Synthesis of Cycloalkyl Substituted Purine Nucleosides via a Metal-Free Radical Route

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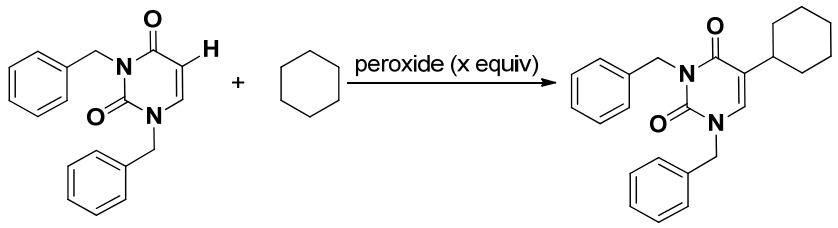
1. General

Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 MHz spectrometer for ^{1}H NMR, 100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to tetramethylsilane as internal standard, residual $CHCl_3$ for ^{1}H or $CDCl_3$ in ^{13}C NMR spectroscopy. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m). High resolution mass spectra are taken using Q-TOF system, with Electrospray Ionization (ESI) as the ionization method used for the HRMS measurement. 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. The optimization of reaction conditions for 5a and 2a.[a,b]



5a **2a** **6a**

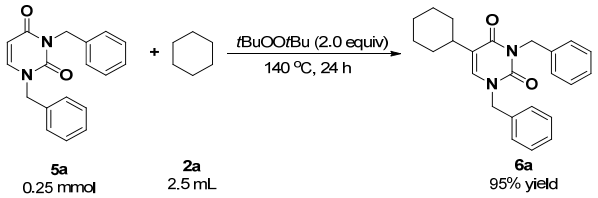
Entry	Peroxide	X [equiv]	T [^{o}C]	Time [h]	Yield [%]
1	*t*BuOO*t*Bu	1.0	reflux	12	0
2	*t*BuOO*t*Bu	1.0	100	12	0
3	*t*BuOO*t*Bu	1.0	120	12	36
4	*t*BuOO*t*Bu	1.0	140	12	55
5	*t*BuOO*t*Bu	1.0	140	24	63
6	***t*BuOO*t*Bu**	**2.0**	**140**	**24**	**95**
7[c]	*t*BuOOH	2.0	140	24	trace
8	dicumyl peroxide	2.0	140	24	81
9[d]	*t*BuOO*t*Bu	2.0	140	24	trace

[a] Unless otherwise mentioned, all of the reactions were carried out with **5a** (0.25 mmol) and **2a** (2.5 mL) under air; [b] The yield referred to isolated yield based on substrate **5a**; [c] 70% Aqueous solution; [d] Toluene (1.0 mL) was added.

3. Typical procedures

(1) The reaction of 1,3-dibenzyluracil (6a) with cyclohexane (2a):

A reaction vessel was charged with 1,3-dibenzyluracil (**5a**, 73 mg, 0.25 mmol), *t*BuOO*t*Bu (0.095 mL, 0.5 mmol) and cyclohexane (2.5 mL). Then, the reaction vessel was sealed and the resulting solution was stirred at 140 ^{o}C for 24 h. After cooling to room temperature, the resulting mixture was removed in vacuo and the residue was purified by column chromatography (SiO_2, petroether/ethyl acetate = 8:1) to give **6a** with 95% yield.



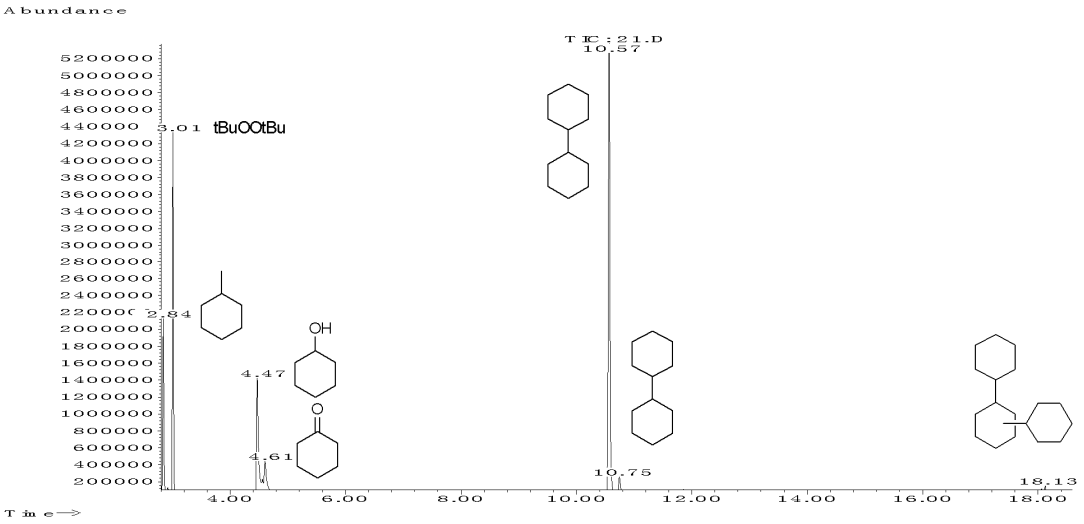
Scheme S1

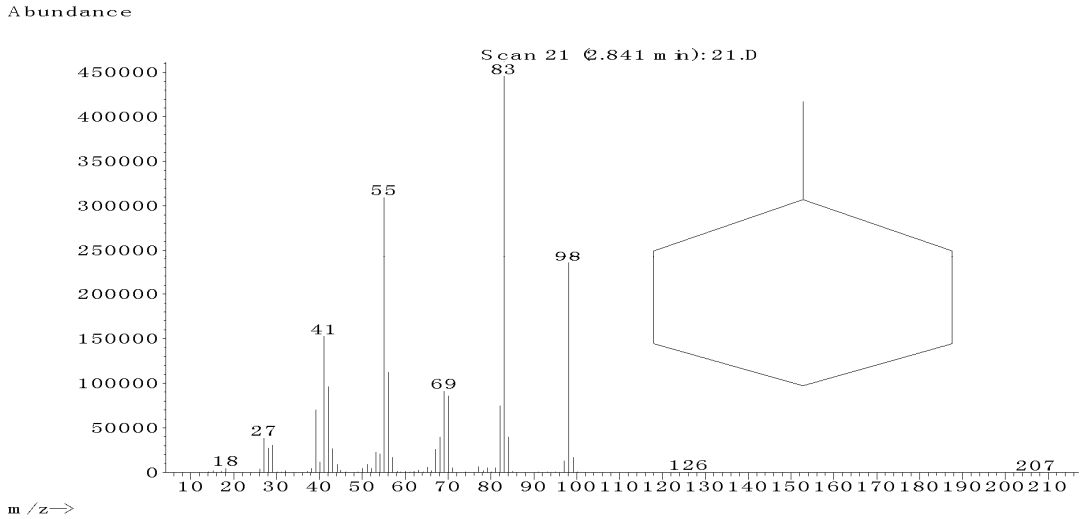
(2) The kinetic isotope effect (KIE) experiment:

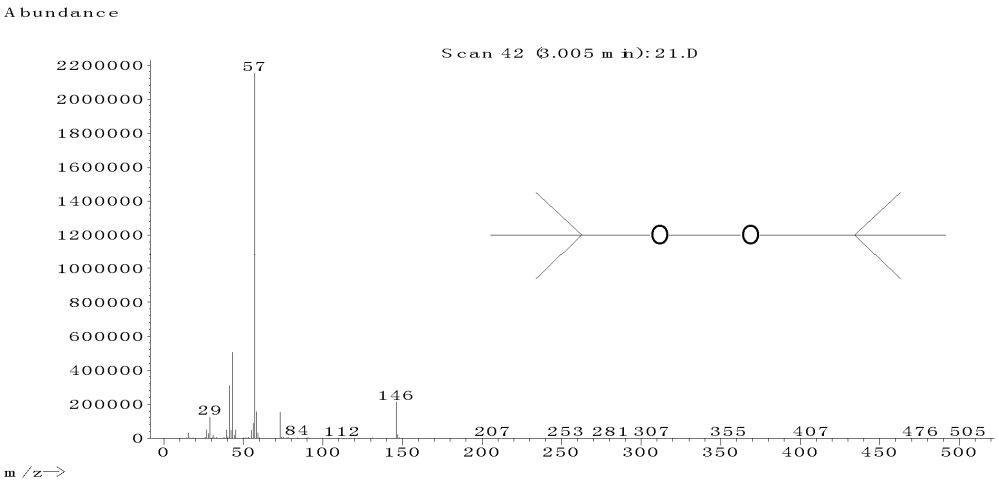
A reaction vessel was charged with 1,3-dibenzyluracil (**5a**, 73 mg, 0.25 mmol), *t*BuOO*t*Bu (0.095 mL, 0.5 mmol), cyclohexane (1.25 mL) and [D_{12}]-cyclohexane (1.25 mL). Then the reaction vessel was sealed and the resulting solution was stirred at 140 ^{o}C for 24 h. After cooling to room temperature, the resulting mixture was removed in vacuo and the residue was purified by column chromatography (SiO_2, petroether/ethyl acetate = 8:1) to give **6a**/[D_{11}]-**6a** with 90% yield.

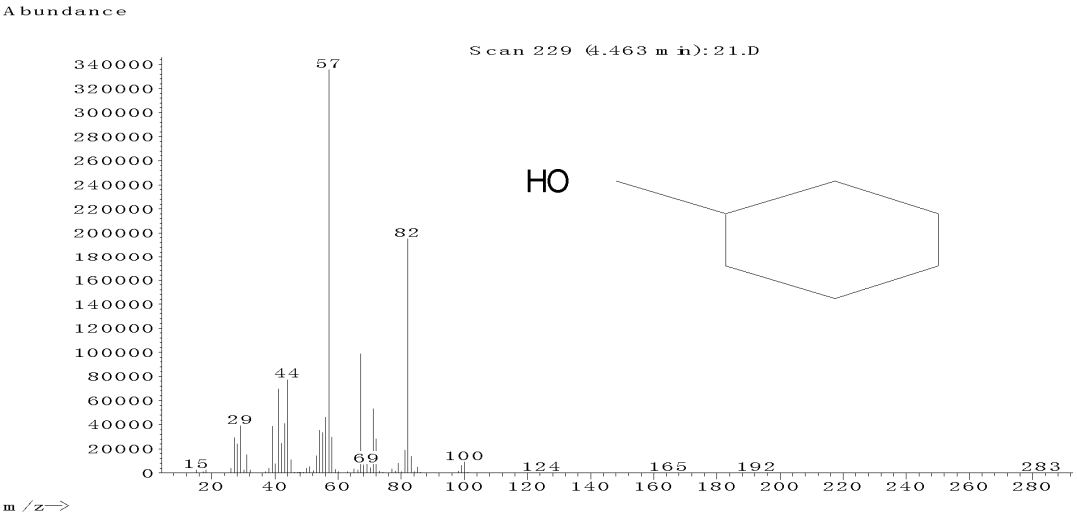
4. Mechanism study

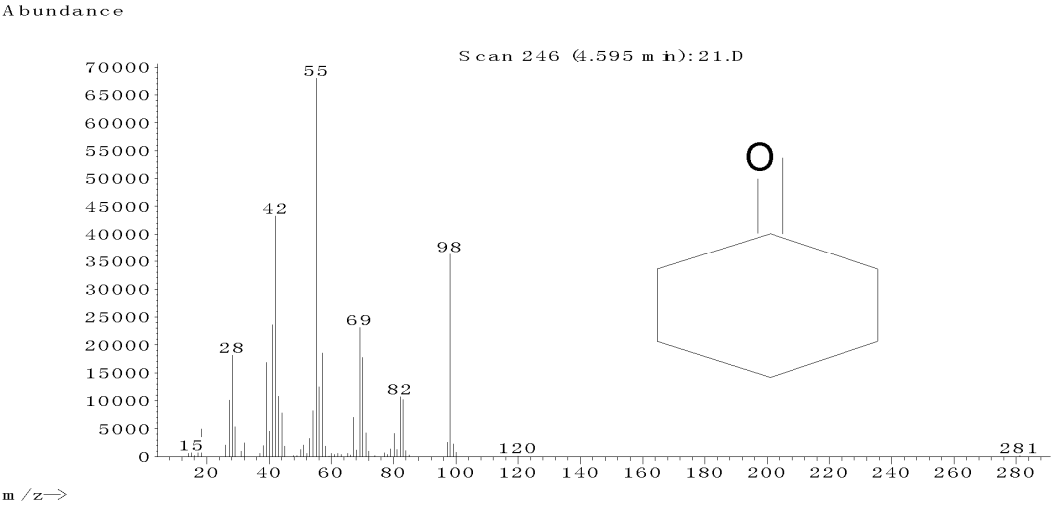
(1). GC-MS of 1a with 2a

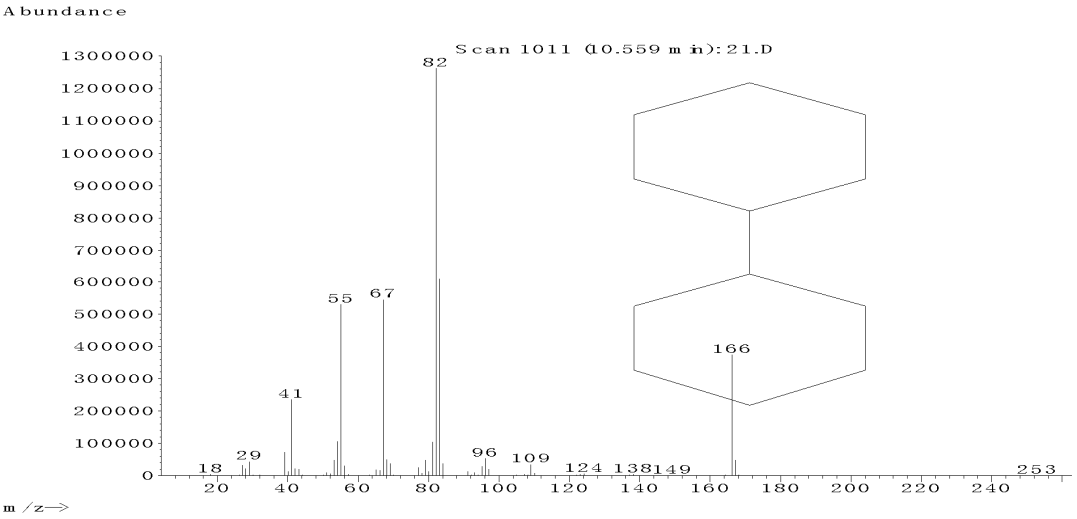


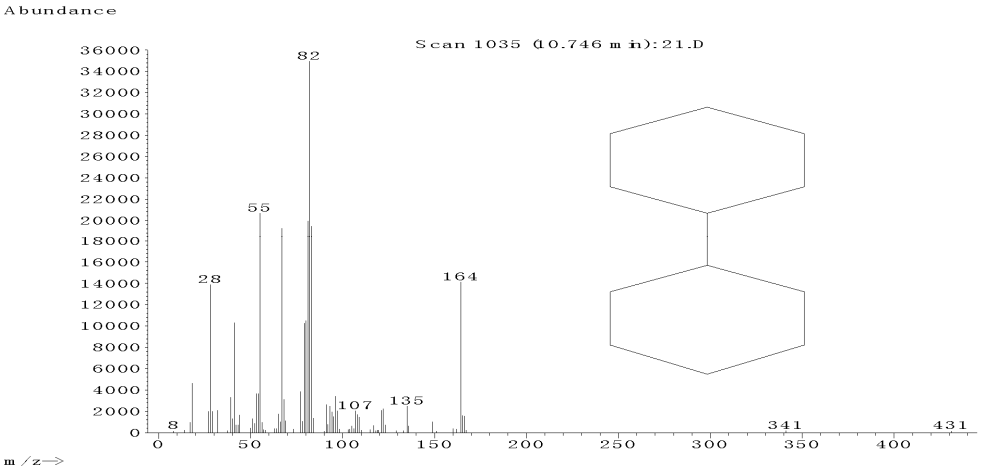


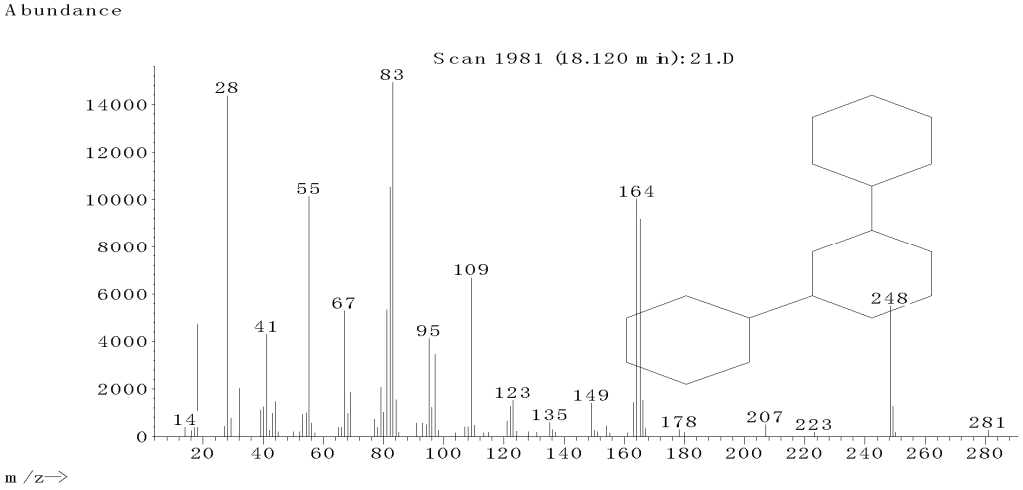



Abundance
Scan 229 (4.463 min): 21.D
HO
57
82
44
29
15
69
100
124
165
192
283
m/z


Abundance
Scan 246 (4.595 min): 21.D
O
55
42
98
69
28
82
15
120
281
m/z


Abundance
Scan 1011 (10.559 min): 21.D
82
55
67
166
41
29
18
96
109
124
138
149
253
m/z

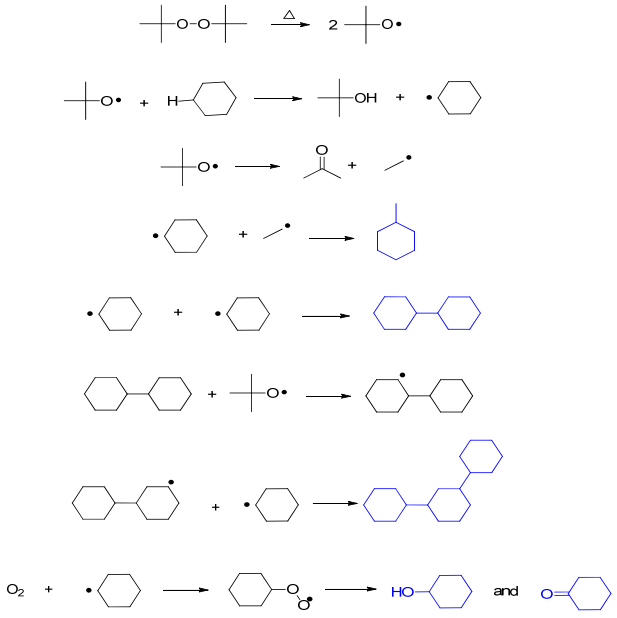




Signal report of GC-MS:

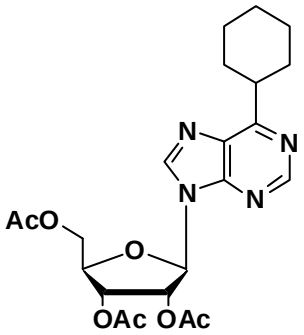
peak	R.T.min	first scan	Max scan	last scan	PK TY	peak height	corr. area	corr. % max.	% of total
1	2.841	4	21	28	BV	1909119	26225130	24.69%	10.540%
2	3.013	37	43	58	PB	4041516	52041960	49.00%	20.916%
3	4.470	216	230	239	BV	1376674	32371230	30.48%	13.010%
4	4.603	239	247	284	VB	2389058	18715122	17.62%	7.522%
5	10.566	987	1012	1030	BV	5268474	106198974	100.00%	42.682%
6	10.746	1030	1035	1062	VB	223006	7266743	6.84%	2.921%
7	18.128	1978	1982	1998	VV	117334	3041533	2.86%	1.222%

(2). The proposed transformation of radicals



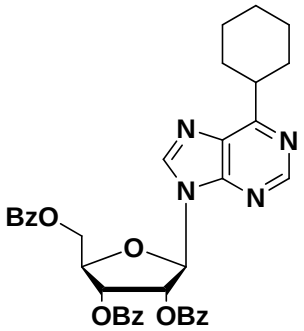
5. Characterization of compounds

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-cyclohexyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3a)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.17 (s, 1H), 6.24 (d, *J* = 5.2 Hz, 1H), 5.96 (t, *J* = 5.2 Hz, 1H), 5. 69 (t, *J* = 5.2 Hz, 1H), 4.47-4.35 (m, 3H), 3.48-3.42 (m, 1H), 2.15 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.04-1.77 (m, 8H), 1.53-1.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 152.6, 151.4, 150.5, 141.9, 132.4, 86.5, 80.3, 70.1, 63.0, 41.8, 31.3, 26.2, 25.9, 20.8, 20.6, 20.5; HRMS calcd for $C_{22}H_{28}N_4NaO_7$[M+Na^+] 483.1850, found 483.1855.

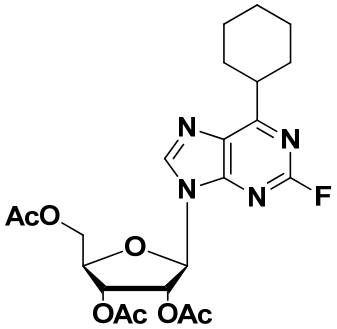
(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(6-cyclohexyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl dibenzoate (3b)



Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.16 (s, 1H), 8.11 (d, *J* = 7.2 Hz, 2H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.60-7.53 (m, 3H), 7.47-7.34 (m, 6H), 6.47 (s, 2H), 6.30 (d, *J* = 3.6 Hz, 1H), 4.93 (dd, J_1 = 3.2 Hz, J_2 = 12 Hz, J_3 = 80.4 Hz, 2H), 4.85-4.82 (m, 1H), 3.47-3.41 (m, 1H), 1.97-1.74 (m, 7H), 1.53-1.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.2, 165.3, 165.2, 152.9, 150.5, 142.1, 133.8, 133.4, 132.5, 129.9, 129.8, 128.8, 128.6, 87.1, 80.8, 73.8, 71.5, 63.6, 41.9, 31.3, 26.3; HRMS calcd for $C_{37}H_{35}N_4O_7$[M+H^+] 647.2500, found

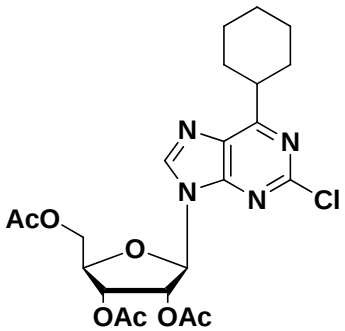
647.2501.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-cyclohexyl-2-fluoro-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3c)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.16 (d, *J* = 5.6 Hz, 1H), 5.84 (d, *J* = 5.6 Hz, 1H), 5.60-5.58 (m, 1H), 4.45-4.34 (m, 3H), 3.43-3.67 (m, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 1.91-1.75 (m, 8H), 1.49-1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 170.3, 169.5, 169.4, 159.9, 157.8, 152.7, 152.5, 142.1, 131.0, 100.0, 86.2, 80.5, 77.4, 77.1, 76.7, 73.0, 70.5, 62.9, 41.9, 31.0, 26.0, 25.8, 20.7, 20.5, 20.4; HRMS calcd for $C_{22}H_{28}FN_4O_7$[M+H$^+$] 479.1937, found 479.1938.

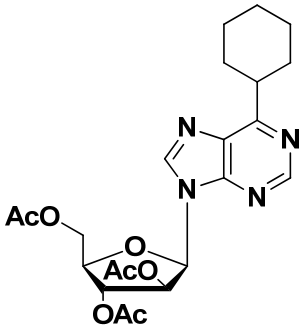
(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(2-chloro-6-cyclohexyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3d)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 6.23 (d, *J* = 5.6 Hz, 1H), 5.82 (d, *J* = 5.2 Hz, 1H), 5.61 (d, *J* = 4.4 Hz, 1H), 4.45-4.36 (m, 3H), 3.40-3.34 (m, 1H), 2.15 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.96-1.71 (m, 8H), 1.50-1.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.6, 169.5, 169.4, 154.6, 152.1, 141.9, 131.4, 86.0, 80.6, 73.2, 70.1, 63.0, 42.4, 31.1, 31.0, 26.1, 25.7, 20.8, 20.5, 20.4; HRMS calcd

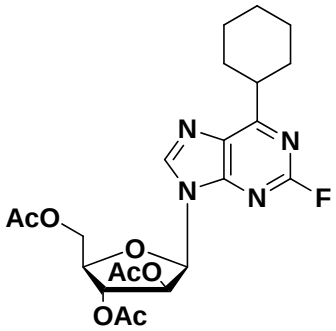
for $C_{22}H_{27}ClN_4NaO_7$[M+Na^+] 517.1460, found 517.1454.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-5-(6-cyclohexyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3e)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.18 (s, 1H), 6.62 (d, *J* = 4.4 Hz, 1H), 5.48-5.40 (m, 2H), 4.43 (d, *J* = 4.8 Hz, 2H), 4.25 (q, J = 4.8 Hz, 1H), 3.42-3.36 (m, 1H), 2.12 (s, 3H), 2.07 (s, 3H), 1.84 (s, 3H), 1.92-1.71 (m, 7H), 1.48-1.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.6, 168.6, 166.8, 152.7, 150.3, 142.4, 131.3, 82.9, 79.9, 75.7, 74.9, 62.9, 42.7, 31.3, 31.2, 26.9, 26.2, 25.9, 20.7, 20.3; HRMS calcd for $C_{22}H_{28}N_4NaO_7$[M+Na^+] 483.1850, found 483.1844.

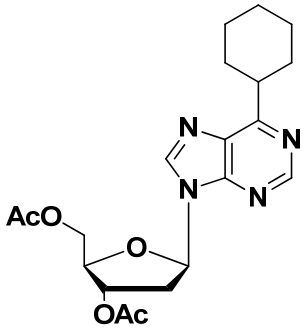
(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-5-(6-cyclohexyl-2-fluoro-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3f)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.56 (d, *J* = 4.4 Hz, 1H), 5.49-5.47 (m, 1H), 5.37-5.35 (m, 1H), 4.46-4.45 (m, 1H), 4.28-4.24 (m, 1H), 3.43-3.37 (m, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 1.93 (s, 3H), 1.96-1.76 (m, 8H), 1.48-1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 169.5, 168.5, 160.0, 157.9, 152.5, 142.8, 131.1, 130.0, 83.1, 80.3, 75.9, 74.8, 62.7, 41.9, 31.1, 31.0, 26.1, 25.8, 20.7, 20.3; HRMS calcd for $C_{22}H_{27}FN_4NaO_7$[M+Na^+] 501.1756, found

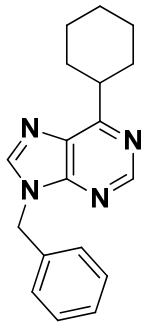
501.1750.

((2*R*,3*S*,5*R*)-3-Acetoxy-5-(6-cyclohexyl-9*H*-purin-9-yl)tetrahydrofuran-2-yl)methyl acetate (3g)



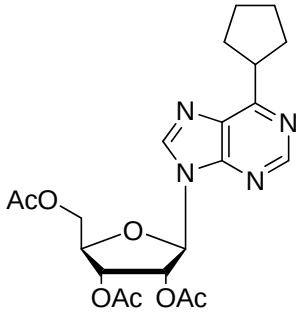
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.62 (s, 1H), 6.62 (d, *J* = 5.4 Hz, 1H), 5.42 (t, *J* = 2.4 Hz, 1H), 4.42-3.38 (m, 3H), 3.56-3.50 (m, 1H), 2.95-2.87 (m, 1H), 2.81-2.73 (m, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 2.06-1.79 (m, 8H), 1.48-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 163.2, 152.2, 148.3, 145.6, 131.6, 85.5, 83.3, 74.0, 63.5, 43.3, 38.1, 30.9, 25.8, 25.2, 20.9, 20.8; HRMS calcd for $C_{20}H_{26}N_4NaO_5$[M+Na^+] 425.1795, found 425.1801.

