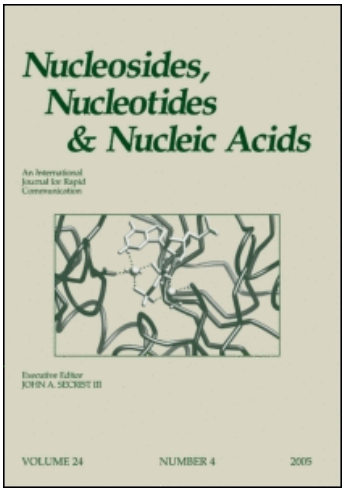

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THE JOURNEY TOWARDS ELUCIDATING THE ANTI-HCMV ACTIVITY OF ALKYLATED BICYCLIC FURANO PYRIMIDINES

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▫ *Bicyclic furanopyrimidines were recently discovered by us to be potent and selective inhibitors of VZV. Related studies to investigate the role of the sugar in this activity uncovered dideoxy furanopyrimidines as inhibitors of HCMV and this led to the preparation of highly modified long alkyl chain furanopyrimidines from the N- and O-alkylation of their parent bases. Herein we describe their synthesis and subsequent biological evaluation against HCMV. O-alkylated derivatives were almost invariably found to be at least equiactive with their N-alkylated counterparts. At this point, little change in activity has been found with large variation in N- and O-substituent.*

Keywords Furanopyrimidines, Human Cytomegalovirus, Antiviral

INTRODUCTION

Following the discovery in our laboratories of the highly potent and selective anti-VZV bicyclic furanopyrimidines (EC_{50} < 1 nM and SI > 1 million),[1–4] modifications on the base, sugar and side chain moieties led to dideoxy derivatives that displayed poor VZV activity, but exhibited anti-HCMV properties.[5]

Evidence was shown in time-of-addition studies of these dideoxy derivatives for a non-nucleosidic mechanism of action early in the viral replication cycle, which implied that phosphorylation is not a requisite of activity, and suggested the possible redundancy of the sugar component. Subsequent work focused on the preparation of a substantial series of highly modified N_1-substituted alkyl furanopyrimidines **3** (and the corresponding O_2-alkylated by-products **4**), obtained from the reaction of the C_4–C_{10} long chain parent base **3** with the corresponding alkylating agent.[6,7]

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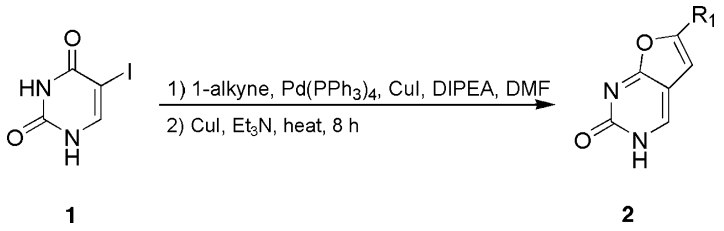


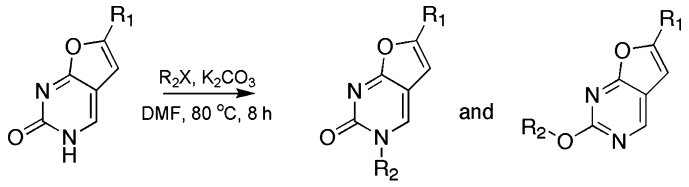
1 **2**

SCHEME 1

Scheme 1 details the preparation of furanopyrimidine bases **2** via the standard protocol of Cu/Pd coupling of the various 1-alkynes to 5-iodouracil **1**, and subsequent cyclization with Cu catalyst and base formed the desired bases in a one-pot synthesis. The corresponding bases **2** were then reacted with a selection of various alkylating agents to form both the N- and O-alkylated products, **3** and **4**, respectively, as shown in Scheme 2 (the yields of **3** and **4** from each reaction is shown in brackets).

Compounds **3** and **4** were then submitted for testing against AD169 and Davis HCMV strains. It was immediately noted that the O-substituted compounds **4** were almost invariably equipotent or more potent than its analogous N-substituted derivatives **3**. Earlier work found **4c** to display the best activity (EC_{50} 3 μM) relative to GCV (2.9 μM).[6,7]

Encouragingly, a recent study into more modified non-sugar-like substituents produced **4v**, the C_{10} O-2-methyltetrahydropyran analogue, which is currently the most potent alkyl furanopyrimidine to date, and the first analogue to exhibit submicromolar potency, with an activity of 0.78 μM. However, this also displays the first example of cytotoxicity observed in this class of compounds (S.I. of 63).



2 **3** **4**

3a (10 %), **4a** (57 %): R_1 = C_4H_9 , R_2 = cyclopentyl
3b (14%), **4b** (79 %): R_1 = C_6H_{13} , R_2 = cyclopentyl
3c (20 %), **4c** (57 %): R_1 = C_7H_{15} , R_2 = cyclopentyl
3d (14 %), **4d** (56 %): R_1 = C_8H_{17} , R_2 = cyclopentyl
3e (14 %), **4e** (66 %): R_1 = $C_{10}H_{21}$, R_2 = cyclopentyl
3f (29 %), **4f** (42 %): R_1 = C_4H_9, R_2 = isopentyl
3g (37 %), **4g** (59 %): R_1 = C_6H_{13}, R_2 = isopentyl
3h (28 %), **4h** (70 %): R_1 = C_7H_{15}, R_2 = isopentyl
3i (18 %), **4i** (43 %): R_1 = C_8H_{17}, R_2 = isopentyl
3j (27 %), **4j** (43 %): R_1 = $C_{10}H_{21}$,R_2 = isopentyl
3k (6 %), **4k** (61 %): R_1 = C_6H_{13}, R_2 = cyclohexyl
3l (6 %), **4l** (20 %): R_1 = $C_{10}H_{21}$, R_2 = cyclohexyl
3m (27 %), **4m** (-) : R_1 = C_6H_{13}, R_2 = 2-tetrahydrofuryl
3n (24 %), **4n** (-) : R_1 = $C_{10}H_{21}$, R_2 = 2-tetrahydrofuryl
3o (55 %), **4o** (29 %): R_1 = $C_{10}H_{21}$, R_2 = n-propyl
3p (32 %), **4p** (57 %): R_1 = $C_{10}H_{21}$, R_2 = n-butyl
3q (53 %), **4q** (35 %): R_1 = $C_{10}H_{21}$, R_2 = n-pentyl
3r (14 %), **4r** (66 %): R_1 = $C_{10}H_{21}$, R_2 = cyclohexyl
3s (65 %), **4s** (14 %): R_1 = $C_{10}H_{21}$, R_2 = benzyl
3t (65 %), **4t** (15 %): R_1 = $C_{10}H_{21}$, R_2 = 4-methylbenzyl
3u (44 %), **4u** (9 %): R_1 = $C_{10}H_{21}$, R_2 = 4-methoxybenzyl
3v (30 %), **4v** (26 %): R_1 = C_{10}, R_2 = 2-methyltetrahydropfuran

SCHEME 2

All compounds were also tested against VZV and no activity was observed, which highlights the requirement of 5′-phosphorylation for VZV inhibition. In the course of these studies, it has been found that varying the size and shape of the substituent at the N- and O-position influences the regioselectivity of reaction and hence the ratio of N-/O-products, but does not appear to play a dominant role in the antiviral activity of these furanopyrimidines.

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