RUTHENIUM(II)-CATALYZED *ortho* HYDROXYMETHYLATION OF 6-ARYLPURINES WITHPARAFORMALDEHYDE VIA PURINE-DIRECTED C-H ACTIVATION

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X-Ray structure of 3a

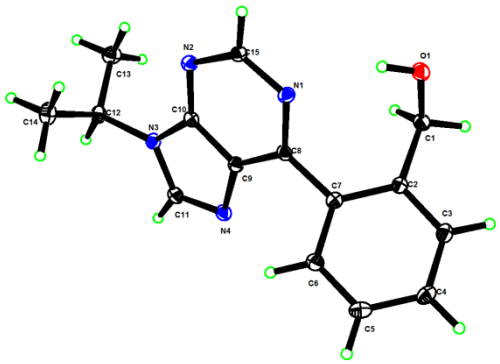
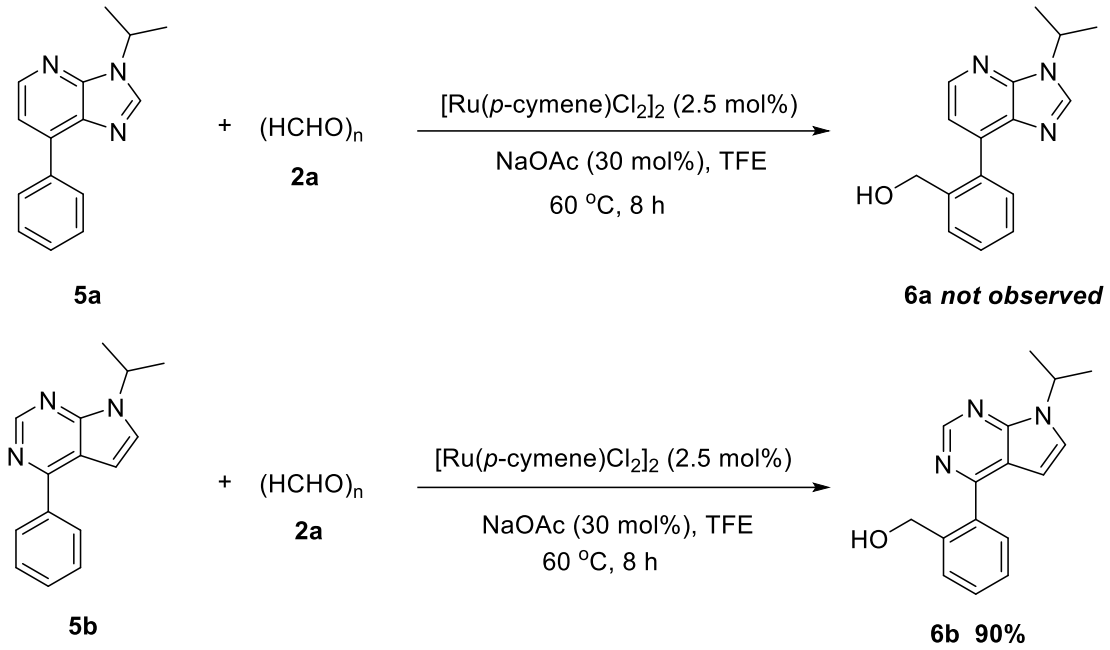


Figure S1. X-Ray structure of **3a**

A single crystal **3a** was obtained by slowly evaporating 99.5% MeOH under Air conditions and at room temperature. The crystal of compound **3a** (CCDC 1995350) belongs to monoclinic, space group $P2_1/n$ (no. 14), a = 10.3596(5) Å, b = 11.0912(5) Å, c = 12.5143(6) Å, β = 112.911(2)°, V = 1324.46(11) Å^3, Z = 4, T = 150.0 K, μ(MoKα) = 0.089 mm^{-1}, *Dcalc* = 1.346 g/cm^3, 13299 reflections measured (5.096° ≤ 2θ ≤ 52.8°), 2691 unique (R_{int} = 0.0837, R_{sigma} = 0.0667) which were used in all calculations. The final R_1 was 0.0522 and wR_2 was 0.1201.

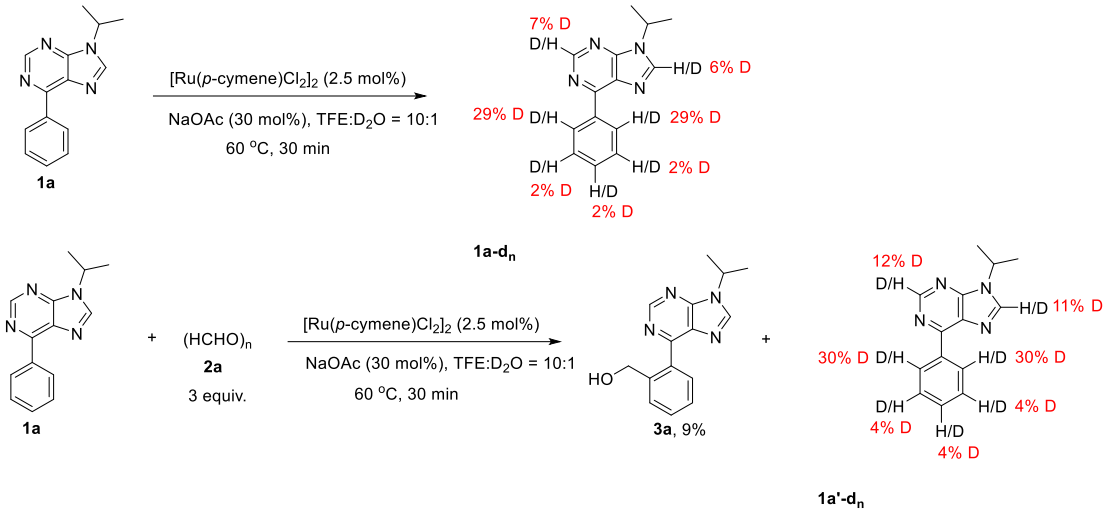
Experimental Procedures of Mechanistic Studies

1) Verification of the directing group



A mixture of **5** (0.2 mmol, 47.4 mg, 1 equiv), **2a** (0.6 mmol, 18 mg, 3 equiv), [$RuCl_2$(*p*-cymene)]$_2$ (0.005 mmol, 3 mg, 2.5 mol%) and NaOAc (0.06 mmol, 8.2 mg, 30 mol%) were dissolved in TFE (2 mL) in a 10 mL round bottom flask and the mixture was stirred at 60 ℃ for 8 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatograph (PE/EA = 1/1) to afford product **6** (**6b**, Yield: 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 7.82 (m, 1H), 7.55 (m, 1H), 7.51 – 7.41 (m, 2H), 7.38 (d, *J* = 3.7 Hz, 1H), 6.66 (d, *J* = 3.7 Hz, 1H), 6.51 (br, 1H), 5.21 (hept, *J* = 6.6 Hz, 1H), 4.48 (s, 2H), 1.56 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.28, 150.81, 149.84, 141.13, 137.52, 131.50, 130.99, 130.17, 127.84, 125.92, 117.18, 100.74, 64.52, 46.26, 22.81; HRMS (ESI) Calcd for $C_{16}H_{18}N_3O$ $[M+H]^+$ 268.1444, found 268.1443.

2) H/D Exchange Studies



To a 10 mL round bottom flask was added **1a** (0.2 mmol, 47.6 mg, 1 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 2.5 mol%), NaOAc (0.06 mmol, 8.2 mg, 30 mol%) and TFE/D_2O (10/1, 2.0 mL /0.2 mL). Meanwhile, to another 10 mL round bottom flask was added **1a** (0.2 mmol, 47.6 mg, 1 equiv), **2a** (0.6 mmol, 18 mg, 3 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 2.5 mol%), NaOAc (0.06 mmol, 8.2 mg, 30 mol%) and TFE/D_2O (10/1, 2.0 mL /0.2 mL). The two mixture were stirred at 60℃ over 30 minutes. The two resulting solution were concentrated in vacuo and purified by column chromatograph on silica gel (Petroleum ether/Ethyl acetate) to afford product. The ratio of the hydrogen-deuterium exchange was determined by ^{1}H NMR analysis.

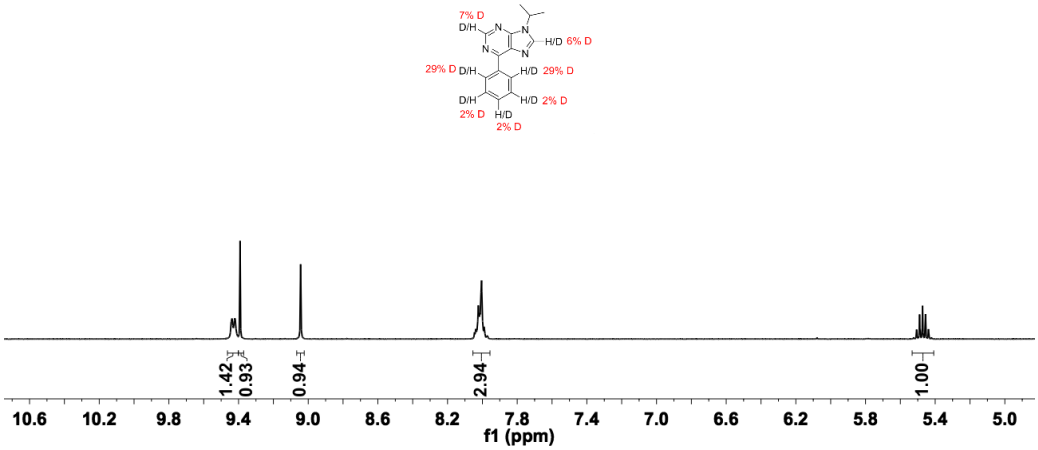


Figure S2. ^{1}H NMR analysis of **1a-d$_n$**

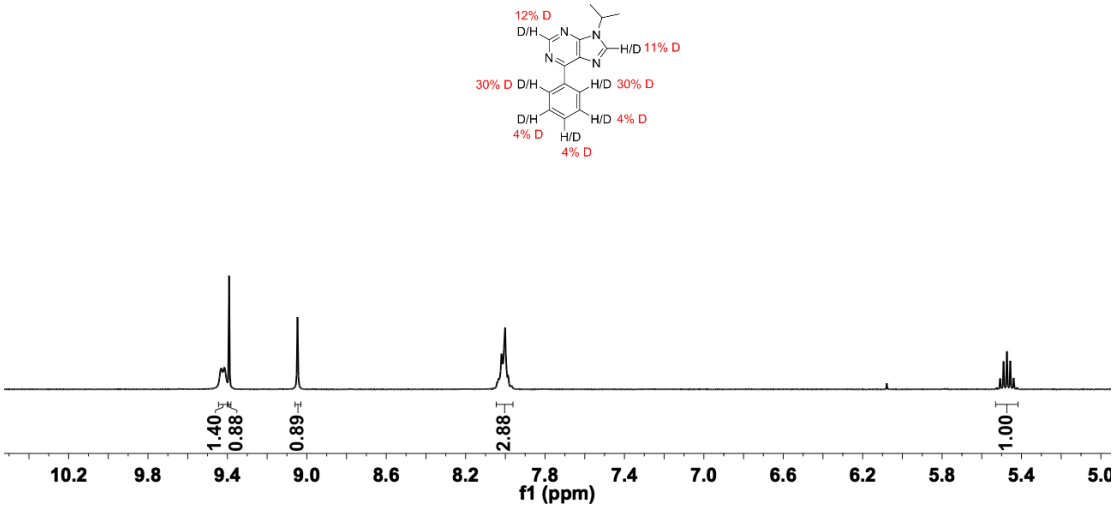
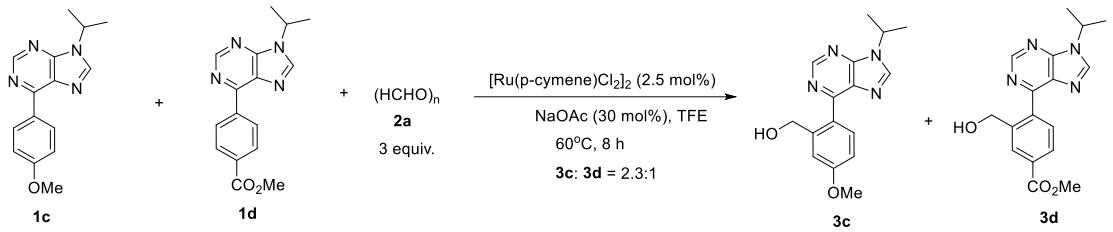


Figure S3. ^{1}H NMR analysis of **1a'-d$_n$**

3) Competitive Experiment



To a 10 mL round bottom flask was added **1c** (0.2 mmol, 53.6 mg, 1 equiv), **1d** (0.2 mmol, 59.2 mg, 1 equiv), **2a** (0.6 mmol, 18 mg, 3 equiv), [Ru(*p*-cymene)Cl_2]$_2$ (0.005 mmol, 3 mg, 2.5 mol%), NaOAc (0.06 mmol, 8.2 mg, 30 mol%) and TFE (2 mL, 0.1

M). After stirring for 8 hours at 60℃, the reaction mixture was evaporated to dryness. The crude product was purified by column chromatograph on silica gel (Petroleum ether/Ethyl acetate) to give a mixture of **3c** and **3d** (2.3:1) by ^{1}H NMR analysis.

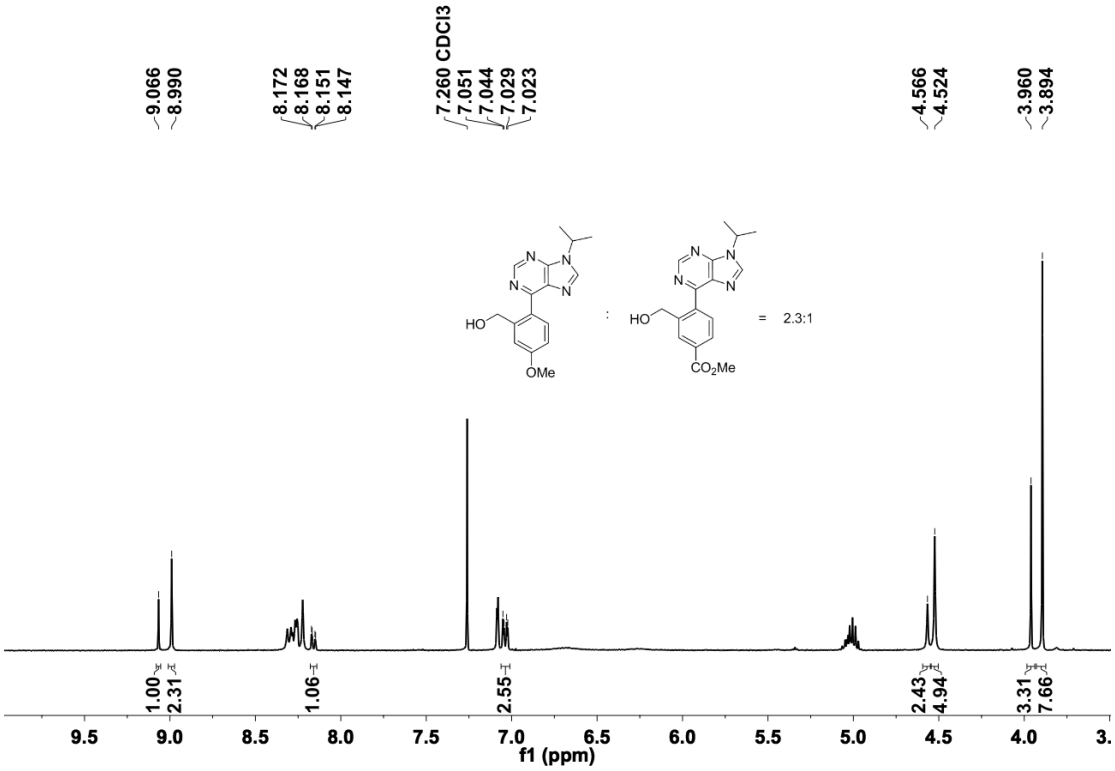
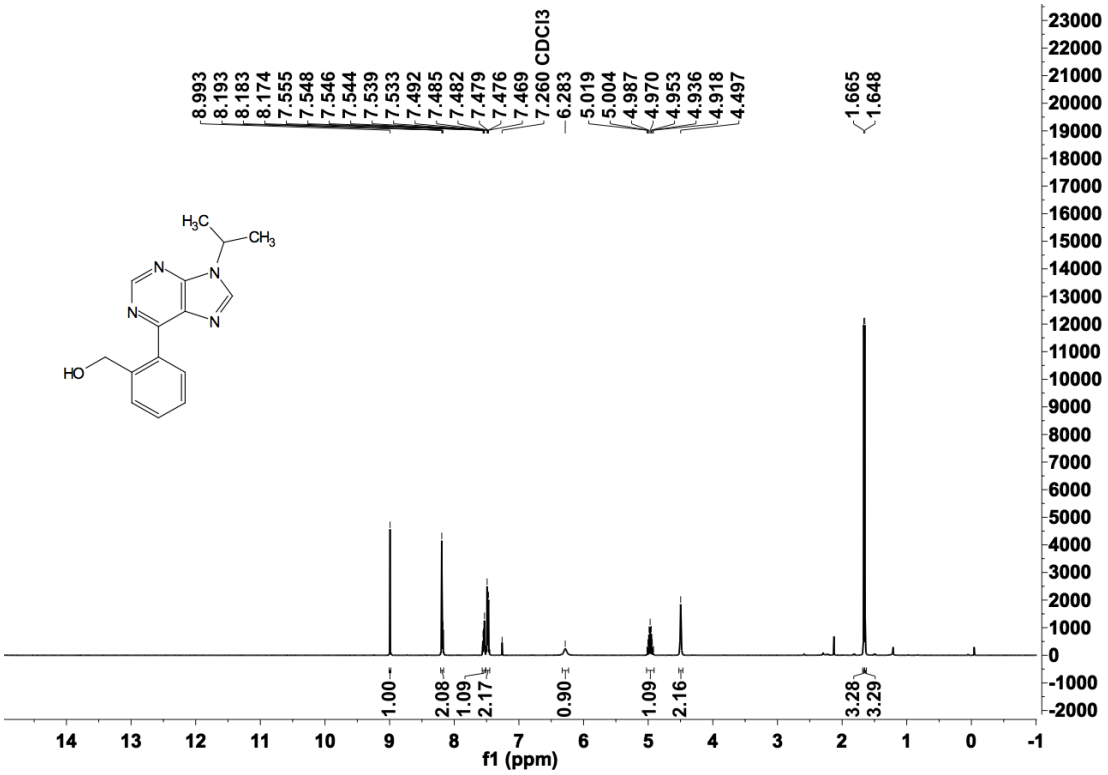
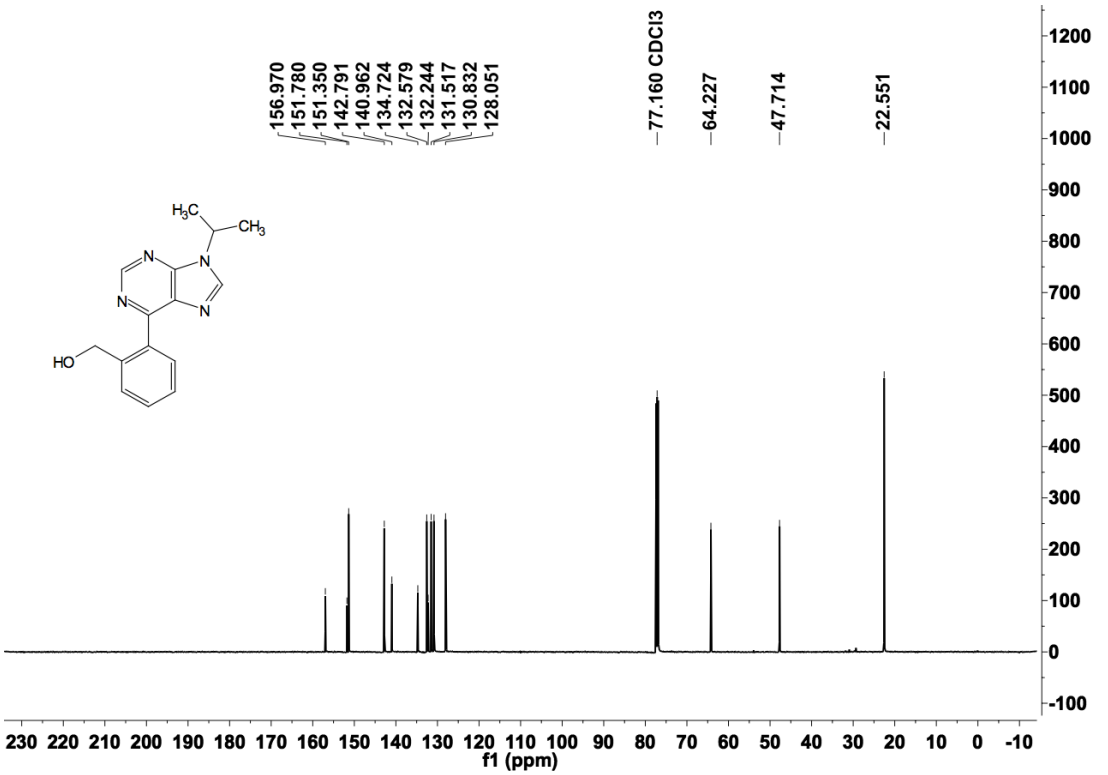
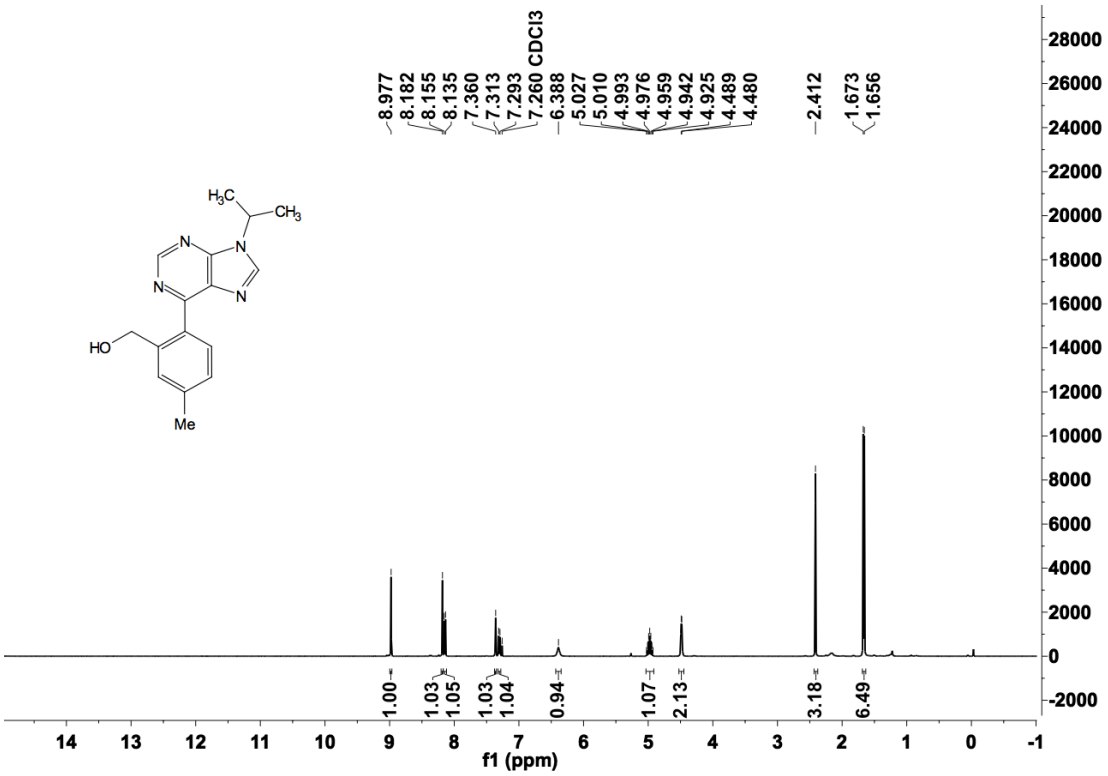


