Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information for

A Facile Transformation of Amino acids to Functionalized Coumarins

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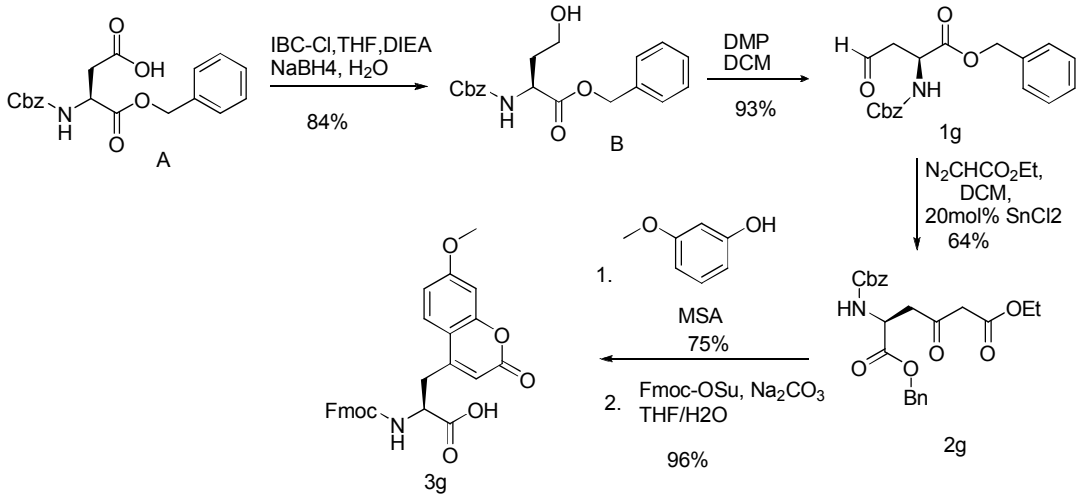
Synthesis of Coumarin 3g starting from Z-Asp(OH)-OBzl



Synthesis of alcohol B starting from Cbz-Asp(OH)-OBzl (A): The Cbz-Asp(OH)-OBzl (10 mmol) was dissolved in dry THF (20 mL) under nitrogen atmosphere, cooled to -15 ^{o}C, and then treated with DiPEA (10.2 mmol, 1.32 g) followed by isobutyl chloroformate (10 mmol, 1.366 g). White hydrochloride salt of DiPEA was precipitated out immediately after addition of isobutyl chloroformate. The reaction was continued to stir for another 10 min. The hydrochloride salt of DiPEA was filtered and washed with THF (2 × 10 mL). The filtrate was again cooled to -15 ^{o}C under nitrogen atmosphere, and then a solution of $NaBH_4$ (20 mmol, 720 mg) in 3 mL of water was added with vigorous stirring. After completion of reaction (~10 min), THF was evaporated and the reaction mixture was diluted with EtOAc (150 mL). The organic layer was washed with 5% HCl (50 mL x 2), 5 % sodium carbonate (50 mL x 2), followed by brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to get crude Cbz-protected alcohol (**B**) which was further purified on silica gel column chromatography.

(*S*)-benzyl 2-(((benzyloxy)carbonyl)amino)-4-oxobutanoate (1g) : The Cbz-amino alcohol **B** (5 mmol) was dissolved in 50 mL of DCM at room temperature and then 2.1 g (7.5 mmol) Dess-Martin periodinane (DMP) was added. Resulting reaction mixture was stirred for about 1 hr and the progress of the reaction was monitored by TLC. After completion of the reaction, it was diluted with diethylether (50 mL) and 10% Na_2CO_3 solution (50 mL) with

vigorous stirring. After 10 min, the organic layer was separated, washed with10% Na_2CO_3 (50 mL × 2), brine (30 mL) and dried over anhydrous Na_2SO_4. The organic layer was evaporated under reduced pressure to get Cbz-Asp(CHO)-OBzl and used immediately for the synthesis of β-keto-esters using the reported procedure.[1]

Crystal Structure analysis

Crystal structure analysis of Boc-Ala-Coumarin (3a): Crystals were grown by slow evaporation from a solution of methanol/water. A single crystal (0.35× 0.30 × 0.20 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 200K temperature on a Bruker APEX DUO CCD diffractometer using Mo K_α radiation (λ = 0.71073 Å), ω-scans (2θ = 56.56), for a total of 3782 independent reflections. Space group P2(1), a = 5.122(3), b = 10.085(6), c = 16.501(10), β = 96.065(13), V = 847.6(8)Å^3, Monoclinic, Z = 2 for chemical formula $C_{17}H_{21}NO_5$, with one molecule in asymmetric unit; ρ calcd. = 1.251gcm^{-3}, μ = 0.092mm^{-1}, F(000) = 340, R_{int} = 0.0468..The final R value was 0.0537 (wR2= 0.1113) 1598 observed reflections ($F_0 \geq 4\sigma$ ($|F_0|$)) and 213 variables, S = 0.899. The structure was obtained by direct methods using SHELXS-97.[2] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. The largest difference peak and hole were 0.126 and -0.143eÅ^3, respectively.

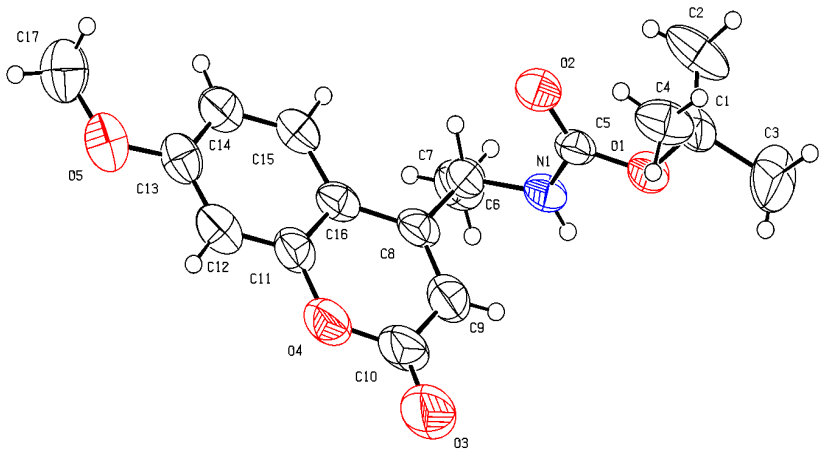


Figure 1. ORTEP diagram of Boc-Alanyl coumarin (3a). Hydrogens are not labelled for clarity.

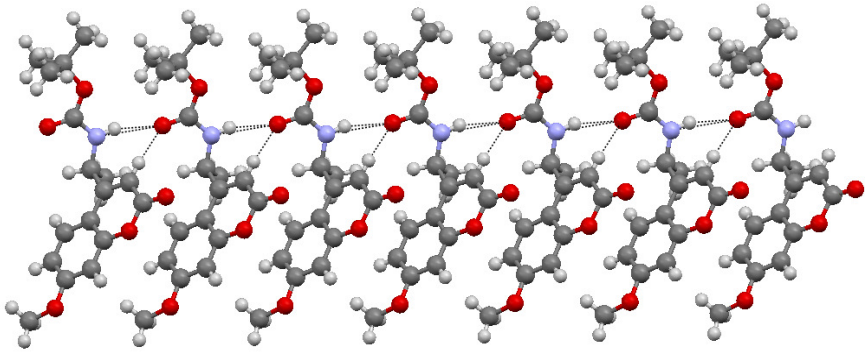


Figure 2: The extended sheet type assembly of Boc-alanylcoumarin

Table 2. Non-covalent interactions observed in the crystal structure of Boc-alanylcoumarin

	D-H---A[Å]	D---A[Å]	D-H---A[deg]	Type of H-bonding
N1---O2	2.128	2.955	161	NH---CO
C9-H---O2	2.664	3.468	145	CH---O
C7-H---O5	2.666	3.367	130	CH---O
C3-H---O3	2.700	3.349	125	CH---O
C17-H---O3	2.459	3.294	145	CH---O

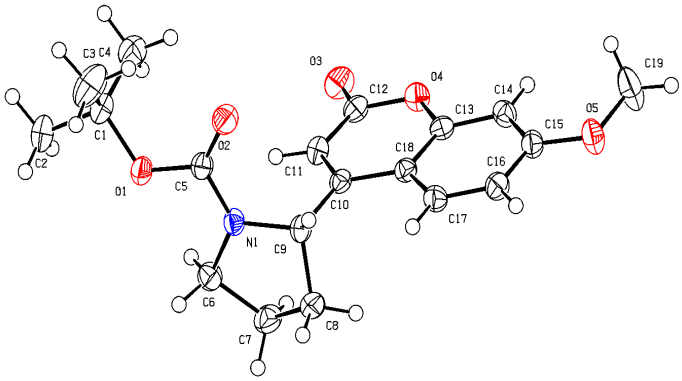


Figure 3: ORTEP diagram of Boc-prolylcoumarin. Hydrogen atoms are not labelled for clarity.

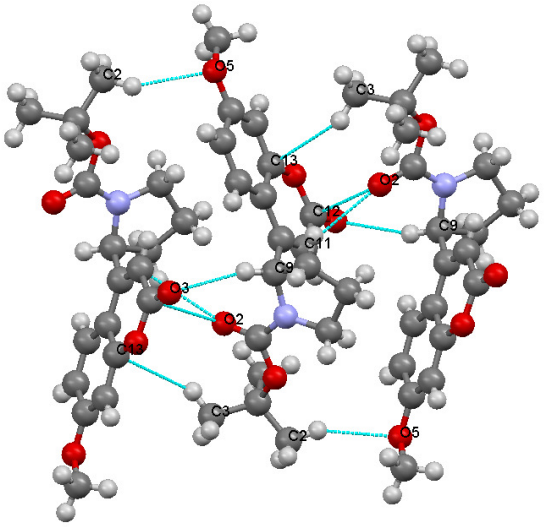


Figure 4: The crystal packing depicting the non-covalent interactions in Boc-prolylcoumarin

Table 2. Non-covalent interactions in the crystal structure of Boc-prolylcoumarin

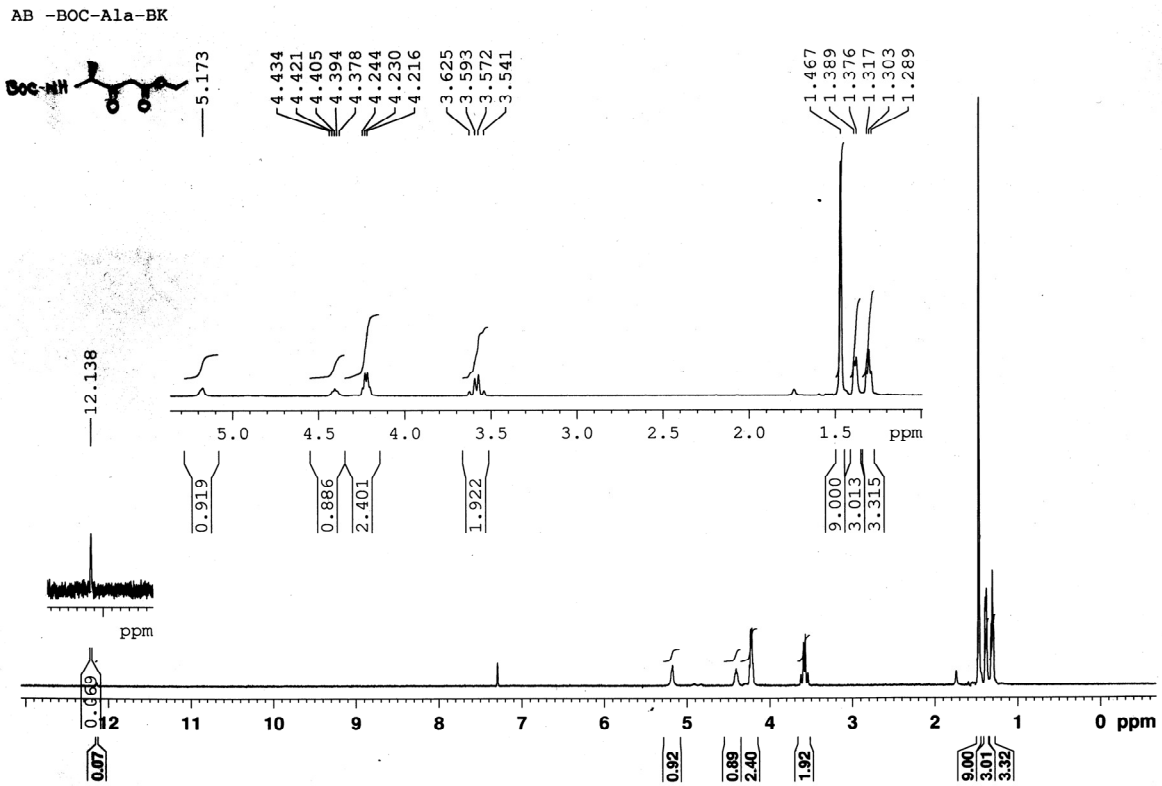
	D-H---A[Å]	D---A[Å]	D-H---A[deg]	Type of H-bonding
C3H---Ar	3.053	---		C-H---π
O2---Ar	----	3.037	---	Lone pair---π
C9-H---O3	2.564	3.514	163	CH---O
C19-H---O3	2.522	3.325	141	CH---O
C4-H---O5	2.614	3.460	147	CH---O

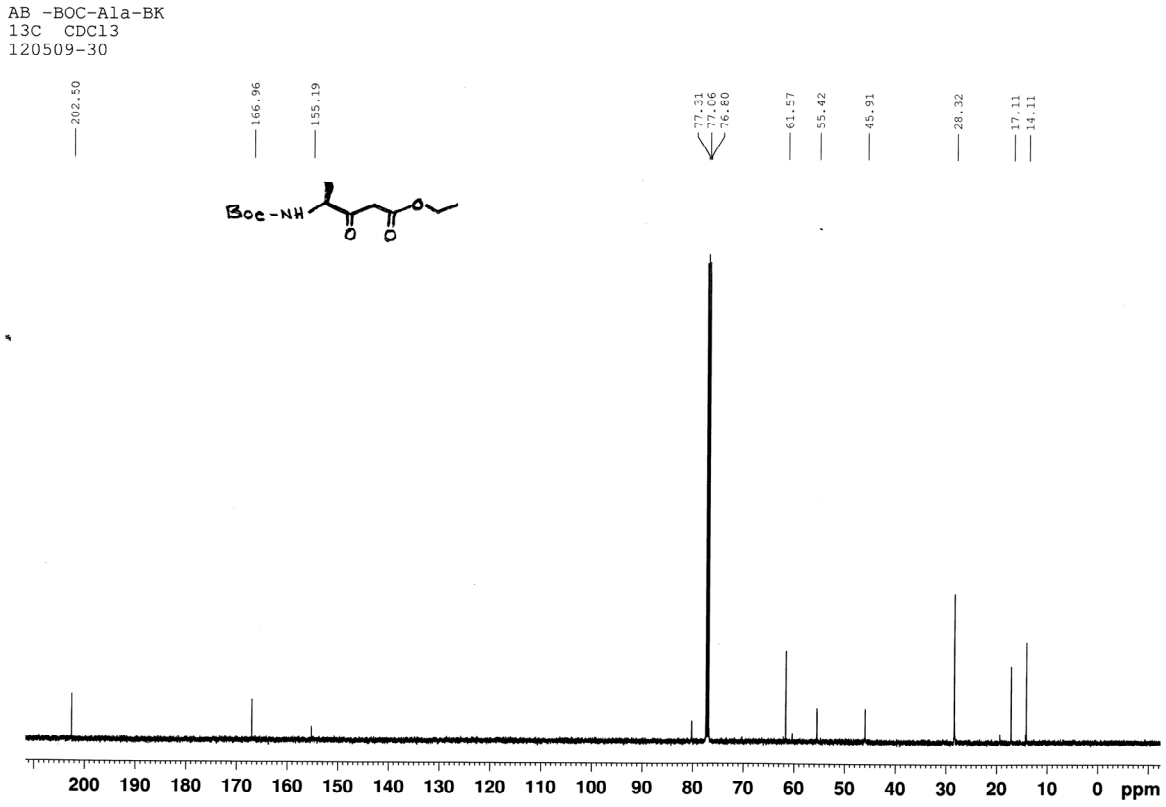
Reference

(1) A. Bandyopadhyay, N. Agrawal, S.M. Mali, S.V. Jadhav, H.N. Gopi, *Org. Biomol. Chem.*, 2010, **8**, 4855–4860.

(2) a) SHELXS-97: G. M. Sheldrick, *Acta Crystallogr. Sect A* 1990, **46**, 467-473. b) G. M. Sheldrick, SHELXL-97, Universitat Gottingen (Germany) 1997.

