A. Supplementary Data

Synthesis and evaluation of analogs of 5'-(((*Z*)-4-amino-2-butenyl)methylamino)-5'-deoxyadenosine (MDL 73811, or AbeAdo), an inhibitor of *S*-adenosylmethionine decarboxylase with antitrypanosomal activity

Anthony J. Brockway[a], Oleg A. Volkov[b], Casey C. Cosner[a], Karen S. MacMillan[a], Stephen A. Wring[c], Thomas E. Richardson[c], Michael Peel[c], Margaret A. Phillips[a,b,*], Jef K. De Brabander[a,*]

[a]Department of Biochemistry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9038, USA

[b]Department of Pharmacology, University of Texas Southwestern Medical Center, 6001 Forest Park Rd., Dallas, Texas 75390-9041, USA

[c]Scynexis, Inc. (now Avista Pharma Solutions), 3501 Tricenter Blvd, Suite C, Durham, NC 27713, USA

* Corresponding authors. E-mail: Margaret.Phillips@UTSouthwestern.edu and Jef.DeBrabander@UTSouthwestern.edu

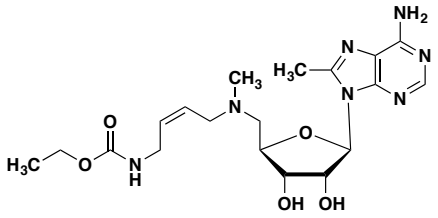
Table of Contents

Chemical synthesis and characterization data

Materials: Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Silica gel chromatographic purifications were performed by flash chromatography with silica gel (Sigma, grade 62, 60-200 mesh) packed in glass columns; the eluting solvent for each purification was determined by thin layer chromatography (TLC). Analytical TLC was performed on glass plates coated with 0.25 mm silica gel using UV for visualization. Experimental procedures and characterization for compound **1** and related intermediates (**9a**, **10a**) can be found in the Supporting Information of Brockway, et al. *Synthesis* **2016**, *48*, 2065–2068.

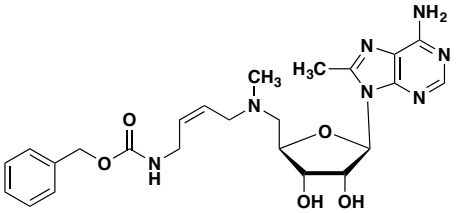
Instrumentation: ^{1}H NMR spectra were obtained on a 400 or 500 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent ($CDCl_3$, s, δ 7.26 ppm). Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), sep (septuplet), m (multiplet). Proton-decoupled ^{13}C NMR spectra were obtained on a 101 MHz NMR spectrometer. ^{13}C chemical shifts are reported relative to $CDCl_3$ (δ 77.2 ppm). IR frequencies are given in cm^{-1} and spectra were obtained on a FT-IR spectrometer. Electrospray ionization mass spectra (ESI-MS) were recorded on a Shimadzu 2010-LCMS. High-resolution mass spectrometry data was collected at the Shimadzu Center for Advanced Analytical Chemistry (SCAAC) at University of Texas at Arlington.

Ethyl ((*Z*)-4-((((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-8-methyl-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (3a)



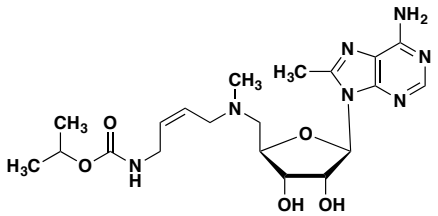
To a slurry of (2*R*,3*S*,4*R*,5*R*)-2-[[[(*Z*)-4-aminobut-2-enyl]-methyl-amino]methyl]-5-(6-amino-8-methyl-purin-9-yl)tetrahydrofuran-3,4-diol (**2**) (22.0 mg, 0.055 mmol) and triethylamine (15.3 µL, 0.110 mmol) in 2 mL THF at room temperature, ethyl(4-nitrophenyl)carbonate (12.7 mg, 0.055 mmol) in 1 mL THF was added. The resulting slurry was stirred for a total of 3 h at room temperature during which time the slurry thinned out to a light yellow solution. The crude reaction solution was coated onto silica gel and then subjected to flash chromatography (neat DCM to 5:95 MeOH:DCM to 1:9 MeOH:DCM to 2:8 MeOH:DCM to 1 liter 2:8 MeOH:DCM mixed with 10 mL Et_3N at 18 mL/min for 60 min). Compound **3a** (20 mg, 84%) was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (s, 1H), 5.93 (d, *J* = 5.2 Hz, 1H), 5.65–5.75 (m, 1H), 5.52–5.63 (m, 1H), 5.17 (s, 1H), 4.39 (d, *J* = 5.3 Hz, 1H), 4.22–4.36 (m, 1H), 4.02 (d, *J* = 7.1 Hz, 2H), 3.71 (d, *J* = 6.8 Hz, 2H), 3.48 (d, *J* = 5.0 Hz, 2H), 3.24–3.28 (m, 1H), 3.20 (q, *J* = 7.3 Hz, 2H), 3.04–3.12 (m, 1H), 2.64 (s, 3H), 2.53 (s, 3H), 1.31 (t, *J* = 7.3 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); LC/MS (ESI) calcd. for $C_{19}H_{30}N_7O_5$ $(M + H)^+$ 436.2, found 436; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{30}N_7O_5$, 436.2303; found, 436.2306.

Benzyl ((*Z*)-4-((((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-8-methyl-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (3b)



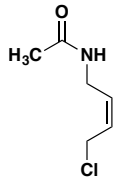
Prepared in a manner similar to that used for **3a**. Compound **3b** (44 mg, 71%) was isolated as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.31–7.35 (m, 4H), 7.25–7.30 (m, 1H), 5.88 (d, *J* = 4.8 Hz, 1H), 5.56 (d, *J* = 5.2 Hz, 2H), 5.19 (s, 1H), 5.05 (s, 2H), 4.38 (t, *J* = 5.4 Hz, 1H), 4.14–4.21 (m, 1H), 3.73 (d, *J* = 5.9 Hz, 2H), 3.20 (d, *J* = 5.4 Hz, 2H), 2.87–2.95 (m, 1H), 2.84 (br s, 1H), 2.63 (s, 3H), 2.31 (s, 3H), 1.24 (s, 1H); HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{32}N_7O_5$, 498.2459; found, 498.2460.

Isopropyl ((*Z*)-4-((((2*R*,3*S*,4*R*,5*R*)-5-(6-amino-8-methyl-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (3c)



Prepared in a manner similar to that used for **3a**. Compound **3c** (48 mg, 86%) was isolated as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 5.93–5.99 (m, 1H), 5.71–5.81 (m, 1H), 5.55–5.65 (m, 1H), 5.12–5.18 (m, 1H), 4.71–4.79 (m, 1H), 4.34–4.44 (m, 2H), 3.63–3.74 (m, 4H), 3.45–3.56 (m, 1H), 2.67 (s, 2H), 2.65 (s, 3H), 1.19 (d, *J* = 6.2 Hz, 6H); HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{20}H_{32}N_7O_5$, 450.2459; found, 450.2461.

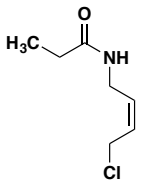
(*Z*)-*N*-(4-Chlorobut-2-en-1-yl)acetamide (7a)



Cis-4-Chloro-2-butenylamine hydrochloride (3.00 g, 21.12 mmol) was suspended in dry THF (100 mL) at 0 °C under an argon atmosphere. Acetic anhydride (3.00 mL, 31.7 mmol) and DIPEA (7.5 mL, 42.2 mmol) were successively added over several minutes. The suspension slowly dissolved and the reaction mixture was stirred overnight at 22 °C. TLC analysis (10% MeOH in CH_2Cl_2; $KMnO_4$ stain) showed the reaction to be complete. The mixture was poured into saturated $NaHCO_3$ (200 mL) and extracted with EtOAc. The organic extracts were then washed with 1 N HCl, separated, dried with $MgSO_4$, filtered, and concentrated to obtain 2.38 g (76%) of **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84–5.77 (m, 1H), 5.67–5.60 (m, 1H), 4.13 (d, *J* = 8.0 Hz, 2H), 3.96 (t, *J* = 6.0 Hz, 2H),

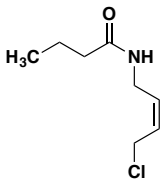
2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 130.2, 128.5, 38.6, 36.2, 23.2; IR (thin film) 3279, 3075, 1653, 1552; LC/MS (ESI) calcd for $C_6H_{11}ClNO$ $(M + H)^+$ 148.1, found 148.1.

(*Z*)-*N*-(4-Chlorobut-2-en-1-yl)propionamide (7b)



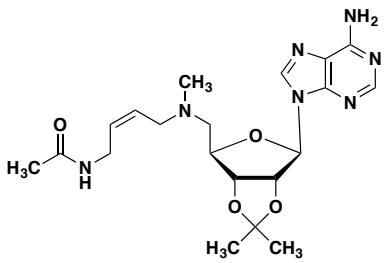
Cis-4-Chloro-2-butenylamine hydrochloride (3.00 g, 21.12 mmol) was suspended in dry THF (100 mL) at 0 °C under an argon atmosphere. Propionic anhydride (4.00 mL, 31.7 mmol) and DIPEA (7.5 mL, 42.2 mmol) were successively added over several minutes. The suspension slowly dissolved and the reaction mixture was stirred for 2 h at 22 °C. TLC analysis (10% MeOH in CH_2Cl_2; $KMnO_4$ stain) showed the reaction to be complete. The mixture was poured into saturated $NaHCO_3$ (200 mL) and extracted with EtOAc. The organic extracts were then washed with 1 N HCl, separated, dried with $MgSO_4$, filtered, and concentrated to afford **7b** (3.40 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (br s, 1H), 5.80–5.73 (m, 1H), 5.65–5.57 (m, 1H), 4.11 (d, *J* = 8.0 Hz, 2H), 3.96–3.91 (m, 2H), 2.21 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 130.3, 128.4, 38.7, 36.1, 29.5, 9.8; IR (thin film) 3288, 3075, 2978, 2881, 1645, 1547; LC/MS (ESI) calcd for $C_7H_{13}ClNO$ $(M + H)^+$ 162.0, found 162.0.

(*Z*)-*N*-(4-Chlorobut-2-en-1-yl)butyramide (7c)



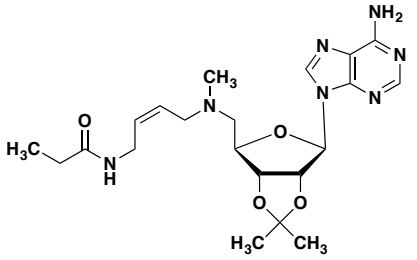
Cis-4-Chloro-2-butenylamine hydrochloride (3.00 g, 21.12 mmol) was suspended in dry THF (100 mL) at 0 °C under an argon atmosphere. Butyric anhydride (5.18 mL, 31.7 mmol) and DIPEA (7.5 mL, 42.2 mmol) were successively added over several minutes. The suspension slowly dissolved and the reaction mixture was stirred for 2 h at 22 °C. TLC analysis (10% MeOH in CH_2Cl_2; $KMnO_4$ stain) showed the reaction to be complete. The mixture was poured into saturated $NaHCO_3$ (200 mL) and extracted with EtOAc. The organic extracts were then washed with 1 N HCl, separated, dried with $MgSO_4$, filtered, and concentrated to afford **7c** as a yellow oil (3.11 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (br s, 1H), 5.68 (m, 1H), 5.55 (m, 1H), 4.06 (d, *J* = 7.6 Hz, 2H), 3.87 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.10 (t, *J* = 7.2 Hz, 2H), 1.58 (m, 2H), 0.86 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 127.9, 38.7, 38.3, 36.0, 19.1, 13.7; IR (thin film) 3289, 3074, 3035, 1713, 1644, 1548; LC/MS (ESI) calcd for $C_8H_{15}ClNO$ $(M + H)^+$ 176.1, found 176.1.

***N*-((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)acetamide (S1)**



Alkyl halide **7a** (127 mg, 0.86 mmol), amine **4** (250 mg, 0.78 mmol), sodium iodide (117 mg, 0.78), and triethylamine (0.11 mL, 0.78 mmol) were allowed to stir at room temperature for 16 h. Afterwards, NH_4Cl was used to wash the mixture, and then CH_2Cl_2 was used to extract the mixture. The mixture was concentrated and purified by Combi-Flash chromatography (12 g column; gradient of 100% CH_2Cl_2 → 10% (1% NH_4OH 99% MeOH) in CH_2Cl_2 over 10 minutes and then continued to run at 10% (1% NH_4OH 99% MeOH) in CH_2Cl_2 for another 10 minutes. This procedure yielded **S1** as a light orange solid (129 mg, 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.95 (s, 1H), 6.08 (d, *J* = 1.6 Hz, 1H), 6.01 (br s, 1H), 5.64 (br s, 2H), 5.52 (dd, *J* = 1.6, 6.4 Hz, 1H), 5.48 (app. sex, *J* = 3.6, 5.6 Hz, 2H), 4.96 (dd, *J* = 3.2, 6.4 Hz, 1H), 4.40 (app. sep, *J* = 3.6, 5.6, 8.8 Hz, 1H), 3.79 (t, *J* = 5.2 Hz, 2H), 3.01–2.98 (m, 2H), 2.62 (dd, *J* = 8.4, 13.2 Hz, 1H), 2.53 (dd, *J* = 5.6, 13.2 Hz, 1H), 2.27 (s, 3H), 1.95 (s, 3H), 1.61 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 155.4, 153.1, 149.3, 140.3, 129.6, 128.9, 120.4, 114.3, 91.0, 85.2, 84.0, 83.3, 58.7, 54.5, 42.6, 36.8, 27.1, 25.3, 23.2; IR (thin film) 3318, 3181, 2987, 1651, 1599, LC/MS (ESI) calcd for $C_{20}H_{30}N_7O_4$ $(M + H)^+$ 432.2, found 432.2; $[\alpha]^{20}_D$ = +7.2 (*c* = 0.2, $CHCl_3$).

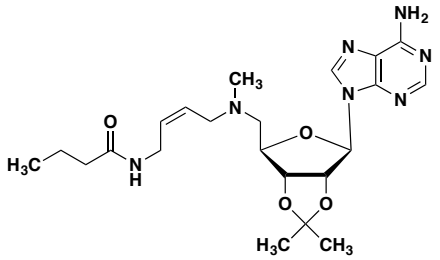
***N*-((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)propionamide (S2)**



In a 5-mL flask, the alkyl chloride **7b** (139 mg, 0.86 mmol), Et_3N (110 µL, 0.78 mmol), and NaI (129 mg, 0.86 mmol) were vigorously stirred in CH_3CN (3 mL) under argon at 22 °C. To this mixture was added amine **4** (250 mg, 0.78 mmol). The mixture was stirred and monitored by TLC analysis (1% NH_4OH, 9% MeOH, 90% CH_2Cl_2). After 4 h, no further product formation was observed, but starting material remained. The reaction mixture was diluted with CH_2Cl_2 and washed with NH_4Cl, dried, filtered, and concentrated. The crude material was purified by flash chromatography (12 g column; gradient of 100% CH_2Cl_2 → 10% MeOH (containing 1% NH_4OH) in CH_2Cl_2 over 18 min) to furnish 180 mg (51%) of the title compound **S2** as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.21 (s, 1H), 6.19 (d, *J* = 2.4 Hz, 1H), 5.52–5.38 (m, 4H), 5.00 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.39 (app. p, *J* = 4.0 Hz,

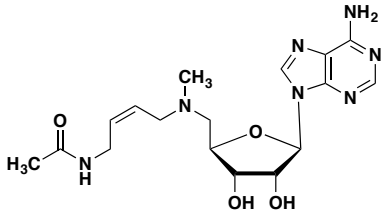
1H), 3.73 (d, *J* = 6.4 Hz, 2H), 3.10 (d, *J* = 6.4 Hz, 2H), 2.79–2.72 (m, 1H), 2.69–2.62 (m, 1H), 2.26 (s, 3H), 2.15 (q, *J* = 7.4 Hz, 2H), 1.59 (s, 3H), 1.38 (s, 3H), 1.09 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 155.9, 152.6, 148.8, 140.7, 129.4, 127.4, 119.2, 114.1, 90.2, 84.6, 83.6, 83.3, 58.5, 53.8, 41.3, 36.0, 28.7, 25.9, 24.1, 9.0; IR (thin film) 3317, 3181, 2982, 2939, 1645, 1598; LC/MS (ESI) calcd for $C_{21}H_{32}N_7O_4$ $(M + H)^+$ 446.1, found 446.1; $[\alpha]^{20}_D$ = +10.0 (*c* = 0.2, $CHCl_3$).

***N*-((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)butyramide (S3)**



Alkyl halide **7c** (302 mg, 1.72 mmol), amine **4** (500 mg, 1.56 mmol), sodium iodide (234 mg, 1.56), and triethylamine (0.22 mL, 1.56 mmol) were allowed to stir at room temperature for 16 h. Afterwards, NH_4Cl was used to wash the mixture, and then CH_2Cl_2 was used to extract the mixture. The mixture was concentrated and purified by Combi-Flash chromatography (12 g column; gradient of 100% CH_2Cl_2 → 10% (1% NH_4OH/99% MeOH) in CH_2Cl_2 over 10 minutes and then continued to run at 10% (1% NH_4OH/99% MeOH) in CH_2Cl_2 for another 10 minutes. This procedure yielded **S3** as a light orange solid (0.34 g, 47%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.21 (s, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 5.52–5.38 (m, 4H), 5.00 (dd, *J* = 3.2, 7.2 Hz, 1H), 4.39 (app, *J* = 4.8, 8.4 Hz, 1H), 3.74 (d, *J* = 6.8 Hz, 2H), 3.12 (d, *J* = 6.4 Hz, 2H), 2.80–2.75 (m, 1H), 2.71–2.66 (m, 1H), 2.27 (s, 3H), 2.12 (t, *J* = 8.0 Hz, 2H), 1.64–1.55 (m, 5H), 1.38 (s, 3H), 0.91 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 174.4, 156.0, 152.6, 148.8, 140.7, 129.5, 127.3, 119.2, 114.1, 90.2, 84.5, 83.6, 83.3, 58.4, 53.7, 41.3, 37.5, 36.0, 26.0, 24.1, 18.9, 12.6; IR (thin film) 3320, 2962, 2404, 1617, LC/MS (ESI) calcd for $C_{22}H_{34}N_7O_4$ $(M + H)^+$ 460.2, found 460.2; $[\alpha]^{20}_D$ = +11.4 (*c* = 0.25, $CHCl_3$).

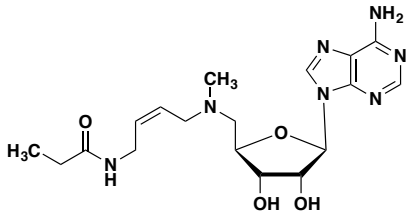
***N*-((*Z*)-4-((((2*R*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(methyl)amino)but-2-en-1-yl)acetamide (5a)**



Amide **S1** (122 mg, 0.283 mmol) was added to 4 mL of 1 M H_2SO_4 and allowed to stir for 16 h at room temperature. Afterwards, NaOH was used to neutralize the mixture, and the solvent was removed *in vacuo*. The resultant white solid was dissolved in a minimal amount of methanol and purified by Combi-Flash chromatography (4 g column; 35% (1% NH_4OH/99% MeOH) in CH_2Cl_2 over 20 min). This procedure yielded 63.6 mg (57% yield) of **5a** as a white

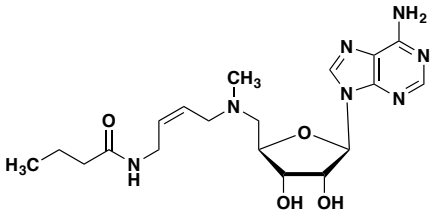
solid; ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.20 (s, 1H), 5.99 (d, *J* = 4.4 Hz, 1H), 5.63–5.55 (m, 2H), 4.70 (app. t, *J* = 4.4 Hz, 1H), 4.25–4.18 (m, 2H), 3.80 (d, *J* = 6.0 Hz, 2H), 3.34 (s, 1H), 3.22–3.17 (m, 2H), 2.85–2.81 (m, 2H), 2.32 (d, *J* = 2.4 Hz, 3H), 1.90 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 171.5, 155.9, 152.4, 149.1, 140.1, 129.0, 128.0, 119.2, 89.3, 81.8, 73.3, 72.3, 58.9, 53.8, 41.6, 36.2, 21.0; IR (thin film) 3320, 3196, 2936, 1645, 1602; LC/MS (ESI) calcd for $C_{17}H_{26}N_7O_4$ $(M + H)^+$ 392.2, found 392.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}N_7O_4$, 392.2041; found, 392.2036; $[\alpha]^{20}_D$ = –3.81 (*c* = 0.21, MeOH).

***N*-((*Z*)-4-((((2*R*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(methyl)amino)but-2-en-1-yl)propionamide (5b)**



In a vial, the alkylated nucleoside **S2** (60 mg, 0.135 mmol) was dissolved in 1 M H_2SO_4 (1.5 mL) and MeOH (2 drops) was added to ensure homogeneity. The reaction was stirred overnight at 22 °C and TLC analysis (1% NH_4OH, 9% MeOH, 90% CH_2Cl_2; neutralize an aliquot of the mixture before analyzing) showed complete consumption of starting material. The pH of the reaction mixture was adjusted to pH 10.0 by addition of 1 N NaOH and the mixture was concentrated. The crude material was purified by Combi-Flash chromatography (4 g column; 35% MeOH (with 1% NH_4OH) in CH_2Cl_2 for 15 min) to furnish 32 mg (59%) of **5b** as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.19 (s, 1H), 5.99 (d, *J* = 4.4 Hz, 1H), 5.63–5.53 (m, 2H), 4.70 (dd, *J* = 5.2, 4.4 Hz, 1H), 4.26–4.18 (m, 2H), 3.80 (d, *J* = 5.6 Hz, 2H), 3.30 (app. p, *J* = 1.6 Hz, 1H), 3.18 (d, *J* = 6.0 Hz, 2H), 2.82 (d, *J* = 5.2 Hz, 2H), 2.31 (s, 3H), 2.15 (q, *J* = 7.6 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 176.7, 157.3, 153.9, 150.5, 141.5, 130.5, 129.4, 120.6, 90.7, 83.3, 74.7, 73.7, 60.4, 55.3, 43.1, 37.5, 30.1, 10.5; IR (thin film) 3322, 2977, 2940, 2418, 1621, 1575; LC/MS (ESI) calcd for $C_{18}H_{28}N_7O_4$ $(M + H)^+$ 406.2, found 406.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}N_7O_4$, 406.2197; found, 406.2190.

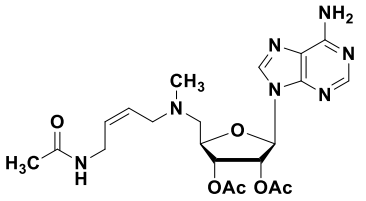
***N*-((*Z*)-4-((((2*R*,3*S*,4*R*,5*R*)-5-(6-Amino-9*H*-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl)(methyl)amino)but-2-en-1-yl)butyramide (5c)**



Amide **S3** (132 mg, 0.286 mmol) was added to 4 mL of 1 M H_2SO_4 and allowed to stir for 16 hours. Afterwards, NaOH was used to neutralize the mixture, and the solvent was removed *in vacuo*. The resultant white solid was dissolved in a minimal amount of methanol and purified by Combi-Flash chromatography (4 g column; 35% (1% NH_4OH/99% MeOH) in CH_2Cl_2 over 20 min). This procedure yielded 82.5 mg (68% yield) of the title compound **5c**

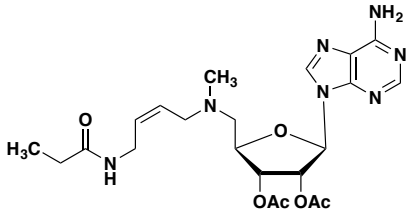
as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.20 (s, 1H), 5.99 (d, *J* = 4.4 Hz, 1H), 5.64–5.54 (m, 2H), 4.70 (dd, *J* = 4.4, 4.8 Hz, 1H), 4.25–4.18 (m, 2H), 3.81 (d, *J* = 5.2 Hz, 2H), 3.30 (p, *J* = 1.6 Hz, 3H), 3.20 (d, *J* = 5.6 Hz, 2H), 2.83 (d, *J* = 5.2 Hz, 2H), 2.32 (s, 3H), 2.12 (t, *J* = 7.6 Hz, 2H), 1.60 (app. sex, *J* = 7.6 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 174.4, 155.9, 152.4, 149.1, 140.1, 129.2, 127.8, 119.2, 89.3, 81.8, 73.3, 72.3, 58.9, 53.8, 41.6, 37.5, 36.0, 18.9, 12.5; IR (thin film) 3319, 2962, 2408, 1619; LC/MS (ESI) calcd for $C_{19}H_{30}N_7O_4$ (M + H)$^+$ 420.2, found 420.2; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{19}H_{30}N_7O_4$, 420.2354; found, 430.2355; $[\alpha]^{20}_D$ = –4.80 (*c* = 0.25, MeOH).

(2*R*,3*R*,4*R*,5*R*)-2-((((*Z*)-4-Acetamidobut-2-en-1-yl)(methyl)amino)methyl)-5-(6-amino-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (6a)



Amide **5a** (39.0 mg, 0.10 mmol), acetic anhydride (25.4 μL, 0.23 mmol), and DMAP on Polystyrene (35 mg) were allowed to stir in acetonitrile at room temperature. After 3 h, TLC (1% NH_4OH, 9% MeOH, 90% DCM) revealed total consumption of starting material and monoacylated intermediate. It was then washed with $NaHCO_3$, extracted with EtOAc, dried with $MgSO_4$, filtered through Celite, concentrated, and purified by Combi-Flash chromatography (4g column; gradient from 0–10% (1% NH_4OH 99% MeOH) in CH_2Cl_2 over 25 min). This procedure yielded 18.7 mg (39.9% yield) of the title compound **6a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.01 (s, 1H), 6.15 (d, *J* = 5.6 Hz, 1H), 6.00 (br s, 1H), 5.95 (t, *J* = 5.6 Hz, 1H), 5.85 (br s, 2H), 5.69–5.53 (m, 3H), 4.30 (dt, *J* = 6.5, 4.3 Hz, 1H), 3.87 (t, *J* = 6.0 Hz, 2H), 3.11 (t, *J* = 5.4 Hz, 2H), 2.88–2.69 (m, 2H), 2.31 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 1.93 (d, *J* = 1.2 Hz, 3H); HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{21}H_{30}N_7O_6$, 476.2252; found, 476.2247.

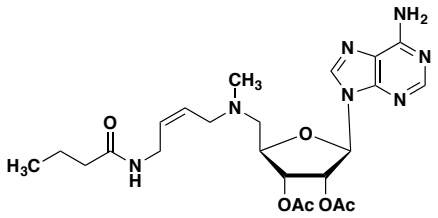
(2*R*,3*R*,4*R*,5*R*)-2-(6-Amino-9*H*-purin-9-yl)-5-((methyl((*Z*)-4-propionamidobut-2-en-1-yl)amino)methyl)tetrahydrofuran-3,4-diyl diacetate (6b)



Amide **5b** (42.9 mg, 0.106 mmol), acetic anhydride (27 μL, 0.244 mmol), and DMAP on Polystyrene (35 mg) were allowed to stir in acetonitrile at room temperature. After 3 h, TLC (1% NH_4OH, 9% MeOH, 90% DCM) revealed total consumption of starting material and monoacylated intermediate. It was then washed with $NaHCO_3$, extracted with EtOAc, dried with $MgSO_4$, filtered through Celite, concentrated, and purified by Combi-Flash chromatography (4 g column; gradient from 0–10% (1% NH_4OH/99% MeOH) in CH_2Cl_2 over 25 min). This procedure yielded 25.2 mg (49.0% yield) of the title compound **6b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.02 (s, 1H), 6.15 (d, *J* = 5.6 Hz,

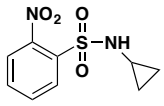
1H), 5.94 (t, *J* = 5.6 Hz, 1H), 5.92–5.80 (m, 3H), 5.67–5.54 (m, 3H), 5.29 (s, 1H), 4.32–4.28 (m, 1H), 3.88 (t, *J* = 6.0 Hz, 2H), 3.12 (t, *J* = 5.6 Hz, 2H), 2.83 (dd, *J* = 6.8, 14.0 Hz, 1H), 2.74 (dd, *J* = 4.4, 14.0 Hz, 1H), 2.31 (s, 3H), 2.19–2.13 (m, 4H), 2.06 (s, 3H), 1.12 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 169.8, 169.5, 155.5, 153.3, 149.8, 139.3, 129.5, 129.3, 120.1, 85.9, 81.3, 72.8, 72.1, 58.1, 54.8, 43.7, 36.6, 29.6, 20.7, 20.5, 9.8; IR (thin film) 3325, 2917, 1748, 1644, 1599,; LC/MS (ESI) calcd for $C_{22}H_{32}N_7O_6$ $(M + H)^+$ 490.2, found 490.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{32}N_7O_6$, 490.2409; found, 490.2404; $[\alpha]^{20}_D$ = –17.9 (*c* = 0.19, $CHCl_3$).

(2*R*,3*R*,4*R*,5*R*)-2-(6-Amino-9*H*-purin-9-yl)-5-((((*Z*)-4-butyramidobut-2-en-1-yl)(methyl)amino)methyl)tetrahydrofuran-3,4-diyl diacetate (6c)



Amide **5c** (39.5 mg, 0.094 mmol), acetic anhydride (18.7 μL, 0.198 mmol), and DMAP on Polystyrene (30 mg) were allowed to stir in acetonitrile at room temperature. After 20 h, TLC (1% NH_4OH, 9% MeOH, 90% DCM) revealed remaining starting material. Acetic anhydride (4.45 μL, 0.047 mmol) was added and allowed to stir for 3 h. TLC revealed total consumption of starting material, but there was still the monoacylated spot; acetic anhydride (2.0 μL, 0.021 mmol) was added and allowed to react for another 15 h. It was washed with $NaHCO_3$, extracted with EtOAc, dried with $MgSO_4$, filtered through Celite, concentrated, and purified by Combi-Flash chromatography (4 g column; gradient from 0–10% (1% NH_4OH/99% MeOH) in CH_2Cl_2 over 25 min). This procedure yielded 24 mg (50.7% yield) of the title compound **6c** as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.01 (s, 1H), 6.15 (d, *J* = 5.2 Hz, 1H), 5.94 (t, *J* = 5.2 Hz, 1H), 5.85 (br s, 1H), 5.71–5.54 (m, 5H), 4.31 (app. q, *J* = 4.8 Hz, 1H), 3.89 (t, *J* = 6.0 Hz, 2H), 3.12 (t, *J* = 5.2 Hz, 2H), 2.84 (dd, *J* = 6.8, 14.0 Hz, 1H), 2.75 (dd, *J* = 4.0, 13.2 Hz, 1H), 2.32 (s, 3H), 2.15–2.10 (m, 5H), 2.06 (s, 3H), 1.64 (app. sex, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 169.8, 169.5, 155.4, 153.3, 150.0, 139.3, 129.5, 129.3, 120.1, 85.9, 81.4, 72.8, 72.1, 58.1, 54.8, 43.7, 38.6, 36.6, 20.7, 20.5, 19.1, 13.8; IR (thin film) 3324, 2919, 1748, 1644, 1599; LC/MS (ESI) calcd for $C_{23}H_{33}N_7O_6$ $(M + H)^+$ 504.2, found 504.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{23}H_{34}N_7O_6$, 504.2565; found, 504.2568; $[\alpha]^{20}_D$ = –3.24 (*c* = 0.19, $CHCl_3$).

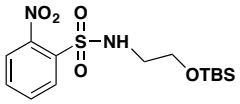
***N*-Cyclopropyl-2-nitrobenzenesulfonamide (S4)**



o-Nitrobenzenesulfonyl chloride (3.0 g, 13.5 mmol) was dissolved in 30 mL of DCM and cooled to 0 °C using an ice-bath. A mixture of Et_3N (2.1 mL, 14.9 mmol) and cyclopropylamine (1.03 mL, 14.9 mmol) in DCM (10 mL) was slowly added and stirring was continued at room temperature for 3–4 h. It was then diluted with DCM (50 mL) and washed with half saturated NaCl in water. The layers were separated and the organic layer was dried over

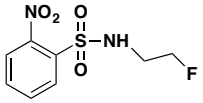
anhydrous $MgSO_4$, filtered, and then concentrated to dryness to yield 3.32 g of the desired sulfonamide **S4** (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.25 (m, 1H), 7.84–7.89 (m, 1H), 7.74–7.80 (m, 2H), 5.59 (br s, 1H), 2.34–2.39 (m, 1H), 0.66–0.78 (m, 4H).

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-2-nitrobenzenesulfonamide (S5)**



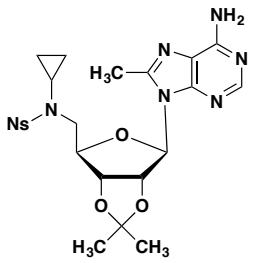
Prepared in a manner similar to that used for **S4**. Product **S5** was obtained (4.5 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.15 (m, 1H), 7.87–7.90 (m, 1H), 7.74–7.77 (m, 2H), 5.80 (m, 1H), 3.70 (t, J = 5.2 Hz, 2H), 3.19–3.23 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H).

***N*-(2-Fluoroethyl)-2-nitrobenzenesulfonamide (S6)**



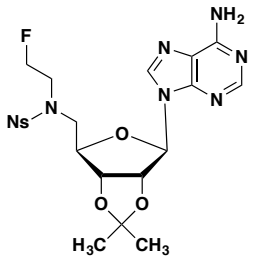
Prepared in a manner similar to that used for **S4**. 2.21 g of product **S6** was obtained (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.16 (m, 1H), 7.89–7.92 (m, 1H), 7.75–7.79 (m, 2H), 5.71 (m, 1H), 5.51 (dt, $J_{F\text{-}H}$ = 46.8 Hz, $J_{H\text{-}H}$ = 4.9 Hz, 2H), 3.48–3.52 (m, 1H), 3.41–3.45 (m, 1H).

***N*-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-8-methyl-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-cyclopropyl-2-nitrobenzenesulfonamide (S7)**



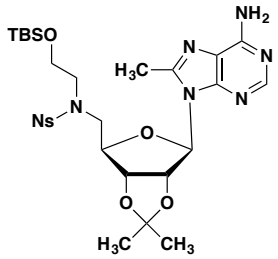
To a solution of acetonide-protected 8-methyl-adenosine **8b** (1.3 g, 4.045 mmol) in 40 mL dry THF was added *N*-cyclopropyl-2-nitrobenzenesulfonamide (**S4**) (2.0 g, 8.1 mmol) in 10 mL of THF, followed by triphenylphosphine (2.12 g, 8.1 mmol) and the resulting mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (1.6 mL, 8.1 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography, eluting with a gradient of 0–10% MeOH/DCM. Fractions containing the desired product were pooled, concentrated, and dried under vacuum to yield to 0.83 g of **S7** (38% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.98–8.00 (m, 1H), 7.51–7.63 (m, 3H), 6.04 (br s, 1H), 5.77 (m, 1H), 5.49 (br s, 2H), 5.23 (dd, J = 6.2, 3.0 Hz, 1H), 4.59–4.63 (m, 1H), 3.43–3.68 (m, 2H), 2.65 (s, 3H), 2.46–2.52 (m, 1H), 1.62 (s, 3H), 1.42 (s, 3H), 0.36–0.53 (m, 4H).

***N*-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-(2-fluoroethyl)-2-nitrobenzenesulfonamide (S8)**



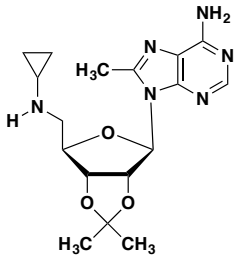
Compound **S8** was prepared in a manner similar to that used for **S7** to afford 0.36 g of product (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.85–7.87 (m, 1H), 7.81 (s, 1H), 7.51–7.57 (m, 2H), 7.41–7.45 (m, 1H), 5.98 (d, *J* = 1.9 Hz, 1H), 5.70 (br s, 2H), 5.38 (dd, *J* = 6.4, 2.0 Hz, 1H), 5.07 (dd, *J* = 6.4, 3.9 Hz, 1H), 4.52 (t, *J* = 4.8 Hz, 1H), 4.39–4.46 (m, 2H), 3.57–3.90 (m, 4H), 3.34–3.41 (m, 1H), 1.58 (s, 3H), 1.36 (s, 3H).

***N*-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-8-methyl-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-nitrobenzenesulfonamide (S9)**



Compound **S9** was prepared in a manner similar to that used for **S7** to afford 0.3 g of product (58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.81–7.83 (m, 1H), 7.44–7.50 (m, 2H), 7.32–7.36 (m, 1H), 5.90 (d, *J* = 1.7 Hz, 1H), 5.52 (dd, *J* = 6.3, 1.6 Hz, 1H), 5.45 (br s, 2H), 5.07 (dd, *J* = 6.3, 3.9 Hz, 1H), 4.38–4.42 (m, 1H), 3.77–3.82 (m, 1H), 3.67–3.70 (t, *J* = 5.9 Hz, 2H), 3.55–3.61 (m, 2H), 3.34–3.41 (m, 1H), 2.62 (s, 3H), 1.57 (s, 3H), 1.36 (s, 3H), 0.84 (s, 9H), –0.01 (s, 6H).

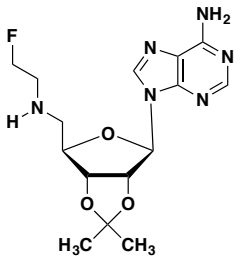
9-((3a*R*,4*R*,6*R*,6a*R*)-6-((Cyclopropylamino)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-8-methyl-9*H*-purin-6-amine (9c)



To a solution of **S7** (1.0 g, 1.83 mmol) in 37 mL dry DMF was added lithium hydroxide mono hydrate (0.35 g, 8.34 mmol), followed by thioglycolic acid (0.29 mL, 4.17 mmol) and the resulting mixture was stirred at room temperature

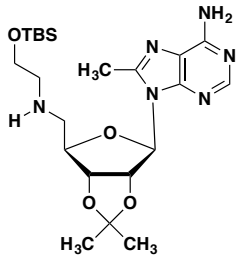
overnight. The reaction mixture was diluted with water (70 mL) and extracted with ethyl acetate (10 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), and then concentrated. The residue was dissolved in methanol and silica gel (10 g) was added. The solvent was removed under reduced pressure and the powder was loaded on 80 g silica gel cartridge, eluting with a gradient of 0–10% MeOH/DCM. Fractions containing the desired product were pooled, concentrated, and dried under vacuum to yield 0.60 g of the desired product (91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.17 (br s, 2H), 6.01 (d, J = 2.5 Hz, 1H), 5.75 (dd, J = 6.4, 2.5 Hz, 1H), 4.98 (dd, J = 6.4, 3.1 Hz, 1H), 4.16 (dt, J = 6.3, 3.1 Hz, 1H), 2.58–2.69 (m, 2H), 2.56 (s, 3H), 1.94–1.99 (m, 1H), 1.53 (s, 3H), 1.32 (s, 3H), 0.23–0.31 (m, 2H), 0.09–0.13 (m, 2H).

9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((2-Fluoroethyl)amino)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (9b)



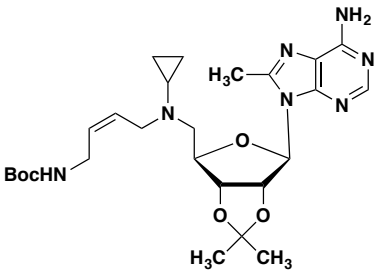
Compound **9b** was synthesized in a manner similar to that used for **9c** to afford 0.17 g of product (85% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.15 (s, 1H), 7.32 (br s, 2H), 6.08 (d, J = 3.1 Hz, 1H), 5.45 (dd, J = 6.3, 3.1 Hz, 1H), 4.97 (dd, J = 6.3, 3.0 Hz, 1H), 4.41 (dt, $J_{F\text{-}H}$ = 47.8 Hz, $J_{H\text{-}H}$ = 5.0 Hz, 1H), 4.21 (dt, J = 5.9, 2.8 Hz, 1H), 2.81–2.96 (m, 4H), 1.54 (s, 3H), 1.32 (s, 3H).

9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((2-((*Tert*-butyldimethylsilyl)oxy)ethyl)amino)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-8-methyl-9*H*-purin-6-amine (9d)



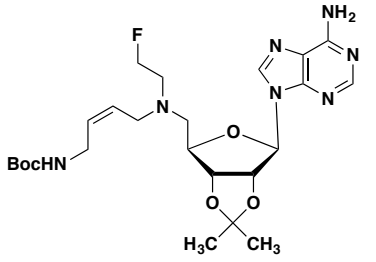
Compound **9d** was synthesized in a manner similar to that used for **9c** to afford 0.167 g of product (77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.16 (br s, 2H), 6.01 (d, J = 2.8 Hz, 1H), 5.71 (dd, J = 6.3, 2.7 Hz, 1H), 4.98 (dd, J = 6.4, 3.4 Hz, 1H), 4.11–4.15 (m, 1H), 3.50–3.55 (m, 2H), 2.61–2.72 (m, 2H), 2.55 (s, 3H), 1.54 (s, 3H), 1.32 (s, 3H), 0.78 (s, 9H), –0.03 (s, 3H), –0.04 (s, 3H).

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-8-methyl-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(cyclopropyl)amino)but-2-en-1-yl)carbamate (10c)**



To a solution of **9c** (0.2 g, 0.56 mmol) in 15 mL dry MeCN was added (*Z*)-*tert*-butyl 4-chlorobut-2-enylcarbamate **13** (0.12 g, 0.56 mmol) followed by DIPEA (0.097 mL, 0.56 mmol) and potassium iodide (0.092 g, 0.56 mmol) and the resulting mixture was stirred at room temperature overnight. Silica gel (5.0 g) was then added and the solvent was removed under reduced pressure and the powder was loaded onto a 40 g silica gel cartridge, eluting with a gradient of 0–10% methanol in DCM. Fractions containing the desired product were pooled, concentrated, and re-dissolved in ethyl acetate (50 mL), washed with sat-$NaHCO_3$ (1 × 50 mL), brine (1 × 25 mL), dried over anhydrous Na_2SO_4, and then concentrated. After drying under vacuum, 0.24 g of **10c** was obtained (81.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 5.99 (d, *J* = 1.6 Hz, 1H), 5.83 (dd, *J* = 6.4, 1.4 Hz, 1H), 5.47 (br s, 2H), 5.41–5.43 (m, 2H), 5.07 (dd, *J* = 6.4, 3.2 Hz, 1H), 4.81 (br s, 1H), 4.49–4.53 (m, 1H), 3.68 (br s, 2H), 3.14–3.25 (m, 2H), 2.66–2.72 (m, 2H), 2.64 (s, 3H), 1.71–1.76 (m, 1H), 1.62 (s, 3H), 1.45 (s, 9H), 1.41 (s, 3H), 0.36–0.45 (m, 4H); LC/MS (ESI) calcd for $C_{26}H_{40}N_7O_5$ $(M + H)^+$ 530.3, found 530.1; HRMS (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{39}N_7O_5Na$, 552.2905; found, 552.2911.

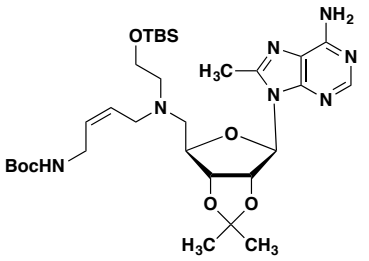
***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(2-fluoroethyl)amino)but-2-en-1-yl)carbamate (10b)**



10b

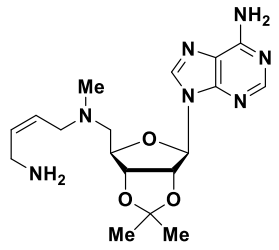
Compound **10b** was synthesized in a manner similar to that used for **10c** to afford 0.48 g of (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.95 (s, 1H), 6.09 (br s, 1H), 5.64 (br s, 2H), 5.51–5.53 (m, 2H), 5.49 (dd, *J* = 6.5, 3.1 Hz, 1H), 5.00 (dd, *J* = 6.5, 3.3 Hz, 1H), 4.93 (br s, 1H), 4.54 (t, *J* = 5.0 Hz, 1H), 4.42 (t, *J* = 5.0 Hz, 1H), 4.34–4.39 (m, 1H), 3.73 (br s, 2H), 3.22–3.24 (m, 2H), 2.86 (t, *J* = 5.1 Hz, 1H), 2.79 (t, *J* = 5.1 Hz, 1H), 2.74–2.82 (m, 2H), 2.64 (s, 3H), 1.62 (s, 3H), 1.45 (s, 9H), 1.41 (s, 3H).

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-8-methyl-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)but-2-en-1-yl)carbamate (10d)**



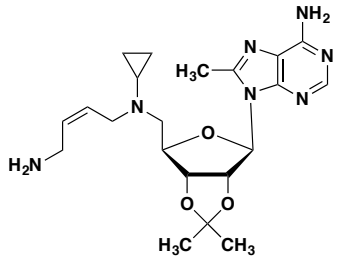
Compound **10d** was synthesized in a manner similar to that used for **10c** to afford 1.01 g of product (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 5.98 (d, *J* = 1.8 Hz, 1H), 5.77–5.78 (m, 1H), 5.45 (br s, 4H), 5.09 (dd, *J* = 6.3, 3.5 Hz, 1H), 4.83 (br s, 1H), 4.27–4.31 (m, 1H), 3.68 (br s, 2H), 3.08–3.18 (m, 2H), 2.57–2.72 (m, 4H), 2.64 (s, 3H), 1.61 (s, 3H), 1.45 (s, 9H), 1.41 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H).

(*Z*)-*N*^{1}-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*^{1}-methylbut-2-ene-1,4-diamine (11a)



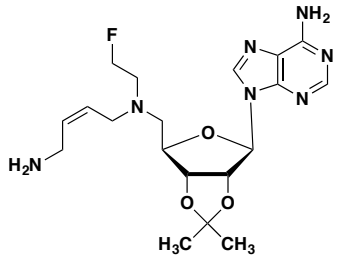
To a stirred solution of carbamate **10a** (0.15 g, 0.31 mmol) in 2 mL of anhydrous DCM was added 2,6-lutidine (0.18 mL, 1.53 mmol) followed by TMSOTf (0.22 mL, 1.23 mmoL). The solution was stirred at rt for one hour and was then quenched with 5 mL of MeOH. The solution was then concentrated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography gradient from 0–10% (1% NH_4OH/99% MeOH) in CH_2Cl_2 to afford amine **11a** as a foam (0.13 g, 95%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1H), 8.27 (s, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 5.84 (m, 1H), 5.57 (m, 1H), 5.46 (dd, *J* = 6.3, 2.4 Hz, 1H), 5.15 (dd, *J* = 6.3, 3.3 Hz, 1H), 4.67 (m, 1H), 3.97–3.76 (m, 4H), 3.68 (m, 2H), 3.51 (m, 1H), 2.84 (s, 3H), 1.61 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.1, 152.7, 148.5, 140.9, 128.9, 121.9, 119.4, 114.7, 90.8, 83.8, 82.7, 81.8, 57.2, 53.1, 48.0, 39.9, 35.9, 25.9, 24.0; LC/MS (ESI) calcd for $C_{18}H_{28}N_7O_3$ $(M + H)^+$ 390.2, found 390.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{28}N_7O_3$, 390.2248; found, 390.2246.

(*Z*)-*N*^{1}-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-8-methyl-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*^{1}-cyclopropylbut-2-ene-1,4-diamine (11c)



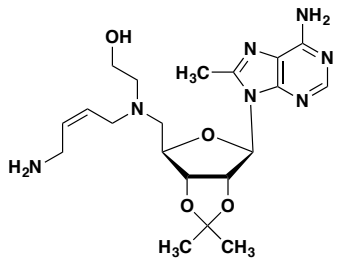
To a solution of **10c** (0.2 g, 0.38 mmol) in 15 mL dry DCM was added TFA (3.5 mL) and the resulting mixture was stirred at 0 °C for 1.5 h. The solvent was removed under reduced pressure and the residue was washed with diethyl ether (20 mL). The supernatant was decanted and the solid was dissolved in methanol (10 mL) and stirred with 0.2 g of $NaHCO_3$ in water (2.0 mL) for 30 min. Silica gel (10 g) was added, the solvent was removed under reduced pressure, and the powder was loaded onto a 40 g silica gel cartridge, eluting first with 4:1:0.1 of DCM/MeOH/NH_4OH and then 1:0.1 MeOH/NH_4OH. Fractions containing the desired product were pooled, concentrated, and lyophilized to yield 100 mg of the product **11c** as its free base (61.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.74 (br s, 2H), 7.16 (br s, 2H), 6.06 (d, *J* = 1.9 Hz, 1H), 5.81 (dd, *J* = 6.4, 1.8 Hz, 1H), 5.59–5.65 (m, 1H), 5.42–5.48 (m, 1H), 4.97 (dd, *J* = 6.3, 2.9 Hz, 1H), 4.35 (dt, *J* = 7.2, 2.9 Hz, 1H), 3.39–3.41 (m, 2H), 3.12–3.24 (m, 2H), 2.52–2.65 (m, 2H), 2.55 (s, 3H), 1.72–1.77 (m, 1H), 1.53 (s, 3H), 1.33 (s, 3H), 0.22–0.37 (m, 4H); LC/MS (ESI) calcd for $C_{21}H_{32}N_7O_3$ $(M + H)^+$ 430.3, found 430.0; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{32}N_7O_3$, 430.2561; found, 430.2560.

(*Z*)-*N*^{1}-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*^{1}-(2-fluoroethyl)but-2-ene-1,4-diamine (11b)



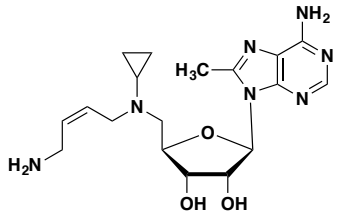
Compound **11b** was synthesized in a manner similar to that used for **11c t**o afford 95 mg of product (48.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.16 (s, 1H), 7.96 (br s, 2H), 7.33 (br s, 2H), 6.15 (d, *J* = 2.4 Hz, 1H), 5.64–5.70 (m, 1H), 5.51–5.55 (m, 1H), 5.48 (dd, *J* = 6.4, 2.3 Hz, 1H), 4.96 (dd, *J* = 6.3, 3.2 Hz, 1H), 4.46–4.50 (m, 1H), 4.34–4.38 (m, 1H), 4.22–4.26 (dt, *J* = 6.9, 2.9 Hz, 1H), 3.44–3.46 (m, 2H), 3.17–3.20 (m, 2H), 2.59–2.78 (m, 4H), 1.53 (s, 3H), 1.33 (s, 3H); LC/MS (ESI) calcd for $C_{19}H_{29}FN_7O_3$ $(M + H)^+$ 422.2, found 422.0; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{29}N_7O_3F$, 422.2310; found, 422.2308.

2-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-8-methyl-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)((*Z*)-4-aminobut-2-en-1-yl)amino)ethan-1-ol (11d)



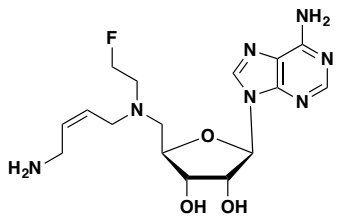
Compound **11d** was synthesized in a manner similar to that used for **11c** to afford 0.2 g of product (65% yield). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.16 (br s, 2H), 6.05 (d, *J* = 2.0 Hz, 1H), 5.76–5.78 (m, 1H), 5.59–5.65 (m, 1H), 5.42–5.48 (m, 1H), 5.19–5.25 (m, 1H), 5.01 (dd, *J* = 6.3, 3.1 Hz, 1H), 4.17 (dt, *J* = 7.0, 3.0 Hz, 1H), 3.36 (t, *J* = 6.4 Hz, 2H), 2.95–3.08 (m, 4H), 2.35–2.59 (m, 4H), 2.55 (s, 3H), 1.53 (s, 3H), 1.33 (s, 3H); LC/MS (ESI) calcd for $C_{20}H_{32}N_7O_4$ (M + H)$^+$ 434.2, found 434.0; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{20}H_{32}N_7O_4$, 434.2510; found, 434.2508.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-8-methyl-9*H*-purin-9-yl)-5-((((*Z*)-4-aminobut-2-en-1-yl)(cyclopropyl)amino)methyl)tetrahydrofuran-3,4-diol (12c)



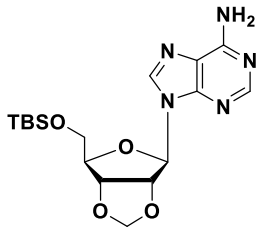
To a solution of **10c** (0.2 g, 0.38 mmol) in 5 mL anhydrous methanol was added 4.0 N HCl in 1,4-dioxane (1.0 mL) and the resulting mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the residue was washed with diethyl ether (20 mL). The supernatant was decanted and the solid was dissolved in methanol (10 mL) and stirred with 0.2 g of $NaHCO_3$ in water (2.0 mL) for 30 min. Silica gel (10 g) was added, the solvent was removed under reduced pressure and the powder was loaded onto a 40 g silica gel cartridge, eluting first with 4:1:0.1 of DCM/MeOH/NH_4OH and then 1:0.1 MeOH/NH_4OH. Fractions containing the desired product were pooled, concentrated, and lyophilized to yield 94.5 mg of the product **12c** as its free base (64.3%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.09 (br s, 2H), 5.74 (d, *J* = 5.7 Hz, 1H), 5.36–5.55 (m, 2H), 5.11–5.13 (m, 1H), 4.08–4.11 (m, 2H), 3.12–3.20 (m, 4H), 2.85–2.90 (m, 1H), 2.71–2.76 (m, 1H), 2.53 (s, 3H), 1.80–1.85 (m, 1H), 0.37–0.41 (m, 2H), 0.27–0.30 (m, 2H); LC/MS (ESI) calcd for $C_{18}H_{28}N_7O_3$ (M + H)$^+$ 390.2, found 390.0; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{18}H_{28}N_7O_3$, 390.2248; found, 390.2241.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-9*H*-purin-9-yl)-5-((((*Z*)-4-aminobut-2-en-1-yl)(2-fluoroethyl)amino)methyl)tetrahydrofuran-3,4-diol (12b)



Compound **12b** was synthesized in a manner similar to that used for **12c** to afford 120 mg of product (68.4% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.23 (s, 1H), 6.01 (d, *J* = 4.2 Hz, 1H), 5.96–6.00 (m, 1H), 5.76–5.82 (m, 1H), 4.74 (dd, *J* = 5.1, 4.3 Hz, 1H), 4.67–4.71 (m, 1H), 4.56–4.59 (m, 1H), 4.28–4.36 (m, 2H), 3.45–3.59 (m, 4H), 2.96–3.24 (m, 4H); LC/MS (ESI) calcd for $C_{16}H_{25}FN_7O_3$ $(M + H)^+$ 382.2, found 382.0; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{25}N_7O_3F$, 382.1997; found, 382.1992.

