Antibody-drug conjugates, compositions and methods of use

Antibody-cytotoxin antibody-drug conjugates and related compounds, such as linker-cytotoxin conjugates and the linkers used to make them, tubulysin analogs, and intermediates synthesis; compositions; and methods, including methods of treating cancers.
INTERNATIONAL SEARCH REPORT  
International application No.  
PCT/US14/41420  

A. CLASSIFICATION OF SUBJECT MATTER  
IPC(8) C07D 413/00, 207/00, 295/00; A01N 43/64; A61K 31/41, 31/40 (2014.01)  
CPC - C07D 207/16, 207/12, 207/27, 207/09, 207/08, 295/023, 295/037; B01J 23/40; A61K 31/40  

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(8): C07D 413/00, 207/00, 295/00; A01N 43/64; A61K 31/41, 31/40 (2014.01)  
CPC: C07D 207/16, 207/12, 207/27, 207/09, 207/08, 295/023, 295/037; B01J 23/40; A61K 31/40  

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 practicable, search terms used)  

C. DOCUMENTS CONSIDERED TO BE RELEVANT  

<table>
<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>Y</td>
<td>WO 2013/009564 A1 [NOVARTIS AG] January 17, 2013; page 6, line 3; page 8, lines 1-10; page 11, lines 11-18; page 21, lines 4-13; page 27, lines 24-28; page 28, line 35</td>
<td>1, 45-49</td>
</tr>
<tr>
<td>Y</td>
<td>US 2012/0190124 A1 [SMITH, M et al.] July 26, 2012; paragraphs [0022], [0076], [0288], [0320], [0322], [0324], [0552], [0554], [0556]</td>
<td>1, 45-49</td>
</tr>
<tr>
<td>Y</td>
<td>WO 2006/056446 A2 [PIERS PROTEOLAB AG] June 1, 2006; page 18, lines 1-10</td>
<td>47</td>
</tr>
</tbody>
</table>

* Further documents are listed in the continuation of Box C.  

* 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 application or patent 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  
  "Z" document member of the same patent family  

Date of the actual completion of the international search  
12 December 2014 (12.12.2014)  

Date of mailing of the international search report  
9 DEC 2014  

Name and mailing address of the ISA/US  
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents  
P.O. Box 1450, Alexandria, Virginia 22313-1450  
Facsimile No. 571-273-3201  

Authorized officer:  Shane Thomas  
PCT Helpdesk: 571-272-4300  
PCT OSP: 571-272-777h  

Form PCT/ISA/2 to (second sheet) (July 2009)
INTERNATIONAL SEARCH REPORT

**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 : 5-41, 43, 44, 51 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:

Please see continuation 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 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.:

   "*Please See Supplemental Page***"

**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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (July 2009)
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I-6: Claims 1-4, 42, 45-50, 52, an antibody conjugate encompassing an antibody conjugated to CTX-I, CTX-II, or CTX-III by a linker encompassing an ether linkage to a pyrrole-2,5-dione; a linker of formula A; a linker of formula AA; and a linker of formula AAA are directed toward an antibody-drug conjugate (ADC) of the formula: A-([=PD-(L1)a-(L2)b-(L3)c-(CTX)m)n]; wherein: A is an antibody; PD is a pyrrole-2,5-dione or a derivative thereof, a pyrrolidine-2,5-dione or derivative thereof; CTX is a cytotoxin; each L1, L2, and L3 is independently a linker, and CTX is a linker-cytotoxin conjugate of formula A, B, or C; a linker of formula AA, BB, CC or DD; and a linker of formula AAA, BBB, CCC or DDD; Exemplary Ejection: an antibody-cytotoxin conjugate; wherein PD is pyrrole-2,5-dione, L1 is absent, L2 is (CH2)3, and L3 is -OC(O)-; a cytotoxin encompassing CTX-IV; a linker-cytotoxin conjugate of formula A, wherein each of R and R' are pyridyl; X is CH2; L1 is absent, L2 is (CH2)3, L3 is -OC(O)-; and D is amino; a linker of formula AA wherein each of R and R' are ethoxy, X is CH2; L1 is absent, L2 is (CH2)3, L3 is -OC(O)-; and D is amino

