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Title	Design and synthesis of alpha-carboxy nucleoside phosphonate analogues and evaluation as HIV-1 reverse transcriptase-targeting agents
Authors	Keane, Sarah J.;Ford, Alan;Mullins, Nicholas D.;Maguire, Nuala M.;Legigan, Thibaut;Balzarini, Jan;Maguire, Anita R.
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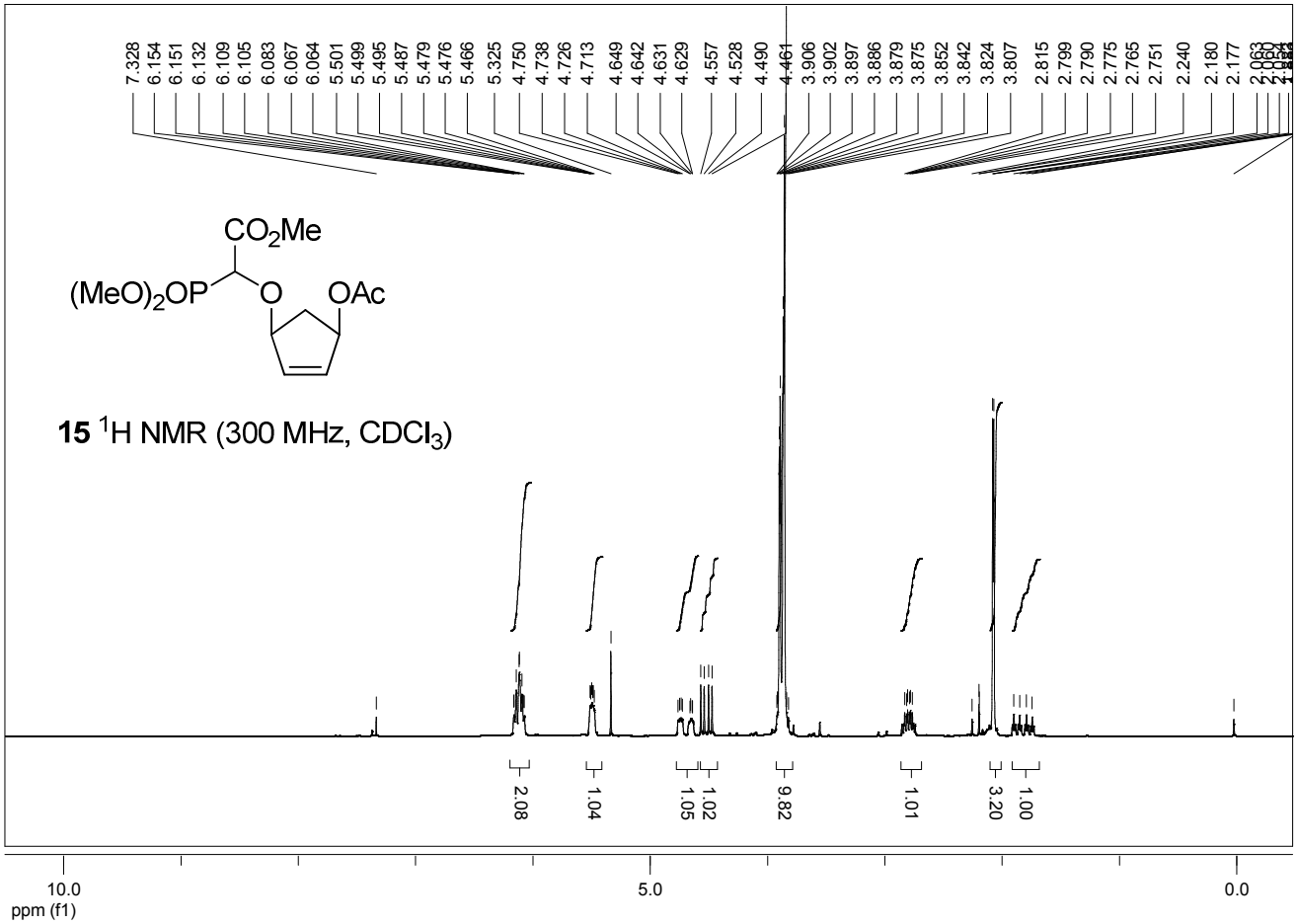
UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Design and synthesis of α-carboxy nucleoside phosphonate (α-CNP) analogues and evaluation as HIV-1 reverse transcriptase-targeting agents

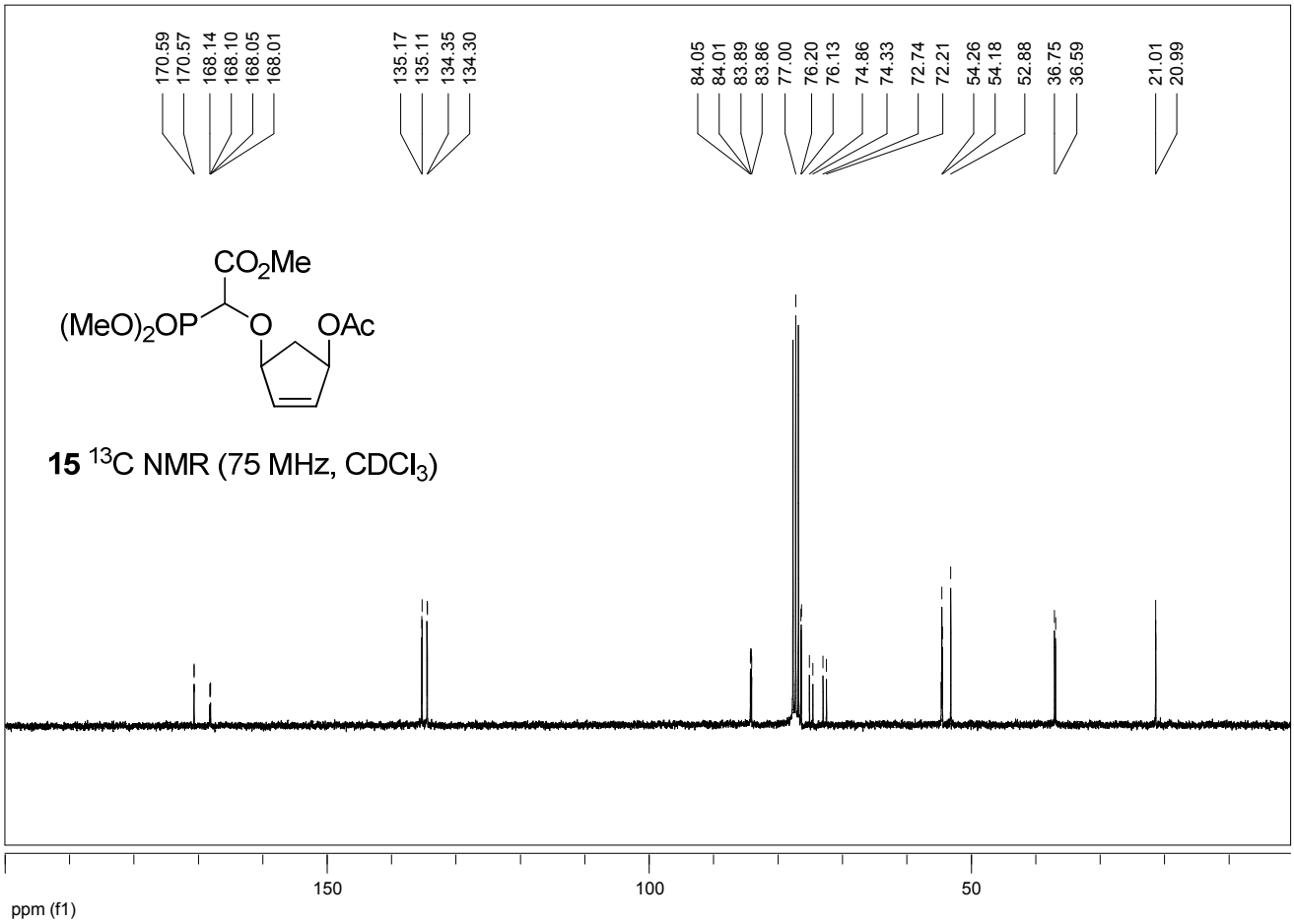
*Sarah J. Keane, Alan Ford, Nicholas D. Mullins, Nuala M. Maguire, Thibaut Legigan, Jan Balzarini and Anita R. Maguire**

Supporting Information

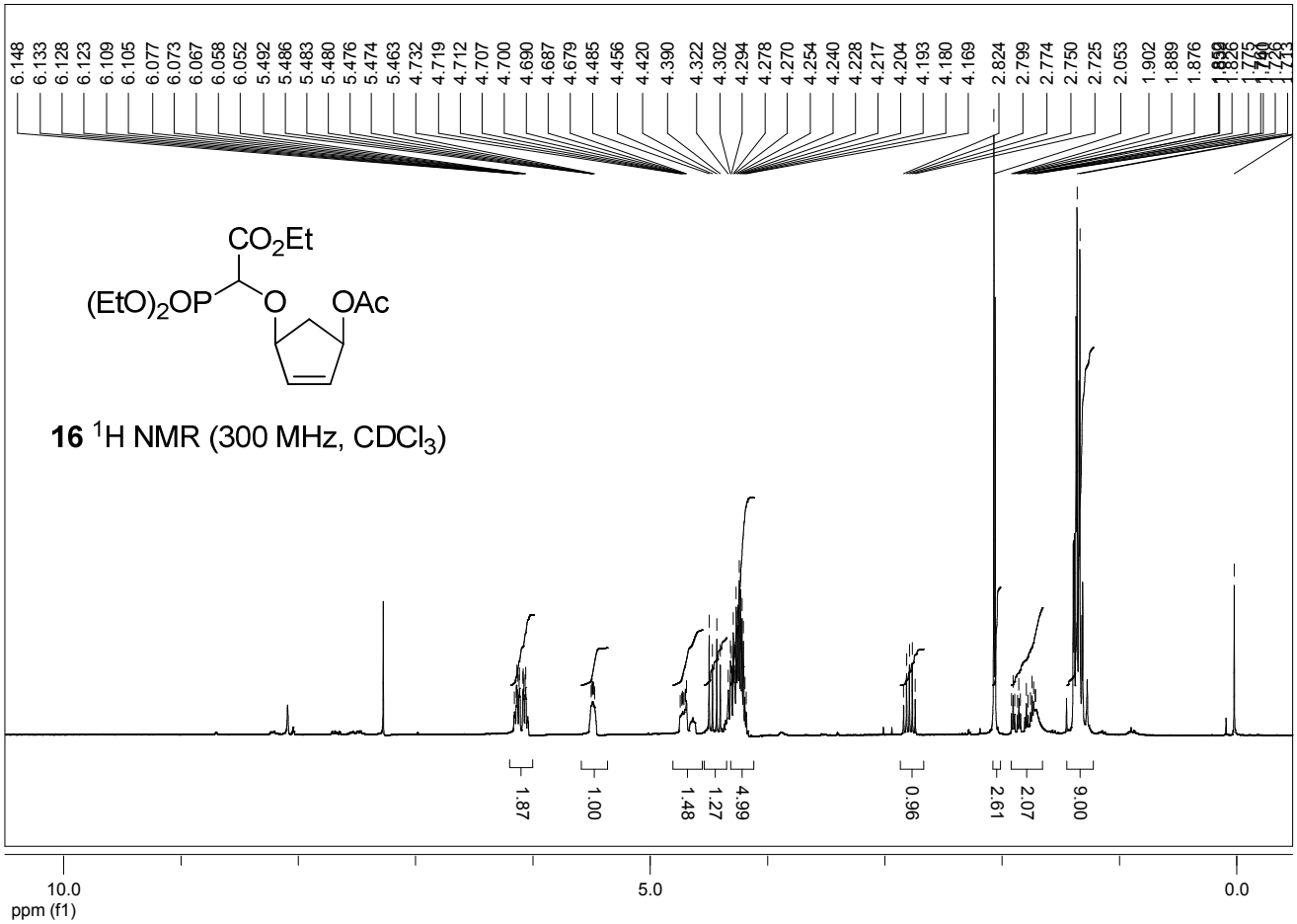
Copies of ^{1}H and ^{13}C Spectra S2–S33

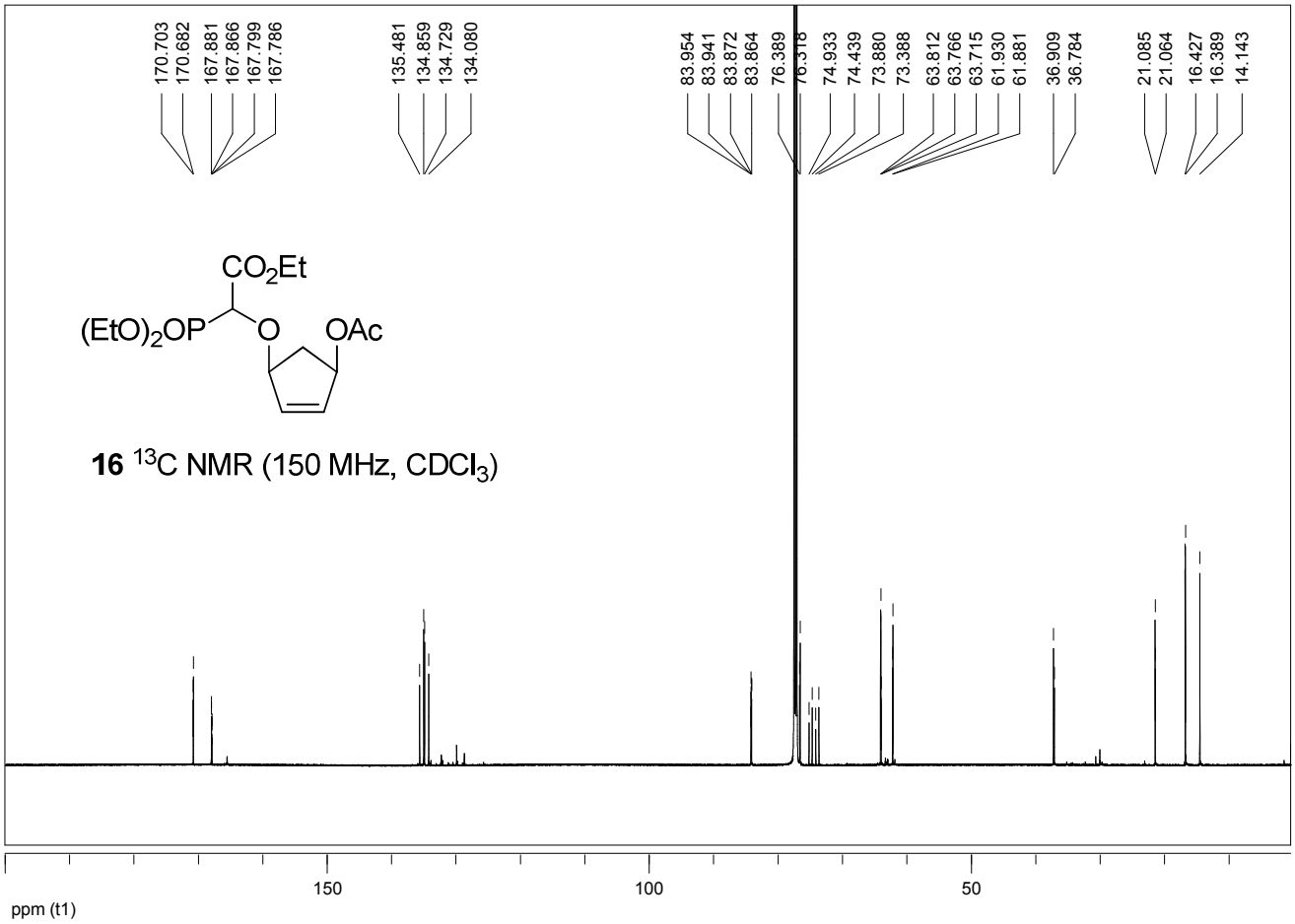


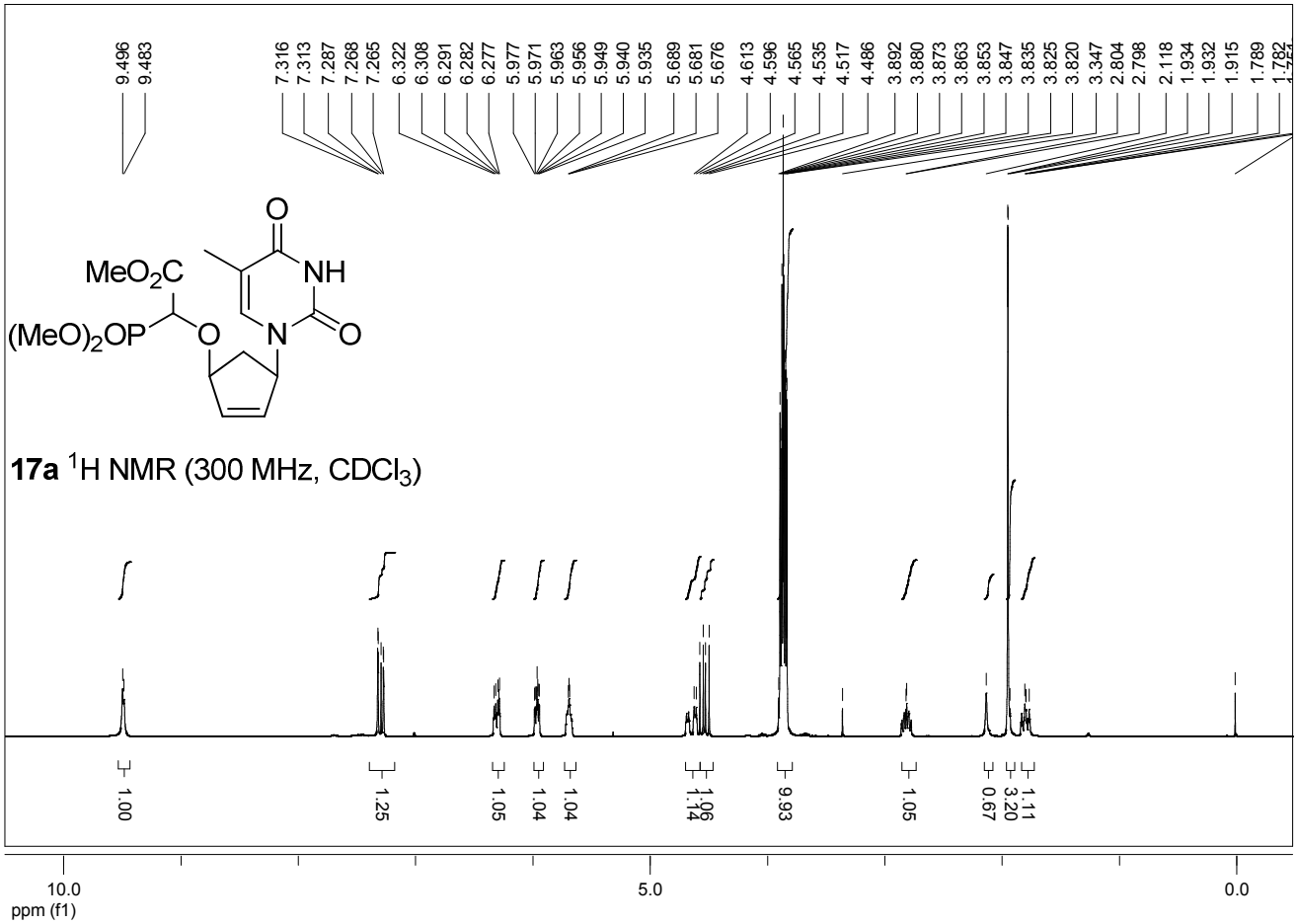
15 ^{1}H NMR (300 MHz, $CDCl_3$)



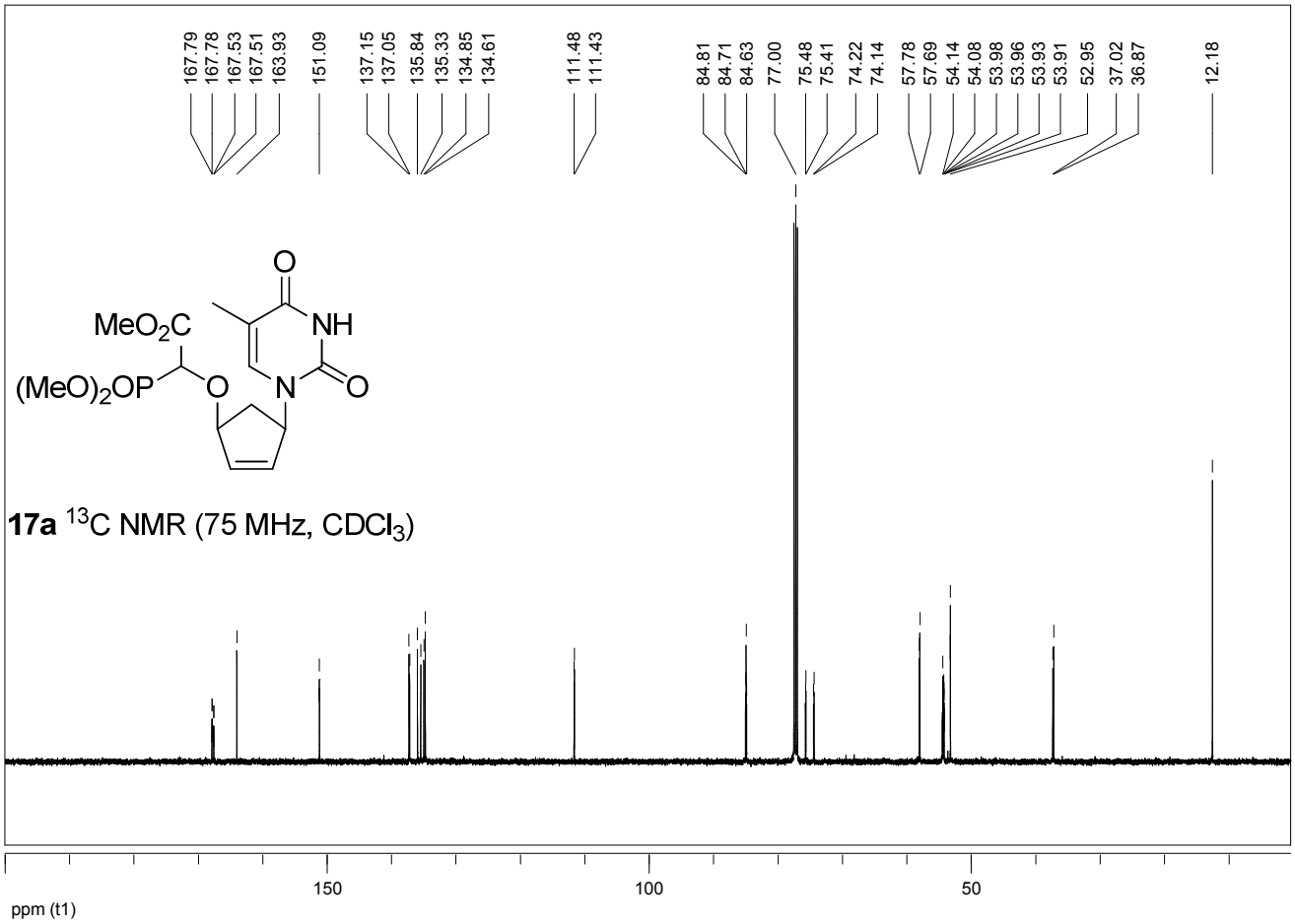
15 ^{13}C NMR (75 MHz, $CDCl_3$)


6.148
6.133
6.128
6.123
6.109
6.105
6.077
6.073
6.067
6.058
6.052
5.492
5.486
5.483
5.480
5.476
5.474
5.463
4.732
4.719
4.712
4.707
4.700
4.690
4.687
4.679
4.485
4.456
4.420
4.390
4.322
4.302
4.294
4.278
4.270
4.254
4.240
4.228
4.217
4.204
4.193
4.180
4.169
2.824
2.799
2.774
2.750
2.725
2.053
1.902
1.889
1.876
CO2Et
(EtO)2OP
O
OAc
16 1H NMR (300 MHz, CDCl3)
1.87
1.00
1.48
1.27
4.99
0.96
2.61
2.07
9.00
10.0
5.0
0.0
ppm (f1)

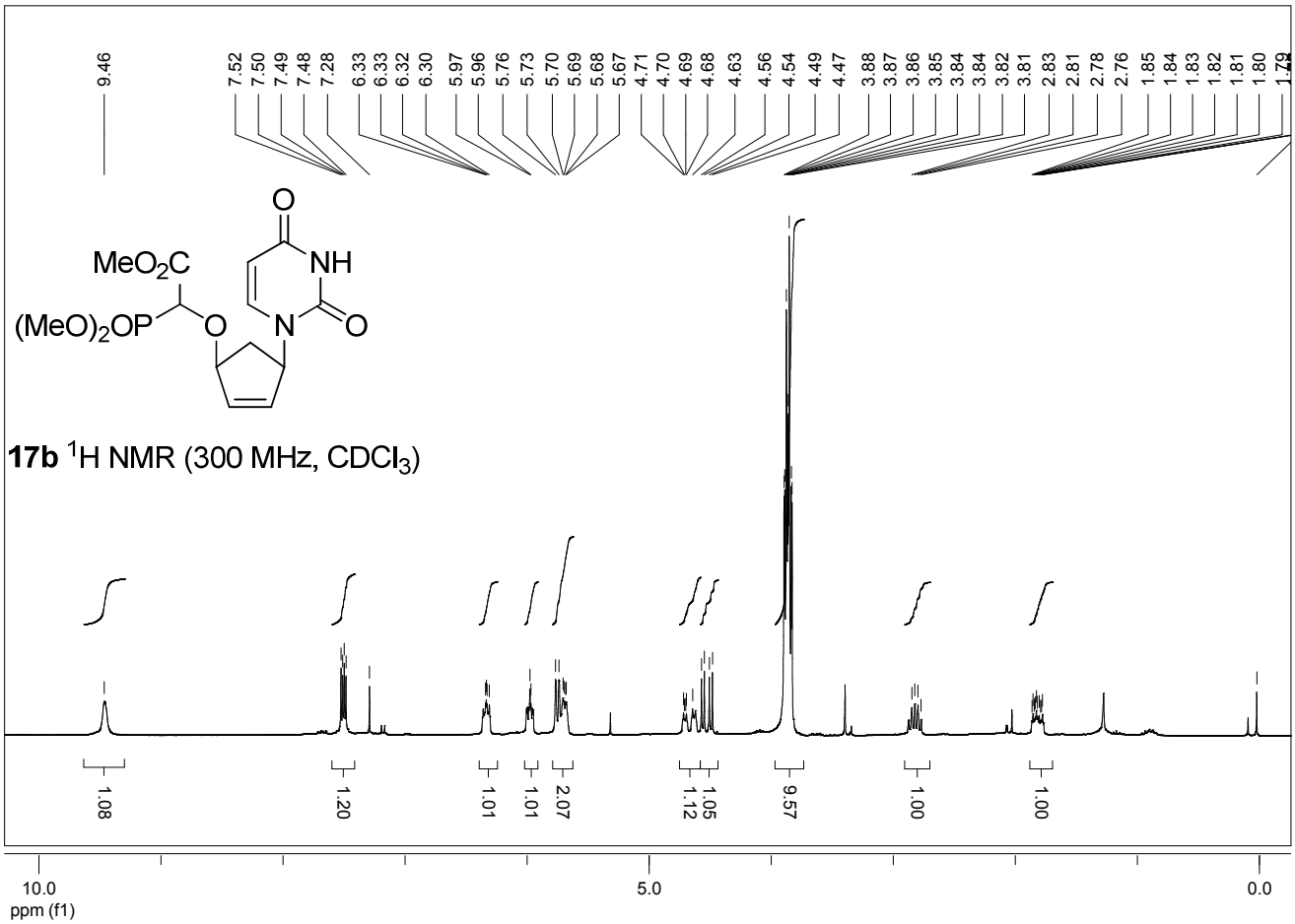

170.703
170.682
167.881
167.866
167.799
167.786
135.481
134.859
134.729
134.080
83.954
83.941
83.872
83.864
76.389
74.933
74.439
73.880
73.388
63.812
63.766
63.715
61.930
61.881
36.909
36.784
21.085
21.064
16.427
16.389
14.143
CO2Et
(EtO)2OP
O
OAc
16 13C NMR (150 MHz, CDCl3)
150
100
50
ppm (t1)