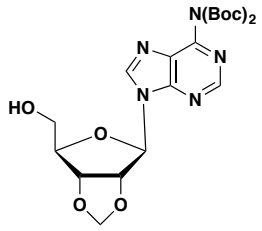
9-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*Tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (15)



To a stirred solution of adenosine **14** (20.0 g, 74.9 mmol) in 100 mL of DMF was added imidazole (5.59 g, 82.4 mmol), the solution was cooled to 0 °C and then TBSCl (12.4 g, 82.4 mmol) was added. The solution was allowed to warm to rt and was stirred at rt for 2 h at which time TLC analysis indicated complete consumption of SM. The solution was then slowly quenched with 50 mL of satd. $NaHCO_3$, and was then extracted with 3 × 50 mL of EtOAc. The combined organic layers were then washed with 3 × 50 mL of water. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford an off-white solid. This solid was used in the next step with no further purification.

To a solution of the intermediate silyl ether in 300 mL of DCM was added 100 mL of water, followed by NaOH (50.0 g, 1.25 mol), CH_2Br_2 (30.0 mL, 430 mmol) and 200 mg of TBAB. The biphasic mixture was vigorously stirred and heated to 40 °C for 72 h. The solution was cooled to rt and the organic layer was washed with 3 × 100 mL of H_2O. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford methylenedioxy compound **15** as an off-white solid (17.9 g, 61% mass recovery over 2 steps).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 1.9 Hz, 1H), 8.14 (s, 1H), 7.33 (s, 2H), 6.16 (d, *J* = 2.5 Hz, 1H), 5.34 (dd, *J* = 6.4, 2.5 Hz, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 4.91 (dd, *J* = 6.4, 3.4 Hz, 1H), 4.18 (ddd, *J* = 5.4, 3.3 Hz, 1H), 3.75 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.69 (dd, *J* = 11.0, 5.9 Hz, 1H), 0.79 (s, 9H), -0.07 (s, 6H).

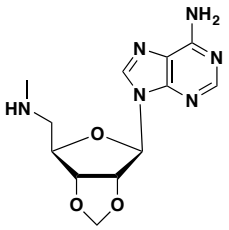
Bis-Boc compound 16



To a solution of **15** (5.95 g, 15.1 mmol) in 45 mL of DMF was added Et_3N (4.64 mL, 33.3 mmol) followed by DMAP (0.18 g, 1.51 mmol). The solution was cooled to 0 °C and then Boc_2O (7.64 mL, 33.3 mmol) was added dropwise via syringe. The solution was then allowed to warm to rt and was stirred at rt for 18 h at which time TLC analysis indicated complete consumption of SM. The solution was then slowly quenched with 50 mL of satd. $NaHCO_3$, the solution was then extracted with 3 × 50 mL of EtOAc, the combined organic layers were then washed with 3 × 50 mL of water. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a colorless oil. This oil was used in the next step with no further purification.

The intermediate bis-Boc protected carbamate was dissolved in 50 mL of anhydrous THF and was cooled to 0 °C before a 1M solution of TBAF was added dropwise via syringe (22.5 mL, 22.5 mmol). The solution was then allowed to warm to rt and was stirred at rt for 18 h at which time TLC analysis indicated complete consumption of SM. The solution was then slowly quenched with 50 mL of satd. $NaHCO_3$, the solution was then extracted with 3 × 50 mL of EtOAc, the combined organic layers were then washed with 3 × 50 mL of water. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford alcohol **16** as colorless oil (2.60 g, 37% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.18 (s, 1H), 5.99 (d, *J* = 4.5 Hz, 1H), 5.38 (s, 1H), 5.13 (s, 1H), 5.03 (m, 1H), 4.56 (m, 1H), 4.01 (m, 1H), 3.85 (m, 2H), 1.48 (s, 18H).

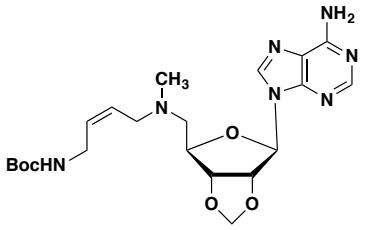
9-((3a*R*,4*R*,6*R*,6a*R*)-6-((Methylamino)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-amine (17)



To a stirred solution of alcohol **16** (0.46 g, 0.96 mmol) in 8 mL of DCM at 0 °C was added Et_3N (0.40 mL, 2.88 mmol) followed by MsCl (0.11 mL, 1.44 mmol) the solution was then allowed to warm to rt and then stirred at rt for 45 min before being quenched with 8 mL of satd. $NaHCO_3$. The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow foam. The foam was immediately dissolved in 5 mL of THF and transferred to a sealed tube. To this solution was added 5 mL of a 33% solution of methylamine in EtOH. The tube was quickly sealed and heated to 50 °C for 18 h before being cooled to rt. The solution was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–50% MeOH/DCM gradient) to give amine **17** as a yellow oil (0.18 g, 65%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (s, 1H), 8.24 (s, 1H), 6.28 (d, *J* = 2.8 Hz,

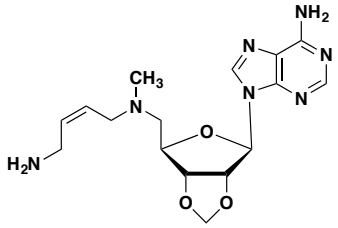
1H), 5.35 (dd, *J* = 6.5, 2.8 Hz, 1H), 5.26 (s, 1H), 5.19 (s, 1H), 5.12 (dd, *J* = 6.6, 4.1 Hz, 1H), 4.53 (dt, *J* = 9.2, 3.7 Hz, 1H), 3.58 (m, 1H), 3.44 (m, 1H), 2.67 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.1, 152.7, 148.6, 140.9, 119.3, 96.0, 89.5, 83.2, 81.5, 80.4, 50.8, 33.0; LC/MS (ESI) calcd for $C_{12}H_{16}N_6NaO_3$ $(M + Na)^+$ 315.1, found 315.1.

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-amino-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (S10)**



To a stirred solution of amine **17** (0.18 g, 0.62 mmol) in 5.0 mL of CH_3CN and 2.0 mL of DMSO was added chlorobuteneamine **13** (0.14 g, 0.68 mmol) followed by Et_3N (0.10 mL, 0.68 mmol) and sodium iodide (0.10 g, 0.68 mmol). The resulting suspension was stirred at rt for 18 h before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (5 mL) and saturated aq. $NaHCO_3$ (5 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–20% MeOH/DCM) to give the alkene **S10** as a clear oil (0.12 g, 42%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.21 (s, 1H), 6.18 (d, *J* = 2.5 Hz, 1H), 5.52–5.33 (m, 3H), 5.21 (s, 1H), 5.15 (s, 1H), 4.96 (dd, *J* = 6.5, 3.9 Hz, 1H), 4.35 (m, 1H), 3.61 (d, *J* = 7.1 Hz, 2H), 3.09 (d, *J* = 6.2 Hz, 2H), 2.82–2.62 (m, 2H), 2.26 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.0, 152.6, 148.8, 140.7, 139.1, 130.3, 126.8, 119.2, 116.7, 95.6, 89.3, 82.8, 82.8, 82.4, 58.5, 53.8, 41.4, 36.9, 27.4; LC/MS (ESI) calcd for $C_{21}H_{32}N_7O_5$ $(M + H)^+$ 462.2, found 462.2.

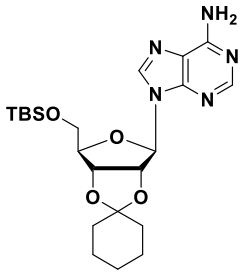
(*Z*)-*N*^{1}-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*^{1}-methylbut-2-ene-1,4-diamine (18)



To a stirred solution of carbamate **S10** (0.03 g, 0.06 mmol) in 2 mL of MeOH was added 2 mL of 1M H_2SO_4. The solution was stirred at rt for 18 h before the reaction was adjusted to pH 10 by the dropwise addition of 10% NaOH. The solution was concentrated *in vacuo*, dissolved in MeOH, dried (Na_2SO_4), filtered through Celite, and the filtrate was concentrated in vacuo. The residual oil was purified by flash chromatography (0–50% (1% NH_4OH in MeOH)/DCM) to give the free amine **18** as a clear oil (0.016 g, 66%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.27 (s, 1H), 8.21 (s, 1H), 6.18 (d, *J* = 2.5 Hz, 1H), 5.55 (m, 1H), 5.43–5.36 (m, 2H), 5.20 (s, 1H), 5.15 (s, 1H), 4.96 (dd, *J* = 6.5, 3.9 Hz, 1H), 4.33 (m, 1H), 3.22 (d, *J* = 7.0 Hz, 2H), 3.02 (d, *J* = 6.9 Hz, 2H), 2.73–2.61 (m, 2H), 2.23 (s, 3H); ^{13}C

NMR (101 MHz, CD_3OD) δ 156.8, 156.0, 152.6, 148.8, 140.7, 132.2, 126.9, 119.2, 95.6, 89.3, 82.8, 82.6, 58.6, 53.8, 41.4, 37.5; IR (thin film) 3324, 3178, 2916, 2849, 1598; LC/MS (ESI) calcd for $C_{16}H_{24}N_7O_3$ $(M + H)^+$ 362.2, found 362.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{24}N_7O_3$, 362.1935; found, 362.135; $[\alpha]^{20}_D$ = –6.66 (*c* = 0.15, MeOH).

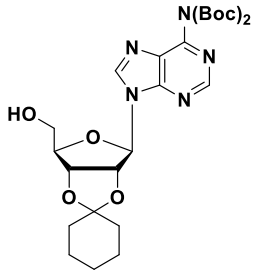
9-((3a'*R*,4'*R*,6'*R*,6a'*R*)-4'-(((*Tert*-butyldimethylsilyl)oxy)methyl)tetrahydrospiro[cyclohexane-1,2'-furo[3,4-*d*][1,3]dioxol]-6'-yl)-9*H*-purin-6-amine (19)



To a stirred solution of adenosine **14** (20.0 g, 74.8 mmol) in 60 mL of TFA was added cyclohexanone (60 mL, 579 mmol). The resulting red solution was stirred at rt for 1 h before being poured slowly into a mixture of 100 g of $NaHCO_3$ in 300 mL of H_2O and 100 g of ice over a period of 30 minutes. The solution was extracted with 3 × 100 mL of EtOAc, and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow solid. The solid was washed with copious amounts of diethyl ether to afford the cyclohexylidene ketal as an off-white solid (21.1 g, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.13 (s, 1H), 7.34 (br s, 2H), 6.10 (d, *J* = 3.1 Hz, 1H), 5.32 (dd, *J* = 6.1, 3.1 Hz, 1H), 5.22 (m, 1H), 4.93 (dd, *J* = 6.1, 2.5 Hz, 1H), 4.18 (td, *J* = 4.8, 2.5 Hz, 1H), 3.59–3.43 (m, 2H), 1.78–1.69 (m, 2H), 1.61–1.39 (m, 6H), 1.37–1.28 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 156.6, 153.1, 149.2, 140.2, 119.5, 114.0, 90.1, 86.9, 83.3, 81.4, 62.0, 41.7, 37.0, 34.7, 26.9, 24.9, 24.7, 24.1, 23.7; IR (thin film) 3411, 1651, 1587; LC/MS (ESI) calcd for $C_{16}H_{22}N_5O_4$ $(M + H)^+$ 348.2, found 348.2; $[\alpha]^{20}_D$ = –73.9 (*c* = 0.85, MeOH).

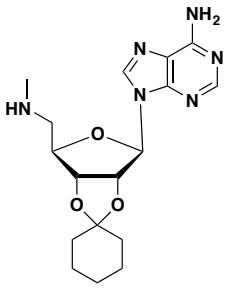
To a solution of cyclohexylidene ketal (9.52 g, 25.4 mmol) in 34 mL of DMF was added imidazole (1.90 g, 27.9 mmol). The solution was then cooled to 0 °C before TBSCl (4.22 g, 27.9 mmol) was added. The solution was allowed to warm to rt and was stirred at rt for 24 h at which time TLC analysis indicated complete consumption of SM. The solution was then slowly quenched with 50 mL of satd. $NaHCO_3$, the solution was then extracted with 3 × 50 mL of EtOAc, the combined organic layers were then washed with 3 × 50 mL of water. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a colorless oil. The oil was purified by flash chromatography (0–10% MeOH/DCM) to afford the silyl ether **19** as a white foam (7.85 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.03 (s, 1H), 6.16 (d, *J* = 2.6 Hz, 1H), 5.91 (br s, 1H), 5.28 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.95 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.41–4.36 (m, 1H), 3.86 (m, 1H), 3.76 (m, 1H), 1.86–1.82 (m, 2H), 1.70–1.55 (m, 6H), 1.43–1.37 (m, 2H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 153.1, 149.5, 139.4, 120.1, 114.8, 91.2, 87.3, 84.3, 81.0, 63.5, 37.1, 34.8, 25.9, 24.9, 24.0, 23.7, 18.3, –5.4.

Bis-boc compound 20



To a stirred solution of silyl ether **19** (4.60 g, 9.7 mmol) in 30 mL of DMF was added DMAP (1.90 g, 28.0 mmol) followed by Et_3N (3.05 mL, 21.9 mmol) and Boc_2O (5.03 mL, 21.9 mmol). The solution was then stirred for 18 h. The reaction was quenched with 50 mL of saturated $NaHCO_3$ and 50 mL of EtOAc was added. The aqueous layer was extracted with 3 × 50 mL of EtOAc then the combined organic layers were washed with 3 × 150 mL of H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. The oil was dissolved in 30 mL of THF and cooled to 0 °C and to this solution was added a 1M solution of TBAF in THF (15 mL, 15.0 mmol). The solution was stirred at rt for 1 h. The reaction was quenched with 50 mL of saturated $NaHCO_3$ and 50 mL of EtOAc was added. The aqueous layer was extracted with 3 × 50 mL of EtOAC then the combined organic layers were washed with 3 × 150 mL of H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography (0–10% MeOH/DCM) to afford the alcohol **20** as a white foam (5.45 g, 70%). ^{1}H NMR 400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.22 (s, 1H), 5.95 (d, *J* = 4.4 Hz, 1H), 5.22 (br s, 1H), 5.11 (dd, *J* = 5.9, 4.4 Hz, 1H), 4.97 (dd, *J* = 5.9, 1.5 Hz, 1H), 4.32 (m, 1H), 3.84 (m, 1H), 3.71 (m, 1H), 1.75 (m, 2H), 1.62–1.43 (m, 8H), 1.36 (s, 18H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 151.6, 150.8, 150.2, 144.4, 129.9, 114.9, 93.4, 86.3, 83.9, 83.0, 81.1, 63.0, 37.3, 34.5, 27.7, 24.8, 23.9, 23.4.

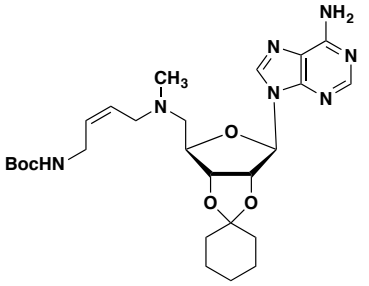
9-((3a'*R*,4'*R*,6'*R*,6a'*R*)-4'-((Methylamino)methyl)tetrahydrospiro[cyclohexane-1,2'-furo[3,4-*d*][1,3]dioxol]-6'-yl)-9*H*-purin-6-amine (21)



To a stirred solution of alcohol **20** (2.00 g, 3.65 mmol) in 30 mL of DCM at 0 °C was added Et_3N (1.5 mL, 2.88 mmol) followed by MsCl (0.42 mL, 5.48 mmol). The solution was allowed to warm to rt and then stirred at rt for 45 minutes before being quenched with 30 mL of satd. $NaHCO_3$. The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow foam. The foam was immediately dissolved in 25 mL of THF and transferred to a sealed tube. To this solution was added 25 mL of a 33% solution of methylamine in EtOH. The tube was quickly sealed and heated to 50 °C for 18 h before being cooled to rt. The solution was concentrated

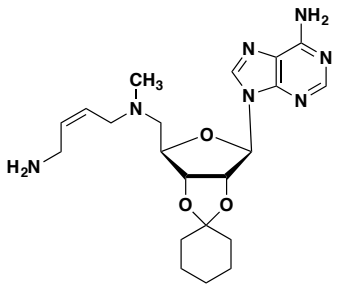
in vacuo. The resulting yellow oil was purified by flash chromatography (0–50% MeOH/DCM gradient) to give the amine **21** as a yellow oil (1.31 g, quant. mass recovery). ^{1}H NMR (400 MHz, CD_3OD) δ 8.36 (s, 1H), 8.26 (s, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 5.40 (dd, *J* = 6.3, 2.7 Hz, 1H), 5.18 (dd, *J* = 6.3, 3.5 Hz, 1H), 4.58 (m, 1H), 3.64 (m, 1H), 3.46 (m, 1H), 2.70 (s, 3H), 1.87–1.82 (m, 2H), 1.70–1.61 (m, 4H), 1.58–1.52 (m, 2H), 1.45–1.38 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.2, 152.6, 148.6, 141.0, 119.4, 115.4, 90.7, 83.4, 82.1, 81.6, 36.7, 34.3, 32.8, 24.6, 24.2, 23.7, 23.3; LC/MS (ESI) calcd for $C_{17}H_{25}N_6O_3$ $(M + H)^+$ 361.2, found 361.2.

***Tert*-butyl ((*Z*)-4-((((3a'*R*,4'*R*,6'*R*,6a'*R*)-4'-(6-amino-9*H*-purin-9-yl)tetrahydrospiro[cyclohexane-1,2'-furo[3,4-*d*][1,3]dioxol]-6'-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (S11)**



To a stirred solution of amine **21** (1.28 g, 3.55 mmol) in 11 mL of CH_3CN and 2.0 mL of DMSO was added chlorobuteneamine **13** (0.80 g, 3.91 mmol) followed by Et_3N (0.55 mL, 3.91 mmol) and sodium iodide (0.59 g, 3.91 mmol). The resulting suspension was stirred at rt for 3 h before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (25 mL) and saturated $NaHCO_3$ (25 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–20% MeOH/DCM) to give the alkene **S11** as a clear oil (1.05 g, 55% mass recovery). ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1H), 8.22 (s, 1H), 6.21 (d, *J* = 2.2 Hz, 1H), 5.88–5.69 (m, 2H), 5.35 (m, 1H), 5.01 (m, 1H), 4.39 (m, 1H), 3.80 (d, *J* = 6.9 Hz, 2H), 3.66–3.59 (m, 2H), 2.87–2.68 (m, 2H), 2.30 (s, 3H), 1.84 (m, 2H), 1.73–1.55 (m, 8H), 1.42 (s, 9H); LC/MS (ESI) calcd for $C_{26}H_{40}N_7O_5$ $(M + H)^+$ 530.3, found 530.3.

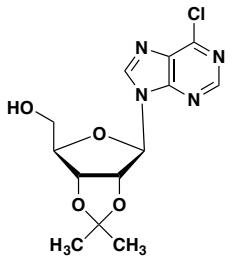
(*Z*)-*N*^{1}-(((3a'*R*,4'*R*,6'*R*,6a'*R*)-4'-(6-Amino-9*H*-purin-9-yl)tetrahydrospiro[cyclohexane-1,2'-furo[3,4-*d*][1,3]dioxol]-6'-yl)methyl)-*N*^{1}-methylbut-2-ene-1,4-diamine (22)



To a stirred solution of carbamate **S11** (0.11 g, 0.21 mmol) in 1.8 mL of DCM was added 0.3 mL of TFA. The solution was stirred at rt for 1 hour before the reaction was adjusted to pH 10 by the dropwise addition of 10% NaOH. The solution was concentrated *in vacuo*, dissolved in MeOH, dried (Na_2SO_4), filtered through Celite, and the

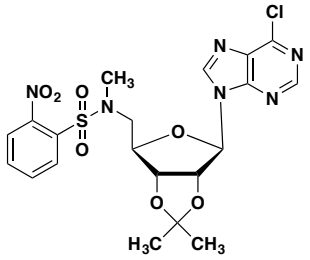
filtrate was concentrated *in vacuo*. The residual oil was purified by flash chromatography (0–50% (1% NH_4OH in MeOH)/DCM) to give the free amine **22** as a clear oil (0.06 g, 64%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1H), 8.25 (s, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 5.81 (m, 1H), 5.65 (m, 1H), 5.43 (dd, *J* = 6.3, 2.2 Hz, 1H), 5.13 (dd, *J* = 6.3, 3.7 Hz, 1H), 4.61 (m, 1H), 3.92 (m, 1H), 3.78–3.70 (m, 3H), 3.63 (d, *J* = 7.1 Hz, 2H), 2.72 (s, 3H), 1.87–1.82 (m, 2H), 1.72–1.54 (m, 6H), 1.45–1.40 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 161.9, 161.6, 152.7, 140.9, 121.1, 118.2, 115.3, 112.4, 90.7, 83.4, 82.4, 82.2, 57.3, 52.9, 36.6, 35.8, 34.2, 27.3, 24.6, 23.7, 23.3; IR (thin film) 3427, 3218, 2957, 1645; LC/MS (ESI) calcd for $C_{21}H_{32}N_7O_3$ $(M + H)^+$ 430.3, found 430.3; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{32}N_7O_3$, 430.2561; found, 430.2563; $[\alpha]^{20}_D$ = –5.44 (*c* = 0.25, MeOH).

((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (S12)



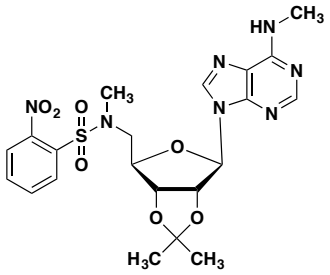
To a stirred solution of chloropurine **23** (15.0 g, 52.2 mmol) in 175 mL of acetone was 2,2-dimethoxypropane (63.0 mL, 538 mmol) followed by *p*-toluenesulfonic acid (10.9 g, 60 mmol). The resulting heterogeneous mixture was stirred for 2.5 h at rt during which time the solution become homogenous and bright yellow. The volatiles were removed *in vacuo* to give a thick yellow oil. The oil was dissolved in 150 mL of EtOAc followed by the addition of 150 mL of saturated $NaHCO_3$ over a period of 5 minutes during which time the yellow color disappeared. The resulting layers were separated and the aqueous layer was extracted with 2 × 150 mL of EtOAc. The combined organic layers were washed with 200 mL of brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the acetonide **S12** as a light yellow solid (16.5 g, 97%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 8.77 (s, 1H), 8.74 (s, 1H), 6.33 (d, *J* = 3.0 Hz, 1H), 5.41 (dd, *J* = 6.1, 3.0 Hz, 1H), 5.10 (dd, *J* = 6.1, 2.3 Hz, 1H), 4.52 (m, 1H), 4.43 (m, 1H), 3.85–3.72 (m, 2H), 1.59 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 151.5, 151.5, 150.1, 145.4, 132.2, 113.4, 91.6, 87.5, 84.4, 81.6, 62.2, 26.7, 24.6; IR (thin film) 3368, 2918, 1593, 1562; LC/MS (ESI) calcd for $C_{13}H_{16}ClN_4O_4$ $(M + H)^+$ 327.1, found 327.1; m.p. 195-196 °C; $[\alpha]^{20}_D$ = –115.6 (*c* = 0.91, $CHCl_3$).

***N*-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Chloro-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-methyl-2-nitrobenzenesulfonamide (24)**



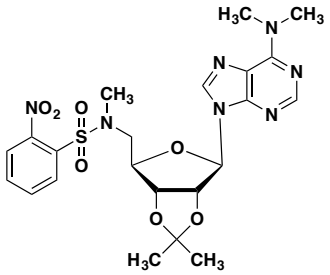
To a stirred solution of chloropurine **S12** (10.0 g, 30.6 mmol) in 115 mL of THF was added sulfonamide (6.23 g, 33.7 mmol). The solution was then cooled to 0 °C before triphenylphosphine (12.0 g, 45.9 mmol) was added in one portion followed by the addition of DIAD (9.03 mL, 45.9 mmol) dropwise by syringe. The residual yellow solution was stirred for 2 h during which time the solution was allowed to warm to rt. The volatiles were removed *in vacuo* to give a thick brown oil. To this oil was added 150 mL of MeOH and the solution was cooled to 0 °C for 0.5 h during which time a white precipitate formed. This precipitate was collected by suction filtration and washed with Et_2O (3 × 50 mL) to give the sulfonamide **24** as a white powder (14.6 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.20 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.71–7.50 (m, 3H), 6.12 (d, *J* = 2.2 Hz, 1H), 5.45 (dd, *J* = 6.4, 2.2 Hz, 1H), 5.14 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.44 (ddd, *J* = 8.2, 5.0, 3.6 Hz, 1H), 3.64 (m, 1H), 3.46 (m, 1H), 2.84 (s, 3H), 1.60 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 151.6, 150.7, 147.9, 144.7, 133.6, 132.4, 131.9, 131.5, 131.2, 124.1, 115.0, 90.9, 85.3, 83.8, 82.2, 51.6, 35.5, 27.1, 25.3; IR (thin film) 3098, 2985, 1593, 1545; LC/MS (ESI) calcd for $C_{20}H_{22}ClN_6O_7S$ $(M + H)^+$ 525.1, found 525.1; $[\alpha]^{20}_D$ = +22.8 (*c* = 0.9, $CHCl_3$); m.p.= 193 °C.

***N*-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(6-(methylamino)-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-methyl-2-nitrobenzenesulfonamide (S13)**



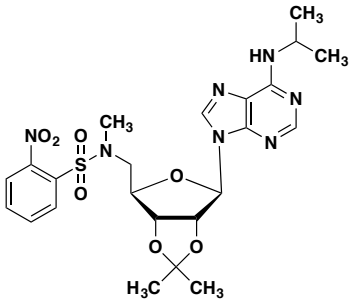
A 2M solution of methylamine in THF (29.0 mL, 58.0 mmol) was added to the chloride **24** (5.00 g, 9.53 mmol) in a sealed tube. The tube was quickly sealed and stirred at rt for 18 h before the volatiles were concentrated *in* vacuo. The resulting yellow oil was purified by flash chromatography (0–10% CH_3OH/DCM gradient) to give the amine **S13** as a white foam (4.85 g, 98%); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.38 (s, 1H), 7.87–7.76 (m, 2H), 7.63–7.44 (m, 3H), 6.02 (d, *J* = 2.1 Hz, 1H), 5.45 (dd, *J* = 6.4, 2.1 Hz, 1H), 5.11 (dd, *J* = 6.4, 3.5 Hz, 1H), 4.42 (m, 1H), 3.66 (m, 1H), 3.50 (m, 1H), 3.19 (s, 3H), 2.83 (s, 3H), 1.58 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CHCl_3$) δ 155.5, 153.3, 148.0, 139.3, 133.4, 132.2, 131.4, 131.0, 124.0, 114.6, 90.7, 85.7, 83.9 82.5, 77.2, 51.8, 35.8, 27.5, 27.1, 25.3; IR (thin film) 3286, 2939, 1625, 1545; LC/MS (ESI) calcd for $C_{21}H_{26}N_7O_7S$ $(M + H)^+$ 520.2, found 520.2; $[\alpha]^{20}_D$ = +14.2 (*c* = 0.76, $CHCl_3$).

***N*-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(Dimethylamino)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-methyl-2-nitrobenzenesulfonamide (S14)**



A 2M solution of dimethylamine in THF (60.0 mL, 120 mmol) was added to the chloride **24** (10.0 g, 19.0 mmol) in a sealed tube. The tube was quickly sealed and stirred at rt for 18 h before the volatiles were concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–10% CH_3OH/DCM gradient) to give the amine **S14** as a yellow solid (9.34 g, 92%); ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.20 (s, 1H), 7.70 (s, 1H), 7.53–7.39 (m, 4H), 5.95 (d, *J* = 2.1 Hz, 1H), 5.35 (dd, *J* = 6.5, 2.1 Hz, 1H), 5.03 (dd, *J* = 6.5, 3.6 Hz, 1H), 4.33 (m, 1H), 3.66–3.34 (m, 8H), 2.74 (s, 3H), 1.48 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, $CHCl_3$) δ 154.7, 152.2, 149.4, 147.9, 137.7, 133.6, 131.5, 130.5, 128.4, 123.9, 120.5, 114.3, 90.3, 85.6, 83.8, 82.4, 51.7, 38.5, 35.9, 27.0; IR (thin film) 3096, 2989, 2937, 1598, 1545; LC/MS (ESI) calcd for $C_{22}H_{28}N_7O_7S$ $(M + H)^+$ 534.2, found 534.2; $[\alpha]^{20}_D$ = +10.3 (*c* = 0.62, $CHCl_3$); m.p.= 75 °C.

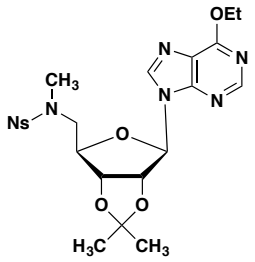
***N*-(((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(Isopropylamino)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*-methyl-2-nitrobenzenesulfonamide (S15)**



To a solution of chloropurine riboside **24** (5.25 g, 10.0 mmol) in 40.0 mL of THF in a sealed tube was added isopropylamine at rt dropwise via syringe, the tube was sealed, and the solution was heated to 55 °C for 3 h. The solution was cooled to rt and the volatiles were concentrated *in vacuo* to give a yellow oil. The oil was dissolved in 100 mL of DCM and was washed with 2 × 100 mL saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (0–10% MeOH/DCM gradient) to give the desired amine **S15** as an off-white foam (3.15 g, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.75 (s, 1H), 7.70 (m, 1H), 7.60–7.31 (m, 4H), 5.96 (d, *J* = 2.1 Hz, 1H), 5.75 (s, 1H), 5.35 (dd, *J* = 6.4, 2.1 Hz, 1H), 5.03 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.44–4.31 (m, 1H), 3.60 (m, 1H), 3.42 (m, 1H), 2.74 (s, 3H), 1.46 (s, 3H), 1.24 (s, 3H), 1.20 (d, *J* = 2.8 Hz, 3H), 1.19 (d, *J* = 2.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 153.2, 147.89, 139.3,

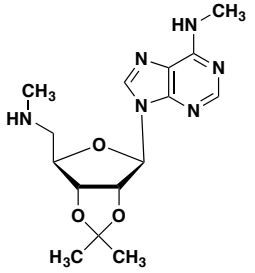
133.5, 132.9, 132.0, 131.9, 131.4, 130.7, 128.5, 128.4, 124.0, 114.4, 90.4, 85.6, 83.8, 82.4, 51.7, 35.8, 27.0, 25.3, 22.9; LC/MS (ESI) calcd for $C_{23}H_{30}N_7O_7S$ $(M + H)^+$ 548.2, found 548.2; $[\alpha]^{20}_D$ = +8.15 (*c* = 0.52, $CHCl_3$).

_N_-(((3a_R_,4_R_,6_R_,6a_R_)-6-(6-Ethoxy-9_H_-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-_d_][1,3]dioxol-4-yl)methyl)-_N_-methyl-2-nitrobenzenesulfonamide (S16)



To a solution of ethanol (0.086 mL, 1.47 mmol) in 16 mL dry THF was added sodium hydride (61 mg, 1.53 mmol, 60% in mineral oil) at 0 °C and the reaction mixture was stirred at this temperature for 30 min. Nosyl-protected chloropurine riboside **24** (0.6 g, 1.18 mmol) in dry THF (5 mL + 1 mL rinse) was then added and the resulting mixture was stirred at room temperature for 3 h under argon. The reaction was quenched with cold sat-NH_4Cl (30 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with sat-NaCl (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was loaded onto a silica gel cartridge and eluted with 0–70% EtOAc/heptane to afford the ethyl ether product **S16** (0.18 g, 29.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.96 (s, 1H), 7.86 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.50–7.63 (m, 3H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.45 (dd, *J* = 6.4, 2.2 Hz, 1H), 5.16 (dd, J_1 = 6.5, 3.7 Hz, 1H), 4.69 (q, *J* = 7.1 Hz, 2H), 4.42–4.46 (m, 1H), 3.46–3.73 (m, 2H), 2.85 (s, 3H), 1.61 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H), 1.39 (s, 3H).

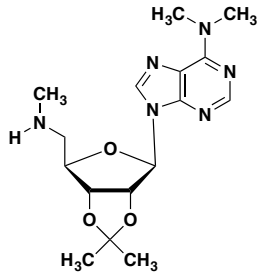
9-((3a_R_,4_R_,6_R_,6a_R_)-2,2-Dimethyl-6-((methylamino)methyl)tetrahydrofuro[3,4-_d_][1,3]dioxol-4-yl)-_N_-methyl-9_H_-purin-6-amine (25a)



To a stirred solution of nosyl-protected amine **S13** (2.62 g, 4.65 mmol) in 25.0 mL of CH_3CN was added Cs_2CO_3 (4.52 g, 13.9 mmol) in one portion followed by the addition of thiophenol (1.54 mL, 13.9 mmol) dropwise via syringe. The resulting solution was stirred at rt for three hours before being filtered through Celite and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–20% CH_3OH/DCM gradient) to give the amine **25a** as a clear waxy oil (1.44 g, 93%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.17 (s, 1H), 6.11 (d, *J* = 2.9 Hz, 1H), 5.45 (dd, *J* = 6.4, 2.9 Hz, 1H), 4.96 (dd, *J* = 6.4, 3.4 Hz, 1H), 4.31 (m, 1H), 3.07 (s, 3H), 2.91–2.73 (m, 2H), 2.32 (s, 3H), 1.56 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 155.3, 152.6, 147.7, 139.8, 119.8,

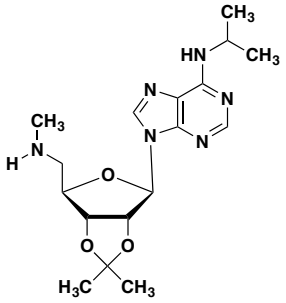
114.2, 90.1, 84.8, 83.5, 82.4, 53.0, 34.8, 26.2, 24.3; IR (thin film) 3286, 2939, 1623, 1581; LC/MS (ESI) calcd for $C_{15}H_{23}N_6O_3$ $(M + H)^+$ 335.2, found 335.2; $[\alpha]^{20}_D = -14.4$ (*c* = 1.82, MeOH).

9-((3a*S*,4*R*,6*R*,6a*S*)-2,2-Dimethyl-6-((methylamino)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-*N*,*N*-dimethyl-9*H*-purin-6-amine (25b)



To a stirred solution of nosyl-protected amine **S14** (7.10 g, 13.3 mmol) in 65 mL of CH_3CN was added Cs_2CO_3 (13.0 g, 40.0 mmol) in one portion followed by the addition of thiophenol (4.40 mL, 40.0 mmol) dropwise via syringe. The resulting solution was stirred at rt for 6 h before being filtered through Celite and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–20% CH_3OH/DCM gradient) to give the amine **25b** as a clear waxy oil (4.07 g, 88%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 8.10 (s, 1H), 6.09 (d, *J* = 2.9 Hz, 1H), 5.42–5.38 (m, 1H), 4.94 (dd, *J* = 6.4, 3.5 Hz, 1H), 4.28 (m, 1H), 3.47–3.30 (m, 8H), 2.30 (s, 3H), 1.56 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 154.6, 151.8, 149.6, 138.4, 120.0, 114.3, 89.9, 84.8, 83.4, 82.4, 53.1, 37.7, 34.8, 26.1, 24.2; IR (thin film) 3310, 2985, 2936, 1597, 1568; LC/MS (ESI) calcd for $C_{16}H_{25}N_6O_3$ $(M + H)^+$ 349.2, found 349.2; $[\alpha]^{20}_D = -20.6$ (c = 1.33, MeOH).

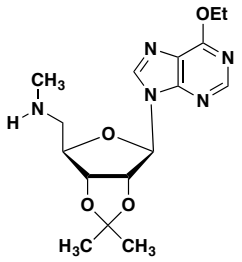
9-((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-((methylamino)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-*N*-isopropyl-9*H*-purin-6-amine (25c)



To a stirred solution of nosyl-protected amine **S15** (2.62 g, 4.65 mmol) in 25.0 mL of CH_3CN was added Cs_2CO_3 (4.52 g, 13.9 mmol) in one portion followed by the addition of thiophenol (1.54 mL, 13.9 mmol) dropwise via syringe. The resulting solution was stirred at rt for 3 h before being filtered through Celite and concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–20% CH_3OH/DCM gradient) to give the amine **25c** as a clear waxy oil (0.72 g, 43%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.20 (s, 1H), 6.12 (d, *J* = 2.9 Hz, 1H), 5.45 (dd, *J* = 6.4, 2.9 Hz, 1H), 4.97 (dd, *J* = 6.4, 3.4 Hz, 1H), 4.48–4.28 (m, 2H), 2.85–2.76 (m, 2H), 2.31 (s, 3H), 1.57 (s, 3H), 1.35 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 154.0, 152.7, 148.0,

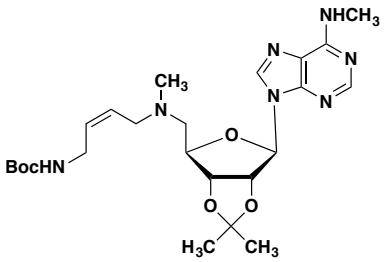
139.8, 119.4, 114.2, 90.1, 85.0, 83.5, 82.5, 53.1, 42.2, 34.8, 26.1, 24.2, 21.5; LC/MS (ESI) calcd for $C_{17}H_{27}N_6O_3$ (M + H)$^+$ 363.2, found 363.2; $[\alpha]^{20}_D$ = –17.4 (*c* = 1.92, MeOH).

1-((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Ethoxy-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-*N*-methylmethanamine (25d)



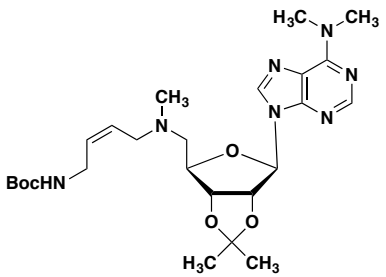
Compound **25d** was synthesized following the same procedure for making amines **15a-c** starting with **S16** (0.1 g, 85%).

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-(6-(methylamino)-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (26a)**



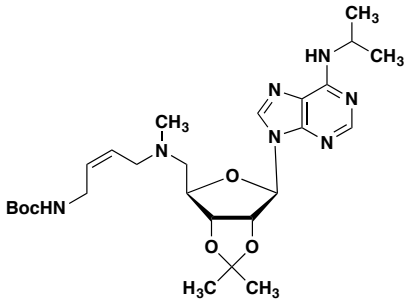
To a stirred solution of amine **25a** (1.33 g, 3.97 mmol) in 20.0 mL of CH_3CN was added Et_3N (0.62 mL, 4.37 mmol) followed by chlorobuteneamine **13** (0.89 g, 4.37 mmol) and sodium iodide (0.66 g, 4.37 mmol). The resulting suspension was stirred at rt for 4 h before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (50 mL) and saturated $NaHCO_3$ (50 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–20% MeOH/DCM) to give the alkene **26a** as a white, fluffy solid (1.02 g, 50%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1H), 8.19 (s, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 5.54–5.32 (m, 3H), 4.96 (dd, *J* = 6.5, 3.3 Hz, 1H), 4.32 (td, *J* = 6.7, 3.3 Hz, 1H), 3.62 (d, *J* = 6.6 Hz, 2H), 3.08 (s, 3H), 3.03–2.94 (m, 2H), 2.56 (d, *J* = 6.7 Hz, 2H), 2.17 (s, 3H), 1.54 (s, 3H), 1.39 (s, 9H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, CD_3O) δ 156.5, 155.3, 152.8, 147.7, 140.0, 130.2, 127.5, 119.9, 114.0, 90.2, 84.8, 83.6, 83.4, 78.5, 58.6, 54.1, 41.8, 37.2, 27.8, 26.6, 26.4, 24.8; IR (thin film) 3306, 3105, 2978, 1694, 1614; LC/MS (ESI) calcd for $C_{24}H_{38}N_7O_5$ (M + H)$^+$ 504.3, found 504.3; $[\alpha]^{20}_D$ = –6.94 (*c* = 0.49, MeOH); m.p = 80 °C.

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(dimethylamino)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (26b)**



To a stirred solution of amine **25b** (1.43 g, 4.10 mmol) in 21 mL of CH_3CN was added Et_3N (0.63 mL, 4.51 mmol) followed by chlorobuteneamine (0.97 g, 4.51 mmol) and sodium iodide (0.68 g, 4.51 mmol). The resulting suspension was stirred at rt for 4 hours before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (50 mL) and saturated $NaHCO_3$ (50 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–20% MeOH/DCM) to give the alkene **26b** as a white foam (1.40 g, 64%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 8.14 (s, 1H), 6.15 (d, *J* = 2.3 Hz, 1H), 5.51–5.32 (m, 3H), 4.96 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.33 (ddd, *J* = 7.7, 5.5, 3.5 Hz, 1H), 3.65–3.37 (m, 8H), 3.03 (m, 2H), 2.67–2.59 (m, 2H), 2.21 (s, 3H), 1.58 (s, 3H), 1.41 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.8, 154.6, 151.9, 149.6, 138.5, 130.0, 127.2, 120.0, 114.1, 89.9, 84.6, 83.6, 83.3, 78.6, 58.6, 53.9, 41.5, 37.7, 37.0, 27.4, 26.1, 24.2; IR (thin film) 3373, 2978, 1709, 1597, 1568; LC/MS (ESI) calcd for $C_{25}H_{40}N_7O_5$ $(M + H)^+$ 518.3, found 518.3; $[\alpha]^{20}_D$ = –14.4 (*c* = 0.66, MeOH).

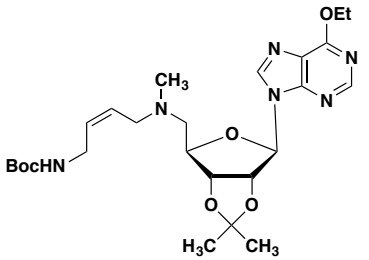
***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(isopropylamino)-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (26c)**



To a stirred solution of amine **25c** (0.33 g, 0.91 mmol) in 5.00 mL of CH_3CN was added Et_3N (0.14 mL, 1.00 mmol) followed by chlorobuteneamine (0.21 g, 1.00 mmol) and sodium iodide (0.15 g, 1.00 mmol). The resulting suspension was stirred at rt for 4 hours before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (25 mL) and saturated $NaHCO_3$ (25 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–20% MeOH/DCM) to give the alkene **26c** as a clear oil (0.26 g, 54%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (s, 1H), 8.22 (s, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.55–5.28 (m, 3H), 4.99 (m, 1H), 4.48–4.32 (m, 2H), 3.61 (d, *J* = 6.6 Hz, 2H), 3.09–3.01 (m, 2H), 2.73–2.57 (m, 2H), 2.23 (s, 3H), 1.59 (s, 3H), 1.42 (s, 9H), 1.37 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 6H);

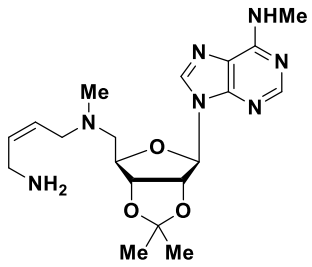
^{13}C NMR (101 MHz, CD_3OD) δ 156.8, 156.2, 154.0 152.9, 140., 130.1, 127.0, 114.1, 90.1, 84.7, 83.6, 83.3, 78.6, 58.5, 53.8, 48.4, 41.4, 36.9, 27.4, 26.0, 24.1, 21.5. LC/MS (ESI) calcd for $C_{26}H_{42}N_7O_5$ $(M + H)^+$ 532.3, found 532.3; $[\alpha]^{20}_D$ = –4.50 (*c* = 0.76, MeOH).

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-ethoxy-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (26d)**



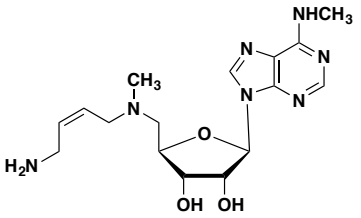
Compound **26d** was synthesized following the same procedure for making **26a-c** starting with **25d** (50 mg, 74.9%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.08 (s, 1H), 6.12 (d, *J* = 2.1 Hz, 1H), 5.48–5.51 (m, 2H), 5.47 (dd, *J* = 6.4, 2.2 Hz, 1H), 4.95 (dd, *J* = 6.4, 3.5 Hz, 1H), 4.71 (br s, 1H), 4.67 (q, *J* = 6.9 Hz, 2H), 4.38–4.42 (m, 1H), 3.73 (br s, 2H), 3.04–3.06 (m, 2H), 2.54–2.64 (m, 2H), 2.27 (s, 3H), 1.63 (s, 3H), 1.52 (t, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 1.40 (s, 3H).

(*Z*)-*N*^{1}-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(6-(methylamino)-9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*^{1}-methylbut-2-ene-1,4-diamine (27)



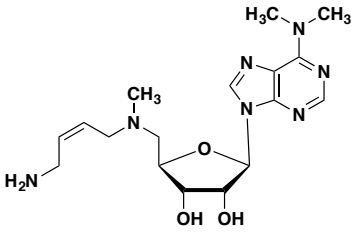
To a stirred solution of **26a** (0.453 g, 0.87 mmol) in 4.5 mL of DCM was added 2,6-lutidine (0.51 mL, 4.35 mmol) followed by the addition of TMSOTf (0.62 mL, 3.48 mmol) dropwise via syringe. The solution was stirred at rt for 1 h before 10 mL of MeOH was added dropwise. The solution was then concentrated *in vacuo* and the residual yellow oil was purified by flash chromatography (0–20% MeOH/DCM gradient) to give the primary amine **27** as a clear viscous oil (0.34 g, 94%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1H), 8.22 (s, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.83 (m, 1H), 5.46 (m, 1H), 5.16 (m, 1H), 4.67 (m, 1H), 3.97–3.82 (m, 4H), 3.67 (m, 2H), 3.50 (m, 1H), 3.10 (s, 3H), 2.84 (s, 3H), 1.62 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 155.3, 152.6, 140.4, 129.8, 123.8, 121.9, 118.8, 114.8, 90.9, 83.9, 82.6, 81.2, 56.9, 53.0, 39.7, 36.0, 26.4, 25.9, 24.0; IR (thin film) 3385, 3053, 1626; LC/MS (ESI) calcd for $C_{19}H_{30}N_7O_3$ $(M + H)^+$ 404.2, found 404.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{30}N_7O_3$, 404.2405; found, 404.2409; $[\alpha]^{20}_D$ = +3.47 (*c* = 0.75, MeOH).

(2*R*,3*S*,4*R*,5*R*)-2-((((*Z*)-4-Aminobut-2-en-1-yl)(methyl)amino)methyl)-5-(6-(methylamino)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (28a)



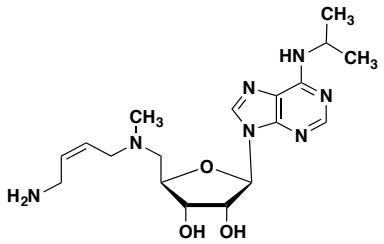
To a stirred solution of carbamate **26a** (0.51 g, 0.99 mmol) in 5 mL of MeOH was added 10 mL of 1M H_2SO_4. The solution was stirred at rt for 18 h before the reaction was adjusted to pH 10 by the dropwise addition of 10% NaOH. The solution was concentrated *in vacuo*, dissolved in MeOH, dried (Na_2SO_4), filtered through Celite, and the filtrate was concentrated *in vacuo*. The residual oil was purified by flash chromatography (0–50% (1% NH_4OH in MeOH)/DCM) to give the free amine **28a** as a thick, clear oil (0.22 g, 62%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (s, 1H), 8.20 (s, 1H), 5.98 (d, *J* = 4.1 Hz, 1H), 5.71–5.47 (m, 2H), 4.68 (m, 1H), 4.29–4.15 (m, 2H), 3.26 (m, 2H), 3.15–3.07 (m, 5H), 2.81–2.78 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 155.3, 152.5, 139.5, 133.1, 126.4, 119.1, 89.3, 81.8, 73.3, 72.3, 58.9, 53.8, 48.4, 41.7, 37.7, 26.3; IR (thin film) 3281, 2939, 1624, 1578; LC/MS (ESI) calcd for $C_{16}H_{26}N_7O_3$ (M + H)$^+$ 364.2, found 364.2; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{16}H_{26}N_7O_3$, 364.2092; found, 364.2095; $[\alpha]^{20}_D$ = –6.80 (*c* = 0.50, MeOH).

(2*R*,3*S*,4*R*,5*R*)-2-((((*Z*)-4-Aminobut-2-en-1-yl)(methyl)amino)methyl)-5-(6-(dimethylamino)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (28b)



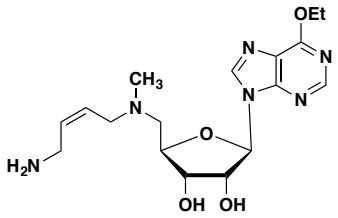
To a stirred solution of carbamate **26b** (0.60, 1.12 mmol) in 5 mL of MeOH was added 10 mL of 1M H_2SO_4. The solution was stirred at rt for 18 h before the reaction was adjusted to pH 10 by the dropwise addition of 10% NaOH. The solution was concentrated *in vacuo*, dissolved in MeOH, dried (Na_2SO_4), filtered through Celite, and the filtrate was concentrated *in vacuo*. The residual oil was purified by flash chromatography (0–50% (1% NH_4OH in MeOH)/DCM) to give the free amine **28b** as a thick, clear oil (0.28 g, 66%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 8.15 (s, 1H), 5.98 (d, *J* = 4.0 Hz, 1H), 5.70–5.61 (m, 1H), 5.60–5.51 (m, 1H), 4.62 (dd, *J* = 4.9, 4.0 Hz, 1H), 4.26–4.12 (m, 2H), 3.56–3.30 (m, 8H overlapping with solvent), 3.28 (d, *J* = 6.8 Hz, 2H) 3.14 (d, *J* = 6.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 154.7, 151.8, 149.8, 137.9, 132.7, 126.8, 120.1, 89.1, 81.7, 73.4, 72.3, 58.9, 53.8, 48.4, 41.7, 37.6; LC/MS (ESI) calcd for $C_{17}H_{28}N_7O_3$ (M + H)$^+$ 378.2, found 378.2; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{17}H_{28}N_7O_3$, 378.2248; found, 378.2241; $[\alpha]^{20}_D$ = –5.67 (*c* = 0.64, MeOH).

(2*R*,3*S*,4*R*,5*R*)-2-((((*Z*)-4-Aminobut-2-en-1-yl)(methyl)amino)methyl)-5-(6-(isopropylamino)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (28c)



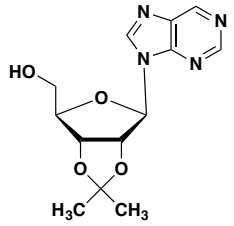
To a stirred solution of carbamate **26c** (0.24 g, 0.44 mmol) in 5 mL of MeOH was added 5 mL of 1M H_2SO_4. The solution was stirred at rt for 18 h before the reaction was adjusted to pH 10 by the dropwise addition of 10% NaOH. The solution was concentrated *in vacuo*, dissolved in MeOH, dried (Na_2SO_4), filtered through Celite, and the filtrate was concentrated *in vacuo*. The residual oil was purified by flash chromatography (0–50% (1% NH_4OH in MeOH)/DCM) to give **28c** as a clear oil (0.18 g, 88%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.23 (s, 1H), 8.21 (s, 1H), 5.97 (d, *J* = 4.1 Hz, 1H), 5.70–5.62 (m, 1H), 5.61–5.52 (m, 1H), 4.67 (dd, *J* = 5.2, 4.1 Hz, 1H), 4.21 (m, 3H), 3.28 (d, *J* = 6.7 Hz, 2H), 3.14 (d, *J* = 6.8 Hz, 2H), 2.82–2.79 (m, 2H), 2.30 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 154.0, 152.6, 140.0, 132.6, 126.8, 89.3, 81.8, 73.3, 72.3, 59.0, 53.7, 48.4, 42.2, 41.6, 37.6, 21.5; LC/MS (ESI) calcd for $C_{18}H_{30}N_7O_3$ $(M + H)^+$ 392.2, found 392.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{30}N_7O_3$, 392.2405; found, 392.2407; $[\alpha]^{20}_D$ = –5.25 (*c* = 2.33, MeOH).

