

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
27 April 2006 (27.04.2006)

PCT

(10) International Publication Number  
WO 2006/044916 A3

- (51) International Patent Classification:  
A61K 31/56 (2006.01)
- (21) International Application Number:  
PCT/US2005/037486
- (22) International Filing Date: 18 October 2005 (18.10.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/619,637 18 October 2004 (18.10.2004) US
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AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

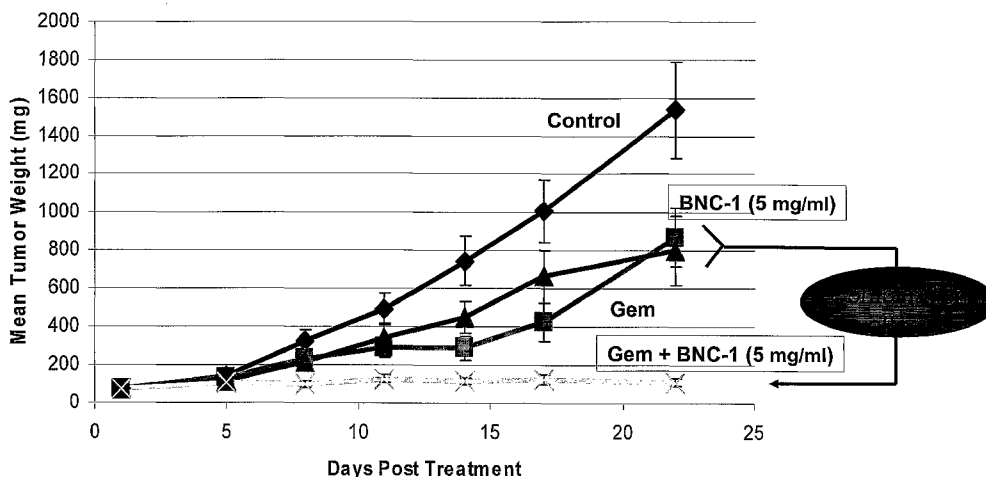
**Published:**  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:  
4 January 2007

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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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

(54) Title: USE OF NA<sup>+</sup>/K<sup>+</sup>-ATPASE INHIBITORS AND ANTAGONISTS THEREOF



(57) Abstract: The reagent, pharmaceutical formulation, kit, and methods of the invention provides a new approach for treating hypoxia-related pathological conditions, such as Alzheimer's Disease, and those involving excessive angiogenesis, especially those non-cancer pathological conditions. The invention provides the use of Na<sup>+</sup>/K<sup>+</sup>-ATPase inhibitors, such as cardiac glycosides (e.g. ouabain and proscillaridin, etc.), either alone or in combination with other standard therapeutic agents for treating such conditions. The invention also relates to the use of cardiac glycoside inhibitors / antagonists as reagents, pharmaceutical formulations, or in kits and methods for treating conditions arising from excessive amount of cardiac glycosides, including all symptoms of digitalis poisoning, depression, hypertension, etc. The pharmaceutical formulation of the invention may be delivered to a patient either systemically or locally, or both. The pharmaceutical formulations of the invention may be delivered either in one dose, or continuously over a sustained period of time using, for example, sustained drug delivery devices.

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# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/037486

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61K31/56

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, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/44931 A (BION, INC) 3 August 2000 (2000-08-03) page 1, lines 7-9 pages 20-21, lines 14-8 pages 28-29, lines 33-1	1-39
Y	W. SCHONER: "Endogenous cardiac glycosides, a new class of steroid hormones" EUR J BIOCHEM, vol. 269, 2002, pages 2440-2448, XP002367830 page 2443; figure 2	1-39

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

20 February 2006

Date of mailing of the international search report

10 Feb 2006

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/037486

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MANSFIELD, SIMON, KEITH: "Hypoxic reduction in cellular glutathione levels requires mitochondrial reactive oxygen species" J APPL PHYSIOL, vol. 97, 2004, pages 1358-1366, XP002367831 page 1358, left-hand column, paragraph 2 -----	1-39

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No  
PCT/US2005/037486

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0044931 A	03-08-2000	AU 2743800 A	18-08-2000
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/037486

## 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:
  
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:

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.:

1-39

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

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

1. claims: 1-39

Na<sup>+</sup>-K<sup>+</sup>-ATPase inhibitors for the treatment of diseases caused by/with pathogenic angiogenesis

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2. claims: 40-57

Na<sup>+</sup>-K<sup>+</sup>-ATPase inhibitor antagonists for the treatment of depression

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