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 C07H 19/20 (2006.01) A61K 31/7125 (2006.01)  
 C07H 19/23 (2006.01) A61K 31/713 (2006.01)  
 A61P 31/20 (2006.01) A61P 35/00 (2006.01)

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English

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(74) Agent: **SCHORR, Kristel et al.**; 3000 K Street, N.W., Suite 600, Washington, District of Columbia 20007-5109 (US).

(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, 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.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

## Published:

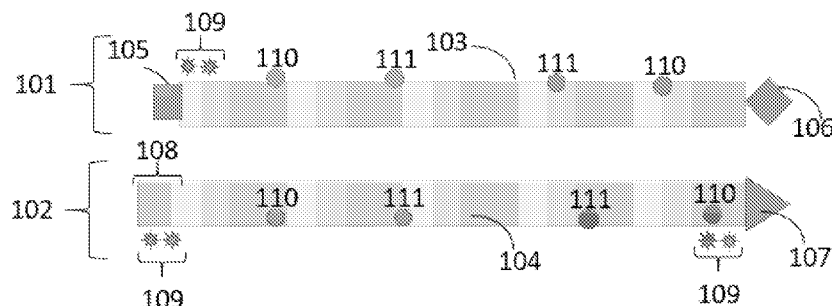
- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

## (88) Date of publication of the international search report:

20 July 2023 (20.07.2023)

(54) Title: MODIFIED SHORT INTERFERING NUCLEIC ACID (SINA) MOLECULES AND USES THEREOF

FIG. 1



(57) Abstract: Described are short interfering nucleic acid (siNA) molecules comprising modified nucleotides, compositions, and methods and uses thereof.



## INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2022/042808

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                  |                                                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                  |                                                    |
| INV.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | C07H21/02                                                                                                                                                                                                                                                                                                        | C07H19/10                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | A61K31/7115                                                                                                                                                                                                                                                                                                      | A61K31/712                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                  | A61K31/7125                                        |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                  | A61K31/713                                         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                  | A61P31/20                                          |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                  | A61P35/00                                          |
| <b>ADD.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                  |                                                    |
| According to International Patent Classification (IPC) or to both national classification and IPC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                  |                                                    |
| <b>B. FIELDS SEARCHED</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                  |                                                    |
| Minimum documentation searched (classification system followed by classification symbols)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                  |                                                    |
| <b>A61P A61K C07H</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                  |                                                    |
| 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)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                  |                                                    |
| <b>EPO-Internal, WPI Data, CHEM ABS Data</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                  |                                                    |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                  |                                                    |
| Category*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                               | Relevant to claim No.                              |
| <b>A</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>HU BO ET AL: "Therapeutic siRNA: state of the art",<br/>SIGNAL TRANSDUCTION AND TARGETED THERAPY,<br/>vol. 5, no. 1,<br/>1 December 2020 (2020-12-01), XP055801687,<br/>DOI: 10.1038/s41392-020-0207-x<br/>Retrieved from the Internet:<br/>URL:https://www.nature.com/articles/s41392-020-0207-x.pdf&gt;</b> | <b>1,2,9,<br/>11,<br/>13-29,<br/>31-75</b>         |
| <b>A</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>CHERNIKOV IVAN V. ET AL: "Current Development of siRNA Bioconjugates: From Research to the Clinic",<br/>FRONTIERS IN PHARMACOLOGY,<br/>vol. 10, 26 April 2019 (2019-04-26),<br/>XP055916231,<br/>DOI: 10.3389/fphar.2019.00444<br/>cited in the application</b>                                               | <b>1,2,9,<br/>11,<br/>13-29,<br/>31-75</b>         |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | -----<br>-/--                                                                                                                                                                                                                                                                                                    |                                                    |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                  |                                                    |
| * Special categories of cited documents :<br>"A" document defining the general state of the art which is not considered to be of particular relevance<br>"E" earlier application or patent but published on or after the international filing date<br>"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)<br>"O" document referring to an oral disclosure, use, exhibition or other means<br>"P" document published prior to the international filing date but later than the priority date claimed<br>"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<br>"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<br>"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<br>"&" document member of the same patent family |                                                                                                                                                                                                                                                                                                                  |                                                    |
| Date of the actual completion of the international search                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                  | Date of mailing of the international search report |
| <b>31 March 2023</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                  | <b>09/06/2023</b>                                  |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                  | Authorized officer<br><br><b>Klein, Didier</b>     |

