

Efficient Synthesis of Nebularine and Vidarabine via Dehydration of (Hetero)aromatics Catalyzed by CuSO₄ in Water

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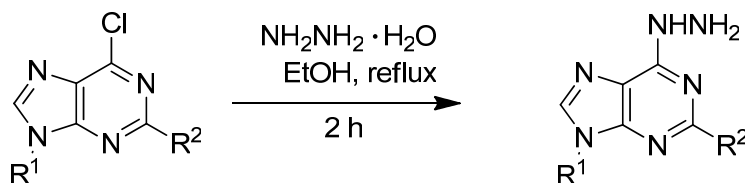
1. General

Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 MHz spectrometer for ^1H NMR, 100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to the residual proton signals of the deuterated solvent CDCl_3 or DMSO for ^1H and ^{13}C NMR. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m). High resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-ToFMS/MS system. For column chromatography silica gel (200-300 mesh) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

2. Procedures for the synthesis of starting compounds

2.1 Procedures for the synthesis of 1a-1q, 3a-3b:

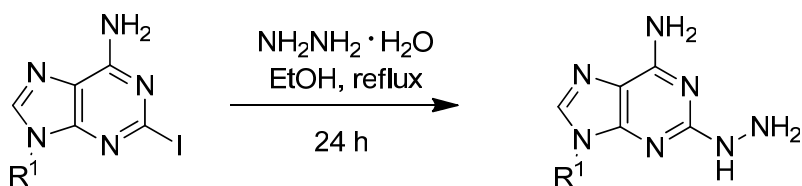
6-Cl Purines or 2-Cl pyridines (1.0 mmol), 80% hydrazine monohydrate (2.0 eq) and EtOH (10.0 mL) were charged in reaction vessel and heated to reflux for 2 h. After cooled to temperature, the crystal or solid precipitated. The crystal or solid was filtrated and washed with EtOH (10.0 mL), dried to afford the pure product.



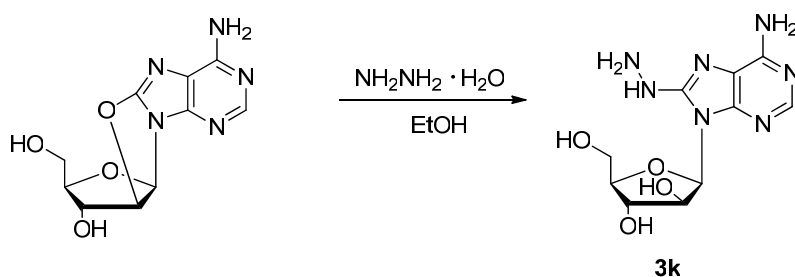
2.2 Procedures for the synthesis of 3i-3j:

2-I Purines (1.0 mmol), 80% hydrazine monohydrate (2.0 eq) and EtOH (10.0 mL) were charged in reaction vessel and heated to reflux for 24 h. After cooled to temperature, the crystal or solid precipitated. The crystal or solid was filtrated and

washed with EtOH (10.0 mL), dried to afford the pure product.

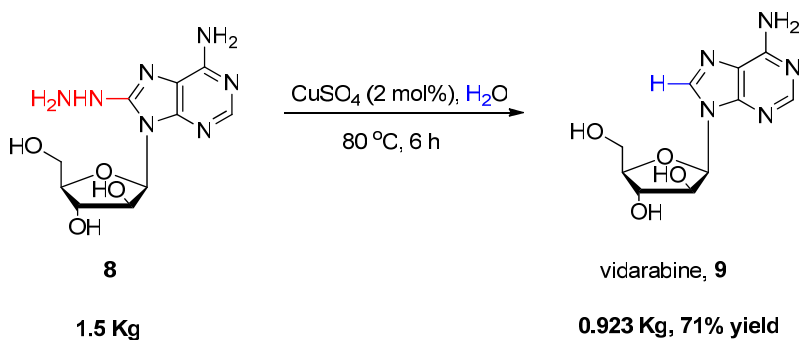


3k was provided by the plant producing vidarabine as an intermediate. The route by the plant is displayed as the following scheme. Other starting materials were purchased from commercial sources.



3. Scalable synthesis procedure of vidarabine

3.1 Synthetic procedure



8-Hydrazine-vidarabine 1.5 Kg (**8**, 5.05 mol) and CuSO₄ 25 g (2 mol %) and H₂O (15 L) were charged into one 100 L reaction vessel. The stirring bar is depicted as follows:



The temperature was tested by thermocouple detector, heated by hot steam and cooled by water. The mixture was stirred and heated slowly, controlling the temperature around at 80 °C (\pm 5 °C) for 6 h. The gas was produced and bubbles yielded (N_2 proposed). The reaction was monitored by thin layer chromatography. Upon completion, the resulting mixture was de-colored by activated carbon and filtrated. The filtrate was evaporated to 0.5 L and cooled. The product precipitated slowly, affording crude vidarabine 0.975 Kg (yield 75%). Recrystallization by water gave pure vidarabine 0.923 Kg (yield 71%).

3.2 The Scene photos of scable production:



Reaction vessle 100 L



Inside of vessle



Outside of vessel

4. Mechanism study

4.1 The isotope effects of H/D

9-Benzyl-6-hydrazine-9*H*-purine 0.06 g (**1a**, 0.25 mmol) and CuSO₄ 0.0008 g (2 mol %) were dissolved in H₂O (1.5 mL) and D₂O (1.5 mL). The mixture was stirred at 80 °C for 6 h and monitored by thin layer chromatography. Upon completion, the resulting mixture was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, concentrated under reduced pressure and purified by silica gel chromatography with ethyl acetate as eluent to give **2a** (H/D).

4.2 Radical scavenged experiments by TEMPO or AIBN

9-Benzyl-6-hydrazine-9*H*-purine 0.06 g (**1a**, 0.25 mmol) and CuSO₄ 0.0008 g (2 mol %) were dissolved in H₂O (3.0 mL). TEMPO (0.05 g, 1.2 eq.) or AIBN (0.05 g, 1.2 eq.) was added. The mixture was stirred at 80 °C for 6 h and monitored by thin

layer chromatography. Upon completion, the resulting mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and purified by silica gel chromatography with ethyl acetate as eluent to give **2a**. The results were shown as follows:

| scavenger | TEMPO | AIBN |
|--------------------|-------|------|
| Yield of 2a | 81% | 85% |

4.3 The air was replaced by $\text{K}_2\text{S}_2\text{O}_8$ as oxidant under N_2 atmosphere

9-Benzyl-6-hydrazine-9*H*-purine 0.06 g (**1a**, 0.25 mmol) and CuSO_4 0.0008 g (2 mol %) were dissolved in H_2O (3.0 mL). $\text{K}_2\text{S}_2\text{O}_8$ (0.135 g, 2.0 eq.) was added. The mixture was charged under N_2 atmosphere and stirred at 80 °C for 6 h and monitored by thin layer chromatography. Upon completion, the resulting mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and purified by silica gel chromatography with ethyl acetate as eluent to give **2a** (yield: 56%).

4.4 The control experiments in anhydrous conditions----testing the source of H atom in new formed C-H bonds

4.4.1 solvent-free process

a) 9-Benzyl-6-hydrazine-9*H*-purine 0.06 g (**1a**, 0.25 mmol), CuSO_4 0.0008 g (2 mol %) and $\text{K}_2\text{S}_2\text{O}_8$ (0.135 g, 2.0 eq.) were grinded thoroughly and charged in reaction vessel. The mixture was stirred at 80 °C for 6 h under N_2 and anhydrous condition. Thin layer chromatography showed no reaction occurred.

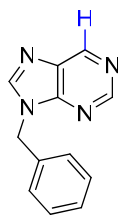
b) 9-Benzyl-6-hydrazine-9*H*-purine 0.06 g (**1a**, 0.25 mmol) and CuSO_4 0.0008 g (2 mol %) were grinded thoroughly and charged in reaction vessel. The mixture was stirred at 80 °C for 6 h under air and anhydrous condition. Thin layer chromatography showed no reaction occurred.

4.4.2 Anhydrous dioxane as solvent

9-Benzyl-6-hydrazine-9*H*-purine 0.06 g (**1a**, 0.25 mmol), CuSO₄ 0.0008 g (2 mol %) and anhydrous dioxane (3.0 mL) were charged in reaction vessel. The mixture was stirred at 80 °C for 6 h under air and anhydrous condition. Thin layer chromatography showed no reaction occurred.

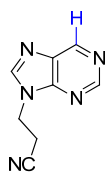
5. Characterization of compounds

9-Benzyl-9H-purine (2a)



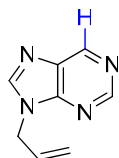
White solid. m.p. 90-92 °C. ^1H NMR (400 MHz, CDCl_3) δ 9.13 (s, 1H), 9.00 (s, 1H), 8.07 (s, 1H), 7.34-7.27 (m, 5H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.8, 151.5, 148.6, 145.2, 134.9, 133.9, 129.2, 128.7, 127.9, 47.2; HRMS calcd for $\text{C}_{12}\text{H}_{11}\text{N}_4$ $[\text{M}+\text{H}^+]$ 211.0978, found 211.0970.

3-(9H-Purin-9-yl)propanenitrile (2b)



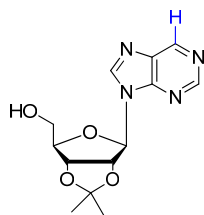
White solid. m.p. 138-140 °C. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 9.18 (s, 1H), 8.96 (s, 1H), 8.66 (s, 1H), 4.58 (t, $J = 6.8$ Hz, 2H), 3.22 (t, $J = 6.4$ Hz, 2H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 18.4, 118.7, 134.0, 147.2, 148.5, 151.5, 152.6; HRMS calcd for $\text{C}_8\text{H}_7\text{NaN}_5$ $[\text{M}+\text{Na}^+]$ 196.0594, found 196.0614.

9-Allyl-9H-purine (2c)



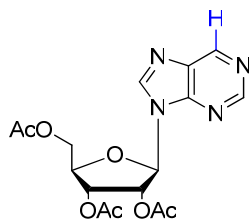
White solid. m.p. 50-52 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 9.16 (s, 1H), 8.99 (s, 1H), 8.11 (s, 1H), 6.00-6.08 (m, 1H), 5.34 (d, $J = 9.6$ Hz, 1H), 5.24 (d, $J = 17.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 45.7, 119.6, 131.2, 148.7, 152.7; HRMS calcd for $\text{C}_8\text{H}_9\text{N}_4$ $[\text{M}+\text{H}^+]$ 161.0822, found 161.0834.

9-[2,3-O-(1-methylethylidene)- β -D-ribofuranosyl]-9H-purine (2d)



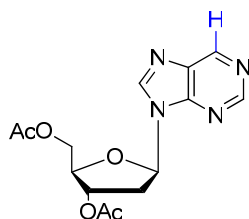
Colorless oil. ^1H NMR (CDCl_3 , 400 MHz) δ 9.21 (s, 1H), 8.98 (s, 1H), 8.18 (s, 1H), 5.97 (d, $J = 4.8$ Hz, 1H), 5.46 (d, $J = 10.4$ Hz, 1H), 5.24 (t, $J = 6.4$ Hz, 1H), 5.13 (d, $J = 6.4$ Hz, 1H), 4.56 (s, 1H), 3.98 (d, $J = 12.4$ Hz, 1H), 3.82 (t, $J = 11.2$ Hz, 1H), 1.66 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 18.4, 25.2, 27.6, 58.4, 63.3, 81.5, 82.9, 86.1, 94.1, 114.3, 135.7, 144.9, 149.9, 152.1; HRMS calcd for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{NaO}_4$ [$\text{M}+\text{Na}^+$] 315.1064, found 315.1068.

9-(2,3,5-Tri-O-acetyl- β -D-ribofuranosyl)-9H-purine (2e)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 9.17 (s, 1H), 9.00 (s, 1H), 8.27 (s, 1H), 6.26 (d, $J = 5.2$ Hz, 1H), 5.97 (s, 1H), 5.67 (s, 1H), 4.47-4.35 (m, 3H), 2.15 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.3, 169.6, 169.4, 152.8, 151.0, 149.0, 143.8, 134.6, 86.5, 80.4, 73.1, 70.5, 63.0, 20.8, 20.6, 20.4; HRMS calcd for $\text{C}_{16}\text{H}_{19}\text{N}_4\text{O}_7$ [$\text{M}+\text{H}^+$] 379.1248, found 379.1247.

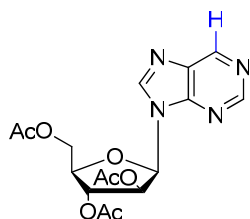
9-(2-Deoxy-3,5-di-O-acetyl- β -D-ribofuranosyl)-9H-purine (2f)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 9.13 (s, 1H), 8.96 (s, 1H), 8.34 (s, 1H), 6.48 (t, $J = 5.2$ Hz, 1H), 5.40 (d, $J = 6$ Hz, 1H), 4.35-4.28 (m, 3H), 3.02-2.95 (m, 1H), 2.65-2.60

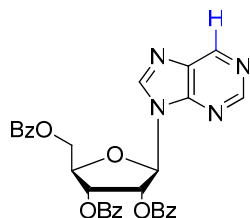
(m, 1H), 2.07 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.4, 170.3, 152.0, 151.1, 148.0, 144.3, 134.4, 84.8, 82.7, 74.3, 63.6, 37.4, 20.9, 20.8; HRMS calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{NaO}_5$ [$\text{M}+\text{Na}^+$] 343.1013, found 343.1014.

9-(2,3,5-Tri-O-acetyl- β -D-arabinofuranosyl)-9H-purine (2g)



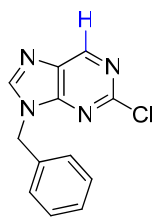
Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 9.19 (s, 1H), 9.03 (s, 1H), 8.41 (s, 1H), 6.67 (t, J = 4.8 Hz, 1H), 5.48 (t, J = 2.8 Hz, 1H), 5.39 (t, J = 3.6 Hz, 1H), 4.44-4.24 (m, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.5, 169.6, 168.7, 151.5, 146.9, 145.7, 133.3, 83.2, 80.2, 75.6, 74.8, 62.8, 20.7, 20.6, 20.2; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{N}_4\text{NaO}_7$ [$\text{M}+\text{Na}^+$] 401.1068, found 401.1060.

9-(2,3,5-Tri-O-benzoyl- β -D-ribofuranosyl)-9H-purine (2h)



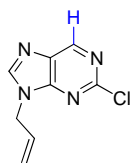
Brown oil. ^1H NMR (CDCl_3 , 400 MHz) δ 9.16 (s, 1H), 8.86 (s, 1H), 8.41 (s, 1H), 8.05-7.87 (m, 6H), 7.56-7.26 (m, 10H), 6.53 (d, J = 5.2 Hz, 1H), 6.42 (t, J = 5.2 Hz, 1H), 6.26 (t, J = 5.2 Hz, 1H), 4.94-4.84 (m, 2H), 4.72-4.68 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.1, 166.0, 165.3, 165.1, 151.6, 151.5, 147.5, 145.2, 134.4, 133.9, 133.8, 133.5, 129.8, 19.7, 129.3, 128.6, 128.5, 128.2, 87.3, 80.9, 73.9, 71.3, 63.3, 60.3; HRMS calcd for $\text{C}_{31}\text{H}_{25}\text{N}_4\text{O}_7$ [$\text{M}+\text{H}^+$] 565.1718, found 565.1719.

9-Benzyl-2-chloro-9H-purine (2i)



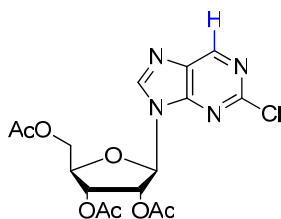
White solid. m.p. 120-122 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 9.02 (s, 1H), 8.09 (s, 1H), 7.26-7.39 (m, 5H), 5.42 (s, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 154.7, 150.2, 134.3, 129.3, 128.9, 128.1, 47.5; HRMS calcd for $\text{C}_{12}\text{H}_9\text{ClNaN}_4$ [$\text{M}+\text{Na}^+$] 267.0408, found 267.0414.

9-Allyl-2-chloro-9H-purine (2j)



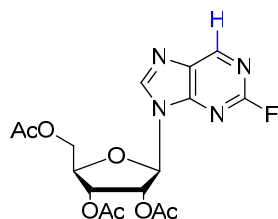
White solid. m.p. 66-68 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 8.96 (s, 1H), 8.09 (s, 1H), 5.97-6.07 (m, 1H), 5.35 (d, $J = 6.0$ Hz, 1H), 5.25 (d, $J = 17.2$ Hz, 1H), 4.86 (d, $J = 6.4$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 45.8, 120.1, 130.8, 133.0, 145.8, 150.2, 153.0, 154.5; HRMS calcd for $\text{C}_8\text{H}_8\text{ClN}_4$ [$\text{M}+\text{H}^+$] 195.0432, found 195.0439.

2-Chloro-9-(2,3,5-tri-*O*-acetyl- β -*D*-ribofuranosyl)-9H-purine (2k)



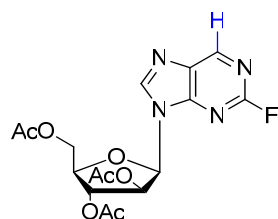
Brown oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.95 (s, 1H), 8.26 (s, 1H), 8.05-7.87 (m, 6H), 6.21 (d, $J = 5.6$ Hz, 1H), 5.78 (t, $J = 5.6$ Hz, 1H), 5.56 (t, $J = 4.8$ Hz, 1H), 4.44-4.35 (m, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.3, 169.6, 169.4, 154.7, 152.7, 150.6, 144.2, 133.6, 86.1, 80.6, 73.1, 70.5, 62.9, 20.8, 20.5, 20.4; HRMS calcd for $\text{C}_{16}\text{H}_{17}\text{ClN}_4\text{NaO}_7$ [$\text{M}+\text{Na}^+$] 435.0678, found 435.0671.

2-Fluoro-9-(2,3,5-tri-*O*-acetyl- β -*D*-ribofuranosyl)-9*H*-purine (2l)



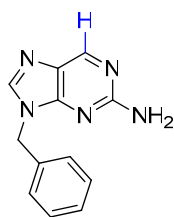
Brown color oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.26 (s, 1H), 8.07 (s, 1H), 6.17 (d, $J = 5.6$ Hz, 1H), 5.82 (t, $J = 5.2$ Hz, 1H), 5.57 (d, $J = 4.8$ Hz, 1H), 4.44-4.36 (m, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.4, 169.6, 169.4, 159.9, 157.7, 153.4, 153.3, 153.2, 153.1, 151.5, 151.3, 151.2, 144.4, 144.3, 133.4, 133.3, 86.2, 80.6, 73.0, 70.5, 62.8, 20.7, 20.5, 20.3; HRMS calcd for $\text{C}_{16}\text{H}_{17}\text{FN}_4\text{NaO}_7$ [$\text{M}+\text{Na}^+$] 419.0973, found 419.0964.

2-Fluoro-9-(2,3,5-Tri-*O*-acetyl- β -*D*-arabinofuranosyl)-9*H*-purine (2m)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.90 (s, 1H), 8.27 (s, 1H), 6.55 (d, $J = 4.4$ Hz, 1H), 5.47-5.45 (m, 1H), 5.34 (t, $J = 2.8$ Hz, 1H), 4.46-4.27 (m, 2H), 4.26-4.23 (m, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.5, 169.6, 168.5, 159.9, 157.7, 153.3, 153.1, 151.2, 151.0, 144.9, 144.8, 132.5, 132.4, 83.1, 80.3, 75.7, 74.7, 62.7, 20.7, 20.6, 20.2; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{FN}_4\text{O}_7$ [$\text{M}+\text{H}^+$] 397.1154, found 397.1158.

9-Benzyl-9H-purin-2-amine (2n)



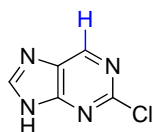
White solid. m.p. 150-152 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 8.71 (s, 1H), 7.71 (s, 1H), 7.25-7.71 (m, 5H), 5.26 (s, 2H), 5.13 (s, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 46.5, 127.7, 128.4, 129.0, 135.4, 142.3, 149.9, 160.0; HRMS calcd for $\text{C}_{12}\text{H}_{11}\text{NaN}_5$ $[\text{M}+\text{Na}^+]$ 248.0907, found 248.0924.

9-Allyl-9H-purin-2-amine (2o)



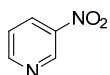
White solid. m.p. 86-88 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 8.75 (s, 1H), 7.89 (s, 1H), 5.95-6.04 (m, 1H), 5.28 (d, $J = 10.4$ Hz, 1H), 5.15-5.21 (m, 3H), 4.69 (d, $J = 5.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 160.0, 149.7, 149.6, 131.4, 118.7, 45.3, 29.7, 23.0, 11.2; HRMS calcd for $\text{C}_8\text{H}_{10}\text{N}_5$ $[\text{M}+\text{H}^+]$ 176.0931, found 176.0940.

2-Chloro-9H-purine (2p)



Yellow solid. m.p. 214-216 °C. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 13.63 (brs, 1H), 9.04 (s, 1H), 8.69 (s, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 154.5, 152.0, 148.2, 146.7, 129.7; HRMS calcd for $\text{C}_5\text{H}_4\text{ClN}_4$ $[\text{M}+\text{H}^+]$ 155.0119, found 155.0127.

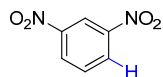
3-Nitropyridine (4a, 4b)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.54-8.45 (m, 2H), 7.63-7.61 (m, 1H), 7.22-7.18

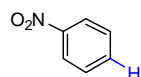
(m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 148.9, 147.5, 135.8, 132.1, 124.3.

1,3-Dinitrobenzene (4c)



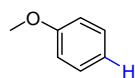
White solid. m.p. 88-90 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 9.08-9.05 (m, 1H), 8.60-8.58 (m, 2H), 7.85-7.81 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 130.8, 128.9, 119.1.

Nitrobenzene (4d)



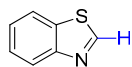
Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.26 (t, $J = 1.2$ Hz, 2H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.58-7.54 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 134.6, 129.3, 123.5.

Anisole (4f)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 7.32-7.28 (m, 2H), 6.98-6.91 (m, 3H), 3.82 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm) 129.5, 120.7, 113.9, 55.2.

Benzo[d]thiazole (4g)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.06 (s, 1H), 7.79-7.62 (m, 1H), 7.57-7.55 (m, 1H), 7.39-7.32 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 152.5, 150.0, 140.0, 125.6, 124.6, 120.6, 111.0.

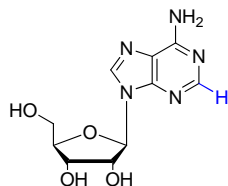
4-(Trifluoromethyl)pyrimidine (4h)



Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.60 (d, $J = 4.8$ Hz, 1H), 7.67 (s, 1H), 7.05 (d, $J =$

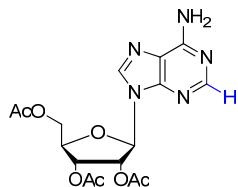
5.2 Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 177.3, 163.2, 160.8, 157.0, 121.6, 118.9, 108.8, 108.7.

Adenosine (4i)



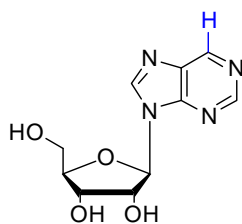
White solid. m.p. 234-236 °C. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz) δ 8.34 (s, 1H), 8.13 (s, 1H), 7.35 (s, 1H), 5.88 (d, $J = 6.4$ Hz, 1H), 5.47-5.44 (m, 2H), 5.21 (d, $J = 4.4$ Hz, 1H), 4.62-4.58 (m, 1H), 4.15-4.12 (m, 1H), 3.97-3.95 (m, 1H), 3.69-3.64 (m, 1H), 3.57-3.52 (m, 1H); ^{13}C NMR ($\text{DMSO}-d_6$, 100 MHz) δ 156.6, 152.9, 149.5, 140.4, 119.8, 88.4, 86.4, 73.9, 71.2, 62.2; HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_5\text{NaO}_4$ [$\text{M}+\text{Na}^+$] 290.0860, found 290.0863.

9-(2,3,5-Tri-O-acetyl- β -D-adenosine (4j)



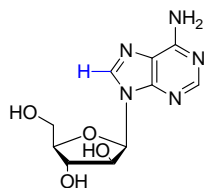
White solid. m.p. 168-170 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 8.33 (s, 1H), 7.95 (s, 1H), 6.17 (d, $J = 5.2$ Hz, 1H), 5.92 (t, $J = 5.2$ Hz, 1H), 5.66 (t, $J = 4.4$ Hz, 1H), 4.45-4.33 (m, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.3, 169.6, 169.4, 155.6, 153.0, 149.7, 138.9, 120.1, 86.3, 80.3, 73.2, 70.7, 63.1, 20.7, 20.5, 20.4.; HRMS calcd for $\text{C}_{16}\text{H}_{20}\text{N}_5\text{O}_7$ [$\text{M}+\text{H}^+$] 394.1357, found 394.1358.

9- β -D-Ribofuranosyl-9H-purine (7)



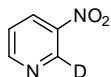
White solid. m.p. 182-184 °C. ^1H NMR (DMSO- d_6 , 400 MHz) δ 9.19 (s, 1H), 8.95 (s, 1H), 8.86 (s, 1H), 6.04 (d, J = 5.6 Hz, 1H), 4.59 (t, J = 5.2 Hz, 1H), 4.18 (t, J = 4.0 Hz, 1H), 3.96 (t, J = 4.4 Hz, 1H), 3.69-3.54 (m, 2H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 152.6, 151.4, 148.7, 145.9, 134.6, 88.1, 86.2, 74.3, 70.7, 61.7; HRMS calcd for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{NaO}_4$ [$\text{M}+\text{Na}^+$] 275.0751, found 275.0745.

Vidarabine (9)



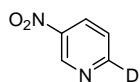
White solid. m.p. 264-266 °C. ^1H NMR (DMSO- d_6 , 400 MHz) δ 8.18 (s, 1H), 8.12 (s, 1H), 7.24 (s, 2H), 6.25 (d, J = 4.4 Hz, 1H), 5.64 (d, J = 4.4 Hz, 1H), 5.56 (t, J = 3.6 Hz, 1H), 5.13 (t, J = 4.4 Hz, 1H), 4.13 (brs, 2H), 3.79-3.76 (m, 1H), 3.69-3.61 (m, 2H); ^{13}C NMR (DMSO- d_6 , 100 MHz) δ 156.3, 152.9, 149.8, 140.8, 118.7, 84.5, 84.0, 76.1, 75.4, 61.3; HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{N}_5\text{NaO}_4$ [$\text{M}+\text{Na}^+$] 290.0860, found 290.0857.

2-D-3-Nitropyridine (5a)



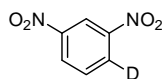
Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.61-8.60 (m, 1H), 8.23-8.21 (m, 1H), 7.49-7.46 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 152.5, 143.4, 134.3, 123.1.

2-D-5-Nitropyridine (5b)



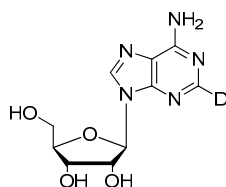
Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 9.22 (d, $J = 2.8$ Hz, 1H), 8.46-8.43 (m, 1H), 7.56 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 157.1, 145.5, 143.3, 13.7, 124.9.

1-D-2,4-Dinitrobenzene (5c)



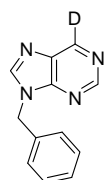
Oil. ^1H NMR (CDCl_3 , 400 MHz) δ 8.68 (d, $J = 2.4$ Hz, 1H), 8.13-8.10 (m, 1H), 7.59 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 130.6, 128.7, 118.9.

