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[Continued on next page]

(54) Title: COMPOUNDS AND METHODS FOR MODULATING RHO GTPASES

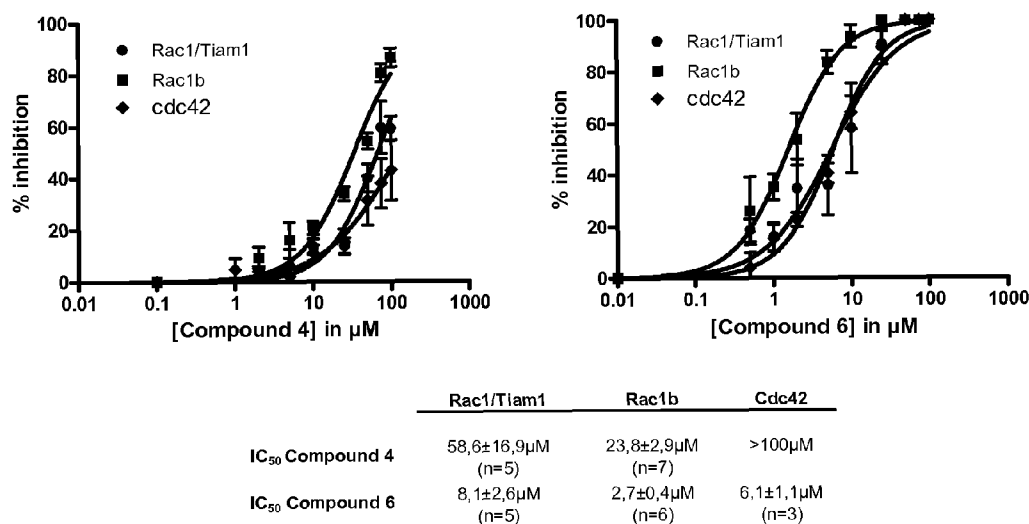


Figure 1

(57) Abstract: The present invention relates to methods and compositions that affect the GTP-binding activity of members of the Rho family GTPases, preferably Rac GTPases (Rac1, Rac1b, Rac2 and/or Rac3).

WO 2009/007457 A3



Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D217/10	C07D217/12	C07D217/14	C07D217/16	C07D217/18
C07D217/20	A61K31/4375	A61K31/47	A61K31/472	A61K31/473
A61P7/02	A61P9/10	A61P9/12	A61P25/28	A61P27/02

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)

C07D A61K A61P

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, BEILSTEIN Data, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X, Y	LIANG K W ET AL: "Berberine inhibits platelet-derived growth factor-induced growth and migration partly through an AMPK-dependent pathway in vascular smooth muscle cells" 20 August 2008 (2008-08-20), EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER BV, NL, PAGE(S) 343 - 354 , XP023438293 ISSN: 0014-2999 [retrieved on 2008-06-14] abstract page 348, left-hand column, lines 6-23 page 350, left-hand column, lines 6-19 page 350, right-hand column, line 27 - page 354, right-hand column, line 8 figure 5	1-13
Y	----- -/--	25

☒ 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

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/059134

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PAN JING ET AL: "PKC mediates cyclic stretch-induced cardiac hypertrophy through Rho family GTPases and mitogen-activated protein kinases in cardiomyocytes" JOURNAL OF CELLULAR PHYSIOLOGY, vol. 202, no. 2, February 2005 (2005-02), pages 536-553, XP002478647 ISSN: 0021-9541 abstract page 540, right-hand column, line 11 - page 541, left-hand column, line 5	1-13
Y	-----	25
Y	MONTESSUIT<A> C ET AL: "Activation of Ras by phorbol esters in cardiac myocytes - Role of guanine nucleotide exchange factor" FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 460, no. 1, 22 October 1999 (1999-10-22), pages 57-60, XP004342719 ISSN: 0014-5793 abstract page 60, left-hand column, lines 30-32	1-13
Y	-----	25
X	EP 0 495 610 A (TOSOH CORP [JP]) 22 July 1992 (1992-07-22) page 3 page 10, lines 8-23 pages 53,54; claims 1,2	14-22,24
X	-----	
X	EP 0 528 553 A (TOSOH CORP [JP]) 24 February 1993 (1993-02-24) page 3, lines 24-52 page 4, line 57 - page 5, line 7	14-22,24
X	-----	
X	CS 225 598 B1 (VALENTA VLADIMIR; PROTIVA MIROSLAV; DLABAC ANTONIN) 13 February 1984 (1984-02-13) page 1; compound I page 2; compound III page 2; example 1	14-22,24
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/059134

