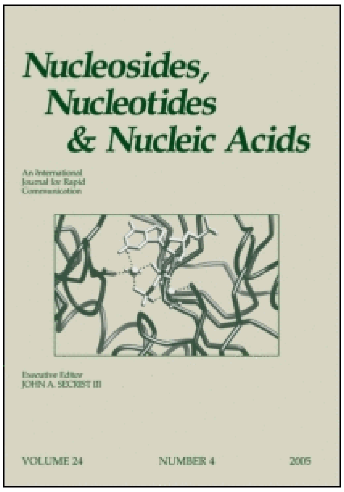

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Acyclic Nucleosides Bearing a Furanyl Scaffold

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ACYCLIC NUCLEOSIDES BEARING A FURANYL SCAFFOLD

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▫ *Synthesis of acyclic nucleosides bearing a furanyl scaffold is described. The approach involved the construction of the base moiety onto a dihydrofuranyl intermediate. While the A and C analogues did exhibit some substrate activity toward deoxycytidine kinase, the compounds were devoid of any significant anti-HIV activity.*

Keywords Furanyl nucleosides, Antiviral, Synthesis

INTRODUCTION

Since the discovery of acyclovir as a potent antiherpetic agent,[1] the structure activity relationship of acyclic nucleosides has been extensively studied. For optimal antiviral activity[2,3] the side chain should be 4 atoms in length and bear a 4′-primary hydroxyl group. Conformationally constricted analogues (type **B** and **C**) of acyclovir, reported previously,[4] showed moderate activity against HSV-1 and HSV-2. Introduction of a rigid methylenecyclopropane moiety between the heterocyclic base and hydroxymethyl group led to the compounds (type **D**)[5] with broad spectrum of antiviral activity. It is of interest to note that 1,2-disubstituted carbonucleosides (type **E**)[6] showed antitumor activity.

Based on the above findings, we designed and synthesized acyclo nucleosides of general structure **F** as potential antiviral agents. In this class of nucleosides, the dihydrofuran moiety can be viewed as a rigid "spacer" between the groups important for antiviral activity, i.e., the heterocyclic base and the hydroxymethyl group.

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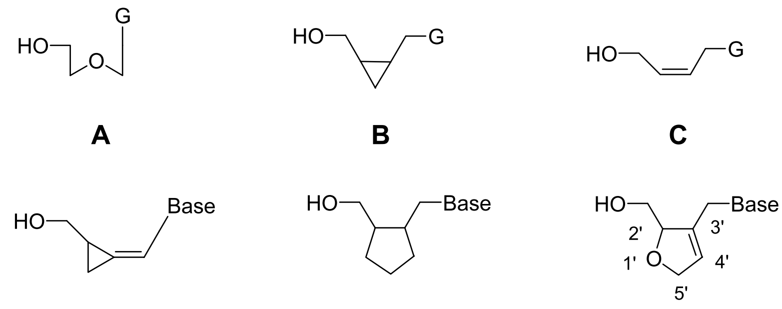
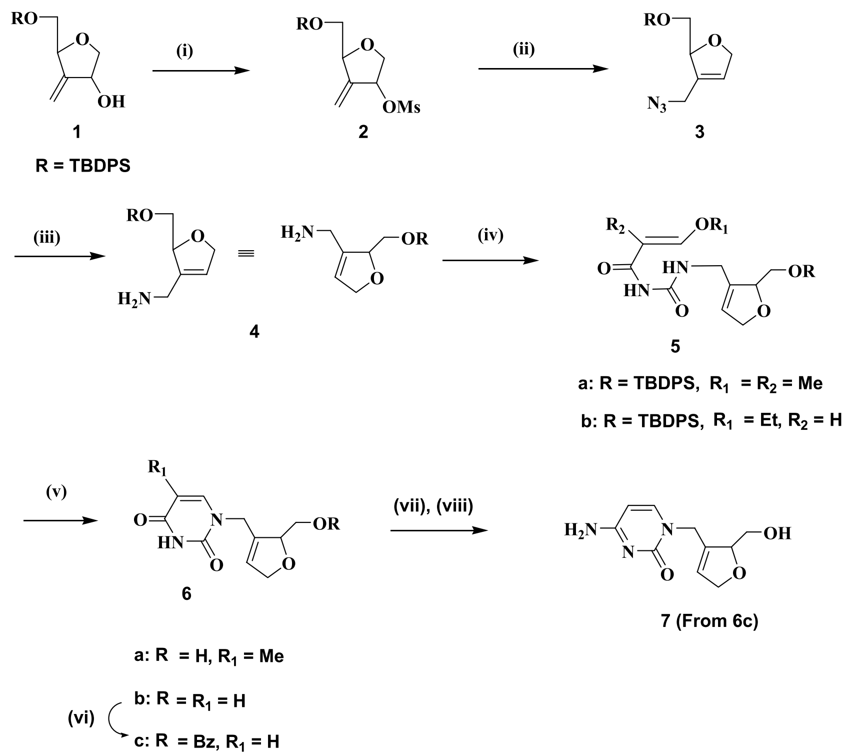
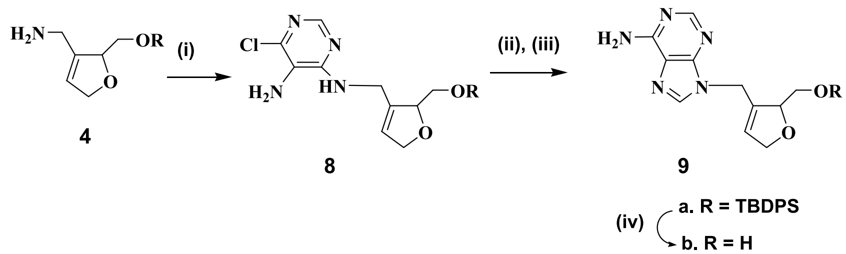


