

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 February 2009 (12.02.2009)

PCT

(10) International Publication Number  
**WO 2009/021085 A1**

(51) International Patent Classification:  
C07D 249/06 (2006.01) A61F 2/16 (2006.01)

(21) International Application Number:  
PCT/US2008/072406

(22) International Filing Date: 7 August 2008 (07.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/954,992 9 August 2007 (09.08.2007) 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, 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, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report



**WO 2009/021085 A1**

(54) Title: OPTHALMIC LENS MATERIALS CONTAINING CHROMOPHORES THAT ABSORB BOTH UV AND SHORT WAVELENGTH VISIBLE LIGHT

(57) Abstract: Chromophores that absorb both UV and short wavelength visible light are disclosed. The chromophores are particularly suitable for use in intraocular lens materials.

## OPHTHALMIC LENS MATERIALS CONTAINING CHROMOPHORES THAT ABSORB BOTH UV AND SHORT WAVELENGTH VISIBLE LIGHT

### 5 Field of the Invention

This invention is directed to chromophores. In particular, this invention relates to chromophores that absorb both UV and short wavelength light.

### 10 Background of the Invention

Many UV light absorbers are known as ingredients for polymeric materials used to make ophthalmic lenses. UV absorbers are preferably covalently bound to the polymeric network of the lens material instead of  
15 simply physically entrapped in the material to prevent the absorber from migrating, phase separating or leaching out of the lens material. Such stability is particularly important for implantable ophthalmic lenses, especially intraocular lenses (IOLs), where the leaching of the UV absorber may present both toxicological issues and lead to the loss of UV blocking activity in the  
20 implant.

Numerous copolymerizable benzotriazole, benzophenone and triazine UV absorbers are known. Many of these UV absorbers contain conventional olefinic polymerizable groups, such as methacrylate, acrylate,  
25 methacrylamide, acrylamide or styrene groups. Copolymerization with other ingredients in the lens materials, typically with a radical initiator, incorporates the UV absorbers into the resulting polymer chain. Incorporation of additional functional groups, on a UV absorber may influence one or more of the UV absorber's UV absorbing properties, solubility or reactivity. If the UV absorber  
30 does not have sufficient solubility in the remainder of the ophthalmic lens material ingredients or polymeric lens material, the UV absorber may coalesce into domains that could interact with light and result in decreased optical clarity of the lens.

Examples of polymeric ophthalmic lens materials that incorporate UV absorbers can be found in U.S. Patent Nos. 5,290,892; 5,331,073 and 5,693,095.

5 Likewise, copolymerizable short wavelength light absorbing chromophores are known as ingredients for polymeric materials used to make ophthalmic lenses. Blue-light absorbing chromophores include those disclosed in U.S. Patent Nos. 5,470,932 and 5,543,504.

10 In order to obtain polymeric lens materials that absorb both UV and short wavelength visible light (e.g., 400 – 500 nm), it is common to add separate UV-absorbing and short wavelength light-absorbing chromophores to the polymeric materials. For example, the AcrySof<sup>®</sup> Natural IOL product, which is commercially available from Alcon Laboratories, Inc., contains a UV  
15 absorber and a blue-light absorber.

Having a single chromophore that absorbs both UV and short wavelength visible light would be advantageous. Such a single chromophore would reduce the number of components that are added to a lens material  
20 formulation and reduce disruption to the primary polymer chain structure produced by the lens formulation's primary monomer constituents.

### Summary of the Invention

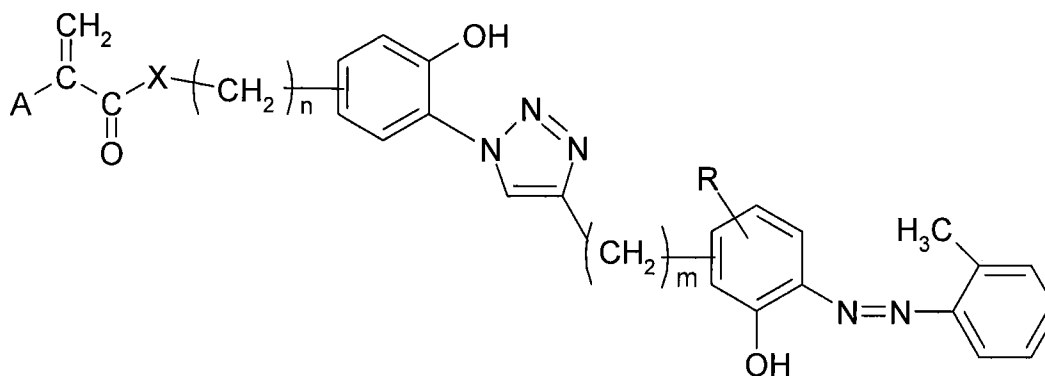
25 The present invention provides chromophores that absorb both UV and short wavelength visible light. These chromophores are suitable for use in ophthalmic lenses, including contact lenses. They are particularly useful in implantable lenses, such as IOLs.

