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(54) Title: TARGETED COMPOSITIONS

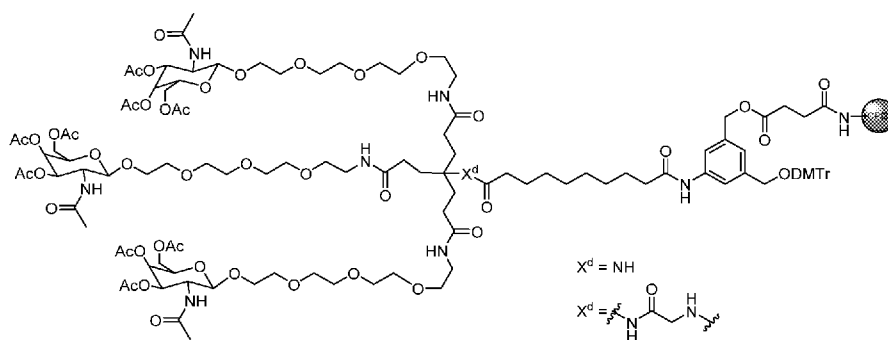


Figure 1: Intermediate compound of formula Ie, wherein a targeting ligand/linker is bound to a solid phase support, and wherein Pg¹ is the protecting group DMTr.

(57) Abstract: The invention provides certain nucleic acids (e.g., double stranded siRNA molecules), as well as conjugates that comprise a targeting moiety, a double stranded siRNA, and optional linking groups. Certain embodiments also provide synthetic methods useful for preparing the conjugates. The conjugates are useful to target therapeutic double stranded siRNA to the liver and to treat liver diseases including hepatitis (e.g. hepatitis B and hepatitis D).



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))*

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22 November 2018 (22.11.2018)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/026918

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C12N15/113 A61K48/00
 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)
 C12N A61K
 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, WPI Data, EMBL, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/077349 A1 (ALNYLAM PHARMACEUTICALS INC [US]) 19 May 2016 (2016-05-19) Whole document, especially Seq ID No 1702, 1793, 1750 table 25.	1-195
A	WO 03/070918 A2 (RIBOZYME PHARM INC [US]; MCSWIGGEN JAMES [US]; BEIGELMAN LEONID [US];) 28 August 2003 (2003-08-28) Whole document, especially Seq ID No 462. ----- -/--	1-195

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
- "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 20 September 2018	Date of mailing of the international search report 08/10/2018
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Kools, Patrick

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/026918

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JAYAPRAKASH K. NAIR ET AL: "Multivalent N-Acetylgalactosamine-Conjugated siRNA Localizes in Hepatocytes and Elicits Robust RNAi-Mediated Gene Silencing", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 136, no. 49, 10 December 2014 (2014-12-10), pages 16958-16961, XP055181463, ISSN: 0002-7863, DOI: 10.1021/ja505986a the whole document	1-195
A	----- YUANYU HUANG: "Preclinical and Clinical Advances of GalNAc-Decorated Nucleic Acid Therapeutics", MOLECULAR THERAPY - NUCLEIC ACIDS, vol. 6, 1 March 2017 (2017-03-01), pages 116-132, XP055485332, GB ISSN: 2162-2531, DOI: 10.1016/j.omtn.2016.12.003 the whole document	1-195
A	----- TRACY S. ZIMMERMANN ET AL: "Clinical Proof of Concept for a Novel Hepatocyte-Targeting GalNAc-siRNA Conjugate", MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY, vol. 25, no. 1, 1 January 2017 (2017-01-01), pages 71-78, XP055448300, US ISSN: 1525-0016, DOI: 10.1016/j.ymthe.2016.10.019 the whole document	1-195
A	----- DATABASE Geneseq [Online] 30 March 2017 (2017-03-30), "Hepatitis B virus mRNA-targeted antisense oligonucleotide, SEQ 1309.", XP002784935, retrieved from EBI accession no. GSN:BEP71596 Database accession no. BEP71596 sequence ----- -/--	1-195

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/026918

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE Geneseq [Online]</p> <p>30 June 2016 (2016-06-30), "Hepatitis B virus X ORF targeted siRNA sense strand, SEQ ID 1793.", XP002784936, retrieved from EBI accession no. GSN:BDA34147 Database accession no. BDA34147 the whole document -----</p>	1-195

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/026918

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:
- in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
- b. furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. furnished subsequent to the international filing date for the purposes of international search only:
- in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/026918

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.:

1-195(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: 1-165, 174-195(all partially)

A nucleic acid molecule with Seq ID No 1. A double stranded siRNA comprising said nucleic acid and the complementary nucleic acid with Seq ID No 2. Said siRNAs having further chemical modifications at one position. Pharmaceutical compositions comprising said molecules. Methods of delivering the modified molecules to a liver. Medical use of the compounds.

2. claims: 1-165, 174-195(all partially)

As for subject 1 but now for sequence with Seq ID No 3 and the complementary sequence with Seq ID No 4.

3. claims: 166, 168, 170, 172(completely); 1-165, 174-195(partially)

As for subject 1 but now for sequence with Seq ID No 5 and the complementary sequence with Seq ID No 6.

4-24. claims: 1-165, 174-195(all partially)

As for subject 1 but now for sequences with Seq ID No 7-47 and the complementary sequences with Seq ID No 8-48.

25. claims: 167, 169, 171, 173(completely); 1-165, 174-195(partially)

As for subject 1 but now for sequence with Seq ID No 49 and the complementary sequence with Seq ID No 50.

26-37. claims: 1-165, 174-195(all partially)

As for subject 1 but now for sequences with Seq ID No 51-73 and the complementary sequences with Seq ID No 52-74.

38. claims: 174-186(partially)

Compounds having a certain formula I, Ia, XX, or specific structure or salts thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/026918

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016077349	A1	19-05-2016	
		AU 2015346513	A1 08-06-2017
		AU 2015346566	A1 08-06-2017
		BR 112017008868	A2 16-01-2018
		CA 2967408	A1 19-05-2016
		CN 108064293	A 22-05-2018
		CN 108064294	A 22-05-2018
		EA 201791014	A1 31-10-2017
		EP 3218487	A1 20-09-2017
		EP 3218489	A1 20-09-2017
		JP 2017534290	A 24-11-2017
		JP 2017538679	A 28-12-2017
		KR 20170077250	A 05-07-2017
		KR 20170077251	A 05-07-2017
		SG 11201703569X	A 30-05-2017
		SG 11201703638X	A 29-06-2017
		TW 201628659	A 16-08-2016
		TW 201631156	A 01-09-2016
		US 2017349900	A1 07-12-2017
		US 2017349901	A1 07-12-2017
		WO 2016077321	A1 19-05-2016
		WO 2016077349	A1 19-05-2016
WO 03070918	A2	28-08-2003	NONE