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13 December 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: MEDICAMENT FOR THE PREVENTION AND/OR THE TREATMENT OF ISCHEMIC HEART AND PERIPHERAL VASCULAR DISEASES, TUMOUR AND WOUNDS

(57) Abstract: The present invention is related to a compound or a pharmaceutical composition thereof for the use of a medicament in the modulation of angiogenesis through the tackling of the intracellular free cholesterol-caveolin1-eNOS-NO pathway. The present invention also provides a method of study, testing, screening and manufacturing of new compounds or compositions which influences the angiogenesis via said pathway with the aim of identifying a compound or composition having possible therapeutic or prophylactic properties upon ischemic heart and peripheral vascular diseases including cerebral diseases, tumour development and wound healing.

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 A61K38/17 A61K31/40 A61K31/70 G01N33/50
A61P9/00 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)
IPC 7 C07K C12N A61K

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, BIOSIS, STRAND, WPI Data, PAJ, MEDLINE, 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.
X	MUROHARA TOYOAKI ET AL: "Nitric oxide synthase modulates angiogenesis in response to tissue ischemia" JOURNAL OF CLINICAL INVESTIGATION,US,NEW YORK, NY, vol. 11, no. 101, 1 June 1998 (1998-06-01), pages 2567-2578, XP002138210 ISSN: 0021-9738 abstract --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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	Date of mailing of the international search report
21 March 2001	06. 04. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Niemann, F

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FERON O ET AL: "High LDL-cholesterol decreases NO production through enhanced caveolin abundance in endothelial cells: Correction by atorvastatin." ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS FOR EXPERIMENTAL BIOLOGY 99;WASHINGTON, D.C., USA; APRIL 17-21, 1999, vol. 13, no. 4 PART 1, 12 March 1999 (1999-03-12), page A201 XP002136666 FASEB Journal March 12, 1999 ISSN: 0892-6638 the whole document	1-6,27, 28,31-33
E	WO 00 67737 A (BRIGHAM & WOMENS HOSPITAL ;KONG DEQUAN (US); GALPER JONAS B (US)) 16 November 2000 (2000-11-16) abstract	1-6, 27-33
P,X	KONG D ET AL: "THE ANTI-ANGIOGENIC EFFECTS OF HMGCOA REDUCTASE INHIBITORS: A NEW ROLE FOR RHOA GTPASE IN THE REGULATION OF ANGIOGENESIS" CIRCULATION,AMERICAN HEART ASSOCIATION, DALLAS, TX,US, vol. 110, no. 18, SUPPL, 2 November 1999 (1999-11-02), page I39 XP000938028 ISSN: 0009-7322 the whole document	1-6,27, 28,31-33
X	WO 99 22773 A (BAYLOR COLLEGE MEDICINE) 14 May 1999 (1999-05-14) cited in the application abstract page 5, line 13 -page 6, line 5 page 6, line 17 - line 22 page 32, line 5 -page 33, line 2; claims 1-8	1,2,13, 14, 17-20, 27,28, 31,32,34
X	MICHEL JEFFREY B ET AL: "Caveolin versus calmodulin. Counterbalancing allosteric modulators of endothelial nitric oxide synthase." JOURNAL OF BIOLOGICAL CHEMISTRY 1997, vol. 272, no. 41, 1997, pages 25907-25912, XP002136661 ISSN: 0021-9258 cited in the application the whole document	1,2, 13-15, 20, 24-32,35

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INTERNATIONAL SEARCH REPORT

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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	OKAMOTO ET AL: "caveolins, a family of scaffolding proteins for organizing "preassembled signaling complexes" at the plasma membrane" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 10, 1998, pages 5419-5422, XP002136663 the whole document ---	1,2, 13-17, 20-28, 31,32
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 1999 (1999-07) BURNETT JOHN R ET AL: "Inhibition of ACAT by avasimibe decreases both VLDL and LDL apolipoprotein B production in miniature pigs." Database accession no. PREV199900374754 XP002156497 abstract & JOURNAL OF LIPID RESEARCH, vol. 40, no. 7, July 1999 (1999-07), pages 1317-1327, ISSN: 0022-2275 ---	1-3,7,8
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 1998 (1998-03) LACOUR ANNE ET AL: "Comparison of efficacy and cost among lipid-lowering agents in patients with primary hypercholesterolemia." Database accession no. PREV199800232626 XP002156498 abstract & CANADIAN JOURNAL OF CARDIOLOGY, vol. 14, no. 3, March 1998 (1998-03), pages 355-361, ISSN: 0828-282X ---	1-3,9,10
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 HANNAH J S ET AL: "Effects of acipimox on the metabolism of free fatty acids and very low density lipoprotein triglyceride." Database accession no. PREV199698650769 XP002156499 abstract & ACTA DIABETOLOGICA, vol. 32, no. 4, 1995, pages 279-283, ISSN: 0940-5429 --- -/--	1-3,11, 12

