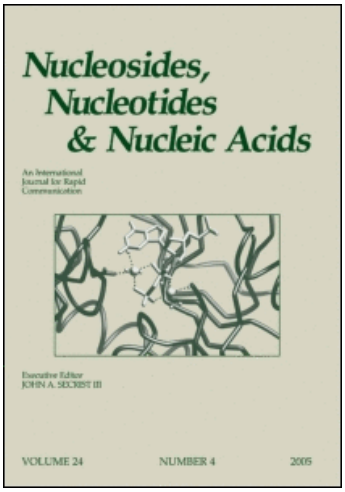

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Synthesis and Biological Evaluation of 1,3-Oxathiolane 5-Azapyrimidine, 6-Azapyrimidine, and Fluorosubstituted 3-Deazapyrimidine Nucleosides

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 Section, Cancer Center, Yale University School of Medicine, New Haven, Connecticut, USA

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(3), 603–618 (2000)

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3-OXATHIOLANE 5-AZAPYRIMIDINE, 6-AZAPYRIMIDINE, AND FLUOROSUBSTITUTED 3-DEAZAPYRIMIDINE NUCLEOSIDES

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 Section, Cancer Center, Yale University School of Medicine, New Haven, Connecticut 06520-8066, *USA*

Abstract: (2*R*,5*S*)-5-Amino-2-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2,4-triazine-3(2H)-one (**8**) and (2*R*,5*R*)-5-amino-2-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2,4-triazine-3(2H)-one (**9**) have been synthesized via a multi-step procedure from 6-azauridine. (2*R*,5*S*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,3,5-triazine-2(1H)-one (**11**) and (2*R*,5*R*)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,3,5-triazine-2(1H)-one (**12**), and the fluorosubstituted 3-deazanucleosides (**19**-**24**) have been synthesized by the transglycosylation of (2*R*,5*S*)-1-{2-[[(*tert*-butyldiphenylsilyl) oxy]methyl]-1,3-oxathiolan-5-yl}cytosine (**2**) with silylated 5-azacytosine and the corresponding silylated fluorosubstituted 3-deazacytosines, respectively, in the presence of trimethylsilyl trifluoromethanesulfonate as the catalyst in anhydrous dichloroethane, followed by deprotection of the blocking groups. These compounds were tested *in vitro* for cytotoxicity against L1210, $B_{16}F_{10}$, and CCRF-CEM tumor cell lines and for antiviral activity against HIV-1 and HBV.

Considerable effort has been expended in the search for novel nucleoside structures for use as antiviral and anticancer agents. Most of these analogues have been synthesized by modification of naturally occurring nucleosides and, therefore, possess the β-D-configuration. In the past, little attention has been given to the synthesis and evaluation of the biological activity of L-nucleosides, the enantiomers of natural D-nucleosides. Recently, however, a number of unnatural L-configuration nucleoside analogues have emerged as potent antiviral agents against human immunodeficiency virus (HIV) and human hepatitis B virus (HBV) including (–)(2*R*,5*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl)cytosine (3TC, Lamivudine),[1-3] (2*R*,5*S*)-5-fluoro-1-(2-hydroxymethyl-1,3-oxathiolan-4-yl)-5-fluorocytosine (FTC, Coviracil),[4,5] 2',3'-dideoxy-β-L-cytidine (β-L-ddC), 2',3'-

