

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 June 2009 (11.06.2009)

PCT

(10) International Publication Number
WO 2009/073460 A2

(51) International Patent Classification:

A61K 31/16 (2006.01) A61P 27/02 (2006.01)
A61K 31/196 (2006.01) A61P 27/06 (2006.01)
A61K 31/52 (2006.01) C07K 14/00 (2006.01)
A61K 31/505 (2006.01) C12N 15/11 (2006.01)
A61K 31/53 (2006.01)

(21) International Application Number:

PCT/US2008/084607

(22) International Filing Date:

25 November 2008 (25.11.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/991,790 3 December 2007 (03.12.2007) US

(71) Applicant (for all designated States except US): **BAUSCH & LOMB INCORPORATED** [US/US]; One Bausch & Lomb Place, Rochester, NY 14604-2701 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **PFEFFER, Bruce, Alan** [US/US]; 9 Old Post Road, Fairport, NY 14450 (US).

(74) Agents: **VO, Toan, P.** et al.; Bausch & Lomb Incorporated, One Bausch & Lomb Place, Rochester, NY 14604-2701 (US).

(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:

— as to the identity of the inventor (Rule 4.17(i))

Published:

— without international search report and to be republished upon receipt of that report

(54) Title: INHIBITION OF 11 BETA-HYDROXYSTEROID DEHYDROGENASE TYPE 1 FOR OCULAR NEUROPROTECTION

(57) Abstract: A composition comprises a material capable of controlling a level of cortisol in an ocular environment for effecting ocular neuroprotection in subjects in risk of developing or worsening an ocular neurodegenerative condition. Such a composition is injected into or implanted in the subject's posterior segment to provide such neuroprotection.



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INHIBITION OF 11 BETA-HYDROXYSTEROID DEHYDROGENASE TYPE 1 FOR OCULAR NEUROPROTECTION

BACKGROUND

The present invention relates to compositions and methods for effecting ocular neuroprotection. In particular, the present invention relates to such compositions comprising antagonists to 11 β -hydroxysteroid dehydrogenase type 1 and such methods using such antagonists.

Endogenous glucocorticoids ("GCs") exert a diverse array of physiological roles including the regulation of carbohydrate and amino acid metabolism, maintenance of blood pressure, modulation of the stress and immune responses, and homeostasis of the central nervous system ("CNS").

Cortisol, the principal circulating GC in human, is secreted from the adrenal gland under the control of the hypothalamo-pituitary-adrenal ("HPA") axis. GCs elicit their hormone action on cells via binding to their cytosolic receptor, the glucocorticoid receptor ("GR"). The GC/GR complex then translocates to the cell nucleus, binds to the glucocorticoid response element ("GRE") of genes, and effects their transcription. Thus, the prereceptor level of active cortisol directly affects the cellular physiology. Two enzymes, exhibiting tissue-specific expression, control the interconversion of cortisol (the active form) and cortisone (the inactive keto form). In vivo, 11 β -hydroxysteroid dehydrogenase type 1 ("11 β -HSD1") functions predominantly as a reductase, generating active cortisol from inactive cortisone, and thereby enhancing activation of the GR. 11 β -HSD1 is broadly distributed among tissues, with predominant expression occurring in hepatic, adipose, gonadal, and central nervous system. 11 β -Hydroxysteroid dehydrogenase type 2 ("11 β -HSD2"), which is mainly expressed in the placenta and aldosterone target tissues such as the kidney and colon, acts almost exclusively as a dehydrogenase converting active cortisol to inactive cortisone, thereby preventing the activation of mineralocorticoid receptor-sensitive genes by excess cortisol. Recent studies have elucidated the potential effects of excess GCs on the CNS. Most neural pathways can be modified by GCs, as their target genes include those for neurotransmitter synthesis, cellular receptor expression, and synthesis of enzymes

involved in calcium activation and ion channels (e.g., K^+ channels). High levels of GCs are deleterious to the homeostasis of the CNS, causing abnormalities in development through potentiation of cognitive deficiencies seen in aging. Although the hippocampus requires GCs for neuronal function and survival, it is also particularly vulnerable to the adverse effect of chronic GC excess, which produces atrophy of dendrites, neuronal and cognitive dysfunction and even neuronal loss, as shown in some strains of rats. M.C. Homes and J.R. Seckl, *Mol. Cell. Endocrinol.*, Vol. 248, 9 (2006). In addition, pharmacological evidence indicates that chronic administration of dexamethasone, a GR agonist, as part of the anti-inflammatory therapy for rheumatoid arthritis, leads to widespread neuronal atrophy in the brain. Consistent with this finding, the results of several clinical studies lend support to the notion that sustained endogenous elevation of plasma cortisol levels may be regarded as a major predisposing factor for neurodegenerative disorders in the human and mammalian brain. Such a hypothesis is further supported by the observation that individuals with Alzheimer's and Parkinson's disease exhibit significantly higher total plasma cortisone concentrations, which are then available for conversion to active cortisol under the action of 11β -HSD1. I.M. Abraham et al., *J. Endocrinol.*, Vol. 13, 749 (2001).

The retina is part of the CNS; like the cerebral and the cerebellar cortices, the neural retina develops into a layered array of different neuronal cell types. Among these are retina ganglion cells, Müller glial cells, amacrine cells, and horizontal neurons, which cooperate in the transmission of electrical impulses from the retinal to the brain. As with the brain, the retina is a target for steroids and produces steroids itself. Recent advances in research have proved the existence of hormone steroid receptors, steroid enzymes for the formation of *ex novo* steroids or neurosteroids and their involvement in the physiology and pathology of visual function. The retina is capable of transforming cholesterol into pregnenolone, which is then converted into other GCs and sex steroids. Recently, high cholesterol in retinal pigment epithelium ("RPE"), changes in apolipoprotein E ("ApoE") expression by Müller glia of the retina, and the apolipoprotein polymorphism have been suggested to increase the risk of age-related macular degeneration ("AMD"), the impairment of visual function during aging, and the progression of glaucoma. See P. Guarnieri et al., *Ann. N.Y. Acad. Sci.*, Vol. 1007, 117 (2003) and references therein. In addition, it was shown that the increased blood level of cortisol in patients with

functional and subclinical stages of diabetic retinopathy was accompanied by disturbed microcirculation in the eye (as exhibited by obliterated regions in microvessels and the presence of microaneurism) and decreased functional activity of the retina outer layers (as measured by electrophysiological parameters). N.A. Gavrilova et al., *Biol. Bull.*, Vol. 29, No. 6, 577 (2002). Furthermore, in a recent study, cortisol level was significantly associated with diabetic retinopathy and neuropathy and tended to be associated with macroangiopathy. I. Chiodini et al., *Diabetes Care*, Vol. 30, No. 1, 83 (2007).

Presently, these ocular neurodegenerative conditions are not medically reversible. There have been some achievements in slowing the progression of these blinding diseases with medicaments or surgery. However, success in treating all cases of ocular degeneration is still elusive. Therefore, continued efforts have been devoted to finding novel and effective compositions and treatment methods for preserving or improving the visual function of patients having these diseases.

SUMMARY

In general, the present invention provides compositions and methods for effecting ocular neuroprotection.

In one aspect, the present invention provides compositions and methods for controlling a progression of ocular neurodegenerative conditions.

In another aspect, such ocular neurodegenerative conditions are selected from the group consisting of glaucoma, retinitis pigmentosa, AMD (including wet and dry AMD), diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.

In still another aspect, a composition of the present invention comprises a material capable of controlling a level of 11 β -HSD1 in an ocular environment when applied thereto.

In yet another aspect, a composition of the present invention comprises an antagonist to 11β -HSD1 in an effective amount for providing ocular neuroprotection.

In a further aspect, a composition comprises an antagonist to 11β -HSD1 in an effective amount for controlling an ocular neurodegenerative condition.

In a further aspect, a composition of the present invention comprises a topical formulation; injectable formulation; or implantable formulation, system, or device.

In still another aspect, a method for controlling a progression of ocular neurodegenerative conditions comprises controlling a level of 11β HSD1 in an ocular environment.

In yet another aspect, a method for controlling a progression of an ocular neurodegenerative condition comprises administering to an eye of a patient in need of such controlling a composition comprising an antagonist of 11β -HSD1 in an amount and at a frequency sufficient to control such progression.

In a further aspect, such administering comprises providing such a composition in the posterior segment of the eye.

Other features and advantages of the present invention will become apparent from the appended figures and the following detailed description and claims.

DETAILED DESCRIPTION

Definition of Terms

As used herein, the term “control” also includes treatment, reduction, amelioration, alleviation, stoppage, and reversing.

As used herein, the term “antagonist to 11β -HSD1” also includes compounds or materials that neutralize, inhibit, or impede the activity, transcription, expression, or

signaling cascade of 11 β -HSD1. The term "antagonist to 11 β -HSD1" also includes a prodrug, a pharmaceutically acceptable salt, hydrate, or ester of such an antagonist.

The term "alkenyl" as used herein, refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl.

The term "alkoxy" as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy and hexyloxy.

The term "alkoxyalkyl" as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkoxyalkyl include, but are not limited to, tert-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl and methoxymethyl.

The term "alkoxycarbonyl" as used herein, refers to an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl and tert-butoxycarbonyl.

The term "alkyl" as used herein, refers to a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl and n-decyl.

The term "alkylcarbonyl," as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined

herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl and 1-oxopentyl.

The term "alkylsulfonyl" as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of alkylsulfonyl include, but are not limited to, methylsulfonyl and ethylsulfonyl.

The term "alkyl-NH" as used herein, refers to an alkyl group, as defined herein, appended to the parent molecular moiety through a nitrogen atom.

The term "alkyl-NH-alkyl" as used herein, refers to an alkyl-NH group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "aryl" as used herein, means a phenyl group, or a bicyclic or a tricyclic fused ring system. Bicyclic fused ring systems are exemplified by a phenyl group appended to the parent molecular moiety and fused to a monocyclic cycloalkyl group, as defined herein, a phenyl group, a monocyclic heteroaryl group, as defined herein, or a monocyclic heterocycle, as defined herein. Tricyclic fused ring systems are exemplified by an aryl bicyclic fused ring system, as defined herein and fused to a monocyclic cycloalkyl group, as defined herein, a phenyl group, a monocyclic heteroaryl group, as defined herein, or a monocyclic heterocycle, as defined herein. Representative examples of aryl include, but are not limited to, anthracenyl, azulenyl, fluorenyl, indenyl, indenyl, naphthyl, phenyl and tetrahydronaphthyl.

The aryl groups may be optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylalkoxy, arylcarbonyl, aryloxy, arylsulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkylalkoxy, ethylenedioxy, formyl, haloalkoxy, haloalkyl, halogen, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylalkoxy, heteroarylcarbonyl, heterocycle, heterocycloalkyl, heterocyclealkoxy, heterocyclecarbonyl, heterocycleoxy,

hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$, wherein R_f and R_g are independently selected from the group consisting of hydrogen, alkyl, alkoxyalkyl, alkylcarbonyl, alkylsulfonyl, cycloalkyl, heterocycloalkyl and cycloalkylalkyl and wherein the cycloalkyl, the heterocycle of heterocycloalkyl and the cycloalkyl of cycloalkylalkyl as represented by R_f and R_g are each independently unsubstituted or substituted with 1, 2 or 3 substituent selected from the group consisting of alkyl, haloalkyl and halogen. The substituent aryl, the aryl of arylalkyl, the aryl of arylalkenyl, the aryl of arylalkoxy, the aryl of arylcarbonyl, the aryl of aryloxy, the aryl of arylsulfonyl, the cycloalkyl of cycloalkylalkoxy, the substituent heteroaryl, the heteroaryl of heteroarylalkyl, the heteroaryl of heteroarylalkenyl, the heteroaryl of heteroarylalkoxy, the heteroaryl of heteroarylcarbonyl, the substituent heterocycle, the heterocycle of heterocycloalkyl, the heterocycle of heterocyclealkoxy, the heterocycle of heterocyclecarbonyl, the heterocycle of heterocycleoxy, the heterocycle of heterocyclesulfonyl may be optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkynyl, carboxy, carboxyalkyl, cyano, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$.

The term "aryl"¹ as used herein, refers to a substituted phenyl group wherein the substituent is a member selected from the group consisting of alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkynyl, aryl, arylcarbonyl, aryloxy, arylsulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, ethylenedioxy, formyl, haloalkoxy, haloalkyl, halogen, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocycle, heterocyclecarbonyl, heterocycleoxy, hydroxy, hydroxyalkyl and nitro, or a bicyclic or a tricyclic fused ring system. Bicyclic fused ring systems are exemplified by a phenyl group appended to the parent molecular moiety, which is fused to a cycloalkyl group, as defined herein, a phenyl group, a heteroaryl, as defined herein, or a heterocycle as defined herein. Tricyclic fused ring systems are exemplified by an aryl bicyclic fused ring system fused to a cycloalkyl group, as defined herein, a phenyl group, a heteroaryl, as defined herein, or a heterocycle as defined herein. Bicyclic and tricyclic fused ring systems of this invention may be optionally substituted with 1, 2, 3, 4 or 5 substituents independently selected from

alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkynyl, aryl, arylcarbonyl, aryloxy, arylsulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, ethylenedioxy, formyl, haloalkoxy, haloalkyl, halogen, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocycle, heterocyclecarbonyl, heterocycleoxy, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$, wherein R_f and R_g are as described herein. Representative examples of aryl.sup.1 include, but are not limited to, anisole, aniline, anthracenyl, azulenyl, fluorenyl, naphthyl, and tetrahydronaphthyl.

The term "arylalkenyl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkenyl group, as defined herein.

The term "arylalkyl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl and 2-naphth-2-ylethyl.

The term "arylalkoxy" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein.

The term "arylcarbonyl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylcarbonyl include, but are not limited to, benzoyl and naphthoyl.

The term "aryl-NH-" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a nitrogen atom.

The term "aryl-NH-alkyl" as used herein, refers to an aryl-NH- group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "aryloxy," as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an oxy moiety, as defined herein. Representative examples of aryloxy include, but are not limited to phenoxy, naphthyloxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy and 3,5-dimethoxyphenoxy.

The term "aryloxyalkyl" as used herein, refers to an aryloxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "arylsulfonyl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of arylsulfonyl include, but are not limited to, phenylsulfonyl, 4-bromophenylsulfonyl and naphthylsulfonyl.

The term "carbonyl" as used herein refers to a -C(O)- group.

The term "carboxy" as used herein refers to a -C(O)-OH group.

The term "carboxyalkyl" as used herein refers to a carboxy group as defined herein, appended to the parent molecular moiety through an alkyl group as defined herein.

