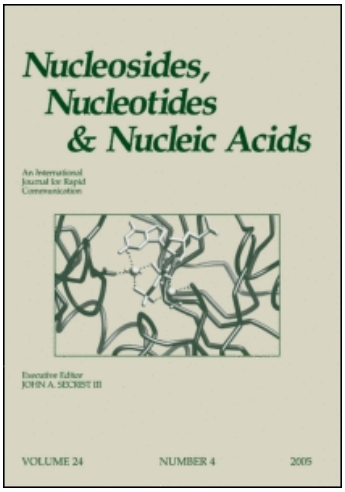

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 2- AND 7-SUBSTITUTED 9-DEAZAADENOSINE ANALOGUES

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▫ *A series of 2-halogen and 7-alkyl substituted analogues of 9-deazaadenosine and 2′-deoxy-9-deazaadenosine was synthesized by new efficient methodology involving transformation of corresponding 9-deazaguanosine and 2′-deoxyguanosine, which in turn were synthesized by direct C-glycosylation of 1-benzyl-9-deazaguanine with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose and methyl 2-deoxy-3,5-di-O-(p-toluoyl)-D-ribofuranoside, respectively. Deoxychlorination of C6 and diazotization/chloro- or fluoro-dediazoniation of the sugar-protected 9-deazaguanosine, followed by selective ammonolysis at C6 and deprotection of the sugar moiety, gave 2-chloro- and 2-fluoro-9-deazaadenosine (***6*** *and* ***9****). Substitution of the 7-position of the dihalogen-intermediate with alkyl groups, followed by ammonolysis and deprotection, provided 2-chloro-7-alkyl-9-deazaadenosines (***13a–e****) and 2-fluoro-7-benzyl-9-deazaadenosine (***13f****). Catalytic hydrogenation of* ***13a–e*** *gave 7-alkyl-9-deazaadenosines* ***14a–e****. Similarly, 2-chloro-2′-deoxy-9-deazaadenosine (***21****), 2-chloro-2′-deoxy-7-methyl-9-deazaadenosine (***25****), 2′-deoxy-9-deazaadenosine (***22****), and 2′-deoxy-7-methyl-9-deazaadenosine (***26****) were prepared from sugar-protected 2′-deoxy-9-deazaguanosine. Among these compounds, 7-benzyl-9-deazaadenosine (***14b****) showed the most potent cytotoxic activity, with IC_{50} values of 0.07, 0.1, 0.2 and 1.5 μM, while both 7-methyl-9-deazaadenosine (***14a****) and 2-fluoro-9-deazaadenosine (***9****) also demonstrated significant cytotoxic activity with IC_{50} values of 0.4, 0.7, 0.3, and 1.5 μM, and 1.5, 0.9, 0.3, and 5 μM against L1210 leukemia, P388 leukemia, CCRF-CEM lymphoblastic leukemia, and $B_{16}F_{10}$ melanoma cells, respectively.*

Keywords C-Glucosylation, New synthetic method for 9-deazaadenosine analogues, 2- and 7-substituted 9-deazaadenosines, Cytotoxic activity

INTRODUCTION

2-Halogen–substituted purine nucleosides have been shown to exhibit cytotoxicity to cultured cell lines and anticancer activity against transplanted experimental neoplasms.[1–4] Prominent among these analogues are fludarabine

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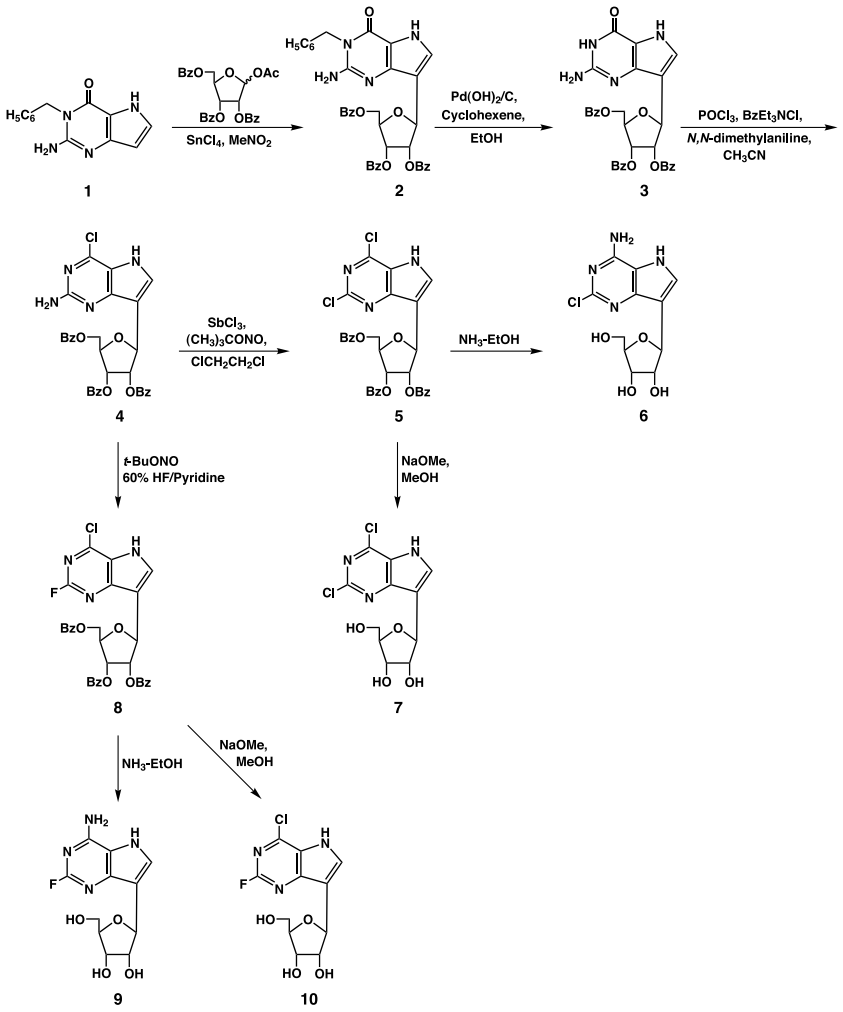
(9-β-D-arabinofuranosyl-2-fluoroadenine 5′-*O*-phosphate) and cladribine (2-chloro-2′-deoxy-β-D-adenosine), which are currently used clinically in the treatment of cancer. A major limitation of many purine nucleosides is that the glycosyl bond is unstable. Thus, for example, the dose-limiting toxicity of fludarabine may be due to its rapid dephosphorylation followed by cleavage of the glycosyl bond to yield 2-fluoroadenine, a toxic purine devoid of therapeutic activity. Carbon–carbon–linked 9-deazapurine nucleosides are resistant to cleavage by purine nucleoside phosphorylase and, as a result, 9-deazaadenosine exhibits pronounced cytotoxicity against several experimental murine and human leukemias.[5,6] Because of these considerations, we have prepared a series of 2-halogen– and 7-alkyl–substituted analogues of 9-deazaadenosine and 2′-deoxy-9-deazaadenosine. In this article, we describe the synthesis and biological evaluation of these nucleoside analogues.