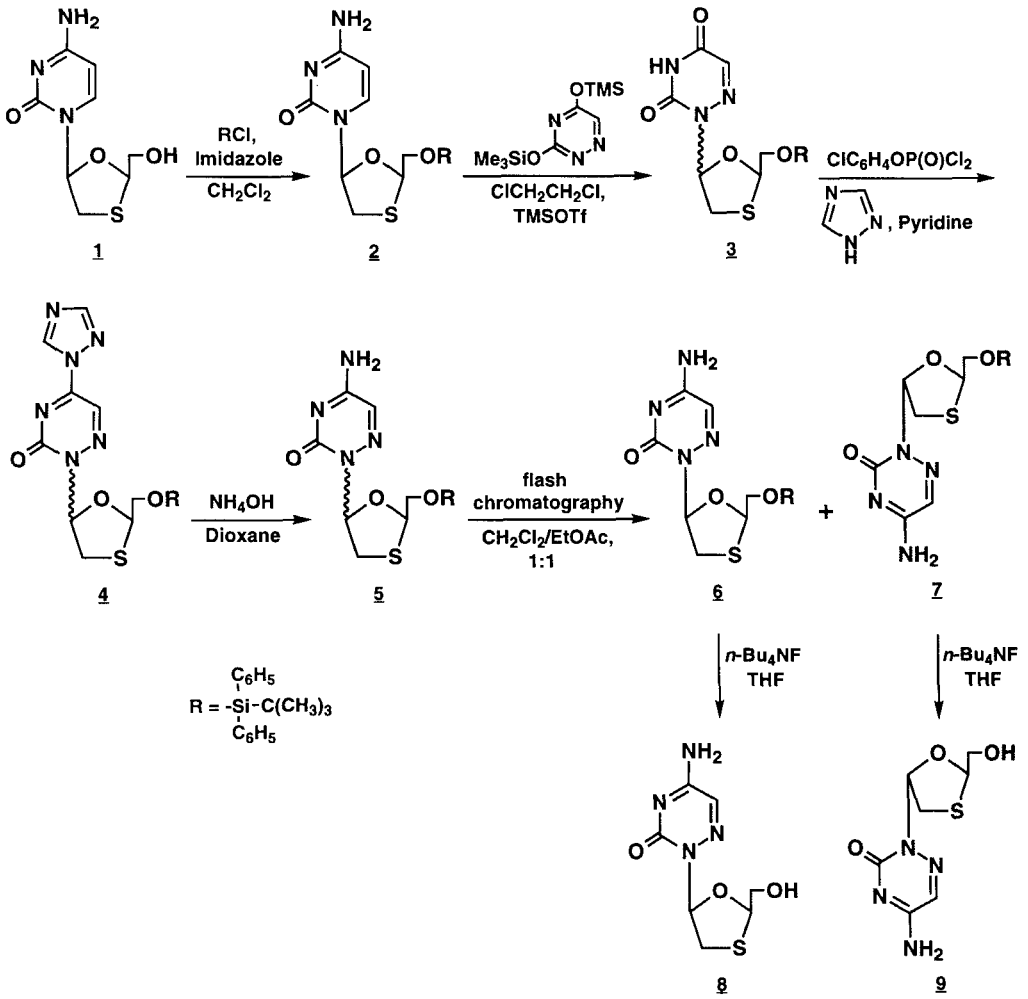
†*Deceased*

dideoxy-β-L-5-fluorocytidine (β-L-FddC),[6-8] 2',3'-dideoxy-2',3'-didehydro-β-L-cytidine (β-L-d4C), 2',3'-dideoxy-2',3'-didehydro-β-L-fluorocytidine (β-L-Fd4C),[9] and 2'-fluoro-5-methyl-β-L-arabinofuranosyluracil (L-FMAU).[10] Among these L-nucleosides, 3TC (Lamivudine) has been used clinically in combination with AZT as first line therapy for the treatment of HIV infection.[11-12] Various aza/deaza nucleoside analogs, in which the carbon or nitrogen atoms in the natural base have been replaced by the bioisosteric nitrogen or carbon, have shown significant anticancer and/or antiviral activity. For example, 5-azacytidine (AZC),[13,14] 5-aza-2'-deoxycytidine (dAZC),[15] 6-azauridine,[16] and 3-deaza-3-fluorocytidine[17] have exhibited significantly antitumor activity. Based upon these findings, it was of interest to evaluate the effects of combining the structural feature of the sulfur-containing sugar of 3TC with various bases of active aza/deaza nucleosides. In this paper, we report the synthesis and biological evaluation of the 1,3-oxathiolane nucleoside derivatives of 5-azapyrimidine, 6-azapyrimidine, and fluorosubstituted 3-deazapyrimidines.

SYNTHESIS

(−)(2*R*,5*S*)-1-[2-(Hydroxymethyl)oxathiolan-5-yl)cytosine (**1**, 3TC, Lamivudine, Epivir) was chosen as the common chiral pool for the preparation of the newly designed aza and deaza nucleosides. β-L-2'-Deoxy-3'-thia-6-azacytidine (**8**) was synthesized by a transglycosylation reaction which was a modification of methodology described by Spadari et al.[18] (**SCHEME 1**). Treatment of **1** with *t*-butylchlorodiphenylsilane and imidazole in anhydrous dichloromethane at room temperature gave its 5'-silyl ether derivative **2**. The transglycosylation reaction of **2** with silylated 6-azauracil in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst in anhydrous dichloroethane afforded a mixture of *cis* and *trans* anomers (**3**). Condensation[19] of **3** with 4-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine at room temperature produced the 4-triazolylpyrimidinone derivative **4**. Subsequent treatment[20] of **4** with aqueous ammonia in dioxane provided a mixture of *cis* and *trans* anomers (**5**), which were separated by chromatography on a silica gel column to give the anomers, **6** and **7**. Deprotection of **6** and **7** with tetra-*n*-butylammonium fluoride in THF furnished the target compound **8** and its *trans* anomer **9**.

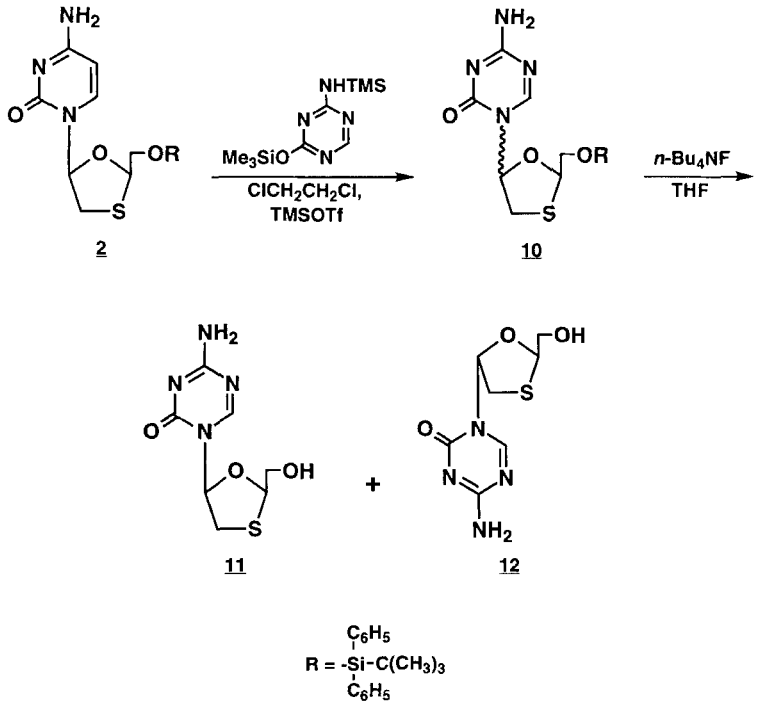
Similarly, the transglycosylation reaction of **2** with silylated 5-azacytosine in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst in anhydrous dichloroethane afforded a mixture of the *cis* and *trans* anomers of L-2'-deoxy-3'-thia-5-azacytidine (**10**). We were unable to separate these anomers (**10**) by silica gel column



SCHEME 1

chromatography. However, deprotection of **10** with tetra-*n*-butylammonium fluoride in THF gave β-L-2'-deoxy-3'-thia-5-azacytidine (**11**) and its *trans* anomer (**12**), which were purified by silica gel column chromatography and separated by crystallization from ethanol (**SCHEME 2**).