9-Benzyl-6-cyclohexyl-9*H*-purine (3h)



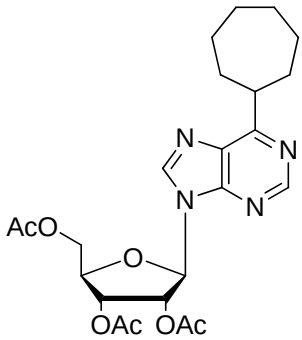
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.47 (s, 1H), 7.40 (s, 5H), 5.57 (s, 2H), 3.58-3.52 (m, 1H), 2.08-1.64 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 153.0, 148.0, 147.8, 133.4, 130.5, 129.5, 128.4, 48.5, 41.2, 30.9, 28.8, 25.7, 25.4, 25.1; HRMS calcd for $C_{18}H_{21}N_4$ [M+H^+] 293.1761, found 293.1752.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-cyclopentyl-9*H*-purin-9-yl)tetrahydrofura n-3,4-diyl diacetate (3i)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.15 (s, 1H), 6.23 (d, J = 5.2 Hz, 1H), 5.98 (t, *J* = 5.2 Hz, 1H), 5.68 (t, *J* = 4.8 Hz, 1H), 4.47-4.44 (m, 2H), 4.39-4.34 (m, 1H), 3.90-3.82 (m, 1H), 2.14 (s, 1H), 2.11 (s, 1H), 2.07 (s, 1H), 2.06-2.00 (m, 2H), 1.96-1.89 (m, 3H), 1.80-1.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 167.0, 152.8, 150.2, 141.8, 132.9, 86.4, 80.3, 73.1, 70.6, 63.0, 42.7, 32.7, 26.3, 20.8, 20.5, 20.4; HRMS calcd for $C_{21}H_{27}N_4O_7$[M+H$^+$] 447.1874, found 447.1877.

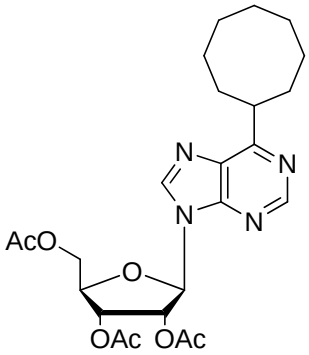
(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-cycloheptyl-9*H*-purin-9-yl)tetrahydrofura n-3,4-diyl diacetate (3j)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.15 (s, 1H), 6.24 (d, *J* = 5.2 Hz, 1H), 5.98 (d, *J* = 5.2 Hz, 1H), 5.70 (d, *J* = 5.2 Hz, 1H), 4.48-4.35 (m, 3H), 3.63-3.56 (m, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.03-1.97 (m, 4H), 1.92-1.85 (m, 2H) , 1.75-1.65 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 170.4, 169.6, 168.6, 152.9, 150.4, 141.7, 131.8, 86.4, 80.3, 73.1, 70.6, 63.1, 43.6, 33.5, 28.1, 27.3, 20.8, 20.6, 20.4; HRMS calcd for $C_{23}H_{31}N_4O_7$[M+H$^+$] 475.2187, found

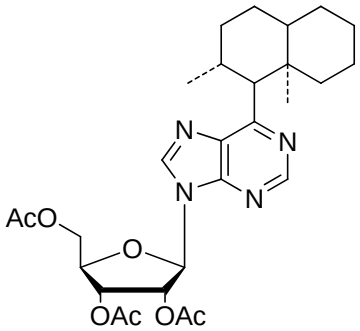
475.2190.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-cyclooctyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3k)



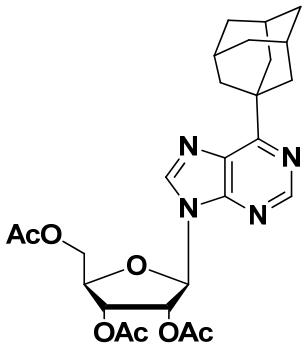
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.15 (s, 1H), 6.23 (d, *J* = 5.2 Hz, 1H), 5.98 (d, *J* = 5.2 Hz, 1H), 5.69 (d, *J* = 5.2 Hz, 1H), 4.47-4.35 (m, 3H), 3.70-3.64 (m, 1H), 2.15 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 1.98-1.82 (m, 7H), 1.72-1.63 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.6, 169.4, 169.2, 152.8, 150.4, 141.8, 131.9, 86.4, 80.3, 73.0, 70.6, 63.1, 41.6, 31.9, 26.6, 26.4, 26.0, 20.8, 20.6, 20.4; HRMS calcd for $C_{24}H_{32}N_4NaO_7$ [M+Na$^+$] 511.2163, found 511.2164.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-(decahydronaphthalen-1-yl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3l)



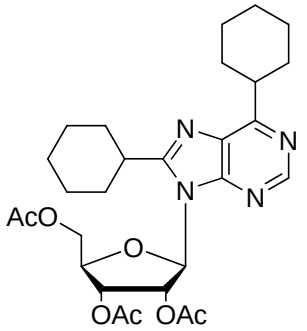
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.14 (s, 1H), 6.22-6.20 (m, 1H), 5.96 (d, *J* = 5.2 Hz, 1H), 5.67 (d, *J* = 5.2 Hz, 1H), 4.47-4.33 (m, 3H), 3.89-3.83 (m, 0.1H), 3.65-3.61 (m, 0.2H), 3.54-3.44 (m, 0.5H), 3.24-3.17 (m, 0.18H), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 1.99-1.49 (m, 12H), 1.43-0.98 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 166.9, 152.8, 150.4, 141.8, 132.4, 86.4, 80.3, 73.1, 70.6, 63.0, 42.9, 42.7, 41.8, 38.3, 33.8, 33.6, 31.1, 26.6, 20.7, 20.5, 20.4; HRMS calcd for $C_{26}H_{35}N_4O_7$ [M+H$^+$] 515.2500, found 515.2506.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6-((3*R*,5*R*,7*R*)-adamantan-1-yl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (3m)



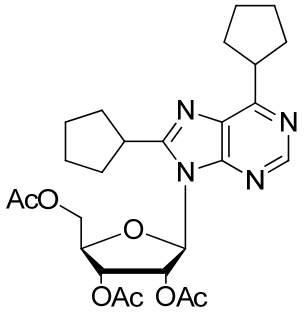
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.14 (s, 1H), 6.22 (d, *J* = 5.2 Hz, 1H), 5.94 (t, *J* = 5.6 Hz, 1H), 5.65 (t, *J* = 5.2 Hz, 1H), 4.42-4.30 (m, 3H), 2.28 (d, *J* = 2.4 Hz, 6H), 2.10 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.84-1.75 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.4, 169.2, 152.1, 151.0, 140.7, 132.2, 86.3, 80.2, 73.0, 70.6, 63.1, 40.8, 40.6, 36.8, 28.5, 26.9, 20.8, 20.5, 20.4; HRMS calcd for $C_{26}H_{33}N_4O_7$[M+H$^+$] 513.2344, found 513.2339.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6,8-dicyclohexyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4a)



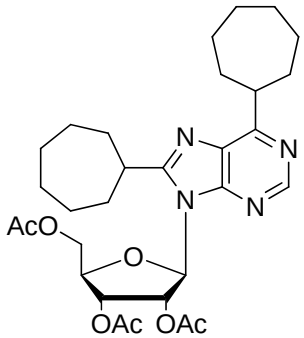
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 6.45-6.43 (m, 1H), 6.02-5.99 (m, 2H), 4.53-4.50 (m, 1H), 4.40-4.30 (m, 2H), 3.47-3.40 (m, 1H), 2.90-2.83 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 2.02 (s, 3H), 1.94-1.76 (m, 13H), 1.51-1.35 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 177.8, 177.7, 169.5, 159.5, 151.5, 131.5, 86.6, 79.9, 72.3, 70.6, 63.0, 40.9, 36.6, 31.7, 31.4, 31.3, 31.1, 26.2, 26.1, 26.0, 20.7, 20.6, 20.5; HRMS calcd for $C_{28}H_{39}N_4O_7$[M+H$^+$] 543.2813, found 543.2820.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6,8-dicyclopentyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4b)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 6.46-6.43 (m, 1H), 6.05 (d, *J* = 4.8 Hz, 1H), 5.99-5.96 (m, 1H), 4.54-4.49 (m, 1H), 4.38-4.30 (m, 2H), 3.87-3.79 (m, 1H), 3.38-3.30 (m, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H), 1.97-1.87 (m, 4H), 1.77-1.68 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 170.6, 169.5, 169.4, 164.9, 159.4, 151.7, 131.9, 86.7, 79.9, 72.1, 70.7, 63.0, 42.2, 37.5, 32.9, 32.8, 32.1, 31.8, 26.4, 25.8, 20.7, 20.6, 20.5; HRMS calcd for $C_{26}H_{35}N_4O_7$[M+H$^+$] 515.2500, found 515.2508.

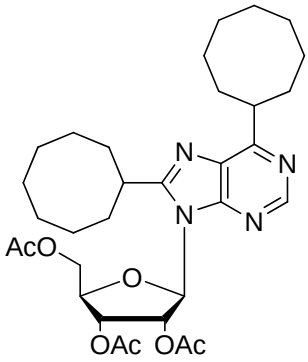
(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6,8-dicycloheptyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4c)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 6.42-6.40 (m, 1H), 6.01-5.97 (m, 2H), 4.54-4.49 (m, 1H), 4.39-4.32 (m, 2H), 3.60-3.53 (m, 1H), 3.11-3.05 (m, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.99-1.86 (m, 10H), 1.74-1.56 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 169.3, 166.6, 160.5, 130.9, 86.8, 79.9, 72.3, 70.6, 63.0, 42.9, 38.2, 33.5, 33.4, 32.9, 29.7, 28.3, 28.2, 28.0,

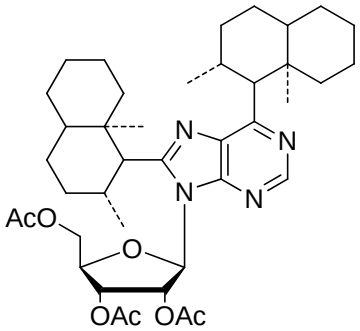
27.1, 26.8, 20.7, 20.6, 20.4; HRMS calcd for $C_{30}H_{42}N_4NaO_7$[M+Na^+] 593.2946, found 593.2941.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6,8-dicyclooctyl-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4d)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 6.41-6.38 (m, 1H), 6.01-5.97 (m, 2H), 4.54-4.51 (m, 1H), 4.39-4.32 (m, 2H), 3.65-3.58 (m, 1H), 3.19-3.13 (m, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.99-1.82 (m, 8H), 1.73-1.59 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 169.3, 167.0, 160.7, 151.5, 130.9, 86.8, 79.9, 72.3, 70.6, 63.0, 41.3, 36.5, 31.5, 31.3, 31.0, 27.0, 26.8, 26.5, 26.4, 26.2, 25.9, 25.8, 25.7, 25.3, 20.7, 20.6, 20.4; HRMS calcd for $C_{32}H_{46}N_4NaO_7$ [M+Na^+] 621.3259, found 621.3252.

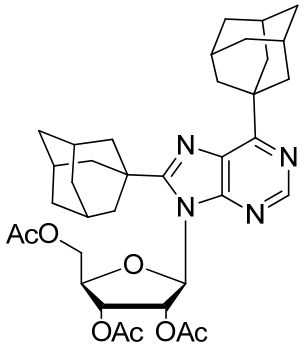
(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6,8-bis(decahydronaphthalen-1-yl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4e)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 6.44-6.40 (m, 1H), 6.02-5.98 (m, 2H), 4.93-4.50 (m, 1H), 4.37-4.32 (m, 2H), 3.62-3.38 (m, 1H), 3.25-2.86 (m, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.01 (s, 3H), 1.95-1.39 (m, 25H),

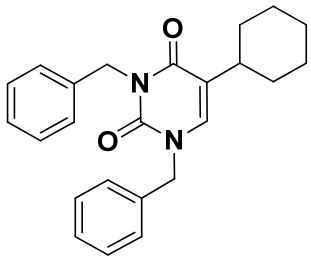
1.28-0.82 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.5, 151.6, 86.6, 72.3, 70.6, 63.0, 42.9, 42.8, 42.7, 42.4, 38.2, 36.7, 34.2, 33.9, 33.7, 33.5, 26.8, 26.7, 26.5, 20.7, 20.6, 20.5; HRMS calcd for $C_{36}H_{50}N_4NaO_7$[M+Na^+] 673.3572, found 673.3572.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(6,8-di-((3*R*,5*R*,7*R*)-adamantan-1-yl)-9*H*-purin-9-yl)tetrahydrofuran-3,4-diyl diacetate (4f)



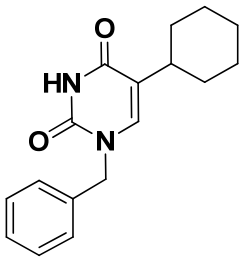
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 6.04 (s, 2H), 5.95 (t, *J* = 5.2 Hz, 1H), 4.55-4.51 (m, 1H), 4.40-4.32 (m, 2H), 2.14-2.02 (m, 19H), 1.82-1.74 (m, 10H), 1.27-1.21 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.1, 168.8, 157.8, 154.6, 151.2, 151.4, 118.1, 87.4, 79.6, 71.8, 70.5, 62.8, 40.7, 36.7, 36.2, 31.7, 29.5, 28.0, 22.5, 22.0, 20.6, 20.4, 20.2, 13.9; HRMS calcd for $C_{36}H_{47}N_4O_7$[M+H^+] 647.3439, found 647.3437.

1,3-Dibenzyl-5-cyclohexylpyrimidine-2,4(1*H*,3*H*)-dione (6a)



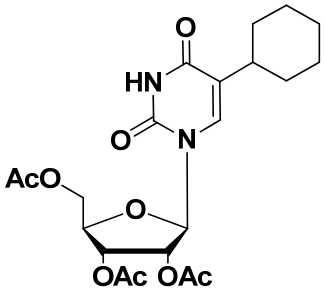
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 11.2 Hz, 2H), 7.40-7.24 (m, 9H), 6.88 (s, 1H), 5.17 (s, 2H), 4.92 (s, 2H), 2.62-2.55 (m, 1H), 1.86-1.70 (m, 5H), 1.43-1.32 (m, 2H), 1.21-1.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 151.5, 137.1, 136.8, 135.8, 129.2, 129.0, 128.4, 128.3, 127.7, 127.6, 119.9, 52.3, 44.7, 35.7, 32.4, 26.6, 26.1; HRMS calcd for $C_{24}H_{26}N_2NaO_2$[M+Na^+] 397.1886, found 397.1879.

1-Benzyl-5-cyclohexylpyrimidine-2,4(1*H*,3*H*)-dione (6b)



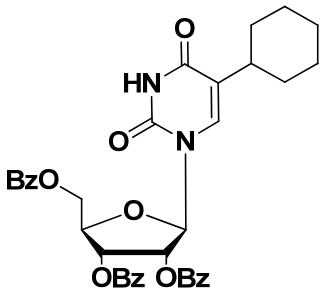
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.37-7.28 (m, 5H), 6.87 (s, 1H), 5.17 (s, 2H), 4.90 (s, 2H), 2.58-2.50 (m, 1H), 1.82-1.67 (m, 7H), 1.38-1.29 (m, 2H), 1.18-1.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 151.1, 138.6, 135.6, 129.0, 128.3, 128.3, 127.8, 120.8, 51.2, 35.0, 32.2, 26.4, 26.0; HRMS calcd for $C_{17}H_{21}N_2O_2$[M+H$^+$] 285.1598, found 285.1598.

(2*R*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-5-(5-cyclohexyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diacetate (6c)



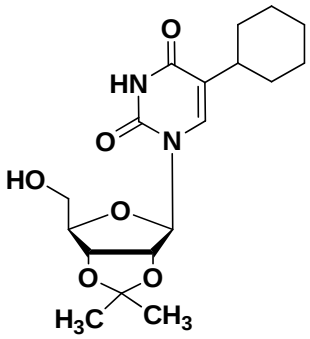
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 6.99 (s, 1H), 6.03 (d, J = 5.6 Hz, 1H), 5.30 (t, J = 1.2 Hz, 2H), 4.38-4.19 (m, 4H), 2.54-2.48 (m, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 1.75-1.62 (m, 5H), 1.38-1.28 (m, 2H), 1.16-1.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.8, 169.7, 163.2, 150.3, 133.7, 121.3, 107.0, 87.1, 79.8, 72.3, 70.3, 63.5, 35.1, 32.2, 32.1, 26.3, 26.0, 20.8, 20.6, 20.5; HRMS calcd for $C_{21}H_{29}N_2O_9$[M+H$^+$] 453.1868, found 453.1860.

(2*R*,3*R*,4*R*,5*R*)-2-((Benzoyloxy)methyl)-5-(5-cyclohexyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl dibenzoate (6d)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.59-7.31 (m, 15H), 7.06 (s, 1H), 6.50 (t, *J* = 4.4 Hz, 1H), 5.96 (t, *J* = 2.8 Hz, 1H), 5.80 (t, *J* = 6.4 Hz, 1H), 4.87-4.54 (m, 4H), 2.38-2.26 (m, 1H), 1.66-1.39 (m, 9H), 1.22-1.15 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 166.1, 165.5, 165.4, 163.2, 150.4, 133.8, 133.7, 133.6, 133.4, 130.0, 129.8, 129.7, 129.6, 128.8, 128.6, 128.3, 121.7, 86.5, 80.6, 73.2, 71.5, 64.5, 35.1, 32.0, 31.6, 26.3, 21.1; HRMS calcd for $C_{36}H_{34}N_2NaO_9$[M+Na^+] 661.2157, found 661.2148.

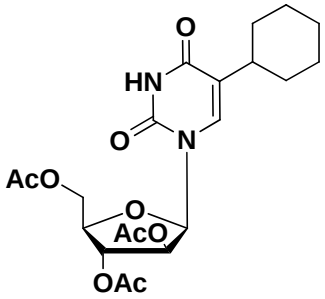
5-Cyclohexyl-1-((3a*R*,4*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)pyrimidine-2,4(1*H*,3*H*)-dione (6e)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.00 (s, 1H), 5.50 (t, *J* = 2.4 Hz, 1H), 5.14-5.11 (m, 1H), 5.01-4.99 (m, 1H), 4.28-4.26 (m, 1H), 3.92-3.78 (m, 2H), 2.99 (s, 1H), 2.56-2.45 (m, 1H), 1.85-1.69 (m, 6H), 1.56 (s, 3H), 1.35 (s, 3H), 1.20-1.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 150.3, 138.0, 120.7, 114.4, 96.8, 87.1, 83.5, 80.4, 62.7, 35.1, 32.2, 27.3, 26.5, 26.1, 25.3; HRMS calcd for

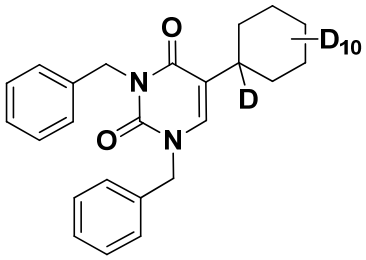
$C_{18}H_{27}N_2O_6[M+H^+]$ 367.1864, found 367.1868.

(2*R*,3*R*,4*S*,5*R*)-2-(Acetoxymethyl)-5-(5-cyclohexyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3,4-diyl diacetate (6f)



Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.16 (s, 1H), 7.06 (s, 1H), 6.29 (d, *J* = 4.0 Hz, 1H), 5.37-5.36 (m, 1H), 5.09 (d, *J* = 2 Hz, 1H), 4.41 (d, *J* = 5.2 Hz, 1H), 4.17-4.14 (m, 1H), 2.59-2.53 (m, 1H), 2.12 (s, 3H), 2.11 (s, 3H), 2.00 (s, 3H), 1.85-1.70 (m, 6H), 1.38-1.31 (m, 2H), 1.16-1.08 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.7, 168.4, 163.1, 149.8, 135.0, 119.5, 84.1, 80.3, 76.4, 74.7, 62.6, 34.8, 32.4, 26.5, 26.4, 26.0, 20.8, 20.7; HRMS calcd for $C_{21}H_{28}N_2NaO_9[M+Na^+]$ 475.1687, found 475.1678.

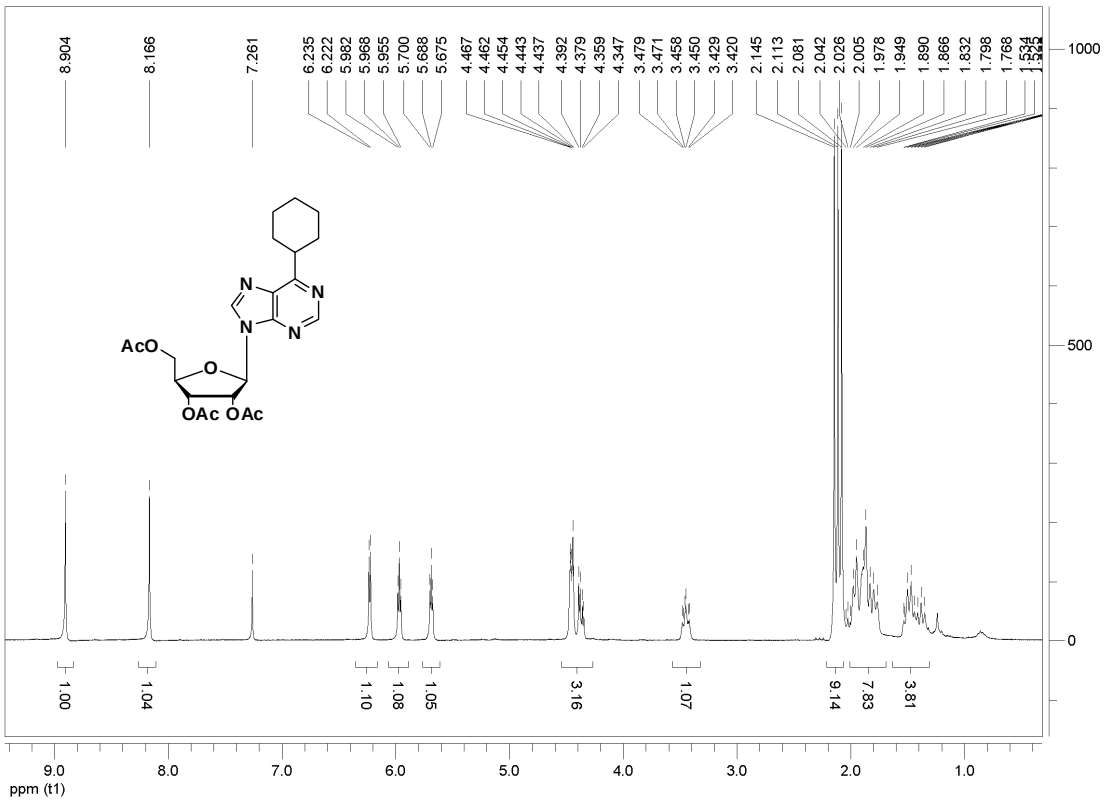
6a-D



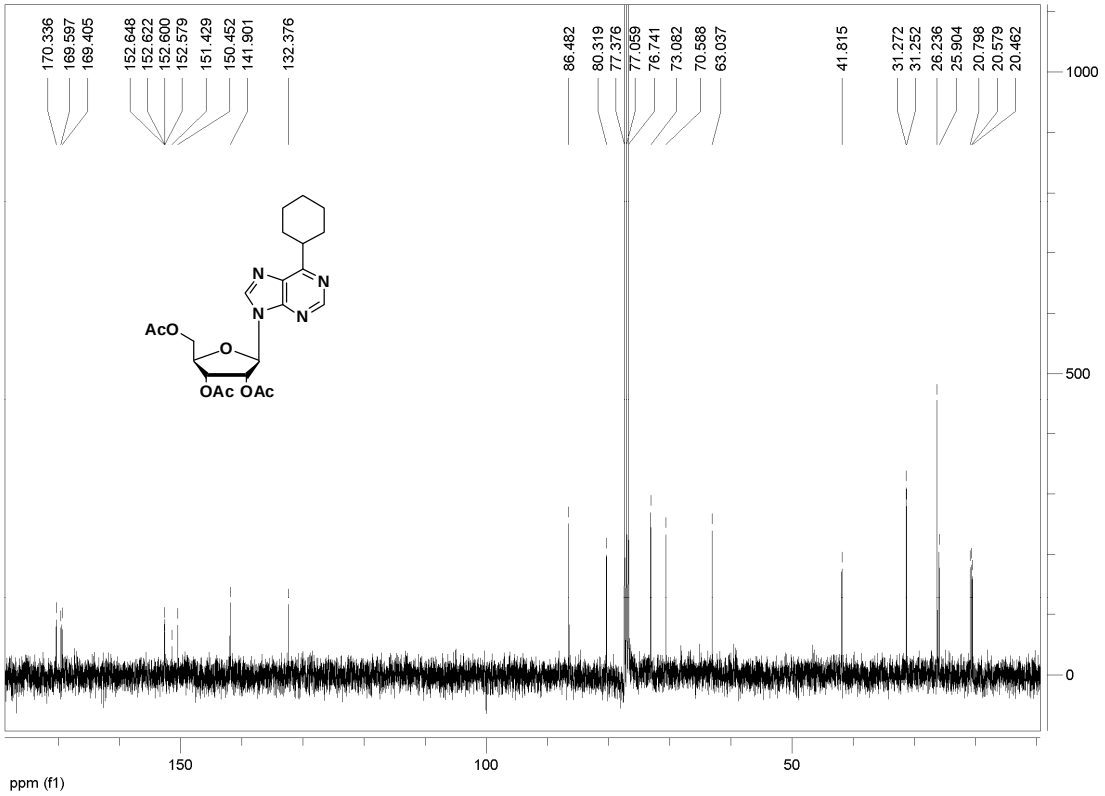
Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.39-7.24 (m, 11H), 6.87 (s, 1H), 5.16 (s, 2H), 4.92 (s, 2H), 2.61-2.55 (m, 0.88H), 1.85-1.69 (m, 5H), 1.42-1.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 151.5, 137.2, 136.8, 135.8, 129.2, 129.1, 129.0, 128.9, 128.4, 128.3, 127.8, 127.5, 120.0, 52.3, 44.8, 35.7, 32.4, 26.6, 26.2; HRMS calcd for $C_{24}H_{15}D_{11}N_2NaO_2[M+Na^+]$ 408.2577, found 408.2585.