The term "carboxycycloalkyl" as used herein refers to a carboxy group as defined herein, appended to the parent molecular moiety through a cycloalkyl group as defined herein.

The term "cycloalkyl" as used herein, refers to a monocyclic, bicyclic, or tricyclic ring system. Monocyclic ring systems are exemplified by a saturated cyclic hydrocarbon group containing from 3 to 8 carbon atoms. Examples of monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Bicyclic fused ring systems are exemplified by a cycloalkyl group appended to the parent molecular moiety, which is fused to an additional cycloalkyl group, as

defined herein, a phenyl group, a heteroaryl, as defined herein, or a heterocycle as defined herein. Tricyclic fused ring systems are exemplified by a cycloalkyl bicyclic fused ring system fused to an additional cycloalkyl group, as defined herein, a phenyl group, a heteroaryl, as defined herein, or a heterocycle as defined herein. Bicyclic ring systems are also exemplified by a bridged monocyclic ring system in which two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms. Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane and bicyclo[4.2.1]nonane. Tricyclic ring systems are also exemplified by a bicyclic ring system in which two non-adjacent carbon atoms of the bicyclic ring are linked by a bond or an alkylene bridge of between one and three carbon atoms. Representative examples of tricyclic-ring systems include, but are not limited to, tricyclo[3.3.1.0^{sup}.3,7]nonane and tricyclo[3.3.1.1^{sup}.3,7]decane (adamantane).

The cycloalkyl groups may be substituted with 1, 2, 3, 4 or 5 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkyl carbonyl, alkynyl, aryl, arylalkyl, aryl carbonyl, aryloxy, arylsulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, ethylenedioxy, formyl, haloalkoxy, haloalkyl, halogen, heteroaryl, heteroarylalkyl, heteroarylcarbonyl, heterocycle, heterocycloalkyl, heterocyclecarbonyl, heterocycleoxy, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$, wherein R_f and R_g are independently selected from the group consisting of hydrogen, alkyl, alkoxyalkyl, alkylcarbonyl, alkylsulfonyl, cycloalkyl and cycloalkylalkyl. The substituent aryl, the aryl of arylalkyl, the aryl of arylcarbonyl, the aryl of aryloxy, the aryl of arylsulfonyl, the substituent heteroaryl, the heteroaryl of heteroarylalkyl, the heteroaryl of heteroarylcarbonyl, the substituent heterocycle, the heterocycle of heterocycloalkyl, the heterocycle of heterocyclecarbonyl, the heterocycle of heterocycleoxy, the heterocycle of heterocyclesulfonyl may be optionally substituted with 0, 1, 2 or 3 substituents independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxy carbonyl, alkyl, alkylcarbonyl, alkynyl, carboxy, carboxyalkyl, cyano, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$.

The term "cycloalkylalkyl" as used herein, refers to a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, 2-cyclobutylethyl, cyclopentylmethyl, cyclohexylmethyl and 4-cycloheptylbutyl.

The term "cycloalkylalkoxy" as used herein, refers to a cycloalkyl group, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein.

The term "cycloalkylcarbonyl" as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of cycloalkylcarbonyl include, but are not limited to, cyclopropylcarbonyl, 2-cyclobutylcarbonyl and cyclohexylcarbonyl.

The term "cycloalkyloxy," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through an oxy group, as defined herein.

The term "cycloalkylsulfonyl," as used herein, refers to cycloalkyl group, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of cycloalkylsulfonyl include, but are not limited to, cyclohexylsulfonyl and cyclobutylsulfonyl.

The term "halo" or "halogen," as used herein, refers to -Cl, -Br, -I or -F.

The term "haloalkyl," as used herein, refers to at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl and 2-chloro-3-fluoropentyl.

The term "heteroaryl," as used herein, refers to an aromatic monocyclic ring or an aromatic bicyclic ring system. The aromatic monocyclic rings are five or six-membered rings containing at least one heteroatom independently selected from the group consisting of N, O and S. The five membered aromatic monocyclic rings have two double bonds and the six membered aromatic monocyclic rings have three double bonds. The bicyclic heteroaryl groups are exemplified by a monocyclic heteroaryl ring appended to the parent molecular moiety and fused to a monocyclic cycloalkyl group, as defined herein, a monocyclic aryl group, as defined herein, a monocyclic heteroaryl group, as defined herein, or a monocyclic heterocycle, as defined herein. Representative examples of heteroaryl include, but are not limited to, benzimidazolyl, benzofuranyl, benzothiazolyl, benzothienyl, benzoxazolyl, furyl, imidazolyl, indazolyl, indolyl, indoliziny, isobenzofuranyl, isoindolyl, isoxazolyl, isoquinoliny, isothiazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, phthalazinyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, quinoliny, quinoliziny, quinoxaliny, quinazolinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl and triazinyl.

The heteroaryls may be optionally substituted with 1, 2 or 3 substituents independently selected from alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkynyl, aryl, arylalkenyl, arylalkyl, arylcarbonyl, aryloxy, arylsulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, ethylenedioxy, formyl, haloalkoxy, haloalkyl, halogen, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heterocycle, heterocycloalkyl, heterocyclecarbonyl, heterocycleoxy, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$, wherein R_f and R_g are as described herein. The substituent aryl, the aryl of arylalkyl, the aryl of arylalkenyl, the aryl of arylcarbonyl, the aryl of aryloxy, the aryl of arylsulfonyl, the substituent heteroaryl, the heteroaryl of heteroarylalkyl, the heteroaryl of heteroarylalkenyl, the substituent heterocycle, the heterocycle of heterocycloalkyl, the heterocycle of heterocyclecarbonyl, the heterocycle of heterocycleoxy, may be optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkynyl, carboxy, carboxyalkyl, cyano, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$.

The term "heteroarylalkenyl" as used herein, refers to a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkenyl group, as defined herein.

The term "heteroarylalkyl" as used herein, refers to a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "heteroarylalkoxy" as used herein, refers to a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein.

The term "heteroaryloxy" as used herein, refers to a heteroaryl, as defined herein, appended to the parent molecular moiety through an oxy group, as defined herein.

The term "heteroaryloxyalkyl" as used herein, refers to a heteroaryloxy, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "heterocycle" as used herein, refers to a non-aromatic monocyclic ring or a non-aromatic bicyclic ring. The non-aromatic monocyclic ring is a three-, four-, five-, six-, seven-, or eight-membered ring containing at least one heteroatom, independently selected from the group consisting of N, O and S. Representative examples of monocyclic ring systems include, but are not limited to, azetidiny, aziridiny, diazepiny, dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydro-2H-pyranyl, tetrahydro-2H-pyran-2-yl, tetrahydro-2H-pyran-4-yl, tetrahydrothienyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone) and thiopyranyl. The bicyclic heterocycles are exemplified by a monocyclic heterocycle appended to the parent molecular moiety and fused to a monocyclic cycloalkyl group, as defined herein, a

monocyclic aryl group, a monocyclic heteroaryl group, as defined herein, or a monocyclic heterocycle, as defined herein. Bicyclic ring systems are also exemplified by a bridged monocyclic ring system in which two non-adjacent atoms of the monocyclic ring are linked by a bridge of between one and three atoms selected from the group consisting of carbon, nitrogen and oxygen. Representative examples of bicyclic ring systems include but are not limited to, for example, benzopyranyl, benzothiopyranyl, benzodioxinyl, 1,3-benzodioxolyl, cinnolinyl, 1,5-diazocanyl, 3,9-diaza-bicyclo[4.2.1]non-9-yl, 3,7-diazabicyclo[3.3.1]nonane, octahydro-pyrrolo[3,4-c]pyrrole, indolinyl, isoindolinyl, 2,3,4,5-tetrahydro-1H-benzo[c]azepine, 2,3,4,5-tetrahydro-1H-benzo[b]azepine, 2,3,4,5-tetrahydro-1H-benzo[d]azepine, tetrahydroisoquinolinyl and tetrahydroquinolinyl.

The heterocycles may be optionally substituted with 1, 2 or 3 substituents independently selected from oxo, alkenyl, alkoxy, alkoxyalkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkynyl, aryl, arylalkyl, arylcarbonyl, aryloxy, arylsulfonyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, ethylenedioxy, formyl, haloalkoxy, haloalkyl, halogen, heteroaryl, heteroarylalkyl, heterocycle, heterocycloalkyl, heterocyclecarbonyl, heterocycleoxy, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$, wherein R_f and R_g are as described herein. The substituent aryl, the aryl of arylalkyl, the aryl of arylcarbonyl, the aryl of aryloxy, the aryl of arylsulfonyl, the heteroaryl, the heteroaryl of heteroarylalkyl, the substituent heterocycle, the heterocycle of heterocycloalkyl, the heterocycle of heterocyclecarbonyl, the heterocycle of heterocycleoxy, may be optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkynyl, carboxy, carboxyalkyl, cyano, haloalkyl, halogen, hydroxy, hydroxyalkyl, nitro, R_fR_gN- , $R_fR_gNalkyl$, $R_fR_gNcarbonyl$ and $R_fR_gNsulfonyl$.

The term "heterocycloalkyl" as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heterocycloalkyl include, but are not limited to, pyridin-3-ylmethyl and 2-pyrimidin-2-ylpropyl.

The term "heterocycloalkylcarbonyl" as used herein, refers to a heterocycloalkyl, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein.

The term "heterocyclealkoxy" as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an alkoxy group, as defined herein.

The term "heterocycleoxy" as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through an oxy group, as defined herein.

The term "heterocycleoxyalkyl" as used herein, refers to a heterocycleoxy, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "heterocycle-NH-" as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a nitrogen atom.

The term "heterocycle-NH-alkyl" as used herein, refers to a heterocycle-NH-, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein.

The term "heterocyclecarbonyl" as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of heterocyclecarbonyl include, but are not limited to, 1-piperidinylcarbonyl, 4-morpholinylcarbonyl, pyridin-3-ylcarbonyl and quinolin-3-ylcarbonyl.

The term "heterocyclesulfonyl" as used herein, refers to a heterocycle, as defined herein, appended to the parent molecular moiety through a sulfonyl group, as defined herein. Representative examples of heterocyclesulfonyl include, but are not

limited to, 1-piperidinylsulfonyl, 4-morpholinylsulfonyl, pyridin-3-ylsulfonyl and quinolin-3-ylsulfonyl.

The term "hydroxy" as used herein, refers to an -OH group.

The term "hydroxyalkyl" as used herein, refers to a hydroxy group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl and 2-ethyl-4-hydroxyheptyl.

The term "oxo" as used herein, refers to an =O group.

The term "oxy" as used herein, refers to an -O- group.

The term "sulfonyl" as used herein, refers to an -SO₂- group.

As discussed above, cells of the retina are capable of producing GCs and also are targets of GCs, including cortisol. In addition, 11 β -HSD1 is expressed in human ciliary nonpigmented epithelium ("NPE"), corneal epithelium, lens epithelium, and trabecular meshwork. S. Rauz et al., *Invest. Ophthalmol. Vis. Sci.*, Vol. 42, No. 9, 2037 (2001); J. Stokes et al., *Invest. Ophthalmol. Vis. Sci.*, Vol. 41, No.7, 1629 (2000). Thus, the action of 11 β HSD1 undoubtedly leads to production of cortisol within these cells and secretion of cortisol into the posterior chamber as a component of aqueous humor, which eventually flows out of the eye through the trabecular meshwork into the Schlemm's canal. Some of the cortisol in the posterior chamber may diffuse into the vitreous and add to the level of cortisol in contact with the retina.

In general, the present invention provides compositions and methods for effecting ocular neuroprotection.

In one aspect, the present invention provides compositions and methods for controlling a progression of ocular neurodegenerative conditions.

In another aspect, such ocular neurodegenerative conditions are selected from the group consisting of glaucoma, retinitis pigmentosa, AMD (including wet and dry AMD), diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.

In one embodiment such ocular neurodegenerative conditions comprise results of optic nerve damage due to hypertensive (high intraocular pressure or IOP) or normotensive glaucoma (normal IOP).

In another embodiment, such ocular neurodegenerative conditions are selected from the group consisting of retinitis pigmentosa, AMD (including wet and dry AMD), diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.

In still another aspect, a composition of the present invention comprises a material capable of controlling a level of 11β -HSD1 in an ocular environment when applied thereto. In one embodiment, such controlling comprises lowering the level of 11β -HSD1 in the ocular environment when the composition is applied thereto.

In yet another aspect, a composition of the present invention comprises an antagonist to 11β -HSD1 in an effective amount for providing ocular neuroprotection.

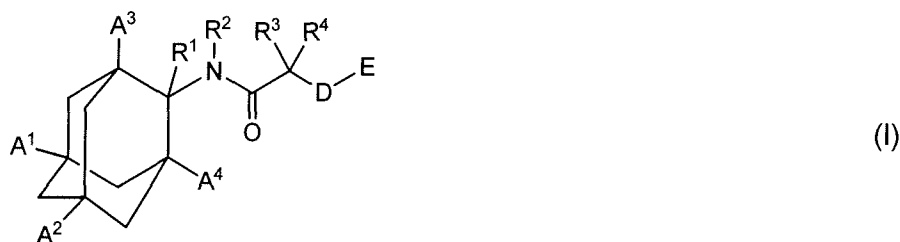
In a further aspect, a composition comprises an antagonist to 11β -HSD1 in an effective amount for controlling an ocular neurodegenerative condition.

In yet another aspect, the antagonist to 11β -HSD1 comprises a compound or material that inhibits the enzymatic activity of 11β -HSD1 (an “inhibitor of 11β -HSD1”).

In a further aspect, such an inhibitor is a selective inhibitor of 11β -HSD1. A selective inhibitor of 11β -HSD1 suitable for use in a composition or method of the present invention has low (preferably insignificant) inhibiting activity toward the 11β -HSD2 enzyme.

Non-limiting examples of inhibitors of 11 β -HSD1 suitable for use in a composition or method of the present invention include inhibitors disclosed in US Patents 7,217,838 (adamantane derivatives); 7,179,802 (triazole derivatives); and 6,849,636 (bicyclo[2.2.2]-oct-1-yl-1,2,4-triazole derivatives); US Patent Application Publications 2007/0270408 (pyrazolo[1,5-a]pyrimidine derivatives); 2007/0207985 (triazine derivatives); 2007/0244108 (phenylsulfonamide derivatives); 2006/0089349 (substituted amides); 2006/0111366 (substituted amides); 2006/0106008 (fused 1,2,4-triazole derivatives); 2006/0100235 (substituted triazoles); and 2005/0154038 (triazole derivatives). Each of these patents and patent applications is hereby incorporated by reference in its entirety.