### Detailed Description of the Invention

  
30

Unless indicated otherwise, all ingredient amounts expressed in percentage terms are presented as % w/w.

The chromophores of the present invention are represented by the formula



5

wherein

A = H or CH<sub>3</sub>;

X = O or NH;

10 n = 2 – 6;

m = 0 – 6; and

R = H, C<sub>1</sub> – C<sub>4</sub> alkyl, or C<sub>1</sub> – C<sub>4</sub> alkoxy.

A preferred chromophore of the present invention has

15 A = CH<sub>3</sub>;

X = NH;

n = 2;

m = 0; and

R = CH<sub>3</sub>.

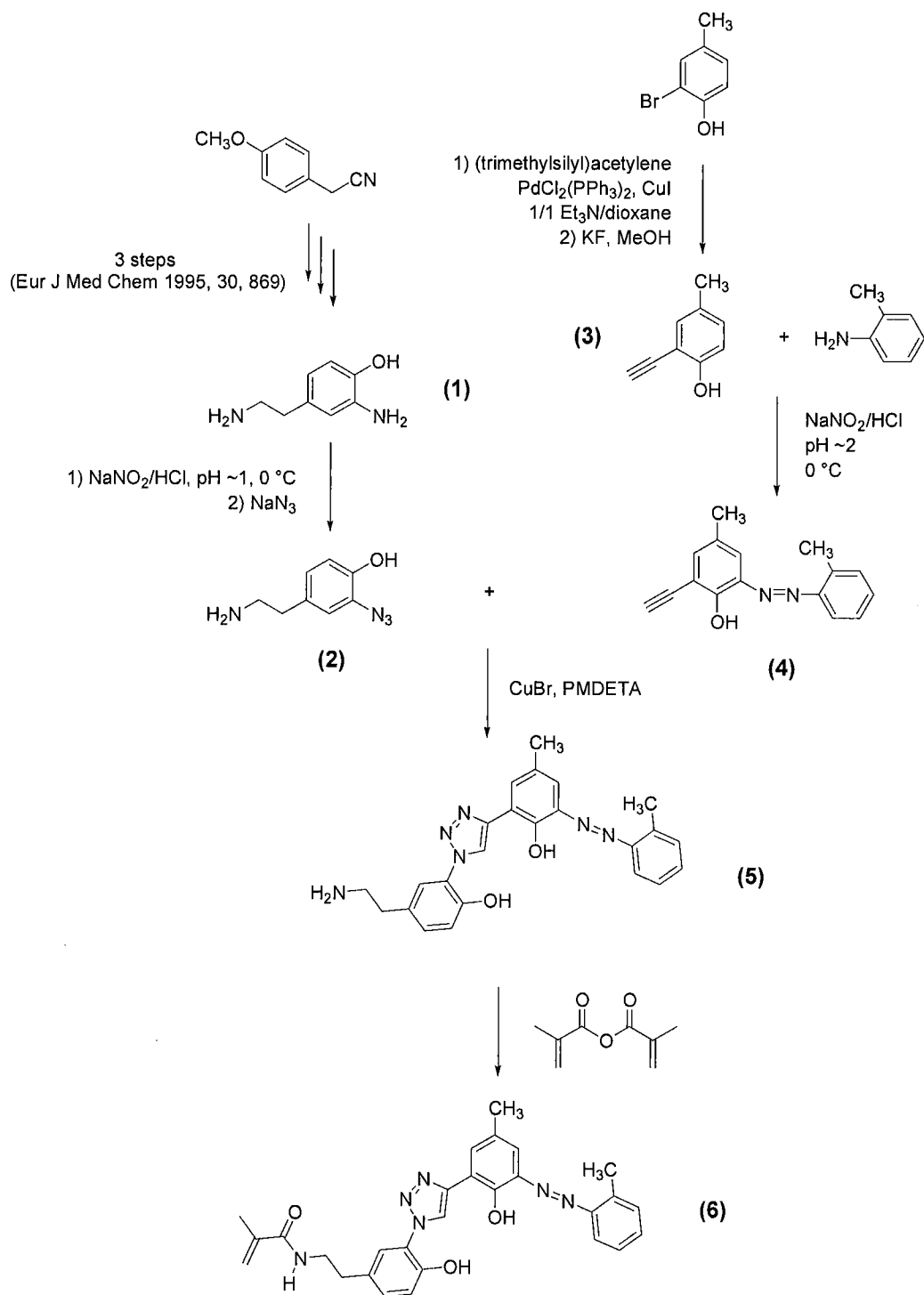
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The synthesis of the chromophores of the present invention is described below. (Scheme 1). 2-Amino-4-(2-amino-ethyl)-phenol (1) is synthesized in 3 steps from 4-methoxyphenylacetonitrile (Macchia, B.; Macchia, M.; Manera, C.; Martinotti, E.; Nencetti, S.; Orlandini, E.; Rossello, A.; Scatizzi, R. *Eur. J. Med. Chem.* **1995**, 30, 869). This is followed by aryl diazonium salt formation at pH 1 (Kornblum, N.; Iffland, D. C. *J. Am. Chem.*

