Synthesis and Antiviral Evaluation of 6-(Alkyl-heteroaryl)furo[2,3-*d*]pyrimidin-2(3*H*)-one Nucleosides and Analogues with Ethynyl, Ethenyl, and Ethyl Spacers at C6 of the Furopyrimidine Core[1]

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Sonogashira coupling strategies were employed to synthesize new furo[2,3-*d*]pyrimidin-2(3*H*)-one (FuPyrm) 2′-deoxynucleoside analogues. Partial or complete reduction of ethyne-linked compounds afforded ethenyl- and ethyl-linked derivatives. Levels of inhibition of varicella-zoster virus (VZV), human cytomegalovirus (HCMV), a broad range of other DNA and RNA viruses, and several cancer cell lines were evaluated in cell cultures. The anti-VZV potency decreased with increasing rigidity of the side chain at C6 of the FuPyrm ring in the order dec-1-yn-1-yl < dec-1-en-1-yl < decan-1-yl. In contrast, compounds with a rigid ethynyl spacer between C6 of the FuPyrm ring and a 4-alkylphenyl moiety were more potent inhibitors of VZV than the corresponding derivatives with an ethyl spacer. Replacement of the phenyl moiety in 6-(4-alkylphenyl) derivatives with a pyridine ring (in either regioisomeric orientation) gave analogues with increased solubility in methanol but reduced anti-VZV potency, and replacement with a pyrimidine ring reduced the anti-VZV activity even further. The pyridine-ring-containing analogues were ∼20-fold more potent inhibitors of VZV than acyclovir but were ∼6-fold less potent than BVDU and ∼60-fold weaker than the most active 6-(4-pentylphenyl)-substituted prototype.

Introduction

In 1981, Robins and Barr[2] reported the first nucleoside analogues with a furo[2,3-*d*]pyrimidin-2(3*H*)-one (FuPyrm) ring system **3** (Figure 1) (as byproducts in Pd/Cu-catalyzed Sonogashira coupling reactions of terminal alkynes with 5-iodouracil nucleosides **1**) and demonstrated that the derivatives **3** were produced by treatment of 5-(alkyn-1-yl)uracil (base and nucleoside) compounds **2** with CuI and Et_3N in MeOH.[2,3] Our shorter-chain 5-(alk-1-yn-1-yl)uracil nucleosides **2** showed antiviral activity that was lost with longer-chain analogues.[4] Two decades later, the remarkable potency and selectivity of longer-chain derivatives of the FuPyrm ring system **3** against varicella-zoster virus (VZV) were discovered.[5] Extensive structure−activity studies have demonstrated that compounds with an extended alkyl chain at C6, an endocyclic oxygen atom in the fused five-membered ring, and a 2-deoxy-β-D-*erythro*-pentofuranosyl moiety at N3 show marked selectivity and potency against VZV.[5] Analogues with even better activity were produced by insertion of a 4-substituted phenyl ring into the alkyl side chain,[6] and such compounds **4** show potencies in the lower nanomolar range against VZV.[7] Additional modifications of the FuPyrm ring system, the 2′-deoxy-β-D-*erythro*-pentofuranosyl sugar moiety, and the side chain on the aryl ring have not produced superior drug candidates.[7,8]

Because of the highly lipophilic nature of the active compounds, a more soluble FuPyrm nucleoside analogue that could retain high potency and selectivity against VZV would be attractive. Nucleosides **3** and **4** are not substrates for human or bacterial thymidine phosphorylase (TP), and the base analogues do not inhibit dihydropyrimidine dehydrogenase (DPD).[9] In contrast, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) (licensed for treatment of herpes zoster in several European countries) is readily cleaved by TP to give (*E*)-5-(2-bromovinyl)-uracil (BVUra), which is an inhibitor of DPD. Catabolism of 5-fluorouracil (FU) is initiated by DPD, and inhibition of DPD by BVUra results in markedly increased plasma levels of FU in cancer patients treated with both FU and BVDU. Initial phosphorylation of FuPyrm nucleosides by a specific VZV thymidine kinase (TK) was indicated because activity was reduced with TK-impaired mutants.[5] However, detailed modes of action of the FuPyrm analogues remain unclear. Therefore, the design, synthesis, and biological evaluation of new structures are highly warranted. We now report two new classes of such analogues. Members of the first class have two-carbon linkers between C6 of the FuPyrm core and the (4-alkylphenyl) side chain. Such analogues are readily available from our 6-bromo-FuPyrm nucleosides[8b] but would require synthesis of more complex alkynes for our original methodology[2−4] that was employed for other syntheses.[5−7] Members of the second class have alkyl-substituted pyridine or pyrimidine rings attached at C6 of the FuPyrm core.

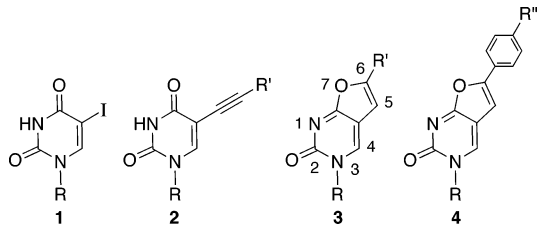

Figure 1. Precursors and drug candidates **3** and **4**.

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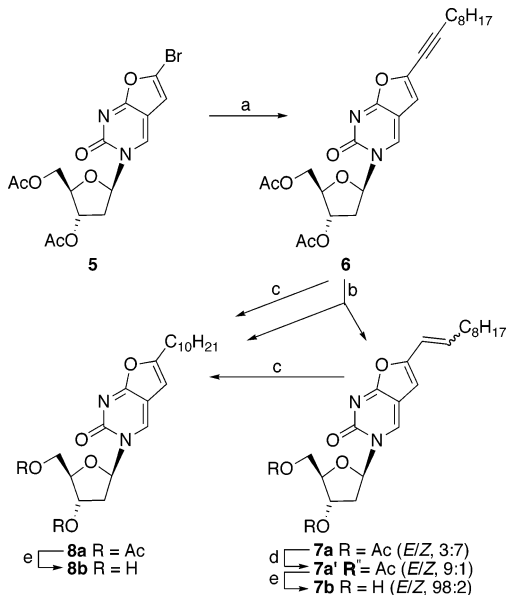
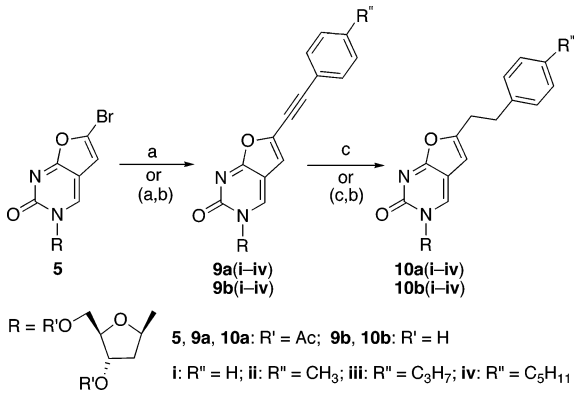
Scheme 1[a]



[a] Reagents and conditions: (a) HC≡CC_8H_{17}, $(Ph_3P)_4Pd$, CuI, Et_3N, DMF; (b) H_2, Pd−$CaCO_3$−Pb; (c) H_2, Pd−C; (d) *hv*; (e) NH_3, MeOH, 0 °C.

Scheme 2[a]



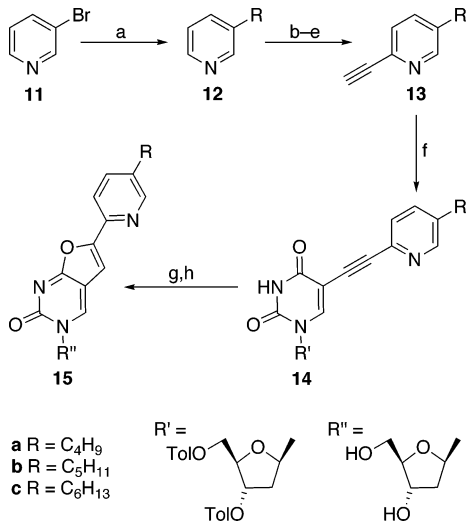
[a] Reagents and conditions: (a) HC≡CC_6H_4R'', $(Ph_3P)_4Pd$, CuI, Et_3N, DMF; (b) NH_3, MeOH (c) H_2, Pd−C.

Results and Discussion

A. Chemistry. Sonogashira coupling of 3-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-bromofuro[2,3-*d*]pyrimidin-2(3*H*)-one (**5**) (Scheme 1) and 1-decyne gave the alkyne **6** in good yield.[8b] Controlled hydrogenation of **6** with a Lindlar catalyst gave an *E*/*Z* (3:7) mixture of alkenes **7a**, which was irradiated with a sun lamp to produce a mixture enriched in the *E* isomer [**7a′**, *E*/*Z* (9:1)]. Deacetylation of **7a′** (NH_3/MeOH) and chromatography gave (*E*)-6-(dec-1-en-1-yl)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)[2,3-*d*]pyrimidin-2(3*H*)-one (**7b**) (containing ∼2% of the *Z* diastereomer). Hydrogenation of **6** or **7** (*E*/*Z*) over Pd−C gave the ethyl-linked derivative **8a**, which was deacetylated to give 6-(decyl)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)[2,3-*d*]pyrimidin-2(3*H*)-one[5] (**8b**). The anti-VZV activities of the alkyne **6′** (deacetylated **6**)[8b] and alkene **7b** (or a mixture containing a higher proportion of the *Z* isomer) were inferior to that of the alkyl analogue **8b**. Therefore, studies on such unsaturated analogues were terminated.

Sonogashira coupling of **5** with (4-alkylphenyl)ethynes (Scheme 2) gave new 6-[2-(4-alkylphenyl)ethynyl]furo[2,3-*d*]-pyrimidin-2(3*H*)-ones **9a**(**i**−**iv**) in good yields (47−84%). The ethynyl linker was hydrogenated to give **10a**(**i**−**iv**) (63−75%) with a more flexible ethyl linker. Deacetylation gave **9b**(**i**−**iv**) and **10b**(**i**−**iv**), respectively. The series of compounds **4** (Figure 1) with a 4-alkylphenyl substituent linked directly from C6 of the furopyrimidine to the phenyl moiety are more potent anti-VZV agents than the series **3** analogues with linear alkanes at C6. It is noteworthy that our compounds **10b**(**i**−**iv**) with an (ethyl)phenyl moiety inserted between C6 of the FuPyrm core and the 4-alkyl substituent, to an even greater extent than the **9b**(**i**−**iv**) series with an ethynyl linker, had limited anti-VZV activity. Thus, positioning of the phenyl ring with direct attachment to the FuPyrm core produces enhancement of the anti-VZV activity of **4** relative to that of **3**, whereas its positioning within the alkyl chain two carbon atoms apart from the FuPyrm ring results in loss of anti-VZV activity.