The antibody-drug conjugate (ADC) of the formula: A-([=PD-(L1)a-(L2)b-(L3)c-(CTX)m)n]; will be searched to the extent that the conjugate encompasses an antibody conjugated to pyrrole-2,5-dione, linked to a cytotoxin by a linker, wherein the linker encompasses -O- (wherein a and b are each 0, c is 1, and L3 is the first available option: -O-); and the cytotoxin encompasses CTX-I, CTX-II, or CTX-III. A linker-cytotoxin conjugate of formula A, B, or C; and a linker of formula AA, BB, CC or DD will be searched to the extent that the linker encompasses a linker of formula AA, and a linker-cytotoxin conjugate of formula A, wherein each of R and R' is C1 alkyl (methyl); each of x and x' is O; Z is N; L1 is a linker defined by -(L1)a-(L2)b-(L3)c-, wherein a and b are both 0, c is 1, L3 is -O-; and D is carboxyl. It is believed that Claims 1 (in-part), 45 (in-part), 46 (in-part), 47 (in-part), 48 (in-part), 49 (in-part) and 52 (in-part) encompass these first named inventions and thus these claims will be searched without fee to the extent that they encompass this previously named conjugate, cytotoxin, cytotoxin-linker conjugate and the previously named linkers. Applicant is invited to elect additional antibody-cytotoxin conjugate(s) and/or cytotoxin(s) and/or cytotoxin-linker conjugate(s) and/or linkers of formulas A, B, C, AA, BB, CC, DD, AAA, BBB, CCC or DDD by fully specifying the molecular structure of the PD and linking groups of the conjugate (e.g., with no optional positions or R groups); and/or the cytotoxin(s) and/or the linker/cytotoxin conjugate(s) and/or linker(s) to be searched. Additional fully specified conjugate(s) and/or cytotoxin(s) and/or cytotoxin-linker conjugate(s) and/or linker(s) will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected fully specified conjugate(s) and/or cytotoxin(s) and/or cytotoxin-linker conjugate(s) and/or linker(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the *+ group(s) will result in only the first claimed invention to be searched/examined. An Exemplary Election would include: an antibody-cytotoxin conjugate; wherein PD is pyrrole-2,5-dione, L1 is absent, L2 is (CH2)3, and L3 is -OC(O)-; a cytotoxin encompassing CTX-IV; a linker-cytotoxin conjugate of formula A, wherein each of R and R' are pyridyl; X is CH2; L1 is absent, L2 is (CH2)3, L3 is -OC(O)-; and D is amino; a linker of formula AA, wherein each of R and R' are ethoxy, X is CH2; L1 is absent, L2 is (CH2)3, L3 is -OC(O)-; and D is amino.

The cytotoxins of Groups I-6 lack unity a priori, since they do not share a common technical feature.
**INTERNATIONAL SEARCH REPORT**

