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(54) Title: COMPOUNDS FOR TARGETING DRUG DELIVERY AND ENHANCING SIRNA ACTIVITY

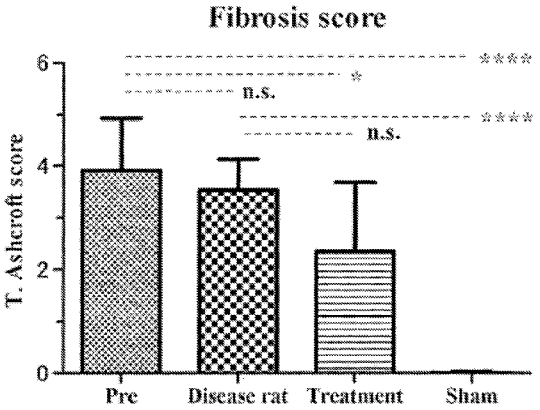
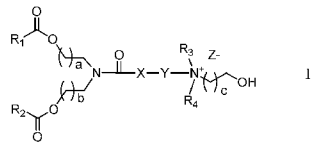


FIG. 7



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(57) Abstract: Here described are compounds of formula I: wherein R_1 and R_2 is independently selected from a group consisting of C_{10} to C_{18} alkyl, C_{12} to C_{18} alkenyl, and oleyl group; wherein R_3 and R_4 are independently selected from a group consisting of C_1 to C_6 alkyl, and C_2 to C_6 alkanol; wherein X is selected from a group consisting of $-CH_2-$, -S-, and -O- or absent; wherein Y is selected from $-(CH_2)n$, $-S(CH_2)_n$, $-O(CH_2)_n-$, thiophene, $-SO_2(CH_2)_n-$, and ester, wherein n = 1 -4; wherein a = 1 -4; wherein b=1 -4; wherein c=1-4; and wherein Z is a counterion; and compounds consisting of the structure $(\text{targeting molecule})_m$-linker-$(\text{targeting molecule})_n$, wherein the targeting molecule is a retinoid or a fat soluble vitamin having a specific receptor on the target cell; wherein m and n are independently 0, 1, 2 or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule, as well as compositions and pharmaceutical formulations including one or both of these compounds which are useful for the delivery of therapeutic agents; and methods of using these compositions and pharmaceutical formulations.

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

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Published:

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C237/08 A61K31/16 A61P1/16 C07C237/22 C07C323/60
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C A61K A61P

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/061880 A1 (CHUGAI PHARMACEUTICAL CO LTD [JP]; TOKYO METROPOLITAN ORG MED RES [JP]) 3 June 2010 (2010-06-03)	1-6,9-32
A	claims 3,4,18 abstract paragraph [0010] - paragraph [0011] -----	7,8
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HORIMOTO, HIKARI ET AL: "Liquid crystal compositions", XP002684897, retrieved from STN Database accession no. 1987:11469 abstract & JP 61 089286 A (TOKUYAMA SODA CO., LTD., JAPAN) 7 May 1986 (1986-05-07) ----- -/--	1

[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

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"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
18 January 2013	30/01/2013

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	Eberhard, Michael

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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	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HORIMOTO, HIKARI ET AL: "Liquid crystal compositions", XP002684898, retrieved from STN Database accession no. 1987:59428 abstract & JP 61 136584 A (TOKUYAMA SODA CO., LTD., JAPAN) 24 June 1986 (1986-06-24) -----	1
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAGAMI, TATSUAKI ET AL: "Effect of siRNA in PEG-coated siRNA -lipoplex on anti-PEG IgM production", XP002684899, retrieved from STN Database accession no. 2009:776119	51-55, 57-62, 64,65
A	abstract * CAS RN 182280-69-9 * -& TAGAMI T ET AL: "Effect of siRNA in PEG-coated siRNA-lipoplex on anti-PEG IgM production", JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 137, no. 3, 4 August 2009 (2009-08-04), pages 234-240, XP026223536, ISSN: 0168-3659, DOI: 10.1016/J.JCONREL.2009.04.006 [retrieved on 2009-04-08] compounds mPEG2000-DSPE -----	1-32
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 8 April 2011 (2011-04-08), HADA, MAGDOLNA ET AL: "The first synthesis of PEG-carotenoid conjugates", XP002690323, retrieved from STN Database accession no. 2011:648518 abstract & MAGDOLNA HDA ET AL: "The first synthesis of PEGcarotenoid conjugates", TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 52, no. 25, 8 April 2011 (2011-04-08), pages 3195-3197, XP028212363, ISSN: 0040-4039, DOI: 10.1016/J.TETLET.2011.04.039 [retrieved on 2011-04-15] -----	33-38, 41, 51-54,57
2	-/--	