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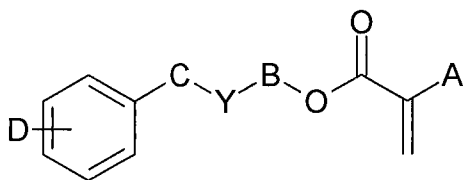
Soc. 1949, 71, 2137) to yield 4-(2-amino-ethyl)-2-azido-phenol (2). Aryl alkyne (4) is available in 2 steps from 2-bromo-4-methylphenol and o-toluidine. This is then combined with an equimolar amount of 4-(2-amino-ethyl)-2-azido-phenol (2) and catalytic CuBr to produce 1,2,3-triazole (5). The free amine is then reacted with methacrylic anhydride to produce polymerizable chromophore (6). Alternatively, (5) can be reacted with 4-vinylbenzoic acid using carbodiimide coupling to produce a vinyl-functional chromophore.

Scheme 1.



The chromophores of the present invention are particularly suitable for use in IOLs. IOL materials will generally contain from 0.1 to 5 % (w/w) of a chromophore of the present invention. Preferably, IOL materials will contain from 0.5 to 3 % (w/w) of a chromophore of the present invention. Such device materials are prepared by copolymerizing the chromophores of the present invention with other ingredients, such as device-forming materials and cross-linking agents.

Many device-forming monomers are known in the art and include both acrylic and silicone-containing monomers among others. See, for example, U.S. Nos. 7,101,949; 7,067,602; 7,037,954; 6,872,793; 6,852,793; 6,846,897; 6,806,337; 6,528,602; and 5,693,095. In the case of IOLs, any known IOL device material is suitable for use in the compositions of the present invention. Preferably, the ophthalmic device materials comprise an acrylic or methacrylic device-forming monomer. More preferably, the device-forming



monomers comprise a monomer of formula [II]:

[II]

where in formula [II]:

A is H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CH<sub>2</sub>OH;

B is (CH<sub>2</sub>)<sub>m</sub> or [O(CH<sub>2</sub>)<sub>2</sub>]<sub>z</sub>;

C is (CH<sub>2</sub>)<sub>w</sub>;

m is 0 – 6;

z is 1 – 10;

Y is nothing, O, S, or NR', provided that if Y is O, S, or NR', then

B is (CH<sub>2</sub>)<sub>m</sub>;

R' is H, CH<sub>3</sub>, C<sub>n</sub>H<sub>2n+1</sub> (n'=1-10), iso-OC<sub>3</sub>H<sub>7</sub>, C<sub>6</sub>H<sub>5</sub>, or

CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>;

w is 0 – 6, provided that m + w ≤ 8; and

D is H, C<sub>1</sub> – C<sub>4</sub> alkyl, C<sub>1</sub> – C<sub>4</sub> alkoxy, C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> or halogen.

