

(43) International Publication Date  
14 January 2010 (14.01.2010)

PCT

(10) International Publication Number  
**WO 2010/004433 A3**

## (51) International Patent Classification:

C07H 13/12 (2006.01) A61K 47/48 (2006.01)  
A61K 31/702 (2006.01) A61P 31/04 (2006.01)  
A61K 31/7028 (2006.01) C07H 15/12 (2006.01)  
A61K 31/7036 (2006.01)

## (21) International Application Number:

PCT/IB2009/006651

## (22) International Filing Date:

9 July 2009 (09.07.2009)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

61/079,338 9 July 2008 (09.07.2008) US  
61/093,199 29 August 2008 (29.08.2008) US

(71) Applicant (for all designated States except US): **UNIVERSITY OF MANITOBA** [CA/CA]; Room 631 Drake Centre, 181 Freedman Crescent, Winnipeg, Manitoba R3M 3N5 (CA).

## (72) Inventors; and

(75) Inventors/Applicants (for US only): **BERA, Smritilekha** [—/CA]; University Of Manitoba, Room 631 Drake Centre, 181 Freedman Crescent, Winnipeg, Manitoba R3M 3N5 (CA). **ZHANEL, George, G.** [CA/CA]; University Of Manitoba, Room 631 Drake Centre, 181 Freedman Crescent, Winnipeg, Manitoba R3M 3N5 (CA). **SCHWEIZER, Frank** [DE/CA]; University Of Manitoba, Room 631 Drake Centre, 181 Freedman Crescent, Winnipeg, Manitoba R3M 3N5 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

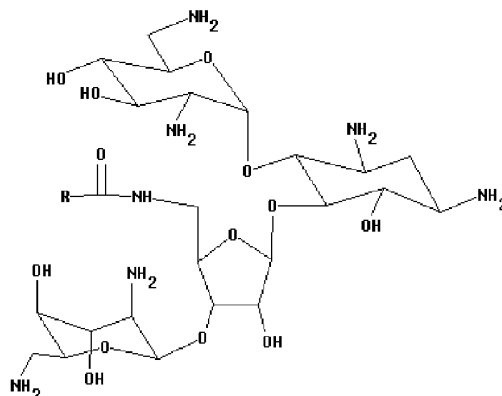
## Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

## (88) Date of publication of the international search report:

8 April 2010

(54) Title: HYDROPHOBICALLY ENHANCED AMINOGLYCOSIDES



R = hydrophobic moiety

(57) Abstract: Hydrophobically enhanced aminoglycosides have been prepared and shown to be effective antibacterial agents. These agents may be used in the treatment or prevention of various bacterial infections. Methods of preparing these agents also permit facile synthetic access. Formula (I).

