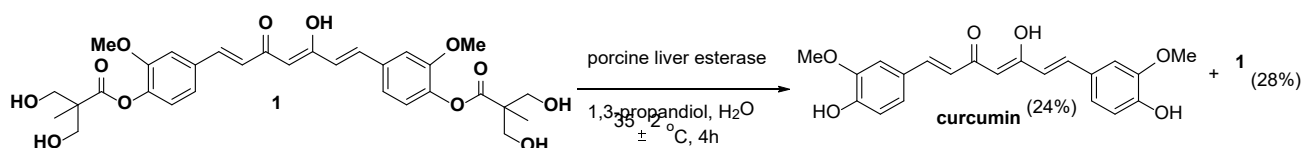# Synthesis, anticancer activity, and preliminary pharmacokinetic evaluation of 4,4-disubstituted curcuminoid 2,2-bis(hydroxymethyl)propionate derivatives

Der-Yen Lee, Yu-Chi Hou, Jai-Sing Yang, Hui-Yi Lin, Tsu-Yuan Chang, Kuo-Hsiung Lee, Sheng-Chu Kuo, Min-Tsang Hsieh

Porcine liver esterase mediated hydrolysis of curcumin 2,2-bis(hydroxymethyl)propionate 1

To a stirred solution of compound **1** (0.200 g, 0.29 mmol) in 1,3-propanediol/water (ratio = 1:3, 4mL) was added porcine liver esterase (10 mg, lyophilized powder, ≥15 units/mg solid) in one portion. The resulting mixture was stirred at 35 ± 2 °C for 4 hours under air atmosphere. H_2O (6 mL) was added to quench the reaction. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was then purified by flash chromatography on silica gel with EtOAc/*n*-hexane/CH_2Cl_2 (1:2:1) to afford curcumin (0.026 g, 24% yield) as an yellow soild and recover compound **1** (0.056 g, 28% yield).
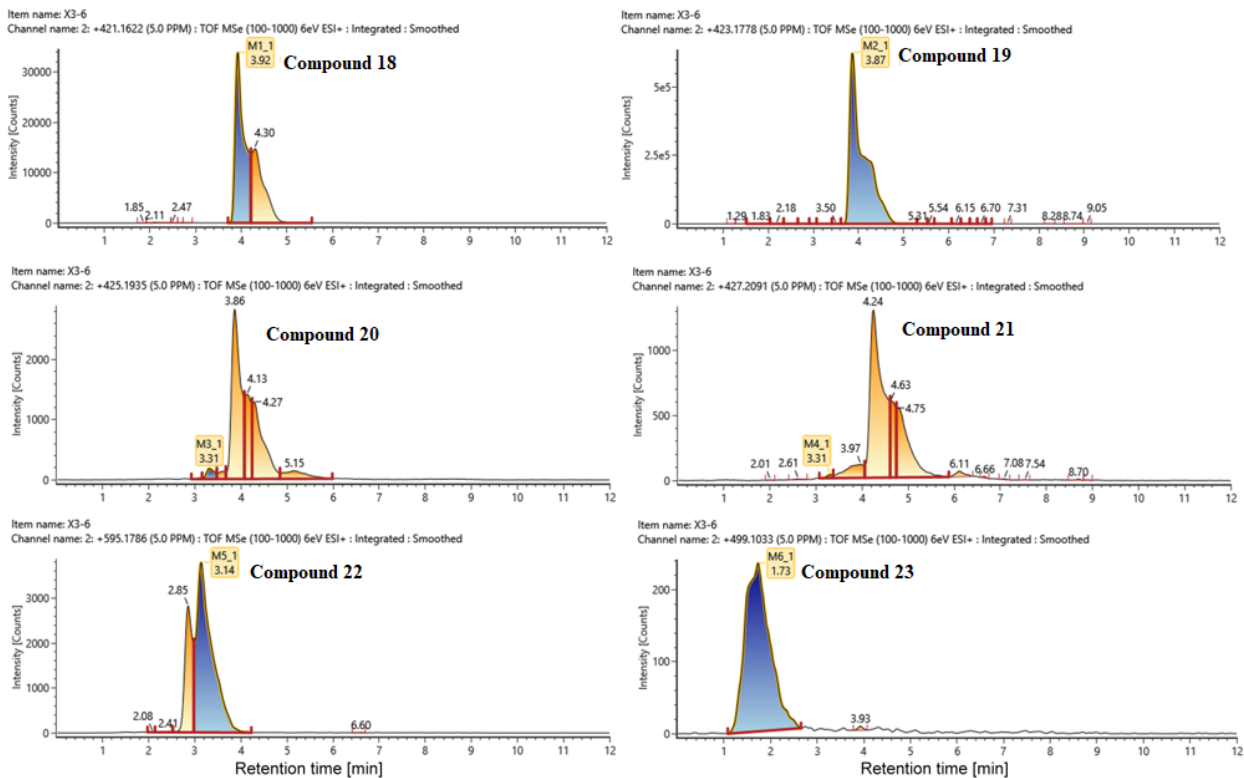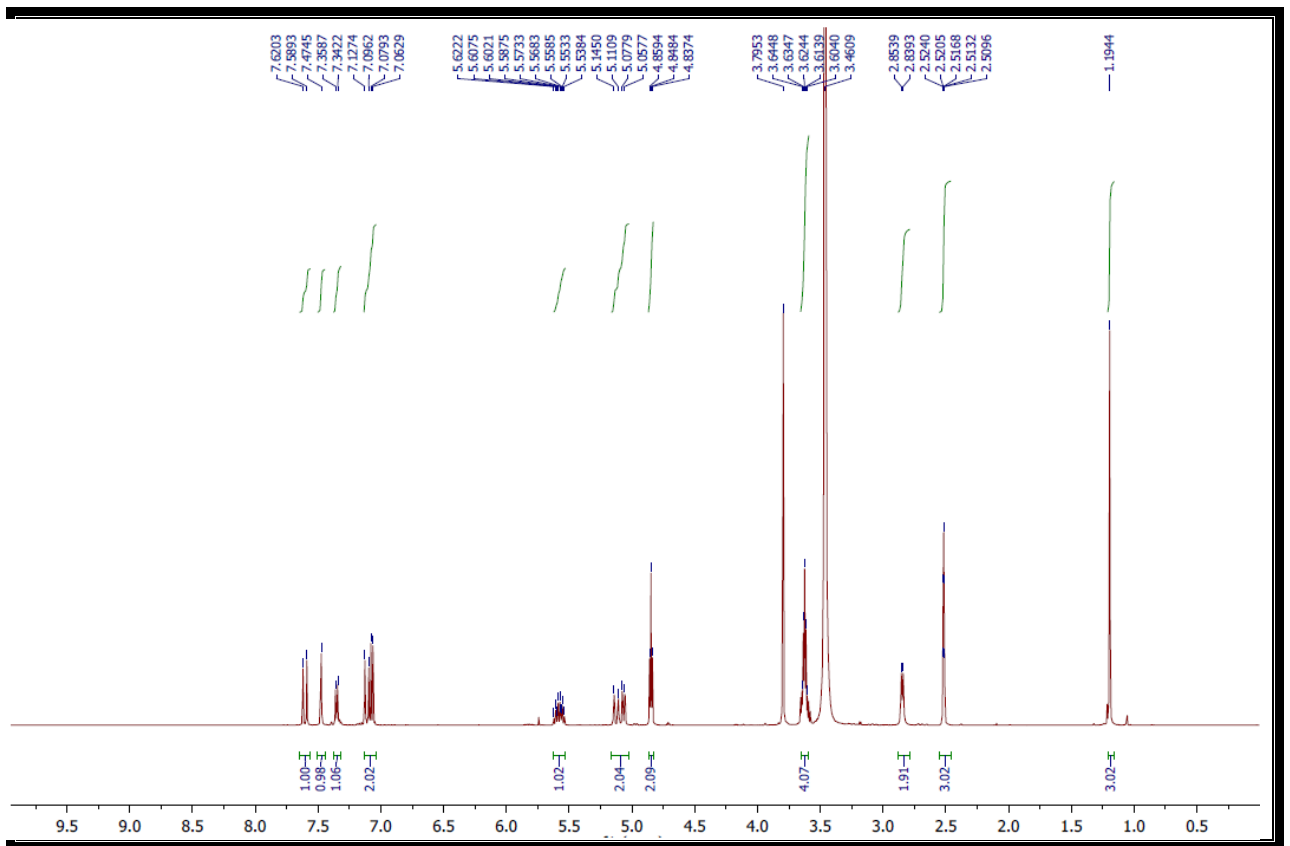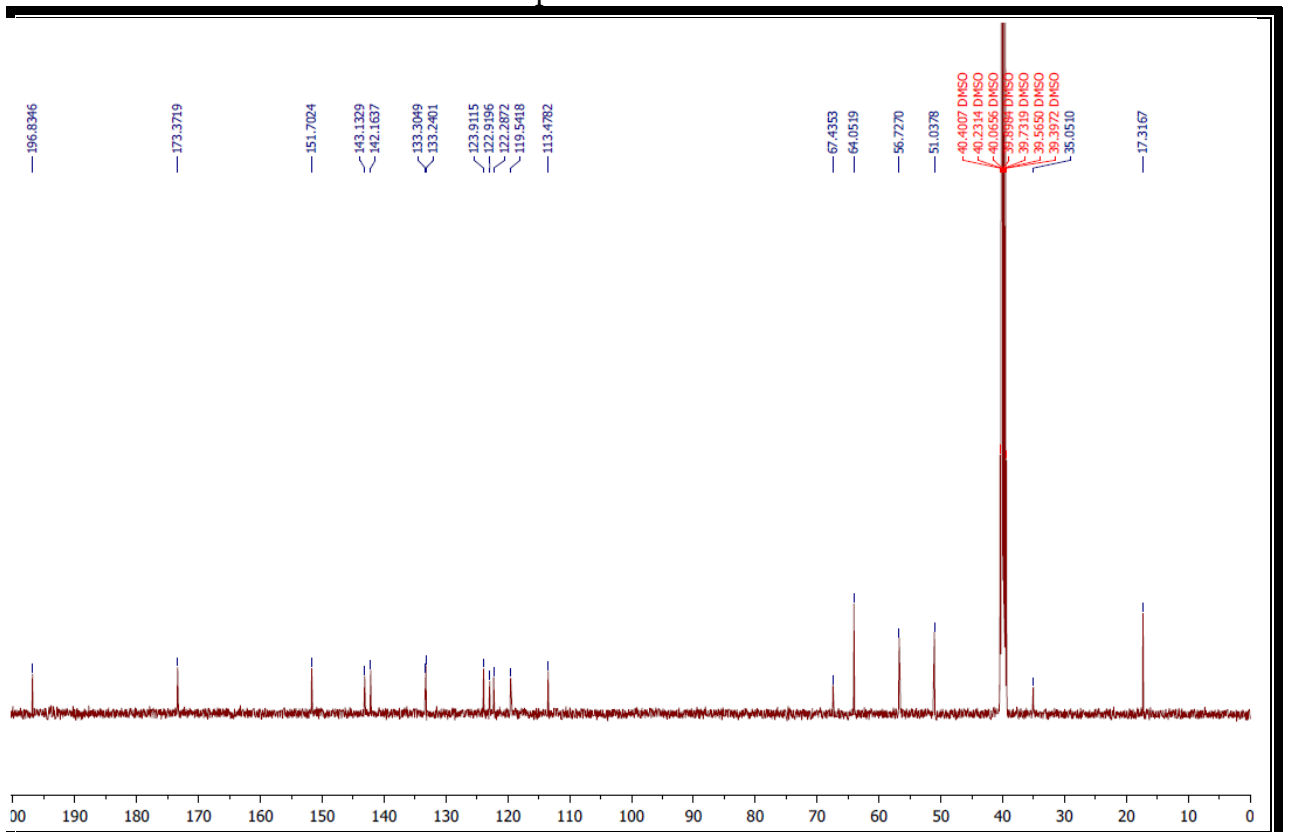
Figure S1. The analysis of compound **18**, **19**, **20**, **21**, **22** and **23** was performed by Waters Vion IMS QTof mass spectrometer. The acquired m/z and isotope pattern were processed by UNIFI software to illustrate chromatogram. The m/z values of the parent ions were set to 421.1622 for **18**, 423.1778 for **19**, 425.1935 for **20**, 427.2091 for **21**, 595.1786 for **22** and 499.1033 for **23**, respectively.
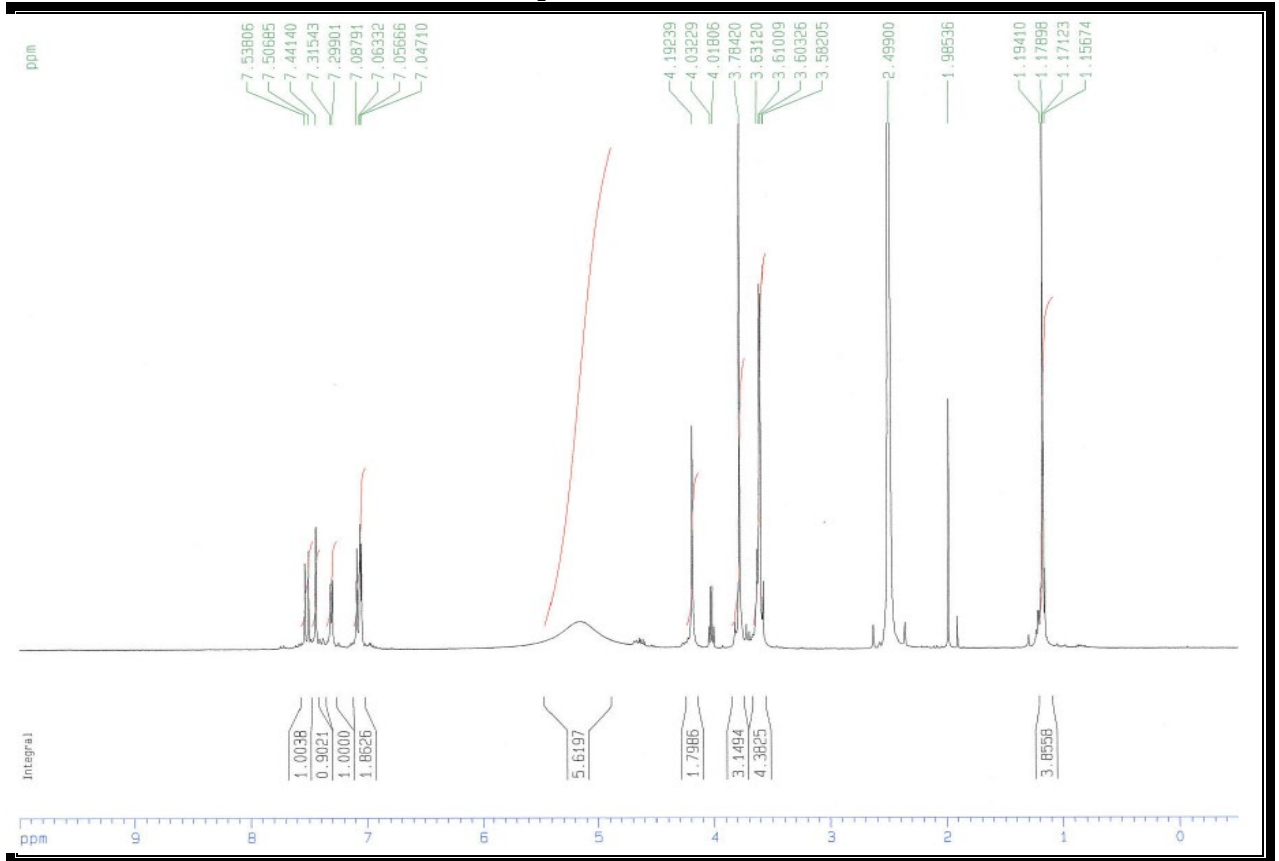
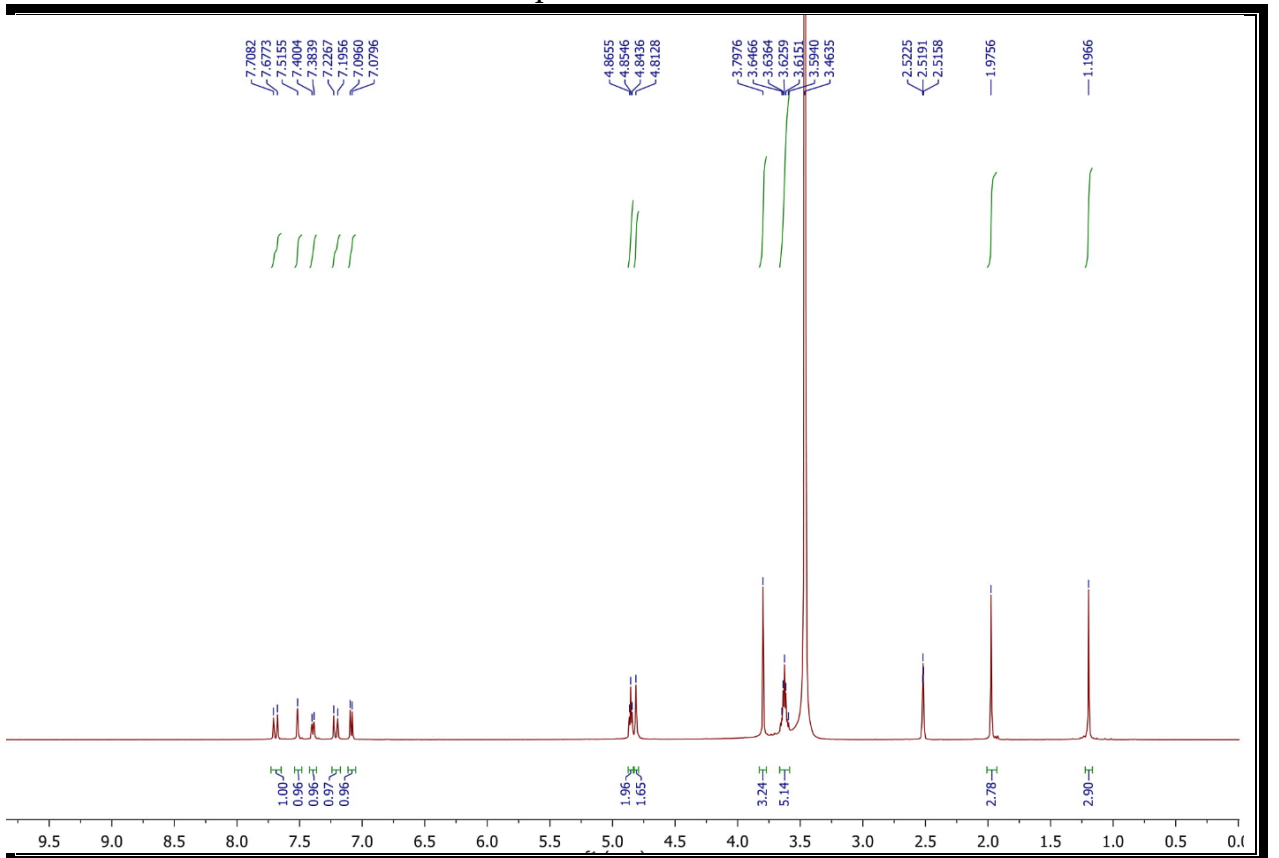**The NMR sepctrums of newly synthesized compounds**
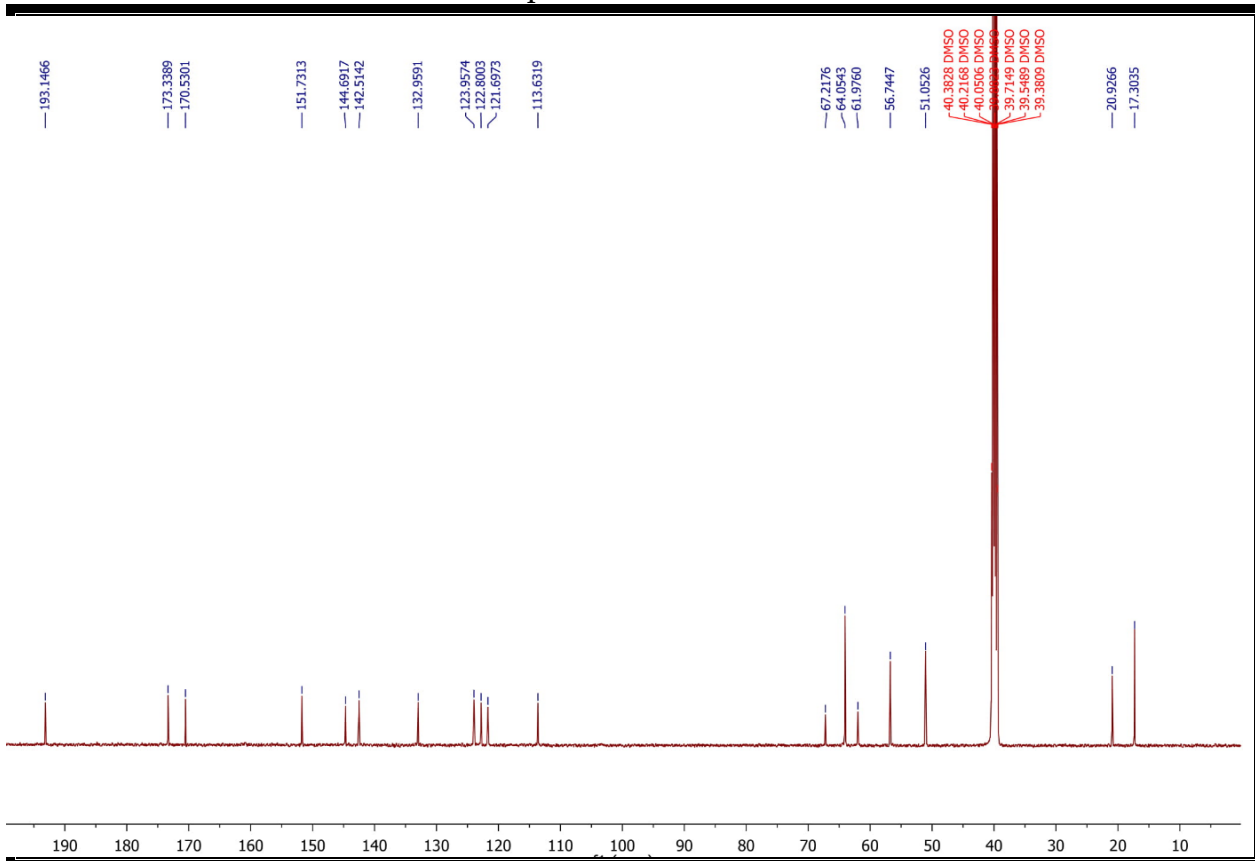

