Supporting Information

Novel HIV-1 Capsid-Targeting Small Molecules of the PF74 Binding Site

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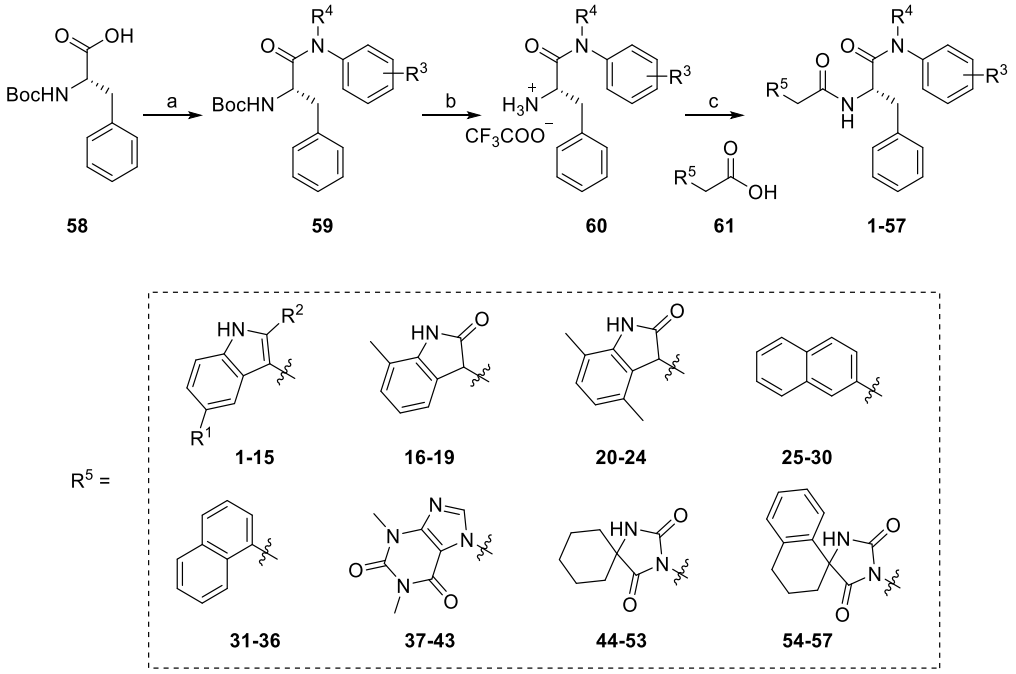
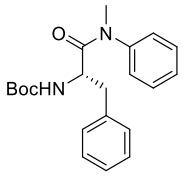
Synthesis of intermediates



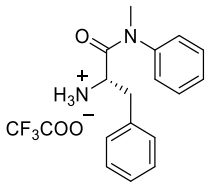
Reagents and conditions: (a) amine, HATU (or T_3P), DIPEA, DMF, rt, 12 h; (b) TFA; DCM, rt, 4-6 h; (c) HATU, DIPEA, DMF, rt, 12 h.

Synthesis of ***59*****:** To a solution of commercially available (*tert*-butoxycarbonyl)-*L*-phenylalanine (1.0 g, 3.8 mmol, 1 equiv.) in DMF (5 mL), HATU or T_3P (2 equiv.) and DIPEA (2 equiv.) were added and the mixture was stirred at room temperature for 20 min before amine (1.5 equiv.) was added. The mixture was further stirred at room temperature overnight. Upon completion, H_2O was added and the reaction mixture was extracted with EtOAc (3x50 mL). The organic phases were combined and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The product was purified by Combi-flash on silica gel using EtOAc/hexane (1:4 to 2:1) as eluent.

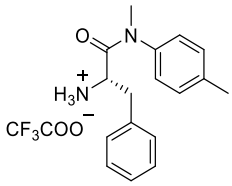


Yield 68-89%. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 3H), 7.20 – 7.19 (m, 3H), 6.94 – 6.80 (m, 4H), 5.17 (d, *J* = 9.0 Hz, 1H), 4.53 (q, *J* = 7.5, 6.8 Hz, 1H), 3.21 (s, 3H), 2.87 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.69 (dd, *J* = 13.0, 6.8 Hz, 1H), 1.38 (s, 9H).

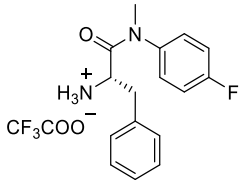
*Synthesis of **60*:** TFA (5 equiv.) was added dropwise to a solution of **59** (1 equiv.) in DCM (5 mL) and the mixture was stirred at room temperature for 4-6 h. The solvent was evaporated to give the product as a TFA salt.



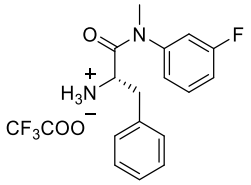
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.36 – 7.31 (m, 3H), 7.20 – 7.14 (m, 3H), 6.96 – 6.90 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 3.30 (t, *J* = 6.8 Hz, 1H), 3.06 (s, 3H), 2.71 (dd, *J* = 12.7, 6.8 Hz, 1H), 2.43 (dd, *J* = 13.2, 7.8 Hz, 1H).



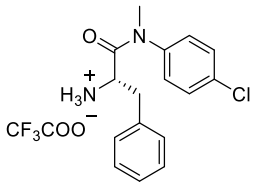
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.20 – 7.12 (m, 5H), 6.86 – 6.80 (m, 4H), 3.33 – 3.30 (m, 1H), 3.02 (s, 3H), 2.71 (dd, *J* = 13.1, 7.3 Hz, 1H), 2.44 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.28 (s, 3H).



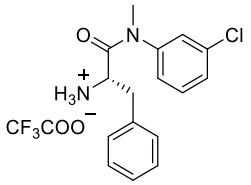
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H), 6.98 – 6.93 (m, 5H), 4.09 – 4.06 (m, 1H), 3.12 (s, 3H), 3.05 – 3.04 (m, 2H).



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 5H), 7.00 – 6.97 (m, 4H), 4.17 – 4.14 (m, 1H), 3.11 (s, 3H), 3.10 – 3.03 (m, 2H).



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 6H), 6.98 – 6.97 (m, 3H), 4.12 – 4.10 (m, 1H), 3.10 (s, 3H), 3.08 – 3.02 (m, 2H).



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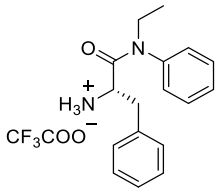
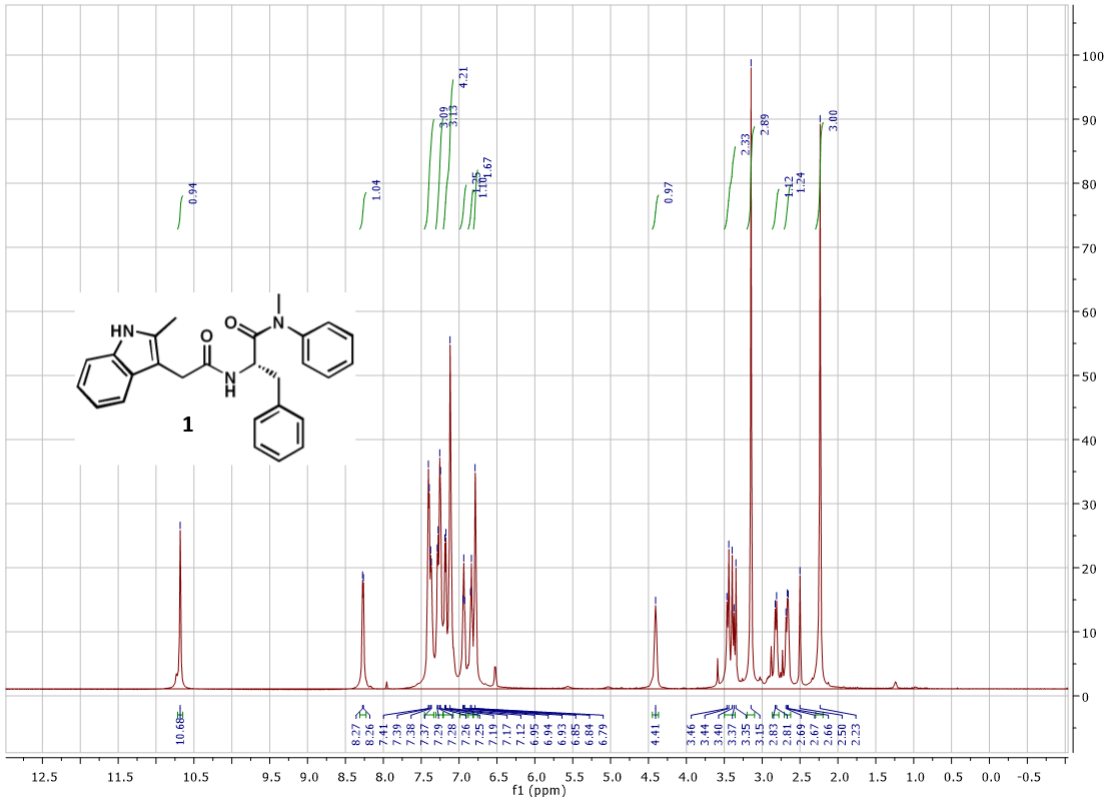
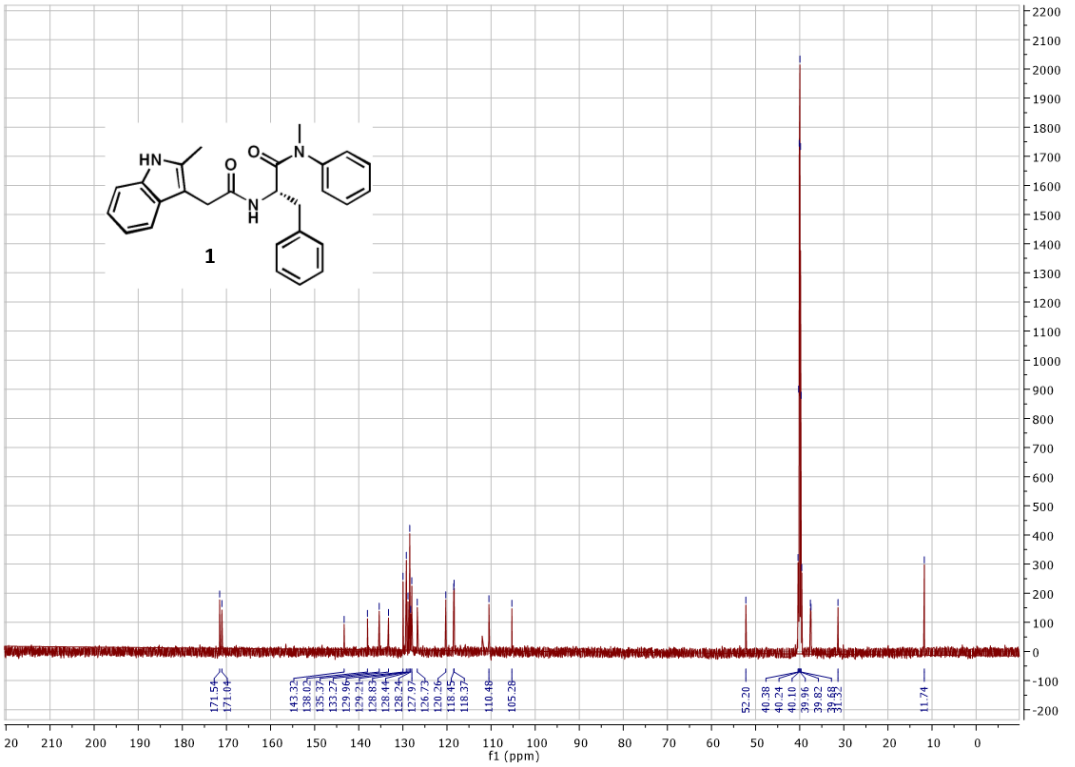


^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 8H), 6.97 – 6.96 (m, 2H), 4.03 – 4.00 (m, 1H), 3.76 – 3.72 (m, 1H), 3.48 – 3.43 (m, 1H), 3.08 – 3.01 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H).

NMR spectra

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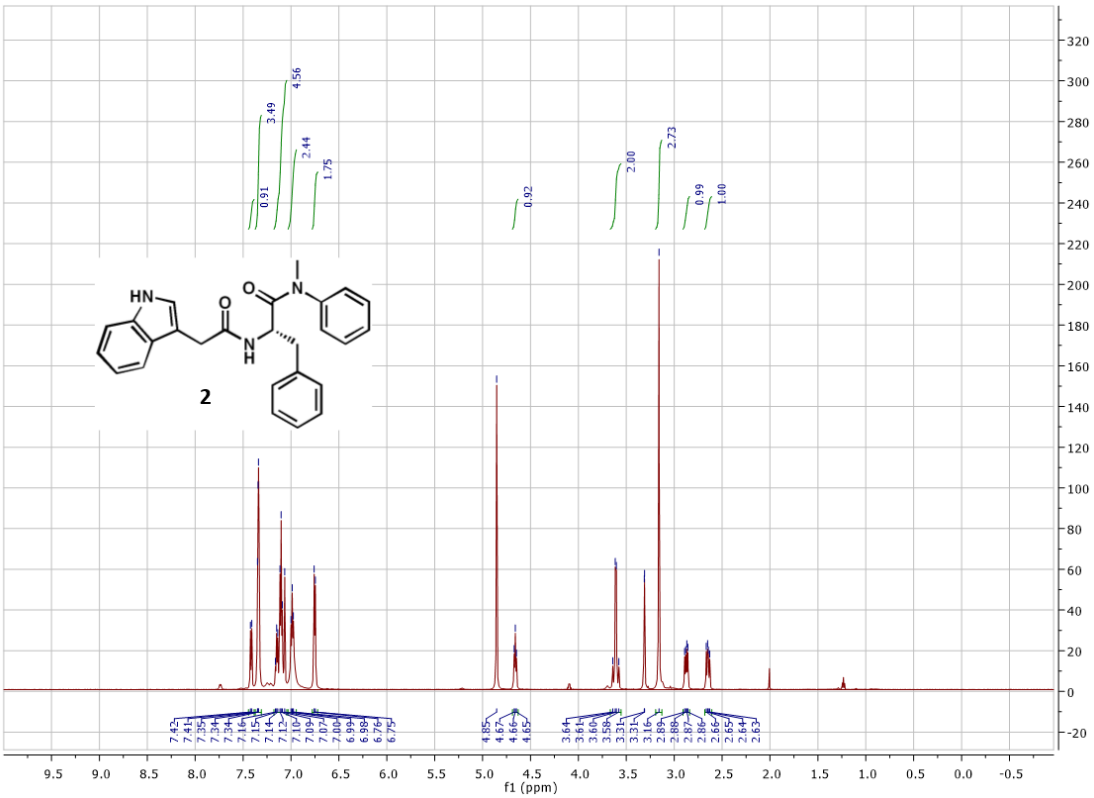
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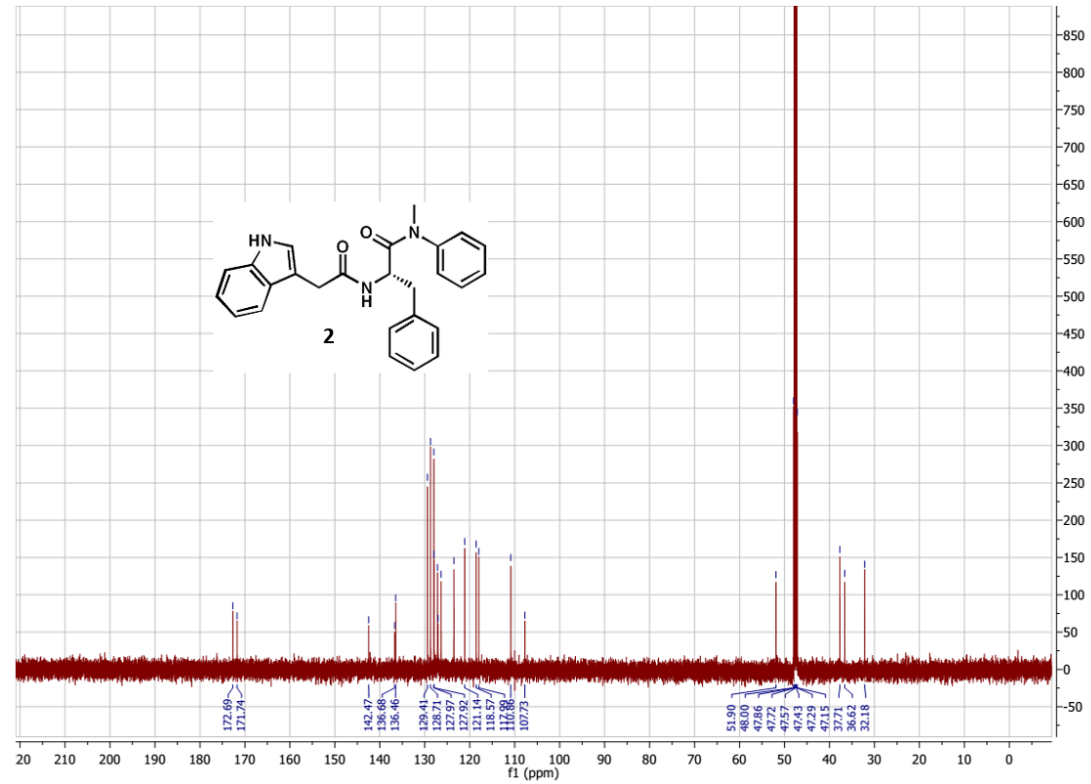
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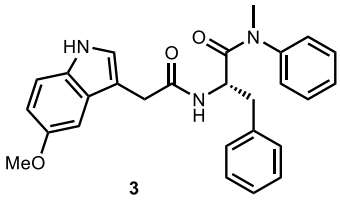
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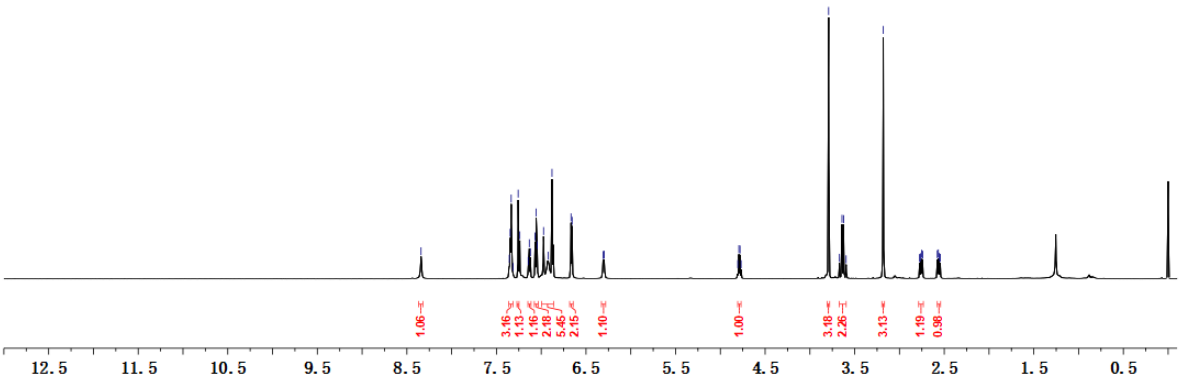

