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### Design, Synthesis, and Biological Evaluation of Novel Anti-VZV Agents

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Varicella zoster virus (VZV) currently affects about 95% of the population of industrialised countries and there are approximately 500,000 cases of shingles reported annually in the U.S. (NIAID, 2007). Previously we reported the potent and selective anti-VZV activity of unusual fluorescent bicyclic nucleosides analogues (BCNAs) characterised by a fused bicyclic pyrimidine ring (McGuigan et al., 1999). Initial studies found that the long alkyl chain on the aglycone to be essential for activity. The optimisation of the lead compound resulted in a series of 6-alkylphenyl derivatives, which showed a greatly improved antiviral activity (McGuigan et al., 2000). In particular Cf1743 (Fig. 1) emerged as the most potent compound reported against VZV to date (EC50 of 0.1 nM) which is ca. 10,000 times more potent than the current treatment acyclovir.

In the present work, we report a series of novel modified derivatives of Cf1743 designed to enhance potency and bioavailability. The synthesis and biological evaluation of these compounds will be presented.

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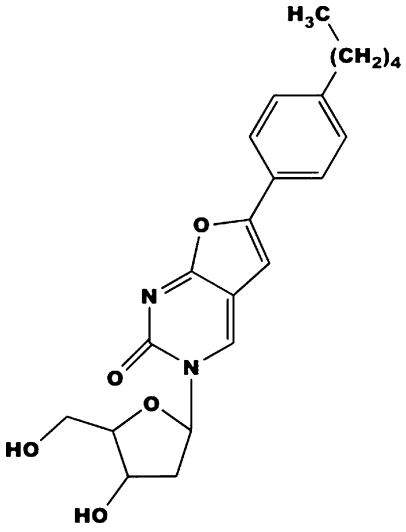


Fig. 1. Structure of Cf1743.

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### Synthesis and Properties of Chiral Open-Ring Acyclic Nucleoside Bisphosphonates

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New generation of acyclic nucleoside phosphonates (ANP, 1) is based on replacement of purine heterocycle by 2,4-diamino-6-hydroxy- or 2-amino-4,6-dihydroxypyrimidine (Fig. 1). The antiviral activity of so-called "open-ring" ANPs (2) is enantiospecific and parallel to that of the corresponding ANPs with the complete purine ring.

In the SAR studies, we prepared open-ring derivatives containing at the positions 4- and 6- of the pyrimidine moiety two identical or different chiral phosphonate-bearing substituents (3). Bisphosphonates (3) were prepared by alkylation of 4,6-dihydroxy-2-methylthiopyrimidine with appropriate synthon and subsequent ammonolysis of 2-methylthio group to amino group. In contrast to alkylation of 2-amino-4,6-dihydroxypyrimidine, which gives mixture of *O*- and *N*-alkylated regioisomers, alkylation of 2-methylthio derivative affords exclusively *O*-alkylated product.

Details of synthesis, biological activities and formation of metal ion complexes will be discussed.

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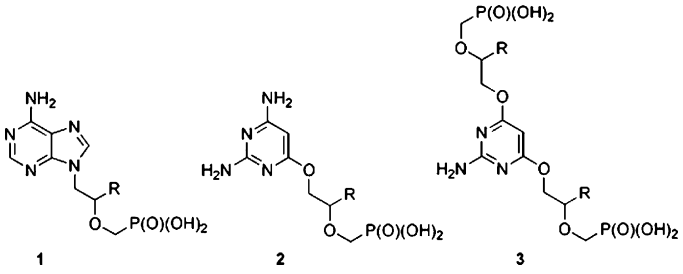


Fig. 1.

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