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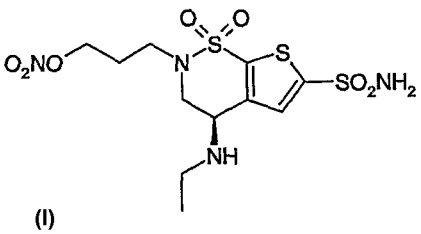
(54) **Title:** THIENO [3, 2-E] [1, 2] THIAZINE DERIVATIVE AS INHIBITOR OF CARBONIC ANHYDRASE



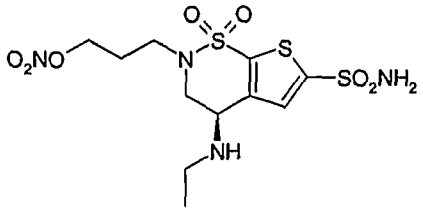
(I)

(57) **Abstract:** The invention relates to a compound of the formula (I): (I) and to pharmaceutically acceptable salts and solvates thereof. The invention also relates to methods of treating glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy, retinal vasculopathies and intraocular pressure in mammals by administering the compound, and to pharmaceutical compositions which contain the compound for such treatments. The invention also relates to methods of preparing the compound.

THIENO[3,2-E][1,2]THIAZINE DERIVATIVE AS INHIBITOR OF CARBONIC ANHYDRASE

Field of the Invention

The present invention relates to a compound of the formula



Methods for its preparation, pharmaceutical compositions containing this compound, and methods of using this compound and compositions for inhibiting carbonic anhydrase, and thereby lowering intraocular pressure and treating glaucoma are also provided.

Background of the Invention

Glaucoma is a disease of the eye characterized by a progressive loss of visual field due to irreversible damage to the optic nerve to the point where, if untreated, may result in total blindness. The chief pathophysiological feature of glaucoma is raised intraocular pressure (IOP). The loss of visual field, in one form of primary open angle glaucoma, or POAG, is associated with a sustained increase in the intraocular pressure of the diseased eye. Moreover, elevated intraocular pressure without visual field loss is thought to be indicative of the early stages of this form of POAG.

Inhibitors of carbonic anhydrase interrupt the enzyme's abililty to catalyze the water-carbon dioxide combination to form bicarbonate ions. Thus, inhibitors acting upon carbonic anhydrase isoenzyme II (CAI-II) in the ciliary body yield a reduction in IOP by decreasing bicarbonate secretion, and correspondingly decreasing aqueous humor secretion, by the ciliary epithelial cells into the posterior chamber.

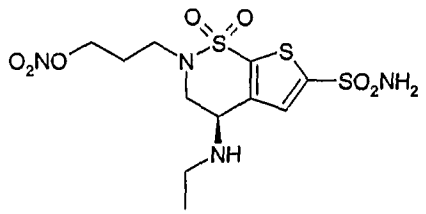
Orally administered carbonic anhydrase inhibitors (CAIs) include acetazolamide and methazolamide. Systemic inhibition of carbonic anhydrase is associated with significant side effects, including aplastic anemia, hypokalemia, nephrolithiasis, paresthesias in the hands and face, malaise, anorexia, and severe weight loss. Accordingly, oral CAIs are typically used only in acute management of raised IOP, and they are used chronically only as a last restort, where topical agents have failed to adequately manage IOP.

There are a number of therapies that target reducing the elevated IOP associated with this form of POAG. The most common are the topical administration of a beta

adrenergic antagonist or a muscarinic agonist. These treatments, while effective in lowering IOP, can also produce significant undesirable side effects. Another treatment of POAG is the systemic administration of carbonic anhydrase inhibitors. For example, U.S. Patent Nos. 5,679,670, 4,797,413, 4,847,289 and 4,731,368 disclose topically dosed thiophene sulfonamides which lower IOP by inhibiting carbonic anhydrase. However, these compounds may also bring about unwanted side effects, such as nausea, dyspepsia, fatigue and metabolic acidosis. Dorzolamide is another carbonic anhydrase inhibitor that is used to treat increased pressure in the eye caused by open-angle glaucoma.

