# *Expedited Articles*

## Potent and Selective Inhibition of Varicella-Zoster Virus (VZV) by Nucleoside Analogues with an Unusual Bicyclic Base

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We herein report the discovery of an entirely new category of potent antiviral agents based on novel deoxynucleoside analogues with unusual bicyclic base moieties. Target structures, previously known as byproducts in Pd-catalyzed coupling of terminal alkynes with 5-iodonucleosides, are recognized herein for the first time to be potent and selective inhibitors of varicella-zoster virus (VZV) in vitro. As an unusual structure−activity relationship we noted the absolute requirement of a long alkyl side chain, with an optimum length of $C_8$−$C_{10}$, for antiviral activity. We thus report the synthesis and characterization of a series of chain-modified analogues and their extensive in vitro evaluation. The lead compounds have a ca. 300-fold enhancement in anti-VZV activity over the reference compound acyclovir, with no detectable in vitro cytotoxicity. The novel structure of these compounds, coupled with their ease of synthesis, excellent antiviral profile, and promising physical properties, makes them of great interest for possible antiviral drug development.

### Introduction

Many nucleoside analogues with potent biological properties have arisen by substitution at the 5-position of the uracil base, particularly in the 2′-deoxyuridine series. The 5-(2-substituted-vinyl)-2′-deoxyuridines in particular have emerged as potent and selective inhibitors of herpes virus replication, especially against HSV-1 (herpes simplex virus type 1).[1,2] 5-Alkynyl-2′-deoxyuridines have also been studied as potential antiviral agents, the parent 5-ethynyl system being a potent inhibitor of HSV-1, HSV-2 (herpes simplex virus type 2), and VV (vaccinia virus).[3,4] However, this compound is also rather cytotoxic and its antiviral selectivity is low.[5] Virus-encoded thymidine kinases (TK) appear often to be able to phosphorylate various 5-substituted 2′-deoxyuridines,[6] and the resulting 5′-monophosphates may be inhibitors of enzymes such as thymidylate synthase,[7] this being one possible target of action/toxicity of these compounds.

We have an ongoing program on the possible activation of poorly active nucleoside analogues via 'kinase bypass'[8] in which lipophilic nucleotide pro-drugs act as intracellular phosphate delivery motifs and achieve the generation of free nucleotides by nucleoside kinase-independent means.[9] In this way unusual, highly modified nucleoside analogues, which would otherwise be inactive due to poor kinase-mediated phosphorylation, may become active via this chemical bypass of the nucleoside kinase.[10] We recently sought to apply this pro-tide methodology to a series of novel long chain 5-alkynyl-2′-deoxyuridines with the view that the parent nucleosides would be inactive due to poor phosphorylation but that the pro-tide kinase bypass would confer activity, while the unusual (long) alkynyl chain may reduce the cytotoxicity associated with the parent ethynyl homologue. These studies will be reported elsewhere. However, we now report for the first time that a synthetic byproduct in the preparation of the parent 5-alkynyl-2′-deoxyuridines displays prominent potency and exclusive selectivity for VZV (varicella-zoster virus). This unusual compound represents the first in an entirely new family of potent antiviral nucleosides which may have considerable potential for the discovery of new and improved antiviral therapies. Furthermore, the novel physical properties of these new analogues, in particular their intrinsic fluorescence, may lead to their wider utility in biochemistry.

Besides the discovery of the parent compound in this new series we herein report a preliminary SAR (structure−activity relationship) study, with evaluation against a series of DNA viruses.

### Results and Discussion

**Chemistry**. The conventional synthesis of 5-alkynyl-2′-deoxyuridines involves the Pd-catalyzed coupling of terminal alkynes with 5-iodo nucleoside.[11,12] A generally unwanted byproduct in such coupling reactions is the fluorescent furano pyrimidine (**1**), noted by a number of researchers as a slower spot on TLC.[11−13] Indeed, it was observed that the use of DMF as solvent could

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**Scheme 1**

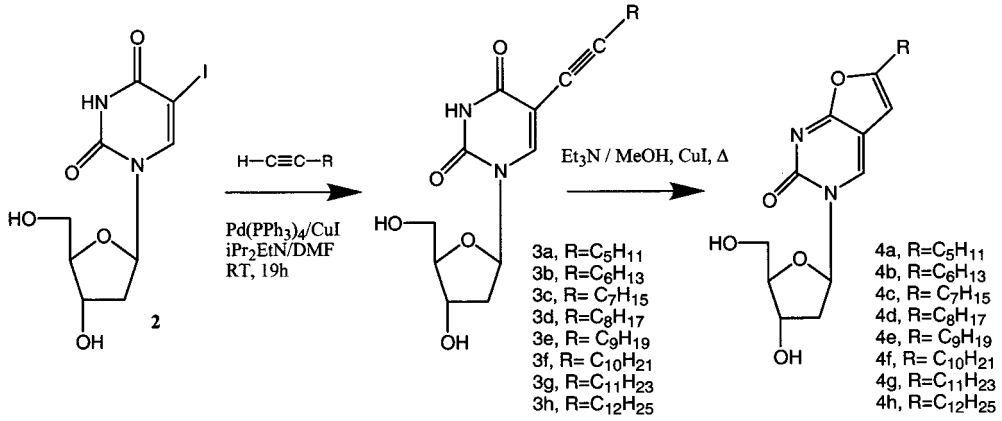
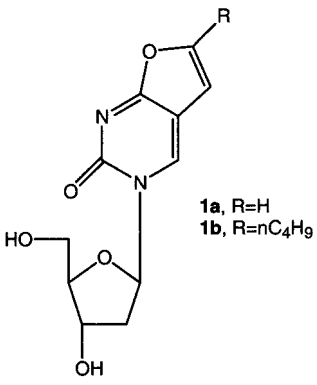