^{1}H ,^{13}C NMR, HPLC profile and MALDI-TOF Mass Data

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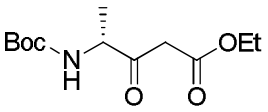
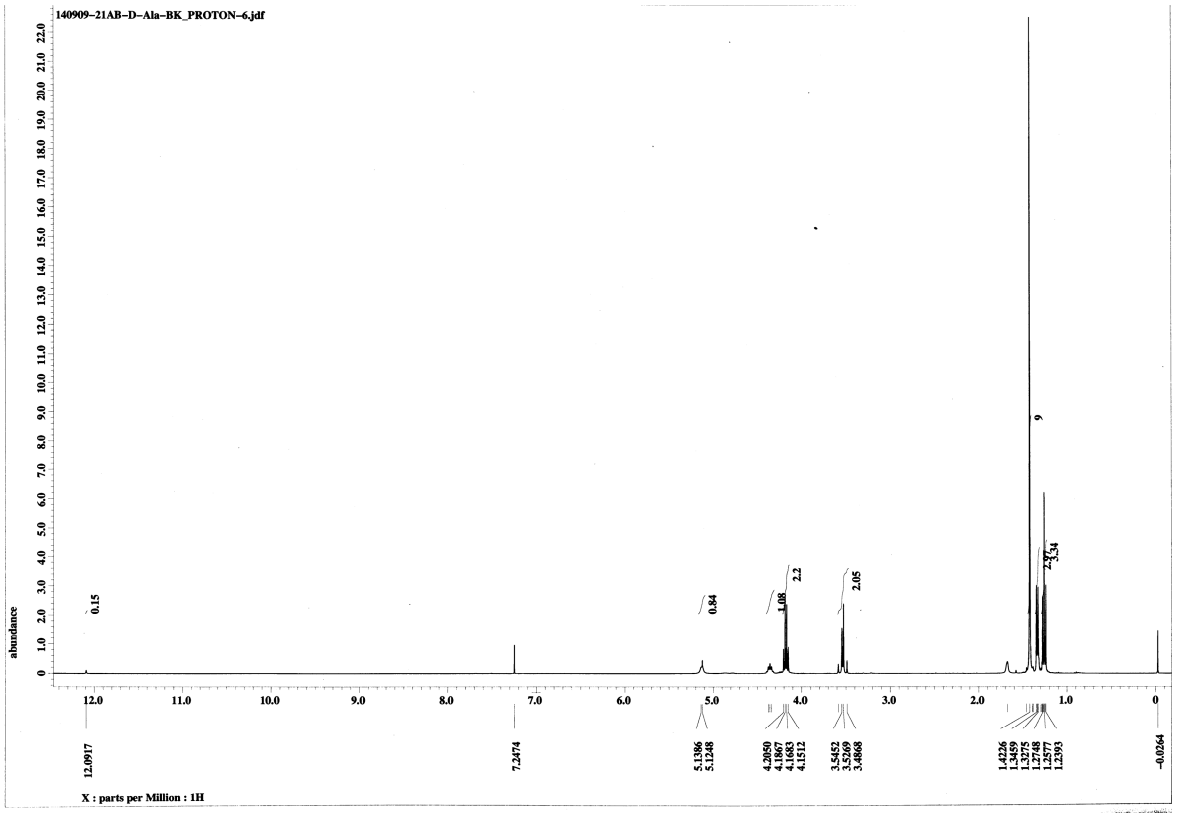
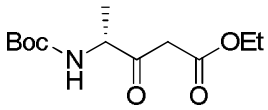
202.50
166.96
155.19
77.31
77.06
76.80
61.57
55.42
45.91
28.32
17.11
14.11
Boc-NH
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm






Boc
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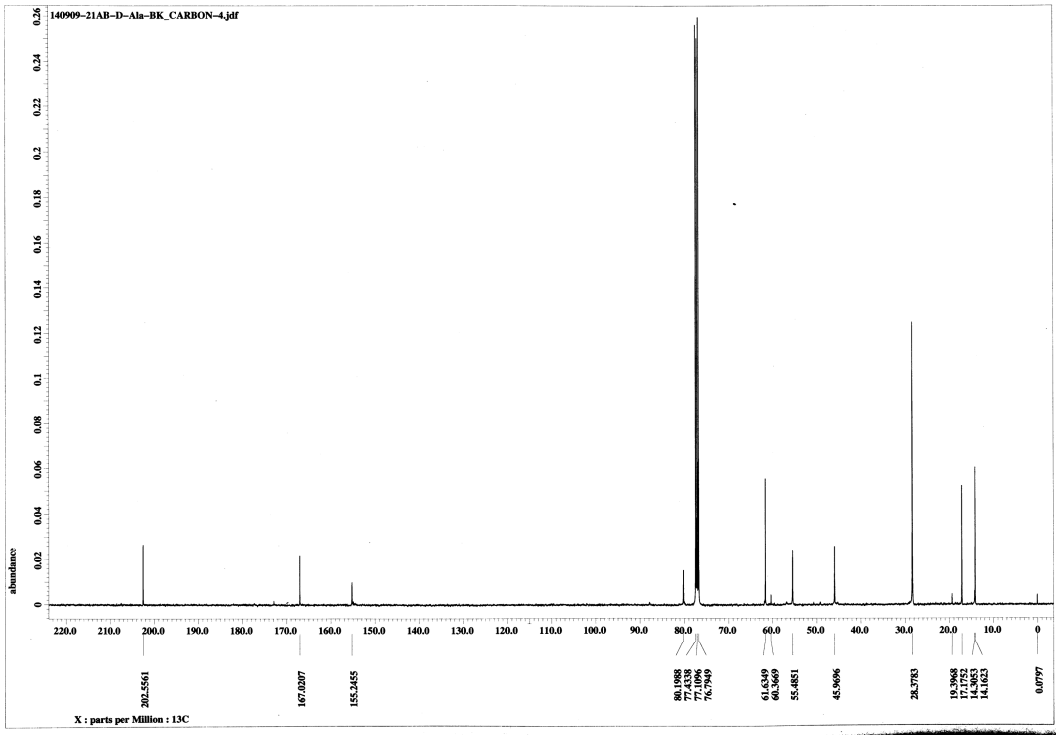
H
O
O
OEt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X : parts per Million : 13C
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167.0207
155.2455
90.1988
77.3183
77.1086
76.7949
61.6349
60.3669
55.4851
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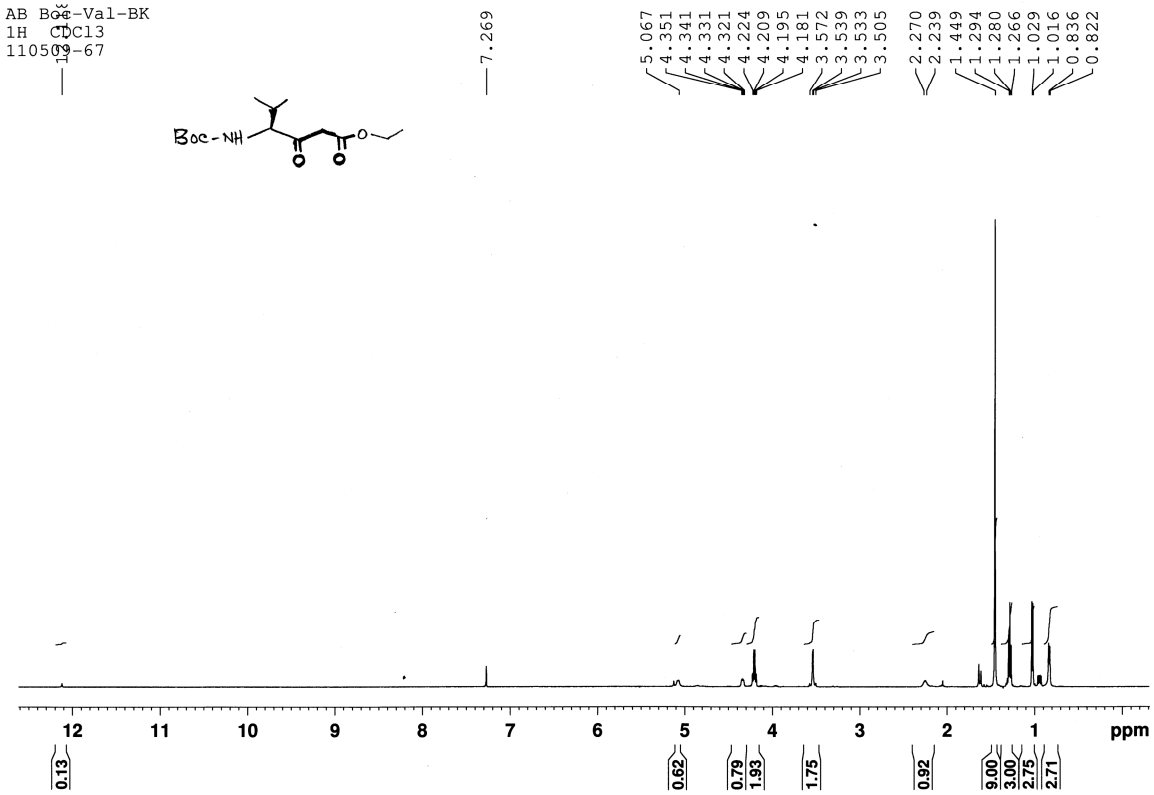
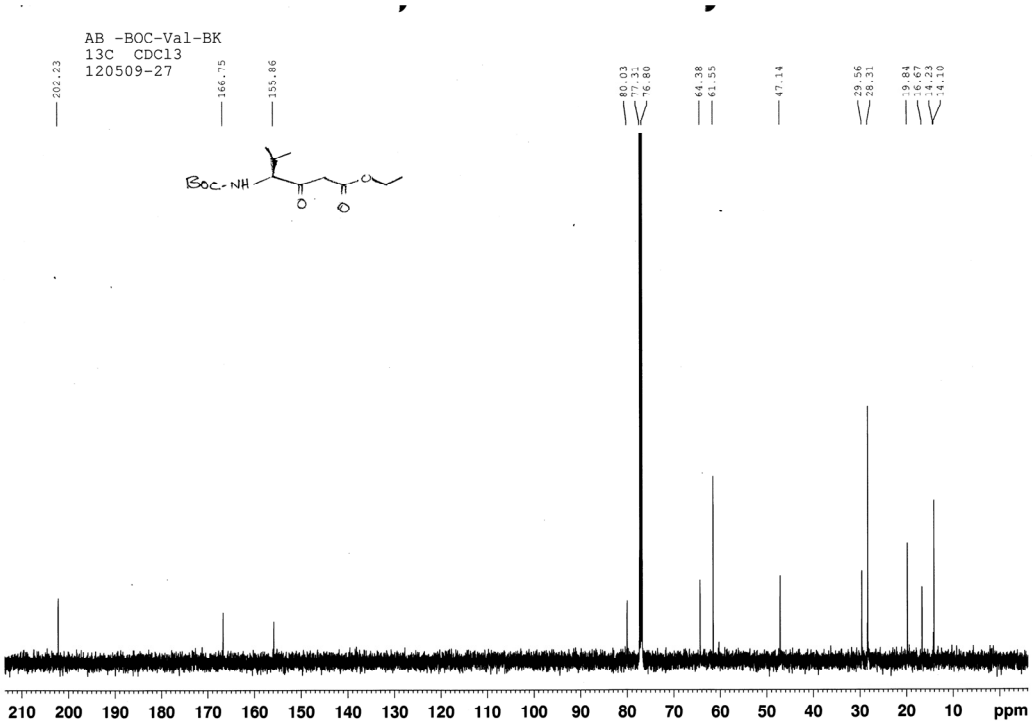
19.3968
17.1752
14.3053
14.1623
0.0797

