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

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(54) Title: SELF-IMMOLATIVE LINKERS AND DRUG CONJUGATES

(57) Abstract: The present disclosure provides drug-ligand conjugates that are potent cytotoxins, wherein the drug is linked to the ligand through either a peptidyl, hydrazine or disulfide self-immolative linker. In a particular embodiment the cytotoxin is represented by duocarmycins and derivatives thereof. The disclosure is also directed to compositions containing the drug-ligand conjugates, and to methods of treatment using them.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61P35/00

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)
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, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUZAWA T ET AL: "Synthesis of a novel duocarmycin derivative DU-257 and its application to immunoconjugate using poly(ethylene glycol)-dipeptidyl linker capable of tumor specific activation" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 8, no. 8, August 2000 (2000-08), pages 2175-2184, XP002342901 ISSN: 0968-0896	1-3, 7-10,14, 18, 21-26, 136-139
Y	Abstract; pag. 2176 Scheme 1; pag. 2177 Scheme 2; pag. 2181 last par.	1-37, 118-139

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
13 October 2006	20/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bettio, Andrea

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SUZAWA T ET AL: "Synthesis and HPLC analysis of enzymatically cleavable linker consisting of poly(ethylene glycol) and dipeptide for the development of immunoconjugate" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 69, no. 1, 3 October 2000 (2000-10-03), pages 27-41, XP004217532 ISSN: 0168-3659 Abstract; fig 2 pag. 33	1,2,7-9, 14-23
X	WO 2004/032828 A (SEATTLE GENETICS, INC; WAHL, ALAN, F; SENTER, PETER, D; LAW, CHE-LEUNG) 22 April 2004 (2004-04-22)	1-5,7-9, 14-26, 29, 136-139
Y	pag. 61 lines 7-16; pag. 65; Claims 35 and 36, 43, 47, 86, 87, 117, 118 Fig 1B	38-77, 100-139
X	US 2003/096743 A1 (SENTER PETER D ET AL) 22 May 2003 (2003-05-22) cited in the application	1-5,7,8, 14-26, 29, 136-139
Y	Abstract; par. 57, 83, 98; claims 1, 3, 56-61; fig. 2B structure (VIIg)	1-37, 118-139
Y	EP 0 624 377 A (BRISTOL-MYERS SQUIBB COMPANY) 17 November 1994 (1994-11-17) cited in the application Abstract; pag. 3 lines 24-54; pag. 23 line 23-pag. 24 line 25	1-37, 118-139
Y	US 5 739 350 A (KELLY ET AL) 14 April 1998 (1998-04-14) cited in the application Example 10 column 40 line 49-column 41 line 3; Chart 10 column 55 and 56.	1-37, 118-139
Y	EP 0 563 475 A (IMMUNOGEN INC) 6 October 1993 (1993-10-06) pag. 18-19; Claim 1 structure A-4	118-139
Y	US 6 214 345 B1 (FIRESTONE RAYMOND ARMAND ET AL) 10 April 2001 (2001-04-10) cited in the application Column 8 formula (IXe); Column 35 and 36 formula 15	1-37, 118-139
Y	EP 0 867 190 A (KYOWA HAKKO KOGYO CO., LTD) 30 September 1998 (1998-09-30) pag. 4 line 47; pag. 5 lines 25-54	10-13, 32,34, 36,37

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/017804

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DUBOWCHIK G M ET AL: "Receptor-mediated and enzyme-dependent trageting of cytotoxic anticancer drugs" PHARMACOLOGY AND THERAPEUTICS, ELSEVIER, GB, vol. 83, 1999, pages 67-123, XP002391774 ISSN: 0163-7258 fig 7 pag. 78, fig. 8 pag. 79, fig. 9 pag. 80	38-77, 100-119
Y	WO 2004/073656 A (SEATTLE GENETICS, INC; LAW, CHE-LEUNG; WAHL, ALAN, F; SCHOLLER, NATHAL) 2 September 2004 (2004-09-02) Pag. 48 formula (IVa), pag. 54-56	38-77, 100-139
Y	HAY M P ET AL: "A 2-nitroimidazole carbamate prodrug of 5-amino-1-(chloromethyl)-3-[5 ,6,7-trimethoxyindol-2-yl)carbonyl]-1,2-di hydro -3H-benz[e]indole (amino-seco-CBI-TMI) for use with ADEPT and GDEPT" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 15, 2 August 1999 (1999-08-02), pages 2237-2242, XP004174167 ISSN: 0960-894X pag. 2237, pag. 2238 first 5 lines	38-77, 100-139
Y	WO 03/043583 A (SEATTLE GENETICS, INC; LAW, CHE-LEUNG; KLUSSMAN, KERRY; WAHL, ALAN, F;) 30 May 2003 (2003-05-30) claims 53,62,67,141,142,189,190,198	38-77, 100-139

INTERNATIONAL SEARCH REPORT

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

Although claims 137-139 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.

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:

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. [X] 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.:

25-28, 31-37, 106-109, 117-135 complete; 1-24, 29, 30, 38-77, 100-105 110-116, 136-139 in part

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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 137-139 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.

Continuation of Box II.1

In reply to the invitation to pay additional fees from the ISA dated 25.08.2006 the applicant has paid an additional search fee corresponding to invention 10 (claims 118-139 in part, 38-77, 100-117 complete) related to conjugates according to the formula of present claim 1 and wherein the cleavable linker contains an hydrazine linkage.