Summary of the Invention

In one aspect according to the invention, there is provided a compound of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof.

In another aspect of the invention, there is provided a compound of formula (I) as described above for use as a medicament.

In yet another aspect of the invention, there is provided a compound of formula (I) as described above for the preparation of a medicament for treating glaucoma or ocular hypertension.

In still another aspect of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formula (I) as described above.

In another aspect of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of formula (I) as described above in a suitable form for topical administration.

In yet another aspect of the invention, there is provided a pharmaceutical composition

as described above for the treatment of glaucoma and ocular hypertension.

In still another aspect of the invention, there is provided a pharmaceutical composition as described above, wherein the compound of formula (I) as described above is administered as a solution, suspension or emulsion in an ophthalmically acceptable vehicle.

In another aspect of the invention, there is provided a method for treating glaucoma or ocular hypertension, wherein the method comprises contacting an effective intraocular pressure reducing amount of a pharmaceutical composition as described above with the eye in order to reduce eye pressure and to maintain the pressure at a reduced level.

In yet another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof comprising administering a therapeutically effective amount of a carbonic anhydrase inhibitor of formula (I) as described above able to release nitric oxide.

In still another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said eye disorder is selected from glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies.

In another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said carbonic anhydrase inhibitor is a compound having an inhibition constant (K_i) against the isoenzyme CAII in the range of 0.01 to 200 nM.

In yet another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said carbonic anhydrase inhibitor is a compound having a dissociation constant (K_d) against the isoenzyme CAII in the range of 0.01 to 200 nM.

In still another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said carbonic anhydrase inhibitor is a compound having an inhibition constant (K_i) against the isoenzyme CAIV in the range of 0.01 to 200 nM.

In another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said carbonic

anhydrase inhibitor is a compound having a dissociation constant (K_d) against the isoenzyme CAIV in the range of 0.01 to 200 nM.

In yet another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said carbonic anhydrase inhibitor able to release nitric oxide is a compound having an EC_{50} value in the range of 1 to 50 μM.

In still another aspect of the invention, there is provided a method for treating eye disorders in a patient in need thereof as described above, wherein said carbonic anhydrase inhibitor able to release nitric oxide is a compound having an IC_{50} value in the range of 1 to 50 μM.

In another aspect of the invention, there is provided a method for the treatment of glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies comprising administering a compound of formula (I) as described above.

In yet another aspect of the invention, there is provided a method for the treatment of glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies comprising administering a pharmaceutical composition as described above.

Definitions

As used herein, the terms "comprising" and "including" are used in their open, non-limiting sense.

As used herein, the term "substituted," means that the specified group or moiety bears one or more substituents. The term "unsubstituted," means that the specified group bears no substituents.

As used herein, the term "optionally substituted" means that the specified group is unsubstituted or is substituted by one or more substituents.

As used herein, the terms "treat," "treating" or "treatment" includes preventative (e.g., prophylactic) and palliative treatment.

As used herein, the term "pharmaceutically acceptable" means the carrier, diluent, excipients and/or salt must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

As used herein, the term "alkyl" means a straight or branched chain saturated hydrocarbon. Exemplary alkyl groups include but are not limited to methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, hexyl, isohexyl, heptyl, octyl and the like.

As used herein, the term "alkenyl" means a straight or branched chain hydrocarbon having at least one double bond, i.e., a C=C. Exemplary alkenyl groups include but are not limited to vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl and the like.

As used herein, the term "alkynyl" means a straight or branched chain hydrocarbon having at least one triple bond, i.e., a C≡C. Exemplary alkynyl groups include but are not limited to acetylenyl, propargyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl and the like.

As used herein, the term "cycloalkyl" means a cyclic saturated hydrocarbon. Exemplary cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

As used herein, the term "cycloalkenyl" means a cyclic hydrocarbon having at least one double bond, i.e., a C=C. Exemplary cycloalkenyl groups include but are not limited to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl and the like.

As used herein, the term "cycloalkynyl" means a cyclic hydrocarbon having at least one triple bond, i.e., a C≡C. Exemplary cycloalkynyl groups include but are not limited to cyclohexynyl, cycloheptynyl, cyclooctynyl and the like.