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61.55
47.14
29.56
28.31
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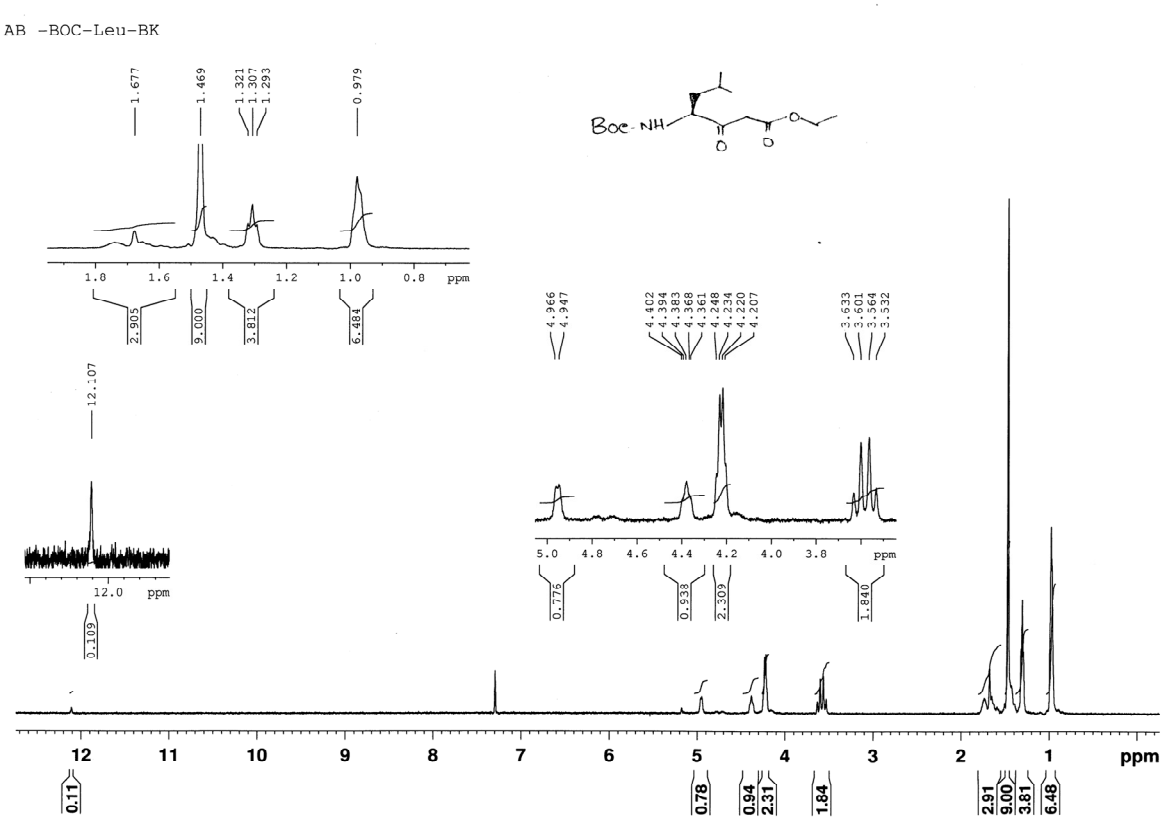
14.10
Boc-NH
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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9.000
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6.484
12.107
0.109
4.366
4.347
4.402
4.394
4.383
4.368
4.361
4.248
4.234
4.220
4.207
3.633
3.601
3.564
3.532
0.776
0.938
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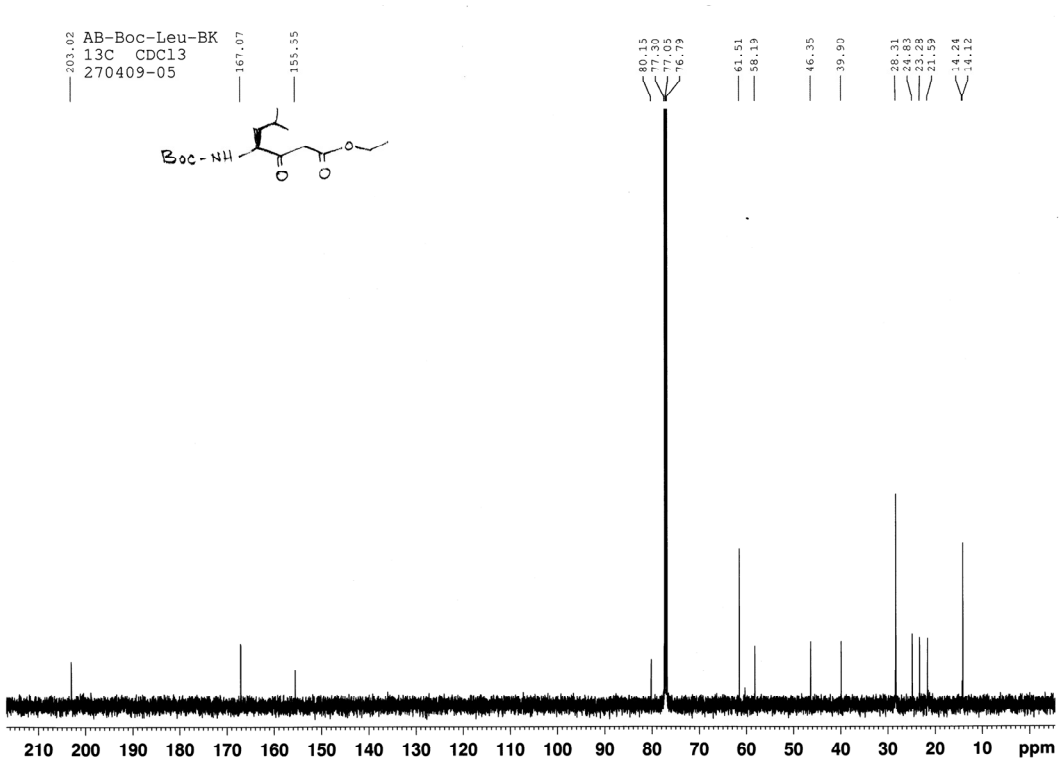
6.48
ppm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77.03
77.05
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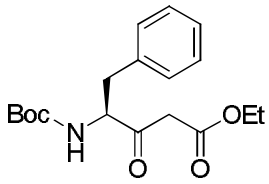
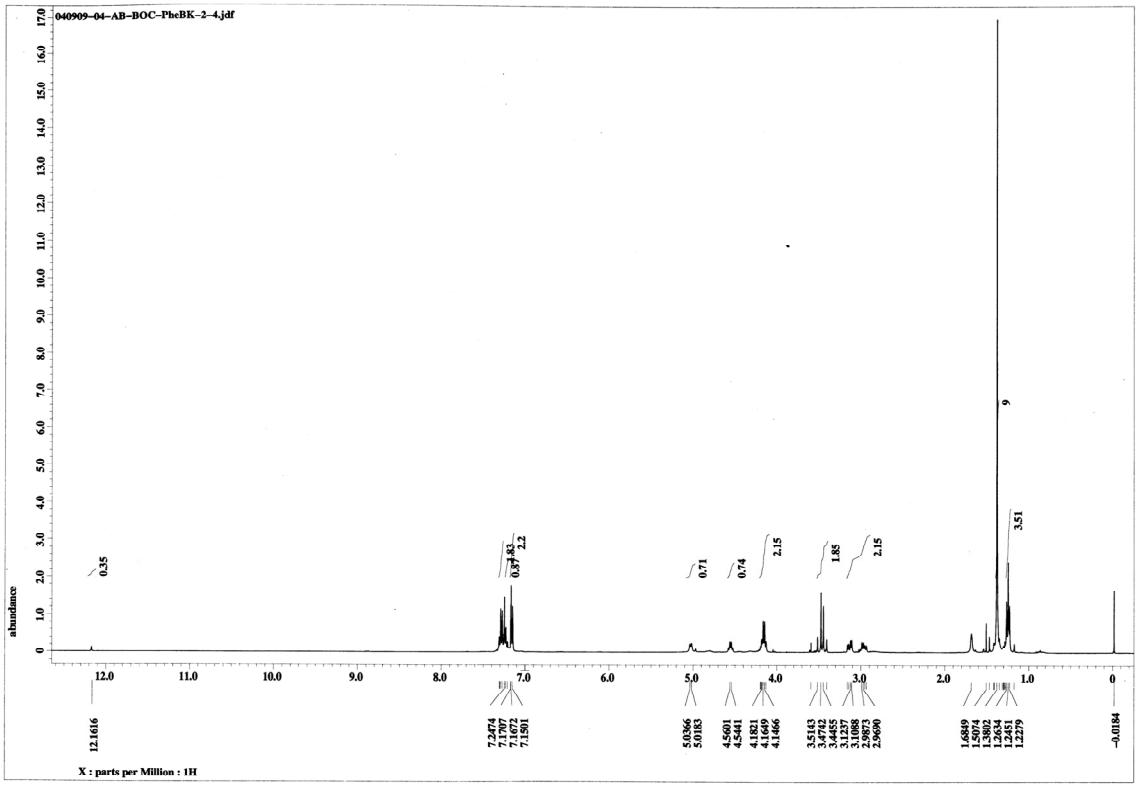
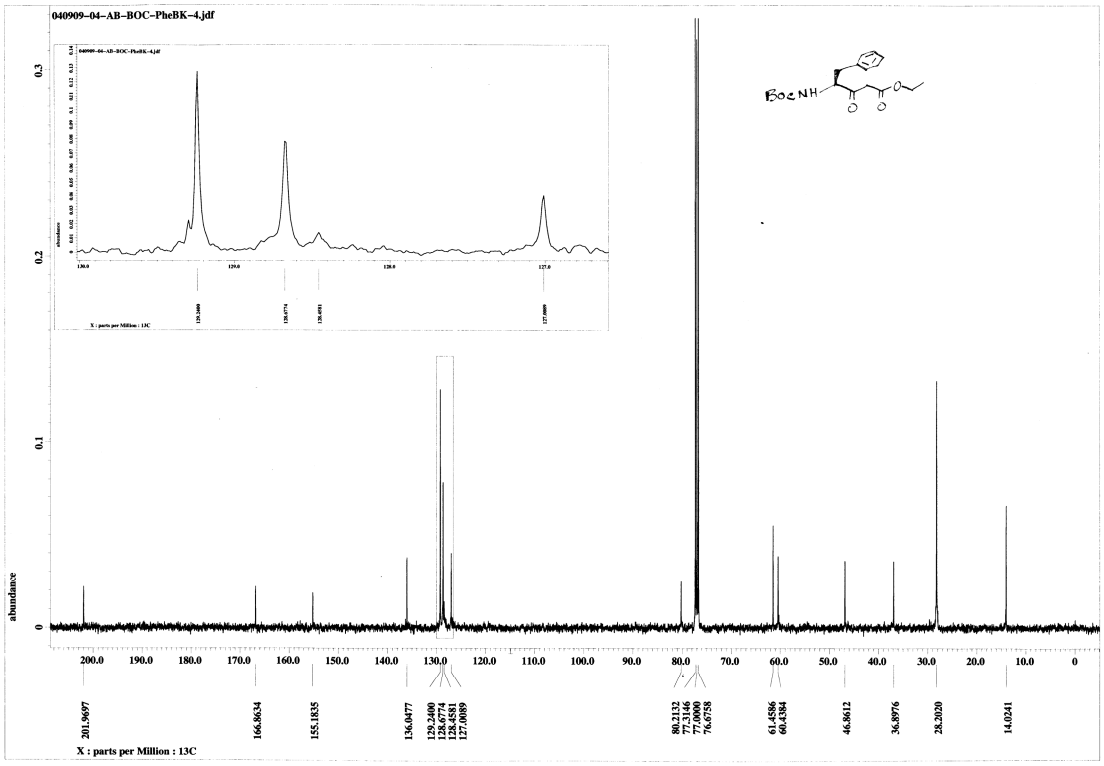
61.51
58.19
46.35
39.90
28.31
24.83
23.23
21.59
14.24
14.12
Boc-NH
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm



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X : parts per Million : 13C
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127.0089
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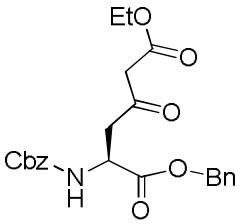

