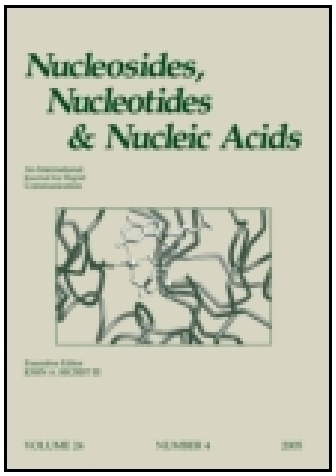

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SYNTHESIS AND IN VITRO EVALUATION OF NOVEL ANTI-VARICELLA-ZOSTER VIRUS (VZV) NUCLEOSIDES

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ABSTRACT

A series of alkyl-aryl, -phenoxy, and -thiophenoxy bicyclic furo pyrimidine nucleosides have been successfully synthesised by Pd-coupling of 5-iodo-2′-deoxyuridine (IDU) with terminal alkynes, followed by *in situ* copper-cyclisation. Synthesised compounds (**4a**-**i**) showed an anti-VZV activity at low μM concentration, comparable to that of current treatment acyclovir.

We have recently reported on the discovery of a new class of anti-VZV nucleosides with unusual bicyclic furo pyrimidine structures (1). Preliminary evaluation pointed out the structural requirement of a long alkyl side-chain on the base moiety for biological activity, with an optimal length of C8-C10 (1) (structure **1**, Fig. 1). Most recently, we observed that introduction of a phenyl group in the side chain of these compounds leads to further significant enhancement of antiviral potency (2) (structure **2**, Fig. 1). Following this extraordinary result, we sought to investigate SARs regarding the aromatic moiety in the lead structure **2** by synthesising a broad series of alkyl-aryl chain-modified analogues.

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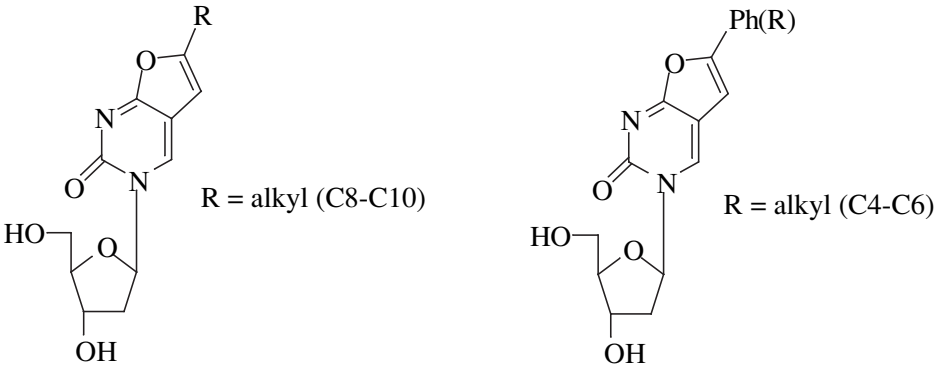

1 **2**

Figure 1.

Effect of introduction of a heteroatom (O, S) on the antiviral activity was also investigated, through the synthesis and *in vitro* evaluation of phenoxy and thiophenoxy analogues.

Chemistry. Target structures have been synthesised in good yield following the previously reported procedure for this family of molecules (1). Thus, we treated 5-iodo-2′-deoxyuridine with the corresponding terminal alkynes in the presence of a catalytic amount of Pd(0). As previously observed (1), the resulting alkynyl-deoxyuridine may be easily cyclised *in situ*, by treatment with copper(I) and Et_3N. The terminal alkynes (**3a**-**h**) used in the coupling step were synthesised in good yields from the appropriate halides, by treatment with lithium acetylide, ethylenediamine complex (3). The whole process is reported in Scheme 1.

Bearing in mind previous observation regarding derivatives with *p*-alkylaryl side-chains, where an alkyl chain of 4–6 carbon atoms was optimal for antiviral activity (2), we synthesised compounds **4a** and **4b**, with 4 and 5 methylene groups between the furo-system and the phenyl moiety. Following previous studies on derivatives bearing an oxygen along the alkyl side chain (4), we synthesised phenoxy-derivatives **4c** and **4d**. Since we previously observed that introduction of an oxygen atom in the side chain, whilst being extremely successful in enhancing water solubility, was detrimental for antiviral activity (4), we replace the oxygen by the more lipophilic sulphur (compounds **4e** and **4f**). Compounds **4g** (5), **4h** and **4i** have been synthesised in order to investigate the effect of a substitution on the phenyl ring, as well as increase the ClogP of the phenoxy-derivatives (Table 1).

Antiviral Activity. The target bicyclic compounds **4a**-**i** were evaluated for their ability to inhibit the replication of VZV *in vitro*, according to previously described methodology (6). Data are shown in Table 1 for the activity of these compounds *versus* two strains of thymidine kinase-competent, and also two strains

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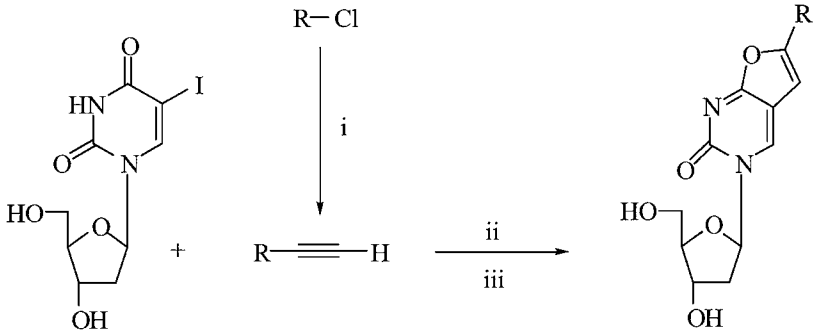

