Electronic Supporting Information

Deep eutectic solvent for an expeditious sono-synthesis of novel series of bis-quinazolin-4-one derivatives as potential anticancer agents

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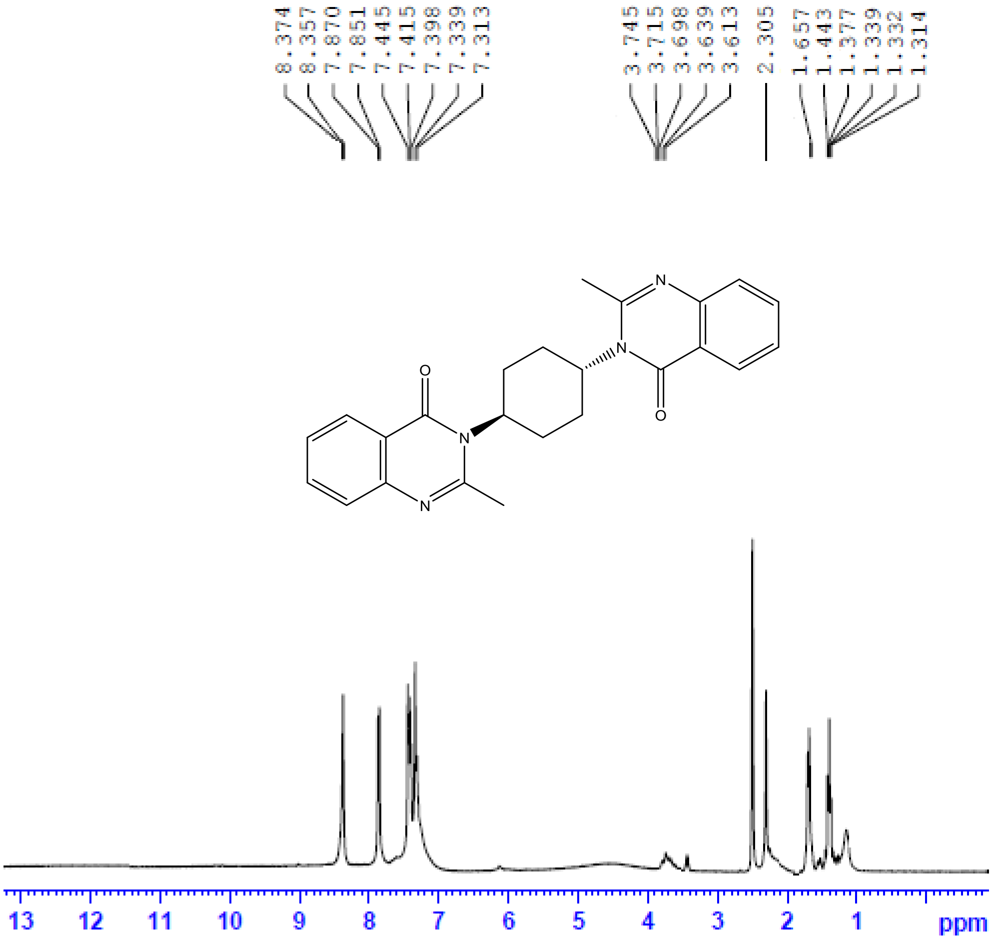
Synthesis of 1a-e

For the synthesis of derivatives **1a-e**, a mixture of anthranilic acid derivatives (1 mmol) and acetic anhydride (≈ 10 mL, 10 mmol) was sonicated at 40 °C for 10 min. The excess of acetic anhydride was distilled off under vacuum and the residue was dissolved in DCM. The obtained crystals filtered, dried and used for the next steps.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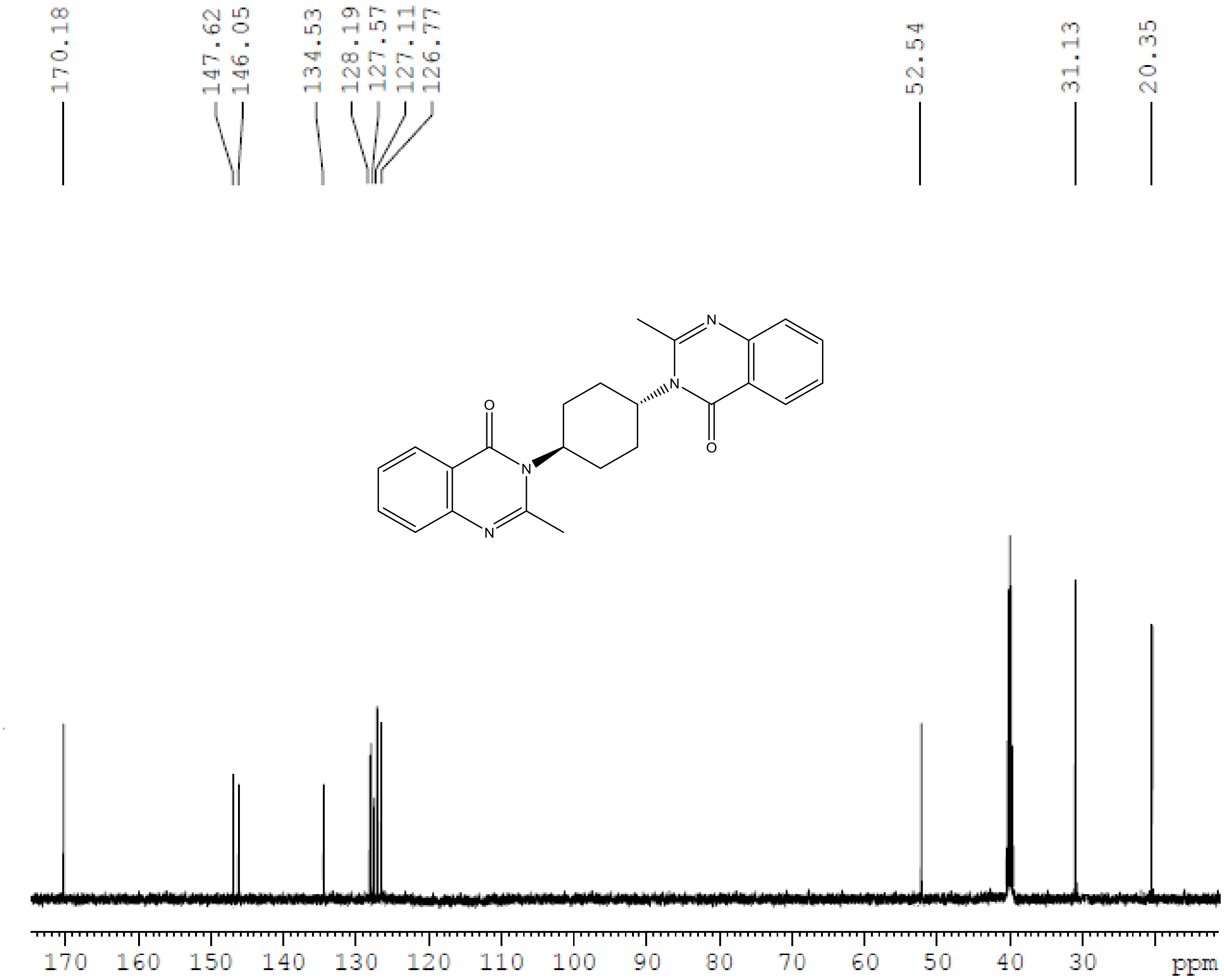
3.639
3.613
2.305
1.657
1.443
1.377
1.339
1.332
1.314
O
N
N
N
O
N
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

^{1}H NMR of **3a**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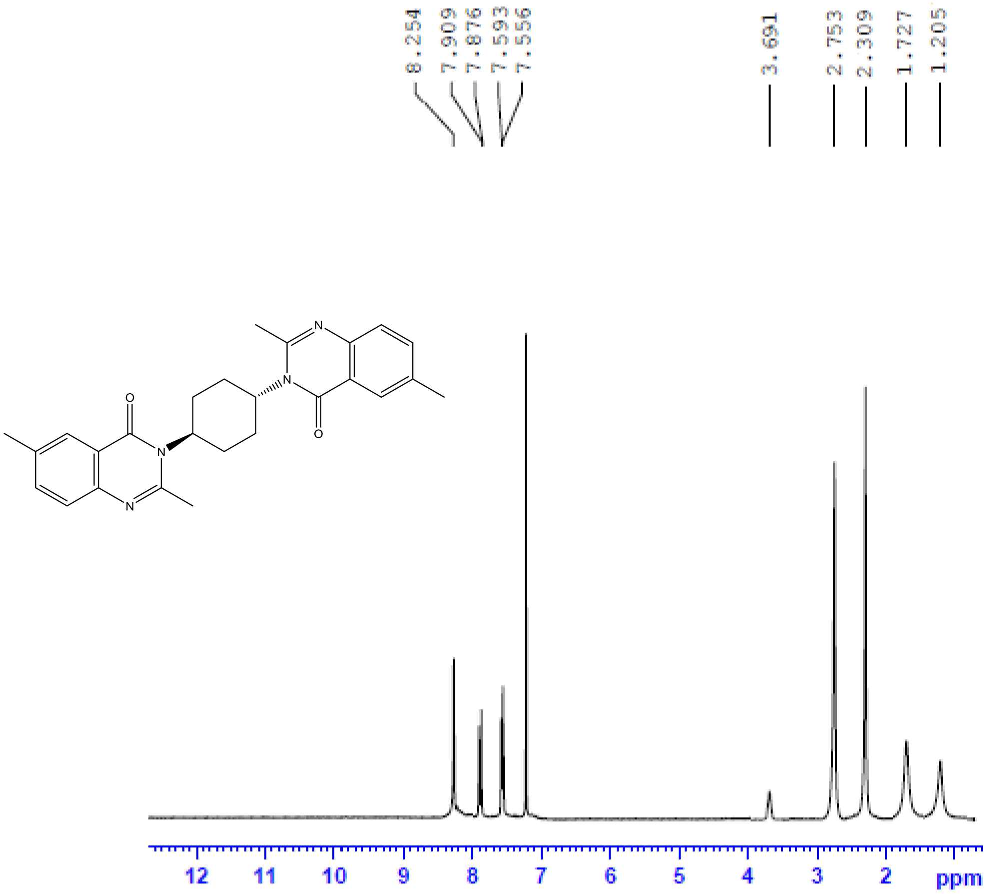
147.62
146.05
134.53
128.19
127.57
127.11
126.77
52.54
31.13
20.35
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

^{13}C NMR of **3a**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2.309
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1.205
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10
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4
3
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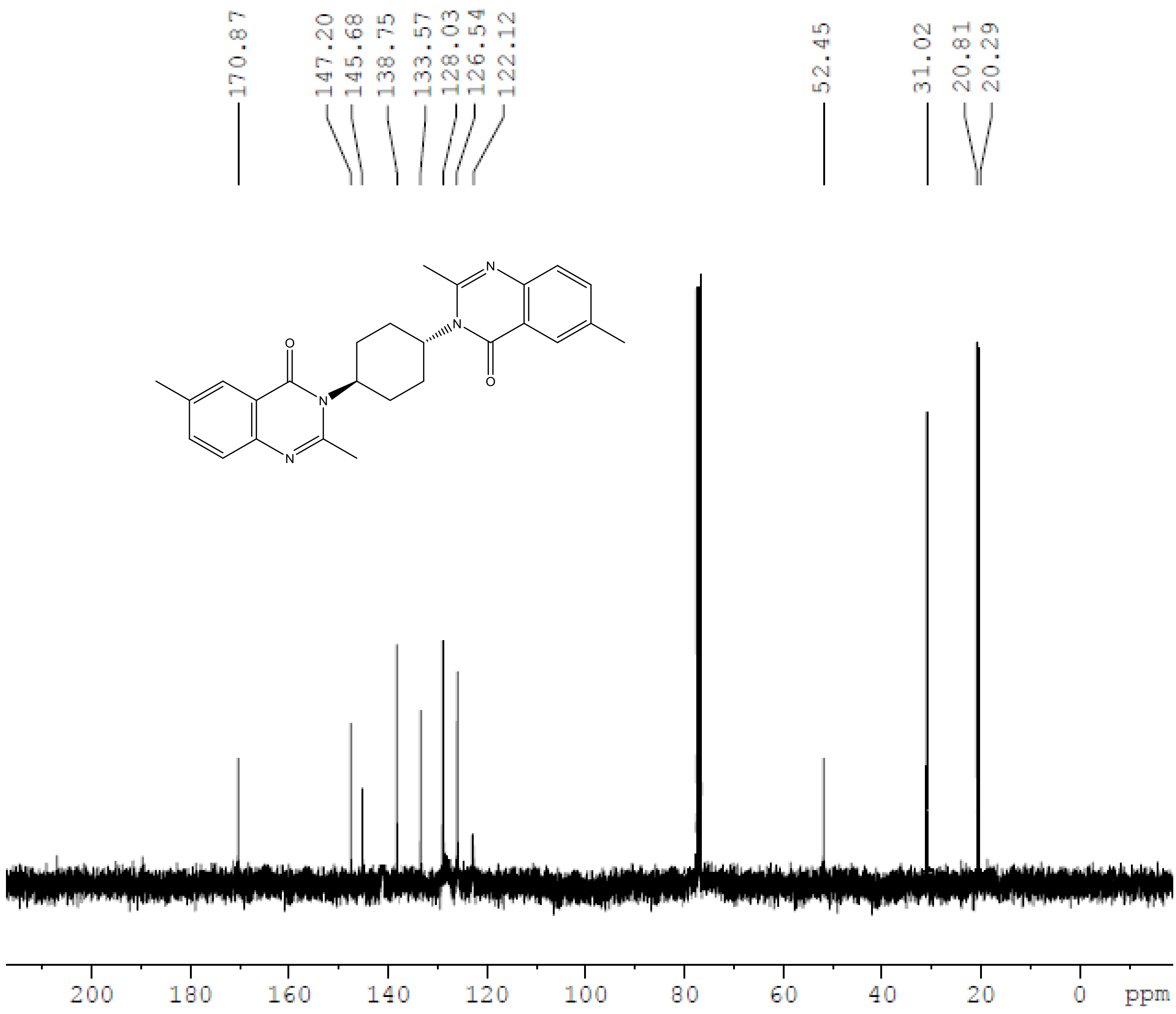
ppm

[1]H NMR of **3b**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20.81
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40
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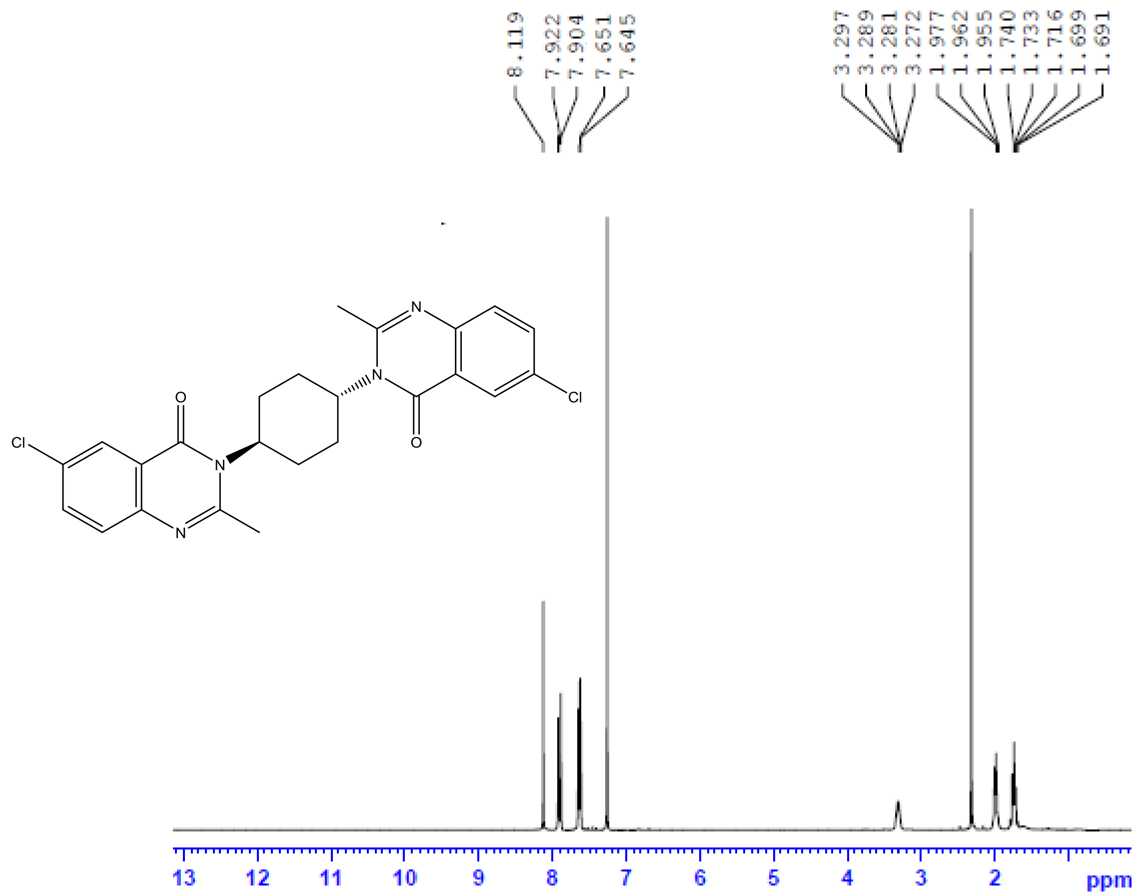
^{13}C NMR of **3b**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1.740
1.733
1.716
1.699
1.691
Cl
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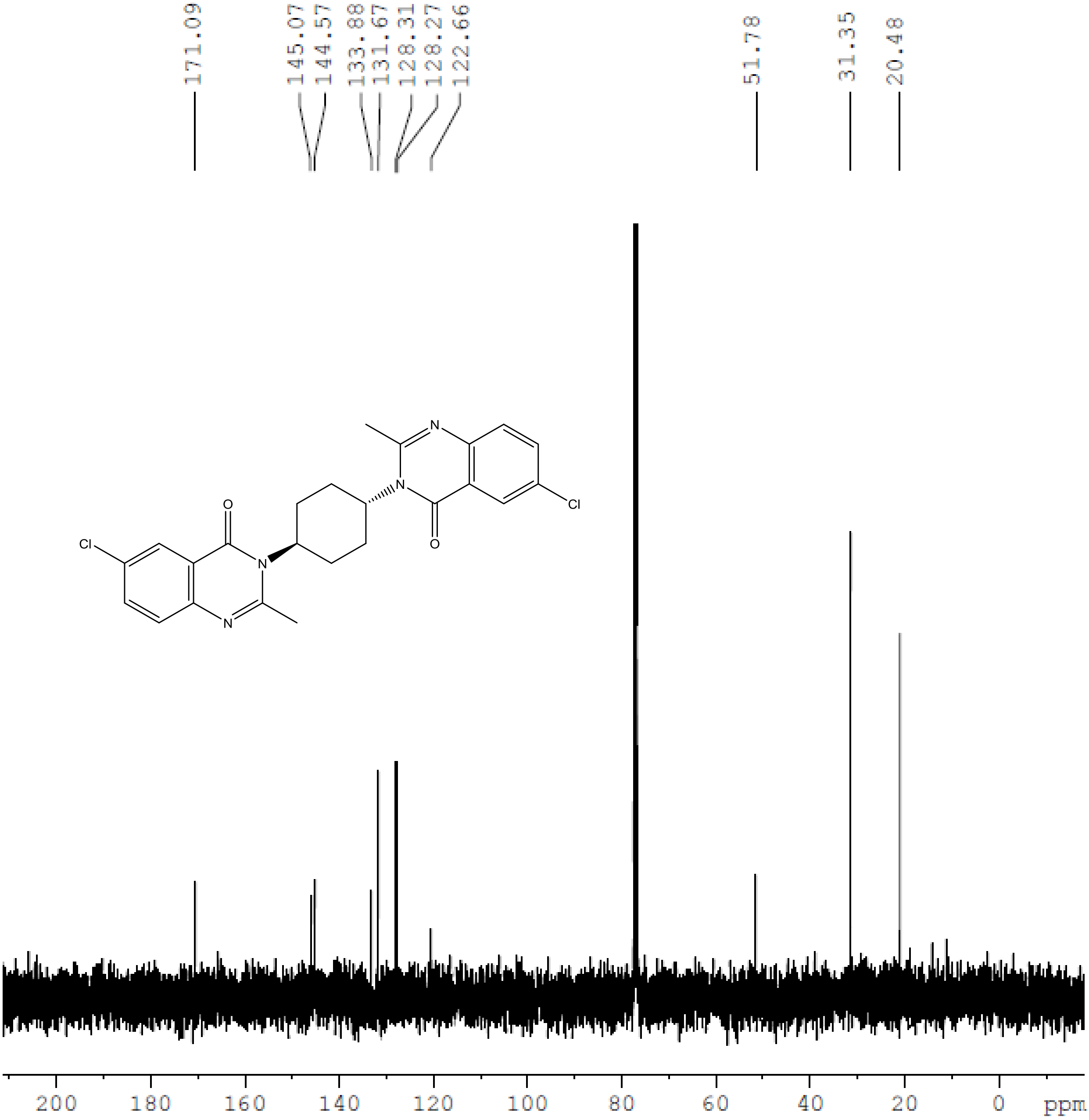
13
12
11
10
9
8
7
6
5
4
3
2
ppm

[1]H NMR of **3c**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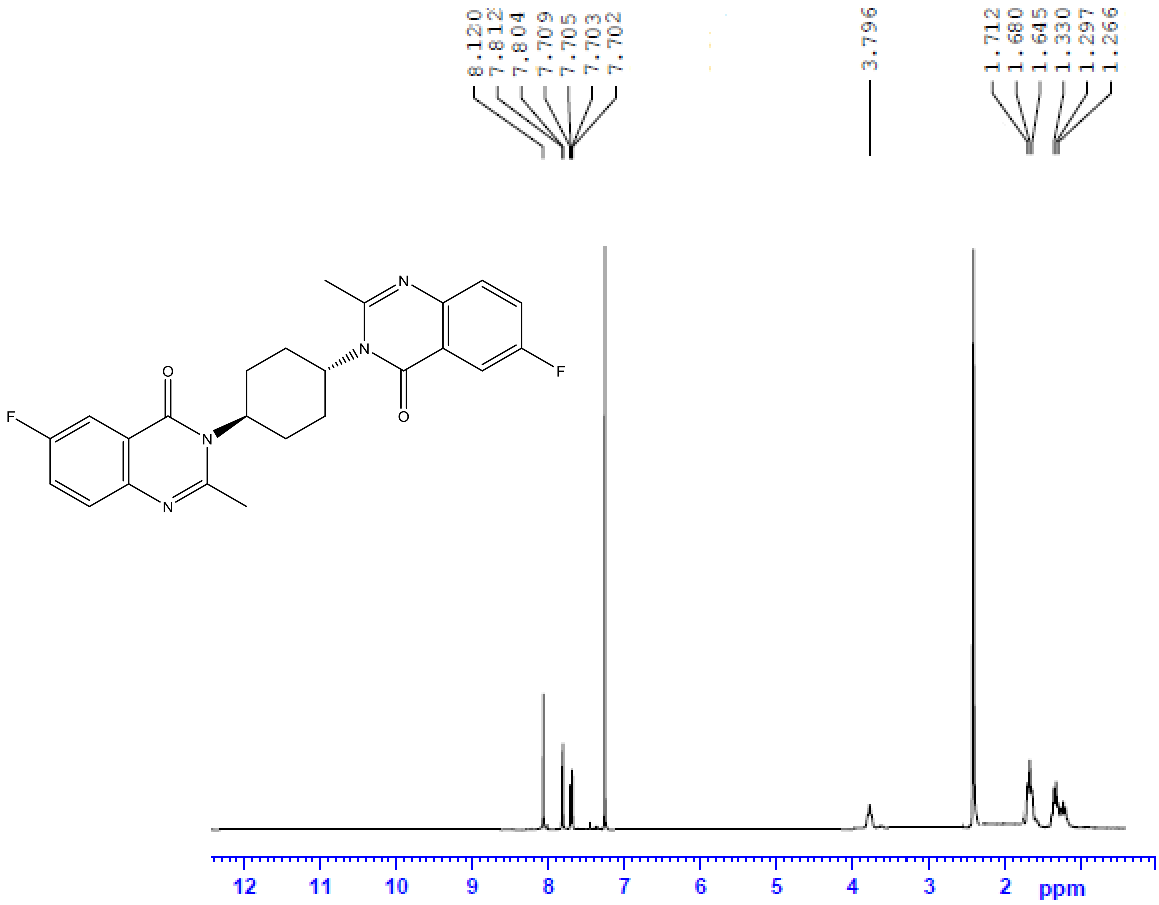
20
0
ppm

