Supplementary Material

Thiophene-expanded guanosine analogues of Gemcitabine

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All chemicals were obtained from commercial sources and used without further purification unless otherwise noted. An-hydrous DMF, MeOH, DMSO and EtOH were purchased from Fisher Scientific. Anhydrous THF, acetone, CH_2Cl_2, CH_3CN, and ether were obtained using a solvent purification system (mBraun Labmaster 130). NMR solvents were purchased from Cambridge Isotope Laboratories (Andover, MA). All ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were obtained either on a JEOL ECX 400 MHz NMR, operated at 400, 100, 376 and 162 MHz, respectively, or a Bruker AVANCE III HD 500 MHz NMR, operated at 500 and 125 MHz, respectively, and referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (trip-let), q (quartet), m (multiplet), and br (broad). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} pre-coated plates. Purification was performed on a Teledyne Isco CombiFlash Rf 200, and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H, ^{13}C, ^{19}F and ^{31}P NMR) homogeneous materials. Mass Spectra were recorded at the Johns Hopkins Mass Spectrometry Facility.

Compound **6** (α/β mixture) can be obtained from lactone **3** in 3 steps with an overall yield of 45% using similar procedures most recently published by our group.[21]

Synthesis of 3',5'-dibenzyloxy-2'-deoxy-2',2'-difluoro-1'-(4,5-diiodoimidazol-3-yl]-α/β-D-ribofuranose (8)
To a solution of **7** (2.2 g, 4.7 mmol) in anhydrous DMF (40 mL) at 0°C was added a suspension of NaH (95%, 268 mg, 11.2 mmol) in anhydrous DMF (20 mL) dropwise over a period of 10 min. The resulting mixture was stirred at 0°C for 2 h, and then BnBr (1.9 mL, 16.3 mmol) was added slowly. The mixture was stirred at room temperature for an additional 4 h. The reaction mixture was quenched by cold water and neutralized by HOAc at 0°C. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (PE/EtOAc = 20:1 - 2:1) to give **8** (2.5 g, 82%) as off-white syrup, β:α = 1:2.6; β isomer: R_f = 0.25, (PE/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57-3.60 (m, 1H, H-5), 3.76-3.79 (m, 1H, H-5'), 4.13-4.15 (m, 1H, H-4), 4.28-4.35 (dd, 1H, J = 10.5 Hz, J = 18.3 Hz, CH_2), 4.47-4.56 (m, 3H, CH_2), 4.81 (d, 1H, J = 11.5Hz, H-3), 5.83 (dd, 1H, J = 3.6 Hz, J= 9.6 Hz, H-1), 7.24-7.37 (m, 10H), 8.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.7, 73.3, 73.6, 79.3, 88.9, 97.3, 122.2, 128.6 (multiple peaks), 136.3, 137.1, 140.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.6, -121.0; HRMS (FAB) calculated for $C_{22}H_{20}F_2I_2N_2O_3$ [M + H^+] 652.96096; Found, 652.96065. α isomer: R_f = 0.24, (PE/EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57-3.68 (m, 2H, H-5 and H-5'), 4.36-4.41 (m, 2H, H-4 and CH_2), 4.49-4.59 (m, 3H, CH_2), 4.84 (d, 1H, J = 11.4Hz, H-3), 6.00 (t, 1H, J = 6.4 Hz, H-1), 7.26-7.39 (m, 10 H, Ar), 7.92 (d, 1H, J = 2.8 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.4, 73.5, 73.7, 82.3, 89.2, 97.2, 122.5, 128.6 (multiple peaks), 136.2, 137.4, 141.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.6, -121.0; MS (ESI, pos), m/z: 653.0 (M + H^+).

Synthesis of 3',5'-dibenzyloxy-2'-deoxy-2',2'-difluoro-1'-[(5-iodo-4-carbaldehyde) imidazole-3-yl]-β-D-ribofuranose (9)
Compound **8** (715 mg, 1.1 mmol) was dissolved in anhydrous THF (20 mL), and then EtMgBr (1 M in THF, 1.2 mL, 1.2 mmol) was added dropwise under nitrogen. The reaction mixture was stirred at 0°C for 30 min. Anhydrous DMF (1.5 mL) was added and the reaction mixture was stirred overnight, quenched with water. The solvent was removed, and the residue was purified by silica gel column chromatography (PE/EtOAc = 10:1-2:1) to give **9** (432 mg, 72%) as colorless syrup; R_f = 0.45, (PE/EtOAc = 5:1).