¹H spectrum of **6**

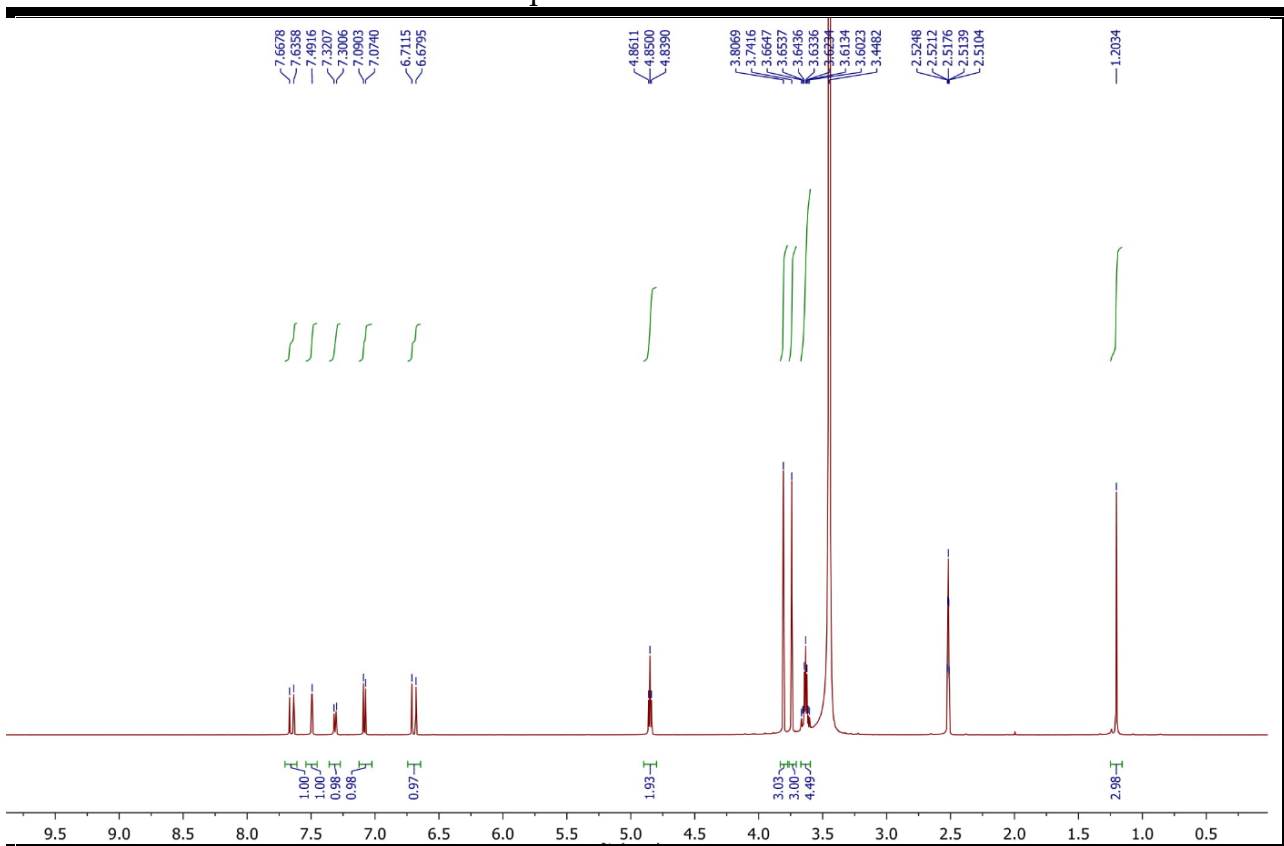## ^{13}C spectrum of 6

^{1}H spectrum of 9

¹H spectrum of 10

193.1466

173.3389
170.5301

151.7313

144.6917
142.5142

132.9591

123.9574
122.8003
121.6973

113.6319

67.2176
64.0543
61.9760

56.7447

51.0526

40.3828 DMSO
40.2168 DMSO
40.0506 DMSO
39.7149 DMSO
39.5489 DMSO
39.3809 DMSO

20.9266
17.3035

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

¹³C spectrum of 10

7.6678
7.6358
7.4916
7.3207
7.3006
7.0903
7.0740

6.7115
6.6795

4.8611
4.8500
4.8390

3.8069
3.7416
3.6647
3.6537
3.6436
3.6336
3.6234
3.6134
3.6023
3.4482

2.5248
2.5212
2.5176
2.5139
2.5104

1.2034

1.00
1.00
0.98
0.98

0.97

1.93

3.03
3.00
4.49

2.98

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

¹H spectrum of **11**

173.4248
167.1919
151.6980
144.4740
141.8538
133.2439
123.8454
121.9067
118.4697
112.6572
64.0627
56.6368
51.9646
51.0382
40.4119 DMSO
40.2455 DMSO
40.0796 DMSO
39.7441 DMSO
39.5777 DMSO
39.4117 DMSO
17.3208

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

¹³C spectrum of **11**

7.5116
7.4806
7.2863
7.2828
7.2559
7.2524
7.2392
7.2357
6.9916
6.9748
6.9563
6.9252
4.7970
4.7871
4.7771
4.1928
4.1829
3.7981
3.7909
3.4497
2.5213
2.5178
2.5144

1.00
1.00
1.02
1.06
1.04
0.97
1.90
6.19

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
f1 (ppm)