In some embodiments, an inhibitor of 11 β -HSD1 suitable for use in a composition or method of the present invention comprises an adamantane derivative having Formula I (as disclosed in US Patent 7,217,838),



wherein one of A¹, A², A³ and A⁴ is selected from the group consisting of alkyl-NH-alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkyl, cycloalkylcarbonyl, cycloalkylsulfonyl, arylcarbonyl, arylsulfonyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heterocyclecarbonyl, heterocyclesulfonyl, aryl¹, arylalkyl, aryloxyalkyl, carboxyalkyl, carboxycycloalkyl, haloalkyl, heterocycloalkyl, heterocycleoxyalkyl, -SO₂-N(R⁵R⁶), -NR⁷-[C(R⁸R⁹)]_n-C(O)-R¹⁰, -O-[C(R¹¹R¹²)]_p-C(O)-R¹³, -OR^{14a}, -N(R¹⁵R¹⁶), -CO₂R¹⁷, -C(O)-N(R¹⁸R¹⁹), -C(R²⁰R²¹)-OR²², -C(R²³R²⁴)-N(R²⁵R²⁶), and heterocycle, with the exception that 5-membered heterocycles may not contain two oxygen atoms, and the remaining members of the group consisting of A¹, A², A³ and A⁴ are each individually selected from the group consisting of hydrogen, alkyl, alkyl-NH-alkyl, alkylcarbonyl, alkylsulfonyl, cycloalkyl, cycloalkylcarbonyl, cycloalkylsulfonyl, arylcarbonyl, arylsulfonyl, heterocyclecarbonyl, heterocyclesulfonyl,

aryl, arylalkyl, aryloxyalkyl, carboxyalkyl, carboxycycloalkyl, halogen, haloalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heterocycle, heterocycloalkyl, heterocycleoxyalkyl, $-\text{SO}_2-\text{N}(\text{R}^5\text{R}^6)$, $-\text{NR}^7-[\text{C}(\text{R}^8\text{R}^9)]_n-\text{C}(\text{O})-\text{R}^{10}$, $-\text{O}-[\text{C}(\text{R}^{11}\text{R}^{12})]_p-\text{C}(\text{O})-\text{R}^{13}$, $-\text{OR}^{14a}$, $-\text{N}(\text{R}^{15}\text{R}^{16})$, $-\text{CO}_2\text{R}^{17}$, $-\text{C}(\text{O})-\text{N}(\text{R}^{18}\text{R}^{19})$, $-\text{C}(\text{R}^{20}\text{R}^{21})-\text{OR}^{22}$, $-\text{C}(\text{R}^{23}\text{R}^{24})-\text{N}(\text{R}^{25}\text{R}^{26})$;

n is 0 or 1;

p is 0 or 1;

D is selected from the group consisting of a bond, $-\text{C}(\text{R}^{27}\text{R}^{28})-\text{X}-$, and $-\text{C}(\text{R}^{27}\text{R}^{28})-\text{C}(\text{R}^{29}\text{R}^{30})-\text{X}-$;

E is selected from the group consisting of a cycloalkyl, alkyl, aryl, heteroaryl and heterocycle, wherein the heteroaryl and the heterocycle are appended to the parent molecular moiety through an available carbon atom, or R^4 and E together with the atoms to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle;

X is selected from the group consisting of a bond, $-\text{N}(\text{R}^{31})-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$ and $-\text{SO}_2-$;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen, alkyl and cycloalkyl;

R^3 and R^4 are each independently selected from the group consisting of hydrogen, alkyl, carboxyalkyl, carboxycycloalkyl, cycloalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocycloalkyl, or R^3 and R^4 together with the atom to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, alkoxy, alkyl, alkylcarbonyl, alkylsulfonyl, carboxy, carboxyalkyl,

carboxycycloalkyl, cycloalkyl, cycloalkyloxy, cycloalkylsulfonyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxy, aryloxyalkyl, arylsulfonyl, heteroaryl, heteroarylalkyl, heteroarylalkylcarbonyl, heteroarylcarbonyl, heteroaryloxyalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkyl, heterocycloalkylcarbonyl, heterocyclecarbonyl, heterocycleoxyalkyl, heterocycleoxy, heterocyclesulfonyl and hydroxy, or R^5 and R^6 together with the atom to which they are attached form a heterocycle;

R^7 is selected from the group consisting of hydrogen, alkyl, carboxyalkyl, cycloalkyl, carboxycycloalkyl, aryl, arylalkyl, aryloxyalkyl, hydroxy, alkoxy, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heterocycle, heterocycloalkyl and heterocycleoxyalkyl;

R^8 and R^9 are each independently selected from the group consisting of hydrogen and alkyl, or R^8 and R^9 taken together with the atom to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle;

R^{10} is selected from the group consisting of hydrogen, alkyl, carboxyalkyl, cycloalkyl, carboxycycloalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, hydroxy, alkoxy, cycloalkyloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroaryloxyalkyl, heterocycle, heterocycloalkyl, heterocycleoxy, heterocycleoxyalkyl and $-N(R^{32}$ and $R^{33})$;

R^{11} and R^{12} are each independently selected from the group consisting of hydrogen and alkyl or R^{11} and R^{12} taken together with the atom to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle;

R^{13} is selected from the group consisting of hydroxy and $-N(R^{34}$ and $R^{35})$;

R^{14a} is selected from the group consisting of carboxyalkyl, cycloalkyl, carboxycycloalkyl, aryl, arylalkyl, aryloxyalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heterocycle, heterocycloalkyl and heterocycleoxyalkyl;

R^{14b} is selected from the group consisting of hydrogen, alkyl, carboxyalkyl, cycloalkyl, carboxycycloalkyl, aryl, arylalkyl, aryloxyalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heterocycle, heterocycloalkyl and heterocycleoxyalkyl;

R¹⁵ and R¹⁶ are each independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, carboxyalkyl, cycloalkyl, carboxycycloalkyl, aryl, arylalkyl, arylalkylcarbonyl, arylcarbonyl, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroarylalkylcarbonyl, heteroarylcarbonyl, heteroaryloxyalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkyl, heterocycloalkylcarbonyl, heterocyclecarbonyl, heterocycleoxyalkyl, heterocyclesulfonyl, alkylsulfonyl, cycloalkylsulfonyl and arylsulfonyl, or R¹⁵ and R¹⁶ together with the atom to which they are attached form a heterocycle;

R¹⁷ is selected from the group consisting of hydrogen, alkyl, carboxyalkyl, cycloalkyl, carboxycycloalkyl, aryl, arylalkyl, aryloxyalkyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heterocycle, heterocycloalkyl and heterocycleoxyalkyl;

R¹⁸ and R¹⁹ are each independently selected from the group consisting of hydrogen, alkoxy, alkyl, alkylsulfonyl, carboxy, carboxyalkyl, carboxycycloalkyl, cycloalkyl, cycloalkyloxy, cycloalkylsulfonyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, arylsulfonyl, heteroaryl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylsulfonyl, heterocycle, heterocycloalkyl, heterocycleoxyalkyl, heterocycleoxy, heterocyclesulfonyl and hydroxy, or R¹⁸ and R¹⁹ together with the atom to which they are attached form a heterocycle;

R²⁰, R²¹ and R²² are each independently selected from the group consisting of hydrogen, alkyl, aryl, arylalkyl, carboxyalkyl, carboxycycloalkyl, cycloalkyl, haloalkyl, heteroaryl, heteroarylalkyl, heterocycle and heterocycloalkyl;

R²³ and R²⁴ are each independently selected from the group consisting of hydrogen, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylcarbonyl, arylsulfonyl, carboxyalkyl, carboxycycloalkyl, cycloalkyl, cycloalkylcarbonyl, cycloalkylsulfonyl,

heteroaryl, heteroarylcarbonyl, heteroarylsulfonyl, heterocycle, heterocyclecarbonyl and heterocyclesulfonyl;

R^{25} and R^{26} are each independently selected from the group consisting of hydrogen, alkoxy, alkyl, alkylcarbonyl, alkylsulfonyl, aryl, arylcarbonyl, aryloxy, arylsulfonyl, carboxyalkyl, carboxycycloalkyl, cycloalkyl, cycloalkylcarbonyl, cycloalkyloxy, cycloalkylsulfonyl, heteroaryl, heteroarylcarbonyl, heteroaryloxy, heteroarylsulfonyl, heterocycle, heterocyclecarbonyl, heterocycleoxy, heterocyclesulfonyl and hydroxy, or R^{25} and R^{26} together with the nitrogen to which they are attached form a ring selected from the group consisting of heteroaryl and heterocycle;

R^{27} and R^{28} are each independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, heteroaryl and heterocycle or R^{27} and R^{28} together with the atom to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle, or R^{27} and R^{28} together with the atoms to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle, or R^{28} and R^4 together with the atoms to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle;

R^{29} and R^{30} are each independently selected from the group consisting of hydrogen, alkyl, alkoxy, aryl, aryloxy, cycloalkyl, cycloalkyloxy, heteroaryl, heterocycle, and $-N(R^{36}R^{37})$, or R^{29} and R^{30} together with the atom to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle, or R^{29} and R^4 together with the atoms to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle, or R^{29} and E together with the atoms to which they are attached form a ring selected from the group consisting of cycloalkyl and heterocycle;

R^{31} is selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, heterocycle and heteroaryl, or R^{31} and E together with the atom to which they are attached form a ring selected from the group consisting of heteroaryl and heterocycle, or R^{31} and R^4 together with the atoms to which they are attached form a heterocycle;

R^{32} and R^{33} are each independently selected from the group consisting of hydrogen, alkyl, carboxy, carboxyalkyl, cycloalkyl, cycloalkyloxy, carboxycycloalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, heterocycle, heterocycloalkyl, heterocycleoxyalkyl, heterocycleoxy, hydroxy, alkoxy, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heterocyclesulfonyl, or R^{32} and R^{33} together with the atom to which they are attached form a heterocycle;

R^{34} and R^{35} are each independently selected from the group consisting of hydrogen, alkyl, carboxy, carboxyalkyl, cycloalkyl, cycloalkyloxy, carboxycycloalkyl, aryl, arylalkyl, aryloxy, aryloxyalkyl, heterocycle, heterocycloalkyl, heterocycleoxyalkyl, heterocycleoxy, hydroxy, alkoxy, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, and heterocyclesulfonyl, or R^{34} and R^{35} together with the atom to which they are attached form a heterocycle; and

R^{36} and R^{37} are each independently selected from the group consisting of hydrogen, alkyl and aryl.

Non-limiting examples of such adamantane derivatives include E-4-{[1-(4-chlorophenyl)-cyclobutanecarbonyl]amino}adamantane-1-carboxylic acid; E-4-{[1-phenyl-cyclopropanecarbonyl]-amino}adamantane-1-carboxylic acid; E-4-(2-methyl-2-phenyl-propionylamino)adamantane-1-carboxylic acid; E-4-{[1-(4-chlorophenyl)-cyclobutanecarbonyl]-amino}adamantane-1-carboxylic acid amide; E-4-{[1-phenyl-cyclopropanecarbonyl]-amino}adamantane-1-carboxylic acid amide; E-4-(2-methyl-2-phenyl-propionylamino)adamantane-1-carboxylic acid amide; E-4-({[1-(4-chlorophenyl)cyclohexyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(4-chlorophenyl)cyclopropyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(4-chlorophenyl)cyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[2-(4-chlorophenyl)-2-methylpropanoyl]amino}adamantane-1-carboxamide; E-4-({[1-phenylcyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(3-fluorophenyl)cyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(2-chloro-4-fluorophenyl)cyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(4-fluorophenyl)cyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(2-fluorophenyl)cyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-

{[(1-methylcyclohexyl)carbonyl]amino}adamantane-1-carboxamide; E-4-({[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(4-methoxyphenyl)cyclopropyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(4-methylphenyl)cyclopropyl]carbonyl}amino)adamantane-1-carboxamide; E-4-({[1-(4-methoxyphenyl)cyclopentyl]carbonyl}amino)adamantane-1-carboxamide; E-4-{{2-(4-bromophenyl)-2-methylpropanoyl}amino}adamantane-1-carboxamide; E-4-{{2-(3-bromophenyl)-2-methylpropanoyl}amino}adamantane-1-carboxamide; and E-4-{{2-(4-hydroxyphenyl)-2-methylpropanoyl}amino}adamantane-1-carboxamide; E-4-{{2-methyl-2-(4-phenoxyphenyl)propanoyl}amino}adamantane-1-carboxamide; methyl(E)-4-[(2-methyl-2-phenylpropanoyl)amino]adamantane-1-carboxylic acid; methyl(E)-4-{{[(1-phenylcyclopropyl)carbonyl]amino}adamantane-1-carboxylic acid; (E)-N-[3-(aminocarbonyl)benzyl]-4-[(2-methyl-2-phenylpropanoyl)amino]adamantane-1-carboxamide; (E)-4-{{2-methyl-2-(4-phenoxyphenyl)propanoyl}amino}adamantane-1-carboxylic acid; N-[(E)-5-(aminosulfonyl)-2-adamantyl]-1-phenylcyclopropanecarboxamide; (E)-4-[(2-methyl-3-phenylpropanoyl)amino]adamantane-1-carboxamide; methyl(E)-4-({[1-(4-chlorophenyl)cyclobutyl]carbonyl}amino)adamantane-1-carboxylic acid; N-[(E)-5-(aminosulfonyl)-2-adamantyl]-2-(4-chlorophenyl)-2-methylpropanamide; (E)-N-[4-(aminosulfonyl)benzyl]-4-[(2-methyl-2-phenylpropanoyl)amino]adamantane-1-carboxamide; (E)-4-({2-methyl-2-[4-(pentyloxy)phenyl]propanoyl}amino)adamantane-1-carboxylic acid; (E)-4-({2-[4-(benzyloxy)phenyl]-2-methylpropanoyl}amino)adamantane-1-carboxylic acid; (E)-4-{{2-(4-chlorophenyl)-2-methylpropanoyl}amino}adamantane-1-carboxylic acid; 4-{{{(E)-4-[(2-methyl-2-phenylpropanoyl)amino]-1-adamantyl}carbonyl}amino}methyl}benzoic acid; 3-{{{(E)-4-[(2-methyl-2-phenylpropanoyl)amino]-1-adamantyl}carbonyl}amino}methyl}benzoic acid; (E)-4-({[1-(4-methylphenyl)cyclopropyl]carbonyl}amino)adamantane-1-carboxylic acid; (E)-4-({[1-(2,4-dichlorophenyl)cyclopropyl]carbonyl}amino)adamantane-1-carboxylic acid; and (E)-4-({2-[4-(cyclohexylmethoxy)phenyl]-2-methylpropanoyl}amino)adamantane-1-carboxylic acid; pharmaceutically acceptable salts; pharmaceutically acceptable esters; prodrugs; and combinations thereof.

