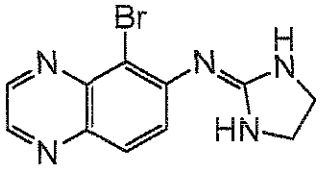
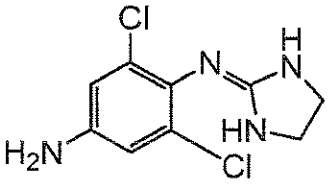
SUMMARY OF THE INVENTION

Three alpha 1 and three alpha 2 adrenergic receptors have been characterized by molecular and pharmacological methods. Activation of these alpha 2 receptors evokes physiological responses and has useful therapeutic actions.

The adrenergic Alpha-2 agonists play a key role in modulating aqueous humor formation and facilitating aqueous outflow; as a result these compounds lower intraocular pressure (IOP) in glaucomatous patients. Two drugs are currently prescribed for glaucoma patients, Apraclonidine (Iopidine® available from Alcon Pharmaceuticals) and Brimonidine (Alphagan P® available from Allergan, Inc.). While these drugs are effective at lowering elevated intraocular pressure, Alphagan P® is the only alpha-2 adrenergic drug approved for chronic treatment of glaucoma, but it loses effect during the day and must be used 2-3 times a day, while Iopidine® is only approved for short term IOP control. Considering the aged glaucoma patient population, a 3 times per day dosing frequency is far from optimal and may result in poor patient compliance.

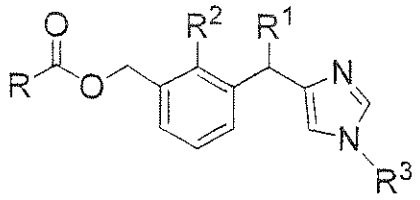


Brimonidine



Apraclonidine

In a first aspect, there is provided a composition for use in lowering intraocular pressure in a subject comprising a therapeutically effective amount of a compound having Formula I, its individual enantiomers, its individual diastereoisomers, its hydrates, its solvates, its crystal forms, its individual isomers, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula I

wherein

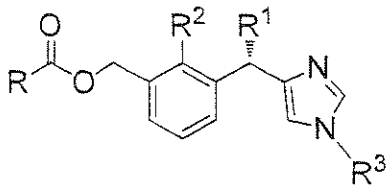
R^1 is H or C_{1-3} alkyl;

R^2 is H or C_{1-3} alkyl;

R^3 is H, C_{1-10} alkyl, heterocycle or aryl; and

R is C_{1-10} alkyl, heterocycle or aryl.

In a second aspect, there is provided a pharmaceutical composition for lowering intraocular pressure in a subject comprising a compound having a structure



Formula II

wherein

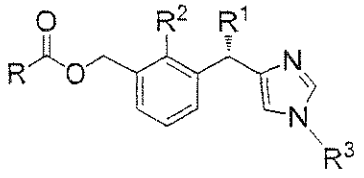
R^1 is H or C $_{1-3}$ alkyl;

R^2 is H or C $_{1-3}$ alkyl;

R^3 is H, C $_{1-10}$ alkyl, heterocycle or aryl; and

R is C $_{1-10}$ alkyl, heterocycle or aryl.

In a third aspect, there is provided an article of manufacture when used as defined herein comprising packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for lowering intraocular pressure and wherein the packaging material comprises a label which indicates the pharmaceutical agent can be used for lowering intraocular pressure and wherein said pharmaceutical agent comprises an effective amount of compound is of Formula II, its individual diastereoisomers, its individual hydrates, its individual solvates, its individual crystal forms, its individual isomers, its individual tautomers or a pharmaceutically acceptable salt thereof,



Formula II

wherein

R^1 is H or C $_{1-3}$ alkyl;

R^2 is H or C $_{1-3}$ alkyl;

R^3 is H, C $_{1-10}$ alkyl, heterocycle or aryl; and

R is C $_{1-10}$ alkyl, heterocycle or aryl.

The present disclosure~~invention~~ relates to a method of lowering intraocular pressure in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

In another embodiment~~aspect~~, the present disclosure~~invention~~ relates to a method of lowering intraocular pressure in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of (*S*)

[3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, or pharmaceutical compositions containing them. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound, active metabolite, (*S*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

In another embodiment~~aspect~~ the present disclosure~~invention~~ provides relates to a method of lowering intraocular pressure in a subject in need of such treatment, which comprises administering a therapeutically effective amount of a composition comprising ester pro-drugs of (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, or pharmaceutical compositions containing them. Upon hydrolytic and/or enzymatic cleavage of the ester functionality the parent compound (*R*) [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol, is released to act as a selective modulator of the alpha 2 adrenergic receptors.

The ester pro-drugs of [3-(1-(1*H*-imidazol-4-yl)ethyl)-2-methylphenyl] methanol are useful for the treatment or prevention of mammals, including humans, in a range of conditions and diseases that are alleviated by alpha 2A, 2B, 2C activation, including but not limited to treating or preventing glaucoma, elevated intraocular pressure, ischemic neuropathies, optic neuropathy, pain, visceral pain, corneal pain, headache pain, migraine, cancer pain, back pain, irritable bowel syndrome pain, muscle pain and pain associated with diabetic neuropathy, the treatment of diabetic retinopathy, other retinal degenerative conditions, stroke, cognitive deficits, neuropsychiatric conditions, drug dependence and addiction, withdrawal of symptoms, obsessive-compulsive disorders, obesity, insulin resistance, stress-related conditions, diarrhea, diuresis, nasal congestion, spasticity, attention deficit disorder, psychoses, anxiety, depression, autoimmune disease, Crohn's disease, gastritis, Alzheimer's, and Parkinson's ALS other neurodegenerative diseases, dermatological conditions, skin erythema (redness) and inflammation, acne, age related macular degeneration, wet macular degeneration, dry macular degeneration, geographic atrophy, diabetic macular edema, tumors, wound healing, inflammation and retinal vein occlusion, enhancing vision in patients with vision loss from conditions including glaucoma, retinitis pigmentosa and neuritis secondary to multiple sclerosis, rosacea (dilation of the blood vessels just under the skin), sunburn, chronic sun damage, discreet