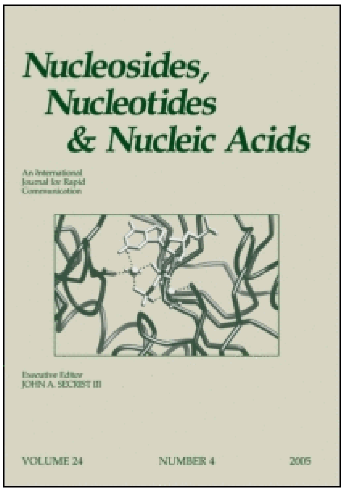


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

SYNTHESIS OF HALOGEN-SUBSTITUTED 3-DEAZAADENOSINE AND 3-DEAZAGUANOSINE ANALOGUES AS POTENTIAL ANTITUMOR/ANTIVIRAL AGENTS

Mao-Chin Liu[a]; Mei-Zhen Luo[a]; Diane E. Mozdziesz[a]; Tai-Shun Lin†[a]; Ginger E. Dutschman[a]; Elizabeth A. Gullen[a]; Yung-Chi Cheng[a]; Alan C. Sartorelli[a]
[a] Department of Pharmacology and Developmental Therapeutics Progam, Cancer Center, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

To cite this Article Liu, Mao-Chin , Luo, Mei-Zhen , Mozdziesz, Diane E. , Lin†, Tai-Shun , Dutschman, Ginger E. , Gullen, Elizabeth A. , Cheng, Yung-Chi and Sartorelli, Alan C.(2001) 'SYNTHESIS OF HALOGEN-SUBSTITUTED 3-DEAZAADENOSINE AND 3-DEAZAGUANOSINE ANALOGUES AS POTENTIAL ANTITUMOR/ANTIVIRAL AGENTS', Nucleosides, Nucleotides and Nucleic Acids, 20: 12, 1975 — 2000

To link to this Article: DOI: 10.1081/NCN-100108327

URL: http://dx.doi.org/10.1081/NCN-100108327

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(12), 1975–2000 (2001)

SYNTHESIS OF HALOGEN-SUBSTITUTED 3-DEAZAADENOSINE AND 3-DEAZAGUANOSINE ANALOGUES AS POTENTIAL ANTITUMOR/ANTIVIRAL AGENTS

**Mao-Chin Liu, Mei-Zhen Luo, Diane E. Mozdziesz, Tai-Shun Lin,[†]
Ginger E. Dutschman, Elizabeth A. Gullen, Yung-Chi Cheng, and
Alan C. Sartorelli***

Department of Pharmacology and Developmental Therapeutics
Progam, Cancer Center, Yale University School of Medicine, New
Haven, Connecticut 06520-8066, USA

ABSTRACT

Various 2-halogen-substituted analogues (**38**, **39**, **43** and **44**), 3-halogen-substituted analogues (**51** and **52**), and 2′,3′-dihalogen-substituted analogues (**57**–**60**) of 3-deazaadenosine and 3-halogen-substituted analogues (**61** and **62**) of 3-deazaguanosine have been synthesized as potential anticancer and/or antiviral agents. Among these compounds, 3-deaza-3-bromoguanosine (**62**) showed significant cytotoxicity against L1210, P388, CCRF-CEM and $B_{16}F_{10}$ cell lines in vitro, producing IC_{50} values of 3, 7, 9 and 7 µM, respectively. Several 3-deazaadenosine analogues (**38**, **51**, **57** and **59**) showed moderate to weak activity against hepatitis B virus.

Considerable progress has been made in the search for novel nucleoside structures with anticancer and/or antiviral activity by modifications in the base portion of the molecule. For example, 3-deazaadenosine[1–3], a potent inhibitor of adenosylhomocysteine hydrolase[4], showed significant activity

---

[†] Deceased.

*Corresponding author.

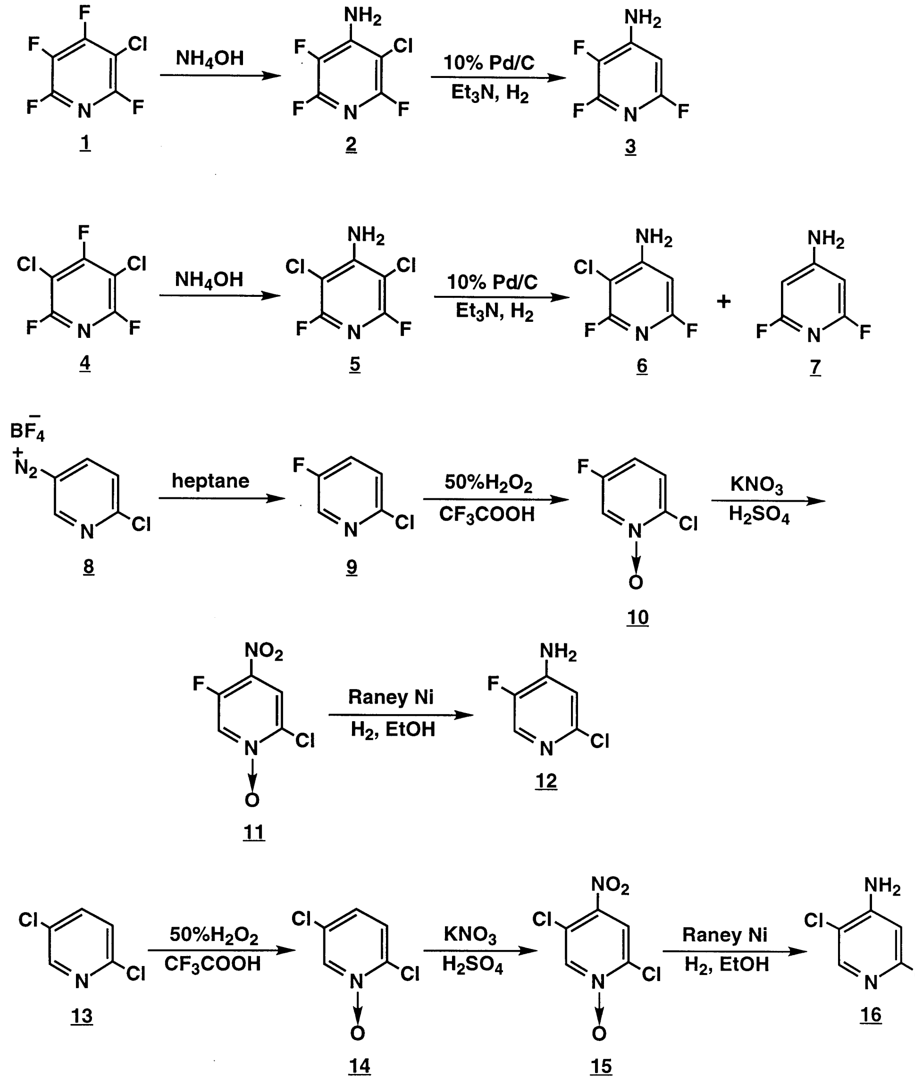
www.dekker.com

against herpes simplex type-1[5], human immunodeficiency virus[6] and oncogenic DNA viruses[7,8]. 3-Deazaguanosine has been reported to possess broad spectrum antiviral activity against a variety of DNA and RNA viruses, as well as antitumor activity against the L1210 leukemia and several mammary adenocarcinomas in mice[9–11]. Certain 2-halogen-substituted purine nucleosides have exhibited cytotoxicity in vitro and anticancer activity in vivo[12–15]. Among these analogues, Fludarabine phosphate (9-β-D-arabinofuranosyl-2-fluoroadenine 5′-*O*-phosphate) and Cladribine (2-chloro-2′-deoxy-β-D-adenosine) are currently used as anticancer agents. On the basis of these findings, we chose to prepare a series of halogen-substituted analogues of 3-deazaadenosine and 3-deazaguanosine, which combine the structural features of 3-deazapurine nucleosides and halogen-substituted purine nucleosides. In this report, we describe the synthesis and biological evaluation of these nucleoside analogues.

CHEMISTRY

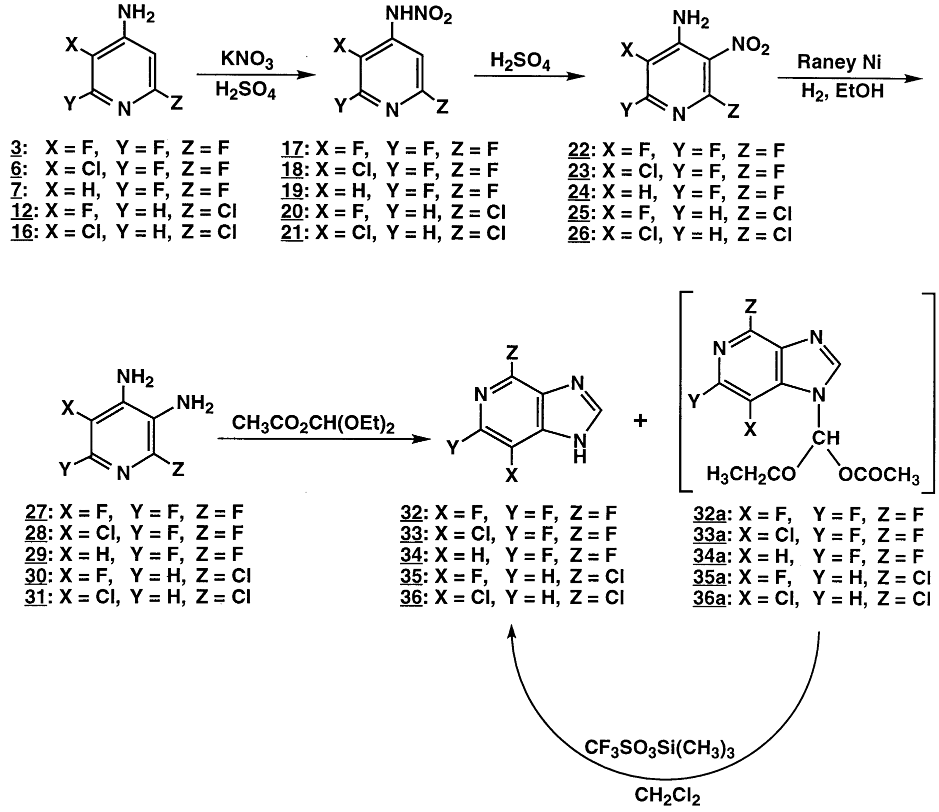
The halogen-substituted 4-aminopyridines were synthesized as depicted in Scheme 1. Treatment of commercially available 3-chlorotetrafluoropyridine (**1**) and 3,5-dichlorotrifluoropyridine (**4**) with ammonium hydroxide at room temperature gave almost quantitatively 4-amino-3-chloro-2,5,6-trifluoropyridine (**2**) and 4-amino-3,5-dichloro-2,6-difluoropyridine (**5**), respectively[16]. Catalytic hydrogenation of **2** afforded **4**-amino-2,3,6-trifluoropyridine (**3**) in high yield. Catalytic hydrogenation of **5** was reported to give 4-amino-2,6-difluoropyridine (7)[17]; however, when the reaction was stopped at an early stage, a mixture of 4-amino-3-chloro-2,6-difluoropyridine (**6**) and **7** were produced, which was easily separated by flash silica gel column chromatography.

