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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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(54) Title: ISOTHIOZOLES FOR TREATING CONDITIONS OF THE EYE

(57) Abstract: Disclosed herein are isothiozoles for treating conditions of the eye.

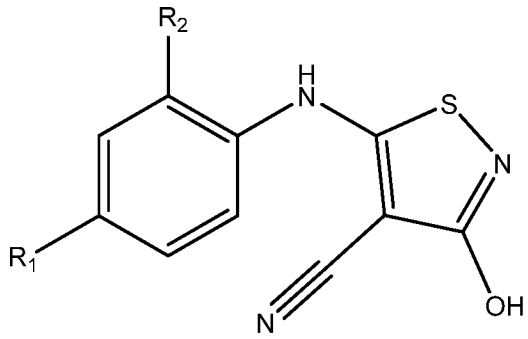
ISOTHIOZOLES FOR TREATING CONDITIONS OF THE EYE

Inventors: Veena Viswanath and John E. Donello

CROSS-REFERENCE

This application claims the benefit of U.S. Provisional Patent Application Serial Number 61/233,047, filed on August 11, 2009, the entire disclosure of which is incorporated herein by this specific reference.

Disclosed herein is a method for treating conditions of the eye, the method comprising administering to a patient in need of such treatment a compound of the formula

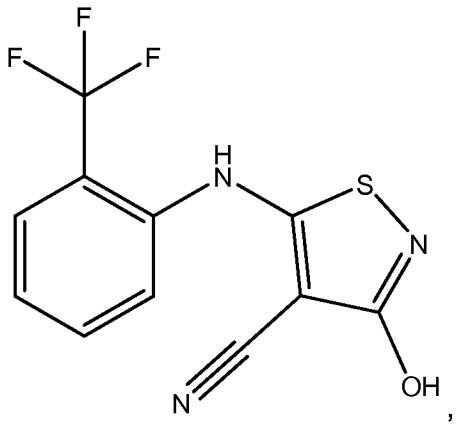


wherein a) R_2 is chlorine or CF_3, and R_1 is H, or b) R_2 is H and R_1 is Cl.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the invention

One can use the following isothiozoles in the method of the invention:



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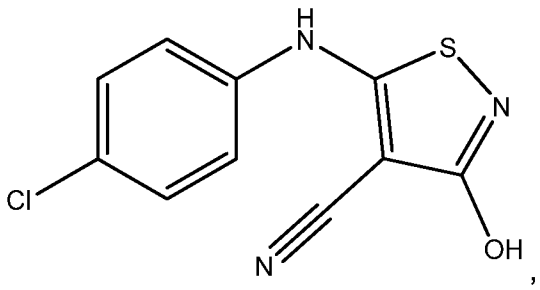
Compound I



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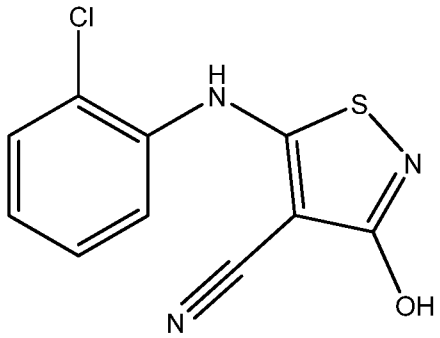
Compound II

Or



Compound III

Compound I is 3-hydroxy-5-(2-(trifluoromethyl)phenylamino)isothiazole-4-carbonitrile, CAS no. 287196-91-2. Compound II is 5-(4-chlorophenylamino)-3-hydroxyisothiazole-4-carbonitrile, CAS no. 287196-70-7. Compound III is 5-(2-chlorophenylamino)-3-hydroxyisothiazole-4-carbonitrile, CAS no. 287196-71-8. All of these compounds are available from commercial sources. One can use in the methods of the invention an enantiomer, stereoisomer, or other isomer of the foregoing compounds.