As used herein, the term "alkoxy" means a straight or branched chain saturated alkyl group bonded through oxygen. Exemplary alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, tert-pentoxy, hexoxy, isohexoxy, heptoxy, octoxy and the like.

As used herein, the term "alkylene" means a straight chain or branched chain saturated hydrocarbon wherein a hydrogen atom is removed from each of the terminal carbons. Exemplary alkylene groups include but are not limited to methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene and the like.

As used herein, the term "cycloalkylaryl" and "$(CH_2)_t(C_3\text{-}C_{12})$cycloalkyl$(C_6\text{-}C_{10})$aryl" includes linear and/or fused ring systems such as 2,3-didydro-1H-indene, 2-methyl-2,3-didydro-1H-indene, 1,2,3,4-tetrahydronaphthalene, 2-methyl-1,2,3,4-

tetrahydronaphthalene, 1-cyclopentylbenzene, 1-(2-methylcyclopentyl)benzene, 1-(3-methylcyclopentyl)benzene, 1-cyclohexylbenzene, 1-(2-methylcyclohexyl)benzene, 1-(3-methylcyclohexyl)benzene, 1-(4-methylcyclohexyl)benzene, and the like,

As used herein, the term "halo" or "halogen" means fluoro, chloro, bromo or iodo.

As used herein, the term "aryl" means an organic radical derived from an aromatic hydrocarbon by removal of hydrogen. Exemplary aryl groups include but are not limited to phenyl, biphenyl, naphthyl, and the like.

As used herein, the terms "heterocyclic" and "heterocyclyl" means an aromatic or non-aromatic cyclic group containing one to four heteroatoms each independently selected from O, S and N, wherein each group has from 3 to 10 atoms in its ring system. Non-aromatic heterocyclic groups include groups having only 3 atoms in their ring system, whereas aromatic heterocyclic groups have at least 5 atoms in their ring system. Heterocyclic groups include fused ring systems such as benzo-fused rings and the like. An exemplary 3 membered heterocyclic group is aziridine; 4 membered heterocyclic group is azetidinyl (derived from azetidine); 5 membered heterocyclic group is thiazolyl; 7 membered ring heterocyclic group is azepinyl; and a 10 membered heterocyclic group is quinolinyl.

Examples of non-aromatic heterocyclic groups include but are not limited to pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl.

Examples of aromatic heterocyclic (heteroaryl) groups include but are not limited to pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl.

The foregoing groups may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole may be imidazol-1-yl (N-attached) or imidazol-3-yl (C-attached). Heterocyclic groups may be optionally substituted on any ring carbon, sulfur or nitrogen atom(s) by one to two oxygens (oxo), per ring. An example of a heterocyclic group wherein 2 ring carbon atoms are substituted with oxo moieties is 1,1-dioxo-thiomorpholinyl.

Exemplary five to six membered heterocyclic aromatic rings having one or two heteroatoms selected independently from oxygen, nitrogen and sulfur include but are not limited to isothiazolyl, pyridinyl, pyridiazinyl, pyrimidinyl, pyrazinyl and the like.

Exemplary partially saturated, fully saturated or fully unsaturated five to eight membered heterocyclic rings having one to four heteroatoms selected independently from oxygen, sulfur and nitrogen include but are not limited to 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl and the like. Further exemplary five membered rings are furyl, thienyl, 2H-pyrrolyl, 3H-pyrroyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, pyrazolinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadizaolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-trizaolyl, 1,3,4-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatrizaolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl. Further exemplary six member rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-trizainyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl. Further exemplary seven membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl. Further exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings are composed of two fused partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur

and oxygen are indolizinyl, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyi, benzthiazolyl, purinyl, 4Hquinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decalinyl, 2H-1-benzopyranyl, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3, 1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