CHEMISTRY

9-Deazaadenosines and their 2′-deoxy-9-deazaadenosine derivatives have been produced previously via a multistep synthetic procedure starting from 2,3-isopropylidene-5-*O*-trityl-D-ribose to form 3-amino-2-cyano-4-(2,3-*O*-isopropylidene-5-*O*-trityl-β-D-ribofuranosyl)pyrrole, which was then cyclized with formamidine to give the 9-deazaadenosine derivative.[7–9] This synthetic route was lengthy and the introduction of a halogen atom onto the 2-position of the 9-deazaadenine ring was difficult using this methodology. Recently, Crigis et al.[10] reported the synthesis of 9-deazaguanosine by direct C-glycosylation of 9-deazaguanine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in the presence of $SnCl_4$-followed by hydrolytic deprotection of the sugar. Several years later, Gibson et al.[11] described the synthesis of 2′-deoxy-9-deazaguanosine by $SnCl_4$-catalyzed condensation of 1-benzyl-9-deazaguanine (**1**) with methyl 2-deoxy-3,5-di-*O*-(*p*-nitrobenzoyl)-D-ribofuranoside, followed by separation of the anomers, hydrolysis, and debenzylation. We explored the possibility of transforming 9-deazaguanosine and 2′-deoxy-9-deazaguanosine to the corresponding 9-deazaadenosine derivatives by transforming the guanosine analogues to the corresponding adenosine derivatives using well-established methodology,[12–17] since this approach offered an efficient alternative method for the synthesis of 9-deazaadenosine derivatives. Furthermore, the 2-amino group of 9-deazaguanosine could be converted to chloro and fluoro substituents for the preparation of target compounds. To facilitate this approach, we recently developed improved methodology for the synthesis of 9-deazaguanine via a 1-benzyloxymethylguanine intermediate.[18] Therefore, we evaluated individual reaction conditions for condensation of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose with 9-deazaguanine, 1-benzyl-9-deazaguanine, and 1-benzyloxymethyl-9-deazaguanine; among these three 9-deazaguanines, 1-benzyl-9-deazaguanine (**1**) gave the best yield. This latter finding might be due to the electron-donating properties of the benzyl group of the 1-benzyl-9-deazaguanine, which contributed to an increase in electron density at the pyrrole carbon atom, thereby facilitating the formation of direct electrophilic

C-glycosylation. The molecular ratio of $SnCl_4$ to the base may also affect the yield, since, after varying the ratios, 2.8:1 produced the optimal yield (70–75%). It is conceivable that the association of $SnCl_4$ with the heteroatoms of the 1-benzyl-9-deazaguanine ring results in more of this agent being necessary, accounting for the large amount of $SnCl_4$ required to complete the Friedel-Crafts type reaction.

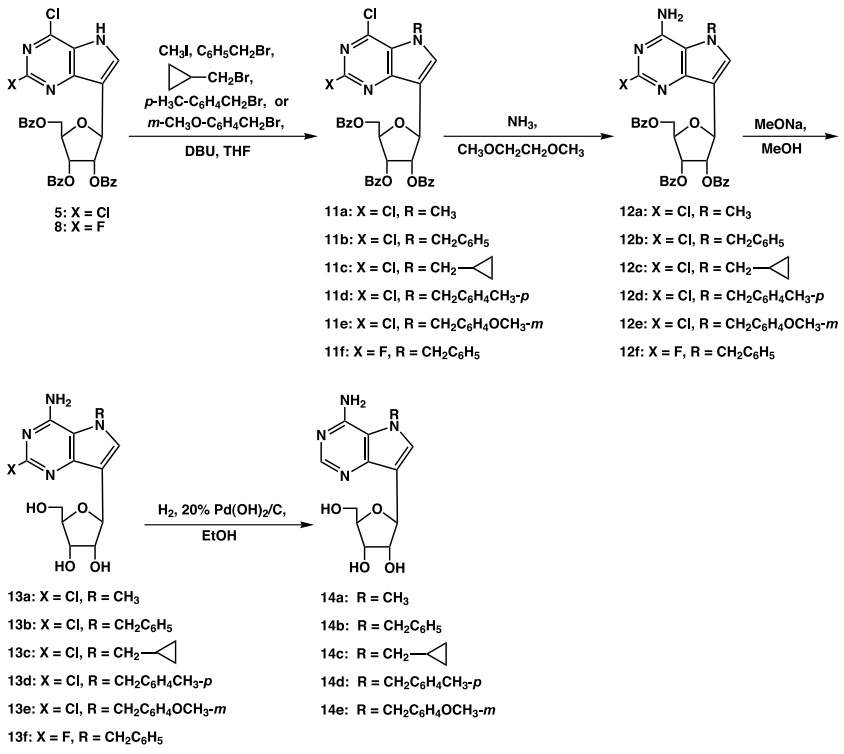
The syntheses of 2-chloro-9-deazaadenosine (**6**) and 2-fluoro-9-deazaadenosine (**9**) are illustrated in Scheme 1. Condensation of 1-benzyl-9-deazaguanine (**1**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in the presence of $SnCl_4$ in nitromethane gave 2-amino-3-benzyl-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (**2**). Removal of the *N*-benzyl group by hydrogenation transfer with palladium hydroxide and cyclohexene in ethanol at elevated



SCHEME 1 Syntheses of 2-chloro-9-deazaadenosine and 2-fluoro-9-deazaadenosine.

temperature gave 2-amino-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3, 2-*d*]pyrimidin-4(3*H*)-one (**3**). Deoxygenative chlorination[12–17] of **3** with phosphoryl chloride, benzyltriethylammonium chloride and *N,N*-dimethylaniline in acetonitrile provided compound **4**. Chloro-dediazoniation[13–15] of **4** with *tert*-butyl nitrite and antimony trichloride in 1,2-dichloroethane yielded the dichloronucleoside **5**. Treatment of compound **5** with ammonia-saturated ethanol at elevated temperature in a steel bomb produced the target compound 2-chloro-9-deazaadenosine (**6**). Deprotection of **5** with sodium methoxide in methanol afforded the dichloronucleoside **7**. Fluoro-dediazoniation[15] of **4** with *tert*-butyl nitrite in 60% anhydrous HF/pyridine gave the 2-fluoronucleoside **8**. Similarly, treatment of compound **8** with ammonia saturated ethanol at elevated temperature in a steel bomb afforded the target compound 2-fluoro-9-deazaadenosine (**9**). Deprotection of **8** with sodium methoxide in methanol gave 2-fluoro-6-chloronucleoside (**10**).

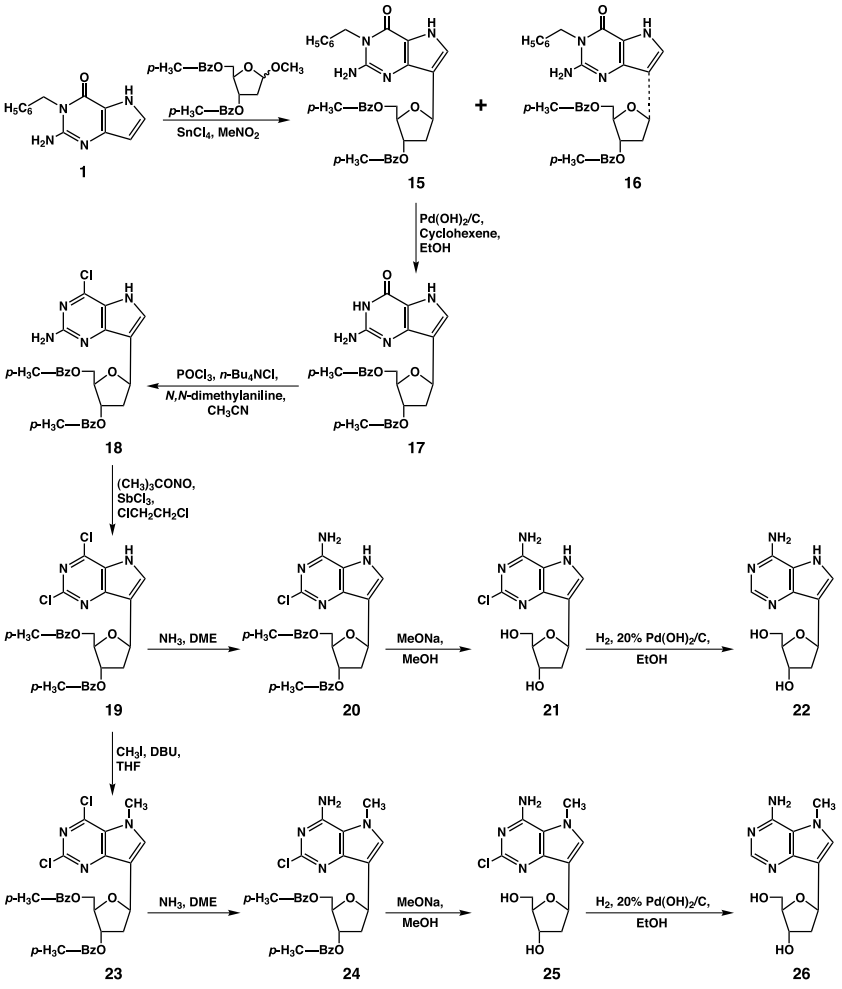
The syntheses of 2-halogen-7-alkyl- and 7-alkyl-9-deazaadenosines **13a–f** and **14a–e**, respectively, are outlined in Scheme 2. Alkylation of **5** with iodomethane, benzyl bromide, cyclopropylmethyl bromide, 4-methylbenzyl bromide and 3-methoxybenzyl bromide in the presence of 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) in dry THF gave compounds **11a–e**, respectively. Similarly, alkylation of



SCHEME 2 Syntheses of 2-halogen-7-alkyl- and 7-alkyl-9-deazaadenosines.

