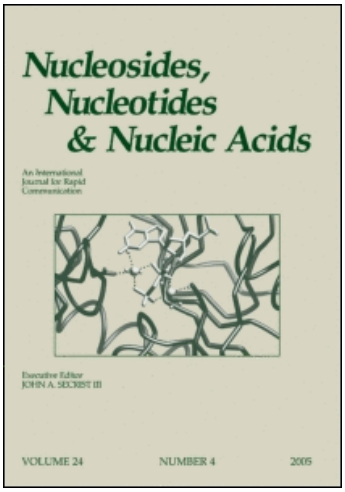

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Synthesis of Certain Acyclic Nucleoside Analogs of 1,2,4-Triazolo[3,4-*f*][1,2,4]triazine and Pyrimido[5,4-*d*]pyrimidine

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SYNTHESIS OF CERTAIN ACYCLIC NUCLEOSIDE ANALOGS OF 1,2,4-TRIAZOLO[3,4-*f*][1,2,4]TRIAZINE AND PYRIMIDO[5,4-*d*]PYRIMIDINE

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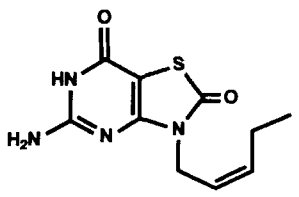
Abstract: Synthesis of 2-penten-1-yl (**8a**) and ganciclovir analog (**8b**) of 1,2,4-triazolo[3,4-*f*][1,2,4]triazine was accomplished by the ring annulation of the corresponding hydrazides (**6a** and **6b**), which in turn was obtained by the dehydrative coupling of **4** with **5a** or **5b**. Base catalysed ring expansion of N9-alkylpurine-6-carbonitriles (**10a, 10c, 10e**) provided the acyclic analogs of 4-aminopyrimido-[5,4-*d*]pyrimidines (**13a, 13d, 13e**). Debenzylation of **13e** afforded the ganciclovir analog (**13f**) of 4-amino-8-(β-*D*-ribofuranosylamino)-pyrimido[5,4-*d*]pyrimidine. However, compound **10b** did not undergo the expected rearrangement but resulted in the formation of the methyl formimidate derivative (**12**).

Recently there has been considerable interest in the synthesis of acyclic purine nucleoside analogs[1], mainly due to the observation that 9-[(2-hydroxyethoxy)methyl]guanine (acyclovir) is a selective antiherpes agent[2], and is the drug of choice in the treatment of diseases caused by herpes simplex virus type-1 (HSV-1). 9-(4-Hydroxybutyl)guanine (HBG), a carba analog of acyclovir, is also found to inhibit HSV-1 in animals[3]. 9-[(1,3-Dihydroxy-2-propoxy)-methyl]guanine (ganciclovir, DHPG), another acyclic guanosine analog, is the current drug of choice for human cytomegalovirus (HCMV) infections[4].



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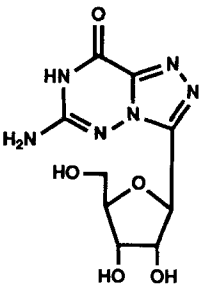

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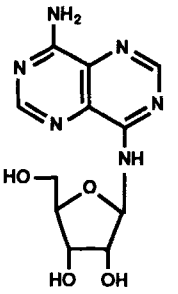
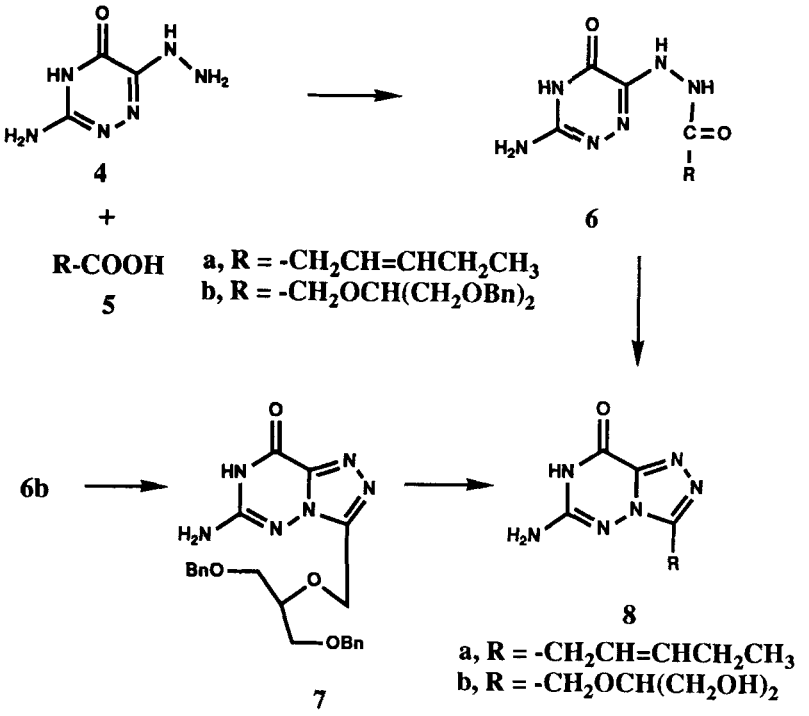


