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Synthesis and antiviral activity of novel acyclic nucleosides in the 5-alkynyl- and 6-alkylfuro[2,3-*d*]pyrimidine series

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Abstract—The synthesis of novel acyclic nucleosides in the 5-alkynyl and 6-alkylfuro[2,3-*d*]pyrimidine series is described. These compounds were evaluated against HIV and HSV in order to determine their spectrum of antiviral activity. Their cytotoxicities against PBM, CEM and VERO cells were also determined. Compounds **21d** and **24b** displayed moderate EC_{50}s of 2.7 and 4.9 μM, respectively, against HIV-1 and of 6.3 and 4.8 μM, respectively, against HSV. Nevertheless, these compounds also showed cellular toxicity, suggesting that the antiviral effects are secondary to the toxic effects.

1. Introduction

Among the antiviral agents developed for several life threatening infections, acyclic nucleosides have been a focus of several recent studies, including variations both of the acyclic glycone and of the heterocyclic base.[1,2] Acyclovir (ACV, **1a**)[3] and ganciclovir (GCV, **1b**)[4] are two important acyclic drugs (Fig. 1) active against herpes simplex virus (HSV), varicella-zoster virus (VZV) and/or cytomegalovirus (CMV). The success of ACV and GCV as antiviral drugs has prompted intensive efforts by several groups to prepare and evaluate many structurally related acyclic nucleoside analogues. In another area, many nucleoside analogues substituted at various positions on the heterocycle,[5] are known to have potent biological properties and have been investigated, for instance, as antiviral agents (against HSV, VZV, CMV, HIV, HBV and HCV), non-radioactive fluorescent labels for DNA and as anticancer drugs. Among them, extensive studies have been carried out on 5-substituted uracils,[6] starting from the anti-HSV BVDU agent, **2**.[6e] Bicyclic pyrimidine nucleosides such as (**3**),[7]

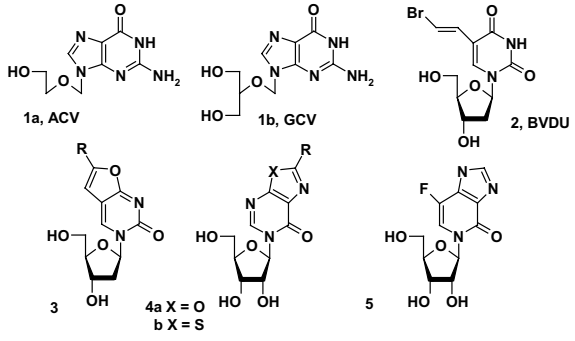

Figure 1.

oxazolo- (**4a**)[8a], thieno (**4b**)[8b] or imidazo (**5**)[8c,d,e] have demonstrated antiviral and antileukemic activity in vitro, which has led to increased interest in preparation of corresponding nucleoside analogues (Fig. 1). Thus, as part of an ongoing program in our drug discovery group, we initiated the preparation of different, hitherto unknown, acyclic analogues of ACV and other bicyclic nucleosides. In the present report, we present the full experimental details and biological evaluation of the first 18 analogues of these novel acyclic nucleosides in the 5-alkynyl- and 6-alkylfuro[2,3-*d*]pyrimidine series with hydrophobic functional groups.

Keywords: Nucleosides; Furopyrimidine; Antiviral activity.
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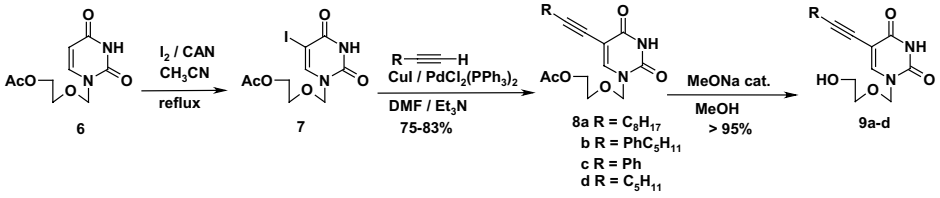
2. Chemistry

The preparation of the desired 5-alkynyl analogues of acyclovir is illustrated in Scheme 1. Thus, starting from the known acetylated uracil analogue of acyclovir **6**, synthesized following a well-known procedure,[9] an iodo group was selectively introduced at the C-5 position on the heterocyclic moiety using I_2/CAN.[10] Different substituents were then introduced by reaction of the 5-iodo acyclic nucleoside **7** under optimized Sonogashira Pd(0)-catalyzed reactions.[11,12] It is important to note that this reaction must be run at room temperature to avoid the formation of co-products produced when heating. Finally, deacylation of C5-alkynyl acyclovir analogues **8a**–**d** was performed using a catalytic solution of MeONa/MeOH to give the desired nucleosides **9a**–**d**.

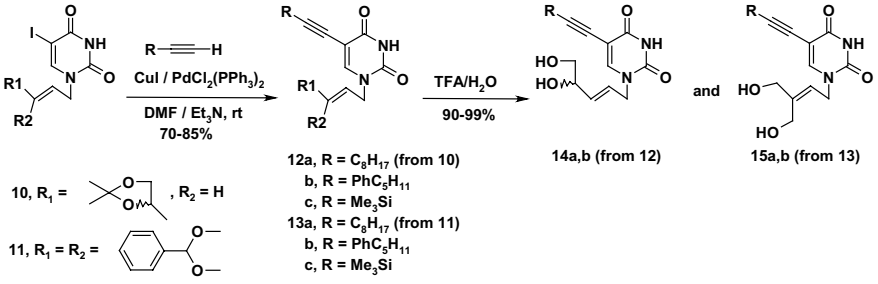
In order to explore more of the acyclic nucleosides family, we applied the same methodology to unsaturated C5-iodinated uracil acyclonucleosides **10** and **11** obtained using a cross metathesis methodology (Scheme 2).[13] The desired C5-alkynyl unsaturated acyclic nucleosides **12a**–**c** and **13a**–**c** were obtained in 70–85% average yield, The acidic deprotection (TFA/H_20, 2:1, v/v) of nucleosides **12** and **13** afforded in >90% yields the acycloalkenyl nucleosides **14a**,**b** and **15a**,**15b**, respectively. It is interesting to note that the two-step deprotection of trimethylsilyl alkyne **12c** and **13c** afforded C5-acylated analogues **18** and **19** due to the in situ acidic hydrolysis of the alkyne (Scheme 3).

Having these C-5-alkynyl nucleosides in hand, we turned our attention to the synthesis of fused bicyclic pyrimidine acyclonucleosides through an *O*-hetero-annulations process (Scheme 4). The most common synthetic pathway for cyclization to the target bicyclic nucleosides consists of the base and copper-catalyzed 5-*endo-dig* cyclization of various alkynyluridines with CuI in triethylamine/methanol at reflux, involving the C-4 pyrimidine oxygen and acetylenic bond.[14] Nevertheless, this approach suffers from poor to moderate yields. Thus, we applied a more versatile and efficient procedure, recently reported by our group, based on a 5*endo-dig* electrophilic cyclization catalyzed by $AgNO_3$.[15]

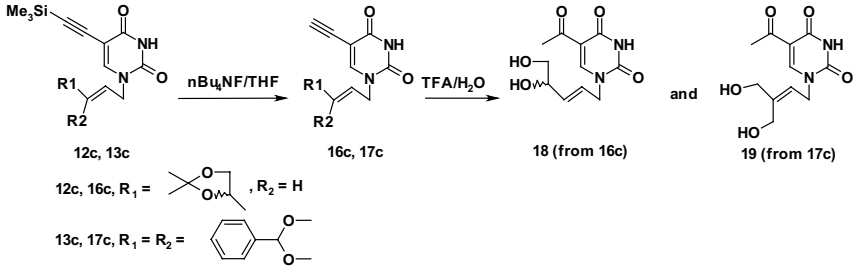
Starting from protected C5-alkynyl acyclic nucleosides **8a**–**d** or unsaturated **12a**,**b** the desired alkyl furanopyr-