In some other embodiments, an inhibitor of 11 β -HSD1 suitable for use in a composition or method of the present invention comprises a substituted triazole (as

disclosed in US Patent 7,179,802) selected from the group consisting of 3-[bis(4-chlorophenyl)methyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(E)-1,2-diphenylethenyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[methoxy(phenyl)-methyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1S)-1-(6-methoxy-2-naphthyl)ethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)cyclopentyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[fluoro(phenyl)-methyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(2-methyl-1-phenyl-butyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-isobutylphenyl)-ethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(ethylthio)(diphenyl)-methyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1S)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1S)-1-phenyl-propyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(2-fluoro-1,1'-biphenyl-4-yl)ethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1S)-1-(2-fluoro-1,1'-biphenyl-4-yl)ethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1S)-1-(4-isobutylphenyl)ethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1R)-1-phenylethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1R)-1-phenyl-propyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-trityl-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-methylphenyl)cyclohexyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)cyclohexyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1,1-diphenylethyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-fluorophenyl)cyclohexyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1,1-diphenylpropyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1,1-diphenylhexyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1-methyl-1-phenylpropyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(8-phenyl-1,4-dioxaspiro[4.5]-dec-8-yl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-cyclohexylphenyl)-1-methylethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(1-naphthyl)cyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; tert-butyl-4-(5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocin-3-yl)-4-phenylpiperidine-1-carboxylic acid; 3-(1-phenylcyclopropyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(2-fluorophenyl)-cyclopentyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1-

phenylcyclopentyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(2-methyl-1-phenylpropyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1-methyl-1-phenylethyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[cyclopentyl-(phenyl)methyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1-phenylcyclobutyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[(1E)-1-phenylprop-1-enyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-methylphenyl)-cyclopropyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[2-methyl-1-(4-methylphenyl)propyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-fluorophenyl)-2-methylpropyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1-cyclobutyl-1-phenylethyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(3-methyl-phenyl)cyclopentyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)cyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-methylphenyl)-cyclopentyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-fluorophenyl)-cyclopentyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(2-methyl-1-phenylcyclobutyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(1-phenyl-2-vinylcyclopropyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]-azocin-3-yl)cyclopentyl]phenol; 3-[1-(4-chlorophenyl)-1-methylethyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]-azocin-3-yl)-1-methylethyl]phenol; 3-[1-(4-chlorophenyl)cyclopropyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(2,4-dichloro-phenyl)cyclopropyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3,4-dicyclopropyl-5-(1-phenylcyclobutyl)-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4,5-dicyclopropyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-phenyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-cyclopropyl-5-(1-methylcyclopropyl)-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-(2,2,2-trifluoroethyl)-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 4-cyclopropyl-3-[1-(4-fluorophenyl)cyclobutyl]-5-(1-methylcyclopropyl)-4H-1,2,4-triazole; 3-[1-(4-fluorophenyl)cyclobutyl]-4-methyl-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3,4-dicyclopropyl-5-[1-(4-fluorophenyl)cyclopropyl]-4H-1,2,4-triazole; 4-cyclopropyl-3-

[1-(4-fluorophenyl)cyclopropyl]-5-(1-methylcyclopropyl)-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclopropyl]-4-cyclopropyl-5-(1-methylcyclopropyl)-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclopropyl]-4-methyl-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3-[1-(4-fluorophenyl)cyclopropyl]-4-methyl-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 4-{5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazol-3-yl}phenol; 2-{5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazol-3-yl}phenol; 3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-(2-naphthyl)-4H-1,2,4-triazole; 3-(2-chlorophenyl)-5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazole; 6-{5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazol-3-yl}-1H-benzimidazole; 6-{5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazol-3-yl}-1-methyl-1H-benzimidazole; 3-[1-(4-chlorophenyl)cyclobutyl]-5-(2,3-dihydro-1-benzofuran-5-yl)-4-methyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-[2-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-5-(2-fluorophenyl)-4-methyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-(2-methylphenyl)-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-5-(2-methoxyphenyl)-4-methyl-4H-1,2,4-triazole; 5-{5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazol-3-yl}-1,2,3-benzothiadiazole; 3-[1-(4-chlorophenyl)cyclopropyl]-4,5-dicyclopropyl-4H-1,2,4-triazole; 3,4-dicyclopropyl-5-[1-(4-fluorophenyl)cyclobutyl]-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-5-(3-fluoro-4-methoxyphenyl)-4-methyl-4H-1,2,4-triazole; 4-{5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazol-3-yl}-2-fluorophenol; 3-[1-(4-chlorophenyl)cyclobutyl]-4-cyclopropyl-5-phenyl-4H-1,2,4-triazole; 3-[4-(benzyloxy)phenyl]-5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazole; 3-(1,1'-biphenyl-4-yl)-5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazole; 3-(3-chlorophenyl)-5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazole; 3-(4-chlorophenyl)-5-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-5-(3-fluorophenyl)-4-methyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-4-methyl-5-[4-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)cyclobutyl]-5-(2,4-dichlorophenyl)-4-methyl-4H-1,2,4-triazole; 3,5-bis[1-(4-chlorophenyl)cyclobutyl]-4-methyl-4H-1,2,4-triazole; 3,5-bis[1-(4-chlorophenyl)cyclopropyl]-4-methyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)-(Z)-3-(methoxymethoxy)cyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-

[1-(4-chlorophenyl)-(E)-3-(methoxymethoxy)cyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(4-chlorophenyl)-cis-3-(5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocin-3-yl)-cyclobutanol; 3-(4-chlorophenyl)-trans-3-(5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocin-3-yl)-cyclobutanol; 3-(4-chlorophenyl)-3-(5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocin-3-yl)cyclobutanone; 3-[1-(4-chlorophenyl)-3-methylenecyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)-3,3-difluorocyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-(3-methyl-1-phenylcyclobutyl)-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine; 3-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-4,5-dicyclopropyl-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-4-cyclopropyl-5-(1-methylcyclopropyl)-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-4-methyl-5-[4-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-4-methyl-5-[2-(trifluoromethoxy)phenyl]-4H-1,2,4-triazole; 3-(2-chlorophenyl)-5-[1-(4-chlorophenyl)-trans-3-fluorocyclobutyl]-4-methyl-4H-1,2,4-triazole; pharmaceutically acceptable salts; pharmaceutically acceptable esters; prodrugs; and combinations thereof.

In still some other embodiments, an inhibitor of 11 β -HSD1 suitable for use in a composition or method of the present invention comprises a triazole derivative (as disclosed in US Patent 6,849,636) selected from the group consisting of 3-methoxy-4-[4-methyl-5-(4-pentylbicyclo[2.2.2]oct-1-yl)-4H-1,2,4-triazol-3-yl]phenol; 3-methyl-4-[4-methyl-5-(4-pentylbicyclo[2.2.2]oct-1-yl)-4H-1,2,4-triazol-3-yl]phenol; 3-chloro-4-[4-methyl-5-(4-pentylbicyclo[2.2.2]oct-1-yl)-4H-1,2,4-triazol-3-yl]phenol; 5-(4-{1-methyl-5-[2-(trifluoromethyl)phenyl]-1-H-1,2,4-triazol-3-yl} bicyclo [2.2.2]oct-1-yl)pentan-2-ol; 3-chloro-4-{5-[4-(4-hydroxypentyl)bicyclo[2.2.2]oct-1-yl]-1-methyl-1-H-1,2,4-triazol-3-yl}phenol; 5-{4-[5-(2-chloro-4-hydroxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl]bicyclo[2.2.2]oct-1-yl}pentan-2-one; 3-(4-fluorophenyl)-5-[4-[4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl]bicyclo[2.2.2]oct-1-yl]-1,2,4-oxadiazole; 4-[4-Methyl-5-(4-phenylbicyclo[2.2.2]oct-1-yl)-4H-1,2,4-triazol-3-yl]-3-(trifluoromethyl)phenol; 3-Chloro-4-[5-(4-ethylbicyclo[2.2.2]oct-1-yl)-4-methyl-4H-

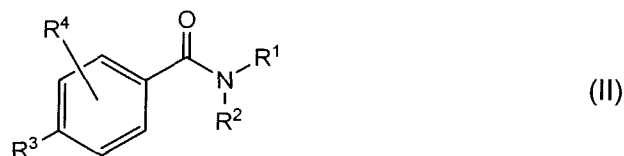
1,2,4-triazol-3-yl]phenol; 3-{4-[2-(ethylsulfonyl)ethyl]bicyclo[2.2. 2]oct-1-yl}-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 3-{4-[3-(ethylsulfonyl)propyl]bicyclo[2.2. 2]oct-1-yl}-4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazole; 4-methyl-3-{4-[4-(methylsulfonyl)phenyl]bicyclo[2.2.2.]oct-1-yl}-5-[2-(trifluoromethyl)phenyl]-4H-1,2,-triazole; 3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-5-(3,3,3-trifluoropropyl)-1,2,4-oxadiazole; 3-(4-{4-methyl-5-[2-(trifluoromethyl)phenyl]-4H-1,2,4-triazol-3-yl}bicyclo[2.2.2]oct-1-yl)-5-(3,3,3-trifluoroethyl)-1,2,4-oxadiazole; 4-methyl-3-[2-(trifluoromethyl)phenyl]-5-(4-{2-[(trifluoromethyl)sulfonyl]ethyl}bicyclo[2.2.2]oct-1-yl)-4H-1,2,4-triazole; pharmaceutically acceptable salts; pharmaceutically acceptable esters; prodrugs; and combinations thereof.

In yet some other embodiments, an inhibitor of 11 β -HSD1 suitable for use in a composition or method of the present invention comprises a pyrazolo[1,5-1]pyrimidine derivative (as disclosed in US Patent Application Publication 2007/0270408) selected from the group consisting of (3-bromo-5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-(2,6-dimethylpiperidin-1-yl)-methanone; (3-bromo-5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-ethyl-piperidin-1-yl)-methanone; (5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)methanone; (3-chloro-5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-methyl-piperidin-1-yl)-methanone; 5-methyl-7-phenyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexyl amide; azepan-1-yl-(3-chloro-5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone; azepan-1-yl-(3-chloro-5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-methanone; (2,6-dimethyl-piperidin-1-yl)-(3-chloro-5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)methanone; 3-bromo-5-furan-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-carboxylic acid cyclohexyl amide; (7-methyl-5-phenyl-pyrazolo[1,5-a]pyrimidin-3-yl)-(4-methyl-piperidin-1-yl)methanone; 5-(4-methoxy-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid benzylmethyl amide; [5-(4-ethoxy-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-2-yl]-piperidin-1-yl-methanone; azepan-1-yl-(3-bromo-5-furan-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)methanone; 5-benzo[1,3]dioxol-5-yl-7-trifluoromethyl-pyrazolo[1,5-

a]pyrimidine-3-carboxylic acid cyclohexylmethyl amide; (3,4-dihydro-1H-isoquinolin-2-yl)-[5-(4-methoxy-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]methanone; azepan-1-yl-[5-(4-bromo-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]methanone; azepan-1-yl-(5,7-diphenyl)-pyrazolo[1,5-a]pyrimidin-3-yl]methanone; [5-(4-bromo-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-(2-methyl-piperidin-1-yl)-methanone; (5-furan-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-(2-methyl-piperidin-1-yl)-methanone; (2,6-dimethyl-piperidin-1-yl)-[7-(4-ethoxy-phenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-2-yl]methanone; 5-(4-ethoxy-phenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexyl amide; piperidin-1-yl-(5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-methanone; (5-furan-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-(2-methyl-piperidin-1-yl)-methanone; (2-methyl-piperidin-1-yl)-(5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-methanone; azepan-1-yl-[5-(4-methoxy-phenyl)-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl]-methanone; 5-thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid benzylmethyl amide; 5-p-tolyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (1,3-dimethyl-1H-pyrazol-4-yl-methyl)methyl amide; 5-methyl-7-phenyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexylmethyl amide; 7-methyl-5-phenyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexylmethyl amide; (5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl-methanone; 5-naphthalen-1-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexylmethyl amide; 5-naphthalen-1-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexyl amide; (5-naphthalen-1-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl-methanone (2-methyl-piperidin-1-yl)-(5-naphthalen-1-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone; 5,7-diphenyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexyl amide; 5,7-diphenyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexylmethyl amide; (5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-2-yl)-(2-methyl-piperidin-1-yl)methanone; (5,7-diphenyl-pyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl-methanone; 5-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexyl amide; (5-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl-methanone; 5-methyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexylmethyl amide; (2-methyl-piperidin-1-yl)-(5-methyl-7-

trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-methanone; 5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexyl amide; (5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-piperidin-1-yl-methanone; 7-phenyl-5-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-2-carboxylic acid cyclohexylmethyl-amide; 5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidine-3-carboxylic acid cyclohexyl amide; and (5-phenyl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-3-yl)-piperidin-1-yl-methanone; pharmaceutically acceptable salts thereof; pharmaceutically acceptable esters thereof; optical isomers thereof; mixtures of optical isomers thereof, racemic mixtures, and combinations thereof.

