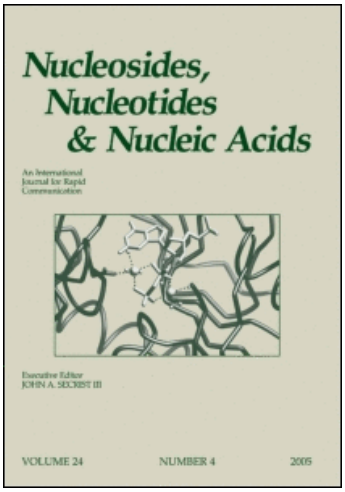


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

An Efficient Alternative Route To 3,6-Disubstituted-Furo[2,3-*d*]Pyrimidin-2-One Analogues

Zlatko Janeba[a]; Noha Maklad[a]; Morris J. Robins[a]
[a] Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah, USA

To cite this Article Janeba, Zlatko , Maklad, Noha and Robins, Morris J.(2005) 'An Efficient Alternative Route To 3,6-Disubstituted-Furo[2,3-*d*]Pyrimidin-2-One Analogues', Nucleosides, Nucleotides and Nucleic Acids, 24: 10, 1729 — 1743
To link to this Article: DOI: 10.1080/10810730500265757
URL: http://dx.doi.org/10.1080/10810730500265757

Nucleosides, Nucleotides, and Nucleic Acids, 24:1729–1743, 2005

ISSN: 1525-7770 print/1532-2335 online
DOI: 10.1080/10810730500265757

Taylor & Francis
Taylor & Francis Group

AN EFFICIENT ALTERNATIVE ROUTE TO 3,6-DISUBSTITUTED-FURO[2,3-*d*]PYRIMIDIN-2-ONE ANALOGUES

Zlatko Janeba, Noha Maklad, and Morris J. Robins □ *Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah, USA*

□ *Copper(I)-catalyzed 5-endo-dig cyclizations of 5-(alkyn-1-yl)uracil derivatives had given poor yields of substituted furo[2,3-d]pyrimidin-2-ones unless the uracil ring was substituted at N1 with alkyl or glycosyl groups. This limited flexibility for the synthesis of analogues with varied substituents at N3 and/or C6 of the furo[2,3-d]pyrimidin-2-one core has been overcome with 5-(3-hydroxyalkyn-1-yl)uracil compounds with no substituent at N1. Manipulation of the side-chain hydroxyl group gives access to additional furo[2,3-d]pyrimidin-2-one analogues.*

Keywords 5-(Alkyn-1-yl)uracil derivatives; Copper(I)-catalyzed cyclizations; Furo[2,3-*d*]pyrimidin-2-ones; Synthesis

INTRODUCTION

Highly potent and selective antiviral activity has been discovered with derivatives of furo[2,3-*d*]pyrimidin-2(3*H*)-one (**1**) (Figure 1). In 1981 Robins and Barr reported the first nucleoside analogues with this ring system, as by-products in Pd/Cu-catalyzed Sonogashira coupling reactions of terminal alkynes with 5-iodouracil nucleosides.[1] We then demonstrated that derivatives of **1** were produced by treatment of 5-(alkyn-1-yl)uracil (base and nucleoside) compounds with CuI and Et_3N in MeOH.[1,2] We had reported antiviral activity with shorter chain 5-(alkyn-1-yl)uracil nucleosides, but the activity was lost with longer chain analogues.[3] Two decades later,

In honor and celebration of the life and career of John. A. Montgomery.

Nucleic Acid Related Compounds. 130. Paper 129 is reference 19.

Current address for Zlatko Janeba: Moravek Biochemicals, Brea, CA.

Current address for Noha Maklad: Pfizer Inc., Groton, CT.

Received 28 December 2004; accepted 6 May 2005.

Pharmaceutical company gift funds (M.J.R.) and Brigham Young University support of this research are gratefully acknowledged.

Address correspondence to Professor Morris J. Robins, Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602-5700. Fax: (801) 422-0153; E-mail: morris_robins@byu.edu

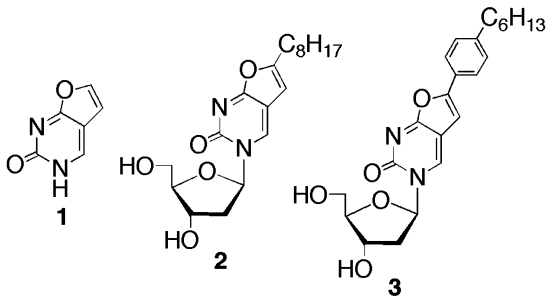


FIGURE 1 Structures of furo[2,3-*d*]pyrimidin-*2*-one (**1**) and potent anti-VZV derivatives.

the remarkable potency and selectivity of longer chain derivatives of ring system **1** against varicella zoster virus (VZV) were discovered.[4–6] Extensive structure-activity studies by McGuigan and coworkers have revealed that 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 (**2**, Figure 1) gave marked selectivity and potency against VZV. Analogues with even greater potency were produced by insertion of a (*para*-substituted) phenyl ring into the alkyl side-chain (**3**, Figure 1).[7] Compounds such as **3** have the greatest potency against VZV with EC_{50} values as low as 1 nM. Initial phosphorylation by a specific VZV kinase was indicated because activity was reduced with kinase-depleted mutants. These analogues were all prepared by minor modifications of the methodology we reported in 1981.[1]

We became interested in different synthetic approaches that would allow greater structural diversity and flexibility of starting materials. We prepared new analogues with different sugar substituents at N3 of the furopyrimidine system, and included a 3-alkyl derivative as a negative control for VZV activity (no kinase activation possible).[8a] As expected, the 3-alkyl compound showed no activity against VZV. However, we were surprised to find that this non-nucleoside derivative had activity against human cytomegalovirus (HCMV).[8b] The De Clercq-Balzarini-McGuigan team have reported anti-HCMV activity with 2′,3′-dideoxynucleoside analogues of the furo[2,3-*d*]pyrimidin-2-one ring, which also function as "non-nucleoside" agents that are not activated by a viral kinase.[9]

Furo[2,3-*d*]pyrimidin-2-one (**1**) has been prepared by cyclization of (*E*)-5-(2-bromovinyl)uracil (BVU) with potassium tert-butoxide,[10,11] or by our Cu(I)-promoted 5-endo-dig cyclization[1,2] of 5-ethynyluracil.[12] However, both of these multistep routes from uracil suffer from very low overall yields. Consistently high yields of the Cu(I)-promoted cyclization products have been realized only with 1-(alkyl or glycosyl)uracil derivatives. A one-pot procedure that involves Sonogashira coupling followed by heating the derived 5-alkynyluracil intermediate with additional CuI has also been

employed.[12–14] However, attempted cyclization of 5-ethynyl-1-tosyluracil with CuI failed to give detected amounts of the targeted furopyrimidin-2-one.[12] Recently, iodo- and bromocyclization of substituted systems to give analogous bicyclo-furano ring systems have been reported.[15,16]