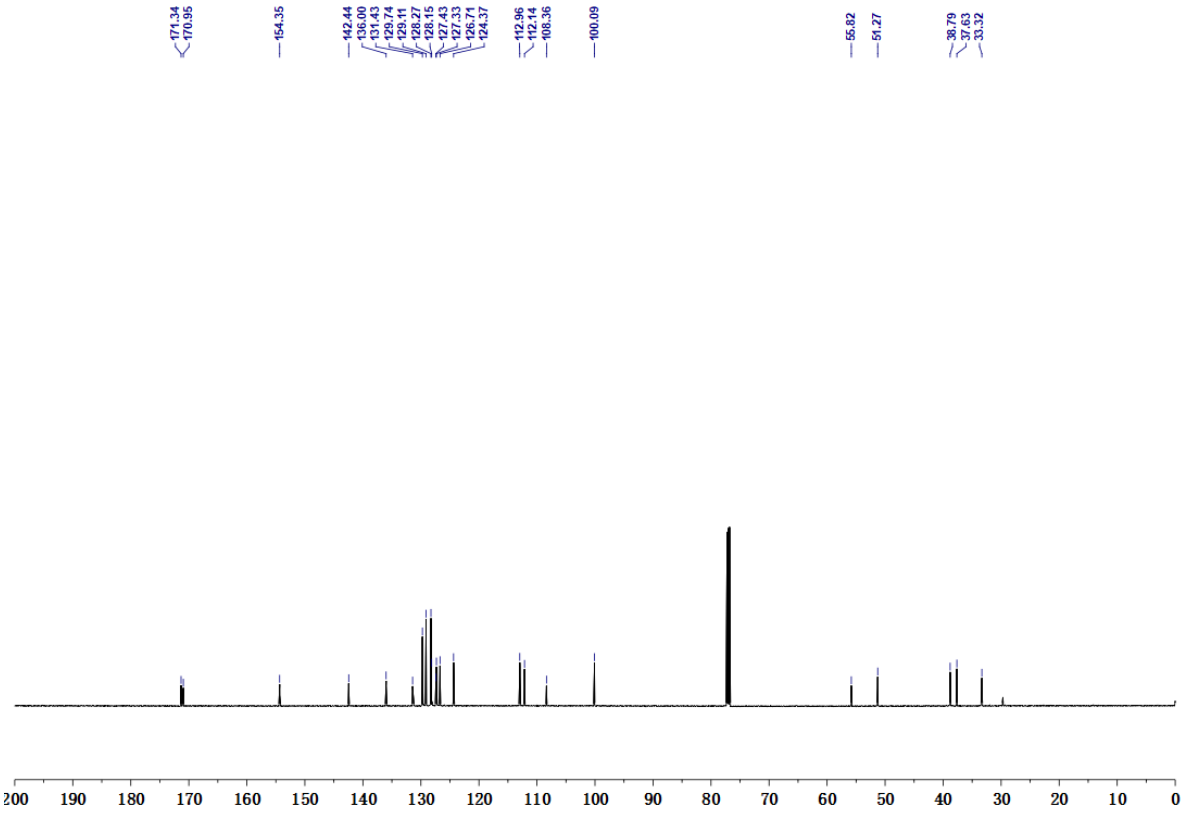
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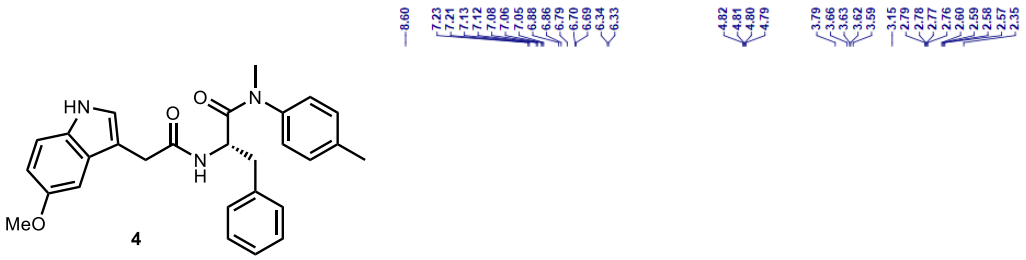
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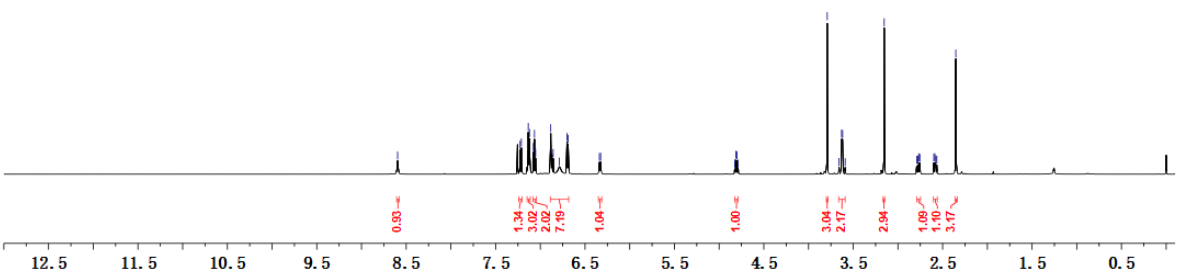
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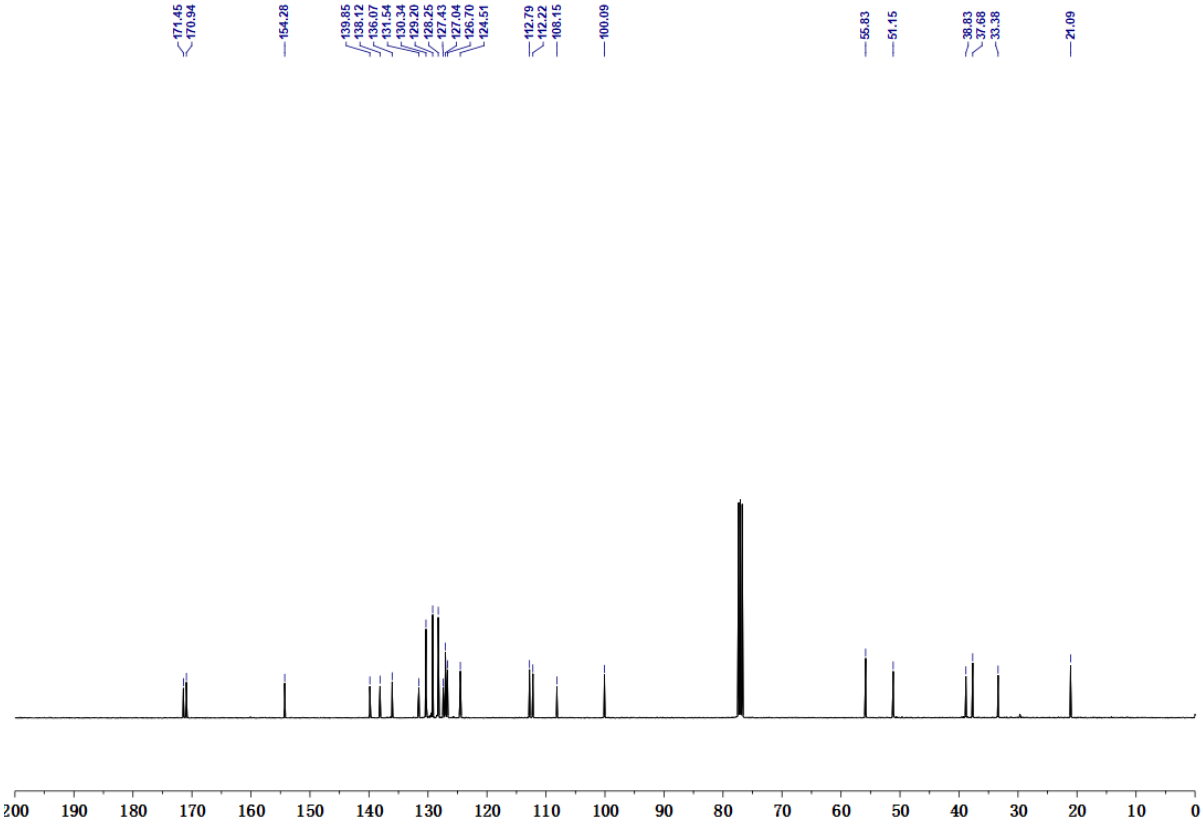
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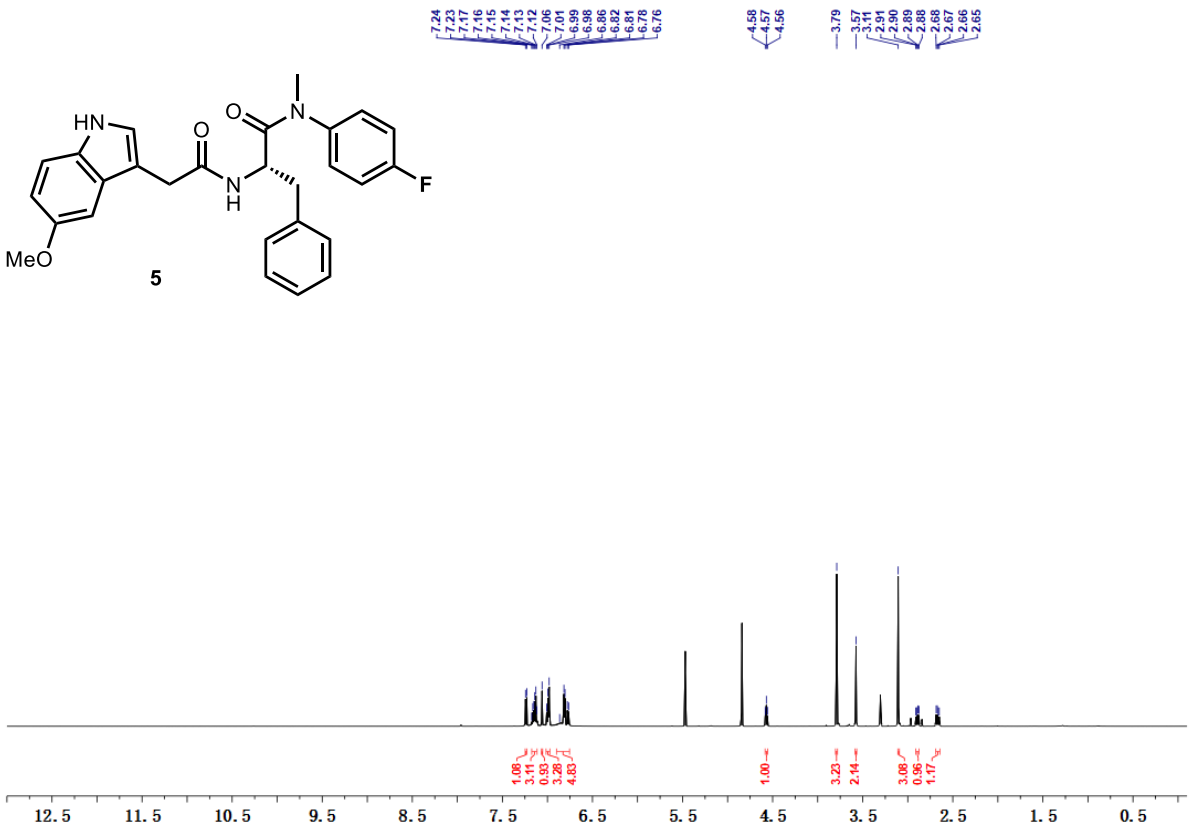
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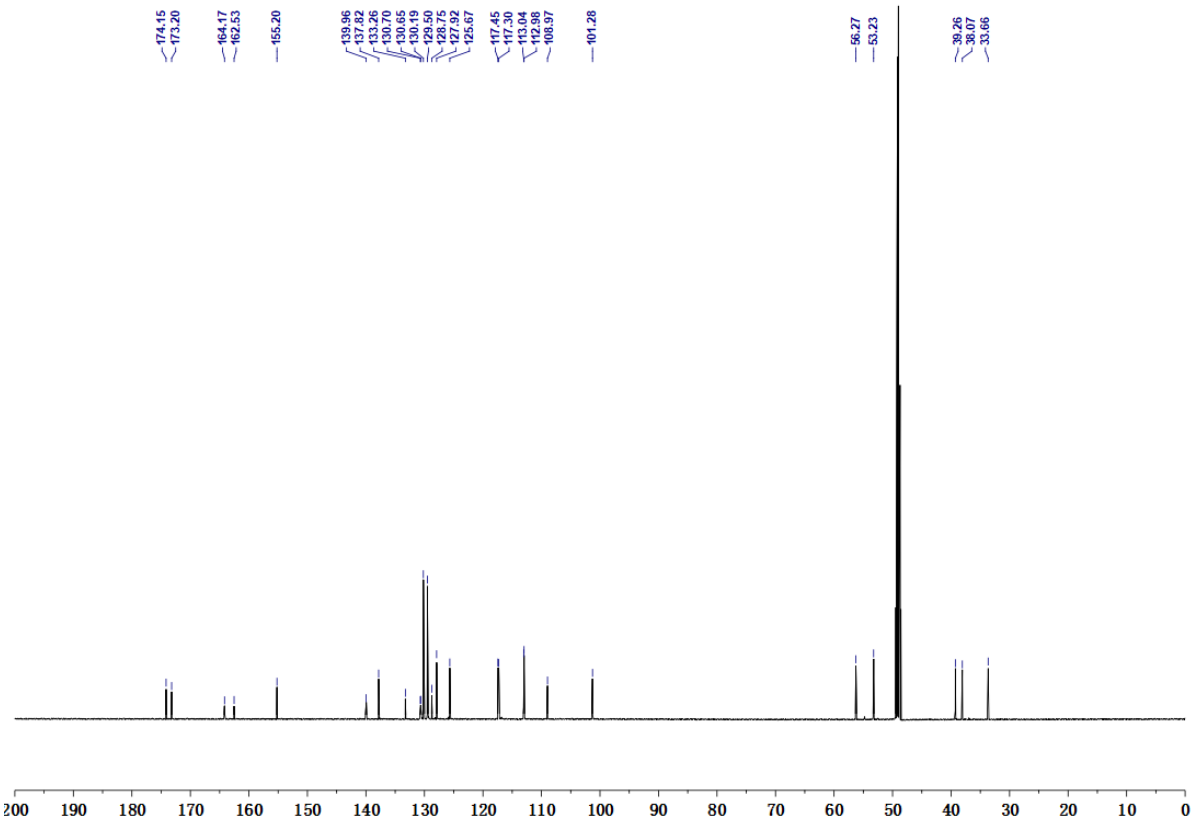
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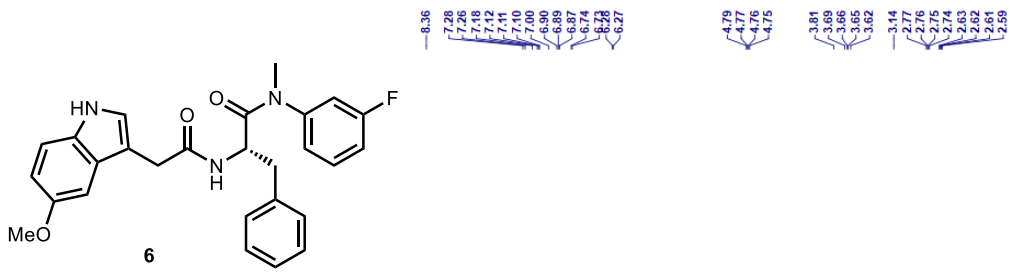
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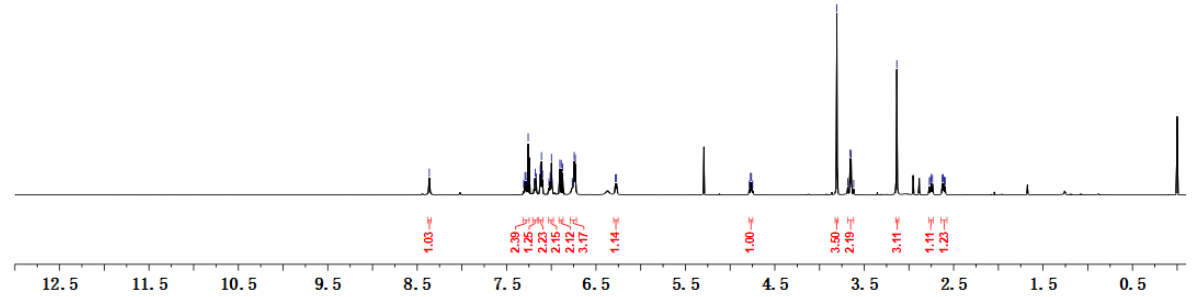
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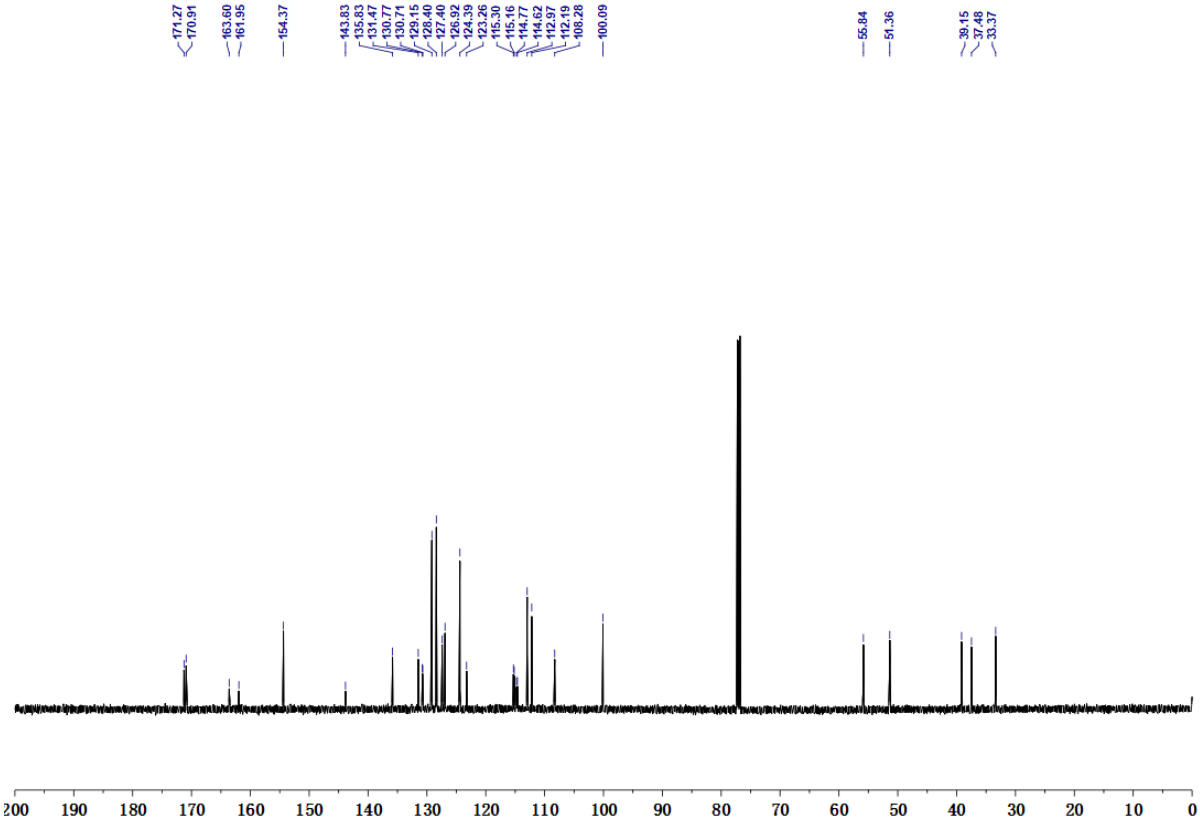
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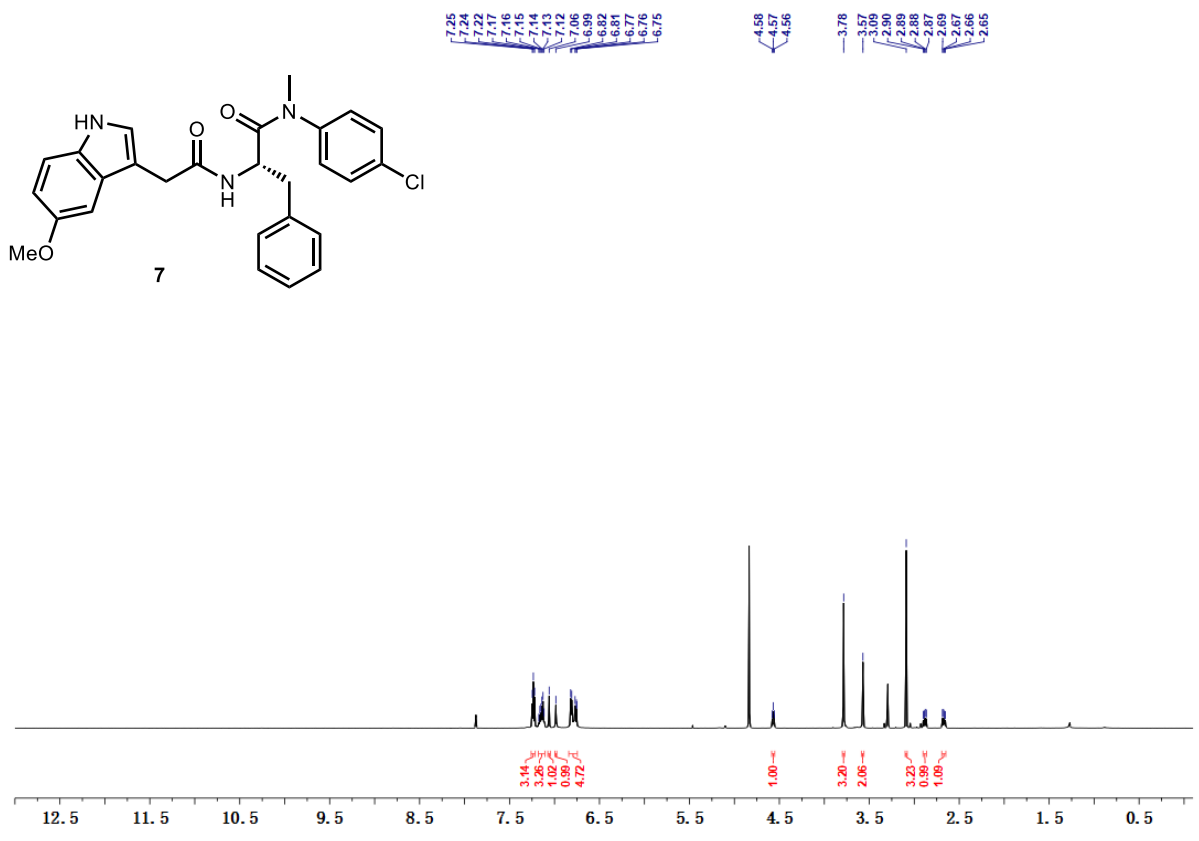
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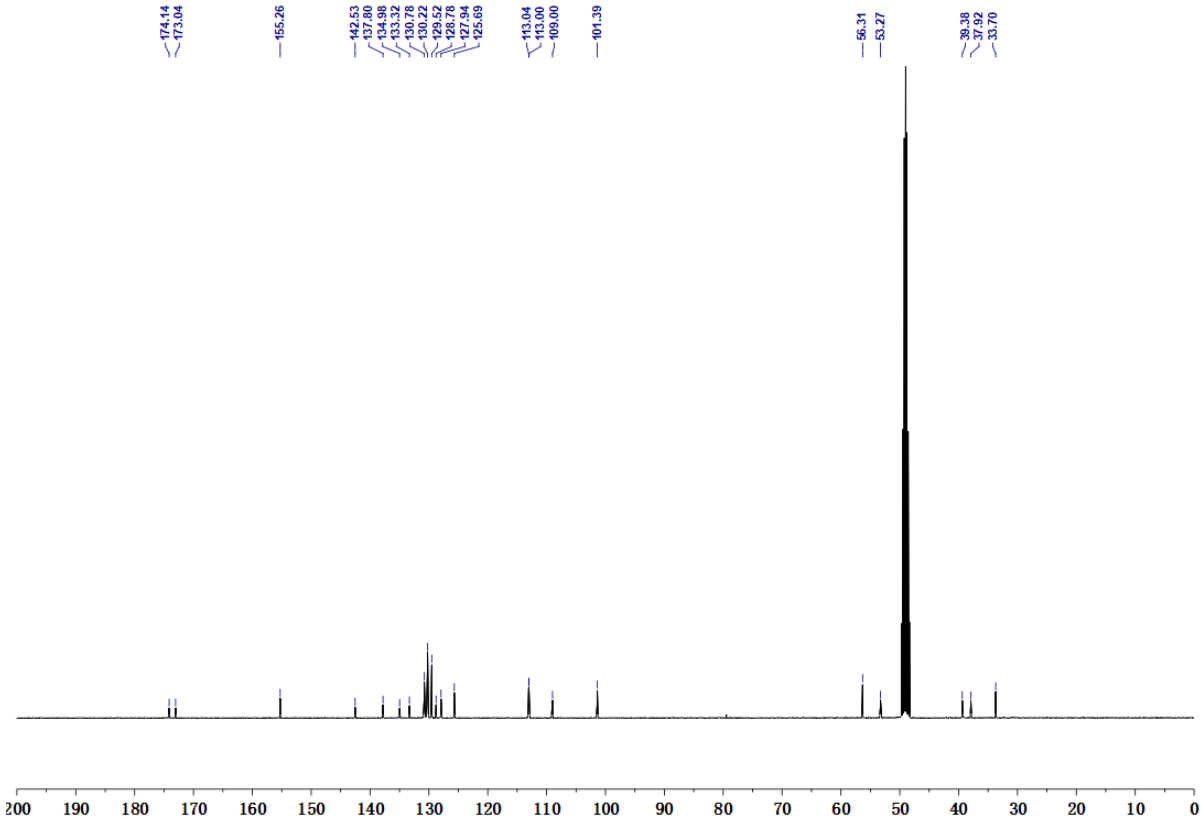
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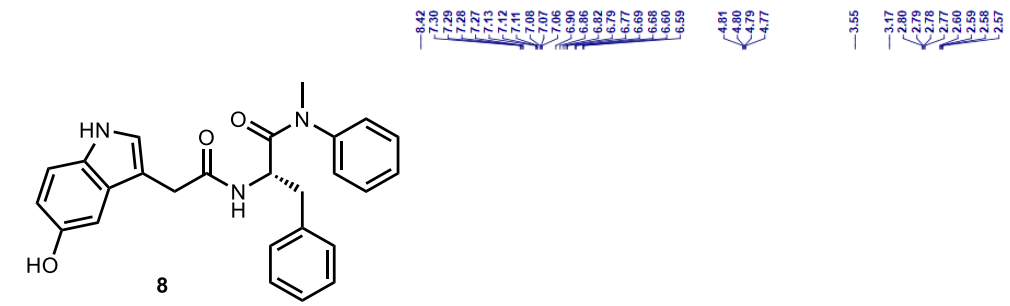
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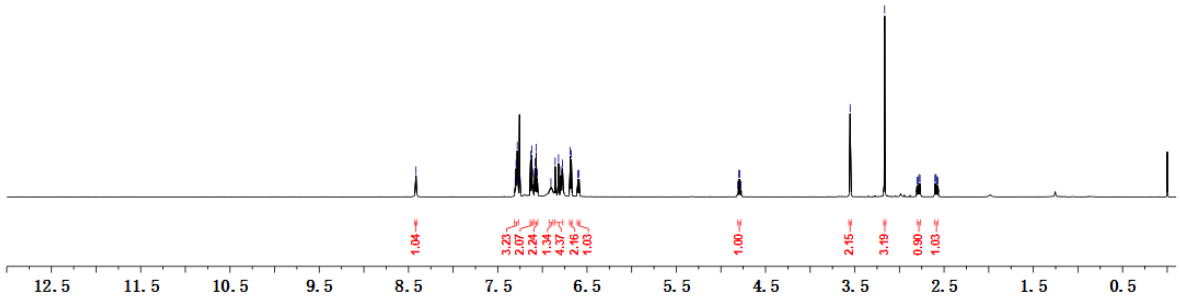
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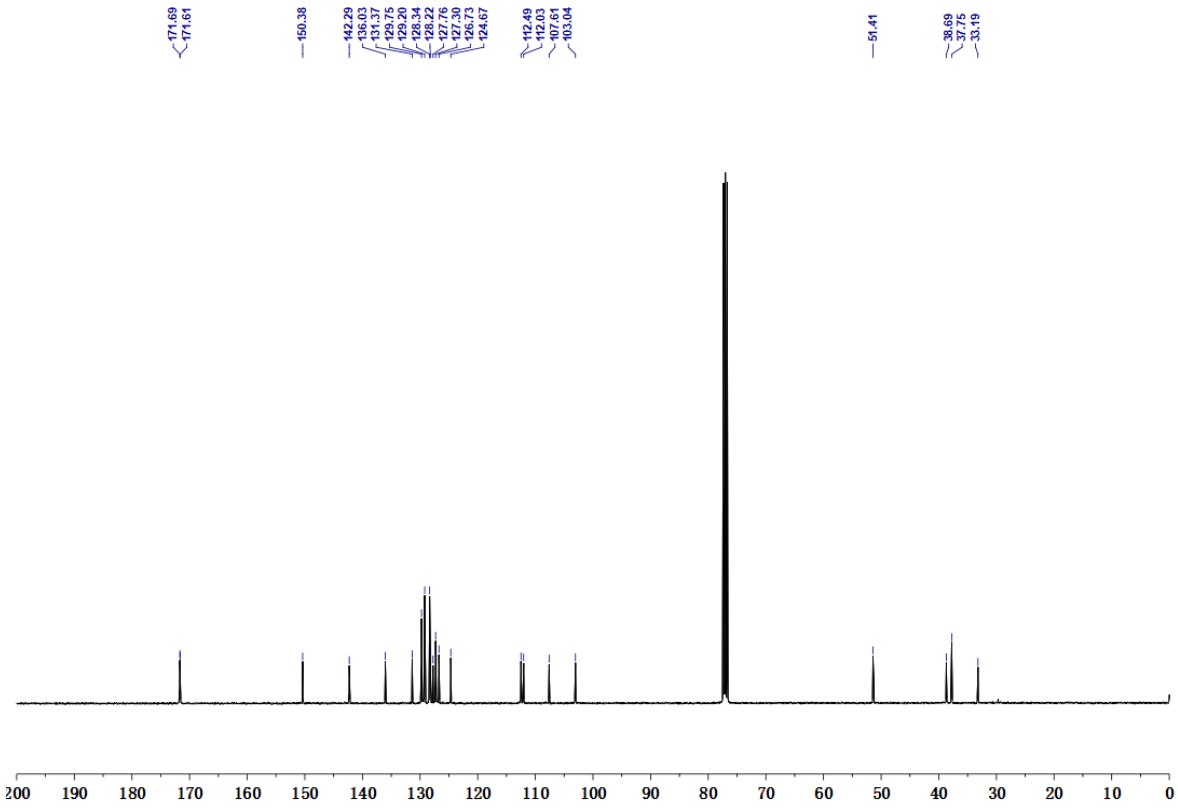
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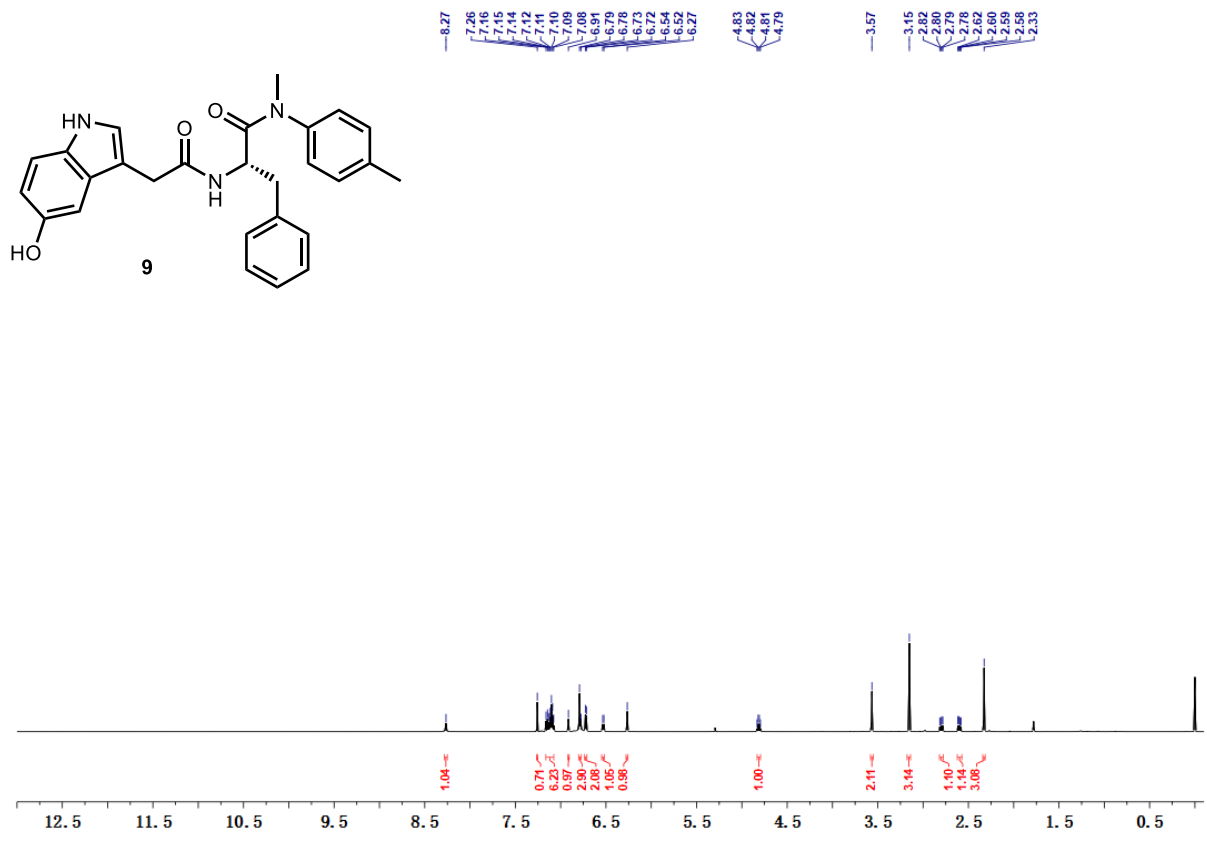
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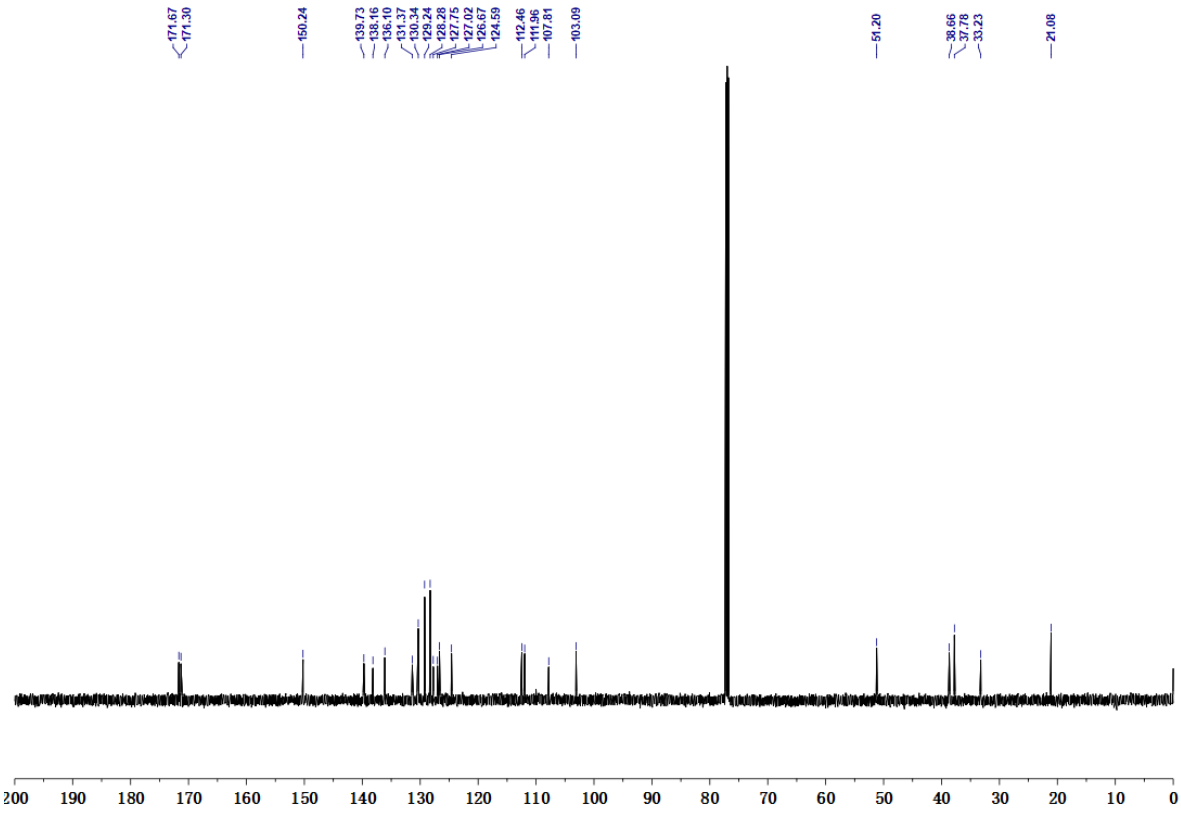