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2022/042808

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                             |                                    |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                          | Relevant to claim No.              |
| A                                                    | WO 2018/045317 A1 (DICERNA PHARMACEUTICALS INC [US]) 8 March 2018 (2018-03-08)<br>cited in the application<br><br>-----                                                                                                                                                     | 1, 2, 9,<br>11,<br>13-29,<br>31-75 |
| A                                                    | WO 2011/139699 A2 (ISIS PHARMACEUTICALS INC [US]; PRAKASH THAZHA P [US] ET AL.)<br>10 November 2011 (2011-11-10)<br><br>-----                                                                                                                                               | 1, 2, 9,<br>11,<br>13-29,<br>31-75 |
| A                                                    | ELAD ELKAYAM ET AL: "Current Development of siRNA Bioconjugates: From Research to the Clinic",<br>NUCLEIC ACIDS RESEARCH,<br>vol. 45, no. 6,<br>28 November 2016 (2016-11-28), pages<br>3528-3536, XP055448298,<br>GB<br>ISSN: 0305-1048, DOI: 10.1093/nar/gkw1171<br>----- | 1, 2, 9,<br>11,<br>13-29,<br>31-75 |
| A                                                    | WO 2019/217397 A2 (ALNYLAM PHARMACEUTICALS INC [US]; PARMAR RUBINA G [US] ET AL.)<br>14 November 2019 (2019-11-14)<br><br>-----                                                                                                                                             | 1, 2, 9,<br>11,<br>13-29,<br>31-75 |

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/042808

### 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 13*ter*.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/US2022/042808**

## 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.:
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.:  
**1, 2 (completely); 9, 11, 13-29, 31-75 (partially)**

### 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, 2(completely); 9, 11, 13-29, 31-75(partially)

a compound of formula of claim 1 and oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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2. claims: 3(completely); 9, 11, 13-29, 31-75(partially)

a compound of formula of claim 3 and oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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3. claims: 4, 5, 7, 8(completely); 9-29, 31-75(partially)

a compound of claim 4 and 7, oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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4. claims: 6, 10, 12-29, 31-75(all partially)

a compound of claim 6 (compounds bearing a 3' O-alkyl phosphonate group), oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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5. claims: 6, 10, 12-29, 31-75(all partially)

a compound of claim 6 (compounds bearing a 2' O-CD<sub>3</sub> moiety), oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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6. claims: 6, 10, 12-29, 31-75(all partially)

a compound of claim 6 (compounds with no 2'-3' covalent bond) and a 4'-phosphonate-vinyl moiety, oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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7. claims: 6, 10, 12-29, 31-75(all partially)

a compound of claim 6 (compounds with no 2'-3' covalent bond) and a 4'-phosphonate-methyloxy moiety, oligonucleotides comprising said compound and dependent claims, composition and uses thereof

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8. claims: 30(completely); 31-75(partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A compound of claim 30 bearing a mesylphosphoramidate  
internucleoside linkage and dependent claims, composition  
and uses thereof

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2022/042808

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| WO 2018045317 A1                          | 08-03-2018          | AU 2017321892 A1           | 28-02-2019          |
|                                           |                     | CA 3033756 A1              | 08-03-2018          |
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|                                           |                     | JP 2019530656 A            | 24-10-2019          |
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| WO 2011139699 A2                          | 10-11-2011          | EP 2625186 A2              | 14-08-2013          |
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|                                           |                     | US 2016046939 A1           | 18-02-2016          |
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| WO 2019217397 A2                          | 14-11-2019          | EP 3790557 A2              | 17-03-2021          |
|                                           |                     | US 2021238594 A1           | 05-08-2021          |
|                                           |                     | WO 2019217397 A2           | 14-11-2019          |