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Bicyclic Nucleoside Inhibitors of Varicella-Zoster Virus (VZV): The Effect of Terminal Unsaturation in the Side Chain

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Abstract—Novel bicyclic nucleoside analogues bearing long alkyl side chains are prepared and tested as inhibitors of VZV. In particular, analogues with terminal unsaturation in the side chain are reported. Whilst terminal alkenyl derivatives are potent antivirals, the corresponding terminal alkynyls are poorly active.

We have recently reported the discovery of an entirely new family of potent and selective inhibitors of Varicella-Zoster Virus (VZV) based on unusual bicyclic furo nucleosides.[1] The lead compounds bear a long alkyl side chain on the base, this unusual structural feature being an absolute requirement for antiviral activity, with optimal activity noted for a C_8–C_{10} alkyl chain,[1] (Fig. 1).

We have recently noted that terminal substitution of halogen atoms within the alkyl side chain is well-tolerated, with retention of potency down the group F, Cl, Br, I.[2,3] On the other hand whilst attempts to boost water solubility by ether substitution along the side chain were successful, they lead to a very significant reduction in antiviral potency,[4] indicating poor tolerance for substitution along the chain, perhaps particularly with polar groups.

With this in mind, we sought to make alternative structural modifications at the terminus of the side chain. We were particularly interested to probe unsaturation at the terminus and herein report for the first time the synthesis and evaluation of terminal alkene and alkyne analogues.

Following procedures we have reported,[1–4] 5-iodo-2′-deoxyuridine was reacted with long chain terminal alkynes under Pd-catalysis, and the resulting C5-alkynes were cyclised under Cu-catalysis to give the target bicyclic furo compounds, either in one pot or with isolation of the alkyne intermediate (Fig. 1). The ω-alkyn-1-enes, which were used in the preparation of series 2, were synthesised via a slightly modified literature procedure,[5] from the corresponding ω-bromoalk-1-enes, and obtained cleanly in good yields (71–99%). Coupling of the ω-alkyn-1-enes with 5-iodo-2′-deoxyuridine, followed by cyclisation afforded the target bicyclic nucleosides **2a**–**d** in variable yields (8–73%). Target compounds in series 3 (**3a**–**d**) were prepared from 5-iodo-2′-deoxyuridine and commercially available 1,ω-dialkynes but were obtained in very poor yields (4–20%). The variable yields noted for the formation of the target nucleosides in series 2 and 3 are most probably due to the fact that unsaturation at the terminus of the side chain provides an extra site for metal chelation, thus resulting in unwanted side reactions and possible polymerisation.

In series 2 a terminal alkene unit was present, with chain lengths of C_5–C_{10} and in series 3 a terminal alkyne unit was present, with chain lengths of C_5–C_8. In each case the compounds chosen were determined by the availability of corresponding alkyne starting materials. However, given prior structure–activity relationships that we have noted,[1] we believed that the C_5–C_{10} alkyl range would give a significant variation in potencies. Spectroscopic data for selected compounds from each series are given.[6,7]

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Antiviral Activity and Cytotoxicity

The compounds noted in Figure 1 (**2a–d**) and (**3a–d**) were evaluated for antiviral activity and cytotoxicity by methods reported elsewhere,[1,8] data for VZV being recorded in Table 1, along with reference data for the lead compounds **1a–e**[1] and the reference compound acyclovir (acycloguanosine, **4**).

It is clear from the data that the terminal alkenes **2a–d** show a significant antiviral effect, with potency increasing from C_5 to C_8 and being fully retained for C_{10}. The hexenyl analogue **2b** is somewhat less active than the corresponding hexyl parent **1b**, this difference being exacerbated for the C_8 compounds (**2c** vs **1d**; 3–30 fold). For the decenyl system there is also a trend (6–12 fold; **2d** vs **1e**) towards greater activity for the parent alkyl compound, although the alkenyl is a significant antiviral. Both **2c** and **2d** are more antivirally potent than the reference compound acyclovir (**4**). The previously noted optimal side-chain lengths of C_8–C_{10} had indicated to us the possibility that there may be a correlation between antiviral activity and an optimal compound lipophilicity, with values of partition coefficients of 2.5–3.5 (calculated octanol–water ClogP[9]) being noted for the most active lead compounds.[1] This may possibly account for the significant potencies noted for the alkenyl compounds **2c–d**, which have ClogP values of 2–3 (Table 1).