2-Deuterium adenosine (5d)



White solid. m.p. 236-238 °C. ^1H NMR ($\text{DMSO-}d_6$, 400 MHz) δ 8.36 (s, 1H), 7.82 (brs, 2H), 5.81 (d, $J = 6.0$ Hz, 1H), 5.46 (d, $J = 6.0$ Hz, 1H), 5.19 (d, $J = 4.8$ Hz, 1H), 5.05 (t, $J = 5.6$ Hz, 1H), 4.51 (q, $J_1 = 11.2$ Hz, $J_2 = 5.6$ Hz, 1H), 4.12 (d, $J = 3.2$ Hz, 1H), 3.94 (d, $J = 2.8$ Hz, 1H), 3.67-3.51 (m, 2H); ^{13}C NMR ($\text{DMSO-}d_6$, 100 MHz) δ 156.6, 152.9, 149.5, 140.4, 119.8, 88.4, 86.4, 73.9, 71.1, 62.2; HRMS calcd for $\text{C}_{10}\text{H}_{13}\text{DN}_5\text{O}_4$ [$\text{M}+\text{H}^+$] 269.1103, found 269.1107.

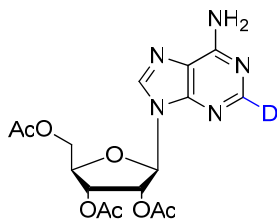
9-Benzyl-6-D-9H-purine (5e)



White solid. m.p. 82-86 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 9.03 (s, 1H), 8.09 (s, 1H), 7.30-7.37 (m, 5H), 5.46 (s, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 152.1, 151.1, 148.7, 145.0, 134.5, 131.4, 129.2, 128.8, 127.9, 47.8; HRMS calcd for $\text{C}_{12}\text{H}_{10}\text{DN}_4$ [$\text{M}+\text{H}^+$]

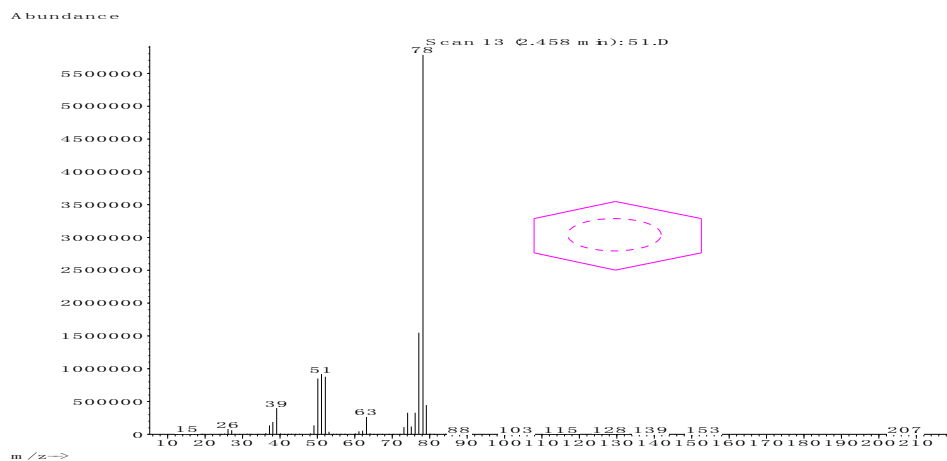
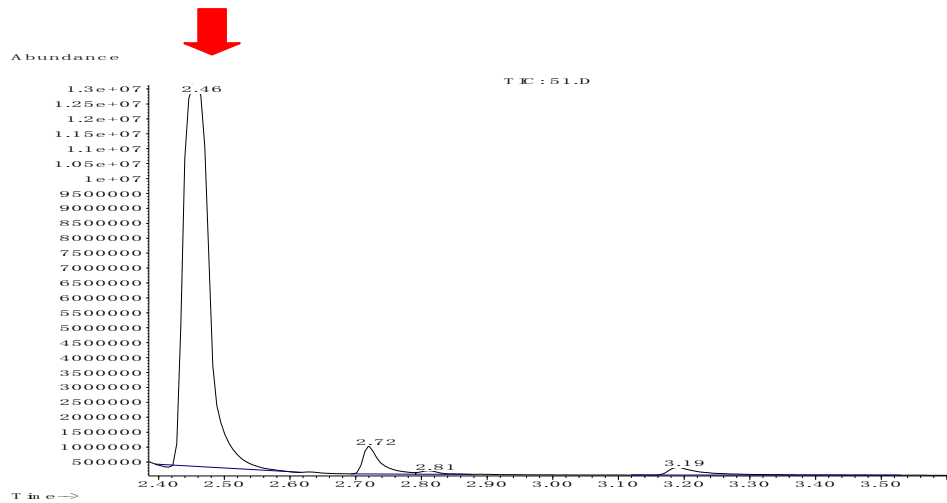
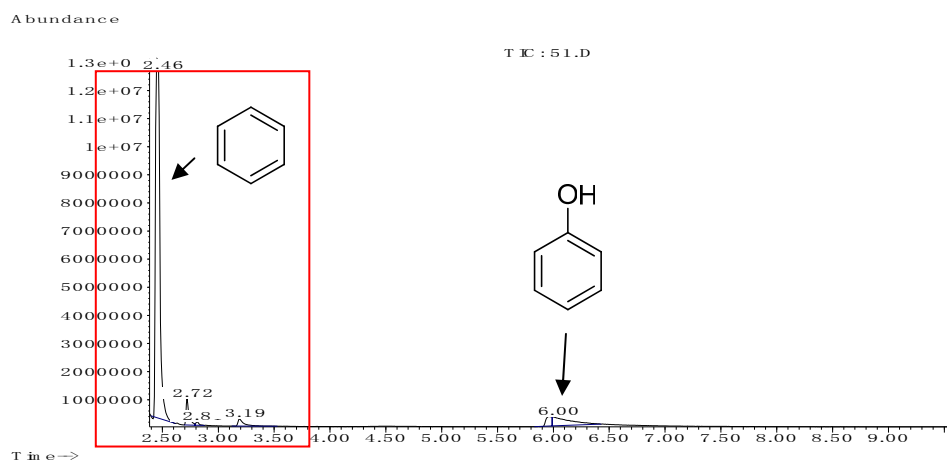
212.1041, found 212.1048.

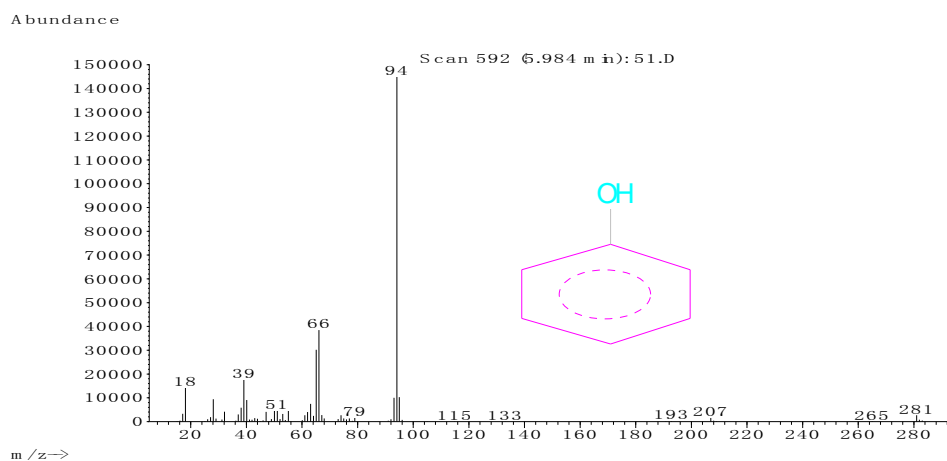
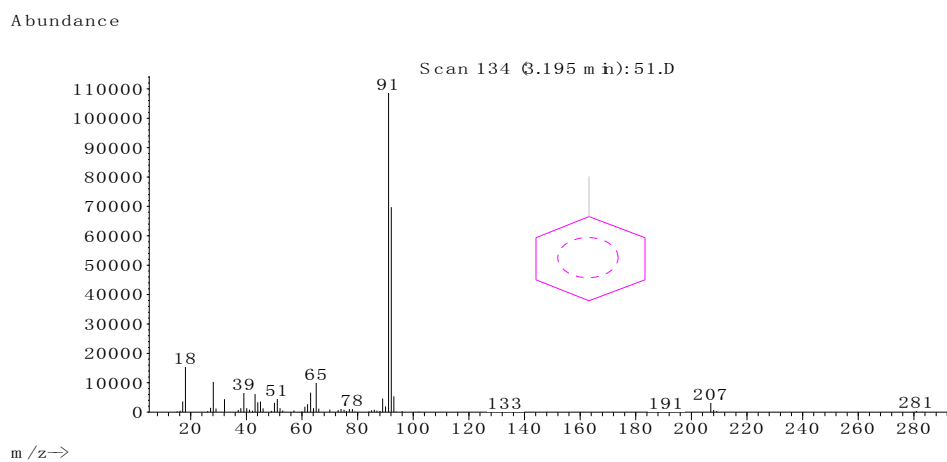
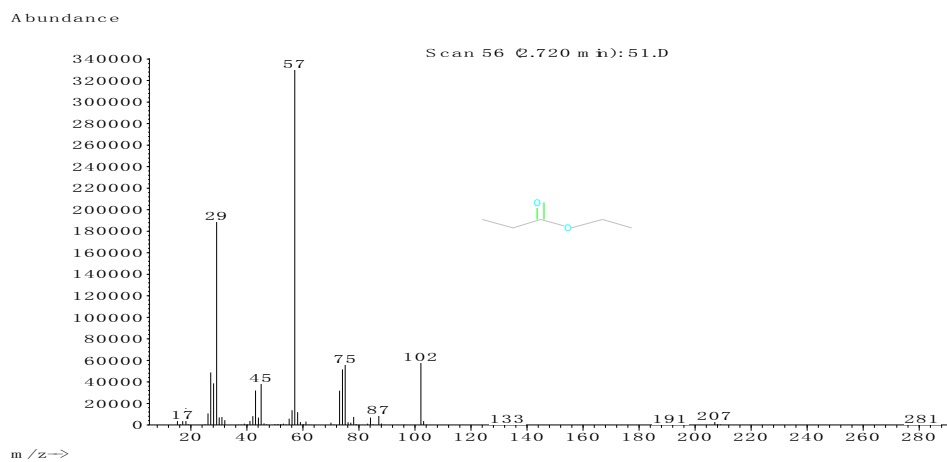
2-Deuterium-9-(2,3,5-Tri-O-acetyl- β -D-adenosine (5f)



White solid. m.p. 168-170 °C. ^1H NMR (CDCl_3 , 400 MHz): δ 8.95 (s, 1H), 8.26 (s, 1H), 6.21 (d, $J = 5.6$ Hz, 1H), 5.78 (d, $J = 5.6$ Hz, 1H), 5.56 (d, $J = 4.8$ Hz, 1H), 4.44-4.35 (m, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.4, 169.7, 169.5, 156.3, 154.5, 150.7, 138.8, 118.6, 85.9, 80.5, 73.3, 70.7, 63.1, 20.8, 20.6, 20.5; HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{DN}_5\text{NaO}_7$ [$\text{M}+\text{Na}^+$] 417.1239, found 417.1242.

6. GC-MS of 4e





GC-MS of 4e report:

Area Percent Report

Data File : D:\MSDCHEM\1\DATA\QUGUIRONG\51.D Vial: 1
Acq On : 18 Jul 2013 11:21 Operator:
Sample : Inst : Instrumen
Misc : Multiplr: 1.00
Sample Amount: 0.00

MS Integration Params: AUTOINT1.E

Method : E:\MSDCHEM\1\METHODS\DEFAULT.M (Chemstation Integrator)
Title :

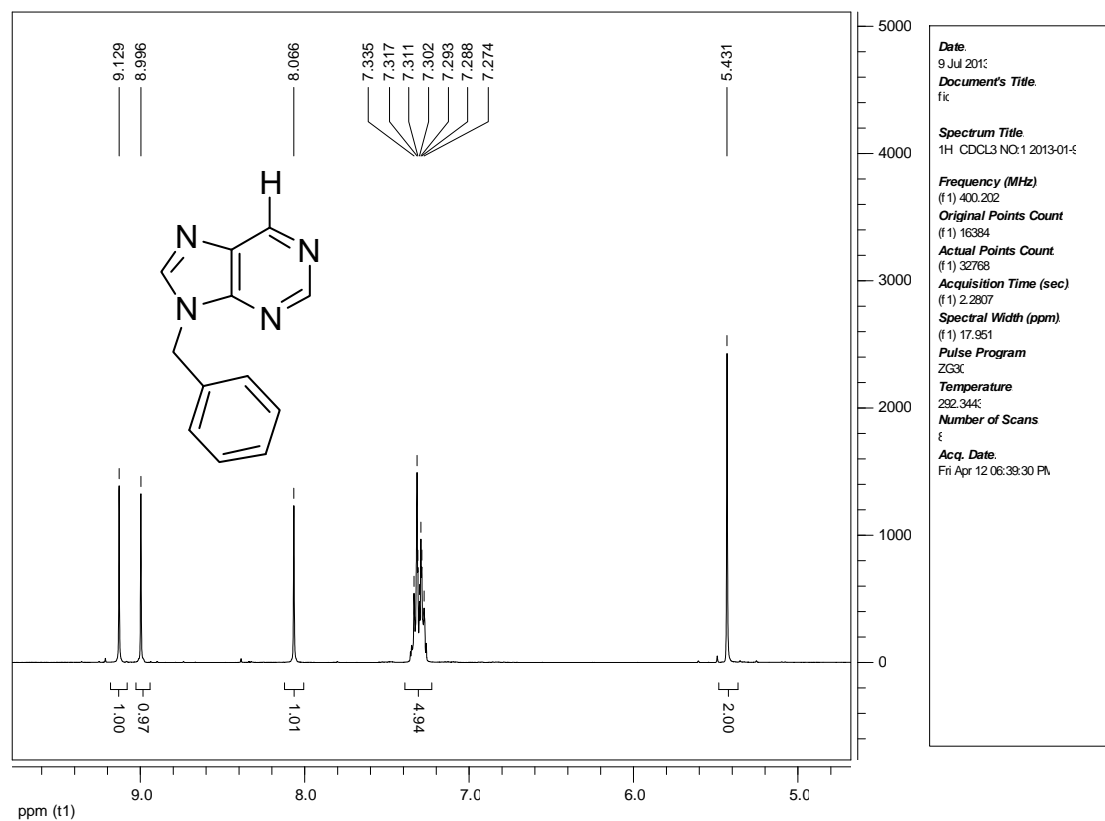
Signal : TIC

| peak # | R.T. min | first scan | max scan | last scan | PK TY | peak height | corr. area | corr. % max. | % of total |
|--------|----------|------------|----------|-----------|-------|-------------|------------|--------------|------------|
| 1 | 2.458 | 3 | 13 | 39 | BV 2 | 12781526 | 347844689 | 100.00% | 82.189% |
| 2 | 2.720 | 52 | 56 | 68 | PV | 906701 | 17217572 | 4.95% | 4.068% |
| 3 | 2.811 | 68 | 71 | 82 | VV | 116044 | 2331221 | 0.67% | 0.551% |
| 4 | 3.195 | 122 | 134 | 189 | BB | 260427 | 9589622 | 2.76% | 2.266% |
| 5 | 5.965 | 567 | 589 | 593 | BV 4 | 338632 | 11177443 | 3.21% | 2.641% |
| 6 | 5.996 | 593 | 594 | 665 | VV 2 | 319978 | 35066387 | 10.08% | 8.285% |

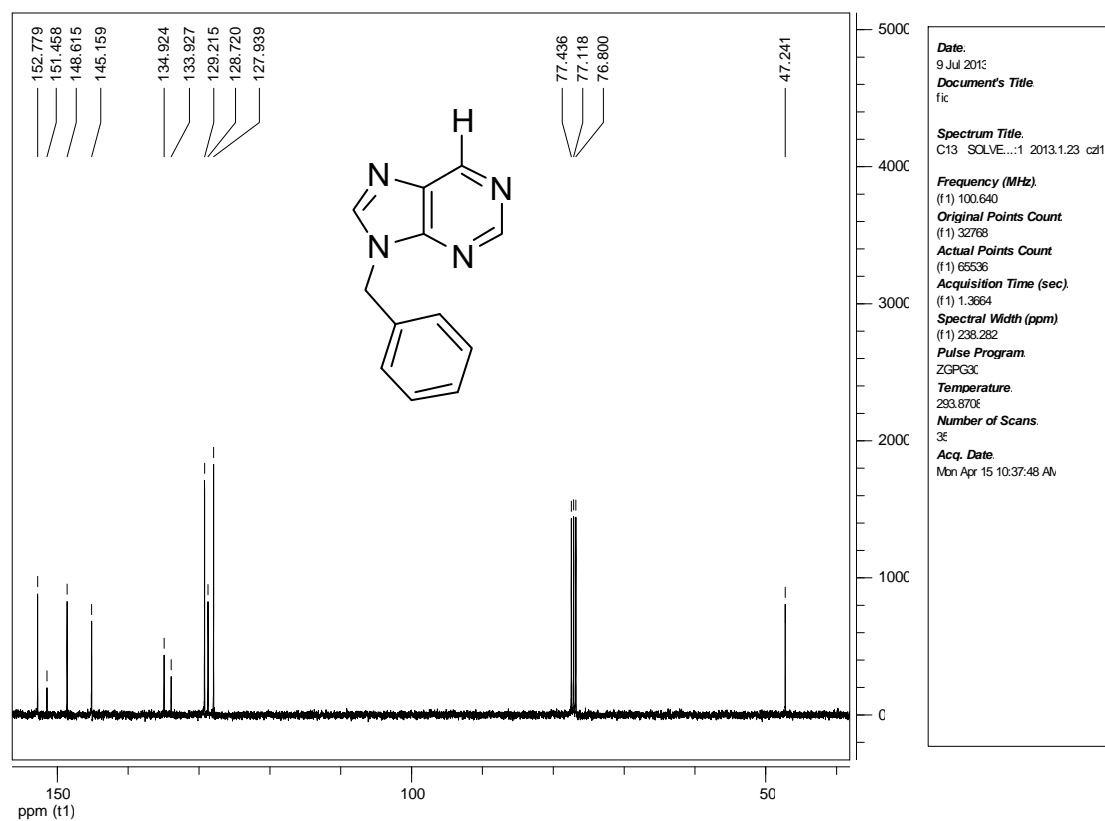
Sum of corrected areas: 423226936

7. ^1H and ^{13}C spectra of products

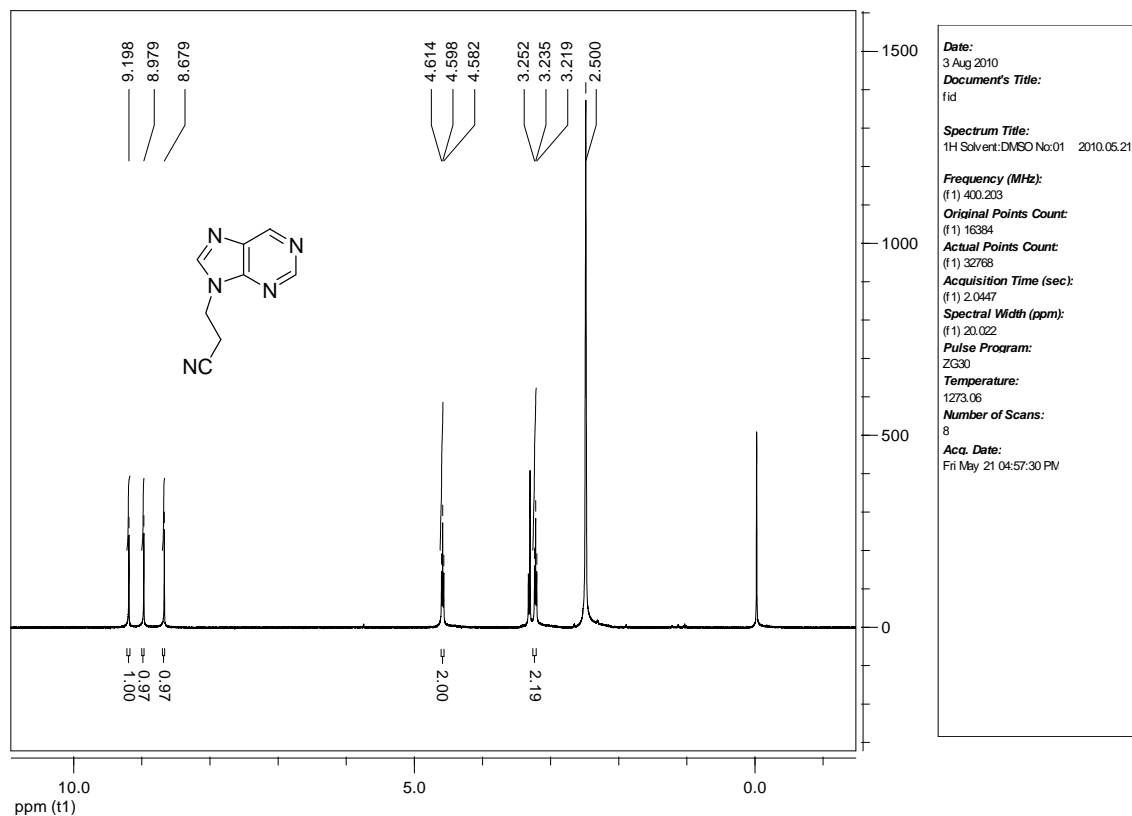
^1H NMR Spectrum for 2a:



