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61/465,847 25 March 2011 (25.03.2011) US
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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, 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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Declarations under Rule 4.17:

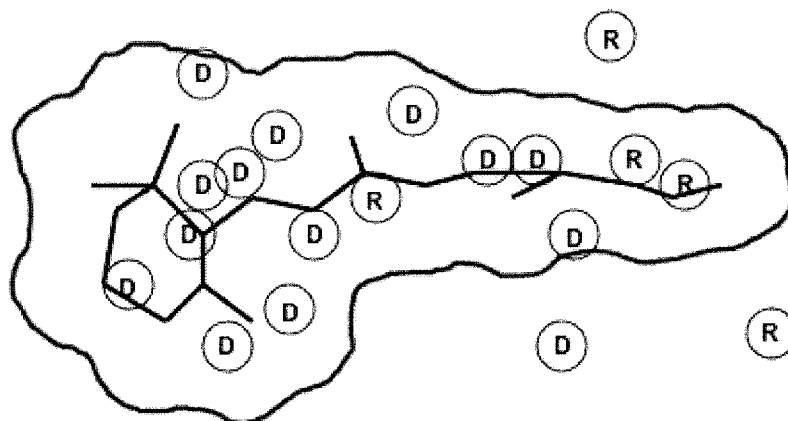
— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

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

1 May 2014

(54) **Title:** OPSIN-BINDING LIGANDS, COMPOSITIONS AND METHODS OF USE**Figure 1**

(57) **Abstract:** Compounds and compositions of said compounds along with methods of use of compounds are disclosed for treating ophthalmic conditions related to mislocalization of opsin proteins, the misfolding of mutant opsin proteins and the production of toxic visual cycle products that accumulate in the eye. Compounds and compositions useful in these methods, either alone or in combination with other therapeutic agents, are also described, along with methods of use.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/30229

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 27/00; A61K 31/015 (2012.01)

USPC - 514/763

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)

USPC - 514/763

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/765; 514/766 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: crystal structure, opsin, binding pocket, retinal binding site, rod cell, method, inhibiting, accumulation, visual cycle product, contacting, opsin protein, opsin-binding agent, A2E, lipofuscin, docking, retinal binding pocket, treating, retinitis pigmentosa, reduces hydration, hydrogen bonding. INTER

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----		1-7
Y	PubChem Public Chemical Database. CID 10081980, Create Date: 25 October, 2006 [http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=10081980]	13-26, 41-42 and 44
Y	WO 2008/013984 A2 (KAUSHAL et al.) 31 January 2008 (31.01.2008) pg 1, ln 20-23; pg 5, ln 30 - pg 6, ln 3; pg 6, ln 18 - pg 7, ln 12; pg 7, ln 14-20; pg 8, ln 1-3, 9-11; pg 18, ln 26 - pg 19, ln 24; pg 22, ln 5 - pg 23, ln 24; pg 23, ln 26 - pg 24, ln 6; pg 32, ln 3-22; pg 53, ln 3-21	13-26, 41-42 and 44
Y	WO 2010/147653 A1 (GARVEY et al.) 23 December 2010 (23.12.2010) pg 37, ln 22 - pg 38, ln 3; pg 39, ln 1 - pg 47, ln 6; pg 61, ln 6-9; pg 65, ln 12-16; pg 66, ln 4-7	13-26, 41-42 and 44
A/P	WO 2011/155983 A1 (GARVEY et al.) 15 December 2011 (15.12.2011) pg 6, ln 26- pg 83, ln 18	1-7, 13-26, 41-42 and 44

☐ Further documents are listed in the continuation of Box C.

* 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

30 August 2012 (30.08.2012)

Date of mailing of the international search report

01 OCT 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/30229

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 extra 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 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.:
Group I: represented by claims 1-7, 13-26, 41-42 and 44

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.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-7, 13-26, 41 (in part), 42, and 44 (in part), directed to compounds having the structure of Formula I: (as shown), and related methods of use, etc.

Group II: claims 8-12, 27-40, 41 (in part), 43, and 44 (in part), directed to compounds having the structure of Formula II: (as shown), and related methods of use, etc.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claims of the various groups I-II as defined above do not share any special technical feature that is an advance over the prior art.

PubChem Public Chemical Database, CID 10081980, Create Date: 25 October, 2006 (25.10.2006)

[<http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=10081980>] (hereinafter 'PC '980') discloses a compound: (4aR,9aS)-1,1,4a-trimethyl-3,4,9,9a-tetrahydro-2H-fluorene, having the structure of Formula I:

wherein x=-y is:

4) C(R4)-C(H)(R5)

T is:

1) CHRd,

R1 and R2 are independently:

2) -CH3

R3 is:

2) -CH3

R4 is:

1) hydrogen,

R5 is:

1) hydrogen,

A is:

1) phenyl

Ra, and Rb, are each independently:

1) hydrogen,

Rc, and Rd, are each independently:

1) hydrogen,

Ro is:

1) hydrogen,

Re, Rf Rg and Rh are each independently:

1) hydrogen,

and provided that if R1 and/or R2 are hydrogen then each of Ra and Rb must be selected from methyl and ethyl, including pharmaceutically acceptable salts, solvates and hydrates thereof, and provided that said compound does not include any compound listed in the Excluded Compound Group.

Thus, the inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

In this case the first named invention that will be searched without additional fees is Group I represented by claims 1-7, 13-26, 41 (in part), 42, and 44 (in part).