By comparison, compounds (**3a–d**) in the alkynyl series are notably less active as antivirals (Table 1). There is some antiviral activity noted down the series, with a mean EC_{50} value of ca. 10 μM, but there is no clear trend with increasing alkynyl chain length, in contrast to that noted above for the alkyl (**1a–e**) and alkenyl (**2a–d**) series. This poor activity is particularly notable for the C_8 compound where direct comparison can be made between the three series (**1d**, **2c**, **3d**); relative EC_{50} values (VZV YS, **1d** = 1.0) are 1, 33, and 625 for the alkyl, alkenyl and alkynyl analogues. To some extent this can be rationalised by reference to the apparently significant impact of the terminal alkyne functionality on compound lipophilicity (Table 1); for each homologue the ClogP values are reduced by ca. 1.5, corresponding to a striking 30-fold reduction in lipophilicity. By comparison the presence of the terminal alkene moiety reduces ClogP by only ca. 0.5 for each homologue, a reduction of only ca. 3-fold in lipophilicity. Comparing compounds of similar lipophilicity across the three series (**3d**, **2b**, **1a**) indicates roughly equal potency, apparently unaffected by the nature of the terminal moiety.

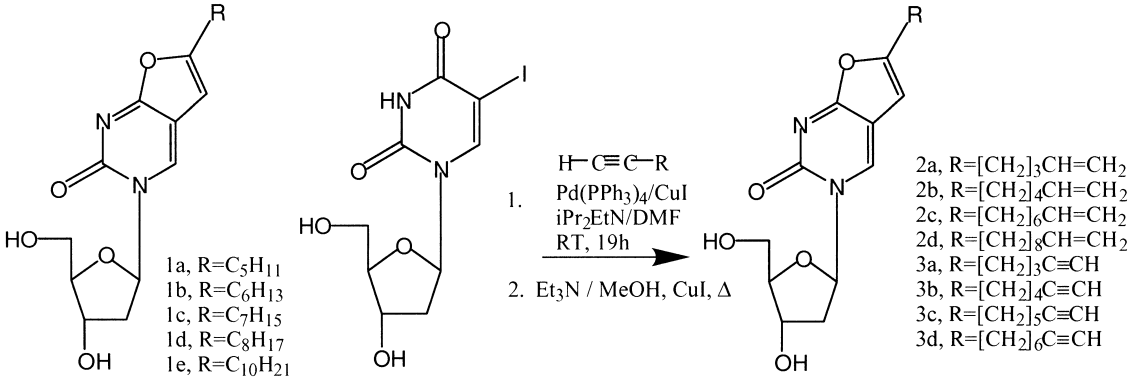

Figure 1.

Table 1. Anti-VZV activity, cytotoxicity and ClogP values for compounds **2a–d, 3a–d** and reference compounds **1a–e** and acyclovir **4**

Cpd	R length	ClogP	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	C5	0.4	>200	>200	>200	>200	>200	>200
2b	C6	0.9	14	13	>200	>200	>200	>200
2c	C8	2.0	0.27	0.06	>200	>50	≥200	>200
2d	C10	3.0	0.09	0.1	>200	>200	≥50	>200
3a	C5	−0.5	8	10	>200	>200	>200	>200
3b	C6	0.0	25	33	>200	>200	>200	>200
3c	C7	0.6	79	37	>200	>200	>200	>200
3d	C8	1.1	5	4	>200	>200	>200	>200
1a	C5	0.9	3.0	4.6	>50	>50	>50	>50
1b	C6	1.4	1.3	2.8	>50	>50	>50	>200
1c	C7	1.9	0.17	0.39	>50	>50	>50	>50
1d	C8	2.5	0.008	0.024	>50	>50	>50	>50
1e	C10	3.5	0.015	0.008	>50	>50	>50	>50
4	acycl	—	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 HEL cell morphology.
[c]CC_{50}, 50% cytotoxic concentration, required to inhibit HEL cell growth by 50%.
[d]TK$^-$, thymidine kinase-deficient.