RESULTS AND DISCUSSION

The protected allyl alcohol **1**[7] was chosen as a starting material. Compound **1**, on treatment with MsCl in CH_2Cl_2 at 0°C, gave the mesylated derivative **2** (83%). Reaction of **2** with NaN_3 in DMF at 90°C resulted in the S_N2' product **3** in almost



SCHEME 1 Reaction conditions: (i) MsCl, CH_2Cl_2, Et_3N; (ii) NaN_3, DMF, 90°C; (iii) Ph_3P, pyridine; (iv) 3-methoxy-2-methyl-2-propenoylisocyanate or 3-ethoxy-2-propenoylisocyanate, toluene; (v) 2N H_2SO_4, dioxane; (vi) BzCl, pyridine, 0°C; (vii) (a) TIPSCI, DMAP, Et_3N, (b) NH_4OH; (viii) NaOMe, MeOH.



SCHEME 2 (i) 5-Amino-4,6-dichloropyrimidine, 1-butanol, Et_3N; (ii) c.HCl, triethylorthoformate; (iii) NH_3/MeOH; (iv) NH_4F, MeOH.

quantitative yield. The azido group was selectively reduced to the amino derivative **4** in 84% yield by treating **3** with Ph_3P in pyridine.[8] Compound **4** was the key starting material for the synthesis of the title nucleosides (Scheme 1).

For the synthesis of the pyrimidine nucleosides, the amine **4** was treated with 3-methoxy-2-methyl-2-propenoyl isocyanate or 3-ethoxy-2-propenoyl isocyanate using reported methodology[9–11] to give the acylurea **5a** or **5b**, which, on treatment with 2N H_2SO_4 in dioxane at 100°C, afforded the thymine and uracil derivatives **6a** (55% for 2 steps) and **6b** (characterized as its benzoylated derivative, **6c**, 29% overall yield for 3 steps). The uracil derivative **6c** was converted to the cytosine derivative **7** in 72% yield following literature methodology.[10–12]

Reaction of **4** with 5-amino-4,6-dichloropyrimidine[13,14] gave compound **8**. Acid catalyzed cyclization of **8** with triethyl orthoformate followed by treatment of the resulting product with methanolic ammonia in a steel bomb gave the adenine derivative **9a** (30% yield for 3 steps). Deprotection of **9a** with NH_4F in MeOH produced **9b** (77%). All target molecules and intermediates were characterized by ^{1}H and ^{13}C NMR spectra and HRMS data (Scheme 2).

While compounds **7** and **9b** were phosphorylated by recombinant deoxycytidine kinase,[15] albeit inefficiently, they and compounds **6a** and **6b** were not found to have in vitro antiviral activity against HIV-1 and HIV-2 in infected human T-lymphocytes (CEM cells) up to 100 μg/mL.

EXPERIMENTAL

Melting points reported were uncorrected and were determined on an Electrothermal Engineering, Ltd., melting point apparatus. Ultraviolet (UV) spectra were recorded on a Cary 3 UV-Visible spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-300 and WM-360 NMR instruments. Chemical shifts are referenced to an internal TMS standard for ^{1}H-NMR spectra and to solvent ($CDCl_3$, DMSO-d6, acetone-d6 or CD_3OD) for ^{13}C NMR spectra. Column chromatographic separations were carried out using 230–400 mesh silica gel. High-resolution FAB mass spectral data were obtained on a VG ZAB-HF high-resolution mass spectrometer.