Exemplary 3-10 membered heterocyclyl groups include but are not limited to oxetane, azetidine, tetrahydrofuran, pyrrolidine, 2,5-dihydro-1H-pyrrole, 1,3-dioxalane, isoxazolidine, oxazolidine, pyrazolidine, imidazolidine, pyrrolidin-2-one, tetrahydrothiophene-1,1-dioxide, pyrrolidine-2,5-dione, tetrahydro-2H-pyran, piperidine, 1,2,3,6-tetrahydropyridine, 1,4-dioxane, morpholine, piperazine, thiomorpholine, piperidin-2-one, piperidin-4-one, thiomorpholine-1,1-dioxide, 1,3-oxazinan-2-one, morpholin-3-one, piperazine-2-one, azepane, 1,4-oxazepane, 1,4-diazepane, azepan-2-one, 1,4-diazepan-5-one, quinuclidine, 2-aza-bicyclo[2.2.1]heptane, 8-aza-bicyclo[3.2.1]octane, 5-oxa-2-aza-bicyclo[2.2.1]heptane, 2-oxa-5-aza-bicyclo[2.2.1]heptan-3-one, 2-oxa-5-aza-bicyclo[2.2.2]octan-3-one, 1-methyl-5,6-pyrrolyl-7-oxa-bicyclo[2.2.1]heptane, 6-aza-bicyclo[3.2.1]octane, 3,8-diaza-bicyclo[3.2.1]octan-2-one, 2,2-dimethyl-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrole, 3,3-cyclohexylpyrrolidine, 1,5-diaxo-9-azaspiro[5.5]undecane, octahydro-1H-isoindole, decahydroquinoline, decahydroisoquinoline, octahydropyrrolo[1,2a]pyrazine, octahydro'1H-pyrido[1,2a]pyrazine, octahydropyrrolo[3,4-c]pyridine-3-one, decahydropyrazino[1,2-a]azepine, furan, 1H-pyrrole, isoxazole, oxazole, 1H-pyrazole, 1H-imidazole, thiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, 4H-1,2,4-triazole, 1H-tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyridine-2(1H)-one, 1,4,5,6-tetrahydrocyclopenta[c]pyrazole, 6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazole, 2,3-dihydroimidazo[2,1-b]thiazole, imidazo[2,1-b][1,3,4-c]pyridine, 4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine, 4,5,6,7-tetrahydrothiazole[5,4-c]pyridine, 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, quinoline, isoquinoline, 2,3-dihydrobenzofuran, 5,6,7,8-tetrahydroquinoline, 3,4-dihydro-1H-isochromene, 1,2,3,4-tetrahydroisoquinoline, 4H-benzo[d][1,3]dioxane, 5,6,7,8-tetrahydropyrido[3,4-d]pyrimidine, benzofuran, 1H-indole, benzo[d]oxazole, 1H-

benzo[d]imidazole, H-imidazo[1,2-a]pyridine, imidazo[1,2-a]pyrimidine, 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine-3(2H)-one, 2,3,4,5-tetrahydro-1H-benzo[d]azepine, 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine, 5,6,7,8-tetrahydro-4H-isoxazolo[4,3-d]azepine and6,7,8,9-tetrahydro-2H-[1,2,4]triazolo[4,3-g][1,4]diazepin-3(5H)-one.

It is to be understood that if a carbocyclic or heterocyclic moiety may be bonded or otherwise attached to a designated substrate, through differing ring atoms without denoting a specific point of attachment, then all possible points are intended, whether through a carbon atom or, for example, a trivalent nitrogen atom. For example, the term "pyridyl" means 2-, 3-, or 4-pyridyl, the term "thienyl" means 2-, or 3-thienyl, and so forth.

Pharmaceutically acceptable salts of the compounds of the invention include the acid addition and base salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of the invention may be readily prepared by mixing together solutions of a compound of the invention and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol, water and the like. The term 'hydrate' is included within the meaning of the term "solvate" and is frequently used when the solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include solvates (hydrates) wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, d_6-DMSO.

The compounds of the invention which are complexes, such as clathrates and drug-host inclusion complexes, are within the scope of the invention. In contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

The compounds of the invention include all polymorphs and isomers thereof, including optical, geometric and tautomeric isomers as hereinafter defined and isotopically-labeled compounds.