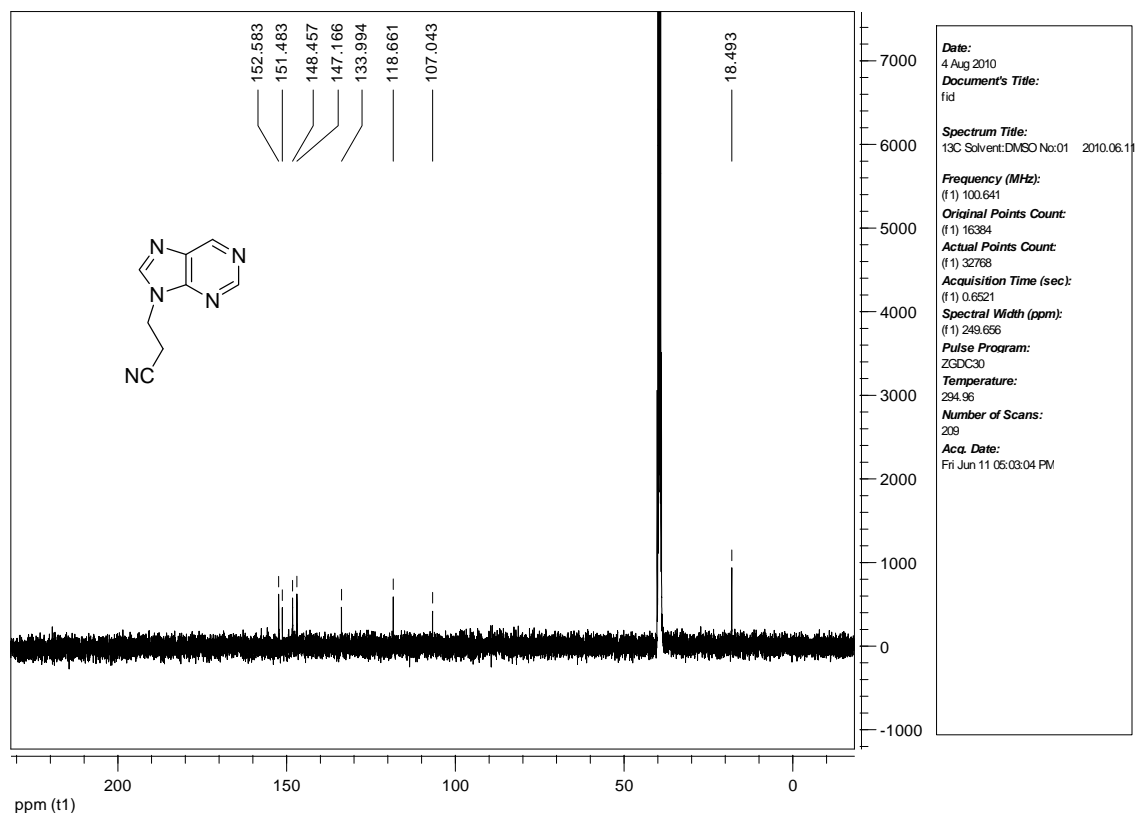
^{13}C NMR Spectrum for 2a



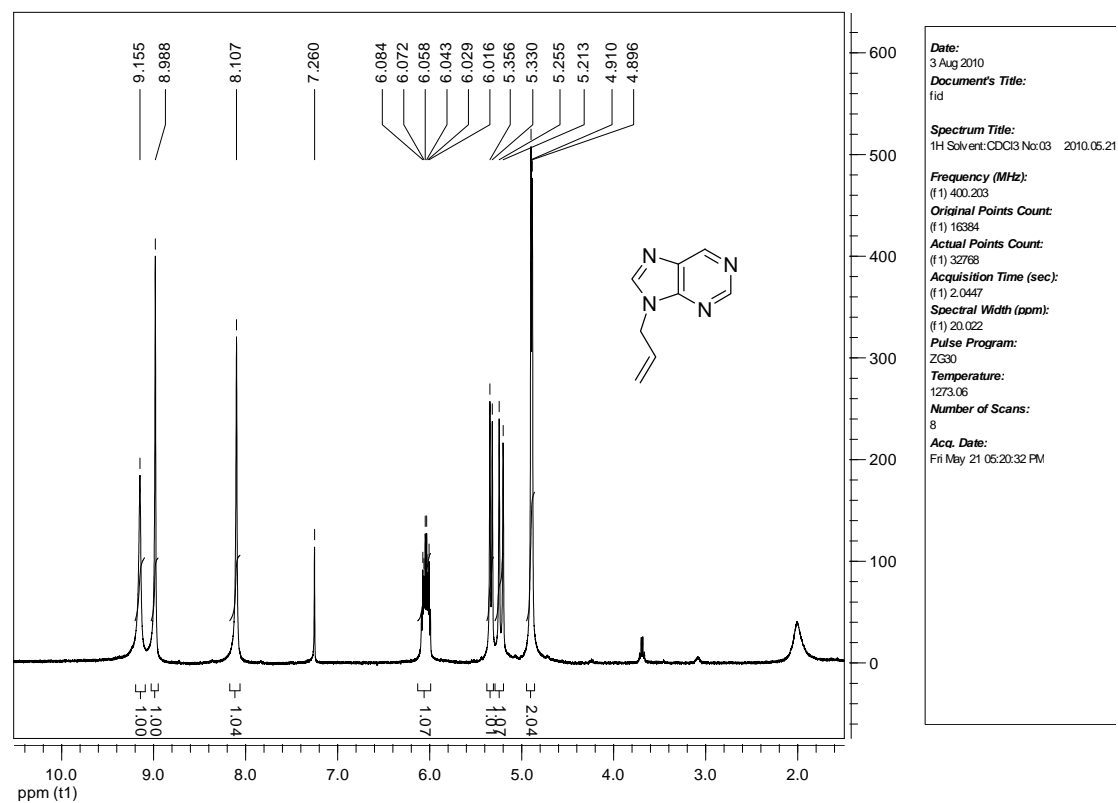
¹H NMR Spectrum for 2b



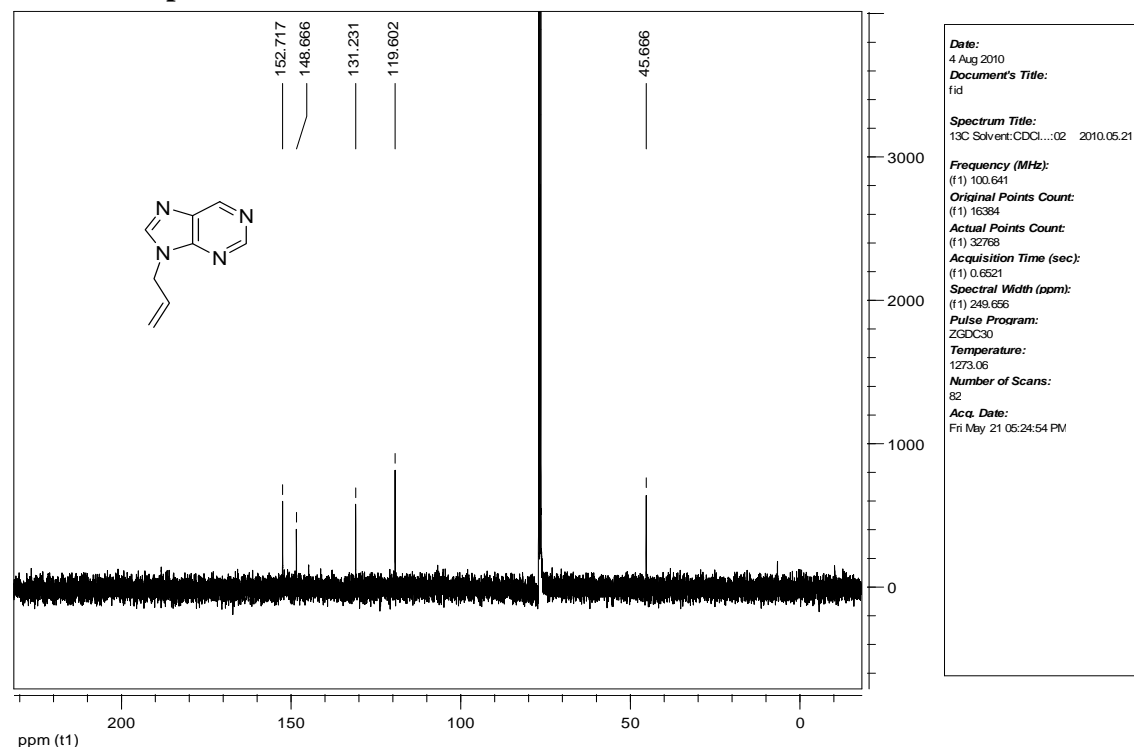
¹³C NMR Spectrum for 2b



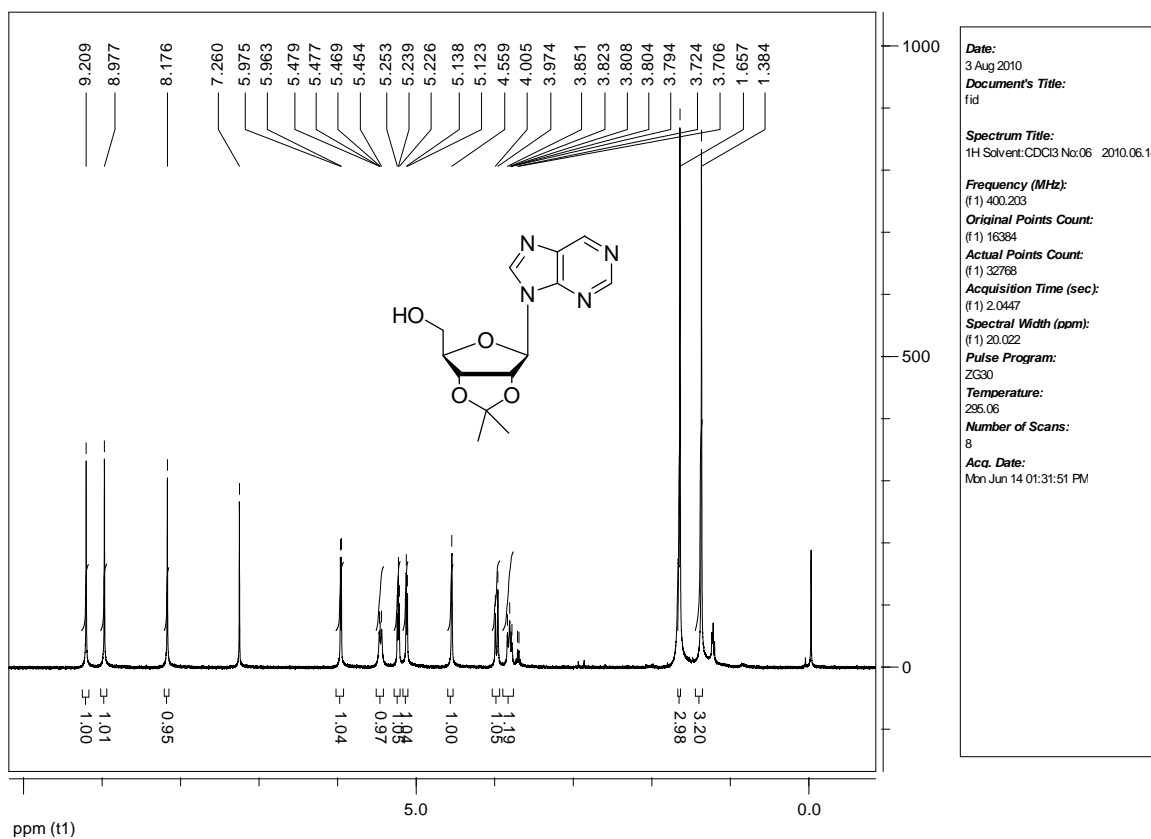
¹H NMR Spectrum for 2c



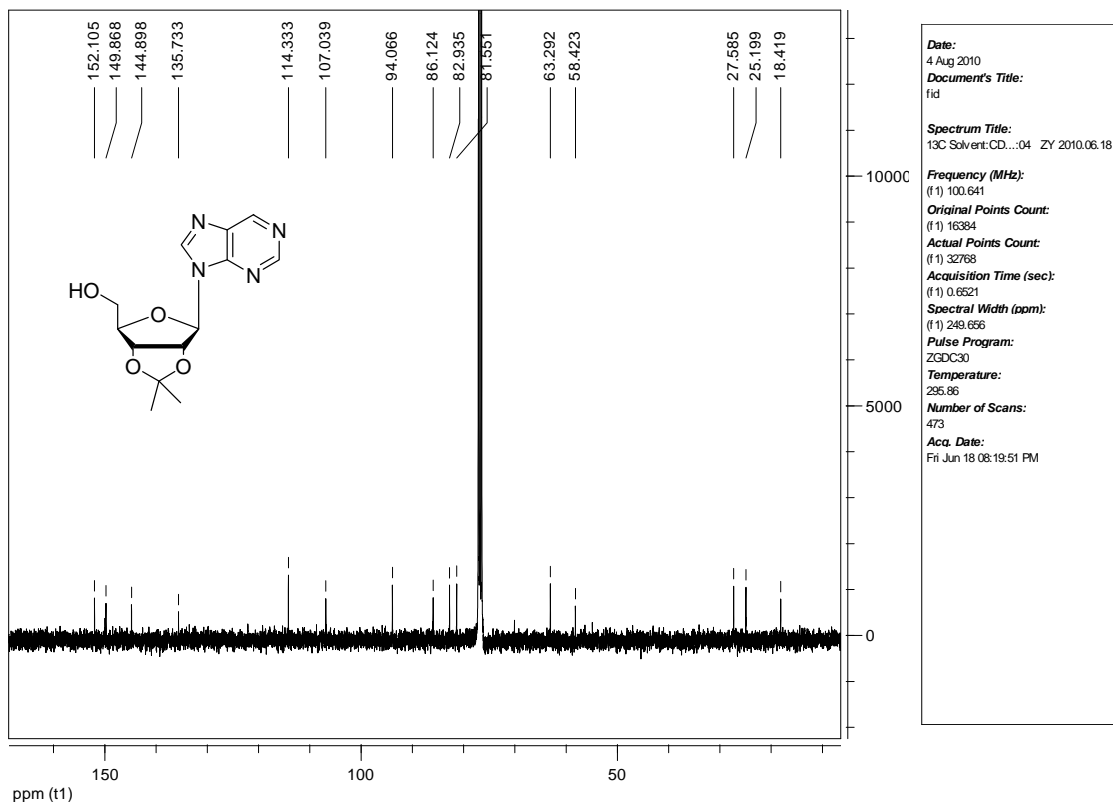
¹³C NMR Spectrum for 2c



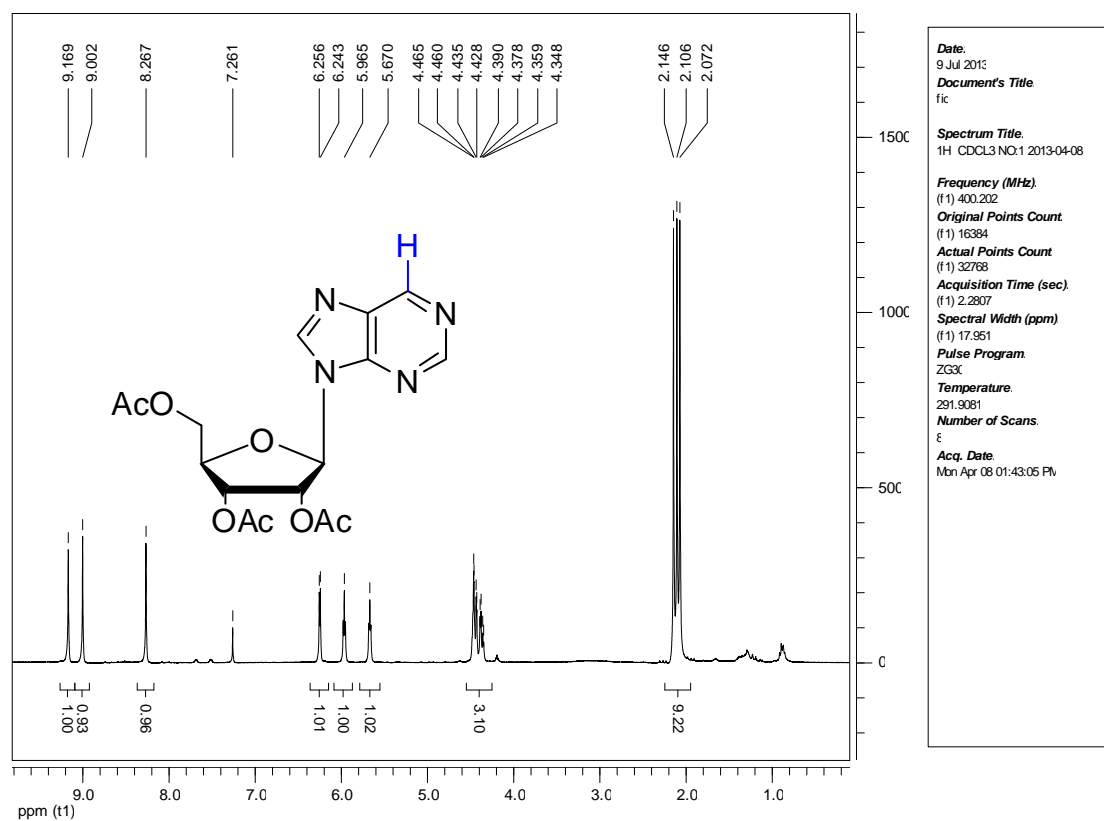
¹H NMR Spectrum for 2d



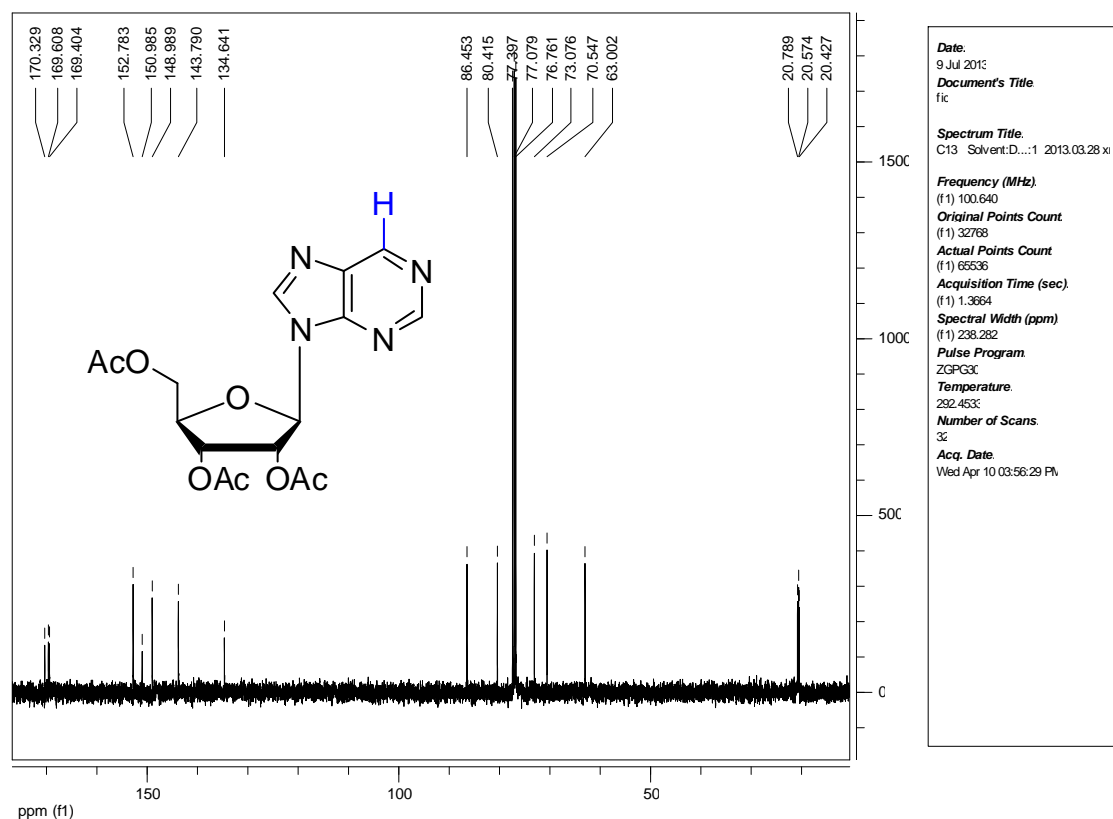
¹³C NMR Spectrum for 2d



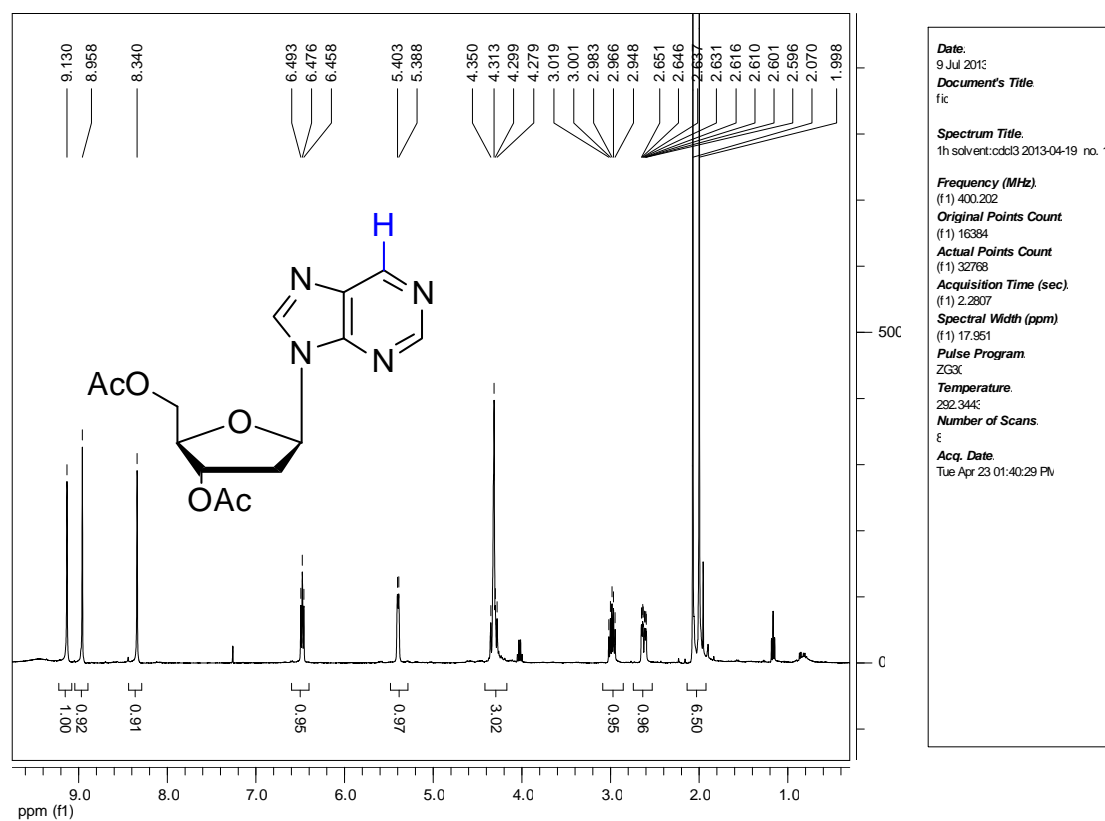
¹H NMR Spectrum for 2e



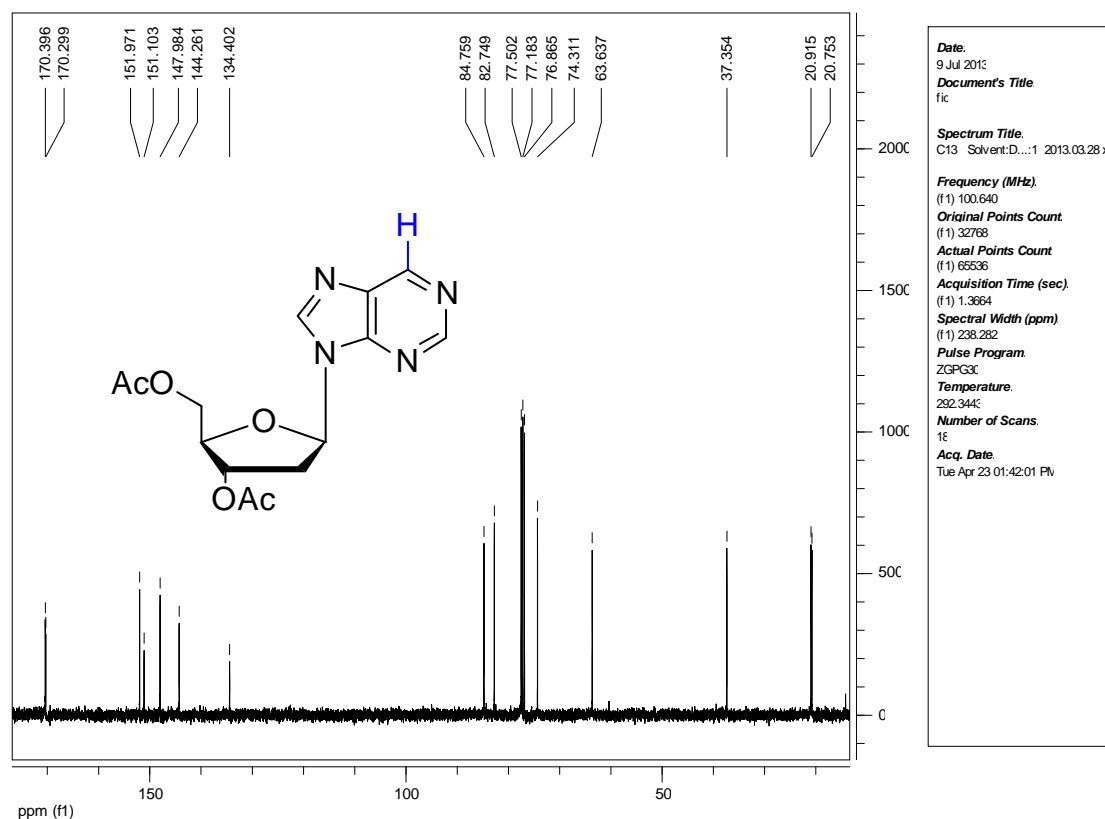
¹³C NMR Spectrum for 2e



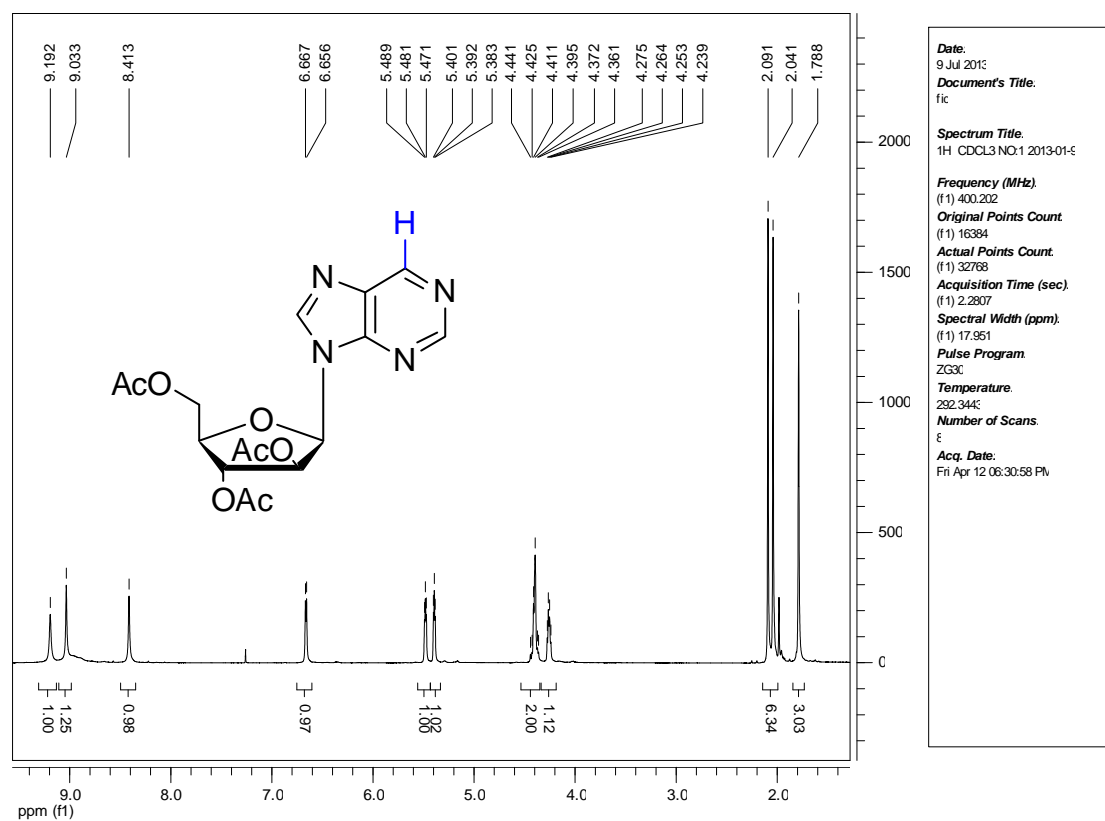
¹H NMR Spectrum for 2f



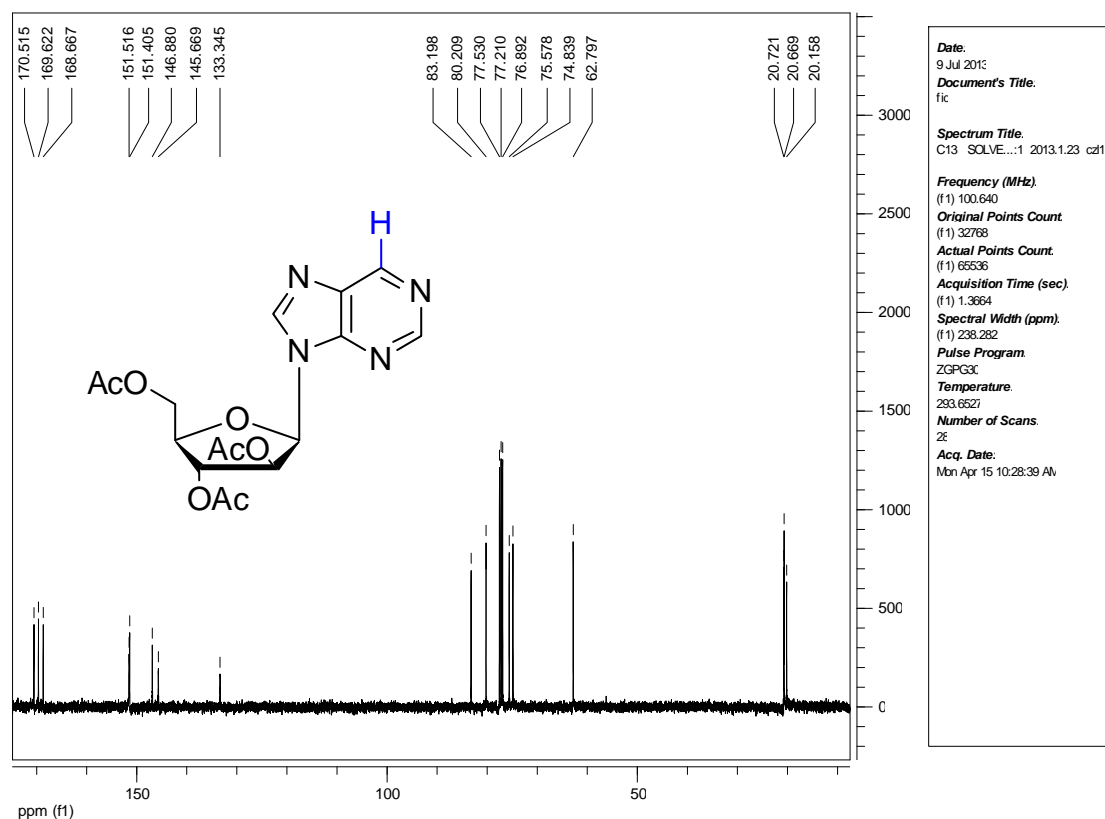