2(*S*)-[*tert*-Butyldiphenylsilyloxy)methyl]-3-(azidomethyl)-2,5-dihydrofuran (3). To a solution of **1**[7] (1.10 g. 3 mmol) in CH_2Cl_2 were added triethylamine (1.66 mL, 12 mmol) and MsCl (0.7 mL, 9 mmol) at 0°C. The reaction mixture was stirred at 0°C for 3 h and then poured into water (75 mL) and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over Na_2SO_4 and evaporated to dryness. The residue was purified over silica gel to produce the mesylated product **2** (1.11 g, 83%) as a viscous oil. To a solution of **2** (0.70 g, 1.56 mmol) in DMF (25 mL) NaN_3 (0.65 g, 10 mmol) was added and the mixture was heated at 90°C for 5 h. The solution was poured into water (150 mL) and extracted with ether (3 × 30 mL). The combined ether layers were washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified over silica gel to give **3** (0.60 g, 98%) as an oil. ^{1}H-NMR ($CDCl_3$): δ 7.68–7.35 (m, 10 H, 2 × phenyl), 5.96 (s, 1H, H-4), 4.79–4.66 (m, 3H, H-2, H-5), 3.99 (d, *J* = 15.0 Hz, 1H), 3.76 (m, 3H), 1.04 (s, 9H, *t*-butyl). ^{13}C-NMR ($CDCl_3$): δ 135.4 (C-3), 135.5, 133.2, 133.1, 129.7, 129.6, 127.6 (2 × phenyl), 125.5 (C-4), 85.9 (C-2), 74.9 (C-5), 65.2 (CH_2-O), 47.9 (CH_2-N), 26.7, 19.1 (t-butyl); HRMS (FAB): $(M + Na)^+$ calc. for $C_{22}H_{27}N_3O_2$-NaSi: 416.1770. Found: 416.1781.

2(*S*)-[*tert*-Butyldiphenylsilyloxy)methyl]-3-(aminomethyl)-2,5-dihydrofuran (4). To a solution of **3** (0.66 g, 1.75 mmol) in pyridine (6 mL) was added triphenylphosphine (0.78 g, 2.97 mmol) and the reaction mixture was stirred at room temperature for 2 h. Aqueous NH_4OH (30%, 6 mL) was added and the solution was stirred for another 2 h. The solvent was removed under reduced pressure and the gummy residue was purified over silica gel column to give **4** (0.52 g, 84%) as a gum. ^{1}H-NMR ($CDCl_3$): δ 7.70–7.34 (m, 10H, 2 × phenyl), 5.73 (s, 1H, H-4), 4.77 (bs, 1H, H-2), 4.63 (m, 2H, H-5), 3.79 (m, 2H, CH_2-O), 3.35 (m, 2H, CH_2-N), 1.02 (s, 9H, *t*-butyl). ^{13}C-NMR ($CDCl_3$): δ 142.9 (C-3), 135.5, 135.4, 133.3, 133.2, 129.6, 129.5, 127.6, 127.5 (2 × phenyl), 120.7 (C-4), 86.4 (C-2), 74.9 (C-5), 65.6 (CH_2-O), 39.4 (CH_2-N), 26.6, 19.1 (t-butyl); HRMS (FAB): $(M + H)^+$ calc. for $C_{22}H_{30}NO_2Si$: 368.2045. Found: 368.2052.

5-Methyl-1-[2′(*S*)-2′-hydroxymethyl-2′,5′-dihydrofuran-3′-yl]-methyl-pyrimidine-2,4(1H,3H)-dione (6a). A solution of 3-methoxy-2-methyl-2-propenoylisocyanate (prepared by refluxing the acid chloride [0.23 g, 1.66 mmol] and silver cyanate [0.45 g, 3 mmol] in toluene [10 mL]) was added drop-wise to a solution of **4** (0.28 g, 0.79 mmol) in DMF (8 mL) and ether (4 mL) at −10°C. After the addition, the reaction mixture was stirred at room temperature for 20 h. Ethanol (2 mL) was added and the solvent was evaporated under reduced pressure. The residue was purified on silica gel to give the urea derivative **5a**, which was dissolved in dioxane (8 mL) and treated with 2N H_2SO_4 (4 mL). The reaction mixture was refluxed for 4 h. After cooling to room temperature the solution was neutralized with 2N NaOH solution and evaporated to dryness under reduced pressure. The residue was purified over silica gel to give **6a** (0.10 g, 0.38 mmol, 23%

