Copper-catalysed difluoroalkylation of aromatic aldehydes via decarboxylation/aldol reaction

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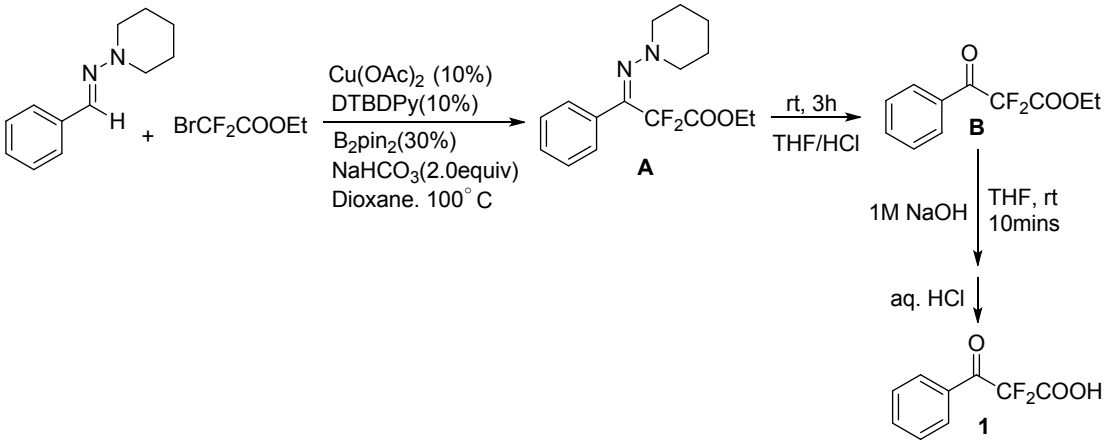
Supporting Information

Experimental

General Procedure for the synthesis of **1**[1-4]**:**



The aldehyde hydrazone (4.0 mmol), bis(pinacolato)diboron (30 mol %, 0.3g), $Cu(OAc)_2$ (10 mol %, 72 mg), 4,4′-dibutyl-2,2′-bipyridyl (10 mol %, 107 mg), and $NaHCO_3$ (8.0 mmol, 672 mg) were placed in a 50 mL Schlenk tube in air. Then the mixture was evacuated and back-filled with N_2 (three times). Ethylbromodifluoroacetate (6.0 mmol, 0.77mL) and dioxane (10 mL) were added subsequently. The Schlenk tube was screw-capped and put into a preheated oil bath (100 °C). The reaction mixture was cooled to room temperature after being stirred for 16 h. After the reaction was finished, the mixture was concentrated under vacuum to remove dioxane, and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate 10/1 to 1/4) to afford the product.

Compound **A** was placed in a 25 mL round-bottom flask with 5 mL of THF and 5 mL of 0.6 M HCl. The reaction was stirred at room temperature and monitored by TLC. The crude product was diluted with ethyl acetate when the raw material **A** was consumed. Then scrubbed with saturated NaCl solution. The organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, the residue was used in the next step directly. Compound **B** was placed in 25 mL round-bottom flask with 5 mL of THF and 5 mL of 1 M NaOH. The mixture was stirred for 10 mins, then added 30mL EtOAc to the mixture. After layering extraction of the lower, adjusted the PH = 3～4, then extracted the aqueous solution using ethyl acetate (20 mL ×2), dried by Na_2SO_4. After evaporation of the EtOAc under vacuum, the product **1** was obtained for direct use without further purification.

General procedure for the reaction:

To a mixture of 2,2-difluoro-3-oxo-3-arylpropanoic acids 1 (1.0 mmol) and aromatic aldehydes 2 (1.5 mmol) and CuI (5% mmol, 9.5 mg), 1,10-phenanthroline (5.0 mmol, 9.0 mg) was added Dimethoxyethane (DME) (5.0 mL). The mixture was stirred at 80 ºC under N_2 for 10 hours. After completion of the reaction as indicated

by TLC, the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (20 mL), washed with saturated brine and NaHCO3, and then dried over anhydrous MgSO4. Evaporation of the solvent followed by purification on silica gel provided the corresponding product 3.

2,2-difluoro-3-oxo-3-phenylpropanoic acid (**1a**) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.7).

2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoic acid (1k) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.06 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.3).

2,2-difluoro-3-oxo-3-(p-tolyl)propanoic acid (1l) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 2.45 (s, 3H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.5).

3-(3-chlorophenyl)-2,2-difluoro-3-oxopropanoic acid (1m) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H), 8.06 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.67 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.6).

3-(4-bromophenyl)-2,2-difluoro-3-oxopropanoic acid (1g) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.7).

3-(4-chlorophenyl)-2,2-difluoro-3-oxopropanoic acid (1n) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.50 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.7).

3-(4-cyanophenyl)-2,2-difluoro-3-oxopropanoic acid (1c) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (s, 1H), 8.24 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -108.1).

2,2-difluoro-3-(4-fluorophenyl)-3-oxopropanoic acid (1o) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H), 8.11-8.14 (m, 2H), 7.19 (t, *J* = 8.0 Hz, 2H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -107.6), (s, -99.8).

2,2-difluoro-1-phenylethanone (4) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 6.30 (t, *J* = 52 Hz, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz): δ (s, -122.1).

References

(1) Xu, P.; Wang, G.; Zhu, Y.; Li, W.; Cheng, Y.; Li, S.; Zhu, C. *Angew. Chem., Int. Ed*. 2016, **55**, 2939.

(2) Xie, J.; Zhang, T.; Sc, M.;Chen, F.; Mehrkens, N.; Rominger, F.; Rudolph, M.; Hashmi, A. S. *Angew. Chem., Int. Ed*. 2016, **55**, 2934

(3) Ke, M.; Song, Q. *J. Org. Chem*. 2016, **81**, 3654.

(4) Alexis, P.; Romain, M.; Didier, B.; Nuno, M. *ACS Catal.*, 2016, **6**, 1093.

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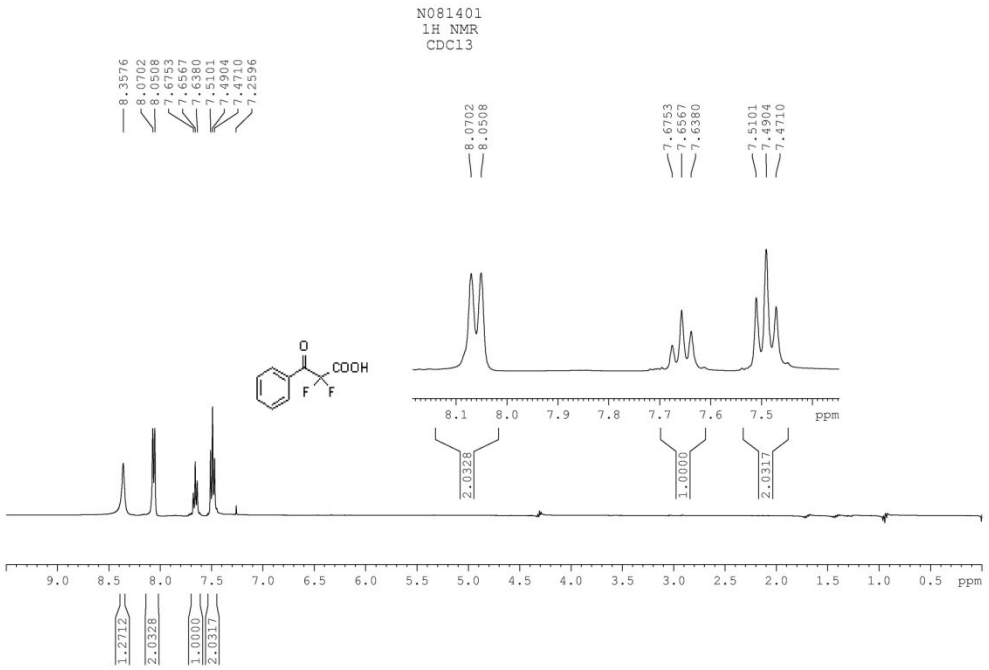