**Table 1.** Anti-VZV Activity and Cytotoxicity for Bicyclic Pyrimidines (**4a**−**h**) and Reference Compounds **5**−**6**

| cpd | R | $EC_{50}$ ($\mu$M) VZV strain OKA | $EC_{50}$ ($\mu$M) VZV strain YS | $EC_{50}$ ($\mu$M) VZV/TK$^-$ strain 07 | $EC_{50}$ ($\mu$M) VZV/TK$^-$ strain YS-R | MCC ($\mu$M) | $IC_{50}$ ($\mu$M) |
|---|---|---|---|---|---|---|---|
| **4a** | 5 | 3.0 | 4.6 | >50 | >50 | >50 | >50 |
| **4b** | 6 | 1.3 | 2.8 | >50 | >50 | 200 | >200 |
| **4c** | 7 | 0.17 | 0.39 | >50 | >50 | >50 | >50 |
| **4d** | 8 | 0.008 | 0.024 | >50 | >50 | >50 | >50 |
| **4e** | 9 | 0.02 | 0.02 | >200 | >200 | ≥200 | >200 |
| **4d** | 10 | 0.015 | 0.008 | >50 | >50 | >50 | >50 |
| **4g** | 11 | 0.5 | 0.5 | >50 | >50 | 200 | >200 |
| **4h** | 12 | 1.3 | 1.1 | >50 | >20 | 50 | >200 |
| ACV, **5** | | 2.9 | 1.0 | 74 | 125 | >200 | >200 |
| BVDU, **6** | | 0.003 | 0.006 | 144 | >300 | >150 | >400 |

reduce the amount of the cyclic byproduct.[14] Conversely, the treatment of the intended 5-alkynyl nucleosides with copper iodide in triethylamine/methanol leads to their smooth conversion to the fluorescent byproducts (**1**).[11] Similar cyclization has been also observed by base treatment of (*E*)-5-(2-bromovinyl) uracil.[15]

Previously, the only well-characterized examples of the fluorescent byproduct in this 2′-deoxy series have been the parent compound (**1a**)[16−18] and the *n*-butyl analogue (**1b**).[11]




Biological evaluation of the cyclic byproduct has not been extensive to date. However, the parent compound (**1a**) was noted to be inactive against HSV-1, HSV-2, CMV (cytomegalovirus), and VZV.[18] Ribo-[19] and xylofuranosyl[20] analogues of compound **1** have also been reported, although no antiviral activity was noted. In this article we describe the synthesis and biological evaluation of novel compounds of type **1** bearing long alkyl side chains. Such materials have not been previously reported, and we now note them to have a surprising and unique biological profile.

Thus, reaction of 5-iodo-2′-deoxyuridine (**2**) with 1-decyne in DMF under cocatalysis of Pd and Cu[13] gave 5-decynyl-2′-deoxyuridine (**3d**) in moderate yield (Scheme 1).

Similarly prepared were other homologues of the *n*-alkynyl series **3a** (R = *n*-$C_5H_{11}$), **3c** (R = *n*-$C_7H_{15}$), **3f** (R = *n*-$C_{10}H_{21}$), **3g** (R = *n*-$C_{11}H_{23}$), and **3h** (R = *n*-$C_{12}H_{25}$). Each of these alkynes was treated with copper iodide in methanol and triethylamine at reflux for 3−8 h to generate the bicyclic fluorescent compounds (**4a**, **4c**−**d**, and **4f**−**h**) in moderate yield (Scheme 1). In the case of products **4b** and **4e**, these were generated in one pot from **2** without the isolation of the intermediates **3b** and **3e**. In general, it appeared that the overall yields of **4** were similar with or without isolation of intermediates **3**. The key spectroscopic evidence for **4** was the absence of the NH seen in the hydrogen-1 NMR of **3** ($\delta_H$ 11.5) and the introduction of a new olefinic signal for **4** ($\delta_H$ ca. 6.4). Carbon-13 NMR, mass spectral data, and elemental analysis also confirmed the structure and purity of compounds **4a**−**f**.

**Antiviral Activity.** The target bicyclic systems **4a**−**f** were evaluated for their ability to inhibit the replication of HSV-1, HSV-2, VV, CMV, and VZV, according to previously described methodology.[21] Data are shown in Table 1 for the activity of **4a**−**f** versus two strains of thymidine kinase-competent VZV and also two strains of thymidine kinase-deficient VZV, with data also included for the reference anti-herpetic agents acyclovir (**5**) and BVDU (**6**). Cytotoxicity data are also given for each compound (**4a**−**f** and **5**−**6**) in two assays (Table 1). It is clear from these data that the long chain bicyclic nucleosides (**4**) are potent and selective inhibitors of VZV, with activity critically depending on the length of the alkyl side chain.

Within this series a $C_8-C_{10}$ side chain appears optimal, with $EC_{50}$ values against VZV of 3−9 nM (compounds **4d**−**f**). These lead compounds are thus ca. 300-fold more potent against VZV than the reference compound acyclovir (**5**) (Table 1). Furthermore, compounds **4a**−**h** show little or no cytotoxicity, and thus the lead compounds display extremely high values of SI (selectivity index = ratio of MCC to $EC_{50}$) in the region of >5000.

A clear SAR emerges from the data in Table 1 regarding the long alkyl chain; short chains ($\leq C_6$) lead to little antiviral activity (similar to that of acyclovir (**5**) in fact), $C_7$ and $C_{11}$ confer moderate activity, and $C_8-C_{10}$ lead to high activity. The apparent reduction in potency noted for the longest chains may in fact be an anomaly caused by the low water solubility of this material (**4h**).