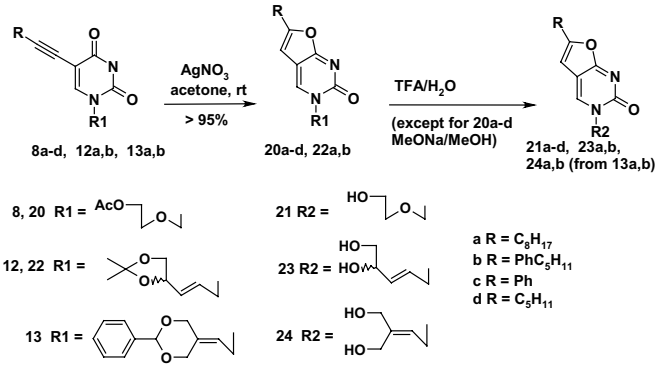
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

imidine nucleosides (**20a**–**d**, **22a**,**b**) were obtained in >95% yield, often requiring no purification. A final deprotection was performed using a catalytic amount of MeONa/MeOH (for **20**) or a TFA/H_2O mixture (for **22**) to yield the desired nucleosides **21a**–**d** and **23a**,**b**, respectively. Alkyl furanopyrimidines **24a**,**b** were directly obtained from a one pot cyclization and deprotection reaction of **13a**,**b**, respectively.

3. Biological assay

All synthesized compounds, the C5-alkynyl derivatives **9a**–**d**, **14a**–**b**, **15a**,**b**, the C5-acetyl derivatives **18** and **19** and the 6-alkylfuro[2,3-*d*]pyrimidine (**21a**–**d**, **23a**,**b** and **24a**,**b**) along with the known antiviral compounds (acyclovir for HSV and AZT for HIV), were tested for their antiviral activities in vitro (results shown in Table 1). The antiviral[16] and cytotoxicity[17] assays were performed as previously described. For the anti-HIV activity, among the C-5-alkynyl acyclonucleoside analogues, **9a**,**b**, **14a**,**b**, **15a**,**b** exhibited moderate anti-HIV activity with EC_{50}s ranging from 18.6 μM to 57.3 μM; among the fused bicyclic pyrimidine acyclonucleosides, the highest anti-HIV activity was achieved for compound **21d** with an EC_{50} of 2.7 μM.

The introduction of a C-5 acetyl group on **18** or **19** led to inactive compounds. The above synthesized acyclonucleosides were also evaluated against HSV-1 and all tested compounds showed either no (EC_{50} > 100 μM) or moderate antiviral activity (EC_{50} ranging from 4.8 to 18.2 μM). The highest anti-HSV activity was achieved by the furano-pyrimidine compounds **21d** and **24b** with an EC_{50} of 6.3 and 4.8 μM, respectively. Nevertheless, all compounds with moderate activity against HIV and HSV showed toxicity against PBM, CEM and VERO cells, probably by inhibiting cell DNA synthesis. The

Table 1. Evaluation of 5-alkynyl- and 6-alkylfuro[2,3-*d*]pyrimidine acyclic nucleosides antiviral activity against human immunodeficiency virus (HIV), herpes simplex virus (HSV-1) and cytotoxicity against PBM, CEM and VERO cells in vitro, expressed in μM

Compd	Anti-HIV-1 activity in PBMCs		HSV-1 plaque reduction assay		Toxicity(IC_{50}) in:		
	EC_{50}	EC_{90}	EC_{50}	EC_{90}	PBM	CEM	VERO
Acyclovir[a]	>100	>100	0.11	0.69	>100	>100	
AZT[a]	0.016	0.20	>10	>10	>100	14.0	29.0
9a	23.7	≈105	>100	>100	72.1	6.4	19.3
9b	18.6	>100	>10	>10	8.3	8.9	7.9
9c	>100	>100	>100	>100	>100	>100	21.6
9d	≈100	>100	>100	>100	>100	>100	39.5
14a	57.3	>100	ND[b]	ND	59.2	15.7	37.03
14b	45.1	91.6	8.5	16.2	19.5	13.9	75.1
15a	33.0	72.3	>10	>100	21.9	31.6	28.8
15b	31.8	69.7	ND	ND	3.4	2.2	6.9
18	>100	>100	100	>100	>100	>100	>100
19	25.1	39.0	>100	>100	>100	>100	>100
21a	49.8	>100	18.2	>100	52.9	17.6	4.97
21b	>100	>100	>100	>100	>100	30.9	4.4
21c	>100	>100	>100	>100	>100	>100	63.1
21d	**2.7**	**19.8**	**6.3**	**16.4**	**54.4**	**4.1**	**3.1**
23a	55.4	>100	>10	10	9.8	16.3	14.9
23b	36.7	>100	>100	>100	>100	>100	>100
24a	25.1	39.0	7.3	53.8	91.0	4.0	78.9
24b	**4.9**	**13.07**	**4.8**	**46.2**	**11.1**	**0.81**	**8.7**

[a] Reference compounds.
[b] ND, not determined.

non-toxic compounds will be evaluated against HBV and HCV.

4. Experimental

4.1. General procedures

Commercially available chemicals and solvents were reagent grade and used as received. Dry tetrahydrofuran, pyridine and dichloromethane were obtained from distillation over CaH_2 or Na, and dry *N*,*N*-dimethylformamide over BaO. Reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel plates (Kieselgel 60 F_{254}, E. Merck). Compounds were visualized by UV irradiation and/or spraying with 20% H_2SO_4 in EtOH, followed by charring at 150 °C. Column chromatography was performed on Silica Gel 60 M (0.040–0.063 mm, E. Merck). Melting points were recorded on a Büchi (Dr. Tottoli) and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX 250 Fourier Transform spectrometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C, using tetramethylsilane as the internal standard; signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were recorded on a Perkin-Elmer SCIEX API-300 (heated nebulizer) spectrometer. HRMS were performed by the CRMPO, University of Rennes 1, France. The nomenclature of the synthesized compounds is in accordance with the IUPAC rules and was checked with Autonome. Evidence of purity has been done from a proton-decoupled ^{13}C NMR spectrum with a signal-to-noise ratio sufficient to permit seeing peak with 5% of the intensity of the strongest peak.