However, this comparison is somewhat limited in the alkynyl series; it would clearly be of interest to prepare and evaluate longer chain ω-alkyne homologues, however this is impeded by the general unavailability of the parent (di)alkynes.

Finally, we also note from Table 1 that all of the target compounds **2a**–**d** and **3a**–**d** lack any detectable activity in two strains of thymidine kinase-deficient VZV, indicating a requirement for thymidine kinase-mediated phosphorylation for activation.[1] Furthermore, all of the compounds display low cytotoxicity, resulting in selectivity index values for lead alkenyl systems **2c**–**d** exceeding 3000.

In conclusion, we note that unsaturation at the terminus of the alkyl side chain of lead bicyclic furo compounds **1a**–**e** is well tolerated in the case of alkenes (**2a**–**d**) but not so in the case of alkynes (**3a**–**d**). To some extent this may correlate with the negative impact of the alkyne moiety on the overall lipophilicity of the compounds, a parameter which appears to be critical for biological potency in these systems.

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6. Selected data for **2b**; δ_H [d_6-DMSO] 1.44 (2H, m, CH_2), 1.65 (2H, m, CH_2), 2.08 (3H, m, CH_2, H-2′), 2.40 (1H, m, H-2′), 2.68 (2H, m, CH_2), 3.66 (2H, m, H-5′), 3.93 (1H, m, H-4′), 4.25 (1H, m, H-3′), 5.01 (2H, m, –CH=CH_2), 5.17 (1H, m, 5′-OH), 5.33 (1H, m, 3′-OH), 5.82 (1H, m, –C$\overline{H}$=C$\overline{H_2}$), 6.19 (1H, m, H-1′), 6.46 (1H, s, H-5), 8.70 (1H, s, H-4); δ_C [d_6-DMSO] 25.13 (CH_2), 26.43 (CH_2), 26.78 (CH_2), 32.02 (CH_2), 40.48 (C-2′), 60.06 (C-5′), 68.95 (C-3′), 86.67 (C-1′), 87.67 (C-4′), 99.12 (C-5), 105.64 (C-4a), 114.26 (–CH=$\overline{CH_2}$), 136.09 (–$\overline{CH}$=CH_2), 137.75 (C-4), 153.08 (C-6), 157.48 (C-2), 170.48 (C-7a); MS [ES(+ve)] 357.1420 (MNa^+), $C_{17}H_{22}N_2O_5Na$ req. 357.1426. Anal. found C 59.52, H 7.00, N 8.01%, $C_{17}H_{22}N_2O_5.0.5H_2O$ req. C 59.46, H 6.75, N 8.16%.
7. Selected data for **3b**; δ_H [d_6-DMSO] 1.49 (2H, m, CH_2), 1.67 (2H, m, CH_2), 2.03 (1H, m, H-2′), 2.19 (2H, m, CH_2), 2.38 (1H, m, H-2′), 2.65 (2H, t, CH_2, *J* 7.0), 2.74 (1H, s, –C≡C$\overline{H}$), 3.61 (2H, m, H-5′), 3.90 (1H, m, H-4′), 4.22 (1H, m, H-3′), 5.14 (1H, t, 5′-OH, *J* 4.6), 5.31 (1H, d, 3′-OH, *J* 3.9), 6.15 (1H, t, H-1′, *J* 5.9), 6.43 (1H, s, H-5), 8.67 (1H, s, H-4); δ_C [d_6-DMSO] 18.13 (CH_2), 26.28 (CH_2), 27.62 (CH_2), 28.00 (CH_2), 42.01 (C-22′), 61.58 (C-5′), 70.47 (C-3′), 72.19 (–C≡CH), 85.06 (–C≡CH), 88.23 (C-1′), 88.91 (C-4′), 100.74 (C-5), 107.17 (C-4a), 137.68 (C-4), 154.64 (C-6), 158.81 (C-2), 172.01 (C-7a); MS [ES(+ve)] 355.1254 (MNa^+), $C_{17}H_{20}N_2O_5Na$ req. 355.1270. Anal. found C 61.15, H 6.27, N 8.35%, $C_{17}H_{20}N_2O_5$ req. 61.44, 6.07, 8.43%.
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9. Values calculated using ClogP version 1.0.0; Biobyte, PO Box 517, Claremont, CA 91711, USA.