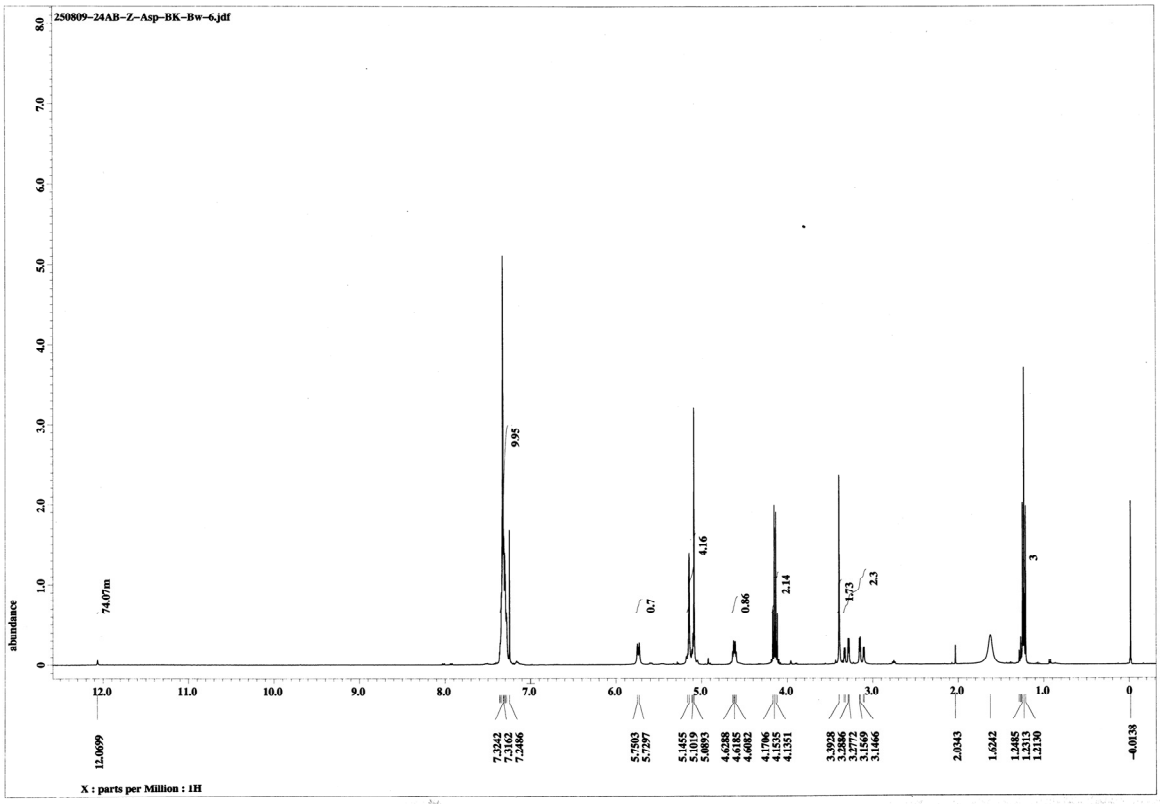

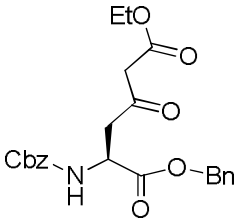

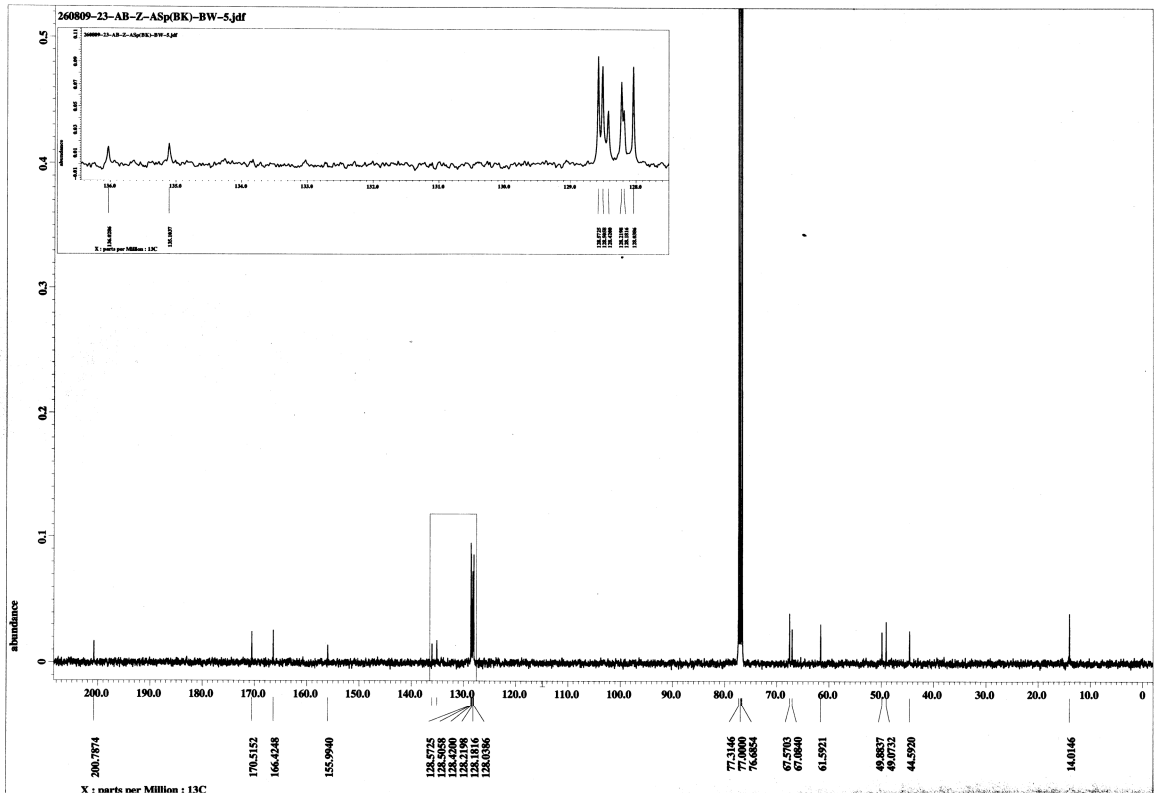

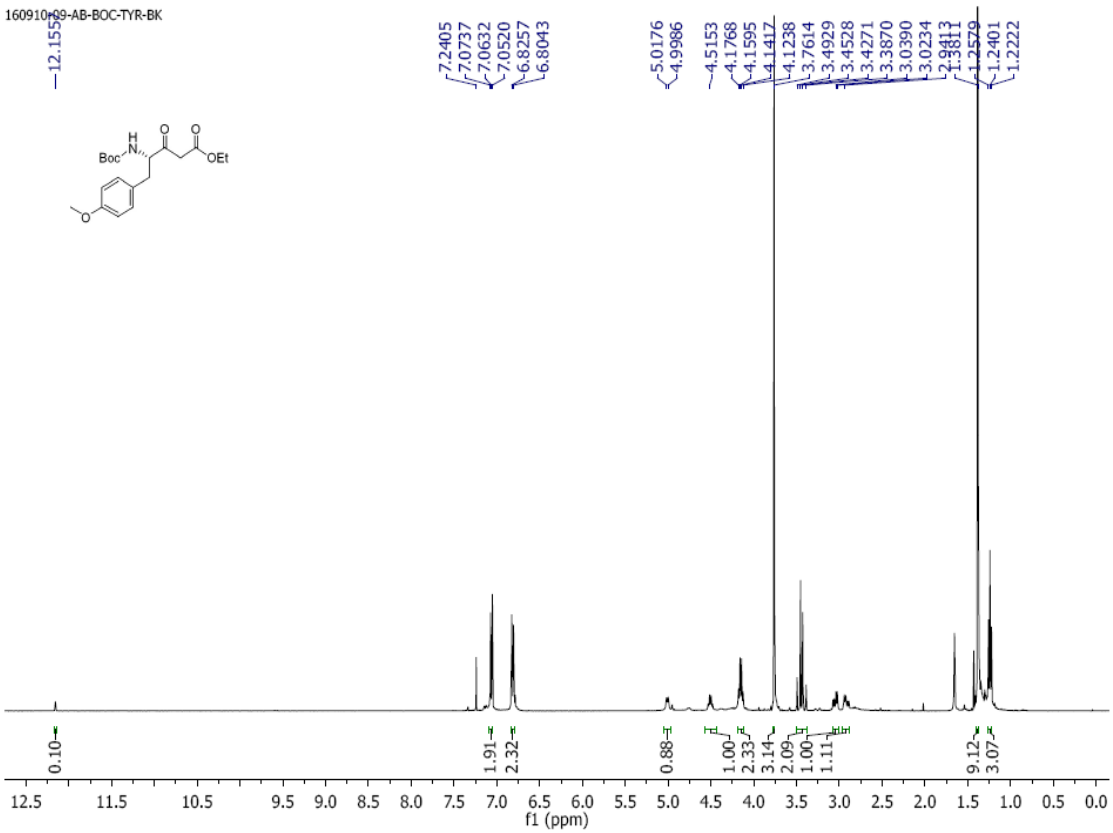

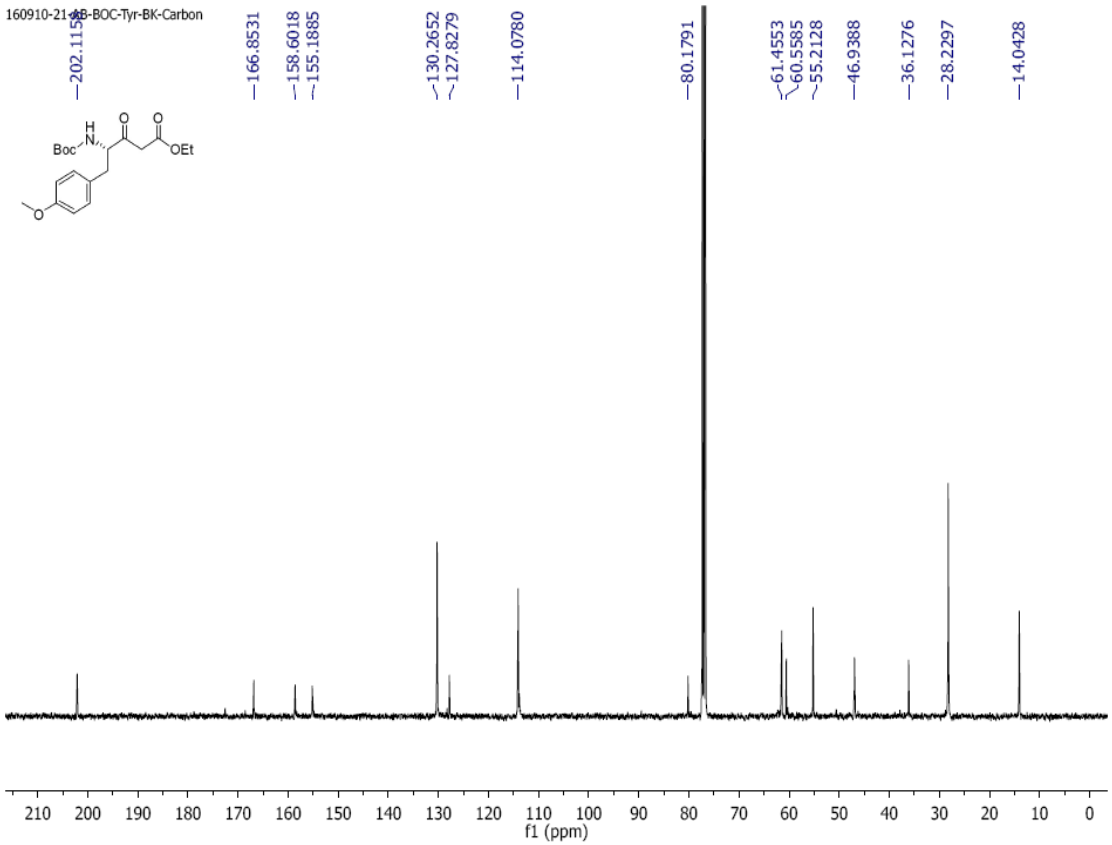
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60.5585
55.2128
46.9388
36.1276
28.2297
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N
H
O
O
OEt
O
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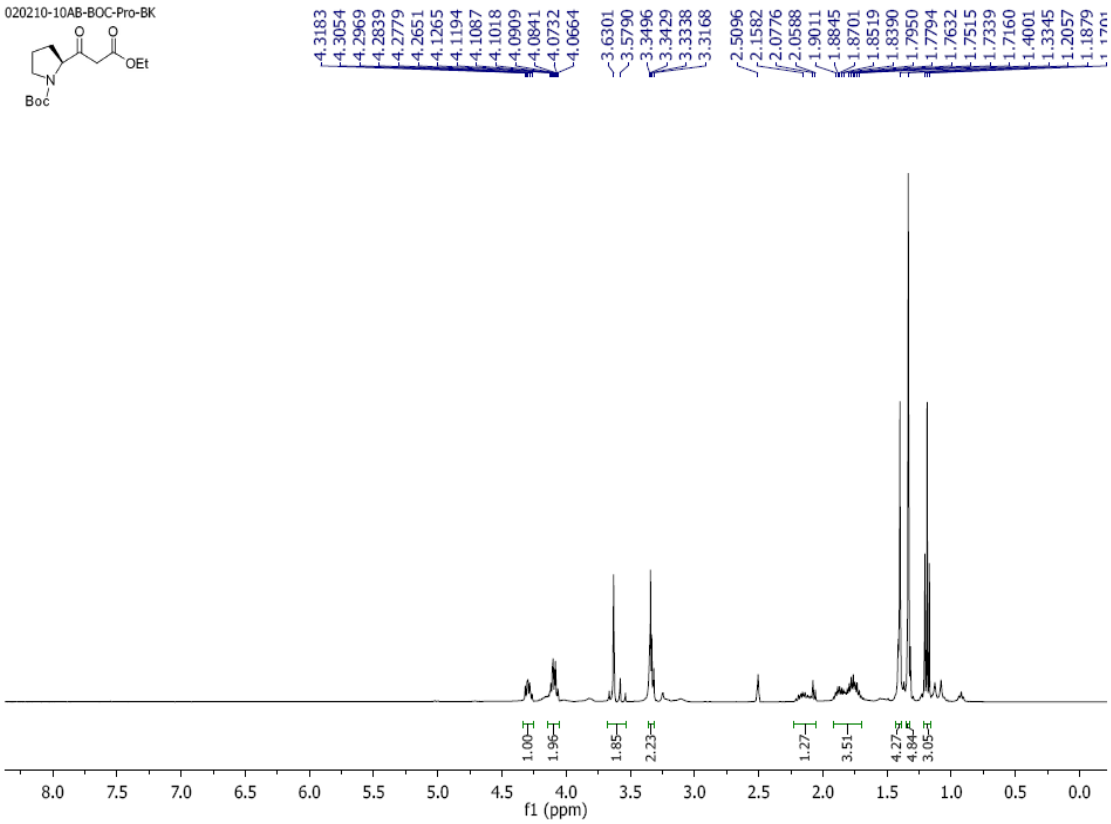
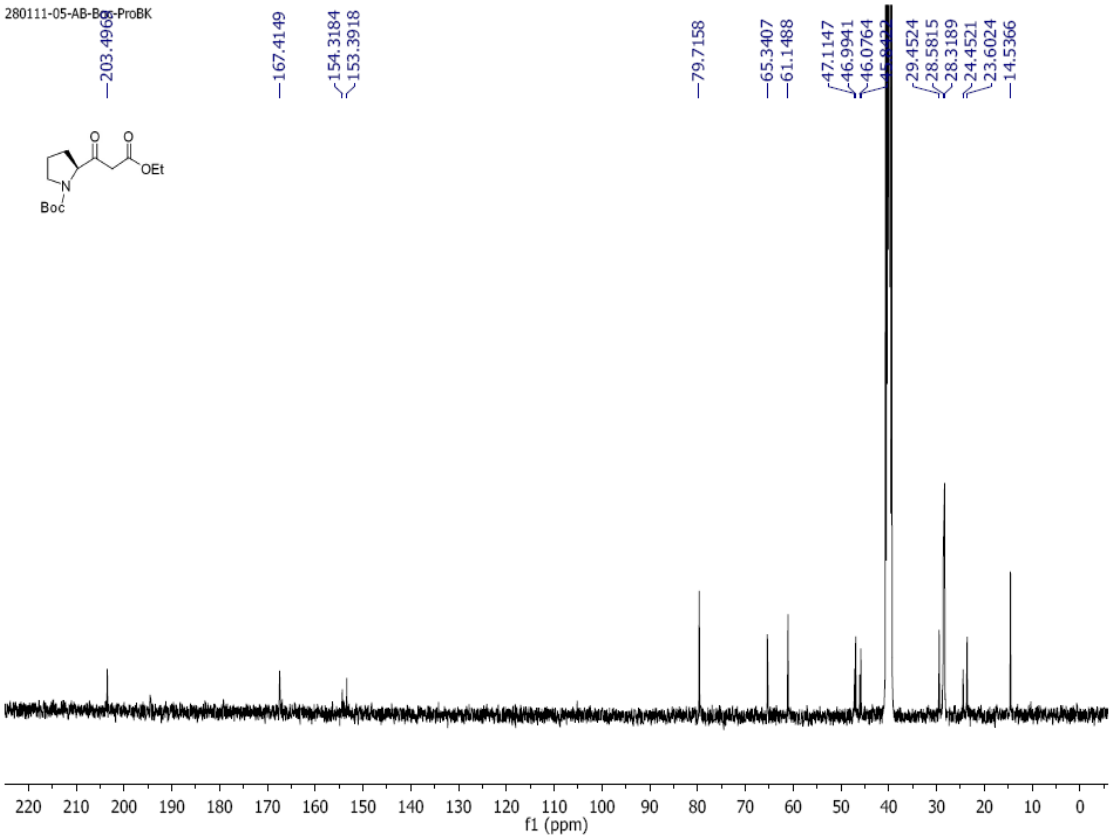
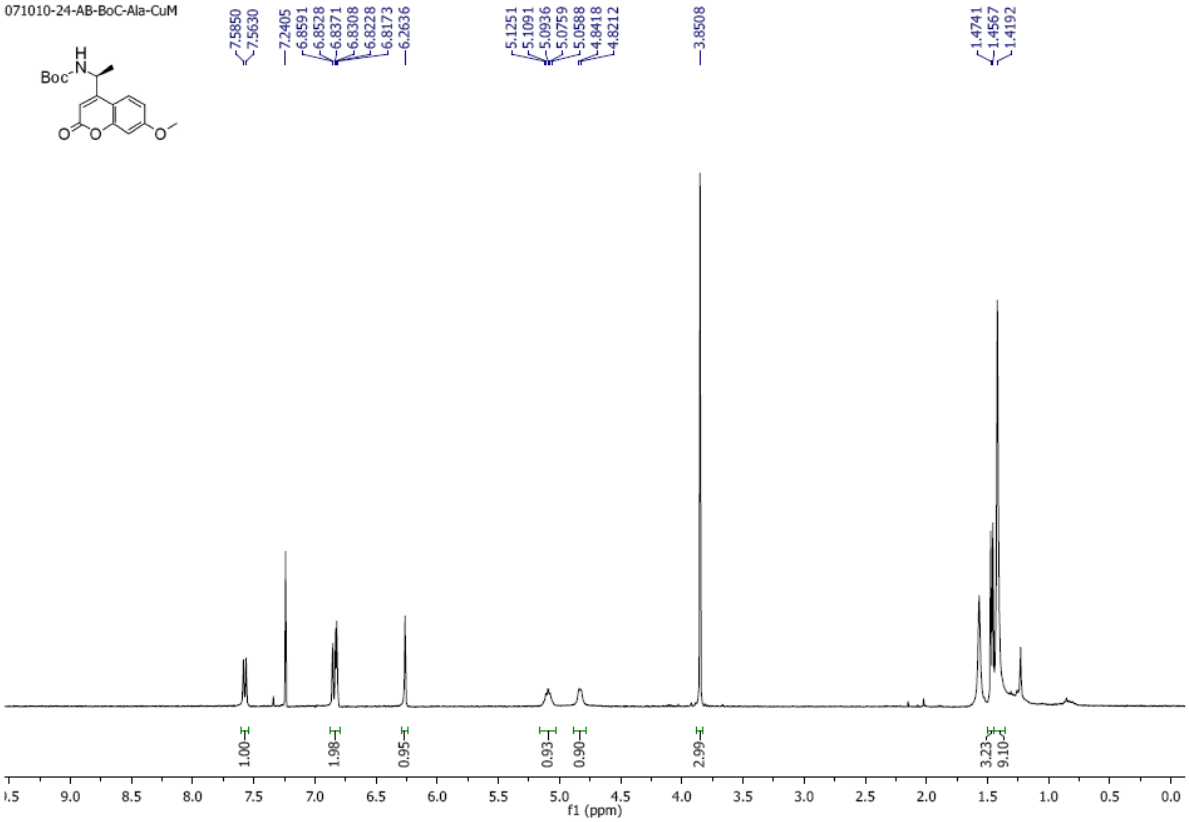
f1 (ppm)