**International application No.**

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Groups I - share the technical features including an antibody-drug conjugate (ADC) of the formula: A=-(PD-(L1)a-(L2)b-(L3)c-(CTX)m)n;
wherein: A is an antibody; PD is a pyrrole-2,5-dione or derivative thereof, a pyrrolidine-2,5-dione or derivative thereof; CTX is a cytotoxin;
each L, L2 and L3 is independently a linker selected from the group consisting of: -O-, -S-, -S(O)-, -S(O)2-, -NH-, -NHS-, -(CH2)q-
-NH(CH2)2NH-, -(OCH2)2-, -(CH2O)2-, -(CH2)q-(OCH2)2-, -(CH2)q-(CH2O)2-, -(CH2O)p-(CH2)q-(CH2O)pCH2CH2-,
-CYC, -(CH2CH2)p-(CH2CH2)q-; cyclopendant, cyclohexyl, unsubstituted phenyl, phenyl substituted by 1 or 2 substituents selected from the group consisting of cyclo-halo, -CN, -NH-, -NH2-, -OH, -NHC3-, -NHC2-, 1-alkylyl and -AAr; a, b and c are each independently 0, 1, 2 or 3, provided that at least one of a, b or c is 1; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 10; each AA is independently an amino acid; each r is 1 to 12; and m is an integer of 1 to 4; and n is an integer of 1 to 4; with the proviso that when -L1a=(L2)b=(L3)c- together is -(CH2)1-12- or -(CH2CH2)1-12CH2CH2- then L1, L2 and L3 are not bonded to CTX by an amide bond; an antibody-drug conjugate recited in Table 1 and a pharmaceutically acceptable excipient thereof; a cytotoxin selected from the group consisting of: CTX-Y, CTX-F, CTX-III, CTX-IV, CTX-V, CTX-VI, CTX-VII and CTX-VIII; wherein the variables i, q, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14 and R15 are as defined herein in the corresponding cytotoxin conjugated residues CTX-I, CTX-II, CTX-III, CTX-IV, CTX-V, CTX-VI, CTX-VII and CTX-VIII, respectively; a linker-cytotoxin conjugate of formula A, B, or C; where each R and R' is independently selected from the group consisting of 1-alkylyl optionally substituted with halo or hydroxyl; phenyl optionally substituted with halo, hydroxyl, carboxyl, C1-3alkoxyacarbonyl, or C1-3alkylyl; naphthyl optionally substituted with halo, hydroxyl, carbonyl, C1-3alkoxyacarbonyl, or C1-3alkylyl; 2-pyrilyl optionally substituted with halo, hydroxyl, carbonyl, C1-3alkoxyacarbonyl or C1-3alkylyl; c1-3alkylsulfonyl, c2-1cycloalkylsulfonyl, c6-10arylsulfonyl, c1-3alkylS-, C6-10arylS- and C6-10heteroarylS-, X is O, S or NR1 where R1 is H or C1-3alkylyl; X is O, S or NR2 where R2 is H or C1-3alkylyl; Z is selected from the group consisting of: N-, CH-, CR3- and CR3-CR4RS- where R3, R4 and R5 are each independently H or C1-3alkylyl, L is a linker defined by -(L1)a-(L2)b-(L3)c-, wherein each L1, L2 and L3 is independently a linker selected from the group consisting of: -O-, -S-, -S(O)-, -S(O)2-, -NH-, -NHC3-, -(CH2)q-, -(CH2)q-(OCH2)2-, -(CH2)q-(CH2O)p-(CH2O)pCH2CH2-, -CH2CH2-(CH2CH2)p-, -OCH2CH2O-,
cyclopendant, cyclohexyl, unsubstituted phenyl, phenyl substituted by 1 or 2 substituents selected from the group consisting of halo, CF3-, CF30-, CH3O-, -C(0)OH-, -C(0)CH3-, -CN-, -NH-, -OCH3-, -NHC3-, -NHC2-, 1-alkylyl and -AAr; a, b and c are each independently 0, 1, 2 or 3, provided that at least one of a, b or c is 1; each AA is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; and CTX is a cytotoxin bonded to L by an amide bond; a linker defined as above for formulas A, B or C; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; D is carbonyl, C1-3alkoxyacarbonyl or amino, and m is an integer of 1 to 12; and a linker of formula AAA, BBB, CCC or DDD; where each R and R' is independently selected from the group consisting of chloro, bromo, iodo, C1-6alkylsulfonyl, C2-1cycloalkylsulfonyl, C6-10aryl sulfonil, L is a linker defined as above for formulas A, B or C; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; and D is carbonyl, C1-6alkoxyacarbonyl or amino.