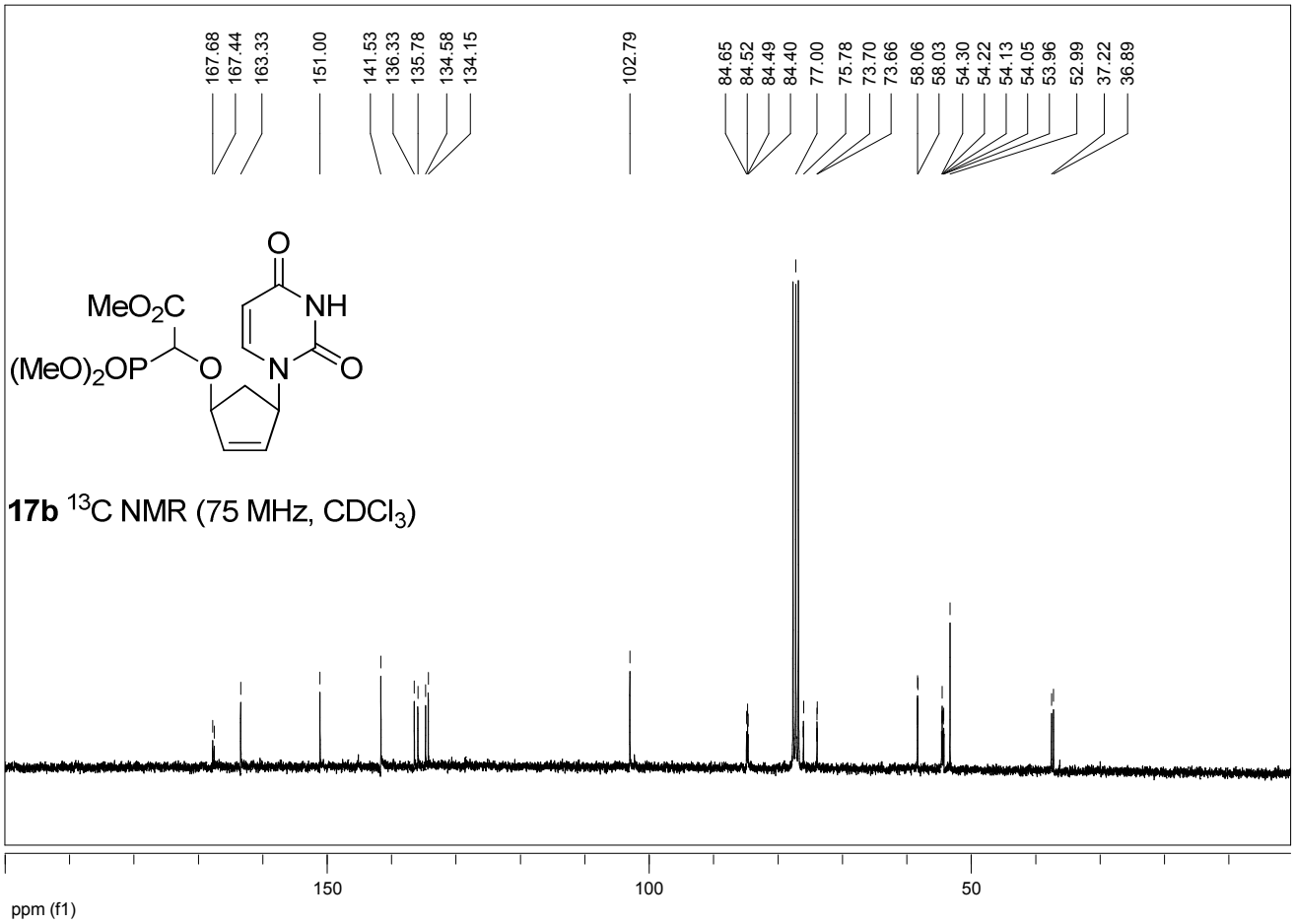
17a ^{1}H NMR (300 MHz, $CDCl_3$)



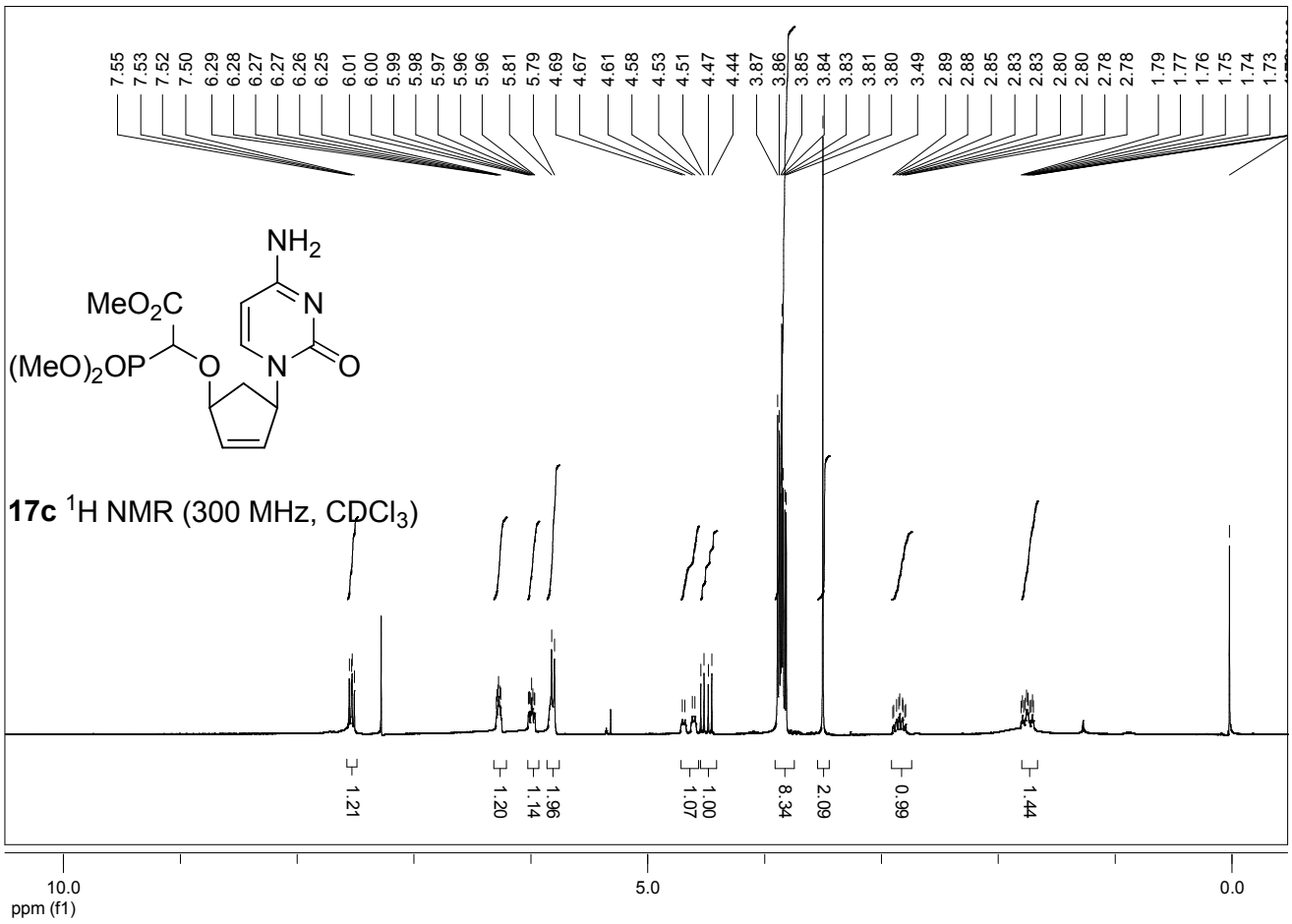
17a ^{13}C NMR (75 MHz, $CDCl_3$)



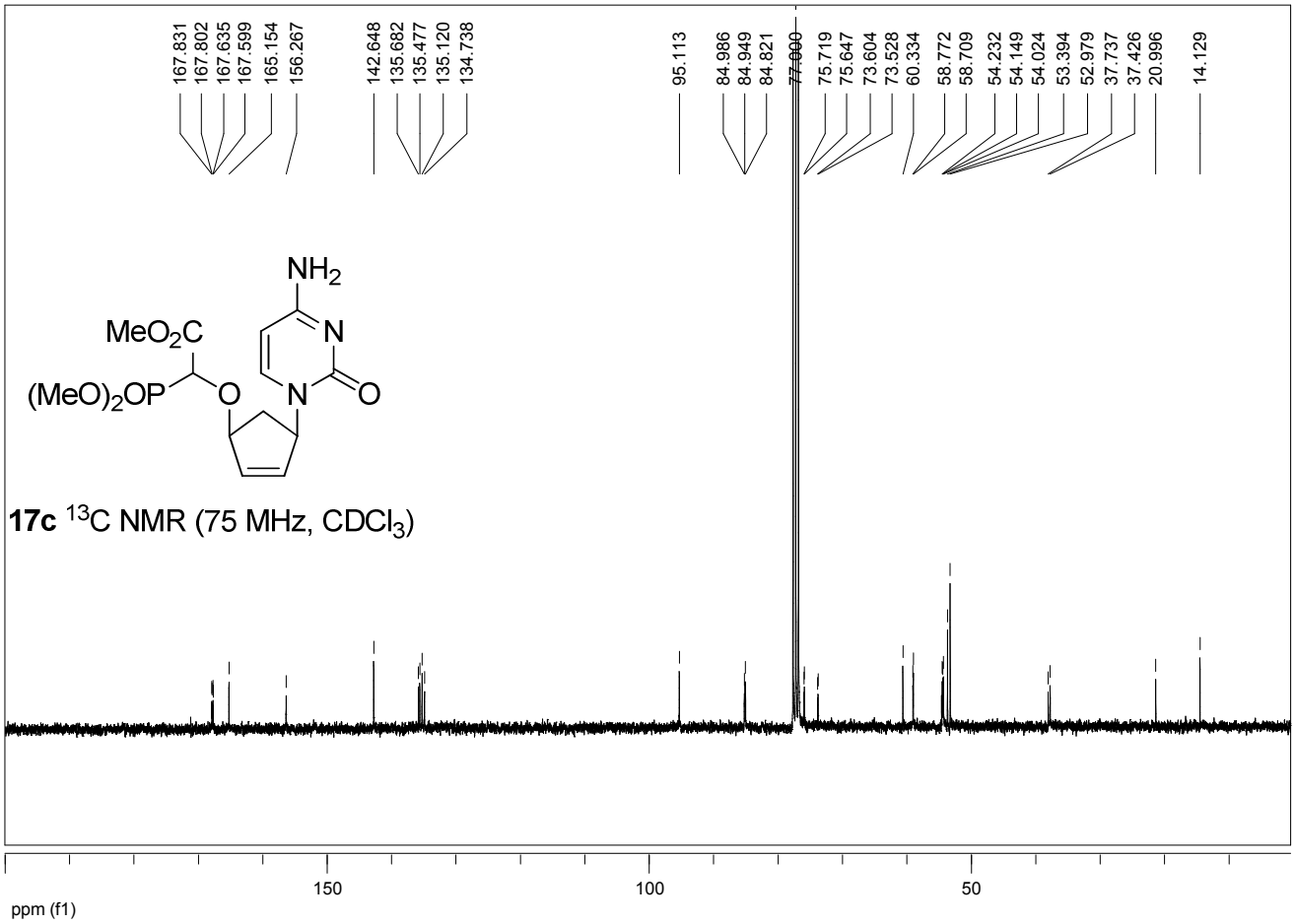
17b ^{1}H NMR (300 MHz, $CDCl_3$)



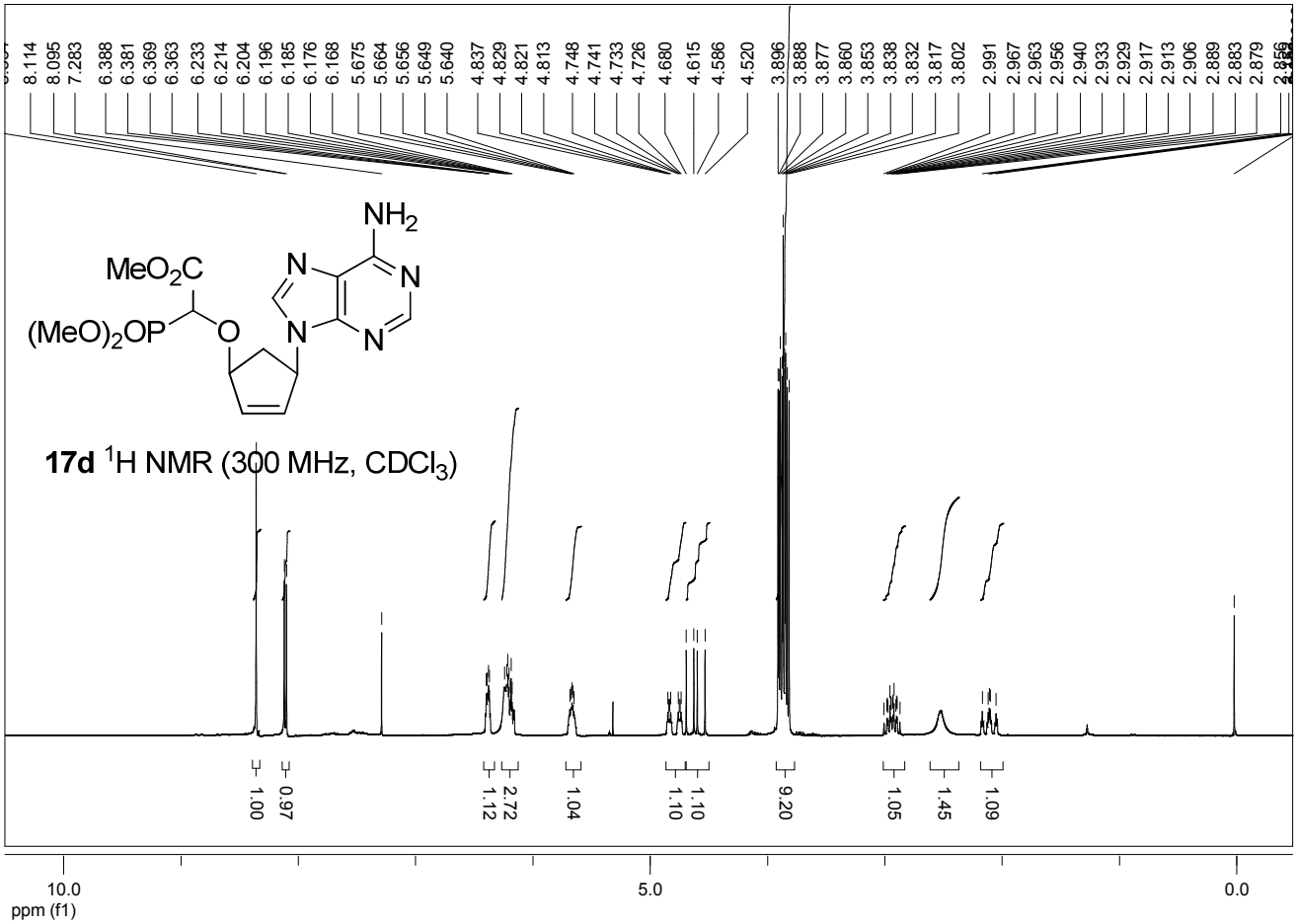
17b ^{13}C NMR (75 MHz, $CDCl_3$)

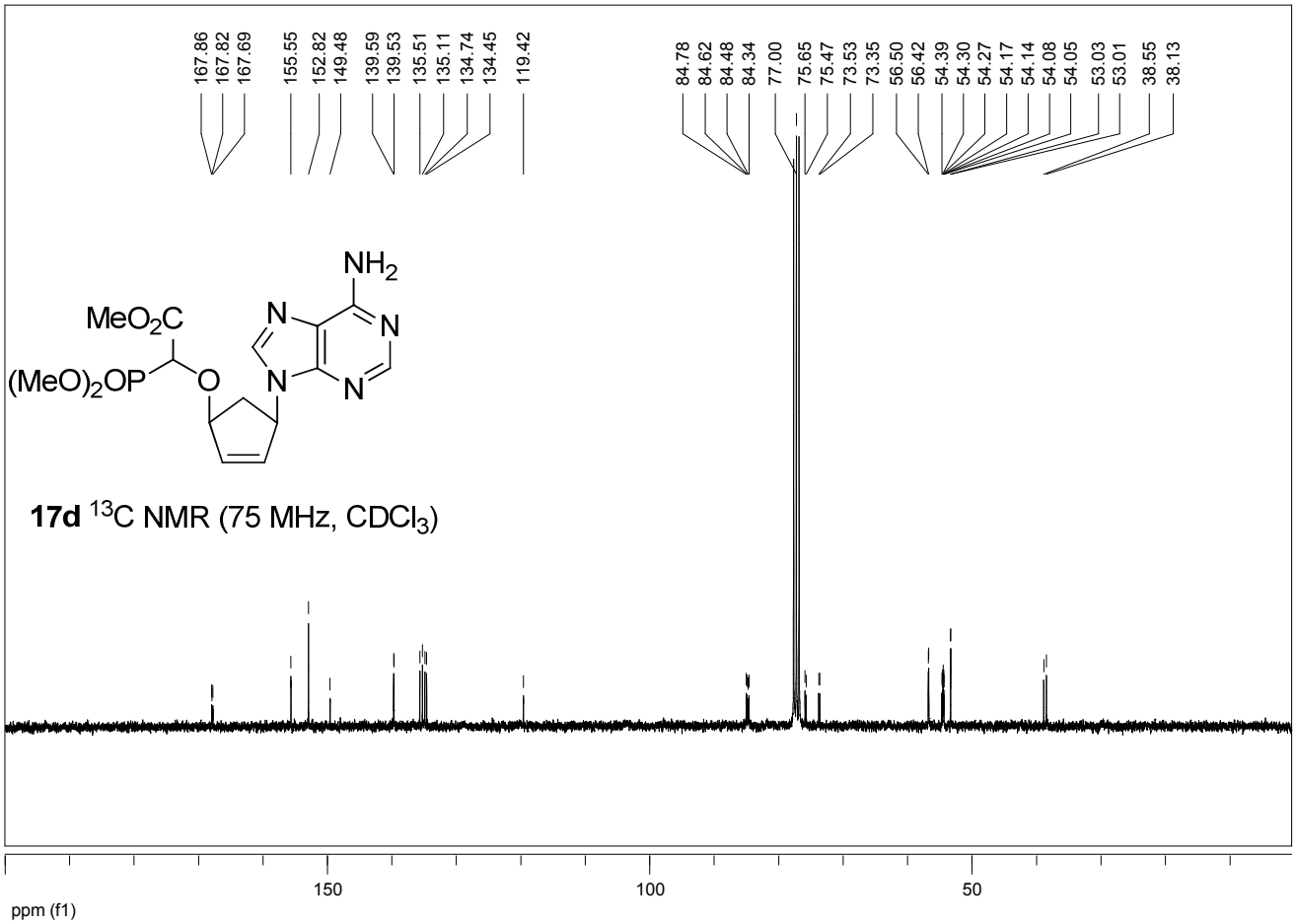


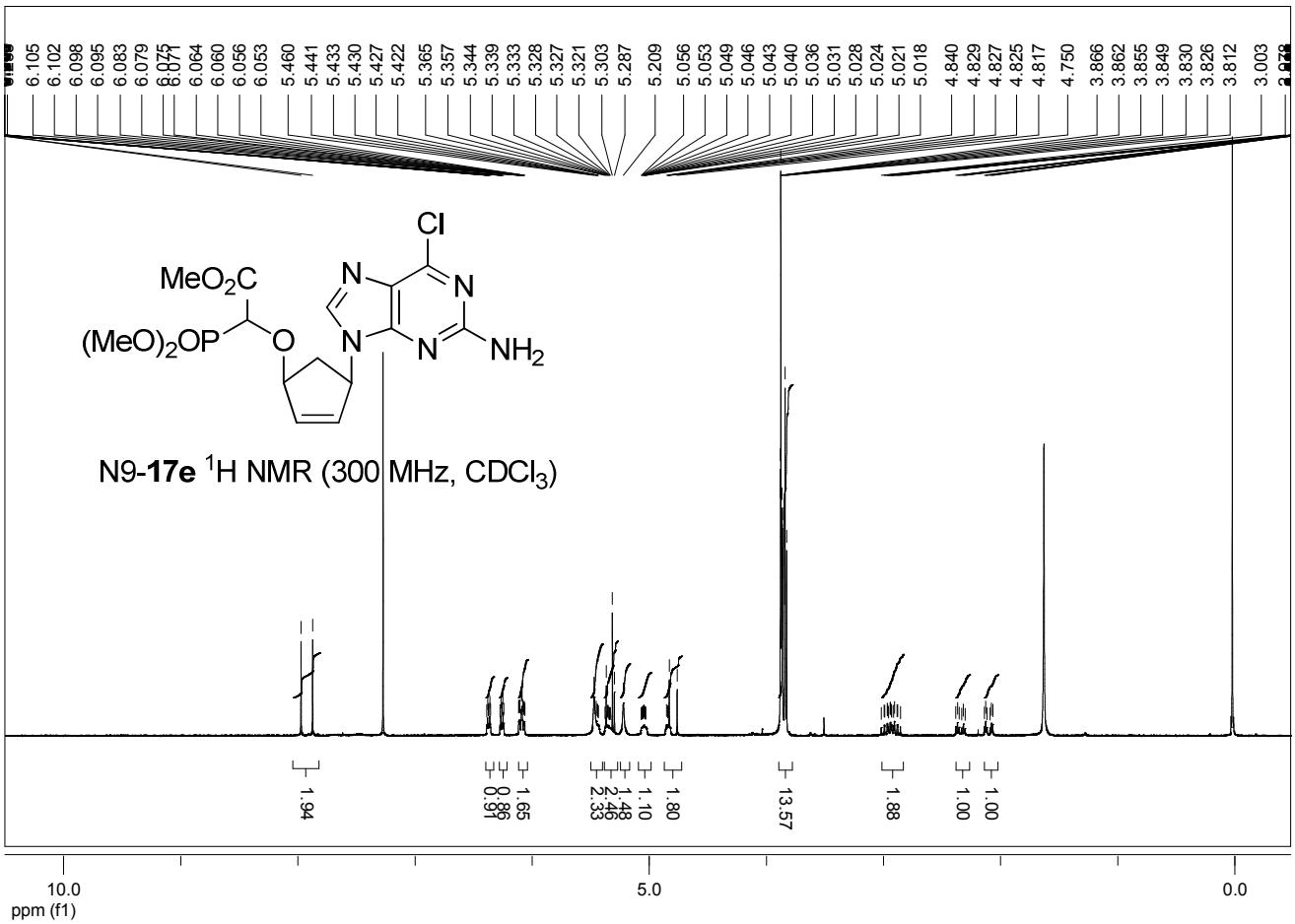
17c ^{1}H NMR (300 MHz, $CDCl_3$)

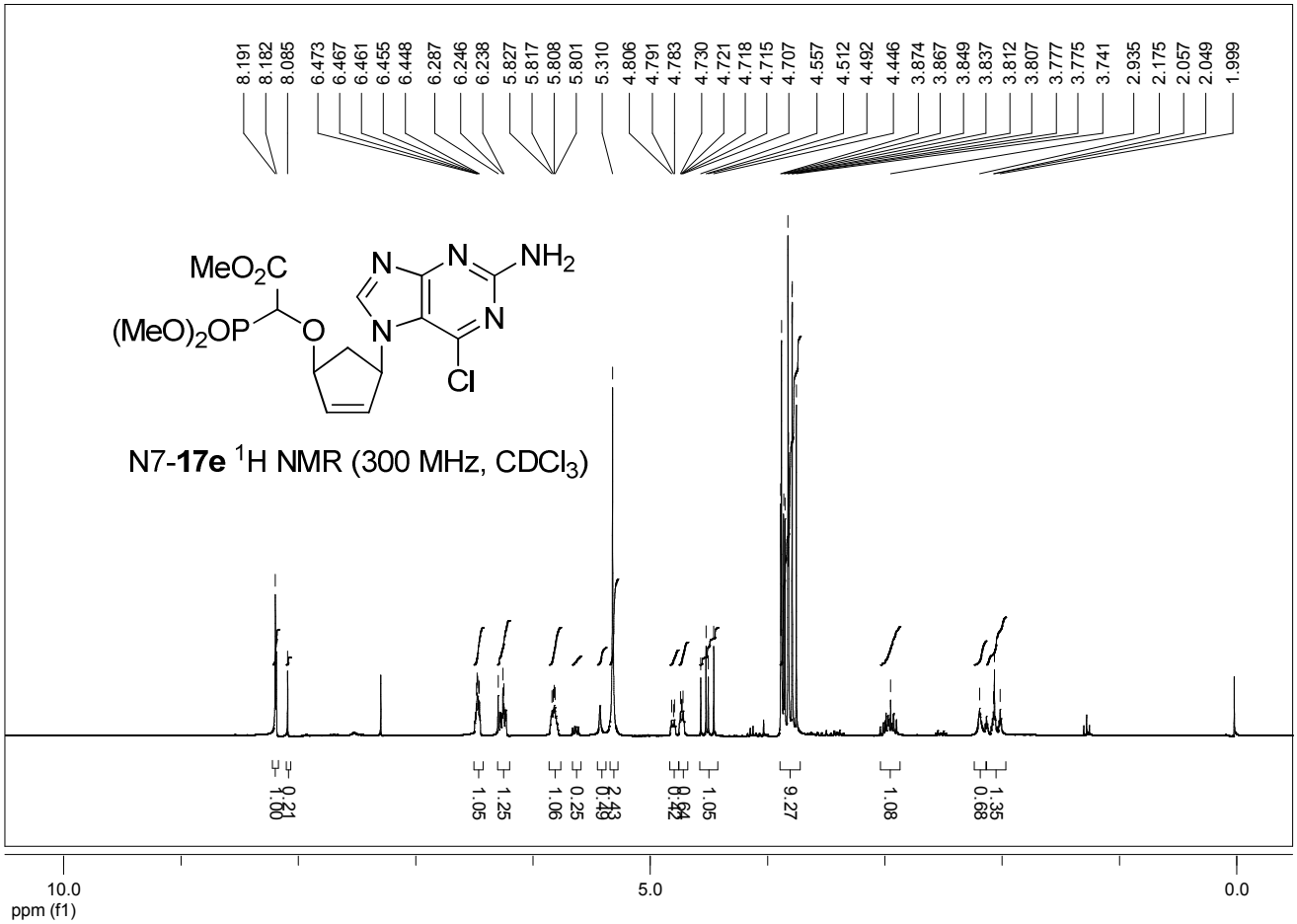


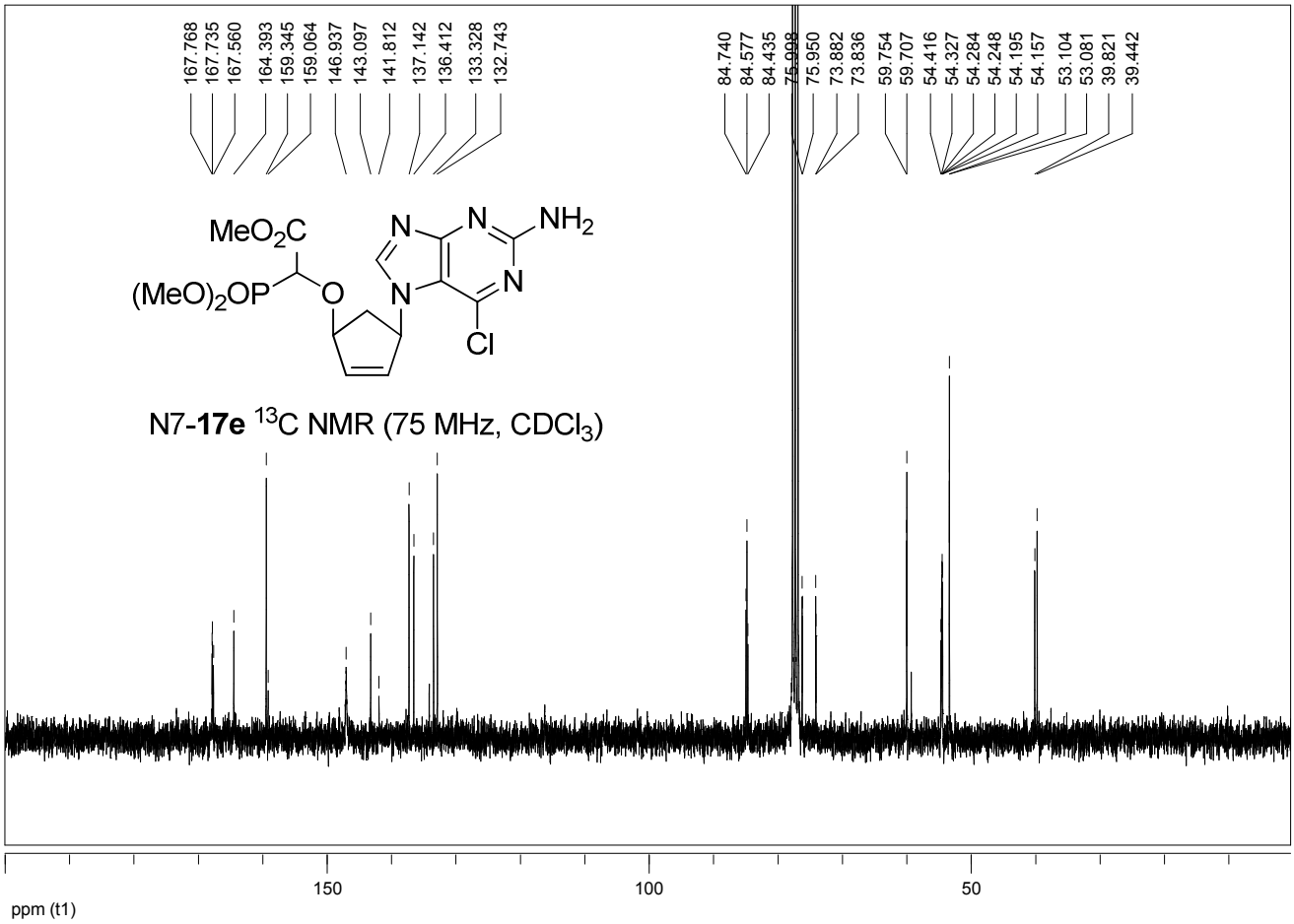
17c ^{13}C NMR (75 MHz, $CDCl_3$)

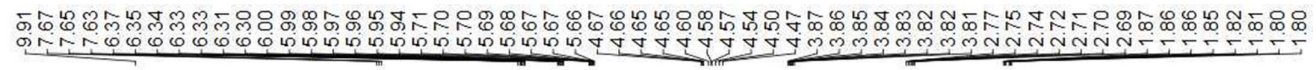

8.114
8.095
7.283
6.388
6.381
6.369
6.363
6.233
6.214
6.204
6.196
6.185
6.176
6.168
5.675
5.664
5.656
5.649
5.640
4.837
4.829
4.821
4.813
4.748
4.741
4.733
4.726
4.680
4.615
4.586
4.520
3.896
3.888
3.877
3.860
3.853
3.838
3.832
3.817
3.802
2.991
2.967
2.963
2.956
2.940
2.933
2.929
2.917
2.913
2.906
2.889
2.883
2.879
NH2
MeO2C
(MeO)2OP
O
N
N
N
N
17d 1H NMR (300 MHz, CDCl3)
1.00
0.97
1.12
2.72
1.04
1.10
1.10
9.20
1.05
1.45
1.09
10.0
5.0
0.0
ppm (f1)

