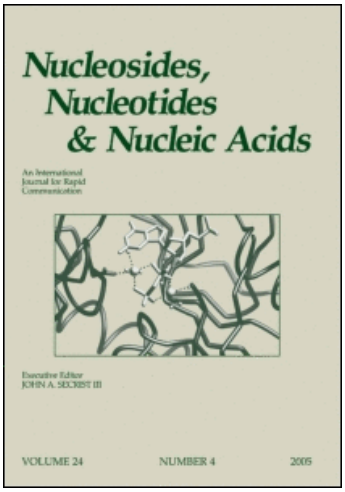

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Synthesis and Biological Evaluation of N- and O-Alkylated Bicyclic Furanopyrimidines as Non-Nucleosidic Inhibitors of Human Cytomegalovirus

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SYNTHESIS AND BIOLOGICAL EVALUATION OF N- AND O-ALKYLATED BICYCLIC FURANOPYRIMIDINES AS NON-NUCLEOSIDIC INHIBITORS OF HUMAN CYTOMEGALOVIRUS

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▫ *2′,3′-Dideoxy furanopyrimidines were shown to display anti-HCMV activity via a non-nucleoside mechanism. Further studies into highly modified sugar derivatives led to the preparation of N-and O-alkylated C_{10} furanopyrimidine analogues, and this work is described herein. These compounds were tested against HCMV strains, and the first case of submicromolar activity was observed.*

Keywords Furanopyrimidines, Human Cytomegalovirus, Antiviral

INTRODUCTION

The pharmacological and therapeutic complications associated with ganciclovir (GCV), cidofovir and foscarnet has fuelled the imperative pursuit of alternative treatments of human cytomegalovirus (HCMV).[1] Interest within our group to modify the sugar moiety of highly active VZV selective bicyclic furanopyrimidine nucleosides[2–5] led to the discovery of 2′,3′-dideoxy furanopyrimidine nucleosides, which were poorly VZV-active, but surprisingly displayed HCMV activity.[6] Time of addition studies showed that these dideoxy nucleosides did not require phosphorylation to inhibit HCMV activity, and thus presented the possibility to introduce non-sugar-like functionalities to probe the structure-activity relationships (SARs). Further work has culminated in a series of novel C_4–C_{10} long chain N- and O-alkylated derivatives, which displayed a comparable potency to GCV in vitro against HCMV AD-169 and Davis strains.[7] Here we present the synthesis and biological evaluation of an extended series of C_{10} long chain N- and O-derivatives in an effort to elucidate the structural requirements at the sugar of such highly modified compounds for HCMV inhibition.

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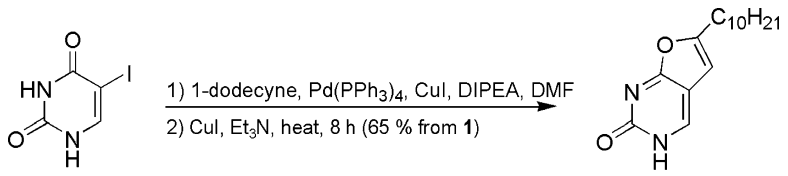
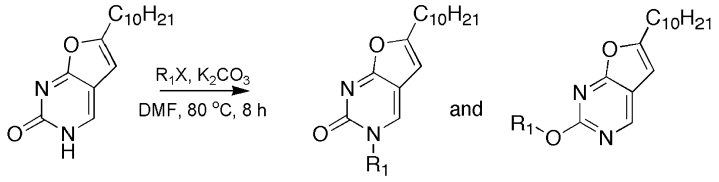


1 2

SCHEME 1



2 3 4

SCHEME 2 (Yields of **3** and **4** in brackets); where R_1 = n-C_3H_7 (**a:** 55% and 29%), n-C_4H_9 (**b:** 32% and 57%), n-C_5H_{11} (**c:** 53% and 35%) i-C_5H_{11} (**d:** 27% and 43%), cyclopentyl (**e:** 14% and 66%), cyclohexyl (**f:** 6% and 20%), 2-methyltetrahydropyranyl (**g:** 30% and 26%), benzyl (**h:** 65% and 14%), 4-methylbenzyl (**i:** 65% and 15%), 4-methoxybenzyl (**j:** 44% and 9%).

The target N- and O-alkylated compounds **3** and **4**, respectively, were prepared from the alkylation of their parent C_{10} furano pyrimidine base **1** (obtained from the Pd and Cu coupling/cyclisation reaction of 5-iodouracil with 1-dodecyne in Scheme 1) with a suite of alkylating reagents, as detailed in Scheme 2.

The antiviral evaluation of these C_{10} compounds against HCMV AD-169 and Davis strains in human embryonic lung (HEL) cells showed that O-alkylated derivatives **4** were as active/more active than their corresponding **3** compounds, although a clear SAR is still not observed despite the large diversity in substituents. The lipophilic C_{10} chain increased the ClogP of these derivatives to between 6 and 10, and so the low activities observed in some cases were not unexpected on the grounds of poor water solubility. Encouragingly, the O-2-methyltetrahydropyran analogue **4g** displayed the first example of submicromolar activity, but with concomitant cytotoxicity.

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