3

Recently, we reported the synthesis and the antiviral properties of 2-penten-1-yl (**1**) and 3-methyl-2-buten-1-yl derivatives of 5-aminothiazolo[4,5-*d*]-pyrimidine-2,7-dione[5,6]. Compound **1** was shown to be approximately 10 fold more active *in vitro* against HCMV than DHPG in similar experiments[5]. In continuation of these studies on the synthesis of acyclic nucleoside analogs[5-8], we now report the synthesis of certain acyclic nucleoside analogs of 1,2,4-triazolo[3,4-*f*][1,2,4]triazine and pyrimido[5,4-*d*]pyrimidine. The synthesis of these acyclic nucleoside analogs is of particular interest, since the ribofuranosyl derivative 6-amino-3-β-*D*-ribofuranosyl-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**2**) exhibited interesting biological properties[9]. Similarly, 4-amino-8-(β-*D*-ribofuranosylamino)pyrimido[5,4-*d*]pyrimidine (ARPP, **3**) was found to possess significant activity against a variety of DNA and RNA viruses[10-13].

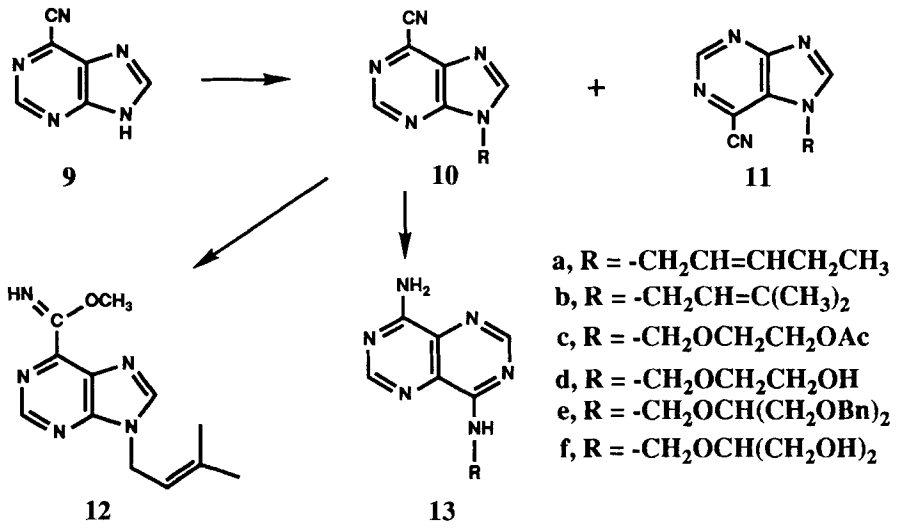
The synthesis of 2-pentenyl derivative (**8a**) and ganciclovir analog (**8b**) of 1,2,4-triazolo[3,4-*f*][1,2,4]triazine was accomplished starting from 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one[14] (**4**) and the corresponding carboxylic acids (**5a** and **5b**, Scheme 1). Thus, dehydrative coupling of **4** with 2-hexenoic acid (**5a**) in dry DMF in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) gave the viable intermediate **6a**, which on heating in ethylene glycol at 200 °C afforded the ring cyclized product 6-amino-3-(2-penten-1-yl)-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**8a**) in a 75.8% yield. Similarly, the synthesis of the ganciclovir congener (**8b**) was accomplished starting from **4** and 1,3-dibenzyloxy-2-propoxyacetic acid (**5b**). The acid **5b** was prepared by the condensation of the sodium salt of 1,3-dibenzyloxy-2-propanol with ethyl chloroacetate in dry CH_3CN, followed by alkaline hydrolysis of the intermediate ester. The dehydrative coupling of **4** with **5b** in dry DMF afforded the hydrazide **6b** in good yield. The ring annulation of **6b** was accomplished by



Scheme 1

heating in ethylene glycol at 200 °C for 2 h and the ring closed product **7** was isolated in 58% yield. Removal of the protecting groups of **7** was carried out by reductive debenzylation by the treatment with $Pd(OH)_2/C$ in absolute EtOH in the presence of cyclohexene. The desired product 6-amino-3-[(1,3-dihydroxy-2-propoxy)methyl]-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (**8b**) was obtained in 74% yield.