2-Chloro-5-fluoropyridine (**9**), a highly volatile substance, was synthesized from thermolysis of 2-chloro-5-pyridinediazonium tetrafluoroborate (**8**)[18]. The isolation of **9** by the literature procedure was very complicated, in that it included repeated extractions, repeated distillations, treatment with sulfuric acid and sodium hydroxide, and steam distillation. In our hands, the reported yield of 70% was difficult to obtain after these operations. To improve upon these complicated procedures, following the thermolysis of compound **8**, the reaction mixture was directly treated with 50% hydrogen peroxide and trifluoroacetic acid to give 2-chloro-5-fluoropyridine-*N*-oxide (**10**), which was easily isolated, with a total yield of 73%. Nitration of **10**, followed by catalytic hydrogenation of the resulting 2-chloro-5-fluoro-4-nitropyridine-1-oxide (**11**) removed the *N*-oxide function, as well as reduced the nitro group to give the desired 4-amino-2-chloro-5-fluoropyridine (**12**). *N*-Oxidation of commercially available 2,5-dichloropyridine (**13**), followed by nitration and reduction yielded 4-amino-2,5-dichloropyridine (**16**).



Scheme 1.

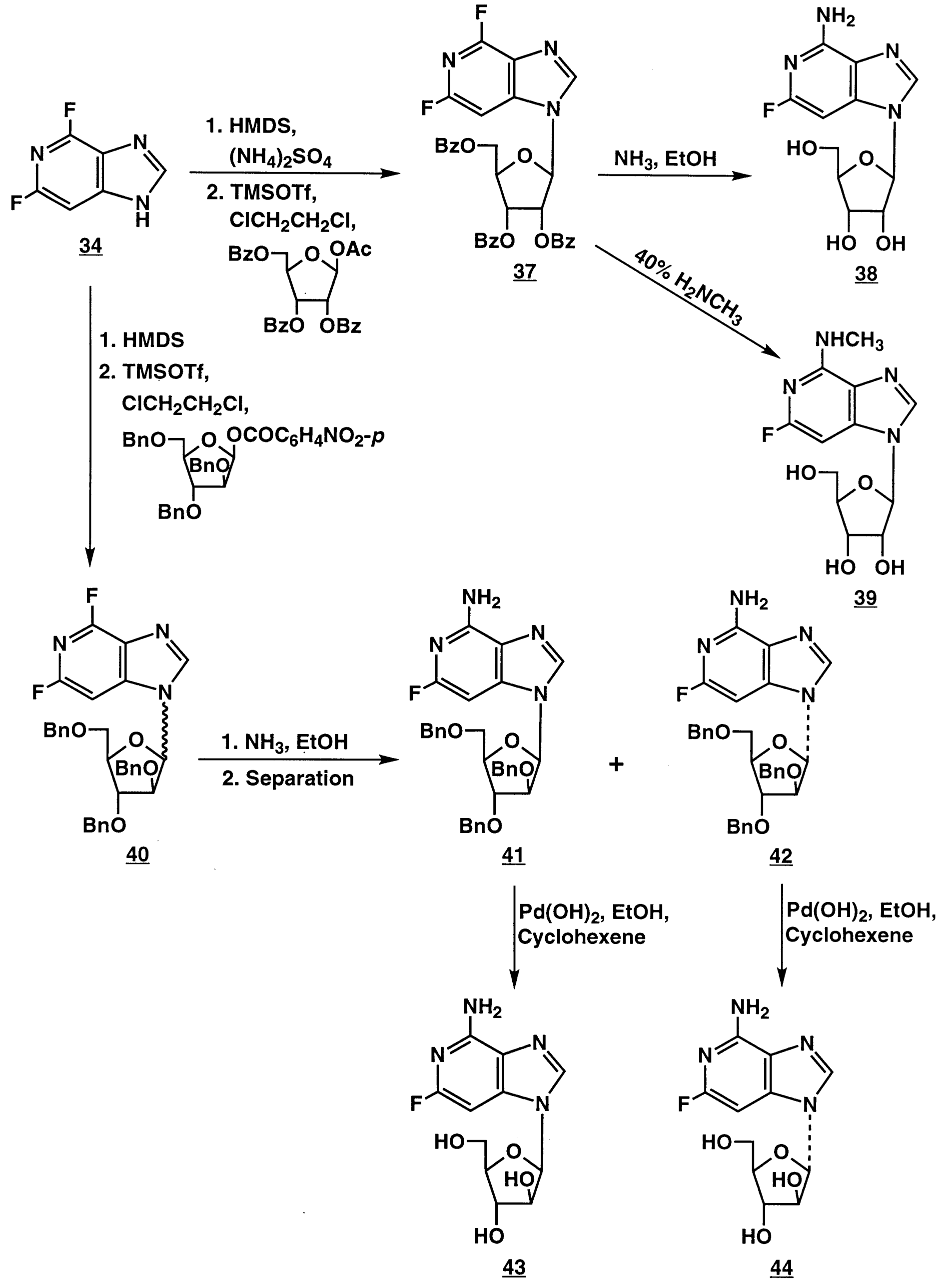
Various halogen-substituted imidazo[4,5-c]pyridines (**32**–**36**) were synthesized from the corresponding halogen-substituted 4-pyridinamines according to methodology similar to that reported by Rousseau and Robins[19] for the synthesis of 4,6-dichloroimidazo[4,5-c]pyridine, with modifications as illustrated in Scheme 2. Nitration of compounds **3**, **6**, **7**, **12** and **16** with potassium nitrate in sulfuric acid gave the respective 4-nitraminopyridines (**17**–**21**). Rearrangement of compounds **17**–**21** in concentrated sulfuric acid produced the respective 4-amino-3-nitropyridine derivatives **22**–**26**. Catalytic hydrogenation of **22**–**26** in the presence of Raney nickel afforded the



Scheme 2.

corresponding 3,4-diaminopyridine derivatives **27**–**31**. Ring closure of compounds **27**–**31** by reaction with diethoxymethyl acetate gave the desired halogen-substituted imidazo[4,5c]pyridines **32**–**36**[20] and *N*-1 substituted compounds **32a**–**36a** which were separated by silica gel column chromatography; these by-products were easily converted back to compounds **32**–**36** by reaction with trimethylsilyl trifluoromethanesulfonate. The synthesis of 4,6-difluoroimidazo[4,5-c]pyridine (**34**) has been previous reported by a different synthetic route; however, this method was rather lengthy and the overall yield was quite low[20].

Treatment of 4,6-difluoroimidazo[4,5-c]pyridine (**34**) with excess hexamethyldisilazane and a catalytic amount of ammonium sulfate gave the trimethylsilyl derivative, which was treated with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst at room temperature to give the tribenzoyl-protected nucleoside derivative **37** (Scheme 3). Treatment of **37** with either saturated ethanolic ammonia or 40% methylamine removed the protecting groups and displaced the 4-fluoro group in one step to produce


34
1. HMDS, (NH4)2SO4
2. TMSOTf, ClCH2CH2Cl,
BzO
OAc
BzO OBz
37
NH3, EtOH
38
40% H2NCH3
39
1. HMDS
2. TMSOTf, ClCH2CH2Cl,
BnO
OCOC6H4NO2-p
BnO
BnO
40
1. NH3, EtOH
2. Separation
41
+
42
Pd(OH)2, EtOH, Cyclohexene
Pd(OH)2, EtOH, Cyclohexene
43
44

Scheme 3.

the respective target nucleosides **38** and **39**. Refluxing of silylated **34** with 2,3,5-tri-*O*-benzyl-1-*O*-(4-nitro-benzoyl)-D-arabinofuranose in 1,2-dichloroethane in the presence of TMSOTf under nitrogen afforded a mixture of α- and β-nucleosides **40**. Treatment of **40** with ammonia saturated ethanol gave the 4-amino-6-fluoro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazo[4, 5-c]pyridine (**41**) and its α-analogue **42**, which were separated by silica gel chromatography. Debenzylation of **41** and **42** with palladium (II) oxide hydrate and cyclohexene in ethanol afforded the target compound **43** and its α-analogue **44**.

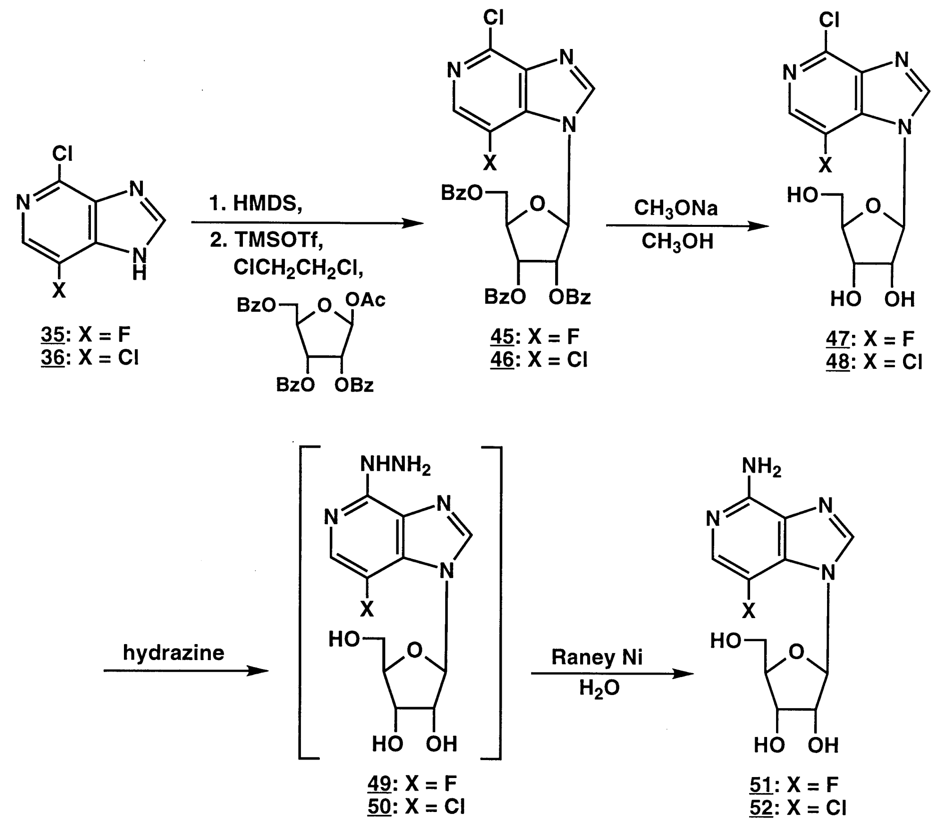
The assignment of the anomeric configurations of these nucleosides (**41**–**44**) was made on the basis of the characteristics of the proton NMR spectra (Table 1). The 4′-H protons of the α-anomers appear at a lower field than those of the β-anomers. Conversely, the 5′-H protons of the α-anomers appear at a higher field than those of the β-anomers. These shifts are attributed to the fact that protons at the syn-position relative to the base are more deshielded than those in the anti-position relative to the base. The 4′-H protons of the α-anomers and the bases are on the same side of the sugar ring and those of β-anomers are on the opposite side. In contrast, the 5′-H protons of the α-anomers and the bases are on the opposite side of the sugar ring and those of β-anomers are on the same side. The findings are consistent with reports by others with both pyrimidine and purine nucleosides[21–23].

