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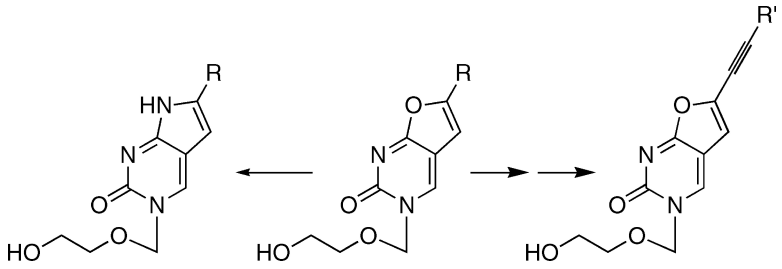

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Synthesis and Biological Evaluation of Acyclic 3-[(2-Hydroxyethoxy)methyl] Analogues of Antiviral Furo- and Pyrrolo[2,3-*d*]pyrimidine Nucleosides[1]

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The remarkably potent and specific activity against varicella-zoster virus (VZV) shown by 2′-deoxynucleosides of furo[2,3-*d*]pyrimidin-2(3*H*)-one and related ring systems is dependent on key structural features including the length and nature of the side-chain at C6 and the structure and stereochemistry of the sugar moiety at N3. Removal of the 3′-hydroxyl group from potent anti-VZV 2′-deoxynucleosides results in loss of the VZV activity, but such 2′,3′-dideoxynucleoside analogues have shown anti-HCMV activity. We now report acyclic analogues with comparable side-chains at C6, but with the sugar moiety at N3 replaced with the (2-hydroxyethoxy)methyl group (present in the antiherpes drug acyclovir). Examples of both furo[2,3-*d*]- and pyrrolo-[2,3-*d*]pyrimidin-2(3*H*)-one acyclic analogues were prepared and evaluated in a number of virus-infected cells and in tumor cell cultures. Certain of the long-chain analogues showed activity against VZV and HCMV. No significant activity against other DNA and RNA virus replication or against tumor cell proliferation was observed.

Introduction

In 1981, Robins and Barr[2a] reported that base and nucleoside derivatives of furo[2,3-*d*]pyrimidin-2(3*H*)-one (Figure 1) were produced as fluorescent byproducts (∼10%) of Sonogashira couplings of 5-iodo-1-methyluracil and 5-iodo-3′,5′-di-*O*-acetyl-2′-deoxyuridine with terminal alkynes. We described the efficient formation of 6-butyl-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)furo-[2,3-*d*]pyrimidin-2(3*H*)-one (82%) upon heating 5-(hexyn-1-yl)-2′-deoxyuridine in CuI/Et_3N/MeOH and assumed that Cu(I)-catalyzed 5-endo-dig cyclization was the mode of formation of these compounds.[2] Antiviral activity[3a] and inhibition of thymidylate synthase[4] were observed with 5-(alkyn-1-yl)uracil nucleoside analogues. Inhibition of incorporation of thymidine and 2′-deoxyuridine into primary rabbit kidney DNA was found with the bicyclic 6-butylfuro[2,3-*d*]pyrimidin-2(3*H*)one 2′-deoxynucleoside, but no antiviral activity was observed with that compound.[3b] Two decades later, the remarkably potent and specific activity against varicella-zoster virus (VZV) was discovered with analogues that had longer alkyl chains at C6.[5]

Potent inhibitory activity against herpes simplex virus type 1 (HSV-1), HSV-2, and vaccinia virus (VV) was observed with 5-ethynyl-2′-deoxyuridine. Other 5-(alkyn-1-yl)uracil nucleosides with short alkynyl chains also had activity, but none exhibited sufficient potency and selectivity for development as antiviral agents.[3] SAR studies of McGuigan, Balzarini, De Clercq, and their co-workers have shown that the length of the alkyl chain at C6 of the furopyrimidine analogues plays a crucial role in the anti-VZV potency. Compounds with shorter alkyl chains (≤C_6) had little or no activity, those with C_7 or C_{11} had moderate activity, and those with C_8 to C_{10} chains had the highest potency.[6] The latter compounds displayed minimal cytotoxicity and were ∼300-fold more active against VZV than the reference drug acyclovir. In contrast, no meaningful activity against HSV-1, HSV-2, VV, and HCMV was observed with these lead compounds.[5,6]

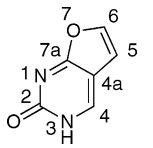

Figure 1. Furo[2,3-*d*]pyrimidin-2(3*H*)-one.

Other SAR studies have involved modifications of the lipophilic chain at C6 of such bicyclic nucleoside analogues (BCNAs). Substitution with F, Cl, Br, or I at the terminal carbon of a nonyl side-chain resulted in retention of anti-VZV activity,[7] and insertion of a (para-oriented) phenyl group into a side-chain of appropriate length gave a significant enhancement of the anti-VZV potency.[8] Analogues with ether- or glycol-containing side-chains had improved water solubility but reduced antiviral activity.[9] Substitution with other (aryl-, phenoxy-, or thiophenoxy)alkyl groups resulted in reduction of the in vitro anti-VZV potencies to levels comparable with that of acyclovir.[10] Terminal alkenyl derivatives retained reasonable anti-VZV potency, whereas those with a terminal alkyne function had poor activity.[11]

The role of the heteroatom (N, O, or S) in the fused ring (7-position) of the bicyclic compounds also was probed. Pyrrolo[2,3-*d*]pyrimidin-2-one analogues (including 7-alkyl derivatives) of the active furo[2,3-*d*]-pyrimidin-2-ones were 20- to 100-fold less potent,[12] but the corresponding thieno[2,3-*d*]pyrimidin-2-ones retained high anti-VZV activity.[13]

Thus, major attention has been focused on successful modifications of the lipophilic side-chain at C6 and the

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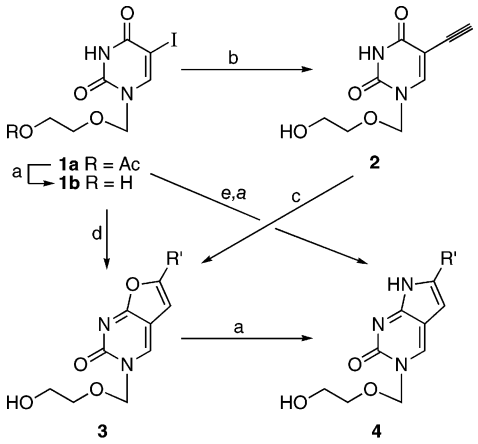
Scheme 1[a]



3 and **4**: **a**, R' = H; **b**, R' = C_4H_9; **c**, R' = C_5H_{11}; **d**, R' = C_6H_{13}; **e**, R' = C_7H_{15}; **f**, R' = C_8H_{17}; **g**, R' = C_9H_{19}; **h**, R' = $C_{10}H_{21}$; **i**, R' = $C_{11}H_{23}$;

[a] Reagents and conditions: (a) NH_3/MeOH/(Δ); (b) (i) TMSA/$Pd(PPh_3)_4$/CuI/Et_3N/DMF/Δ, (ii) TBAF/THF; (c) CuI/Et_3N/DMF/Δ; (d) 1-Alkyne/$Pd(PPh_3)_4$/CuI/Et_3N/DMF/Δ; (e) 1-alkyne/$Pd(PPh_3)_4$/CuI/Et_3N/EtOAc/Δ.

