Supporting Information

A Chelating Nucleophile Plays a Starring Role: 1,8-Naphthyridine Catalyzed Polycomponent α,α-Difluorination of Acid Chlorides

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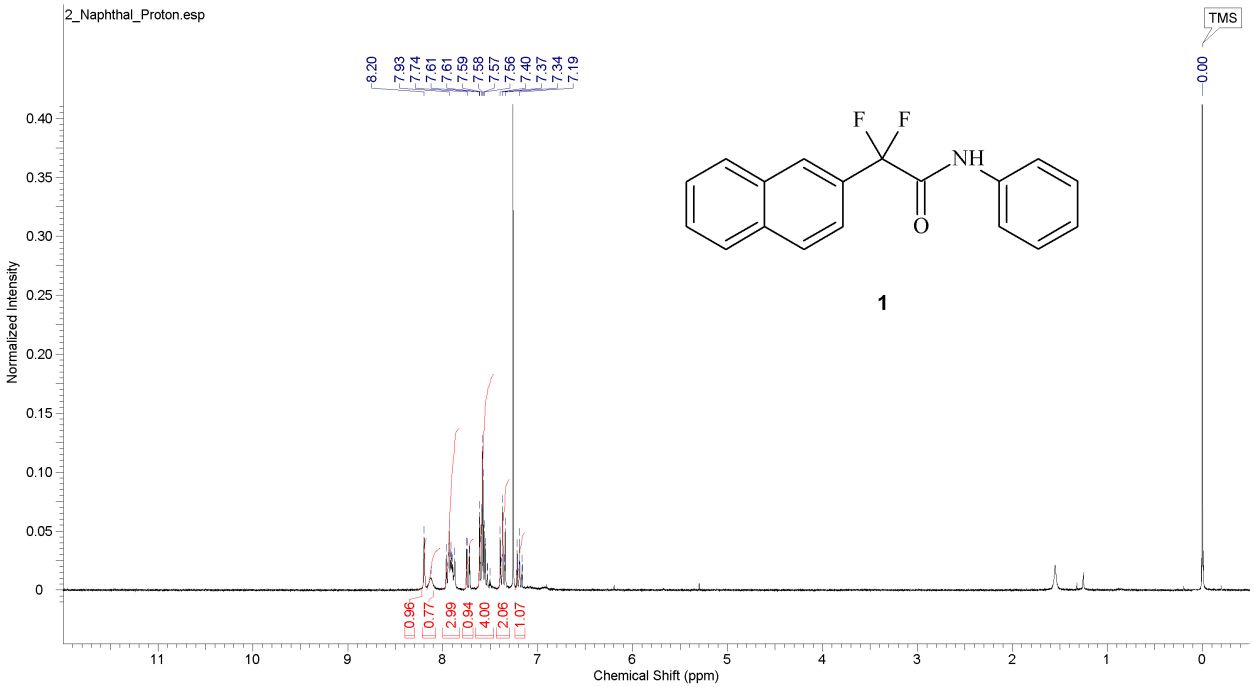
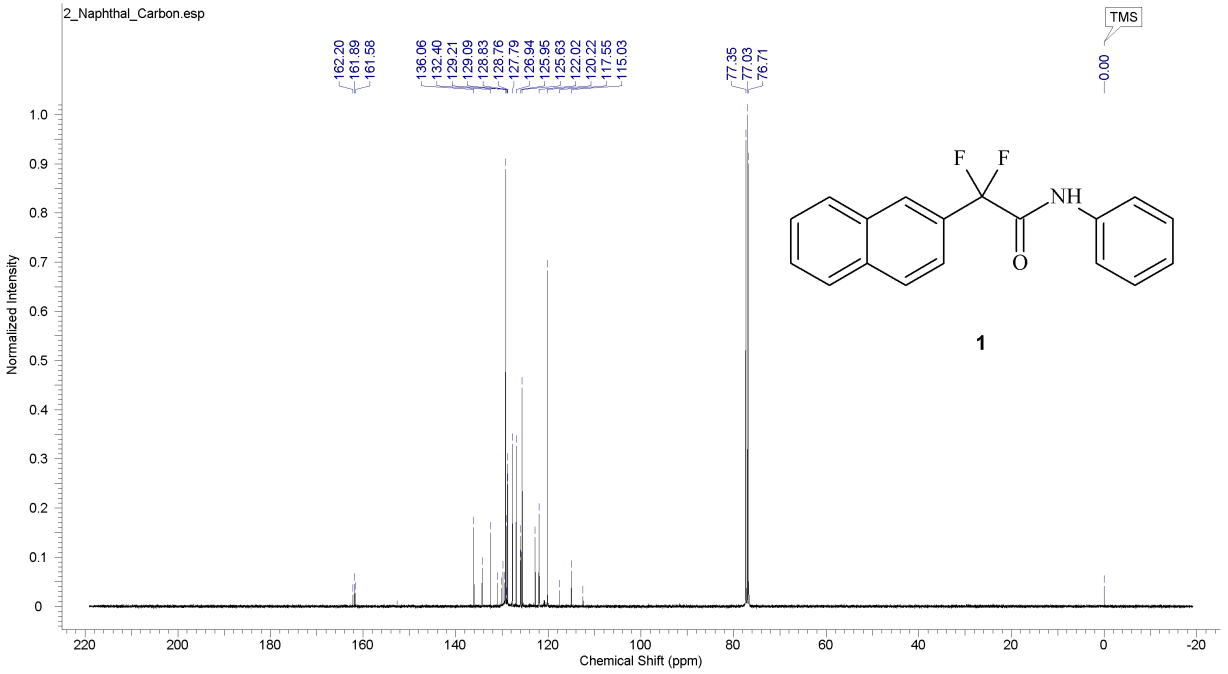
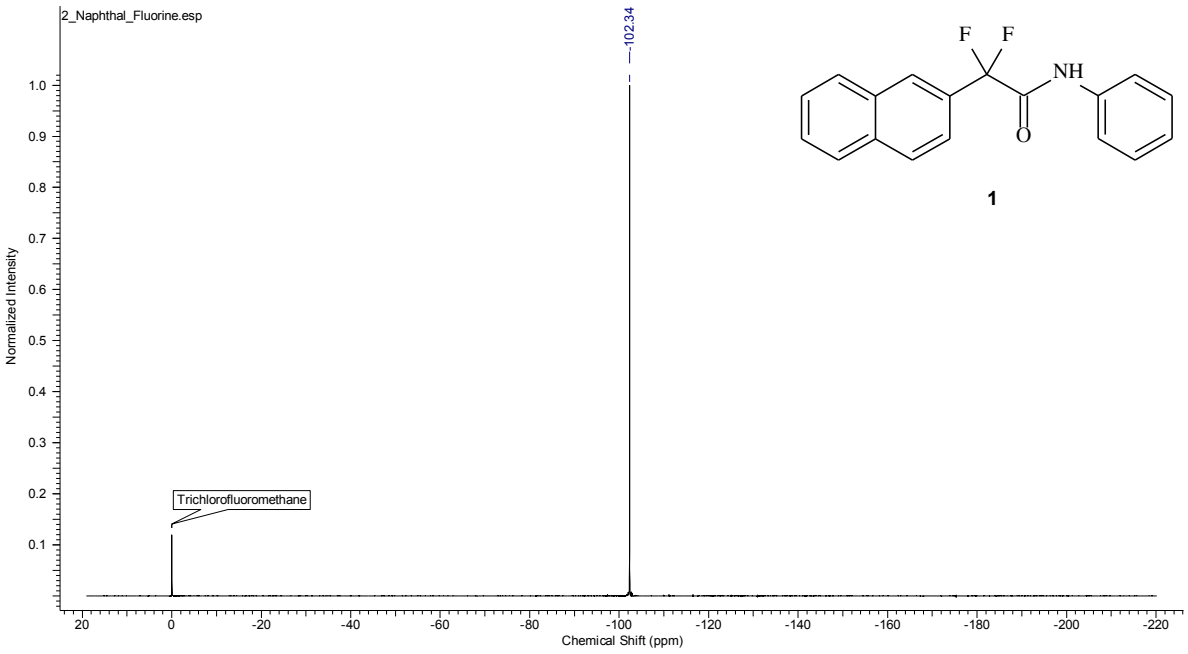
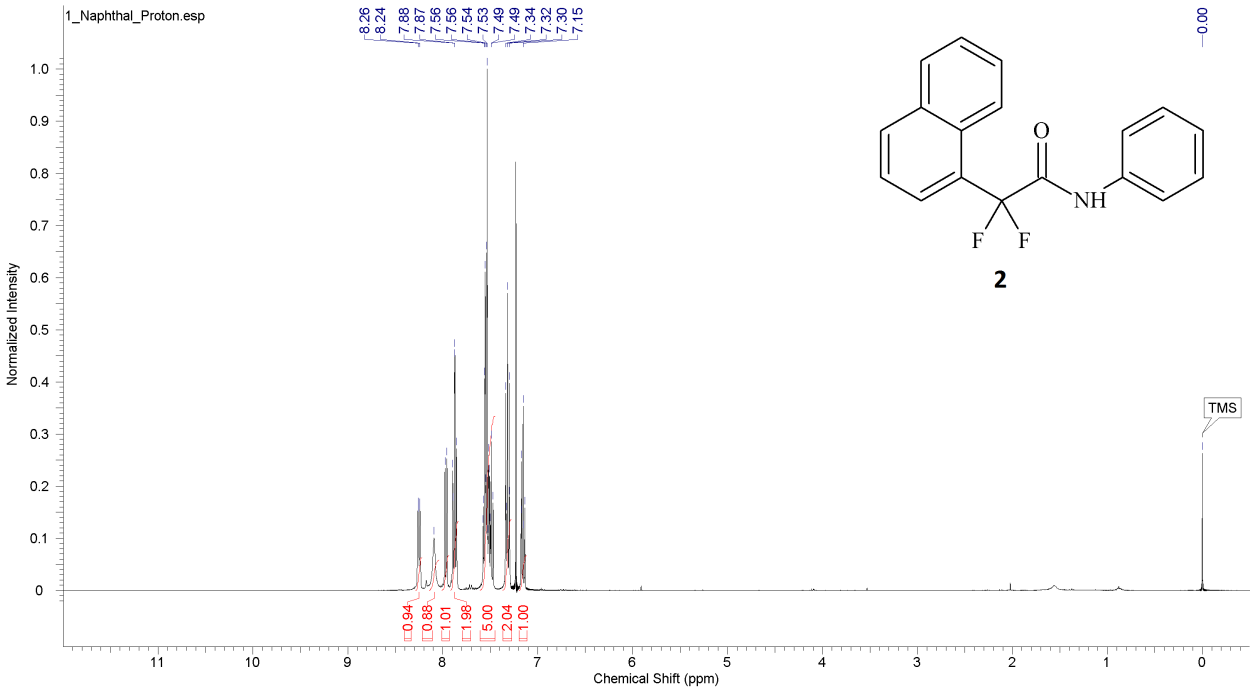
2,2-difluoro-2-(naphthalen-2-yl)-*N*-phenylacetamide (1)

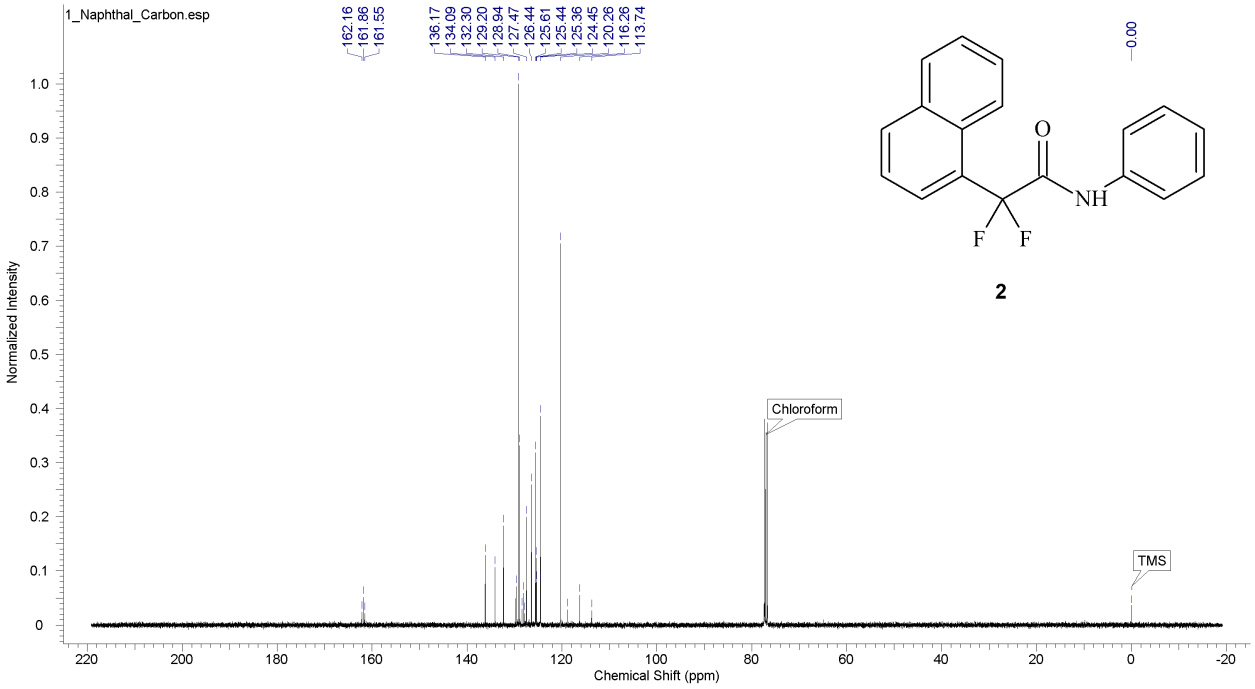




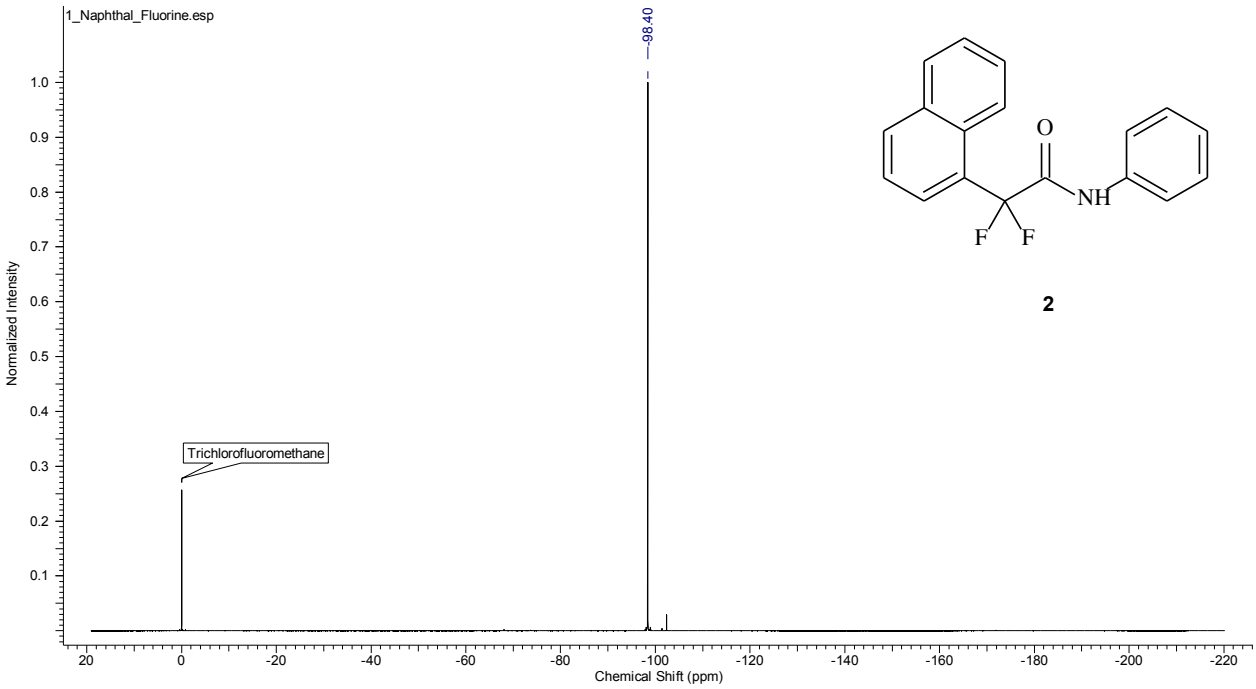


2,2-difluoro-2-(naphthalen-1-yl)-*N*-phenylacetamide (2)



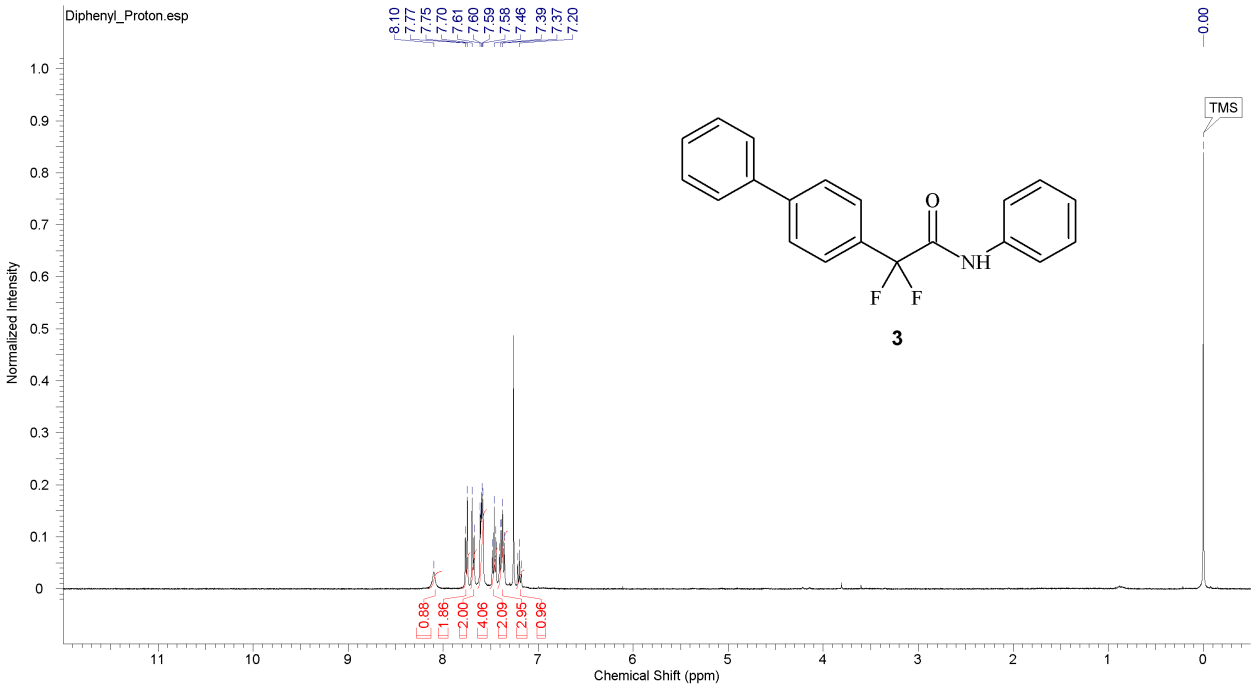

1_Naphthal_Carbon.esp
162.16
161.86
161.55
136.17
134.09
132.30
129.20
128.94
127.47
126.44
125.61
125.44
125.36
124.45
120.26
116.26
113.74
0.00
Chloroform
TMS
Normalized Intensity
Chemical Shift (ppm)
O
NH
F F