The compounds of the invention containing one or more asymmetric carbon atoms may exist as two or more stereoisomers. Where a compound contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

All stereoisomers, geometric isomers and tautomeric forms of the compounds of the invention are included within the scope of the invention, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of the invention contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known to those skilled in the art [see, for example, "Stereochemistry of Organic Compounds" by E.L. Eliel (Wiley, New York, 1994)].

The invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of the invention, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, are

particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refers to a solvent which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

The parenthetical negative or positive sign used herein in the nomenclature denotes the direction plane polarized light is rotated by the particular stereoisomer.

One of ordinary skill will recognize that certain compounds of the invention may contain one or more atoms which may be in a particular stereochemical or geometric configuration, giving rise to stereoisomers and configurational isomers. All such isomers and mixtures thereof are included in the invention. Solvates (hydrates) of the compounds of the invention are also included.

Other features and advantages will be apparent from the specification and claims which describe the invention.

Detailed Description of the Invention

The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations. In the following examples, molecules with a single chiral center, unless otherwise noted, exist as a racemic mixture. Those molecules with two or more chiral centers, unless otherwise noted, exist as a racemic

mixture of diastereomers. Single enantiomers/diastereomers may be obtained by methods known to those skilled in the art.

In general, the compounds of the invention may be prepared by processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of the invention are provided as further features of the invention and are illustrated in the reaction schemes provided below and in the experimental section. The use of various protecting groups in these reactions are also well known and are exemplified in Protective Groups In Organic Synthesis, Second Edition, T.W. Greene and P.G.M. Wuts, John Wiley and Sons, Inc. 1991, pages 227-229, which is hereby incorporated by reference in its entirety for all purposes.

The utility of the compounds of the invention as medical agents for the reduction of intraocular pressure and accordingly to treat glaucoma is demonstrated by the activity of the compounds in conventional assays, including the in vivo assay and a receptor binding assay. Such assays also provide a means whereby the activities of the compounds can be compared to each other and with the activities of other known compounds. The results of these comparisons are useful for determining dosage levels in mammals, including humans, for the treatment of such diseases.

The compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The compounds of the invention intended for pharmaceutical use may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).]

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations, such as tablets, capsules containing particulates, liquids, or powders; lozenges (including liquid-filled), chews; multi- and nano-particulates; gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol,

natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

The foregoing formulations for the various types of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Thus, compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA [define] microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated [see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).]

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1 µg to 20 mg of the compound of the invention per actuation and the actuation volume may vary from 1 µl to 100 µl. A typical formulation may comprise a compound of the invention, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid; a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose; or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

The compounds of the invention can be incorporated into various types of ophthalmic formulations for delivery to the eye. These compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride and water to form an aqueous, sterile ophthalmic suspensions or solutions. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the active ingredient in a hydrophilic base prepared from the combination of, for example, carbopol-940 or the like according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated. Ophthalmic solution formulations may be prepared by dissolving the active ingredient in a physiologically acceptable isotonic aqueous

buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the active ingredient. Furthermore, the ophthalmic solution may contain a thickener such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methyl-cellulose, polyvinylpyrrolidone, or the like to improve the retention of the medicament in the conjunctival sac.

The compounds of the invention are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 4.5 to 7.8. The compounds will normally be contained in these formulations in an amount of 0.1% to 10% by weight, but preferably in an amount of 0.25% to 5.0% by weight. Thus, for topical presentation, 1 to 3 drops of these formulations would be delivered to the surface of the eye 1 to 4 times a day according to the routine discretion of a skilled clinician.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Dosage ranges are based on an average human subject having a weight of about 65 kg to 70 kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly. Depending on the disease and condition of the patient, the term "treatment" as used herein may include one or more of curative, palliative and prophylactic treatment.

The following non-limiting preparations and Examples illustrate the preparation of the compounds of the invention.

Examples

^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 M Hz, 400 M Hz or 500 M Hz and ^{13}C-NMR spectra were recorded operating at 75 M Hz.

NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or DMSO-D_6 (2.50 ppm and 39.51 ppm) or CD_3OD (3.4 ppm and 4.8 ppm and 49.3 ppm), or internal tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Atmospheric pressure chemical ionization mass spectra (APCI) were obtained on a Fisons.TM. Platform II Spectrometer (carrier gas: acetonitrile: available from Micromass Ltd, Manchester, UK). Chemical ionization mass spectra (CI) were obtained on a Hewlett-Packard.TM. 5989 instrument (ammonia ionization, PBMS: available from Hewlett-Packard Company, Palo Alto, Calif.). Electrospray ionization mass spectra (ES) were obtained on a Waters.TM. ZMD instrument (carrier gas: acetonitrile: available from Waters Corp., Milford, Mass.). Where the intensity of chlorine or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for $^{35}Cl/^{37}Cl$-containing ions and 1:1 for $^{79}Br/^{81}Br$-containing ions) and the intensity of only the lower mass ion is given. In some cases only representative ^1H NMR peaks are given. MS peaks are reported for all examples.

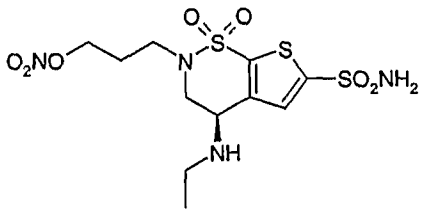
Column chromatography was performed with either Baker.TM. silica gel (40 .mu.m; J. T. Baker, Phillipsburg, N.J.) or Silica Gel 50 (EM Sciences.TM., Gibbstown, N.J.) in glass columns or in Flash 40 Biotage.TM. columns (ISC, Inc., Shelton, Conn.) under low nitrogen pressure.

The following abbreviations may be used herein: AcOH (acetic acid); MeCN (acetonitrile); Et_2O (diethyl ether); DMF (*N,N*-dimethylformamide); DMSO (dimethylsulfoxide); MeOH (methanol); EtOH (ethanol); EtOAc (ethyl acetate); THF (tetrahydrofuran).

Method A

Example A-1

3-[(4R)-6-(aminosulfonyl)-4-(ethylamino)-1,1-dioxido-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazin-2-yl]propyl nitrate

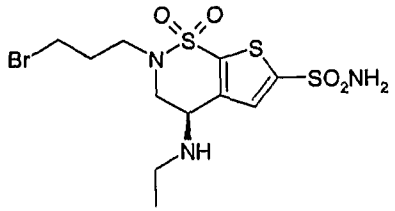


To a solution of the nitrate salt of (4R)-2-(3-bromopropyl)-4-(ethylammmonium)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine-6-sulfonamide 1,1-dioxide (738 mg, 1.49 mmol) in acetonitrile (25 mL) was added concentrated nitric acid (1.0 mL) and silver nitrate (726 mg, 3.0 equiv) sequentially. The solution was then heated at 60 °C for 24 hours, at which point additional silver nitrate (508 mg, 2 equiv) was added in one portion and heated at 60 °C for an additional 24 h. The mixture was allowed to cool to ambient temperature and diluted with ethyl acetate (50 mL) and brine (25 mL). The heterogeneous mixture was allowed to vigorously stir for 1 h then the layers were separated and the organics were washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude oil was dissolved in dimethylsulfoxide (4 mL) and deionized water (1 mL) and purified by reverse phase preparatory HPLC (0-30%, MeCN/H_2O, 0.1% AcOH). The pure fractions were collected and lyophilized to dryness to provide the title compound as a fluffy off-white solid (174 mg, 28%).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.05 (br. s., 2 H) 7.69 (s, 1 H) 4.59 (t, J = 6.1 Hz, 2 H) 4.14 (br. s., 1 H) 3.84 (s, 2 H) 3.45 (dt, J = 14.1, 7.3 Hz, 1 H) 3.21 - 3.32 (m, 1 H) 2.56 - 2.67 (m, 2 H) 2.02 (dt, J = 12.8, 6.4 Hz, 2 H) 1.04 (t, J = 6.4 Hz, 3 H); LRMS (ES) *m/z* 415.0 ([M + H]$^+$; calcd for $C_{11}H_{19}N_4O_7S_3$ 415.0).