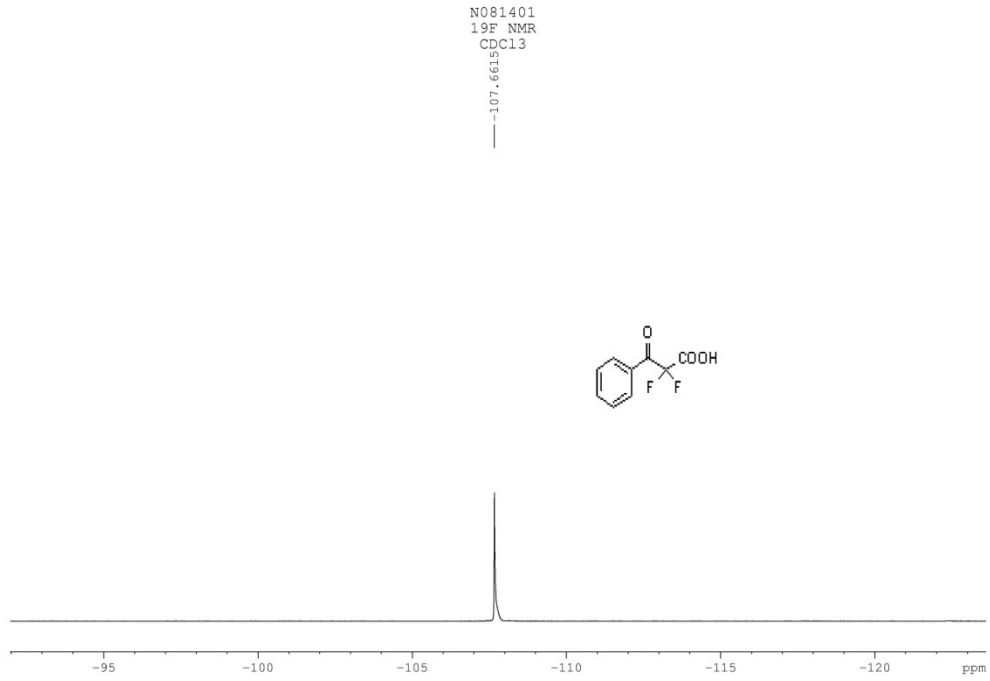


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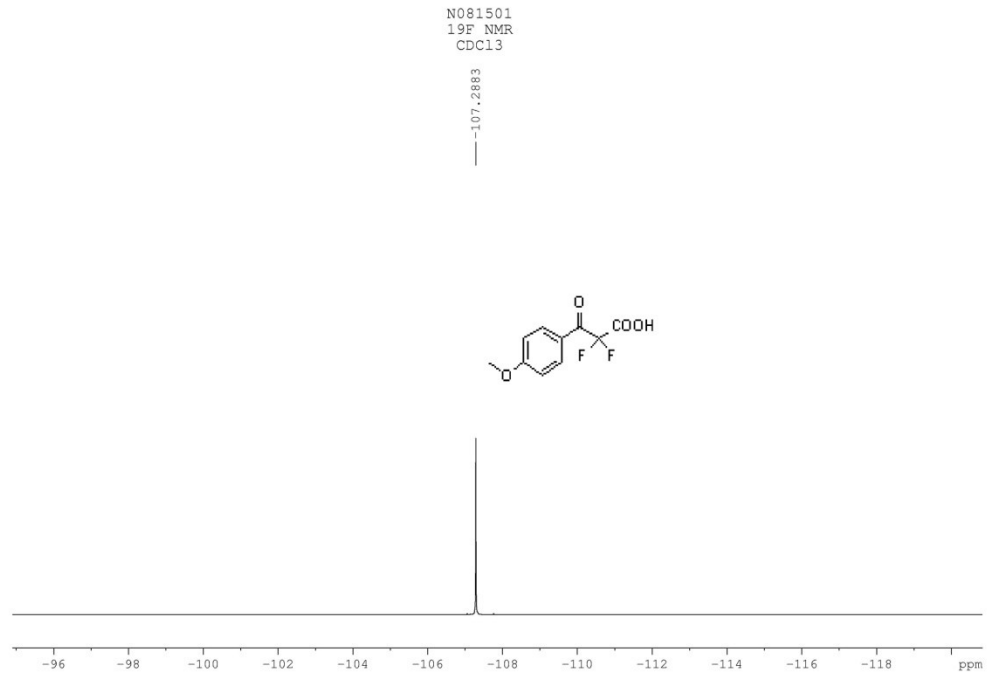
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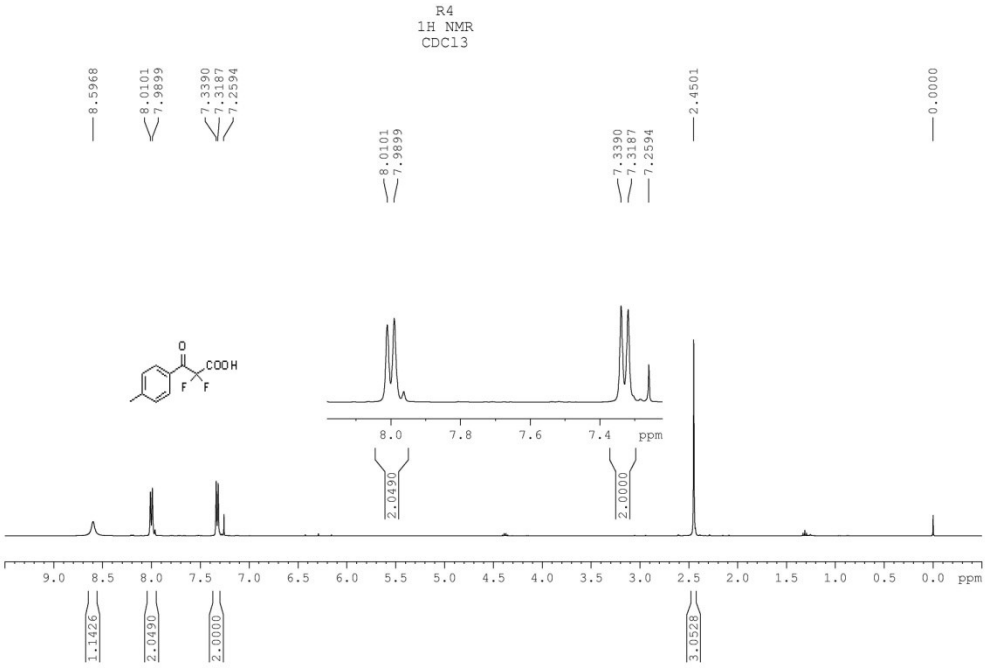
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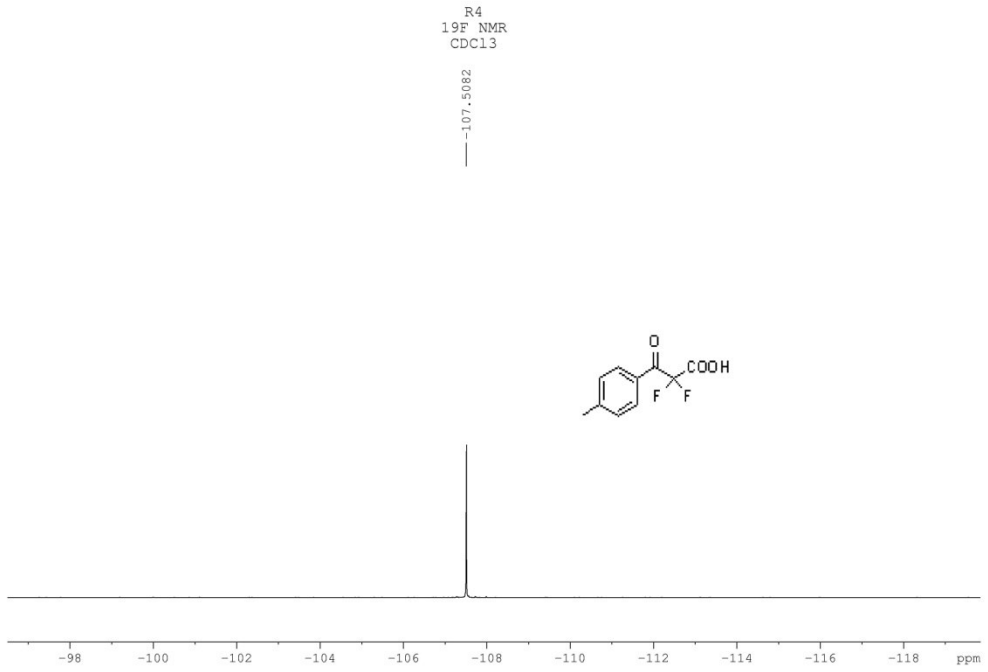
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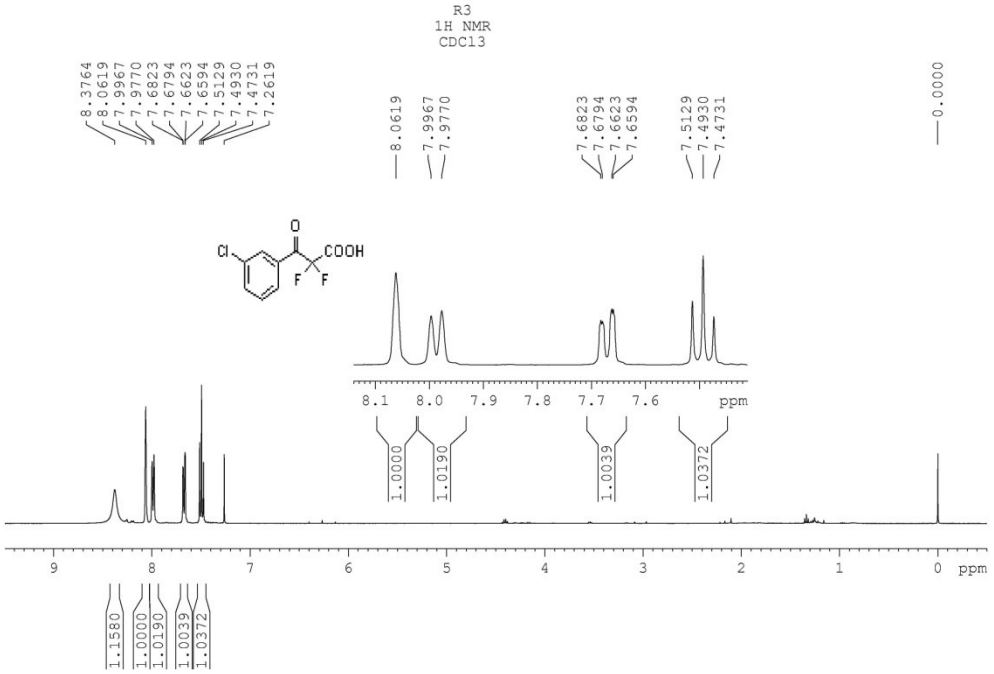
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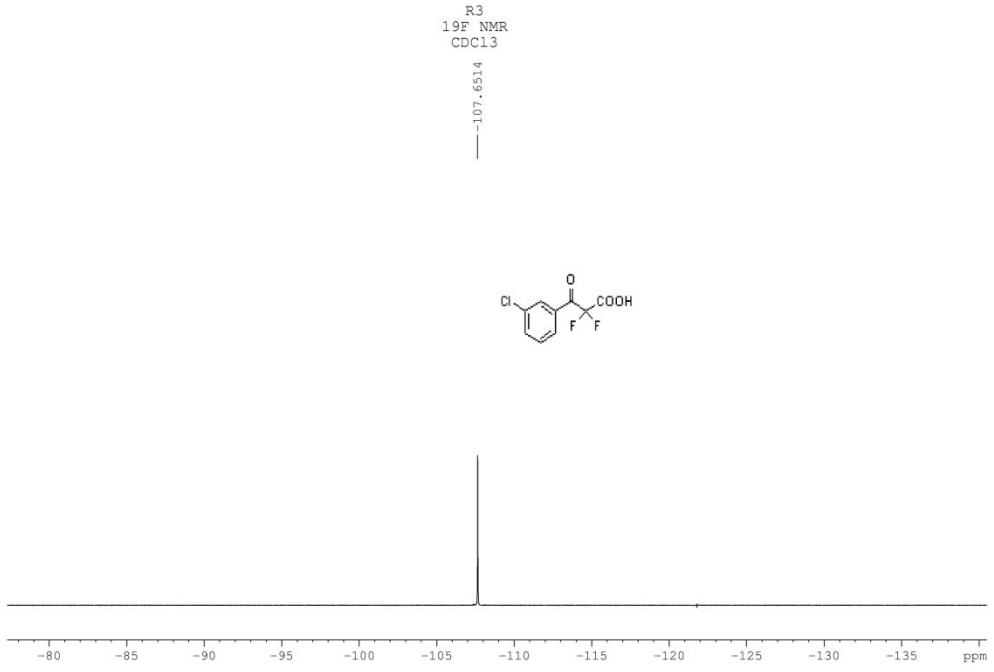
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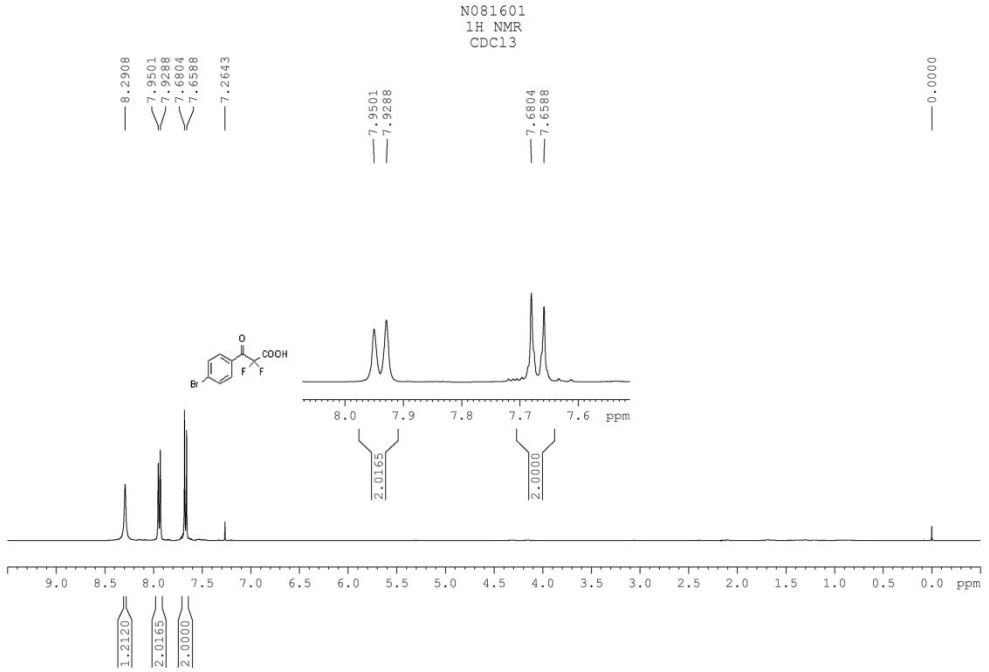
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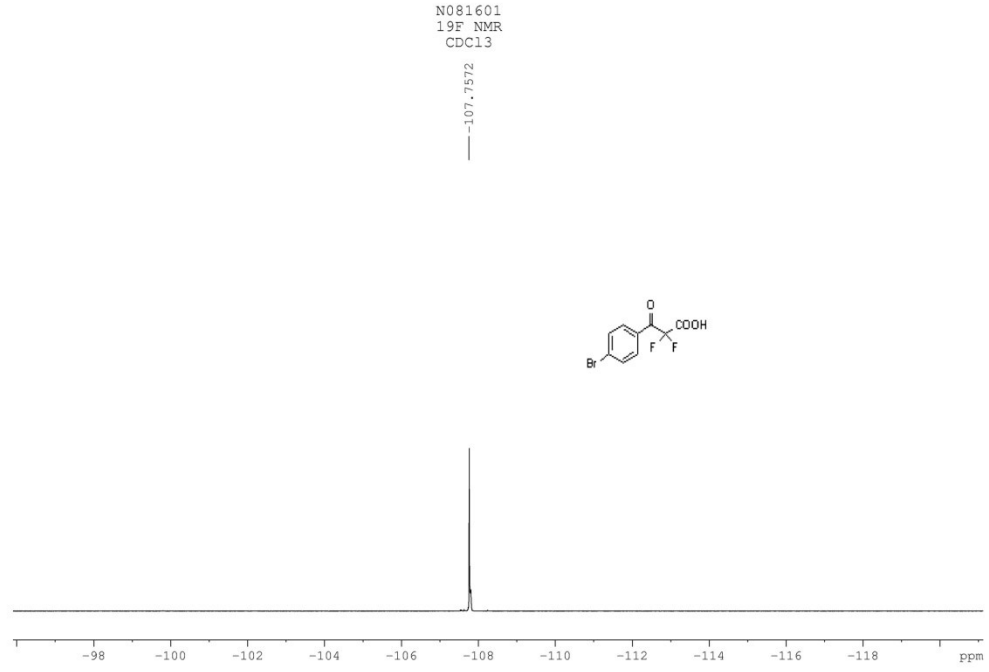
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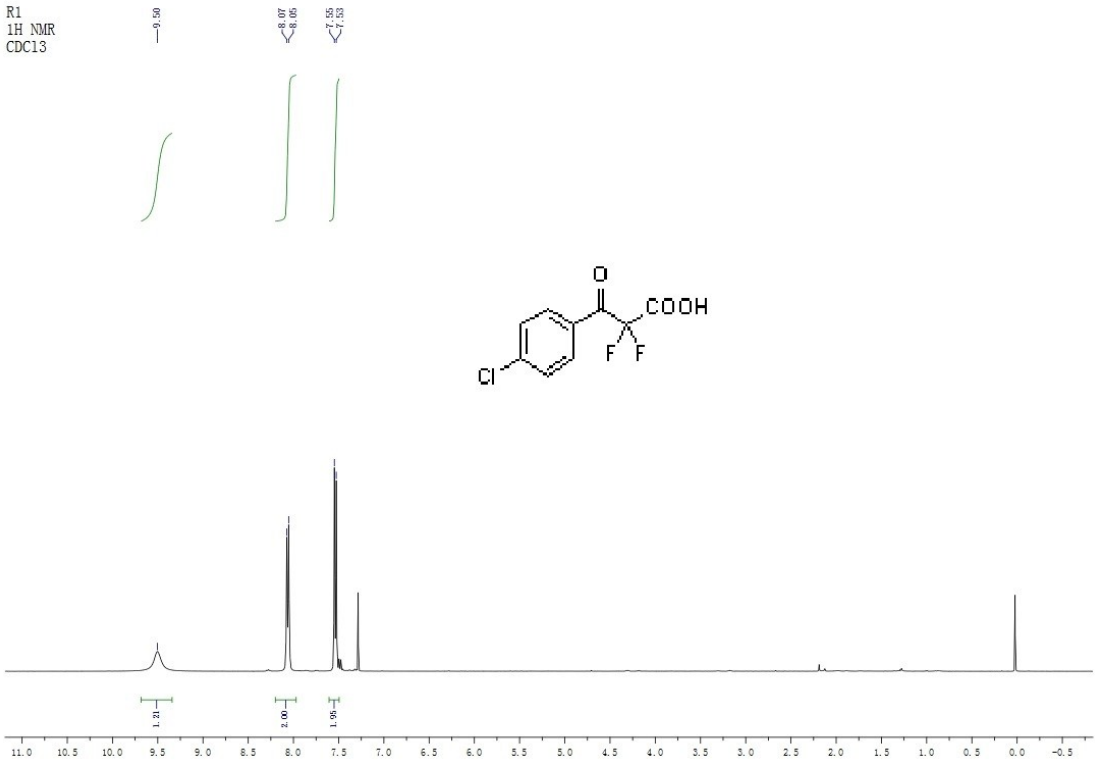
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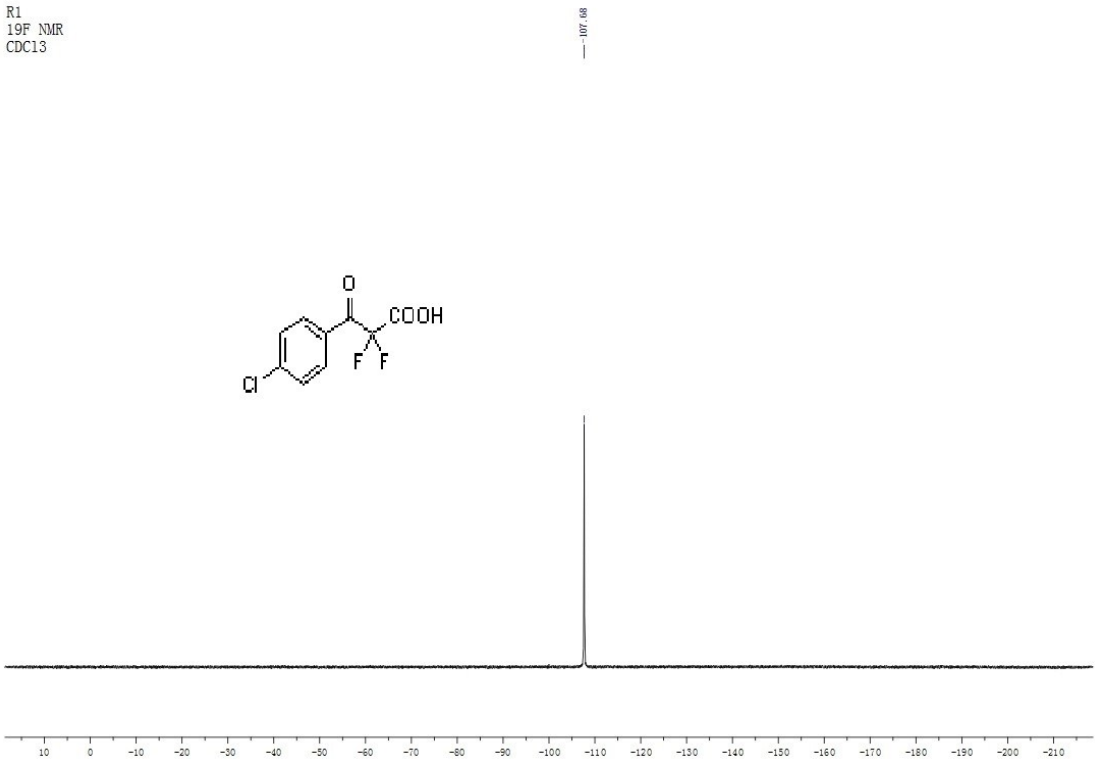
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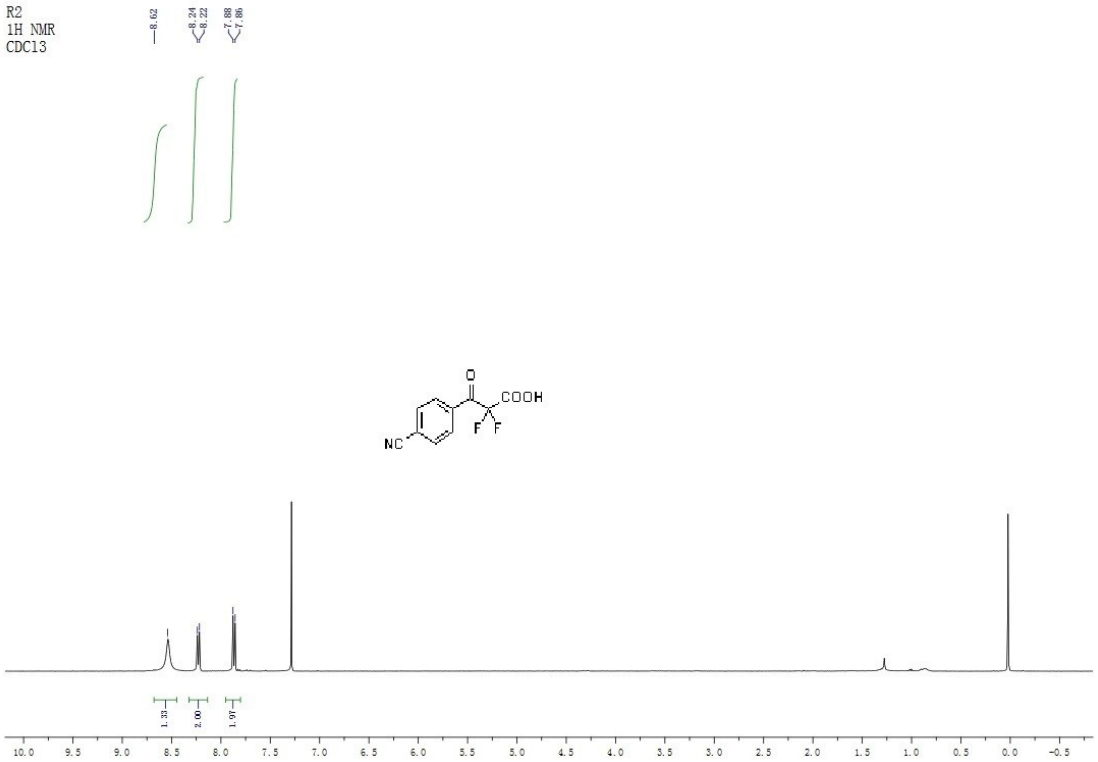
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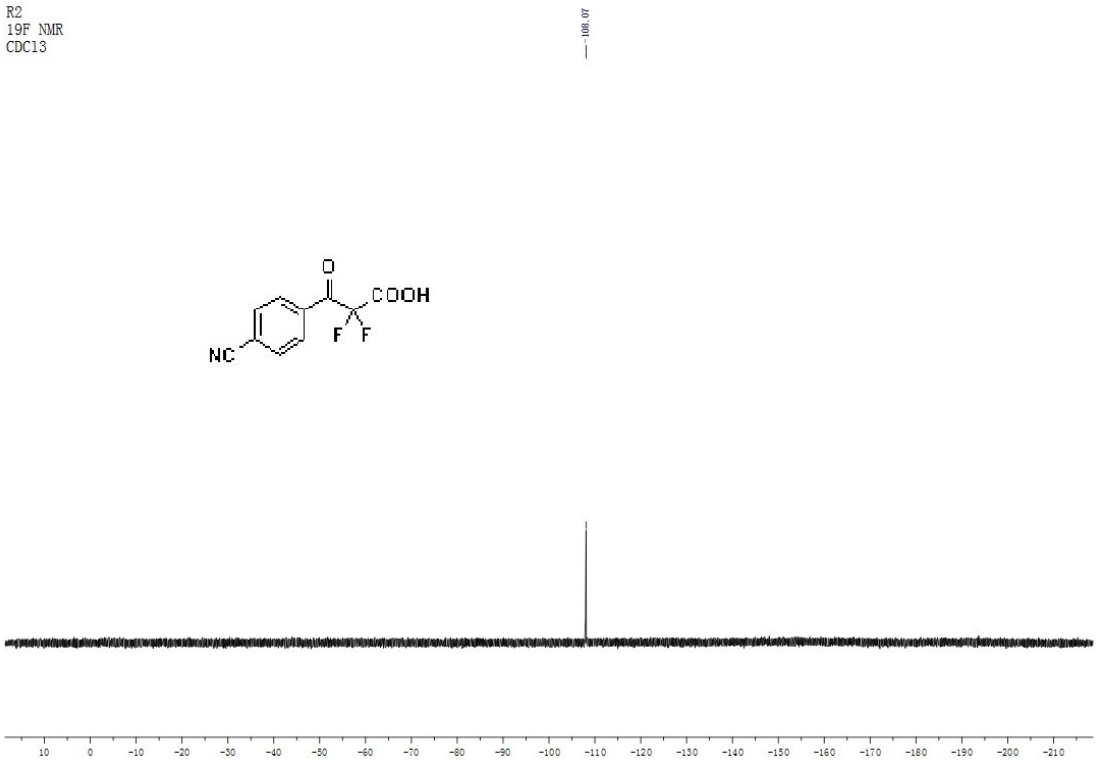
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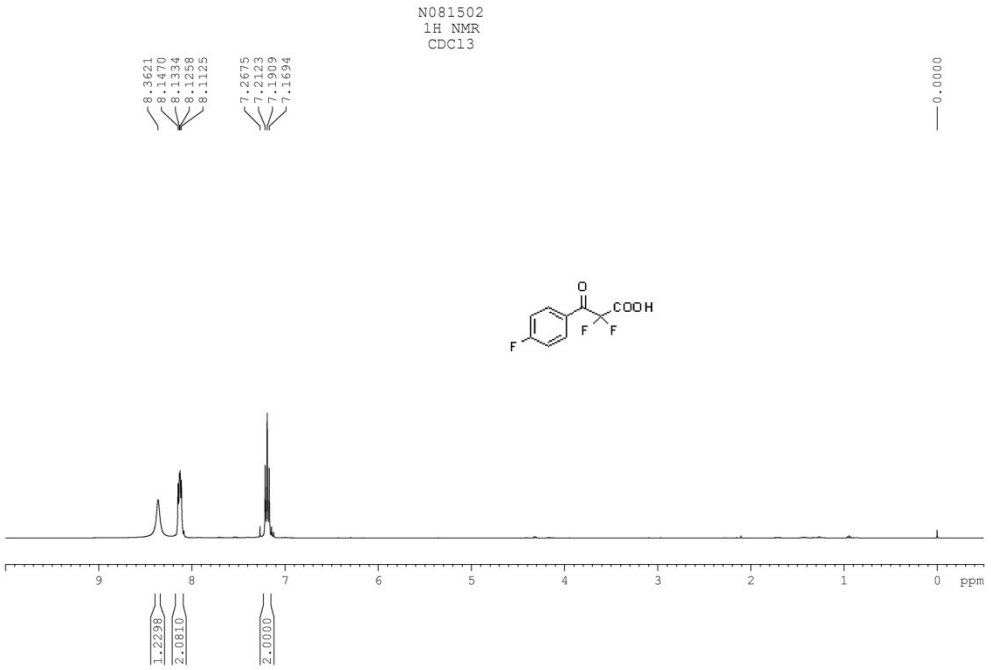
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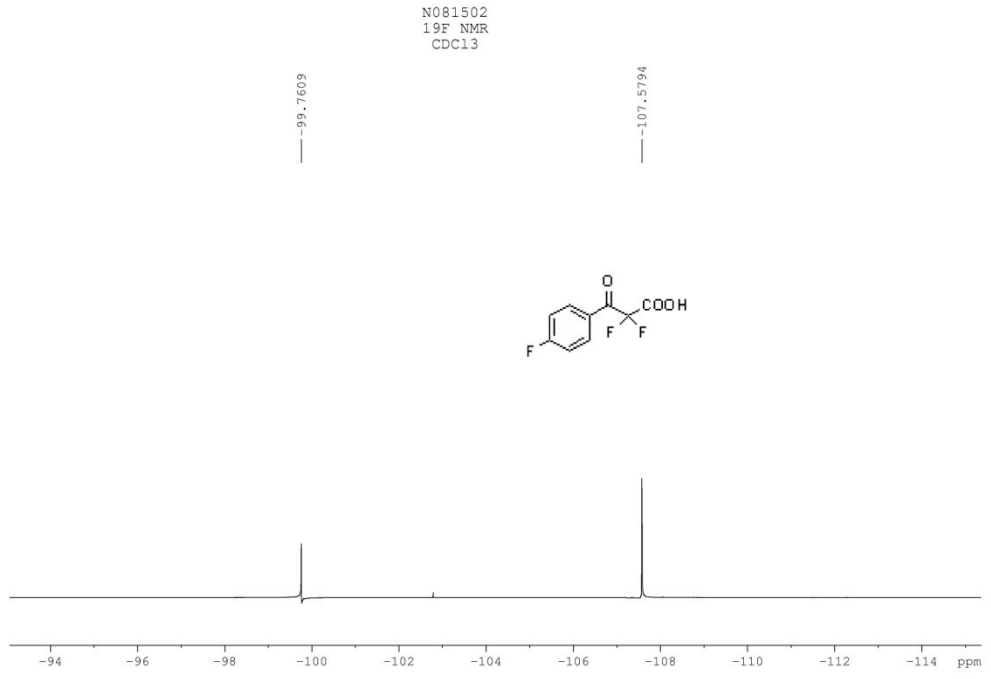
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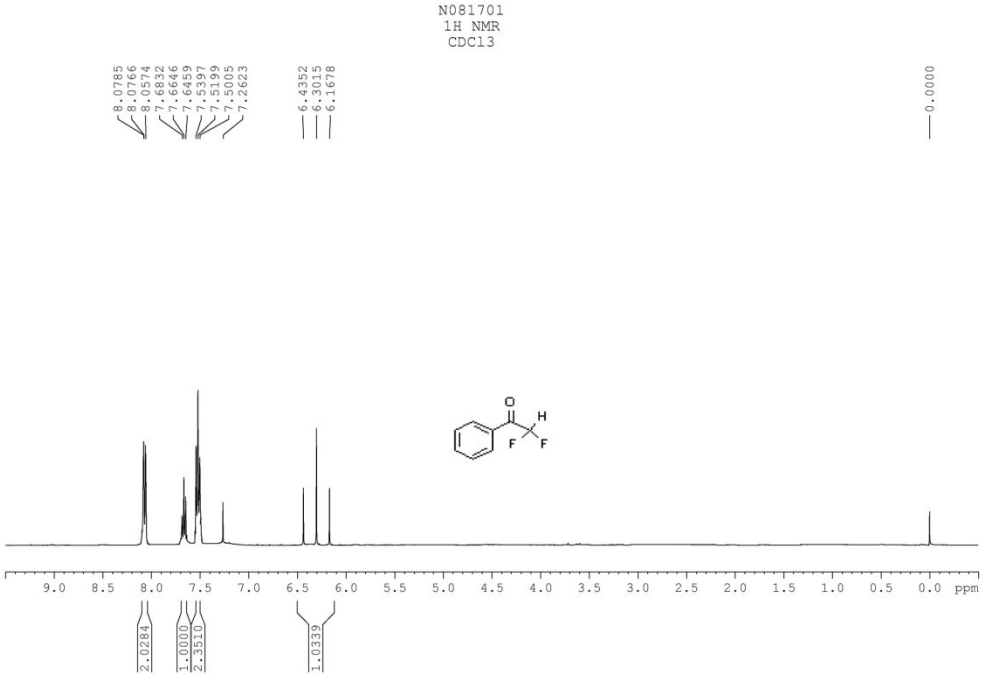
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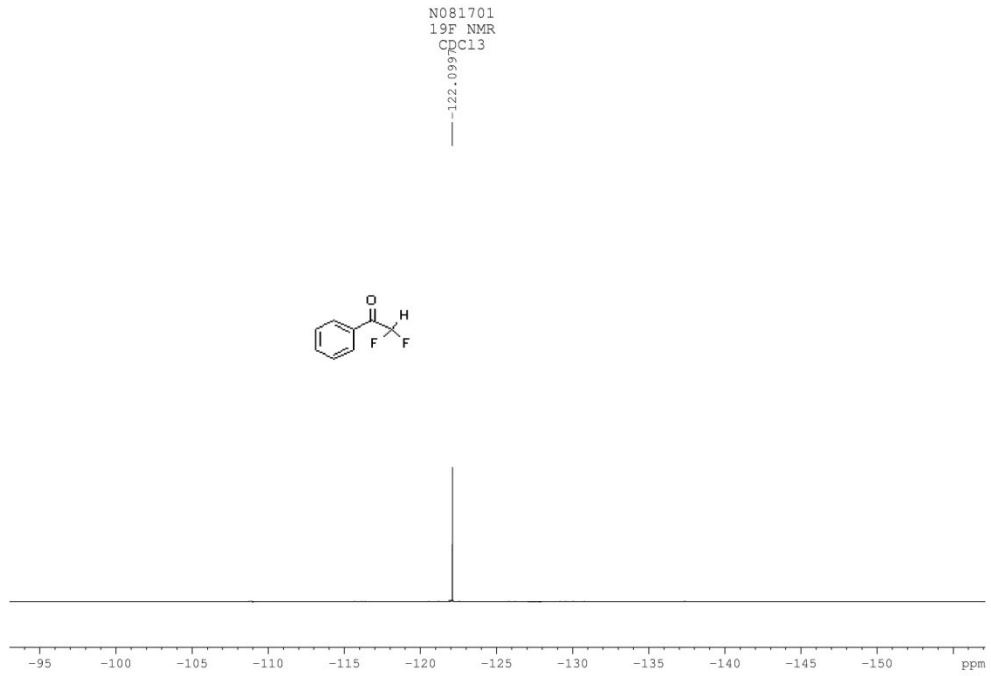
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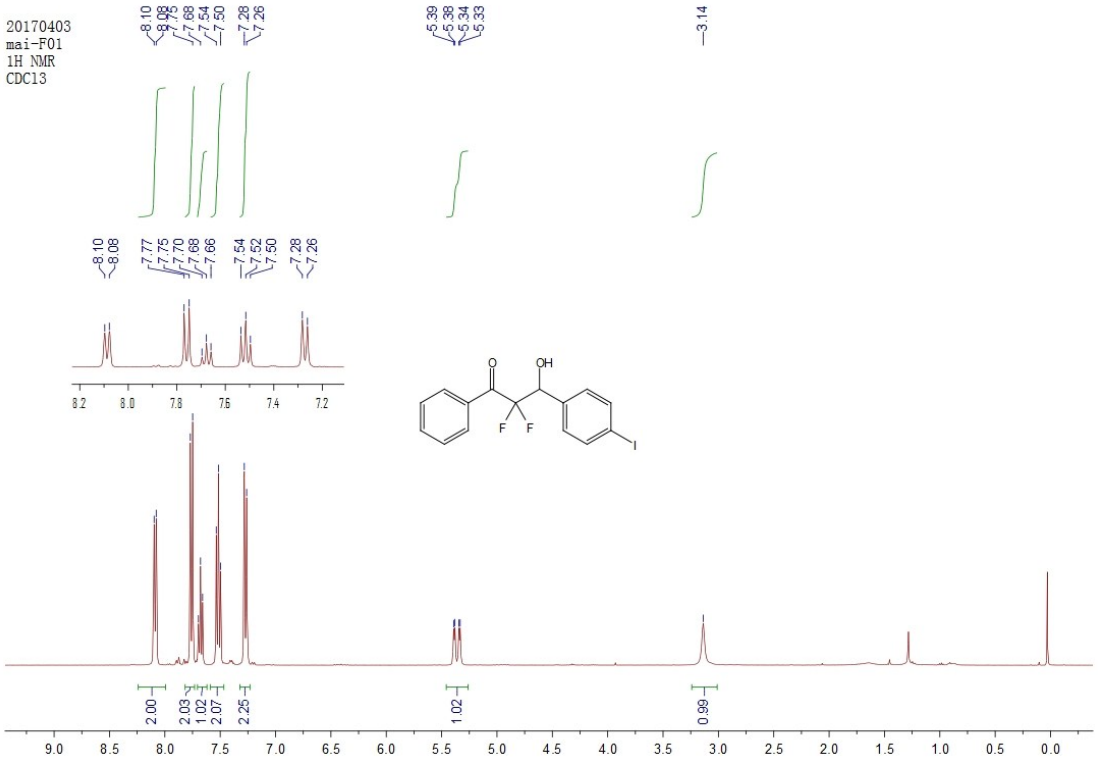
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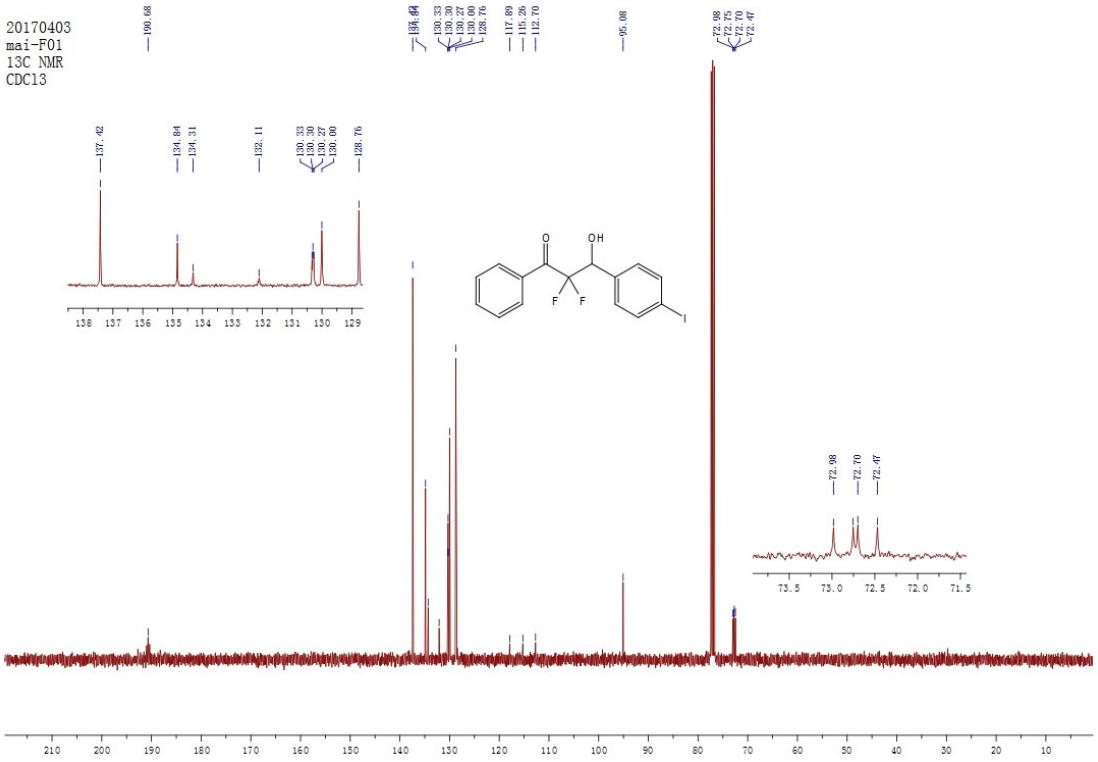
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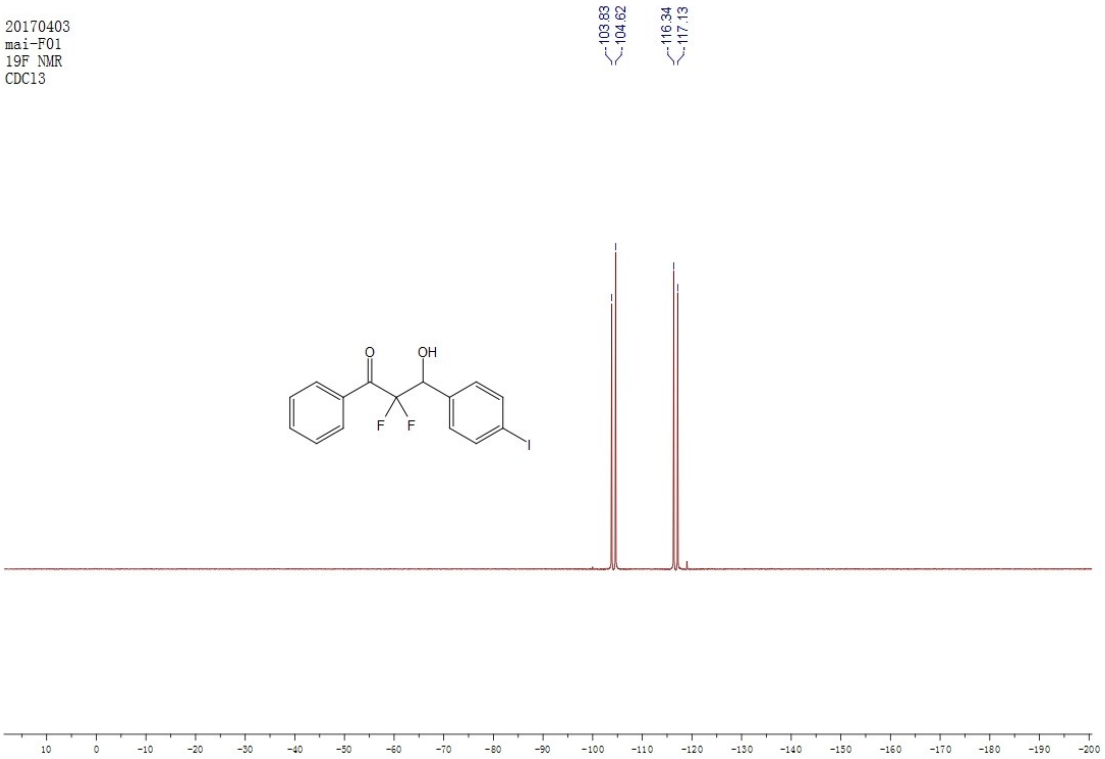
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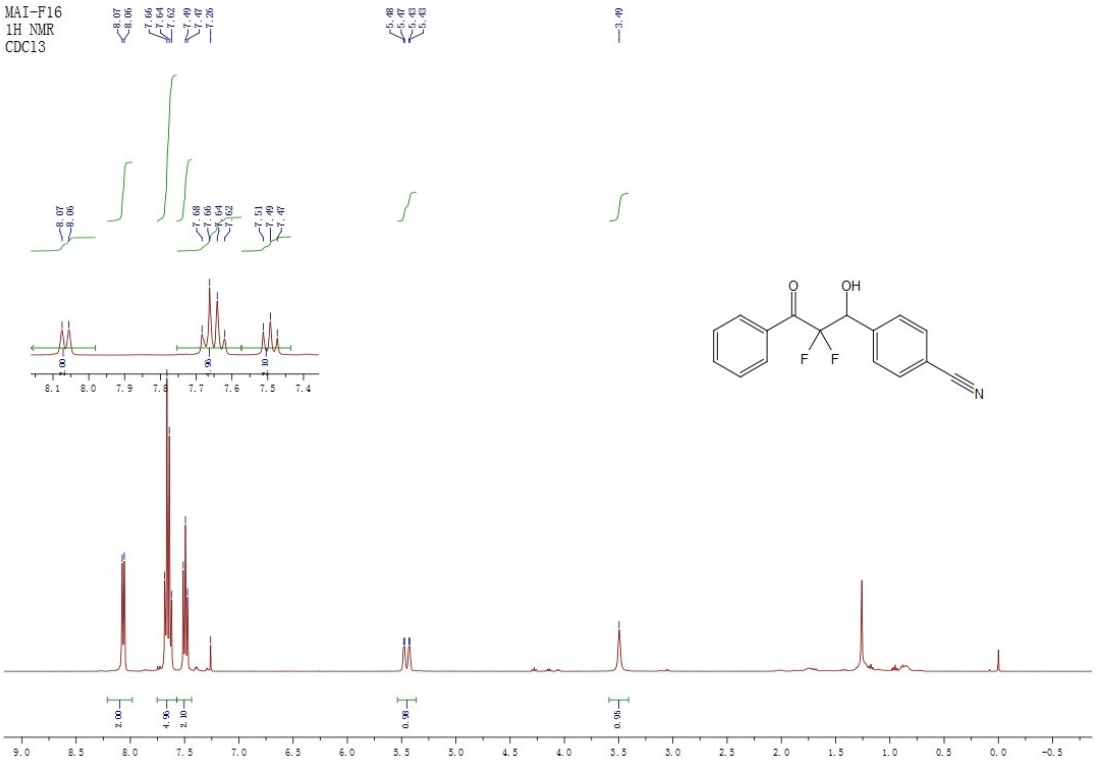
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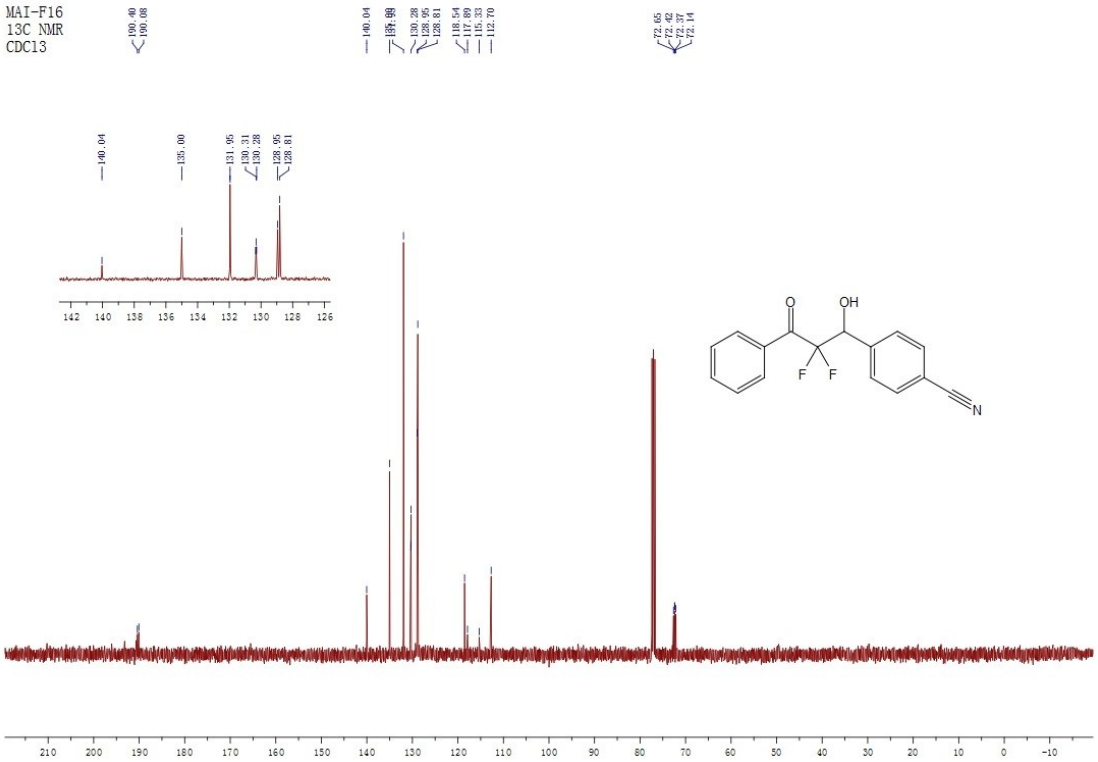
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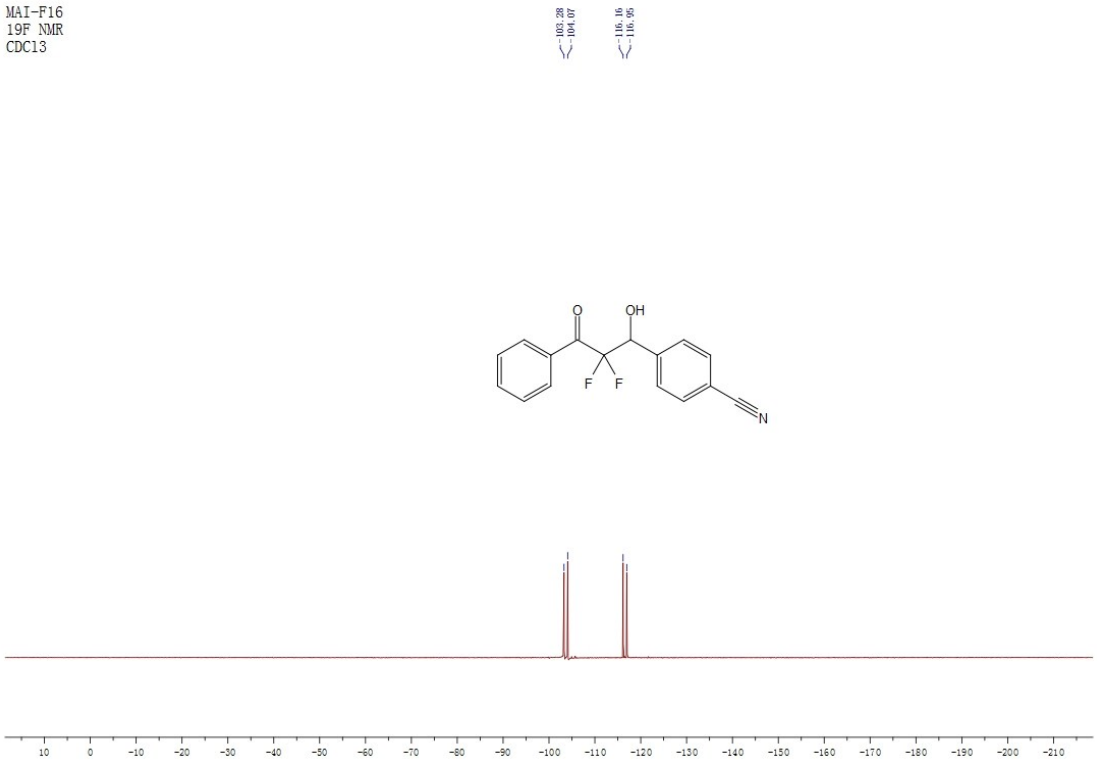
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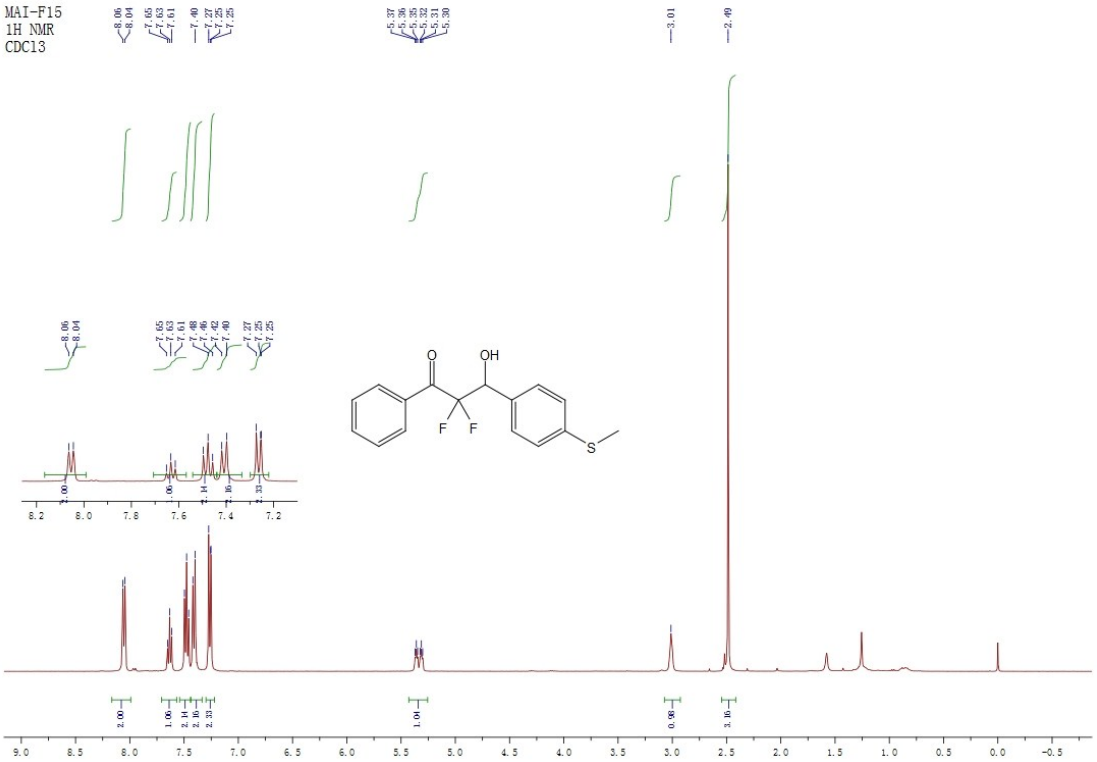
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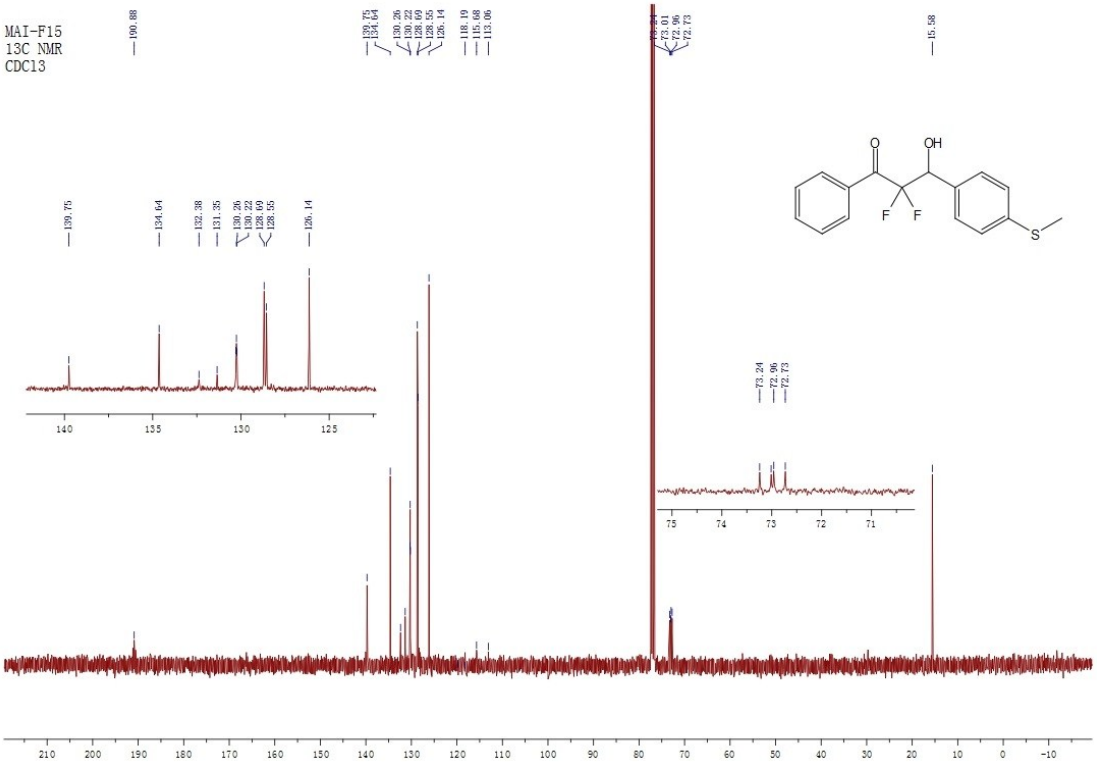
5.35
5.32
5.31
5.30
3.01
2.49
O
OH
F
F
S