(2*R*,3*S*,4*R*,5*R*)-2-((((*Z*)-4-Aminobut-2-en-1-yl)(methyl)amino)methyl)-5-(6-ethoxy-9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (28d)



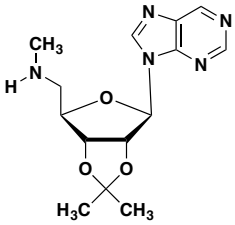
Compound **28d** was synthesized following the same procedure for making **28a-c** starting with **26d** (80 mg as HCl salt, 100%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.26 (s, 1H), 9.13 (d, *J* = 4.0 Hz, 1H), 8.70 (d, *J* = 2.5 Hz, 1H), 8.31 (s, 1H), 6.22–6.23 (m, 1H), 6.19 (d, *J* = 3.6 Hz, 1H), 5.94–6.08 (m, 4H), 4.80–4.93 (m, 2H), 4.76 (q, *J* = 7.1 Hz, 2H), 4.54–4.59 (m, 2H), 4.45–4.48 (m, 1H), 4.37–4.41 (m, 1H), 4.02–4.19 (m, 4H), 3.86–3.98 (m, 2H), 3.70–3.82 (m, 5H), 3.58–3.63 (m, 1H), 2.96–3.00 (m, 4H), 1.52 (t, *J* = 7.1 Hz, 3H); LC/MS (ESI) calcd for $C_{17}H_{27}N_6O_4$ $(M + H)^+$ 379.2, found 379.0; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{27}N_6O_4$, 379.2088; found, 379.2087.

((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (29)



To a stirred solution of **S12** (7.00 g, 21.5 mmol) in 80 mL of THF was added K_2CO_3 (5.90 g, 42.9 mmol) followed by 1.5 g of 10% Pd/C. The solution was purged with Ar for 30 min before being stirred under H_2 (1 atm) for 18 h. The solution was then filtered through Celite and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (10% MeOH/DCM) to give the product **29** as an off-white foam (6.54 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.56 (s, 1H), 8.17 (s, 1H), 5.88 (d, *J* = 3.5 Hz, 1H), 5.36 (s, 1H), 4.98 (dd, *J* = 6.2, 3.5 Hz, 1H), 4.78–4.76 (m, 1H), 4.21–4.16 (m, 1H), 3.68–3.56 (m, 1H), 3.56–3.43 (m, 1H), 1.29 (s, 3H), 1.04 (s, 3H); LC/MS (ESI) calcd for $C_{13}H_{17}N_4O_4$ $(M + H)^+$ 293.1, found 293.1; $[\alpha]^{20}_D$ = –128.6 (*c* = 2.92, $CHCl_3$).

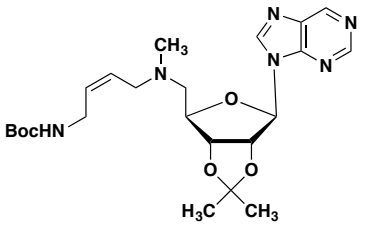
1-((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-*N*-methylmethanamine (S17)



To a stirred solution of **29** (3.0 g, 10.3 mmol) in 33 mL THF was added *N*-(2-nosyl)-*N*-methylamine (2.1 g, 11.3 mmol). The solution was then cooled to 0 °C before triphenylphosphine (4.59 g, 17.5 mmol) was added in one portion followed by the addition of DEAD (7.62 mL, 17.5 mmol) dropwise by syringe. The solution was stirred overnight during which time the solution was allowed to warm to rt. The volatiles were removed *in vacuo* to give a thick brown oil. The residue was purified by chromatography (SiO_2, 0–25% MeOH/DCM) to afford the nosylated product as a mixture with reduced DEAD and sulfonamide.

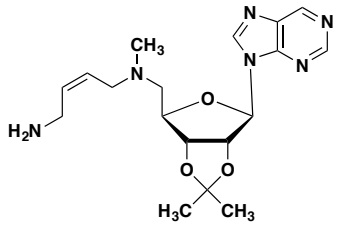
To a stirred solution of impure sulfonamide (1.00 g, 1.97 mmol) in 10 mL of CH_3CN was added Cs_2CO_3 (1.92 g, 5.92 mmol) followed by dropwise addition of thiophenol (0.66 g, 5.92 mmol). The suspension was stirred at rt for 6 h before being filtered through celite and concentrated *in vacuo* to give a yellow oil. The oil was purified by flash chromatography (0-20 (1% NH_4OH in MeOH)/100-80 DCM gradient) to give **S17** as a clear viscous oil (0.28 g, 46%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.97 (s, 1H), 8.69 (s, 1H), 6.30 (d, *J* = 2.7 Hz, 1H), 5.54 (dd, *J* = 6.4, 2.7 Hz, 1H), 5.03 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.37 (m, 1H), 2.87–2.85 (m, 2H), 2.33 (s, 3H), 1.61 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 152.0, 150.7, 147.7, 146.3, 134.2, 114.4, 90.3, 85.2, 83.6, 82.5, 53.0, 34.7, 26.1, 24.1; LC/MS (ESI) calcd for $C_{14}H_{20}N_5O_3$ $(M + H)^+$ 306.2, found 306.2; $[\alpha]^{20}_D$ = –2.03 (*c* = 0.69, MeOH).

***Tert*-butyl ((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-(9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)carbamate (S18)**



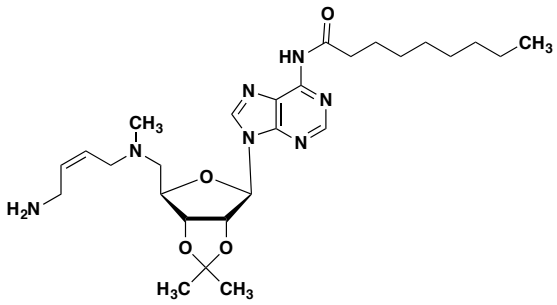
To a stirred solution of amine **S17** (0.10 g, 0.33 mmol) in 1 mL of CH_3CN was added the chloride **13** (0.07 g, 0.36 mmol) followed by NaI (0.05 g, 0.36 mmol) and Et_3N (0.05 mL, 0.36 mmol). The solution was stirred at rt for 4 h before being quenched with 5 mL of saturated $NaHCO_3$. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a clear oil. The oil was purified by flash chromatography (0–20% MeOH/DCM gradient) to give the carbamate **S18** as a clear oil (0.09 g, 56%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.97 (s, 1H), 8.70 (s, 1H), 6.32 (m, 1H), 5.57 (m, 1H), 5.48–5.31 (m, 2H), 5.03 (dd, *J* = 6.4, 3.5 Hz, 1H), 4.42 (m, 1H), 3.67–3.54 (m, 2H), 3.05 (d, *J* = 6.8 Hz, 2H), 2.75–2.57 (m, 2H), 2.23 (s, 3H), 1.60 (s, 3H), 1.42 (s, 9H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.8, 152.1, 150.6, 147.7, 146.4, 134.2, 130.2, 127.0, 114.2, 90.4, 84.9, 83.6, 83.3, 78.6, 58.5, 53.8, 41.4, 36.9, 27.4, 26.0, 24.1; LC/MS (ESI) calcd for $C_{23}H_{35}N_6O_5$ $(M + H)^+$ 475.3, found 475.3; $[\alpha]^{20}_D$ = +11.6 (*c* = 1.12, MeOH).

(*Z*)-*N*^{1}-(((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(9*H*-purin-9-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)-*N*^{1}-methylbut-2-ene-1,4-diamine (30)



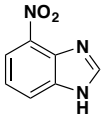
To a stirred solution of carbamate **S18** (0.59 g, 1.23 mmol) in 6.20 mL of DCM was added 2,6-lutidine (0.71 mL, 6.15 mmol) followed by TMSOTf (0.89 mL, 4.92 mmol). The solution was stirred at rt for 1 h before being quenched with 10 mL of MeOH. The volatiles were then concentrated *in vacuo* and purified by flash chromatography (0–20% MeOH/DCM gradient) to give **30** as a light yellow oil (0.40 g, 86%). ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 9.02 (s, 1H), 8.68 (s, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 5.88 (m, 1H), 5.62 (m, 1H), 5.51 (dd, *J* = 6.3, 2.4 Hz, 1H), 5.22 (dd, *J* = 6.4, 3.7 Hz, 1H), 4.71 (m, 1H), 3.98–3.77 (m, 3H), 3.74–3.55 (m, 3H), 2.87 (s, 3H), 1.64 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 152.2, 150.4, 147.9, 146.6, 134.3, 130.0, 123.6, 115.0, 90.7, 83.8, 82.5, 81.2, 56.9, 52.9, 39.6, 36.0, 26.0, 24.1; LC/MS (ESI) calcd for $C_{18}H_{27}N_6O_3$ $(M + H)^+$ 375.2, found 375.2; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{27}N_6O_3$, 375.2139; found, 375.2142.

***N*-(9-((3a*R*,4*R*,6*R*,6a*R*)-6-((((*Z*)-4-Aminobut-2-en-1-yl)(methyl)amino)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-9*H*-purin-6-yl)nonanamide (31)**



To a cold solution (0 °C, ice bath) of carbamate **10a** (0.56 g, 1.14 mmol) in DCM (23 mL) was added triethylamine (0.8 mL, 5.73 mmol) followed by nonanoyl chloride (0.52 mL, 2.86 mmol). The resulting solution was stirred for at 0 °C for 2 h. The mixture was then washed with water and volatiles were evaporated under vacuum. The residue was dissolved in methanol (25 mL) and treated with 28% NH_4OH in water (1.0 mL) and stirred at room temperature for 1.5 h. It was diluted with ethyl acetate (50 mL) and washed with water (4 × 25 mL). The solvent was removed at reduced pressure and the residue was purified via silica gel column chromatography (100% heptanes to 100% of 5% methanol in ethyl acetate) to yield 400 mg of the product, which was de-protected by treatment with TFA in DCM to afford **31** (250 mg as free base, 41.4%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.73 (s, 1H), 8.60 (s, 1H), 6.45 (d, *J* = 2.0 Hz, 1H), 5.50 (dd, *J* = 6.3, 1.7 Hz, 1H), 5.22 (dd, *J* = 6.3, 3.7 Hz, 1H), 4.35 (dt, *J* = 10.7, 3.2 Hz, 1H), 2.65 (t, *J* = 7.4 Hz, 2H), 1.72–1.80 (m, 2H), 1.64 (s, 3H), 1.40 (s, 3H), 0.89–0.92 (m, 3H); LC/MS (ESI) calcd for $C_{27}H_{44}N_7O_4$ $(M + H)^+$ 530.3, found 530.2; HRMS (TIC): $[M+H–C(O)(CH_2)_7CH_3]^+$ calcd for $C_{18}H_{28}N_7O_3$, 390.2248; found, 390.2213.

4-Bitro-1*H*-benzo[*d*]imidazole (34)

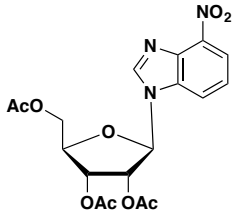


To a stirred solution of 2,6-dinitroaniline (10.0 g, 54.6 mmol) in 250 mL of EtOH was added 0.5 g of 5% Ru/C. To this suspension was then added hydrazine monohydrate (5.0 mL 82.8 mmol) dropwise via syringe pump over 30 minutes. The solution was heated to reflux for 3 h before being cooled to rt. The solution was filtered through Celite and concentrated *in vacuo* to afford the desired di-aniline product **33** as an orange solid. The solid was taken onto the next step with no further purification.

The unpurified **33** was dissolved in 150 mL of formic acid and was then heated to reflux for 18 h. The solution was then cooled to rt and concentrated *in vacuo* to afford a brown solid. The solid was cooled to 0 °C before 100 mL of 30% NH_4OH was added slowly over a period of 30 minutes. The solution was then allowed to warm to rt and stirred at rt for 1 h during which time a tan precipitate formed. The precipitate was collected by filtration to afford benzimidazole **34** as a tan solid (8.51 g, 95% over 2 steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (m, 1H), 8.13 (d,

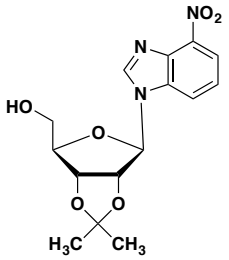
J = 8.1 Hz, 2H), 7.40 (t, *J* = 8.1 Hz, 1H); ^{1}H NMR in accordance with literature values;[1] ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.7, 141.2, 134.5, 127.1, 121.7, 119.4, 114.2.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(4-nitro-1*H*-benzo[*d*]imidazol-1-yl)tetrahydrofuran-3,4-diyl diacetate (35)



To a stirred suspension of benzimidazole **34** (4.11 g, 30.6 mmol) in 230 mL of CH_3CN was added BSA (8.22 mL, 39.8 mmol), and the solution was stirred for 10 min during which time the reaction mixture became homogenous. TAR (9.65 g, 39.8 mmol) was added followed by TMSOTf (5.88 mL, 38.8 mmol) and the reaction was heated to reflux for 3 h before being cooled to rt and diluted with 200 mL of EtOAc. The organic layer was washed with 200 mL of satd. $NaHCO_3$ and 200 mL of brine. The organic layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography (0–20% MeOH/DCM) to afford the triacetate **35** as a yellow foam (10.1 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.96 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 6.15 (d, *J* = 5.5 Hz, 1H), 5.56 (t, *J* = 5.5 Hz, 1H), 5.40 (t, *J* = 5.1 Hz, 1H), 4.52 (m, 1H), 4.45 (m, 1H), 4.39 (m, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 2.10 (s, 3H). ^{1}H NMR in accordance with literature values.[2]

((3a*R*,4*R*,6*R*,6a*R*)-2,2-Dimethyl-6-(4-nitro-1*H*-benzo[*d*]imidazol-1-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (36)

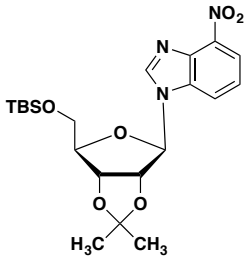


To a stirred solution of tri-acetate **35** (17.0 g, 40.4 mmol) in 100 mL of MeOH in a sealed tube was added 12 mL of 7N ammonia in methanol. The tube was sealed and the mixture was stirred at rt for 18 h before being concentrated *in vacuo* to afford a brown solid. The solid was used in the next step immediately with no additional purification.

The intermediate triol was suspended in 200 mL of acetone followed by addition of 45 mL of 2,2-dimethoxy propane, and *p*-TsOH (8.45 g, 44.4 mmol). The resulting suspension was heated to reflux for 2 h, during which time the reaction mixture became homogenous After 2 h, TLC analysis indicated complete consumption of SM. The volatiles were removed *in vacuo* to give a thick yellow oil. The oil was dissolved in 150 mL of EtOAc followed by the addition of 150 mL of saturated $NaHCO_3$ over a period of 5 minutes during which time the yellow color disappeared. The resulting layers were separated and the aqueous layer was extracted with 2 × 150 mL of EtOAc. The combined

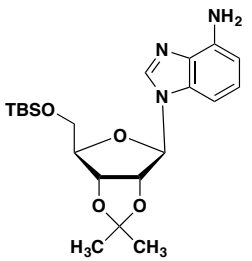
organic layers were washed with 200 mL of brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the acetonide **36** as a light orange solid (7.50 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 6.15 (d, *J* = 3.1 Hz, 1H), 5.50 (br s, 1H), 5.11 (m, 1H), 4.98 (m, 1H), 4.21–4.03 (m, 2H). 1.69 (s, 3H), 1.41 (s, 3H).

1-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-4-nitro-1*H*-benzo[*d*]imidazole (S19)



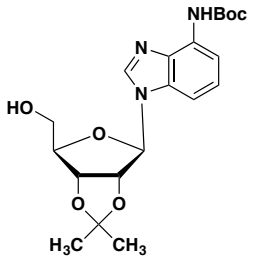
To a stirred solution of alcohol **36** (1.00 g, 2.98 mmol) in 15 mL DCM was added imidazole (0.47 g, 7.15 mmol) followed by TBSCl (0.54 g, 3.58 g). The solution was then stirred at rt for 3 h before being quenched with 15 mL of satd $NaHCO_3$. The resulting layers were separated and extracted with 3 × 15 mL of DCM. The combined organic layers were then washed with 30 mL of brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford an orange oil. The oil was purified by flash chromatography (0–40% EtOAc/Hexanes) to afford silyl ether **S19** as an orange foam (1.25 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 4.79 (m, 2H), 4.43 (m, 1H), 3.95–3.72 (m, 2H), 1.57 (s, 3H), 1.31 (s, 3H), 0.72 (s, 9H), –0.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 139.3, 137.8, 134.9, 122.3, 119.5, 117.4, 114.6, 93.4, 86.2, 85.1, 81.1, 63.3, 27.3, 25.7, 25.2, 18.2, –5.5.

1-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-benzo[*d*]imidazol-4-amine (37)



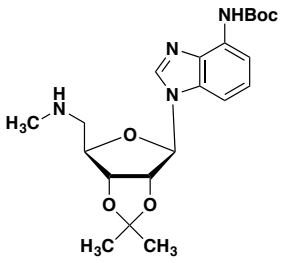
To a stirred solution of nitro compound **S19** (0.70 g, 1.56 mmol) in 95 mL of methanol and 9.5 mL of H_2O was added Fe powder (0.96 g, 17.2 mmol) and $FeSO_4$ (0.48 g, 1.72 mmol). The resulting solution was heated to 50 °C for 2 h before being cooled to rt. The solution was filtered through Celite and concentrated *in vacuo* to afford the desired aniline **37** as a yellow oil (0.65 g, quant. yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.06 (m, 1H), 6.89 (m, 1H), 6.53 (m, 1H), 5.94 (m, 3H), 4.88 (m,1H), 4.44 (m, 2H), 3.86 (m, 2H), 1.63 (s, 3H), 1.36 (s, 3H), 0.86 (s, 9H), 0.06 (s, 6H).

***Tert*-butyl (1-((3a*R*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-benzo[*d*]imidazol-4-yl)carbamate (38)**



To a stirred solution of silyl ether **37** (0.65 g, 1.56 mmol) in 3 mL of DMF was added DMAP (0.04 g, 0.34 mmol) followed by Et_3N (0.53 mL, 3.78 mmol) and Boc_2O (0.83 g, mL, 3.78 mmol). The solution was then stirred for 18 h. The reaction was quenched with 5 mL of saturated $NaHCO_3$ and 5 mL of EtOAc was added. The aqueous layer was extracted with 3 × 5 mL of EtOAc, and the combined organic layers were washed with 3 × 15 mL of H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. The oil was dissolved in 10 mL of THF and cooled to 0 °C and to this solution was added a 1M solution of TBAF in THF (2.58 mL, 2.58 mmol). The solution was stirred at rt for 1 hour. The reaction was quenched with 5 mL of saturated $NaHCO_3$ and 5 mL of EtOAc was added. The aqueous layer was extracted with 3 × 5 mL of EtOAc, and the combined organic layers were washed with 3 × 15 mL of H_2O. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography (0–10% MeOH/DCM) to afford the mono-Boc protected aniline **38** as a yellow foam (0.40 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.16 (s, 1H), 7.81 (m, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 5.99 (d, *J* = 3.4 Hz, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 4.51 (m, 1H), 4.02 (m, 1H), 3.86 (m, 1H), 1.64 (s, 3H), 1.53 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 138.9, 133.2, 132.4, 130.4, 124.5, 114.3, 110.6, 104.5, 93.2, 86.7, 85.4, 81.4, 80.3, 62.0, 28.5, 27.2, 25.2; IR (thin film) 3319, 2981, 1731, 1620; LC/MS (ESI) calcd for $C_{20}H_{28}N_3O_6$ $(M + H)^+$ 406.2, found 406.2.

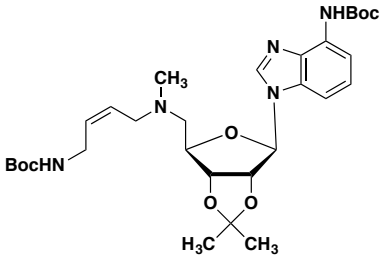
***Tert*-butyl (1-((3a*R*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-((methylamino)methyl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-benzo[*d*]imidazol-4-yl)carbamate (S20)**



To a stirred solution of alcohol **38** (0.09 g, 0.23 mmol) in 1.0 mL of DCM at 0 °C was added Et_3N (0.09 mL, 0.68 mmol) followed by MsCl (0.03 mL, 0.34 mmol). The solution was allowed to warm to rt and then stirred at rt for 45 min before being quenched with 1 mL of satd. $NaHCO_3$. The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow foam. The foam was immediately dissolved in 2.0 mL of THF and transferred to a sealed tube. To this solution was added 2.0 mL of a 33 % solution of methylamine in EtOH.

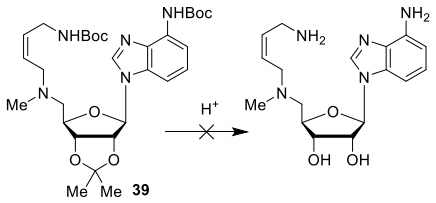
The tube was quickly sealed and heated to 50 °C for 18 h before being cooled to rt. The solution was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–20% MeOH/DCM gradient) to give the amine **S20** as a yellow oil (0.06 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.88 (m, 2H), 7.79 (s, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 5.91 (d, *J* = 3.4 Hz, 1H), 4.98 (dd, *J* = 6.9, 3.4 Hz, 1H), 4.81 (dd, *J* = 6.9, 4.1 Hz, 1H), 4.29 (dt, *J* = 6.1, 4.1 Hz, 1H), 3.44 (s, 2H), 2.90 (m, 1H), 2.77 (m, 1H), 2.42 (s, 3H), 1.60 (s, 3H), 1.51 (s, 9H), 1.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 139.1, 134.2, 132.3, 130.8, 124.5, 115.4, 109.9, 104.5, 91.4, 84.5, 83.97, 81.9, 80.4, 53.4, 36.7, 28.3, 27.1, 25.3; LC/MS (ESI) calcd for $C_{21}H_{31}N_4O_5$ $(M + H)^+$ 419.2, found 419.2.

***Tert*-butyl (1-((3a*R*,4*R*,6*R*,6a*R*)-6-((((*Z*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)(methyl)amino)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-1*H*-benzo[*d*]imidazol-4-yl)carbamate (39)**



To a stirred solution of amine **S20** (0.21 g, 0.51 mmol) in 5 mL of CH_3CN was added chlorobuteneamine **13** (0.16 g, 0.56 mmol) followed by Et_3N (0.08 mL, 0.56 mmol) and sodium iodide (0.08 g, 0.56 mmol). The resulting suspension was stirred at rt for 3 h before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (5 mL) and saturated $NaHCO_3$ (5 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–10% MeOH/DCM) to give the alkene **39** as a clear oil (0.16 g, 55%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.32 (s, 1H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.34–7.18 (m, 2H), 6.08 (d, *J* = 3.2 Hz, 1H), 5.60–5.38 (m, 2H), 5.14 (dd, *J* = 6.8, 3.2 Hz, 1H), 4.82 (m, 1H), 4.32 (m, 1H), 3.63 (br s, 2H), 3.20–3.03 (br s, 2H), 2.68–2.58 (m, 2H), 2.26 (s, 3H), 1.60 (s, 3H), 1.53 (s, 9H), 1.39 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 156.8, 153.3, 140.2, 133.8, 132.7, 130.4, 130.1, 127.0, 124.0, 114.9, 111.2, 105.3, 91.0, 83.5, 82.8, 80.0, 78.6, 58.5, 53.8, 41.5, 37.0, 29.3, 27.3, 27.2, 25.9, 24.1.

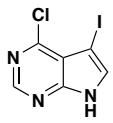
Table S1. Deprotection screening conditions for the attempted conversion of **39** to **40**.



Acid/Lewis Acid	Cosolvent	Time	Temp.	Yield[a]
1M H_2SO_4	MeOH	18 h	rt	0%
1M HCl	MeOH	18 h	rt	0%
TFA	THF/H_2O	2 h	0 °C to rt	0%
TFA	THF/H_2O	1 h	0 °C to rt	0%
TsOH	THF/H_2O	18 h	rt	0%
Formic Acid	H_2O	18 h	rt	0%
DOWEX 50W	MeOH	2 h	rt	0%
4M HCl (dioxane)	MeCN	6 h	rt	0%
4M HCl (dioxane)	MeCN	1 h	rt	0%
TMSBr	DCM	0.5 h	rt	0%
BF_3•Et_2O, EtSH	DCM	18 h	rt	0%
BF_3•Et_2O, DMS	DCM	18 h	rt	0%
BF_3•Et_2O	DCM	18 h	rt	0%
CAN	MeCN	0.5 h	rt	0%
BCl_3	DCM	0.5 h	-78 °C	0%
TMSOTf, 2,6-lut.	DCM	0.5 h	0 °C to rt	0%

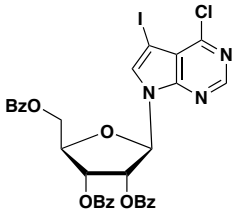
a) Decomposition of SM was observed in all cases; no product was identified

4-Iodo-7*H*-pyrrolo[2,3-*d*]pyrimidine (41b)



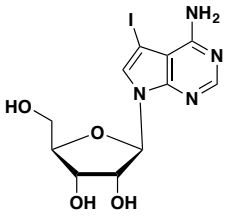
To a stirred solution of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **41a** (7.19 g, 46.8 mmol) in 70 mL of DMF was added *N*-iodosuccinimide (11.06 g, 49.2 mmol). The solution was stirred in the dark for 18 h at rt before being poured into 100 mL of H_2O. The resulting tan precipitate was collected by suction filtration and dried under high vacuum to afford iodide **41b** (11.8 g, 90%) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.91 (s, 1H). ^{1}H NMR in accordance with literature values.[3]

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(4-chloro-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)tetrahydrofuran-3,4-diyl dibenzoate (42)



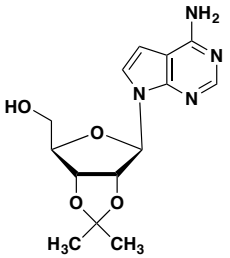
To a stirred suspension of pyrimidine **S21** (2.89 g, 10.4 mmol) in 52 mL of CH_3CN was added BSA (2.79 mL, 11.42 mmol). The solution was stirred for 10 minutes during which time the reaction mixture became homogenous. 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (5.75 g, 11.4 mmol) was added followed by TMSOTf (2.15 mL, 11.4 mmol), and the reaction was heated to reflux for 2 h before being cooled to rt and diluted with 100 mL of EtOAc. The organic layer was washed with 100 mL of satd. $NaHCO_3$ and 100 mL of brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a yellow oil. The oil was purified by flash chromatography (40% EtOAc/Hexanes) to afford the riboside **42** as a yellow foam (4.51 g, 60%). ^{1}H NMR in accordance with literature values.[4]

(2*R*,3*R*,4*S*,5*R*)-2-(4-Amino-5-iodo-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (43)



Tri-benzoyl compound **42** (3.70 g, 5.31 mmol) was dissolved in a mixture of 53 mL of 1,4-dioxane and 53 mL of 30% aqueous NH_4OH in a sealed tube. The tube was sealed and heated to 60 °C for 72 h before being cooled to rt and concentrated *in vacuo* to afford a brown oil. The oil was purified by flash chromatography (0–20% MeOH/DCM) to give the triol **43** as a white solid (1.20 g, 57%). ^{1}H NMR in accordance with literature values.[5]

((3a*R*,4*R*,6*R*,6a*R*)-6-(4-Amino-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol (S22)

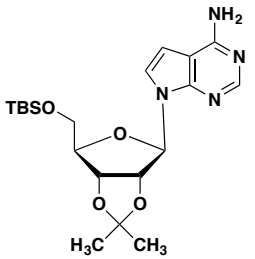


To a stirred solution triol **43** (0.38 g, 0.97 mmol) in 5 mL of DMF was added Et_3N (0.28 mL, 2.00 mmol) and 0.15 g of Pd/C. The solution was stirred under H_2 balloon for 18 h before being filtered through Celite and concentrated *in vacuo* to afford a brown oil. The oil was used in the next step with no further purification.

To a solution of the intermediate triol in 20 mL of acetone and 1.0 mL of 2,2-DMP was added *p*-TsOH (0.21 g, 1.1 mmol). The resulting suspension was heated to reflux for 2 h, during which time the reaction mixture became homogenous After 2 h, TLC analysis indicated complete consumption of SM. The volatiles were removed *in vacuo* to give a thick yellow oil. The oil was dissolved in 15 mL of EtOAc followed by the addition of 15 mL of saturated $NaHCO_3$ over a period of 5 minutes during which time the yellow color disappeared. The resulting layers were

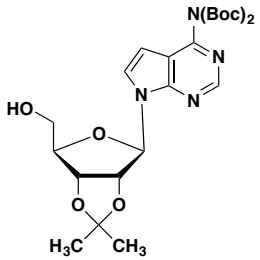
separated and the aqueous layer was extracted with 2 × 15 mL of EtOAc. The combined organic layers were washed with 20 mL of brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford an orange oil. The oil was purified by flash chromatography (0–20% MeOH/DCM) to give the acetonide **S22** as an off-white foam (0.14 g, 47%). ^{1}H NMR (500 MHz, CD_3OD) δ 8.10 (s, 1H), 7.31 (d, *J* = 3.7 Hz, 1H), 6.62 (d, *J* = 3.7 Hz, 1H), 6.16 (d, *J* = 4.0 Hz, 1H), 5.16 (dd, *J* = 6.3, 4.0 Hz, 1H), 5.00 (dd, *J* = 6.3, 2.7 Hz, 1H), 4.30 (m, 1H), 3.86–3.69 (m, 2H), 1.62 (s, 3H), 1.37 (s, 3H).

7-((3a*R*,4*R*,6*R*,6a*R*)-6-(((*Tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (44)



To a stirred solution of alcohol **S22** (0.14 g, 0.45 mmol) in 5 mL DCM was added imidazole (0.07 g, 0.99 mmol) followed by TBSCl (0.08 g, 0.50 g). The solution was then stirred at rt for 18 h before being quenched with 5 mL of satd $NaHCO_3$. The resulting layers were separated and extracted with 3 × 5 mL of DCM. The combined organic layers were washed with 15 mL of brine, dried (Na_2SO_4) and concentrated *in vacuo* to afford an orange oil. The oil was purified by flash chromatography (0–10% MeOH/DCM) to afford silyl ether **44** as an off-white foam (0.17 g, 88%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.26 (d, *J* = 3.7 Hz, 1H), 6.60 (d, *J* = 3.7 Hz, 1H), 6.25 (d, *J* = 3.1 Hz, 1H), 5.12 (dd, *J* = 6.3, 3.1 Hz, 1H), 4.94 (dd, *J* = 6.3, 3.1 Hz, 1H), 4.20 (m, 1H), 3.87–3.62 (m, 2H), 1.57 (s, 3H), 1.33 (s, 3H), 0.86 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (101 MHz, CD_3OD) δ 157.6, 151.1, 149.5, 122.2, 113.8, 103.3, 99.9, 89.5, 85.8, 84.3, 81.1, 63.3, 26.2, 25.0, 24.2, 17.8, –6.7; LC/MS (ESI) calcd for $C_{20}H_{33}N_4O_4$ $(M + H)^+$ 421.2, found 421.2.

Bis-boc compound 45

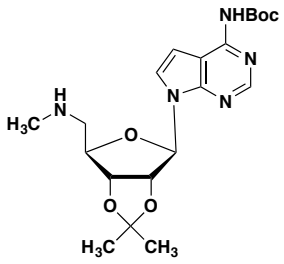


To a solution of 5'-TBS ether **44** (0.06 g, 0.14 mmol) in 5 mL of DMF was added Et_3N (0.04 mL, 0.29 mmol) followed by 10 mg of DMAP. The solution was cooled to 0 °C and Boc_2O (0.07 g, 0.30 mmol) was added dropwise via syringe. The solution was allowed to warm to rt and was stirred at rt for 18 h, at which time TLC analysis indicated complete consumption of SM. The solution was slowly quenched with 5 mL of satd. $NaHCO_3$, and was then extracted with 3 × 5 mL of EtOAc. The combined organic layers were washed with 3 × 5 mL of water. The

organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a colorless oil. This oil was used in the next step with no further purification.

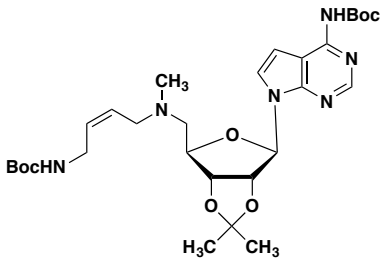
The intermediate bis-Boc protected carbamate was dissolved in 5 mL of anhydrous THF and was cooled to 0 °C before a 1M solution of TBAF was added dropwise via syringe (0.21 mL, 0.21 mmol). The solution was allowed to warm to rt and was stirred at rt for 1 h at which time TLC analysis indicated complete consumption of SM. The solution was slowly quenched with 5 mL of satd. $NaHCO_3$, and was then extracted with 3 × 5 mL of EtOAc. The combined organic layers were washed with 3 × 5 mL of water. The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the crude alcohol as a yellow oil. The oil was purified by flash chromatography (0–50% EtOAc/Hexanes) to afford carbamate **45** as a yellow oil (0.04 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 6.41 (br s, 1H), 5.84 (br s, 1H), 5.64 (br s, 1H), 5.23 (br s, 1H), 5.10 (br s, 1H), 4.47 (br s, 1H), 3.96 (m, 1H), 3.79 (m, 1H), 1.62 (s, 3H), 1.42 (s, 18H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 151.3, 150.4, 129.3, 116.2, 114.1, 99.6, 95.8, 85.4, 83.9, 82.9, 81.4, 77.2, 63.3, 27.8, 27.6, 25.3; LC/MS (ESI) calcd for $C_{24}H_{35}N_4O_8$ $(M + H)^+$ 507.2, found 507.2.

Bis-boc compound S23



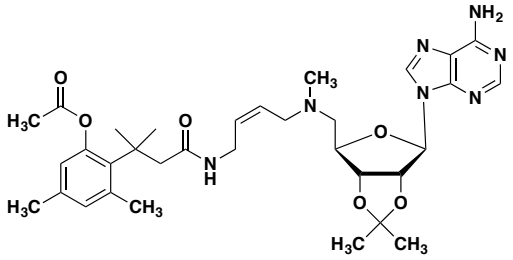
To a stirred solution of alcohol **45** (0.77 g, 1.53 mmol) in 30 mL of DCM at 0 °C was added Et_3N (0.64 mL, 4.60 mmol) followed by MsCl (0.18 mL, 2.30 mmol). The solution was allowed to warm to rt and then stirred at rt for 45 min before being quenched with 15 mL of satd. $NaHCO_3$. The layers were separated and the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a yellow foam. The foam was immediately dissolved in 20 mL of THF and transferred to a sealed tube. To this solution was added 20 mL of a 33% solution of methylamine in EtOH. The tube was quickly sealed and heated to 50 °C for 18 h before being cooled to rt. The solution was concentrated *in vacuo*. The resulting yellow oil was purified by flash chromatography (0–20% MeOH/DCM gradient) to give the amine **S23** as a yellow oil (0.53 g, 82%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 7.44 (d, *J* = 3.8 Hz, 1H), 6.91 (d, *J* = 3.8 Hz, 1H), 6.27 (d, *J* = 2.8 Hz, 1H), 5.32 (dd, *J* = 6.5, 2.8 Hz, 1H), 5.02 (dd, *J* = 6.5, 4.0 Hz, 1H), 4.35 (m, 1H), 3.23–3.14 (m, 2H), 2.50 (s, 3H), 1.58 (s, 3H), 1.56 (s, 9H), 1.35 (s, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 151.9, 151.6, 151.4, 150.3, 125.4, 114.6, 107.9, 102.1, 90.6, 84.0, 82.5, 82.1, 81.0, 51.7, 33.5, 27.1, 26.1, 24.1; LC/MS (ESI) calcd for $C_{20}H_{30}N_5O_5$ $(M + H)^+$ 420.2, found 420.2.

***Tert*-butyl (7-((3a*R*,4*R*,6*R*,6a*R*)-6-((((*Z*)-4-((*tert*-butoxycarbonyl)amino)but-2-en-1-yl)(methyl)amino)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)carbamate (46)**



To a stirred solution of amine **S23** (0.09 g, 0.21 mmol) in 5 mL of CH_3CN was added chlorobuteneamine **13** (0.05 g, 0.26 mmol) followed by Et_3N (0.04 mL, 0.26 mmol) and sodium iodide (0.04 g, 0.26 mmol). The resulting suspension was stirred at rt for 18 h before being concentrated *in vacuo* to give a clear oil. The oil was partitioned between EtOAc (5 mL) and saturated $NaHCO_3$ (5 mL). The layers were separated and the organic layer was dried and concentrated *in vacuo*. The residual yellow oil was purified by flash chromatography (0–10% MeOH/DCM) to give the alkene **46** as a clear oil (0.05 g, 44%).^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (s, 1H), 7.42 (d, *J* = 3.8 Hz, 1H), 6.92 (d, *J* = 3.8 Hz, 1H), 6.29 (d, *J* = 2.7 Hz, 1H), 5.53–5.34 (m, 2H), 5.30 (dd, *J* = 6.6, 2.7 Hz, 1H), 4.89 (dd, *J* = 6.6, 4.0 Hz, 1H), 4.27 (m, 1H), 3.60 (d, *J* = 6.3 Hz, 2H), 3.13–2.97 (m, 2H), 2.70–2.58 (m, 2H), 2.21 (s, 3H), 1.57 (s, 3H), 1.55 (s, 9H), 1.40 (s, 9H), 1.35 (s, 3H); LC/MS (ESI) calcd for $C_{29}H_{45}N_6O_7$ $(M + H)^+$ 589.3, found 589.3.

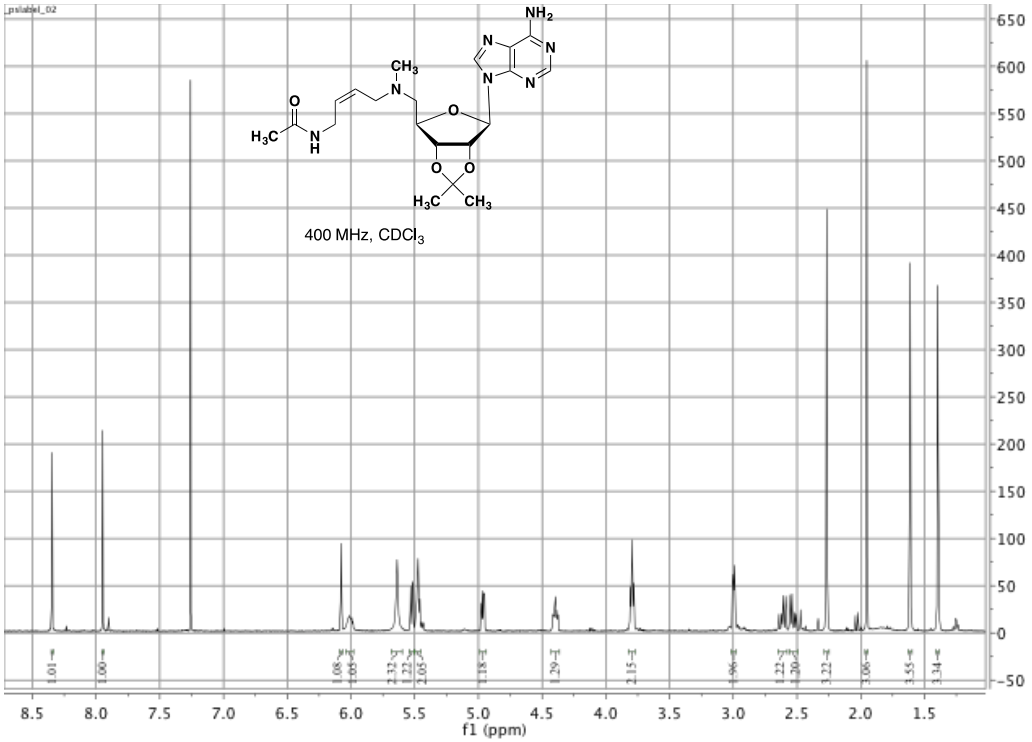
2-(4-(((*Z*)-4-((((3a*R*,4*R*,6*R*,6a*R*)-6-(6-Amino-9*H*-purin-9-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methyl)(methyl)amino)but-2-en-1-yl)amino)-2-methyl-4-oxobutan-2-yl)-3,5-dimethylphenyl acetate (49)



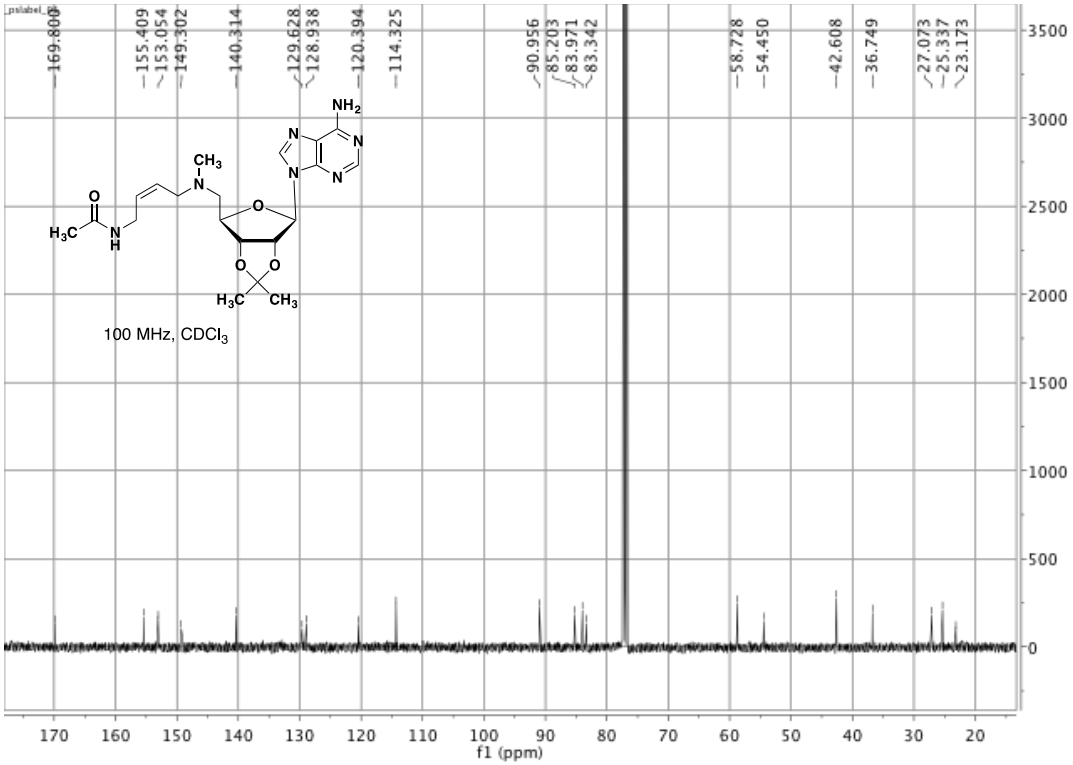
To a stirred suspension of amine **11a** (0.02 g, 0.05 mmol) and 3-(2-acetoxy-4,6-dimethylphenyl)-3-methylbutanoic acid (trimethyl-lock acid[6], **48**) (0.014 g, 0.05 mmol) in 1 mL of DCM was added EDC (0.01 g, 0.06 mmol) followed by polystyrene bound DMAP (40 mg). The mixture was stirred at rt for 22 h, loaded directly onto a flash column and purified by flash chromatography (gradient from 0–10% MeOH in DCM) to give the amide **49** (0.03 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.95 (s, 1H), 6.80 (s, 1H), 6.56 (s, 1H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.66 (br s, 2H), 5.56 (br s, 1H), 5.46 (dd, *J* = 6.4, 2.0 Hz, 1H), 5.36 (m, 1H), 5.10 (m, 1H), 4.93 (dd, *J* = 6.4, 3.6 Hz, 1H), 4.37 (m, 1H), 3.58 (app. t, *J* = 6.0 Hz, 2H); 3.29–3.19 (m, 2H), 2.96 (br s, 2H), 2.47 (s, 3H), 2.45 (s, 3H), 2.32 (s, 3H), 2.21 (m, 6H), 1.61 (m, 8H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 171.4, 155.6, 153.1, 149.7, 148.7, 138.5, 136.6, 133.1, 132.5, 123.3, 121.9, 119.8, 118.7, 114.9, 90.9, 83.9, 82.9, 57.4, 48.9, 39.7, 36.3, 31.9, 31.8, 26.9, 25.4, 25.1, 21.9, 20.1; LC/MS (ESI) calcd for $C_{33}H_{46}N_7O_6$ $(M + H)^+$ 636.4, found 636.4; HRMS (*m*/*z*): $[M+H]^+$ calcd for $C_{33}H_{46}N_7O_6$, 636.3504; found, 636.3515; $[\alpha]^{20}_D$ = +14.5 (*c* = 1.32, $CHCl_3$).

