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Design and Synthesis of Novel Anti-HCMV Agents: Modifications to the Bicyclic Pyrimidine Base

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We have previously reported bicyclic furanopyrimidines as potent and selective inhibitors of Varicella Zoster Virus (VZV). Modifications on the base, sugar and side chain led to 2′,3′-dideoxy derivatives that were poorly VZV-active but exhibited 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. Following this, long chain N- and O-alkylated derivatives have been presented showing comparable activity to ganciclovir (GCV) (Kelleher et al., 2005).

The synthesis and biological evaluation of a novel series of long chain *N*- and *O*-alkylated derivatives are described herein (Scheme 1).

The target structures were prepared by the Pd-catalysed coupling of various alkynes with 5-iodouracil, to give intermediate 5-alkynyl bases 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 the *N*- and *O*-alkylated products. The antiviral activity against HCMV AD-169 and Davis strains along with the cytotoxicity of these compounds are to be reported.

References

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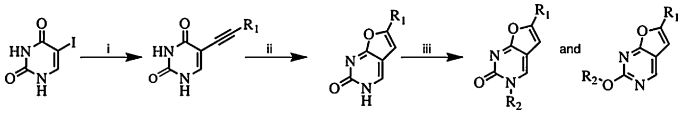

Scheme 1. (i) 1-Alkyne, DIPEA, $Pd(PPh_3)_4$, CuI; (ii) CuI, Et_3N; (iii) R_2X DMF.

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HINT as Putative Phosphoramidase Responsible of ProTides Activation: Molecular Modelling Studies

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The ProTide approach was developed by McGuigan et al. as a method to improve the biological activity of poorly active nucleoside analogues by “kinase bypass” in which lipophilic nucleotide pro-drugs act as intracellular phosphate delivery motifs and achieve the generation of free nucleotides by nucleoside kinase-independent means.

The activation of phosphoramidates is considered to be based upon two enzymatic cleavages: the hydrolysis of the amino acid ester moiety as the trigger of the process, and the P–N bond cleavage as the final step that would release the corresponding nucleoside analogue monophosphate. The latter step is carried out by an enzyme with phosphoramidase activity and it has been proposed that the protein responsible of the cleavage of the P–N bond belongs to the HINT family: adenosine monophosphoramidates AMP-NH2, AMP-*N*-ε-(*N*-α-acetyl lysine methyl ester) and AMP-*para*-nitroaniline were identified as rabbit Hint and yeast Hint1 substrates. Notably, AMP-*N*-alanine methyl ester was also reported as a substrate for the same enzymes, which might indicate their role in the activation of our phosphoramidates.

We have recently reported some initial docking studies on a series BVDU phosphoramidate analogues in the human HINT-1 active site, which showed that indeed this enzyme could be able to bind and process the phosphoramidates. In the work presented here, we have extended the modelling simulations to different antiviral nucleoside analogues and examined their binding to HINT-1, as well as to the homology models of HINT-2 and HINT-3, with the aim of developing a predictive computational model which could be used in the design of more potent and selective phosphoramidate analogues (Fig. 1).

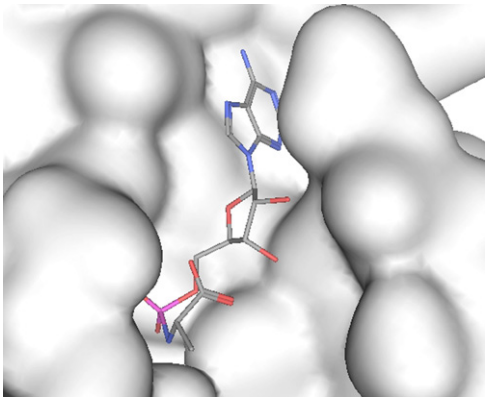

Fig. 1.

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