for 3 steps) as a foamy solid. ^{1}H-NMR (acetone-d$_6$): δ 10.3 (bs, 1H, NH), 7.40 (d, *J* = 1.1 Hz, 1H, H-6), 5.85 (s, 1H, H-4′), 4.68 (m, 1H, H-2′), 4.58–4.39 (m, 4H, H-5′, CH$_2$-N), 3.67 (m, 2H, CH$_2$-O), 1.81 (d, *J* = 1.0 Hz, 3H, –CH$_3$). ^{13}C-NMR (acetone-d$_6$): δ 165.1 (C-4), 151.9 (C-2), 141.6 (C-6), 137.4 (C-3′), 126.1 (C-4′), 110.6 (C-5), 87.2 (C-2′), 75.2 (C-5′), 64.1 (CH$_2$-O), 44.8 (CH$_2$-N), 12.2 (CH$_3$); HRMS (FAB): $(M + Na)^+$ calc. for $C_{11}H_{14}N_2O_4Na$: 261.0851. Found: 261.0850.

1-[2′(*S*)-Benzoyloxymethyl-2′,5′-dihydrofuran-3′-yl]-methyl-pyrimidine-2,4(1H,3H)-dione (6c). A solution of 3-ethoxy-2-propenoyl isocyanate (prepared from 3-ethoxy-2-propenoyl chloride [0.29 g, 2.1 mmol] and silver cyanate [0.64 g, 4.2 mmol] by heating under reflux in toluene for 30 min) was added drop-wise to a solution of **4** (0.3 g, 0.85 mmol) in toluene (20 mL) at 0°C. After the addition, the reaction mixture was stirred at room temperature for 3 h. The solution was poured into saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 25 mL). The combined EtOAc layers were dried over Na_2SO_4 and evaporated to dryness. The residue on purified over silica gel gives the urea derivative **5b**, which was dissolved in dioxane (12 mL) and 2N H_2SO_4 (6 mL) was added. The solution was heated under reflux for 4 h. The solution was cooled to room temperature, neutralized with 2N NaOH, and evaporated to dryness under reduced pressure. The residue was purified over silica gel column to give the uracil derivative **6b**, which was characterized as its benzoate derivative. Compound **6b** was dissolved in anhydrous pyridine (10 mL) and benzoyl chloride (0.17 mL, 1.5 mmol) was added at 0°C. The reaction mixture was stirred at 0°C for 3 h and then quenched with water (0.5 mL) and evaporated to dryness. The residue was taken up in EtOAc (40 mL) and washed with saturated aqueous $NaHCO_3$ (25 mL) and water (30 mL). The organic phase was dried over Na_2SO_4, evaporated to dryness, and purified over silica gel to give **6c** (0.08 g, 29% for 3 steps). ^{1}H-NMR (CDCl$_3$): δ 10.01 (bs, 1H, NH), 7.97–7.16 (m, 6H, H-6, phenyl), 5.80 (s, 1H, H-4′), 5.64 (d, *J* = 8.0 Hz, 1H, H-5), 4.98 (bs, 1H, H-2′), 4.60 (m, 4H), 4.41 (m, 2H). ^{13}C-NMR (CDCl$_3$): δ 166.2 (CO), 163.8 (C-4), 150.8 (C-2), 143.8 (C-6), 134.2 (C-3′), 133.1, 129.4, 128.3, 127.1 (phenyl), 126.0 (C-4′), 102.7 (C-5), 83.8 (C-2′), 75.0 (C-5′), 64.9 (CH$_2$-O), 44.5 (CH$_2$-N); HRMS (FAB): $(M + H)^+$ calc. for $C_{17}H_{17}N_2O_5$: 329.1137. Found: 329.1139.

4-Amino-1-[2′(*S*)-hydroxymethyl-2′,5′-dihydrofuran-3′-yl]-methyl-pyrimidine-2(1H)-one (7). Triethylamine (0.06 mL, 0.42 mmol) was added to a solution of **6c** (0.055 g, 0.167 mmol), TIPSCl (0.126 g, 0.42 mmol), and DMAP (0.051 g, 0.42 mmol) at 0°C. The reaction mixture was stirred at room temperature for 3 h. Aqueous NH_4OH (28%, 2 mL) was added and stirring was continued for a further for 1.5 h at room temperature. The solution was evaporated to dryness under reduced pressure and purified over silica gel. The O-benzoyl protection of the product was removed by treatment with NaOMe (0.05 g) in MeOH (10 mL) at room temperature for 4 h. The solution was neutralized by 10%