Copies of NMR Spectra

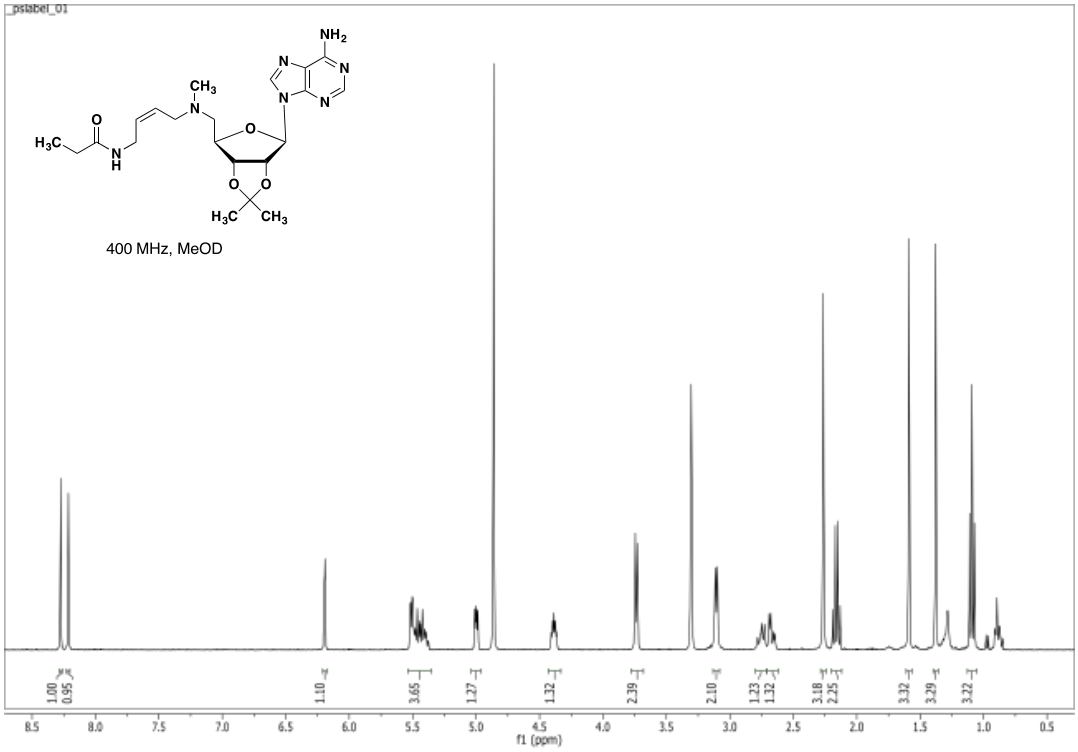
S1 ^{1}H NMR



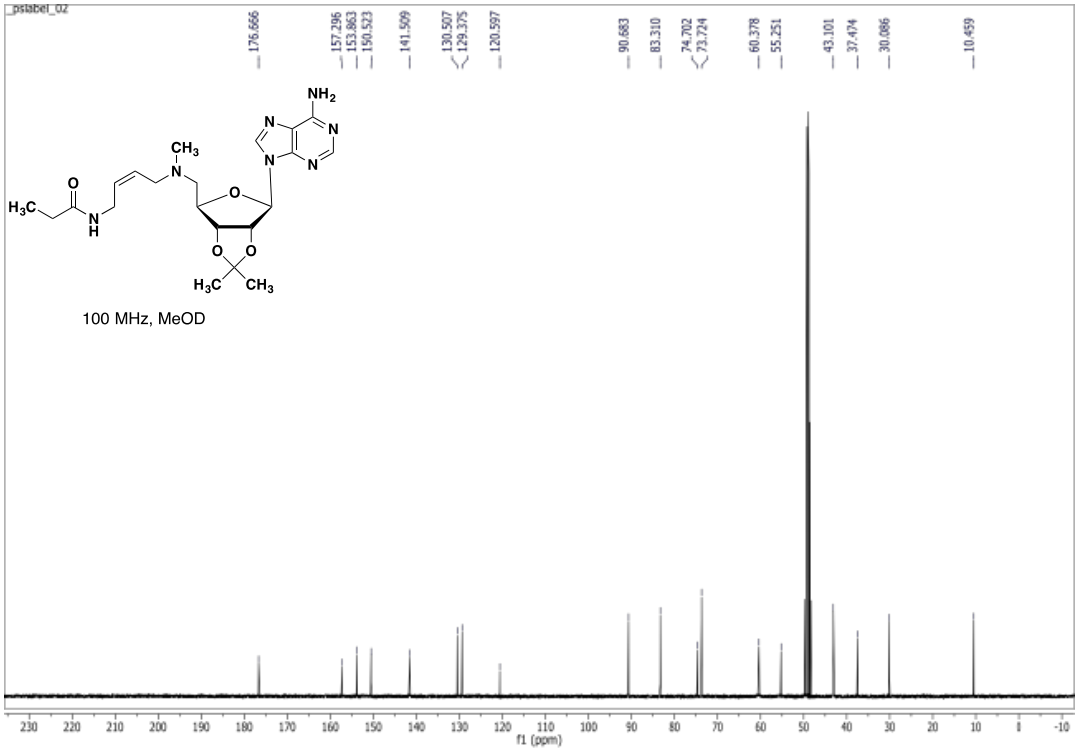
S1 ^{13}C NMR



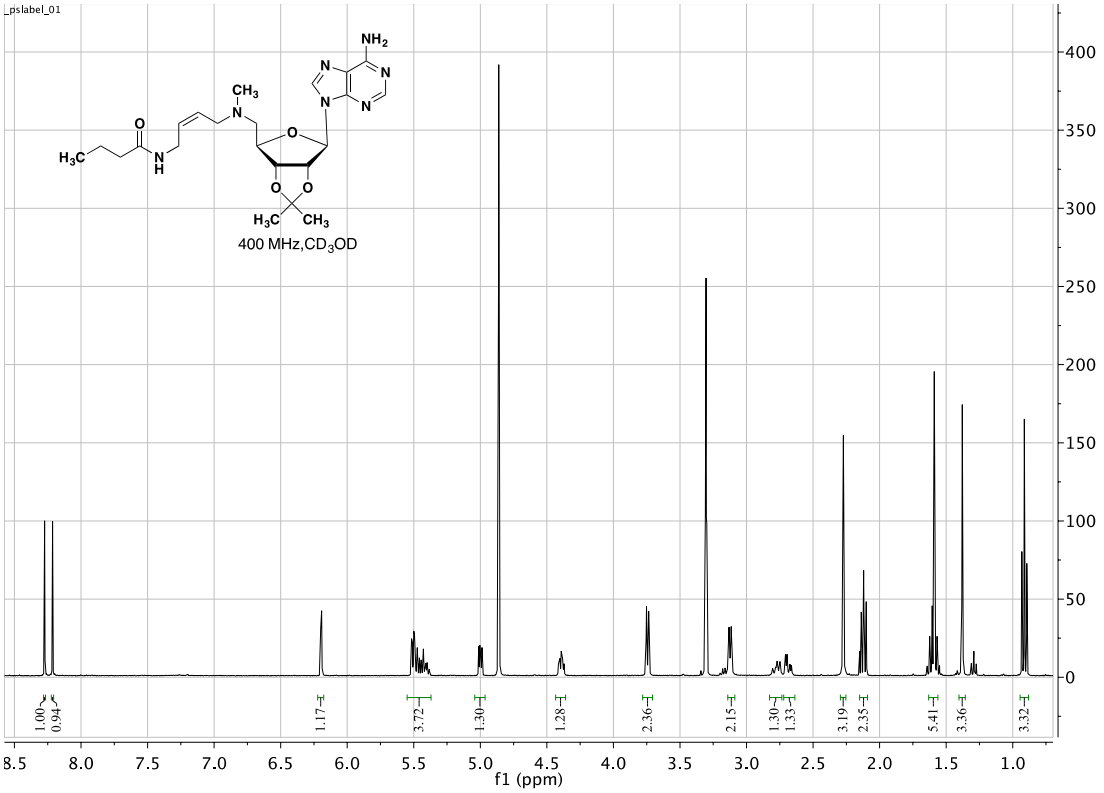
S2 ^{1}H NMR



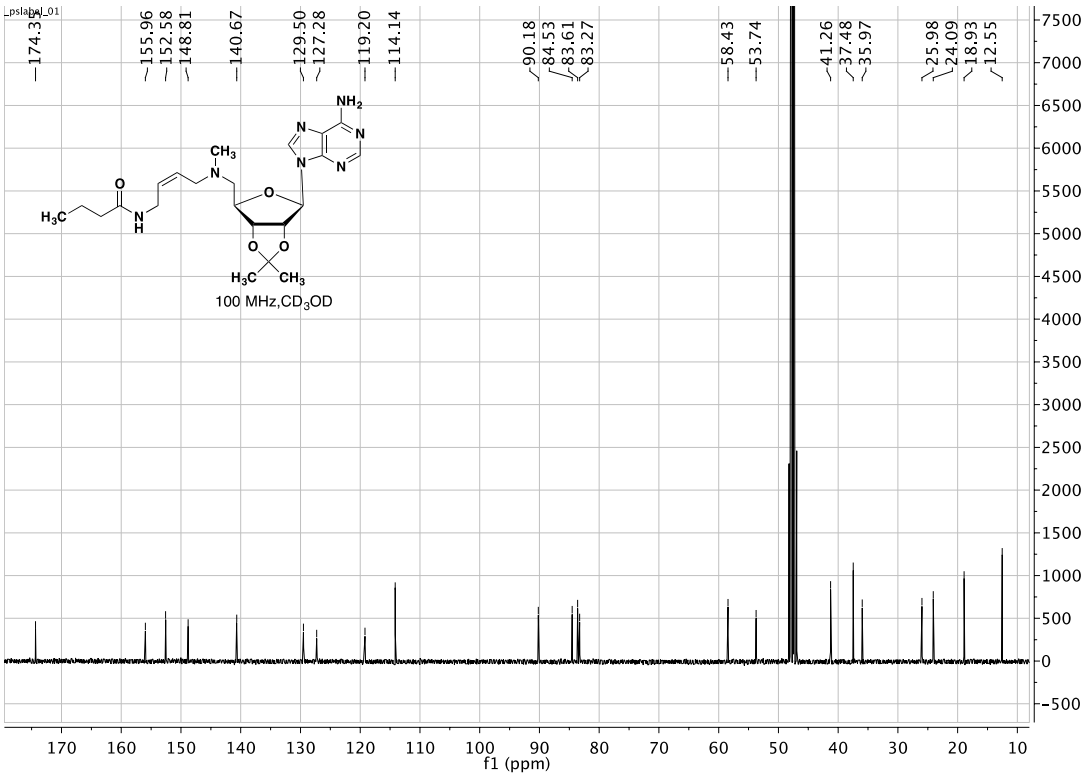
S2 ^{13}C NMR



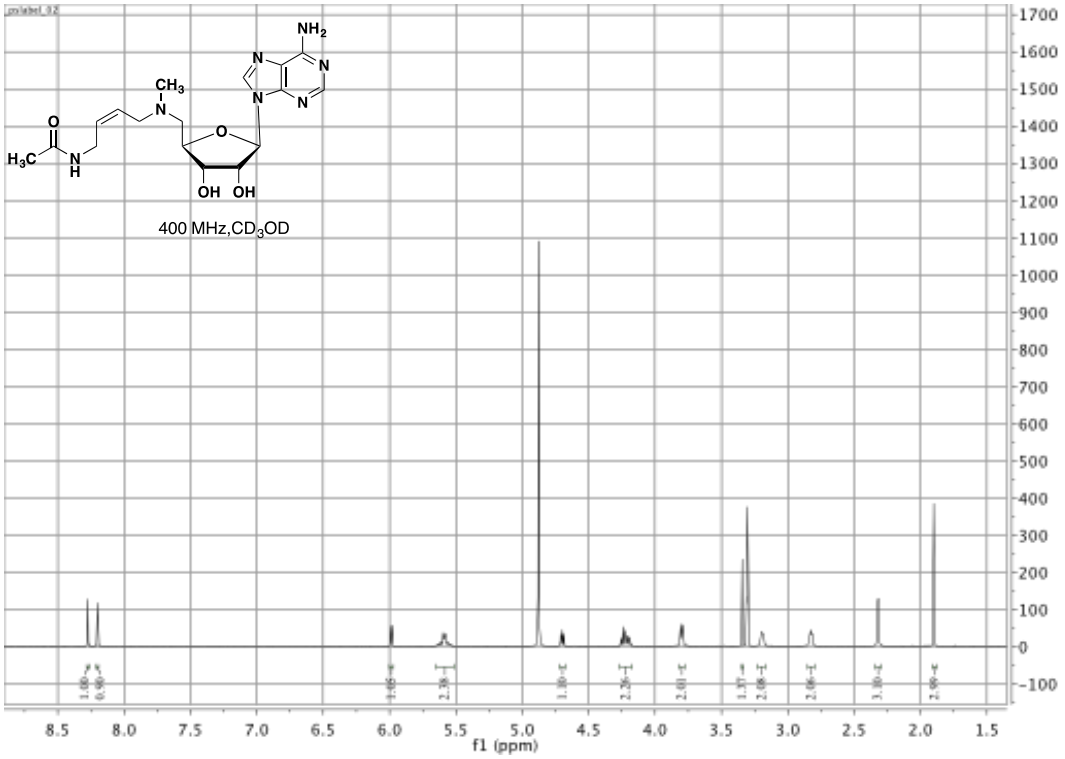
S3 ^{1}H NMR



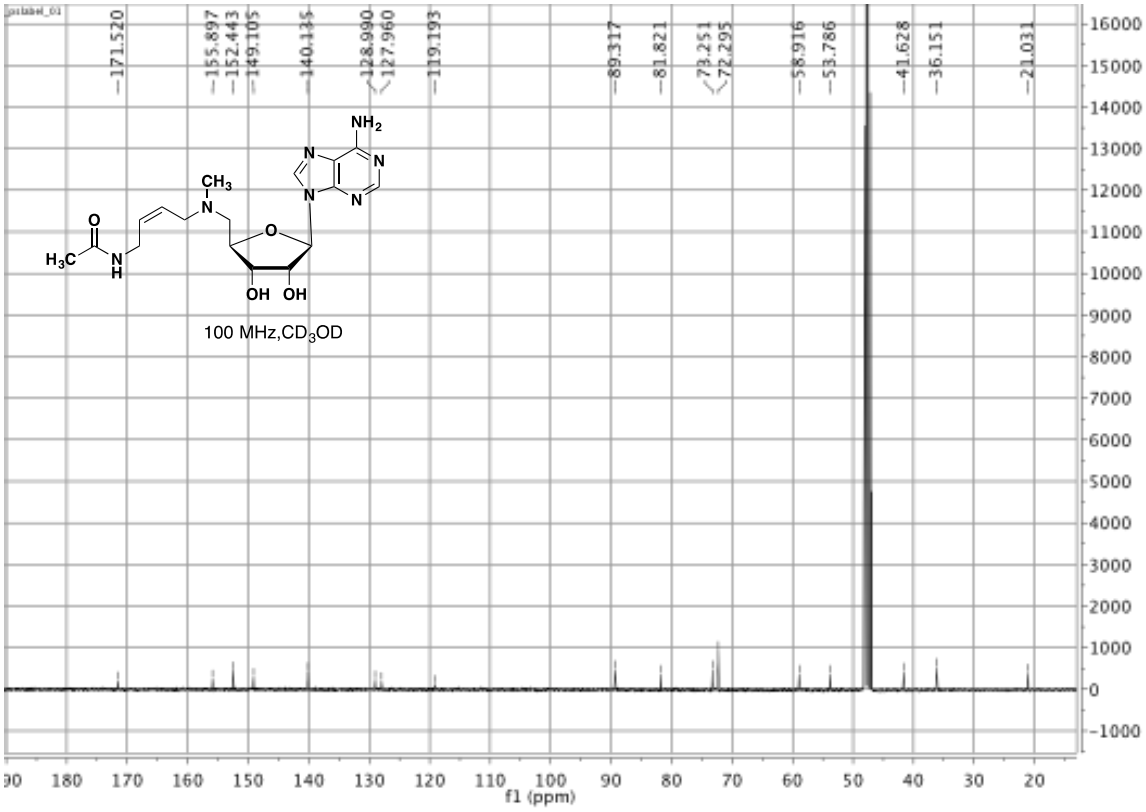
S3 ^{13}C NMR



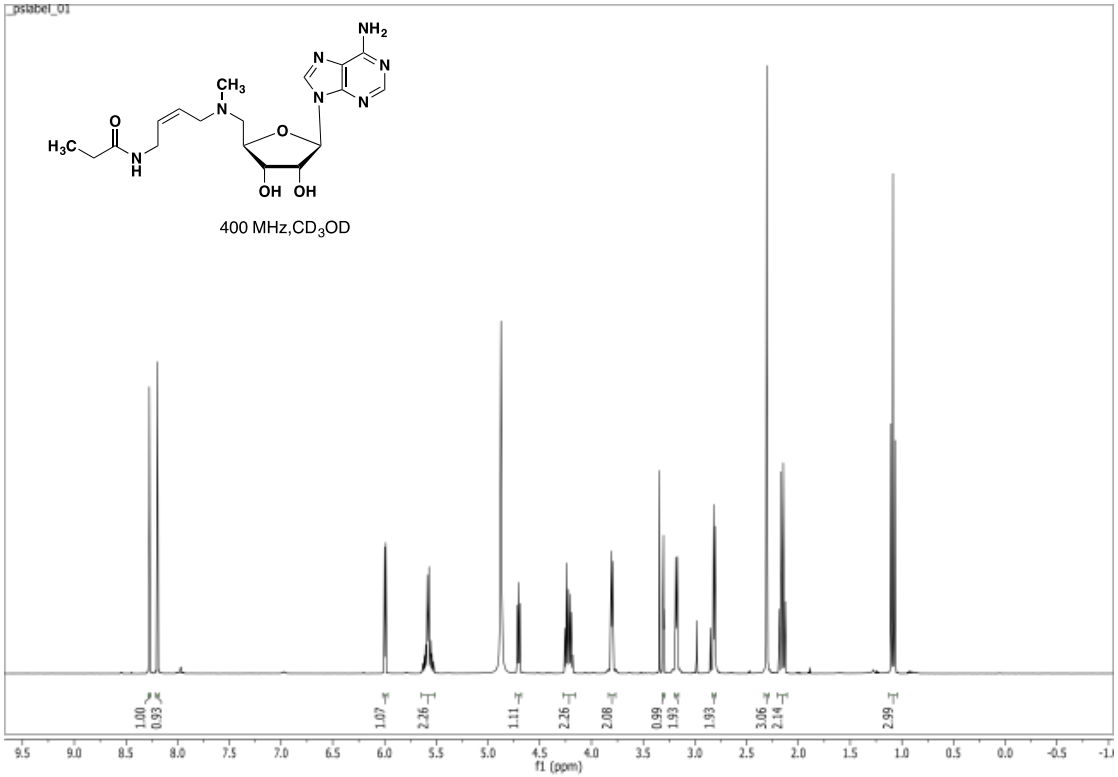
5a ^{1}H NMR



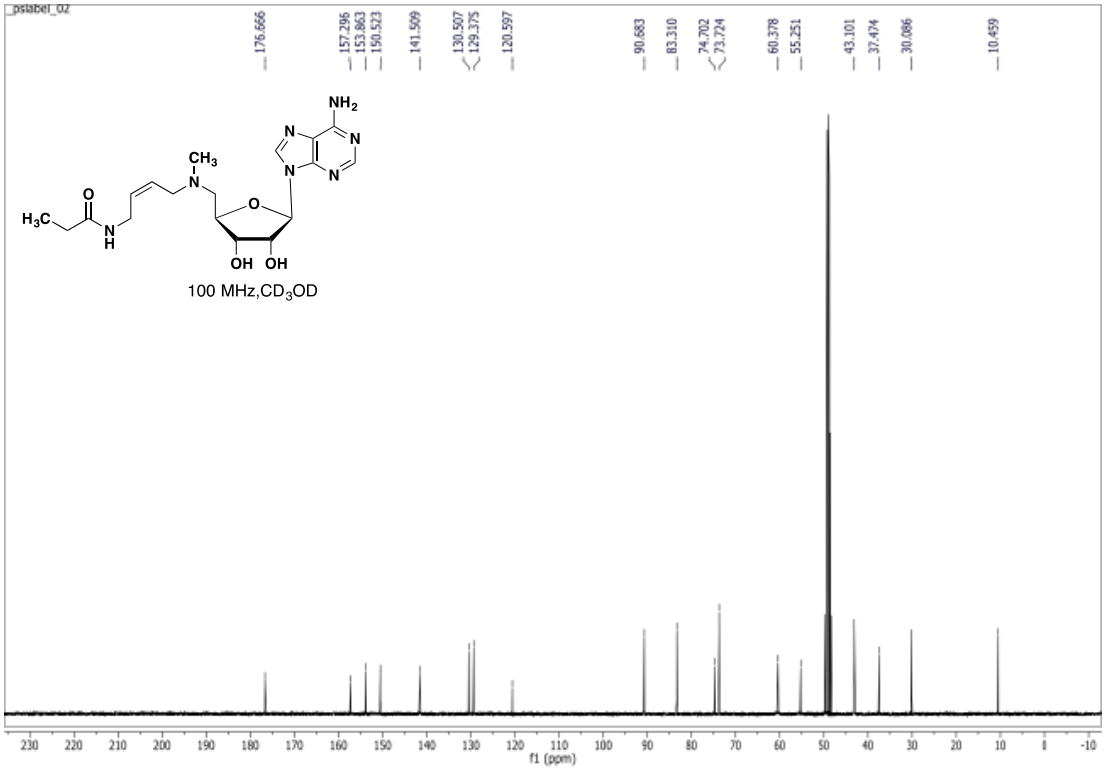
5a ^{13}C NMR



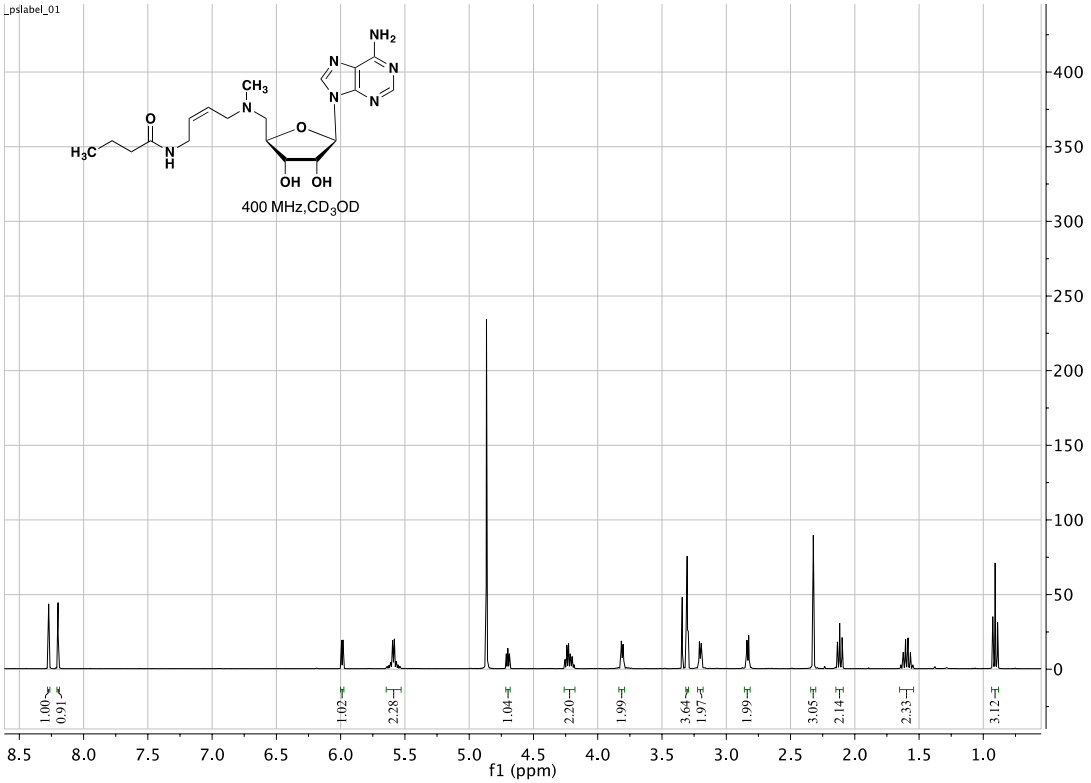
5b ^{1}H NMR



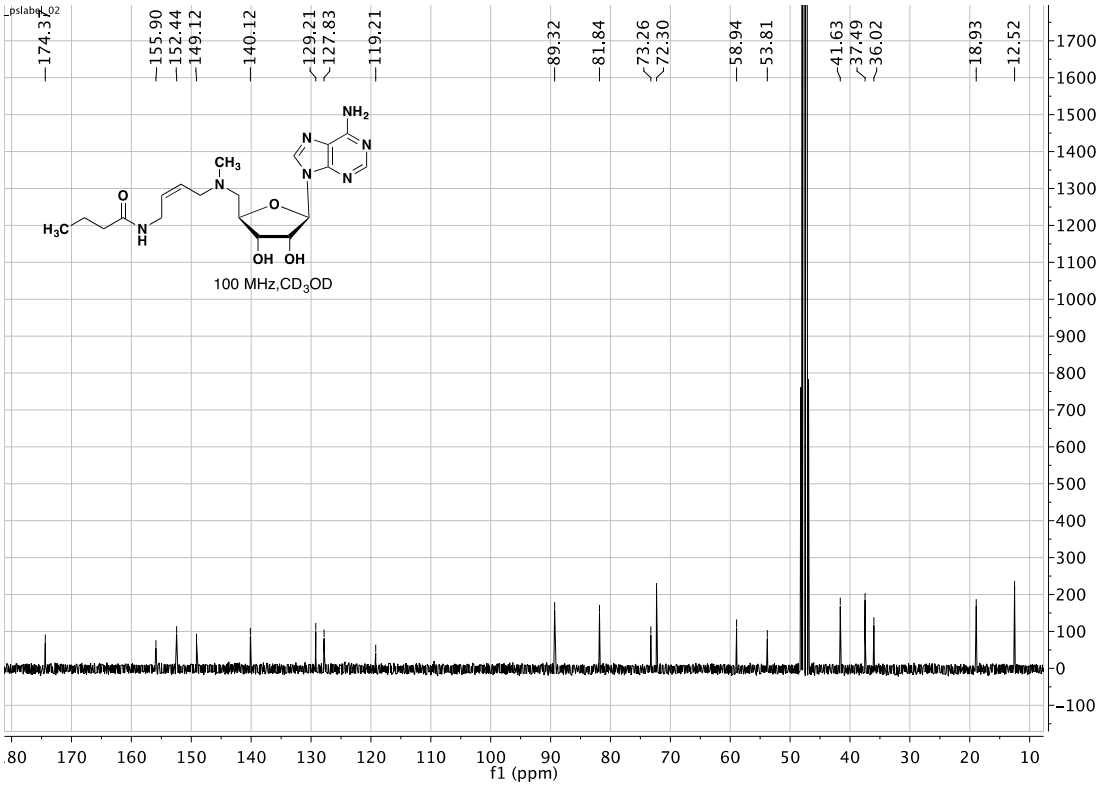
5b ^{13}C NMR



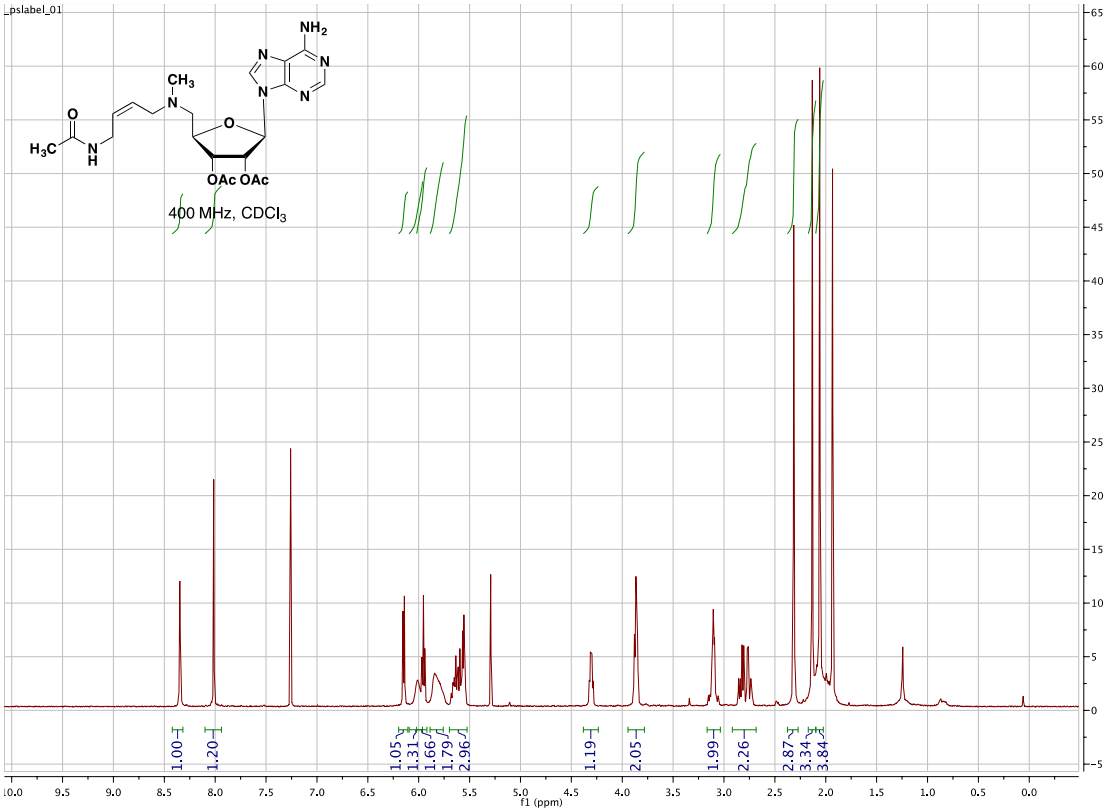
5c ^{1}H NMR



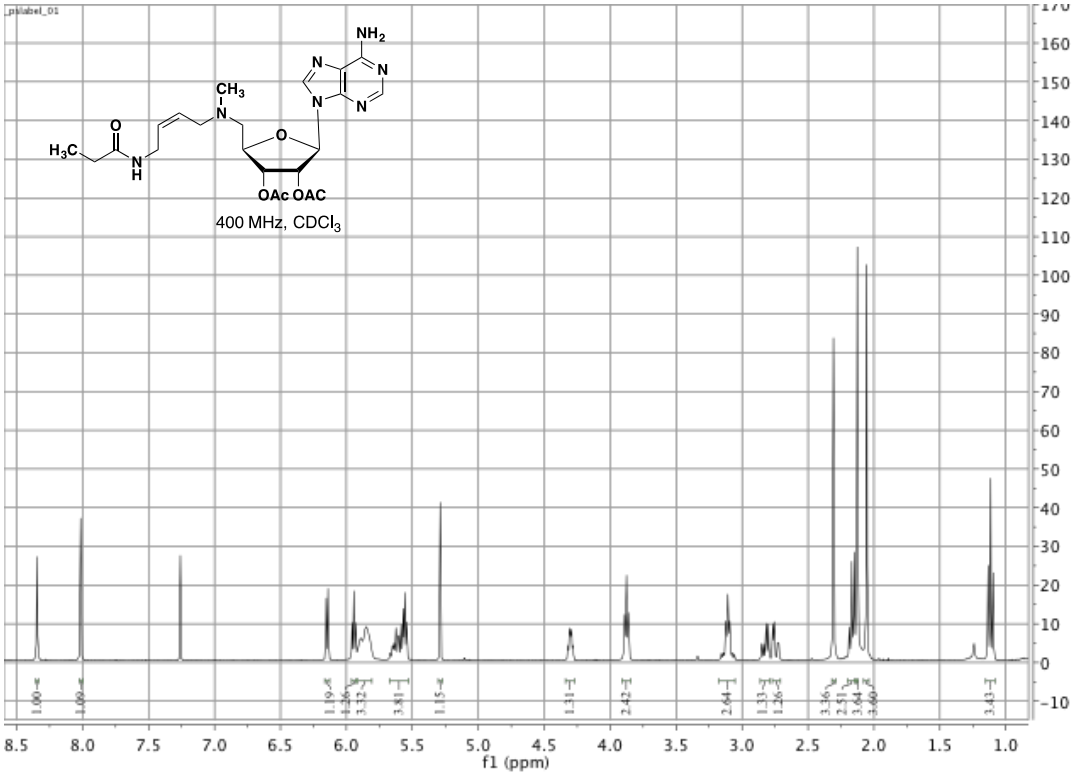
5c ^{13}C NMR



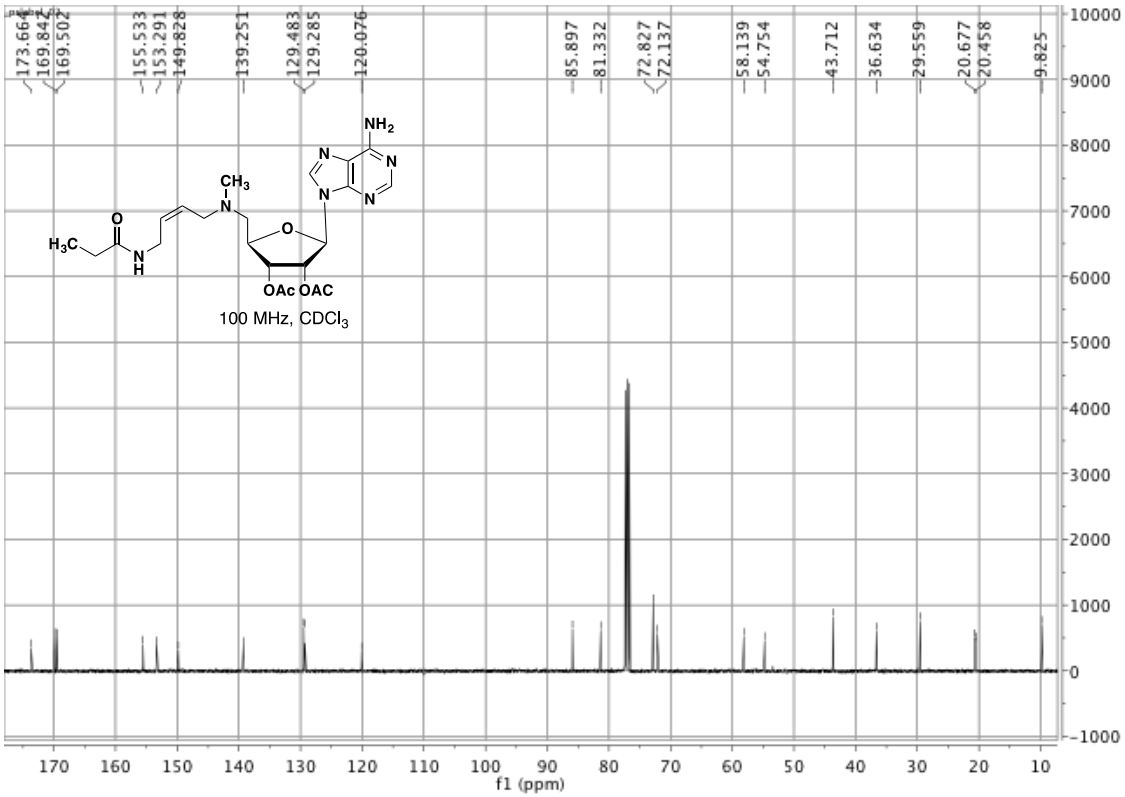
6a ^{1}H NMR


_pslabel_01
NH2
N
N
N
N
CH3
N
O
O
H3C
N
H
OAc OAc
400 MHz, CDCl3
1.00
1.20
1.05
1.31
1.66
1.79
2.96
1.19
2.05
1.99
2.26
2.87
3.34
3.84
f1 (ppm)

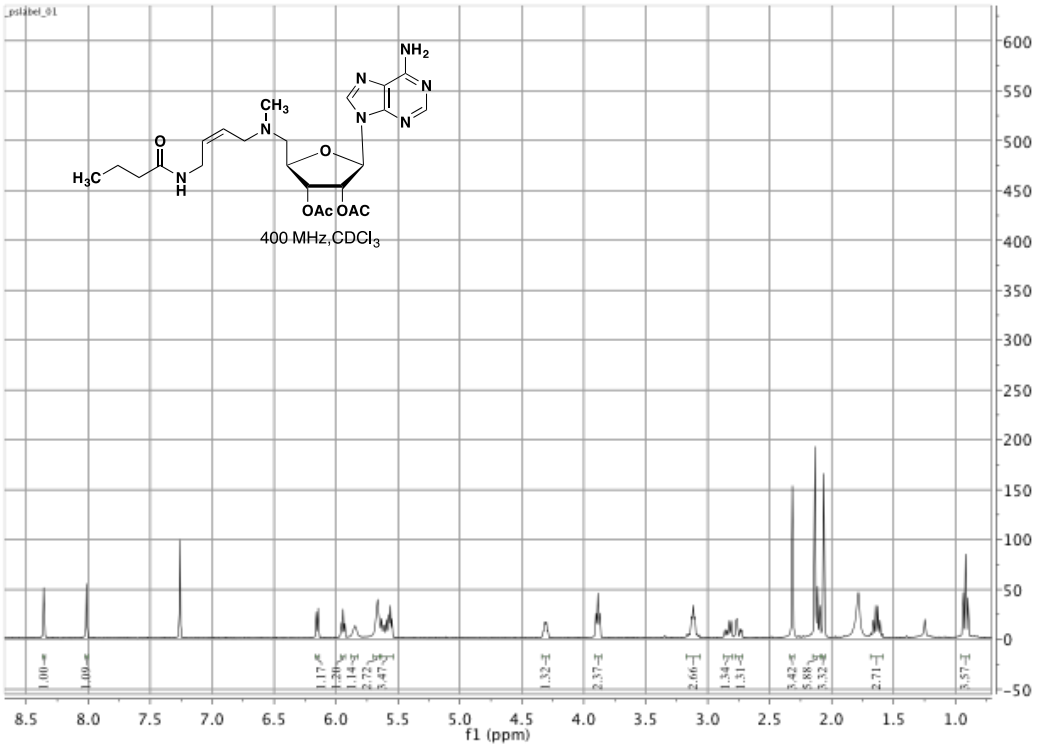
6b ^{1}H NMR



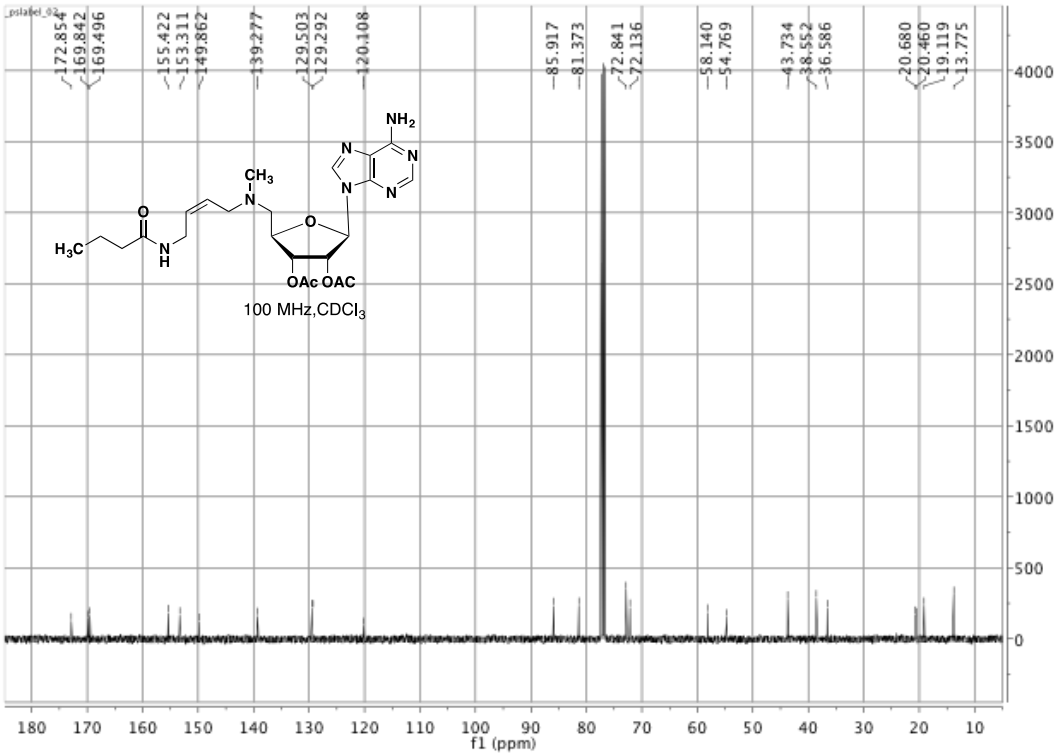
6b ^{13}C NMR



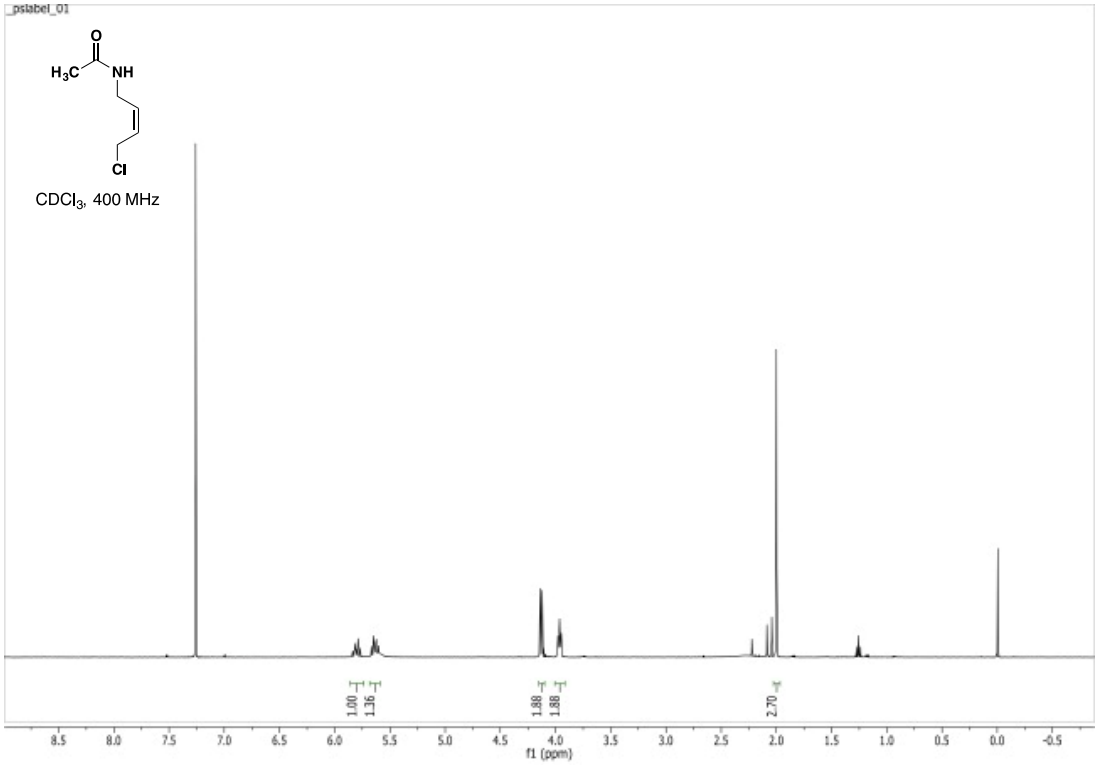
6c ^{1}H NMR



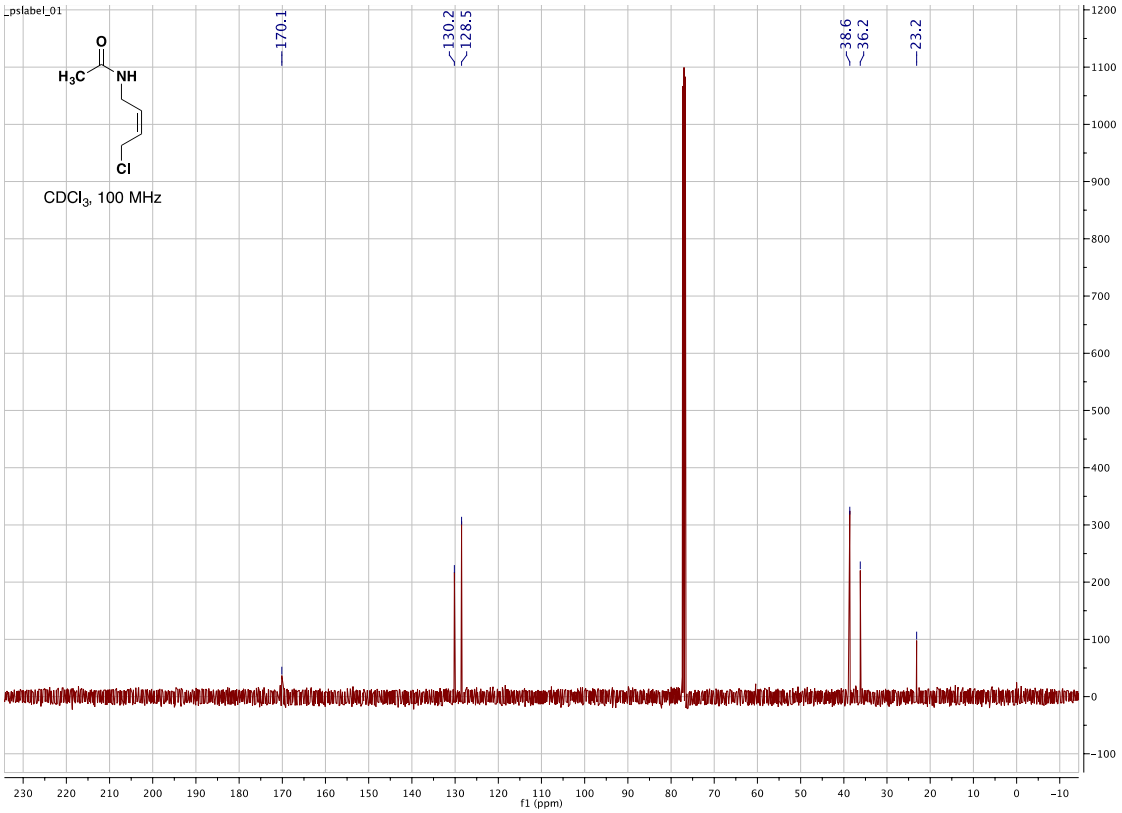
6c ^{13}C NMR



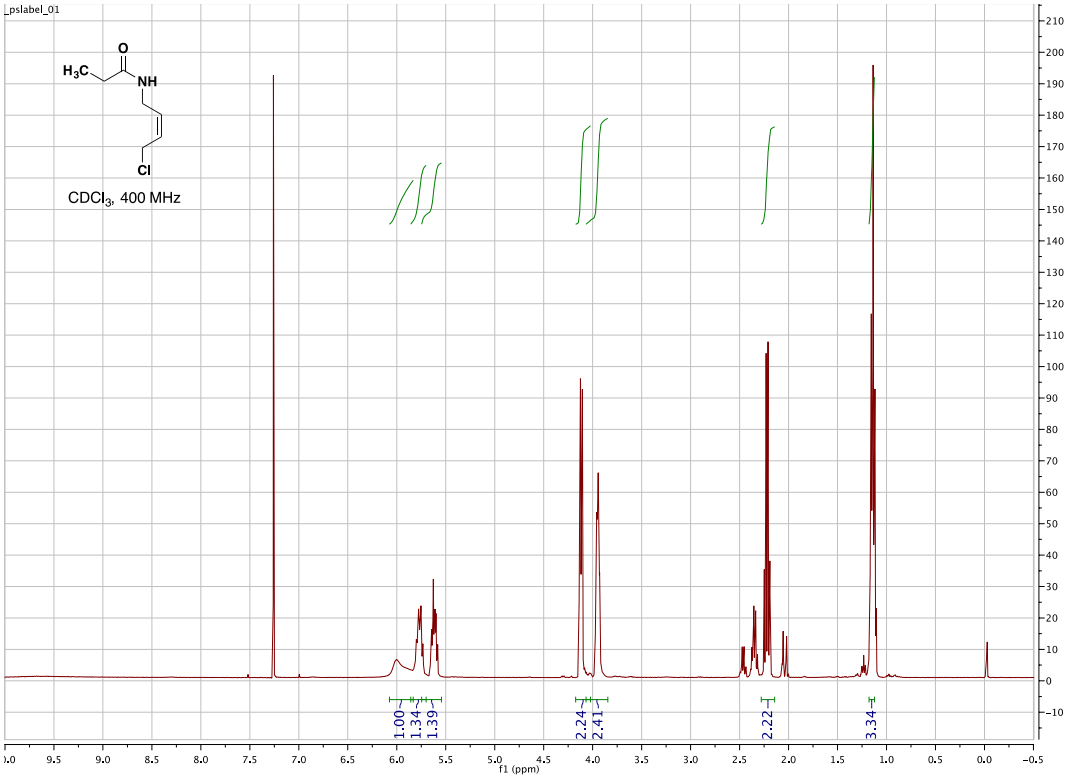
7a ^{1}H NMR



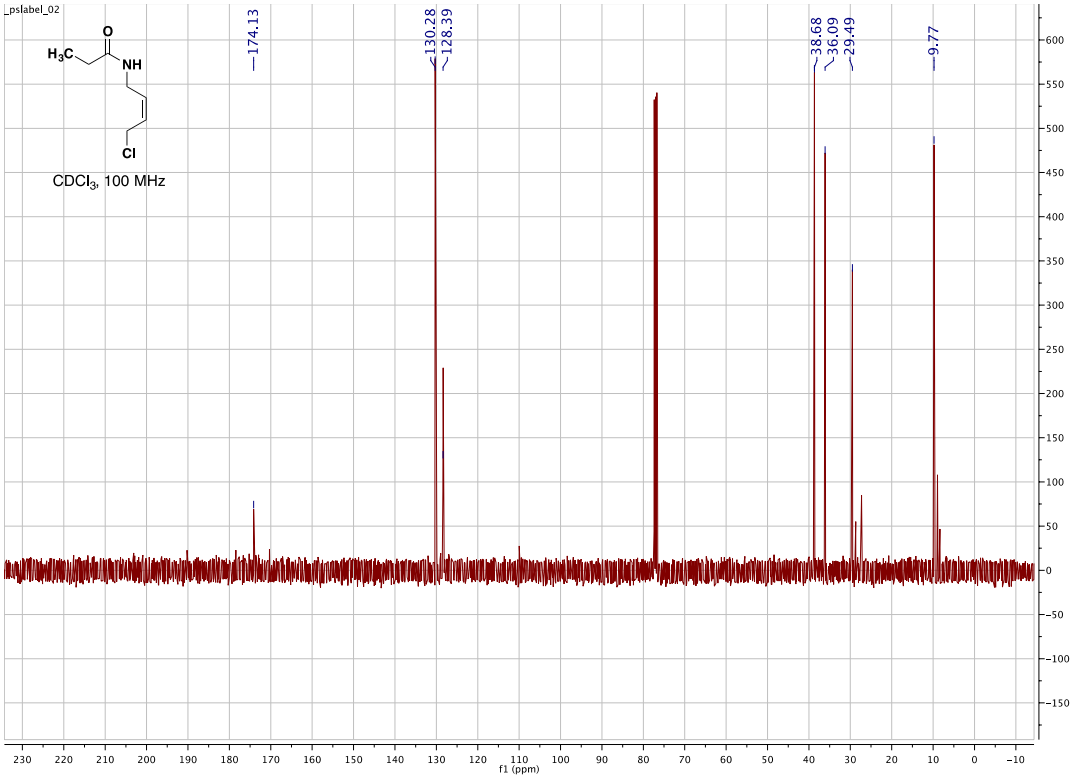
7a ^{13}C NMR



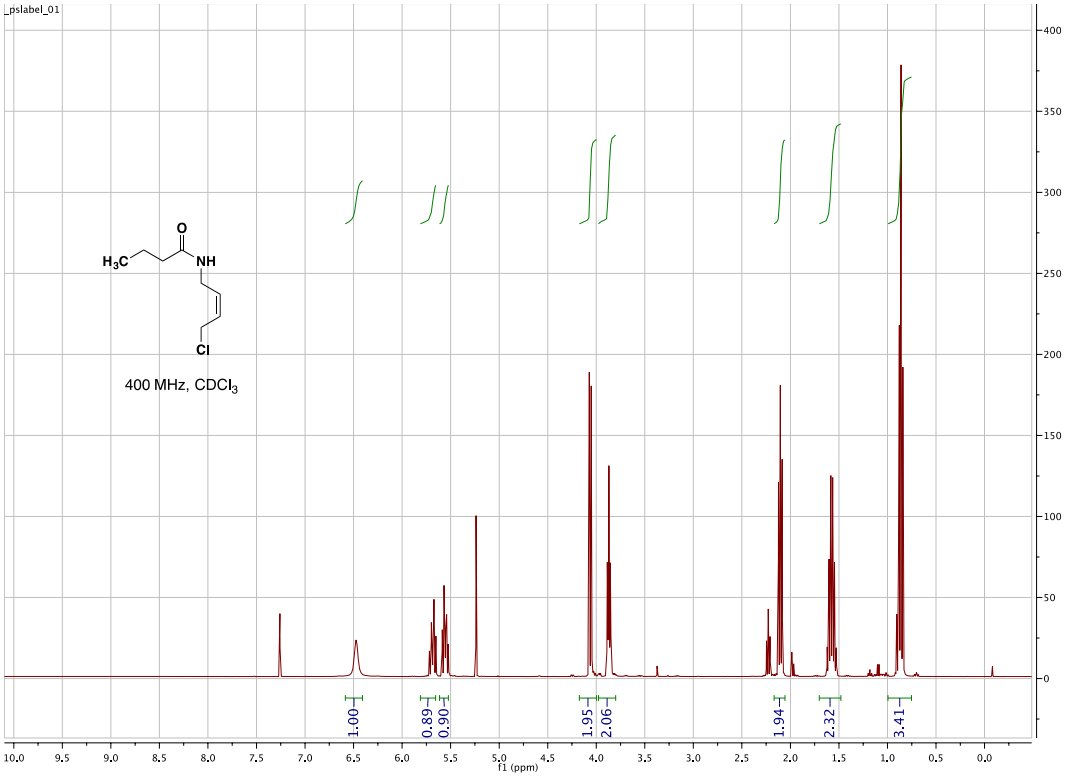
7b ^{1}H NMR



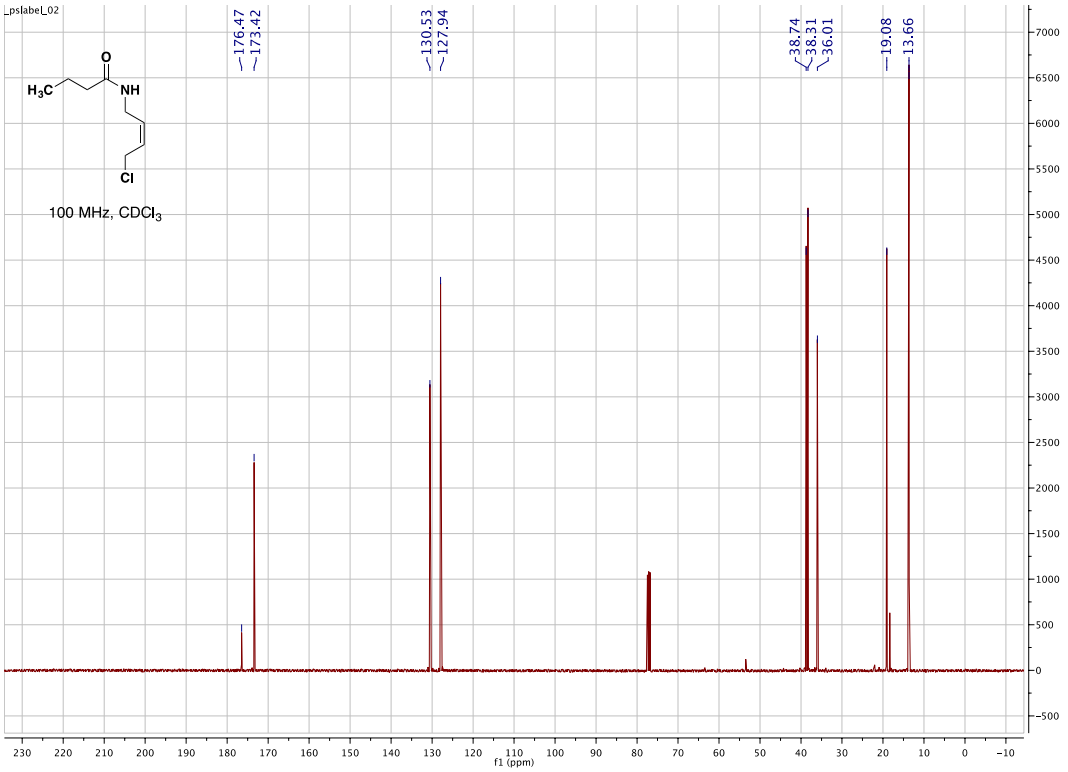
7b ^{13}C NMR



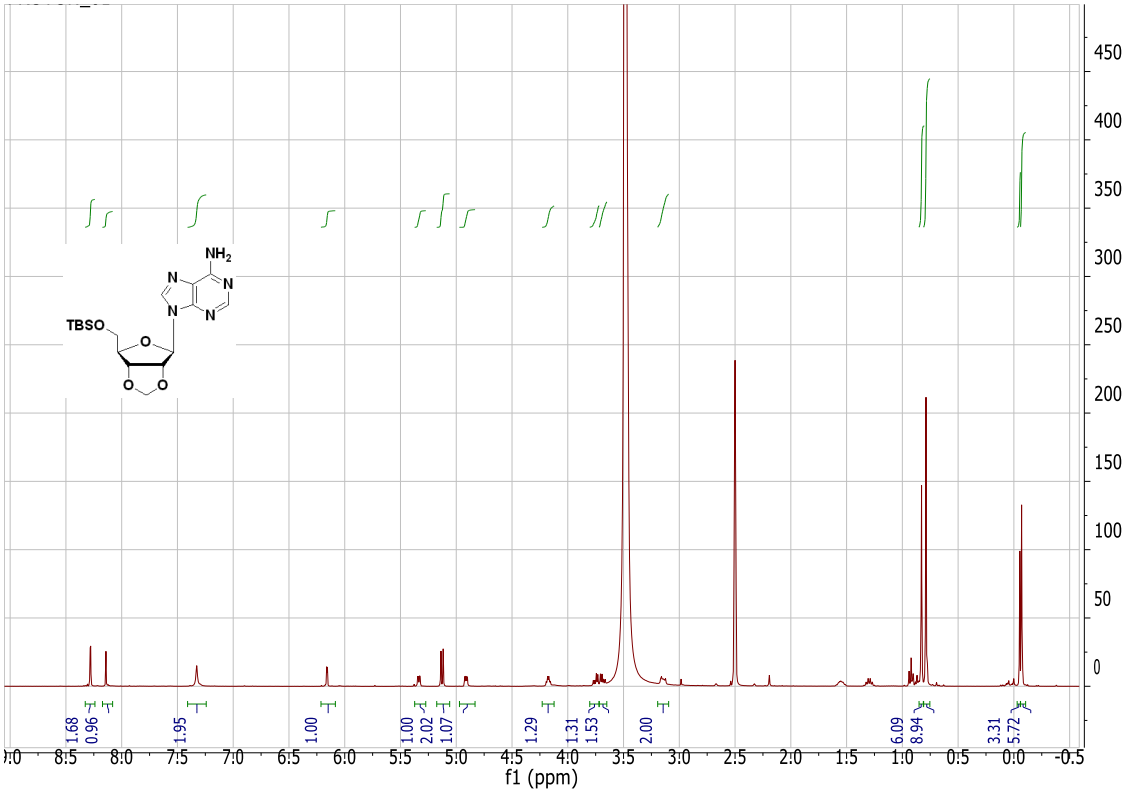
7c ^{1}H NMR



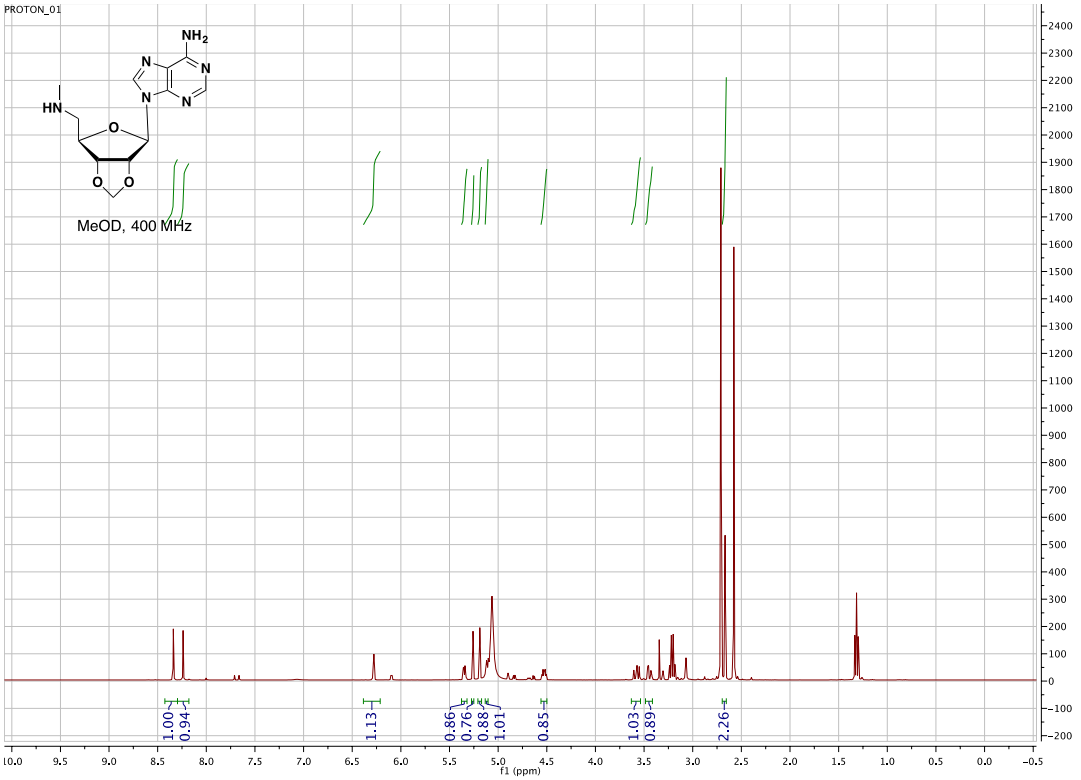
7c ^{13}C NMR



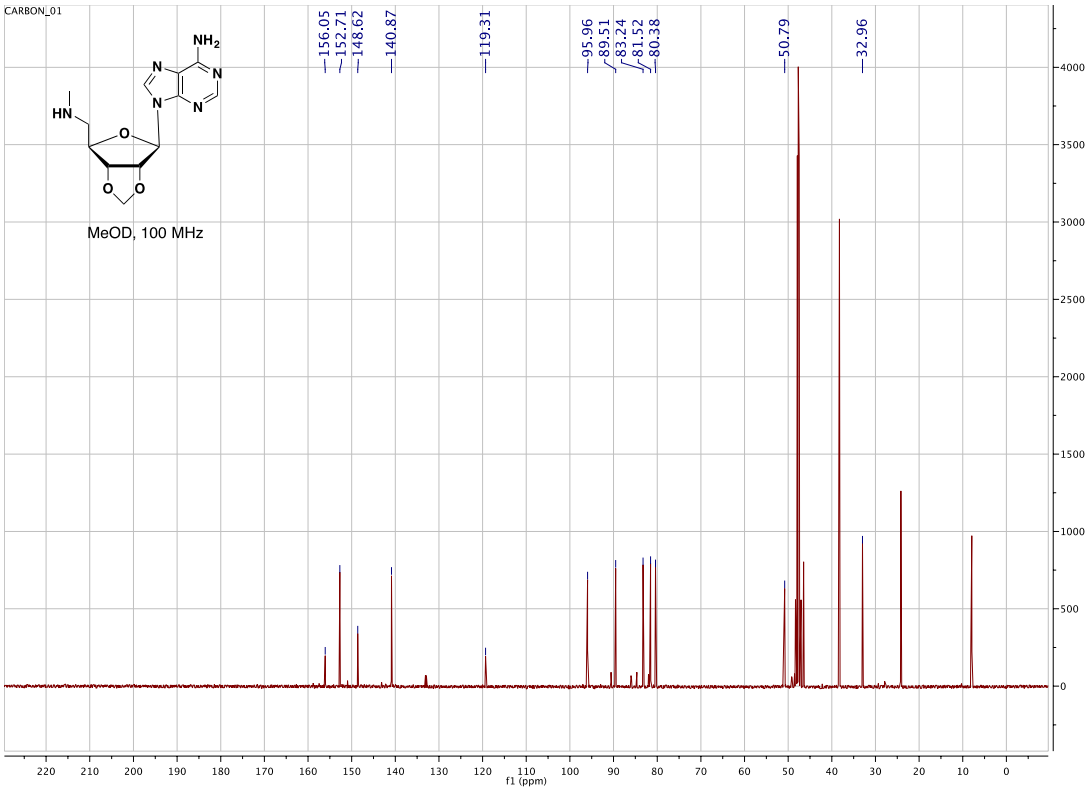
15 ^{1}H NMR


NH2
N
N
N
N
TBSO
O
O
O
450
400
350
300
250
200
150
100
50
0
1.68
0.96
1.95
1.00
1.00
2.02
1.07
1.29
1.31
1.53
2.00
6.09
8.94
3.31
5.72
8:5
8:0
7:5
7:0
6:5
6:0
5:5
5:0
4:5
4:0
3:5
3:0
2:5
2:0
1:5
1:0
0:5
0:0
-0.5
f1 (ppm)

