Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Synthesis of Morpholino Nucleosides Starting From Enantiopure Glycidol

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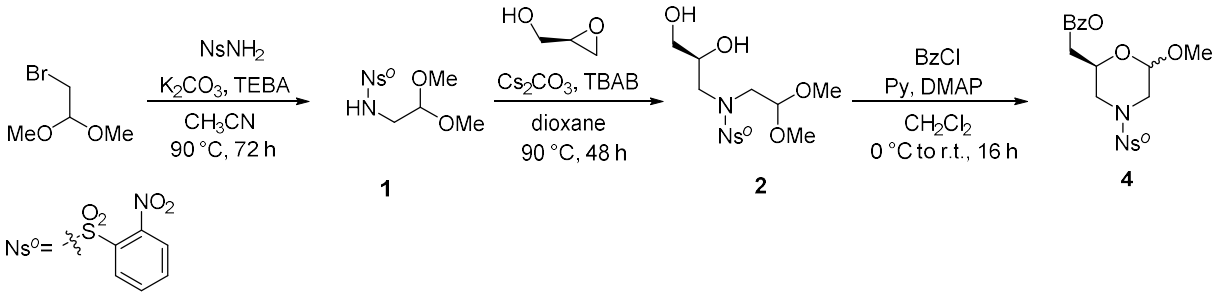
Supporting Information

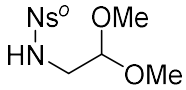
Materials and methods

All available chemicals and solvents were purchased from commercial sources and were used without any further purification. Thin layer chromatography (TLC) was performed using 0.25 mm silica gel precoated plates Si 60-F254 (Merck, Darmstadt, Germany) visualized by UV-254 light and CAM staining. Purification by flash column chromatography (FCC) was conducted by using silica gel Si 60, 230-400 mesh, 0.040-0.063 mm (Merck). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 (400 and 101 MHz, respectively) or Bruker Fourier 300 (300 and 75 MHz , respectively); chemical shifts are indicated in parts per million downfield from $SiMe_4$, using the residual proton (DMSO = 2.54; CH_3CN = 1.96; $CHCl_3$ = 7.26 ppm; CH_3OH = 3.30; H_2O = 4.70) and carbon (DMSO = 39.0 CH_3CN = 30.9 and 118.1; $CDCl_3$ = 77.0 ppm; CH_3OH = 49.0) solvent resonances as internal reference. Protons and carbon assignments were achieved by ^{13}C-APT, ^{1}H-^{1}H COSY, and ^{1}H-^{13}C heteronuclear correlation experiments. Coupling constants values *J* are given in Hz. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at 589 nm, using a 10 cm x 5 ml cell and c is in g/100 ml. FTIR spectra were recorded on a Tensor 27 (ATR Diamond) Bruker infrared spectrophotometer and are reported in frequency of absorption (cm^{-1}).

Procedure for the synthesis of morpholine acetals 4α, β



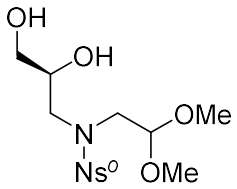
***N*-(2,2-Dimethoxyethyl)-2-nitrobenzenesulfonamide (1)**



1

To a heterogeneous mixture of 2-nitrobenzenesulfonamide (606 mg, 3.00 mmol), TEBA (69 mg, 0.30 mmol) and bromoacetaldehyde dimethyl acetal (507 mg, 3.00 mmol) dissolved in anhydrous CH_3CN (6.0 mL) was added anhydrous K_2CO_3 (455 mg, 3.3 mmol). The resulting mixture was magnetically stirred at 90 °C for 72 hours. After cooling, the crude was diluited with CH_2Cl_2 (10 mL) and filtered through a celite pad. The solvent was evaporated under vacuum (RV) and the residue was purified by FCC (AcOEt/hexane 1:2) providing **1** as white solid (653 mg, 75%), m.p.: 62.0-66.2 °C. The characterization of product **1** is consistent with that reported in the literature.[1]

(*S*)-*N*-(2,3-Dihydroxypropyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide (2)



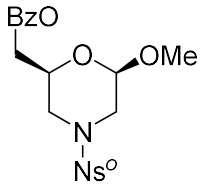
2

In a screw cap vial, a heterogeneous mixture of sulfonamide **1** (639 mg, 2.20 mmol), TBAB (64 mg, 0.20 mmol), (*R*)-glycidol (148 mg, 2.00 mmol) and anhydrous Cs_2CO_3 (66 mg, 0.2 mmol) in anhydrous dioxane (4 mL), was magnetically stirred at 90 °C for 48 hours. After cooling, the crude was diluted with AcOEt (20 mL) and filtered through a celite pad. The solvent was evaporated under reduced pressure (RV) and the residue was purified by FCC (AcOEt/hexane 1:1) providing **2** as yellow wax (634 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 6.8 Hz, 1H), 7.74 – 7.65 (m, 3H), 4.63 (t, *J* = 5.3 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.70 (dd, *J* = 4.1, 11.4 Hz, 1H), 3.56 (dd, *J* = 4.9, 11.7 Hz, 1H), 3.51 – 3.40 (m, 10H), 2.64 (bs, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 144.2, 129.9, 129.6, 128.5, 127.4, 105.4, 70.0, 58.9, 51.6 (2 CH_3), 45.0, 44.9. Anal. Calcd. for $C_{13}H_{20}N_2O_8S$: C, 42.85; H, 5.53; N, 7.69. Found: C, 42.94; H, 5.58; N, 7.61.

[1] Y. Miyauchi, K. Noguchi, K. Tanaka, Rhodium-Catalyzed One-Pot Intermolecular [2 + 2 + 2] Trimerization/Asymmetric Intramolecular [4 + 2] Cycloaddition of Two Aryl Ethynyl Ethers and 5-Alkynals, *Org. Lett.,* 2012, **23**, 5856-5859.

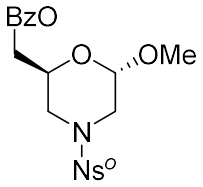
{(2*R*,6*S*)-2-Methoxy-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (4β) *and* **{(2*S*,6*S*)-2-methoxy-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (4α)**

To a solution of sulfonamido diol **2** (364 mg, 1.00 mmol), DMAP (12 mg, 0.10 mmol), pyridine (81 µL, 79 mg, 1.00 mmol), in dry CH_2Cl_2 (3 mL) benzoyl chloride (141 mg, 1.00 mmol) was added dropwise at 0 °C. The resulting solution was stirred at 35 °C for 16 h, then the reaction was diluted with CH_2Cl_2 (10 ml), washed with saturated NH_4Cl solution (2×10 mL), saturated $NaHCO_3$ solution (2×10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent under vacuum (RV), the crude was purified by FCC (AcOEt/hexane 1:2) affording morpholines **4α, β.**



4β

4β (300 mg, 69%), yellow wax, $[\alpha]_D^{20}$: – 11.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10-8.00 (m, 3H), 7.80 – 7.61 (m, 4H), 7.49 (t, *J* = 7.4 Hz, 2H), 4.60 (d, *J* = 8.0 Hz, 1H), 4.50 (dd, *J* = 5.3, 11.6 Hz, 1H), 4.41 (dd, *J* = 5.3, 11.5 Hz, 1H), 4.10-4.07 (m, 1H), 3.89 – 3.81 (m, 2H), 3.56 (s, 3H), 2.89 (t, *J* = 11.3 Hz, 1H), 2.74 (dd, *J* = 8.7, 12.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 148.3, 142.2, 134.2, 133.4, 132.4, 131.9, 131.0, 129.7 (2 CH_{ar}), 128.5 (2 CH_{ar}), 124.4, 99.3, 71.8, 64.2, 56.6, 48.5, 46.7. IR ν_{max} 3356, 3338, 1749, 1354, 928, 768 cm^{-1}. Anal. Calcd. for $C_{19}H_{20}N_2O_8S$: C, 52.29; H, 4.62; N, 6.42. Found: C, 52.45; H, 4.70; N, 6.36.



4α

4α (100 mg, 23%), yellow wax, $[\alpha]_D^{20}$: – 10.9 (*c* 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 8.05 (m, 3H), 7.71 – 7.58 (m, 4H), 7.49 – 7.45 (m, 2H), 4.76 (s, 1H), 4.47 – 4.35 (m, 3H), 3.95 (d, *J* = 12.8 Hz, 1H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.34 (s, 3H), 3.17 (dd, *J* = 1.9, 13.1 Hz, 1H), 3.00 (dd, *J* = 10.0, 12.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 148.4, 141.4, 134.0, 133.7, 132.8, 131.7, 131.0 (2 CH_{ar}), 130.2 (2 CH_{ar}), 128.6, 124.2, 101.1, 71.3, 64.4, 56.8, 49.0, 46.7. Anal. Calcd. for $C_{19}H_{20}N_2O_8S$: C, 52.29; H, 4.62; N, 6.42. Found: C, 52.47; H, 4.73; N, 6.32.

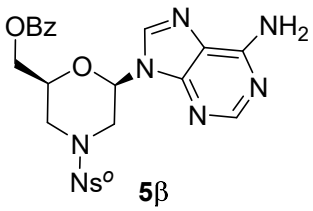
General procedure for the preparation of protected morpholino compounds

Method A: synthesis of 5- and 6- α,β; 8β

In a round bottom flask, TMSOTf (272 μL, 333 mg, 1.5 mmol) was added dropwise at 0 °C to a mixture of morpholines **4** (218 mg, 0.5 mmol) and the appropriate nucleobase (1.0 mmol) in anhydrous CH_3CN (1.0 mL). The reaction was allowed to warm to room temperature until completion (4 hours). The reaction was then cooled to 0 °C, diluted with AcOEt (10 mL), quenched and washed with saturated $NaHCO_3$ solution (2×10 mL), NH_4Cl solution (5 mL), brine (5 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent under vacuum (RV), the crude was purified by FCC affording the correspondent analogue. Reaction time, yield, physical, spectroscopic, and analytical data of compound **5- and 6- α,β; 8β** are as follows.

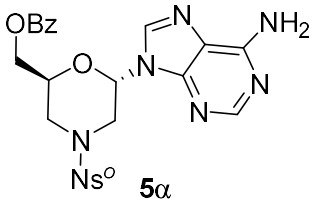
{(2*R*,6*S*)-2-(6-Amino-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (5β) *and* **{(2*S*,6*S*)-2-(6-amino-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (5α)**

Adenine (135 mg); FCC (AcOEt/hexane 3:1) + 10% CH_3OH.



5β

5β (138 mg, 51%), white wax $[\alpha]_D^{20}$: – 10.6 (*c* 0.5, CH_3CN). ^1H NMR (300 MHz, CD_3CN) δ 8.24 (s, 1H), 8.07 – 8.00 (m, 4H), 7.91 – 7.78 (m, 3H), 7.75 – 7.48 (m, 3H), 6.22 (bs, 2H), 5.96 (dd, *J* = 2.4, 10.2 Hz, 1H), 4.45 – 4.30 (m, 3H), 4.10 (d, *J* =12.1 Hz, 1H), 3.95 (d, *J* =12.4 Hz, 1H), 3.56 (t, *J* = 11.6 Hz, 1H), 3.10 (t, *J* = 11.4 Hz, 1H). ^{13}C NMR (75 MHz, CD_3CN) δ 166.2, 157.4, 153.4, 148.3, 146.3, 138.4, 136.7, 135.0, 134.5, 134.1, 132.7, 131.1, 130.3 (2 CH_{ar}), 123.0 (2 CH_{ar}), 129.4, 124.7, 80.8, 77.1, 66.6, 49.5, 48.2. IR ν_{max} 3356, 3338, 1749, 1354, 928, 768 cm^{-1}. Anal. Calcd. for $C_{23}H_{21}N_7O_7S$: C, 51.20; H, 3.92; N, 18.17. Found: C, 51.31; H, 3.97; N, 18.04.

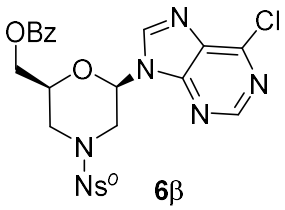


5α

5α (59 mg, 22%), white amorphous solid, $[\alpha]_D^{20}$ = – 13.9 (*c* 0.5, CH_3CN). ^1H NMR (300 MHz, CD_3OD) δ 8.42 (s, 1H), 8.11 – 8.05 (m, 2H), 7.91 – 7.79 (m, 5H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 6.32 (s, 1H), 4.48 (dd, *J* = 6.5, 11.9 Hz, 1H), 4.37 (dd, *J* = 3.8, 12.1 Hz, 1H), 4.20 - 4.13 (m, 1H), 3.92 (d, *J* = 12.7 Hz, 1H), 3.69 – 3.64 (m, 2H), 3.27 – 3.20 (m, 1H) *NH protons not visible*. ^{13}C NMR (75 MHz, CD_3OD) δ 160.0, 156.6, 153.2, 152.5, 143.2, 143.1, 138.9, 137.0, 135.8, 135.0, 134.1, 133.2 (2 CH_{ar}), 132.8, 132.1 (2 CH_{ar}), 128.3, 125.0, 80.5, 72.6, 67.1, 50.2, 33.3. IR ν_{max} 3365, 3358, 1749, 1348, 940, 785 cm^{-1}. Anal. Calcd. for $C_{23}H_{21}N_7O_7S$: C, 51.20; H, 3.92; N, 18.17. Found: C, 51.35; H, 4.00; N, 18.02.

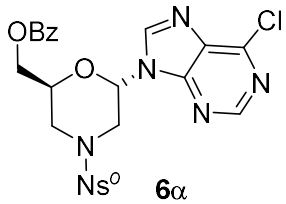
{(2*R*,6*S*)-2-(6-Chloro-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (6β) *and* **{(2*S*,6*S*)-2-(6-chloro-9*H*-purin-9-yl)-4-[(2-nitrophenyl]sulfonyl)morpholin-6-yl}methyl benzoate (6α)**

6-Chloropurine (154 mg); FCC (AcOEt/hexane 3:1).



6β

6β (134 mg, 48%), yellow wax, $[\alpha]_D^{20}$ = – 31.1 (*c* 0.5, CH_3CN). ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.27 (s, 1H), 8.12 – 8.01 (m, 3H), 7.80 – 7.68 (m, 3H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 6.03 (dd, *J* = 1.7, 9.9 Hz, 1H), 4.53 – 4.45 (m, 2H), 4.38 – 4.25 (m, 2H), 4.02 (d, *J* = 13.0 Hz, 1H), 3.50 (t, *J* = 11.9 Hz, 1H), 3.11 (t, *J* = 12.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 152.2, 151.3, 150.9, 148.0, 142.8, 134.5, 133.3, 132.1, 131.6, 131.1, 130.9, 129.6 (2 CH_{ar}), 129.1, 128.4 (2 CH_{ar}), 124.5, 79.9, 74.6, 63.5, 48.2, 46.3. IR ν_{max} 1744, 1359, 1361, 1024, 912, 777 cm^{-1}. Anal. Calcd. for $C_{23}H_{19}ClN_6O_7S$: C, 49.42; H, 3.43; N,15.04. Found: C, 49.58; H, 3.50; N,14.88.

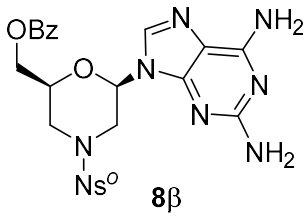


6α

6α (59 mg, 21%), yellow wax, $[\alpha]_D^{20}$ = – 42.7 (*c* 0.5, CH_3CN). ^1H NMR *impure compound* (300 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.57 (s, 1H), 8.03 – 7.97 (m, 3H), 7.79 – 7.64 (m, 3H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.48 – 7.37 (m, 2H), 6.42 (t, *J* = 3.1 Hz, 1H), 4.64 (dd, *J* = 11.6, 6.0 Hz, 1H), 4.54 – 4.18 (m, 3H), 3.95 (d, *J* = 12.1 Hz, 1H), 3.81 (dd, *J* = 13.3, 3.3 Hz, 1H), 3.32 (dd, *J* = 12.5, 8.2 Hz, 1H).