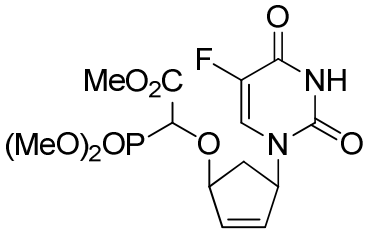

167.86
167.82
167.69
155.55
152.82
149.48
139.59
139.53
135.51
135.11
134.74
134.45
119.42
84.78
84.62
84.48
84.34
77.00
75.65
75.47
73.53
73.35
56.50
56.42
54.39
54.30
54.27
54.17
54.14
54.08
54.05
53.03
53.01
38.55
38.13
NH2
MeO2C
(MeO)2OP
O
N
N
N
N
17d 13C NMR (75 MHz, CDCl3)
150
100
50
ppm (f1)


6.105
6.102
6.098
6.095
6.083
6.079
6.064
6.060
6.056
6.053
5.460
5.441
5.433
5.430
5.427
5.422
5.365
5.357
5.344
5.339
5.333
5.328
5.327
5.321
5.303
5.287
5.209
5.056
5.053
5.049
5.046
5.043
5.040
5.036
5.031
5.028
5.024
5.021
5.018
4.840
4.829
4.827
4.825
4.817
4.750
3.866
3.862
3.855
3.849
3.830
3.826
3.812
3.003
Cl
MeO2C
(MeO)2OP
O
N
N
N
N
NH2
N9-17e 1H NMR (300 MHz, CDCl3)
1.94
0.91
0.86
1.65
2.33
1.48
1.10
1.80
13.57
1.88
1.00
1.00
10.0
5.0
0.0
ppm (f1)

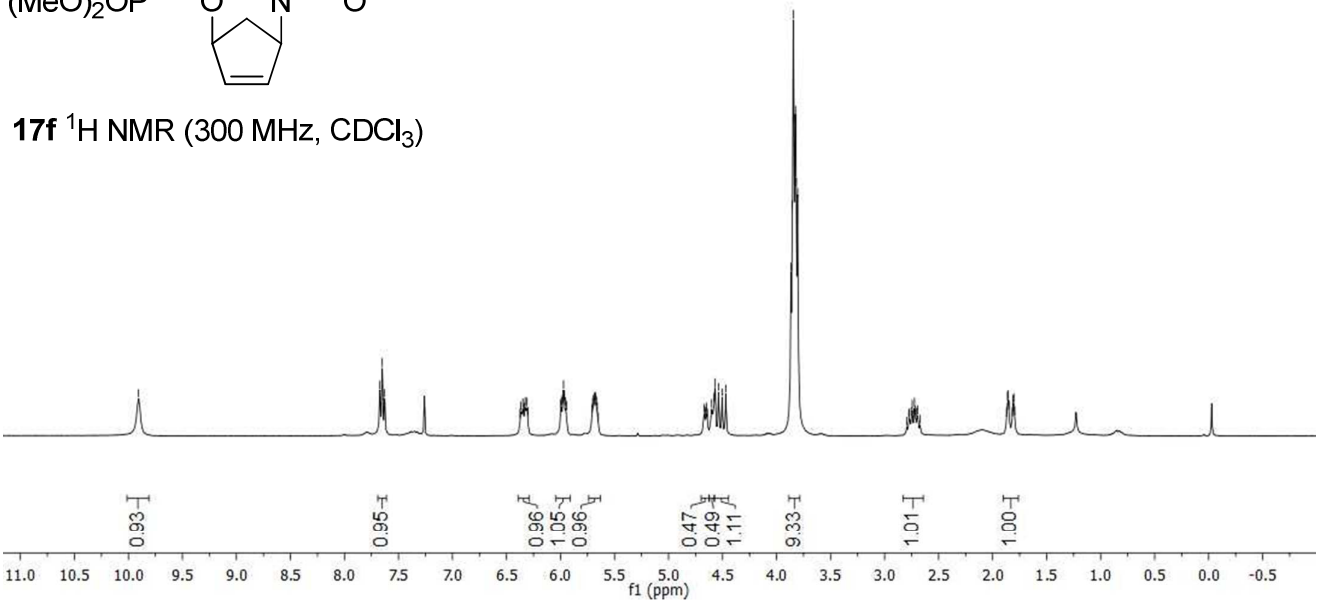

8.191
8.182
8.085
6.473
6.467
6.461
6.455
6.448
6.287
6.246
6.238
5.827
5.817
5.808
5.801
5.310
4.806
4.791
4.783
4.730
4.721
4.718
4.715
4.707
4.557
4.512
4.492
4.446
3.874
3.867
3.849
3.837
3.812
3.807
3.777
3.775
3.741
2.935
2.175
2.057
2.049
1.999
MeO2C
(MeO)2OP
O
N
N
NH2
N
N
Cl
N7-17e 1H NMR (300 MHz, CDCl3)
1.00
0.21
1.05
1.25
1.06
0.25
2.43
0.42
0.64
1.05
9.27
1.08
0.88
1.35
10.0
5.0
0.0
ppm (f1)


167.768
167.735
167.560
164.393
159.345
159.064
146.937
143.097
141.812
137.142
136.412
133.328
132.743
84.740
84.577
84.435
75.950
73.882
73.836
59.754
59.707
54.416
54.327
54.284
54.248
54.195
54.157
53.104
53.081
39.821
39.442
MeO2C
(MeO)2OP
O
N
N
NH2
N
N
Cl
N7-17e 13C NMR (75 MHz, CDCl3)
150
100
50
ppm (t1)

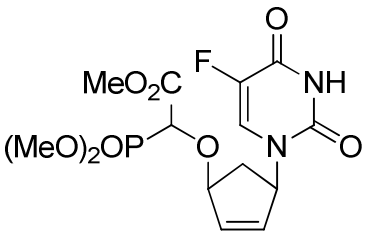




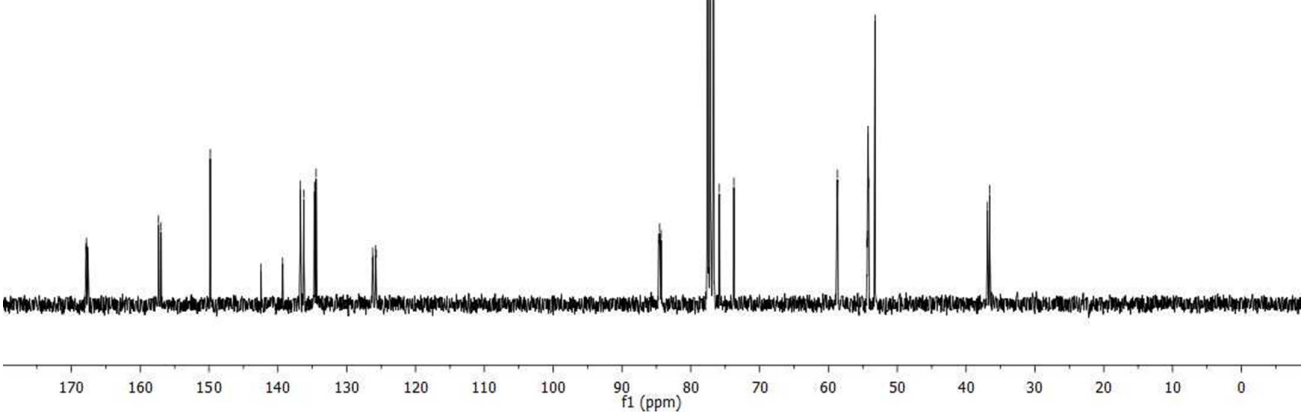
17f ^{1}H NMR (300 MHz, $CDCl_3$)

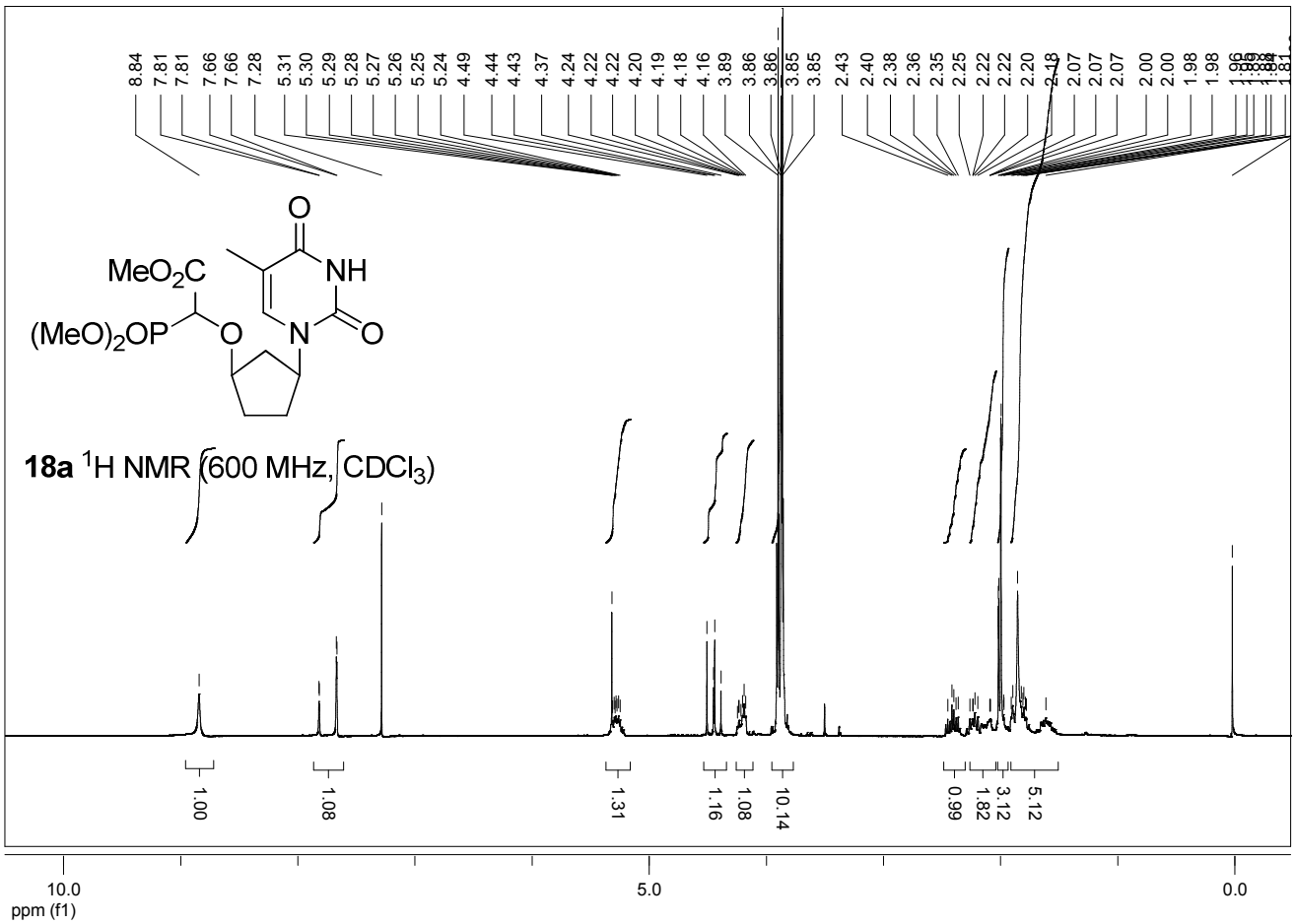


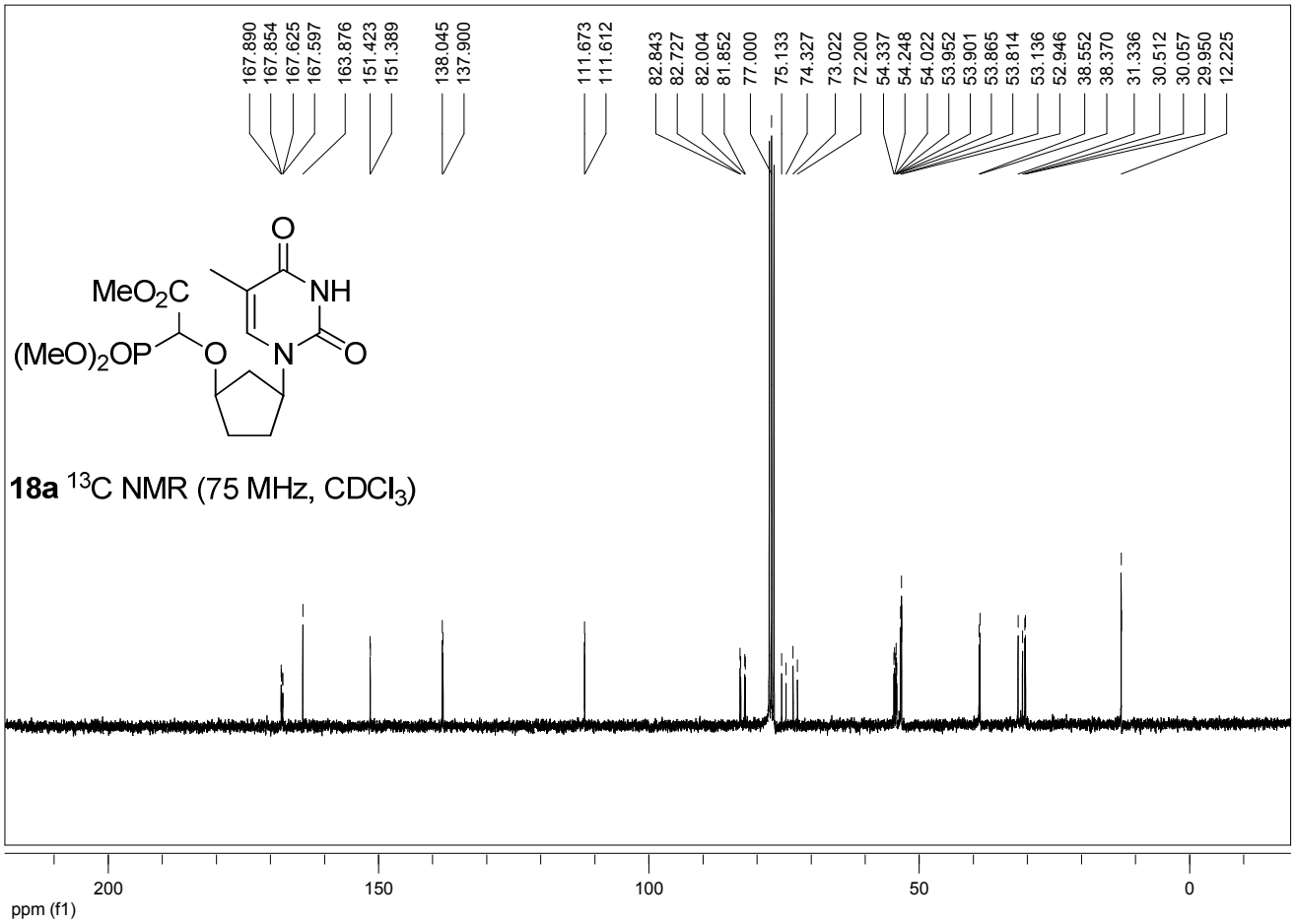


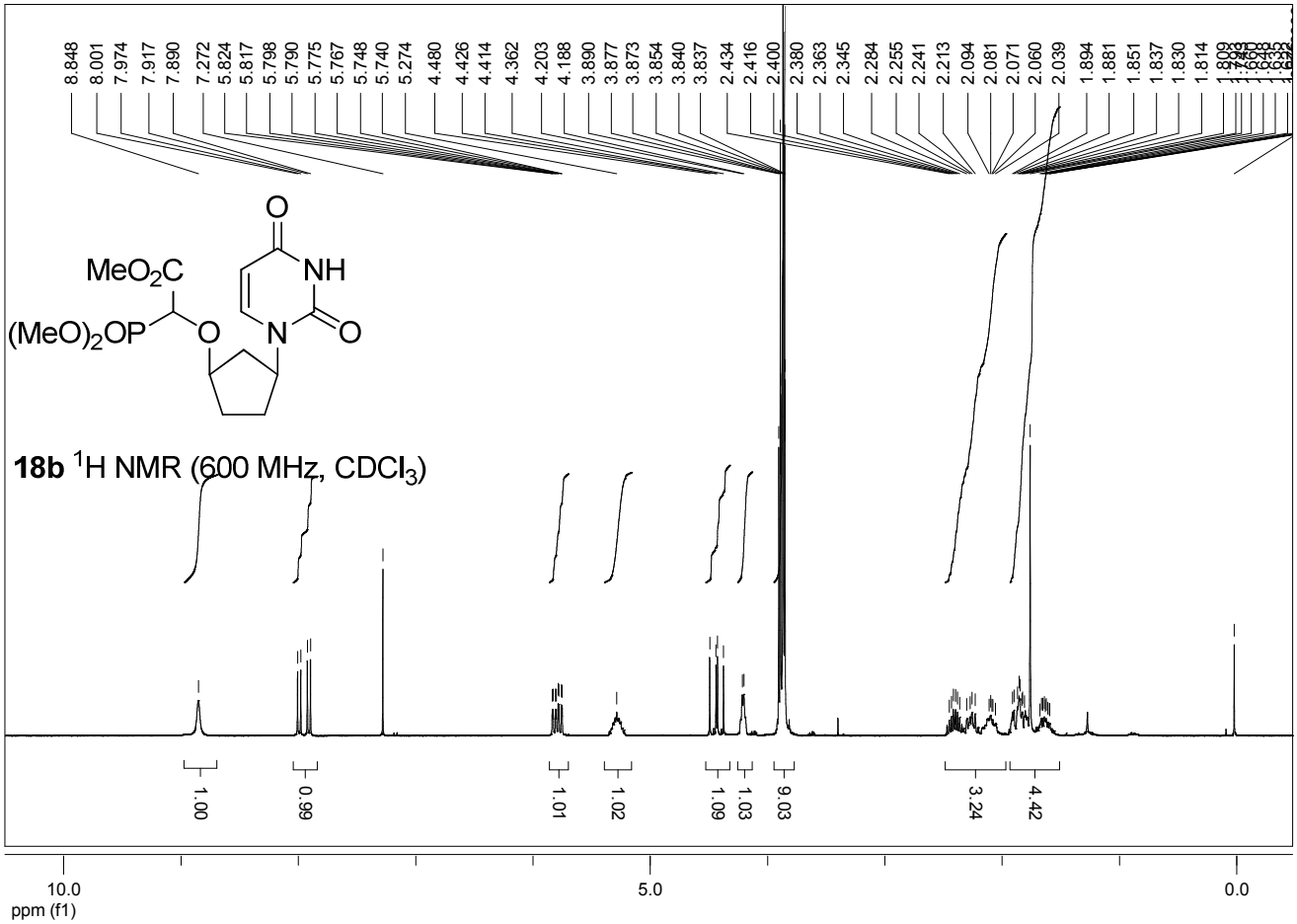


17f ^{13}C NMR (75 MHz, $CDCl_3$)

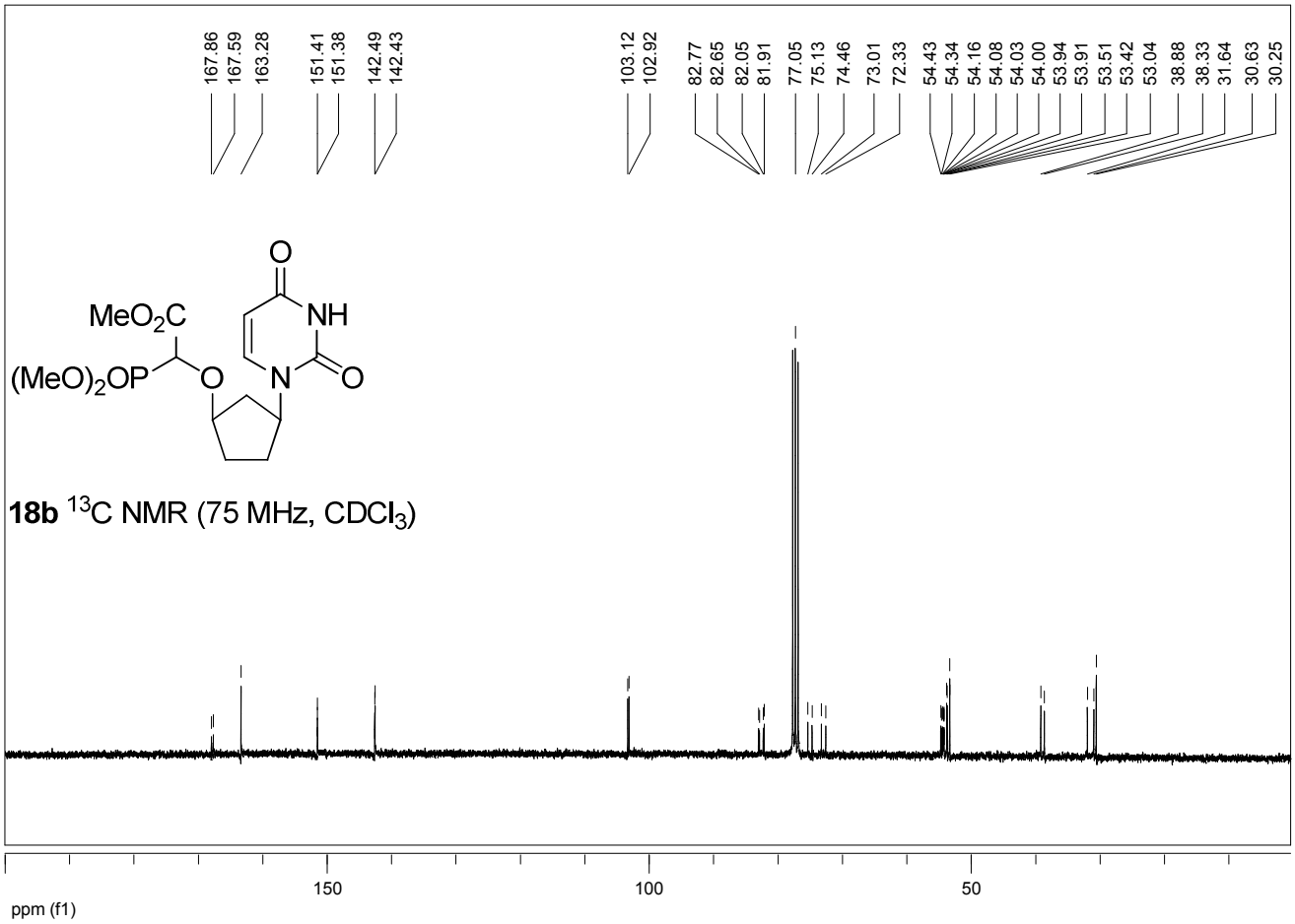



8.84 7.81 7.81 7.66 7.66 7.28 5.31 5.30 5.29 5.28 5.27 5.26 5.25 5.24 4.49 4.44 4.43 4.37 4.24 4.22 4.22 4.20 4.19 4.18 4.16 3.89 3.86 3.86 3.85 3.85 2.43 2.40 2.38 2.36 2.35 2.25 2.22 2.22 2.20 2.18 2.07 2.07 2.07 2.00 2.00 1.98 1.98
MeO2C
(MeO)2OP
O
NH
N
O
18a 1H NMR (600 MHz, CDCl3)
1.00 1.08 1.31 1.19 1.08 10.14 0.99 1.28 3.12 5.12
10.0
5.0
0.0
ppm (f1)

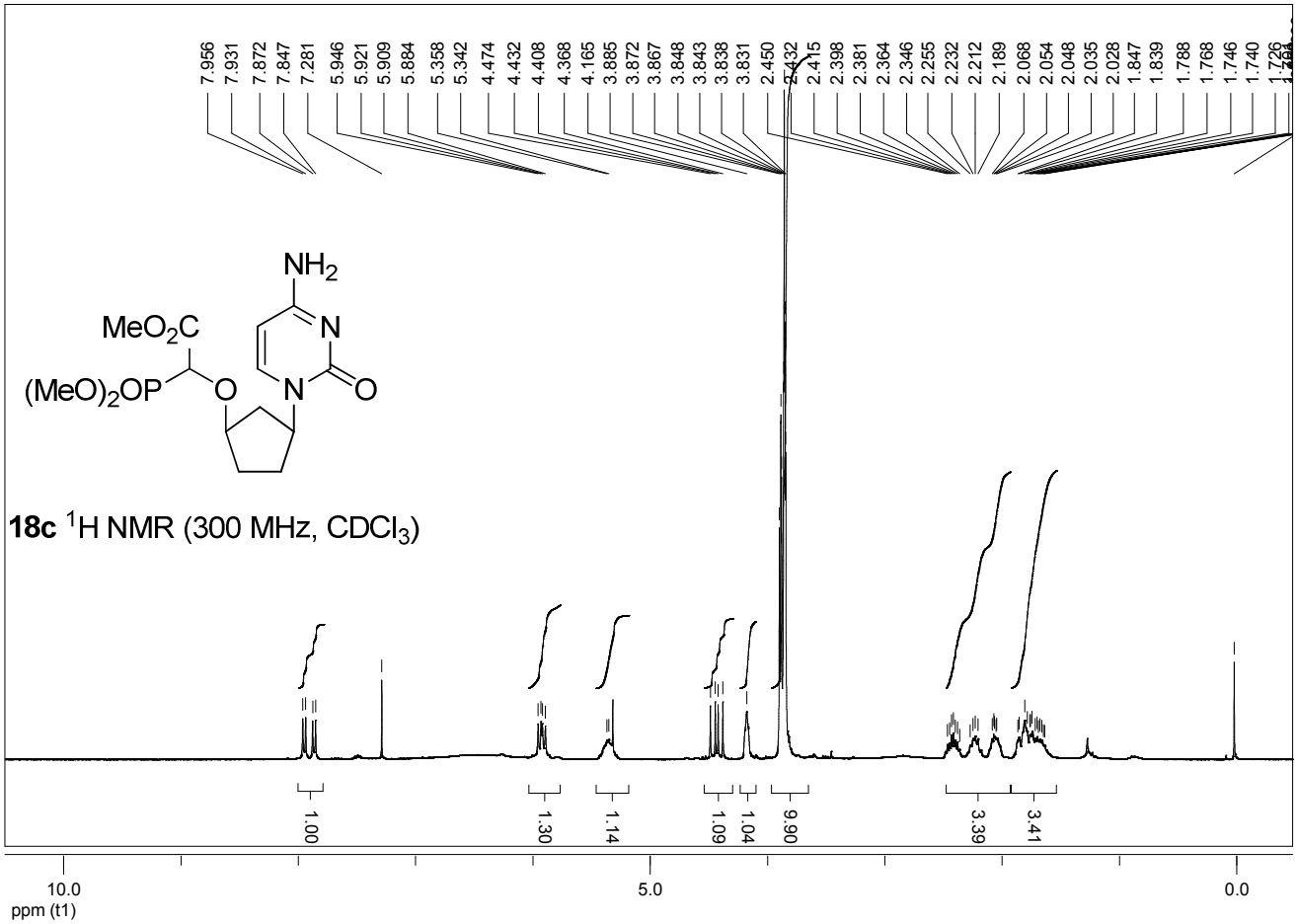

167.890 167.854 167.625 167.597 163.876 151.423 151.389 138.045 137.900 111.673 111.612 82.843 82.727 82.004 81.852 77.000 75.133 74.327 73.022 72.200 54.337 54.248 54.022 53.952 53.901 53.865 53.814 53.136 52.946 38.552 38.370 31.336 30.512 30.057 29.950 12.225
MeO2C
(MeO)2OP
O
NH
N
O
18a 13C NMR (75 MHz, CDCl3)
200
150
100
50
0
ppm (f1)



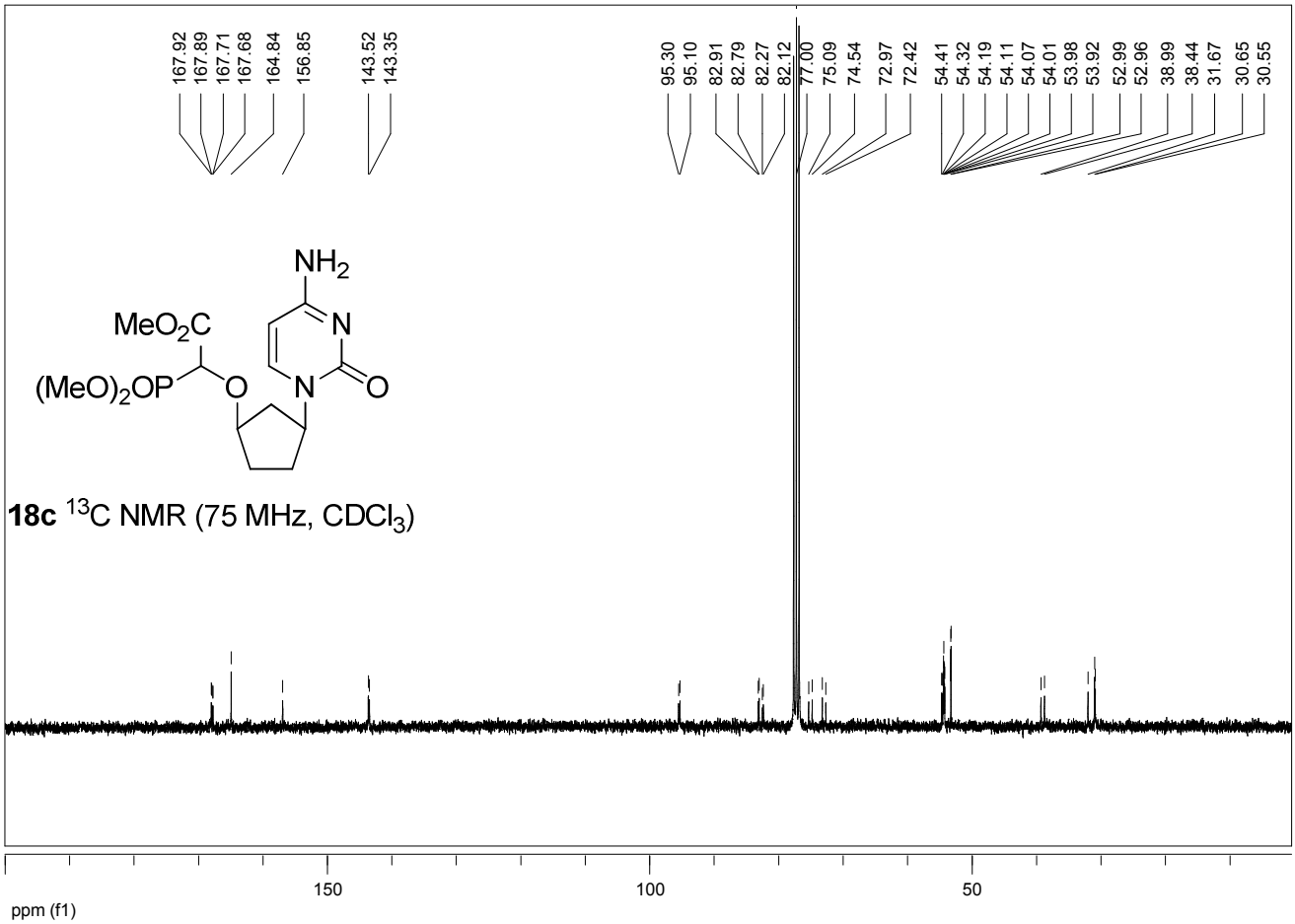
18b ^{1}H NMR (600 MHz, $CDCl_3$)