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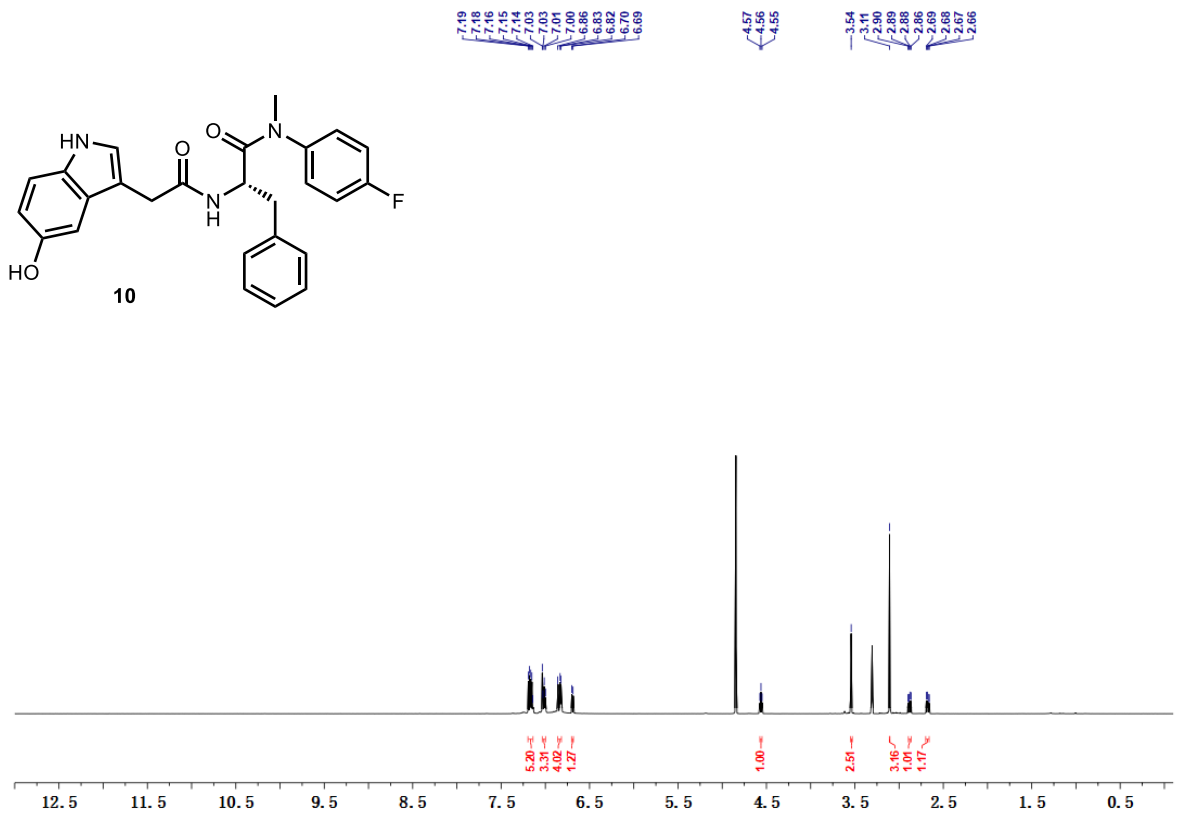
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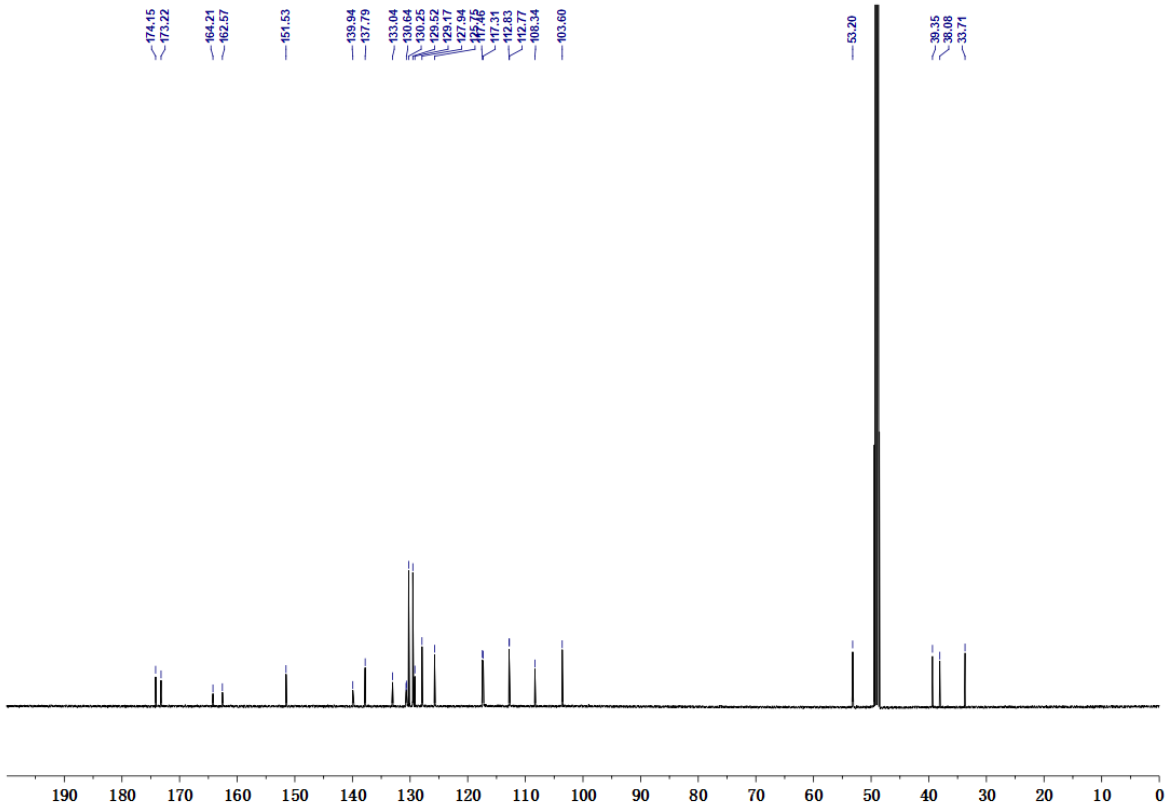
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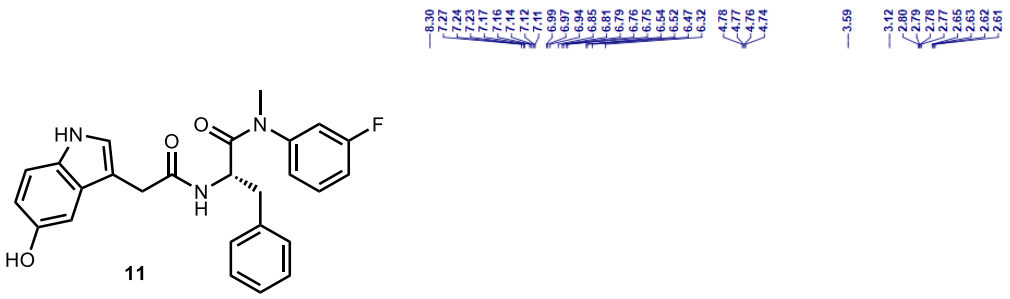
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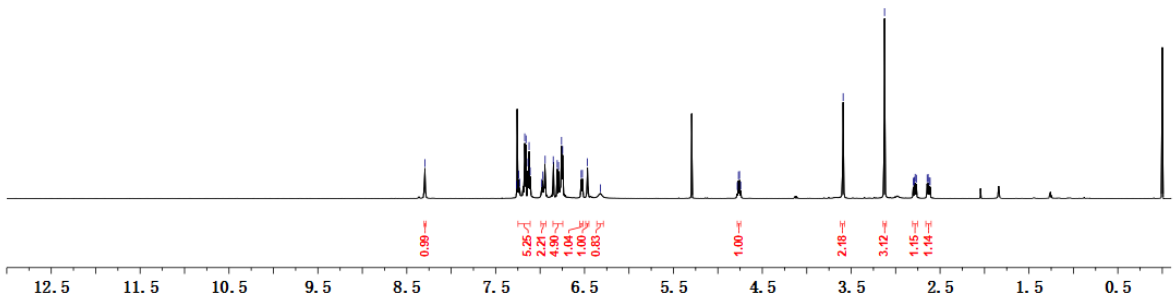
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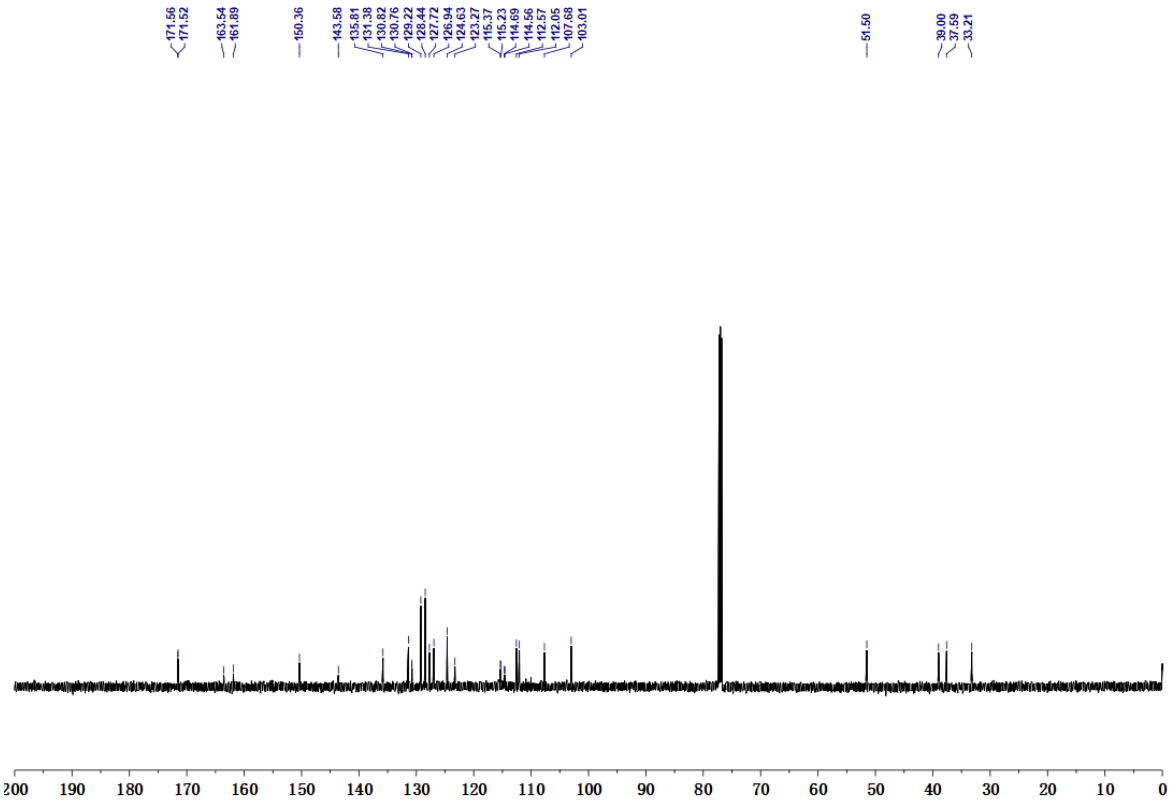
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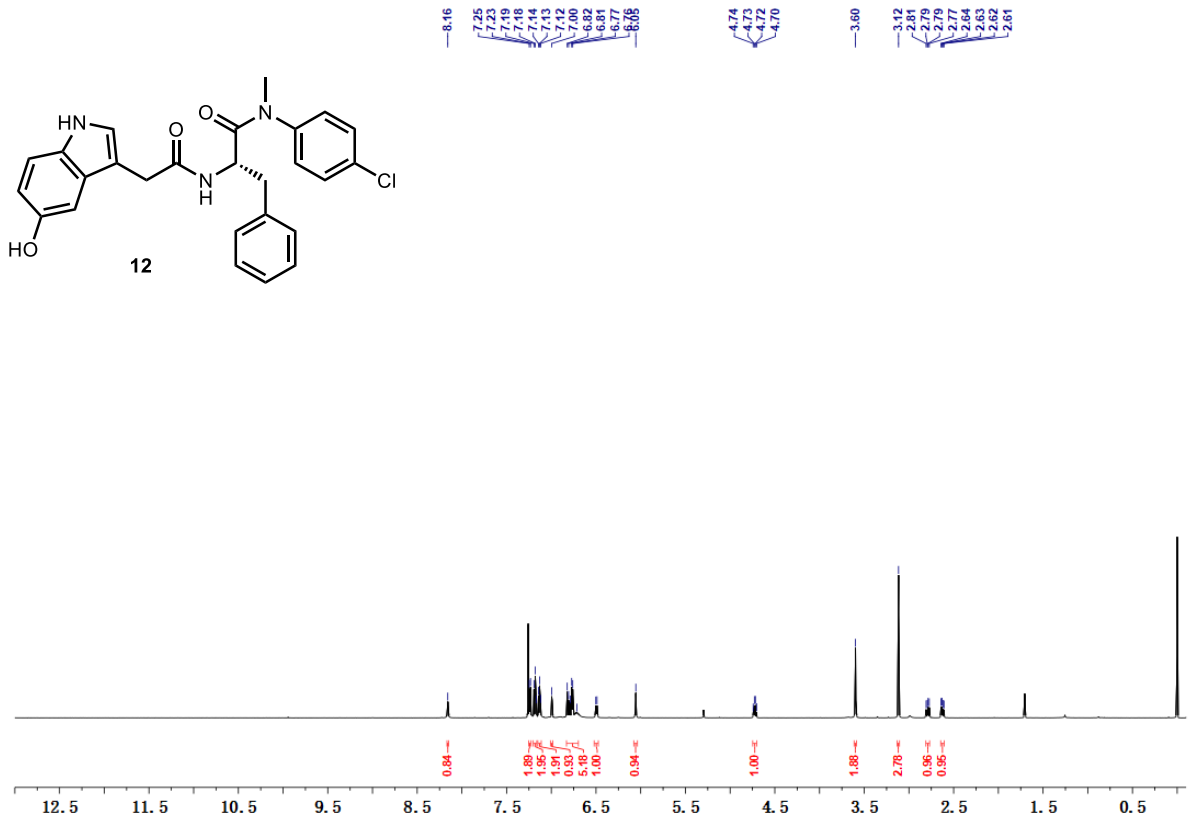
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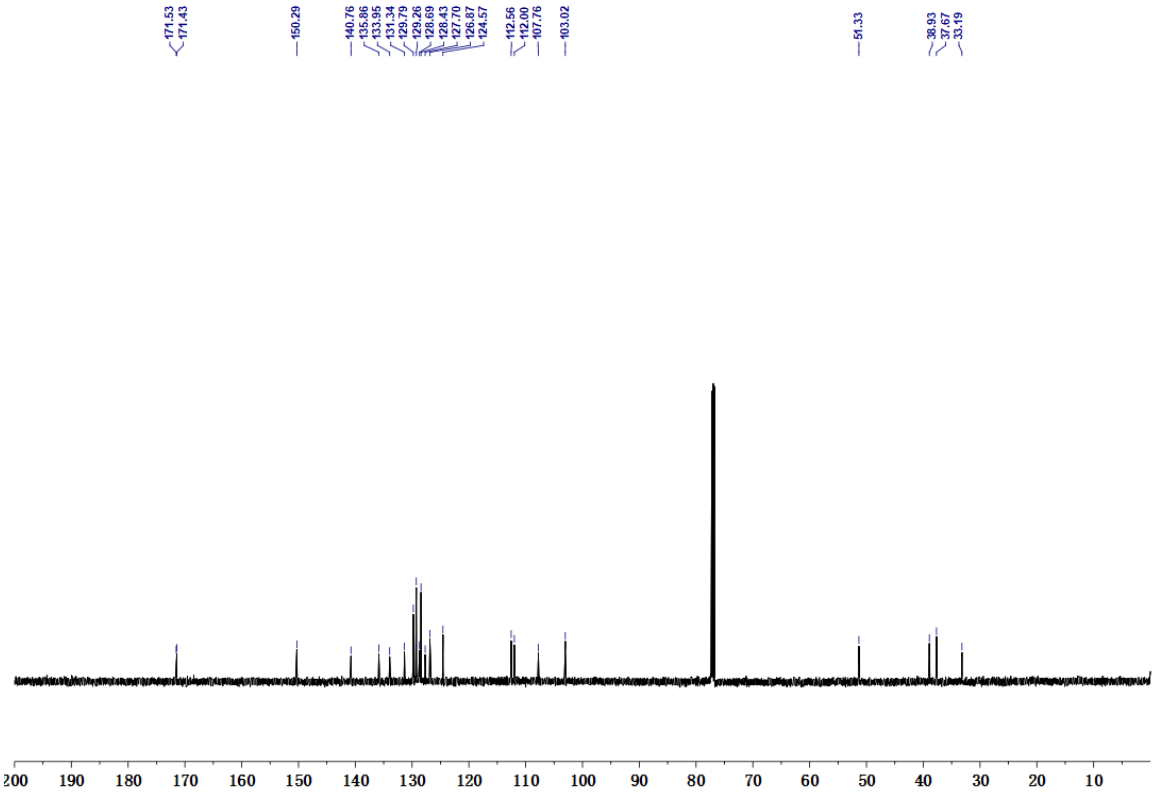
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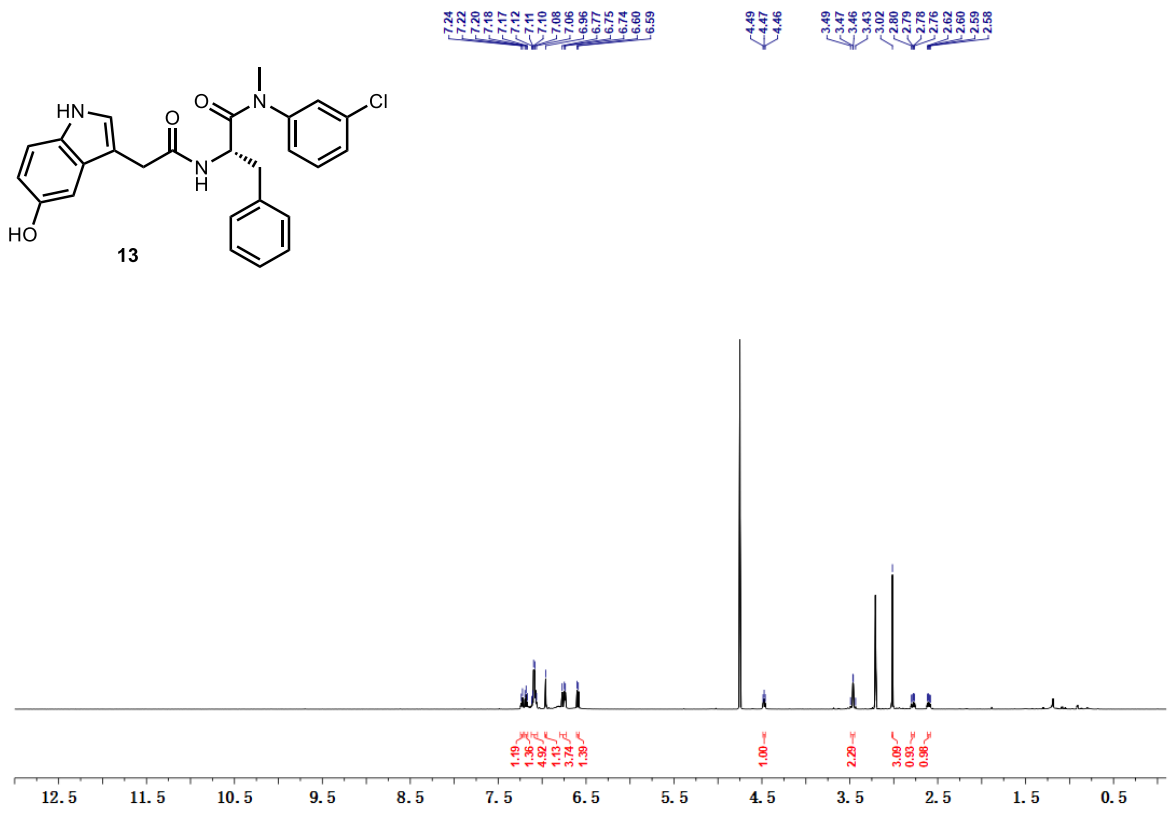
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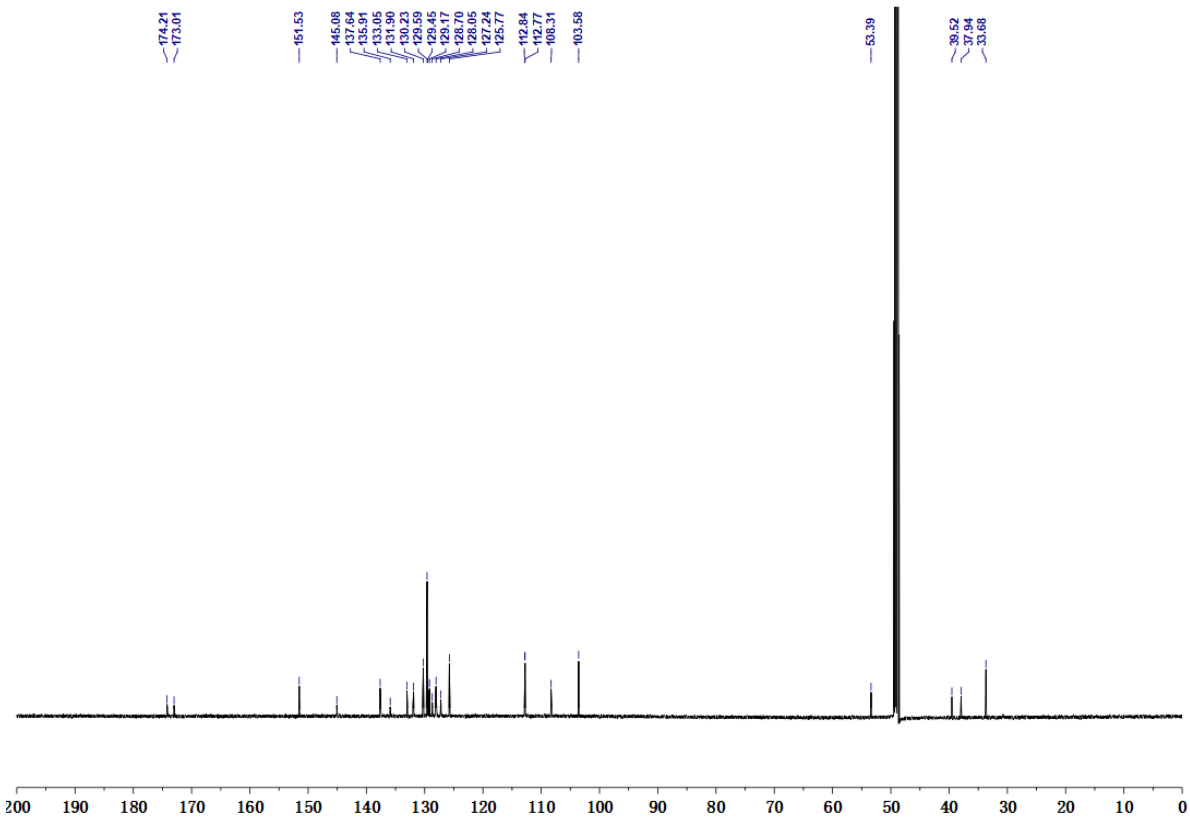
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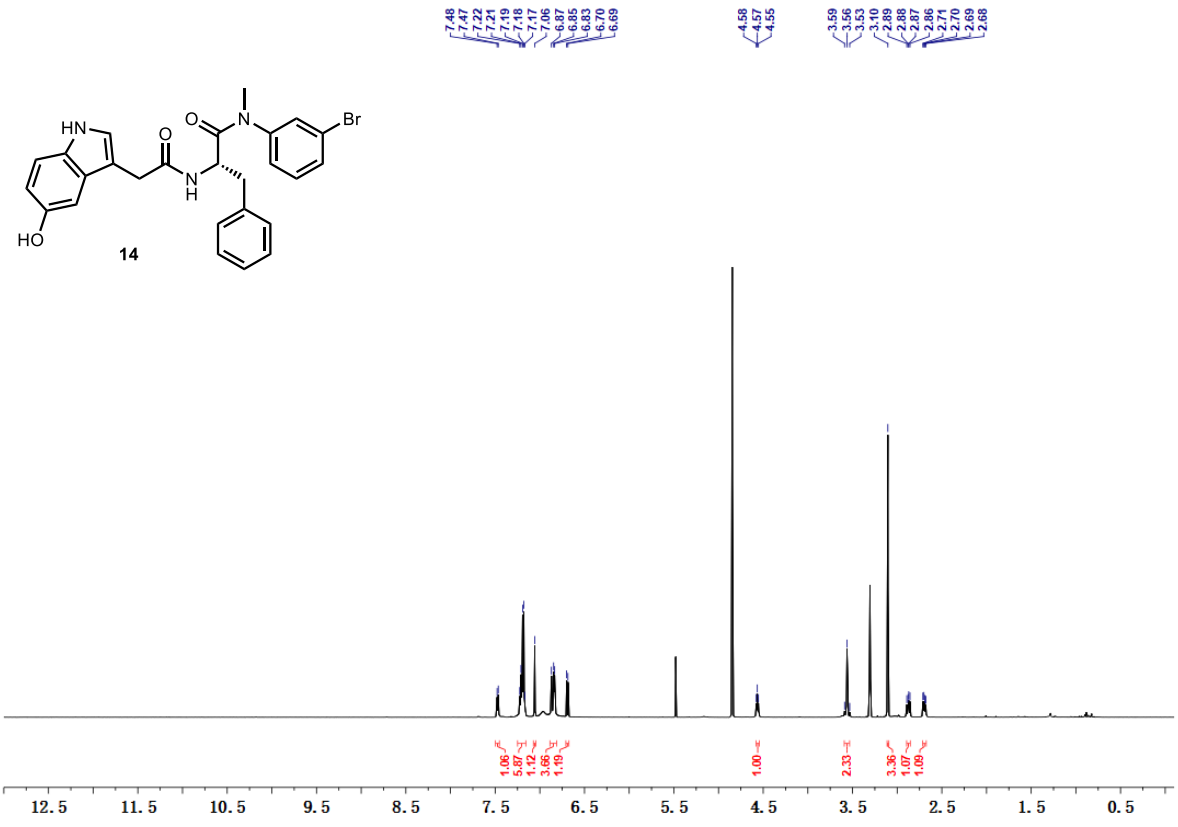
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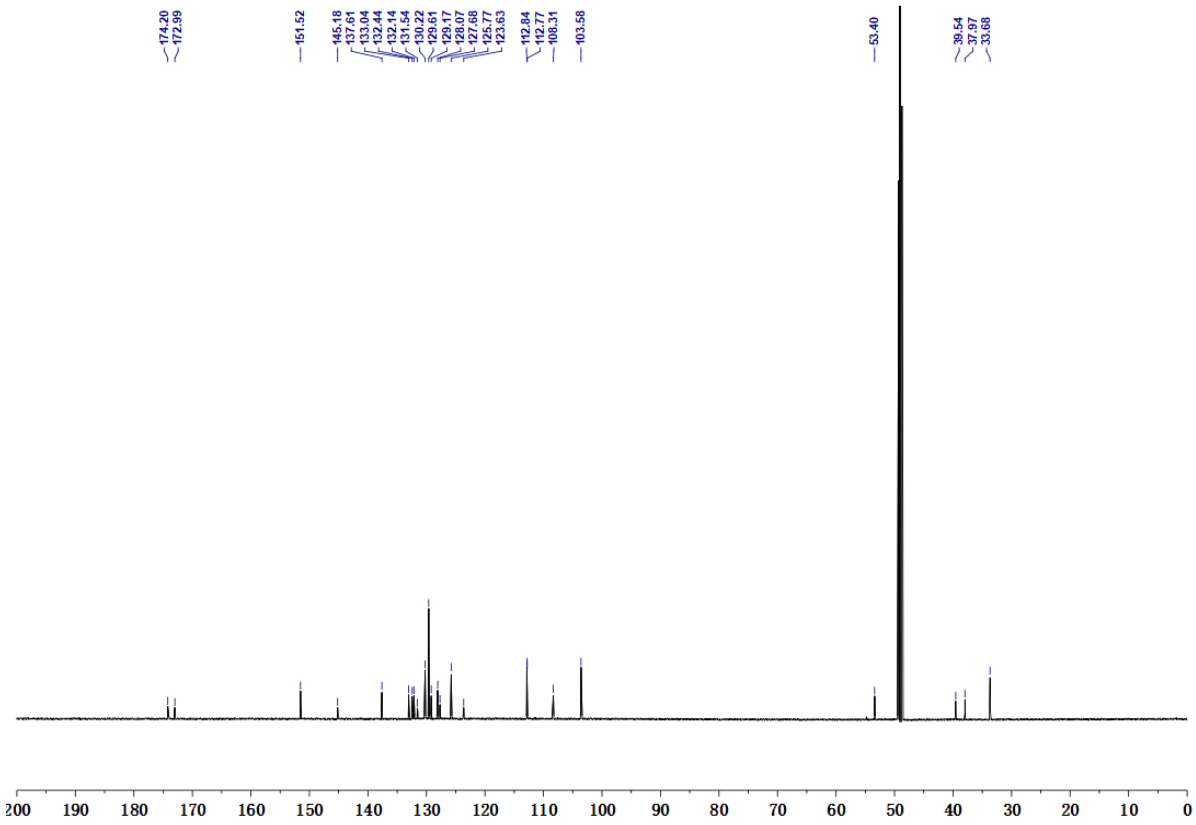
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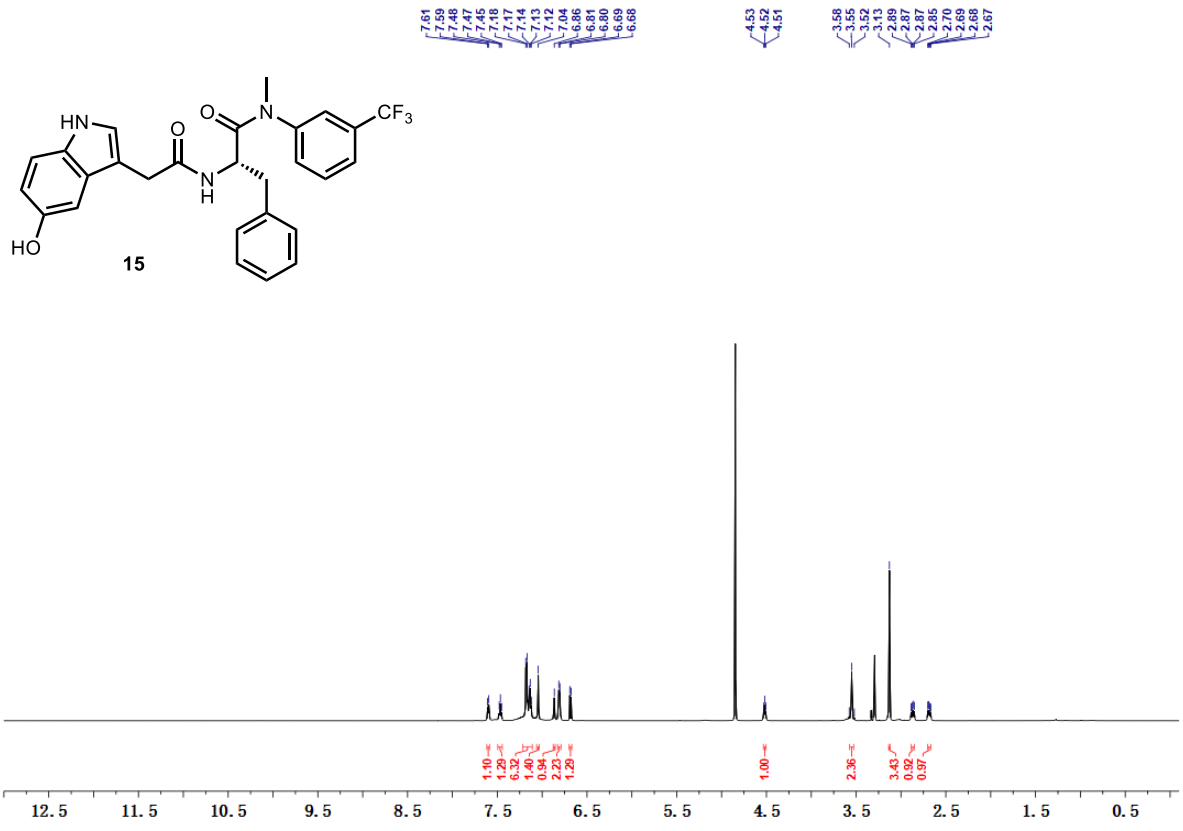
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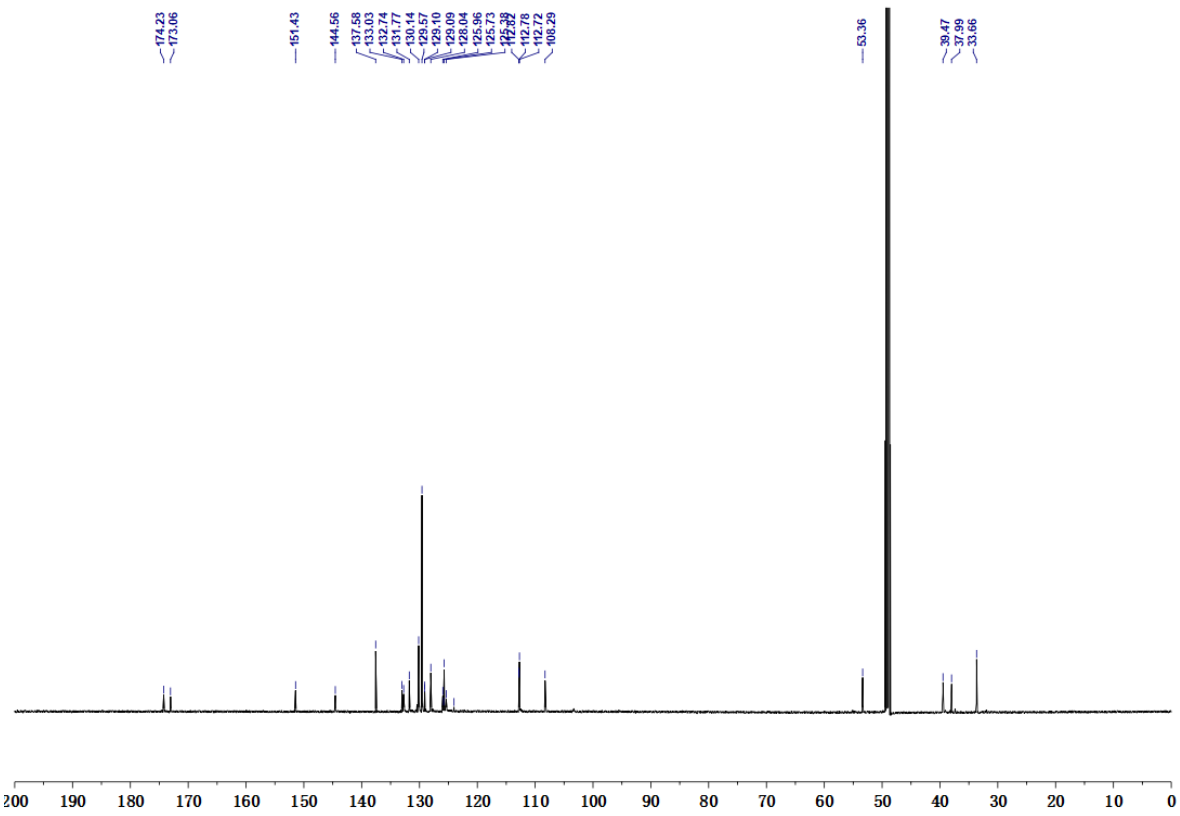
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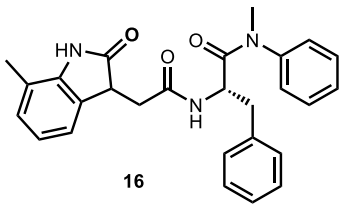
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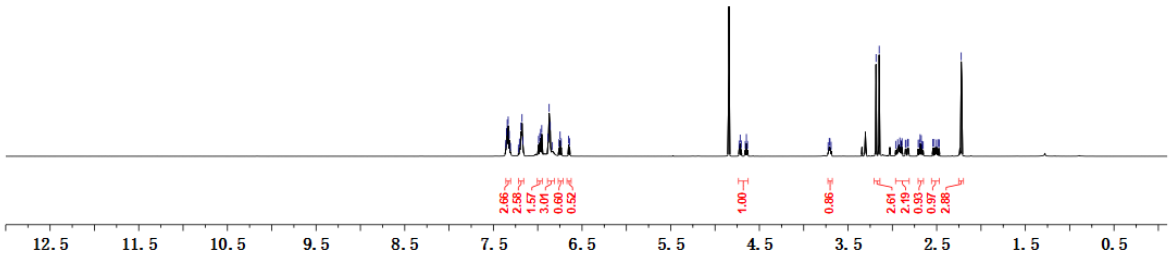
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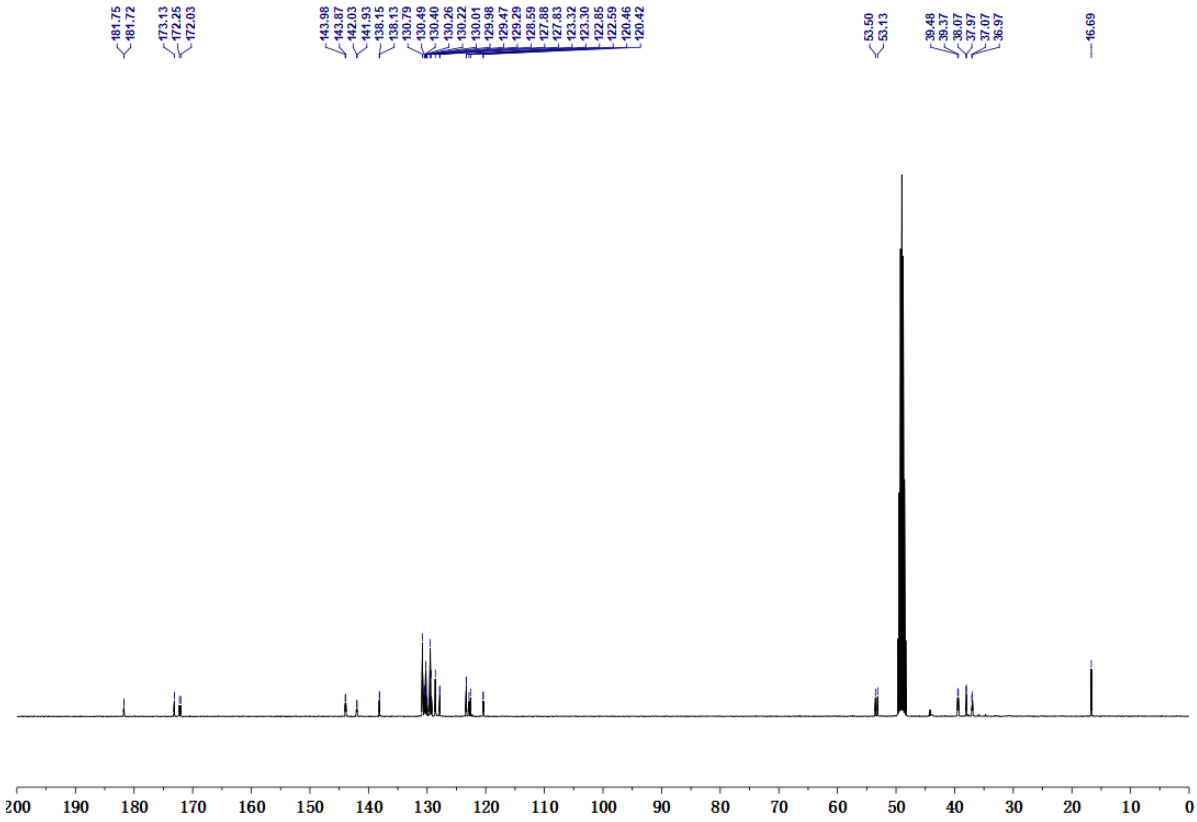