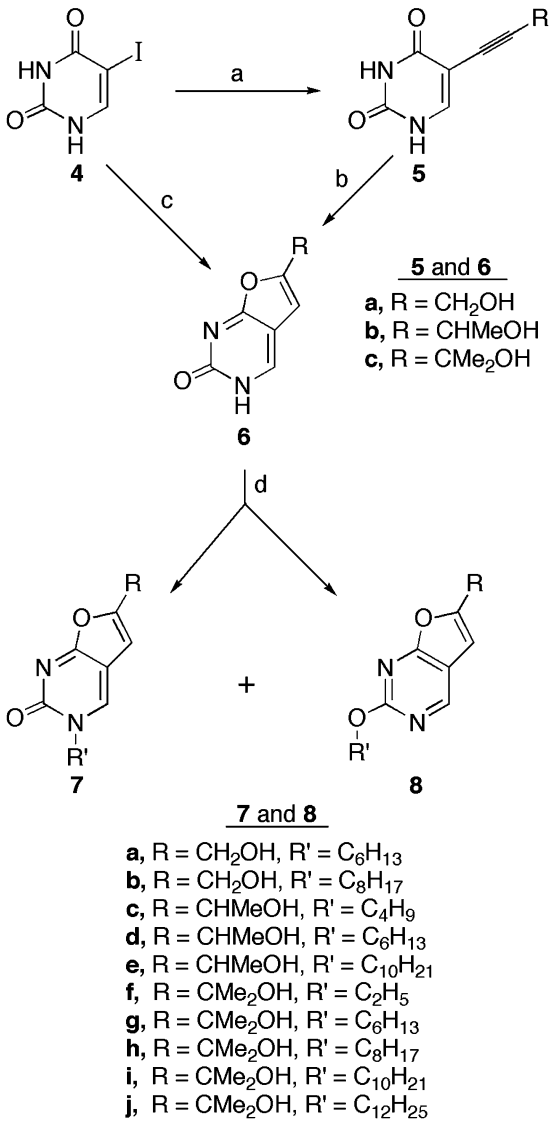
It is noteworthy that Botta and coworkers[17] failed to obtain 5-(3-hydroxypropyn-1-yl)uracil derivatives by attempted Sonogashira coupling of the corresponding 5-iodouracil derivatives and propargyl alcohol (under usual conditions with DMF as solvent at ambient temperature[18]). Instead, moderate yields of the cyclized furopyrimidine derivatives were noted, and microwave irradiation was employed to enhance yields of those cyclized products.[17] We now describe successful Sonogashira couplings of 5-iodouracil with propargyl alcohol and related alkynols with ethyl acetate as solvent at ambient temperature, and Cu(I)-promoted 5-endo-dig cyclizations of the 5-(3-hydroxyalkyn-1-yl)uracil bases without N1 substituents.

RESULTS AND DISCUSSION

Sonogashira couplings of 5-iodouracil (**4**, Scheme 1) with propargyl alcohol, 3-butyn-2-ol, and 2-methyl-3-butyn-2-ol at ambient temperature afforded the 5-alkynyl uracils **5a–c**, respectively, in good yields (56–89%). Longer reaction times resulted in the formation of additional intensely fluorescent spots (TLC), which indicated generation of furo[2,3-*d*]pyrimidin-2-one by-products. Cu(I)-promoted cyclization of such 5-alkynyluracil derivatives usually required elevated temperatures for reasonable reaction rates. Observation of fluorescent by-products during ambient-temperature Sonogashira couplings indicated more readily promoted cyclizations of **5** (with a side-chain hydroxyl group) relative to those of previously studied 5-alkynyluracils.[12] We then evaluated cyclizations of **5** under standard reaction conditions (1 equiv. of CuI, Et_3N, MeCN, 80°C). These proceeded quite cleanly (TLC), and the purified bicyclic derivatives **6a–c** were isolated in yields of 60, 60, and 49%, respectively.

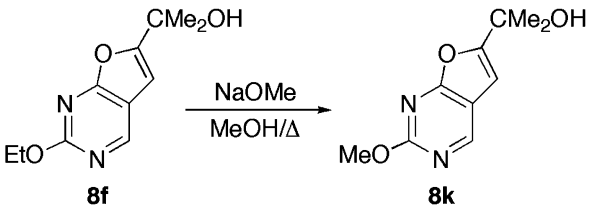
We next performed the cyclization step without purification of the coupled intermediates **5**. The coupling mixture (2-methyl-3-butyn-2-ol/$Pd(PPh_3)_4$/CuI/Et_3N/EtOAc) was stirred at room temperature until **4** was no longer detected (TLC). The solid precipitate was filtered, washed (EtOAc, Et_2O), and dried. This material was treated with fresh CuI (1 equiv.) in Et_3N/MeCN (1:20) at 80°C for 5 h to give **6c** (73% overall from **4**). Acetonitrile was the best solvent we tried for this cyclization.

We then studied the in situ coupling/cyclization of **4** with 3-butyn-2-ol. The best result (of the combinations of DMF, EtOAc, and MeOH we examined) was obtained with a mixture of EtOAc/MeOH/DMF (10:2.5:1). Sonogashira coupling of **4** with 3-butyn-2-ol was performed at room temperature, and then CuI (0.5 equiv.) and Et_3N were added. The reaction mixture was heated at 80°C, and **6b** was obtained in 61% yield.



SCHEME 1 Reagents and conditions: (a) RC≡CH/$Pd(PPh_3)_4$/CuI/Et_3N/EtOAc; (b) CuI/Et_3N/MeCN/Δ; (c)(i) RC≡CH/$Pd(PPh_3)_4$/CuI/Et_3N/EtOAc/DMF/MeOH; (ii) CuI/Et_3N/Δ; (d) R′I/K_2CO_3/DMF.

The 6-substituted-furo[2,3-*d*]pyrimidin-2-one derivatives **6** are new substrates for further modifications. A straightforward approach involves alkylation at N3 of the fused pyrimidine ring, followed by transformations of the hydroxyalkyl substituents at C6 of the furan ring. Treatment of **6** with iodoalkanes/K_2CO_3/DMF at ambient temperature gave the targeted 3-substituted derivatives **7** (33–63%) plus their *O*-alkylated isomers **8** (12–32%).



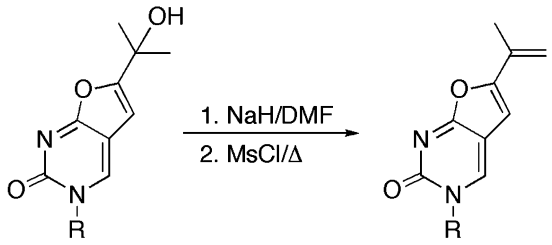
8f **8k**

SCHEME 2 S_NAr displacement of ethoxide by methoxide at C2.

Compounds with an alkyl group at N1 were not detected. The N3-alkyl derivatives **7** were recrystallized easily (EtOAc or EtOAc/EtOH), whereas the isomers **8** were oils that solidified under vacuum. Certain of these alkoxy compounds were recrystallized (quite low recovery) from either a nonpolar solvent (**8d**; hexanes) or a polar solvent mixture (**8f–8j**; H_2O/MeOH). Melting points of the N3-alkyl compounds **7** were greater than 140°C, whereas the O-alkyl isomers **8** had mp <100°C. The site of alkylation at O2 for the **8** isomers was indicated by HMBC NMR experiments with **8f** [coupling of the proximal methylene protons of the ethyl group was observed only with C2 (^3J)]. Chemical corroboration was provided by S_NAr replacement of the ethoxyl group at C2 of **8f** by a methoxyl group. Thus, heating a solution of **8f** in MeONa/MeOH gave **8k** (Scheme 2).