¹H spectrum of **12**

¹³C spectrum of **12**

¹H spectrum of **14**

—193.3450

—174.6422

152.1694
149.4337
145.0523

127.1264
124.7191

—119.5853

112.0815
111.4838

66.9135
63.9959
62.3695

56.1670
56.1025

—50.7052

40.4040 DMSO
40.2384 DMSO
40.0704 DMSO
39.7366 DMSO
39.5705 DMSO
39.4022 DMSO

—17.0591

| 00 | 190 | 180 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |

^{13}C spectrum of **14**

7.6450
7.6141

7.2332
7.0652
7.0493
6.9535
6.8626
6.8462
6.6088
6.5779

—3.8837

1.9924
1.9822
1.9757
1.9583

1.1085
1.0960
1.0807
1.0633
1.0476
1.0241
0.9091
0.8948
0.8803

1.00

1.09
1.00
1.04

0.97

0.93

3.22

1.94

2.26
3.03

| 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 |

^{1}H spectrum of **15**

^{13}C spectrum of **15**
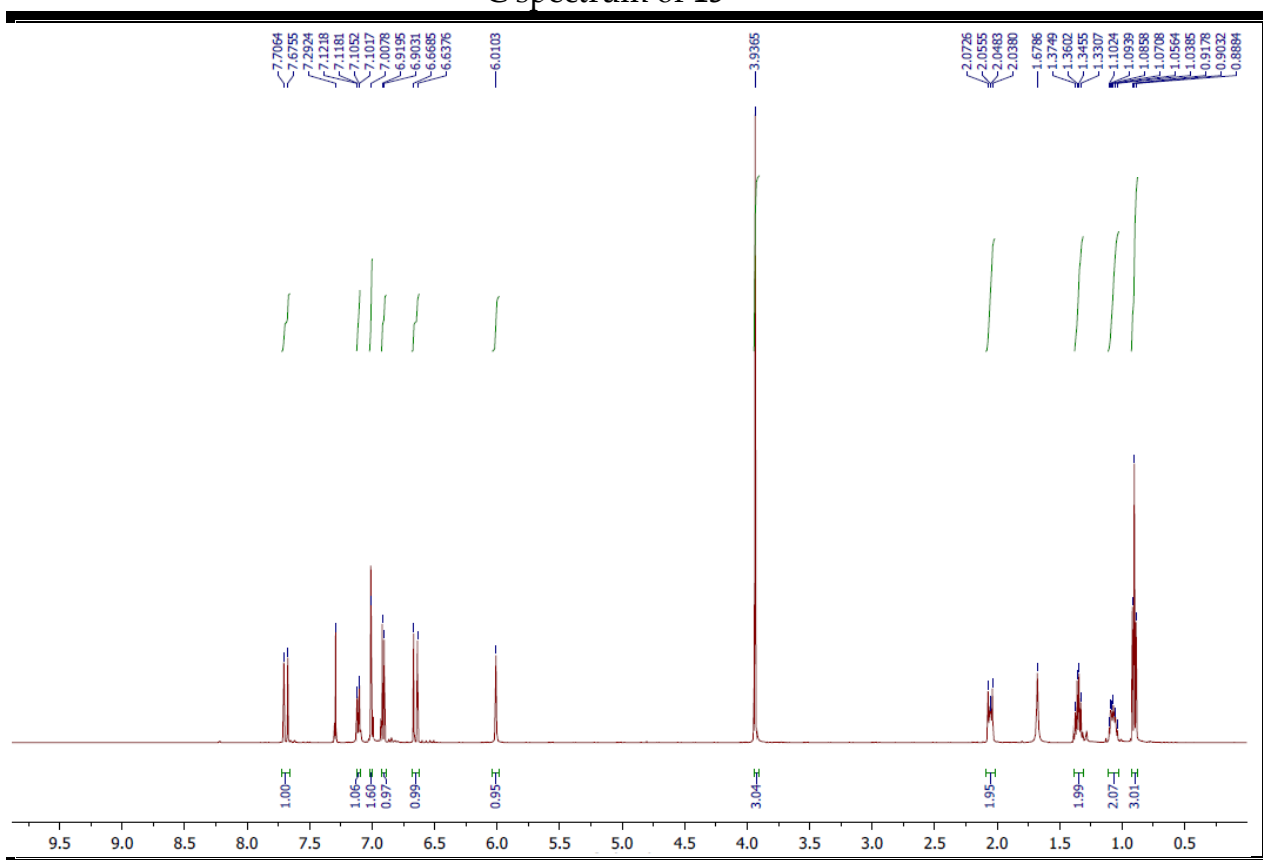
^{1}H spectrum of **16**
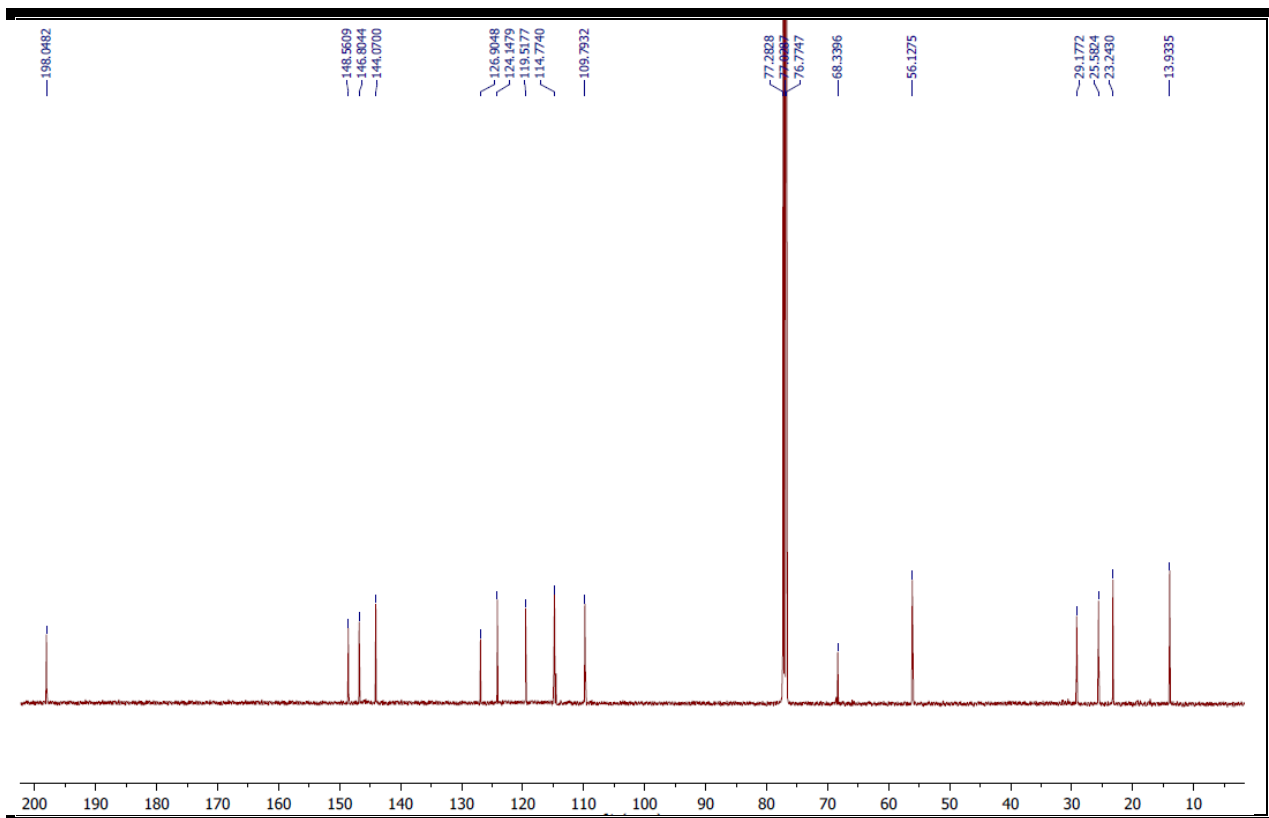
¹³C spectrum of **16**
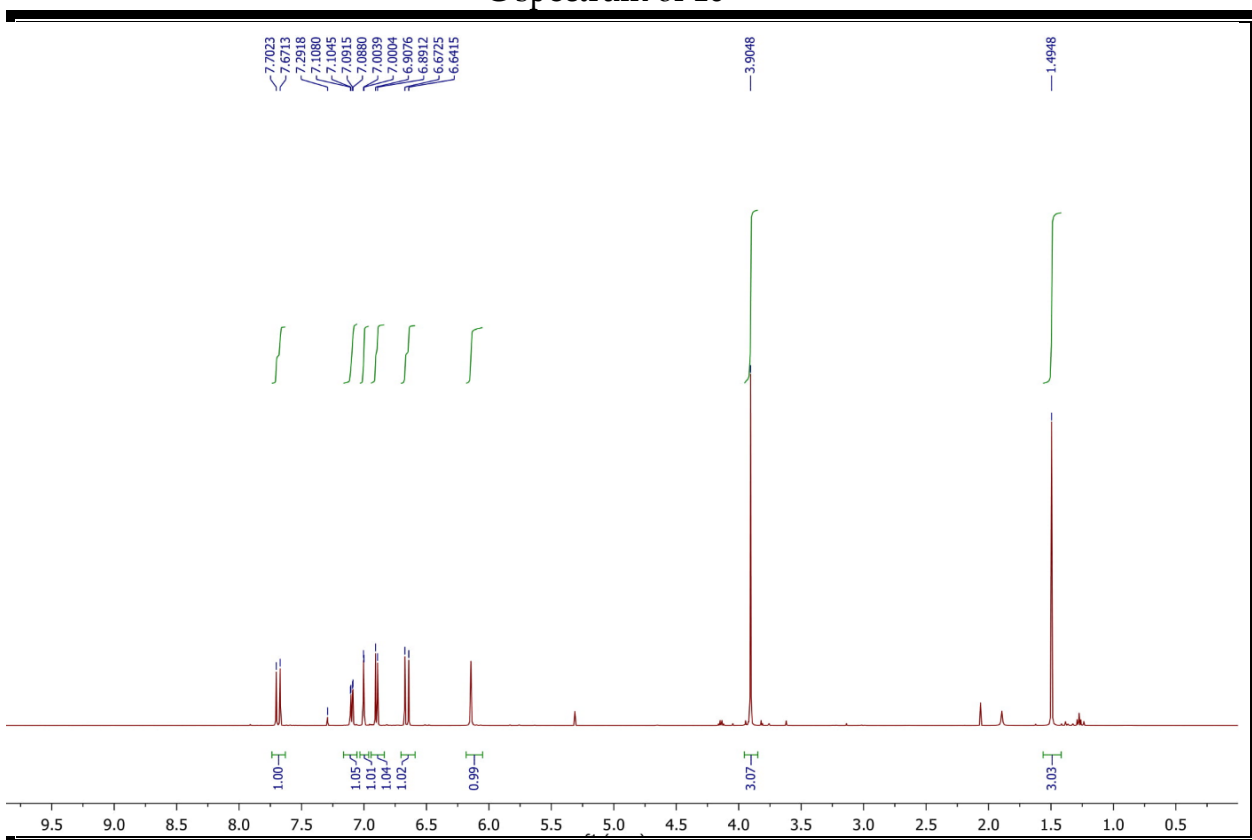
¹H spectrum of **2m**