In still some other embodiments, an inhibitor of 11 β -HSD1 suitable for use in a composition or method of the present invention comprises a bicyclic or tricyclic amide having Formula II (as disclosed in US Patent Application Publication 2006/0089349), pharmaceutically acceptable salts thereof, pharmaceutically acceptable esters thereof, optical isomers thereof, mixtures of optical isomers thereof, or racemic mixtures thereof,



wherein R¹ and R² together with the nitrogen to which they are attached, are forming a saturated or partially saturated bicyclic or tricyclic ring system containing from 4 to 12 carbon atoms and from 0 to 2 additional heteroatoms selected from nitrogen or oxygen, the ring system optionally being substituted with at least one of R⁵, -OR⁵, R⁶, hydroxy, oxo, cyano, C₁-C₆ alkyl, aryl, heteroaryl, aryl-C₁-C₆ alkyl, heteroaryl-C₁-C₆ alkyl or C₁-C₆ alkyloxy-C₁-C₆ alkyl, wherein the alkyl and aryl groups independently are optionally substituted with one or more of R⁷;

R³ is C₁-C₆ alkyl, -NR⁸R⁹, -C(O)NR⁸R⁹ or -OR¹⁰, wherein the alkyl group is optionally substituted with one or more of R¹¹;

R⁴ is hydrogen, halo, hydroxy, cyano, trihalomethyl or C₁-C₆ alkyl;

R^5 is C_1 - C_6 alkylcarbonyl-, C_3 - C_{10} cycloalkylcarbonyl-, C_3 - C_{10} cycloalkyl-
 C_1 - C_6 alkylcarbonyl-, arylcarbonyl-, aryl- C_1 - C_6 alkylcarbonyl-, heteroarylcarbonyl- or
heteroaryl- C_1 - C_6 alkylcarbonyl-;

R^6 is C_1 - C_6 alkyloxy-, aryloxy-, aryl- C_1 - C_6 alkyloxy-, heteroaryloxy- or
heteroaryl- C_1 - C_6 alkyloxy-;

R^7 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy or aryl- C_1 - C_6 alkyl;

R^8 is hydrogen, C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkyl- C_1 - C_6
alkyl, C_1 - C_6 alkyloxy- C_1 - C_6 alkyl, aryl- C_1 - C_6 alkyloxy- C_1 - C_6 alkyl or C_2 - C_6 alkenyl;

R^9 is C_1 - C_6 alkyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkyl- C_1 - C_6 alkyl, C_3 - C_{10}
cycloalkylcarbonyl-, C_3 - C_{10} heterocycloalkylcarbonyl-, arylcarbonyl-,
heteroarylcarbonyl-, C_1 - C_6 alkyloxy- C_1 - C_6 alkyl, $NR^{12}R^{13}$ -carbonyl- C_1 - C_6 alkyl-, R^{14} - C_1 -
 C_6 alkylcarbonyl-, $-COR^{15}$, C_1 - C_6 alkyl-S(O) $_n$ -, aryl-S(O) $_n$ -, aryl- C_1 - C_6 alkyl-S(O) $_n$ -, aryl-
 C_1 - C_6 alkyl or heteroaryl- C_1 - C_6 alkyl, wherein the alkyl, cycloalkyl, aryl and heteroaryl
groups independently are optionally substituted with one or more R^{11} ;

R^{10} is C_1 - C_6 alkyl, aryl- C_1 - C_6 alkyl or $NR^{12}R^{13}$ -carbonyl- C_1 - C_6 alkyl, wherein
the alkyl and aryl groups independently are optionally substituted with one or more R^{11} ;

R^{11} is R^5 , R^6 , halo, hydroxy, oxo, cyano, $-COR^{15}$, C_1 - C_8 alkyl, C_1 - C_8
alkyloxy, C_3 - C_{10} cycloalkyl, trihalomethyl, trihalomethyloxy, aryl, aryl- C_1 - C_6 alkyl, C_1 -
 C_6 alkyloxy- C_1 - C_6 alkyl, aryloxy- C_1 - C_6 alkyl, aryl- C_1 - C_6 alkyloxy- C_1 - C_6 alkyl,
heteroaryl, heteroaryl- C_1 - C_6 alkyl, heteroaryloxy- C_1 - C_6 alkyl, heteroaryl- C_1 - C_6 alkyloxy-
 C_1 - C_6 alkyl, $-NR^{12}R^{13}$, $-SO_2-NR^{12}R^{13}$, $NR^{12}R^{13}$ -carbonyl- C_1 - C_6 alkyl, R^{16} -carbonyl-
 $N(R^{12})$ -, aryl-S(O) $_n$ -, heteroaryl-S(O) $_n$ - or R^{17} -S(O) $_nN(R^{12})$ -; wherein the aryl and
heteroaryl groups independently are optionally substituted with one or more R^{18} ;

R^{12} and R^{13} independently are hydrogen, C_1 - C_8 alkyl, C_3 - C_{10} cycloalkyl, C_3 -
 C_{10} cycloalkyl- C_1 - C_6 alkyl, C_3 - C_{10} heterocycloalkyl, aryl, heteroaryl, aryl- C_1 - C_6 alkyl or
heteroaryl- C_1 - C_6 alkyl, wherein the alkyl, aryl and heteroaryl groups independently are

optionally substituted with one or more of R^{18} ; or R^{12} and R^{13} together with the nitrogen to which they are attached, are forming a saturated or partially saturated cyclic, bicyclic or tricyclic ring system containing from 4 to 12 carbon atoms and from 0 to 2 additional heteroatoms selected from nitrogen or oxygen, the ring system optionally being substituted with at least one R^5 , R^5O- , R^6 , halo, cyano, hydroxy, oxo, C_1-C_8 alkyl, aryl, heteroaryl, aryl- C_1-C_6 alkyl, heteroaryl- C_1-C_6 alkyl, C_1-C_6 alkyloxy- C_1-C_6 alkyl, $NR^{12}R^{13}-C(O)-C_1-C_6$ alkyl, $NR^{12}R^{13}-C_1-C_6$ alkylcarbonyl-, $R^{14}-C_1-C_6$ alkylcarbonyl- or $-C(O)R^{15}$;

R^{14} is C_1-C_6 alkyloxy, C_3-C_{10} cycloalkyloxy-, C_3-C_{10} cycloalkyl- C_1-C_6 alkyloxy-, C_3-C_{10} heterocycloalkyloxy-, aryl, heteroaryl, aryl- C_1-C_6 alkyloxy, heteroaryl- C_1-C_6 alkyloxy, $-NR^{12}R^{13}$, $-C(O)R^{15}$, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups independently are optionally substituted with one or more of R^{20} ;

R^{15} is C_1-C_6 alkyl, hydroxy, C_1-C_8 alkyloxy, $-NR^{12}R^{13}$, aryl, aryloxy or aryl- C_1-C_6 alkyloxy;

R^{16} is R^6 , C_1-C_6 alkyl, C_2-C_6 alkenyl, aryl, aryl- C_1-C_6 alkyl, heteroaryl, heteroaryl- C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, aryl- C_1-C_6 alkyloxy- C_1-C_6 alkyl-, heteroaryl- C_1-C_6 alkyloxy- C_1-C_6 alkyl- or $R^{12}R^{13}N-C_1-C_6$ alkyl-, wherein the alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups are optionally substituted with R^{19} ;

R^{17} is C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocycloalkyl, aryl, aryl- C_1-C_6 alkyl, heteroaryl, heteroaryl- C_1-C_6 alkyl; R^{18} is R^6 , $-NR^{12}R^{13}$, oxo, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl or C_3-C_{10} heterocycloalkyl, wherein the alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups independently are optionally substituted with one or more of R^7 ;

R^{19} is hydrogen, halo, hydroxy, oxo, nitro, cyano or $-COR^{15}$;

R^{20} is hydrogen, C_1-C_8 alkyl, $-NR^{12}R^{13}$, C_1-C_6 alkyloxy or aryl- C_1-C_6 alkyl;

X and Y independently are carbon or nitrogen;

n is 1 or 2.

Non-limiting examples of such compounds include (as disclosed in US Patent Application Publication 2006/0089349) [4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]carbamic acid tert-butyl ester; (4-amino-phenyl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (4-amino-phenyl)-(4-aza-tricyclo[4.3.1.1^{3,8}]undec-4-yl)-methanone; (4-methylaminophenyl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzenesulfonamide; N-methyl-(phenyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; N-ethyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; N-cyclopropylmethyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-isonicotinamide; 2,4-dichloro-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 2,4-dimethoxy-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 4-trifluoromethoxy-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3,4-dimethoxy-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3,5-dimethyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3-trifluoromethoxy-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3,5-dimethoxy-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3-cyano-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzenesulfonamide; phenyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-methanesulfonamide; butane-1-sulfonic acid [4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-amide; 3-trifluoromethyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzenesulfonamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-

phenyl]-isophthalamic acid methyl ester; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-isophthalamic acid; 4-methoxy-cyclohexanecarboxylic acid [4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-amide; 6-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylcarbamoyl]-nicotinic acid methyl ester; 6-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylcarbamoyl]-nicotinic acid; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-malonamic acid ethyl ester; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-malonamic acid tert-butyl ester; 3-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylcarbamoyl]-cyclohexane carboxylic acid methyl ester; 3-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylcarbamoyl]-cyclohexane carboxylic acid; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-isonicotinamide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-nicotinamide; pyridine-2-carboxylic acid [4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-amide; 1-acetyl-piperidine-4-carboxylic acid [4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-amide; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-succinamic acid methyl ester; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-succinamic acid; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-malonamic acid; 2-amino-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-acetylamino-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-succinamic acid methyl ester; 2-acetylamino-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-succinamic acid; N-methyl-N'-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-succinamide; N,N-dimethyl-N'-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-succinamide; N-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-pyridin-2-yl]-benzamide; N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3,5,N-trimethyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 2,4-dimethoxy-N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 3,5-dichloro-N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; 4-bromo-

N,N-dimethyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-isonicotinamide; N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-nicotinamide; 2-piperidin-1-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-morpholin-4-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-methylpiperazin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-dimethylamino-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-[(2-dimethylaminoethyl)-methylamino]-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(3,4-dihydro-2H-quinolin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-acetyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-dimethylamino-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-oxo-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-[methyl-(1-methyl-piperidin-4-yl)-amino]-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(3,6-dihydro-2H-pyridin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 1-{[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylcarbonyl]-methyl}-piperidine-4-carboxylic acid ethyl ester; N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-acetamide; 2-(4-acetyl-piperazin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(cyclohexyl-methyl-amino)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(2,4-dimethoxy-benzyloxy)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-benzyloxy-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(6-aza-bicyclo[3.2.1]oct-6-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-azepan-1-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-

(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-indol-1-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-benzimidazol-1-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(2,3-dihydroindol-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-benzotriazol-1-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-benzoyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-tert-butyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-phenyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-hydroxy-4-phenyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-pyridin-2-yl-piperazin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-phenyl-piperazin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-pyrimidin-2-yl-piperazin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-acetyl-4-phenyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-cyano-4-phenyl-piperidin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(4-pyridin-4-yl-piperazin-1-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-[4-(2-pyrrolidin-1-yl-acetyl)-piperazin-1-yl]-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(piperidin-4-yloxy)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 2-(2H-tetrazol-5-yl)-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 3-piperidin-1-yl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-propionamide; 3-benzylamino-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-propionamide; 2-(3,4-dihydro-2H-quinolin-1-yl)-N-methyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-acetamide; 1-morpholin-4-yl-2-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylamino]-ethanone; [4-(2-piperidin-1-yl-ethylamino)-phenyl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; N-methyl-N-phenyl-2-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl-amino]-acetamide; N-(2-methoxy-ethyl)-N-

[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; N-allyl-N-[4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]-benzamide; [4-(2-methoxy-ethylamino)-phenyl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (4-benzyloxy-phenyl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; pharmaceutically acceptable salts thereof; pharmaceutically acceptable esters thereof; optical isomers thereof; mixtures of optical isomers thereof, racemic mixtures, and combinations thereof.

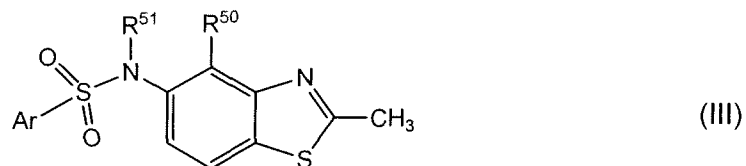
In yet some other embodiments, an inhibitor of 11 β -HSD1 suitable for use in a composition or method of the present invention comprises a substituted amide (as disclosed in US Patent Application Publication 2006/0111366) selected from the group consisting of (1H-indol-7-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (1H-indol-6-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; 1H-indole-6-carboxylic acid adamantan-2-yl amide; (6-aza-bicyclo[3.2.1]oct-6-yl)-(1H-indol-6-yl)-methanone; 1H-indole-6-carboxylic acid (8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-amide; 1H-indole-5-carboxylic acid adamantan-2-yl amide; (6-aza-bicyclo[3.2.1]oct-6-yl)-(1H-indol-5-yl)-methanone; (1H-indol-4-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (1H-indol-2-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (1-methyl-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (3-aza-bicyclo[3.2.2]non-3-yl)-(1H-indol-3-yl)-methanone; 1-methyl-1H-indole-3-carboxylic acid cycloheptyl amide; 1-methyl-1H-indole-3-carboxylic acid adamantan-1-yl amide; (3-aza-bicyclo[3.2.2]non-3-yl)-(1-methyl-1H-indol-3-yl)-methanone; (1-methyl-1H-indol-3-yl)-(4-methyl-piperazin-1-yl)-methanone; 1-methyl-1H-indole-3-carboxylic acid (3-hydroxy-adamantan-1-yl)-amide; 1-methyl-1H-indole-3-carboxylic acid azepan-1-ylamide; 1-methyl-1H-indole-3-carboxylic acid (2-oxo-azepan-3-yl)-amide; (4-benzyl-piperidine-1-yl)-(1-methyl-1H-indol-3-yl)-methanone; 1-methyl-1H-indole-3-carboxylic acid (2,6-dimethyl-piperidin-1-yl)-amide; 1-methyl-1H-indole-3-carboxylic acid (2-methyl-piperidin-1-yl)-amide; (1-cyclopropylmethyl-6-fluoro-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; azepan-1-yl-(1-methyl-1H-indol-3-yl)-methanone; (5-benzyloxy-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (5H-[1,3]dioxolo[4,5]indol-7-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (5-chloro-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-

bicyclo[3.2.1]oct-6-yl)-methanone; (6-trifluoromethyl-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (6-methyl-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (6-nitro-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (5-methoxy-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (6-fluoro-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (6-methoxy-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (7-nitro-1H-indol-3-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (1H-indol-4-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; 2-(1H-indol-3-yl)-1-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethanone; 1-(3-aza-bicyclo[3.2.2]non-3-yl)-2-(1H-indol-3-yl)-ethanone; 1-(3-aza-bicyclo[3.2.2]non-3-yl)-2-(1-methyl-1H-indol-3-yl)-ethanone; 2-(1-methyl-1H-indol-3-yl)-1-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethanone; [3-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indol-6-yloxy]-acetic acid tert-butyl ester; 6-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid; 6-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid ethyl ester; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid ethyl ester; 4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid; 4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid ethyl ester; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid ethyl ester; 4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid; 4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid ethyl ester; [3-(piperidine-1-carbonyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid cyanomethyl-amide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid benzylamide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid dimethylamide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid allyl amide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (2-dimethylamino-ethyl)-methyl amide; 5-(1,3,3-trimethyl-