Figure S4. ^{1}H NMR analysis of **3c** and **3d**

^{1}H and ^{13}C NMR Spectra of Compounds



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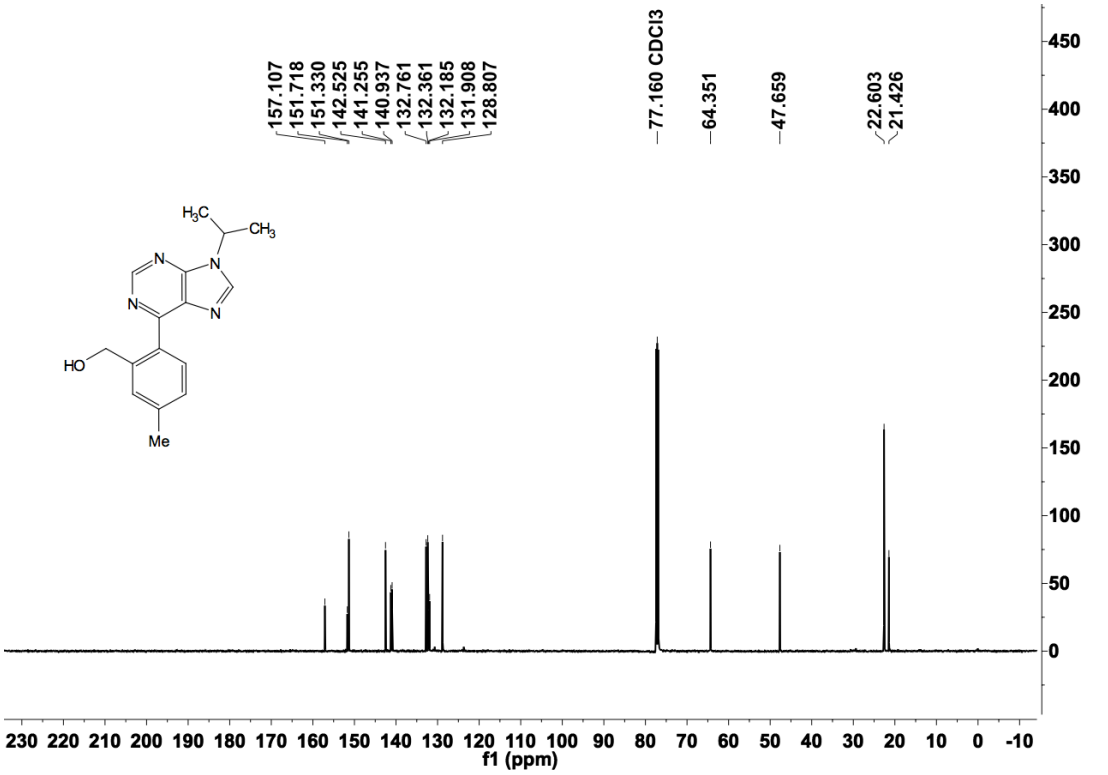
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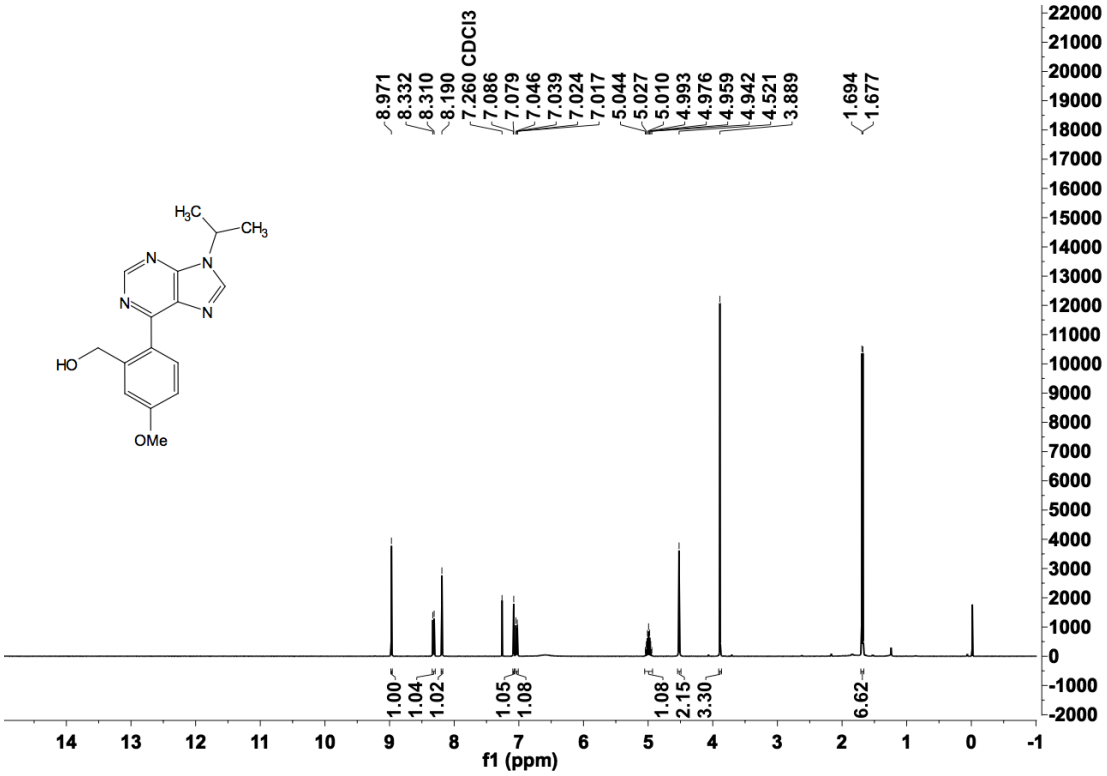
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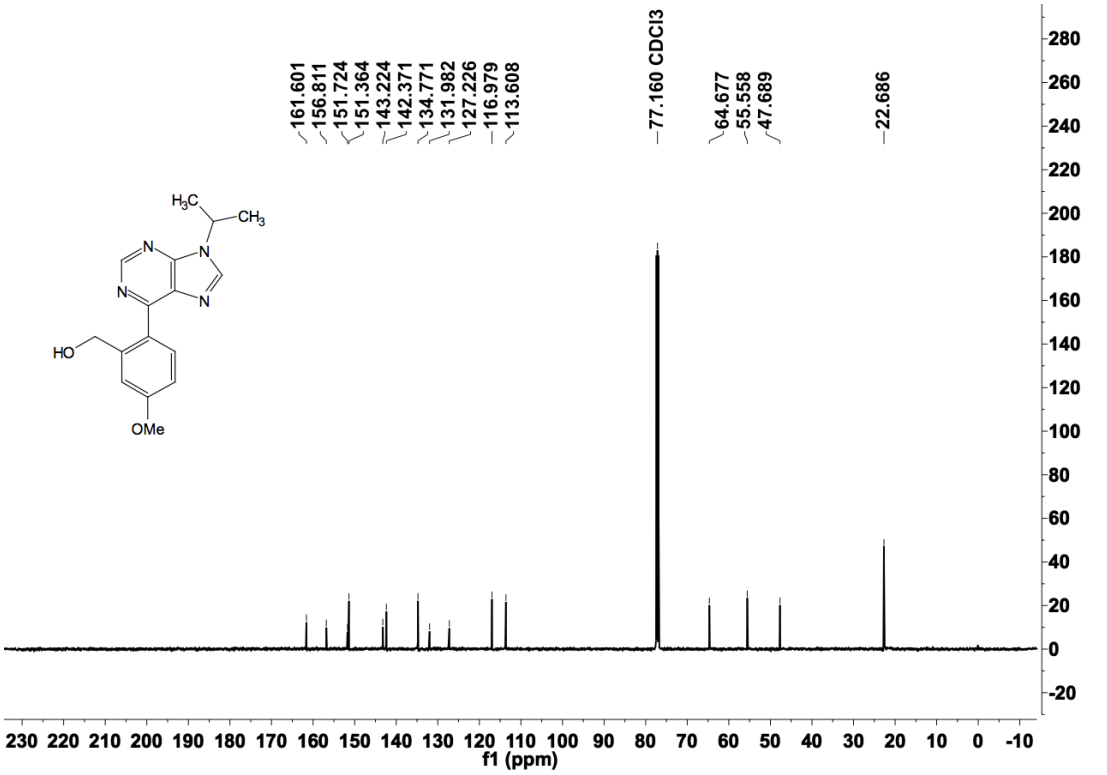
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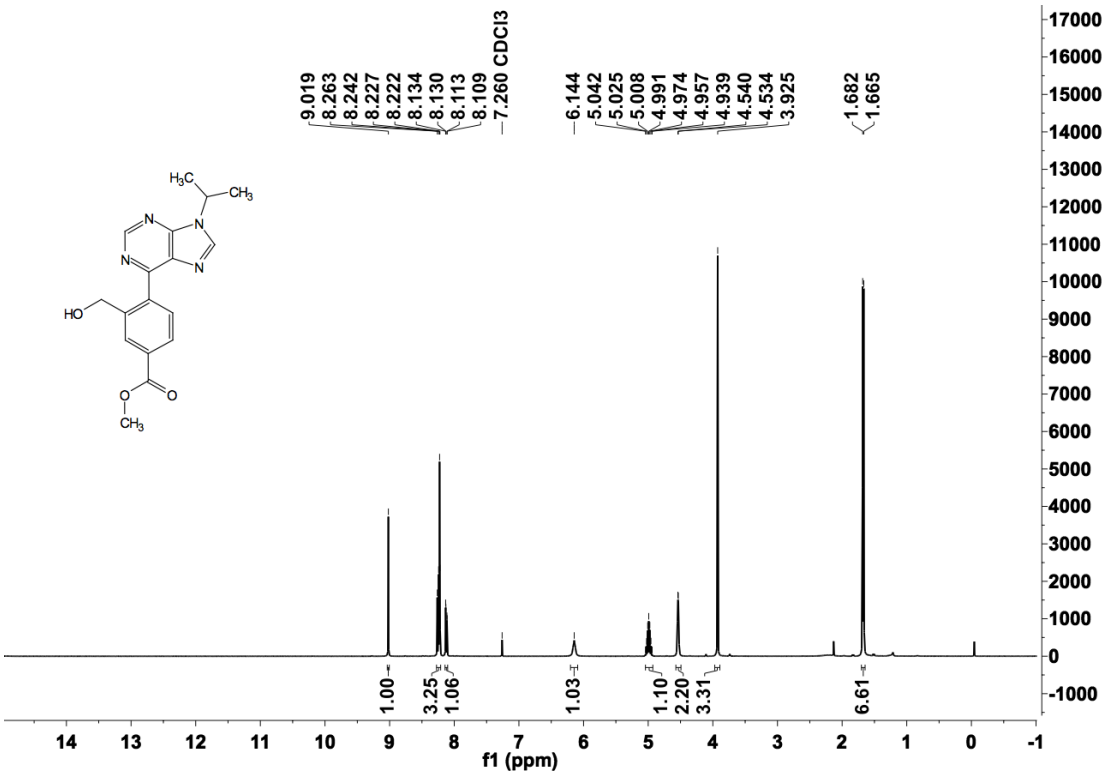
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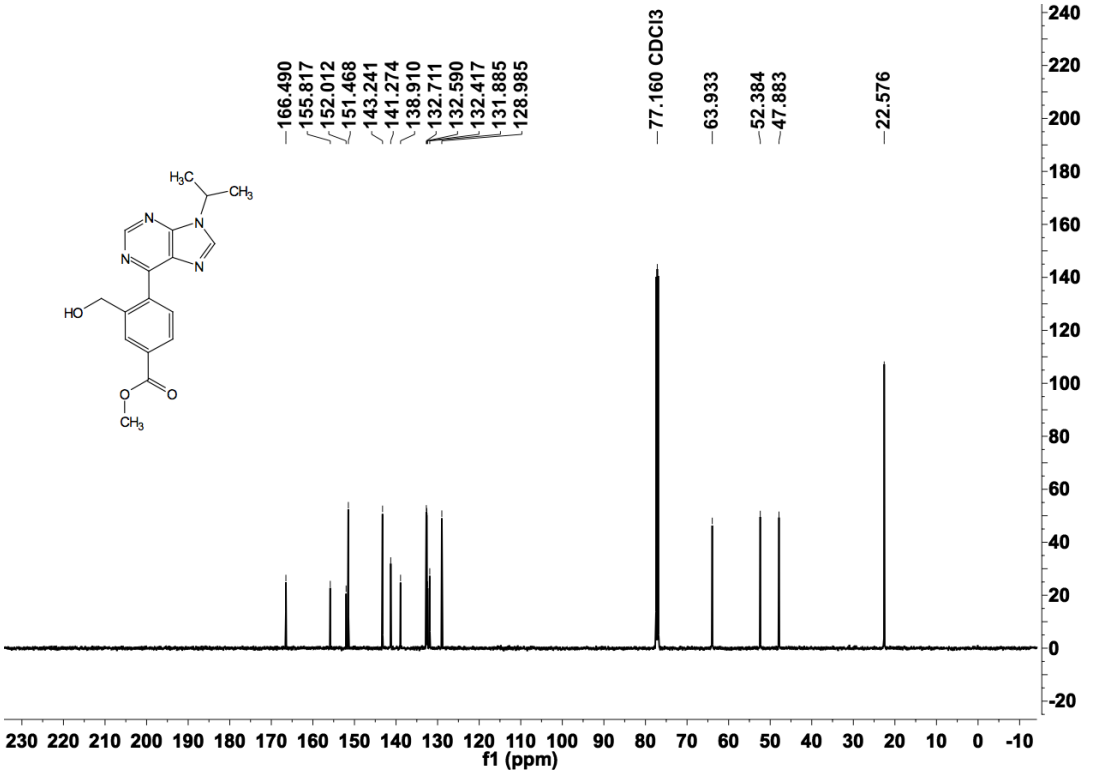
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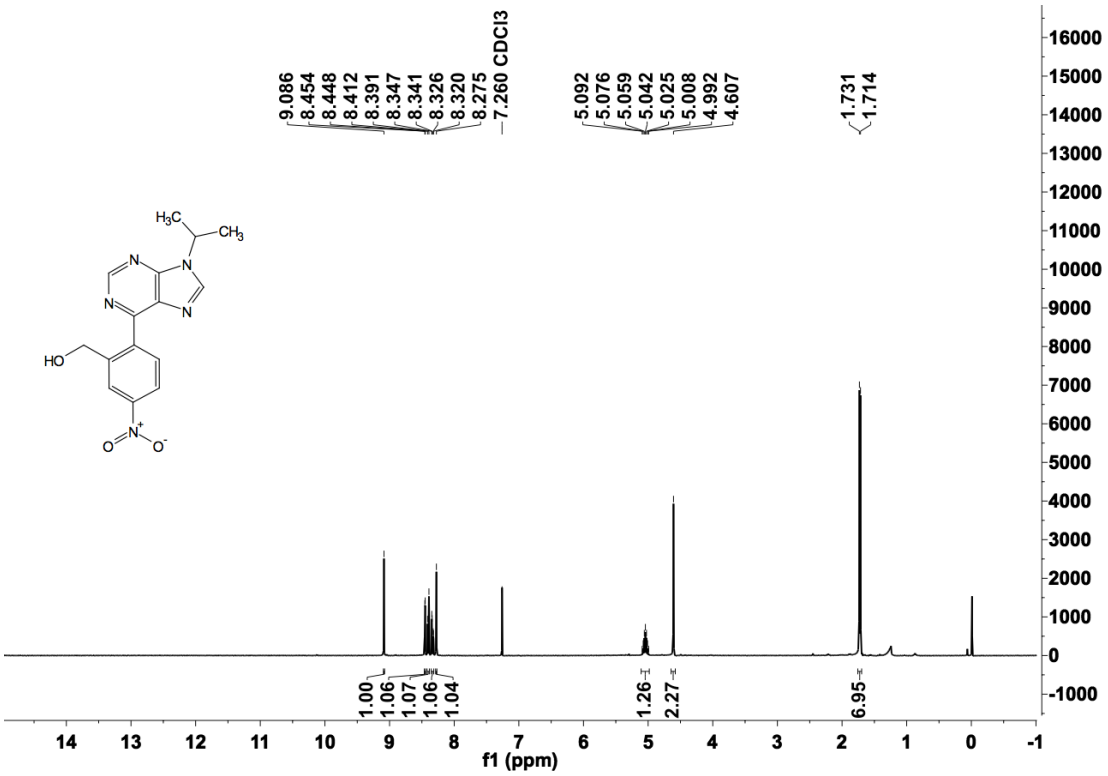
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5.042
5.025
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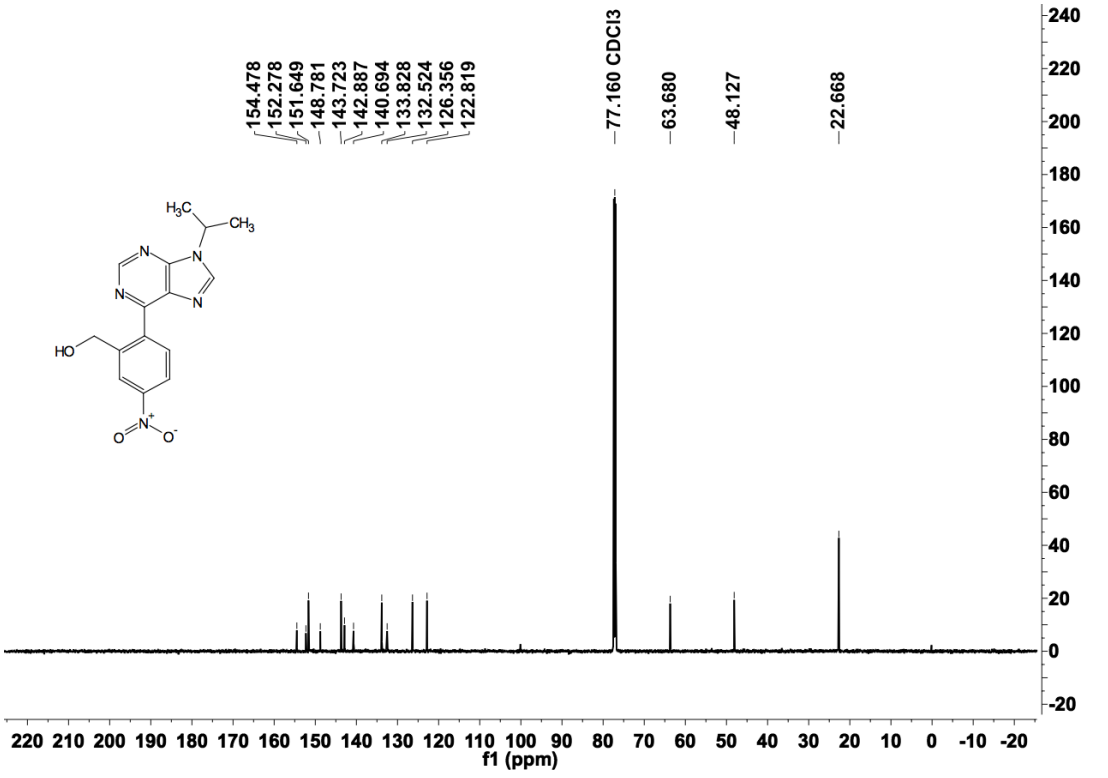
f1 (ppm)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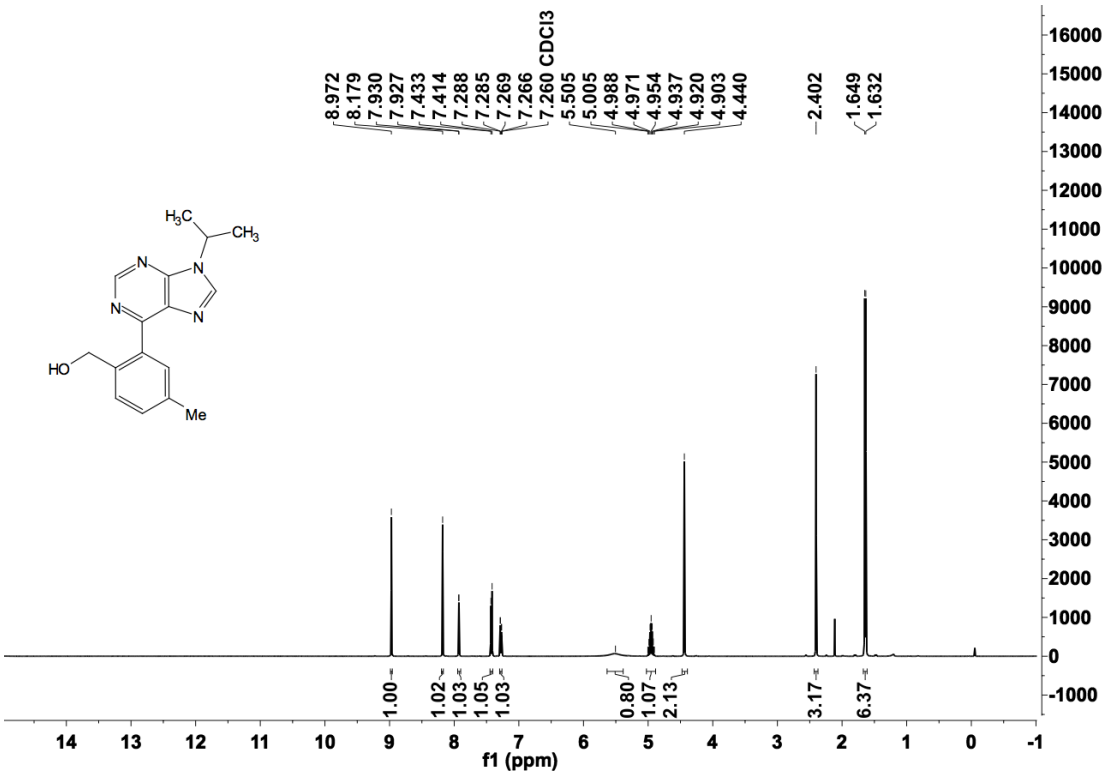
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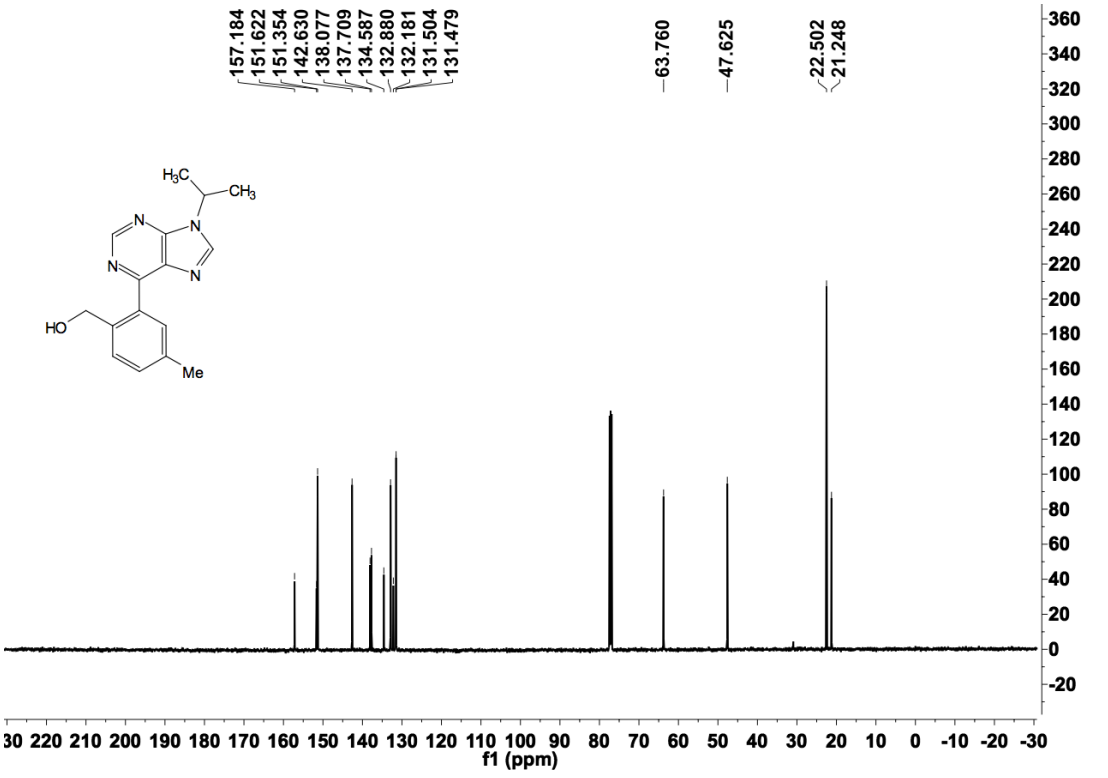
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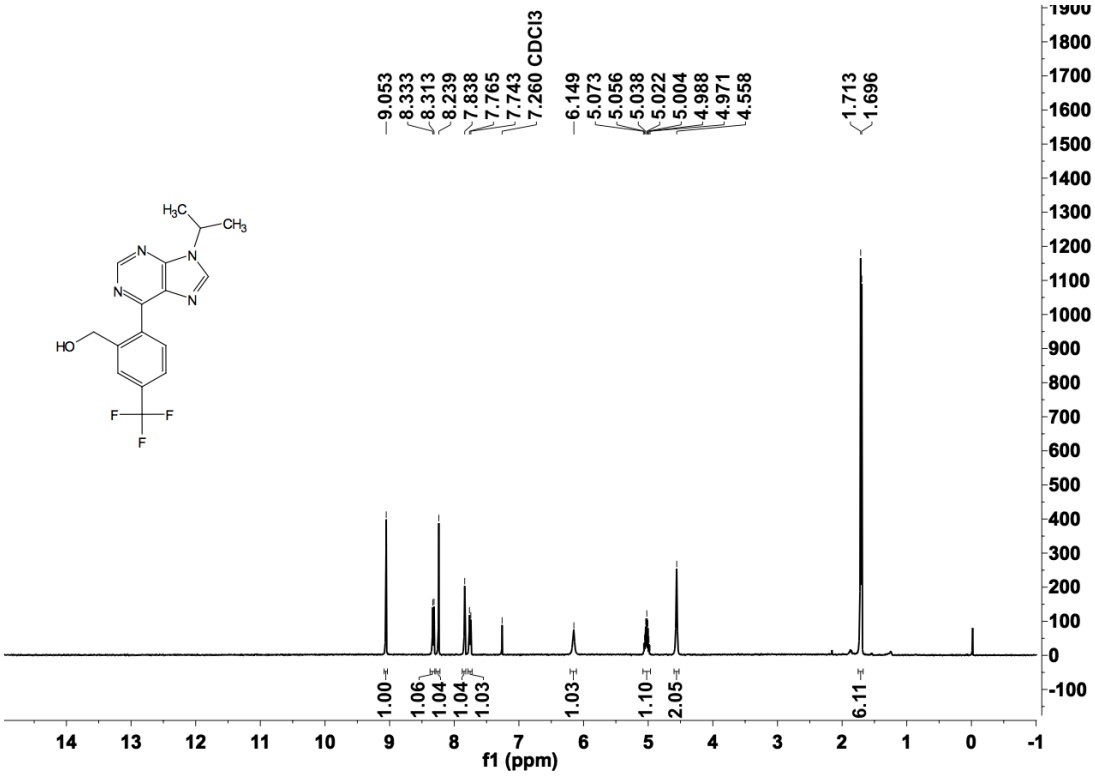
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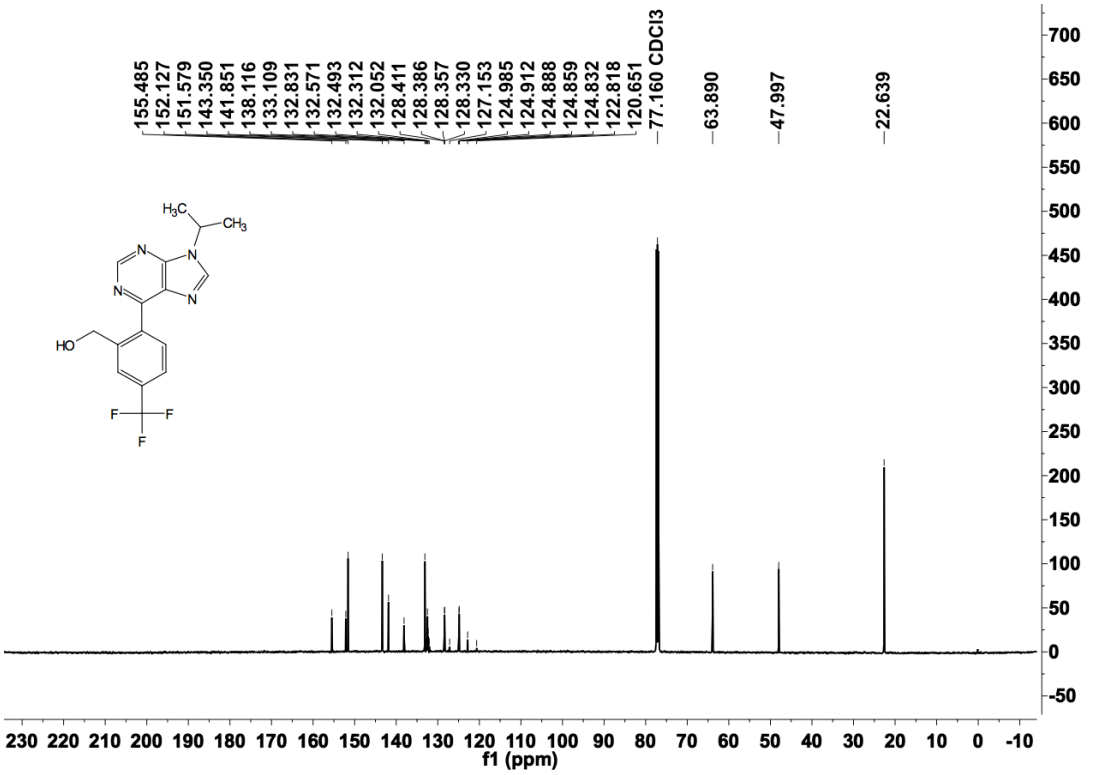