However, these shared technical features are previously disclosed by WO 2013/078377 A1 to Lippincott, et al. (hereinafter Lippincott) and further in view of US 2011/0021568 A1 to Ellman, et al. (hereinafter Ellman) and US 2012/0190124 A1 to Smith, et al. (hereinafter Smith). Lippincott discloses a conjugate [paragraph [0216]] comprising an antibody [paragraph [0216]] linked to a cytotoxic [comprising a cytotoxic agent; paragraph [0216]] and a linking group comprising a pyrrole 2,5-dione ring (and a bifuncional coupling agent, such as BMPS, EMCS, sulfo-EMCS, sulfo-GMBS, and SVSB (a linking group comprising a pyrrole 2,5-dione ring); paragraph [0216]); and a pharmaceutical composition comprising the conjugate and a pharmaceutically acceptable carrier (a pharmaceutical composition comprising the conjugate and a pharmaceutically acceptable carrier; paragraphs [0036], [0216]); and wherein the cytotoxin may be a tubulin depolymerizing agent, including a maytansinoid [paragraph [0216]].

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Lippincott does not disclose a conjugate comprising a cytotoxin and a linking group comprising a 5-membered ring; an antibody-daig conjugate (ADC) of the formula: A-(PD-L1(a)-(L2(b)-(L3)-(L4)-(L5)-(L6)-L7b)-CTX) wherein: A is an antibody; PD is a pyrrole-2,5-dione or derivative thereof, a pyrrolidine-2,5-dione or derivative thereof; CTX is a cytotoxin; each L1, L2 and L3 is independently a linker selected from the group consisting of O-C(=O)-, S-O-C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)C(=O)-, NHC(H)C(=O)C(=O)C(=O)-, NHC(H)C(=O)C(=O)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C(=O)-, NHC(H)C=O-,

Ellman discloses tubulinyl analogs (tubulinyl analogs: abstract) and conjugates thereof (and conjugates thereof: abstract), wherein the tubulinyl analog comprises a structure according to CTX-IV (comprising a structure according to formula II, wherein R1 is a nitrogen containing moiety; R2 is substituted or unsubstituted alkyl or heteroalkyl, R3 is H, and Y is (CH2)nC00H (comprising a structure according to CTX-V)); paragraphs [0011], [0013]), and including antibody conjugates thereof (antibody conjugates: paragraphs [0023]).

Smith discloses compounds for linking compounds (compounds for linking compounds: paragraph [0019]), including linking compounds comprising pyrrole 2,5-dione rings (maleimide type linking reagents (linking compounds comprising pyrrole 2,5-dione rings): paragraph [0007]), which react with and can be functionalized to contain a R group by an ether linkage [react with and can be functionalized to contain a R group through an ether linkage; illustrated in paragraph [0007]; as well as linking reagents (linking reagents: paragraphs [0019], [0037]) comprising pyrrole 2,5-dione rings (wherein R3a and R3a' together form a group of formula N(R3a)3a and X and Y represent oxygen (comprising pyrrole 2,5-dione rings); paragraphs [0037], [0041], [0046]) comprising an alkyl chain including a reactive carbonyl or amide linked to a nitrogen heteroatom (wherein R3a represents a group of formula L/Zn; wherein L is a linker group and Z is a reactive group capable of reacting with a compound to form a link (comprising an alkyl chain including a reactive carbonyl or amide linked to a nitrogen heteroatom); paragraphs [004], [0053], [0054], [0024], as well as reactive halogen pyrrole ring substituents (electrolytic leaving group, including halogen atom (reactive halogen pyrrole ring substituents): paragraphs [0051], [0052]), or other electrolytic leaving groups (electrolytic leaving groups: paragraphs [0050], [0056]-[0058]). Continued on Next Supplemental Page...
INTERNATIONAL SEARCH REPORT

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Continued from Previous Supplemental Page...