A variety of compounds can be prepared from alkenes. Treatment of **6c** and **7f–h** with NaH/MsCl/DMF resulted in mesylation of the side-chain hydroxyl group followed by in situ elimination to give the corresponding 6-(1-methylvinyl) derivatives **9** (62–74%) (Scheme 3).

In conclusion, we have developed an alternative approach for the synthesis of 6-substituted-furo[2,3-*d*]pyrimidin-2-ones, which can be modified at N3 and C6 to afford potential new antiviral compounds. The first clean and efficient Cu(I)-promoted 5-endo-dig cyclizations of 5-(alkyn-1-yl)uracil



6c, R = H
7f, R = C_2H_5
7g, R = C_6H_{13}
7h, R = C_8H_{17}

9a, R = H
9b, R = C_2H_5
9c, R = C_6H_{13}
9d, R = C_8H_{17}

SCHEME 3 In situ mesylation/elimination to give 1-methylvinyl derivatives.

derivatives without N1 alkyl or glycosyl substituents are described. Sonogashira couplings with 5-iodouracil followed by in situ cyclizations constitute a superior method (73% overall yield of **6c**), which can be scaled (~14 g) for the preparation of this key 6-substituted-furo[2,3-*d*]pyrimidin-2-one derivative. A possible reason for the enhanced ease of cyclization of these 5-(3-hydroxyalkyn-1-yl)uracils is an increased equilibrium complexation of Cu(I) with the hydroxyl group in proximity with the alkyne triple bond. Treatment of such 6-substituted-furo[2,3-*d*]pyrimidine-2-ones with iodoalkanes gave N3/O2 (average ratio of ~2.5:1) alkylated derivatives, with no N1 alkylation observed. Synthesis of various 3,6-disubstituted-furo[2,3-*d*]pyrimidin-2-one analogues for biological evaluation are in progress.

EXPERIMENTAL SECTION

General Methods

Uncorrected melting points were determined with a hot-stage apparatus. All UV spectra were determined 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 peaks were poorly resolved. 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 CH_2Cl_2/MeOH solutions.

Method 1, Sonogashira coupling, (5-iodouracil/1-alkyne/$Pd(PPh_3)_4$/CuI/Et_3N/EtOAc) is described in detail for **4** → **5a**. Method 2, CuI-promoted 5-endo-dig cyclization, (**5**/CuI/Et_3N/MeCN) is described for **5a** → **6a**. Method 3, alkylation, (**6**/iodoalkane/K_2CO_3/DMF) is described for **6a** → **7a** + **8a**. Method 4, in situ mesylation/elimination, (**7**/NaH/MsCl/DMF) is described for **7f** → **9b**.

5-(3-Hydroxypropyn-1-yl)uracil (5a). Method 1. 5-Iodouracil (**4**, 15 g, 63 mmol), propargyl alcohol (4.8 mL, 4.6 g, 82 mmol), $Pd(Ph_3P)_4$ (800 mg, 0.69 mmol), and CuI (1.3 g, 6.8 mmol) were added to a deoxygenated solution of Et_3N (21 mL) and EtOAc (600 mL). The solution was stirred at ambient temperature overnight (or until the reaction was completed, TLC). Volatiles were evaporated under vacuum, and toluene was added and evaporated (3 × 20 mL). The residue was dissolved in hot MeOH (150 mL), and the insoluble solids were filtered. Volatiles were evaporated, cold Me_2CO (100 mL) was added, and the suspension was filtered. The collected solid was recrystallized (EtOH) to give **5a** (9.3 g, 89%): mp >200°C (dec.); UV max 287, 230 nm (ε 10,500, 12,300); ^{1}H NMR δ 4.21 (d, J = 4.0 Hz, 2H), 7.73 (d, J = 4.0 Hz, 1H), 11.30 (br s, 2H); ^{13}C NMR δ 162.6, 150.4,

145.4, 96.8, 92.1, 76.5, 49.5; HRMS (EI) *m/z* 166.0375 ($M^+[C_7H_6N_2O_3]$ = 166.0378).

5-(3-Hydroxybutyn-1-yl)uracil (5b). Treatment of **4** (2.4 g, 10 mmol) and 3-butyn-2-ol (1.0 mL, 0.9 g, 13 mmol) by method 1 gave **5b** (1.01 g, 56%): mp 239–240°C; UV max 287, 228 nm (ε 11,900, 13,400); ^{1}HNMR δ 1.32 (d, J = 6.6 Hz, 3H), 4.50–4.52 (m, 1H), 5.37 (d, J = 5.5 Hz, 1H), 7.69 (d, J = 6.0 Hz, 1H), 11.21 (d, J = 5.5 Hz, 1H), 11.33 (s, 1H); ^{13}C NMR δ 162.7, 150.5, 145.3, 96.9, 95.6, 75.0, 56.7, 24.6; HRMS (EI) *m/z* 180.0536 ($M^+[C_8H_8N_2O_3]$ = 180.0535). Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.23; H, 4.60; N, 15.45.

5-(3-Hydroxy-3-methylbutyn-1-yl)uracil (5c). Treatment of **4** (2.4 g, 10 mmol) and 2-methyl-3-butyn-2-ol (1.3 mL, 1.1 g, 13 mmol) by method 1 gave **5c** (1.53 g, 79%): mp >210°C (dec.); UV max 287, 228 nm (ε 10,300, 12,000); ^{1}H NMR δ 1.40 (s, 6H), 5.37 (s, 1H), 7.65 (d, J = 5.5 Hz, 1H), 11.20 (d, J = 3.5 Hz, 1H), 11.31 (s, 1H); ^{13}C NMR δ 162.6, 150.5, 145.2, 98.2, 97.0, 73.3, 63.6, 31.7; HRMS (EI) *m/z* 194.0703 (M^+ $[C_9H_{10}N_2O_3]$ = 194.0691). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.40; H, 5.29; N, 14.30.

6-Hydroxymethylfuro[2,3-*d*]pyrimidin-2-one (6a). Method 2. CuI (1.14 g, 6.0 mmol) and **5a** (1.0 g, 6.0 mmol) were added to a deoxygenated solution of Et_3N (2.5 mL) and MeCN (10 mL). The solution was heated at 80°C for 12 h, and volatiles were evaporated under vacuum. Toluene was added and evaporated (2 × 5 mL). Chromatography ($MeOH/CH_2Cl_2$) gave **6a** (0.60 g, 60%) as a yellow solid with mp >200°C (dec.); UV max 325, 243 nm (ε 5000, 13,400); ^{1}H NMR δ 4.42 (d, J = 5.5 Hz, 2H), 5.51 (t, J = 6.0 Hz, 1H), 6.53 (s, 1H), 8.24 (s, 1H), 12.05 (br s, 1H); ^{13}C NMR δ 172.2, 156.8, 155.9, 140.2, 105.5, 100.9, 55.8; HRMS (EI) *m/z* 166.0378 (M^+ $[C_7H_6N_2O_3]$ = 166.0378). Anal. Calcd for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.55; H, 3.92; N, 16.72.