Preferred monomers of formula [II] are those wherein A is H or CH<sub>3</sub>, B is (CH<sub>2</sub>)<sub>m</sub>, m is 1 - 5, Y is nothing or O, w is 0 – 1, and D is H. Most preferred are benzyl methacrylate; 2-phenylethyl methacrylate; 4-phenylbutyl methacrylate; 5-phenylpentyl methacrylate; 2-benzyloxyethyl methacrylate; and 3-benzyloxypropyl methacrylate; and their corresponding acrylates.

Monomers of formula [II] are known and can be made by known methods. For example, the conjugate alcohol of the desired monomer can be combined in a reaction vessel with methyl methacrylate, tetrabutyl titanate (catalyst), and a polymerization inhibitor such as 4-benzyloxy phenol. The vessel can then be heated to facilitate the reaction and distill off the reaction by-products to drive the reaction to completion. Alternative synthesis schemes involve adding methacrylic acid to the conjugate alcohol and catalyzing with a carbodiimide or mixing the conjugate alcohol with methacryloyl chloride and a base such as pyridine or triethylamine.

Device materials generally comprise a total of at least about 75%, preferably at least about 80%, of device-forming monomers.

In addition to a chromophore of the present invention and a device-forming monomer, the device materials of the present invention generally comprise a cross-linking agent. The cross-linking agent used in the device materials of this invention may be any terminally ethylenically unsaturated compound having more than one unsaturated group. Suitable cross-linking agents include, for example: ethylene glycol dimethacrylate; diethylene glycol dimethacrylate; allyl methacrylate; 1,3-propanediol dimethacrylate; 2,3-propanediol dimethacrylate; 1,6-hexanediol dimethacrylate; 1,4-butanediol dimethacrylate; CH<sub>2</sub>=C(CH<sub>3</sub>)C(=O)O-(CH<sub>2</sub>CH<sub>2</sub>O)<sub>p</sub>-C(=O)C(CH<sub>3</sub>)=CH<sub>2</sub> where p = 1 – 50; and CH<sub>2</sub>=C(CH<sub>3</sub>)C(=O)O(CH<sub>2</sub>)<sub>t</sub>O-C(=O)C(CH<sub>3</sub>)=CH<sub>2</sub> where t = 3 - 20; and their corresponding acrylates. A preferred cross-linking monomer is

$\text{CH}_2=\text{C}(\text{CH}_3)\text{C}(=\text{O})\text{O}-(\text{CH}_2\text{CH}_2\text{O})_p-\text{C}(=\text{O})\text{C}(\text{CH}_3)=\text{CH}_2$  where  $p$  is such that the number-average molecular weight is about 400, about 600, or about 1000.

5 Generally, the total amount of the cross-linking component is at least 0.1% by weight and, depending on the identity and concentration of the remaining components and the desired physical properties, can range to about 20% by weight. The preferred concentration range for the cross-linking component is 0.1 – 17% (w/w).

10 Suitable polymerization initiators for device materials containing a chromophore of the present invention include thermal initiators and photoinitiators. Preferred thermal initiators include peroxy free-radical initiators, such as *t*-butyl (peroxy-2-ethyl)hexanoate and di-(*tert*-butylcyclohexyl) peroxydicarbonate (commercially available as Perkadox<sup>®</sup> 16 from Akzo  
15 Chemicals Inc., Chicago, Illinois). Initiators are typically present in an amount of about 5% (w/w) or less. The total amount of initiator is customarily not included when determining the amounts of other ingredients.

IOLs constructed of the materials of the present invention can be of  
20 any design capable of being rolled or folded into a small cross section that can fit through a relatively smaller incision. For example, the IOLs can be of what is known as a one piece or multipiece design, and comprise optic and haptic components. The optic is that portion which serves as the lens. The haptics are attached to the optic and hold the optic in its proper place in the  
25 eye. The optic and haptic(s) can be of the same or different material. A multipiece lens is so called because the optic and the haptic(s) are made separately and then the haptics are attached to the optic. In a single piece lens, the optic and the haptics are formed out of one piece of material. Depending on the material, the haptics are then cut, or lathed, out of the  
30 material to produce the IOL.