8 with benzyl bromide and DBU in dry DHF produced the 2-fluoro-7-benzyl derivative **11f**. Treatment of **11a**–**f** with anhydrous ammonia in 1,2-dimethoxyethane at elevated temperature in a steel bomb afforded the 9-deazaadenosine analogues **12a**–**f**. Deprotection of **12a**–**f** with sodium methoxide in methanol gave the 2-chloronucleoside derivatives **13a**–**e** and 2-fluoro-7-benzyl-9-deazaadenosine (**13f**). Removal of the 2-chloro moiety of **13a**–**e** by catalytic hydrogenation in the presence of 10% palladium on carbon in ethanol produced the 7-alkyl–substituted 9-deazaadenosine derivatives **14a**–**e**.

The syntheses of 2′-deoxy-9-deazaadenosine analogues are shown in Scheme 3. Condensation of **1** with methyl 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-D-ribofuranoside and $SnCl_4$ in nitromethane afforded a mixture of anomers **15** and **16**, which were



SCHEME 3 Syntheses of 2′-deoxy-9-deazaadenosine analogues.

separated by repeat silica gel column chromatography. Treatment of the major β-anomer **15** with cyclohexene and palladium hydroxide in ethanol at elevated temperature gave compound **17**. Deoxygenative chlorination of **17** with phosphorus oxychloride, benzyltriethylammonium chloride, and *N,N*-dimethylaniline in acetonitrile, followed by separation on a silica gel column provided the chloro derivative **18**. Treatment of **18** with *tert*-butyl nitrite and antimony trichloride in 1,2-dichloroethane gave the dichloronucleoside **19**. Treatment of **19** with anhydrous ammonia in 1,2-dimethoxyethane at an elevated temperature in a steel bomb yielded the 2-chloro-2′-deoxy-3-deazaadenosine analogue **20**, which was deprotected with sodium methoxide in methanol to give the target compound 2-chloro-2′-deoxy-9-deazaadenosine (**21**). Catalytic hydrogenation of **21** with palladium hydroxide in ethanol gave 2′-deoxy-9-deazaadenosine (**22**). Alkylation of **19** with iodomethane and DBU in anhydrous THF produced the 7-methyl derivative **23**. Treatment of **23** with anhydrous ammonia in 1,2-dimethoxyethane and subsequently with sodium methoxide in methanol afforded the 2-chloronucleoside (**25**) via the intermediate **24**. Catalytic hydrogenation of **25** with palladium hydroxide in ethanol gave 2′-deoxy-7-methyl-9-deazaadenosine (**26**).

The assignment of the anomeric configurations of **15** and **16** was made on the basis of proton NMR spectroscopy. The ^{1}H signal of the major product **15** appeared as a double doublet, whereas the corresponding signal of the minor product **16** was an apparent triplet. These results were consistent with those reported in the literature[9,11,19–21] that stated for C-2′-deoxypurine nucleosides the H-1′ signal for β-nucleosides appears as a double doublet, whereas an apparent triplet appears for α-nucleosides. Furthermore, the ^{1}H NMR spectrum of **22** was consistent with that reported in the literature,[9] although it was synthesized by a different approach.

BIOLOGICAL EVALUATION

The synthesized compounds **6**, **7**, **9**, **10**, **13a–f**, **14a–e**, **21**, **22**, **25** and **26** were evaluated in vitro for their cytotoxicities against the L1210 and P388 leukemias, the CCRF-CEM lymphoblastic leukemia, and the $B_{16}F_{10}$ melanoma by previously reported methodologies[22] and the results are shown in Table 1. Among the tested compounds, 7-benzyl-9-deazaadenosine (**14b**) exhibited the greatest potency, with IC_{50} values of 0.07, 0.1, 0.2, and 1.5 μM against L1210, P388, CCRF-CEM, and $B_{16}F_{10}$ cells, respectively; both 7-methyl-9-deazaadenosine (**14a**) and 2-fluoro-9-deazaadenosine (**9**) also showed potent activity against these tumor cell lines with IC_{50} values of 0.4, 0.7, 0.3, and 1.5 μM, and 1.5, 0.9, 3, and 5 μM, respectively. The introduction of a halogen atom onto the 2-position of 9-deazaadenosine led to the reduction or abolishment of cytotoxic activity. Thus, the 9-deaza analogue (**21**) of 2-chloro-2′-deoxyadenosine (cladribine) showed no cytotoxity, and the 2-chloro derivatives (**13a** and **13b**) of the active compounds, 7-methyl-9-deazaadenosine (**14a**), and 7-benzyl-9-deazaadenosine (**14b**) also did

TABLE 1 Evaluation of the Cytotoxicity of 2- and 7-Substituted 9-Deazaadenosine Analogues Against L1210, P388, CCRF-CEM, and $B_{16}F_{10}$ Cell Lines in Vitro[a]

	IC_{50} (μM)[b]			
Compound	L1210	P388	CCRF-CEM	$B_{16}F_{10}$
7	20	18	11	20
9	1.5	0.9	3	5
10	37	18	18	37
14a	0.4	0.7	0.3	1.5
14b	0.07	0.1	0.2	0.3
14c	50	50	>100	>100
14d	>100	50	>100	>100
26	40	70	>100	>100

[a]Compounds **6**, **13a**–**f**, **14e**, **21**, **22**, and **25** were also tested in each of the cell lines, but showed no activity up to concentrations of 100 μM.

[b]IC_{50} values represent the concentrations (μM) required to inhibit cell replication by 50%.

not produce cytotoxity. In addition, introduction of a substituent onto the benzene ring of 7-benzyl-9-deazaadenosine (**15b**) caused a loss of activity, while the dihalogen nucleosides **7** and **10** exhibited moderate activity.

In summary, new and efficient methodology for the synthesis of 2- and 7-substituted 9-deazaadenosine derivatives has been developed and three of the compounds synthesized by these procedures, **9**, **14a**, and **14b**, had significant cytotoxic activity against four different neoplastic cell lines in vitro.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or Gemini-300 (300 MHz) NMR spectrometer with Me_4Si as the internal reference. The UV spectra were recorded on a Beckman-25 spectrophotometer. Mass spectra were recorded on a VG-ZAB-SE mass spectrometer in the fast bombardment (FAB) mode (glycerol matrix). Column chromatography was conducted with Merck silica gel 60, 230–400 mesh. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT, USA.

2-Amino-3-benzyl-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2). To a suspension of 1-benzyl-9-deazaguanine[11] (**1**, 9.6 g, 40 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose (24 g, 48 mmol) in dry nitromethane (200 mL) was added $SnCl_4$ (13.2 mL, 112 mmol). The reaction mixture was stirred at room temperature to form a clear solution and stirred at 55–60°C for 3 h. The cooled solution was diluted with ethyl acetate (300 mL) and gradually added to a mixture of $NaHCO_3$ (45 g) and water (540 mL). The reaction mixture was stirred for 20 min, filtered, and washed with ethyl acetate. The

organic layer was separated and the water layer was extracted with ethyl acetate (200 mL). The combined organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 40:1, v/v) to give 20 g (73%) as an off-white foam: TLC, R_f 0.22 (CH_2Cl_2/EtOH, 15:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.15 (br s, 2H, 2-NH_2, D_2O exchangeable), 4.64 (2 m, 2H, 5′-H), 4.82 (m, 1H, 4′-H), 5.34 (s, 1H, $ArCH_2$), 5.44 (d, 1H, 1′-H, J=5.5 Hz), 6.15 (m, 1H, 3′-H), 6.28 (m, 1H, 2′-H), 7.18–7.50 and 7.90–8.10 (2 m, 16H, ArH, and 6-H), 9.92 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{39}H_{32}N_4O_8$: C, 68.42; H, 4.71; N, 8.18. Found: C, 68.14; H, 4.90; N, 8.43.