The synthesis of 3-halogen-substituted 3-deazaadenosine analogues **51** and **52** is shown in Scheme 4. Condensation of silylated 4-chloro-7-fluoroimidazo[4,5-c]pyridine (**35**) and silylated 4,7-dichloroimidazo[4,5-c]pyridine (**36**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroe thane in the presence of TMSOTf gave the 3-deaza-3-halogen-substituted purine nucleosides **45** and **46**, respectively. Deblocking of **45** and **46** with sodium methoxide in methanol yielded the corresponding nucleoside derivatives **47** and **48**. Attempts at conversion of the 4-chloro substituents on **45**

Table 1. Proton NMR Chemical Shifts δ (ppm)

Compound	4′-H[a]	Δδ	5′-H[a]	Δδ
41 (β)[b]	4.10 (anti)		3.70 (syn)	
		0.15		0.12
42 (α)[b]	4.25 (syn)		3.58 (anti)	
43 (β)[c]	3.73 (anti)		3.65 (syn)	
		0.29		0.13
44 (α)[c]	4.02 (syn)		3.52 (anti)	

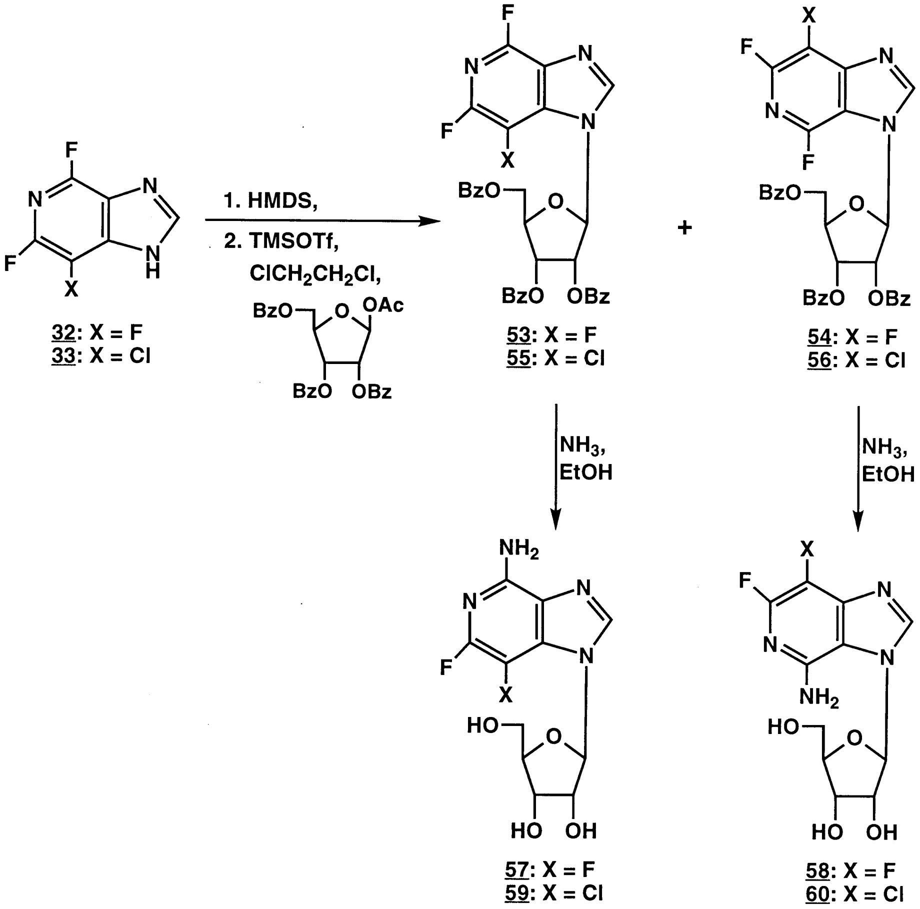
[a] stereochemistry relative to the base. [b] spectra were recorded in $CDCl_3$; [c] in DMSO-d_6.



Scheme 4.

and **46** to the corresponding amino functions by either ammonia saturated ethanol or liquid ammonia at various temperatures were unsuccessful and resulted in either a decomposed by-product or recovery of the starting material. However, treatment of **47** and **48** with anhydrous hydrazine[24], followed by catalytic hydrogenation of compounds **49** and **50** with Raney nickel furnished **51** and **52**.

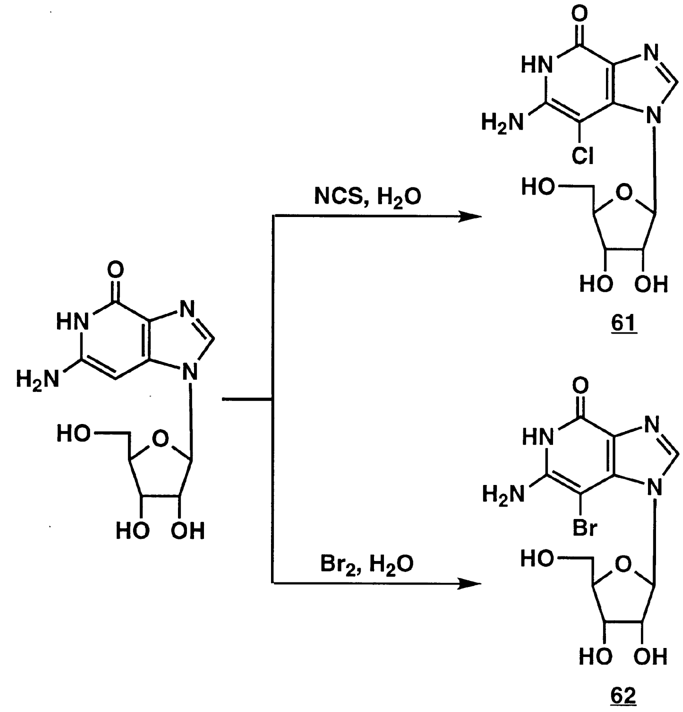
The synthesis of 2,3-dihalogen-substituted 3-deazaadenosine analogues **57**–**60** is depicted in Scheme 5. Condensation of silylated 4,6,7-trifluoroimidazo[4,5-c]pyridine (**32**) and silylated 7-chloro-4,6-difluoroimidazo[4,5-c]pyridine (**33**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane in the presence of TMSOTf gave the corresponding protected 1-ribosides **53** and **55**, and 3-ribosides **54** and **56**. Treatment of compounds **53**–**56**, with ammonia saturated ethanol afforded the respective target compounds **57**–**60**. The assignment of the *N*-glycosidic linkage of the N^1- and N^3-isomers of compounds **57**–**60** was based upon the UV spectra of these derivatives. The UV spectra of the N^1-3-deazapurine nucleoside



Scheme 5.

isomers showed a maximum peak at 274 nm (**57** and **59**), while the N^3-isomers showed a maximum peak at 292 nm (**58** and **60**). Furthermore, the NMR spectra of the 2-H protons of the N^3-isomers were downfield from those of the corresponding N^1-isomers. For example, the chemical shifts of the 2-H protons of the N^3-isomers **58** and **60** appeared at 8.54 and 8.55 ppm and for the N^1-isomers **57** and **59** at 8.43 and 8.51 ppm, respectively. These results are similar to those obtained with other 3-deazapurine nucleosides[25,26].

The synthesis of 3-deaza-3-halogen-substituted 3-deazaguanosine analogues is illustrated in Scheme 6. Halogenation of 3-deazaguanosine, which was synthesized by a known procedure[11,27], with *N*-chlorosuccinimide in water and bromine-water, respectively, gave the corresponding 3-deaza-3-chloroguanosine (**61**) and 3-deaza-3-bromoguanosine (**62**).



Scheme 6.

BIOLOGICAL EVALUATION

The synthesized compounds were evaluated in vitro for their cytotoxicity against the L1210 and P388 leukemias, the CCRF-CEM lymphoblastic leukemia, and the $B_{16}F_{10}$ melanoma cell lines and the results are shown in Table 2. Among these compounds, 3-deaza-3-chloroguanosine (**61**) showed activity with IC_{50} values of 12, 40, 30 and 35 μM and 3-deaza-3-bromoguanosine (**62**) produced IC_{50} values of 3, 7, 9 and 7 μM against L1210, P388, CCRF-CEM and $B_{16}F_{10}$ cells, respectively. The halogen-substituted 3-deazaadenosine derivatives **38**, **51**, **57** and **59** showed moderate to weak activities, and the other compounds had only slight or no activity in concentrations up to 100 μM against these neoplastic cell lines.

Antiviral assays were performed against hepatitis B virus (HBV) and human immunodeficiency virus (HIV-IIIB) in vitro as previously described[28]. Among these compounds, 3-deaza-3-chloro-2-fluoroadenosine (**59**), 3-deaza-3-fluoroadenosine (**51**) and 4-amino-6,7-difluoro-3-(β-D-ribfuranosyl)imidazo[4,5c]pyridine (**58**) showed moderate activity against HBV with EC_{50}

Table 2. Evaluation of the Cytotoxicity of Halogen-Substituted 3-Deazaadenosine and 3-Deazaguanosine Analogues Against L1210, P388, CCRF-CEM, and $B_{16}F_{10}$ Cell Lines In Vitro

	$IC_{50}(\mu M)^a$			
Compound	L1210	P388	CCRF-CEM	B16F10
38	35	50	100	40
39	> 100	> 100	100	> 100
43	> 100	> 100	> 100	> 100
44	> 100	> 100	> 100	> 100
51	15	100	60	45
52	> 100	> 100	> 100	> 100
57	90	90	40	100
58	> 100	> 100	> 100	> 100
59	55	90	60	100
60	> 100	> 100	> 100	> 100
61	12	40	30	35
62	3	7	9	7

[a] IC_{50} values represent the drug concentration (μM) required to inhibit cancer cell replication by 50%. The compounds were tested up to a concentration of 100 μM.

values of 7.5, 9.2 and 10 μM, respectively. The remaining compounds showed little or no activity against HBV and HIV-IIIB up to their maximum tested concentrations of 10 and 100 μM, respectively.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H 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.

4-Amino-3-chloro-2,5,6-trifluoropyridine (2). This compound was prepared by a modification of the procedure of Chambers et al.[16] A mixture of

3-chloro-2,4,5,6-tetrafluoropyridine (**1**, 37.4 g, 201 mmol) and 150 mL of 28% ammonium hydroxide was stirred at room temperature for 5 h. The resulting white crystals were collected and carefully washed with ice water to give **2** as a white solid (35 g). The combined filtrate and washings were extracted with ether. The ether extract was dried ($MgSO_4$), filtered and evaporated in vacuo to give additional **2** (1.3 g); total yield: 26.3 g (99%). The product was used directly for the next step in the reaction. A small sample was purified by silica gel column chromatography: mp 118-120°C (Lit.16 mp 117-118°C).

4-Amino-3,5-dichloro-2,6-difluoropyridine (5). This compound was prepared from 3,5-dichloro-2,4,6-trifluoropyridine (24.5 g) by a procedure similar to that described for compound **2**: yield, 23.7 g (98%); mp 110°C (Lit[16]. mp 112–113°C).

4-Amino-2,3,6-trifluoropyridine (3). A suspension of 4-amino-3-chloro-2,5,6-trifluoropyridine (**2**, 19.7 g, 108 mmol), 10% Pd/C (1.8 g) and triethylamine (20 mL, 140 mmol) in 150 mL of anhydrous ethanol was hydrogenated at 50 psi in a Parr hydrogenation apparatus until TLC showed the reaction was completed (~ 18 h). The catalyst was removed by filtration and carefully washed with ethanol. The combined filtrate and washings were evaporated to dryness in vacuo. The residue was stirred with 80 mL of water for 1 h, filtered, and washed with water to give **3** (14 g) as a white solid. The filtrate and washings were combined and extracted with ether. The combined ether layers were then dried ($MgSO_4$) and concentrated to give an additional 1.3 g of **3** (total yield: 15.3 g, 96%). A small analytical sample was purified by silica gel column chromatography (R_f 0.47, CH_2Cl_2): mp 94–96°C; ^1H NMR ($CDCl_3$) δ 4.78 (br s, 2 H, 4-NH_2, D_2O exchangeable), 6.20 (d, 1 H, 5-H). Anal. Calcd. for $C_5H_3F_3N_2$: C, 40.55; H, 2.04; N, 18.92. Found: C, 40.60; H, 2.16; N, 18.67.