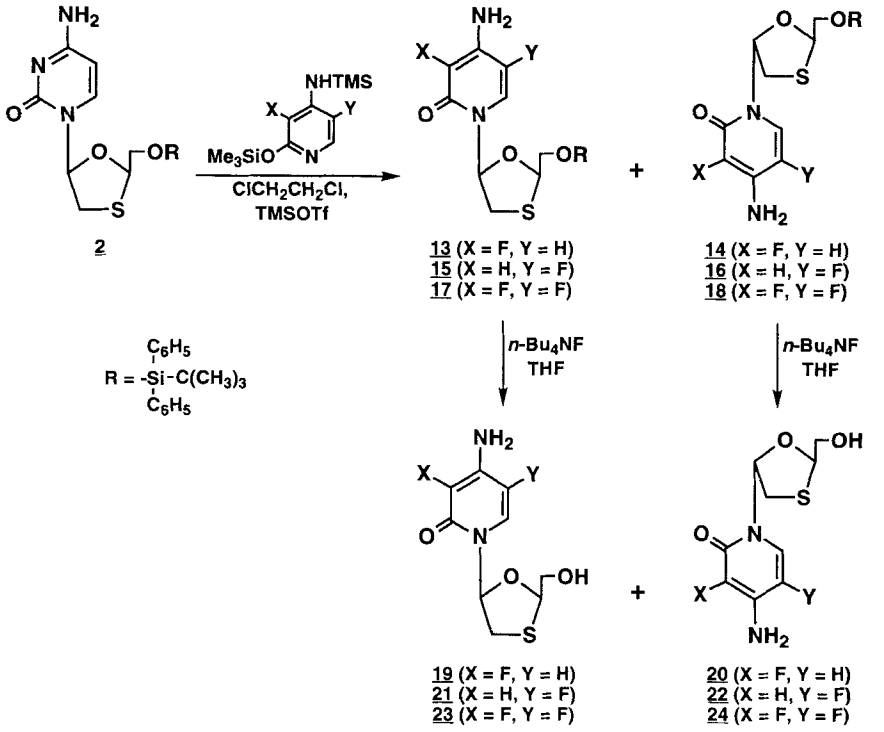
Treatment of **2** with silylated 3-deaza-3-fluorocytosine, 3-deaza-5-fluorocytosine, and 3-deaza-3,5-difluorocytosine, respectively, in the presence of trimethylsilyl trifluoromethanesulfonate in anhydrous dichloroethane afforded the corresponding *cis* and



SCHEME 2

trans anomers **13-18**, which were successfully separated by silica gel column chromatography. Treatment of the *cis* and *trans* anomers **13-18**, respectively, with tetra-*n*-butylammonium fluoride in THF gave the corresponding *cis* anomers L-2'-deoxy-3'-thia-3-deaza-3-fluorocytidine (**19**), L-2'-deoxy-3'-thia-3-deaza-5-fluorocytidine (**21**), and L-2'-deoxy-3'-thia-3-deaza-3,5-difluorocytidine (**23**), and their *trans* anomers **20**, **22**, and **24** (**SCHEME 3**).

Transglycosylation from 3TC to the compounds containing the respective aza and deazapyrimidine bases results in a complicated reaction. First, the silylated 3TC, catalyzed by trimethylsilyl trifluoromethanesulfonate, is split into silylated cytosine and the active sulfur sugar with a carbonium cation at the C-1' position. The active sugar is then attacked by the silylated aza and deazapyrimidine bases, as well as the split silylated cytosine from both sides of the sugar ring to produce the α- and β-anomers of the corresponding aza and deazanucleosides, along with 3TC, its α-anomer, and a trace amount of unidentified side products. The yields of the products are moderate (~ 40-60%) and repeated separations by silica gel chromatography are needed to obtain the pure anomers. However, in comparison



SCHEME 3

to the lengthy synthesis of the sulfur sugar intermediate,[2] the advantage of the transglycosylation reaction, which allows use of the commercially available 3TC as the sulfur sugar donor, outweighs its disadvantage of the many side products.

The assignment of the anomeric configuration of these nucleosides was made on the basis of the characteristics of the proton NMR spectra. The 4'-H protons of the α-anomers appeared at a lower field than those of the β-anomers. Conversely, the 5'-H protons of the α-anomers appeared at a higher field than those of the β-anomers (**TABLE 1**). These shifts were attributed to the fact that protons at the syn-position relative to the base are more deshielded than those in an anti-position 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 the 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, whereas those of the β-anomers are on the same side. The findings are consistent with reports by others with similar pyrimidine nucleosides.[20-22]

TABLE 1. Proton NMR chemical shifts δ (ppm).

Compd	4'-H[a]	δ	5'-H[a]	δ
6 (β)[b]	5.33 (anti)		3.78 (syn)	
7 (α)[b]	5.42 (syn)	0.09	3.76 (anti)	0.02
8 (β)[c]	5.12 (anti)		3.58 (syn)	
9 (α)[c]	5.27 (syn)	0.15	3.50 (anti)	0.08
11 (β)[c]	5.20 (anti)		3.80 (syn)	
12 (α)[c]	5.55 (syn)	0.35	3.50 (anti)	0.30
13 (β)[c]	5.25 (anti)		4.05 (syn)	
14 (α)[c]	5.55 (syn)	0.30	3.86 (anti)	0.19
15 (β)[b]	5.20 (anti)		3.95 (syn)	
16 (α)[b]	5.60 (syn)	0.40	3.82 (anti)	0.13
17 (β)[c]	5.25 (anti)		4.10 (syn)	
18 (α)[c]	5.60 (syn)	0.35	3.82 (anti)	0.28
19 (β)[c]	5.17 (anti)		3.70 (syn)	
20 (α)[c]	5.50 (syn)	0.33	3.52 (anti)	0.18
21 (β)[c]	5.18 (anti)		3.74 (syn)	
22 (α)[c]	5.53 (syn)	0.35	3.52 (anti)	0.22
23 (β)[c]	5.20 (anti)		3.78 (syn)	
24 (α)[c]	5.60 (syn)	0.40	3.55 (anti)	0.23

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

BIOLOGICAL EVALUATION

The synthesized compounds **8**, **9**, **11**, **12**, and **19-24** were evaluated *in vitro* for their cytotoxicity against the L1210 leukemia, $B_{16}F_{10}$ melanoma, and CCRF-CEM lymphoblastic leukemia cell lines by previously reported methodology.[7] (2*R*,5*S*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,3,5-triazine-2(1H)-one (**11**) produced EC_{50} values of 50, 80, and 60 μM against L1210, $B_{16}F_{10}$, and CCRF-CEM cells, respectively, and (2*R*,5*R*)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,3,5-triazine-2(1H)-one (**12**) produced an EC_{50} value of 90 and 70 μM against $B_{16}F_{10}$

and CCRF-CEM cells, respectively. The remaining compounds had no activity up to 100 μM against these three tumor cell lines. Evaluation of the compounds for antiviral activity[7,23] against HIV-1 and HBV demonstrated that compound **12** was active against HBV with an EC_{50} value of 0.4 μM and the remaining compounds were inactive up to 15 μM. 3TC at a fixed concentration of 50 nm was used as a positive control. The EC_{50} for 3TC against HBV was 10 nm. These compounds were also inactive against HIV-1 up to 100 μM.