Thus, the compounds of the present study emerge as unusual antiviral nucleosides in respect of the requirement for the long alkyl chain. Furthermore, this structural feature has a significant impact on the physical properties of these compounds; their water solubility is in general low, while their lipophilicity is rather high. Calculated octanol−water logP values for lead structures **4d**−**e** are in the range 2.5−3.5.[22]

This may have important repercussions for the formulation, dosing, and pharmacokinetics of the present compounds, an early assessment being that topical dosing may be a promising approach.

The precise mechanism of action of these compounds remains unclear. However, in keeping with previous antiviral nucleosides we would anticipate the necessity for the VZV kinase-mediated activation to their 5′-phosphate forms. This would appear to be supported by the data in Table 1 for the thymidine kinase-deficient VZV assays. Thus, the complete absence of antiviral activity in the VZV $TK^-$ assays strongly implicates TK-mediated phosphorylation of compounds **4** to give bioactive nucleotides. While activity as the corresponding 5′-triphosphate would appear most likely, present data cannot exclude activity as the mono- or diphosphate.

Further evaluation of **4a**−**h** against HSV-1, HSV-2, CMV, and VV indicated a complete absence of antiviral activity at 100 $\mu$M (data not shown), indicating the compounds to be entirely VZV-specific in their action. Such high anti-VZV specificity, with no activity against herpes simplex, for example, is unusual in nucleoside analogues; both **5** and **6** are far more potent against HSV1 than against VZV. However, a number of recent analogues such as 5-propynyl araU (882C, zonavir)[23,24] do show some anti-VZV selectivity, though with far less antiviral potency than in the present case. The molecular origins of this specificity, and the precise mechanism of action, are the subject of current extensive investigation in our laboratories.

## Experimental Section

The numbering of the bicyclic ring follows the recommended IUPAC nomenclature guidelines. The naming of compounds follows IUPAC nomenclature and/or standard accepted nomenclature for nucleoside chemistry.

For thin layer chromatography, precoated, aluminum-backed sheets with silica gel (60 F-54, 0.2 mm thickness; supplied by E. Merck AG, Darmstadt, Germany) were used and were developed by the ascending method. After solvent evaporation, compounds were detected by quenching of the fluorescence at 254 or 366 nm, depending on the compound, on irradiation with a UV lamp. For column chromatography, glass columns were slurry packed in the appropriate eluent under gravity with silica gel (C-gel 60A, 40−60 mm, Phase Sep, U.K.). Samples were applied as a concentrated solution in the same eluent or preabsorbed onto silica gel. Fractions containing the product were identified by TLC and were pooled, and the solvent was removed in vacuo. Flash column chromatography was performed with the aid of a hand pump.

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance DPX300 spectrometer (300 and 75 MHz, respectively) and autocalibrated to the deuterated solvent reference peak. All $^{13}C$ NMR spectra were proton decoupled. Mass spectra were obtained from a Fisons VG Platform 8070 micromass spectrometer. All spectra were produced by electrospray (ES+), using a mobile phase of acetonitrile/water (1:1).

Elemental analyses were performed by the service at the Department of Chemistry, University of Wales, Cardiff, U.K. All solvents used were anhydrous and used as supplied by Aldrich. All nucleosides and solid reagents were either dried for several hours while being heated under high vacuum over phosphorus pentoxide or dried by coevaporation with dry pyridine. All glassware was oven dried at 130 °C for several hours or overnight and was allowed to cool in a desiccator or under a stream of dry nitrogen. All analytical high-performance liquid chromatography (HPLC) experiments were done on an ACS 350/04 system provided with an ACS 351/04 gradient controller and using an ACS 750/12 detector set at 254 nm. The analysis involved an Ultratech50DS (25 × 4.6 mm) reverse phase column, with a mobile phase of 55/45 acetonitrile/water.

**Preparation of 5-Alkynyl Nucleosides.** A full procedure is listed for **3d**; only brief spectroscopic data are presented for other analogues.

**5-Heptynyl-2′-deoxyuridine (3a)**: yield 66%; mp 129−132 °C (lit.[11,12] mp 130−132 ∞C) (from EtOH-diffusion $Et_2O$); $\delta_H$ (DMSO-$d_6$) 11.57 (1H, bs, NH), 8.11 (1H, s, H-6), 6.12 (1H, t, $J$ = 6.5 Hz, H-1′), 5.26 (1H, d, OH-3′), 5.11 (1H, t, OH-5′), 4.23 (1H, m, H-3′), 3.79 (1H, m, H-4′), 3.58 (2H, m, 2H-5′), 2.36 (2H, t, $J$ = 7 Hz, C≡C−$CH_2$), 2.12 (2H, m, H-2′), 1.48 (6H, m, 3×$CH_2$), 0.88 (3H, t, Me); HPLC (retention time) 2.59 min.

**5-Nonynyl-2′-deoxyuridine (3c)**: yield 61%; mp 146−148 ∞C (from EtOH-diffusion $Et_2O$); $\delta_H$ (DMSO-$d_6$) 8.11 (1H, s, H-6), 6.12 (1H, t, $J$ = 6.5 Hz, H-1′), 5.25 (1H, d, OH-3′), 5.08 (1H, t, OH-5′), 4.24 (1H, m, H-3′), 3.80 (1H, m, H-4′), 3.57 (2H, m, 2H-5′),2.36 (2H, t, $J$ = 6.8 Hz, C≡C−$CH_2$), 2.12 (2H, m, H-2′), 1.35 (10H, m, 5$CH_2$), 0.87 (3H, t, Me); $\delta_C$ (DMSO-$d_6$) 15.9 (Me), 20.7, 24.0, 30.2 (5×$CH_2$), 33.1 (α-$CH_2$), 42.0 (C-2′), 62.9 (C-5′), 72.2 (C-3′), 74.8 (C-$\beta$), 86.5 (C-4′), 89.5 (C-1′), 95.2 (C-α), 101.0 (C-5), 144.5 (C-6), 151.4 (C-2), 163.7 (C-4); MS-($ES^+$) 373 ($MNa^+$, 100%); HPLC (retention time) 3.38 min.