Synthesis of 3',5'-dibenzyloxy-2'-deoxy-2',2'-difluoro-1'-[(5-iodo-4-carbonitrile) imidazole-3-yl]-β-D-ribofuranose (11)

To a stirred solution of **9** (800 mg, 1.4 mmol) in anhydrous EtOH (30 mL) was added hydroxylamine hydrochloride (400 mg, 5.7 mmol) and $NaHCO_3$ (480 mg, 5.7 mmol). The resulting mixture was heated to reflux for 4 h. The solvent was removed under reduced pressure, and the crude product was extracted in EtOAc (2 x 25 mL) and excess water. The combined organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give the crude oxime intermediate **10** as syrup (920 mg), which was then used for the next step without further purification. Oxime intermediate **10** (920 mg) was dissolved in anhydrous THF (30 mL) and CDI (1.3 g, 8.0 mmol) was added to the mixture. The resulting solution was stirred at reflux for 6 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (PE/EtOAc = 8:1) to provide the cyano nucleoside **11** as a light yellow syrup (362 mg, 45% in 2 steps); R_f = 0.40, (PE/EtOAc = 3:1).

Synthesis of 3',5'-dibenzoyloxy-2'-deoxy-2',2'-difluoro-1'-[(5-carboxamide)[2, 3-d]imidazole-3-yl]-β-D-ribofuranose (13)

To a solution of **11** (350 mg, 0.6 mmol) in anhydrous DMF (80 mL), was added thioglycolamide (347 mg, 3.8 mmol) and K_2CO_3 (439 mg, 3.2 mmol). The resulting mixture was heated to 65°C for 24 h under nitrogen. The crude mixture was filtered over a pad of Celite and the solid was washed with DMF. The solvent was removed under reduced pressure to give crude mixture **12**, which was then heated to reflux in a NaOEt (21%, 0.5 mL) and anhydrous EtOH (40 mL) mixture for 4 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (DCM/MeOH = 50:1 - 10:1) to afford compound **13** as a yellow foam (185 mg, 57%); R_f = 0.50, DCM/MeOH = 15:1. ^{1}H NMR (400 MHz, MeOH-d_4) δ 3.60-3.64 (m, 1H, H-5), 3.91-3.93(m, 1H, H-5'), 4.12-4.14 (m, 1H, H-4), 4.36-4.62 (m, 4H, CH_2), 4.79-4.87 (m, 1H, H-3), 6.18 (dd, 1H, J = 7.8 Hz, J = 11.4 Hz, H-1), 7.22-7.38 (m, 10H, Ar), 8.16 (s, 1H, Ar). ^{13}C NMR (100 MHz, MeOH-d_4) δ 65.7, 73.0, 73.3, 74.8, 79.3, 86.8, 98.3, 125.4, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 136.8, 139.3, 143.7, 145.4, 169.4; ^{19}F NMR (376 MHz, MeOH-d_4) δ -111.9, -120.4.

Synthesis of 3',5'-dibenzyloxy-2'-deoxy-2',2'-difluoro-1'-[(2-amino-imidazo-[4',5':4,5]-thieno-[3,2-d]pyrimidin-3-yl-7-one)]-β-D-ribofuranose (14)

To a stirred solution of **13** (135 mg, 0.26 mmol) in anhydrous MeOH (12 mL) was added NaOH (52 mg, 1.3 mmol). The resulting mixture was stirred at room temperature until the mixture was homogeneous. Carbon disulfide (120 mg, 1.6 mmol) was added, and the resulting mixture was heated in a steel bomb for 18 h at 150°C. The mixture was cooled to 0°C. H_2O_2 (0.9 mL, 30%) was then added dropwise and allowed to stir at 0°C for 2 h. The resulting suspension was added to a steel bomb and anhydrous ammonia was bubbled in at -40°C for 20 minutes. The bomb was then heated at 130°C for 12 h. The solvent was removed under reduced pressure, and the crude yellow residue was purified by silica gel column chromatography to afford **14** (77 mg, 54%) as a yellow foam. HRMS (FAB) calculated for $C_{26}H_{23}F_2N_5O_4S$ [M + H$^+$] 540.15171; Found, 540.15032.