During the further search the document "Dubowchik G.M and Walker M. A. , Pharmacology and Therapeutics 83 (1999), 67-123" (XP-002391774) has been retrieved.

Said document (fig 7 pag. 78, fig. 8 pag. 79, fig. 9 pag. 80) dislcoses a series of doxorubycin-antibody conjugates wherein the linker contains an hydrazine linkage.

Consequently said document provides evidence of non unity "a posteriori" for the subject matter of invention 10.

No further invitation to pay further additional fees will be issued. This is because Article 17(3)(a) PCT stipulates that the ISA shall establish the International Search Report on those parts of the international application which relate to the invention first mentioned in the claims ('main invention') and for those parts which relate to inventions in respect of which the additional fees were paid. Neither the PCT nor the PCT guidelines provide a legal basis for further invitations to pay further additional search fees (W17/00, point 11 and W1/97, points 11-16).

Consequently the search for the subject matter of invention 10 has been limited to the following subject:

conjugates according to the formula of present claims 38 and 100 and wherein the cleavable linker contains an hydrazine linkage and the drug is a duocarmycin or CC-1065; except the subject matter of inventions 1-9, 11-19 ((claims 38-77, 100-105, 110-116, 118-139 in part, 106-109, 117 complete)

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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: 1-24, 29, 30,118-139 in part, 25-28, 31-37, complete

Conjugates according to the formula of present claim 1, wherein the cleavable linker contains a peptide or an amino acid and the drug is a duocarmycin or CC-1065; except the subject matter of inventions 2-19.

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2. claims: 1-24, 29, 30,136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, daunorubicin; except the subject matter of inventions 1, 3-19.

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3. claims: Claims 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from dolestatin-10, combretastatin , auristatin E, auristatin EB (AEB), auristatin EFP (AEFP), monomethyl auristatin E (MMAE), actinomycin , mitomycin C, mitomycin a, carminomycin, tallysomycin; except the subject matter of inventions 1, 2, 4-19.

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4. claims: 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from calicheamicin, maytansine, epothilones, 5-benzoylvaleric acid-AE ester (AEVB), butyric acid, SN-38
retinoic acid, , N8 -acetyl spermidine, camptothecin, topotecan, rhizoxin, echinomycin, colchicine, vinblastin, vindesine, estramustine, cemadotin, eleutherobin vincristine, melphalan, leurosine, leurosideine; except the subject matter of inventions 1-3, 5-19.

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5. claims: 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is a tubulysin; except the subject matter of inventions 1-4, 6-19.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. claims: Claims 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from Paclitaxel (taxol), docetaxel (taxotere); except the subject matter of inventions 1-5, 7-19.

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7. claims: 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from methotrexate, methopterin, dichloromethotrexate, aminopterin; except the subject matter of inventions 1-6, 8-19.

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8. claims: 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside; except the subject matter of inventions 1-7, 9-19.

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9. claims: 1-24, 29, 30, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a peptide or an amino acid and the drug is selected from podophyllotoxin and podophyllotoxin derivatives such as etoposide or etoposide phosphate; except the subject matter of inventions 1-8, 10-19.

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10. claims: Claims 118-139 in part, 38-77, 100-117 complete

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains an hydrazine linkage; except the subject matter of inventions 1-9, 11-19

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11. claims: Claims 78-86, 91-97, 118-139 in part, 87-90, 98, 99 complete

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is a duocarmycin or CC-1065;except the subject matter of inventions 1-10, 12-19.

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12. claims: 78-86, 91-97, 136-139 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is selected from doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, daunorubicin; except the subject matter of inventions 1-11, 13-19.

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13. claims: Claims 78-86, 91-97, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains an hydrazine linkage and the drug is selected from dolestatin-10, combretastatin , auristatin E, auristatin EB (AEB), auristatin EFP (AEFP), monomethyl auristatin E (MMAE), actinomycin , mitomycin C, mitomycin a, carminomycin, tallysomycin; except the subject matter of inventions 1-12, 14-19.

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14. claims: 78-86, 91-97, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is selected from calicheamicin, maytansine, epothilones, 5-benzoylvaleric acid-AE ester (AEVB), butyric acid, SN-38 retinoic acid, N8 -acetyl spermidine, camptothecin, topotecan, rhizoxin, echinomycin, colchicine, vinblastin, vindesine, estramustine, cemadotin, eleutherobin vincristine, melphalan, leurosine, leurosideine; except the subject matter of inventions 1-13, 15-19.

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15. claims: 78-86, 91-97, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is a tubulysin; except the subject matter of inventions 1-14, 16-19.

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16. claims: 78-86, 91-97, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is selected from paclitaxel (taxol), docetaxel (taxotere); except the subject matter of inventions 1-15, 17-19.

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17. claims: 78-86, 91-97, 136-139 in part

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is selected from methotrexate, methopterin, dichloromethotrexate, aminopterin; except the subject matter of inventions 1-16, 18-19.

---

18. claims: 78-86, 91-97, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is selected from 5-fluorouracil, 6-mercaptopurine, cytosine arabinoside; except the subject matter of inventions 1-17, 19.

---

19. claims: 78-86, 91-97, 136-139 in part

Conjugates according to the formula of present claim 1 and wherein the cleavable linker contains a disulfide linkage and the drug is selected from podophyllotoxin and podophyllotoxin derivatives such as etoposide or etoposide phosphate; except the subject matter of inventions 1-18.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2005/017804

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