6. ^{1}H and ^{13}C spectra of products

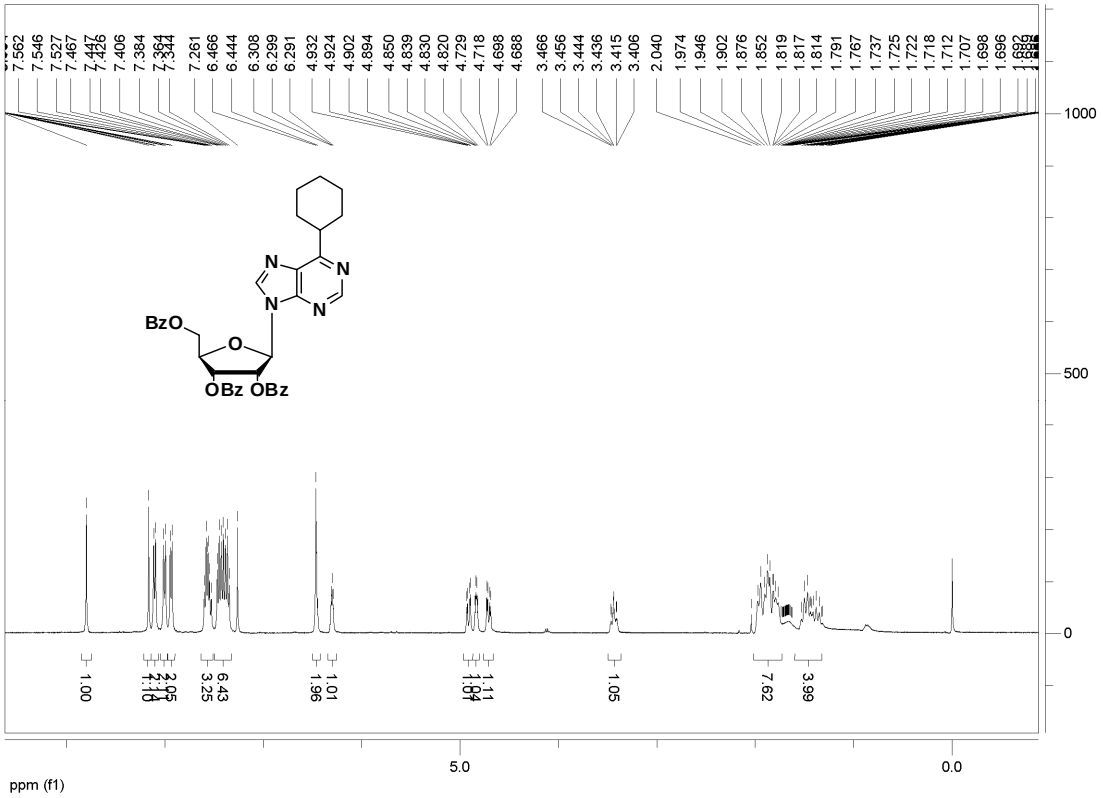
^{1}H NMR Spectrum for 3a



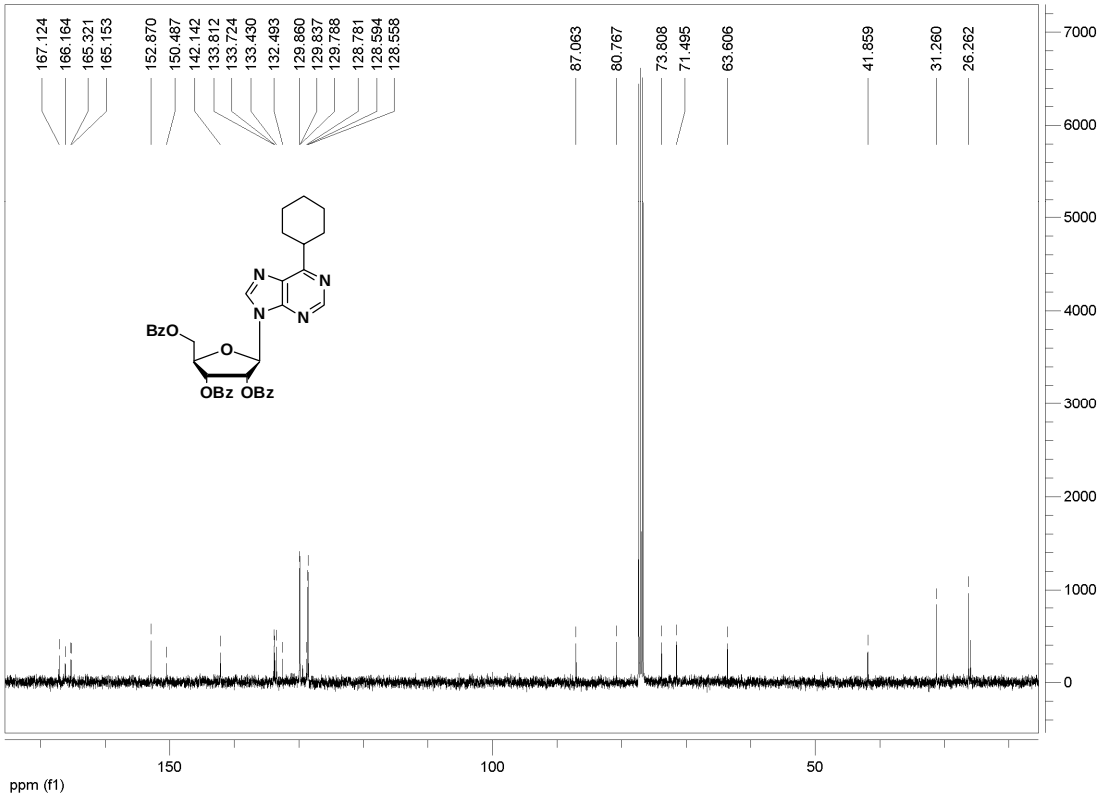
^{13}C NMR Spectrum for 3a



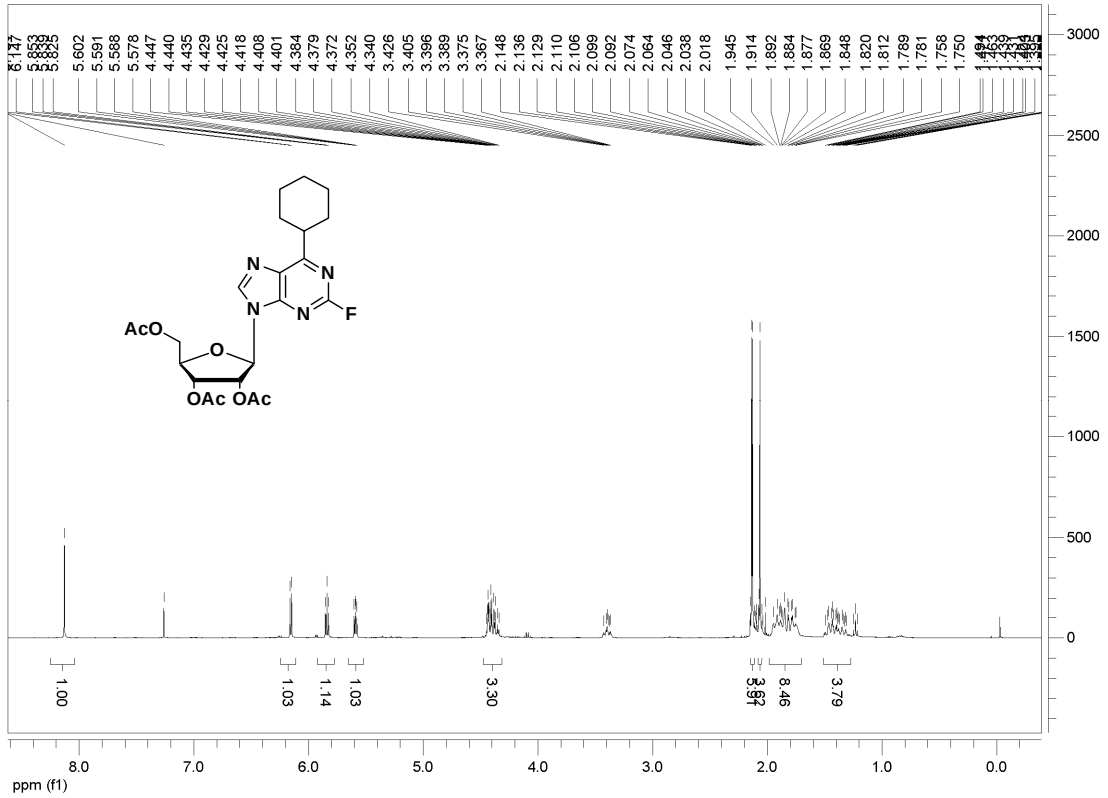
^{1}H NMR Spectrum for 3b



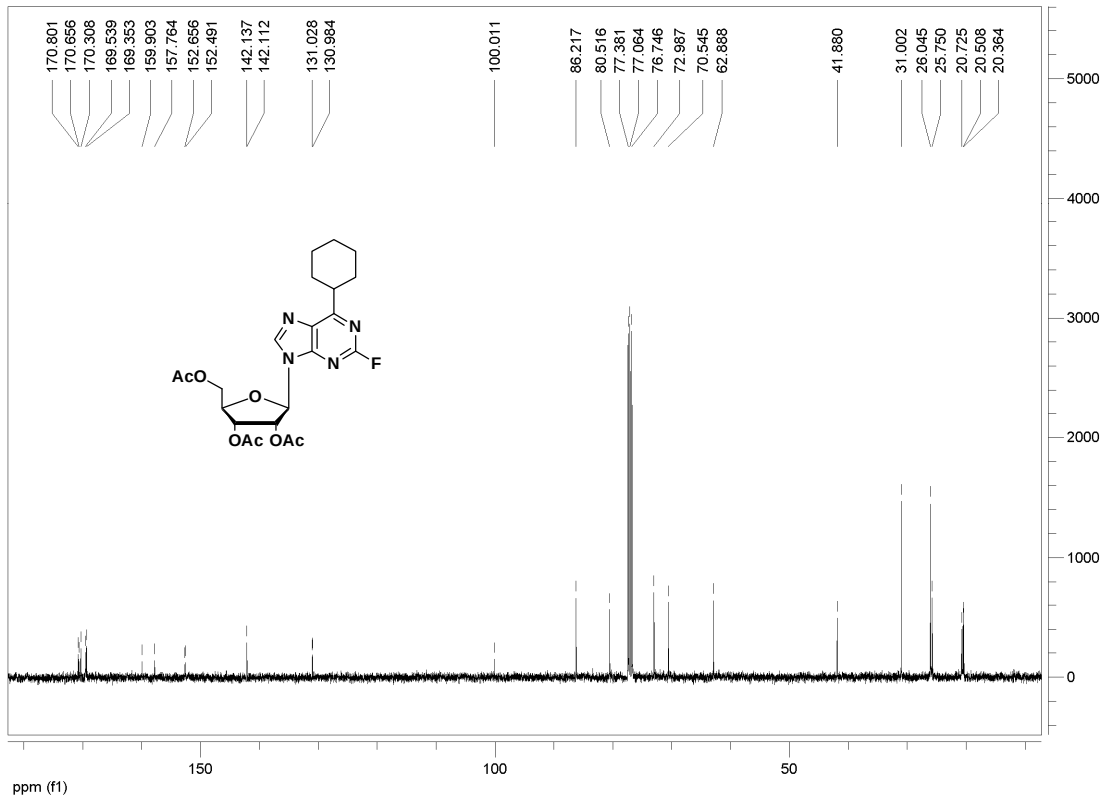
^{13}C NMR Spectrum for 3b



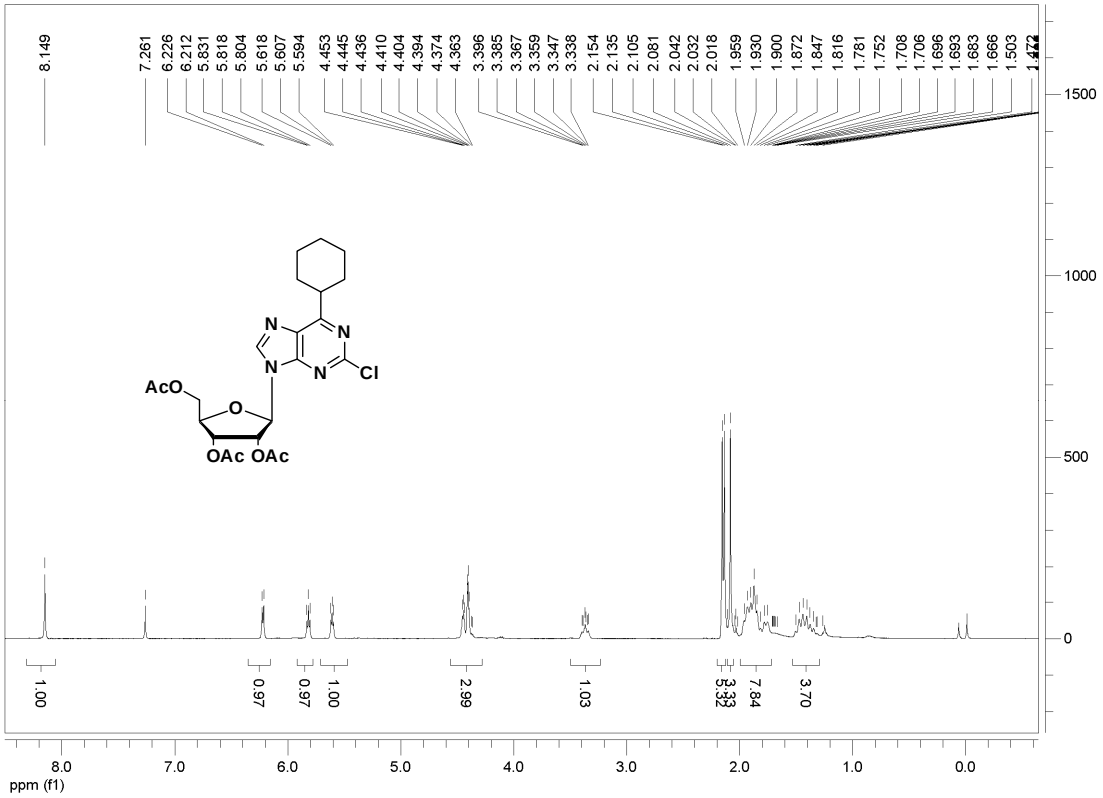
^{1}H NMR Spectrum for 3c



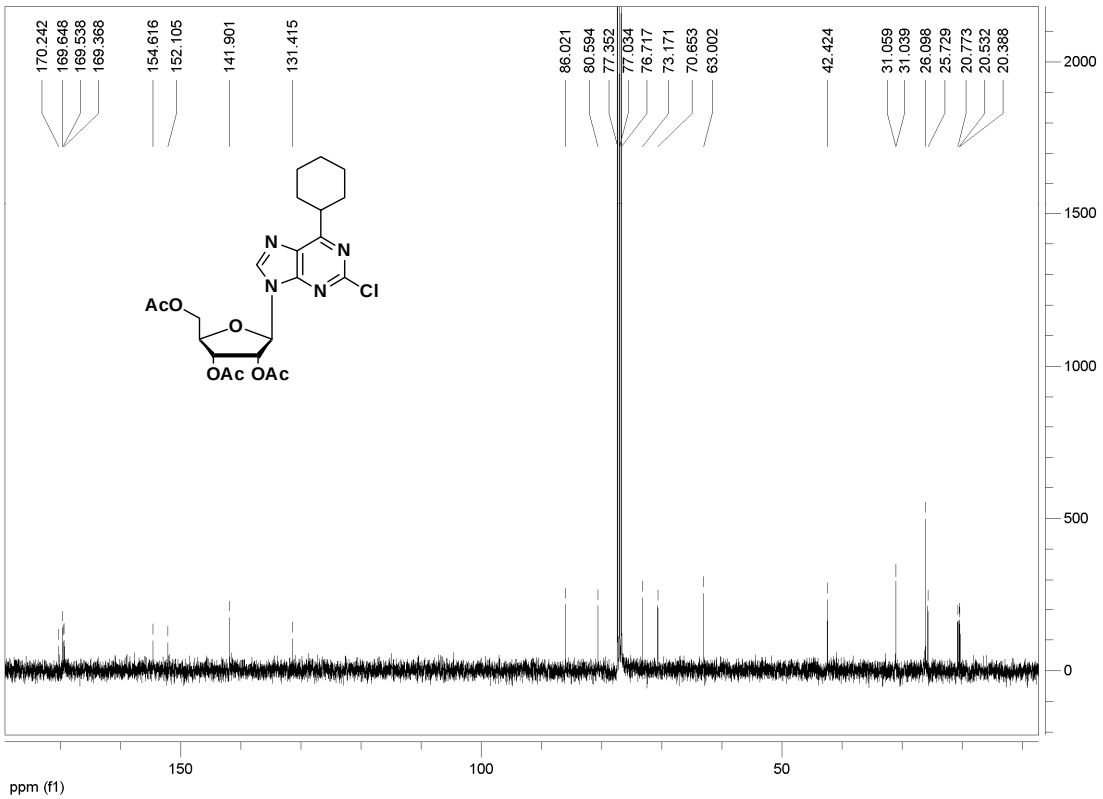
^{13}C NMR Spectrum for 3c



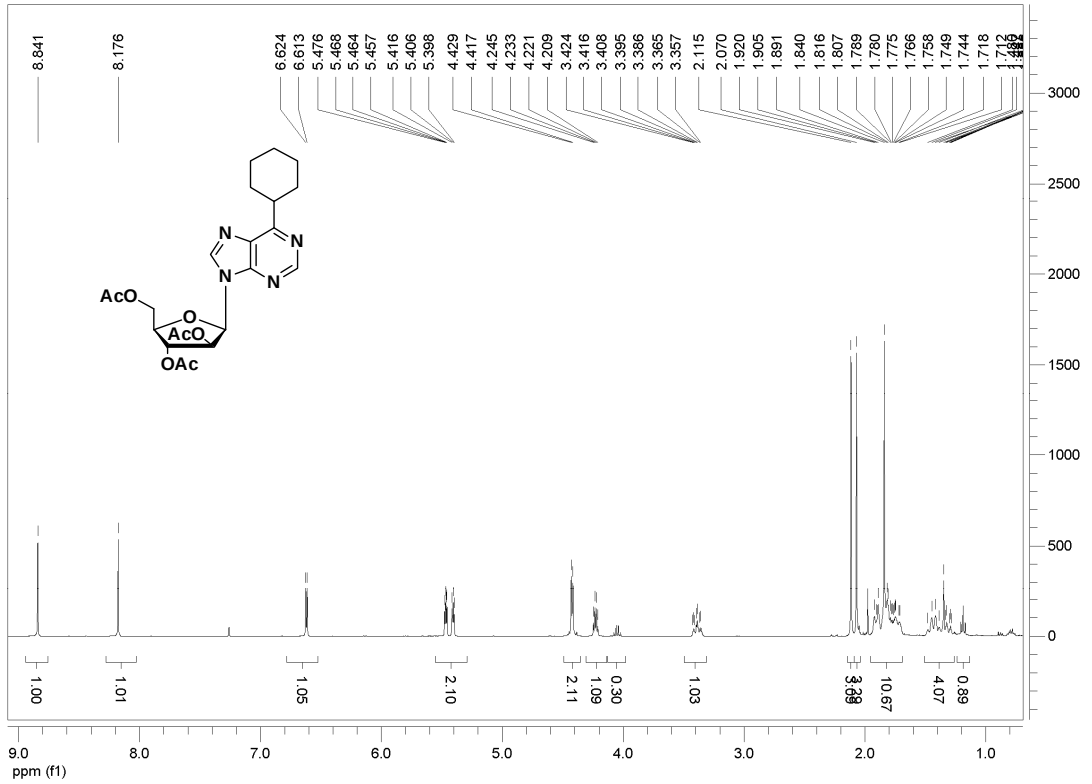
^{1}H NMR Spectrum for 3d



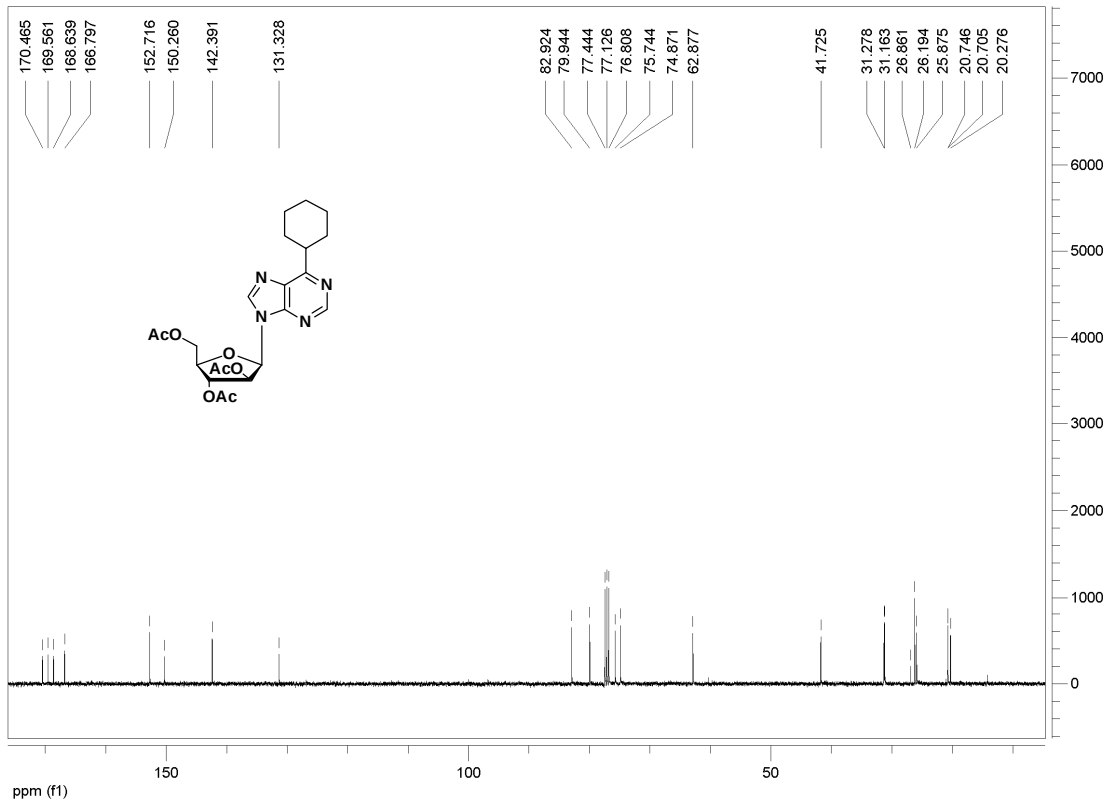
^{13}C NMR Spectrum for 3d



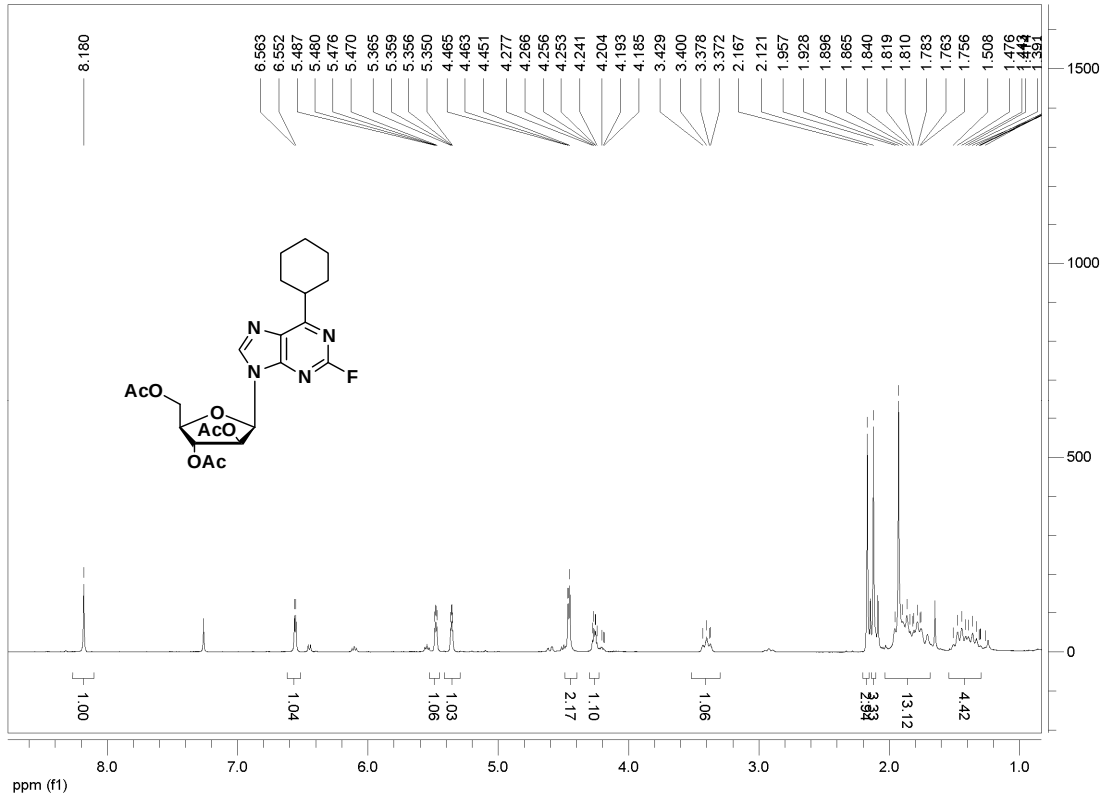
^{1}H NMR Spectrum for 3e



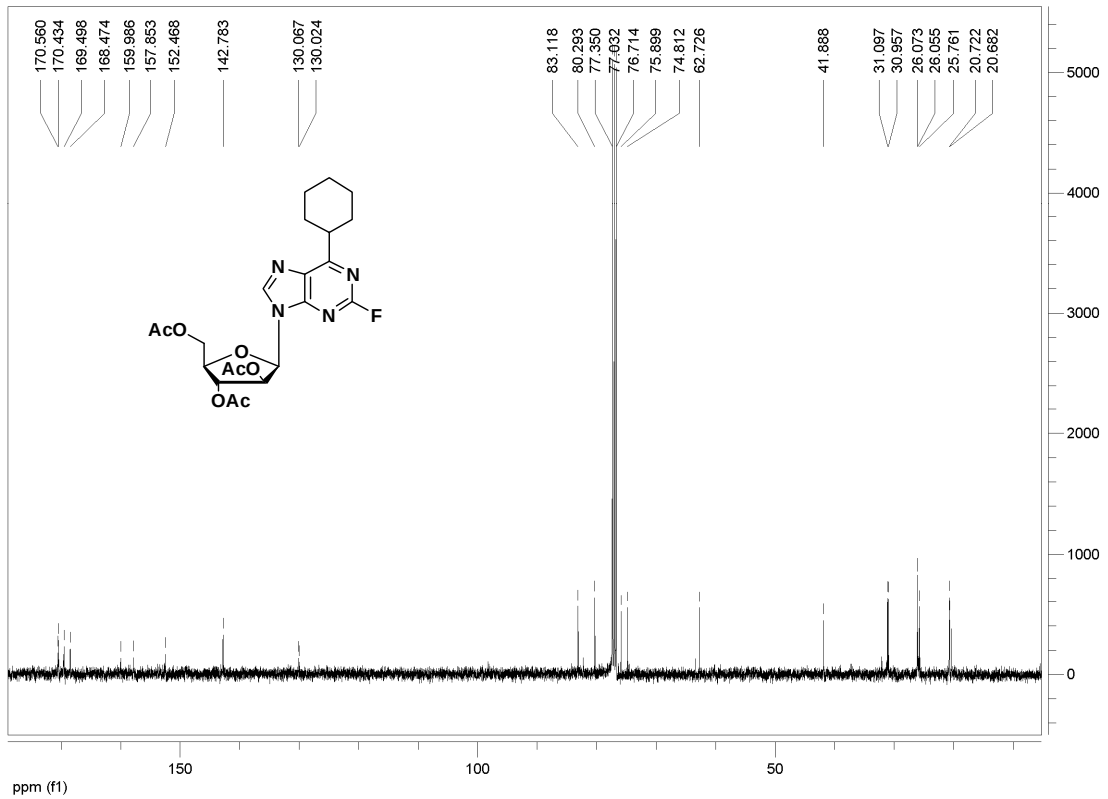
^{13}C NMR Spectrum for 3e