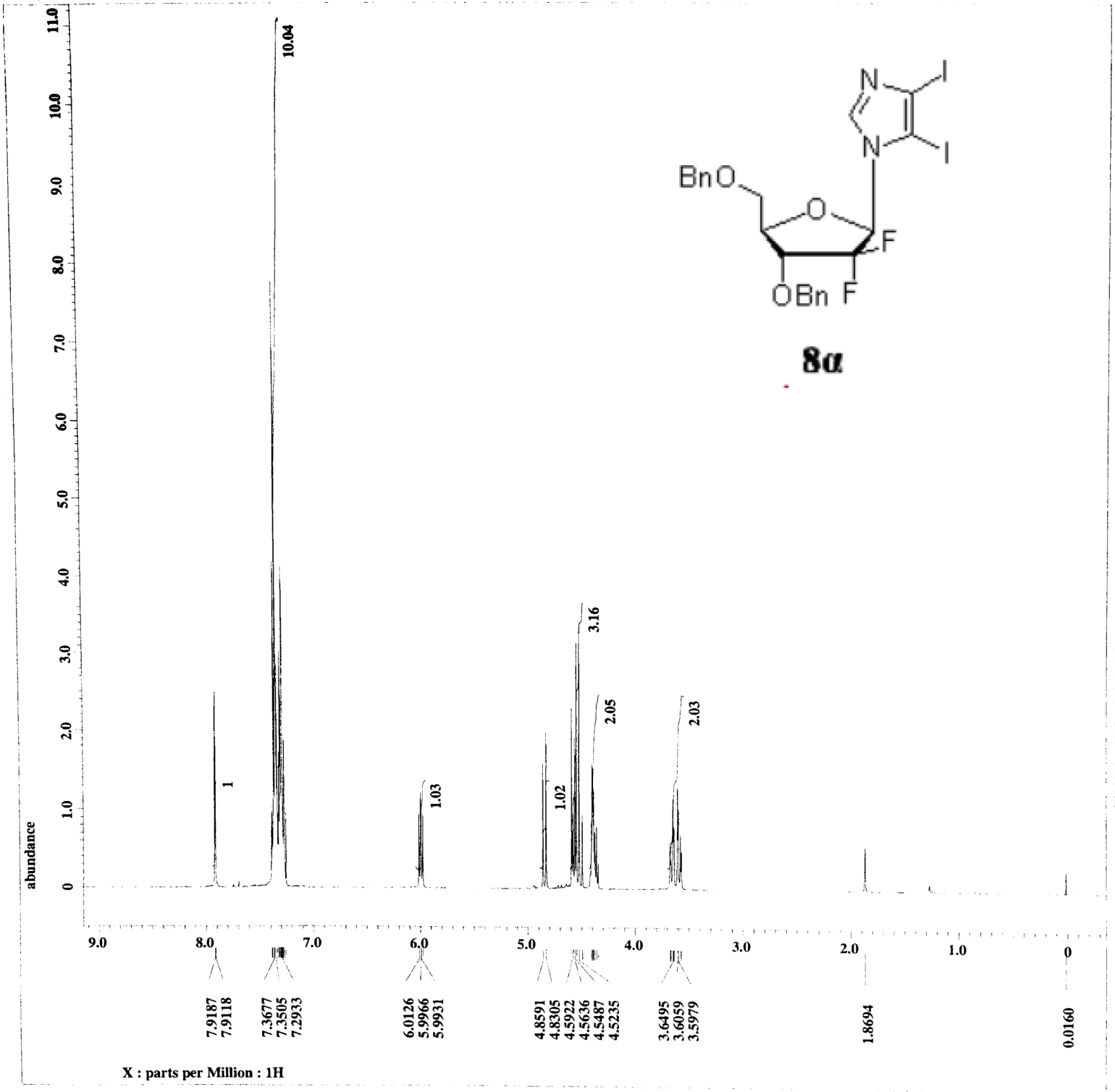
Synthesis of 2'-deoxy-2',2'-difluoro-1'-[(2-amino-imidazo-[4',5':4,5]-thieno-[3, 2-d]pyrimidin-3-yl-7-one)]-β-D-ribofura-nose (1)