^{13}C NMR of **3c**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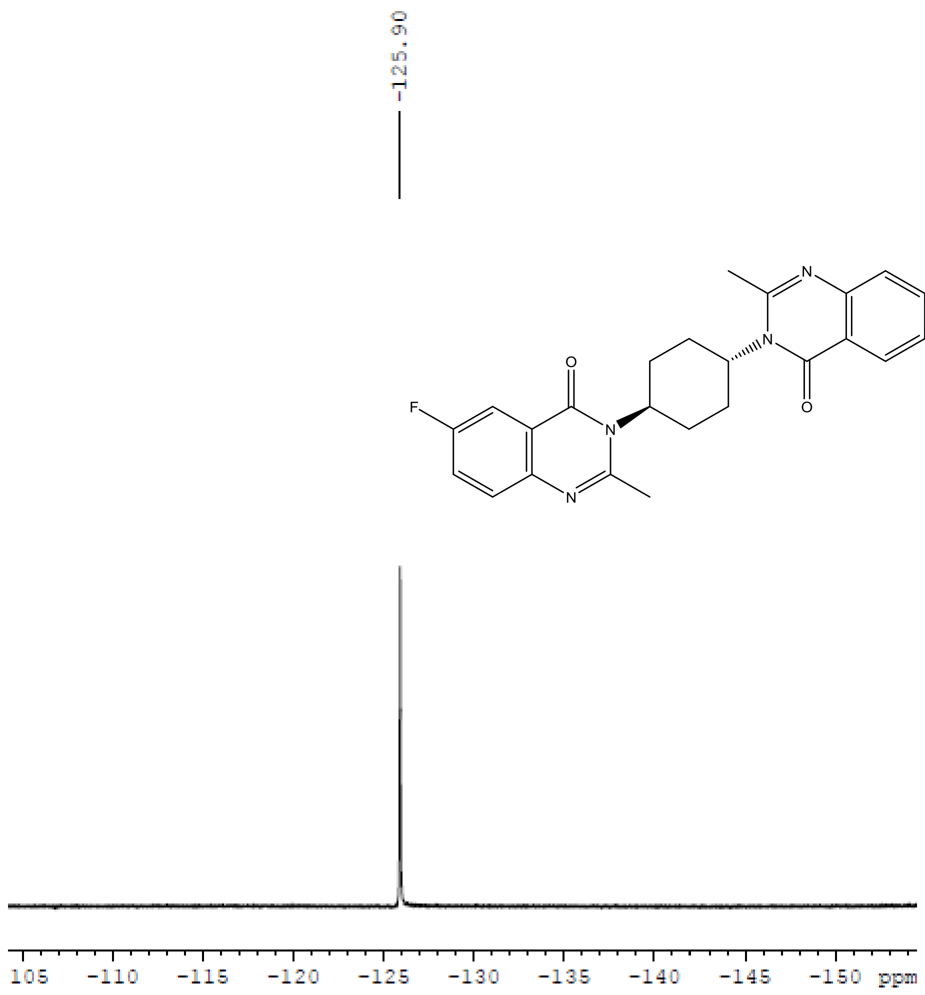
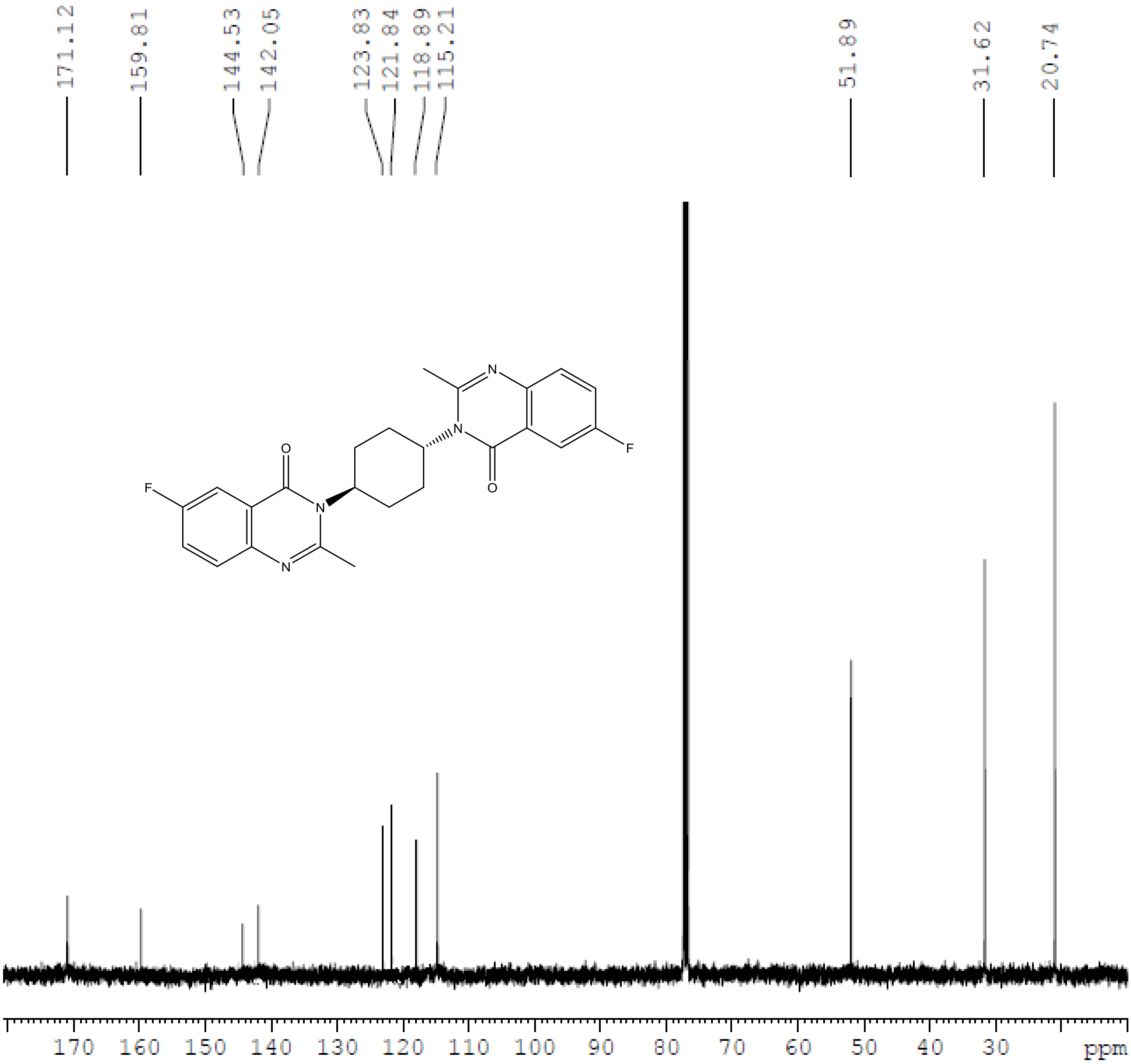
1.266
F
O
N
N
N
N
O
F
12
11
10
9
8
7
6
5
4
3
2
ppm

^{1}H NMR of **3d**



^{19}F NMR of **3d**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123.83
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118.89
115.21
51.89
31.62
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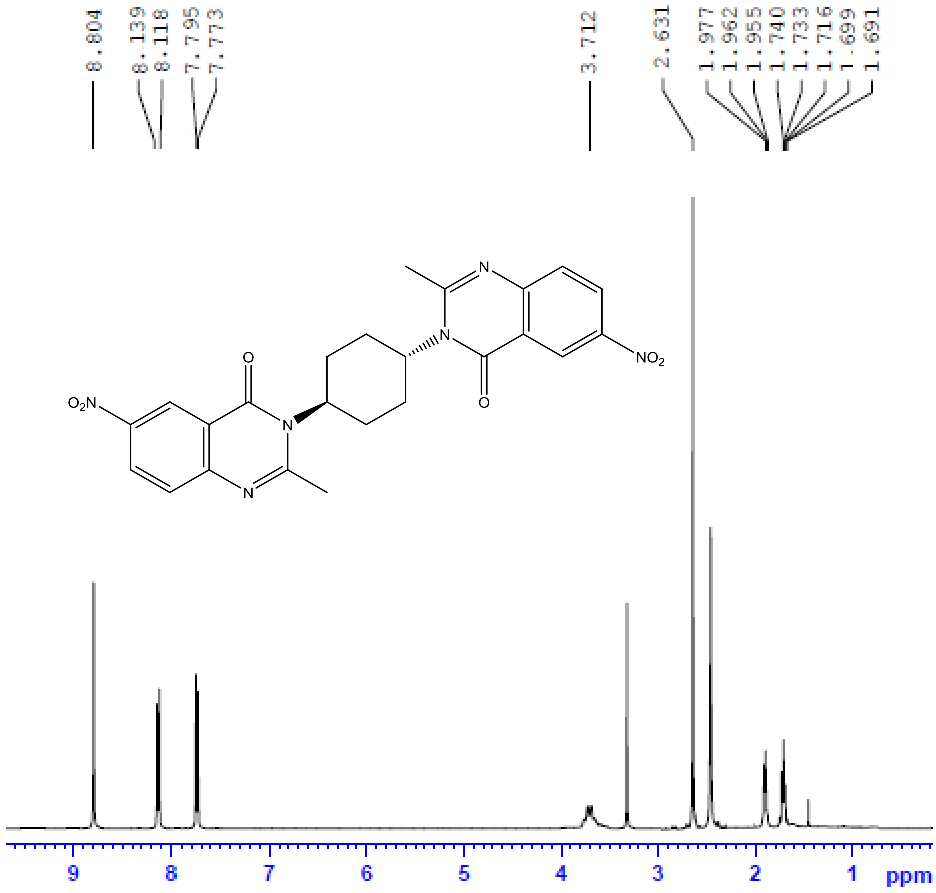
N
F
O
N
N
F
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

[12]C NMR of **3d**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O
N
O_2N
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O
NO_2
9
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7
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5
4
3
2
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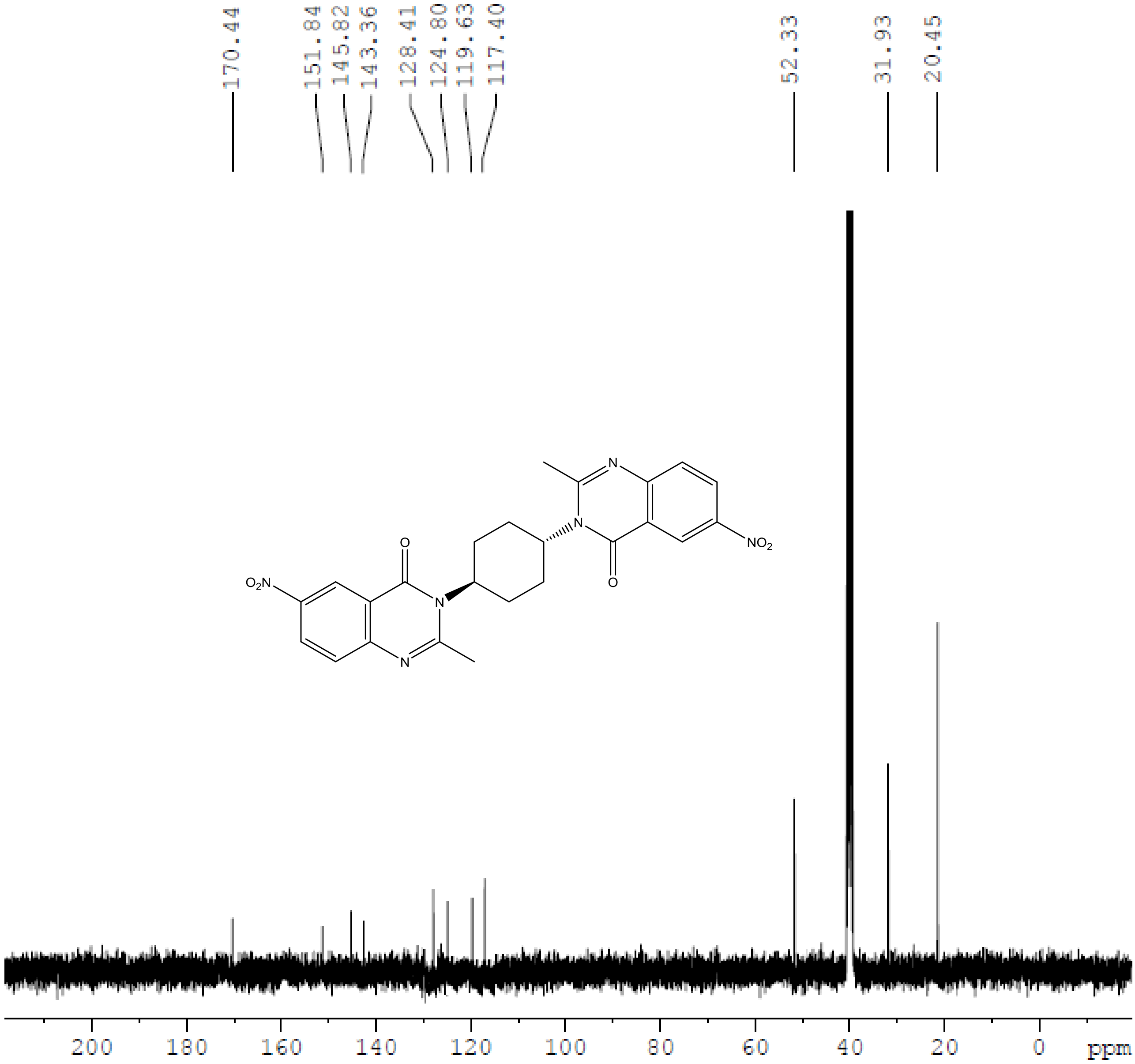
ppm

[1]H NMR of **3e**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O_2N
N
N
N
N
O
NO_2
200
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160
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80
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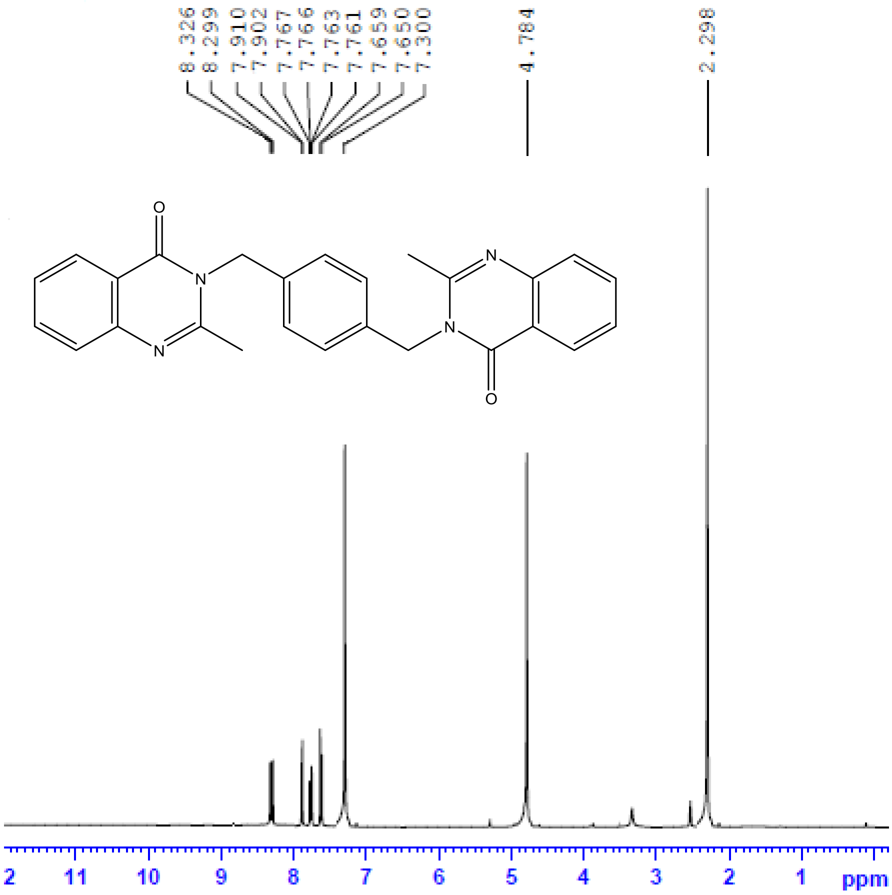
40
20
0
ppm

^{13}C NMR of **3e**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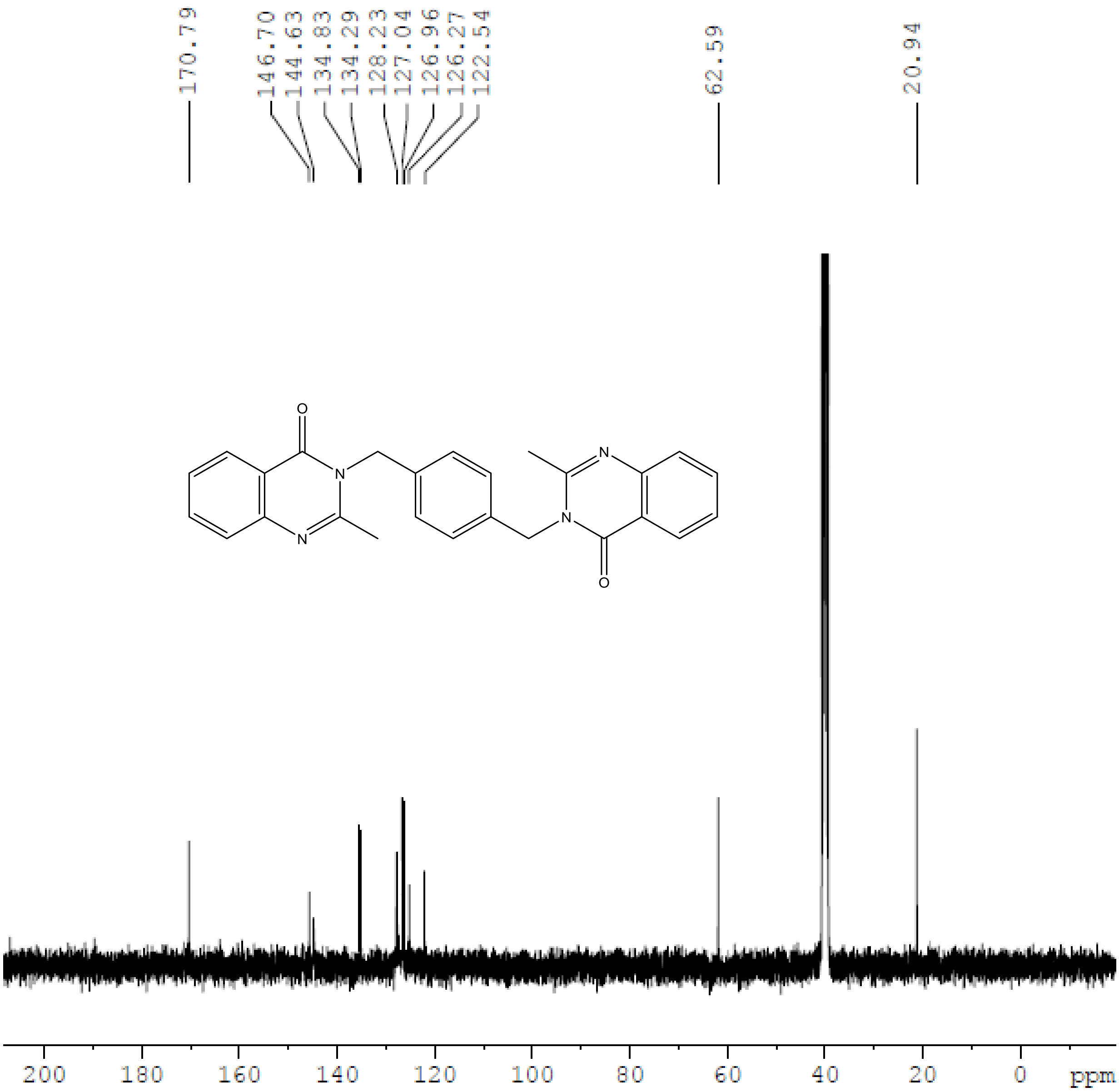
O
N
N
N
N
O
2
11
10
9
8
7
6
5
4
3
2
1
ppm

^{1}H NMR of **4a**



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N
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60
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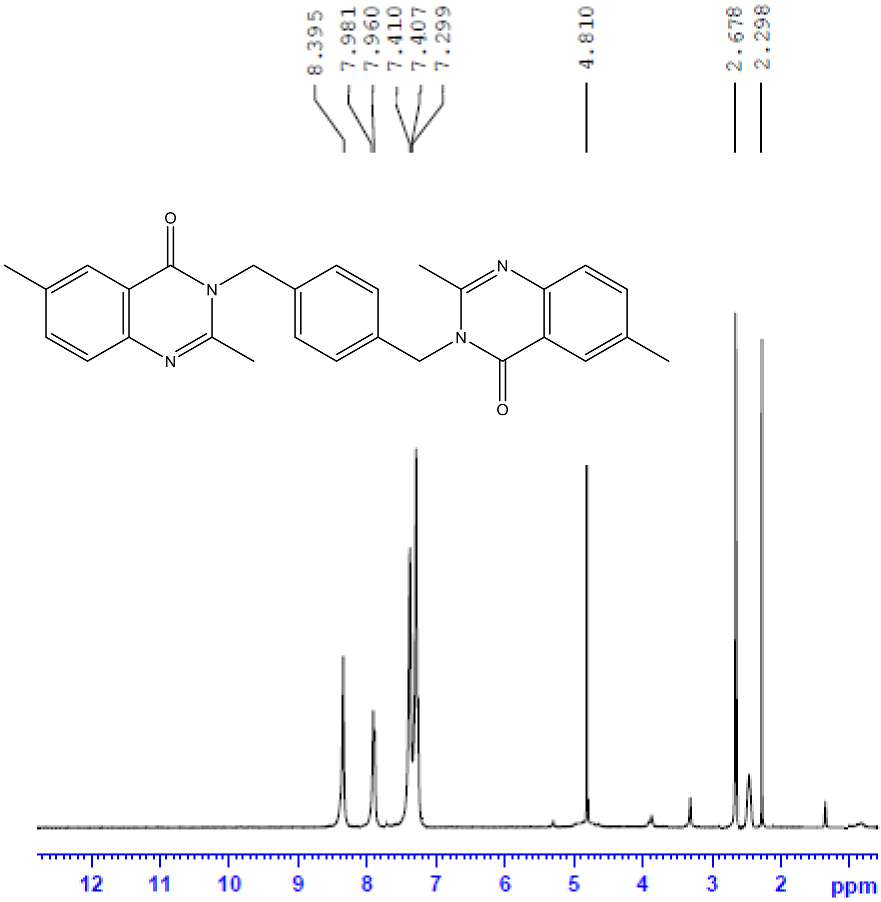
^{13}C NMR of **4a**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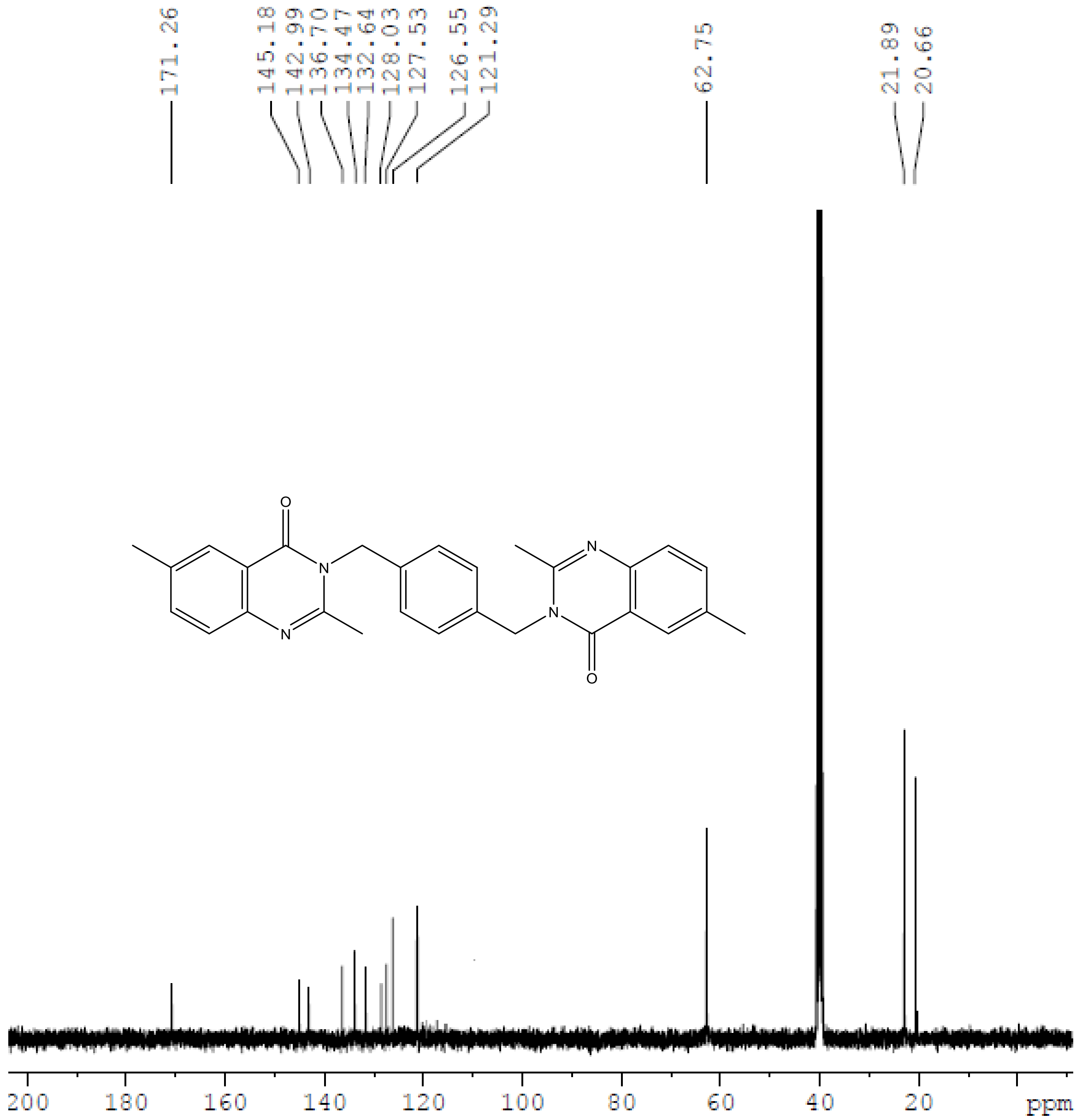
^{1}H NMR of **4b**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60
40
20
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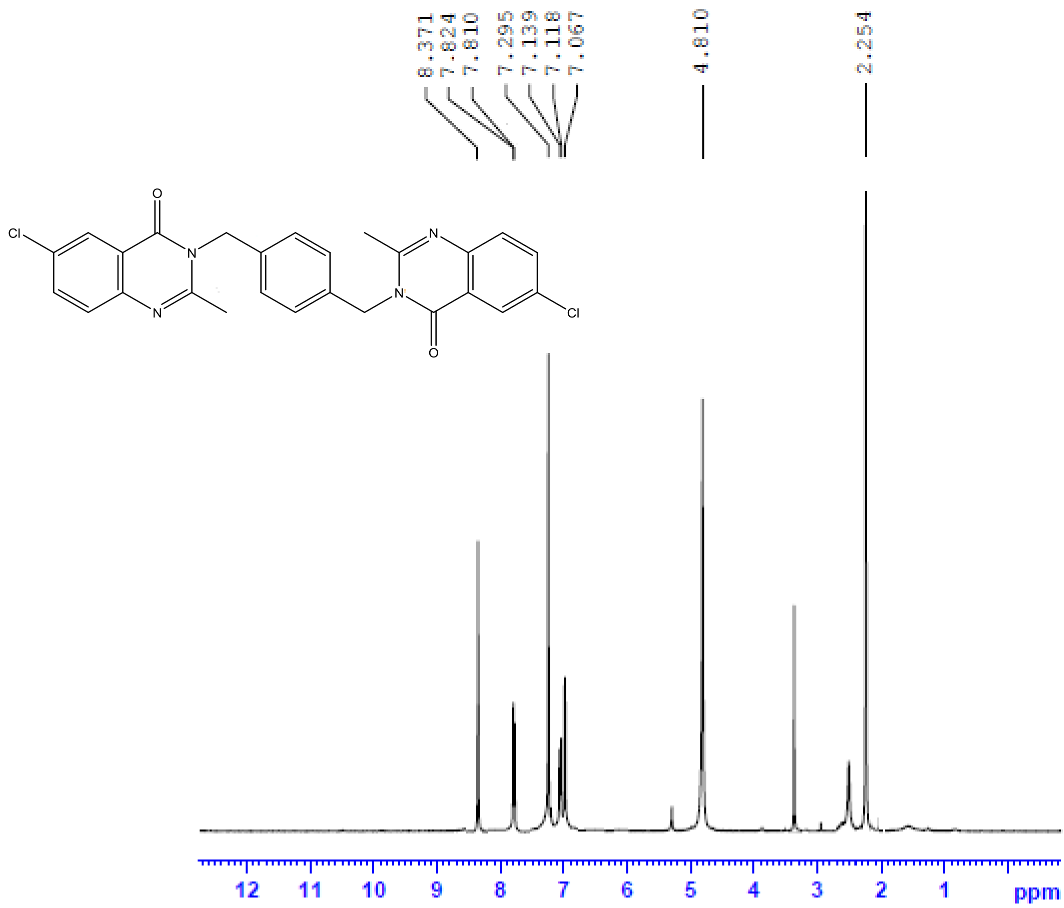
^{13}C NMR of **4b**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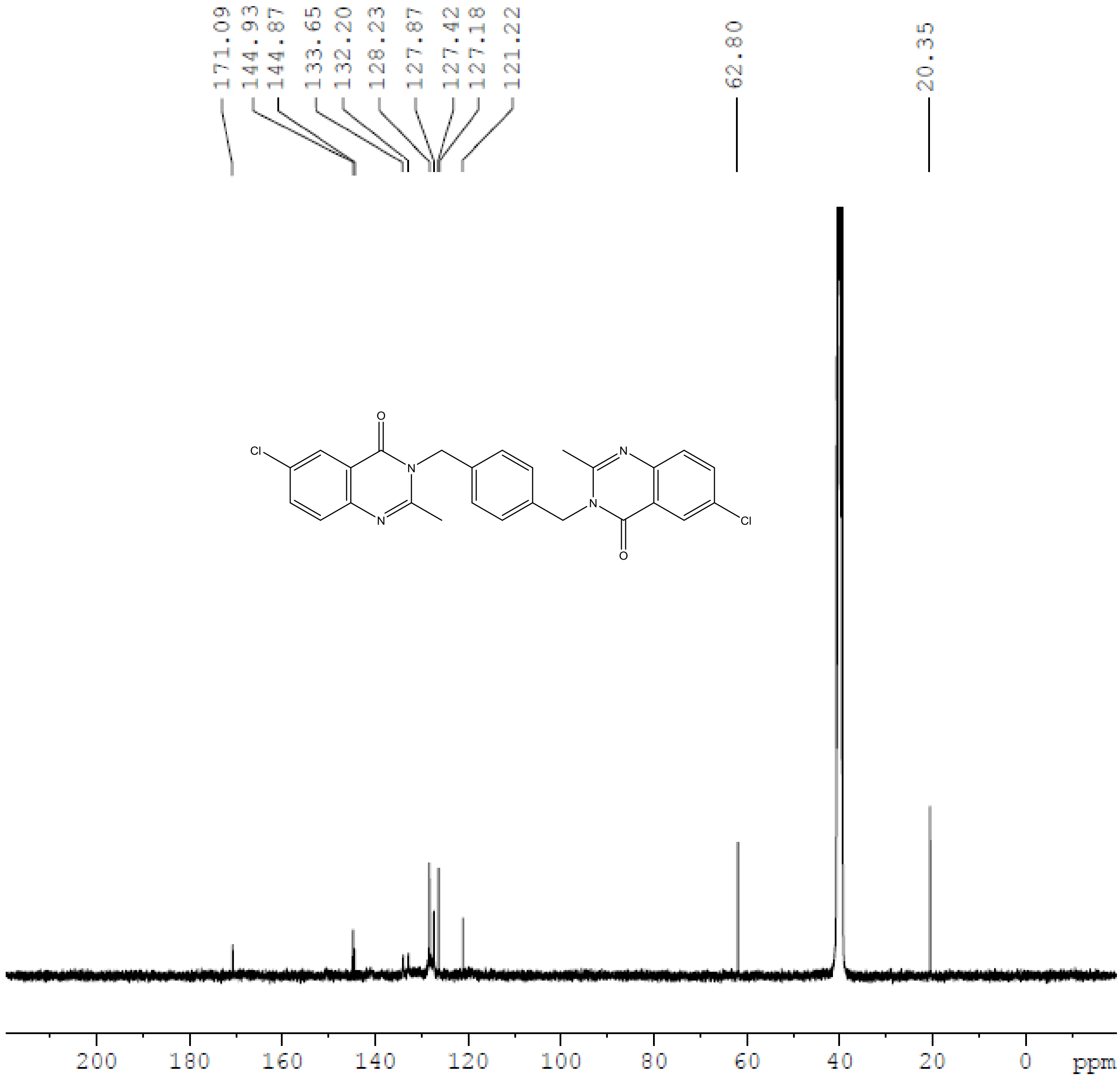
^{1}H NMR of **4c**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O
N
N
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Cl
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40
20
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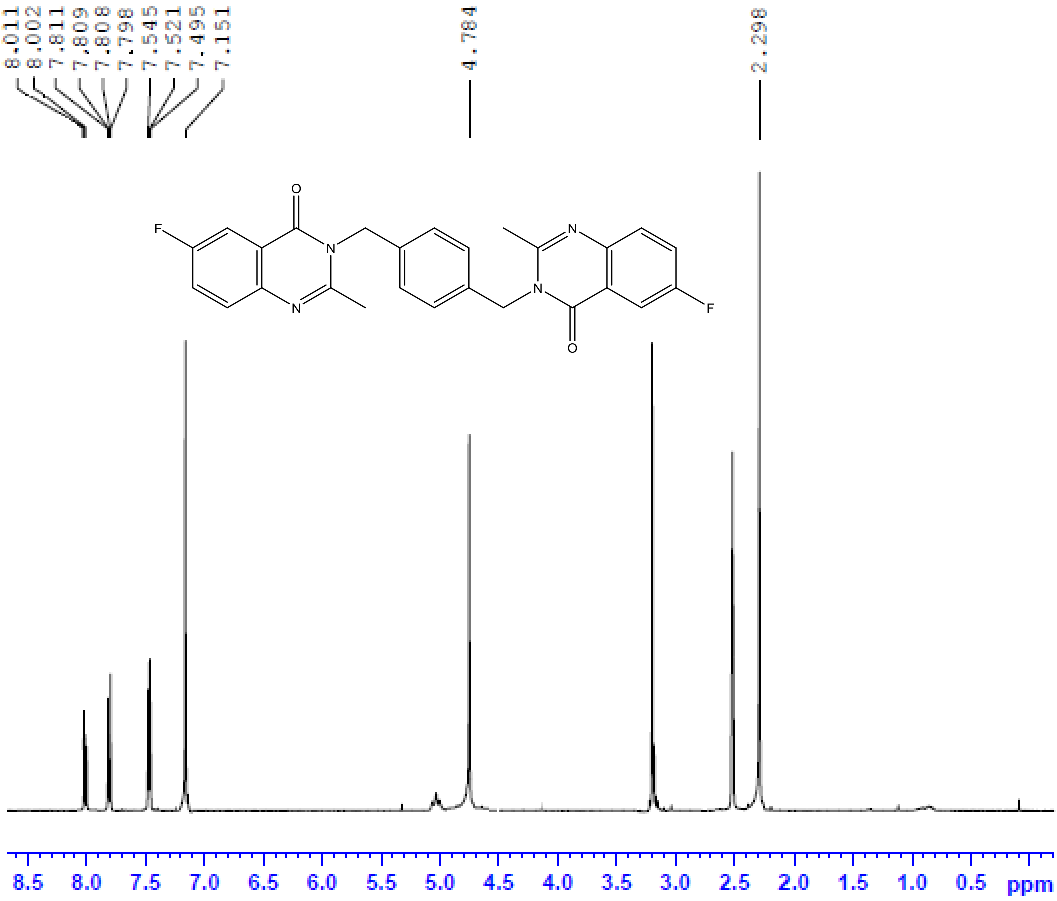
ppm