4.2. Chemistry

4.2.1. 1-*N*-(2-Acetoxy-ethoxymethyl)-5-iodo-uracil[9a] (7). 1-*N*-(2-Acetoxy-ethoxymethyl)-uracil (**6**, 3.42 g, 15 mmol) was dissolved in 150 mL dry CH_3CN. CAN (4.94 g, 0.6 equiv) and 2.28 g I_2 (0.6 equiv) were added and the resulting solution was refluxed for 1 h. After cooling to rt, solvents were evaporated in vacuo and the dark oily residue was dissolved in 300 mL AcOEt and 50 mL H_2O. The biphasic mixture was cooled in an ice bath and a saturated $Na_2S_2O_3$ solution was slowly added until complete decolouration. The organic layer was washed with water (2×50 mL) and brine (50 mL) then dried over $MgSO_4$ and concentrated in vacuo. The yellow solid was submitted to flash column chromatography (eluent:CH_2Cl_2 then 2% MeOH/CH_2Cl_2) to yield pure iodinated nucleoside **7** as a white solid (4.25, 80%); ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H), 3.81 (t, 2H, $J = 4.6$ Hz), 4.23 (t, 2H, $J = 4.6$ Hz), 5.21 (s, 2H), 7.79 (s, 1H), 9.25–9.35 (br s, 1H); other spectral data were identical to those previously reported.[9a]

4.3. General procedure for Sonogashira cross-coupling

The iodinated nucleoside (2 mmol) was dissolved in a mixture of 6 mL dry DMF, 824 μL dry Et_3N (3 equiv) and 3 mmol of the desired alkyne (3 equiv). CuI (76 mg, 0.2 equiv) and 140 mg $PdCl_2(PPh_3)_2$ (0.1 equiv) were added and the reaction mixture was stirred at rt until completion (typically 5–20 h, checked by TLC). Solvents were evaporated in vacuo. The oily residue was dissolved in 100 mL AcOEt then washed with water (7×10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvents were evaporated in vacuo to give a dark oil. A first purification using a short path flash chromatography (eluent:CH_2Cl_2 then MeOH/CH_2Cl_2 5%) gave the desired compound contaminated with coloured reaction co-products. Pure alkynes were obtained after a second round of flash chromatography (eluent:pet. eth./AcOEt, 8:2 then 1:1).

4.3.1. 1-*N*-(2-Acetoxy-ethoxymethyl)-5-(dec-1-ynyl)-uracil (8a). Yield 78%, white solid; mp (CH_2Cl_2) 55–57 °C; ^1H NMR ($CDCl_3$): δ 0.98 (m, 3H, $J = 7.2$ Hz), 1.24–1.64 (m, 12H), 2.08 (s, 3H), 2.39 (t, 2H, $J = 7.2$ Hz), 3.80 (t, 2H, $J = 4.6$ Hz), 4.22 (t, 2H), 5.20 (s, 2H), 7.52 (s, 1H), 9.43–9.53 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 19.7 (CH_2), 20.9 (CH_3), 22.7, 28.6, 29.0, 29.1, 29.2 and 31.9 ($6 \times CH_2$), 63.0 (CH_2), 67.8 (CH_2), 70.6, 76.9 (CH_2), 96.1, 102.0, 144.7 (CH), 150.4, 162.1, 171.0 (CO); HRMS: $C_{19}H_{28}N_2O_5Na$ calcd 387.4352 $[M+Na]^+$, found 387.4355.

4.3.2. 1-*N*-(2-Acetoxy-ethoxymethyl)-5-(*p*-pentylphenylethynyl)-uracil (8b). Yield 80%, white solid; mp (CH_2Cl_2) 100–102 °C; ^1H NMR ($CDCl_3$): δ 0.97 (m, 3H, $J = 6.9$ Hz), 1.25–1.66 (m, 6H), 2.09 (s, 3H), 2.60 (t, 2H, $J = 7.6$ Hz), 3.81 (t, 2H, $J = 4.5$ Hz), 4.23 (t, 2H, $J = 4.5$ Hz), 5.23 (s, 2H), 7.14 (d, 2H, $J = 8.2$ Hz), 7.41 (d, 2H, $J = 8.2$ Hz), 7.65 (s, 1H), 8.51–8.58 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_2), 20.9 (CH_3), 22.5, 30.9, 31.5, 35.9 ($4 \times CH_2$), 63.0 (CH_2), 67.8 (CH_2), 77.0 (CH_2), 79.1, 94.5, 101.6, 119.8 (CH), 128.5 (CH), 130.0 (CH), 145.0 (CH), 148.5, 150.3, 161.6, 170.9 (CO); HRMS: $C_{22}H_{26}N_2O_5Na$ calcd 412.4527 $[M+Na]^+$, found 412.4528.

4.3.3. 1-*N*-(2-Acetoxy-ethoxymethyl)-5-(phenylethynyl)-uracil (8c). Yield 83%, white solid; mp (CH_2Cl_2) 85–87 °C; ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H), 3.81 (t, 2H, $J = 4.6$ Hz), 4.22 (t, 2H, $J = 4.6$ Hz), 5.23 (s, 2H), 7.30–7.38 (m, 3H), 7.47–7.54 (m, 5H), 7.68 (s, 1H), 9.63–9.78 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.9 (CH_3), 63.0 (CH_2), 67.9 (CH_2), 77.1 (CH_2), 79.7, 94.3, 101.4, 122.4 (CH), 128.4 (CH), 128.8 (CH), 131.7, 145.3 (CH), 150.3, 161.7, 171.0 (CO); HRMS: $C_{17}H_{16}N_2O_4Na$ calcd 351.3173 $[M+Na]^+$, found 351.3174.

4.3.4. 1-*N*-(2-Acetoxy-ethoxymethyl)-5-(hept-1-ynyl)-uracil (8d). Yield 75%, white solid; mp (CH_2Cl_2) 50–52 °C; ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H, $J = 7.0$ Hz), 1.24–1.64 (m, 6H), 2.09 (s, 3H), 2.39 (t, 2H, $J = 7.2$ Hz), 3.80 (t, 2H, $J = 4.7$ Hz), 4.22 (t, 2H, $J = 4.2$ Hz), 5.21 (s, 2H), 7.52 (s, 1H), 9.48–9.58 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 19.6 (CH_2), 20.9 (CH_3), 22.2 (CH_2), 28.2 (CH_2), 31.2 (CH_2), 63.0 (CH_2), 67.8 (CH_2), 70.6, 77.1 (CH_2), 96.0, 102.0, 144.7 (CH), 150.4, 162.1, 171.0 (CO); HRMS: $C_{16}H_{22}N_2O_5Na$ calcd 345.3539 $[M+Na]^+$, found 345.3537.

4.4. General procedure for deacetylation under basic conditions

Acetylated acyclonucleoside (0.5 mmol) was dissolved in 5 mL dry MeOH. Freshly prepared (500 μL, 0.1 equiv) 0.1 M MeONa solution in MeOH were added and the reaction mixture was stirred at rt until completion (typically 1–6 h, checked by TLC). The reaction mixture was neutralized with Dowex [H^+] resin then filtered through a fritted glass funnel. Solvents were evaporated in vacuo and the residue was submitted to flash column chromatography using an appropriate eluent (typically AcOEt then MeOH/AcOEt 1% then MeOH/AcOEt 5%) to yield pure acyclonucleosides.

4.4.1. 1-*N*-(2-Hydroxy-ethoxymethyl)-5-(dec-1-ynyl)-uracil (9a). Yield 95%, white solid; mp (MeOH) 104–106 °C; ^{1}H NMR (CD_3OD): δ 0.90 (t, 3H, J = 7.2 Hz), 1.25–1.64 (m, 12H), 2.38 (t, 2H, J = 7.3 Hz), 3.62–3.54 (m, 4H), 5.19 (s, 2H), 7.84 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.4 (CH_3), 20.1 (CH_2), 23.7 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 30.3 (CH_2), 30.4 (CH_2), 33.0 (CH_2), 61.9 (CH_2), 72.1 (CH_2), 72.2, 78.5 (CH_2), 95.5, 101.6 (CH_2), 147.8 (CH_2), 152.0 (CH_2), 164.8 (CH_2); HRMS: $C_{17}H_{26}N_2O_4Na$ calcd 345.3976 $[M+Na]^+$, found 345.3981.