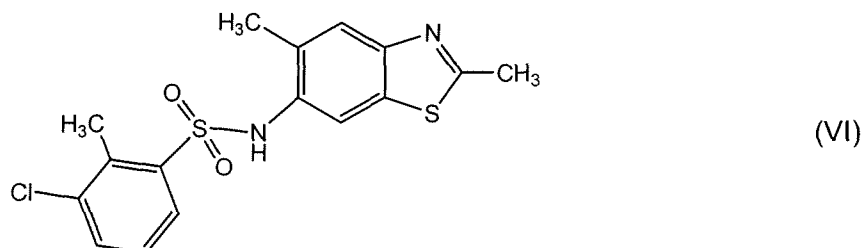
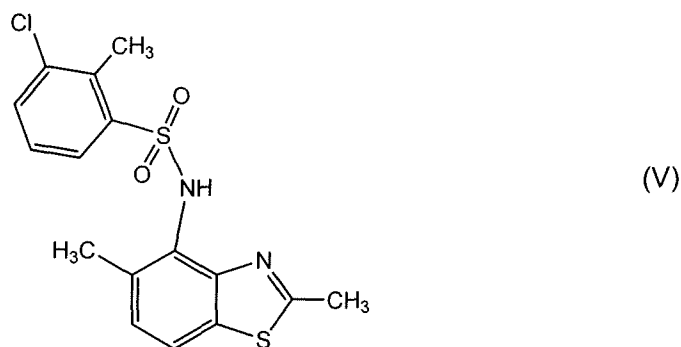
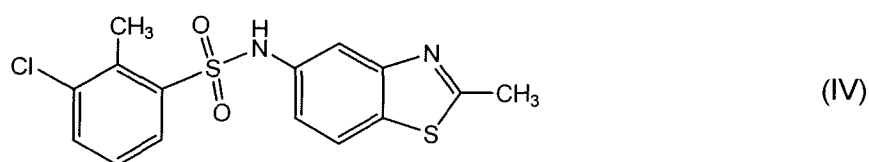
6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (2-methoxy-ethyl) amide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid 4-methoxybenzyl amide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (tetrahydrofuran-2-ylmethyl)-amide; [3-(2-methoxymethyl-pyrrolidine-1-carbonyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; [3-(2,6-dimethylmorpholine-4-carbonyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (1,1-dioxo-tetrahydrothiophen-3-yl)-amide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid [3-(4-methyl-piperazin-1-yl)-propyl]-amide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid 4-trifluoromethylbenzylamide; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (furan-2-ylmethyl)-amide; [3-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-carbonyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (2H-tetrazol-5-ylmethyl)-amide; [3-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; 3-{[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carbonyl]-amino}-propionic acid ethyl ester; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid (4-methoxy-phenyl)-amide; 3-{[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carbonyl]-amino}-propionic acid; azepan-1-yl-(1H-indol-5-yl)-methanone; 1H-indole-5-carboxylic acid dibenzyl amide; (3-aza-bicyclo[3.2.2]non-3-yl)-(1H-indol-5-yl)-methanone; (4-benzyl-piperidin-1-yl)-(1H-indol-5-yl)-methanone; 8-(1H-indole-5-carbonyl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one; [4-(4-chloro-phenyl)-4-hydroxy-piperidin-1-yl]-(1H-indol-5-yl)-methanone; 1-[1-(1H-indole-5-carbonyl)-piperidin-4-yl]-1,3-dihydrobenzoimidazol-2-one; (4-tert-butyl-piperidin-1-yl)-(1H-indol-5-yl)-methanone; (1H-indole-5-carbonyl)-4-phenyl-piperidine-4-carbonitrile; (1H-indol-5-yl)-(4-phenyl-piperidin-1-yl)-methanone; (5-benzyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-(1H-indol-5-yl)-methanone; (1H-indol-5-yl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone; 1H-indole-5-carboxylic acid (5-hydroxy-1,3,3-trimethyl-cyclohexylmethyl)-amide; 1H-indole-5-carboxylic acid (3,4-dihydrospiro(1H-indene-1,4-piperidine)-amide; (3-

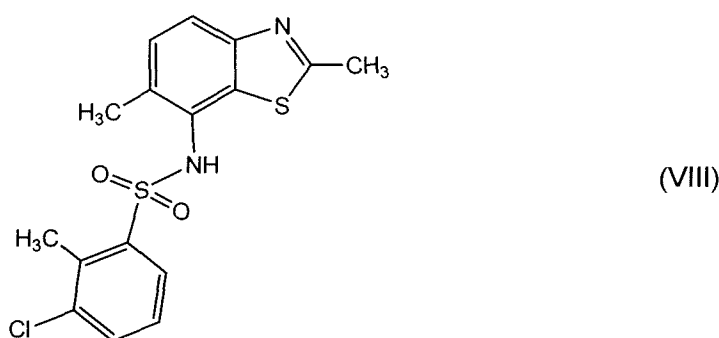
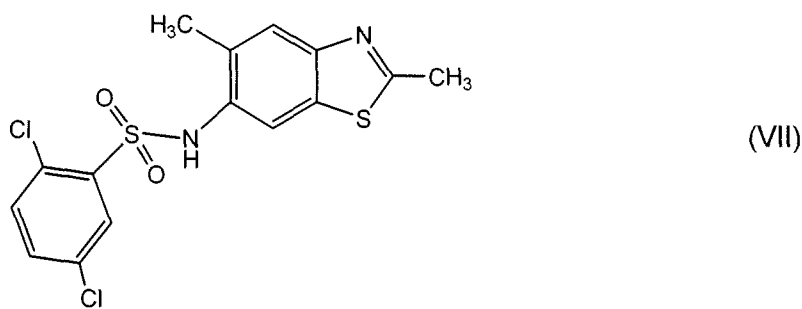
methanesulfonylmethyl-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; (3-dimethylaminomethyl-1H-indol-6-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; 1-{3-acetyl-2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indol-3-yl]-2,3-dihydro-imidazol-1-yl}-ethanone; 1-ethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indol-3-yl]-pyrrolidine-2,5-dione; (3-thiazol-2-yl-1H-Indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (3-iodo-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; 6-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carbonitrile; 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carbonitrile; 6-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-3-carboxylic acid amide; [3-(2H-tetrazol-5-yl)-1H-indol-6-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; N-[3-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indol-7-yl]-acetamide; (1-benzenesulfonyl-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; (1-benzenesulfonyl-2-methyl-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; (1-methyl-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-m-ethanone; (1-benzyl-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; [6-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid ethyl ester; [1-(2-ethoxy-ethyl)-1H-indol-6-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; {1-[2-(2-methoxyethoxy)-ethyl]-1H-indol-6-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; 3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester; (1-phenethyl-1H-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone; [1-(tetrahydrofuran-2-ylmethyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; 2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetamide; [1-(4-trifluoromethoxy-benzyl)-1H-indol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone; 3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid methyl ester; and 4-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzonitrile; pharmaceutically acceptable salts thereof; pharmaceutically acceptable esters thereof; optical isomers thereof; mixtures of optical isomers thereof, racemic mixtures, and combinations thereof.

In still another aspect, an antagonist to 11 β -HSD1 comprises a benzothiazol derivative represented by having Formula III, IV, V, VI, VII, or VIII,



wherein R⁵⁰ is H or Cl; R⁵¹ is H, CH₃, or C₂H₅; and Ar is 2,5-dichlorophenyl, 4-n-propylphenyl, 2-methyl-3-chlorophenyl, 2-methyl-4-bromophenyl, 4-biphenyl, 4-phenoxyphenol, 2,4-dichloro-5-carboxyphenyl, or 2,5-dichlorophenyl.





These compounds and methods for their synthesis are disclosed in X. Su et al., *Mol. Cell. Endocrinol.*, Vol. 248, 214 (2006).

Other inhibitors of 11 β -HSD1 are also suitable for a composition or method of the present invention. Inhibitory activity of a candidate compound can be assessed by performing an 11 β -HSD1 enzyme assay as disclosed in US Patent Application Publication 2006/0111366, which is incorporated herein by reference in its entirety.

In addition, the selectivity of a test 11 β -HSD1 inhibitor with respect to its ability also to inhibit 11 β -HSD2 may also be assessed by performing the same assay with the 11 β -HSD2 enzyme and cortisol substrate. A desirable 11 β -HSD1 inhibitor has a high activity for inhibiting 11 β -HSD1 but a low, preferably insignificant or non-existent, activity for inhibiting 11 β -HSD2.

In a further aspect, an antagonist to 11 β -HSD1 comprises a compound or material that interferes with the transcription of 11 β -HSD1 or modulates the stability or functionality of mRNA for 11 β -HSD1.

In one embodiment, an antagonist to 11 β -HSD1 comprises a small nucleic acid molecule that downregulates, inhibits, or reduces the expression of 11 β -HSD1, or the expression or activity of another gene involved in a pathway of 11 β -HSD1 gene expression. Non-limiting examples of such nucleic acid molecules include short interfering nucleic acid ("siNA"), short interfering RNA ("siRNA"), double stranded RNA ("dsRNA"), micro-RNA ("miRNA"), and short hairpin RNA ("shRNA"), as disclosed in US Patent Application Publication 2007/0049543, which is incorporated herein by reference in its entirety. In particular, this document discloses siNA constructs that can downregulate, inhibit, or reduce the expression of 11 β -HSD1, methods for their preparation, assays for identifying activity of the constructs, and methods for delivering such molecules to cells or tissues of a subject. Alternatively, useful 11 β -HSD1 siRNAs may be those available from Santa Cruz Biotechnology, Inc., Santa Cruz, California (catalog No. sc-41377) or from Applied Biosystems, Foster City, California (catalog No. 107743, 16400, or 212848).

In another aspect, an antagonist to 11 β -HSD1 comprises an inhibitor of hexose-6-phosphate dehydrogenase ("H6PDH"). Recent studies suggested that *in vivo* H6PDH generates NADPH (nicotinamide adenine dinucleotide phosphate, reduced form) in the endoplasmic reticulum ("ER") lumen, which stimulates the 11 β -HSD1 reductase activity. I. Czegle et al., *Mol. Cell. Endocrinol.*, Vol. 248, 24 (2006); I.J. Bujalska et al., *J. Mol. Endocrinol.*, Vol. 34, 675 (2005). Thus, a tightly controlled ratio of H6PDH to 11 β -HSD1 is crucial for controlling the magnitude of cortisol activity, and inhibiting the activity of H6PDH can inhibit the activity of 11 β -HSD1.

In one embodiment, an antagonist to 11 β -HSD1 comprises an H6PDH siRNA, such as those available from Applied Biosystems, Foster City, California (catalog No. 289474, 113106, or 14466).

In still another aspect, the antagonist to 11 β -HSD1 comprises a peroxisome proliferators-activated receptor ("PPAR") agonist. In one embodiment, such PPAR agonist is selected from the group consisting of PPAR α agonists, PPAR γ agonists, and combinations thereof. Such a PPAR agonist binds to and activates PPAR to modulate the expression of genes containing the appropriate peroxisome proliferator response

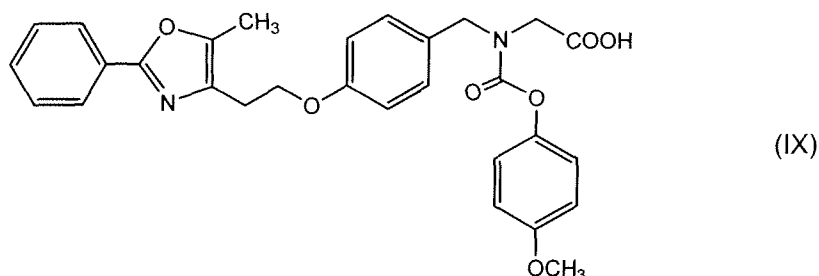
element in its promoter region. PPAR α and PPAR γ agonists have been shown to inhibit 11 β HSD1 expression and activity. J. Berger et al., *J. Biol. Chem.*, Vol. 276, No. 16, 12629 (2001); A. Hermanowski-Vosatka et al., *Biochem. Biophys. Res. Comm.*, Vol. 279, No. 2, 330 (2000).

Spiegelman et al., in U.S. Patent 6,242,196, which is incorporated herein by reference, disclose several synthetic PPAR γ agonists, as well as methods for diagnosing PPAR γ -responsive cells. PPARs are differentially expressed in diseased versus normal cells. PPAR γ is expressed to different degrees in the various tissues of the eye, such as some layers of the retina and the cornea, the choriocapillaris, uveal tract, conjunctival epidermis, and intraocular muscles (see, e.g., U.S. Patent 6,316,465). Therefore, administration of PPAR γ to an eye can be a particularly effective way to control the level of 11 β HSD1 therein.

In one aspect, a PPAR γ agonist used in a composition or a method of the present invention is a thiazolidinedione, a derivative thereof, or an analog thereof. Non-limiting examples of thiazolidinedione-based PPAR γ agonists include pioglitazone, troglitazone, ciglitazone, englitazone, rosiglitazone, and chemical derivatives thereof. Other PPAR γ agonists include clofibrate (ethyl 2-(4-chlorophenoxy)-2-methylpropionate), clofibric acid (2-(4-chlorophenoxy)-2-methylpropanoic acid), GW 1929 (N-(2-benzoylphenyl)-O-{2-(methyl-2-pyridinylamino)ethyl}-L-tyrosine), GW 7647 (2-{4-{2-{{(cyclohexylamino)carbonyl}}(4-cyclohexylbutyl)amino}ethyl}phenyl}thio}-2-methylpropanoic acid), and WY 14643 ({4-chloro-6-{{(2,3-dimethylphenyl)amino}-2-pyrimidinyl}thio}acetic acid). GW 1929, GW 7647, and WY 14643 are commercially available, for example, from Koma Biotechnology, Inc. (Seoul, Korea). In one embodiment, the PPAR γ agonist is 15-deoxy- Δ -12, 14-PG J2.

Non-limiting examples of PPAR- α agonists include the fibrates, such as fenofibrate and gemfibrozil.

In another embodiment, an antagonist to 11 β -HSD1 comprises a dual PPAR α /PPAR γ agonist such as muraglitazar (having Formula IX) developed by Bristol-Myers Squibb and Merck.



In still another aspect, an ophthalmic pharmaceutical composition of the present invention comprises at least an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof. Non-limiting examples of such an antagonist to 11 β HSD1 include those disclosed hereinabove.

In one embodiment, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier. In another aspect, said carrier is an ophthalmically acceptable carrier.

In a further aspect, a composition of the present invention comprises a topical formulation; injectable formulation; or implantable formulation, system, or device.

In another aspect, the present invention provides an ophthalmic pharmaceutical composition for effecting ocular neuroprotection in a subject in need thereof. The ophthalmic pharmaceutical composition comprises at least an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof.

In still another aspect, such ocular neuroprotection comprises controlling a progression of an ocular neurodegenerative condition.

In yet another aspect, such an ocular neurodegenerative condition is selected from the group consisting of glaucoma, retinitis pigmentosa, AMD (including wet and dry AMD), diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.