The synthesis of the acyclic derivatives of pyrimido[5,4-*d*]pyrimidine was achieved by utilizing the base catalysed rearrangement[15,16] of 9-substituted-purine-6-carbonitriles. The required intermediates for the ring transformation reaction were prepared by direct alkylation of the sodium salt of purine-6-carbonitrile[17] (**9**), generated *in situ* by the treatment with NaH, with the appropriate alkyl halide. Thus, alkylation of the sodium salt of **9** either with 1-bromo-2-pentene or 4-bromo-2-methyl-2-butene in dry CH_3CN afforded the N-9 and N-7 alkylated products (**10a**, **10b**, and **11a**, **11b**) (Scheme 2). However, in



Scheme 2

both the cases N-9 isomer was found to be the major component. The positional isomers **10a** and **11a** were separated into the pure components by silica gel column chromatography and were isolated in 56% and 11% yields, respectively. Similarly, 3-methyl-2-butenyl derivatives **10b** and **11b** were isolated in 59% and 17% yields, respectively. The structural assignment of the N-9 positional isomers **10a** and **10b** was based on the comparison of the uv spectral data to that of the corresponding ribonucleoside[11]. Treatment of **10a** with large excess of NH_4OH in MeOH gave the rearranged product 4-amino-8-(2-penten-1-ylamino)-pyrimido[5,4-*d*]pyrimidine (**13a**). However, a similar treatment of **10b** with methanolic NH_4OH did not give the rearranged product, but resulted in the formation of methyl 9-(3-methyl-2-buten-1-yl)purine-6-formimidate (**12**). Although the addition of MeOH to a carbonitrile functionality to give the methylformimidate is well documented[18,19], the reason for resistance of the imidazole moiety to ring open under the conditions used is not clear at this time.

Alkylation of **9** either with [(2-acetoxyethoxy)methyl] bromide[20] or 1,3-dibenzyloxy-2-chloromethylglycerol[21] resulted mainly in the formation of N-9 substituted derivatives (**10c**, **10e**). Although the formation of a minor amount of N-7 isomer was detected by TLC procedures, no attempts were made to isolate

these compounds. The N-9 isomeric products **10c** and **10e** were isolated in 84% and 78% yields, respectively. Treatment of **10c** with NH_4OH/MeOH at room temperature for 22 h gave the acyclovir analog 4-amino-8-[(2-hydroxy-ethoxy)methylamino]pyrimido[5,4-*d*]pyrimidine (**13d**). A similar treatment of **10e** with NH_4OH/MeOH resulted in an intractable reaction mixture from which the desired rearrangement product **13e** was isolated and subsequently subjected to reductive debenzylation with $Pd(OH)_2/C$ in absolute EtOH in the presence of cyclohexene. The product 4-amino-8-[(1,3-dihydroxy-2-propoxy)methylamino]-pyrimido[5,4-*d*]pyrimidine (**13f**) was isolated in rather low yield. The compounds **8a, 8b, 13a, 13d** and **13f** were tested against HCMV (strain AD 169) in MRC5 cells using the plaque reduction assay[22]. None of the compounds tested showed any activity against HCMV.

In summary the synthesis of 2-penten-1-yl derivative and ganciclovir analog of 1,2,4-triazolo[3,4-f][1,2,4]triazine and the novel acyclic analogs of ARPP is accomplished in good yields.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Thomas-Hoover capillary melting-point apparatus. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. The presence of solvent as indicated by elemental analysis was verified by ^1H NMR spectroscopy. Thin layer chromatography (TLC) was performed on aluminum plates coated (0.2 mm) with silica gel $60F_{254}$ (EM Reagents). Silica gel (Whatman; 230-400 mesh) was used for flash column chromatography. All solvents and chemicals used were reagent grade and the solvent mixtures are in volumes. The detection of nucleoside components on TLC was by uv light. Evaporations were conducted under diminished pressure with the bath temperature below 30 °C. Infrared (IR) spectra were recorded in KBr with Perkin-Elmer 1420 IR spectrophotometer and ultraviolet spectra (UV) were recorded with a Hewlett-Packard 8452 diode array spectrophotometer. Mass spectra (MS) were obtained from Baylor College of Medicine, Houston, Texas. Nuclear magnetic resonance (^1H NMR) spectra were recorded in DMSO-d_6 at 400 MHz with a Bruker AM400 wide bore spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as the internal standard (key: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad).