To a solution of **14** (95 mg, 0.18 mmol) in anhydrous DCM (8 mL) was added EtSH (0.26 mL, 3.5 mmol) and $BF_3.Et_2O$ (48%, 0.9 mL, 3.5 mmol) at 0°C. The reaction was allowed to proceed for 72 h at room temperature before TLC analysis confirmed complete product formation. The solvent was removed under reduced pressure, and the residue was purified by CombiFlash silica column chromatography ($CHCl_3$/MeOH = 100:1 - 1:1) to afford target nucleoside **1** (51 mg, 81%) as off-white powder; R_f = 0.32, (DCM: MeOH = 4:1). ^{1}H NMR (400 MHz, MeOH-d_4) δ 3.83-3.86 (m, 1H, H-5), 3.99-4.01 (m, 2H, H-5' and H-4), 4.58-4.66 (m, 1H, H-3), 6.53 (dd, 1H, J = 6.0 Hz, J = 8.7 Hz, H-1), 8.47 (s, 1H, Ar); ^{19}F NMR (376 MHz, MeOH-d_4) δ -119.2, -122.0; MS (ESI, pos), m/z: 359.9 (M + H$^+$).

Synthesis of tricyclic nucleoside prodrugs (2 and 15).

To a stirred solution of free nucleoside **1** (10-20 mg, 1.00 eq.) in anhydrous DMF (3-6 mL), was added tert-butyl magnesium chloride (1.50 eq., 1 M solution in THF) slowly at 0°C. After completion of the addition, the mixture was stirred at 0°C for 1 h. To the above mixture was added freshly prepared phosphorous reagent (S)-2-[(2,3,4,5,6-pentafluoro-phenoxy)-phenoxy-phos-phorylamino] propionic acid isopropyl ester (1.50 eq., 1 M solution in THF) dropwise, and the resulting mixture was stirred at 0°C for 1 h and then slowly allowed to warm to room temperature overnight. The mixture was quenched with cold water, and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was

removed under reduced pressure. The residue was purified by CombiFlash silica gel column chromatography (DCM/MeOH = 100:1 - 10:1) to give target nuc-leoside prodrugs **2** and **15**, respectively. **Compound 2:** Off-white powder, ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.10-1.29 (m, 9H), 3.83-3.91 (m, 1H), 4.14-4.20 (m, 1H), 4.45-4.60 (m, 2H), 4.69-4.82 (m, 1H), 4.92-4.96 (m, 1H), 6.56-6.60 (m, 1H), 7.14-7.23 (m, 3H), 7.28-7.32 (m, 2H), 8.25 (s, 1H); ^{19}F NMR (376 MHz, MeOH-d_4) δ -118.4, -120.1; ^{31}P NMR (400 MHz, MeOH-d_4) δ 4.53, 4.58, two isomers: S_p/R_p or R_p/S_p = 3:1; HRMS (FAB) calculated for $C_{24}H_{28}F_2N_6O_8PS$ [M + H^+] 629.13950; Found, 629.13985. **Compound 15:** Colorless syrup, ^{1}H NMR (400 MHz, MeOH-d_4) δ 1.03-1.14 (m, 10H), 1.18-1.38 (m, 8H), 3.61-3.72 (m, 1H), 3.93-4.00 (m, 1H), 4.23-4.42 (m, 2H), 4.55-4.83 (m, 2H), 4.96-5.01 (m, 2H), 6.39-6.44 (m, 1H), 7.05-7.36 (m, 10H), 8.29 (s, 1H); ^{19}F NMR (376 MHz, MeOH-d_4) δ -114.0, -117.2; ^{31}P NMR (400 MHz, MeOH-d^4) δ 4.02, 4.21, 5.49, 5.63, two isomers: S_p/R_p or R_p/S_p = 6:5; HRMS (FAB) calculated for $C_{36}H_{44}F_2N_7O_{12}P_2S$ [M + H^+] 898.22120; Found, 898.22221.