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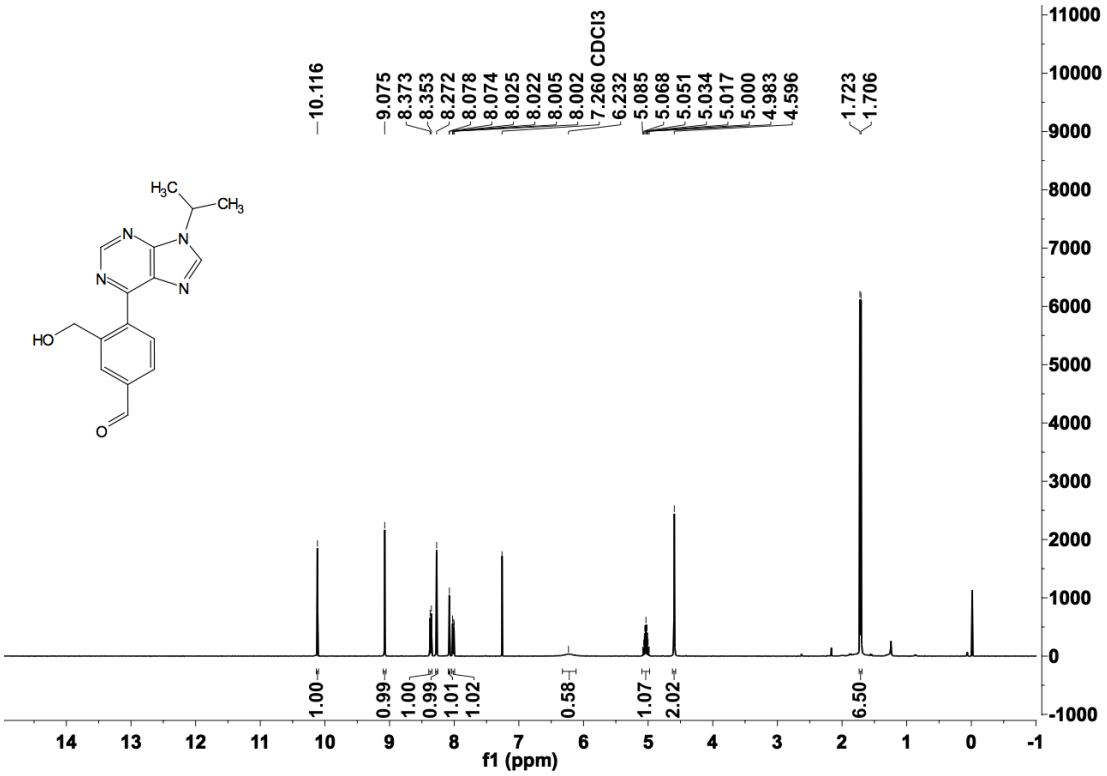
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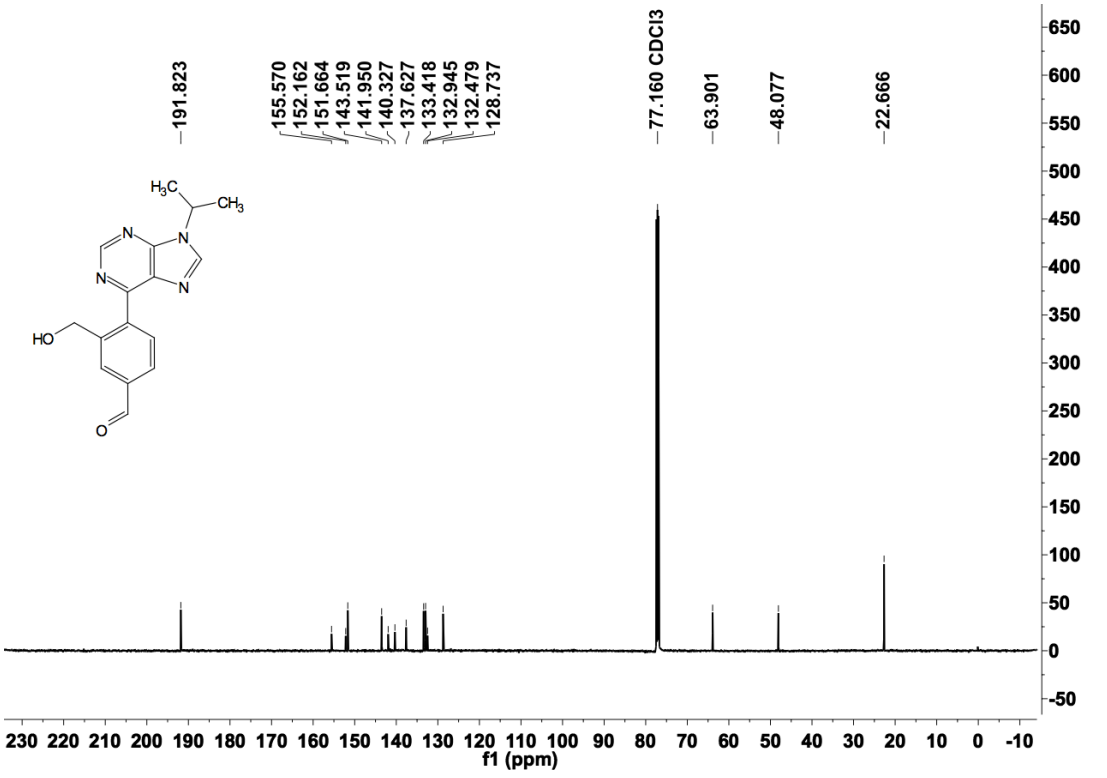
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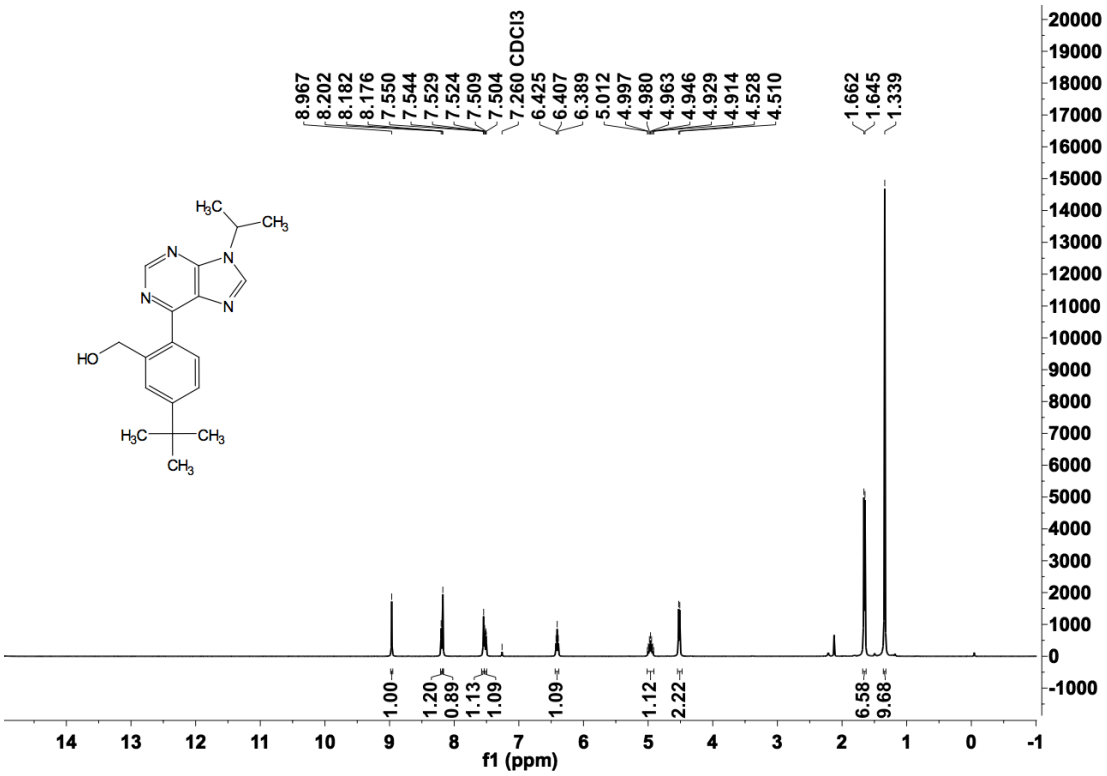
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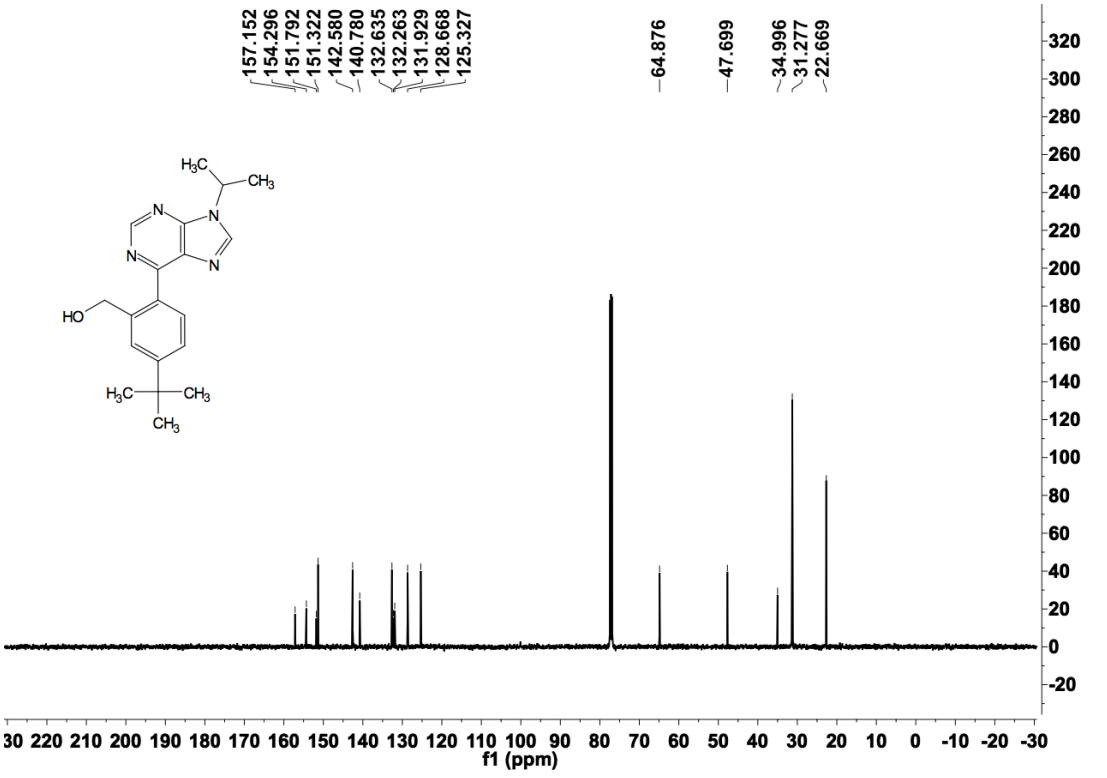
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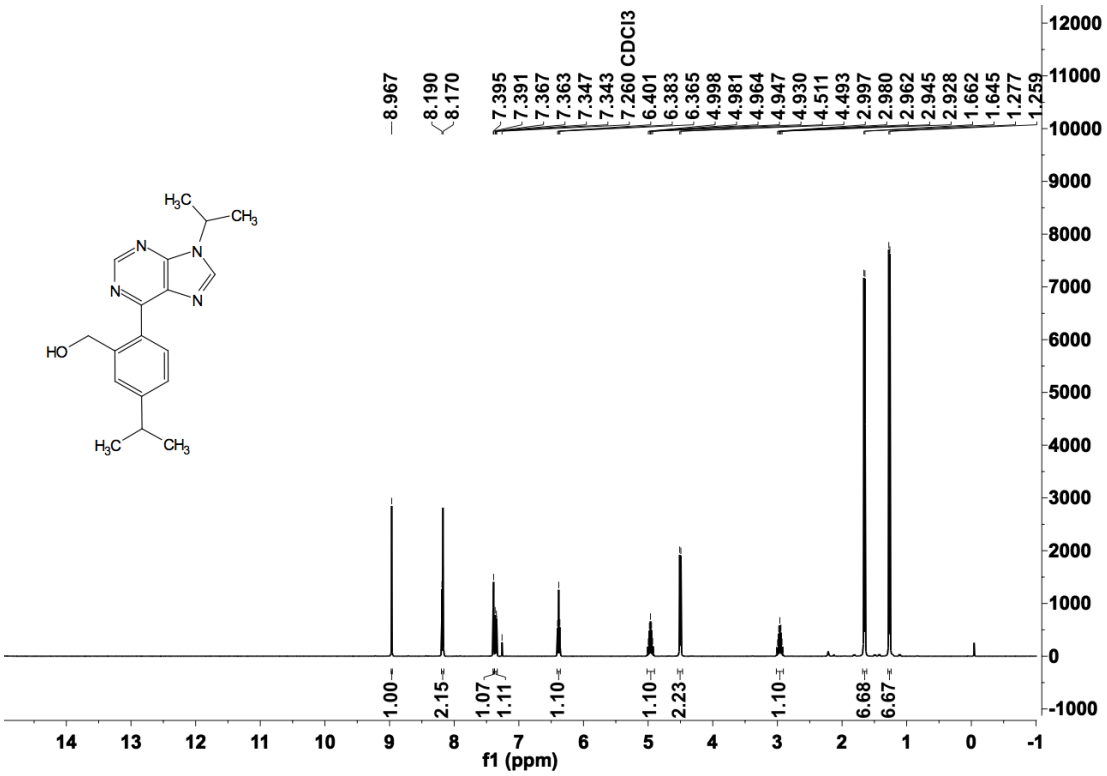
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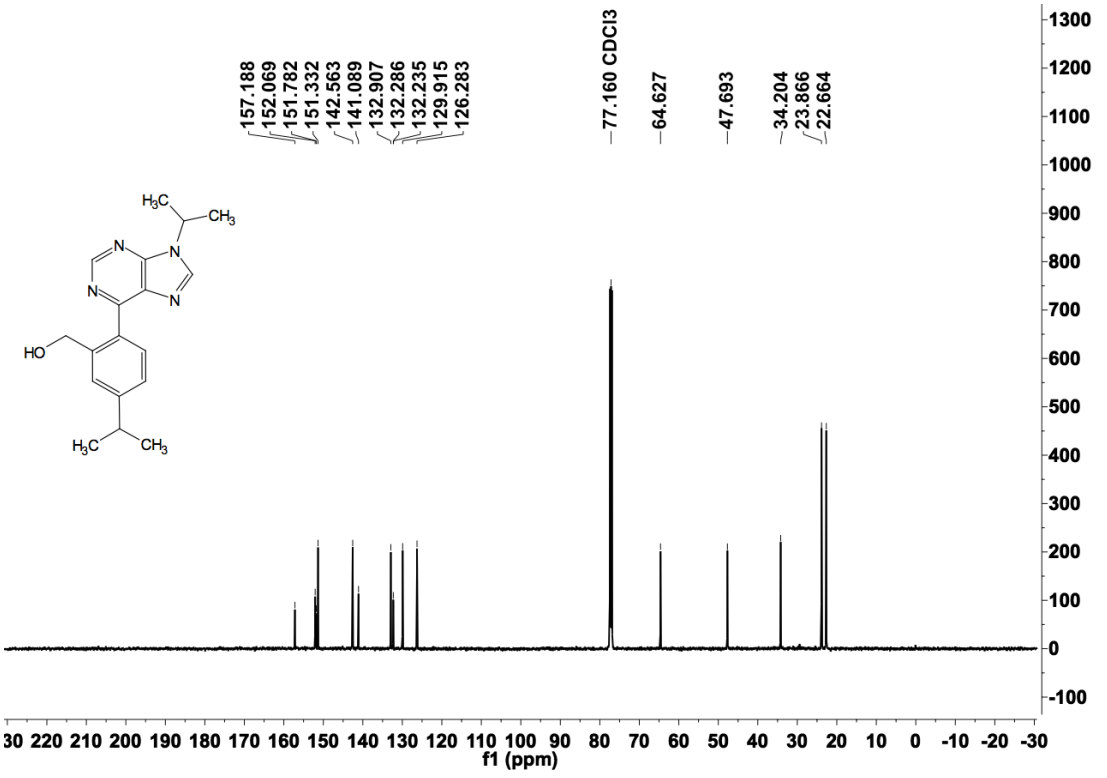
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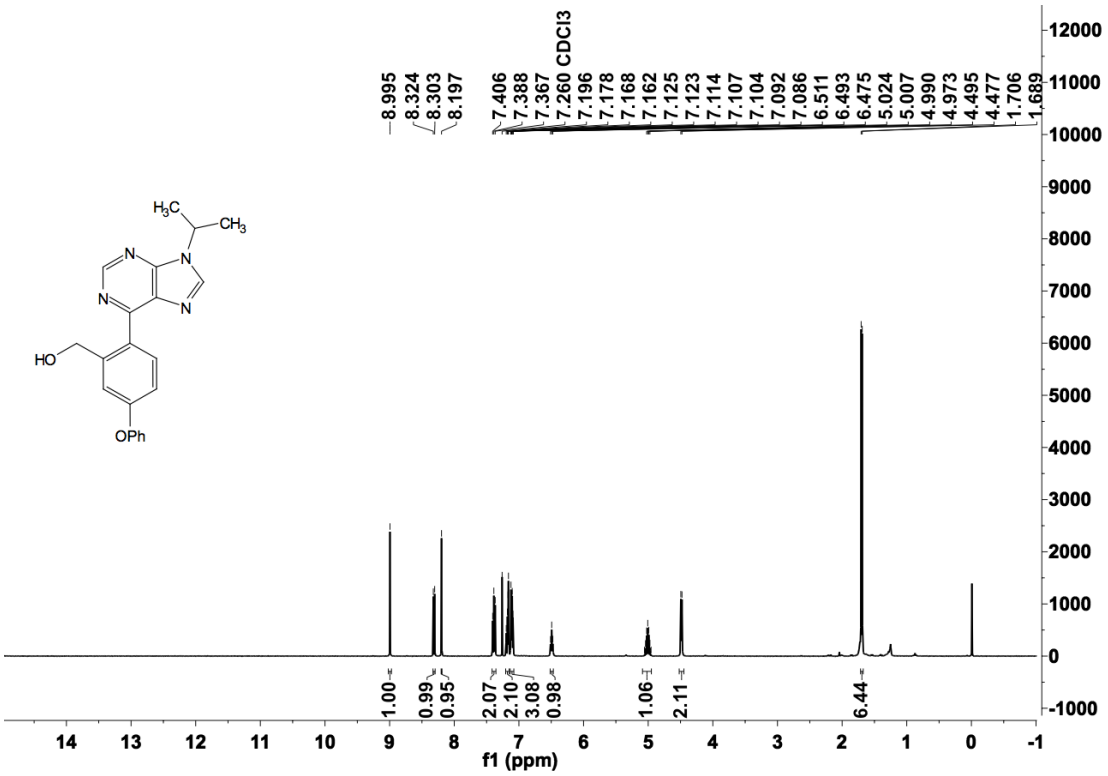
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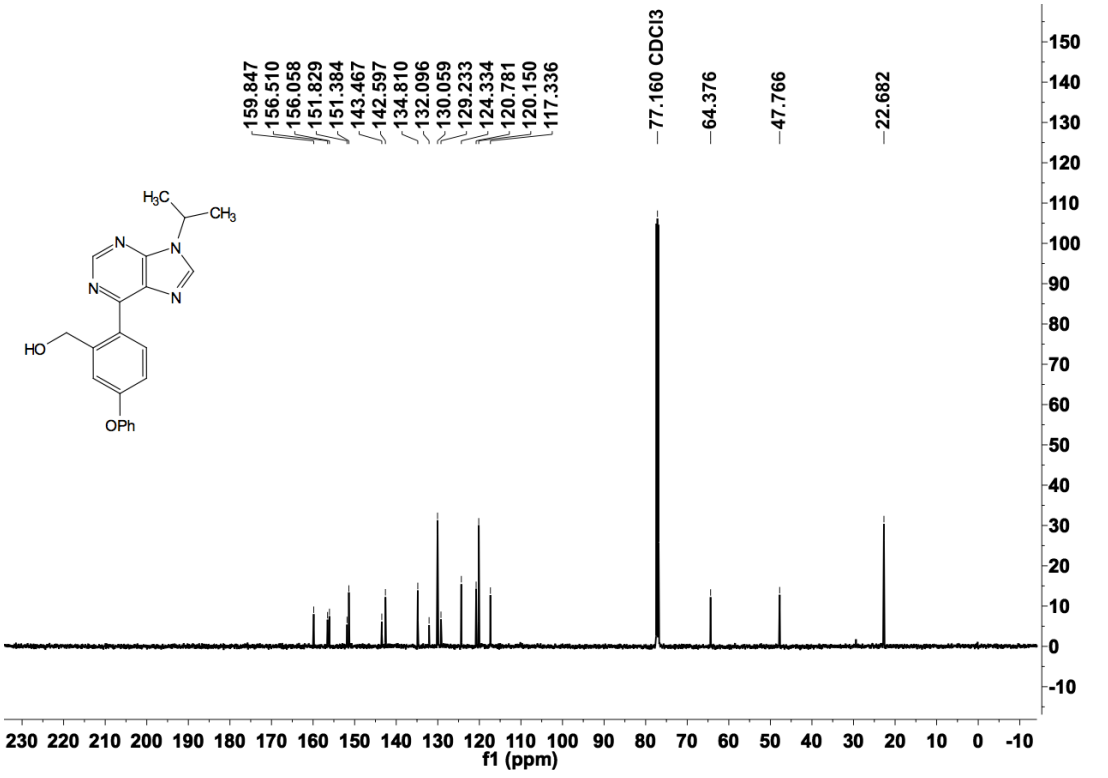
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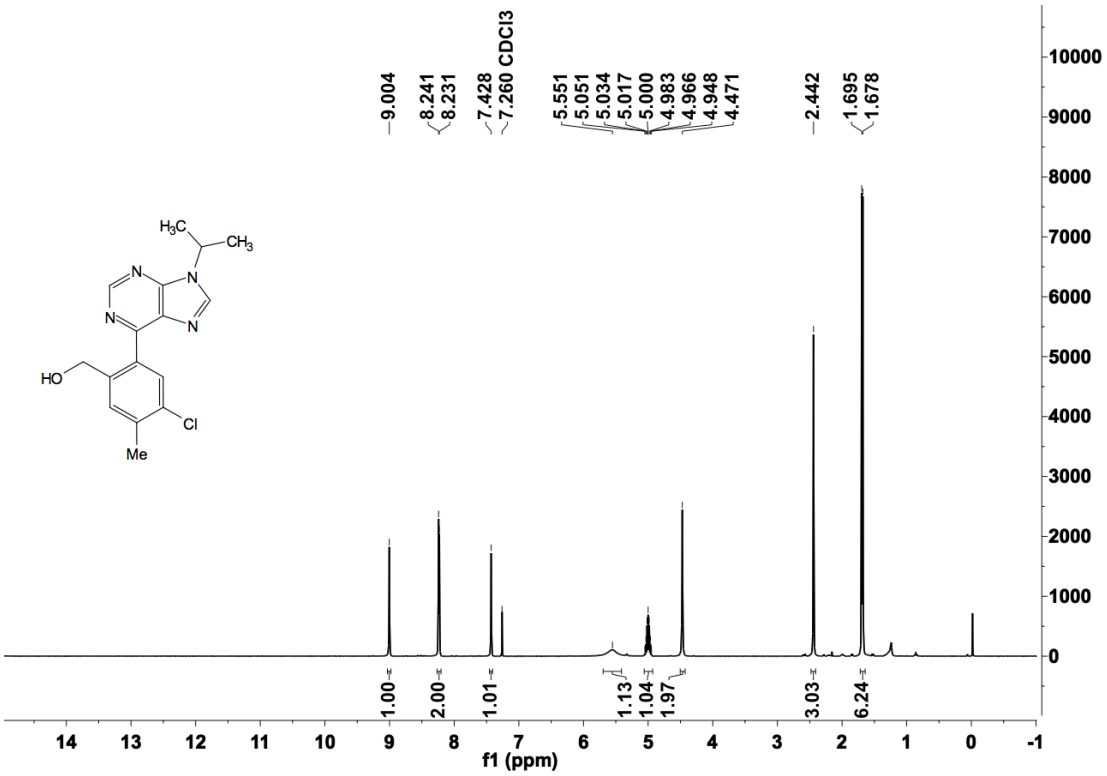
22.682
f1 (ppm)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8.231
7.428
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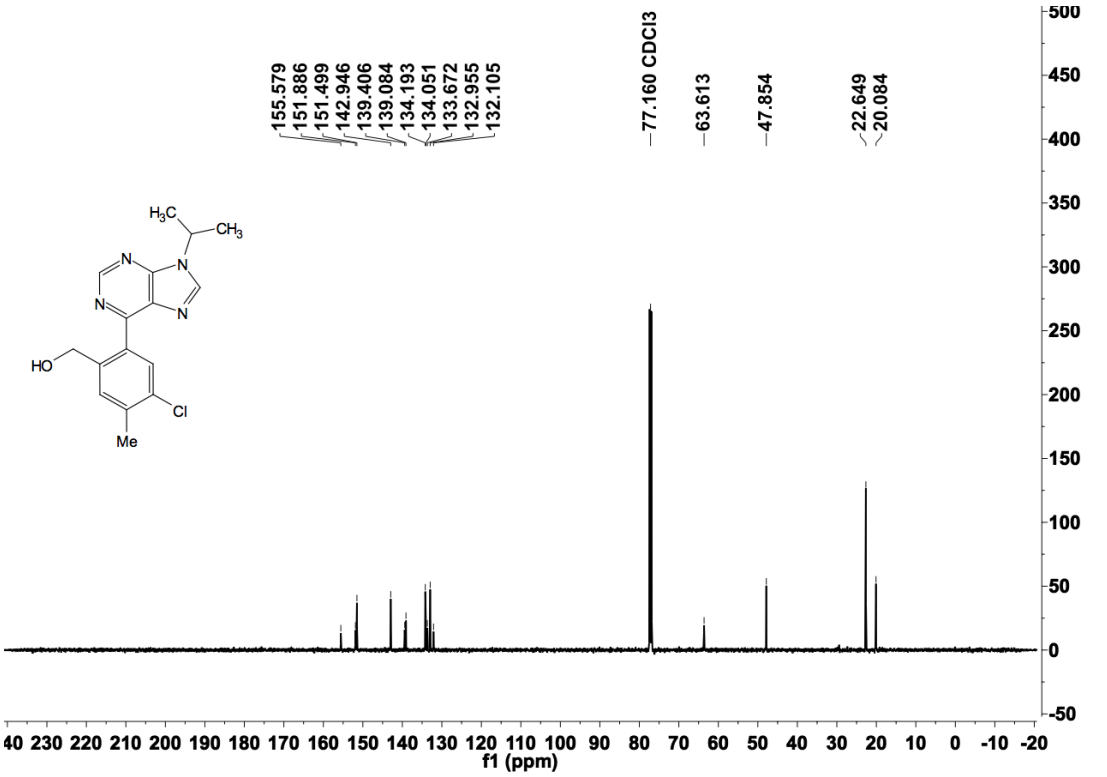
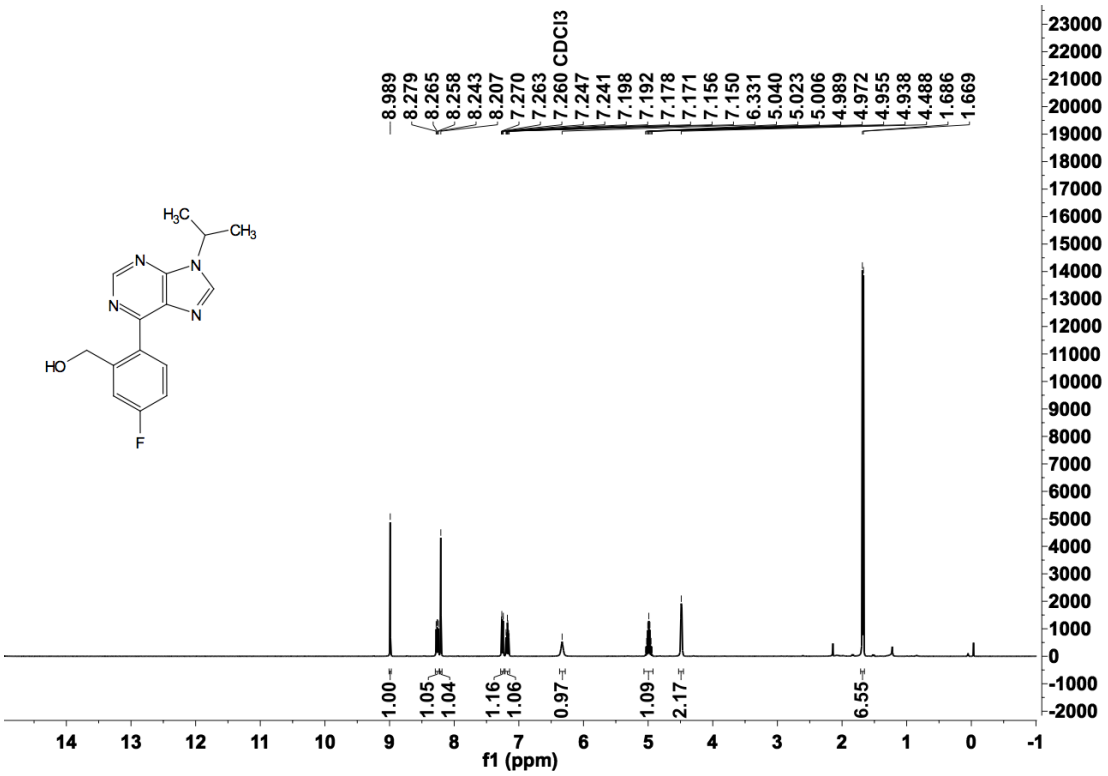
5.051
5.034
5.017
5.000
4.983
4.966
4.948
4.471
2.442
1.695
1.678
1.00
2.00
1.01
1.13
1.04
1.97
3.03
6.24
f1 (ppm)


