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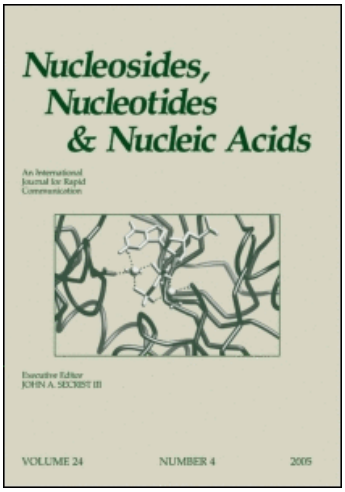

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BICYCLIC NUCLEOSIDE INHIBITORS OF VARICELLA-ZOSTER VIRUS (VZV): EFFECT OF TERMINAL UNSATURATION IN THE SIDE-CHAIN

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BICYCLIC NUCLEOSIDE INHIBITORS OF VARICELLA-ZOSTER VIRUS (VZV): EFFECT OF TERMINAL UNSATURATION IN THE SIDE-CHAIN

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ABSTRACT

As part of an ongoing research program, we have prepared novel bicyclic nucleoside inhibitors bearing long alkyl side-chains for evaluation against VZV. In particular, we report the synthesis of analogues with terminal unsaturation in the side-chain. Terminal alkenyl derivatives were found to be potent antivirals whereas the terminal alkynyls displayed poor activity.

We have recently identified an entirely new family of extremely potent and selective antiviral nucleosides bearing a highly unusual bicyclic furo base moiety (1). The lead compounds have long alkyl side-chains at the 6-position of the furo ring and preliminary investigative studies have indicated that this structural feature is an absolute requirement for antiviral activity, with optimal activity observed for compounds with chain lengths of C_8-C_{10} (1).

We have also recently noted the effects of structural modifications within the alkyl side-chain of the lead compounds. Terminal substitution with halogen atoms is well tolerated and full retention of antiviral potency, down the group F, Cl, Br, I, is observed (2). However, although attempts to increase the overall water solubility

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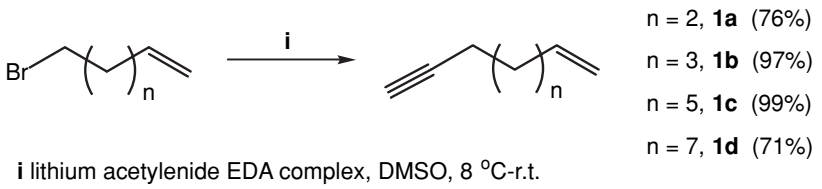

Figure 1.

of the lead compounds by ether substitution along the side-chain proved successful, the resulting derivatives displayed a significant reduction in antiviral potency (3), suggesting that substitution along the side-chain, perhaps with particularly polar groups, is not tolerated.

Bearing this in mind, we sought to make alternative structural modifications at the terminus of the side-chain: in particular, we wanted to probe the effect on antiviral activity of unsaturation at the terminus and now report the preparation and evaluation of terminal (ω) alkenyl and alkynyl derivatives (4).

The ω-alkyn-1-enes (**1a**–**d**, Fig. 1), used in the preparation of ω-alkenyl derivatives, were synthesised from the corresponding bromoalk-1-enes in good yields (71–99%) (5). Using established methodology (1–3), coupling of **1a**–**d** with 5-iodo-2′-deoxyuridine, followed by cyclisation afforded the target bicyclic nucleosides **2a**–**d** (Fig. 2) in variable yields (8–73%). The ω-alkynyl derivatives (**3a**–**d**, Fig. 2), prepared from 5-iodo-2′-deoxyuridine and commercially available 1,ω-di-alkynes, were obtained in lower yields than the ω-alkenyl derivatives (4–20%). The variable yields noted for **2a**–**d** and **3a**–**d** are probably due to the presence of the unsaturated moieties at the terminus of the side-chain, which provide extra sites for metal chelation and thus, result in unwanted side-reactions and possible polymerisation.