MAI-F15
13C NMR
CDC13
190.88
139.75
134.64
132.38
131.35
130.26
130.22
128.69
128.55
126.14
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113.06
73.24
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72.96
72.73
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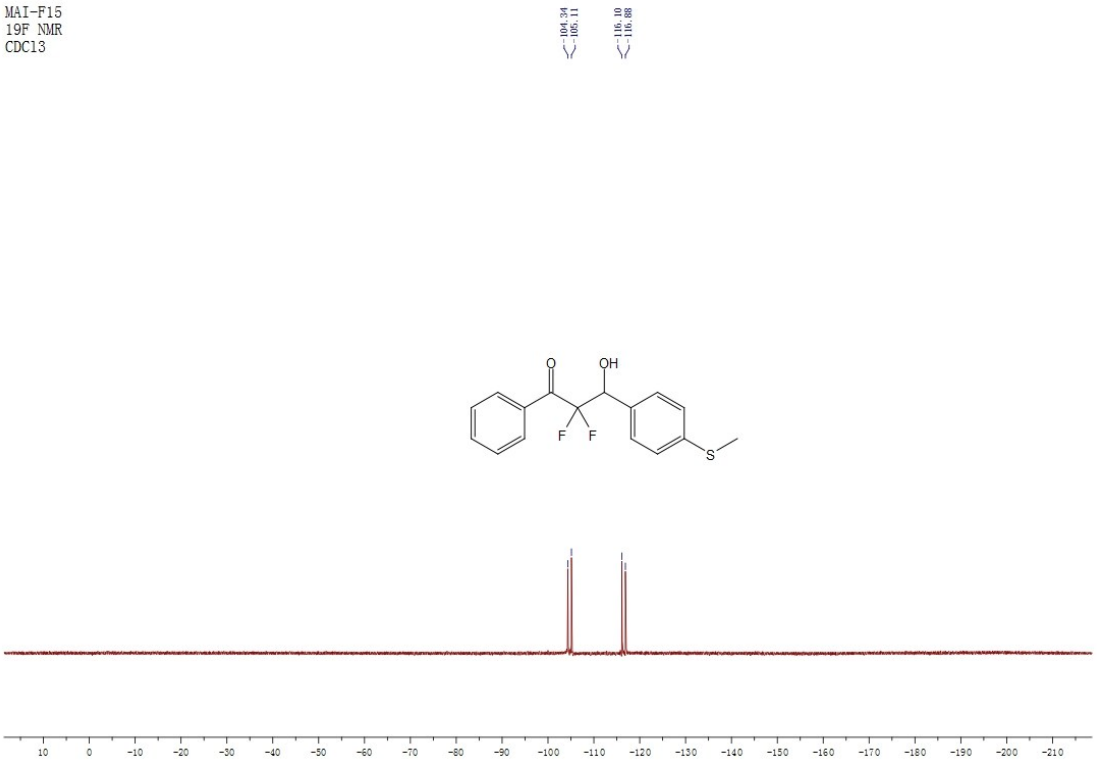
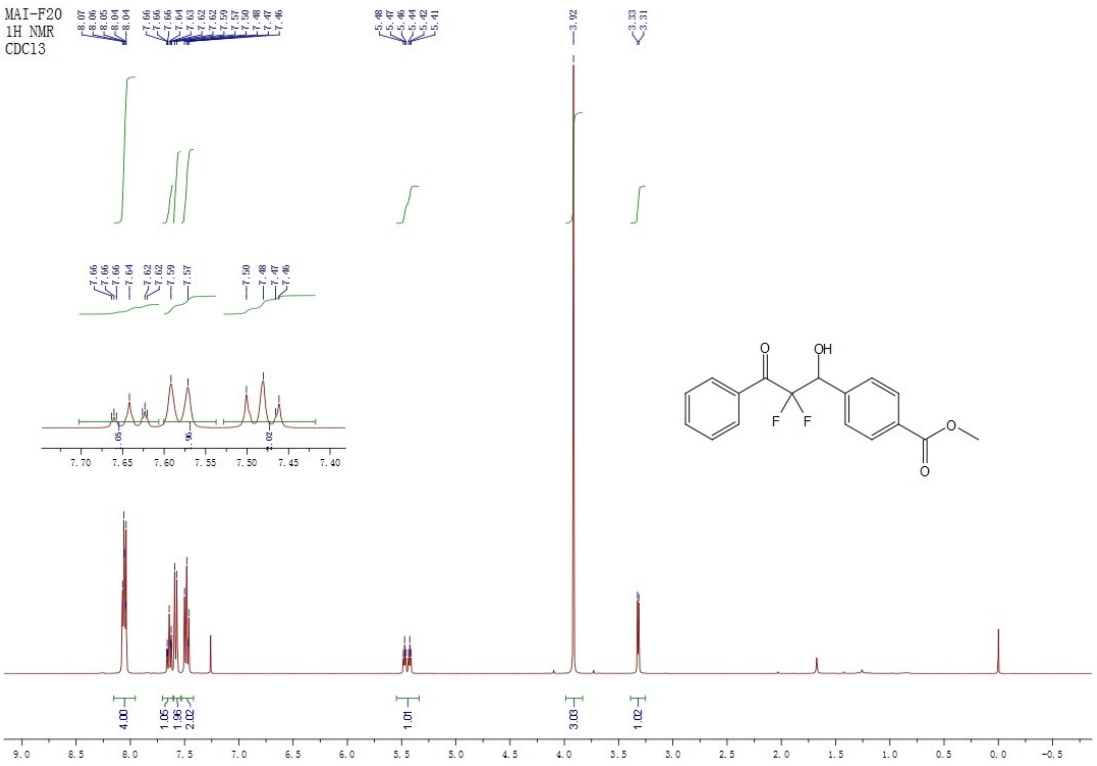
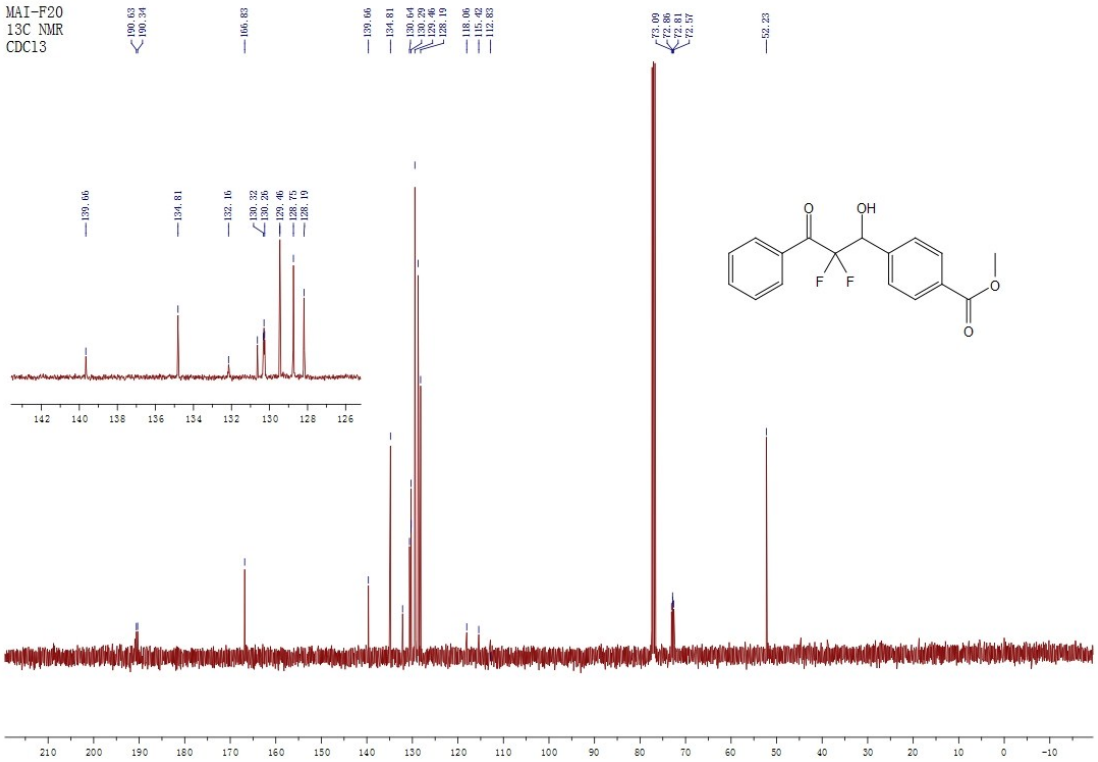
OH
F
F
S


