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Novel Bicyclic Furanopyrimidines with Dual Anti-VZV and -HCMV Activity

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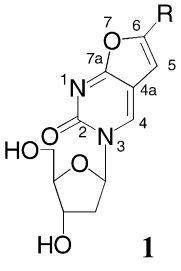
Abstract—Several novel bicyclic furanopyrimidine deoxy nucleosides have been designed, prepared and evaluated as anti-Varicella Zoster Virus agents. The compounds have long ether side chains. Uniquely amongst compounds of this family to date the present agents show dual anti- (VZV) and human cytomegalovirus (HCMV) activity. The lead compounds inhibit VZV at 10 nM and HCMV at 5 μM.

We have discovered furano pyrimidine based deoxynucleosides as potent and selective inhibitors of Varicella Zoster Virus (VZV).[1] In the general structure (**1**) the optimal activity resides with long alkyl side chains of the order C8–C10. There is an apparent correlation between lipophilicity, as measured by calculated logP (ClogP), and antiviral potency.[2] Activity is retained with ω-substitution of halogens in the alkyl side chain,[3] as with the introduction of an alkene function at the terminus,[4] but potency is diminished with a (more polar) alkynyl terminus.[4] Finally, we noted that replacement of the alkyl side chain by a *p*-alkylphenyl unit, as in (**2**) lead to a very significant potency boost, to yield compounds that are inhibitors of VZV below 1 nM.[5]



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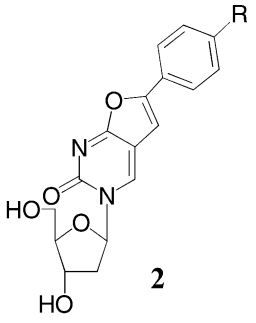

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One of the challenges facing the further development of these agents is their very poor water solubility. Compounds **1** ($R = C_8H_{17}$) and **2** ($R = C_5H_{11}$) each have water solubility of <0.01 mg/mL.[6] With this in mind, we recently prepared a series of analogues of **1** with ether, and glycol, linkages in the side chain.[6]

However, although these agents were significantly (>100-fold) more water soluble than the parent alkyl compounds, they had very considerably reduced antiviral potency. Again, to a large extent this was predicted by ClogP (Table 1). With this in mind we wondered if we might be able to boost liphophilicity (and hence potency) by further lengthening the alkyl side chain of the ethers, whilst retaining water solubility. In silico prediction indicated that a ca. 14 atom side chain with one ether oxygen may have approximately the optimal ClogP (3.5). Thus, we designed a series of alkyloxynonyl substituted systems (**3**) with some variation in the alkyl terminus.

These compounds were prepared by procedures analogous to those we have reported.[1,6] Thus, the corresponding primary alcohol was allowed to react with the mesylate prepared from 11-hydroxyundecyne in the presence of NaH in THF at reflux to give synthons **4** in 80–88%. These were coupled with 5-iodo-2′-deoxyuridine (IDU) **5** and the intermediate 5-alkynyl nucleosides cyclised in situ with CuI to give **3a–d** in moderate yield.[7] The calculated logP values for **3a–d** are 3.7, 4.2,

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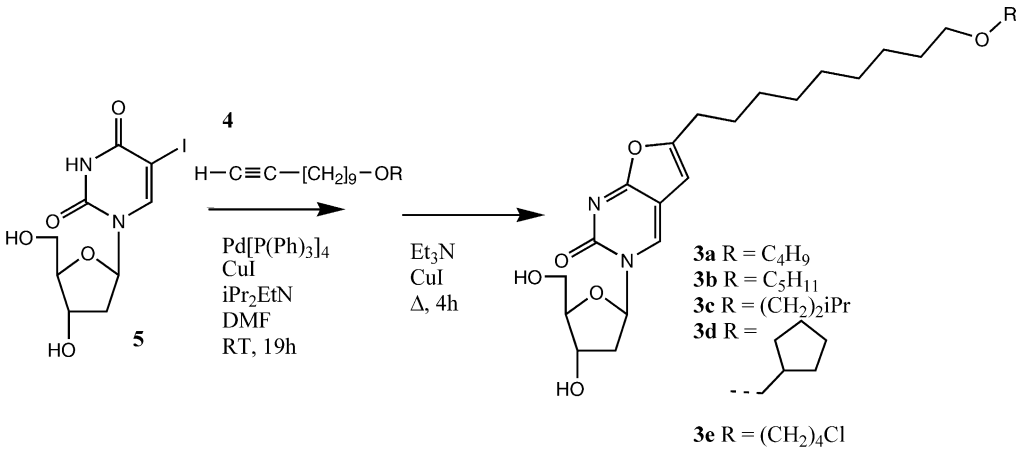

Table 1.