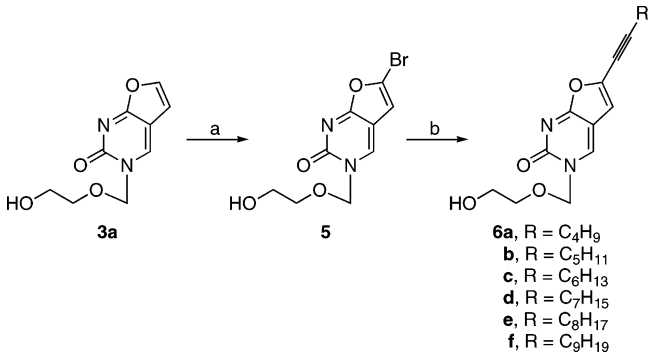
fused-ring heteroatom. In contrast, ribo and arabino nucleoside analogues and those with modifications of the sugar moiety (methylation of the 2′-deoxynucleoside at O3′, inversion at C3′ to give the 2′-deoxy *threo* analogue, and chlorination at C3′ or C5′) did not have potent anti-VZV activity.[6a]

Our observation of anti-HCMV activity with 6-(alkyn-1-yl)-3-alkylfuro[2,3-*d*]pyrimidin-2(3*H*)-one derivatives[14] suggested that a more systematic study of substituents at N3 could be promising. It was recently reported that 2′,3′-dideoxynucleoside analogues with alkyl groups at C6 have anti-HCMV activity,[15] and they also function by a "nonnucleoside" mechanism [i.e., activation by nucleoside kinase(s) is not required]. We now report the synthesis and biological evaluation of 3-[(2-hydroxyethoxy)methyl]furo- and pyrrolo[2,3-*d*]pyrimidin-2(3*H*)-one analogues of antivirally active nucleoside derivatives.[16] These new compounds combine the bicyclic heterobases of anti-VZV nucleosides and the acyclic sugar surrogate of the anti-HSV drug acyclovir.

Results and Discussion

Chemistry. Several methods have been developed for efficient syntheses of heterocyclic acyclonucleoside analogues.[17,18] We used the procedures of Robins and Hatfield[18] for the preparation of 1-[(2-acetoxyethoxy)-methyl]-5-iodouracil (**1a**) and its deacetylated product **1b**. Treatment of **1b** with trimethylsilylacetylene (TMSA) under the Sonogashira coupling conditions, followed by removal of the TMS group with tetrabutylammonium fluoride (TBAF), gave 5-ethynyl-1-[(2-hydroxyethoxy)-methyl]uracil (**2**, 80%) (Scheme 1). Cyclization of **2** with CuI/Et_3N in DMF gave the parent fused-ring product **3a** (20%). Such Cu(I)-promoted cyclizations can be executed in situ or performed after purification of the coupled 5-(alkyn-1-yl)uracils. Recent applications of both approaches have provided 6-alkylfuro[2,3-*d*]pyrimidin-2-ones in ∼30% yields.[19,20] Treatment of 3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one (**3a**) with hot methanolic ammonia gave 3-[(2-hydroxyethoxy)-methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*)-one (**4a**) (60%).

Scheme 2[a]



[a] Reagents and conditions: (a) Br_2/KOAc/CH_2Cl_2/DMF/0 °C; (b) 1-alkyne/$Pd(PPh_3)_4$/CuI/Et_3N/DMF.

The 6-alkyl-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-ones **3** were prepared by the sequential in situ procedure. Treatment of **1b** with the terminal alkynes (1.2 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and CuI (1 equiv) in Et_3N/DMF (1:20) at 70 °C gave the cyclized products **3** in 51−83% yields. Clearly, 1-substituted-5-(alkyn-1-yl)uracil derivatives cyclize much more readily than analogues with hydrogen at N1.[20]

Treatment of the furanopyrimidine compounds **3** with hot methanolic ammonia[12] gave the corresponding 6-alkyl-3-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*, 7*H*)-ones **4** in 53−84% yields. Other pyrrolo analogues were prepared from the acetylated 5-iodouracil derivative **1a** by the one-pot coupling and in situ cyclization procedure with EtOAc as solvent at 60 °C, followed by column chromatography and treatment with NH_3/MeOH (concomitant deacetylation and fused-ring transformation from the furano to pyrrolo analogues) in yields of 30−53% (**1a** → **4**, overall).

As noted, the most potent of the furanopyrimidine derivatives against VZV are the 6-(4-alkylphenyl)furo-[2,3-*d*]pyrimidin-2-one 2′-deoxynucleosides with a *p*-alkylphenyl ring at C6.[8] We had decided to probe antiviral effects of the formal replacement of the *p*-alkylphenyl ring by alkyl-substituted acetylenes.[14a] An ethynyl moiety is rigid and can function as a π-donor analogous to a phenyl ring. McGuigan and co-workers had prepared the latter analogues by application of our Cu(I)-mediated cyclization[2] of 5-[(4-alkylphenyl)ethynyl]-2′-deoxyuridine derivatives.[8] However, this approach is not applicable for direct introduction of substituted-alkynyl groups at C6 because a 1,3-diyne substituent (difficult accessibility and questionable stability) would be required at C5 of a 2′-deoxyuridine precursor.

Bromination at C6 of the furan ring[14a] of **3a** (Scheme 2) (TLC showed complete conversion) afforded 6-bromo-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2-one (**5**) (47%). The instability of **5** during workup resulted in its isolation in moderate yields, and attempted recrystallization of **5** (hot MeOH) caused extensive decomposition.

Sonogashira coupling of **5** with terminal alkynes under our standard conditions [$Pd(PPh_3)_4$/CuI/Et_3N/DMF] gave the corresponding 6-(alkyn-1-yl) derivatives **6** (41−77%). Treatment of **6c** and **6e** with NH_3/MeOH resulted in decomposition of the starting materials. A major new fluorescent spot (TLC) for the targeted

Table 1. Antiviral and Cytostatic Activity of the Test Compounds in Cell Cultures