^{13}C NMR of **4c**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2.298
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O
N
N
F
O
N
N
8.5
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7.5
7.0
6.5
6.0
5.5
5.0
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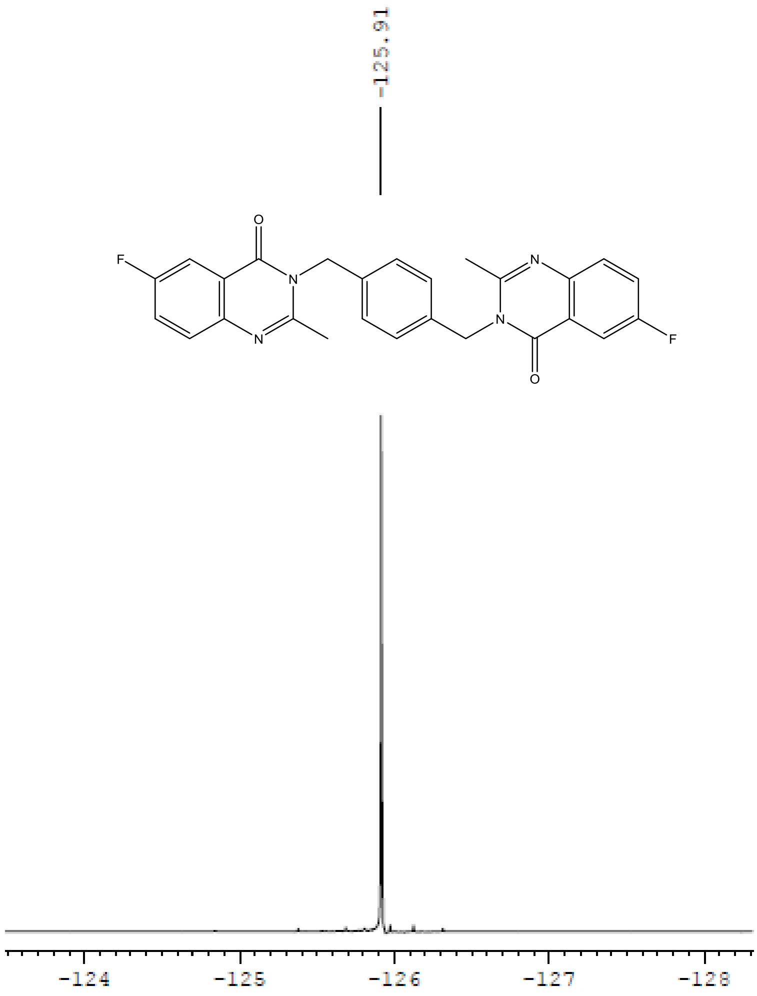
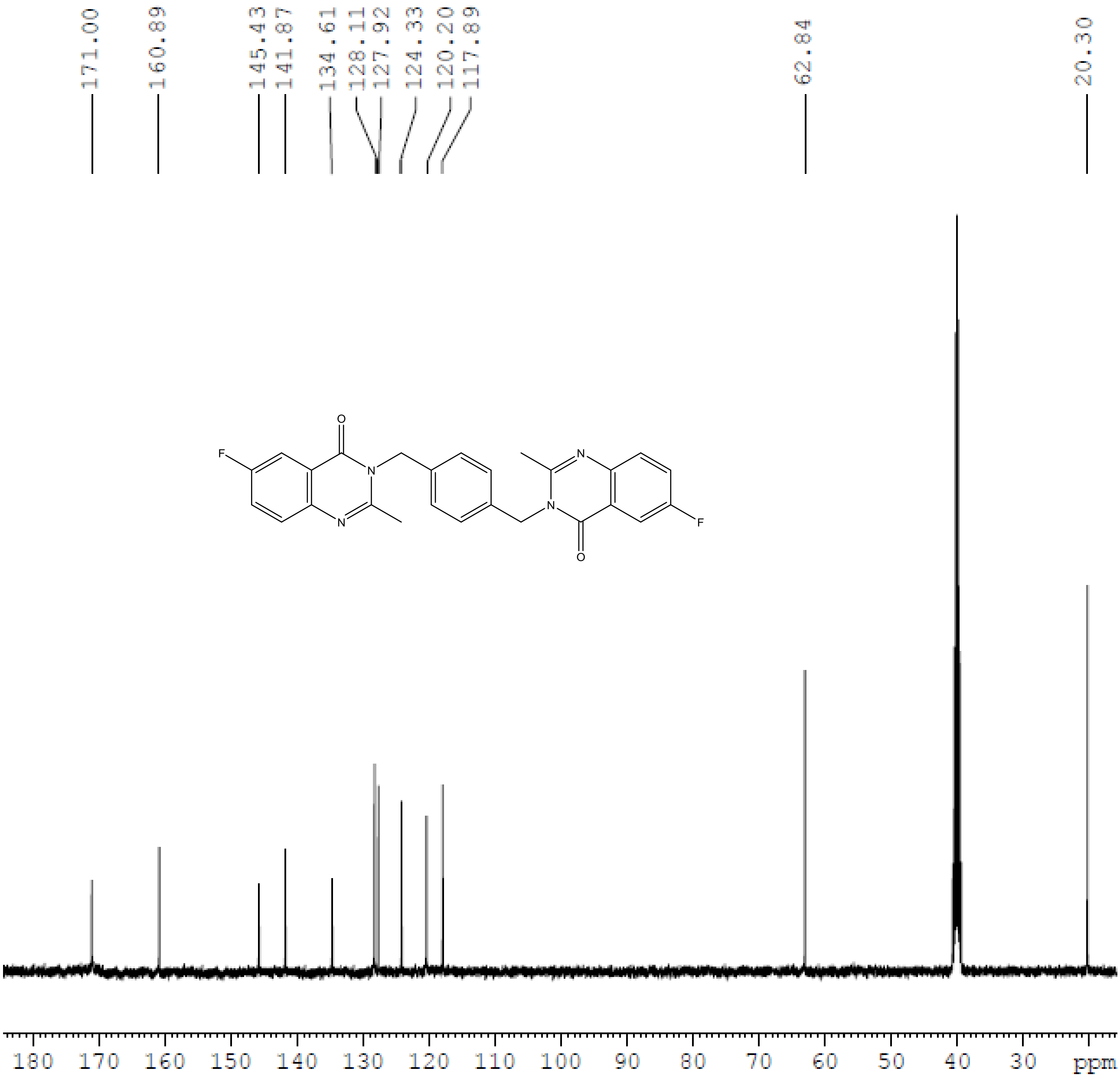
^{1}H NMR of **4d**



^{19}F NMR of **4d**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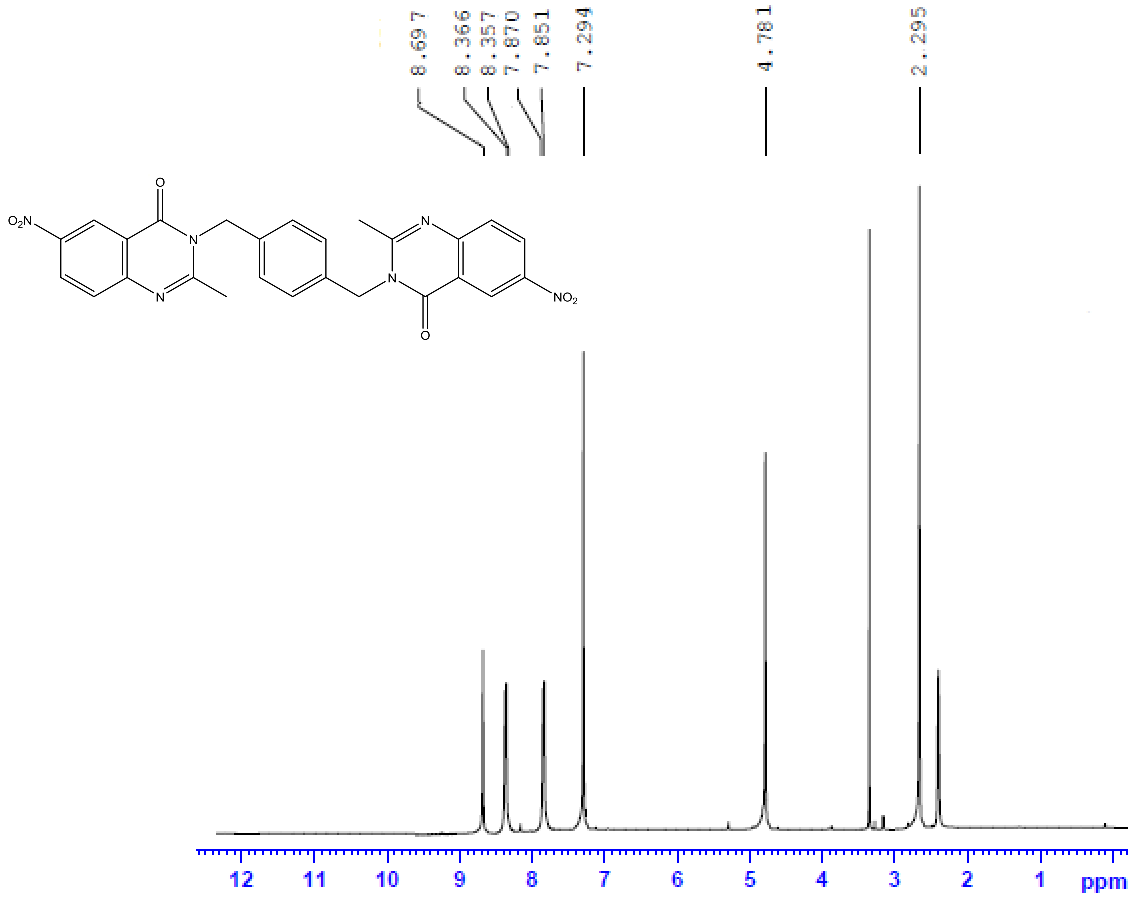
^{13}C NMR of **4d**



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7.870
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7.294
4.781
2.295
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O_2N
N
N
N
N
O
NO_2
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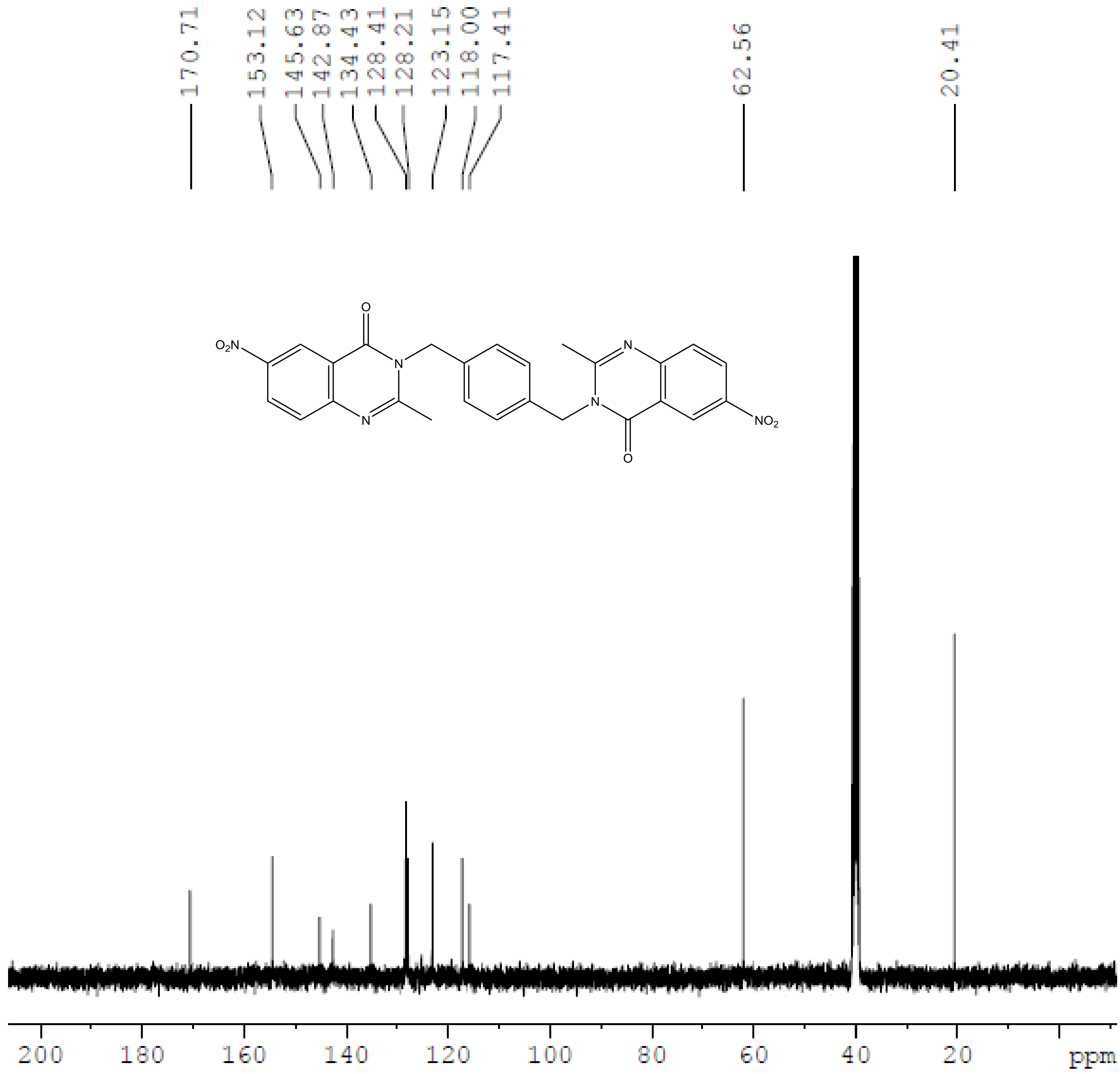
11
10
9
8
7
6
5
4
3
2
1
ppm

^{1}H NMR of **4e**



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128.21
123.15
118.00
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62.56
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NO_2
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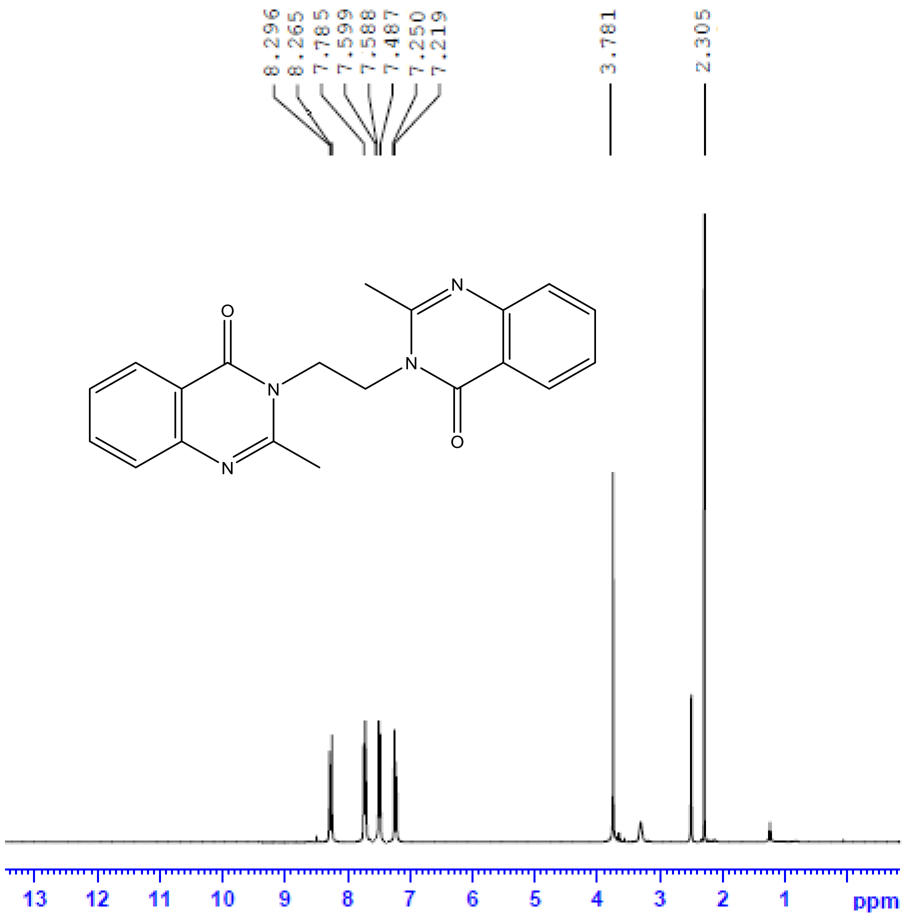
100
80
60
40
20
ppm

^{13}C NMR of **4e**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N
N
N
N
O
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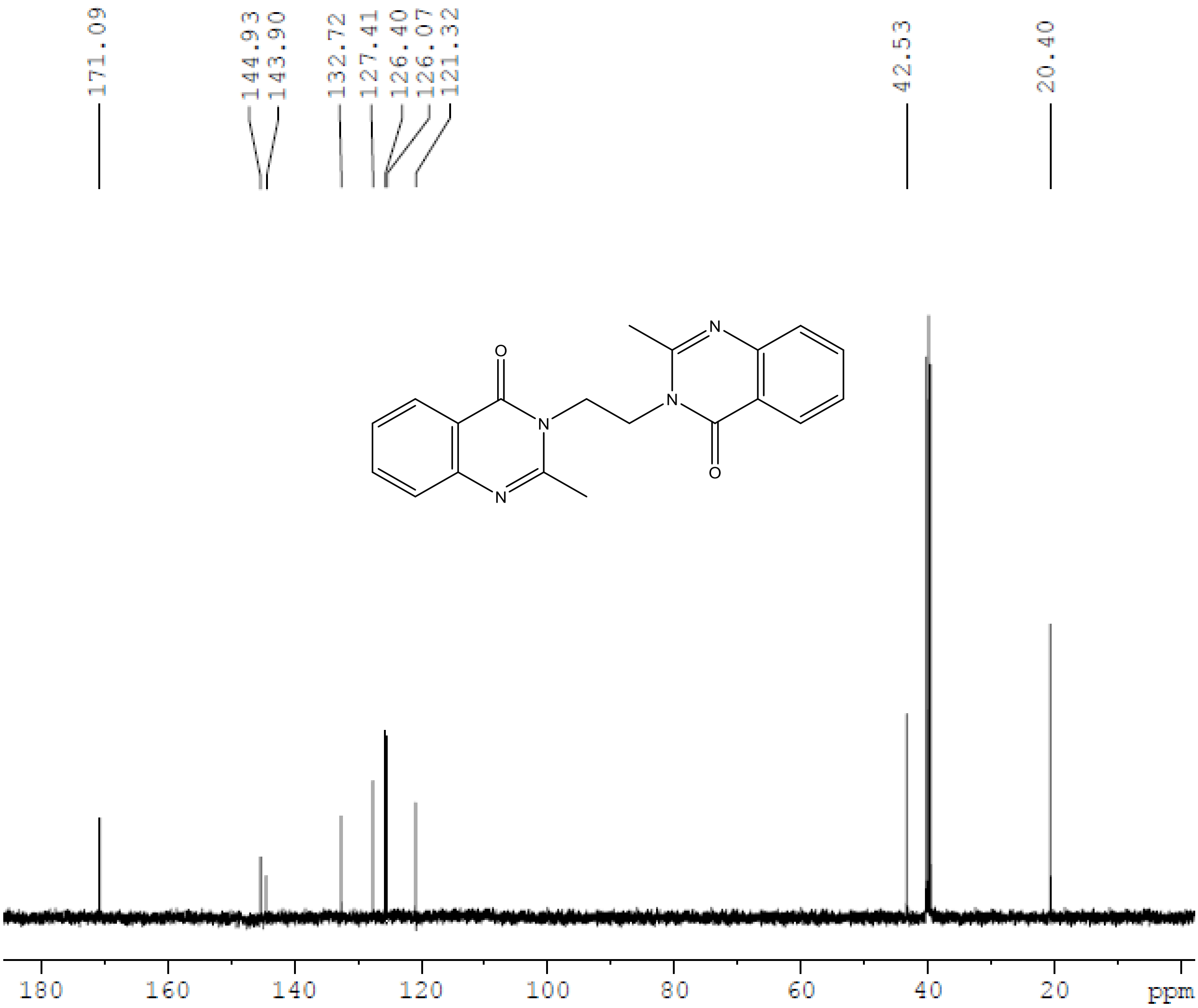
12
11
10
9
8
7
6
5
4
3
2
1
ppm