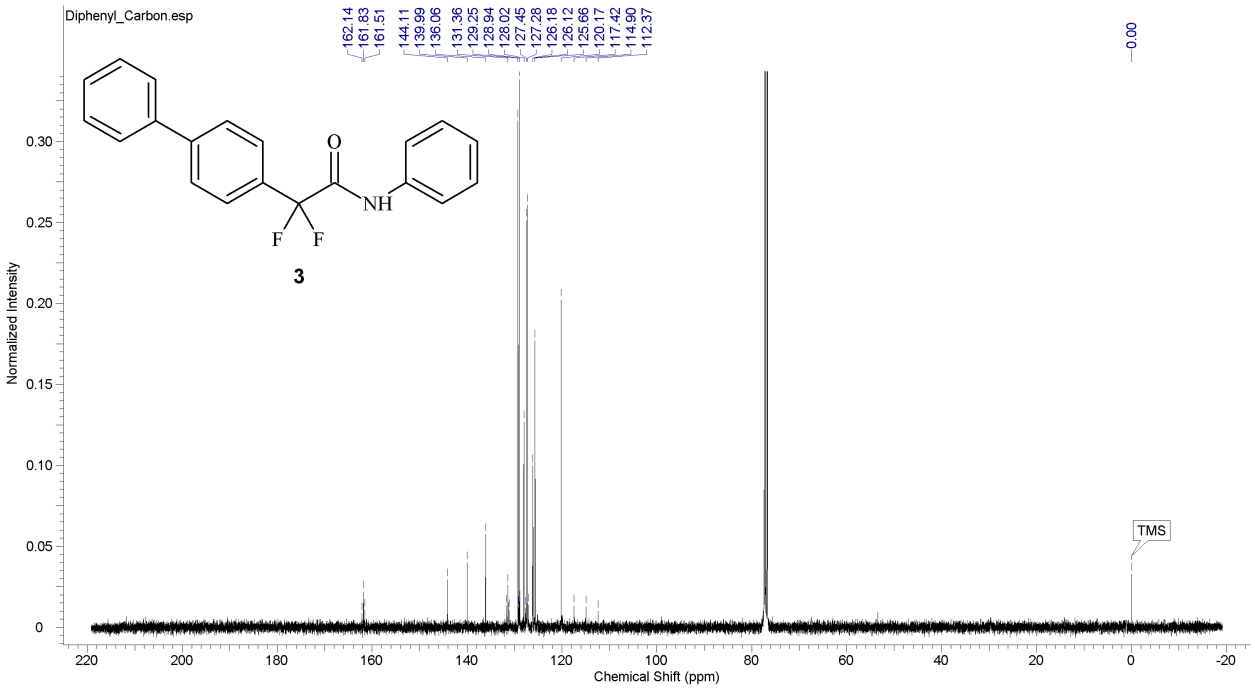
2

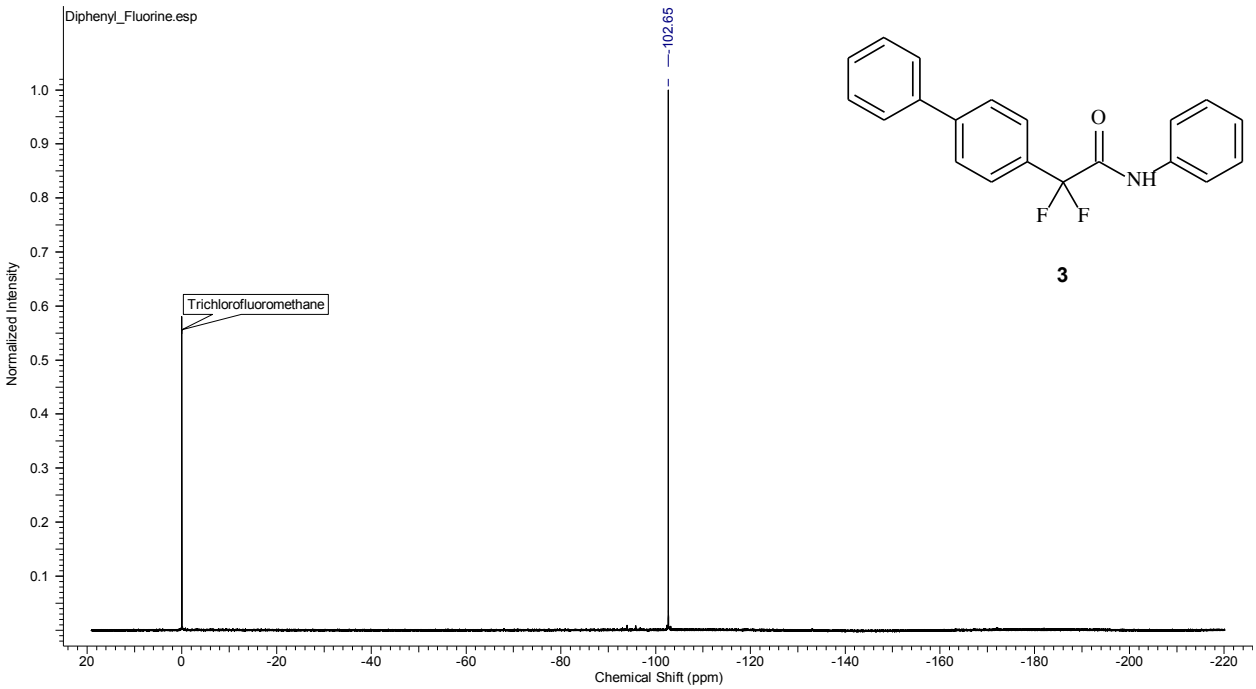

1_Naphthal_Fluorine.esp
-98.40
Trichlorofluoromethane
Normalized Intensity
Chemical Shift (ppm)
O
NH
F F

2

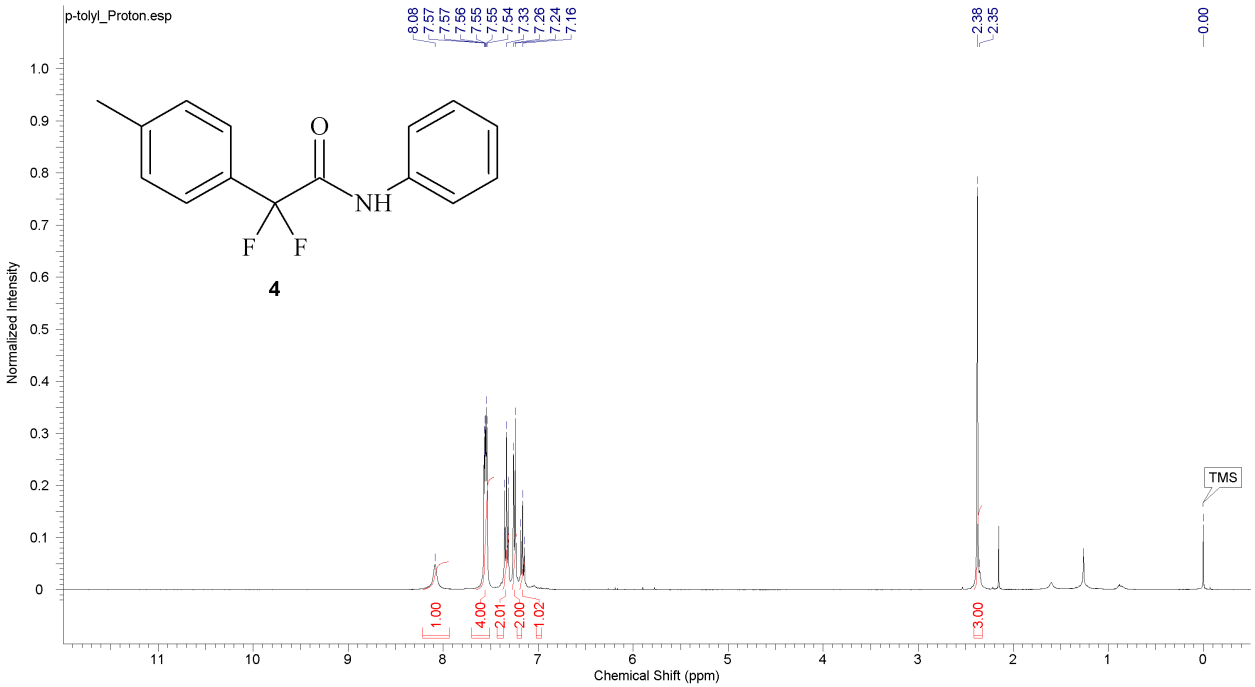
2-([1,1'-biphenyl]-4-yl)-2,2-difluoro-*N*-phenylacetamide (3)

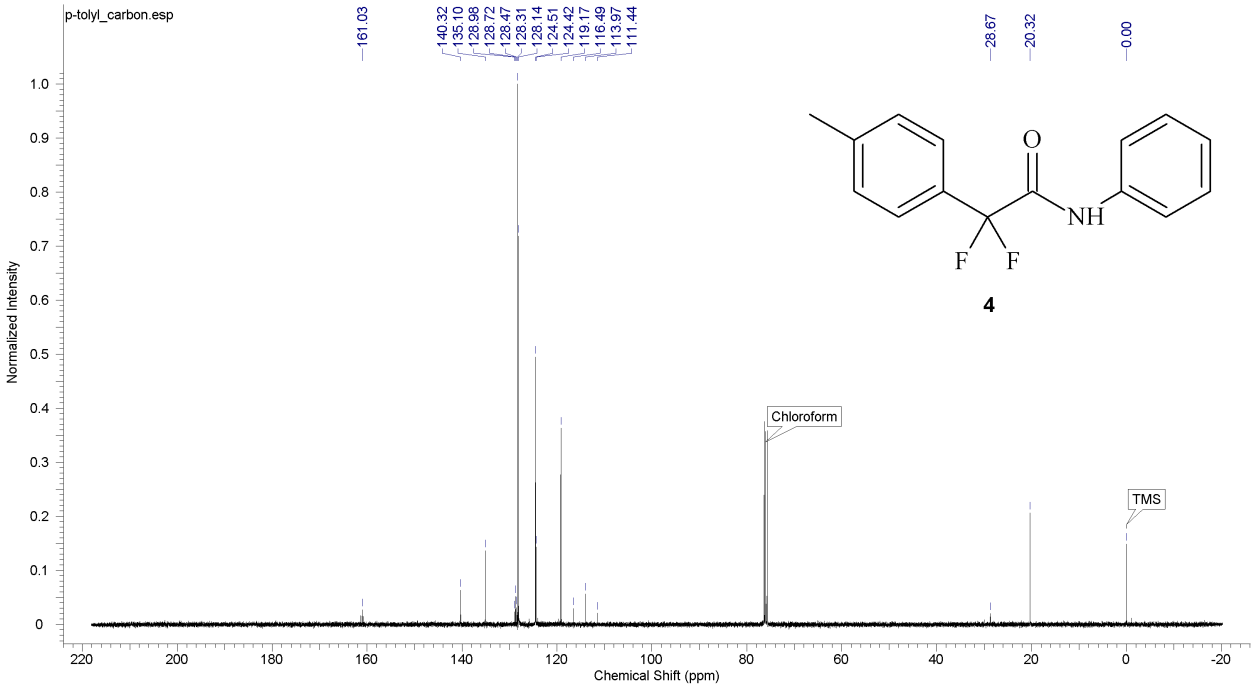


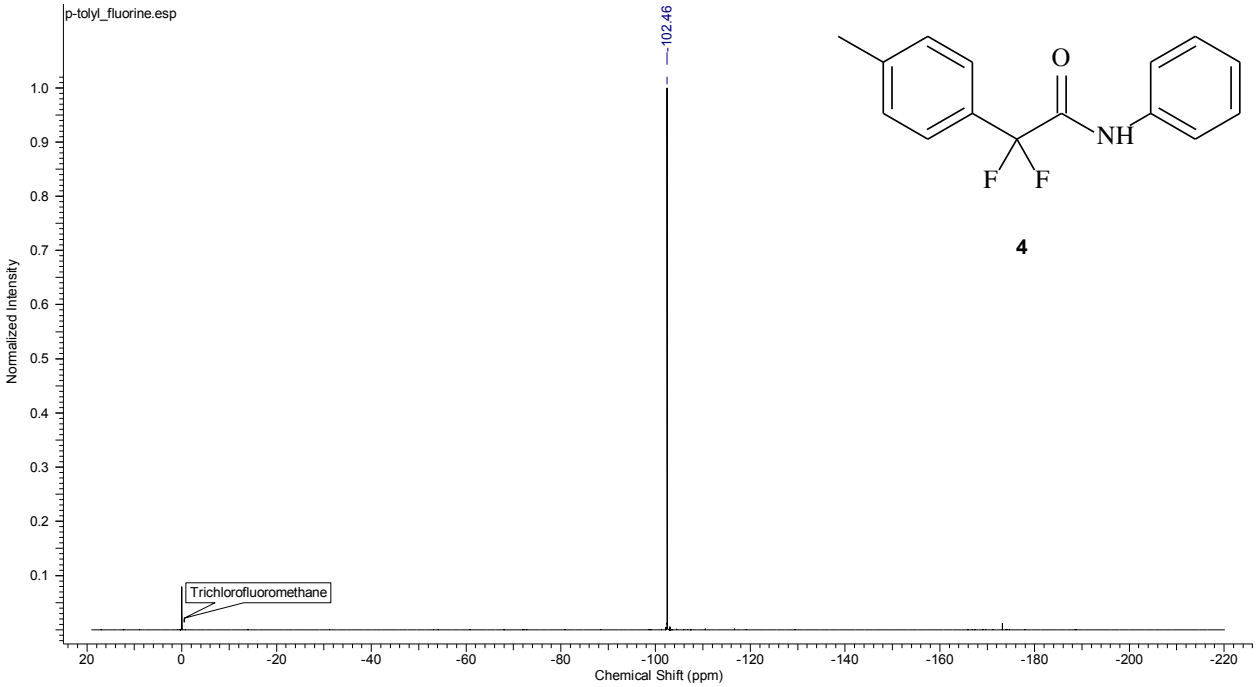




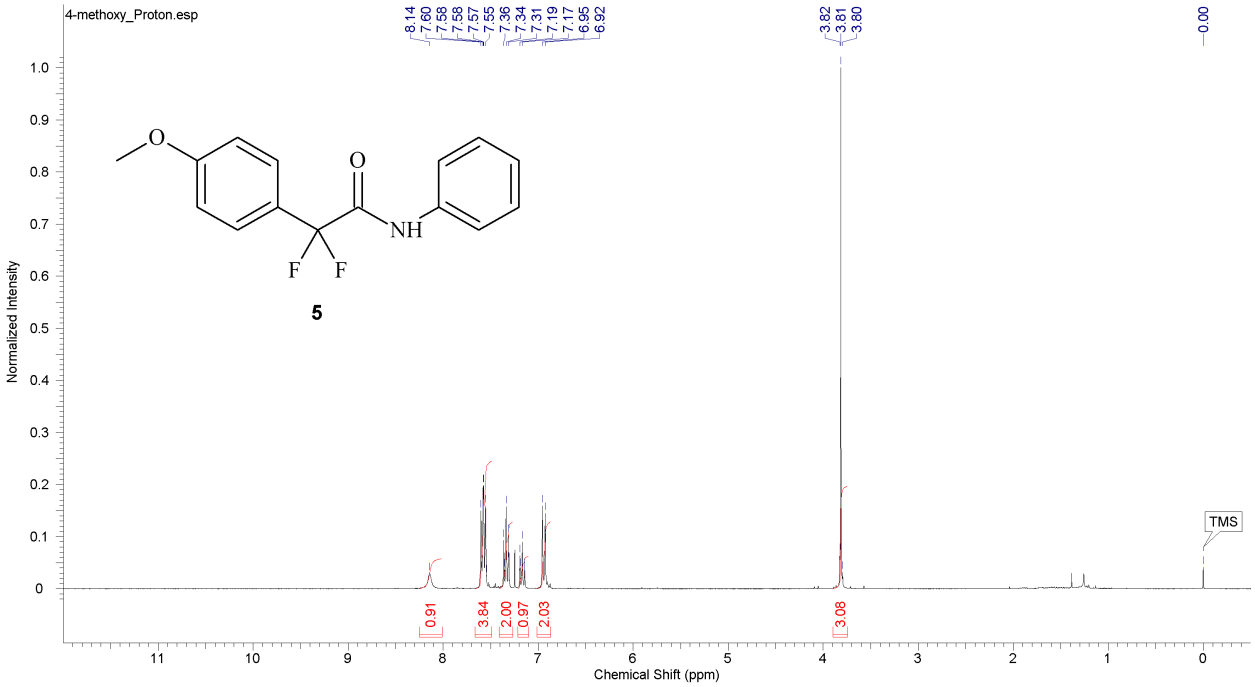
2,2-difluoro-*N*-phenyl-2-(*p*-tolyl)acetamide (4)

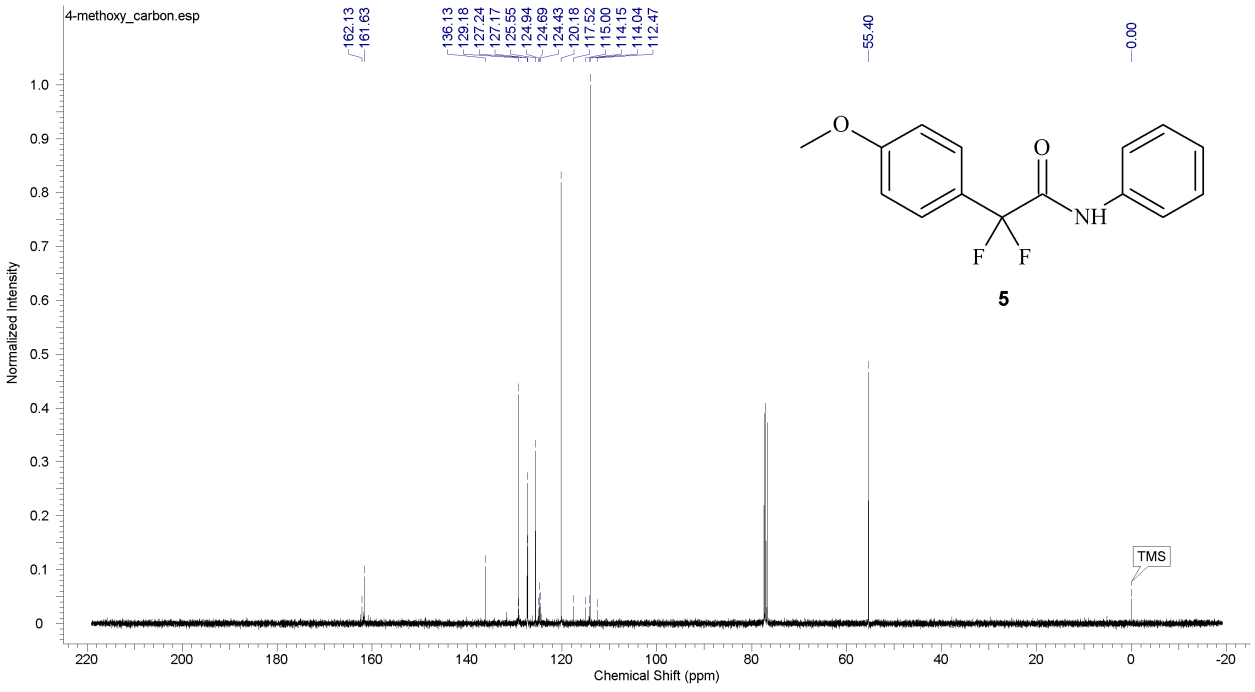


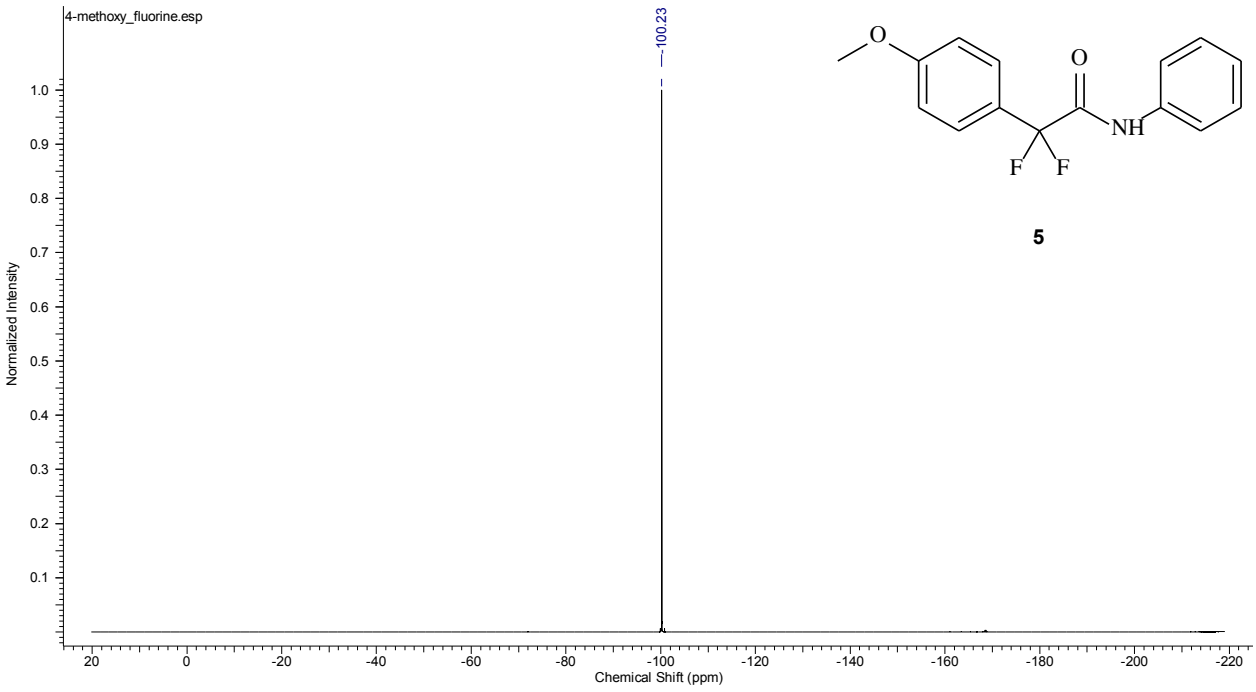

p-tolyl_carbon.esp
161.03
140.32
135.10
128.98
128.72
128.47
128.31
128.14
124.51
124.42
119.17
116.49
113.97
111.44
28.67
20.32
0.00
Normalized Intensity
Chemical Shift (ppm)
Chloroform
TMS
O
NH
F
F
4


p-tolyl_fluorine.esp
102.46
Normalized Intensity
Chemical Shift (ppm)
Trichlorofluoromethane
O
NH
F
F
4