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O
O
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6.8308
6.8228
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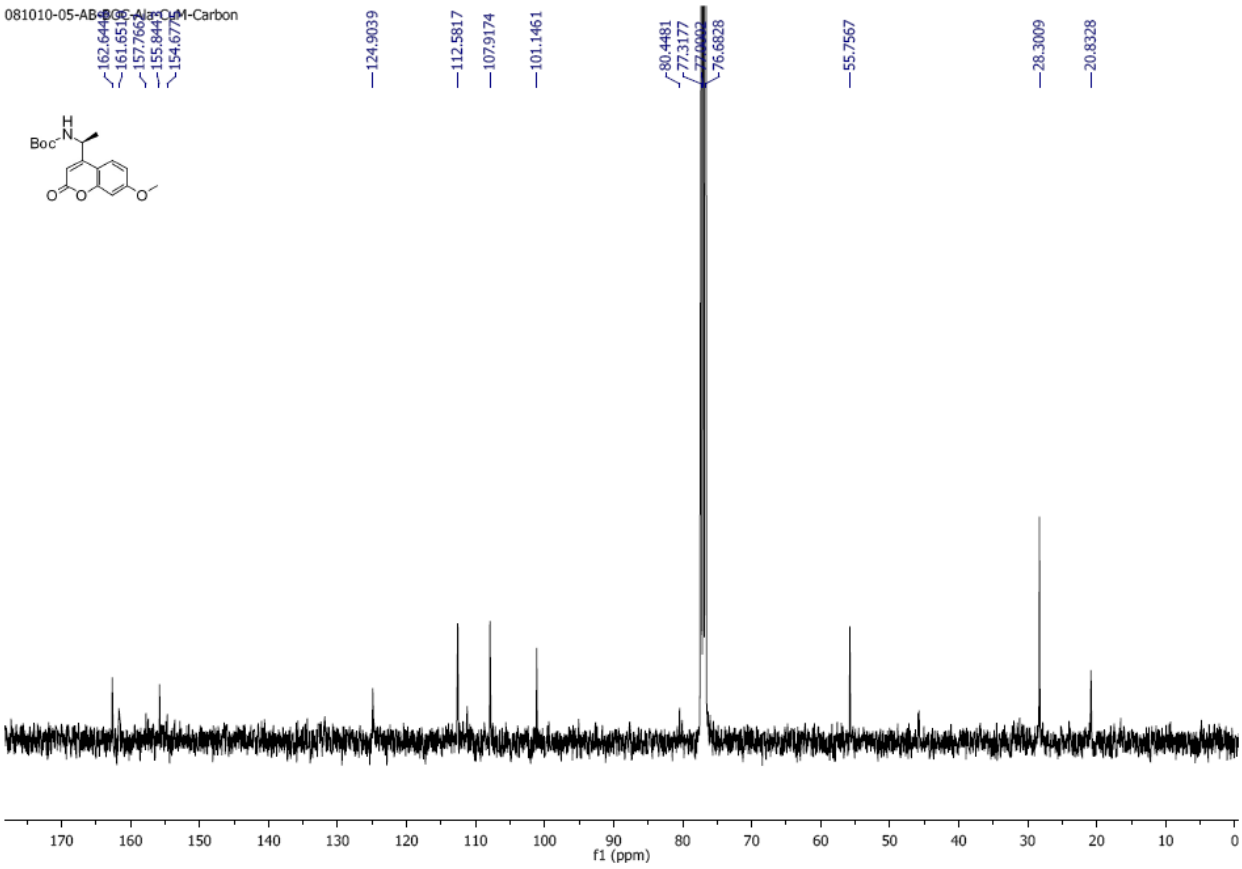
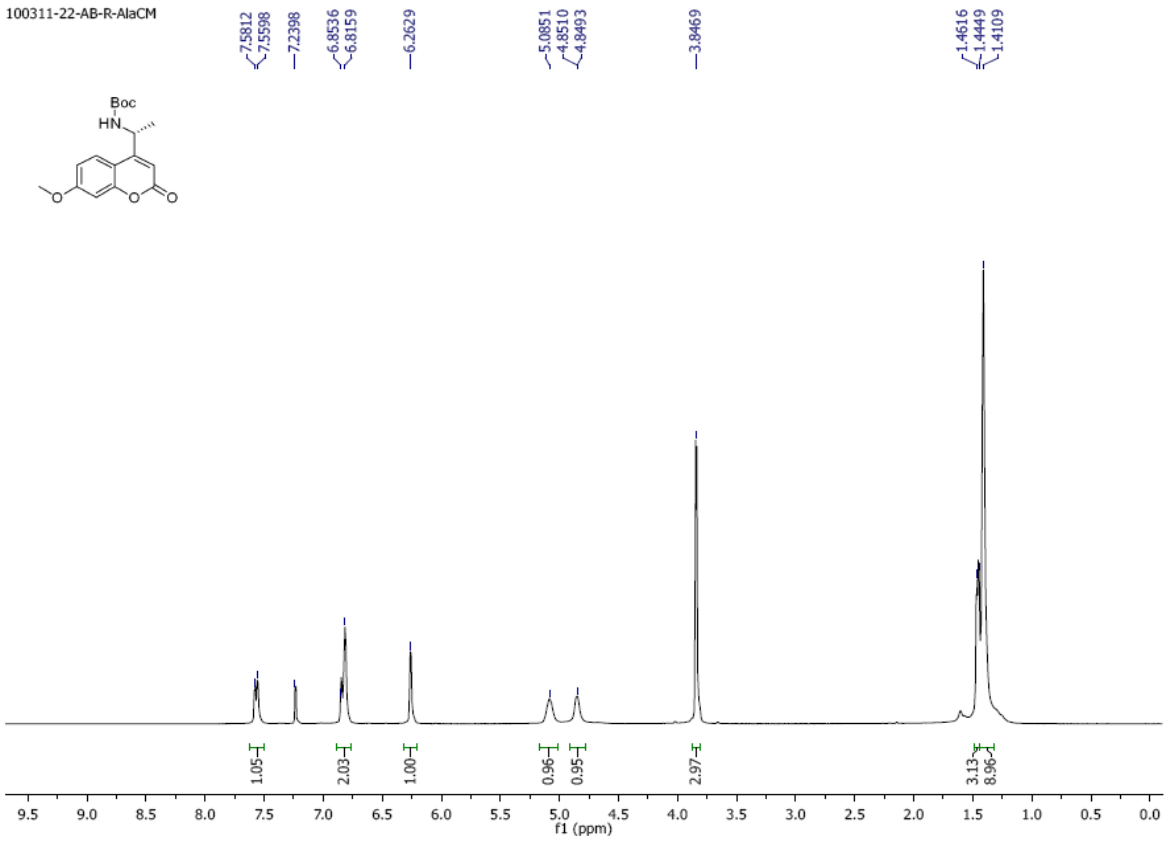
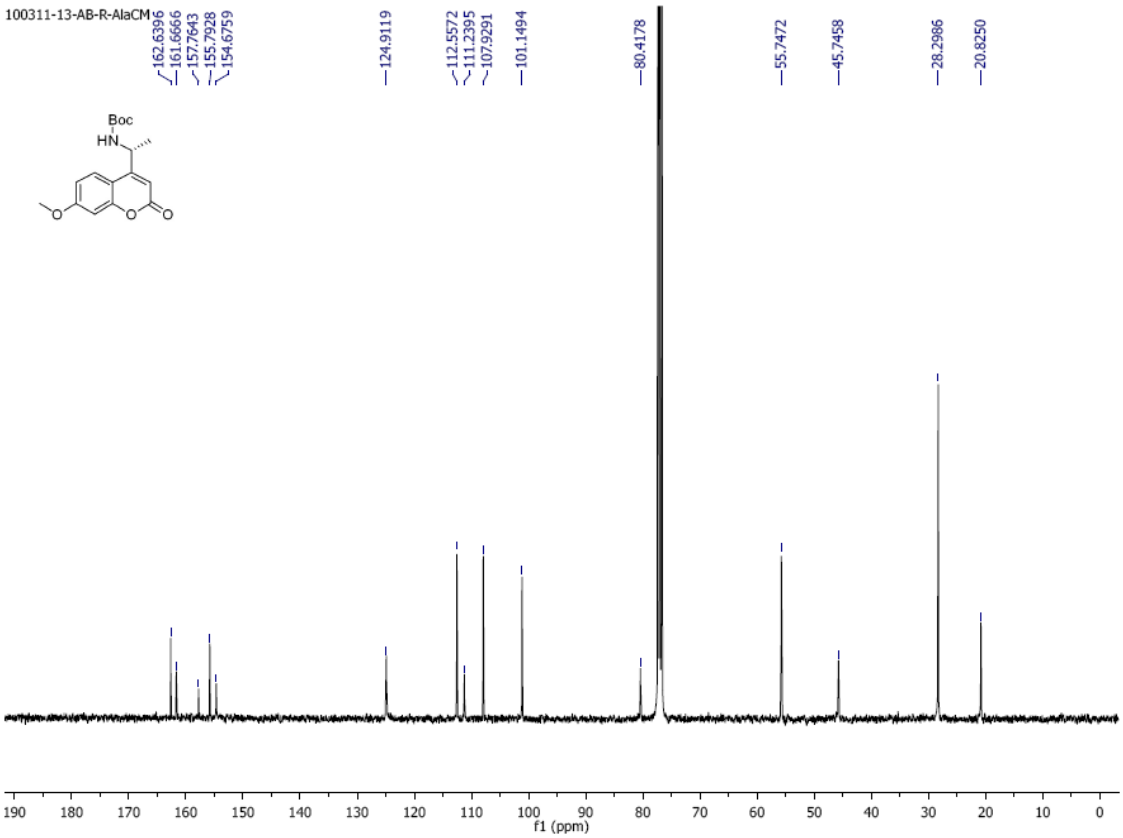
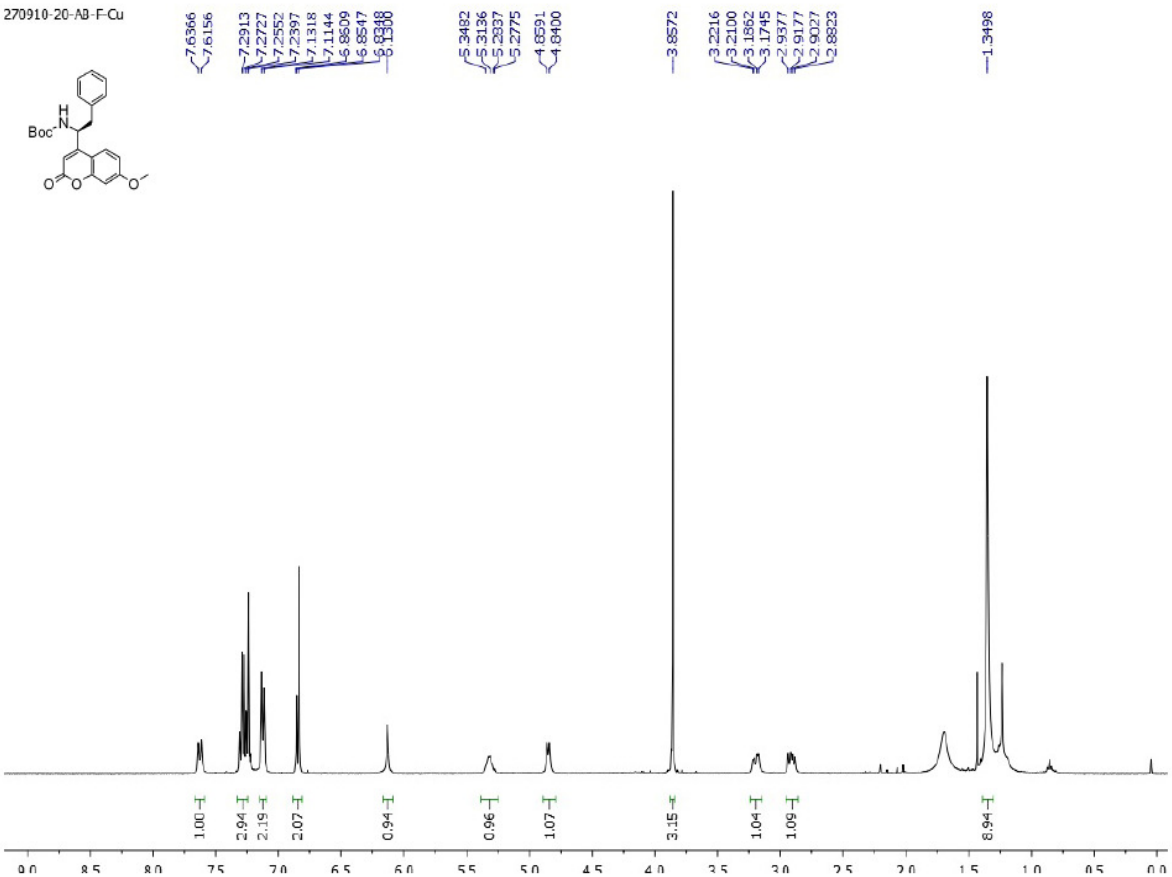
f1 (ppm)





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3.1862
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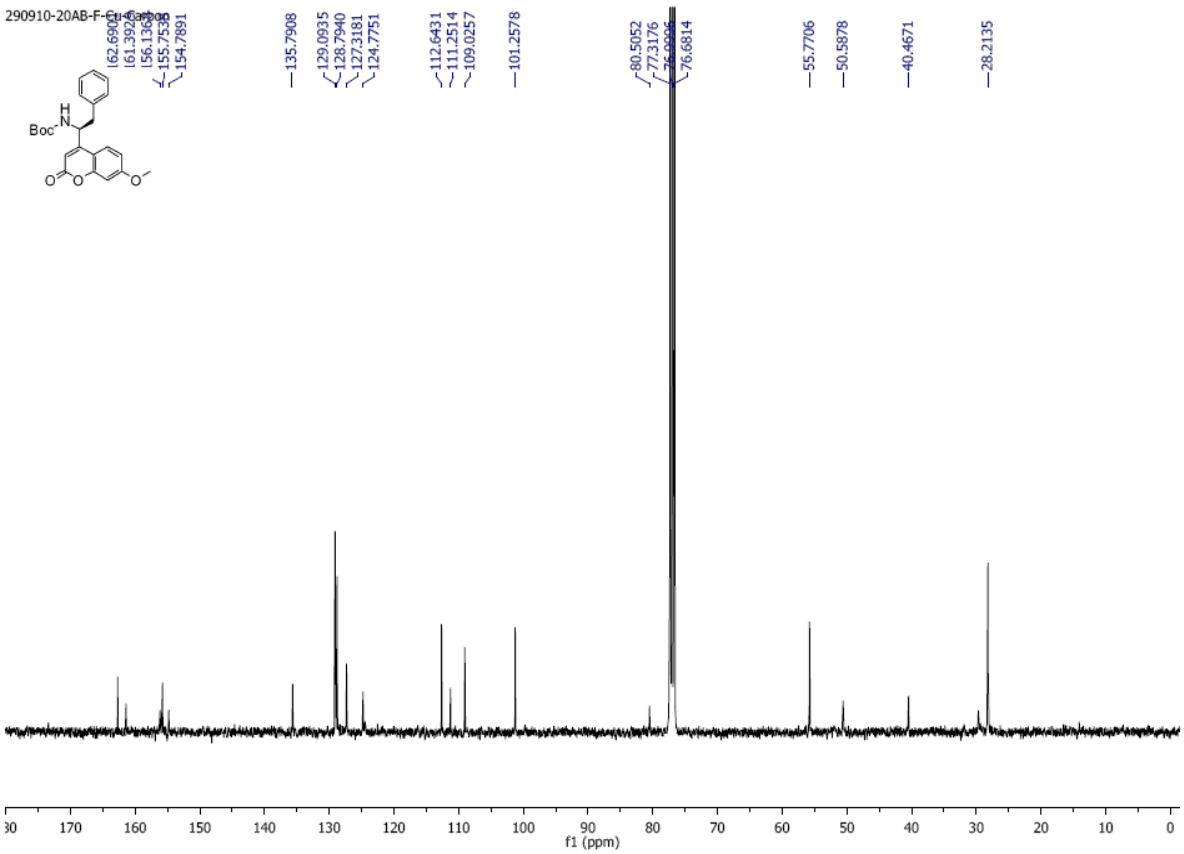
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127.3181
124.7751
112.6431
111.2514
109.0257
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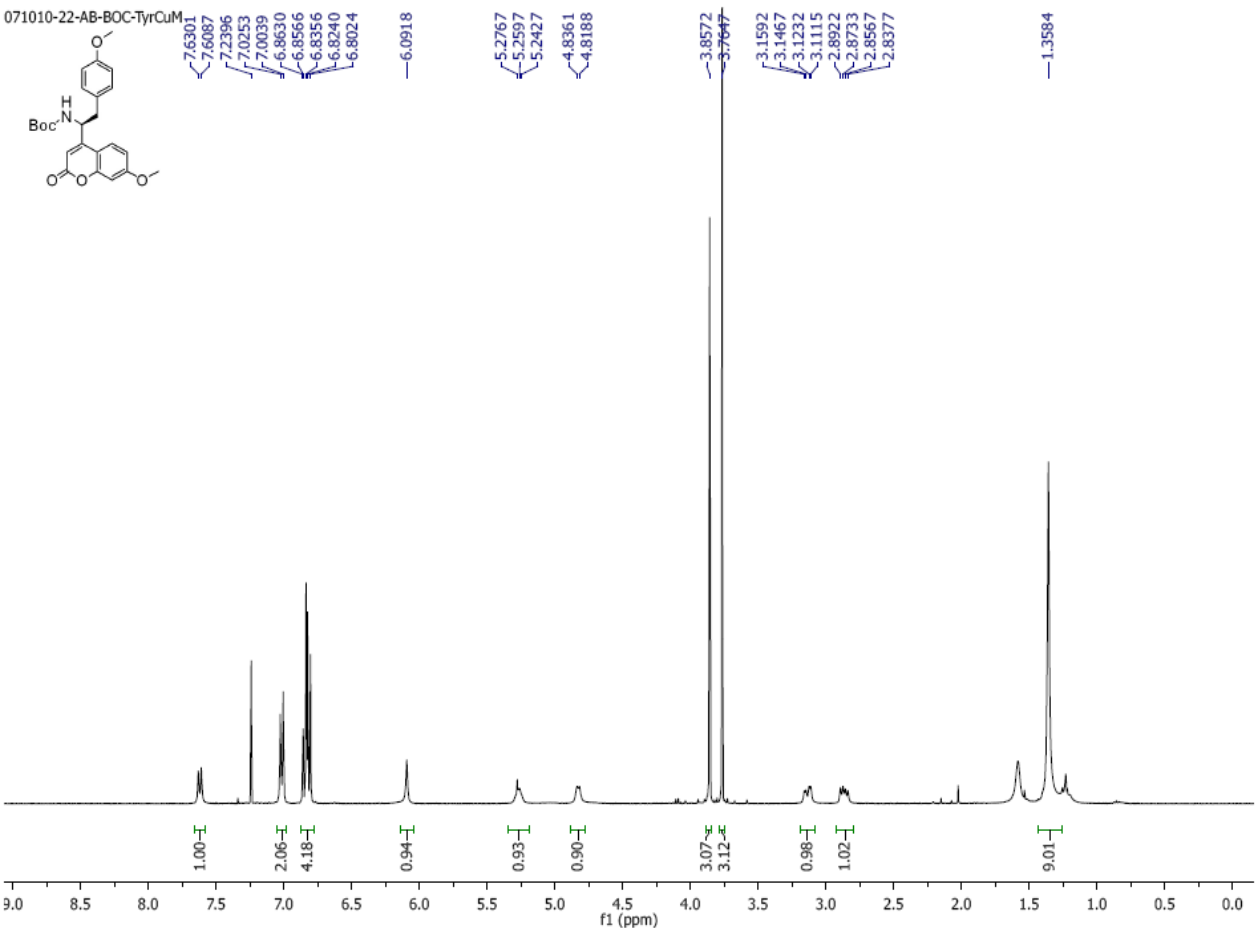
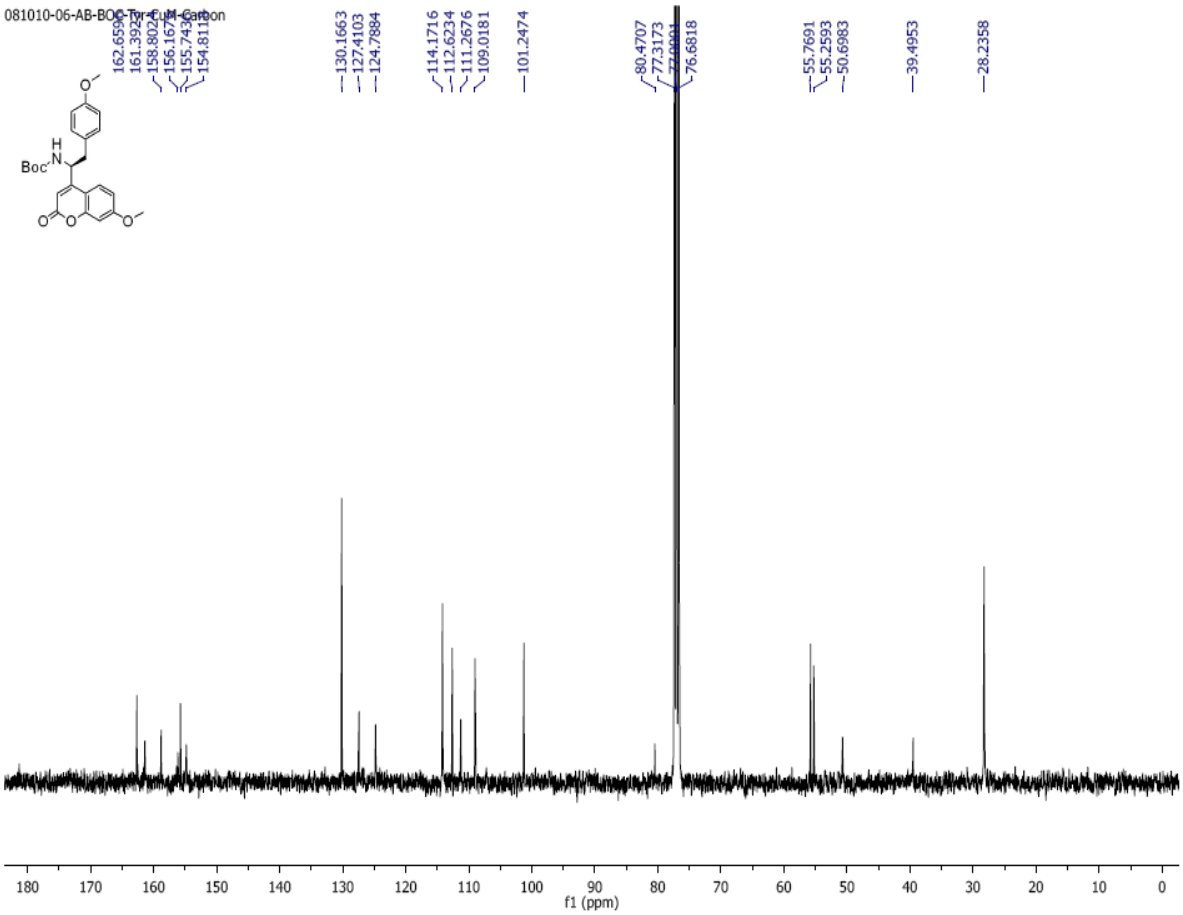
28.2135
Boc
f1 (ppm)