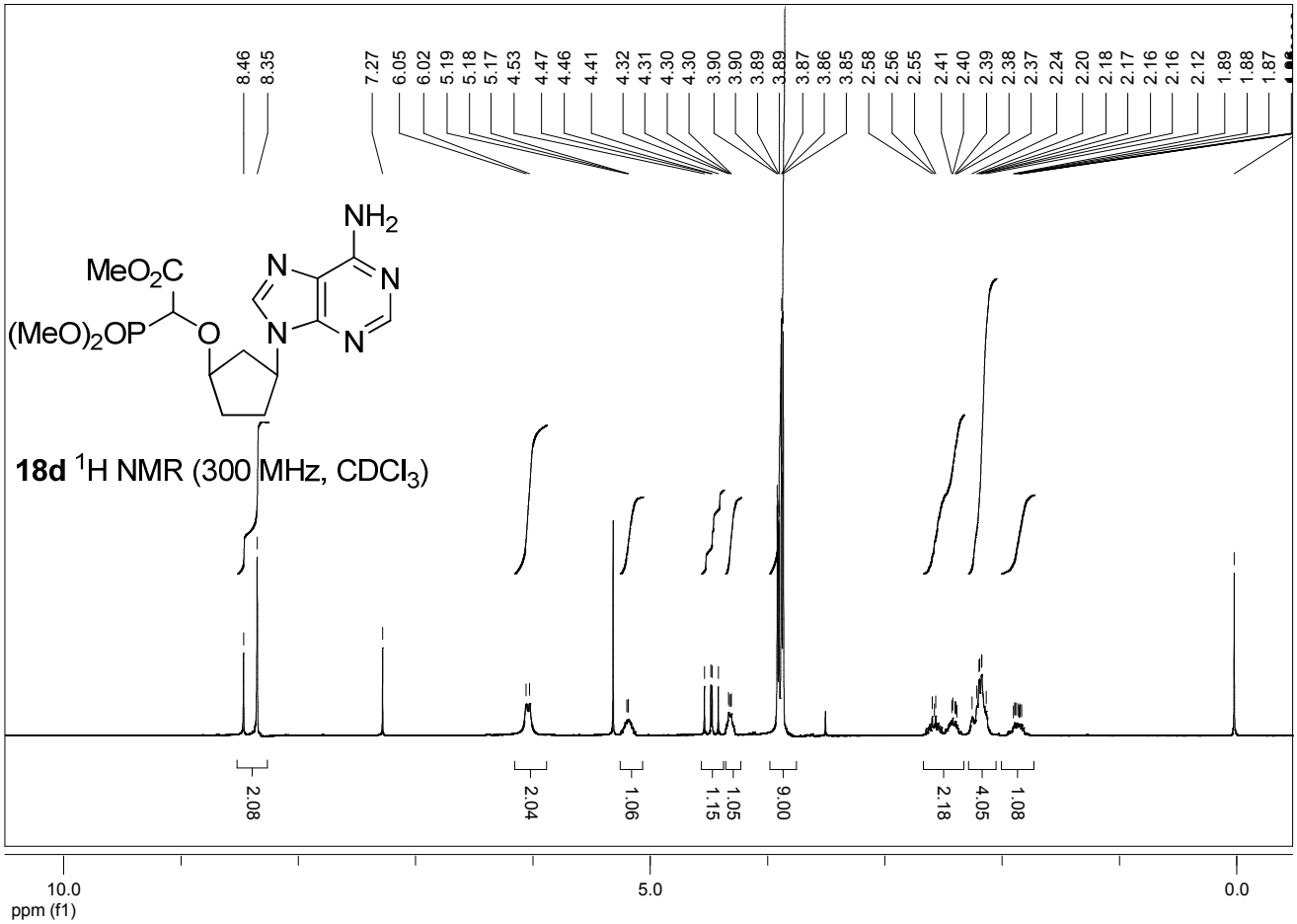
18b ^{13}C NMR (75 MHz, $CDCl_3$)

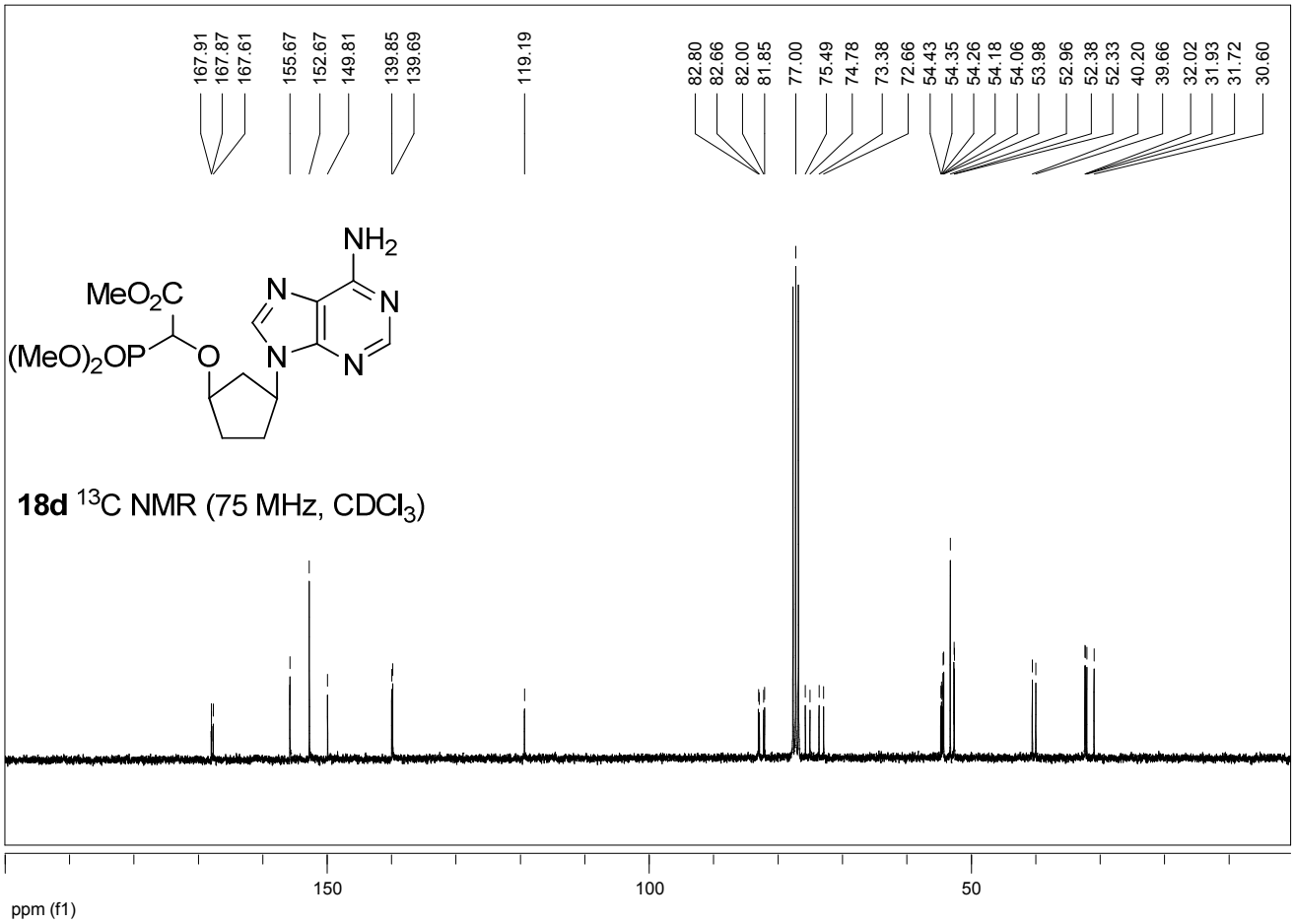


18c ^{1}H NMR (300 MHz, $CDCl_3$)

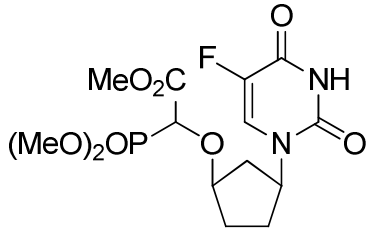


18c ^{13}C NMR (75 MHz, $CDCl_3$)

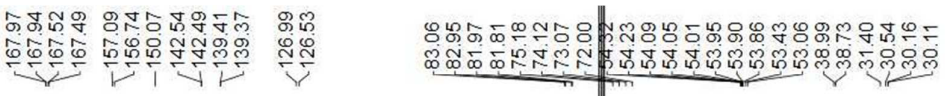

8.46
8.35
7.27
6.05
6.02
5.19
5.18
5.17
4.53
4.47
4.46
4.41
4.32
4.31
4.30
4.30
3.90
3.90
3.89
3.89
3.87
3.86
3.85
2.58
2.56
2.55
2.41
2.40
2.39
2.38
2.37
2.24
2.20
2.18
2.17
2.16
2.16
2.12
1.89
1.88
1.87
NH2
MeO2C
(MeO)2OP
O
N
N
N
N
18d 1H NMR (300 MHz, CDCl3)
2.08
2.04
1.06
1.15
1.05
9.00
2.18
4.05
1.08
10.0
5.0
0.0
ppm (f1)

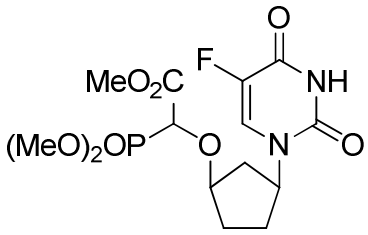

167.91
167.87
167.61
155.67
152.67
149.81
139.85
139.69
119.19
82.80
82.66
82.00
81.85
77.00
75.49
74.78
73.38
72.66
54.43
54.35
54.26
54.18
54.06
53.98
52.96
52.38
52.33
40.20
39.66
32.02
31.93
31.72
30.60
NH2
MeO2C
(MeO)2OP
O
N
N
N
N
18d 13C NMR (75 MHz, CDCl3)
150
100
50
ppm (f1)



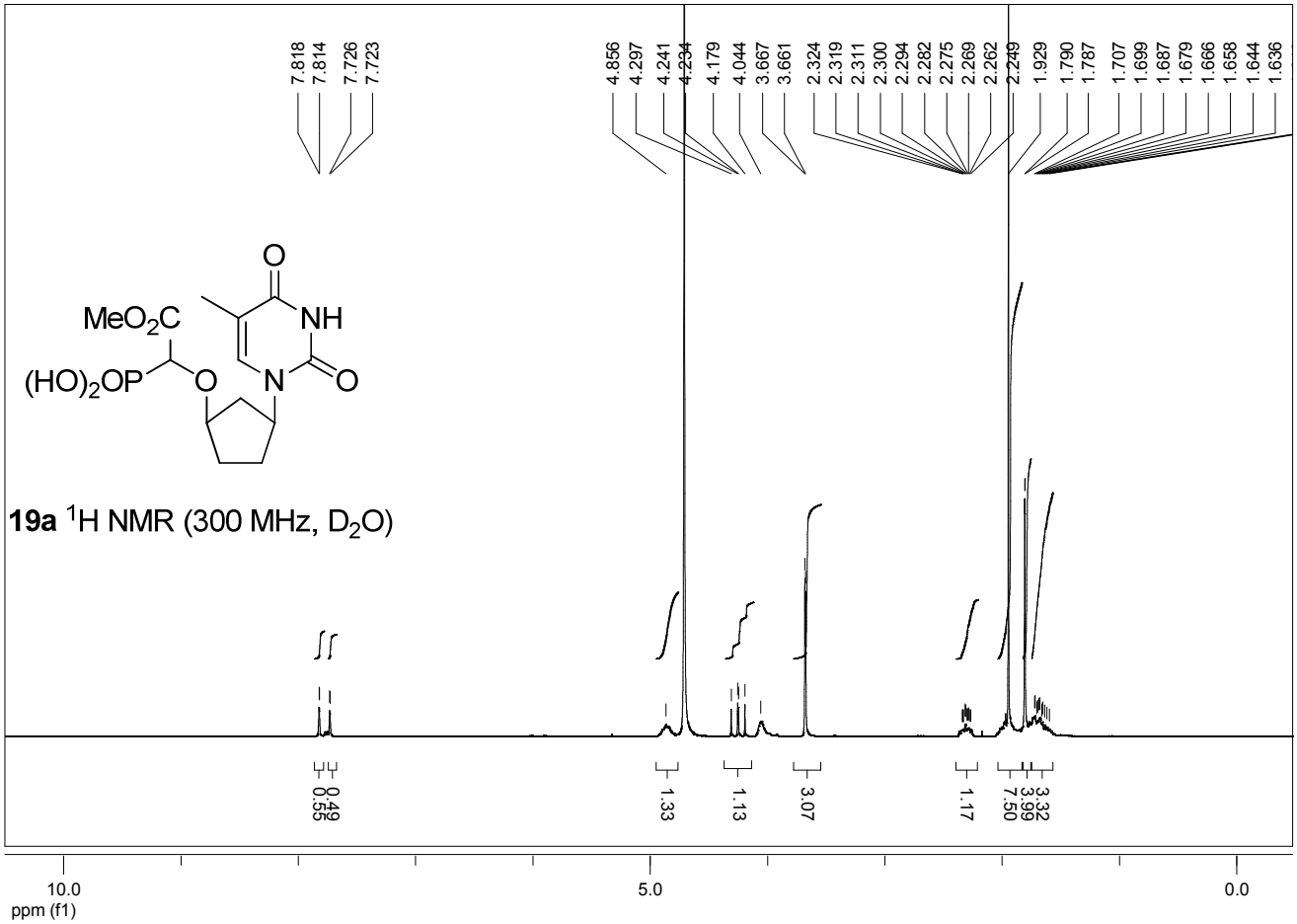


18f ^{1}H NMR (300 MHz, $CDCl_3$)

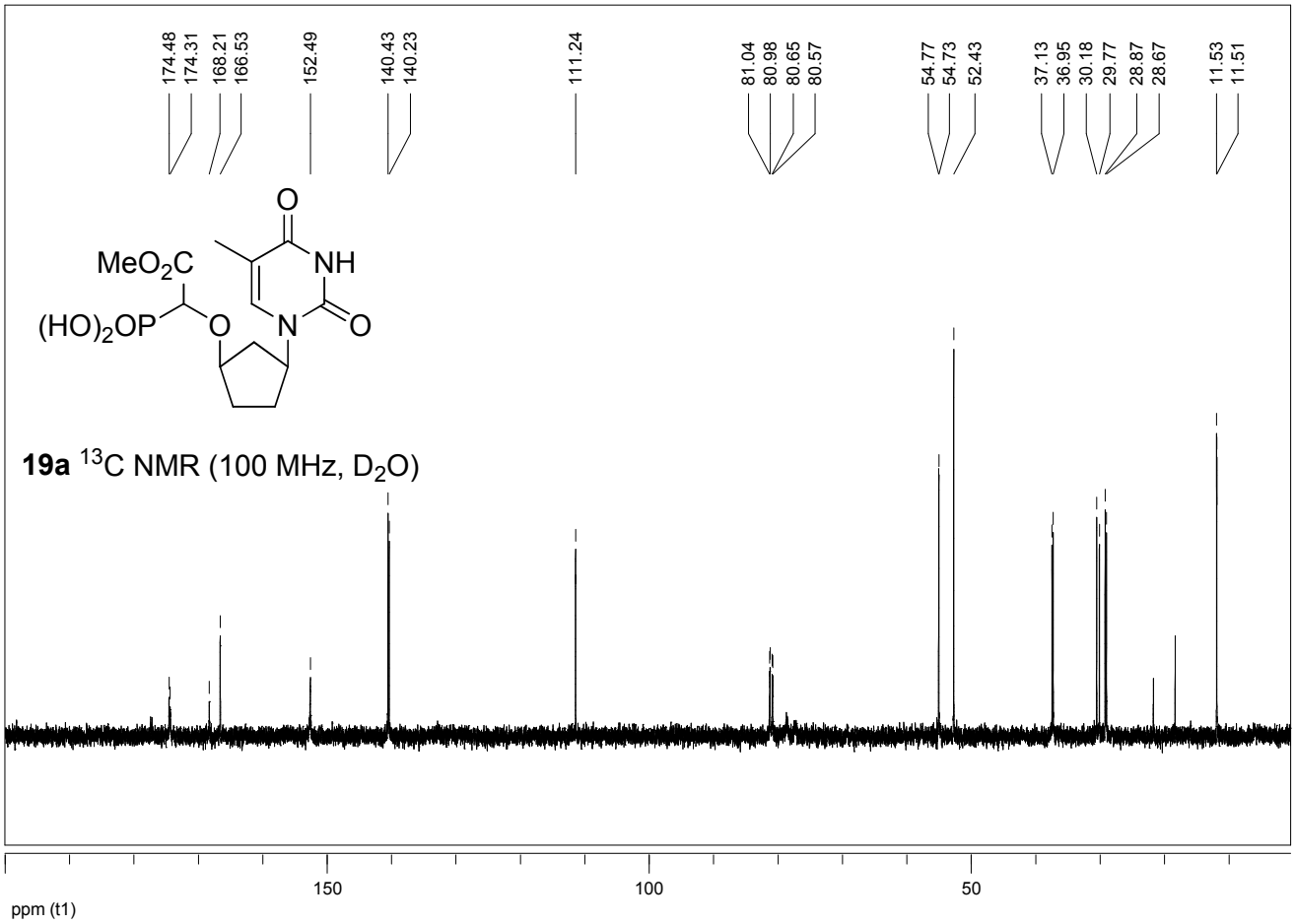




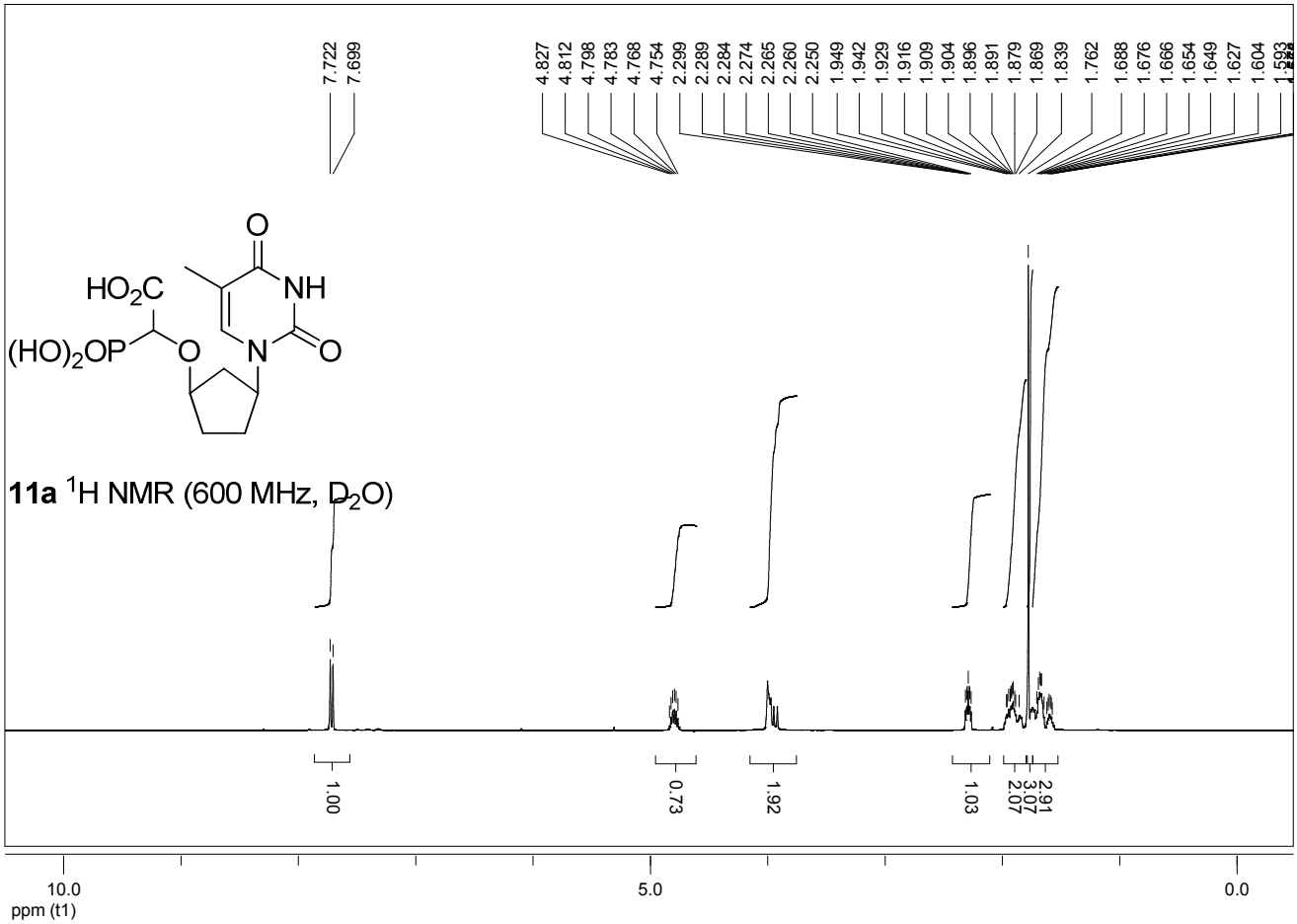
18f ^{13}C NMR (75 MHz, $CDCl_3$)

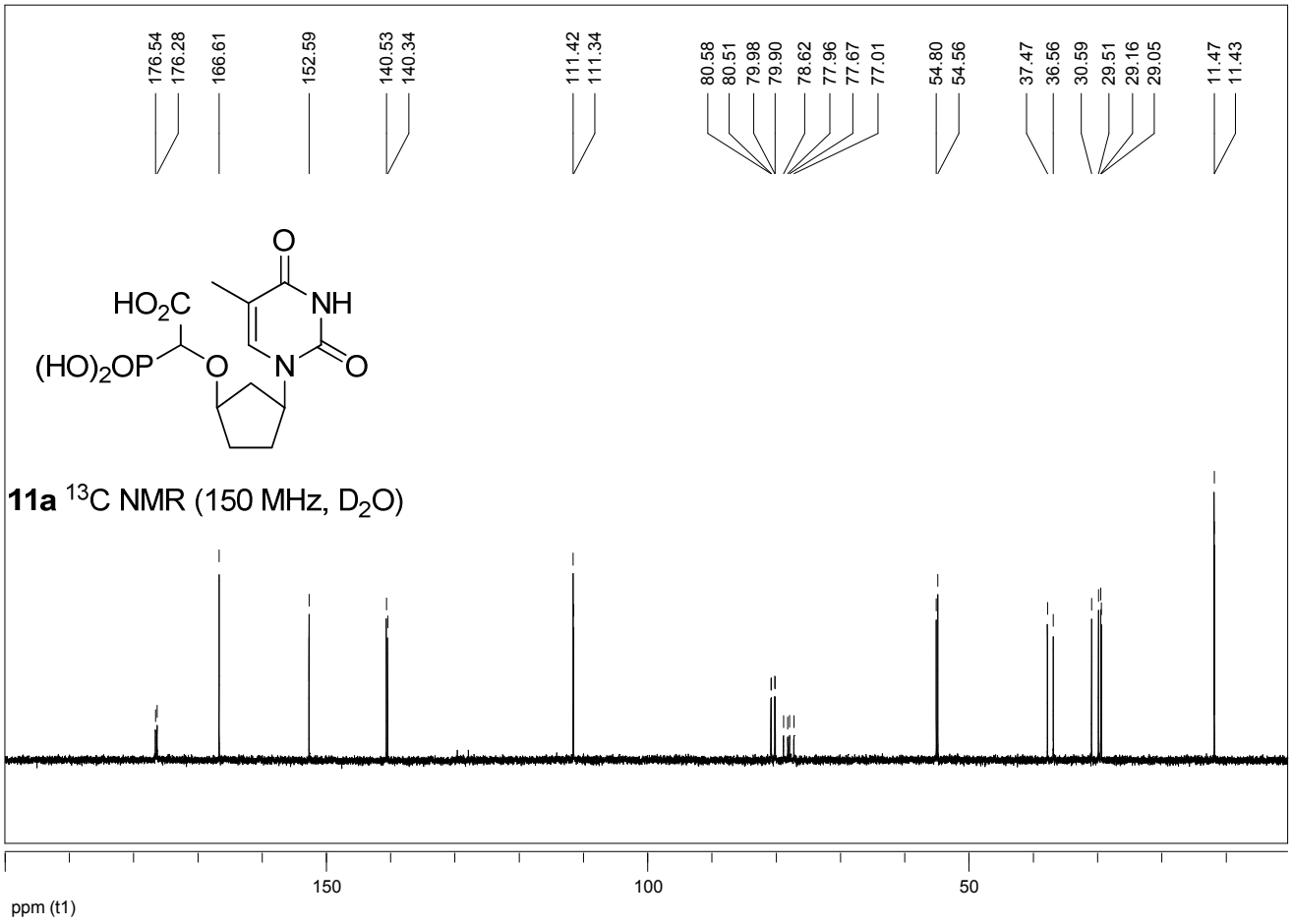


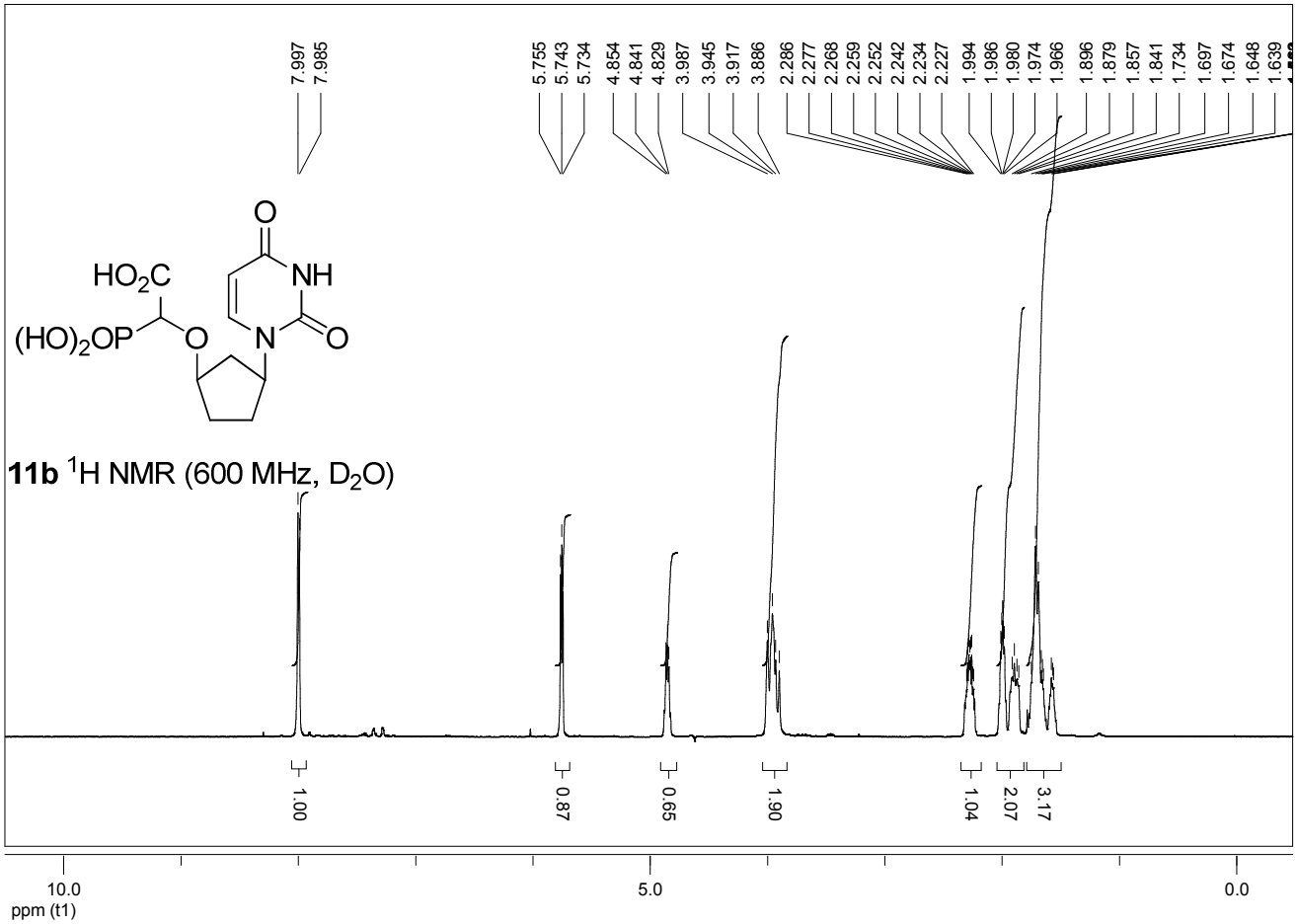
19a ^{1}H NMR (300 MHz, D_2O)