Scheme 3[a]

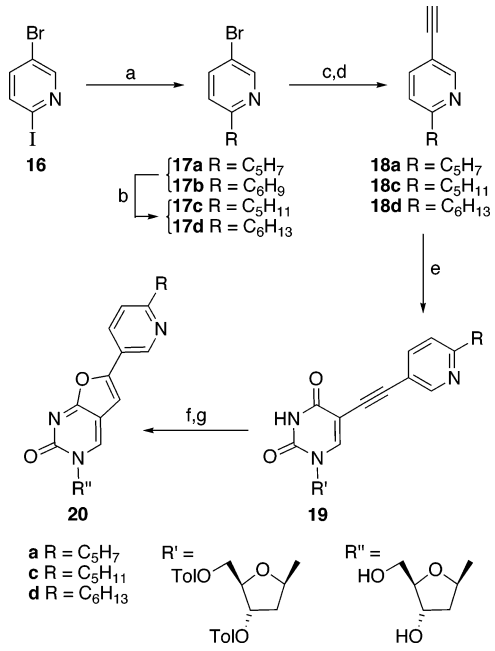


[a] Reagents and conditions: (a) CuBr, RMgBr, THF; (b) BuLi, LiDMAE, hexanes, 0 °C; (c) CBr_4, THF; (d) HC≡CTMS, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 50 °C; (e) $Bu_4N^+F^-$, THF; (f) 2′-deoxy-5-iodo-3′,5′-di-*O*-(*p*-toluoyl)uridine, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 50 °C; (g) (i) KOH, MeOH, (ii) HCl, H_2O; (h) CuI, Et_3N, DMF, 80 °C.

We considered that replacement of the phenyl moiety in **4** by a heteroaromatic ring might attenuate the extreme insolubility[10] of analogues of **4** and/or increase binding affinities for the target protein(s). Our first analogue was derived from commercially available 3-butylpyridine, and other 3-alkylpyridines were prepared in low yields (20−25%) from 3-bromopyridine (**11**) (Scheme 3) by an oxidative coupling procedure with alkylmagnesium bromides.[11] Adaptation of a lithiation−bromination procedure used previously for 3-methylpyridine[12] gave selective bromination at C6 of **12a**−**c**. The resulting 5-alkyl-2-bromopyridines were subjected to Sonogashira coupling with TMS−acetylene (80−86%) followed by desilylation to give the 5-alkyl-2-ethynylpyridines **13a**−**c** (∼60% yields). Additional Sonogashira couplings of **13a**−**c** with 2′-deoxy-5-iodo-3′,5′-di-*O*-(*p*-toluoyl)uridine gave the internal alkynes **14a**−**c** in excellent yields (92−97%), whereas difficulties had been reported for the inverted couplings with 2′-deoxy-5-ethynyluridine and aryl iodides.[10] Because furo[2,3-*d*]pyrimidin-2(3*H*)-one nucleosides undergo conversion to their pyrrolo[2,3-*d*]pyrimidin-2(3*H*)-one counterparts upon heating with NH_3/MeOH, we performed O-deacylation prior to the cyclization step. Treatment of **14a** with NH_3/MeOH at 80 °C gave a complex mixture, but rapid and selective hydrolysis of the ester groups was effected by stirring **14a**−**c** with 1% KOH/MeOH at ambient temperature. Cyclization of the deprotected alkynes proceeded without difficulty to give high yields of **15a**−**c**.

Pyridine regioisomers of **15** were synthesized by a similar sequence beginning with 5-bromo-2-iodopyridine (**16**) (Scheme

Scheme 4[a]



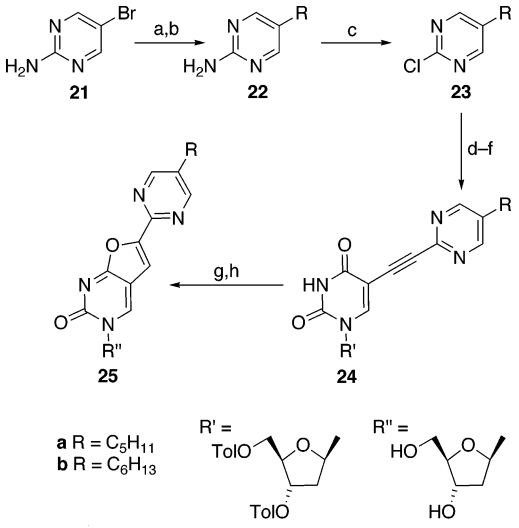
[a] Reagents and conditions: (a) HC≡CR, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 60 °C; (b) H_2, PtO_2, Et_3N, EtOH; (c) HC≡CTMS, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 50 °C; (d) $Bu_4N^+F^-$, THF; (e) 2′-deoxy-5-iodo-3′,5′-di-*O*-(*p*-toluoyl)uridine, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 50 °C; (f) (i) KOH, MeOH, (ii) HCl, H_2O; (g) CuI, Et_3N, DMF, 80 °C.

4). Sonogashira coupling of **16** with terminal alkynes occurred selectively at the iodinated site to give the 2-alkynyl-5-bromopyridines **17a** and **17b**. Hydrogenation of the triple bonds with PtO_2 (modified conditions of Tilley and Zawoiski)[13] gave **17c** and **17d**, respectively, without hydrogenolysis of the C−Br bonds. Sonogashira coupling of **17a**, **17c**, and **17d** with TMS−acetylene followed by desilylation gave the alkynes **18a**, **18c**, and **18d** in overall yields of ∼60%. A third series of Sonogashira couplings with 2′-deoxy-5-iodo-3′,5′-di-*O*-(*p*-toluoyl)uridine gave the internal alkynes **19a**, **19c**, and **19d** (67−95%). Removal of the ester protecting groups followed by CuI-promoted cyclization gave **20a**, **20c**, and **20d** (43−70% combined yields).

Replacement of the phenyl ring with a pyrimidine was also probed. The aminopyrimidine **21** is poorly soluble in most solvents, but Sonogashira coupling with terminal alkynes in DMSO[14] was successful. Hydrogenation of the triple bond (H_2 at 60 psi/Pd−C) gave the intermediate 2-amino-5-alkylpyrimidines **22a** and **22b** (Scheme 5). Our nonaqueous diazotization/chlorodediazoniation procedure[15] converted **22a** and **22b** into 2-chloro-5-alkylpyrimidines **23a** and **23b**, which were subjected to Sonogashira coupling with TMS−acetylene (activation by the two endocyclic nitrogens was sufficient for successful coupling with the chloro substituent).[16] Desilylation gave the respective 5-alkyl-2-ethynylpyrimidines (54−69% for two steps), which were coupled with 2′-deoxy-5-iodo-3′,5′-di-*O*-(*p*-toluoyl)uridine to give the 5-alkynyluracil derivatives **24a** and **24b** (∼95% yields). Hydrolysis of the ester protecting groups and CuI-catalyzed cyclization proceeded without problems to give **25a** and **25b** (∼70% yields).

No solubility in water had been detected[10] with the most active anti-VZV 2′-deoxynucleoside prototype **4** (R″ = C_5H_{11}). Our butylpyridine compound **15a** (R = C_4H_9) was ∼3× more soluble (MeOH) than the butylphenyl analogue **4** (R″ = C_4H_9). There was no significant difference in solubility between the pentylpyridine regioisomers **15b** and **20c**, which were slightly less soluble than the butylphenyl compound **4** (R″ = C_4H_9).

Scheme 5[a]



[a] Reagents and conditions: (a) HC≡CR, $(Ph_3P)_4Pd$, CuI, Et_3N, DMSO, 55 °C; (b) H_2 (60 psi), Pd−C, MeOH; (c) TMS−Cl, $TEA^+NO_2^-$, CH_2Cl_2; (d) HC≡CTMS, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 50 °C; (e) $Bu_4N^+F^-$, THF; (f) 2′-deoxy-5-iodo-3′,5′-di-*O*-(*p*-toluoyl)uridine, $(Ph_3P)_4Pd$, CuI, Et_3N, CH_2Cl_2, 50 °C; (g) (i) KOH, MeOH, (ii) HCl, H_2O; (h) CuI, Et_3N, DMF, 80 °C.

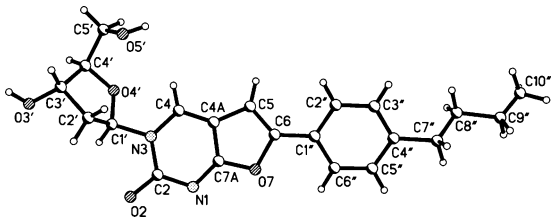


Figure 2. X-ray crystal structure of **4** (R″ = C_4H_9).

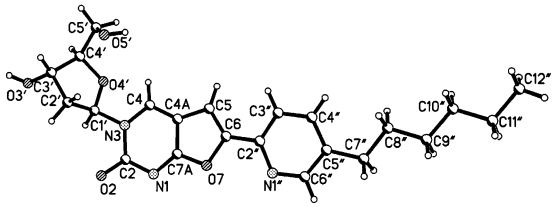


Figure 3. X-ray crystal structure of **15c**.

Thus, homologation of the side chain decreased the solubility to a greater extent than deletion of the pyridine ring nitrogen. The solubility of the pentylpyrimidine derivative **25a** was about half that of the pyridine analogues **15b** and **20c**. Thus, the qualitative solubility order (MeOH) was **15** ≈ **20** > **25** > **4** (with equivalent alkyl groups on the aryl/heteroaryl rings).

In view of the differences in antiviral activities of analogues containing a benzene or pyridine ring at C6, X-ray crystal structures were determined for the reference compound 6-(4-butylphenyl)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (**4**, R″ = C_4H_9) (Figure 2) and our 3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(4-hexylpyrid-2-yl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (**15c**) (Figure 3). There are only minor differences in the crystal structures (for example, an angle of 19.1° between the planes of the phenyl and FuPyrm rings in Figure 2 and 11.0° between the pyridine and FuPyrm rings in Figure 3), and the two extended conformations show much greater similarities than differences.

