.A1 (SUTO et al.) 16 September 2004 (16.09.2004) para [0178], Table 1	16-17 ----- 1-10
Y	US 2003/0134904 A1 (GIORDANO et al.) 17 July 2003 (17.07.2003) para [0008]-[0012], [0087], [0162]-[0163], [0165]	1-10
Y	US 6,936,432 B2 (GOPALAN et al.) 30 August 2005 (30.08.2005) col 1, ln 58 to col 2, ln 8	1-10
Y	US 2002/0123077 A1 (O'TOOLE et al.) 5 September 2002 (05.09.2002) para [0106]	7, 10/7
Y	PubChem CID 1268985 http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1268985&loc=ec_rcs . Retrieved 16 April 2012 Create Date: 2005-07-10	9, 10/9

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 2 July 2012 (02.07.2012)	Date of mailing of the international search report 17 JUL 2012
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/22662

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.: 14-15
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:
Group I: claims 1-10 and 16-17 drawn to a method of treating or preventing a microbial infection in a subject, comprising administering to the subject an effective amount of an RNase inhibitor of the structure represented in Claim 1.

Group II: claims 11-13 and 16-17 drawn to a method of inhibiting a bacterial ribonuclease comprising contacting the bacterial ribonuclease with an effective amount of an RNase inhibitor of the the structure represented in Claim 11.

- Please see extra sheet for continuation -

- 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.:
1-10, 16-17

- 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.

Continuation of:

Box NO III. Observations where unity of invention is lacking

Group III: claim 18, drawn to a method of identifying a compound for treating or preventing a microbial infection, comprising the steps of:

a) combining RNA, RnpA, and a fluorescent dye to form a mixture;

b) contacting the mixture with the compound; and

c) monitoring RnpA-mediated total bacterial RNA degradation in the cell using fluorescence, wherein decreased fluorescence, as compared to a control, indicates RNA degradation,

wherein a compound that decreases the RnpA-mediated total bacterial RNA degradation, as compared to a control, is identified as the compound for treating or preventing the microbial infection.

The inventions listed as Groups I through III 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 inventions of Group I-II do not include the inventive concept of a method of identifying a compound for treating or preventing a microbial infection, as required by Group III.

The inventions of Group I and III do not include the inventive concept of a method of inhibiting a bacterial ribonuclease, as required by Group II.

The inventions of Groups I-III share the technical feature of an RNase inhibitor. The inventions of Groups II-III share the technical feature of a bacterial ribonuclease inhibitor. The inventions of Groups I and III share the technical feature of preventing the microbial infection. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2005/0187409 A1 to Powers et al. (hereinafter 'Powers'). Powers discloses a method of treating or preventing a microbial infection in a subject, comprising administering to the subject an effective amount of a bacterial RNase inhibitor (para [0006], [0008] and [0088]-[0089]). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

In addition, the inventions of Groups I and II share the technical feature of the specific formula recited therein. The inventions do not share a special technical feature, because CID 1268985 (retrieved from <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=1268985> on 17 April 2012) (Create Date 2005-07-10) teaches the compound represented in Claim 9. As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I-III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.