4-Amino-3-chloro-2,6-difluoropyridine (6) and 4-amino-2,6-difluoropyridine (7). A suspension of 19.9 g (100 mmol) of **5**, 2.2 g of 10% Pd/C and 27 mL (190 mmol) of triethylamine in 100 mL of anhydrous ethanol was hydrogenated at 50 psi in a Parr hydrogenation apparatus overnight (~ 18 h). The catalyst was filtered and carefully washed with ethanol. The combined filtrate and washings were evaporated to dryness in vacuo. The residue was partitioned between ether and water, and the water layer was extracted with ether. The combined ether layers were dried ($MgSO_4$) and concentrated to dryness. The residue was dissolved in ethanol and the solution was treated with 50 g of silica gel. The solvent was removed in vacuo to give a powder, which was purified by silica gel column chromatography, eluted with CH_2Cl_2 to afford 9.4 g (57%) of **6** and 4.3 g (33%) of **7**.

Compound **6** was isolated as a white solid: mp 84–85°C; TLC, R_f 0.55 (CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.15 (br s, 2 H, NH_2, D_2O exchangeable), 6.20 (s, 1 H, 5-H). Anal. Calcd. for $C_2H_3ClF_2N_2$: C, 36.49; H, 1.84; N, 17.02. Found: C, 36.78; H, 2.09; N, 16.89.

Compound **7** was isolated as a white solid: mp 126–128°C (Lit.14 mp 125–127°C); TLC, R_f 0.37 (CH_2Cl_2); ^1H NMR (DMSO-d_6) δ 6.00 (s, 2 H, 3- and 5-H), 6.70 (br s, 2H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_5H_4F_2N_2$: C, 46.16; H, 3.10; N, 21.54. Found: C, 46.01; H, 3.39; N, 21.29.

2-Chloro-5-fluoropyridine-1-oxide (10). A suspension of 2-chloro-5-pyridinediazonium tetrafluoroborate[18] (8, 7.6 g, 33.4 mmol) in dry heptane (50 mL) was heated to 105°C (oil bath temperature) for 2 h. A rapid evolution of nitrogen was observed after 10–15 min, which lasted for about 30 min. The reaction mixture formed two layers: the clear upper heptane layer and the blackened dark lower layer. The temperature was then lowered to 70°C, and 100 mL of trifluoroacetic acid and 11 mL of 50% hydrogen peroxide were subsequently added from the top of the condenser. The reaction mixture was stirred at 70–75°C until TLC showed that the reaction was complete (~20 h). The lower dark layer gradually changed to a clear orange solution during the reaction process. The two-layer mixture was evaporated to dryness in vacuo and co-evaporated with toluene (50 mL). To the residue were added 20 mL of water and 100 mL of methylene chloride, and the mixture was neutralized by dropwise addition of 28% ammonium hydroxide solution with stirring. The aqueous layer was further extracted with methylene chloride and the combined organic layer was dried, filtered and evaporated to give the crude product, which was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 1:1, v/v, R_f 0.23) to give 3.6 g (73%) of product as a white solid: mp 98–100°C; ^1H NMR ($CDCl_3$) δ 7.15 (m, 1 H, 3-H), 7.60 (m, 1H, 4-H), 8.40 (dd, 1 H, 6-H, $J = 2.0$ Hz, 8.5 Hz). Anal. Calcd. for $C_5H_3ClFNO \cdot 0.5\ H_2O$: C, 38.36; H, 2.56; N, 8.95. Found: C, 38.13; H, 2.19; N, 8.65.

2-Chloro-5-fluoro-4-nitropyridine-1-oxide (11). 2-Chloro-5-fluoropyridine-*N*-oxide (**10**, 3.5 g, 23.7 mmol) was gradually added to 46 mL of concentrated sulfuric acid, followed by 10 g of potassium nitrate with stirring. The reaction mixture was heated at 120°C for 2 h, cooled and poured onto 160 g of crushed ice. The solution was neutralized by dropwise addition of 28% ammonium hydroxide with stirring, while the temperature was maintained below 15°C with an ice bath. The light yellow crystals which precipitated were collected by filtration, washed with ice water, and dried to yield 2.7 g (59%) of product. A small sample was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 4:1, v/v, R_f 0.71): mp 131–132°C; ^1H NMR (DMSO-d_6) δ 8.70 (m, 1 H, 3-H), 9.12 (m, 1 H, 6-H). Anal. Calcd. for $C_5H_2ClFN_2O_3$: C, 31.19; H, 1.05; N, 14.55. Found: C, 31.36; H, 1.16; N, 14.75.

4-Amino-2-chloro-5-fluoropyridine (12). A mixture of 2-chloro-5-fluoro-4-nitropyridine-1-oxide (**11**, 1.3 g, 6.8 mmol) and 1.6 g of Raney nickel in 80 mL of anhydrous ethyl alcohol was hydrogenated at 40 psi in a Parr hydrogenation apparatus for 3 h when TLC showed that the starting material had disappeared and a new spot was detected (CH_2Cl_2/EtOAc, 4:1, v/v, R_f 0.78 and 0.71, for the starting material and the product, respectively). The catalyst was removed by filtration and washed carefully with ethyl alcohol. The filtrate and washings were combined and evaporated in vacuo to give 0.9 g (91%) of product as an off-white solid. A small analytical sample was purified by recrystallization from hot water to afford white crystals: mp 110–111°C; ^1H NMR ($CDCl_3$) δ 4.50 (br s, 2 H, NH_2, D_2O exchangeable), 7.15 (d, 1H, 3-H, $J = 6\,Hz$), 7.95 (d, 1H, 6-H, $J = 2\,Hz$). Anal. Calcd. for $C_5H_4ClFN_2$: C, 40.97; H, 2.75; N, 19.12. Found: C, 41.18; H, 2.39; N, 18.89.

2,5-Dichloropyridine-1-oxide (14). A mixture of 2,5-dichloropyridine (10 g, 67 mmol), 180 mL of trifluoroacetic acid and 22 mL of 50% hydrogen peroxide was heated at 70–75°C with stirring until TLC showed the reaction to be complete. The reaction mixture was evaporated to dryness in vacuo and co-evaporated with water twice. The residue was stirred with 40 mL of water and 200 mL of methylene chloride and neutralized by dropwise addition of 28% ammonium hydroxide solution. The aqueous layer was further extracted with methylene chloride and the combined organic layer was dried, filtered and evaporated to give 10 g (91%) of product, which was used directly for the next step. A small sample was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 10:1, v/v, R_f 0.24): mp 73–75°C; ^1H NMR ($CDCl_3$) δ 7.13 (dd, 1 H, 4-H, $J = 10\,Hz$, 2 Hz), 7.45 (d, 1H, 3-H, $J = 10\,Hz$), 8.35 (d, 1 H, 6-H, $J = 2\,Hz$). Anal. Calcd. for $C_5H_3Cl_2NO \cdot 0.5\ H_2O$: C, 36.62; H, 1.84; N, 8.54. Found: C, 36.43; H, 2.01; N, 8.25.

Compounds **15** and **16** were synthesized by methodology similar to that described for compounds **11** and **12**, respectively.

2,5-Dichloro-4-nitropyridine-1-oxide (15). Compound **15** was isolated as light yellow crystals (6.5 g, 50.5%): mp 137–139°C; ^1H NMR (DMSO-d_6) δ 8.70 (s, 1 H, 3-H), 9.05 (s, 1 H, 6-H). Anal. Calcd. for $C_5H_2Cl_2N_2O_3$: C, 28.73; H, 0.96; N, 13.41. Found: C, 28.39; H, 1.06; N, 13.55.

2,5-Dichloro-4-aminopyridine (16). Compound **16** was isolated as a white solid (4.0 g, 85%): mp 122–123°C; ^1H NMR ($CDCl_3$) δ 4.75 (br s, 2 H, NH_2, D_2O exchangeable), 6.63 (s, 1 H, 3-H), 8.05 (s, 1H, 6-H). Anal. Calcd. for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47; N, 17.19. Found: C, 36.58; H, 2.30; N, 16.88.

4-Nitramino-2,3,6-trifluoropyridine (17). 4-Amino-2,4,6-trifluoropyri dine (3, 7 g, 47.3 mmol) was carefully added to 75 mL of concentrated sulfuric acid at 0–5°C (ice-bath) with stirring to form a solution. Potassium nitrate (10.1 g, 100 mmol) was gradually added to the solution during a period of 20 min while the internal temperature was maintained below 5°C. The reaction mixture was further stirred at 0–5°C for 1 h and at room temperature for 15 min, then poured onto 300 g of crushed ice. The resulting acidic solution was extracted with methylene chloride. The methylene chloride extracts were combined, dried, filtered and concentrated to give 8 g (88%) of product as a yellow solid. It was used directly for the next step in the reaction without further purification. A small analytical sample was purified by silica gel chromatography: mp 135–137°C; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 1 H, 3-H, $J = 2$ Hz), 10.70 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_5H_2F_3N_3O_2$: C, 31.10; H, 1.04; N, 21.76. Found: C, 31.23; H, 1.23; N, 21.60.

Compounds **18**–**21** were synthesized by methodology similar to that described for compound **17**.

3-Chloro-2,6-difluoro-4-nitraminopyridine (18). Compound **18** was isolated as a light yellow solid (10.7 g, 76.4%): mp 100–102°C; ^{1}H NMR ($CDCl_3$) δ 7.62 (d, 1 H, 5-H, $J = 2$ Hz), 10.48 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_5H_2ClF_2N_3O_2$: C, 28.66; H, 0.96; N, 20.05. Found: C, 29.02; H, 1.25; N, 20.40.

2,6-Difluoro-4-nitraminopyridine (19). Compound **19** was isolated as an off-white solid (4.2 g, 76%): mp 140°C (dec.); ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 2 H, 3- and 5-H), 7.62 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_5H_3F_2N_3O_2$: C, 34.30; H, 1.73; N, 24.00. Found: C, 34.42; H, 1.85; N, 24.05.

2-Chloro-5-fluoro-4-nitraminopyridine (20). Compound **20** was isolated as a light yellow solid (2.0 g, 83%): mp 160°C (dec.); ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H, 3-H), 8.32 (d, 1H, 6-H, $J = 2$ Hz), 12.70 (br s, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_5H_3ClFN_3O_2$: C, 37.17; H, 3.12; N, 26.01. Found: C, 37.36; H, 3.16; N, 25.75.

2,5-Dichloro-4-nitraminopyridine (21). Compound **21** was isolated as a light yellow solid (1.2 g, 65%): mp 154°C (dec.) ^{1}H NMR (DMSO-d_6) δ 6.90 (br s, 1H, NH, D_2O exchangeable), 7.85 (s, 1H, 3-H), 8.45 (s, 1H, 6-H). Anal. Calcd. for $C_5H_3Cl_2N_3O_2$: C, 28.87; H, 1.45; N, 20.20. Found: C, 28.55; H, 1.26; N, 20.45.

