

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

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Date of mailing
(day/month/year)

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Applicant's or agent's file reference
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FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 23/72120

International filing date (day/month/year)

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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

Applicant SEAGEN INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
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Facsimile No. 571-273-8300

Date of completion of this opinion

9 January 2024 (09.01.2024)

Authorized officer

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**WRITTEN OPINION OF THE
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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established 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.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 7-34, 42-65, 71-103, 107-117

because:

- ☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 7-34, 42-65, 71-103, 107-117 are so unclear that no meaningful opinion could be formed (*specify*):

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).

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☒ no international search report has been established for said claims Nos. 7-34, 42-65, 71-103, 107-117

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

- ☐ See Supplemental Box for further details.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☒ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

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').

--continued in first Supplemental Box--

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1, 3, 5, 35-36

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	see below	YES
	Claims	see below	NO
Inventive step (IS)	Claims	see below	YES
	Claims	see below	NO
Industrial applicability (IA)	Claims	1,3,5,35-36	YES
	Claims	None	NO

2. Citations and explanations:

--first species--

Novelty - Yes: 1, 3, 5
No: None

Inventive Step - Yes: 1, 3, 5
No: None

--second species--

Novelty - Yes: 1, 3, 5, 35-36
No: None

Inventive Step - Yes: 1, 3, 5, 35-36
No: None

--first species--

Claims 1, 3 and 5 meet the criteria set out under PCT Article 33(2)-(3) because the prior art doesn't teach or fairly suggest the claimed invention.

Regarding claim 1, WO 2015/183978 A1 to Agensys, Inc. (hereinafter 'Agensys-978') teaches a compound of Formula (I); wherein Xb is -NR1R2; Xa is the substructure listed in claim 1; R3 and R4 are H; R10 is H; X is OH; 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 (para [0170], Example 14, formula), but Agensys-978 doesn't teach wherein R1 and R2 are H (Agensys-978 teaches C1 alkyl instead); R6 is unsubstituted C1 alkyl (Agensys-978 teaches C3 alkyl instead); and R7 is H (Agensys-978 teaches a carboxylic acid moiety instead).

US 2017/0190735 A1 to Agensys, Inc. (hereinafter 'Agensys-735') teaches a compound of Formula (I); wherein Xb is -NR1R2; Xa is the substructure listed in claim 1; R3 and R4 are H; R10 is H; X is OH; 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 (para [0329] Example 15, formula), but Agensys-735 doesn't teach wherein R1 and R2 are H (Agensys-735 teaches C1 alkyl instead); R6 is unsubstituted C1 alkyl (Agensys-735 teaches C3 alkyl instead); and R7 is H (Agensys-735 teaches a carboxylic acid moiety instead).

The article entitled "Hydrophilic Auristatin Glycoside Payload Enables Improved Antibody-Drug Conjugate Efficacy and Biocompatibility" by Satomaa et al. (hereinafter 'Satomaa') teaches a compound that is similar to Formula (I) wherein Xb is -NR1R2; Xa is the substructure listed in claim 1; R1 is H; R3 is H; R10 is H; E is phenyl; R9 is H; n is 0; and q is 0 (pg 2, Figure 1. Structures of the payloads and linkers in the present study... (b) MMAE, monomethylauristatin E), but Satomaa doesn't teach wherein R2 is H (Satomaa teaches C1 alkyl instead); R4 is H (Satomaa teaches C1 alkyl instead) X is OH (Satomaa teaches H instead), thus Satomaa doesn't teach wherein when X is H, at least two of R7, R8, R9, and R11 comprise an OH moiety. Satomaa also doesn't teach wherein R6 is unsubstituted C1 alkyl (Satomaa teaches C3 alkyl instead); R7 is H (Satomaa teaches C1 alkyl instead); R8 is H (Satomaa teaches OH instead). Therefore the prior art doesn't teach or fairly suggest the claimed invention.

Regarding claims 3 and 5, these claims are dependent on claim 1, thus these claims also meet the criteria set out under PCT Article 33(2)-(3).

--second species--

Claims 1, 3, 5 and 35-36 meet the criteria set out under PCT Article 33(2)-(3) because the prior art doesn't teach or fairly suggest the claimed invention.

--continued in first Supplemental Box--

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--Box IV - Lack of Unity--

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.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

--Box V.2 - Citations and Explanations--

Regarding claim 1, Agensys-978 teaches a compound of Formula (I): wherein Xb is -NR₁R₂; R₁ and R₂ are C₁ alkyl; Xa is the substructure listed in claim 1; R₃ and R₄ are H; R₁₀ is H; X is OH; R₆ is unsubstituted C₃ alkyl; R₇ is C₁ alkyl substituted with one OH moiety; 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 (para [0170], Example 14, formula), but Agensys-978 teaches an additional oxo substituent on R₇ that is not present in the claimed compound. It would not have been obvious to prepare the derivative of the compound of Agensys-978 wherein the oxo group is not present because there is no motivation for preparing this compound.

Agensys-735 teaches a compound of Formula (I): wherein Xb is -NR₁R₂; R₁ and R₂ are C₁ alkyl; Xa is the substructure listed in claim 1; R₃ and R₄ are H; R₁₀ is H; X is OH; R₆ is unsubstituted C₃ alkyl; R₇ is C₁ alkyl substituted with one OH moiety; 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 (para [0329] Example 15, formula), but Agensys-735 teaches an additional oxo substituent on R₇ that is not present in the claimed compound. It would not have been obvious to prepare the derivative of the compound of Agensys-735 wherein the oxo group is not present because there is no motivation for preparing this compound.

Satoma teaches a compound that is similar to Formula (I) wherein Xb is -NR₁R₂; Xa is the substructure listed in claim 1; R₁ is C₁ alkyl; R₃ is H; R₁₀ is H; R₆ is unsubstituted C₃ alkyl; E is phenyl; R₉ is H; n is 0; and q is 0 (pg 2, Figure 1. Structures of the payloads and linkers in the present study... (b) MMAE, monomethylauristatin E), but Satoma doesn't teach wherein R₂ is C₁ alkyl (Satoma teaches H instead); R₄ is H (Satoma teaches C₁ alkyl instead) X is OH (Satoma teaches H instead), thus Satoma doesn't teach wherein when X is H, at least two of R₇, R₈, R₉, and R₁₁ comprise an OH moiety. Satoma also doesn't teach wherein R₈ is H (Satoma teaches OH instead). Therefore the prior art doesn't teach or fairly suggest the claimed invention.

Regarding claims 3, 5 and 35-36 these claims are dependent on claim 1, thus these claims also meet the criteria set out under PCT Article 33(2)-(3).

Claims 1, 3, 5 and 35-36 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.