**5-Decynyl-2′-deoxyuridine (3d).** To a stirred solution of 5-iodo-2′-deoxyuridine (800 mg, 2.26 mmol) in dry DMF (8 mL), at room temperature under a nitrogen atmosphere, was added dry diisopropylethylamine (584 mg, 0.80 mL, 4.52 mmol), 1-decyne (937 mg, 1.22 mL, 6.78 mmol), tetrakis(triphenylphosphine)palladium(0) (261 mg, 0.226 mmol), and copper(I) iodide (86 mg, 0.452 mmol). The reaction mixture was stirred at room temperature for 19 h, after which time the mixture was concentrated in vacuo. The resulting residue was dissolved in dichloromethane/methanol (1:1) (6 mL), an excess of Amberlite IRA-400 ($HCO_3^-$ form) was added, and the mixture was stirred for 30 min. The resin was then filtered and washed with methanol, and the combined filtrate was evaporated to dryness in vacuo. The crude product was purified by flash silica gel column chromatography using an initial eluent of ethyl acetate and then changing to ethyl acetate/methanol (9:1) via a gradient. The appropriate fractions were combined, and the solvent was removed in vacuo to yield the product as a cream solid (490 mg, 60%). Crystallization of the product from hot dichloromethane yielded the pure product as fine white crystals (376 mg, 46%): $\delta_H$ (DMSO-$d_6$) 11.56 (1H, bs, NH), 8.11 (1H, s, H-6), 6.12 (1H, dd, $J$ = 6.6 Hz, H-1′), 5.25 (1H, d, $J$ =

4.2 Hz, 3′-OH), 5.09 (1H, t, 5′-OH), 4.24 (1H, m, H-3′), 3.79 (1H, m, H-4′), 3.59 (2H, m, H-5′), 2.36 (2H, t, $J$ = 6.8 Hz, α-$CH_2$), 2.12 (2H, m, H-2), 1.47 (2H, m, β-$CH_2$), 1.38−1.26 (10H, m, 5×$CH_2$), 0.87 (3H, t, Me); $\delta_C$ (DMSO-$d_6$) 16.2 (Me), 21.0, 24.3, 30.4, 30.5, 30.8, 30.9 (6×$CH_2$), 33.5 (α-$CH_2$), 41.7 (C-2′), 63.2 (C-5′), 72.4 (C-3′), 75.1, 86.8, 89.8, 95.5 (C-4′, C-β, C-1′, C-α), 101.3 (C-5), 144.9 (C-6), 151.7 (C-2), 164.0 (C-4); MS(ES$^+$) *m/e* 428 (MCu$^+$, 55%), 403 (MK$^+$, 25%), 387 (MNa$^+$, 45%), 365 (MH$^+$, 50%), 249 (baseH$^+$, 100%). Found: C, 62.77%; H, 7.98%; N, 7.97%. $C_{19}H_{28}N_2O_5$ requires: C, 62.62%; H, 7.74%; N, 7.69%.

**5-Dodecynyl-2′-deoxyuridine (3f).** yield 57%; mp 144−146 °C (recrystallized EtOH-difusion $Et_2O$); $\delta_H$ (DMSO-$d_6$) 11.56 (1H, bs, NH), 8.11 (1H, s, H-6), 6.12 (1H, t, $J$ = 6.5 Hz, H-1′), 5.25 (1H, d, OH-3′), 5.09 (1H, t, OH-5′), 4.23 (1H, m, H-3′), 3.78 (1H, m, H-4′), 3.63 (2H, m, H-5′), 2.35 (2H, t, $J$ = 6.7 Hz, C≡C−$CH_2$), 2.12 (2H, m, H-2′), 1.25 (16H, m, 8×$CH_2$), 0.86 (3H, t, Me); $\delta_C$ (DMSO-$d_6$) 16.0 (Me), 20.7, 24.0, 30.1, 30.2, 30.5, 30.6, 30.9 (8×$CH_2$), 33.2 (α-$CH_2$), 41.7 (C-2′), 63.0 (C-5′), 72.2 (C-3′), 74.8 (C-β), 86.5 (C-4′), 89.5 (C-1′), 95.2 (C-α), 101.0 (C-5), 144.6 (C-6), 151.4 (C-2), 163.7 (C-4); MS(ES$^+$) *m/e* 415 (MNa$^+$, 100%); HPLC (retention time) 7.80 min.

