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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, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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))*

(88) Date of publication of the international search report:
13 August 2020 (13.08.2020)

(54) Title: TRACELESS LINKERS AND PROTEIN-CONJUGATES THEREOF

(57) Abstract: Provided herein are compounds, compounds including traceless linkers, protein conjugates thereof, and compositions thereof. Also provided herein are methods for the treatment of diseases, disorders, and conditions, and/or the management of the symptoms thereof, associated with inflammatory diseases and autoimmune disorders further associated with the glucocorticoid receptor, glucocorticoid binding, and/or glucocorticoid receptor signalling, including administration of the compounds or payloads via traceless linker-payloads, and protein conjugates thereof.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/012798

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/68 A61K47/65 A61K47/61 C07J41/00 C07J43/00
C07J71/00 C08B37/16
ADD.
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 C07J C08B

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)
EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/155998 A1 (DAIICHI SANKYO CO LTD [JP]) 15 October 2015 (2015-10-15) page 156 - page 166; examples 12-16d claims ----- -/--	1-7, 10-16, 19-22, 25-27, 32, 123-131, 133-136

[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 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	Date of mailing of the international search report
2 July 2020	13/07/2020

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, Fax: (+31-70) 340-3016	Dullaart, Anwyn

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAJAJ S ET AL: "Topochemical model for prediction of anti-HIV activity of HEPT analogs", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 15, no. 2, 17 January 2005 (2005-01-17), pages 467-469, XP027800977, ISSN: 0960-894X [retrieved on 2005-01-17] abstract page 468	1-7, 10-16, 19-22, 25-27, 32, 123-131, 133-136
X	FRANZ EFFENBERGER ET AL: "Trifluormethansulfonate von [alpha]-Hydroxycarbonsäureestern - Edukte zur racemisierungsfreien Synthese N-substituierter [alpha]-Aminosäuren", ANGEWANDTE CHEMIE, vol. 95, no. 1, 1 January 1983 (1983-01-01), pages 50-50, XP055685197, ISSN: 0044-8249, DOI: 10.1002/ange.19830950111 abstract page 50; table 1	1-7, 10-16, 19-22, 25-27, 32, 123-131, 133-136
X	CHO ET AL: "The first preparation of alpha-functionalized benzylamine", TETRAHEDRON LETTERS, vol. 40, no. 47, 19 November 1999 (1999-11-19), pages 8215-8217, XP005024955, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(99)01713-X page 8215; figure 1; compound 1	1-7, 10-16, 19-22, 25-27, 32, 123-131, 133-136
X	SAMANT ET AL: "Synthesis of 3-hydroxypyrid-2-ones from furfural for treatment against iron overload and iron deficiency", EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 9, 1 September 2008 (2008-09-01), pages 1978-1982, XP025404797, ISSN: 0223-5234, DOI: 10.1016/J.EJMECH.2007.11.013 [retrieved on 2007-11-28] page 1980	1-7, 10-16, 19-22, 25-27, 32, 123-131, 133-136

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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	CN 108 853 514 A (SICHUAN BAILI PHARMACEUTICAL CO LTD) 23 November 2018 (2018-11-23)	90,94, 98-101, 103,117, 123,132
Y	page 15 page 19 examples	91-93, 95, 141-144

X	CN 109 106 951 A (SICHUAN BAILI PHARMACEUTICAL CO LTD) 1 January 2019 (2019-01-01)	90,94, 98-101, 103,117, 123,132
Y	page 28 claims	91-93, 95, 141-144

Y	JEFFREY C. KERN ET AL: "Novel Phosphate Modified Cathepsin B Linkers: Improving Aqueous Solubility and Enhancing Payload Scope of ADCs", BIOCONJUGATE CHEMISTRY, vol. 27, no. 9, 28 July 2016 (2016-07-28), pages 2081-2088, XP055557206, ISSN: 1043-1802, DOI: 10.1021/acs.bioconjchem.6b00337 abstract figures page 2085, right-hand column, paragraph Conclusions	90-92, 94-132, 141-144

Y	PIA SVENDSEN ET AL: "Antibody-Directed Glucocorticoid Targeting to CD163 in M2-type Macrophages Attenuates Fructose-Induced Liver Inflammatory Changes", MOLECULAR THERAPY - METHODS & CLINICAL DEVELOP, vol. 4, March 2017 (2017-03), pages 50-61, XP055578466, ISSN: 2329-0501, DOI: 10.1016/j.omtm.2016.11.004 abstract figures	90-92, 94-132, 141-144