2,2-difluoro-2-(4-methoxyphenyl)-*N*-phenylacetamide (5)

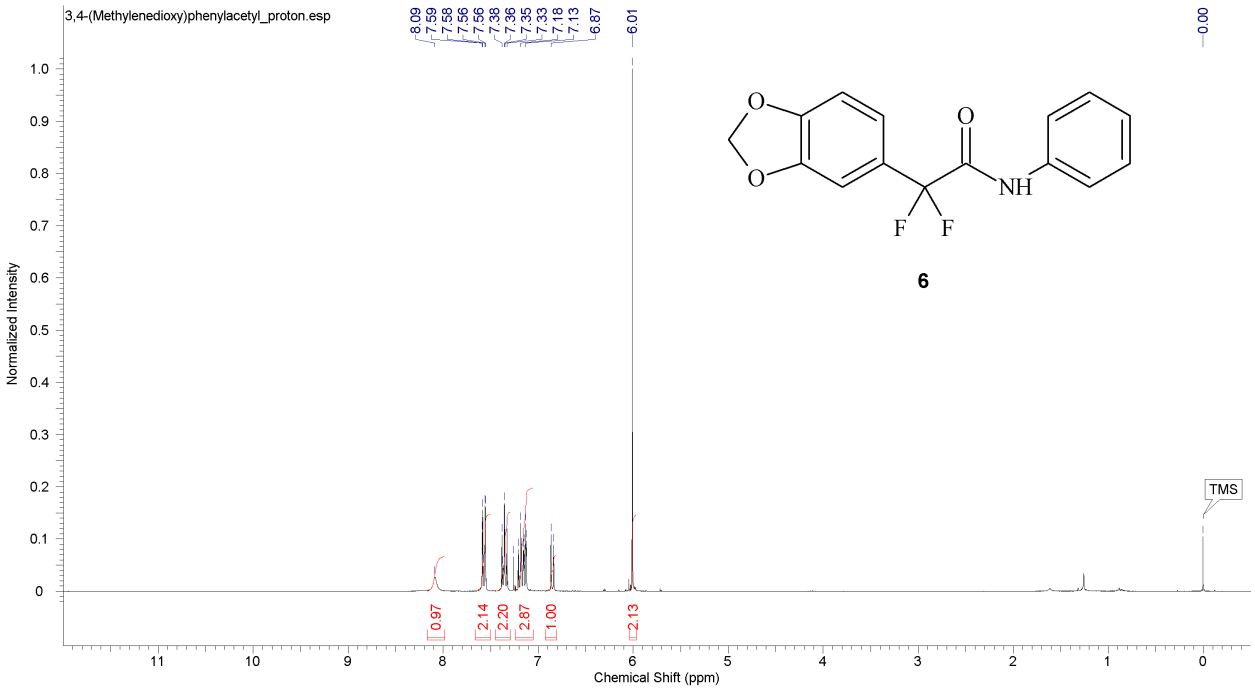




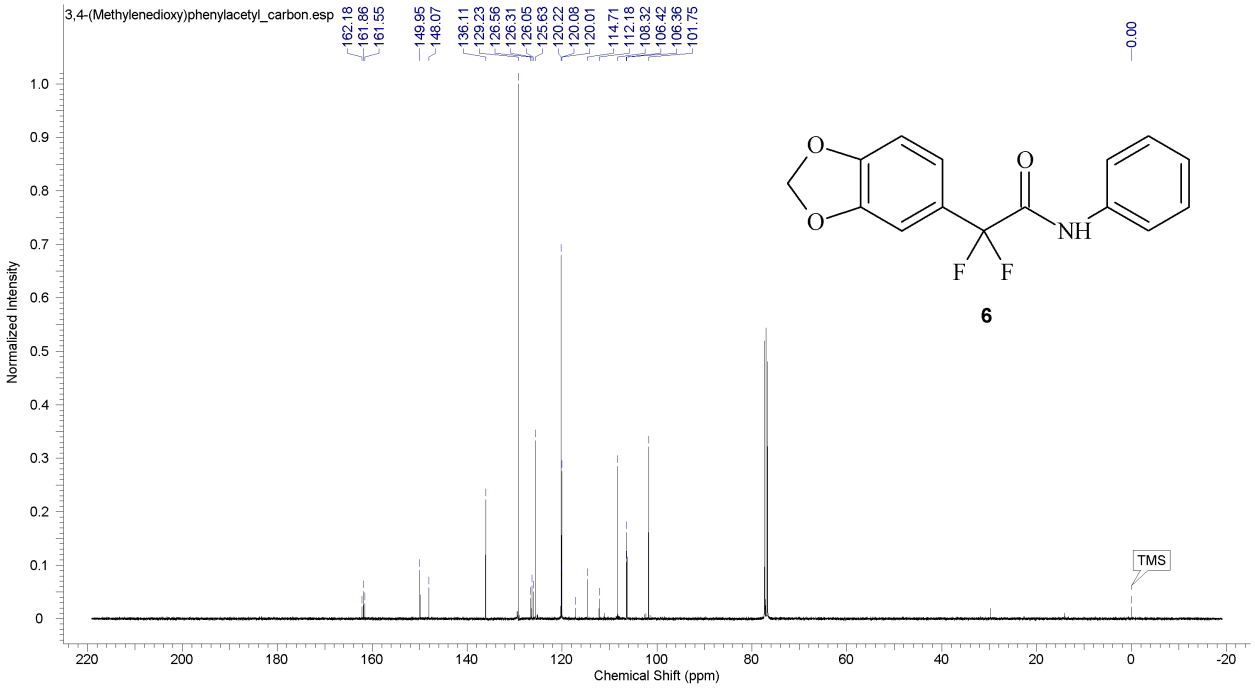


5

2-(benzo[*d*][1,3]dioxol-5-yl)-2,2-difluoro-*N*-phenylacetamide (6)

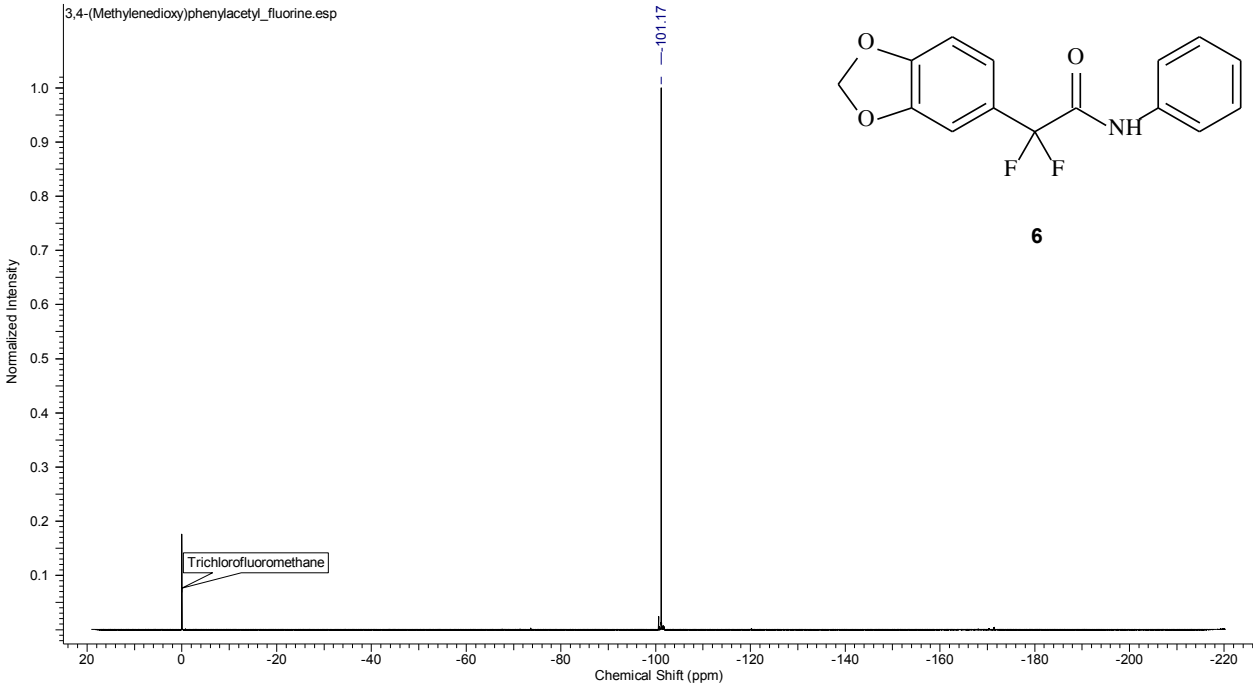


6


3,4-(Methylenedioxy)phenylacetyl_carbon.esp
162.18
161.86
161.55
149.95
148.07
136.11
129.23
126.56
126.31
126.05
125.63
120.22
120.08
120.01
114.71
112.18
108.32
106.42
106.36
101.75
0.00
TMS
Normalized Intensity
Chemical Shift (ppm)

O
O
O
NH
F
F

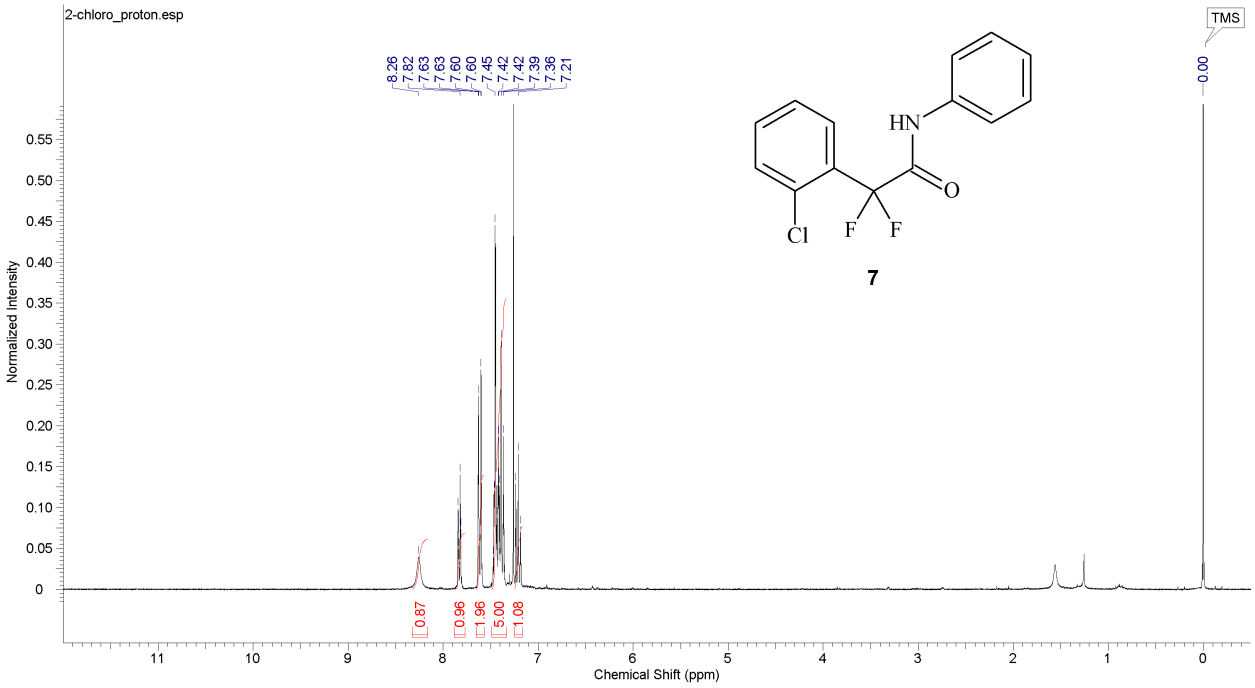
6

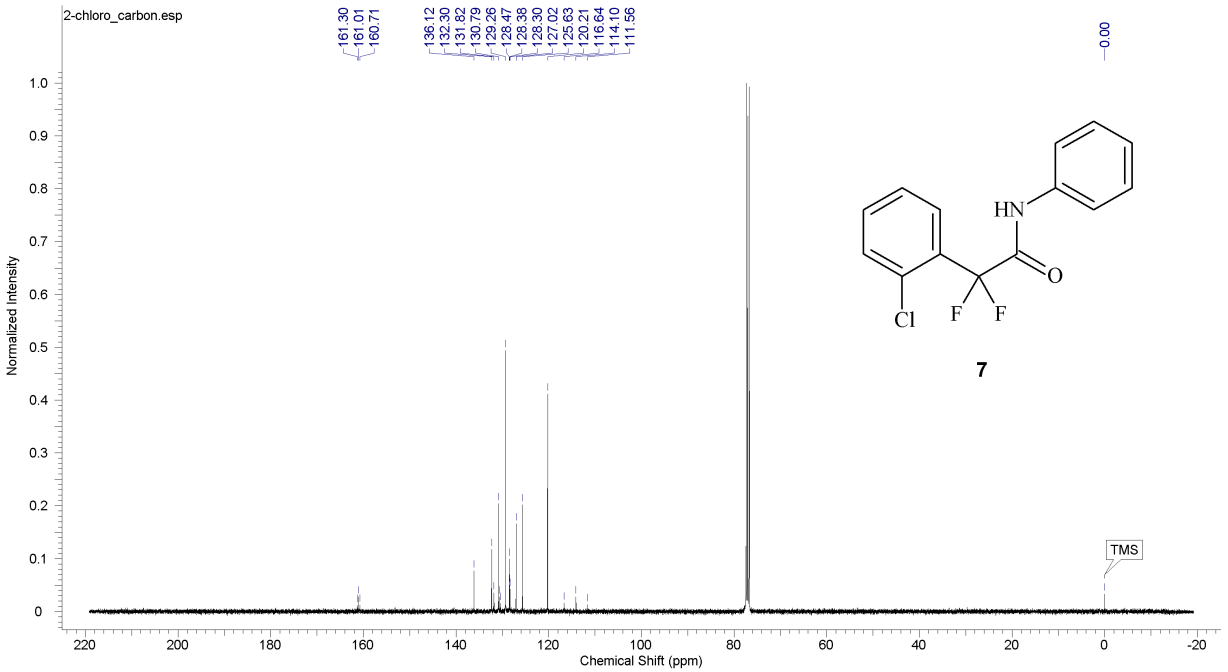

3,4-(Methylenedioxy)phenylacetyl_fluorine.esp
101.17
Trichlorofluoromethane
Normalized Intensity
Chemical Shift (ppm)

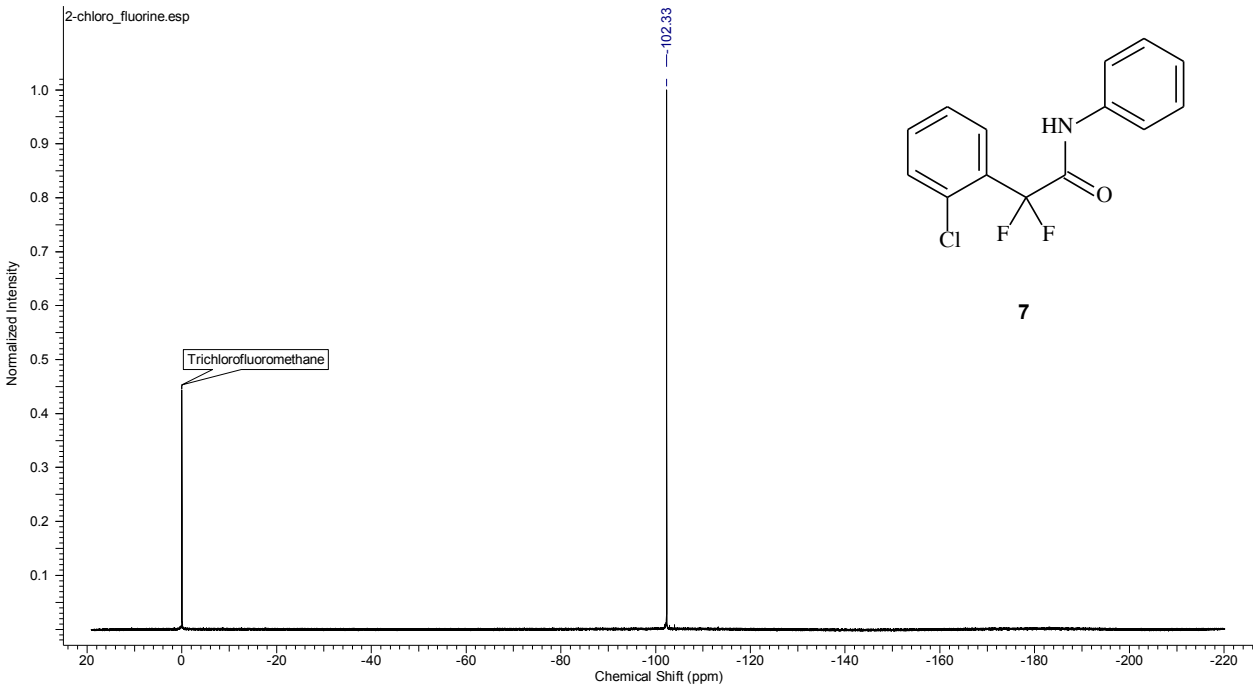
O
O
O
NH
F
F

6

2-(2-chlorophenyl)-2,2-difluoro-*N*-phenylacetamide (7)