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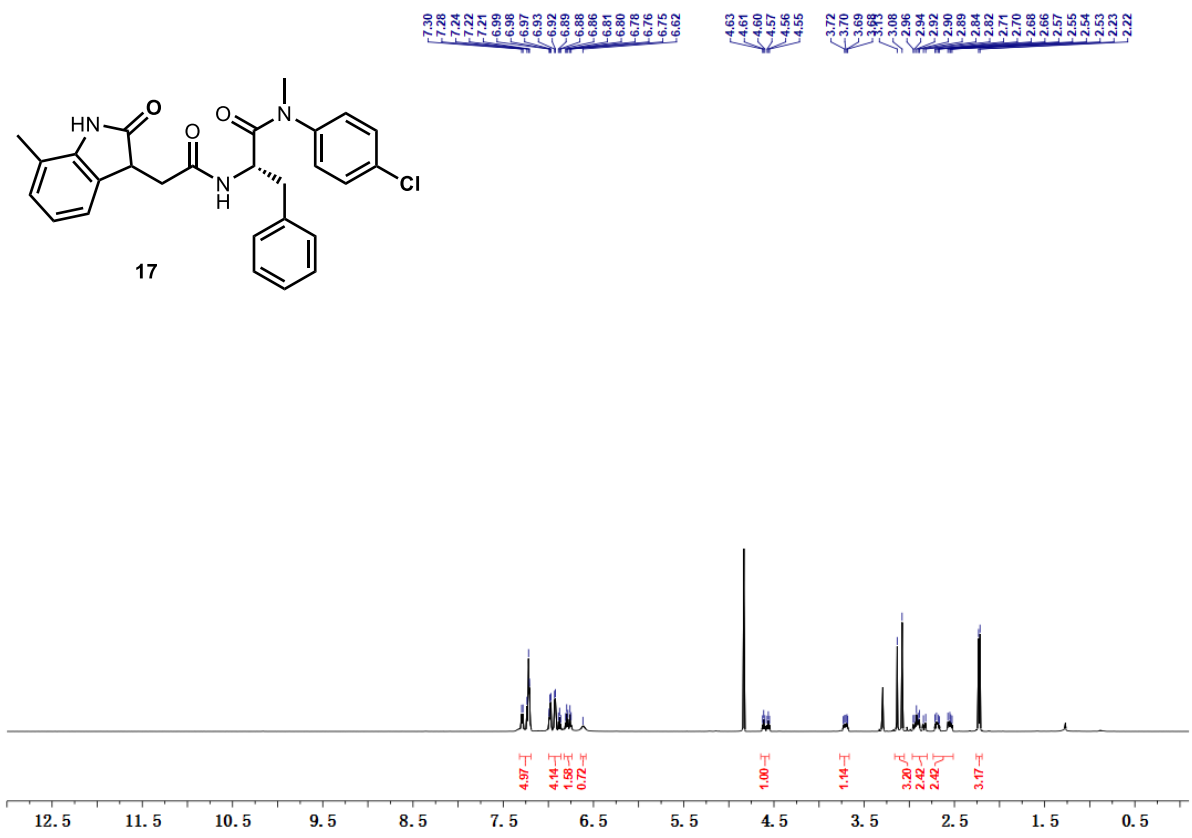