**5-Tridecynyl-2′-deoxyuridine (3g).** yield 56%; $\delta_H$ (DMSO-$d_6$) 11.50 (1H, bs, NH), 8.09 (1H, s, H6), 6.12 (1H, dd, $J$ = 6.6 Hz, H1′), 5.20 (1H, d, $J$ = 3.9 Hz, 3′-OH), 5.03 (1H, t, $J$ = 4.7 Hz, 5′-OH), 4.24 (1H, m, H3′), 3.80 (1H, m, H4′), 3.59 (2H, m, H5′), 2.35 (2H, t, $J$ = 6.9 Hz, α-$CH_2$), 2.12 (2H, m, H2′), 1.49 (2H, m, β-$CH_2$), 1.40−1.26 (16H, m, 8×$CH_2$), 0.86 (3H, t, $J$ = 6.9 Hz, Me); $\delta_C$ (DMSO-$d_6$) 14.2 (Me), 19.2, 22.4, 28.5, 28.6, 28.9, 29.0, 29.1, 29.2, 29.3, 31.7 (10×$CH_2$), 40.4 (C-2′), 61.4 (C-5′), 72.4 (C-3′), 73.2 (α-alkynyl), 85.0, 88.0 (C-4′, C-1′), 93.6 (β-alkynyl), 99.5 (C-5), 142.9 (C-6), 149.8 (C-2), 162.7 (C-4); MS (ES$^+$) *m/e* 445 (MK$^+$, 20%), 429 (MNa$^+$, 90%), 407 (MH$^+$, 60%), 291 (baseH$^+$, 100%). Found: C, 65.03%; H, 8.38%; N, 6.98%. $C_{22}H_{34}N_2O_5$ requires: C, 65.00%; H, 8.43%; N, 6.89%.

**5-Tetradecynyl-2′-deoxyuridine (3h).** yield 60%; $\delta_H$ (DMSO-$d_6$) 11.59 (1H, s, NH), 8.13 (1H, s, H-6), 6.14 (1H, dd, $J$ = 6.4 Hz, 6.8 Hz, H-1′), 5.27 (1H, d, $J$ = 3.8 Hz, 3′-OH), 5.09 (1H, t, $J$ = 4.5 Hz, 5′-OH), 4.26 (1H, m, H-3′), 3.81 (1H, m, H-4′), 3.61 (2H, m, H-5′), 2.37 (2H, t, α-$CH_2$), 2.13 (2H, m, H-2′), 1.50 (2H, m, β-$CH_2$), 1.40−1.26 (18H, m, 9×$CH_2$), 0.88 (3H, t, Me); $\delta_C$ (DMSO-$d_6$) 14.8 (Me), 19.6, 23.0, 29.0, 29.1, 29.4, 29.6, 29.8, 29.9, 32.1 (11×$CH_2$), 41.2 (C-2′), 61.9 (C-5′), 71.1 (C-3′), 73.7 (quaternary β-alkynyl), 85.4, 88.4 (C-4′, C-1′), 94.1 (quaternary α-alkynyl), 99.9 (C-5), 143.4 (C-6), 150.3 (C-2), 162.6 (C-4); MS (ES$^+$) *m/e* 484 (MCu$^+$, 25%), 459 (MK$^+$, 15%), 443 (MNa$^+$, 50%), 421 (MH$^+$, 50%), 305 (baseH$^+$, 100%). Found: C, 65.94%; H, 8.85%; N, 6.95%. $C_{23}H_{36}N_2O_5$ requires: C, 65.69%; H, 8.63%; N, 6.66%.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-pentyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one (4a).** To a stirred solution of (**3a**) (125 mg, 0.39 mmol) in methanol/triethylamine (7:3) (14 mL), at room temperature under a nitrogen atmosphere, was added copper(I) iodide (15 mg, 0.075 mmol). The reaction mixture was then heated to reflux and stirred for 8 h. The solvent was removed in vacuo and the crude product purified by silica gel column chromatography, using an initial eluent of ethyl acetate, followed by an eluent of ethyl acetate/methanol (9:1). The appropriate fractions were combined and the solvent removed in vacuo, yielding the product as an off-white solid (85 mg, 68%). The product was isolated by trituration with diethyl ether, followed by drying, yielding the pure product as a fine white powder (55 mg, 44%): $\delta_H$ (DMSO-$d_6$) 8.67 (1H, s, H-4), 6.43 (1H, s, H-5), 6.16 (1H, dd, $J$ = 6.0 Hz, H-1′), 5.29 (1H, d, $J$ = 4.1 Hz, 3′-OH), 5.13 (1H, m, 5′-OH), 4.22 (1H, m, H-3′), 3.89 (1H, m, H-4′), 3.63 (2H, m, H-5′), 2.64 (2H, t, α-$CH_2$), 2.35 and 2.06 (2H, m, H-2′), 1.61 (2H, m, β-$CH_2$), 1.30 (4H, m, 2×$CH_2$), 0.87 (3H, m, Me); $\delta_C$ (DMSO-$d_6$) 14.1 (Me), 22.0, 26.3 (2×$CH_2$), 27.5 (β-$CH_2$), 30.8 (α-$CH_2$), 41.4 (C-2′), 60.9 (C-5′), 69.8 (C-3′), 87.6, 88.3 (C-1′, C-4′), 100.0 (C-5), 106.6 (C-4a), 137.0 (C-4), 154.0 (C-2), 158.5 (C-6), 171.4 (C-7a); MS (ES$^+$) *m/e* 386 (MCu$^+$, 15%), 361 (MK$^+$, 15%), 345 (MNa$^+$, 15%), 323 (MH$^+$, 20%), 207 (baseH$^+$, 10%).

