

Eye drops for the delivery of an anti-glycation agent that prevents and treats diabetes- and age-related pathologies

SUMMARY

Glycation is a non enzymatic chemical process in which human DNA, lipids and proteins are damaged by the attachment of reducing sugars such as glucose, ultimately leading to the formation of highly reactive Advanced Glycation Endproducts (AGEs). This process has been associated with deleterious health effects. The present invention provides a potent inhibitor of protein glycation and AGEs formation that is particularly advantageous for eye-drop delivery in the prevention and treatment of diabetes- and age-related pathologies.

APPLICATIONS

- An anti-glycation agent that inhibits the glycation process and prevents the formation of AGEs (e.g. free radicals, α -dicarbonyl species, protein cross-links, etc.).
- Eye drops for prevention and treatment of ocular pathologies such as diabetic retinopathy.
- Anti-aging protection of long-lived ocular proteins, such as collagen and lens crystalline.

CONCEPT

Protein glycation has been implicated in the development of pathologies associated with diabetes, smoking and normal ageing including vision impairment. Drug candidates that exhibit anti-glycation activities are being sought for the treatment of these disorders. D-isoproterenol, a structurally related analog of adrenaline, was identified as a highly potent inhibitor of protein glycation. Administered by conventional eye drop as a dipivalyl

prodrug derivative, this agent could prevent and treat glycation-related ocular pathologies such as diabetic retinopathy. Broadly classified as an anti-oxidant and known for having significantly lower adrenergic activities than its L-isomer, D-isoproterenol directly protects proteins from reducing sugars, thereby inhibiting their glycation (see Figure; lysozyme is used as a model protein).

FEATURES AND BENEFITS

Prevents initial step of protein glycation

D-isoproterenol directly protects amino groups of proteins against glycation, especially those of lysine residues, by blocking the initial reaction with a reducing sugar. This in turn prevents the formation of highly reactive AGEs that increase the oxidative stress of biological systems.

High potency anti-glycation

The anti-glycation activity of D-isoproterenol (IC_{50} of 21 μ M) compares favorably to that of aminoguanidine (IC_{50} of 350 μ M). This value is also within the effective concentration range reported for the choroid/retinal distribution of dipivefrin, a structurally related anti-glaucoma eye drop.

Non-toxicity to the surface of the eye at high concentration

Response to a single eye drop application of D-isoproterenol at high concentration (10-20% solution) was reported to be physiologically acceptable however long term use was not tested. The anticipated concentration of D-isoproterenol prodrug is 0.1%.

Enhanced absorption of prodrug formulation

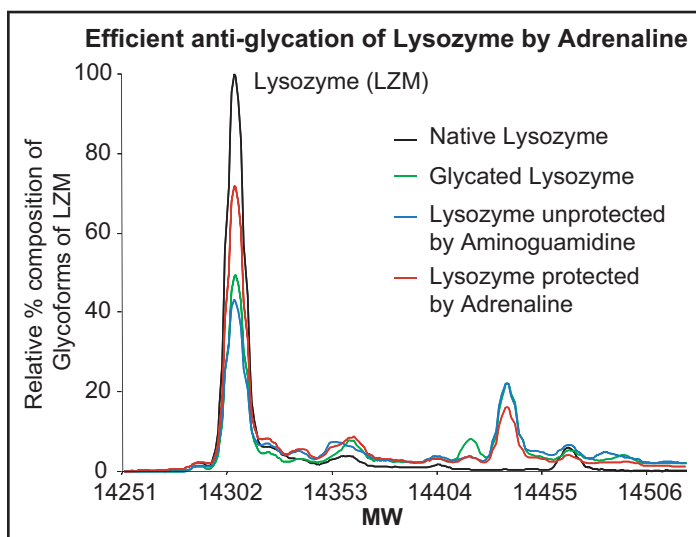
Dipivalyl D-isoproterenol is a prodrug of D-isoproterenol that can be administered topically by eye drop. The dipivalyl portion of the drug facilitates absorption and penetration of the prodrug across the corneal epithelium as is well documented for the prodrug dipivalyl D,L-adrenaline (dipivefrin).

Suitable for long-term preventive treatment

The previously described low beta-adrenergic receptor affinity of D-isoproterenol and the absence of systemic toxicity make this drug suitable for long-term use. Continuous eye drop administration of its prodrug will ultimately prevent glycation allowing for ocular protection from diabetic retinopathy and other diabetes- and age-related complications.

PROTECTION STATUS

Anti-glycation agents for preventing age- diabetes- and smoking-related complications (NRC no. 11323).



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