	EC_{50}[a] (μM)											
			VZV		HCMV							
compd	HIV-1 (III_B) (CEM)	HIV-2 (ROD) (CEM)	(OKA) (HEL)	(07/1) (HEL)	AD169 (HEL)	Davis (HEL)	HSV-1 (HEL)	HSV-2 (HEL)	VV (HEL)	VSV (HEL)	MCC[b](μM) (HEL)	CC_{50}[c](μM) (HEL)
2	>250	>250	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200
3a	>250	>250	>100	>400	>400	>400	>400	>400	>400	>400	>400	>200
3b	>250	>250	≥100	>400	>400	>400	>400	>400	>400	>400	>400	>200
3c	>50	>250	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200
3d	>50	>50	173	151	>80	>80	>16	>16	>16	>16	≥400	>200
3e	>50	>50	>80	>80	>80	>80	>200	>200	>200	>200	400	140
3f	>50	>50	11	>16	31	10	>16	>16	>16	>16	≥80	>200
3g	>250	>250	41	10	>400	>400	>200	>200	>200	>200	≥16	≥100
3h	>250	>250	>80	>80	>400	>80	>16	>16	>16	>16	400	>200
3i	>250	>250	>16	>16	>16	>16	>40	>40	>40	>40	80	132
4a	>250	>250	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200
4b	>250	>250	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200
4c	>250	>250	>400	>400	>400	>400	>400	>400	>400	>400	>400	>200
4d	>50	>50	206	151	400	253	>80	>80	>80	>80	>400	>200
4e	>250	>250	149	156	>400	400	>200	>200	>200	>200	≥400	119
4f	>50	>50	>16	>16	>16	>16	>80	>80	>80	>80	80	65
4g	>50	>50	>16	>16	>16	>16	>80	>80	>80	>80	80	ND[d]
4h	>10	>10	6.4	5.8	5.1	1.8	>16	>16	>16	>16	80	32
4i	>10	>10	16	10	>16	>16	>40	>40	>40	>40	80	41
6a	>50	>50	>50	>50	>100	>100	>200	>200	>200	>200	>100	>50
6b	>50	>50	>50	>50	>20	58	>200	>200	>200	>200	≥100	>50
6c	>50	>10	100	100	40	>20	>200	>200	>200	>200	>200	>50
6d	>10	>10	>20	>20	>20	>20	>40	>40	>40	>40	200	>50
6e	>10	>10	>5	8.5	>4	5.2	>40	>40	>40	>40	≥20	42
6f	>10	>10	2.6	7.1	>4	5.2	>40	>40	>40	>40	≥20	>50
GCV	>50	>50	–	–	5.1	2.5	0.032	0.032	>100	>100	>100	130
CDV	>50	>50	–	–	0.47	0.79	–	–	–	–	>400	63
BVDU	>50	>50	0.03	108	>100	>100	0.16	300	60	>500	>400	≥400

[a] 50% Effective concentration, or compound concentration required to inhibit virus-induced cytopathogenicity or plaque formation (VZV) by 50%. [b] Minimum cytotoxic concentration, or compound concentration required to cause a microscopically visible alteration of cell morphology. [c] 50% Cytostatic concentration, or compound concentration required to inhibit cell proliferation by 50%. [d] Not determined.

6-(alkyn-1-yl)pyrrolo[2,3-*d*]pyrimidin-2-one derivatives was not observed.

Biological Evaluations. The compounds were evaluated against herpesviruses including HSV-1, HSV-2, VZV, and HCMV, and also against vaccinia virus (VV), HIV-1, HIV-2, and vesicular stomatitis virus (VSV) in cell cultures. The 5-ethynyl compound **2** was devoid of antiviral activity. Only the **3f** (octyl) and **3g** (nonyl) acyclic furo[2,3-*d*]pyrimidin-2(3*H*)-one derivatives showed marginal anti-VZV activity (EC_{50}: 10−41 μM). Compound **3f** also showed weak anti-HCMV activity (EC_{50}: 10−31 μM). Little or no cytotoxicity and no significant cytostatic effects on proliferation of HEL cells was observed with compounds **3b**−**e** (C_4−C_7 alkyl chains at C6) or **3f**−**i** (C_8−C_{11}) (Table 1). These compounds were poorly cytostatic against murine leukemia L1210, human mammary carcinoma FM3A, human lymphocyte CEM, and human cervix carcinoma HeLa cells (IC_{50}: 32 to >500 μM) (data not shown). The series **3** compounds were not inhibitory to other DNA viruses, HIV, or other RNA viruses evaluated [VSV, Coxsackie B4, and respiratory syncytial virus (RSV) in HeLa cell cultures; parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 virus, and Punta Toro virus in Vero cell cultures] (data not shown).

Similar trends were observed with the pyrrolo derivatives **4**. No anti-VZV/HCMV activity was seen with the shorter-chain 6-alkyl derivatives, and the longer-chain analogues showed weak anti-VZV/HCMV activity. Compound **4h** (decyl) was most inhibitory against VZV (5.8−6.4 μM) and HCMV (1.8−5.1 μM) but not inhibitory against the other viruses investigated. There also was a trend toward increased cytotoxic potency with the longer-chain compounds (**4f**−**i**).

The 6-(alkyn-1-yl)-substituted furo compounds (**6** series) were also evaluated. Compounds **6e** (decyn-1-yl) and **6f** (undecyn-1-yl) showed selective activity against VZV (EC_{50}: 2.6−8.5 μM) and HCMV (5.2 μM) but not against the other herpesviruses (HSV-1 and HSV-2), vaccinia virus, VSV, HIV-1, or HIV-2.

Compounds **3f**, **3g**, **4h**, **4i**, **6e**, and **6f** are 4 to 5 orders of magnitude less potent against VZV than the most active *bic*yclic furanopyrimidine *n*ucleoside *a*nalogues (BCNAs).[9] All of those highly potent and selective BCNAs contain an intact 2-deoxy-β-D-*erythro*-pentofuranosyl moiety at N3 of the furo[2,3-*d*]pyrimidin-2(3*H*)-one ring, whereas the **3**, **4**, and **6** series of compounds have a 2-(hydroxyethoxy)methyl group (present in acyclovir) at N3. This acyclic surrogate failed to maintain the marked anti-VZV activity, but it is noteworthy that the compounds that showed activity against VZV (OKA) also were active against its TK-deficient VZV (07/1) mutant—and also against HCMV. This suggests another mechanism of antiviral activity, which is different from that found with the nucleoside analogues. The activity retained against VZV TK^- emphasizes the lack of a prominent role of the viral TK for antiviral activity. Comparable activities of the compounds against VZV and HCMV might indicate a common mechanism of action. Recent studies on some BCNAs as inhibitors of HCMV (and in some cases also of VZV) suggest interference with virus entry as the target site for these compounds.[15]

Summary and Conclusions

Acyclic analogues of antiviral furano- and pyrrolopyrimidine nucleosides were synthesized for SAR studies. Sonogashira coupling of terminal alkynes with 1-[(2-hydroxyethoxy)methyl]-5-iodouracil (**1b**) and Cu(I)-promoted in situ cyclization gave the 6-alkyl-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-ones **3** in good yields. Pyrrolopyrimidine analogues **4** were prepared directly from the furano derivatives **3** by treatment with NH_3/MeOH or by sequential Sonogashira coupling of the terminal alkynes and 1-[(2-acetoxyethoxy)methyl]-5-iodouracil (**1a**) and in situ cyclization, followed by treatment of the acetylated furano intermediates with NH_3/MeOH. Bromination of **3a** followed by coupling with 1-alkynes gave the 6-(alkyn-1-yl)furo[2,3-*d*]pyrimidin-2-one analogues **6**. Decomposition, rather than transformation into pyrrolopyrimidine derivatives, occurred upon treatment of **6** with NH_3/MeOH. Compounds **3f** and **3g** showed weak anti-VZV/HCMV activity (EC_{50}: 10−41 μM), **4h** and **4i** at EC_{50}: 1.8−16 μM, and **6e** and **6f** at EC_{50}: 2.6−8.5 μM in HEL cell cultures. None of the compounds showed significant antiviral activity against other DNA and RNA viruses or cytotoxic/cytostatic effects in these cells.