^{1}H NMR of **5a**



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132.72
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126.40
126.07
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140
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60
40
20
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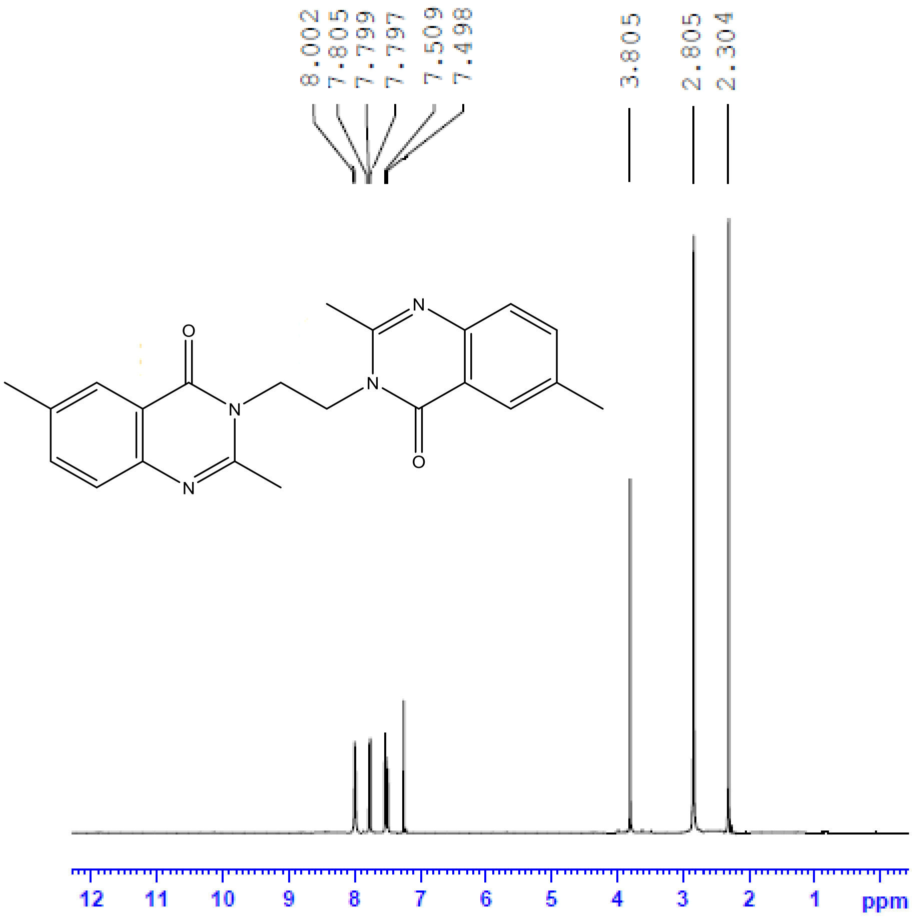
^{13}C NMR of **5a**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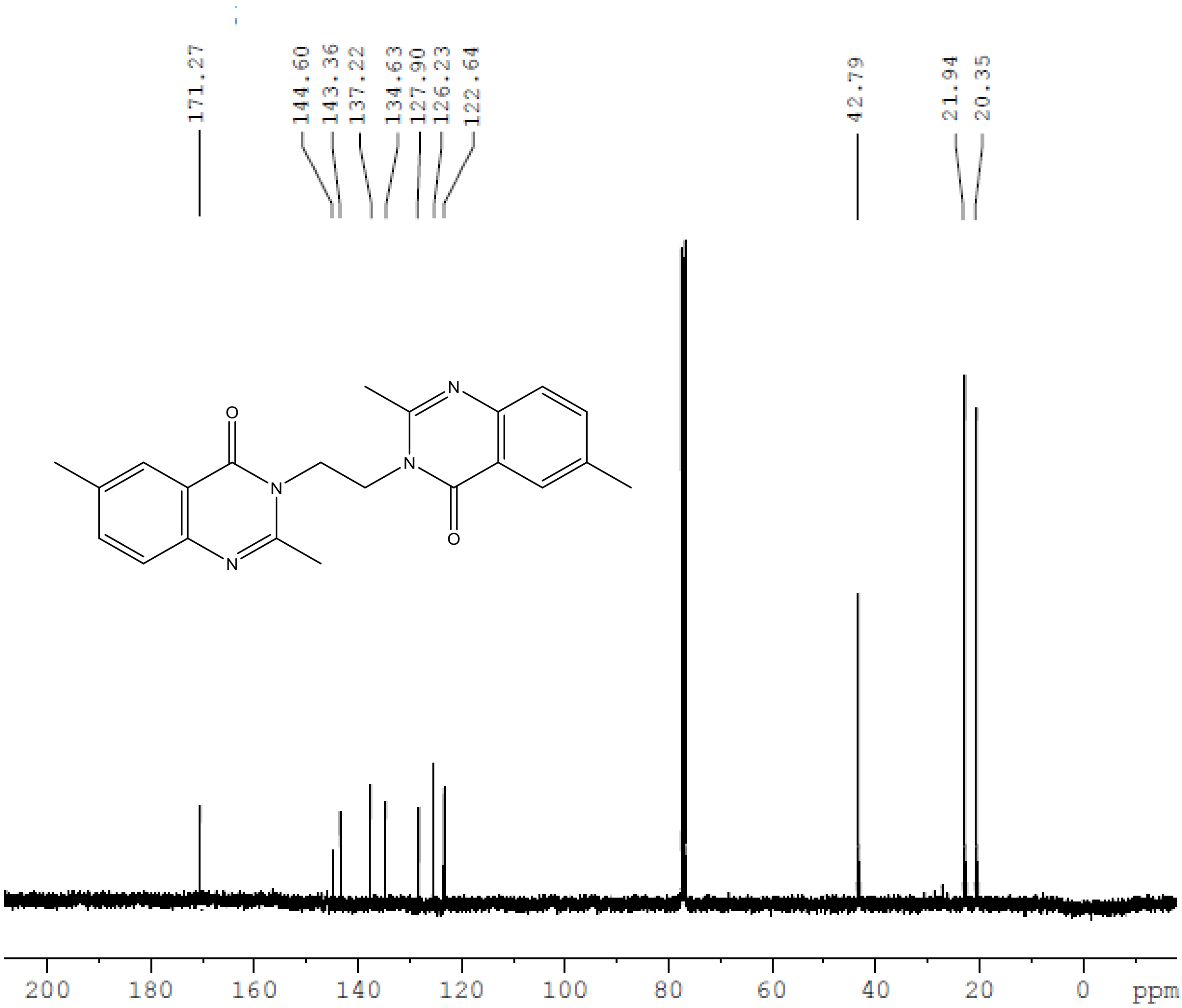
^{1}H NMR of **5b**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20.35
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80
60
40
20
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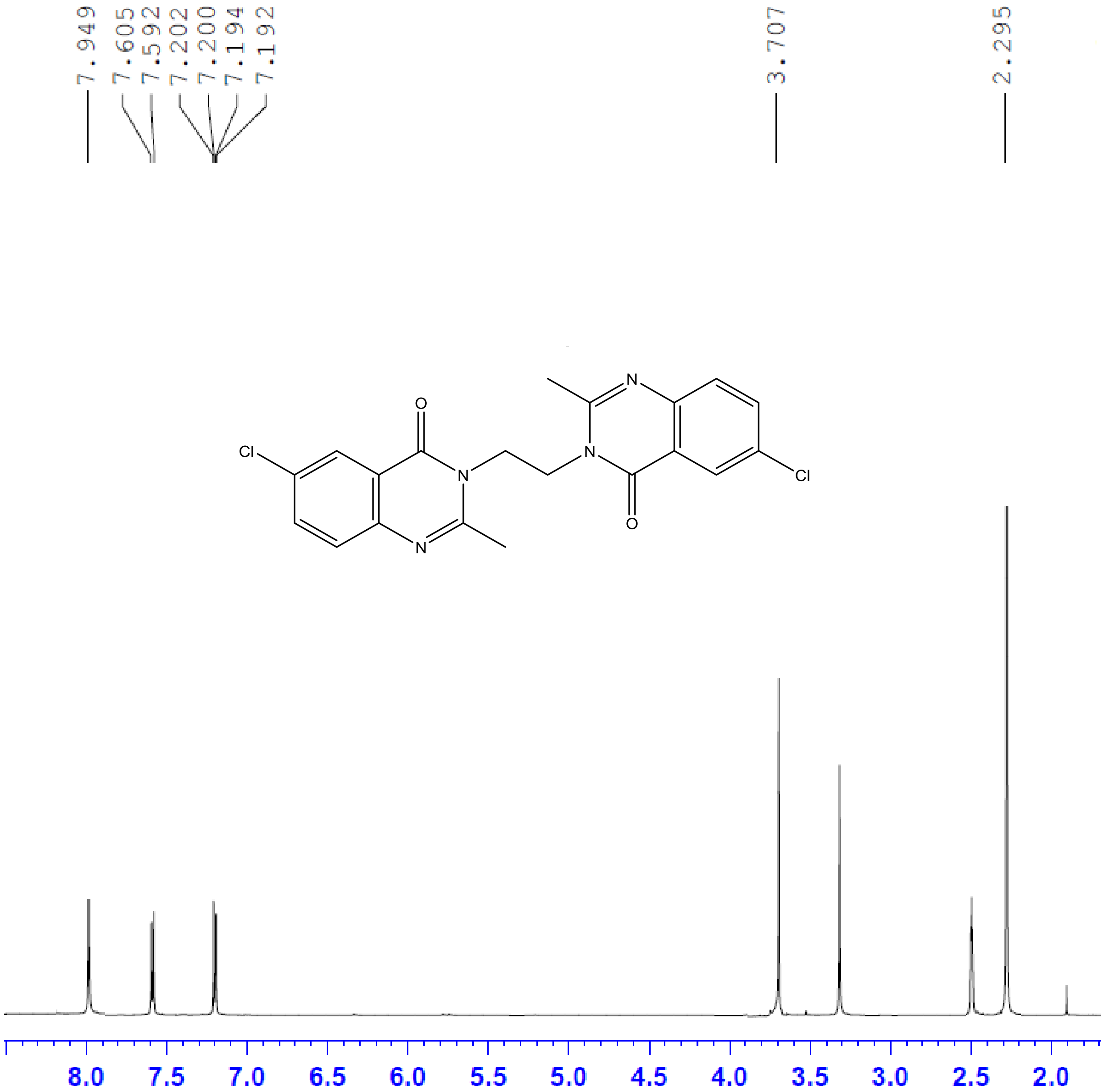
^{13}C NMR of **5b**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Cl
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7.0
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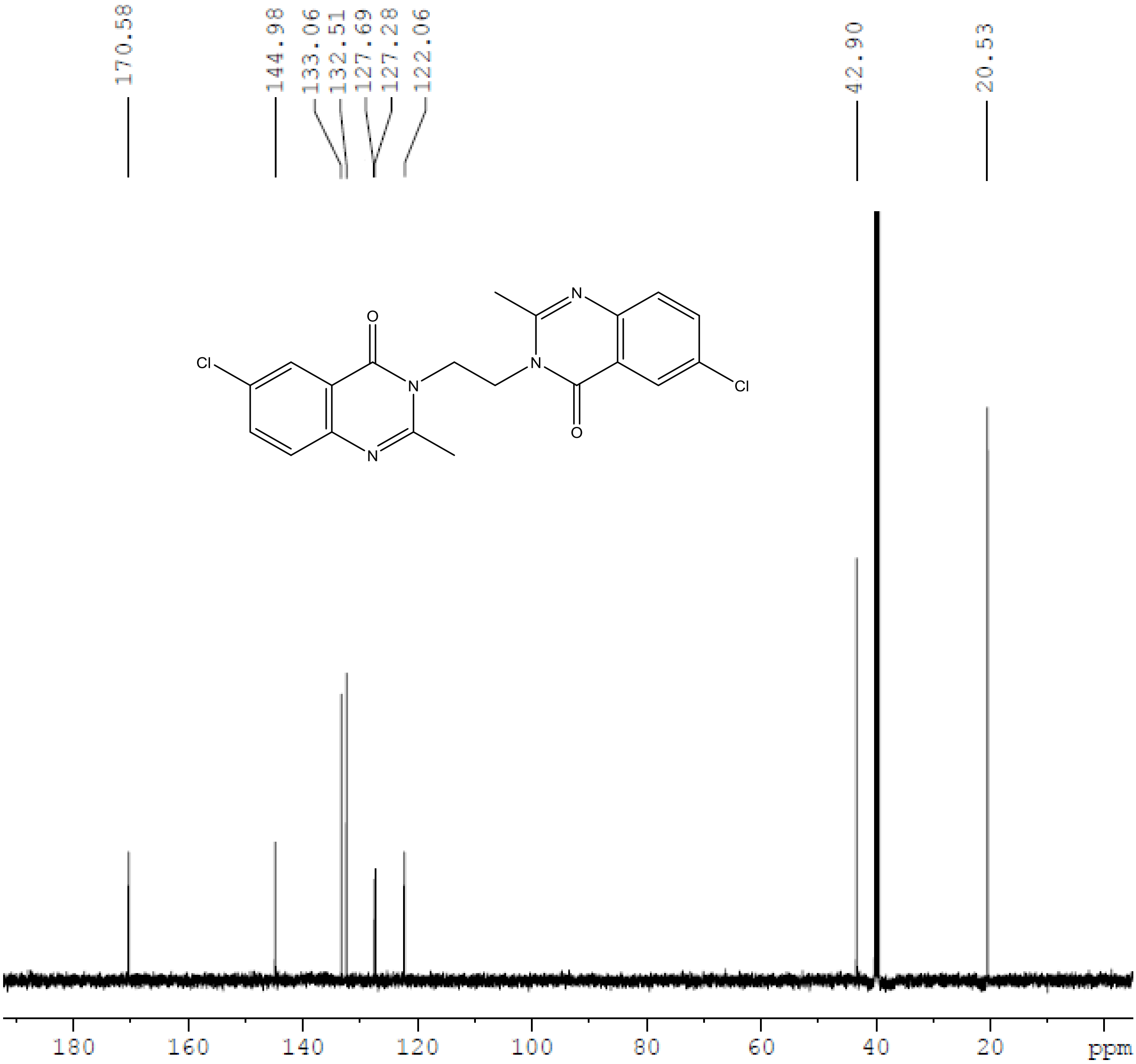
2.5
2.0

^{1}H NMR of **5c**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127.28
122.06
42.90
20.53
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N
N
O
Cl
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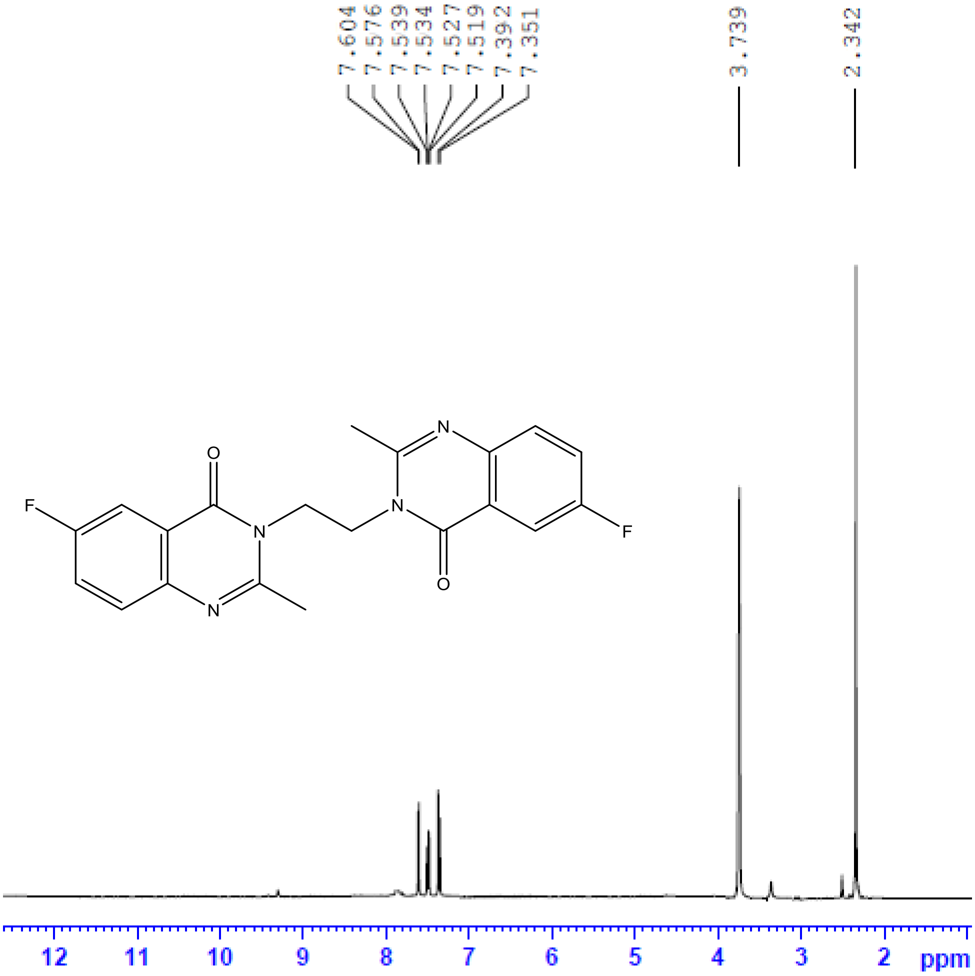
160
140
120
100
80
60
40
20
ppm

^{13}C NMR of **5c**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7.351
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N
N
N
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F
12
11
10
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8
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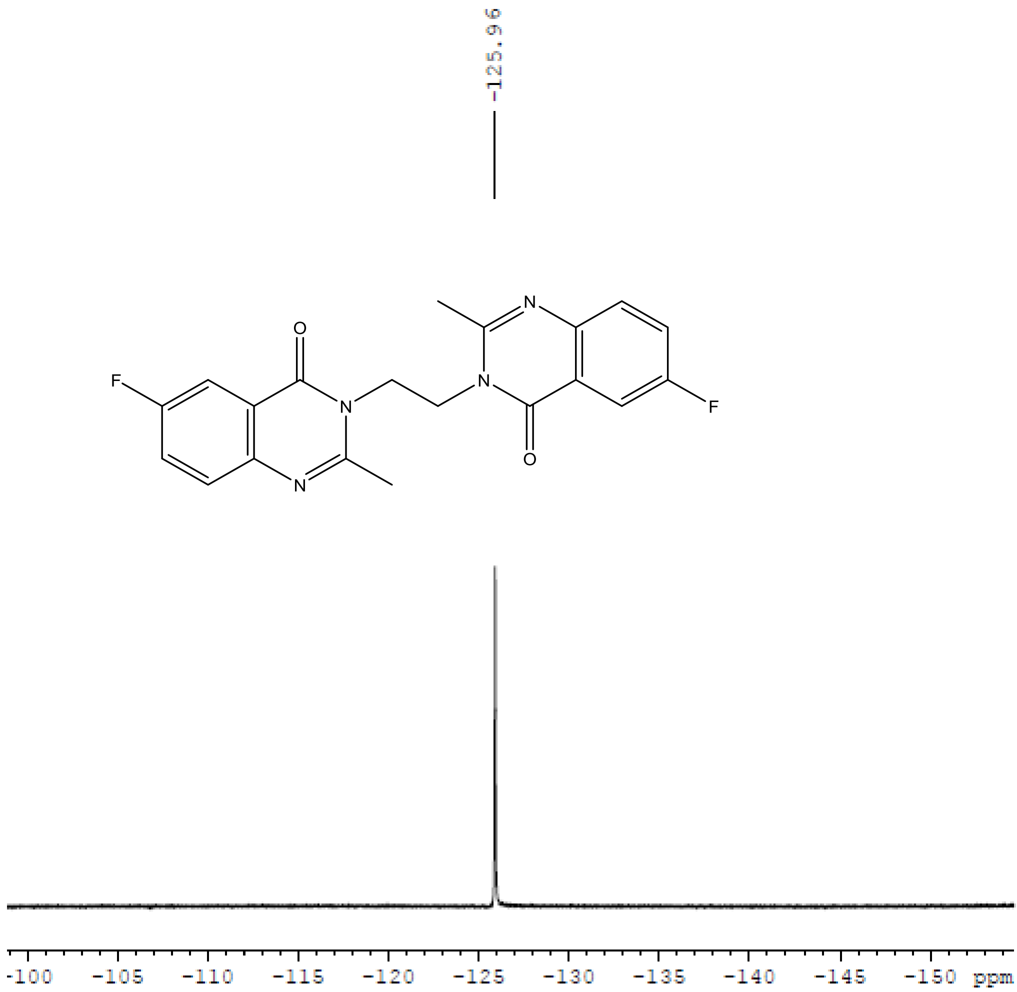
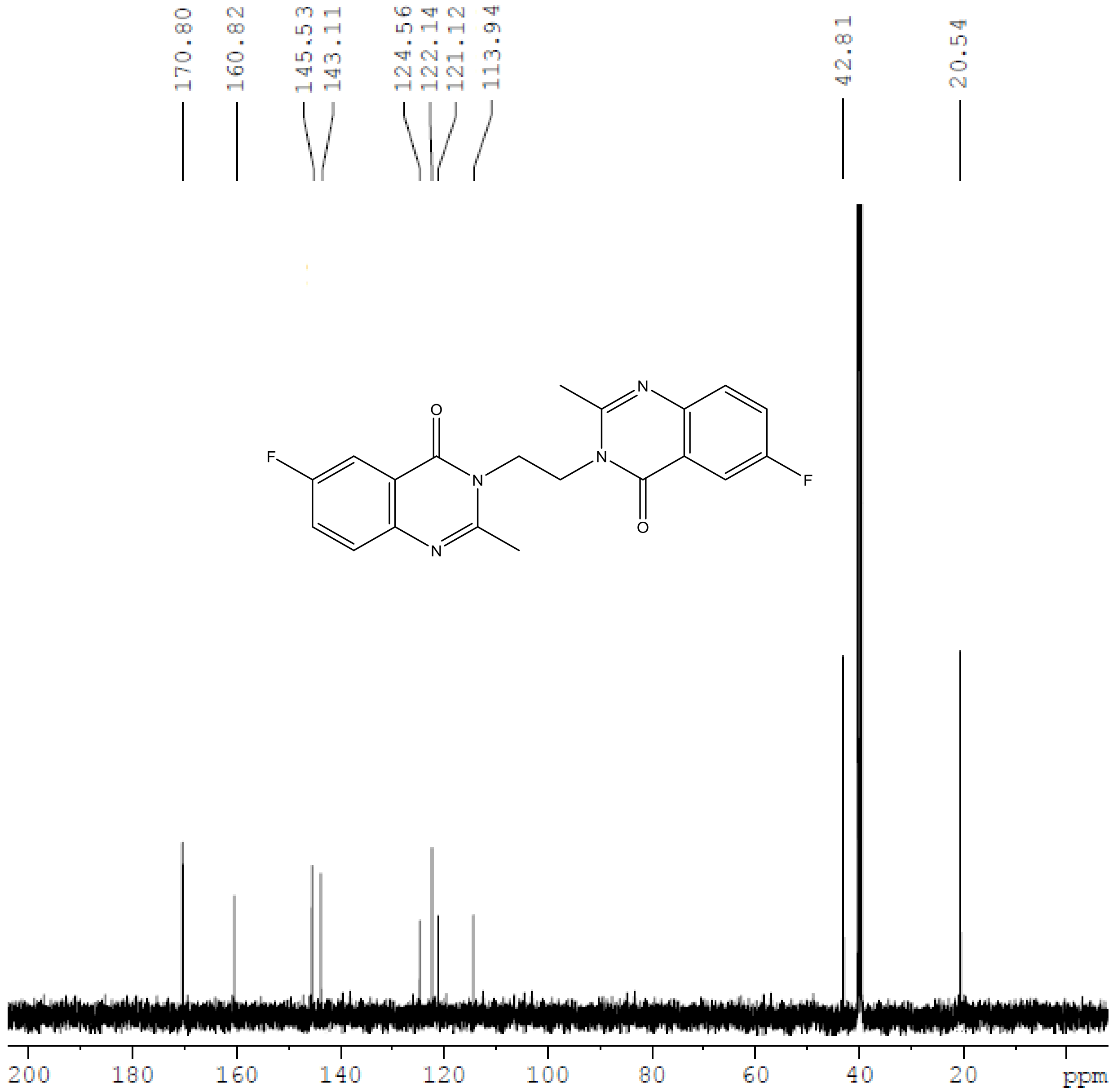
6
5
4
3
2
ppm