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109.0181
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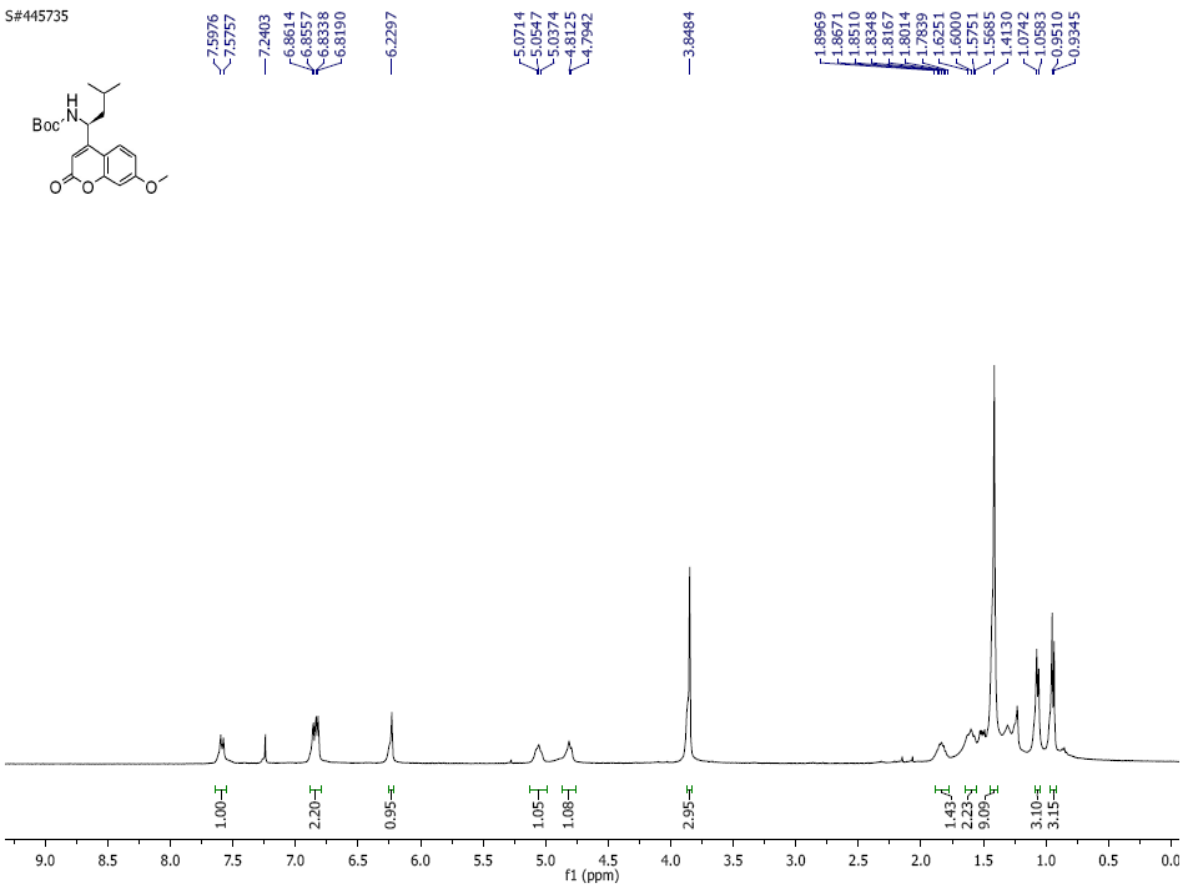
Boc
H
N
O
O
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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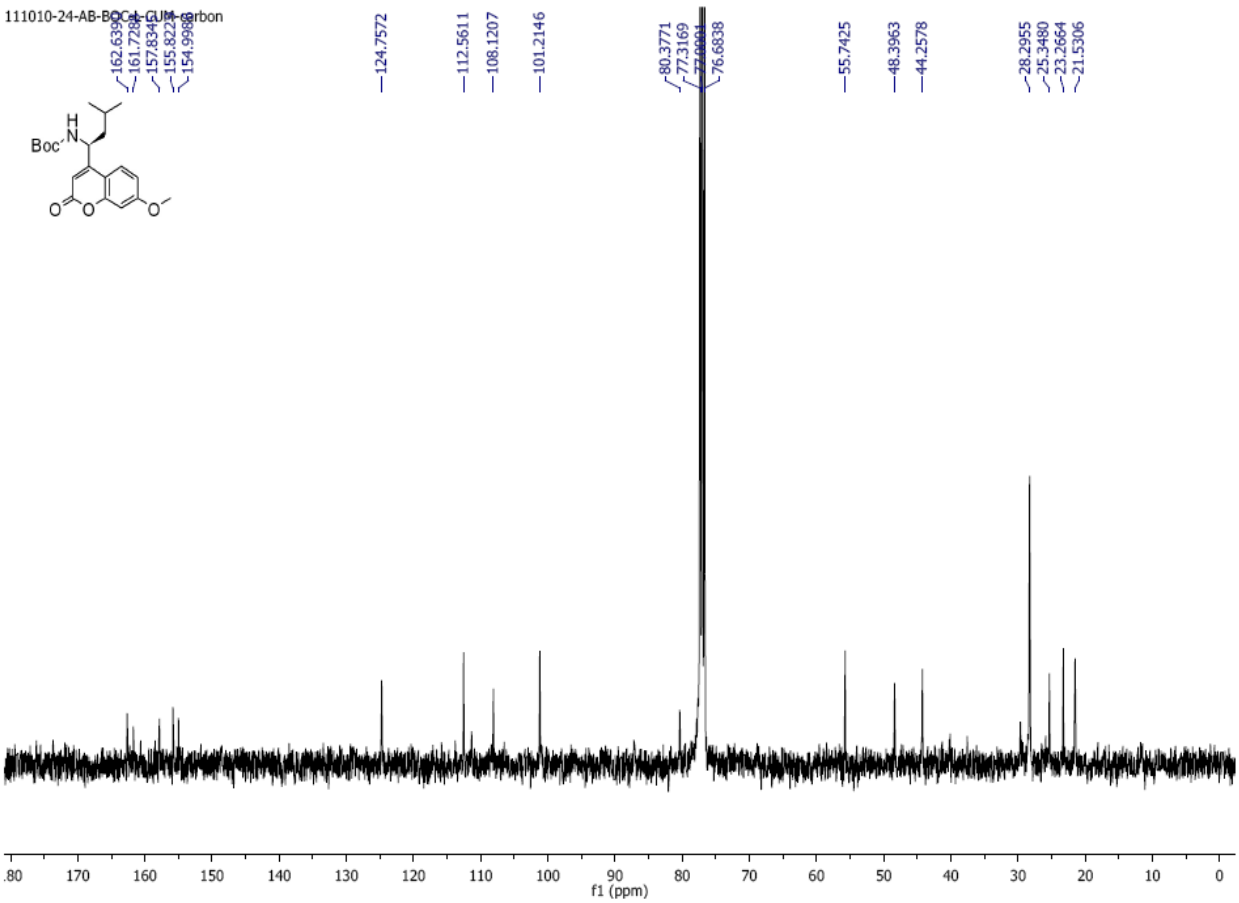
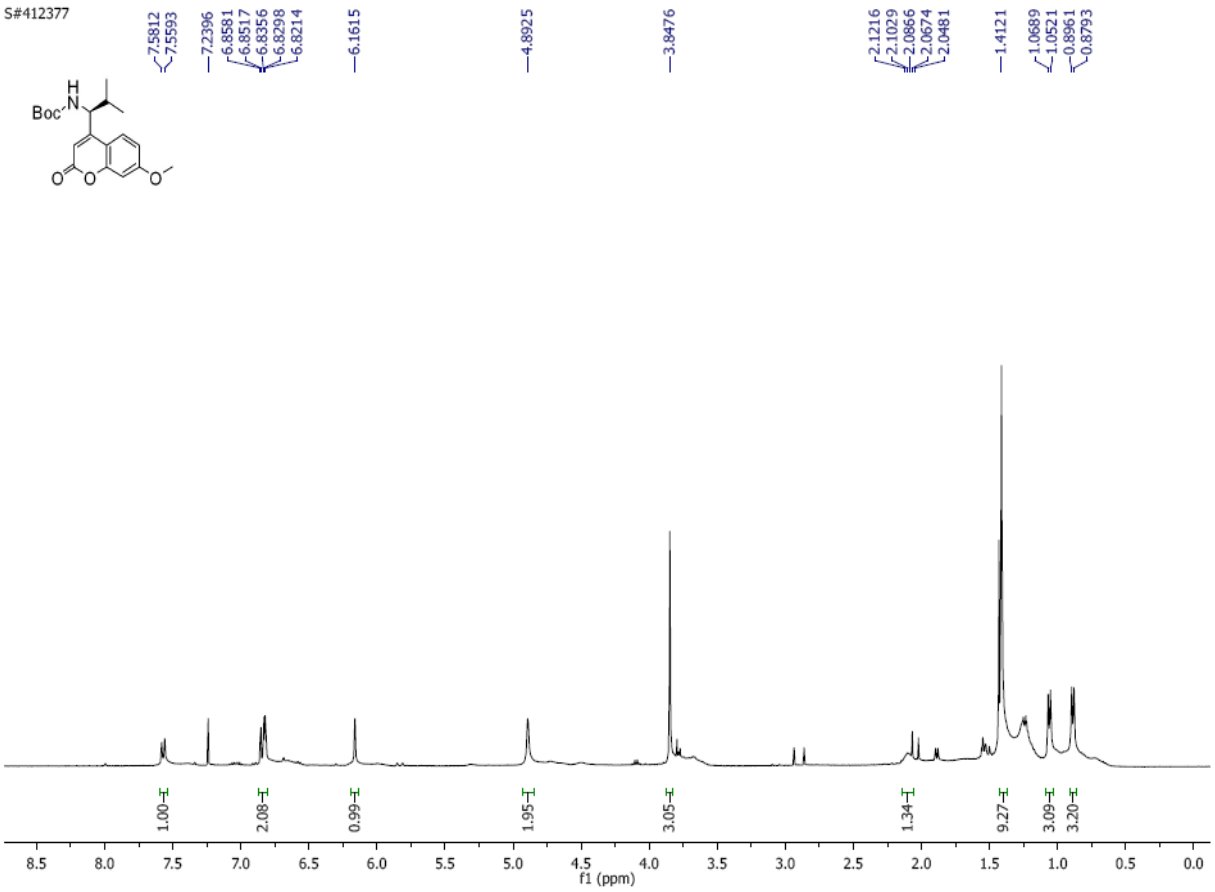
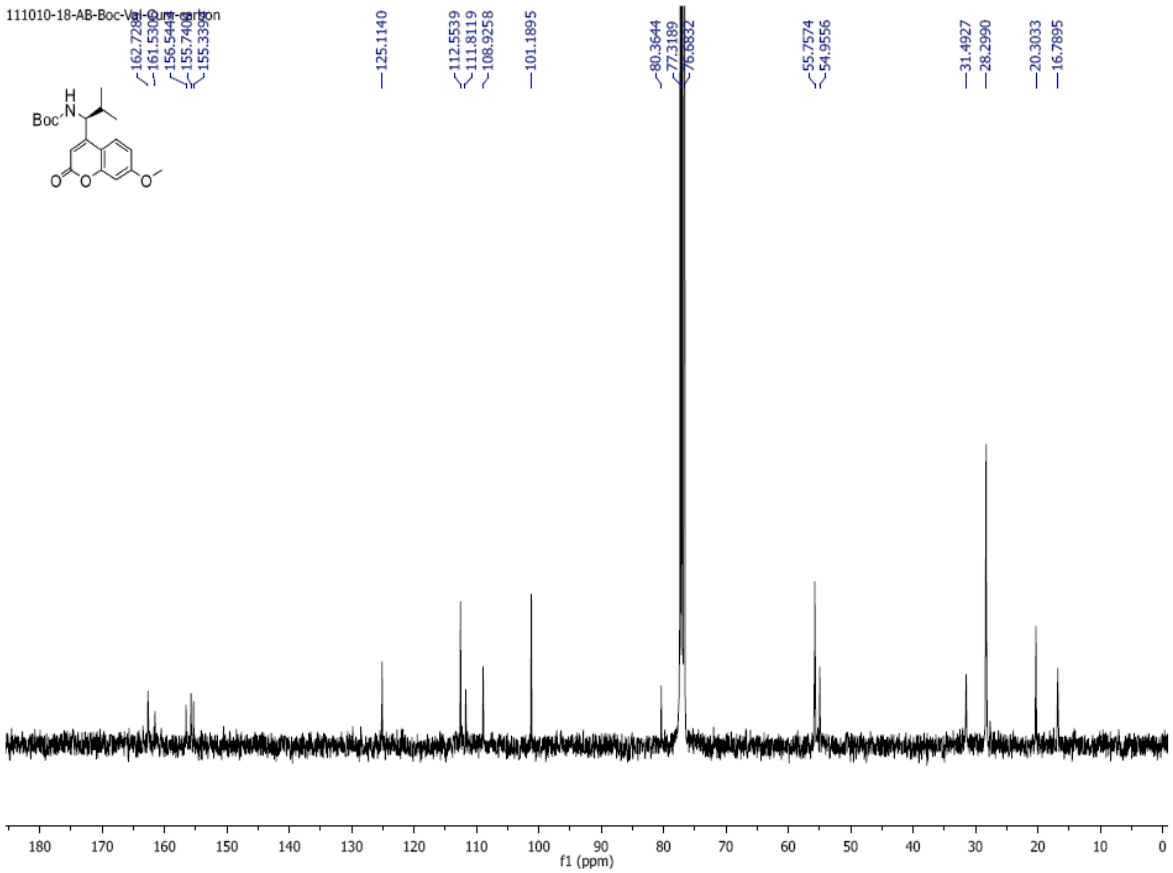
7.5757
7.2403
6.8614
6.8557
6.8338
6.8190
6.2297
5.0714
5.0547
5.0374
4.8125
4.7942
3.8484
1.8969
1.8671
1.8510
1.8348
1.8167
1.8014
1.7839
1.6251
1.6000
1.5751
1.5685
1.4130
1.0742
1.0583
0.9510
0.9345
Boc
N
H
O
O
O
1.00
2.20
0.95
1.05
1.08
2.95
1.43
2.23
9.09
3.10
3.15
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)




