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(88) Date of publication of the international search report:
18 December 2008

(54) Title: DRUG DISCOVERY METHODS FOR AURORA KINASE INHIBITORS

(57) Abstract: The present invention relates to drug discovery methods, particularly methods for assaying compounds for activity as Aurora kinase inhibitors. This invention also relates to a pharmacophore describing compounds that are able to promote a conformational change in the protein AuroraB and whose binding constant for the two-step process is given as K_i^* . Finally, this invention also relates to compounds having the features of the pharmacophore.



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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV: C12Q1/48 G06F19/00 A61P35/00 A61K31/00 C07D403/12

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)

C12Q G06F

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 practical, search terms used)

EPO-Internal, EMBASE, BIOSIS, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CARVAJAL RICHARD D ET AL: "Aurora kinases: new targets for cancer therapy." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 1 DEC 2006, vol. 12, no. 23, 1 December 2006 (2006-12-01), pages 6869-6875, XP002487803 ISSN: 1078-0432 the whole document in particular: abstract page 6872; table 2 ----- -/--	1-4

☒ 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 document 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

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/060635

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LIU YI ET AL: "Rational design of inhibitors that bind to inactive kinase conformations." NATURE CHEMICAL BIOLOGY JUL 2006, vol. 2, no. 7, July 2006 (2006-07), pages 358-364, XP002487804 ISSN: 1552-4450 published online 16.06.2006 the whole document in particular: abstract page 358, left-hand column, paragraph 2 - right-hand column, paragraph 2 page 359; figure 1 page 359, left-hand column, paragraph 1 page 360; figure 2 page 360; table 1 page 364, left-hand column, paragraph 2</p>	1-4
A	<p>HERON ET AL: "SAR and inhibitor complex structure determination of a novel class of potent and specific Aurora kinase inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 16, no. 5, 1 March 2006 (2006-03-01), pages 1320-1323, XP005263944 ISSN: 0960-894X page 1322, right-hand column, paragraph 2 - page 1323, left-hand column, paragraph 1 in particular: abstract the whole document</p>	1-4
A	<p>JUNG F H ET AL: "Discovery of novel and potent thiazoloquinazolines as selective Aurora A and B kinase inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, vol. 49, no. 3, 9 February 2006 (2006-02-09), pages 955-970, XP002441806 ISSN: 0022-2623 the whole document in particular: abstract page 961, left-hand column, paragraph 2 - page 961, right-hand column, paragraph 1 page 961; figure 1</p>	1-4

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/060635

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>EP 1 715 036 A (BOEHRINGER INGELHEIM INT [DE]) 25 October 2006 (2006-10-25) the whole document in particular: abstract claim 27 page 3, paragraph 11 page 13, paragraph 107 page 18, paragraph 140</p>	1-4
A	<p>SESSA F ET AL: "Mechanism of Aurora B activation by INCENP and inhibition by Hesperadin" MOLECULAR CELL, CELL PRESS, CAMBRIDGE, MA, US, vol. 18, no. 3, 28 April 2005 (2005-04-28), pages 379-391, XP002342809 ISSN: 1097-2765 the whole document page 388, left-hand column, paragraph 3 - page 389, left-hand column, paragraph 3 page 381, right-hand column, paragraph 3 page 380, left-hand column, paragraph 2 in particular: abstract</p>	1-4
A	<p>WO 03/031606 A (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; ANDERSON MALCOLM [GB]; K) 17 April 2003 (2003-04-17) the whole document in particular: abstract page 3, line 20 - line 28 page 7, compound of formula I (AMP-PNP) page 8, compound of formula II page 114, line 23 - line 28 page 128, line 23 - line 32 claim 11</p>	1-4

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 5, 8-40

Due to lack of unity (Rules 13.1 and 13.2 PCT), the search was restricted to the first group of inventions claimed, i.e. on methods for selecting Aurora B inhibitors based on a structural analysis (claims 1 (partially), 2-4 (fully), 6-7 (partially)).

Furthermore, the applicant claims a method for selecting an Aurora B inhibitor comprising identifying an inhibitor through its interactions with a first hydrophobic pocket and a second hydrophobic pocket of the Aurora B kinase in the closed/inactive conformation. The applicant failed to identify in a clear way said pockets (by, for example, identifying residues involved) both in the claims and in the description (Articles 5 and 6 PCT).

The absence of these essential features of the invention in the claims (Article 6 PCT) and the lack of their disclosure (Article 5 PCT) is such that a meaningful search of the subject-matter of claims 1-4 and 6-7 could not be carried out (Article 17(2) PCT and PCT Guidelines 9.30).

The concepts searched are: the rational design of Aurora kinase inhibitors based on the inactive/closed conformation of Aurora kinase and using a structural approach.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

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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.: 5, 8-40
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an 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.:

see annex

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1 (partially), 2-4 (fully), 6-7 (partially)

Methods for selecting Aurora B kinase inhibitors based on a structural analysis;

2. claims: 1 (partially), 5 (fully), 6-7 (partially), 8-13 (fully) and 38-40 (fully)

Methods for selecting Aurora B kinase inhibitors based on binding kinetics;

3. claims: 14-37 (fully)

Compounds, pharmacophores and their use

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/060635

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1715036	A	25-10-2006	NONE	
WO 03031606	A	17-04-2003	AU 2002334125 A1	22-04-2003
			EP 1485472 A2	15-12-2004
			JP 2005504548 T	17-02-2005
			US 2006078975 A1	13-04-2006