4.4.2. 1-*N*-(2-Hydroxy-ethoxymethyl)-5-(*p*-pentylphenyl-ethynyl)-uracil (9b). Yield 97%, white solid; mp (MeOH) 110–112 °C; ^{1}H NMR (DMSO-d_6): δ 0.84 (m, 3H, J = 6.8 Hz), 1.18–1.64 (m, 6H), 2.58 (t, 2H, J = 7.7 Hz), 3.45–3.59 (m, 4H), 4.65–4.73 (br s, 1H), 5.14 (s, 2H), 7.22 (d, 2H, J = 8.4 Hz), 7.37 (d, 2H, J = 8.4 Hz), 8.21 (s, 1H), 11.69–11.74 (br s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_2), 21.9 (CH_2), 30.3 (CH_2), 30.9 (CH_2), 35.0 (CH_2), 60.0 (CH_2), 70.8 (CH_2), 76.9 (CH_2), 81.4, 92.1, 98.2, 119.6 (CH), 128.7 (CH), (CH), 143.3 (CH), 148.0, 150.1, 161.7; HRMS: $C_{20}H_{24}N_2O_4$ Na calcd 379.4151 $[M+Na]^+$, found 379.4153.

4.4.3. 1-*N*-(2-Hydroxy-ethoxymethyl)-5-(phenylethynyl)-uracil (9c). Yield 95%, white solid; mp (MeOH) 140–142 °C; ^{1}H NMR (DMSO-d_6): δ 3.45–3.59 (m, 4H), 4.62–4.75 (br s, 1H), 5.14 (s, 2H), 7.37–7.51 (m, 5H), 8.25 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 60.0 (CH_2), 70.8 (CH_2), 77.0 (CH_2), 82.0, 91.9, 98.0, 122.3 (CH), 125.4 (CH), 128.7 (CH), 128.8 (CH), 131.1, 148.3 (CH), 150.1, 161.8; HRMS: $C_{15}H_{14}N_2O_4Na$ calcd 309.2796 $[M+Na]^+$, found 309.2797.

4.4.4. 1-*N*-(2-Hydroxy-ethoxymethyl)-5-(hept-1-ynyl)-uracil (9d). Yield 98%, white solid; mp (MeOH) 104–106 °C; ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, J = 7.0 Hz), 1.20–1.57 (m, 6H), 2.36 (t, 2H, J = 7.0 Hz), 3.44–3.54 (m, 4H), 4.62–4.70 (br s, 1H), 5.19 (s, 2H), 7.99 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 18.7 (CH_2), 21.7 (CH_2), 27.9 (CH_2), 30.5 (CH_2), 60.0 (CH_2), 70.7 (CH_2), 72.5, 76.8 (CH_2), 93.4, 98.8, 147.2 (CH), 150.1, 162.2; HRMS: $C_{14}H_{20}N_2O_4$ Na calcd 303.3163 $[M+Na]^+$, found 303.3161.

4.5. 5-(1-Decynyl)-1-[(*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-2,4(3*H*)-pyrimidinedione (12a)

In an analogous manner to the preparation of **8a**, the title compound **12a** was prepared in a yield of 72% as a pale yellow gum; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 6.9 Hz), 1.15–1.48 (m, 16H), 1.50–1.63 (m, 1H), 2.36 (t, 2H, J = 6.9 Hz), 3.58 (dd, 1H, J = 8.0 Hz), 4.10 (dd, 1H, J = 6.3 Hz, J = 8.0 Hz), 4.22–4.41 (m, 2H), 4.48–4.61 (m, 1H), 5.72 (dd, 1H, J = 6.0 Hz, J = 15.4 Hz), 5.83 (dt, 1H, J = 5.7 Hz, J = 15.4 Hz), 7.31 (s, 1H), 9.17 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 19.7 (CH_2), 22.7 (CH_2), 25.8 (CH_3), 26.7 (CH_3), 28.6 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 49.3 (CH_2), 69.3 (CH_2), 70.8, 75.9 (CH), 95.9, 101.3, 109.8, 126.6 (CH), 133.4 (CH), 145.4 (CH), 149.8, 162.2; HRMS: $C_{22}H_{32}N_2O_4Na$ calcd 411.2260 $[M+Na]^+$, found 411.2259.

4.6. 1-[(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-[2-(4-pentylphenyl)ethynyl]-2,4(3*H*)-pyrimidinedione (12b)

In an analogous manner to the preparation of **8a**, the title compound **12b** was prepared in a yield of 85% as a white solid; mp (CH_2Cl_2) 131–133 °C; ^{1}H NMR ($CDCl_3$): δ 0.90 (t, 3H, J = 11.25 Hz), 1.22–1.38 (m, 4H), 1.39 (s, 3H), 1.44 (s, 3H), 1.55–1.68 (m, 2H), 2.59 (t, 2H, J = 7.4 Hz), 3.61 (dd, 1H, J = 8.1 Hz), 4.13 (dd, 1H, J = 6.4 Hz, J = 8.1 Hz), 4.30–4.48 (m, 2H), 4.50–4.60 (m, 1H), 5.76 (dd, 1H, J = 5.85 Hz, J = 15.7 Hz), 5.87 (dt, 1H, J = 5.3 Hz, J = 15.7 Hz), 7.13 (d, 2H, J = 8.0 Hz), 7.40 (d, 2H, J = 8.0 Hz), 7.46 (s, 1H), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 25.9 (CH_3), 26.8 (CH_3), 31.0 (CH_2), 31.6 (CH_2), 36.0 (CH_2), 49.6 (CH_2), 69.4 (CH_2), 75.9 (CH), 94.7, 101.0, 109.9, 119.6, 126.4 (CH), 128.6 (CH × 2), 131.7 (CH × 2), 133.8 (CH), 144.1, 145.7 (CH), 149.5, 161.3; HRMS: $C_{25}H_{30}N_2O_4$ calcd 422.22056 $[M]^+$, found 422.2202.

4.7. 1-[(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-[2-(trimethylsilyl)ethynyl]-2,4(3*H*)-pyrimidinedione (12c)

In an analogous manner to the preparation of **8a**, the title compound **12c** was prepared in a yield of 83% as a pale yellow gum. ^{1}H NMR ($CDCl_3$): δ 0.20 (s, 9H), 1.37 (s, 3H), 1.42 (s, 3H), 3.58 (dd, 1H, J = 8.0 Hz), 4.10 (dd, 1H, J = 6.5 Hz, J = 8.0 Hz), 4.22–4.52 (m, 2H), 4.47–4.58 (m, 1H), 5.65–5.88 (m, 2H), 7.42 (s, 1H), 9.53 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 0.1 ($CH_3 \times 3$), 25.8 (CH_3), 26.6 (CH_3), 49.4 (CH_2), 69.2 (CH_2), 75.8 (CH), 95.0, 100.0, 100.5, 109.8, 126.4 (CH), 133.5 (CH), 147.0 (CH), 149.8, 161.9; HRMS: $C_{17}H_{24}N_2O_4$ SiNa calcd 371.2318 $[M+Na]^+$, found 371.2221.

4.8. 5-(1-Decynyl)-1-[2-(2-phenyl-1,3-dioxan-5-ylidene)ethyl]-2,4(3*H*)-pyrimidinedione (13a)

In an analogous manner to the preparation of **8a**, the title compound **13** was prepared in a yield of 75% as a

pale yellow gum. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6.8 Hz), 1.18–1.42 (m, 10H), 1.49–1.67 (m, 2H), 2.38 (t, 2H, J = 7.1 Hz), 4.10–4.20 (m, 1H), 4.40–4.61 (m, 4H), 4.91–4.98 (m, 1H), 5.41 (t, 1H, J = 6.6 Hz), 5.67 (s, 1H), 7.29–7.42 (m, 4H), 7.43–7.51 (m, 2H), 9.42 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 19.7 (CH_2), 22.7 (CH_2), 28.6 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 44.5 (CH_2), 65.8 (CH_2), 70.7, 71.6 (CH_2), 96.1, 101.4 (CH), 101.6 (CH), 118.5 (CH), 126.2 (CH × 2), 128.4 (CH × 2), 129.2 (CH), 136.0, 137.7, 145.3 (CH), 150.0, 162.3; HRMS: $C_{26}H_{32}N_2O_4$ Na calcd 459.1817 $[M+Na]^+$, found 459.1814.