R	ClogP	EC_{50}
$C_{10}H_{21}$	4.1	0.015
C_8H_{17}	3.0	0.008
C_6H_{13}	1.9	1.3
C_2-O-C_7	1.7	6

R, refers to the side chain in (**1**); ClogP is calculated via Chemdraw 7.0.3 and EC_{50} is the concentration in μM required to give 50% inhibition of replication of VZV OKA in tissue culture.[1,6]

4.1 and 4.2, respectively. Our prior experience with (**1**) would thus predict EC_{50} values of ca. 0.01 μM.[2]

Compounds **3a–d** were evaluated as inhibitors of two strains of thymidine kinase competent (TK^+) VZV and two strains of thymidine kinase deficient virus (TK^-) by methods we have described.[1,8] We have noted TK to be a pre-requisite for agents of this family, being regarded as the putative essential activation step for these compounds.[9] As shown in Table 2, compounds **3a–d** do indeed show a potent and selective TK dependent anti-VZV activity, with EC_{50} values entirely as were predicted from their ClogP values.

Further elaboration of the structure lead to **3e**, with a chlorobutyl terminus (**3**, R = ClC_4H_8). This more or less retains the potency of **3a**,**d** but with reduced cytotoxicity. All compounds of this general class reported by us to date have complete selectivity for VZV, with no other antiviral activity against a range of DNA or RNA viruses. However, unique to the present agents we also note a modest anti-human cytomegalovirus (HCMV) activity in the low μM range (Table 3).[10]

As noted in Table 3, the chlorobutyl compound **3e** is a particularly promising lead compound, with 9.7–30 μM activity against both strains of HCMV and cytotoxicity at 200 μM. The reference compound ganciclovir, is only 3- to 5-fold more active. Whilst among **3a–d** several compounds also display some HCMV activity, they also show higher toxicity, as measured by MCC. Thus, in conclusion, we report the synthesis and evaluation of a series of long-chain alkyl ether bicyclic furanopyrimidines. These

Table 2.

	EC_{50}(μM)				MCC (μM)	CC_{50} (μM)
Compd	VZV (OKA)	VZV (YS)	VZV TK^-(07)	VZV TK^-(YS)		
3a	0.02	0.03	>5	>5	20	>200
3b	0.01	0.02	>5	>5	10	>200
3c	0.05	0.06	>5	>5	10	>200
3d	0.09	0.10	>5	>5	≥5	>200
3e	0.05	0.03	≥200	≥50	≥200	>200

Table 3.

Compd	EC_{50} (μM)		MCC (μM)	CC_{50} (μM)
	HCMV AD169	HCMV Davis		
3a	>5	>5	20	>200
3b	>5	>5	20	>200
3c	>5	5	20	>200
3d	>5	5	20	>200
3e	9.7	30	200	>200
Ganciclovir	4.0	5.7	>150	>150

compounds represent the first class of compounds that show dual anti-VZV and anti-HCMV activity. The chlorobutyloxy nonyl analogue **3e** is of particular interest on account of its poor cytotoxicity. This, coupled with its high inherent lipophilicity make it of interest for onward antiviral evaluation.