In addition to IOLs, the materials of the present invention are also suitable for use in other ophthalmic devices, such as contact lenses, keratoprostheses, and corneal inlays or rings.

5 The invention will be further illustrated by the following examples, which are intended to be illustrative, but not limiting.

**Example 1: Synthesis of (2).**

2-Amino-4-(2-amino-ethyl)-phenol (1) (1 mmol) is dissolved in aqueous HCl. The solution is cooled to 0 °C and 1 mmol of NaNO<sub>2</sub> dissolved in H<sub>2</sub>O is added slowly with stirring. The reaction mixture is maintained at 0 °C for 1 hr, then NaN<sub>3</sub> (2 mmol) dissolved in water is added dropwise with stirring. The resulting mixture is maintained at 0 °C for 1 hr, then the cooling bath is removed and the mixture stirred overnight at ambient temperature. The product is extracted with ethyl acetate, washed with saturated NaHCO<sub>3</sub> and H<sub>2</sub>O. The organic phase is dried with Na<sub>2</sub>SO<sub>4</sub>, then the solvent removed under vacuum. The crude product is purified by column chromatography to yield 4-(2-amino-ethyl)-2-azido-phenol (2).

20 **Example 2: Synthesis of (3).**

A flask is flushed with N<sub>2</sub> and charged with 2-Bromo-4-methylphenol (20 mmol) and dissolved in 1/1 Et<sub>3</sub>N/dioxane. Bis(triphenylphosphine)palladium(II) dichloride (PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>) (0.2 mmol) is added, followed by 0.4 mmol of CuI. Trimethylsilylacetylene (24 mmol) is added drop-wise to the reaction mixture. The reaction mixture is stirred overnight under N<sub>2</sub>. The solvents are removed under vacuum and the resulting liquid is extracted by washing with ethyl ether. The ethyl ether extracts are combined and washed with H<sub>2</sub>O, then dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the product is purified by column chromatography. The purified product is placed in a N<sub>2</sub>-flushed flask and dissolved in methanol. Potassium fluoride (65 mmol) is added and the reaction stirred under a N<sub>2</sub> blanket for 16 h. The reaction mixture is poured into CH<sub>2</sub>Cl<sub>2</sub> and extracted with H<sub>2</sub>O, then dried

over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent is removed under vacuum. The resulting product is purified by column chromatography to yield 2-ethynyl-4-methyl-phenol (3).

5 **Example 3: Synthesis of (4).**

A flask is charged with 100 mmol of boric acid followed by 6N HCl solution to adjust the reaction solution to a pH of 2. Once the salt dissolves, 20 mmol of *o*-toluidine is added to the reaction solution, followed by enough ice to reduce solution temperature to 0 °C. In a separate flask, 20 mmol of sodium nitrite  
10 (NaNO<sub>2</sub>) is dissolved in ice water. The NaNO<sub>2</sub> solution is added drop wise with constant stirring to the *o*-toluidine solution. The pH of the reaction solution is maintained by addition of 6N HCl. After the addition of sodium nitrite solution is complete, ice is added to maintain the 0 °C reaction temperature. A 3<sup>rd</sup> flask is charged with 20 mmol of 2-ethynyl-4-methyl-phenol  
15 (3), water and 2.5 N NaOH (20 mmol), which is then added drop wise to the ice cooled reaction with constant stirring. The reaction mixture is allowed to stir for 15 min at pH 2.0 – 2.5. NaOH (2.5 N) is added in small aliquots to the reaction solution to increase the pH to 8.5. The reaction solution is allowed to warm to room temperature. Dibasic sodium phosphate solution (100 mmol) is  
20 added and the pH is adjusted to 6.0 with 6 N HCl. The product is filtered, rinsed with ice water and air dried. The product is purified by column chromatography to yield 2-ethynyl-4-methyl-6-*o*-tolylazo-phenol (4).