6-[(1-Hydroxy)ethyl]furo[2,3-*d*]pyrimidin-2-one (6b). Procedure A. Treatment of **5b** (200 mg, 1.1 mmol) by method 2 gave **6b** (120 mg, 60%) as a yellow solid. An analytical sample was recrystallized (EtOH) to give white crystals with mp 215–216°C; UV max 326, 244 nm (ε 5200, 15,500); ^{1}H NMR δ 1.37 (d, J = 6.5 Hz, 3H), 4.66–4.69 (m, 1H), 5.58 (d, J = 5.5 Hz, 1H), 6.45 (s, 1H), 8.22 (s, 1H), 12.03 (s, 1H); ^{13}C NMR δ 172.1, 160.2, 155.9, 140.1, 105.5, 98.9, 61.8, 21.3; HRMS (EI) *m/z* 180.0545 (M^+ $[C_8H_8N_2O_3]$ = 180.0535). Anal. Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.23; H, 4.60; N, 15.45.

Procedure B. Compound **4** (11.9 g, 50 mmol), $Pd(Ph_3P)_4$ (2.9 g, 2.5 mmol), and CuI (775 mg, 4.1 mmol) were added to a deoxygenated mixture

of DMF (12 mL), EtOAc (120 mL), and MeOH (30 mL). 3-Butyn-2-ol (5.0 mL, 4.5 g, 64 mmol) and Et_3N (40 mL) were added, and the reaction mixture was stirred at ambient temperature for 20 h. CuI (4.75 g, 25 mmol) and Et_3N (15 mL) were added, and the mixture was heated at reflux (80°C) for 3 h. Solids were filtered (hot), and volatiles were evaporated. Chromatography ($MeOH/CH_2Cl_2$, 8:92) gave **6b** (5.5 g, 61%) as a white solid. A recrystallized sample (MeOH) had identical spectral data as the material prepared in procedure A.

6-[(1-Hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidin-2-one (6c). Procedure A. Treatment of **5c** (2.1 g, 10.8 mmol) by method 2 gave **6c** (1.03 g, 49%): mp >250°C (dec.); UV max 326, 243 nm (ε 4800, 14,500); ^{1}H NMR δ 1.43 (s, 6H), 5.47 (s, 1H), 6.41(s, 1H), 8.21 (s, 1H), 12.03 (br s, 1H); ^{13}C NMR δ 172.1, 162.7, 155.9, 140.0, 105.7, 97.6, 67.2, 28.3; HRMS (EI) *m/z* 194.0682 (M^+ [$C_9H_{10}N_2O_3$] = 194.0691). Anal. Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.40; H, 5.29; N, 14.30.

Procedure B. 2-Methyl-3-butyn-2-ol (12.5 mL, 10.85 g, 0.13 mol) and then deoxygenated Et_3N (70 mL) were added to a deoxygenated mixture of **4** (23.8 g, 0.10 mol), $Pd(Ph_3P)_4$ (3.5 g, 3.0 mmol), and CuI (1.55 g, 8.1 mmol) in EtOAc (300 mL). The reaction mixture was stirred at ambient temperature for 3.5 h (TLC), and cooled at 4°C. The precipitated solid was filtered, washed (cold EtOAc, Et_2O), and dried in vacuo. The dried solid and CuI (18.0 g, 95 mmol) were added to a deoxygenated solution of MeCN (500 mL) and Et_3N (50 mL), and the stirred mixture was heated at reflux for 5 h. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 1:9). Recrystallization of the residue ($EtOH/H_2O$) gave **6c** (14.2 g, 73%) as white crystals with identical spectral data as material prepared in procedure A.

3-Hexyl-6-(hydroxymethyl)furo[2,3-*d*]pyrimidin-2-one (7a) and 2-Hexyloxy-6-(hydroxymethyl)furo[2,3-*d*]pyrimidine (8a). Method 3. A mixture of **6a** (530 mg, 3.2 mmol), K_2CO_3 (484 mg, 3.5 mmol), and 1-iodohexane (0.57 mL, 814 mg, 3.8 mmol) in DMF (8 mL) was stirred at ambient temperature for 20 h. The mixture was filtered with Celite, and the filter cake was washed with DMF (10 mL). The combined volatiles were evaporated in vacuo, and toluene was added and evaporated (2 × 10 mL). Chromatography of the residue ($MeOH/CHCl_3$, 5:95) gave **7a** and **8a**. Recrystallization (EtOAc/EtOH) gave **7a** (376 mg, 47%) as white crystals: mp 178–179°C; UV max 331, 245 nm (ε 6600, 11,800); ^{1}H NMR δ 0.84 (t, J = 5.9 Hz, 3H), 1.26 (s, 6H), 1.64–1.66 (m, 2H), 3.92 (t, J = 7.3 Hz, 2H), 4.42 (d, J = 5.85 Hz, 2H), 5.52 (t, J = 5.86 Hz, 1H), 6.57 (s, 1H), 8.55 (s, 1H); ^{13} C NMR δ 171.3, 157.0, 154.5, 143.1, 105.6, 100.7, 55.8, 50.9, 30.8, 28.3, 25.5, 21.9, 13.9; HRMS *m/z* 273.1208 (MNa^+ [$C_{13}H_{18}N_2O_3Na$] = 273.1215). Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 61.96; H, 7.40; N, 10.88.

Yellow solid **8a** (152 mg, 19%) had: mp 77–78°C; UV max 289, 240 nm (ε 7400, 12,400); ^{1}H NMR ($CDCl_3$) δ 0.85–0.87 (m, 3H), 1.28–1.31 (m, 4H), 1.43–1.44 (m, 2H), 1.76–1.80 (m, 2H), 3.94 (br s, 1H), 4.35 (t, J = 6.8 Hz, 2H), 4.75 (s, 2H), 6.61 (s, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.7, 162.9, 156.3, 151.9, 113.3, 101.2, 68.4, 57.6, 31.7, 28.9, 25.7, 22.7, 14.2; HRMS *m/z* 273.1219 (MNa^+ [$C_{13}H_{18}N_2O_3Na$] = 273.1215).

6-Hydroxymethyl-3-octylfuro[2,3-*d*]pyrimidin-2-one (7b) and 6-Hydroxymethyl-2-(octyloxy)furo[2,3-*d*]pyrimidine (8b). Treatment of **6a** (390 mg, 2.4 mmol), K_2CO_3 (365 mg, 2.6 mmol), and 1-iodooctane (0.52 mL, 692 mg, 2.9 mmol) in DMF (7 mL) by method 3 gave **7b** (295 mg, 45%) as white crystals: mp 176–177°C; UV max 331, 245 nm (ε 6100, 11,000); ^{1}H NMR δ 0.84 (t, J = 6.8 Hz, 3H), 1.24–1.26 (m, 10H), 1.64–1.67 (m, 2H), 3.92 (t, J = 7.3 Hz, 2H), 4.43 (d, J = 5.9 Hz, 2H), 5.51 (t, J = 5.9 Hz, 1H), 6.57 (s, 1H), 8.55 (s, 1H); ^{13}C NMR δ 171.3, 157.0, 154.4, 143.0, 105.6, 100.6, 55.6, 50.8, 31.1, 28.6, 28.5, 28.3, 25.8, 22.0, 13.9; HRMS (EI) *m/z* 278.1638 (M^+ [$C_{15}H_{22}N_2O_3$] = 278.1630). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.53; H, 7.88; N, 9.89.