Additional hydrogen bonding is possible with the heteroaryl analogues, which should be more polar and subject to different solvation effects, but π-electron densities decrease in the order

Table 1. Antiviral and Cytotoxic Activity of the Test Compounds against Varicella-Zoster Virus (VZV) and Human Cytomegalovirus (HCMV) in Human Embryonic Lung (HEL) Cell Cultures

	EC_{50} [a] (μM)							
	VZV				HCMV		cytotoxicity (μM)	
compd	YS[b]	OKA[b]	07/1[c]	YS/R[c]	AD-169	Davis	MCC[d]	CC_{50} [e]
6′ [f]	2.7		>13	6.5	7.4	7.6	52	77
7b	0.72	1.2	>48	26	22	8.4	≥120	230
8b	0.066	0.094	>51	>51	>130	64	≥130	>510
9b(i)	99	≥140	>140	>140	>140	>140	>570	>570
9b(ii)	41	66	36	-	510	>130	≥510	510
9b(iii)	27	41	>50	>50	15	8.7	87	>120
9b(iv)	19	17	71		13	11	470	110
10b(i)		380	>560		>560	>560	>560	>560
10b(ii)		>140	>140		>540	>540	540	>540
10b(iii)	≥50	>130	>50	>130	>130	>130	≥130	>130
10b(iv)		18	>120		>120	>120	≥470	>470
15a	0.36	0.23	>100	>100	>100	>100	>100	>50
15b	0.58	0.07	>100	>100	>100	>100	>100	>50
15c	0.045	0.06	>100	70	>100	>100	>100	>50
20a	0.06	0.09	>20	>20	>20	>20	≥100	>50
20c	0.09	0.13	>20	>20	>20	>20	100	>50
20d	0.09	0.14	>20	>20	>20	>20	100	>50
25a	2.0	1.9	>100	>100	>100	>100	>100	>50
25b	0.71	0.63	>100	>100	>100	>100	>100	>50
ACV	1.4	4.0	36	24	ND	ND	>220	>890
BVDU	0.01	0.01	≥99	≥130	ND	ND	>150	>150
4[g]	0.001	0.004	>1.3	>0.5	>10	>10	>1.3	>50
GCV	2.3	ND	ND	ND	5.1	8.7	>200	>200

[a] Inhibitory concentration required to reduce virus plaque formation by 50%. Virus input was 100 plaque forming units (pfu). [b] TK^+ strain. [c] TK^- strain. [d] Minimum cytotoxic concentration that caused a microscopically visible alteration of cell morphology. [e] Cytostatic concentration required to reduce cell growth by 50%. [f] 6-(Dec-1-yn-1-yl)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (data from ref 8b). [g] 3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(4-pentylphenyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one.

benzene > pyridine > pyrimidine. It must be remembered that nucleoside analogues are almost always prodrugs of metabolically activated phosphate derivatives. Thus, a nucleoside prodrug must undergo transport (active, facilitated, or passive diffusion) across cellular membranes, phosphorylation by nucleoside (and usually nucleotide) kinases, and only then is the "active drug" available for binding to a target receptor (usually an enzyme or other protein). The phenyl compounds of type **4** apparently have fortuitous combinations of structural features that give globally favorable combinations of such interactions, which result in enhanced in vitro anti-VZV activity.

B. Biological Evaluation. Table 1 contains data with thymidine kinase competent (TK^+) and impaired (TK^-) VZV- and HCMV-infected HEL cell cultures. Our new analogues had no significant inhibitory activity against a broad variety of other DNA and RNA viruses or tumor cell proliferation, in agreement with prior results with FuPyrm nucleosides.[5,7]

The more flexible decyl derivative **8b** (EC_{50} = 0.066−0.094 μM) was ~10-fold more inhibitory to VZV than the decenyl derivative **7b** (EC_{50} = 0.72−1.2 μM), which in turn was more potent than the decynyl analogue **6′** (EC_{50} = 2.7 μM). In contrast, the rigid (4-alkylphenyl)ethynyl compounds **9b(i−iv)** were more inhibitory than their more flexible (4-alkylphenyl)-ethyl analogues **10b(i−iv)**. Within these two series of compounds, the activity increased progressively with longer R″ alkyl groups (H < CH_3 < C_3H_7 < C_5H_{11}), a trend also observed within the **4** series that has no linker between the 4-alkylphenyl group and C6 of the FuPyrm ring.[5] The *m*-alkylpyridine derivatives **15a−c** showed pronounced anti-VZV activity. The pentyl- and hexylpyridine analogues were ~3- to 8-fold more potent than the butyl compound (EC_{50} = 0.045−0.07 μM versus 0.23−0.36 μM). The *o*-alkylpyridine derivatives **20a**, **20c**, and **20d** showed similarly potent anti-VZV activity (EC_{50} = 0.06−0.14 μM). It is noteworthy that the alkylpyrimidine compounds **25a** and **25b** were less active (EC_{50} = 0.63−2.0 μM) than the alkylpyridine derivatives of series **15** and **20**. Overall, insertion of one or two endocyclic nitrogen atoms into the alkylphenyl moiety of **4** resulted in significantly decreased anti-VZV activity in cell culture. Generally, the test compounds were devoid of antiviral activity against TK^- strains of VZV. These observations suggest a pivotal role for VZV TK as an activating enzyme. However, evaluation of the affinity of the test compounds for VZV TK (Table 2) showed no direct correlation with their antiviral potency, as also had been observed with the **4** series of compounds.[5] Thus, although VZV TK is absolutely required for activation of the compounds, the SARs for binding of such compounds to VZV TK differ from the SARs for their antiviral efficacies. Compounds **6′**, **7b**, **9b(ii)**, **9b(iii)**, and **9b(iv)** showed limited antiviral activity against VZV TK^-, and **6′**, **7b**, **9b(iii)**, and **9b(iv)** showed limited activity against HCMV (Table 1). These effects might result from interference with virus entry or other modes of action as observed with some 2′,3′-dideoxy analogues of **4**.[17] No significant inhibitory activity against other DNA and RNA viruses or cancer cells was observed (data not shown).

Table 2. Inhibitory Activity of the Test Compounds against VZV TK-Catalyzed Conversion of [^{3}H]dThd to [^{3}H]dTMP

compd	IC_{50} [a] (μM)	compd	IC_{50} [a] (μM)
6′	217 ± 179	**15a**	34 ± 5.0
7b	65 ± 4.0	**15b**	4.2 ± 0.3
8b	≥500	**15c**	3.7 ± 0.7
9b(i)	493 ± 9	**20a**	2.9 ± 0.2
9b(iii)	>500	**20c**	18 ± 2.0
10b(iii)	>500	**20d**	30 ± 1.0
		25a	24 ± 5.0
		25b	15 ± 4.0

[a] 50% inhibitory concentration (compound concentration required to inhibit VZV TK-catalyzed phosphorylation of 1 μM [^{3}H]dThd to [^{3}H]dTMP).

Summary and Conclusions

We have developed efficient methods for synthesis of a variety of furo[2,3-*d*]pyrimidin-2(3*H*)-one (FuPyrm) nucleosides with lipophilic substituents at C6. Analogues with alkyl, alkenyl, and alkynyl chains at C6 were produced by Sonogashira coupling of 6-bromo derivatives with alkynes, followed by partial or complete hydrogenation of the alkyne triple bond. Analogues with *p*-alkylphenyl substituents at C6 are readily accessible by our prior methods [Sonogashira coupling with *p*-alkylphenylethynes followed by cyclization with Cu(I)]. Coupling of *p*-alkylphenylethynes with the 6-bromo derivative gave access to lipophilic analogues with two-carbon spacers between the phenyl and FuPyrm moieties. However, the anti-VZV potency was diminished with such compounds relative to those with the directly bonded phenyl and FuPyrm rings. Finally, regioisomeric pyridine and pyrimidine analogues were prepared with alkyl-substituted heteroaromatic rings directly connected to C6 of the FuPyrm core. Although such derivatives have the potential for additional hydrogen bonding and other polarity-enhanced association with proteins relative to their phenyl counterparts (and have greater solubility in methanol), their anti-VZV potencies were diminished. Fortuitous combinations of structural features with the strongly hydrophobic *p*-alkylphenyl prodrugs result in unmatched anti-VZV potencies in vitro.

Experimental Section

Chemistry. UV spectra were determined with solutions in MeOH. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded with solutions in $CDCl_3$ unless otherwise noted. ^{13}C peaks

with the same chemical shifts for more than one carbon are specified, and overlapping peaks for multiple carbons are indicated by a shift range (ovlp). HRMS were obtained with a Joel SX 102A double-focusing mass spectrometer with an HP-9000 workstation. Elemental analyses were determined by M-H-W Laboratories, Phoenix, AZ. The (4-alkylphenyl)ethyne, 3-bromopyridine, 3-butylpyridine, 3-bromo-6-iodopyridine, and 2-amino-5-bromopyrimidine starting materials were purchased from Aldrich. Compounds **5** and **6** were prepared as described,[8b] and **8a** and **8b** had spectroscopic data in agreement with reported values.[18] General procedures A−C were performed with the quantities and conditions noted for the individual compounds.

Procedure A (Synthesis of 6 and 9a). A solution of **5**, the alkyne (4−5 equiv), $(Ph_3P)_4Pd$ (0.1 equiv), and CuI (0.2 equiv) in deoxygenated DMF/Et_3N (2:1, v/v) was stirred under an inert atmosphere until the 6-bromofuro[2,3-*d*]pyrimidin-2(3*H*)-one starting material had reacted completely (1−3 h, TLC). Volatiles were evaporated under reduced pressure, and the residue was purified by flash chromatography.

Procedure B (Deacetylation of 7a, 7a′, 8a, 9a, and 10a). A solution of the *O*-acetyl nucleoside derivative in NH_3/MeOH (saturated at 0 °C) was stirred at 0 °C until deacetylation was complete (3−6 h, TLC). Volatiles were evaporated under reduced pressure, and the residue was purified by flash chromatography.

Procedure C (Hydrogenation of 6 and 9). A mixture of **6** (or **9**) and 10% Pd−C in EtOH (100%) was shaken with H_2 (25 psi) in a Parr apparatus at ambient temperature (3−11 h). The mixture was filtered (Celite), and the filter cake was washed with EtOH. Volatiles were evaporated under reduced pressure, and the residue was purified by flash chromatography.