^{1}H NMR of **5d**



^{19}F NMR of **5d**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145.53
143.11
124.56
122.14
121.12
113.94
42.81
20.54
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O
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F
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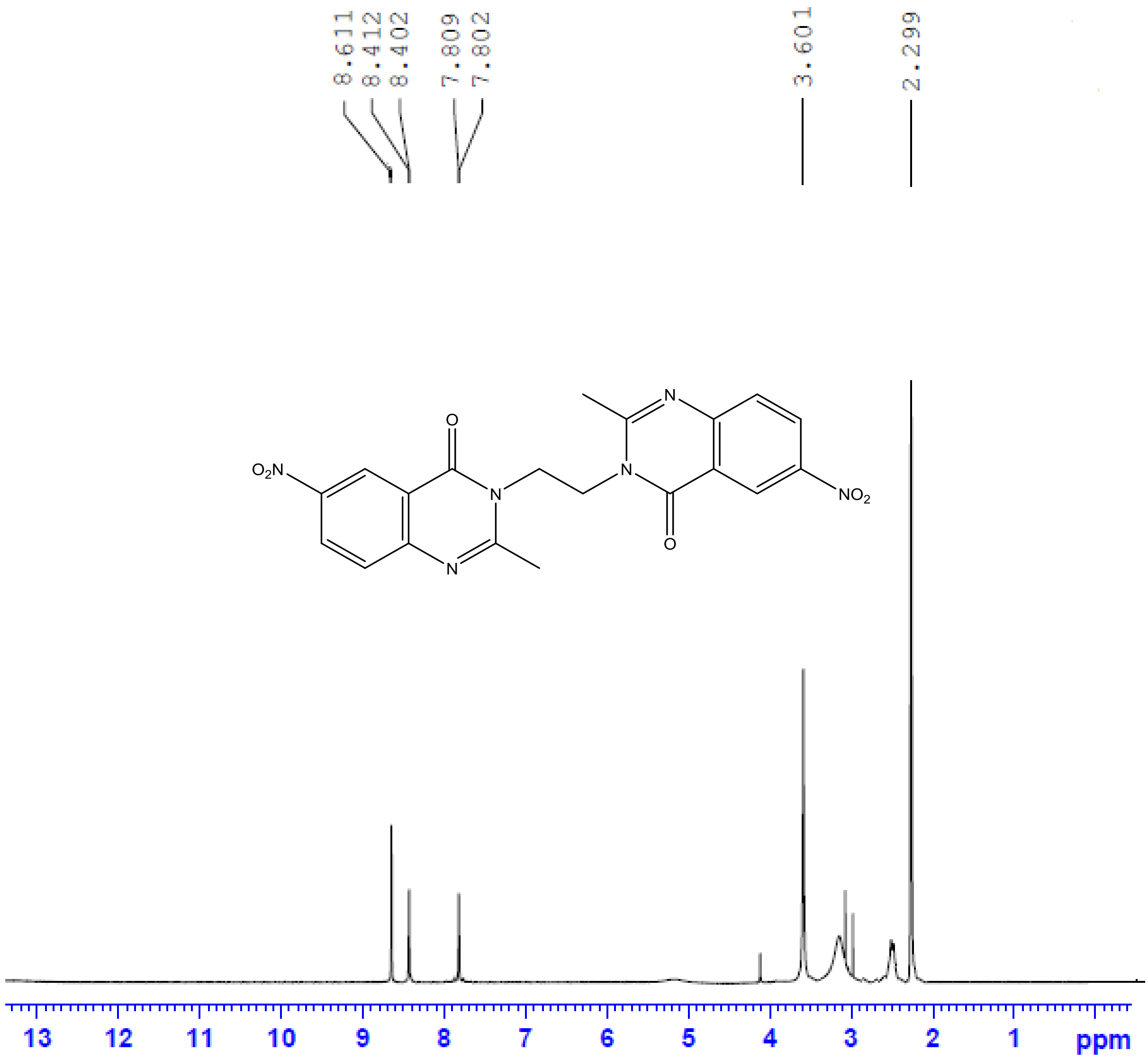
100
80
60
40
20
ppm

^{13}C NMR of **5d**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7.802
3.601
2.299
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O2N
N
N
N
N
NO2
O
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11
10
9
8
7
6
5
4
3
2
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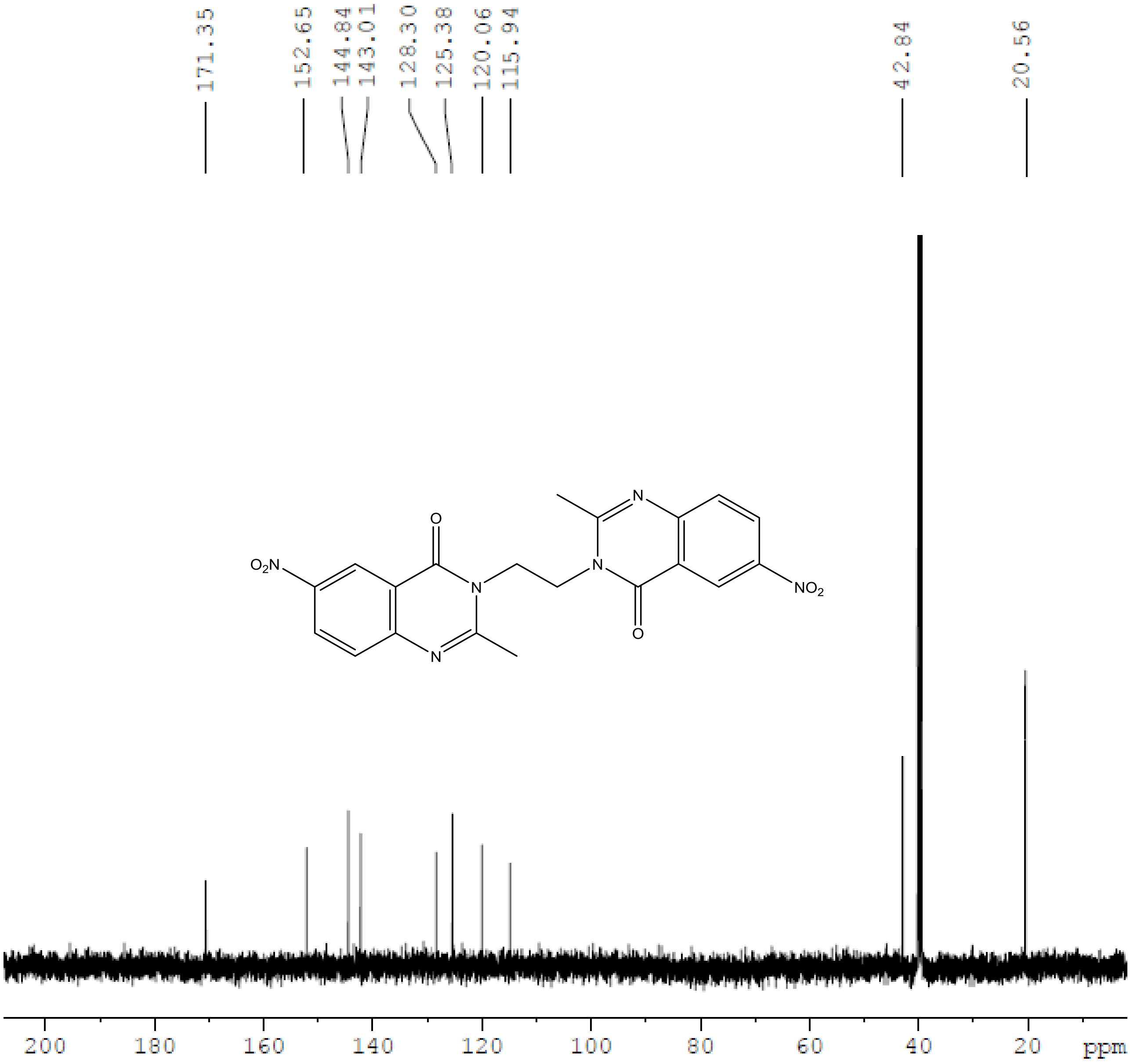
ppm

[1]H NMR of **5e**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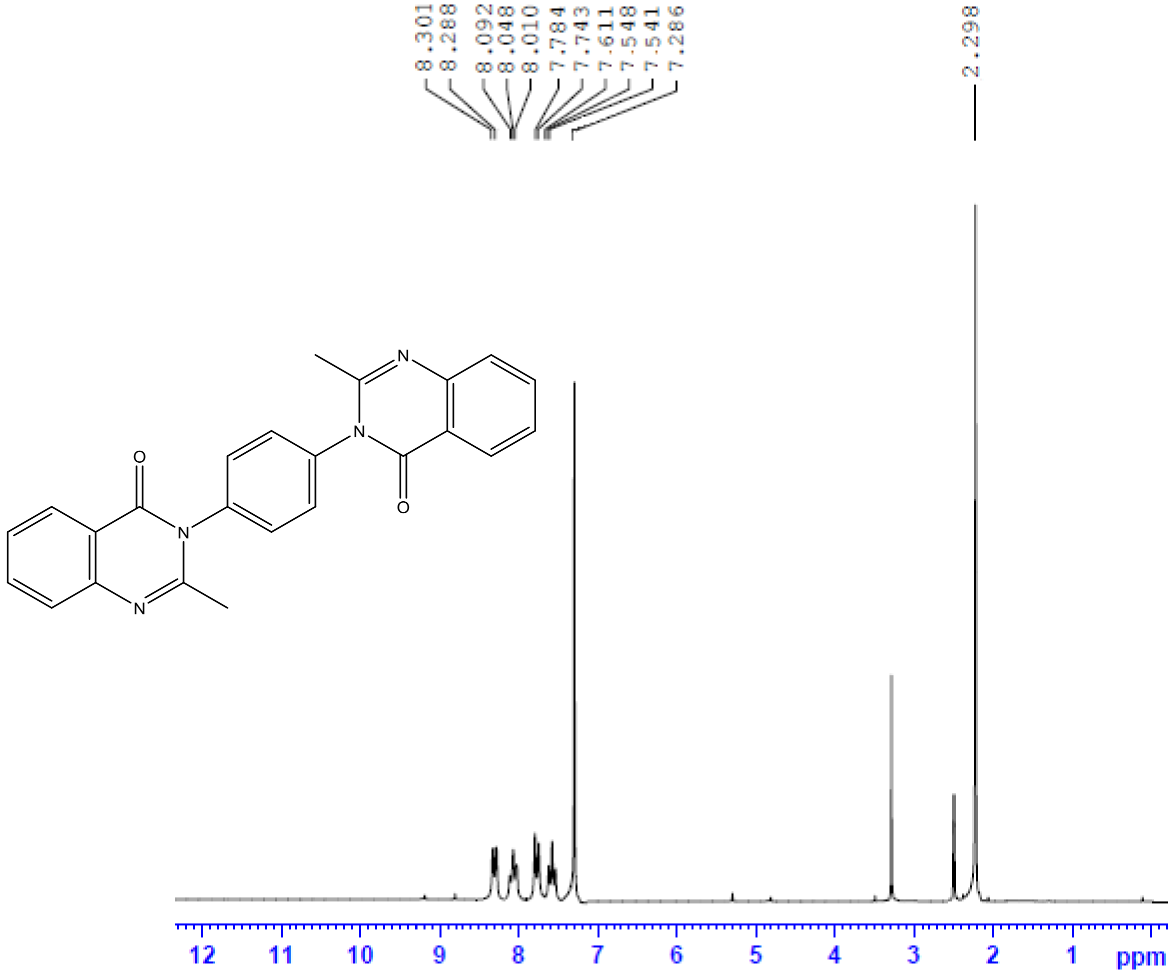
143.01
128.30
125.38
120.06
115.94
42.84
20.56
O_2N
O
N
N
N
N
O
NO_2
200
180
160
140
120
100
80
60
40
20
ppm

^{13}C NMR of **5e**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7.743
7.611
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7.286
2.298
O
N
N
N
N
O
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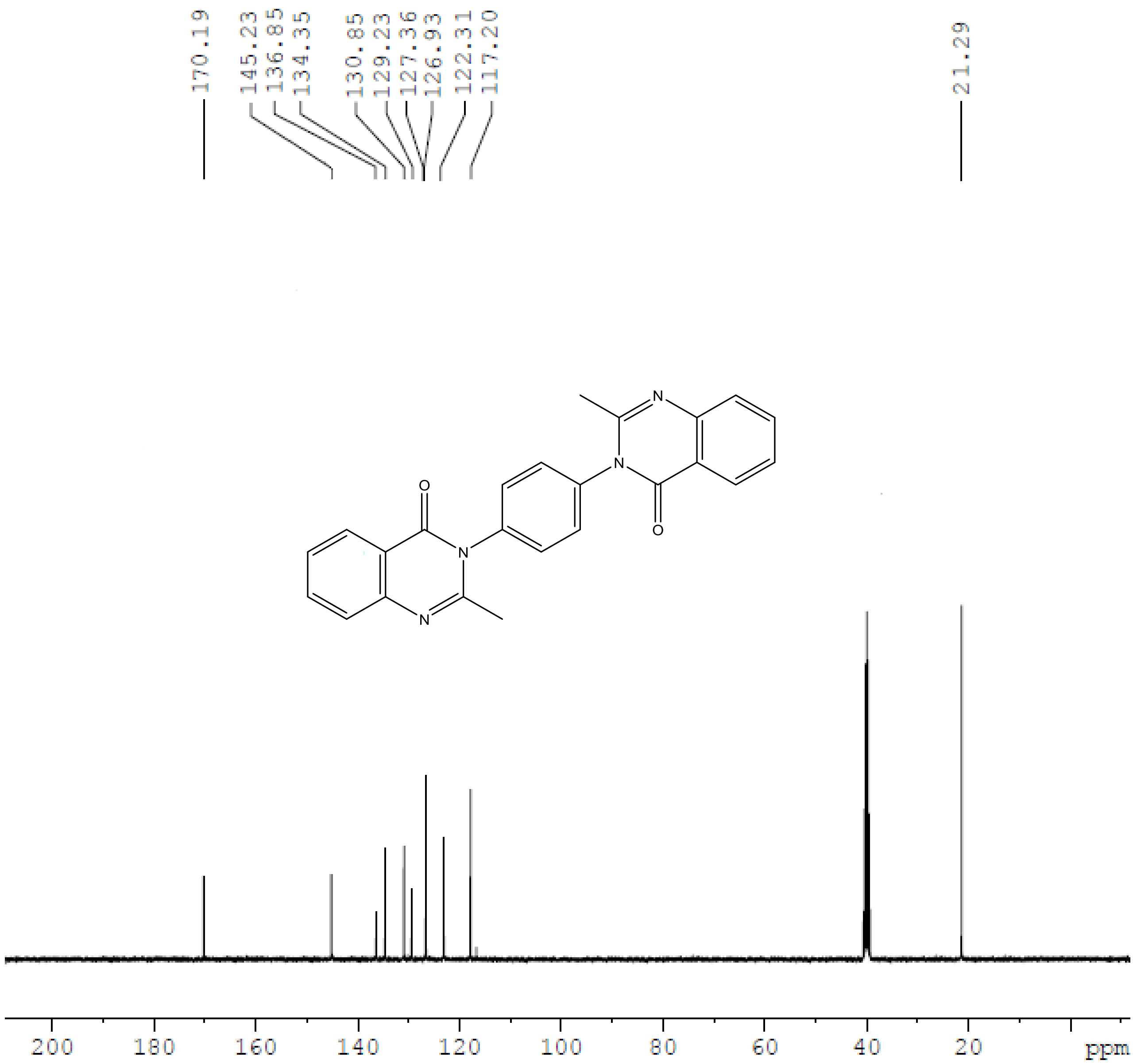
11
10
9
8
7
6
5
4
3
2
1
ppm

^1H NMR of **6a**


170.19
145.23
136.85
134.35
130.85
129.23
127.36
126.93
122.31
117.20
21.29
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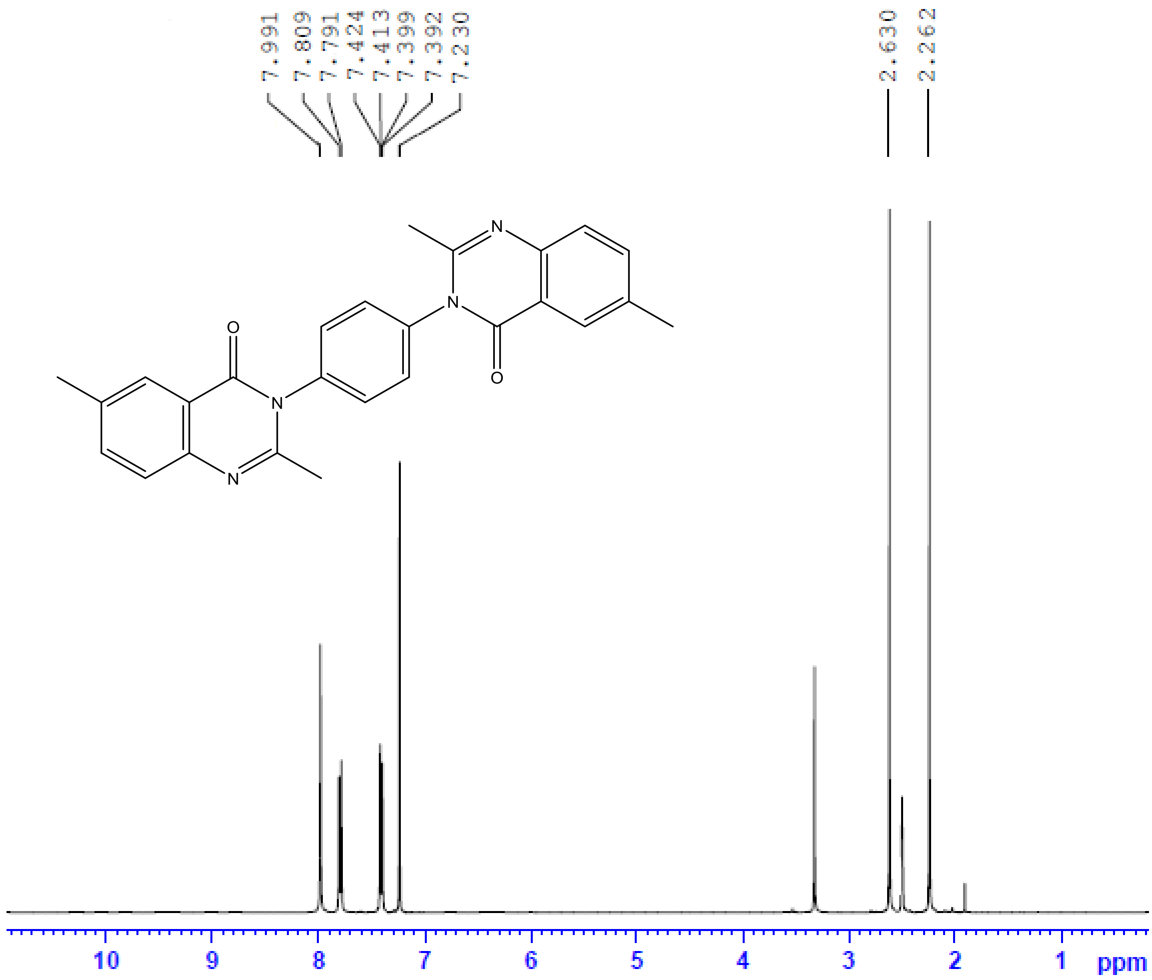
N
N
200
180
160
140
120
100
80
60
40
20
ppm

^{13}C NMR of **6a**


7.991
7.809
7.791
7.424
7.413
7.399
7.392
7.230
2.630
2.262
N
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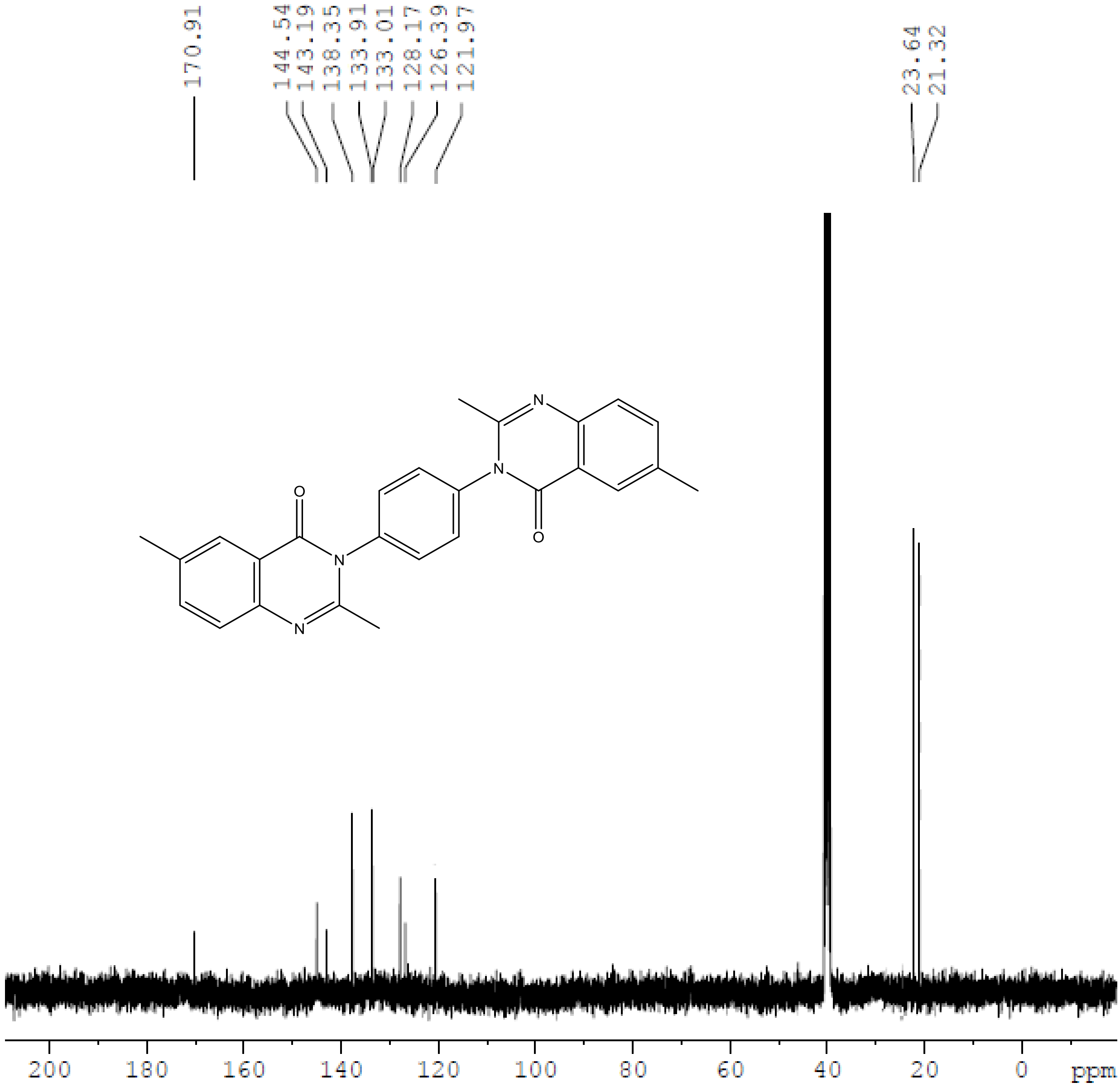
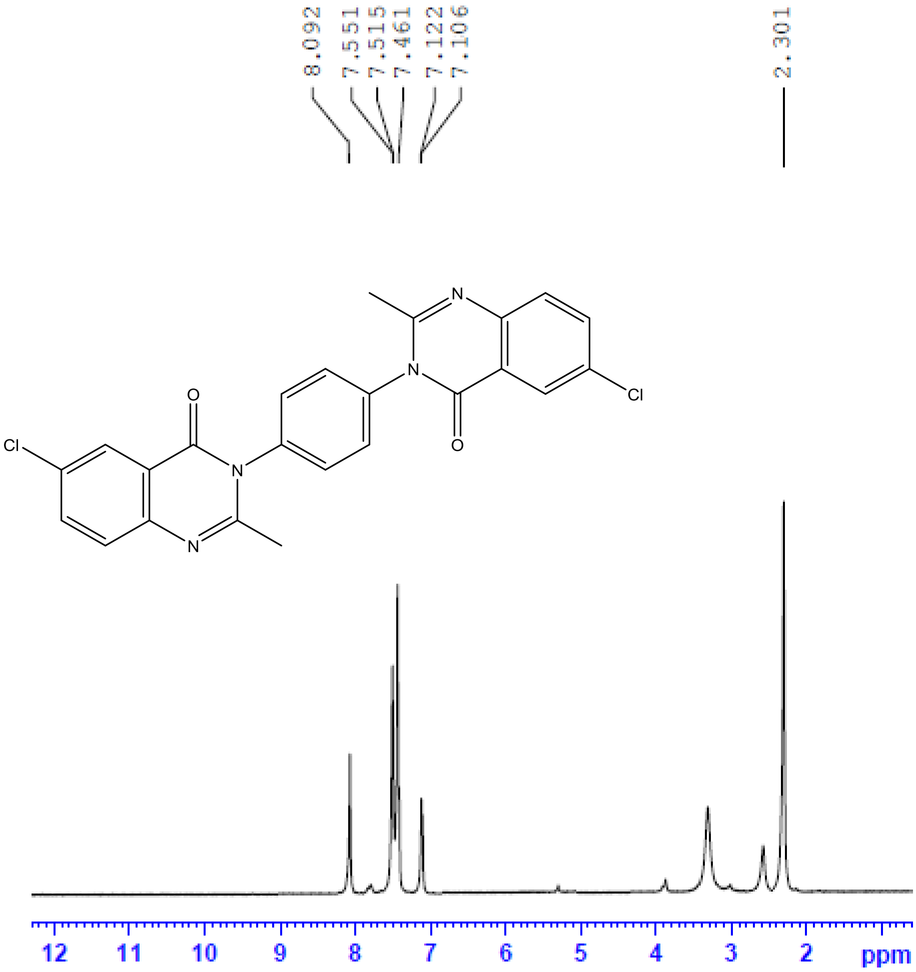
O
N
N
10
9
8
7
6
5
4
3
2
1
ppm

^{1}H NMR of **6b**

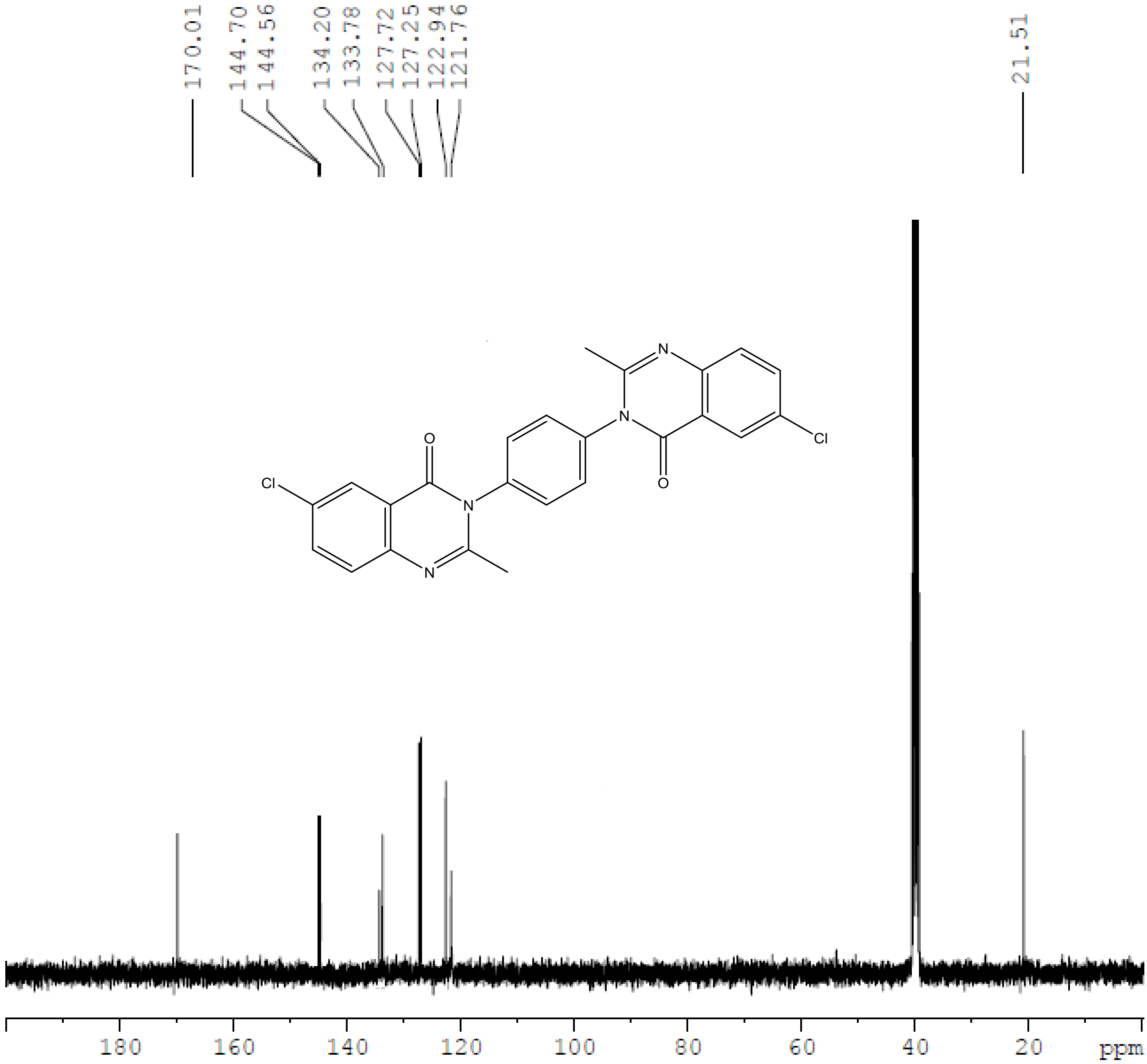


170.91
144.54
143.19
138.35
133.91
133.01
128.17
126.39
121.97
23.64
21.32
200
180
160
140
120
100
80
60
40
20
0
ppm