Conditions of the eye

Conditions of the eye that may be treated with the method of the invention include the following: conditions affecting the posterior part of the eye, such as maculopathies and retinal degeneration including non-exudative age related macular degeneration, exudative age related macular degeneration, choroidal neovascularization, diabetic retinopathy, acute macular neuroretinopathy, central serous chorioretinopathy, cystoid macular edema, and diabetic macular edema; uveitis, retinitis, and choroiditis such as acute multifocal placoid pigment epitheliopathy, Behcet's disease, birdshot retinochoroidopathy, infectious (syphilis,

lyme, tuberculosis, toxoplasmosis), intermediate uveitis (pars planitis), multifocal choroiditis, multiple evanescent white dot syndrome (mewds), ocular sarcoidosis, posterior scleritis, serpiginous choroiditis, subretinal fibrosis and uveitis syndrome, Vogt-Koyanagi-and Harada syndrome; vasuclar diseases/ exudative diseases such as retinal arterial occlusive disease, central retinal vein occlusion, disseminated intravascular coagulopathy, branch retinal vein occlusion, hypertensive fundus changes, ocular ischemic syndrome, retinal arterial microaneurysms, Coat's disease, parafoveal telangiectasis, hemi-retinal vein occlusion, papillophlebitis, central retinal artery occlusion, branch retinal artery occlusion, carotid artery disease (CAD), frosted branch angiitis, sickle cell retinopathy and other hemoglobinopathies, angioid streaks, familial exudative vitreoretinopathy, and Eales disease; traumatic/ surgical conditions such as sympathetic ophthalmia, uveitic retinal disease, retinal detachment, trauma, conditions caused by laser, conditions caused by photodynamic therapy, photocoagulation, hypoperfusion during surgery, radiation retinopathy, and bone marrow transplant retinopathy; proliferative disorders such as proliferative vitreal retinopathy and epiretinal membranes, and proliferative diabetic retinopathy; infectious disorders such as ocular histoplasmosis, ocular toxocariasis, presumed ocular histoplasmosis syndrome (POHS), endophthalmitis, toxoplasmosis, retinal diseases associated with HIV infection, choroidal disease associate with HIV infection, uveitic disease associate with HIV infection, viral retinitis, acute retinal necrosis, progressive outer retinal necrosis, fungal retinal diseases, ocular syphilis, ocular tuberculosis, diffuse unilateral subacute neuroretinitis, and myiasis; genetic disorders such as retinitis pigmentosa, systemic disorders with accosiated retinal dystrophies, congenital stationary night blindness, cone dystrophies, Stargardt's disease and fundus flavimaculatus, Best's disease, pattern dystrophy of the retinal pigmented epithelium, X-linked retinoschisis, Sorsby's fundus dystrophy, benign concentric maculopathy, Bietti's crystalline dystrophy, and pseudoxanthoma elasticum; retinal tears/ holes such as retinal detachment, macular hole, and giant retinal tear; tumors such as retinal disease associated with tumors, congenital hypertrophy of the retinal pigmented epithelium, posterior uveal melanoma, choroidal hemangioma, choroidal osteoma, choroidal metastasis, combined hamartoma of the retina and retinal pigmented epithelium, retinoblastoma, vasoproliferative tumors of the ocular fundus, retinal astrocytoma,

and intraocular lymphoid tumors; and miscellaneous other diseases affecting the posterior part of the eye such as punctate inner choroidopathy, acute posterior multifocal placoid pigment epitheliopathy, myopic retinal degeneration, and acute retinal pigement epitheliitis.

Administration

One can use any of the compounds described above to treat conditions of the eye. To "treat," as used here, means to deal with medically. It includes both preventing conditions of the eye and relieving symptoms associated with the conditions, whether such prevention or relief is complete or partial.

Dose

The precise dose and frequency of administration depends on the severity and nature of the patient's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound employed, and on the judgment of the prescribing physician. Determining dose is a routine matter that is well within the capability of someone of ordinary skill in the art.

The compositions of the invention may be administered orally or parenterally, the later by subcutaneous injection, intramuscular injection, intravenous administration, or other route, or by delivering the compositions locally to the eye, as by topically instilling them on the eye or by injecting them into the eye.