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2009/006651

| <p>A. CLASSIFICATION OF SUBJECT MATTER</p> <p>IPC: <b>C07H 13/12</b> (2006.01) , <b>A61K 31/702</b> (2006.01) , <b>A61K 31/7028</b> (2006.01) , <b>A61K 31/7036</b> (2006.01) , <b>A61K 47/48</b> (2006.01) , <b>A61P 31/04</b> (2006.01) , <b>C07H 15/12</b> (2006.01)</p> <p>According to International Patent Classification (IPC) or to both national classification and IPC</p>  |  |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
|---|--|--|---|---|--|--|--|--|---|---|--|------|---|--|---|---|--|
| <p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols)</p> <p><b>C07H 13/12</b> (2006.01)</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched</p> <p>Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)</p> <p>STN (Structure search in Registry; CAplus, Keywords: neomycin, kanamycin, paromomycin, amikacin, gentamicin, netilmicin, streptomycin, tobramycin, hygromycin, spectinomycin, lipid, conjugate), EPODOC (Keywords: neomycin, kanamycin, paromomycin, amikacin, gentamicin, netilmicin, streptomycin, tobramycin, hygromycin, spectinomycin, lipid, conjugate; and Inventors)</p>  |  |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| <p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <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>P, X</td> <td>BERA et al: "Design, synthesis, and antibacterial activities of neomycin-lipid conjugates: polycationic lipids with potent gram-positive activity"; <i>J. Med. Chem.</i> <b>2008</b>, <i>51</i>, 6160-6164.<br/>See the whole document.</td> <td>1-20, 27, 29-30, 43-50, 61-62, 64-65, 68-73, 75-79, 87-93, 95-114, 121, 123-124, 137-144, 155-156, 158-159, 162-167, 169-173, 181-187</td> </tr> <tr> <td>P, X</td> <td>ZHANG et al: "Surprising alteration of antibacterial activity of 5"-modified neomycin against resistant bacteria"; <i>J. Med. Chem.</i> <b>2008</b>, <i>51</i>, 7563-7573.<br/>See the whole document.</td> <td>1-18, 20, 27, 29-30, 43-50, 61-62, 64-65, 68-73, 75-79, 87-93, 95-112, 114, 121, 123-124, 137-144, 155-156, 158-159, 162-167, 169-173, 181-187</td> </tr> <tr> <td>P, X</td> <td>CA 2,687,689 (ZHANEL et al) 26 March 2009 (26-03-2009)<br/>See pages 5-7, claims 21, 23, 78 and 60, and Figures 1 and 4-7.</td> <td>1-2, 5-10, 20, 27, 29, 61-62, 64-65, 68-71, 87-92, 95-96, 99-114, 121, 123, 155-156, 158-159, 162-165, 181-186</td> </tr> <tr> <td>X</td> <td>WO 03/066648 (YU et al) 14 August 2003 (14-08-2003)<br/>See pages 5, 8 and 10; and claims 1 and 6.</td> <td>1-2, 5-10, 20, 27, 29, 61-62, 64-65, 68-71, 81, 87-92, 95-96, 99-104, 114, 121, 123, 155-156, 158-159, 162-165, 175, 181-186</td> </tr> </tbody> </table> |  |  | Category*                                 | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  | P, X   | BERA et al: "Design, synthesis, and antibacterial activities of neomycin-lipid conjugates: polycationic lipids with potent gram-positive activity"; <i>J. Med. Chem.</i> <b>2008</b> , <i>51</i> , 6160-6164.<br>See the whole document. | 1-20, 27, 29-30, 43-50, 61-62, 64-65, 68-73, 75-79, 87-93, 95-114, 121, 123-124, 137-144, 155-156, 158-159, 162-167, 169-173, 181-187  | P, X  | ZHANG et al: "Surprising alteration of antibacterial activity of 5"-modified neomycin against resistant bacteria"; <i>J. Med. Chem.</i> <b>2008</b> , <i>51</i> , 7563-7573.<br>See the whole document. | 1-18, 20, 27, 29-30, 43-50, 61-62, 64-65, 68-73, 75-79, 87-93, 95-112, 114, 121, 123-124, 137-144, 155-156, 158-159, 162-167, 169-173, 181-187 | P, X | CA 2,687,689 (ZHANEL et al) 26 March 2009 (26-03-2009)<br>See pages 5-7, claims 21, 23, 78 and 60, and Figures 1 and 4-7. | 1-2, 5-10, 20, 27, 29, 61-62, 64-65, 68-71, 87-92, 95-96, 99-114, 121, 123, 155-156, 158-159, 162-165, 181-186 | X | WO 03/066648 (YU et al) 14 August 2003 (14-08-2003)<br>See pages 5, 8 and 10; and claims 1 and 6. | 1-2, 5-10, 20, 27, 29, 61-62, 64-65, 68-71, 81, 87-92, 95-96, 99-104, 114, 121, 123, 155-156, 158-159, 162-165, 175, 181-186 |
| Category*   | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| P, X  | BERA et al: "Design, synthesis, and antibacterial activities of neomycin-lipid conjugates: polycationic lipids with potent gram-positive activity"; <i>J. Med. Chem.</i> <b>2008</b> , <i>51</i> , 6160-6164.<br>See the whole document.         | 1-20, 27, 29-30, 43-50, 61-62, 64-65, 68-73, 75-79, 87-93, 95-114, 121, 123-124, 137-144, 155-156, 158-159, 162-167, 169-173, 181-187          |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| P, X  | ZHANG et al: "Surprising alteration of antibacterial activity of 5"-modified neomycin against resistant bacteria"; <i>J. Med. Chem.</i> <b>2008</b> , <i>51</i> , 7563-7573.<br>See the whole document.  | 1-18, 20, 27, 29-30, 43-50, 61-62, 64-65, 68-73, 75-79, 87-93, 95-112, 114, 121, 123-124, 137-144, 155-156, 158-159, 162-167, 169-173, 181-187 |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| P, X  | CA 2,687,689 (ZHANEL et al) 26 March 2009 (26-03-2009)<br>See pages 5-7, claims 21, 23, 78 and 60, and Figures 1 and 4-7.  | 1-2, 5-10, 20, 27, 29, 61-62, 64-65, 68-71, 87-92, 95-96, 99-114, 121, 123, 155-156, 158-159, 162-165, 181-186                                 |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| X   | WO 03/066648 (YU et al) 14 August 2003 (14-08-2003)<br>See pages 5, 8 and 10; and claims 1 and 6.  | 1-2, 5-10, 20, 27, 29, 61-62, 64-65, 68-71, 81, 87-92, 95-96, 99-104, 114, 121, 123, 155-156, 158-159, 162-165, 175, 181-186                   |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| <p>[X] Further documents are listed in the continuation of Box C.      [X] See patent family annex.</p> <table border="1"> <tbody> <tr> <td>* Special categories of cited documents :</td> <td>"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</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </tbody> </table>                           |  |  | * Special categories of cited documents : | "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 | "A" document defining the general state of the art which is not considered to be of particular relevance | "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 | "E" earlier application or patent but published on or after the international filing date  | "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 | "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) | "&" document member of the same patent family   | "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                    |  |   |   |  |
| * Special categories of cited documents :   | "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  |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| "A" document defining the general state of the art which is not considered to be of particular relevance  | "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   |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| "E" earlier application or patent but published on or after the international filing date   | "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 |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| "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)   | "&" document member of the same patent family  |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| "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  |  |  |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| <p>Date of the actual completion of the international search</p> <p>28 January 2010 (28-01-2010)</p>  |  | <p>Date of mailing of the international search report</p> <p>17 February 2010 (17-02-2010)</p>   |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |
| <p>Name and mailing address of the ISA/CA</p> <p>Canadian Intellectual Property Office</p> <p>Place du Portage I, C114 - 1st Floor, Box PCT</p> <p>50 Victoria Street</p> <p>Gatineau, Quebec K1A 0C9</p> <p>Facsimile No.: 001-819-953-2476</p>  |  | <p>Authorized officer</p> <p>Lu Jiang (819) 934-6738</p>   |   |   |  |  |  |  |   |   |  |      |   |  |   |   |  |

