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DZ, EC, EE, EG, ES, FI, 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,
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(54) Title: SMALL MOLECULE INHIBITORS OF MUC1 AND METHODS OF IDENTIFYING THE SAME

(57) Abstract: The invention provides methods for the identification of small molecules that inhibit MUC1 oligomerization, and the functions flowing therefrom. In addition, small molecules that prevent MUC1 oligomerization, such as some flavonoids, are disclosed. Identified molecules will find use in treating a variety of MUC1 -related inflammatory conditions, including MUC1 -related cancers. The screening methods involve two MUC1 -derived peptides comprising at least four consecutive residues of the MUC1 sequence and the motive CQC, e.g. CQCR, CQCRR, CQCRRR, CQCRRRR, CQCRRK and CQCRRKN.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER INV. G01N33/68 G01N33/574 G01N33/50 C07K14/47 A61K31/35 ADD. C07K7/06 C07K5/00 A61P29/00 A61P35/00		
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) C07K G01N		
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, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAINA DEEPAK ET AL: "Direct targeting of the mucin 1 oncoprotein blocks survival and tumorigenicity of human breast carcinoma cells", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER REREARCH, US, vol. 69, no. 12, 15 June 2009 (2009-06-15) , pages 5133-5141, XP002604940, ISSN: 0008-5472, DOI: DOI:10.1158/0008-5472.CAN-09-0854 abstract; page 5134, left-hand column, second full paragraph -----	1-20
X,P	WO 2010/045586 A2 (DANA FARBER CANCER INST INC [US]; KUFFE DONALD W [US]; KHARBANDA SUREND) 22 April 2010 (2010-04-22) abstract; claim 1; figure 1A; examples 2-3 ----- -/--	1-20
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> 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 21 October 2011		Date of mailing of the international search report 21/11/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Fausti, Simone

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LENG YUMEI ET AL: "Nuclear import of the MUC1-C oncoprotein is mediated by nucleoporin Nup62", JOURNAL OF BIOLOGICAL CHEMISTRY, THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INC., BALTIMORE, MD, US, vol. 282, no. 27, 6 July 2007 (2007-07-06), pages 19321-19330, XP002604941, ISSN: 0021-9258, DOI: DOI:10.1074/JBC.M703222200 cited in the application last paragraphs on page 19321 and 19329</p> <p>-----</p>	1-20
A	<p>REHAN AHMAD ET AL: "MUC1-C Oncoprotein Functions as a Direct Activator of the Nuclear Factor-kappa B p65 Transcription Factor", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 69, no. 17, 1 September 2009 (2009-09-01), pages 7013-7021, XP007919020, ISSN: 0008-5472, DOI: DOI:10.1158/0008-5472.CAN-09-0523 [retrieved on 2009-08-25] abstract; page 7013, left-hand column, lines 8-10 of the introduction; figure 6</p> <p>-----</p>	1-20
A	<p>MAYA DATT JOSHI ET AL: "MUC1 oncoprotein is a druggable target in human prostate cancer cells", MOLECULAR CANCER THERAPEUTICS, AMERICAN ASSOCIATION OF CANCER RESEARCH, US, vol. 8, no. 11, 11 January 2009 (2009-01-11), pages 3056-3065, XP007919019, ISSN: 1535-7163, DOI: DOI:10.1158/1535-7163.MCT-09-0646 [retrieved on 2009-03-11] abstract; figure 2</p> <p>-----</p>	1-20
X,P	<p>ZHOU YONGCHUN ET AL: "Mucin 1 C-Terminal Subunit Oncoprotein Is a Target for Small-Molecule Inhibitors", MOLECULAR PHARMACOLOGY, vol. 79, no. 5, 23 February 2011 (2011-02-23), pages 886-893 URL, XP9149947, ISSN: 0026-895X abstract; figures 2-3</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-45