(*E*/*Z*)-3-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl-6-(dec-1-en-1-yl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (7a). A mixture of 3-(3,5-di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-(dec-1-yn-1-yl)furo[2,3-*d*]pyrimidin-2(3*H*)-one[8b] (**6**) (217 mg, 0.46 mmol), quinoline (0.87 mL, freshly distilled), and Lindlar catalyst (220 mg) in acetone (60 mL) was shaken with H_2 (13 psi) at ambient temperature for 8 h in a Parr apparatus. (The reaction vessel was protected from light with aluminum foil to minimize isomerization; after 8 h, a 500 MHz ^{1}H NMR spectrum indicated almost complete conversion of **6**.) The suspension was filtered, the filter cake was washed with acetone (100 mL), and volatiles were evaporated from the combined filtrates. The residual yellow oil was flash-chromatographed (EtOAc/hexanes, 1:1) to give **7a** (*E*/*Z*, 3:7) as a light-yellow oil (142 mg, 65%): UV max 347, 266, 228 nm; UV min 308, 245 nm; ^{1}H NMR δ 8.24 (s, 0.7H), 8.17 (s, 0.3H), 6.52 (dt, *J*= 7.4, 15.2 Hz, 0.3H), 6.32 (dd, *J* = 6.0, 7.5 Hz, 1H), 6.28 (s, 1H), 6.18−6.10 (m, 1H), 5.87 (dt, *J* = 7.6, 11.8 Hz, 0.7H), 5.23 (d, *J* = 6.0 Hz, 1H), 4.43−4.39 (m, 3H), 2.99−2.94 (m, 1H), 2.53 (ddd, *J* = 1.5, 7.5, 15.0 Hz, 1.4H), 2.25−2.19 (m, 0.6H), 2.12−2.05 (m, 1H), 2.12 (s, 3H), 2.07 (s, 3H), 1.49−1.45 (m, 2H), 1.36−1.25 (m, 10H), 0.89−0.86 (m, 3H); ^{13}C NMR δ (172.0), 171.8, 170.6, 170.5, 155.7, (155.6), (154.74), 154.69, 139.1, (137.9), 134.4, (133.8), (117.0), 115.8, (108.6), 108.1, 101.4, (98.6), 88.7, (88.6), 83.40, (83.37), 74.29, (74.27), 63.9, 39.50, (39.46), (33.2), 32.0, 30.0, 29.70, 29.64, 29.59, 29.53, 29.44, 29.41, 29.38, 28.9, 22.7, 21.10, 21.09, 21.03, 21.02, 14.3 (identifiable minor isomer peaks in parentheses); HRMS (EI) *m*/*z* 474.2378 (M^+ $[C_{25}H_{34}N_2O_7]$ = 474.2366).

A solution of **7a** (*E*/*Z*, 3:7) (132 mg, 0.28 mmol) in $CDCl_3$ (5 mL) was stirred for 6.5 h at 25−32 °C (circulating water bath) with irradiation by a sun lamp (250 W, 150 V). Diastereoisomerization was monitored by ^{1}H NMR (500 MHz) until equilibrium was attained (**7a′**; *E*/*Z*, 9:1): UV max 339, 277, 251, 230 nm; UV min 309, 269, 244 nm; ^{1}H NMR δ 8.24 (s, 0.1H), 8.17 (s, 0.9H), 6.52 (dt, *J* = 7.3, 15.8 Hz, 0.9H), 6.32 (dd, *J* = 5.5, 7.5 Hz, 1H), 6.28 (s, 0.1H), 6.16 (dt, *J* = 1.5, 15.5 Hz, 0.9H), 6.15 (s, 0.9H), 6.13−6.11 (m, 0.1H), 5.87 (dt, *J* = 7.6, 11.8 Hz, 0.1H), 5.23 (m, 1H), 4.41−4.39 (m, 3H), 2.94 (ddd, *J* = 2.4, 5.6, 14.6 Hz, 1H), 2.52 (ddd, *J* = 1.5, 7.5, 15.0 Hz, 0.2H), 2.23 (ddd, *J* = 1.5, 7.0, 15.0 Hz, 1.8H), 2.15−2.06 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 1.47 (pent, *J* = 7.1 Hz, 2H), 1.34−1.25 (m, 10H), 0.874 (t, *J* = 7.3 Hz, 2.7 H), 0.968 (t, *J* = 7.1 Hz, 0.3H); ^{13}C NMR δ 172.0, 170.7, 170.5, 155.6, 154.8, 137.9, 133.8, 117.0, 108.6, 98.6, 88.6, 83.4, 74.3, 63.9, 39.5, 33.2, 32.0, 29.6, 29.41, 29.37, 28.9, 22.8, 21.1, 21.0, 14.3; HRMS (FAB) *m*/*z* 497.2269 (M + Na^+ $[C_{25}H_{34}N_2O_7Na]$ = 497.2264).

(*E*)-6-(Dec-1-en-1-yl)-3-(2-deoxy-*β*-D-*erythro*-pentofuranosyl)-furo[2,3-*d*]pyrimidin-2(3*H*)-one (7b). Treatment of **7a′** (*E*/*Z*, 9:1) (130 mg, 0.27 mmol) with NH_3/MeOH (20 mL) by procedure B [4 h, chromatography (MeOH/EtOAc, 1:20] gave **7b** (*E*/*Z*, ∼98:2) as a white solid (57 mg, 53%): UV max 346, 277, 226 nm (ϵ 9800, 13 700, 14 000); UV min 309, 244 nm (ϵ 4200, 11 300); ^{1}H NMR (DMSO-d_6) δ 8.71 (s, 1H), 6.56 (s, 1H), 6.37−6.32 (m, 2H), 6.15 (t, *J* = 6.3 Hz, 1H), 5.30 (d, *J* = 4.0 Hz, 1H), 5.14 (t, *J* = 5.3 Hz, 1H), 4.24−4.21 (m, 1H), 3.91 (dd, *J* = 3.3, 7.3 Hz, 1H), 3.69−3.64 (m, 1H), 3.64−3.58 (m, 1H), 2.38 (ddd, *J* = 4.0, 5.8, 13.5 Hz, 1H), 2.23−2.19 (m, 2H), 2.05 (dt, *J*= 6.5, 13.0 Hz, 1H), 1.44−1.42 (m, 2H), 1.28−1.25 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.1, 153.9, 153.2, 137.4, 134.9, 117.7, 106.8, 100.5, 88.2, 87.5, 69.7, 60.8, 41.2, 32.3, 31.3, 28.9, 28.7, 28.3, 22.1, 14.0; HRMS (FAB) *m*/*z* 391.2216 (M + H^+ $[C_{21}H_{31}N_2O_5Na]$ = 391.2233). Anal. Calcd for $C_{21}H_{30}N_2O_5 \cdot 1.5H_2O$: C, 60.83; H, 8.07; N, 6.60. Found: C, 61.50; H, 7.67; N, 7.00.

3-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-decylfuro[2,3-*d*]pyrimidin-2(3*H*)-one (8a). Treatment of **6** (89 mg, 0.19 mmol), 10% Pd−C (10 mg), and EtOH (12 mL) by procedure C [3 h, chromatography (EtOAc/hexanes, 1:1 → 3:2)] gave **8a** as a white solid (67 mg, 74%): UV max 332, 245 nm; UV min 269, 237 nm; ^{1}H NMR δ 8.16 (s, 1H), 6.32 (dd, *J* = 5.5, 7.5 Hz, 1H), 6.11 (s, 1H), 5.22 (dt, *J* = 2.1, 6.5 Hz, 1H), 4.41−4.38 (m, 3H), 2.93 (ddd, *J* = 2.1, 5.4, 14.6 Hz, 1H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.11−2.05 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 1.67 (pent, *J* = 7.3 Hz, 2H), 1.36−1.25 (m, 14H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 172.2, 170.6, 170.5, 160.7, 154.7, 133.6, 108.1, 98.8, 88.5, 83.3, 74.3, 63.9, 39.5, 32.1, 29.7, 29.6, 29.5, 29.4, 29.2, 28.5, 26.9, 22.8, 21.1, 21.0, 14.3; HRMS (FAB) *m*/*z* 477.2599 (M + H^+ $[C_{25}H_{37}N_2O_7]$ = 477.2602).

6-Decyl-3-(2-deoxy-*β*-D-*erythro*-pentofuranosyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (8b). Treatment of **8a** (65 mg, 0.14 mmol) with NH_3/MeOH (10 mL) by procedure B [3 h, chromatography (MeOH/EtOAc, 1:30 → 1:15)] gave **8b** as a white solid (28 mg, 51%) with spectral data as reported.[18]

3-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-(phenylethynyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one [9a(i)]. Treatment of **5** (80 mg, 0.19 mmol), phenylacetylene (106 μL, 99 mg, 0.97 mmol), $(Ph_3P)_4Pd$ (22 mg, 0.019 mmol), CuI (8 mg, 0.04 mmol), Et_3N (1 mL), and DMF (2 mL) by general procedure A [1 h, chromatography (EtOAc/hexanes, 3:2)] gave **9a(i)** (66 mg, 79%) as an off-white solid: UV max 353, 286, 225 nm; UV min 319, 253 nm; ^{1}H NMR δ 8.38 (s, 1H), 7.57−7.56 (m, 2H), 7.42−7.37 (m, 3H), 6.73 (s, 1H), 6.31 (dd, *J* = 5.8, 7.8 Hz, 1H), 5.24 (d, *J* = 6.5 Hz, 1H), 4.43−4.41 (m, 3H), 2.99 (ddd, *J* = 2.4, 5.9, 14.4 Hz, 1H), 2.14−2.09 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H); ^{13}C NMR δ 171.4, 170.6, 170.5, 154.6, 139.2, 135.9, 132.0, 130.0, 128.8, 121.1, 108.3, 106.9, 97.9, 88.9, 83.6, 78.2, 74.2, 63.8, 39.5, 21.1, 21.0; HRMS (EI) *m*/*z* 436.1287 (M^+ $[C_{23}H_{20}N_2O_7]$ = 436.1271).

3-(2-Deoxy-*β*-D-*erythro*-pentofuranosyl)-6-(phenylethynyl)-furo[2,3-*d*]pyrimidin-2(3*H*)-one [9b(i)]. Treatment of **9a(i)** (63 mg, 0.14 mmol) with NH_3/MeOH (14 mL) by procedure B [5 h, chromatography (MeOH/EtOAc, 1:50 → 1:25)] gave **9b(i)** as a light-yellow solid (41 mg, 83%): UV max 353, 285 (ϵ 26 000, 25 570); UV min 319, 253 nm (ϵ 11 190, 10 500); ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 1H), 7.64−7.63 (m, 2H), 7.51−7.47 (m, 3H), 7.23 (s, 1H), 6.14 (t, *J* = 6.0 Hz, 1H), 5.30 (d, *J* = 3.5 Hz, 1H), 5.15 (t, *J* = 5.5 Hz, 1H), 4.24−4.21 (m, 1H), 3.94 (dd, *J* = 3.8, 7.8 Hz, 1H), 3.67 (dd, *J* = 3.8, 12.3 Hz, 1H), 3.59 (dd, *J* = 4.5, 12.5 Hz, 1H), 2.43 (ddd, *J* = 4.4, 6.4, 13.4 Hz, 1H), 2.07 (dt, *J* = 6.1, 13.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 170.4, 153.7, 139.7, 136.0, 131.5, 130.1, 129.0, 120.2, 110.7, 105.1, 96.5, 88.3, 87.9, 78.6, 69.6, 60.7, 41.2; HRMS (FAB) *m*/*z* 375.0941 (M + Na^+ $[C_{19}H_{16}N_2O_5Na]$ = 375.0957). Anal. ($C_{19}H_{16}N_2O_5$) C, H, N.

3-(3,5-Di-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)-6-[(4-pentylphenyl)ethynyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one [9a(iv)].