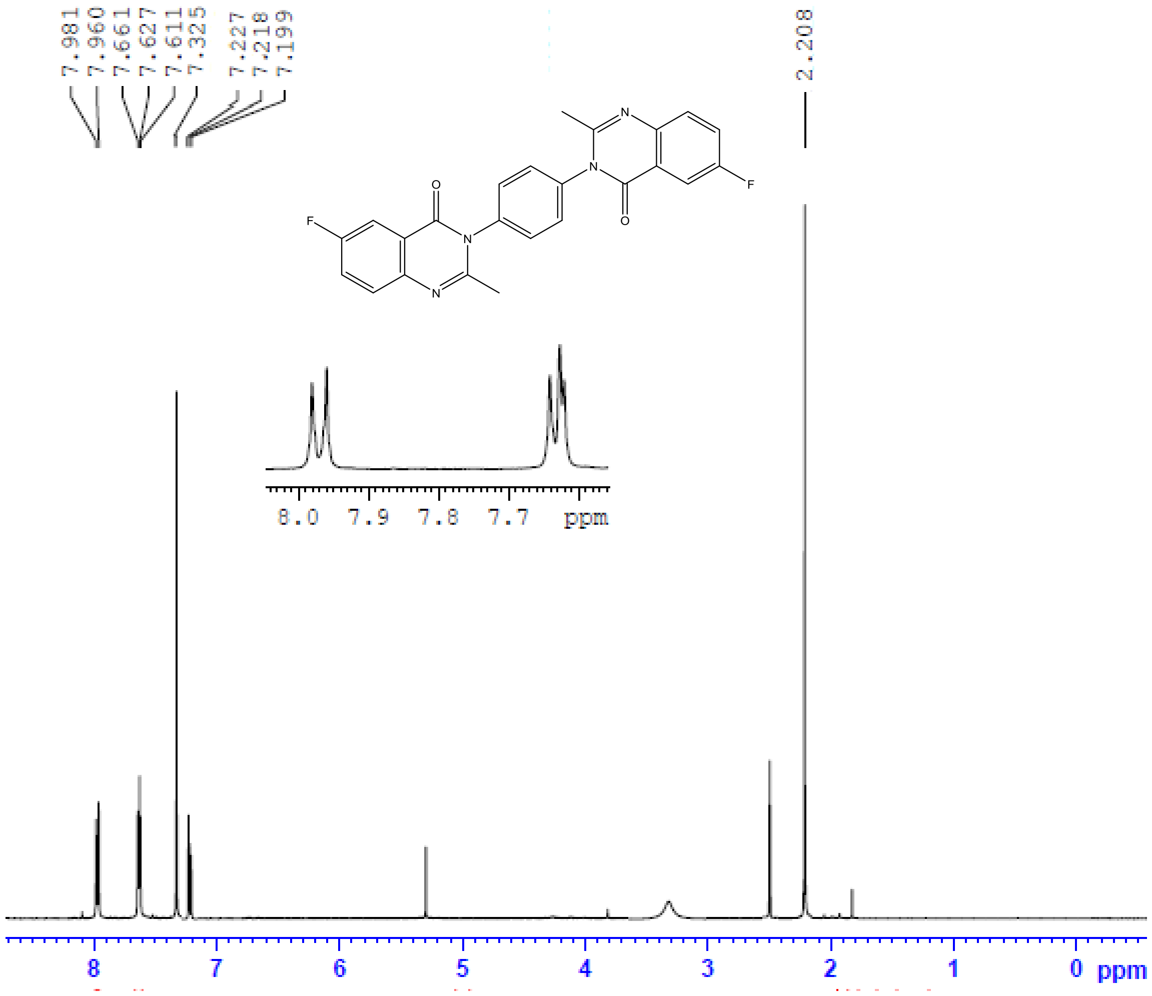
^{13}C NMR of **6b**


8.092
7.551
7.515
7.461
7.122
7.106
2.301
Cl
O
N
N
Cl
O
N
N
12
11
10
9
8
7
6
5
4
3
2
ppm

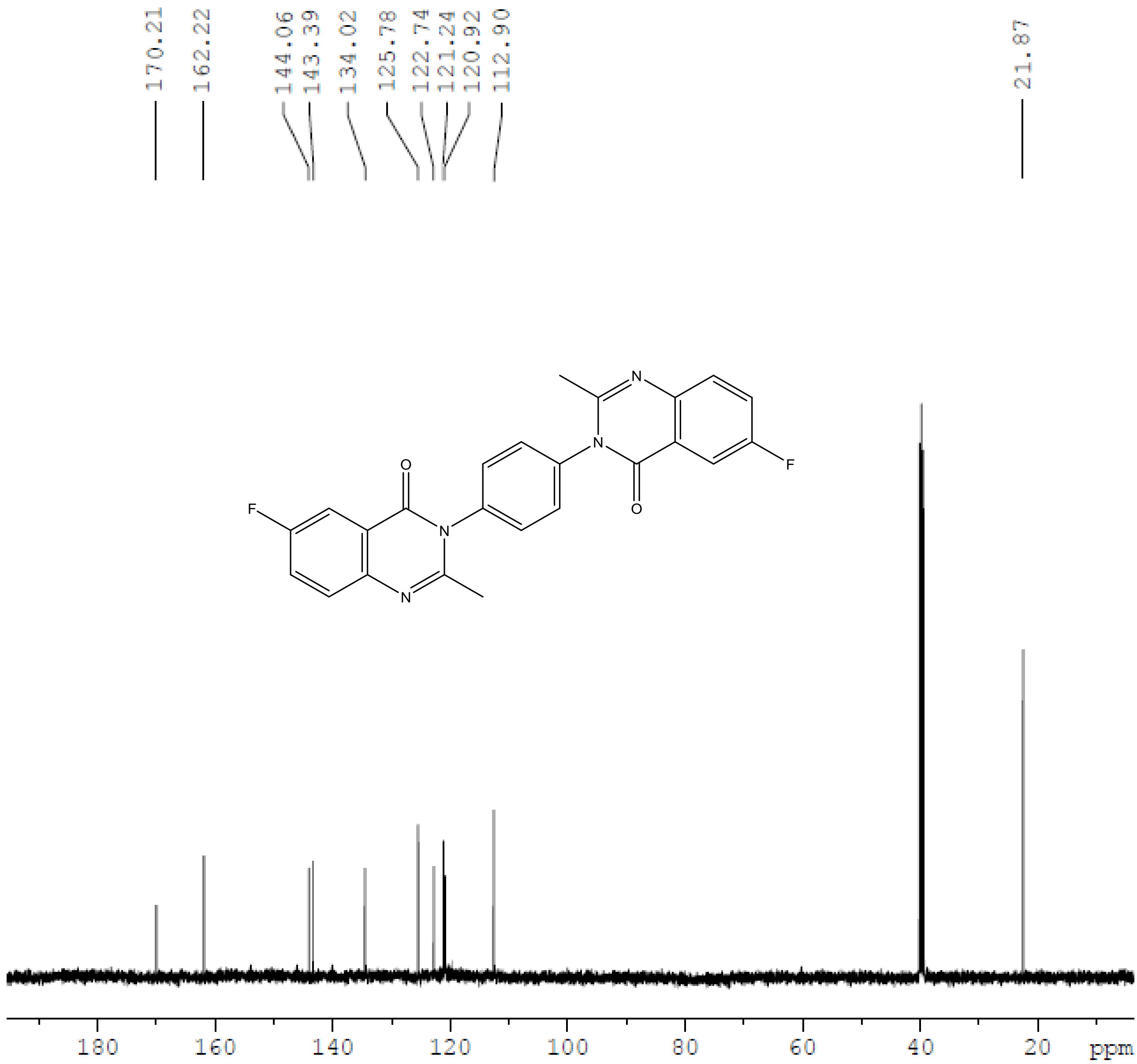
^{1}H NMR of **6c**


170.01
144.70
144.56
134.20
133.78
127.72
127.25
122.94
121.76
21.51
Cl
O
N
N
O
N
N
Cl
180
160
140
120
100
80
60
40
20
ppm

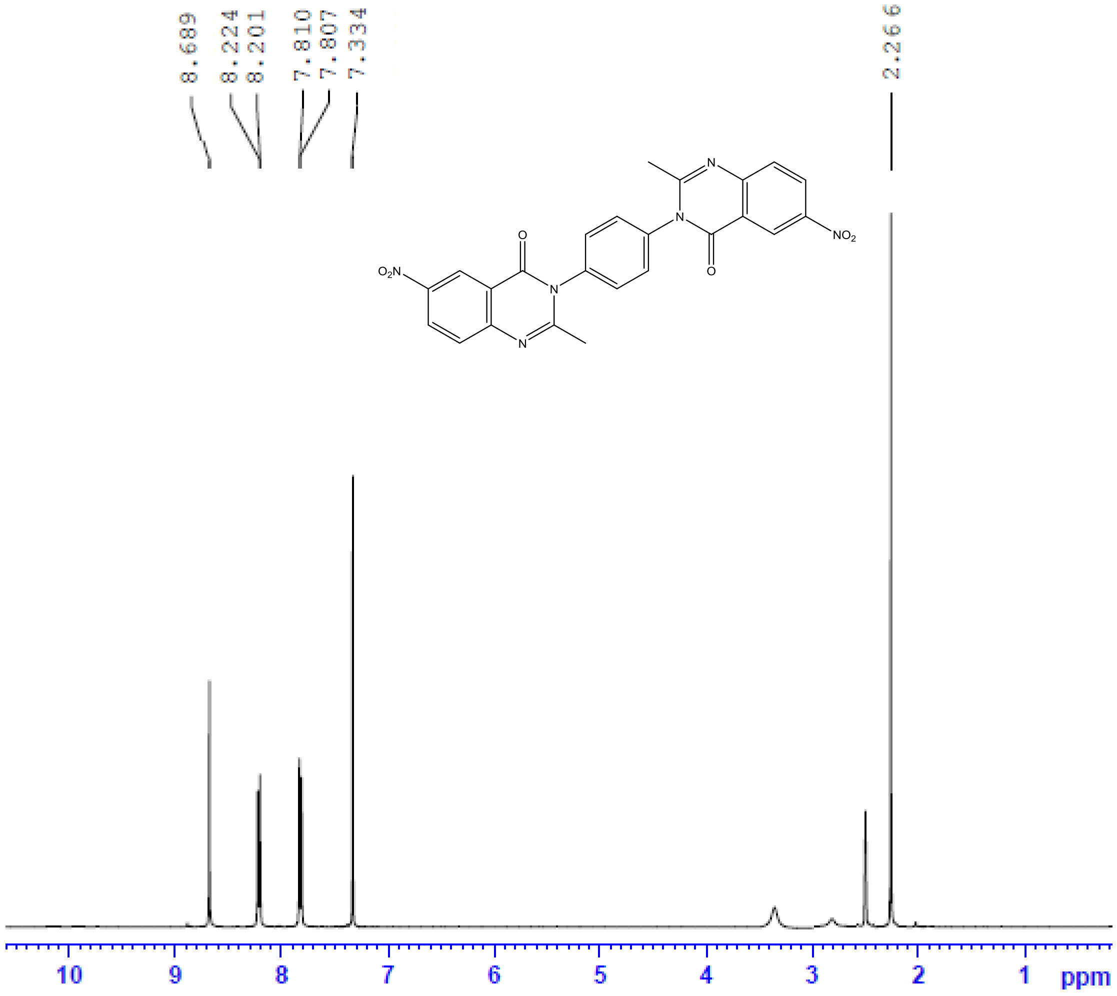
^{13}C NMR of **6c**


7.981
7.960
7.661
7.627
7.611
7.325
7.227
7.218
7.199
2.208
O
F
N
N
N
N
O
F
8.0
7.9
7.8
7.7
ppm
8
7
6
5
4
3
2
1
0
ppm

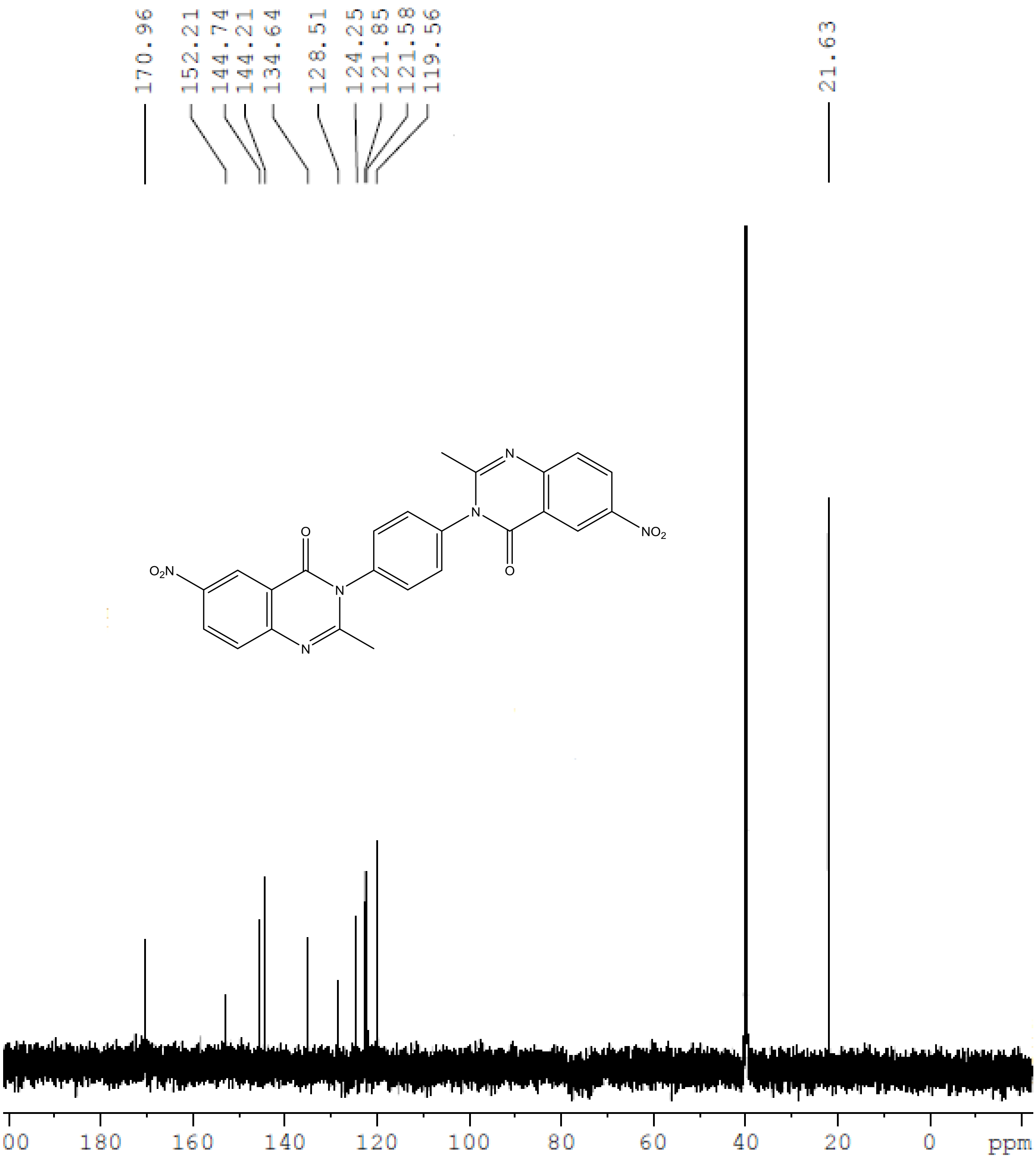
^{1}H NMR of **6d**


170.21
162.22
144.06
143.39
134.02
125.78
122.74
121.24
120.92
112.90
21.87
F
O
N
N
N
N
O
F
180
160
140
120
100
80
60
40
20
ppm

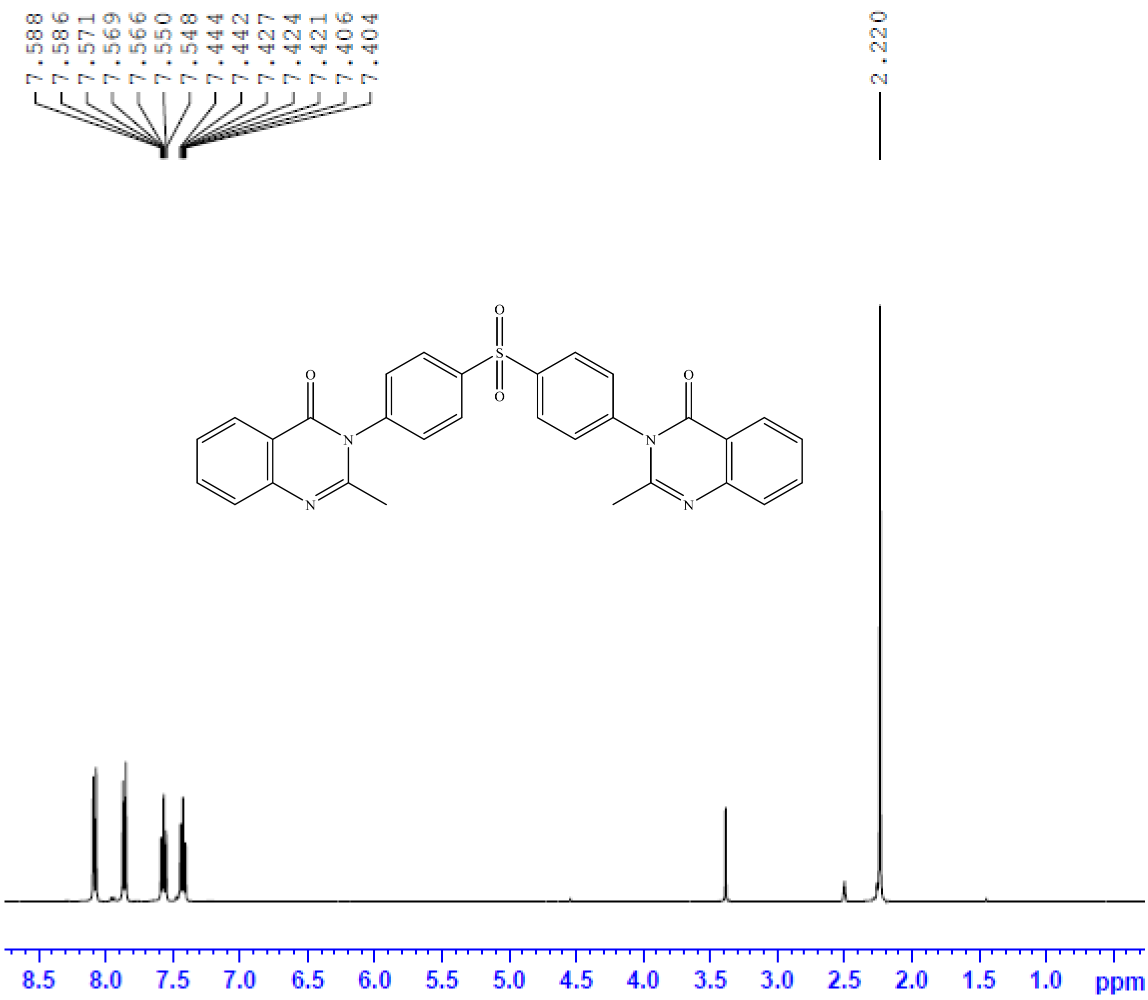
^{13}C NMR of **6d**



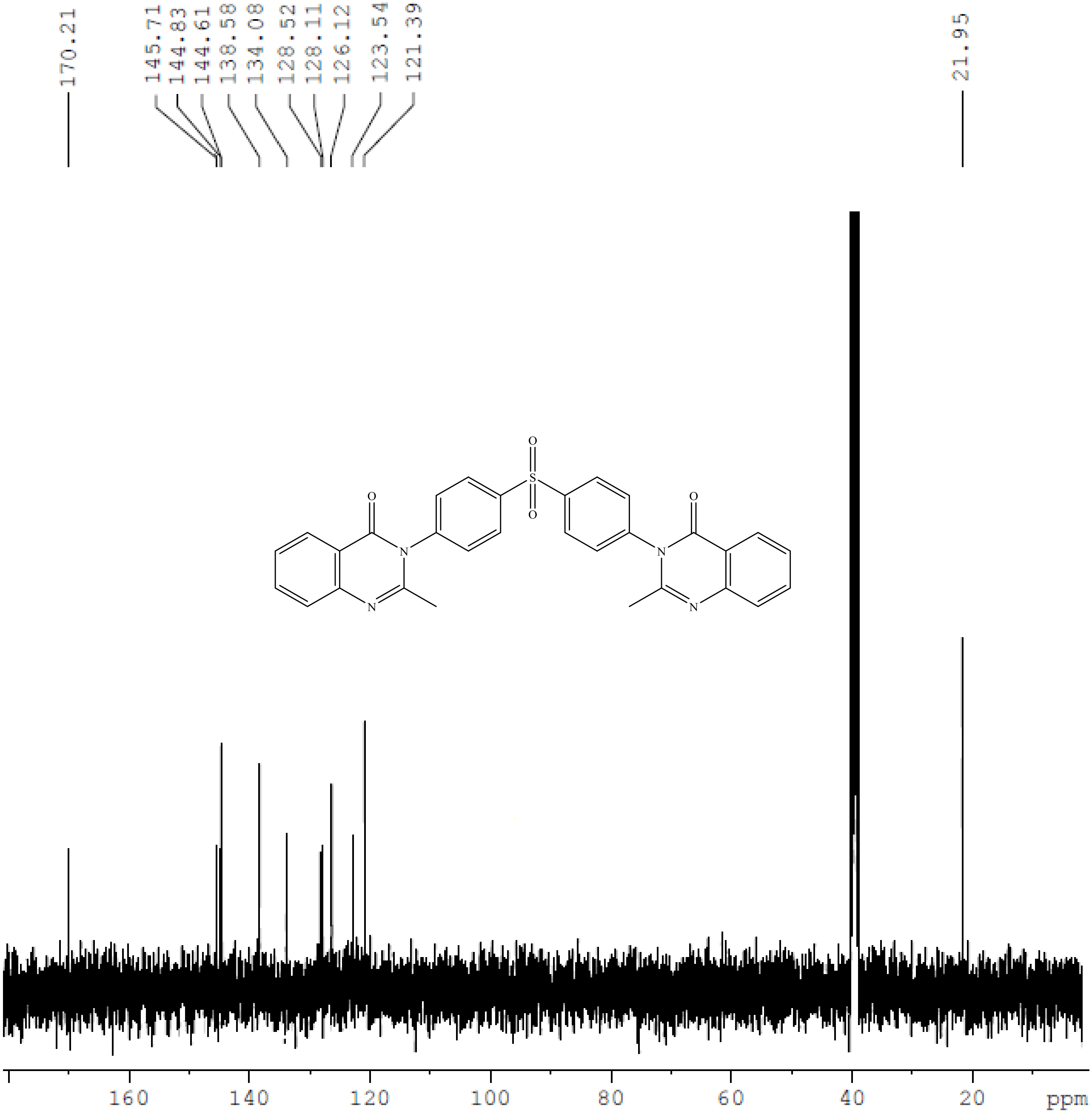
[1]H NMR of **6e**


170.96
152.21
144.74
144.21
134.64
128.51
124.25
121.85
121.58
119.56
21.63
N
N
O
NO_2
O_2N
O
N
N
00
180
160
140
120
100
80
60
40
20
0
ppm

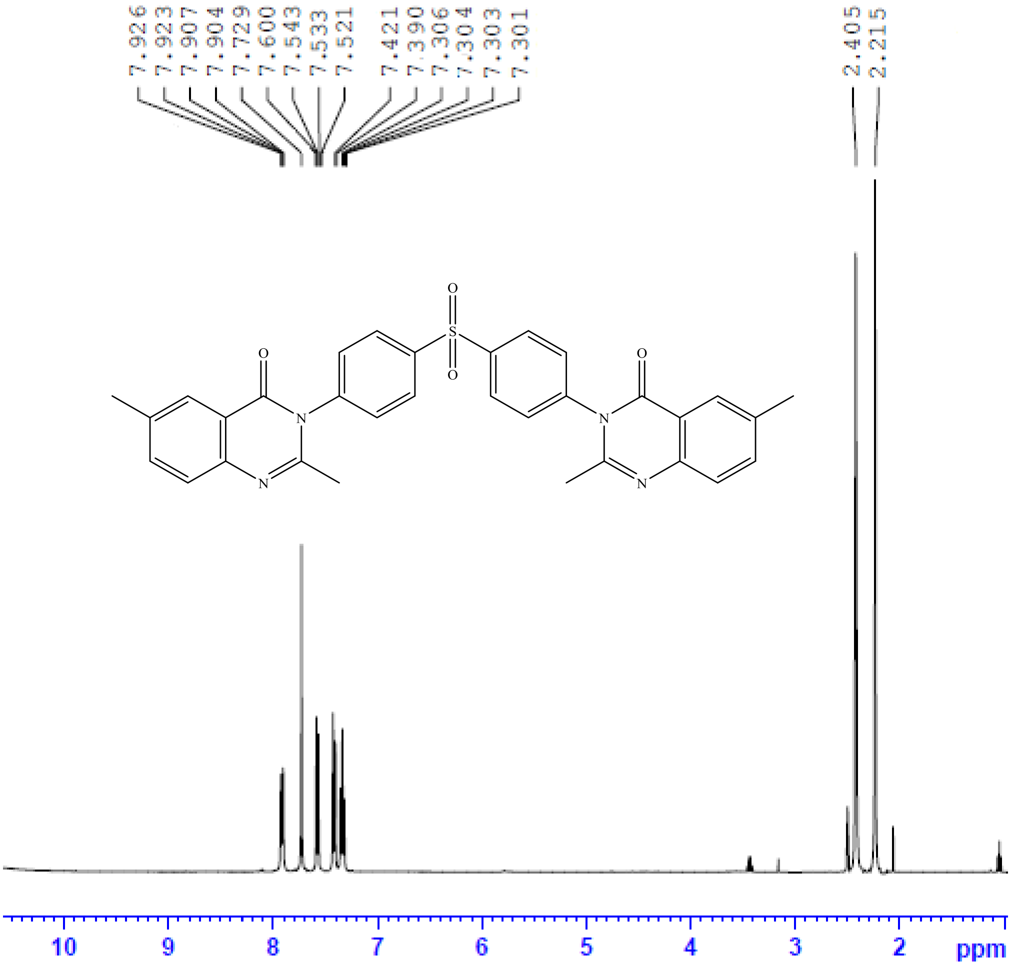
^{13}C NMR of **6e**


7.588
7.586
7.571
7.569
7.566
7.550
7.548
7.444
7.442
7.427
7.424
7.421
7.406
7.404
2.220
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
ppm