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-hexyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one (4b).** To a stirred solution of **2** (800 mg, 2.26 mmol) in dry dimethylformaldehyde (8 mL), at room temperature under a nitrogen atmosphere, were added dry diisopropylethylamine (584 mg, 0.80 mL, 4.52 mmol), 1-octyne (747 mg, 1.00 mL, 6.78 mmol), tetrakis(triphenylphosphine)-palladium(0) (261 mg, 0.226 mmol), and copper(I) iodide (86 mg, 0.452 mmol). The reaction mixture was stirred at room temperature for 19 h, after which time TLC (ethyl acetate/methanol (95:5)) of the reaction mixture showed complete conversion of the starting material. Copper(I) iodide (80 mg, 0.40 mmol) and triethylamine (15 mL) were then added to the reaction mixture, which was subsequently heated at 70−80 °C for 4 h. The reaction mixture was then concentrated in vacuo, the resulting residue was dissolved in dichloromethane/methanol (1:1) (8 mL), an excess of Amberlite IRA-400 ($HCO_3^-$ form) was added, and the mixture was stirred for 30 min. The resin was then filtered and washed with methanol, and the combined filtrate was evaporated to dryness. The crude product was initially triturated with acetone and then purified by silica gel column chromatography using an initial eluent of dichloromethane/methanol (95:5), followed by an eluent of dichloromethane/methanol (9:1). The appropriate fractions were combined, and the solvent was removed in vacuo to yield the product as a cream solid (196 mg, 26%). Trituration of the product with petroleum ether yielded the pure product as a fine white solid (176 mg, 23%): $\delta_H$ (DMSO-$d_6$) 8.64 (1H, s, H-4), 6.40 (1H, s, H-5), 6.13 (1H, dd, $J$ = 6.0 Hz, 6.4 Hz, H-1′), 5.25 (1H, d, $J$ = 4.1 Hz, 3′-OH), 5.10 (1H, t, 5′-OH), 4.19 (1H, m, H-3′), 3.87 (1H, m, H-4′), 3.60 (2H, m, H-5′), 2.61 (2H, t, $J$ = 7.2 Hz, α-$CH_2$), 2.33, 2.01 (2H, m, H-2′), 1.57 (2H, m, β-$CH_2$), 1.25 (6H, m, 3×$CH_2$), 0.82 (3H, m, Me); $\delta_C$ (DMSO-$d_6$) 16.2 (Me), 24.2, 28.6, 29.6 (3×$CH_2$), 30.3 (β-$CH_2$), 33.1 (α-$CH_2$), 43.4 (C-2′), 63.0 (C-5′), 71.9 (C-3′), 89.6, 90.3 (C-1′, C-4′), 102.0 (C-5), 108.6 (C-4a), 139.0 (C-4), 156.0 (C-2), 161.7 (C-6), 173.4 (C-7a); MS (ES$^+$) *m/e* 400 (MCu$^+$, 5%), 375 (MK$^+$, 5%), 359 (MNa$^+$, 15%), 337 (MH$^+$, 20%), 221 (baseH$^+$, 100%). Found: C, 60.90%; H, 7.37%; N, 8.61%. $C_{17}H_{24}N_2O_5$ requires: C, 60.70%; H, 7.19%; N, 8.33%.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-heptyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one (4c).** This was prepared as described for **4a**. The appropriate column fractions were combined, and the solvent was removed in vacuo to yield the product as a yellow solid (660 mg, 84%). Trituration of the product with dichloromethane yielded the pure product as a cream solid (484 mg, 61%): $\delta_H$ (DMSO-$d_6$) 8.67 (1H, s, H-4), 6.43 (1H, s, H-5), 6.16 (1H, dd, $J$ = 5.3 Hz, 6.0 Hz, H-1′), 5.29 (1H, d, $J$ = 4.0 Hz, 3′-OH), 5.13 (1H, t, 5′-OH), 4.22 (1H, m, H-3′), 3.90 (1H, m, H-4′), 3.63 (2H, m, H-5′), 2.63 (2H, t, $J$ = 7.2 Hz, α-$CH_2$), 2.35, 2.06 (2H, m, H-2′), 1.60 (2H, m, β-$CH_2$), 1.25 (8H, m, 4×$CH_2$), 0.85 (3H, m, Me); $\delta_C$ (DMSO-$d_6$) 16.3 (Me), 24.5, 28.8, 29.8, 30.8 (5×$CH_2$), 33.6 (α-$CH_2$), 43.6 (C-2′), 63.2 (C-5′), 72.1 (C-3′), 89.8, 90.5 (C-1′, C-4′), 102.2 (C-5), 108.8 (C-4a), 139.2 (C-4), 156.2 (C-2), 160.7 (C-6), 173.6 (C-7a); MS (ES$^+$) *m/e* 414 (MCu$^+$, 15%), 389 (MK$^+$, 15%), 373 (MNa$^+$, 25%), 351 (MH$^+$, 100%), 235 (baseH$^+$, 35%). Found: C, 61.99%; H, 7.62%; N, 8.11%. $C_{18}H_{26}N_2O_5$ requires: C, 61.70%; H, 7.48%; N, 7.99%.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-octyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one (4d).** This was prepared as described for **4a** above except that the reaction was conducted for 5 h and the column chromatographic purification was conducted on two columns, the first using an eluent of dichloromethane/methanol (9:1) and the second an eluent of dichloromethane/methanol (8:2). The appropriate fractions were combined, and the solvent was removed in vacuo, yielding an orange/brown solid. The crude product was triturated and washed with acetone, followed by drying, yielding the pure product as a fine white powder (118 mg, 55%): $\delta_H$ (DMSO-$d_6$) 8.63 (1H, s, H-4), 6.39 (1H, s, H-5), 6.12 (1H, dd, $J$ = 6.0 Hz, 6.4 Hz, H-1′), 5.25 (1H, d, $J$ = 4.5 Hz, 3′-OH), 5.09 (1H, t, 5′-OH), 4.19 (1H, m, H-3′), 3.86 (1H, m, H-4′), 3.60 (2H, m, H-5′), 2.60 (2H, t, $J$ = 7.2 Hz, α-$CH_2$), 2.33, 2.00 (2H, m, H-2′), 1.57 (2H, m, β-$CH_2$), 1.21 (10H, m, 5×$CH_2$), 0.81 (3H, t, Me); $\delta_C$ (DMSO-$d_6$): 14.4 (Me), 22.5, 26.8, 27.8, 28.8, 29.1 (5×$CH_2$), 31.7 (β-$CH_2$), 39.1 (α-$CH_2$), 41.6 (C-2′), 61.2 (C-5′), 70.1 (C-3′), 87.8, 88.5 (C-1′,