155.579
151.886
151.499
142.946
139.406
139.084
134.193
134.051
133.672
132.955
132.105
77.160 CDCl3
63.613
47.854
22.649
20.084
f1 (ppm)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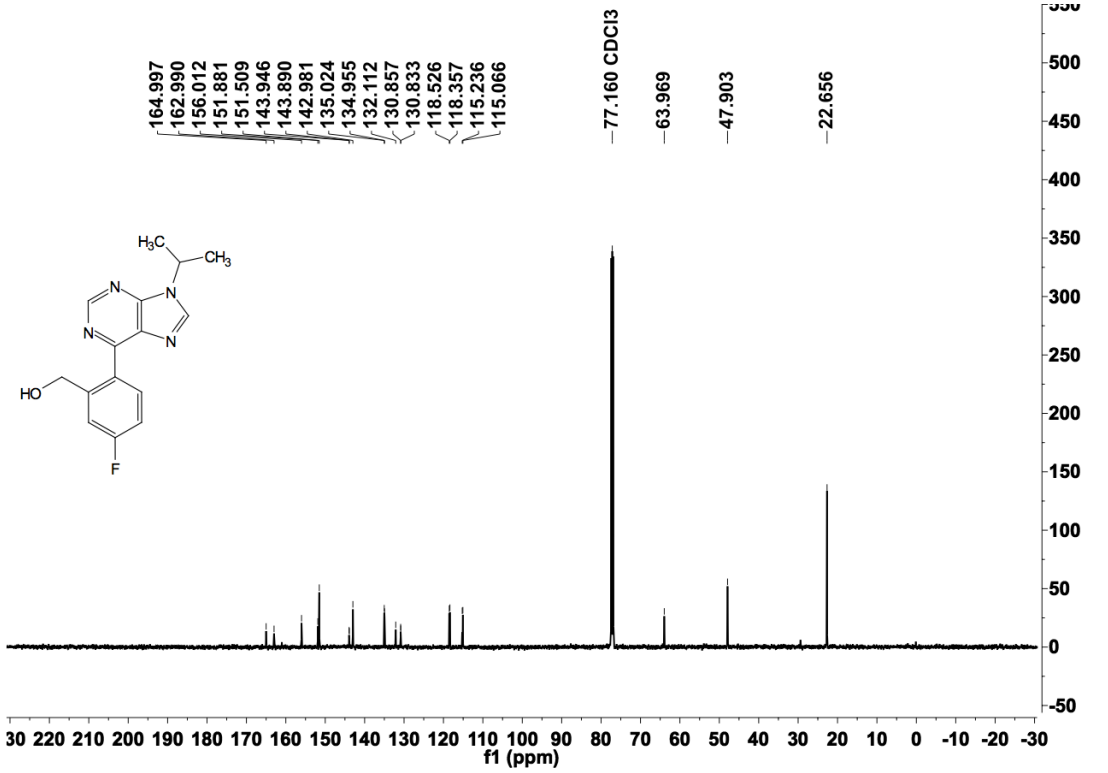
8.265
8.258
8.243
8.207
7.270
7.263
7.260 CDCl3
7.247
7.241
7.198
7.192
7.178
7.171
7.156
7.150
6.331
5.040
5.023
5.006
4.989
4.972
4.955
4.938
4.488
1.686
1.669
1.00
1.05
1.04
1.16
1.06
0.97
1.09
2.17
6.55
f1 (ppm)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151.509
143.946
143.890
142.981
135.024
134.955
132.112
130.857
130.833
118.526
118.357
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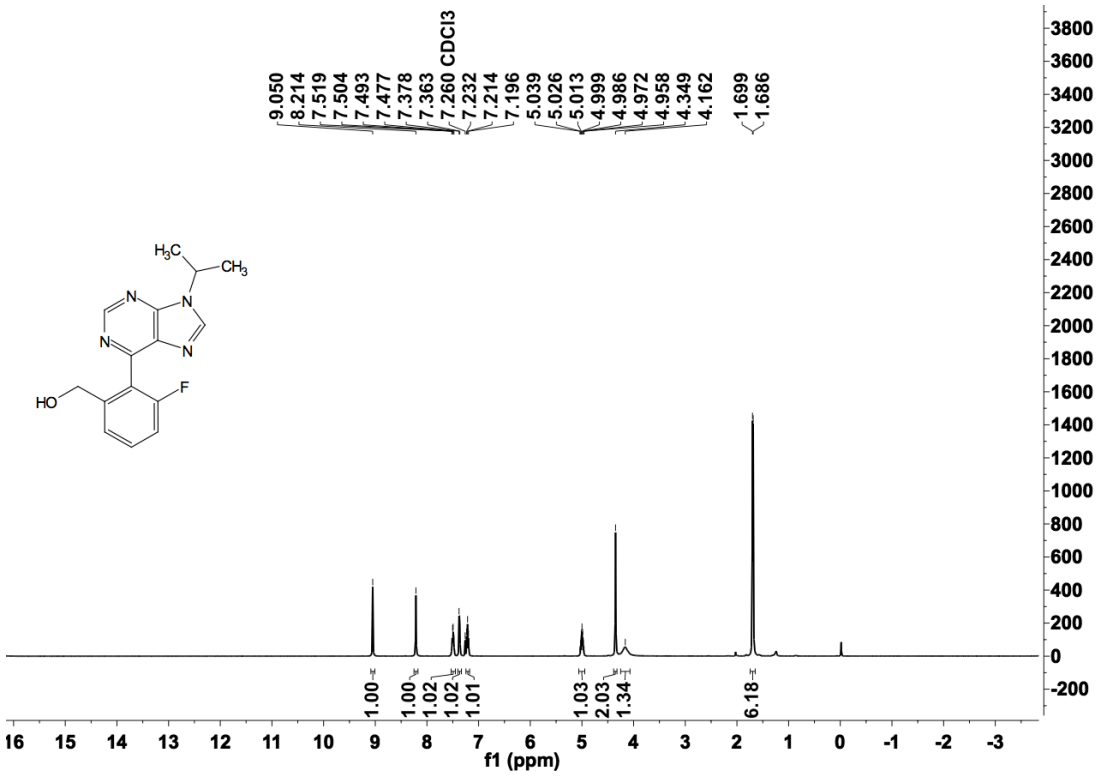
115.066
77.160 CDCl3
63.969
47.903
22.656
f1 (ppm)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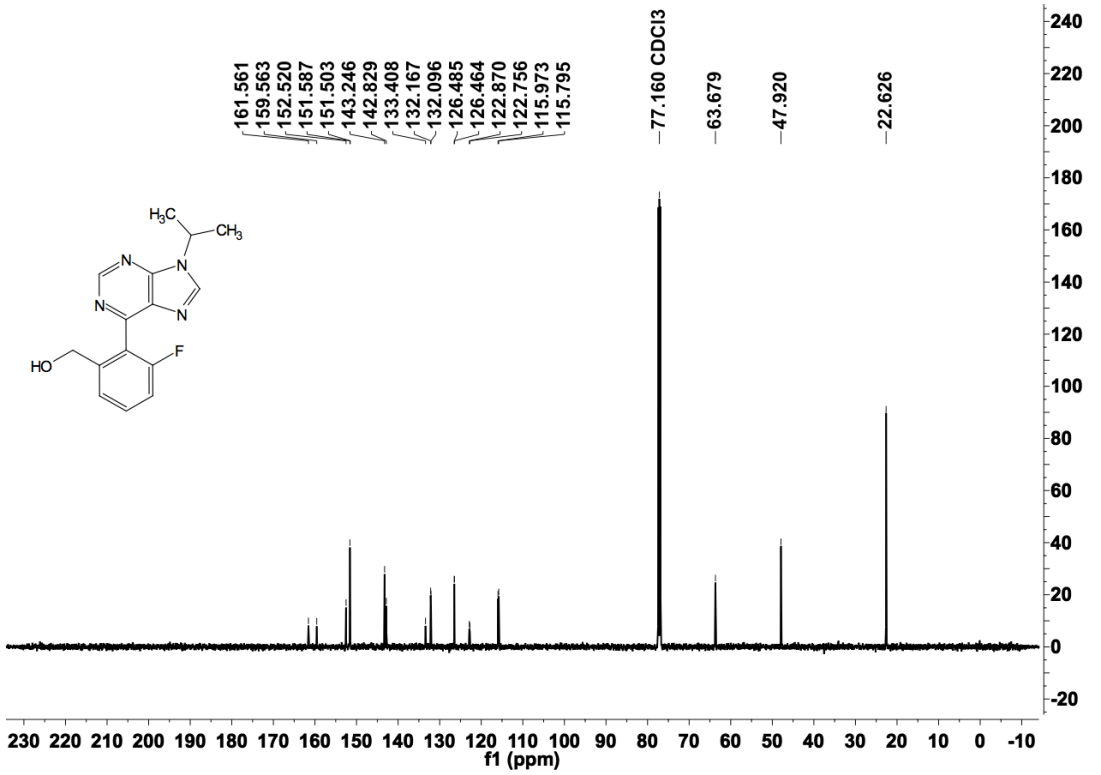
8.214
7.519
7.504
7.493
7.477
7.378
7.363
7.260 CDCl3
7.232
7.214
7.196
5.039
5.026
5.013
4.999
4.986
4.972
4.958
4.349
4.162
1.699
1.686
1.00
1.00
1.02
1.02
1.01
1.03
2.03
1.34
6.18
f1 (ppm)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159.563
152.520
151.587
151.503
143.246
142.829
133.408
132.167
132.096
126.485
126.464
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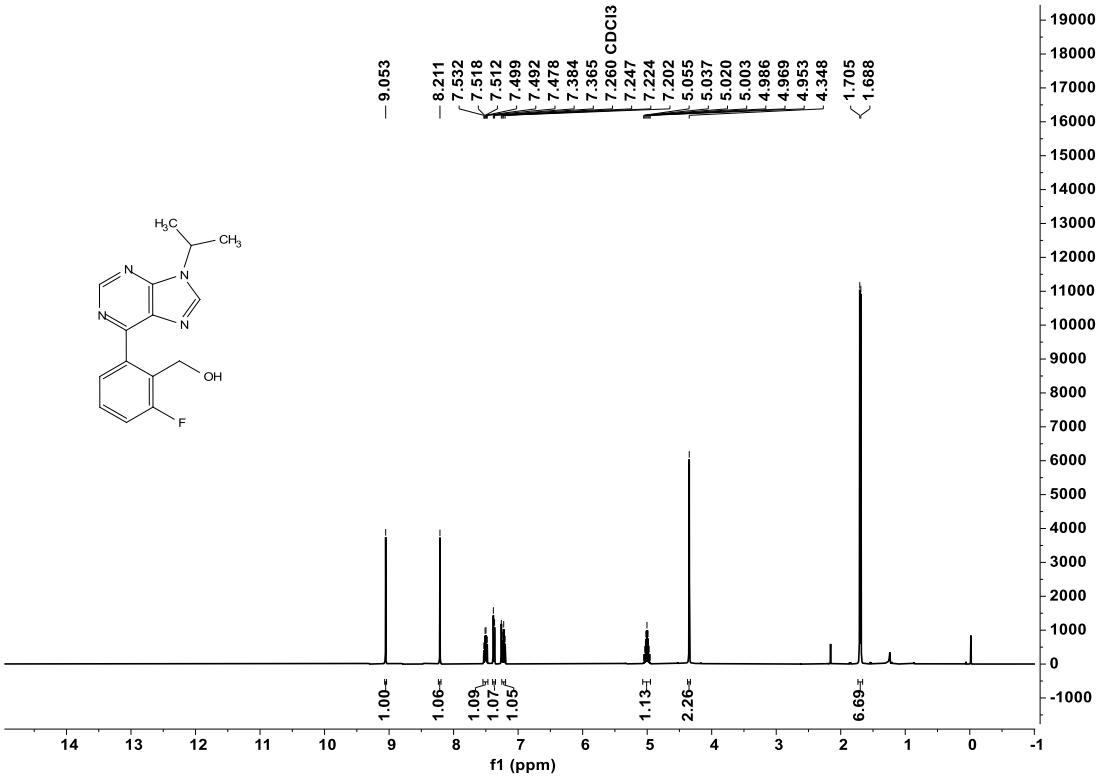
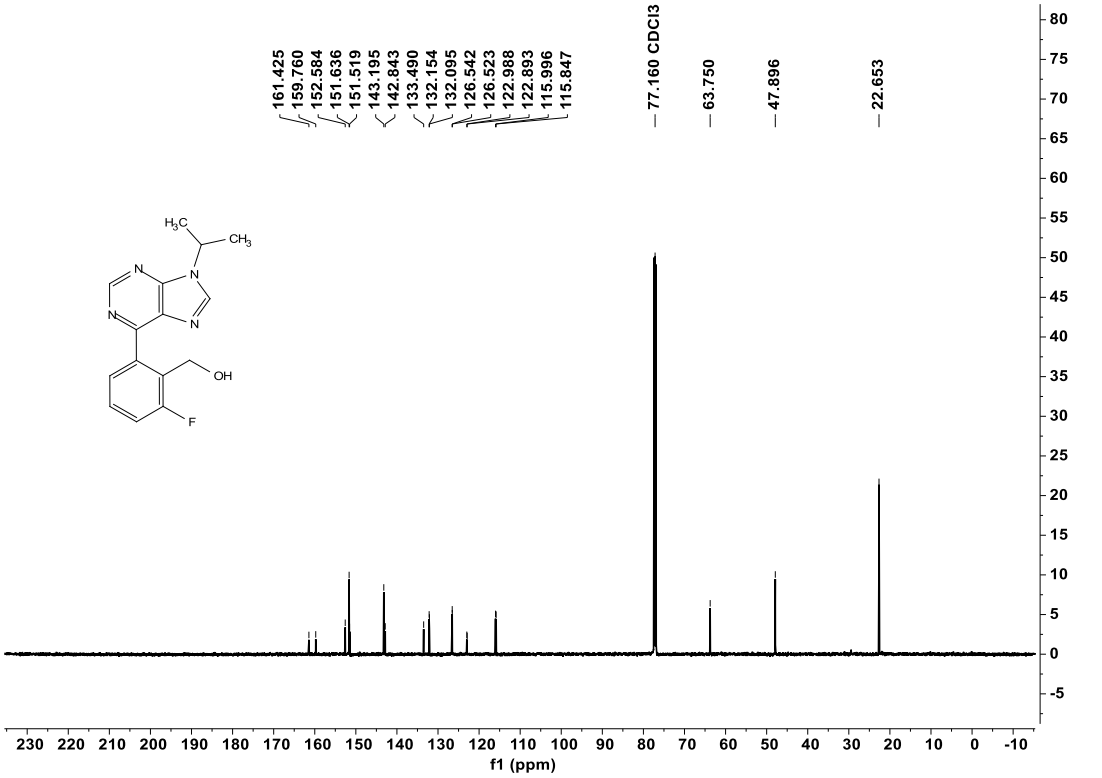
122.756
115.973
115.795
77.160 CDCl3
63.679
47.920
22.626
f1 (ppm)