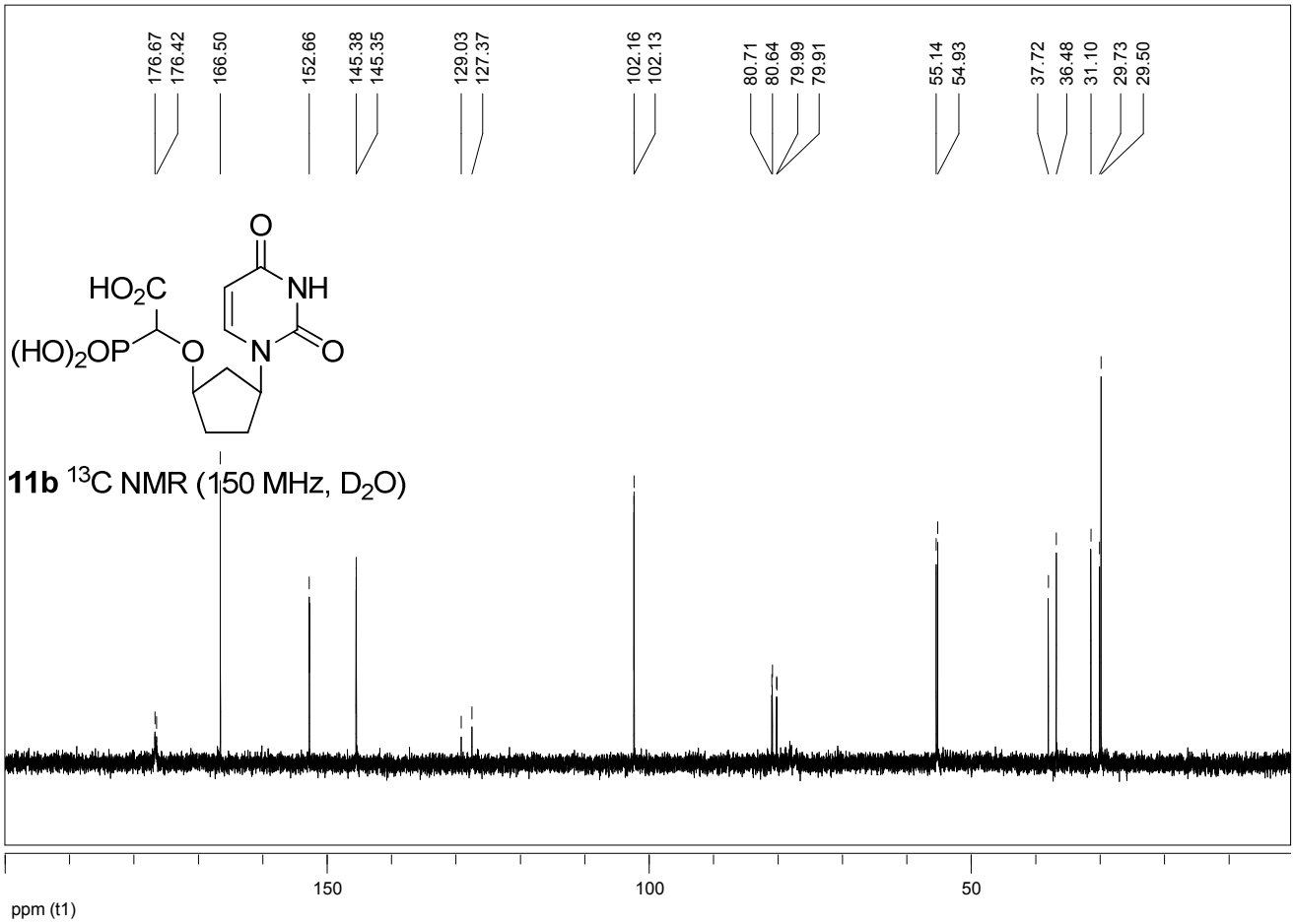


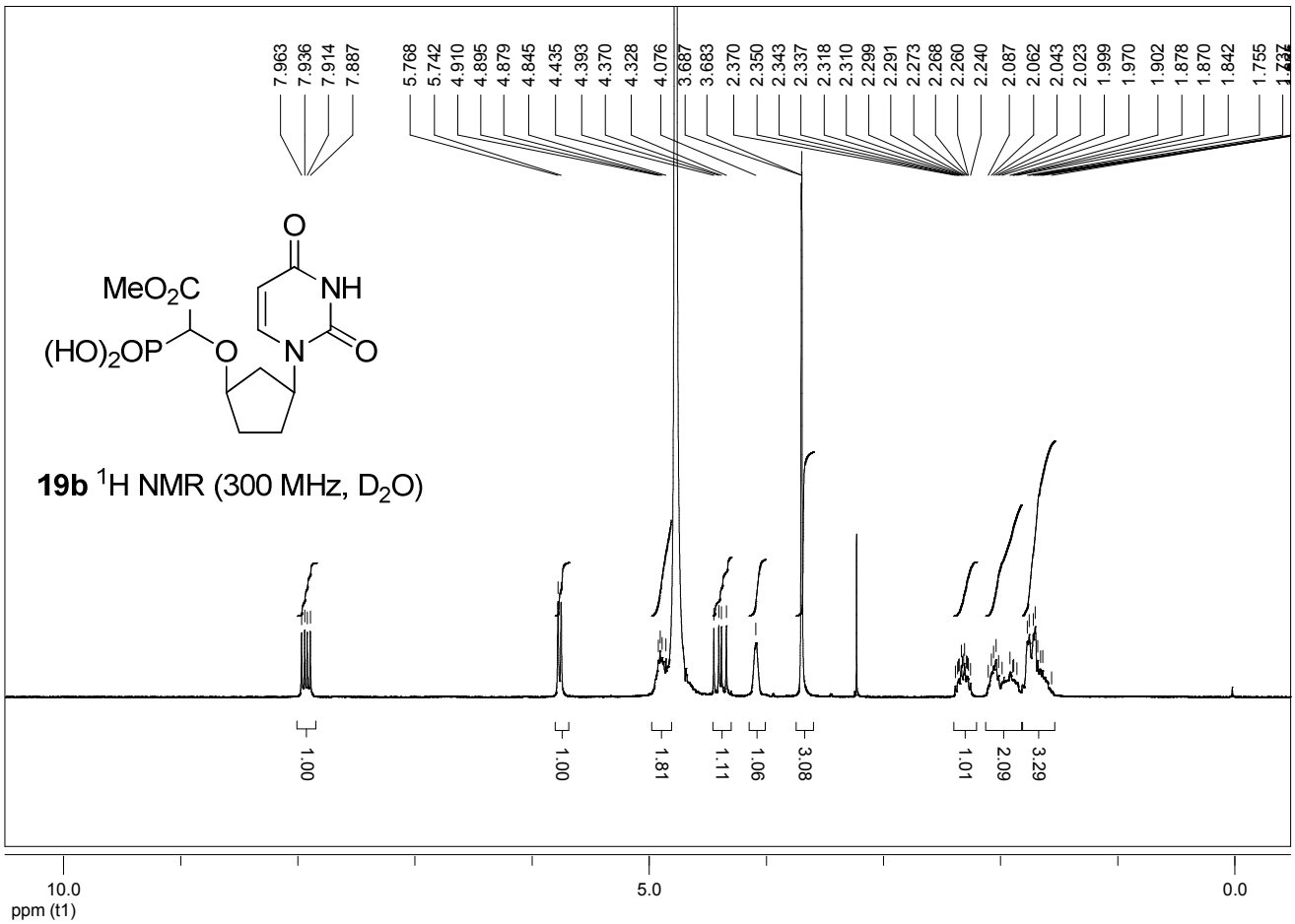
19a ^{13}C NMR (100 MHz, D_2O)

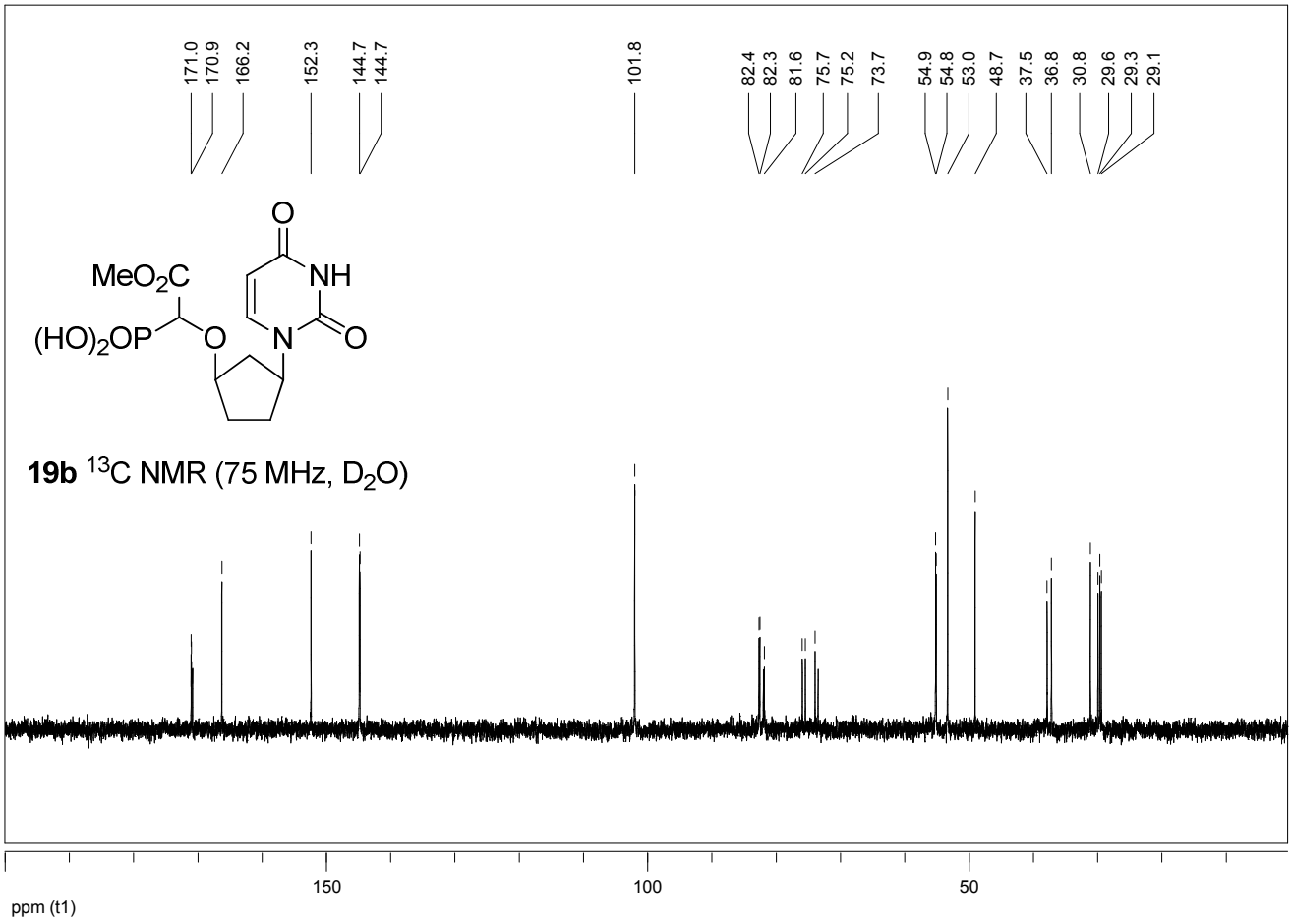

7.722
7.699
4.827
4.812
4.798
4.783
4.768
4.754
2.299
2.289
2.284
2.274
2.265
2.260
2.250
1.949
1.942
1.929
1.916
1.909
1.904
1.896
1.891
1.879
1.869
1.839
1.762
1.688
1.676
1.666
1.654
1.649
1.627
1.604
HO2C
NH
(HO)2OP
O
N
O
11a 1H NMR (600 MHz, D2O)
1.00
0.73
1.92
1.03
3.07
2.91
10.0
5.0
0.0
ppm (t1)

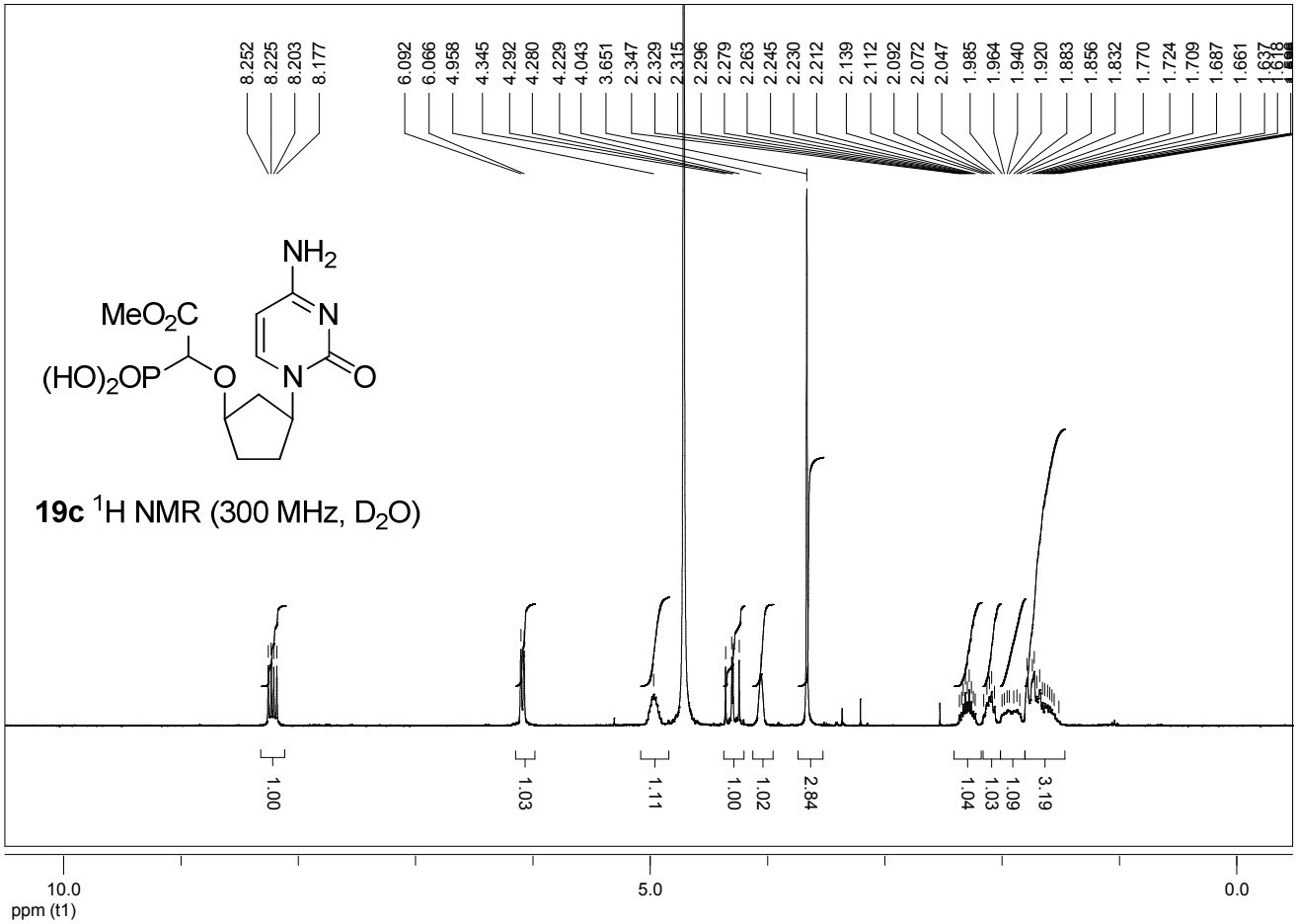

176.54
176.28
166.61
152.59
140.53
140.34
111.42
111.34
80.58
80.51
79.98
79.90
78.62
77.96
77.67
77.01
54.80
54.56
37.47
36.56
30.59
29.51
29.16
29.05
11.47
11.43
HO2C
NH
(HO)2OP
O
N
O
11a 13C NMR (150 MHz, D2O)
150
100
50
ppm (t1)

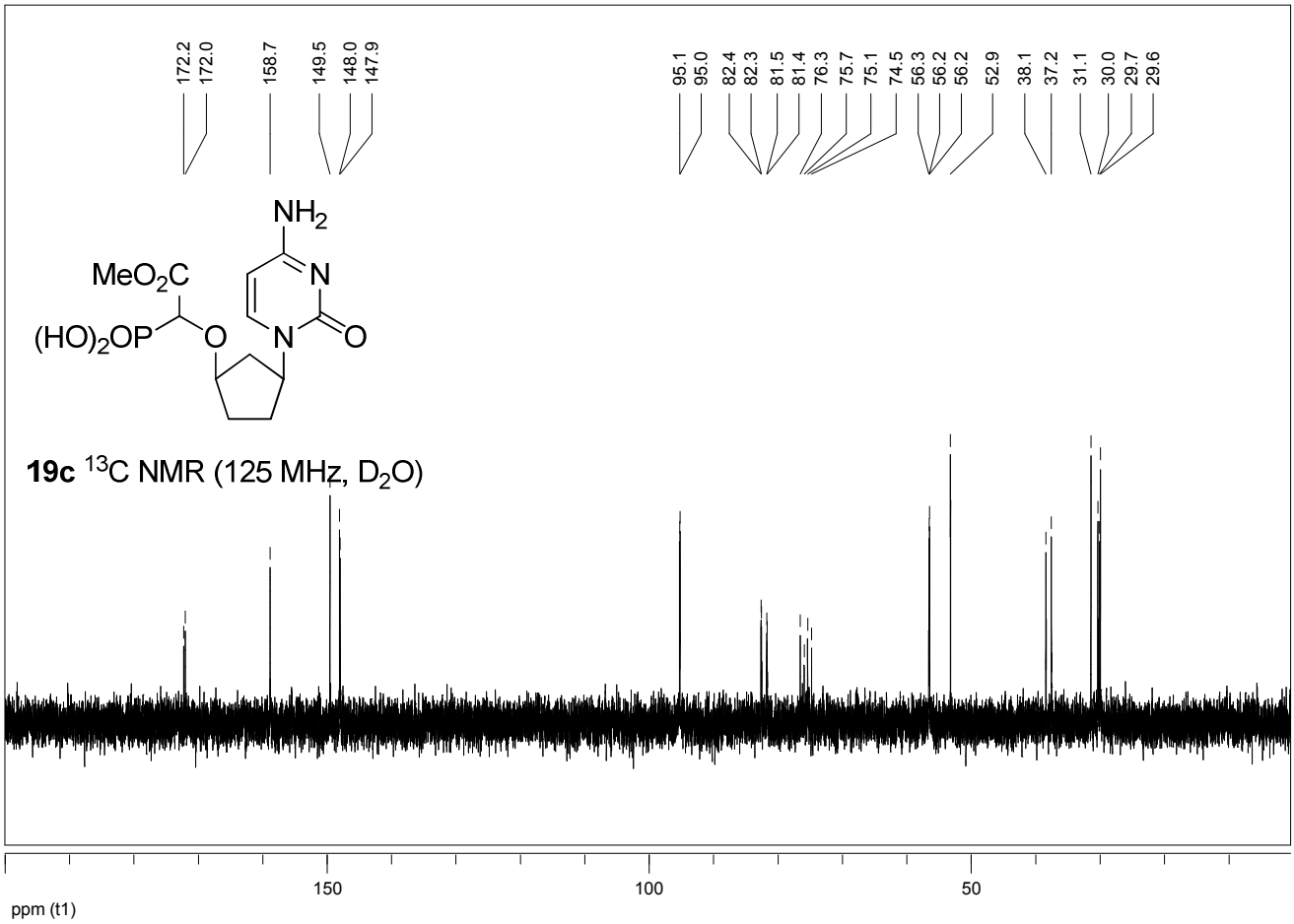

7.997
7.985
5.755
5.743
5.734
4.854
4.841
4.829
3.987
3.945
3.917
3.886
2.286
2.277
2.268
2.259
2.252
2.242
2.234
2.227
1.994
1.986
1.980
1.974
1.966
1.896
1.879
1.857
1.841
1.734
1.697
1.674
1.648
1.639
HO2C
(HO)2OP
O
NH
N
O
11b 1H NMR (600 MHz, D2O)
1.00
0.87
0.65
1.90
1.04
2.07
3.17
10.0
5.0
0.0
ppm (t1)

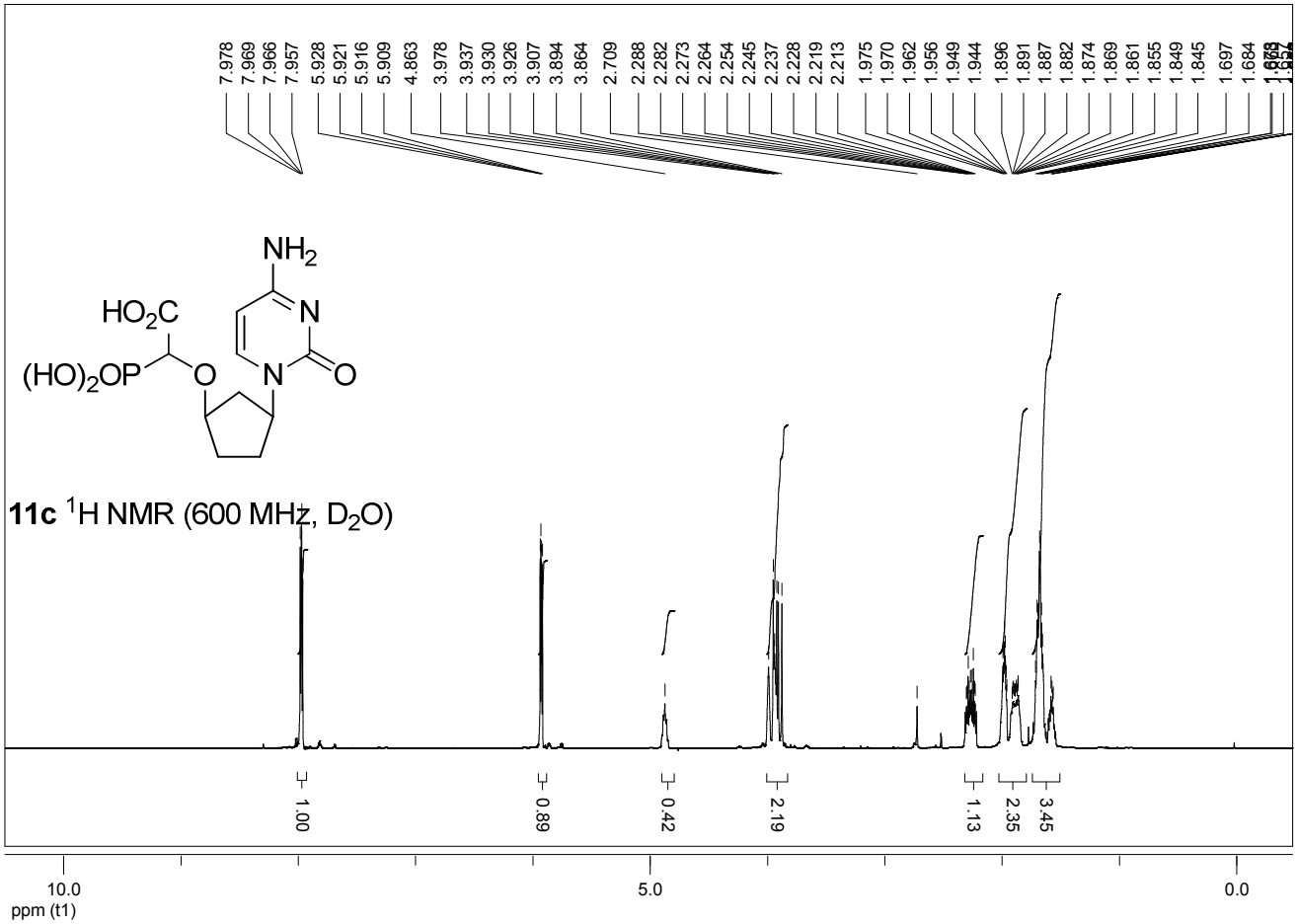

176.67
176.42
166.50
152.66
145.38
145.35
129.03
127.37
102.16
102.13
80.71
80.64
79.99
79.91
55.14
54.93
37.72
36.48
31.10
29.73
29.50
HO2C
(HO)2OP
O
NH
N
O
11b 13C NMR (150 MHz, D2O)
150
100
50
ppm (t1)

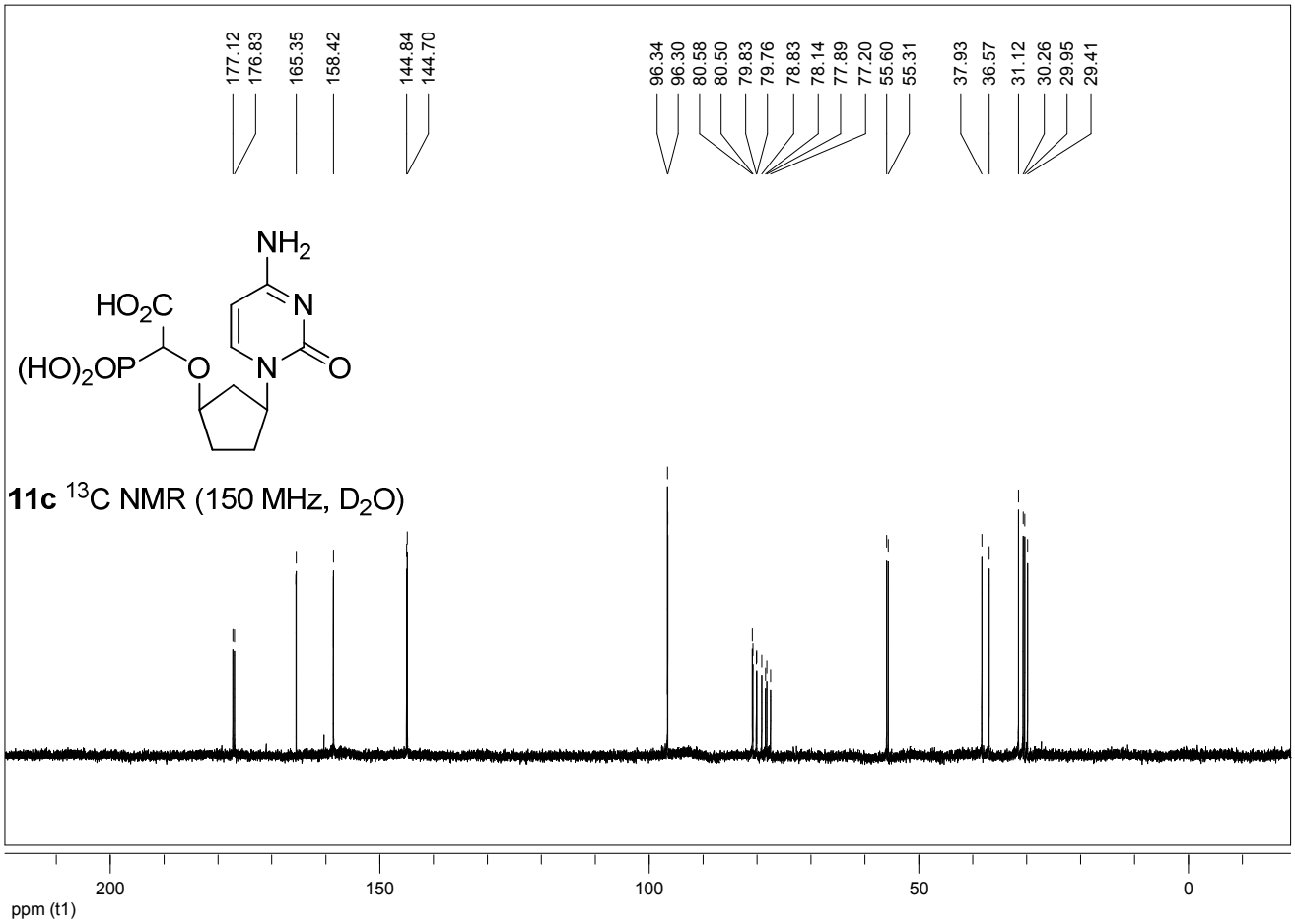

7.963
7.936
7.914
7.887
5.768
5.742
4.910
4.895
4.879
4.845
4.435
4.393
4.370
4.328
4.076
3.687
3.683
2.370
2.350
2.343
2.337
2.318
2.310
2.299
2.291
2.273
2.268
2.260
2.240
2.087
2.062
2.043
2.023
1.999
1.970
1.902
1.878
1.870
1.842
1.755
MeO2C
(HO)2OP
O
NH
N
O
19b 1H NMR (300 MHz, D2O)
1.00
1.00
1.81
1.11
1.06
3.08
1.01
2.09
2.29
10.0
5.0
0.0
ppm (t1)