4-Amino-3-nitro-2,5,6-trifluoropyridine (22). 4-Nitramino-2,3,6-trifluoropyridine (**17**, 9.3 g, 48 mmol) was carefully added to 70 mL of concentrated sulfuric acid. The mixture was stirred at room temperature overnight (18 h), then poured onto 170 g of crushed ice with stirring. The resulting acidic solution was mixed with 100 mL of methylene chloride and neutralized by dropwise addition of 28% ammonium hydroxide with stirring while the internal temperature was maintained below 5°C in a salted ice bath. The organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic extracts were dried, filtered, evaporated in vacuo to dryness and purified by silica gel column chromatography (CH_2Cl_2/hexane, 1:1, v/v) to give 3.7 g (40%) of off-white crystals: mp 99–100°C; ^1H NMR ($CDCl_3$) δ 6.80 (br s, 2H, 4-NH_2, D_2O exchangeable). Anal. Calcd. for $C_5H_2F_3N_3O_2$: C, 31.10; H, 1.04; N, 21.76. Found: C, 31.01; H, 1.34; N, 21.43.

Compounds **23**–**26** were synthesized by a procedure similar to that described for compound **22**.

4-Amino-3-chloro-2,6-difluoro-5-nitropyridine (23). Compound **23** was isolated as an off-white solid (4.1 g, 82%): mp 84–85°C; ^1H NMR ($CDCl_3$) δ 6.20 (br s, 2H, 4-NH_2, D_2O exchangeable). Anal. Calcd. for $C_5H_2ClF_2N_3O_2$: C, 28.66; H, 0.96; N, 20.05. Found: C, 28.99; H, 0.78; N, 19.66.

4-Amino-2,6-difluoro-5-nitropyridine (24). Compound **24** was isolated as an off-white solid (1.7 g, 89%): mp 149–150°C (lit.20 147°C); ^1H NMR (DMSO-d_6) δ 6.40 (s, 1 H, 5-H), 8.20 (br s, 2H, 4-NH_2, D_2O exchangeable).

4-Amino-2-chloro-5-fluoro-3-nitropyridine (25). Compound **25** was isolated as an off-white solid (1.7 g, 90%): mp 154–155°C; ^1H NMR ($CDCl_3$) δ 6.70 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.00 (d, 1 H, 6-H, $J = 2$ Hz). Anal. Calcd. for $C_5H_3ClFN_3O_2$: C, 31.35; H, 1.58; N, 21.94. Found: C, 31.55; H, 1.60; N, 21.77.

4-Amino-2,5-dichloro-3-nitropyridine (26). Compound **26** was isolated as an off-white solid (1.8 g, 97%): mp 168–170°C; ^1H NMR (DMSO-d_6) δ 7.45 (br s, 2H, 4-NH_2, D_2O exchangeable), 8.20 (s, 1 H, 6-H). Anal. Calcd. for $C_5H_3Cl_2N_3O_2$: C, 28.87; H, 1.45; N, 20.20. Found: C, 28.60; H, 1.31; N, 20.02.

3,4-Diamino-2,5,6-trifluoropyridine (27). A mixture of 4-amino-3-nitro-2,5,6-trifluoropyridine (22, 1.08 g, 5.6 mmol) and 1.5 g of Raney nickel in 50 mL of anhydrous ethyl alcohol was hydrogenated at 36 psi in a Parr hydrogenation apparatus for 2 h. The catalyst was removed by filtration and washed carefully with ethyl alcohol. The filtrate and washings were combined and evaporated in vacuo to give 0.9 g (98%) of product as an off-white solid. A small analytical sample was purified by silica gel chromatography (CH_2Cl_2/EtOH, 20:1, v/v, R_f 0.48) to give white crystals: mp 116–117°C; ^1H NMR (DMSO-d_6) δ 3.35 (br s, 2 H, NH_2, D_2O exchangeable), 5.10 (br s, 2 H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_5H_4F_3N_3$: C, 36.82; H, 2.47; N, 25.76. Found: C, 37.20; H, 2.59; N, 25.40.

Compounds **28**–**31** were synthesized by methodology similar to that described for compound **27**.

5-Chloro-3,4-diamino-2,6-difluoropyridine (28). Compound **28** was isolated as a white solid (2.9 g, 92%): mp 178–179°C; ^{1}H NMR (DMSO-d_6) δ 3.00 (br s, 2 H, NH_2, D_2O exchangeable), 4.80 (br s, 2 H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_5H_4Cl\ F_2N_3$: C, 3.44; H, 2.24; N, 23.40. Found: C, 33.80; H, 2.45; N, 23.03.

3,4-Diamino-2,6-difluoropyridine (29). Compound **29** was isolated as a white solid (3.3 g, 92%): mp 135–136°C (lit.17 mp 132°C); ^{1}H NMR (DMSO-d_6) δ 4.23 (br s, 2 H, NH_2, D_2O exchangeable), 6.05 (s, 1 H, 5-H), 6.20 (br s, 2 H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_5H_5F_2N_3$: C, 41.38; H, 3.47; N, 28.96. Found: C, 41.10; H, 3.68; N, 28.64.

2-Chloro-3,4-diamino-5-fluoropyridine (30). Compound **30** was isolated as an off-white solid (1.4 g, 94%): mp 178–179°C; ^{1}H NMR (DMSO-d_6) δ 4.95 (br s, 2 H, NH_2, D_2O exchangeable), 5.80 (br s, 2 H, NH_2, D_2O exchangeable), 7.42 (d, 1 H, 6-H, $J = 2$ Hz). Anal. Calcd. for $C_5H_5ClFN_3$: C, 37.17; H, 3.12; N, 26.01. Found: C, 37.36; H, 3.16; N, 25.75.

3,4-Diamino-2,5-dichloropyridine (31). Compound **31** was isolated as a white solid (1.9 g, 94%): mp 197–199°C; ^{1}H NMR (DMSO-d_6) δ 5.05 (br s, 2 H, NH_2, D_2O exchangeable), 5.95 (br s, 2 H, NH_2, D_2O exchangeable), 7.45 (s, 1 H, 6-H). Anal. Calcd. for $C_5H_5Cl_2N_3$: C, 33.73; H, 2.83; N, 23.60. Found: C, 33.60; H, 3.11; N, 23.22.

4,6,7-Trifluoroimidazo[4,5-c]pyridine (32) and 1-[(1-acetyloxy-1-ethoxy) methyl]-4,6,7-trifluoroimidazo[4,5-c]pyridine (32a). A mixture of 3,4-diamino-2,5,6-trifluoropyridine (**27**, 0.9 g, 5.5 mmol) and 9 mL of diethoxymethyl acetate was heated at 100°C for 1 h with exclusion of moisture. The reaction mixture was then evaporated to dryness in vacuo and the residue was purified on a silica gel column, eluted with CH_2Cl_2/EtOAc, first (10:1, v/v), then (1:1, v/v) to give compounds **32** (0.45 g, 47%) and 32a (0.45 g, 28%).

Compound **32** was isolated as white crystals: TLC, R_f 0.35 (CH_2Cl_2/EtOH, 20:1, v/v); mp 182–184°C; ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 1 H, 2-H), 10.60 (br s, 1 H, NH, D_2O exchangeable). Anal. Calcd. for $C_6H_2F_3N_3$: C, 41.90; H, 1.16; N, 24.27. Found: C, 42.00; H, 1.42; N, 23.87.

Compound **32a** was isolated as a syrup: TLC, R_f 0.77 (CH_2Cl_2/EtOAc, 10:1, v/v); ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3 H, CH_3), 2.25 (s, 3 H, acetyl), 4.20 (m, 2 H, CH_2), 7.62 (s, 1 H, CH), 8.45 (d, 1 H, 2-H); MS, m/e 290 ($M^+ + 1$). Compound **32a** in methylene chloride (30 mL) was treated with trimethylsilyl trifluoromethanesulfonate (1 mL). The mixture was stirred at room temperature overnight, then neutralized with 10% sodium bicarbonate solution and co-evaporated with 5 g of silica gel. The residue was purified by silica gel column chromatography to give 0.25 g of 32. The total yield of 32 was 0.7 g (74%).

Compounds **33–36** were synthesized by methodology similar to that described for compound **32**.

7-Chloro-4,6-difluoroimidazo[4,5-c]pyridine (33). Compound **33** was isolated as off-white crystals (2.07; g, 74%): TLC, R_f 0.45 (CH_2Cl_2/EtOH, 20:1, v/v); mp 225–227°C; ^1H NMR (DMSO-d_6) δ 8.50 (s, 1 H, 2-H), 10.45 (br s, 1 H, NH, D_2O exchangeable). Anal. Calcd. for $C_6H_2ClF_2N_3$: C, 38.02; H, 1.06; N, 22.17. Found: C, 38.33; H, 1.08; N, 21.84.

1-[(1-Acetyloxy-1-ethoxy)methyl]-7-chloro-4,6-difluoroimidazo[4,5-c]pyridine (33a). Compound **33a** was isolated as a syrup: TLC, R_f 0.77 (CH_2Cl_2/EtOAc, 10:1, v/v); ^1H NMR ($CDCl_3$) δ 1.40 (t, 3 H, CH_3), 2.23 (s, 3 H, acetyl), 4.18 (m, 2 H, CH_2), 7.58 (s, 1 H, CH), 8.42 (d, 1 H, 2-H); MS, m/e 307 ($M^+ + 1$).

4,6-Difluoroimidazo[4,5-c]pyridine (34). Compound **34** was isolated as a white solid (0.96 g, 90%): TLC, R_f 0.35 (CH_2Cl_2/EtOH, 20:1, v/v); mp 170–171°C (lit.20 169°C); ^1H NMR (DMSO-d_6) δ 7.15 (t, 1 H, 2-H, $J = 1.5$ Hz), 8.40 (s, 1 H, 7-H), 12.60 (br s, 1 H, NH, D_2O exchangeable).

1-[(1-Acetyloxy-1-ethoxy)methyl]-4,6-difluoroimidazo[4,5-c]pyridine (34a). Compound **34a** was isolated as a syrup: TLC, R_f 0.84 (CH_2Cl_2/EtOH, 20:1, v/v); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, CH_3), 2.20 (s, 3 H, acetyl), 3.90 (q, 2 H, CH_2), 7.05 (d, 1 H, 7 H, $J = 2$ Hz), 7.32 (s, 1 H, CH), 8.21 (d, 1 H, 2-H); MS, m/e 272 ($M^+ +1$).

4-Chloro-7-fluoroimidazo[4,5-c]pyridine (35). Compound **35** was isolated as white crystals (1.11 g, 80%): TLC, R_f 0.19 (CH_2Cl_2/EtOAc, 1:1, v/v); mp 232–234°C; 1H NMR (DMSO-d_6) δ 8.12 (d, 1 H, 6-H, $J = 2$ Hz), 8.56 (s, 1 H, 2-H), 13.80 (br s, 1 H, NH, D_2O exchangeable). Anal. Calcd. for $C_6H_3ClFN_3$: C, 37.17; H, 3.12; N, 26.01. Found: C, 37.36; H, 3.16; N, 25.75.

1-[(1-Acetyloxy-1-ethoxy)methyl]-4-chloro-7-fluoroimidazo[4,5-c]pyridine (35a). Compound **35a** was isolated as a syrup: TLC, R_f 0.29 (CH_2Cl_2/EtOAc, 10:1, v/v); ^1H NMR ($CDCl_3$) δ 1.37 (t, 3 H, CH_3), 2.20 (s, 3 H, acetyl), 3.95 (q, 2 H, CH_2), 7.57 (s, 1 H, CH), 8.15 (d, 1 H, 6-H, $J = 2$ Hz), 8.35 (s, 1 H, 2-H); MS, m/e 289 ($M^+ +1$).