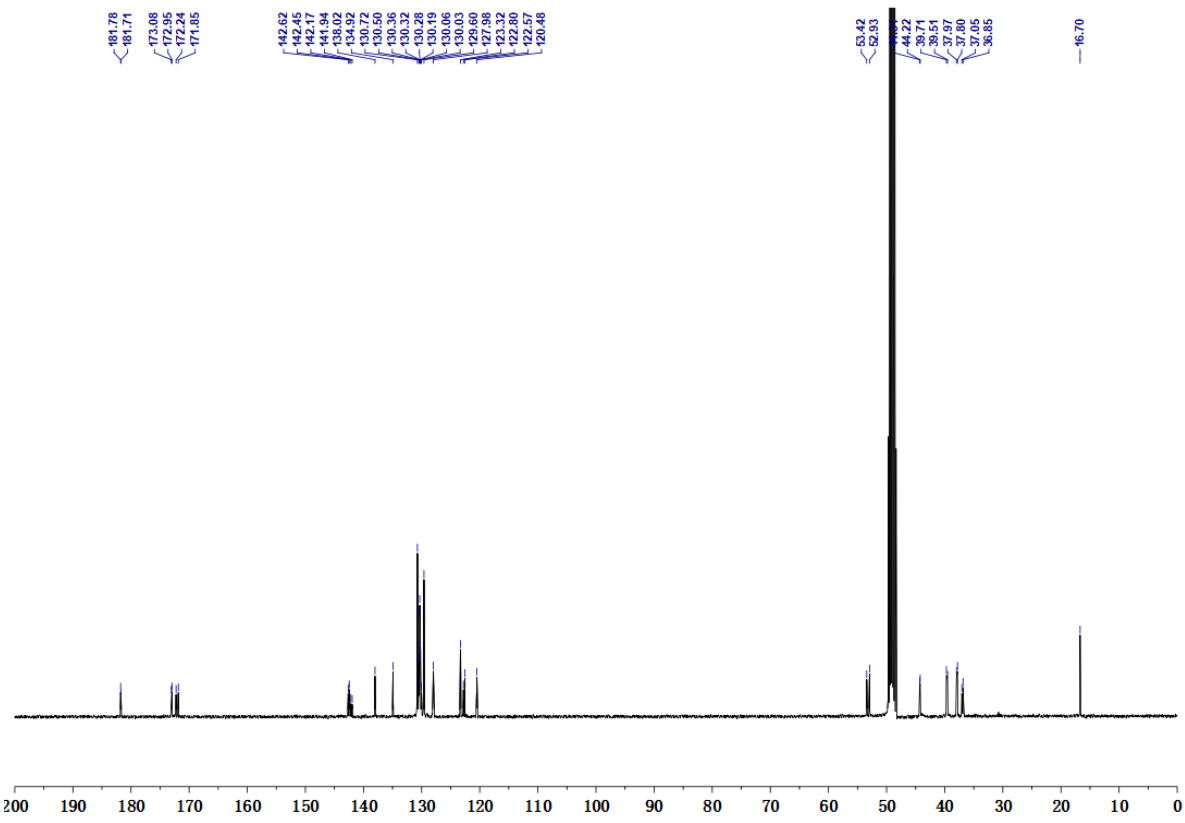

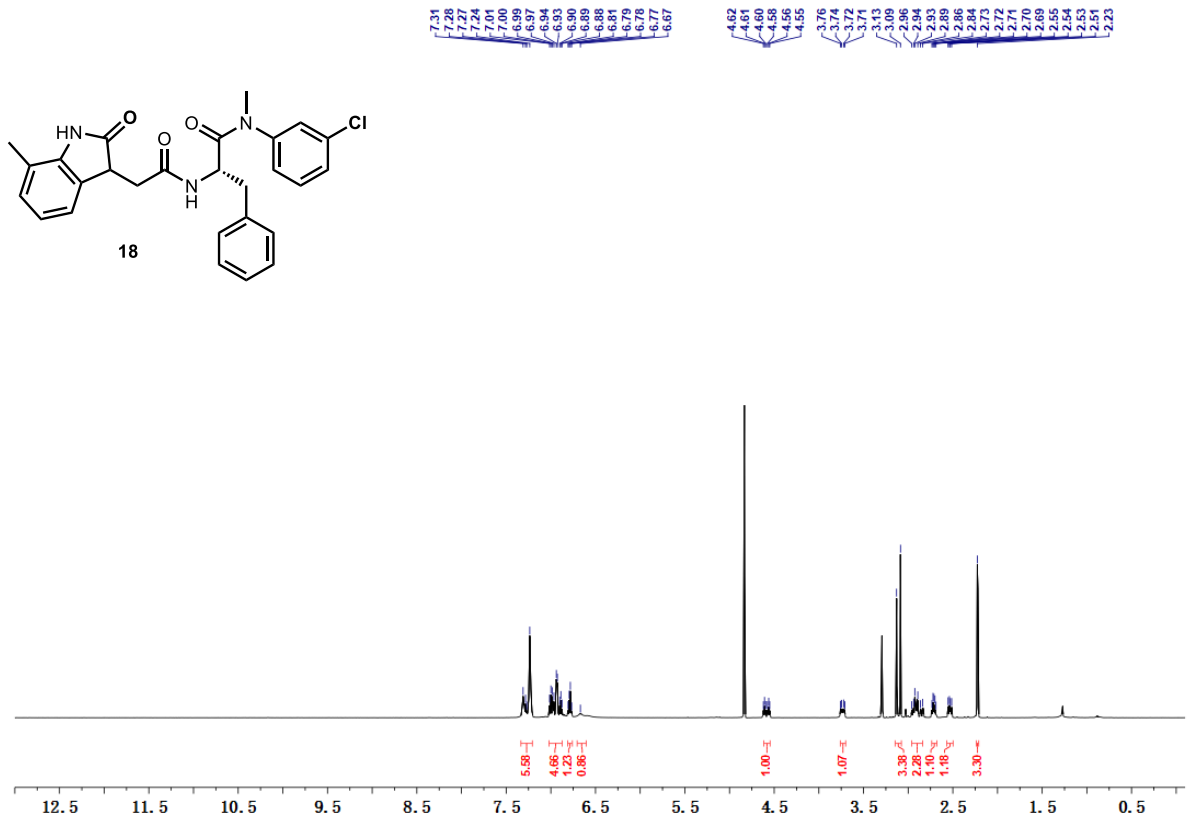

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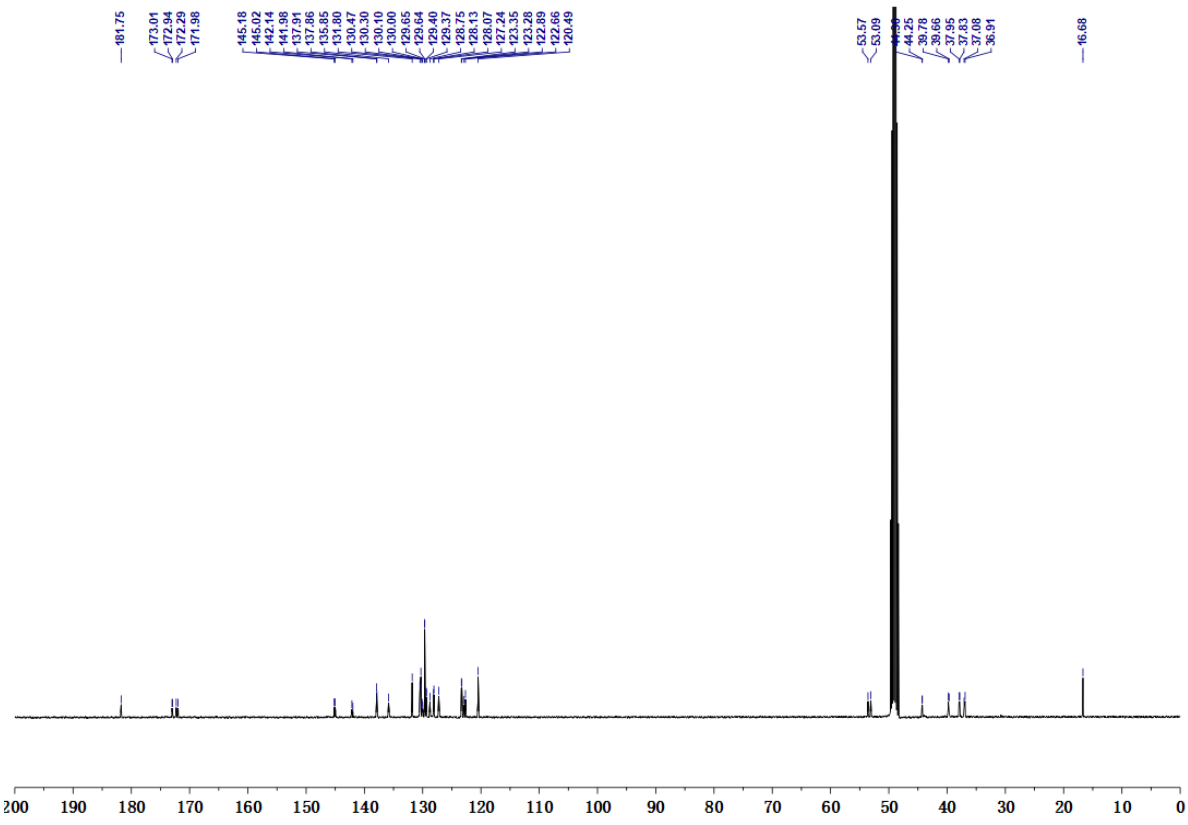
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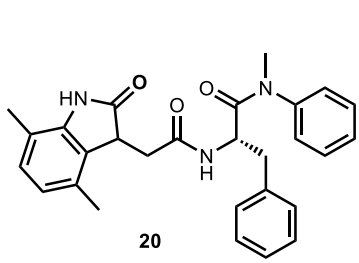
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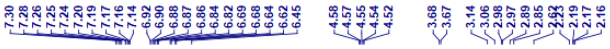
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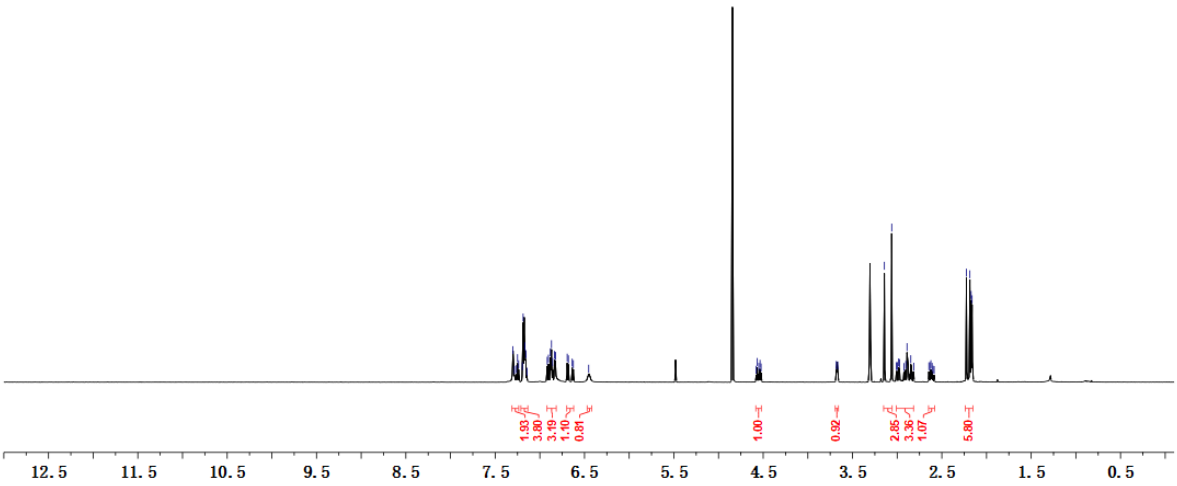
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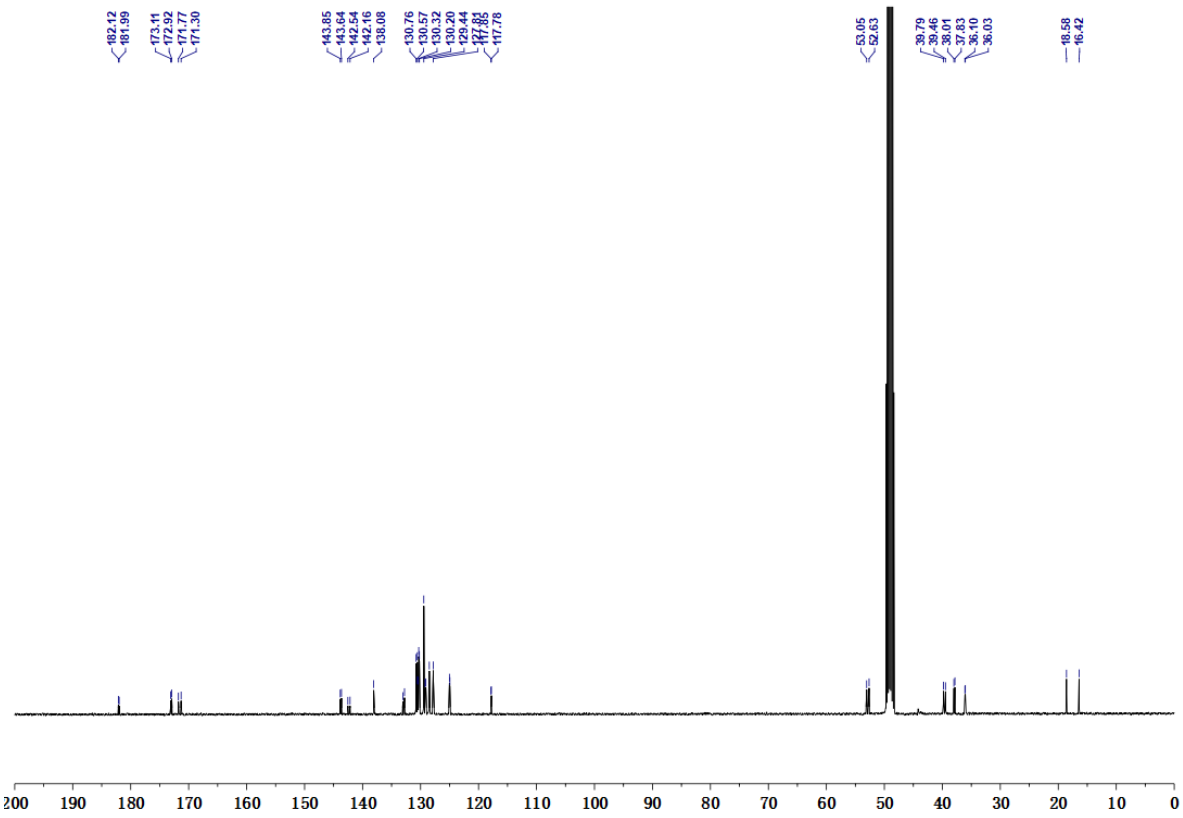
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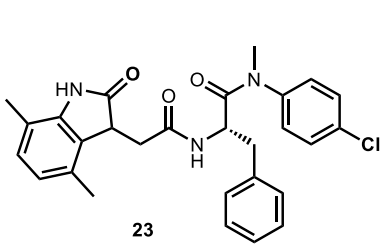
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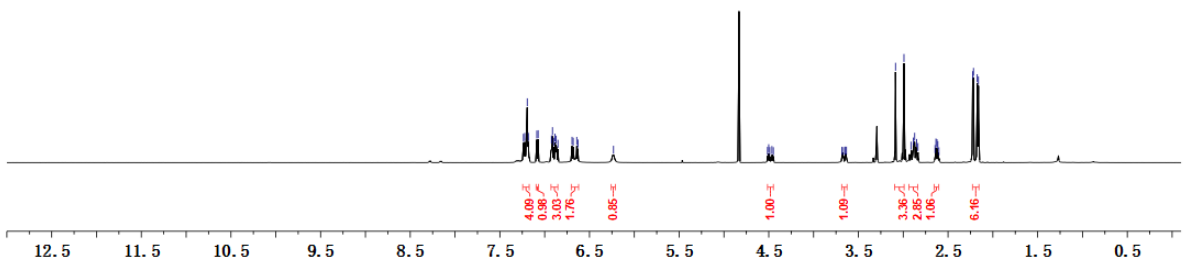
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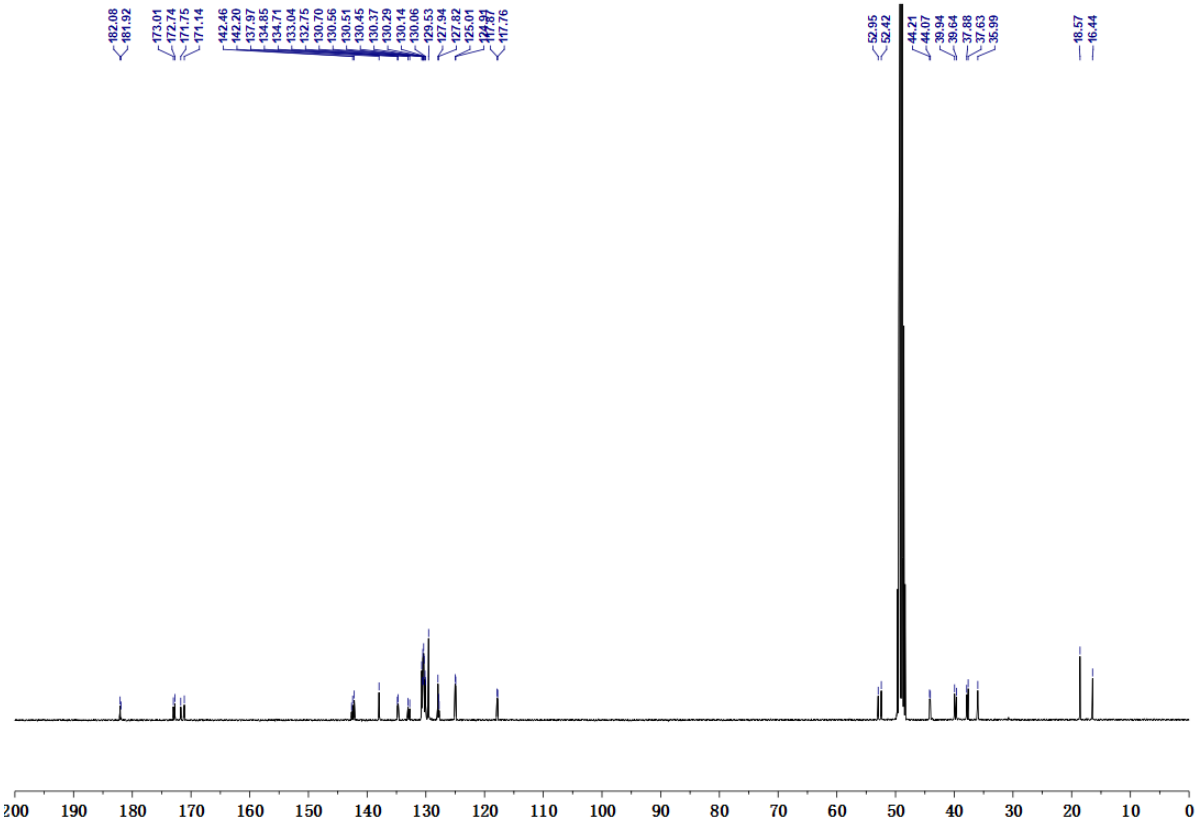
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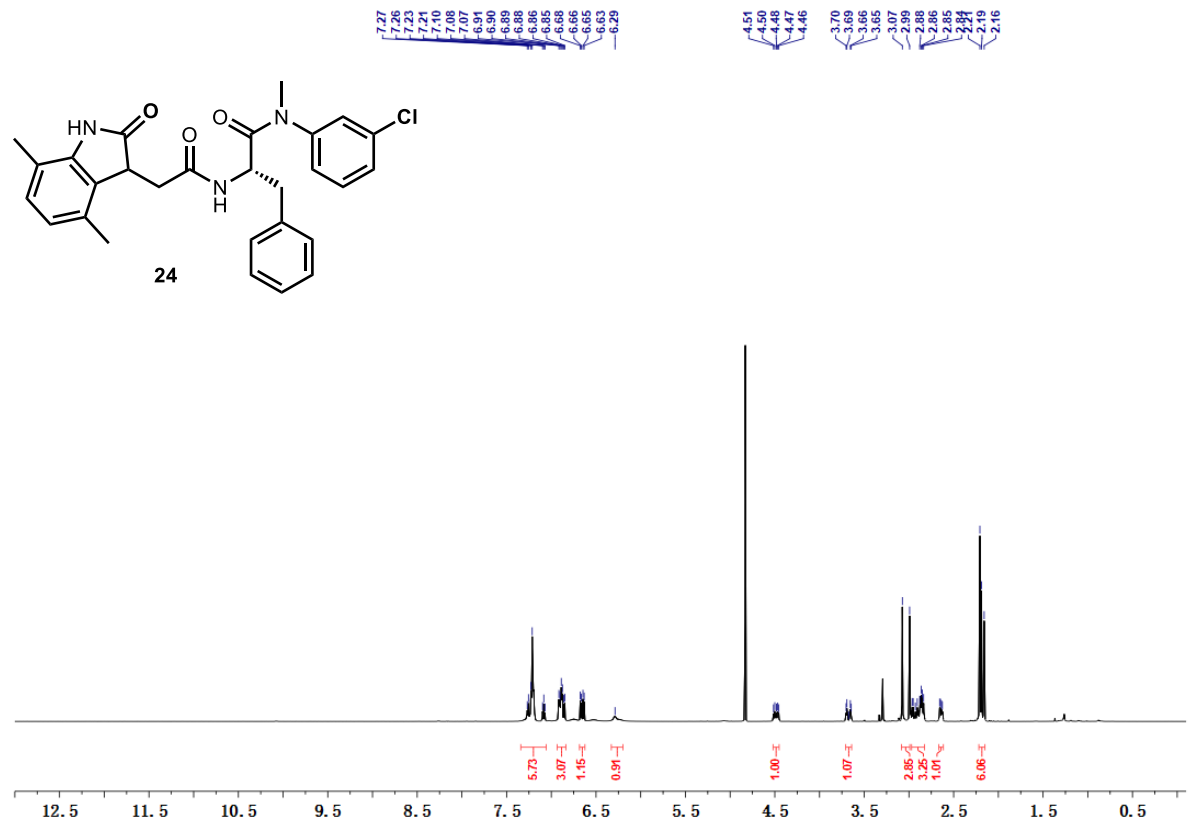
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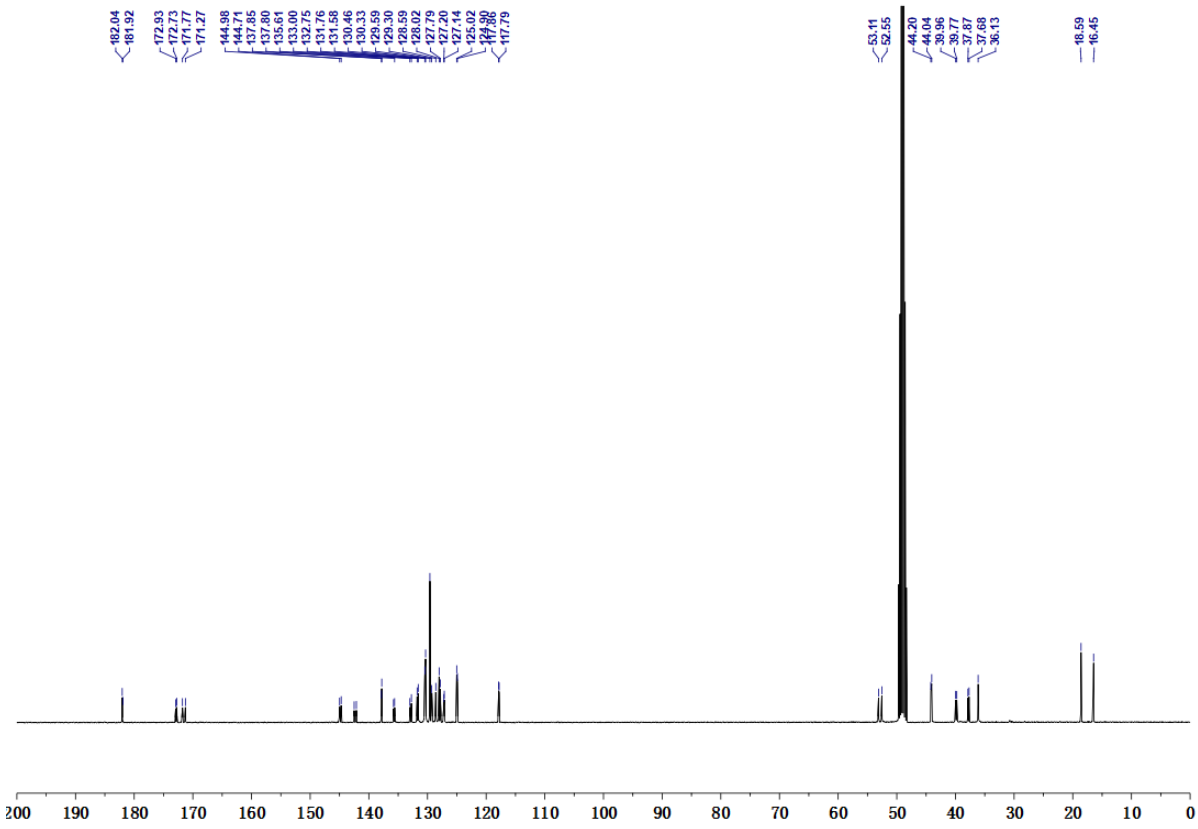

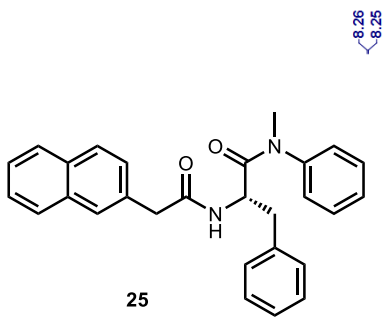

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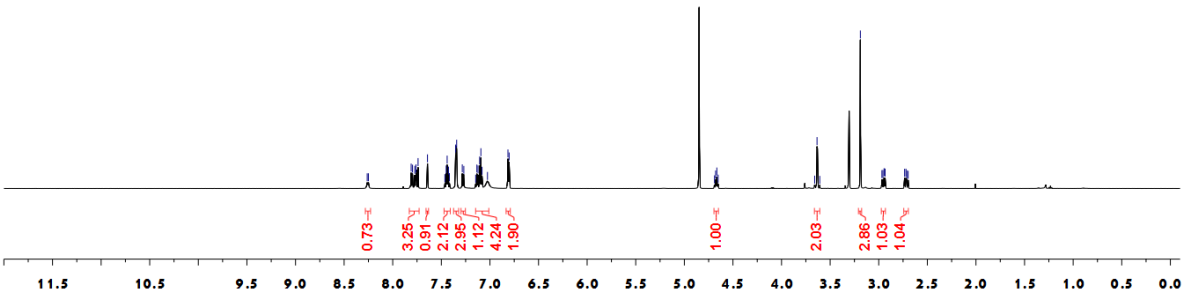