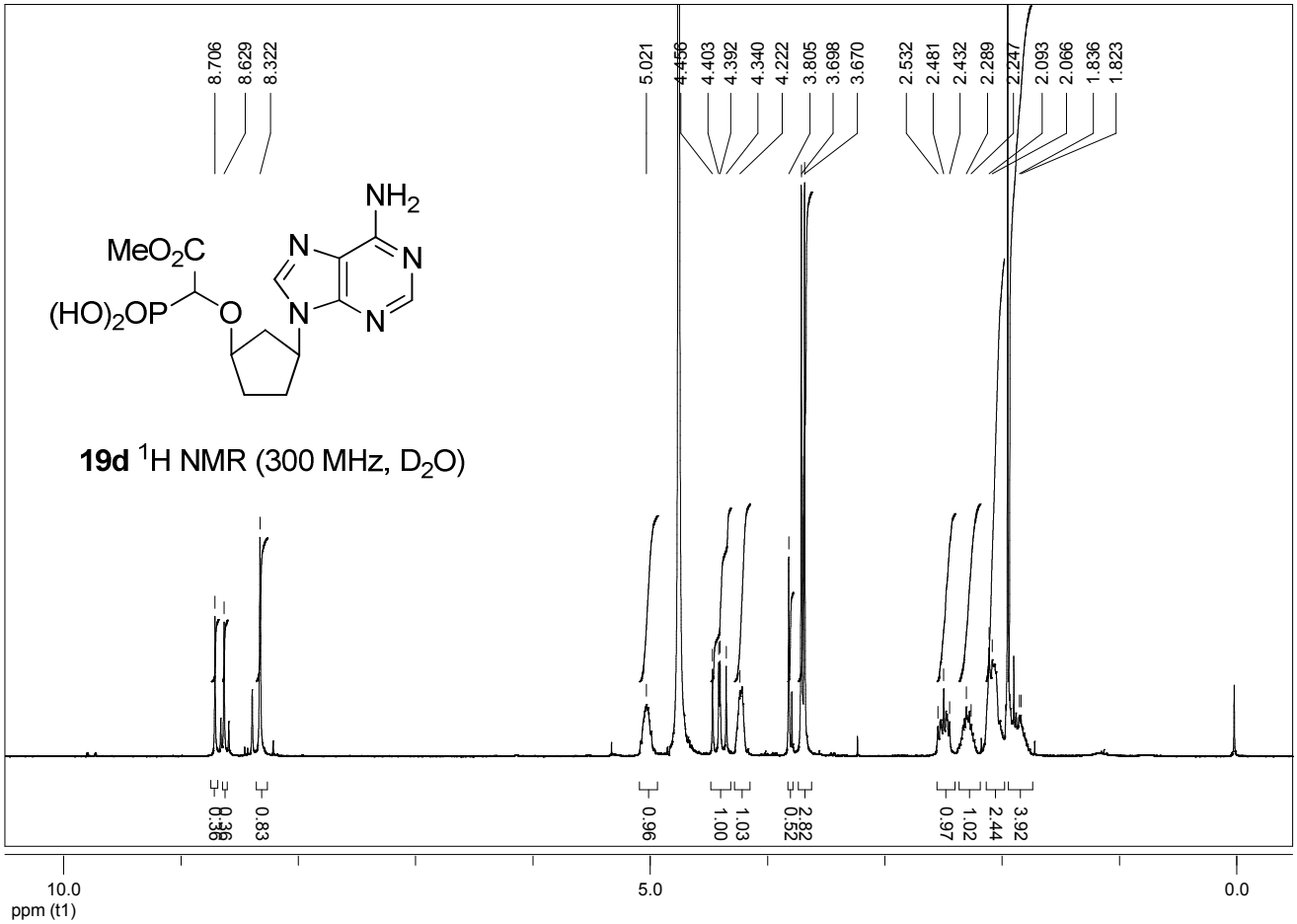

171.0
170.9
166.2
152.3
144.7
144.7
101.8
82.4
82.3
81.6
75.7
75.2
73.7
54.9
54.8
53.0
48.7
37.5
36.8
30.8
29.6
29.3
29.1
MeO2C
(HO)2OP
O
NH
N
O
19b 13C NMR (75 MHz, D2O)
150
100
50
ppm (t1)


8.252
8.225
8.203
8.177
6.092
6.066
4.958
4.345
4.292
4.280
4.229
4.043
3.651
2.347
2.329
2.315
2.296
2.279
2.263
2.245
2.230
2.212
2.139
2.112
2.092
2.072
2.047
1.985
1.964
1.940
1.920
1.883
1.856
1.832
1.770
1.724
1.709
1.687
1.661
NH2
MeO2C
N
(HO)2OP
O
N
O
19c 1H NMR (300 MHz, D2O)
1.00
1.03
1.11
1.00
1.02
2.84
1.04
1.03
1.09
3.19
10.0
5.0
0.0
ppm (t1)

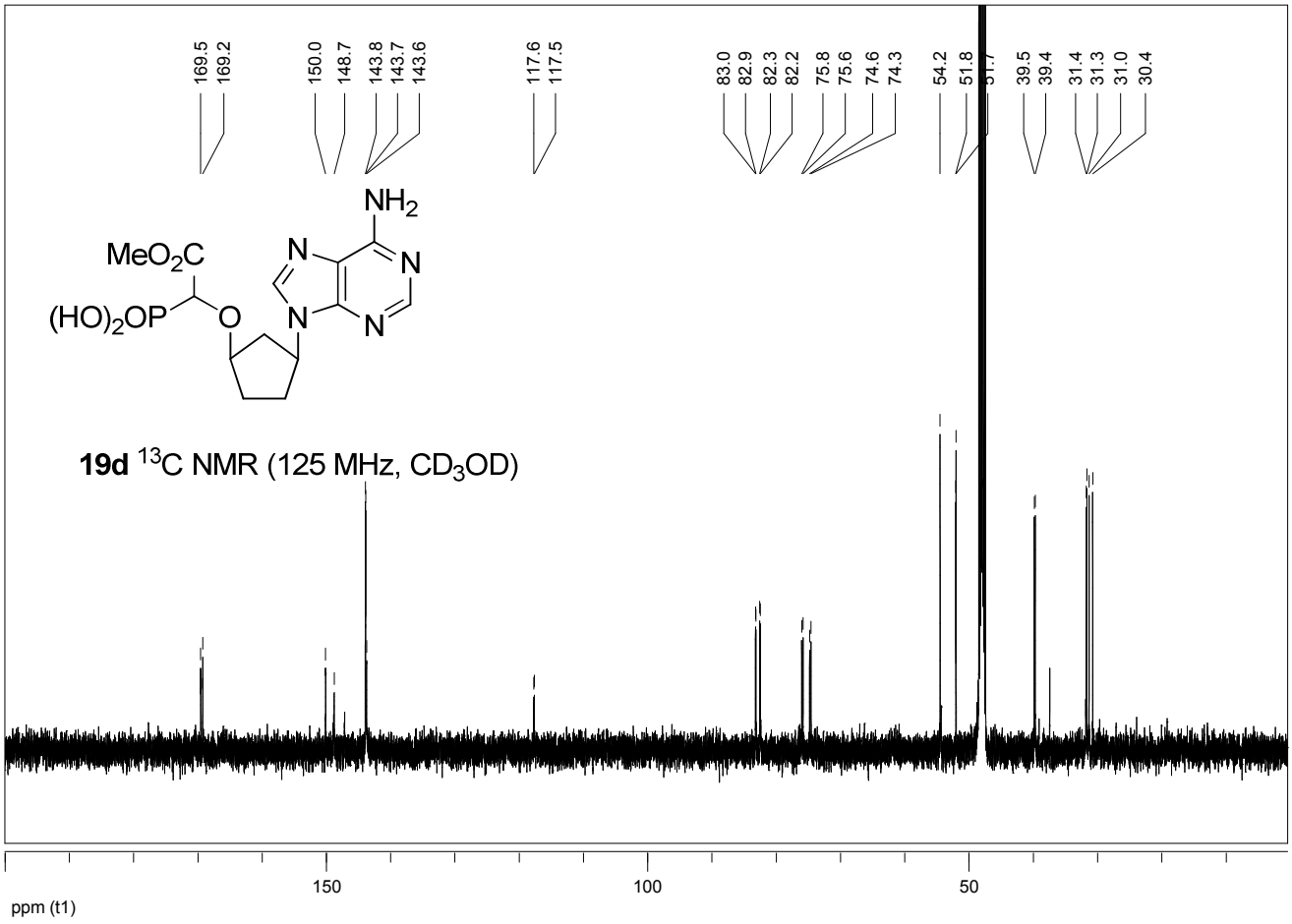

172.2
172.0
158.7
149.5
148.0
147.9
95.1
95.0
82.4
82.3
81.5
81.4
76.3
75.7
75.1
74.5
56.3
56.2
56.2
52.9
38.1
37.2
31.1
30.0
29.7
29.6
NH2
MeO2C
N
(HO)2OP
O
N
O
19c 13C NMR (125 MHz, D2O)
150
100
50
ppm (t1)


7.978
7.969
7.966
7.957
5.928
5.921
5.916
5.909
4.863
3.978
3.937
3.930
3.926
3.907
3.894
3.864
2.709
2.288
2.282
2.273
2.264
2.254
2.245
2.237
2.228
2.219
2.213
1.975
1.970
1.962
1.956
1.949
1.944
1.896
1.891
1.887
1.882
1.874
1.869
1.861
1.855
1.849
1.845
1.697
1.684
NH2
HO2C
N
(HO)2OP
O
N
O
11c 1H NMR (600 MHz, D2O)
1.00
0.89
0.42
2.19
1.13
2.35
3.45
10.0
5.0
0.0
ppm (t1)

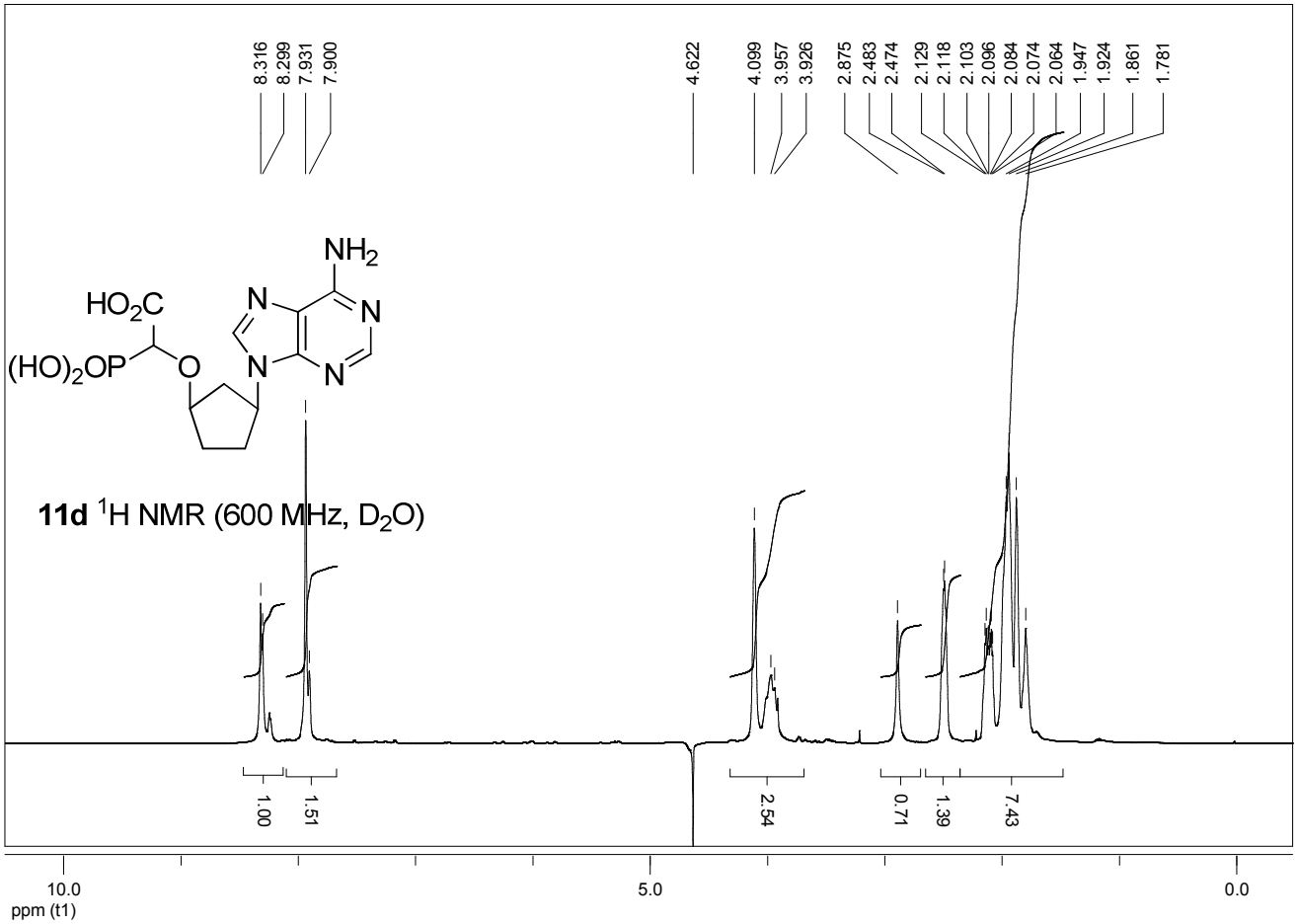

177.12
176.83
165.35
158.42
144.84
144.70
96.34
96.30
80.58
80.50
79.83
79.76
78.83
78.14
77.89
77.20
55.60
55.31
37.93
36.57
31.12
30.26
29.95
29.41
NH2
HO2C
N
(HO)2OP
O
N
O
11c 13C NMR (150 MHz, D2O)
200
150
100
50
0
ppm (t1)

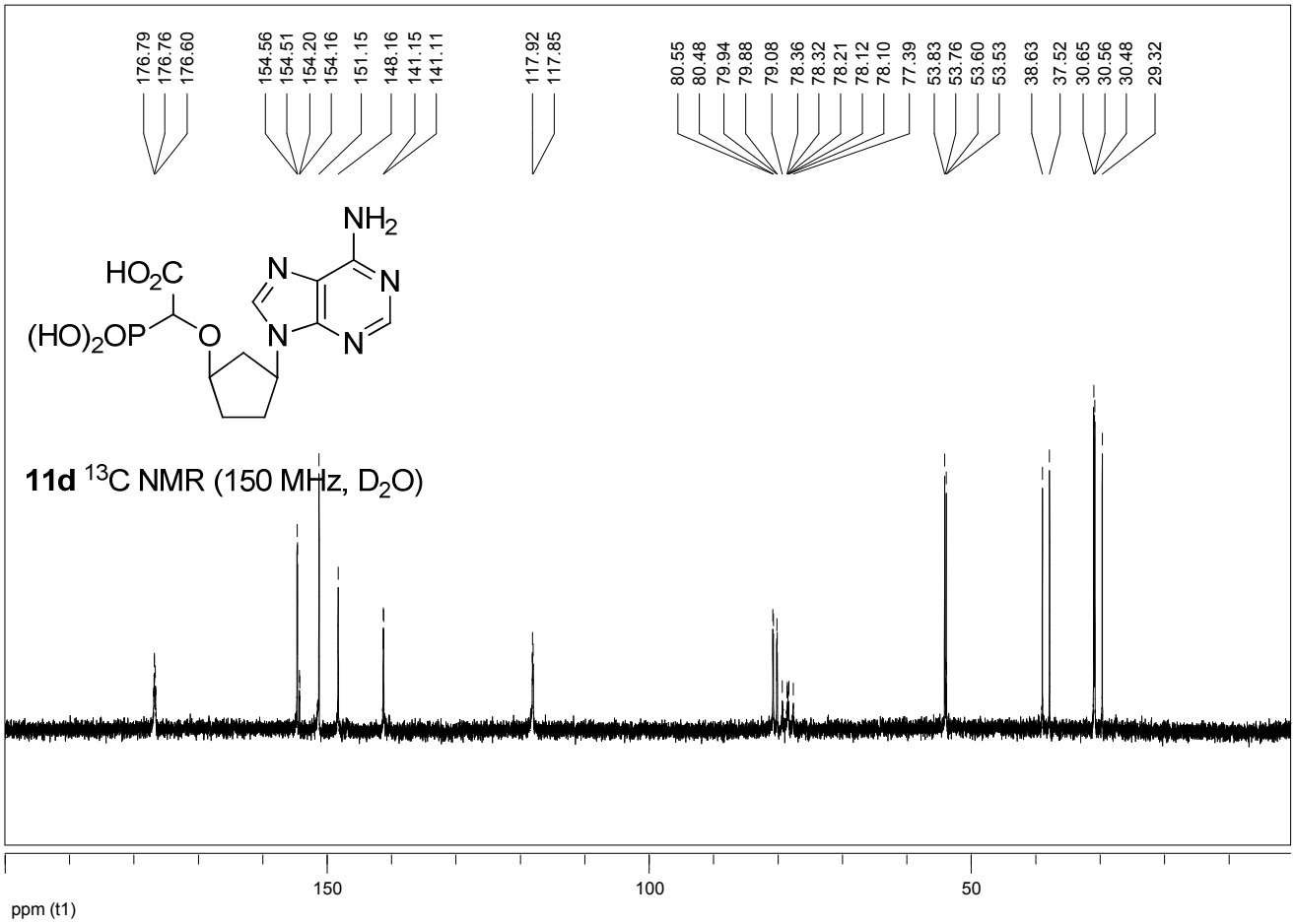


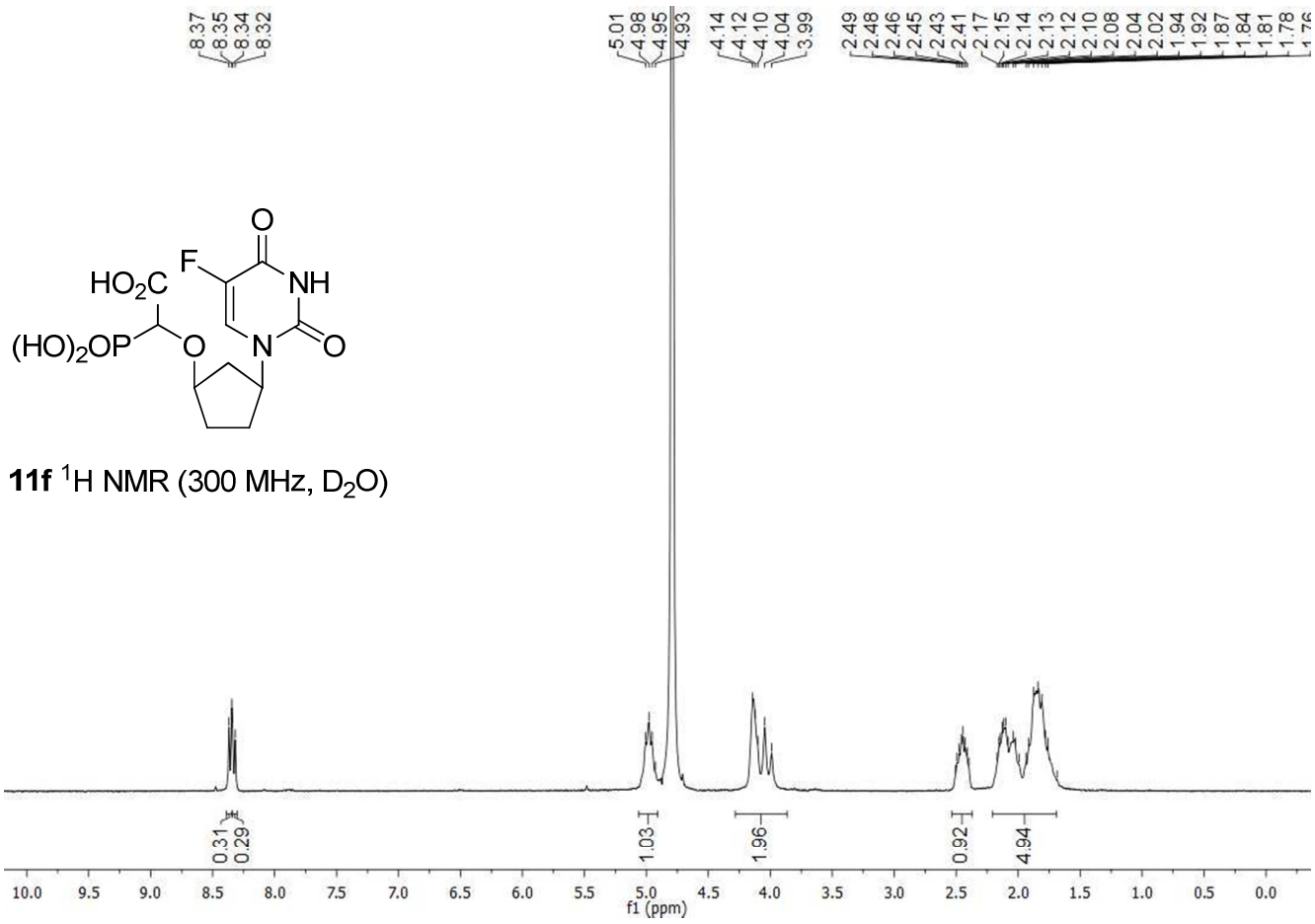
19d ^{1}H NMR (300 MHz, D_2O)



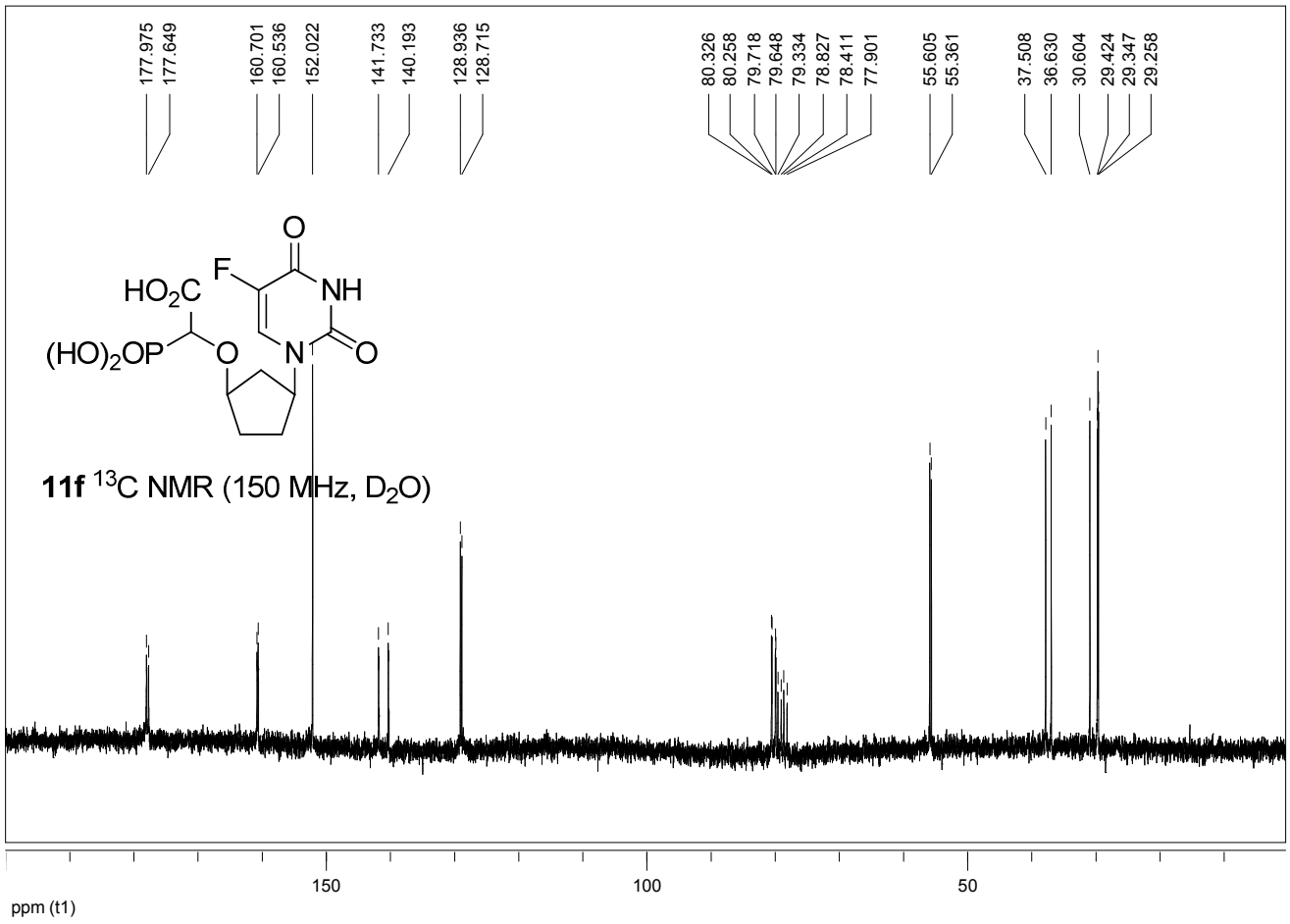
19d ^{13}C NMR (125 MHz, CD_3OD)


8.316
8.299
7.931
7.900
4.622
4.099
3.957
3.926
2.875
2.483
2.474
2.129
2.118
2.103
2.096
2.084
2.074
2.064
1.947
1.924
1.861
1.781
NH2
HO2C
(HO)2OP
O
N
N
N
N
11d 1H NMR (600 MHz, D2O)
1.00
1.51
2.54
0.71
1.39
7.43
10.0
5.0
0.0
ppm (t1)

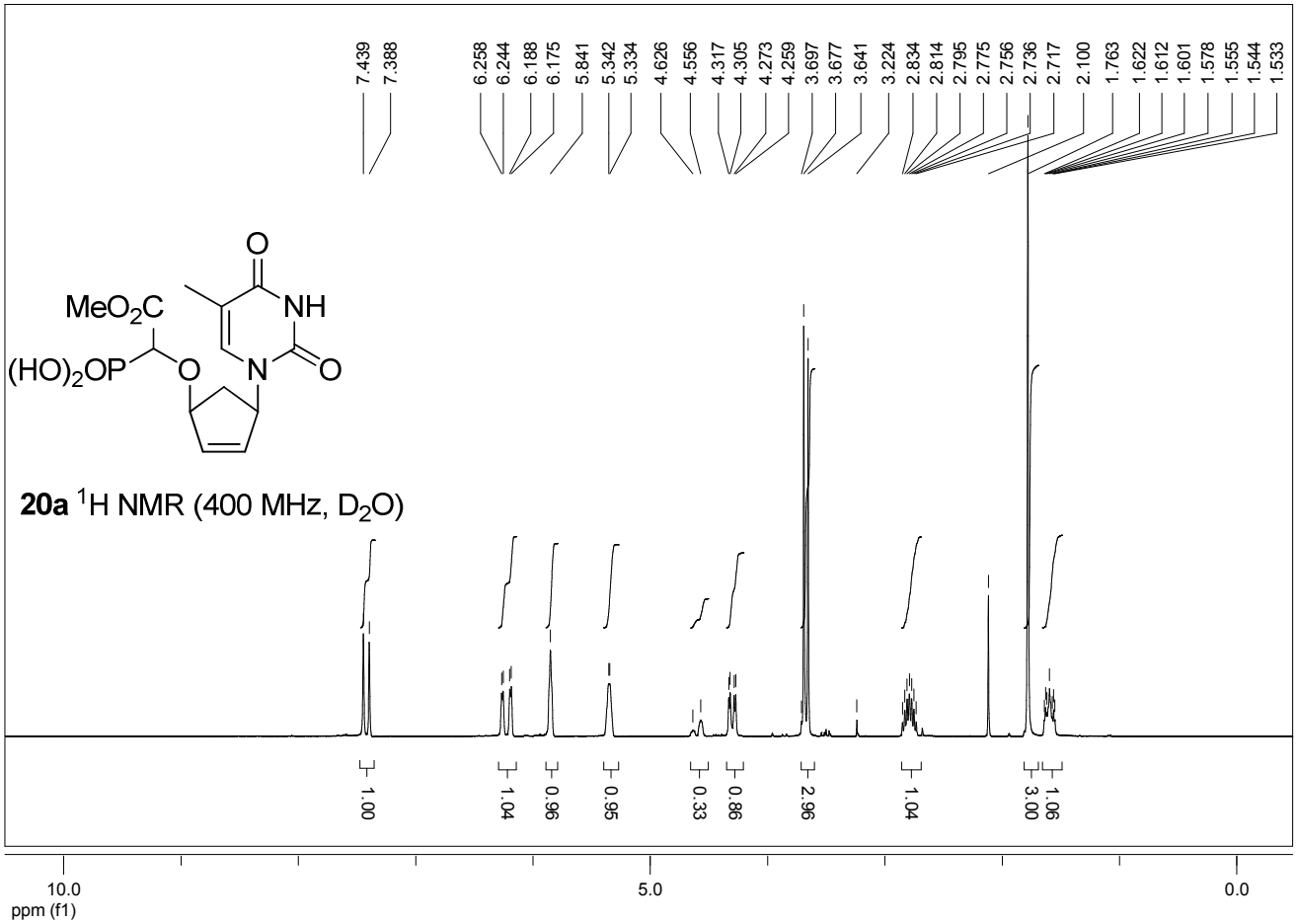

176.79
176.76
176.60
154.56
154.51
154.20
154.16
151.15
148.16
141.15
141.11
117.92
117.85
80.55
80.48
79.94
79.88
79.08
78.36
78.32
78.21
78.12
78.10
77.39
53.83
53.76
53.60
53.53
38.63
37.52
30.65
30.56
30.48
29.32
NH2
HO2C
(HO)2OP
O
N
N
N
N
11d 13C NMR (150 MHz, D2O)
150
100
50
ppm (t1)



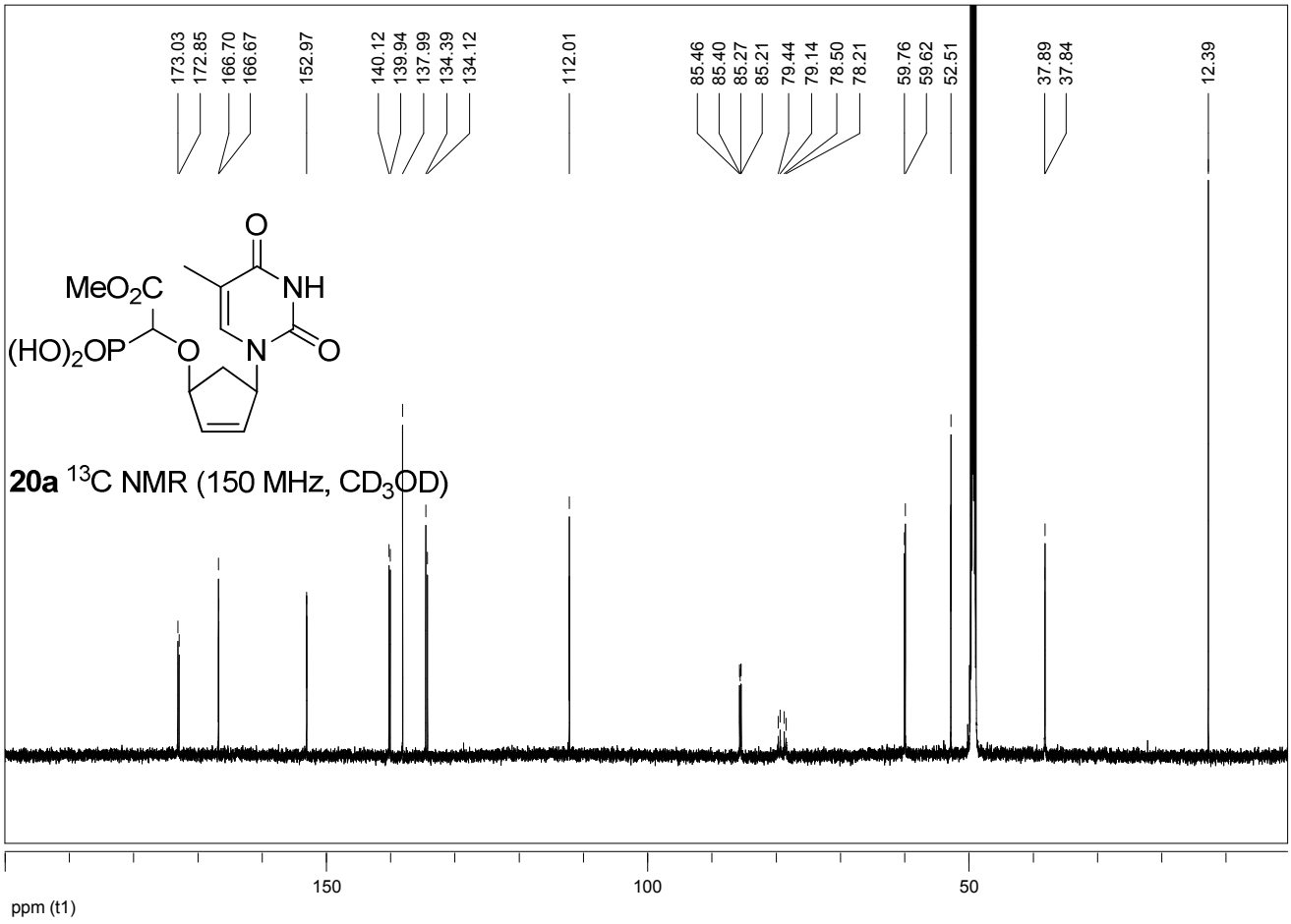
11f ^{1}H NMR (300 MHz, D_2O)