¹³C NMR Spectrum for 2f



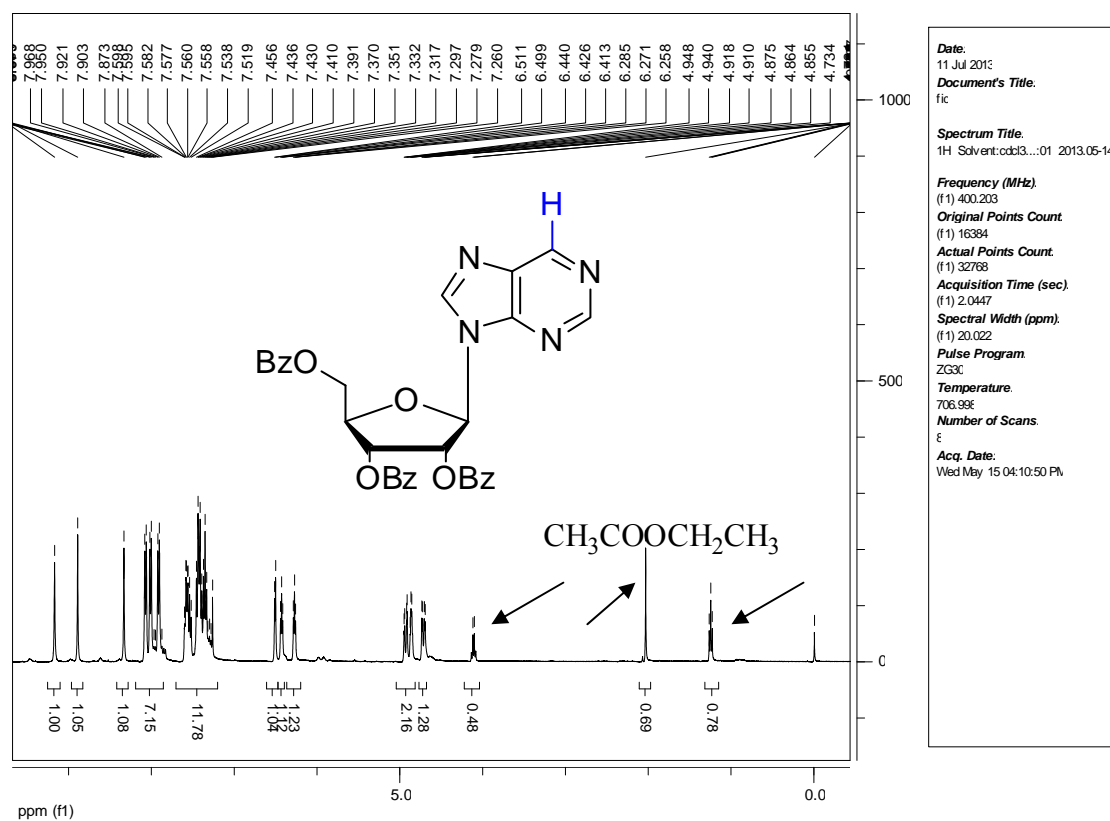
¹H NMR Spectrum for 2g



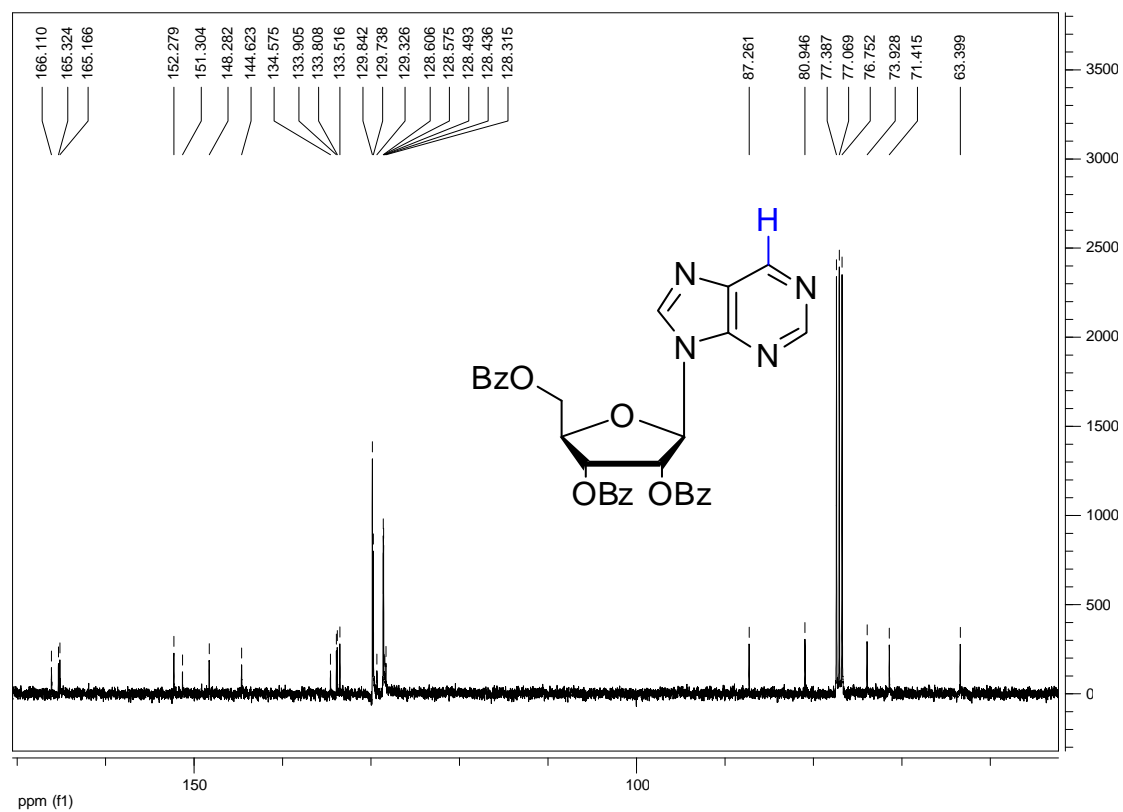
¹³C NMR Spectrum for 2g



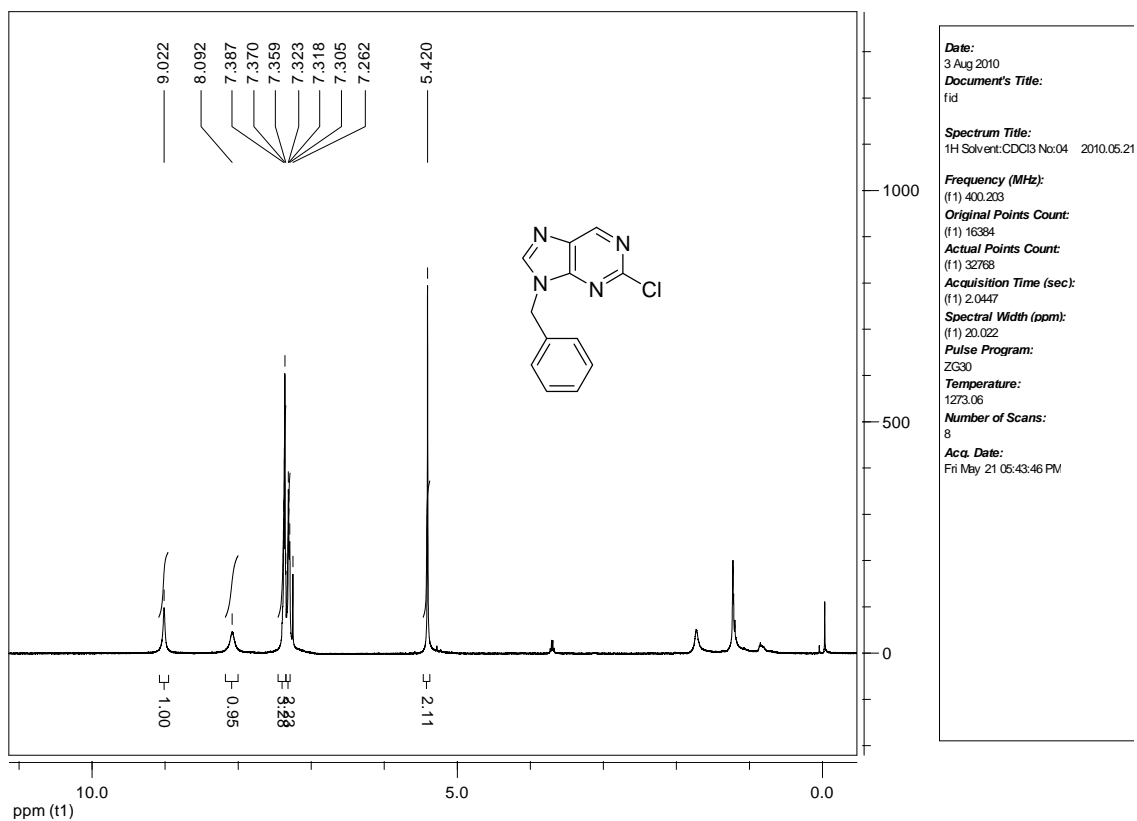
¹H NMR Spectrum for 2h



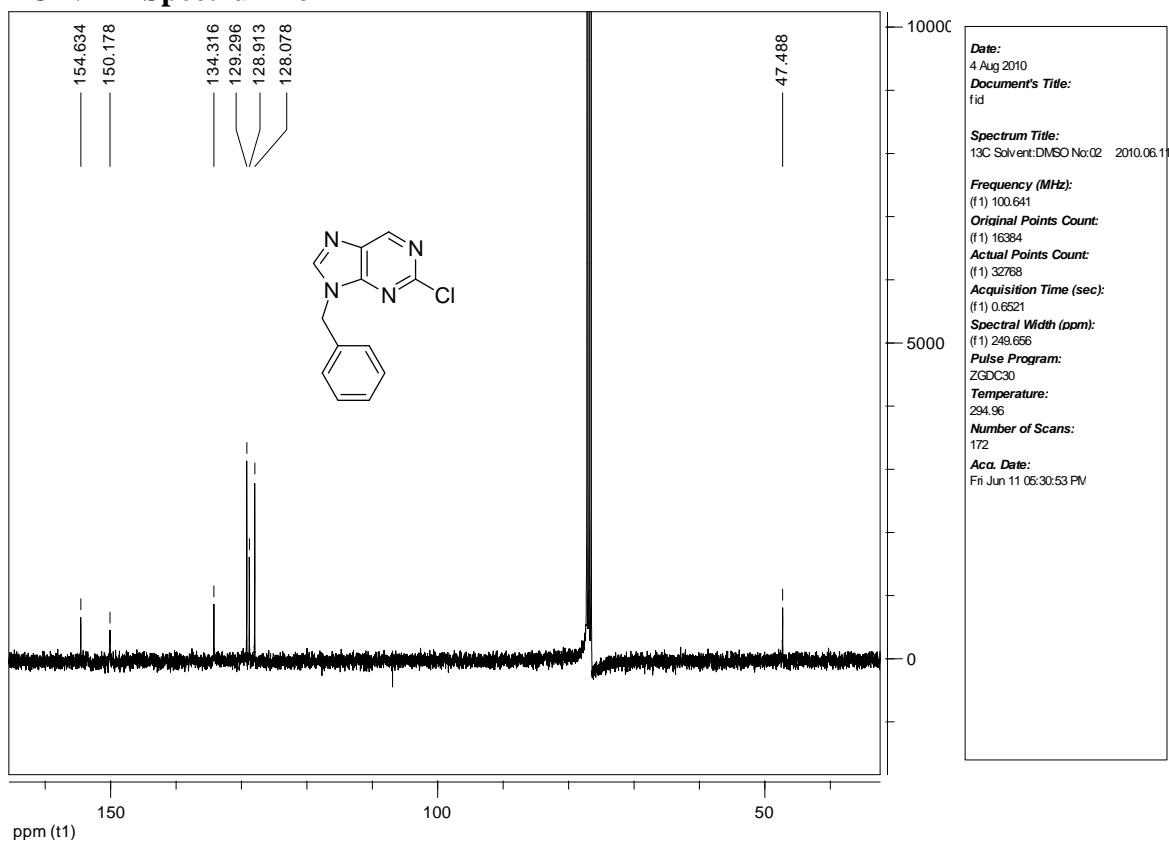
¹³C NMR Spectrum for 2h



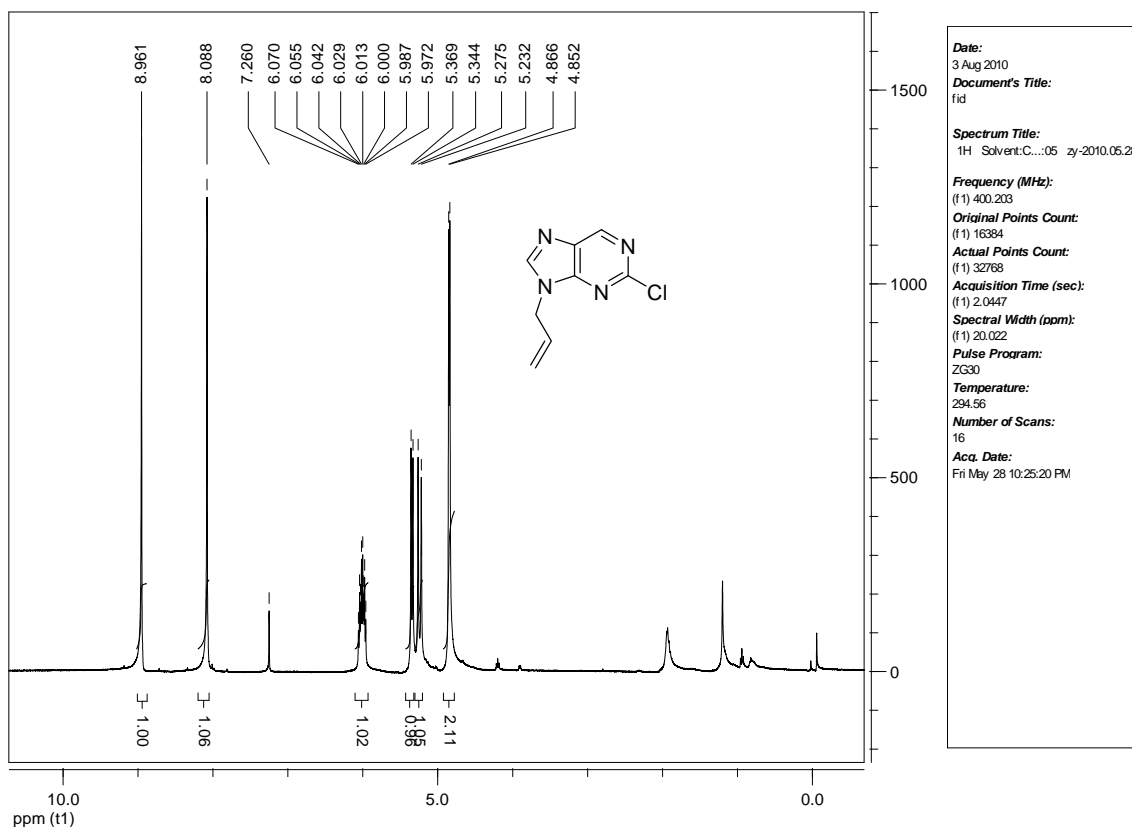
¹H NMR Spectrum for 2i



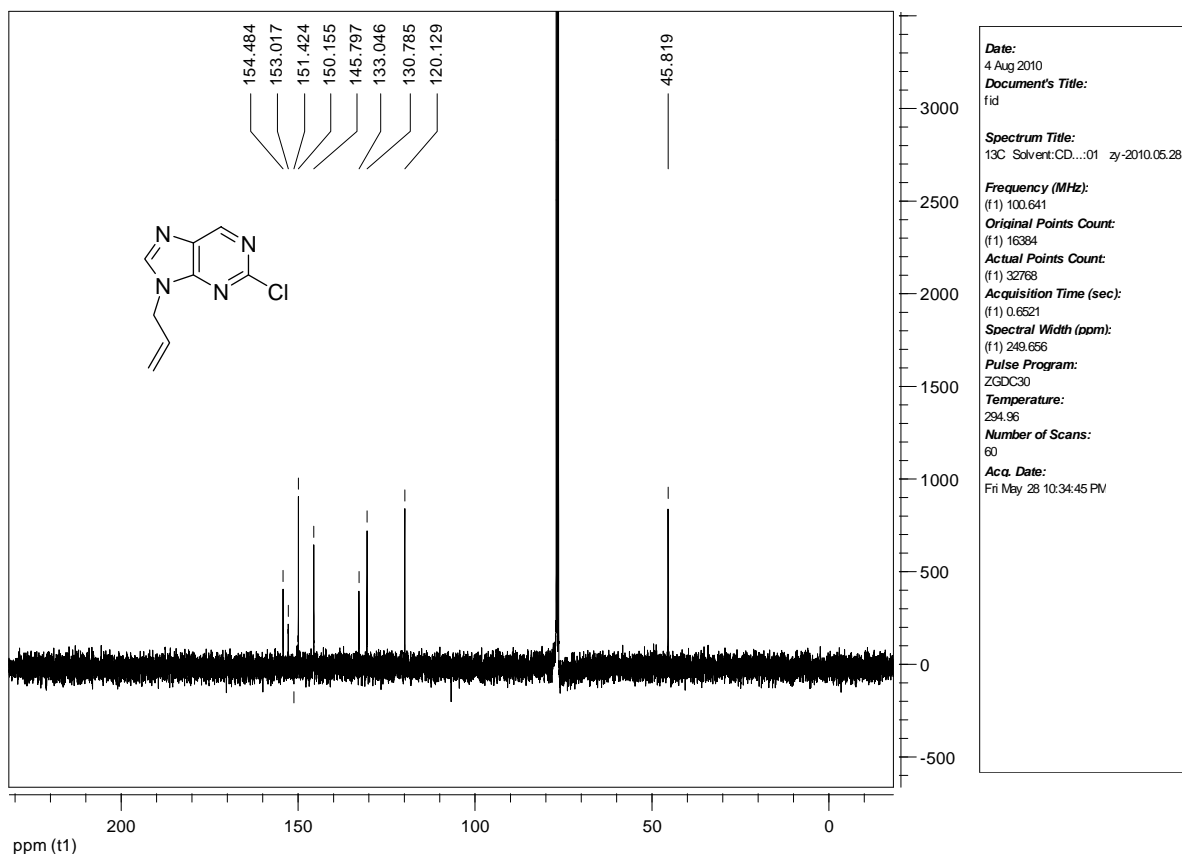
¹³C NMR Spectrum for 2i



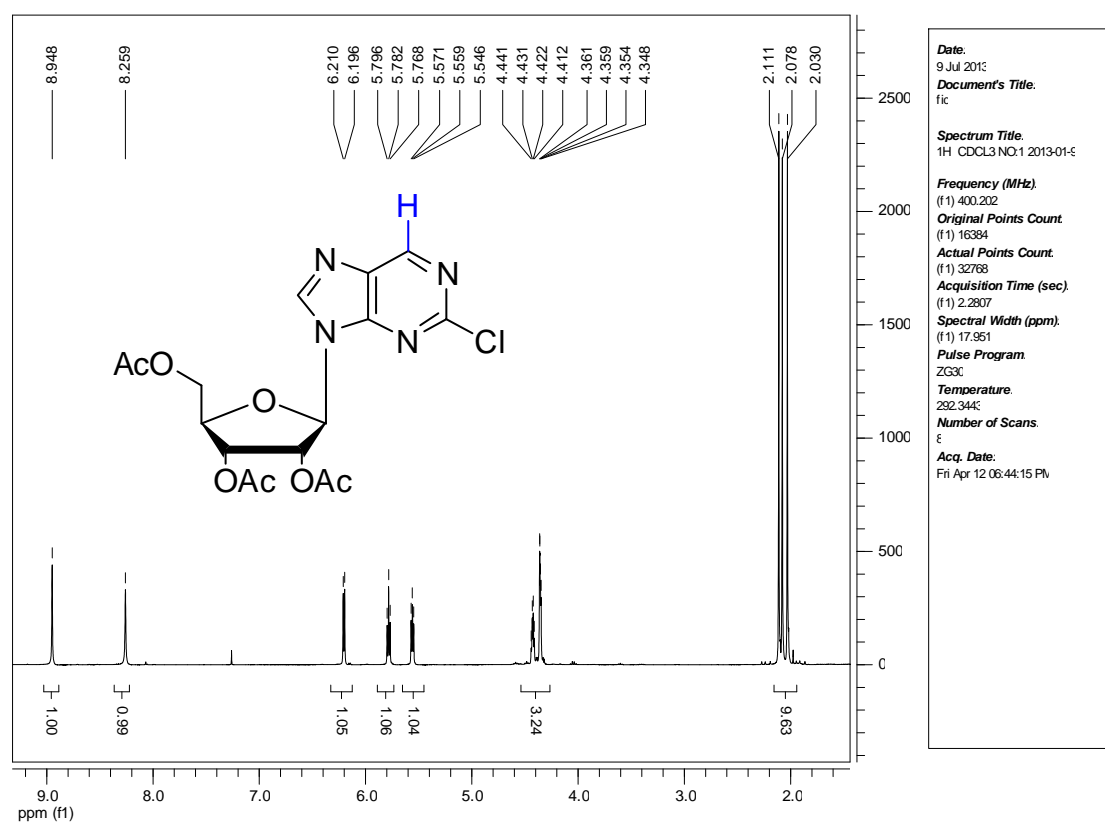
¹H NMR Spectrum for 2j



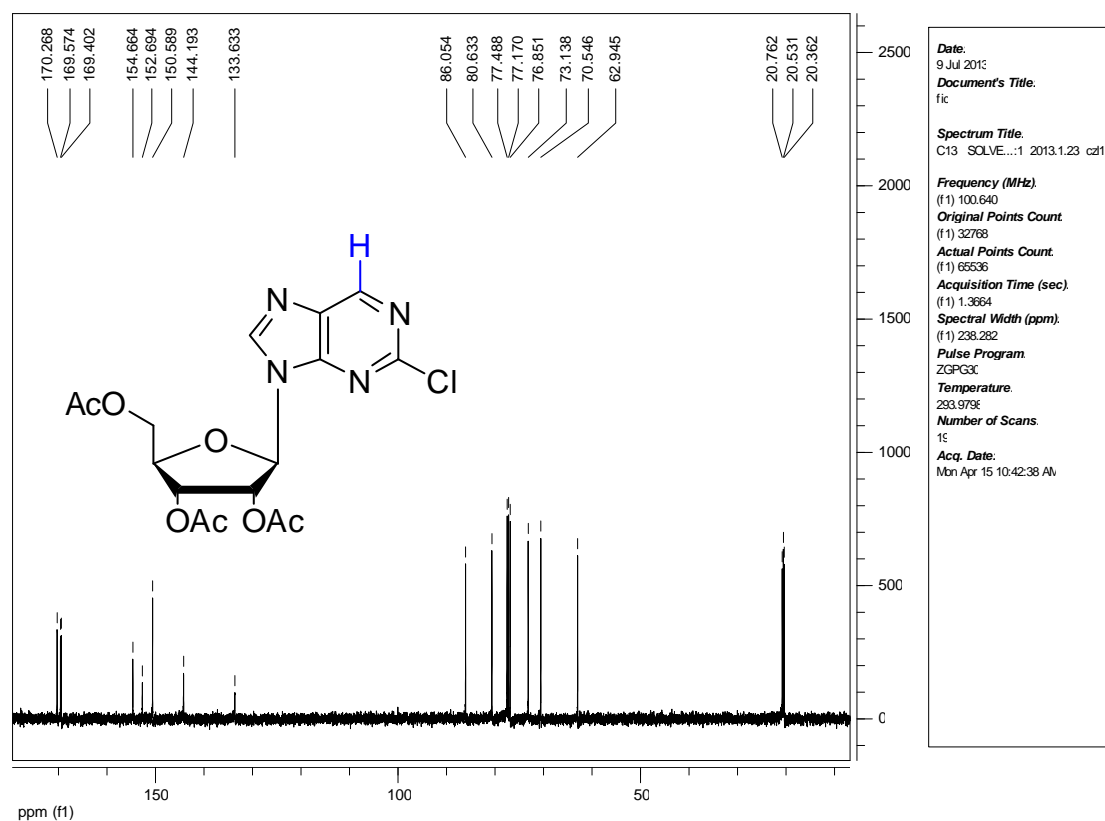
¹³C NMR Spectrum for 2j



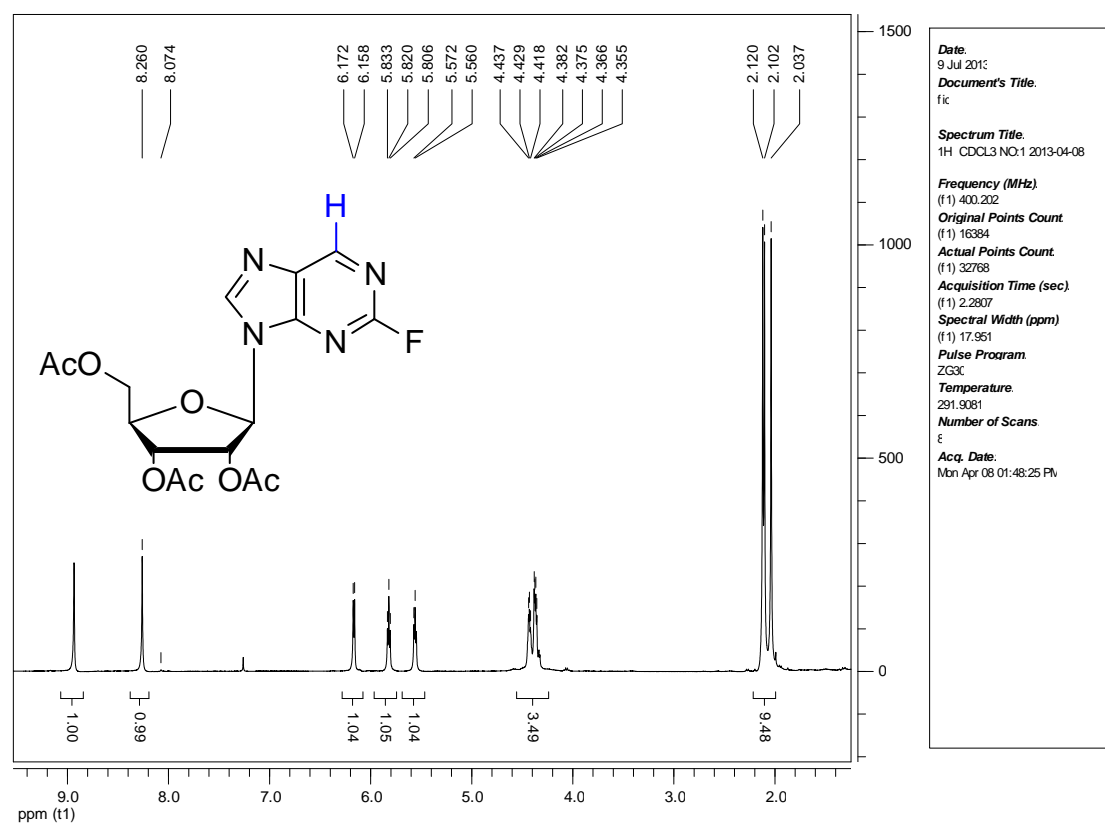
¹H NMR Spectrum for 2k



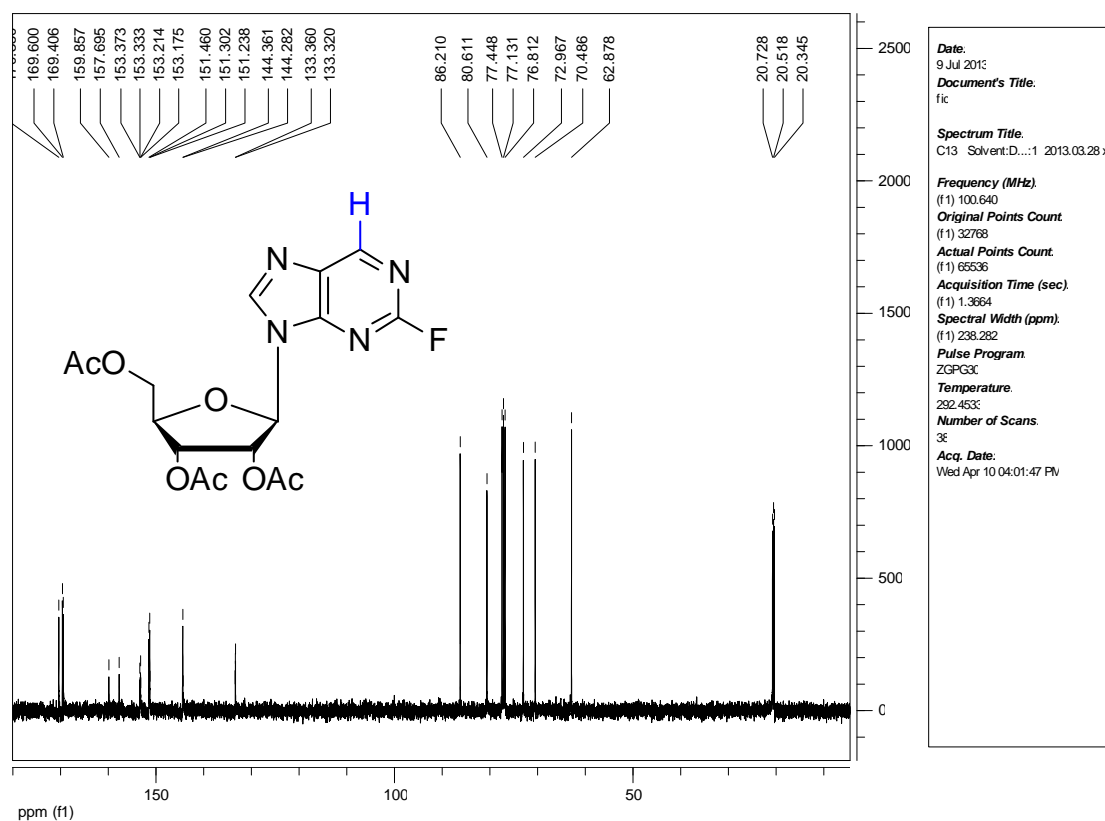
¹³C NMR Spectrum for 2k



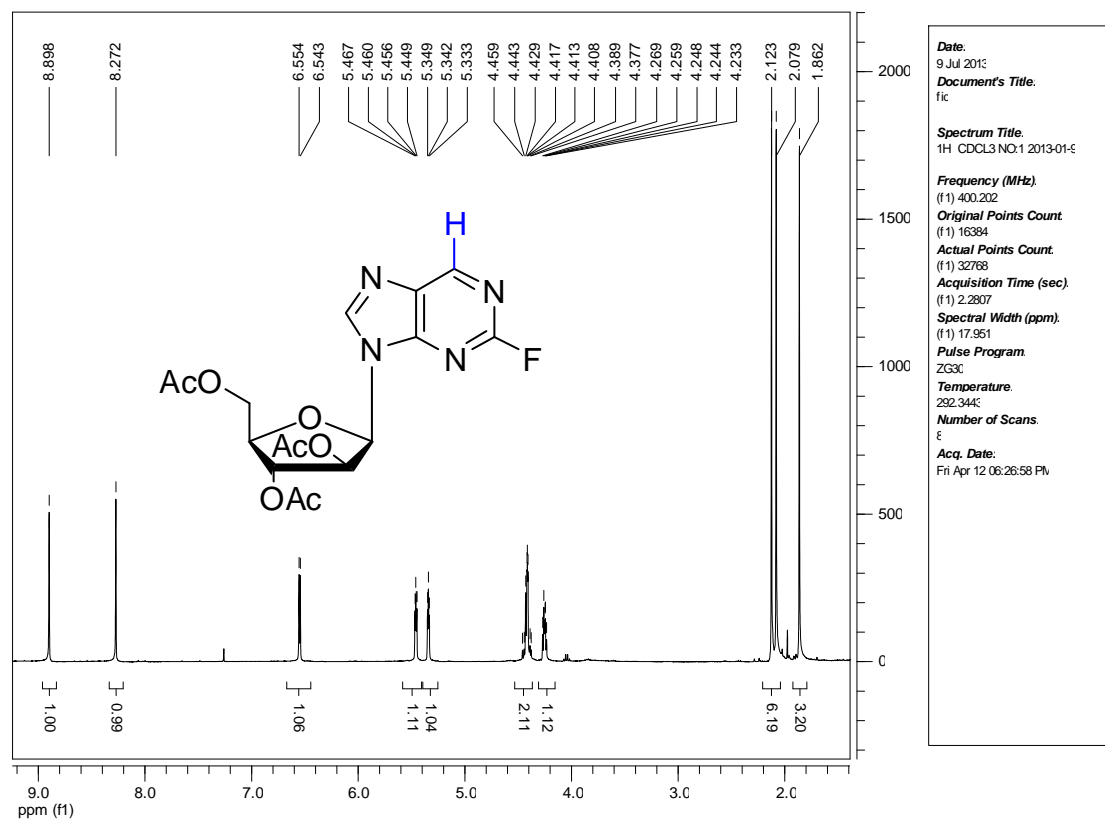