Experimental Section

Uncorrected melting points were determined with a hot-stage apparatus. UV spectra were measured with solutions in MeOH. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were determined with solutions in DMSO-d_6 unless otherwise indicated. "Apparent" peak shapes are in quotation marks when the first-order splitting should be more complex or when the peaks were poorly resolved. Several ^{1}H and ^{13}C NMR spectra of especially lipophilic compounds were measured at an elevated probe temperature (50 °C) because of their limited solubility in DMSO-d_6. High-resolution mass spectra (HRMS) were determined with FAB (thioglycerol, NaOAc) unless otherwise indicated. Chemicals and solvents were of reagent quality. Column chromatography (silica gel, 230−400 mesh) was performed with 5% MeOH/CH_2Cl_2 unless otherwise indicated. Experimental procedures are described in detail for the preparation of one compound, and characterization data are provided for all target compounds. Method 1 [**1b**/1-alkyne/$Pd(PPh_3)_4$/CuI/Et_3N/DMF] is described for **1b** → **3b**; method 2 [(a) **1a**/1-alkyne/$P(PPh_3)_4$/CuI/Et_3N/EtOAc, (b) NH_3/MeOH] for **1a** → **4b**; method 3 (**3**/NH_3/MeOH) for **3e** → **4e**; and method 4 [**5**/1-alkyne/$P(PPh_3)_4$/CuI/Et_3N/DMF] for **5** → **6a**.

5-Ethynyl-1-[(2-hydroxyethoxy)methyl]uracil (2). TMSA (0.59 mL, 409 mg, 4.16 mmol) and then Et_3N (4 mL) were added to a suspension of **1b** (1.0 g, 3.2 mmol), $Pd(PPh_3)_4$ (186 mg, 0.16 mmol), and CuI (49 mg, 0.26 mmol) in deoxygenated DMF (20 mL). The reaction mixture was sealed in a pressure tube and stirred at 60 °C for 4 h. TLC (10% MeOH/CH_2Cl_2) showed complete conversion to a faster-migrating product. Volatiles were evaporated, and toluene was added and evaporated (2 × 5 mL). The residue was chromatographed to give a slightly yellow solid, which was dissolved in THF (50 mL). TBAF/THF (1 M, 3.2 mL) was added, and the reaction mixture was stirred at ambient temperature for 30 min. Volatiles were evaporated, and the residue was chromatographed and recrystallized (EtOAc/EtOH, 1:1) to give slightly yellow crystals of **2**: mp 149−150 °C; UV max 285, 224 nm (ϵ 11 700, 11 200); ^{1}H NMR δ 3.46−3.49 (m, 2H), 3.51−3.53 (m, 2H), 4.12 (s, 1H), 4.68 (t, J = 5.1 Hz, 1H), 5.10 (s, 2H), 8.17 (s, 1H), 11.66 (s, 1H); ^{13}C NMR δ 162.1, 150.1, 149.0, 97.4, 83.8, 76.9, 76.0, 70.8, 60.0; HRMS *m/z* 211.0707 (MH^+ [$C_9H_{11}N_2O_4$] = 211.0719). Anal. ($C_9H_{10}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one (3a). A mixture of **2** (600 mg, 2.85 mmol), CuI (543 mg, 2.85 mmol), and Et_3N (6 mL) in DMF (50 mL) was stirred at 80 °C for 12 h. Volatiles were evaporated, and toluene was added and evaporated (2 × 10 mL). The residue was extracted with hot MeOH (50 mL), and the solid was filtered. Volatiles were evaporated from the filtrate, and the residue was chromatographed and recrystallized (EtOAc/EtOH, 1:1) to give slightly yellow crystals of **3a**: mp 148 °C; UV max 329, 241 nm (ϵ 6800, 11 400); ^{1}H NMR δ 3.48−3.51 (m, 2H), 3.57−3.59 (m, 2H), 4.69 (t, J = 5.4 Hz, 1H), 5.38 (s, 2H), 6.81 (d, J = 2.9 Hz, 1H), 7.74 (d, J = 2.5 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR δ 171.9, 154.7, 145.1, 143.1, 105.13, 105.06, 79.5, 71.3, 60.0; HRMS (EI) *m/z* 210.0652 (M^+ [$C_9H_{10}N_2O_4$] = 210.0641). Anal. ($C_9H_{10}N_2O_4$) C, H, N.

6-Butyl-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(1*H*)-one (3b). Method 1. A stirred suspension of **1b** (312 mg, 1.0 mmol), $Pd(Ph_3P)_4$ (58 mg, 0.05 mmol), and CuI (190 mg, 1.0 mmol) in DMF (20 mL) was purged with N_2 at room temperature. 1-Hexyne (0.15 mL, 107 mg, 1.3 mmol) and then dried Et_3N (1 mL) were added, and the reaction mixture was stirred under N_2 at 70 °C for ∼8 h (TLC). Volatiles were evaporated, and toluene was added and evaporated (2 × 5 mL). The residue was extracted with hot MeOH (40 mL), and the solid was filtered and washed (MeOH). Volatiles were evaporated in vacuo from the combined filtrate, and the residue was chromatographed and recrystallized (MeOH, two crops) to give white crystals (146 mg, 55%). This material was recrystallized (EtOAc, 80% recovery) to give **3b**: mp 122 °C; UV max 332, 245 nm (ϵ 6100, 12 400); ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3H), 1.33−1.37 (m, 2H), 1.60 ("quint", J = 7.4 Hz, 2H), 2.65 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.54−3.56 (m, 2H), 4.69 (t, J = 5.4 Hz, 1H), 5.35 (s, 2H), 6.45 (s, 1H), 8.46 (s, 1H); ^{13}C NMR δ 171.9, 158.7, 154.7, 140.9, 106.8, 99.5, 79.3, 71.1, 60.0, 28.4, 27.0, 21.5, 13.6; HRMS *m/z* 289.1174 (MNa^+ [$C_{13}H_{18}N_2O_4Na$] = 289.1164). Anal. ($C_{13}H_{18}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-pentylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (3c). Treatment of **1b** (312 mg, 1.0 mmol) with 1-heptyne (0.16 mL, 115 mg, 1.2 mmol) by method 1 gave **3c** (148 mg, 53%) as white crystals (EtOAc): mp 122 °C; UV max 333, 245 nm (ϵ 6100, 12 300); ^{1}H NMR δ 0.87 (t, J = 6.6 Hz, 3H), 1.30−1.34 (m, 4H), 1.60−1.63 (m, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.54−3.57 (m, 2H), 4.69 (t, J = 5.5 Hz, 1H), 5.35 (s, 2H), 6.44 (s, 1H), 8.46 (s, 1H); ^{13}C NMR δ 171.9, 158.7, 154.7, 140.9, 106.8, 99.6, 79.3, 71.1, 60.0, 30.6, 27.3, 26.0, 21.8, 13.8; HRMS *m/z* 281.1665 (MH^+ [$C_{14}H_{21}N_2O_4$] = 281.1501). Anal. ($C_{14}H_{20}N_2O_4$) C, H, N.