In still another aspect, the ophthalmic pharmaceutical composition comprises: (a) at least an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof; and (b) 11 β HSD2. In one embodiment, the 11 β HSD2 is recombinant human 11 β HSD2, which may be obtained from, for example, Scottish Biomedical, Glasgow, Great Britain (such as catalog No. HSD10002). The concentration of 11 β HSD2 in the composition is typically high enough to effect conversion of part of the endogenous cortisol to the inactive form of cortisone to enhance the therapeutic efficacy of the composition.

In one aspect, the concentration of an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof in such an ophthalmic composition can be in the range from about 0.0001 to about 500 mg/ml (or, alternatively, or from about 0.001 to about 300 mg/ml, or from about 0.001 to about 250 mg/ml, or from about 0.001 to about 100 mg/ml, or from about 0.001 to about 50 mg/ml, or from about 0.01 to about 300 mg/ml, or from about 0.01 to about 250 mg/ml, or from about 0.01 to about 100 mg/ml, or from about 0.1 to about 100 mg/ml, or from about 0.1 to about 50 mg/ml).

In another aspect, the concentration of 11 β HSD2 in such an ophthalmic composition can be in the range from about 0.0001 to about 100 mg/ml (or, alternatively, or from about 0.001 to about 50 mg/ml, or from about 0.001 to about 25 mg/ml, or from about 0.001 to about 10 mg/ml, or from about 0.001 to about 5 mg/ml, or from about 0.01 to about 30 mg/ml, or from about 0.01 to about 25 mg/ml, or from about 0.01 to about 10 mg/ml, or from about 0.1 to about 10 mg/ml, or from about 0.1 to about 5 mg/ml).

In one embodiment, an ophthalmic composition of the present invention is in a form of an emulsion, suspension, or dispersion. In another embodiment, the

suspension or dispersion is based on an aqueous solution. For example, a composition of the present invention can comprise sterile saline solution. In still another embodiment, the composition comprises an oil-in-water emulsion, which can be desirable for sustained-release purposes.

In another aspect, the an antagonist to 11β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof is present in an amount effective to provide ocular neuroprotection to a subject in whom an ocular degenerative disease has begun or who has shown signs of such disease.

In still another aspect, the an antagonist to 11β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof is present in an amount effective to control a progression of an ocular neurodegenerative disease in a subject.

In another aspect, a composition of the present invention can further comprise an anti-inflammatory drug, such as a non-steroidal anti-inflammatory drug ("NSAID"). Such anti-inflammatory drug can be present in the range from about 0.0001 to about 100 mg/ml (or, alternatively, or from about 0.001 to about 50 mg/ml, or from about 0.001 to about 25 mg/ml, or from about 0.001 to about 10 mg/ml, or from about 0.001 to about 5 mg/ml, or from about 0.01 to about 30 mg/ml, or from about 0.01 to about 25 mg/ml, or from about 0.01 to about 10 mg/ml, or from about 0.1 to about 10 mg/ml, or from about 0.1 to about 5 mg/ml).

Non-limiting examples of the NSAIDs are: aminoarylcarboxylic acid derivatives (e.g., enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, tolfenamic acid), arylacetic acid derivatives (e.g., aceclofenac, acemetacin, alclofenac, amfenac, amtolmetin guacil, bromfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac, isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, zomepirac), arylbutyric acid derivatives (e.g., bumadizon, butibufen, fenbufen, xenbucin), arylcarboxylic acids (e.g.,

clidanac, ketorolac, tinoridine), arylpropionic acid derivatives (e.g., alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprolen, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, zaltoprofen), pyrazoles (e.g., difenamizole, eprizole), pyrazolones (e.g., apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone, thiazolinobutazone), salicylic acid derivatives (e.g., acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalimide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine), thiazinecarboxamides (e.g., ampiroxicam, droxicam, isoxicam, lornoxicam, piroxicam, tenoxicam), ϵ -acetamidocaproic acid, S-(5'-adenosyl)-L-methionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, α -bisabolol, bucolome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, superoxide dismutase, tenidap, zileuton, their physiologically acceptable salts, combinations thereof, and mixtures thereof.

In another aspect, a composition of the present invention can further comprise a non-ionic or ionic surfactant. Non-limiting examples of non-ionic surfactants include polysorbates (such as polysorbate 80 (polyoxyethylene sorbitan monooleate), polysorbate 60 (polyoxyethylene sorbitan monostearate), polysorbate 20 (polyoxyethylene sorbitan monolaurate), commonly known by their trade names of Tween® 80, Tween® 60, Tween® 20), poloxamers (synthetic block polymers of ethylene oxide and propylene oxide, such as those commonly known by their trade names of Pluronic®; e.g., Pluronic® F127 or Pluronic® F108), or poloxamines (synthetic block polymers of ethylene oxide and propylene oxide attached to ethylene diamine, such as those commonly known by their trade names of Tetronic®; e.g., Tetronic® 1508 or Tetronic® 908, etc., other nonionic surfactants such as Brij®, Myrj®, and long chain fatty alcohols (i.e., oleyl alcohol, stearyl alcohol, myristyl alcohol, docosohexanoyl alcohol, etc.) with carbon chains having about 12 or more carbon atoms

(e.g., such as from about 12 to about 24 carbon atoms). Such compounds are delineated in Martindale, 34th ed., pp. 1411-1416 (Martindale, "The Complete Drug Reference," S. C. Sweetman (Ed.), Pharmaceutical Press, London, 2005) and in Remington, "The Science and Practice of Pharmacy," 21st Ed., p. 291 and the contents of chapter 22, Lippincott Williams & Wilkins, New York, 2006).

A popular group of anionic surfactants are long alkyl chain sulfonates and alkyl aryl sulfonates, such as dialkyl sodium sulfosuccinates. Alkyl sulfates are another suitable group of anionic surfactants for pharmaceutical use, such as sodium lauryl sulfate. Phospholipids comprise still another group of anionic surfactants, such as lecithin esterified to two long-chain fatty acids (often oleic, palmitic, stearic, and linoleic).

Cationic surfactants are another group that finds use in pharmaceutical formulations. Such compounds can also provide preservative effect to the formulation. Popular cationic surfactants include the quaternary ammonium compounds (such as polyquaternium-1, polyquaternium-10, benzalkonium chloride, or cetalkonium chloride) and the amine salts.

The concentration of a surfactant, when present, in a composition of the present invention can be in the range from about 0.001 to about 5 weight percent (or alternatively, from about 0.01 to about 4, or from about 0.01 to about 2, or from about 0.01 to about 1, or from about 0.01 to about 0.5 weight percent).

In addition, a composition of the present invention can include additives such as buffers, diluents, carriers, adjuvants, or other excipients. Any pharmacologically acceptable buffer suitable for application to the eye may be used. Other agents may be employed in the composition for a variety of purposes. For example, buffering agents, preservatives, co-solvents, oils, humectants, emollients, stabilizers, or antioxidants may be employed. Water-soluble preservatives which may be employed include sodium bisulfite, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, chlorobutanol, thimerosal, ethyl alcohol, methylparaben, polyvinyl alcohol, benzyl alcohol, and phenylethyl alcohol. These agents may be present in individual amounts of from about

0.001 to about 5% by weight (alternatively, from about 0.01% to about 2%, or from about 0.01% to about 1% by weight). Suitable water-soluble buffering agents that may be employed are sodium carbonate, sodium borate, sodium phosphate, sodium acetate, sodium bicarbonate, etc., as approved by the United States Food and Drug Administration ("US FDA") for the desired route of administration. These agents may be present in amounts sufficient to maintain a pH of the system of between about 2 and about 11. As such, the buffering agent may be as much as about 5% on a weight to weight basis of the total composition. Electrolytes such as, but not limited to, sodium chloride and potassium chloride may also be included in the formulation.

In one aspect, the pH of the composition is in the range from about 4 to about 11. Alternatively, the pH of the composition is in the range from about 5 to about 9, from about 6 to about 9, or from about 6.5 to about 8, or from about 5.5 to about 6.8. In another aspect, the composition comprises a buffer having a pH in one of said pH ranges.

In another aspect, the composition has a pH of about 7. Alternatively, the composition has a pH in a range from about 7 to about 7.5.

In still another aspect, the composition has a pH of about 7.4.

In yet another aspect, a composition also can comprise a viscosity-modifying compound designed to facilitate the administration of the composition into the subject or to promote the bioavailability in the subject. In still another aspect, the viscosity-modifying compound may be chosen so that the composition is not readily dispersed after being administered into an environment of an eye. Such compounds may enhance the viscosity of the composition, and include, but are not limited to: monomeric polyols, such as, glycerol, propylene glycol, ethylene glycol; polymeric polyols, such as, polyethylene glycol; various polymers of the cellulose family, such as hydroxypropylmethyl cellulose ("HPMC"), carboxymethyl cellulose ("CMC") sodium, hydroxypropyl cellulose ("HPC"); polysaccharides, such as hyaluronic acid and its salts, chondroitin sulfate and its salts, dextrans, such as, dextran 70; water soluble proteins, such as gelatin; vinyl polymers, such as, polyvinyl alcohol, polyvinylpyrrolidone, povidone; carbomers, such as carbomer 934P, carbomer 941, carbomer 940, or carbomer

974P; and acrylic acid polymers. In general, a desired viscosity can be in the range from about 1 to about 400 centipoises ("cps") or mPa.s.

In still another aspect, a material that provides an enhanced solubility of an active ingredient (a "solubility enhancer") can be included in a composition of the present invention. Such a solubility enhancer can comprises cyclodextrin, such as α -cyclodextrin, β -cyclodextrin, γ -cyclodextrin, or a combination thereof, in anhydrous or hydrated form. Cyclodextrin derivatives are also suitable in certain embodiments, such as hydroxypropyl and sulfobutyl ether cyclodextrins, and others. Such derivatives are described for example, in U.S. Pat. Nos. 4,727,064 and 5,376,645. In addition, hydroxypropyl- β -cyclodextrin and sulfobutyl- β -cyclodextrin are commercially available. Other suitable cyclodextrin derivatives include methylated cyclodextrins, ethylated cyclodextrins, cyclodextrins with other hydroxyalkyl groups, branched cyclodextrins, cationic cyclodextrins, anionic cyclodextrins, amphoteric cyclodextrins and cyclodextrins wherein at least one glucopyranose unit has a 3,6-anhydro-cyclomalto structure.

In yet another aspect, a method for preparing a composition of the present invention comprises combining: (i) at least an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof; and (ii) a pharmaceutically acceptable carrier. In one embodiment, such a carrier can be a sterile saline solution or a physiologically acceptable buffer. In another embodiment, such a carrier comprises a hydrophobic medium, such as a pharmaceutically acceptable oil. In still another embodiment, such a carrier comprises an emulsion of a hydrophobic material and water.

Physiologically acceptable buffers include, but are not limited to, a phosphate buffer or a Tris-HCl buffer (comprising tris(hydroxymethyl)aminomethane and HCl). For example, a Tris-HCl buffer having pH of 7.4 comprises 3 g/l of tris(hydroxymethyl)aminomethane and 0.76 g/l of HCl. In yet another aspect, the buffer is 10X phosphate buffer saline ("PBS") or 5X PBS solution.

Other buffers also may be found suitable or desirable in some circumstances, such as buffers based on HEPES (N-{2-hydroxyethyl}piperazine-N'-{2-ethanesulfonic acid}) having pK_a of 7.5 at 25 °C and pH in the range of about 6.8-8.2; BES (N,N-bis{2-hydroxyethyl}2-aminoethanesulfonic acid) having pK_a of 7.1 at 25°C and pH in the range of about 6.4-7.8; MOPS (3-{N-morpholino}propanesulfonic acid) having pK_a of 7.2 at 25°C and pH in the range of about 6.5-7.9; TES (N-tris{hydroxymethyl}-methyl-2-aminoethanesulfonic acid) having pK_a of 7.4 at 25°C and pH in the range of about 6.8-8.2; MOBS (4-{N-morpholino}butanesulfonic acid) having pK_a of 7.6 at 25°C and pH in the range of about 6.9-8.3; DIPSO (3-(N,N-bis{2-hydroxyethyl}amino)-2-hydroxypropane)) having pK_a of 7.52 at 25°C and pH in the range of about 7-8.2; TAPSO (2-hydroxy-3 {tris(hydroxymethyl)methylamino}-1-propanesulfonic acid)) having pK_a of 7.61 at 25°C and pH in the range of about 7-8.2; TAPS ({(2-hydroxy-1,1-bis(hydroxymethyl)ethyl)amino}-1-propanesulfonic acid)) having pK_a of 8.4 at 25°C and pH in the range of about 7.7-9.1; TABS (N-tris(hydroxymethyl)methyl-4-aminobutanesulfonic acid) having pK_a of 8.9 at 25°C and pH in the range of about 8.2-9.6; AMPSO (N-(1,1-dimethyl-2-hydroxyethyl)-3-amino-2-hydroxypropanesulfonic acid)) having pK_a of 9.0 at 25°C and pH in the range of about 8.3-9.7; CHES (2-cyclohexylamino)ethanesulfonic acid) having pK_a of 9.5 at 25°C and pH in the range of about 8.6-10.0; CAPSO (3-(cyclohexylamino)-2-hydroxy-1-propanesulfonic acid) having pK_a of 9.6 at 25°C and pH in the range of about 8.9-10.3; or CAPS (3-(cyclohexylamino)-1-propane sulfonic acid) having pK_a of 10.4 at 25°C and pH in the range of about 9.7-11.1.

In certain embodiments, a composition of the present invention is formulated in a buffer having an acidic pH, such as from about 4 to about 6.8, or alternatively, from about 5 to about 6.8, or from about 5.5 to about 6.8, or from about 6 to about 6.5. In such embodiments, the buffer capacity of the composition desirably allows the composition to come rapidly to a physiological pH after being administered into the patient.

It should be understood that the proportions of the various components or mixtures in the following examples may be modified for the appropriate circumstances.

EXAMPLE 1

Two mixtures I and II are made separately by mixing the ingredients listed in Table 1. Five parts (by weight) of mixture I are mixed with one part (by weight) of mixture II for 15 minutes or more. The pH of the combined mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 1

Ingredient	Amount
Mixture I	
Carbopol 934P NF	0.25 g
Purified water	99.75 g
Mixture II	
Propylene glycol	5 g
EDTA	0.1 mg
E-4- {[1-(4-chlorophenyl)-cyclobutanecarbonyl]amino}adamantane-1-carboxylic acid	0.5 g

Alternatively, purified water may be substituted with an oil, such as fish-liver oil, peanut oil, sesame oil, coconut oil, sunflower oil, corn oil, or olive oil to produce an oil-based formulation comprising E-4- {[1-(4-chlorophenyl)-cyclobutanecarbonyl]amino}adamantane-1-carboxylic acid.