2-Amino-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (3). A mixture of **2** (8.0 g, 11.65 mmol), cyclohexene (110 mL), and 20% $Pd(OH)_2$/C (2.5 g) in ethanol (350 mL) was stirred and heated in a steel bomb at 120–125°C overnight. The cooled reaction mixture was filtered, washed with ethanol, and the combined filtrate and washings were evaporated to dryness in vacuo. The residue was purified by silica gel column chromatography, eluted initially with CH_2Cl_2/EtOAc, 1:1, v/v, then with CH_2Cl_2/EtOH, 10:1, v/v to give 6.8 g (78%) as a white foam: TLC, R_f 0.56 (CH_2Cl_2/EtOAc, 10:1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.60 (2 m, 2H, 5′-H), 4.70 (m, 1H, 4′-H), 4.72 (br s, 2H, 2-NH_2, D_2O exchangeable), 5.33 (d, 1H, 1′-H, J=5.5 Hz), 5.94 (m, 2H, 2′-H and 3′-H), 7.27 (d, 1H, 6-H, J=3.0 Hz), 7.40–7.54 and 7.70–8.00 (2 m, 15H, ArH), 10.50 and 11.50 (2 s, 2H, 2 NH, D_2O exchangeable). Anal. Calcd. for $C_{32}H_{26}N_4O_8$: C, 64.64; H, 4.43; N, 9.42. Found: C, 64.20; H, 4.23; N, 9.03.

2-Amino-4-chloro-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (4). To a suspension of compound **3** (8 g, 13.4 mmol) in dry acetonitrile (40 mL) was added benzyltriethylammonium chloride (8 g, 35 mmol) and the mixture was stirred at room temperature to form a clear solution, followed by *N,N*-dimethylaniline (2 mL, 20 mmol) and phosphorus oxychloride (7.4 mL). The reaction mixture was stirred under nitrogen and heated under gentle reflux for 30 min and the cooled solution was evaporated in vacuo to dryness. The resulting yellow foam was stirred with chloroform (80 mL) and ice-water (60 g) for 30 min, then the layers were separated. The aqueous phase was washed with chloroform and the organic phase was combined and washed with water (4 × 60 mL), 5% sodium bicarbonate solution, dried ($MgSO_4$), and filtered. The filtrate and washings were evaporated in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 30:1, v/v) to give 3.3 g (40%) of product as an off-white foam: TLC, R_f 0.43 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.59 (m, 2H, 5′-H), 4.72 (m, 1H, 4′-H), 5.43 (d, 1H, 1′-H, J=8.1 Hz), 5.97 (m, 2H, 2′-H and 3′-H), 6.03 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.42–7.93 (m, 16H, ArH, and 6-H), 11.92 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{32}H_{25}ClN_4O_7$: C, 62.69; H, 4.11; N, 9.14. Found: C, 63.02; H, 4.23; N, 9.03.

2,4-Dichloro-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (5). Compound **4** (7.1 g, 11.6 mmol) was dissolved in dichloroethane (150 mL), cooled to −10°C and a solution of antimony trichloride (6.0 g, 26 mmol) in dichloroethane (20 mL) also cooled to −10°C was added to the above solution with stirring, followed by *tert*-butyl nitrite (8.2 mL, 71 mmol). The mixture was stirred at −10°C for 4 h, poured onto ice-water (100 mL), and the mixture was stirred for 10 min, filtered, and washed with chloroform. The organic layer was then washed successively with water (3 × 60 mL), 5% sodium bicarbonate (60 mL) and brine (60 mL), dried ($MgSO_4$), and filtered. The filtrate and washings were evaporated in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 30:1, v/v) to give 5.2 g (71%) of product as a pale yellow foam: TLC, R_f 0.50 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR (DMSO-d_6) δ 4.72 (m, 2H, 5′-H), 4.95 (m, 1H, 4′-H), 5.70 (d, 1H, 1′-H, J=7.2 Hz), 5.81 (m, 1H, 3′-H), 6.02 (m, 1H, 2′-H), 7.26−7.56 and 8.00−8.10 (m, 15H, ArH), 7.73 (d, 1H, 6-H, J=1.7 Hz), 11.90 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{32}H_{23}Cl_2N_3O_7$: C, 60.77; H, 3.67; N, 6.64. Found: C, 60.98; H, 4.01; N, 6.53.

4-Amino-2-chloro-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (6, 2-chloro-9-deazaadenosine). A suspension of compound **5** (0.61 g, 0.96 mmol) in 60 mL of saturated ethanolic ammonia solution was stirred in a steel bomb at 115°C for 20 h. The cooled reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 10:1 to 4:1, v/v) to give 0.13 g (43%) of product as a white solid: mp 112°C (dec); TLC, R_f 0.33 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.58 and 3.60 (2 m, 2H, 5′-H), 3.82 (m, 1H, 4′-H), 3.97 (m, 1H, 3′-H), 4.23 (m, 1H, 2′-H), 4.54 (br s 1H, OH, D_2O exchangeable), 4.73 (d, 1H, 1′-H, J=7.3 Hz), 5.10 and 5.25 (2 br s, 2H, 2OH, D_2O exchangeable), 7.28 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.56 (d, 1H, 6-H, J=2.5 Hz), 11.01 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}ClN_4O_4$: C, 43.93; H, 4.36; N, 18.63. Found: C, 44.17; H, 4.56; N, 18.38.

2,4-Dichloro-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (7). To a suspension of compound **5** (1.1 g, 1.7 mmol) in dry methanol (40 mL) was added sodium methoxide solution until the pH reached ∼ 12. The mixture was stirred at room temperature for 4 h, at which time TLC showed the reaction to be complete. The solution was neutralized with glacial acidic acid, evaporated with 2 g of silica gel to dryness in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 4:1, v/v) to give 0.3 g (54%) of product as a white solid: mp 181−183°C; TLC, R_f 0.49 (CH_2Cl_2/EtOH, 4:1, v/v) ^{1}H NMR (DMSO-d_6) δ 3.51 and 3.61 (2 m, 2H, 5′-H), 3.81 (m, 1H, 4′-H), 4.00 (m, 1H, 3′-H), 4.22 (m, 1H, 2′-H), 4.89 (d, 1H, 1′-H, J=7.0 Hz), 5.05 and 5.35 (2 br s, 3H, 3OH, D_2O exchangeable), 8.15 (d, 1H, 6-H, J=1.8 Hz), 11.25 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}Cl_2N_3O_3$: C, 41.27; H, 3.70; N, 13.13. Found: C, 41.02; H, 3.95; N, 12.92.

4-Chloro-2-fluoro-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (8). Compound **4** (0.94 g, 1.53 mmol) was added to a solution of 60% HF/pyridine (17 mL) at −35°C in a dry-ice acetone bath and stirred to form a solution, followed by addition of *tert*-butyl nitrite (0.4 mL, 3.4 mmol). The mixture was stirred for 5 min at −35°C, followed by additional *tert*-butyl nitrite (0.4 mL, 3.4 mmol) and removal of the dry-ice acetone bath. The reaction mixture was stirred until the temperature reached −10°C and the solution was poured into ice-water (25 g) with stirring. The mixture was extracted with chloroform (3 × 45 mL) and the combined organic phase was washed with water (3 × 15 mL), dried ($MgSO_4$), filtered, and evaporated to give 0.94 g (100%) of crude product, which was used directly for the next step. A small sample was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 40:1, v/v; R_f 0.42) as a white foam: ^{1}H NMR ($CDCl_3$) δ 4.85 (2 m, 2H, 5′-H), 4.95 (m, 1H, 4′-H), 5.62 (d, 1H, 1′-H, J=6.1 Hz), 5.95 (m, 1H, 3′-H), 6.12 (m, 1H, 2′-H), 7.20−7.50 and 8.10−8.21 (2 m, 15H, ArH), 7.82 (d, 1H, 6-H, J=2.0 Hz), 9.82 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{32}H_{23}ClFN_3O_7$: C, 62.39; H, 3.76; N, 6.82. Found: C, 62.04; H, 3.97; N, 6.63.