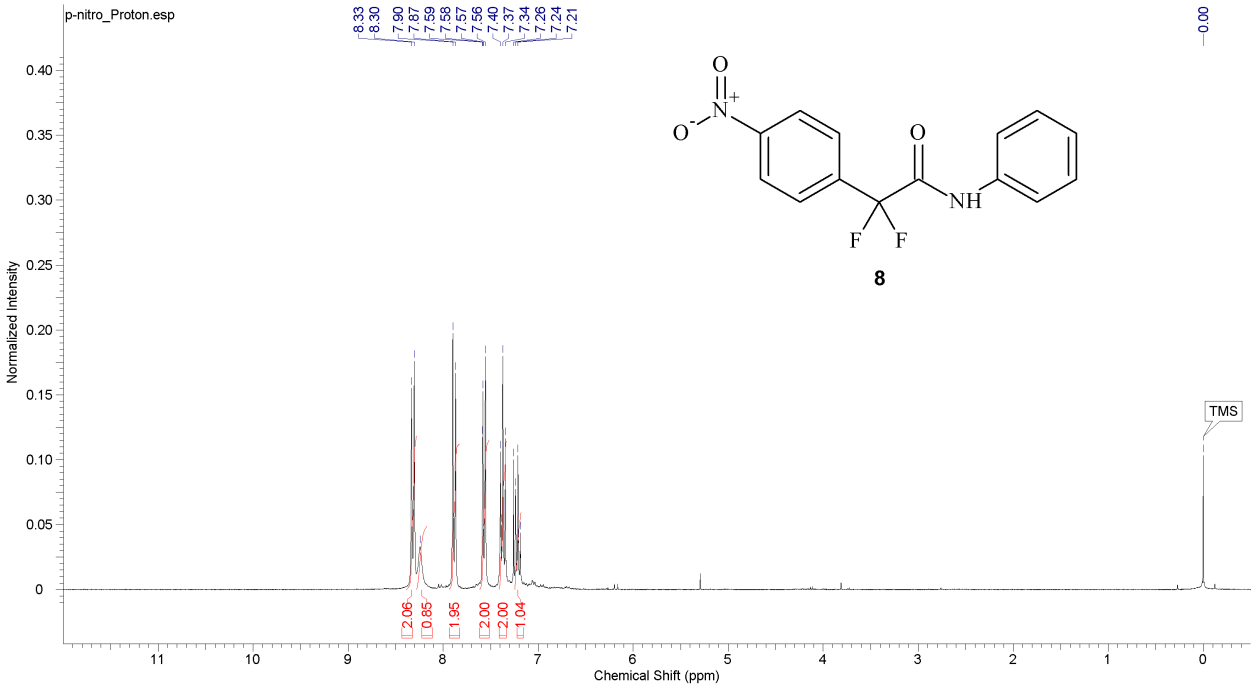




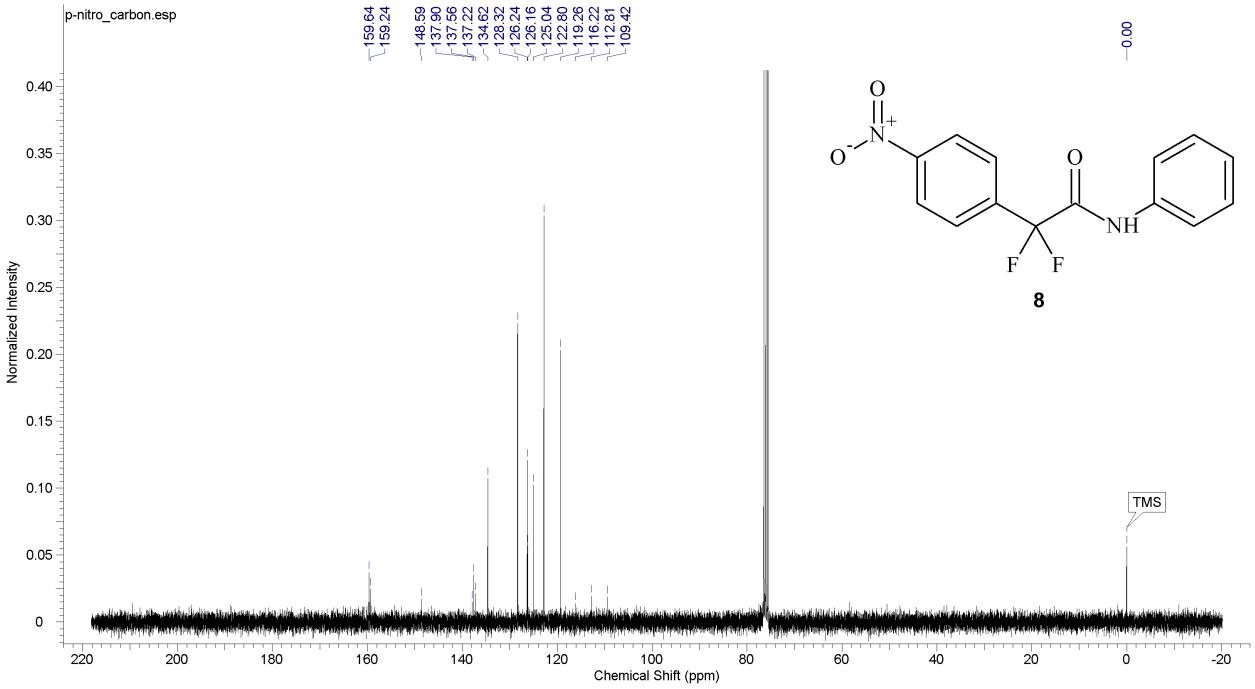


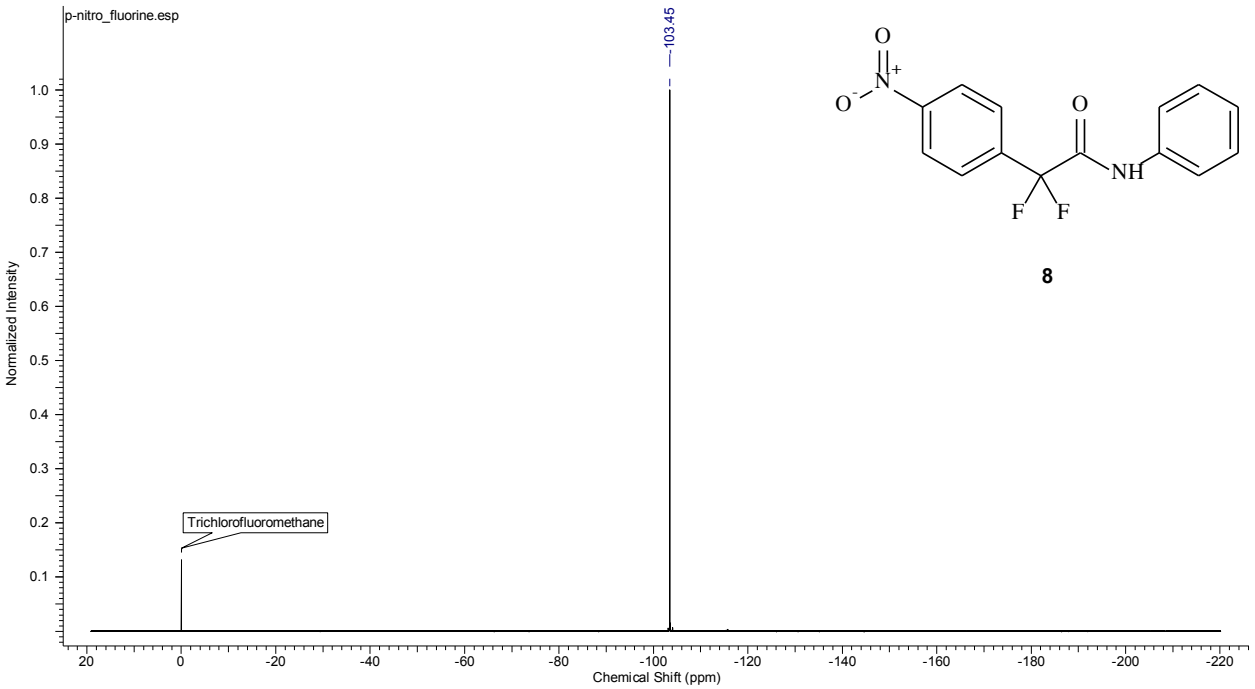
7

2,2-difluoro-2-(4-nitrophenyl)-*N*-phenylacetamide (8)

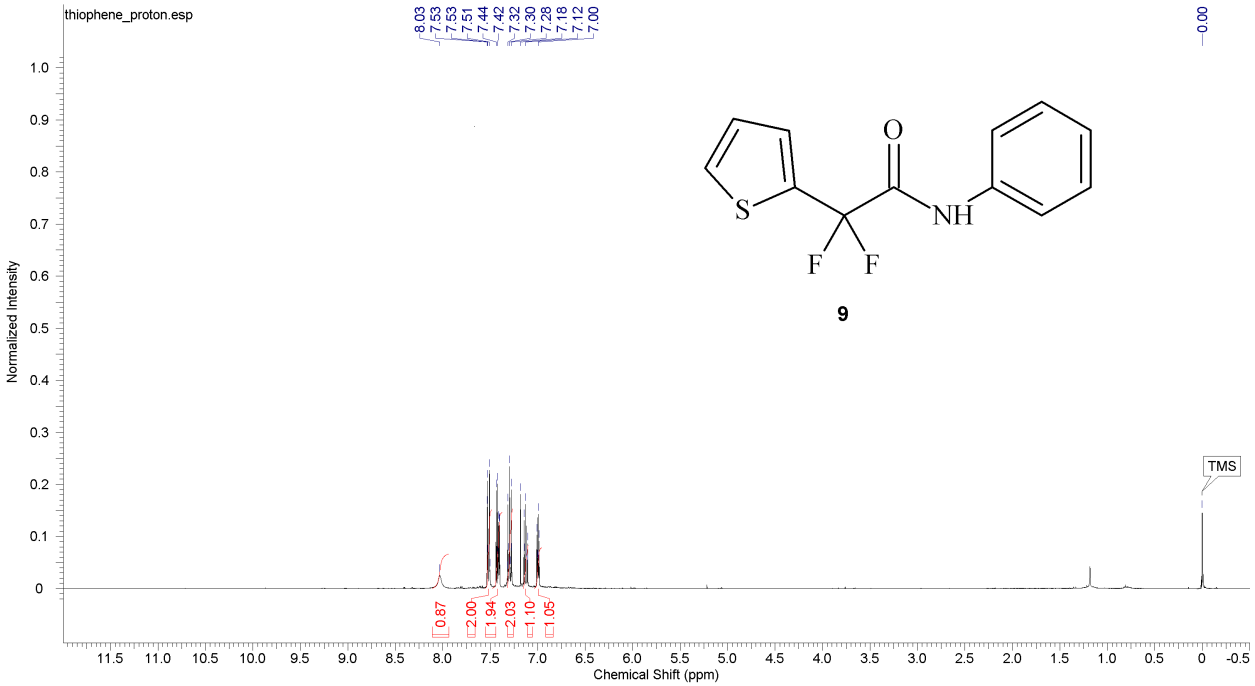


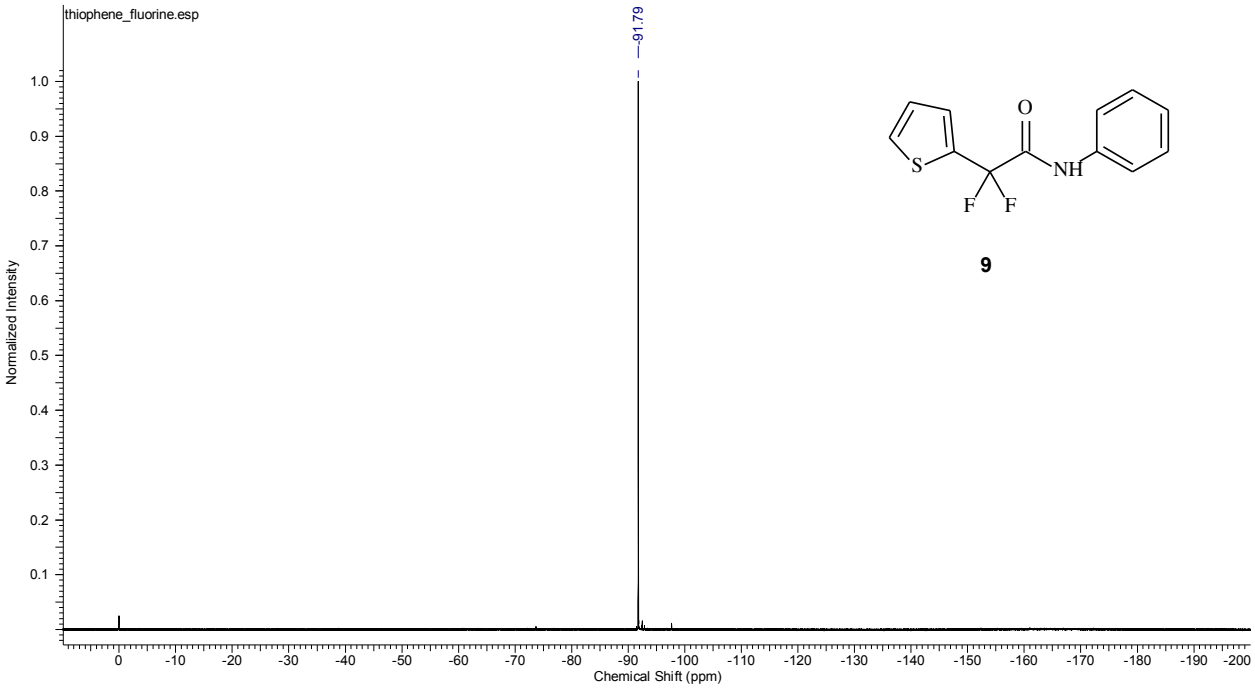
8


p-nitro_carbon.esp
159.64
159.24
148.59
137.90
137.56
137.22
134.62
128.32
126.24
126.16
125.04
122.80
119.26
116.22
112.81
109.42
0.00
TMS
Normalized Intensity
Chemical Shift (ppm)
8


p-nitro_fluorine.esp
103.45
Trichlorofluoromethane
Normalized Intensity
Chemical Shift (ppm)
8

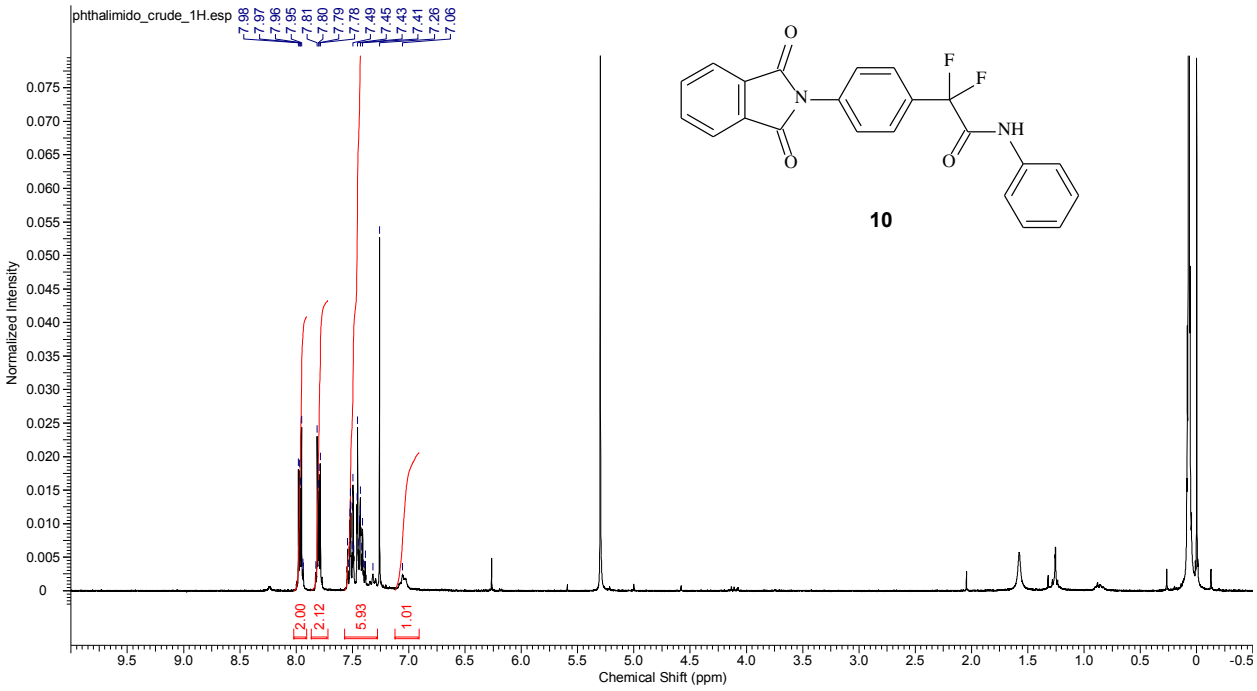
2,2-difluoro-*N*-phenyl-2-(thiophen-2-yl)acetamide (9)

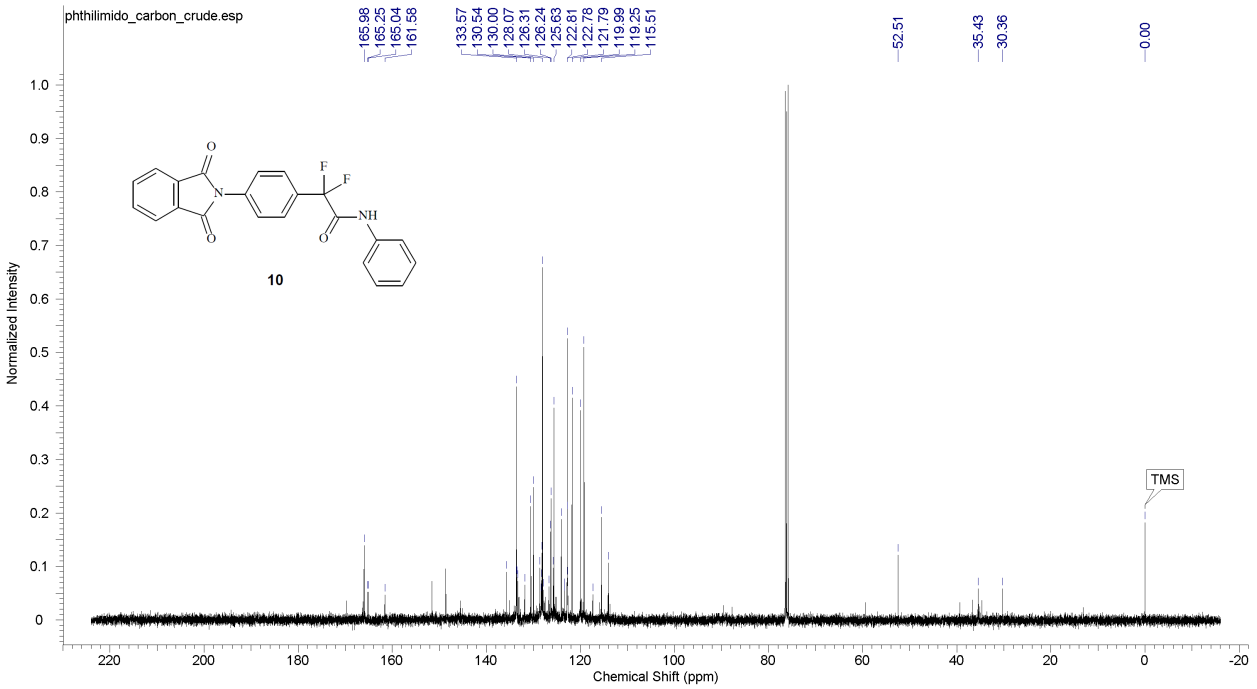


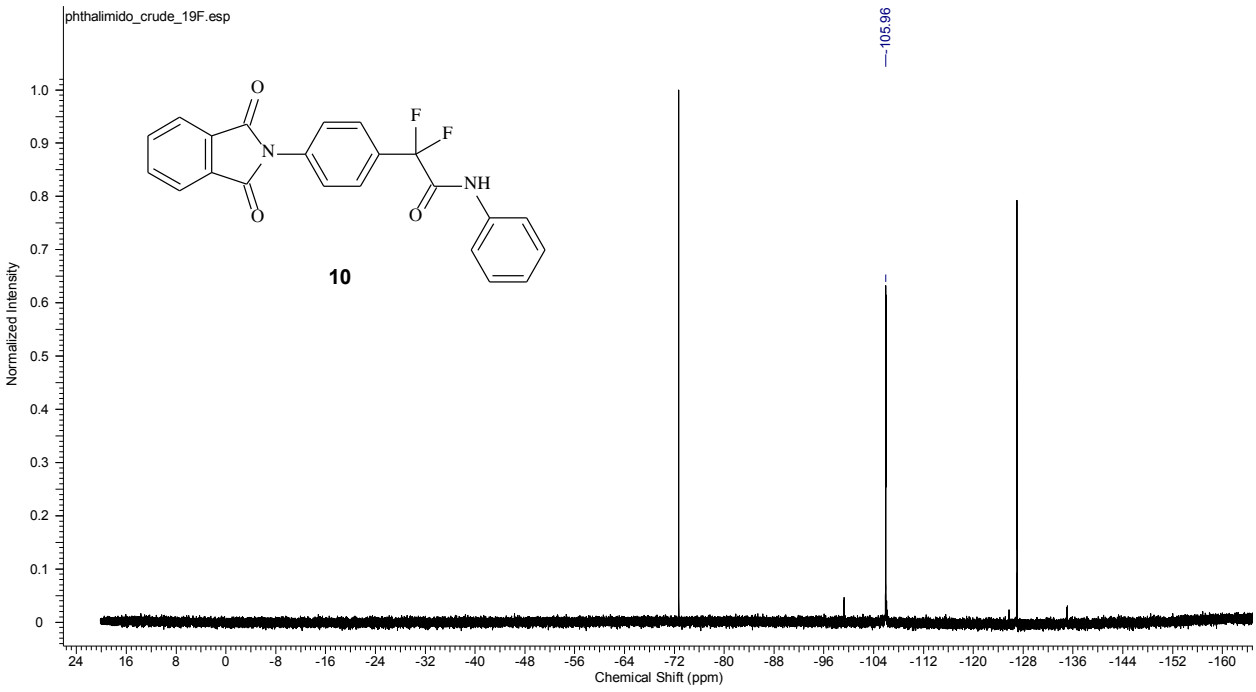


2-(4-(1,3-dioxoisoindolin-2-yl)phenyl)-2,2-difluoro-*N*-phenylacetamide (10)