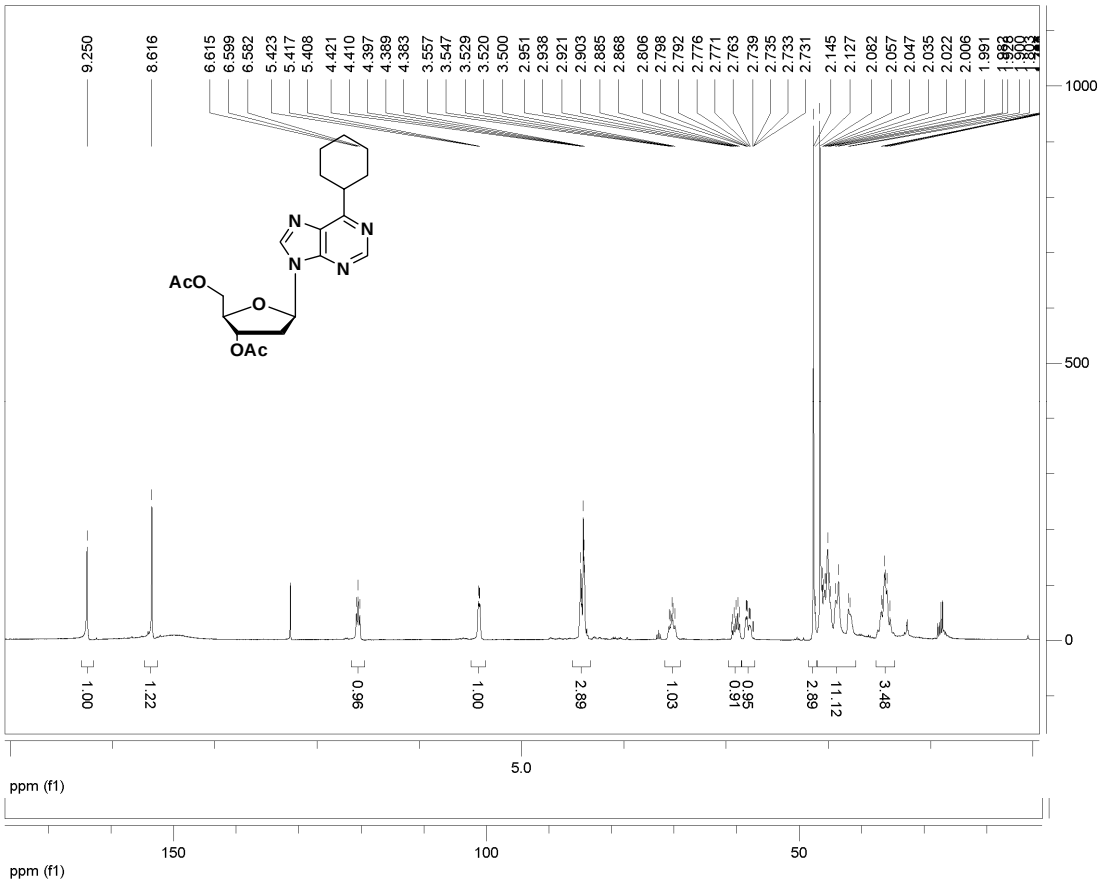
^{1}H NMR Spectrum for 3f



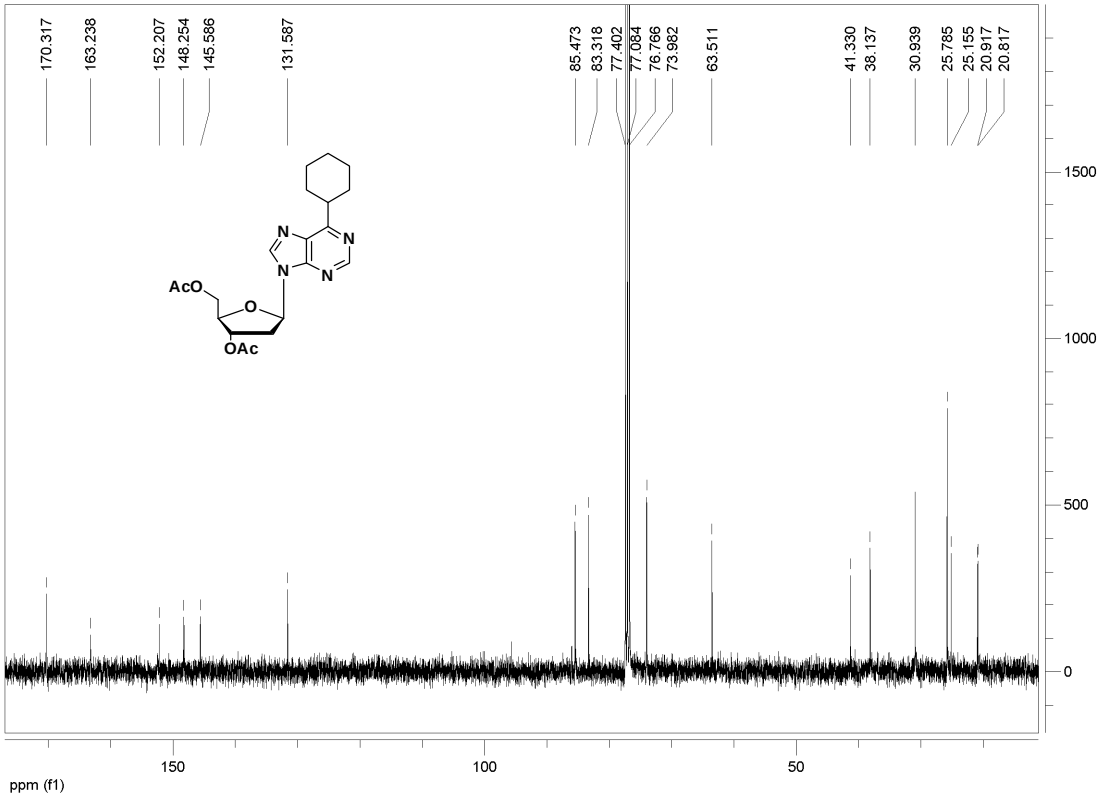
^{13}C NMR Spectrum for 3f



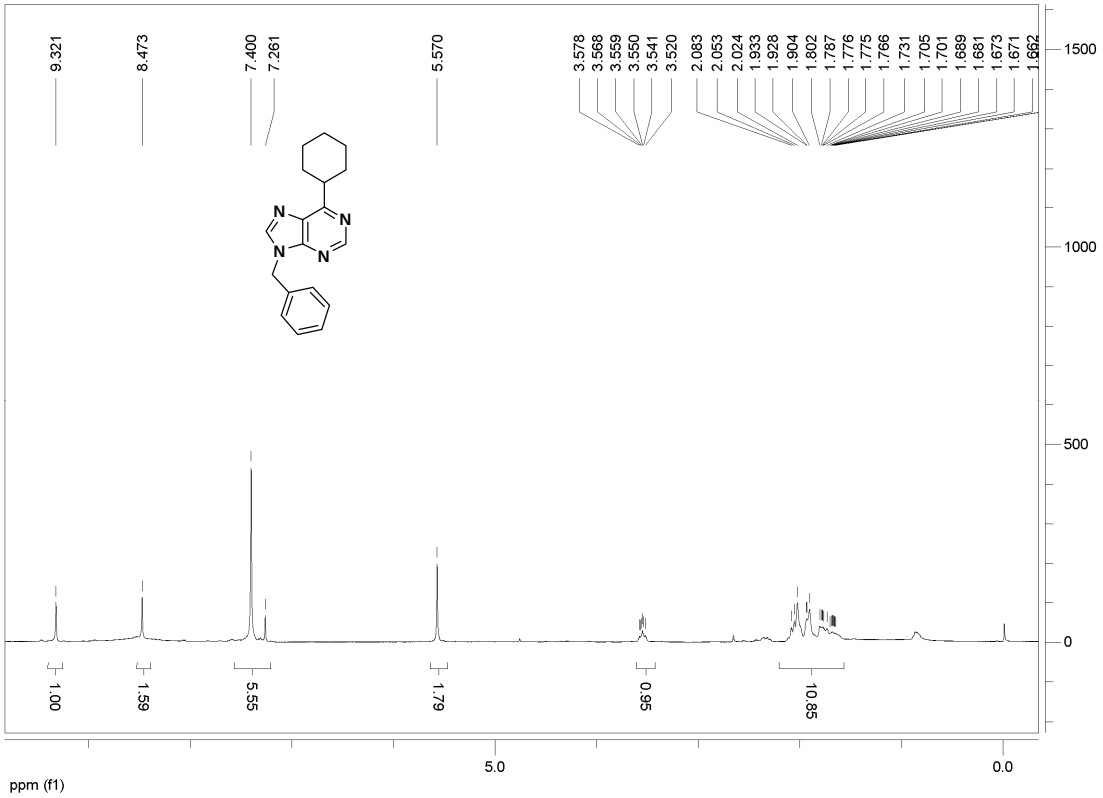
^{1}H NMR Spectrum for 3g



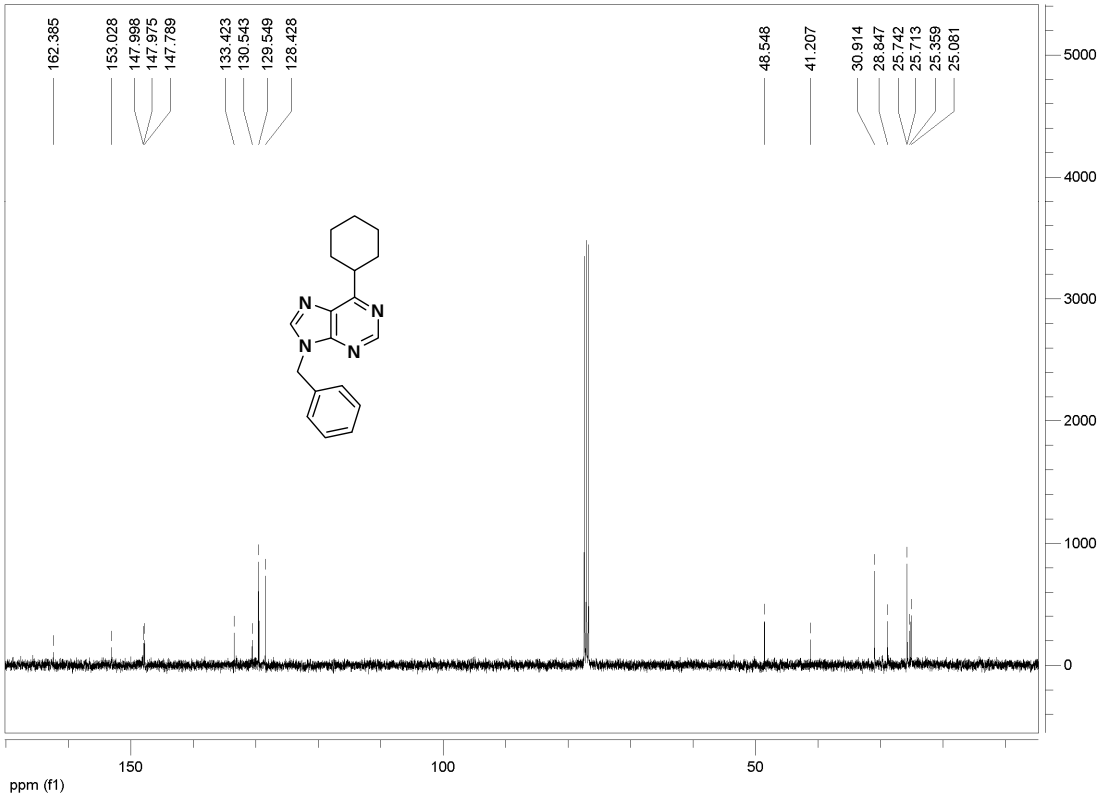
^{13}C NMR Spectrum for 3g



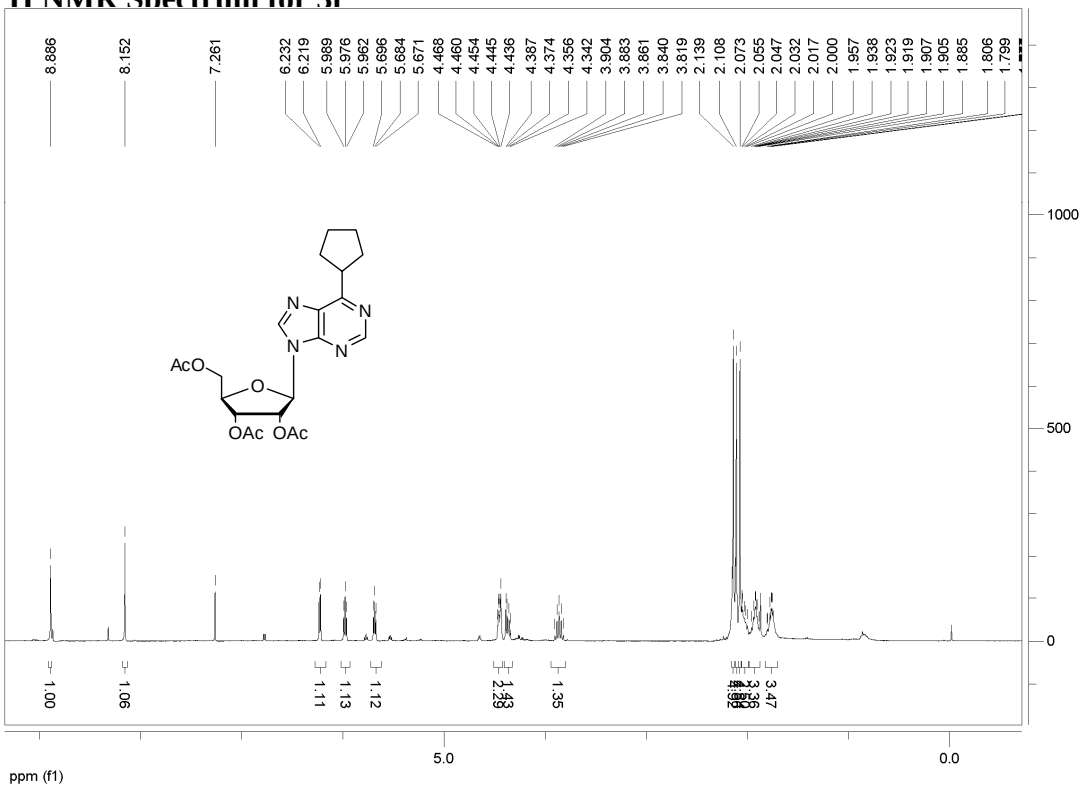
^{1}H NMR Spectrum for 3h



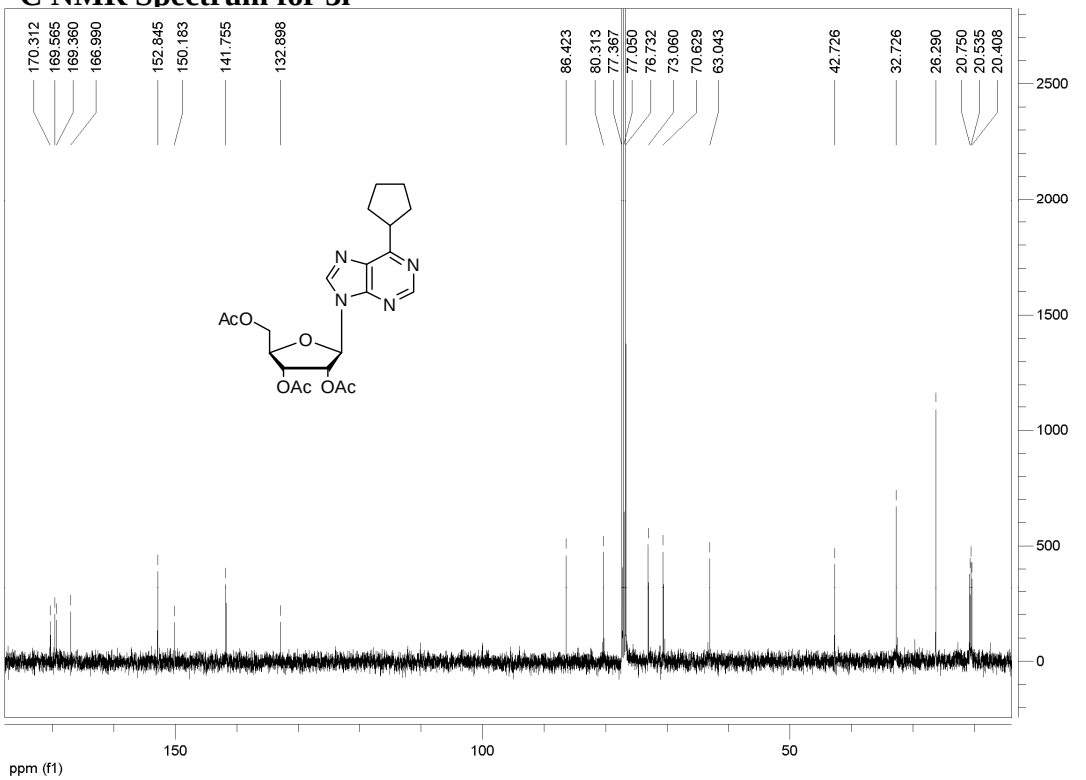
^{13}C NMR Spectrum for 3h



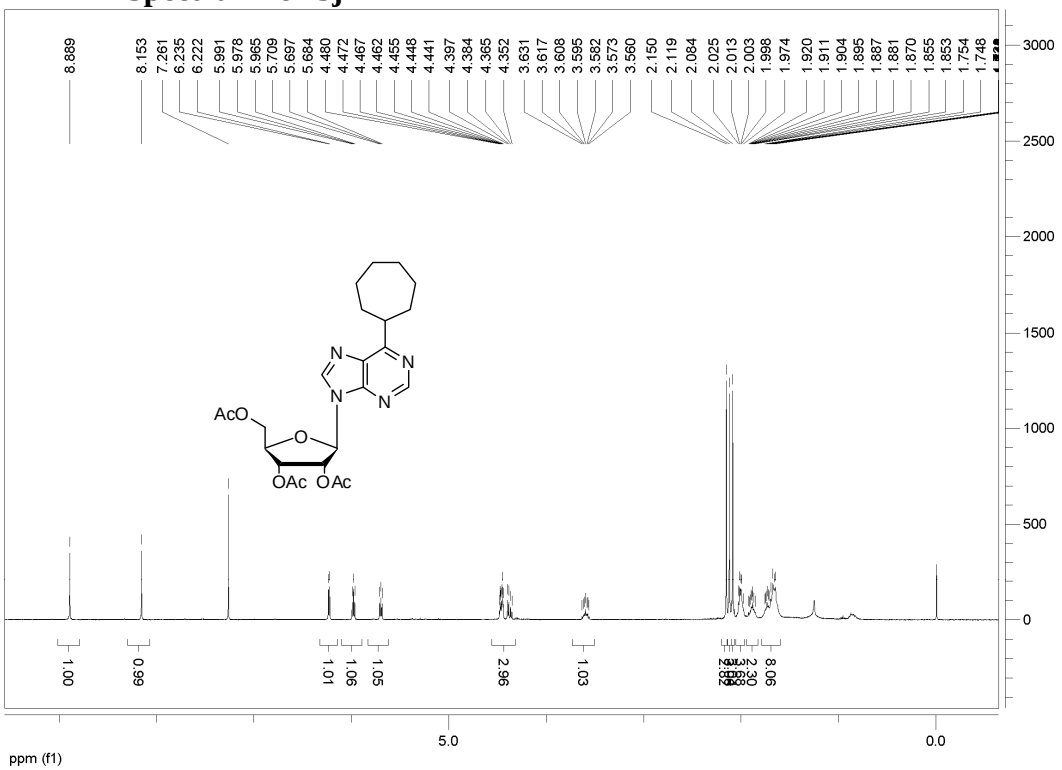
^{1}H NMR Spectrum for 3i



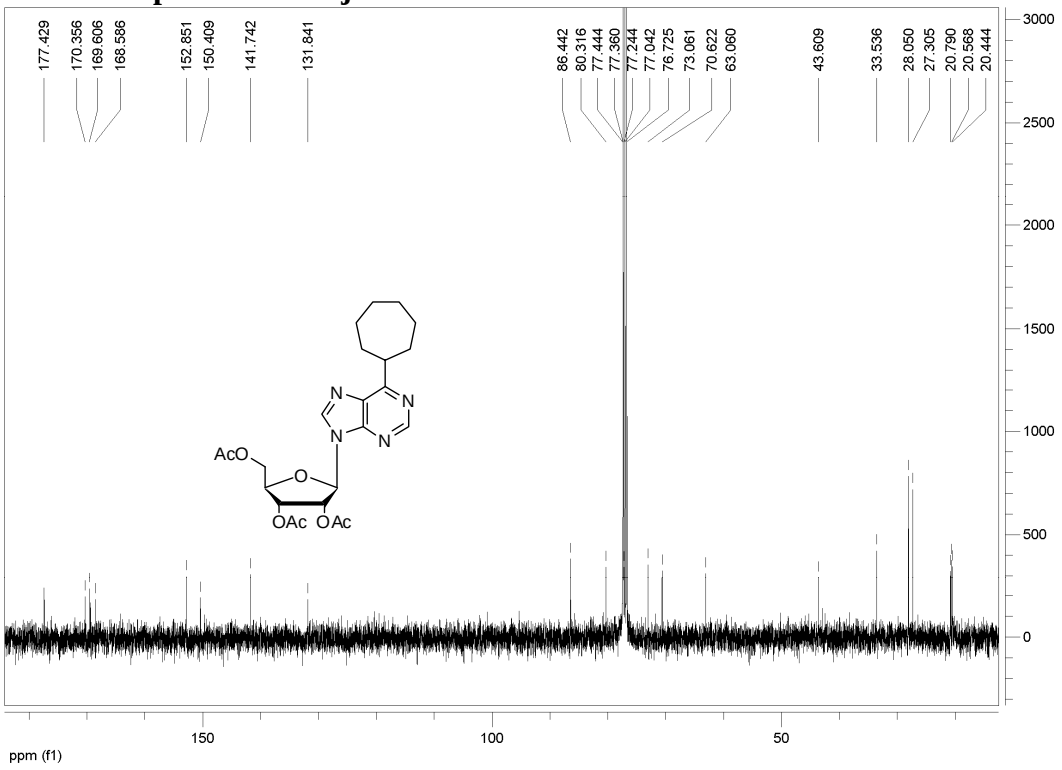
^{13}C NMR Spectrum for 3i



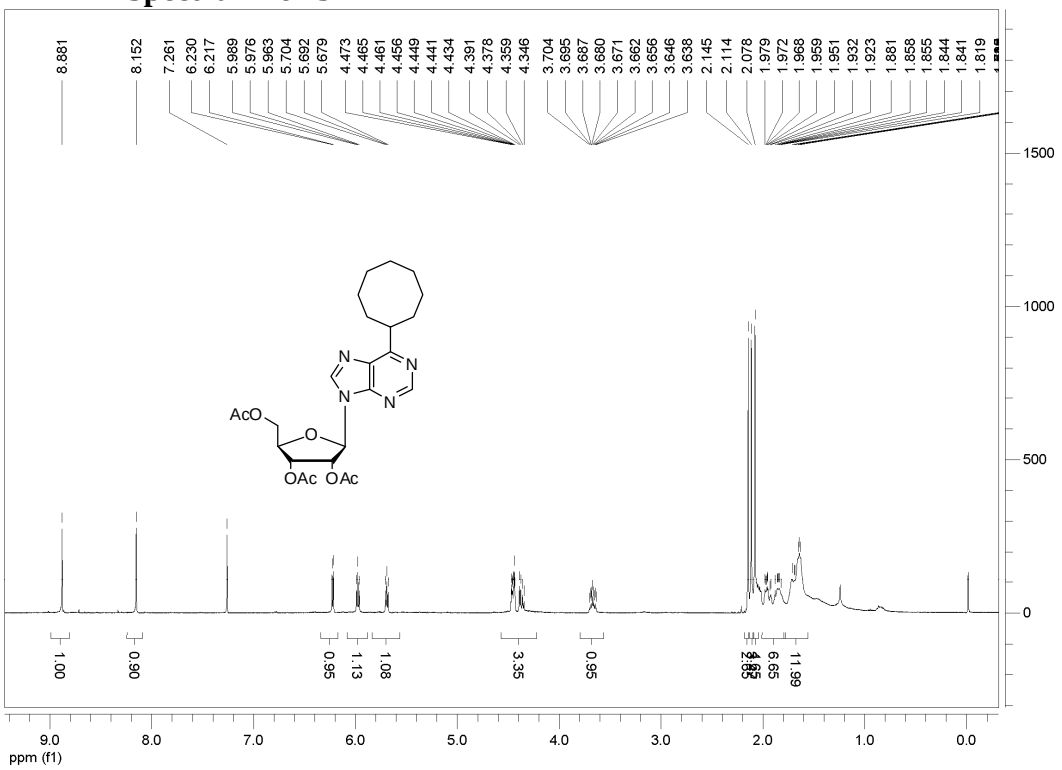
^{1}H NMR Spectrum for 3j



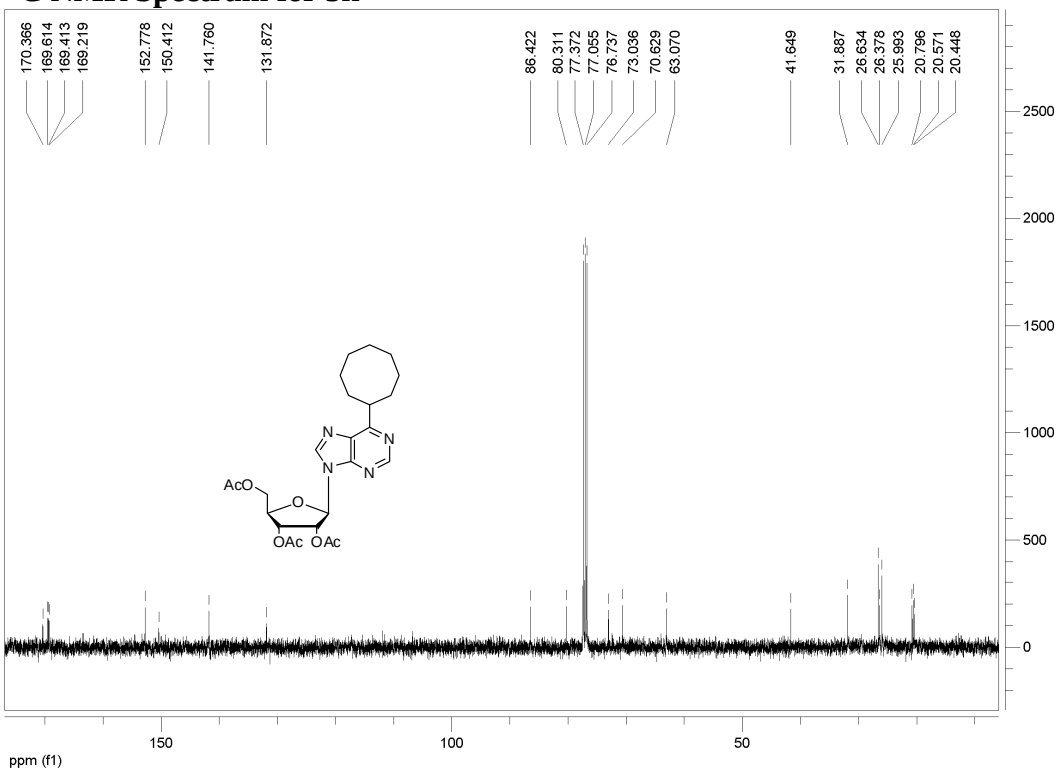
^{13}C NMR Spectrum for 3j



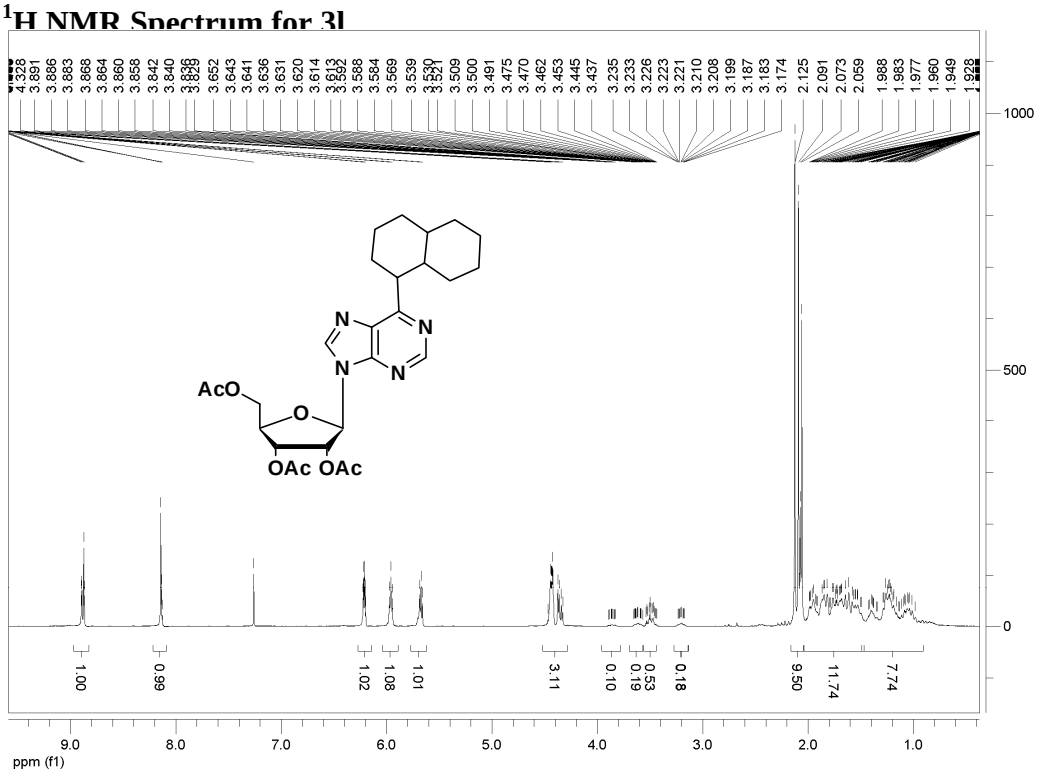
^{1}H NMR Spectrum for 3k



