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13 November 2008

(54) Title: CRYSTALS OF A BACTERIAL METABOLITE-SENSING RIBOZYME AND USE THEREOF FOR ANTIBIOTIC DISCOVERY

(57) Abstract: A crystalline GlmS ribozyme, optionally but in some embodiments preferably in dehydrated (including partially dehydrated) form is described, along with the crystal structure thereof. The invention provides a method of identifying a GlmS binding compound (or compound that facilitates or inhibits cleavage of GlmS), comprising: (a) providing in a computer a three-dimensional structural representation of GlmS or a glucosamine-6-phosphate (GlcN6P) and/or glucose-6-phosphate (Glc6P) binding portion thereof; and (b) screening in the computer a candidate compound for an ability to bind to said three-dimensional structural representation. In some embodiments the three-dimensional structural representation is provided at a resolution of from 4.0 or 3.0 Å, to 2.0 or 1.0 Å.



WO 2007/120657 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/08834

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07H 21/02(2006.01)

USPC: 536/23.1

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)

U.S. : 536/23.1

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

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

Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BARRICK, J. et al. New RNA motifs suggest an expanded scope for riboswitches in bacterial genetic control. Proc. Natl. Acad. Sci. 2004 Vol. 101, pages 6421-6426, particularly page 6421, column 2, bottom.	1-2
A	KLEIN, D.J. et al. Structural Basis of glms Ribozyme Activation by Glucosamine-6-Phosphate. Science 2006, Vol. 313, pages 1752-1756.	



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

"E" earlier application or patent 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

14 August 2008 (14.08.2008)

Date of mailing of the international search report

09 SEP 2008

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/08834

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:
Please See Continuation 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 any 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.: 1-4

- 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. 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.

Group I, claim(s) 1-4, drawn to the special technical feature of a crystal of GlmS ribozyme.

Group II, claim(s) 5-11, drawn to the special technical feature of a method of identifying a GlmS ribozyme binding compound by computerized screening.

Group III, claim(s) 12, drawn to the special technical feature of a method of identifying a non-naturally occurring GlmS ribozyme analog.

Group IV, claim(s) 13, drawn to the special technical feature of a non-naturally occurring GlmS ribozyme analog.

Group V, claim(s) 14-17, drawn to the special technical feature of a computer containing atomic coordinates for a 3-D structural representation of a GlmS ribozyme.

Group VI, claim(s) 18, drawn to the special technical feature of a method of screening a test compound for binding to GlmS ribozyme by co-crystallization.

The inventions listed as Groups I to VI 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:

According to PCT Rule 13.2 unity of invention exists only when there is a shared same or corresponding special technical feature among the claimed inventions. The crystal of Group I, the methods of Groups II-III and VI, the GlmS variant of Group IV, and the computer of Group V share no special technical feature. The crystal of Group I and the methods of Groups II-III share no same or corresponding special technical feature because the crystal of Group I is neither made nor used by the methods of Groups II-III. The crystal of Group I and the GlmS ribozyme variant of Group IV share no same or corresponding special technical feature because the GlmS ribozyme variant of Group IV encompasses those that are unable to crystallize and the crystal of Group I does not require the GlmS ribozyme variant of Group IV, *i.e.*, the crystal of Group I encompasses naturally-occurring and non-naturally occurring GlmS ribozymes. The crystal of Group I and the computer of Group V share no same or corresponding special technical feature because the atomic coordinates of the computer of Group V are not required to be the atomic coordinates of the GlmS ribozyme of the crystal of Group I and instead encompass atomic coordinates of GlmS ribozyme homology models. The crystal of Group I and the method of Group VI share no same or corresponding special technical feature because the crystal made by the method of Group VI encompasses crystals other than the crystal of Group I, *i.e.*, the crystal of Group I is not required to be made by the method of Group VI. For at least the reasons noted above, the methods of Groups II-III and VI, the GlmS variant of Group IV, and the computer of Group V do not share the same or corresponding special technical feature of the crystal of Group I.

In the absence of any response from Applicant, this Authority will establish the International Search Report based on the main invention, *i.e.*, the claims of Group I. The claims drawn to the main invention are as follows: claims 1-4.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/08834

Continuation of B. FIELDS SEARCHED Item 3:
MEDLINE, AGRICOLA, CAPLUS, EMBASE, WPIDS, SCISEARCH, EAST
Search terms: glms, glucosamine-6-phosphate synthase, RNA, ribozyme