Excipients and dosage forms

Those skilled in the art will readily understand that for administering pharmaceutical compositions of the invention the S1P3 receptor inhibitor may be admixed with pharmaceutically acceptable excipients which are well known in the art.

A pharmaceutical composition to be administered systemically may be confected as a powder, pill, tablet or the like, or as a solution, emulsion, suspension, aerosol, syrup or elixir suitable for oral or parenteral administration or inhalation.

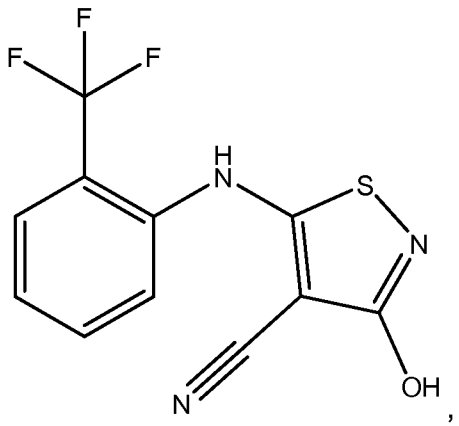
For solid dosage forms or medicaments, non-toxic solid carriers include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. The solid dosage forms may be uncoated or

they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in U.S. Patent No. 4,256,108, No. 4,166,452, and No. 4,265,874 to form osmotic therapeutic tablets for control release. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjutants in a carrier, such as for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like. Typical examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, Pa., 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

What is claimed is

1. A method for treating a condition of the eye, the method comprising the step of administering to a patient in need of such treatment a compound selected from the group consisting of the following:



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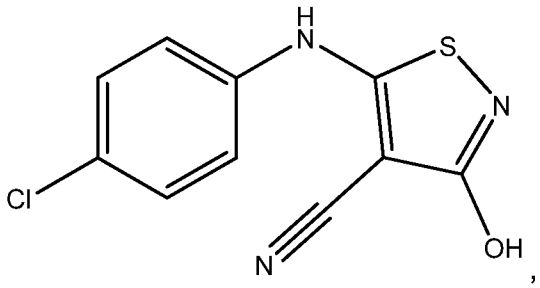

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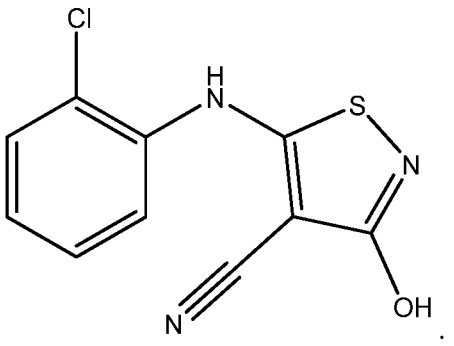
and



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2. The method of claim 1, wherein the condition of the eye is age related macular degeneration.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044946

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/425 A61P27/02
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)
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 practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, 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.
X Y	US 2004/039037 A1 (ZHANG WEIJIAN [US] ET AL) 26 February 2004 (2004-02-26) * abstract page 11; compounds 9,11,19 claims 1,20	1 1,2
Y	WO 2006/045514 A1 (APPLIED RESEARCH SYSTEMS [NL]; ABEL ULRICH [DE]; DEPPE HOLGER [DE]; FE) 4 May 2006 (2006-05-04) * abstract claims 1,9	1,2

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[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 document 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	Date of mailing of the international search report
2 November 2010	11/11/2010

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	Garabatos-Perera, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/044946

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GLOTIN ANNE-LISE ET AL: "Sustained versus transient ERK1/2 signaling underlies the anti- and proapoptotic effects of oxidative stress in human RPE cells" IOVS, vol. 47, no. 10, October 2006 (2006-10), pages 4614-4623, XP002607635 ISSN: 0146-0404 * abstract page 4621; figure 8 page 4622, left-hand column, last paragraph	1,2
A	WO 2008/014338 A2 (ALCON MFG LTD [US]; FLEENOR DEBRA L [US]; SHEPARD ALLAN R [US]; PANG I) 31 January 2008 (2008-01-31) the whole document	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/044946

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