Compounds **9** and **10** were synthesized by methodology similar to that described for compounds **6** and **7**.

4-Amino-2-fluoro-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (9, 2-fluoro-9-deazaadenosine). Compound **9** was isolated as a white solid (0.122 g, 45%): mp 201−203°C (dec.); UV (MeOH) λ_{max} 288 nm (ε 12,026), λ_{min} 234 nm; MS m/z 285 $(M + H)^+$; TLC, R_f 0.31 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.47 and 3.61 (2 m, 2H, 5′-H), 3.81 (m, 1H, 4′-H), 3.97 (m, 1H, 3′-H), 4.21 (m, 1H, 2′-H), 4.50 (br s 1H, OH, D_2O exchangeable), 4.72 (d, 1H, 1′-H, J=7.1 Hz), 5.13 and 5.35 (2 br s, 2H, 2OH, D_2O exchangeable), 7.57 (d, 1H, 6-H, J=2.2 Hz), 7.69 (br s, 2H, 4-NH_2, D_2O exchangeable), 11.03 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; N, 19.71. Found: C, 46.12; H, 4.44; N, 19.39.

4-Chloro-2-fluoro-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (10). Compound **10** was isolated as a white solid (0.13 g, 66%): mp 126°C (dec.); TLC, R_f 0.49 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.50 and 3.63 (2 m, 2H, 5′-H), 3.79 (m, 1H, 4′-H), 4.00 (m, 1H, 3′-H), 4.23 (m, 1H, 2′-H), 4.78, 4.82 and 4.92 (3 br s 3H, 3OH, D_2O exchangeable), 4.87 (d, 1H, 1′-H, J=6.4 Hz), 8.16 (d, 1H, 6-H, J=1.8 Hz), 11.69 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}ClFN_3O_4$: C, 43.50; H, 3.65; N, 13.84. Found: C, 43.14; H, 4.01; N, 13.48.

2,4-Dichloro-5-methyl-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11a). To a stirred solution of compound **5** (0.8 g, 1.3 mmol) in 25 mL of dry THF was added 0.4 mL (2.6 mmol) of DBU, followed by 0.8 mL (12 mmol) of iodomethane. The reaction mixture

was stirred at room temperature until TLC showed it to be complete (~2 h). The mixture was then evaporated to dryness and the residue dissolved in methylene chloride (60 mL), washed with water, 5% sodium bicarbonate solution and brine, dried ($MgSO_4$), and filtered. The filtrate and washings were evaporated to a small volume and purified by silica gel column chromatography (CH_2Cl_2/EtOH, 50:1, v/v) to give 0.73 g (89%) of product as an off-white foam: TLC, R_f 0.41 (CH_2Cl_2/EtOH, 50:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.98 (d, 3H, N-Me, J=3.4 Hz), 4.63 and 4.70 (2 m, 2H, 5′-H), 4.94 (m, 1H, 4′-H), 5.69 (d, 1H, 1′-H, J=6.9 Hz), 5.79 (m, 1H, 3′-H), 6.00 (m, 1H, 2′-H), 7.26–7.55 and 8.00–8.11 (m, 16H, ArH and 6-H). Anal. Calcd. for $C_{33}H_{25}Cl_2N_3O_7$: C, 61.31; H, 3.90; N, 6.50. Found: C, 61.44; H, 4.24; N, 6.44.

Compounds **11b–f** were prepared by a procedure similar to that described for the synthesis of compound **11a**.

2,4-Dichloro-5-benzyl-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11b). Compound **11b** was isolated as a foam (1.73 g, 85%): TLC, R_f 0.64 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.63 and 4.70 (2 m, 2H, 5′-H), 4.82 (m, 2H, $ArCH_2$), 4.92 (m, 1H, 4′-H), 5.70 (d, 1H, 1′-H, J=7.1 Hz), 5.79 (m, 1H, 3′-H), 6.02 (m, 1H, 2′-H), 7.37–8.07 (m, 21H, ArH and 6-H). Anal. Calcd. for $C_{39}H_{29}Cl_2N_3O_7$: C, 64.82; H, 4.05; N, 5.82. Found: C, 65.08; H, 4.38; N, 5.72.

2,4-Dichloro-5-cyclopropylmethyl-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11c). Compound **11c** was isolated as a foam (0.84 g, 88%): TLC, R_f 0.84 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H NMR (DMSO-d_6) δ 0.34–0.51 (m, 4H, CH_2CH_2), 1.10 (m, 1H, CH), 4.10 (m, 2H, NCH_2), 4.53 and 4.63 (2 m, 2H, 5′-H), 4.80 (m, 1H, 4′-H), 5.49 (d, 1H, 1′-H, J=7.0 Hz), 5.77 (m, 1H, 3′-H), 5.90 (m, 1H, 2′-H), 7.23–7.55 and 8.03–8.21 (m, 16H, ArH and 6-H). Anal. Calcd. for $C_{36}H_{29}Cl_2N_3O_7$: C, 62.98; H, 4.26; N, 6.12. Found: C, 62.75; H, 4.42; N, 6.38.

2,4-Dichloro-5-(*p*-methylbenzyl)-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11d). Compound **11d** was isolated as a foam (0.44 g, 95%): TLC, R_f 0.74 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H, Me), 4.60 and 4.68 (2 m, 2H, 5′-H), 4.80 (m, 2H, $ArCH_2$), 4.90 (m, 1H, 4′-H), 5.70 (d, 1H, 1′-H, J=7.0 Hz), 5.77 (m, 1H, 3′-H), 5.88 (m, 1H, 2′-H), 7.30–8.10 (m, 20H, ArH and 6-H). Anal. Calcd. for $C_{40}H_{31}Cl_2N_3O_7$: C, 65.22; H, 4.24; N, 5.70. Found: C, 65.01; H, 4.45; N, 5.40.

2,4-Dichloro-5-(*m*-methoxybenzyl)-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11e). Compound **11e** was isolated as a foam (1.1 g, 93%): TLC, R_f 0.76 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H

NMR ($CDCl_3$) δ 3.71 (s, 3H, Me), 4.62 and 4.72 (2 m, 2H, 5′-H), 4.91 (m, 1H, 4′-H), 5.30 (m, 2H, $ArCH_2$), 5.71 (d, 1H, 1′-H, J=7.0 Hz), 5.75 (m, 1H, 3′-H), 5.86 (m, 1H, 2′-H), 7.15–8.15 (m, 20H, ArH and 6-H). Anal. Calcd. for $C_{40}H_{31}Cl_2N_3O_8$: C, 63.82; H, 4.15; N, 5.58. Found: C, 63.74; H, 4.36; N, 5.33.

4-Chloro-2-fluoro-5-benzyl-7-(2,3,5-tri-*O*-benzoyl)-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (11f). Compound **11f** was isolated as a foam (0.7 g, 90%): TLC, R_f 0.64 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.75 and 4.76 (2 m, 2H, 5′-H), 4.87 (m, 1H, 4′-H), 4.92 (m, 2H, $ArCH_2$), 5.83 (m, 1H, 3′-H), 5.90 (d, 1H, 1′-H, J=7.2 Hz), 6.12 (m, 1H, 2′-H), 7.39–8.17 (m, 21H, ArH and 6-H). Anal. Calcd. for $C_{39}H_{29}ClFN_3O_7$: C, 66.34; H, 4.14; N, 5.95. Found: C, 65.98; H, 4.34; N, 5.78.