6-Amino-3-(2-penten-1-yl)-1,2,4-triazolo[3,4-*f*][1,2,4]-triazin-8(7*H*)-one (8a). To a suspension of 3-amino-6-hydrazino-1,2,4-triazin-5(4*H*)-one[14] (**4**, 0.71 g, 5 mmol), *trans*-3-hexenoic acid (**5a**, 0.59 mL, 5 mmol) and 1-hydroxybenzotriazole monohydrate (HOBT, 0.67 g, 5 mmol) in dry DMF (30 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 0.96 g, 5 mmol). The mixture was stirred at room temperature overnight and the insoluble material was removed by filtration. The solid was washed with MeOH (10 mL) and the combined filtrates was allowed to stand at room temperature overnight. The product that crystallized was collected by filtration and dried to yield 0.5 g (42%) of **6a**, mp 254-256 °C; UV (MeOH): λmax 274 nm (ε 4700); ^{1}H NMR: δ 0.94 (t, 3 H, C*H*$_3$), 2.00 (m, 2 H, C*H*$_2$CH$_3$), 2.84 (d, 2 H, C*H*$_2$CO), 5.47, 5.55 (2m, 2 H, C*H*=C*H*), 6.36 (s, 2 H, N*H*$_2$), 7.77 (s, 1 H, N*H*), 9.52 (s, 1 H, N*H*), 11.14 (s, 1 H, N*H*). *Anal.* Calcd. for $C_9H_{14}N_6O_2$: C, 45.37; H, 5.92; N, 35.28. Found: C, 45.13; H, 5.84; N, 35.14.

A mixture of **6a** (0.3 g, 1.26 mmol) and ethylene glycol (20 mL) was heated at 200 °C (bath temperature) for 2 h. The reaction mixture was cooled to room temperature and poured into cold H_2O (100 mL). After stirring for 15 min the precipitated product was collected by filtration. The filtrate was extracted with EtOAc (2 × 250 mL) and the combined organic phase was washed with saturated $NaHCO_3$ solution (50 mL). Organic layer was evaporated to give a total yield of 0.21 g (75.8%) of **8a** as a colorless solid, mp > 290 °C; UV (MeOH): λmax 276 nm (ε 3600); IR: ν 3190, 3340 (NH, NH$_2$), 1720 (C=O) cm^{-1}; ^{1}H NMR: δ 0.94 (t, 3 H, C*H*$_3$), 2.01 (m, 2 H, C*H*$_2$CH$_3$), 3.57 (d, 2 H, CC*H*$_2$), 5.61 (m, 2 H, C*H*=C*H*), 6.32 (s, 2 H, N*H*$_2$), 11.40 (brs, 1 H, N*H*). *Anal.* Calcd. for $C_9H_{12}N_6O$: C, 49.08; H, 5.49; N, 38.16. Found: C, 49.14; H, 5.43; N, 37.92.

1,3-Dibenzyloxy-2-propoxyacetic acid (5b). To a solution of 1,3-dibenzyloxy-2-propanol (2.72 g, 10 mmol) in anhydrous CH_3CN (25 mL) was added NaH (0.3 g, 10 mmol, 60% dispersion in oil). The mixture was stirred at room temperature for 20 min and $ClCH_2COOEt$ (1.23 g, 10 mmol) was added. The reaction mixture was stirred at room temperature for 20 h and the solvent was evaporated. The residue was partitioned between H_2O and CH_2Cl_2 (150 mL). Dichloromethane layer was separated, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography over a silica gel column (2 × 25 cm) and the product was eluted with hexane:CH_2Cl_2 (1:1) to hexane:CH_2Cl_2 (1:4) to yield 1.0 g (27.9%) of pure 1,3-dibenzyloxy-2-propoxyethyl acetate. ^{1}H NMR: δ 1.16 (t,

3 H, CH_3), 3.56 (d, 4 H, 2 OCH_2), 3.80 (m, 1 H, OC*H*), 4.07 (q, 2 H, CH_2), 4.23 (s, 2 H, CH_2), 4.48 (s, 4 H, 2 CH_2Ph), 7.27-7.34 (m, 10 H, Aryl *H*).