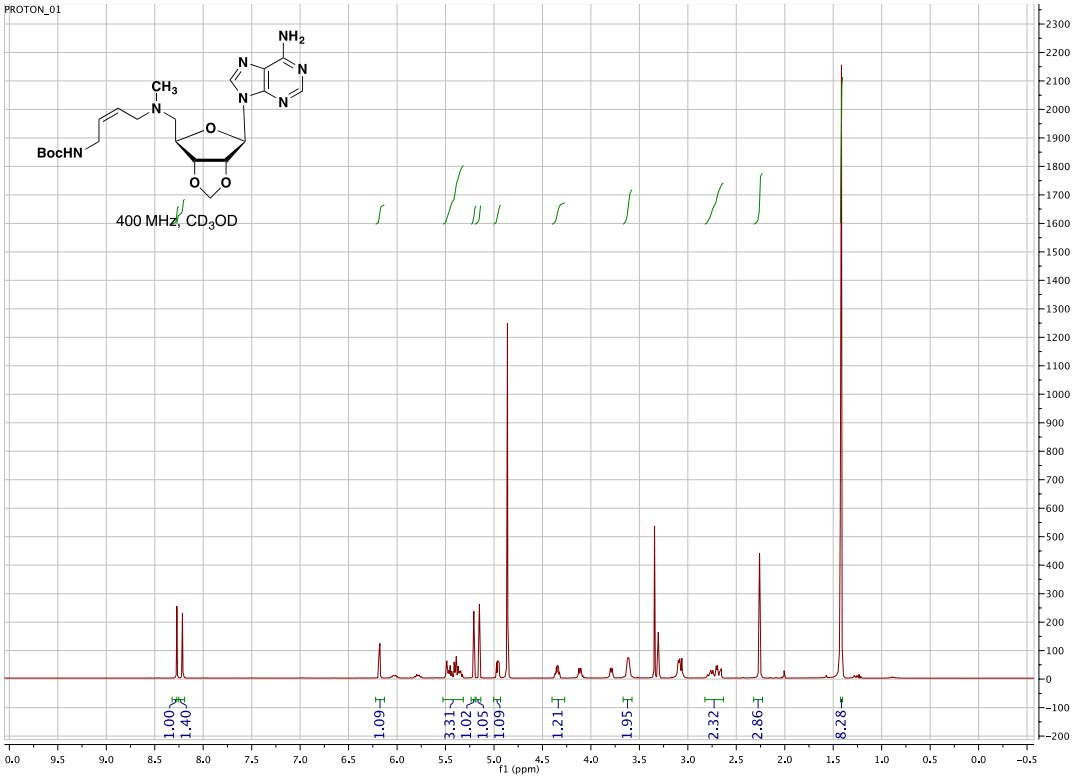
17 ^{1}H NMR



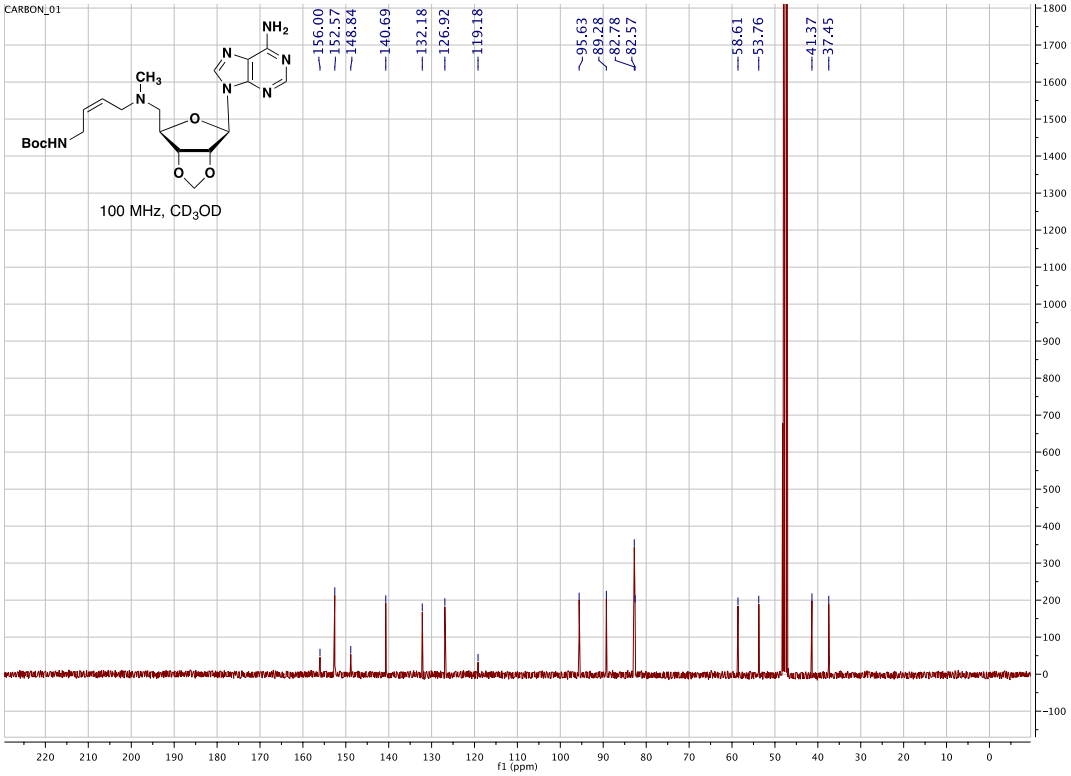
17 ^{13}C NMR



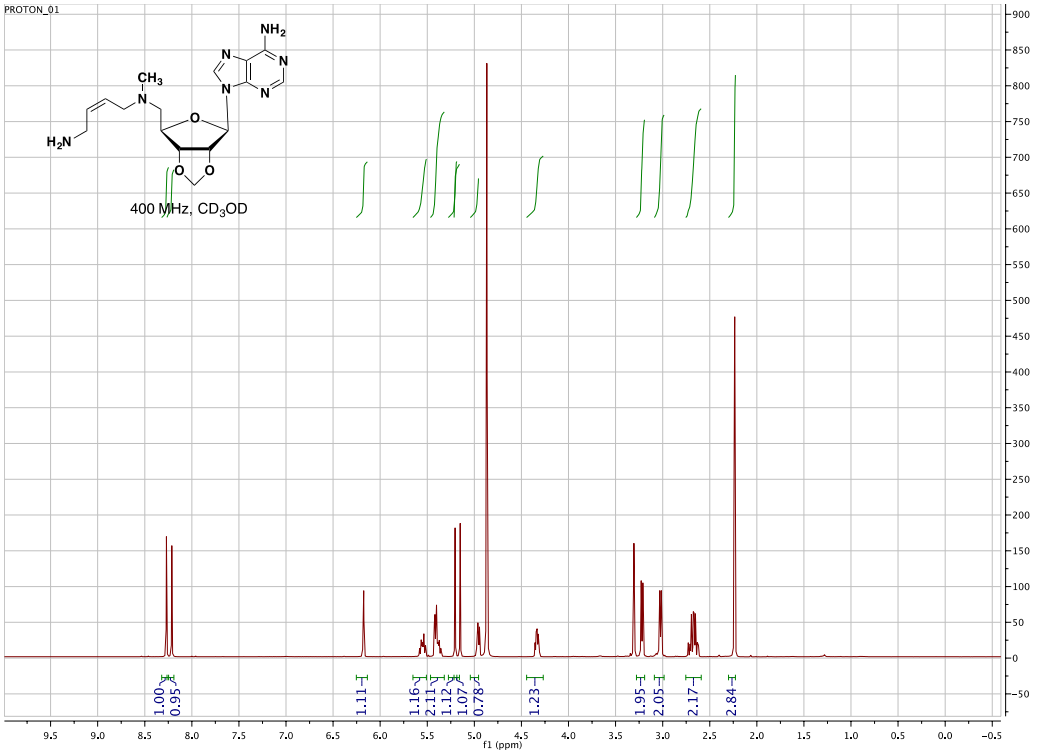
S10 ^{1}H NMR



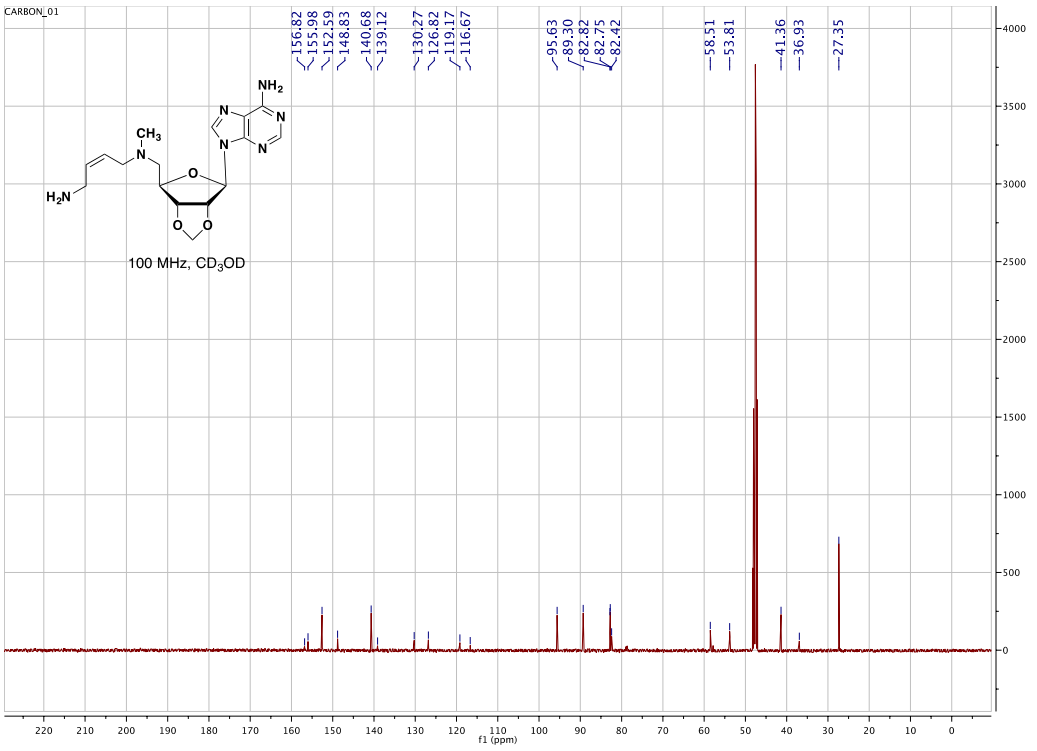
S10 ^{13}C NMR



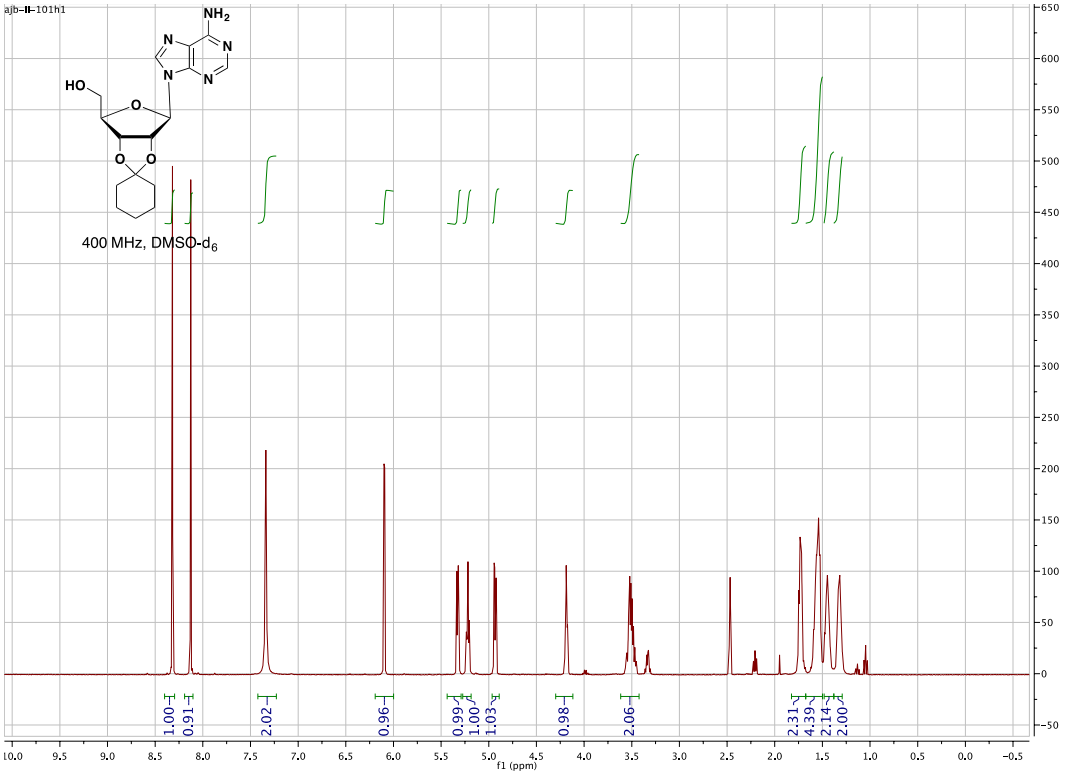
18 ^{1}H NMR



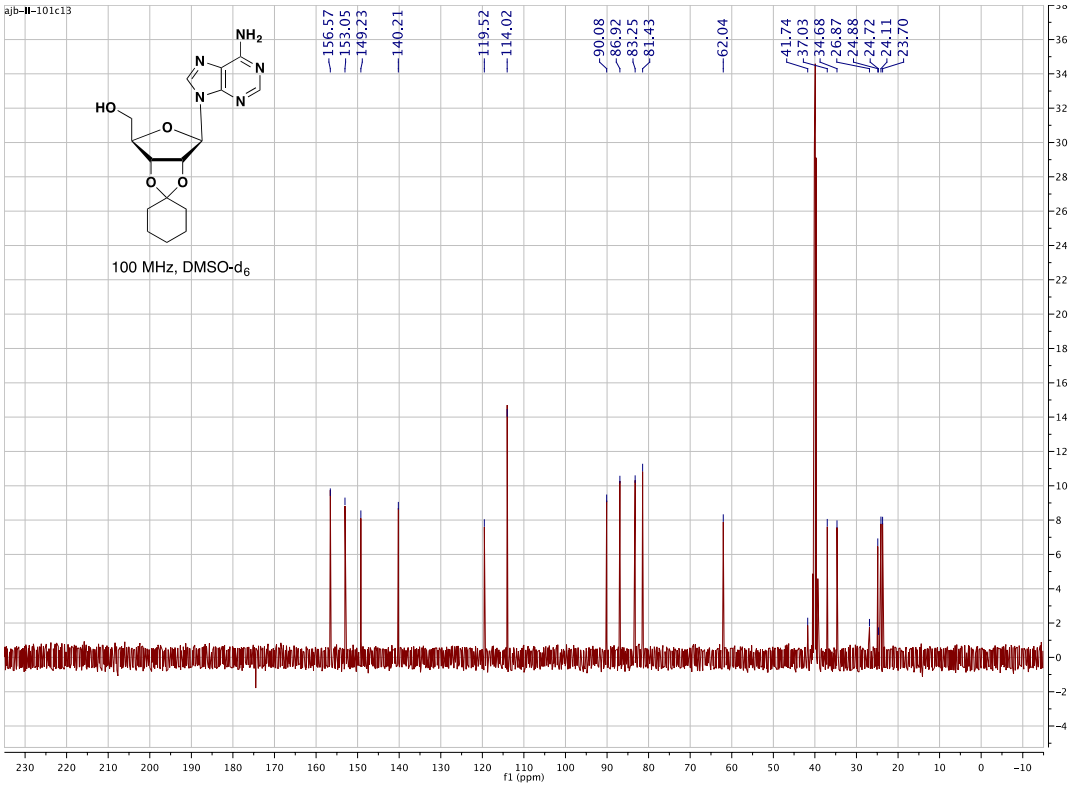
18 ^{13}C NMR



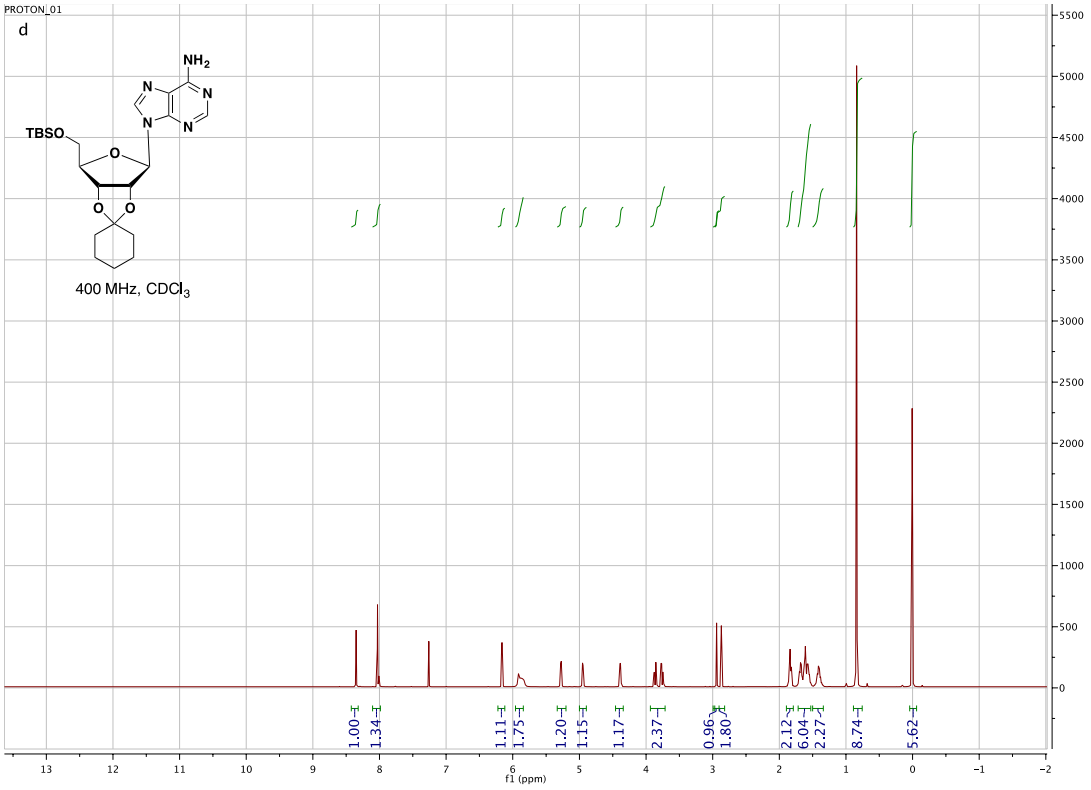
19-intermediate ^{1}H NMR



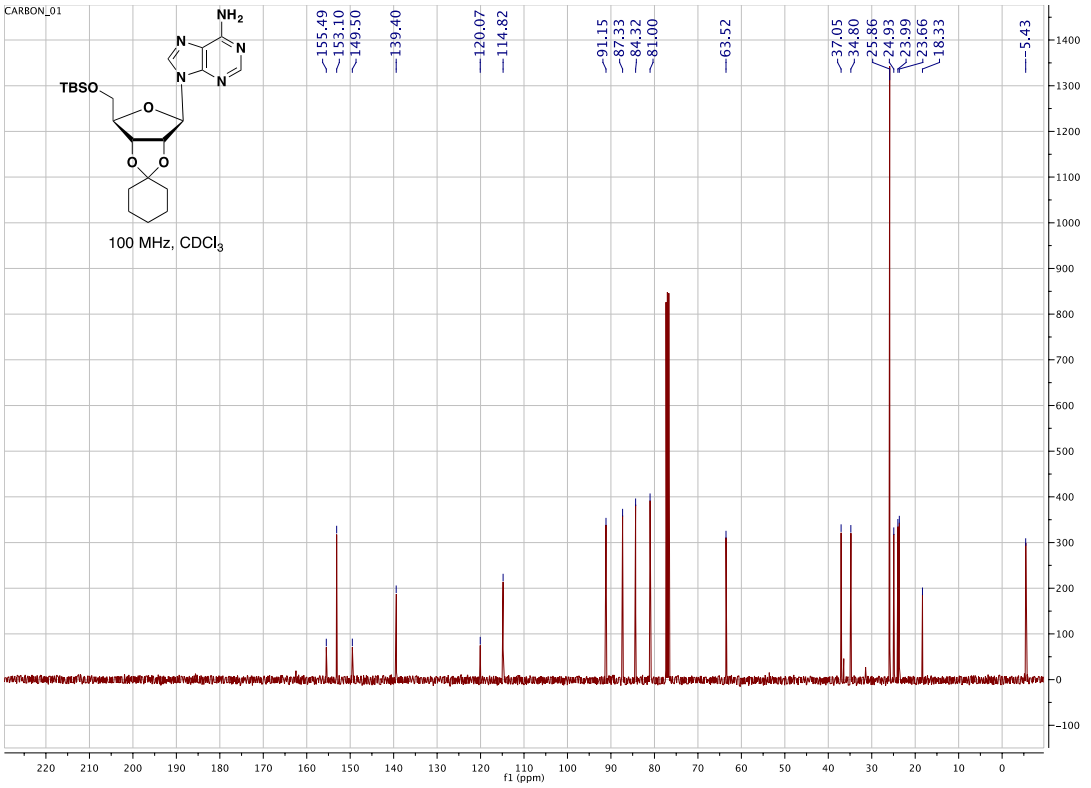
19-intermediate ^{13}C NMR



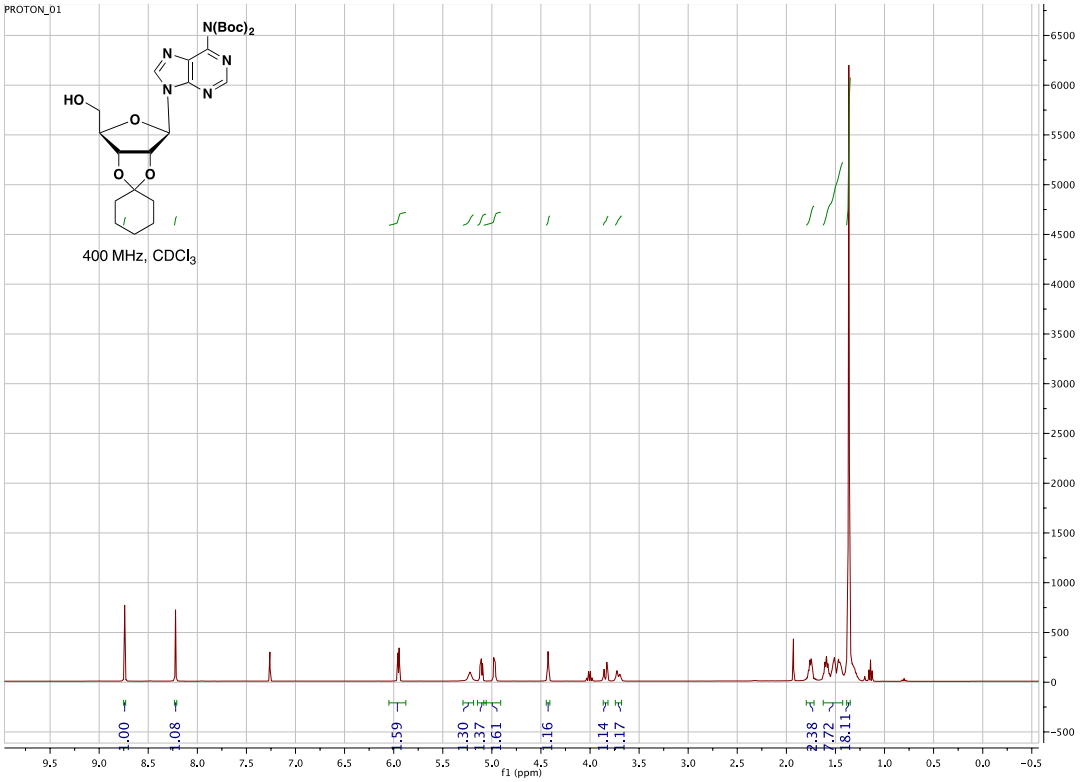
19 ^{1}H NMR



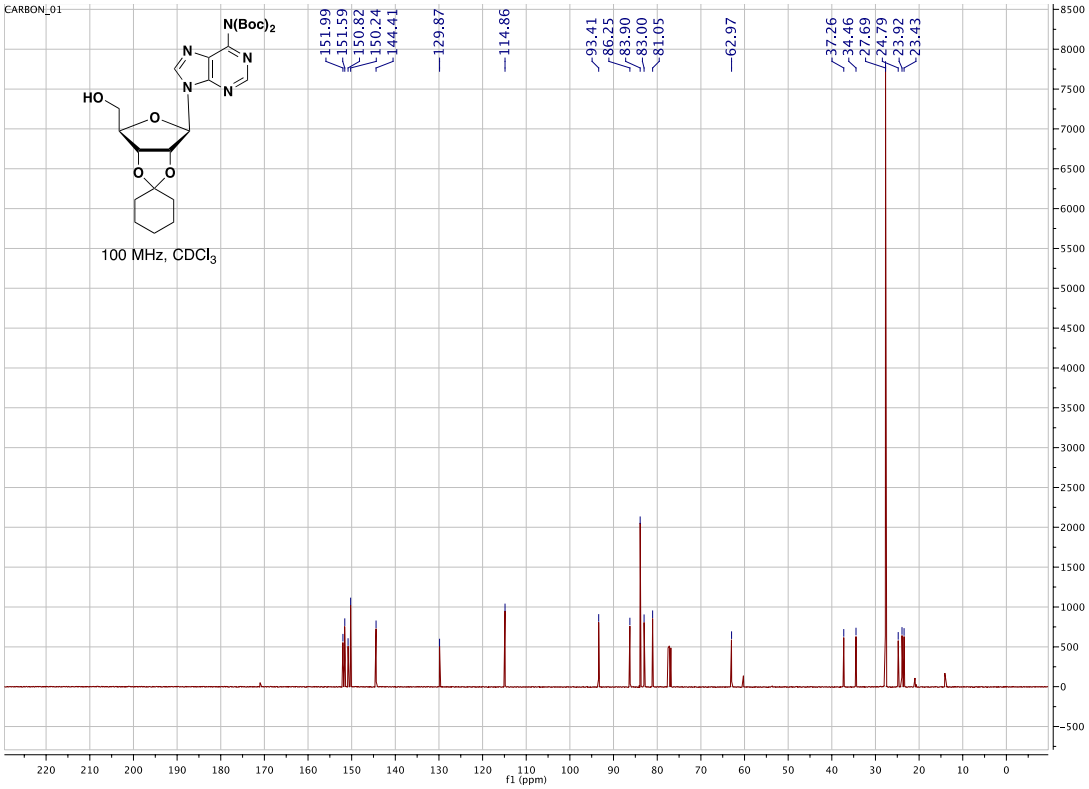
19 ^{13}C NMR



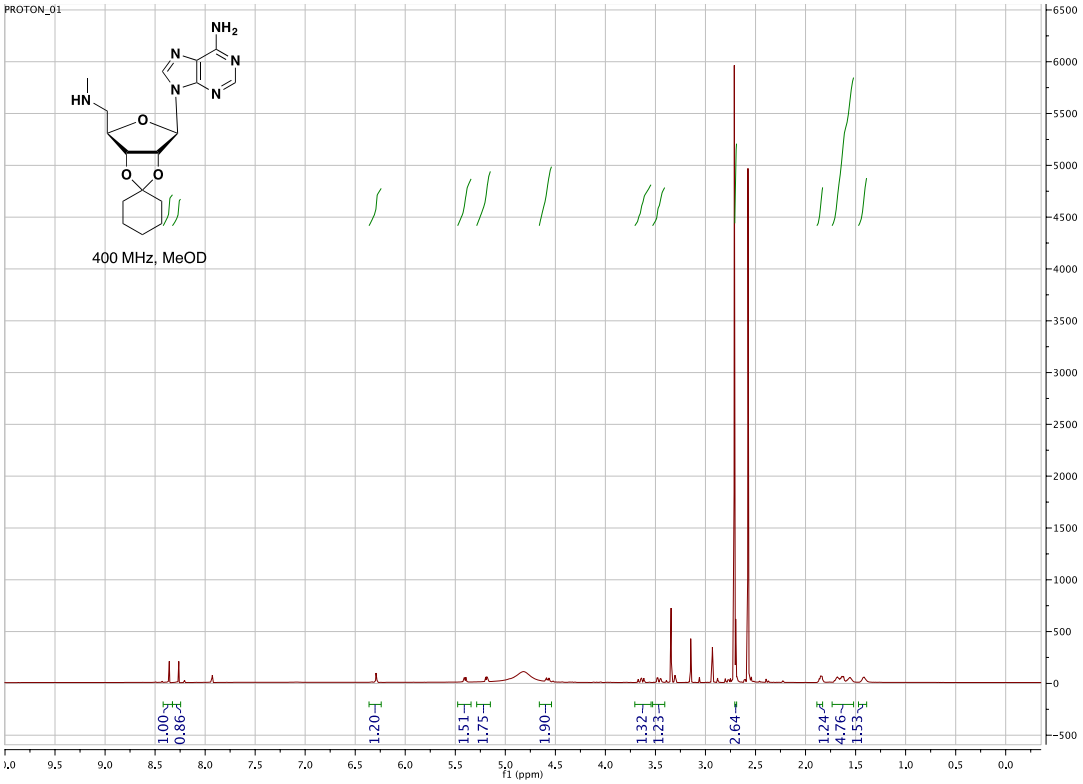
20 ^{1}H NMR



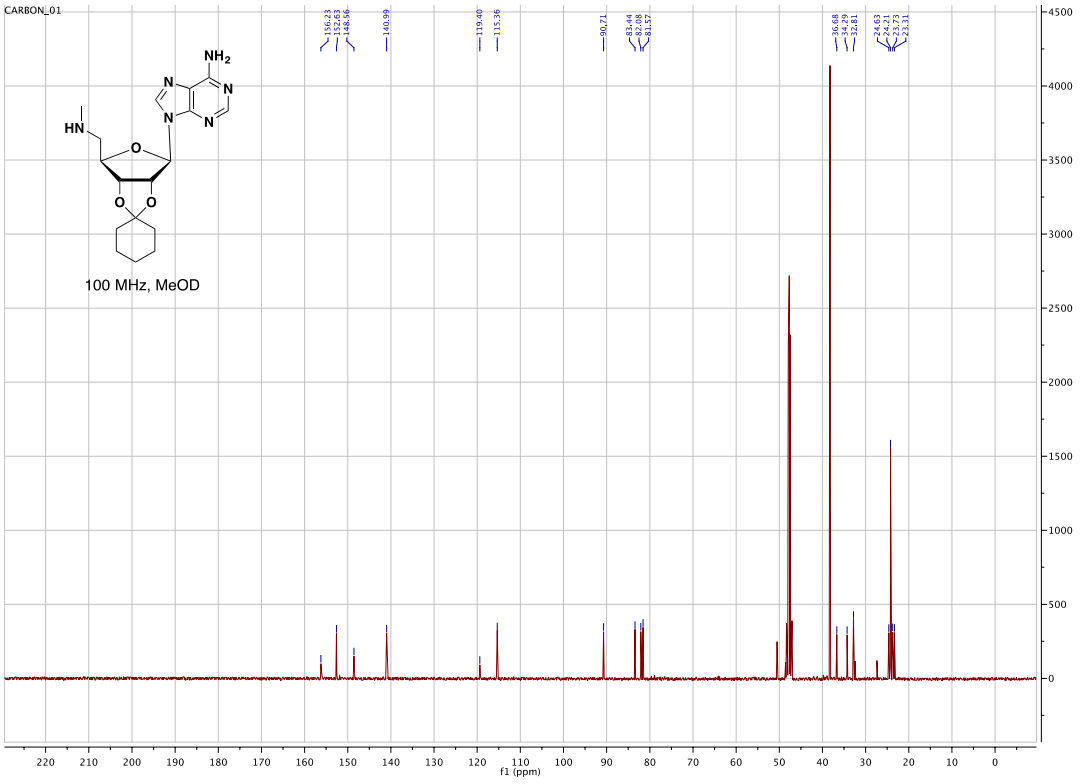
20 ^{13}C NMR



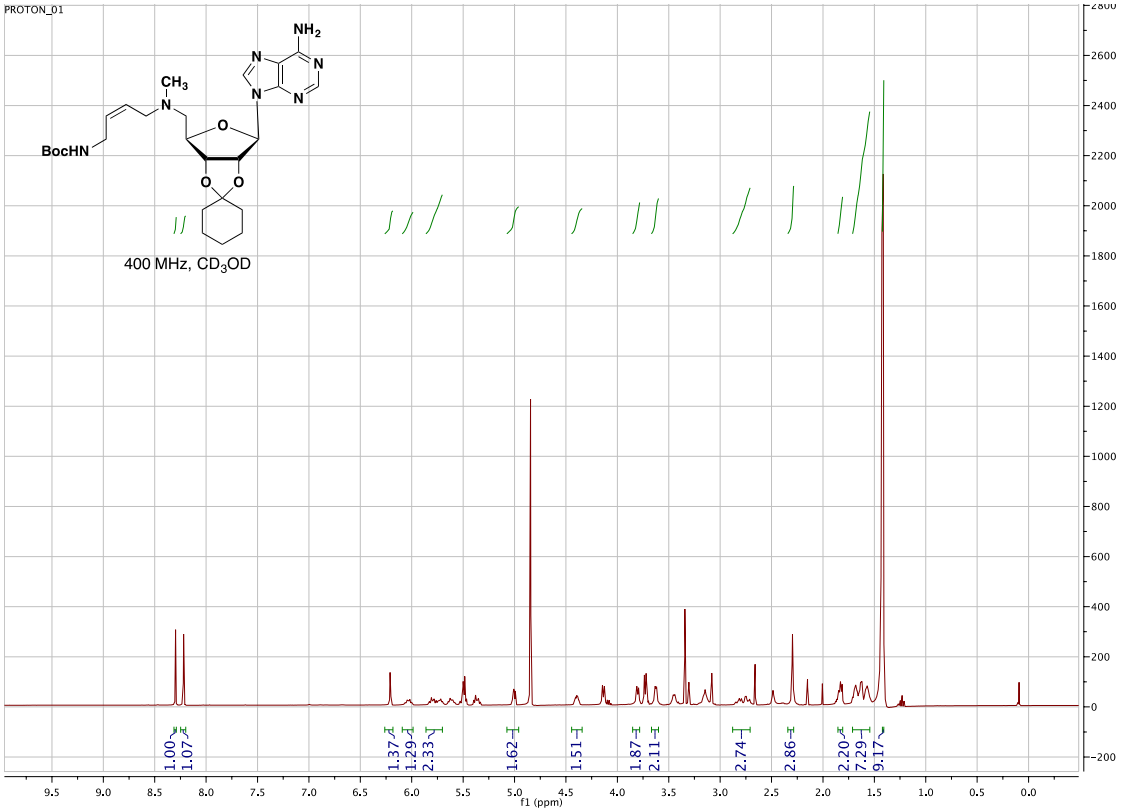
21 ^{1}H NMR



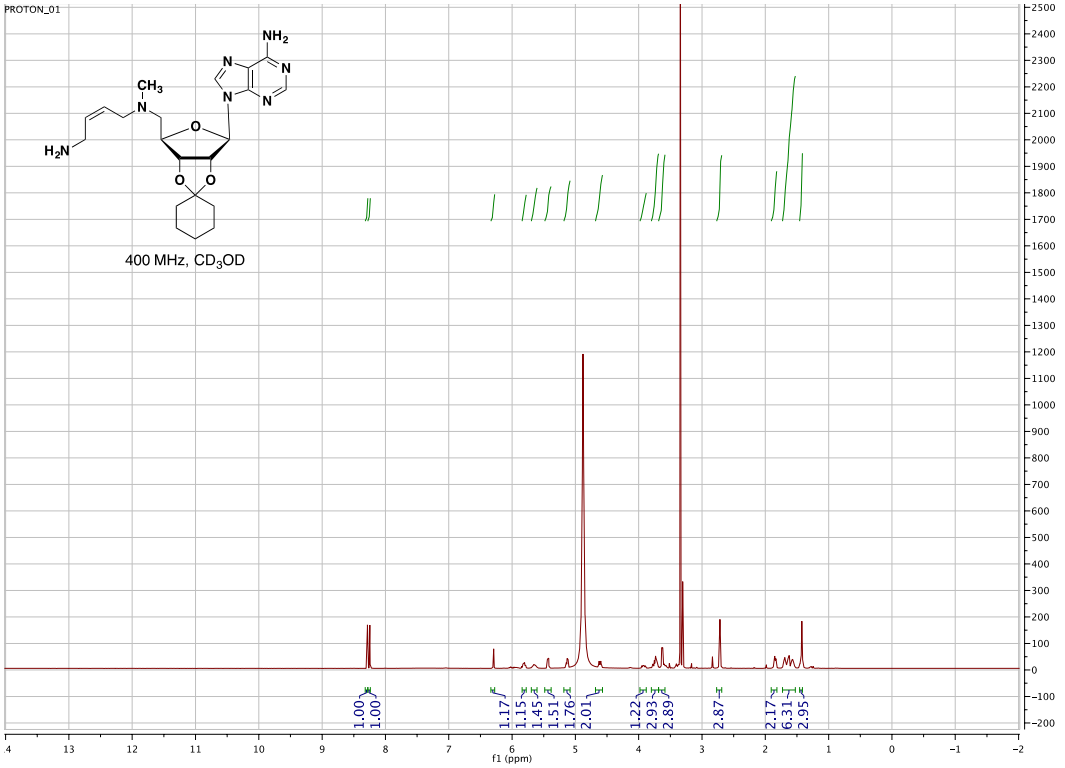
21 ^{13}C NMR



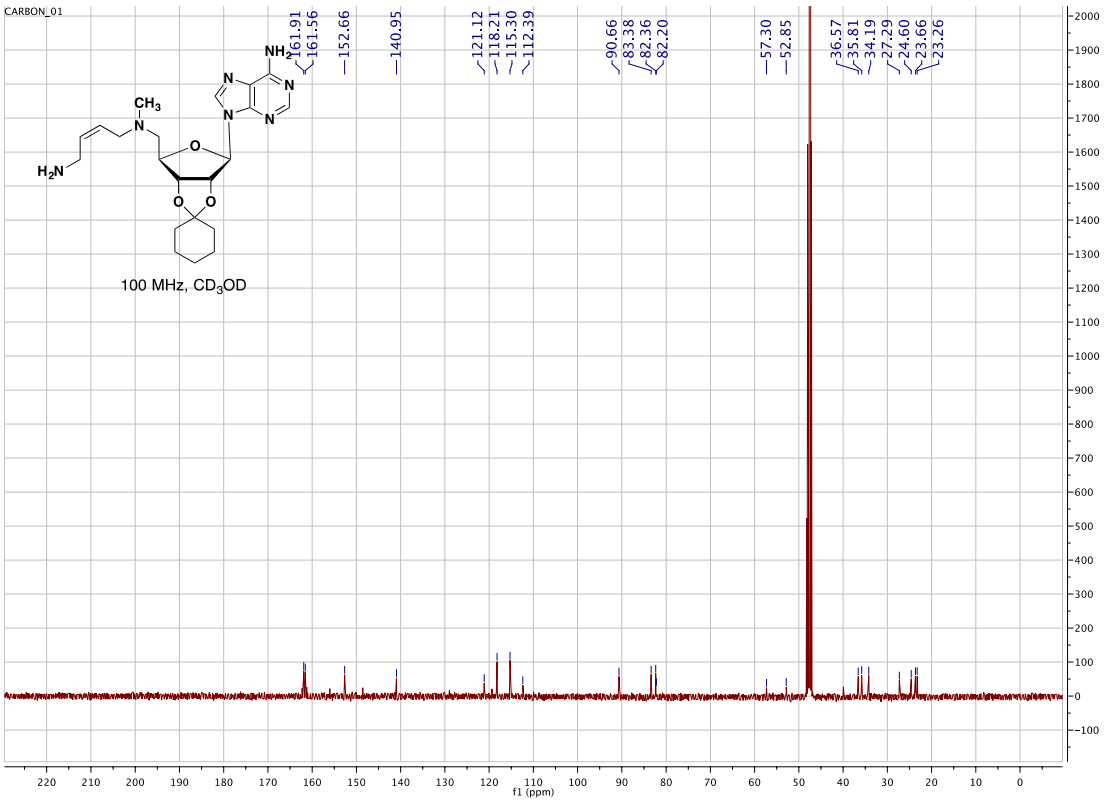
S11 ^{1}H NMR


PROTON_01
NH2
N
N
N
N
CH3
N
O
BocHN
O
O
400 MHz, CD3OD
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
1.00
1.07
1.37
1.29
2.33
1.62
1.51
1.87
2.11
2.74
2.86
2.20
7.29
9.17
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