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07731

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	LIU JUN ET AL: "Angiogenesis activators and inhibitors differentially regulate caveolin-1 expression and caveolae formation in vascular endothelial cells: Angiogenesis inhibitors block vascular endothelial growth factor-induced down-regulation of caveolin-1." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 22, 28 May 1999 (1999-05-28), pages 15781-15785, XP002156496 ISSN: 0021-9258 cited in the application abstract page 15782, left-hand column, paragraph 1 ---	
A	KERWIN ET AL: "the arginine-nitric oxide pathway : a target for new drugs" MEDICINAL RESEARCH REVIEWS, vol. 14, no. 1, 1994, pages 23-74, XP000906832 page 47, line 7 -page 60, line 30 page 61, line 13 -page 62, line 45 ---	
X	EP 0 471 236 A (TAKEDA CHEMICAL INDUSTRIES LTD) 19 February 1992 (1992-02-19) page 2, line 30 - line 35 page 69, line 34 -page 70, line 19; claims 1-31 ---	1,2,13, 14,20, 27-32,36
X	WO 99 18801 A (UNIV FORDHAM) 22 April 1999 (1999-04-22) abstract ---	1,2,13, 14,20, 27-32,37
A	GARCIA-CARDENA GUILLERMO ET AL: "Dynamic activation of endothelial nitric oxide synthase by Hsp90." NATURE (LONDON), vol. 392, no. 6678, 23 April 1998 (1998-04-23), pages 821-824, XP002163482 ISSN: 0028-0836 cited in the application the whole document ---	37
A	MICHEL JEFFREY B ET AL: "Reciprocal regulation of endothelial NO synthase by Ca2+ calmodulin and caveolin" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 25, 1997, pages 15583-15586, XP002136665 ISSN: 0009-7322 the whole document -----	36

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28, 32-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] 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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] 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 fee, this Authority did not invite payment of any additional fee.

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.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-3,13,14,17,20,27,28,31-37 relate to compounds which have only been defined by a certain characteristic, that is "modulate cholesterol metabolism and/or flux, caveolin-1, eNOS, calmodulin, Hsp90 abundance/activity" whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds which are described in the description of the application (see detailled description of the invention p8 -p10).

The applicant's attention is drawn to the fact that claims, or parts of 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. Claims: 1,2,13,14,17,20,27,28-32 (partially), 3-12,15,16, 18,19,21-26,33-35

1.1. Claims: 1,2,27,28-32 (partially), 3-12,33
a compound for use as a medicament for the modulation of angiogenesis wherein said compound has its angiogenic effect via : the modulation of the cholesterol metabolism and/or flux

1.2. Claims: 1,2,13,14, 20,27,28-32 (partially), 15,18,19, 21,34

a compound for use as a medicament for the modulation of angiogenesis wherein said compound has its angiogenic effect via :the modulation of the caveolin-1 abundance/activity

1.3. Claims: 1,2,13,14, 20,27,28-32 (partially),16,22-26, 35

a compound for use as a medicament for the modulation of angiogenesis wherein said compound has its angiogenic effect via :the modulation of the eNOS abundance/activity

2. Claims: 1,2,13,14, 20,27,28-32 (partially), 36

a compound for use as a medicament for the modulation of angiogenesis wherein said compound has its angiogenic effect via :the modulation of the calmodulin abundance/activity

3. Claims: 1,2,13,14, 20,27,28-32 (partially), 37

a compound for use as a medicament for the modulation of angiogenesis wherein said compound has its angiogenic effect via :the modulation of the Hsp90 abundance/activity

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/07731

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0067737 A	16-11-2000	AU 4988100 A	21-11-2000
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