4-Amino-2-chloro-5-methyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (13a, 2-chloro-7-methyl-9-deazaadenosine). A suspension of compound **11a** (0.63 g, 0.96 mmol) in 50 mL of saturated 1,2-dimethoxyethane ammonia solution was stirred in a steel bomb at 100°C for 24 h. The cooled reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 20:1, v/v, R_f 0.42) to give the benzoylated product **12a** (0.52 g, 86%) as a white foam, which was dissolved in methanol (40 mL), followed by addition of sodium methoxide solution until the pH reached ~12. The reaction mixture was stirred at room temperature until TLC showed the reaction to be complete (~2 h). The solution was neutralized with glacial acidic acid, evaporated with 1 g of silica gel to dryness in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 6:1, v/v) to give 0.21 g (69%) of product as a white solid: mp 123–125°C; TLC, R_f 0.31 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.47 and 3.57 (2 m, 2H, 5′-H), 3.80 (m, 1H, 4′-H), 3.94 (m, 4H, N-Me and 3′-H), 4.18 (dd, 1H, 2′-H, J=7.2, 5.2 Hz), 4.69 (d, 1H, 1′-H, J=7.2 Hz), 4.77, 4.85 and 5.14 (3 br s, 3H, 3OH, D_2O exchangeable), 7.21 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.46 (d, 1H, 6-H, J=2.0 Hz). Anal. Calcd. for $C_{21}H_{15}ClN_4O_4 \cdot 0.5CH_3OH$: C, 45.39; H, 5.18; N, 16.94. Found: C, 45.46; H, 5.60; N, 17.07.

Compounds **13b–f** were synthesized by methodology similar to that described for compound **13a**.

4-Amino-2-chloro-5-benzyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (13b, 2-chloro-7-benzyl-9-deazaadenosine). Compound **13b** was isolated as a white solid (0.16 g, 65%): mp 136°C (dec); TLC, R_f 0.31 (CH_2Cl_2/EtOH, 10:1, v/v) ^{1}H NMR (DMSO-d_6) δ 3.45 and 3.48 (2 m, 2H, 5′-H), 3.81 (m, 1H, 4′-H), 3.94 (m, 1H, 3′-H), 3.99 (m, 1H, 2′-H), 4.74 (d, 1H, 1′-H, J=7.2 Hz), 4.79, 4.87 and 5.12 (3 br s, 3H, 3OH, D_2O exchangeable), 5.78 (s, 2H, $ArCH_2$), 7.05 (d, 2H, ArH), 7.27–7.35 (m, 3H, ArH), 8.10 (d, 2H, 4-NH_2, D_2O exchangeable), 8.51 (d, 1H, 6-H, J=2.0 Hz). Anal. Calcd. for $C_{18}H_{19}ClN_4O_4$: C, 55.31; H, 4.90; N, 14.34. Found: C, 55.44; H, 5.08; N, 14.08.

4-Amino-2-chloro-5-cyclopropylmethyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (13c, 2-chloro-7-cyclopropylmethyl-9-deazaadenosine). Compound **13c** was isolated as a white solid (0.71 g, 70%): mp 110−112°C; TLC, R_f 0.38 (CH_2Cl_2/EtOH, 5:1, v/v); ^{1}H NMR (DMSO-d_6) δ 0.34 and 0.48 (2 m, 4H, CH_2CH_2), 1.12 (m, 1H, CH), 3.46 and 3.58 (2 m, 2H, 5′-H), 3.80 (m, 1H, 4′-H), 3.96 (m, 1H, 3′-H), 4.14 (m, 2H, N-CH_2), 4.24 (m, 1H, 2′-H), 4.71 (d, 1H, 1′-H, J=7.1 Hz), 4.76 (d, 1H, OH, D_2O exchangeable), 4.86 (d, 1H, OH, D_2O exchangeable), 5.14 (t, 1H, 5′-OH, D_2O exchangeable), 7.20 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.60 (s, 1H, 6-H). Anal. Calcd. for $C_{15}H_{19}ClN_4O_4$: C, 50.78; H, 5.40; N, 15.79. Found: C, 50.56; H, 5.68; N, 15.68.

4-Amino-2-chloro-5-(*p*-methylbenzyl)-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (13d, 2-chloro-7-(*p*-methylbenzyl)-9-deazaadenosine). Compound **13d** was isolated as a white solid (0.16 g, 67%): mp 120−122°C; TLC, R_f 0.76 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.24 (m, 3H, CH_3), 3.47 and 3.59 (2 m, 2H, 5′-H), 3.81(m, 1H, 4′-H), 3.96 (m, 1H, 3′-H), 4.12 (m, 1H, 2′-H), 4.72 (d, 1H, 1′-H, J=7.2 Hz), 4.77, 4.87, and 5.10 (3 br s, 3H, 3OH, D_2O exchangeable), 5.51 (s, 2H, $ArCH_2$), 6.93 (d, 2H, ArH, J=8.0 Hz), 7.11 (d, 2H, ArH, J=8.0 Hz), 7.10 (s, 2H, 4-NH_2, D_2O exchangeable), 7.65 (d, 1H, 6-H, J=2.0 Hz). Anal. Calcd. for $C_{19}H_{21}ClN_4O_4$: C, 56.37; H, 5.23; N, 13.84. Found: C, 56.67; H, 5.01; N, 13.51.

4-Amino-2-chloro-5-(*m*-methoxybenzyl)-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (13e, 2-chloro-7-(*m*-methoxybenzyl)-9-deazaadenosine). Compound **13e** was isolated as a white solid (0.16 g, 50%): mp 123−124°C; TLC, R_f 0.39 (CH_2Cl_2/EtOH, 10:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.46 and 3.57 (2 m, 2H, 5′-H), 3.69 (s, 3H, CH_3), 3.81 (m, 1H, 4′-H), 3.96 (m, 1H, 3′-H), 4.25 (m, 1H, 2′-H), 4.74 (d, 1H, 1′-H, J=7.1 Hz), 4.79 (d, 1H, OH, D_2O exchangeable), 4.87 (d, 1H, OH, D_2O exchangeable), 5.11 (t, 5′-OH, D_2O exchangeable), 5.53 (s, 2H, $ArCH_2$), 6.55−6.82 (m, 3H, ArH), 7.10 (s, 2H, 4-NH_2, D_2O exchangeable), 7.22 (t, 1H, ArH, J=7.8, 8.0 Hz), 7.68 (s, 1H, 6-H). Anal. Calcd. for $C_{19}H_{21}ClN_4O_5$: C, 54.22; H, 5.03; N, 13.31. Found: C, 54.01; H, 5.40; N, 13.12.

4-Amino-2-fluoro-5-benzyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (13f, 2-fluoro-7-benzyl-9-deazaadenosine). Compound **13f** was isolated as a white solid (0.27 g, 48%): mp 108°C (dec); TLC, R_f 0.27 (CH_2Cl_2/EtOH, 10:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.47 and 3.58 (2 m, 2H, 5′-H), 3.80 (m, 1H, 4′-H), 4.05 (m, 1H, 3′-H), 4.29 (m, 1H, 2′-H), 4.71 (d, 1H, 1′-H, J=7.1 Hz), 4.17, 4.87, and 5.14 (3 br s, 3H, 3OH, D_2O exchangeable), 5.57 (s, 2H, $ArCH_2$), 7.04 (d, 2H, ArH), 7.25−7.30 (m, 3H, ArH), 7.26 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.67 (s, 1H, 6-H). Anal. Calcd. for $C_{18}H_{19}FN_4O_4$: C, 57.75; H, 5.12; N, 14.97. Found: C, 57.31; H, 5.22; N, 14.78.