...Continued from Previous Supplemental Page... It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Lippincott, for implementing antibody conjugates including conjugates of trastuzumab and a maytansinoid (applicant's admitted prior art (instant PCT application; paragraph [0008]), wherein the conjugates disclosed by Lippincott could readily be modified to have included tubulin derivatives, based on the previous disclosure of Ellman, for producing an antibody-drug conjugate (ADC) of the formula: (A)=[(L1)-(L2)(L3)]-CTX/n; wherein: L is an antibody; PD is a pyrrole-2,3-dione or derivative thereof, a pyrroline-2,3-dione or derivative thereof; CTX is a cytotoxic; each L1, L2 and L3 is independently a linker selected from the group consisting of -O-(CH2)n, -S-(CH2)n, -NH-(CH2)n, -(CH2)nO-(CH2)n, -(CH2)CH2O(CH2)n, -(CH2)O(CH2)n, -O(CH2)O(CH2)n, cyclopentany1, cyclohexany1, unsubstituted phenylethyl, phenethyl substituted by 1 or 2 substituents selected from the group consisting of halo, CFS, CF3O, CH3O, -(CH2)nOH, -(CH2)nOC1-3alkyl, -(CH2)nCH3, -(CH2)nNH, -(CH2)nNH2, -OH, -NHCH3, -(CH2)n2, -CH1alkyl and -(AA); a, b and c are independently 0, 1, 2 or 3, provided that at least one of a, b or c is 1; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; and m is an integer of 1 to 4; and n is an integer of 1 to 4 with the proviso that when -(L1)-(L2)-(L3)= together is -(CH2)n -OCH(CH20)2-, -(CH2)nO-(CH2)n, -(CH2)nO(CH2)n, -(CH2)nCH2O(CH2)n, -(CH2)O(CH2)n, cyclopentany1, cyclohexany1, unsubstituted phenylethyl, phenethyl substituted by 1 or 2 substituents selected from the group consisting of halo, CFS, CF3O, CH3O, -(CH2)nOH, -(CH2)nOC1-3alkyl, -(CH2)nCH3, -(CH2)nNH, -(CH2)nNH2, -OH, -NHCH3, -(CH2)n2, -CH1alkyl and -(AA); a, b and c are independently 0, 1, 2 or 3, provided that at least one of a, b or c is 1; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; and CTX is a cytotoxic bonded to L by an amide bond using the cytotoxins previously disclosed by Lippincott, and a linker, as previously disclosed by Smith, for producing antibody-cytotoxin conjugates using the linker-cytotoxin conjugate and an antibody directed to a desirable target. Additionally, a person of ordinary skill in the art would have been readily able to have implemented a conjugate using a range of linker structures and functional groups, as previously disclosed by Smith, wherein the conjugate would have produced a linked cytotoxin that was pharmaceutically active with desirable dose-response properties. Moreover, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Lippincott regarding the linking agents useful for joining a cytotoxin and an antibody to have included a linker of formula AA, BB or CC: wherein each R and R' is as described above for formulas A, B or C; L is a linker defined as above for formulas A, B or C; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; D is carboxyl, C1alkoxy carbonyl or amino, and m is an integer of 1 to 12; and a linker of formula AAA, BBB, CCC or DDD; wherein each R and R' is independently selected from the group consisting of chlorine, bromine, iodine, C1-6alkylsulfonyl, C2-10cy cloalkylsulfonyl, C6-10arilsulfonyl; L is as disclosed above for formulas A, B or C; each p is independently an integer of 1 to 14; each q is independently an integer from 1 to 12; each AA is independently an amino acid; each r is 1 to 12; and D is carboxyl, C1alkoxy carbonyl or amino, provided the previous disclosure of Smith, wherein a range of appropriate linker structures and functionalities would have been useful for producing an antibody-cytotoxin conjugates having different specific attachment points to the antibody, and attachment chemistries, for enabling the identification of conjugates having desirable pharmacological activity and dose-response properties.

Since none of the special technical features of the inventions of Groups I-1 is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by a combination of the Lippincott, Ellman and Smith references, unity of invention is lacking.

Form PCT/ISA/210 (extra sheet) (July 2009)