MAI-F15
19F NMR
CDC13
-104.34
-105.11
-116.10
-116.88
O
OH
F
F
S


MAI-F20
1H NMR
CDC13
O
OH
F
F
O
O


MAI-F20
13C NMR
CDC13
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166.83
139.66
134.81
130.64
130.32
129.46
128.19
118.06
115.42
112.83
73.09
72.86
72.81
72.57
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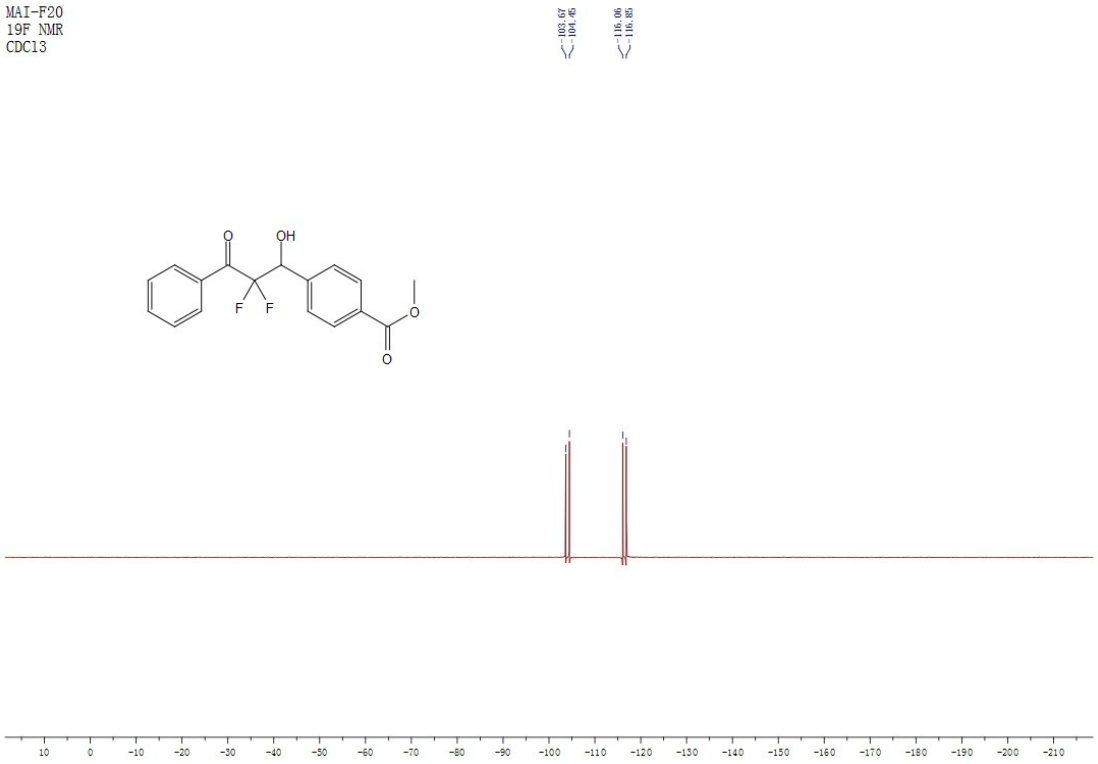
132.16
130.32
130.26
129.46
128.75
128.19
O
OH
F
F
O
O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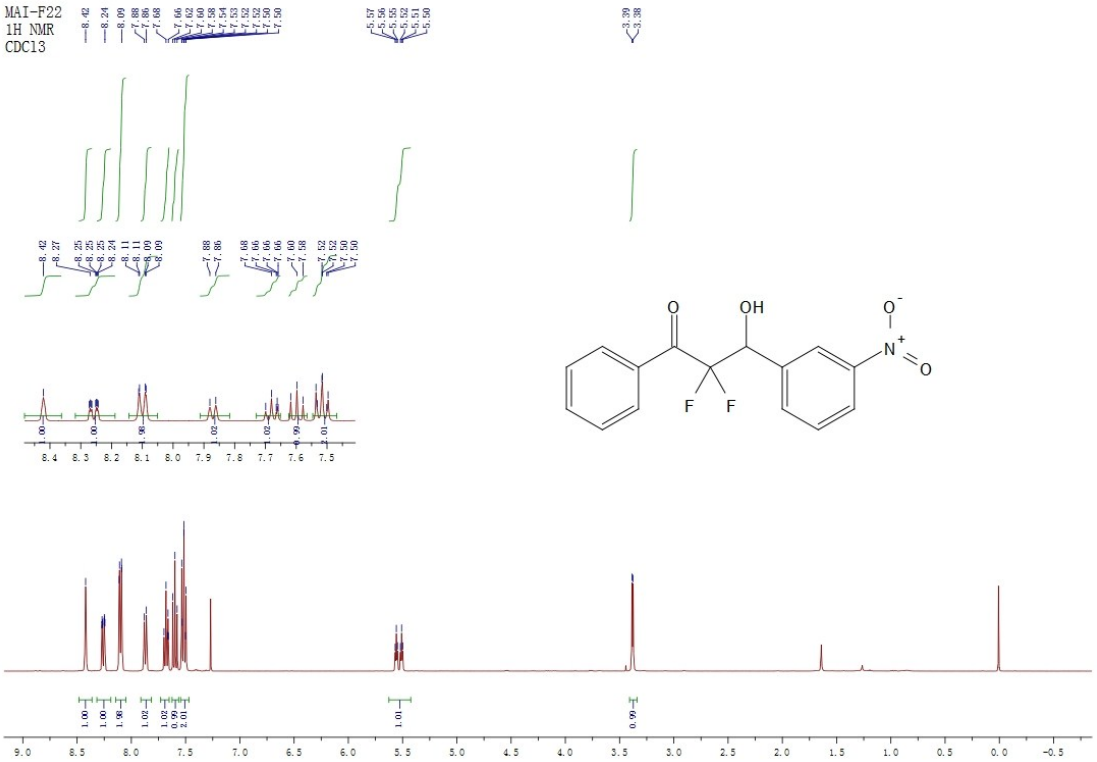
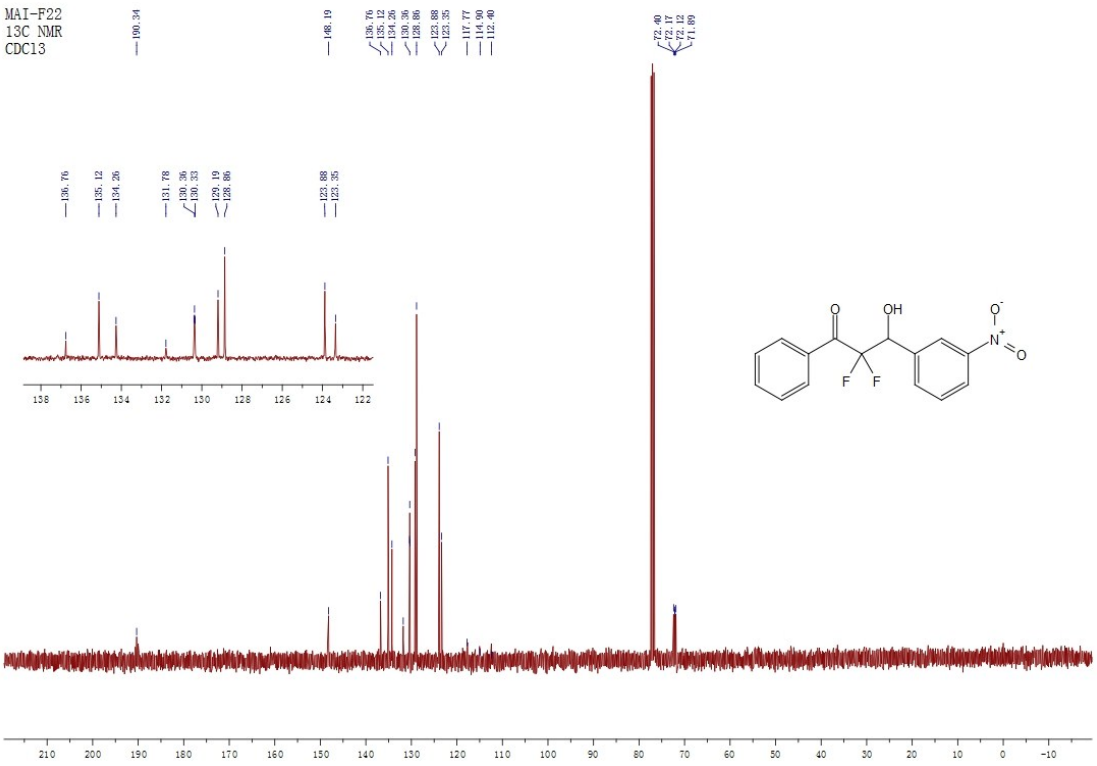
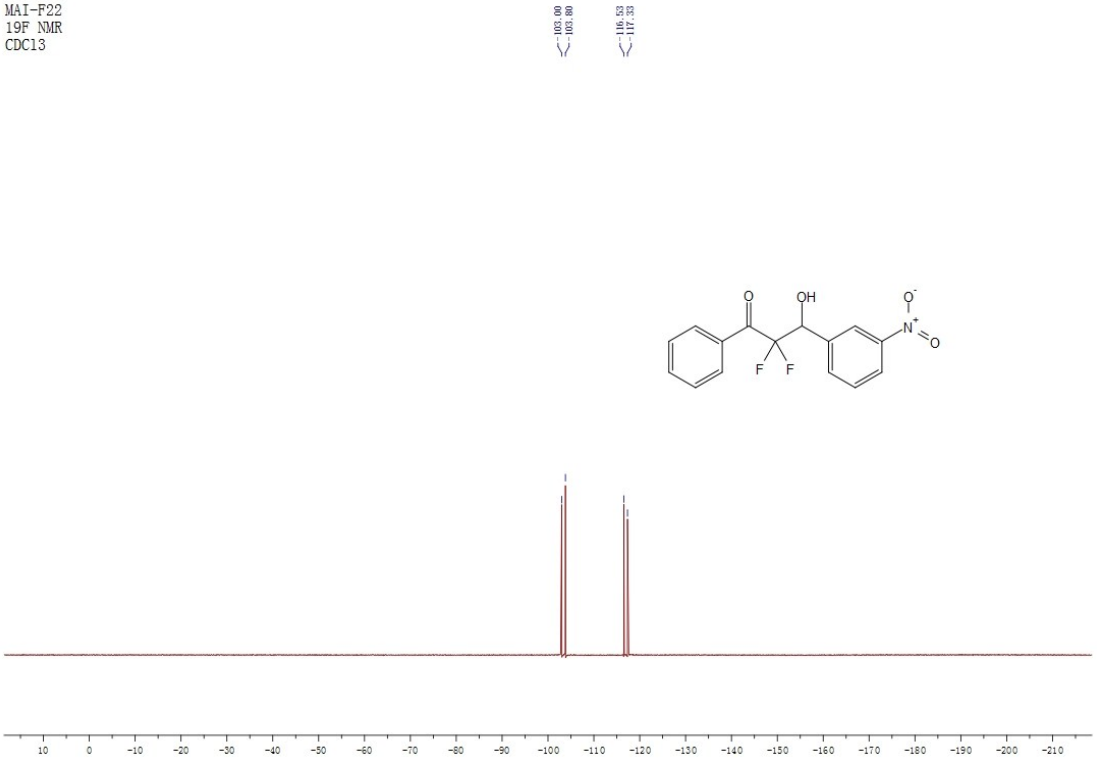
19F NMR
CDC13
103.67
104.46
116.06
116.85
O
OH
F
F
O
O

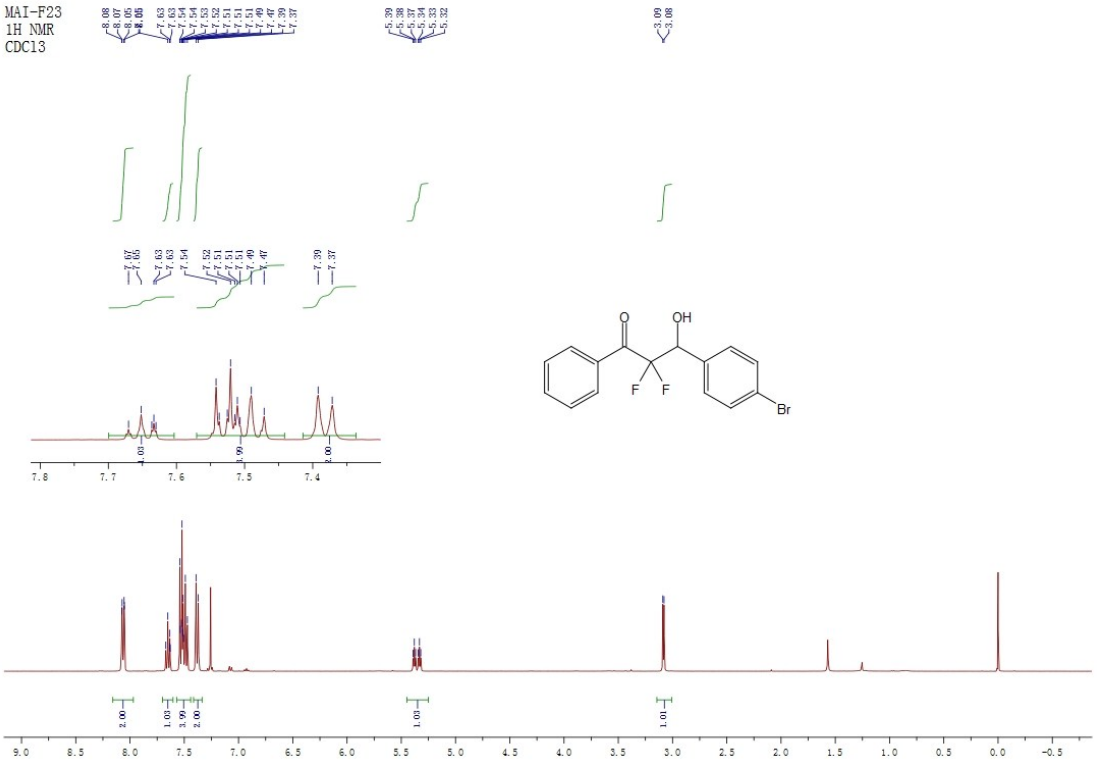

MAI-F22
1H NMR
CDC13
O
OH
F
F
N+
O-

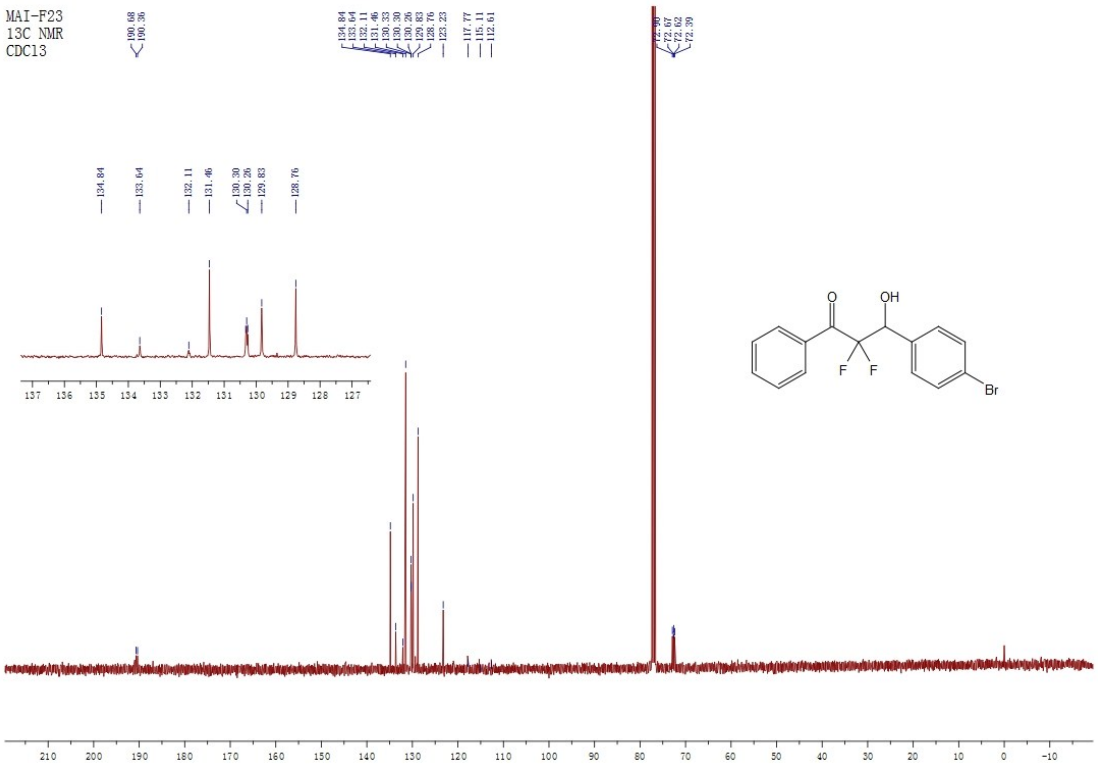

MAI-F22
13C NMR
CDC13
O
OH
F
F
N+
O-

MAI-F22
19F NMR
CDC13



MAI-F23
1H NMR
CDC13




MAI-F23
13C NMR
CDC13
190.68
190.36
134.84
133.64
132.11
131.46
130.33
130.30
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129.83
128.76
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117.77
115.11
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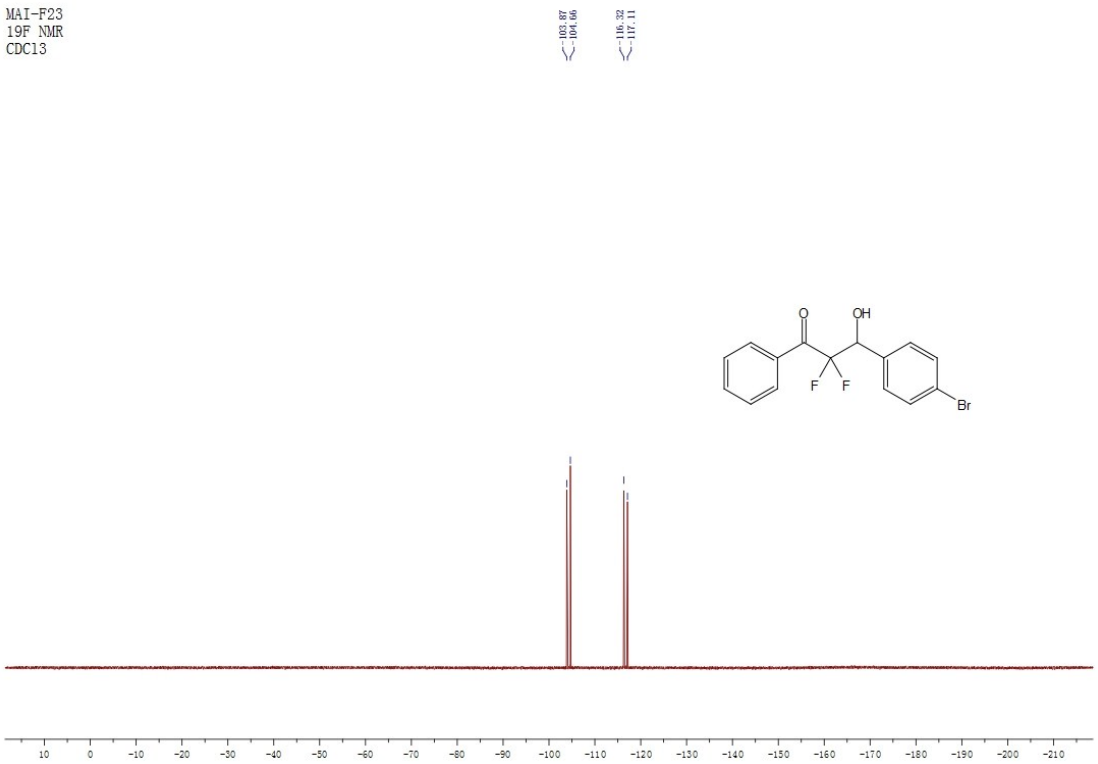
72.67
72.62
72.39
O
OH
F
F
Br