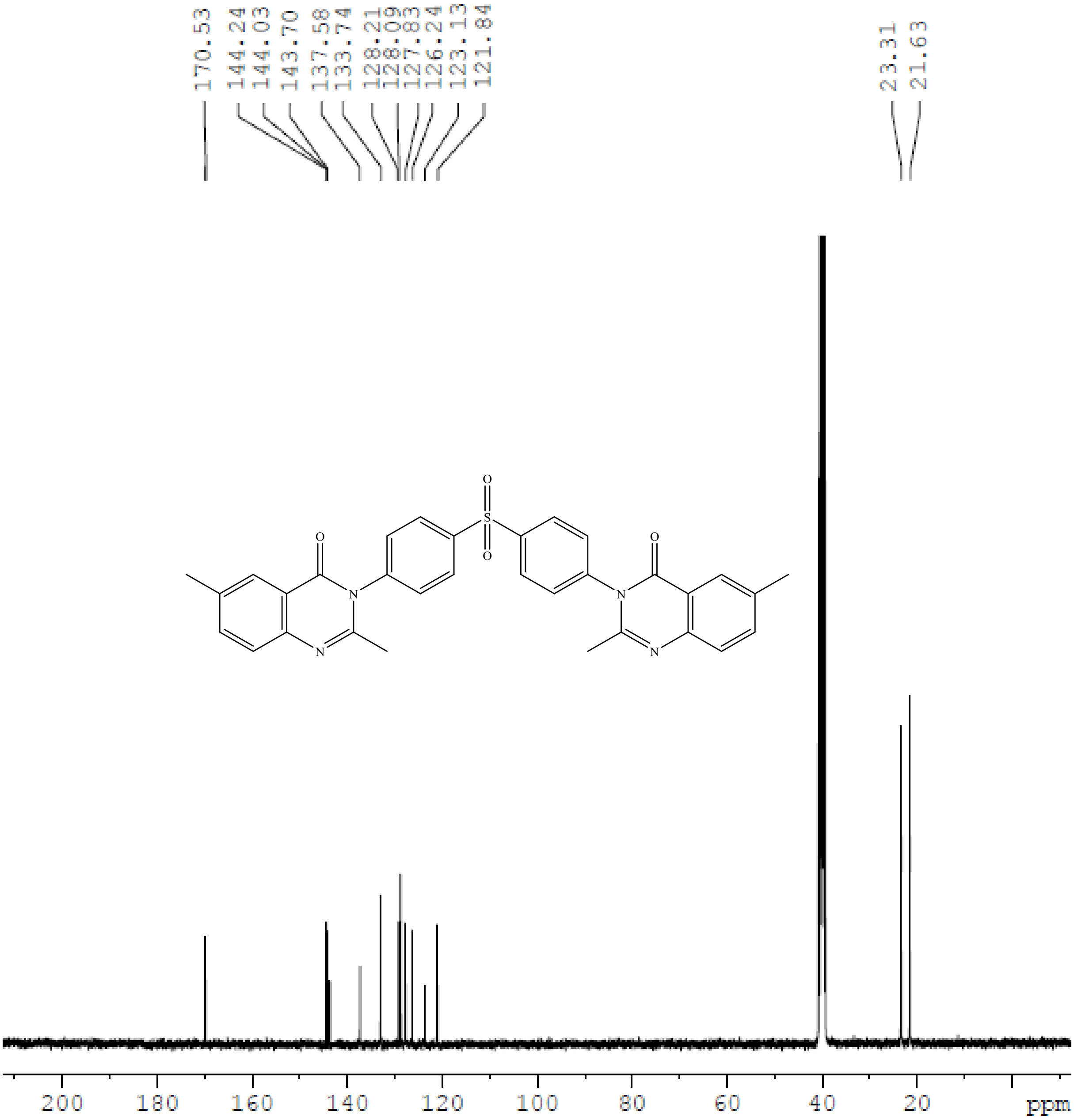
^{1}H NMR of **7a**


170.21
145.71
144.83
144.61
138.58
134.08
128.52
128.11
126.12
123.54
121.39
21.95
O
O
S
O
O
N
N
O
N
N
160
140
120
100
80
60
40
20
ppm

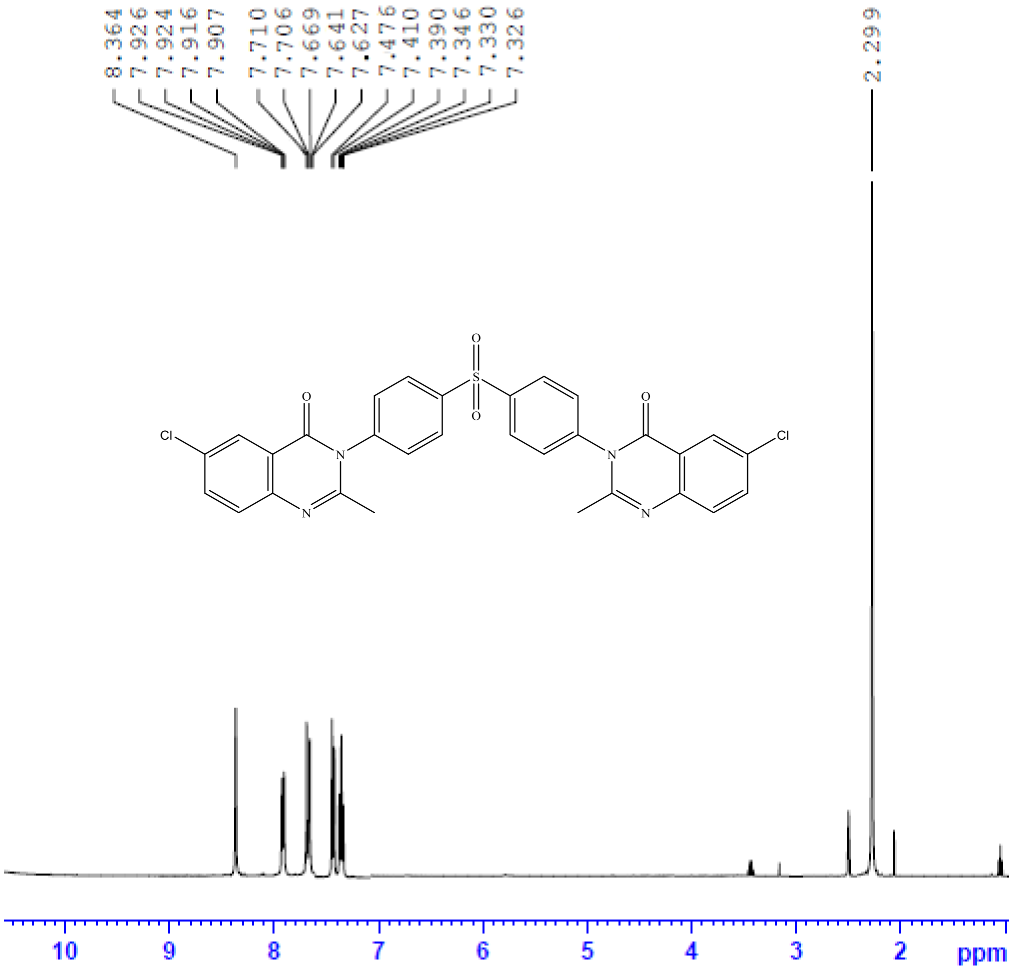
^{13}C NMR of **7a**


7.926
7.923
7.907
7.904
7.729
7.600
7.543
7.533
7.521
7.421
7.390
7.306
7.304
7.303
7.301
2.405
2.215
O
S
O
O
N
N
O
N
N
10
9
8
7
6
5
4
3
2
ppm

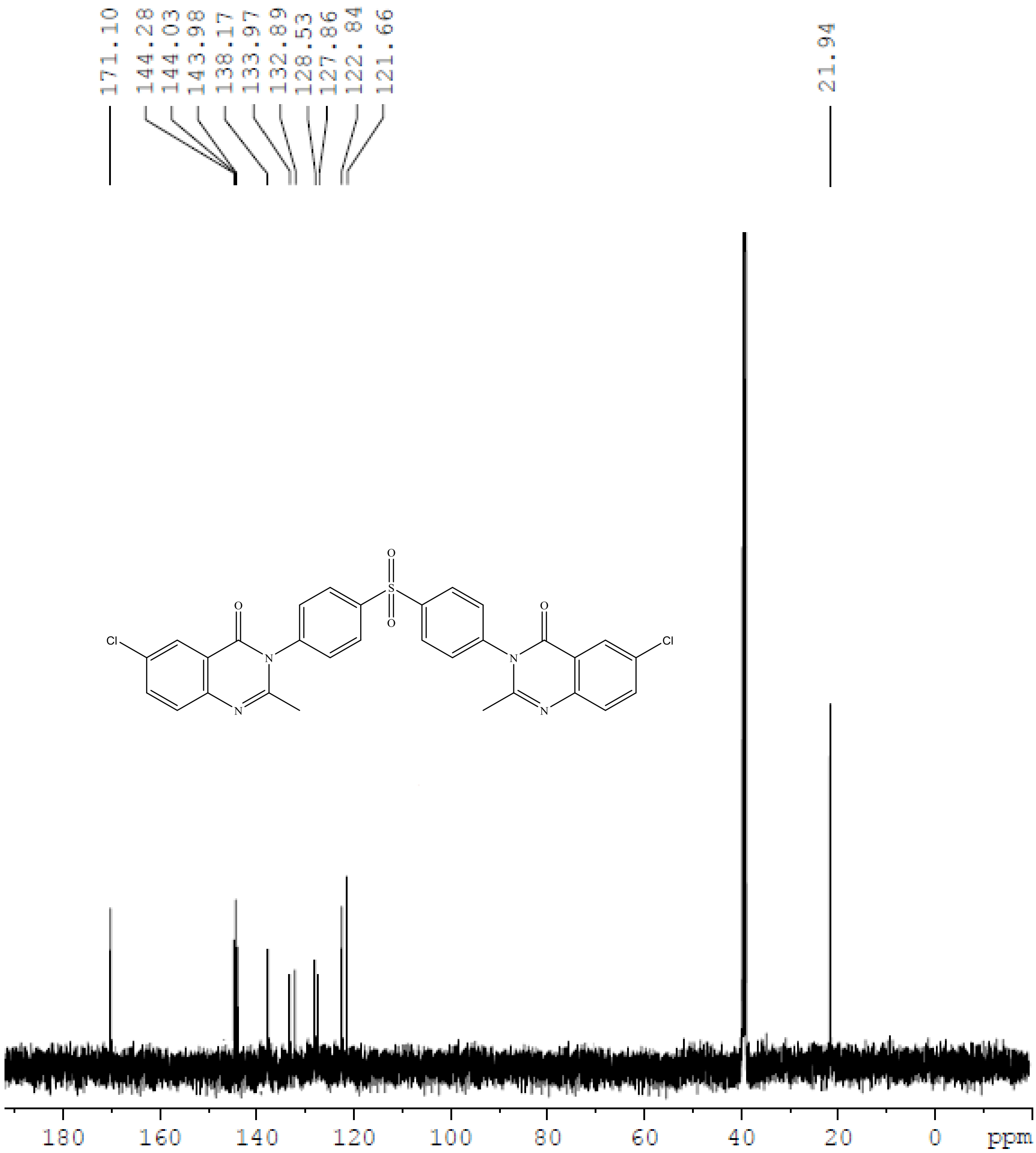
^{1}H NMR of **7b**


170.53
144.24
144.03
143.70
137.58
133.74
128.21
128.09
127.83
126.24
123.13
121.84
23.31
21.63
200
180
160
140
120
100
80
60
40
20
ppm

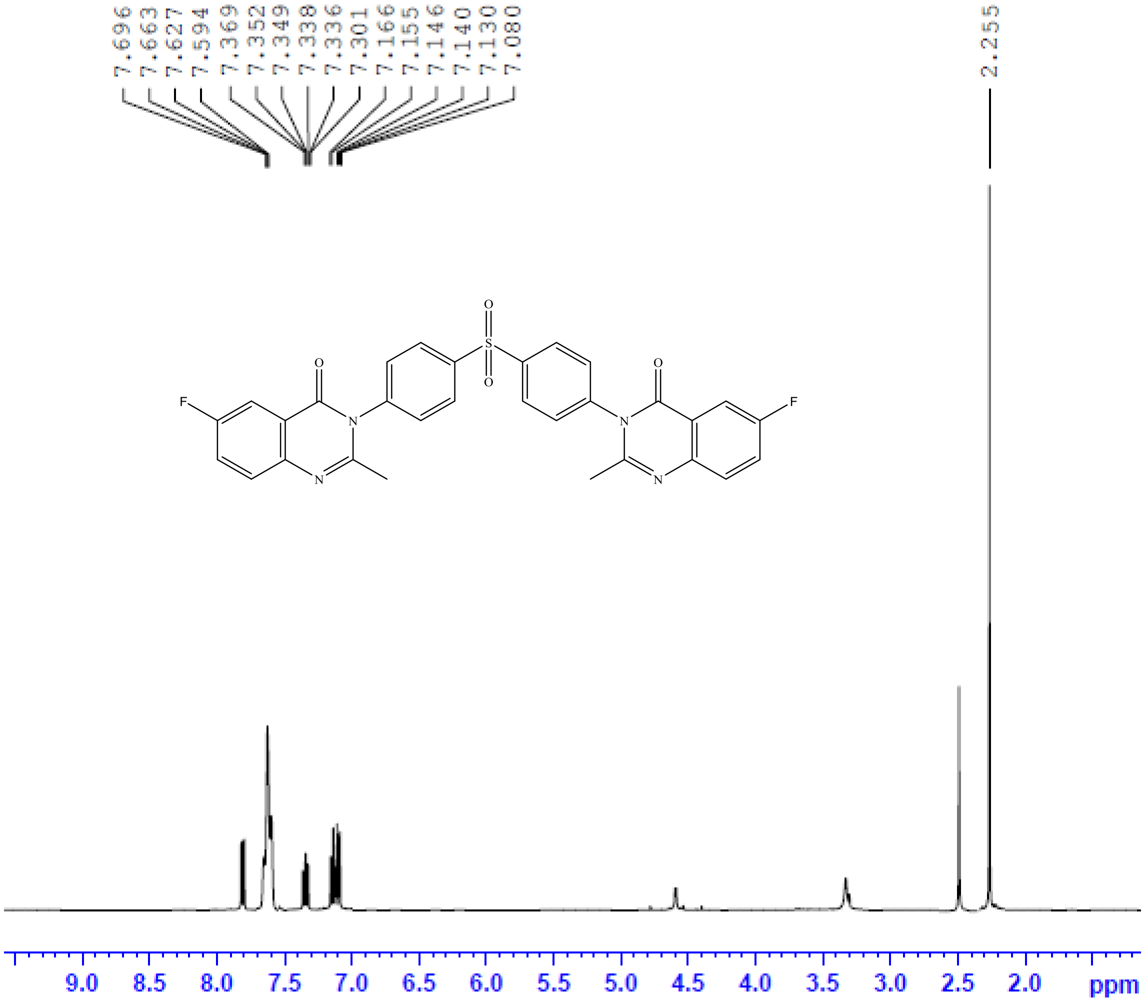
^{13}C NMR of **7b**


8.364
7.926
7.924
7.916
7.907
7.710
7.706
7.669
7.641
7.627
7.476
7.410
7.390
7.346
7.330
7.326
2.299
Cl
O
N
N
S
O
O
O
N
N
Cl
10
9
8
7
6
5
4
3
2
ppm

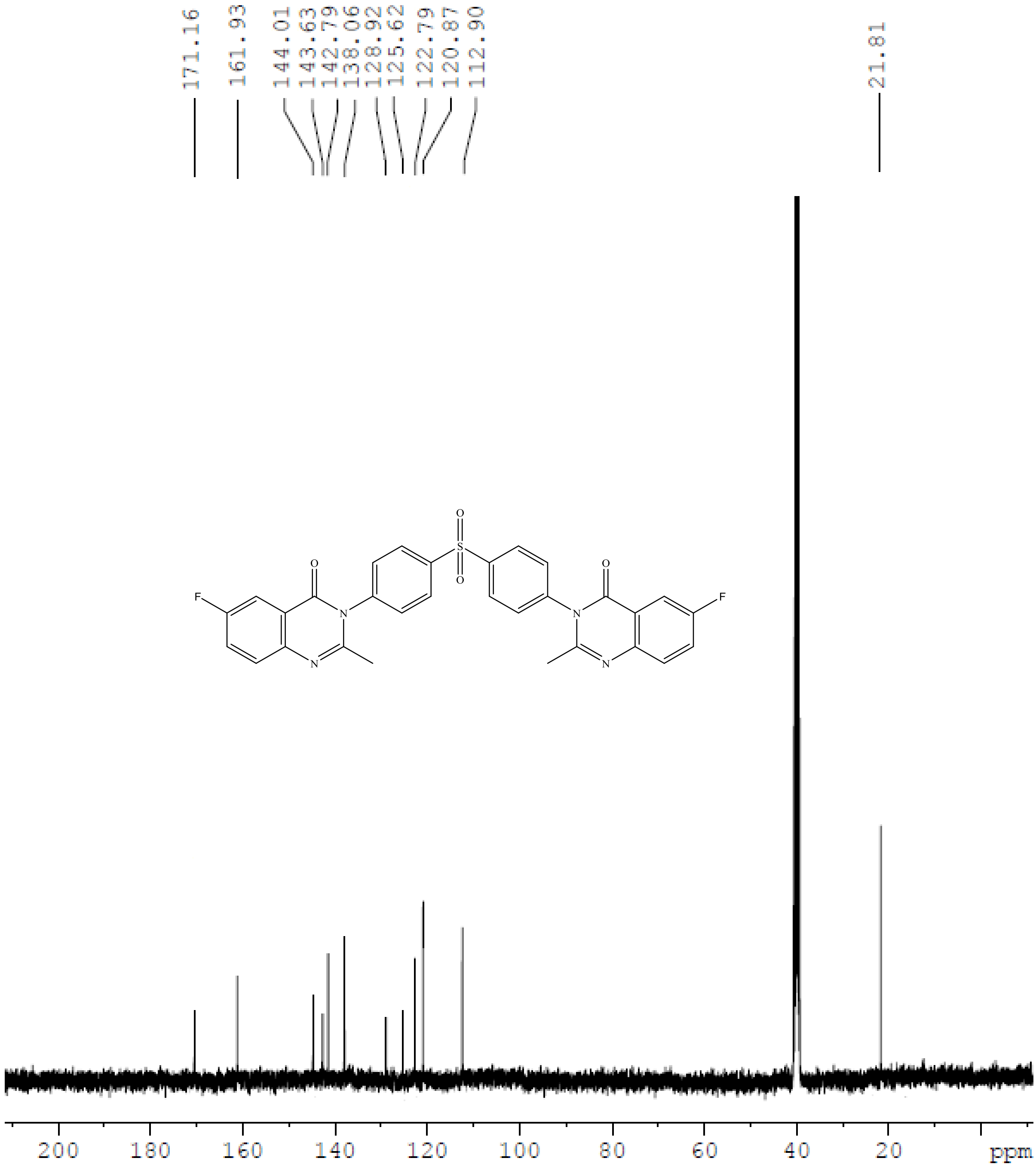
[1]H NMR of **7c**


171.10
144.28
144.03
143.98
138.17
133.97
132.89
128.53
127.86
122.84
121.66
21.94
Cl
O
N
N
O
S
O
O
N
N
Cl
180
160
140
120
100
80
60
40
20
0
ppm

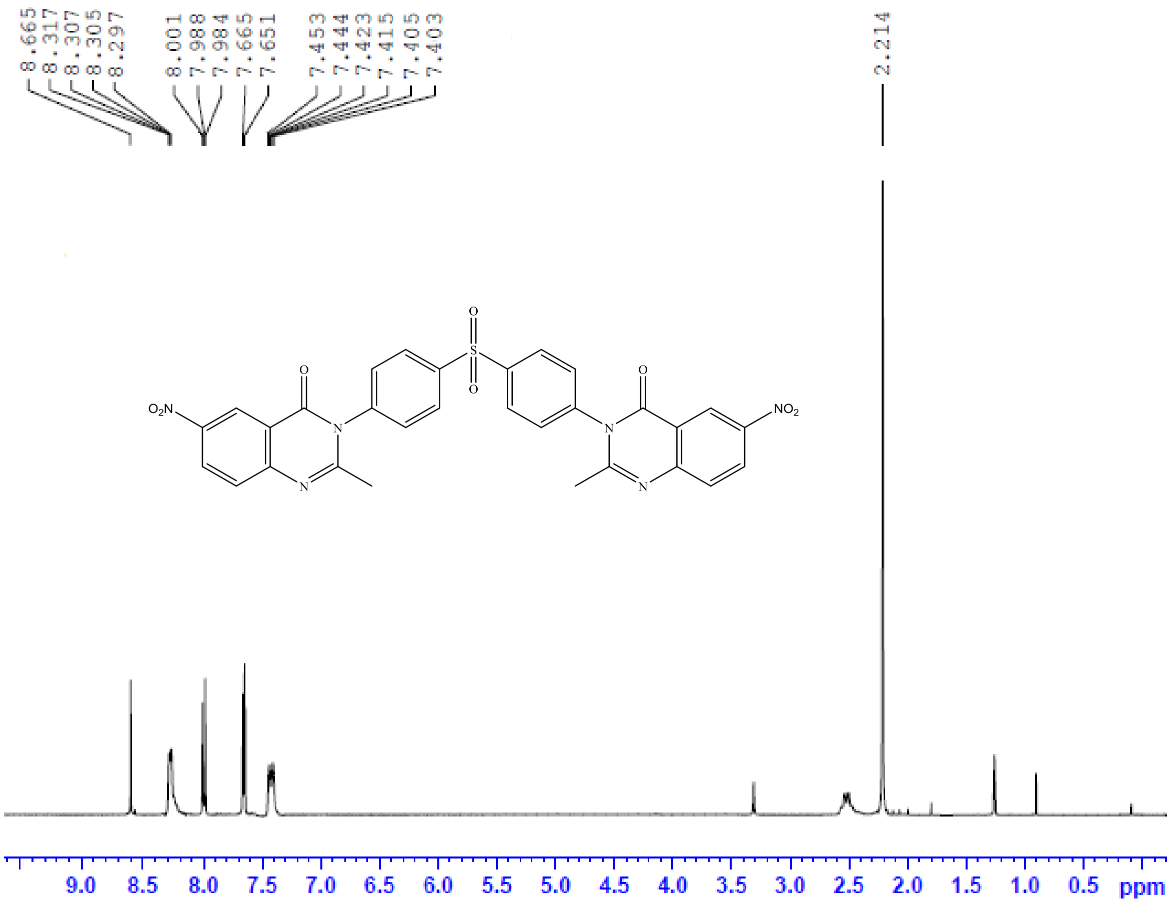
^{13}C NMR of **7c**


7.696
7.663
7.627
7.594
7.369
7.352
7.349
7.338
7.336
7.301
7.166
7.155
7.146
7.140
7.130
7.080
2.255
F
O
N
N
S
O
O
O
N
N
F
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 ppm

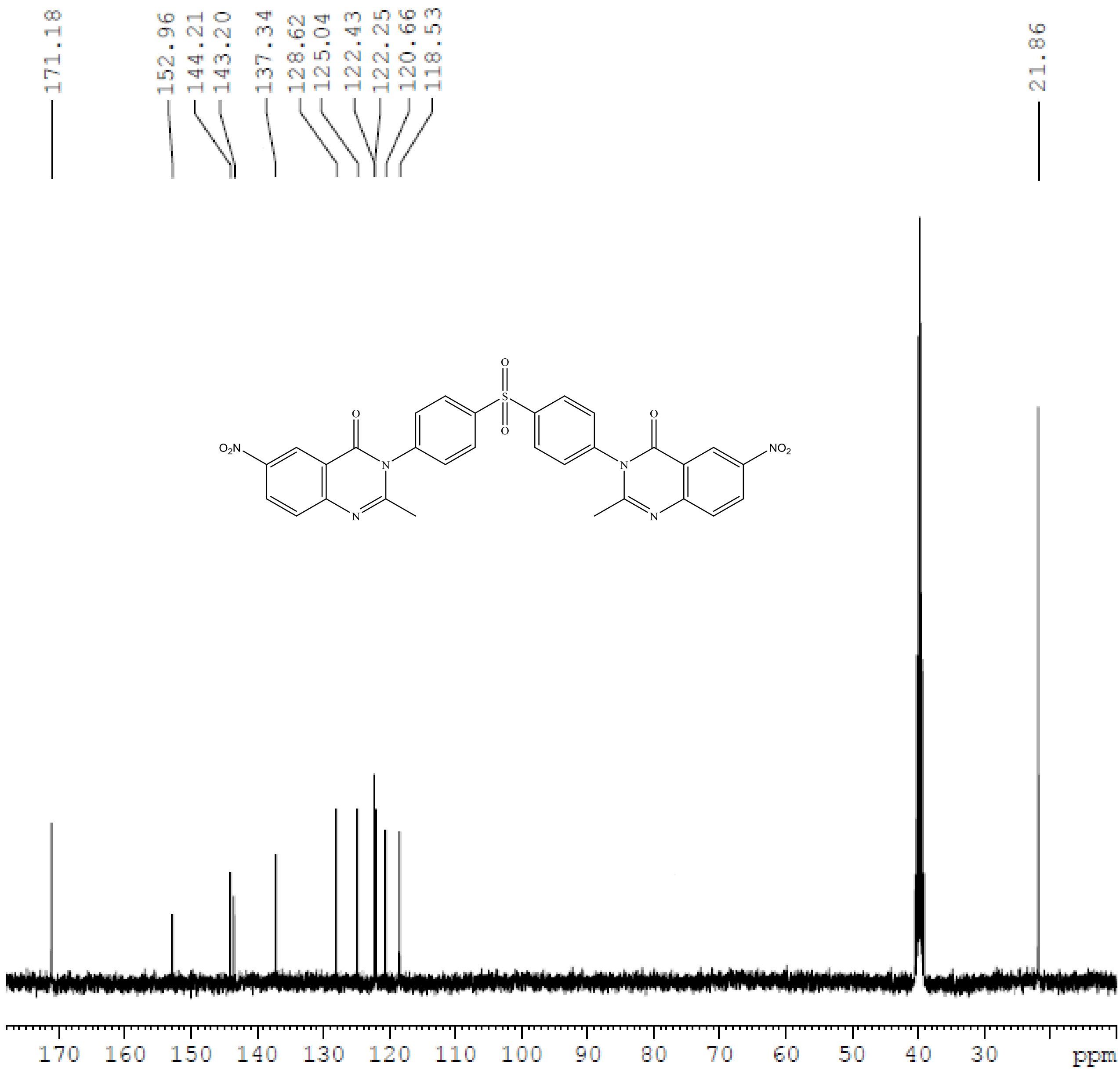
^{1}H NMR of **7d**


171.16
161.93
144.01
143.63
142.79
138.06
128.92
125.62
122.79
120.87
112.90
21.81
200
180
160
140
120
100
80
60
40
20
ppm