3a, R = $(CH_2)_3CH_2Ph$ (86%)
3b, R = $(CH_2)_4CH_2Ph$ (76%)
3c, R = $(CH_2)_3OPh$ (56%)
3d, R = $(CH_2)_4OPh$ (70%)
3e, R = $(CH_2)_3SPh$ (30%)
3f, R = $(CH_2)_4SPh$ (40%)
3g, R = $(CH_2)_3OPh(Me)$ (73%)
3i, R = $(CH_2)_3OPh(Et)$ (53%)
3h, R = $(CH_2)_3OPh(Pr)$ (60%)

4a, R = $(CH_2)_3CH_2Ph$ (81%)
4b, R = $(CH_2)_4CH_2Ph$ (66%)
4c, R = $(CH_2)_3OPh$ (48%)[a]
4d, R = $(CH_2)_4OPh$ (45%)
4e, R = $(CH_2)_3SPh$ (41%)
4f, R = $(CH_2)_4SPh$ (42%)
4g, R = $(CH_2)_3OPh(Me)$ (63%)[a]
4i, R = $(CH_2)_3OPh(Et)$ (64%)
4h, R = $(CH_2)_3OPh(Pr)$ (86%)

[a] Yield of the cyclisation step

i) lithium acetylide, EDA complex, DMSO/Et_2O 7/3, r.t., 17 h.
ii) $Pd(PPh_3)_4$, CuI, DIPEA, DMF, r.t., 17h.
iii) CuI, MeOH/TEA (7/3), reflux, 4-6 h.

Scheme 1.

Table 1.

Cpd	EC_{50}[a] (μM) TK^+ YS	EC_{50}[a] (μM) TK^+ OKA	EC_{50}[a] (μM) TK^-[d] 07/1	EC_{50}[a] (μM) TK^-[d] YS/R	MCC[b] (μM)	CC_{50}[c] (μM)	ClogP[e]
4a	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	1.76
4b	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	2.29
4c	92	77	>200	>200	>200	>200	0.65
4d	13	25	>200	>200	≥200	>200	1.18
4e	0.67	0.90	>50	>50	200	>200	1.29
4f	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	N.D.[f]	1.82
4g	11	5	>50	>50	200	>200	1.15
4h	10.8	8.4	>50	>50	200	165	1.68
4i	2.8	3.2	>20	>20	≥50	>200	2.21
ACV	1.0	2.9	74	125	>200	>200	–

[a] EC_{50}, effective concentration (μM), required to reduce virus plaque formation by 50%.
[b] MCC, minimal cytotoxic concentration (μM), required to alter microscopically detectable cell morphology.
[c] CC_{50}, 50% cytotoxic concentration, required to inhibit Hel cell growth by 50%.
[d] TK; thymidine kinase-deficient.
[e] Values calculated using ClogP version 1.0.0.. Biobyte, P.O. Box 517, Claremont, CA 91711, USA.
[f] N.D., not determined: data awaited (Sept. 2000).

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of thymidine kinase-deficient VZV, with data also included for the reference antiherpetic agent acyclovir (ACV).

A preliminary evaluation shows that target nucleosides retain an anti-VZV activity comparable to that of acyclovir, although their antiviral activity is considerably less pronounced than that of our previously reported analogues (1,2). No cytotoxicity is detectable *in vitro* at the concentration required for antiviral activity.

The clear absence of antiviral activity against thymidine kinase-deficient VZV strains remains a constant characteristic of this family of compounds (7), and strongly suggests the absolute requirement for a thymidine kinase-mediated phosphorylation for antiviral activity.

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5-. **3[4-hydroxy-5-(hydroxymethyl)tetrahydrofuro-2-furanyl]-6-(3-*p*-methyl-phenoxypropyl)-2,3-dihydrofuro[2,3,*d*]pyrimidin-2-one (4g).** ^{1}H-nmr (d_6-DMSO; 300 MHz): 9.00 (1H, s, H-4), 7.07 (2H, d, $^{3}J = 7.9$ Hz., *m*-Ph), 6.80 (2H, d, $^{3}J = 7.9$ Hz., *o*-Ph), 6.49 (1H, s, H-5), 6.17 (1H, dd, $^{3}J = 5.6$ Hz, H-1′), 5.30 (1H, d, $^{3}J = 4.1$ Hz, 3′-OH), 5.13 (1H, t, $^{3}J = 4.9$ Hz, 5′-OH), 4.23 (1H, m, H-3′), 3.98 (2H, t, $^{3}J = 5.9$, OCH_2), 3.91 (1H, m, H-4′), 3.63 (2H, m, H-5′), 2.82 (2H, t, $^{3}J = 6.9$ Hz, α-CH_2), 2.38 and 2.16 (2H, m, H-2′), 1.38 (2H, m, CH_2). ^{13}C-nmr (d_6-DMSO; 75 MHz): 19.2 (CH_3) 24.6, 26.65 (2 × CH_2) 41.5 (C-2′), 61.1 (C-5′), 66.6 (OCH_2), 70.0 (C-3′), 87.7 (C-4′), 88.4 (C-1′), 100.4 (C-5), 106.7 (C-4a), 114.6 (*o*-Ph), 129.5 (*p*-Ph), 130.1 (*m*-Ph), 137.2 (C-4), 154.1 (*ipso*-Ph), 156.7 (C-6), 157.9 (C-2), 171.5 (C-7a). MS (ES^+) m/e 423 (MNa^+, 100%), 307 (baseNa^+, 10%). Accurate mass: $C_{21}H_{24}N_2O_6Na$ requires: 423.1532. Found: 423.1534.

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