Treatment of **5** (265 mg, 0.638 mmol), (4-pentylphenyl)acetylene (0.40 mL, 350 mg, 2.1 mmol), $(Ph_3P)_4Pd$ (74 mg, 0.064 mmol), CuI (26 mg, 0.14 mmol), Et_3N (8 mL), and DMF (16 mL) by procedure A [2 h, chromatography (EtOAc/hexanes, 3:2)] gave **9a**(**iv**) (160 mg, 49%) as a yellow solid: UV max 355, 292, 225 nm; UV min 321, 254 nm; ^{1}H NMR δ 8.36 (s, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 6.70 (s, 1H), 6.32 (dd, J = 5.5, 7.5 Hz, 1H), 5.24 (d, J = 6.5 Hz, 1H), 4.43−4.41 (m, 3H), 3.00 (ddd, J = 2.4, 5.8, 14.4 Hz, 1H), 2.63 (t, J = 7.8 Hz, 2H), 2.14−2.08 (m, 1H), 2.13 (s, 3H), 2.08 (s, 3H), 1.65−1.61 (m, 2H), 1.36−1.31 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 171.5, 170.6, 170.5, 154.6, 145.5, 139.5, 135.6, 132.0, 130.4, 128.9, 118.2, 107.9, 107.1, 98.4, 88.9, 83.6, 77.7, 74.2, 63.9, 39.6, 36.2, 31.6, 31.0, 22.7, 21.1, 21.0, 14.2; HRMS (FAB) *m*/*z* 529.1949 (M + Na^+ [$C_{28}H_{30}N_2O_7Na$] = 529.1951).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-[(4-pentylphenyl)-ethynyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one [9b(iv)]. Treatment of **9a**(**iv**) (100 mg, 0.20 mmol) with NH_3/MeOH (20 mL) by procedure B [5.5 h, chromatography (MeOH/EtOAc, 1:20 → 1:15)] gave **9b**(**iv**) as a yellow solid (61 mg, 70%): UV max 354, 291 nm (ϵ 30 500, 31 300); UV min 321, 253 nm (ϵ 13 800, 12 900); ^{1}H NMR (DMSO-d_6) δ 8.89 (s, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.18 (s, 1H), 6.14 (t, J = 6.0 Hz, 1H), 5.28 (d, J = 4.5 Hz, 1H), 5.13 (t, J = 5.3 Hz, 1H), 4.25−4.22 (m, 1H), 3.94 (dd, J = 3.8, 7.8 Hz, 1H), 3.71−3.67 (m, 1H), 3.65−3.60 (m, 1H), 2.62 (t, J = 7.5 Hz, 2H), 2.42 (ddd, J = 4.4, 6.1, 13.6 Hz, 1H), 2.09 (dt, J = 6.5, 13.0 Hz, 1H), 1.58 (pent, J = 7.4 Hz, 2H), 1.33−1.23 (m, 4H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 170.4, 153.7, 145.0, 139.5, 136.2, 131.5, 128.9, 117.4, 110.2, 105.2, 96.8, 88.3, 87.9, 78.0, 69.6, 60.7, 41.2, 35.0, 30.8, 30.2, 21.9, 13.8; HRMS (FAB) *m*/*z* 445.1749 (M + Na^+ [$C_{24}H_{26}N_2O_5Na$] = 445.1740). Anal. ($C_{24}H_{26}N_2O_5$) C, H, N.

3-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-phenylethyl)furo[2,3-*d*]pyrimidin-2(3*H*)-one [10a(i)]. Treatment of **9a**(**i**) (136 mg, 0.312 mmol), 10% Pd−C (14 mg), and EtOH (35 mL) by procedure C [3 h, chromatography (EtOAc/hexanes, 3:2)] gave **10a**(**i**) as a white solid (94 mg, 68%): UV max 332, 245 nm; UV min 272, 238 nm; ^{1}H NMR δ 8.15 (s, 1H), 7.50−7.28 (m, 2H), 7.23−7.18 (m, 3H), 6.33 (dd, J = 5.5, 7.5 Hz, 1H), 6.06 (s, 1H), 5.23 (d, J = 6.0 Hz, 1H), 4.43−4.38 (m, 3H), 3.05−2.94 (m, 5H), 2.14−2.06 (m, 1H), 2.13 (s, 3H), 2.04 (s, 3H); ^{13}C NMR δ 172.2, 170.7, 170.5, 159.2, 154.7, 140.1, 134.0, 128.8, 128.5, 126.7, 107.9, 99.7, 88.6, 83.4, 74.3, 63.9, 39.5, 33.1, 30.3, 21.1, 21.0; HRMS (FAB) *m*/*z* 463.1483 (M + Na^+ [$C_{23}H_{24}N_2O_7$-Na] = 463.1481).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-phenylethyl)-furo[2,3-*d*]pyrimidin-2(3*H*)-one [10b(i)]. Treatment of **10a**(**i**) (86 mg, 0.2 mmol) with NH_3/MeOH (15 mL) by procedure B [4.5 h, chromatography (MeOH/EtOAc, 1:20 → 1:10)] gave **10b**(**i**) as a white solid (60 mg, 85%): UV max 331, 245 nm (ϵ 6700, 13 100); UV min 272, 239 nm (ϵ 600, 12 500); ^{1}H NMR (DMSO-d_6) δ 8.66 (s, 1H), 7.29−7.24 (m, 4H), 7.20−7.17 (m, 1H), 6.39 (s, 1H), 6.15 (t, J = 6.3 Hz, 1H), 5.28 (d, J = 4.0 Hz, 1H), 5.12 (t, J = 5.3 Hz, 1H), 4.23−4.20 (m, 1H), 3.89 (dd, J = 3.5, 7.8 Hz, 1H), 3.67 (dt, J = 4.5, 11.5 Hz, 1H), 3.60 (dt, J = 4.5, 12.2 Hz, 1H), 3.00−2.93 (m, 4H), 2.37 (ddd, J = 4.3, 6.0, 13.5 Hz, 1H), 2.04 (dt, J = 6.4, 13.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 171.2, 157.4, 153.8, 140.3, 137.0, 128.4, 128.3, 126.2, 106.2, 100.3, 88.1, 87.4, 69.7, 60.8, 41.2, 32.2, 29.1; HRMS (FAB) *m*/*z* 379.1269 (M + Na^+ [$C_{19}H_{20}N_2O_5Na$] = 379.1270). Anal. ($C_{19}H_{20}N_2O_5$) C, H, N.

3-(3,5-Di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-[2-(4-pentylphenyl)ethyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one [10a(iv)]. Treatment of **9a**(**iv**) (53 mg, 0.11 mmol), 10% Pd−C (8 mg), and EtOH (20 mL) by procedure C [11 h, chromatography (EtOAc/hexanes, 3:2)] gave **10a**(**iv**) as a white solid (42 mg, 75%): UV max 331, 245, 225 nm; UV min 273, 239 nm; ^{1}H NMR δ 8.15 (s, 1H), 7.12−7.09 (m, 4H), 6.33 (dd, J = 5.5, 7.5 Hz, 1H), 6.08 (s, 1H), 5.23 (d, J = 6.0 Hz, 1H), 4.42−4.38 (m, 3H), 2.99−2.93 (m, 5H), 2.60 (t, J = 7.8 Hz, 2H), 2.13 (s, 3H), 2.12−2.06 (m, 1H), 2.04 (s, 3H), 1.59 (pent, J = 7.4 Hz, 2H), 1.34−1.23 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 172.2, 170.7, 170.5, 159.4, 154.7, 141.3, 137.3, 133.9, 128.8, 128.3, 107.9, 99.6, 88.6, 83.4, 74.3, 63.9, 39.5, 35.7, 32.7, 31.7, 31.4, 30.4, 22.7, 21.1, 21.0, 14.3; HRMS (FAB) *m*/*z* 533.2269 (M + Na^+ [$C_{28}H_{34}N_2O_7Na$] = 533.2264).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-[2-(4-pentylphenyl)-ethyl]furo[2,3-*d*]pyrimidin-2(3*H*)-one [10b(iv)]. Treatment of **10a**(**iv**) (39 mg, 0.076 mmol) with NH_3/MeOH (10 mL) by procedure B [3 h, chromatography (MeOH/EtOAc, 1:20)] gave **10b**(**iv**) as a white solid (24 mg, 73%): UV max 331, 245 (ϵ 6100, 12 600); UV min 273, 239 nm (ϵ 600, 12 100); ^{1}H NMR (DMSO-d_6) δ 8.65 (s, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 6.39 (s, 1H), 6.15 (t, J = 6.3 Hz, 1H), 5.29 (d, J = 4.5 Hz, 1H), 5.11 (t, J = 5.3 Hz, 1H), 4.23−4.20 (m, 1H), 3.89 (dd, J = 3.8, 7.8 Hz, 1H), 3.67−3.63 (m, 1H), 3.61−3.57 (m, 1H), 2.97−2.94 (m, 2H), 2.91−2.88 (m, 2H), 2.53−2.49 (m, 2H), 2.36 (ddd, J = 4.1, 6.1, 13.1 Hz, 1H), 2.03 (dt, J = 6.5, 13.0 Hz, 1H), 1.52 (pent, J = 7.5 Hz, 2H), 1.30−1.20 (m, 4H), 0.84 (t, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 171.2, 157.6, 153.8, 140.1, 137.5, 137.0, 128.3, 128.2, 106.3, 100.3, 88.1, 87.4, 69.7, 60.8, 41.2, 34.8, 31.8, 30.9, 30.7, 29.1, 22.0, 14.0; HRMS (FAB) *m*/*z* 449.2048 (M + Na^+ [$C_{24}H_{30}N_2O_5Na$] = 449.2052). Anal. ($C_{24}H_{30}N_2O_5$) C, H, N.

General Procedures for Synthesis of 14 and 15. We first employed a procedure reported for the synthesis of 2-bromo-5-methylpyridine,[12] which involves lithiation of 3-alkylpyridines[11] **12** (12 mmol) at C6 followed by C6 bromination.[12] The resulting 5-alkyl-2-bromopyridine intermediates were subjected to Sonogashira coupling with TMS−acetylene followed by desilylation with TBAF to give **13**.

