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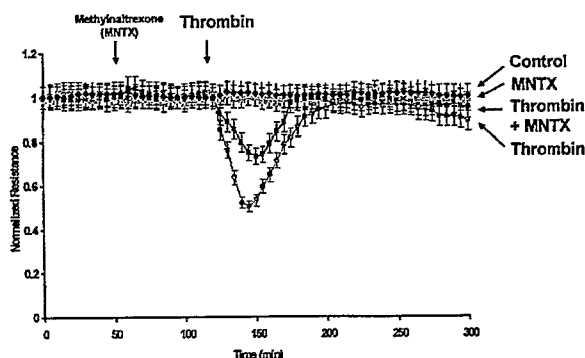
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[Continued on next page]

(54) Title: MODULATION OF CELL BARRIER DYSFUNCTION



(57) Abstract: The invention provides prophylactic and therapeutic methods for administering a  $\mu$ -opioid receptor antagonist to treat cell barrier diseases and disorders, such as endothelial and epithelial cell barrier diseases and disorders. The diseases or disorders may amenable to the methods include inflammation, such as acute lung injury, atherosclerosis, gut-derived sepsis, a burn injury, neonatal necrotizing enterocolitis, severe neutropenia, toxic colitis, inflammatory bowel disease, enteropathy, transplant rejection, pouchitis, pig belly (pig-bel), Pseudomonas-mediated ophthalmologic infection, Pseudomonas-mediated otologic infection and Pseudomonas-mediated cutaneous infection. More generally, epithelial cell barrier disorders are contemplated as amenable to the prophylactic and therapeutic methods.. The diseases and disorders may be induced by microbial pathogens, including bacterial pathogens such as Pseudomonas aeruginosa. The invention further provides prophylactic and therapeutic methods for inhibiting the expression of bacterial PA-I lectin/adhesin and for inhibiting bacterial MvIR activity levels. Also provided is a method of using a  $\mu$ -opioid receptor antagonist in the manufacture of a medicament for use in the methods described herein.

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**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2006/021604

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. A61K31/451 A61K31/485 A61K39/395 A61K45/06 A61P31/04 A61P35/00		
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) 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, EMBASE, WPI Data, PAJ, BIOSIS		
<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 6 384 044 B1 (BIHARI BERNARD [US]) 7 May 2002 (2002-05-07) paragraph [0031]; claims 1-17; examples 1-4	1-14, 19, 20, 22-26
X	ZAGON I S ET AL: "OPIOID ANTAGONISTS INHIBIT THE GROWTH OF METASTATIC MURINE NEURO BLASTOMA" CANCER LETTERS, vol. 21, no. 1, 1983, pages 89-94, XP009083862 ISSN: 0304-3835 page 90, paragraph 5; figure 1	1-14, 19, 20, 22-26
X	US 2004/024006 A1 (SIMON DAVID LEW [US]) 5 February 2004 (2004-02-05) paragraph [0102]	1-13, 19, 20, 22-25, 28
-/--		
<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  22 May 2007		Date of mailing of the international search report  05/06/2007
Name and mailing address of the ISA/ 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		Authorized officer  Loher, Florian

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2006/021604

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/173466 A1 (CRAIN STANLEY M [US] ET AL) 21 November 2002 (2002-11-21) paragraphs [0036], [0050] - [0054]; claims 1-15 -----	1-13,20, 22-26
X	US 4 863 928 A (ATKINSON DAVID C [US] ET AL) 5 September 1989 (1989-09-05)  claims 1-10; example 1 -----	1-13,19, 20, 22-27,32
E	WO 2006/132963 A (UNIV CHICAGO [US]; ALVERDY JOHN C [US]) 14 December 2006 (2006-12-14) paragraph [0040]; claims 30-53 -----	1-35

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2006/021604

## 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 1-26 and 28-35 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 compounds.
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 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 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.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/021604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6384044	B1	07-05-2002	NONE
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