¹H NMR Spectrum for 2l



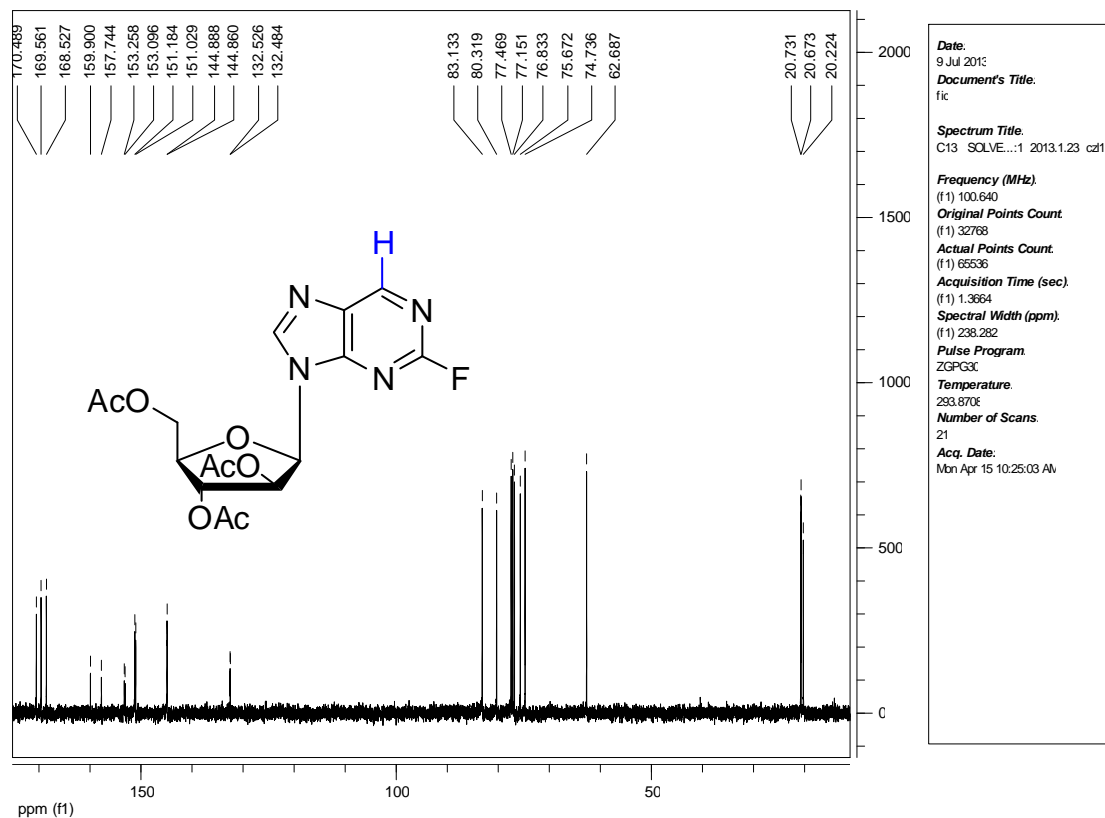
¹³C NMR Spectrum for 2l



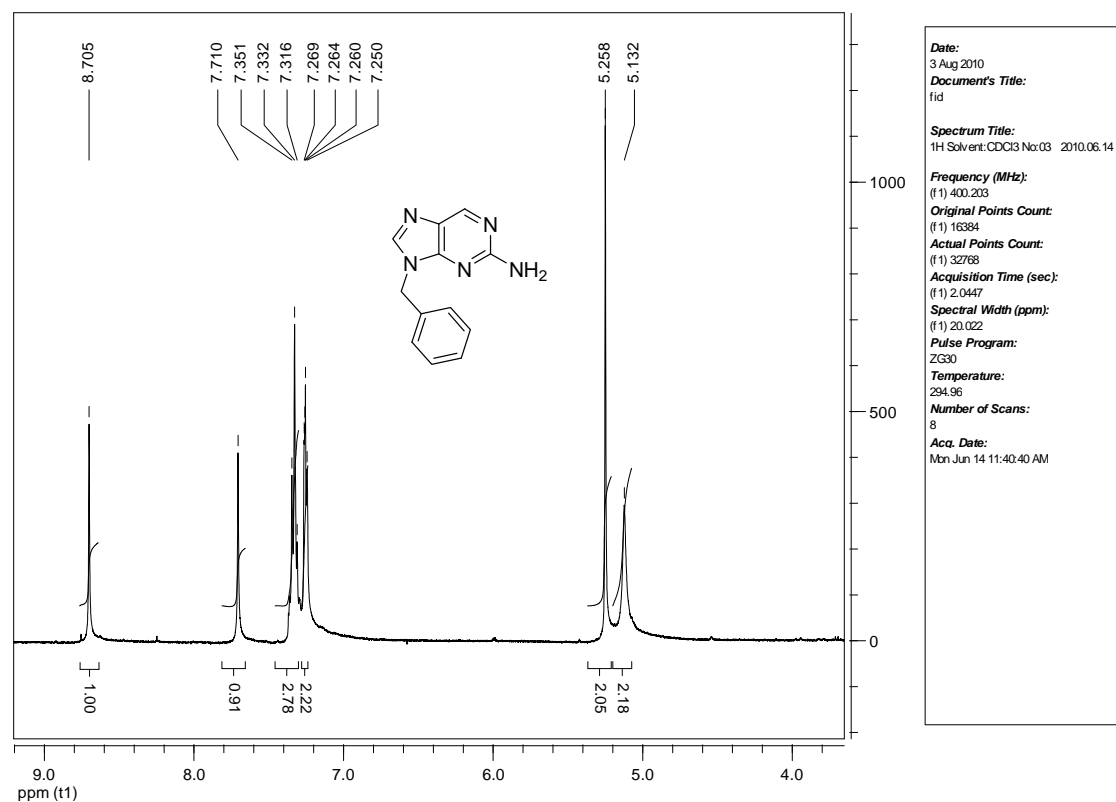
¹H NMR Spectrum for 2m



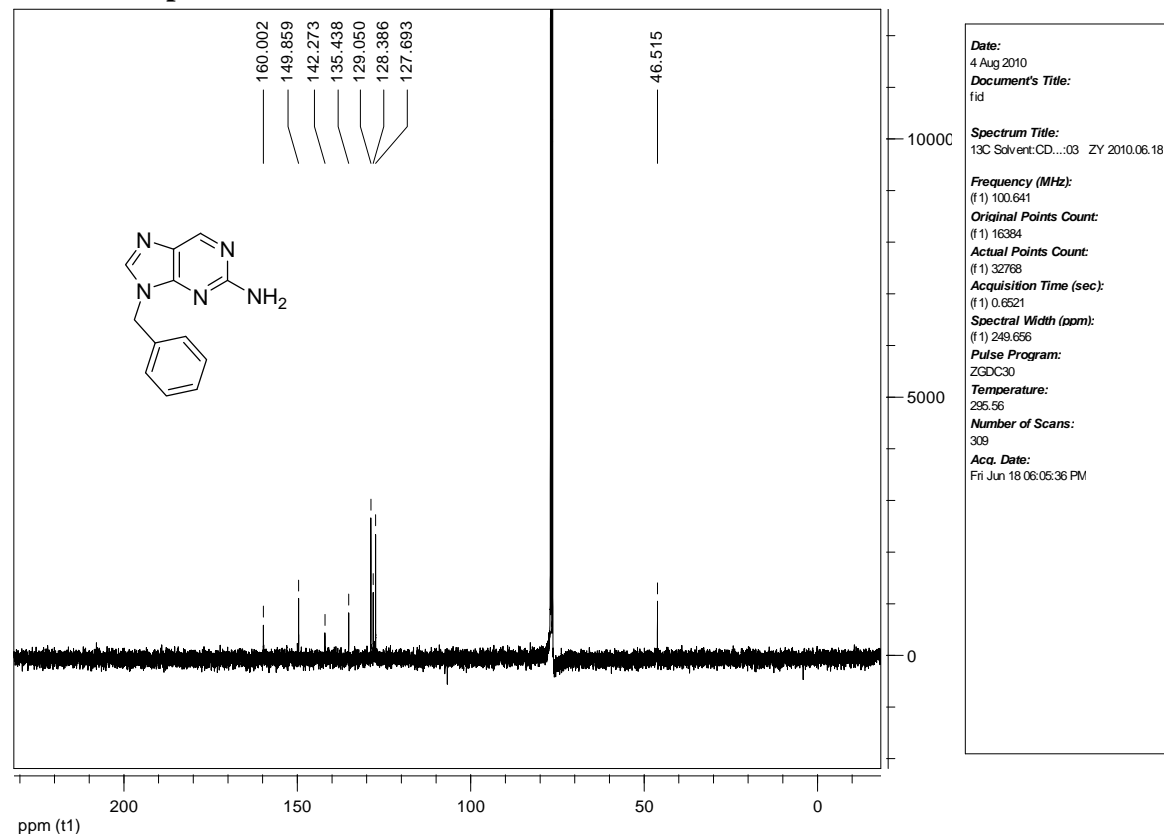
¹³C NMR Spectrum for 2m



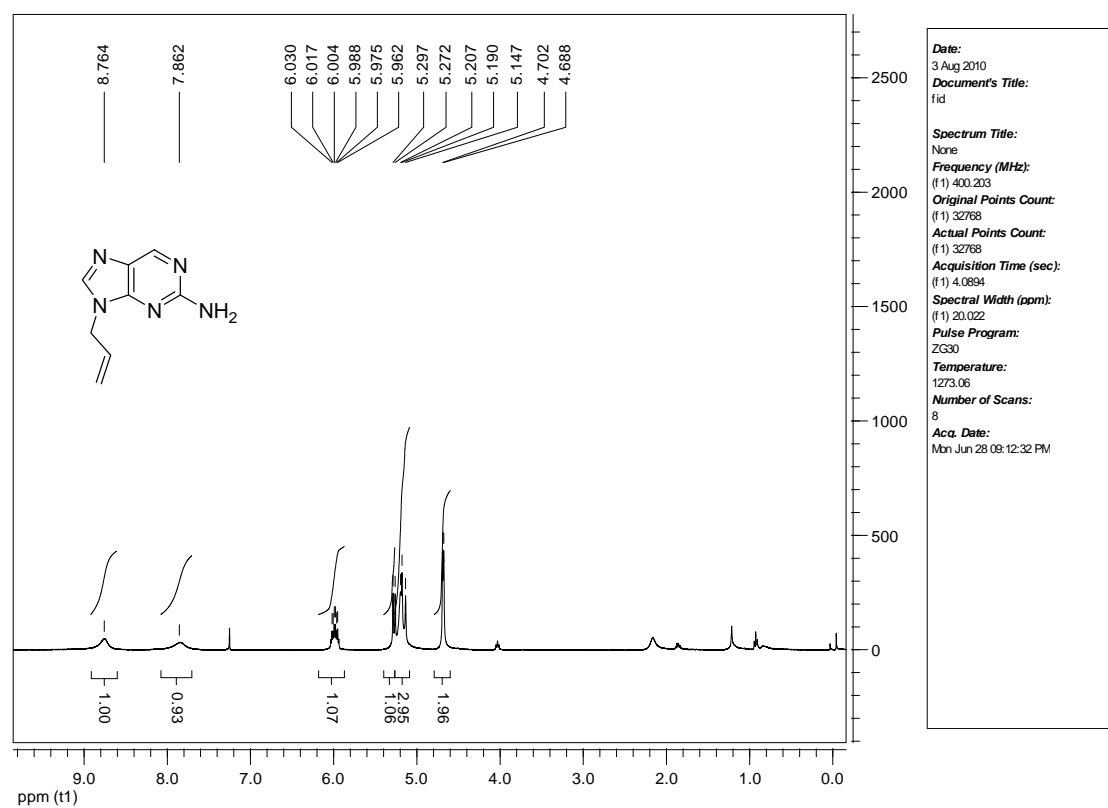
¹H NMR Spectrum for 2n



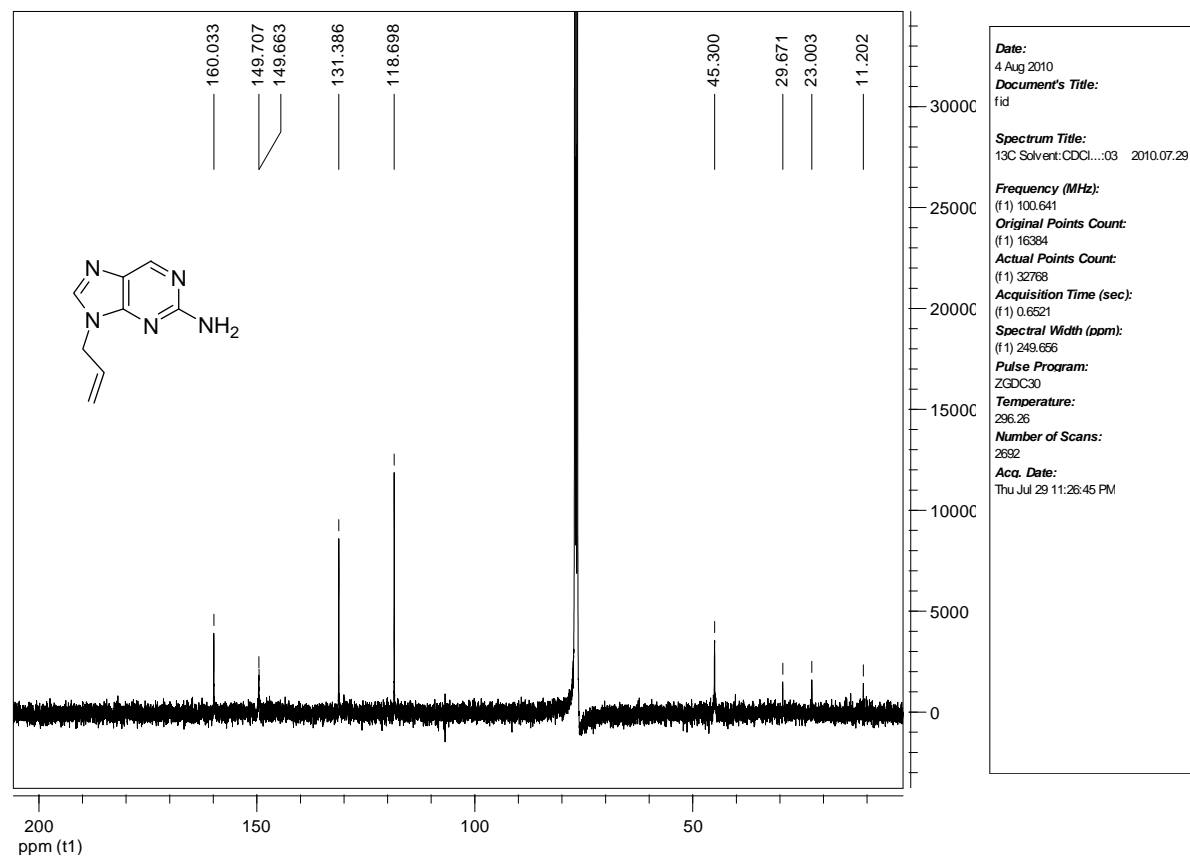
¹³C NMR Spectrum for 2n



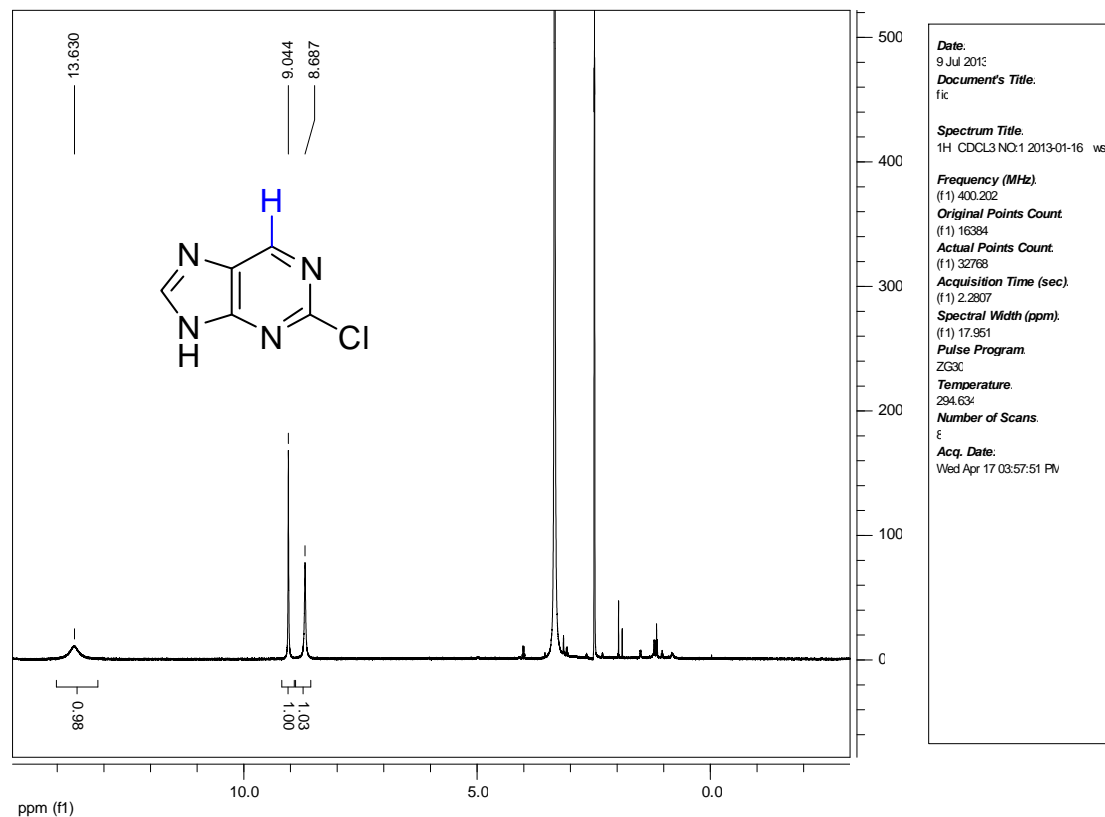
¹H NMR Spectrum for 2o



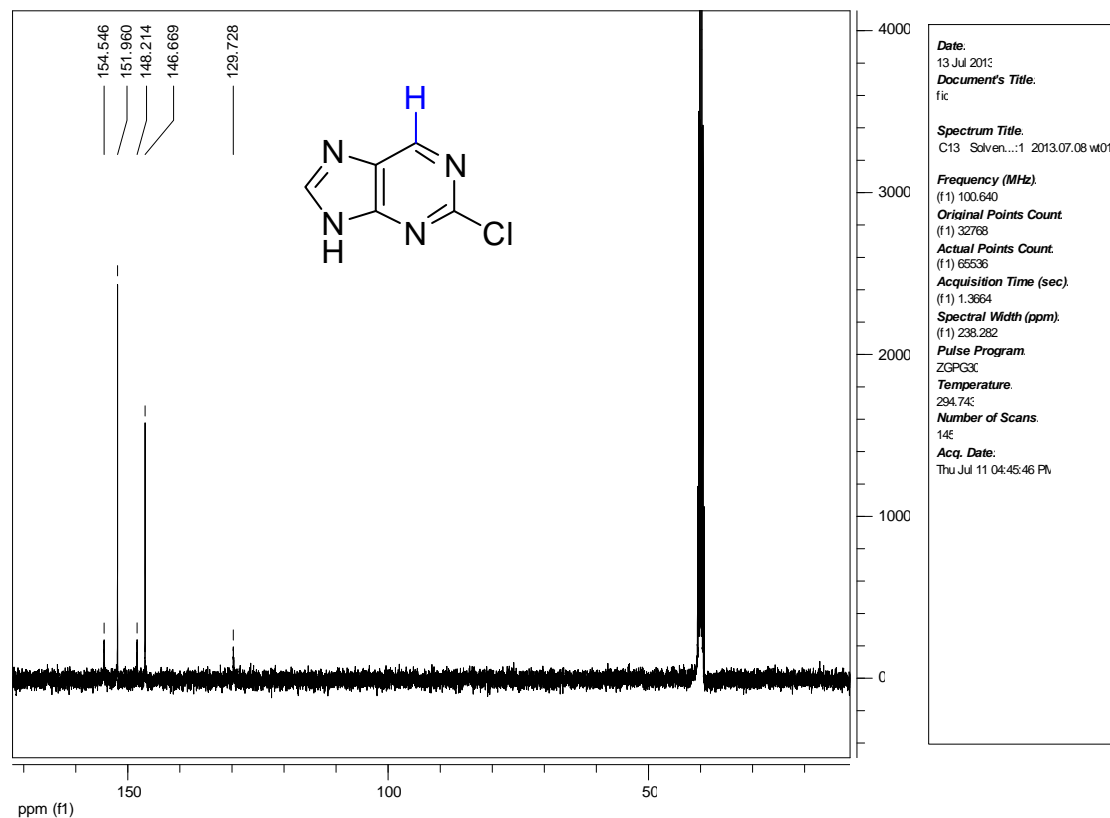
¹³C NMR Spectrum for 2o



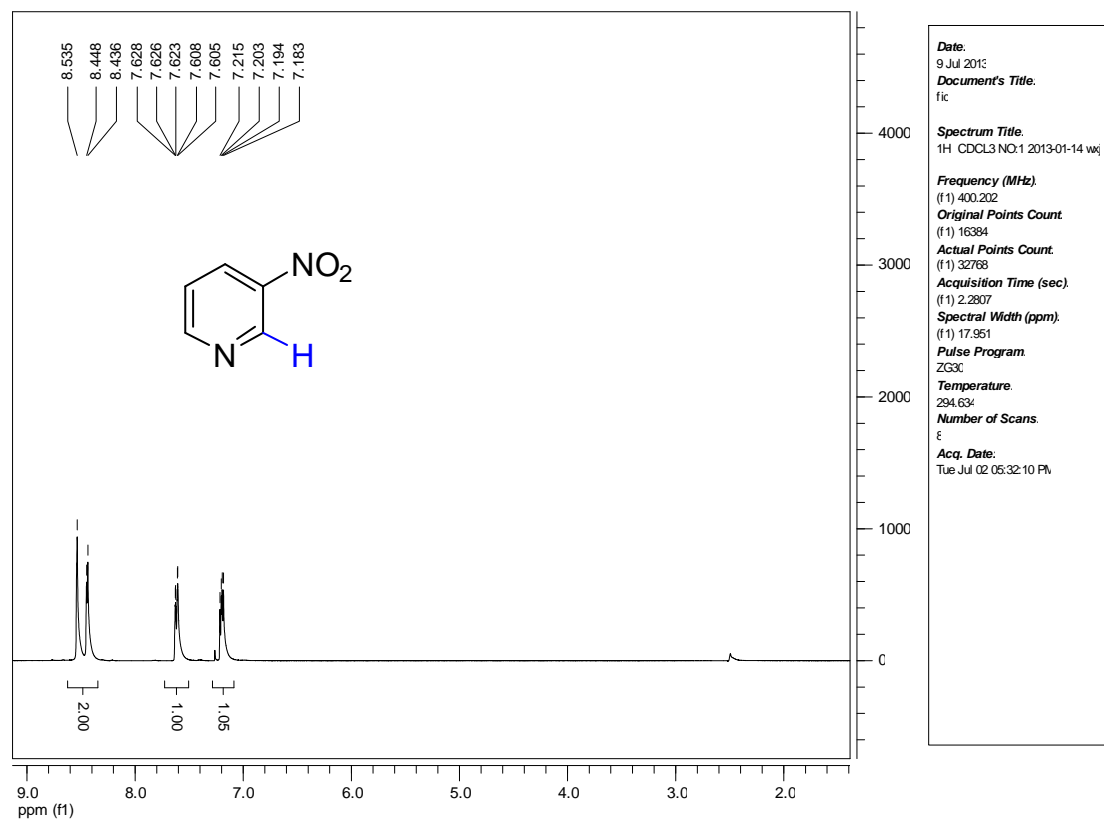
¹H NMR Spectrum for 2p



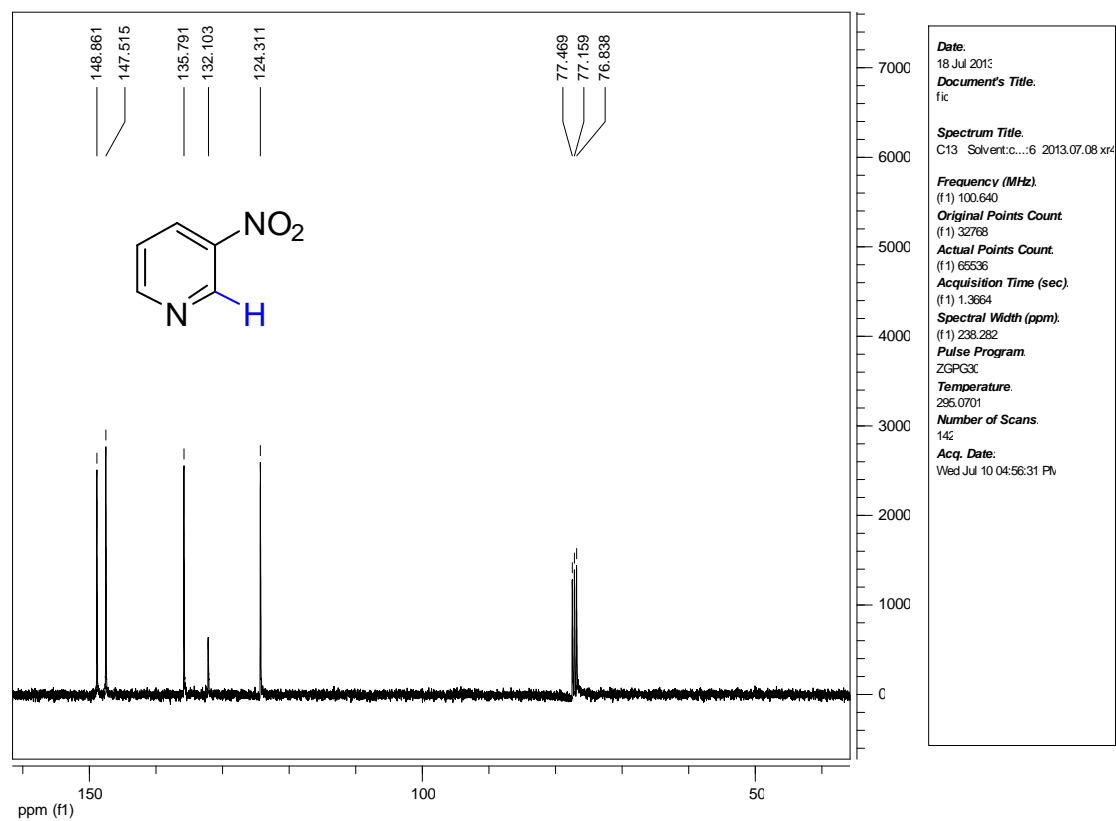
¹³C NMR Spectrum for 2p



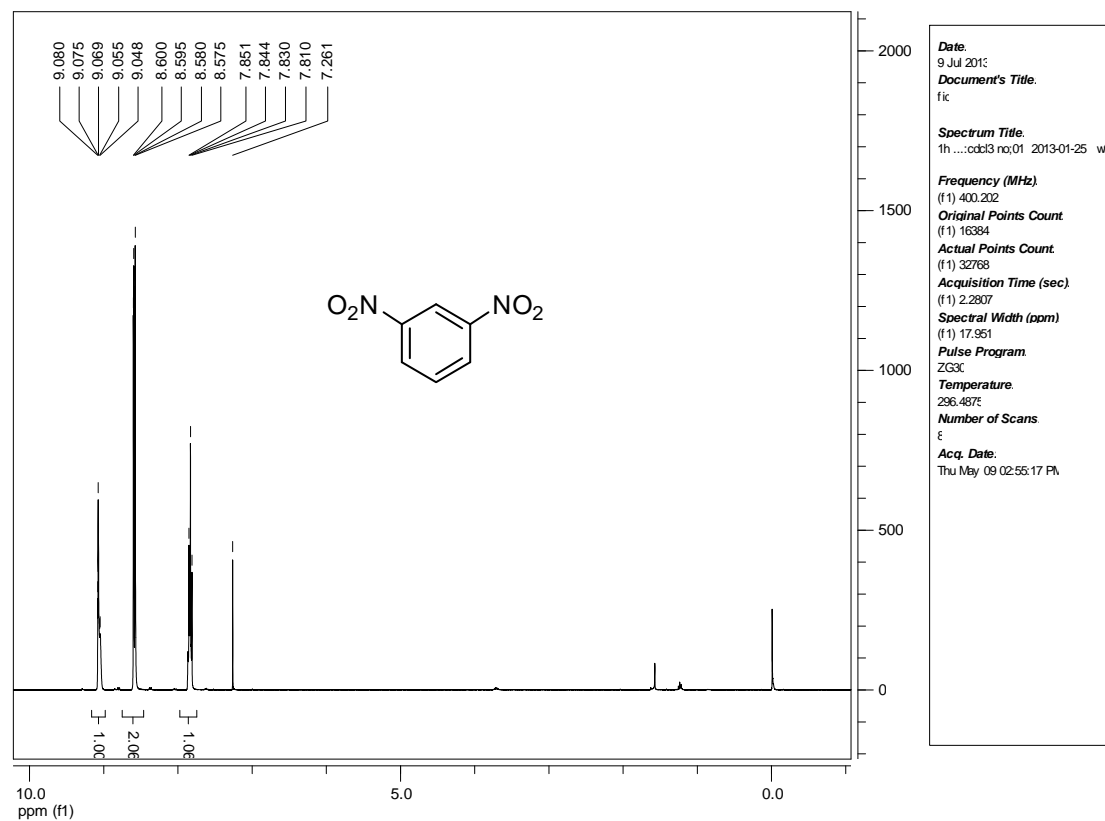
¹H NMR Spectrum for 4a, 4b