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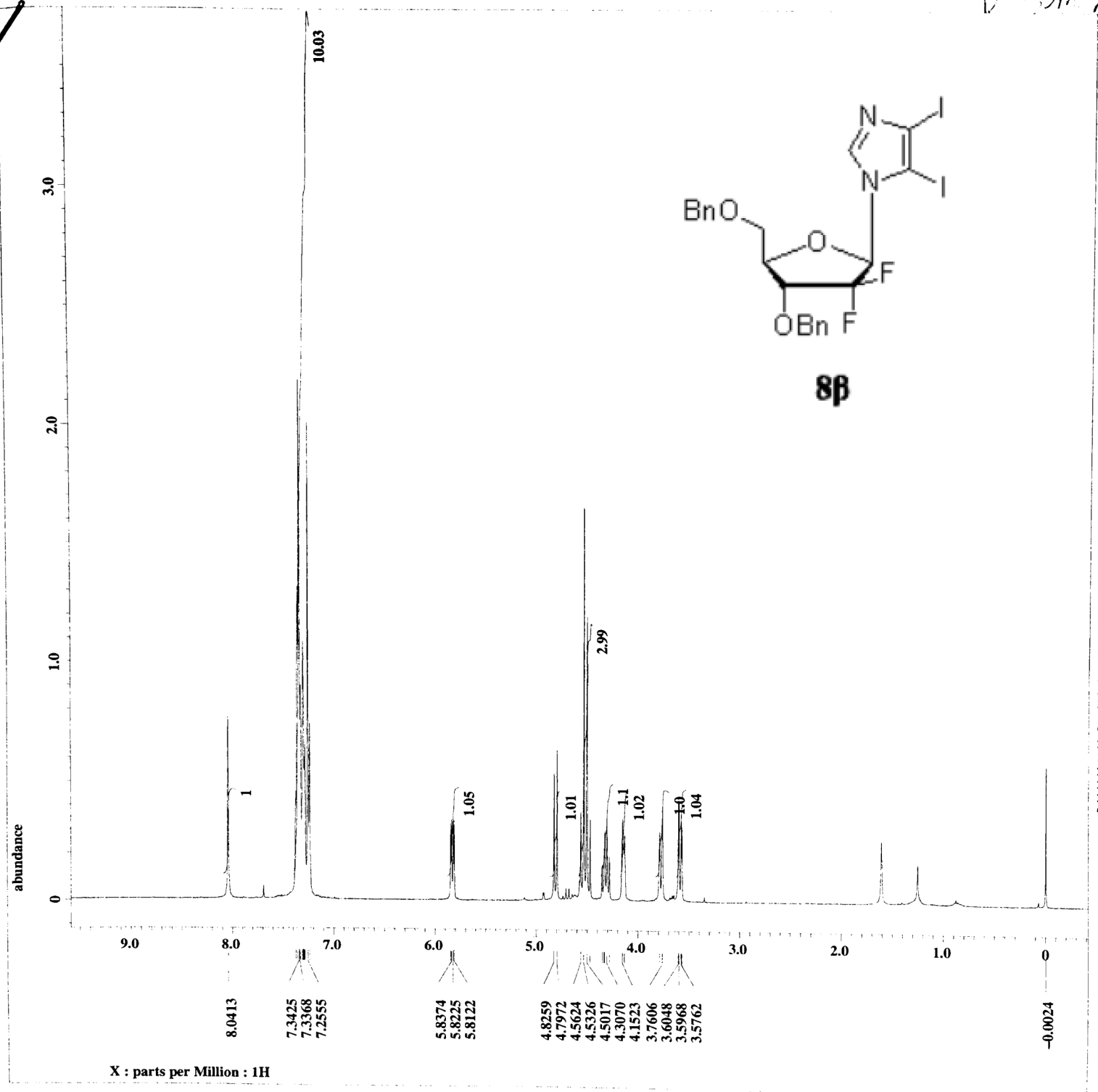