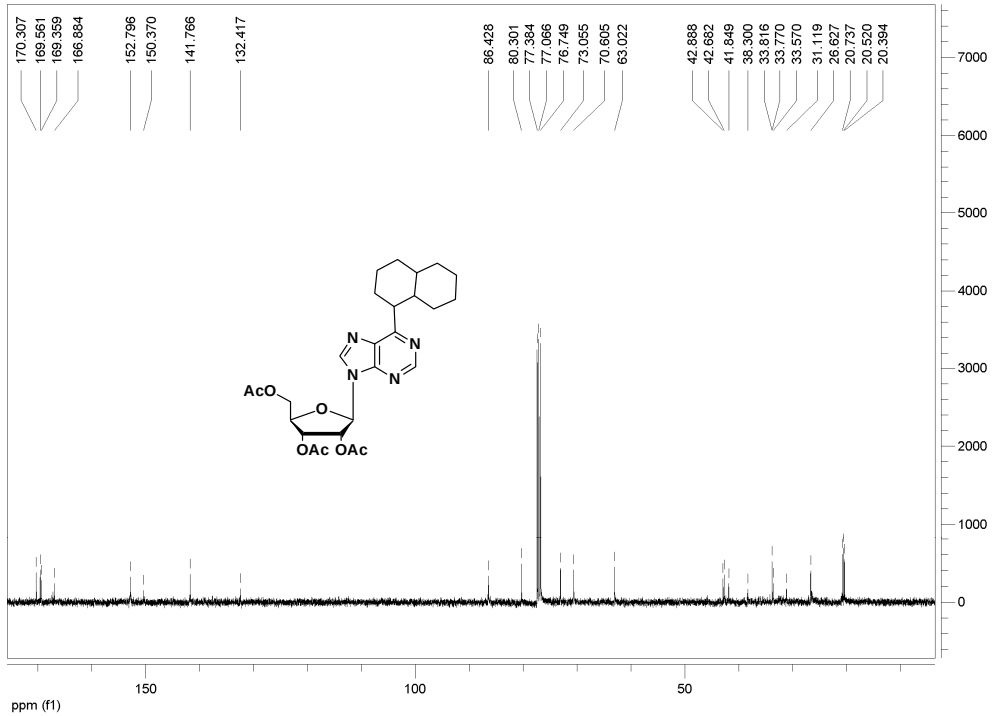
^{13}C NMR Spectrum for 3k



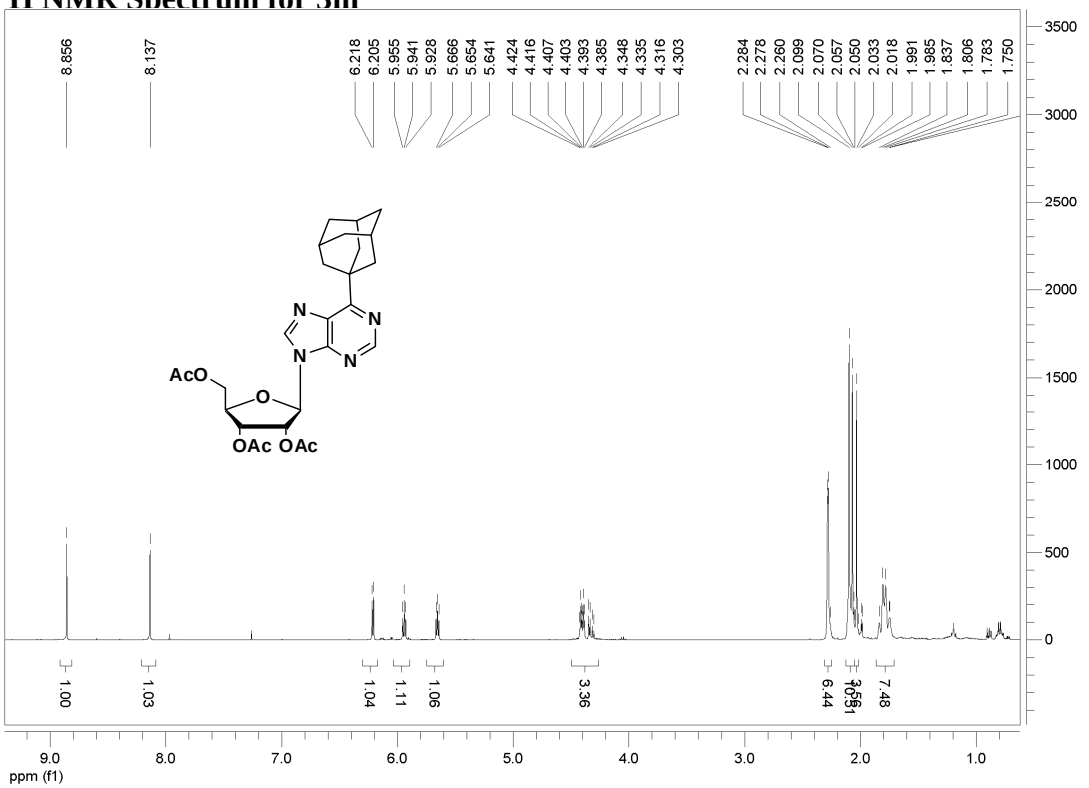
^{1}H NMR Spectrum for 3l



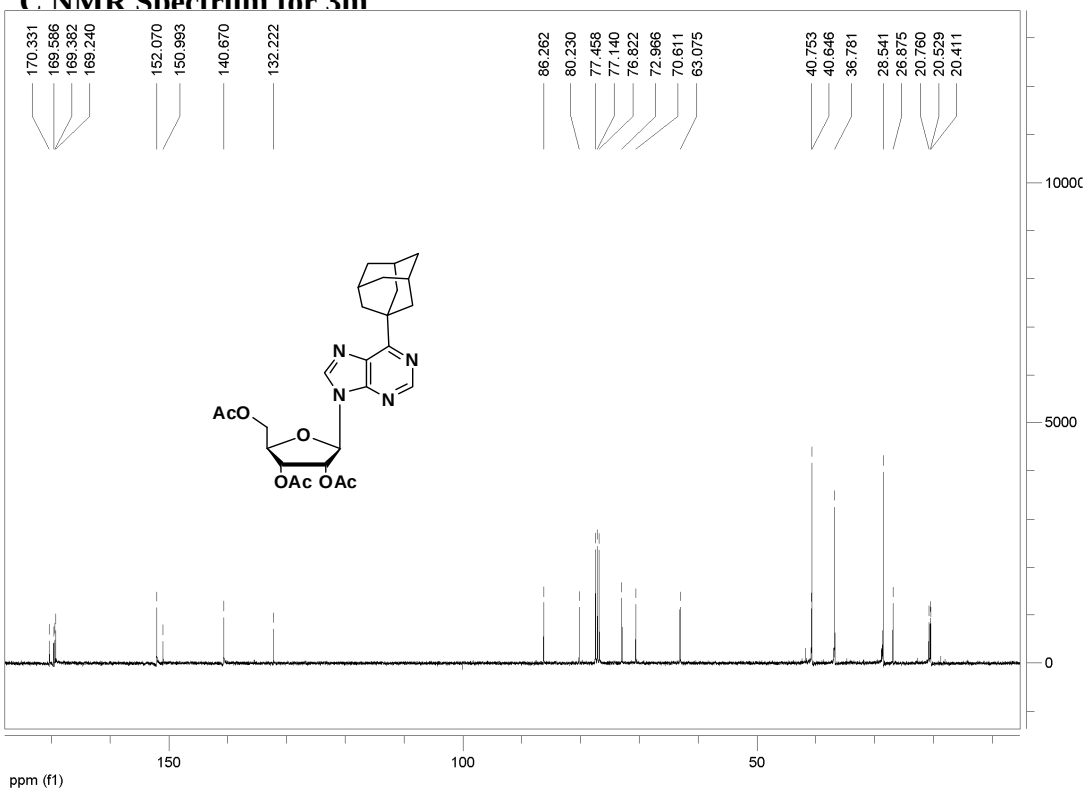
^{13}C NMR Spectrum for 3l



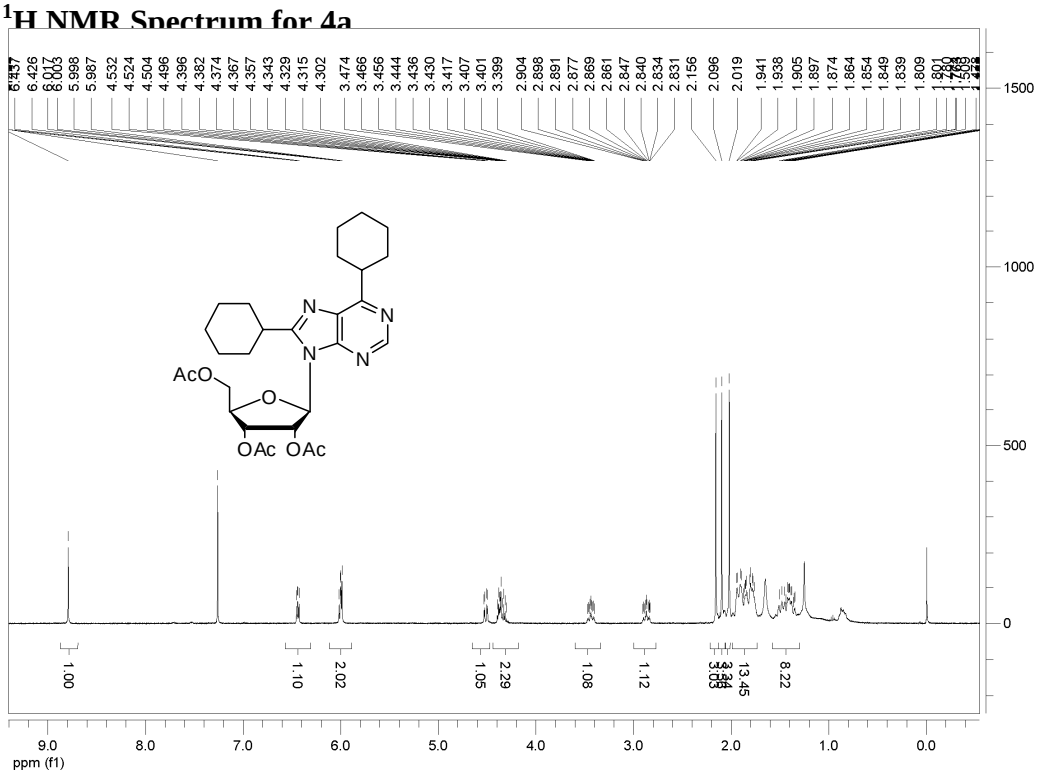
^{1}H NMR Spectrum for 3m



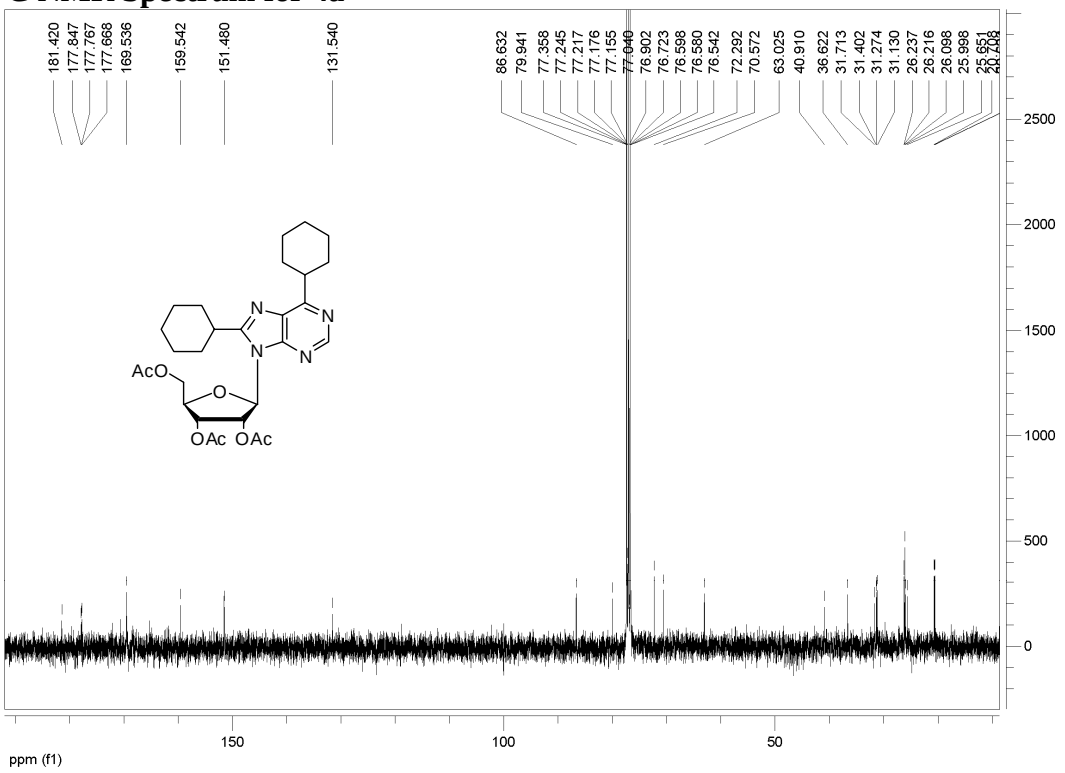
^{13}C NMR Spectrum for 3m



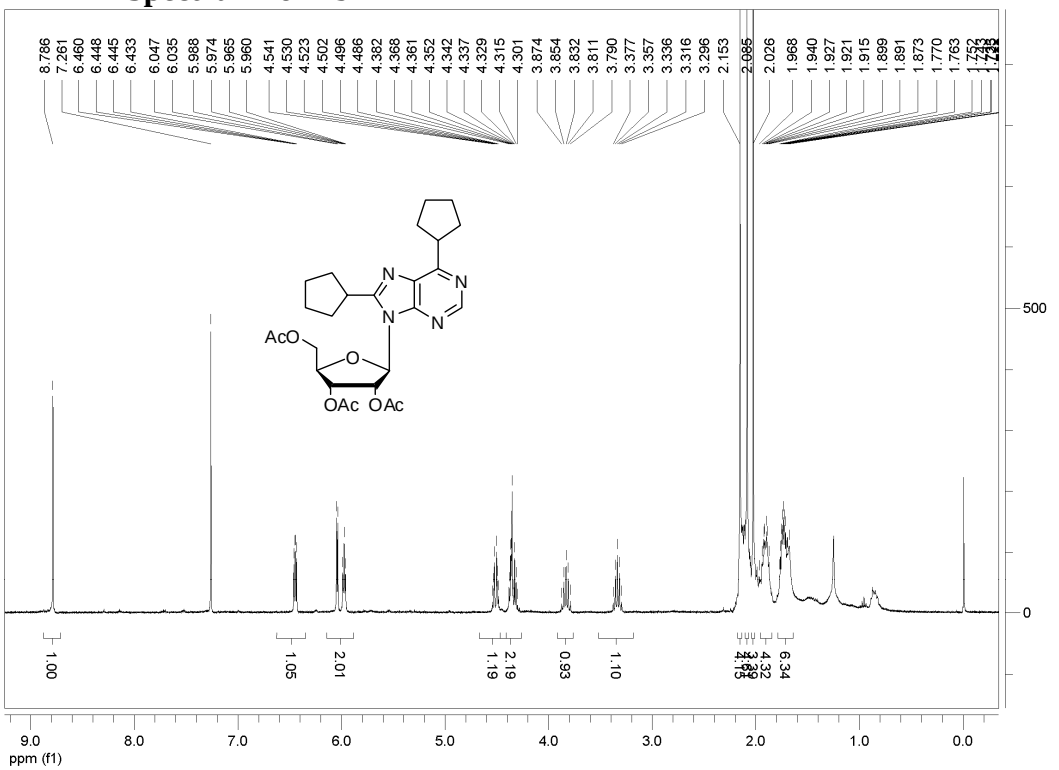
^{1}H NMR Spectrum for 4a



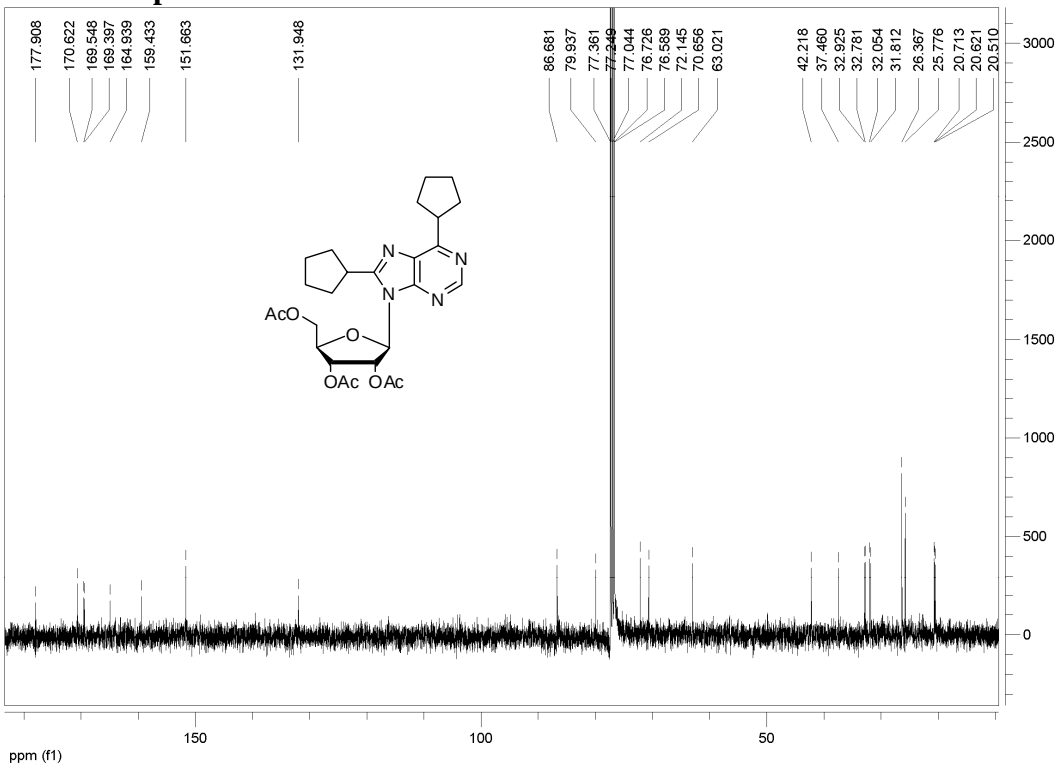
^{13}C NMR Spectrum for 4a



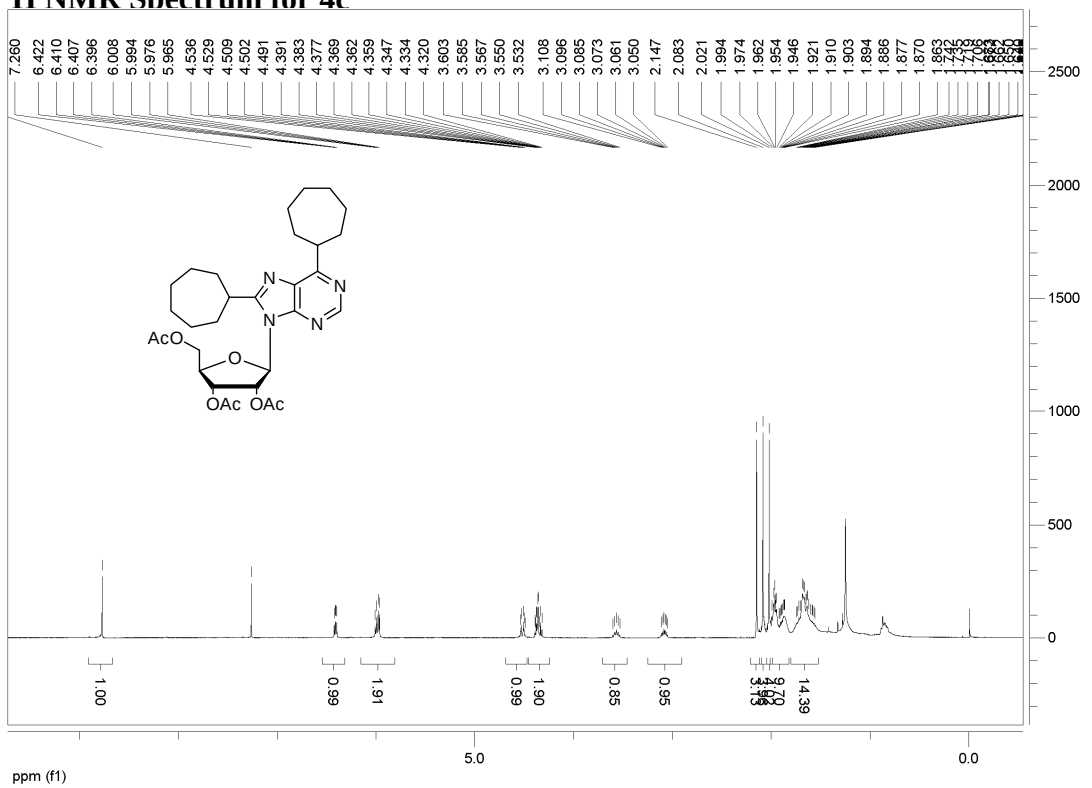
^{1}H NMR Spectrum for 4b



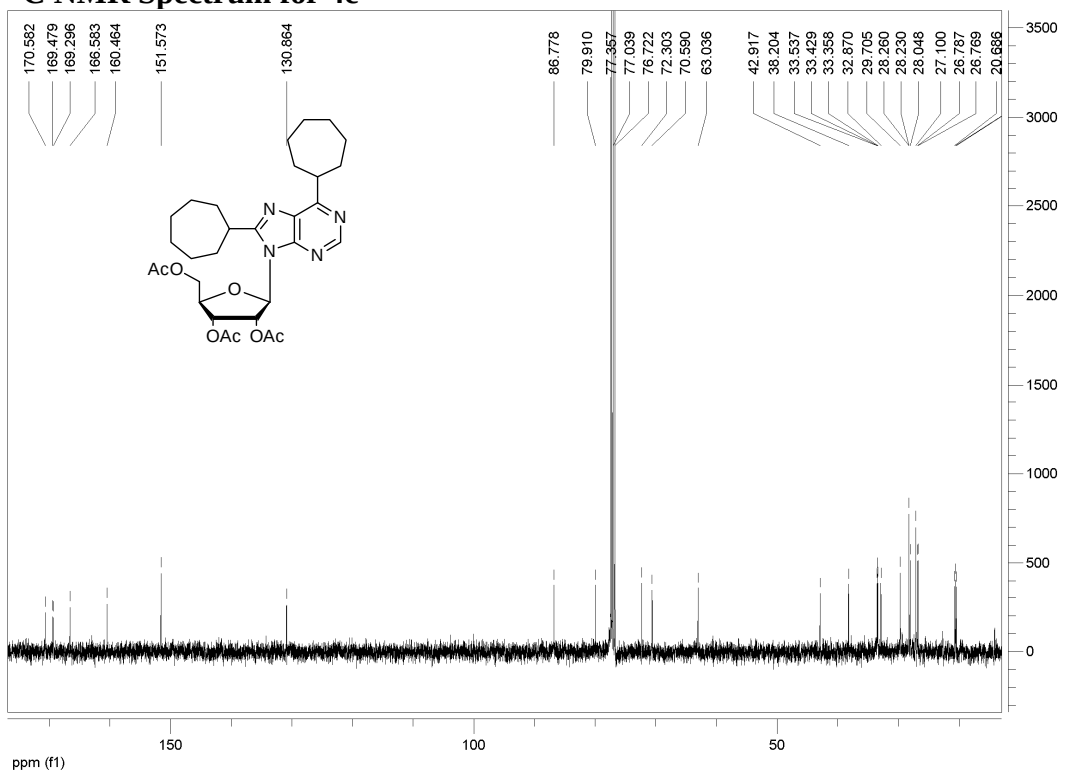
^{13}C NMR Spectrum for 4b



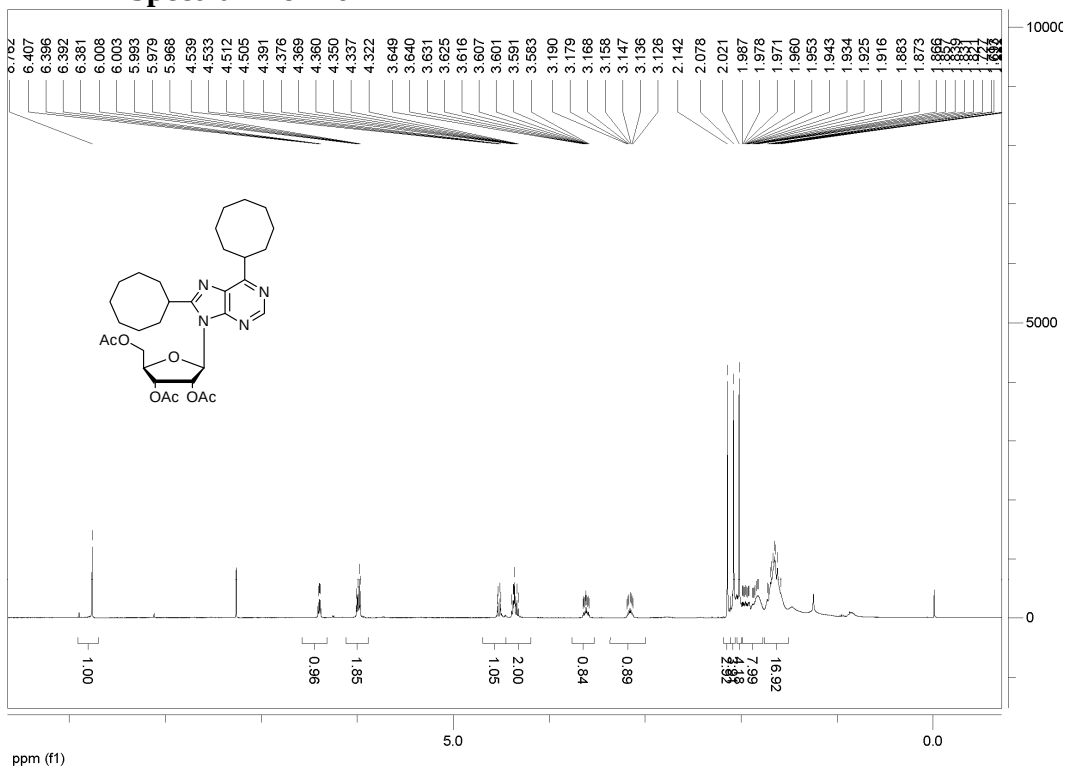
^{1}H NMR Spectrum for 4c



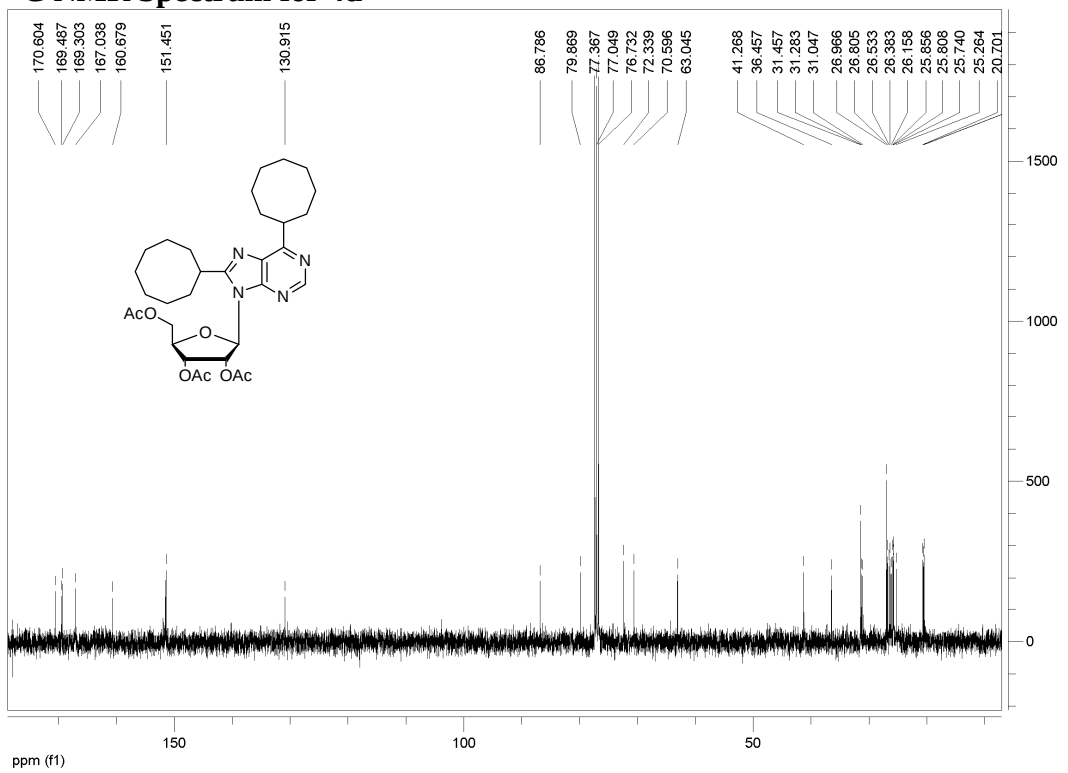