6-Hexyl-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one (3d). Treatment of **1b** (312 mg, 1.0 mmol) with 1-octyne (0.18 mL, 132 mg, 1.2 mmol) by method 1 gave **3d** (158 mg, 56%) as white crystals (EtOAc): mp 131 °C; UV max 332, 245 nm (ϵ 5500, 11 300); ^{1}H NMR δ 0.86 (t, J = 7.1 Hz, 3H), 1.26−1.34 (m, 6H), 1.61 ("quint", J = 7.4 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.54−3.57 (m, 2H), 4.69 (t, J = 5.5 Hz, 1H), 5.35 (s, 2H), 6.44 (s, 1H), 8.46 (s, 1H); ^{13}C NMR δ 171.9, 158.7, 154.7, 140.9, 106.8, 99.6, 79.3, 71.1, 60.0, 30.9, 28.0, 27.4, 26.3, 22.0, 13.9; HRMS *m/z* 317.1495 (MNa^+ [$C_{15}H_{22}N_2O_4Na$] = 317.1477). Anal. ($C_{15}H_{22}N_2O_4$) C, H, N.

6-Heptyl-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one (3e). Treatment of **1b** (500 mg, 1.6 mmol) with 1-nonyne (0.32 mL, 239 mg, 1.9 mmol) by method 1 gave **3e** (410 mg, 83%) as white crystals (EtOAc): mp 134−135 °C; UV max 332, 245 nm (ϵ 6500, 13 100); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.26−1.32 (m, 8H), 1.61 ("quint", J = 7.2 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.55−3.57 (m, 2H), 4.67 (t, J = 5.4 Hz, 1H), 5.35 (s, 2H), 6.43 (s, 1H), 8.45 (s, 1H); ^{13}C NMR δ 171.8, 158.6, 154.7, 140.8, 106.8, 99.5, 79.3, 71.1, 60.0, 31.1, 28.3, 27.3, 26.3, 22.0, 13.9; HRMS (EI) *m/z* 308.1740 (M^+ [$C_{16}H_{24}N_2O_4$] = 308.1736). Anal. ($C_{16}H_{24}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-octylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (3f). Treatment of **1b** (312 mg, 1.0 mmol) with 1-decyne (0.22 mL, 166 mg, 1.2 mmol) by method 1 gave **3f** (225 mg, 70%) as white crystals (EtOAc): mp 140 °C; UV max 332, 245 nm (ϵ 5400, 11 300); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.24−1.30 (m, 10H), 1.60−1.62 (m, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.54−3.56 (m, 2H), 4.69 (t, J

= 5.4 Hz, 1H), 5.35 (s, 2H), 6.44 (s, 1H), 8.46 (s, 1H); ^{13}C NMR δ 171.9, 158.7, 154.7, 140.9, 106.8, 99.6, 79.3, 71.1, 60.0, 31.3, 28.62, 28.59, 28.4, 27.3, 26.3, 22.1, 14.0; HRMS *m/z* 345.1781 (MNa^+ [$C_{17}H_{26}N_2O_4Na$] = 345.1790). Anal. ($C_{17}H_{26}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-nonylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (3 g). Treatment of **1b** (624 mg, 2 mmol) with 1-undecyne (0.47 mL, 365 mg, 2.4 mmol) by method 1 gave **3g** (357 mg, 53%) as white crystals (EtOAc): mp 142 °C; UV max 332, 245 nm (ϵ 5300, 11 000); ^{1}H NMR (50 °C) δ 0.86 (t, J = 7.1 Hz, 3H), 1.26−1.36 (m, 12H), 1.63 ("quint", J = 7.3 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.49−3.52 (m, 2H), 3.57−3.59 (m, 2H), 4.56 (t, J = 5.6 Hz, 1H), 5.35 (s, 2H), 6.42 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (50 °C) δ 171.7, 158.5, 154.5, 140.3, 106.6, 99.2, 79.1, 71.0, 59.9, 31.0, 28.6, 28.4, 28.1, 27.2, 26.1. 21.8, 13.6; HRMS *m/z* 359.1948 (MNa^+ [$C_{18}H_{28}N_2O_4Na$] = 359.1947). Anal. ($C_{18}H_{28}N_2O_4$) C, H, N.

6-Decyl-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one (3h). Treatment of **1b** (500 g, 1.6 mmol) with 1-dodecyne (0.41 mL, 319 mg, 1.9 mmol) by method 1 gave **3h** (285 mg, 51%) as white crystals (EtOAc): mp 145 °C; UV max 332, 245 nm (ϵ 5700, 11 800); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.24−1.30 (m, 14H), 1.61 ("quint", J = 7.3 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.48−3.50 (m, 2H), 3.54−3.56 (m, 2H), 4.70 (t, J = 5.5 Hz, 1H), 5.35 (s, 2H), 6.44 (s, 1H), 8.46 (s, 1H); ^{13}C NMR (50 °C) δ 171.7, 158.5, 154.5, 140.3, 106.6, 99.2, 79.1, 71.0, 59.9, 31.0, 28.7, 28.4, 28.1, 27.2, 26.1. 21.8, 13.6; HRMS *m/z* 373.2099 (MNa^+ [$C_{19}H_{30}N_2O_4Na$] = 373.2103). Anal. ($C_{19}H_{30}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-undecylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (3i). Treatment of **1b** (624 g, 2.0 mmol) with 1-tridecyne (0.55 mL, 433 mg, 2.4 mmol) by method 1 gave **3i** (500 mg, 68%) as white crystals (EtOAc): mp 143−144 °C; UV max 332, 245 nm (ϵ 5300, 11 000); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.24−1.30 (m, 16H), 1.61 ("quint", J = 7.1 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.54−3.56 (m, 2H), 4.69 (t, J = 5.4 Hz, 1H), 5.35 (s, 2H), 6.44 (s, 1H), 8.46 (s, 1H); ^{13}C NMR (50 °C) δ 171.7, 158.5, 154.6, 140.6, 106.7, 99.4, 79.2, 71.1, 59.9, 31.1, 28.8, 28.7, 28.5, 28.2, 27.2, 26.2, 21.9, 13.8; HRMS *m/z* 387.2256 (MNa^+ [$C_{20}H_{32}N_2O_4Na$] = 387.2260). Anal. ($C_{20}H_{32}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4a). Treatment of **3a** (210 mg, 0.83 mmol) by method 3 gave **4a** (105 mg, 60%) as slightly yellow crystals (MeOH): mp >190 °C dec; UV max 345, 270 nm (ϵ 3200, 3500); ^{1}H NMR δ 3.47−3.50 (m, 2H), 3.54−3.56 (m, 2H), 4.68 (t, J = 5.4 Hz, 1H), 5.35 (s, 2H), 6.23 (d, J = 3.9 Hz, 1H), 7.11 (d, J = 3.9 Hz, 1H), 8.47 (s, 1H), 11.18 (s, 1H); ^{13}C NMR δ 159.7, 154.7, 141.1, 127.7, 108.3, 100.5, 79.2, 70.8, 60.0; HRMS (EI) *m/z* 209.0807 (M^+ [$C_9H_{11}N_3O_3$] = 209.0800). Anal. ($C_9H_{11}N_3O_3$) C, H, N.