4-Amino-5-methyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (14a, 7-methyl-9-deazaadenosine). A suspension of compound **13a** (0.34 g, 1.1 mmol) and 20% $Pd(OH)_2/C$ (80 mg) in 80 mL of ethanol was hydrogenated at 45 psi in a Parr hydrogenation apparatus until TLC showed the reaction to be complete (~18 h). The catalyst was removed by filtration and carefully washed with ethanol. The combined filtrate and washings were evaporated to dryness in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 4:1, v/v) to give 0.21 g (69%) of product as a white solid: mp 173–175°C; TLC, R_f 0.31 (CH_2Cl_2/EtOH, 3:2, v/v); UV (MeOH) λ_{max} 286 nm (ε 10,272), λ_{min} 235 nm; MS *m/z* 281 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 3.50 and 3.58 (2 m, 2H, 5′-H), 3.86 (m, 1H, 4′-H), 4.00 (m, 4H, N-Me and 3′-H), 4.69 (dd, 1H, 2′-H, *J*=7.2, 5.0 Hz), 4.73 (d, 1H, 1′-H, *J*=7.8 Hz), 4.80, 4.90, and 5.78 (3 br s, 3H, 3OH, D_2O exchangeable), 7.20 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.47 (s, 1H, 6-H), 8.10 (s, 1H, 2H). Anal. Calcd. for $C_{12}H_{16}N_4O_4 \cdot 0.25C_2H_5OH$: C, 49.39; H, 6.04; N, 19.20. Found: C, 49.44; H, 5.80; N, 19.00.

Compounds **14b–e** were synthesized by methodology similar to that described for compound **14a**.

4-Amino-5-benzyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (14b, 7-benzyl-9-deazaadenosine). Compound **14b** was isolated as a white solid (0.1 g, 85%): mp 136°C (dec); TLC, R_f 0.34 (CH_2Cl_2/EtOH, 4:1, v/v); UV (MeOH) λ_{max} 288 nm (ε 10,440), λ_{min} 235 nm; MS *m/z* 357 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 3.55 (2 m, 2H, 5′-H), 3.91 (m, 1H, 4′-H), 3.94 (m, 1H, 3′-H), 3.99 (m, 1H, 2′-H), 4.87 (d, 1H, 1′-H, *J*=7.4 Hz), 5.73 (s, 2H, $ArCH_2$), 7.05 (d, 2H, ArH), 7.27–7.35 (m, 3H, ArH), 8.01 (s, 1H, 6-H), 8.10 (d, 2H, 4-NH_2, D_2O exchangeable), 8.51 (s, 1H, 2-H). Anal. Calcd. for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.49; H, 5.27; N, 15.58.

4-Amino-5-cyclopropylmethyl-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (14c, 7-cyclopropylmethyl-9-deazaadenosine). Compound **14c** was isolated as a white solid (0.13 g, 86%): mp 145°C (dec); TLC, R_f 0.25 (CH_2Cl_2/EtOH, 3:1, v/v); ^1H NMR (DMSO-d_6) δ 0.38 and 0.50 (2 m, 4H, CH_2CH_2), 1.18 (m, 1H, CH), 3.46 and 3.55 (2 m, 2H, 5′-H), 3.87 (m, 1H, 4′-H), 3.99 (m, 1H, 3′-H), 4.25 (m, 2H, N-CH_2), 4.30 (m, 1H, 2′-H), 4.77 (d, 1H, 1′-H, *J*=7.6 Hz), 4.87, 4.90, and 4.91 (3 br s, 3H, 3OH, D_2O exchangeable), 7.60 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.71 (s, 1H, 6-H), 8.24 (s, 1H, 2-H). Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.49. Found: C, 56.58; H, 6.60; N, 17.33.

4-Amino-5-*p*-(methylbenzyl)-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (14d, 7-*p*-methylbenzyl-9-deazaadenosine). Compound **14d** was isolated as a white solid (0.074 g, 67%): mp 171°C (dec); TLC, R_f 0.30 (CH_2Cl_2/EtOH, 4:1, v/v); ^1H NMR (DMSO-d_6) δ 2.24 (m, 3H, CH_3), 3.48 and 3.59 (2 m, 2H, 5′-H), 3.86 (m, 1H, 4′-H), 4.00 (m, 1H, 3′-H), 4.35 (m, 1H, 2′-H), 4.74 (d,

1H, 1′-H, *J*=7.2 Hz), 4.75, 4.87, and 4.90 (3 br s, 3H, 3OH, D_2O exchangeable), 5.53 (s, 2H, $ArCH_2$), 6.96 (d, 2H, ArH, *J*=8.0 Hz), 7.00 (br s, 2H, 4-NH_2, D_2O exchangeable), 7.11 (d, 2H, ArH, *J*=8.0 Hz), 7.50 (s, 1H, 6-H), 8.04 (s, 1H, 2-H). Anal. Calcd. for $C_{19}H_{29}N_4O_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.89; H, 5.63; N, 15.50.

4-Amino-2-chloro-5-(*m*-methoxybenzyl)-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (14e, 7-*m*-methoxybenzyl-9-deazaadenosine). Compound **14e** was isolated as a white solid (0.31 g, 91%): mp 157−159°C; TLC, R_f 0.34 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 3.51 and 3.59 (2 m, 2H, 5′-H), 3.69 (s, 3H, CH_3), 3.87 (m, 1H, 4′-H), 4.01 (m, 1H, 3′-H), 4.28 (m, 1H, 2′-H), 4.76 (d, 1H, 1′-H, *J*=7.6 Hz), 4.87, 4.90, and 4.92 (m, 3H, 3OH, D_2O exchangeable), 5.53 (s, 2H, $ArCH_2$), 6.55−6.82 (m, 3H, ArH), 7.10 (s, 2H, 4-NH_2, D_2O exchangeable), 7.22 (t, 1H, ArH, *J*=7.8, 8.0 Hz), 7.68 (s, 1H, 6-H), 8.11 (s, 1H, 2-H). Anal. Calcd. for $C_{19}H_{22}N_4O_5 \cdot 0.2C_2H_5OH$: C, 57.68; H, 5.91; N, 14.16. Found: C, 57.55; H, 5.68; N, 14.12.

2-Amino-3-benzyl-2′-deoxy-7-(3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (15) and 2-amino-3-benzyl-2′-deoxy-7-(3,5-di-*O*-toluoyl-α-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (16). To a suspension of 1-benzyl-9-deazaguanine (**1**, 2.4 g, 10 mmol) and methyl 2-deoxy-3,5-di-*O*-toluoyl-D-ribofuranoside (4 g, 10.4 mmol) in dry nitromethane (60 mL) was added $SnCl_4$ (3.3 mL, 28 mmol). The reaction mixture was stirred at room temperature to form a clear solution and stirred at 55−60°C for 3 h. The cooled solution was diluted with ethyl acetate (200 mL) and gradually added to a mixture of $NaHCO_3$ (12.5 g) and water (200 mL). The reaction mixture was stirred for 20 min, filtered, and washed with ethyl acetate. The organic layer was then separated and the water layer was extracted with ethyl acetate (100 mL). The combined organic solutions were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was repeatedly purified by silica gel column chromatography (CH_2Cl_2/EtOAc/EtOH, 50:10:1, v/v) to yield the faster migrating β-anomer (1.5 g, 25%) followed by the α-anomer (0.5 g, 8.4%). Both anomers were isolated as white foams. β-Anomer (**15**): TLC, R_f 0.60 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 6H, ArMe), 2.60 (m, 2H, 2′-H), 4.55 (2 m, 2H, 5′-H), 4.73 (m, 1H, 4′-H), 5.32 (s, 1H, $ArCH_2$), 5.34 (br s, 2H, NH_2, D_2O exchangeable), 5.49 (dd, 1H, 1′-H, *J*=4.5, 10.5 Hz), 5.87 (d, 1H, 3′-H, *J*=3.5 Hz), 7.18−7.38 and 7.92−7.99 (2 m, 14H, ArH, and 6-H), 10.05 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{34}H_{32}N_4O_6$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.57; H, 5.80; N, 9.13. α-Anomer (**16**): TLC, R_f 0.58 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 6H, ArMe), 2.62 (m, 2H, 2′-H), 4.56 (2 m, 2H, 5′-H), 4.75 (m, 1H, 4′-H), 5.35 (s, 1H, $ArCH_2$), 5.40 (br s, 2H, NH_2, D_2O exchangeable), 5.52 (t, 1H, 1′-H, *J*=6.7 Hz), 5.68 (d, 1H, 3′-H, *J*=4.3 Hz), 7.17−7.37 and 7.93−7.97 (2 m, 14H, ArH, and 6-H), 10.01 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{34}H_{32}N_4O_6$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.71; H, 5.77; N, 9.06.