{(2*R*,6*S*)-2-(2,6-Diamino-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (8β)

2,6-Diaminopurine (150 mg); FCC (AcOEt/hexane 9:1) + 10% CH_3OH.



8β

8β (116 mg, 42%, 6 h), white amorphous solid, $[\alpha]_D^{20}$ = – 32.0 (*c* 0.4, CH_3CN). ^1H NMR (300 MHz, CD_3CN) δ 8.00 – 7.91 (m, 3H), 7.85 – 7.70 (m, 3H), 7.66 (s, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.89 (bs, 2H), 5.71 (dd, *J* = 2.8, 10.3 Hz, 1H), 5.10 (bs, 2H), 4.49 – 4.36 (m, 2H), 4.32 – 4.20 (m, 1H), 4.00 (dd, *J* = 1.9, 12.5 Hz, 1H), 3.90 (dd, *J* = 1.9, 14.2 Hz, 1H), 3.46 (dd, *J* = 10.3, 12.2 Hz, 1H), 3.02 (dd, *J* = 10.9, 12.4 Hz, 1H). ^{13}C NMR (75 MHz, CD_3CN) δ 169.8, 161.1, 157.1, 151.9, 149.9, 142.1, 140.4, 138.7, 138.1, 137.7, 136.3, 134.7 (2 CH_{ar}), 133.9 (2 CH_{ar}), 133.6, 133.1, 128.4, 84.4, 80.7, 70.2, 53.2, 51.8. IR ν_{max} 3399, 3390, 3350,

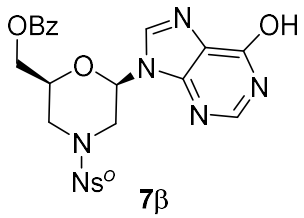
1721, 1339, 879, 752 cm^{-1}. Anal. Calcd. for $C_{23}H_{22}N_8O_7S$: C, 49.82; H, 4.00; N, 20.21. Found: C, 50.00; H, 4.13; N, 20.08.

Method B: synthesis of 7- and 9- α, β

In a round bottom flask, a mixture of the appropriate nucleobase (1.0 mmol), HMDS (323 mg, 2.0 mmol) and saccharin (3.5 mg, 0.02 mmol) was refluxed in anhydrous CH_3CN (3 ml) for 3 hours to get a clear solution. The solvent was evaporated under reduced pressure and a solution of morpholines **4** (218 mg, 0.5 mmol) in anhydrous CH_3CN (1.0 ml) was then added to the silylated base. The reaction mixture was then cooled to 0°C in an ice bath and TMSOTf (272 µL, 333 mg, 1.5 mmol) was added dropwise. After 15 minutes, the reaction was allowed to warm to room temperature until completion (4 h). The reaction was then cooled to 0 °C, diluted with AcOEt (10 mL), quenched and washed with saturated $NaHCO_3$ solution (2×10 mL), NH_4Cl solution (5 mL), and brine (10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent under vacuum (RV), the crude was purified by FCC affording the correspondent analogue. Reaction time, yield and physical, spectroscopic, and analytical data of compounds **7-** and **9- α,β** are as follows.

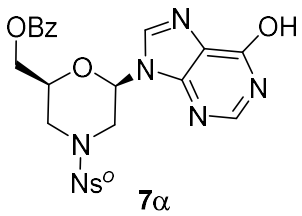
{(2*R*,6*S*)-2-(6-Hydroxy-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (7β) *and* **{(2*S*,6*S*)-2-(6-hydroxy-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (7α)**

Hypoxanthine (136 mg); FCC (AcOEt/hexane 8:2).



7β

7β (138 mg, 51%), pale yellow amorphous solid, $[\alpha]_D^{20}$ = – 27.4 (*c* 0.5, CH_3CN). ^1H NMR(300 MHz, CD_3OD) δ 8.20 (s, 1H), 8.10 (dd, *J* = 1.8, 7.8 Hz, 1H), 8.03–7.98 (m, 3H), 7.85 – 7.77 (m, 3H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.98 (dd, *J* = 2.9, 10.3 Hz, 1H), 4.63 (bs, 1H), 4.47 (d, *J* = 5.0 Hz, 2H), 4.36 – 4.29 (m, 1H), 4.20 – 4.14 (m, 1H), 4.04 – 3.98 (m, 1H), 3.57 (dd, *J* = 10.2, 12.4 Hz, 1H), 3.08 (dd, *J* = 10.9, 12.8 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 170.7, 161.7, 153.1, 151.5, 150.5, 143.6, 140.6, 138.8, 138.0, 136.1, 134.5 (2 CH_{ar}), 134.3, 134.1 (2 CH_{ar}), 131.6, 129.8, 129.4, 83.8, 78.9, 69.2, 52.4, 51.0. IR ν_{max} 3579, 1734, 1361, 1349, 900, 752 cm^{-1}. Anal. Calcd. for $C_{23}H_{20}N_6O_8S$: C, 51.11; H, 3.73; N, 15.55. Found: C, 51.26; H, 3.83; N, 15.41.



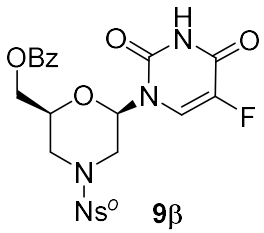
7α

7α (59 mg, 22%), pale yellow wax, $[\alpha]_D^{20}$ = – 22.4 (*c* 0.5, CH_3CN). ^1H NMR (300 MHz, DMSO-*d6*) δ 12.31 (bs, 1H), 8.27 (s, 1H), 7.97 (s, 1H), 7.81 (d, *J* = 9.4 Hz, 2H), 7.70 – 7.63 (m, 3H), 7.49-7.44 (m, 4H), 6.19 (s, 1H), 4.33 – 4.32 (m, 2H) 4.22 – 3.97 (m, 2H), 3.73 – 3.69 (m, 1H), 3.07–2.99 (m, 1H), 2.77-2.74 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ 165.5, 156.3, 148.6, 145.9, 141.5, 137.6, 135.0, 133.2, 132.3, 131.1, 130.1, 129.9, 129.5 (2 CH_{ar}), 128.6 (2 CH_{ar}), 124.8, 124.4, 79.3, 74.3, 63.9, 48.1, 46.3. IR ν_{max} 3467, 1758, 1350, 920, 781 cm^{-1}. Anal. Calcd. for $C_{23}H_{20}N_6O_8S$: C, 51.11; H, 3.73; N, 15.55. Found: C, 51.43; H, 3.97; N, 15.24.

{(2*R*,6*S*)-2-[5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-4-](2-nitrophenyl)sulfonyl[morpholin-6-yl}methyl benzoate (9β) *and*

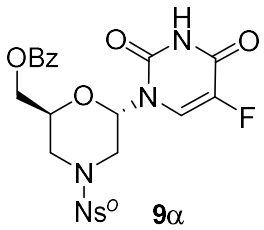
{(2*S*,6*S*)-2-[5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (9α)

5-Fluorouracil (130 mg); FCC (AcOEt/hexane 6:4).



9β

9β (171 mg, 64%), yellow wax, $[\alpha]_D^{20}$ = – 31.8 (*c* 1.0, CH_3CN). ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 4.3 Hz, 1H), 8.15 – 803 (m, 4H), 7.79 – 7.68 (m, 3H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50-7.41 (m, 2H), 5.75 (d, *J* = 8.6 Hz, 1H), 4.50-4.39 (m, 2H), 4.30 – 4.23 (m, 1H), 4.09 – 3.95 (m, 2H), 2.96 (dd, *J* = 11.2, 12.7 Hz, 1H), 2.82 (dd, *J* = 10.8, 12.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 160.2, 158.7 (d, *J* = 30.8 Hz, 1 C), 154.5, 146.7 (d, *J* = 252.9 Hz, 1 CF), 135.8, 133.5, 133.4, 131.8, 131,4, 130.2 (2 CH_{ar}), 129.7 (2 CH_{ar}), 128.0, 125.0 (d, *J* = 33.1 Hz, 1 CH), 124.5., 79.5, 75.7, 63.9, 47.2, 46.7. IR ν_{max} 3389, 1780, 1754, 1358, 1296, 891 cm^{-1}. Anal. Calcd. for $C_{22}H_{19}FN_4O_9S$: C, 49.44; H, 3.58; N, 10.48. Found: C, 49.54; H, 3.64; N, 10.39.

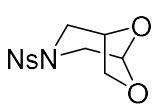


9α

9α (26 mg, 21%), yellow wax, $[\alpha]_D^{20}$ = – 25.7 (*c* 0.5, CH_3CN). ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (bs, 1H), 8.02 (d, *J* = 7.4 Hz, 3H), 7.77-7.50 (m, 5H), 7.46 (t, *J* = 7.5 Hz, 2H), 6.11 (s, 1H), 4.68 (dd, *J* = 5.4, 10.4 Hz, 1H), 4.51 – 4.40 (m, 2H), 3.91 (dd, *J* =3.4, 12.8 Hz, 1H), 3.58 (m, 2H), 3.32 (dd, *J* = 7.2, 12.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 159.6 (d, *J* = 15.6 Hz, 1C), 157.2, 125.2, 150.0, 147.0, 139.8, 135.3, 133.3, 131.1 – 128.0 (m, 7C), 124.6, 75.8, 74.6, 63.5, 47.2, 47.0. IR ν_{max} 3341, 1766, 1749, 1360, 1299, 729 cm^{-1}. Anal. Calcd. for $C_{22}H_{19}FN_4O_9S$: C, 49.44; H, 3.58; N, 10.48. Found: C, 49.61; H, 3.69; N, 10.31.

Method C: synthesis of 9α, β; 12

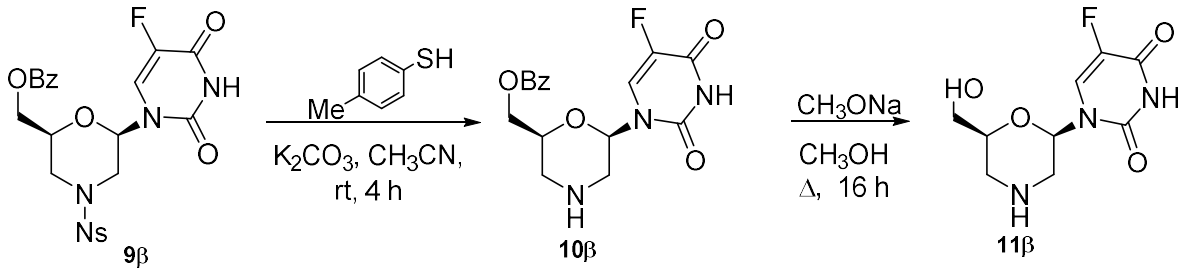
In a round bottom flask, a mixture of 5-Fluorouracil (130 mg, 1.0 mmol), HMDS (323 mg, 2.0 mmol) and saccharin (3.5 mg, 0.02 mmol) was refluxed in anhydrous CH_3CN (3 ml) for 3 hours to get a clear solution. The solvent was evaporated under reduced pressure. A solution of diol **2** (182 mg, 0.5 mmol) and benzoylchloride (98 mg, 0.7 mmol) in anhydrous CH_3CN (1.0 ml) was then added to the silylated base. The reaction mixture was then cooled to 0°C in an ice bath and TMSOTf (272 µL, 333 mg, 1.5 mmol) was added dropwise. After 15 minutes, the reaction was allowed to warm to room temperature and stirred for 8 hours. The reaction was then cooled to 0 °C, diluted with AcOEt (10 mL), quenched and washed with saturated $NaHCO_3$ solution (2×10 mL), NH_4Cl solution (5 mL), and brine (10 mL), dried over $MgSO_4$ and filtered. After evaporation of the solvent under vacuum (RV), the crude was purified by FCC (AcOEt/hexane 1:1) affording products **9α,β** (14% yield) and *(1R,5S)*-3-[(3-nitrophenyl)sulfonyl,]-6,8-dioxa-3-azabicyclo[3.2.1]octane **12**.



12

12 (75 mg, 50%), clear wax, $[\alpha]_D^{20}$ = +3.3 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 – 7.92 (m, 1H), 7.85 – 7.55 (m, 3H), 5.53 (s, 1H), 4.62 (d, *J* = 5.1 Hz, 1H), 4.17 (d, *J* = 7.1 Hz, 1H), 3.84 – 3.79 (m, 1H), 3.72 (d, *J* = 12.4 Hz, 1H), 3.64 (d, *J* = 12.0 Hz, 1H), 3.36 (d, *J* = 12.4 Hz, 1H), 3.08 (d, *J* = 12.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 134.1, 133.7, 131.5, 130.7, 124.1, 97.9, 71.5, 67.0, 49.4, 48.6. Anal. Calcd. for $C_{11}H_{12}N_2O_6S$: C, 44.00; H, 4.03; N, 9.33. Found: C, 44.10; H, 4.09; N, 9.27

***N,O* Deprotection of uridine analogue 9β: synthesis of 11β**

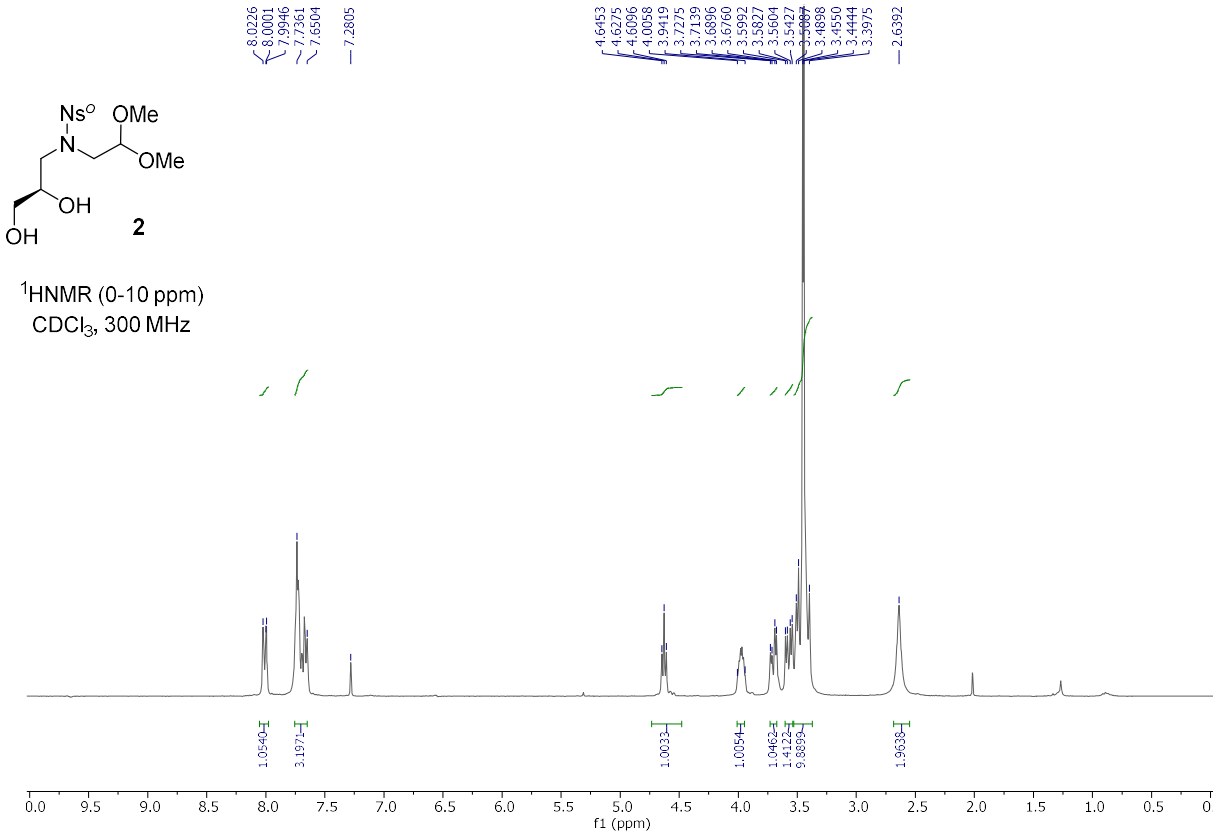


In a round bottom flask, to a solution of **9β** (160 mg, 0.3 mmol) in CH_3CN (3.0 mL), K_2CO_3 (138 mg, 1.0 mmol) and 4-methylbenzenethiol (50 mg, 0.4 mmol) were added. The reaction was