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 on a 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*R*,5*S*)-1-{2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}cytosine (2). To a suspension of (–)(2*R*,5*S*)-1-[2-(hydroxymethyl)oxathiolan-5-yl)cytosine (**1**, Glaxo Wellcome, 2.0 g, 8.9 mmol) and imidazole (1.7 g, 25 mmol) in methylene chloride (85 mL), *tert*-butylchlorodiphenylsilane (2.68 g, 9.7 mmol) was added dropwise with stirring. Stirring was continued at room temperature until TLC showed that the reaction was completed (~ 3 h). The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 15:1, v/v) to yield 3.75 g (90%) of product as a white form: TLC, R_f 0.40 (CH_2Cl_2/EtOH, 10:1, v/v); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.10 (s, 9 H, *tert*-butyl), 3.10-3.50 (m, 2 H, 2'-H), 3.95-4.10 (m, 2 H, 5'-H), 5.20 (t, 1 H, 4'-H), 5.50 (d, 1 H, 5-H), 6.33 (m, 1 H, 1'-H), 7.00 (br s, 2 H, NH_2, D_2O exchangeable), 7.30-7.70 (m, 10 H, Ar-H), 7.90 (d, 1 H, 6-H). Anal. Calcd. for $C_{23}H_{27}N_3O_4SSi$: C, 61.64; H, 6.25; N, 8.99. Found: C, 61.53; H, 6.61; N, 9.17.

(2*R*,5*S*)- and (2*R*,5*R*)-2-{2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-1,2,4-triazine-3,5(2*H*,4*H*)-dione (3). A suspension of 6-azauracil (0.5 g, 4.4 mmol), (2*R*,5*S*)-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}cytosine (**2**, 1.6 g, 3.4 mmol) and ammonium sulfate (50 mg) in 1,1,1,3,3,3-hexamethyldisilazane (30 mL) was refluxed for 3 h to form a clear solution.

The reaction mixture was cooled and evaporated *in vacuo* to give a residue, to which 20 mL of anhydrous dichloroethane was added, followed by 1.1 mL of trimethylsilyl trifluoromethanesulfonate. The reaction mixture was stirred at room temperature overnight and then poured into a mixture of methylene chloride (20 mL) and 5% sodium bicarbonate solution (20 mL) with stirring. The mixture was filtered and the organic layer was washed with brine and water, and then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 20:1, v/v) to give **3** (0.95 g, 60%) as a white foam: TLC, R_f 0.58 (CH_2Cl_2/EtOH, 15:1, v/v); ^1H NMR showed **3** to be a mixture of β- and α-anomers; MS, m/e 470 ($M^+ + 1$). Anal. Calcd. for $C_{23}H_{27}N_3O_4SSi$: C, 58.82; H, 5.80; N, 8.95. Found: C, 58.71; H, 5.66; N, 8.86.

(2*R*,5*S*)-5-Amino-2-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-1,2,4-triazine-3(2H)-one (6) and (2*R*,5*R*)-5-amino-2-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-1,2,4-triazine-3(2H)-one (7). To a stirred solution of compound **3** (0.90 g, 1.92 mmol) in dry pyridine (17 mL), 4-chlorophenyl phosphorodichloridate (1.35 mL, 8.4 mmol) was added dropwise, followed by the addition of 1,2,4-triazole (1.85 g, 26.4 mmol) in an ice/water bath. The reaction mixture was stirred at room temperature for 48 h, and the solvent was evaporated to dryness *in vacuo* to give a dark syrup, which was dissolved in 120 mL of NH_4OH/dioxane (1:2, v/v) and stirred for 3 h at room temperature. The solution was evaporated to dryness under diminished pressure. The resulting residue was then dissolved in methylene chloride (50 mL), washed with water, and dried ($MgSO_4$). The methylene chloride solution was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of methylene chloride and purified by silica gel column chromatography (EtOAc/EtOH, 10:1, v/v) to afford anomers **5** (0.44 g, 49%) as a white foam: TLC, R_f 0.58 (EtOAc/EtOH, 10:1, v/v). Anomers **5** were further separated by silica gel column chromatography (CH_2Cl_2/EtOAc, 1:1, v/v) to provide compound **6** (β-anomer, 0.28 g, 31%) and compound **7** (α-anomer, 0.12 g, 13%).

Compound **6** was isolated as a white foam: TLC, R_f 0.38 (CH_2Cl_2/EtOAc, 1:1, v/v); ^1H NMR (90 MHz, DMSO-d_6) δ 1.00 (m, 9 H, *tert*-butyl), 3.27-3.33 (m, 2 H, 2'-H), 3.78 (m, 2 H, 5'-H), 5.33 (t, 1 H, 4'-H), 6.45 (t, 1 H, 1'-H), 7.40-7.65 (m, 11 H, Ar-H, and 5-H), 7.97 and 8.12 (two s, 2 H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{28}N_4O_3SSi$: C, 58.94; H, 6.02; N, 11.96. Found: C, 58.58; H, 6.36; N, 11.82.

Compound **7** was isolated as a white foam: TLC, R_f 0.32 (CH_2Cl_2/EtOAc, 1:1, v/v); ^1H NMR (90 MHz, DMSO-d_6) δ 1.00 (m, 9 H, *tert*-butyl), 3.28-3.44 (m, 2 H, 2'-H), 3.76 (m, 2 H, 5'-H), 5.42 (t, 1 H, 4'-H), 6.69 (t, 1 H, 1'-H), 7.41-7.65 (m, 11 H, Ar-H,

and 5-H), 7.95 and 8.07 (two s, 2 H, NH_2, D_2O exchangeable). Anal. Calcd. for $C_{23}H_{28}N_4O_3SSi$: C, 58.94; H, 6.02; N, 11.96. Found: C, 58.70; H, 6.37; N, 11.82.