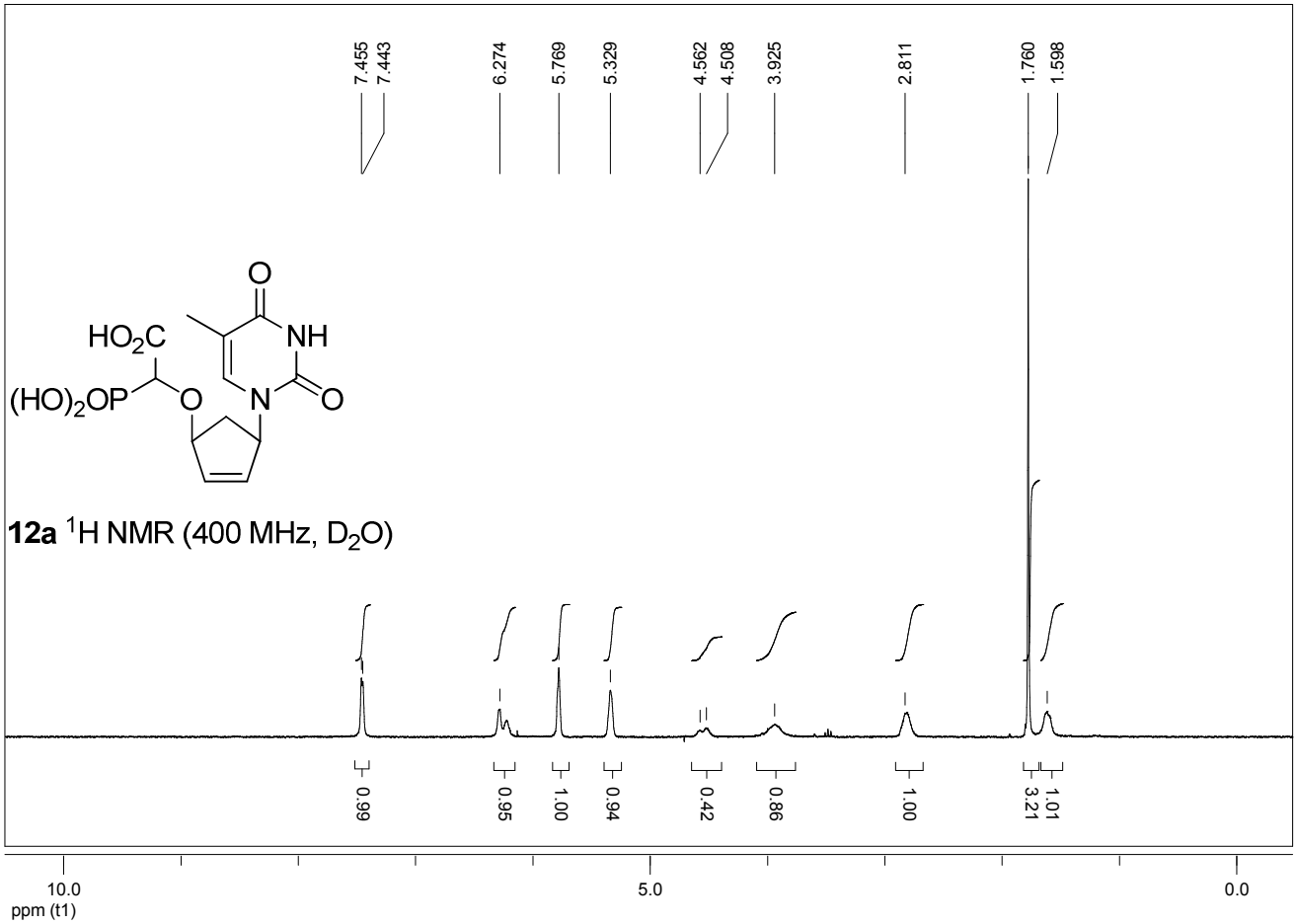
11f ^{13}C NMR (150 MHz, D_2O)

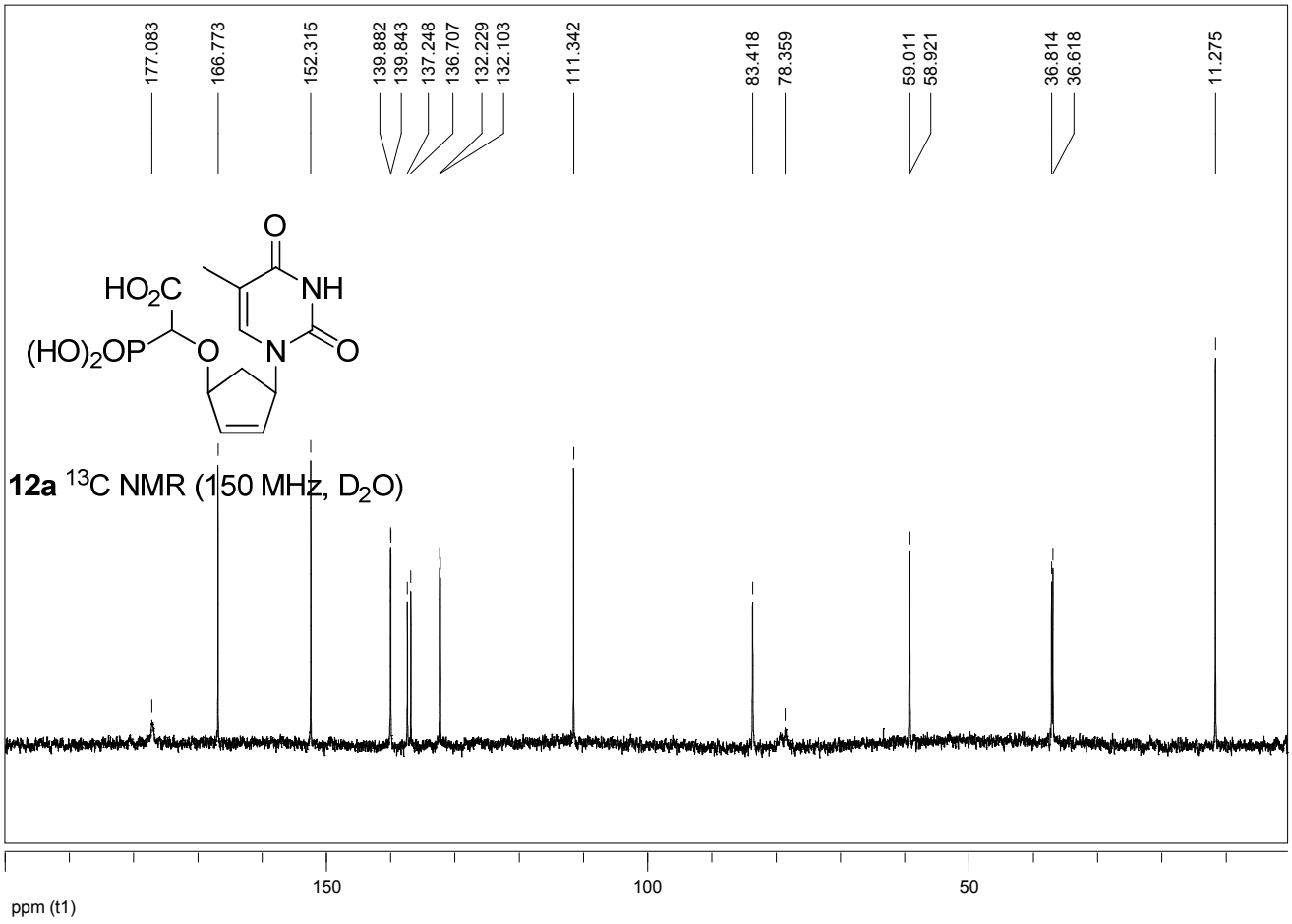


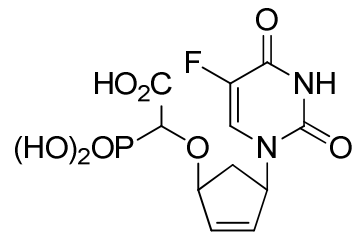
20a ^{1}H NMR (400 MHz, D_2O)



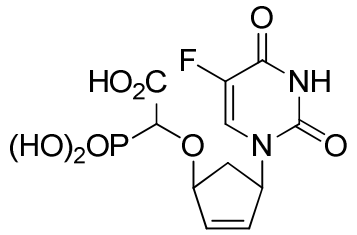
20a ^{13}C NMR (150 MHz, CD_3OD)


7.455
7.443
6.274
5.769
5.329
4.562
4.508
3.925
2.811
1.760
1.598
HO2C
(HO)2OP
O
NH
N
O
12a 1H NMR (400 MHz, D2O)
0.99
0.95
1.00
0.94
0.42
0.86
1.00
3.21
1.01
10.0
5.0
0.0
ppm (t1)

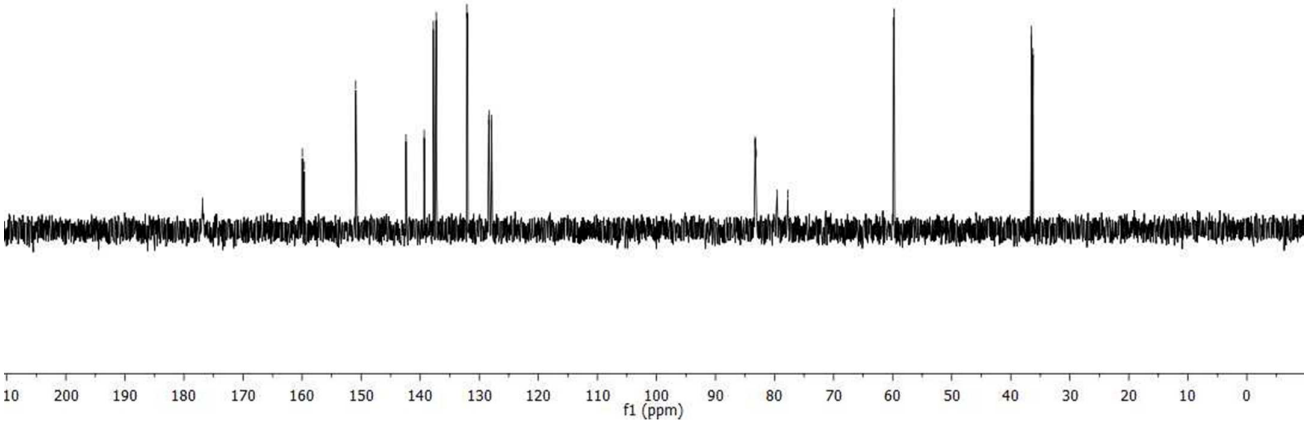

177.083
166.773
152.315
139.882
139.843
137.248
136.707
132.229
132.103
111.342
83.418
78.359
59.011
58.921
36.814
36.618
11.275
HO2C
(HO)2OP
O
NH
N
O
12a 13C NMR (150 MHz, D2O)
150
100
50
ppm (t1)

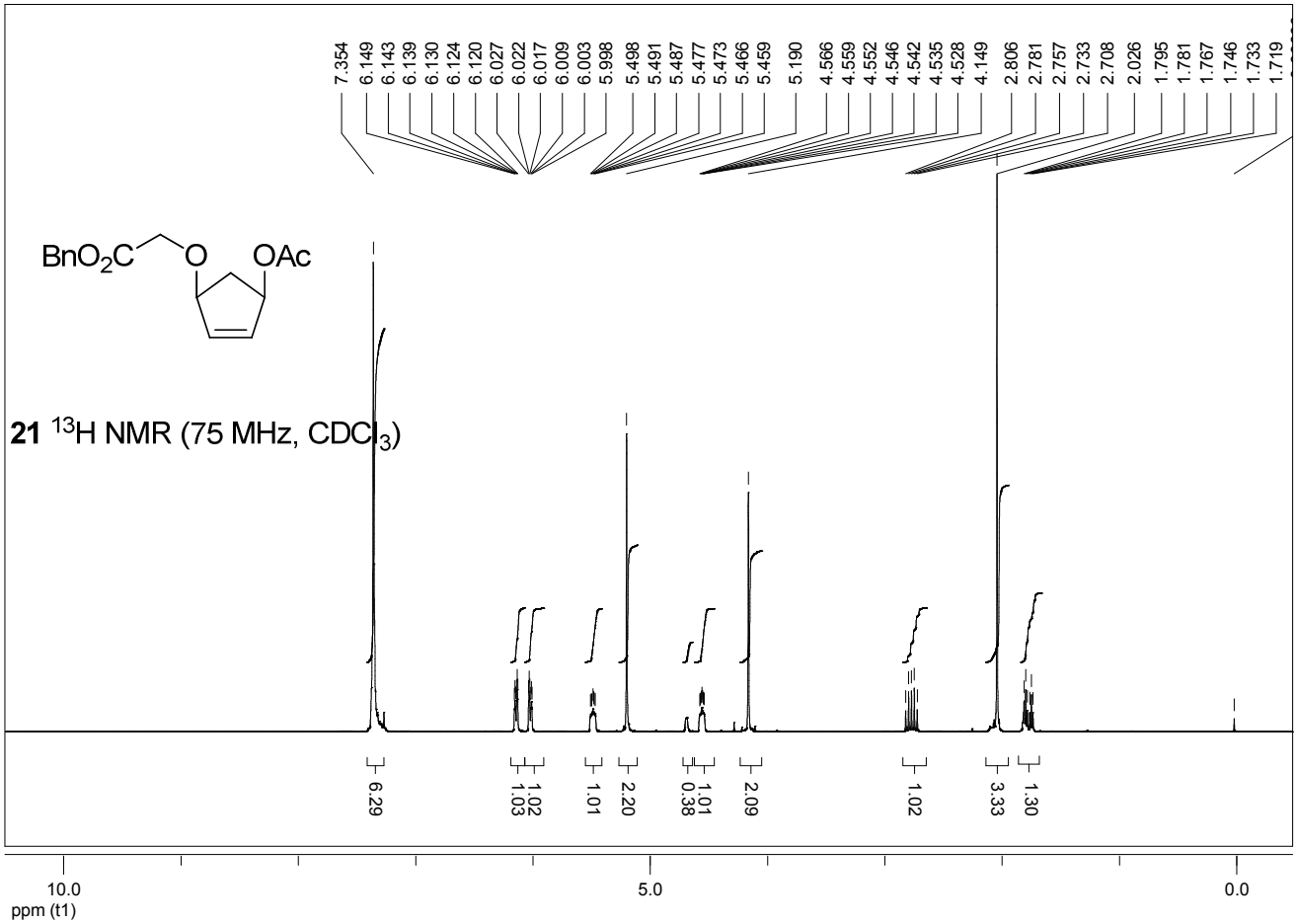


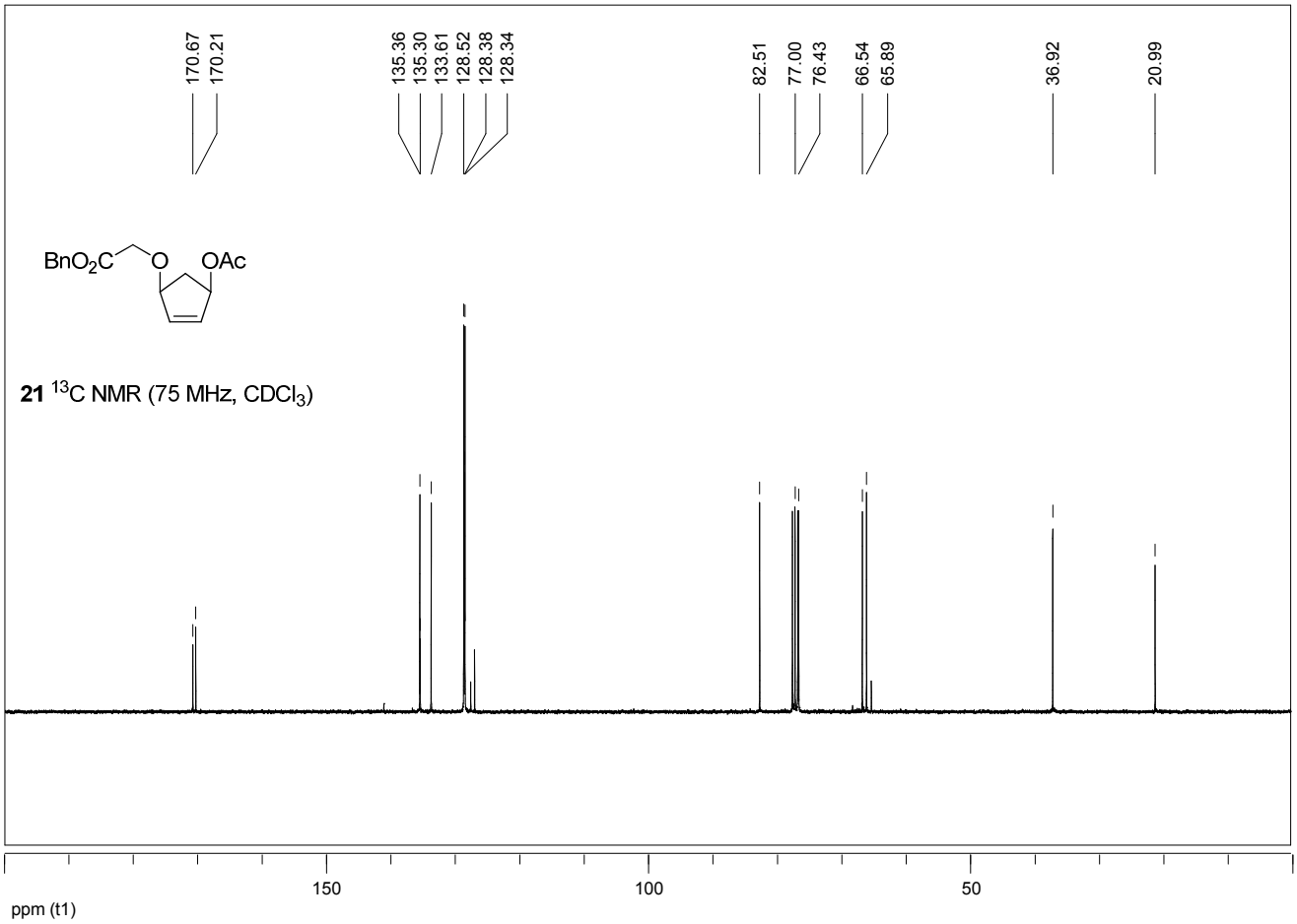
12f ^{1}H NMR (300 MHz, D_2O)

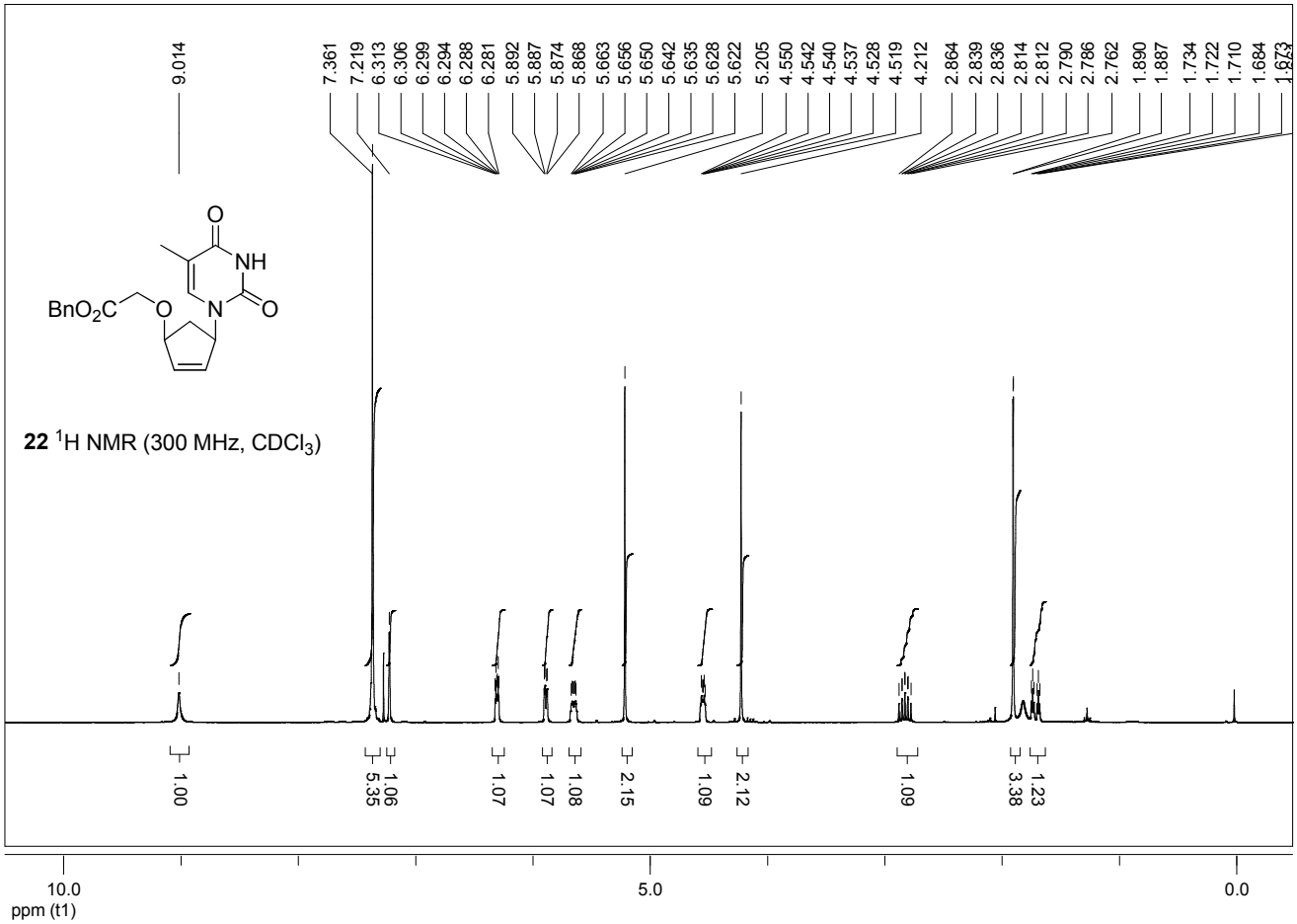


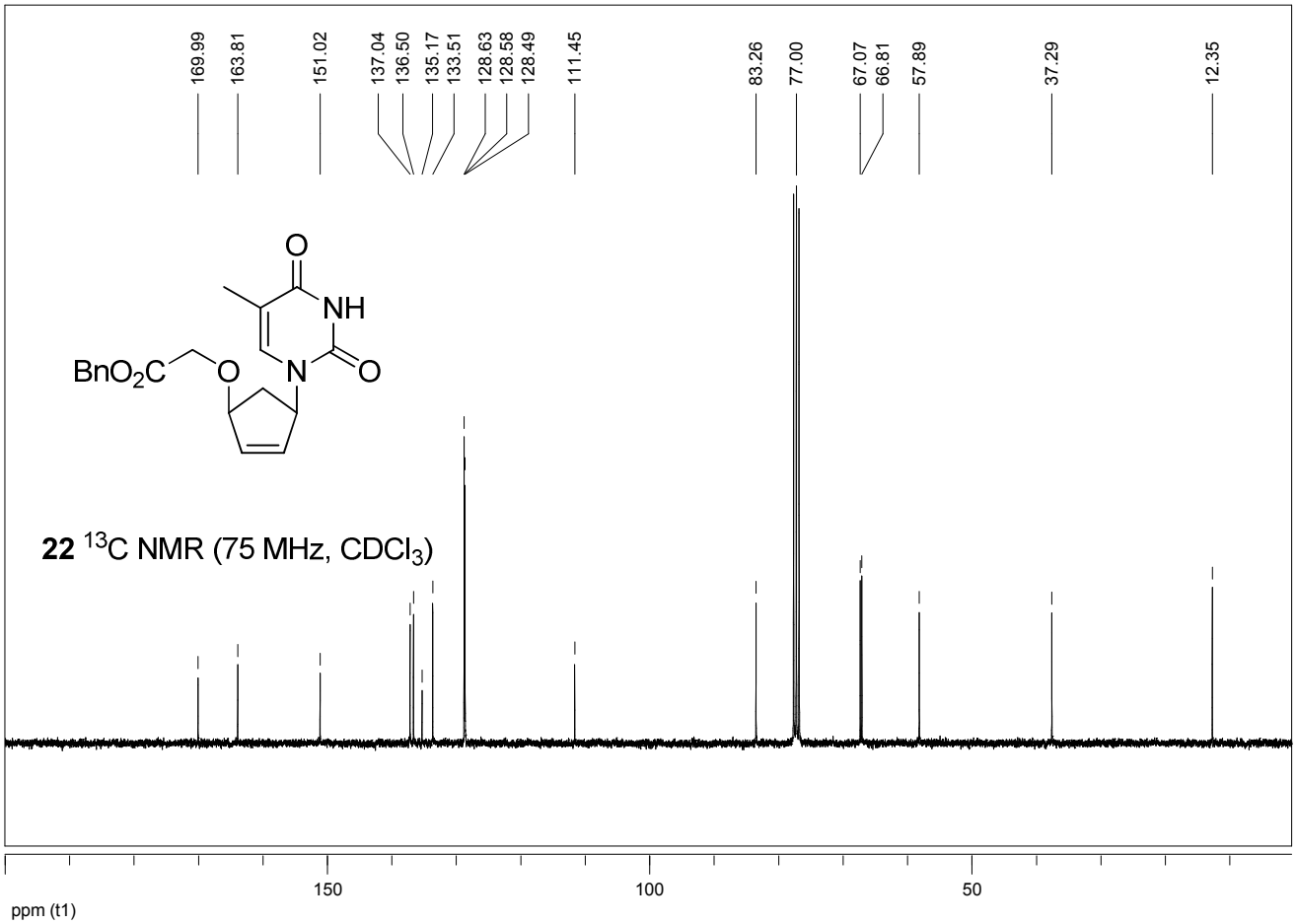
12f ^{1}H NMR (75 MHz, D_2O)

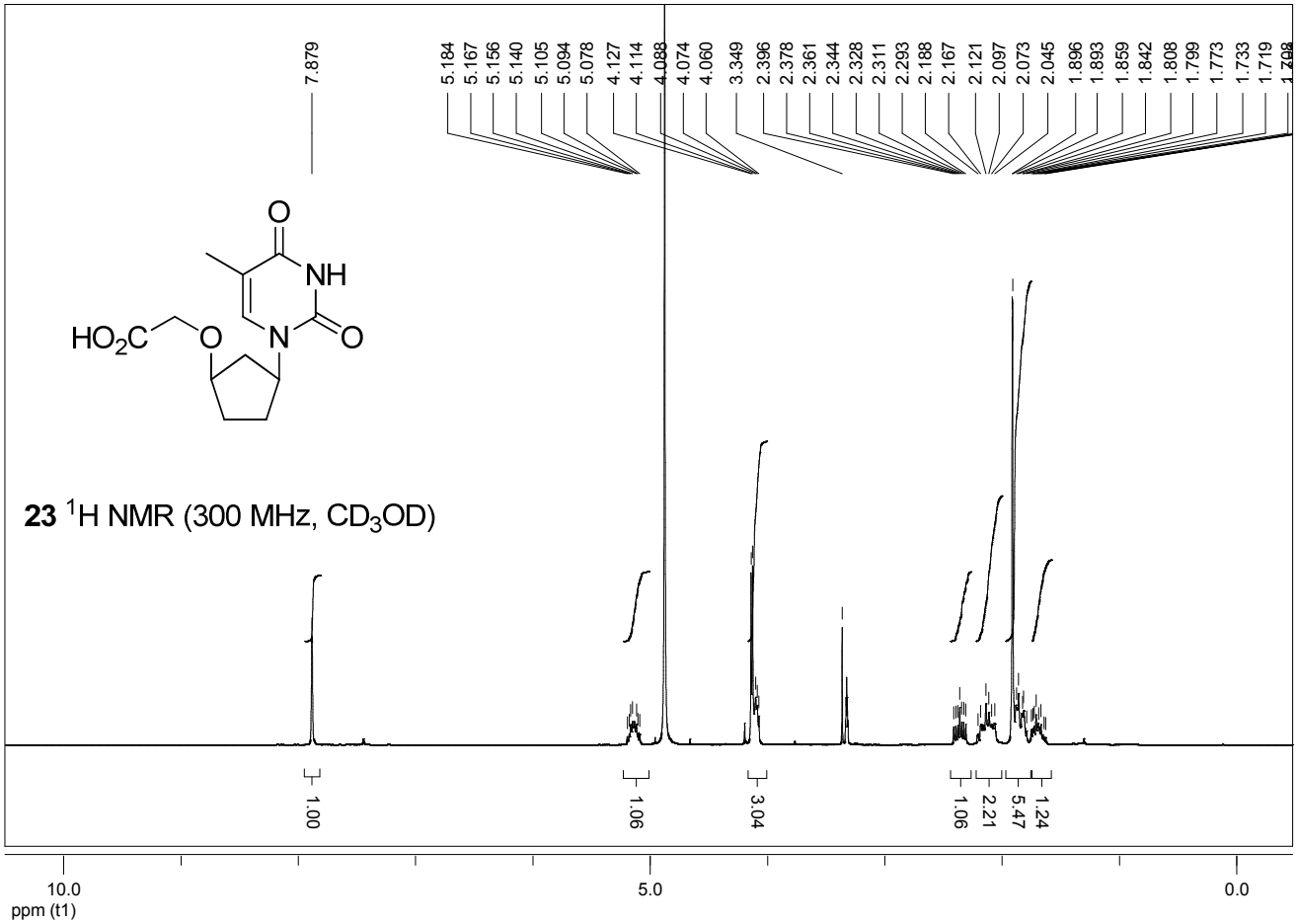



7.354
6.149
6.143
6.139
6.130
6.124
6.120
6.027
6.022
6.017
6.009
6.003
5.998
5.498
5.491
5.487
5.477
5.473
5.466
5.459
5.190
4.566
4.559
4.552
4.546
4.542
4.535
4.528
4.149
2.806
2.781
2.757
2.733
2.708
2.026
1.795
1.781
1.767
1.746
1.733
1.719
BnO2C
O
OAc
21 13H NMR (75 MHz, CDCl3)
6.29
1.03
1.02
1.01
2.20
0.38
1.01
2.09
1.02
3.33
1.30
10.0
5.0
0.0
ppm (t1)