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/IB2009/006651**Box No. II      Observations where certain claims were found unsearchable (Continuation of item 2 of the 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.    ☒ Claim Nos. :    64-94, 158-188

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

Although claims 64-94 and 158-188 are directed to methods of medical treatment of the human or animal body, the search has been carried out based on the alleged effects of the compounds thereof.

2.    ☐ Claim 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.    ☐ Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. 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 additional fees, this Authority did not invite payment of additional fees.

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 claim 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 claim Nos. :

**Remark on Protest**    ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB2009/006651

| 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 2008/040792 (LEHN et al) 10 April 2008 (10-04-2008)<br>See pages 8-11, claim 7, and Figure 2.  | 1-11, 13, 17-18, 20, 27, 29, 40-46, 48-50, 61-63, 95-105, 107, 111-112, 114, 121, 123, 134-140, 142-144, 155-157 |
| X   | US 2003/0054556 (LEHN et al) 20 March 2003 (20-03-2003)<br>See pages 2-3 and Figure 1.  | 1-11, 13, 17-18, 20, 27, 29, 40-46, 48-50, 61-63, 95-105, 107, 111-112, 114, 121, 123, 134-140, 142-144, 155-157 |
| X   | SAINLOS et al: "Kanamycin A-derived cationic lipids as vectors for gene transfection"; <i>ChemBioChem</i> <b>2005</b> , 6, 1023-1033.<br>See the whole document.  | 40-42, 61, 63, 134-136, 155, 157   |
| X   | SAINLOS et al: "Aminoglycoside-derived cationic lipids for gene transfection: synthesis of Kanamycin A derivatives"; <i>Eur. J. Org. Chem.</i> <b>2003</b> , 2764-2774.<br>See the whole document.  | 40-42, 61, 63, 134-136, 155, 157   |
| X   | LI et al: "Investigation of the regioselectivity for the Staudinger reaction and its application for the synthesis of aminoglycosides with N1 modification"; <i>J. Org. Chem.</i> <b>2007</b> , 72, 4055-4066.<br>See compounds 2 and 5 on page 4057. | 31-36, 56, 58, 125-130, 150, 152   |

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

International application No.  
**PCT/IB2009/006651**

| Patent Document<br>Cited in Search Report | Publication<br>Date | Patent Family<br>Member(s) | Publication<br>Date |
|---|---------------------|----------------------------|---------------------|
| CA2687698A1                               | 04-04-2002          | AU9157501A                 | 08-04-2002          |
|   |                     | CA2422823A1                | 04-04-2002          |
|   |                     | CA2422823C                 | 30-06-2009          |
|   |                     | EP1320348A2                | 25-06-2003          |
|   |                     | US6920656B2                | 26-07-2005          |
|   |                     | US7185377B2                | 06-03-2007          |
|   |                     | US2003172459A1             | 18-09-2003          |
|   |                     | US2005283912A1             | 29-12-2005          |
|   |                     | WO0226187A2                | 04-04-2002          |
|   |                     | WO0226187A3                | 19-09-2002          |
| WO03066648A1                              | 14-08-2003          | AU2002315931A1             | 02-09-2003          |
|   |                     | KR20030067355A             | 14-08-2003          |
|   |                     | US2005222055A1             | 06-10-2005          |
| WO2008040792A2                            | 10-04-2008          | CA2665403A1                | 10-04-2008          |
|   |                     | EP2069500A2                | 17-06-2009          |
|   |                     | WO2008040792A3             | 28-08-2008          |
| US2003054556A1                            | 20-03-2003          | AT430758T                  | 15-05-2009          |
|   |                     | AU2002334051B2             | 15-05-2008          |
|   |                     | CA2458626A1                | 06-03-2003          |
|   |                     | DE60232258D1               | 18-06-2009          |
|   |                     | EP1430074A1                | 23-06-2004          |
|   |                     | EP1430074B1                | 06-05-2009          |
|   |                     | FR2829136A1                | 07-03-2003          |
|   |                     | FR2829136B1                | 17-11-2006          |
|   |                     | JP2005504061T              | 10-02-2005          |
|   |                     | WO03018603A1               | 06-03-2003          |