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Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

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16 April 2009

(54) Title: METHIONINE AMINOPEPTIDASE AND METHODS OF USE

(57) Abstract: MetAP crystalline structures are disclosed. Also disclosed are inhibitors of bacterial methionine aminopeptidases, useful in treating bacterial infections and methods of identifying inhibitors of this aminopeptidase and methods of inhibiting MetAP using inhibitors with certain structural and spatial characteristics.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/14258

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C12N 9/48(2006.01);G01N 31/00(2006.01)

USPC: 435/212;436/4

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. : 435/212; 436/4

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.
X	RODERICK et al. Structure of Cobalt-Dependent Methionine Aminopeptidase from Escherichia coli: A New Type of Protelytic Enzyme. 1993, Vol. 32, pages 3907-3912, especially page 3907, column 2, bottom.	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	"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
"E"	earlier application or patent published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"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

09 January 2008 (09.01.2008)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US04/14258

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.: 1-5

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) 1-5, drawn to the special technical feature of a composition comprising a bacterial methionine aminopeptidase (MetAP), including *Staphylococcus aureus* MetAP, in crystalline form.

Group II, claim(s) 1-3 and 6-7, drawn to the special technical feature of a second crystal of *S. aureus* MetAP.

Group III, claim(s) 1-3, 8-9, and 10 (in part), drawn to the special technical feature of a crystal of *S. aureus* MetAP in complex with 5-(3-iodo-phenyl)-1-H-[1,2,3]triazole.

Group IV, claim(s) 1-3, 8-9, and 10 (in part), drawn to the special technical feature of a crystal of *S. aureus* MetAP in complex with 5-benzofuran-2-yl-1-H-[1,2,3]triazole.

Group V, claim(s) 1 and 11-14, drawn to the special technical feature of a crystal of *Streptococcus pneumoniae* methionine aminopeptidase MetAP.

Group VI, claim(s) 15-16, drawn to the special technical feature of a *S. pneumoniae* MetAP in complex with a MetAP inhibitor.

Group VII, claim(s) 17, drawn to the special technical feature of a process for determining a bacterial crystalline form using structural coordinates of a *S. aureus* MetAP crystal.

Group VIII, claim(s) 18, drawn to the special technical feature of a process for determining a bacterial crystalline form using structural coordinates of a *S. pneumoniae* MetAP crystal.

Group IX, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table I.

Group X, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table II.

Group XI, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table III.

Group XII, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table IV.

Group XIII, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table V.

Group XIV, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table VI.

Group XV, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table VII.

Group XVI, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table VIII.

Group XVII, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table IX.

Group XVIII, claim(s) 19 (in part), 20, and 23, drawn to the special technical feature of a process for identifying a bacterial MetAP inhibitor using the structural coordinates of Table X.

Group XIX, claim(s) 21, drawn to the special technical feature of a method of modifying a test bacterial MetAP polypeptide.

Group XX, claim(s) 22, drawn to the special technical feature of a method for the treatment of an individual.

The inventions listed as Groups I-XX 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 technical feature linking groups I-XX is a composition comprising a bacterial MetAP in crystalline form. The inventions listed as Groups I-XX 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 and to the guidelines in Section (f)(i)(B)(1) of Annex B of the PCT Administrative Instructions, all alternatives of a Markush Group must have a common structure that is a substantial structural feature. Although the structural coordinates of Tables I to X share a common structure, the structural coordinates are not regarded as being of similar nature because all alternatives do not share a common structure that is a substantial structural feature.

According to PCT Rule 13.2 unity of invention exists only when the shared same or corresponding special technical feature is a contribution over the prior art. The inventions of Groups I-XX do not relate to a single general inventive concept because they lack the same or corresponding special technical feature. The technical feature of Group I, which includes claim 1, is a bacterial MetAP polypeptide in crystalline form, which is shown by Desmarais et al. (*Structure* 10:1063-1072, 2002) to lack novelty or inventive step because the reference of Desmarais et al. discloses a crystal of methionine aminopeptidase from *Aeromonas proteolytica*, which, as evidenced by Merkel et al. (*J. Bacteriol.* 87:1227-1233, 1964), is a marine bacterium. Thus, the technical feature of Group I is not a contribution over the prior art.

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 1-5.

Continuation of B. FIELDS SEARCHED Item 3:

MEDLINE, AGRICOLA, CAPLUS, WPIDS, BIOSIS, SCISEARCH, EAST, PROTEIN DATA BANK; search terms: methionine aminopeptidase, methionyl aminopeptidase, metap, aureus, crystal, crystalline