(2*R*,5*S*)-5-Amino-2-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2,4-triazine-3(2H)-one (8). To a stirred solution of β-anomer **6** (0.27 g, 0.6 mmol) in THF (17 mL), tetra-*n*-butylammonium fluoride in THF (1 mL, 1 mmol) was added dropwise at ambient temperature. The reaction mixture was stirred for 1 h and evaporated *in vacuo* to dryness. The residue was chromatographed on a silica gel column, eluted first with CH_2Cl_2, then CH_2Cl_2/EtOH, 10:1, v/v) to give **8** (0.11 g, 80%) as white crystals: mp 122-124 °C; TLC, R_f 0.35 (EtOH/EtOAc, 1:1, v/v); UV (MeOH) λ_{max} 264 nm (ε 11,604), λ_{min} 228 nm; UV (0.01 N HCl) λ_{max} 264 nm (ε 9,762), λ_{min} 228 nm; UV (0.01 N NaOH) λ_{max} 264 nm (ε 11,144), λ_{min} 228 nm; ^1H NMR (300 MHz, DMSO-d_6) δ 3.20-3.40 (m, 2 H, 2'-H), 3.58 (m, 2 H, 5'-H), 5.12 (t, 1 H, 4'-H, $J_{4',5'}$ = 5.4 Hz), 5.16 (t, 1 H, 5'-OH, D_2O exchangeable), 6.38 (t, 1 H, 1'-H, $J_{1',2'}$ = 6 Hz), 7.56 (s, 1 H, 5-H), 8.00 and 8.12 (two s, 2 H, 5-NH_2, D_2O exchangeable). Anal. Calcd. for $C_7H_{10}N_4O_3S{\cdot}0.5C_2H_5OH$: C, 37.93; H, 5.17; N, 22.12. Found: C, 37.91; H, 5.35; N, 21.97.

(2*R*,5*R*)-5-Amino-2-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2,4-triazine-3(2H)-one (9). Compound **9** was synthesized by the same procedure described for **8** and was isolated as a white solid (75 mg, 82%): mp 118-120 °C; TLC, R_f 0.31 (EtOAc/EtOH, 6:1, v/v); UV (MeOH) λ_{max} 265 nm (ε 9,762), λ_{min} 227 nm; UV (0.01 N HCl) λ_{max} 265 nm (ε 10,610), λ_{min} 228 nm; UV (0.01 N NaOH) λ_{max} 264 nm (ε 10,929), λ_{min} 228 nm; ^1H NMR (300 MHz, DMSO-d_6) δ 3.30-3.31 (m, 1H, 2'-H_A), 3.39-3.40 (m, 1 H, 2'-H_B), 3.50 (m, 1 H, 5'-H),), 5.16-5.18 (t, 1 H, 5'-OH, D_2O exchangeable), 5.27 (t, 1 H, 4'-H, $J_{4',5'}$ = 5.1 Hz), 6.67-6.68 (dd, 1 H, 1'-H, $J_{1',2'a}$ = 5.2 Hz, $J_{1',2'b}$ = 3.0 Hz), 7.51 (s, 1 H, 5-H), 7.95 and 8.05 (two s, 2 H, 5-NH_2, D_2O exchangeable). Anal. Calcd. for $C_7H_{10}N_4O_3S{\cdot}0.8C_2H_5OH$: C, 38.67; H, 5.57; N, 20.98. Found: C, 39.01; H, 5.76; N, 21.36.

(2*R*,5*S*)- and (2*R*,5*R*)-4-Amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-1,3,5-triazine-2(1H)-one (10). A suspension of 5-azacytosine (0.5 g, 4.5 mmol), (2*R*,5*S*)-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}cytosine (**2**, 1.5 g, 3.2 mmol), and ammonium sulfate (50 mg) in 1,1,1,3,3,3-hexamethyldisilazane (30 mL) was refluxed overnight (~18 h) to form a clear solution. The solution was evaporated *in vacuo* to dryness and the residue was dissolved in anhydrous dichloroethane (30 mL), followed by addition of trimethylsilyl trifluoromethanesulfonate (1 mL, 5.5 mmol) with stirring. Stirring was continued at room

temperature overnight, then the mixture was diluted with 30 mL of CH_2Cl_2 and washed with 5% sodium bicarbonate solution (50 mL), brine, and water. The organic layer was dried with anhydrous $MgSO_4$ and filtered. The filtrate was reduced to a small volume *in vacuo* and chromatographed on a silica gel column (CH_2Cl_2/EtOH, 20:1, v/v) to give **10** (0.65 g, 43%) as a white foam: TLC, R_f 0.58 (CH_2Cl_2/EtOH, 15:1, v/v); ^1H NMR showed **3** to be a mixture of β- and α-anomers; MS, m/e 469 ($M^+ + 1$). Anal. Calcd. for $C_{23}H_{28}N_4O_3SSi$: C, 58.94; H, 6.02; N, 11.96. Found: C, 58.71; H, 5.86; N, 11.68.

(2*R*,5*S*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,3,5-triazine-2(1H)-one (11) and (2*R*,5*R*)-4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,3,5-triazine-2(1H)-one (12). To a stirred solution of **10** (0.25 g, 0.53 mmol) in THF (15 mL), tetra-*n*-butylammonium fluoride in THF (0.55 mL, 0.55 mmol) was added dropwise at ambient temperature. The reaction mixture was stirred for 1 h and evaporated *in vacuo* to dryness. The residue was chromatographed on a silica gel column, eluted first with CH_2Cl_2, then with CH_2Cl_2/EtOH (10:1, v/v) to give a syrup, which was stirred with 5 mL of anhydrous ethanol at 0-5 °C overnight. The resulting solid was collected by filtration and recrystallized from ethanol to give compound **11** (47 mg, 38%). The filtrates were concentrated to a small volume and purified by silica gel column chromatography (CH_2Cl_2/dioxane/EtOH, 10:2:0.5, v/v) to give compound **12** (20 mg, 15%).