(i) TMS−acetylene (0.60 mL, 420 mg, 4.25 mmol) and then $(Ph_3P)_4Pd$ (190 mg, 0.16 mmol) and CuI (22 mg, 0.26 mmol) were added to a deoxygenated solution of 2-bromo-5-butylpyridine (700 mg, 3.27 mmol) in CH_2Cl_2/Et_3N (3:2, 10 mL), and the mixture was stirred at 50 °C for 2 h. Volatiles were evaporated, and the residue was chromatographed (hexanes → EtOAc/hexanes, 1:10) to give an oil (650 mg), which was dissolved in THF (3 mL). (ii) TBAF/THF (1 M, 3 mL) was added to the solution, which was stirred for 30 min. Volatiles were evaporated, and the residue was chromatographed (hexanes → EtOAc/hexanes, 1:10) to give **13a** as an unstable oil [300 mg, 57% (two steps)]. (iii) CH_2Cl_2 (6 mL) and Et_3N (5 mL) were added to 1-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-iodouracil (900 mg, 1.59 mmol) in a 30 mL flask equipped with a Teflon valve, and N_2 was bubbled through the stirred solution for 10 min. Addition of **13a** (254 mg, 1.60 mmol) was followed by $(Ph_3P)_4Pd$ (72 mg, 0.06 mmol) and CuI (19 mg, 0.08 mmol), and stirring was continued for 1.5 h at 50 °C. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:2 → EtOAc) to give **14a** (745 mg, 97%). (iv) A portion of **14a** (240 mg, 0.39 mmol) was stirred with KOH (65 mg, 1.16 mmol) in MeOH (6.5 mL) for 1 h at ambient temperature. The solution was neutralized (37% HCl/H_2O), and volatiles were evaporated. Chromatography (EtOAc → EtOAc/MeOH, 10:1) gave 5-[(5-butylpyrid-2-yl)ethynyl]-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)uracil (116 mg, 78%). (v) A solution of this alkyne (230 mg, 0.60 mmol) and CuI (113 mg, 0.60 mmol) in DMF (3 mL) and Et_3N (3 mL) was stirred for 3 h at 80 °C. Volatiles were evaporated, and the residue was chromatographed (first with EtOAc → EtOAc/MeOH, 10:1, and then with CH_2Cl_2 → CH_2Cl_2/MeOH, 10:1) to give **15a** (220 mg, 96%), which was recrystallized (MeOH).

5-[2-(5-Butylpyrid-2-yl)ethynyl]-1-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]uracil (14a). ^{1}H NMR δ 0.93 (t, J = 7.3 Hz, 3H), 1.31−1.40 (m, 2H), 1.54−1.64 (m, 2H), 2.24, 2.41 (2 × s, 2 × 3H), 2.24−2.40 (m, 1H), 2.59 (t, J = 7.8 Hz, 2H), 2.77 (dd, J = 5.4, 14.2 Hz, 1H), 4.57−4.59 (m, 1H), 4.65 (dd, J = 3.4, 12.2 Hz, 1H), 4.79 (dd, J = 3.9, 12.2 Hz, 1H), 5.59 (d, J = 6.3 Hz, 1H), 6.40 (dd, J = 5.9, 8.8 Hz, 1H), 7.14−7.28 (m, 5H), 7.42 (dd, J = 2.0, 7.8 Hz, 1H), 7.91−7.94 (m, 4H), 8.08 (s, 1H), 8.42 (d, J = 2.0 Hz, 1H), 9.80 (br s, 1H); ^{13}C NMR δ 13.6, 21.3, 21.5, 22.0, 32.3, 32.7, 37.9, 64.0, 74.7, 80.0, 82.9, 85.6, 92.3, 99.9, 126.1, 126.2, 126.6, 129.0, 129.1, 129.4, 129.5, 135.6,

137.4, 139.8, 142.7, 143.8, 144.1, 149.4, 149.7, 161.1, 165.6, 165.9; FAB-MS *m/z* 622 ([M + H$^+$], 10%), 270 (100%); HRMS *m/z* 622.2550 (M + H$^+$ [$C_{36}H_{36}N_3O_7$] = 622.2553).

6-(5-Butylpyrid-2-yl)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-furo[2,3-*d*]pyrimidin-2(3*H*)-one (15a). ^{1}H NMR (CD_3OD) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.35−1.43 (m, 2H), 1.60−1.66 (m, 2H), 2.24 (td, *J* = 6.1, 13.7 Hz, 1H), 2.63 (ddd, *J* = 4.4, 5.9, 12.2 Hz, 1H), 2.67 (t, *J* = 7.8 Hz, 2H), 3.81, 3.92 (2 × dd, *J* = 3.4, 12.2 Hz, 2 × 1H), 4.07−4.09 (m, 1H), 4.23−4.39 (m, 1H), 7.24, 7.735, 7.738, 8.41, 9.05 (5 × s, 5 × 1H); ^{13}C NMR (CD_3OD) δ 14.3, 23.5, 33.6, 34.5, 43.0, 62.4, 71.4, 89.9, 90.2, 102.9, 109.3, 121.3, 138.8, 140.8, 140.9, 146.1, 151.2, 155.6, 156.9, 172.9; FAB-MS *m/z* 408 ([M + Na$^+$], 45%), 270 (100%); HRMS *m/z* 408.1520 (M + Na$^+$ [$C_{20}H_{23}N_3O_5Na$] = 408.1535).

1-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl)-5-[2-(5-hexylpyrid-2-yl)ethynyl]uracil (14c). ^{1}H NMR δ 0.88 (t, *J* = 7.3 Hz, 3H), 1.26−1.38 (m, 6H), 1.56−1.65 (m, 2H), 2.25, 2.43 (2 × s, 2 × 3H), 2.30−2.36 (m, 1H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.77 (dd, *J* = 5.4, 14.2 Hz, 1H), 4.56−4.58 (m, 1H), 4.65, 4.80 (2 × dd, *J* = 3.4, 12.2 Hz, 2 × 1H), 5.60 (d, *J* = 6.3 Hz, 1H), 6.39 (dd, *J* = 5.9, 8.8 Hz, 1H), 7.15−7.30 (m, 5H), 7.43 (dd, *J* = 2.0, 7.8 Hz, 1H), 7.91−7.94 (m, 4H), 8.06 (s, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 8.99 (br s, 1H); ^{13}C NMR δ 14.0, 21.5, 21.6, 22.5, 28.7, 30.8, 31.5, 32.8, 38.3, 64.1, 74.8, 79.6, 83.1, 85.8, 92.7, 100.2, 126.2 (2C), 126.3, 126.8, 129.2, 129.4, 129.5, 129.7, 135.7, 137.7, 139.9, 142.5, 144.1, 144.4, 149.3, 150.0, 161.0, 165.8, 166.1; FAB-MS *m/z* 650 ([M + H$^+$], 50%), 298 (100%); HRMS *m/z* 650.2858 (M + H$^+$ [$C_{38}H_{40}N_3O_7$] = 650.2866).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(5-hexylpyrid-2-yl)-furo[2,3-*d*]pyrimidin-2(3*H*)-one (15c). ^{1}H NMR (DMSO-d_6) δ 0.85 (t, *J* = 7.3 Hz, 3H), 1.24−1.36 (m, 6H), 1.55−1.64 (m, 2H), 2.12 (td, *J* = 6.1, 13.7 Hz, 1H), 2.42−2.47 (m, 1H), 2.41−2.44 (m, 1H), 2.63 (t, *J* = 7.8 Hz, 2H), 3.63−3.75 (m, 2H), 3.95−3.98 (m, 1H), 4.25−4.29 (m, 1H), 5.19 (t, *J* = 5.4 Hz, 1H), 5.34 (d, *J* = 4.4 Hz, 1H), 6.19 (t, *J* = 6.1 Hz, 1H), 7.30, 8.52, 8.92 (3 × s, 3 × 1H), 7.74−7.78 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 14.0, 22.1, 28.3, 30.5, 31.1, 32.0, 41.2, 60.8, 69.7, 87.8, 88.3, 101.7, 106.4, 119.4, 136.9, 138.3, 139.3, 144.6, 150.2, 153.3, 153.8, 171.1; FAB-MS *m/z* 436 ([M + Na$^+$], 25%), 298 (100%); HRMS *m/z* 436.1848 (M + Na$^+$ [$C_{22}H_{27}N_3O_5Na$] = 436.1848).

General Procedures for Synthesis of 20. (i) A solution of 5-bromo-2-iodopyridine (**6**) (1.6 g, 5.63 mmol) in CH_2Cl_2 (10 mL) and Et_3N (8 mL) was deoxygenated with a stream of nitrogen. Addition of 1-hexyne (0.70 mL, 500 mg, 6.1 mmol) was followed by $(Ph_3P)_4Pd$ (320 mg, 0.28 mmol, 0.05 equiv) and CuI (80 mg, 0.42 mmol, 0.07 equiv), and the mixture was stirred for 7 h at 60 °C. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:6) to give crude 5-bromo-2-(hex-1-yn-1-yl)-pyridine (**17b**) (1.34 g): ^{1}H NMR δ 0.94 (m, 3H), 1.45−1.52 (m, 2H), 1.58−1.64 (m, 2H), 2.43 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.74 (dd, *J* = 2.4, 8.3 Hz, 1H), 8.59 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR δ 13.2, 18.6, 21.6, 29.8, 79.1, 92.0, 118.8, 127.3, 138.1, 141.8, 150.3.

(ii) A solution of this material in EtOH (25 mL) and Et_3N (0.5 mL) was hydrogenated[13] over PtO_2 (80 mg) for 24 h. Volatiles were evaporated to give 5-bromo-2-hexylpyridine (**17d**): ^{1}H NMR δ 0.86−0.92 (m, 3H), 1.24−1.38 (m, 6H), 1.66−1.74 (m, 2H), 2.74 (t, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.07 (dd, *J* = 2.4, 8.3 Hz, 1H), 8.57 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR δ 13.8, 22.3, 28.8, 29.5, 31.4, 37.5, 117.5, 123.7, 138.4, 149.9, 160.8; FAB-MS *m/z* 242 ([M + H$^+$], 100%); HRMS *m/z* 242.0538 (M + H$^+$ [$C_{11}H_{17}BrN$] = 242.0539).

[The intermediate 2-(2-alkylpyrid-5-yl)ethynes **18c** and **18d** were prepared from the respective 2-alkyl-5-bromopyridines **17c** and **17d** (by the procedure described for the conversion of 5-alkyl-2-bromopyridines → **13**) and used directly (**18c** and **18d** → **19c** and **19d**). The pyridine-2,5-diyne **18a** was obtained from **17a** by the same procedure.]