Y	WO 2017/210471 A1 (ABBVIE INC [US]) 7 December 2017 (2017-12-07) examples	90-92, 94-132, 141-144

Y	US 2018/334426 A1 (HAN AMY [US] ET AL) 22 November 2018 (2018-11-22) examples	90,91, 93,94, 96-132, 141-144

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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.
Y	WO 2018/213077 A1 (REGENERON PHARMA [US]) 22 November 2018 (2018-11-22) examples	90-132, 141-144

Y	TUMEY L NATHAN ET AL: "ADME Considerations for the Development of Biopharmaceutical Conjugates Using Cleavable Linkers", CURRENT TOPICS IN MEDICINAL CHEMISTRY, vol. 17, no. 32, 2017, pages 3444-3462, XP009517545, ISSN: 1568-0266, DOI: 10.2174/1568026618666180118154017 the whole document	90-132, 141-144

Y	Simone Jeger: "Site-specific conjugation of tumour-targeting, antibodies using transglutaminase", Ph.D. thesis , 2009, XP055208841, ETH Zürich, CH DOI: 10.3929/ethz-a-005963273 Retrieved from the Internet: URL:http://dx.doi.org/10.3929/ethz-a-005963273 page 41 - page 46	90-132, 141-144

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/012798

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.:

1-7, 10-16, 19-22, 25-27, 32, 90-131, 133-136(all partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-7, 10-16, 19-22, 25-27, 32, 123-131, 133-136(all partially)

   Compound as defined in these claims, i.e., without moiety L and without binding agent BA, and its use in medical treatment, wherein D* is acyl

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2. claims: 9, 18, 24, 29-31, 34(completely); 1-8, 10-17, 19-23, 25-28, 32, 33, 123-131, 133-136(partially)

   Compound as defined in these claims, i.e., without moiety L and without binding agent BA, and its use in medical treatment, wherein D* is the residue of a biologically active agent, more specifically a steroid

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3. claims: 1-8, 10-17, 19-23, 25-28, 32, 33, 123-131, 133-136(all partially)

   Compound as defined in these claims, i.e., without moiety L and without binding agent BA, and its use in medical treatment, wherein D* is the residue of a biologically active agent, more specifically an LXR agonist

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4. claims: 35, 39-51, 54, 57, 60, 63, 67, 70, 73, 76, 79, 123-131, 137-140(all partially)

   Compound as defined in these claims, i.e., with moiety L, but without binding agent BA, and its use in medical treatment, wherein D* is acyl

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5. claims: 37, 53, 59, 62, 65, 66, 69, 75, 78, 81, 84-89(completely); 35, 36, 39-52, 54-58, 60, 61, 63, 64, 67, 68, 70-74, 76, 77, 79, 80, 82, 83, 123-131, 137-140(partially)

   Compound as defined in these claims, i.e., with moiety L, but without binding agent BA, and its use in medical treatment, wherein D* is the residue of a biologically active compound, more specifically of an anti-inflammatory biologically active compound, more specifically a steroid

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6. claims: 38(completely); 35, 36, 39-52, 54-58, 60, 61, 63, 64, 67, 68, 70-74, 76, 77, 79, 80, 82, 83, 137-140(partially)

   Compound as defined in these claims, i.e., with moiety L, but without binding agent BA, and its use in medical

treatment, wherein D* is the residue of a biologically active compound, more specifically of an anti-inflammatory biologically active compound, more specifically an LXR agonist

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7. claims: 92, 95(completely); 90, 91, 94, 96-132, 141-144(partially)

Compound as defined in these claims, i.e., with moiety L and with binding agent BA, and its use in medical treatment, wherein D* is the residue of a biologically active compound, more specifically of an anti-inflammatory compound, more specifically of a steroid

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8. claims: 93(completely); 90, 91, 94, 96-132, 141-144(partially)

Compound as defined in these claims, i.e., with moiety L and with binding agent BA, and its use in medical treatment, wherein D* is the residue of a biologically active compound, more specifically of an anti-inflammatory compound, more specifically of an LXR agonist

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9. claims: 115, 116(partially)

Compound as defined in these claims, i.e., without moiety L, but with binding agent BA (i.e., the result of binding a compound as defined in claim 5 with an antibody), and its use in medical treatment

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2020/012798

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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