4,7-Dichloroimidazo[4,5-c]pyridine (36). Compound **36** was isolated as a white solid (1.52 g, 80%): TLC, R_f 0.09 (CH_2Cl_2/EtOAc, 5:1, v/v); mp 270–272°C; ^1H NMR (DMSO-d_6) δ 8.25 (s, 1 H, 6-H), 8.60 (s, 1 H, 7-H), 13.60 (br s, 1 H, NH, D_2O exchangeable). Anal. Calcd. for $C_6H_3Cl_2N_3$: C, 38.33; H, 1.61; N, 22.35. Found: C, 38.52; H, 1.90; N, 22.17.

1-[(1-Acetyloxy-1-ethoxy)methyl]-4,7-dichloroimidazo[4,5-c]pyridine (36a). Compound **36a** was isolated as a syrup: TLC, R_f 0.58 (CH_2Cl_2/EtOAc, 5:1, v/v); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H, CH_3), 2.15 (s, 3 H, acetyl), 4.10 (m, 2 H, CH_2), 7.95 (s, 1 H, CH), 8.25 (s, 1 H, 2-H), 8.44 (s, 1 H, 6-H); MS, m/e 304 (M^++1).

4,6-Difluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (37). A suspension of 4,6-difluoroimidazo[4,5-c]pyridine (**34**, 0.34 g, 2.2 mmol) in hexamethyldisilazane (10 mL) and ammonium sulfate (a catalytic amount) was refluxed for 2 h under anhydrous conditions. The resulting clear solution was cooled and concentrated in vacuo to yield the silylated base as a white solid, which was dissolved in 12 mL of dichloroethane. 1-*O*-Acetyl-2,3,5-*O*-benzoyl-D-ribofuranose (1.2 g, 2.4 mmol) was added to the solution, followed by 1 mL of TMSOTf and the reaction mixture was stirred at room temperature under nitrogen overnight. The reaction mixture was quenched by addition of a saturated sodium bicarbonate solution (10 mL) and further stirred for 10 min at room temperature. The organic layer was separated and the aqueous layer was extracted with methylene chloride (30 mL × 2). The combined organic layers were washed with a saturated sodium bicarbonate solution, then water and dried (anhydrous $MgSO_4$). After filtration, the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 30:1, v/v) to yield **37** (1.0 g, 77%) as a foam: ^1H NMR ($CDCl_3$) δ 4.62–4.82 (m, 3 H, 4′- and 5′-H), 5.85–5.92 (m, 2 H, 2′- and 3′-H), 6.20 (d, 1 H, 1′-H, $J = 5$ Hz), 7.05 (d, 1 H, 7-H, $J = 1.5$ Hz), 7.20–7.90 (m, 15 H, ArH), 8.15 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{23}F_2N_3O_7$: C, 64.10; H, 3.87; N, 7.01. Found: C, 64.28; H, 4.06; N, 6.93.

4-Amino-6-fluoro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (38). A suspension of 4,6-difluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (**37**, 0.6 g, 1 mmol) in 50 mL of saturated ethanolic ammonia solution was stirred in a pressure bottle at room temperature for 4 days. The cooled reaction mixture was evaporated to dryness and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 10:1, v/v) to give 0.2 g (70%) of product as a white solid: mp 171–172°C; UV (MeOH) λ_{max} 274 nm (ε 15,026), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 276 nm (ε 11,863), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 14,027), λ_{min} 232 nm; ^1H NMR (DMSO-d_6) δ 3.63 (m, 2 H, 5′-H), 3.94 (m, 1 H, 4′-H), 4.10 (m, 1 H, 3′-H), 4.28 (m, 1 H, 2′-H), 5.12 [t, 1 H, 5′-OH, D_2O exchangeable), 5.20 (d, 1 H, OH, D_2O exchangeable), 5.45 (d, 1 H, OH, D_2O exchangeable), 5.71 (d, 1 H, 1′-H, $J = 6.0$ Hz), 6.55 (d, 1 H, 7-H, $J = 1.5$ Hz), 6.55 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.25 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; N, 19.70. Found: C, 46.12; H, 4.44; N, 19.39.

6-Fluoro-4-methylamino-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine-(39). A mixture of 4,6-difluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo-[4,5-c]pyridine (**37**, 0.3 g, 0.5 mmol) and 10 mL of 40% methylamine was stirred at room temperature until TLC showed the reaction to be complete (~ 3 days). The reaction mixture was evaporated to dryness and purified by silica gel column chromatography (CH_2Cl_2/EtOH, 10:1, v/v) to give 0.12 g (77%) of product as a white solid: mp 175–177°C; UV (MeOH) λ_{max} 280 nm (ε 19,306), λ_{min} 238 nm; UV (0.01 N HCl) λ_{max} 282 nm (ε 15,835), λ_{min} 242 nm; UV (0.01 N NaOH) λ_{max} 280 nm (ε 18,221), λ_{min} 238 nm; ^1H NMR (DMSO-d_6) δ 2.88 (d, 3 H, CH_3, $J = 4.5$), 3.62 (m, 2 H, 5′-H), 3.75 (m, 1 H, 4′-H), 4.07 (m, 1 H, 3′-H), 4.26 (m, 1 H, 2′-H), 5.15 [t, 1 H, 5′-OH, D_2O exchangeable), 5.20 (d, 1 H, OH, D_2O exchangeable), 5.44 (d, 1 H, OH, D_2O exchangeable), 5.71 (d, 1 H, 1′-H, $J = 6.3$ Hz), 6.55 (d, 1 H, 7-H, $J = 1.5$ Hz), 6.53 (br s, 1 H, 4-$NHCH_3$, D_2O exchangeable), 8.25 (s, 1 H, 2-H). Anal. Calcd. for $C_{12}H_{15}FN_4O_4$: C, 48.32; H, 5.07; N, 18.78. Found: C, 47.94; H, 5.01; N, 18.39.

4-Amino-6-fluoro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)imidazo[4,5-c]pyridine (41) and 4-amino-6-fluoro-1-(2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl)imidazo[4,5-c]pyridine (42). A mixture of 4,6-difluoroimidazo[4,5-c]pyridine (**34**, 0.5 g, 3.2 mmol) and ammonium sulfate (a catalytic amount) in hexamethyldisilazane (15 mL) was refluxed for 2 h. The resulting clear solution was cooled and concentrated *in vacuo* under anhydrous conditions to dryness. The residue was dissolved in 15 mL of dichloroethane, followed by addition of 1-*O*-(4-nitrobenzoyl)-2,3,5-tri-*O*-benzyl-D-arabinofuranose (2 g, 3.6 mmol) and TMSOTf (1 mL) and the reaction mixture was refluxed with stirring under nitrogen for 2 h. The reaction mixture was cooled and stirred with saturated sodium bicarbonate solution (15 mL) for 10 min at room temperature. The organic layer was separated and the aqueous layer was extracted with methylene chloride (30 mL × 2). The combined organic layer was washed with saturated sodium bicarbonate solution, then water and dried (anhydrous $MgSO_4$). After filtration, the filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 20:1, v/v) to yield **40** (1.2 g, 67%) as a syrup. NMR showed it to be a mixture of α- and β-anomers. Compound **40** (1.1 g, 2.0 mmol) was dissolved in 60 mL of ethanol, saturated with anhydrous ammonia and heated in a stainless steel bomb at 100–105°C overnight. The reaction mixture was cooled, evaporated to dryness and separated by silica gel column chromatography (CH_2Cl_2/EtOH, 20:1, v/v) to yield **41** (0.30 g, 27%), **42** (0.34 g, 31%) and a mixture of **41** and **42** (0.17 g, 15%).

Compound **41** was isolated as a white foam: TLC, R_f 0.63 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR ($CDCl_3$) δ 3.70 (m, 2 H, 5′-H), 4.10 (m, 1 H, 4′-H), 4.25 (m, 2 H, 2′- and 3′-H), 4.65 (s, 6 H, $ArCH_2$), 5.75 (br s, 2 H, NH_2, D_2O exchangeable), 5.96 (d, 1 H, 1′-H, $J = 5$ Hz), 6.14 (s, 1 H, 7-H), 6.80–7.40 (m, 15 H, ArH), 8.01 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{31}FN_4O_4$: C, 69.28; H, 5.63; N, 10.10. Found: C, 69.10; H, 5.40; N, 9.96.

Compound **42** was isolated as a white foam: TLC, R_f 0.53 (CH_2Cl_2/EtOH, 20:1, v/v); ^{1}H NMR ($CDCl_3$) δ 3.58 (m, 2 H, 5′-H), 4.25 (m, 1 H, 4′-H), 4.30 (m, 2 H, 2′- and 3′-H), 4.50 (s, 6 H, $ArCH_2$), 5.60 (br s, 2 H, NH_2, D_2O exchangeable), 5.85 (d, 1 H, 1′-H, $J = 5.2$ Hz), 6.20 (s, 1 H, 7-H), 7.00–7.40 (m, 15 H, ArH), 7.84 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{31}FN_4O_4 \cdot 0.05EtOH$: C, 69.01; H, 5.67; N, 10.06. Found: C, 68.87; H, 5.30; N, 9.98.

4-Amino-6-fluoro-1-β-D-arabinofuranosylimidazo[4,5-c]pyridine (43). A mixture of 4-amino-6-fluoro-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl) imidazo[4,5-c]pyridine (**41**, 0.15 g, 0.27 mmol), palladium (II) oxide hydrate (0.25 g), cyclohexene (20 mL) and ethanol (20 mL) was refluxed overnight. The reaction mixture was cooled, filtered and washed with ethanol. The combined filtrate and washings were evaporated in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 6:1, v/v) to give 45 mg (58%) of product as white crystals: mp 215°C (dec.); UV (MeOH) λ_{max} 274 nm (ε 14,127), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 275 nm (ε 9,701), λ_{min} 235 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 12,595), λ_{min} 234 nm; ^{1}H NMR (DMSO-d_6) δ 3.65 (m, 2 H, 5′-H), 3.73 (m, 1 H, 4′-H), 4.06 (m, 1 H, 3′-H), 4.15 (m, 1 H, 2′-H), 5.08 [t, 1 H, 5′-OH, D_2O exchangeable), 5.05 (d, 1 H, OH, D_2O exchangeable), 5.50 (d, 1 H, OH, D_2O exchangeable), 6.08 (d, 1 H, 1′-H, $J = 5.1$ Hz), 6.42 (d, 1 H, 7-H, $J = 1.2$ Hz), 6.59 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.17 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; N, 19.70. Found: C, 46.70; H, 5.00; N, 19.35.

4-Amino-6-fluoro-1-α-D-arabinofuranosylimidazo[4,5-c]pyridine (44). This compound was synthesized by a procedure similar to that described for compound **43**. Compound **44** was isolated as white crystals (60 mg, 65%): mp 198°C (dec.); UV (MeOH) λ_{max} 272 nm (ε 12,344), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 274 nm (ε 10,232), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 11,532), λ_{min} 234 nm; ^{1}H NMR (DMSO-d_6) δ 3.52 (m, 2 H, 5′-H), 4.02 (m, 1 H, 4′-H), 4.08 (m, 1 H, 3′-H), 4.33 (m, 1 H, 2′-H), 4.90 (t, 1 H, 5′-OH, D_2O exchangeable), 5.50 (d, 1 H, OH, D_2O exchangeable), 5.72 (d, 1 H, 1′-H, $J = 5.4$ Hz), 5.84 (d, 1 H, OH, D_2O exchangeable), 6.41 (d, 1 H, 7-H, $J = 1.5$ Hz), 6.69 (br s, 2 H, 4-NH_2, D_2O exchangeable), 8.20 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; N, 19.71. Found: C, 46.68; H, 4.87; N, 19.43.