9.053
8.211
7.532
7.518
7.512
7.499
7.492
7.478
7.384
7.365
7.260 CDCl3
7.247
7.224
7.202
5.055
5.037
5.020
5.003
4.986
4.969
4.953
4.348
1.705
1.688
1.00
1.06
1.09
1.07
1.05
1.13
2.26
6.69
f1 (ppm)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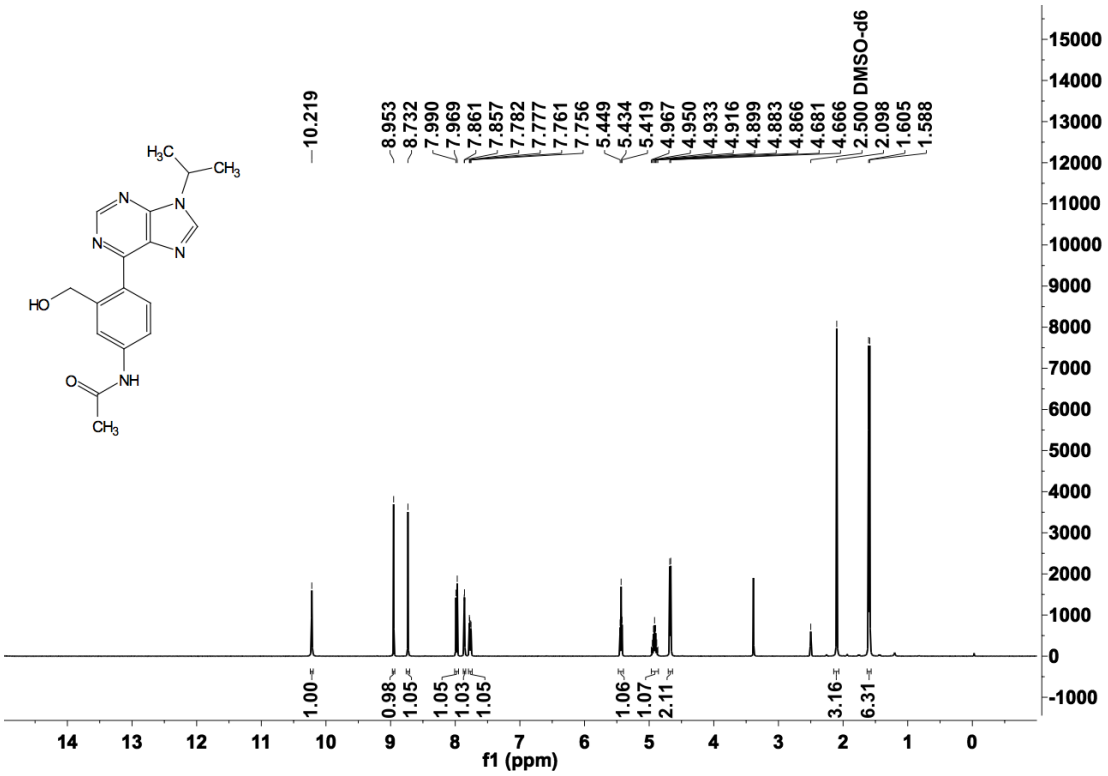
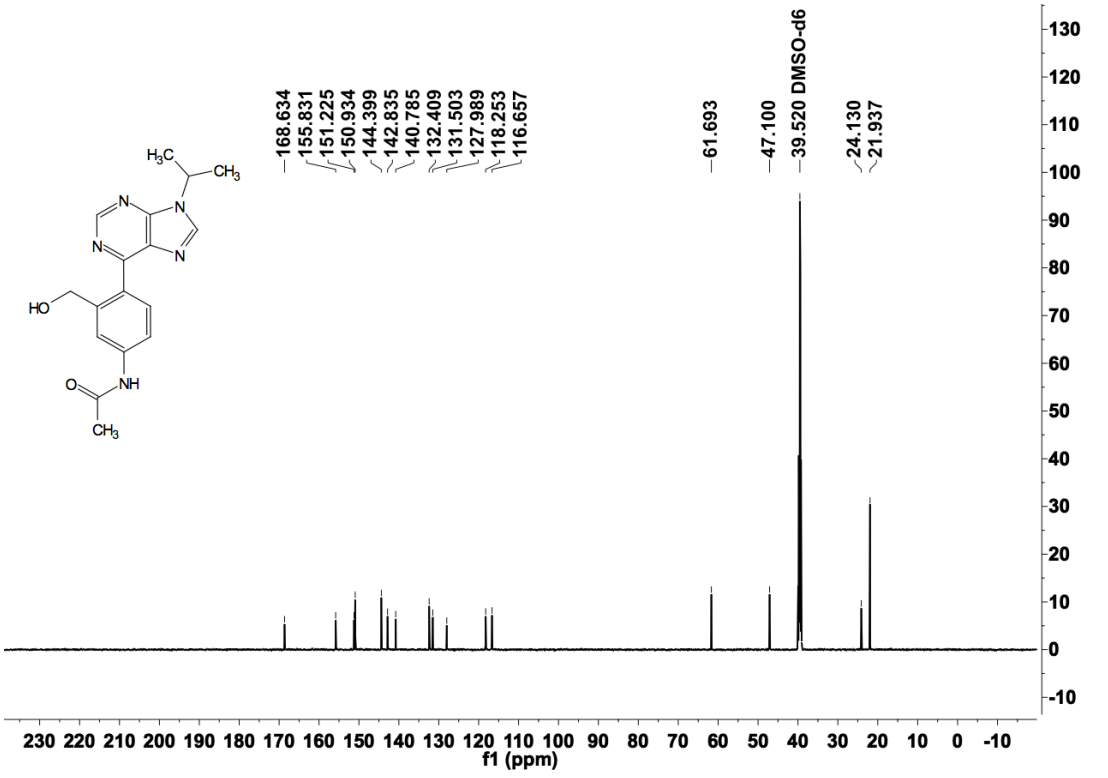
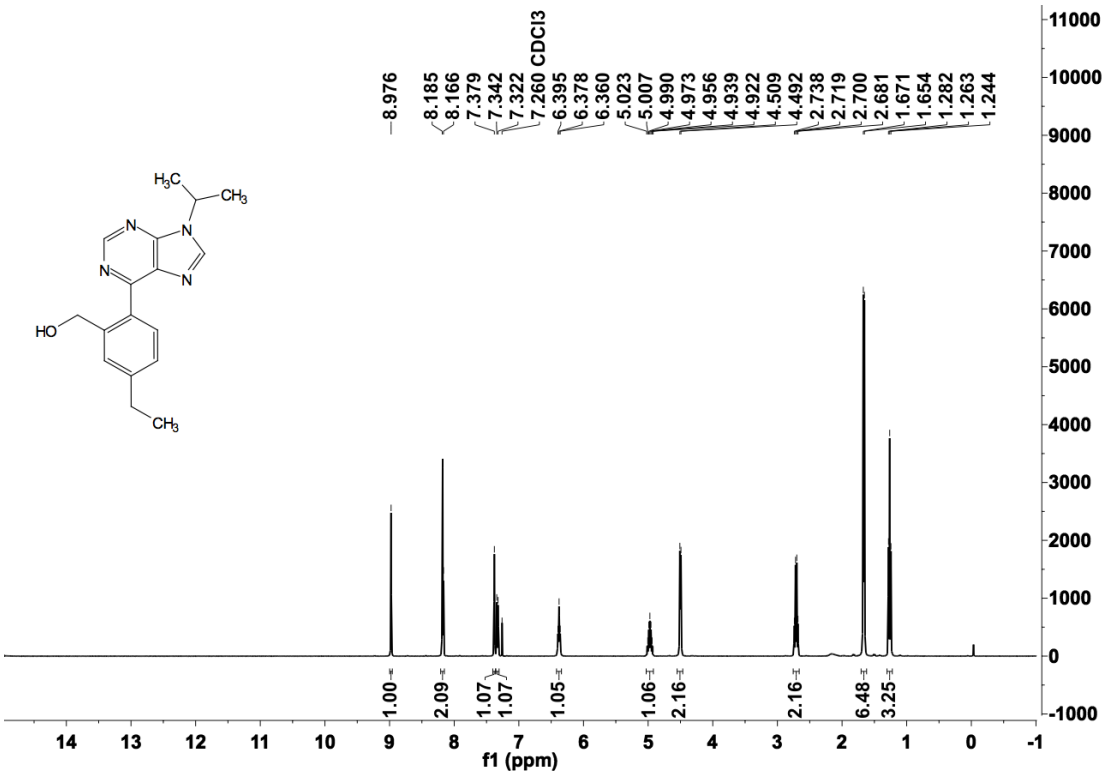
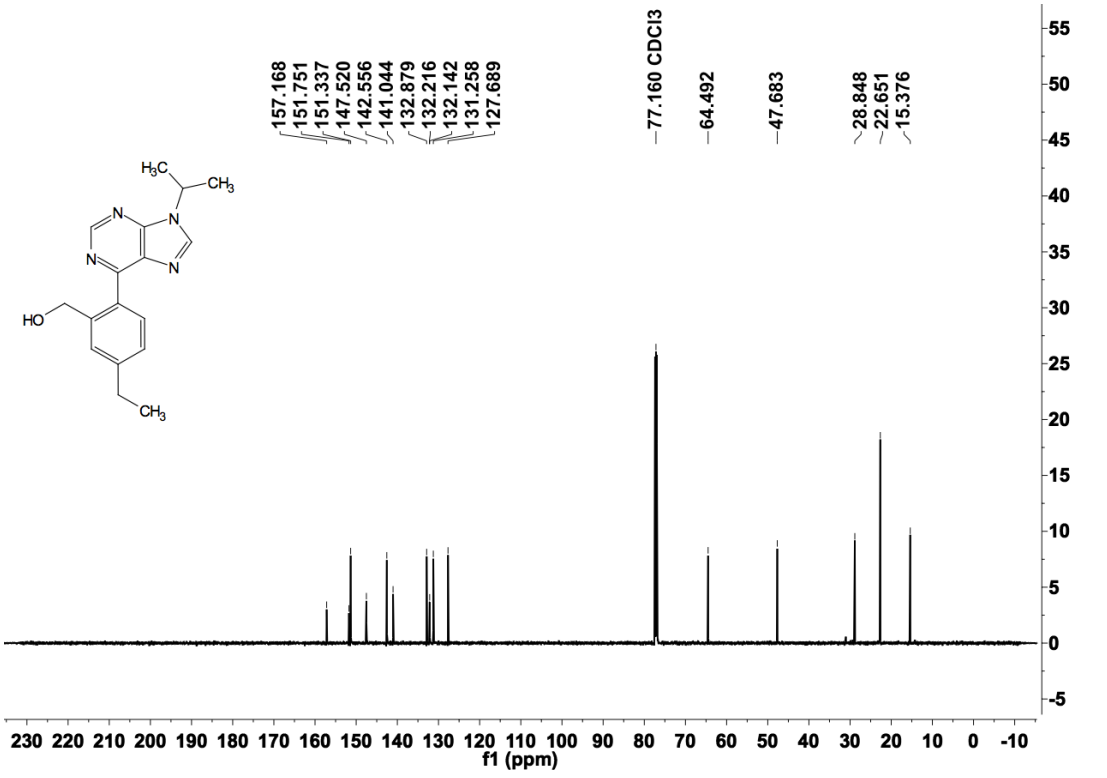
159.760
152.584
151.636
151.519
143.195
142.843
133.490
132.154
132.095
126.542
126.523
122.988
122.893
115.996
115.847
77.160 CDCl3
63.750
47.896
22.653
f1 (ppm)