4.9. 5-[2-(4-Pentylphenyl)ethynyl]-1-[2-(2-phenyl-1,3-dioxan-5-yliden)ethyl]-2,4(3*H*)-pyrimidinedione (13b)

In an analogous manner to the preparation of **8a**, the title compound **13b** was prepared in a yield of 85% as a pale yellow gum. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, 3H, J = 6.8 Hz), 1.25–1.39 (m, 4H), 1.54–1.67 (m, 2H), 2.59 (t, 2H, J = 8.0 Hz), 4.16–4.25 (m, 1H), 4.42–4.63 (m, 4H), 4.94–4.99 (m, 1H), 5.46 (t, 1H, J = 7.0 Hz), 5.67 (s, 1H), 7.13 (d, 2H, J = 8.1 Hz), 7.34–7.51 (m, 8H), 9.25 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 30.9 (CH_2), 31.5 (CH_2), 36.0 (CH_2), 44.6 (CH_2), 65.8 (CH_2), 71.6 (CH_2), 79.2, 94.6, 101.1, 101.7 (CH), 118.4 (CH), 119.6, 126.2 (CH × 2), 128.5 (CH × 2), 129.2 (CH), 131.7 (CH), 136.3, 137.7, 144.1 (CH), 145.6, 149.8, 161.7; HRMS: $C_{29}H_{30}N_2O_4$Na calcd 493.3112 $[M+Na]^+$, found 493.3117.

4.10. 1-[2-(2-Phenyl-1,3-dioxan-5-yliden)ethyl]-5-[2-(trimethylsilyl)ethynyl]-2,4(3*H*)-pyrimidinedione (13c)

In an analogous manner to the preparation of **8a**, the title compound **13c** was prepared in a yield of 70% as a white solid. mp (CH_2Cl_2) 213–215 °C; ^{1}H NMR (DMSO-d_6): δ 0.18 (s, 9H), 4.31–4.54 (m, 5H), 4.96–5.04 (m, 1H), 5.48 (t, 1H, J = 7.0 Hz), 5.69 (s, 1H), 7.28–7.45 (m, 5H), 8.15 (s, 1H), 11.64 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 0.1 (CH_3 × 3), 44.2 (CH_2), 65.3 (CH_2), 70.6 (CH_2), 96.9, 97.6, 97.8, 100.5 (CH), 119.3 (CH), 126.1 (CH × 2), 128.0 (CH × 2), 128.7 (CH), 134.0, 138.3, 149.6 (CH), 149.8, 161.9; HRMS: $C_{21}H_{24}N_2O_4$NaSi calcd 419.1403 $[M+Na]^+$, found 419.1402.

4.11. General procedure for deprotection under acidic conditions

Acetal derivatives (0.22 mmol) were stirred at room temperature for 3 h in a 2:1 mixture of TFA/H_2O (15 mL). After evaporation of volatiles, the crude residue was purified by flash chromatography (CH_2Cl_2/MeOH, 92:8).

4.11.1. 5-(1-Decynyl)-1-[(*E*)-4,5-dihydroxy-2-pentenyl]-2,4(1*H*,3*H*)-pyrimidinedione (14a). Yield 92%, pale yellow gum, ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H, J = 6.3 Hz), 1.18–1.38 (m, 10H), 1.41–1.58 (m, 2H), 2.34 (t, 2H, J = 7.0 Hz), 3.21–3.30 (m, 2H), 3.88–4.01 (m, 1H), 4.21–4.31 (m, 2H), 4.51–4.68 (m, OH), 4.84 (d, OH, J = 4.8 Hz), 5.65–5.78 (m, 2H), 7.87 (s, 1H), 11.52 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 18.7 (CH_2), 22.1 (CH_2), 28.2 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 31.2 (CH_2), 48.6 (CH_2), 65.7 (CH_2), 71.2 (CH), 72.7, 93.2, 98.3, 123.7 (CH), 135.7 (CH), 147.5 (CH), 149.8, 162.3; HRMS: $C_{19}H_{28}N_2O_4$ Na calcd 371.1947, found 371.1945.

4.11.2. 1-[(*E*)-4,5-Dihydroxy-2-pentenyl]-5-[2-(4-pentylphenyl)ethynyl]-2,4(1*H*,3*H*)-pyrimidinedione (14b). Yield 95%, white solid, mp (MeOH) 255–257 °C; ^{1}H NMR (DMSO-d_6): δ 0.73–0.91 (m, 3H), 1.18–1.37 (m, 4H), 1.49–1.68 (m, 2H), 2.57 (t, 2H, J = 7.5 Hz), 3.22–3.33 (m, 2H), 3.91–4.03 (m, 1H), 4.25–4.39 (m, 2H), 4.51–4.61 (m, OH), 4.86 (d, OH, J = 4.5 Hz), 5.69–5.85 (m, 2H), 7.22 (d, 2H, J = 8.0 Hz), 7.36 (d, 2H, J = 8.0 Hz), 8.10 (s, 1H) 11.64 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 21.9 (CH_2), 30.3 (CH_2), 30.8 (CH_2), 34.9 (CH_2), 48.9 (CH_2), 65.7 (CH_2), 71.4 (CH), 81.6, 92.0, 97.7, 119.6, 123.7 (CH), 128.7 (CH × 2), 131.0 (CH × 2), 135.8 (CH), 143.2, 148.3 (CH), 149.8, 161.9; HRMS: $C_{22}H_{26}N_2O_4$ Na calcd 405.1790, found 405.1791.

4.11.3. 5-(1-Decynyl)-1-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]-2,4(1*H*,3*H*)-pyrimidinedione (15a). Yield 97%, pale yellow gum, ^{1}H NMR (DMSO-d_6): δ 0.82–8.88 (m, 3H), 1.18–1.51 (m, 12H), 2.35 (t, 2H, J = 7.1 Hz), 3.95 (d, 2H, J = 4.8 Hz), 4.02 (d, 2H, J = 5.0 Hz), 4.39 (d, 2H, J = 7.1 Hz), 4.71–4.88 (m, OH × 2), 5.44 (t, 1H, J = 7.1 Hz), 7.88 (s,1H), 11.51 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 18.8 (CH_2), 22.1 (CH_2), 28.2 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 31.2 (CH_2), 44.5 (CH_2), 56.8 (CH_2), 62.4 (CH_2), 72.7, 93.2, 98.3, 118.5 (CH), 144.9 (CH), 147.5, 149.9, 162.3; HRMS: $C_{19}H_{28}N_2O_4$Na calcd 371.1221, found 377.1227.

4.11.4. 1-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-5-[2-(4-pentylphenyl)ethynyl]-2,4(1*H*,3*H*)-pyrimidinedione (15b). Yield 98%, white solid, mp (MeOH) 131-133 °C; ^{1}H NMR (DMSO-d_6): δ 0.85 (t, 3H, J = 6.9 Hz), 1.18–1.37 (m, 4H), 1.50–1.65 (m, 2H), 2.58 (t, 2H, J = 7.3 Hz), 3.96 (d, 2H, J = 5.4 Hz), 4.04 (d, 2H, J = 5.4 Hz), 4.45 (d, 2H, J = 7.2 Hz), 4.75 (t, OH, J = 5.4 Hz), 4.82 (t, OH, J = 5.4 Hz), 5.49 (t, 1H, J = 7.2 Hz), 7.21 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.2 Hz), 8.10 (s, 1H), 11.65 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 12.7 (CH_3), 20.7 (CH_2), 29.12 (CH_2), 29.64 (CH_2), 33.7 (CH_2), 44.2 (CH_2), 55.7 (CH_2), 61.2 (CH_2), 80.5, 90.8, 96.5, 117.3, 118.5 (CH), 127.5 (CH × 2), 129.8 (CH × 2), 141, 143 (CH), 147.1, 148.7, 160.7; HRMS: $C_{22}H_{26}N_2O_4$Na calcd 405.0821, found 405.0826.