Compounds **45** and **46** were synthesized by methodology similar to that described for compound **37**.

4-Chloro-7-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (45). Compound **45** was isolated as a white foam (0.77 g, 61%): ^{1}H NMR ($CDCl_3$) δ 4.82 (m, 2 H, 5′-H), 4.92 (m, 1 H, 4′-H), 5.94 (m, 2 H, 2′- and 3′-H), 6.58 (d, 1 H, 1′-H, $J = 5$ Hz), 7.30–8.10 (m, 15 H, ArH), 8.13 (d, 1 H, 7-H, $J = 1.5$ Hz), 8.27 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{23}ClFN_3O_7$: C, 62.39; H, 3.76; N, 6.82. Found: C, 62.12; H, 4.02; N, 6.63.

4,7-Dichloro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (46). Compound **46** was isolated as a foam (2.4 g, 47%): ^{1}H NMR ($CDCl_3$) δ 4.75 (m, 2 H, 5′-H), 4.80 (m, 1 H, 4′-H), 5.95 (m, 1 H, 3′-H), 6.00 (m, 1 H, 2′-H), 7.15 (d, 1 H, 1′-H, $J = 6$ Hz), 7.25–8.00 (m, 15 H, ArH), 8.15 (s, 1 H, 6-H), 8.40 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{23}Cl_2N_3O_7$: C, 60.87; H, 3.67; N, 6.66. Found: C, 61.10; H, 3.84; N, 6.30.

4-Chloro-7-fluoro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (47). To a suspension of 4-chloro-7-fluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-imidazo[4,5-c]pyridine (**45**, 0.73 g, 1.2 mmol) in dry methanol (50 mL) was added sodium methoxide until pH 10 was reached. The reaction mixture was refluxed for 30 min, cooled, neutralized with glacial acetic acid, and evaporated to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 10:1, v/v) to give 0.29 g (78%) as a white solid: mp 187–189°C; ^{1}H NMR (DMSO-d_6) δ 3.58 (m, 1 H, 5′-H_A), 3.70 (m, 1 H, 5′-H_B), 3.99 (m, 1 H, 4′-H), 4.13 (m, 1 H, 3′-H), 4.36 (m, 1 H, 2′-H), 5.16 (t, 1 H, 5′-OH, D_2O exchangeable), 5.28 (d, 1 H, OH, D_2O exchangeable), 5.63 (d, 1 H, OH, D_2O exchangeable), 6.03 (d, 1 H, 1′-H, $J = 5.1$ Hz), 8.27 (d, 1 H, 6-H, $J = 2.1$ Hz), 8.88 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{11}ClFN_3O_4$: C, 43.50; H, 3.65; N, 13.84. Found: C, 43.43; H, 3.26; N, 13.81.

4,7-Dichloro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (48). Compound **48** was synthesized by a procedure similar to that described for compound **47** and was isolated as white crystals (0.2 g, 56%): mp 172–174°C; ^{1}H NMR (DMSO-d_6) δ 3.53 (m, 1 H, 5′-H_A), 3.65 (m, 1 H, 5′-H_B), 4.15 (m, 1 H, 4′-H), 4.28 (m, 1 H, 3′-H), 4.45 (m, 1 H, 2′-H), 4.94 (t, 1 H, 5′-OH, D_2O exchangeable), 5.27 (d, 1 H, OH, D_2O exchangeable), 5.43 (d, 1 H, OH, D_2O exchangeable), 6.79 (d, 1 H, 1′-H, $J = 5.1$ Hz), 8.27 (s, 1 H, 6-H), 8.72 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O_4$: C, 41.27; H, 3.46; N, 13.13. Found: C, 41.00; H, 3.57; N, 12.91.

4-Amino-7-fluoro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (51). A suspension of 4-chloro-7-fluoro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (**47**, 0.51 g, 1.7 mmol) in 30 mL of anhydrous hydrazine was refluxed for

1 h. The reaction mixture was evaporated *in vacuo* to dryness and the residue was co-evaporated with ethanol (30 mL) and deoxygenated water twice (2 × 30 mL). The residue was dissolved in 40 mL of deoxygenated water containing 3.0 g (wet weight) of Raney Nickel and was refluxed with stirring under hydrogen (1 atm) for 8 h. The reaction mixture was filtered through Celite while hot, and the catalyst was washed with hot deoxygenated water. The combined filtrate and washings were evaporated *in vacuo* to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 6:1, v/v) to give 0.26 g (54%) of product as a white solid: mp 160–161°C; UV (MeOH) λ_{max} 270 nm (ε 7,145), λ_{min} 238 nm; UV (0.01 N HCl) λ_{max} 268 nm (ε 8,077), λ_{min} 238 nm; UV (0.01 N NaOH) λ_{max} 268 nm (ε 7,445), λ_{min} 238 nm; ^{1}H NMR (DMSO-d_6) δ 3.58 (m, 1 H, 5′-H$_A$), 3.62 (m, 1 H, 5′-H$_B$), 3.94 (m, 1 H, 4′-H), 4.10 (m, 1 H, 3′-H), 4.35 (m, 1 H, 2′-H), 5.07 (t, 1 H, 5′-OH, D_2O exchangeable), 5.24 (d, 1 H, OH, D_2O exchangeable), 5.54 (d, 1 H, OH, D_2O exchangeable), 5.91 (d, 1 H, 1′-H, $J = 5.1$ Hz), 6.22 (br s, 2 H, NH_2, D_2O exchangeable), 7.67 (d, 1 H, 6-H, $J = 2.1$ Hz), 8.48 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{13}FN_4O_4$: C, 46.48; H, 4.61; N, 19.71. Found: C, 46.52; H, 4.50; N, 19.50.

4-Amino-7-chloro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (52). Compound **52** was synthesized by a procedure similar to that described for compound **51** and was isolated as a white solid (0.14 g, 49%): mp 169°C (dec); UV (MeOH) λ_{max} 271 nm (ε 7,010), λ_{min} 237 nm; UV (0.01 N HCl) λ_{max} 269 nm (ε 7,900), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 269 nm (ε 7,400), λ_{min} 236 nm; ^{1}H NMR (DMSO-d_6) δ 3.45 (m, 1 H, 5′-H$_A$), 3.56 (m, 1 H, 5′-H$_B$), 4.12 (m, 1 H, 4′-H), 4.20 (m, 1 H, 3′-H), 4.34 (m, 1 H, 2′-H), 4.92 (t, 1 H, 5′-OH, D_2O exchangeable), 5.27 (d, 1 H, OH, D_2O exchangeable), 5.61 (d, 1 H, OH, D_2O exchangeable), 6.08 (br s, 2 H, NH_2, D_2O exchangeable), 6.41 (d, 1 H, 1′-H, $J = 4.5$ Hz), 7.72 (s, 1 H, 6-H), 8.41 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{13}ClN_4O_4$: C, 43.93; H, 4.36; N, 18.63. Found: C, 43.70; H, 4.32; N, 18.51.

Compounds **53**–**56** were synthesized by methodology similar to that described for compound **37**.

4,6,7-Trifluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (53). Compound **53** was isolated as a foam (0.76 g, 36%): TLC, R$_f$ 0.47 (CH_2Cl_2/EtOAc, 30:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.80–4.90 (m, 3 H, 4′- and 5′-H), 5.94 (m, 2 H, 2′- and 3′-H), 6.55 (d, 1 H, 1′-H, $J = 5.2$ Hz), 7.30–8.05 (m, 15 H, ArH), 8.25 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{22}F_3N_3O_7$: C, 62.24; H, 3.59; N, 6.80. Found: C, 62.25; H, 3.49; N, 6.51.

4,6,7-Trifluoro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (54). Compound **54** was isolated as a foam (0.53 g, 25%): TLC, R$_f$ 0.55 (CH_2Cl_2/EtOAc, 30:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.80–4.92 (m, 3

H, 4′- and 5′-H), 5.95 (m, 2 H, 2′- and 3′-H), 6.53 (d, 1 H, 1′-H, $J = 5.5$ Hz), 7.30–8.20 (m, 15 H, ArH), 8.43 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{22}F_3N_3O_7$: C, 62.24; H, 3.59; N, 6.80. Found: C, 62.06; H, 3.31; N, 6.69.

7-Chloro-4,6-difluoro-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (55). Compound **55** was isolated as a foam (0.57 g, 34%): TLC, R_f 0.38 (CH_2Cl_2/EtOAc, 30:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.78–4.90 (m, 3 H, 4′- and 5′-H), 5.97 (m, 2 H, 2′- and 3′-H), 6.50 (d, 1 H, 1′-H, $J = 5.1$ Hz), 7.30–8.12 (m, 15 H, ArH), 8.35 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{22}ClF_2N_3O_7$: C, 60.62; H, 3.50; N, 6.63. Found: C, 60.46; H, 3.40; N, 6.49.

7-Chloro-4,6-difluoro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (56). Compound **56** was isolated as a foam (0.50 g, 26%): TLC, R_f 0.47 (CH_2Cl_2/EtOAc, 30:1, v/v); ^{1}H NMR ($CDCl_3$) δ 4.77–4.85 (m, 3 H, 4′- and 5′-H), 5.92 (m, 2 H, 2′- and 3′-H), 6.50 (d, 1 H, 1′-H, $J = 5.2$ Hz), 7.25–8.15 (m, 15 H, ArH), 8.40 (s, 1 H, 2-H). Anal. Calcd. for $C_{32}H_{22}ClF_2N_3O_7$: C, 60.62; H, 3.50; N, 6.63. Found: C, 60.87; H, 3.39; N, 6.52.

Compounds **57**–**60** were synthesized by methodology similar to that described for compound **38**.

4-Amino-6,7-difluoro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (57). Compound **57** was isolated as a white solid (0.17 g, 77%): mp 163–165°C; UV (MeOH) λ_{max} 274 nm (ε 13,510), λ_{min} 232 nm; UV (0.01 N HCl) λ_{max} 274 nm (ε 12,256), λ_{min} 232 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 11,421), λ_{min} 232 nm; ^{1}H NMR (DMSO-d_6) δ 3.65 (m, 1 H, 5′-H_A), 3.67 (m, 1 H, 5′-H_B), 3.93 (m, 1 H, 4′-H), 4.02 (m, 1 H, 3′-H), 4.32 (m, 1 H, 2′-H), 5.07 (t, 1 H, 5′-OH, D_2O exchangeable), 5.22 (d, 1 H, OH, D_2O exchangeable), 5.54 (d, 1 H, OH, D_2O exchangeable), 5.87 (d, 1 H, 1′-H, $J = 5.6$ Hz), 6.65 (br s, 2 H, NH_2, D_2O exchangeable), 8.43 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{12}F_2N_4O_4$: C, 43.71; H, 4.00; N, 18.54. Found: C, 43.92; H, 3.91; N, 18.59.

4-Amino-6,7-difluoro-3-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (58). Compound **58** was isolated as a white solid (0.14 g, 88%): mp 155–157°C; UV (MeOH) λ_{max} 292 nm (ε 5,742), λ_{min} 264 nm; UV (0.01 N HCl) λ_{max} 292 nm (ε 6,045), λ_{min} 262 nm; UV (0.01 N NaOH) λ_{max} 292 nm (ε 5,440), λ_{min} 262 nm; ^{1}H NMR (DMSO-d_6) δ 3.65 (m, 1 H, 5′-H_A), 3.68 (m, 1 H, 5′-H_B), 4.01 (m, 1 H, 4′-H), 4.11 (m, 1 H, 3′-H), 4.22 (m, 1 H, 2′-H), 5.13 (t, 1 H, 5′-OH, D_2O exchangeable), 5.20 (d, 1 H, OH, D_2O exchangeable), 5.30 (d, 1 H, OH, D_2O exchangeable), 5.90 (d, 1 H, 1′-H, $J = 6.6$ Hz), 6.34 (br s, 2 H, NH_2, D_2O exchangeable), 8.54 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{12}F_2N_4O_4$: C, 43.71; H, 4.00; N, 18.54. Found: C, 43.90; H, 4.02; N, 18.16.

