

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 October 2006 (05.10.2006)

PCT

(10) International Publication Number
WO 2006/105237 A3

(51) International Patent Classification:
A01N 61/00 (2006.01)

(74) Agent: ADLER, Benjamin, A.; Adler & Associates, 8011
Candle Lane, Houston, TX 77071 (US).

(21) International Application Number:
PCT/US2006/011536

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 29 March 2006 (29.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/666,206 29 March 2005 (29.03.2005) US

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): THE
UNIVERSITY OF MARYLAND, BALTIMORE
[US/US]; 515 West Lombard Street, Baltimore, Maryland
21201-1627 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): SHAPIRO, Paul
[US/US]; 6408 Sherwood Road, Baltimore, Maryland
21239 (US). MACKERREL, Alexander [US/US]; 515
W. L Ombard St., Baltimore, Maryland 21301 (US).

Published:

— with international search report

(88) Date of publication of the international search report:
16 April 2009

(54) Title: INHIBITORS FOR EXTRACELLULAR SIGNAL-REGULATED KINASE DOCKING DOMAINS AND USES THEREFOR

(57) Abstract: Provided herein are compounds and methods of using compounds that selectively inhibit binding to one or more docking domain regions of an extracellular signal- recognition kinase to inhibit in a cell having an extracellular signal-regulated kinase activity. Such methods may be used to inhibit cell proliferation of a neoplastic cell, to treat a cancer and further may be used in conjunction with administration of an anticancer drug at a reduced dosage to treat a cancer with a concomitant reduction in toxicity to an individual receiving the treatment. Also provided is a method to design and screen for compounds to inhibit binding within the extracellular signal-regulated kinase docking domain region, using at least in part computer-aided drug design modeling.



WO 2006/105237 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/11536

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A01N 61/00(2006.01)

USPC: 514/1

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. : 514/1

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.
x	RAZANDI et al. "BRCA1 Inhibits Membrane Estrogen and Growth Factor Receptor Signaling to Cell Proliferation in Breast Cancer," Molecular and Cellular Biology (2004) Volume 24, Number 13, pages 5900-5913, especially 5904 and 5906.	1, 2, 5, 6
---		-----
y		3, 4, 7-10
A	TANOUE et al. "Identification of a Docking Groove on ERK and p38 MAP Kinases that Regulates the Specificity of Docking Interactions," the EMBO Journal (2001) Volume 20, Number 3, pages 466-479.	1-10
A	JOHNSON et al., "Mitogen-Activated Protein Kinase Pathways Medicated by ERK, JNK, and p38 Protein Kinases," Science (2002) Volume 298, pages 1911-1912.	1-10
A	ZHANG et al. "A Bipartite Mechanism for ERK2 Recognition by its Cognate Regulators and Substrates," The Journal of Biological Chemistry (2003) Volume 278, Number 32, pages 29901-29912.	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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 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

18 June 2008 (18.06.2008)

Date of mailing of the international search report

03 JUL 2008

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

/Jerry Lin/

Telephone No. (571) 272 1600

Janice Ford for

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/11536

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.: 1-10

- 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) 1-10, drawn to a method of inhibiting the activity of a neoplastic cell.

Group II, claim(s) 11-20, drawn to a method of treating cancer.

Group III, claim(s) 21-28, drawn to a method of reducing toxicity of a cancer therapy.

Group IV, claim(s) 29-37, drawn to a method of identifying an inhibitor.

Group V, claim(s) 38-47, drawn to an extracellular signal-regulated kinase inhibitory compound.

The inventions listed as Groups I-V 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:

Each of the Groups I-IV claim a distinct and separate method or product (Group I - a method of inhibiting the activity of a neoplastic cell; Group II - a method of treating cancer; Group III - a method for reducing toxicity; Group IV - a method of identifying an inhibitor). The methods do not share a special technical feature because each method contains specific and unique method steps which are not shared by each of the other methods and each method has a unique and distinct outcome. Thus, Groups I-IV do not share a corresponding special technical feature. Furthermore Group V recites a specific special technical feature of heterocyclic aromatic ring moieties that are not a shared special technical feature in Groups I-IV. Thus the, Group I-IV do not share a corresponding special technical feature.

Continuation of B. FIELDS SEARCHED Item 3:

West, STN

ERK, CD, SB, MS, ED, domain, inhibit, cancer, ras, mutation