Yellow solid **8b** (137 mg, 21%) had: mp 65–67°C; UV max 289, 240 nm (ε 7000, 10,800); ^{1}H NMR ($CDCl_3$) δ 0.85–0.87 (m, 3H), 1.27–1.34 (m, 8H), 1.45–1.48 (m, 2H), 1.78–1.84 (m, 2H), 3.02 (br s, 1H), 4.37–4.39 (m, 2H), 4.76 (s, 2H), 6.63 (s, 1H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.8, 163.2, 156.0, 152.1, 113.3, 101.4, 68.5, 57.8, 32.0, 29.5, 29.4, 29.0, 26.1, 22.8, 14.3; HRMS *m/z* 301.1532 (MNa^+ [$C_{15}H_{22}N_2O_3Na$] = 301.1528).

3-Butyl-6-(1-hydroxyethyl)furo[2,3-*d*]pyrimidin-2-one (7c) and 2-Butyloxy-6-(1-hydroxyethyl)furo[2,3-*d*]pyrimidine (8c). Treatment of **6b** (500 mg, 2.8 mmol), K_2CO_3 (422 mg, 3.1 mmol), and 1-iodobutane (0.38 mL, 618 mg, 3.4 mmol) in DMF (10 mL) by method 3 gave **7c** (305 mg, 46%) as white crystals (EtOAc): mp 141°C; UV max 331, 245 nm (ε 6800, 12,500); ^{1}H NMR δ 0.89 (t, J = 7.3 Hz, 3H), 1.24–1.31 ("hex", J = 7.4 Hz, 2H), 1.38 (d, J = 6.8 Hz, 3H), 1.61–1.67 ("quint", J = 7.3 Hz, 2H), 3.93 (t, J = 7.1 Hz, 2H), 4.66–4.71 ("quint", J = 6.2 Hz, 1H), 5.59 (d, J = 5.4 Hz, 1H), 6.51 (s, 1H), 8.54 (s, 1H); ^{13}C NMR δ 171.2, 160.4, 154.5, 143.0, 105.6, 98.8, 61.8, 50.6, 30.5, 21.3, 19.1, 13.6; HRMS (EI) *m/z* 236.1152 (M^+ [$C_{12}H_{16}N_2O_3$] = 236.1161). Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.85; H, 7.05; N, 11.65.

Yellow solid **8c** (120 mg, 18%) had: mp 79–80°C; UV max 290, 240 nm (ε 7100, 11,600); ^{1}H NMR δ 0.92 (t, J = 7.3 Hz, 3H), 1.38–1.49 (m, 5H), 1.68–1.74 ("quint", J = 7.1 Hz, 2H), 4.31 (t, J = 6.6 Hz, 2H), 4.78–4.83 ("quint", J = 6.2 Hz, 1H), 5.65 (d, J = 5.4 Hz, 1H), 6.75 (s, 1H), 8.80 (s, 1H); ^{13}C NMR δ 167.9, 162.0, 160.6, 152.1, 113.2, 99.0, 67.0, 62.0, 30.4, 21.6, 18.7, 13.7; HRMS (EI) *m/z* 236.1156 (M^+ [$C_{12}H_{16}N_2O_3$] = 236.1161).

3-Hexyl-6-(1-hydroxyethyl)furo[2,3-*d*]pyrimidin-2-one (7d) and 2-Hexyloxy-6-(1-hydroxyethyl)furo[2,3-*d*]pyrimidine (8d). Treatment of **6b** (1.0 g, 5.6 mmol), K_2CO_3 (851 mg, 6.2 mmol), and 1-iodohexane (1.0 mL, 1.4 g, 6.7 mmol) in DMF (15 mL) by method 3 gave **7d** (758 mg, 51%) as white crystals (EtOAc): mp 141–142°C; UV max 331, 245 nm (ε 7400, 13,500); ^{1}H NMR δ 0.83 (t, J = 6.4 Hz, 3H), 1.25–1.28 (m, 6H), 1.38 (d, J = 6.4 Hz, 3H), 1.63–1.66 (m, 2H), 3.92 (t, J = 7.3 Hz, 2H), 4.67–4.71 (m, 1H), 5.59 (d, J = 5.4 Hz, 1H), 6.51 (s, 1H), 8.54 (s, 1H); ^{13}C NMR δ 171.2, 160.4, 154.5, 143.0, 105.6, 98.8, 61.8, 50.9, 30.8, 28.4, 25.5, 21.9, 21.3, 13.9; HRMS (EI) *m/z* 264.1474 (M^+ [$C_{14}H_{20}N_2O_3$] = 264.1474). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.80; H, 7.52; N, 10.44.

Yellow solid **8d** (280 mg, 19%) was recrystallized (hexanes) to give white crystals of **8d**: mp 58–59°C; UV max 290, 240 nm (ε 7100, 12,300); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.32–1.35 (m, 4H), 1.47–1.49 (m, 2H), 1.62 (d, J = 6.4 Hz, 3H), 1.79–1.85 ("quint", J = 7.1 Hz, 2H), 2.75 (d, J = 5.4 Hz, 1H), 4.38 (t, J = 6.8 Hz, 2H), 4.99–5.01 (m, 1H), 6.58 (s, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.6, 163.1, 159.6, 152.0, 113.3, 99.3, 68.4, 64.0, 31.7, 29.0, 25.8, 22.8, 21.5, 14.2; HRMS *m/z* 287.1373 (MH^+ [$C_{14}H_{20}N_2O_3Na$] = 287.1372). Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.69; H, 7.50; N, 10.71.

3-Decyl-6-(1-hydroxyethyl)furo[2,3-*d*]pyrimidin-2-one (7e) and 2-Decyloxy-6-(1-hydroxyethyl)furo[2,3-*d*]pyrimidine (8e). Treatment of **6b** (1.0 g, 5.6 mmol), K_2CO_3 (851 mg, 6.2 mmol), and 1-iododecane (1.44 mL, 1.8 g, 6.7 mmol) in DMF (15 mL) by method 3 gave **7e** (588 mg, 33%) as white crystals (EtOAc): mp 142–144°C; UV max 331, 245 nm (ε 7200, 12,900); ^{1}H NMR δ 0.84 (t, J = 6.8 Hz, 3H), 1.22–1.25 (m, 14H), 1.38 (d, J = 6.8 Hz, 3H), 1.65–1.66 (m, 2H), 3.91 (t, J = 7.3 Hz, 2H), 4.67–4.70 (m, 1H), 5.59 (d, J = 5.4 Hz, 1H), 6.51 (s, 1H), 8.54 (s, 1H); ^{13}C NMR δ 171.2, 160.4, 154.5, 143.0, 105.6, 98.8, 61.8, 50.9, 31.3, 28.93, 28.90, 28.7, 28.6, 28.4, 25.8, 22.1, 21.3, 14.0; HRMS (EI) *m/z* 320.2092 (M^+ [$C_{18}H_{28}N_2O_3$] = 320.2099). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.62; H, 8.69; N, 8.51.