References and Notes

1. McGuigan, C.; Yarnold, C. J.; Jones, G.; Velázquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **1999**, *42*, 4479.
2. McGuigan, C.; Barucki, H.; Brancale, A.; Blewett, S.; Carangio, A.; Jones, G.; Pathirana, R.; Srinivasan, S.; Velázquez, S.; Yarnold, C. J.; Alvarez, R.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Drugs Future* **2000**, *25*, 1151.
3. Brancale, A.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1215.
4. Srinivasan, S.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 391.
5. McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem.* **2000**, *43*, 4993.
6. Brancale, A.; Srinivasan, S.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Antivir. Chem. Chemother.* **2000**, *11*, 383.
7. Selected data for compound **3a**, other compounds were similarly characterised: **3-(2-deoxy-β-D-ribofuranosyl)-6-(9-(butoxy)nonyl)-2,3-dihydrofuro[2,3-*d*]pyrimidin-2-one (3a).** To a stirred solution of 5-iodo-2′-deoxyuridine (100 mg, 0.282 mmol) in dry dimethylformamide (1 mL), at room temperature under a nitrogen atmosphere, was added diisopropylethylamine (73 mg, 0.10 mL, 0.564 mmol), butoxyundecyne (189.5 mg, 0.846 mmol), *tetrakis*(triphenylphosphine)palladium(0) (32.62 mg, 0.028 mmol) and copper(I) iodide (10.75 mg, 0.056 mmol). The reaction mixture was stirred at room temperature for 19 h, after which time copper(I) iodide (10 mg), triethylamine (2 mL) and methanol (3 mL) were added. The reaction mixture was then heated to 75 °C and stirred for 4 h, then concentrated in vacuo. The resulting residue was dissolved in dichloromethane/methanol (1:1) (6 mL) and an excess of Amberlite IRA-400 (HCO_3^- form) was added and the mixture was stirred for 30 min. The resin was filtered, washed with methanol and the combined filtrate was evaporated to dryness. The crude product purified by silica 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 pure product as a white solid (52 mg, 42%). ^{1}H NMR (DMSO-d_6; 300 MHz): 8.68 (1H, s, H-4), 6.44 (1H, s, H-5), 6.17 (1H, dd, ^3J = 6.0 Hz, H-1′), 5.30 (1H, d, ^3J = 4.1 Hz, 3′-OH), 5.14 (1H, t, ^3J = 5.1 Hz, 5′-OH), 4.24 (1H, m, H-3′), 3.92 (1H, m, H-4′), 3.65 (2H, m, H-5′), 3.34 (4H, m, $C\underline{H}_2OC\underline{H}_2$), 2.65 (2H, t, ^3J = 6.9 Hz, α-CH_2), 2.38 and 2.04 (2H, m, H-2′a and H-2′b), 1.61–1.26 (18H, m, 9×CH_2), 0.87 (3H, t, ^3J = 7.0 Hz, CH_3). ^{13}C NMR (DMSO-d_6; 75 MHz): 14.1 (CH_3), 19.3, 26.0, 26.8, 27.7, 28.7, 29.0, 29.2, 29.3, 29.6, 31.7 (10×CH_2), 41.6 (C-2′), 61.1 (C-5′), 69.9, 70.3 ($\underline{C}H_2O\underline{C}H_2$), 70.0 (C-3′), 87.7, 88.5 (C-1′ and C-4′), 100.1 (C-5), 106.7 (C-4a), 137.1 (C-4), 154.1 (C-2), 158.6 (C-6), 171.5 (C-7a). Mass spectrum [ES–MS (+ve)]; *m*/*z* 473 (100%, $[MNa]^+$). FAB *m*/*e* 473.2624 (MNa^+ $C_{24}H_{38}N_2O_6Na$ requires 473.2628).
8. Stock solutions of test compounds were made up in pure DMSO at 20 or 50 mM. Dilutions were made in cell-culture medium. Some of the compounds partly precipitate when brought into aqueous solution, and were added to the virus-infected cells as fine suspensions at their higher concentrations. MCC is the minimal cytotoxic concentration, or compound concentration required to cause a morphological alteration of the human embryonic lung fibroblast (HEL) cell cultures; CC_{50} is the compound concentration required to inhibit HEL cell proliferation by 50%. For full details, see: Andrei, G.; Snoeck, R.; Reymen, D.; Liesnard, C.; Goubau, P.; Desmyter, J.; De Clercq, E. *Eur. J. Clin. Microbiol. Infect. Dis* **1995**, *14*, 318.
9. Sienaert, R.; Naesens, L.; Brancale, A.; De Clercq, E.; McGuigan, C.; Balzarini, J. *Mol. Pharmacol.* **2002**, *61*, 249.
10. For full details of the HCMV assay see: Snoeck, R.; Andrei, G.; Bodaghi, B.; Lagneaux, L.; Daelemans, D.; de Clercq, E.; Neyts, J.; Schols, D.; Naesens, L.; Michelson, S.; Bron, D.; Otto, M. J.; Bousseau, A.; Nemecek, C.; Roy, C. *Antiviral Res.* **2002**, *55*, 413.