

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 November 2007 (22.11.2007)

PCT

(10) International Publication Number
WO 2007/134014 A3

(51) International Patent Classification:

A61K 31/70 (2006.01) C12N 5/00 (2006.01)
C07H 21/02 (2006.01) C12Q 1/68 (2006.01)
C07H 21/04 (2006.01)

[IN/US]; 896 Kestral Drive, San Marcos, CA 92078 (US). **SIWKOWSKI, Andrew, M.** [US/US]; 7317-B Alicante Rd., Carlsbad, CA 92009 (US). **SWAYZE, Eric, E.** [US/US]; 7789 Palenque Street, Carlsbad, CA 92009 (US). **WANCEWICZ, Edward** [US/US]; 12326 Colony Dr., Poway, CA 92064 (US).

(21) International Application Number:

PCT/US2007/068412

(74) Agent: **KURLANDSKY, David, R;** Butzel Long, 350 S. Main Street, Ste. 300, Ann Arbor, MI 48140 (US).

(22) International Filing Date: 7 May 2007 (07.05.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/746,631 5 May 2006 (05.05.2006) US
60/747,059 11 May 2006 (11.05.2006) US
60/805,660 23 June 2006 (23.06.2006) US
60/864,554 6 November 2006 (06.11.2006) US
PCT/US2007/061183
27 January 2007 (27.01.2007) US

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(71) Applicant (*for all designated States except US*): **ISIS PHARMACEUTICALS, INC.** [US/US]; 1896 Rutherford Road, Carlsbad, CA 92009 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BHANOT, Sanjay** [CA/US]; 8094 Paseo Arrayan, Carlsbad, CA 92009 (US). **GEARY, Richard, S.** [US/US]; 3352 Avenida Nieve, Carlsbad, CA 92009 (US). **MCKAY, Robert** [US/US]; 12467 Golden Eye Lane, Poway, CA 92064 (US). **MONIA, Brett, P.** [US/US]; 2306 Casa Hermosa Court, Encinitas, CA 92024 (US). **SETH, Punit, P.**

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report:
9 April 2009

(54) Title: COMPOUNDS AND METHODS FOR MODULATING EXPRESSION OF GCGR

(57) Abstract: The present disclosure describes short antisense compounds, including such compounds comprising chemically-modified high-affinity monomers 8-16 monomers in length. Certain such short antisense compound are useful for the reduction of target nucleic acids and/or proteins in cells, tissues, and animals with increased potency and improved therapeutic index. Thus, provided herein are short antisense compounds comprising high-affinity nucleotide modifications useful for reducing a target RNA *in vivo*. Such short antisense compounds are effective at lower doses than previously described antisense compounds, allowing for a reduction in toxicity and cost of treatment. In addition, the described short antisense compounds have greater potential for oral dosing.



WO 2007/134014 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/68412

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8): A61K 31/70;C07H 21/02,21/04;C12N 5/00
C12Q 1/68

USPC: 514/44;536/24.1,24.5;435/6,375,377

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)

U.S. : 514/44; 536/24.1, 24.5; 435/6, 375, 377

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)

WEST, CAPLUS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 20040266714 A1 (FREIER et al) 30 December 2004 (30.12.2004, see entire document.	1-37 and 43-46
X	US 20050014713 A1 (FREIER) 20 January 2005 (20.01.2005), see entire document.	1-37 and 43-46
X,P	US 20070087987 A1 (MONIA et al) 19 April 2007 (19.04.2007), see entire document.	1-37 and 43-46
T	US 20070238688 A1 (BHANOT et al) 11 October 2007 (11.10.2007), see entire document.	1-37 and 43-46
T	US 20070238698 (BHANOT et al) 11 October 2007 (11.10.2007), see entire document.	1-37 and 43-46



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 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

10 April 2008 (10.04.2008)

Date of mailing of the international search report

24 APR 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Authorized officer

Sean R. McGarry

Telephone No. (571) 272 0763

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/68412

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.: 38-42 and 47-52
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:

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 additional fees, this Authority did not invite payment of any 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.