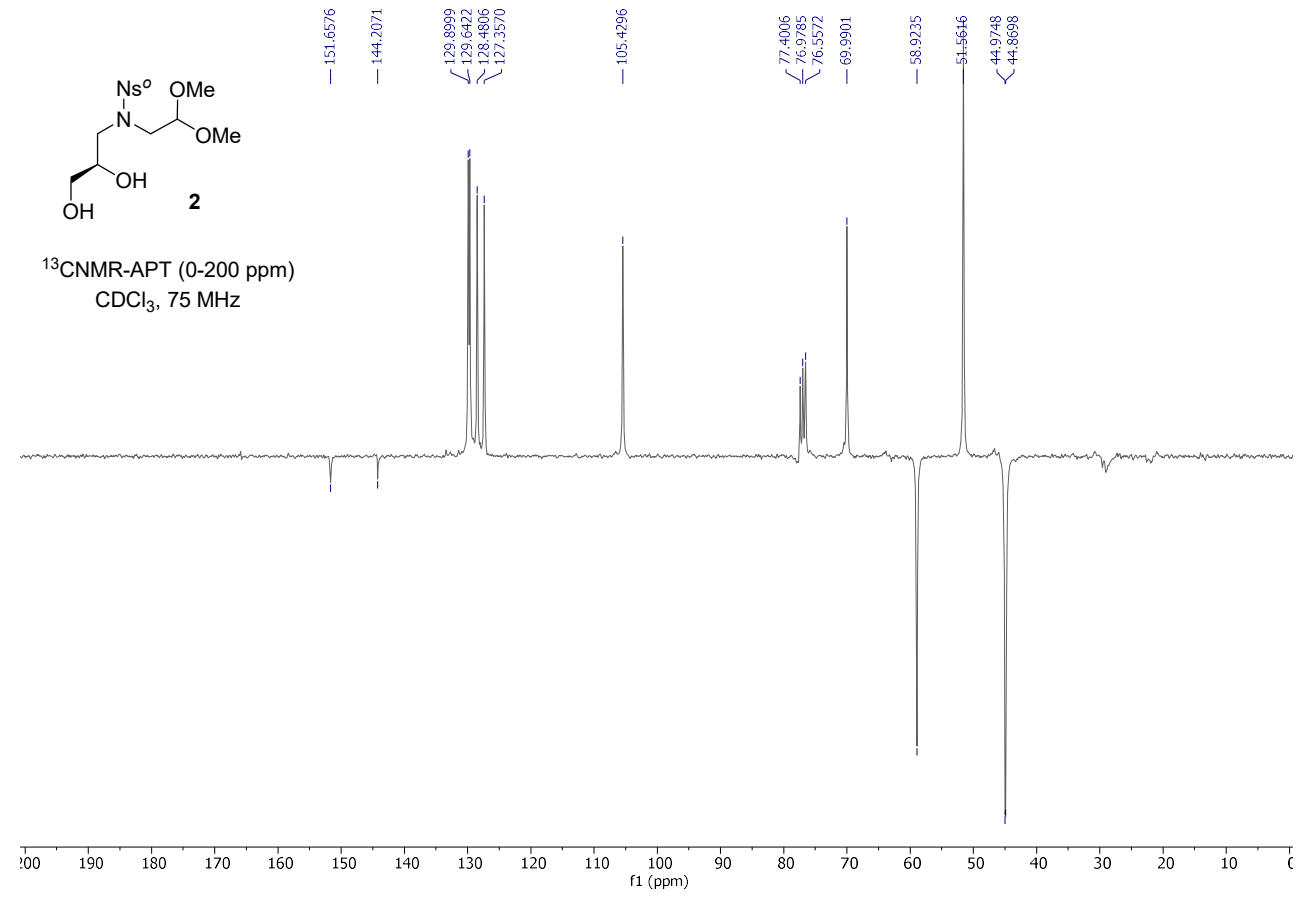
stirred at reflux for 1 hour. After cooling, it was filtered through a celite pad and it was diluted with CH_2Cl_2 (10 mL). the filtrate was transferred into a separating funnel and HCl 10% solution was added up to acid pH. The solution was washed with CH_2Cl_2 (2 x 10 mL) and the aqueous layer was basified and extracted with CH_2Cl_2 (3 x 10 mL). The solvent was evaporated under reduced pressure providing 82 mg (0.23 mmol, 72%) of a white solid which was used without any further purification. {{*(2R,6S)*-6-[5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]morpholin-2-yl}methylbenzoate **10β**: ^{1}H NMR *of the crude* (300 MHz, CH_3OD) δ 8.19 – 7.87 (m, 2H), 7.85 (d, *J* = 6.5 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 3H), 5.73 (d, *J* = 9.6 Hz, 1H), 4.48 – 4.31 (m, 2H), 4.25 – 4.13 (m, 1H), 3.05-2.96 (m, 2H), 2.78 – 2.6 (m, 2H) *NH proton not visible*. The crude *O*-protected uridine analogue **10β** (82 mg, 0.23 mmol) was dissolved in CH_3CN (1.0 mL) and CH_3OH (2.0 mL). Then, CH_3ONa 95% (28 mg, 0.5 mmol) was added. The reaction was stirred at reflux for 16 hours. After cooling, the reaction was quenched with acetic acid (0.5 mL). The solvent was evaporated under reduced pressure and the residue was filtered through RP C-18 – CH_3CN/H_2O (99.5:0.5) providing 5-fluoro-1-[(2*R,6S*)-6-(hydroxymethyl)morpholin-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione **11β** (44 mg, 78%) as white solid; $[\alpha]_D^{20}$: – 88.5 (*c* 1.1, D_2O). ^{1}H NMR (300 MHz, D_2O) δ 8.10 (d, *J* = 5.1 Hz, 1H), 6.14 (d, *J* = 9.2 Hz, 1H), 4.34 (d, *J* = 7.1 Hz, 1H), 3.93 – 3.80 (m, 3H), 3.70 (d, *J* = 11.7 Hz, 1H), 3.55 (d, *J* = 12.2 Hz, 1H), 3.36 – 3.18 (m, 2H) *OH and aminic NH protons not visible*. ^{13}C NMR (75 MHz, D_2O) δ 165.6 (d, *J* = 30.1 Hz, 1C), 152.0, 127.7 (d, *J* = 33.5 Hz, 1CH), 119.0 (d, *J* = 284.1 Hz, 1CF), 80.2, 77.2, 63.7, 46.3, 45.1. IR ν_{max} 3598, 3556, 3389, 1780, 1724 cm^{-1}. Anal. Calcd. For $C_9H_{12}FN_3O_4$: C, 44.08; H, 4.93; N, 17.14. Found: C, 44.24; H, 5.01; N, 17.01.

^{1}H-NMR and ^{13}C-NMR spectra

(*S*)-*N*-(2,3-Dihydroxypropyl)-*N*-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide (2)

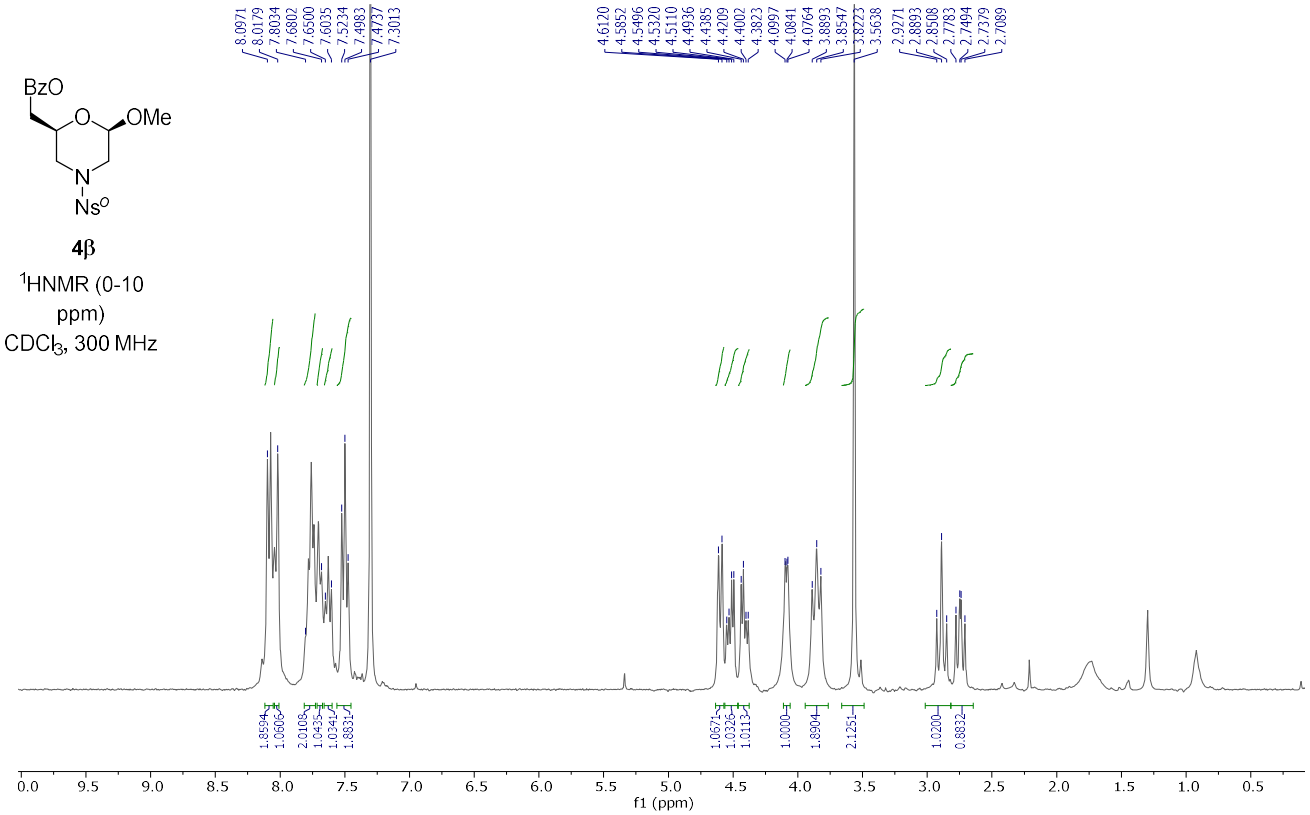


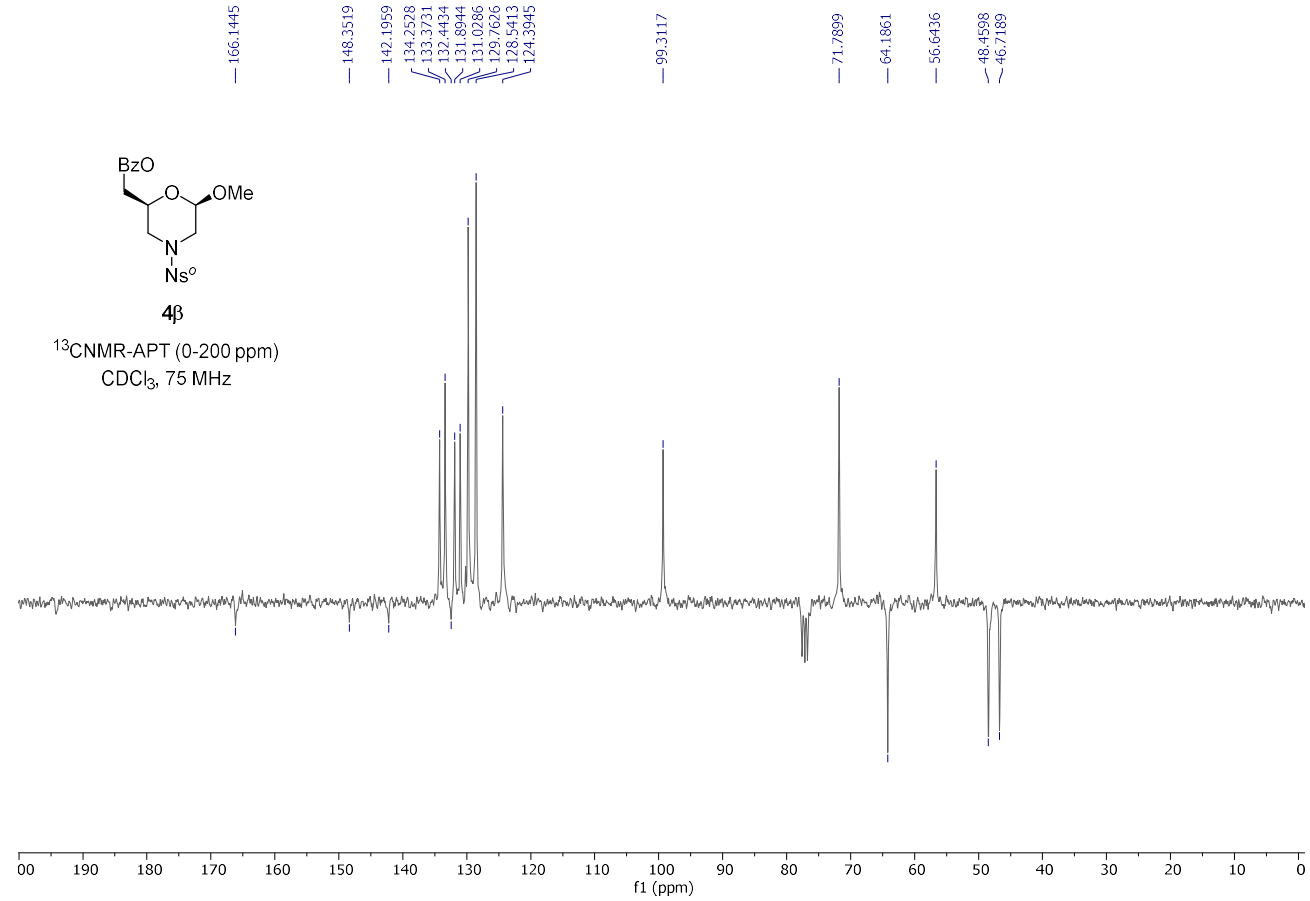
^{1}HNMR (0-10 ppm)
$CDCl_3$, 300 MHz



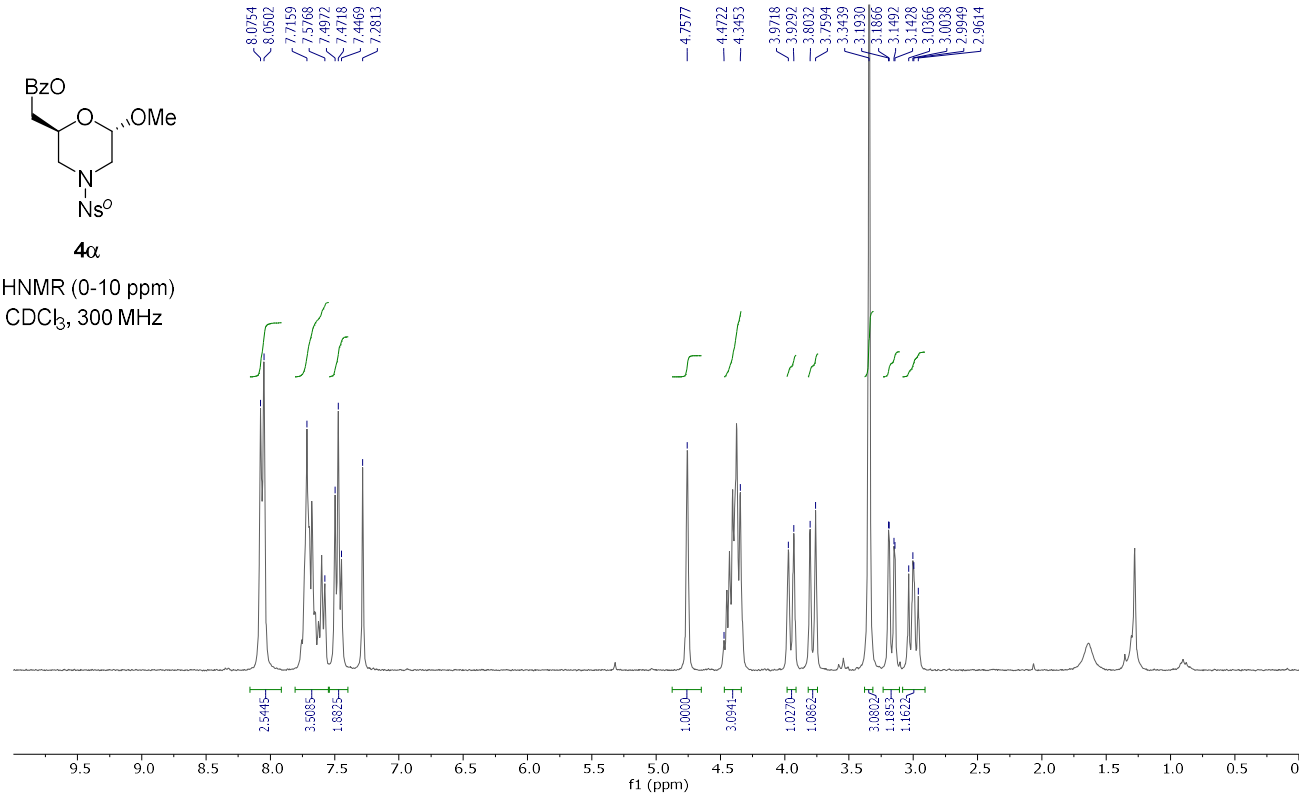
^{13}CNMR-APT (0-200 ppm)
$CDCl_3$, 75 MHz