^{13}C NMR Spectrum for 4c



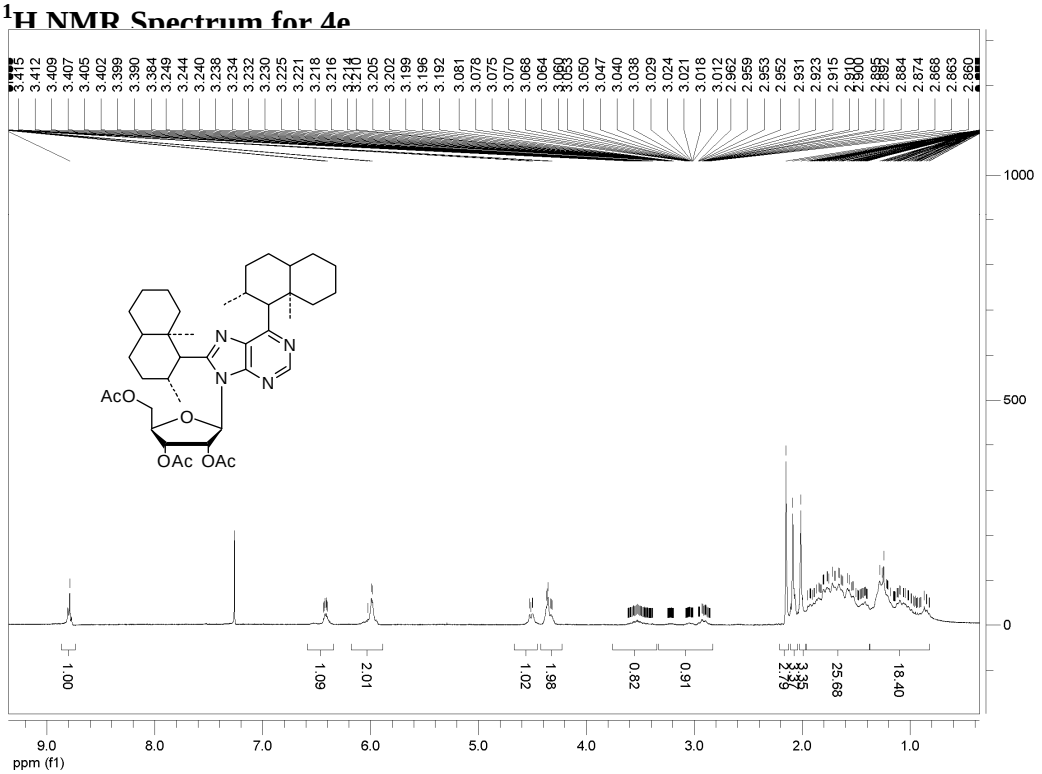
^{1}H NMR Spectrum for 4d



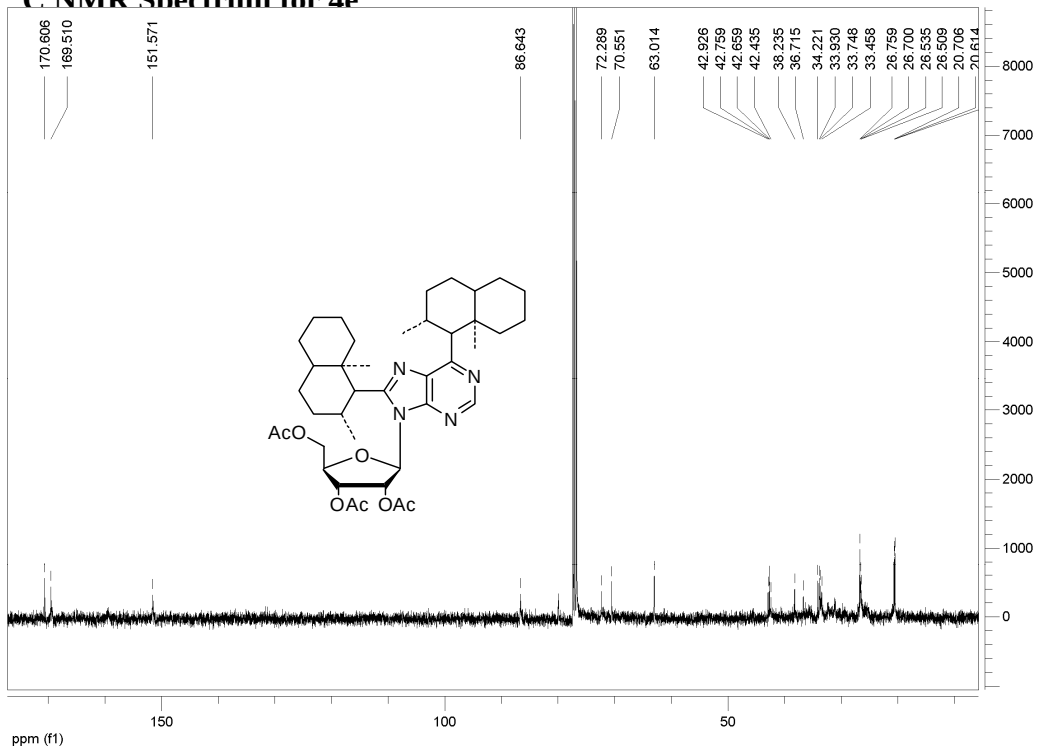
^{13}C NMR Spectrum for 4d



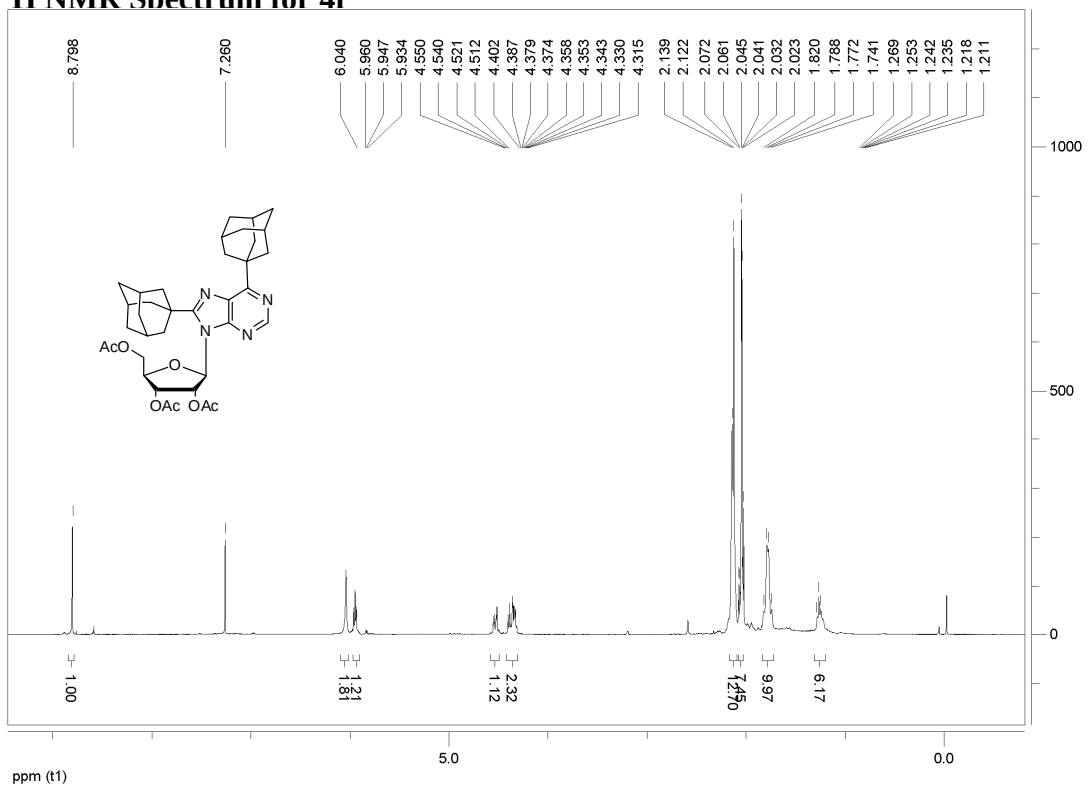
^{1}H NMR Spectrum for 4e



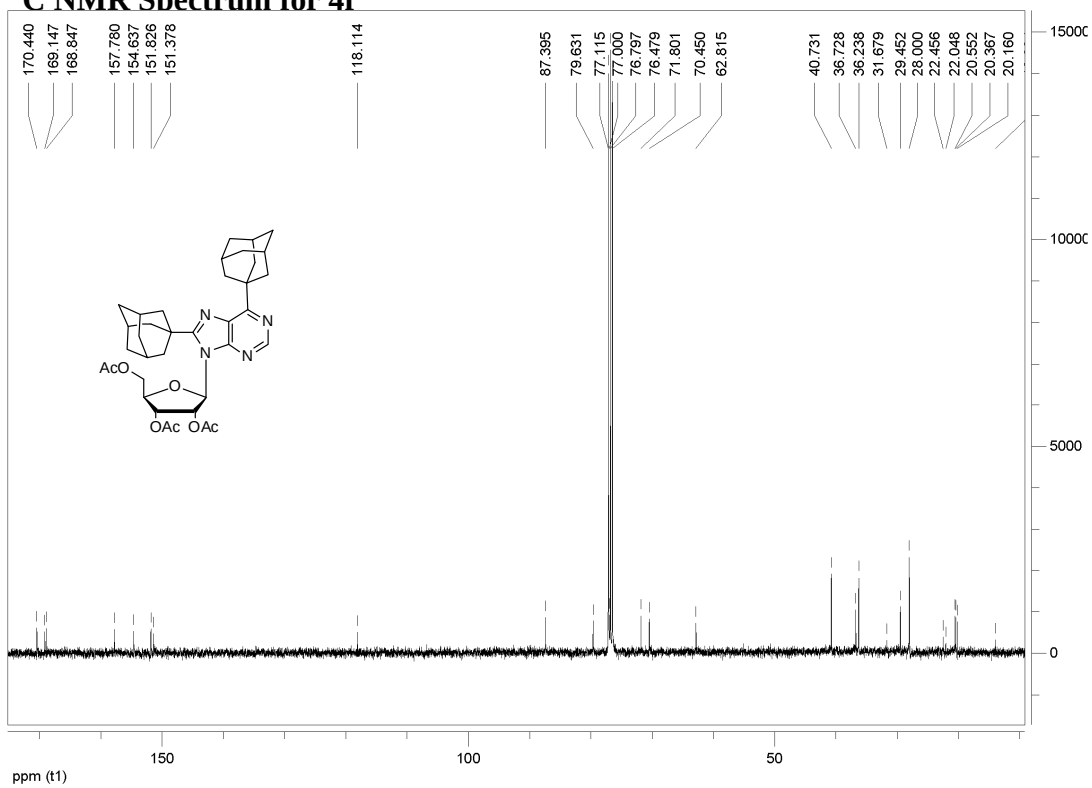
^{13}C NMR Spectrum for 4e



^{1}H NMR Spectrum for 4f

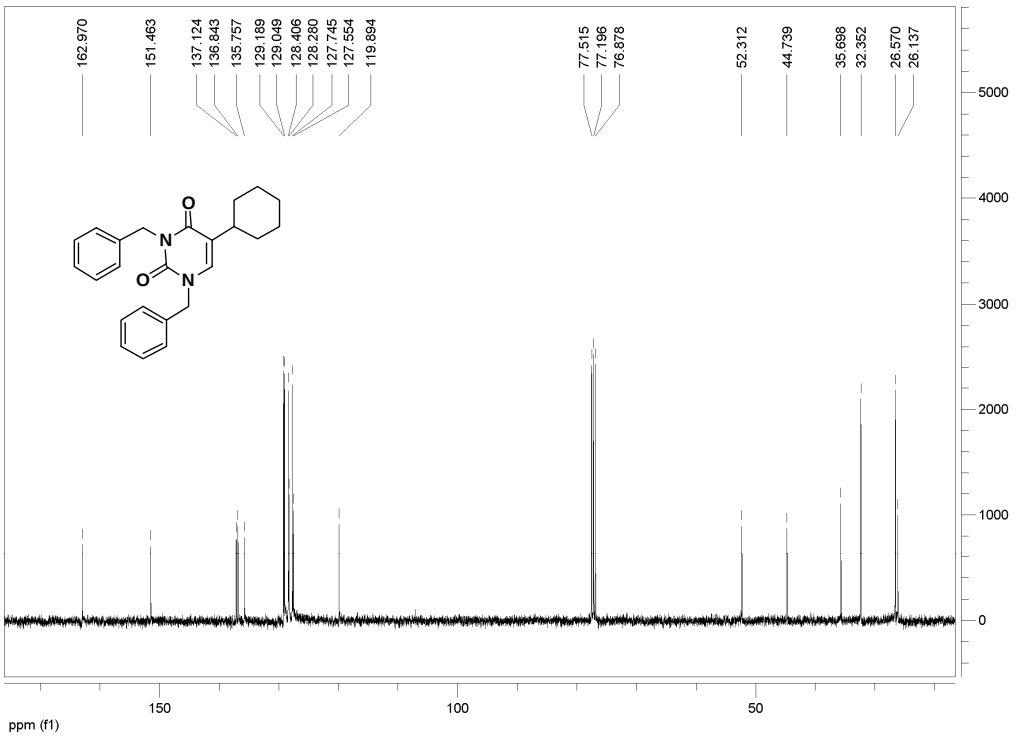


^{13}C NMR Spectrum for 4f

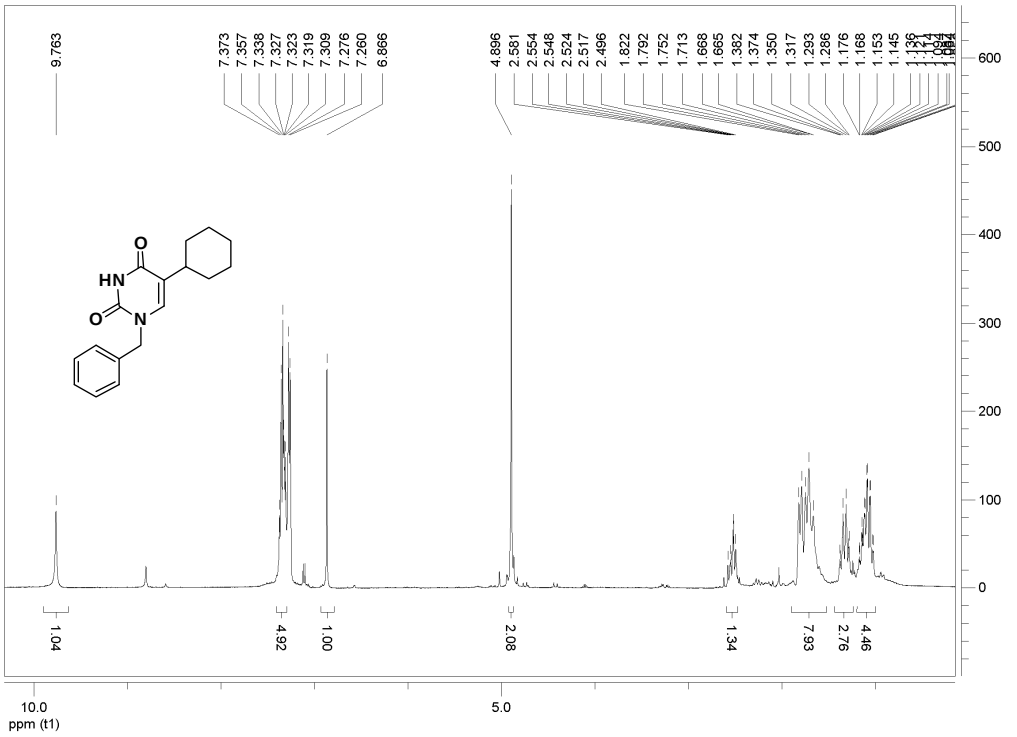


^{1}H NMR Spectrum for 6a

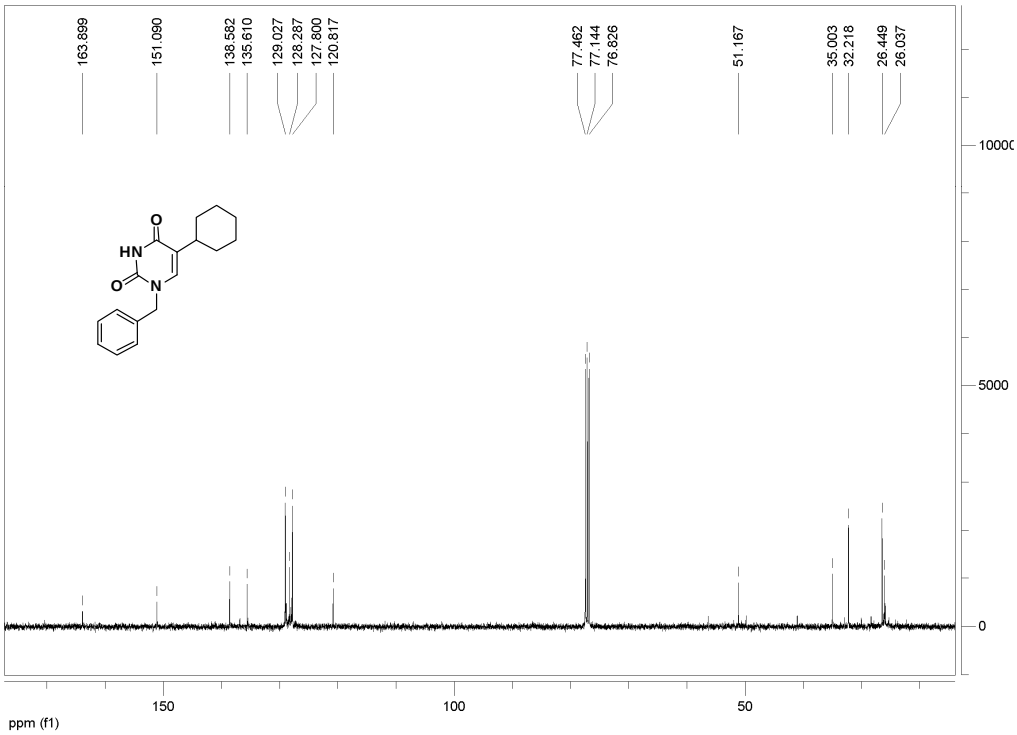
^{13}C NMR Spectrum for 6a



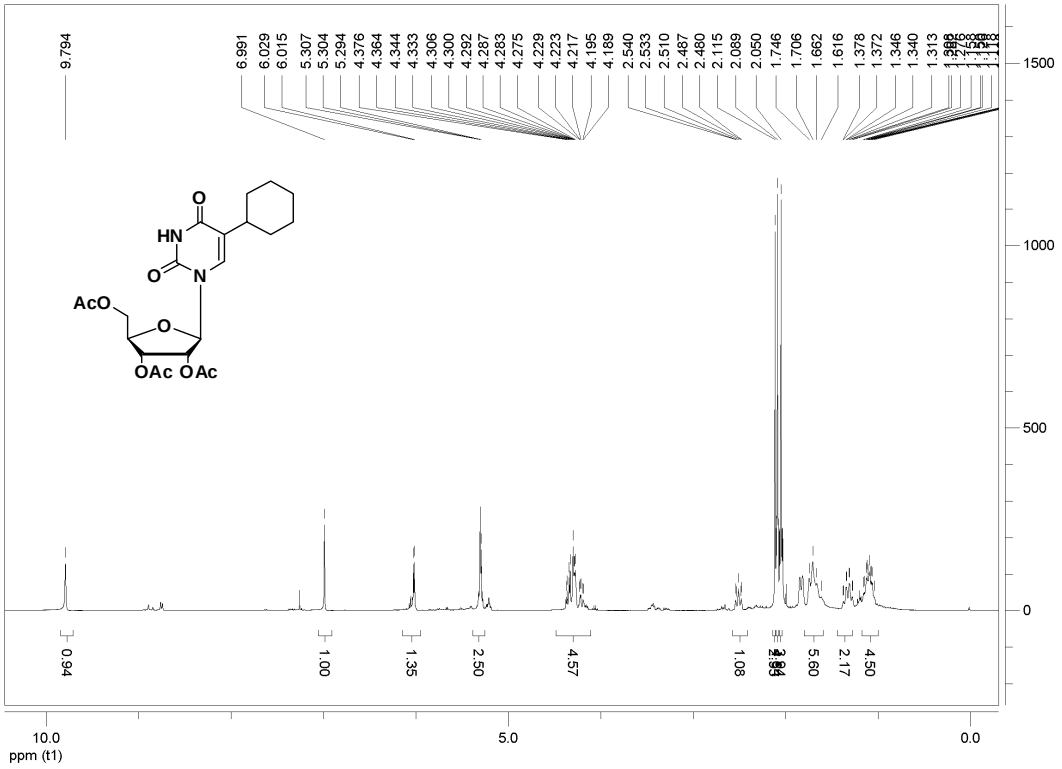
^{1}H NMR Spectrum for 6b



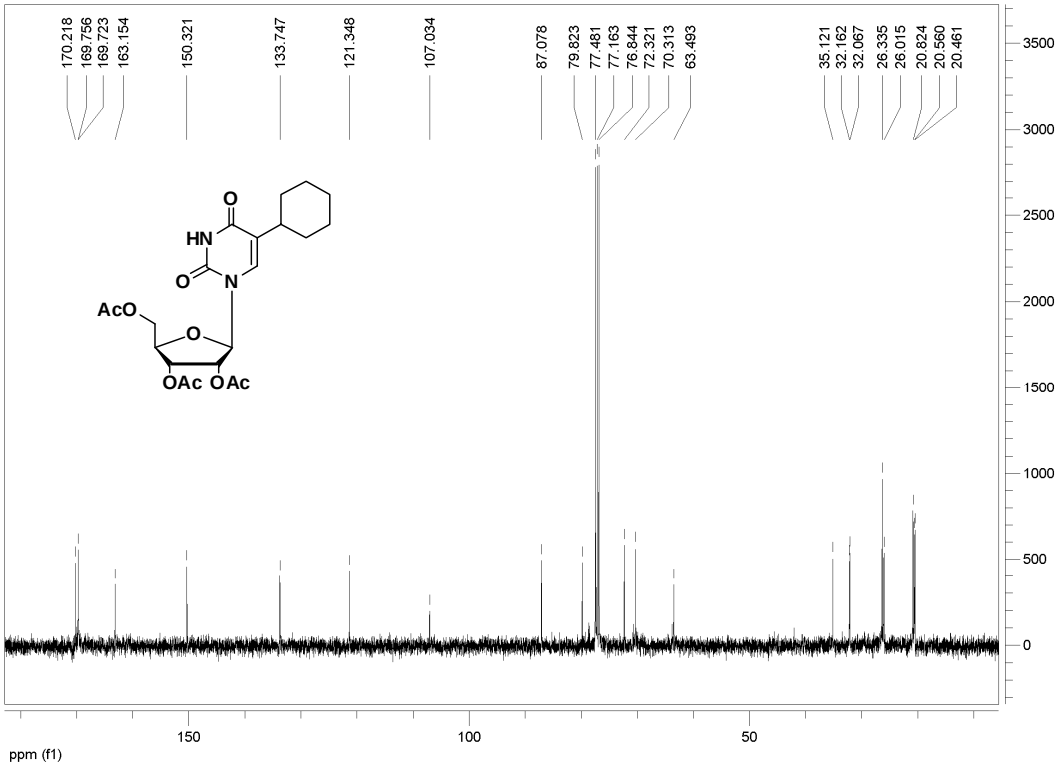
^{13}C NMR Spectrum for 6b



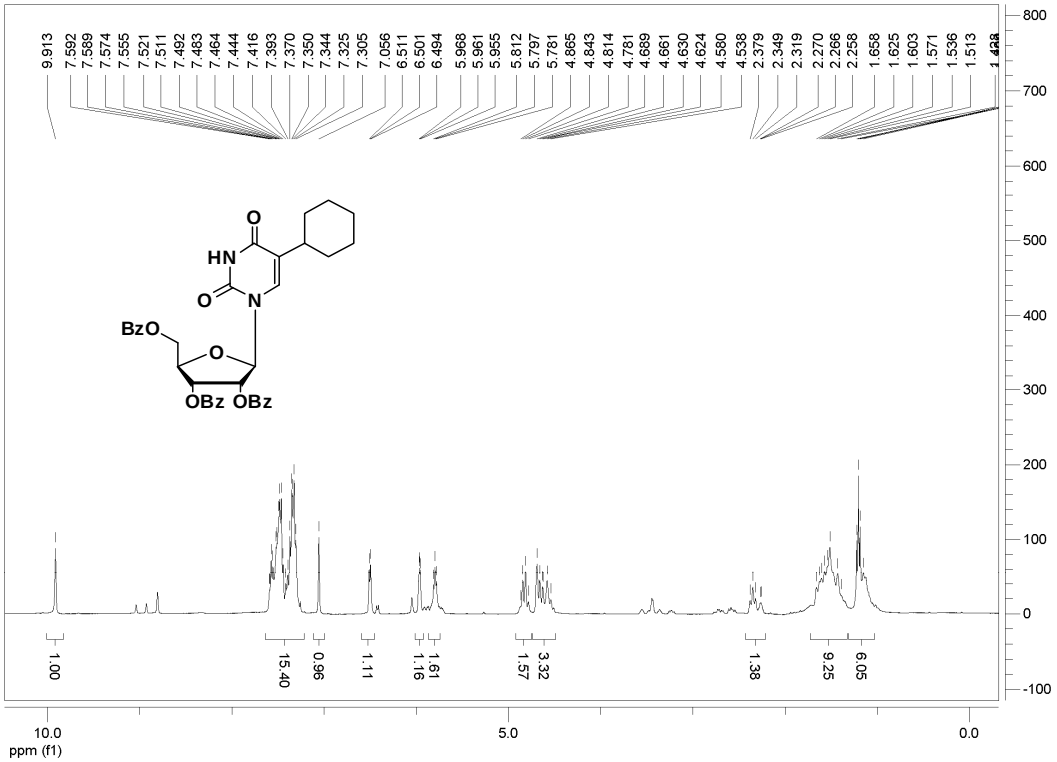
^{1}H NMR Spectrum for 6c



