

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
3 July 2008 (03.07.2008)

PCT

(10) International Publication Number  
**WO 2008/079945 A3**

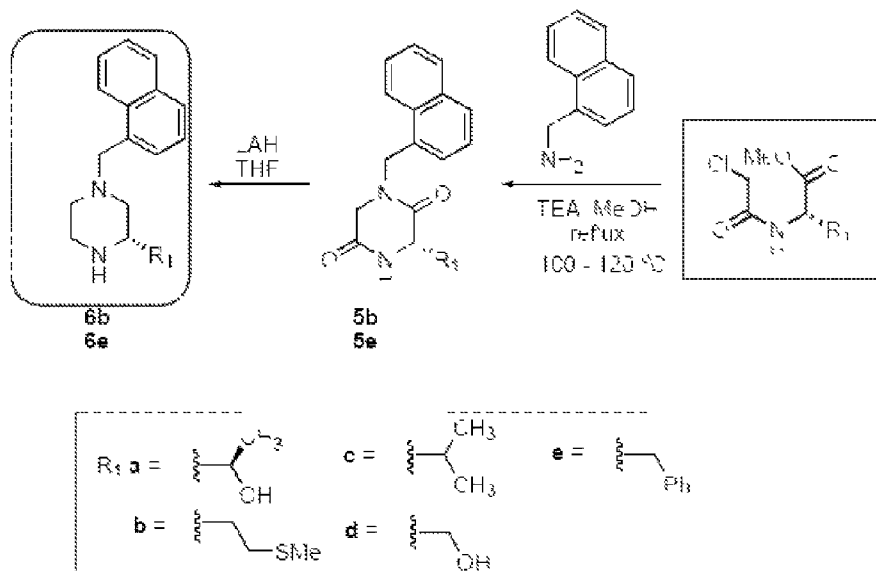
- (51) **International Patent Classification:**  
A61K 31/497 (2006.01)
- (21) **International Application Number:**  
PCT/US2007/088316
- (22) **International Filing Date:**  
20 December 2007 (20.12.2007)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**  
60/871,026 20 December 2006 (20.12.2006) US
- (71) **Applicants (for all designated States except US):** UNIVERSITY OF SOUTH FLORIDA [US/US]; 3802 Spectrum Blvd., Suite 100, Tampa, Florida 33612 (US). YALE UNIVERSITY [US/US]; 2 Whitney Avenue, New Haven, Connecticut 06511 (US).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** SEBTL, Said M. [US/US]; 8957 Magnolia Chase Circle, Tampa, Florida 33612 (US). HAMILTON, Andrew D. [US/US]; One White Pine Lane, New Haven, Connecticut 06437 (US).

- (74) **Agent:** TONER, Thomas E.; 180 Pine Avenue North, Oldsmar, Florida 34677 (US).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FT, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
- (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, MT, 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).

**Published:**  
— with international search report

[Continued on next page]

(54) **Title:** ROCK INHIBITORS AND USES THEREOF



(57) **Abstract:** The subject invention concerns compositions and methods for blocking cancer cell growth or proliferation and/or inducing cancer cell death. Compositions of the present invention are compounds that inhibit Rho - protein associated kinase function. Compounds of the invention include piperazinyl pyridines, piperazinylmethyl pyridines, piperazinyl ureas and carbamates, piperazinyl pyridines and quinolines (including isoquinolines) as well as piperazinyl (including piperazinylmethyl) pyridines and quinolines (including isoquinolines). Compounds of the invention disrupt Rho-kinase activation and function and significantly inhibit tumor cell growth and induce tumor cell death.

WO 2008/079945 A3



---

(88) Date of publication of the international search report:  
16 October 2008

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US 07/88316

<b>A CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61 K 31/497 (2008.04) USPC - 514/252.12 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) USPC - 514/252 12		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 514/187, 252 13, 253 05, 253 06, 307, 310, 311, 314 (see search terms below)		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST (USPT, PGPB, EPAB, JPAB), google com Search Terms Used rho, kinase, piperazinyl, cancer, tumor, melanoma, piperazinylmethyl, protein, alkyl, alkoxy, cycloalkyl, cycloalkoxy, aryl, aryloxy, alkylcarbonyl, alkoxy carbonyl, cycloalkylcarbonyl, h $\beta$ tereoalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, heteroaryl		
<b>C DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 6,906,061 B2 (Uehata et al) 14 June 2005 (14 06 2005) entire document, especially Abstract, col 24, ln 53-67, col 26, ln 51-52	1, 19, 20
-		2-4
Y	US 2006/0142313 A1 (Nagarathnam et al ) 29 June 2006 (29 06 2006) Abstract, para [001 1], [0086], [0117]	2-4
Y		2-4
A	US 2005/0182102 A1 (Hong et al ) 18 August 2005 (18 08 2005) Abstract	1-4, 19-20
<input type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/>		
* 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 but published on or after the international filing date "L" document which may throw doubts on pntny 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 pntny date claimed "T" > later document published after the international filing date or pntny 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 25 June 2008 (25 06 2008)		Date of mailing of the international search report <b>21 JU) 2008</b>
Name and mailing address of the ISA/US Mall 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 PCTOSP 571-272-7774

**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:  
see extra 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 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 and 19-20 (in part).

**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.
- D** No protest accompanied the payment of additional search fees.

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 Claims 1-4 and 19-20 (in part) are drawn to the compounds and the methods of use of compounds represented by the formula I (as shown in claim 1),

Group II Claims 5-8 and 19-20 (in part) are drawn to the compounds and the methods of use of compounds represented by the formula II (as shown in claim 5),

Group III Claims 9-11 and 19-20 (in part) are drawn to the compounds and the methods of use of compounds represented by the formula III (as shown in claim 9),

Group IV Claims 12 and 18-20 (in part) are drawn to the compounds and the methods of use of compounds represented by the formula IV (as shown in claim 12) wherein R1 is as specified in claim 12,

Group V Claims 13-14 and 18-20 (in part) are drawn to the compounds and the methods of use of compounds represented by formula IV and V (as shown in claim 13) wherein R1 is specified by formula V,

Group VI Claims 13-14 and 18-20 (in part) are drawn to the compounds and the methods of use of compounds represented by formula IV and VI (as shown in claim 13) wherein R1 is specified by formula VI,

Group VII Claims 15-16 and 18-20 (in part) are drawn to the compounds and the methods of use of compounds represented by formula IV and VII (as shown in claim 15) wherein R1 is specified by formula VII, and

Group VIII Claims 17 and 18-20 (in part) are drawn to the compounds and the methods of use of compounds represented by formula IV and VIII (as shown in claim 17) wherein R1 is specified by formula VIII.

The inventions listed as Groups I - VIII 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:

Although all of the compounds of groups I-VIII may share a common activity for inhibiting Rho-associated protein kinase in a target cell, the compounds of groups I-VIII do not share a common structure which is a significant structural element. Because of the variables in the ring structures and substituents, there is no shared core structural characteristic required for all the instant compounds of groups I-VIII and so groups I-VIII lack unity of invention.

The inventions listed as Groups I-VIII 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 feature.

In this case the first named invention that will be searched without additional fees is Group I represented by claims 1-4 and 19-20 (in part).