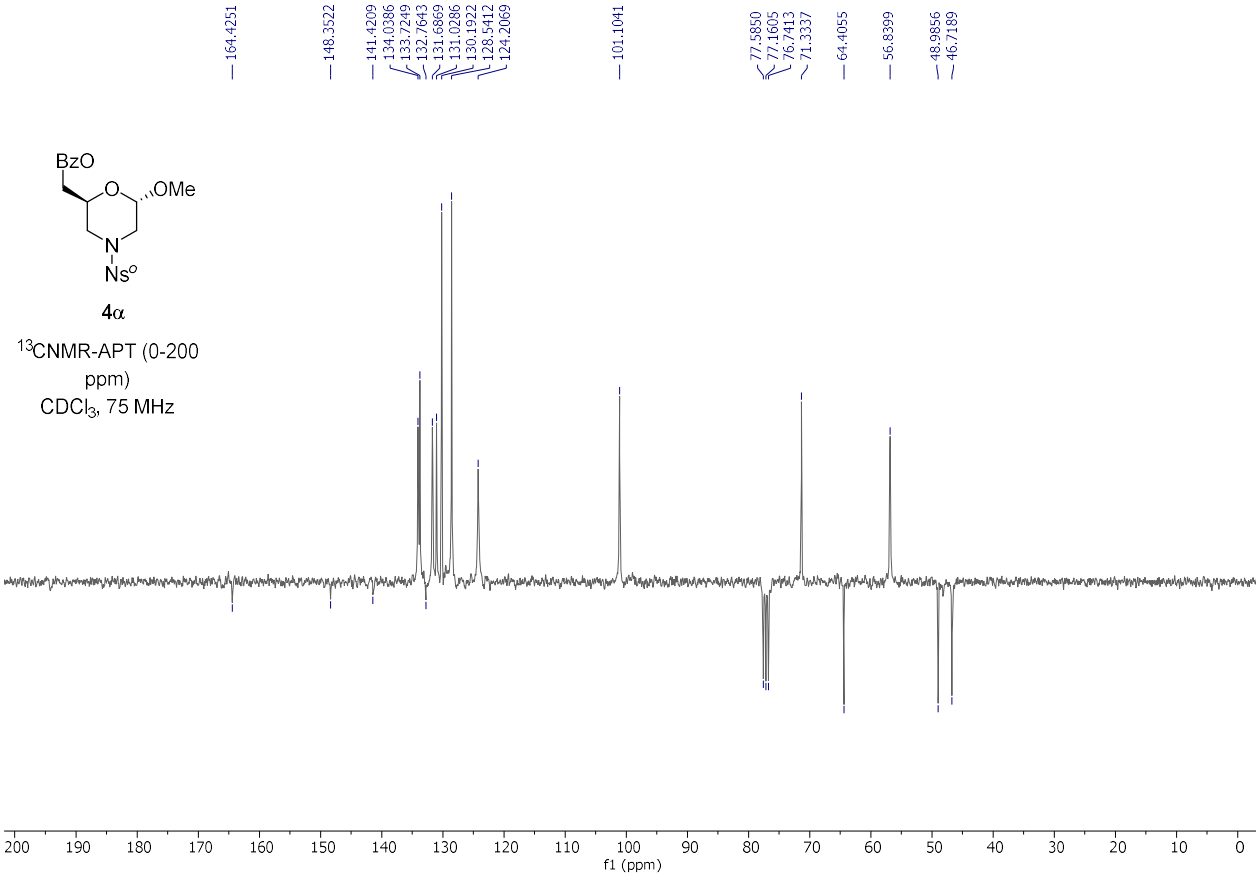
{(2*R*,6*S*)-2-Methoxy-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (4β)



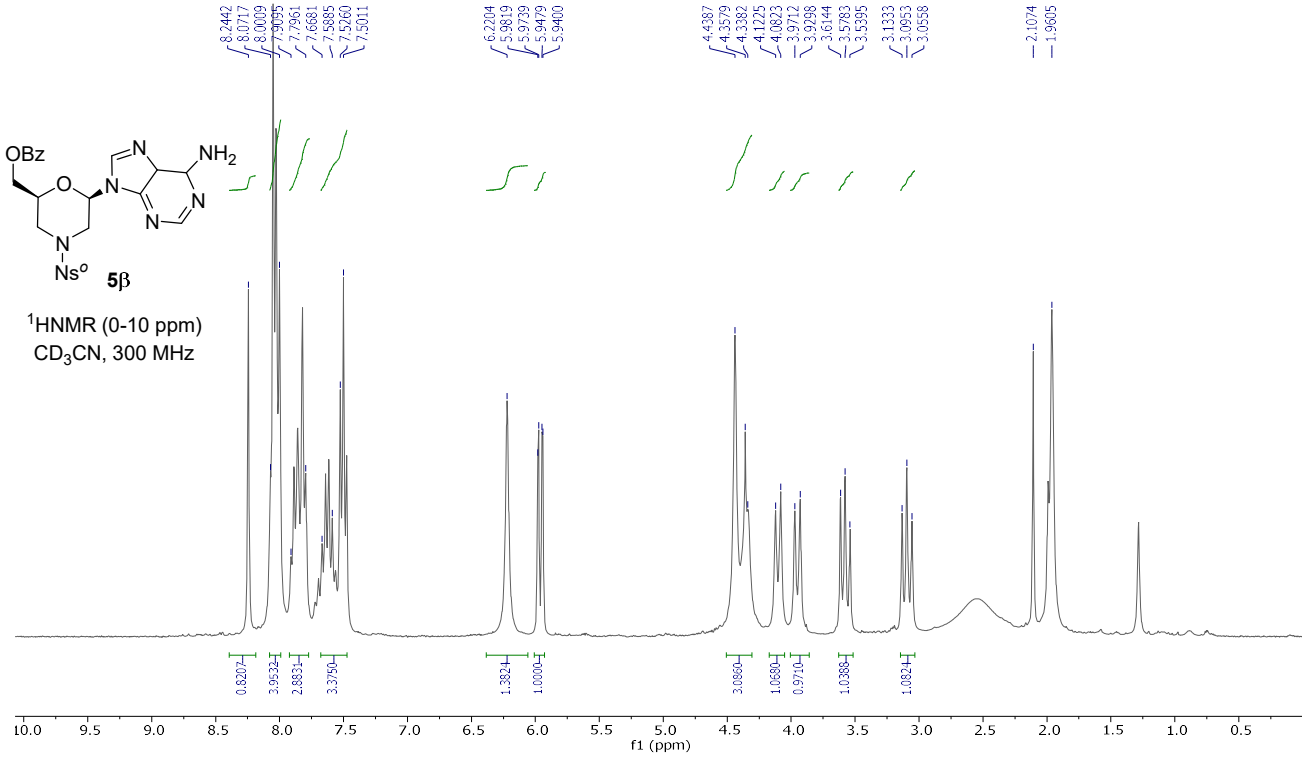


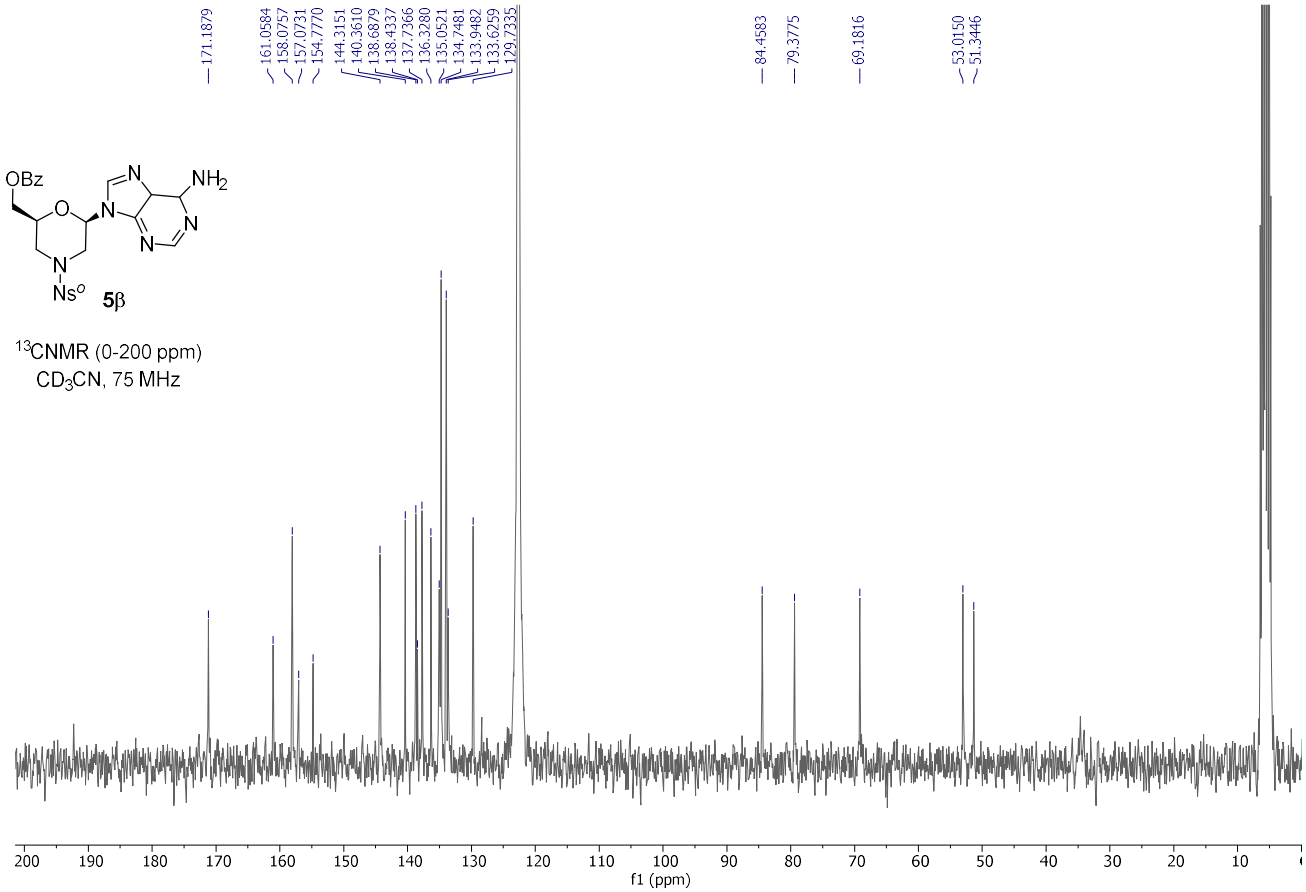
((2*S*,6*S*)-2-Methoxy-4-(2-nitrophenyl)sulfonyl)morpholin-6-yl)methylbenzoate (4α)



