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Published:

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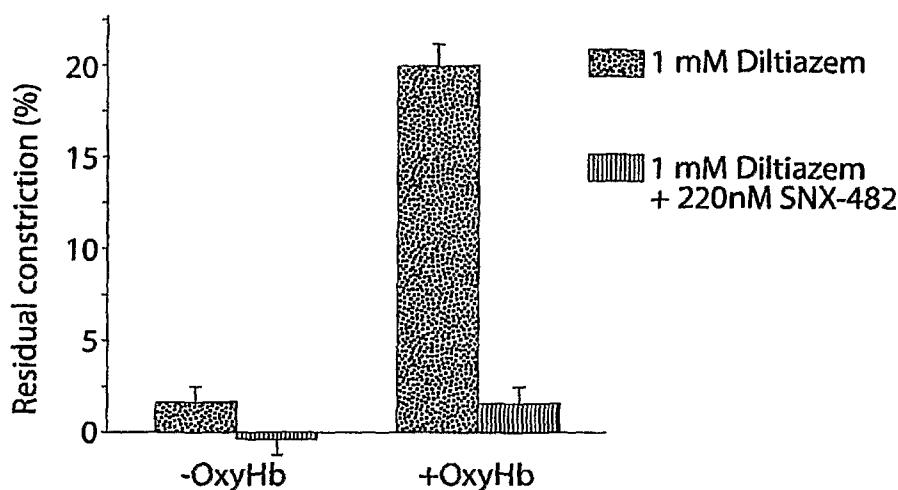
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: EMERGENCE OF A R-TYPE Ca^{2+} CHANNEL(CA_v2.3) CONTRIBUTES TO CEREBRAL ARTERY CONSTRICTION FOLLOWING SUBARACHNOID HEMORRHAGE

R-type Ca^{2+} channel blocker SNX-482 relieves residual constriction



(57) Abstract: The invention relates to methods and products for treatment of a neurological defect such as a subarachnoid hemorrhage or cerebral vasospasm. Specifically, R-type voltage-gated calcium channel inhibitors and related compositions and kits are described.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/003643

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 C12N15/11

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)

A61K C12N

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, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ISHIGURO MASANORI ET AL: "Emergence of a R-type Ca ²⁺ channel (CaV 2.3) contributes to cerebral artery constriction after subarachnoid hemorrhage" CIRCULATION RESEARCH, vol. 96, no. 4, 4 March 2005 (2005-03-04), pages 419-426, XP002393813 ISSN: 0009-7330 the whole document ----- -/--	1-22, 25-39



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

Date of the actual completion of the international search

8 August 2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/003643

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARROYO GLORIA ET AL: "SNX482 selectively blocks P/Q Ca²⁺ channels and delays the inactivation of Na⁺ channels of chromaffin cells." EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 475, no. 1-3, 15 August 2003 (2003-08-15), pages 11-18, XP002393814 ISSN: 0014-2999 the whole document	25-27, 30-32, 34,36-38
X	PIEDRAS-RENTERIA ERIKA ET AL: "Antisense oligonucleotides against alpha1E reduce R-type calcium currents in cerebellar granule cells" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 95, no. 13, 23 June 1998 (1998-06-23), pages 7760-7765, XP002393815 ISSN: 0027-8424 the whole document	36-38
A	ISHIGURO MASANORI ET AL: "The Emergence of a Ca²⁺ Channel with Distinct Biophysical Properties in Cerebral Arteries Following Subarachnoid Hemorrhage" FASEB JOURNAL, vol. 18, no. 4-5, 2004, pages Abst. 671.15 URL-http://ww, XP002393816 & FASEB MEETING ON EXPERIMENTAL BIOLOGY: TRANSLATING THE GENOME; WASHINGTON, DISTRICT OF COLUMBIA, USA; APRIL 17-21, 2004 ISSN: 0892-6638	
A	ISHIGURO MASANORI ET AL: "Altered Ca²⁺ channel properties in cerebral arteries following subarachnoid hemorrhage." FASEB JOURNAL, vol. 17, no. 4-5, March 2003 (2003-03), pages Abstract No. 315.5 URL-http://ww, XP002393817 & FASEB MEETING ON EXPERIMENTAL BIOLOGY: TRANSLATING THE GENOME; SAN DIEGO, CA, USA; APRIL 11-15, 2003 ISSN: 0892-6638	

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/003643

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BARKER FRED G II ET AL: "Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: A metaanalysis" JOURNAL OF NEUROSURGERY, vol. 84, no. 3, 1996, pages 405-414, XP009070799 ISSN: 0022-3085 -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/003643

Box 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:

Although claims 1-22 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. ☒ 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 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 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.:

1-22, 25-39

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 1-22 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.

Continuation of Box II.2

Claims Nos.:

Present claims 1-7, 9, 11-20, 25, 26, 28, 30-32, 36-39 encompass compounds defined only by their desired function (their ability to inhibit a R-type voltage-dependent calcium channel) contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the compounds disclosed in dependent claims 8, 10, 21, 27, 29. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration this non-compliance. The search for claims 1-7, 9, 11-20, 25, 26, 28, 30-32, 36-39 was consequently restricted to the inhibitor SNX-482 (as specified in claims 8 and 27), an antisense directed to a R-type voltage-dependent calcium channel inhibitor (as specified in claims 10 and 21), a siRNA directed to a R-type voltage-dependent calcium channel inhibitor (as specified in claims 10 and 29).

Present claim 2 encompasses compounds defined only by their desired function (their ability to inhibit a L-type voltage-dependent calcium channel) contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the compounds disclosed in the dependent claim 22. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration this non-compliance. The search for claim 2 was consequently restricted to an antisense directed to a L-type voltage-dependent calcium channel inhibitor (as specified in claim 22).

Present claims 25-32 encompass compounds defined only by their desired function (their ability to work as cerebral vasospasm drug and being a L-type voltage-dependent calcium channel inhibitor) contrary to the requirements of clarity of Article 6 PCT, because the result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the compounds disclosed in the dependent claims

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

33-35. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration this non-compliance. The search for claims 25-32 was consequently restricted the L-type voltage-dependent calcium channel inhibitors diltiazem, nisoldipine, nicardipine, nifedipine and verapamil (as specified in claims 33-35).

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, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-22, 25-39

a method for treating cerebral vasospasm comprising administering a R-type voltage-dependent calcium channel inhibitor, a composition comprising a R-type voltage-dependent calcium channel inhibitor and an anticerebral vasospasm drug, a kit comprising a container housing a R-type voltage-dependent calcium channel inhibitor, a composition comprising a R-type voltage-dependent calcium channel inhibitor, use of R-type voltage-dependent calcium channel inhibitor in the manufacture of a medicament for the treatment of cerebral vasospasm.

2. claims: 23, 24, 40

a method for treating cerebral vasospasm comprising administering a L-type voltage-dependent calcium channel inhibitor wherein the L-type voltage dependent calcium channel inhibitor is an antisense oligonucleotide of a L-type VDCC smooth muscle splice variant, use of L-type voltage-dependent calcium channel inhibitor in the manufacture of a medicament for the treatment of cerebral vasospasm.
