Title: CYCLIC ADENOSINE MONOPHOSPHATE COMPOUNDS FOR THE TREATMENT OF IMMUNE-RELATED DISORDERS

Abstract: The present invention is related to the finding that certain analogues of cAMP such as 8-(4-chlorophenylthio)-2'-O- methyladenosine- 3', 5'- cyclic monophosphate (8-pCPT-2'-O-Me-cAMP) specifically blocks the production of IL-10 in human T cells. It is also related to the finding that the production of other cytokines (e.g. IL-2, IL-4, IL-5, IL-6, IL-12 and IFN-gamma) is not affected by these analogues. The finding may be used as a treatment of conditions which respond to a reduced level of IL-10 and/or by a change in the balance of the Th1 and Th2 responses. It may be used in research and in testing for dysfunctional EPAC protein and IL-10 producing pathways.
# INTERNATIONAL SEARCH REPORT

**A. CLASSIFICATION OF SUBJECT MATTER**

<table>
<thead>
<tr>
<th>INV.</th>
<th>A61K31/0076</th>
<th>A61P11/06</th>
<th>A61P17/00</th>
<th>A61P19/02</th>
<th>A61P31/00</th>
</tr>
</thead>
</table>

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

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, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 03/104250 A (KYLIX B V [NL]; DE KONING JOHN [NL]; CHRISTENSEN ANNE [NO]; SCHWEDE FR) 18 December 2003 (2003-12-18)</td>
<td>1-31,34, 35, 37-41, 43-47</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

| X | See patent family annex. |

* Spacial 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

* 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.

"R" document member of the same patent family

**Date of the actual completion of the international search**

22 January 2007

**Date of mailing of the international search report**

03/04/2007

**Name and mailing address of the ISA/**

European Patent Office, P.B. 5816 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx: 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Taylor, Mark
## INTERNATIONAL SEARCH REPORT

**International application No**  
PCT/EP2006/006761

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| X        | WO 00/66131 A (E L MANAGEMENT CORP [US])  
9 November 2000 (2000-11-09)  
abstract  
page 2, line 18 - line 26  
page 4, line 28 - page 5, line 4  
examples 1,2  
claims 1-14 | 1-31,34, 35, 37-41, 43-47 |
| E        | WO 2006/133128 A (UNIV CALIFORNIA [US]; LEVINE JON D [US]; MESSING ROBERT O [US])  
14 December 2006 (2006-12-14) | 1-31,34, 35, 37-41, 43-47 |
| P,A      | WO 2005/123755 A2 (LAURAS AS [NO]; UNDHEIM KJELL [NO]; TASKEN KJETIL [NO]; KLAVENESS JO []) 29 December 2005 (2005-12-29) | 1-31,34, 35, 37-41, 43-47 |
INTERNATIONAL SEARCH REPORT

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. X Claims Nos.: 32, 33, 37  
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 42-47 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. X Claims Nos.: 1-28, 32-41, 43-47  
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. X 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.:

see annex

Remark on Protest  
□ The additional search fees were accompanied by the applicant’s protest.

□ No protest accompanied the payment of additional search fees.
Continuation of Box II.1

Although claims 42-47 are directed to a diagnostic method practised on 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.: 1-28, 32-41, 43-47

Present claim 1-28, 32-41 and 43-47 relate to medical indications defined by their mechanism(s) of action, namely:

"a disorder which responds to a decrease in the production of IL-10 and/or a change in the balance of the Th1 and Th2 response which increases the Th1 response" (claim 1);
"said disorder characterised a least in part by an imbalance in the Th1 and Th2 response where the Th1 response is low" (claim 27);
"said disorder characterised a least in part by a high level of IL-10 production" (claim 28);
"changing the balance of the Th1 and Th2 response towards an increased Th1 response" (claim 39).

However, the description does not provide support and disclosure in the sense of Art. 6 and 5 PCT which enables the skilled man to determine whether any given disease falls within the scope of such a definition, or not. Moreover, there is no common general knowledge of this kind available to the person skilled in the art. This non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claim (PCT Guidelines 9.19 and 9.20).

It should also be noted that expressions such as "at least in part", "increased", "high" and "low" have no generally-accepted meanings for their upper/lower limits. As a consequence, these expressions are unclear under Art. 6 PCT.

The search of these claim was consequently restricted to the diseases specifically disclosed in claims 29-31.

In addition, claims 26 ("analogues") and 43 ("prodrug", "metabolite", "structurally-related derivative") are unclear (Art. 6 PCT) because the said expressions and vague and indefinite. These expressions have therefore been ignored for the purposes of the search.

Claims 32, 33 and 37 have not been searched because their characterising features relate to results of use which have no bearing on the claimed preparation of a medicament. It is therefore unclear (Art. 6 PCT) how these affect the subject-matter of the claims.
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.
This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-41, 43-47(part)

    Compounds and methods for the inhibition of IL-10 and or effecting a change in the Th1/Th2 balance, for use in the treatment of diseases as defined in claims 29-31.

2. claims: 42, 43-47(part)

    A method of diagnosing a dysfunction of EPAC and/or the IL-10 production in a mammalian system comprising contacting samples with compounds according to claims 1-26.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 03104250</td>
<td>18-12-2003</td>
<td>AU 2003242672 A1</td>
<td>22-12-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2488611 A1</td>
<td>18-12-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005532360 T</td>
<td>27-10-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2006100166 A1</td>
<td>11-05-2006</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2881800 A</td>
<td>17-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2336362 A1</td>
<td>09-11-2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2002543138 T</td>
<td>17-12-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2002090384 A1</td>
<td>11-07-2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZA 200006213 A</td>
<td>21-05-2001</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2358155 A1</td>
<td>10-02-1978</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>WO 2006133128</td>
<td>14-12-2006</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>WO 2006038865</td>
<td>13-04-2006</td>
<td>NONE</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>WO 2005123755</td>
<td>29-12-2005</td>
<td>AU 2005254790 A1</td>
<td>29-12-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2568907 A1</td>
<td>29-12-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1765844 A2</td>
<td>28-03-2007</td>
</tr>
</tbody>
</table>