10.219
8.953
8.732
7.990
7.969
7.861
7.857
7.782
7.777
7.761
7.756
5.449
5.434
5.419
4.967
4.950
4.933
4.916
4.899
4.883
4.866
4.681
4.666
2.500 DMSO-d6
2.098
1.605
1.588
1.00
0.98
1.05
1.05
1.03
1.05
1.06
1.07
2.11
3.16
6.31
f1 (ppm)


168.634
155.831
151.225
150.934
144.399
142.835
140.785
132.409
131.503
127.989
118.253
116.657
61.693
47.100
39.520 DMSO-d6
24.130
21.937
f1 (ppm)


8.976
8.185
8.166
7.379
7.342
7.322
7.260 CDCl3
6.395
6.378
6.360
5.023
5.007
4.990
4.973
4.956
4.939
4.922
4.509
4.492
2.738
2.719
2.700
2.681
1.671
1.654
1.282
1.263
1.244
1.00
2.09
1.07
1.07
1.05
1.06
2.16
2.16
6.48
3.25
f1 (ppm)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151.337
147.520
142.556
141.044
132.879
132.216
132.142
131.258
127.689
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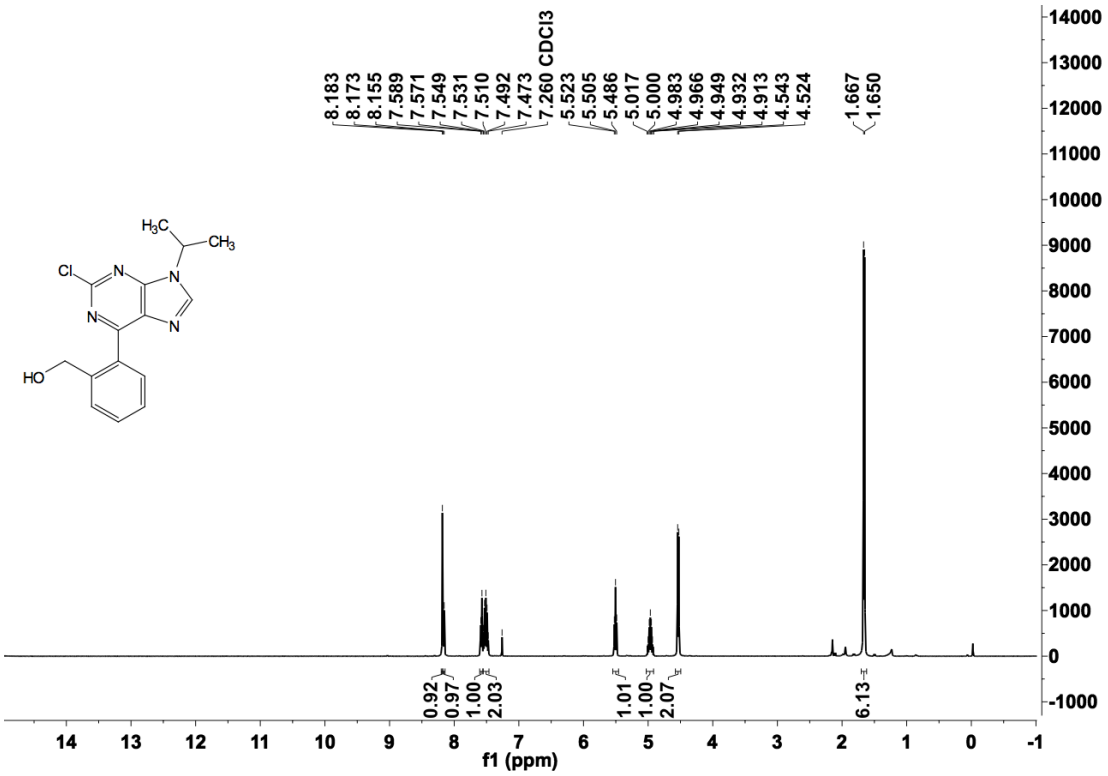
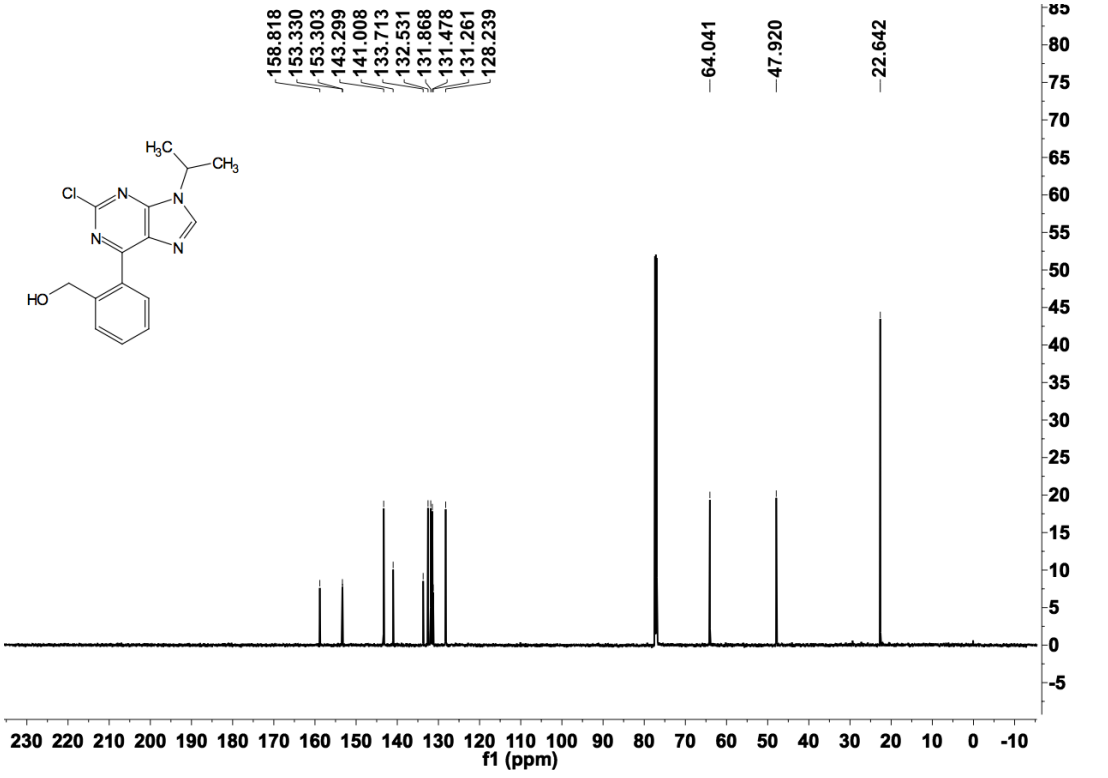
64.492
47.683
28.848
22.651
15.376
f1 (ppm)