6-Butyl-3-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4b). Method 2. A stirred suspension of **1a** (1.0 g, 2.8 mmol), $Pd(Ph_3P)_4$ (160 mg, 0.14 mmol), and CuI (533 mg, 2.8 mmol) in EtOAc (50 mL) was purged with N_2 at room temperature. 1-Hexyne (0.37 mL, 263 mg, 3.2 mmol) and then dried Et_3N (3 mL) were added, and the reaction mixture was stirred under N_2 at 60 °C for ∼15 h (TLC). The mixture was filtered while hot (filter paper), and the filter cake was washed with EtOAc. Volatiles were evaporated from the combined filtrate, and the residue was transferred into a pressure tube with CH_2Cl_2 (10 mL). NH_3/MeOH (20 mL, presaturated at 0 °C) was added, the tube was sealed, and the reaction mixture was stirred at 50 °C for 6 h. Volatiles were evaporated, and the residue was chromatographed and recrystallized (EtOAc) to give **4b** (395 mg, 53%) as slightly yellow crystals: mp 132 °C; UV max 347, 262 nm (ϵ 3600, 3800); ^{1}H NMR δ 0.88 (t, J = 7.3 Hz, 3H), 1.28−1.34 (m, 2H), 1.58 ("quint", J = ∼7.6 Hz, 2H), 2.51 (t, J = 7.6 Hz, 2H), 3.47−3.49 (m, 2H), 3.51−3.53 (m, 2H), 4.70 (t, J = 5.8 Hz, 1H), 5.32 (s, 2H), 5.91 (s, 1H), 8.26 (s, 1H), 11.14 (s, 1H); ^{13}C NMR δ 160.2, 154.8, 142.9, 138.8, 109.3, 96.2, 79.1, 70.7, 60.1, 29.6, 27.2, 21.7, 13.7; HRMS (EI) *m/z* 265.1431 (M^+ [$C_{13}H_{19}N_3O_3$] = 265.1426). Anal. ($C_{13}H_{19}N_3O_3$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-pentylpyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4c). Treatment of **1a** (1.0 g, 2.8 mmol) with 1-heptyne (0.44 mL, 323 mg, 3.4 mmol) by method 2 gave **4c** (234 mg, 30%) as white crystals (EtOAc): mp 158−160 °C; UV max 348, 262 nm (ϵ 3700, 3800); ^{1}H NMR δ 0.87 (t, J = 6.8 Hz, 3H), 1.28−1.32 (m, 4H), 1.61 ("quint", J = ∼7.2 Hz, 2H), 2.52 (t, J = 7.6 Hz, 2H), 3.48−3.50 (m, 2H), 3.53−3.55 (m, 2H), 4.70 (t, J = 5.6 Hz, 1H), 5.34 (s, 2H), 5.92 (s, 1H), 8.27 (s, 1H), 11.15 (s, 1H); ^{13}C NMR δ 160.3, 154.8, 142.9, 138.7, 109.2, 96.1, 79.1, 70.7, 60.1, 30.8, 27.5, 27.2, 21.8, 13.9; HRMS *m/z* 280.1661 (MH^+ [$C_{14}H_{22}N_3O_3$] = 280.1661). Anal. ($C_{14}H_{21}N_3O_3$) C, H, N.

6-Hexyl-3-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4d). Treatment of **1a** (1.0 g, 2.8 mmol) with 1-octyne (0.53 mL, 397 mg, 3.4 mmol) by method 2 gave **4d** (286 mg, 35%) as white crystals (EtOAc): mp 155−156 °C; UV max 348, 262 nm (ϵ 3800, 4000); ^{1}H NMR δ 0.86 (t, J = 6.6 Hz, 3H), 1.28−1.31 (m, 6H), 1.60 ("quint", J = ∼6.8 Hz, 2H), 2.52 (t, J = 7.6 Hz, 2H), 3.47−3.50 (m, 2H), 3.53−3.55 (m, 2H), 4.70 (t, J = 5.8 Hz, 1H), 5.34 (s, 2H), 5.92 (s, 1H), 8.27 (s, 1H), 11.14 (s, 1H); ^{13}C NMR δ 160.2, 154.8, 142.9, 138.7, 109.2, 96.1, 79.1, 70.7, 60.1, 30.1, 28.2, 27.5, 27.4, 22.0, 13.9; HRMS *m/z* 316.1639 (MNa^+ [$C_{15}H_{23}N_3O_3Na$] = 316.1637). Anal. ($C_{15}H_{23}N_3O_3$) C, H, N.