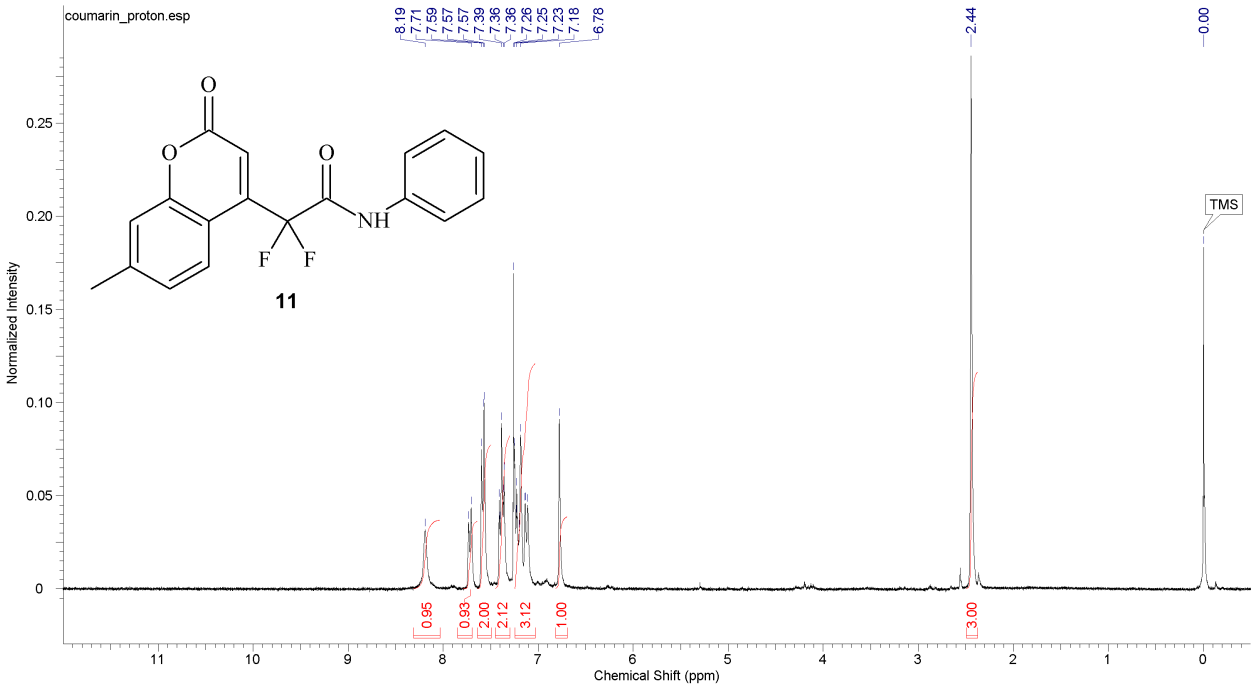
Reported as crude spectra due to product instability

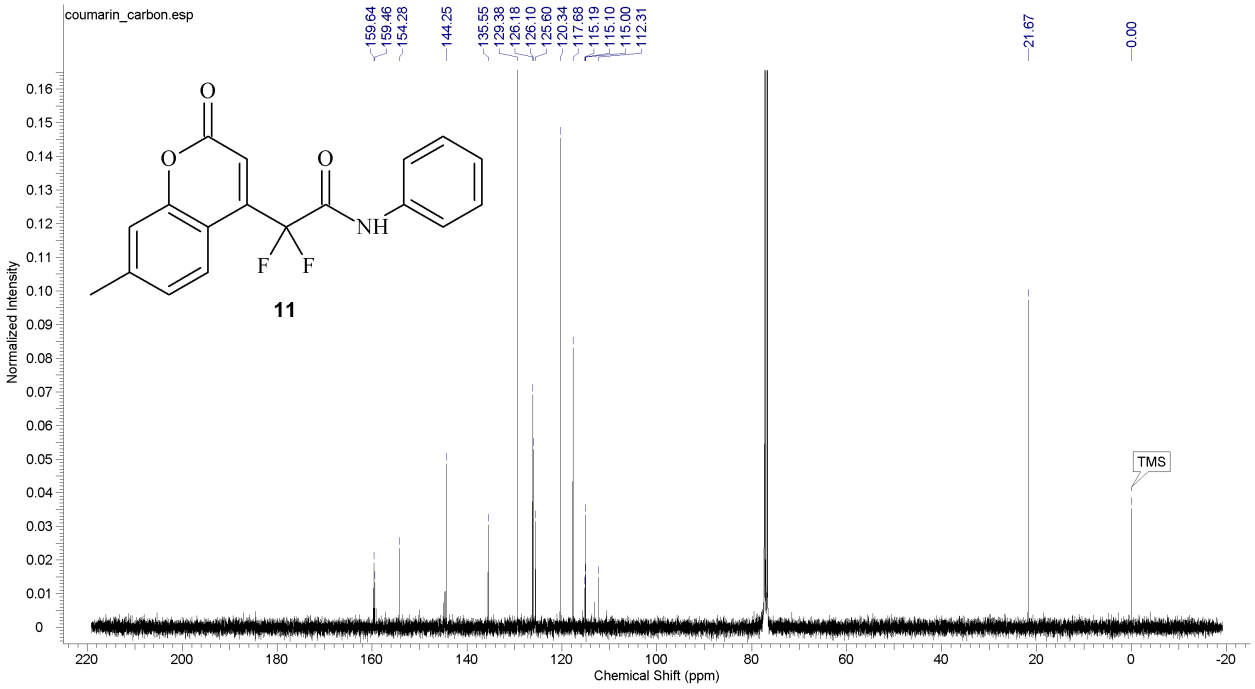


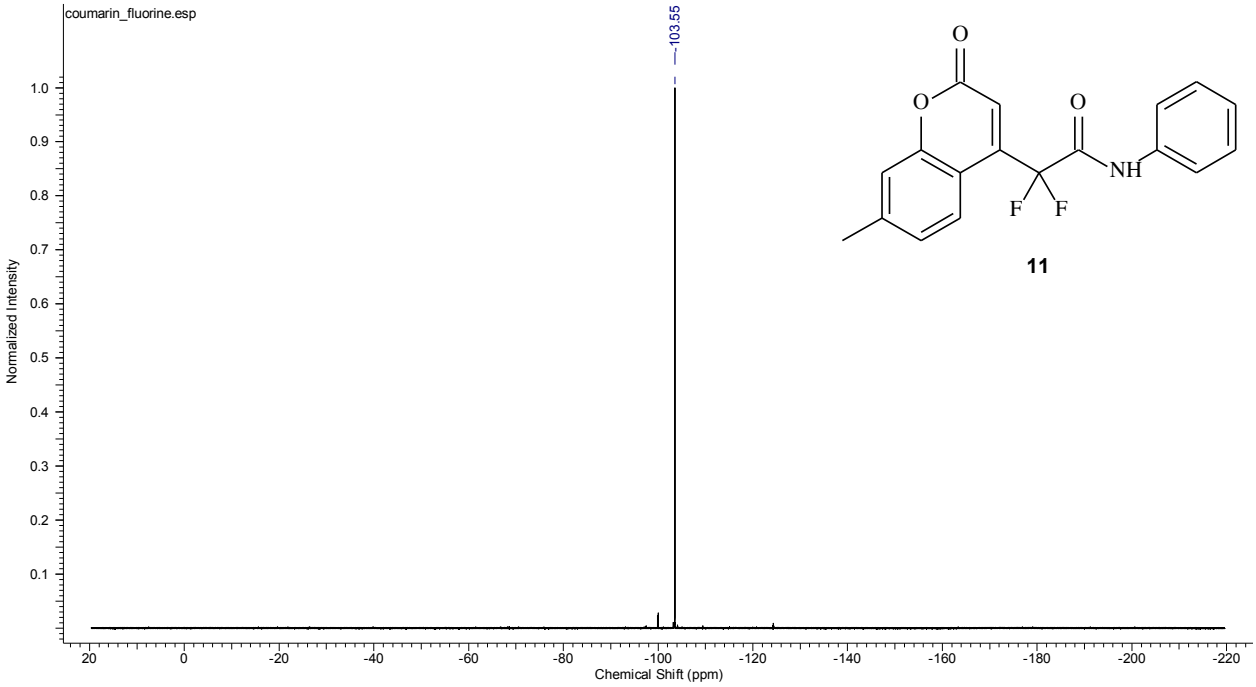




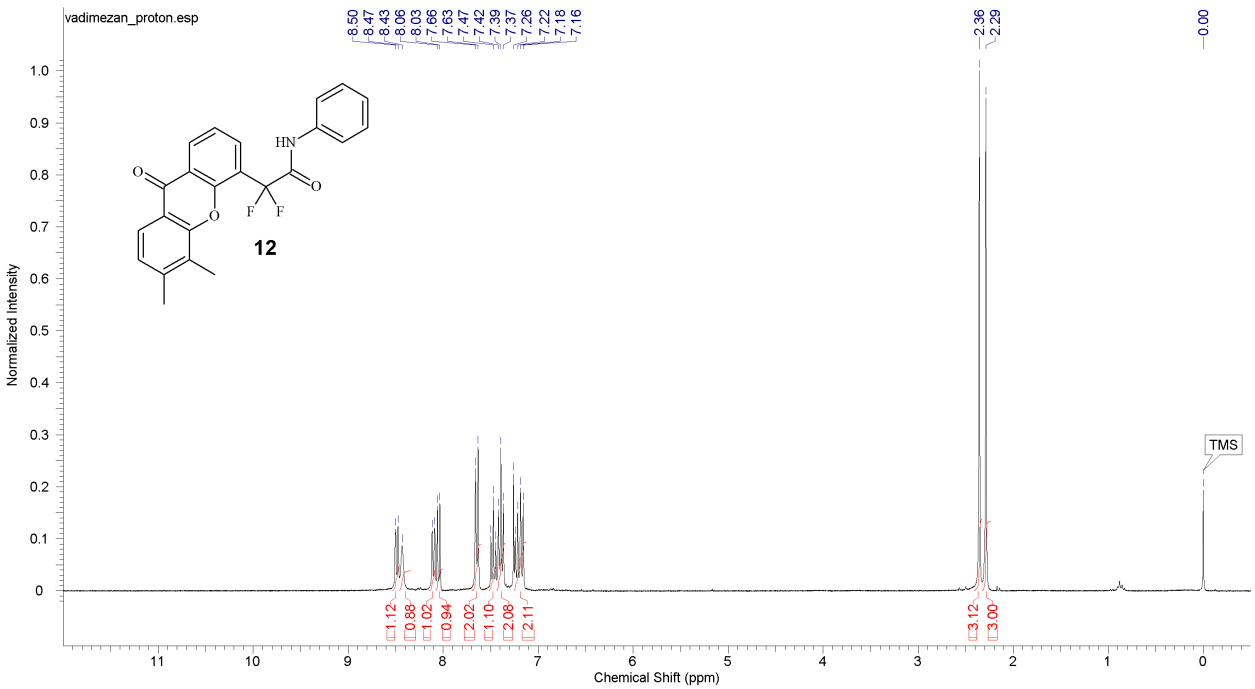
2,2-difluoro-2-(7-methyl-2-oxo-2*H*-chromen-4-yl)-*N*-phenylacetamide (11)

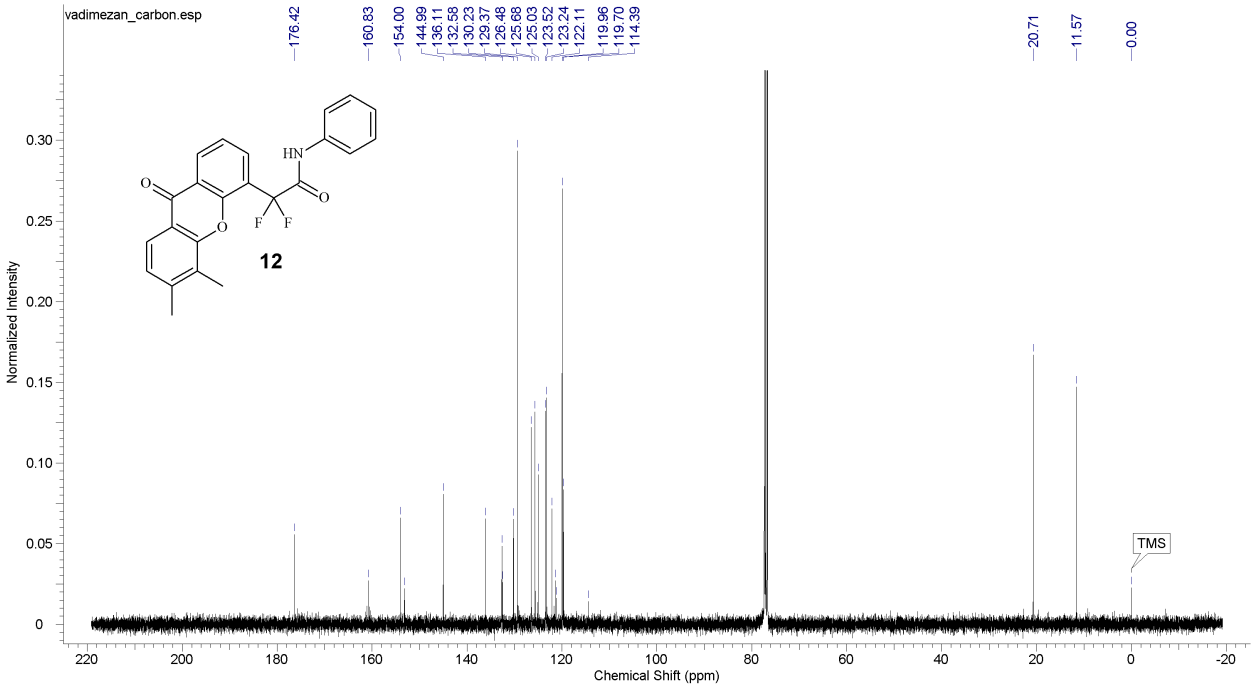


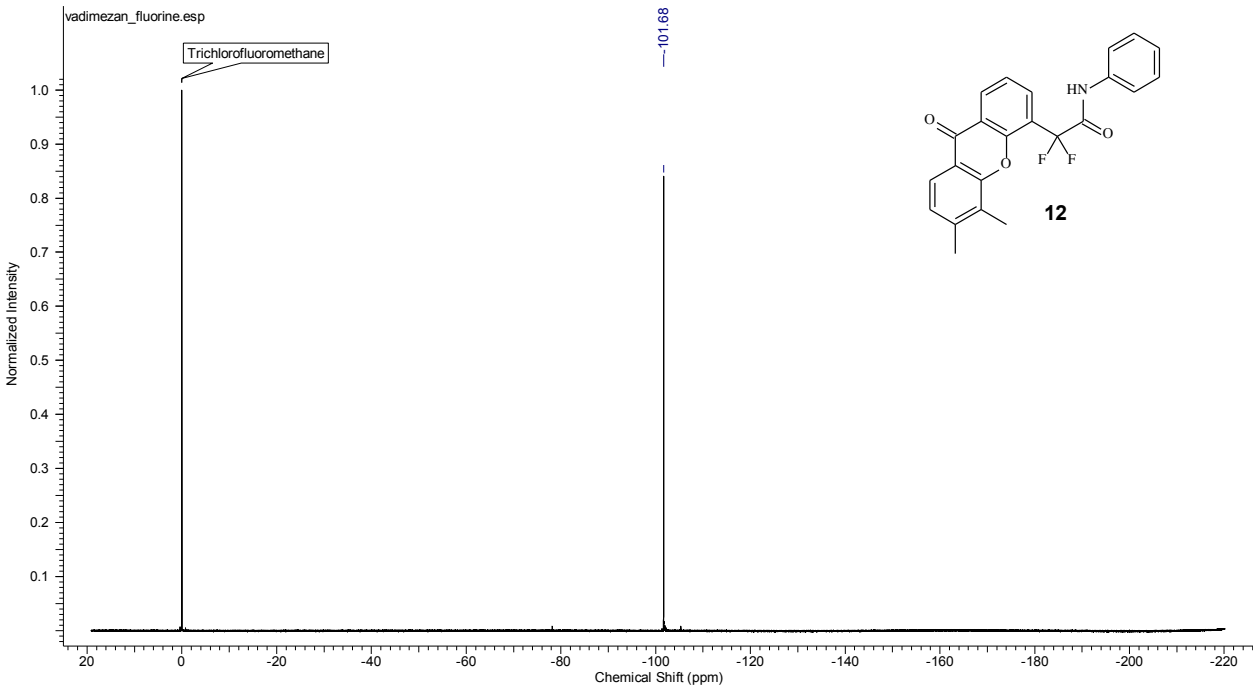

coumarin_carbon.esp
159.64
159.46
154.28
144.25
135.55
129.38
126.18
126.10
125.60
120.34
117.68
115.19
115.10
115.00
112.31
21.67
0.00
TMS
Normalized Intensity
Chemical Shift (ppm)
11


coumarin_fluorine.esp
103.55
Normalized Intensity
Chemical Shift (ppm)
11

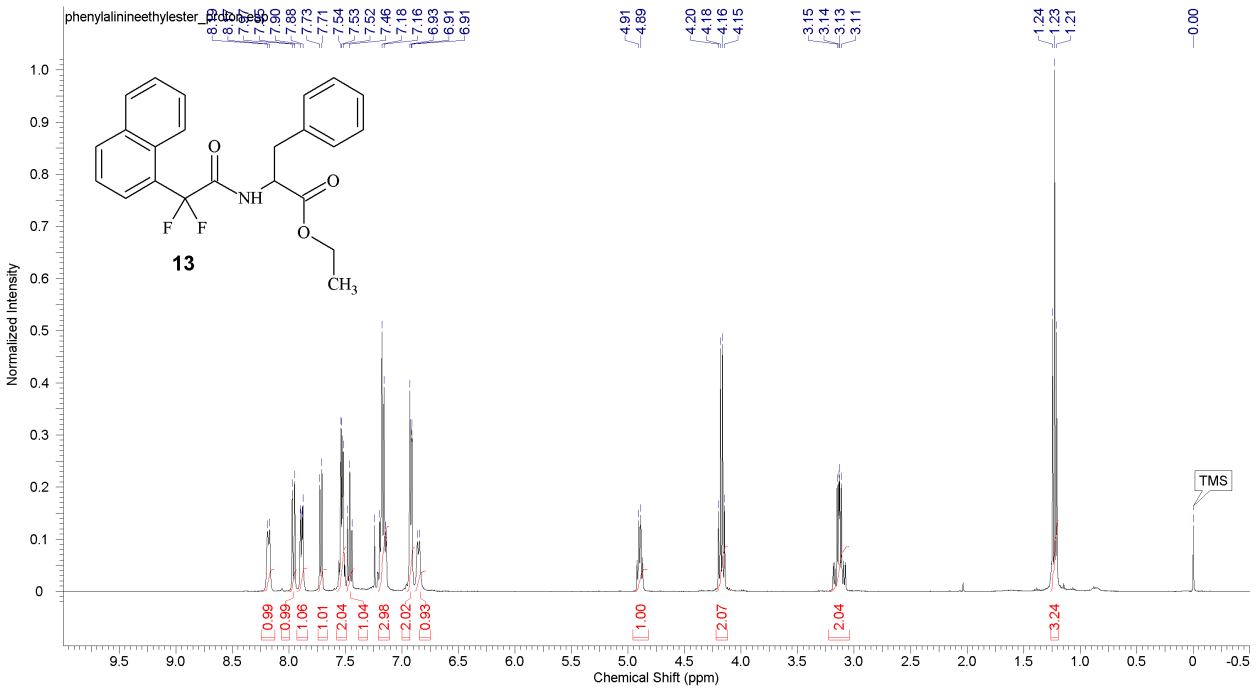
2-(5,6-dimethyl-9-oxo-9*H*-xanthen-4-yl)-2,2-difluoro-*N*-phenylacetamide (12)

