Poster Session II: Herpesviruses, Topical Microbicides, Poxviruses, Other Antiviral Agents, Medicinal

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Design and Synthesis of Novel Non-nucleoside Anti-HCMV Agents

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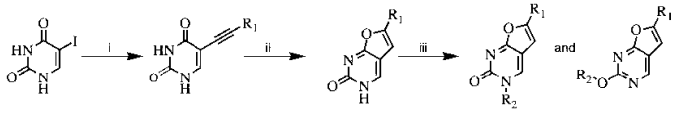
Bicyclic furanopyrimidines are potent and selective inhibitors of Varicella Zoster Virus (VZV) (McGuigan et al., 1999). SAR studies have shown 2′,3′-dideoxynucleoside derivatives to be poorly VZV-active but exhibit activity against human cytomegalovirus (HCMV) (McGuigan et al., 2004). Phosphorylation was shown not to be a requisite for activity presenting the possibility to introduce non-sugar moieties. Many long chain N- and O-alkylated derivatives have been presented, some showing comparable activity to ganciclovir (GCV) supporting a non-nucleoside meachanism of action (Kelleher et al., 2005; Adak et al., 2007). The target structures were prepared by the Pd-catalysed coupling of various alkynes with 5-iodouracil (Scheme 1), to give intermediate 5-alkynyl nucleosides which were subsequently cyclised in the presence of CuI to give the bicyclic systems. The corresponding bases were then reacted with a selection of alkylating agents to form N- and O-alkylated products. The synthesis, biological evaluation and cytotoxicity of novel long chain N- and O-alkylated derivatives will be presented.



Scheme 1. (i) 1-Alkyne, DIPEA, $Pd(PPh_3)_4$, CuI, DMF; (ii) CuI, Et_3N; (iii) R_2X, DMF.

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Susceptibility of Human Cytomegalovirus (HCMV) Drug-resistant Viruses to a New Class of Acyclic Nucleoside Phosphonate Analogues (ANPs)

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We have recently reported on the selective and potent antiviral activity of a new class of ANPs, i.e. HPMP-5-azaC [a 5-azacytosine analogue of cidofovir (HPMPC)] and its cyclic form, against herpesviruses and poxviruses. We describe here the susceptibility of drug-resistant human cytomegalovirus (HCMV) mutants to this new class of ANPs. The antiviral activity against DNA pol mutants of HCMV isolated from clinical samples or selected under pressure with 3-hydroxy-2-phosphylmethoxypropyl derivatives of adenine (HPMPA) and cytosine (HPMPC), 9-(2-phosphonylmethoxyethyl)-2,6-diaminopurine (PMEDAP), ganciclovir (GCV), acyclovir (ACV) and foscarnet (PFA), was evaluated by cytopathic effect reduction assay in human fibroblasts. These mutants bore the following mutations: F412L ($HPMPA^r$), K513N (GCV^r), V715M (PFA^r), L773V ($PMEDAP^r$), H729Y (ACV^r), A987G ($HPMPC^r$) and P522S + G687S (clinical sample). Mutants that showed resistance to the HPMP derivatives and GCV (i.e. F412L, K513N, A987G and P522S + G687S) remained sensitive to the PME derivatives, ACV and PFA, while mutants resistant to the PME derivatives (i.e. H729Y, L773V and V715M) showed cross-resistance to ACV and the pyrophosphate analogue PFA but remained sensitive to the HPMP derivatives and to the 5-azacytosine analogues of HPMPC. The increase in EC_{50} values obtained for the different $HPMPC^r$ viruses compared to the wild-type strain was approximately of 16.9-fold (A987G), 6.8-fold (K513N), 23-fold (F412L) and 6.1-fold (P522S + G687S) for HPMPC and of 1.3-fold (A987G), 1.4-fold (K513N), 5.7-fold (F412L) and 1.7-fold (P522S + G687S) for HPMP-5-azaC. Thus, the A987G, K513N and the P522S + G687S mutations in the HCMV DNA pol were not associated with resistance to HPMP-5-azaC, while the F412L mutation confered a higher level of resistance to HPMPC than to HPMP-5-azaC. These findings indicate that HPMP-5-azaC compares favorably to HPMPC in its activity against $HPMPC^r$ HCMV mutants. Furthermore, these results are in agreement with our previous data on $HPMPC^r$ herpes simplex virus and vaccinia virus mutants

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