(iii) A 30 mL round-bottom flask equipped with a Teflon valve was charged with 1-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-iodouracil (1.00 g, 1.76 mmol), CH_2Cl_2 (6 mL), and Et_3N (5 mL), and N_2 was bubbled through the stirred solution for 10 min. Alkyne **18a** (300 mg, 1.75 mmol) was added followed by $(Ph_3P)_4Pd$ (100 mg, 0.09 mmol, 0.05 equiv) and CuI (27 mg, 0.14 mmol, 0.08 equiv). Stirring was continued for 7 h at 60 °C, and volatiles were evaporated. Chromatography of the residue (EtOAc/hexanes, 1:2 → EtOAc) gave **19a** (0.85 g, 79%). (iv) This material was stirred for 1 h in a solution of KOH (150 mg, 2.68 mmol) in MeOH (20 mL). Neutralization (37% HCl/H_2O), evaporation of volatiles, and chromatography (EtOAc → EtOAc/MeOH, 10:1) gave a solid (510 mg, 92%). (v) A solution of this material (510 mg, 1.28 mmol) and CuI (240 mg, 1.28 mmol) in DMF (3.5 mL) and Et_3N (3.5 mL) was stirred for 4 h at 80 °C. Volatiles were evaporated, and the residue was chromatographed (first with EtOAc → EtOAc/MeOH, 10:1, and second with CH_2Cl_2 → CH_2Cl_2/MeOH, 10:1) to give **20a** (460 mg, 90%), which was recrystallized (MeOH).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-[2-(pent-1-yn-1-yl)-pyrid-5-yl]furo[2,3-*d*]pyrimidin-2(3*H*)-one (20a). ^{1}H NMR (DMSO-d_6) δ 1.02 (t, *J* = 7.3 Hz, 3H), 1.56−1.64 (m, 2H), 2.12 (td, *J* = 6.1, 13.2 Hz, 1H), 2.40−2.53 (m, 4H), 3.62−3.75 (m, 2H), 3.92−3.96 (m, 1H), 4.24−4.28 (m, 1H), 5.23 (t, *J* = 5.1 Hz, 1H), 5.33 (d, *J* = 4.4 Hz, 1H), 6.18 (t, *J* = 6.1 Hz, 1H), 7.49, 8.96 (2 × s, 2 × 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 8.15 (dd, *J* = 1.9, 8.3 Hz, 1H), 9.00 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.4, 20.5, 21.4, 41.3, 60.6, 69.4, 80.9, 87.8, 88.2, 92.5, 102.0, 106.4, 122.3, 126.9, 131.9, 139.1, 142.7, 145.9, 150.6, 153.7, 171.0; FAB-MS *m/z* 418 ([M + Na$^+$], 25%), 279 (100%); HRMS *m/z* 418.1378 (M + Na$^+$ [$C_{21}H_{21}N_3O_5Na$] = 418.1379).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(2-pentylpyrid-5-yl-)furo[2,3-*d*]pyrimidin-2(3*H*)-one (20c). ^{1}H NMR (DMSO-d_6) δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.25−1.37 (m, 4H), 1.64−1.74 (m, 2H), 2.12 (td, *J* = 6.1, 13.2 Hz, 1H), 2.40−2.46 (m, 1H), 2.50−2.54 (m, 1H), 2.77 (t, *J* = 7.8 Hz, 2H), 3.62−3.76 (m, 2H), 3.92−3.96 (m, 1H), 4.24−4.29 (m, 1H), 5.18 (t, *J* = 5.4 Hz, 1H), 5.30 (d, *J* = 4.4 Hz, 1H), 6.19 (t, *J* = 6.1 Hz, 1H), 7.36, 8.91 (2 × s, 2 × 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 8.08 (dd, *J* = 1.9, 8.3 Hz, 1H), 8.95 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.9, 21.9, 28.6, 30.9, 37.3, 41.3, 60.6, 69.4, 87.7, 88.2, 100.3, 106.5, 122.1, 122.8, 132.1, 138.5, 145.1, 151.4, 153.7, 162.6, 171.0; FAB-MS *m/z* 400 ([M + H$^+$], 35%), 117 (100%); HRMS *m/z* 400.1882 (M + H$^+$ [$C_{21}H_{26}N_3O_5$] = 400.1867).

General Procedures for Synthesis of 22 and 23. (i) A solution of 2-amino-5-bromopyrimidine (**21**) (1.6 g, 9.2 mmol) in DMSO (12 mL) and Et_3N (6 mL) was deoxygenated with a stream of N_2. Addition of 1-pentyne (0.70 g, 1.0 mL, 10.25 mmol) was followed by $(Ph_3P)_4Pd$ (530 mg, 0.46 mmol) and CuI (140 mg, 0.74 mmol). The mixture was stirred for 5 h at 55 °C, and volatiles were evaporated. The residue was suspended in hot MeOH and filtered. Recrystallization (MeOH) gave 2-amino-5-(pent-1-yn-1-yl)pyrimidine (1.67 g, 79%): ^{1}H NMR δ 1.04 (t, *J* = 7.3 Hz, 3H), 1.58−1.66 (m, 2H), 2.38 (t, *J* = 6.8 Hz, 2H), 5.20 (br s, 2H), 8.32 (s, 2H); ^{13}C NMR δ 13.5, 21.4, 22.1, 74.6, 93.5, 109.9, 160.4, 160.9; FAB-MS *m/z* 162 ([M + H$^+$], 100%); HRMS *m/z* 162.1025 (M + H$^+$ [$C_9H_{12}N_3$] = 162.1031). (ii) A solution of this material (700 mg, 4.35 mmol) in MeOH (20 mL) was hydrogenated at 60 psi over 10% Pd−C (80 mg) for 24 h. Volatiles were evaporated, and the residue was chromatographed (CH_2Cl_2 → EtOAc) to give 2-amino-5-pentylpyridine (**22a**): ^{1}H NMR δ 0.84 (t, *J* = 6.8 Hz, 3H), 1.22−1.34 (m, 4H), 1.46−1.55 (m, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 5.44 (br s, 2H), 8.08 (s, 2H); ^{13}C NMR δ 13.9, 22.3, 29.4, 30.7, 31.0, 124.6, 157.8, 161.8; FAB-MS *m/z* 166 ([M + H$^+$], 100%); HRMS *m/z* 166.1339 (M + H$^+$ [$C_9H_{16}N_3$] = 166.1344).

(i) 2-Amino-5-(hex-1-yn-1-yl)pyrimidine was used for hydrogenation. ^{1}H NMR δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.42−1.62 (m, 4H), 2.40 (t, *J* = 7.3 Hz, 2H), 5.30 (br s, 2H), 8.31 (s, 2H); ^{13}C NMR δ 13.5, 19.1, 22.0, 30.7.1, 74.5, 93.5, 109.5, 160.3, 161.0; FAB-MS *m/z* 176 ([M + H$^+$], 100%); HRMS *m/z* 176.1179 (M + H$^+$ [$C_{10}H_{14}N_3$] = 176.1088). (ii) Hydrogenation of this material gave 2-amino-5-hexylpyridine (22b). (iii) Benzyltriethylammonium nitrite[15] ($BTEANO_2$) (2.60 g, 10.9 mmol) in CH_2Cl_2 (20 mL) was added to a stirred solution of **22b** (600 mg, 3.35 mmol) and TMSCl

(4.28 mL, 3.67 g, 33.8 mmol) in CH_2Cl_2 (16 mL). Stirring was continued for 3 h at ambient temperature, and volatiles were evaporated. The residue was chromatographed (CH_2Cl_2) to give 2-chloro-5-(hexyl)pyrimidine (**23b**) (450 mg, 68%): ^{1}H NMR δ 0.89 (t, J = 6.8 Hz, 3H), 1.27−1.38 (m, 6H), 1.59−1.65 (m, 2H), 2.60 (t, J = 7.8 Hz, 2H), 8.45 (s, 2H); ^{13}C NMR δ 13.6, 22.1, 28.2, 29.1, 30.1, 31.0, 133.8, 158.6, 158.9; FAB-MS *m*/*z* 199 ([M + H$^+$], 100%); HRMS *m*/*z* 199.1003 (M + H$^+$ [$C_{10}H_{16}ClN_2$] = 199.1002).

General Procedures for Synthesis of 24 and 25. (i) Sonogashira couplings of **23** and TMS−acetylene followed by desilylation were performed as described for conversions of the 5-alkyl-2-bromopyridines → **13**. (ii) Sonogashira couplings of the resulting 5-alkyl-2-ethynylpyrimidines with 1-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-iodouracil were followed by (iii) removal of the *p*-toluoyl groups and (iv) cyclization (as described for **13** → **14** → **15**).

1-[2-Deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]-5-[2-(5-pentylpyrimid-2-yl)ethynyl]uracil (24a). ^{1}H NMR δ 0.91 (t, J = 7.3 Hz, 3H), 1.31−1.38 (m, 4H), 1.60−1.67 (m, 2H), 2.29, 2.43 (2 × s, 2 × 3H), 2.26−2.32 (m, 1H), 2.60 (t, J = 7.8 Hz, 2H), 2.77 (ddd, J = 1.5, 5.4, 14.2 Hz, 1H), 4.56−4.59 (m, 1H), 4.65, 4.82 (2 × dd, J = 3.4, 12.2 Hz, 2 × 1H), 5.59 (d, J = 6.3 Hz, 1H), 6.35 (dd, J = 5.4, 8.3 Hz, 1H), 7.18, 7.27, 7.91, 7.93 (4 × d, J = 8.3 Hz, 4 × 2H), 7.26, 8.13, 8.54 (3 × s, 3 × 1H), 8.39 (br s, 1H); ^{13}C NMR δ 13.8, 21.5, 21.6, 22.2, 30.1, 30.2, 31.1, 38.2, 64.0, 74.9, 78.7, 83.2, 86.0, 91.7, 99.3, 126.3, 126.5, 129.1, 129.2, 129.6, 129.7, 134.1, 143.9, 144.0, 144.3, 149.3, 150.3, 156.8, 160.7, 165.7, 166.1; FAB-MS *m*/*z* 637 ([M + H$^+$], 70%), 285 (100%); HRMS *m*/*z* 637.2657 (M + H$^+$ [$C_{36}H_{37}N_4O_7$] = 637.2662).

3-(2-Deoxy-β-D-*erythro*-pentofuranosyl)-6-(5-pentylpyrimid-2-yl)furo[2,3-*d*]pyrimidin-2(3*H*)-one (25a). ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 7.3 Hz, 3H), 1.26−1.36 (m, 4H), 1.59−1.66 (m, 2H), 2.12 (td, J = 5.8, 13.7 Hz, 1H), 2.45 (ddd, J = 4.4, 5.9, 13.7 Hz, 1H), 2.50−2.54 (m, 1H), 2.64 (t, J = 7.8 Hz, 2H), 3.62−3.74 (m, 2H), 3.94−3.97 (m, 1H), 4.23−4.27 (m, 1H), 5.13 (t, J = 5.1 Hz, 1H), 5.30 (d, J = 3.9 Hz, 1H), 6.17 (t, J = 6.1 Hz, 1H), 7.51, 8.99 (2 × s, 2 × 1H), 8.79 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 13.8, 21.8, 29.3, 29.7, 30.7, 41.2, 60.8, 69.7, 88.0, 88.4, 105.9, 106.5, 134.4, 140.6, 151.6, 153.8, 154.1, 157.3, 171.2; FAB-MS *m*/*z* 423 ([M + Na$^+$], 60%), 285 (100%); HRMS *m*/*z* 423.1648 (M + Na$^+$ [$C_{20}H_{24}N_4O_5Na$] = 423.1639).