4.12. General procedure for desilylation

A solution of silylated derivative (0.24 mmol) and TBAFxH_2O (64 mg, 0.25 mmol) in acetonitrile (2 mL) was stirred at room temperature for 30 min. Solvents were evaporated in vacuo and the residue was submitted to flash column chromatography (AcOEt/Pet. eth. 7:3) to give pure desilylated compound.

4.12.1. 5-Ethynyl-1-[2-(2-phenyl-1,3-dioxan-5-yliden)-ethyl]-2,4(1*H*,3*H*)-pyrimidinedione (16c). The title compound was prepared from **12c**; yield 62%, pale white gum, ^{1}H NMR ($CDCl_3$): δ 4.11 (s, 1H), 4.31–4.52 (m, 5H), 4.94–5.03 (m, 1H), 5.49 (t, 1H, J = 7.0 Hz), 5.69 (s, 1H), 7.31–7.45 (m, 5H), 8.13 (s, 1H), 11.64 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 44.2 (CH_2), 65.3 (CH_2), 70.6 (CH_2), 76.2, 83.7, 97.0, 100.5 (CH), 119.3 (CH), 126.1 (CH × 2), 128.0 (CH × 2), 128.7 (CH), 134.1, 138.3, 149.3 (CH), 149.8, 162.1; HRMS: $C_{18}H_{16}N_2O_4Na$ calcd 347.1201, found 347.1205.

4.12.2. 1-[(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-5-ethynyl-2,4(1*H*,3*H*)-pyrimidinedione (17c). The title compound was prepared from **13c**; yield 94%, pale white gum, ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.41 (s, 3H), 3.18 (s, 1H), 3.58 (dd, 1H, J = 8.0 Hz), 4.10 (dd, 1H, J = 6.3 Hz, J = 8.0 Hz), 4.26–4.41 (m, 2H), 4.48–4.56 (m, 1H), 5.69–5.88 (m, 2H), 7.48 (s, 1H), 9.75 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 23.7 (CH_3), 25.7 (CH_3), 47.5 (CH_2), 67.2 (CH_2), 72.4, 73.8, 80.5, 97.3, 107.8, 124.3 (CH), 131.8 (CH), 145.5 (CH), 147.9, 160.1; HRMS: $C_{14}H_{16}N_2O_4$ Na calcd 299.1008, found 299.1003.

4.13. 5-Acetyl-1-[(*E*)-4,5-dihydroxy-2-pentenyl]-2,4(1*H*,3*H*)-pyrimidinedione (18)

In an analogous manner to the preparation of **14a**, the title compound **18** was prepared in 92% yield as a pale yellow gum; ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H), 3.22–3.31 (m, 2H), 3.88–4.01 (m, 1H), 4.40 (d, 2H, J = 4.4 Hz), 4.63 (t, OH, J = 5.6 Hz), 4.90 (d, OH, J = 5.0 Hz), 5.63–5.82 (m, 2H), 8.35 (s, 1H), 11.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 30.3 (CH_3), 49.3 (CH_2), 65.7 (CH_2), 71.3 (CH), 111.6, 123.6 (CH), 136.1 (CH), 150.1, 151.4 (CH), 162.7, 193.5; HRMS: $C_{11}H_{14}N_2O_5Na$ calcd 277.0936, found 277.0942.

4.14. 5-Acetyl-1-[4-hydroxy-3-(hydroxymethyl)-2-butenyl]-2,4(1*H*,3*H*)-pyrimidinedione (19)

In analogous manner to the preparation of **14a**, the title compound **19** was prepared in 93% yield as a pale yellow gum; ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H), 3.94 (d, 2H, J = 5.0 Hz), 4.03 (d, 2H, J = 5.3 Hz), 4.53 (d, 2H, J = 7.0 Hz), 4.77–4.87 (m, 2H), 5.46 (t, 1H, J = 7.0 Hz), 8.38 (s, 1H), 11.62 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 30.3 (CH_3), 45.3 (CH_2), 57.0 (CH_2), 62.4 (CH_2), 111.6, 118.2 (CH), 145.3, 150.3, 151.4 (CH), 161.7, 193.5; HRMS: $C_{11}H_{14}N_2O_5$ Na calcd 277.0800, found 277.0802.

4.15. General procedure for $AgNO_3$-mediated ring closure

To a solution of 5-alkynyl-acyclonucleosides (0.5 mmol) in acetone (5 mL) was added $AgNO_3$ (17 mg, 0.2 equiv) and the reaction mixture stirred in the dark until completion (typically 5–20 h). Solvents were removed in vacuo and the residue dissolved in 20 mL CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (2 × 5 mL) and brine (5 mL) then dried over $MgSO_4$ and concentrated in vacuo to give the desired furopyrimidone acyclic nucleoside.

4.15.1. 3-*N*-(2-Acetoxy-ethoxymethyl)-6-octyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (20a). White solid; mp (CH_2Cl_2) 111–113 °C; ^{1}H NMR ($CDCl_3$): δ 0.98 (m, 3H, J = 7.2 Hz), 1.21–1.68 (m, 12H), 2.05 (s, 3H), 2.65 (t, 2H, J = 7.5 Hz), 3.88 (t, 2H, J = 4.6 Hz), 4.21 (t, 2H), 5.49 (s, 2H), 6.16 (s, 1H), 7.99 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 20.8 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 26.7 (CH_2) 28.2 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 63.1 (CH_2), 68.2 (CH_2), 79.4 (CH_2), 98.6, 108.7, 137.5, 155.8 (CH), 160.7, 170.7 (CO), 172.4; HRMS: $C_{19}H_{28}N_2O_5Na$ calcd 387.4352 $[M+Na]^+$, found 387.4351.

4.15.2. 3-*N*-(2-Acetoxy-ethoxymethyl)-6-*p*-pentylphenyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (20b). White solid; mp (CH_2 Cl_2) 158–160 °C; ^{1}H NMR ($CDCl_3$): δ 0.85–0.95 (m, 3H), 1.24–1.72 (m, 6H), 2.05 (s, 3H), 2.64 (t, 2H, J = 7.7 Hz), 3.90 (t, 2H, J = 4.7 Hz), 4.22 (t, 2H), 5.50 (s, 2H), 6.70 (s, 1H), 7.24 (d, 2H, J = 8.2 Hz), 7.65 (d, 2H, J = 8.2 Hz), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 20.9 (CH_3), 22.5 (CH_2), 30.9 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 63.1 (CH_2), 68.5 (CH_2), 79.6 (CH_2), 96.5, 109.3, 125.1 (CH), 125.6 (CH), 129.1 (CH), 138.3, 145.4 (CH), 155.7, 156.7, 170.8 (CO), 172.3; HRMS: $C_{22}H_{26}N_2O_5Na$ calcd 412.4527 $[M+Na]^+$, found 412.4525.

