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*A61K 8/37* (2006.01)      *A61P 31/04* (2006.01)  
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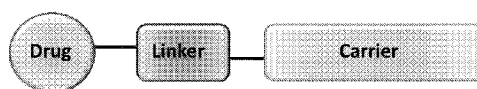
## (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,

[Continued on next page]

## (54) Title: CONJUGATE-BASED ANTIFUNGAL AND ANTIBACTERIAL PRODRUGS

Figure 22

## Antifungal Agent-Carrier Conjugates as Prodrugs



- Drug** - Antifungal Agent, more specifically antidandruff agent (including azole-based, hydroxy antifungals, and others)
- Linker** - Cleavable either spontaneously or easily by lipases from *Malassezia*
- Carrier** - A variety of fatty acids, surfactants, polymers, etc to formulate the prodrug into nanoparticles



(57) **Abstract:** The invention provides conjugate-based antifungal or antibacterial prodrugs formed by coupling at least one antifungal agent or antibacterial agent with at least one linker and/or carrier. The prodrugs are of formula: (i)  $(AFA)_m-X-(L)_n$ ; (ii)  $[(AFA)_m-X]_p-L$ ; (iii)  $AFA-[X-(L)_n]_q$ ; or (iv)  $(AFA)_m-X$ , wherein: AFA is an antifungal agent or an antibacterial agent; L is a carrier; X is a linker; m ranges from 1 to 10; n ranges from 2 to 10; m' is 1 to 10; p is 1 to 10; n' is 1 to 10; and q is 1 to 10, provided that q' and n are not both 1; and m" is 1 to 10. The invention also provides nanoparticles comprising the conjugate-based prodrugs. Additionally, the invention also provides non-conjugated antifungal and antibacterial agents in the form of nanoparticles.



MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

14 March 2013

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2012/043717

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>INV. A61Q17/00 A61K8/37 A61Q5/02 A61K47/48 A61P31/04<br>A61P17/10<br>ADD.<br>According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                |                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>A61Q A61K<br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                |                                                                  |
| <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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | WO 2008/089185 A2 (ENZON PHARMACEUTICALS INC [US]; ZHAO HONG [US])<br>24 July 2008 (2008-07-24)<br>claims 1-18<br>-----                                                        | 1-18,20,<br>21,23,<br>41-46,<br>48,50-61                         |
| X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | WO 2008/034019 A2 (POLYMERIX CORP [US]; KANAMATHAREDDY SUSEELA [US]; GIROUX KAREN J [US])<br>20 March 2008 (2008-03-20)<br>page 6, line 25 - page 16, line 26<br>-----<br>-/-- | 1-21,23,<br>41-61                                                |
| <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 :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"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)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"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<br>"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<br>"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<br>"&" document member of the same patent family |                                                                                                                                                                                |                                                                  |
| Date of the actual completion of the international search<br>2 October 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                | Date of mailing of the international search report<br>11/01/2013 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                | Authorized officer<br>Kukolka, Florian                           |

# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/043717

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                                     | Relevant to claim No.                                             |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| X         | <p>YANG H ET AL: "Penicillin V-conjugated PEG-PAMAM star polymers", JOURNAL OF BIOMATERIALS SCIENCE. POLYMER EDITION, VSP, UTRECHT, NL, vol. 14, no. 10, 1 October 2003 (2003-10-01), pages 1043-1056, XP008085754, ISSN: 0920-5063, DOI: 10.1163/156856203769231556 the whole document</p> <p>-----</p>                                                                                               | <p>1-8,<br/>10-15,<br/>17-21,<br/>23,<br/>41-46,<br/>48,50-61</p> |
| X         | <p>WO 2007/023398 A2 (UNIV GENEVE [CH]; LANGE NORBERT [CH]; CAMPO MARINO A [CH]) 1 March 2007 (2007-03-01)</p> <p>claims 1-33</p> <p>-----</p>                                                                                                                                                                                                                                                         | <p>1-8,<br/>10-15,<br/>18,20,<br/>21,23,<br/>41-46,<br/>48-61</p> |
| X         | <p>US 2007/292404 A1 (WALSH SCOTT M [US] ET AL) 20 December 2007 (2007-12-20)</p> <p>claims 1-25</p> <p>-----</p>                                                                                                                                                                                                                                                                                      | <p>1-8,<br/>10-16,<br/>18,20,<br/>21,23,<br/>41-46,<br/>50-61</p> |
| X         | <p>AGNIESZKA K MUSZANSKA ET AL: "Pluroniclysozyme conjugates as anti-adhesive and antibacterial bifunctional polymers for surface coating", BIOMATERIALS, ELSEVIER SCIENCE PUBLISHERS BV., BARKING, GB, vol. 32, no. 26, 5 May 2011 (2011-05-05), pages 6333-6341, XP028097289, ISSN: 0142-9612, DOI: 10.1016/J.BIOMATERIALS.2011.05.016 [retrieved on 2011-05-11] the whole document</p> <p>-----</p> | <p>1-8,<br/>10-16,<br/>18,20,<br/>21,23,<br/>41-46,<br/>50-61</p> |
| X         | <p>GUIOTTO ANDREA ET AL: "PEGylation of the antimicrobial peptide nisin A: Problems and perspectives", IL FARMACO, ELSEVIER FRANCE * EDITIONS SCIENTIFIQUES ET MEDICALES, IT, vol. 58, no. 1, 1 January 2003 (2003-01-01), pages 45-50, XP002513890, ISSN: 0014-827X, DOI: 10.1016/S0014-827X(02)01301-0 the whole document</p> <p>-----</p> <p>-/--</p>                                               | <p>1-8,<br/>10-16,<br/>18,20,<br/>21,23,<br/>41-46,<br/>50-61</p> |

# INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/043717

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                        | Relevant to claim No.                                             |
|-----------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| X         | <p>W0 90/15628 A1 (CETUS CORP [US])<br/>27 December 1990 (1990-12-27)</p> <p>claims 1-23</p> <p>-----</p> | <p>1-8,<br/>10-16,<br/>18,20,<br/>21,23,<br/>41-46,<br/>50-61</p> |

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2012/043717

### Box No. 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 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:

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 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 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.:

see annex

#### 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/US2012/043717

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)                                                                                                      | Publication<br>date                                                                            |
|-------------------------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| WO 2008089185 A2                          | 24-07-2008          | CA 2675411 A1<br>EP 2125014 A2<br>JP 2010515762 A<br>TW 200838561 A<br>US 2008171013 A1<br>US 2010056543 A1<br>WO 2008089185 A2 | 24-07-2008<br>02-12-2009<br>13-05-2010<br>01-10-2008<br>17-07-2008<br>04-03-2010<br>24-07-2008 |
| WO 2008034019 A2                          | 20-03-2008          | EP 2102144 A2<br>US 2010310498 A1<br>WO 2008034019 A2                                                                           | 23-09-2009<br>09-12-2010<br>20-03-2008                                                         |
| WO 2007023398 A2                          | 01-03-2007          | EP 1888115 A2<br>US 2009209508 A1<br>WO 2007023398 A2                                                                           | 20-02-2008<br>20-08-2009<br>01-03-2007                                                         |
| US 2007292404 A1                          | 20-12-2007          | NONE                                                                                                                            |                                                                                                |
| WO 9015628 A1                             | 27-12-1990          | AU 5858690 A<br>CA 2018833 A1<br>WO 9015628 A1                                                                                  | 08-01-1991<br>14-12-1990<br>27-12-1990                                                         |

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

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

1. claims: 23(completely); 1-21, 24, 25, 41-61(partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is a polymer. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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2. claims: 22(completely); 1-21, 24, 25, 41-61(partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is a fatty acid. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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3. claims: 1-21, 24-61(all partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is an amino acid. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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4. claims: 1-21, 24-61(all partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is a peptide. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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5. claims: 1-21, 24-61(all partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is a nucleic acid. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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6. claims: 1-21, 24-61(all partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is a glycerol. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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7. claims: 1-21, 24-61(all partially)

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is an antibacterial agent. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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8. claims: 1-21, 24-61(all partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is an antifungal agent. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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9. claims: 1-21, 24-61(all partially)

A conjugate-based antifungal or antibacterial prodrug according to claim 1, wherein the carrier is a alpha or beta-hydroxy acid. A personal care composition comprising said prodrug and use of said prodrug in a treatment as specified in claims 47,49-61.

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10. claims: 26-40(completely); 41-61(partially)

A nanoparticle as defined in claims 26-40, a personal care composition comprising said nanoparticle and use of said nanoparticle in a treatment as specified in claims 47,49-61.

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