Yellow solid **8e** (213 mg, 12%) was recrystallized (H_2O/EtOH) to give white crystals of **8e**: mp 64°C; UV max 289, 240 nm (ε 6600, 11,600); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.26–1.36 (m, 12H), 1.44–1.49 ("quint", J = 7.3 Hz, 2H), 1.63 (d, J = 6.8 Hz, 3H), 1.80–1.86 ("quint", J = 7.2 Hz, 2H), 2.57 (br s, 1H), 4.39 (t, J = 6.6 Hz, 2H), 4.98–5.02 ("q", J = 6.5 Hz, 1H), 6.58 (s, 1 H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.6, 163.1, 159.5, 152.1, 113.3, 99.3, 68.4, 64.1, 32.1, 29.8, 29.6, 29.5, 29.0, 26.1, 22.9, 21.5, 14.3; HRMS (EI) *m/z* 320.2096 (M^+ [$C_{18}H_{28}N_2O_3$] = 320.2099). Anal. Calcd for $C_{18}H_{28}N_2O_3 \cdot 0.25H_2O$: C, 66.54; H, 8.84; N, 8.62. Found: C, 66.56; H, 8.50; N, 8.55.

3-Ethyl-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidin-2-one (7f) and 2-Ethyloxy-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidine (8f). Treatment of **6c** (2.0 g, 10.3 mmol), K_2CO_3 (1.57 g, 11.3 mmol), and 1-iodoethane (1.00 mL, 1.93 g, 12.4 mmol) in DMF (30 mL) by method 3 gave **7f** (1.45 g, 63%) as white crystals (EtOAc): mp 179–180°C; UV max 331, 245 nm (ε 6600, 12,700); ^{1}H NMR δ 1.24 (t, J = 6.8 Hz, 3H), 1.44 (s, 6H), 3.96 (q, J = 6.8 Hz, 2H), 5.47 (s, 1H), 6.46 (s, 1H), 8.54 (s, 1H); ^{13}C NMR δ 171.2, 162.9, 154.3, 142.6, 105.9, 97.4, 67.2, 46.1, 28.3, 14.3; HRMS (EI) *m/z* 222.1007 (M^+ [$C_{11}H_{14}N_2O_3$] = 222.1004). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.37; H, 6.24; N, 12.46.

Yellow solid **8f** (360 mg, 16%) was recrystallized (H_2O/EtOH) to give white crystals of **8f**: mp 99°C; UV max 290, 240 nm (ε 8500, 14,000); ^{1}H NMR ($CDCl_3$) δ 1.44 (t, J = 7.1 Hz, 3H), 1.66 (s, 6H), 2.59 (br s, 1H), 4.45 (q, J = 7.1 Hz, 2H), 6.55 (s, 1H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.5, 162.8, 162.3, 152.0, 113.4, 97.9, 69.4, 64.0, 28.7, 14.6; HRMS (EI) *m/z* 222.1007 (M^+ [$C_{11}H_{14}N_2O_3$] = 222.1004). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.60; H, 6.52; N, 12.85.

3-Hexyl-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidin-2-one (7g) and 2-Hexyloxy-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidine (8g). Treatment of **6c** (2.0 g, 10.3 mmol), K_2CO_3 (1.57 g, 11.3 mmol), and 1-iodohexane (1.83 mL, 2.63 g, 12.4 mmol) in DMF (30 mL) by method 3 gave **7g** (1.52 g, 53%) as white crystals (EtOAc): mp 180°C; UV max 332, 244 nm (ε 7600, 13,600); ^{1}H NMR δ 0.84 (t, J = 6.5 Hz, 3H), 1.25–1.26 (m, 6H), 1.44 (s, 6H), 1.64–1.65 (m, 2H), 3.92 (t, J = 7.3 Hz, 2H), 5.47 (s, 1H), 6.46 (s, 1H), 8.52 (s, 1H); ^{13}C NMR δ 171.2, 162.9, 154.5, 142.9, 105.8, 97.5, 67.2, 50.8, 30.8, 28.4, 28.3, 25.5, 22.0, 13.9; HRMS (EI) *m/z* 278.1619 (M^+ [$C_{15}H_{22}N_2O_3$] = 278.1630). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.94; H, 8.14; N, 10.18.

Yellow solid **8g** (920 mg, 32%) was recrystallized (H_2O/EtOH) to give white crystals of **8g**: mp 84°C; UV max 291, 240 nm (ε 8100, 13,800); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.0 Hz, 3H), 1.33–1.36 (m, 4H), 1.47–1.48 (m, 2H), 1.67 (s, 6H), 1.82–1.85 (m, 2H), 2.58 (br s, 1H), 4.39 (t, J = 6.8 Hz, 2H), 6.56 (s, 1H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.5, 163.1, 162.2, 152.1, 113.4, 98.0, 69.5, 68.4, 31.8, 29.0, 28.8, 25.9, 22.8, 14.3; HRMS (EI) *m/z* 278.1625 (M^+ [$C_{15}H_{22}N_2O_3$] = 278.1630). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.91; H, 7.79; N, 9.94.

6-[(1-Hydroxy-1-methyl)ethyl]-3-octylfuro[2,3-*d*]pyrimidin-2-one (7h) and 6-[(1-Hydroxy-1-methyl)ethyl]-2-(octyloxy)furo[2,3-*d*]pyrimidine (8h). Treatment of **6c** (2.0 g, 10.3 mmol), K_2CO_3 (1.57 g, 11.3 mmol), and 1-iodooctane (2.98 g, 2.26 mL, 12.4 mmol) in DMF (30 mL) by method 3 gave **7h** (1.47 g, 47%) as white crystals: mp 164–165°C; UV max 332, 244 nm

(ε 7300, 13,100); ^{1}H NMR δ 0.84 (t, J = 6.8 Hz, 3H), 1.23–1.26 (m, 10H), 1.44 (s, 6H), 1.64–1.66 (m, 2H), 3.91 (t, J = 7.1 Hz, 2H), 5.47 (s, 1H), 6.46 (s, 1H), 8.52 (s, 1H); ^{13}C NMR δ 171.2, 162.9, 154.5, 142.9, 105.8, 97.5, 67.2, 50.9, 31.2, 28.6, 28.5, 28.4, 28.3, 25.8, 22.1, 13.9; HRMS (EI) *m/z* 306.1941 (M^+ [$C_{17}H_{26}N_2O_3$] = 306.1943). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.84; H, 8.36; N, 9.31.

Yellow solid **8h** (619 mg, 20%) was recrystallized (H_2O/EtOH) to give slightly yellow crystals of **8h**: mp 72–73°C; UV max 291, 240 nm (ε 7900, 13,400); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H), 1.28–1.36 (m, 8H), 1.48 ("q", J = 7.2 Hz, 2H), 1.67 (s, 6H), 1.84 ("q", J = 7.1 Hz, 2H), 2.26 (br s, 1H), 4.40 (t, J = 6.6 Hz, 2H), 6.56 (s, 1H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.6, 163.1, 162.2, 152.1, 113.4, 97.9, 69.5, 68.4, 32.0, 29.5, 29.4, 29.0, 28.8, 26.2, 22.9, 14.3; HRMS *m/z* 307.2008 (MH^+ [$C_{17}H_{27}N_2O_3$] = 307.2022). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.72; H, 8.64; N, 9.10.