MAI-F23
19F NMR
CDC13
-103.87
-104.66
-116.32
-117.11
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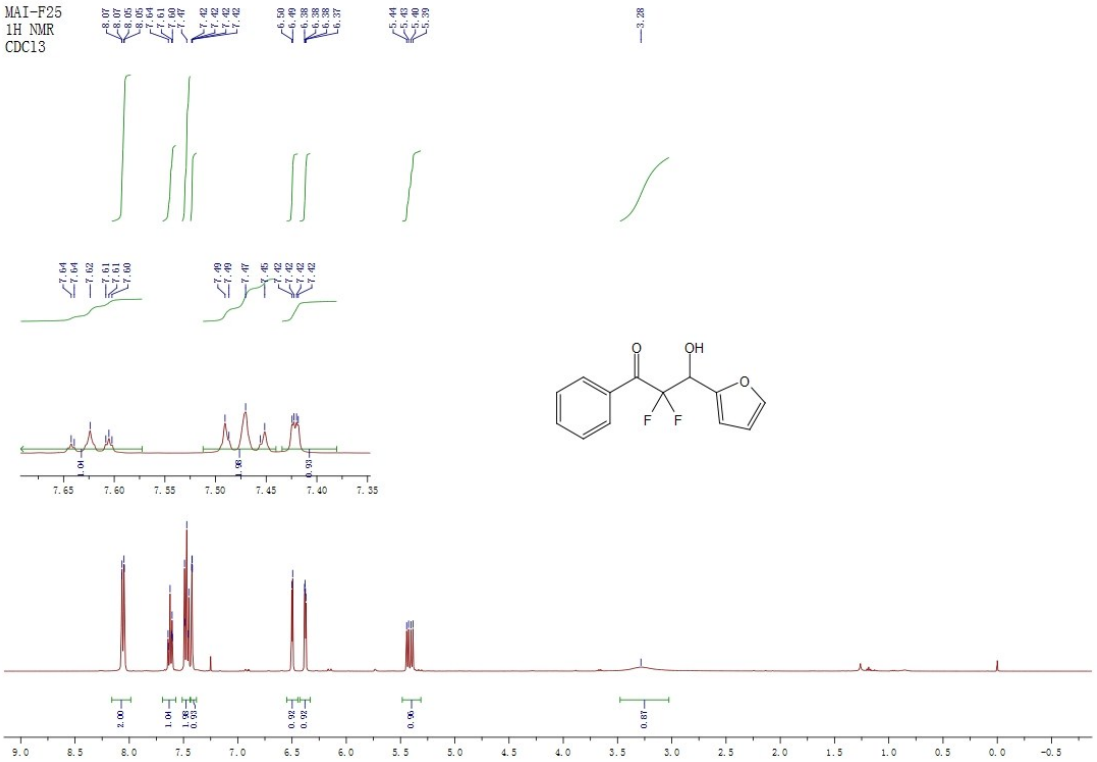
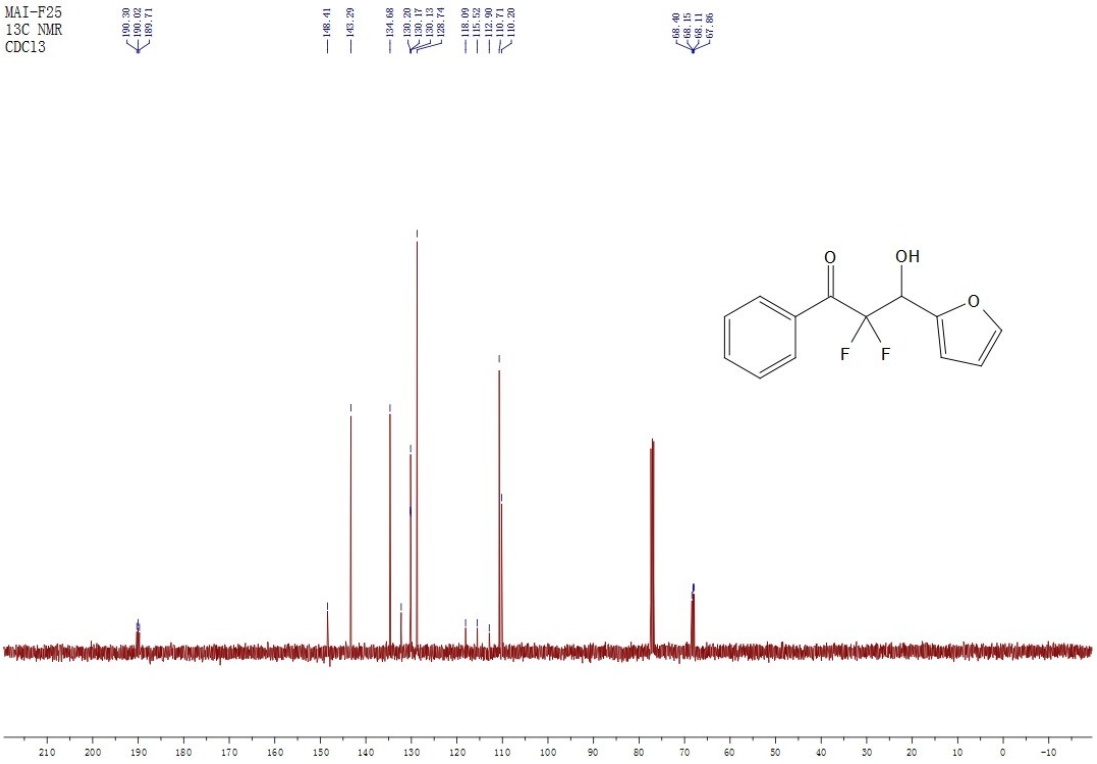
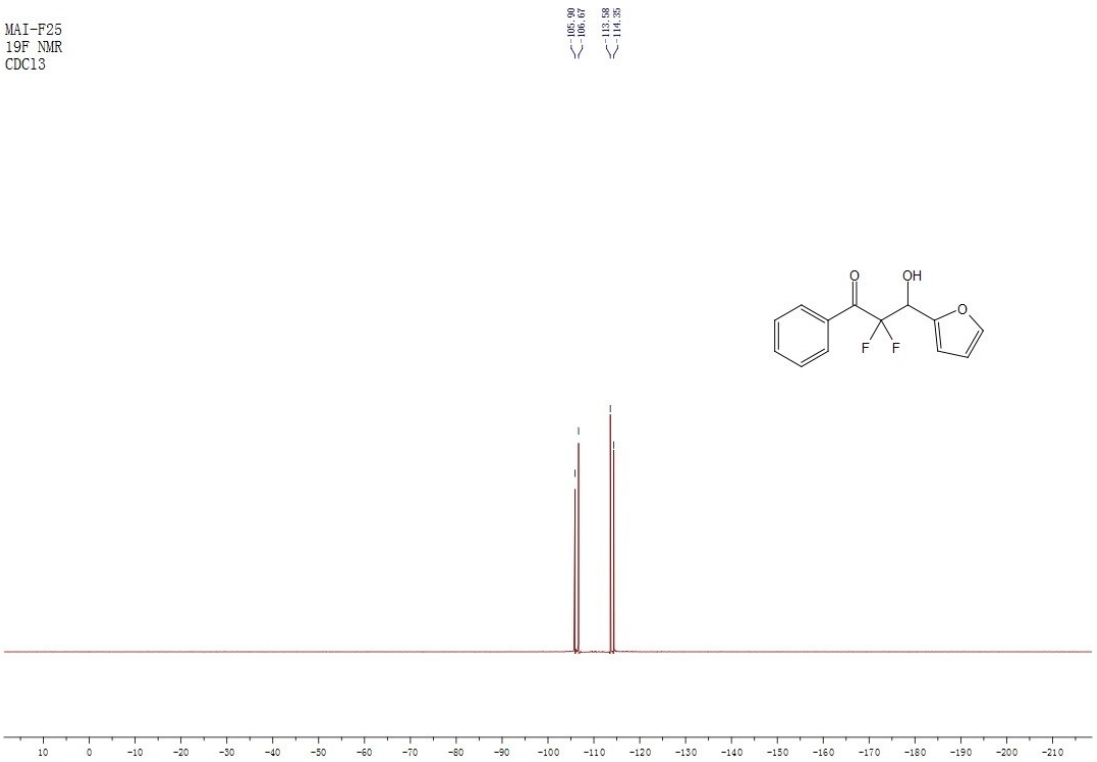
OH
F
F
Br

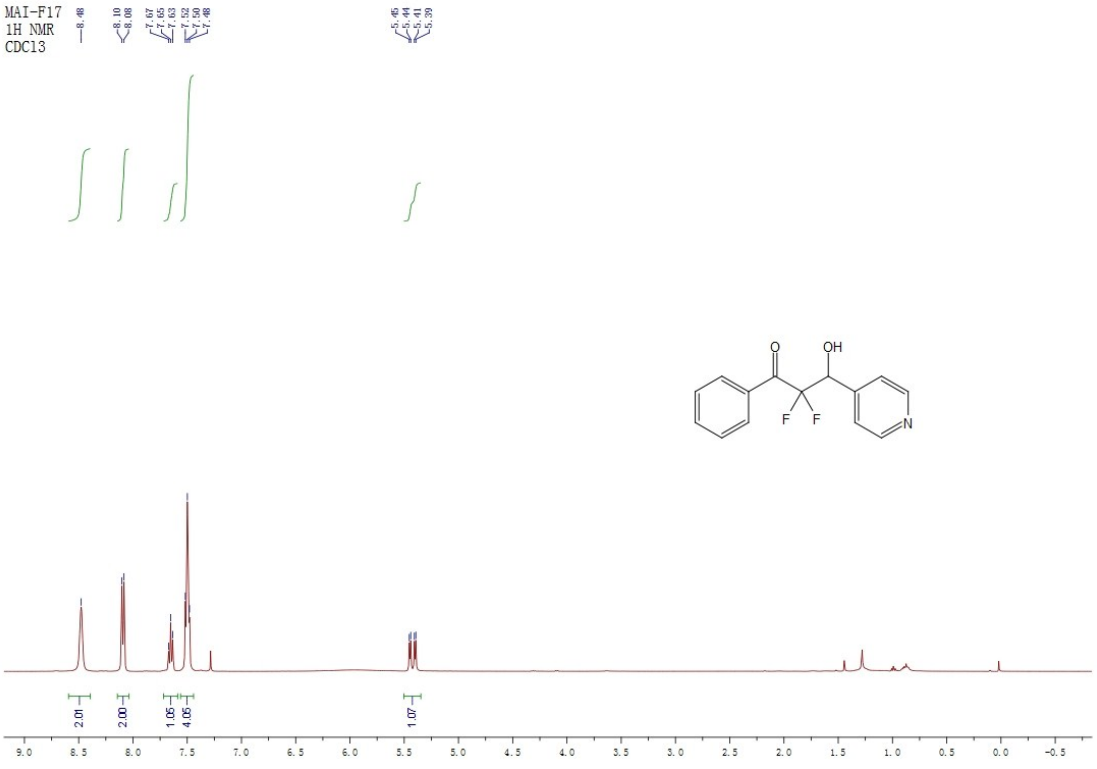

MAI-F25
1H NMR
CDC13
O
OH
O
F
F

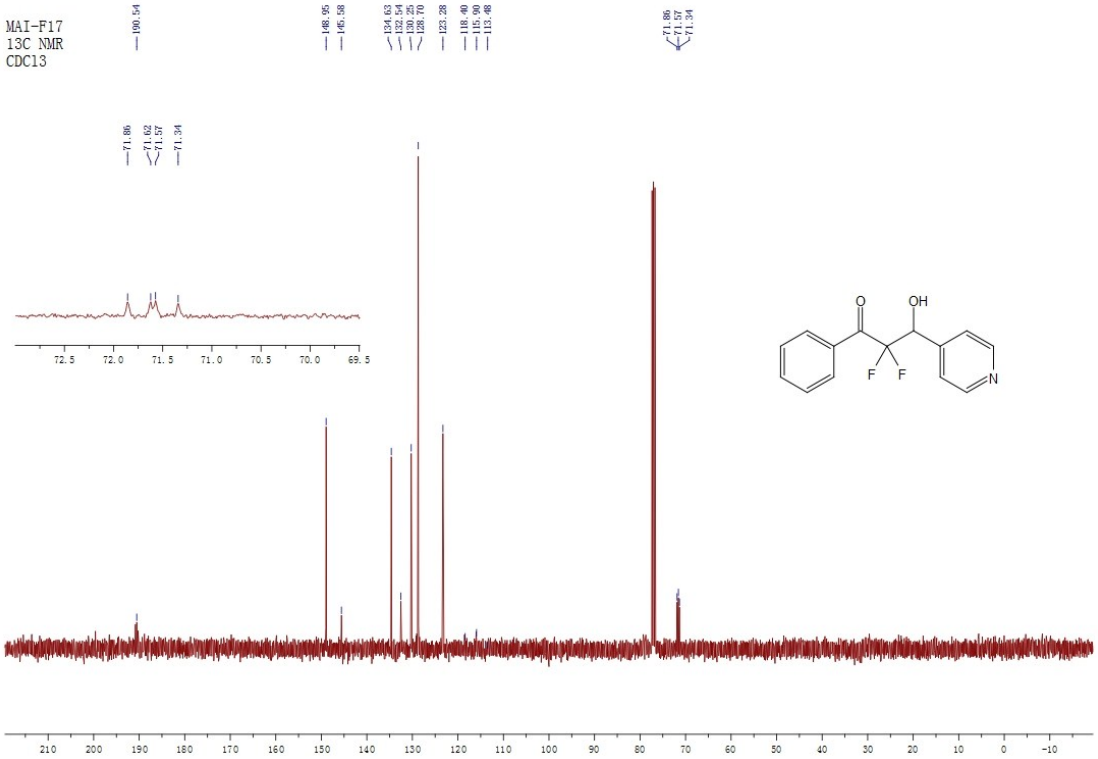

MAI-F25
13C NMR
CDC13
O
OH
O
F
F

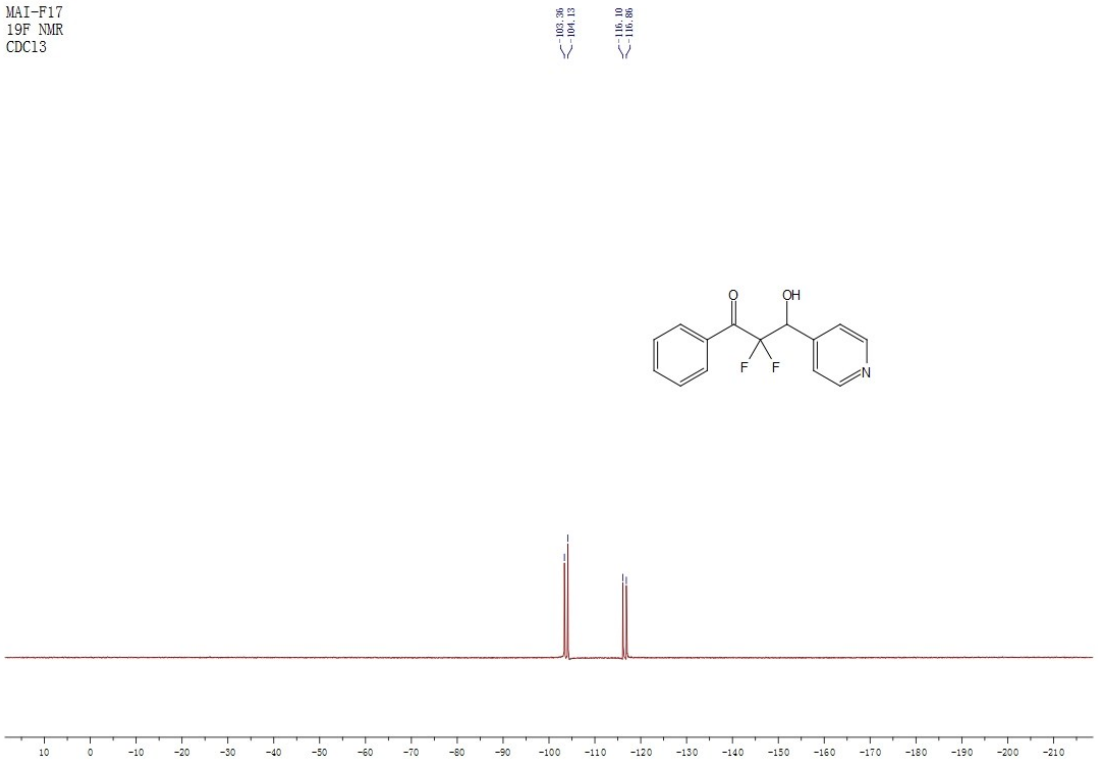
MAI-F25
19F NMR
CDC13

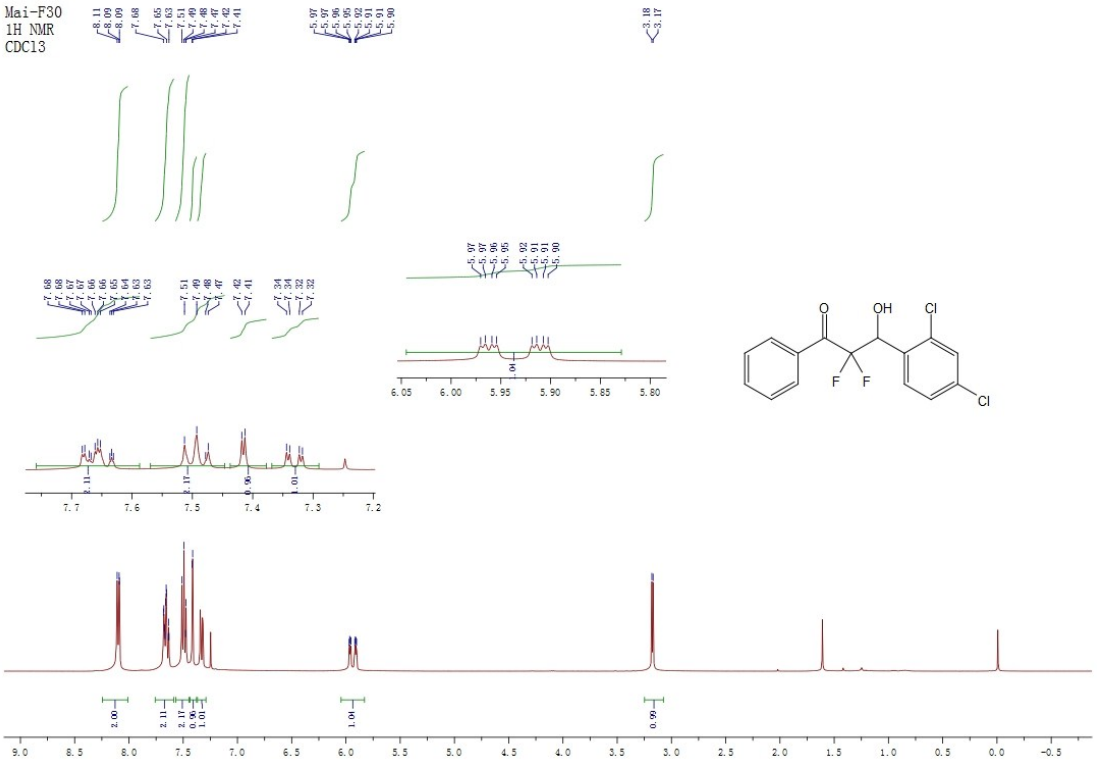


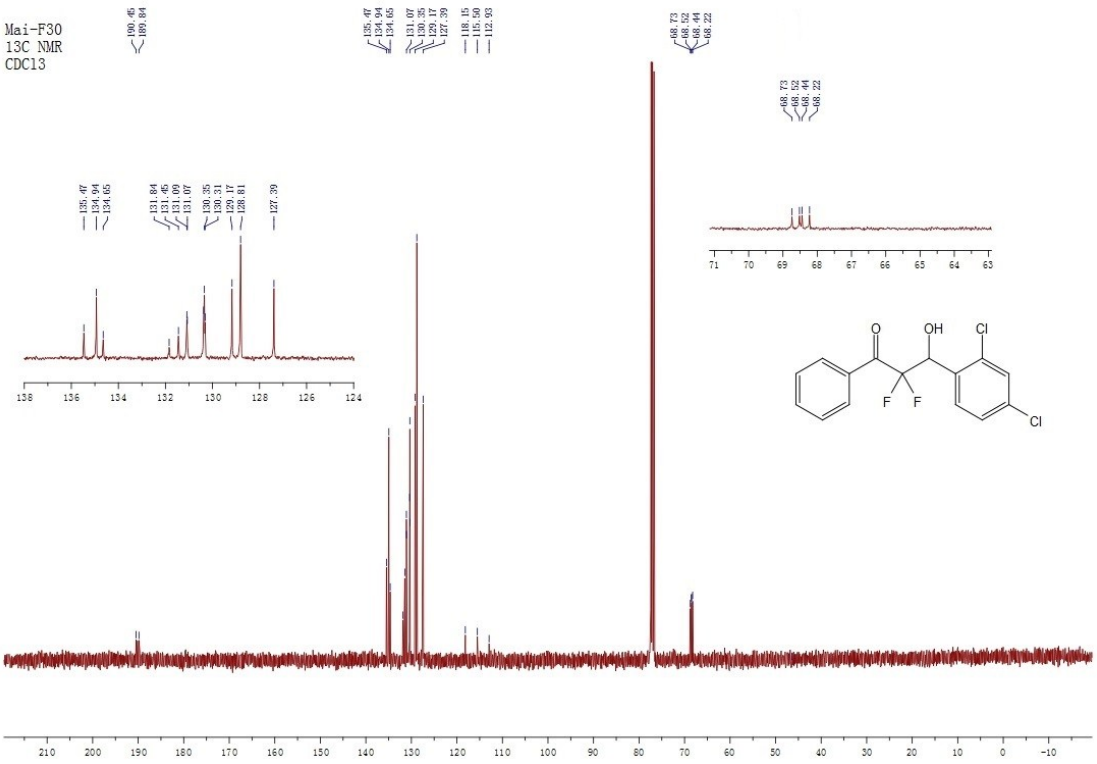
MAI-F17
1H NMR
CDC13



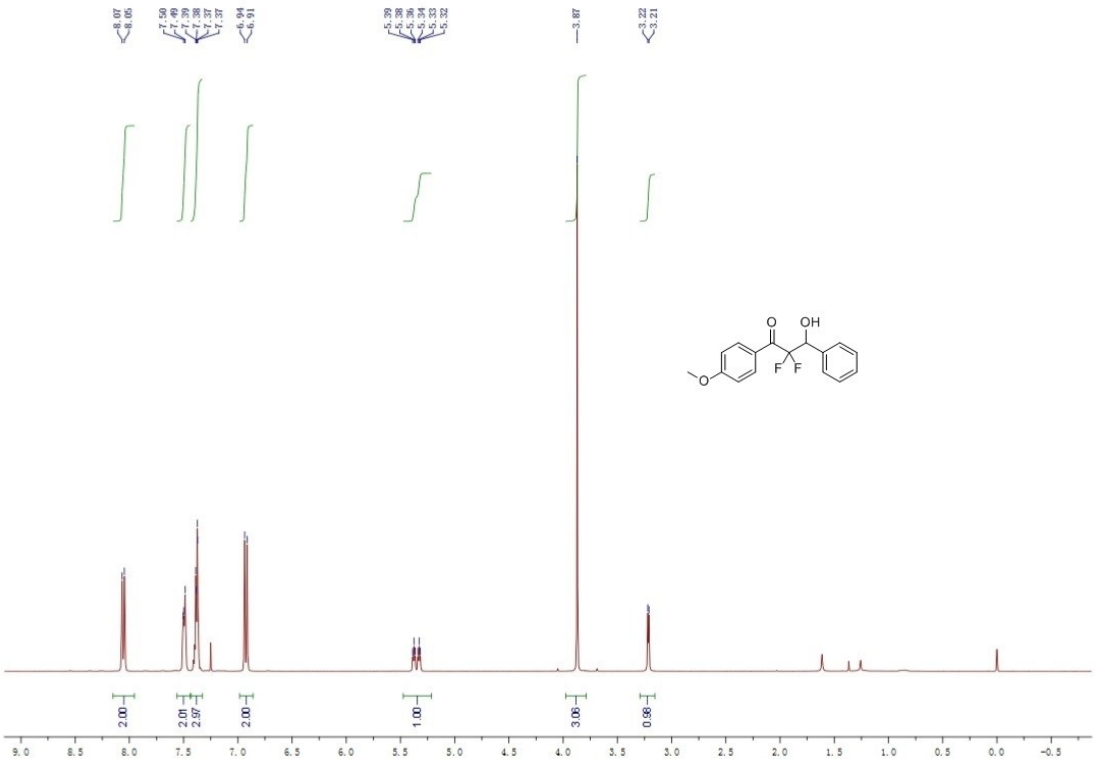

MAI-F17
13C NMR
CDC13
190.54
148.95
145.58
134.63
132.54
130.25
128.10
123.28
118.40
115.90
113.48
71.86
71.57
71.34
O
OH
F
F
N