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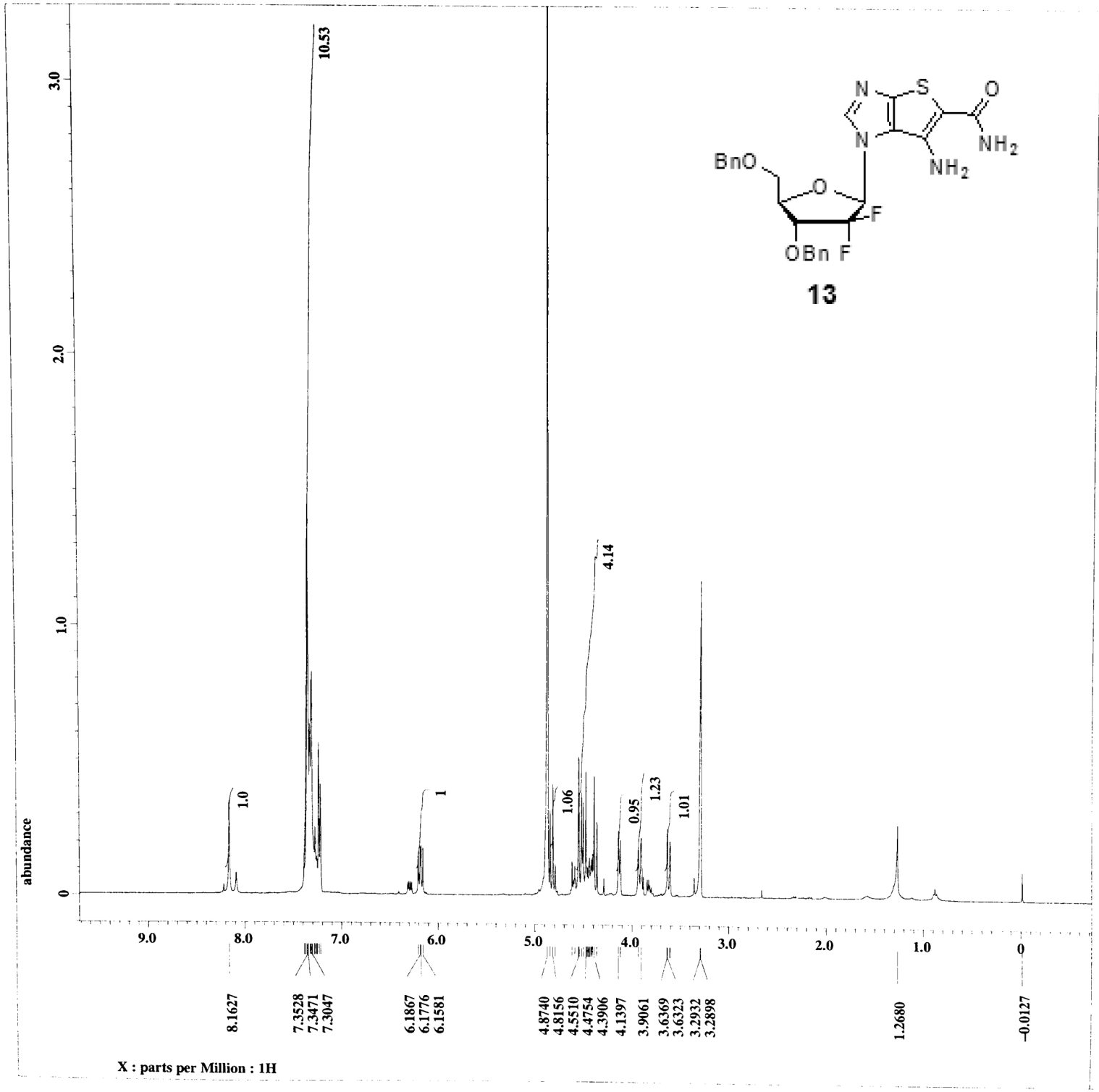