aqueous acetic acid and evaporated to dryness. The residue was purified over silica gel to give **7** (0.026 g, 72%) as a white powder. ^{1}H-NMR (MeOH-d$_4$): δ 7.60 (d, J = 7.3 Hz, 1H, H-6), 5.89 (d, J = 7.3 Hz, 1H, H-5), 5.74 (s, 1H, H-4′), 4.70–4.39 (m, 5H, H-2′, H-5′, CH$_2$-N), 3.70 (d, J = 3.5 Hz, 2H, CH$_2$-O); ^{13}C-NMR (MeOH-d$_4$): δ 167.3 (C-2), 157.9 (C-4), 147.6 (C-6), 137.4 (C-3′), 126.7 (C-4′), 96.1 (C-5), 87.8 (C-2′), 75.8 (C-5′), 64.1 (CH$_2$-O), 46.9 (CH$_2$-N); HRMS (FAB): $(M + H)^+$ calc. for $C_{10}H_{14}N_3O_3$: 224.1035. Found: 224.1035.

6-Amino-9-[2′(*S*)-hydroxymethyl-2′,5′-dihydrofuran-3′-yl]-methylpurine (9b). To a solution of **4** (0.135 g, 0.38 mmol) in 1-butanol (10 mL), 5-amino 4,6-dichloropyrimidine (0.065 g, 0.38 mmol) and triethylamine (0.1 mL) was added and the reaction mixture was heated at 110°C for 2 days. The reaction mixture was evaporated under reduced pressure and the residue was purified over silica gel to give **8** (0.12 g), which was dissolved in triethyl orthoformate (3 mL) and treated with conc. HCl (0.025 mL). This solution was stirred at room temperature for 6 h and poured into saturated $NaHCO_3$ solution and extracted with EtOAc (3 × 15 mL). The combined EtOAc layers were dried over Na_2SO_4, evaporated to dryness, and purified over silica gel to give the 6-chloropurine derivative, which was dissolved in methanolic ammonia (10 mL) and heated at 80°C in a steel bomb for 15 h. The solvent was evaporated to dryness and the residue was purified over silica gel to give **9a** (0.55 g, 30% overall yield for 3 steps). ^{1}H-NMR (CDCl$_3$): δ 8.35 (s, 1H, H-2), 7.74–7.34 (m, 11H, H-8, 2 × phenyl), 6.44 (bs, 2H, NH$_2$), 5.59 (H-4′), 4.91 (s, 2H, H-5′), 4.78 (bs, 1H, H-2′), 4.61 (m, 2H, CH$_2$-N), 3.85 (d, J = 4.0 Hz, 2H, CH$_2$-O), 1.02 (s, 9H, *t*-butyl); ^{13}C-NMR (CDCl$_3$): δ 155.7 (C-6), 153.1 (C-2), 149.8 (C-4), 140.2 (C-8), 136.3 (C-3′), 135.5, 133.1, 133.0, 129.8, 129.7, 127.7, 127.6 (phenyl), 125.4 (C-4′), 119.2 (C-5), 85.9 (C-2′), 74.9 (C-5′), 65.3 (CH$_2$-O), 40.6 (CH$_2$-N), 26.7, 19.1 (*t*-butyl). To a solution of **9a** (0.05 g, 0.1 mmol) in MeOH (10 mL), NH_4F (0.05 g) was added and the solution was heated under reflux for 4 h. The solution was adsorbed on silica gel and purified over silica gel to give **9b** (0.019 g, 77%). ^{1}H-NMR (CDCl$_3$+ MeOH-d$_4$): δ 8.03 (s, 1H, H-2), 7.81 (s, 1H, H-8), 5.38 (s, 1H, H-4′), 4.72 (s, 2H), 4.55 (bs, 1H, H-2′), 4.43–4.33 (m, 2H), 3.55 (m, 2H, CH$_2$-O); ^{13}C-NMR (CDCl$_3$+ MeOH-d$_4$): δ 155.4 (C-6), 152.4 (C-2), 148.8 (C-4), 140.6 (C-8), 135.2 (C-3′), 125.5 (C-4′), 118.4 (C-5), 85.8 (C-2′), 74.6 (C-5′), 62.7 (CH$_2$-O), 40.3 (CH$_2$-N); HRMS (FAB): $(M + H)^+$ calc. for $C_{11}H_{14}N_5O_2$: 248.1147. Found: 248.1146.

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