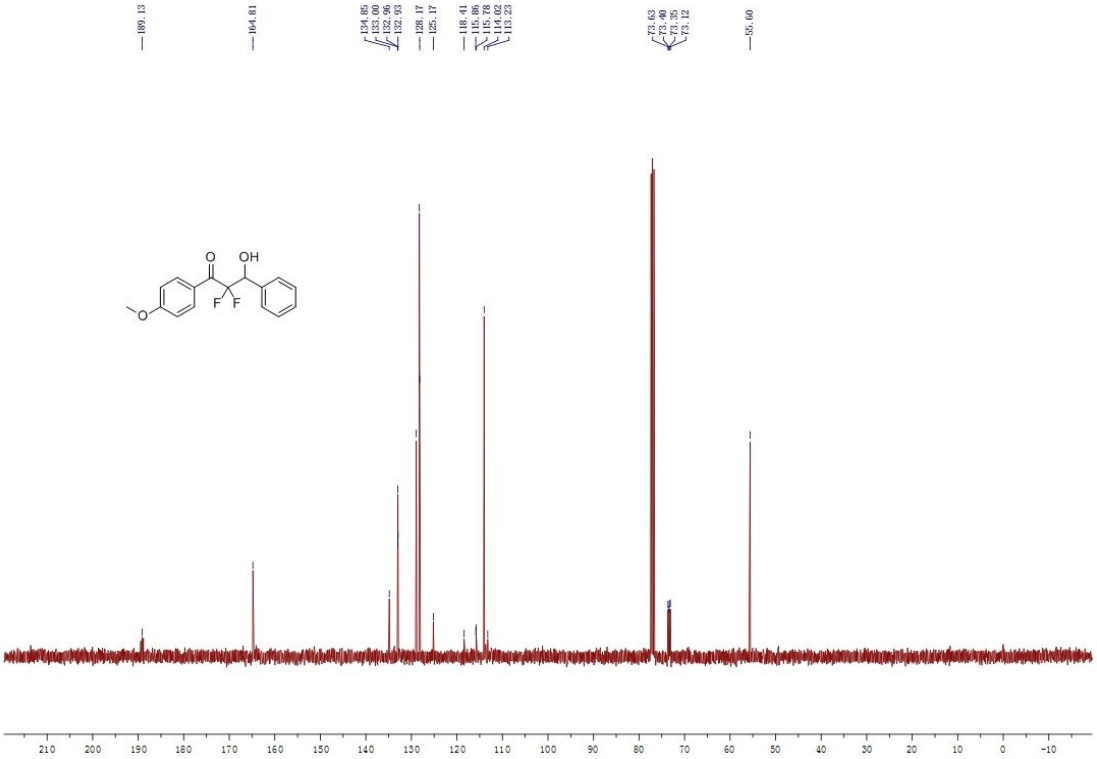

MAI-F17
19F NMR
CDC13
-103.36
-104.13
-116.10
-116.86
O
OH
F
F
N


Mai-F30
1H NMR
CDC13
O
OH
Cl
F
F
Cl

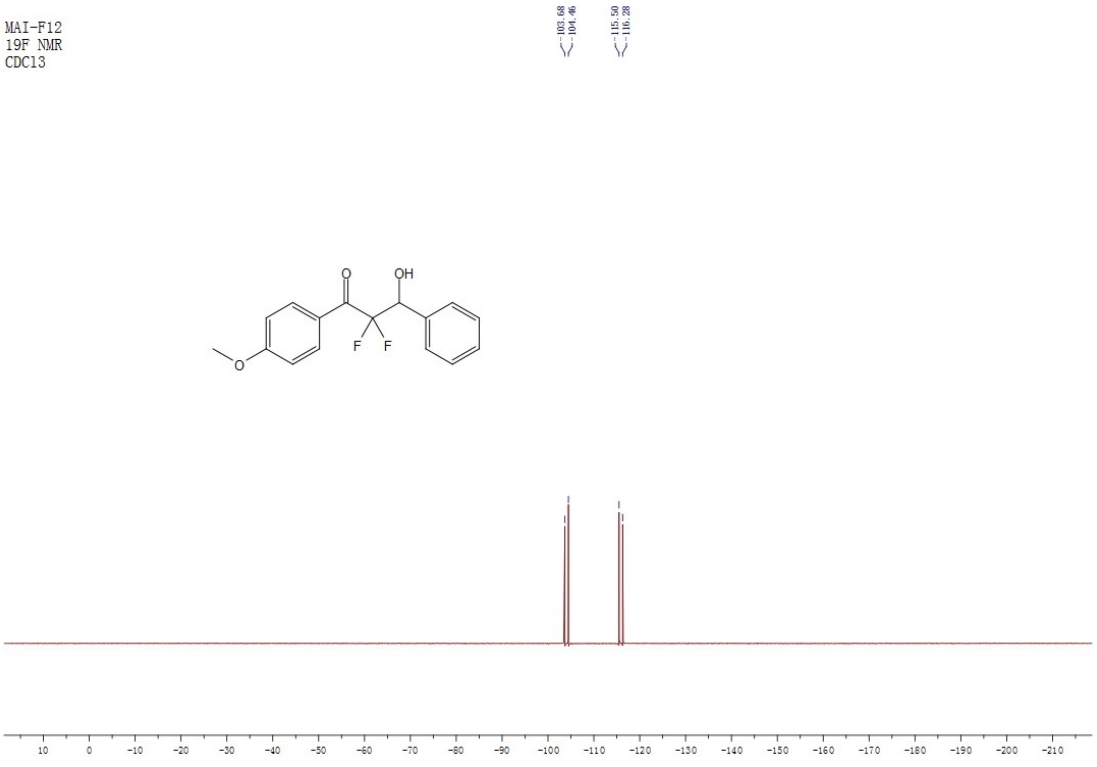

Mai-F30
13C NMR
CDC13
O
OH
Cl
F
F
Cl

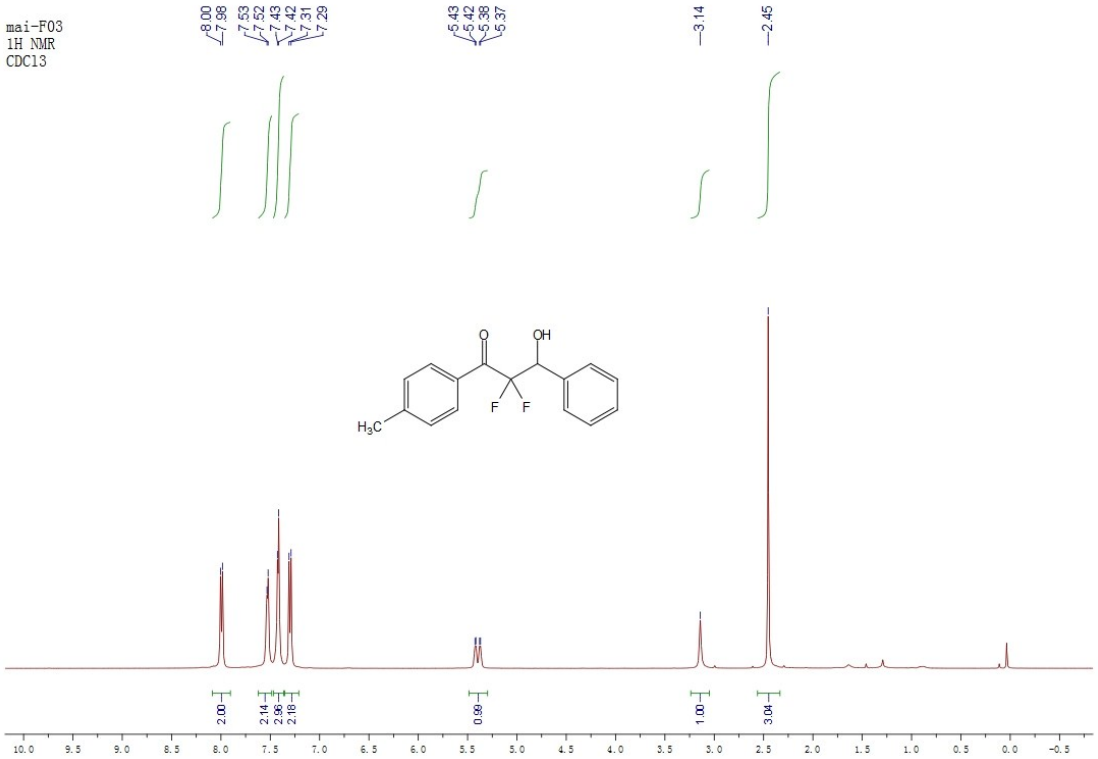

Mai-F30
19F NMR
CDC13
103.19
103.99
117.56
118.36
O
OH
Cl
F
F
Cl


8.07
8.05
7.50
7.49
7.39
7.38
7.37
7.37
6.94
6.91
5.39
5.38
5.36
5.34
5.33
5.32
3.87
3.22
3.21
O
OH
F
F
O
2.00
2.01
2.97
2.00
1.00
3.00
0.98



MAI-F12
19F NMR
CDC13




mai-F03
1H NMR
CDC13
8.00
7.98
7.53
7.52
7.43
7.42
7.31
7.29
5.43
5.42
5.38
5.37
3.14
2.45
O
OH
F
F
H3C
2.00
2.14
2.96
2.18
0.99
1.00
3.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
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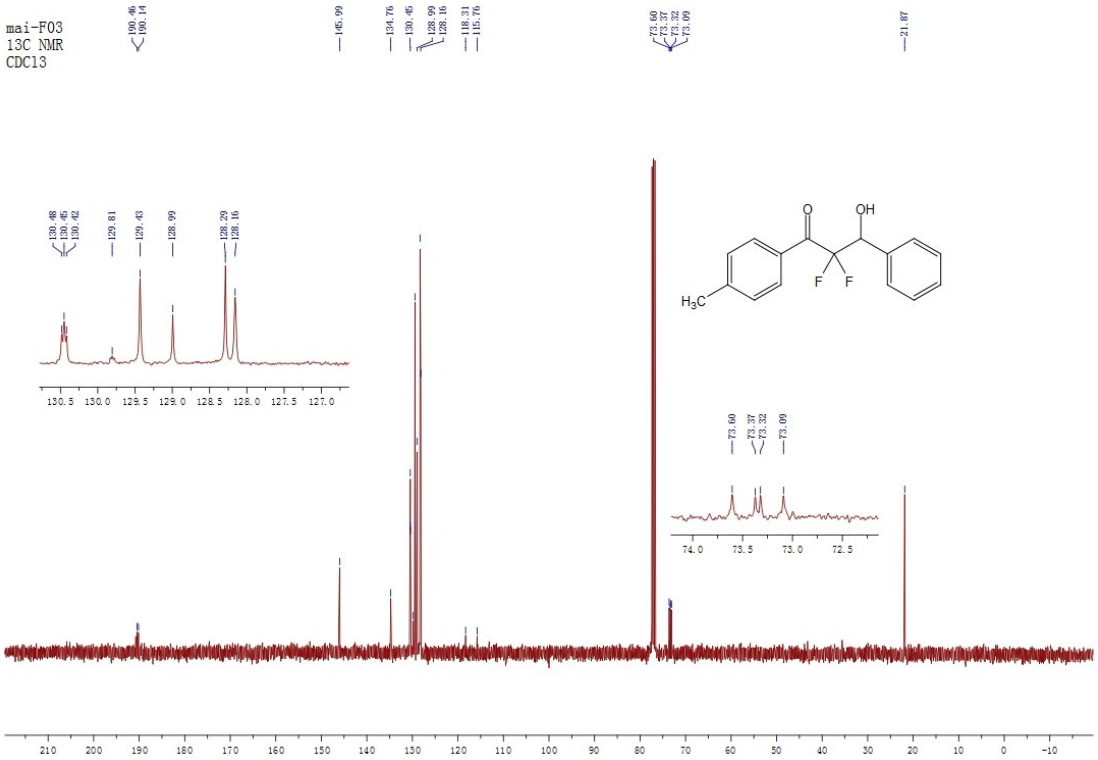
1.0
0.5
0.0
-0.5


mai-F03
13C NMR
CDC13
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128.99
128.16
118.31
115.76
73.60
73.37
73.32
73.09
21.87
130.48
130.45
130.42
129.81
129.43
128.99
128.29
128.16
130.5
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129.0
128.5
128.0
127.5
127.0
O
OH
F
F
H3C
73.60
73.37
73.32
73.09
74.0
73.5
73.0
72.5
210
200
190
180
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100
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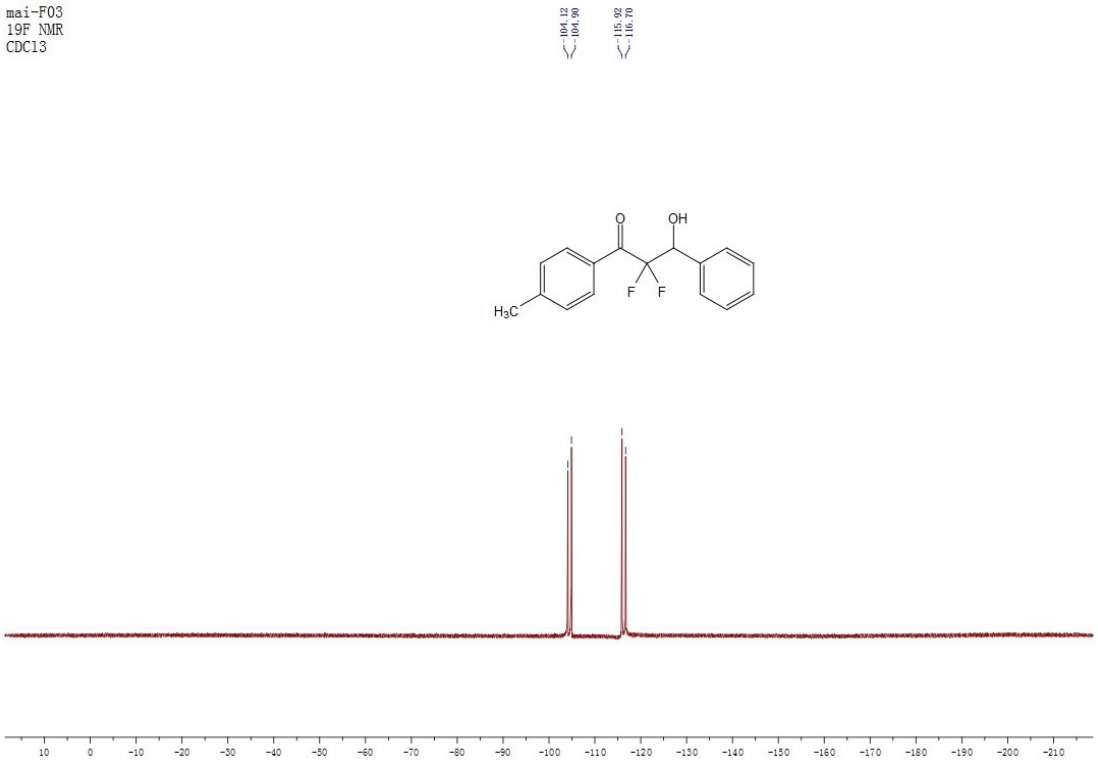
0
-10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19F NMR
CDC13
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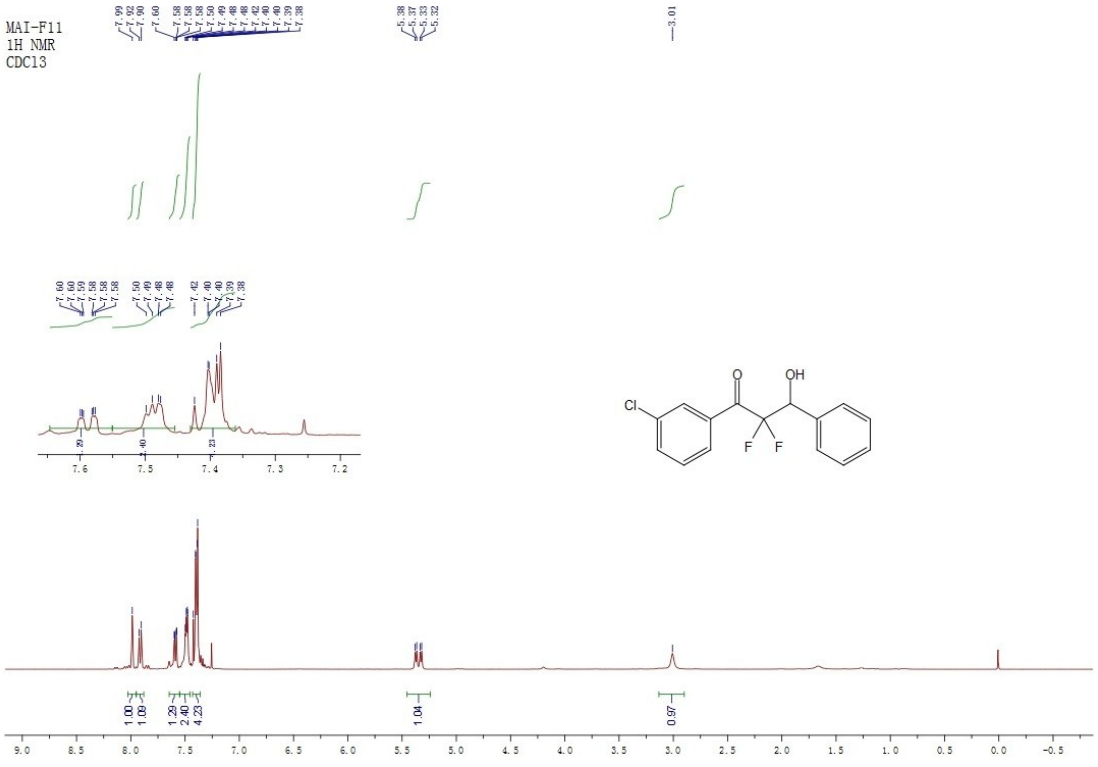
-115.92
-116.70
O
OH
F
F
H3C


MAI-F11
1H NMR
CDC13
7.99
7.92
7.90
7.60
7.58
7.58
7.56
7.56
7.49
7.48
7.48
7.42
7.40
7.40
7.39
7.38
5.38
5.37
5.33
5.32
3.01
O
OH
Cl
F
F
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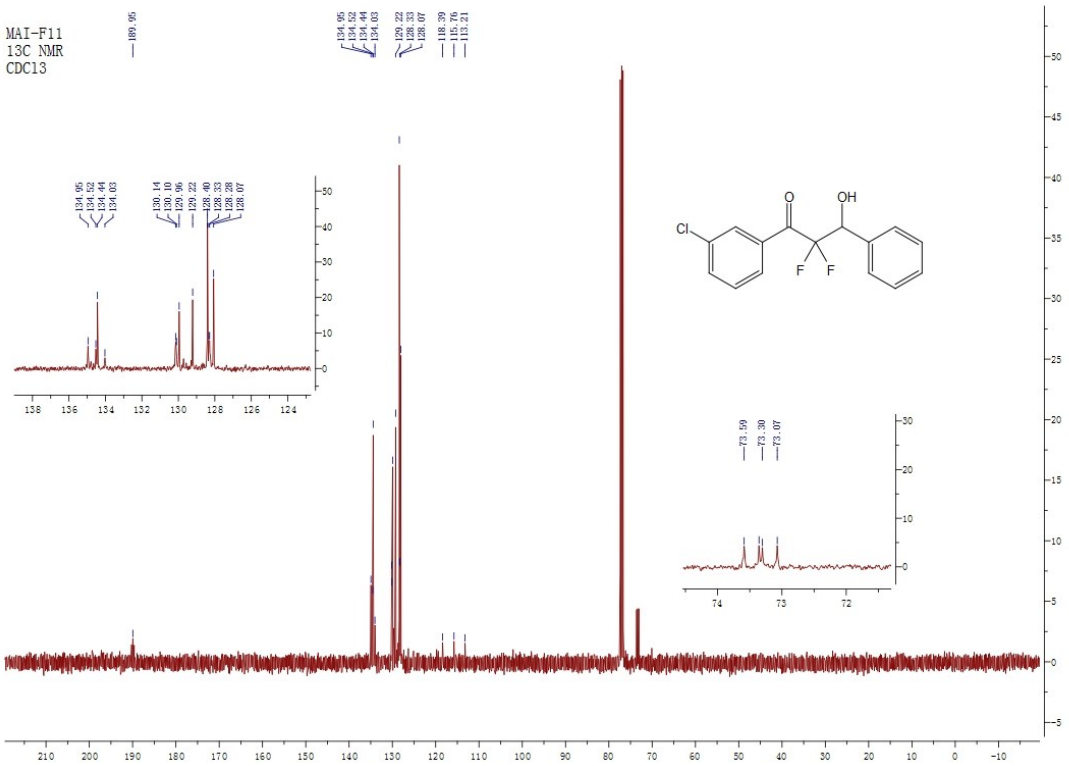
1.00
1.20
2.40
4.23
1.04
0.97


MAI-F11
13C NMR
CDC13
189.95
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134.52
134.44
134.03
129.22
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128.07
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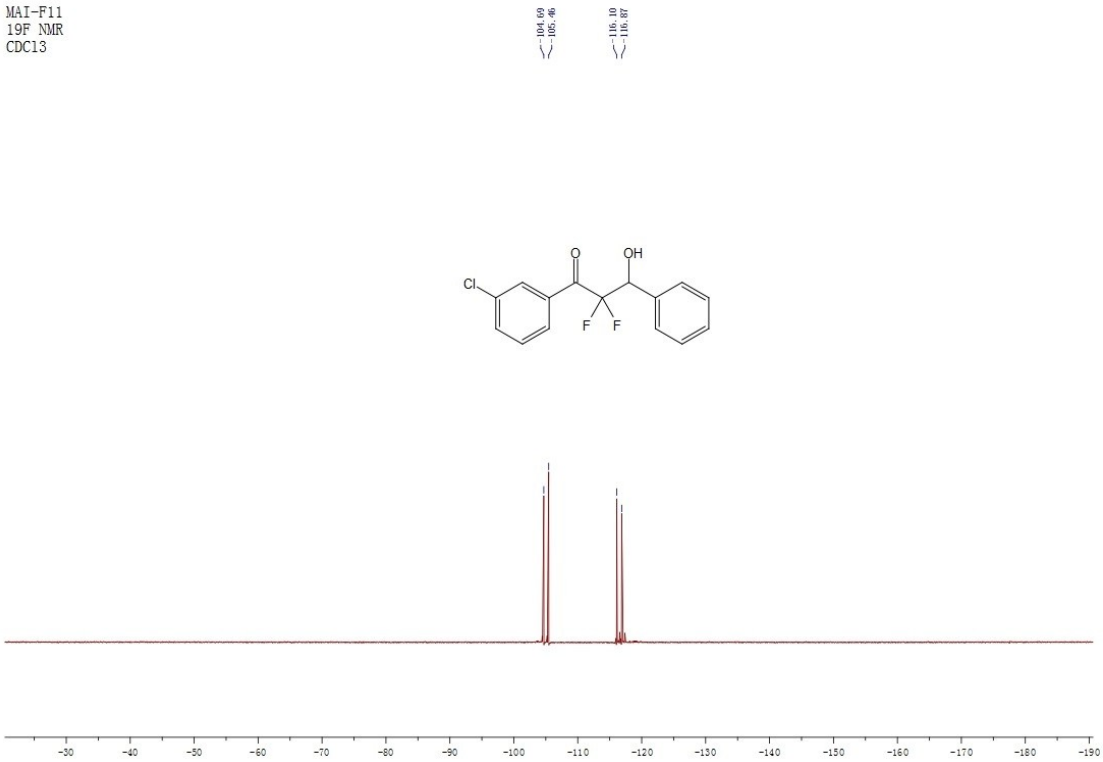
115.21
O
OH
Cl
F
F
73.59
73.30
73.07


MAI-F11
19F NMR
CDC13
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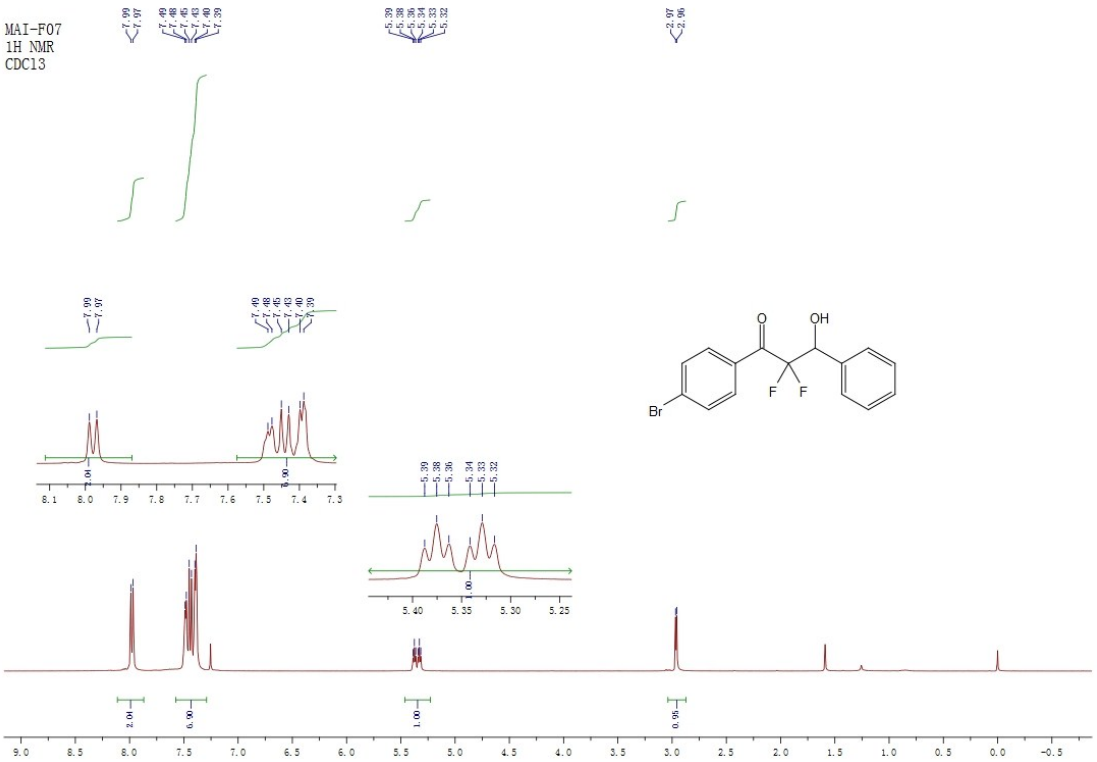
O
OH
Cl
F
F