S#412377
7.5812
7.5593
7.2396
6.8581
6.8517
6.8356
6.8298
6.8214
6.1615
4.8925
3.8476
2.1216
2.1029
2.0866
2.0674
2.0481
1.4121
1.0689
1.0521
0.8961
0.8793
Boc
H
N
O
O
O
1.00
2.08
0.99
1.95
3.05
1.34
9.27
3.09
3.20
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
f1 (ppm)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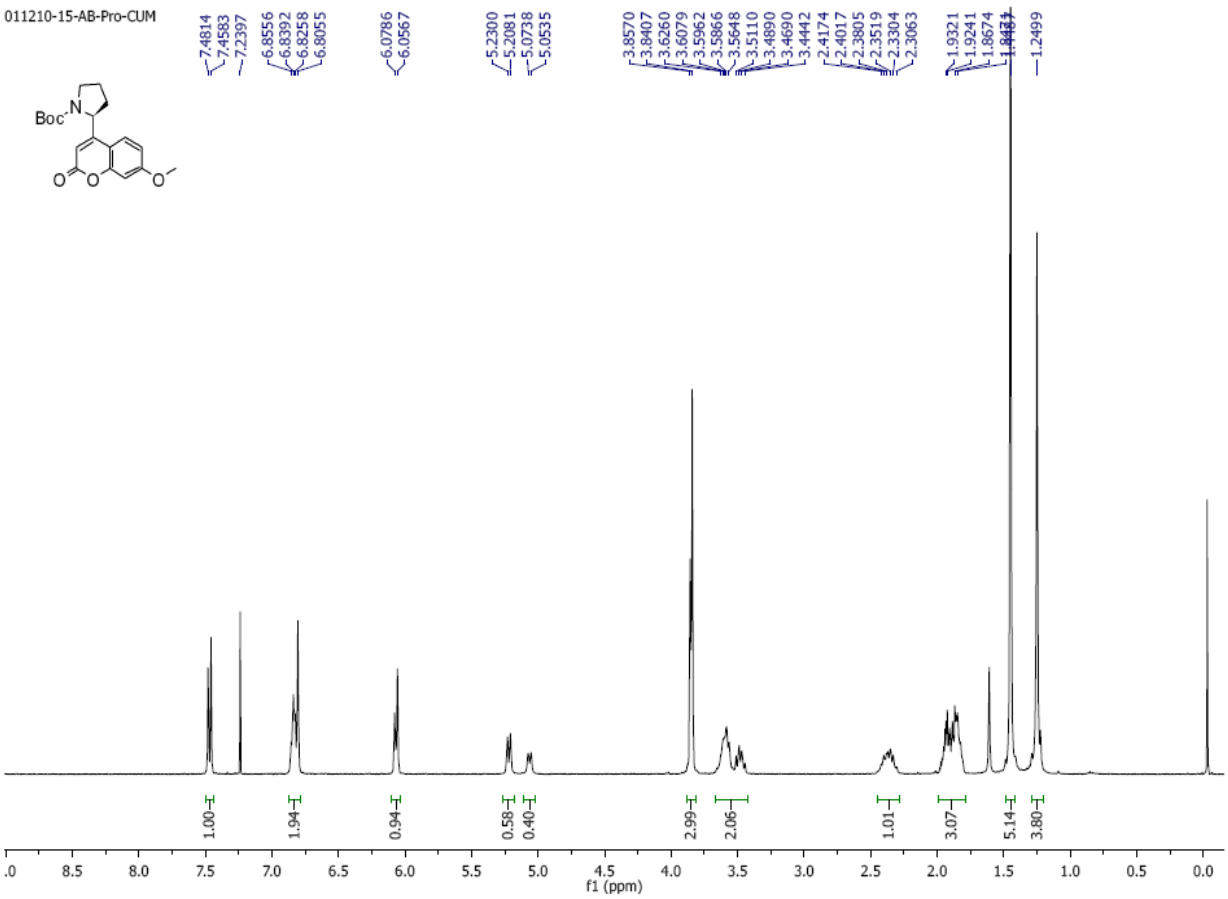
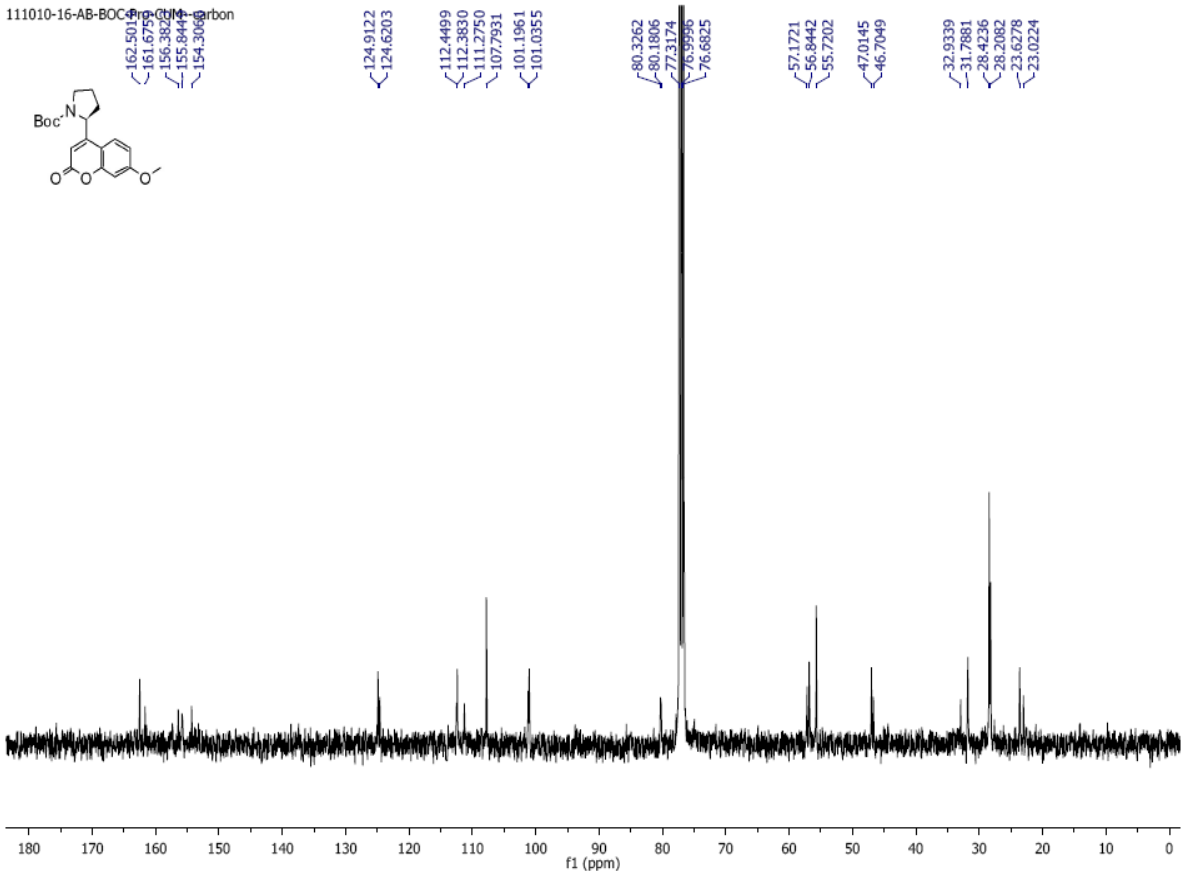
162.7284
161.5307
156.5443
155.7405
155.3397
125.1140
112.5539
111.8119
108.9258
101.1895
80.3644
77.3189
76.6832
55.7574
54.9556
31.4927
28.2990
20.3033
16.7895
Boc
H
N
O
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

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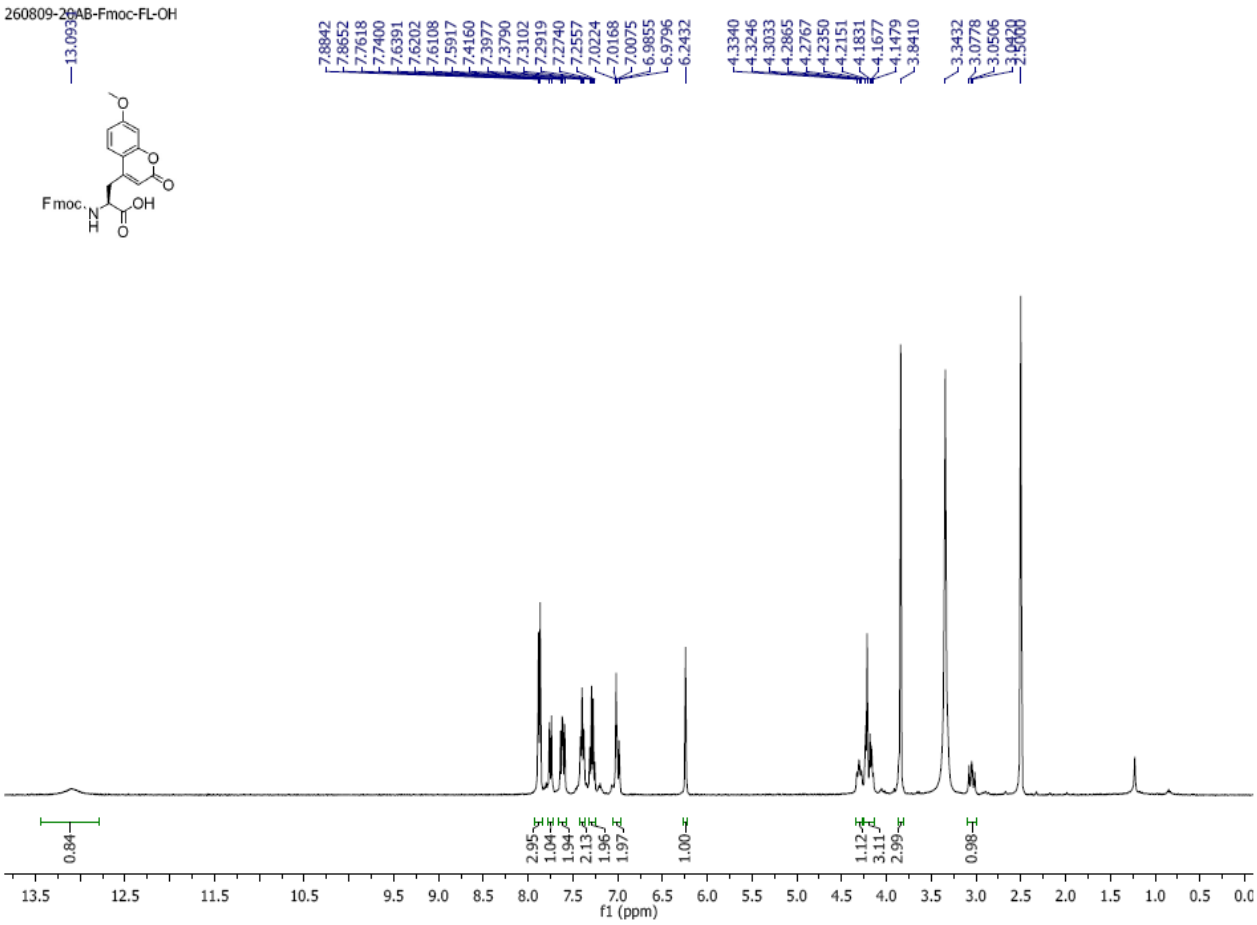
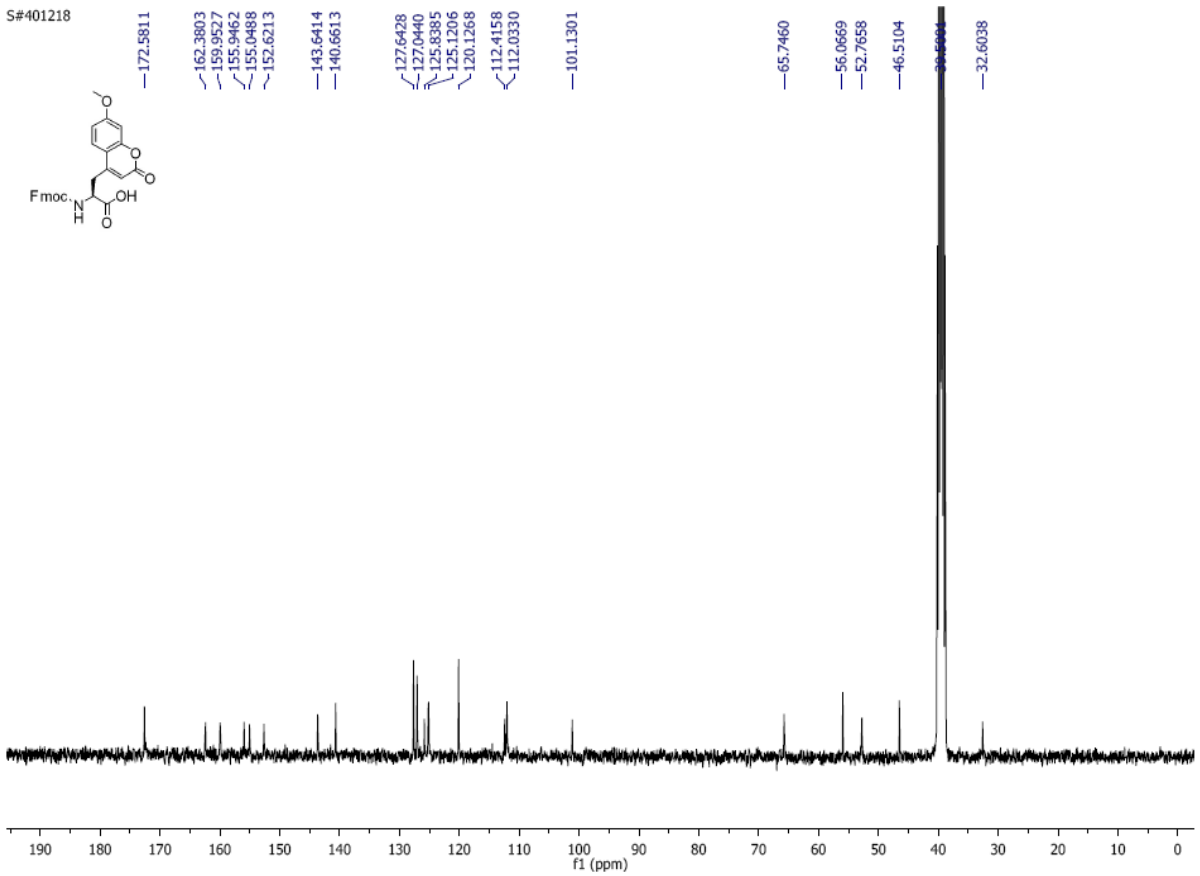
156.3824
155.8444
154.3068
124.9122
124.6203
112.4499
112.3830
111.2750
107.7931
101.1961
101.0355
80.3262
80.1806
77.3174
76.9996
76.6825
57.1721
56.8442
55.7202
47.0145
46.7049
32.9339
31.7881
28.4236
28.2082
23.6278
23.0224
Boc
N
O
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


260809-20AB-Fmoc-FL-OH
13.0938
7.8842
7.8652
7.7618
7.7400
7.6391
7.6202
7.6108
7.5917
7.4160
7.3977
7.3790
7.3102
7.2919
7.2740
7.2557
7.0224
7.0168
7.0075
6.9855
6.9796
6.2432
4.3340
4.3246
4.3033
4.2865
4.2767
4.2350
4.2151
4.1831
4.1677
4.1479
3.8410
3.3432
3.0778
3.0506
3.0420
2.5000
Fmoc
N
H
OH
O
0.84
2.95
1.04
1.94
2.13
1.96
1.97
1.00
1.12
3.11
2.99
0.98
13.5
12.5
11.5
10.5
9.5
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
f1 (ppm)