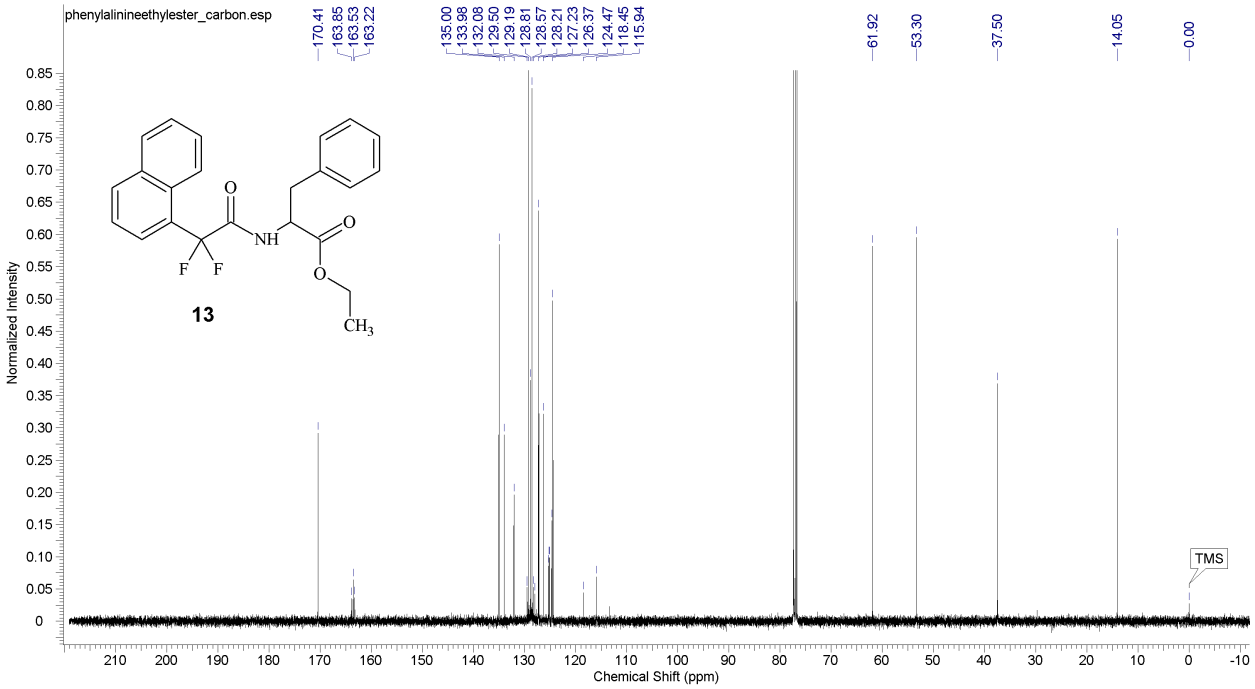


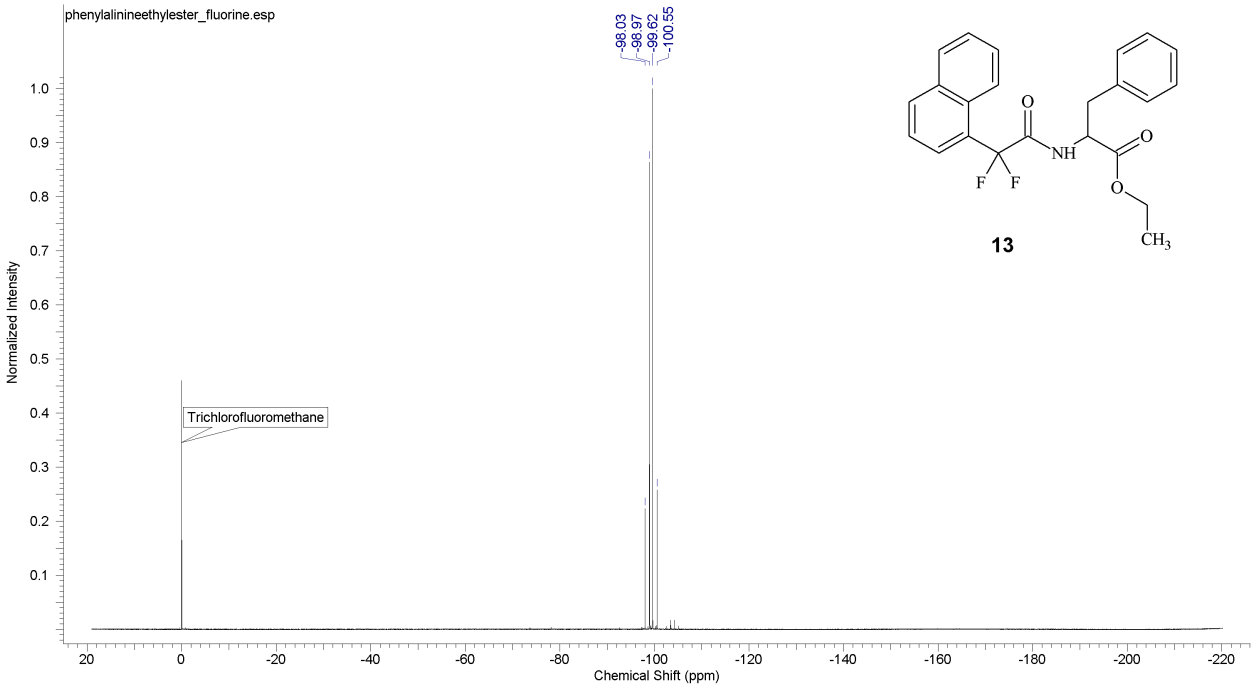




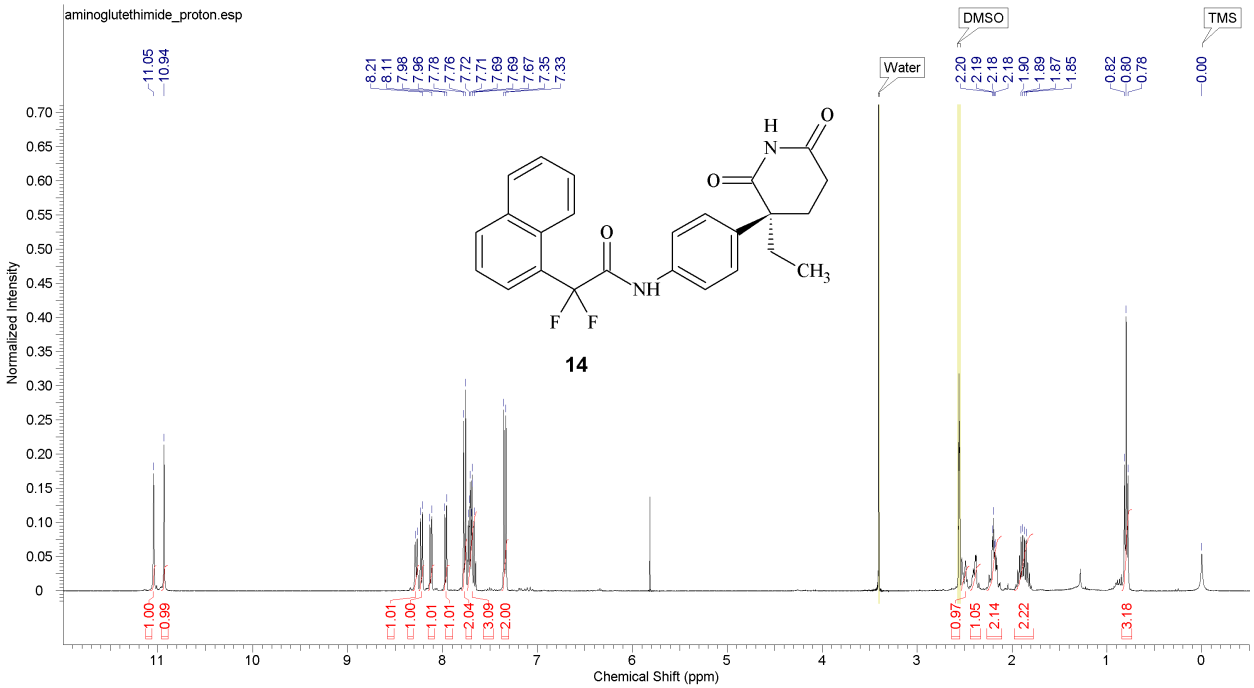
ethyl (2,2-difluoro-2-(naphthalen-1-yl)acetyl)phenylalaninate (13)

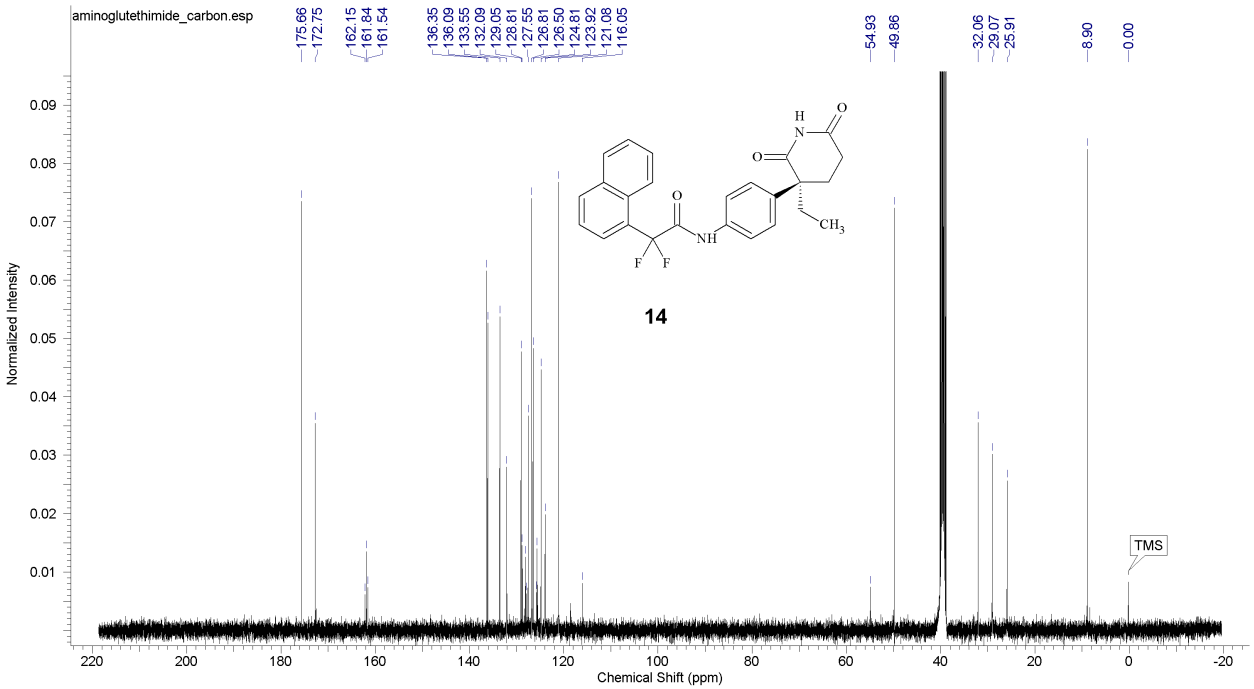


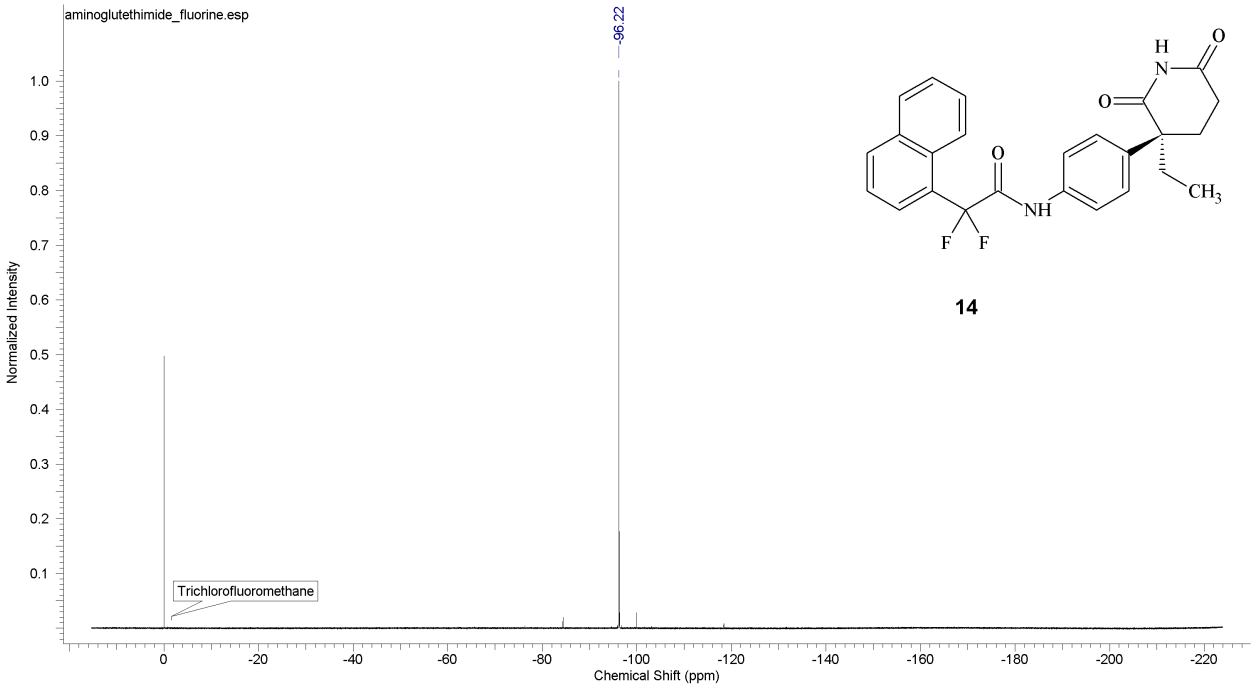

phenylalinineethylester_carbon.esp
170.41
163.85
163.53
163.22
135.00
133.98
132.08
129.50
129.19
128.81
128.57
128.21
127.23
126.37
124.47
118.45
115.94
61.92
53.30
37.50
14.05
0.00
TMS
Normalized Intensity
Chemical Shift (ppm)
13


phenylalinineethylester_fluorine.esp
-98.03
-98.97
-99.62
-100.55
Trichlorofluoromethane
Normalized Intensity
Chemical Shift (ppm)
13

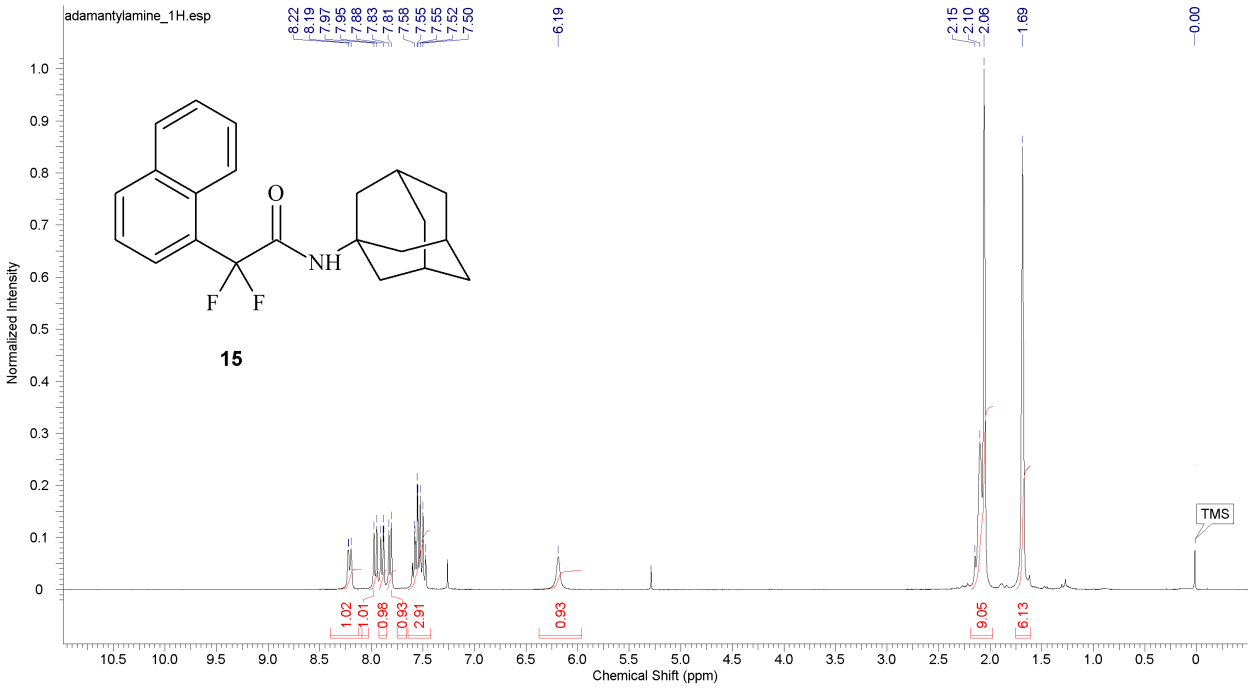
(*S*)-*N*-(4-(3-ethyl-2,6-dioxopiperidin-3-yl)phenyl)-2,2-difluoro-2-(naphthalen-1-yl)acetamide (14)