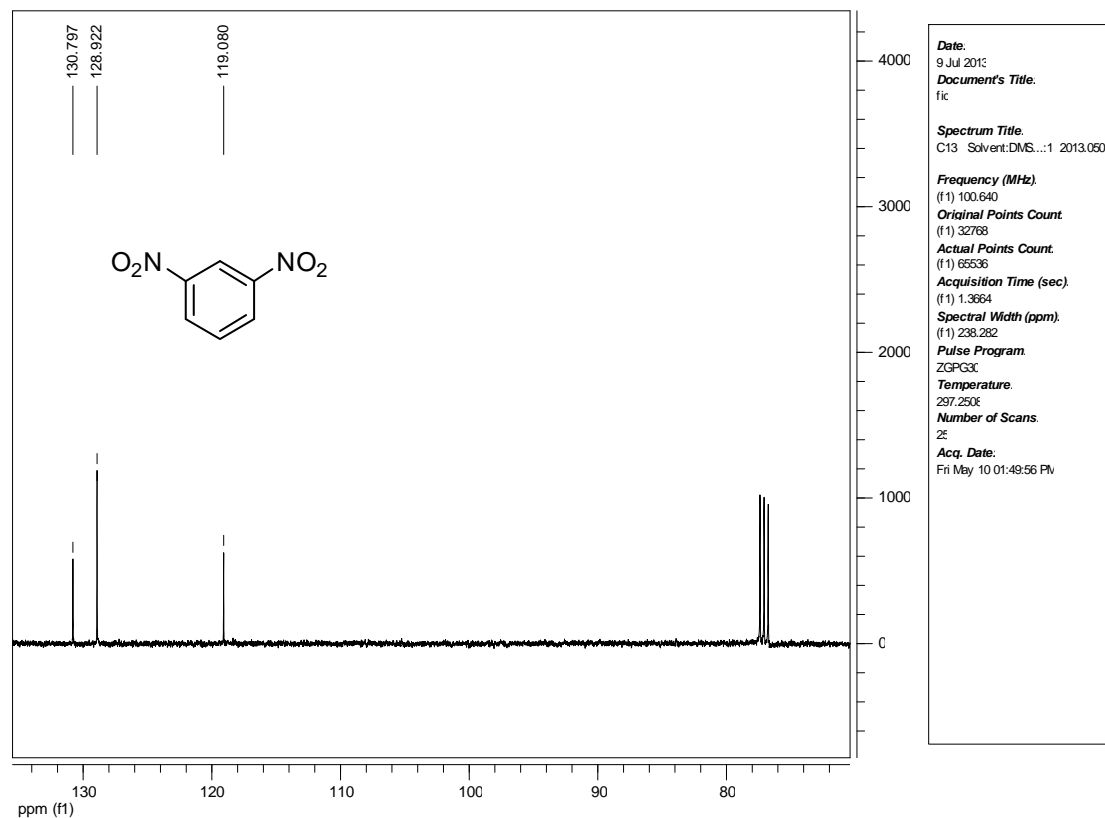
¹³C NMR Spectrum for 4a, 4b



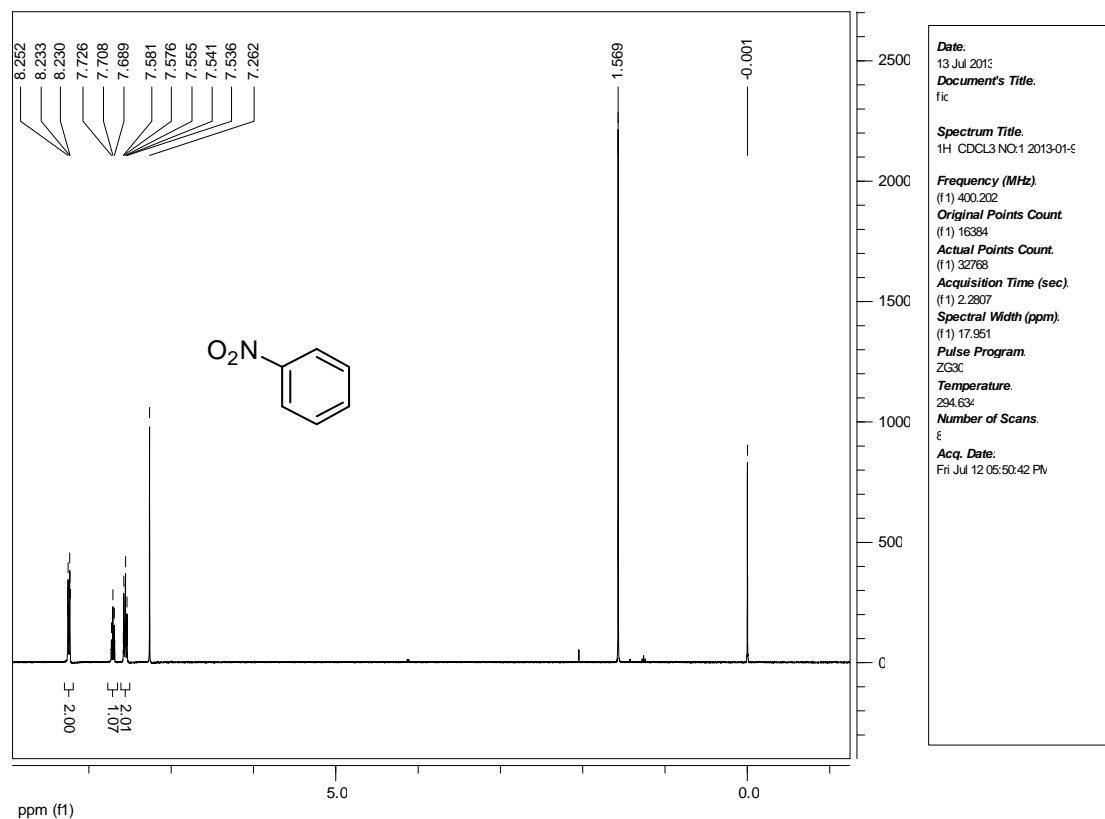
¹H NMR Spectrum for 4c



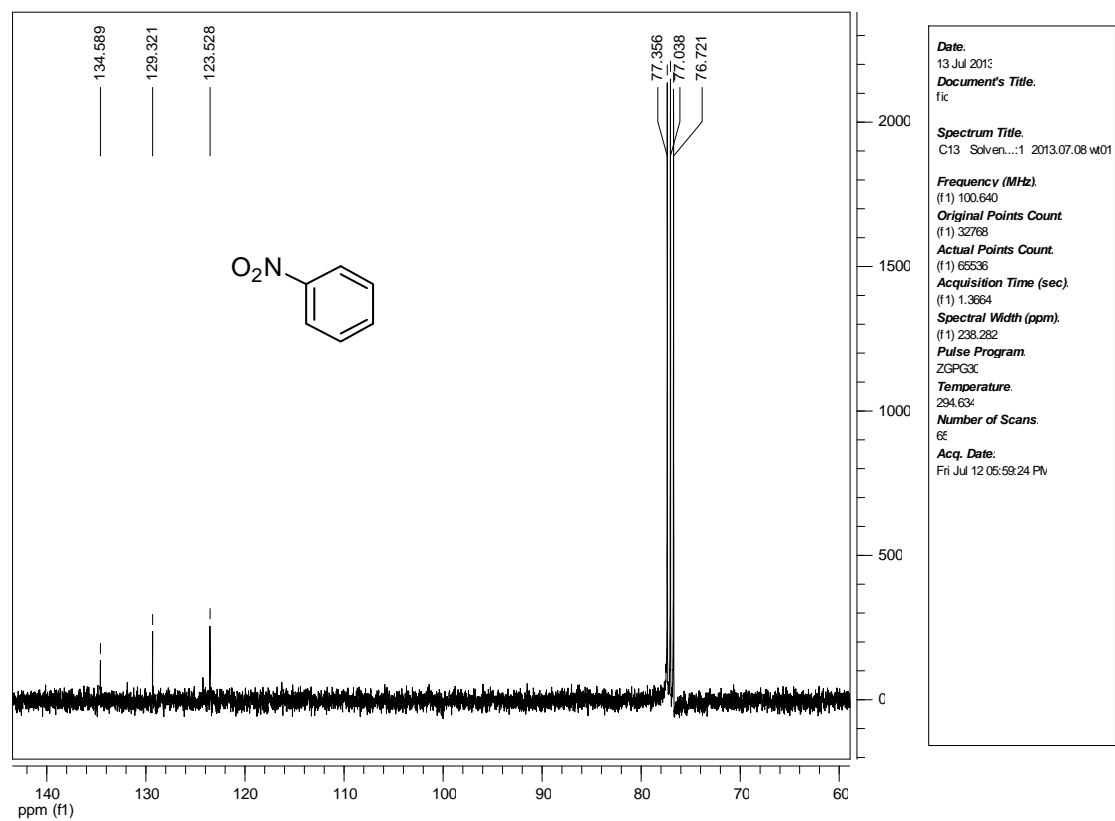
¹³C NMR Spectrum for 4c



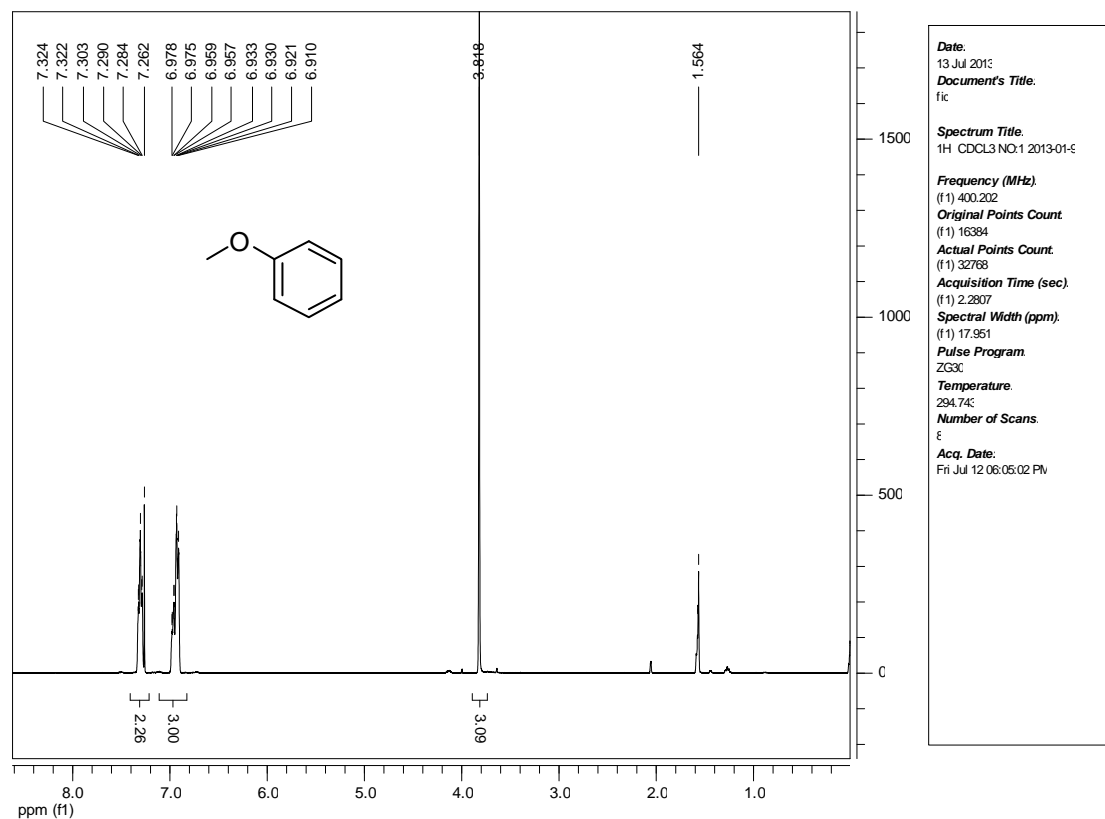
¹H NMR Spectrum for 4d



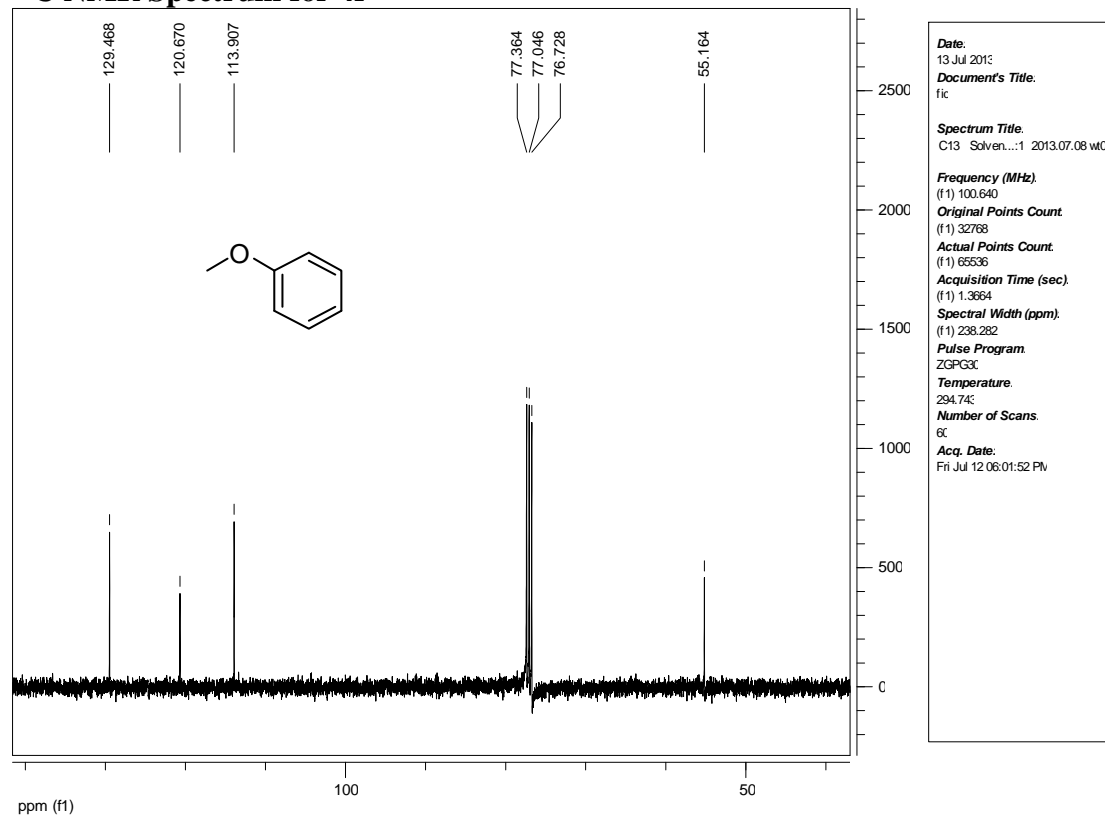
¹³C NMR Spectrum for 4d



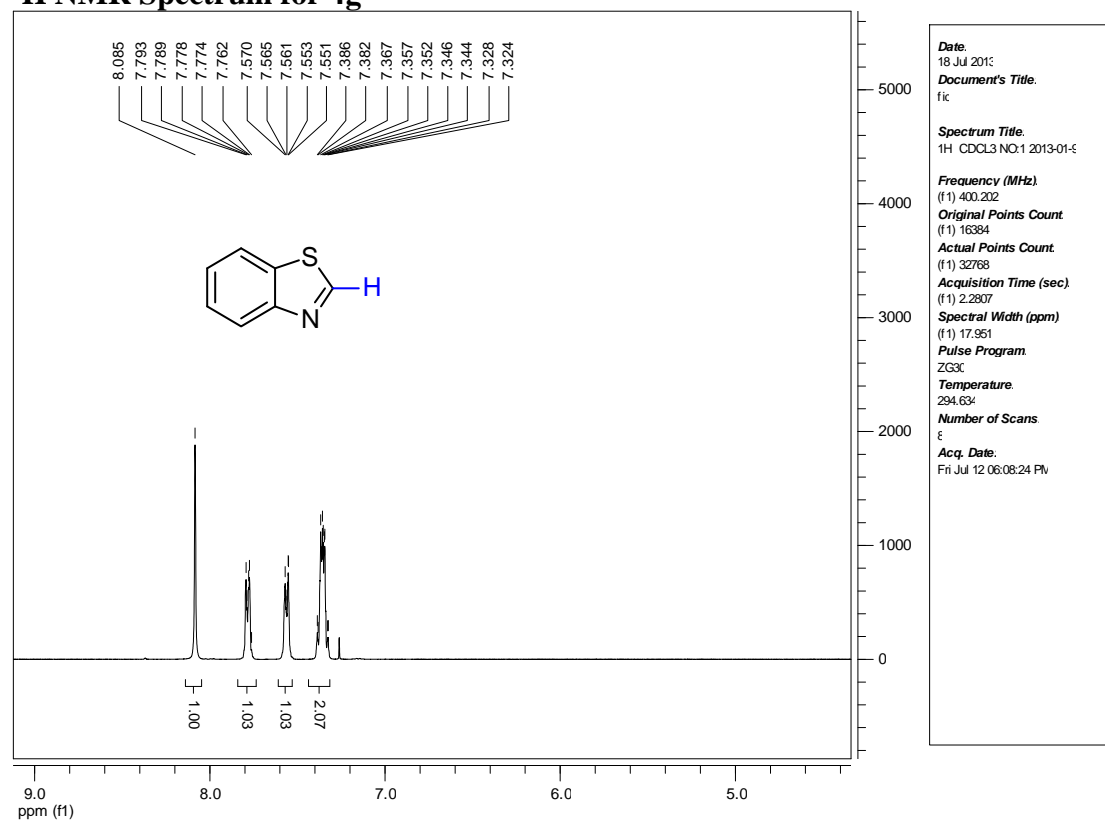
¹H NMR Spectrum for 4f



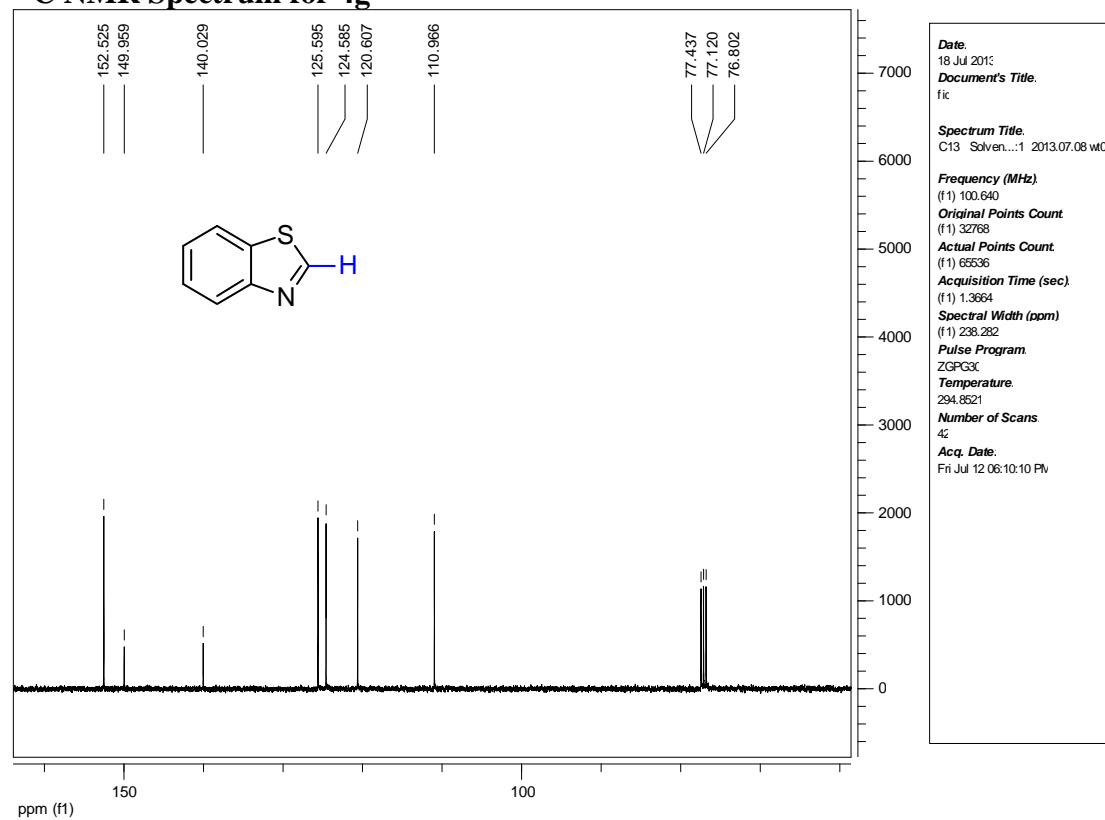
¹³C NMR Spectrum for 4f



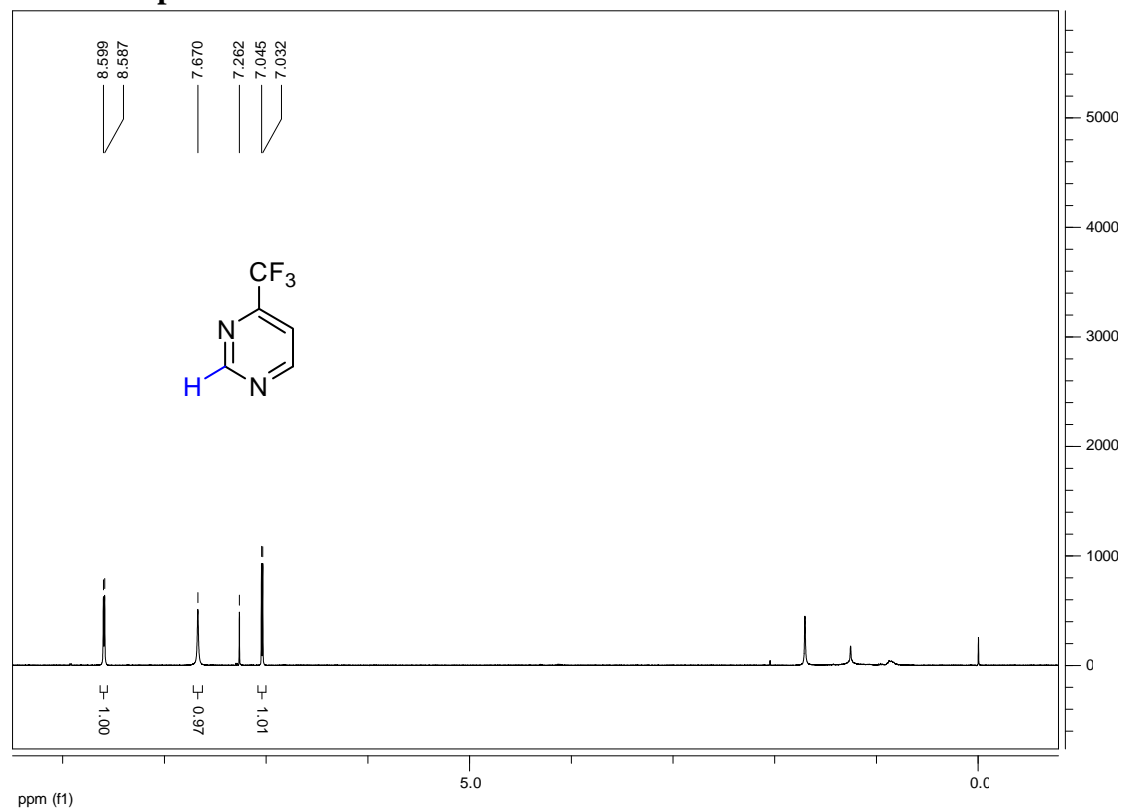
¹H NMR Spectrum for 4g



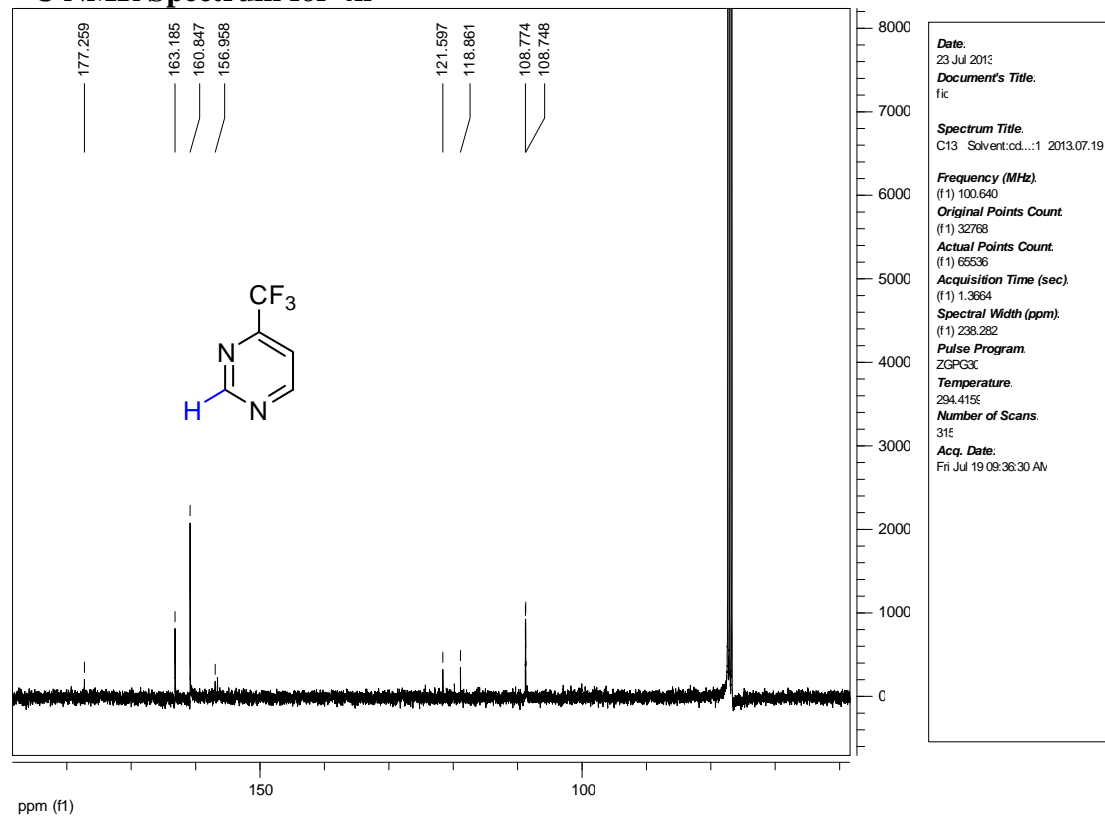
¹³C NMR Spectrum for 4g



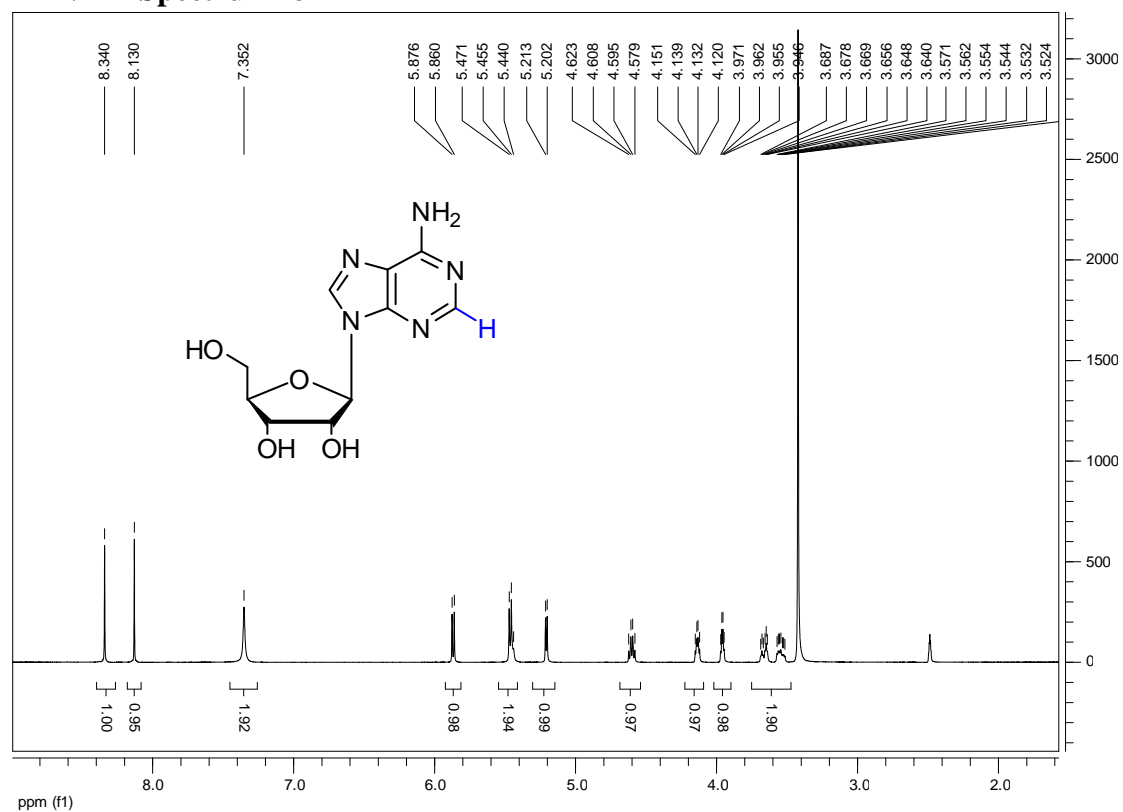
¹H NMR Spectrum for 4h



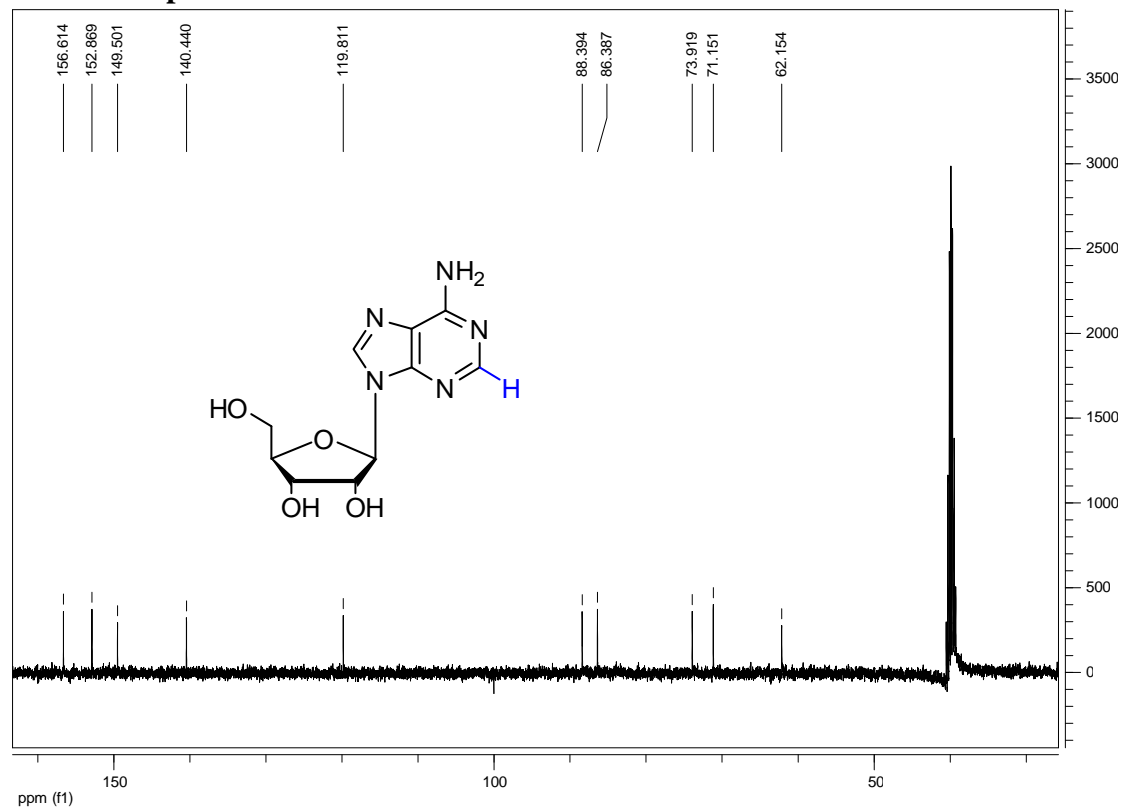