Compound **11** was isolated as white crystals: mp 210 °C; TLC, R_f 0.23 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 244 nm (ε 8,174), λ_{min} 222 nm; UV (0.01 N HCl) λ_{max} 252 nm (ε 4,605), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 230 nm (ε 12,663); ^1H NMR (300 MHz, DMSO-d_6) δ 3.10-3.15 (m, 1 H, 2'-H_A), 3.44-3.50 (m, 1 H, 2'-H_B), 3.80 (m, 2 H, 5'-H), 5.20 (m, 1 H, 4'-H, $J_{4',5'}$ = 4.0 Hz), 5.40 (t, 1 H, 5'-OH, D_2O exchangeable), 6.12 (t, 1 H, 1'-H, $J_{4',5'}$ = 4.5 Hz), 7.52 (br s, 2 H, 5-NH_2, D_2O exchangeable), 8.63 (s, 1 H, 6-H). Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.51; H, 4.38; N, 24.33. Found: C, 36.20; H, 4.04; N, 24.02.

Compound **12** was isolated as a white solid: mp 188-189 °C; TLC, R_f 0.21 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 243 nm (ε 8,289), λ_{min} 223 nm; UV (0.01 N HCl) λ_{max} 252 nm (ε 4,259), λ_{min} 233 nm; UV (0.01 N NaOH) λ_{max} 230 nm (ε 12,894); ^1H NMR (300 MHz, DMSO-d_6) δ 3.10-3.15 (m, 1 H, 2'-H_A), 3.44-3.50 (m, 1 H, 2'-H_B), 3.50 (m, 2 H, 5'-H), 5.10 (t, 1 H, 5'-OH, D_2O exchangeable), 5.55 (t, 1 H, 4'-H, $J_{4',5'}$ = 5.1 Hz), 6.25 (dd, 1 H, 1'-H, $J_{1',2'a}$ = 5.4 Hz, $J_{1',2'b}$ = 3.0 Hz), 7.42 (br s, 2 H, 5-NH_2, D_2O exchangeable), 8.23 (s, 1 H, 6-H). Anal. Calcd. for $C_7H_{10}N_4O_3S$: C, 36.51; H, 4.38; N, 24.33. Found: C, 36.34; H, 4.10; N, 24.11.

(2*R*,5*S*)-4-Amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-3-fluoro-2(1H)-pyridinone (13) and (2*R*,5*R*)-4-amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-3-fluoro-2(1H)-pyridinone (14). A suspension of 3-fluoro-3-deazacytosine (0.4 g, 3.6 mmol), (2*R*,5*S*)-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}cytosine (**2**, 1.5 g, 3.2 mmol) and ammonium sulfate (50 mg) in 1,1,1,3,3,3-hexamethyldisilazane (30 mL) was refluxed overnight (~18 h). The resulting solution was cooled and evaporated *in vacuo* to dryness. The residue was dissolved in anhydrous dichloroethane (20 mL), followed by addition of trimethylsilyl trifluoromethanesulfonate (1 mL, 5.5 mmol) with stirring. Stirring was continued at room temperature overnight, then the mixture was diluted with 50 mL of CH_2Cl_2 and stirred with 50 mL of 5% sodium bicarbonate solution for 20 min. The organic layer was separated, washed with brine and water, then dried with anhydrous $MgSO_4$ and filtered. The filtrate was reduced to a small volume *in vacuo* and chromatographed on a silica gel column (CH_2Cl_2/EtOH, 30:1, v/v) to give 0.47 g (43%) of product as a mixture of α- and β-anomers, which was further resolved by silica gel column chromatography (CH_2Cl_2/dioxane/CH_3CN/CH_3OH, 65:3.5:3.5:0.5, v/v) to give compound **13** (β-anomer) 0.18 g (11.8%) and compound **14** (α-anomer) 0.19 g (12%).

Compound **13** was isolated as a white foam: TLC, R_f 0.47 (CH_2Cl_2/dioxane/CH_3CN/CH_3OH, 65:3.5:3.5:0.5, v/v); ^1H NMR (90 MHz, $CDCl_3$) δ 1.10 (m, 9 H, *tert*-butyl), 3.05-3.25 (m, 2 H, 2'-H), 4.05 (m, 2 H, 5'-H), 4.50 (br s, 2 H, NH_2, D_2O exchangeable), 5.25 (t, 1 H, 4'-H), 5.65 (t, 1 H, 5-H), 6.50 (t, 1 H, 1'-H), 7.45-7.80 (m, 11 H, Ar-H and 6-H). Anal. Calcd. for $C_{25}H_{29}FN_2O_3SSi$: C, 61.95; H, 6.03; N, 5.78. Found: C, 61.70; H, 6.16; N, 5.86.

Compound **14** was isolated as a white foam: TLC, R_f 0.55 (CH_2Cl_2/dioxane/CH_3CN/CH_3OH, 65:3.5:3.5:0.5, v/v); ^1H NMR (90 MHz, $CDCl_3$) δ 1.10 (m, 9 H, *tert*-butyl), 3.10-3.30 (m, 2 H, 2'-H), 3.86 (m, 2 H, 5'-H), 4.55 (br s, 2 H, NH_2, D_2O exchangeable), 5.55 (t, 1 H, 4'-H), 5.80 (t, 1 H, 5-H), 6.60 (t, 1 H, 1'-H), 7.15 (d, 1 H, 6-H), 7.40-7.70 (m, 10 H, Ar-H). Anal. Calcd. for $C_{25}H_{29}FN_2O_3SSi$: C, 61.95; H, 6.03; N, 5.78. Found: C, 61.80; H, 6.27; N, 5.47.

Compounds **15-18** were synthesized by a similar methodology as described for the synthesis of compounds **13** and **14**.