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MAKHEY D ET AL: "Coralyne and related compounds as mammalian topoisomerase I and topoisomerase II poisons" BIOORGANIC AND MEDICINAL CHEMISTRY 199606 GB, vol. 4, no. 6, June 1996 (1996-06), pages 781-791, XP002511123 ISSN: 0968-0896 abstract page 783, left-hand column; figure 2; compounds 15, 14A, 14B page 790, left-hand column, lines 9-52 -----	14-22, 24
X	EP 0 110 372 A (HOECHST AG [DE]) 13 June 1984 (1984-06-13) example 1 page 4; compound III pages 12, 13 -----	14-22, 24
Y	US 5 786 362 A (KRONGRAD ARNON [US]) 28 July 1998 (1998-07-28) column 1, lines 46-65 column 8, line 39 - column 9, line 14 claims 1, 2 -----	23, 25
Y	DATABASE WPI Week 200442 Thomson Scientific, London, GB; AN 2004-441504 XP002478650 & CN 1 486 694 A (QIN J) 7 April 2004 (2004-04-07) abstract -----	23, 25
A	WO 97/29106 A (UNIV RUTGERS [US]; LAVOIE EDMOND J [US]) 14 August 1997 (1997-08-14) page 3, line 30 - page 4, line 10 figures Scheme, 1 table 1 claims 1-35 -----	1-25
A	US 2002/035090 A1 (ZELDIS JEROME B [US] ET AL) 21 March 2002 (2002-03-21) page 1, paragraph 1 page 4, paragraph 44 page 5, paragraphs 44, 45 page 11, paragraphs 89, 90 claims 1-5 -----	1-25
A	WO 2006/029577 A (EMY OF MEDICAL SCIENCES INST O [CN]; JIANG JIAN-DONG [CN]; KONG WEI-JI) 23 March 2006 (2006-03-23) page 5, paragraphs 16, 17 page 7, paragraph 18 -----	1-25
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/059134

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 513 997 A (CHINOIN GYOGYSZER ES VEGYESZET [HU]) 19 November 1992 (1992-11-19) page 1, lines 1-13 page 1, lines 29-35 -----	1-25
A	IWASA K ET AL: "In vitro cytotoxicity of the protoberberine-type alkaloids." JOURNAL OF NATURAL PRODUCTS JUL 2001, vol. 64, no. 7, July 2001 (2001-07), pages 896-898, XP002462488 ISSN: 0163-3864 abstract figure 1 table 1 compounds 1-5 -----	1-25
A	LOPUS M ET AL: "The benzophenanthridine alkaloid sanguinarine perturbs microtubule assembly dynamics through tubulin binding: A possible mechanism for its antiproliferative activity" FEBS JOURNAL 200605 GB, vol. 273, no. 10, May 2006 (2006-05), pages 2139-2150, XP002478646 ISSN: 1742-464X 1742-4658 abstract page 2140, left-hand column, line 10 - right-hand column, line 26 figure 1 -----	1-25
A	US 5 137 912 A (TENG CHE-MING [TW] ET AL) 11 August 1992 (1992-08-11) abstract column 2, lines 41-68 claims 1,2 -----	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2008/059134

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:
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:

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.:

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

Continuation of Box II.2

Claims Nos.: -

The expression "a member of the Rho GTPase family" according to the subject-matter of claim 1 of the present application is not clear because it is not unambiguously derivable for the person skilled in the art which G proteins fall within or without of the expression. Thus it has been interpreted in light of the G proteins disclosed on page 27; lines 18-30 of the description of the present application.

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

Information on patent family members

International application No

PCT/EP2008/059134

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0495610	A	22-07-1992	CA 2059388 A1 DE 69220389 D1 DE 69220389 T2 ES 2102453 T3	17-07-1992 24-07-1997 29-01-1998 01-08-1997
EP 0528553	A	24-02-1993	US 5330991 A	19-07-1994
CS 225598	B1	13-02-1984	NONE	
EP 0110372	A	13-06-1984	DE 3244594 A1 JP 59110691 A US 4547508 A	07-06-1984 26-06-1984 15-10-1985
US 5786362	A	28-07-1998	NONE	
CN 1486694	A	07-04-2004	NONE	
WO 9729106	A	14-08-1997	AU 710070 B2 AU 2115597 A BR 9707425 A CA 2241551 A1 CN 1211252 A CZ 9802544 A3 DE 69705112 D1 DE 69705112 T2 EP 0888346 A1 ES 2161442 T3 HU 9900413 A2 JP 2000504687 T NO 983669 A NZ 330705 A PL 328402 A1 PT 888346 T TR 9801555 T2	16-09-1999 28-08-1997 20-07-1999 14-08-1997 17-03-1999 16-12-1998 12-07-2001 21-03-2002 07-01-1999 01-12-2001 28-05-1999 18-04-2000 23-09-1998 27-03-2000 18-01-1999 31-10-2001 23-11-1998
US 2002035090	A1	21-03-2002	US 2005148524 A1	07-07-2005
WO 2006029577	A	23-03-2006	AU 2005284528 A1 BR PI0515393 A CA 2620208 A1 CN 1759834 A EP 1796666 A1 JP 2008513382 T KR 20070095279 A US 2006223838 A1 US 2008081781 A1	23-03-2006 22-07-2008 23-03-2006 19-04-2006 20-06-2007 01-05-2008 28-09-2007 05-10-2006 03-04-2008
EP 0513997	A	19-11-1992	AU 1482292 A CA 2065689 A1 HU 60926 A2 JP 6145058 A LT 3045 B LV 10049 A ZA 9202354 A	15-10-1992 13-10-1992 30-11-1992 24-05-1994 25-09-1994 10-05-1994 24-02-1993
US 5137912	A	11-08-1992	NONE	