**Example 4: Synthesis of (5).**

25 A flask containing a PTFE coated stir bar is flushed with N<sub>2</sub> and charged with 15 mmol of aryl azide (2), 15 mmol of aryl acetylene (4), N,N-dimethylformamide, 3.0 mmol of N,N,N',N'',N'''-pentamethyldiethylenetriamine, and 1.5 mmol of CuBr. The flask is stirred 20 h at ambient temperature. The reaction mixture is then exposed to air and purified by passing through a  
30 chromatographic alumina column. The eluent is collected and the solvent is removed under vacuum to yield product (5).

**Example 5: Synthesis of (6).**

A flask containing a PTFE coated stir bar is flushed with N<sub>2</sub> and charged with 10 mmol of amino functional triazole (5) and THF. Methacrylic acid (10 mmol) was added drop-wise to the stirring THF solution. Once the addition is complete the reaction is stirred at ambient temperature for 2 hrs. The solvent is evaporated under vacuum and the crude product is purified by column chromatography. The eluent is collected and the solvent is removed under vacuum to yield product (6).

**EXAMPLES 6 – 9. Copolymerization of a chromophore with a device-forming monomer.**

A vial is charged with ingredients as listed in Table 1 except for the initiator. The solution is mixed thoroughly and de-gassed by bubbling with N<sub>2</sub>. The initiator is added and the solution is again mixed thoroughly. The solution is filtered through a 0.2 micron PTFE filter and transferred to polypropylene molds. The molds are heated in a mechanical convection oven at 70 °C for 1 hr, then 110 °C for 2 hrs. The resulting copolymer samples are removed from the polypropylene molds and extracted in refluxing acetone for at least 3 hr, then rinsed with fresh acetone and allowed to air dry. The extracted polymer is dried under vacuum at 70 °C for at least 3 hr.

**Table 1. Representative Copolymer Formulations**

Ingredient	Amount (% w/w)			
	6	7	8	9
PEA	65.0	80.0	0.0	65.0
PEMA	29.95	0.0	0.0	31.25
PBMA	0.0	0.0	82.15	0.0
HEMA	0.0	14.95	0.0	0.0
PEG(1000)DMA	0.0	0.0	15.0	0.0
EGDMA	0.0	0.0	1.0	0.0
BDDA	3.2	3.2	0.0	3.2
o-MTP	1.8	1.8	1.8	0.0
Chromophore (6)	0.05	0.05	0.05	0.5
Perkadox <sup>®</sup> 16S	1.0	1.0	1.0	1.0

PEA = 2-phenylethyl acrylate

PEMA = 2-phenylethyl methacrylate

PBMA = 4-phenylbutyl methacrylate

HEMA = 2-hydroxyethyl methacrylate

PEG(1000)DMA = polyethylene glycol (1000) dimethacrylate

EGDMA = ethylene glycol dimethacrylate

BDDA = 1,4-butanediol diacrylate

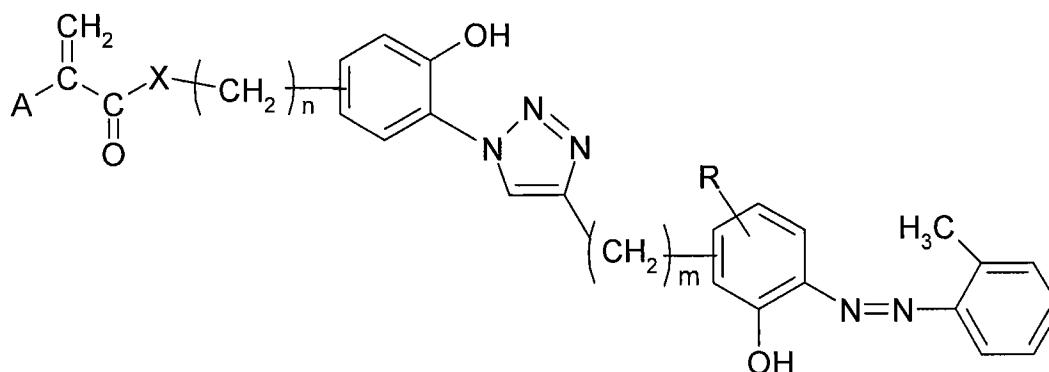
oMTP = *o*-methallyl Tinuvin P

This invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its special or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

We claim:

1. A chromophore of the formula

5



wherein

A = H or CH<sub>3</sub>;

X = O or NH;

10 n = 2 – 6;

m = 0 – 6; and

R = H, C<sub>1</sub> – C<sub>4</sub> alkyl, or C<sub>1</sub> – C<sub>4</sub> alkoxy.