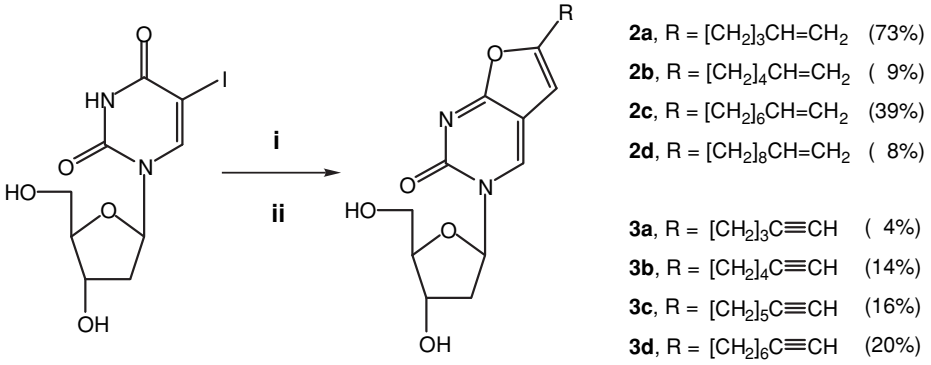

Figure 2.

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Table 1. Antiviral Activity and Cytotoxicity Data for **2a–d** and **3a–d** and Reference Compounds Cf1369 and Acyclovir (ACV)

Cpd	ClogP[7]	EC_{50} (μM)[a] VZV OKA Strain	EC_{50} (μM)[a] VZV YS Strain	EC_{50} (μM)[a] TK$^-$VZV[d] 07/1 Strain	EC_{50} (μM)[a] TK$^-$VZV[d] YS/R Strain	MCC[b] (μM)	CC_{50}[c] (μM)
2a	**0.4**	>200	>200	>200	>200	>200	>200
2b	**0.9**	14	13	>200	>200	>200	>200
2c	**2.0**	0.27	0.06	>200	>50	≥200	>200
2d	**3.0**	0.09	0.1	>200	>200	≥50	>200
3a	**−0.5**	8	10	>200	>200	>200	>200
3b	**0.0**	25	33	>200	>200	>200	>200
3c	**0.6**	79	37	>200	>200	>200	>200
3d	**1.1**	5	4	>200	>200	>200	>200
Cf1369	**3.5**	0.015	0.008	>50	>50	>50	>50
ACV	–	2.9	1.0	>4	125	>200	>200

[a]EC_{50}, 50% effective concentration, required to reduce plaque formation by 50%.
[b]MCC, minimal cytotoxic concentration, required to alter microscopically detectable cell morphology.
[c]CC_{50}, 50% cytotoxic concentration, required to inhibit He1 cell growth by 50%.
[d]TK$^-$, thymidine kinase-deficient.

Compounds **2a–d** and **3a–d** were evaluated for antiviral activity and cytotoxicity (1,6) (data presented in Table 1, along with reference data for the lead parent C_{10}-alkyl compound Cf1369, and acyclovir, ACV). Within the ω-alkenyl series, potency increases from C_5 to C_8 with full retention of potency for the C_{10} analogue. Compounds **2c** and **2d** are notably more active than ACV but are less active than their corresponding *n*-alkyl counterparts (4). The ω-alkynyls **3a–d**, however are much less effective as antivirals, with no apparent trend arising with increasing chain length. We previously noted that the most active bicyclic nucleosides have calculated octanol-water ClogP (7) values in the range 2.5–3.5, indicating a possible correlation between activity and optimal compound lipophilicity (1). Thus, it is interesting to note the significantly negative impact that the ω-alkynyl functionality has on overall compound lipophilicity (∼30-fold reduction compared to parent *n*-alkyl analogues), which may possibly account for the observed loss of activity.

In agreement with earlier observations (1–3), no antiviral activity is observed in thymidine kinase-deficient VZV strains, implying a need for thymidine kinase-mediated activation of these types of compounds. Furthermore, compounds **2a–d** and **3a–d** display low *in vitro* cytotoxicity, resulting in selectivity index values for **2c** and **2d** exceeding 3000.

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