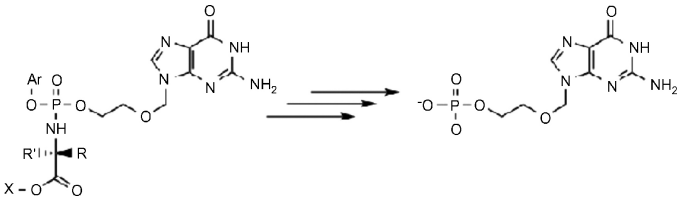

Fig. 1. Bioactivation of acyclovir ProTides.

cant improvement in antiviral activity was observed (McGuigan et al., 2000). In the present work, a new series of optimised acyclovir ProTides with an enhanced biological profile is reported (Fig. 1).

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Vidarabine Prodrugs as Potential Inhibitors of Adenosine Deaminase

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Vidarabine (9-(β-D-arabinofuranosyl)adenine or ara-A) is active against herpes simplex virus (HSV) types 1 and 2, cytomegalovirus, and chronic hepatitis B virus (HBV) infections through inhibition of viral DNA synthesis. Although supplanted by acyclovir and other analogs for most applications, vidarabine is still an alternative therapy for acyclovir-resistant HSV and varicella-zoster virus infections. We recently reported that vidarabine was three- to fivefold more active than cidofovir against cow pox and vaccinia viruses in plaque reduction assays [Antiviral Res. 70 (2006) A14]. However, despite the proven efficacy against a variety of viruses, vidarabine suffers some limitations. First and most importantly, it is readily metabolized by adenosine deaminase (ADA) to 9-(β-D-arabinofuranosyl)hypoxanthine (ara-H), which has very low antiviral activity. Secondly, as a nucleoside, vidarabine has low lipophilicity and thus has low intestinal membrane permeability. Finally, it is also poorly soluble in aqueous solutions, thereby limiting options for both parenteral and peroral formulations. To address these concerns, vidarabine 5′-amino acid prodrugs were synthesized and, when perfused intestinally, resulted in increased plasma concentrations. Since it was previously discovered that vidarabine 5′-valerate inhibits metabolism of ara-A to ara-H by ADA [Mol. Pharm. 14 (1978) 366], we confirmed this inhibition ($K_i = 9.5$ μM) and demonstrated that this prodrug was more active verses vaccinia virus in vitro. In contrast, unlike its fatty acid counterpart, the vidarabine 5′-amino acid prodrugs did not inhibit the metabolism of ara-A to ara-H. We conclude that despite certain advantages over vidarabine, the amino acid prodrugs do not inhibit the deamination of the active compound.

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Megaribavirin Aerosol for the Treatment of Influenza A Virus Infections in Mice

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Clinical efficacy of ribavirin aerosol treatment in mice translated well to natural influenza infections in college students. While newer neuraminidase inhibitors have been developed to treat influenza A and B infections, emergence of drug resistance poses potential problems. Because of this resistance, combination drug treatments have been evaluated. Ribavirin alone or in combination would be an ideal antiviral since it inhibits both influenza A and B viruses and drug resistance has not occurred in the clinical setting. To make ribavirin aerosol treatment a quicker process, limited to once or twice daily treatments, and be more cost effective, a MegaRibavirin formulation (reservoir concentration, 100 mg of ribavirin/mL) was developed that when used with the more efficient nebulizer, the Aerotech II nebulizer, was effective in preventing death in a lethal influenza A/HK/8/68 (H3N2) virus-mouse model. Aerosol generated with the MegaRibavirin formulation using the Aerotech II nebulizer flowing at 10 L of air/min produced aerosol droplets that contained 2.3 mg of ribavirin/L with a mass median aerodynamic diameter of 1.8 μm and a geometric standard deviation of 2.6. Thus, compared to the standard (20 mg/mL) or "high dose" (60 mg/mL) ribavirin concentrations used with the SPAG2-6000 nebulizer that has been used for both influenza and RSV infections, ribavirin aerosol generation was twice as efficient with the Aerotech II nebulizer while maintaining the same aerosol characteristics. Using this system for treatment, a single daily 30-min exposure on days 1–4 produced a survival rate of greater than 90% compared to 0% of animals without treatment. In addition, delaying the start of aerosol treatment for 48 or 72 h and treating just once daily for 30 min for only 2 days (days 2–3 and 3–4, respectively) still significantly increased the rate of survival and mean time to death. For the treatment of influenza in general and specially for pandemic avian influenza, the MegaRibavirin-Aerotech II method of aerosol treatment allows for short treatment periods (30 min once or twice daily), minimizes environmental issues and should