S#401218
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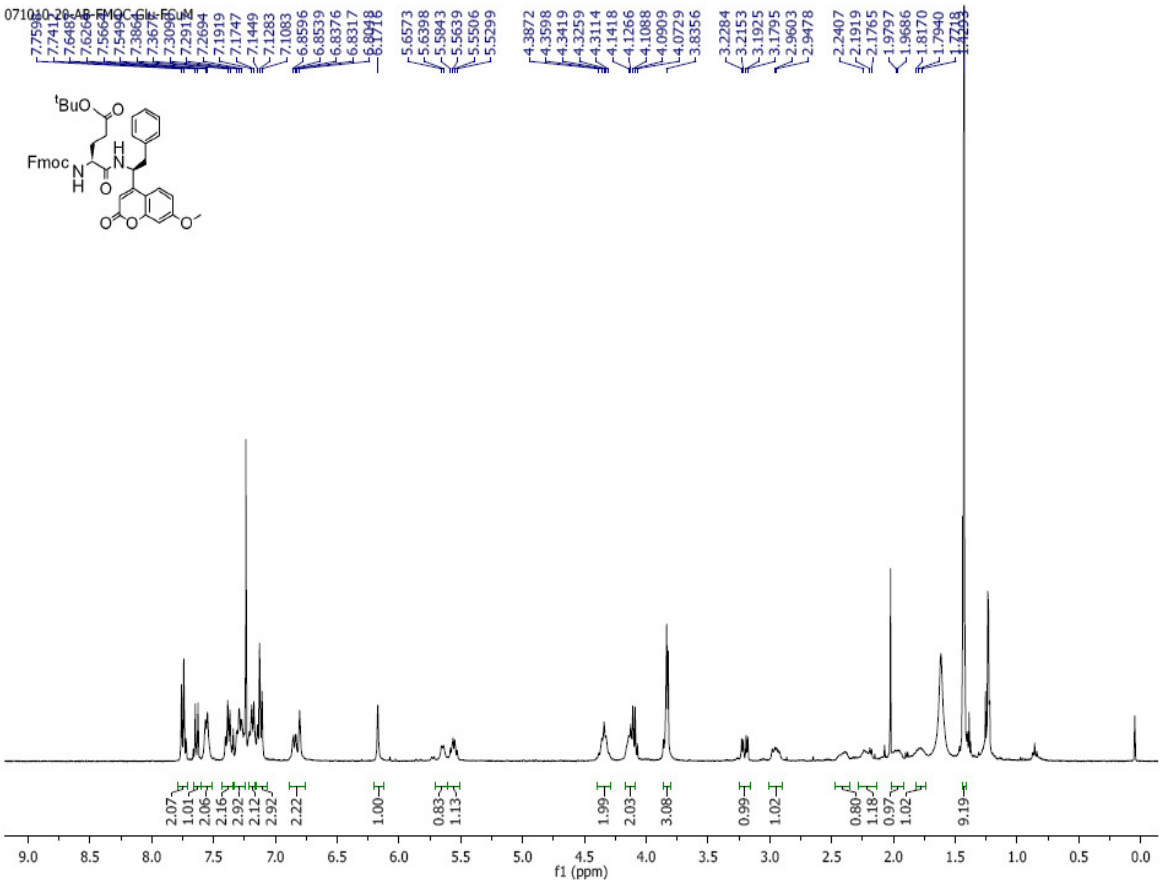
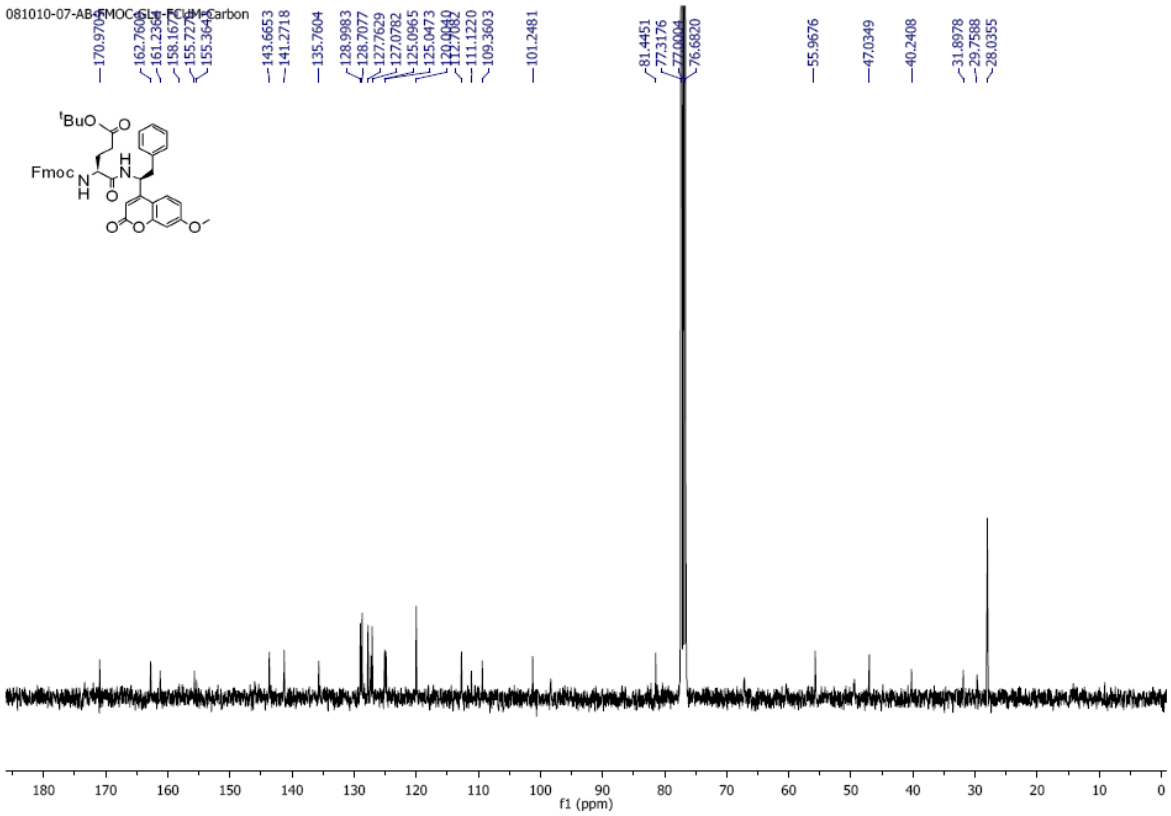
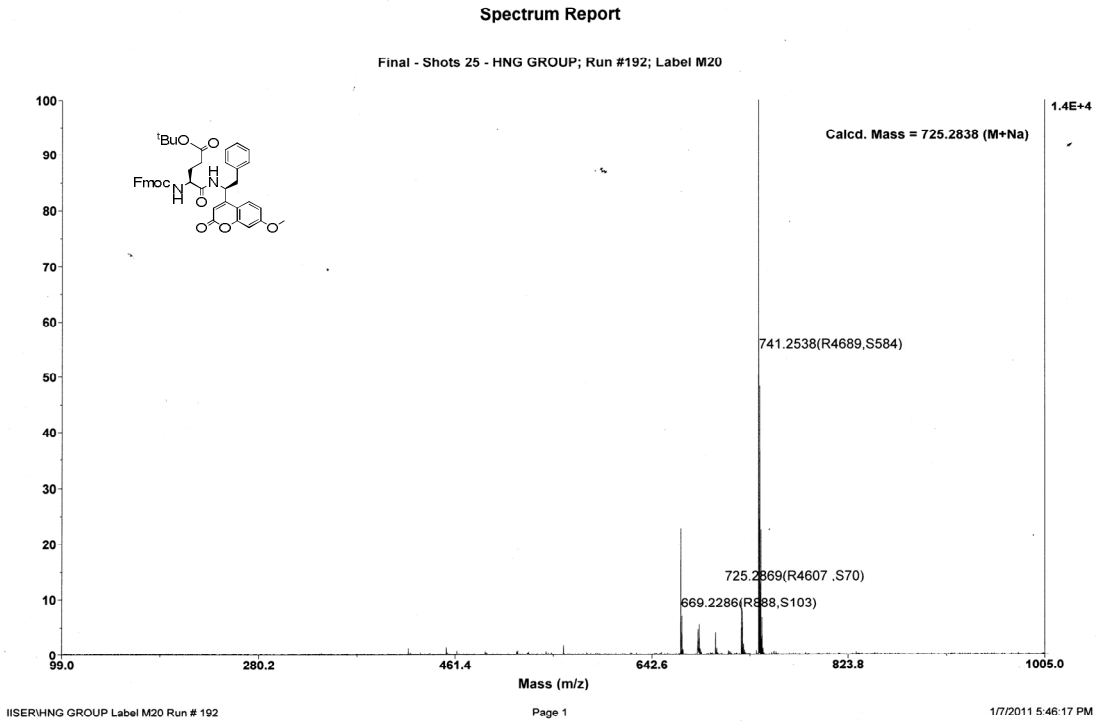
162.3803
159.9527
155.9462
155.0488
152.6213
143.6414
140.6613
127.6428
127.0440
125.8385
125.1206
120.1268
112.4158
112.0330
101.1301
65.7460
56.0669
52.7658
46.5104
39.5694
32.6038
Fmoc
NH
OH
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)






Spectrum Report
Final - Shots 25 - HNG GROUP; Run #192; Label M20
Calcd. Mass = 725.2838 (M+Na)
741.2538(R4689,S584)
725.2869(R4607 ,S70)
669.2286(R888,S103)
Mass (m/z)
IISER\HNG GROUP Label M20 Run # 192
Page 1
1/7/2011 5:46:17 PM

HPLC profile of Fmoc-Glu(OBu^t)-PheCoumarin

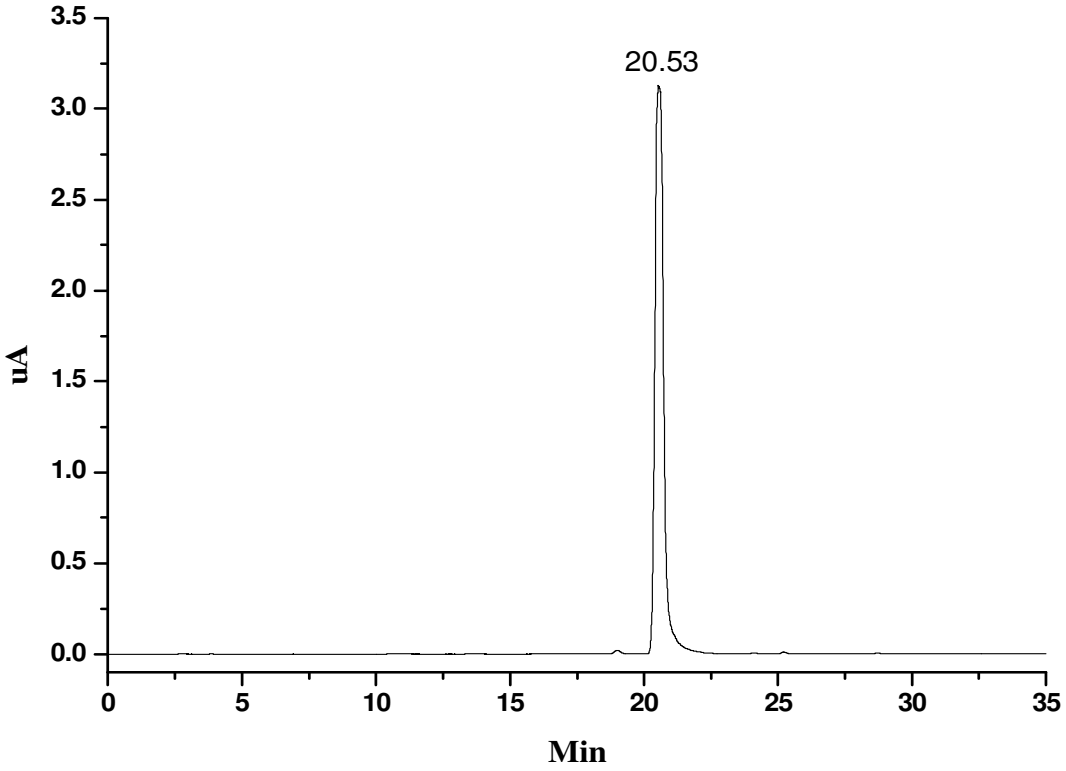
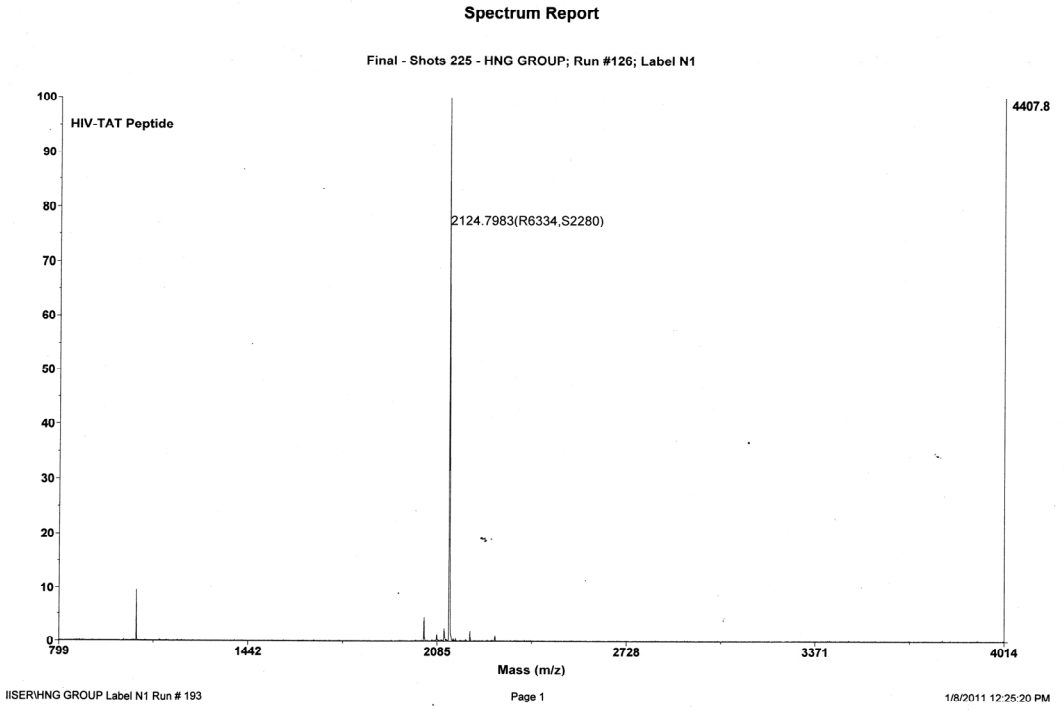


Figure 7: Analytical reverse phase HPLC profile of dipeptide 4 in methanol/water gradient system; λ=254 nm, gradient 60 to 95 % MeOH in 0 →35 min.

MALDI TOF/TOF mass of Coumarin Tagged HIV-1 TAT peptide



HPLC profile of Coumarin Tagged HIV-1 TAT Peptide

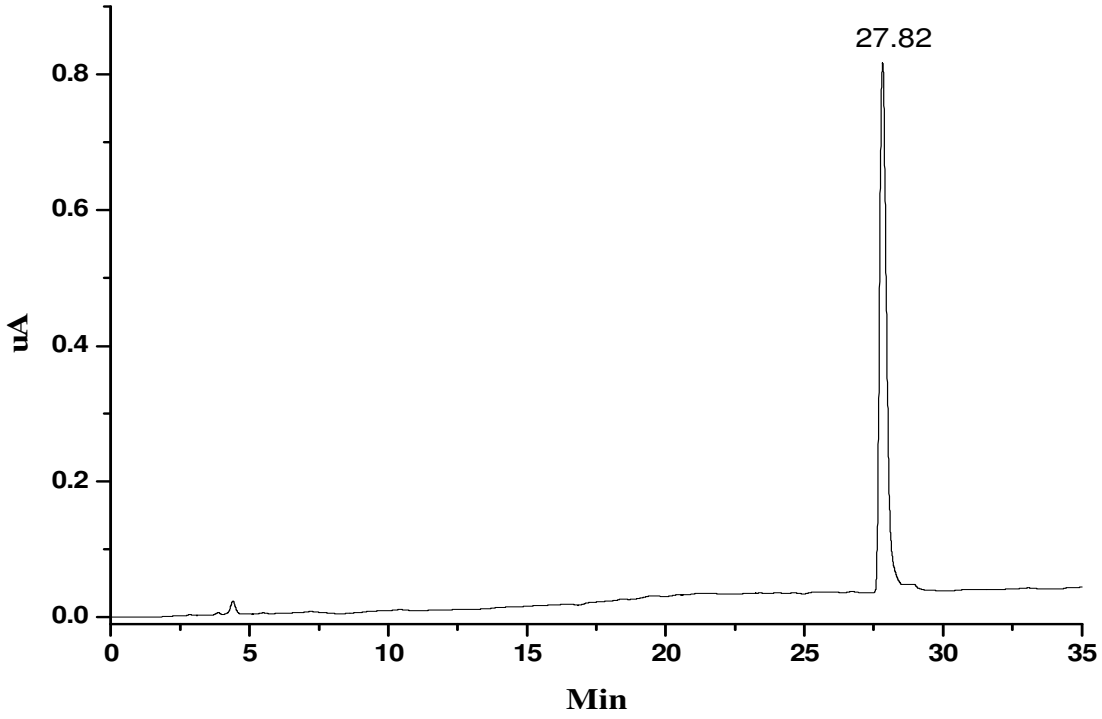


Figure 8: Analytical reverse phase HPLC profile of P1 in acetonitrile/water gradient system; λ=220 nm, gradient 20 to 95 % acetonitrile in 0 →35 min**.**