4-Amino-7-chloro-6-fluoro-1-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (59). Compound **59** was isolated as a white solid (0.10 g, 85%): mp 175–177°C; UV (MeOH) λ_{max} 274 nm (ε 14,503), λ_{min} 234 nm; UV (0.01 N HCl) λ_{max} 274 nm (ε 12,997), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 15,367), λ_{min} 235 nm; ^{1}H NMR (DMSO-d_6) δ 3.52 (m, 1 H, 5′-H$_A$), 3.62 (m, 1 H, 5′-H$_B$), 3.95 (m, 1 H, 4′-H), 4.10 (m, 1 H, 3′-H), 4.37 (m, 1 H, 2′-H), 5.12 (t, 1 H, 5′-OH, D_2O exchangeable), 5.22 (d, 1 H, OH, D_2O exchangeable), 5.58 (d, 1 H, OH, D_2O exchangeable), 6.34 (d, 1 H, 1′-H, $J = 4.5$ Hz), 6.94 (br s, 2 H, NH_2, D_2O exchangeable), 8.51 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{12}ClFN_4O_4$: C, 41.45; H, 3.80; N, 17.58. Found: C, 41.17; H, 4.00; N, 17.35.

4-Amino-7-chloro-6-fluoro-3-(β-D-ribofuranosyl)imidazo[4,5-c]pyridine (60). Compound **60** was isolated as a white solid (0.13 g, 53%): mp 166–168°C; UV (MeOH) λ_{max} 292 nm (ε 8,631), λ_{min} 268 nm; UV (0.01 N HCl) λ_{max} 292 nm (ε 8,465), λ_{min} 266 nm; UV (0.01 N NaOH) λ_{max} 292 nm (ε 7,967), λ_{min} 268 nm; ^{1}H NMR (DMSO-d_6) δ 3.55 (m, 1 H, 5′-H$_A$), 3.65 (m, 1 H, 5′-H$_B$), 3.98 (m, 1 H, 4′-H), 4.11 (m, 1 H, 3′-H), 4.20 (m, 1 H, 2′-H), 5.25 (t, 1 H, 5′-OH, D_2O exchangeable), 5.35 (d, 1 H, OH, D_2O exchangeable), 5.65 (d, 1 H, OH, D_2O exchangeable), 5.87 (d, 1 H, 1′-H, $J = 6.6$ Hz), 6.63 (br s, 2 H, NH_2, D_2O exchangeable), 8.55 (s, 1 H, 2-H). Anal. Calcd. for $C_{11}H_{12}ClFN_4O_4$: C, 41.45; H, 3.80; N, 17.58. Found: C, 41.31; H, 4.10; N, 17.27.

6-Amino-7-chloro-1,5-dihydro-1-β-D-ribofuranosylimidazo[4,5-c]pyridin-4-one (3-chloro-3-deazaguanosine, 61). To a stirred suspension of 3-deazaguanosine[8,24] (0.25 g, 0.9 mmol) in 7 mL of water was added *N*-chlorosuccimide (0.14 g, 1.0 mmol) at 0–5°C in an ice-water bath. The reaction mixture was stirred at 0–5°C for 1 h. The solid was collected, washed with cold water and then cold acetone. Crystallization from water provided 0.12 g (42%) of product: mp 195–196°C (dec.); UV (MeOH) λ_{max} 273 nm (ε 11,000), λ_{min} 238 nm; UV (0.01 N HCl) λ_{max} 285 nm (ε 13,200), λ_{min} 242 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 11,200), λ_{min} 240 nm; ^{1}H NMR (DMSO-d_6) δ 3.52 (m, 2 H, 5′-H), 3.90 (m, 1 H, 4′-H), 4.10 (m, 1 H, 3′-H), 4.25 (m, 1 H, 2′-H), 5.02 (d, 1 H, OH, D_2O exchangeable), 5.10 (t, 1 H, OH, D_2O exchangeable), 5.40 (d, 1 H, OH, D_2O exchangeable), 5.70 (br s, 2 H, NH_2, D_2O exchangeable), 6.25 (d, 1 H, 1′-H, $J = 7.0$ Hz), 8.10 (s, 1 H, 2-H), 10.70 (br s, 1 H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}ClN_4O_5$: C, 41.71; H, 4.14; N, 17.69. Found: C, 41.80; H, 4.00; N, 17.38.

6-Amino-7-bromo-1,5-dihydro-1-β-D-ribofuranosylimidazo[4,5-c]pyridin-4-one (3-bromo-3-deazaguanosine, 62). To a stirred suspension of 3-deazaguanosine[8,24] (0.5 g, 1.8 mmol) in 6 mL of water was added gradually 12 mL of saturated bromine-water at such a rate that the yellow color of the reaction mixture disappeared between each addition (~ 5 min). The reaction mixture was stirred for another 5 min and the solid was collected by filtration, and washed with cold water and cold acetone. The solid was crystallized from water to give 0.45 g (70%) of product: mp 174°C (dec.); UV (MeOH) λ_{max} 274 nm (ε 11,200), λ_{min} 240 nm; UV (0.01 N HCl) λ_{max} 284 nm (ε 13,200), λ_{min} 238 nm; UV (0.01 N NaOH) λ_{max} 274 nm (ε 11,600), λ_{min} 240 nm; ^{1}H NMR (DMSO-d_6) δ 3.50 (m, 2 H, 5′-H), 3.80 (m, 1 H, 4′-H), 4.05 (m, 1 H, 3′-H), 4.28 (m, 1 H, 2′-H), 5.20-5.40 (br s, 2 H, OH, D_2O exchangeable), 5.40 (t, 1 H, OH, D_2O exchangeable), 5.62 (br s, 2 H, NH_2, D_2O exchangeable), 6.38 (d, 1 H, 1′-H, $J = 6.8$ Hz), 8.12 (s, 1 H, 2-H), 10.62 (br s, 1 H, NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{13}BrN_4O_5$: C, 36.58; H, 3.62; N, 15.51. Found: C, 36.41; H, 3.43; N, 15.23.

ACKNOWLEDGMENT

This research was supported in part by Connecticut Innovations, Inc.

REFERENCES

1. May, J.A., Jr.; Townsend, L.B. J. Chem. Soc. Perkin Trans. **1975**, *1*, 125–129.
2. Krenitsky, T.A.; Rideout, J.L.; Chao, E.Y.; Koszalka, G.W.; Gurney, F.; Crouch, R.C.; Cohn, N.K.; Wolberg, G.; Vinegar, R. J. Med. Chem. **1986**, *29*, 138–143.
3. Minakawa, N.; Matsuda, A. Tetrahedron Lett. **1993**, *34*, 661–664.
4. Guranowski, A.; Montgomery, J.A.; Cantoni, G.L.; Chiang, P.K. Biochemistry **1981**, *20*, 110–115.
5. Bodner, A.J.; Cantoni, G.L.; Chiang, P.K. Biochem. Biophys. Res. Commun. **1981**, *98*, 476–481.
6. Flexner, C.W.; Hildreth, J.E.; Kuncl, R.W.; Drachman, D.B. Lancet **1992**, *339*, 438.
7. Bader, J.P.; Brown, N.R.; Chiang, P.K.; Cantoni, G.L. Virology **1978**, *89*, 494–505.
8. Chiang, P.K.; Cantoni, G.L.; Bader, J.P.; Shannon, W.M.; Thomas, H.J.; Montgomery, J.A. Biochem. Biophys. Res. Commun. **1978**, *82*, 417–423.
9. Allen, L.B.; Huffman, J.H.; Cook, P.D.; Meyer, R.B., Jr.; Robins, R.K.; Sidwell, R.W. Antimicrob. Agents Chemother. **1977**, *12*, 114–119.
10. Saunders, P.P.; Chao, L.Y.; Loo, T.L.; Robins, R.K. Biochem. Pharmacol. **1981**, *30*, 2374–2376.
11. Revankar, G.R.; Gupta, P.K.; Adams, A.D.; Dalley, N.K.; McKernan, P.A.; Cook, P.D.; Canonico, P.G.; Robins, R.K. J. Med. Chem. **1984**, *27*, 1389–1396.
12. Carson, D.A.; Wasson, D.B.; Kaye, J.; Ullman, B.; Martin, D.W., Jr.; Robins, R.K.; Montgomery, J.A. Proc. Natl. Acad. Sci. USA **1980**, *77*, 6865–6869.
13. Hutton, J.J.; Von Hoff, D.D.; Kuhn, J.; Phillips, J.; Hersh, M.; Clark, G. Cancer Res. **1984**, *44*, 4183–4186.
14. Secrist, J.A., III; Shortnacy, A.T.; Montgomery, J.A. J. Med. Chem. **1988**, *31*, 405–410.

15. Montgomery, J.A.; Shortnacy-Fowler, A.T.; Clayton, S.D.; Riordan, J.M.; Secrist, J.A., III. J. Med. Chem. **1992**, *35*, 397–401.
16. Chambers, R.D.; Hutchinson, J.; Musgrave, W.K.R. J. Chem. Soc. **1964**, 5634–5640.
17. McNamara, D.J.; Cook, P.D. J. Med. Chem. **1987**, *30*, 340–347.
18. Hand, E.S.; Baker, D.C. Synthesis **1989**, 905–908.
19. Rousseau, R.J.; Robins, R.J. J. Heterocycl. Chem. **1965**, *2*, 196–201.
20. Kroon, C.; van den Brink, A.M.; Vlietstra, E.J.; Salemink, C.A. Rec. Trav. Chim. **1976**, *95*, 127–156.
21. Okabe, M.; Sun, R.C.; Tam, S.Y.K; Todaro, L.J.; Coffen, D.L. J. Org. Chem. **1988**, *53*, 4780–4786.
22. Chu, C.K.; Ullas, G.V.; Jeong, L.S.; Ahn, S.K.; Doboszewski, B.; Lin, Z.X.; Beach, J.W.; Schinazi, R.F. J. Med. Chem. **1990**, *33*, 1553–1561.
23. Tiwari, K.N.; Montgomery, J.A.; Secrist, J.A., III. Nucleosides & Nucleotides **1993**, *12*, 841–846.
24. Secrist, J.A., III; Comber, R.N.; Gray, R. J.; Gilroy, R.B.; Montgomery, J.A. J. Med. Chem. **1993**, *36*, 2102–2106.
25. Montgomery, J.A.; Shortnacy, A.T.; Clayton, S.D. J. Heterocycl. Chem. **1977**, *14*, 195–197.
26. Poonian, M.S.; McComas, W.W. J. Med. Chem. **1979**, *22*, 958–962.
27. Cook, P.D.; Rousseau, R.J.; Mian, A.M.; Dea, P.; Meyer, R.B., Jr.; Robins, R.K. J. Amer. Chem. Soc. **1976**, *98*, 1492–1498.
28. Lin, T.S.; Luo, M.Z.; Liu, M.C.; Pai, S.B.; Dutschman, G.E.; Cheng, Y.C. J. Med. Chem. **1994**, *37*, 798–803.

Received June 28, 2001
Accepted September 26, 2001