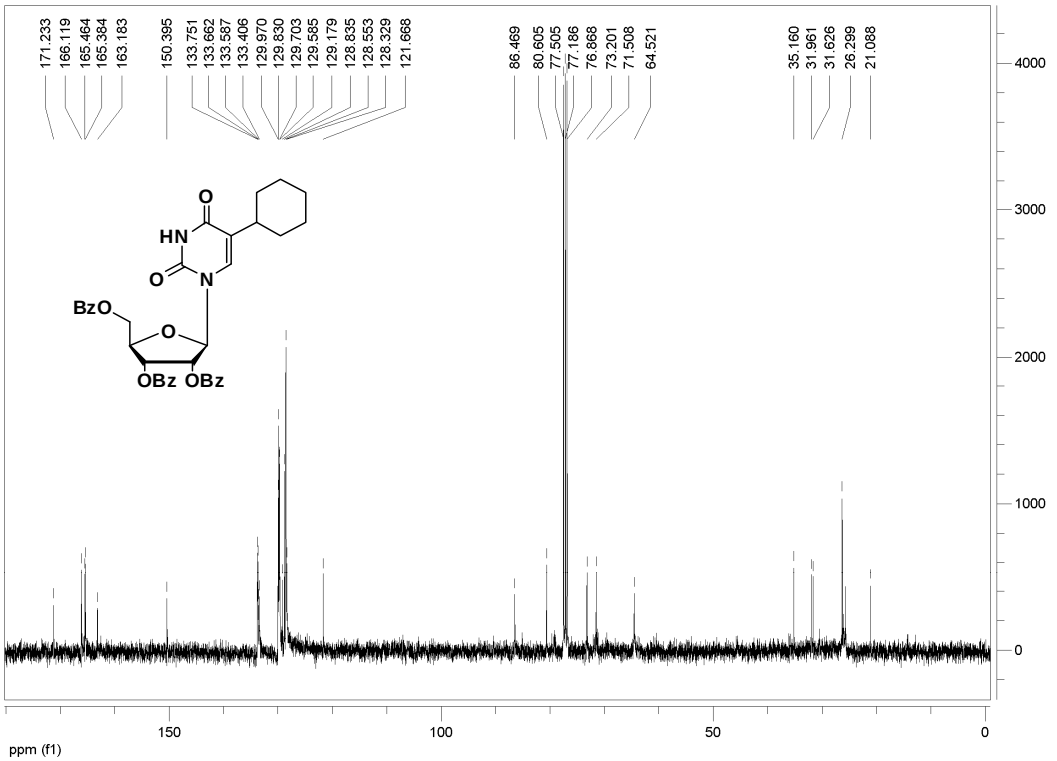
^{13}C NMR Spectrum for 6c



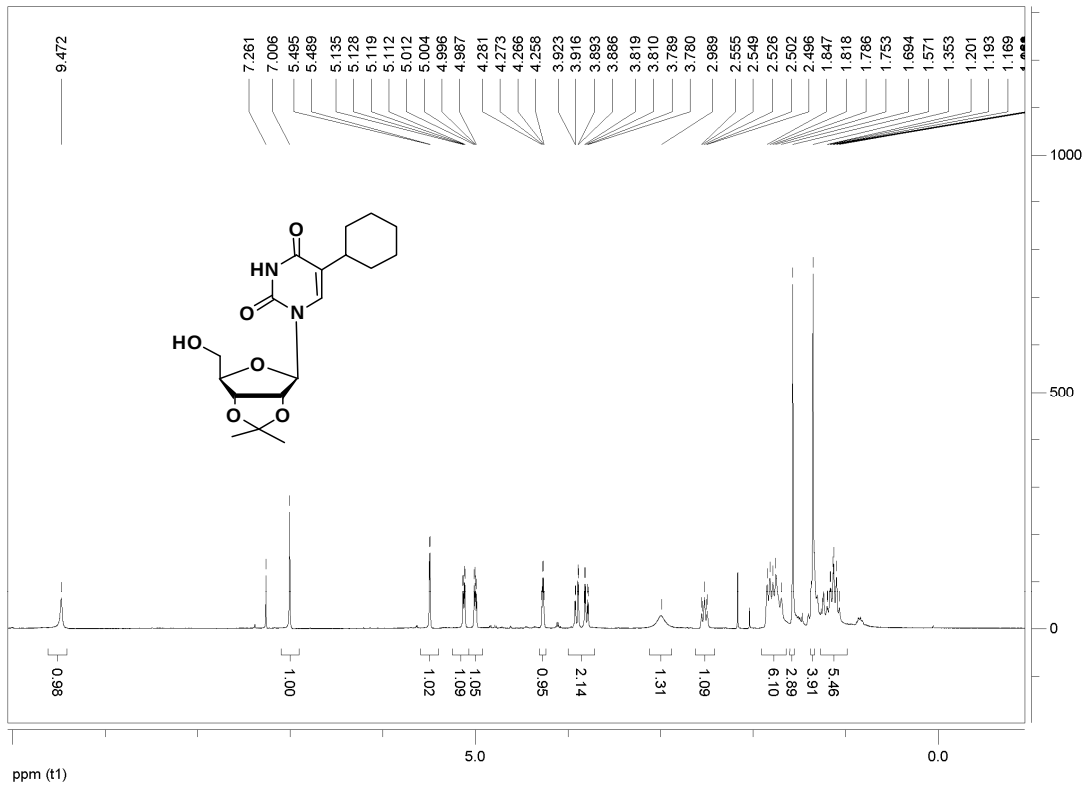
^{1}H NMR Spectrum for 6d



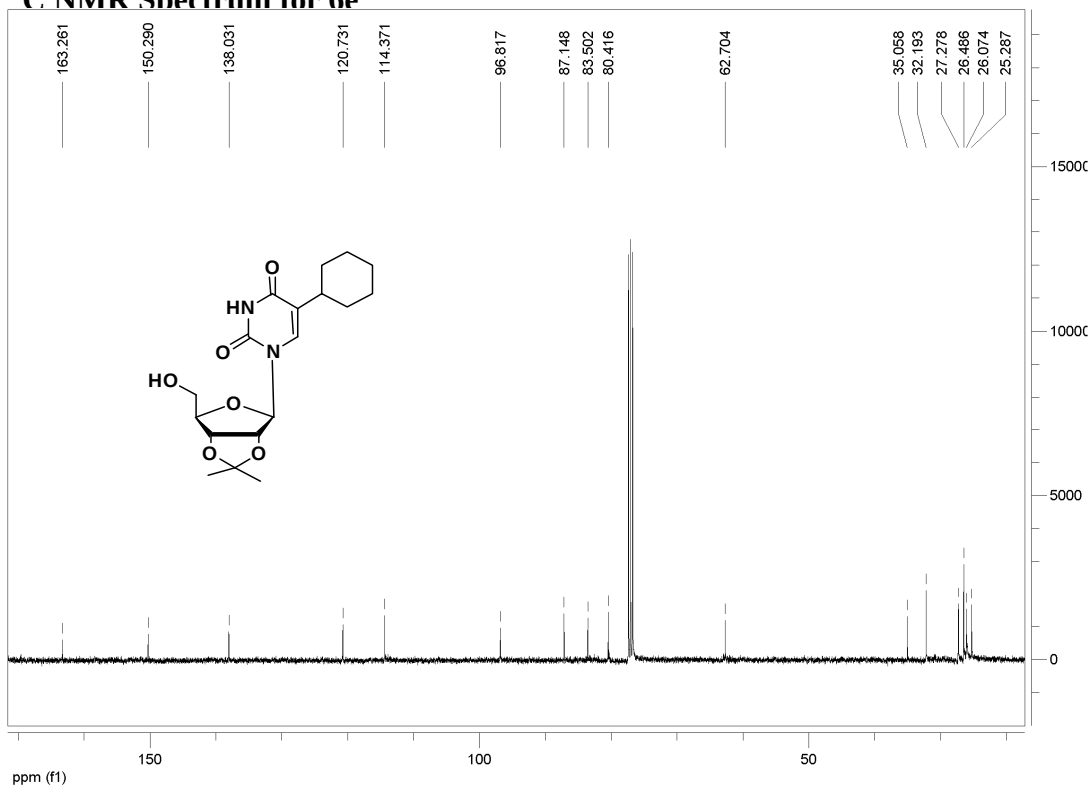
^{13}C NMR Spectrum for 6d



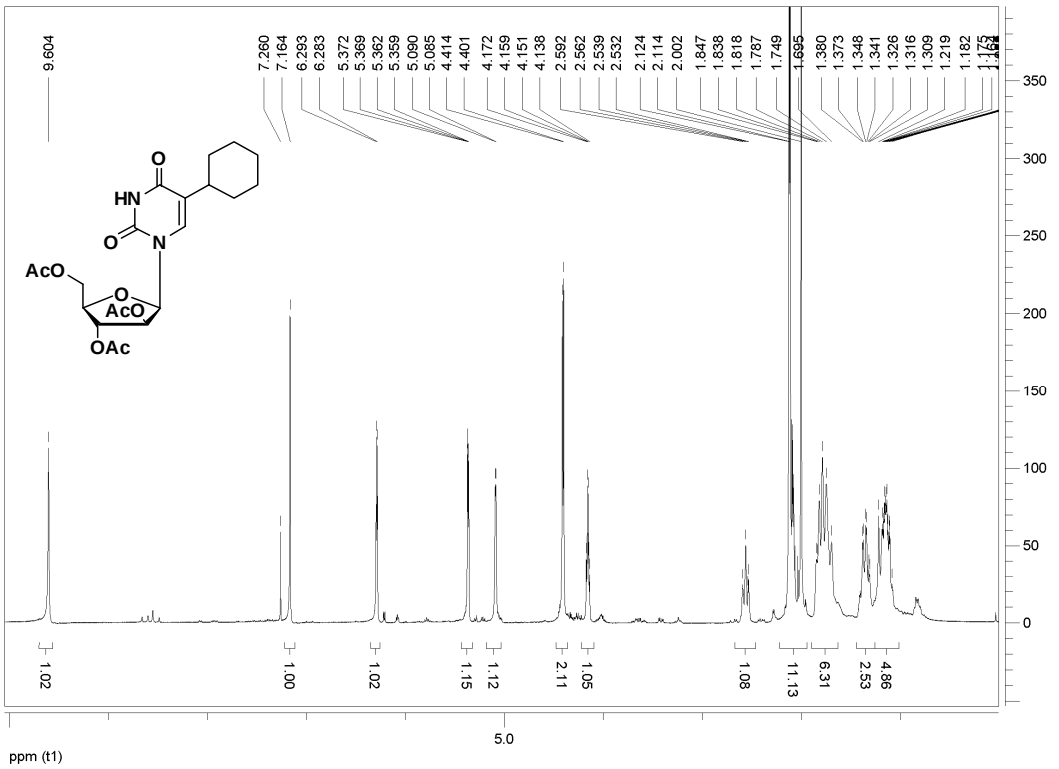
^{1}H NMR Spectrum for 6e



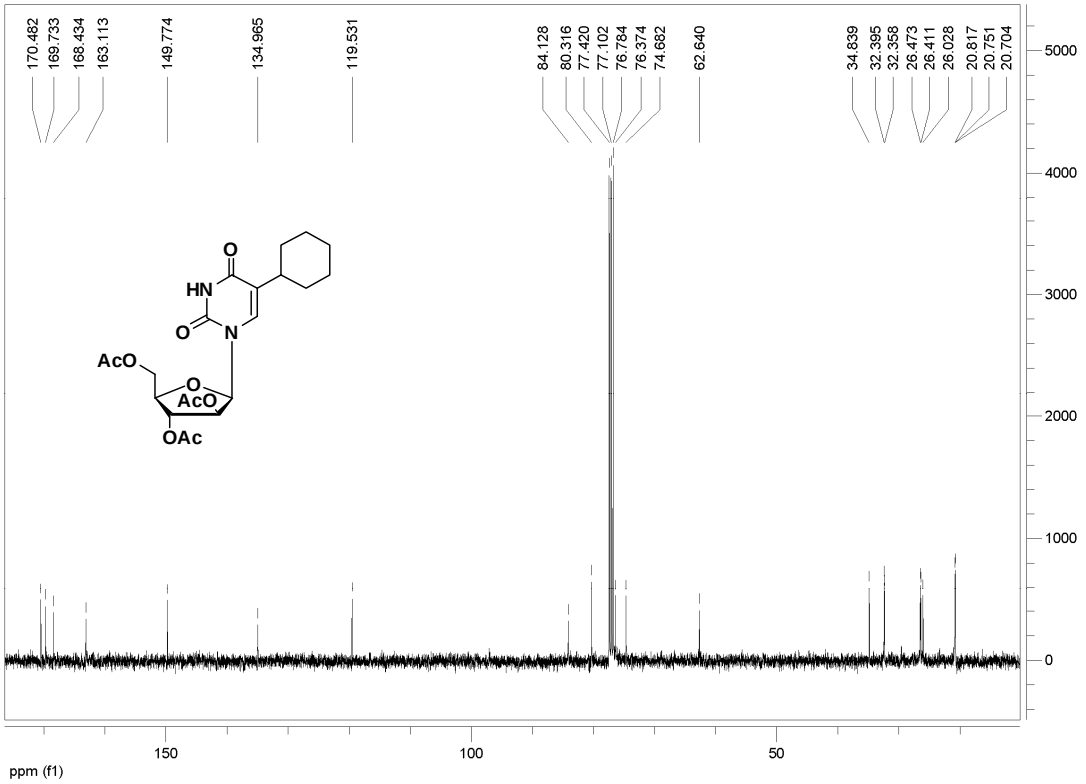
^{13}C NMR Spectrum for 6e



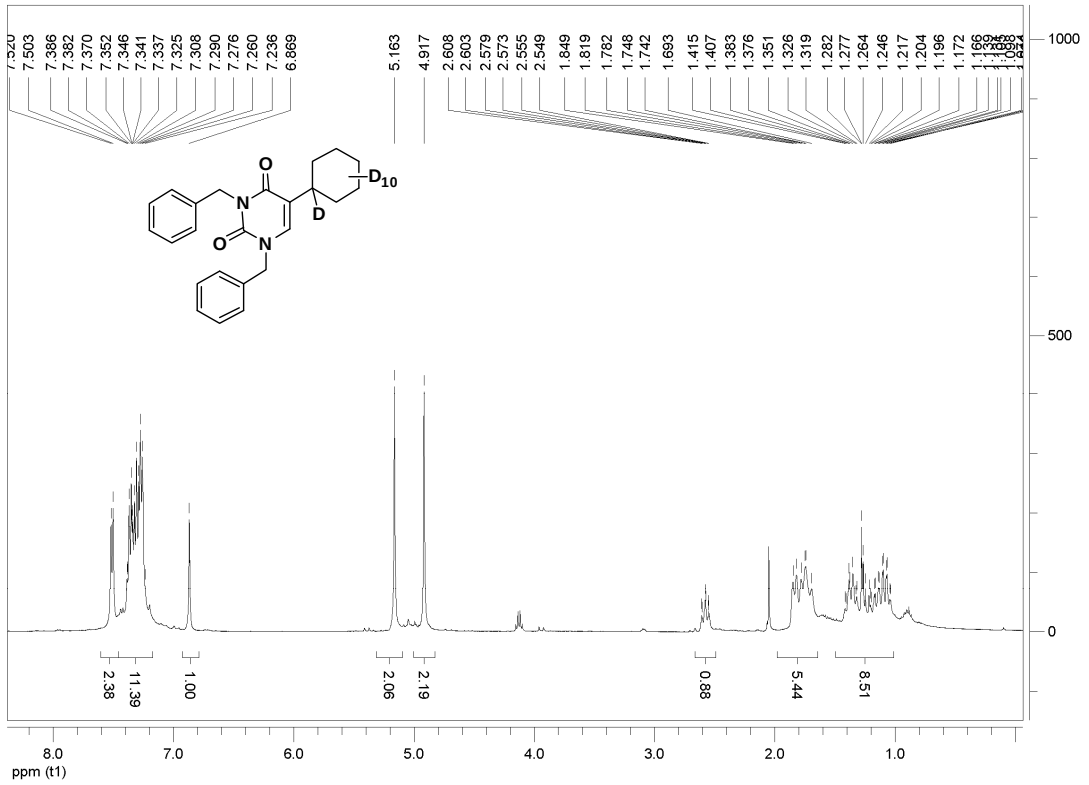
^{1}H NMR Spectrum for 6f



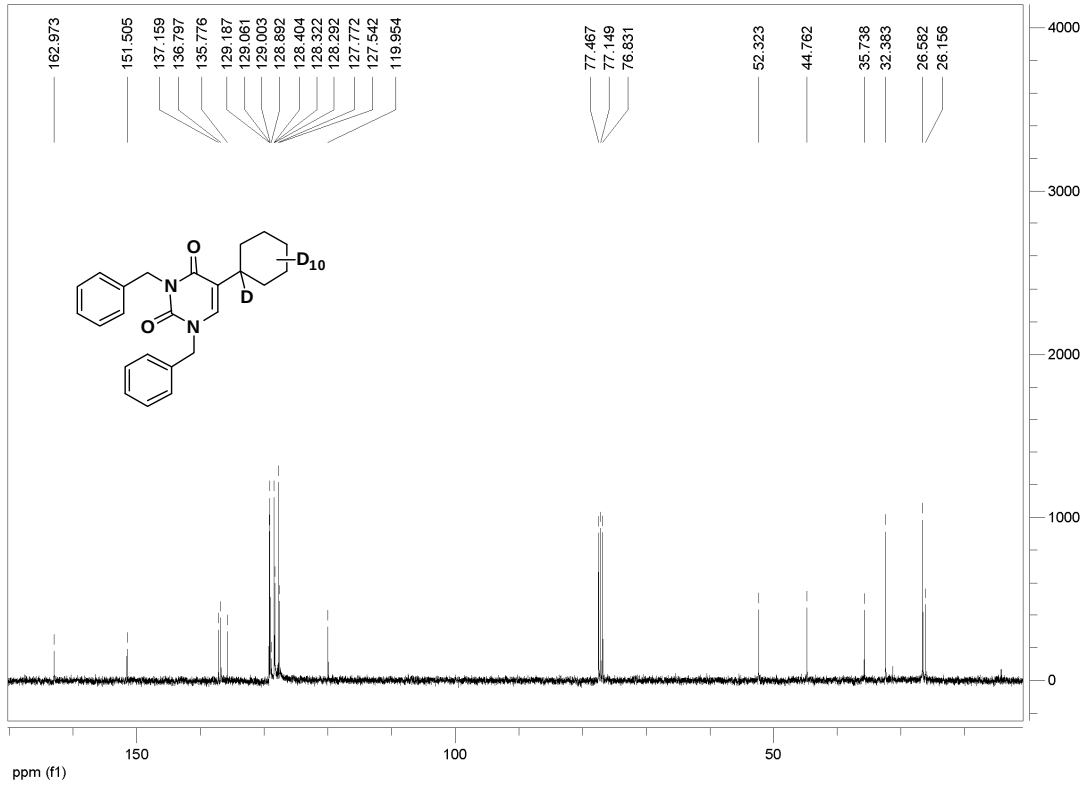
^{13}C NMR Spectrum for 6f



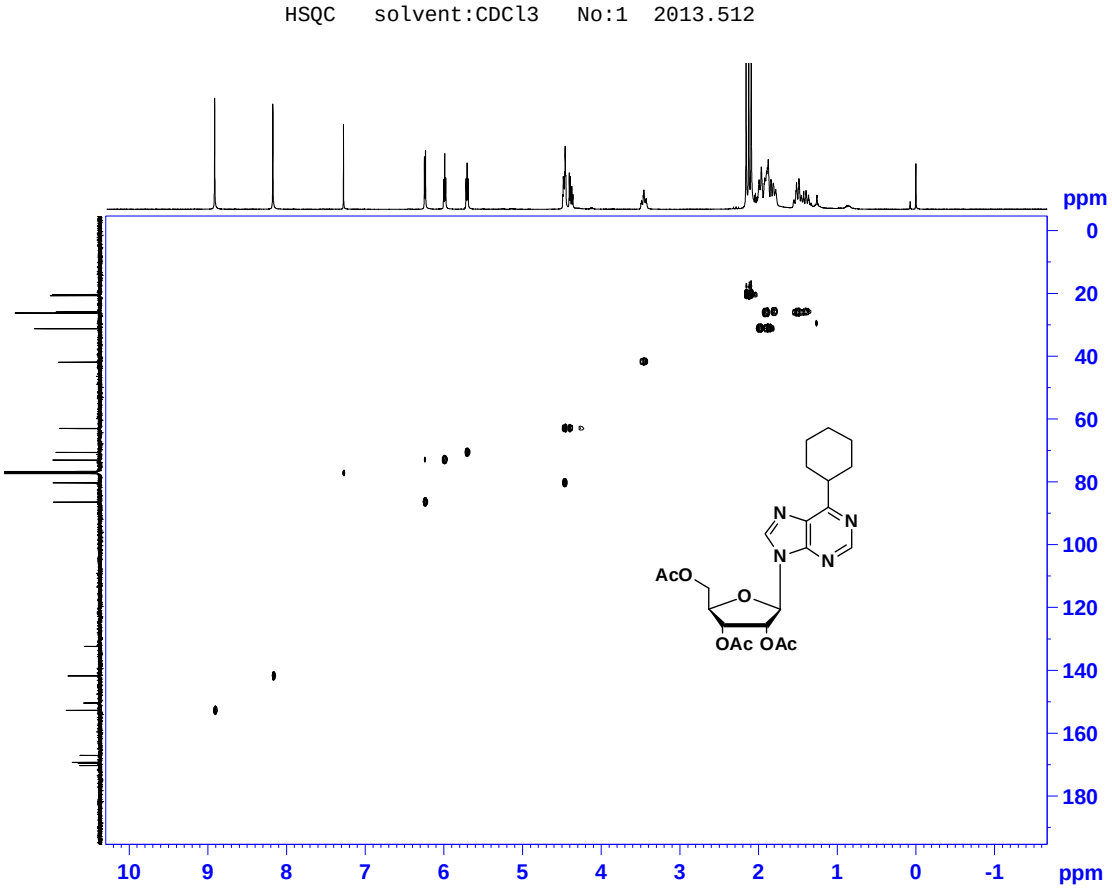
^{1}H NMR Spectrum for 6a-D$_{11}$

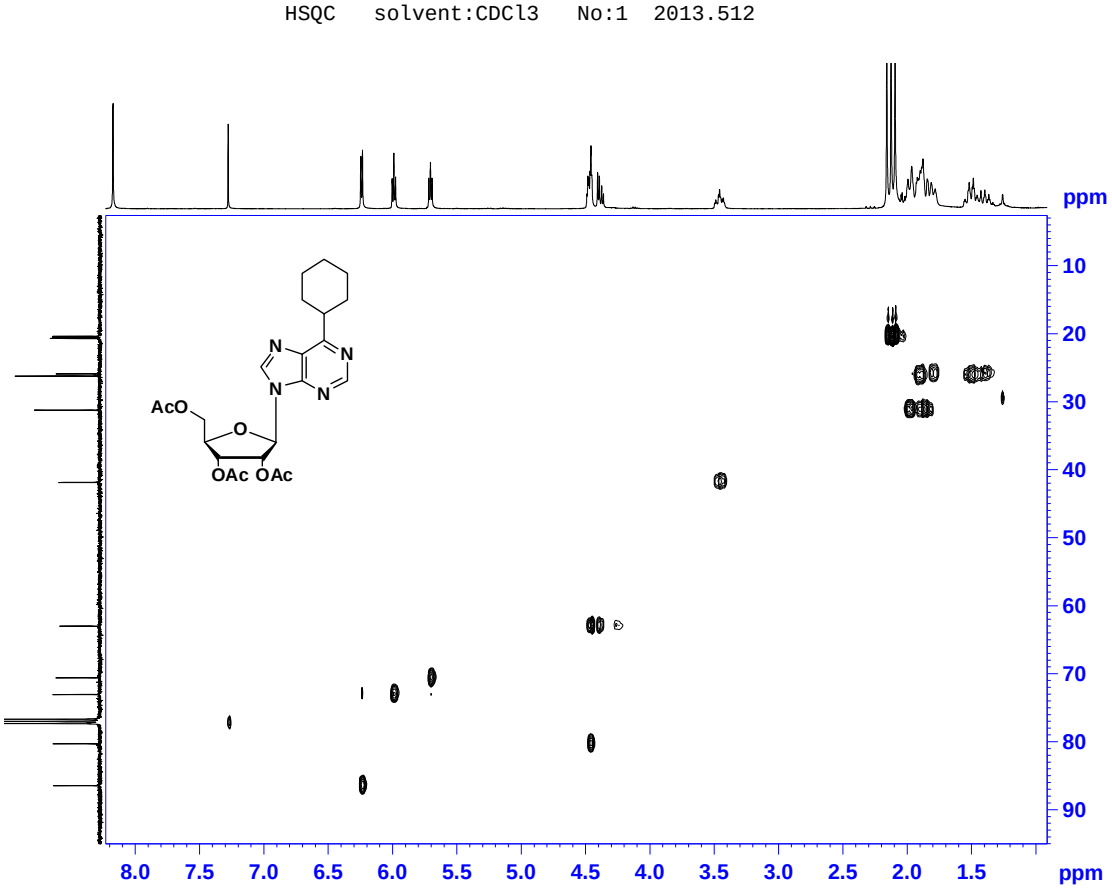


^{13}C NMR Spectrum for 6a-D

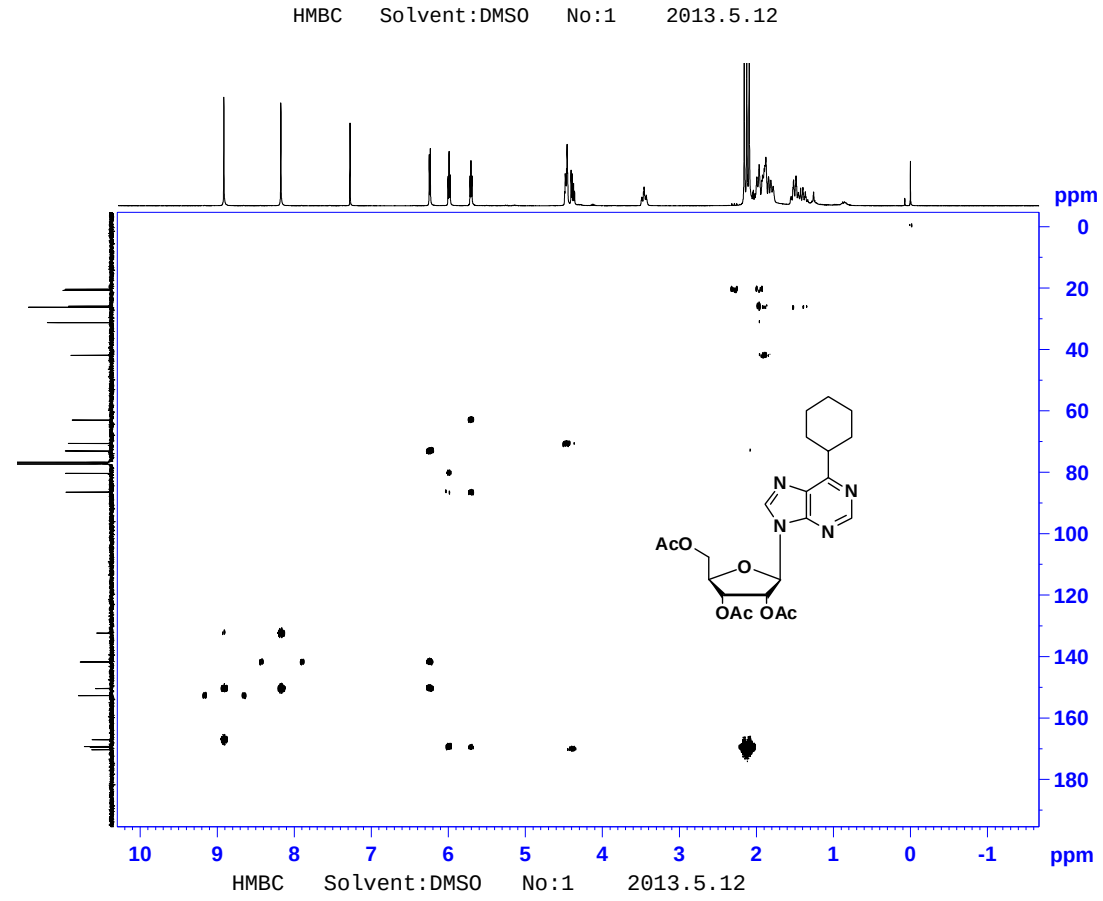


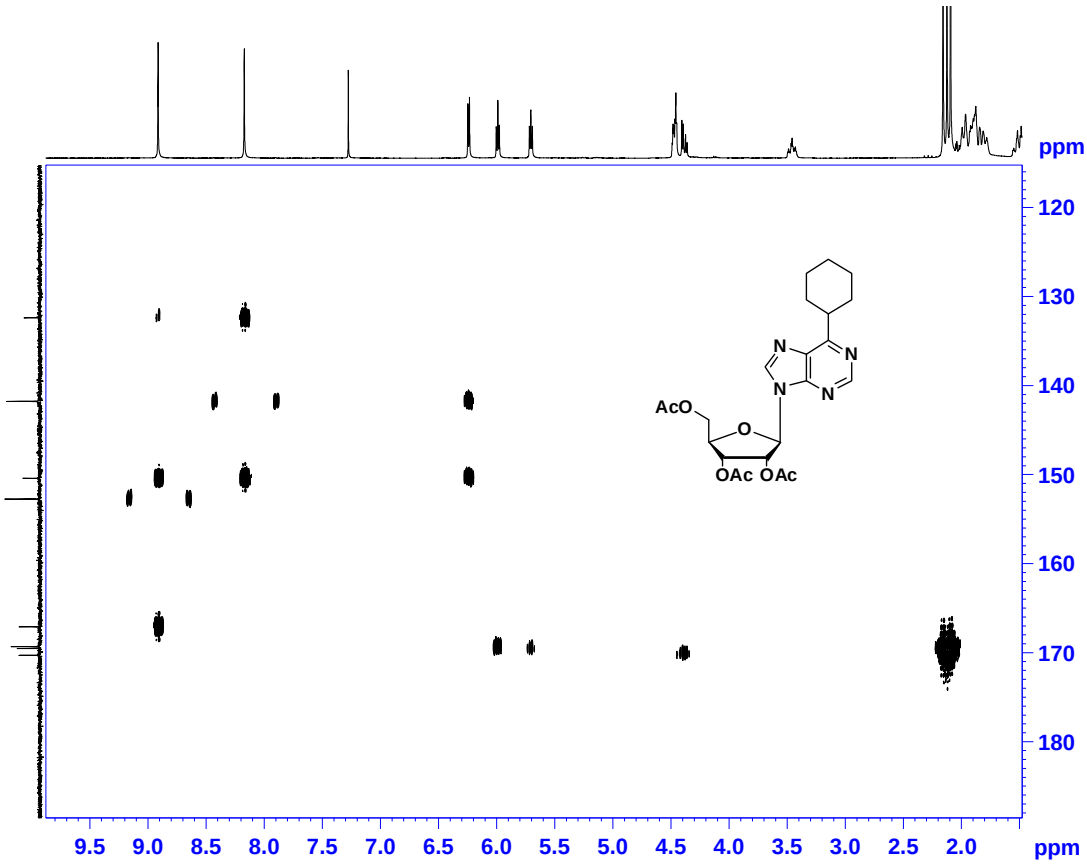
HSQC NMR Spectrum for 3a