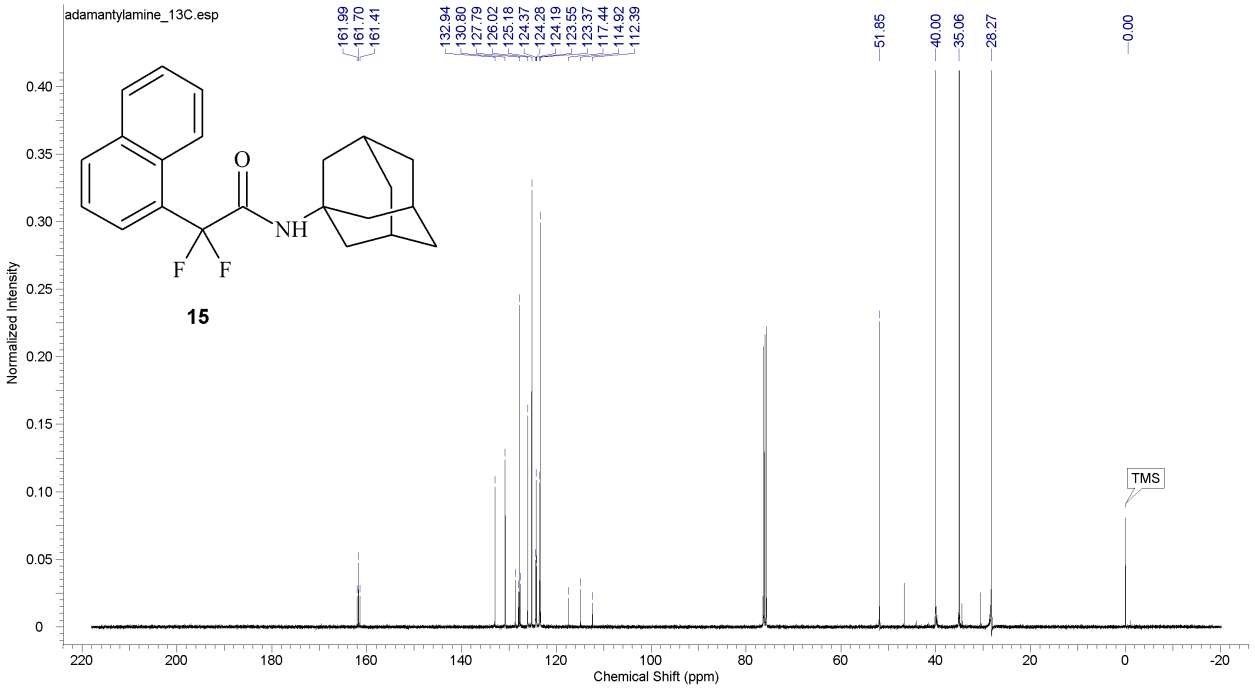


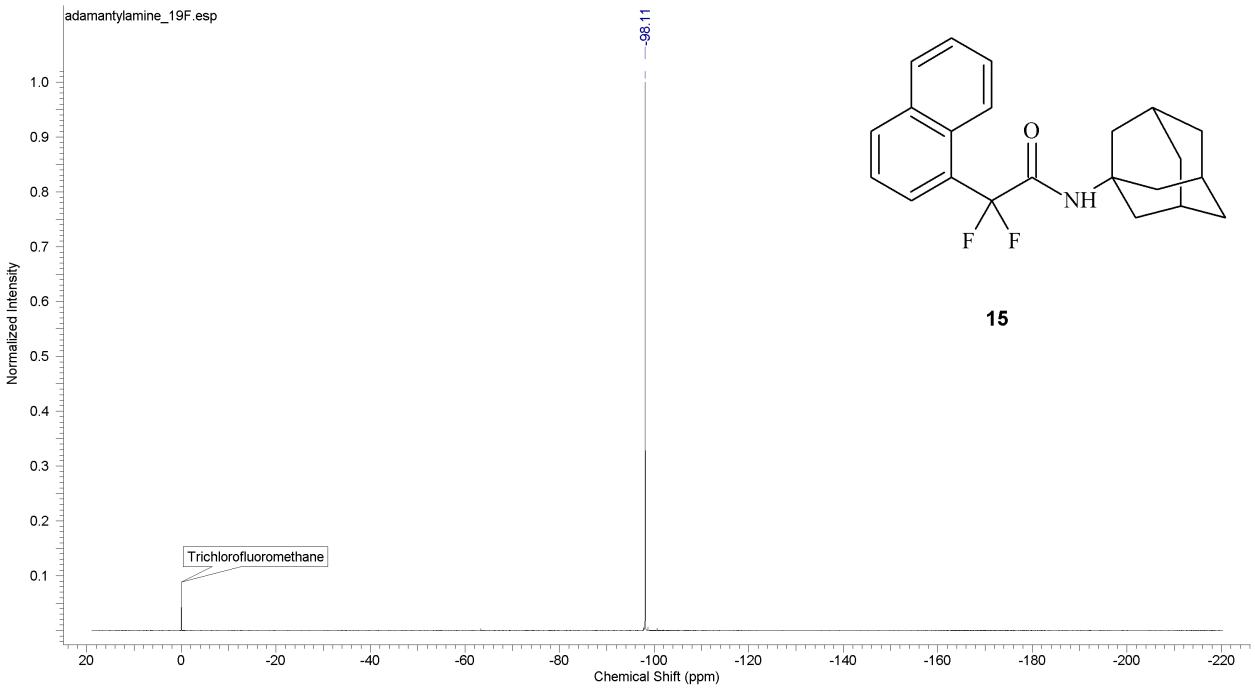




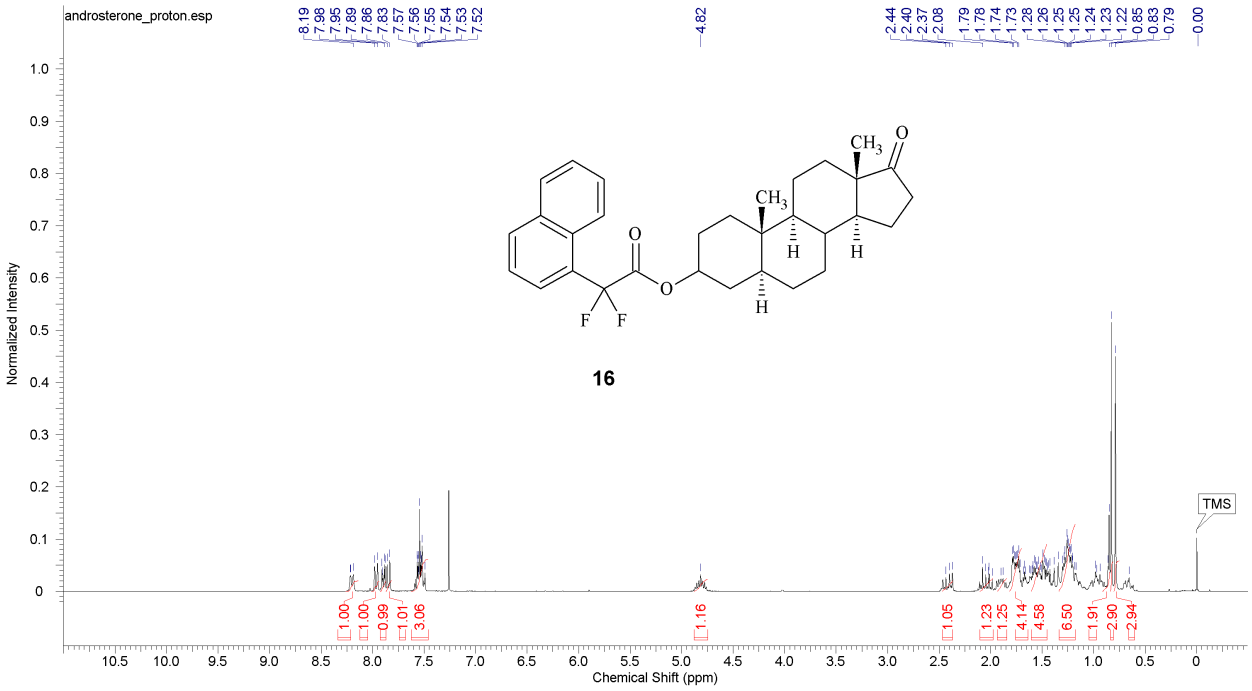
***N*-((3*s*,5*s*,7*s*)-adamantan-1-yl)-2,2-difluoro-2-(naphthalen-1-yl)acetamide (15)**

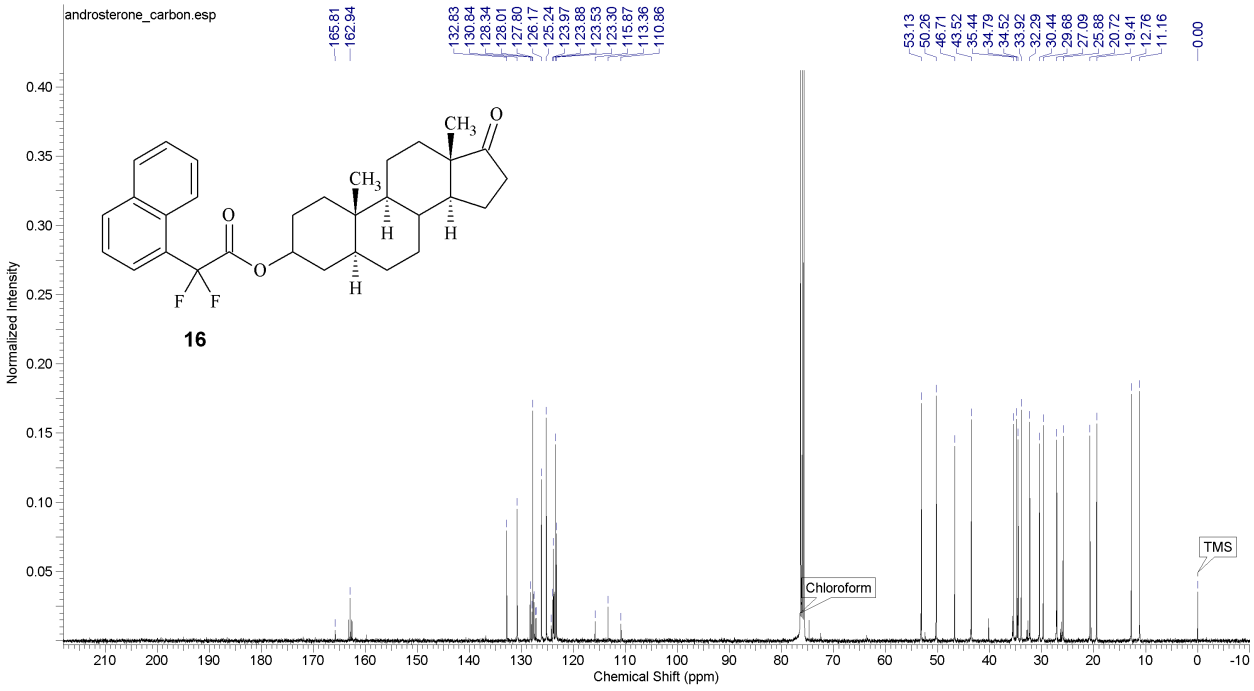


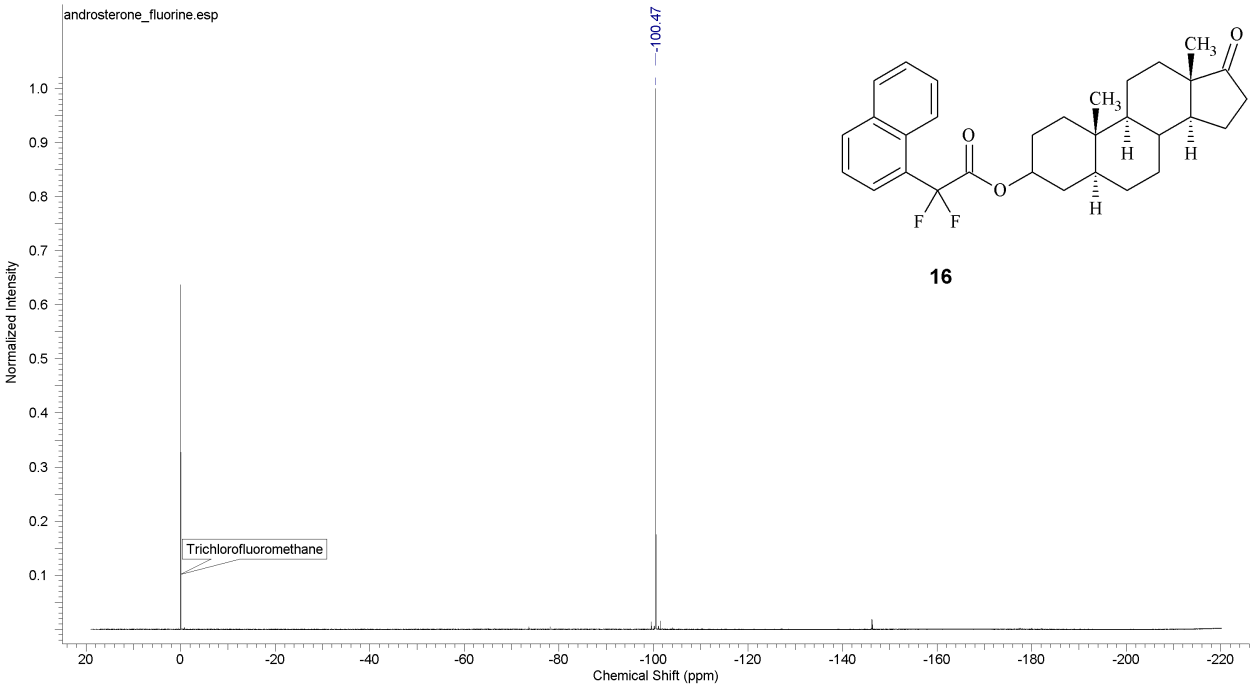

adamantylamine_13C.esp
161.99
161.70
161.41
132.94
130.80
127.79
126.02
125.18
124.37
124.28
124.19
123.55
123.37
117.44
114.92
112.39
51.85
40.00
35.06
28.27
0.00
TMS
O
NH
F F
15
Normalized Intensity
Chemical Shift (ppm)


adamantylamine_19F.esp
-98.11
Trichlorofluoromethane
O
NH
F F
15
Normalized Intensity
Chemical Shift (ppm)

(5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 2,2-difluoro-2-(naphthalen-1-yl)acetate (16)






androsterone_fluorine.esp
-100.47
Trichlorofluoromethane
Normalized Intensity
Chemical Shift (ppm)
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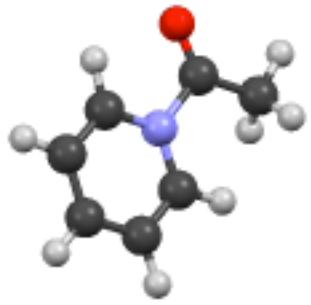
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
CH3
O
CH3
O
O
H
H
H
F
F

16

Acyl pyridine

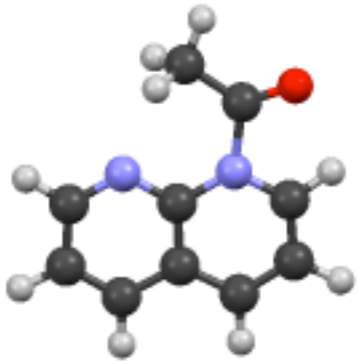


SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-311++G**
Number of shells: 94
Number of basis functions: 254
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization

Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-401.3961113	0.029854	0.113431
2	-401.4015372	0.008402	0.028658
3	-401.4020804	0.003656	0.012766
4	-401.4021856	0.001139	0.003240
5	-401.4021957	0.000617	0.002694
6	-401.4021984	0.000098	0.000451

Acyl naphthyridine



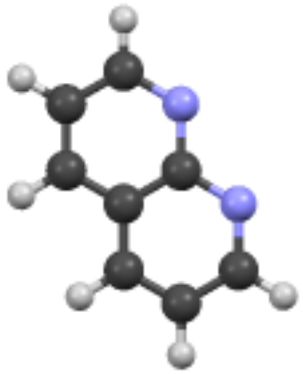
SPARTAN '06 Quantum Mechanics Program: (PC/x86) Release 129v3
Job type: Reading previous wavefunction
Program Wall Time: 0:01:43.0
Job type: Geometry optimization.
Method: RB3LYP
Basis set: 6-311++G**
Number of shells: 123
Number of basis functions: 349
SCF model:
A restricted hybrid HF-DFT SCF calculation will be
performed using Pulay DIIS + Geometric Direct Minimization

Optimization:

Step	Energy	Max Grad.	Max Dist.
1	-571.1218898	0.026687	0.127275
2	-571.1139464	0.056993	0.160596
3	-571.1118790	0.043438	0.127290
4	-571.1152007	0.063914	0.121107
5	-571.1173585	0.040548	0.154239
6	-571.1174501	0.048978	0.167773
7	-571.1159446	0.046017	0.137321
8	-571.1156235	0.041520	0.142244
9	-571.1182594	0.043872	0.123582
10	-571.1195774	0.034803	0.109485
11	-571.1193406	0.040878	0.159332
12	-571.1159352	0.037554	0.137704
13	-571.1179932	0.037640	0.127465
14	-571.1163104	0.045528	0.153135
15	-571.1175983	0.035723	0.114653
16	-571.1172826	0.032827	0.126958
17	-571.1173800	0.028489	0.113692
18	-571.1188846	0.033501	0.136040

19	-571.1200098	0.024799	0.108856
20	-571.1170009	0.028922	0.120453
21	-571.1212102	0.018048	0.112961
22	-571.1191474	0.027907	0.120189
23	-571.1223488	0.019356	0.095078
24	-571.1179763	0.028446	0.088185
25	-571.1243509	0.010815	0.112012
26	-571.1157264	0.030318	0.100130
27	-571.1246245	0.010266	0.131685
28	-571.1201839	0.024836	0.082638
29	-571.1252698	0.002850	0.038118
30	-571.1249947	0.007064	0.027975
31	-571.1253159	0.001115	0.005791
32	-571.1252933	0.001675	0.005674
33	-571.1253224	0.000397	0.004479
34	-571.1253183	0.000669	0.002966
35	-571.1253265	0.000240	0.002238
36	-571.1253241	0.000583	0.001639
37	-571.1253245	0.000116	0.001649

1,8-naphthyridine

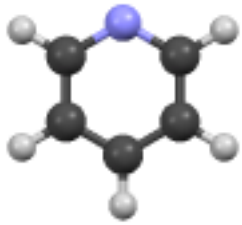


---

opt b3lyp/6-311++g(d,p) maxdisk=3GB geom=connectivity

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	3.196354	-1.366971	0.000004
2	6	0	2.291255	-0.763543	-0.000080
3	7	0	1.154917	-1.423803	-0.000092
4	6	0	1.248325	1.393596	0.000031
5	6	0	0.000002	-0.705629	-0.000040
6	6	0	2.399723	0.649527	0.000062
7	6	0	0.000000	0.725970	-0.000005
8	7	0	-1.154917	-1.423805	0.000112
9	1	0	3.377349	1.116341	0.000201
10	1	0	-1.276090	2.478766	-0.000146
11	1	0	1.276092	2.478767	0.000167
12	6	0	-2.291253	-0.763546	0.000094
13	1	0	-3.196354	-1.366970	-0.000019
14	6	0	-2.399724	0.649529	-0.000063
15	1	0	-3.377353	1.116338	-0.000203
16	6	0	-1.248327	1.393594	-0.000024

Pyridine

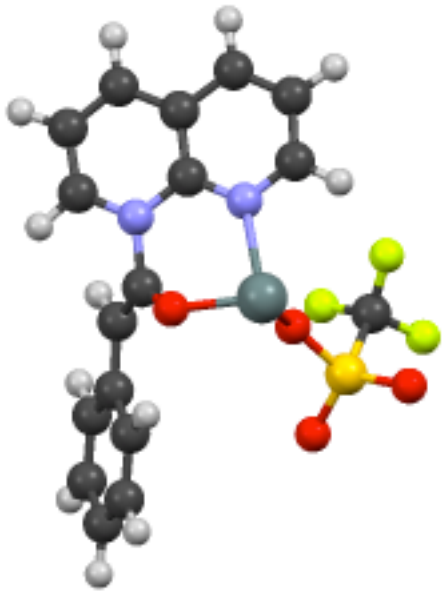


---

opt b3lyp/6-311++g(d,p) maxdisk=3GB geom=connectivity

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	7	0	0.000000	0.000000	1.416604
2	6	0	0.000000	0.000000	-1.383044
3	6	0	0.000000	1.141771	0.721225
4	6	0	0.000000	-1.141771	0.721225
5	6	0	0.000000	-1.196725	-0.671625
6	6	0	0.000000	1.196725	-0.671625
7	1	0	0.000000	2.056782	1.307240
8	1	0	0.000000	-2.056782	1.307240
9	1	0	0.000000	-2.153718	-1.180132
10	1	0	0.000000	2.153718	-1.180132
11	1	0	0.000000	0.000000	-2.467371

Proposed chelated intermediate



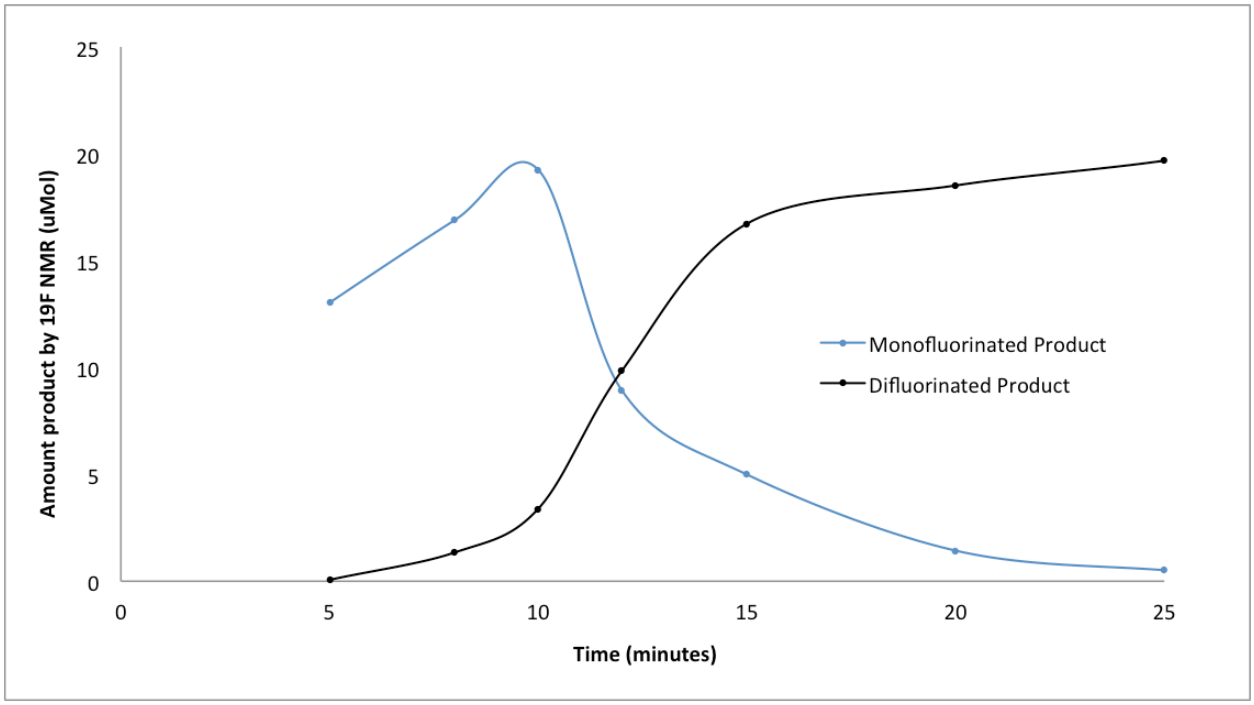
---

opt b3lyp/lanl2dz scrf=(solvent=acetonitrile) maxdisk=24GB geom=connectivity

---

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	1	0	-4.704408	2.497544	-0.340375
2	6	0	-4.167817	1.557673	-0.316295
3	1	0	-5.663114	0.395214	-1.350817
4	6	0	-4.686979	0.399766	-0.876445
5	7	0	-2.174531	0.358875	0.410690
6	6	0	-3.924718	-0.805361	-0.837843
7	6	0	-2.917078	1.488461	0.336432
8	6	0	-2.636909	-0.775047	-0.212505
9	6	0	-4.403119	-2.014435	-1.420419
10	1	0	-2.520359	2.366139	0.835803
11	6	0	-3.611177	-3.154311	-1.378896
12	1	0	-5.383742	-2.030905	-1.884797
13	1	0	-3.944718	-4.100745	-1.784196
14	6	0	-2.334892	-3.079850	-0.798428
15	1	0	-1.688990	-3.945283	-0.740835
16	7	0	-1.835461	-1.924059	-0.274626
17	6	0	-0.419199	-1.923837	0.168051
18	6	0	0.503272	-2.452447	-0.683756
19	1	0	0.151033	-2.753593	-1.667286
20	6	0	1.937472	-2.642792	-0.442684
21	6	0	4.725692	-3.097178	-0.124925
22	6	0	2.566430	-2.437018	0.815416
23	6	0	2.735179	-3.086542	-1.532355
24	6	0	4.112854	-3.308442	-1.377519
25	6	0	3.944586	-2.664533	0.966948
26	1	0	1.972456	-2.112735	1.661548
27	1	0	2.268817	-3.255611	-2.500887
28	1	0	4.705069	-3.645094	-2.224444
29	1	0	4.411441	-2.505641	1.935870
30	1	0	5.791816	-3.269109	-0.001470
31	8	0	-0.225179	-1.407690	1.395943
32	50	0	-0.460432	0.494465	2.022266
33	8	0	2.006789	3.509792	1.017758
34	16	0	1.908016	2.255185	-0.003242
35	8	0	0.669961	1.186800	0.379523
36	8	0	3.264709	1.482398	-0.426842
37	6	0	1.088681	2.967047	-1.702377
38	9	0	-0.208078	3.368352	-1.454049
39	9	0	1.090595	1.976648	-2.661478
40	9	0	1.824605	4.045285	-2.148635