Solubility Estimates. The UV absorbance of a known concentration (weight/volume) of a *solution* of the test compound in MeOH was determined. A suspension of the same test compound in MeOH in a sealed vial was agitated, and the suspension was allowed to settle periodically. A carefully measured aliquot of the supernatant solution was added to a 50 mL volumetric flask, and MeOH was added to a total of 50 mL. Carefully measured aliquots were diluted to known volumes that gave UV absorbance values between 0.6 and 1.0. Concentrations of the solutions were calculated by the formula $C_x = C_s(A_x/A_s)$ where C_s is the concentration of the known standard solution and A_x and A_s are UV absorbance values for the unknown and standard solutions, respectively. This process was repeated until an approximately constant value was obtained for C_x (usually within 24 h).

Antiviral Assays. The antiviral assays measured inhibition of viral plaque formation or virus-induced cytopathicity in human embryonic lung (HEL) fibroblasts. Varicella-zoster virus (VZV) wild-type strains YS and OKA, thymidine kinase-deficient (TK$^-$) VZV strains 07/1 and YS/R, and human cytomegalovirus (HCMV) strains AD-169 and Davis were used. Confluent HEL cells were grown in 96-well microtiter plates and infected at 20 (VZV) or 100 (HCMV) pfu per well. After a 2 h incubation period, residual virus was removed and the infected cells were further incubated with the medium containing different concentrations of the test compounds (in duplicate). After incubation for 5 days (VZV) or 7 days (HCMV) at 37 °C, plaque formation (VZV) or virus-induced cytopathicity (HCMV) was monitored microscopically after ethanol fixation and staining with Giemsa. Antiviral activity was expressed as the EC_{50} value or concentration of test compound required to reduce viral plaque formation (VZV) or virus-induced cytopathicity (HCMV) by 50%. EC_{50} values were calculated from graphic plots of the percentage of cytopathicity or viral plaque formation as a function of concentration of the test compounds.

Cytotoxicity Assays. Cytotoxicity assays measured inhibition of HEL cell growth. HEL cells were seeded into 96-well microtiter plates (5×10^3 cells/well) and allowed to proliferate for 24 h, and medium containing different concentrations of the test compounds was added. After 3 days of incubation at 37 °C, the cell number was determined with a Coulter counter. The cytostatic concentrations of test compounds required to reduce cell growth by 50% relative to the number of cells in the untreated controls (CC_{50} values) were estimated from graphic plots of the number of cells (percentage of control) as a function of the concentration of the test compounds. Cytotoxicity was expressed as the minimum cytotoxic concentration (MCC) or the concentration that caused a microscopically visible alteration of cell morphology.

Enzyme Assays. IC_{50} values for the test compounds were measured relative to phosphorylation of the labeled natural substrate [CH_3-^{3}H]dThd by VZV TK under the following conditions: the standard reaction mixture (50 μL) contained 50 mM Tris-HCl (pH 8.0), 2.5 mM $MgCl_2$, 10 mM dithiothreitol, 2.5 mM ATP, 10 mM NaF, 1.0 mg/mL bovine serum albumin, 1 μM [CH_3-^{3}H]dThd (0.1 μCi), an appropriate amount of the test compound, and 5 μL of Milli-Q water. The reaction was initiated by addition of enzyme, incubation was continued at 37 °C for 30 min, and an aliquot (45 μL) was applied to DE-81 discs (Whatman, Maidstone, England). The discs were washed 3 times (5 min each) by shaking in 1 mM $HCOONH_4/H_2O$ followed by 5 min in ethanol (70%). The filters were then dried and assayed for radioactivity in a scintillant. IC_{50} values were defined as the test compound concentration required to inhibit phosphorylation of labeled thymidine by 50%.

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Supporting Information Available: Complete chemistry experimental details, spectral data, elemental analysis data, ^{1}H and ^{13}C NMR spectra for test compounds for which elemental analyses were not obtained; X-ray crystallographic data (in CIF format) for the structures in Figures 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) This is Paper 145 in the series "Nucleic Acid Related Compounds". Paper 144 is the following: Liu, J.; Robins, M. J. S_NAr Displacements with 6-(Fluoro, Chloro, Bromo, Iodo, and Alkylsulfonyl)purine Nucleosides: Synthesis, Kinetics, and Mechanism. *J. Am. Chem. Soc.* **2007**, *129*, 5962−5968.

(2) Robins, M. J.; Barr, P. J. Nucleic Acid Related Compounds. 31. Smooth and Efficient Palladium−Copper Catalyzed Coupling of Terminal Alkynes with 5-Iodouracil Nucleosides. *Tetrahedron Lett.* **1981**, *22*, 421−424.

(3) Robins, M. J.; Barr, P. J. Nucleic Acid Related Compounds. 39. Efficient Conversion of 5-Iodo to 5-Alkynyl and Derived 5-Substituted Uracil Bases and Nucleosides. *J. Org. Chem.* **1983**, *48*, 1854−1862.

(4) De Clercq, E.; Descamps, J.; Balzarini, J.; Giziewicz, J.; Barr, P. J.; Robins, M. J. Nucleic Acid Related Compounds. 40. Synthesis and Biological Activities of 5-Alkynyluracil Nucleosides. *J. Med. Chem.* **1983**, *26*, 661−666.

(5) Reviews: (a) McGuigan, C.; Brancale, A.; Barucki, H.; Srinivasan, S.; Jones, G.; Pathirana, R.; Blewett, S.; Alvarez, R.; Yarnold, C. J.; Carangio, A.; Velázquez, S.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Fluorescent Bicyclic Furo Pyrimidine Deoxynucleoside Analogs as Potent and Selective Inhibitors of VZV and Potential Future Drugs for the Treatment of Chickenpox and Shingles. *Drugs Future* **2000**, *25*, 1151−1161. (b) Balzarini, J.; McGuigan, C. Bicyclic Pyrimidine Nucleoside Analogues (BCNAs) as Highly Selective and

Potent Inhibitors of Varicella-Zoster Virus Replication. *J. Antimicrob. Chemother*. **2002**, *50*, 5−9. (c) De Clercq, E. Highly Potent and Selective Inhibition of Varicella-Zoster Virus Replication by Bicyclic Furo[2,3-*d*]pyrimidine Nucleoside Analogues. *Med. Res. Rev.* **2003**, *23*, 253−274.

(6) McGuigan, C.; Barucki, H.; Blewett, S.; Carangio, A.; Erichsen, J. T.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Highly Potent and Selective Inhibition of Varicella-Zoster Virus by Bicyclic Furopyrimidine Nucleosides Bearing an Aryl Side Chain. *J. Med. Chem.* **2000**, *43*, 4993−4997.

(7) McGuigan, C.; Balzarini, J. Aryl Furano Pyrimidines: The Most Potent and Selective Anti-VZV Agents Reported to Date. *Antiviral Res.* **2006**, *71*, 149−153.

(8) (a) Janeba, Z.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E.; Robins, M. J. Synthesis and Biological Evaluation of Acyclic 3-[(2-Hydroxyethoxy)methyl] Analogues of Antiviral Furo- and Pyrrolo-[2,3-*d*]pyrimidine Nucleosides. *J. Med. Chem.* **2005**, *48*, 4690−4696. (b) Robins, M. J.; Miranda, K.; Rajwanshi, V. K.; Peterson, M. A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Synthesis and Biological Evaluation of 6-(Alkyn-1-yl)furo[2,3-*d*]pyrimidin-2(3*H*)-one Base and Nucleoside Derivatives. *J. Med. Chem.* **2006**, *49*, 391−398.

(9) Balzarini, J.; Sienaert, R.; Liekens, S.; Van, Kuilenburg, A.; Carangio, A.; Esnouf, R.; De Clercq, E.; McGuigan, C. Lack of Susceptibility of Bicyclic Nucleoside Analogs, Highly Potent Inhibitors of Varicella-Zoster Virus, to the Catabolic Action of Thymidine Phosphorylase and Dihydropyrimidine Dehydrogenase. *Mol. Pharmacol.* **2002**, *61*, 1140−1145.

(10) Luoni, G.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Bicyclic Nucleoside inhibitors of Varicella−Zoster Virus: The Effect of Branching in the *p*-Alkylphenyl Side Chain. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3791−3796.

(11) Schwab, P. F. H.; Fleischer, F.; Michl, J. Preparation of 5-Brominated and 5,5′-Dibrominated 2,2′-Bipyridines and 2,2′-Bipyrimidines. *J. Org. Chem.* **2002**, *67*, 443−449.

(12) Mathieu, J.; Gros, P.; Fort, Y. Unprecedented C-6 Functionalisation of 3-Picosine Induced by a Methyl to C-6 Lithium Shift. *J. Chem. Soc., Chem. Commun.* **2000**, 951−952.

(13) Tilley, J. W.; Zawoiski, S. A Convenient Palladium-Catalyzed Coupling Approach to 2,5-Disubstituted Pyridines. *J. Org. Chem.* **1988**, *53*, 386−390.

(14) Conde, J. J.; Mendelson, W. Synthesis of SB 222618. A Potential PDE IV Inhibitor. *Tetrahedron Lett.* **2000**, *41*, 811−814.

(15) (a) Francom, P.; Janeba, Z.; Shibuya, S.; Robins, M. J. Nucleic Acid Related Compounds. 116. Nonaqueous Diazotization of Aminopurine Nucleosides. Mechanistic Considerations and Efficient Procedures with *tert*-Butyl Nitrite or Sodium Nitrite. *J. Org. Chem.* **2002**, *67*, 6788−6796. (b) Francom, P.; Robins, M. J. Nucleic Acid Related Compounds. 118. Nonaqueous Diazotization of Aminopurine Derivatives. Convenient Access to 6-Halo- and 2,6-Dihalopurine Nucleosides with Acyl or Silyl Halides. *J. Org. Chem.* **2003**, *68*, 666−669.

(16) Littke, A. F.; Fu, G. C. Palladium-Catalyzed Coupling Reactions of Aryl Chlorides. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4176−4211.

(17) McGuigan, C.; Pathirana, R. N.; Snoeck, R.; Andrei, G.; De Clercq, E.; Balzarini, J. Discovery of a New Family of Inhibitors of Human Cytomegalovirus (HCMV) Based upon Lipophilic Alkyl Furano Pyrimidine Dideoxy Nucleosides: Action via a Novel Non-Nucleosidic Mechanism. *J. Med. Chem.* **2004**, *47*, 1847−1851.

(18) McGuigan, C.; Yarnold, C. J.; Jones, G.; Velazquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. Potent and Selective Inhibition of Varicella-Zoster Virus (VZV) by Nucleoside Analogues with an Unusual Bicyclic Base. *J. Med. Chem.* **1999**, *42*, 4479−4484.

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