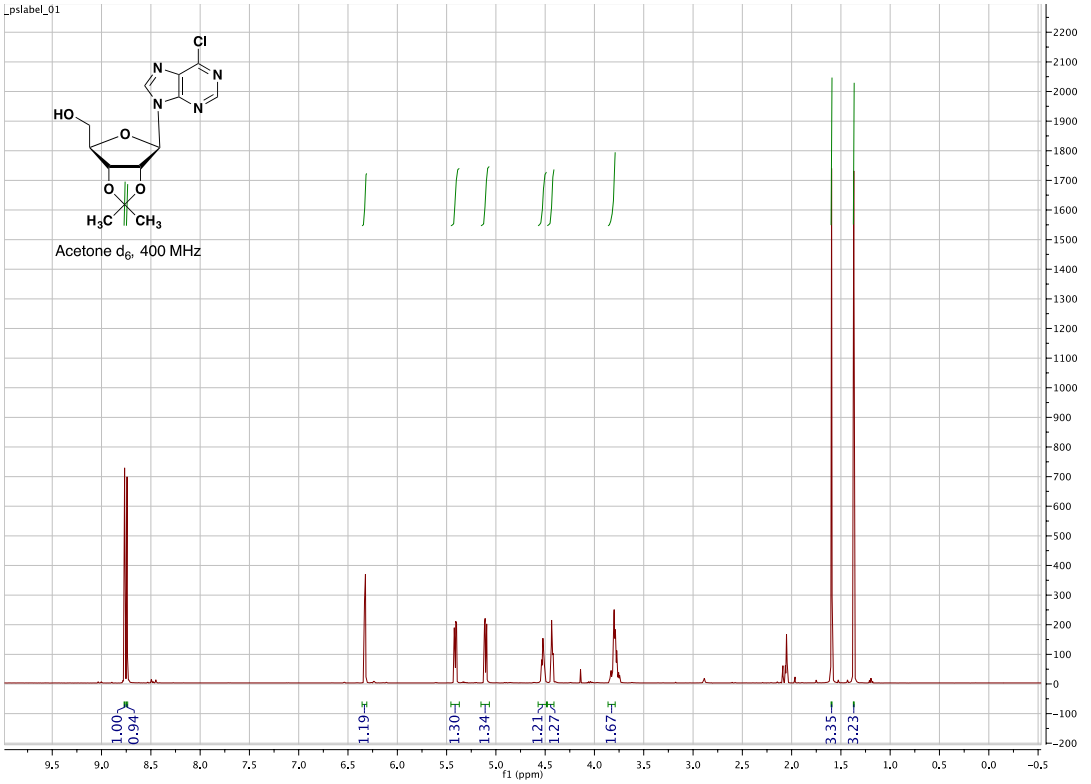
22 ^{1}H NMR



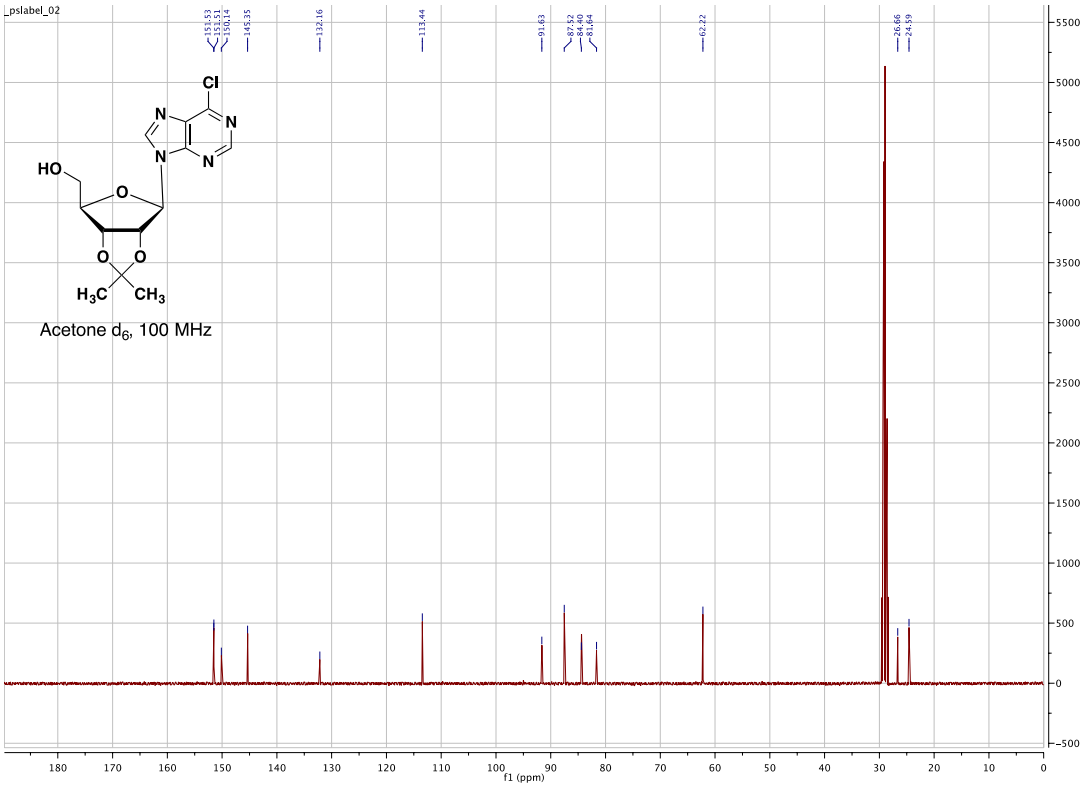
22 ^{13}C NMR



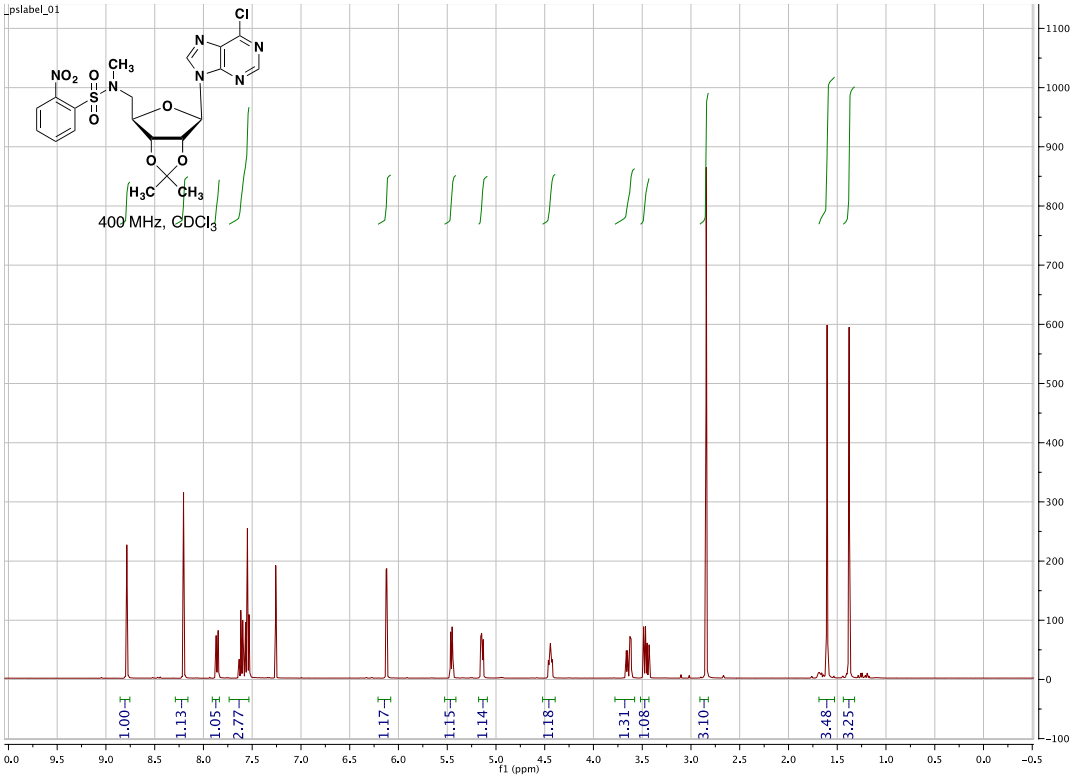
S12 ^{1}H NMR



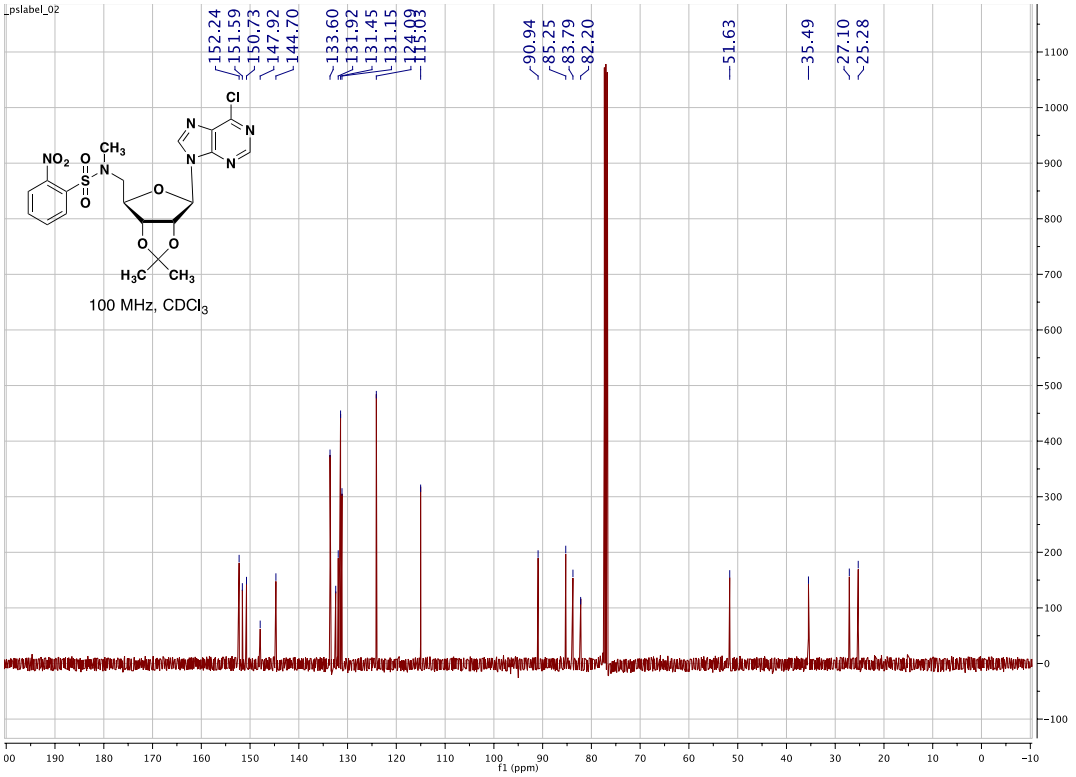
S12 ^{13}C NMR



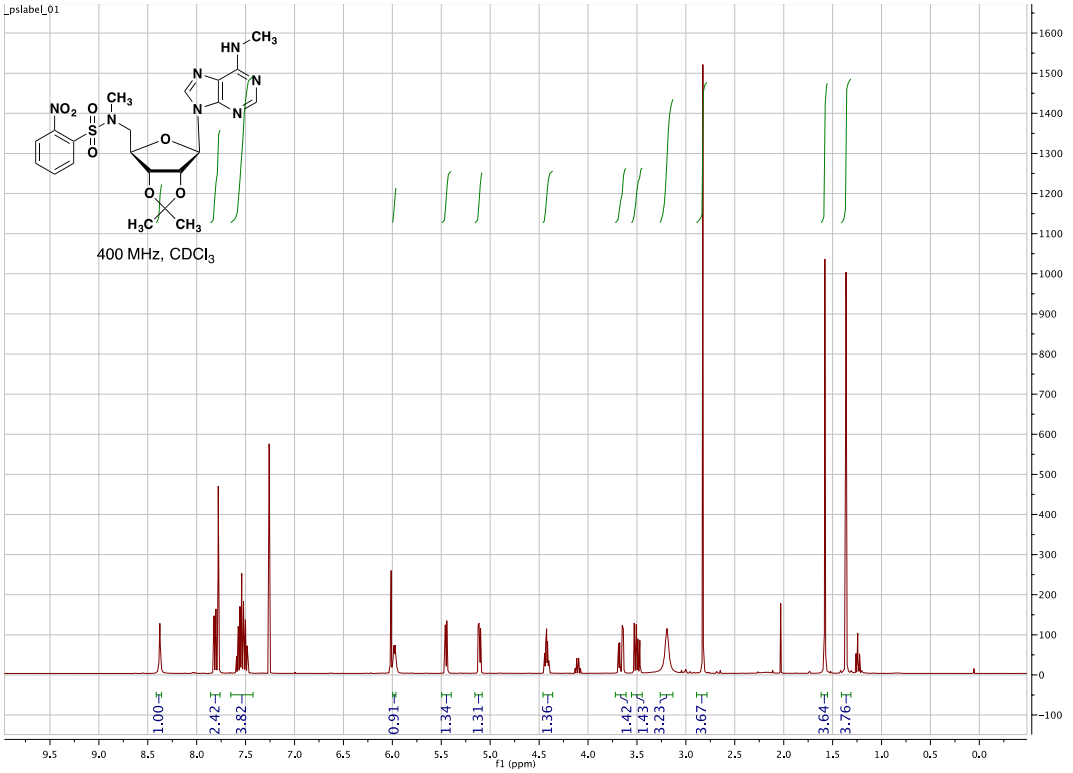
24 ^{1}H NMR



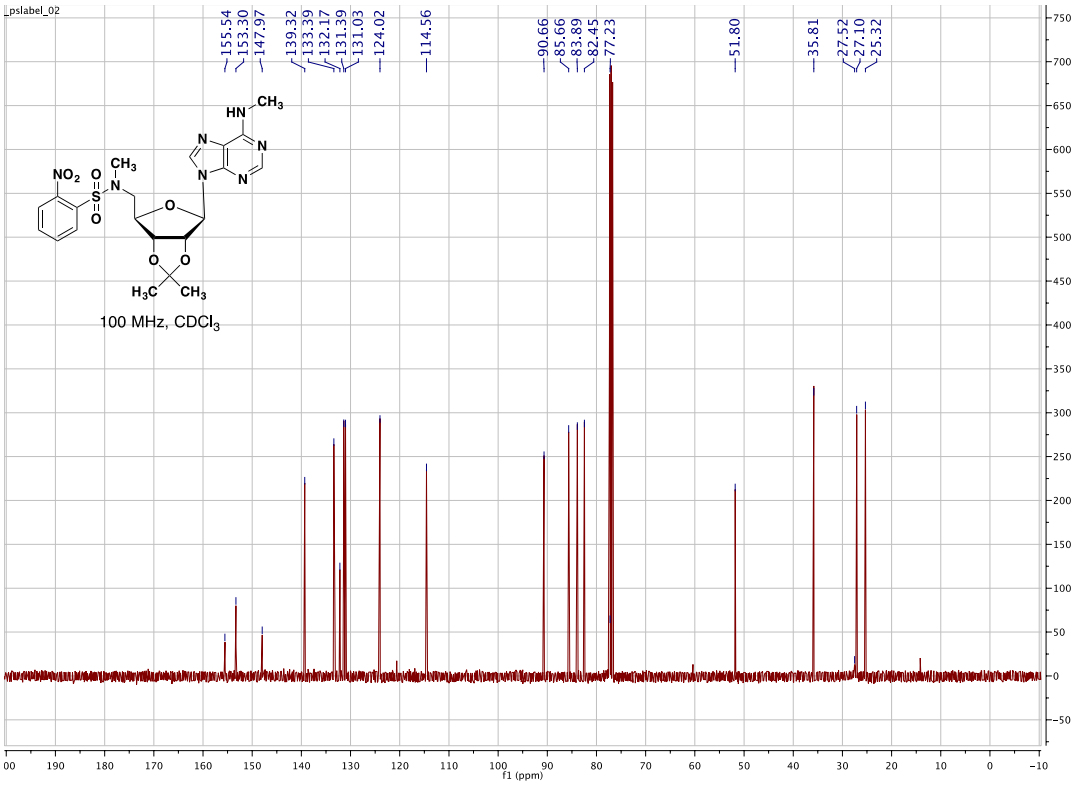
24 ^{13}C NMR



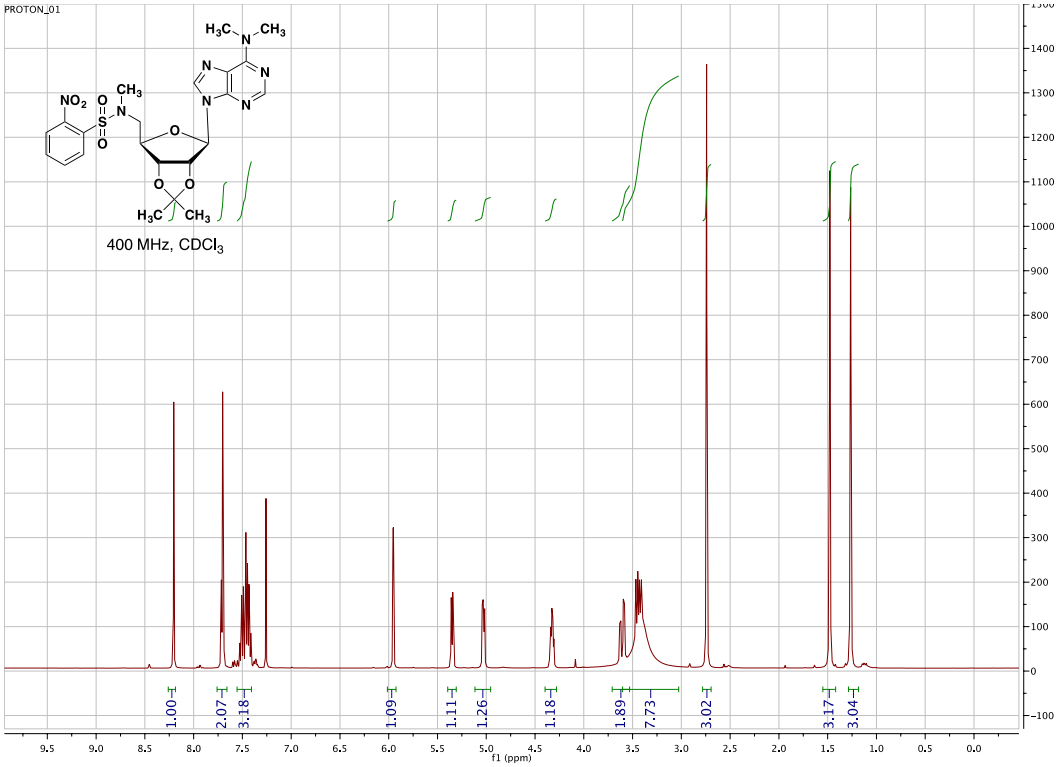
S13 ^{1}H NMR



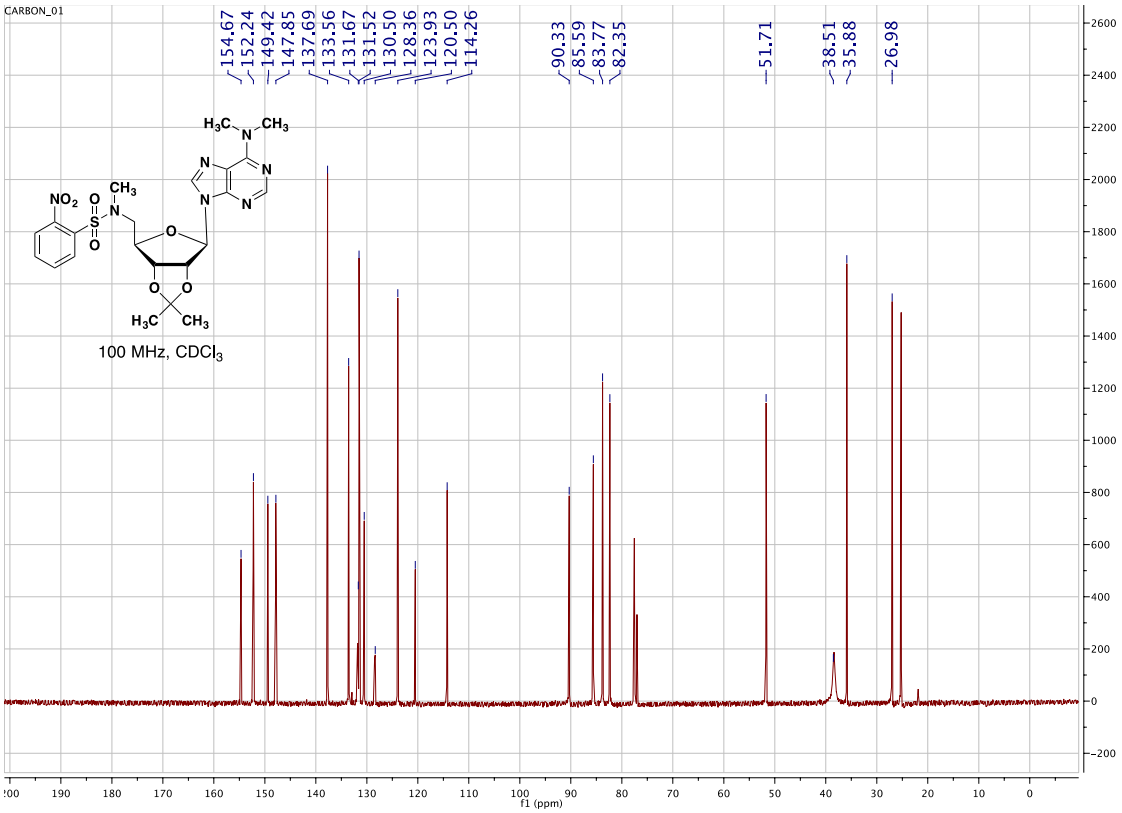
S13 ^{13}C NMR



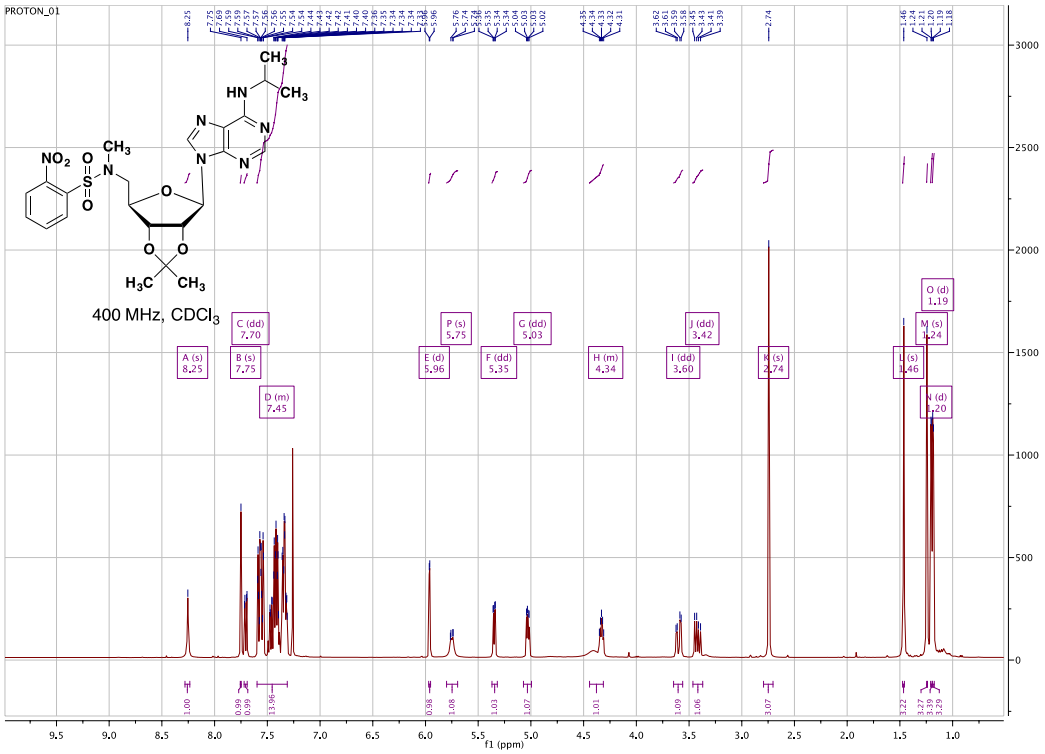
S14 ^{1}H NMR



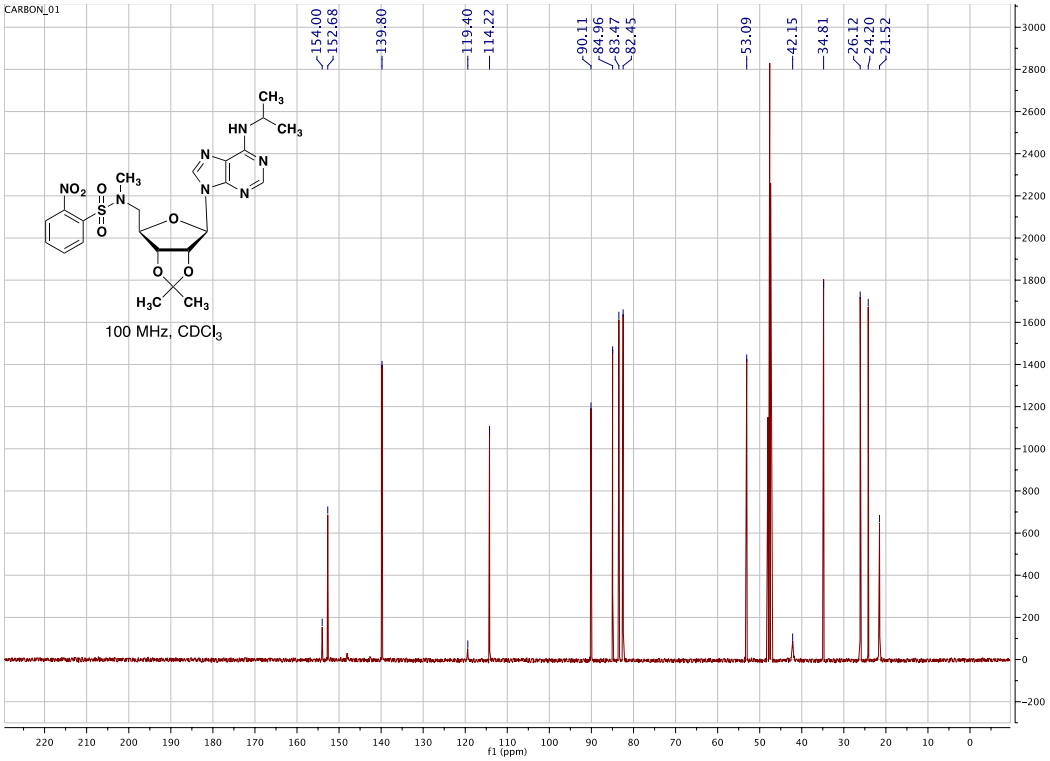
S14 ^{13}C NMR



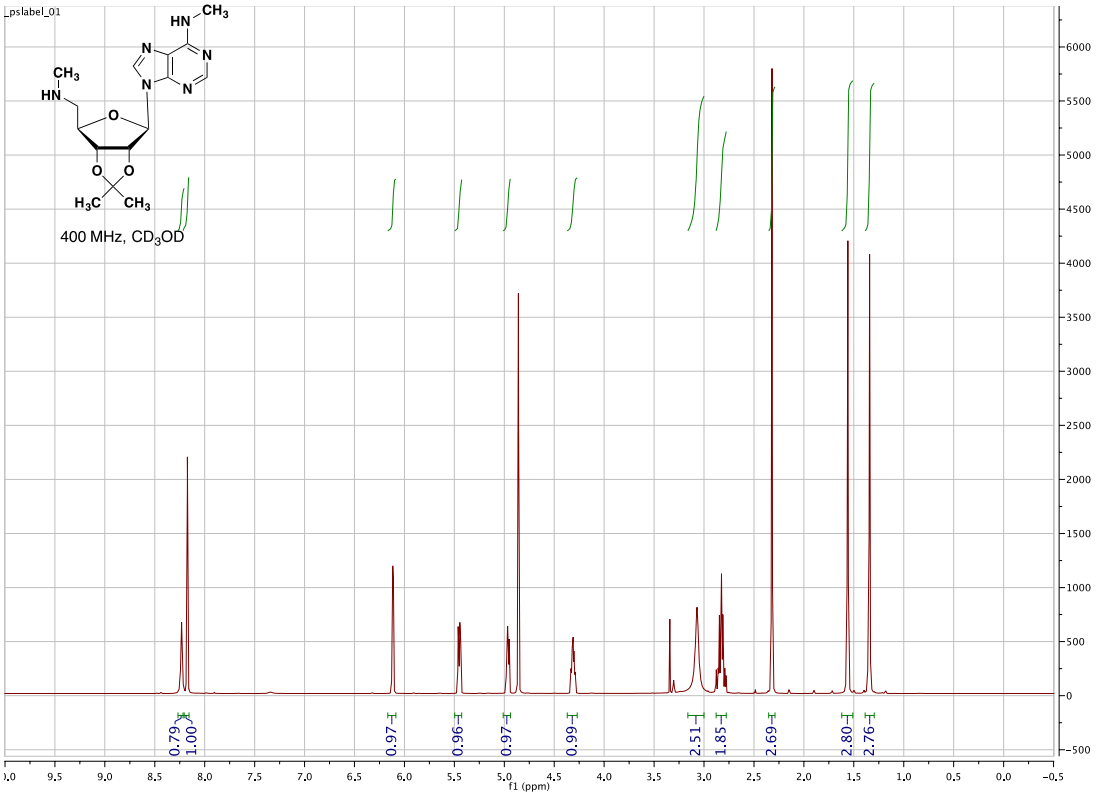
S15 ^{1}H NMR



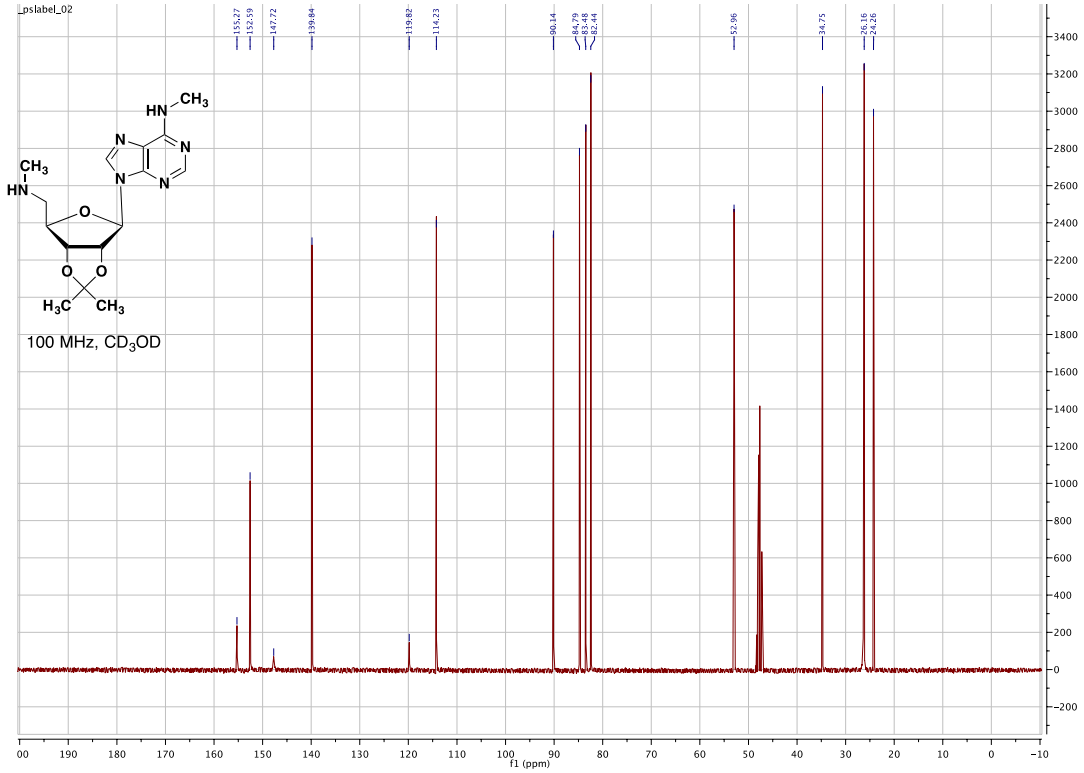
S15 ^{13}C NMR



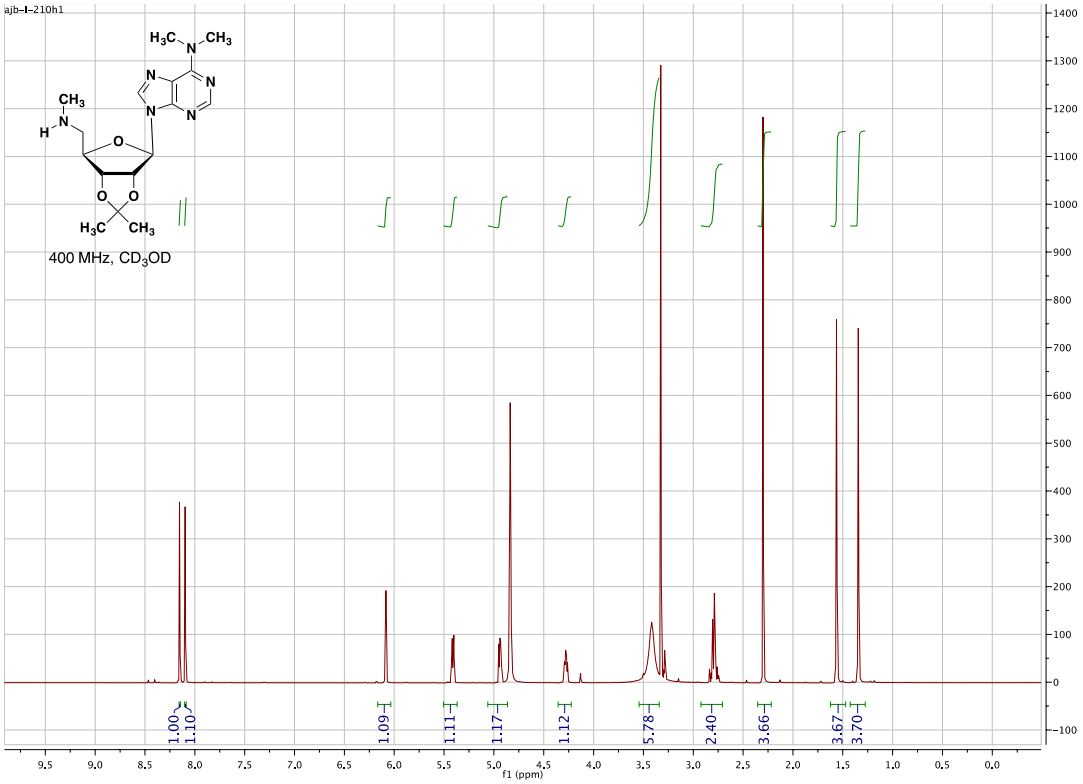
25a ^{1}H NMR



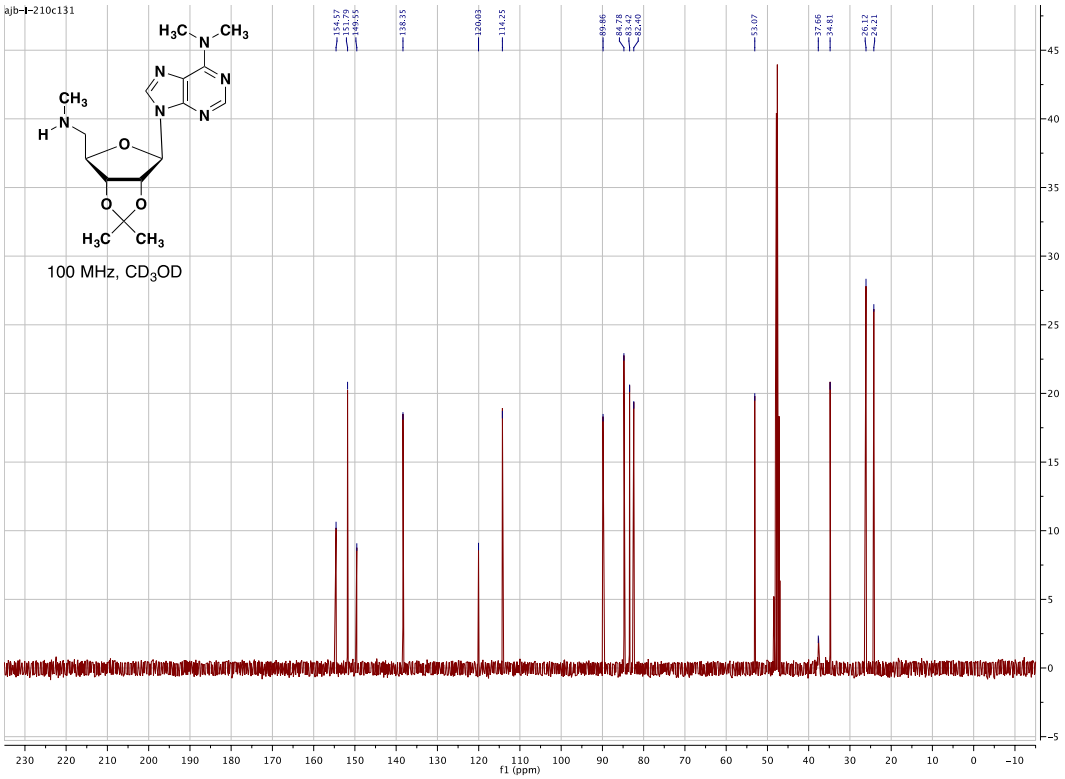
25a ^{13}C NMR



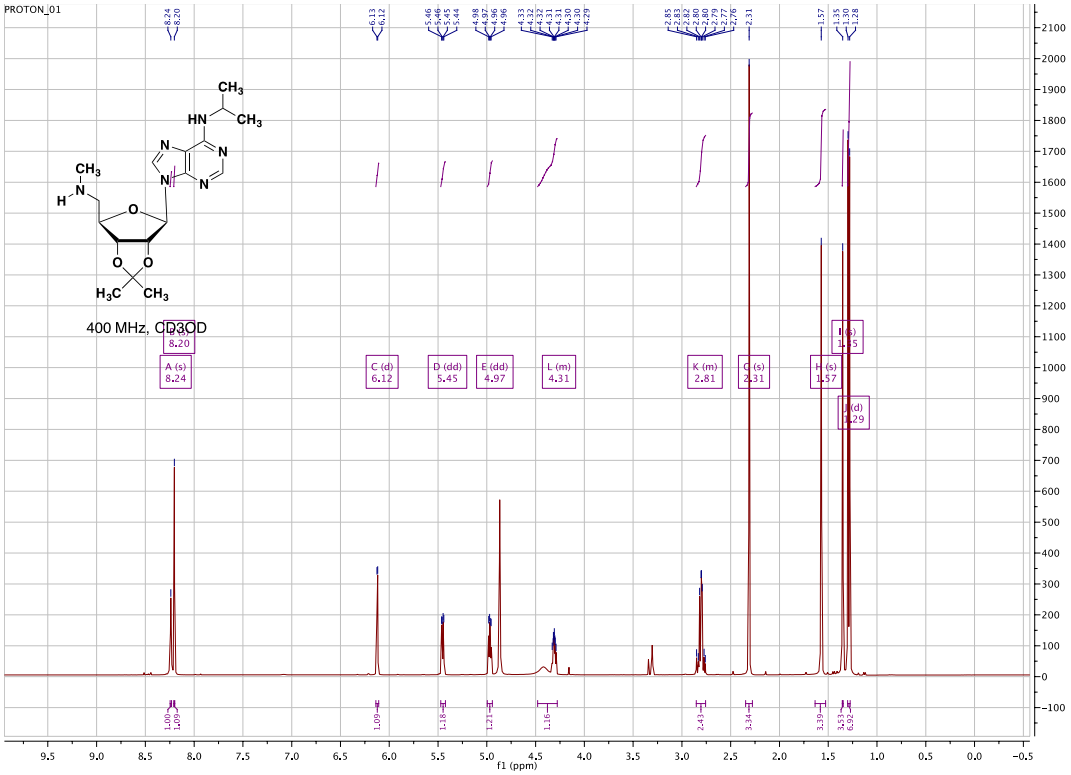
25b ^{1}H NMR



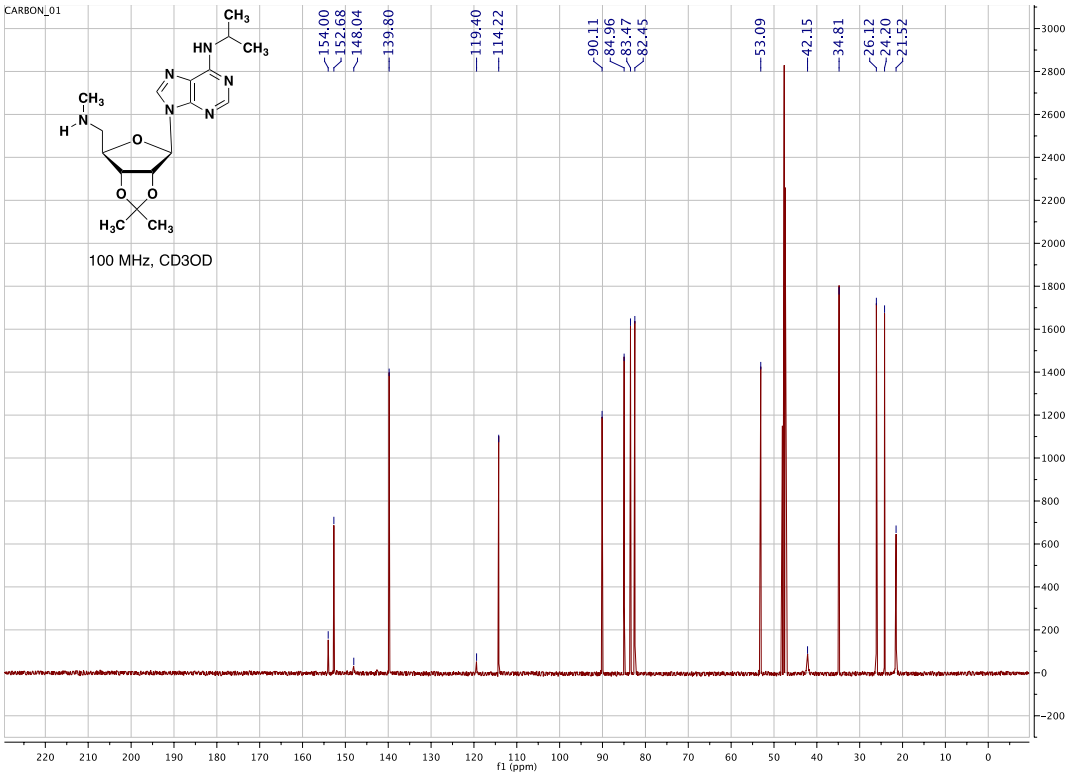
25b ^{13}C NMR



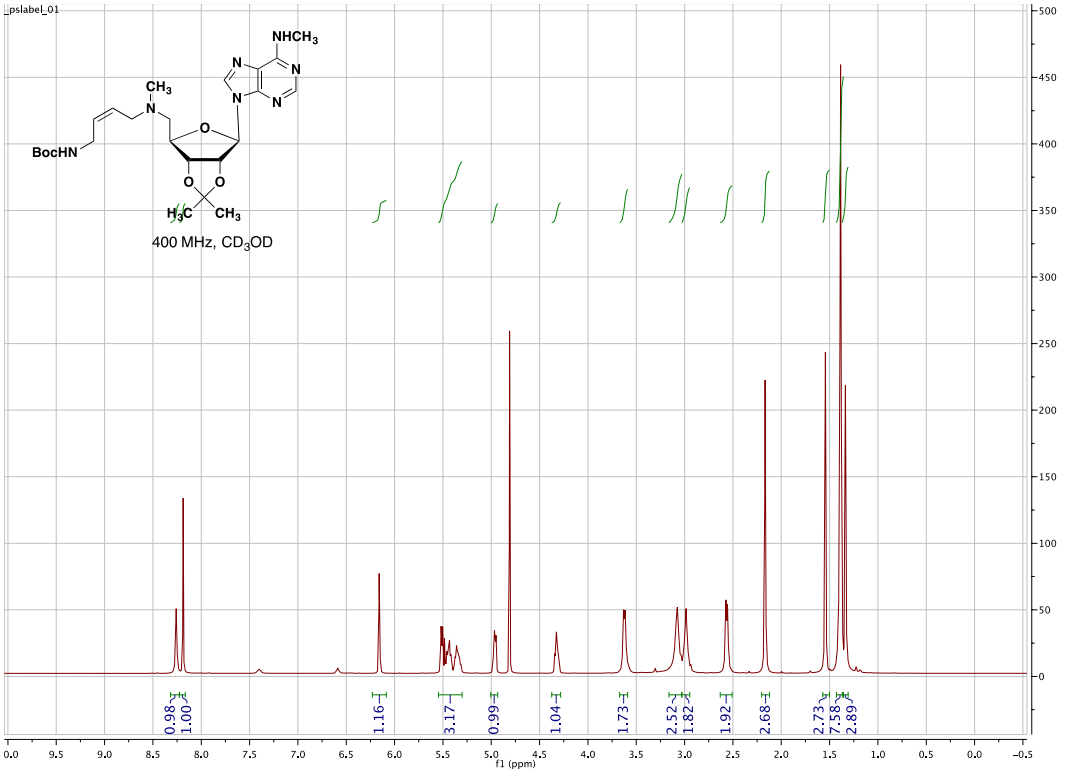
25c ^{1}H NMR



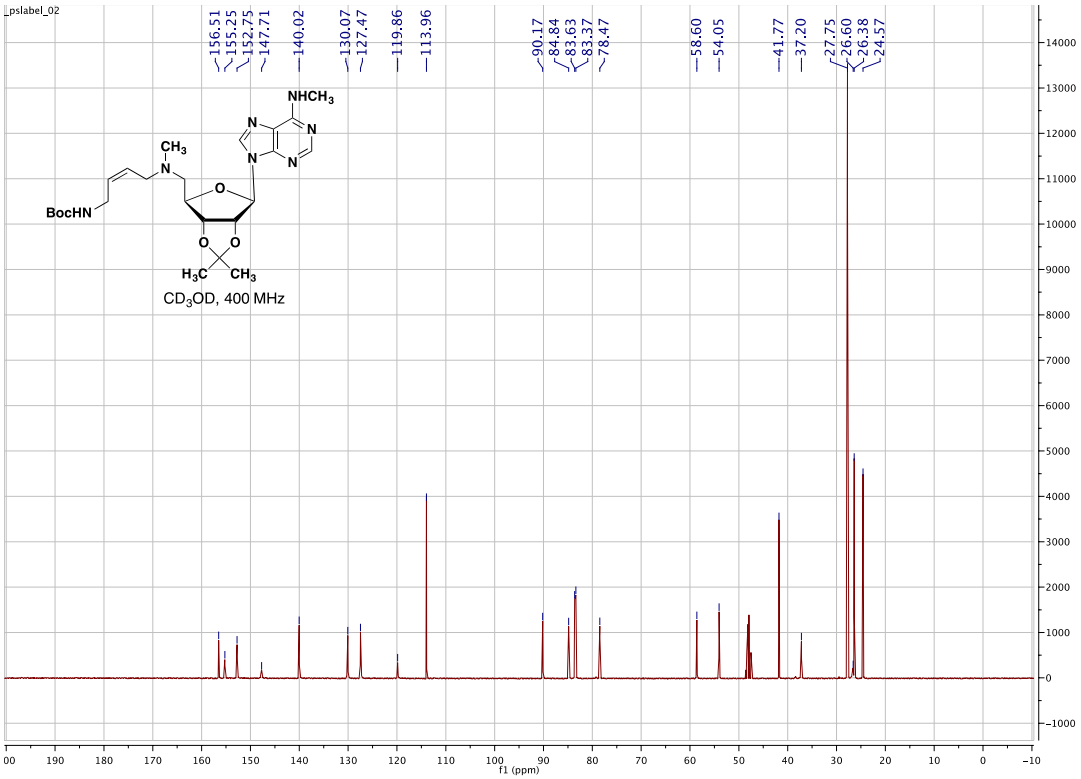
25c ^{13}C NMR



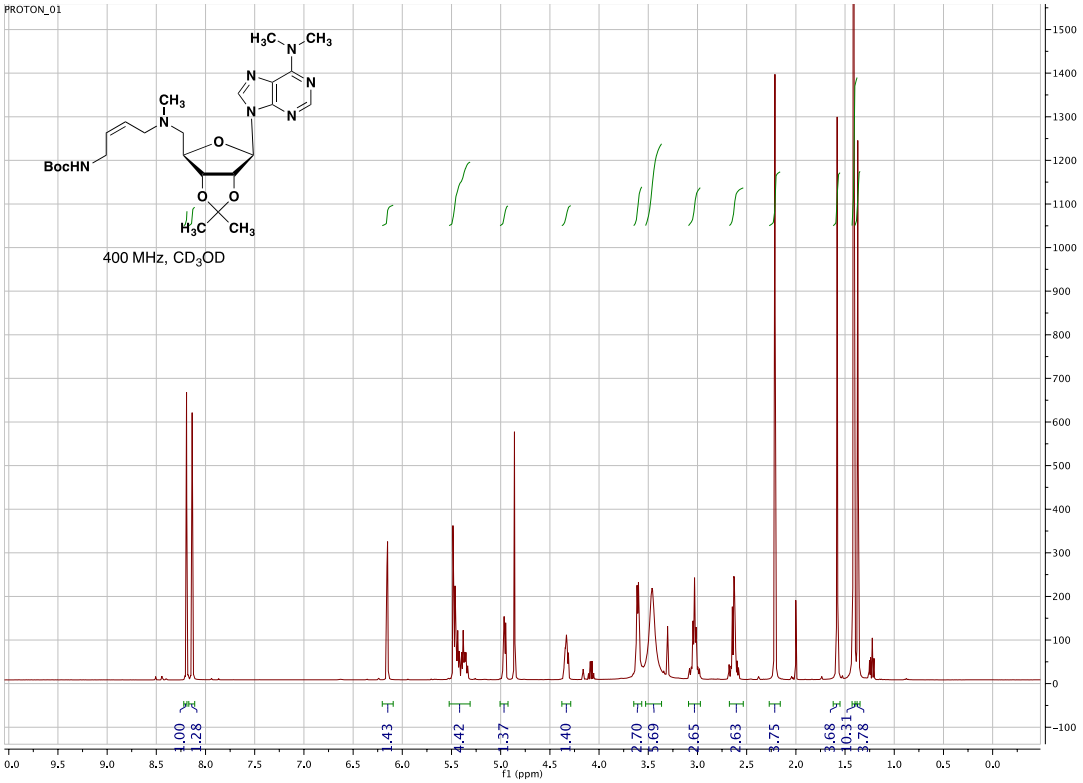
26a ^{1}H NMR



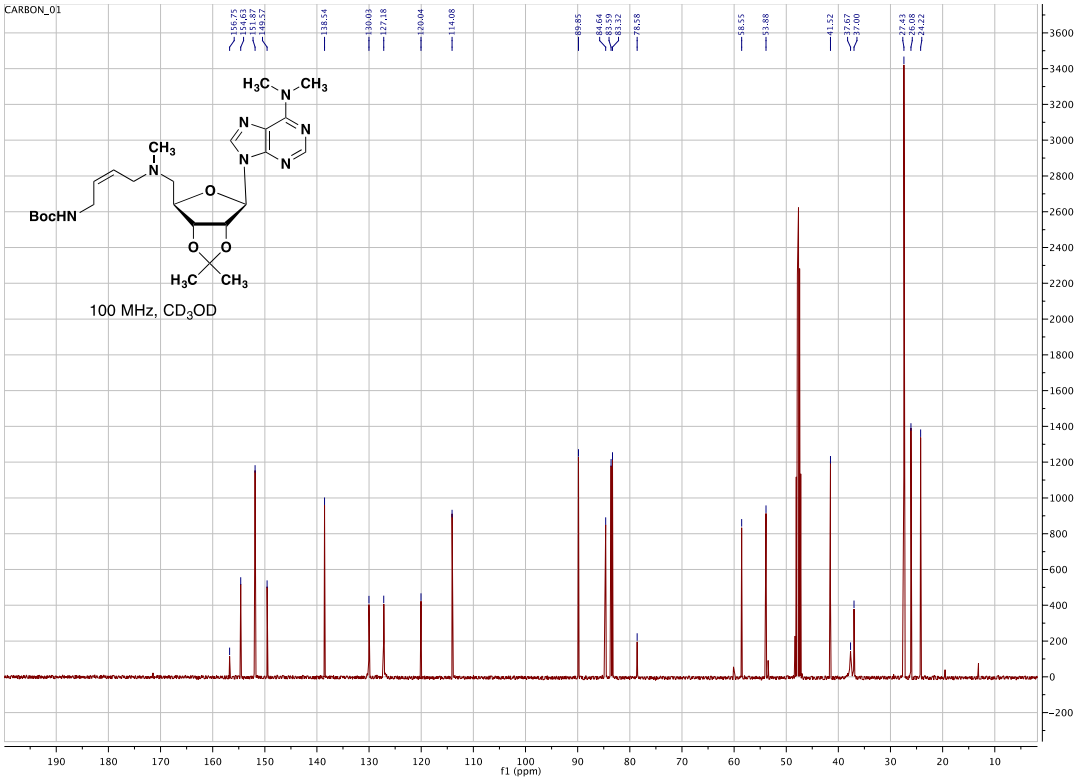
26a ^{13}C NMR



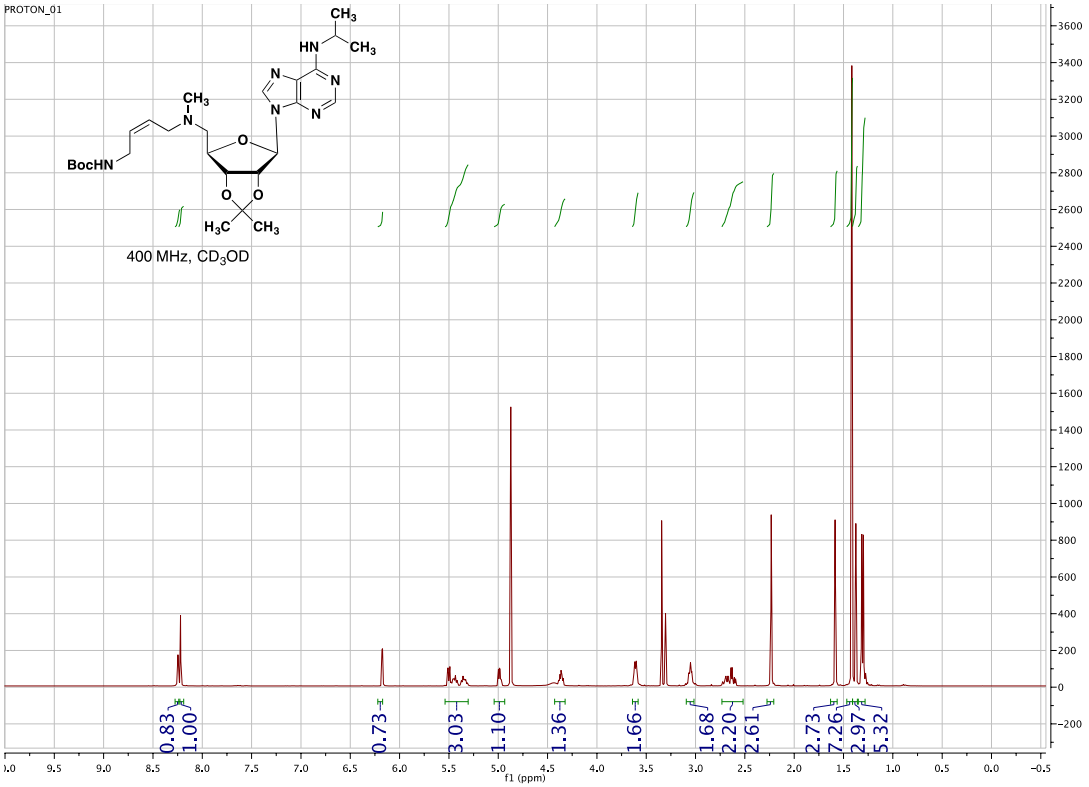
26b ^{1}H NMR



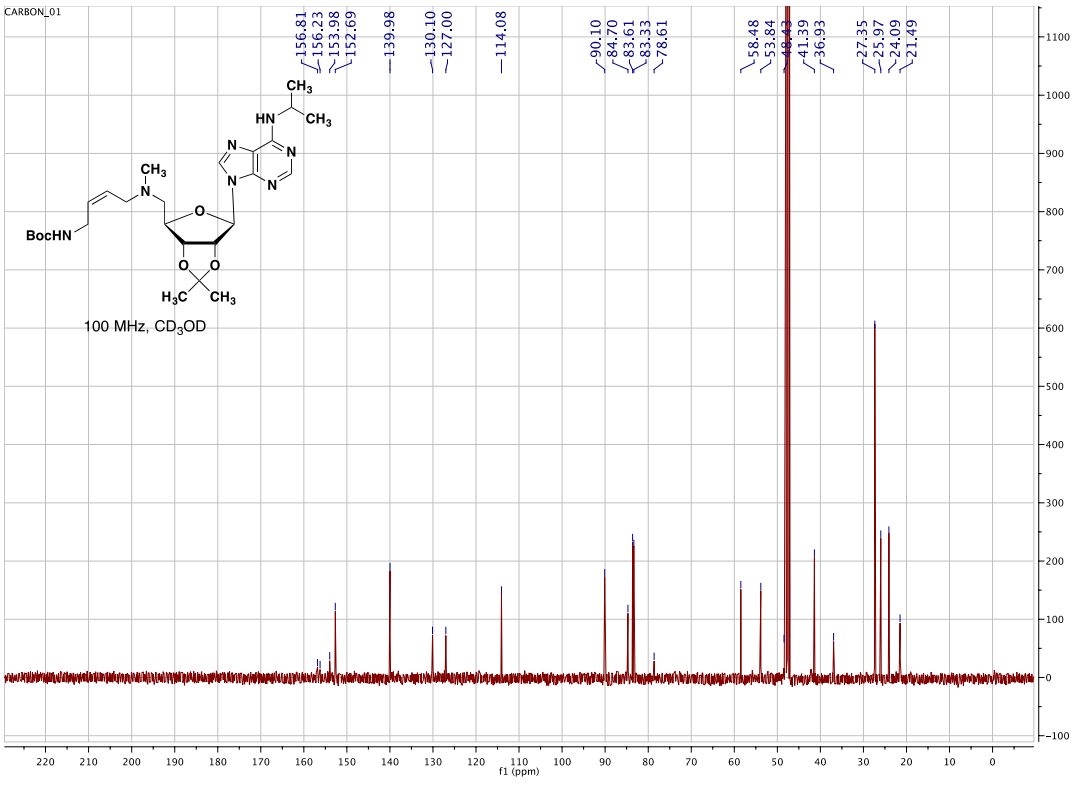
26b ^{13}C NMR



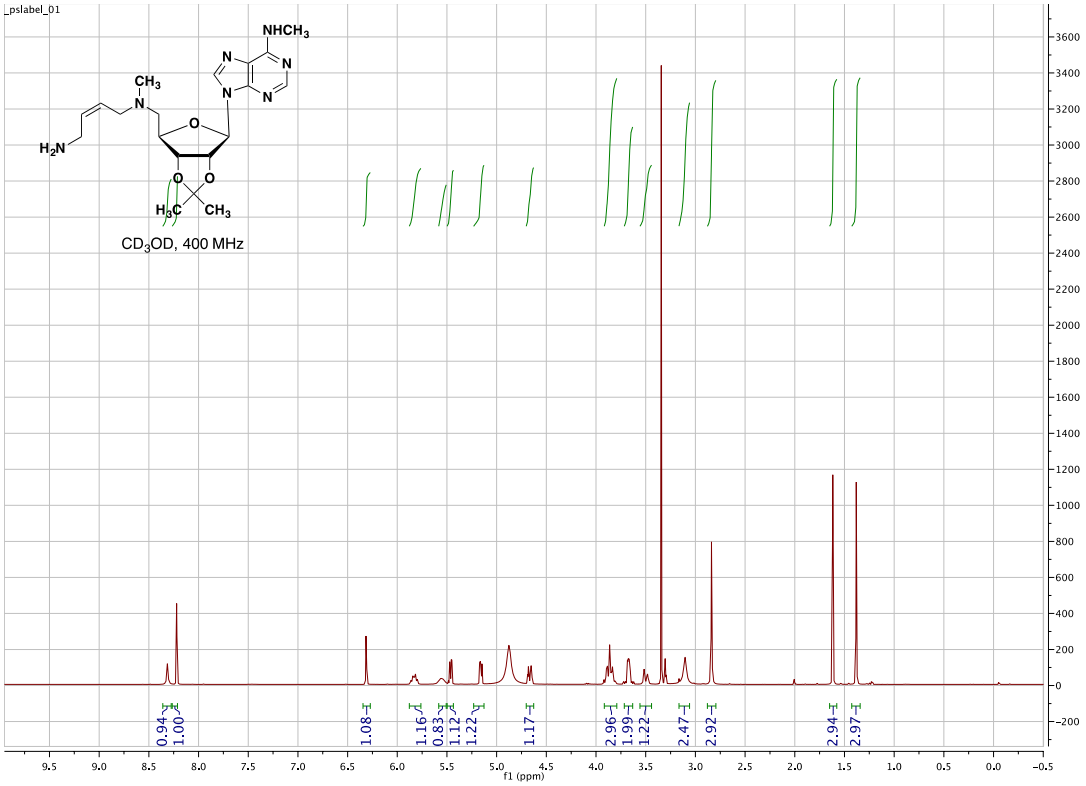
26c ^{1}H NMR