C-4′), 100.2 (C-5), 106.8 (C-4a), 137.2 (C-4), 154.2 (C-2), 158.7 (C-6), 171.6 (C-7a); MS ($ES^+$) *m/e* 428 ($MCu^+$, 15%), 403 ($MK^+$, 10%), 387 ($MNa^+$, 15%), 365 ($MH^+$, 30%), 249 ($baseH^+$, 100%). Found: C, 62.83%; H, 7.88%; N, 7.86%. $C_{19}H_{28}N_2O_5$ requires: C, 62.62%; H, 7.74%; N, 7.69%. UV $\lambda$ max 242 nm ($\epsilon$ 12 700), 329 nm ($\epsilon$ 6 600). Fluorescence excitation $\lambda$ optimal ca. 330 nm; emission maximal ca. $\lambda$ 410−420 nm.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-nonyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one (4e).** This was prepared as described for **4b** above, except that the final column chromatographic purification was conducted with an initial eluent of ethyl acetate, followed by ethyl acetate/methanol (9:1). The appropriate fractions were combined, where the solvent was removed in vacuo, to give the crude product, which was further purified by crystallizing from methanol to give pure product (180 mg, 21%): $\delta_H$ (DMSO-$d_6$) 8.71 (1H, s, H4), 6.45 (1H, s, H5), 6.21 (1H, dd, $J$ = 6.2 Hz, H1′), 5.31 (1H, d, $J$ = 3.9 Hz, 3′-OH), 5.25 (1H, t, $J$ = 5.1 Hz, 5′-OH), 4.18 (1H, m, H3′), 3.87 (1H, m, H4′), 3.59 (2H, m, H5′), 2.71 (2H, t, $J$ = 7.1 Hz, α-$CH_2$), 2.31, 2.01 (2H, m, H2′), 1.49 (2H, m, $CH_2$), 1.26−1.21 (12H, m, 6×$CH_2$), 0.84 (3H, t, $J$ = 6.9 Hz, Me); $\delta_C$ (DMSO-$d_6$) 14.3 (Me), 22.5, 26.7, 27.6, 28.6, 29.1, 29.47, 31.6 (7×$CH_2$), 41.5 (C-2′), 61.1 (C-5′), 70.1 (C-3′), 87.6, 88.5 (C-1′, C-4′), 100.6 (C-5), 107.7 (C-4a), 137.1 (C-4), 154.13 (C-6), 160.8 (C-2), 171.5 (C-7a); MS ($ES^+$) *m/e* 417 ($MK^+$, 20%), 401 ($MNa^+$, 30%), 379 ($MH^+$, 50%), 263 ($base^+$, 100%). Found: C, 62.95%; H, 7.99%; N, 7.28%. $C_{20}H_{30}N_2O_5$ requires: C, 63.47%; H, 7.99%; N, 7.39%.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-decyl-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one (4f).** This was prepared as described for **4a** above except that the reaction was conducted for 5 h and the column chromatographic purification was conducted using EtOAc as eluant to give the product which was further purified by crystallization from diisopropyl ether/ethanol (118 mg, 58%): mp 178−180 °C. $\delta_H$ (DMSO-$d_6$) 8.67 (1H, s, H4), 6.43 (1H, s, H5), 6.16 (1H, t, $J$ = 6.07 Hz, H1′), 5.28 (1H, d, 3′-OH, $J$ = 4.23 Hz) 5.12 (1H, t, $J$ = 5.1 Hz, 5′-OH), 4.22 (1H, m, H3′), 3.89 (1H, m, H4′), 3.63 (2H, m, H5′), 2.64 (2H, t, $J$ = 7.25 Hz, α-$CH_2$), 2.33, 2.04 (2H, m, H2′), 1.60 (2H, m, β-$CH_2$), 1.28−1.23 (14H, m, 7×$CH_2$), 0.85 (3H, t, $J$ = 6.9 Hz, Me); $\delta_C$ (DMSO-$d_6$) 14.2 (Me), 31.5, 29.2, 29.1, 28.9, 28.9, 28.6, 27.6, 26.6, 22.3 (9 x $CH_2$), 41.4 (C-2′), 61.0 (C-5′), 69.7 (C-3′), 88.3, 87.6 (C-1′, C-4′), 106.6, 100.0 (C-4a, C-5), 137.0 (C-4), 154.0 (C-2), 158.5 (C-6), 171.4 (C-7a); MS ($ES^+$) *m/e* 415 ($MNa^+$, 100%). Found: C, 64.37%; H, 8.12%; N, 7.09%. $C_{21}H_{32}N_2O_5$ requires: C, 64.26%; H, 8.22%; N, 7.14%.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-undecyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one (4g).** This was prepared as described for **4d** above except that the column chromatographic purification was conducted using first an eluent of ethyl acetate, followed by an eluent of ethyl acetate/methanol (9:1). The appropriate fractions were combined, and the solvent was removed in vacuo, yielding an orange/brown solid. The crude product was crystallized from methanol, yielding the pure product as white crystals (120 mg, 60%): $\delta_H$ (DMSO-$d_6$) 8.67 (1H, s, H4), 6.42 (1H, s, H5), 6.18 (1H, dd, $J$ = 6.1 Hz, H1′), 5.27 (1H, d, $J$ = 4.1 Hz, 3′-OH), 5.10 (1H, t, $J$ = 5.0 Hz, 5′-OH), 4.24 (1H, m, H3′), 3.92 (1H, m, H4′), 3.63 (2H, m, H5′), 2.64 (2H, t, $J$ = 7.2 Hz, α-$CH_2$), 2.38, 2.04 (2H, m, H-2′), 1.61 (2H, m, β-$CH_2$), 1.29−1.23 (16H, m, 8×$CH_2$), 0.85 (3H, t, $J$ = 6.7 Hz, Me); $\delta_C$ (DMSO-$d_6$) 14.2 (Me), 22.4, 26.7, 27.7, 28.6, 28.9, 29.0, 29.1, 29.2, 29.3, 31.6 (9×$CH_2$), 41.6 (C-2′), 61.2 (C-5′), 70.1 (C-3′), 87.8, 88.5 (C-1′, C-4′), 100.1 (C-5), 106.8 (C-4a), 137.1 (C-4), 154.2 (C-2), 158.7 (C-6), 171.6 (C-7a); MS ($ES^+$) *m/e* 445 ($MK^+$, 25%), 429 ($MNa^+$, 100%), 407 ($MH^+$, 50%), 291 ($baseH^+$, 85%). Found: C, 65.02%; H, 8.36%; N, 6.89%. $C_{22}H_{34}N_2O_5$ requires: C, 65.00%; H, 8.43%; N, 6.89%.