(2*R*,5*S*)-4-Amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-5-fluoro-2(1H)-pyridinone (15). Compound **15** was isolated as a white foam (0.32 g, 14%): TLC, R_f 0.38 (CH_2Cl_2/dioxane/CH_3CN/CH_3OH, 43:3.5:3.5:2, v/v); ^1H NMR (90 MHz, $CDCl_3$) δ 1.10 (m, 9 H, *tert*-butyl), 3.05-3.60 (m, 2 H, 2'-H), 3.95 (m, 2 H, 5'-H), 4.65-4.75 (br s, 2 H, NH_2, D_2O exchangeable),

5.20 (t, 1 H, 4'-H), 5.65 (d, 1 H, 3-H), 6.45 (t, 1 H, 1'-H), 7.35-7.75 (m, 11 H, Ar-H and 6-H). Anal. Calcd. for $C_{25}H_{29}FN_2O_3SSi$: C, 61.95; H, 6.03; N, 5.78. Found: C, 61.93; H, 6.08; N, 5.49.

(2*R*,5*R*)-4-Amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-5-fluoro-2(1H)-pyridinone (16). Compound **16** was isolated as a white foam (0.44 g, 19%): TLC, R_f 0.43 (CH_2Cl_2/dioxane/CH_3CN/CH_3OH, 43:3.5:3.5:2, v/v); ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (m, 9 H, *tert*-butyl), 3.15-3.60 (m, 2 H, 2'-H), 3.82 (m, 2 H, 5'-H), 4.65-4.80 (br s, 2 H, NH_2, D_2O exchangeable), 5.60 (t, 1 H, 4'-H), 5.72 (d, 1 H, 3-H), 6.55 (t, 1 H, 1'-H), 7.30-7.70 (m, 11 H, Ar-H and 6-H). Anal. Calcd. for $C_{25}H_{29}FN_2O_3SSi$: C, 61.95; H, 6.03; N, 5.78. Found: C, 61.85; H, 6.34; N, 5.55.

(2*R*,5*S*)-4-Amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-3,5-difluoro-2(1H)-pyridinone (17). Compound **17** was isolated as a white foam (0.48 g, 19%): TLC, R_f 0.40 (CH_2Cl_2/EtOAc, 1:1, v/v); ^1H NMR (90 MHz, $CDCl_3$) δ 1.05 (m, 9 H, *tert*-butyl), 3.00-3.60 (m, 2 H, 2'-H), 4.10 (m, 2 H, 5'-H), 4.55-4.65 (br s, 2 H, NH_2, D_2O exchangeable), 5.25 (t, 1 H, 4'-H), 6.55 (t, 1 H, 1'-H), 7.30-7.70 (m, 11 H, Ar-H and 6-H). Anal. Calcd. for $C_{25}H_{28}F_2N_2O_3SSi$: C, 59.73; H, 5.61; N, 5.57. Found: C, 59.87; H, 5.92; N, 5.57.

(2*R*,5*R*)-4-Amino-1-{2-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-1,3-oxathiolan-5-yl}-3,5-difluoro-2(1H)-pyridinone (18). Compound **18** was isolated as a white foam (0.45 g, 18%): TLC, R_f 0.51 (CH_2Cl_2/EtOAc, 1:1, v/v); ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (m, 9 H, *tert*-butyl), 3.15-3.60 (m, 2 H, 2'-H), 3.82 (m, 2 H, 5'-H), 4.65-4.80 (br s, 2 H, NH_2, D_2O exchangeable), 5.60 (t, 1 H, 4'-H), 6.60 (t, 1 H, 1'-H), 7.25-7.70 (m, 11 H, Ar-H and 6-H). Anal. Calcd. for $C_{25}H_{28}F_2N_2O_3SSi$: C, 59.73; H, 5.61; N, 5.57. Found: C, 60.03; H, 5.90; N, 5.55.

Compounds **19-24** were synthesized by the same procedure described for compound **8**.

(2*R*,5*S*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-3-fluoro-2(1H)-pyridinone (19). Compound **19** was isolated as white crystals (0.19 g, 78%): mp 185-187 °C; TLC, R_f 0.36 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 277 nm (ε 9,708), λ_{min} 268 nm; UV (0.01 N HCl) λ_{max} 275 nm (ε 10,300), λ_{min} 265 nm; UV (0.01 N NaOH) λ_{max} 276 nm (ε 9,472), λ_{min} 267 nm; ^1H NMR (300 MHz, DMSO-d_6) δ 2.95-3.05 (m, 1 H, 2'-H_A), 3.35-3.45 (m, 1 H, 2'-H_B), 3.70 (m, 2 H, 5'-H), 5.17 (m, 1 H, 4'-H, $J_{4',5'}$ = 3.8 Hz), 5.20 (t, 1 H, 5'-OH, D_2O exchangeable), 5.87 (t, 1 H, 5-H, $J_{5,6}$ = 7.8 Hz, $J_{5,3F}$ = 7.8 Hz), 6.25 (br s, 2 H, 5-NH_2, D_2O exchangeable), 6.35

(t, 1 H, 1'-H, $J_{1',2'}$ = 4.2 Hz), 7.42 (d, 1 H, 6-H, $J_{5,6}$ = 7.8 Hz). Anal. Calcd. for $C_9H_{11}FN_2O_3S$: C, 43.89; H, 4.50; N, 11.38. Found: C, 43.81; H, 4.24; N, 11.08.

(2*R*,5*R*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-3-fluoro-2(1H)-pyridinone (20). Compound **20** was isolated as white crystals (0.19 g, 78%): mp 189-191 °C; TLC, R_f 0.30 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 278 nm (ε 8,318), λ_{min} 268 nm; UV (0.01 N HCl) λ_{max} 276 nm (ε 9,851), λ_{min} 266 nm; UV (0.01 N NaOH) λ_{max} 276 nm (ε 10,288), λ_{min} 266 nm; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00-3.20 (m, 2 H, 2'-H), 3.52 (m, 2 H, 5'-H), 5.15 (t, 1 H, 5'-OH, D_2O exchangeable), 5.50 (t, 1 H, 4'-H, $J_{4',5'}$ = 4.2 Hz), 5.85 (t, 1 H, 5-H, $J_{5,6}$ = 7.6 Hz, $J_{5,3F}$ = 7.6 Hz), 6.15 (br s, 2 H, 5-NH_2, D_2O exchangeable), 6.50 (t, 1 H, 1'-H, $J_{1',2'}$ = 4.6 Hz), 7.25 (d, 1 H, 6-H, $J_{6,5}$ = 7.6 Hz). Anal. Calcd. for $C_9H_{11}FN_2O_3S$: C, 43.89; H, 4.50; N, 11.38. Found: C, 44.12; H, 4.55; N, 11.09.