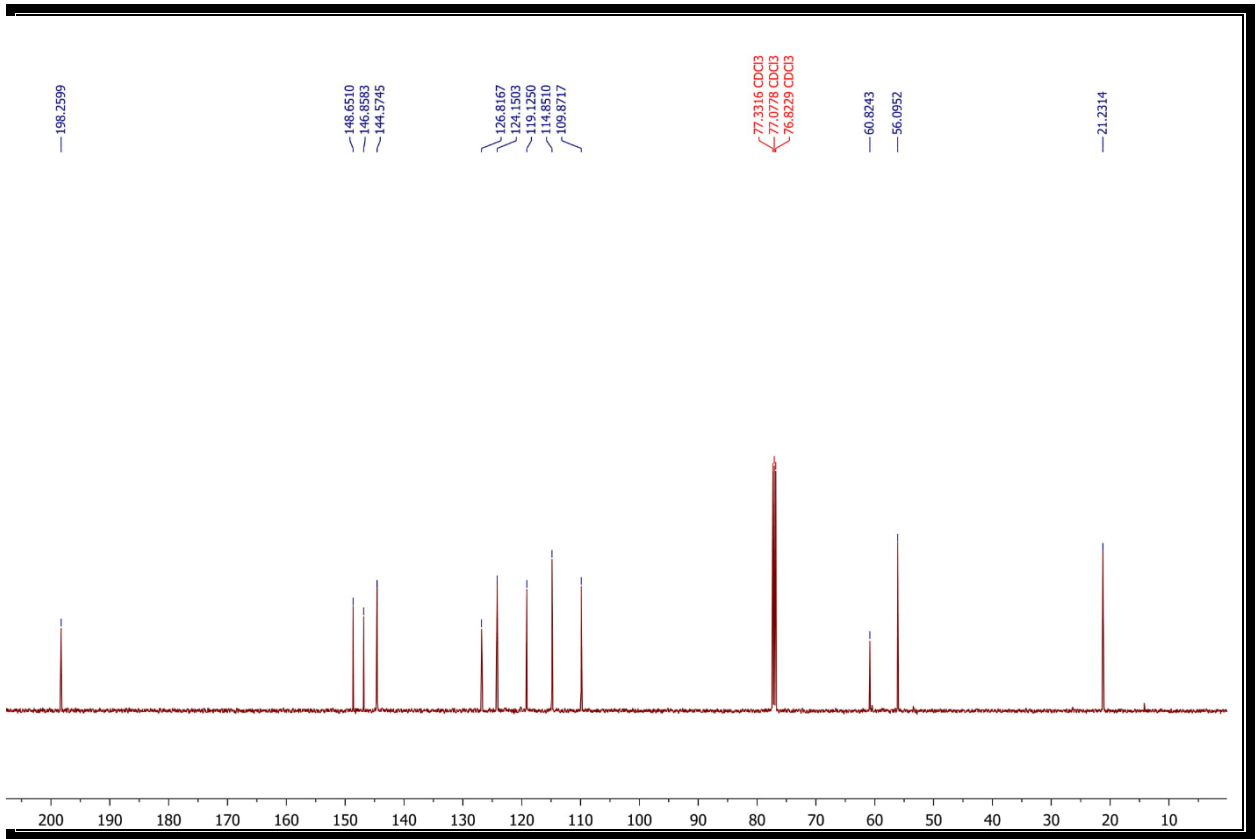
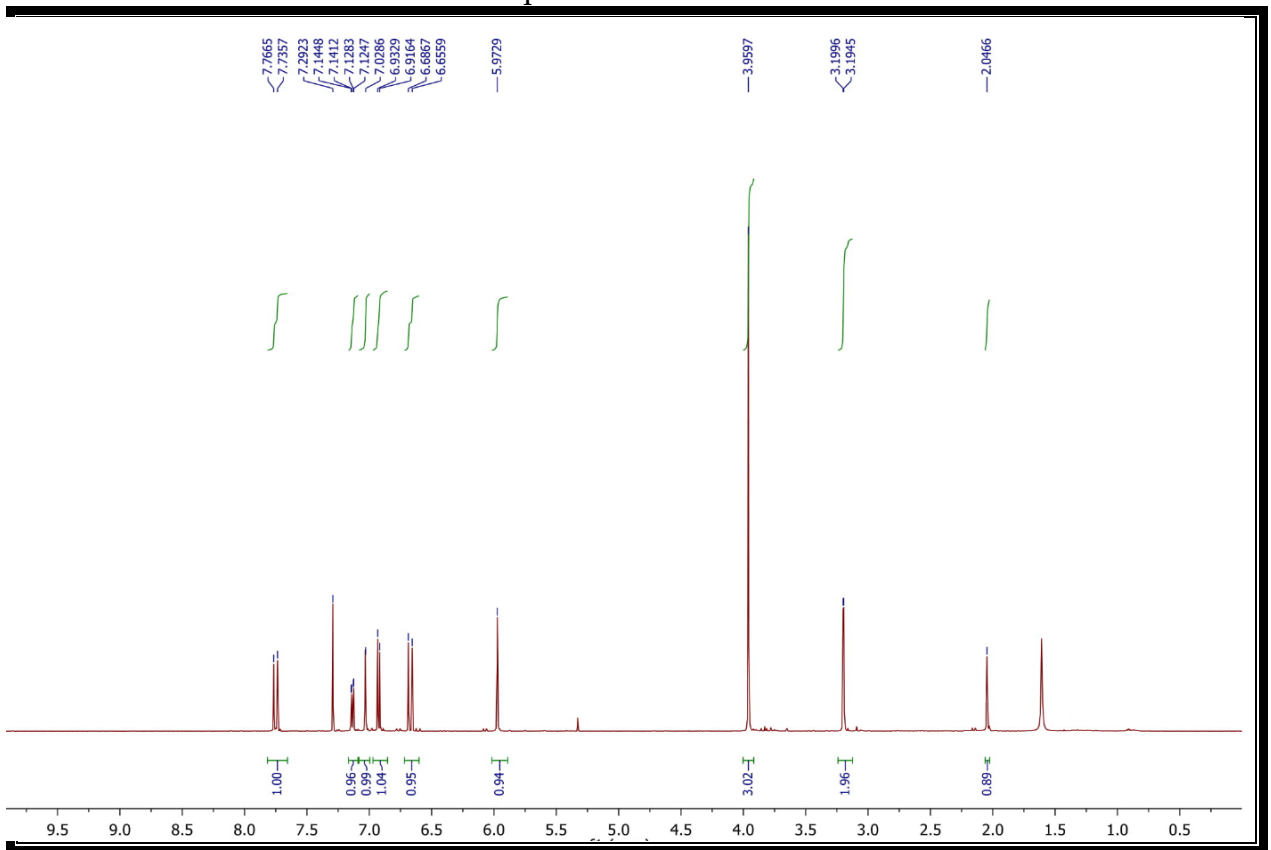^{13}C spectrum of **2m**
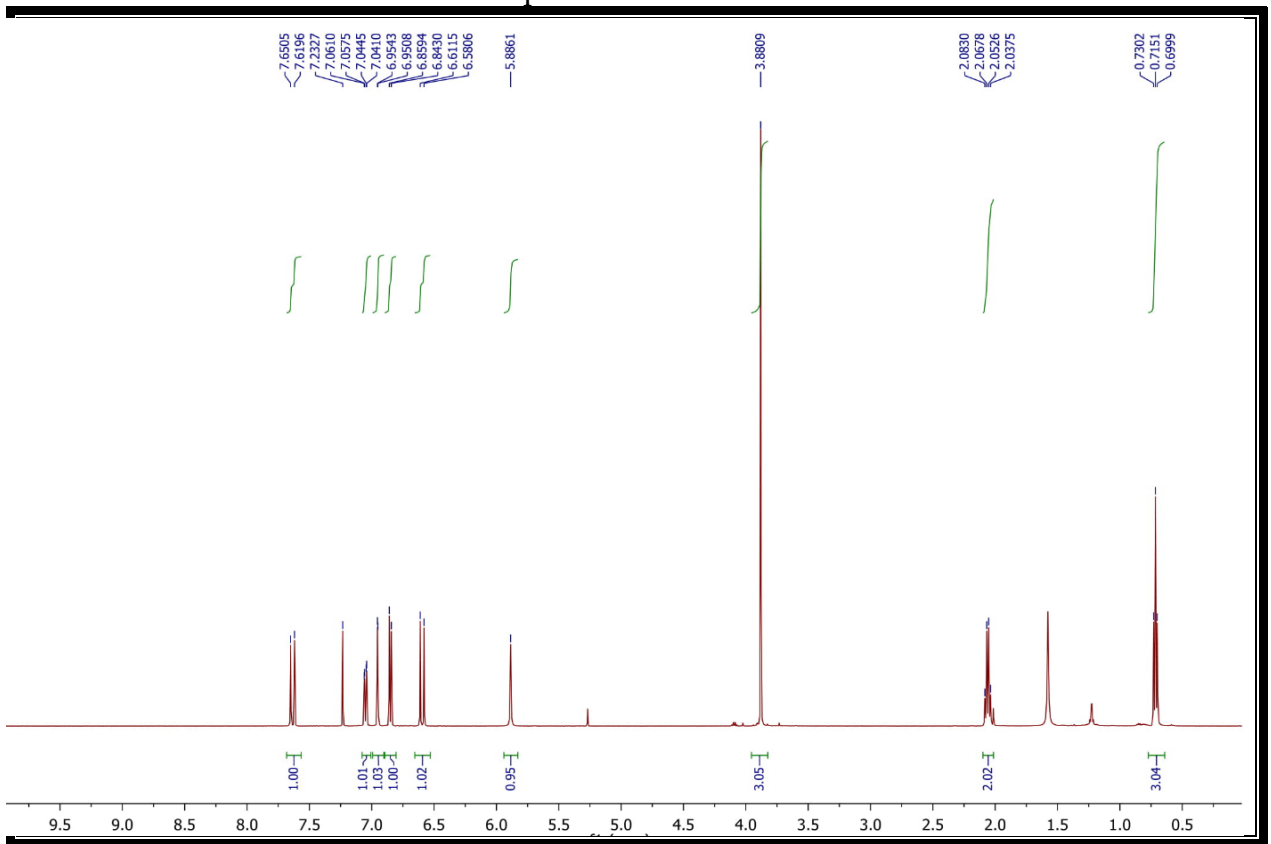
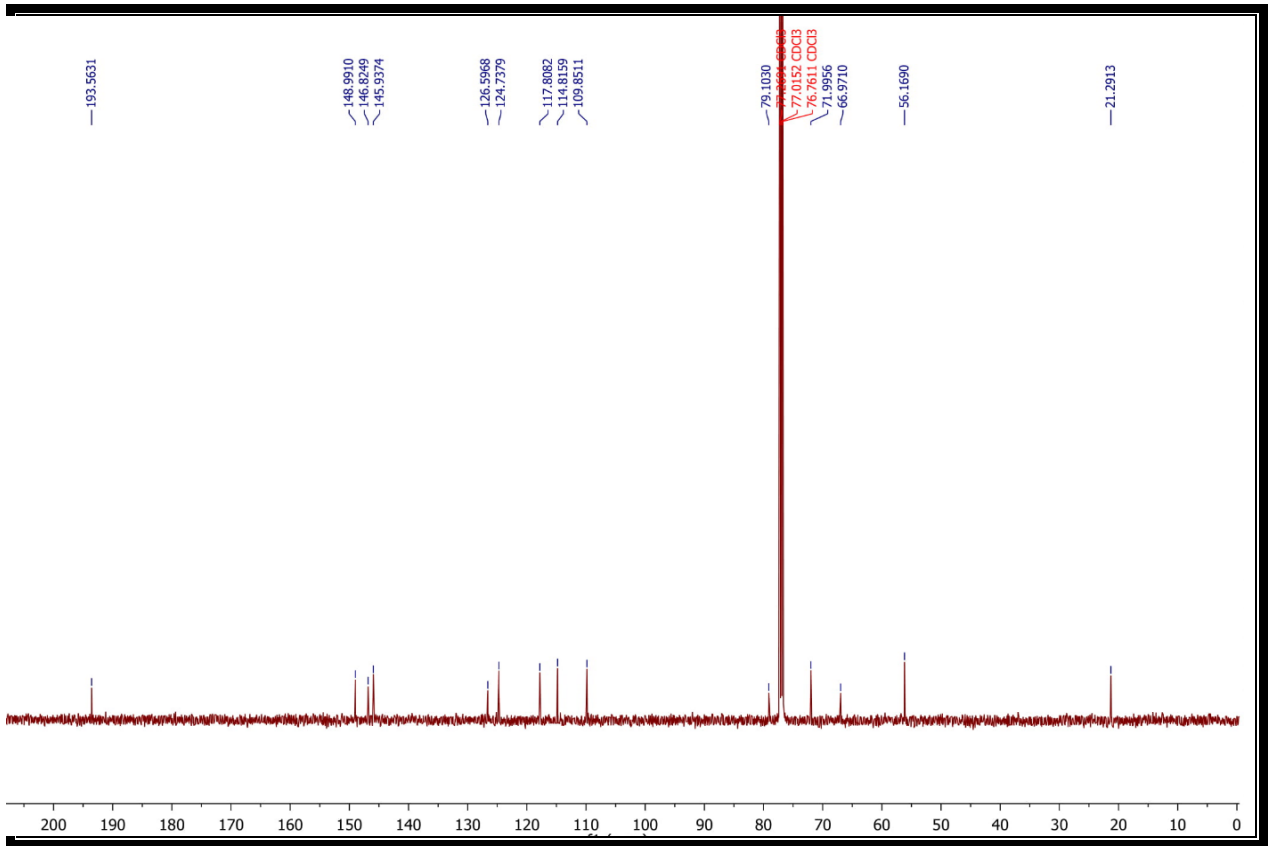^{1}H spectrum of **3m**
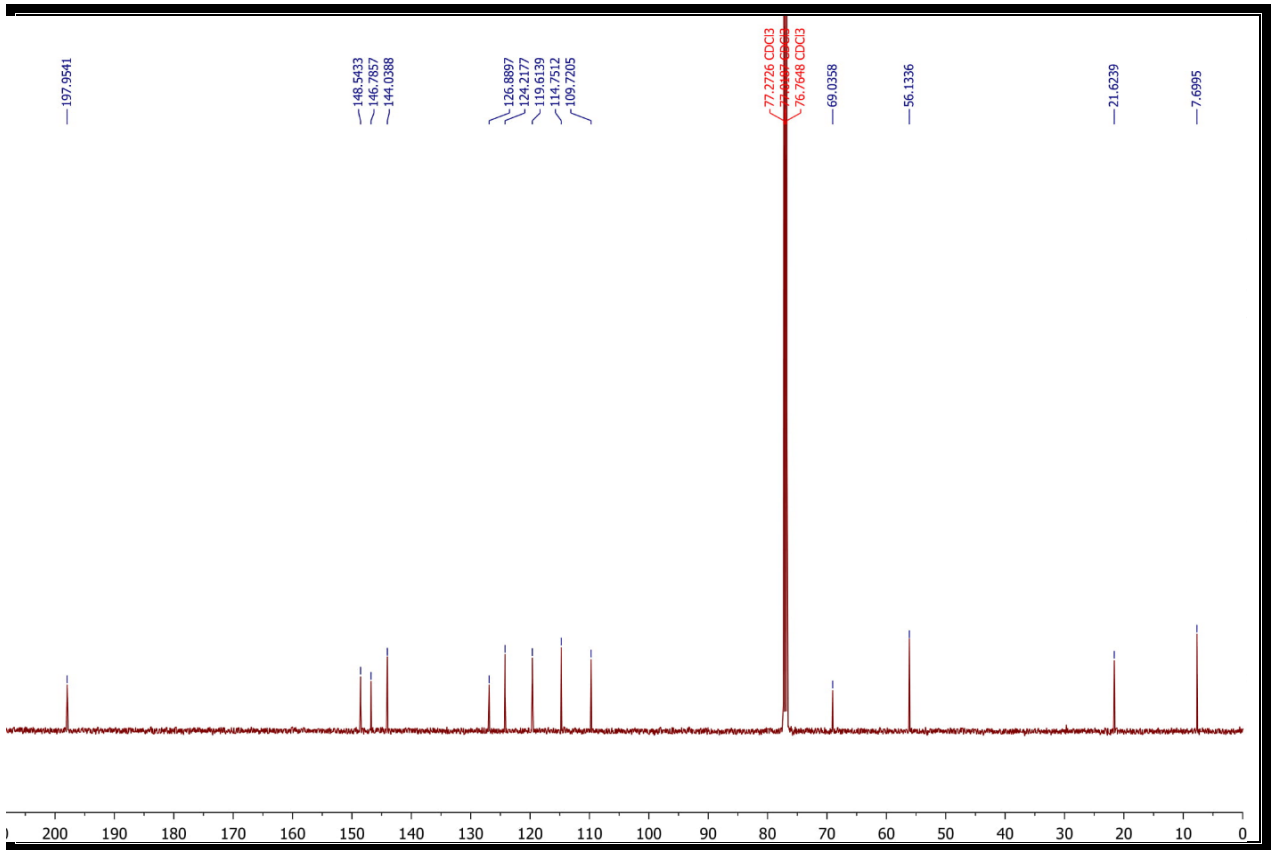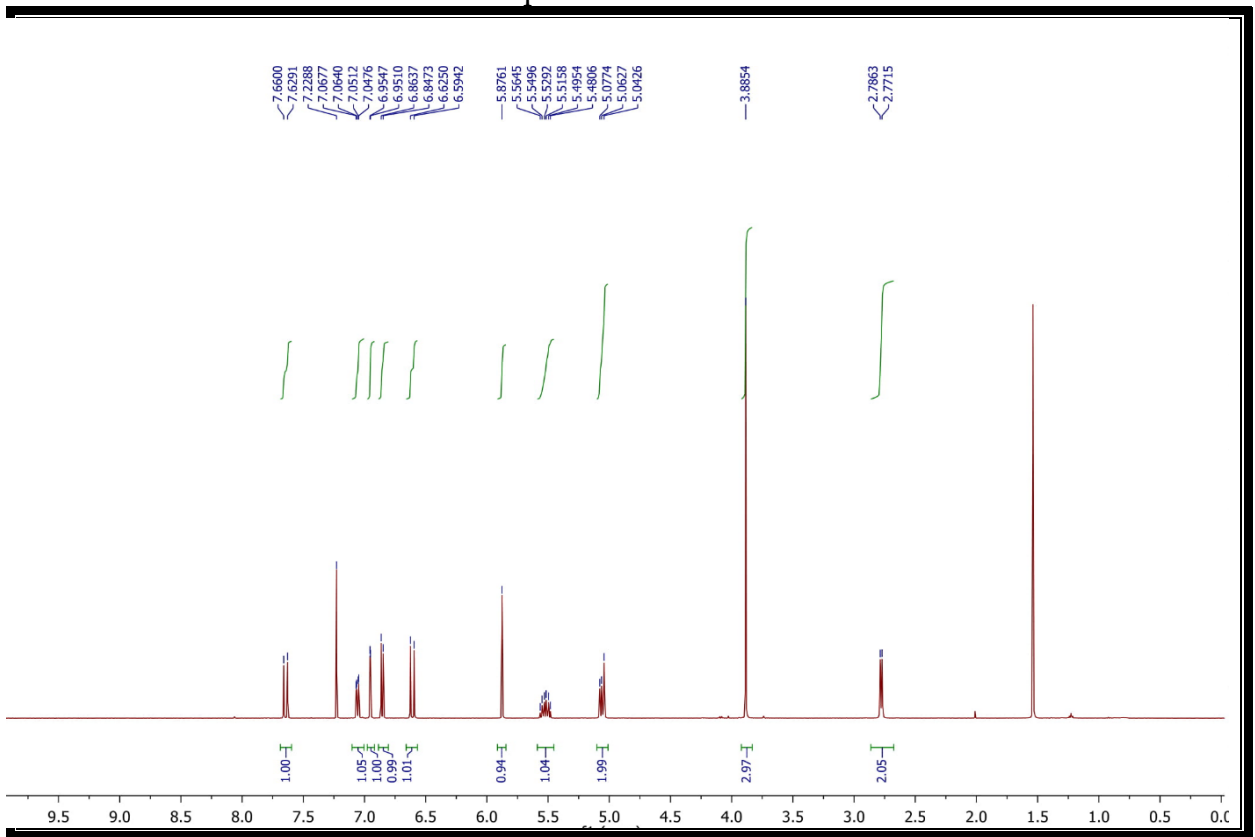
^{13}C spectrum of **3m**
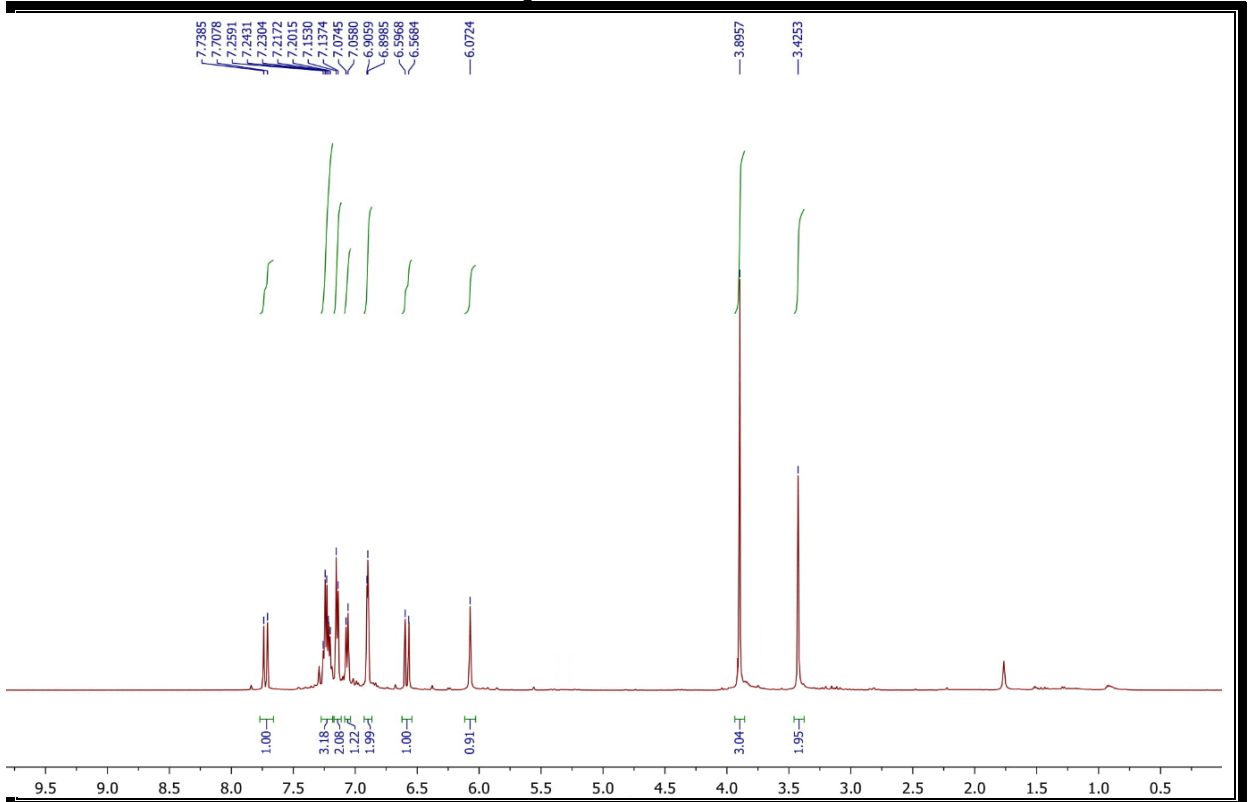
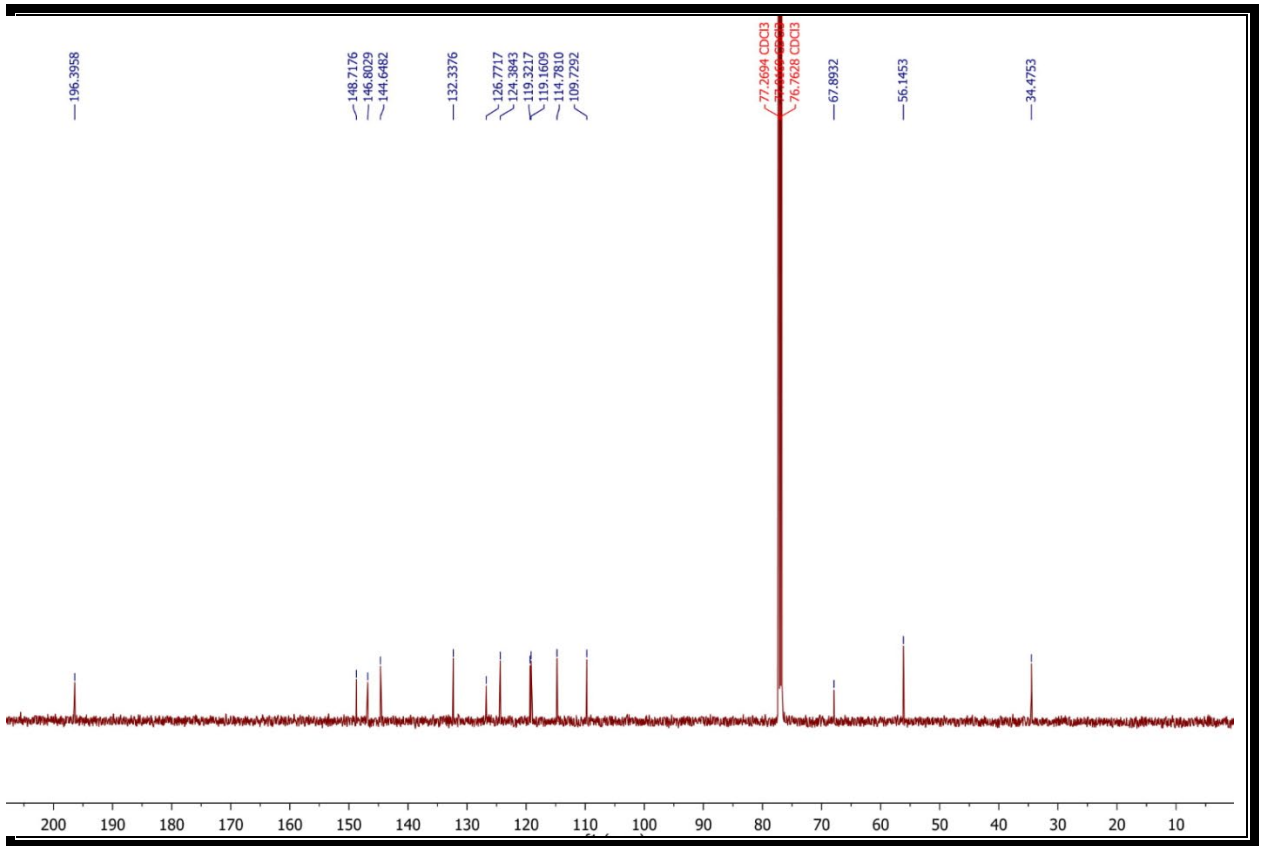^{1}H spectrum of **4m**
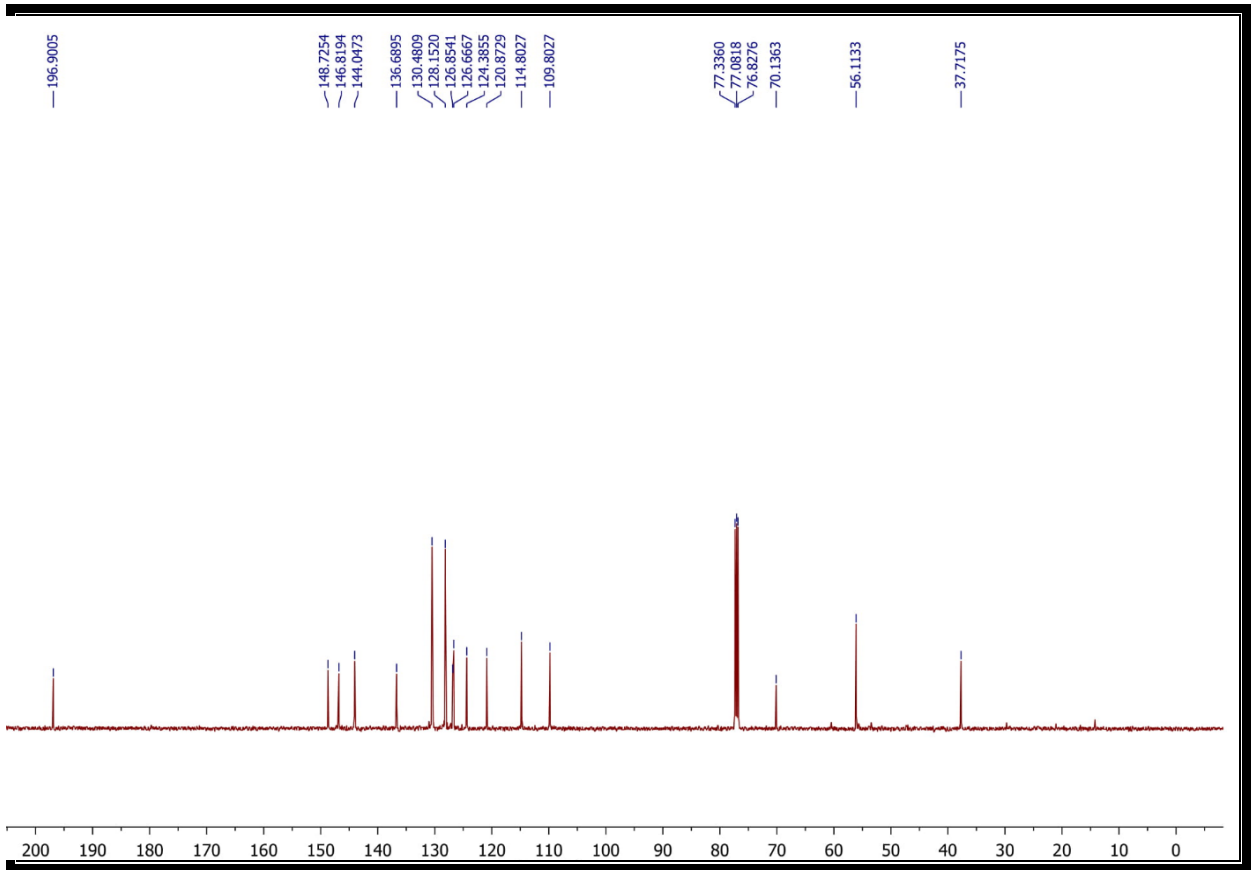
^{13}C spectrum of **4m**