6-Heptyl-3-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4e). Method 3. A stirred mixture of **3e** (100 mg, 0.32 mmol) in NH_3/MeOH (8 mL, presaturated at 0 °C) in a pressure tube was heated at 70 °C for 7 h. Volatiles were evaporated, and the residue was chromatographed and crystallized (EtOAc) to give **4e** (74 mg, 74%) as slightly yellow crystals: mp 159−160 °C; UV max 348, 263 nm (ϵ 3800, 4000); ^{1}H NMR δ 0.86 (t, J = 6.8 Hz, 3H), 1.25−1.29 (m, 8H), 1.59−1.62 (m, 2H), 2.52 (t, J = 7.3 Hz, 2H), 3.46−3.50 (m, 2H), 3.52−3.54 (m, 2H); 4.69 (t, J = 5.6 Hz, 1H), 5.33 (s, 2H), 5.91 (s, 1H), 8.26 (s, 1H), 11.13 (bs, 1H); ^{13}C NMR δ 160.3, 154.8, 142.9, 138.7, 109.2, 96.1, 79.1, 70.7, 60.1, 31.2, 28.5, 28.4, 27.5, 22.1, 14.0; HRMS *m/z* 330.1791 (MNa^+ [$C_{16}H_{25}N_3O_3Na$] = 330.1794). Anal. ($C_{16}H_{25}N_3O_3$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-octylpyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4f). Treatment of **1a** (1.0 g, 2.8 mmol) with 1-decyne (0.61 mL, 465 mg, 3.4 mmol) by method 2 gave **4f** (322 mg, 36%) as white crystals (EtOAc): mp 140−142 °C; UV max 347, 262 nm (ϵ 4100, 4200); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.25−1.29 (m, 10H), 1.60 ("quint", J = ∼7.2 Hz, 2H), 2.52 (t, J = 7.3 Hz, 2H), 3.47−3.50 (m, 2H), 3.53−3.55 (m, 2H), 4.67 (t, J = 5.4 Hz, 1H), 5.33 (s, 2H), 5.91 (s, 1H), 8.26 (s, 1H), 11.11 (s, 1H); ^{13}C NMR δ 160.2, 154.8, 142.9, 138.7, 109.2, 96.1, 79.0, 70.7, 60.0, 31.2, 28.7, 28.6, 28.5, 27.4, 22.0, 13.9; HRMS (EI) *m/z* 321.2046 (M^+ [$C_{17}H_{27}N_3O_3$] = 321.2052). Anal. ($C_{17}H_{27}N_3O_3$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-nonylpyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4g). Treatment of **3g** (200 mg, 0.59 mmol) by method 3 gave **4g** (144 mg, 72%) as white crystals (EtOAc): mp 149 °C; UV max 348, 262 nm (ϵ 4000, 4200); ^{1}H NMR δ 0.84 (t, J = 6.8 Hz, 3H), 1.23−1.28 (m, 12H), 1.59−1.61 (m, 2H), 2.51−2.53 (m, 2H), 3.47−3.50 (m, 2H), 3.52−3.54 (m, 2H), 4.67 (t, J = 5.4, 1H), 5.32 (s, 2H), 5.90 (s, 1H), 8.25 (s, 1H), 11.10 (s, 1H); ^{13}C NMR δ 160.2, 154.8, 142.9, 138.7, 109.2, 96.1, 79.0, 70.7, 60.0, 31.3, 28.9, 28.71, 28.66, 28.5, 27.4, 22.1, 13.9; HRMS *m/z* 358.2103 (MNa^+ [$C_{18}H_{29}N_3O_3Na$] = 358.2107). Anal. ($C_{18}H_{29}N_3O_3$) C, H, N.

6-Decyl-3-[(2-hydroxyethoxy)methyl]pyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4h). Treatment of **3h** (200 mg, 0.59 mmol) by method 3 gave **4h** (92 mg, 84%) as white crystals (EtOAc): mp 145−146 °C; UV max 348, 262 nm (ϵ 4700, 4900); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.23−1.28 (m, 14H), 1.59−1.61 (m, 2H), 2.51 (t, J = 7.6 Hz, 2H), 3.47−3.50 (m, 2H), 3.52−3.54 (m, 2H), 4.69 (t, J = 5.4 Hz, 1H), 5.33 (s, 2H), 5.91 (s, 1H), 8.26 (s, 1H), 11.13 (s, 1H); ^{13}C NMR δ 160.3, 154.8, 142.9, 138.7, 109.2, 96.1, 79.1, 70.7, 60.1, 31.3, 29.0, 28.7, 28.5, 27.5, 22.1, 14.0; HRMS *m/z* 350.2433 (MH^+ [$C_{19}H_{32}N_3O_3$] = 350.2444). Anal. ($C_{19}H_{31}N_3O_3$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-undecylpyrrolo[2,3-*d*]pyrimidin-2(3*H*,7*H*)-one (4i). Treatment of **3i** (180 mg, 0.49

mmol) by method 3 gave **4i** (95 mg, 53%) as slightly yellow crystals (EtOAc): mp 144−146 °C; UV max 347, 262 nm (ϵ 4000, 4100); ^{1}H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.23−1.28 (m, 16H), 1.59−1.61 (m, 2H), 2.50−2.53 (m, 2H), 3.48−3.50 (m, 2H), 3.52−3.54 (m, 2H), 4.67 (t, J = 5.4 Hz, 1H), 5.33 (s, 2H), 5.91 (s, 1H), 8.26 (s, 1H), 11.11 (s, 1H); ^{13}C NMR δ 160.2, 154.8, 142.9, 138.6, 109.2, 96.1, 79.0, 70.7, 60.0, 31.3, 29.0, 28.7, 28.5, 27.4, 22.1, 14.0; HRMS *m/z* 386.2435 (MNa^+ [$C_{20}H_{33}N_3O_3$-Na] = 386.2420). Anal. ($C_{20}H_{33}N_3O_3$) C, H, N.

6-Bromo-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2-one (5). A stirred suspension of **3a** (1.50 g, 7.1 mmol) and KOAc (840 mg, 8.6 mmol) in CH_2Cl_2 (80 mL) and DMF (10 mL) was cooled to 0 °C. A solution of Br_2/CH_2Cl_2 (0.3 M, 25 mL) was added dropwise, and the mixture was stirred at 0 °C for 3 h. The mixture was neutralized (Et_3N), and solids were filtered and washed (CH_2Cl_2,10 mL). Volatiles were evaporated from the combined filtrate, and the residue was chromatographed (MeOH/CH_2Cl_2, 8:92) to give **5** (960 mg, 47%) as a slightly yellow solid: mp 135−145 °C; UV max 330, 258 nm (ϵ 9000, 800); ^{1}H NMR δ 3.47−3.50 (m, 2H), 3.57 (t, J = 4.8 Hz, 2H), 4.70 (t, J = 5.3 Hz, 1H), 5.36 (s, 2H), 7.02 (s, 1H), 8.63 (s, 1H); ^{13}C NMR δ 171.6, 154.2, 142.3, 127.4, 106.9, 106.8, 79.4, 71.1, 60.1; HRMS *m/z* 310.9642 (MNa^+ [$C_9H_9{}^{79}BrN_2O_4$-Na] = 310.9643).

6-(Hexyn-1-yl)-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2-one (6a). Method 4. A stirred suspension of **5** (250 mg, 0.86 mmol), $Pd(Ph_3P)_4$ (50 mg, 43.3 μmol), and CuI (17 mg, 89.3 μmol) in DMF (8.0 mL) and Et_3N (1.7 mL) was purged with N_2. 1-Hexyne (0.125 mL, 90 mg, 1.1 mmol) was added, and the mixture was stirred at ambient temperature for 10 h. Volatiles were evaporated, and toluene was added and evaporated (2 × 5 mL). The residue was chromatographed (MeOH/CH_2Cl_2, 7:93) and treated with charcoal in hot MeOH. Filtration, evaporation of volatiles, and recrystallization of the residue (EtOAc/hexanes, 1:1) gave **6a** (159 mg, 63%) as yellow crystals: mp 140−143 °C; UV max 344, 278, 266 nm (ϵ 10 600, 14 700, 20 900); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, J = 7.1 Hz, 3H), 1.43−1.47 (m, 2H), 1.60 ("quint", J = 7.1 Hz, 2H), 2.47 (t, J = 7.1 Hz, 2H), 3.07 (br s, 1H), 3.78 (br s, 4H), 5.49 (s, 2H), 6.57 (s, 1H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.5, 155.9, 139.7, 139.6, 108.0, 107.0, 100.6, 80.2, 71.9, 70.0, 61.7, 30.1, 22.2, 19.5, 13.7; HRMS *m/z* 313.1151 (MNa^+ [$C_{15}H_{18}N_2O_4$Na] = 313.1164). Anal. ($C_{15}H_{18}N_2O_4 \cdot 0.333H_2O$) C, H, N.