(2*R*,5*S*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-5-fluoro-2(1H)-pyridinone (21). Compound **21** was isolated as white crystals (0.11 g, 77%): mp 157-159 °C; TLC, R_f 0.22 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 264 nm (288 nm shoulder) (ε 14,776), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 265 nm (288 nm shoulder) (ε 13,791), λ_{min} 236 nm; UV (0.01 N NaOH) λ_{max} 264 nm (286 nm shoulder) (ε 13,791), λ_{min} 234 nm; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00-3.10 (m, 1 H, 2'-H_A), 3.35-3.40 (m, 1 H, 2'-H_B), 3.74 (m, 2 H, 5'-H), 5.18 (t, 1 H, 4'-H, $J_{4',5'}$ = 3.8 Hz), 5.30-5.35 (t, 1 H, 5'-OH, D_2O exchangeable), 5.37 (d, 1 H, 3-H, $J_{3,5F}$ = 8.6 Hz), 6.31 (t, 1 H, 1'-H, $J_{1',2'}$ = 4.2 Hz), 6.50 (br s, 2 H, 5-NH_2, D_2O exchangeable), 7.83 (d, 1 H, 6-H, $J_{6,5F}$ = 7.8 Hz). Anal. Calcd. for $C_9H_{11}FN_2O_3S$·0.2 C_2H_5OH: C, 43.19; H, 4.81; N, 10.96. Found: C, 44.40; H, 4.76; N, 10.68.

(2*R*,5*R*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-5-fluoro-2(1H)-pyridinone (22). Compound **22** was isolated as white crystals (0.10 g, 72%): mp 159-161 °C; TLC, R_f 0.17 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 266 nm (284 nm shoulder) (ε 12,609), λ_{min} 237 nm; UV (0.01 N HCl) λ_{max} 262 nm (282 nm shoulder) (ε 12,707), λ_{min} 234 nm; UV (0.01 N NaOH) λ_{max} 262 nm (282 nm shoulder) (ε 14,185), λ_{min} 234 nm; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.00-3.07 (m, 1 H, 2'-H_A), 3.30-3.40 (m, 1 H, 2'-H_B), 3.52 (m, 2 H, 5'-H), 5.15 (t, 1 H, 5'-OH, D_2O exchangeable), 5.35 (d, 1 H, 3-H, $J_{3,5F}$ = 7.9 Hz), 5.53 (t, 1 H, 4'-H, $J_{4',5'}$ = 4.1 Hz), 6.45 (t, 1 H, 1'-H, $J_{1',2'}$ = 4.0 Hz), 6.50 (br s, 2 H, 5-NH_2, D_2O exchangeable), 7.53 (d, 1 H, 6-H, $J_{6,5F}$ = 7.8 Hz). Anal. Calcd. for $C_9H_{11}FN_2O_3S$: C, 43.89; H, 4.50; N, 11.38. Found: C, 43.65; H, 4.59; N, 11.22.

(2*R*,5*S*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-3,5-difluoro-2(1H)-pyridinone (23). Compound **23** was isolated as white crystals (0.15 g, 80%): mp 152-154 °C; TLC, R_f 0.36 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 262 nm (288 nm shoulder) (ε 14,776), λ_{min} 236 nm; UV (0.01 N HCl) λ_{max} 260 nm (286 nm shoulder) (ε 13,001), λ_{min} 237 nm; UV (0.01 N NaOH) λ_{max} 260 nm (286 nm shoulder) (ε 14,375), λ_{min} 238 nm; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.09-3.14 (m, 1 H, 2'-H_A), 3.43-3.49 (m, 1 H, 2'-H_B), 3.78 (m, 2 H, 5'-H), 5.20 (t, 1 H, 4'-H, $J_{4',5'}$ = 3.8 Hz), 5.40 (t, 1 H, 5'-OH, D_2O exchangeable), 6.40 (t, 1 H, 1'-H, $J_{1',2'}$ = 5 Hz), 6.60 (br s, 2 H, 5-NH_2, D_2O exchangeable), 7.88 (dd, 1 H, 6-H, $J_{6,5F}$ = 8.1 Hz, $J_{6,3F}$ = 1.8 Hz). Anal. Calcd. for $C_9H_{10}F_2N_2O_3S$: C, 40.90; H, 3.81; N, 10.60. Found: C, 41.14; H, 4.04; N, 10.42.

(2*R*,5*R*)-4-Amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-3,5-difluoro-2(1H)-pyridinone (24). Compound **24** was isolated as white crystals (0.11 g, 81%): mp 147-149 °C; TLC, R_f 0.45 (CH_2Cl_2/EtOH, 10:1, v/v); UV (MeOH) λ_{max} 260 nm (288 nm shoulder) (ε 12,135), λ_{min} 238 nm; UV (0.01 N HCl) λ_{max} 260 nm (286 nm shoulder) (ε 15,764), λ_{min} 238 nm; UV (0.01 N NaOH) λ_{max} 260 nm (286 nm shoulder) (ε 16,331), λ_{min} 238 nm; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.13-3.18 (m, 1 H, 2'-H_A), 3.46-3.52 (m, 1 H, 2'-H_B), 3.55 (m, 2 H, 5'-H), 5.19 (t, 1 H, 5'-OH, D_2O exchangeable), 5.60 (t, 1 H, 4'-H, $J_{4',5'}$ = 5.2 Hz), 6.54 (t, 1 H, 1'-H, $J_{1',2'}$ = 3.8 Hz), 6.58 (br s, 2 H, 5-NH_2, D_2O exchangeable), 7.55 (dd, 1 H, 6-H, $J_{6,5}$ = 7.5 Hz, $J_{6,5F}$ = 1.8 Hz). Anal. Calcd. for $C_9H_{10}F_2N_2O_3S$: C, 40.90; H, 3.81; N, 10.60. Found: C, 41.28; H, 4.15; N, 10.24.

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