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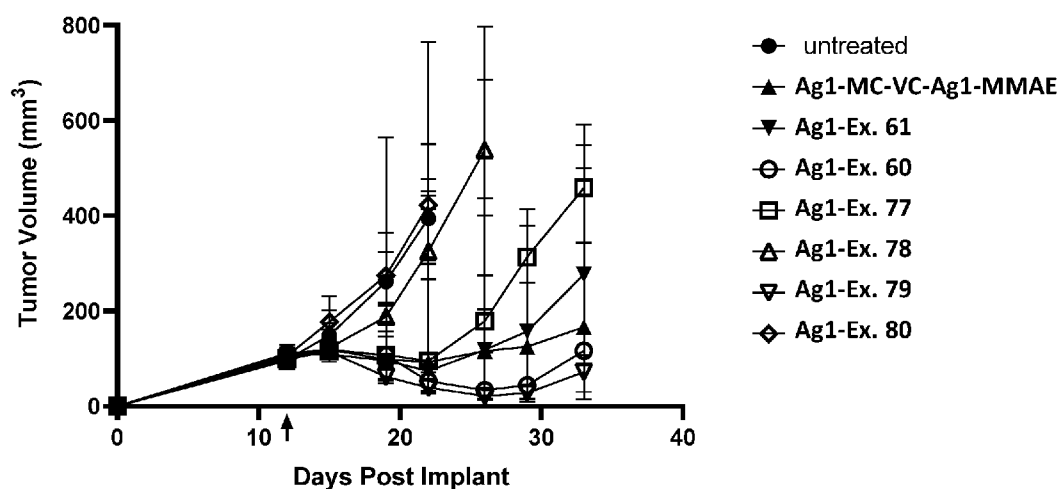
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(54) Title: CYTOTOXIC COMPOUNDS AND CONJUGATES THEREOF

Ag1 ADC efficacy in the A2058 melanoma xenograft model

FIG. 1



(57) Abstract: Hydrophilic auristatin compounds are described, including Drug-Linker compounds, Ligand-Drug Conjugate compounds, methods of use, and preparations thereof.



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))*
- *with sequence listing part of description (Rule 5.2(a))*

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/72120

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/40, A61K 31/395, A61K 31/16 (2023.01)

ADD. A61K 31/33 (2023.01)

CPC - INV. A61K 31/40, A61K 31/395, A61K 31/16

ADD. A61K 31/33

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)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
--	--first species--	-----
A	WO 2015/183978 A1 (AGENSYS, INC.) 3 December 2015 (03.12.2015), especially: abstract; para [0001]; para [0006] para [0170], Example 14, formula; (para [0253] Example 47, formula), but Agensys-978	1, 3, 5
A	US 2017/0190735 A1 (AGENSYS, INC.) 6 July 2017 (06.07.2017), especially: abstract; para [0007]; para [0322] formula; para [0329] Example 15, formula.	1, 3, 5
A	SATOMAA et al. "Hydrophilic Auristatin Glycoside Payload Enables Improved Antibody-Drug Conjugate Efficacy and Biocompatibility", Antibodies. 2018. 7, 15, 13 pages, especially: pg 2, Figure 1.	1, 3, 5
A	AKAIWA et al. "Antibody-Drug Conjugate Payloads; Study of Auristatin Derivatives", Chem. Pharm. Bull. 2020. 68, pp 201-211, entire document.	1, 3, 5
--	--second species--	-----
A	WO 2015/183978 A1 (AGENSYS, INC.) 3 December 2015 (03.12.2015), especially: abstract; para [0001]; para [0006] para [0170], Example 14, formula; (para [0253] Example 47, formula), but Agensys-978	1, 3, 5, 35-36



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"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

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/72120

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/0190735 A1 (AGENSYS, INC.) 6 July 2017 (06.07.2017), especially: abstract; para [0007]; para [0322] formula; para [0329] Example 15, formula.	1, 3, 5, 35-36
A	SATOMAA et al. "Hydrophilic Auristatin Glycoside Payload Enables Improved Antibody-Drug Conjugate Efficacy and Biocompatibility", Antibodies. 2018. 7, 15, 13 pages, especially: pg 2, Figure 1.	1, 3, 5, 35-36
A	AKAIWA et al. "Antibody-Drug Conjugate Payloads; Study of Auristatin Derivatives", Chem. Pharm. Bull. 2020. 68, pp 201-211, entire document.	1, 3, 5, 35-36

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/72120

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/72120

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.: 7-34, 42-65, 71-103, 107-117
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 extra 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.:
1, 3, 5, 35-36
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 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/US 23/72120