EXAMPLE 2

Two mixtures I and II are made separately by mixing the ingredients listed in Table 2. Five parts (by weight) of mixture I are mixed with two parts (by weight) of mixture II for 15 minutes or more. The pH of the combined mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 2

Ingredient	Amount
Mixture I	
Diclofenac	0.3g
Carbopol 934P NF	0.25 g
Purified water	99.25 g
Mixture II	
Propylene glycol	5 g
EDTA	0.1 mg
E-4- {[1-(4-chlorophenyl)-cyclobutanecarbonyl]amino}adamantane-1-carboxylic acid	0.5 g

Alternatively, purified water may be substituted with an oil, such as fish-liver oil, peanut oil, sesame oil, coconut oil, sunflower oil, corn oil, or olive oil to produce an oil-based formulation comprising E-4- {[1-(4-chlorophenyl)-cyclobutanecarbonyl]amino}adamantane-1-carboxylic acid.

EXAMPLE 3

Two mixtures I and II are made separately by mixing the ingredients listed in Table 3. Five parts (by weight) of mixture I are mixed with two parts (by weight) of mixture II for 15 minutes or more. The pH of the combined mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 3

Ingredient	Amount
Mixture I	
[4-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenyl]carbamic acid tert-butyl ester	0.2g
Carbopol 934P NF	0.25 g
Purified water	99.35 g
Mixture II	
Propylene glycol	3 g
sc-41377 (siRNA)	0.25 g
EDTA	0.1 mg

EXAMPLE 4:

Two mixtures I and II are made separately by mixing the ingredients listed in Table 4. Five parts (by weight) of mixture I are mixed with one part (by weight) of mixture II for 15 minutes or more. The pH of the combined mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 4

Ingredient	Amount
Mixture I	
3-[Bis(4-chlorophenyl)methyl]-5,6,7,8,9,10-hexahydro-[1,2,4]-triazolo-[4,3-a]azocine	0.3g
Carbopol 934P NF	0.25 g
Olive oil	99.15 g
Mixture II	
Propylene glycol	7 g
Glycerin	3 g
Muratiglazar	1 g
HAP (30%)	0.5 mg
PHMB	1-20 ppm

Note: "HAP" denotes hydroxyalkyl phosphonates, such as those known under the trade name Dequest®. "PHMB" denotes polyhexamethylene biguanide (a preservative).

EXAMPLE 5:

The ingredients listed in Table 5 are mixed together for at least 15 minutes. The pH of the mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 5

Ingredient	Amount (% by weight, except where "ppm" is indicated)
Povidone	1
HAP (30%)	0.05
Glycerin	3
Propylene glycol	3
Compound of Formula III ($R^{50} = Cl$, $R^{51} = H$, Ar = 2,5-dichlorophenyl)	0.5
Tyloxapol	0.25
BAK	10-100 ppm
Purified water	q.s. to 100

Note: "BAK" denotes benzalkonium chloride (a preservative).

EXAMPLE 6:

The ingredients listed in Table 6 are mixed together for at least 15 minutes. The pH of the mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 6

Ingredient	Amount (% by weight, except where "ppm" is indicated)
Povidone	1.5
HAP (30%)	0.05
Glycerin	3
Propylene glycol	3
Compound of Formula III ($R^{50} = Cl$, $R^{51} = H$, Ar = 4-n-propylphenyl)	0.75
Pioglitazone	0.1
Tyloxapol	0.25
PHMB	10-50 ppm
Purified water	q.s. to 100

EXAMPLE 7:

The ingredients listed in Table 7 are mixed together for at least 15 minutes. The pH of the mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 7

Ingredient	Amount (% by weight, except where "ppm" is indicated)
CMC (MV)	0.5
HAP (30%)	0.05
Glycerin	3
Propylene glycol	3
(1H-Indol-7-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone	0.25
Ketorolac	0.3
Tyloxapol (a surfactant)	0.25
PHMB	1-5 ppm
Sunflower oil	q.s. to 100

EXAMPLE 8:

The ingredients listed in Table 8 are mixed together for at least 15 minutes. The pH of the mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 8

Ingredient	Amount (% by weight, except where "ppm" is indicated)
CMC (MV)	0.5
HAP (30%)	0.05
Glycerin	3
Propylene glycol	3
(4-Amino-phenyl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone	0.3
Recombinant 11 β HSD2 (from Scottish Biomedical, catalog No. HSD1002)	0.1
Diclofenac sodium	0.3
Tyloxapol (a surfactant)	0.25
PHMB	10-20 ppm
Purified water	q.s. to 100

EXAMPLE 9:

The ingredients listed in Table 9 are mixed together for at least 15 minutes. The pH of the mixture is adjusted to 6.2-6.4 using 1 N NaOH or 1 N HCl to yield a composition of the present invention.

Table 9

Ingredient	Amount (% by weight, except where "ppm" is indicated)
CMC (MV)	0.5
HAP (30%)	0.05
Glycerin	3
Propylene glycol	3
(5-Thiophen-2-yl-7-trifluoromethyl-pyrazolo[1,5-a]pyrimidin-2-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)methanone	0.5
H6PDH siRNA from Applied Biosystems, Foster City, California (catalog No. 289474)	0.2
Clofibrate (a PPAR γ agonist)	0.15
Tyloxapol (a surfactant)	0.25
PHMB	10-50 ppm
Corn oil	q.s. to 100

In another aspect, one or more antagonists to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof is incorporated into a formulation for topical administration, systemic administration, periocular injection, or intravitreal injection. A formulation can desirably comprise a carrier that provides a sustained-release of the active ingredients, such as for a period longer than about 1 week (or longer than about 1, 2, 3, 4, 5, or 6 months). In certain embodiments, the sustained-release formulation desirably comprises a carrier that is insoluble or only sparingly soluble in the ocular environment. Such a carrier can be an oil-based liquid, emulsion, gel, or semisolid. Non-limiting examples of oil-based liquids include castor oil, peanut oil, olive oil, coconut oil, sesame oil, cottonseed oil, corn oil, sunflower oil, fish-liver oil, arachis oil, and liquid paraffin.

In one embodiment, a composition of the present invention can be injected intravitreally to control the progression of an ocular neurodegenerative disease, using a fine-gauge needle, such as 25-30 gauge. Typically, an amount from about 25 μ l to about

100 μ l of a composition comprising one or more antagonists to 11 β HSD1, prodrugs thereof, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable esters thereof is administered into a patient. A concentration of such antagonists to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof is selected from the ranges disclosed above.

In still another aspect, one or more antagonists to 11 β HSD1, prodrugs thereof, pharmaceutically acceptable salts thereof, or pharmaceutically acceptable esters thereof is incorporated into an ophthalmic device or system that comprises a biodegradable material, and the device is implanted into the posterior cavity of a diseased eye to provide a long-term (e.g., longer than about 1 week, or longer than about 1, 2, 3, 4, 5, or 6 months) control of progression of an ocular degenerative disease. In one aspect, such control is achieved by reducing the level of 11 β HSD1 in the vitreous over a long period of time.

In still another aspect, a method for controlling progression of an ocular degenerative disease comprises: (a) providing a composition comprising an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof; and (b) administering to a subject an effective amount of the composition at a frequency sufficient to control the progression of the ocular degenerative disease.

In one embodiment, the antagonist to 11 β HSD1 is selected from among those disclosed above.

In still another embodiment, the present invention provides a method for controlling progression of optic nerve degeneration in a subject having hypertensive glaucoma. The method comprises: (a) administering a composition comprising an antagonist to 11 β HSD1, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof to an eye of said subject; and (b) administering to the subject an intraocular-pressure ("IOP") lowering drug, wherein the composition and the IOP lowering drug are administered in effective amounts at a frequency sufficient to control the progression of optic nerve degeneration. Non-limiting

examples of IOP lowering drugs include prostaglandin analogs (latanoprost, travoprost, bimatoprost), β -adrenergic receptor antagonists (timolol maleate), α_2 -adrenergic receptor agonists (brimonidine, clonidine), carbonic anhydrase inhibitors (dorzolamide, brinzolamide), cholinomimetics (pilocarpine, carbachol), and inhibitors of acetylcholinesterase such as Echothiophate (phospholine iodide).

In preferred embodiment, a composition of the present invention is administered intravitreally. In still another aspect, a composition of the present invention is incorporated into an ophthalmic implant system or device, and the implant system or device is surgically implanted in the vitreous cavity of the patient for the sustained or long-term release of the active ingredient or ingredients. A typical implant system or device suitable for use in a method of the present invention comprises a biodegradable matrix with the active ingredient or ingredients impregnated or dispersed therein. Non-limiting examples of ophthalmic implant systems or devices for the sustained-release of an active ingredient are disclosed in U.S. Patents 5,378,475; 5,773,019; 5,902,598; 6,001,386; 6,051,576; and 6,726,918; which are incorporated herein by reference.

In yet another aspect, a composition of the present invention is injected into the vitreous once a month, or once every two, three, four, five, or six months. In another aspect, the composition is implanted in the patient and is replaced at a frequency of, for example, once a year or at a suitable frequency that is determined to be appropriate for controlling the progression of the ocular degenerative disease.

COMBINATION THERAPY

A composition or a method of the present invention can be used in conjunction with other therapeutic and adjuvant or prophylactic agents commonly used to control (a) an increase of intraocular pressure, (b) a loss of neuronal cells of the retinal layers (such as retinal ganglion cells, Müller cells, amacrine cells, bipolar cells, horizontal cells, and photoreceptors) or (c) both, thus providing an enhanced overall treatment or enhancing the effects of the other therapeutic agents, prophylactic agents, and adjunctive agents used to treat and manage the different ocular neurodegenerative diseases.

High doses may be required for some currently used therapeutic agents to achieve levels to effectuate the target response, but may often be associated with a greater frequency of dose-related adverse effects. Thus, combined use of a composition of the present invention, with agents commonly used to control progression of ocular nerve damage allows the use of relatively lower doses of such other agents, resulting in a lower frequency of potential adverse side effects associated with long-term administration of such therapeutic agents. Thus, another indication of the compositions in this invention is to reduce adverse side effects of prior-art drugs used to control optic nerve degeneration, such as the development of cataracts with long-acting anticholinesterase agents including demecarium, echothiophate, and isofluorophate.

While specific embodiments of the present invention have been described in the foregoing, it will be appreciated by those skilled in the art that many equivalents, modifications, substitutions, and variations may be made thereto without departing from the spirit and scope of the invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method for effecting ocular neuroprotection in a subject in need thereof, the method comprising administering to an ocular environment of said subject a composition that comprises a material capable of controlling a level of cortisol in said ocular environment in an effective amount and at an effective frequency to provide said neuroprotection.
2. The method of claim 1, wherein said effecting ocular neuroprotection comprises controlling a progression of an ocular neurodegenerative condition.
3. The method of claim 2, wherein said ocular neurodegenerative condition is selected from the group consisting of glaucoma, retinitis pigmentosa, wet AMD, dry AMD, diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.
4. The method of claim 2, wherein said material comprises an antagonist to 11 β -HSD1, a prodrug, a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.
5. The method of claim 4, wherein said antagonist to 11 β -HSD1 is capable of neutralizing, inhibiting, or impeding an activity, transcription, expression, or signaling cascade of 11 β HSD1.
6. The method of claim 5, wherein said ocular neurodegenerative condition is selected from the group consisting of glaucoma, retinitis pigmentosa, wet AMD, dry AMD, diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.
7. The method of claim 6, wherein said administering to an ocular environment comprises administering into a vitreous of said subject.
8. The method of claim 7, wherein said administering comprises injecting a composition or implanting an implant, device, or system, and said composition, implant,

device or system comprises said antagonist to 11 β -HSD1, a prodrug, a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

9. The method of claim 5, wherein said ocular neurodegenerative condition is selected from the group consisting of hypertensive and normotensive glaucoma

10. The method of claim 5, wherein said ocular neurodegenerative condition is selected from the group consisting of retinitis pigmentosa, wet AMD, dry AMD, diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.

11. The method of claim 1, wherein said administering comprises injecting a composition or implanting an implant, device, or system, and said composition, implant, device or system comprises said antagonist to 11 β -HSD1, a prodrug, a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

12. The method of claim 11, wherein said composition, implant, device, or system further comprises a recombinant human 11 β -HSD2.

13. The method of claim 1, wherein said administering is performed in conjunction with another therapy or medical procedure directed to control progression of an ocular neurodegenerative condition.

14. A pharmaceutical composition comprising a material capable of controlling a level of 11 β -HSD1 in an ocular environment when applied thereto, wherein the material is present in the composition in an effective amount for effecting ocular neuroprotection.

15. The composition of claim 14, wherein said effecting neuroprotection comprises controlling progression of an ocular neurodegenerative disease.

16. The composition of claim 15, wherein said composition comprises an antagonist to 11 β -HSD1, a prodrug, a pharmaceutically acceptable salt, or a pharmaceutically acceptable ester thereof.

17. The composition of claim 16, wherein said antagonist to 11 β -HSD1 is capable of neutralizing, inhibiting, or impeding an activity, transcription, expression, or signaling cascade of 11 β HSD1.
18. The composition of claim 17, wherein said antagonist to 11 β -HSD1 comprises an inhibitor of H6PDH.
19. The composition of claim 18, wherein said antagonist to 11 β -HSD1 comprises a PPAR α agonist, a PPAR γ agonist, or a combination thereof.
20. The composition of claim 16, wherein said antagonist to 11 β -HSD1 comprises a nucleic acid molecule that is capable of downregulating, inhibiting, or reducing an expression of 11 β -HSD1.
21. The composition of claim 20, wherein said nucleic acid molecule comprises an siRNA acting on 11 β -HSD1 gene transcription.
22. The composition of claim 16, wherein said composition is injectable or implantable.
23. The composition of claim 16, further comprising recombinant human 11 β HSD2.
24. The composition of claim 16, wherein said material comprises a compound selected from the group consisting of adamantane derivatives, triazole derivatives, pyrazolo[1,5-a]pyrimidine derivatives, triazine derivatives, substituted amides, fused 1,2,4-triazole derivatives, substituted triazoles, and combinations thereof.
25. The composition of claim 15, wherein said material is effective for controlling progression of an ocular neurodegenerative condition selected from the group consisting of glaucoma, retinitis pigmentosa, wet AMD, dry AMD, diabetic retinopathy, optic neuritis, optic neuropathy, retinal detachment, and combinations thereof.