2. The chromophore of Claim 1 wherein

15 A = CH<sub>3</sub>;

X = NH;

n = 2;

m = 0; and

R = CH<sub>3</sub>.

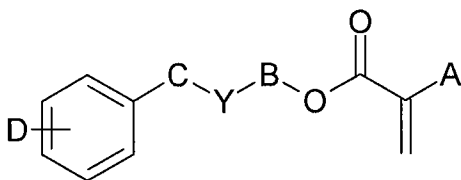
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3. An ophthalmic device material comprising the chromophore of Claim 1 and a device-forming monomer selected from the group consisting of acrylic monomers and silicone-containing monomers.

4. The ophthalmic device material of Claim 3 wherein the ophthalmic device material comprises from 0.1 to 5 % (w/w) of the chromophore of Claim 1.

5. The ophthalmic device material of Claim 4 wherein the ophthalmic device material comprises from 0.5 to 3 % (w/w) of the chromophore of Claim 1.

6. The ophthalmic device material of Claim 3 wherein the ophthalmic device material comprises a device-forming monomer of formula [II]:



[II]

where in formula [II]:

A is H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, or CH<sub>2</sub>OH;

B is (CH<sub>2</sub>)<sub>m</sub> or [O(CH<sub>2</sub>)<sub>2</sub>]<sub>z</sub>;

C is (CH<sub>2</sub>)<sub>w</sub>;

m is 0 – 6;

z is 1 – 10;

Y is nothing, O, S, or NR', provided that if Y is O, S, or NR', then

B is (CH<sub>2</sub>)<sub>m</sub>;

R' is H, CH<sub>3</sub>, C<sub>n'</sub>H<sub>2n'+1</sub> (n'=1-10), iso-OC<sub>3</sub>H<sub>7</sub>, C<sub>6</sub>H<sub>5</sub>, or

CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>;

w is 0 – 6, provided that m + w ≤ 8; and

D is H, C<sub>1</sub> – C<sub>4</sub> alkyl, C<sub>1</sub> – C<sub>4</sub> alkoxy, C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> or halogen.

7. The ophthalmic device material of Claim 6 wherein in formula [II]:  
A is H or CH<sub>3</sub>;  
B is (CH<sub>2</sub>)<sub>m</sub>;  
m is 1 – 5;  
5 Y is nothing or O;  
w is 0 – 1; and  
D is H.
8. The ophthalmic device material of Claim 7 wherein the ophthalmic  
10 device material comprises a monomer selected from the group consisting of:  
benzyl methacrylate; 2-phenylethyl methacrylate; 4-phenylbutyl methacrylate;  
5-phenylpentyl methacrylate; 2-benzyloxyethyl methacrylate; and 3-  
benzyloxypropyl methacrylate; and their corresponding acrylates.
- 15 9. The ophthalmic device material of Claim 3 wherein the ophthalmic  
device material comprises a cross-linking agent.
10. An intraocular lens comprising the chromophore of Claim 1.
- 20 11. An ophthalmic device comprising the ophthalmic device material of  
Claim 3.
12. The ophthalmic device of Claim 11 wherein the ophthalmic device is  
selected from the group consisting of an intraocular lens; a contact lens; a  
25 keratoprosthesis; and a corneal inlay or ring.

INTERNATIONAL SEARCH REPORT

International application No  
PCT/US2008/072406

A. CLASSIFICATION OF SUBJECT MATTER  
INV. C07D249/06 A61F2/16

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)  
C07D A61F

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95/11279 A (ALCON LAB INC [US]) 27 April 1995 (1995-04-27) cited in the application the whole document	1-12
A	US 4 652 656 A (BESECKE SIEGMUND [DE] ET AL) 24 March 1987 (1987-03-24) the whole document	1-12
A	JIN, MING ET AL: "Synthesis and photoinduced birefringence of polymethacrylates with azo-substituted pyrazoline in the side chain" MATERIALS CHEMISTRY AND PHYSICS, 82(1), 246-252 CODEN: MCHPDR; ISSN: 0254-0584, 2003, XP002503300 the whole document	1-12

Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/072406

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