3-Decyl-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidin-2-one (7i) and 2-Decyloxy-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidine (8i). Treatment of **6c** (2.0 g, 10.3 mmol), K_2CO_3 (1.57 g, 11.3 mmol), and 1-iododecane (2.66 mL, 3.33 g, 12.4 mmol) in DMF (30 mL) by method 3 gave **7i** (2.05 g, 60%) as white crystals (EtOAc): mp 158–160°C; UV max 332, 245 nm (ε 7000, 12,500); ^{1}H NMR δ 0.83 (t, J = 6.6 Hz, 3H), 1.22–1.31 (m, 14H), 1.43 (s, 6H), 1.64–1.65 (m, 2H), 3.91 (t, J = 7.3 Hz, 2H), 5.47 (s, 1H), 6.45 (s, 1H), 8.53 (s, 1H); ^{13}C NMR δ 171.2, 162.9, 154.5, 142.9, 105.8, 97.4, 67.2, 50.8, 31.3, 28.93, 28.89, 28.7, 28.6, 28.4, 28.3, 25.8, 22.1, 13.9; HRMS (EI) *m/z* 334.2263 (M^+ [$C_{19}H_{30}N_2O_3$] = 334.2256). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.40; H, 8.90; N, 8.32.

Yellow solid **8i** (815 mg, 24%) was recrystallized (H_2O/EtOH) to give slightly yellow crystals of **8i**: mp 81–82°C; UV max 291, 240 nm (ε 7900, 13,600); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H), 1.26–1.35 (m, 12H), 1.44–1.50 ("quint", J = 7.4 Hz, 2H), 1.66 (s, 6H), 1.80–1.85 ("quint", J = 7.1 Hz, 2H), 2.48 (br s, 1H), 4.38 (t, J = 6.6 Hz, 2H), 6.56 (s, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.6, 163.0, 162.3, 152.0, 113.4, 97.9, 69.4, 68.4, 32.1, 29.8, 29.7, 29.6, 29.5, 29.0, 28.7, 26.1, 22.9, 14.3; HRMS (EI) *m/z* 334.2263 (M^+ [$C_{19}H_{30}N_2O_3$] = 334.2256). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C, 68.23; H, 9.04; N, 8.38. Found: C, 68.00; H, 8.85; N, 8.17.

3-Dodecyl-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidin-2-one (7j) and 2-Dodecyloxy-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidine (8j). Treatment of **6c** (300 mg, 1.5 mmol), K_2CO_3 (235 mg, 1.7 mmol), and 1-iododododecane (0.46 mL, 549 mg, 1.9 mmol) in DMF (5 mL) by method 3 gave **7j** (195 mg, 35%) as white crystals (EtOAc): mp 165°C; UV max 332, 244 nm (ε 7200, 12,900); ^{1}H NMR δ 0.84 (t, J = 6.8 Hz, 3H), 1.22–1.26 (m,

18H), 1.44 (s, 6H), 1.63–1.66 (m, 2H), 3.91 (t, $J = 7.3$ Hz, 2H), 5.47 (s, 1H), 6.46 (s, 1H), 8.52 (s, 1H); ^{13}C NMR δ 171.2, 162.9, 154.5, 142.9, 105.8, 97.4, 67.2, 50.8, 31.3, 29.02, 28.96, 28.88, 28.7, 28.6, 28.4, 28.3, 25.8, 22.1, 14.0; HRMS (EI) *m/z* 362.2569 (M^+ [$C_{21}H_{34}N_2O_3$] = 362.2569). Anal. Calcd for $C_{21}H_{34}N_2O_3$: C, 69.58; H, 9.45; N, 7.73. Found: C, 69.40; H, 9.24; N, 7.66.

Yellow solid **8j** (115 mg, 21%) was recrystallized (H_2O/EtOH) to give yellow crystals of **8j**: mp 79–80°C; UV max 291, 240 nm (ε 8000, 13,600); ^{1}H NMR δ 0.84 (t, $J = 6.8$ Hz, 3H), 1.23–1.31 (m, 16H), 1.36–1.42 (m, 2H), 1.49 (s, 6H), 1.70–1.74 (m, 2H), 4.30 (t, $J = 6.5$ Hz, 2H), 5.53 (s, 1H), 6.71 (s, 1H), 8.79 (s, 1H); ^{13}C NMR δ 167.8, 163.1, 162.0, 152.1, 113.3, 97.8, 67.4, 67.3, 31.3, 29.03, 29.01, 28.98, 28.7, 28.6, 28.3, 25.4, 22.1, 14.0; HRMS *m/z* 385.2477 (MNa^+ [$C_{21}H_{34}N_2O_3Na$] = 385.2467). Anal. Calcd for $C_{21}H_{34}N_2O_3$: C, 69.58; H, 9.45; N, 7.73. Found: C, 69.70; H, 9.24; N, 7.83.

2-Methoxy-6-[(1-hydroxy-1-methyl)ethyl]furo[2,3-*d*]pyrimidine (8k). A solution of **8f** (90 mg, 0.4 mmol) in NaOMe/MeOH (1 M, 10 mL) was heated at reflux for 30 h (**8f** was completely reacted, some decomposition products were also formed, TLC), and allowed to cool to ambient temperature. Dowex 50 × 8 (H^+) was added, the mixture was stirred, and the resin was filtered and washed (MeOH). Preparative TLC (MeOH/CH_2Cl_2, 6:94) gave **8k** (25 mg, 30%) as a slightly yellow solid foam: UV max 290, 240 nm (ε 6900, 10,900); ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 6H), 4.06 (s, 3H), 6.58 (s, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 168.6, 163.3, 162.4, 152.0, 113.6, 97.9, 69.4, 55.4, 28.7; HRMS (EI) *m/z* 208.0856 (M^+ [$C_{10}H_{12}N_2O_3$] = 208.0848).

6-(1-Methylvinyl)furo[2,3-*d*]pyrimidin-2-one (9a). NaH (60 mg of a 60% dispersion, 7.3 mmol) was added to a solution of **6c** (97 mg, 0.5 mmol) in DMF (5 mL), and the mixture was stirred at ambient temperature for 30 min. MsCl (0.10 mL, 143 mg, 1.25 mmol) was added, and the reaction mixture was stirred at 50°C for 3 h. The mixture was neutralized (NH_3/H_2O), and volatiles were evaporated. Toluene was added and evaporated (2 × 5 mL), and the residue was chromatographed (MeOH/CH_2Cl_2, 1:9) to give **9a** (58 mg, 66%) as a yellow solid: mp >250°C (dec.); ^{1}H NMR δ 2.01 (s, 3H), 5.26 (s, 1H), 5.58 (s, 1H), 6.69 (s, 1H), 8.28 (s, 1H), 12.14 (bs, 1H); ^{13}C NMR δ 171.9, 155.9, 154.1, 140.5, 131.5, 114.4, 106.3, 101.1, 18.3; HRMS (EI) *m/z* 176.0580 (M^+ [$C_9H_8N_2O_2$] = 176.0586).