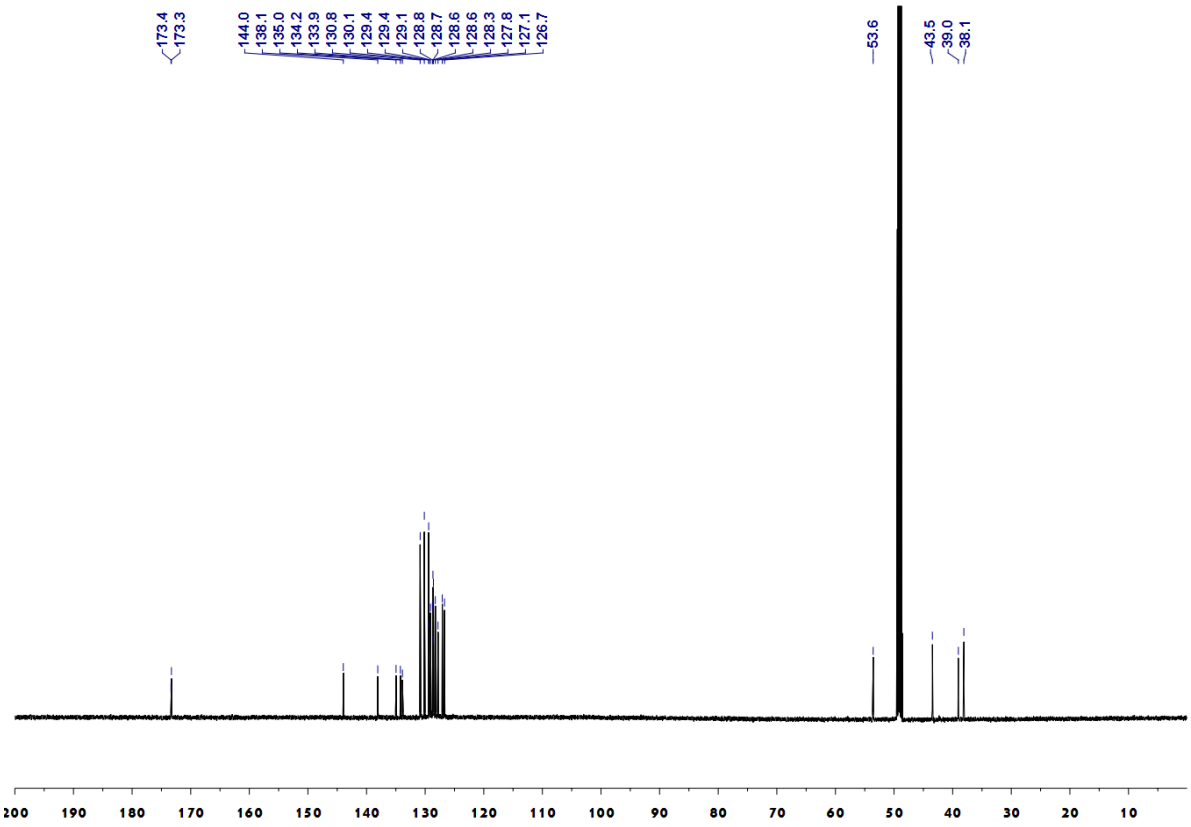
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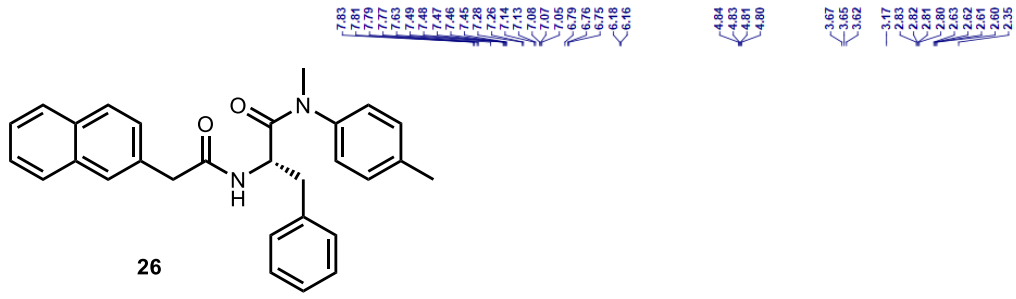
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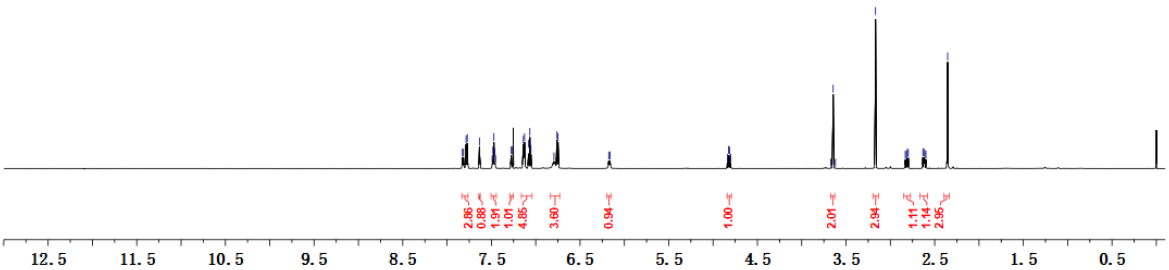
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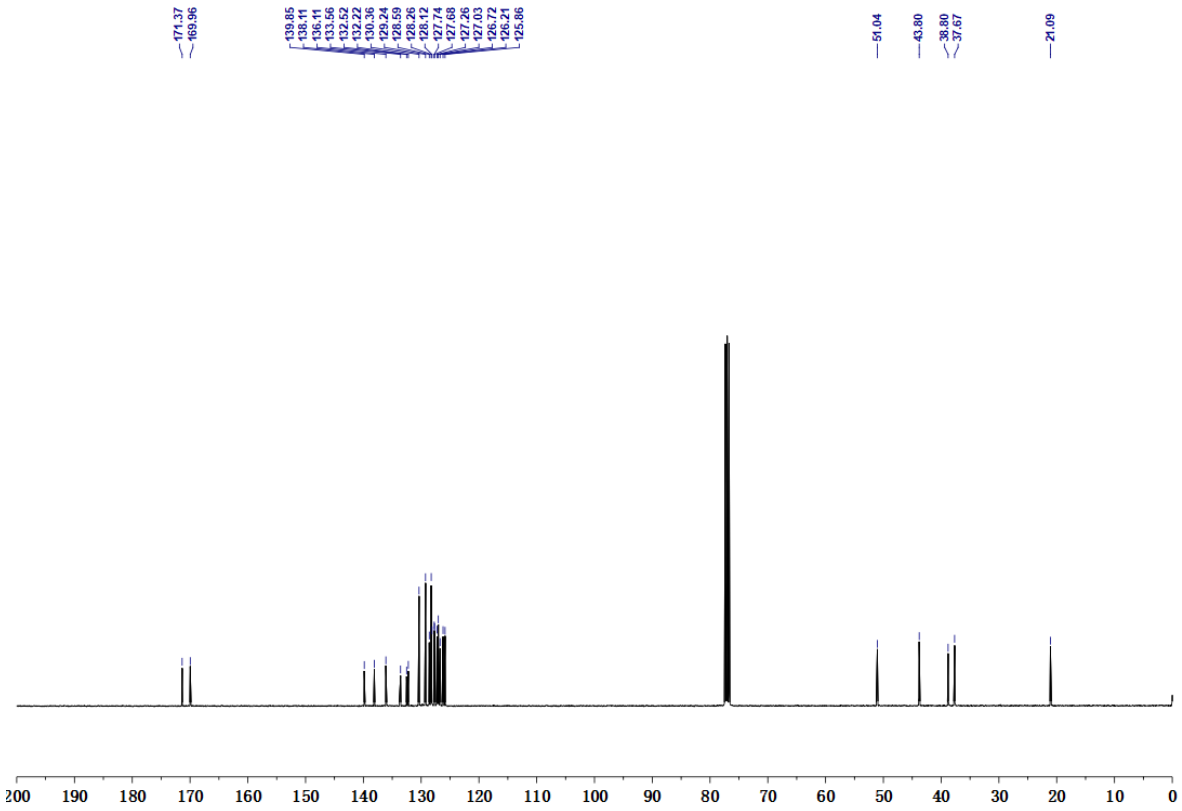
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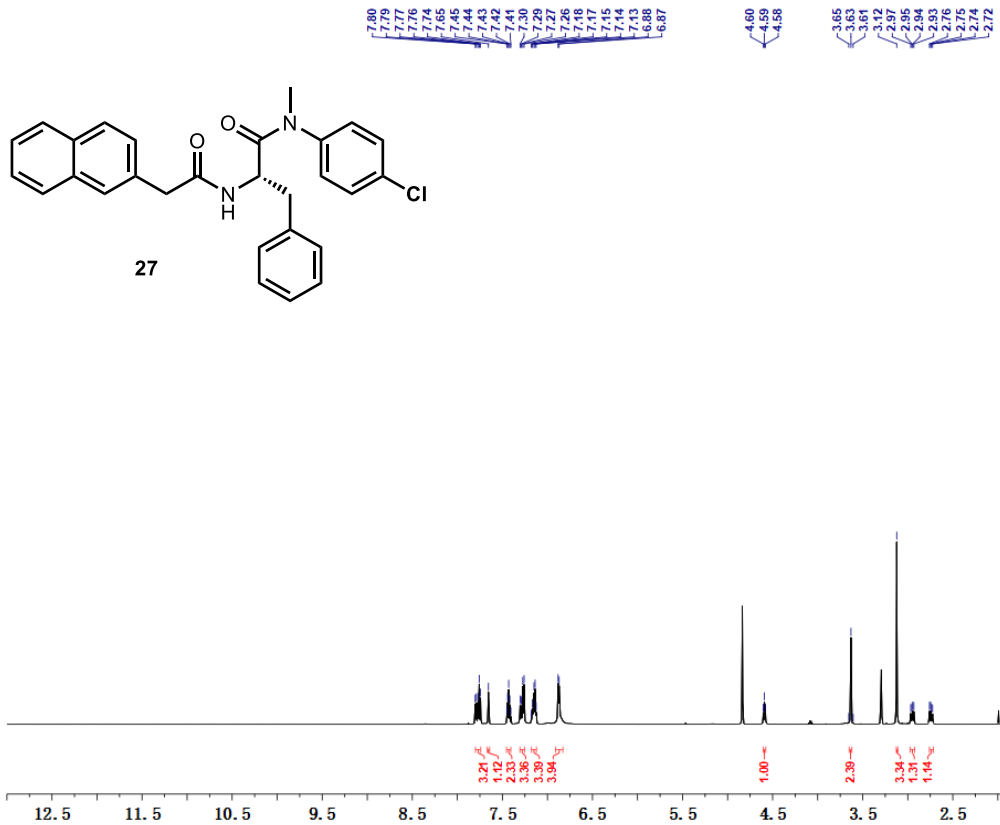
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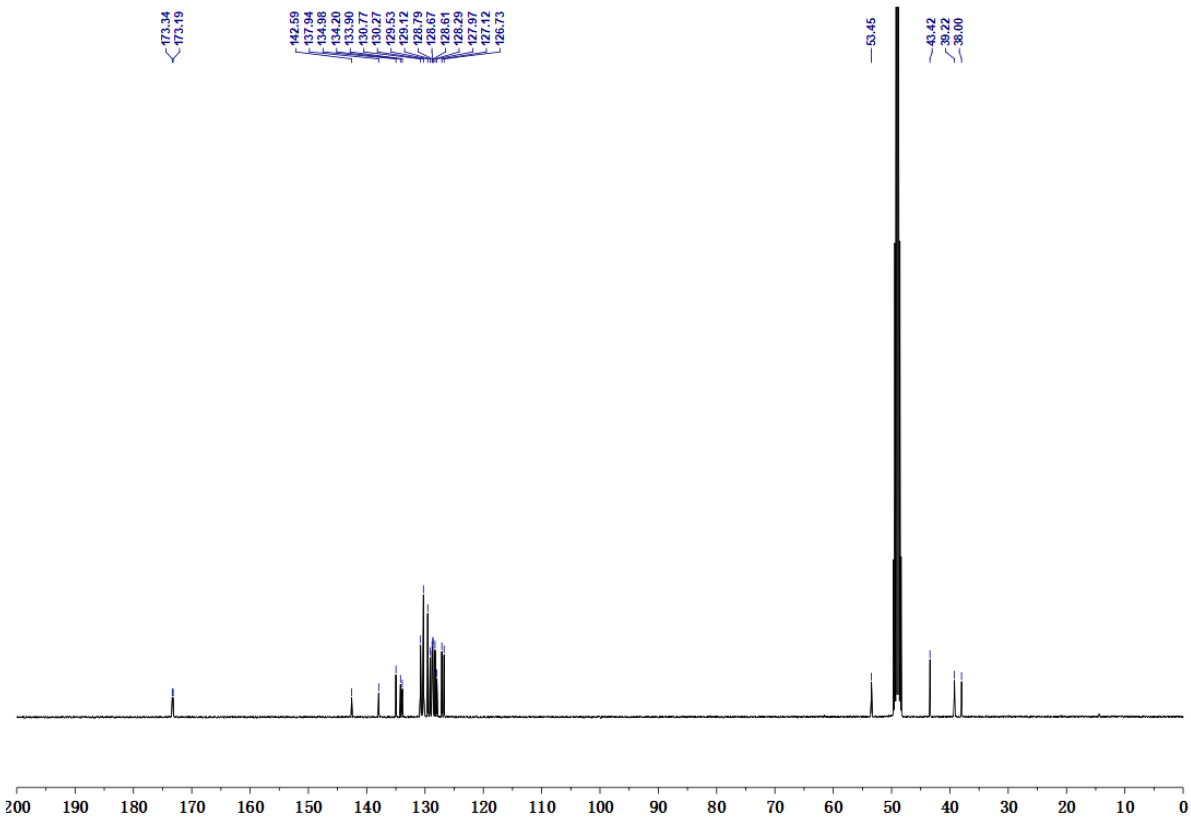
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127.97
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53.45
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39.22
38.60
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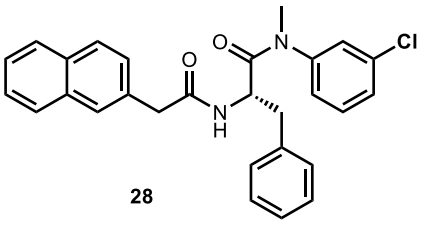
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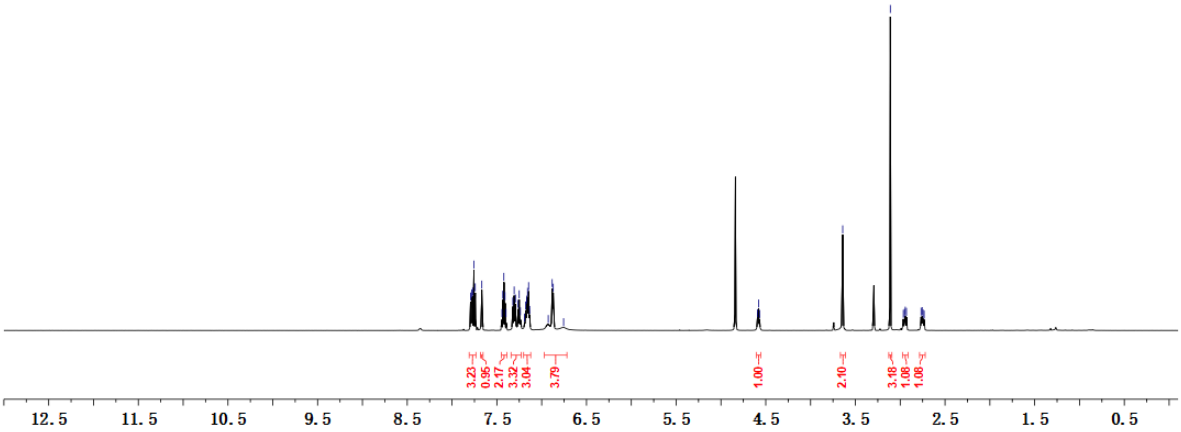
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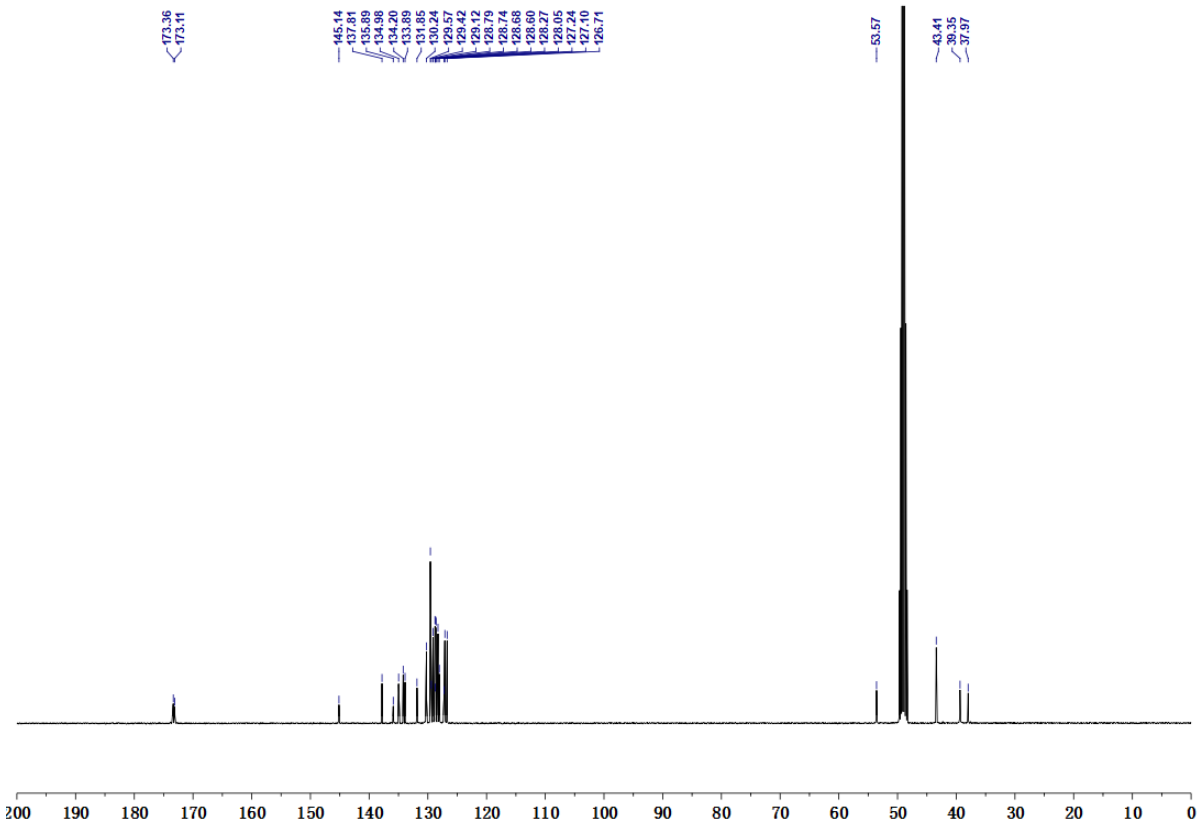
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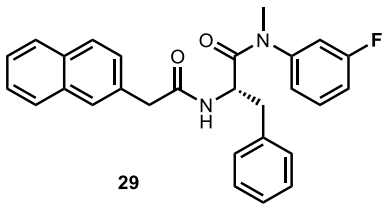
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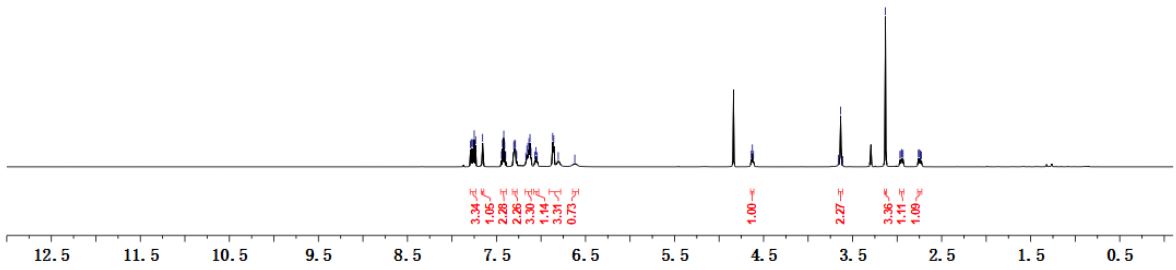
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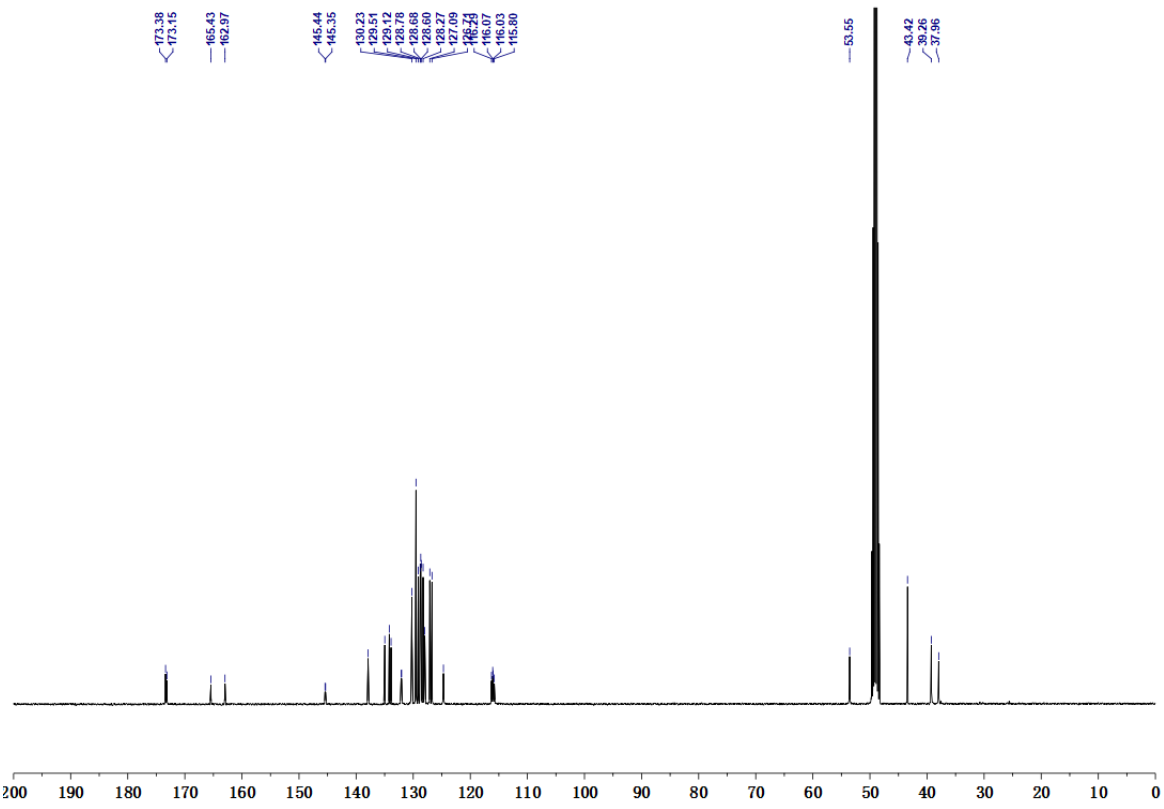
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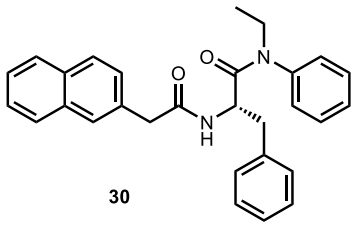
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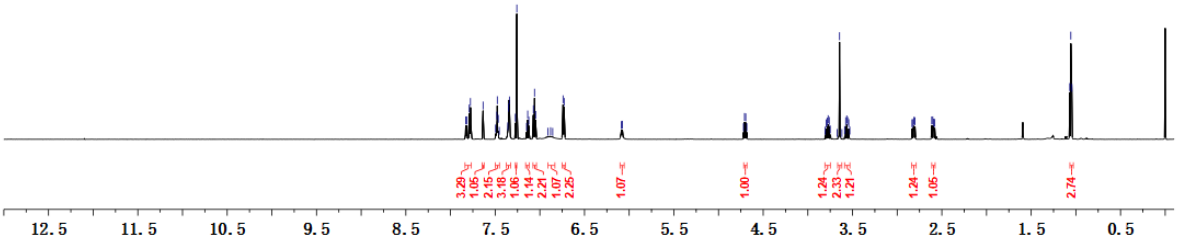
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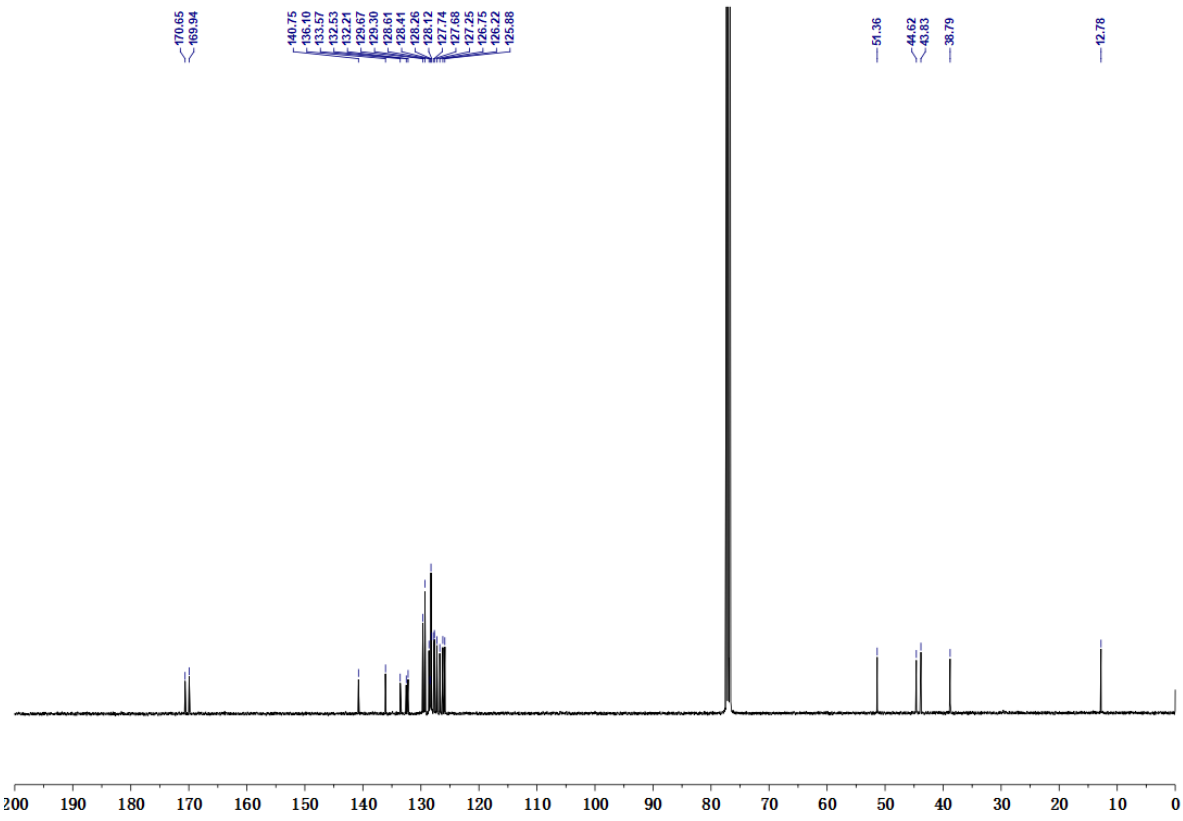
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200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


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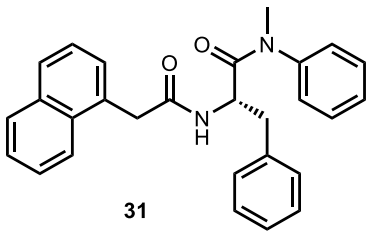
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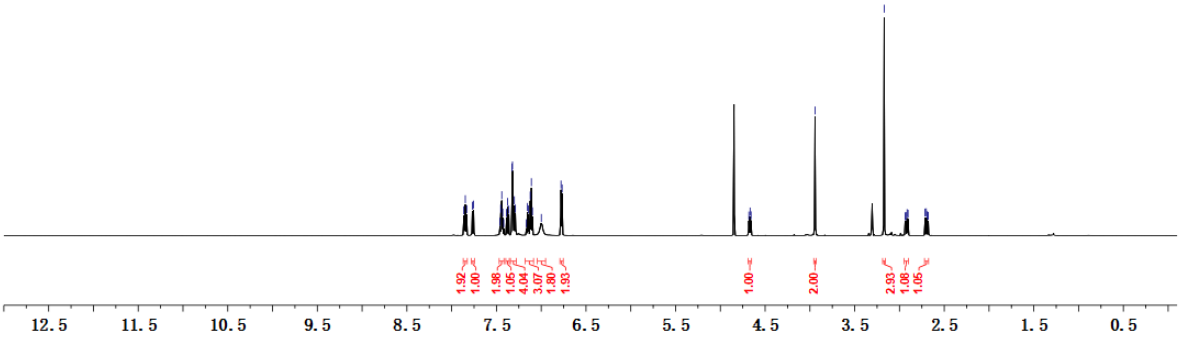
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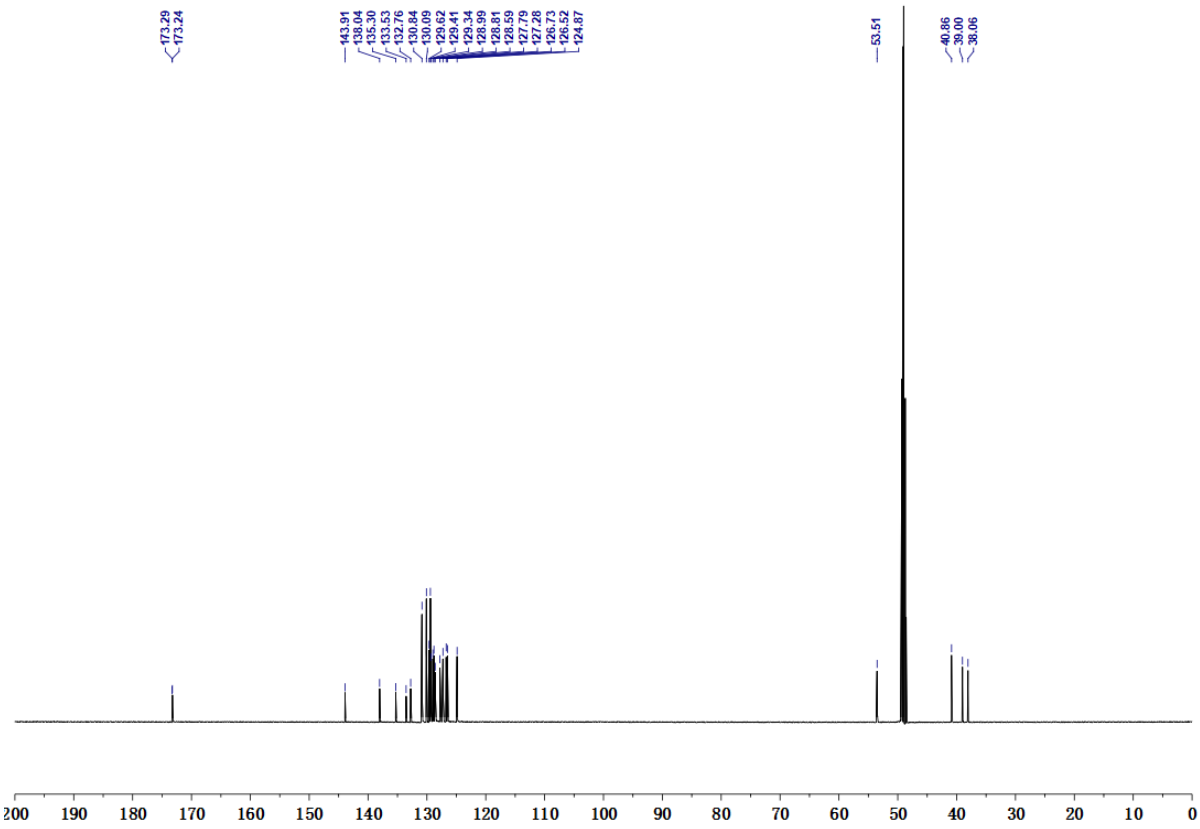
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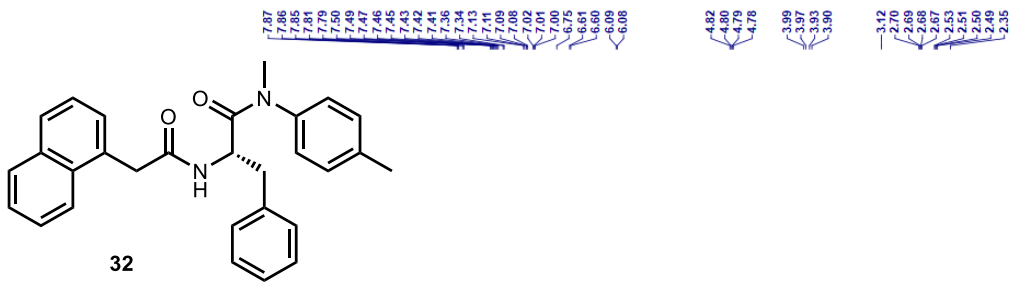
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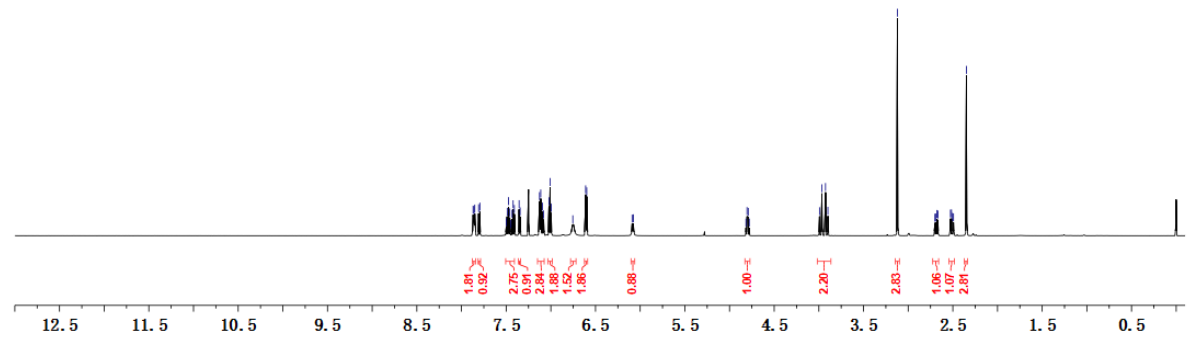
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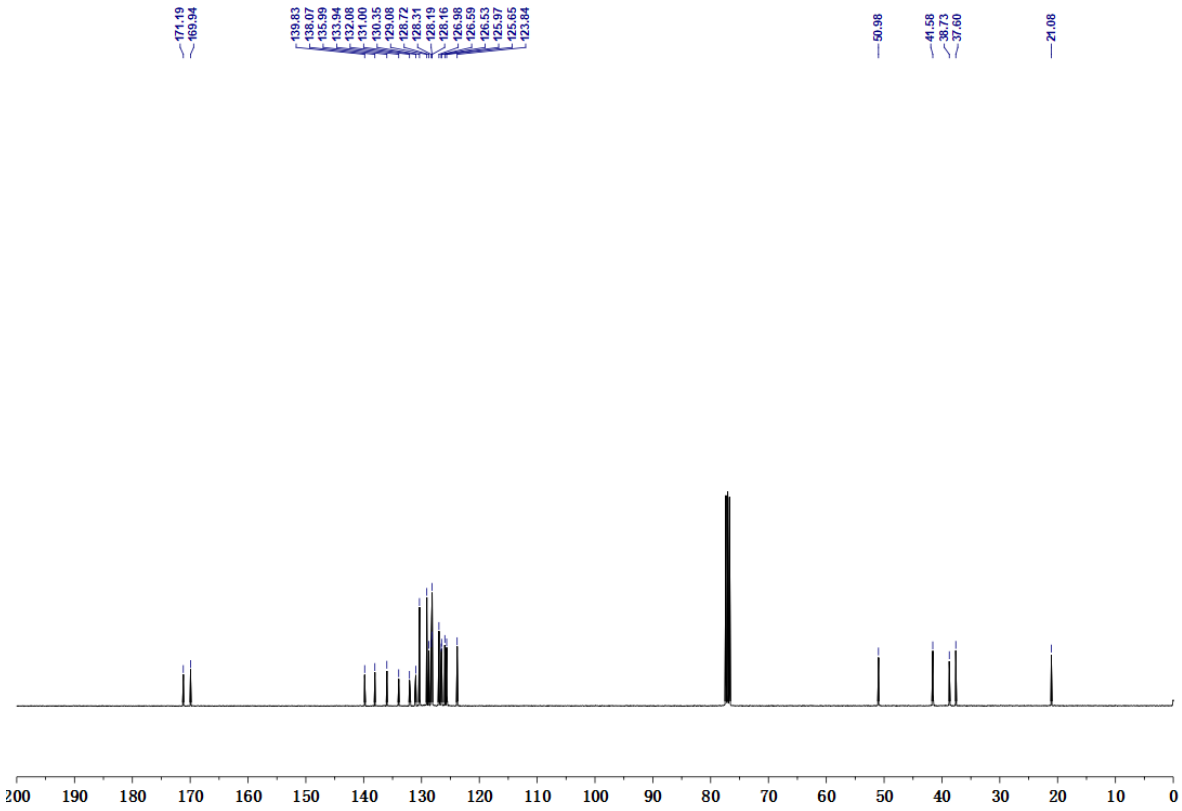
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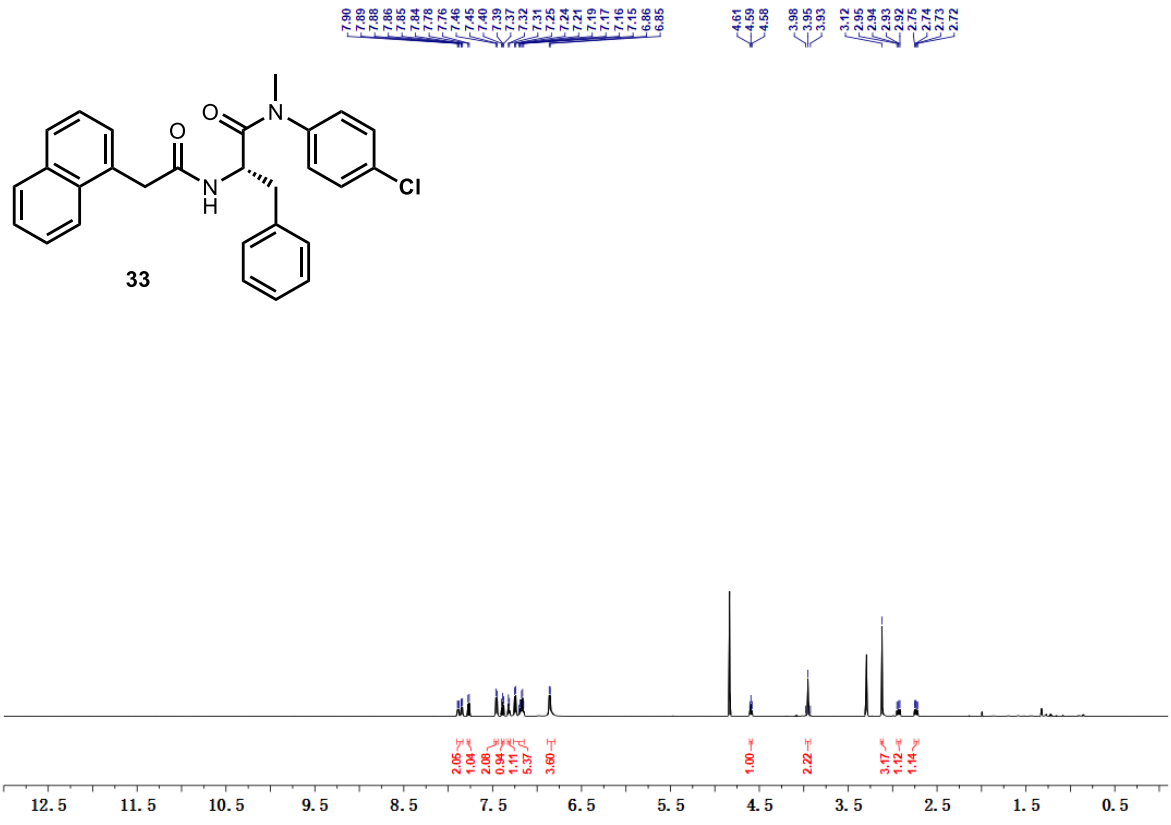
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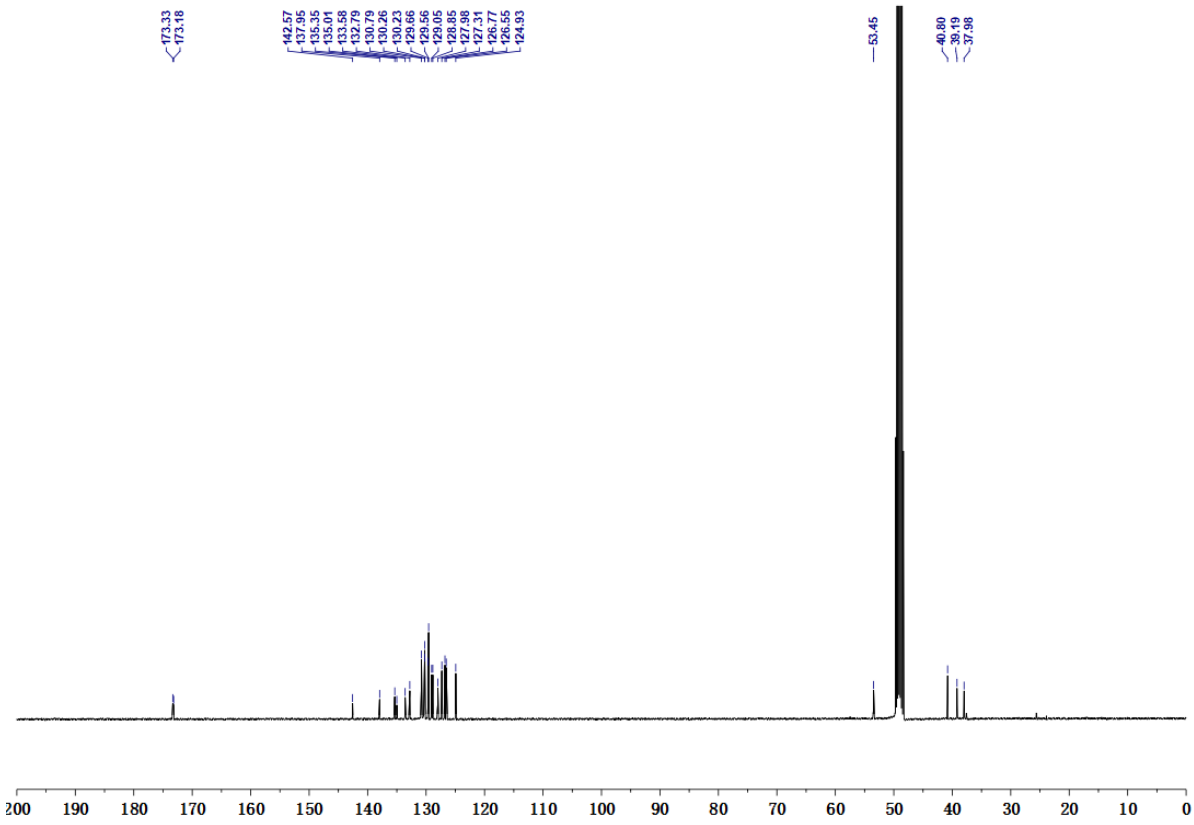
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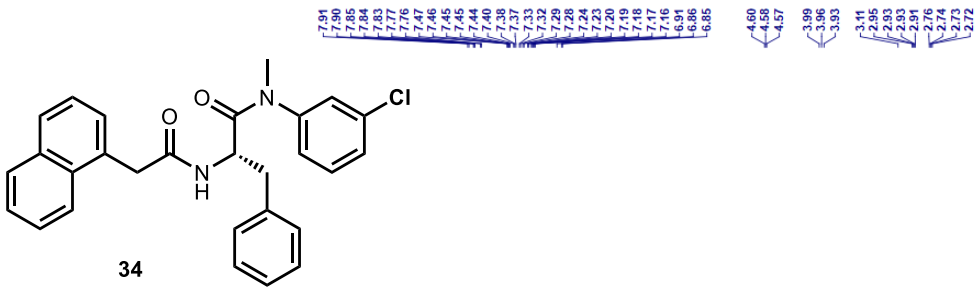
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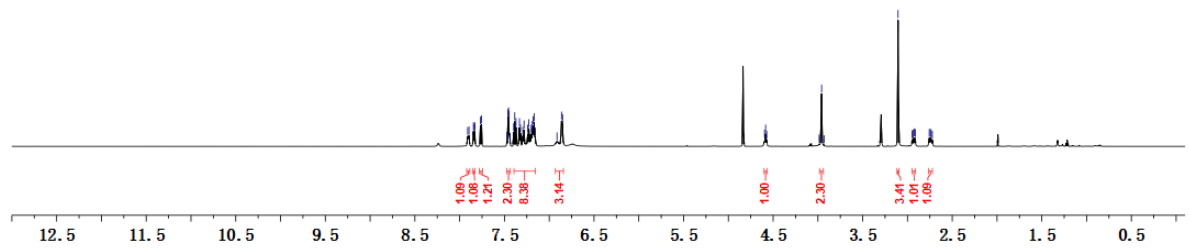
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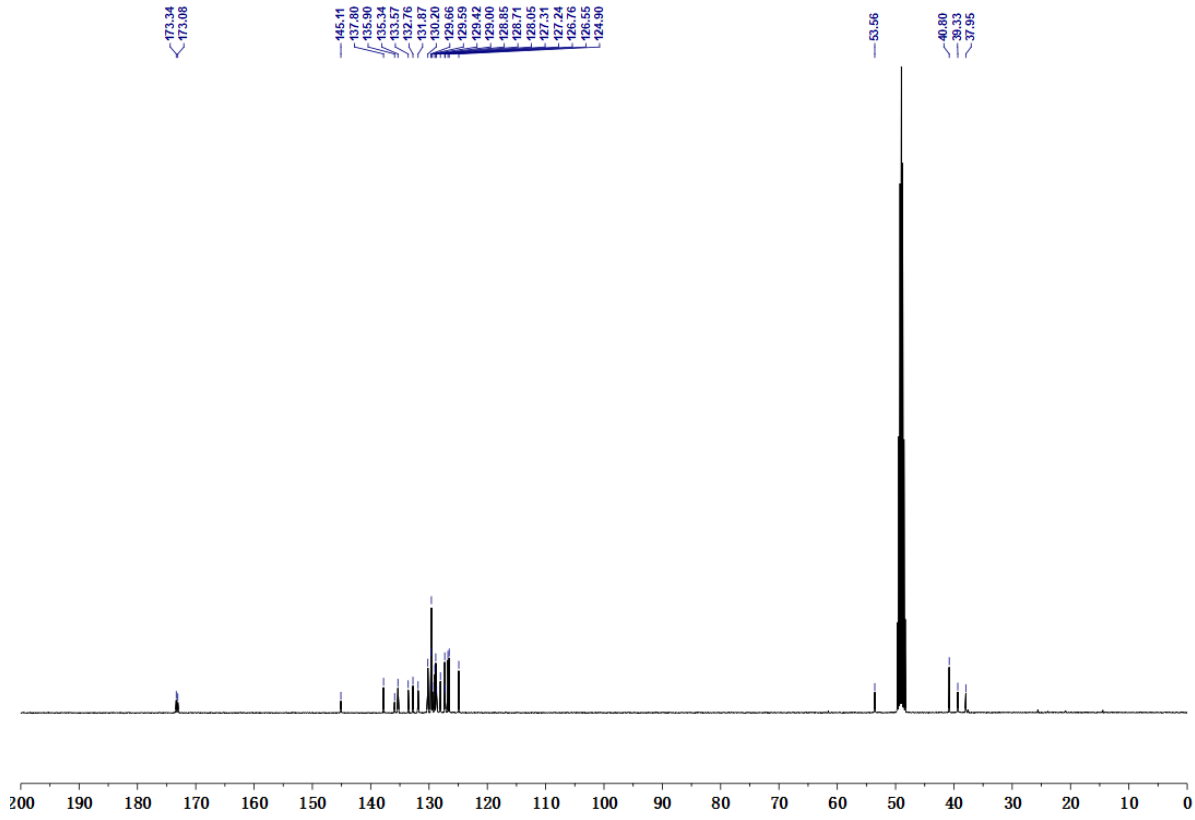
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39.33
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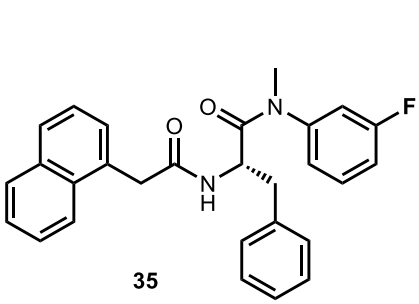
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F
O
N
H