**3-(2′-Deoxy-β-D-ribofuranosyl)-6-dodecyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one (4h).** This was prepared as described for **4d** above except that the column chromatographic purification was conducted using an initial eluent of dichloromethane/methanol (9:1), followed by an eluent of dichloromethane/methanol (8:2). The appropriate fractions were combined, and the solvent was removed in vacuo, yielding the pure product as a white solid (188 mg, 49%): $\delta_H$ (DMSO-$d_6$) 8.70 (1H, s, H-4), 6.27 (1H, s, H-5), 6.18 (1H, dd, $J$ = 5.7 Hz, 6.0 Hz, H-1′), 5.19 (1H, d, $J$ = 4.2 Hz, 3′-OH), 5.05 (1H, t, $J$ = 4.9 Hz, 5′-OH), 4.25 (1H, m, H-3′), 3.91 (1H, m, H-4′), 3.66 (2H, m, H-5′), 2.60 (2H, t, α-$CH_2$), 2.42, 2.03 (2H, m, H-2′), 1.61 (2H, m, β-$CH_2$), 1.21 (18H, m, 9×$CH_2$), 0.83 (3H, m, Me); $\delta_C$ (DMSO-$d_6$) 14.7 (Me), 23.0, 27.2, 28.4, 29.3, 2 × 29.6, 2 × 29.8, 2 × 29.9 (10×$CH_2$), 32.2 (α-$CH_2$), 42.3 (C-2′), 61.5 (C-5′), 70.3 (C-3′), 88.2, 88.9 (C-1′, C-4′), 100.2 (C-5), 107.6 (C-4a), 137.3 (C-4), 154.8 (C-2), 159.1 (C-6), 172.0 (C-7a); MS ($ES^+$) *m/e* 484 ($MCu^+$, 15%), 459 ($MK^+$, 20%), 443 ($MNa^+$, 40%), 421 ($MH^+$, 40%), 305 ($baseH^+$, 100%). Found: C, 65.62%; H, 8.82%; N, 6.90%. $C_{23}H_{36}N_2O_5$ requires: C, 65.69%; H, 8.63%; N, 6.66%.

**Materials and Experimental Procedures: Virology. Cells.** Human embryonic lung (HEL) fibroblasts and $E_6$SM cells were grown in minimum essential medium (MEM) supplemented with 10% inactivated fetal calf serum (FCS), 1% L-glutamine, and 0.3% sodium bicarbonate.

**Viruses.** The laboratory wild-type VZV strains Oka and YS, the thymidine kinase-deficient VZV strains 07-1 and YS-R, HSV-1 (KOS), HSV-2 (G), the thymidine kinase-deficient HSV-1 stains B-2006 and VMW 1837, cytomegalovirus strains Davis and AD-169, and vaccinia virus were used in the virus inhibition assays.

**Antiviral Assays.** Confluent HEL cells grown in 96-well microtiter plates were inoculated with VZV at an input of 20PFU (plaque forming units) per well or with CMV at an input of 100PFU per well. Confluent $E_6$SM cells were inoculated with HSV at 100 $CCID_{50}$ (50% cell culture infective doses) per well. After a 1−2 h incubation period, residual virus was removed and the infected cells were further incubated with MEM (supplemented with 2% inactivated FCS, 1% L-glutamine, and 0.3% sodium bicarbonate) containing varying concentrations of the compounds. Antiviral activity was expressed as $EC_{50}$ (50% effective concentration), or compound concentration required to reduce viral plaque formation after 5 days (VZV) or virus-induced cytopathicity (CMV after 7 days and HSV, VV after 3 days) by 50% compared to the untreated control.

**Cytotoxicity Assays.** Confluent monolayers of HEL cells as well as growing HEL cells in 96-well microtiter plates were treated with different concentrations of the experimental drugs. Cell cultures were incubated for 3 (growing cells) or 5 (confluent cells) days. At the indicated time, the cells were trypsinized, and the cell number was determined using a Coulter counter. The 50% cytostatic concentration ($CC_{50}$) was defined as the compound concentration required to reduce the cell number by 50%.

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