^{1}H spectrum of **5m**

^{13}C spectrum of **5m**

^{1}H spectrum of **6m**

^{13}C spectrum of **6m**
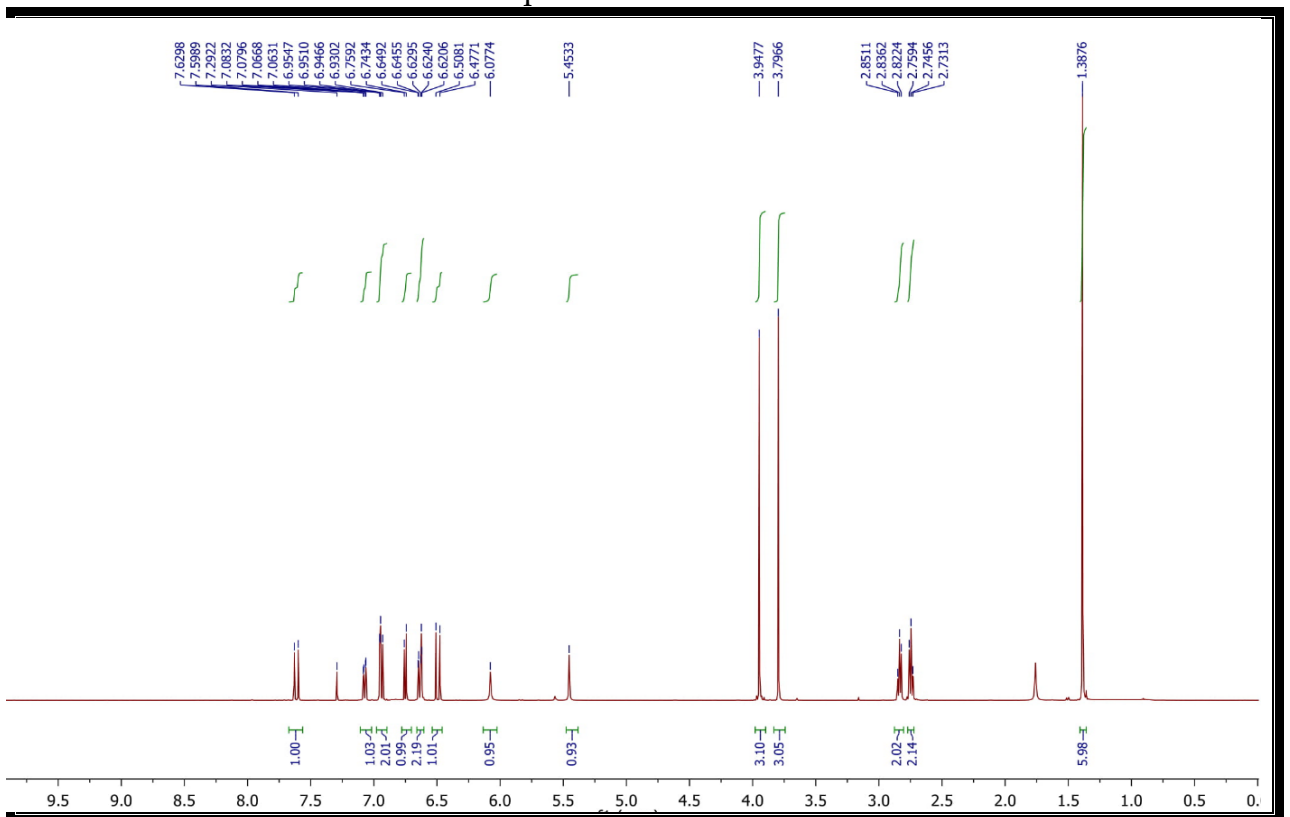
^{1}H spectrum of **18**
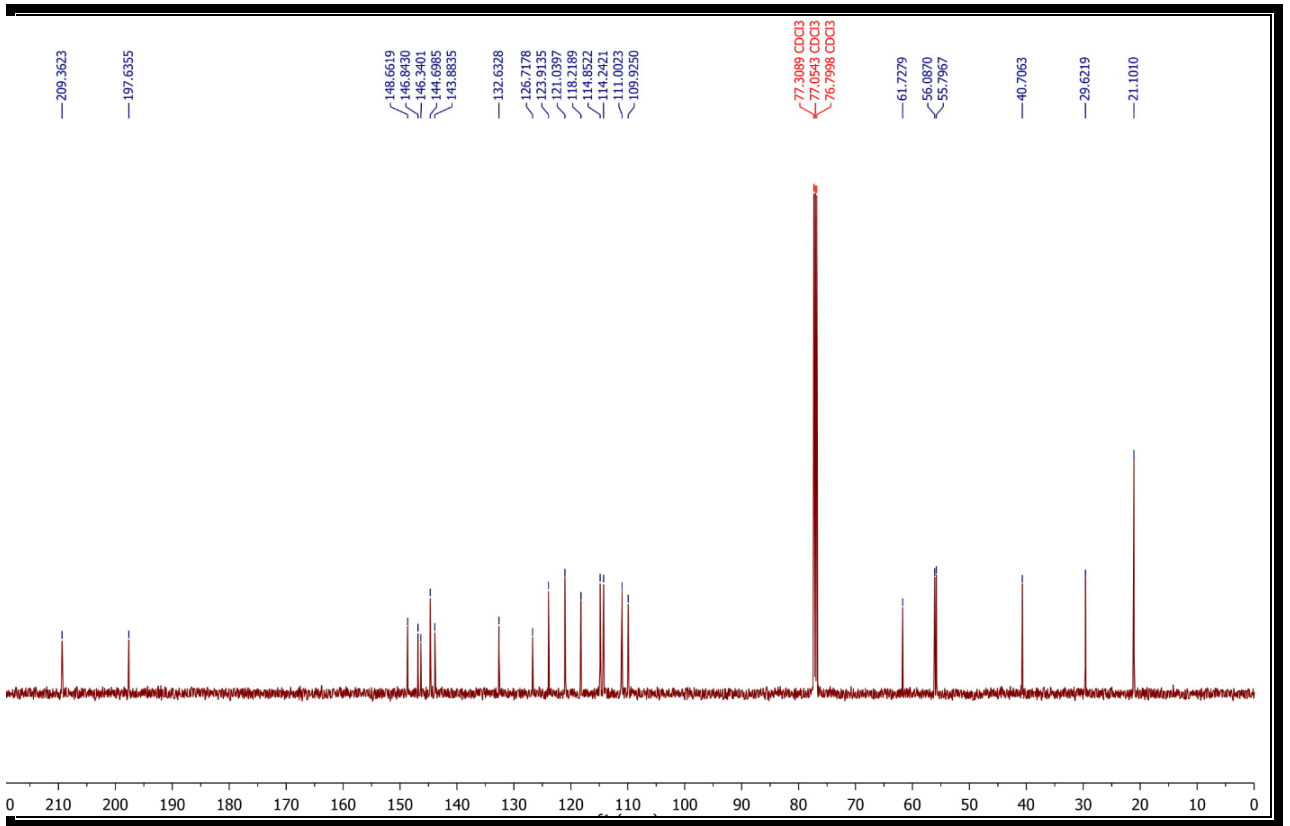
^{13}C spectrum of **18**
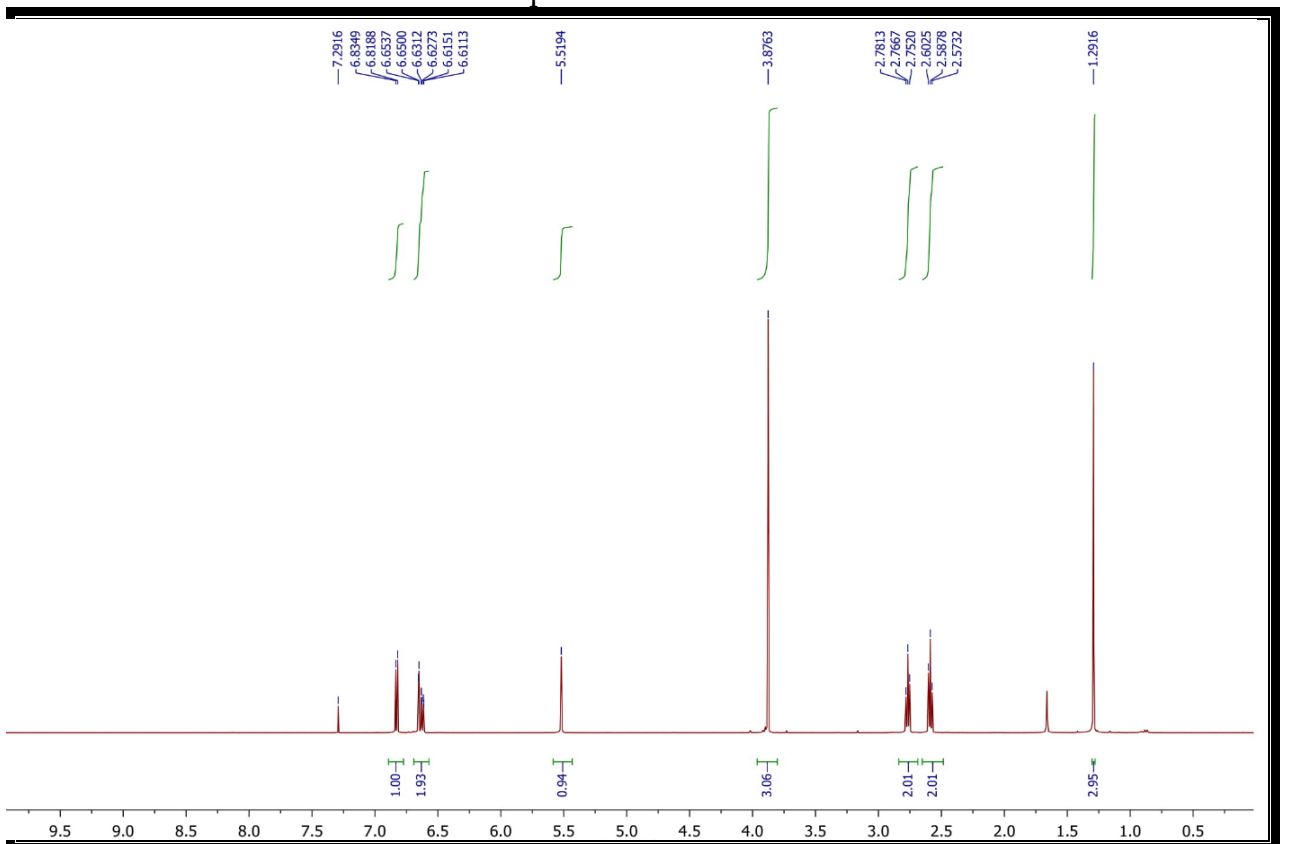
^{1}H spectrum of **19**