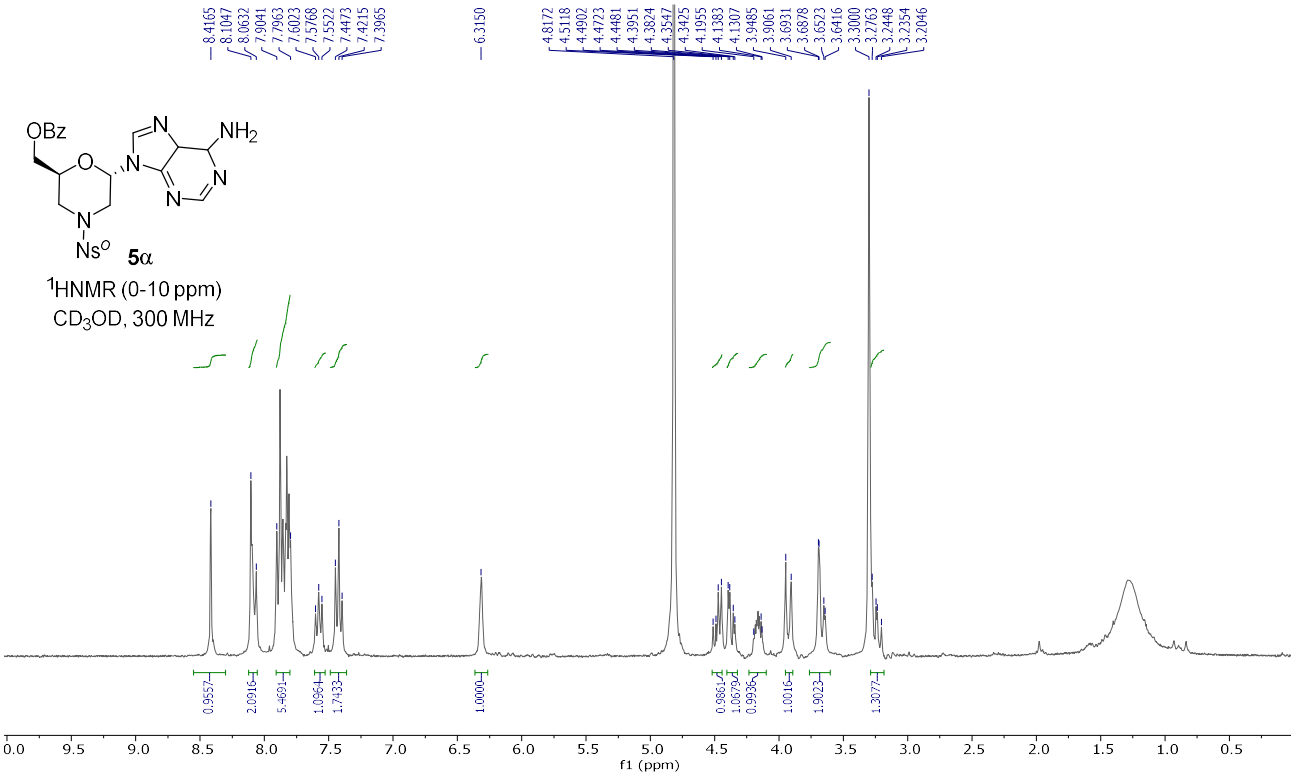


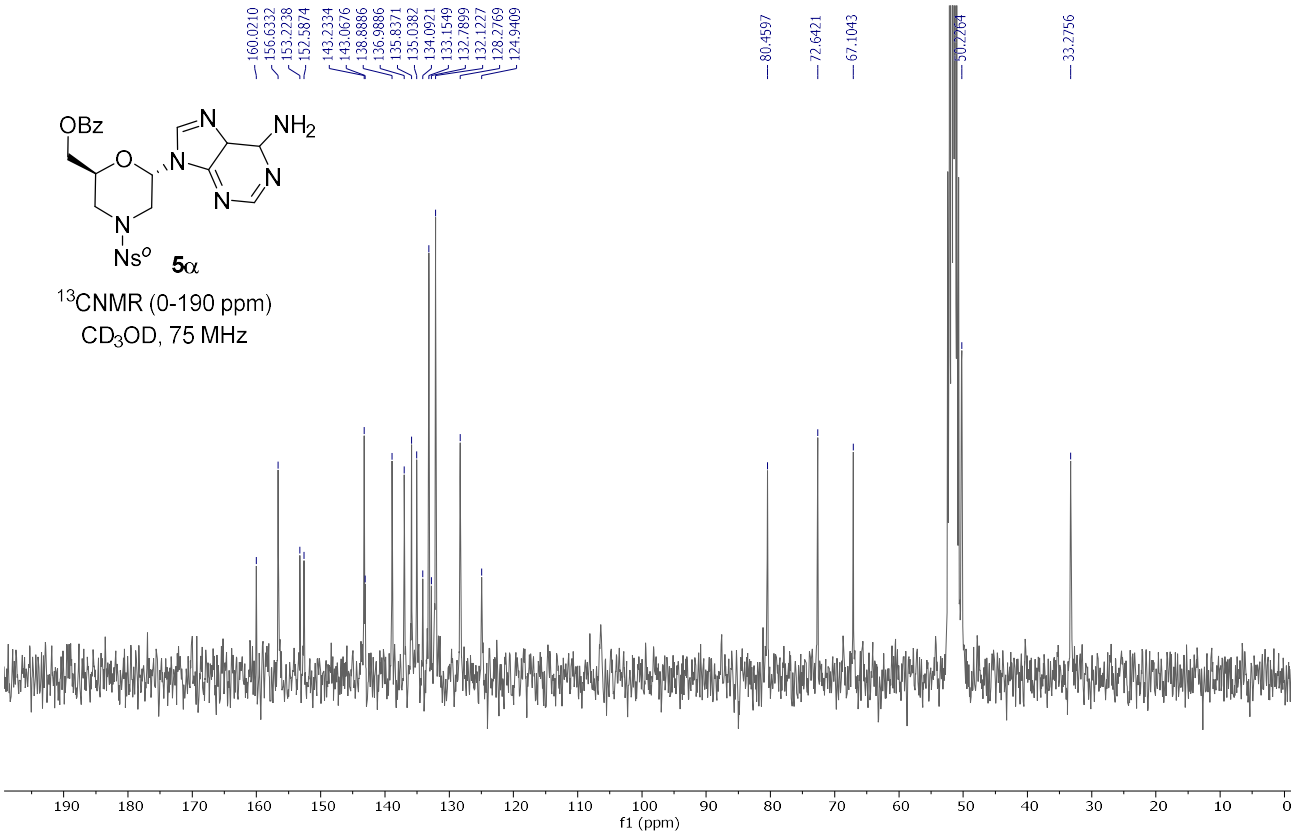
{(2*R*,6*S*)-2-(6-Amino-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (5β)



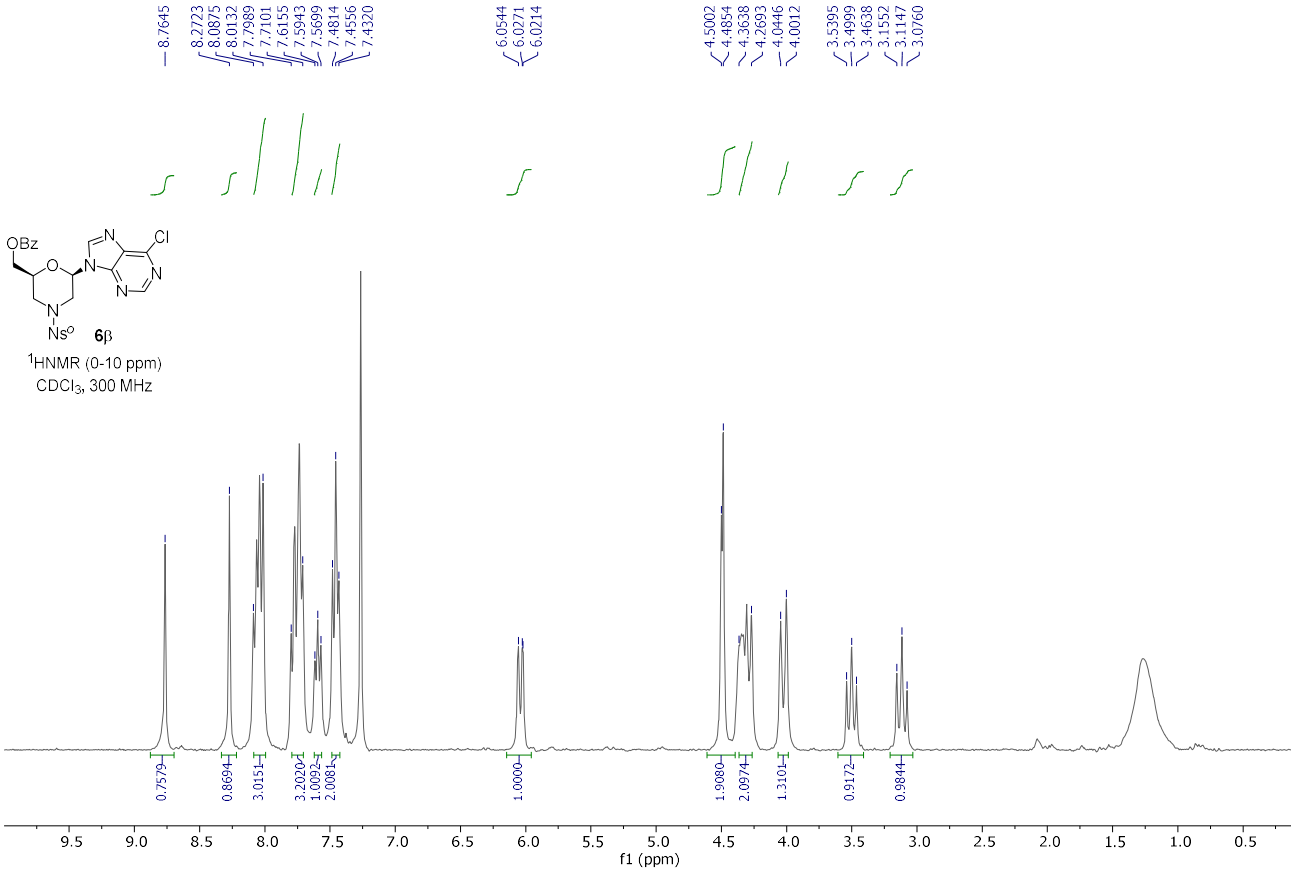


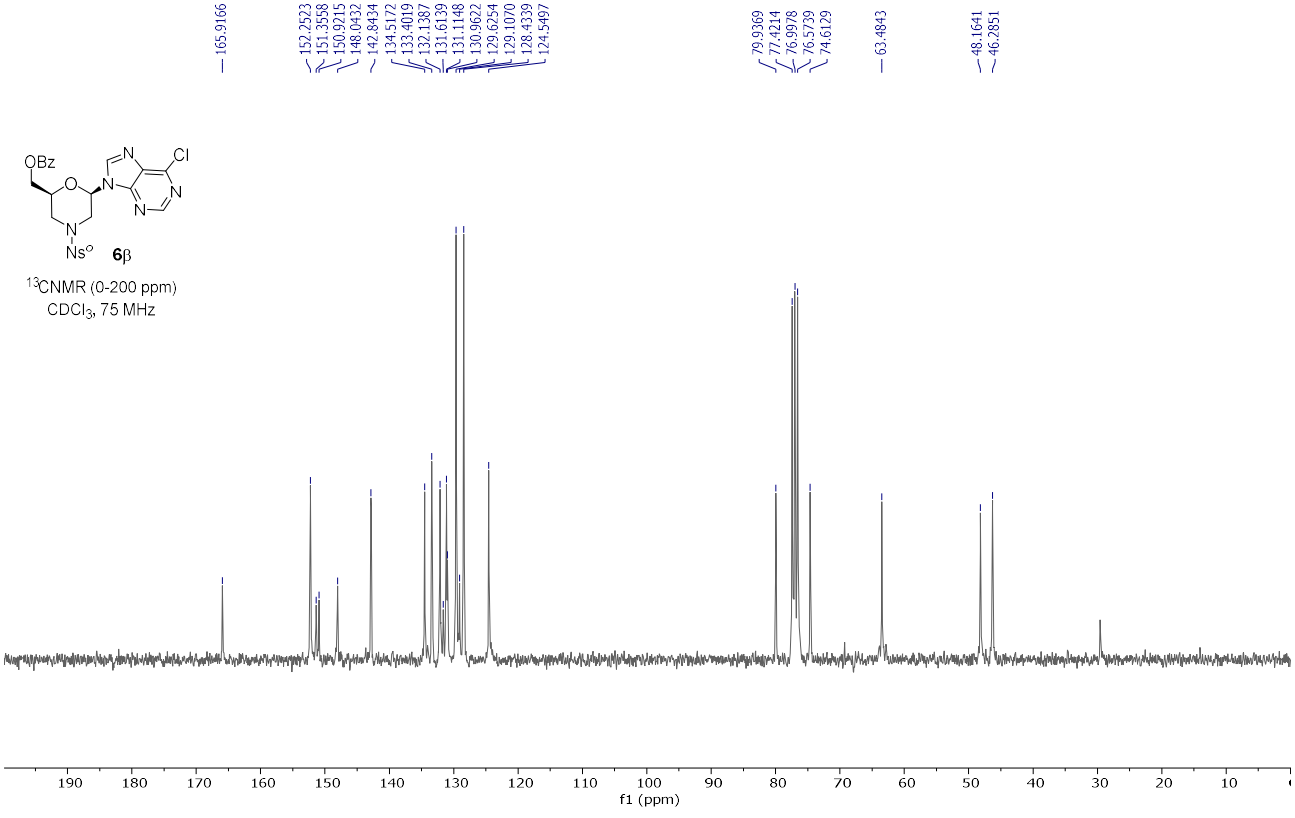
{(2*S*,6*S*)-2-(6-Amino-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methy benzoate (5α)



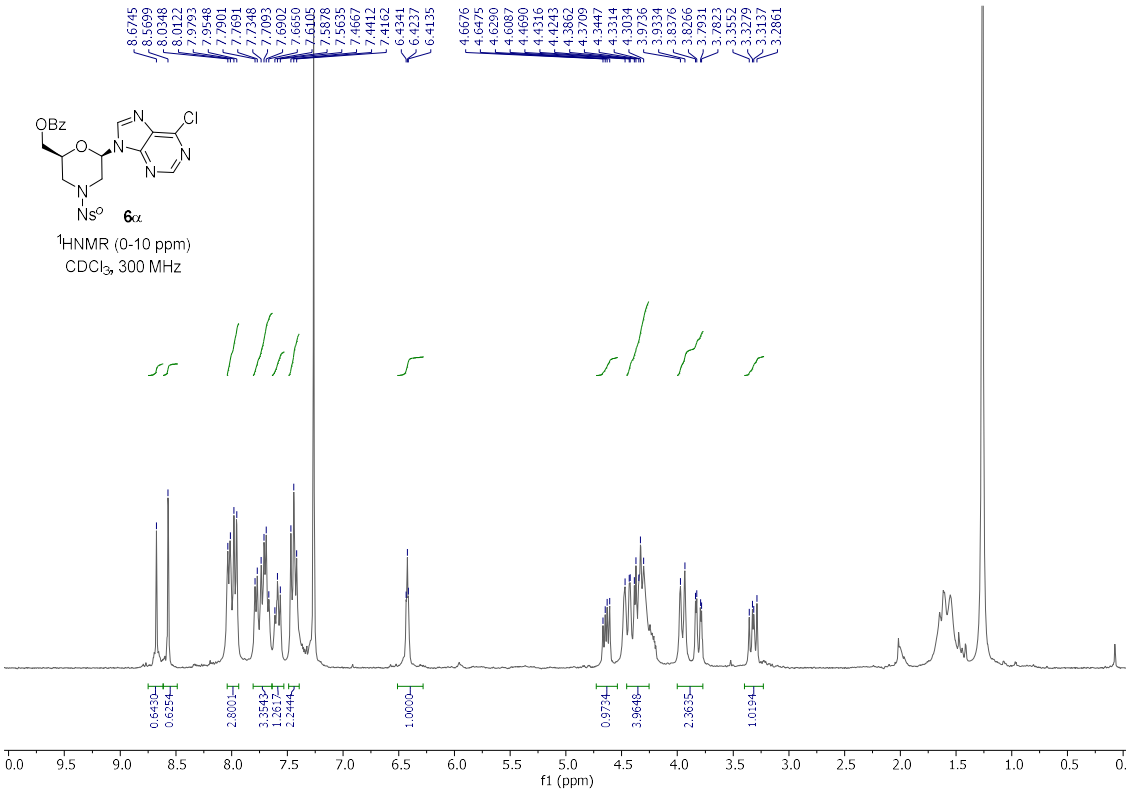


{(2*R*,6*S*)-2-(6-Chloro-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (6β)