¹³C NMR Spectrum for 4h



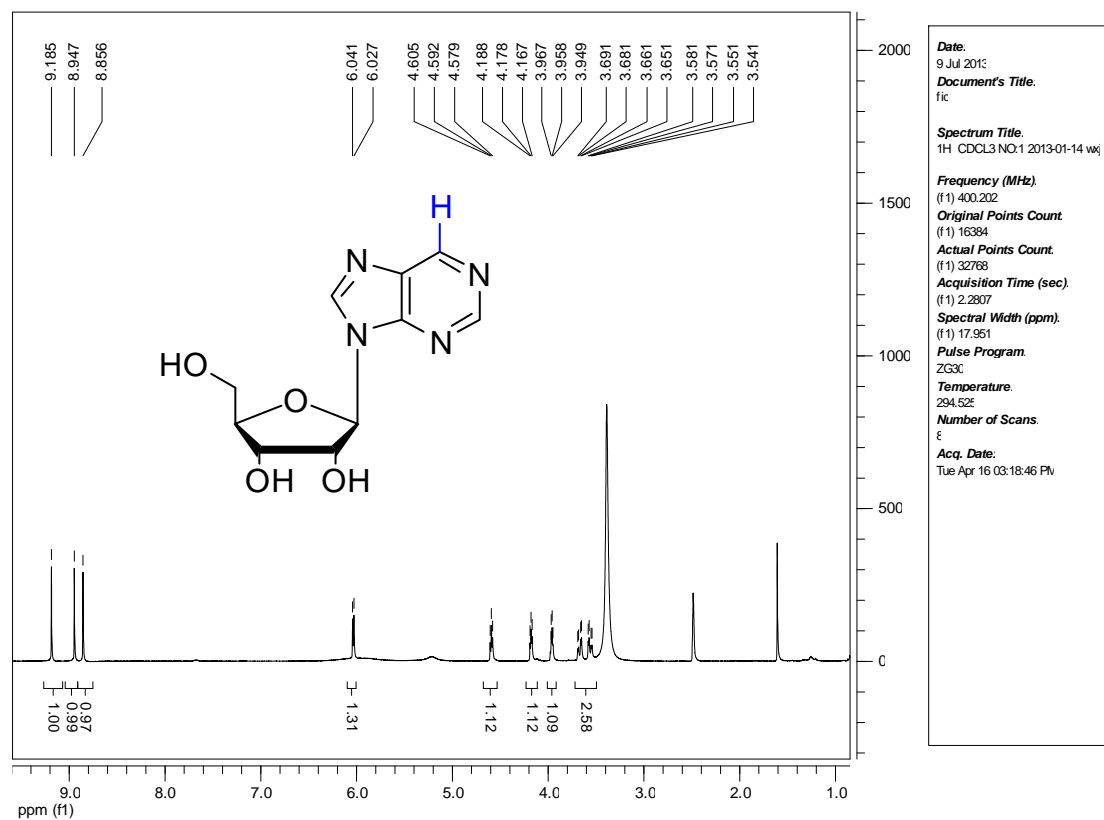
¹H NMR Spectrum for 4i



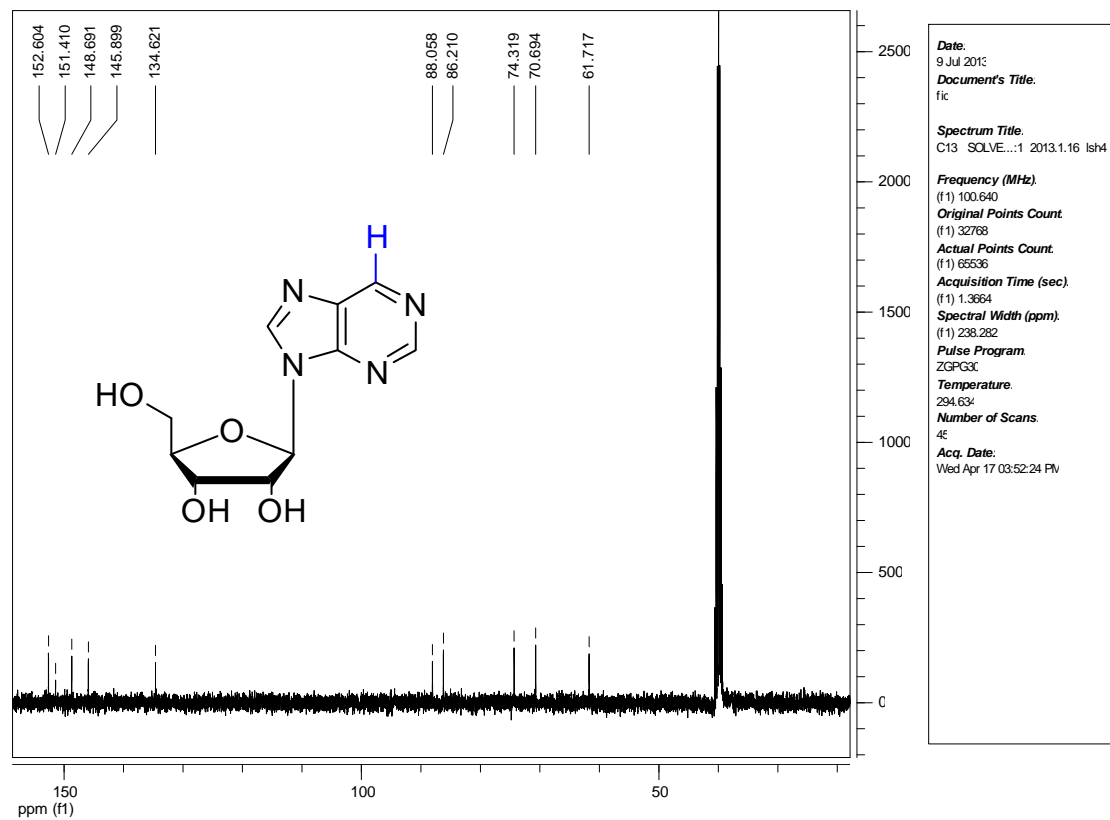
¹³C NMR Spectrum for 4i



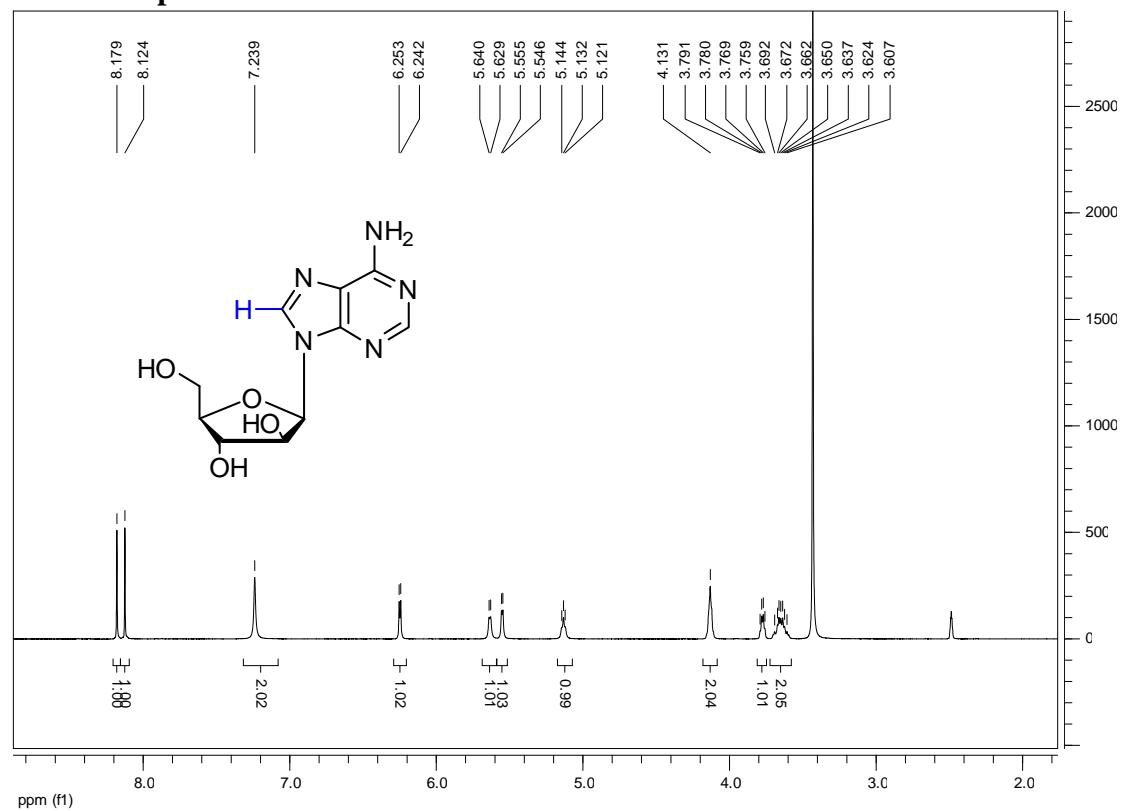
¹H NMR Spectrum for 7



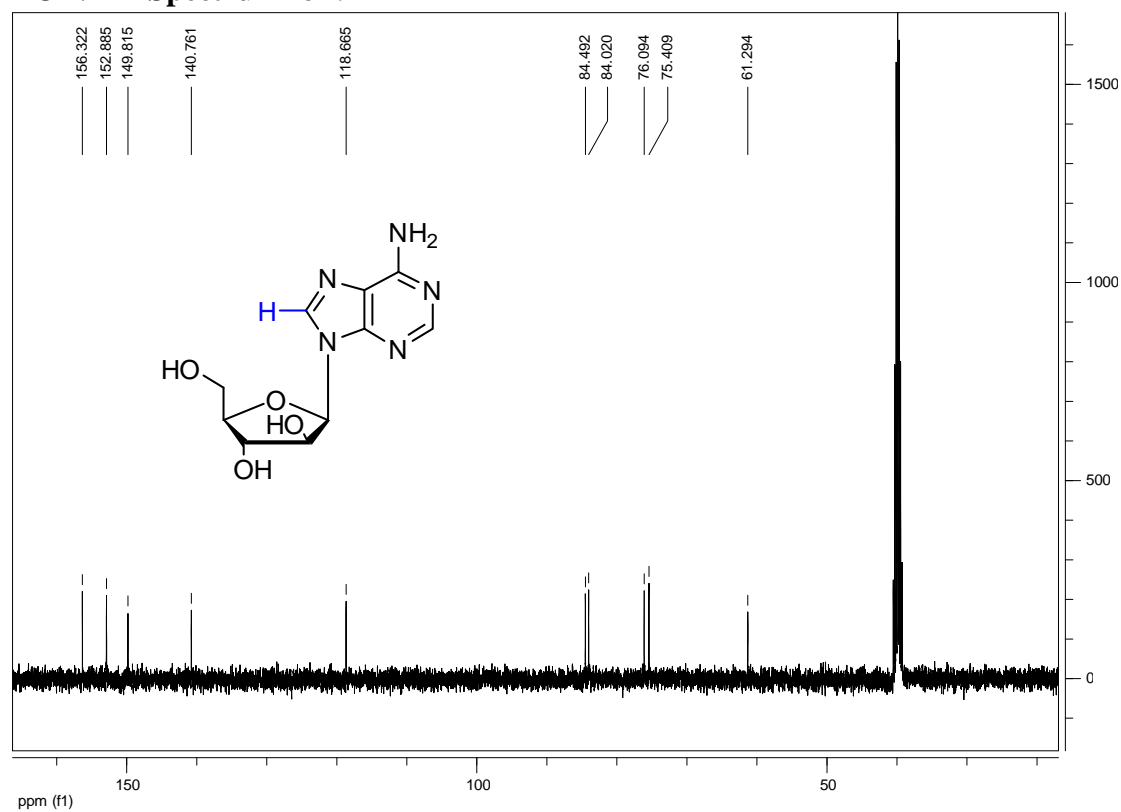
¹³C NMR Spectrum for 7



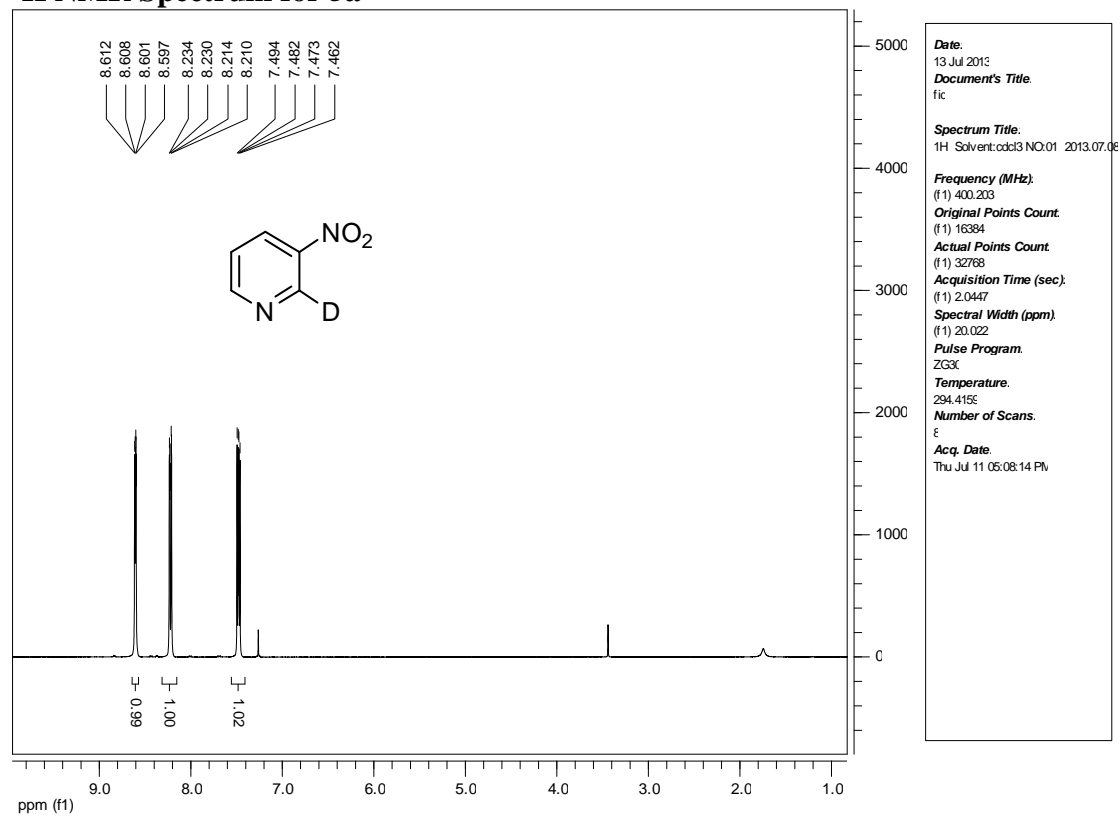
¹H NMR Spectrum for 9



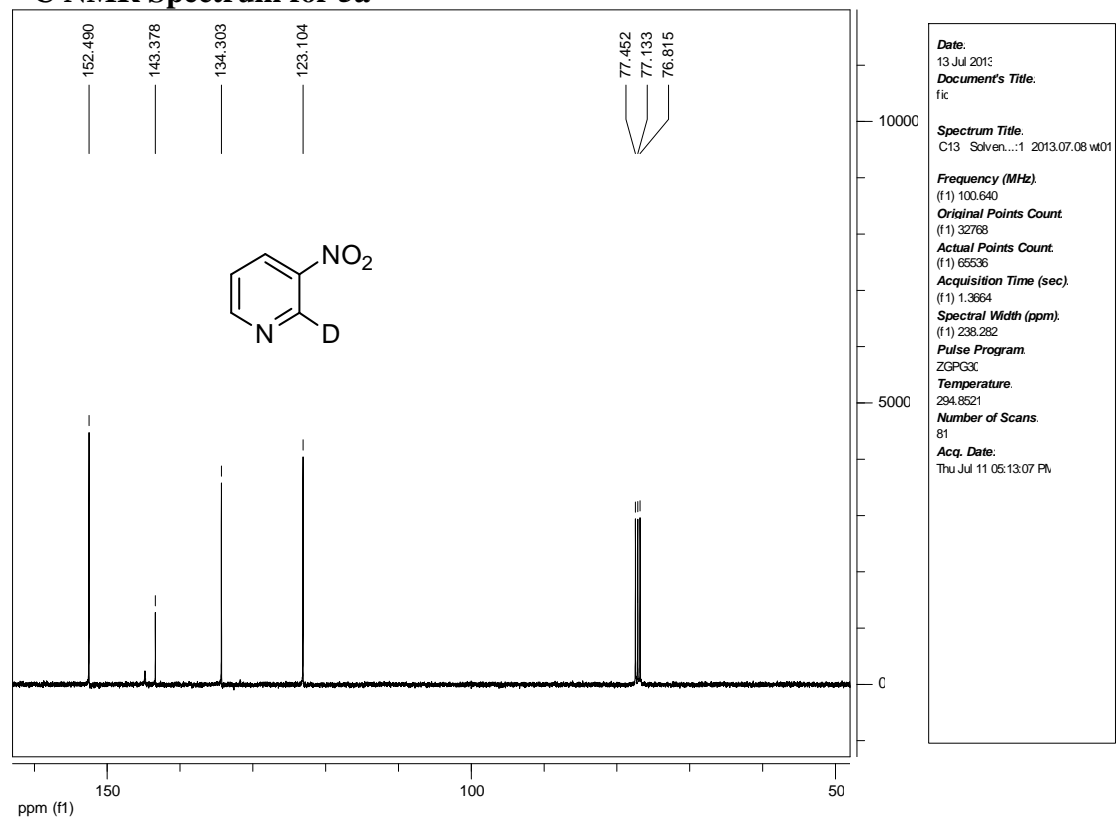
¹³C NMR Spectrum for 9



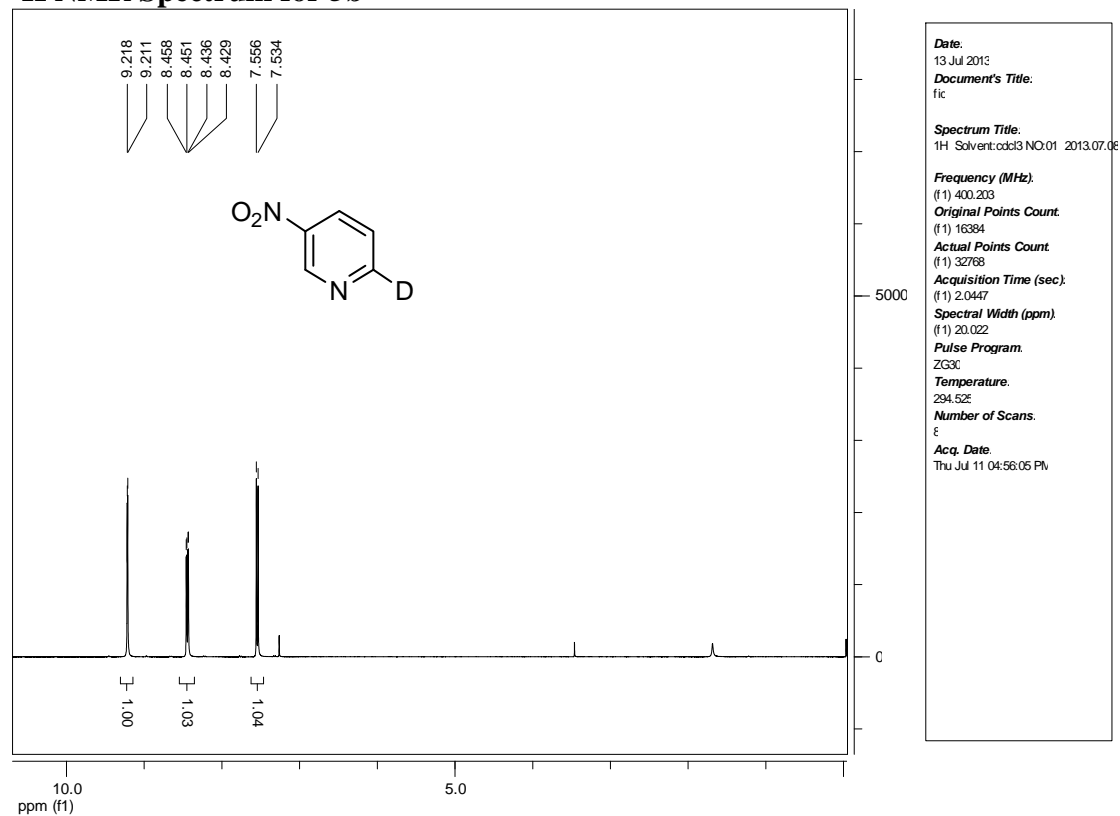
¹H NMR Spectrum for 5a



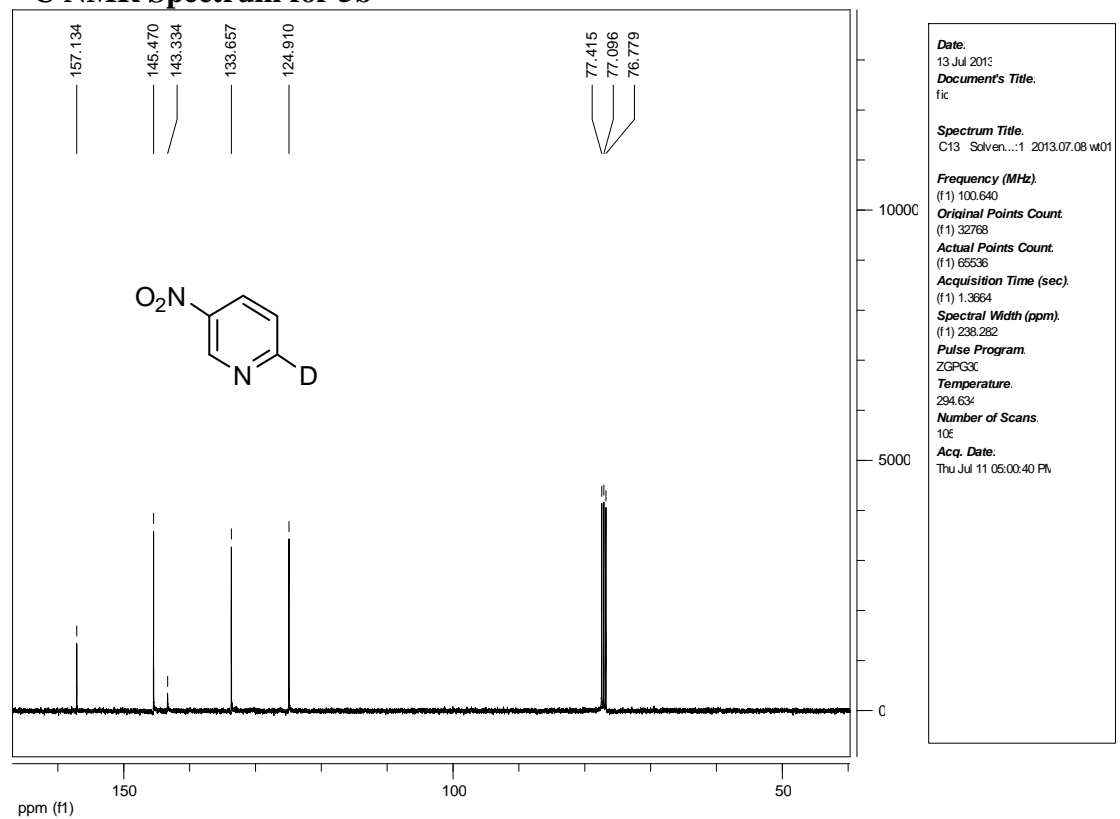
¹³C NMR Spectrum for 5a



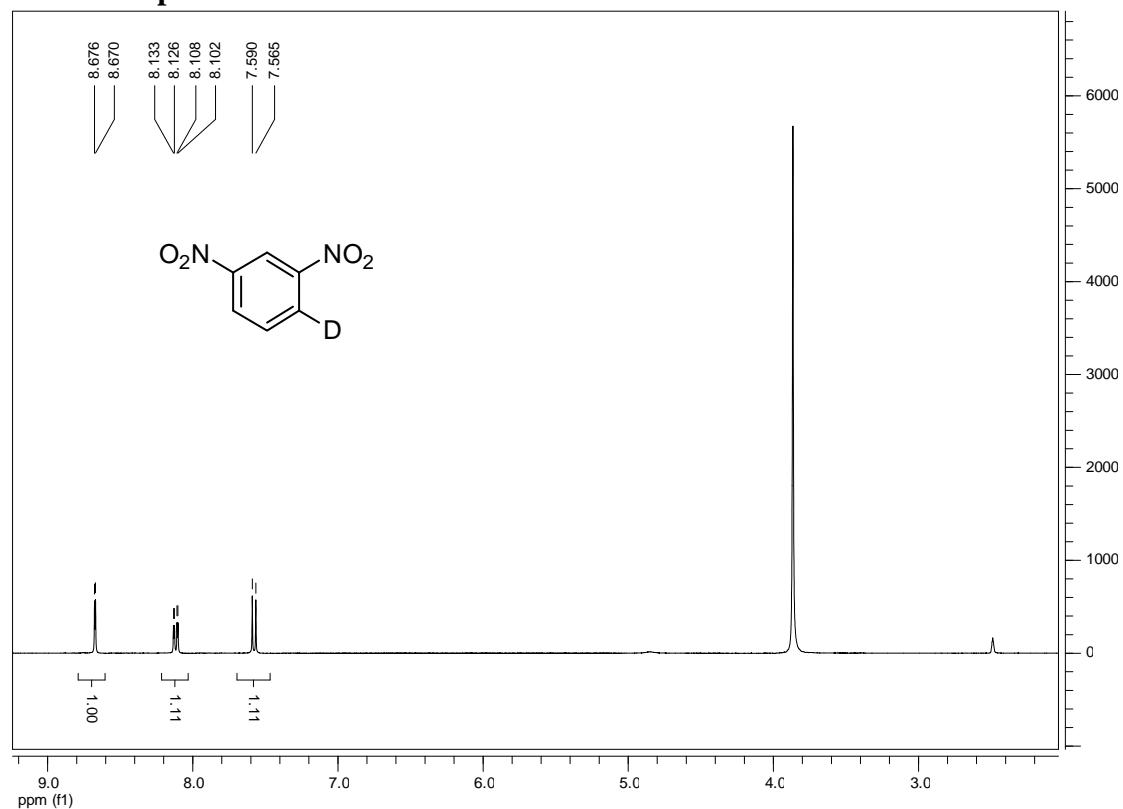
¹H NMR Spectrum for 5b



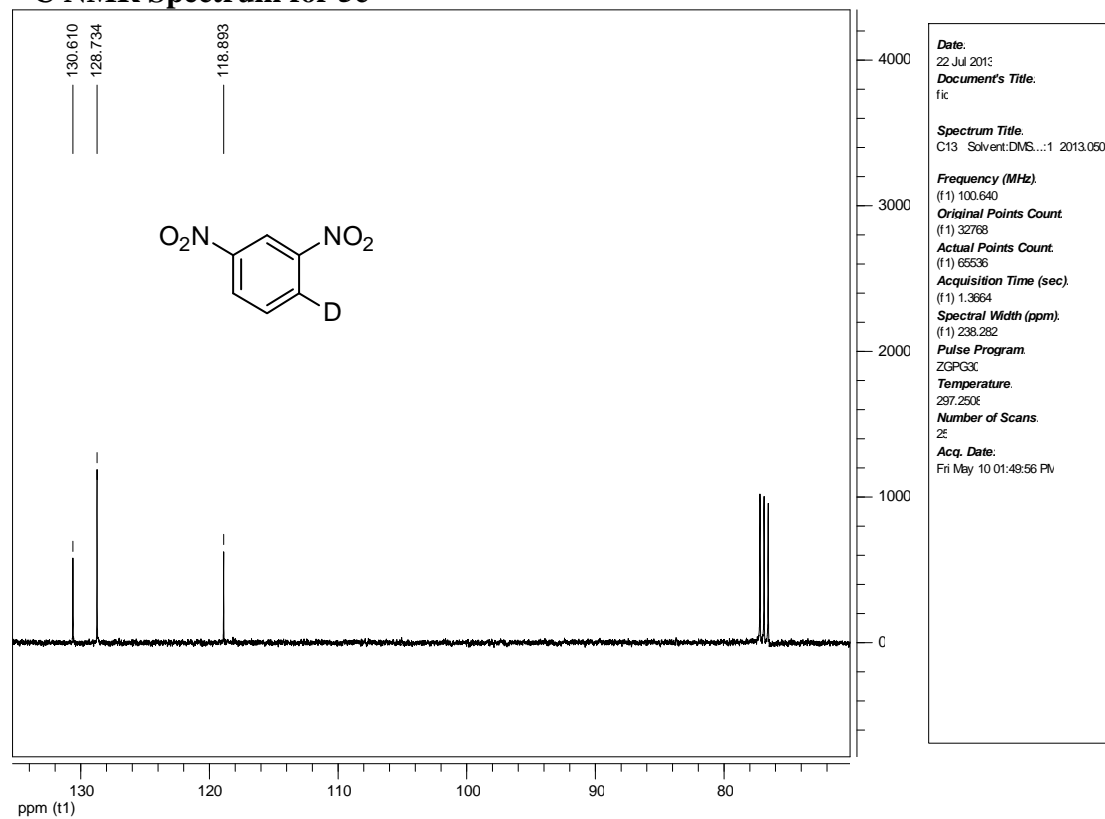
¹³C NMR Spectrum for 5b



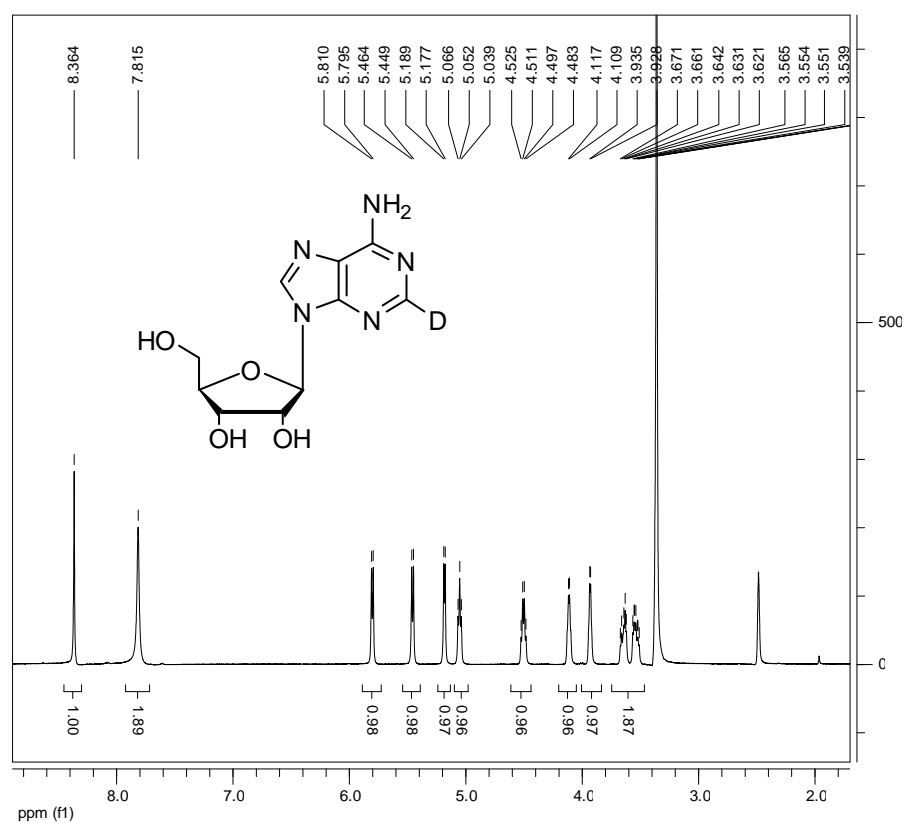