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 2003, BENTLEY, MICHAEL DAVID ET AL: "Water-soluble polymer conjugates of retinoic acid", XP002690324, retrieved from STN Database accession no. 2003:356296 abstract & WO 03/037385 A1 (SHEARWATER CORP [US]; BENTLEY MICHAEL DAVID [US]; ZHAO XUAN [US]; LEAC) 8 May 2003 (2003-05-08) -----	33-38, 41, 51-54,57
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1999, SCHREIBER, JORG ET AL: "Disperse multiphase systems linked by covalent bonds into a network", XP002690325, retrieved from STN Database accession no. 1999:12437 abstract -----	33-38, 41-46, 51-54, 57-61
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1998, DIEC, KHIET HIEN ET AL: "Cosmetic or dermatological crosslinked microemulsions", XP002690326, retrieved from STN Database accession no. 1998:239092 abstract & DE 196 41 672 A1 (BEIERSDORF A.-G., GERMANY; DIEC, KHIET HIEN; MEIER, WOLFGANG; SCHREIBE) 16 April 1998 (1998-04-16) -----	33-38, 41-46, 51-54, 57-61
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1998, SCHREIBER, JOERG ET AL: "Crosslinked structures with double lipid membranes or based on peptides", XP002690327, retrieved from STN Database accession no. 1998:208404 abstract -/--	33-38, 41-46, 51-54, 57-61

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-& WO 98/13025 A1 (BEIERSDORF A.-G., GERMANY; SCHREIBER, JOERG; MEIER, WOLFGANG) 2 April 1998 (1998-04-02)	

X	MOON ET AL: "Regulation of adipocyte differentiation by PEGylated all-trans retinoic acid: reduced cytotoxicity and attenuated lipid accumulation", JOURNAL OF NUTRITIONAL BIOCHEMISTRY, BUTTERWORTH PUBLISHERS, STONEHAM, GB, vol. 18, no. 5, 19 April 2007 (2007-04-19) , pages 322-331, XP022035106, ISSN: 0955-2863, DOI: 10.1016/J.JNUTBIO.2006.06.004	41-46, 51-53, 55,57-61
A	compound (PRA) page 323, column 2, line 1 - page 324, column 1, line 2	33-40, 47-50

X	LI JING ET AL: "Synthesis of polyethylene glycol (PEG) derivatives and PEGylated-peptide biopolymer conjugates", BIOMACROMOLECULES, AMERICAN CHEMICAL SOCIETY; US, vol. 4, no. 4, 17 May 2003 (2003-05-17), pages 1055-1067, XP002328259, ISSN: 1525-7797, DOI: 10.1021/BM034069L figures 1-3 abstract	33,42, 51,57

X,P	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; NIITSU, YOSHIRO ET AL: "Retinoid-liposomes for enhancing modulation of human hsp47 expression for treatment of fibrosis", XP002690328, retrieved from STN Database accession no. 2012:1819002 abstract & WO 2012/170957 A2 (NITTO DENKO CORP [JP]; QUARK PHARMACEUTICALS INC [US]; NNTSU YOSHIRO [) 13 December 2012 (2012-12-13)	33-65

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/041753

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.:

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: 1-32

A compound of formula I; and a stellate-cell-specific drug carrier comprising a stellate cell specific amount of a retinoid molecule and a cationic lipid consisting of the compound according to claim 3.

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2. claims: 33-50

A compound for facilitating drug delivery to a target cell, consisting of the structure (targeting molecule)n -linker-(targeting molecule)n, wherein the targeting molecule is a retinoid or a fat soluble vitamin having a specific receptor on the target cell; wherein n=0, 1, 2 or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule; and a stellate-cell-specific drug carrier comprising a stellate cell specific amount of a retinoid molecule consisting of the structure (retinoid)m -linker-(retinoid)n; wherein m and n are independently 0, 1, 2, or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule.

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3. claims: 51-65

A compound for facilitating drug delivery to a target cell, consisting of the structure (lipid)m- linker-(targeting molecule)n , wherein the targeting molecule is a retinoid or a fat soluble vitamin having a specific receptor on the target cell; wherein m and n are independently 0, 1, 2, or 3; and wherein the linker comprises a polyethylene glycol (PEG) molecule; and a stellate-cell-specific drug carrier comprising a stellate cell specific amount of a targeting molecule consisting of the molecule (lipid)m- linker-(retinoid)n , wherein m and n are independently 0, 1, 2 or 3; and wherein the linker comprises a polyethylene glycol (PEG) or PEG-like molecule.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/041753

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010061880 A1	03-06-2010	CN 102292069 A	21-12-2011
		KR 20110112305 A	12-10-2011
		WO 2010061880 A1	03-06-2010
WO 9813025 A1	02-04-1998	DE 19640092 A1	16-04-1998
		EP 0928188 A1	14-07-1999
		JP 2001500886 A	23-01-2001
		WO 9813025 A1	02-04-1998