8.183
8.173
8.155
7.589
7.571
7.549
7.531
7.510
7.492
7.473
7.260 CDCl3
5.523
5.505
5.486
5.017
5.000
4.983
4.966
4.949
4.932
4.913
4.543
4.524
1.667
1.650
0.92
0.97
1.00
2.03
1.01
1.00
2.07
6.13
f1 (ppm)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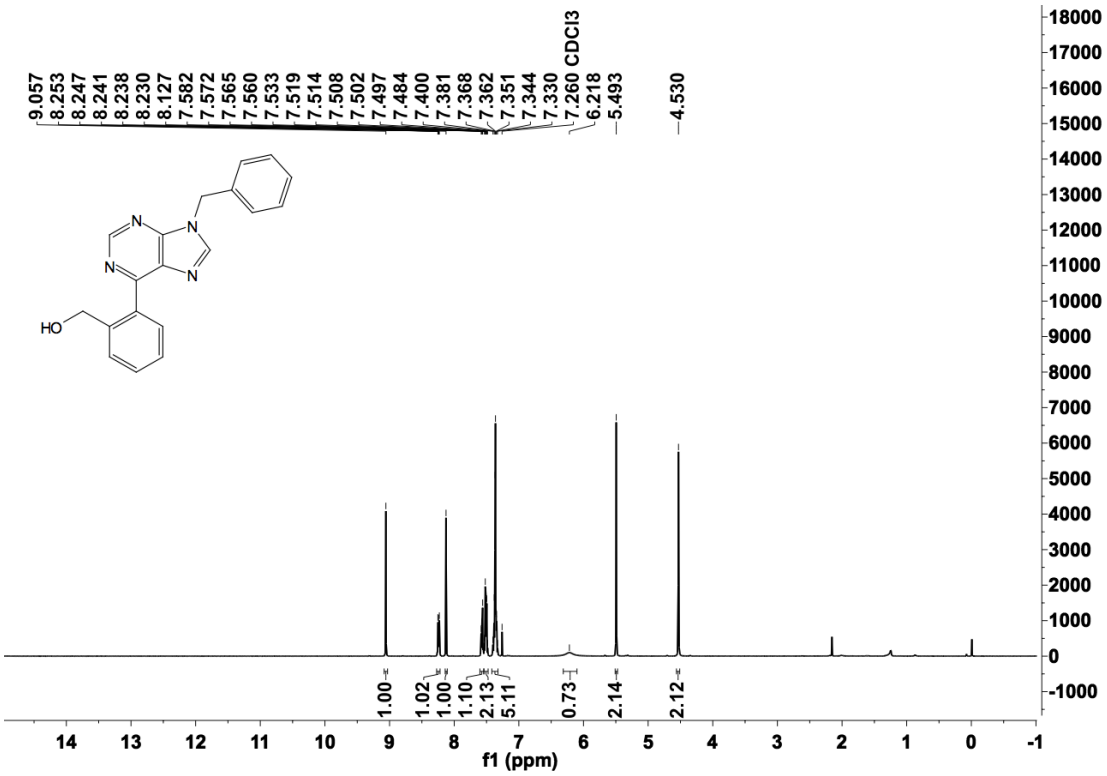
153.303
143.299
141.008
133.713
132.531
131.868
131.478
131.261
128.239
64.041
47.920
22.642
f1 (ppm)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8.247
8.241
8.238
8.230
8.127
7.582
7.572
7.565
7.560
7.533
7.519
7.514
7.508
7.502
7.497
7.484
7.400
7.381
7.368
7.362
7.351
7.344
7.330
7.260 CDCl3
6.218
5.493
4.530
HO
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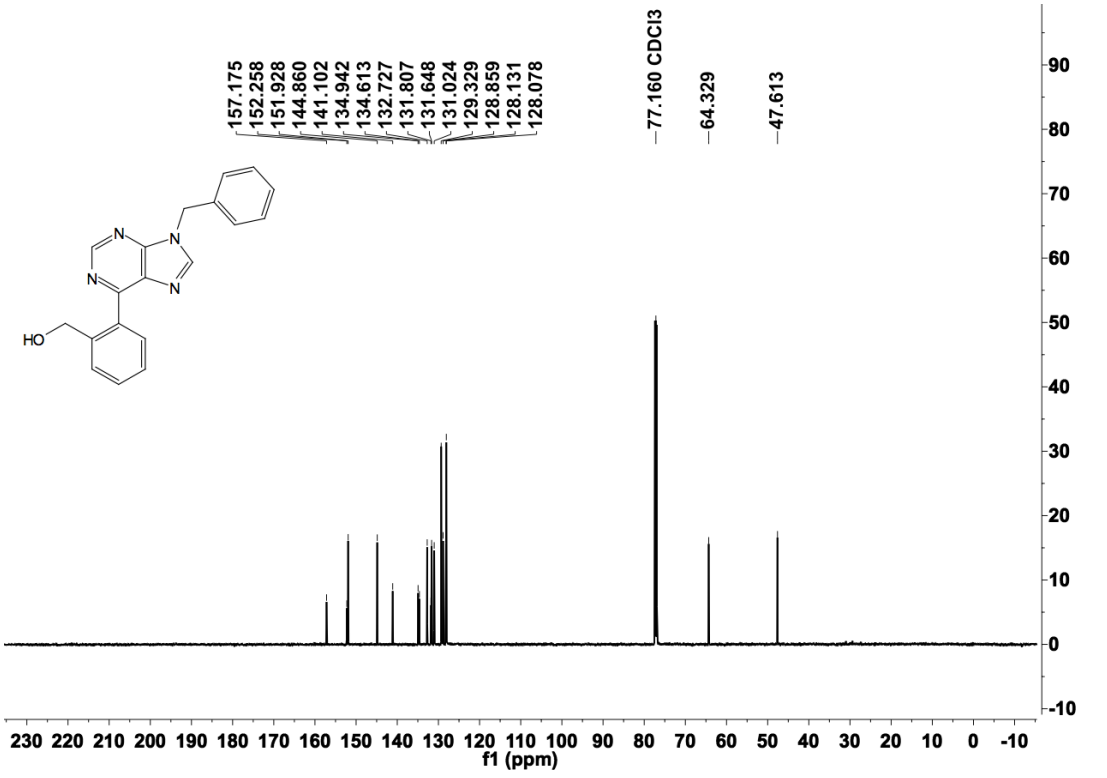
1.02
1.00
1.10
2.13
5.11
0.73
2.14
2.12
f1 (ppm)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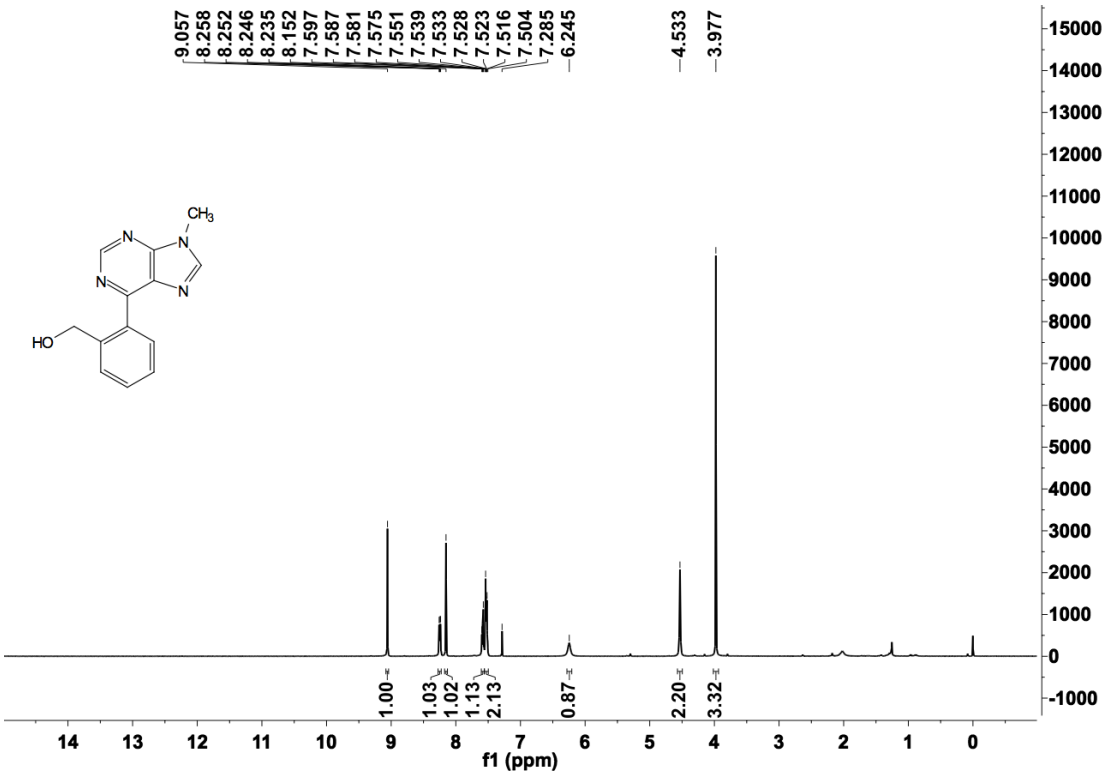
152.258
151.928
144.860
141.102
134.942
134.613
132.727
131.807
131.648
131.024
129.329
128.859
128.131
128.078
77.160 CDCl3
64.329
47.613
HO
f1 (ppm)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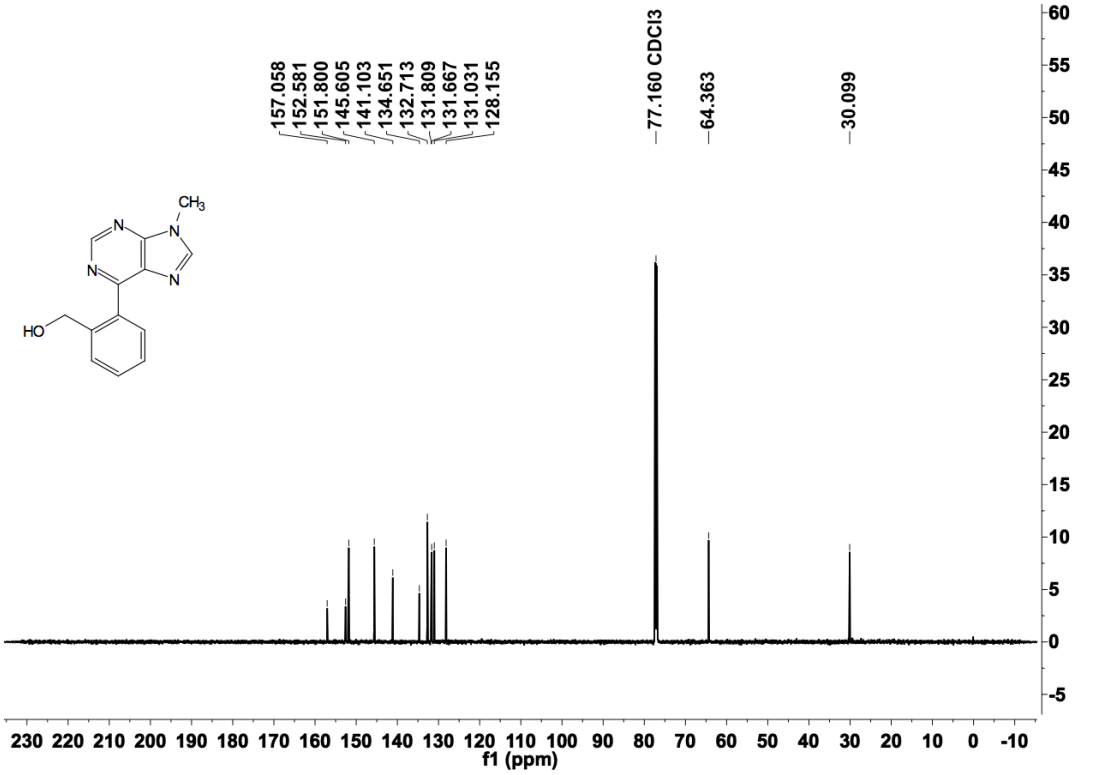
8.252
8.246
8.235
8.152
7.597
7.587
7.581
7.575
7.551
7.539
7.533
7.528
7.523
7.516
7.504
7.285
6.245
4.533
3.977
CH3
N
N
N
N
HO
1.00
1.03
1.02
1.13
2.13
0.87
2.20
3.32
f1 (ppm)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151.800
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141.103
134.651
132.713
131.809
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128.155
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CH3
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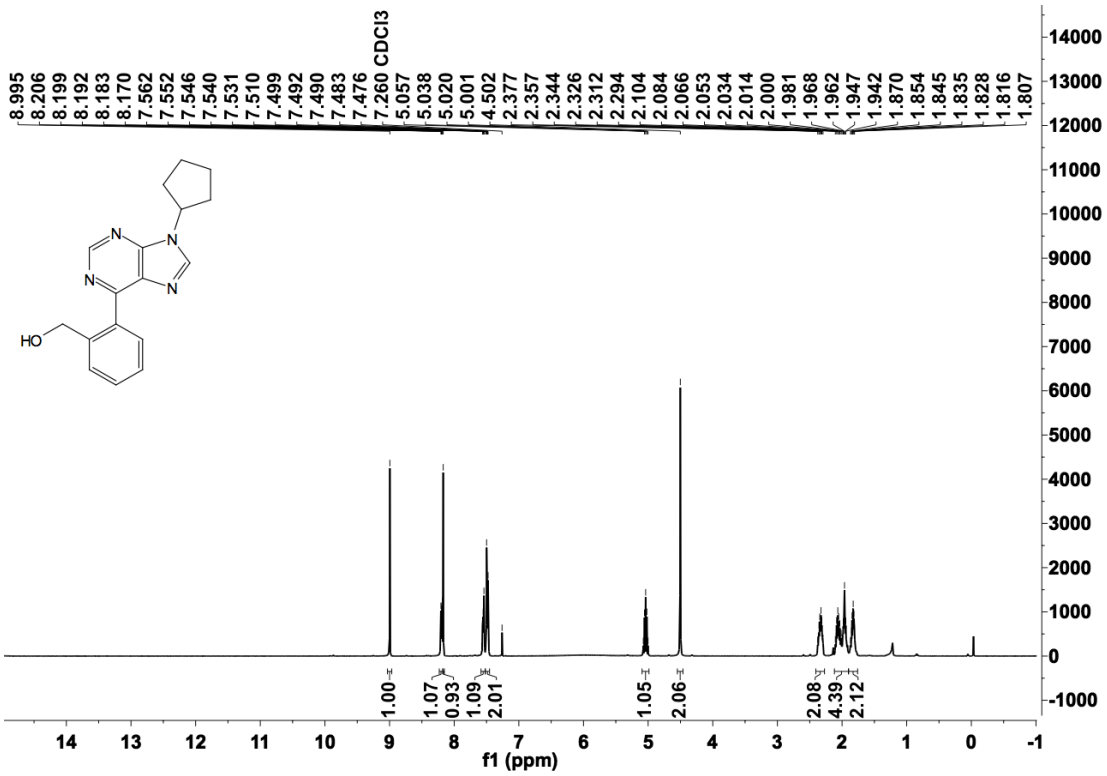
N
N
HO
f1 (ppm)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7.562
7.552
7.546
7.540
7.531
7.510
7.499
7.492
7.490
7.483
7.476
7.260 CDCl3
5.057
5.038
5.020
5.001
4.502
2.377
2.357
2.344
2.326
2.312
2.294
2.104
2.084
2.066
2.053
2.034
2.014
2.000
1.981
1.968
1.962
1.947
1.942
1.870
1.854
1.845
1.835
1.828
1.816
1.807
HO
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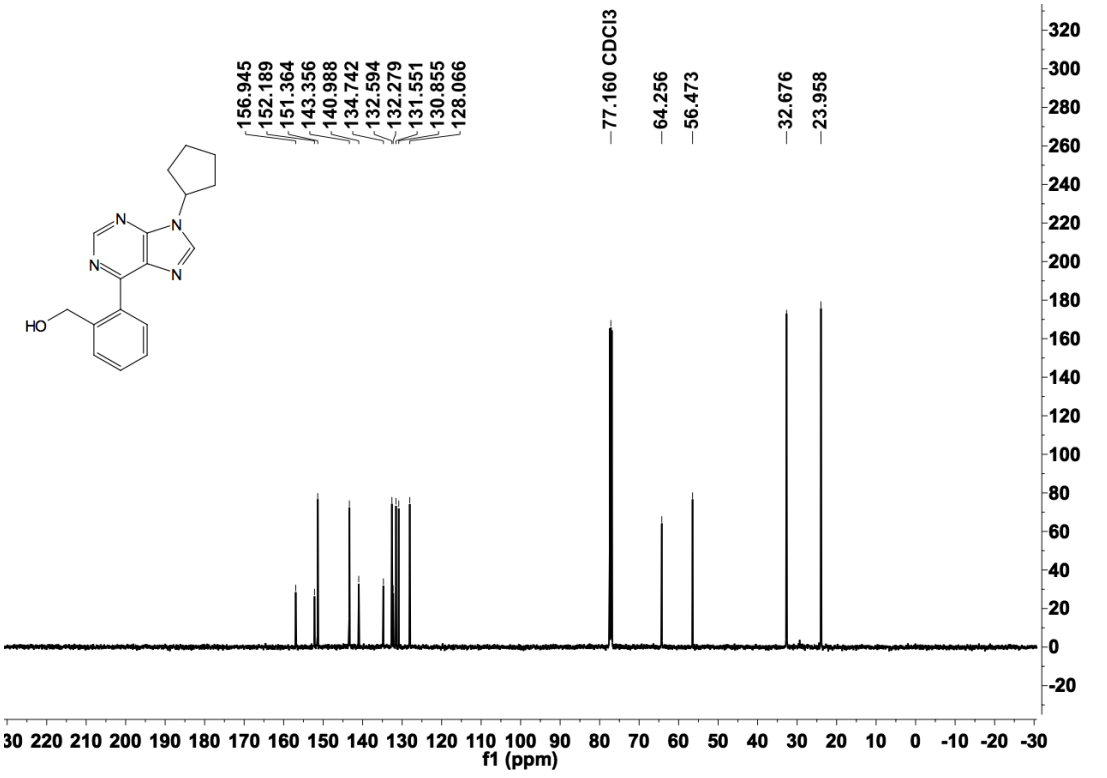
1.07
0.93
1.09
2.01
1.05
2.06
2.08
4.39
2.12
f1 (ppm)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152.189
151.364
143.356
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134.742
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132.279
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130.855
128.066
77.160 CDCl3
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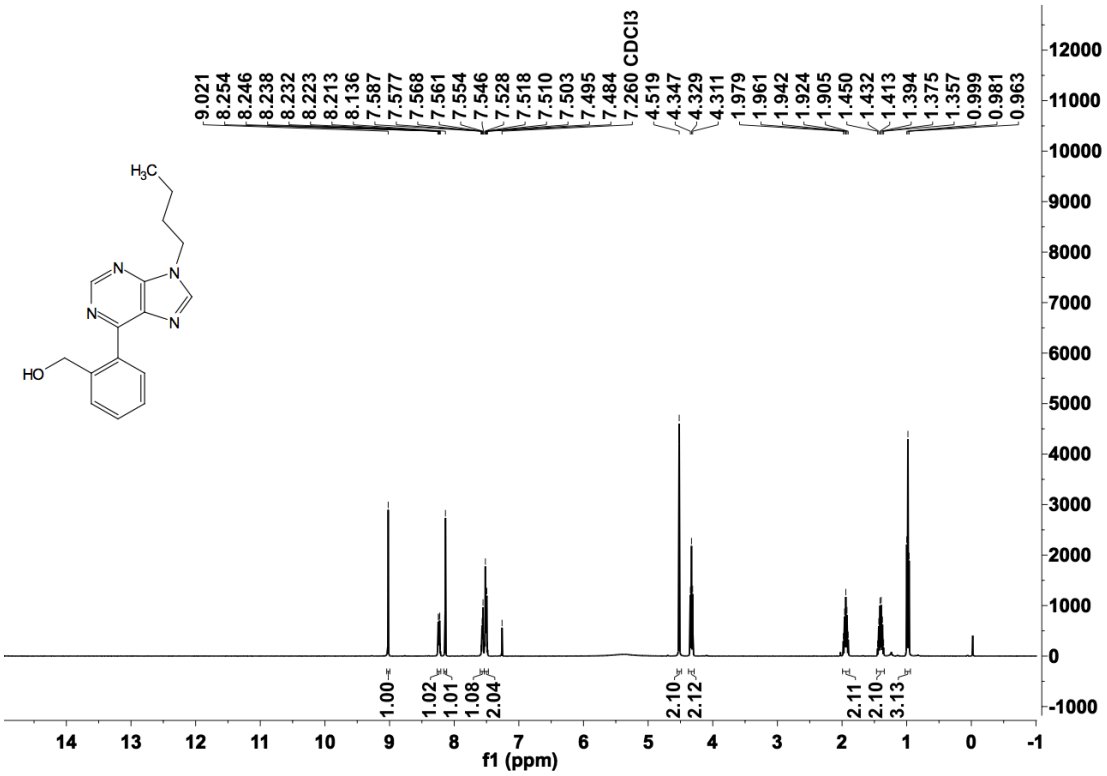
HO
f1 (ppm)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8.136
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7.568
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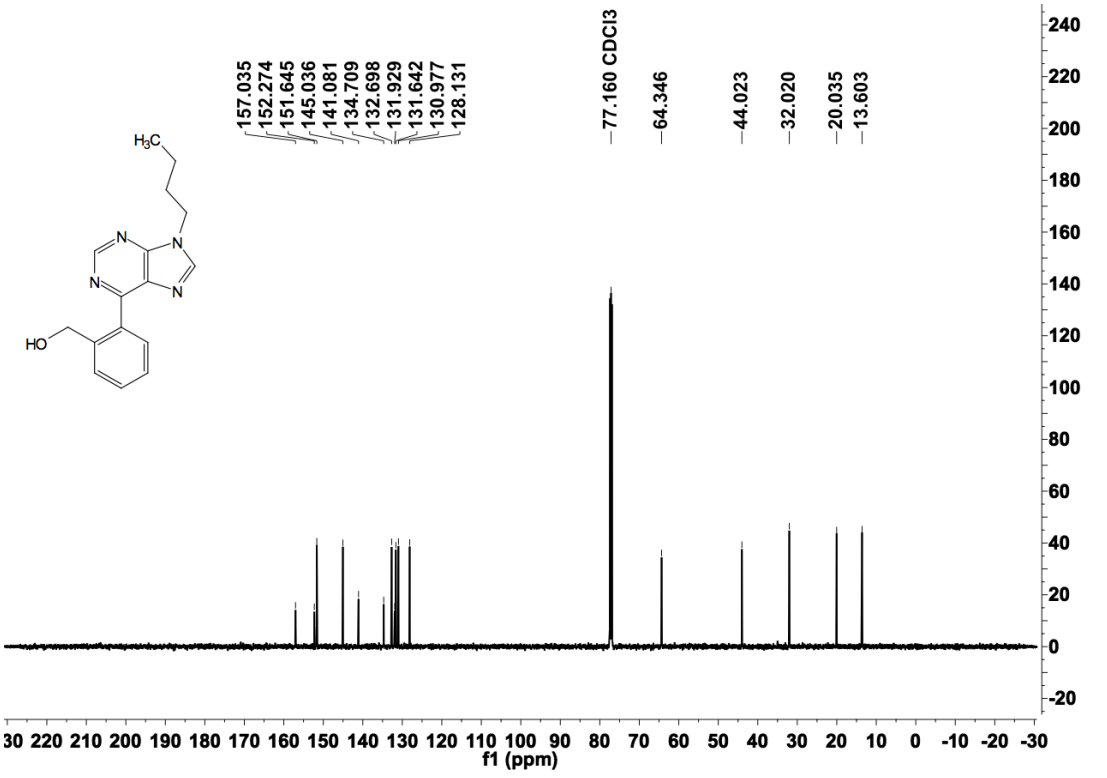
7.554