--Box III - Lack of Unity--

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 searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-6, 35-41, 66-70, 104-106 and 118-119, directed to a compound of Formula (I); or a salt thereof; a compound of Formula (II); or a salt thereof; a Drug-Linker compound of the following formula: listed in claim 37, or a salt thereof; a Ligand-Drug Conjugate compound of the formula: listed in claim 66, or a pharmaceutically acceptable salt thereof; a compound, wherein the compound is selected from the group consisting of the compounds listed in Table 1 or a salt thereof; a Drug-Linker compound, wherein the Drug-Linker compound is selected from the group consisting of the compounds listed in Table 2 or a salt thereof; or a Ligand-Drug Conjugate compound, wherein the Ligand-Drug Conjugate compound is selected from the group consisting of the compounds listed in Table 3, or a salt thereof, and p is an integer ranging from 1 to 12, or a Ligand-Drug Conjugate of the following formula: listed in claim 118. The compound of Formula (I) will be searched to the extent that it encompasses the first species of claim 1, wherein Xb is -NR1R2; Xa is the substructure listed in claim 1; R1 and R2 are H; R3 and R4 are H; R10 is H; X is OH; R6 is unsubstituted C1 alkyl; R7 is H; E is phenyl; R8 is H; R9 is H; n is 0; and q is 0, wherein when X is H, at least two of R7, R8, R9, and R11 comprise an OH moiety. It is believed that claims 1, 3 and 5 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of Formula (I), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. 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. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein Xb is -NR1R2; Xa is the substructure listed in claim 1; R1 is C1 alkyl and R2 are H; R3 and R4 are H; R10 is H; X is OH; R6 is unsubstituted C1 alkyl; R7 is H; E is phenyl; R8 is H; R9 is H; n is 0; and q is 0, wherein when X is H, at least two of R7, R8, R9, and R11 comprise an OH moiety (i.e. claims 1, 3 and 5).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of Formula (I), which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of Formula (I).

These shared technical features, however, do not provide a contribution over the prior art, as being obvious over WO 2015/183978 A1 to Agensys Inc (hereinafter 'Agensys-978') in view of US 2017/0190735 A1 to Agensys Inc (hereinafter 'Agensys-735').

Agensys teaches a compound of Formula (I): wherein Xb is -NR1R2; Xa is the substructure listed in claim 1; R1 and R2 are C1 alkyl; R3 and R4 are C1 alkyl; R10 is H; X is H; R6 is C2 alkyl substituted with OH; R7 is unsubstituted C1 alkyl; E is phenyl; R8 is OH; R9 is H; n is 0; and q is 0 (para [0253] Example 47, formula), but Agensys doesn't teach wherein when X is H, at least two of R7, R8, R9, and R11 comprise an OH moiety. However, Agensys-735 teaches a highly similar compound wherein X is OH (para [0322] formula) and it would have been obvious to a person having ordinary skill in the art to combine Agensys-735 with Agensys-978 because Agensys-735 (abstract, Provided are peptide analogs, pharmaceutical compositions comprising such compounds, and methods of treating cancer with such compounds; see also para [0322] formula) and Agensys-978 (abstract, Provided are peptide analogs, pharmaceutical compositions comprising such compounds, and methods of treating cancer with such compounds; see also para [0253] Example 47, formula) teach highly similar peptide analogs that are used to treat cancer, and Agensys-978 further teaches that there is a need for new analogs (para [0006] Despite significant advances, there remains a need for new anticancer therapeutics with desirable pharmaceutical properties; see also para [0001] Provided herein are dolaproine-dolaisoleuine peptide analogs, pharmaceutical compositions comprising such compounds, and methods of treating cancer with such) and Agensys-735 further teaches new analogs (para [0007] Provided herein are novel dolaproine-dolaisoleuine peptide analogs. Thus, provided herein are compounds of Formula (I)) and the high similarity between the compounds suggests similar activity, and preparing the derivative of the compound of Agensys-978 wherein X is OH could lead to a compound with enhanced activity. Thus it would have been obvious to prepare the compound that meets the provision wherein when X is H, at least two of R7, R8, R9, and R11 comprise an OH moiety in order to identify a more effective compound.

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Item 4 Cont.: Claims 7-34, 42-65, 71-103 and 107-117 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are therefore, not included in the above analysis.

Note: Applicant states for second elected species that claims encompassed are: 3, 5, 7-10, 14-15, 17, 19-20, 22-23, 28, 30-31, 33 and 35-36. However, claims 7-10, 14-15, 17, 19-20, 22-23, 28, 30-31 and 33 are unsearchable.