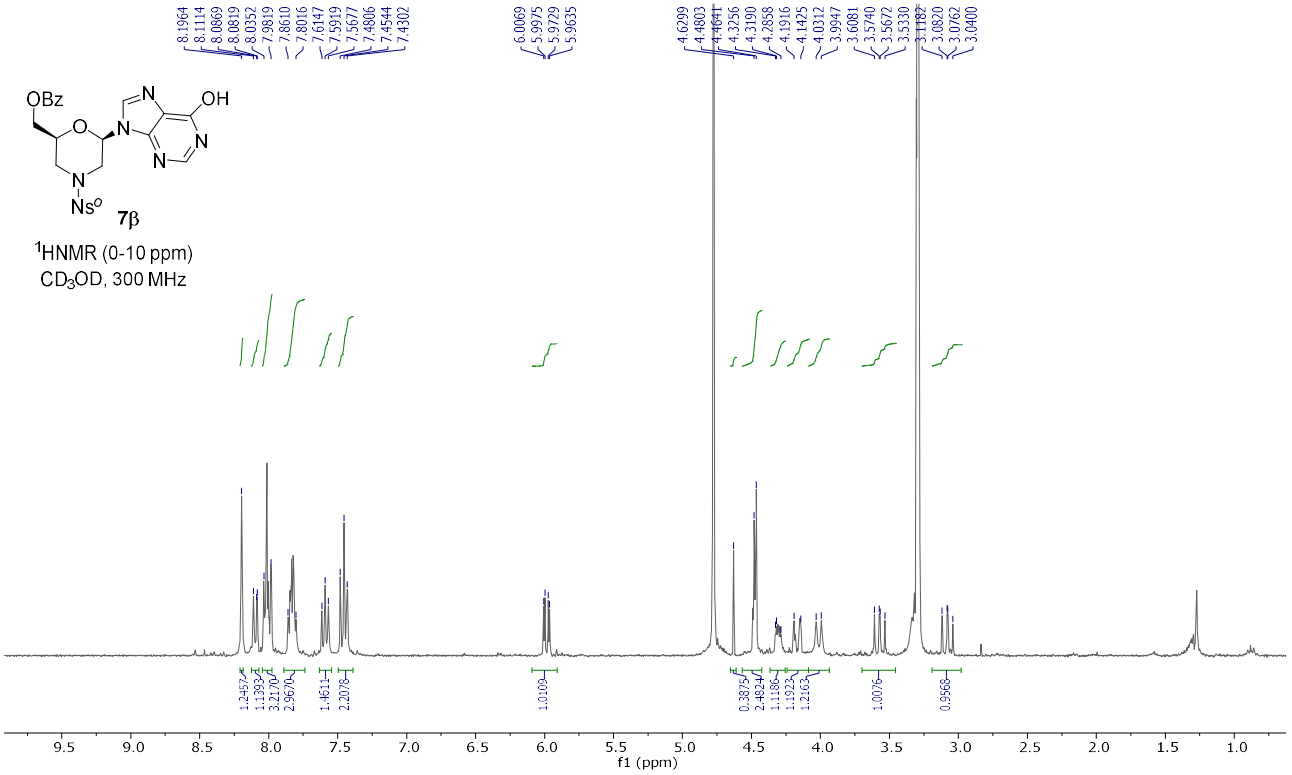


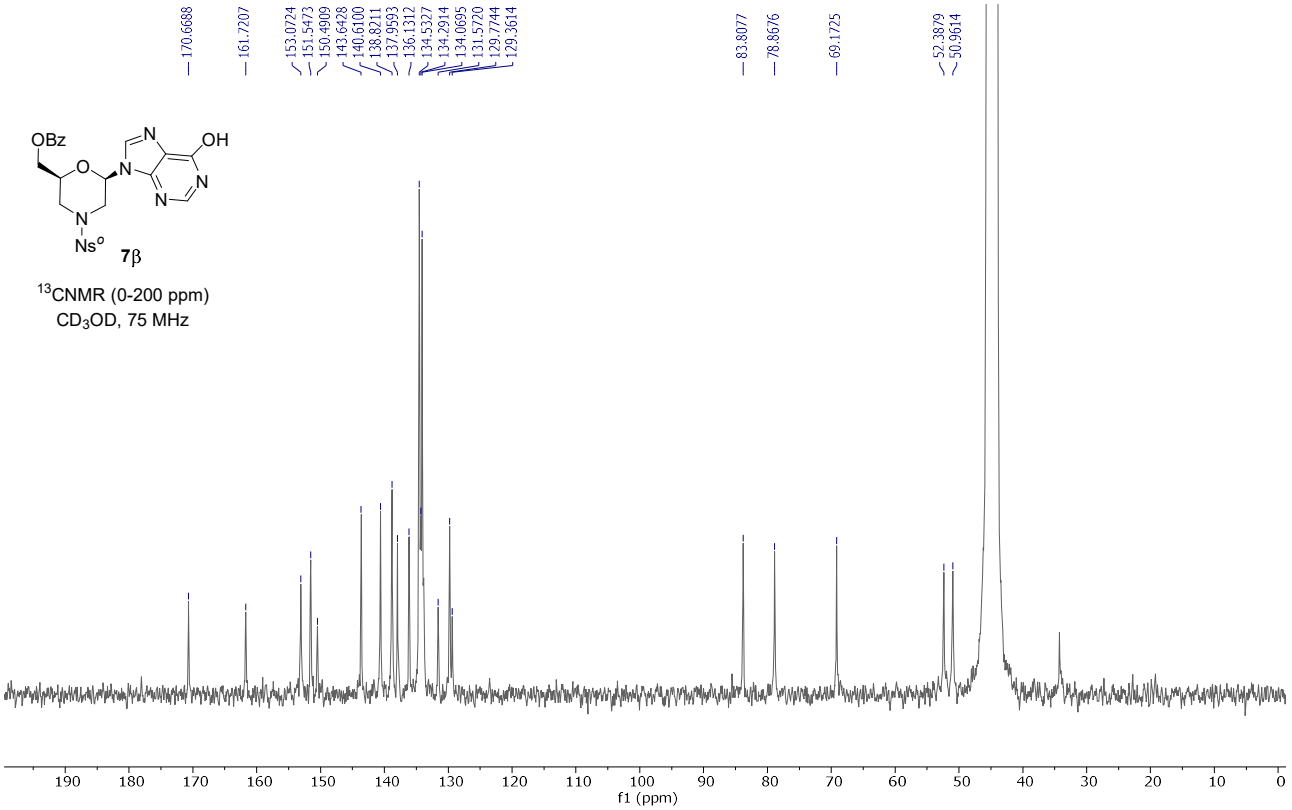


{(2*S*,6*S*)-2-(6-Chloro-9*H*-purin-9-yl)-4-[(2-nitrophenyl]sulfonyl)morpholin-6-yl}methyl benzoate (6α)

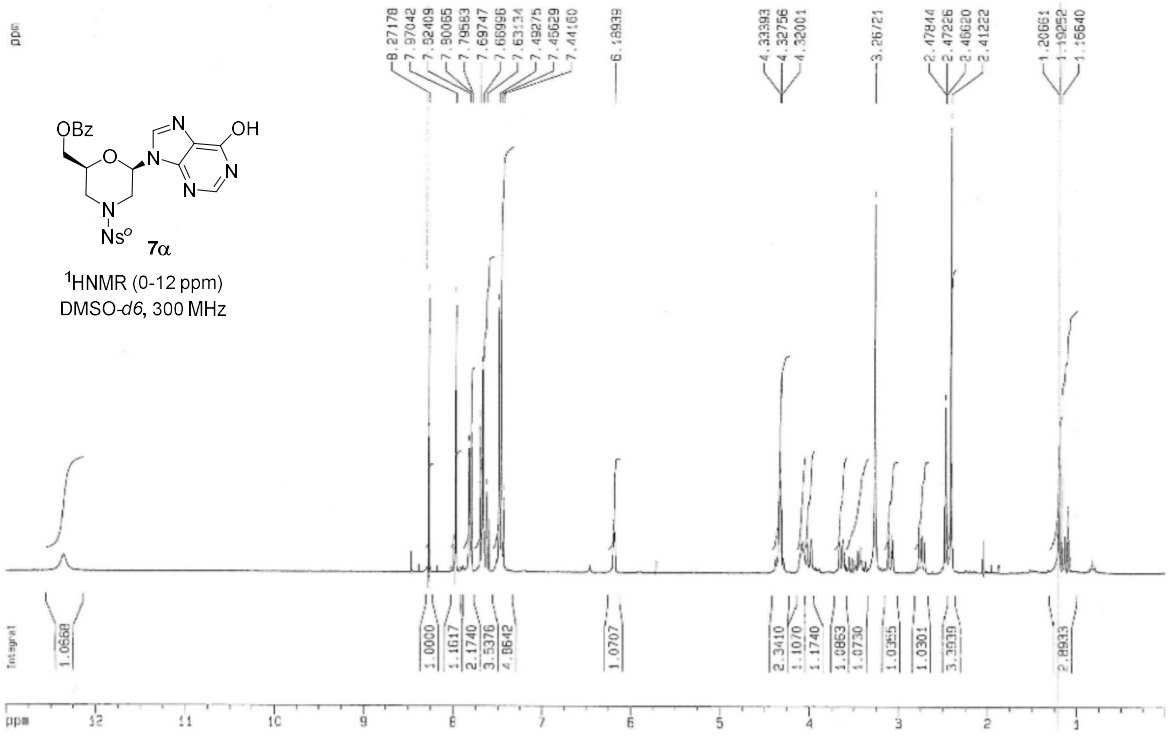


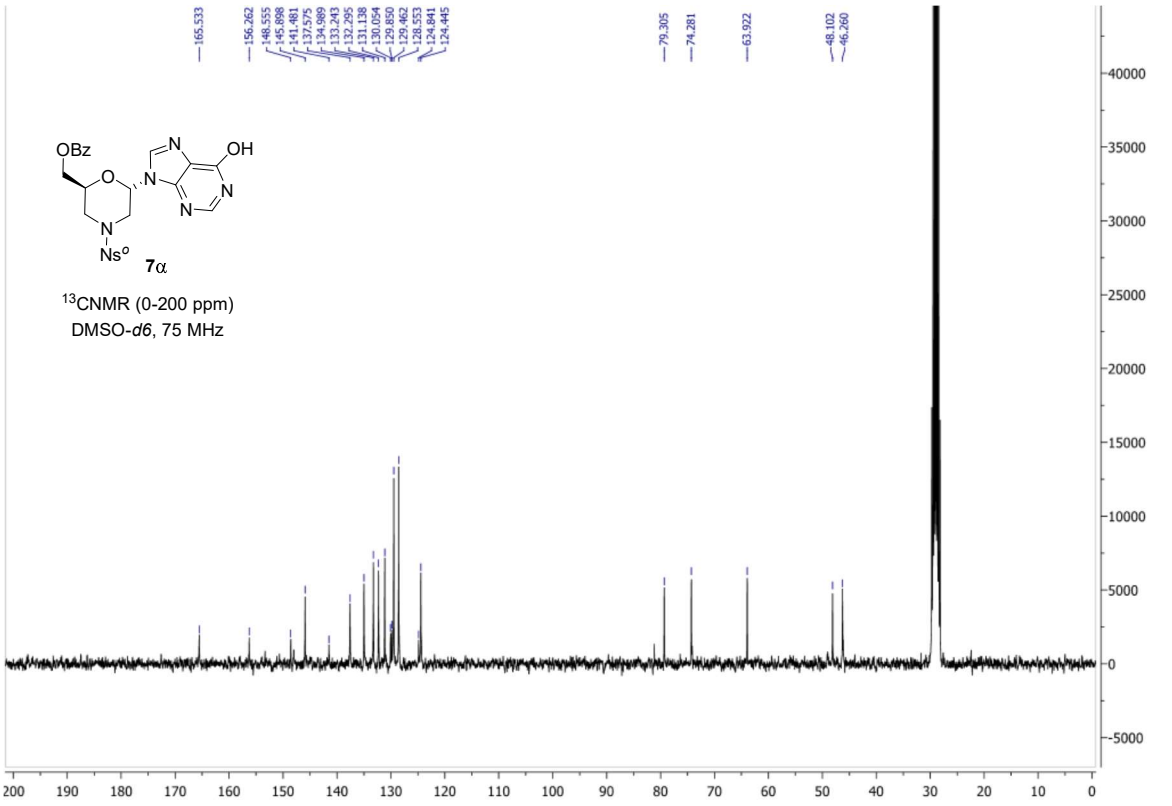
{(2R,6*S*)-2-(6-Hydroxy-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (7β)



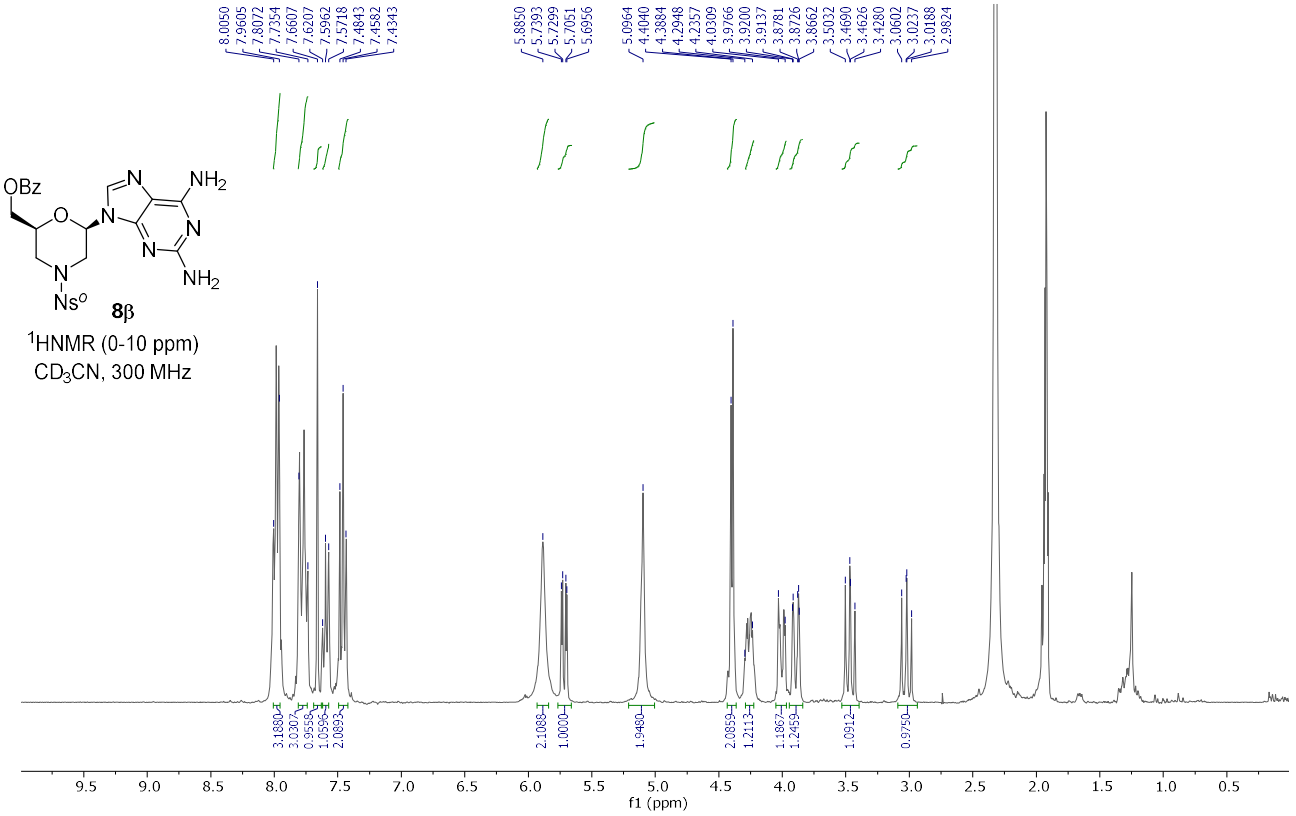


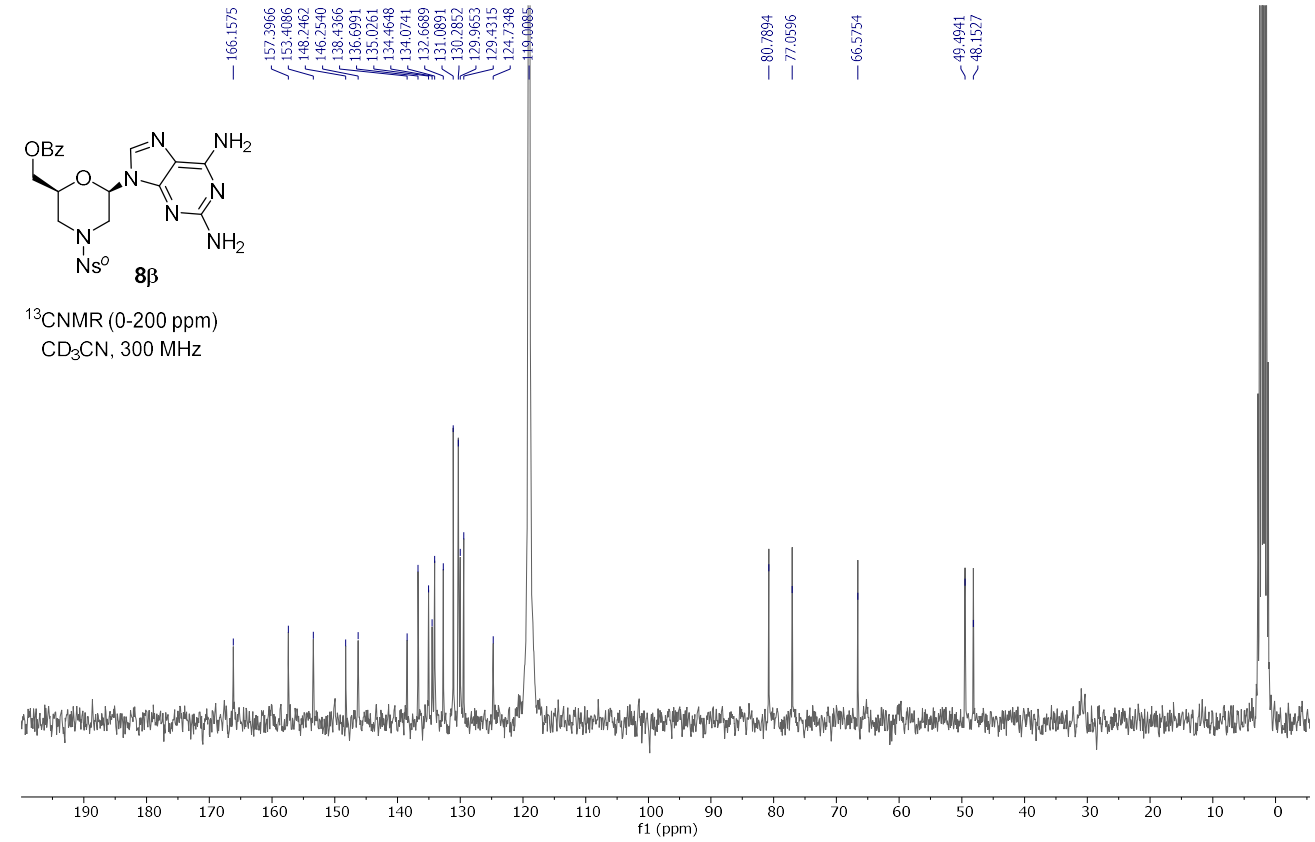
{(2*S*,6*S*)-2-(6-Hydroxy-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (7α)