MAI-F07
1H NMR
CDC13
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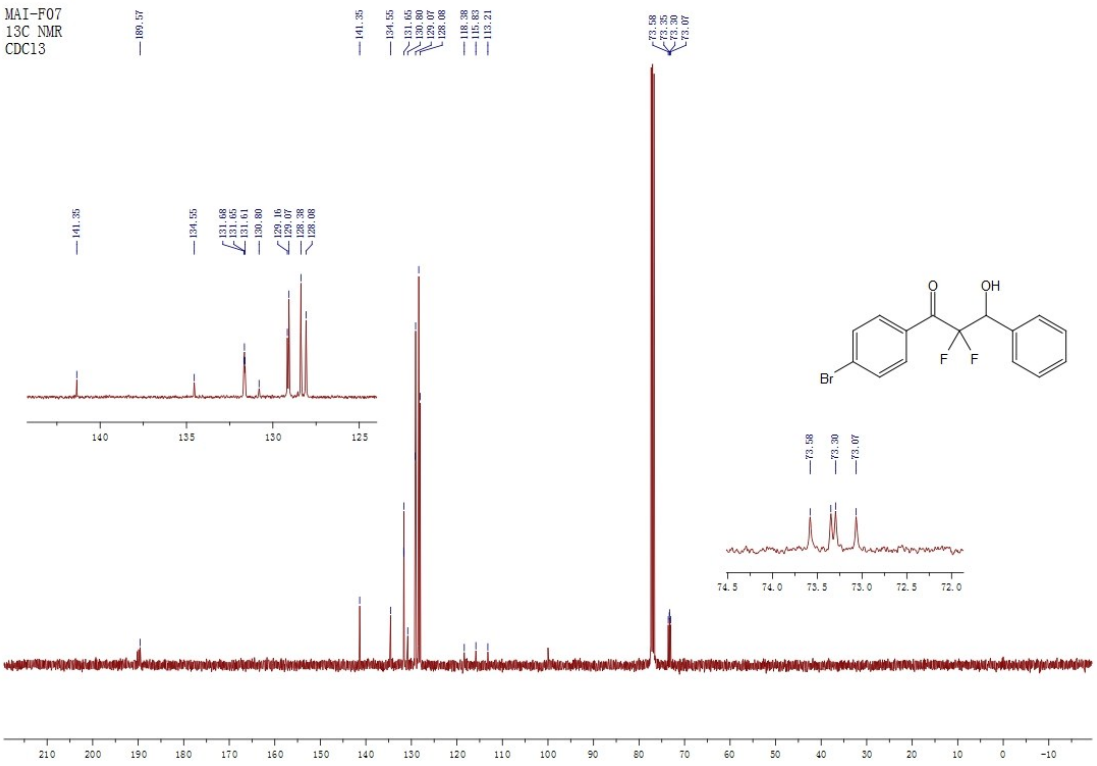
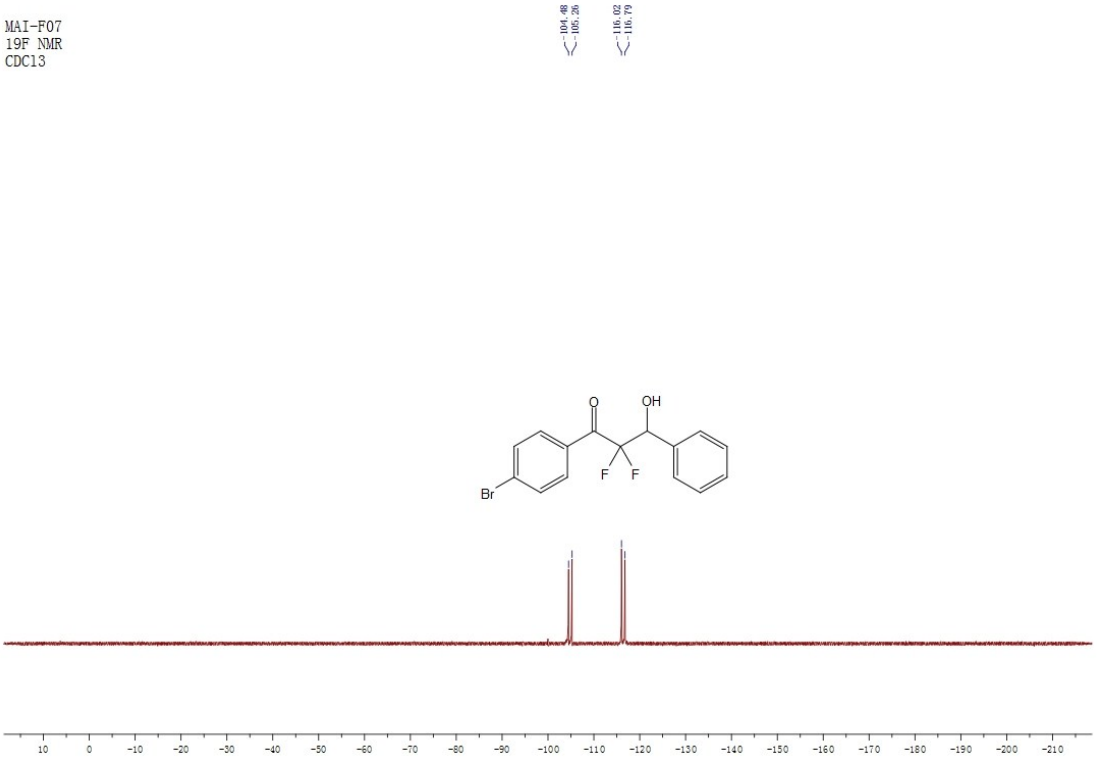
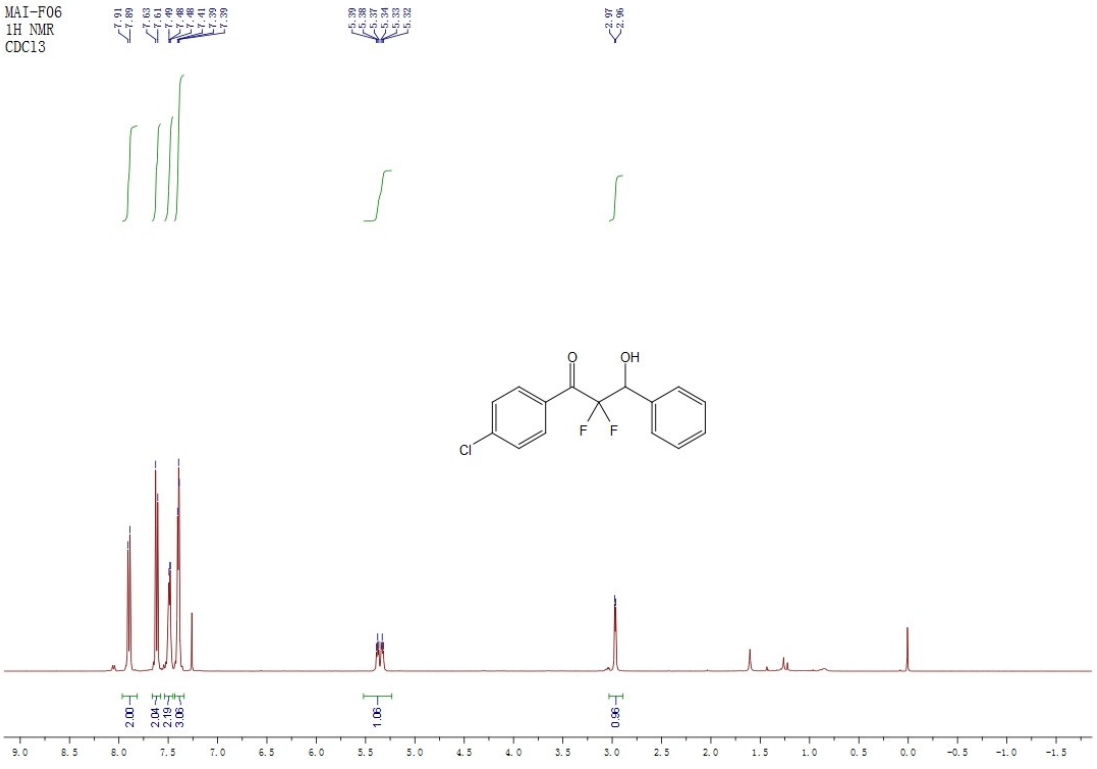
OH
F
F
Br

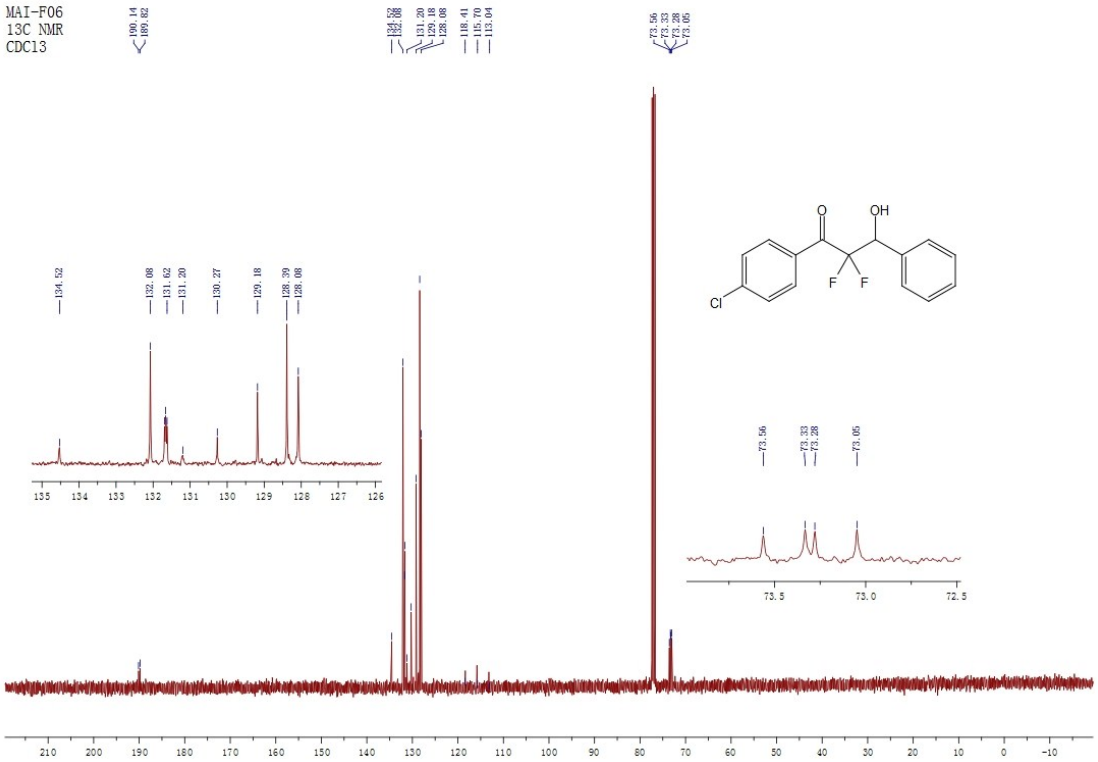

MAI-F07
13C NMR
CDC13
O
OH
F
F
Br

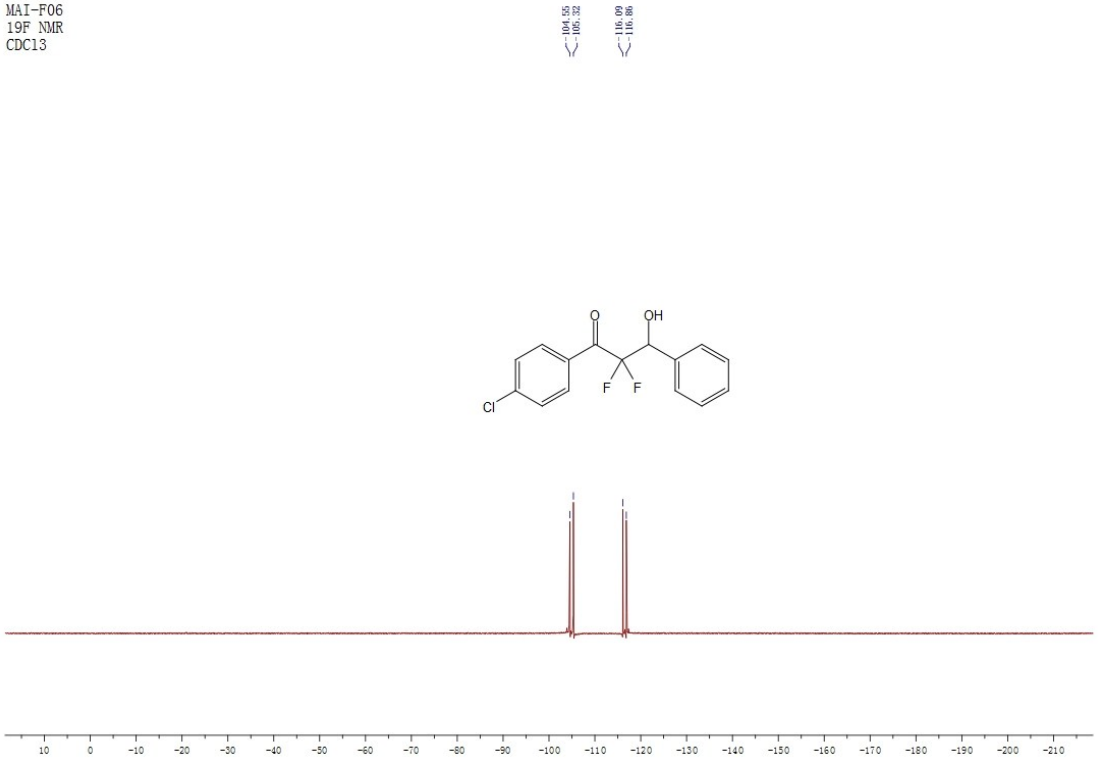
MAI-F07
19F NMR
CDC13



MAI-F06
1H NMR
CDC13




MAI-F06
13C NMR
CDC13
190.14
189.62
134.52
132.08
131.20
129.18
128.08
118.41
115.70
113.04
73.56
73.33
73.28
73.05
O
OH
F
F
Cl


MAI-F06
19F NMR
CDC13
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-105.32
-116.09
-116.86
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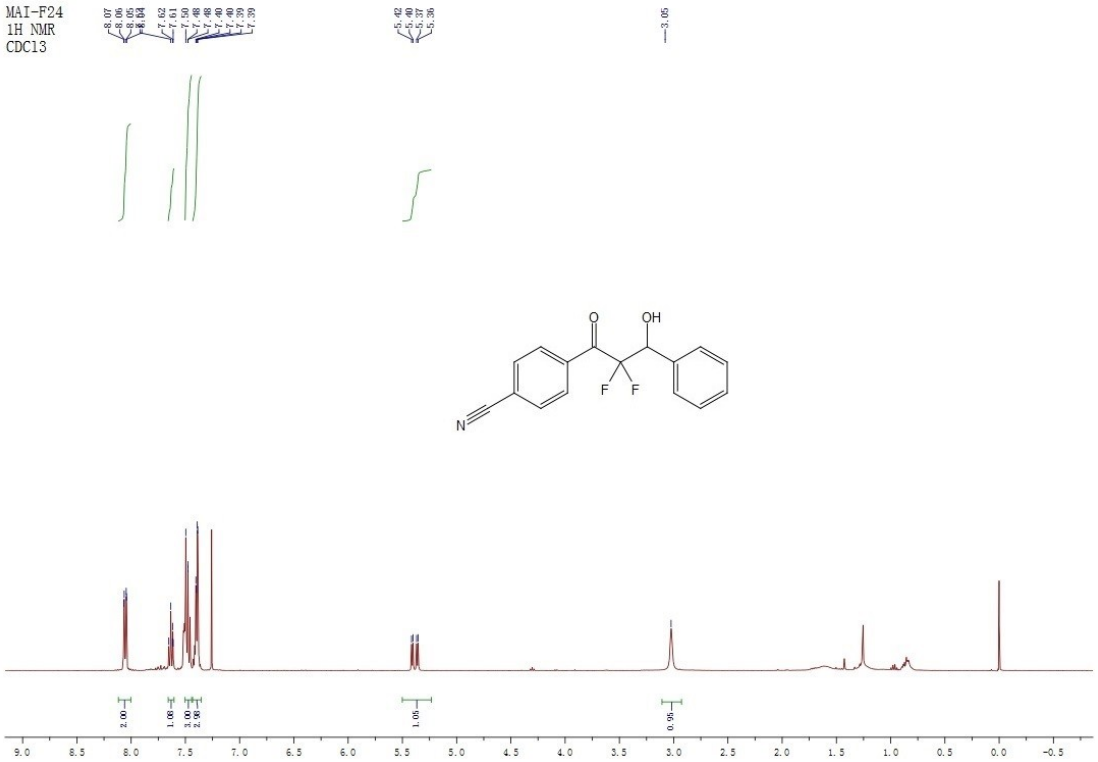
OH
F
F
Cl