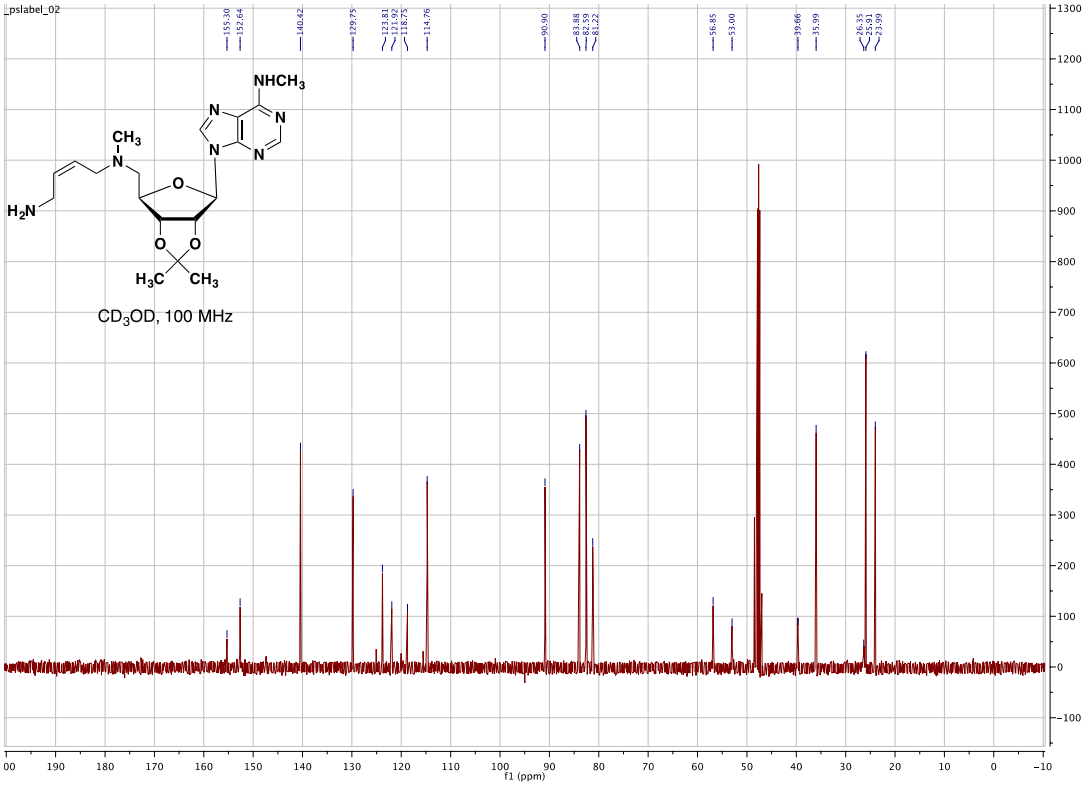
26c ^{13}C NMR



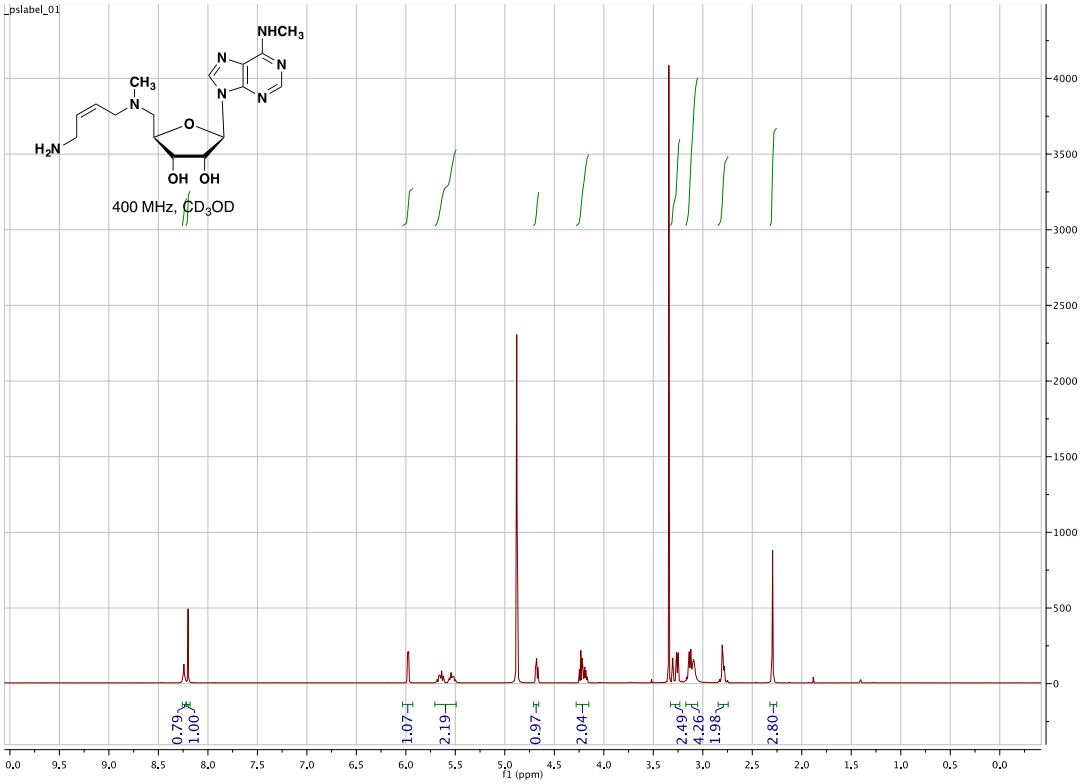
27 ^{1}H NMR



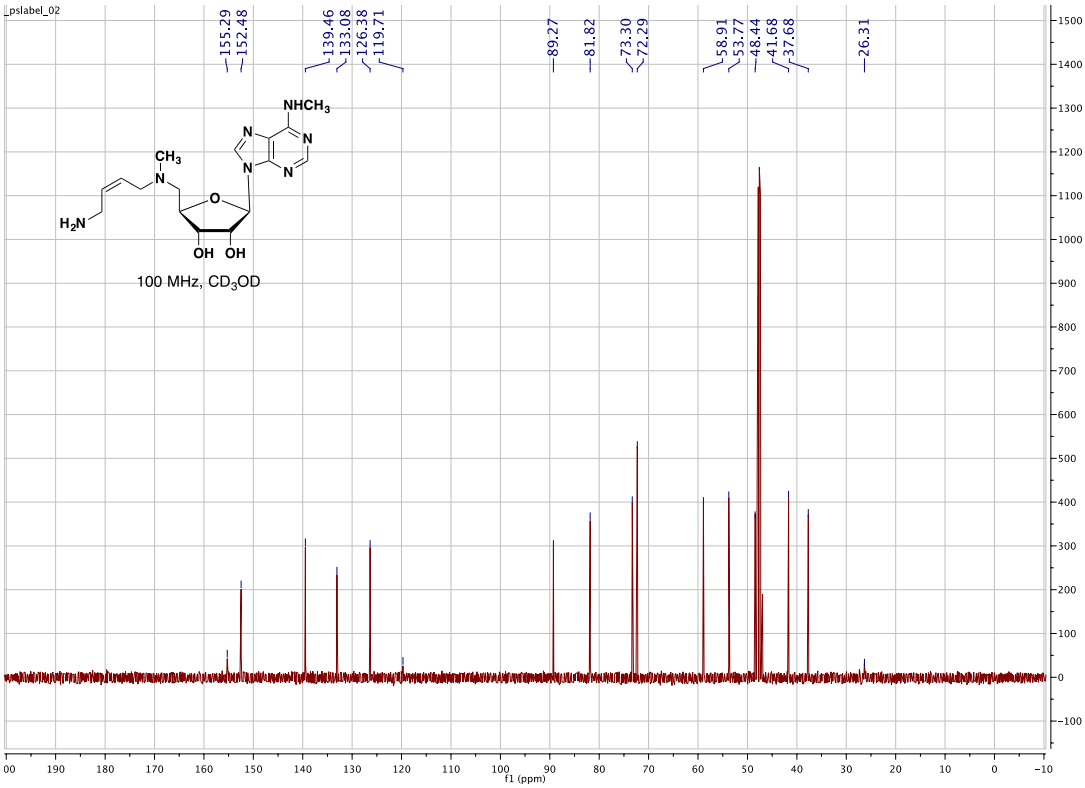
27 ^{13}C NMR



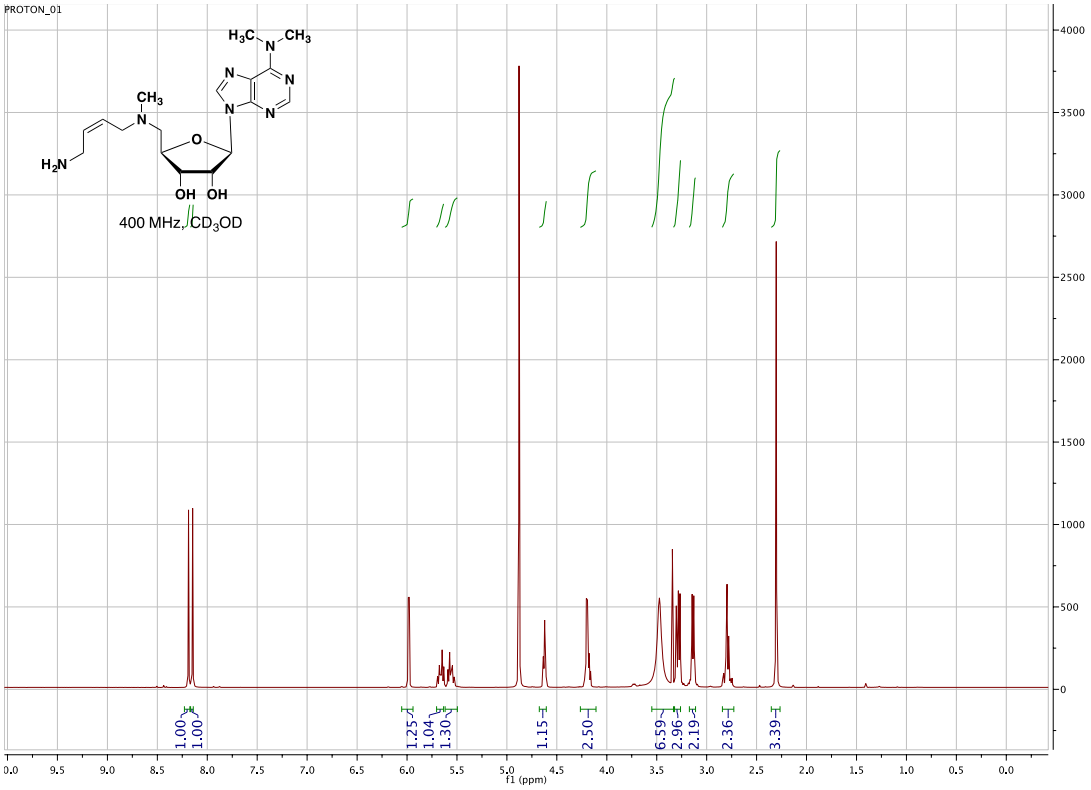
28a ^{1}H NMR



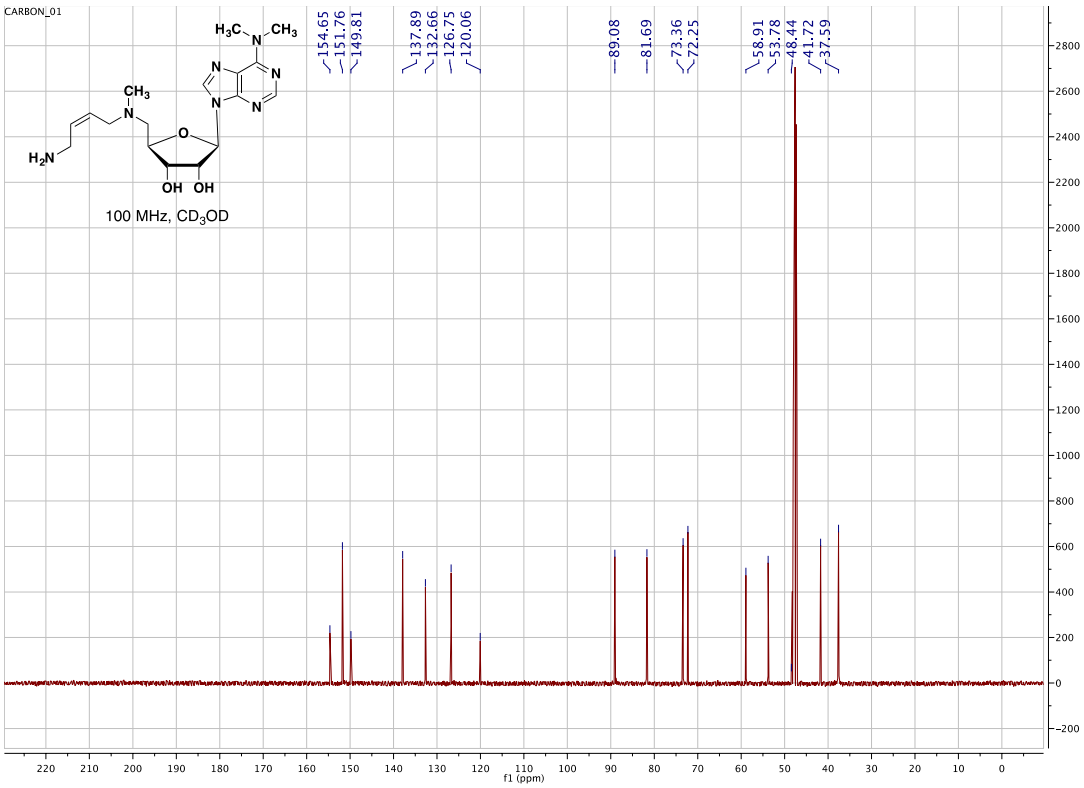
28a ^{13}C NMR



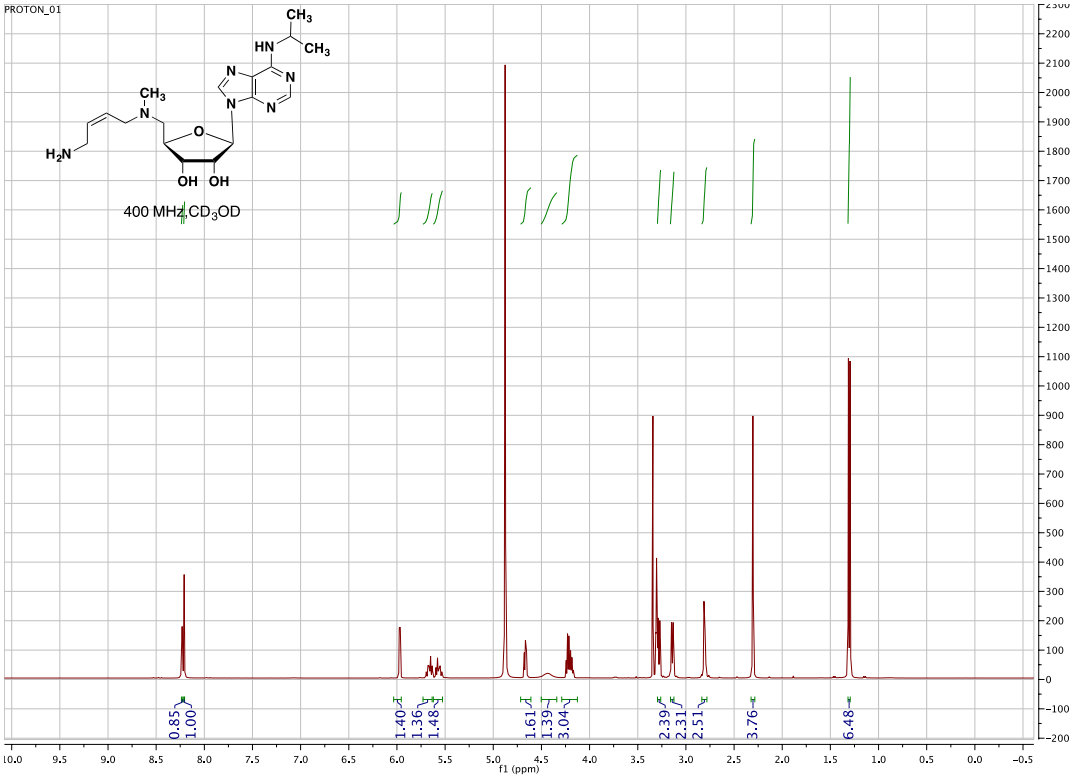
28b ^{1}H NMR



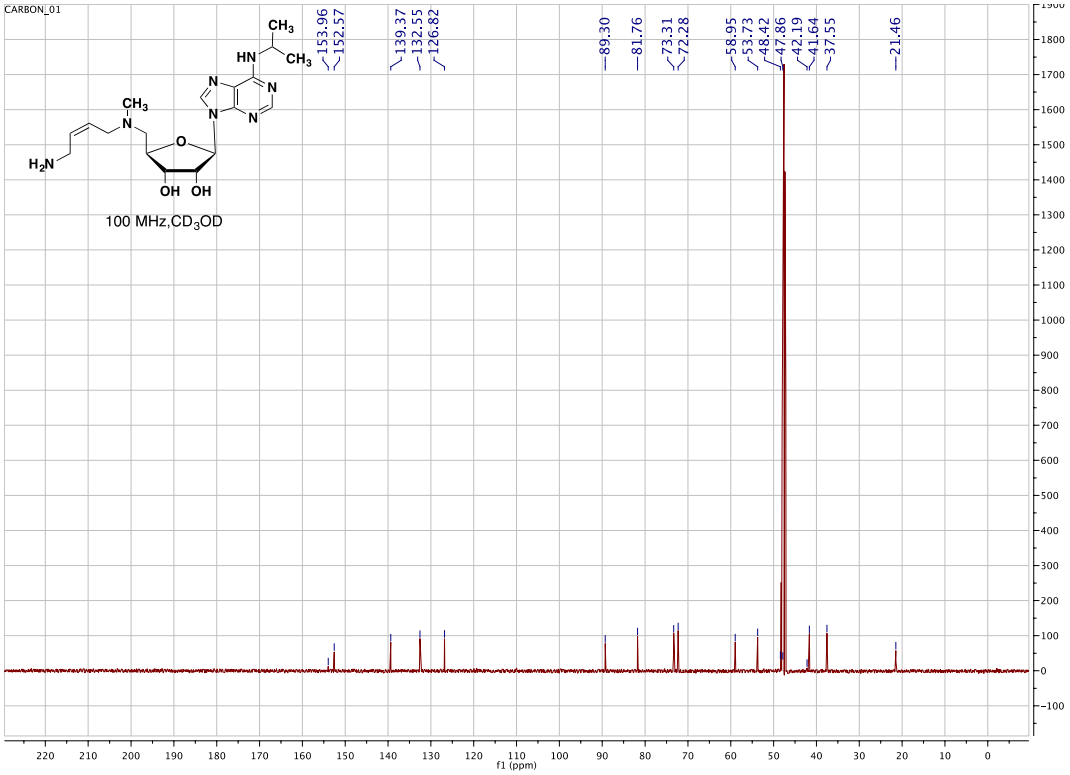
28b ^{13}C NMR



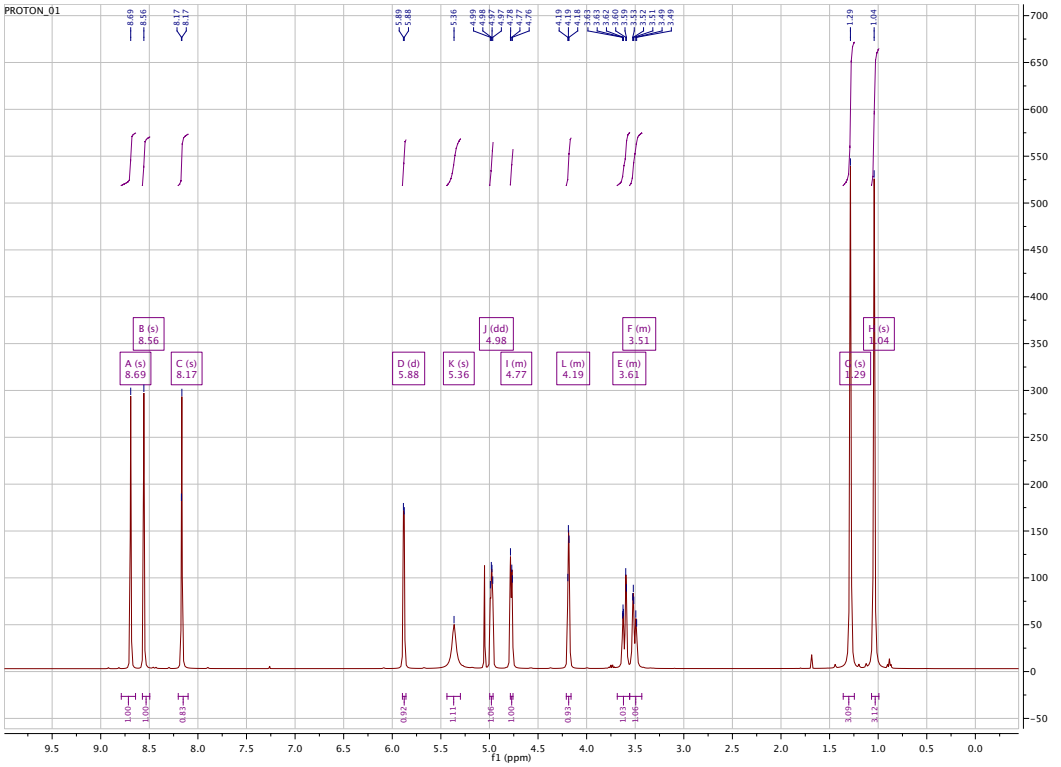
28c ^{1}H NMR



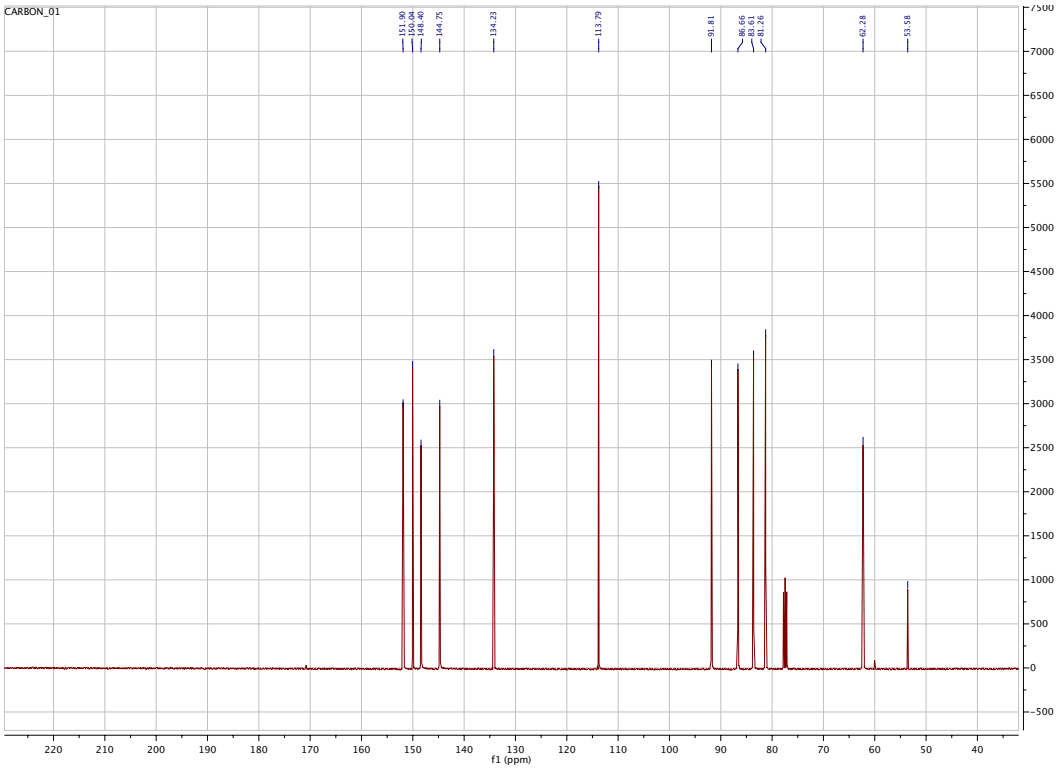
28c ^{13}C NMR



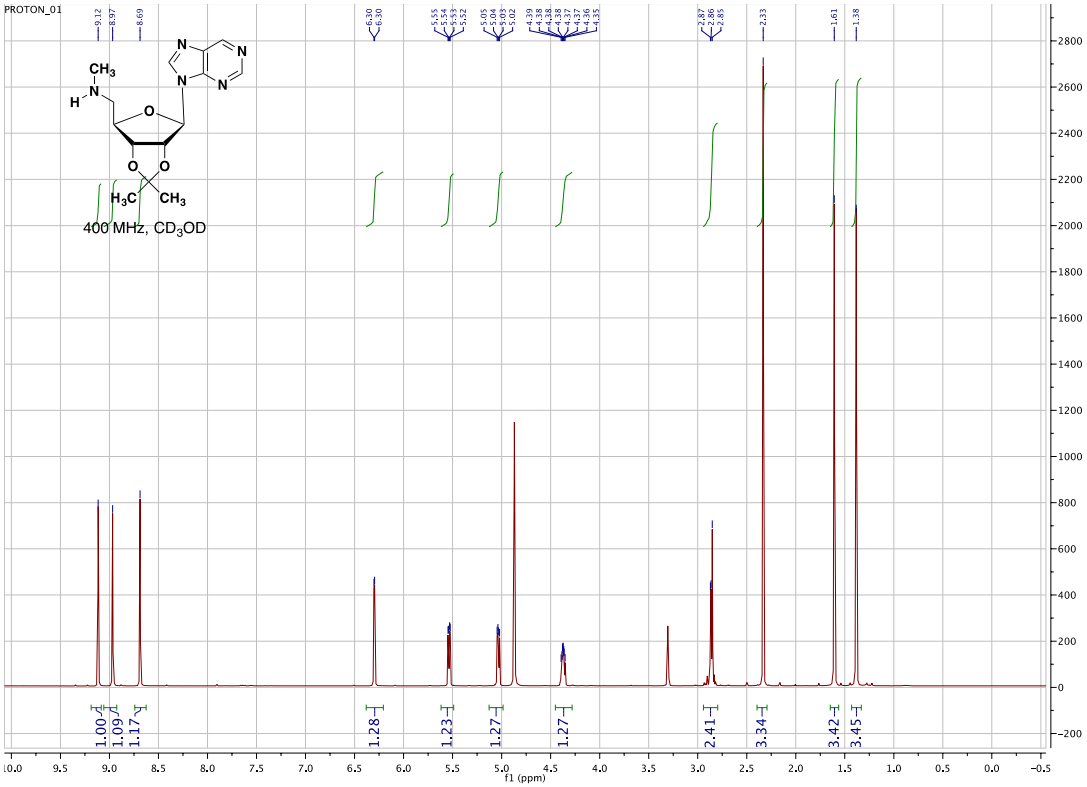
29 ^{1}H NMR



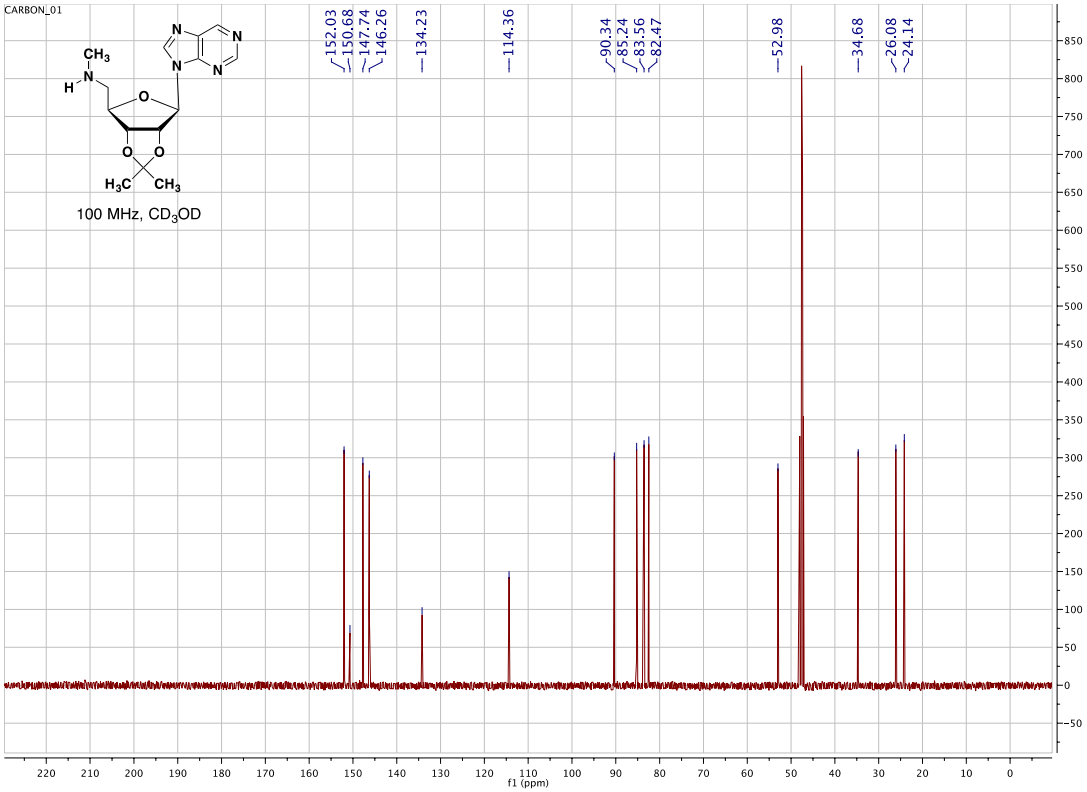
29 ^{13}C NMR



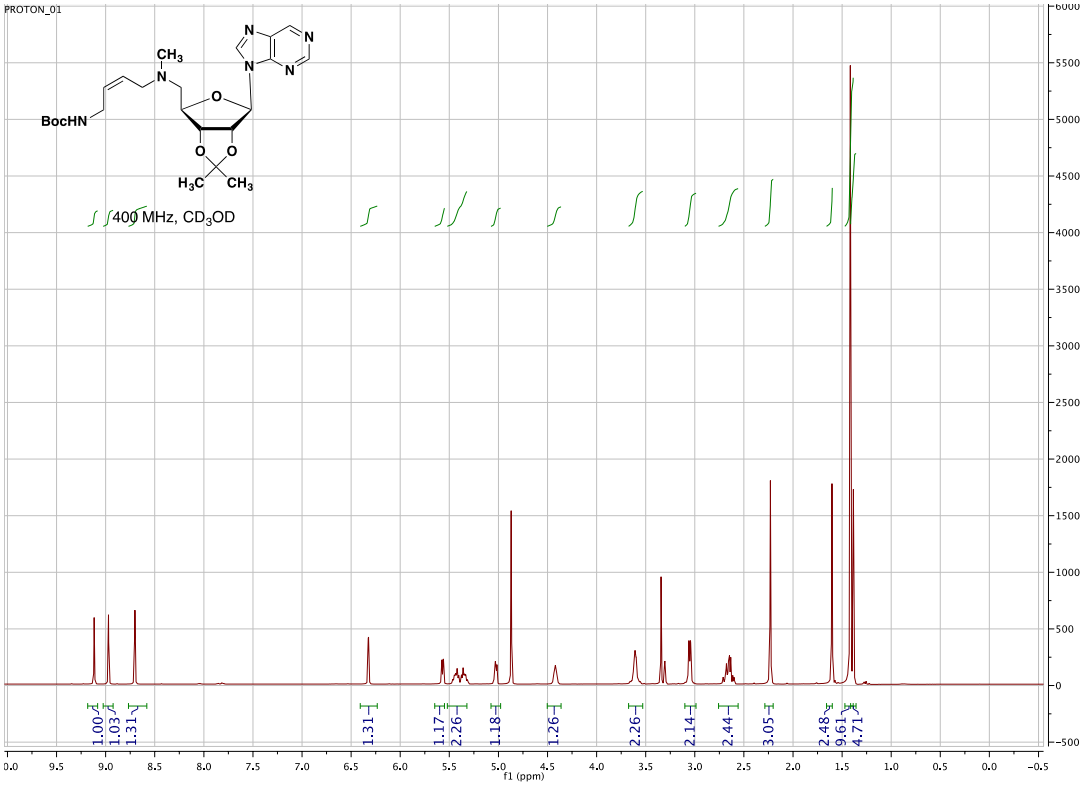
S17 ^{1}H NMR



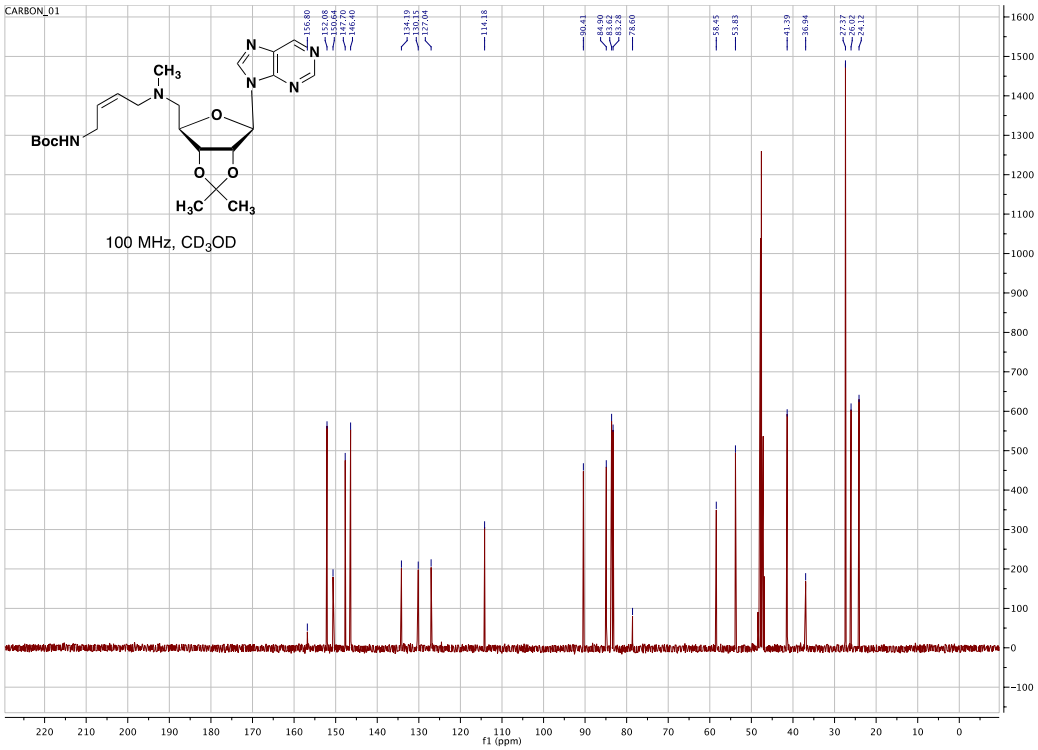
S17 ^{13}C NMR



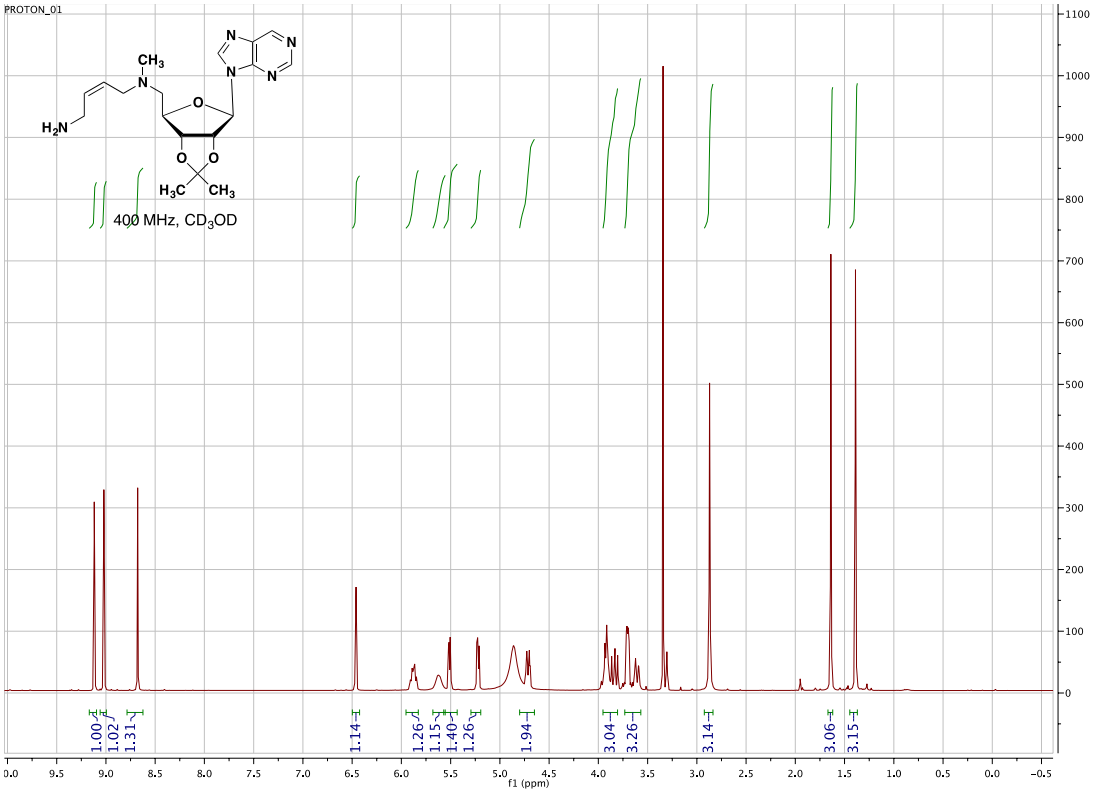
S18 ^{1}H NMR



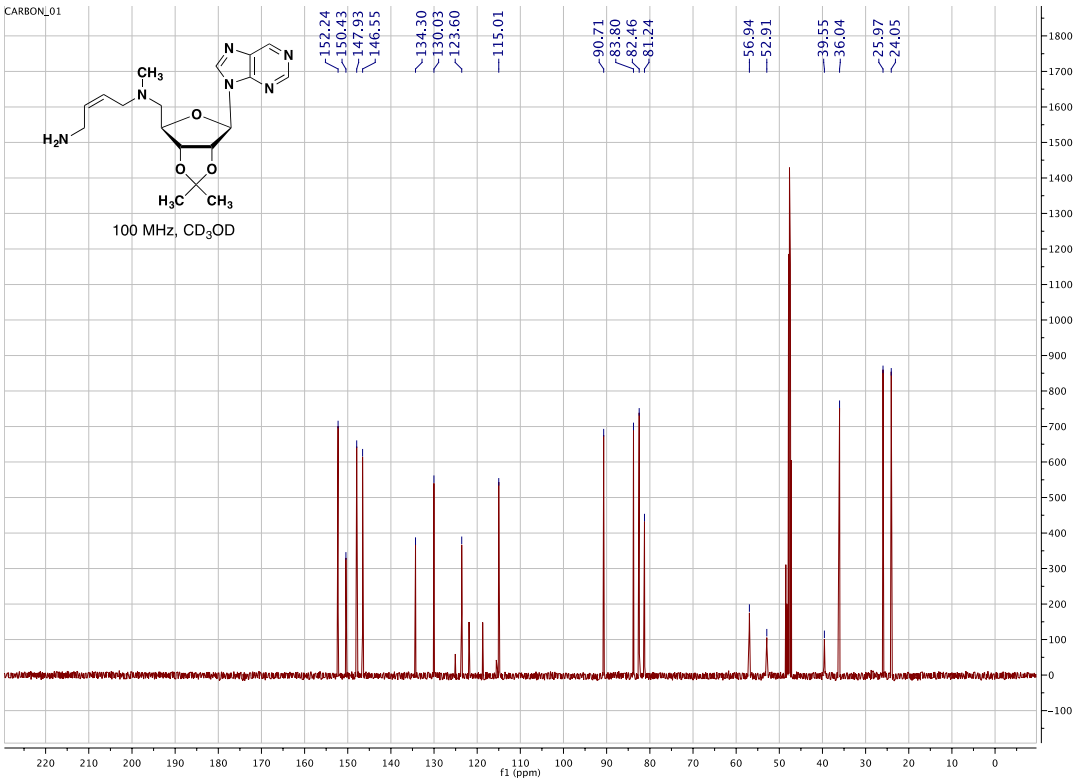
S18 ^{13}C NMR



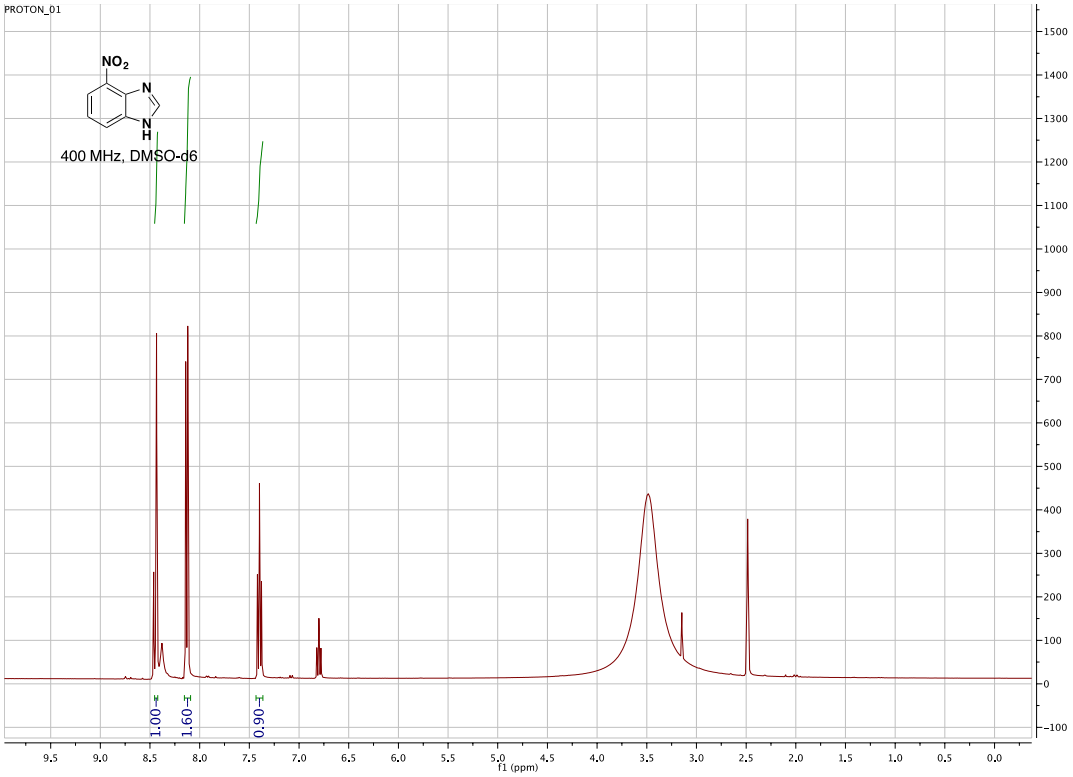
30 ^{1}H NMR



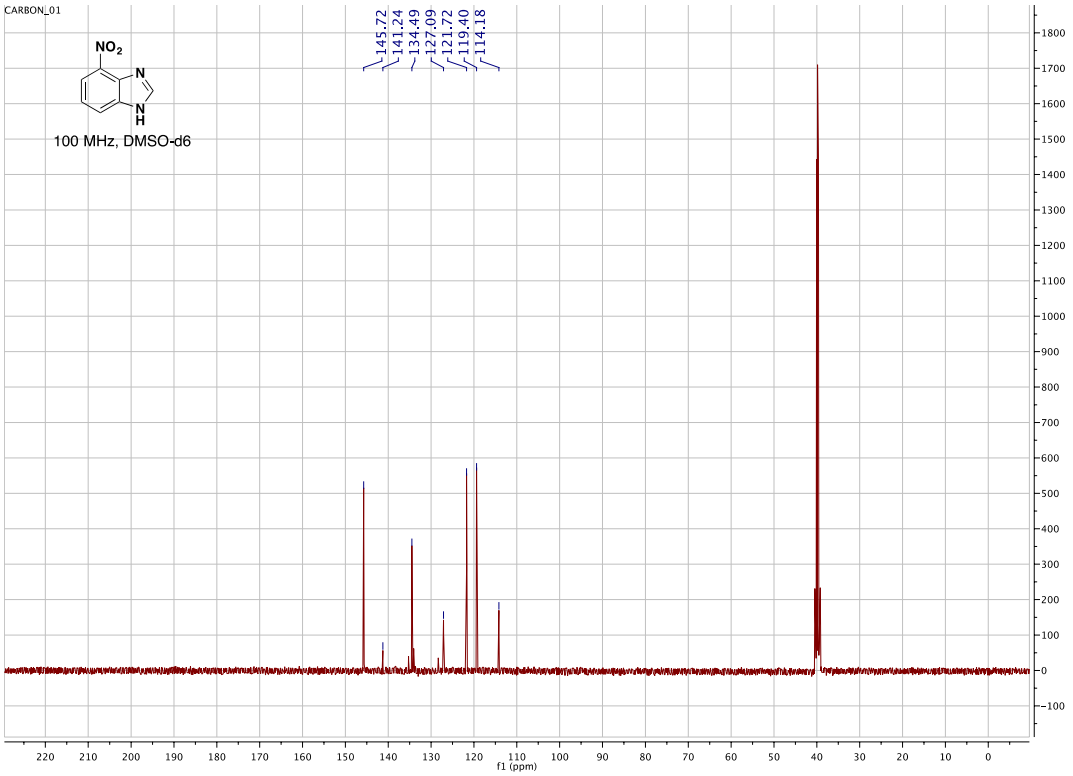
30 ^{13}C NMR



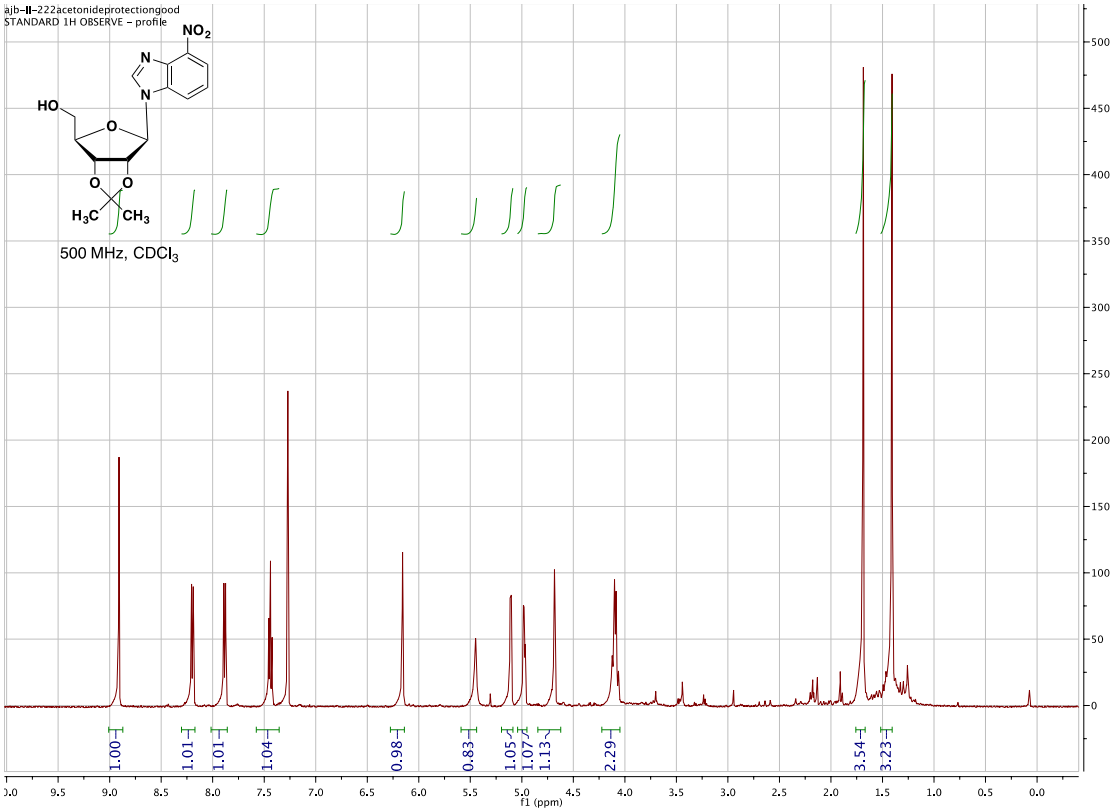
34 ^{1}H NMR



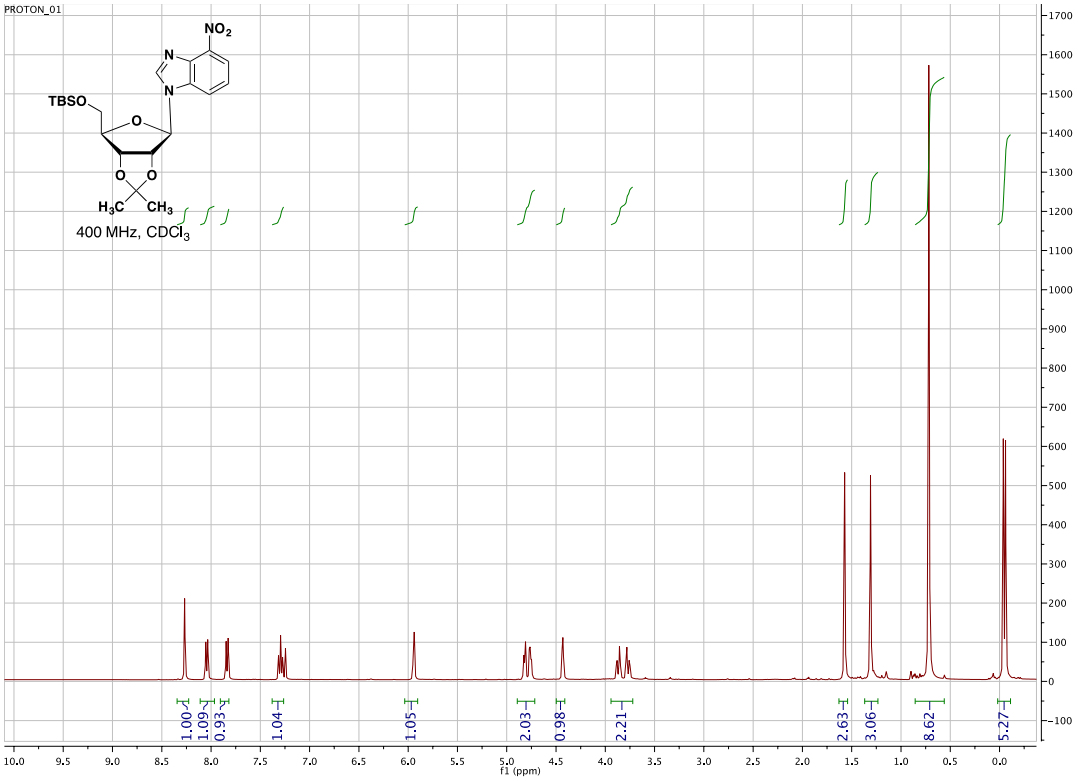
34 ^{13}C NMR



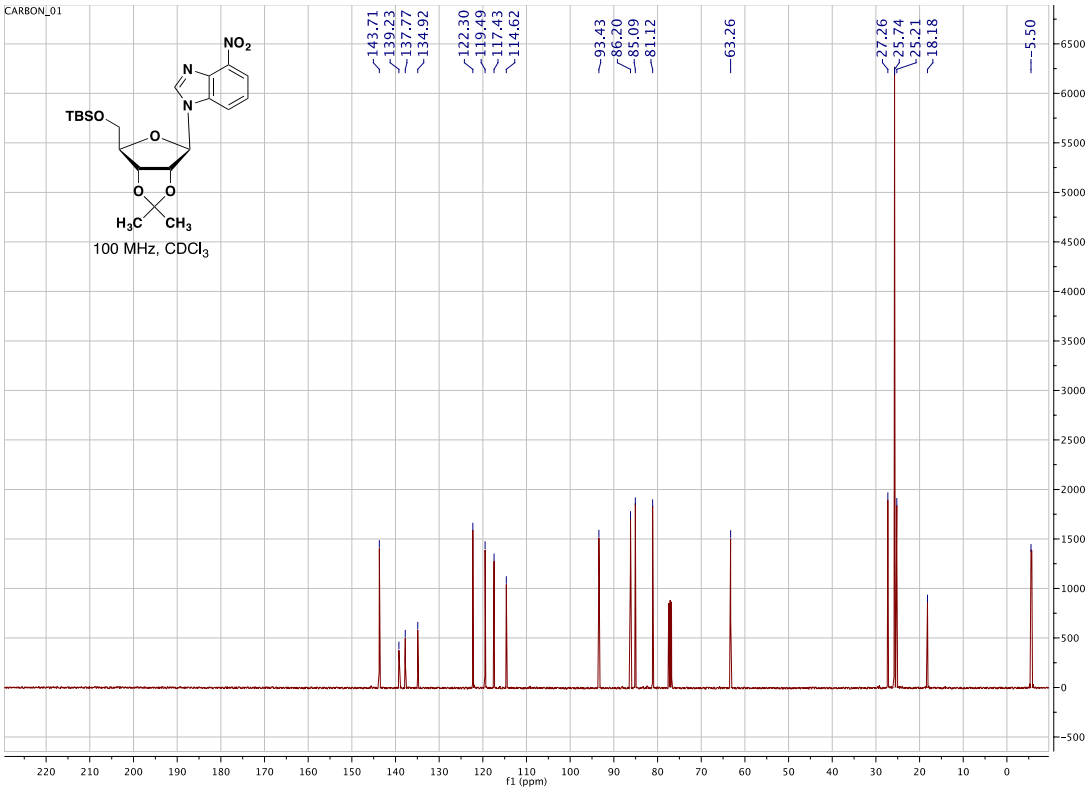
36 ^{1}H NMR


ajb-II-222acetonideprotectiongood
STANDARD 1H OBSERVE - profile
NO2
N
N
HO
O
O
O
H3C
CH3
500 MHz, CDCl3
1.00
1.01
1.01
1.04
0.98
0.83
1.05
1.07
1.13
2.29
3.54
3.23
f1 (ppm)