To a solution of 1,3-dibenzyloxy-2-propoxyethyl acetate (0.8 g, 2.23 mmol) in absolute EtOH (6 mL) was added 1 *N* NaOH solution (3 mL) and the mixture was heated at 85 °C for 2 h. The reaction mixture was allowed to cool to room temperature and the pH of the solution was adjusted to 4. The aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic phase was dried (Na_2SO_4). The solvent was evaporated to give 0.65 g (88.2%) of **5** as a colorless oil. ^1H NMR: δ 3.54 (d, 4 H, 2 OCH_2), 3.75 (m, 1 H, OC*H*), 3.98 (s, 2 H, $COCH_2$), 4.48 (s, 4 H, 2 CH_2Ph), 7.27-7.36 (m, 10 H, Aryl *H*). *Anal.* Calcd. for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.53; H, 6.73.

3-[(1,3-Dibenzyloxy-2-propoxy)methyl]-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)-one (7). A suspension of **4** (284 mg, 2 mmol) and 1,3-dibenzyloxy-2-propoxyacetic acid (**5b**, 0.66 g, 2 mmol) was co-evaporated with anhydrous DMF (2 × 20 mL). The mixture was suspended in dry DMF (15 mL) to which HOBT (0.27 g, 2 mmol) and EDC (0.38 g, 2 mmol) were added. The mixture was stirred at room temperature for 18 h. DMF was evaporated and the residue was dissolved in a small amount of CH_2Cl_2 (20 mL). The insoluble material was removed by filtration and the solid was washed with CH_2Cl_2 (30 mL). The combined filtrates were evaporated and the residue was purified by chromatography on a silica gel column (2 × 15 cm). The product was eluted with 0-10% MeOH in CH_2Cl_2 to yield 0.68 g (72.26%) of **6b**, mp 84-87 °C; UV (MeOH): λmax 276 nm (ε 6300);^1H NMR: δ 3.57 (m, 4 H, 2 OCH_2), 3.85 (m, 1 H, OC*H*), 4.13 (s, 2 H, CH_2), 4.51 (s, 4 H, 2 CH_2Ph), 6.47 (s, 2 H, NH_2), 7.25-7.35 (m, 10 H, Aryl*H*), 7.95 (d, 1 H, N*H*), 9.35 (d, 1 H, N*H*), 11.20 (s, 1 H, N*H*). *Anal.* Calcd. for $C_{22}H_{26}N_6O_5 \cdot 1.5\ H_2O$: C, 54.87; H, 6.06. Found: C, 54.75; H, 5.72.

A suspension of **6b** (0.39 g, 0.83 mmol) in ethylene glycol (25 mL) was heated at 200 °C for 2 h. The reaction flask was allowed to cool to room temperature and the solution was poured into H_2O (100 mL). The product that precipitated was collected by filtration and dried under vaccum to yield 0.21 g (55.8%) of **7**, mp 175-176 °C; UV (MeOH): λmax 276 nm (ε 3620); ^1H NMR: δ 3.53 (m, 4 H, 2 OCH_2), 3.92 (m, 1 H, OC*H*), 4.44 (s, 4 H, 2 CH_2Ph), 4.86 (s, 2 H, CH_2), 6.44 (s, 2 H, NH_2), 7.24-7.34 (m, 10 H, Aryl *H*), 11.56 (s, 1 H, N*H*). *Anal.* Calcd. for $C_{22}H_{24}N_6O_4$: C, 60.54; H, 5.54; N, 19.26. Found: C, 60.56; H, 5.48; N, 18.85.

6-Amino-3-[(1,3-dihydroxy-2-propoxy)methyl]-1,2,4-triazolo[3,4-*f*][1,2,4]-triazin-8(7*H*)-one (8b). To a suspension of **7** (0.17 g, 0.37 mmol) in absolute EtOH (35 mL) and cyclohexene (8 mL) was added $Pd(OH)_2/C$ (20%, 35 mg) and the mixture was heated under reflux overnight. Water (50 mL) was added and the mixture was refluxed for additional one hour. The hot solution was filtered. The solid was again extracted by boiling with MeOH:H_2O (1:1, 50 mL). The combined filtrates were evaporated to give a colorless solid. The solid was triturated with CH_2Cl_2 (10 mL) and the product was collected by filtration to yield 75 mg (74.2%) of **8b**, mp 240-242 °C; UV (MeOH): λmax 276 nm (ε 3650); IR: ν 3180, 3310, 3380, 3500 (OH, NH, NH_2), 1725 (C=O) cm^{-1}; ^1H NMR: δ 3.49 (m, 5 H, OC*H*, 2 OCH_2), 4.57 (br s, 2 H, 2 O*H*), 4.85 (s, 2 H, CH_2), 6.46 (s, 2 H, NH_2); MS (FAB): m/e 257.3 (M+H). *Anal.* Calcd. for $C_8H_{12}N_6O_4$: C, 37.50; H, 4.72; N, 32.80. Found: C, 37.32; H, 4.69; N, 31.20.