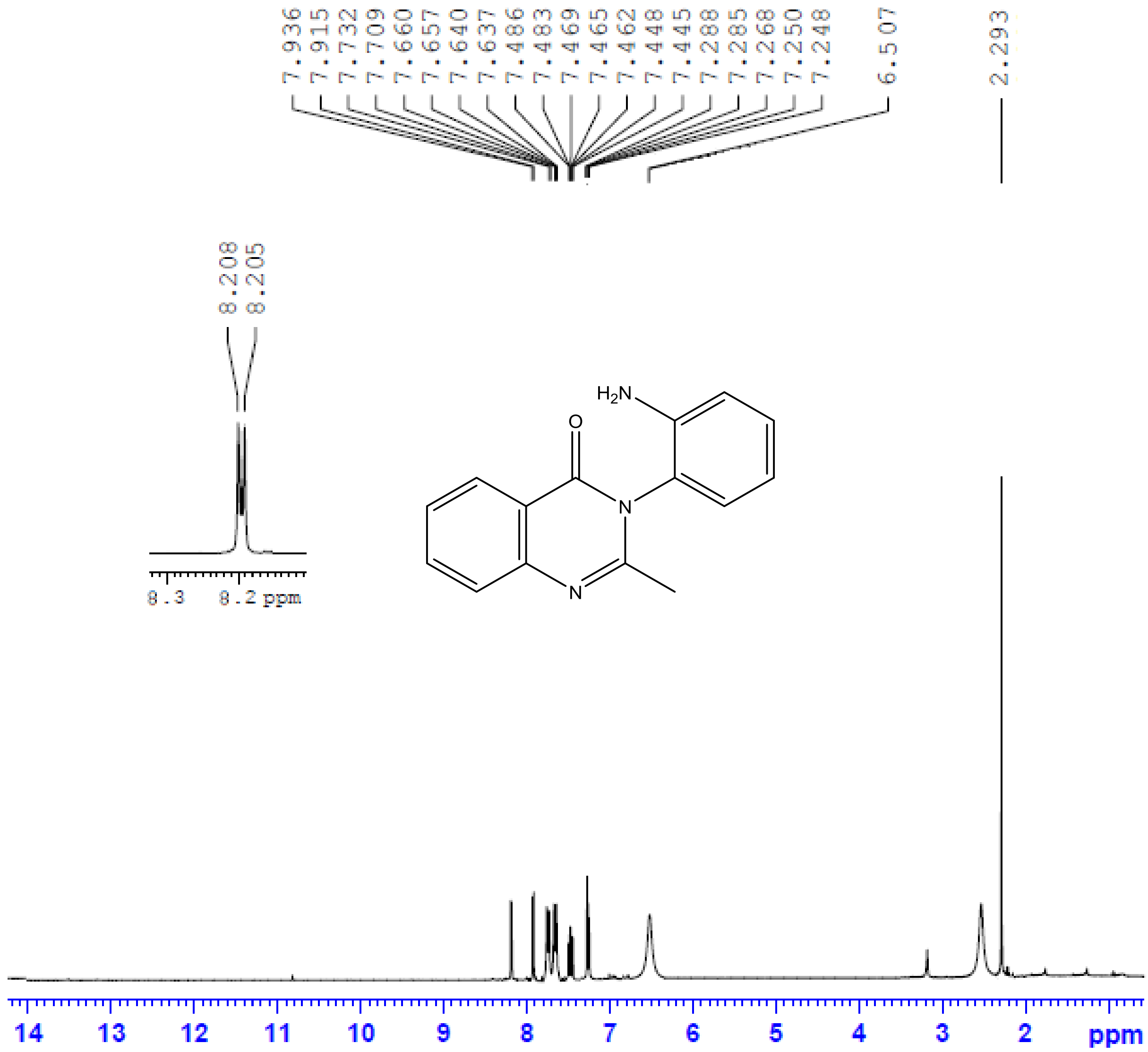
^{13}C NMR of **7d**


8.665
8.317
8.307
8.305
8.297
8.001
7.988
7.984
7.665
7.651
7.453
7.444
7.423
7.415
7.405
7.403
2.214
O
S
O
O
O
O₂N
N
N
N
N
NO₂
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
ppm

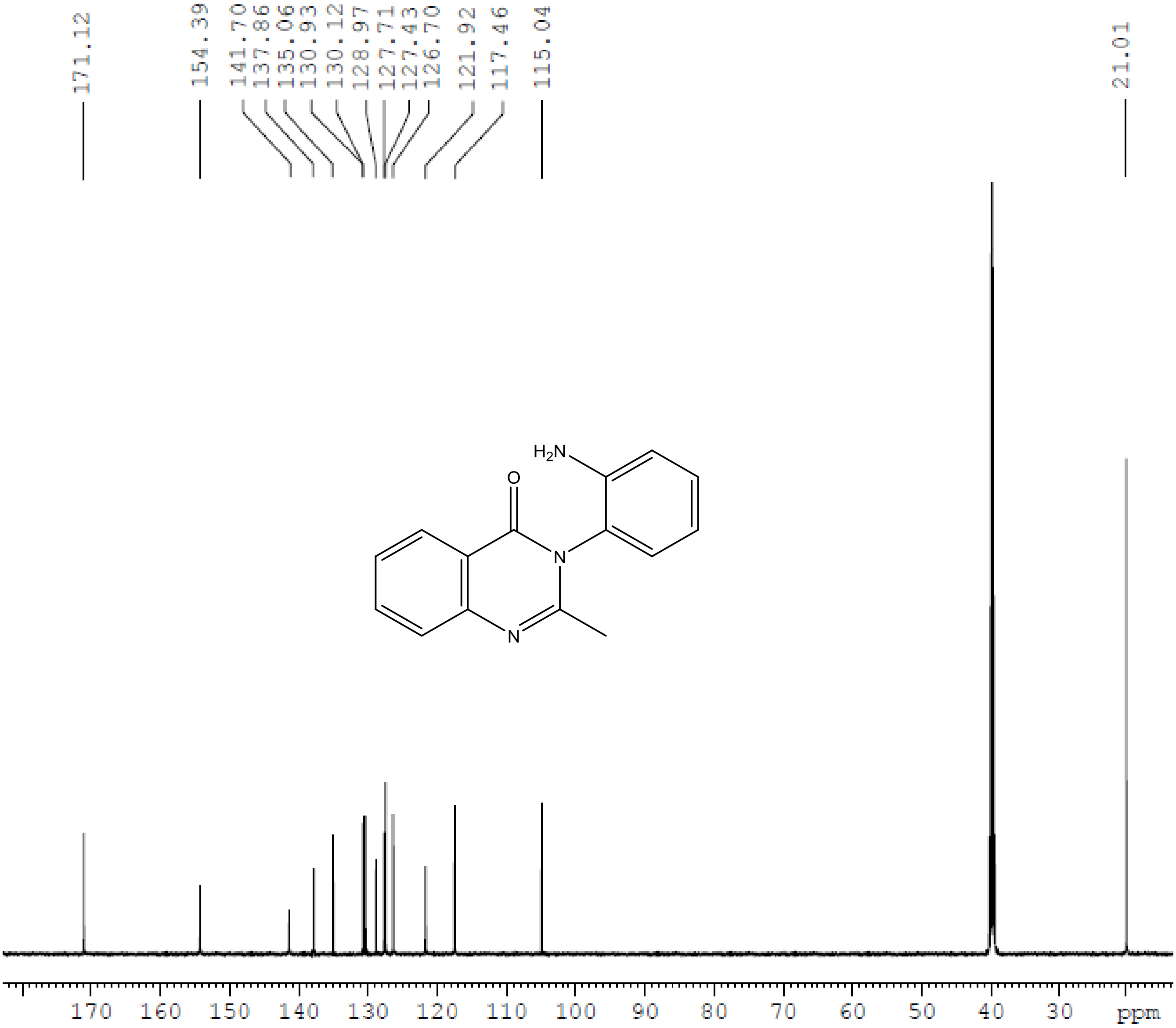
^{1}H NMR of **7e**


171.18
152.96
144.21
143.20
137.34
128.62
125.04
122.43
122.25
120.66
118.53
21.86
O
O
S
O
O
O_2N
N
N
N
N
NO_2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

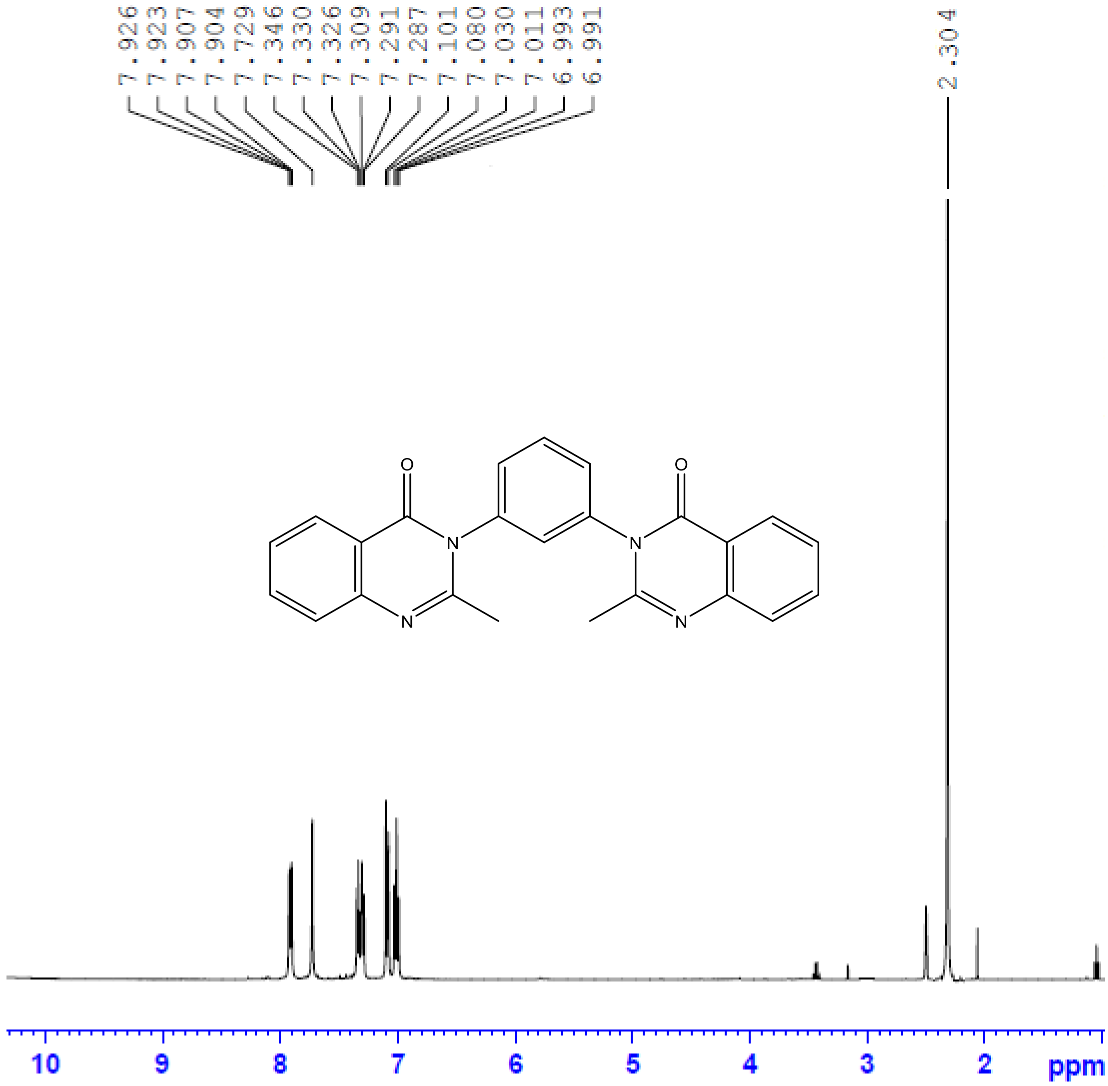
^{13}C NMR of **7e**


7.936
7.915
7.732
7.709
7.660
7.657
7.640
7.637
7.486
7.483
7.469
7.465
7.462
7.448
7.445
7.288
7.285
7.268
7.250
7.248
6.507
2.293
8.208
8.205
8.3
8.2 ppm
H2N
O
N
N
14
13
12
11
10
9
8
7
6
5
4
3
2
ppm

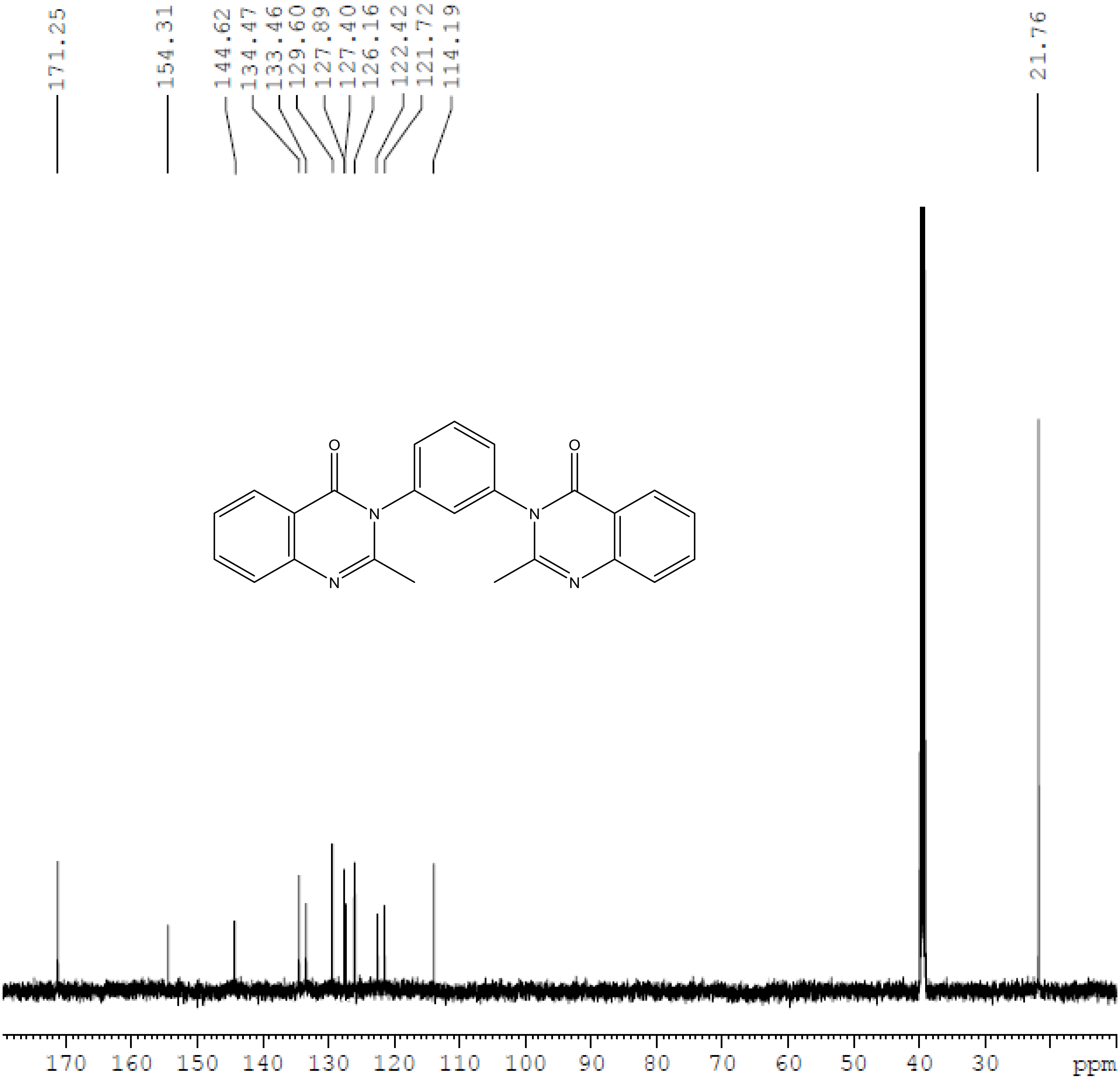
^{1}H NMR of **8**


171.12
154.39
141.70
137.86
135.06
130.93
130.12
128.97
127.71
127.43
126.70
121.92
117.46
115.04
21.01
H2N
O
N
N
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

^{13}C NMR of **8**

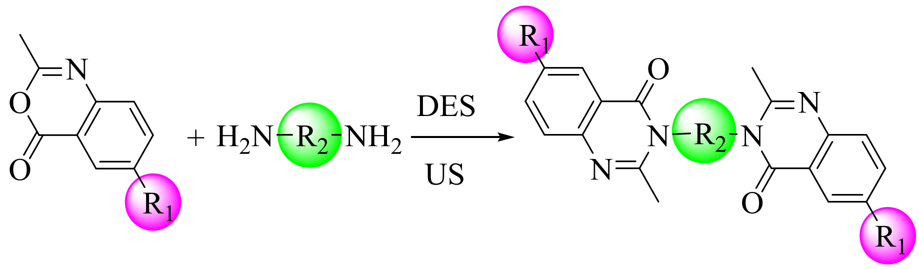

7.926
7.923
7.907
7.904
7.729
7.346
7.330
7.326
7.309
7.291
7.287
7.101
7.080
7.030
7.011
6.993
6.991
2.304
O
N
N
O
N
N
10
9
8
7
6
5
4
3
2
ppm

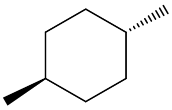
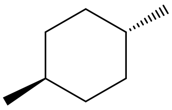
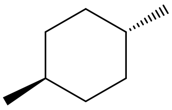
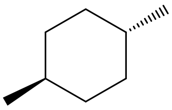
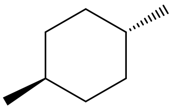
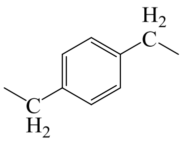
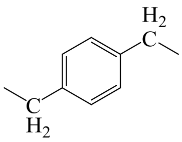
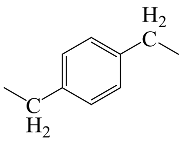
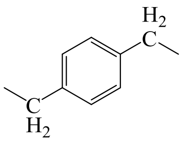
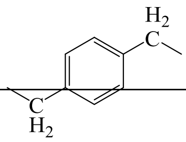
^{1}H NMR of **11**

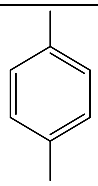
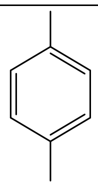
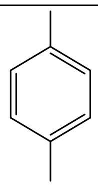
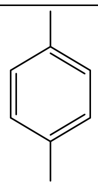
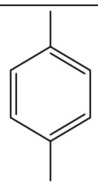
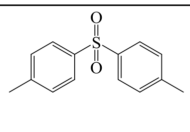

171.25
154.31
144.62
134.47
133.46
129.60
127.89
127.40
126.16
122.42
121.72
114.19
21.76
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
ppm

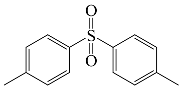
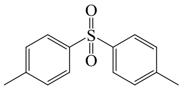
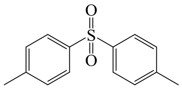
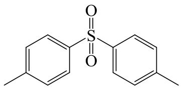
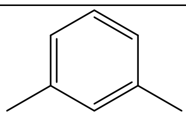
^{13}C NMR of **11**

Table 3. The anti-proliferative activities of the newly prepared bis-quinazolinone derivatives against human cancer cell lines.



Compd.	R_1	R_2	Conc.&IC_{50}	Cells viability (%)	
				MCF-7 (µM)	A549 (µM)
3a	H		10 µM	51.00 ± 2.02	60.16 ± 1.56
			30 µM	57.95 ± 1.45	97.20 ± 0.41
			IC_{50} µM	9.78	8.15
3b	CH_3		10 µM	31.52 ± 1.82	39.33 ± 2.76
			30 µM	94.90 ± 0.46	90.12 ± 0.25
			IC_{50} µM	12.70	15.70
3c	Cl		10 µM	56.64 ± 2.23	61.12 ± 1.82
			30 µM	86.85 ± 0.89	96.98 ± 0.40
			IC_{50} µM	9.05	8.14
3d	F		10 µM	69.73 ± 2.31	67.49 ± 0.27
			30 µM	89.10 ± 1.93	89.95 ± 043
			IC_{50} µM	7.11	8.11
3e	NO_2		10 µM	83.12 ± 1.61	77.06 ± 1.78
			30 µM	81.18 ± 0.55	82.85 ± 1.64
			IC_{50} µM	4.55	5.34
4a	H		10 µM	79.06 ± 2.70	60.37 ± 3.31
			30 µM	89.85 ± 1.02	62.90 ± 1.45
			IC_{50} µM	5.38	6.11
4b	CH_3		10 µM	78.02 ± 2.63	75.98 ± 2.21
			30 µM	96.50 ± 0.20	78.71 ± 1.76
			IC_{50} µM	6.73	6.79
4c	Cl		10 µM	76.84 ± 1.24	79.50 ± 2.61
			30 µM	81.08 ± 1.72	81.75 ± 0.87
			IC_{50} µM	4.65	6.07
4d	**F**		10 µM	60.25 ± 3.31	94.29 ± 0.39
			30 µM	61.92 ± 1.01	96.09 ± 0.244
			IC_{50} µM	6.19	5.55
4e	NO_2		10 µM	95.58 ± 0.26	80.22 ± 2.10
			30 µM	95.26 ± 0.90	87.03 ± 1.45

			IC_{50} µM	2.75	2.98
5a	H	$-CH_2-CH_2-$	10 µM	51.03 ± 1.92	32.44 ± 2.91
			30 µM	58.07 ± 1.55	88.68 ± 1.83
			IC_{50} µM	9.79	12.32
5b	CH_3	$-CH_2-CH_2-$	10 µM	27.07 ± 1.70	39.99 ± 2.11
			30 µM	87.65 ± 1.24	89.67 ± 1.76
			IC_{50} µM	13.55	15.73
5c	Cl	$-CH_2-CH_2-$	10 µM	80.22 ± 2.10	61.87 ± 2.34
			30 µM	87.03 ± 1.45	82.10 ± 1.93
			IC_{50} µM	6.12	7.98
5d	**F**	$-CH_2-CH_2-$	10 µM	76.84 ± 1.24	54.49 ± 0.27
			30 µM	81.08 ± 1.72	89.95 ± 043
			IC_{50} µM	5.39	7.95
5e	NO_2	$-CH_2-CH_2-$	10 µM	91.11 ± 1.87	91.54 ± 0.56
			30 µM	92.80 ± 2.52	97.83 ± 0.24
			IC_{50} µM	5.21	5.05
6a	H		10 µM	75.50 ± 2.17	54.49 ± 0.27
			30 µM	79.02 ± 0.90	89.95 ± 043
			IC_{50} µM	6.98	8.41
6b	CH_3		10 µM	61.13 ± 2.35	59.16 ± 1.53
			30 µM	82.84 ± 0.92	95.12 ± 0.22
			IC_{50} µM	7.48	8.13
6c	Cl		10 µM	94.78 ± 0.49	91.98 ± 0.49
			30 µM	96.88 ± 0.21	98.02 ± 0.21
			IC_{50} µM	5.53	5.15
6d	**F**		10 µM	54.22 ± 2.78	82.65 ± 1.67
			30 µM	86.56 ± 1.54	81.78 ± 0.45
			IC_{50} µM	5.70	4.54
6e	NO_2		10 µM	95.26 ± 0.45	95.40 ± 0.24
			30 µM	95.87 ± 0.21	97.60 ± 0.21
			IC_{50} µM	2.73	3.43
7a	H		10 µM	72.68 ± 0.79	82.73 ± 1.63
			30 µM	89.08 ± 0.94	82.10 ± 0.50
			IC_{50} µM	4.24	4.58

7b	CH_3		10 µM	53.03 ± 2.29	53.13 ± 2.20
			30 µM	86.90 ± 1.24	86.84 ± 1.19
			IC_{50} µM	5.78	5.77
7c	Cl		10 µM	93.82 ± 0.49	72.34 ± 0.78
			30 µM	96.21 ± 0.34	88.43 ± 0.19
			IC_{50} µM	3.91	4.21
7d	**F**		10 µM	61.03 ± 2.82	96.46 ± 0.65
			30 µM	78.09 ± 1.79	96.68 ± 0.17
			IC_{50} µM	1.46	3.45
7e	NO_2		10 µM	81.08 ± 1.77	95.99 ± 0.14
			30 µM	86.97 ± 1.26	96.76 ± 0.87
			IC_{50} µM	1.26	2.75
11	H		10 µM	61.80 ± 1.11	79.8 ± 1.05
			30 µM	88.54 ± 1.09	83.20 ± 1.02
			IC_{50} µM	5.42	5.94
Sorafenib			10 µM	69.85 ± 1.02	89.8 ± 1.14
			30 µM	90.79 ± 1.43	91.21 ± 1.44
			IC_{50} µM	4.03	5.20

Green Metrics Calculations[1,2]

$$\textbf{\% Atomic Efficiency (AE)} = \frac{\text{Mol Wt. of desired product}}{\text{Mol Wt. of all reagents}} \times 100$$

$$\textbf{\% Carbon Efficiency (CE)} = \frac{\text{Mass of carbon in product}}{\text{Totall mass of carbon in the reactants}} \times 100$$

$$\textbf{Reaction Mass Efficiency (RME)} = \frac{\text{Mass of the isolated product}}{\text{Total mass of reactants used in the reaction}} \times 100$$

$$\textbf{\% Yield Economy (YE)} = \frac{\text{Reaction percent}}{\text{Time in min}} \times 100$$

$$\textbf{E-Factor (EF)} = \frac{\text{Mass of the total waste}}{\text{Mass of the crude product}}$$

$$\textbf{Process Mass Intensity (PMI)} = \frac{\text{Total mass used in process}}{\text{Mass of product}}$$

References

1. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1-6.
2. C. Jimenez-Gonzalez, D. J. C. Constable and C. S. Ponder, *Chem. Soc. Rev.*, 2012, **41**, 1485-1498.