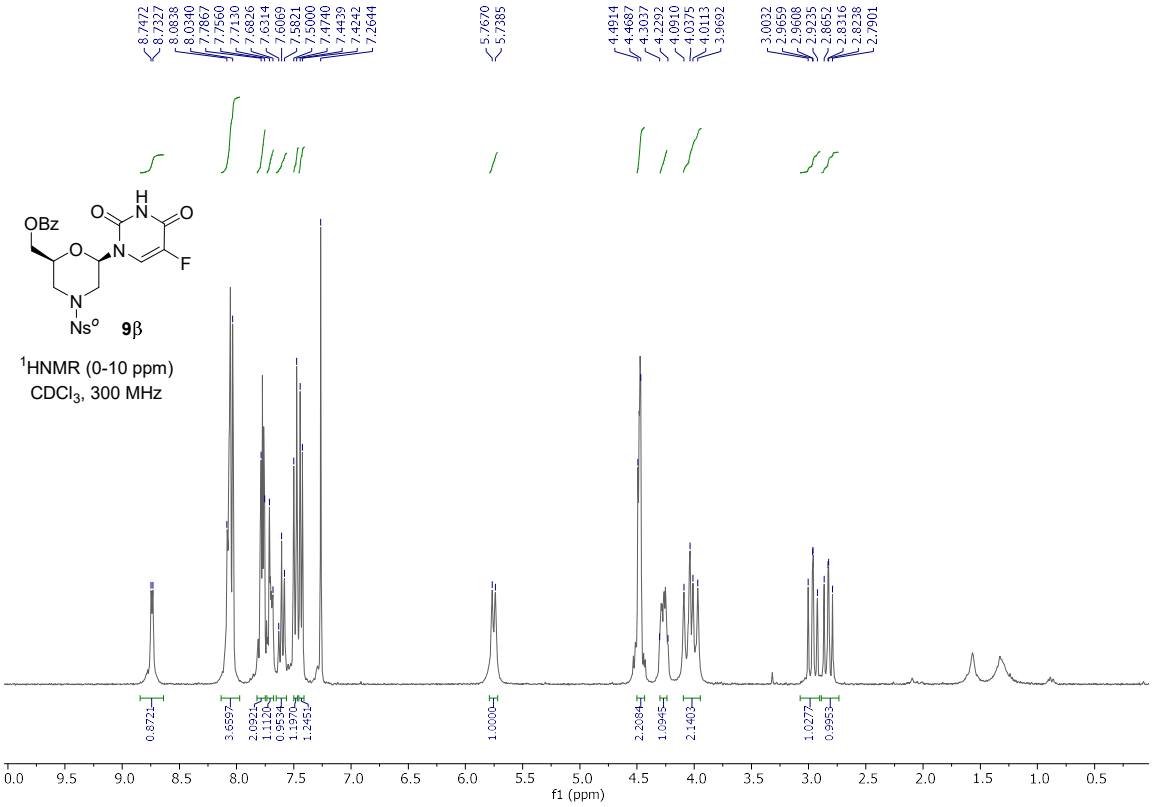


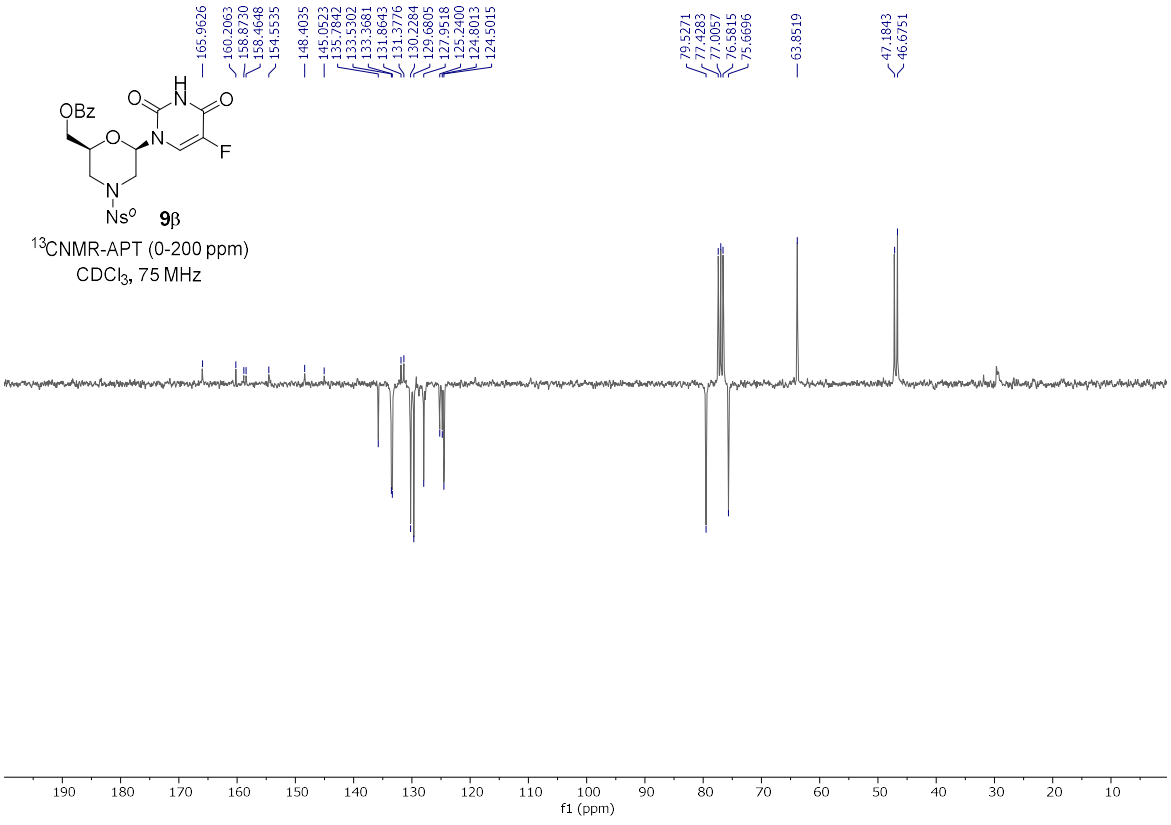
{(2*R*,6*S*)-2-(2,6-Diamino-9*H*-purin-9-yl)-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methylbenzoate (8β)



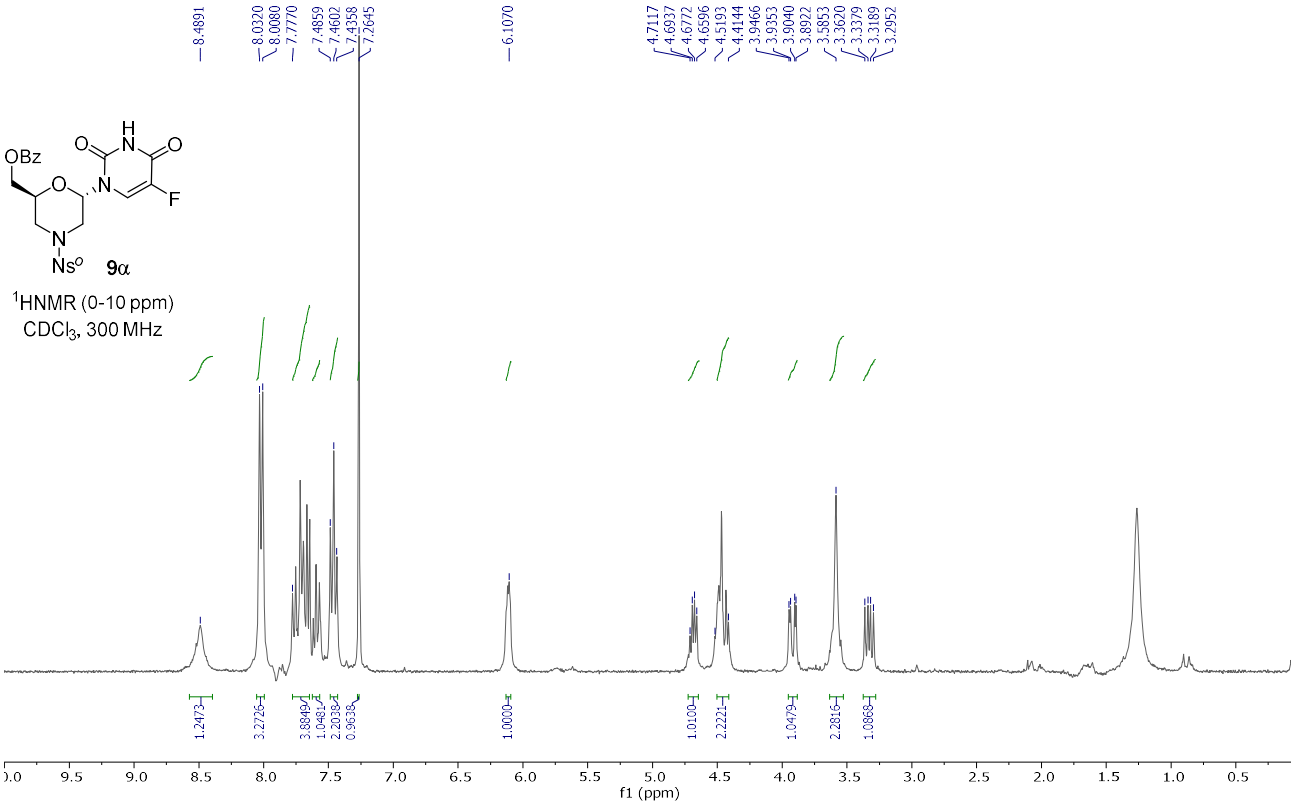


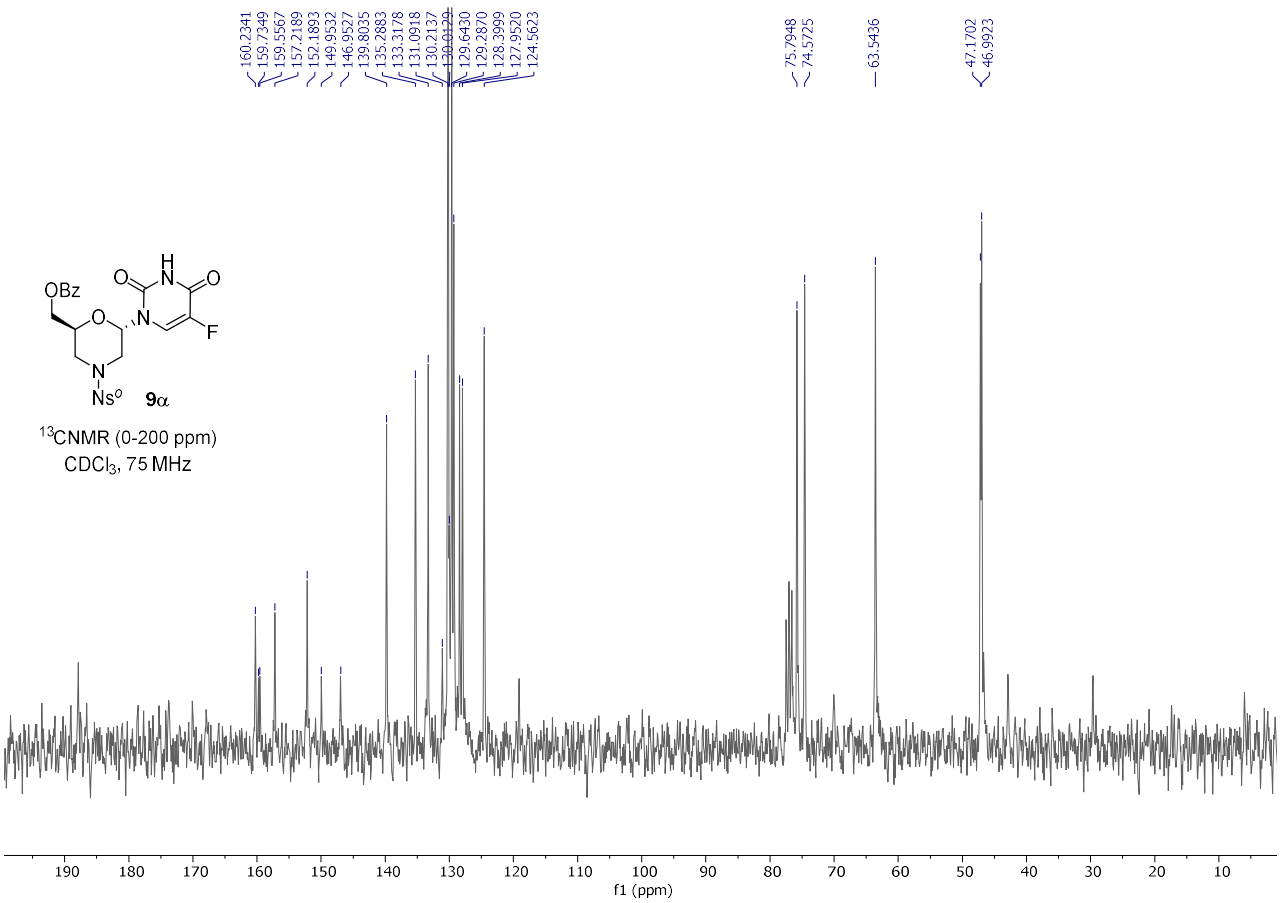
{(2*R*,6*S*)-2-[5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl} methyl benzoate(9β)



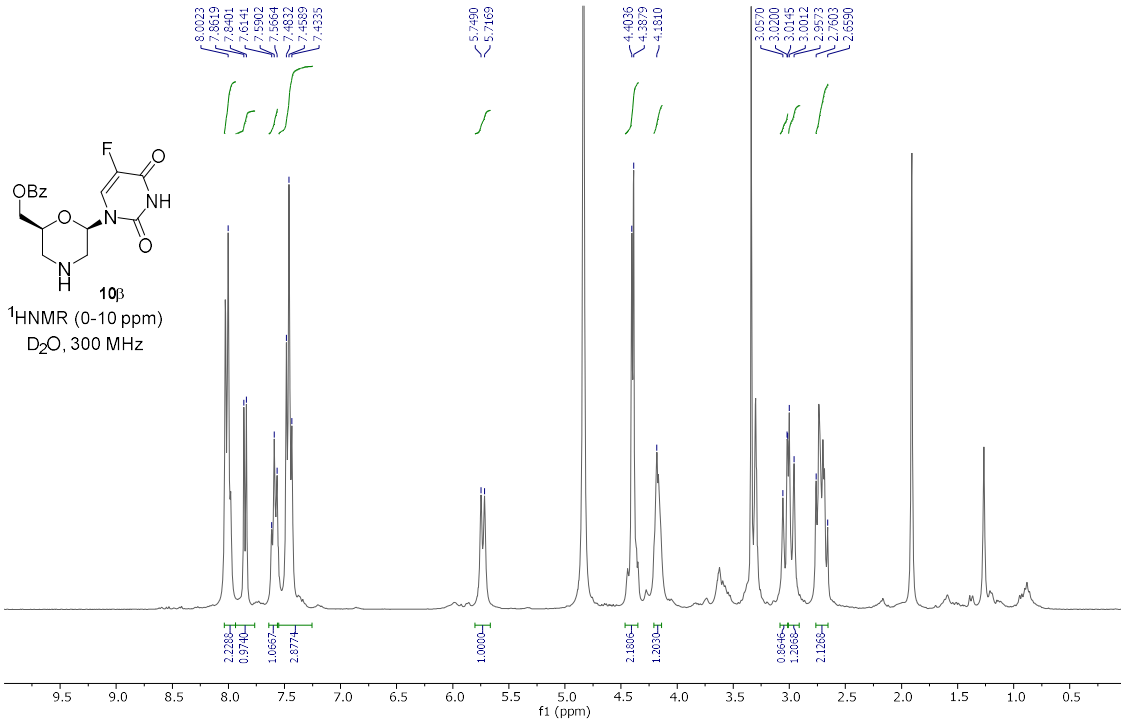


{(2*R*,6*S*)-2-[5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-4-[(2-nitrophenyl)sulfonyl]morpholin-6-yl}methyl benzoate (9α)