3-Ethyl-6-(1-methylvinyl)furo[2,3-*d*]pyrimidin-2-one (9b). Method 4. NaH (216 mg of a 60% dispersion, 5.4 mmol) was added to a solution of **7f** (1.0 g, 4.5 mmol) in DMF (30 mL), and the mixture was stirred at ambient temperature for 20 min. MsCl (0.42 mL, 621 mg, 5.4 mmol) was added, and stirring at 50°C was continued for 6 h. The mixture was neutralized (NH_3/H_2O), and volatiles were evaporated. Toluene was added and evaporated

(2 × 5 mL), and the residue was dissolved (CH_2Cl_2, 100 mL) and the solution was washed (H_2O, 2 × 20 mL) and dried ($MgSO_4$). Volatiles were evaporated, and the brown solid residue was dissolved (MeOH, 100 mL). Charcoal was added, and the mixture was heated at reflux for 10 min. The hot mixture was filtered with Celite, and the filter cake was washed with MeOH. The combined filtrate was evaporated, and the residue was recrystallized (EtOAc) to give **9b** (680 mg, 74%) as white crystals: mp 195°C; UV max 342, 271, 262, 227 nm (ε 11,000, 13,000, 13,700, 13,900); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.3 Hz, 3H), 2.02 (s, 3H), 4.07 (q, J = 7.3 Hz, 2H), 5.24 (s, 1H), 5.76 (s, 1H), 6.32 (s, 1H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.9, 156.6, 155.5, 139.6, 131.1, 116.4, 108.4, 99.1, 47.5, 18.8, 14.9; HRMS (EI) *m/z* 204.0903 (M^+ [$C_{11}H_{12}N_2O_2$] = 204.0899). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.47; H, 5.89; N, 13.49.

3-Hexyl-6-(1-methylvinyl)furo[2,3-*d*]pyrimidin-2-one (9c). Treatment of **7g** (688 mg, 2.5 mmol), NaH (119 mg of a 60% dispersion, 3.0 mmol), and MsCl (0.19 mL, 283 mg, 3.0 mmol) in DMF (20 mL) by method 4 gave **9c** (437 mg, 68%) as white crystals (EtOAc): mp 198°C; UV max 343, 272, 262, 228 nm (ε 11,100, 12,700, 13,300, 14,000); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H), 1.29–1.36 (m, 6H), 1.77–1.83 ("quint", J = 7.3 Hz, 2H), 2.03 (s, 3H), 4.00 (t, J = 7.5 Hz, 2H), 5.26 (s, 1H), 5.78 (s, 1H), 6.31 (s, 1H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.9, 156.7, 155.6, 139.9, 131.1, 116.5, 108.2, 99.0, 52.6, 31.6, 29.3, 26.5, 22.7, 18.8, 14.2; HRMS (EI) *m/z* 260.1527 (M^+ [$C_{15}H_{20}N_2O_2$] = 260.1525). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.10; H, 7.62; N, 10.58.

6-(1-Methylvinyl)-3-octylfuro[2,3-*d*]pyrimidin-2-one (9d). Treatment of **7h** (500 mg, 1.6 mmol), NaH (78 mg of a 60% dispersion, 2.0 mmol), and MsCl (0.15 mL, 225 mg, 2.0 mmol) in DMF (15 mL) by method 4 gave **9d** (290 mg, 62%) as white crystals (EtOAc): mp 196°C; UV max 343, 272, 262, 228 nm (ε 12,400, 14,000, 14,600, 15,200); ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 6.8 Hz, 3H), 1.24–1.32 (m, 10H), 1.76–1.81 ("quint", J = 7.1 Hz, 2H), 2.03 (s, 3H), 3.99 (t, J = 7.5 Hz, 2H), 5.25 (s, 1H), 5.77 (s, 1H), 6.31 (s, 1H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 171.9, 156.6, 155.6, 140.0, 131.1, 116.4, 108.1, 99.0, 52.5, 31.9, 29.33, 29.30, 26.8, 22.8, 18.8, 14.2; HRMS (EI) *m/z* 288.1832 (M^+ [$C_{17}H_{24}N_2O_2$] = 288.1838). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.94; H, 8.14; N, 9.56.

REFERENCES

1. 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.

2. 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.
3. 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.
4. 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 of the Fut. **2000**, 25, 1151–1161.
5. 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.
6. 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.
7. 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.
8. (a) Miranda, K. Approaches to the synthesis of potential antiviral nucleosides. M.S. Thesis, Brigham Young University, 2001. (b) Robins, M.J.; Miranda, K.; De Clercq, E; Balzarini, J. Unpublished results.
9. 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.
10. Bleackley, R.C.; Jones, A.S.; Walker, R.T. Incorporation of 5-substituted uracil derivatives into nucleic acids-III. Synthesis of 5-substituted uracils derived from 5-acetyluracil. Tetrahedron **1976**, 32, 2795–2797.
11. Eger, K.; Jalalian, M.; Schmidt, M. Steric fixation of bromovinyluracil: Synthesis of furo[2,3-*d*]pyrimidine nucleosides. J. Heterocycl. Chem. **1995**, 32, 211–218.
12. Janeba, Z.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E.; Robins, M.J. Synthesis and biological evaluation of 5-(alkyn-1-yl)-1-(*p*-toluenesulfonyl)uracil derivatives. Abstracts of Papers, 229th National Meeting of the American Chemical Society, San Diego, CA; American Chemical Society: Washington, DC, 2005; MEDI 435 (manuscript submitted for publication).
13. 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.
14. Janeba, Z.; Robins, M.J. *N*-[(2-Hydroxyethoxy)methyl] derivatives of bicyclic furano and pyrrolo pyrimidines and their antiviral evaluation. Antiviral Res. **2004**, 62, A64.
15. Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. Electrophilic cyclization of *o*-acetoxy- and *o*-benzyloxyalkynylpyridines: An easy entry into 2,3-disubstituted furopyridines. Org. Lett. **2002**, 4, 2409–2412.
16. Rao, M.S.; Esho, N.; Sergeant C.; Dembinski, R. 5-*Endo-dig* electrophilic cyclization of α-alkynyl carbonyl compounds: Synthesis of novel bicyclic 5-iodo- and 5-bromofuranopyrimidine nucleosides. J. Org. Chem. **2003**, 68, 6788–6790.
17. Petricci, E.; Radi, M.; Corelli, F.; Botta, M. Microwave-enhanced Sonogashira coupling reaction of substituted pyrimidinones and pyrimidine nucleosides. Tetrahedron Lett. **2003**, 44, 9181–9184.
18. Robins, M.J.; Vinayak, R.S.; Wood, S.G. Solvent, not palladium oxidation state, is the primary determinant for successful coupling of terminal alkynes with iodo-nucleosides. Tetrahedron Lett. **1990**, 31, 3731–3734.
19. Nowak, I.; Robins, M.J. Hydrothermal deamidation of 4-*N*-acylcytosine nucleoside derivatives: Efficient synthesis of uracil nucleoside esters. Org. Lett. **2005**, 7, 4903–4905.