9-(2-Penten-1-yl)purine-6-carbonitrile (10a) and 7-(2-Penten-1-yl)purine-6-carbonitrile (11a). To a suspension of purine-6-carbonitrile[17] (**9**, 0.72 g, 5 mmol) in dry CH_3CN (80 mL) was added NaH (0.2 g, 5 mmol, 60% dispersion in oil). After stirring the mixture at room temperature for 25 min, 1-bromo-2-pentene (predominantly *Z* olefin, 0.6 mL, 5 mmol) was added and the stirring was continued for 20 h. The insoluble material was removed by filtration. The filtrate was evaporated and the residue containing a mixture of positional isomers were separated by flash column (2 × 25 cm) chromatography using 0-12% EtOAc in CH_2Cl_2 as the eluent. The initial fractions contained the N-9 isomer and the subsequent fractions contained the N-7 isomer. The fractions were collected separately and evaporated to give the pure isomers **10a** and **11a** as viscous liquids.

9-(2-Penten-1-yl)purine-6-carbonitrile (10a). Yield, 0.6 g (56.28%); UV (MeOH): λmax 290 nm (ε 12,600); ^1H NMR: δ 1.00 (t, 3 H, CH_3), 2.23 (m, 2 H, CH_2CH_3), 5.18 (d, 2 H, NCH_2), 5.67 (m, 2 H, *CH*=*CH*), 9.02 (s, 1 H, C_8H), 9.16 (s, 1 H, C_2H). *Anal.* Calcd. for $C_{11}H_{11}N_5 \cdot 0.1\ H_2O$: C, 61.43; H, 5.25; N, 32.57. Found: C, 61.36; H, 4.99; N, 32.74.

7-(2-Penten-1-yl)purine-6-carbonitrile (11a). Yield: 0.12 g (11.26%); UV (MeOH): λmax 298 nm (ε 7000); ^1H NMR: δ 1.00 (t, 3 H, CH_3), 2.28 (m, 2 H, CH_2CH_3), 5.00 (d, 2 H, NCH_2), 5.63 (m, 2 H, *CH*=*CH*), 8.94 (s, 1 H, C_8H), 9.13 (s, 1 H, C_2H). *Anal.* Calcd. for $C_{11}H_{11}N_5 \cdot 0.1\ H_2O$: C, 61.43; H, 5.25; N, 32.57. Found: C, 61.34; H, 5.27; N, 32.73.

4-Amino-8-(2-penten-1-ylamino)pyrimido[5,4-*d*]pyrimidine (13a). To a solution of **10a** (0.5 g, 2.34 mmol) in MeOH (30 mL) was added NH_4OH (70 mL) and the mixture was stirred at room temperature for 22 h. The solvent was evaporated and the residue was purified by chromatography on a silica gel column (2 × 10 cm). The product was eluted with 0-8% MeOH in CH_2Cl_2 to yield 0.26 g (48.2%) of **13a**, mp 185-186 °C; UV (MeOH): λmax 298 nm (ε 18,100), 318 (15,200), 336 (9700); IR: ν 3295, 3460 (NH, NH_2) cm^{-1}; ^1H NMR: δ 0.97 (t, 3 H, CH_3), 2.15 (m, 2 H, CH_2CH_3), 4.13 (t, 2 H, NCH_2, collapsed to a doublet on D_2O exchange), 5.48 (m, 2 H, *CH*=*CH*), 7.65, 7.89 (2s, 2 H, NH_2), 8.34 (t, 2 H, C_6H, N*H*, collapsed to a singlet on D_2O exchange), 8.42 (s, 1 H, C_2H). *Anal.* Calcd. for $C_{11}H_{14}N_6 \cdot 0.25$ MeOH: C, 56.70; H, 6.34; N, 35.28. Found: C, 56.88; H, 6.03; N, 35.54.

