

NANTIVIRAL COMPOUNDS FOR IMPROVED TREATMENT OF EYE INFECTIONS

Infections with the herpes simplex virus can lead to severe corneal scarring and opacity. The currently available therapy for HSV keratitis involves the use of a 1% trifluorothymidine(TFT) solution. However, one of the major problems associated with TFT therapy is cytotoxicity, which restricts its use in long-term treatment. Due to problems associated with the use of ointments in the eye, acyclovir (ACV) ointment has not been approved for clinical use in HSV keratitis patients in the United States. In addition, ACV ointment is not effective against stromal keratitis or when the deeper ocular tissues are involved, suggesting that ACV has poor permeation characteristics across the corneal epithelium. The corneal epithelium is composed of 5 to 6 layers of columnar epithelium with tight junctions, making paracellular diffusion across this epithelium minimal. Beneath the epithelial layer is the stroma, which contains more than 90% water, and hence presents a barrier to hydrophobic compounds.

UMKC researchers have developed esters with sufficient hydrophilicity to be formulated into pharmacologically active compositions, such as aqueous solutions (e.g., eye drops). Compounds of the invention can be effectively transported into the ocular tissues. Specifically, such compounds effectively reach the anterior segment and/or the vitreo-retinal segment when administered either topically or systemically. The compounds formulated have been shown to be effective against viral infections, particularly the herpes group of viruses (e.g., herpes simplex types 1 and 2, *varicella zoster virus* (VZV) and human cytomegalovirus (HCMV)).

The present compounds employ oligopeptide transporters for delivery to the deeper tissues of the cornea. Thus, the present compounds are effective in cases where the corneal stroma and underlying tissues have been infected. These compounds have shown excellent *in vitro* antiviral activity against HSV 1 in HFF cells and *in vivo* rabbit epithelial keratitis with no significant cytotoxicity.

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