6-(Heptyn-1-yl)-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2-one (6b). Treatment of **5** (100 mg, 0.35 mmol) with 1-heptyne (58 μL, 42 mg, 0.44 mmol) by method 4 gave **6b** (60 mg, 57%) as yellow crystals (EtOAc/hexanes, 1:1): mp 127−128 °C; UV max 344, 278, 266 nm (ϵ 11 300, 15 600, 22 400); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.33−1.44 (m, 4H), 1.62 ("quint", J = 7.3 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 3.01 (br s, 1H), 3.78 (br s, 4H), 5.49 (s, 2H), 6.55 (s, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.7, 155.9, 139.8, 139.6, 107.9, 107.0, 100.8, 80.3, 72.0, 70.1, 61.8, 31.3, 27.9, 22.4, 19.8, 14.1; HRMS (EI) *m/z* 304.1429 (M^+ [$C_{16}H_{20}N_2O_4$] = 304.1423). Anal. ($C_{16}H_{20}N_2O_4 \cdot 0.5H_2O$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-(octyn-1-yl)furo[2,3-*d*]pyrimidin-2-one (6c). Treatment of **5** (150 mg, 0.52 mmol) with 1-octyne (0.10 mL, 75 mg, 0.68 mmol) by method 4 gave **6c** (127 mg, 77%) as yellow crystals (EtOAc/hexanes, 1:1): mp 125−127 °C; UV max 344, 278, 266 nm (ϵ 10 000, 13 700, 19 600); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.1 Hz, 3H), 1.30−1.31 (m, 4H), 1.41−1.44 (m, 2H), 1.58−1.63 (m, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.98 (br s, 1H), 3.77 (br s, 4H), 5.48 (s, 2H), 6.54 (s, 1H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.7, 155.9, 139.8, 139.5, 107.8, 106.9, 100.7, 80.2, 72.0, 70.0, 61.7, 31.4, 28.7, 28.1, 22.7, 19.8, 14.2; HRMS *m/z* 341.1489 (MNa^+ [$C_{17}H_{22}N_2O_4$Na] = 341.1477).

3-[(2-Hydroxyethoxy)methyl]-6-(nonyn-1-yl)furo[2,3-*d*]pyrimidin-2-one (6d). Treatment of **5** (110 mg, 0.38 mmol) with 1-nonyne (80 μL, 61 mg, 0.49 mmol) by method 4 gave **6d** (64 mg, 51%) as slightly yellow crystals (EtOAc/hexanes, 1:1): mp 128−131 °C; UV max 344, 278, 266 nm (ϵ 10 200, 14 200, 20 200); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.0 Hz, 3H), 1.28 (m, 6H), 1.41 (br s, 2H), 1.61 ("quint", J = 7.1 Hz, 2H), 2.45 (t, J = 7.1 Hz, 2H), 3.02 (br s, 1H), 3.77 (br s, 4H), 5.49 (s, 2H), 6.57 (s, 1H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.5, 155.9, 139.7, 139.6, 107.9, 107.0, 100.7, 80.3, 71.9, 70.0, 61.7, 31.8, 29.0, 28.9, 28.1, 22.8, 19.8, 14.2; HRMS *m/z* 355.1647 (MNa^+ [$C_{18}H_{24}N_2O_4$Na] = 355.1634).

6-(Decyn-1-yl)-3-[(2-hydroxyethoxy)methyl]furo[2,3-*d*]pyrimidin-2-one (6e). Treatment of **5** (150 mg, 0.52 mmol) with 1-decyne (0.12 mL, 93 mg, 0.67 mmol) by method 4 gave **6e** (119 mg, 66%) as slightly yellow crystals (EtOAc/hexanes, 1:1): mp 130−132 °C; UV max 344, 278, 266 nm (ϵ 11 200, 15 300, 22 000); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.28−1.30 (m, 8H), 1.41 (br s, 2H), 1.61 ("quint", J = 7.3 Hz, 2H), 2.45 (t, J = 7.1 Hz, 2H), 3.04 (br s, 1H), 3.77 (br s, 4H), 5.48 (s, 2H), 6.54 (s, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.6, 155.9, 139.8, 139.6, 107.8, 107.0, 100.7, 80.2, 72.0, 70.0, 61.7, 32.0, 29.3, 29.2, 29.1, 28.1, 22.8, 19.8, 14.2; HRMS *m/z* 369.1798 (MNa^+ [$C_{19}H_{26}N_2O_4$Na] = 369.1790). Anal. ($C_{19}H_{26}N_2O_4$) C, H, N.

3-[(2-Hydroxyethoxy)methyl]-6-(undecyn-10yl)furo[2,3-*d*]pyrimidin-2-one (6f). Treatment of **5** (150 mg, 0.52 mmol) with 1-undecyne (0.13 mL, 100 mg, 0.66 mmol) by method 4 gave **6f** (77 mg, 41%) as slightly yellow crystals (EtOAc/hexanes, 1:1): mp 128−130 °C; UV max 344, 278, 266 nm (ϵ 10 600, 14 700, 20 800); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.26−1.29 (m, 10H), 1.42 (br s, 2H), 1.61 ("quint", J = 7.1 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 2.88 (br s, 1H), 3.78 (br s, 4H), 5.49 (s, 2H), 6.54 (s, 1H), 8.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.6, 155.9, 139.8, 139.4, 107.9, 106.9, 100.8, 80.2, 71.9, 70.0, 61.7, 32.0, 29.6, 29.4, 29.3, 29.1, 28.1, 22.8, 19.8, 14.3; HRMS *m/z* 383.1961 (MNa^+ [$C_{20}H_{28}N_2O_4$Na] = 383.1947). Anal. ($C_{20}H_{28}N_2O_4 \cdot 0.5H_2O$) C, H, N.

Antiviral Assays. The antiviral assays, other than anti-HIV assays, were based on inhibition of virus-induced cytopathicity in HEL [herpes simplex virus type 1 (HSV-1) (KOS), HSV-2 (G), vaccinia virus, and vesicular stomatitis virus], Vero (parainfluenza-3, reovirus-1, Sindbis, Coxsackie B4, and Punta Toro virus), or HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus) cell cultures. Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures). After a 1-h virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (200, 40, 8, ... μM) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. The methodology of the anti-HIV assays was as follows: human CEM ($\sim 3 \times 10^5$ cells/cm^3) cells were infected with 100 $CCID_{50}$ of HIV(III_B) or HIV-2(ROD)/mL and seeded in 200-μL wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37 °C, HIV-induced CEM giant cell formation was examined microscopically.

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Supporting Information Available: Elemental analysis data and ^{1}H NMR spectra of **5**, **6c**, and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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