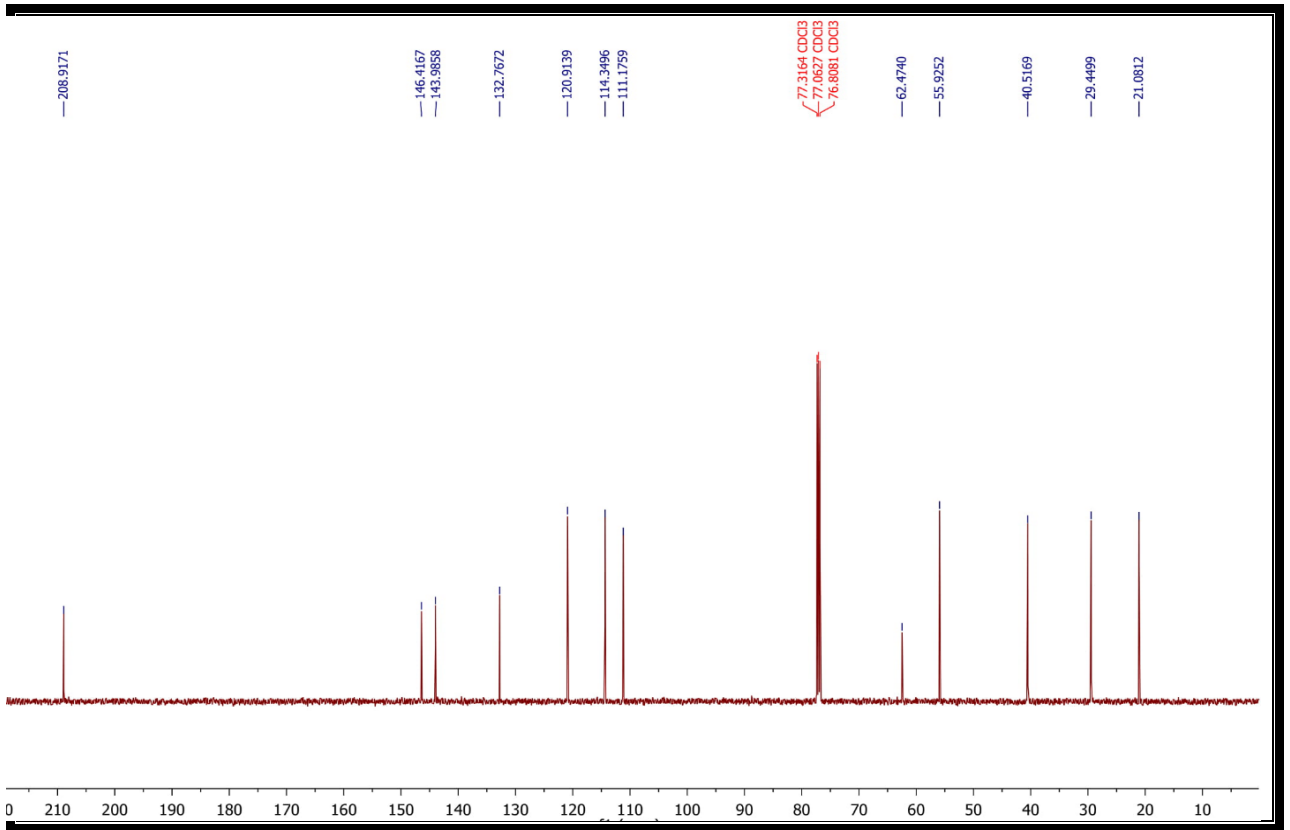
^{13}C spectrum of **19**
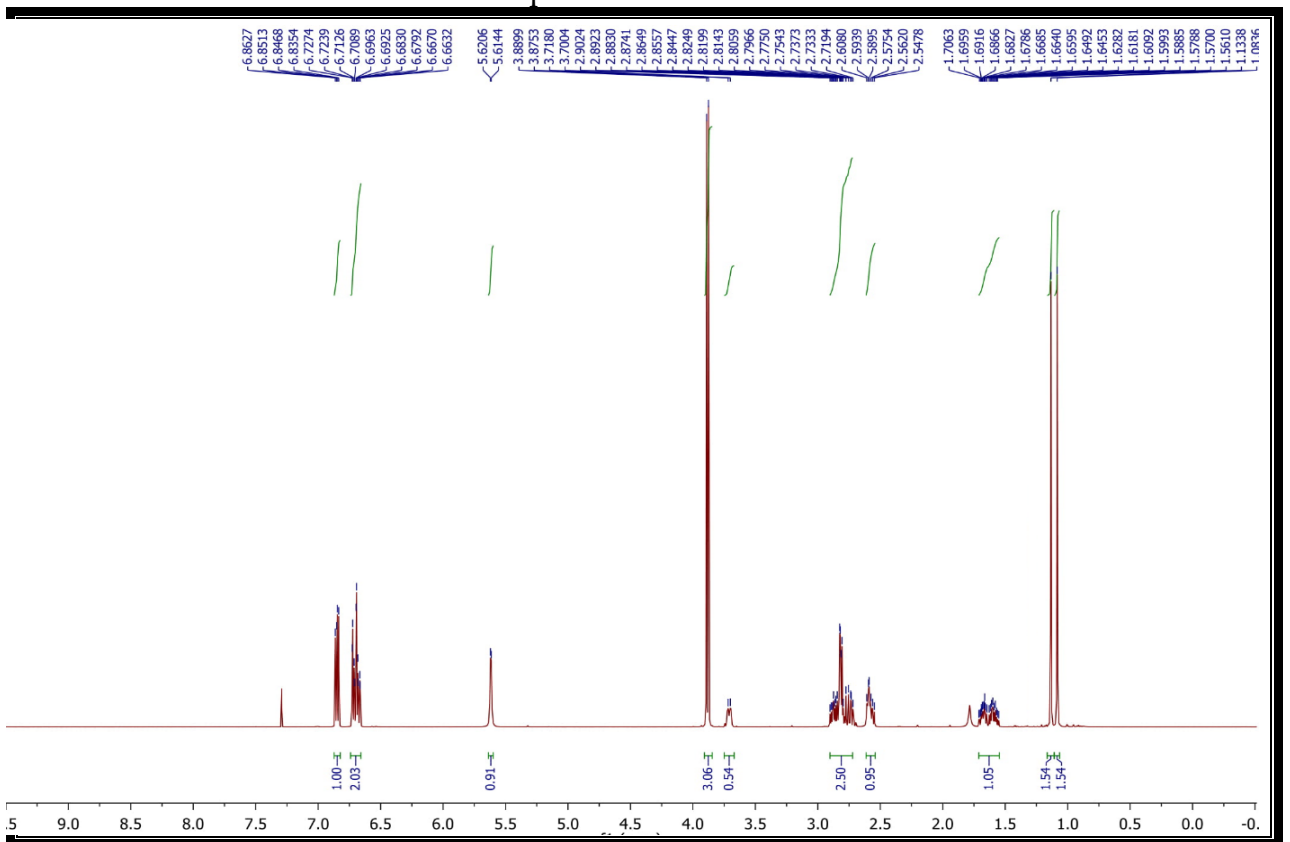
^{1}H spectrum of **20**
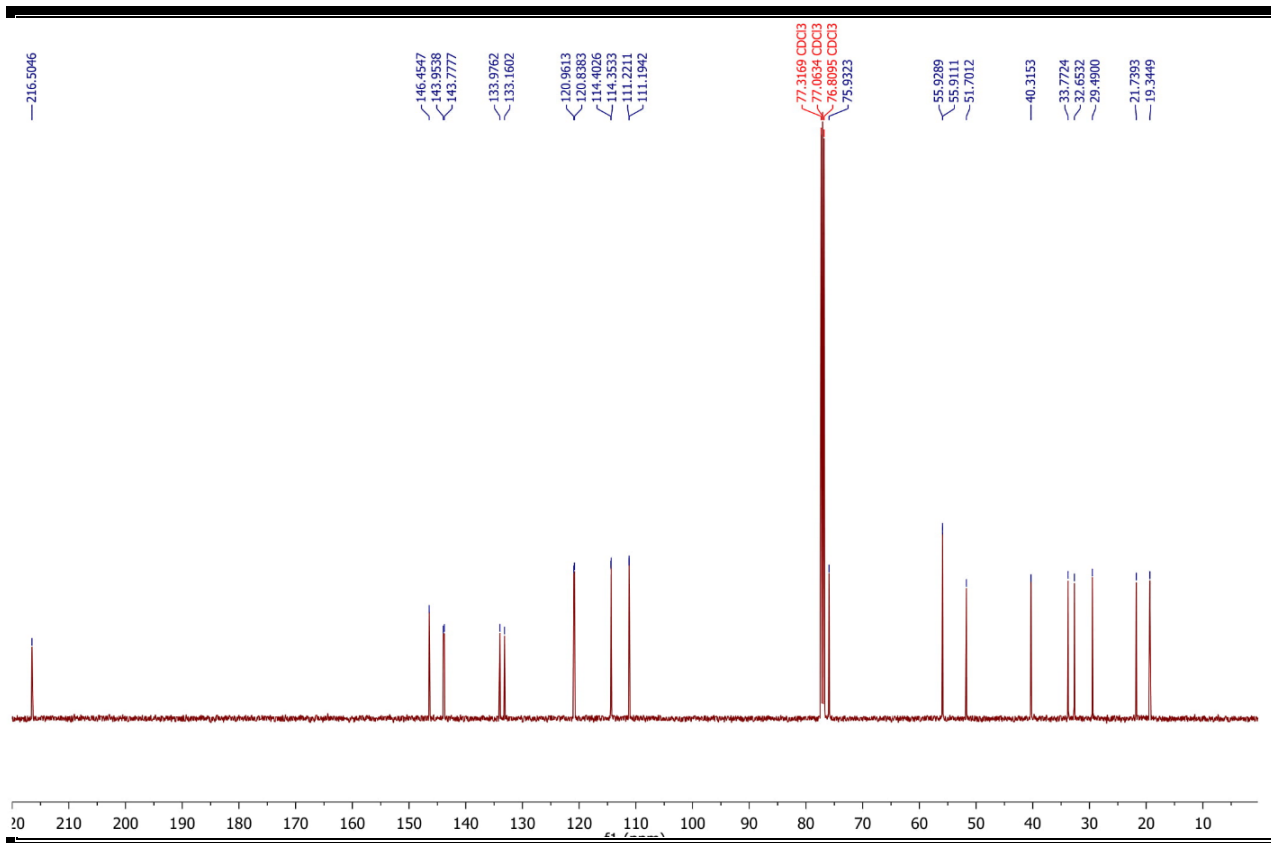
^{13}C spectrum of **20**
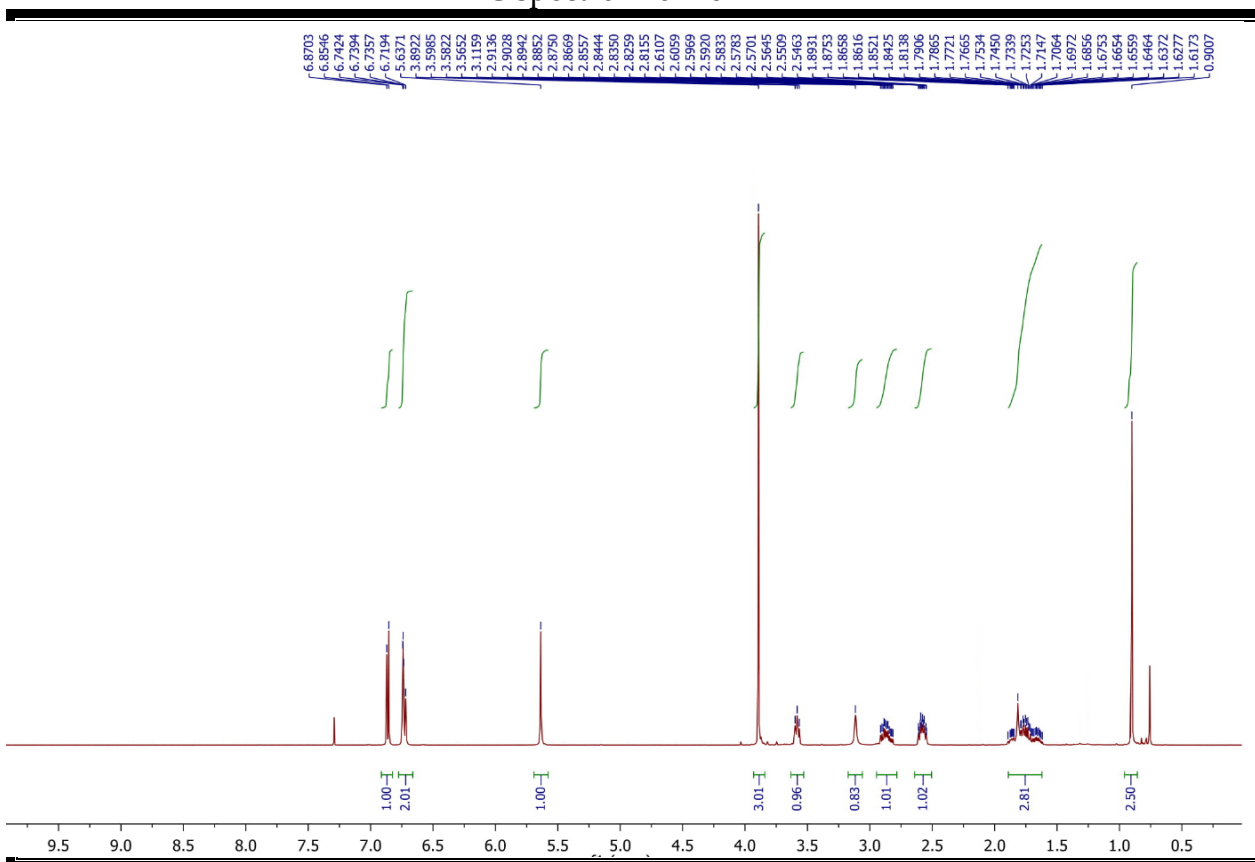
^{1}H spectrum of **21**

^{13}C spectrum of **21**