9-(3-Methyl-2-buten-1-yl)purine-6-carbonitrile (10b) and 7-(3-Methyl-2-buten-1-yl)purine-6-carbonitrile (11b). In a similar manner as described for the preparation of **10a** and **11a,** alkylation of **9** (0.73 g , 5 mmol) in dry CH_3CN (80 mL) containing NaH (60% dispersion in oil, 0.2 g, 5 mmol) with 4-bromo-2-methyl-2-butene (0.75 mL, 6.5 mmol) gave a mixture of positional isomers which were separated by silica gel column (2 × 20 cm) chromatography. The products were eluted with CH_2Cl_2 containing 0-20% EtOAc. The initial fractions contained the pure N-9 isomer and the subsequent fractions contained the pure N-7 isomer.

9-(3-Methyl-2-buten-1-yl)purine-6-carbonitrile (10b). Yield, 0.63 g (59%); mp 64-66 °C; UV (MeOH): λmax 290 nm (ε 11,000); ^1H NMR: δ 1.73, 1.84 (2s, 6 H, 2 CH_3), 4.94 (d, 2 H, NCH_2), 5.45 (m, 1 H, *CH*), 8.93 (s, 1 H, C_8H), 9.14 (d, 1 H, C_2H). *Anal.* Calcd. for $C_{11}H_{11}N_5$: C, 61.95; H, 5.20; N, 32.85. Found: C, 61.83; H, 5.09; N, 32.75.

7-(3-Methyl-2-buten-1-yl)purine-6-carbonitrile (11b). Yield, 0.18 g (17%); mp 90-92 °C; UV (MeOH): λmax 298 nm (ε 10,200); ^1H NMR: δ 1.76, 1.81 (2s, 6 H, 2 CH_3), 4.92 (d, 2 H, NCH_2), 5.45 (m, 1 H, *CH*), 8.77 (s, 1 H, C_8H), 9.03 (d, 1 H, C_2H). *Anal.* Calcd. for $C_{11}H_{11}N_5$: C, 61.95; H, 5.20; N, 32.85. Found: C, 61.77; H, 5.17; N, 31.97.

Methyl 9-(3-methyl-2-buten-1-yl)purine-6-formimidate (12). To a solution of **10b** (0.35 g, 1.64 mmol) in MeOH (15 mL) was added concd. NH_4OH (25 mL). The mixture was stirred at room temperature for 16 h and allowed to stand

at 0 °C for 4 h. The colorless solid that deposited was collected by filtration and washed with a small amount of cold MeOH. The solid was dried under vaccum to give 0.24 g (59%) of pure **12**, mp 140-42 °C; UV (MeOH): λmax 286 nm (ε 12,700); IR: ν 3290 (NH) cm^{-1}; ^1H NMR: δ 1.72, 1.84 (2s, 6 H, 2 CH_3), 3.93 (s, 3 H, OCH_3), 4.92 (d, 2 H, NCH_2), 5.45 (m, 1 H, CH), 8.77 (s, 1 H, C_8H), 9.03 (d, 1 H, C_2H), 9.85 (s, 1 H, NH). *Anal.* Calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.69; H, 6.07; N, 28.61.

9[(2-Acetoxyethoxy)methyl]purine-6-carbonitrile (10c). To a solution of **9** (0.72 g, 5 mmol) in dry CH_3CN (75 mL) was added NaH (0.2 g, 5 mmol, 60% dispersion in oil). After stirring the mixture at room temperature for 30 min, [(2-acetoxyethoxy)methyl] bromide[20] (1.28 g, 6.5 mmol) was added and the reaction was continued overnight. The insoluble material was removed by filtration and the filtrate was evaporated to dryness. The residue which contained mainly one isomer was purified by silica gel column chromatography using 0-2% MeOH in CH_2Cl_2 as the eluent to yield 1.10 g (84.2%) of **10c** as a viscous liquid. UV (MeOH): λmax 288 nm (ε 9300); ^1H NMR: δ 1.92 (s, 3 H, $COCH_3$), 3.77 (t, 2 H, OCH_2CH_2O), 4.07 (t, 2 H, OCH_2CH_2O), 5.78 (s, 2 H, NCH_2), 9.09 (s, 1 H, C_8H), 9.19 (s, 1 H, C_2H). *Anal.* Calcd. for $C_{11}H_{11}N_5O_3$: C, 50.57; H, 4.24; N, 26.81. Found: C, 50.67; H, 4.14; N, 26.80.