¹H NMR Spectrum for 5c



¹³C NMR Spectrum for 5c

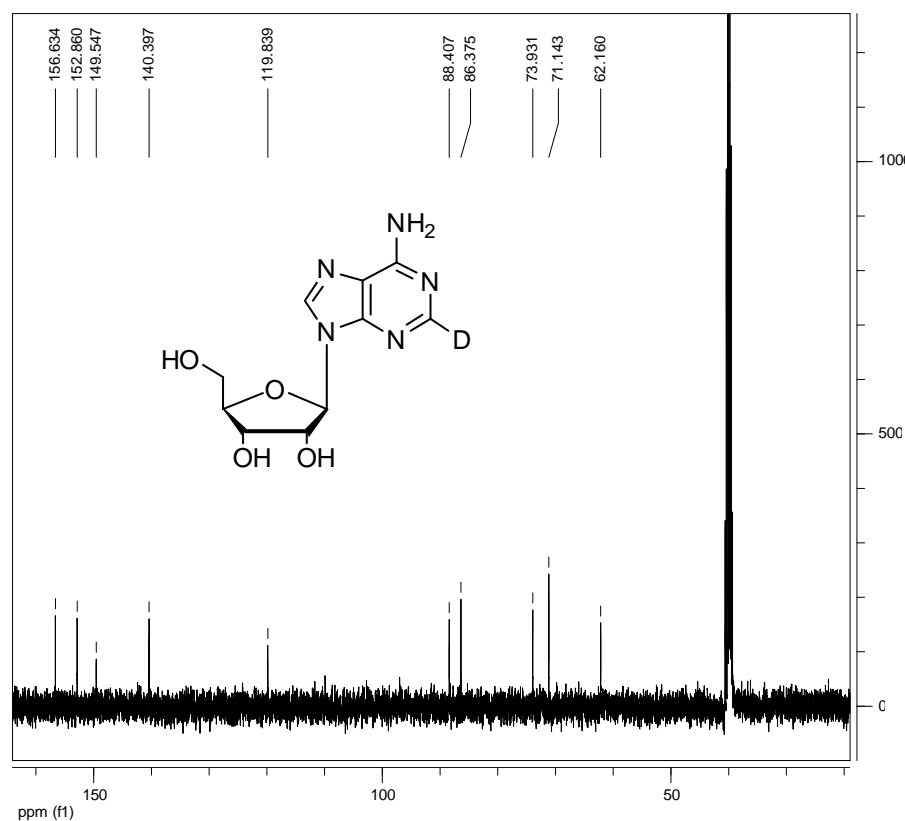


¹H NMR Spectrum for 5d



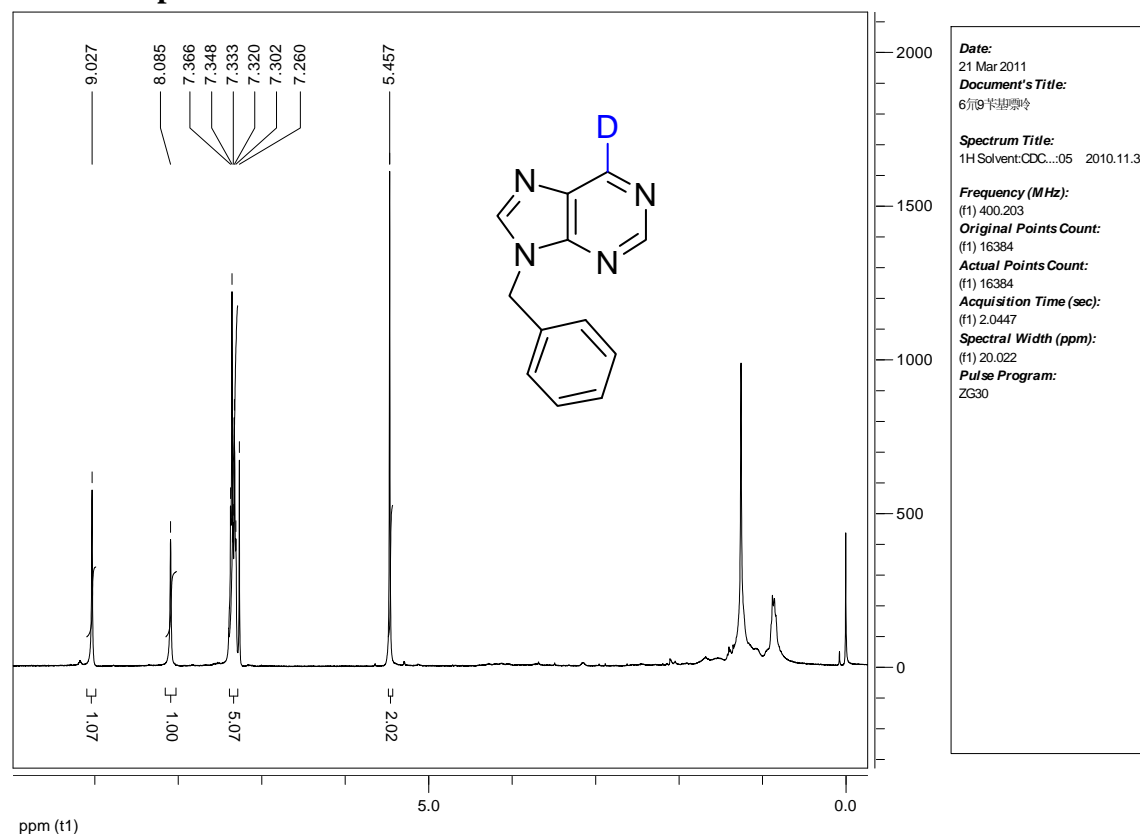
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10 Jul 2013
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Temperature:
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6
Acq. Date:
Fri May 17 05:08:33 PM

¹³C NMR Spectrum for 5d

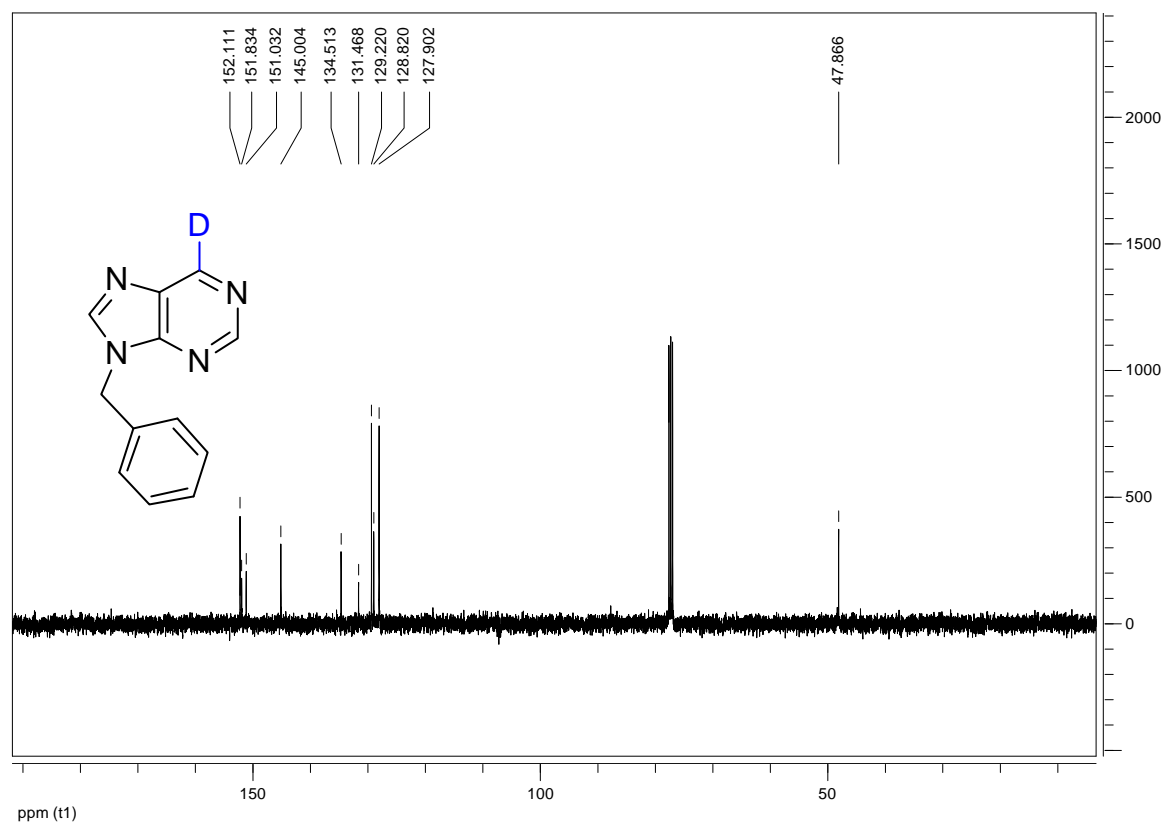


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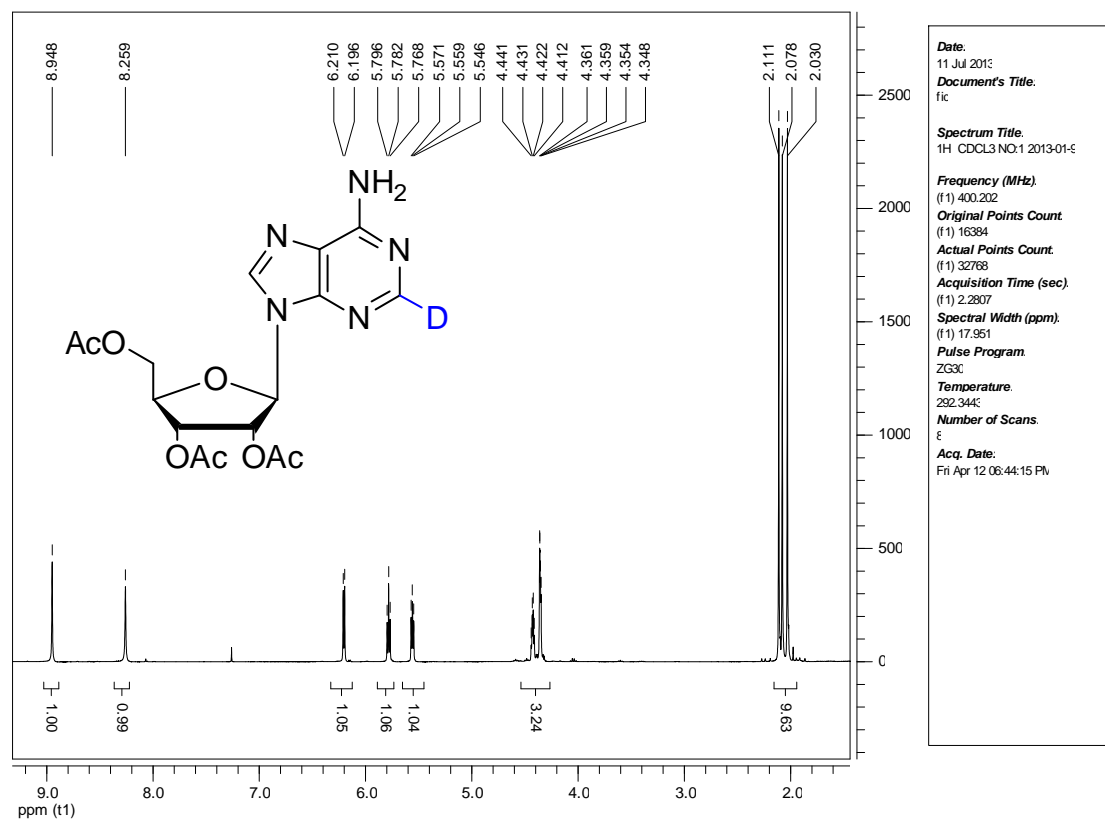
¹H NMR Spectrum for 5e



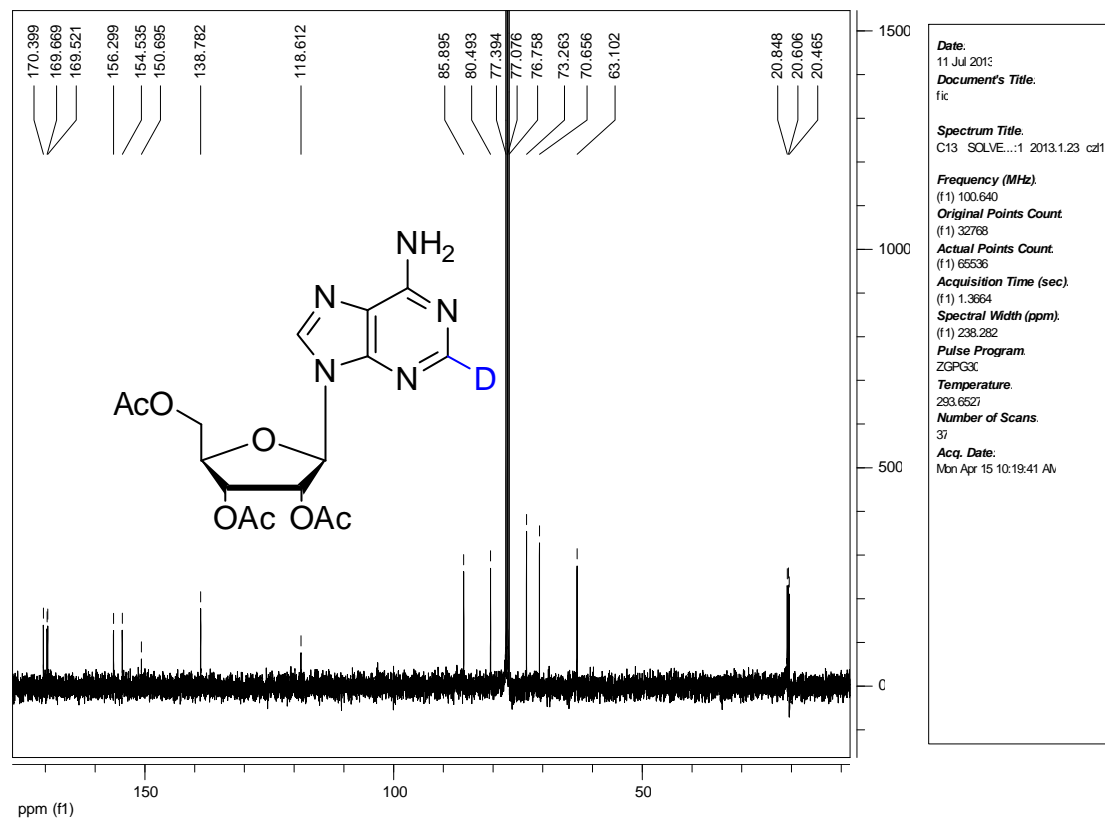
¹³C NMR Spectrum for 5e



¹H NMR Spectrum for 5f



¹³C NMR Spectrum for 5f



¹H NMR Spectrum for 2a-H/D