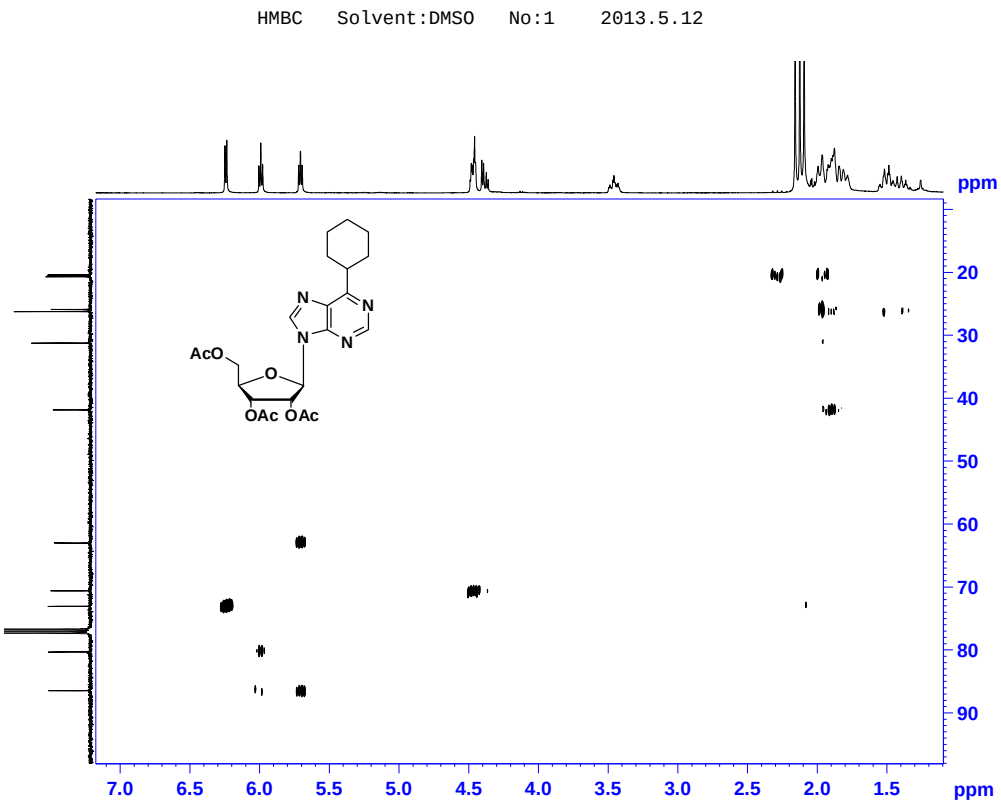




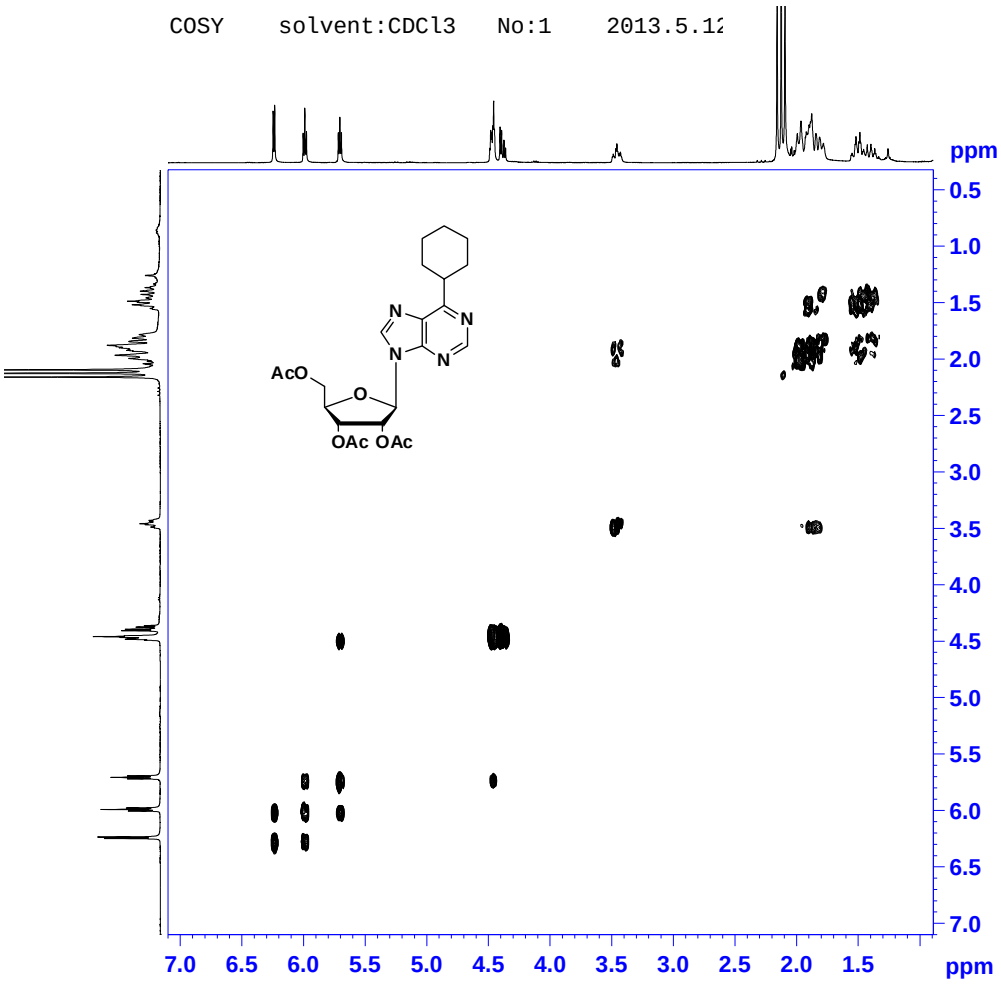
HMBC NMR Spectrum for 3a



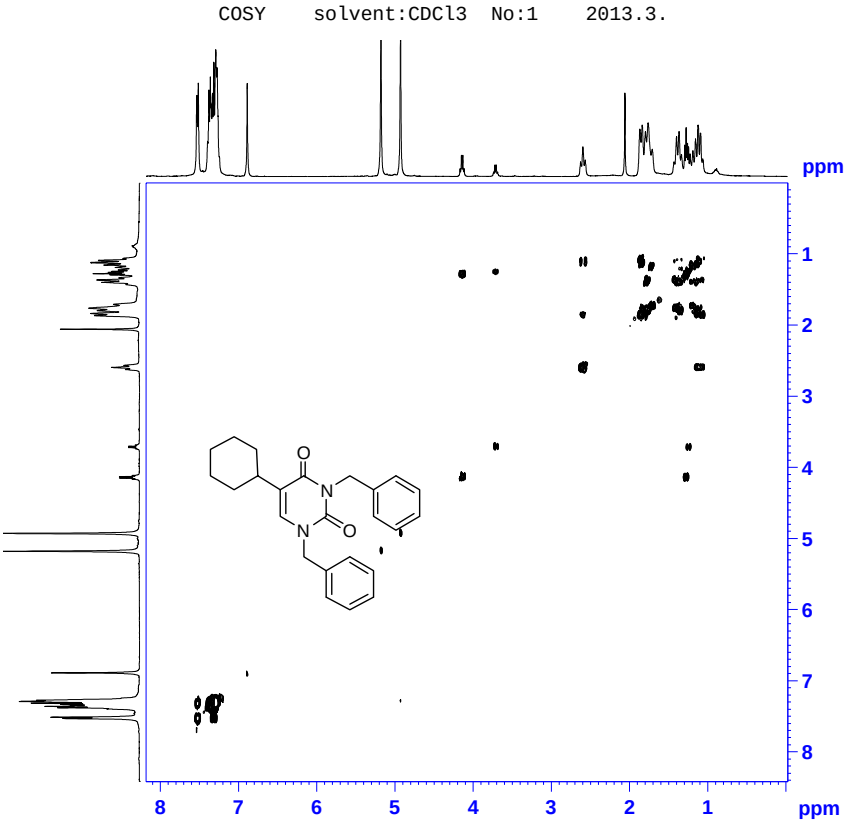




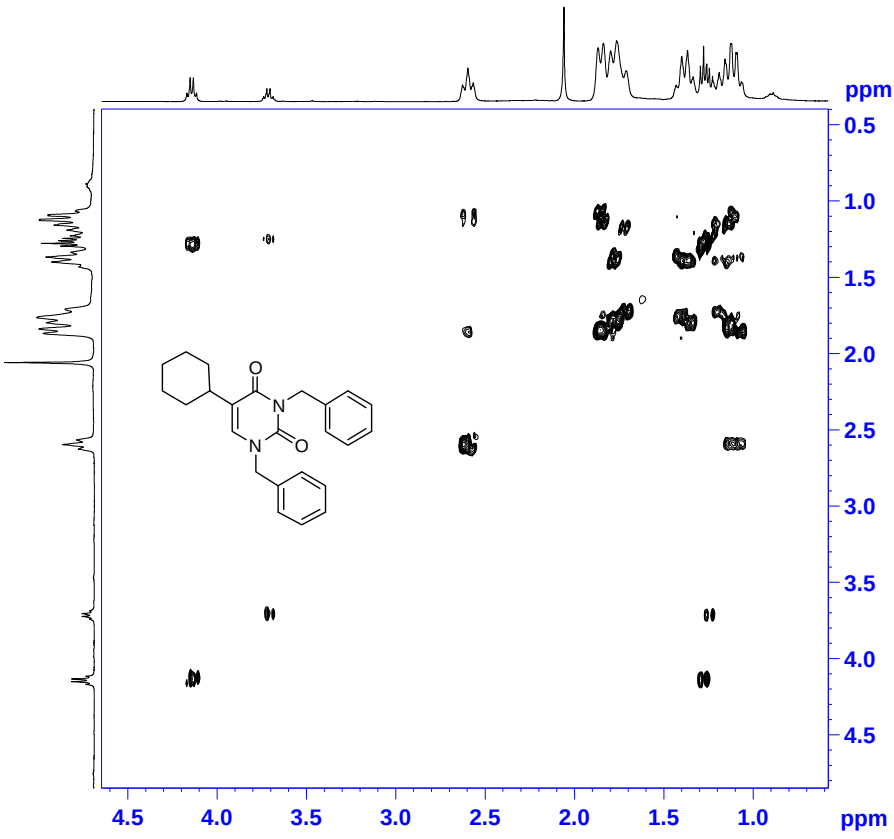
COSY NMR Spectrum for 3a



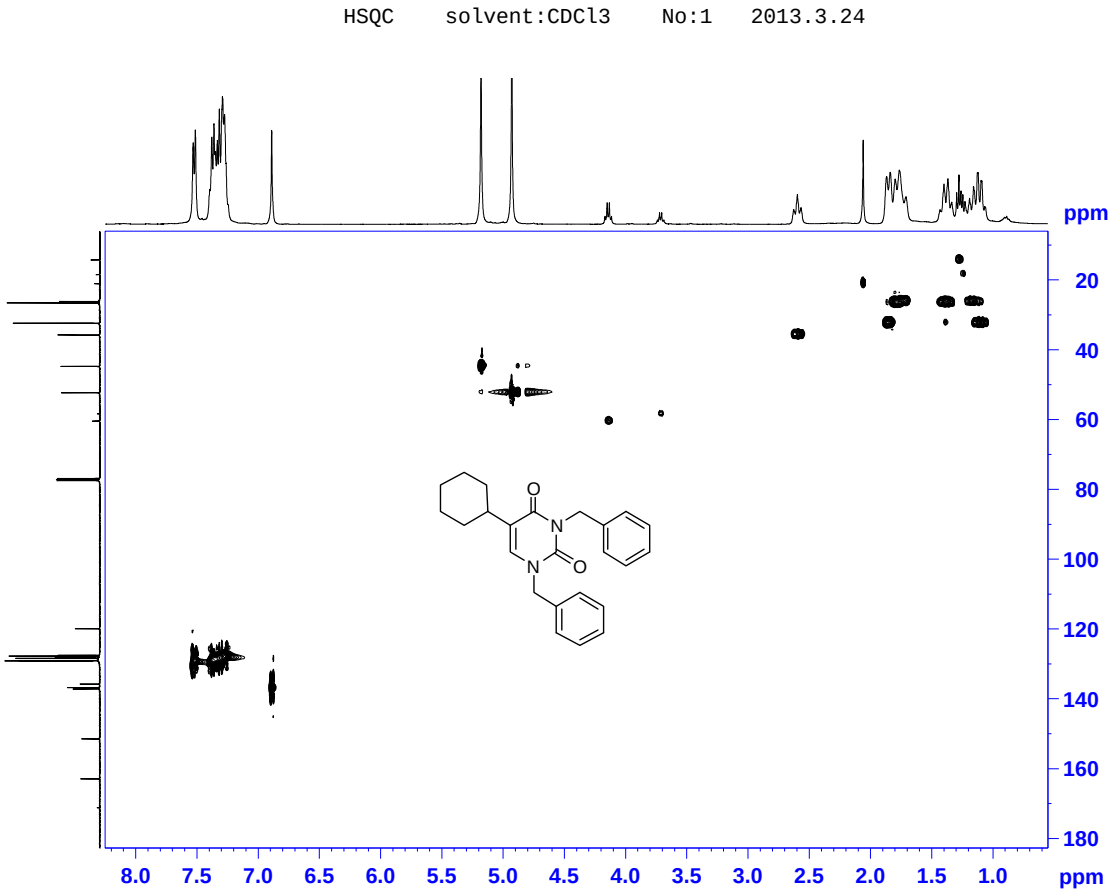
COSY NMR Spectrum for 6a

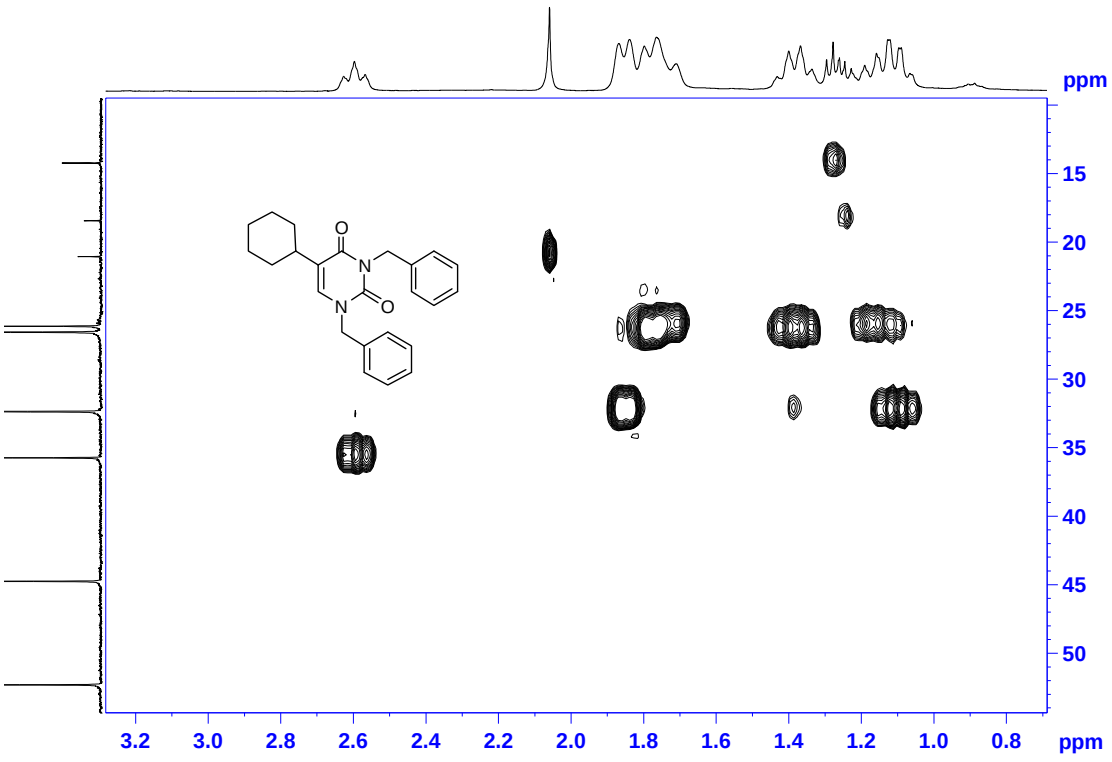


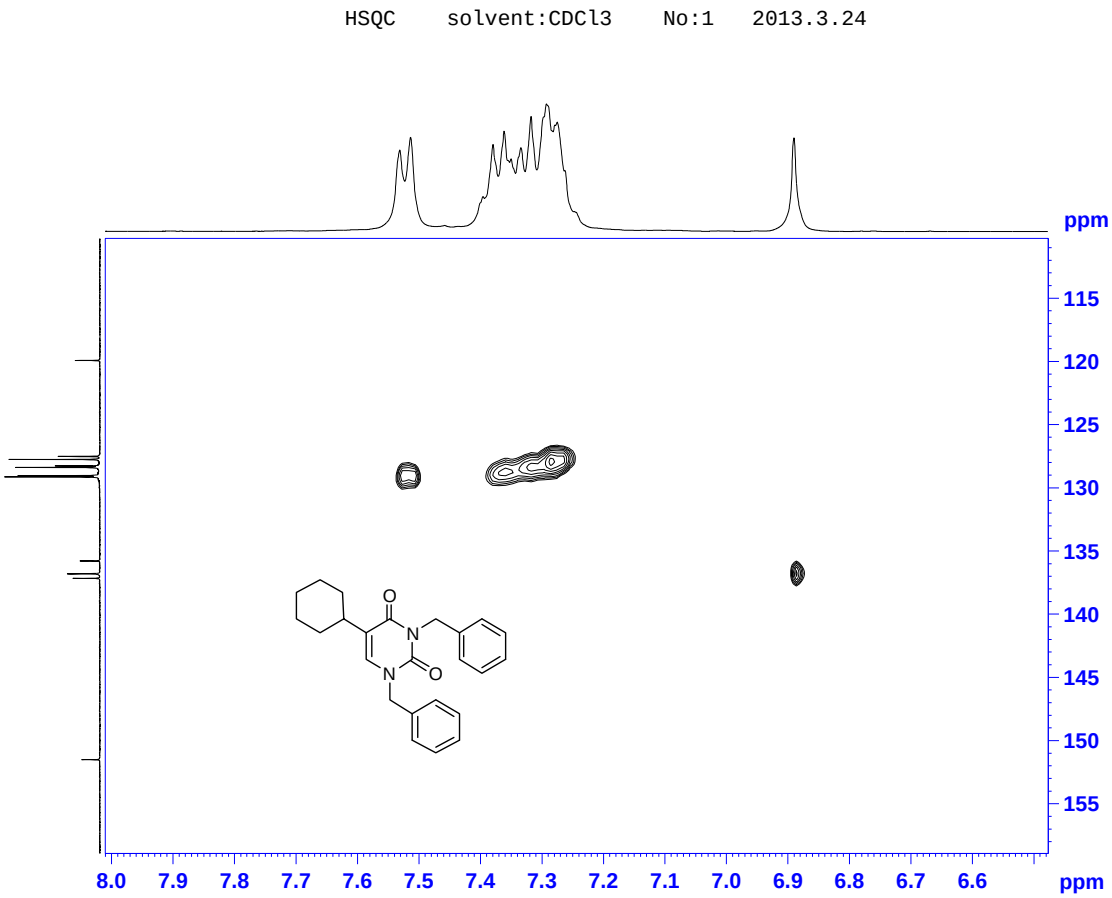
COSY solvent:CDCl3 No:1 2013.3.



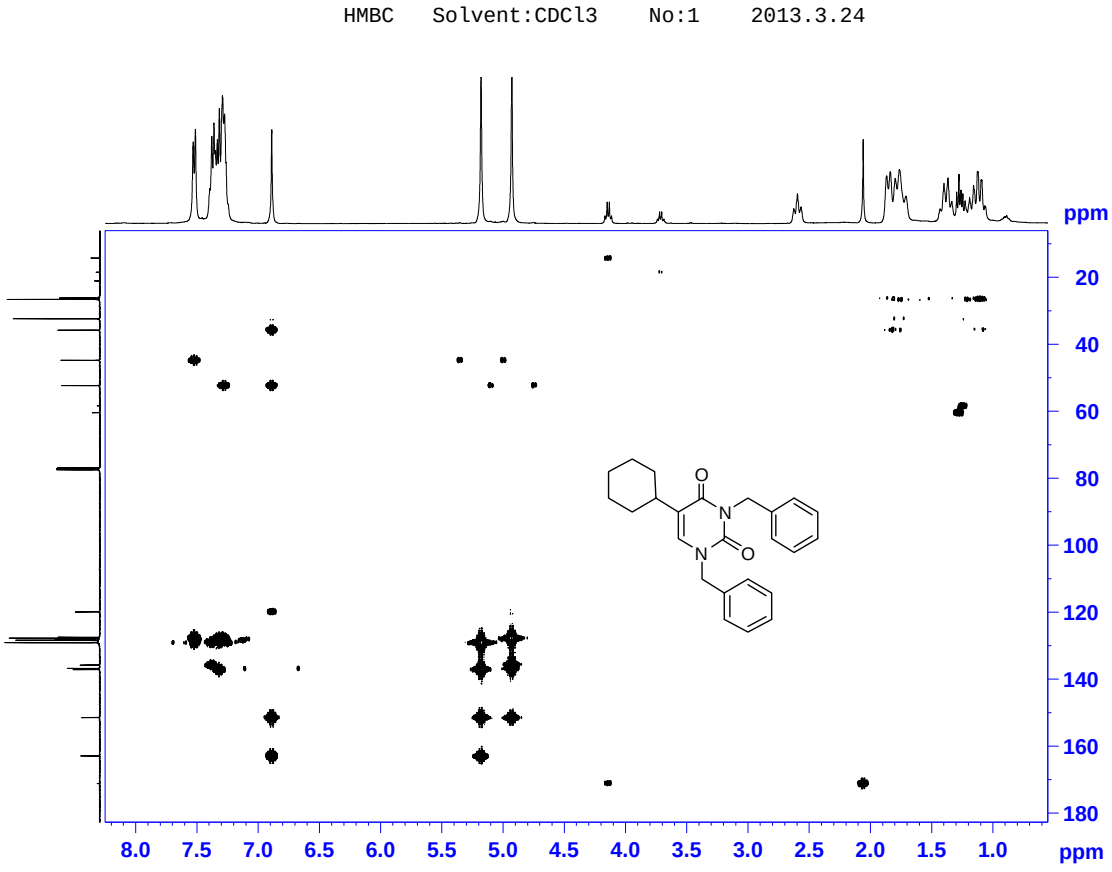
HSQC NMR Spectrum for 6a

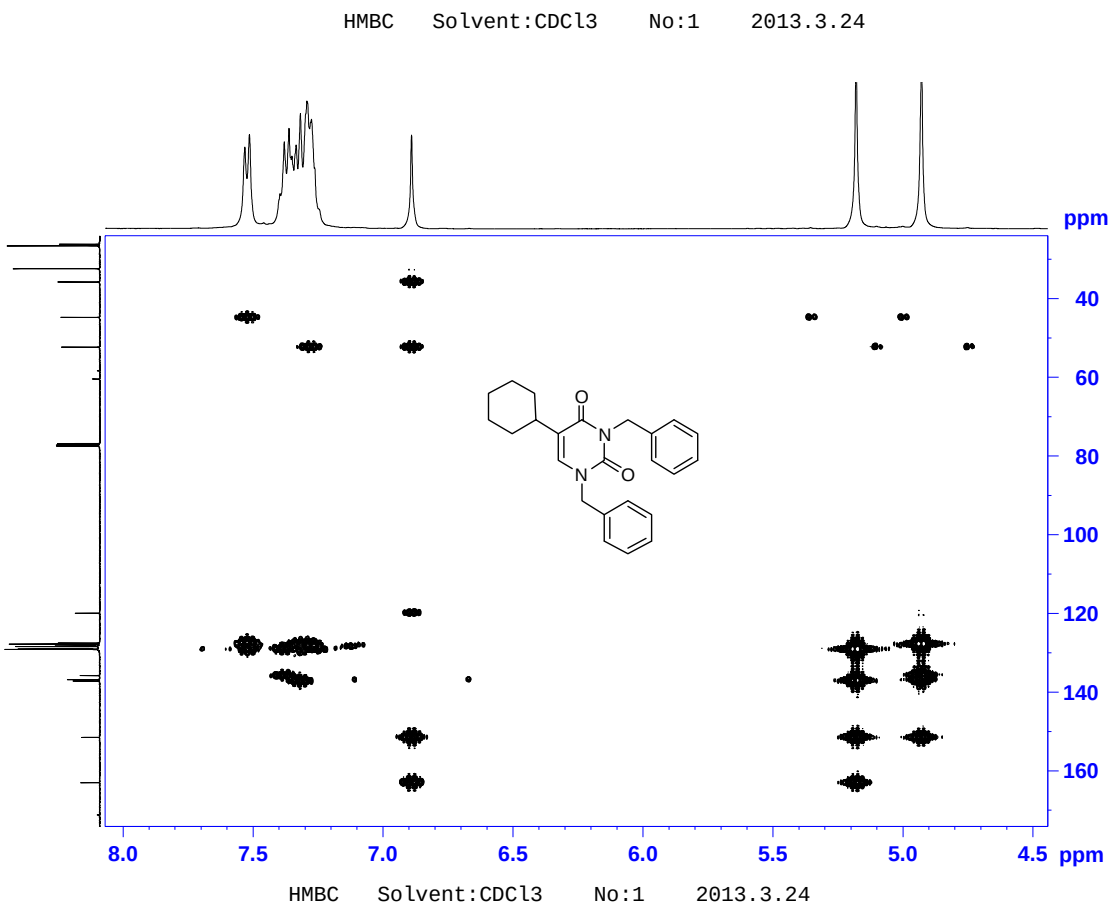






HMBC NMR Spectrum for 6a

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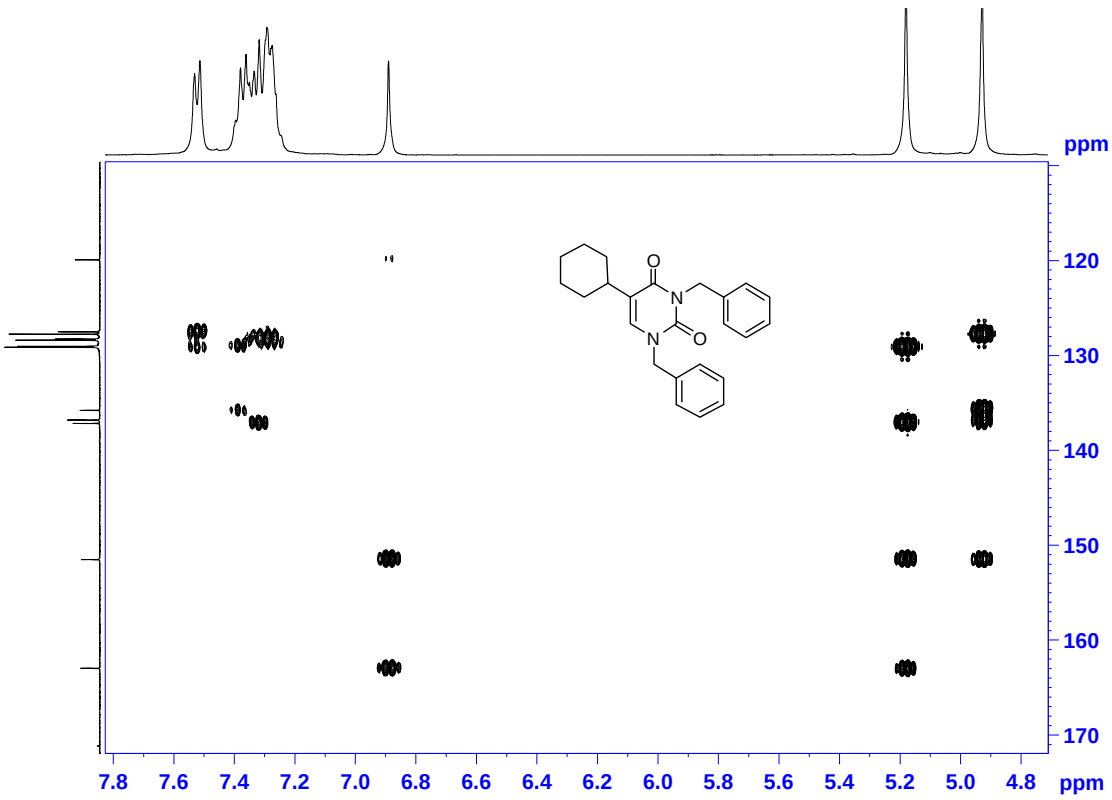
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5.2
5.0
4.8
ppm

HMBC Solvent:CDCl3 No:1 2013.3.24