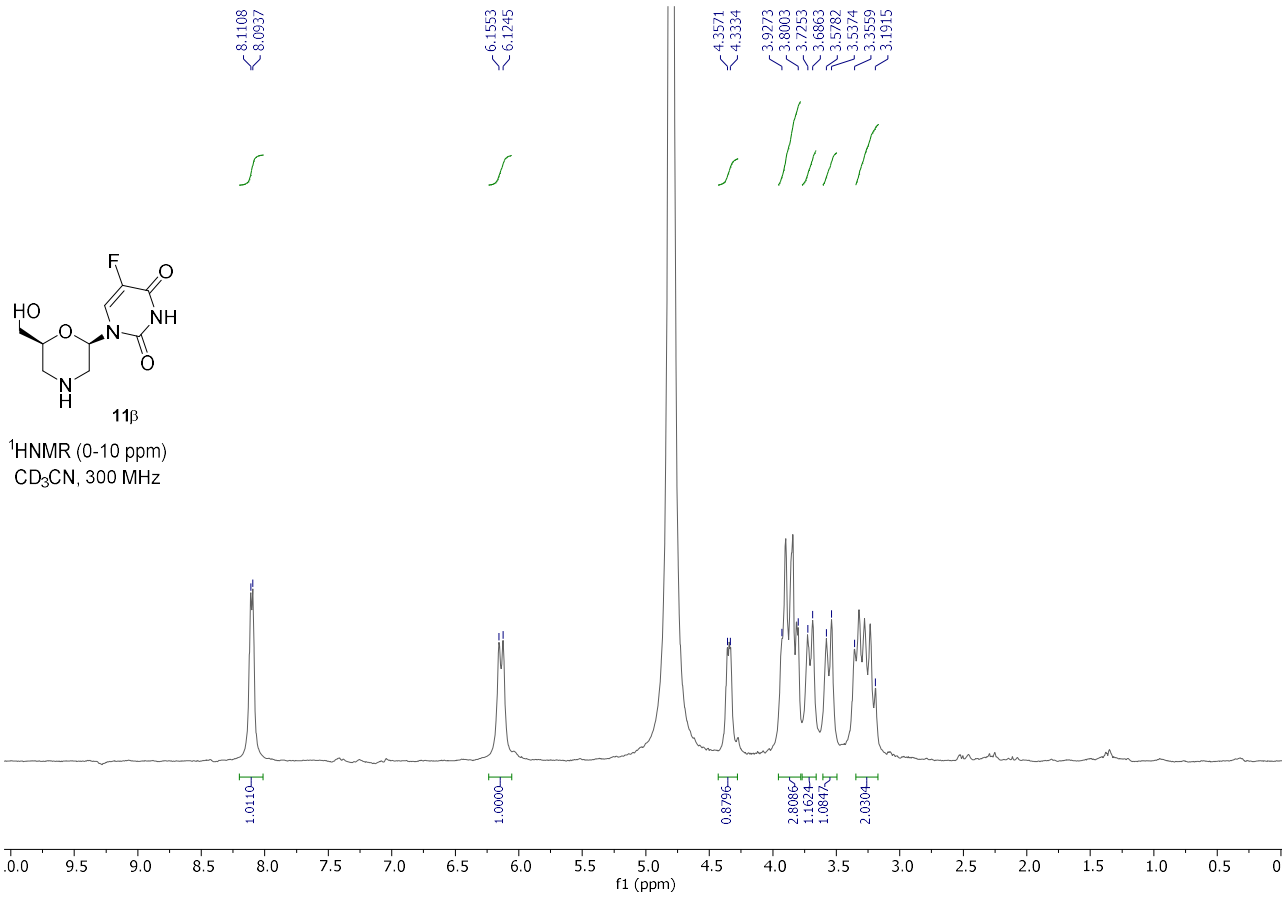


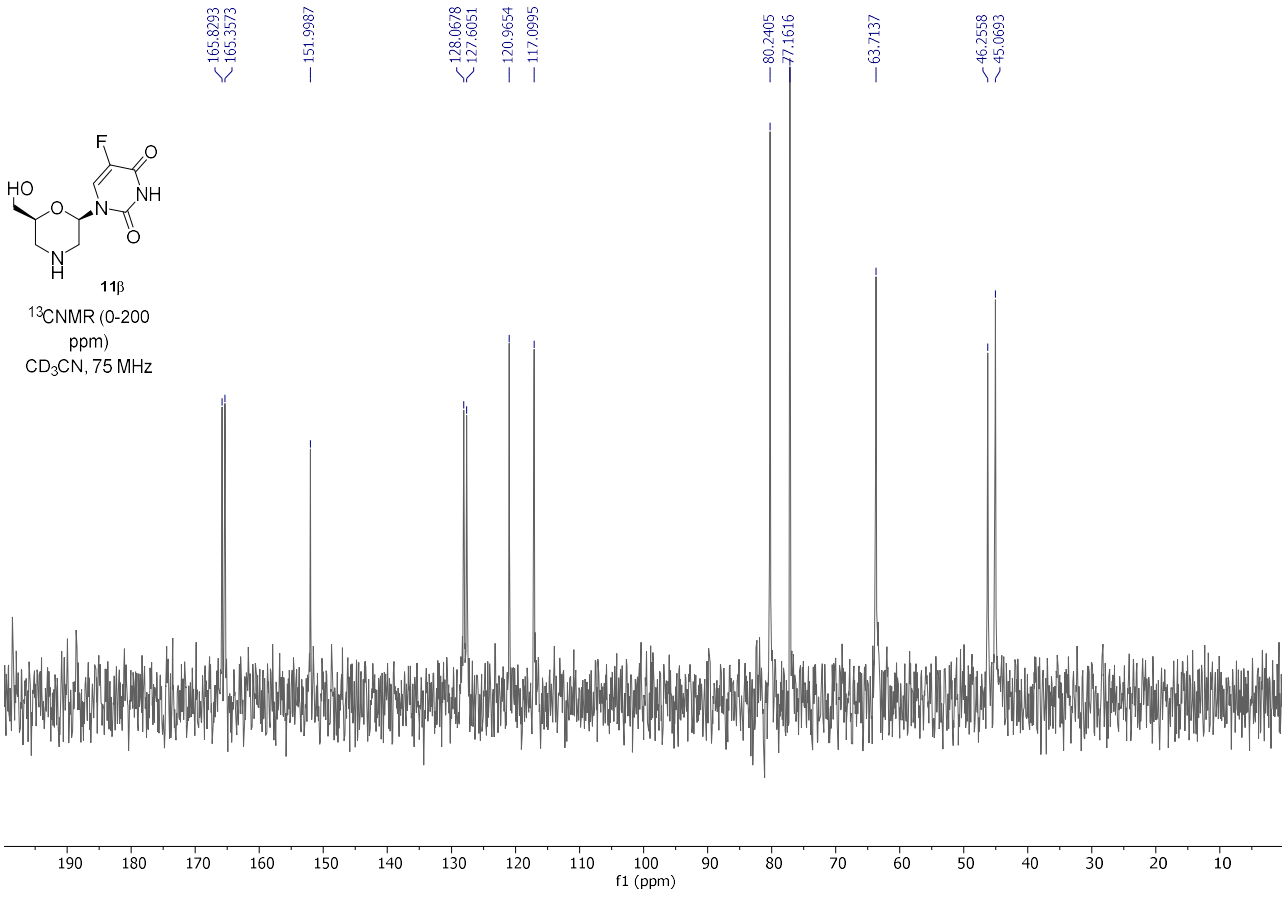


(2*R*,6*S*)-2-[5-Fluoro-2,4-dioxo-3,4-dihydropyrimidin-1-(2*H*)-yl)morpholin-6-yl]methylbenzoate (10β)

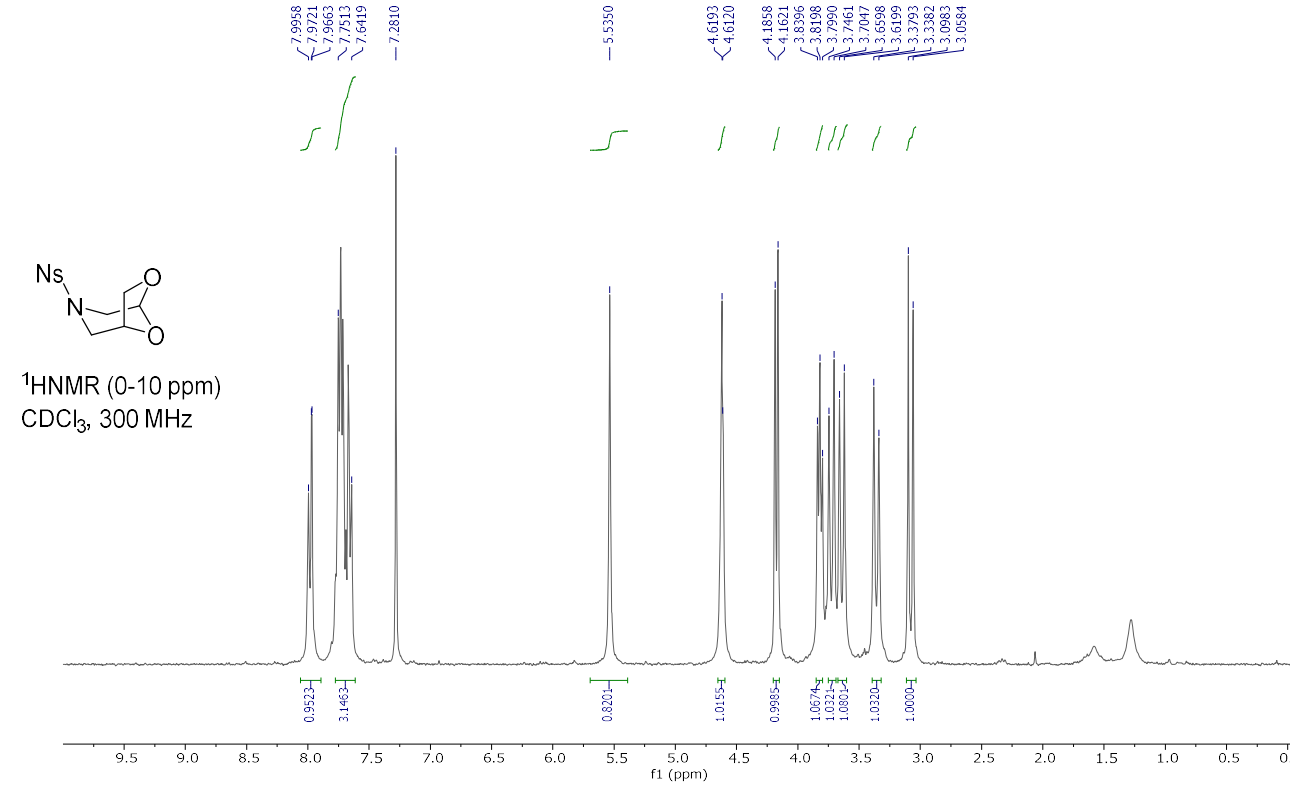


5-Fluoro-1-[(2*R*,6*S*)-6-(hydroxymethyl)morpholin-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (11β)



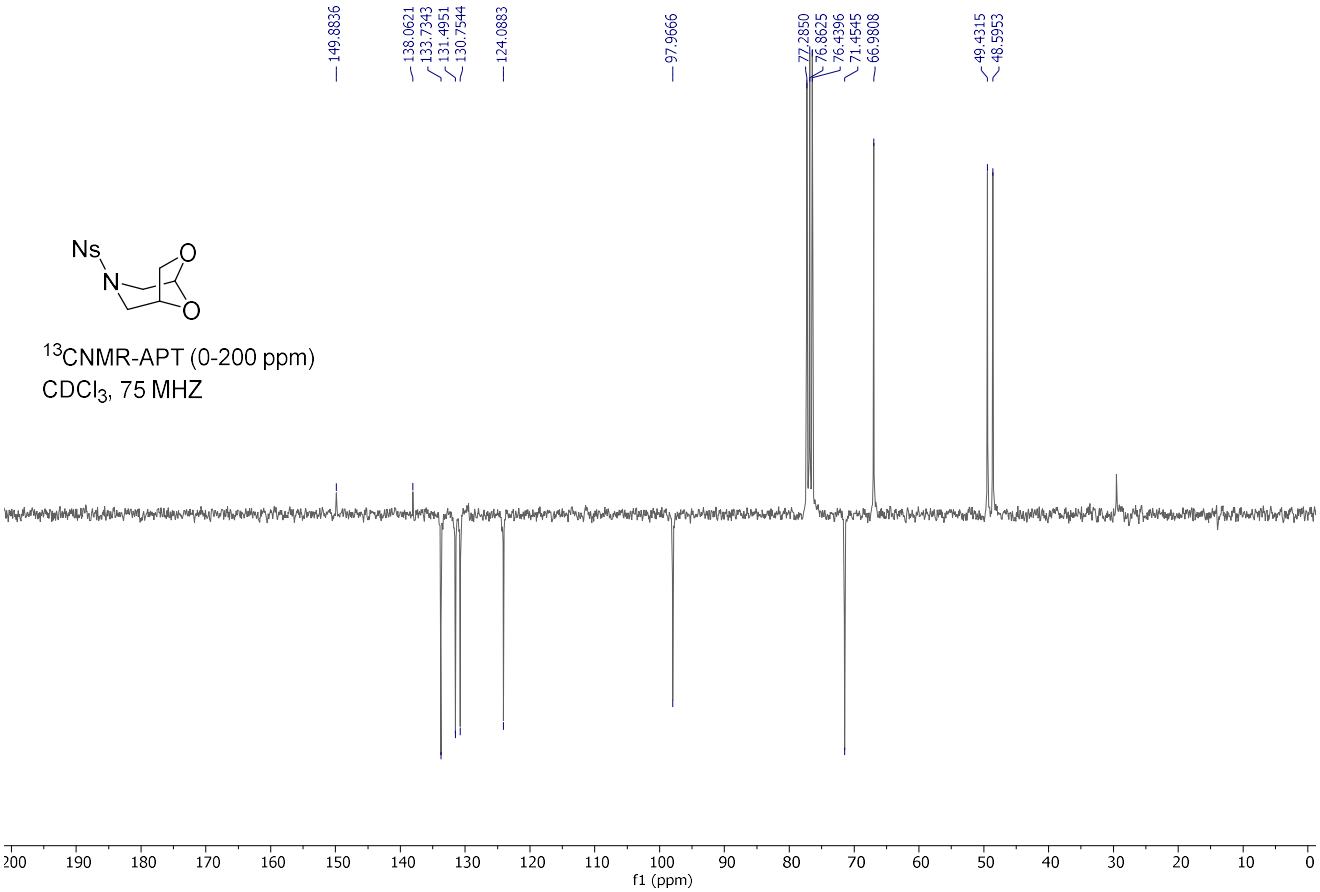


(1*R*,5*S*)-3-[(2-nitrophenyl)sulfonyl]-6,8-dioxa-3-azabicyclo[3.2.1]octane (12)



Ns, N, O, O

^{1}HNMR (0-10 ppm)
$CDCl_3$, 300 MHz



Ns, N, O, O

^{13}CNMR-APT (0-200 ppm)
$CDCl_3$, 75 MHZ