7.546
7.528
7.518
7.510
7.503
7.495
7.484
7.260 CDCl3
4.519
4.347
4.329
4.311
1.979
1.961
1.942
1.924
1.905
1.450
1.432
1.413
1.394
1.375
1.357
0.999
0.981
0.963
H3C
N
N
N
N
HO
1.00
1.02
1.01
1.08
2.04
2.10
2.12
2.11
2.10
3.13
f1 (ppm)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152.274
151.645
145.036
141.081
134.709
132.698
131.929
131.642
130.977
128.131
77.160 CDCl3
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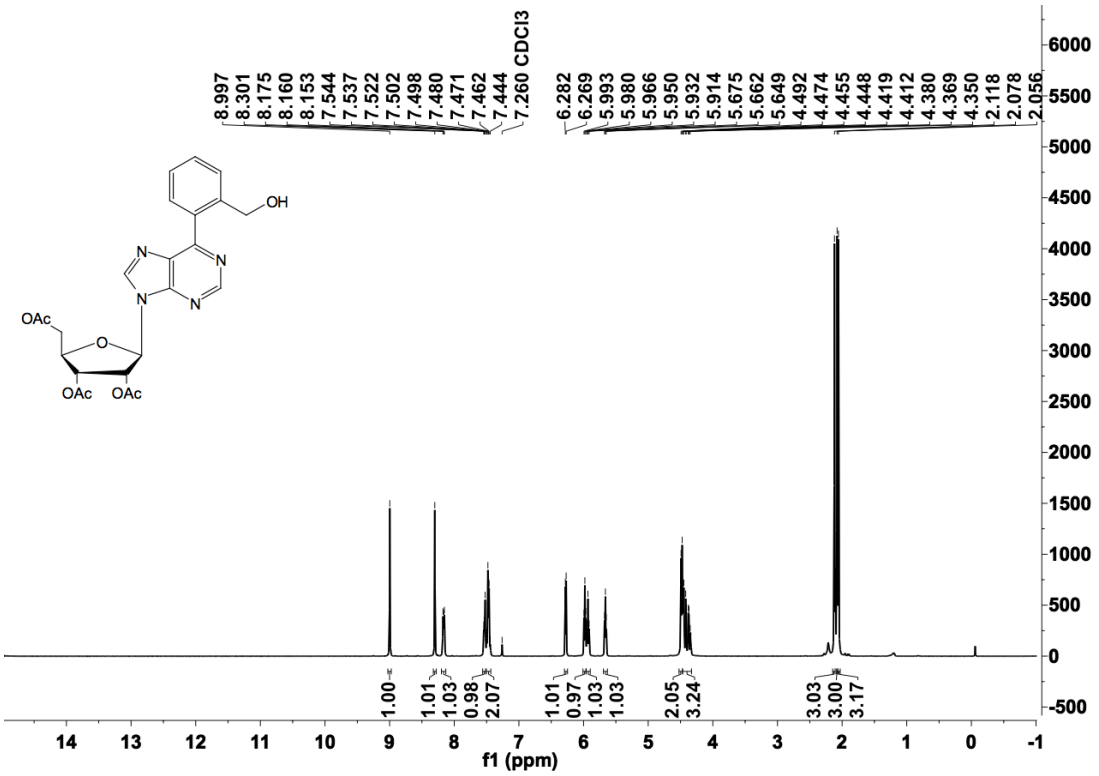
32.020
20.035
13.603
H3C
N
N
N
N
HO
f1 (ppm)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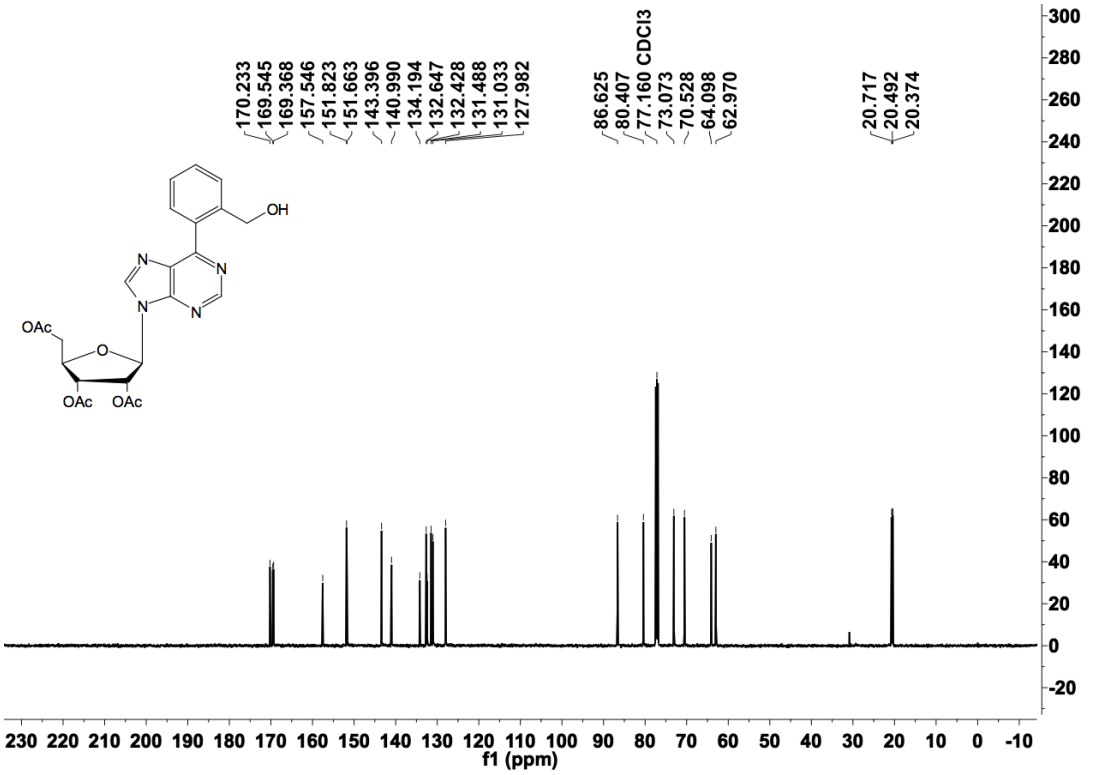
7.537
7.522
7.502
7.498
7.480
7.471
7.462
7.444
7.260 CDCl3
6.282
6.269
5.993
5.980
5.966
5.950
5.932
5.914
5.675
5.662
5.649
4.492
4.474
4.455
4.448
4.419
4.412
4.380
4.369
4.350
2.118
2.078
2.056
OH
OAc
OAc
OAc
1.00
1.01
1.03
0.98
2.07
1.01
0.97
1.03
1.03
2.05
3.24
3.03
3.00
3.17
f1 (ppm)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140.990
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132.428
131.488
131.033
127.982
86.625
80.407
77.160 CDCl3
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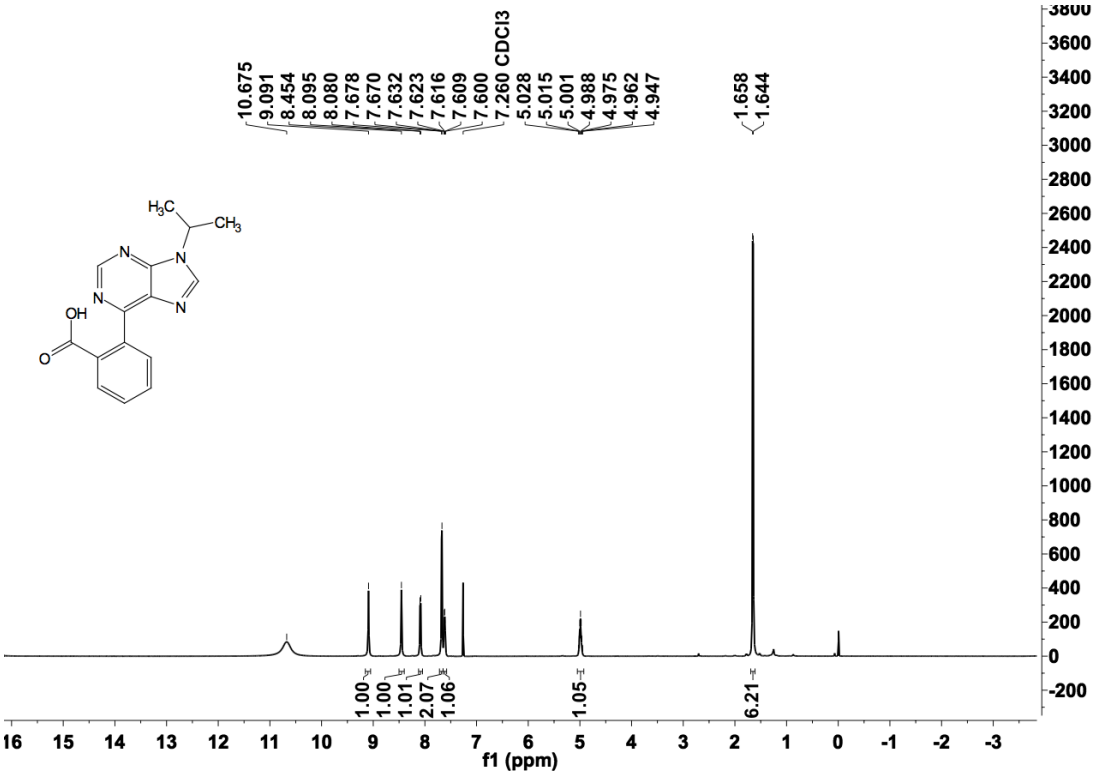
70.528
64.098
62.970
20.717
20.492
20.374
OH
OAc
OAc
OAc
f1 (ppm)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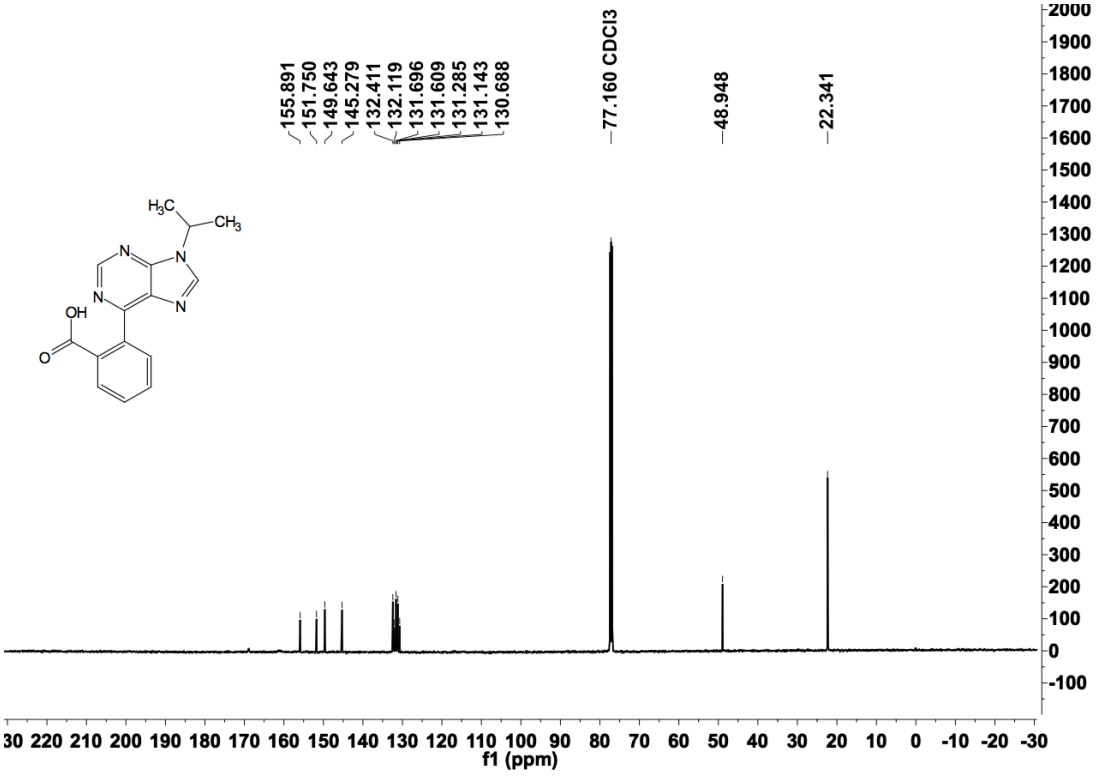
7.678
7.670
7.632
7.623
7.616
7.609
7.600
7.260 CDCl3
5.028
5.015
5.001
4.988
4.975
4.962
4.947
1.658
1.644
1.00
1.00
1.01
2.07
1.06
1.05
6.21
f1 (ppm)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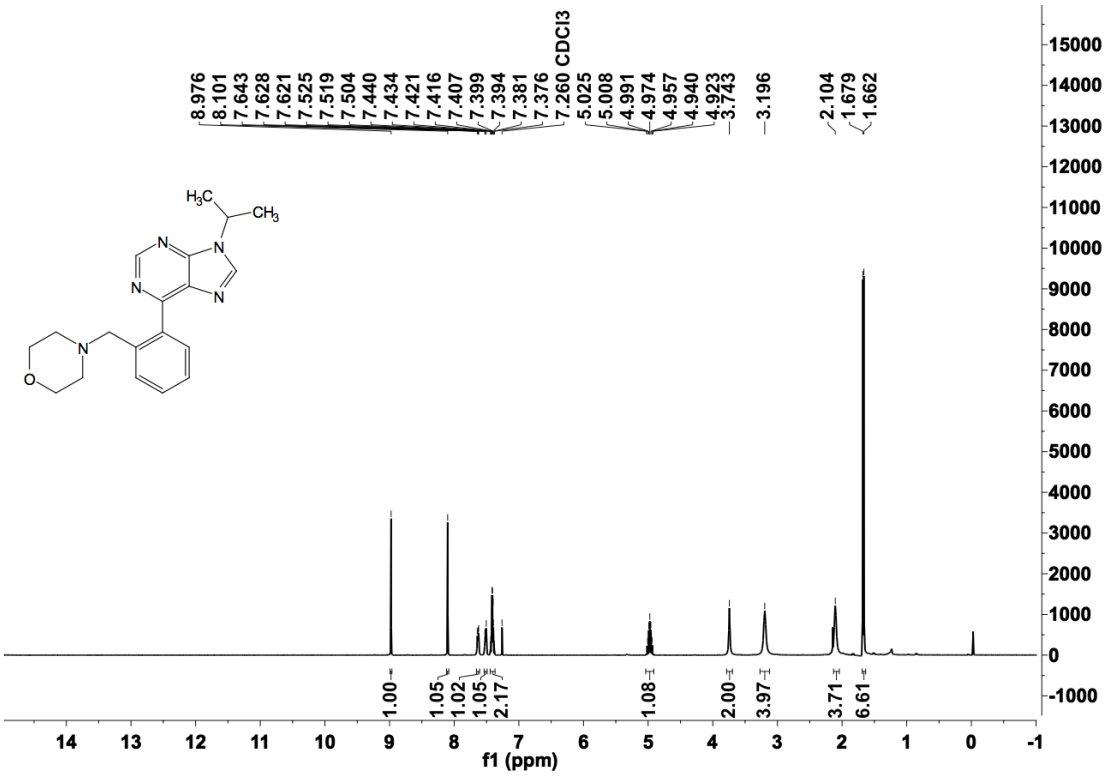
131.609
131.285
131.143
130.688
77.160 CDCl3
48.948
22.341
f1 (ppm)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7.504
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7.416
7.407
7.399
7.394
7.381
7.376
7.260 CDCl3
5.025
5.008
4.991
4.974
4.957
4.940
4.923
3.743
3.196
2.104
1.679
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1.02
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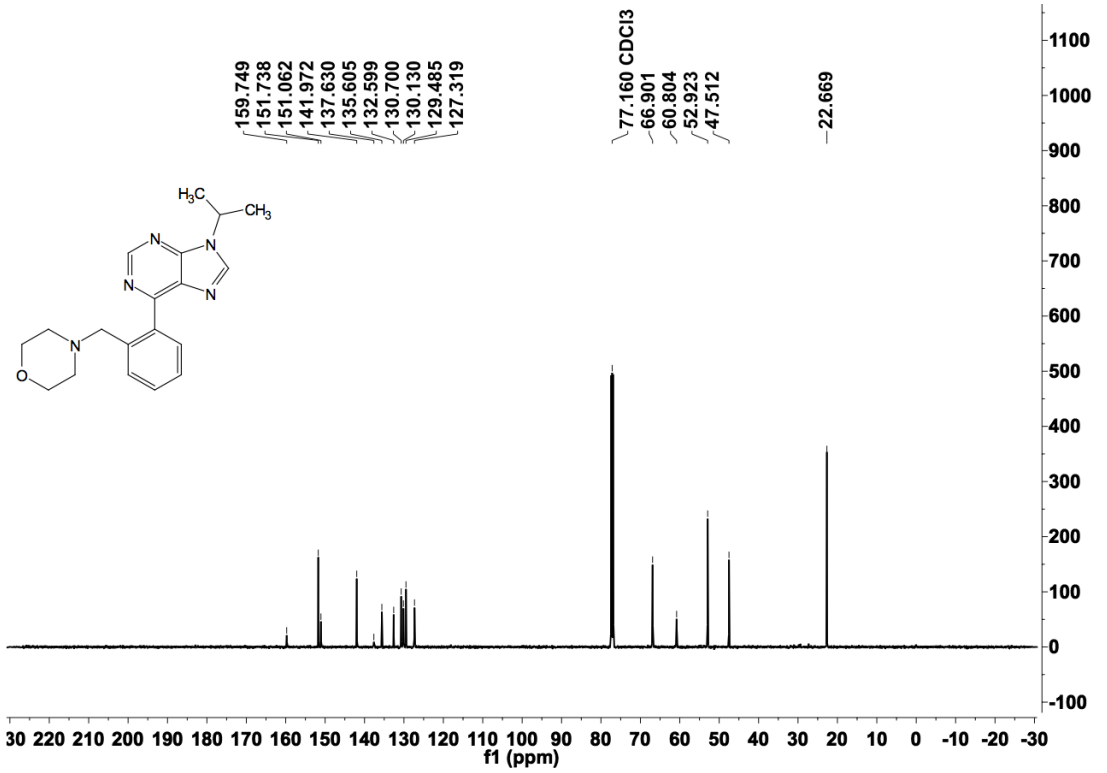
f1 (ppm)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141.972
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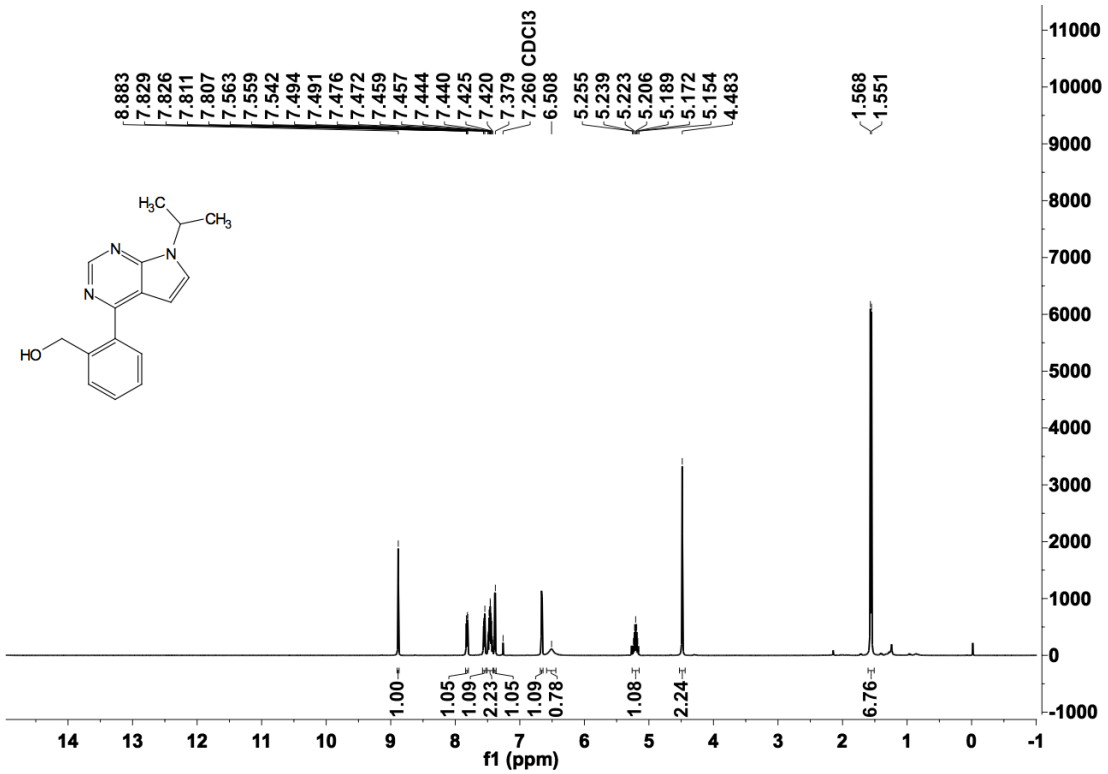
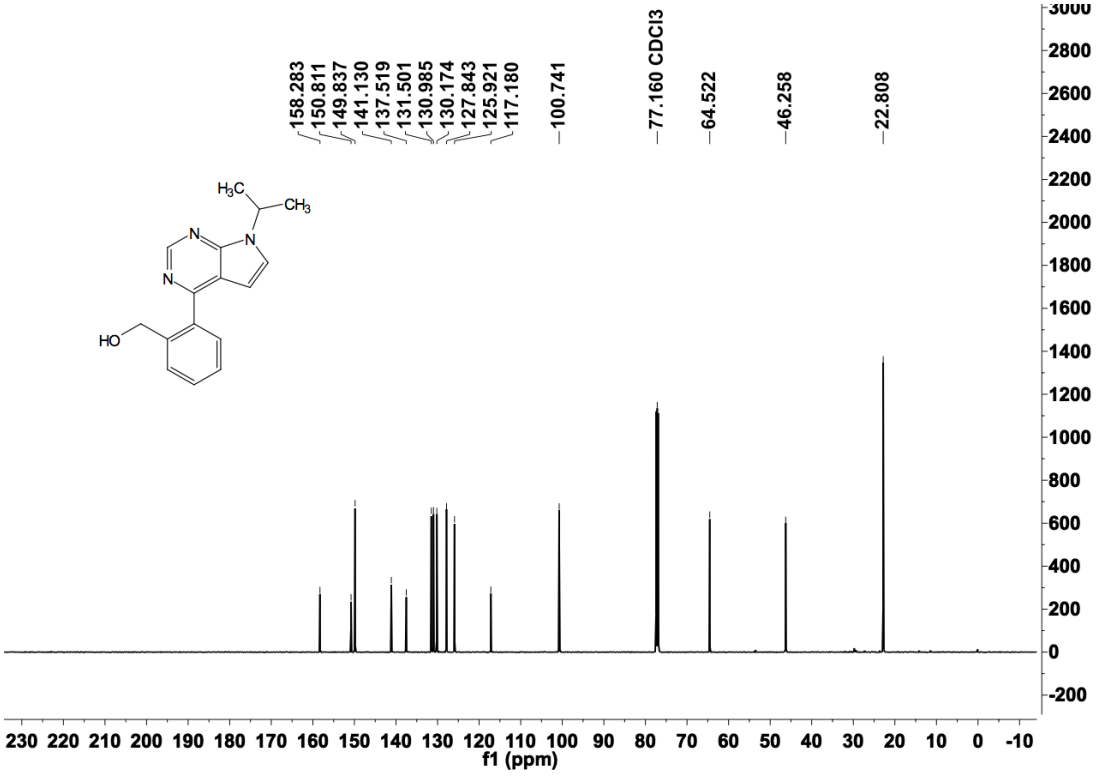
135.605
132.599
130.700
130.130
129.485
127.319
77.160 CDCl3
66.901
60.804
52.923
47.512
22.669
f1 (ppm)


8.883
7.829
7.826
7.811
7.807
7.563
7.559
7.542
7.494
7.491
7.476
7.472
7.459
7.457
7.444
7.440
7.425
7.420
7.379
7.260 CDCl3
6.508
5.255
5.239
5.223
5.206
5.189
5.172
5.154
4.483
1.568
1.551
1.00
1.05
1.09
2.23
1.05
1.09
0.78
1.08
2.24
6.76
f1 (ppm)


158.283
150.811
149.837
141.130
137.519
131.501
130.985
130.174
127.843
125.921
117.180
100.741
77.160 CDCl3
64.522
46.258
22.808
f1 (ppm)