4.15.3. 3-*N*-(2-Acetoxy-ethoxymethyl)-6-phenyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (20c). White solid; mp (MeOH) 188–190 °C; ^{1}H NMR (DMSO-d_6, 80 °C): δ 1.99 (s, 3H), 3.83 (t, 2H, J = 4.8 Hz), 4.15 (t, 2H), 5.43 (s, 2H), 7.20 (s, 1H), 7.40–7.85 (m, 5H), 8.57 (s, 1H); ^{13}C NMR (DMSO-d_6, 80 °C): δ 20.0 (CH_3), 62.5 (CH_2), 67.3 (CH_2), 79.0 (CH_2), 98.8, 107.0, 124.3 (CH), 128.0 (CH), 128.6 (CH), 129.1, 141.6, 153.8 (CH), 160.9, 170.4 (CO), 172.6; HRMS: $C_{17}H_{16}N_2O_4Na$ calcd 351.3173 $[M+Na]^+$, found 351.3176.

4.15.4. 3-*N*-(2-Acetoxy-ethoxymethyl)-6-pentyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (20d). White solid; mp (CH_2Cl_2) 80–82 °C; ^{1}H NMR ($CDCl_3$): δ 0.85–1.08 (m, 3H), 1.24–1.82 (m, 6H), 2.05 (s, 3H), 2.66 (t, 2H, J = 7.5 Hz), 3.90 (t, 2H, J = 4.6 Hz), 4.21 (t, 2H, J = 4.6 Hz), 5.50 (s, 2H), 6.17 (s, 1H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9 (CH_3), 20.8 (CH_3), 22.2 (CH_2), 26.3 (CH_2), 28.2 (CH_2), 31.1 (CH_2), 63.0 (CH_2), 68.2 (CH_2), 79.4 (CH_2), 98.6, 108.7, 137.7, 155.7 (CH), 160.7, 170.7 (CO), 172.4; HRMS: $C_{16}H_{22}N_2O_5Na$ calcd 345.3539 $[M+Na]^+$, found 345.3536.

4.15.5. 3-[(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-6-octylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (22a). Yield 96%, pale white gum, ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 6.3 Hz), 1.24–1.42 (m, 10H), 1.60–1.72 (m, 2H), 2.62 (t, 2H, J = 7.2 Hz), 3.58 (dd, 1H, J = 8.0 Hz), 4.11 (dd, 1H, J = 6.2 Hz, J = 8.0 Hz), 4.47–4.71 (m, 3H), 5.72 (dd, 1H, J = 6.9 Hz, J = 15.4 Hz), 5.96 (dt, 1H, J = 5.9 Hz, J = 15.4 Hz), 6.06 (s, 1H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.2 (CH_3), 22.7 (CH_2), 25.8 (CH_3), 26.7 (CH_2), 26.8

(CH_3), 28.4 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.9 (CH_2), 52.2 (CH_2), 69.3 (CH_2), 76.1 (CH), 98.4 (CH), 108.3, 109.7, 127.6 (CH), 133.1 (CH), 138.0 (CH), 155.4, 160.5, 172.2; HRMS: $C_{22}H_{32}N_2O_4Na$ calcd 411.2260 $[M+Na]^+$, found 411.2256.

4.15.6. 3-[(*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-propenyl]-6-(4-pentylphenyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (22b). Yield 97%, pale white gum, ^1H NMR ($CDCl_3$): δ 0.90 (t, 3H, $J = 6.7$ Hz), 1.21–1.41 (m, 4H), 1.38 (s, 3H), 1.42 (s, 3H), 1.55–1.71 (m, 2H), 2.64 (t, 2H, $J = 7.3$ Hz), 3.61 (dd, 1H, $J = 8.0$ Hz), 4.11 (dd, 1H, $J = 6.1$ Hz, $J = 8.0$ Hz), 4.50–4.76 (m, 3H), 5.77 (dd, 1H, $J = 7.0$ Hz, $J = 15.5$ Hz), 6.01 (dt, 1H, $J = 6.0$ Hz, $J = 15.5$ Hz), 6.64 (s, 1H), 7.25 (d, 2H, $J = 8.1$ Hz), 7.66 (d, 2H, $J = 8.1$ Hz), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 22.6 (CH_2), 25.9 (CH_3), 26.7 (CH_3), 31.0 (CH_2), 31.5 (CH_2), 35.9 (CH_2), 52.4 (CH_2), 69.3 (CH_2), 76.1 (CH), 96.4 (CH), 108.9, 109.8, 125.1 (CH × 2), 125.7, 127.5 (CH), 129.2 (CH × 2), 133.4 (CH), 138.9 (CH), 145.4, 155.2, 156.4, 171.9; HRMS: $C_{22}H_{26}N_2O_4$ Na calcd 405.1790 $[M+Na]^+$, found 405.1795.

4.16. 3-*N*-(2-Hydroxy-ethoxymethyl)-6-octyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (21a)

The title compound was prepared from **20a** in an analogous manner to the preparation of **9a** in the yield of 93% as a white solid; mp (MeOH) 124–126 °C; ^1H NMR (DMSO-d_6, 80 °C): δ 0.81–0.93 (m, 3H), 1.21–1.72 (m, 12H), 2.64 (t, 2H, $J = 7.3$ Hz), 3.50–3.55 (m, 4H), 5.34 (s, 2H), 6.38 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (DMSO-d_6, 80 °C): δ 13.3 (CH_3), 21.5, 25.9, 27.0, 28.0, 28.1 and 30.7 (8 × CH_2), 59.8 (CH_2), 71.0 (CH_2), 79.0 (CH_2), 99.0, 106, 139.9, 154.3 (CH), 158.4, 171.5; HRMS: $C_{17}H_{26}N_2O_4$ Na calcd 345.3976 $[M+Na]^+$, found 345.3978.

4.17. 3-*N*-(2-Hydroxy-ethoxymethyl)-6-*p*-pentyl-phenyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (21b)

The title compound was prepared from **20b** in an analogous manner to the preparation of **9a** in a 92% yield as a white solid; mp (CH_2Cl_2) 240–245 °C (dec); ^1H NMR (DMSO-d_6): δ 0.82–0.95 (m, 3H), 1.22–1.70 (m, 6H), 2.58–2.72 (m, 2H), 3.48–3.72 (m, 4H), 4.37–4.54 (br s, 1H), 5.41 (s, 2H), 7.12 (s, 1H), 7.22 (d, 2H, $J = 7.8$ Hz), 7.72 (d, 2H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.2 (CH_3), 21.4, 29.7, 30.4 and 34.5 (4 × CH_2), 59.8 (CH_2), 71.1 (CH_2), 79.2 (CH_2), 98.0, 107.0, 124.3 (CH), 125.5 (CH), 128.5 (CH), 141.0, 143.9 (CH), 154.0, 154.2, 171.4; HRMS: $C_{20}H_{24}N_2O_4Na$ calcd 379.4151 $[M+Na]^+$, found 379.4149.

4.18. 3-*N*-(2-Hydroxy-ethoxymethyl)-6-phenyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (21c)

The title compound was prepared from **20c** in an analogous manner to the preparation of **9a** in a 95% yield as a white solid; mp (MeOH) 205–207 °C (dec); ^1H NMR (DMSO-d_6, 80 °C): δ 3.50–3.72 (m, 4H), 4.37–4.54 (br s, 1H), 5.41 (s, 2H), 7.19 (s, 1H), 7.40–7.90 (m, 5H), 8.58 (s, 1H); ^{13}C NMR (DMSO-d_6, 80 °C): δ 61.1 (CH_2), 72.4 (CH_2), 80.5 (CH_2), 100.1, 108.1, 125.5 (CH), 129.3 (CH), 129.9 (CH), 130.3, 142.7, 155.0 (CH), 162.1, 172.7; HRMS: $C_{15}H_{14}N_2O_4Na$ calcd 309.2796 $[M+Na]^+$, found 309.2795.