35


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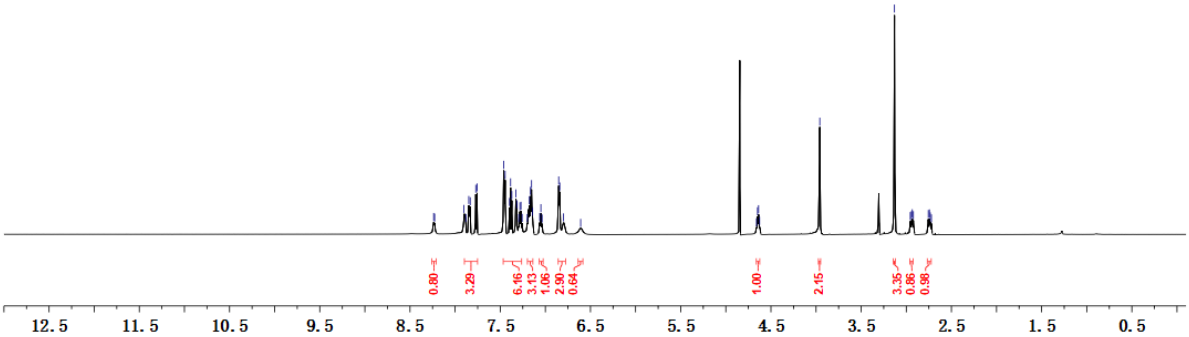
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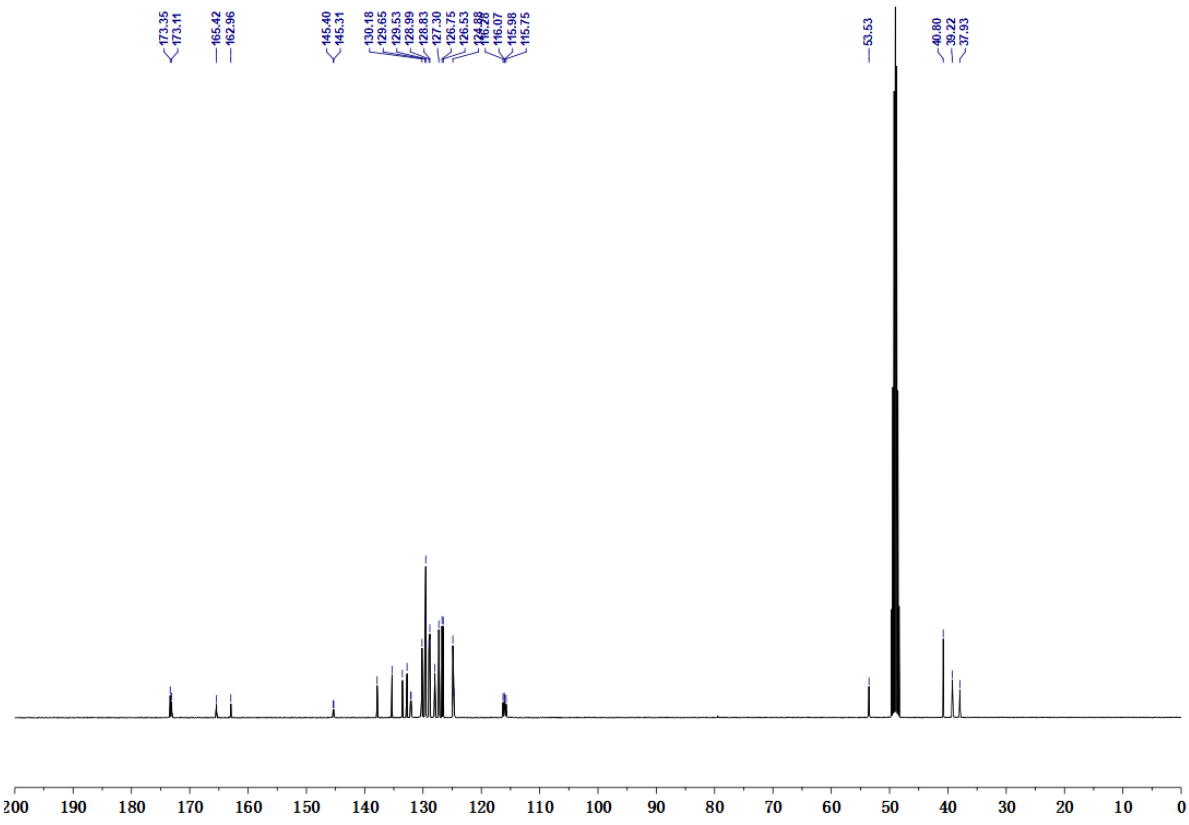

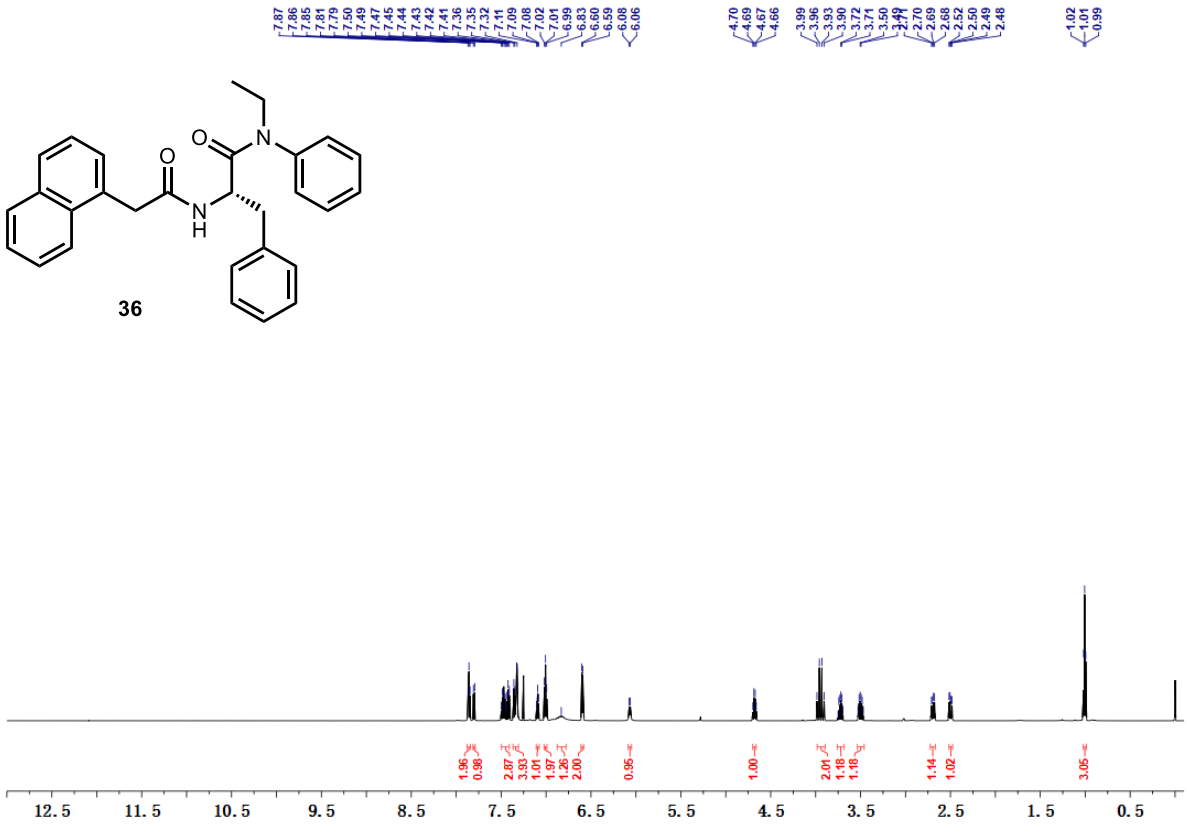

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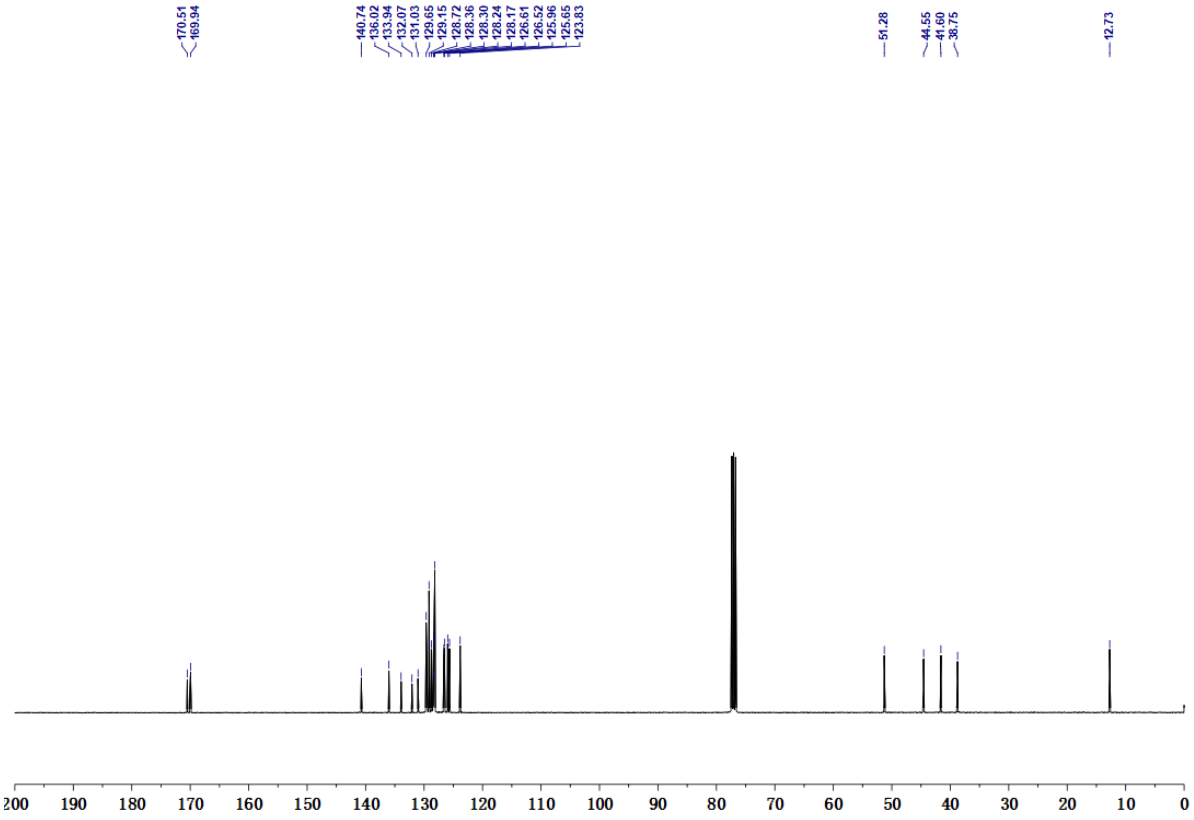
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126.52
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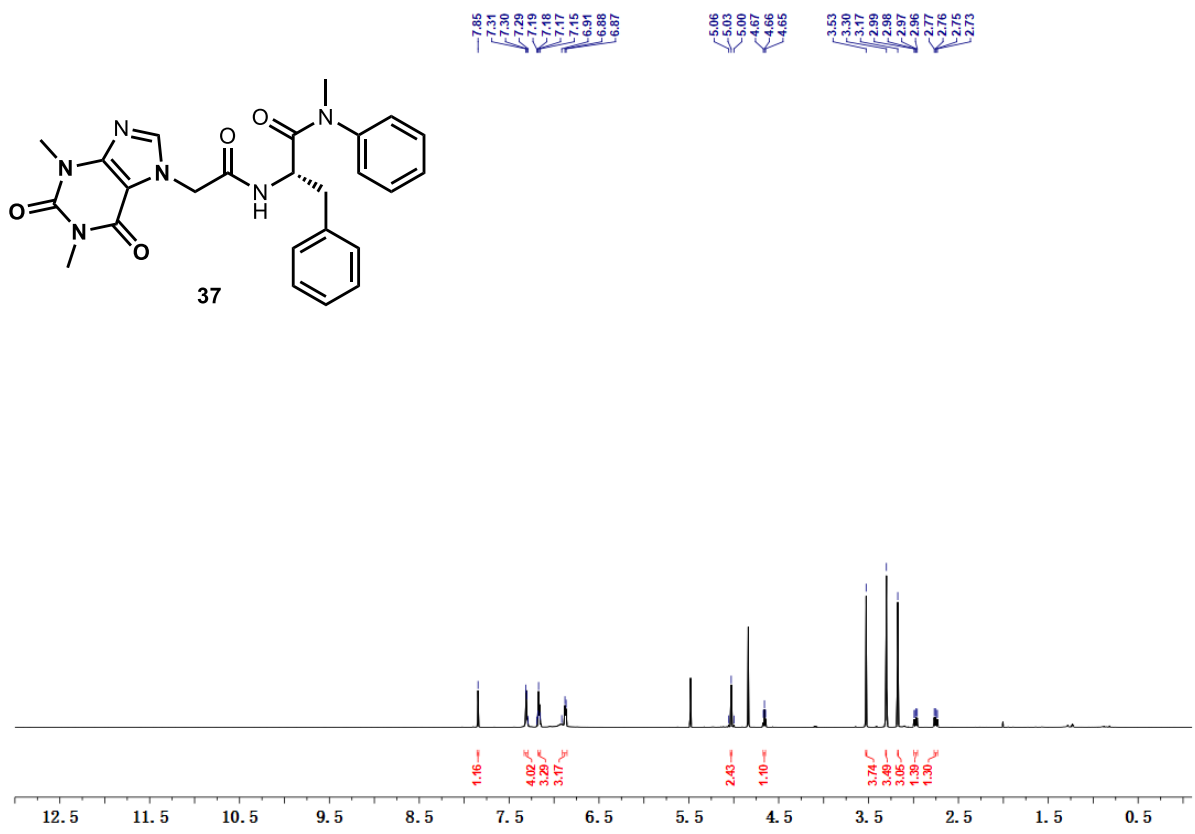
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2.75
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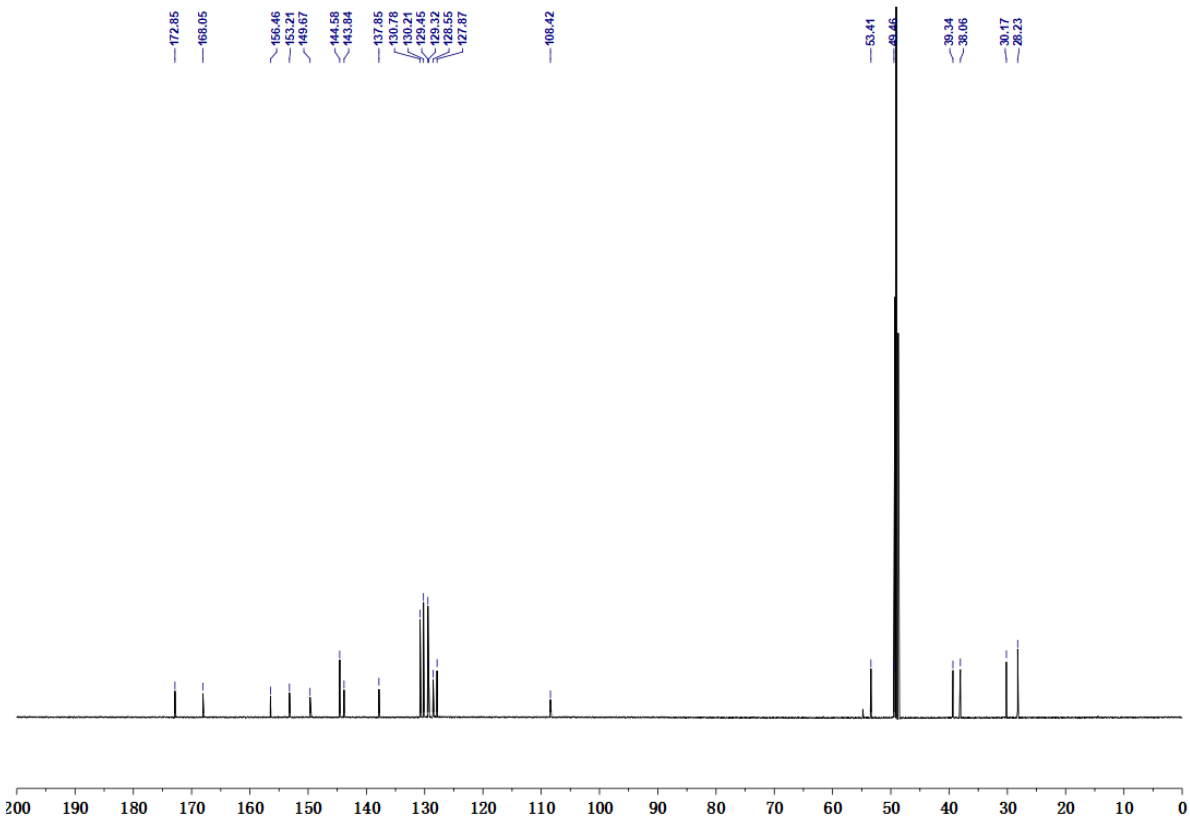
37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39.34
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30.17
28.23
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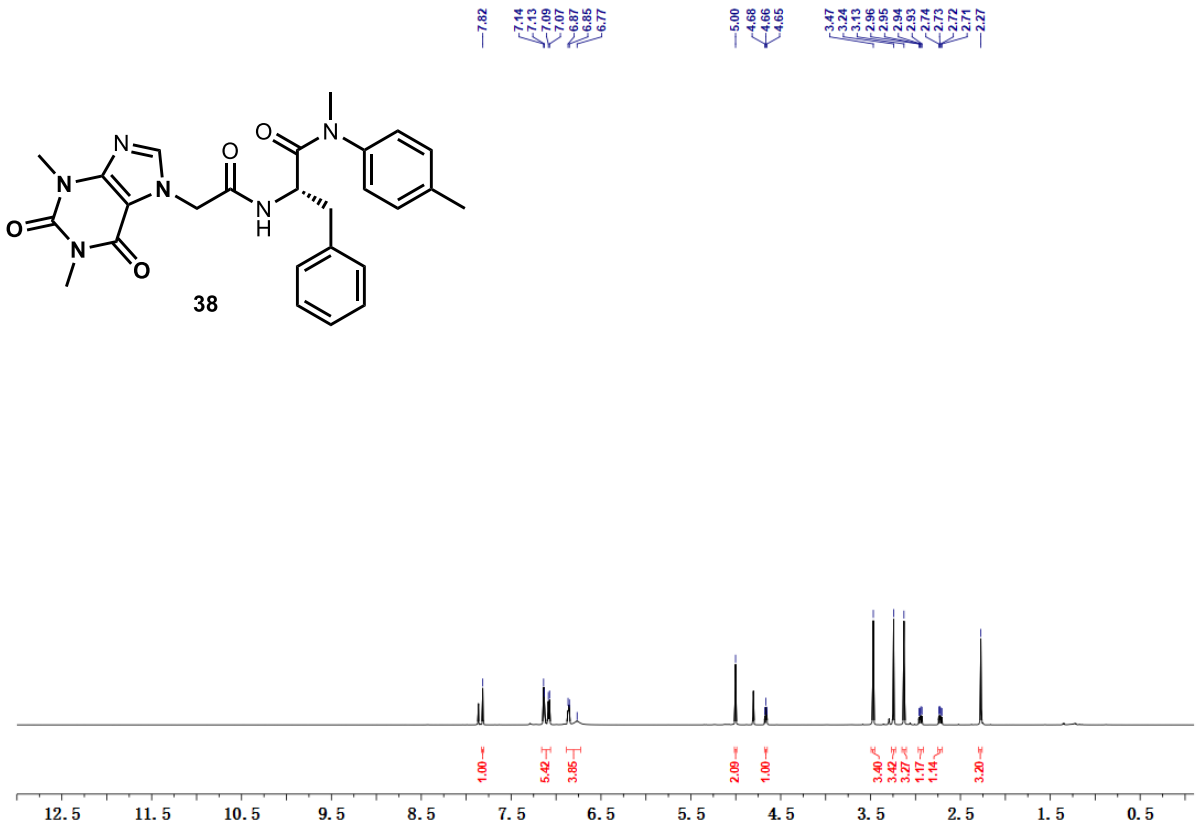
38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2.71
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2.09
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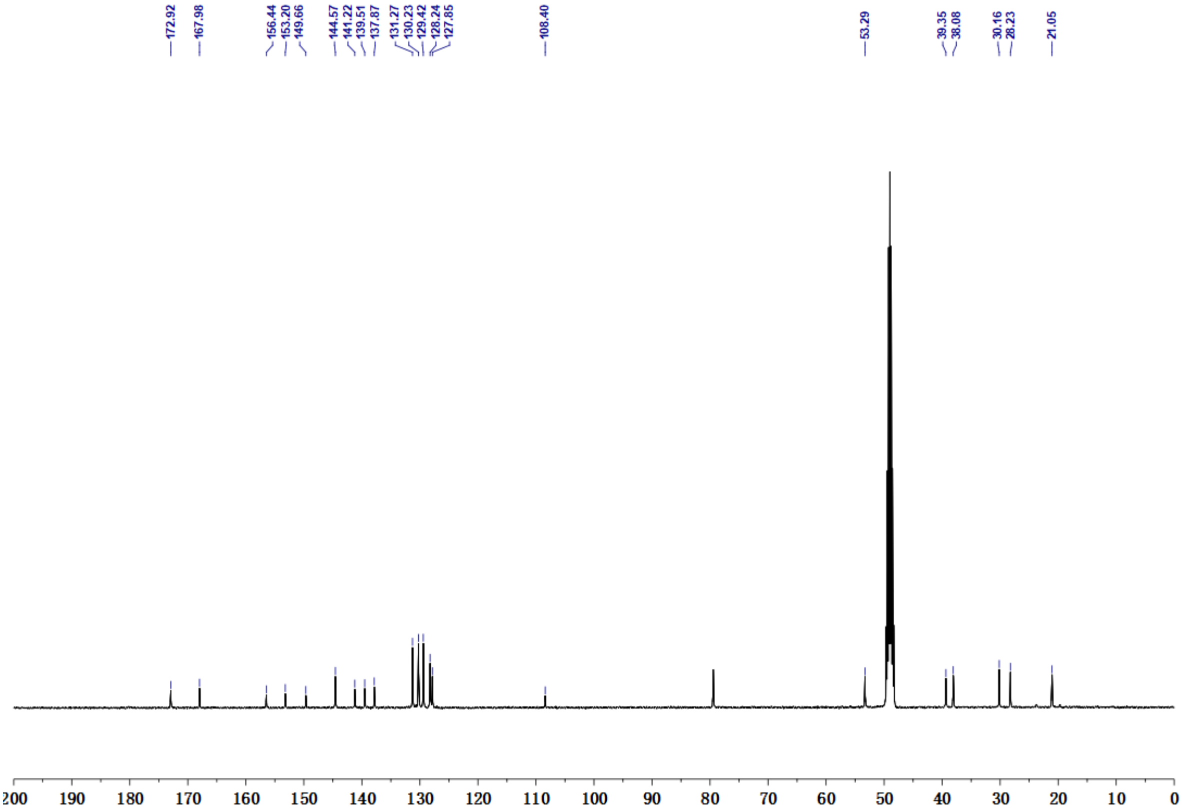
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128.24
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28.23
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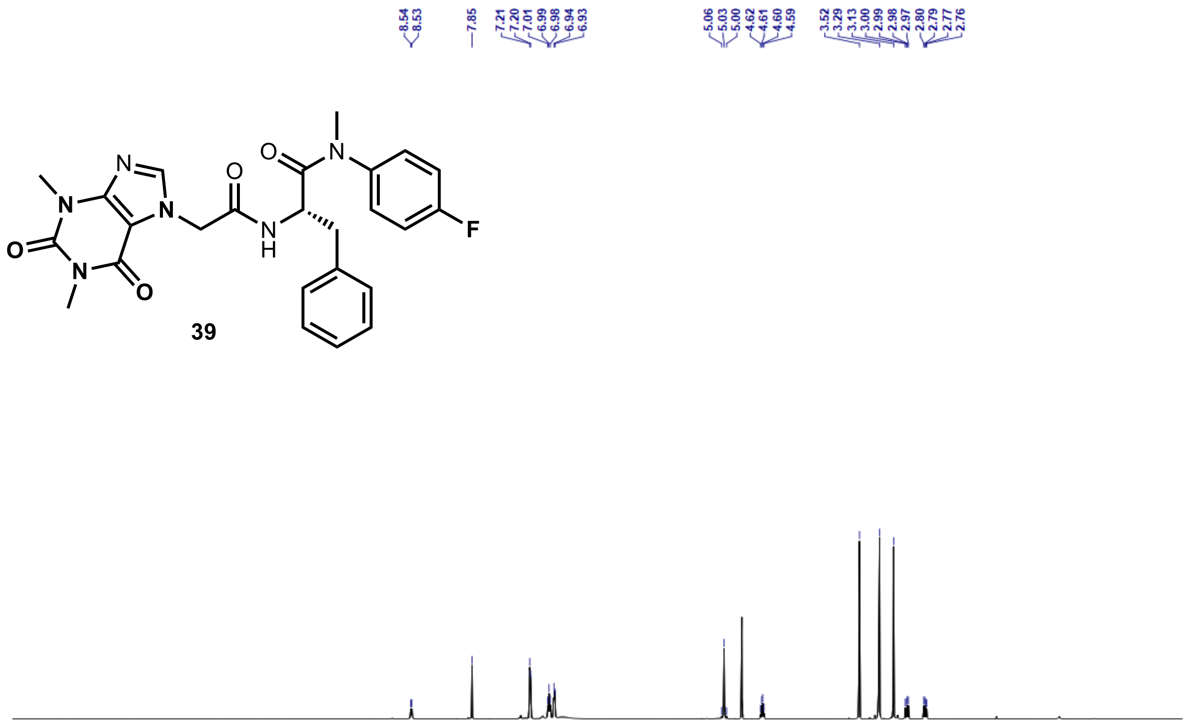
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O
N
F