MAI-F24
1H NMR
CDC13
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8.05
8.04
7.62
7.61
7.50
7.48
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7.40
7.39
7.39
5.42
5.40
5.37
5.36
3.65
O
OH
F
F
N
2.00
1.08
3.00
2.05
1.00
0.99
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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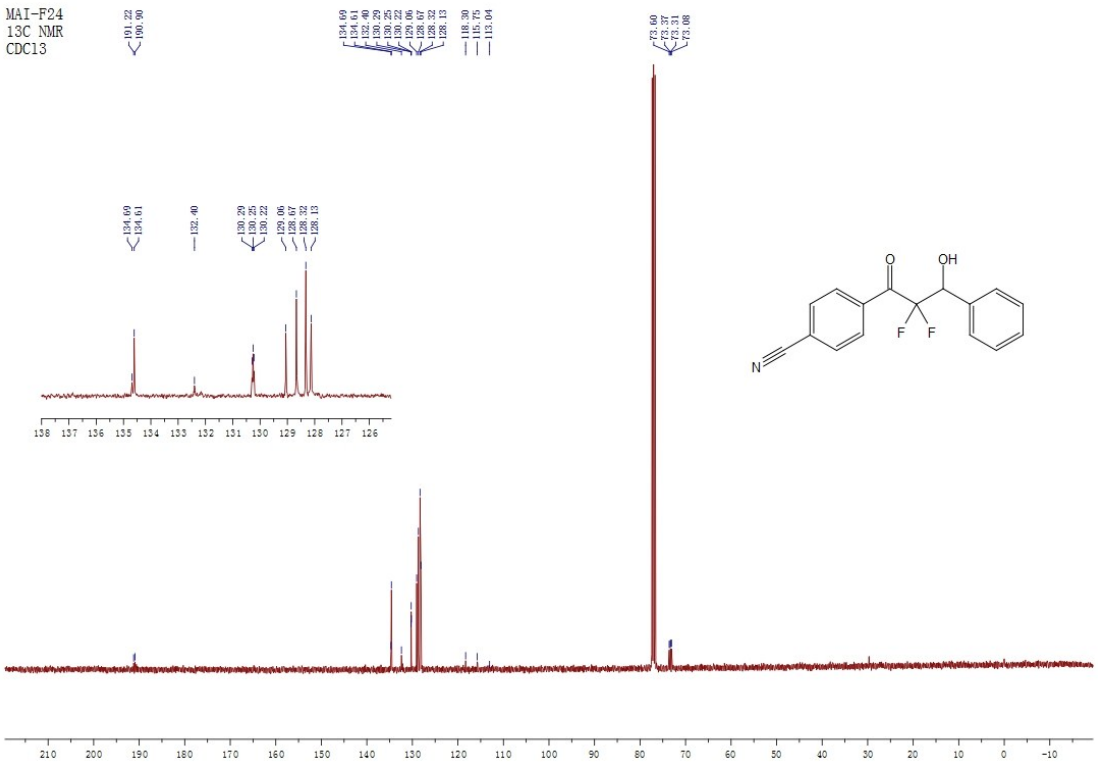
MAI-F24
13C NMR
CDC13
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134.69
134.61
132.40
130.29
130.25
130.22
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128.67
128.32
128.13
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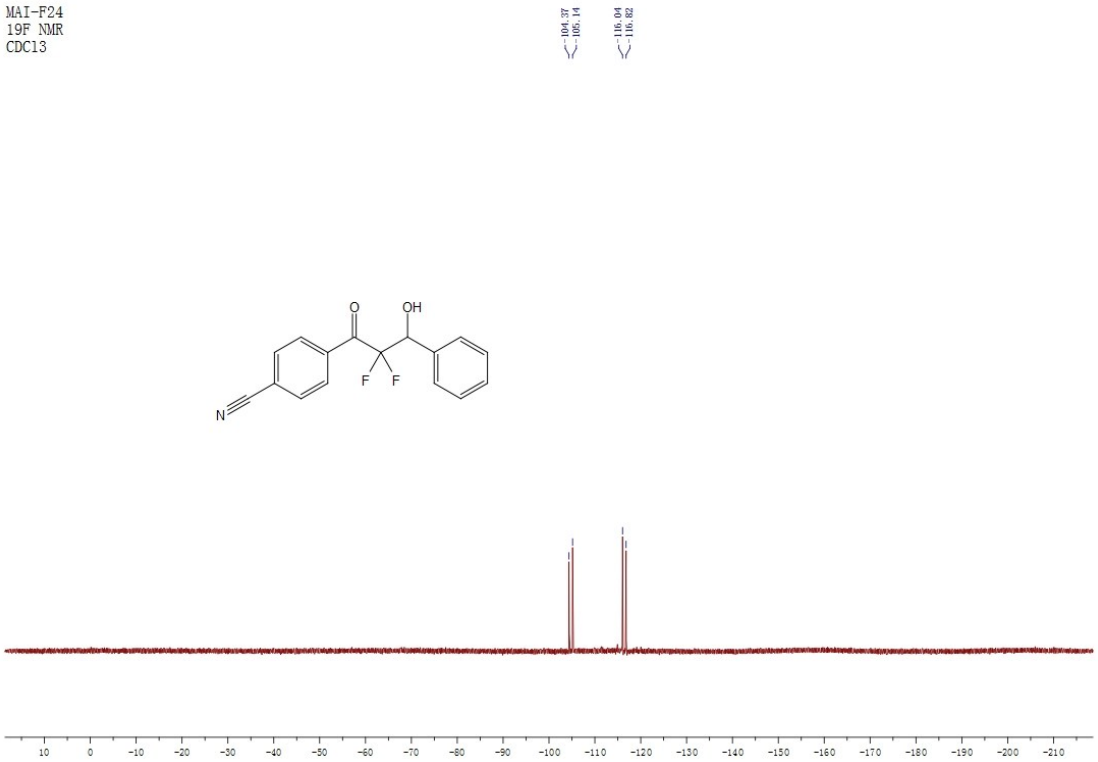
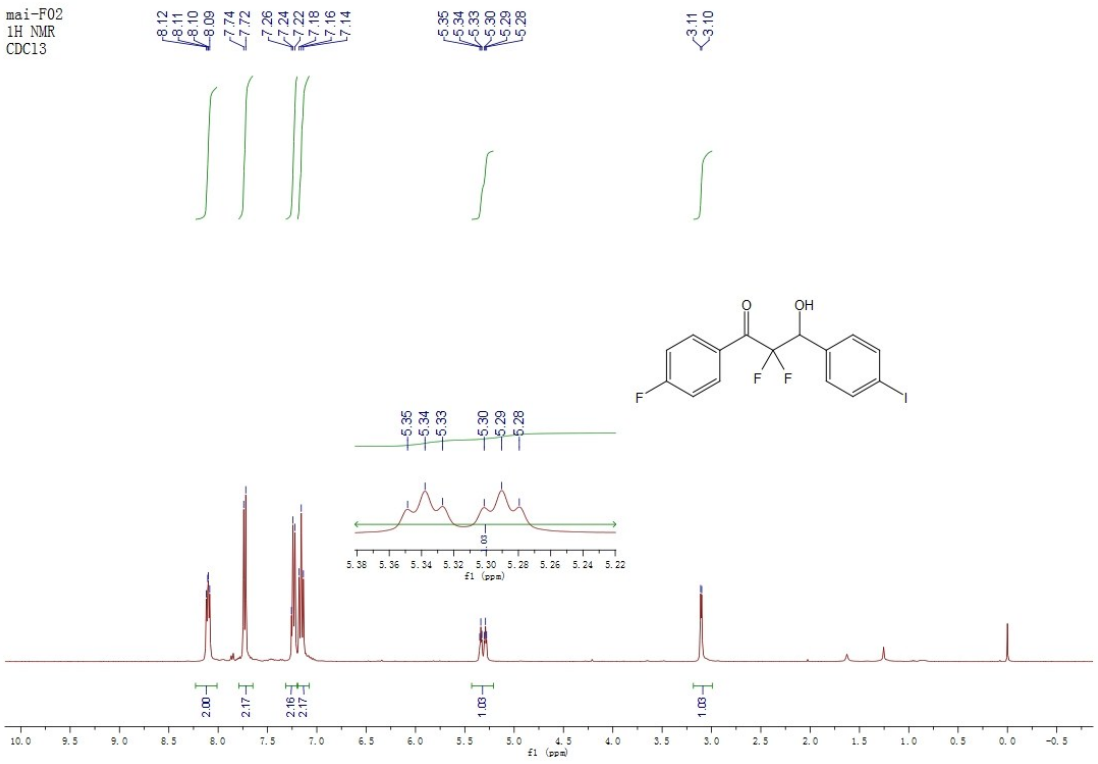
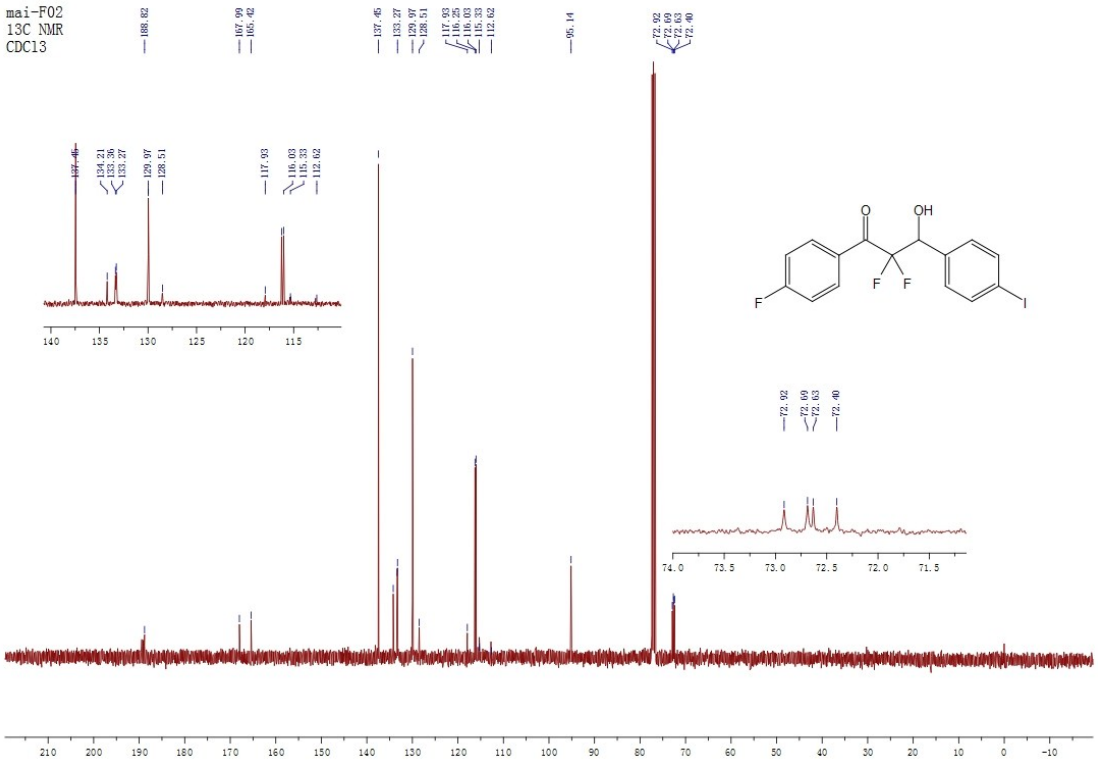
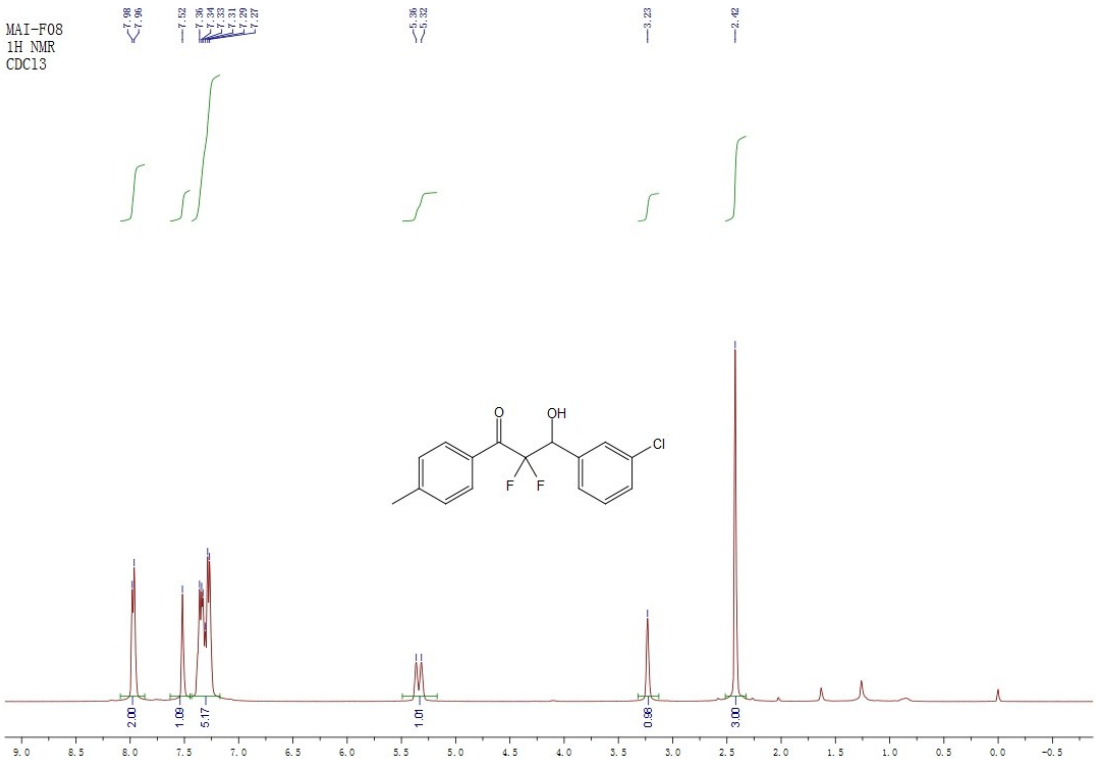
73.60
73.37
73.31
73.08
O
OH
F
F
N
138
137
136
135
134
133
132
131
130
129
128
127
126
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

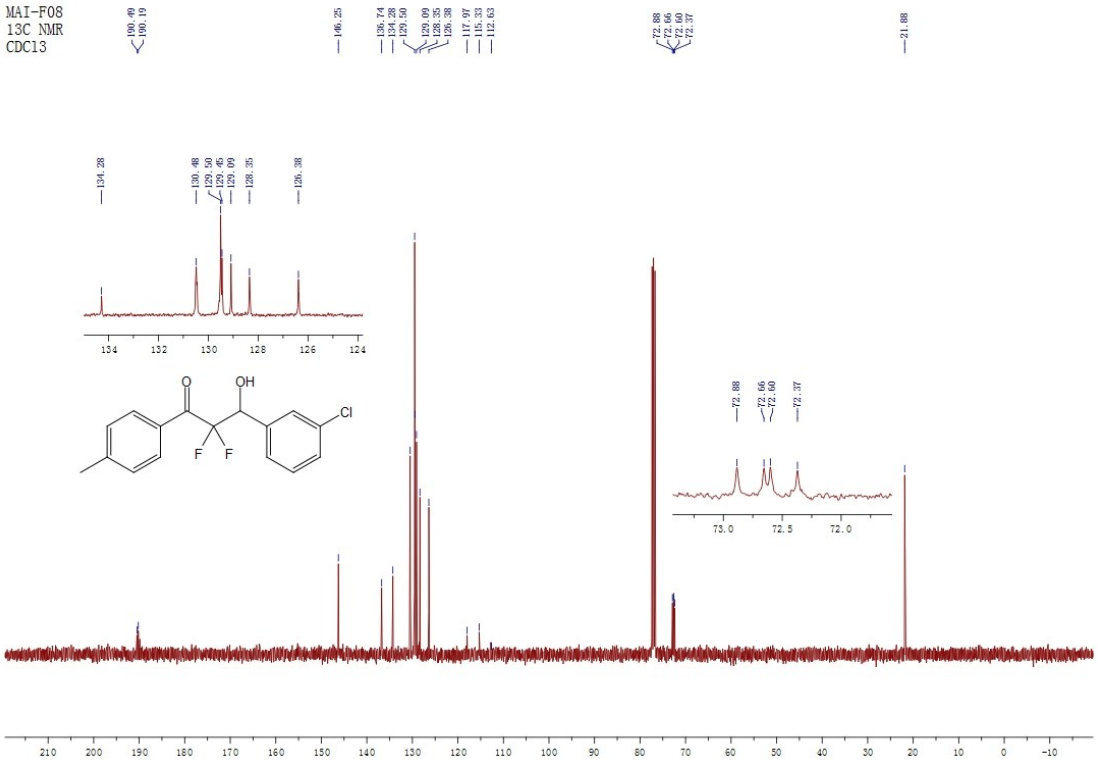

MAI-F24
19F NMR
CDC13
-104.37
-105.14
-116.04
-116.82
O
OH
F
F
N

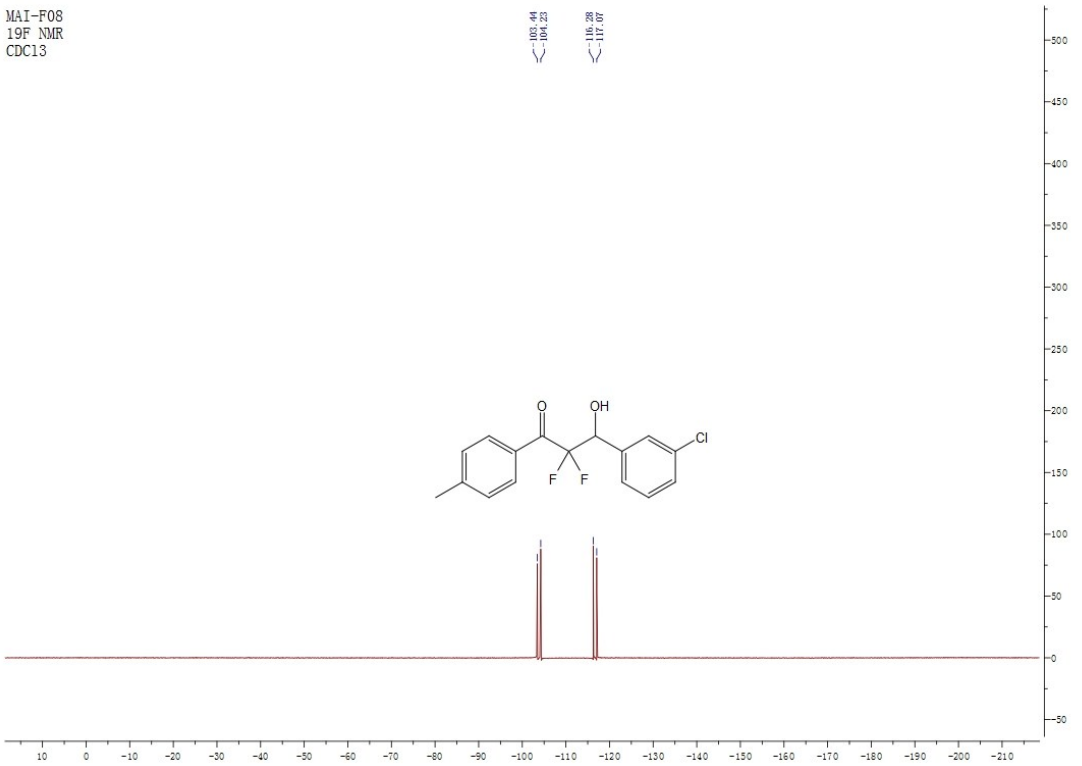

mai-F02
1H NMR
CDC13
8.12
8.11
8.10
8.09
7.74
7.72
7.26
7.24
7.22
7.18
7.16
7.14
5.35
5.34
5.33
5.30
5.29
5.28
3.11
3.10
O
OH
F
F
F
I
2.00
2.17
2.16
2.17
1.03
1.03
f1 (ppm)

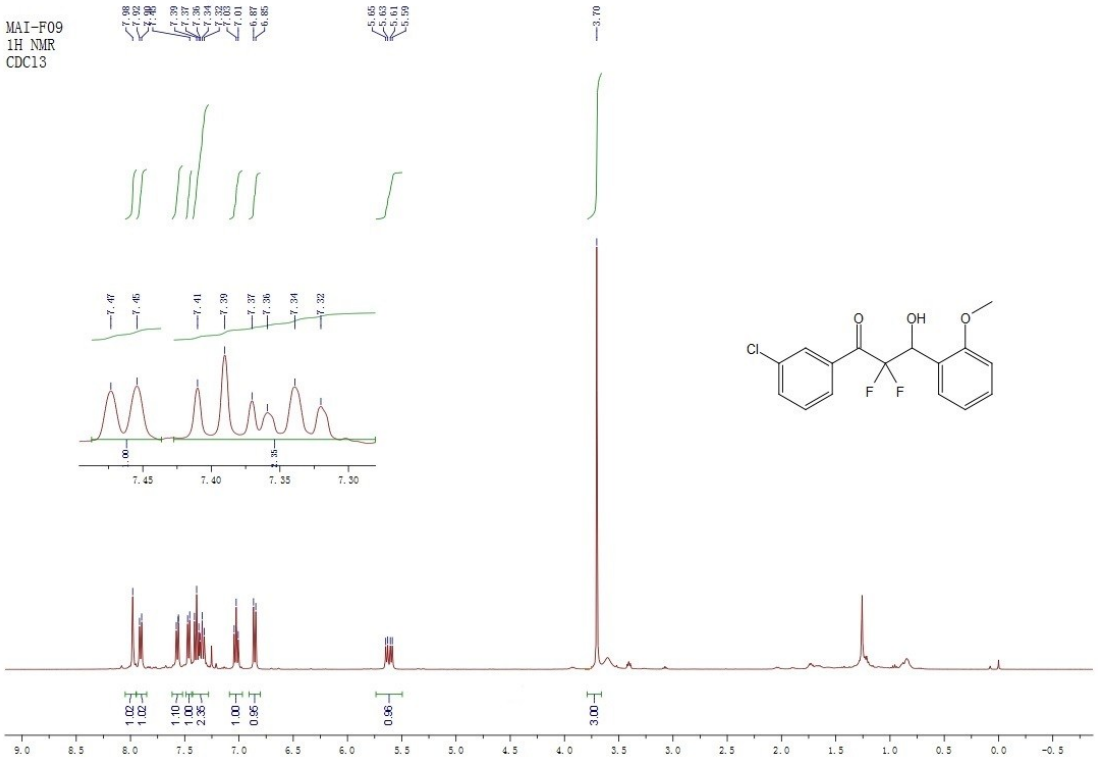

mai-F02
13C NMR
CDC13
188.62
167.99
165.42
137.45
133.27
129.97
128.51
117.93
116.25
116.03
115.33
112.62
95.14
72.92
72.69
72.63
72.40
O
OH
F
F
F
I

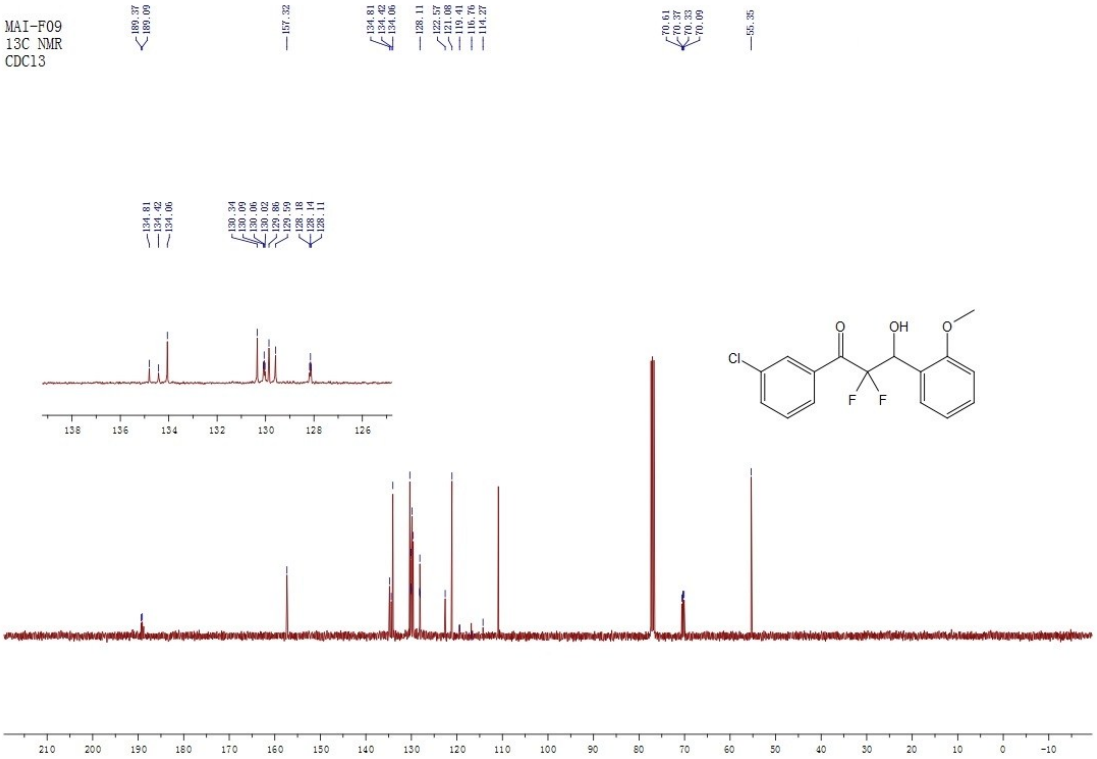

mai-F02
19F NMR
CDC13
-101.01
-103.63
-104.42
-116.19
-116.98
O
OH
F
F
F
I

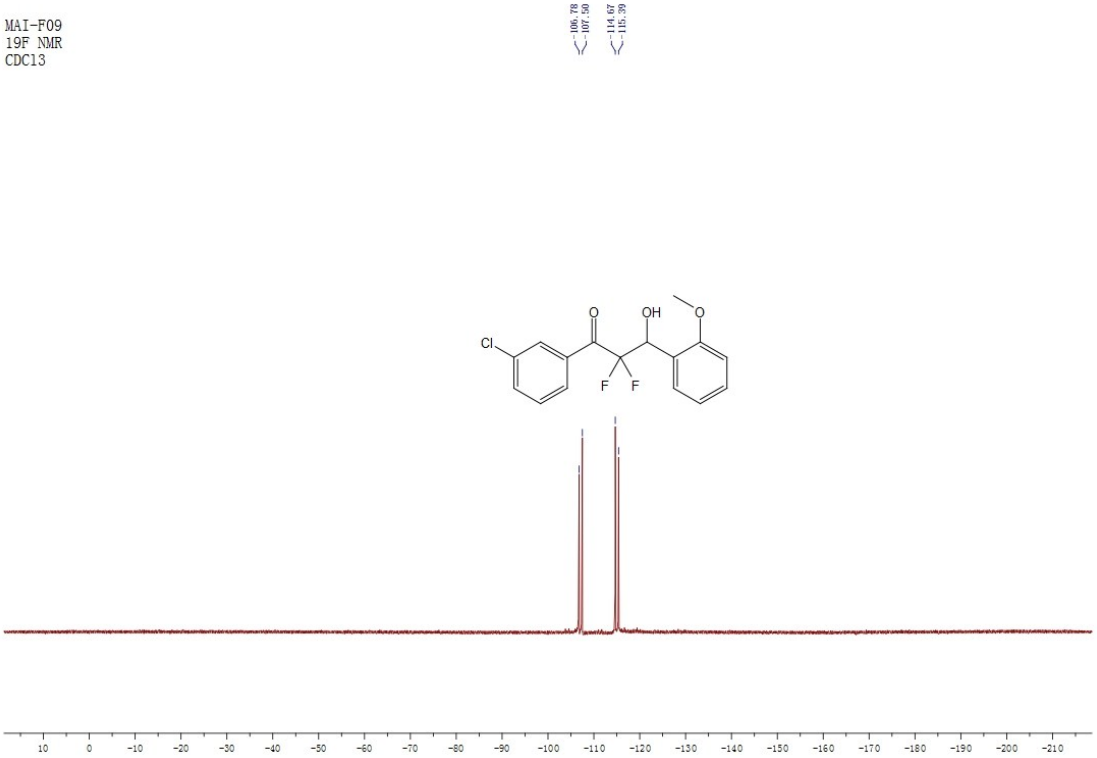

MAI-F08
1H NMR
CDC13
7.98
7.96
7.52
7.36
7.34
7.33
7.31
7.29
7.27
5.36
5.32
3.23
2.42
O
OH
Cl
F
F
2.00
1.09
5.17
1.01
0.98
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


MAI-F08
13C NMR
CDC13
190.49
190.19
146.25
136.74
134.28
129.50
129.09
128.35
126.38
117.97
115.33
112.63
72.88
72.66
72.60
72.37
21.88
134.28
130.48
129.50
129.45
129.09
128.35
126.38
134
132
130
128
126
124
O
OH
Cl
F
F
72.88
72.66
72.60
72.37
73.0
72.5
72.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


MAI-F08
19F NMR
CDC13
-103.44
-104.23
-116.28
-117.07
O
OH
Cl
F
F


MAI-F09
1H NMR
CDC13
7.98
7.92
7.39
7.37
7.36
7.34
7.33
7.01
6.87
6.85
5.65
5.63
5.61
5.59
3.70
7.47
7.45
7.41
7.39
7.37
7.36
7.34
7.32
O
OH
O
Cl
F
F


MAI-F09
13C NMR
CDC13
189.37
189.09
157.32
134.81
134.42
134.06
128.11
122.57
121.88
119.41
116.76
114.27
70.61
70.37
70.33
70.09
55.35
134.81
134.42
134.06
130.34
130.09
130.06
130.02
129.86
129.59
128.18
128.14
128.11
Cl
O
OH
O
F
F


MAI-F09
19F NMR
CDC13
-106.78
-107.50
-114.67
-115.39
Cl
O
OH
O
F
F