Preparation a-1-a

(4R)-2-(3-bromopropyl)-4-(ethylamino)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine-6-sulfonamide1,1-dioxide

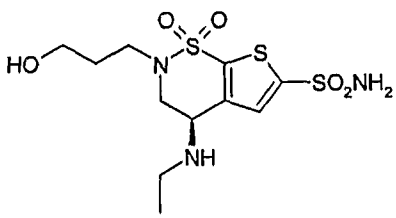


A solution of (4R)-4-(ethylamino)-2-(3-hydroxypropyl)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine-6-sulfonamide 1,1-dioxide (1.05 g, 2.74 mmol) in concentrated hydrobromic acid (10 mL) was heated to 80 °C for 18 h. The slightly brown homogeneous solution was allowed to cool to ambient temperature and purified by reverse phase preparatory HPLC (1-30%, MeCN/H_2O, 0.1% AcOH). The fractions were collected and concentrated nitric acid (1.0 mL) was added the solution was concentrated *in vacuo* to provide the nitrate salt of the title compound as a white solid (738 mg, 54%).

^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 8.21 (s, 2 H) 7.99 (s, 1 H) 4.97 (s, 1 H) 4.05 - 4.23 (m, 2 H) 3.40 - 3.71 (m, 4 H) 3.23 - 3.39 (m, 1 H) 2.98 - 3.21 (m, 2 H) 2.17 (dt, *J* = 13.2, 6.6 Hz, 2 H) 1.25 (t, *J* = 7.1 Hz, 3 H); LRMS (ES) *m/z* 432.0 ($[M + H]^+$; calcd for $C_{11}H_{19}BrN_3O_4S_3$ 432.0).

Preparation a-1-b

(4R)-4-(ethylamino)-2-(3-hydroxypropyl)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine-6-sulfonamide1,1-dioxide



To a slurry of (4R)-4-(ethylamino)-2-(3-methoxypropyl)-3,4-dihydro-2H-thieno[3,2-e][1,2]thiazine-6-sulfonamide 1,1-dioxide (397 mg, 1.04 mmol) in dichloromethane (20 mL) under nitrogen was cooled to -78 °C. To this chilled slurry was added a solution of

boron tribromide (4.1 mL, 1.0 M) in dichloromethane dropwise *via* syringe pump (0.25 mL/min). The slurry was allowed to stir for 10 min at -78 °C before gradually warming to ambient temperature. The mixture was then allowed to stir at ambient temperature for 24 h. The excess boron tribromide was quenched by slow addition of methanol (20 mL) by syringe at 0 °C. Upon complete addition the reaction was a colorless homogeneous solution that was allowed to stir for 30 min at ambient temperature. The solution was then concentrated *in vacuo* to provide an oil that was azeotroped with methanol (3 x 10 mL). The crude oil was then dissolved in a 2:1 mixture of dimethylsulfoxide and hydrochloric acid (0.1 N) (5 mL) and purified by reverse phase HPLC (1-30% MeCN/H_2O (0.1% AcOH)). The collected fractions were lyophilized to dryness to provide the title compound as a white solid (255 mg, 66%).

^{1}H NMR (300 MHz, D_2O) δ ppm 7.82 (s, 1 H) 4.76 - 4.80 (m, 1 H) 4.23 (dd, *J* = 15.6, 4.3 Hz, 1 H) 4.09 (dd, *J* = 15.6, 5.8 Hz, 1 H) 3.68 (t, *J* = 6.0 Hz, 2 H) 3.53 (dt, *J* = 14.3, 7.3 Hz, 1 H) 3.38 (dt, *J* = 13.8, 6.8 Hz, 1 H) 3.14 (q, *J* = 7.3 Hz, 2 H) 1.82 - 2.01 (m, 2 H) 1.28 (t, *J* = 7.2 Hz, 3 H); LRMS (ES) *m/z* 370.0 ($[M + H]^+$; calcd for $C_{11}H_{20}N_3O_5S_3$ 370.1).

