

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 2003/103675 A3

(51) International Patent Classification⁷: **A61K 31/522**,
31/675, A61P 9/00, 11/00

(21) International Application Number:
PCT/US2003/017964

(22) International Filing Date: 6 June 2003 (06.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/386,769 6 June 2002 (06.06.2002) US

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
25 March 2004

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: COMBINATION TREATMENTS FOR PURINOCEPTOR-RELATED DISORDERS

(57) Abstract: The present invention provides methods of preventing and treating purinoceptor-related disorders comprising con-
currently administering an A1 adenosine receptor antagonist or a P_{2x} purinoceptor antagonist with an at least one additional active
agent effective to treat purinoceptor-related disorders. The present invention also provides pharmaceutical formulations suitable for
preventing and treating purinoceptor-related disorders.



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/17964

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/522 A61K31/675 A61P09/00 A61P11/00

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 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, WPI Data, PAJ, EMBASE, MEDLINE, BIOSIS, FSTA, 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.
P,X	WO 02/094317 A (ENDACEA INC ;WILSON CONSTANCE NEELY (US)) 28 November 2002 (2002-11-28) the whole document	1-7, 9-25, 27-38, 40,41
X	WO 99/34803 A (NEELY CONSTANCE F ;UNIV PENNSYLVANIA (US)) 15 July 1999 (1999-07-15) the whole document	1-7, 9-25, 27-38, 40,41
X	US 5 733 916 A (NEELY CONSTANCE F) 31 March 1998 (1998-03-31) the whole document	1-7, 9-25, 27-38, 40,41
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☒ Further documents are listed in the continuation of box C.

☒ 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

18 September 2003

Date of mailing of the international search report

30. 01. 04

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 03/17964

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/26728 A (NEELY CONSTANCE F ;UNIV PENNSYLVANIA (US)) 12 October 1995 (1995-10-12) the whole document -----	1-7, 9-25, 27-38, 40,41
X	WO 99/38532 A (LINK TECHNOLOGY INC ;NEELY CONSTANCE F (US)) 5 August 1999 (1999-08-05) the whole document -----	1-7, 9-25, 27-38, 40,41
X	STEINMETZ M ET AL: "Influence of purinoceptor antagonism on diadenosine pentaphosphate-induced hypotension in anesthetized rats." THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS. UNITED STATES SEP 2000, vol. 294, no. 3, September 2000 (2000-09), pages 963-968, XP001154546 ISSN: 0022-3565 the whole document -----	1-7, 9-25, 27-38, 40,41
X	NEELY C ET AL: "A1 adenosine receptor antagonist, 8-benzyl-7,(2-(ethyl(2-hydroxyethyl)amino)-ethyl)theophylline, and/or the P2X purinoceptor antagonist, pyridoxalphosphate-6-azophenyl-2',4'-disulfonic acid block endotoxin-induced lung injury." DRUG DEVELOPMENT RESEARCH, vol. 43, no. 1, January 1998 (1998-01), page 76, XP009016775 6th International Symposium on Adenosine and Adenine Nucleotides: New Frontiers in the 3rd Millennium;Ferrara, Italy; May 19-24, 1998 ISSN: 0272-4391 abstract -----	1-7, 9-25, 27-38, 40,41
A	NEELY CONSTANCE F ET AL: "A-1 adenosine receptor antagonists block ischemia-reperfusion injury of the heart." CIRCULATION, vol. 94, no. 9 SUPPL., 1996, pages II376-II380, XP009017123 ISSN: 0009-7322 abstract -----	1-7, 9-25, 27-38, 40,41
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/17964

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NEELY CONSTANCE F ET AL: "A-1-adenosine receptor antagonists block endotoxin-induced lung injury." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 272, no. 2 PART 1, 1997, pages L353-L361, XP000901722 ISSN: 0002-9513 abstract -----	1-7, 9-25, 27-38, 40,41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/17964

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. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-7, 9-25, 27-38, 40, 41 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.: 1-7, 9-25, 27-38, 40, 41 (all in part)
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. ☐ 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.:

1-7,9-25,27-38,40,41 (in part)

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 I.2

Claims Nos.: 1-7, 9-25, 27-38, 40, 41 (all in part)

Present independent claims 1, 37-39 relate to a compounds defined by reference to a desirable characteristic or property, namely "an A1 adenosine receptor antagonist" and "a P2x purinoceptor antagonist" (component (a)) and the "at least one additional active agent effective to treat said purinoceptor related disorder (component (b)).

Moreover, a "purinoceptor related disorder" is not considered a clear definition of the therapeutical application.

For the above reasons, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed (Articles 5,6 PCT), namely the use of PPADS and an an A1 adenosine receptor antagonist according to generic formula (I) in combination for the treatment of diseases as listed in claims 2-7.

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: 1-7,9-25,27-38,40,41 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being inflammatory disorder, congestive heart failure, systemic hypertension, pulmonary hypertension, ischemia-reperfusion organ injury, endotoxin-related tissue injury, anaphylactic shock, allergic rhinitis, asthma, cystic fibrosis, allergic conditions, chronic obstructive pulmonary disorder, chronic cough, coronary artery disease, ARDS, ALI, septicemia.

2. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being Alzheimer's disease or Parkinson's disease.

3. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being depression.

4. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being obesity or diabetes.

5. claims: 1,3,10-19,21,28-36 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being biliary colic.

6. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being fibrosis or sclerosis.

7. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being renal failure.

8. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being SARS.

9. claims: 1,3,10-19,21,28-36 (in part)

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being substance abuse or drug dependence.

10. claims: 1,3,8,10-19,21,26,28-36,39-41 (in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of treating a purinoceptor-related disorder in a subject in need thereof, comprising concurrently administering (a) an A1 adenosine receptor antagonist or a P2x purinoceptor antagonist with (b) at least one additional active agent effective to treat said purinoceptor-related disorder, said purinoceptor-related disorder being an autoimmune disorder.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 03/17964

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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