4-Amino-8-[(2-hydroxyethoxy)methylamino]pyrimido[5,4-*d*]pyrimidine (13d). To a solution of **10c** (0.75 g, 2.87 mmol) in MeOH (20 mL) was added NH_4OH (40 mL) and the mixture was stirred at room temperature for 20 h. The solvents were evaporated and the solid was washed with a small amount of H_2O and MeOH to yield 0.28 g (41%) of **13d**, mp 216-218 °C; UV (MeOH): λmax 292 nm (ε 18,600), 304 (16,200), 318 (13,700), 334 (9700); IR: ν 3170, 3320 (OH, NH, NH_2) cm^{-1}; ^1H NMR: δ 3.49, 3.52 (2s, 4 H, OCH_2CH_2O), 4.59 (s, 1 H, OH), 4.99 (d, 2 H, NCH_2), 7.74, 7.95 (2s, 2 H, NH_2), 8.40 (s, 1 H, C_6H), 8.50 (s, 1 H, C_2H), 8.90 (br s, 1 H, NH); MS: m/e 237.3 (M+H). *Anal.* Calcd. for $C_9H_{12}N_6O_2$: C, 45.75; H, 5.12; N, 35.58. Found: C, 45.37; H, 4.83; N, 35.49.

9-[(1,3-Dibenzyloxy-2-propoxy)methyl]purine-6-carbonitrile (10e). To a solution of **9** (1.0 g, 6.89 mmol) in dry CH_3CN (75 mL) was added NaH (0.28 g, 7 mmol, 60% dispersion in oil). The mixture was stirred at room temperature for 30 min before a solution of 1,3-dibenzyloxy-2-chloromethyl glycerol (prepared from 2.72 g, 10 mmol of 1,3-dibenzyloxy-2-propanol) in CH_3CN (20 mL) was added. The mixture was stirred overnight and the insoluble material was

removed by filtration. The filtrate was evaporated and the residue containing mainly N-9 isomer was purified by silica gel column chromatography using 0-2% MeOH in CH_2Cl_2 as the eluent to yield 2.3 g (77.7%) of **10e** as a viscous oil. UV (MeOH): λmax 290 nm (ε 8300); ^{1}H NMR: δ 3.44 (m, 4 H, 2 OCH_2), 4.12 (m, 1 H, OC*H*), 4.33, 4.34 (2s, 4 H, 2 CH_2Ph), 5.85 (s, 2 H, CH_2), 7.10-7.33 (m, 10 H, 2 *Ph*), 9.06 (s, 1 H, C_8H), 9.13 (s, 1 H, C_2H). *Anal.* Calcd. for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.40; N, 16.31. Found: C, 66.96; H, 5.21; N, 15.47.

4-Amino-8-[(1,3-dihydroxy-2-propoxy)methylamino]pyrimido[5,4-*d*]-pyrimidine (13f). To a solution of **10e** (1 g, 2.33 mmoles) in MeOH (50 mL) was added NH_4OH (50 mL). The mixture was stirred at room temperature for 20 h. The solvents were evaporated to give a solid, which was found to be a complex mixture of compounds by TLC procedures. The desired product **13e** was isolated by silica gel column chromatography using 0-3% MeOH in CH_2Cl_2 as the eluent. To a solution of the pure **13e** (0.2 g) in absolute EtOH (100 mL) were added cyclohexene (20 mL) and $Pd(OH)_2$ (100 mg, 20% on carbon). The mixture was heated under reflux for 40 h. The reaction mixture was filtered hot through a Celite pad and the pad was washed with hot MeOH (2 × 30 mL). The combined filtrates were evaporated. The solid thus obtained was dissolved in MeOH and adsorbed onto silica gel. The dried silica gel was loaded on a silica gel column and the product was eluted with 0-12% MeOH in CH_2Cl_2. Yield: 50 mg (8 %); mp 162-164 °C; UV (MeOH): λmax 292 nm (ε 14,800), 304 (12,700), 318 (10,500), 336 (7500); IR: ν 3180, 3310 (OH, NH, NH_2) cm^{-1}; ^{1}H NMR: δ 3.40 (m, 4 H, 2OCH_2), 3.61 (m, 1 H, OC*H*), 4.58 (t, 2 H, 2 O*H*), 5.09 (d, 2 H, CH_2), 7.75, 7.96 (2s, 2 H, NH_2), 8.40 (s, 1 H, C_6H), 8.49 (s, 1 H, C_2H), 8.85 (t, 1 H, N*H*); MS: m/e 267.3 (M+H).

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