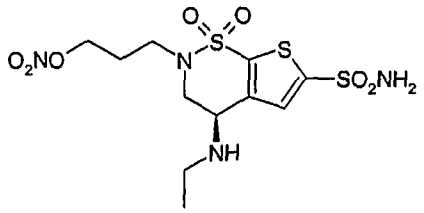
The ability of the compounds of the invention to reduce intraocular pressure may be measured using the assay described below. The compound of the invention has been tested for activities against Carbonic Anhydrase II and Carbonic Anhydrase IV. The activities are tabulated below in K_d (dissociation constant (nM)), or IC_{50} (the inhibitor concentration resulting in 50% inhibition of the enzyme activity (nM)).

Example #	Carbonic Anhydrase II K_d (nM)	Carbonic Anhydrase IV IC_{50} (nM)
A-1	0.0900	31.0

While the invention has been illustrated by reference to specific and preferred embodiments, those skilled in the art will recognize that variations and modifications may be made through routine experimentation and practice of the invention. Thus, the invention is intended not to be limited by the foregoing description, but to be defined by the appended claims and their equivalents.

We Claim:

1. A compound of formula:



or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 for use as a medicament.

3. The use of a compound according to claim 1 for the preparation of a medicament for treating glaucoma or ocular hypertension.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to claim 1.

5 A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to claim 1 in a suitable form for topical administration.

6. A pharmaceutical composition according to claim 4 or 5 for the treatment of glaucoma and ocular hypertension.

7. A pharmaceutical composition according to claim 4 or 5, wherein the compound of formula I is administered as a solution, suspension or emulsion in an ophthalmically acceptable vehicle.

8. A method for treating glaucoma or ocular hypertension, wherein the method comprises contacting an effective intraocular pressure reducing amount of a pharmaceutical composition according to claim 4 or 5 with the eye in order to reduce eye pressure and to maintain the pressure at a reduced level.

9. A method for treating eye disorders in a patient in need thereof comprising administering a therapeutically effective amount of a carbonic anhydrase inhibitor according to claim 1 able to release nitric oxide.

10. A method according to claim 9 wherein said eye disorder is selected from glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies.

11. A method according to claim 9 wherein said carbonic anhydrase inhibitor is a compound having an inhibition constant (K_i) against the isoenzyme CAII in the range of 0.01 to 200 nM.

12. A method according to claim 9 wherein said carbonic anhydrase inhibitor is a compound having a dissociation constant (K_d) against the isoenzyme CAII in the range of 0.01 to 200 nM.

13. A method according to claim 9 wherein said carbonic anhydrase inhibitor is a compound having an inhibition constant (K_i) against the isoenzyme CAIV in the range of 0.01 to 200 nM.

14. A method according to claim 9 wherein said carbonic anhydrase inhibitor is a compound having a dissociation constant (K_d) against the isoenzyme CAIV in the range of 0.01 to 200 nM.

15. A method according to claim 9 wherein said carbonic anhydrase inhibitor able to release nitric oxide is a compound having an EC_{50} value in the range of 1 to 50 μM.

16. A method according to claim 9 wherein said carbonic anhydrase inhibitor able to release nitric oxide is a compound having an IC_{50} value in the range of 1 to 50 μM.

17. A method for the treatment of glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive

retinopathy and retinal vasculopathies comprising administering a compound according to claim 1.

18. A method for the treatment of glaucoma, ocular hypertension, age-related macular degeneration, diabetic macular edema, diabetic retinopathy, hypertensive retinopathy and retinal vasculopathies comprising administering a pharmaceutical composition according to any one of claims 4 to 7.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/000813

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D513/04 A61K31/542 A61P27/06

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

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, WPI Data, BEILSTEIN Data, CHEM ABS 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 91/15486 A (ALCON LAB INC [US]) 17 October 1991 (1991-10-17) claims; examples 19-25; table 1	1-18
A	US 5 240 923 A (DEAN THOMAS R [US] ET AL) 31 August 1993 (1993-08-31) claims; examples 25,29,32-38; table 1	1-18

☐ 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 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
17 June 2008	25/06/2008

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, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gavriliu, Daniela

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2008/000813

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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable 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 reportcovers 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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/000813

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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