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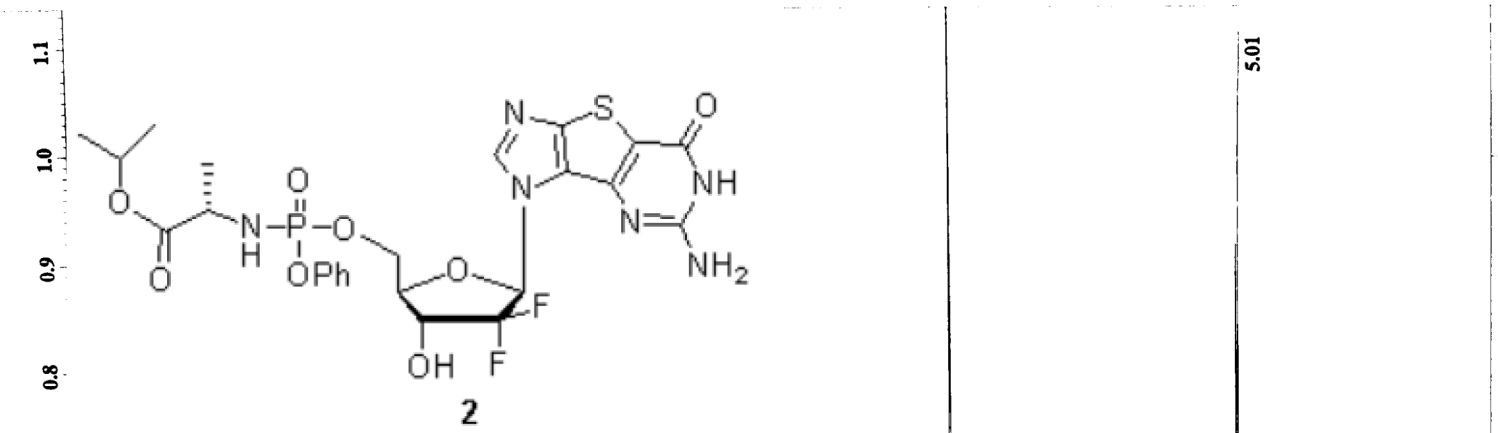

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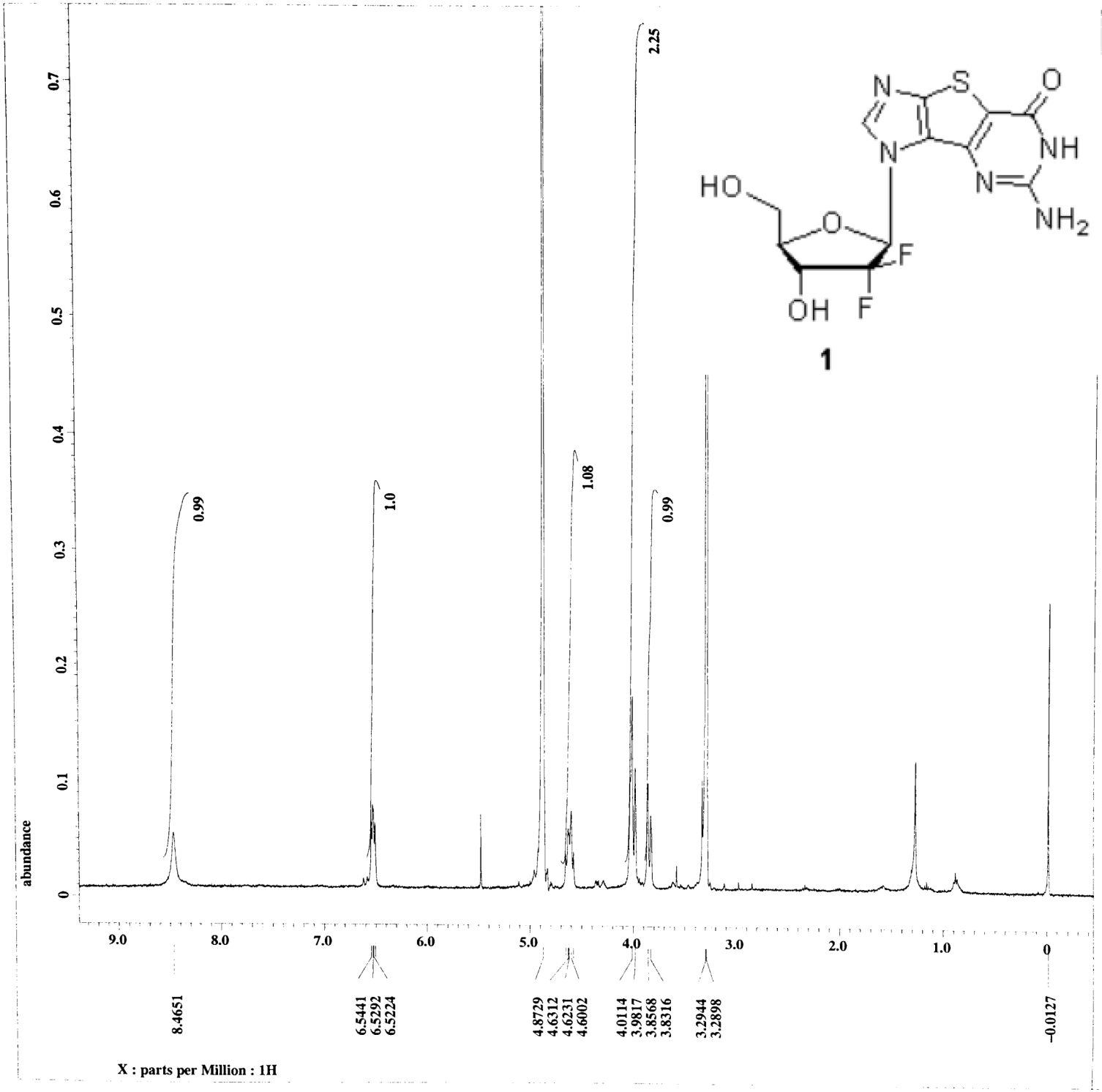