Compounds **17**–**19** and **21** were synthesized by methodology similar to that described for compounds **3**–**5** and **13a**, respectively.

2-Amino-2′-deoxy-7-(3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (17). Compound **17** was isolated as a foam (1.3 g, 59%): TLC, R_f 0.15 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.34 and 2.38 (2 s, 6H, ArMe), 2.56 (m, 2H, 2′-H), 4.43 (2 m, 2H, 5′-H), 4.55 (m, 1H, 4′-H), 5.26 (dd, 1H, 1′-H, J=5.0, 11.5 Hz), 5.53 (d, 1H, 3′-H, J=5.0 Hz), 5.82 (br s, 2H, NH_2, D_2O exchangeable), 7.13 (s, 1H, 6-H), 7.20–7.37 and 7.82–7.93 (2 m, 8H, ArH), 10.40 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{27}H_{26}N_4O_6$: C, 64.53; H, 5.22; N, 11.15. Found: C, 64.20; H, 5.60; N, 11.02.

2-Amino-4-chloro-7-(3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (18). Compound **18** was isolated as a foam (0.8 g, 35%): TLC, R_f 0.21 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.38 and 2.40 (2 s, 6H, ArMe), 2.80 and 2.90 (2 m, 2H, 2′-H), 4.58 (2 m, 2H, 5′-H), 4.66 (m, 1H, 4′-H), 4.85 (br s, 2H, NH_2, D_2O exchangeable), 5.57–5.62 (m, 2H, 1′-H, and 3′-H), 7.17–7.23 and 7.49–7.96 (2 m, 9H, ArH and 6-H), 9.24 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{27}H_{25}$ ClN_4O_5: C, 62.25; H, 4.84; N, 10.76. Found: C, 62.10; H, 4.61; N, 10.52.

2,4-Dichloro-7-(3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (19). Compound **19** was isolated as a foam (0.41 g, 53%): TLC, R_f 0.32 (CH_2Cl_2/EtOH, 40:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.43 and 2.48 (2 s, 6H, ArMe), 2.49 and 2.82 (2 m, 2H, 2′-H), 4.55 (m, 2H, 5′-H), 4.77 (m, 1H, 4′-H), 5.63 (dd, 1H, 1′-H, J=5.3, 10.4 Hz), 5.68 (m, 1H, 3′-H), 7.20–7.29 and 7.87–7.98 (2 m, 8H, ArH), 7.60 (d, 1H, 6-H, J=2,5 Hz), 8.75 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{27}H_{23}Cl_2N_3O_5 \cdot 0.3C_2H_5OH$: C, 58.51; H, 4.50; N, 7.58. Found: C, 58.40; H, 4.34; N, 7.42.

4-Amino-2-chloro-7-(2-deoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (21, 2-chloro-2′-deoxy-9-deazaadenosine). Compound **21** was isolated as a white solid (0.1 g, 43%): mp 96–98°C; TLC, R_f 0.43 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 1.97 and 2.35 (2 m, 2H, 2′-H), 3.53 (m, 2H, 5′-H), 3.83 (m, 1H, 4′-H), 4.27 (d, 1H, 3′-H, J=5.2 Hz), 4.72 and 5.00 (2 br s, 2H, 2OH, D_2O exchangeable), 5.26 (dd, 1H, 1′-H, J=5.4, 10.7 Hz), 7.50 (br s, 2H, NH_2, D_2O exchangeable), 7.60 (d, 1H, 6-H, J=2.5 Hz), 11.60 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}ClN_4O_3$: C, 46.40; H, 4.60; N, 19.68. Found: C, 46.67; H, 4.38; N, 19.32.

4-Amino-7-(2-deoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (22, 2′-deoxy-9-deazaadenosine). Compound **22** was synthesized by a procedure similar to that described for compound **14a** and was isolated

as a white foam (0.04 g, 43%): TLC, R_f 0.34 (CH_2Cl_2/EtOH, 1:1, v/v); ^{1}H NMR (DMSO-d_6) δ 1.97 (dd, 1H, 2′-H_A, J=12.6, 5.4 Hz), 2.35 (ddd, 1H, 2′-H_B, J=12.4, 10.4, 5.1 Hz), 3.53 (m, 2H, 5′-H), 3.83 (s, 1H, 4′-H), 4.27 (d, 1H, 3′-H, J=5.2 Hz), 4.72 and 5.00 (2 br s, 2H, 2OH, D_2O exchangeable), 5.25 (dd, 1H, 1′-H, J=10.5, 5.4 Hz), 7.59 (br s, 2H, NH_2, D_2O exchangeable), 7.60 (s, 1H, 6-H), 8.15 (s, 1H, 2-H), 11.60 (s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.80; H, 5.88; N, 22.10.

Compounds **23**–**26** were synthesized from compound **19** by methodology similar to that described for compounds **11a**–**14a**.

2,4-Dichloro-5-methyl-7-(3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (23). Compound **23** was isolated as a foam (0.30 g, 73%): TLC, R_f 0.60 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR (DMSO-d_6) δ 2.42 and 2.47 (2 s, 6H, ArMe), 2.49 and 2.76 (2 m, 2H, 2′-H), 3.90 (s, 2H, Me), 4.51 (m, 2H, 5′-H), 4.74 (m, 1H, 4′-H), 5.58 (m, 1H, 3′-H), 5.62 (dd, 1H, 1′-H, J=10.1, 5.2 Hz), 7.22–7.29 and 7.87–7.97 (2 m, 8H, ArH), 7.62 (s, 1H, 6-H). Anal. Calcd. for $C_{28}H_{25}Cl_2N_3O_5$: C, 60.66; H, 4.55; N, 7.58. Found: C, 60.80; H, 4.21; N, 7.39.

4-Amino-2-chloro-5-methyl-7-(2-deoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (25, 2-chloro-2′-deoxy-7-methyl-9-deazaadenosine). Compound **25** was isolated as an off-white solid (0.12 g, 71%): mp 120–122°C: TLC, R_f 0.36 (CH_2Cl_2/EtOH, 4:1, v/v); ^{1}H NMR (DMSO-d_6) δ 1.96 and 2.18 (2 m, 2H, 2′-H), 3.46 (m, 2H, 5′-H), 3.75 (m, 1H, 4′-H), 3.94 (s, 3H, Me), 4.22 (m, 1H, 3′-H), 4.98 and 5.00 (2 br s, 2H, 2OH, D_2O exchangeable), 5.15 (dd, 1H, 1′-H, J=10.7, 5.3 Hz), 7.16 (br s, 2H, NH_2, D_2O exchangeable), 7.46 (s, 1H, 6-H). Anal. Calcd. for $C_{12}H_{15}ClN_4O_3$: C, 48.25; H, 5.06; N, 18.76. Found: C, 48.34; H, 4.88; N, 18.54.

4-Amino-5-methyl-7-(2-deoxy-β-D-ribofuranosyl)-5H-pyrrolo[3,2-d]pyrimidine (26, 2′-deoxy-7-methyl-9-deazaadenosine). Compound **26** was isolated as a white solid (0.05 g, 71%): mp 78–80°C; TLC, R_f 0.18 (CH_2Cl_2/EtOH, 2:1, v/v); ^{1}H NMR (DMSO-d_6) δ 1.92 and 2.30 (2 m, 2H, 2′-H), 3.46 and 3.52 (2 m, 2H, 5′-H), 3.81 (m, 1H, 4′-H), 3.95 (s, 3H, Me), 4.25 (m, 1H, 3′-H), 4.94 and 5.90 (2 br s, 2H, 2OH, D_2O exchangeable), 5.19 (dd, 1H, 1′-H, J=10.9, 5.3 Hz), 6.69 (br s, 2H, NH_2, D_2O exchangeable), 7.39 (s, 1H, 6-H), 7.99 (s, 1H, 2-H). Anal. Calcd. for $C_{12}H_{16}N_4O_3 \cdot 0.3C_2H_5OH$: C, 51.82; H, 6.45; N, 20.14. Found: C, 52.12; H, 6.50; N, 20.04.

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