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/027970

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HAMALAINEN MARI ET AL: "Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF-kappa B activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF-kappa B activation along with their inhibitory effect on iNOS expression and NO production in", MEDIATORS OF INFLAMMATION, RAPID COMMUNICATION OF OXFORD LTD., OXFORD, GB, vol. 2007, 1 January 2007 (2007-01-01), pages 45673/1-10, XP009135366, ISSN: 0962-9351, DOI: 10.1155/2007/45673 abstract; tables 1-2</p> <p>-----</p>	21-45
X	<p>PATEL DEENDAYAL ET AL: "Apigenin and cancer chemoprevention: Progress, potential and promise (Review)", INTERNATIONAL JOURNAL OF ONCOLOGY, LYCHNIA, GR, vol. 30, no. 1, 1 January 2007 (2007-01-01), pages 233-245, XP009137744, ISSN: 1019-6439 abstract; table 1; second full paragraph on page 236, left-hand column</p> <p>-----</p>	21-45
X	<p>RUELA-DE-SOUSA R R ET AL: "Cytotoxicity of apigenin on leukemia cell lines: implications for prevention and therapy", CELL DEATH & DISEASE, vol. 1, January 2010 (2010-01), page E19, XP7919598, ISSN: 2041-4889 abstract</p> <p>-----</p>	21-45
X	<p>LIN YONG ET AL: "Luteolin, a Flavonoid with Potential for Cancer Prevention and Therapy", CURRENT CANCER DRUG TARGETS, vol. 8, no. 7, November 2008 (2008-11), pages 634-646, XP7919593, ISSN: 1568-0096 abstract</p> <p>-----</p> <p style="text-align: center;">-/--</p>	21-45

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HSIEH CHIA-JUNG ET AL: "Baicalein inhibits IL-1 β - and TNF- α -induced inflammatory cytokine production from human mast cells via regulation of the NF- κ B pathway", CLINICAL AND MOLECULAR ALLERGY, BIOMED CENTRAL LTD., LONDEN, GB, vol. 5, no. 1, 26 November 2007 (2007-11-26), page 5, XP021037104, ISSN: 1476-7961 abstract	21-45
X	----- CHUANG JING-YUAN ET AL: "Coumarin induces cell cycle arrest and apoptosis in human cervical cancer HeLa cells through a mitochondria- and caspase-3 dependent mechanism and NF-kappaB down-regulation.", IN VIVO (ATHENS, GREECE) 2007 NOV-DEC LNKD- PUBMED:18210747, vol. 21, no. 6, November 2007 (2007-11), pages 1003-1009, XP002661860, ISSN: 0258-851X abstract; figure 5	21-45
X	----- MOON ET AL: "Use of scopoletin to inhibit the production of inflammatory cytokines through inhibition of the IkappaB/NF-kappaB signal cascade in the human mast cell line HMC-1", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 555, no. 2-3, 10 January 2007 (2007-01-10), pages 218-225, XP005826604, ISSN: 0014-2999, DOI: 10.1016/J.EJPHAR.2006.10.021 abstract; figure 5	21-45
X	----- CHU C-Y ET AL: "Induction of apoptosis by esculetin in human leukemia cells", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 416, no. (1,2), 1 January 2001 (2001-01-01), pages 25-32, XP002518255, ISSN: 0014-2999, DOI: 10.1016/S0014-2999(01)00859-7 abstract; figure 1	21-45
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/027970

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WU CHI-HAO ET AL: "Naturally occurring flavonoids attenuate high glucose-induced expression of proinflammatory cytokines in human monocytic THP-1 cells", MOLECULAR NUTRITION & FOOD RESEARCH, vol. 53, no. 8, August 2009 (2009-08), pages 984-995, XP002661861, ISSN: 1613-4125 abstract; figure 8</p> <p>-----</p>	21-45
X	<p>WO 2010/012037 A1 (NOVOGEN RES PTY LTD [AU]; HUSBAND ALAN JAMES [AU]; JAMES MICHAEL [AU];) 4 February 2010 (2010-02-04) page 3 - page 4; claims 1,16,20,21; compounds 1-8</p> <p>-----</p>	21-45

INTERNATIONAL SEARCH REPORT

International application No.
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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.:
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 additional 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 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

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

1. claims: 1-20

Methods for identifying inhibitors of the MUC1
oligomerization involving MUC1 peptides containing the CQC
motive

2. claims: 21-45

Flavone analogues for use in the inhibition of the
inflammatory signalling.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/027970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010045586 A2	22-04-2010	AU 2009305550 A1 CA 2741065 A1 EP 2352508 A2 US 2010125055 A1	22-04-2010 22-04-2010 10-08-2011 20-05-2010
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WO 2010012037 A1	04-02-2010	AU 2009276293 A1 CA 2738510 A1 CN 102164904 A EP 2324003 A1	04-02-2010 04-02-2010 24-08-2011 25-05-2011
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