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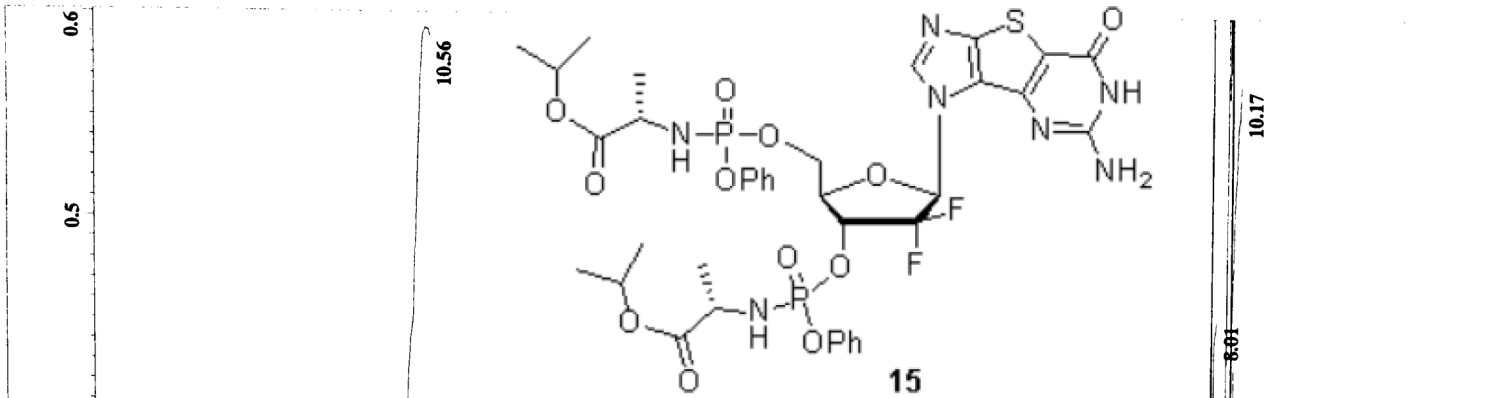

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Clipped	= FALSE
Mod_return	= 1
Scans	= 8
Total_scans	= 8
X_90_width	= 14.21[us]
X_acq_time	= 2.18365952[s]
X_angle	= 45[deg]
X_atn	= 3[dB]
X_pulse	= 7.105[us]
Irr_mode	= Off
Tri_mode	= Off
Dante_presat	= FALSE
Initial_wait	= 1[s]
Recvr_gain	= 42
Relaxation_delay	= 5[s]
Repetition_time	= 7.18365952[s]
Temp_get	= 21.3[dC]