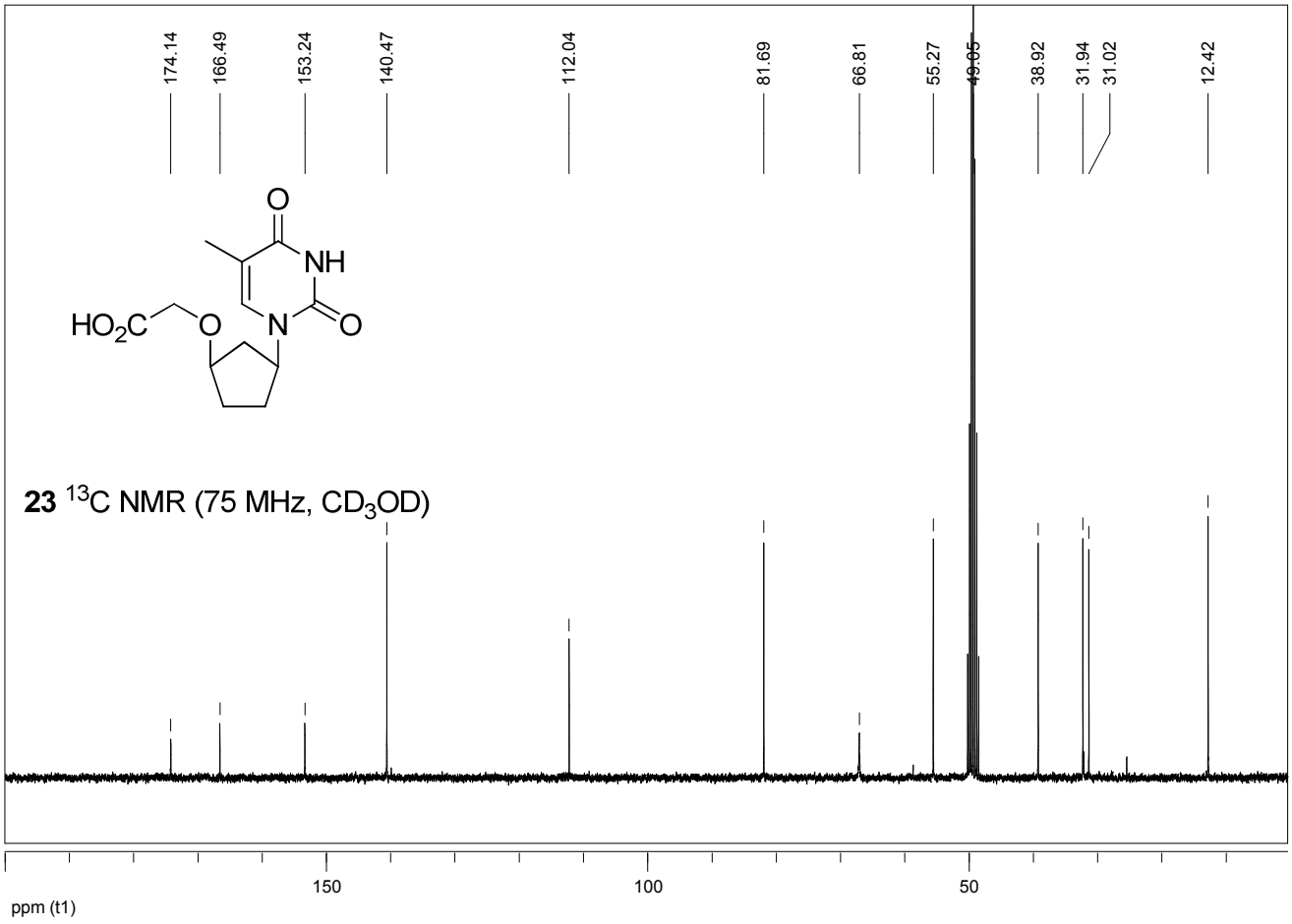

170.67
170.21
135.36
135.30
133.61
128.52
128.38
128.34
82.51
77.00
76.43
66.54
65.89
36.92
20.99
BnO2C
O
OAc
21 13C NMR (75 MHz, CDCl3)
150
100
50
ppm (t1)


9.014
7.361
7.219
6.313
6.306
6.299
6.294
6.288
6.281
5.892
5.887
5.874
5.868
5.663
5.656
5.650
5.642
5.635
5.628
5.622
5.205
4.550
4.542
4.540
4.537
4.528
4.519
4.212
2.864
2.839
2.836
2.814
2.812
2.790
2.786
2.762
1.890
1.887
1.734
1.722
1.710
1.684
1.673
O
NH
BnO2C
O
N
O
22 1H NMR (300 MHz, CDCl3)
1.00
5.35
1.90
1.07
1.07
1.08
2.15
1.09
2.12
1.09
3.38
1.23
10.0
5.0
0.0
ppm (t1)

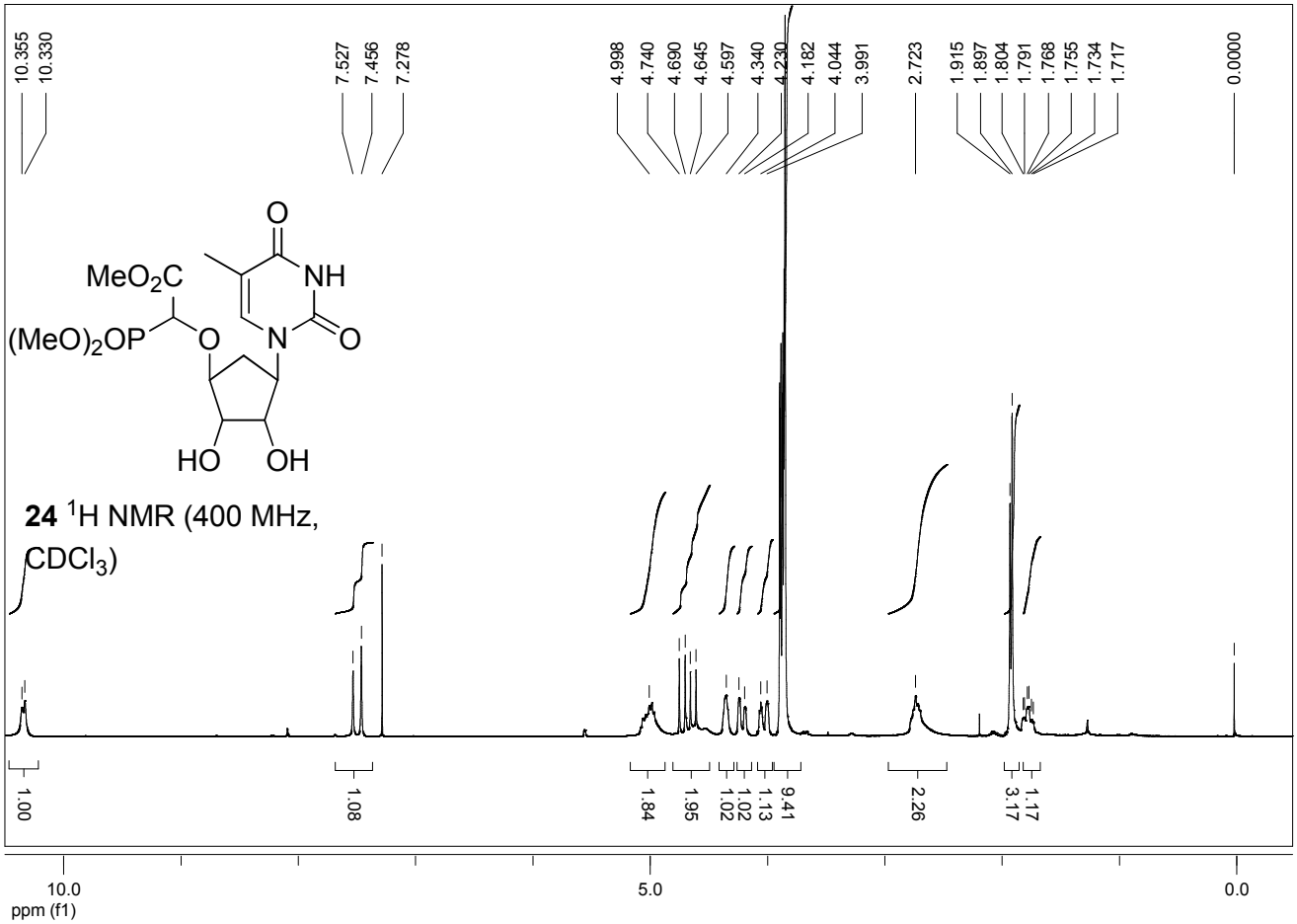

169.99
163.81
151.02
137.04
136.50
135.17
133.51
128.63
128.58
128.49
111.45
83.26
77.00
67.07
66.81
57.89
37.29
12.35
O
NH
BnO2C
O
N
O
22 13C NMR (75 MHz, CDCl3)
150
100
50
ppm (t1)



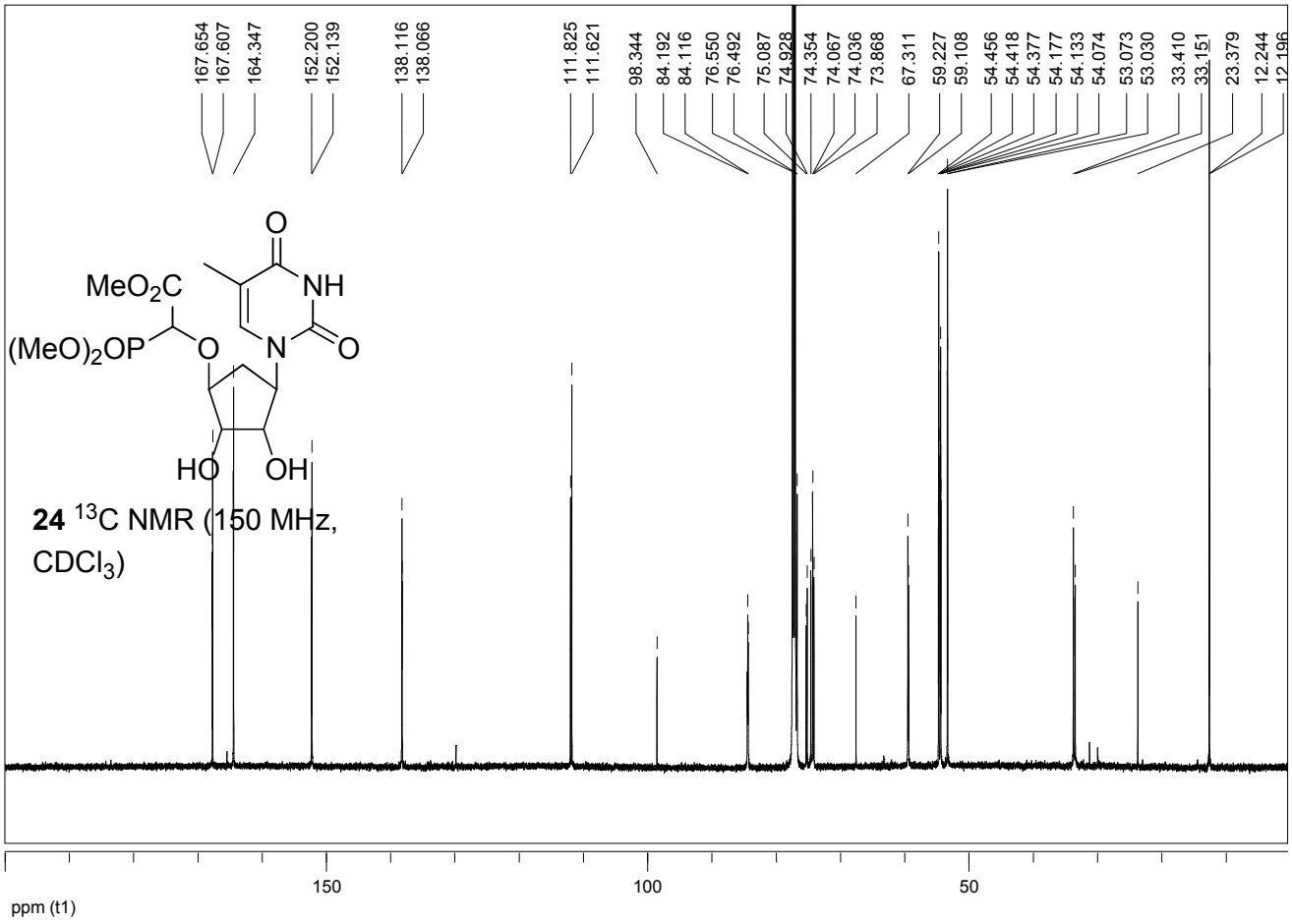
23 ^{1}H NMR (300 MHz, CD_3OD)



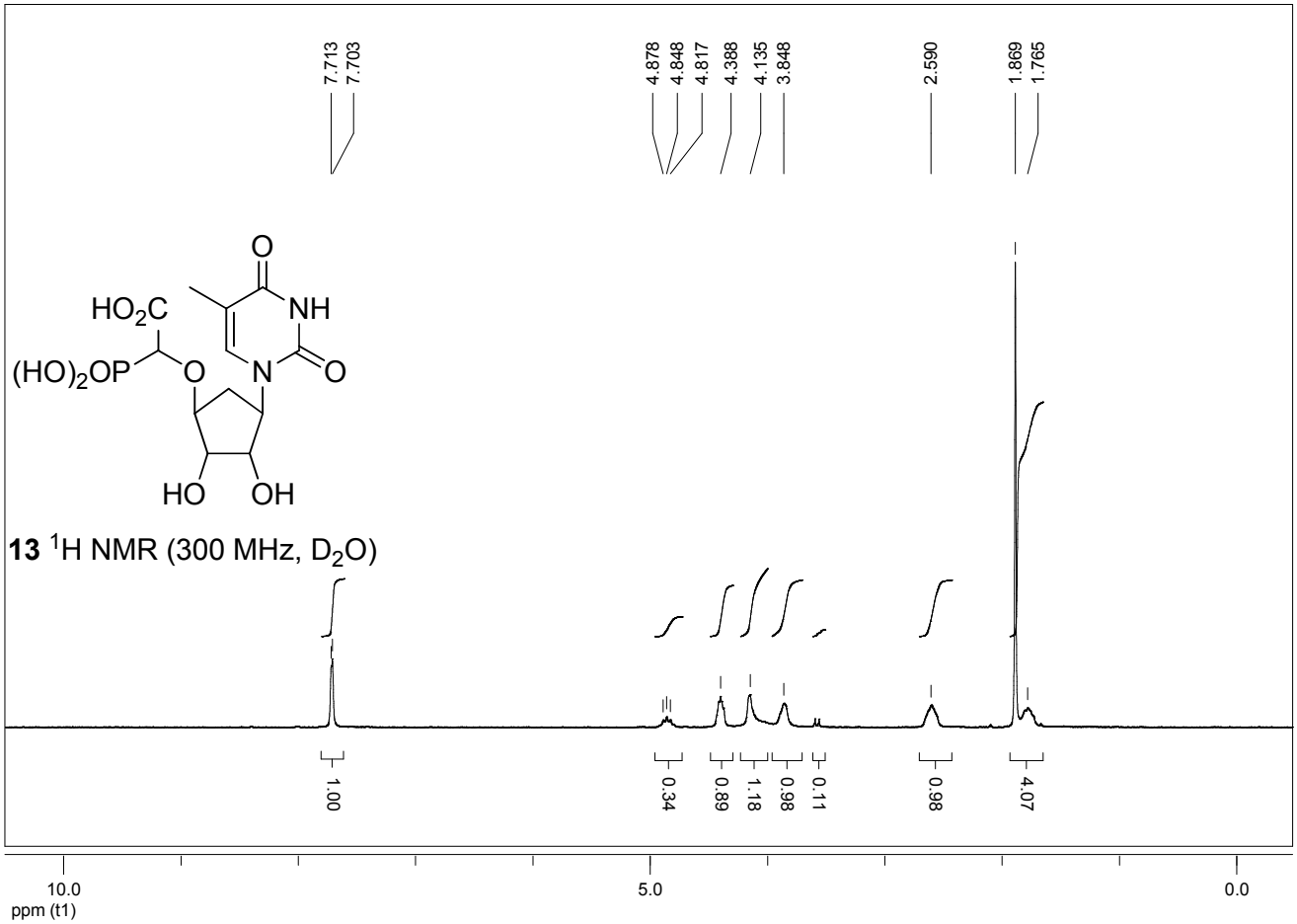
23 ^{13}C NMR (75 MHz, CD_3OD)



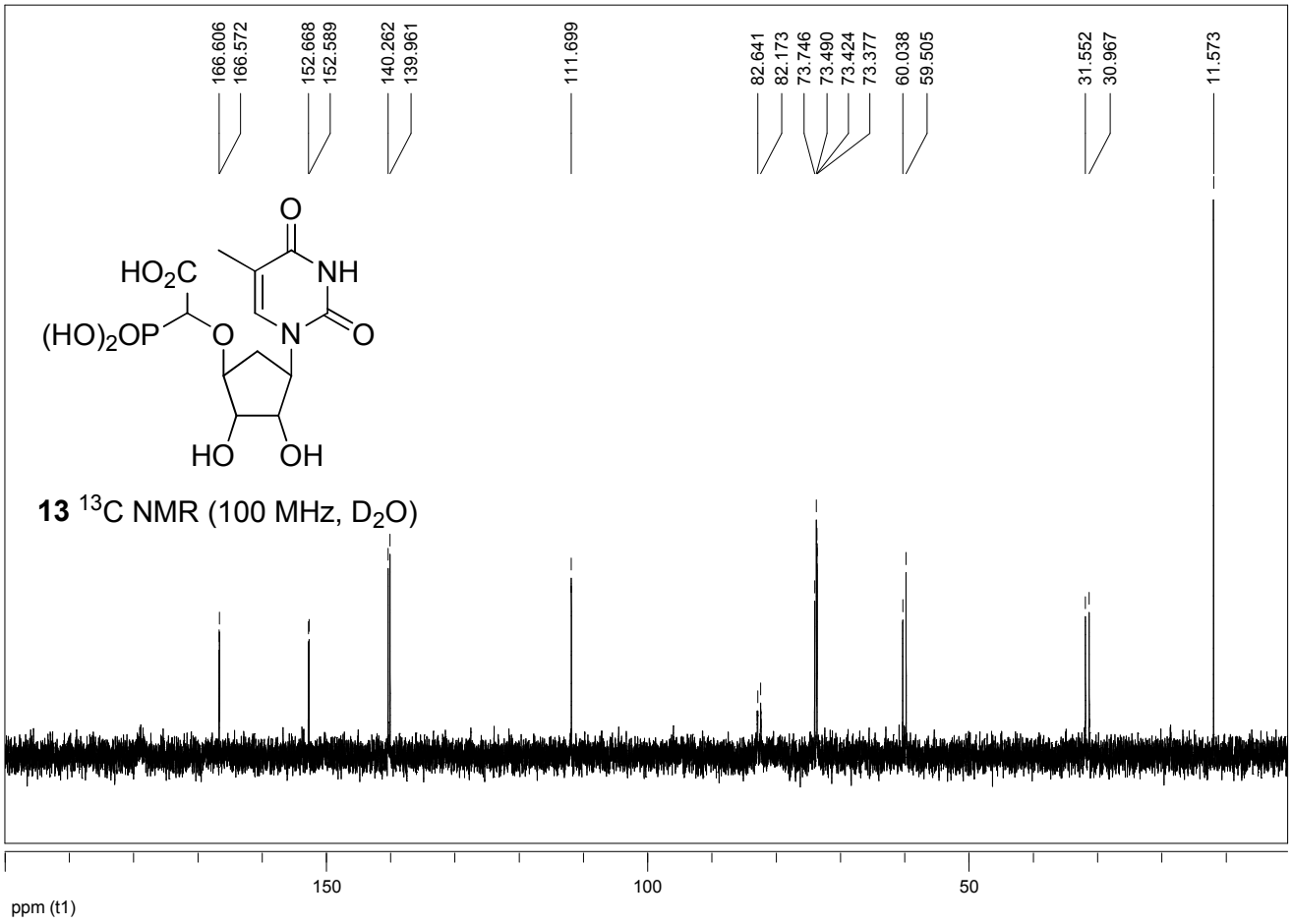
24 ^{1}H NMR (400 MHz, $CDCl_3$)



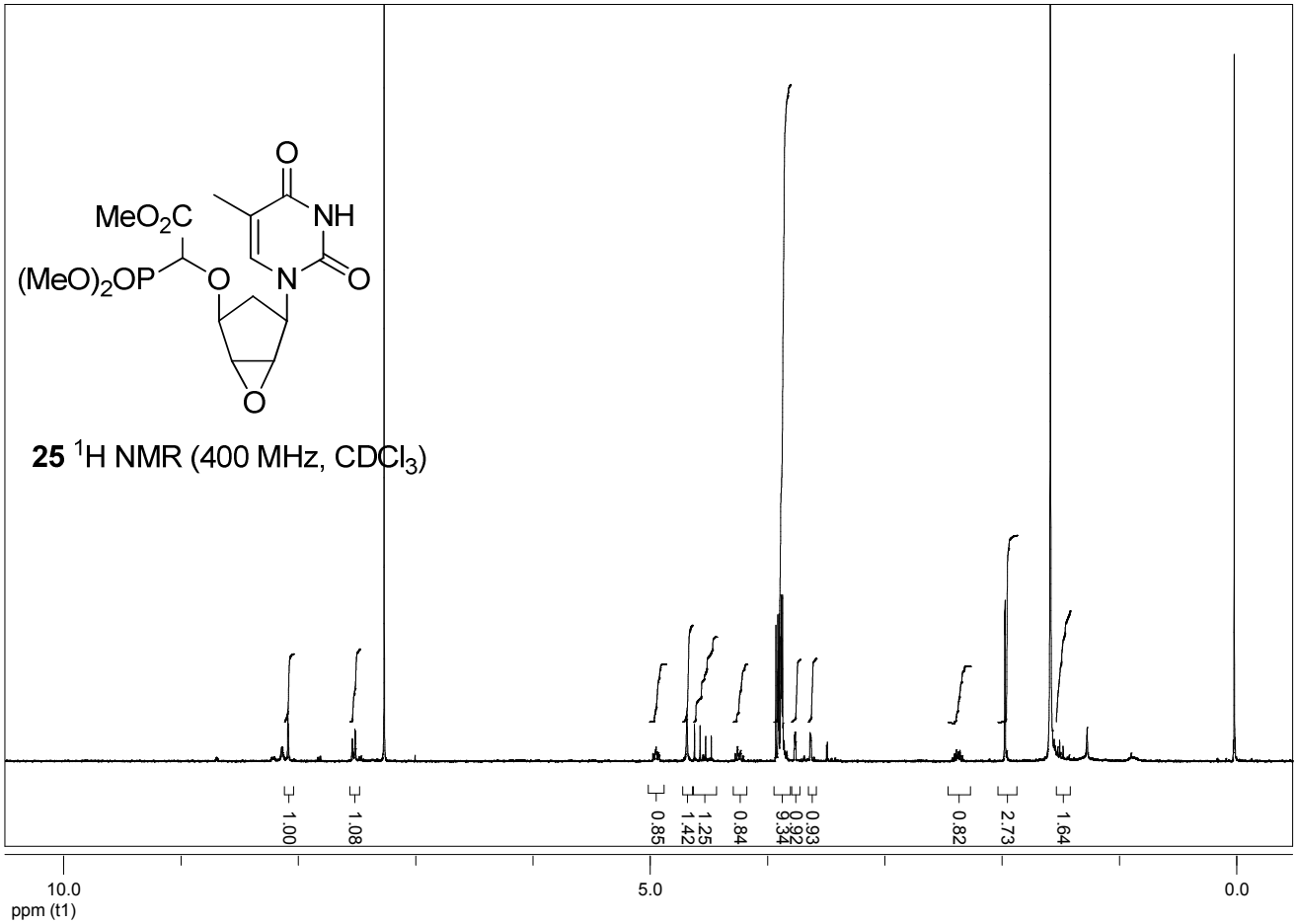
24 ^{13}C NMR (150 MHz, $CDCl_3$)



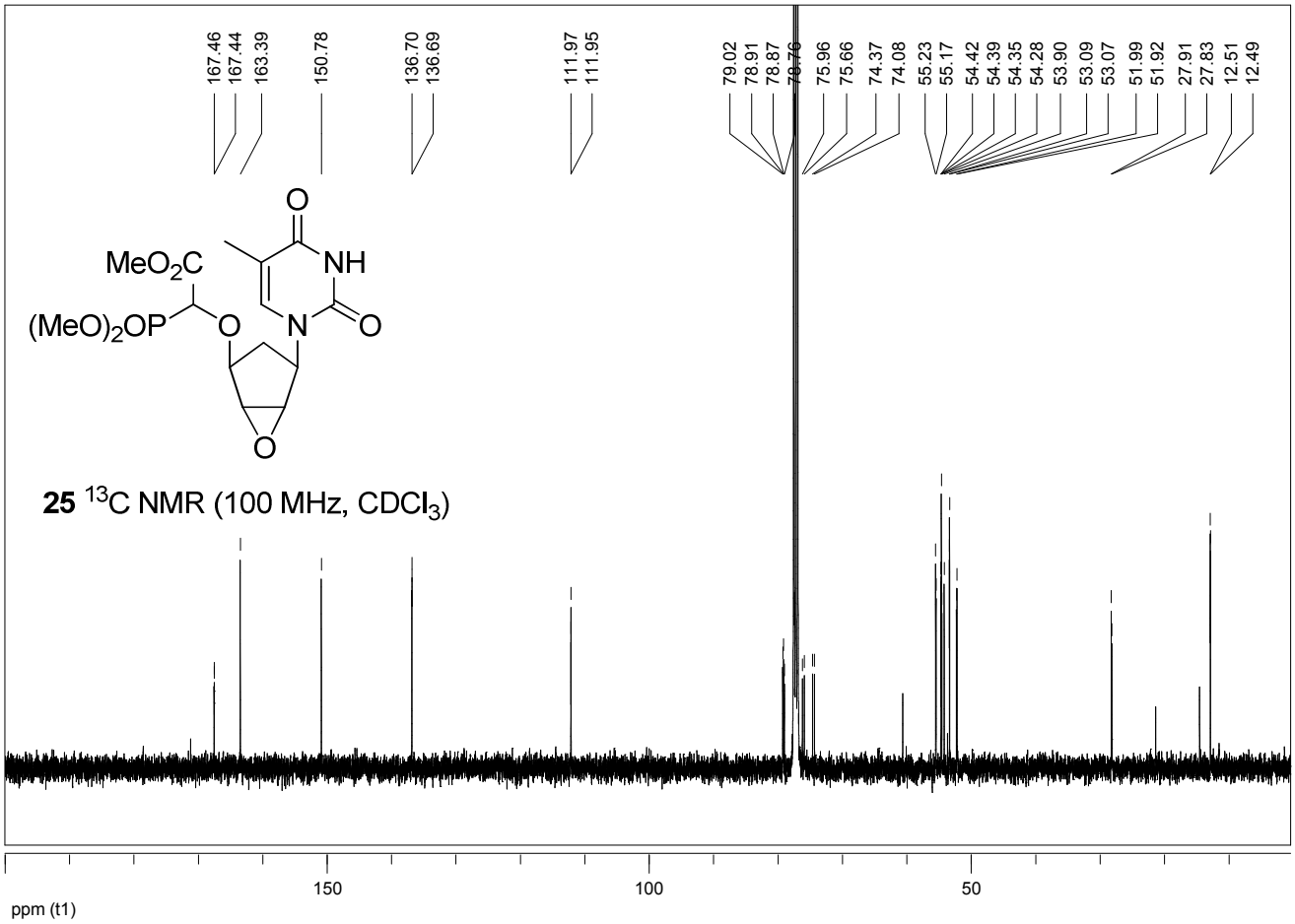
13 ^{1}H NMR (300 MHz, D_2O)



13 ^{13}C NMR (100 MHz, D_2O)



25 ^{1}H NMR (400 MHz, $CDCl_3$)



25 ^{13}C NMR (100 MHz, $CDCl_3$)