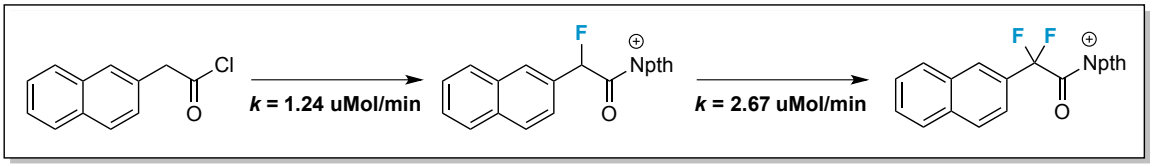
^{19}F NMR Kinetic Data



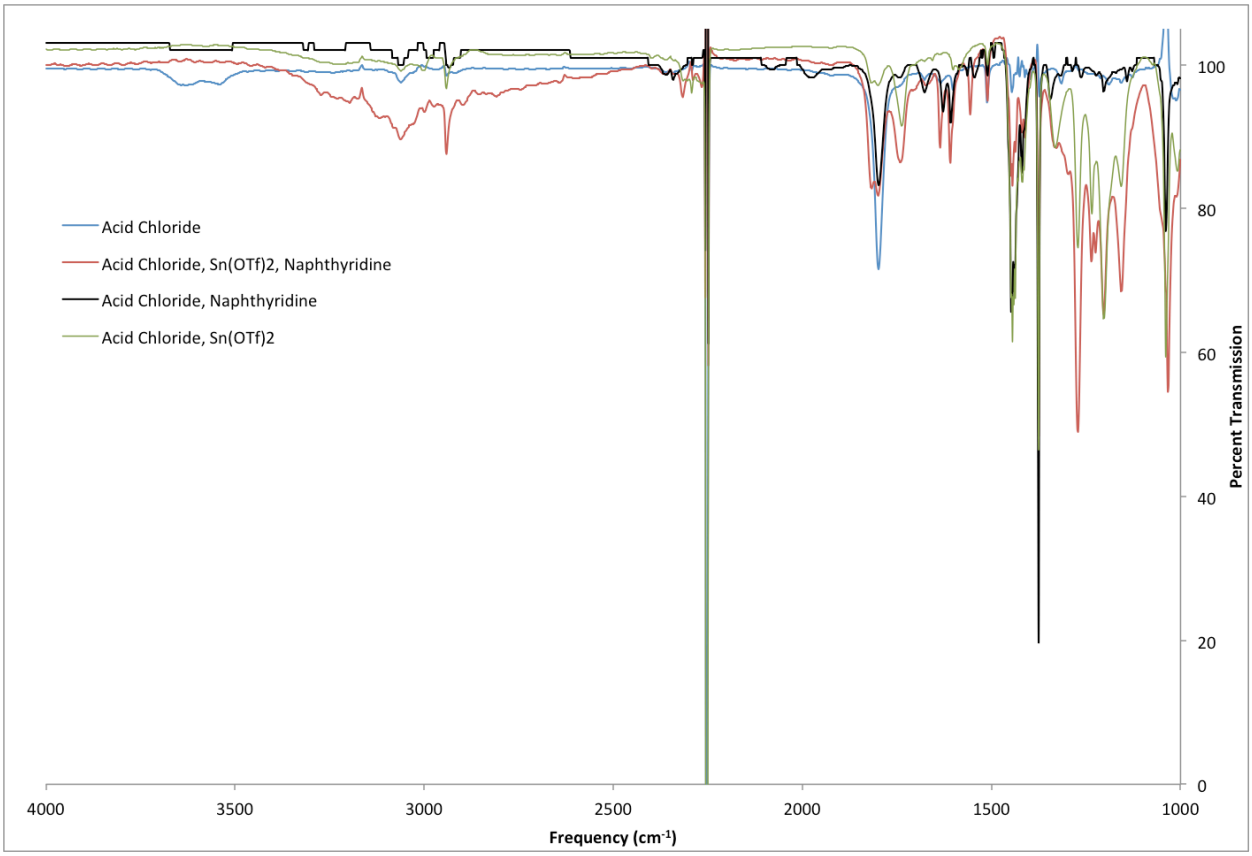
Initial rates calculated:

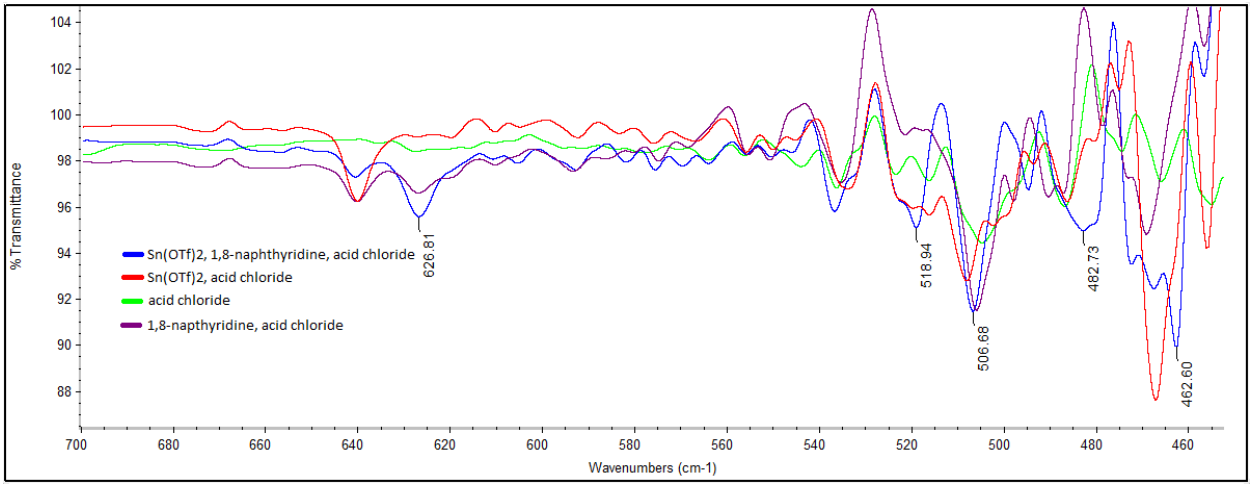
First fluorination – 1.24 uMol/min

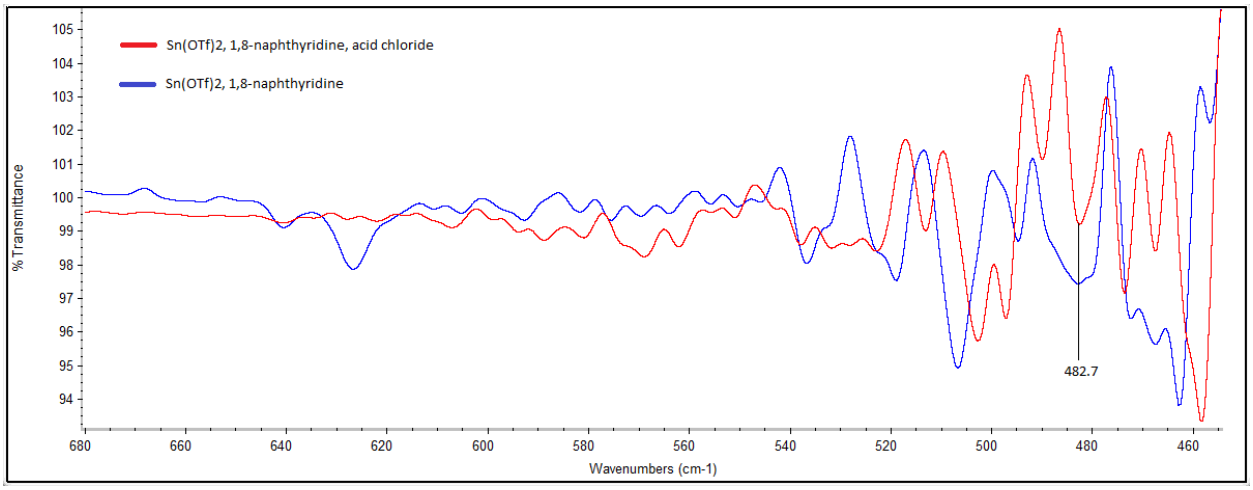
Second fluorination – 2.67 uMol/min



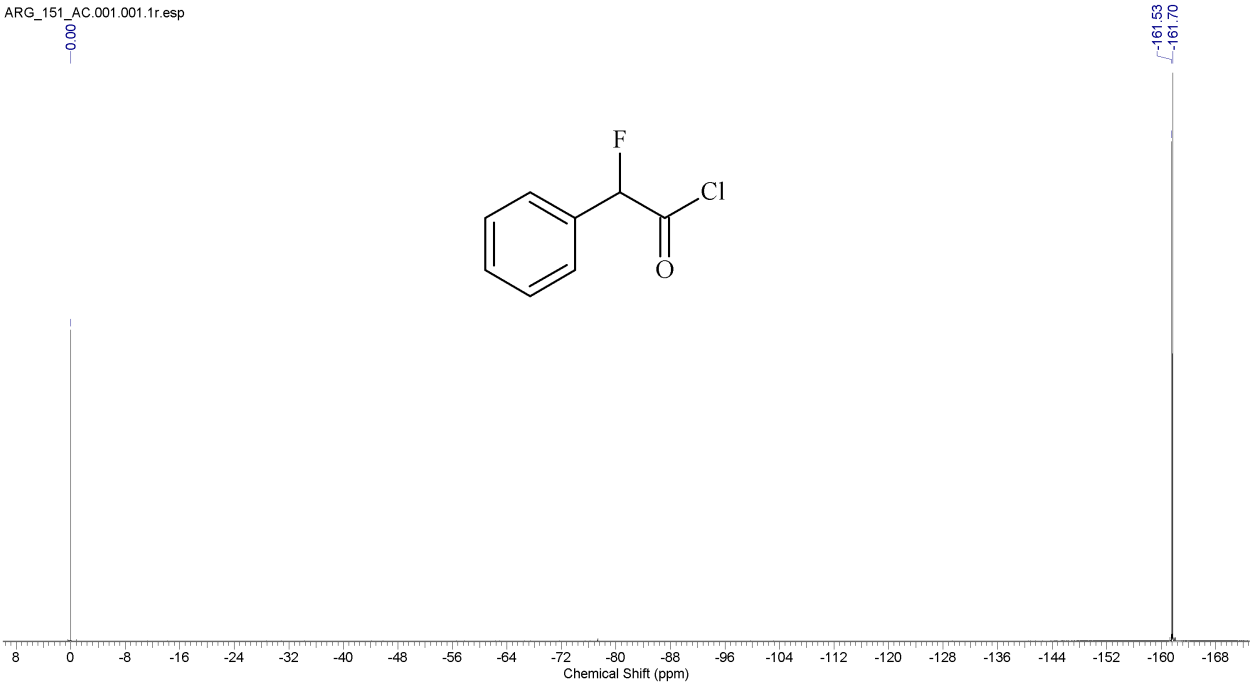
Infrared Spectroscopy Data

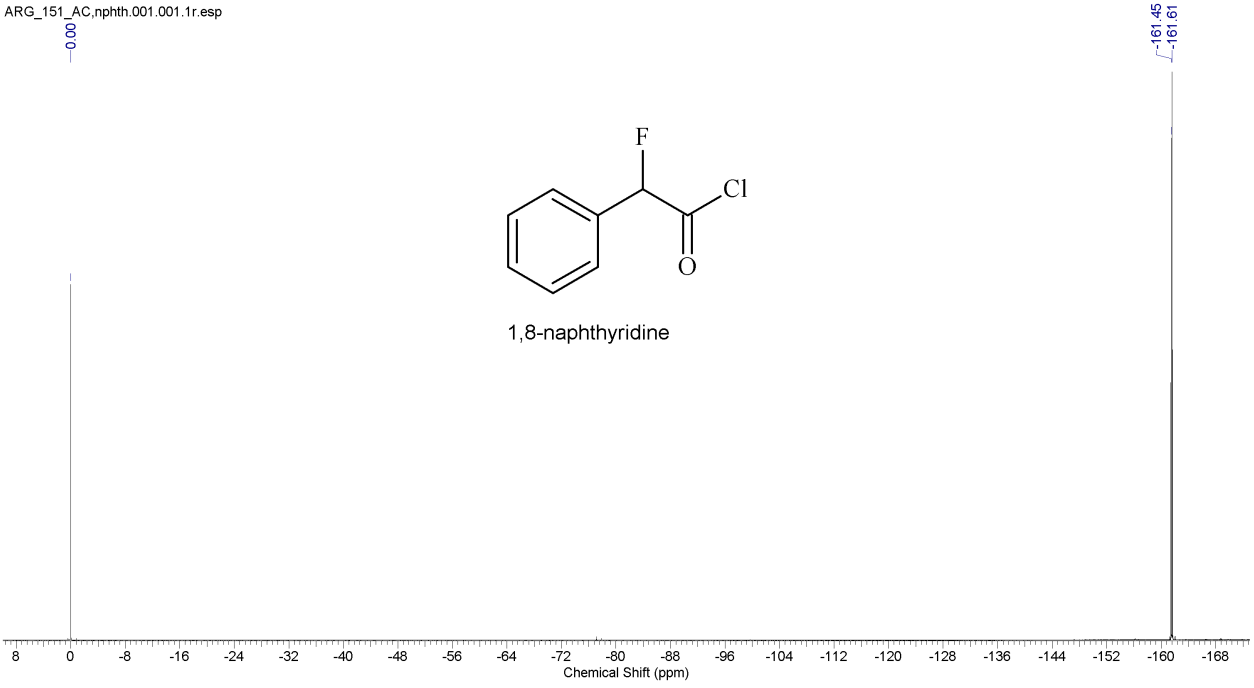


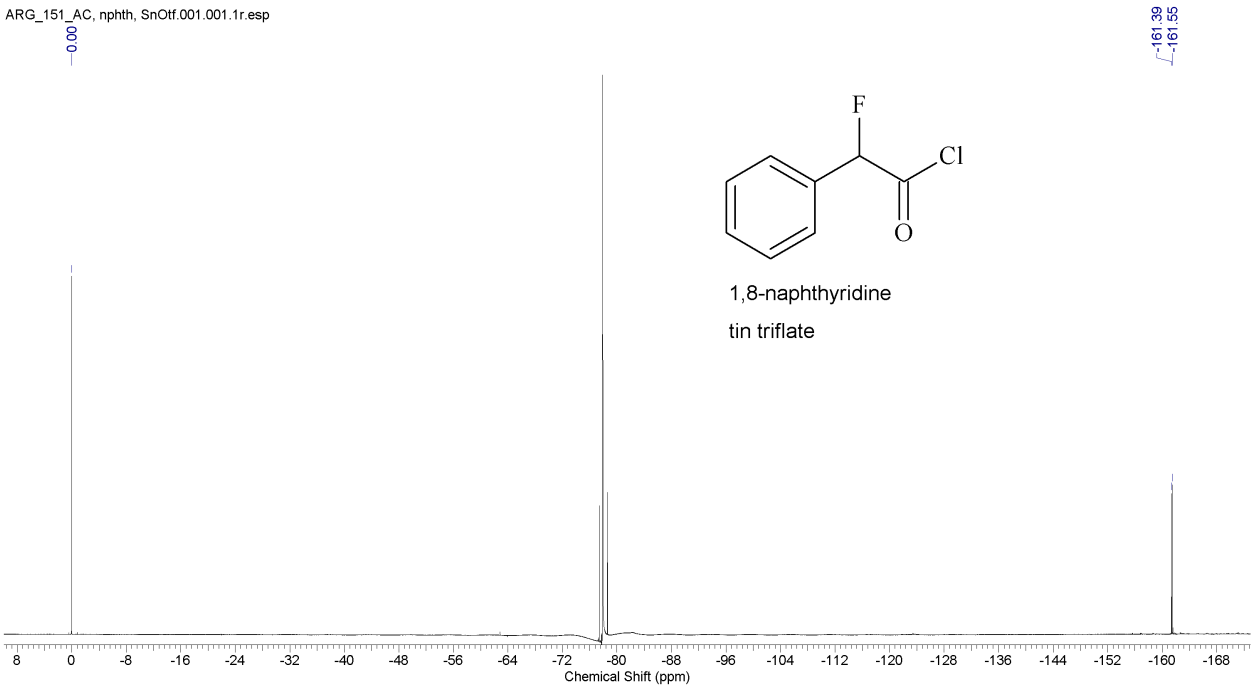

% Transmittance
Wavenumbers (cm-1)
Sn(OTf)2, 1,8-naphthyridine, acid chloride
Sn(OTf)2, acid chloride
acid chloride
1,8-napthyridine, acid chloride
626.81
518.94
506.68
482.73
462.60


% Transmittance
Wavenumbers (cm-1)
Sn(OTf)2, 1,8-naphthyridine, acid chloride
Sn(OTf)2, 1,8-naphthyridine
482.7

^{19}F NMR Studies for 2-fluoro-2-phenylacetyl chloride



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0.00
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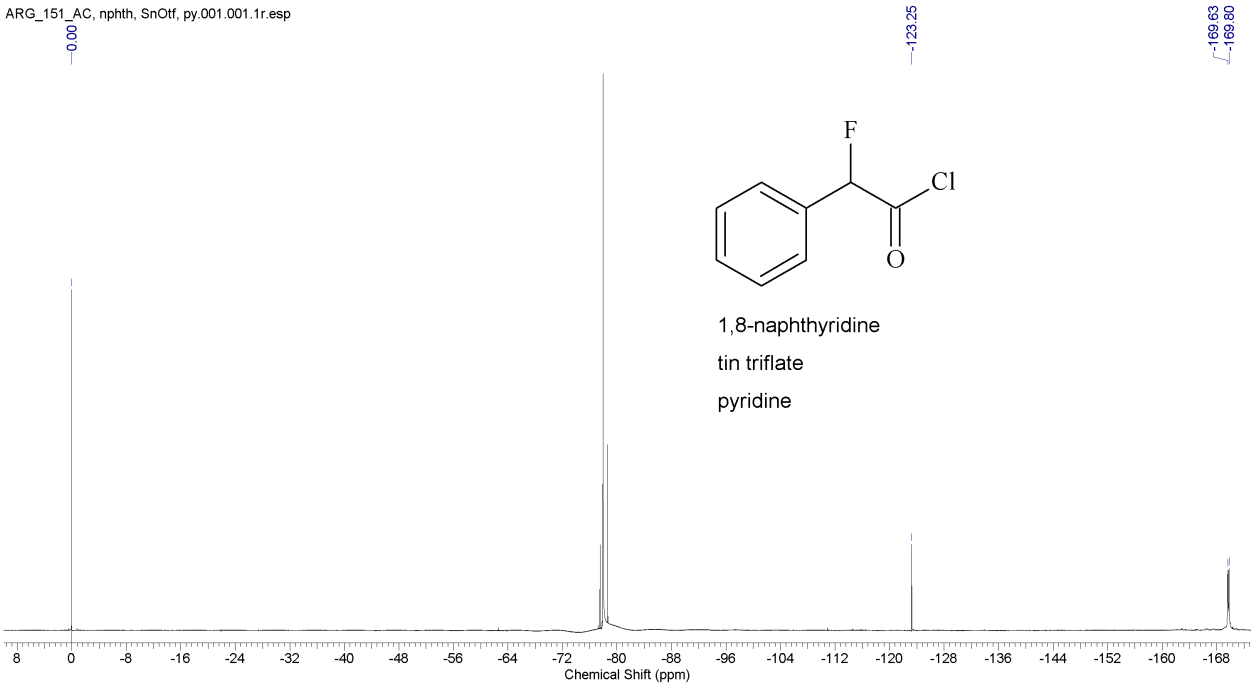
-161.55
F
Cl
O
1,8-naphthyridine
tin triflate
8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168
Chemical Shift (ppm)


ARG_151_AC, nphth, SnOtf, py.001.001.1r.esp
0.00
-123.25
-169.63
-169.80
F
Cl
O
1,8-naphthyridine
tin triflate
pyridine
8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168
Chemical Shift (ppm)