4.19. 3-*N*-(2-Hydroxy-ethoxymethyl)-6-pentyl-2,3-dihydrofuro[2,3-*d*]pyrimidin-2one (21d)

The title compound was prepared from **20d** in an analogous manner to the preparation of **9a** in a 94% yield as a white solid; mp (MeOH) 104–106 °C; ^1H NMR (CD_3 OD): δ 0.82–0.92 (m, 3H), 1.20–1.66 (m, 6H), 2.63 (t, 2H, $J = 7.7$ Hz), 3.44–3.61 (m, 4H), 4.69 (t, 1H, $J = 5.2$ Hz), 5.35 (s, 2H), 6.43 (s, 1H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8 (CH_3), 21.8, 26.0, 27.3 and 30.6 (4 × CH_2), 60.0 (CH_2), 71.2 (CH_2), 79.4 (CH_2), 99.6, 106.8, 140.9, 154.8 (CH), 158.7, 171.9; HRMS: $C_{14}H_{20}N_2O_4Na$ calcd 303.3163 $[M+Na]^+$, found 303.3165.

4.20. 3-[(*E*)-4,5-Dihydroxy-2-pentenyl]-6-octylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (23a)

The title compound was prepared from **22a** in an analogous manner to the preparation of **14a** in a 91% yield as a white solid; ^1H NMR (DMSO-d_6): δ 0.84 (t, 3H, $J = 6.3$ Hz), 1.18–1.39 (m, 10H), 1.52–1.65 (m, 2H), 2.62 (t, 2H, $J = 7.2$ Hz), 3.20–3.30 (m, 2H), 3.90–4.01 (m, 1H), 5.42 (d, 2H, $J = 4.8$ Hz), 4.60 (t, 1H, $J = 5.8$ Hz), 4.85 (d, 1H, $J = 4.8$ Hz), 5.65–5.85 (m, 2H), 6.42 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.7 (CH_3), 22.9 (CH_2), 27.1 (CH_2), 28.2 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 32.0 (CH_2), 52.3 (CH_2), 66.5 (CH_2), 72.1 (CH), 100.2 (CH), 107.2, 124.8 (CH),136.7 (CH), 142.2 (CH), 155.2, 159.0, 172.1; HRMS: $C_{19}H_{28}N_2O_4Na$ calcd 371.1947, found 371.1947.

4.21. 3-[(*E*)-4,5-Dihydroxy-2-pentenyl]-6-(4-pentylphenyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (23b)

The title compound was prepared from **22b** in analogous manner to the preparation of **14a** in the yield 95% as a pale yellow solid; mp (MeOH) 227–229 °C; ^1H NMR (DMSO-d_6): δ 0.85 (t, 3H, $J = 7.1$ Hz), 1.20–1.32 (m, 4H), 1.51–1.63 (m, 2H), 2.61 (t, 2H, $J = 7.5$ Hz), 3.25–3.32 (m, 2H), 3.91–4.03 (m, 1H), 4.56 (d, 2H, $J = 4.8$ Hz), 4.63 (t, 1H, $J = 6.0$ Hz), 4.89 (d, 1H, $J = 5.0$ Hz), 5.75–5.85 (m, 2H), 7.21 (s, 1H), 7.31 (d, 2H, $J = 8.1$ Hz), 7.72 (d, 2H, $J = 8.1$ Hz), 8.59 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 22.0 (CH_2), 30.4 (CH_2), 30.9 (CH_2), 34.9 (CH_2), 48.6 (CH_2), 65.7 (CH_2), 71.4 (CH), 98.5 (CH), 107.0, 124.0 (CH), 124.6 (CH × 2), 126.0, 129.0 (CH × 2), 136.1 (CH), 142.6 (CH), 144.1, 153.8, 154.4, 171.1; HRMS: $C_{22}H_{26}N_2O_4$-Na calcd 405.1790, found 405.1795.

4.22. General synthesis of 6-alkylfuro[2,3-*d*]pyrimidine acyclonucleosides (24a) and (24b)

5-Alkynyl-acyclonucleoside (0.5 mmol) was dissolved in 5 mL acetone. $AgNO_3$ (17 mg, 0.2 equiv) was added and

the reaction mixture stirred in the dark until completion. Solvents were removed in vacuo and the residue was dissolved in CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (2 × 5 mL) and brine (5 mL) then dried over $MgSO_4$ and concentrated in vacuo. The residue was then stirred at room temperature for 3 h in a 2:1 mixture of TFA/H_2O (15 mL). After evaporation of volatiles, the crude was purified by flash chromatography (CH_2Cl_2/MeOH, 92:8).

4.22.1. 3-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-6-octylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (24a). Yield 98%, pale white gum; ^{1}H NMR (DMSO-d_6): δ 0.78–8.89 (m, 3H), 1.18–1.38 (m, 10H), 1.55–1.67 (m, 2H), 2.63 (t, 2H, J = 7.0 Hz), 3.95 (d, 2H, J = 4.8 Hz), 4.07 (d, 2H, J = 5.0 Hz), 4.65 (d, 2H, J = 7.1 Hz), 4.75–4.85 (m, OH × 2), 5.51 (t, 1H, J = 7.1 Hz), 6.42 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 18.8 (CH_2), 22.1 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 28.4 (CH_2), 28.6 (CH_2), 31.2 (CH_2), 47.5 (CH_2), 57.1 (CH_2), 62.5 (CH_2), 99.5 (CH), 106.5, 118.8 (CH), 141.52, 145.0 (CH), 154.6, 158.2, 171.2; HRMS: $C_{19}H_{28}N_2O_4Na$ calcd 371.1947, found 371.1949.

4.22.2. 3-[4-Hydroxy-3-(hydroxymethyl)-2-butenyl]-6-(4-pentylphenyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (24b). Yield 95%, pale white gum; ^{1}H NMR (DMSO-d_6): δ 0.85 (t, 3H, J = 6.5 Hz), 1.18–1.33 (m, CH_2 × 2), 1.51–1.68 (m, CH_2), 2.61 (t, CH_2, J = 7.2 Hz), 3.97 (s, CH_2), 4.10 (s, CH_2), 4.70 (d, CH_2, J = 7.2 Hz), 5.56 (t, 1H, J = 7.2 Hz), 7.20 (s, 1H), 7.32 (d, 2H, J = 8.1 Hz), 7.73 (d, 2H, J = 8.1 Hz), 8.60 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.9 (CH_3), 21.9 (CH_2), 30.4 (CH_2), 30.8 (CH_2), 34.9 (CH_2), 47.8 (CH_2), 57.1 (CH_2), 98.4 (CH), 107.0, 118.7 (CH), 124.5 (CH × 2), 125.9, 129.0 (CH × 2), 142.6 (CH), 144.1, 145.2, 153.8, 154.6, 171.0; HRMS: $C_{22}H_{26}N_2O_4Na$ calcd 405.1790, found 405.1790.

4.23. Antiviral and cytotoxicity assays for HIV-1 and HBV

Antiviral and cytotoxicity assays were conducted as described recently by Stuyver et al.[17] HIV assays were performed in activated primary human peripheral blood mononuclear (PBM) cells.

4.24. Antiviral and cytotoxicity assays for HSV

The newly synthesized nucleosides were evaluated for activity against HSV-1 (strain F) by plaque reduction assay in Vero cells using methodologies described previously.[18] Cytotoxicity assays were conducted in rapidly dividing Vero cells as previously described.[16] The median effective concentration was determined by the median effect method.

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