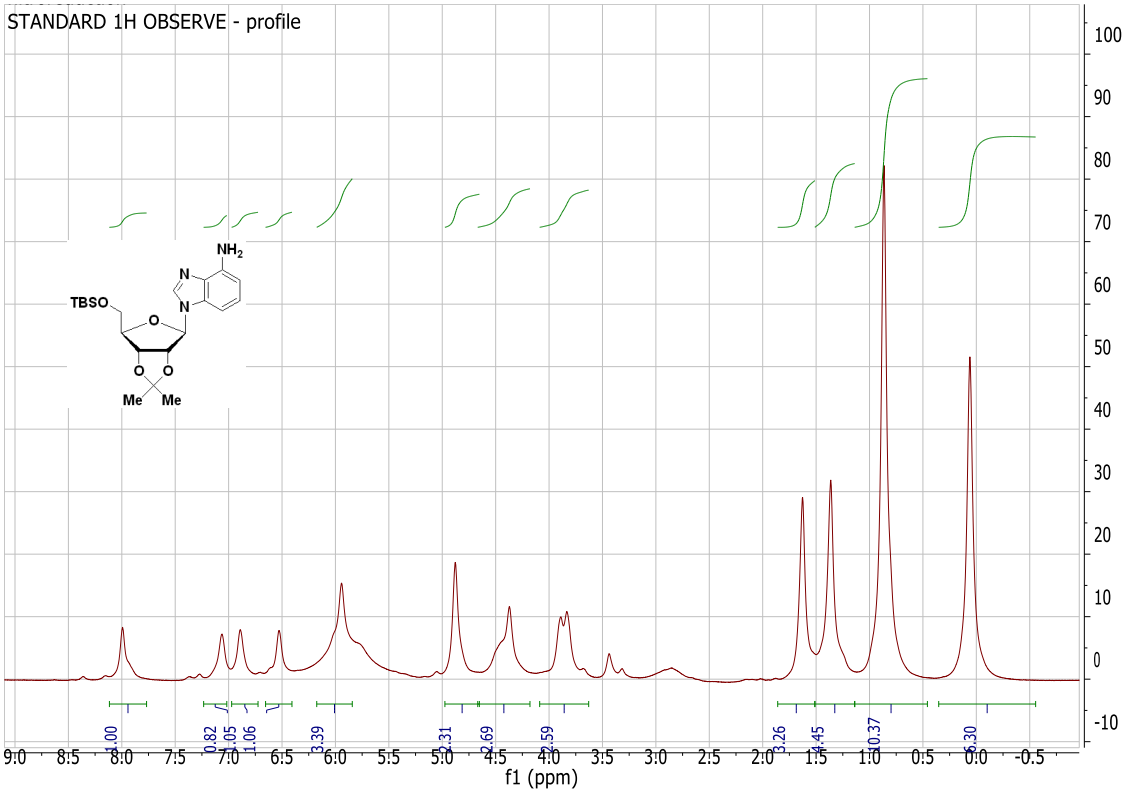
S19 ^{1}H NMR



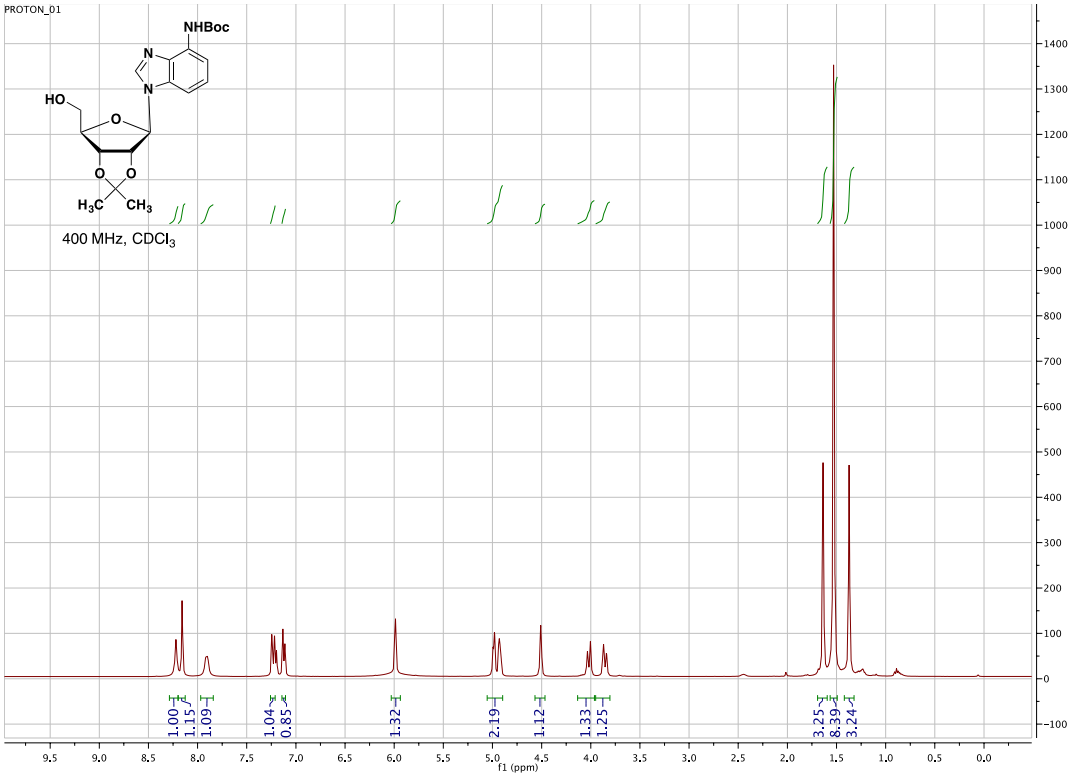
S19 ^{13}C NMR



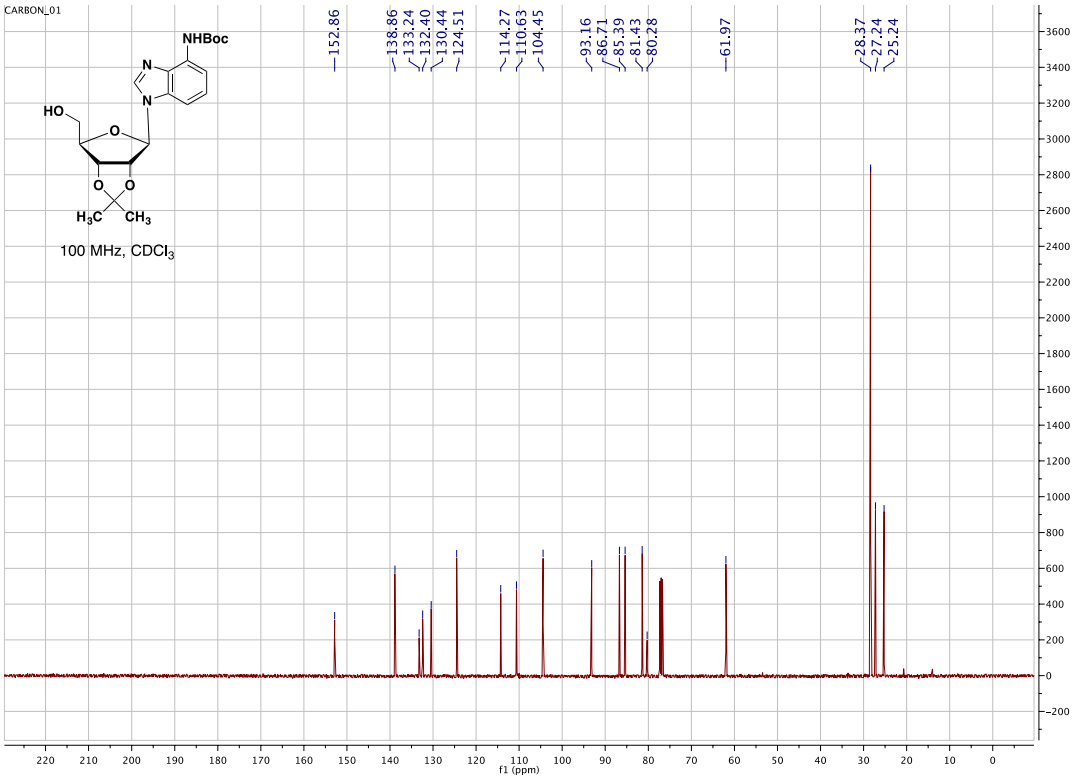
37 ^{1}H NMR


STANDARD 1H OBSERVE - profile
NH2
N
N
TBSO
O
O
O
Me
Me
1.00
0.82
1.05
1.06
3.39
5.31
2.69
2.59
3.26
4.45
10.37
6.30
f1 (ppm)

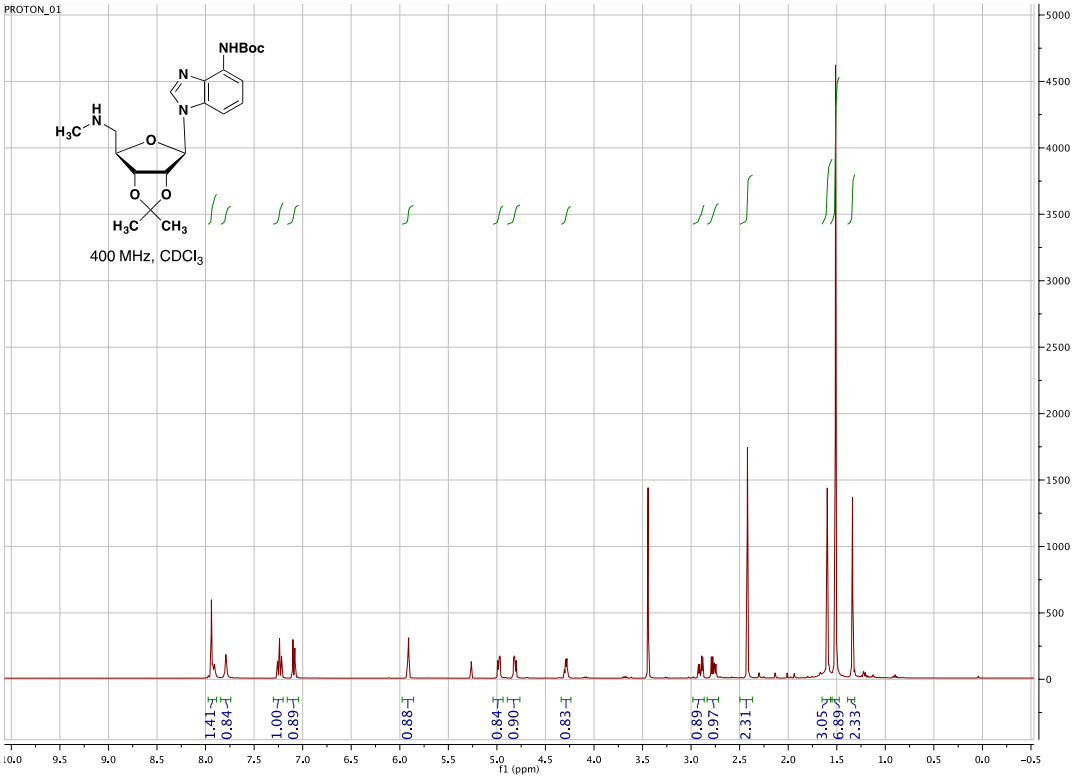
38 ^{1}H NMR



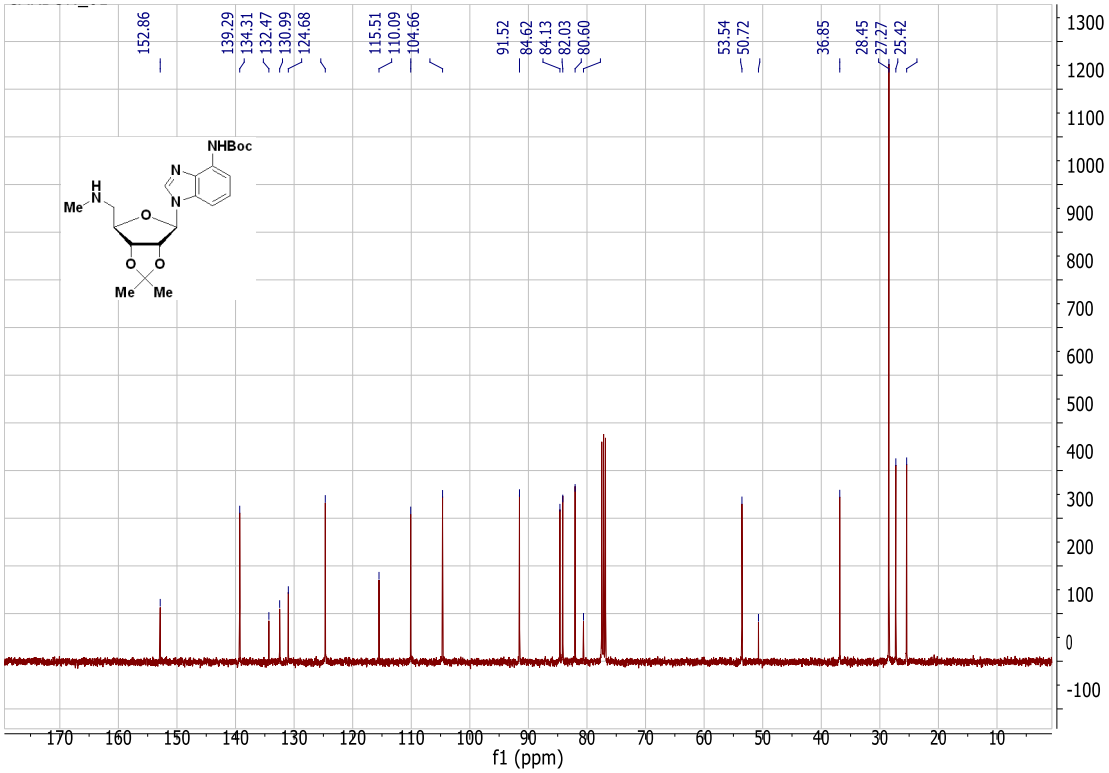
38 ^{13}C NMR



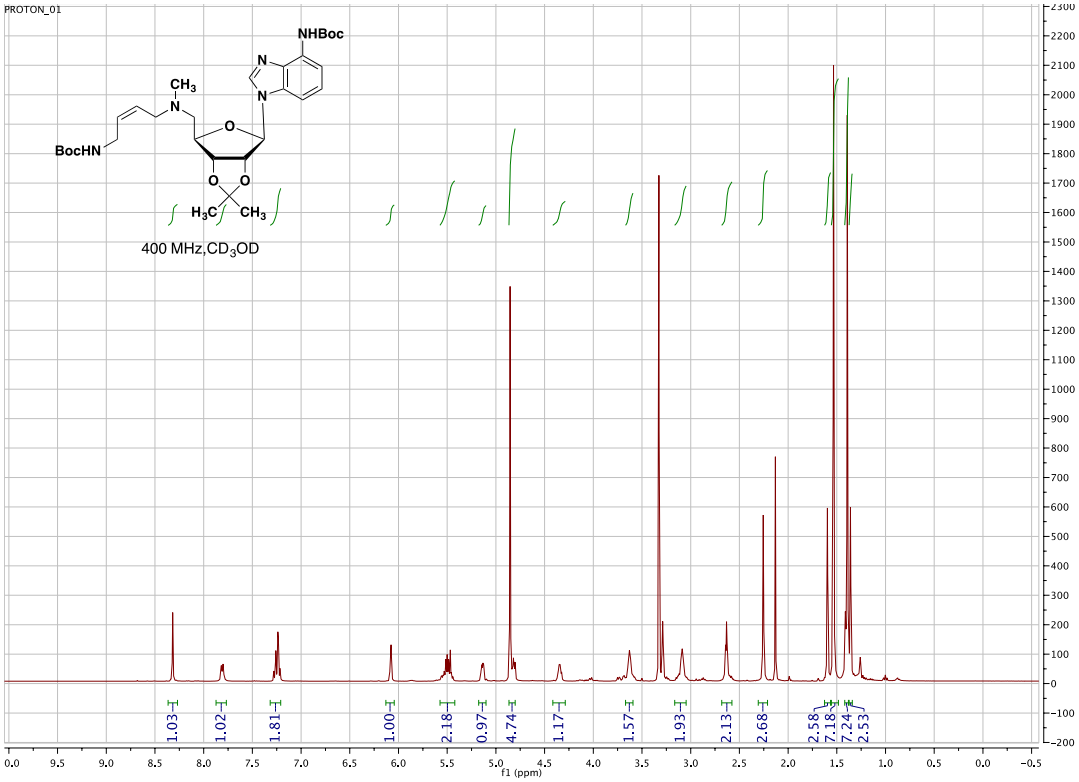
S20 ^{1}H NMR



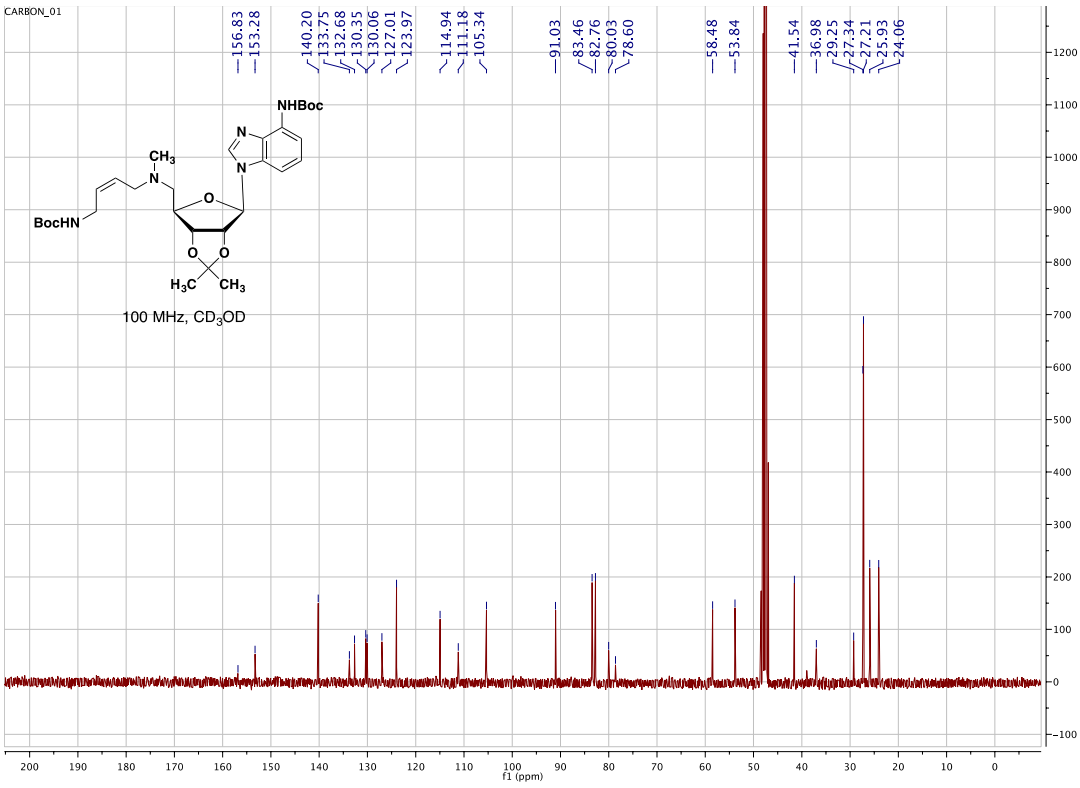
S20 ^{13}C NMR



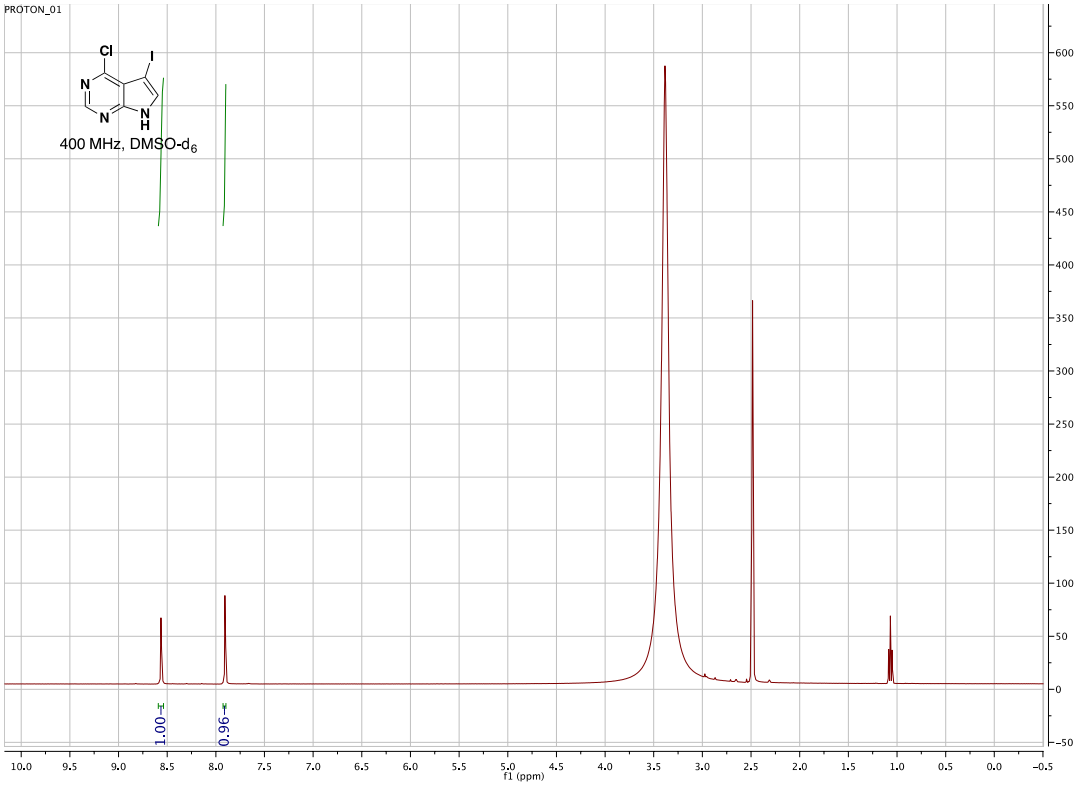
39 ^{1}H NMR



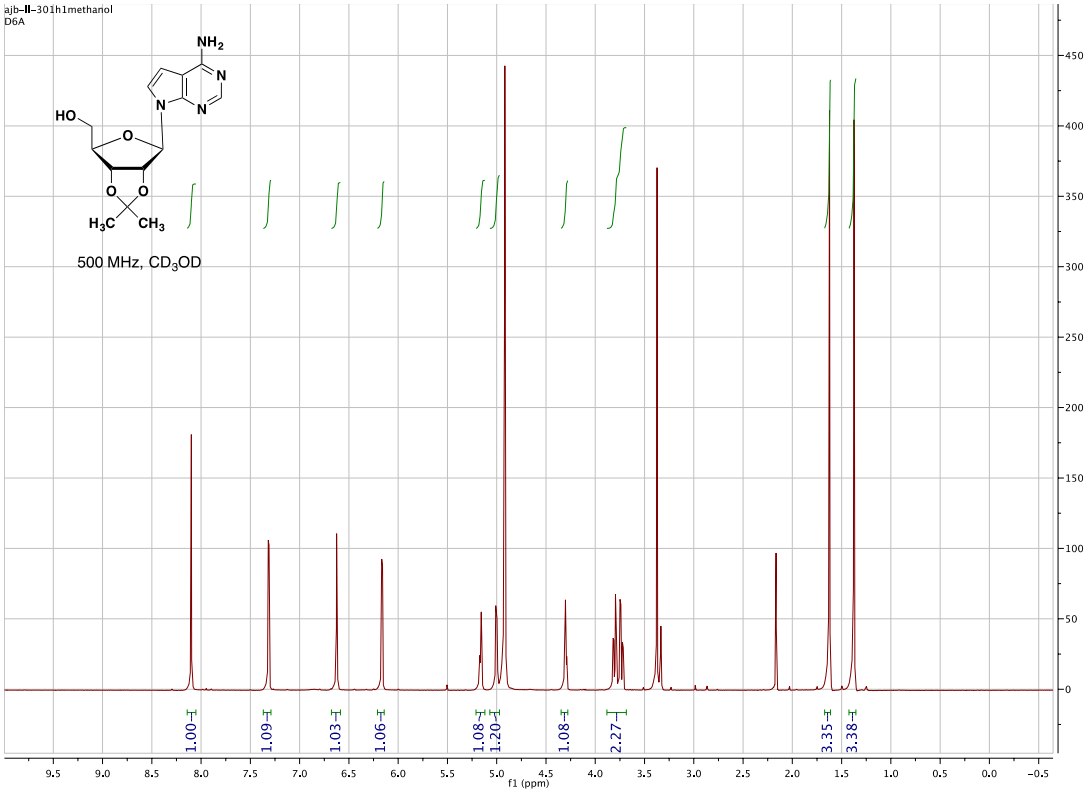
39 ^{13}C NMR



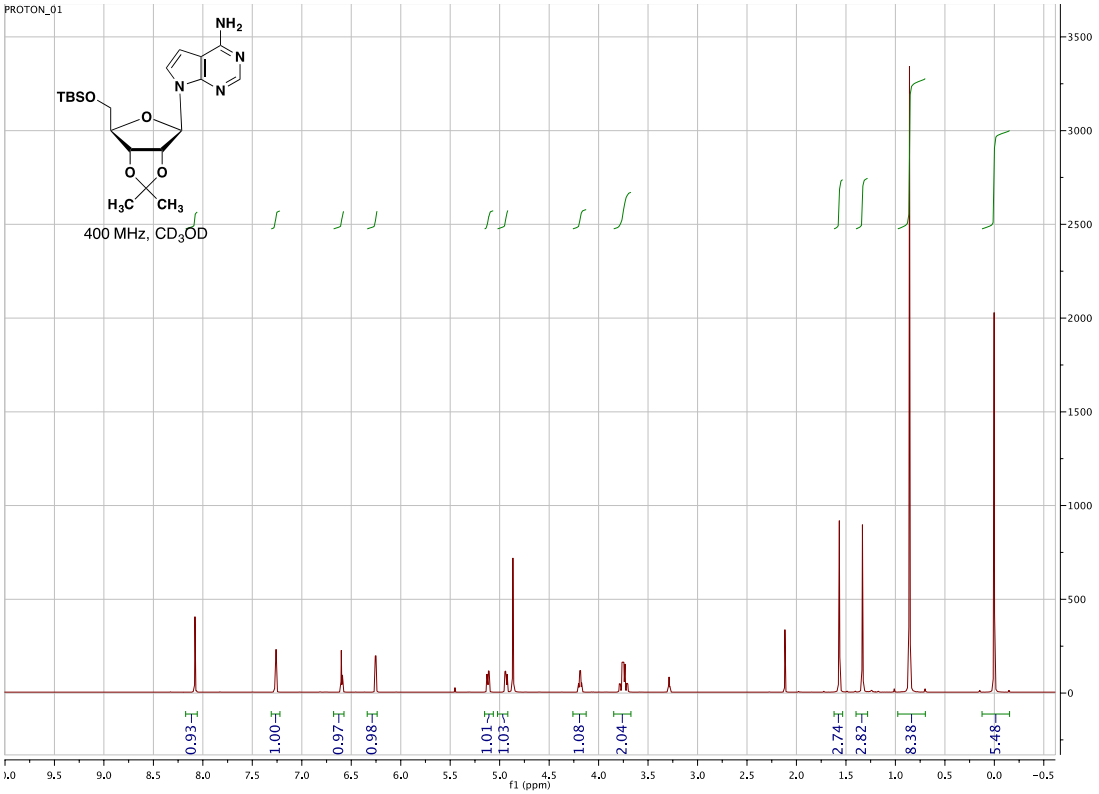
41b ^{1}H NMR



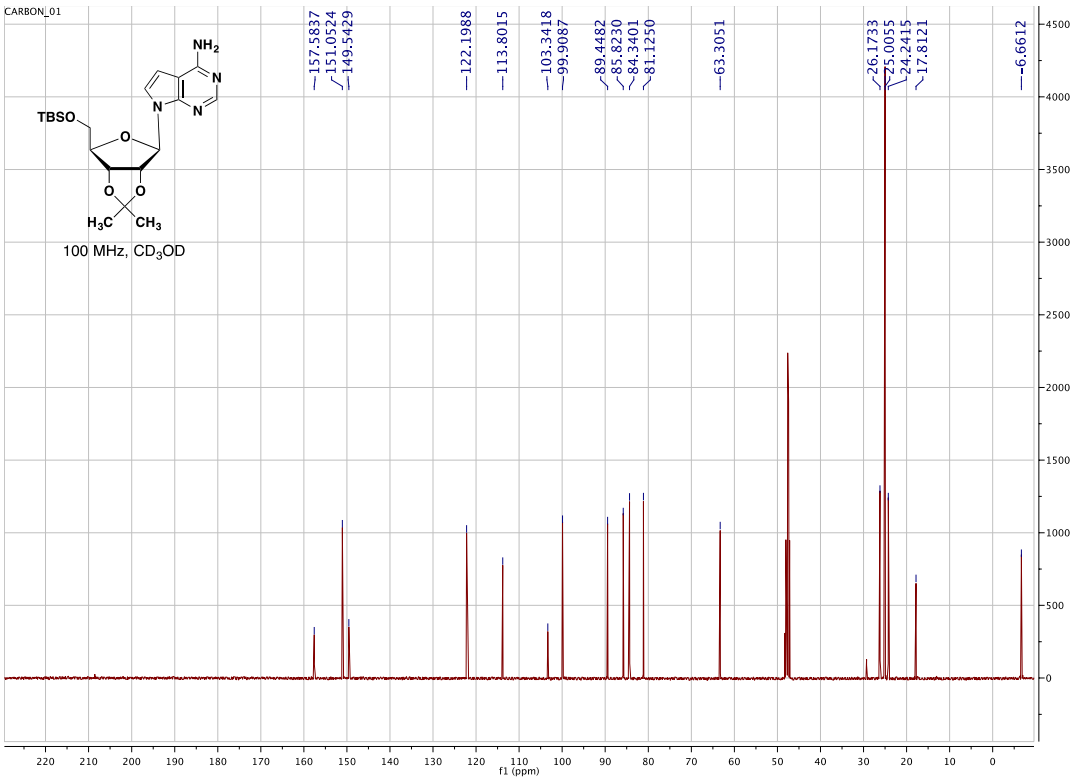
S22 ^{1}H NMR



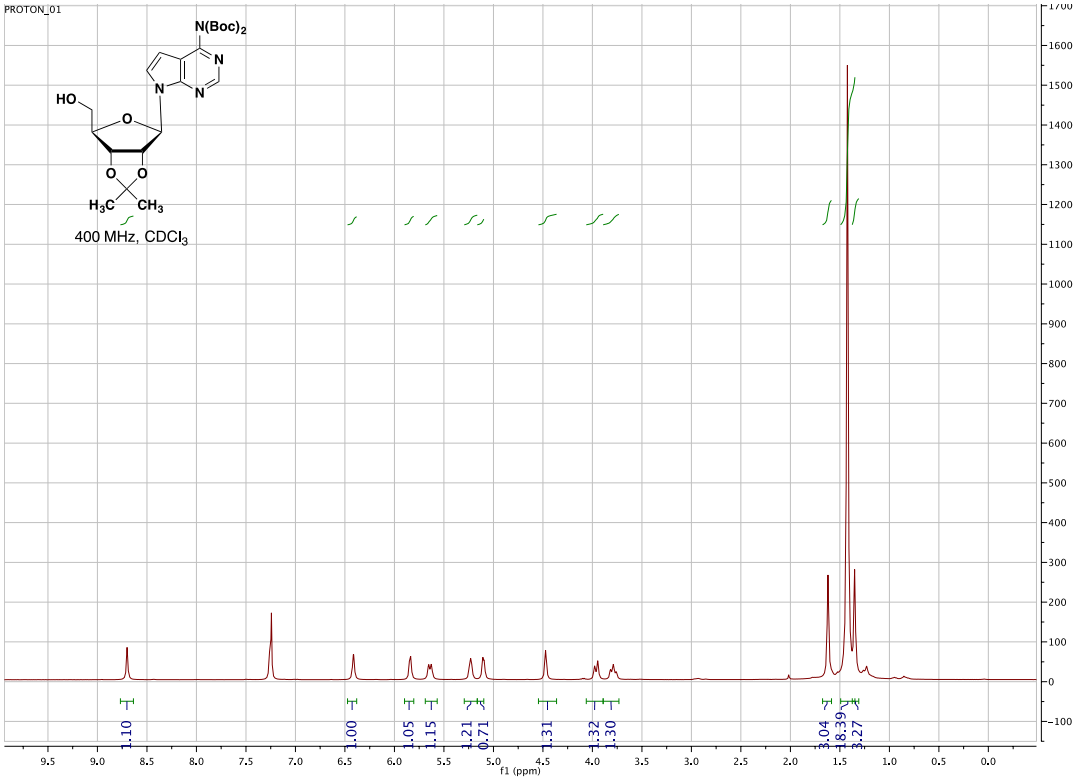
44 ^{1}H NMR



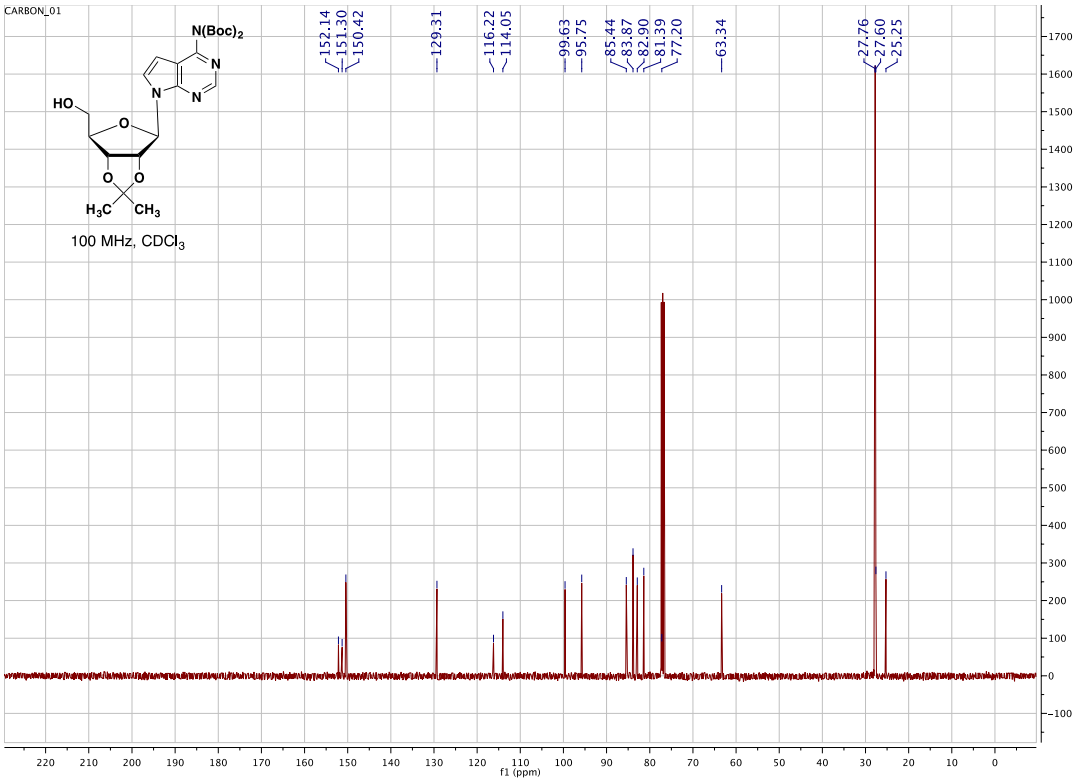
44 ^{13}C NMR



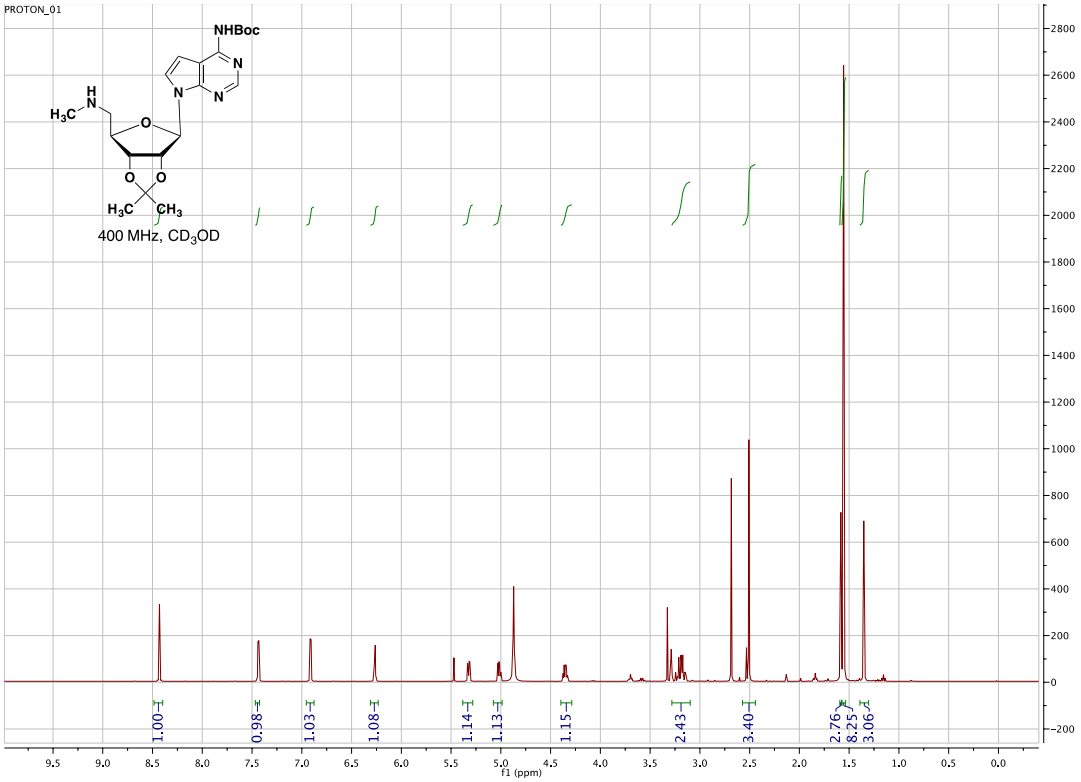
45 ^{1}H NMR



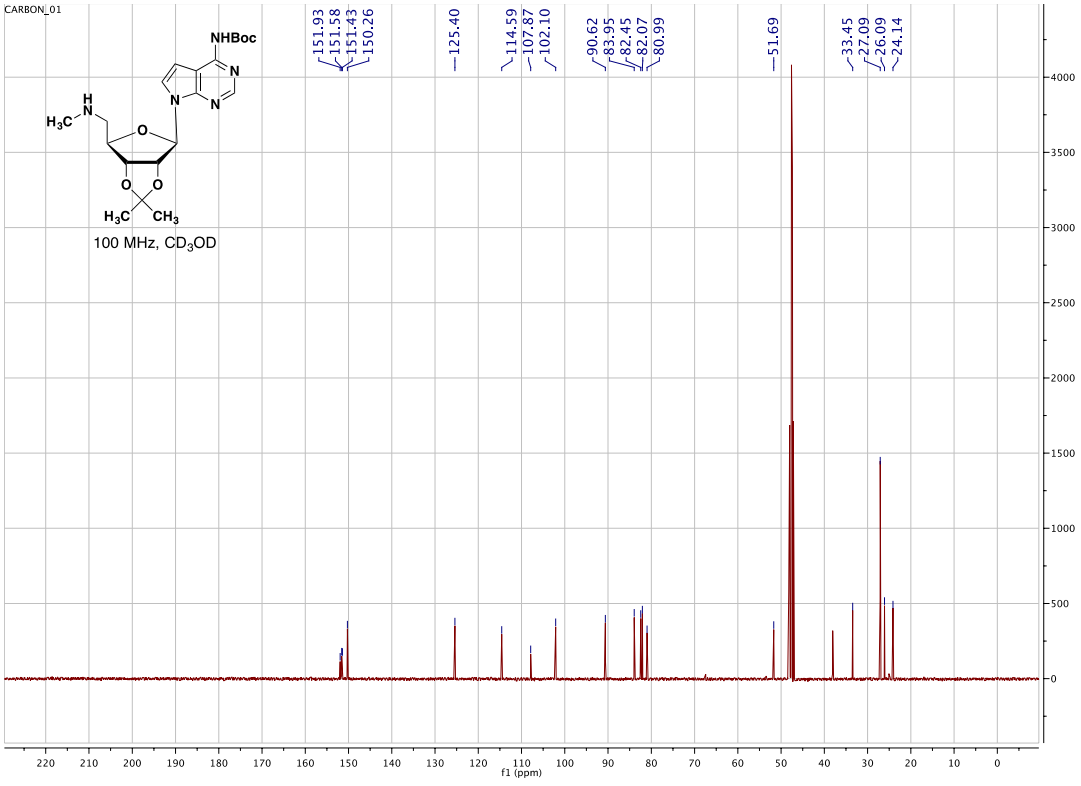
45 ^{13}C NMR



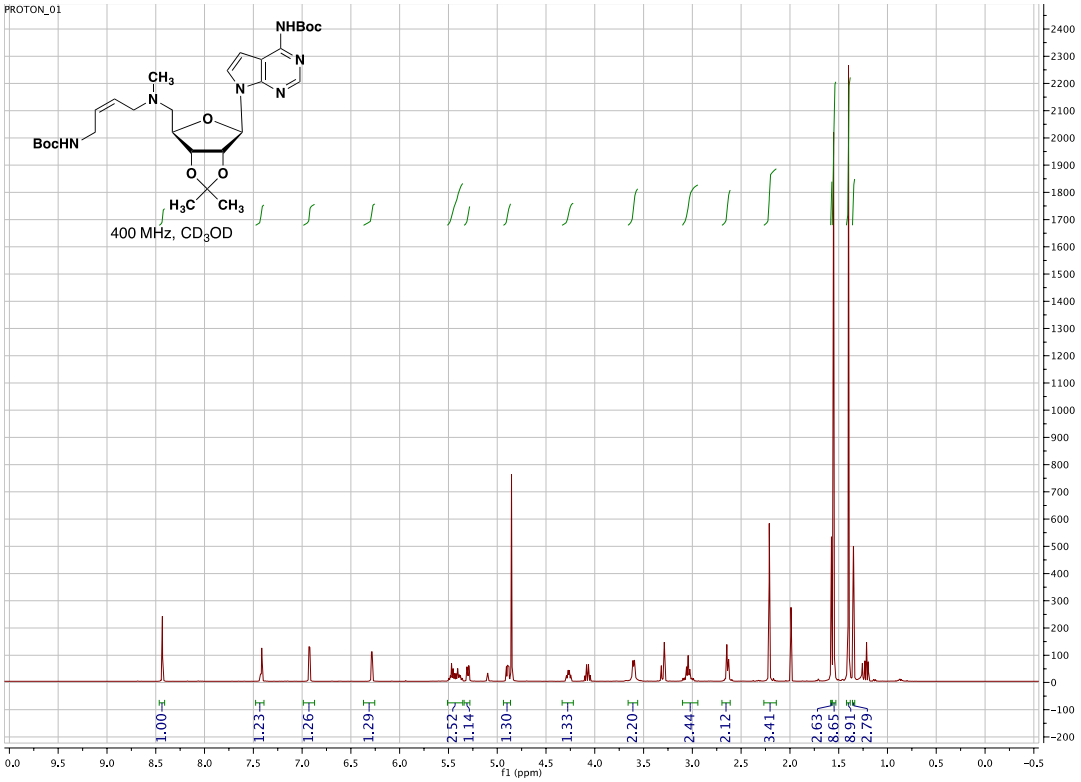
S23 ^{1}H NMR



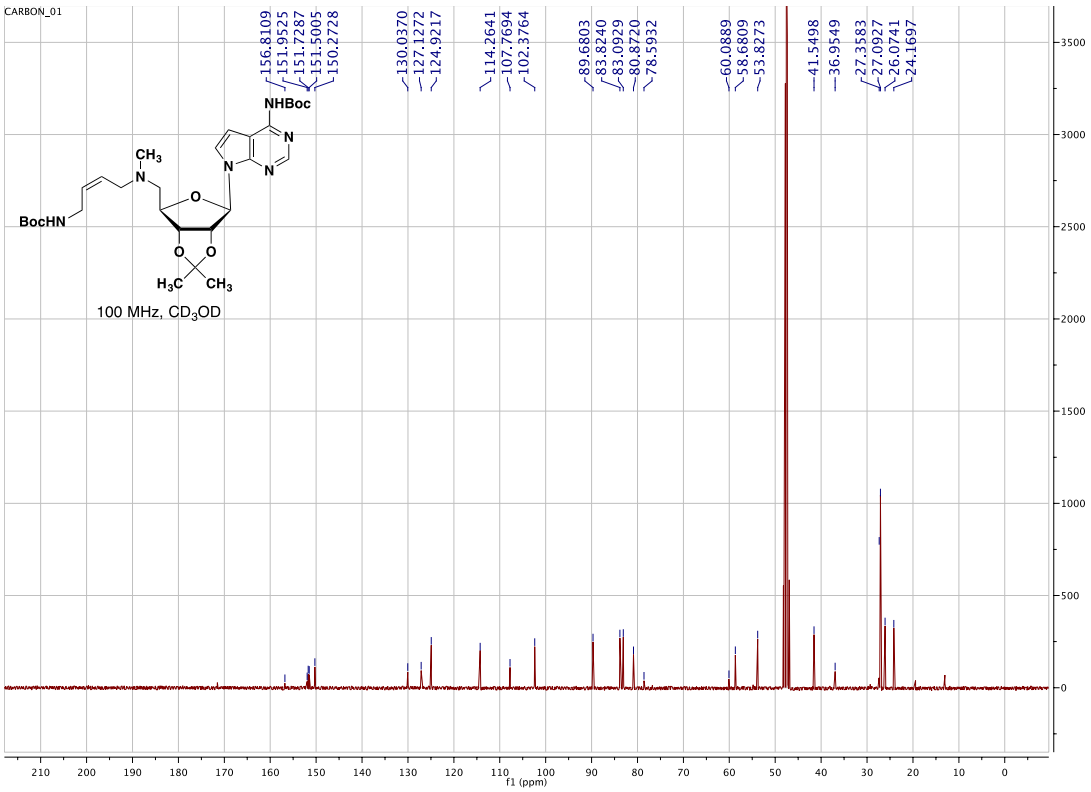
S23 ^{13}C NMR



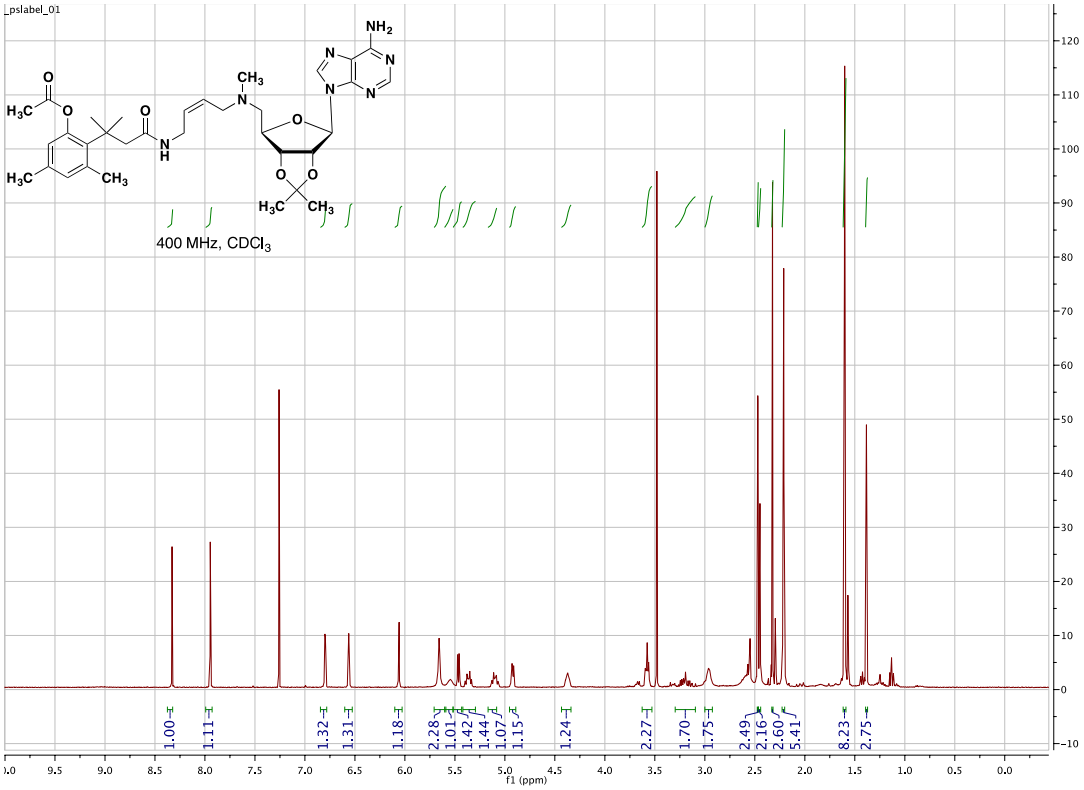
46 ^{1}H NMR



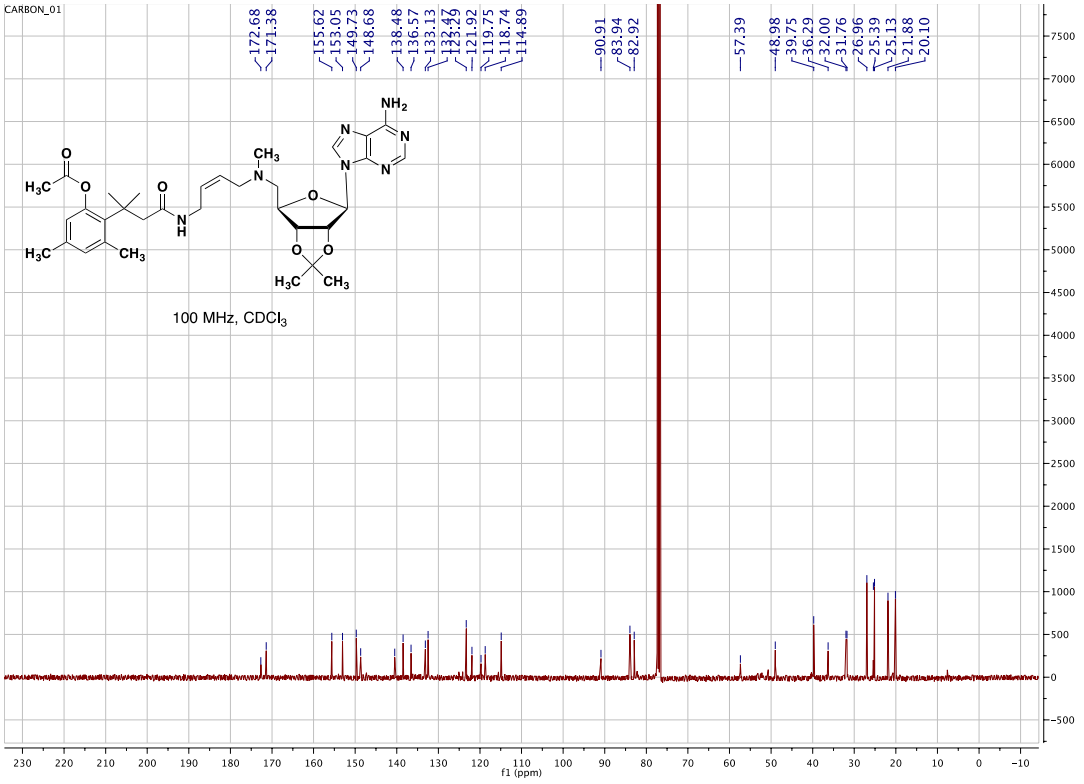
46 ^{13}C NMR



49 ^{1}H NMR



49 ^{13}C NMR



References:

1. Nosenko, Y.; Kunitski, M.; Stark, T.; Gobel, M.; Tarakeshwar, P.; Brutschy, B., 4-Aminobenzimidazole-1-Methylthymine: A Model for Investigating Hoogsteen Base-Pairing between Adenine and Thymine. *J. Phys. Chem. A* **2011,** *115* (41), 11403-11411.
2. Gadakh, B.; Vondenhoff, G.; Lescrinier, E.; Rozenski, J.; Froeyen, M.; Van Aerschot, A., Base substituted 5'-O-(N-isoleucyl)sulfamoyl nucleoside analogs as potential antibacterial agents. *Bioorg. Med. Chem.* **2014,** *22* (10), 2875-2886.
3. Song, Y.; Ding, H.; Dou, Y.; Yang, R.; Sun, Q.; Xiao, Q.; Ju, Y., Efficient and practical synthesis of 5'-deoxytubercidin and its analogues via vorbruggen glycosylation. *Synthesis* **2011,** (9), 1442-1446.
4. Naus, P.; Perlikova, P.; Bourderioux, A.; Pohl, R.; Slavetinska, L.; Votruba, I.; Bahador, G.; Birkus, G.; Cihlar, T.; Hocek, M., Sugar-modified derivatives of cytostatic 7-(het)aryl-7-deazaadenosines: 2'-C-methylribonucleosides, 2'-deoxy-2'-fluoroarabinonucleosides, arabinonucleosides and 2'-deoxyribonucleosides. *Bioorg. Med. Chem.* **2012,** *20* (17), 5202-5214.
5. De Ornellas, S.; Slattery, J. M.; Edkins, R. M.; Beeby, A.; Baumann, C. G.; Fairlamb, I. J. S., Design and synthesis of fluorescent 7-deazaadenosine nucleosides containing π-extended diarylacetylene motifs. *Org. Biomol. Chem.* **2015,** *13* (1), 68-72.
6. Liu, R.; Aw, J.; Teo, W.; Padmanabhan, P.; Xing, B., Novel trimethyl lock based enzyme switch for the self-assembly and disassembly of gold nanoparticles. *New J. Chem.* **2010,** *34* (4), 594-598.