39

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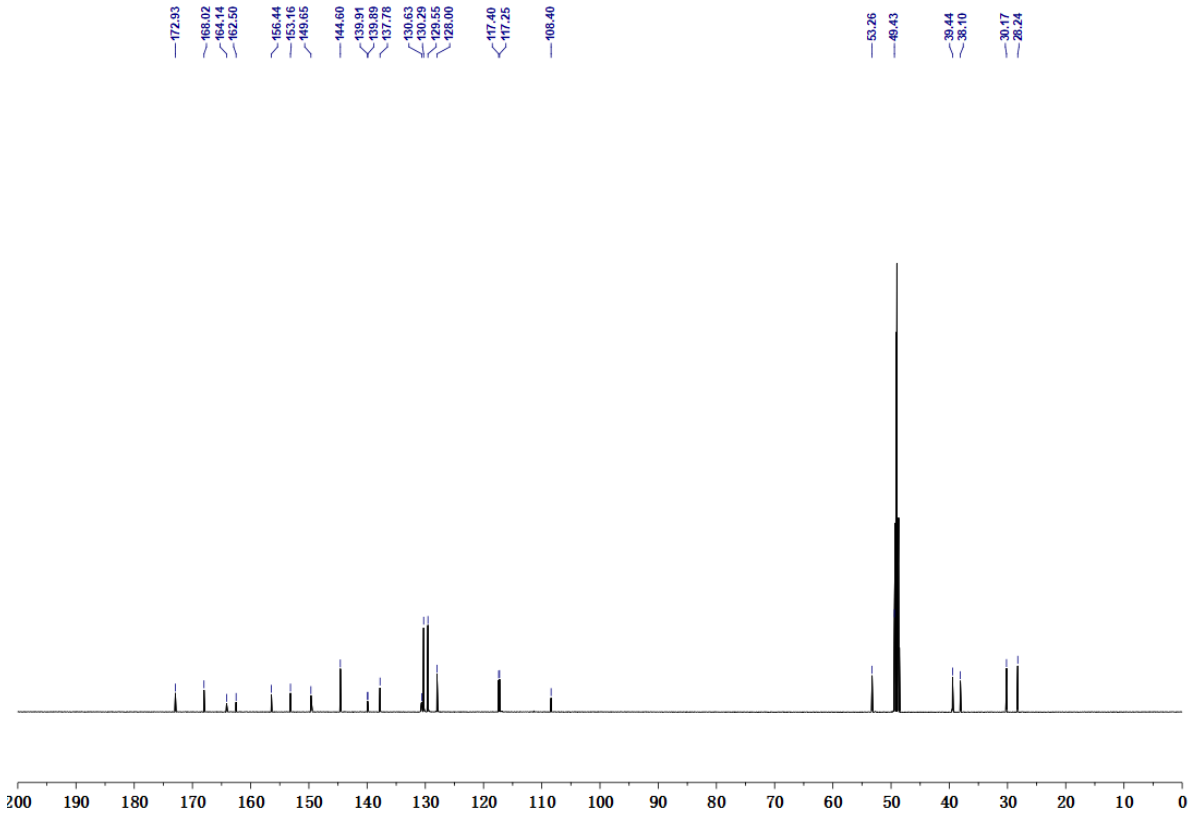
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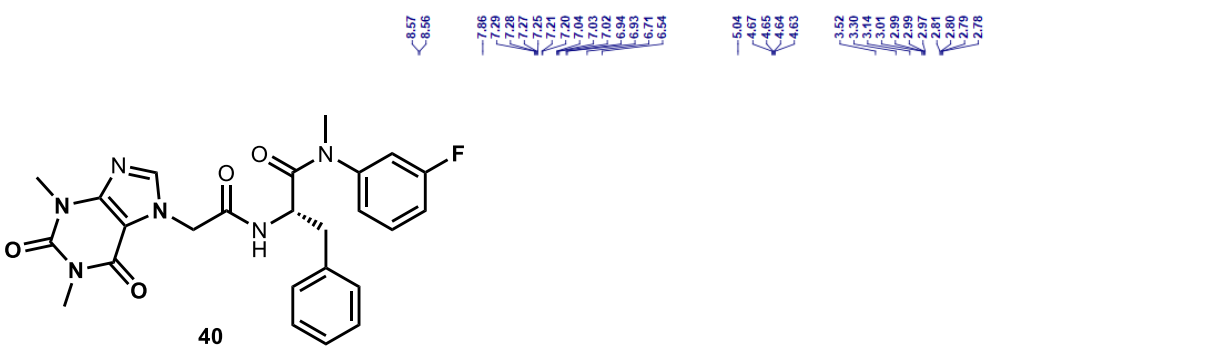
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3.30
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2.99
2.99
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2.79
2.78

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O
N
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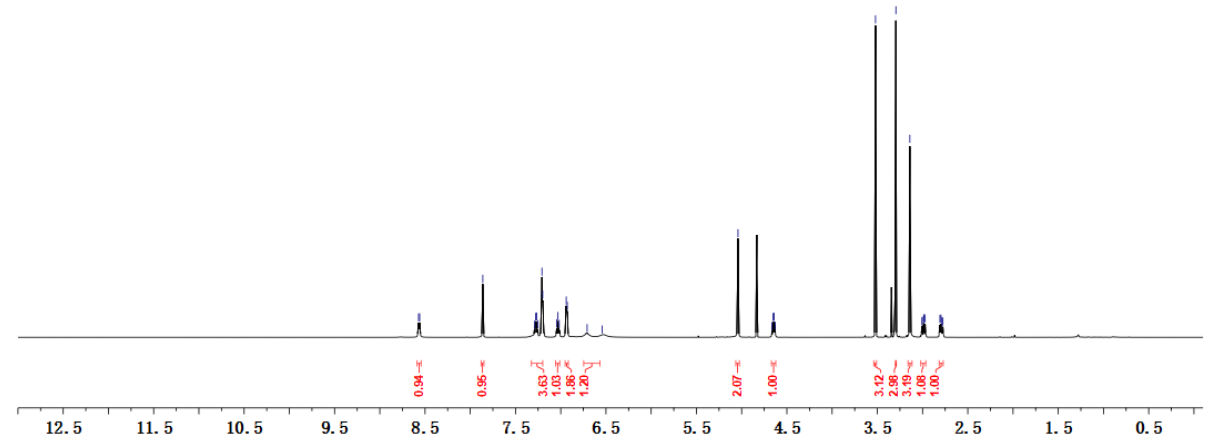
N
N
O
O

40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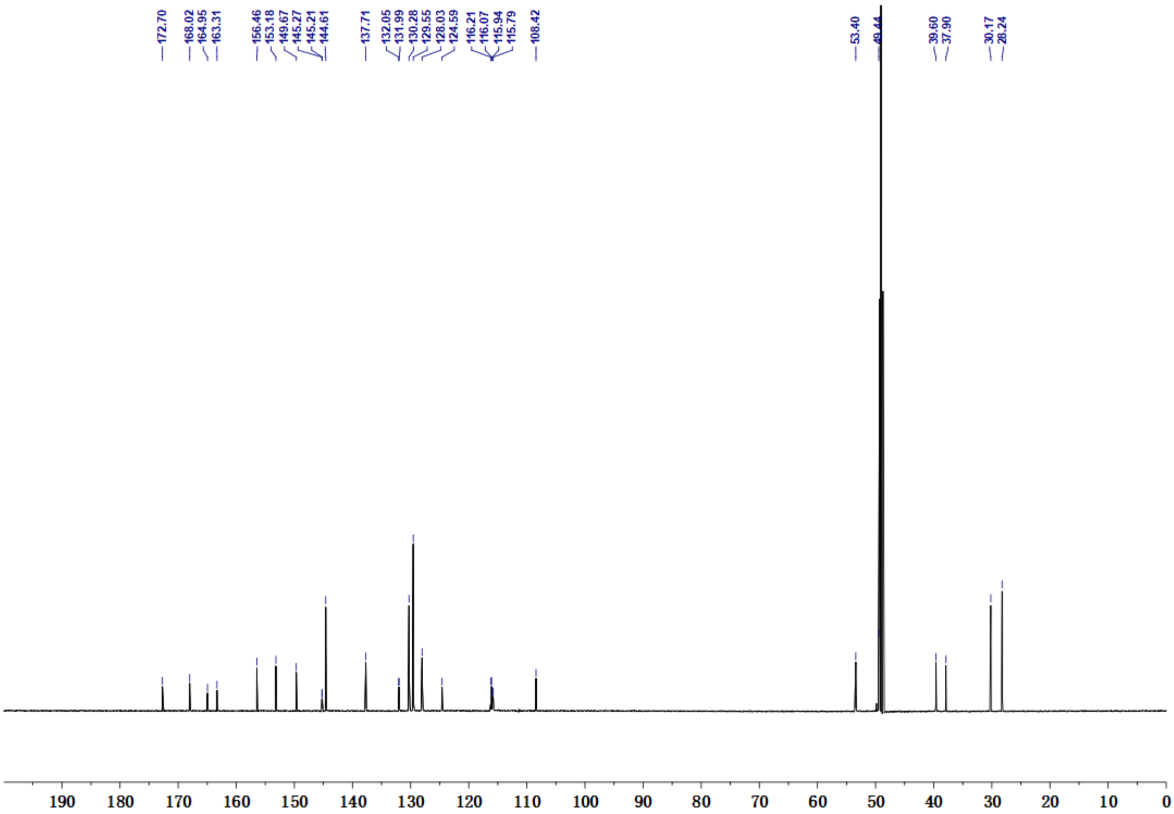
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128.03
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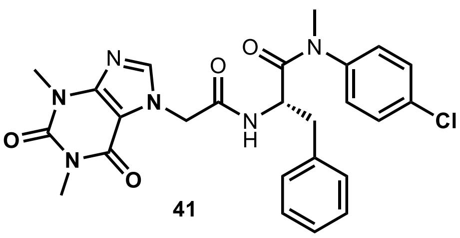
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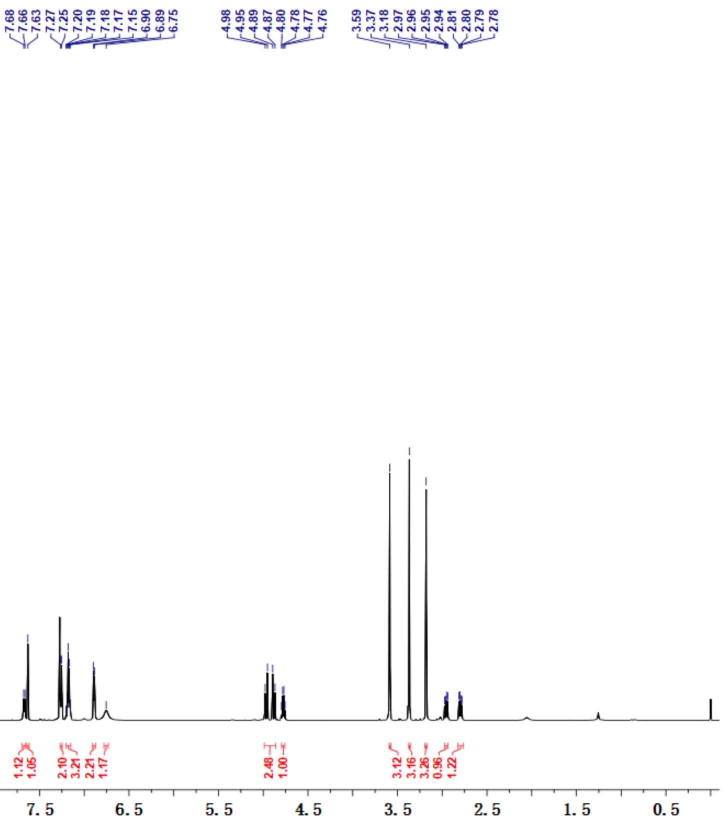
Cl

41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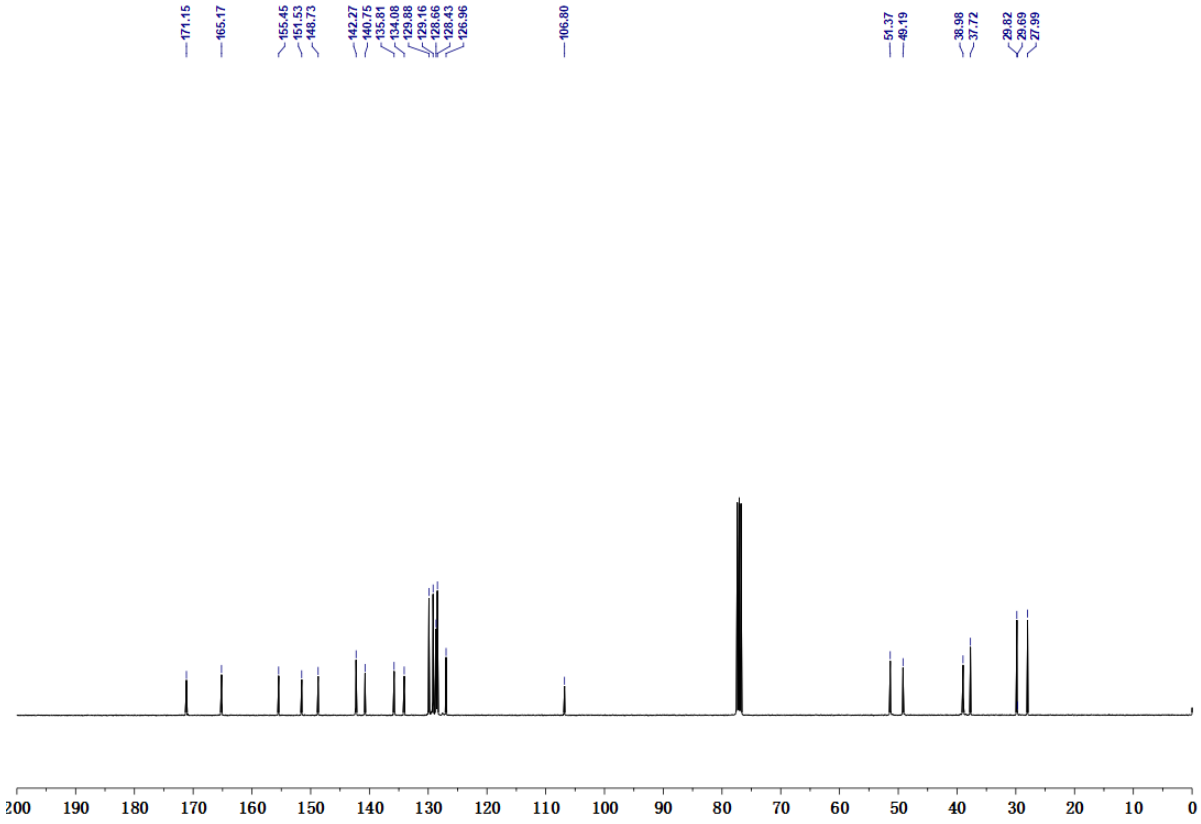
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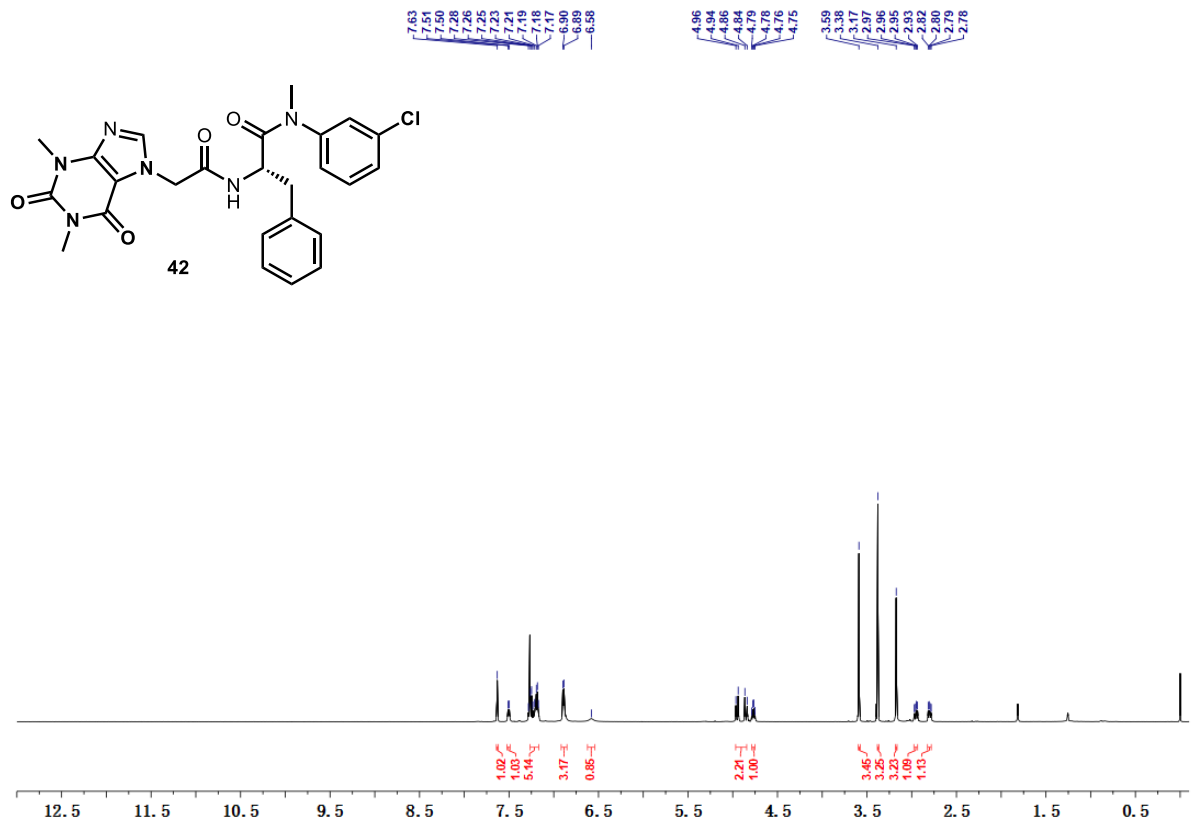
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Cl
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N
H
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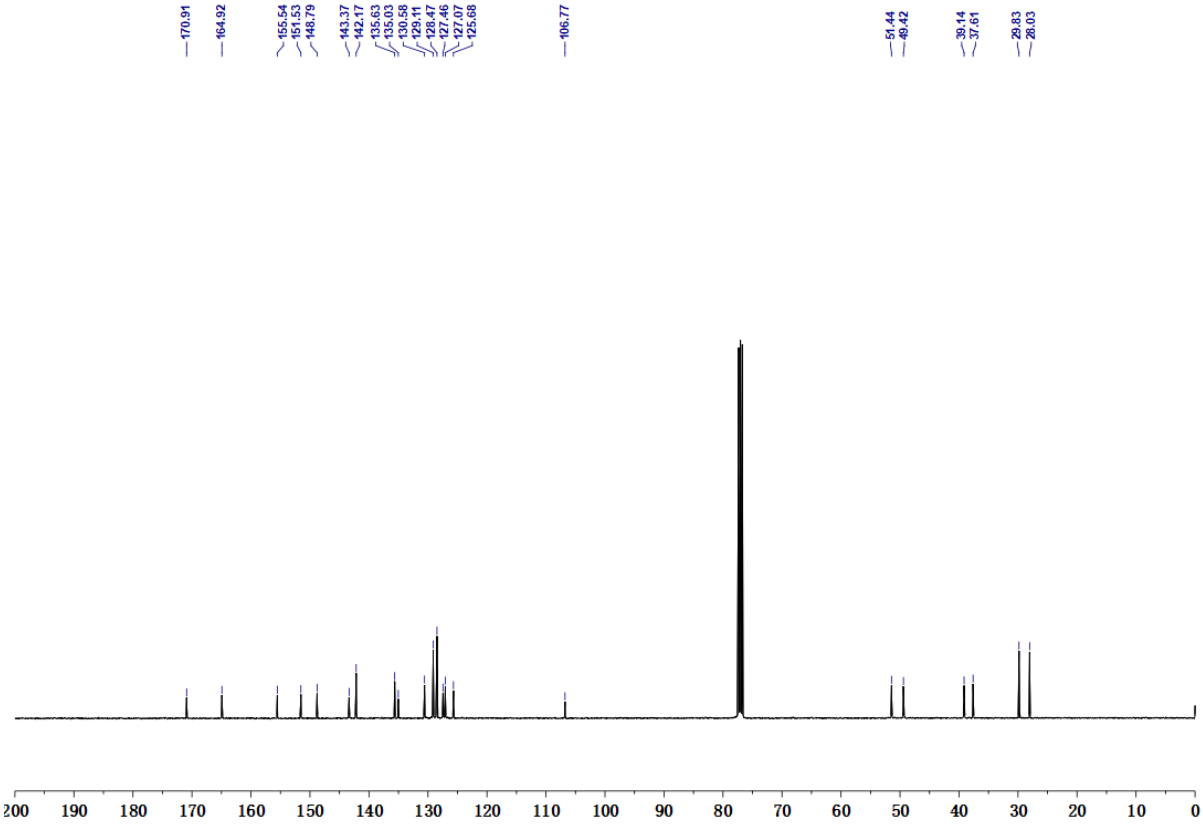
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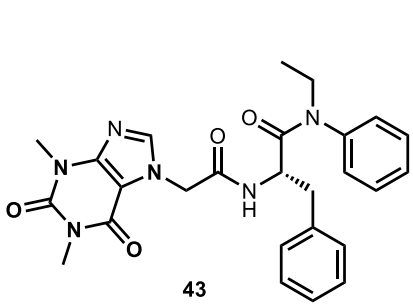
O
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N
H

43


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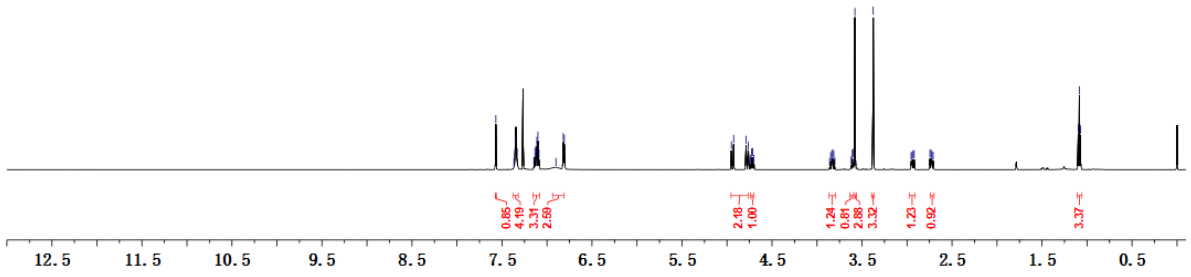
1.07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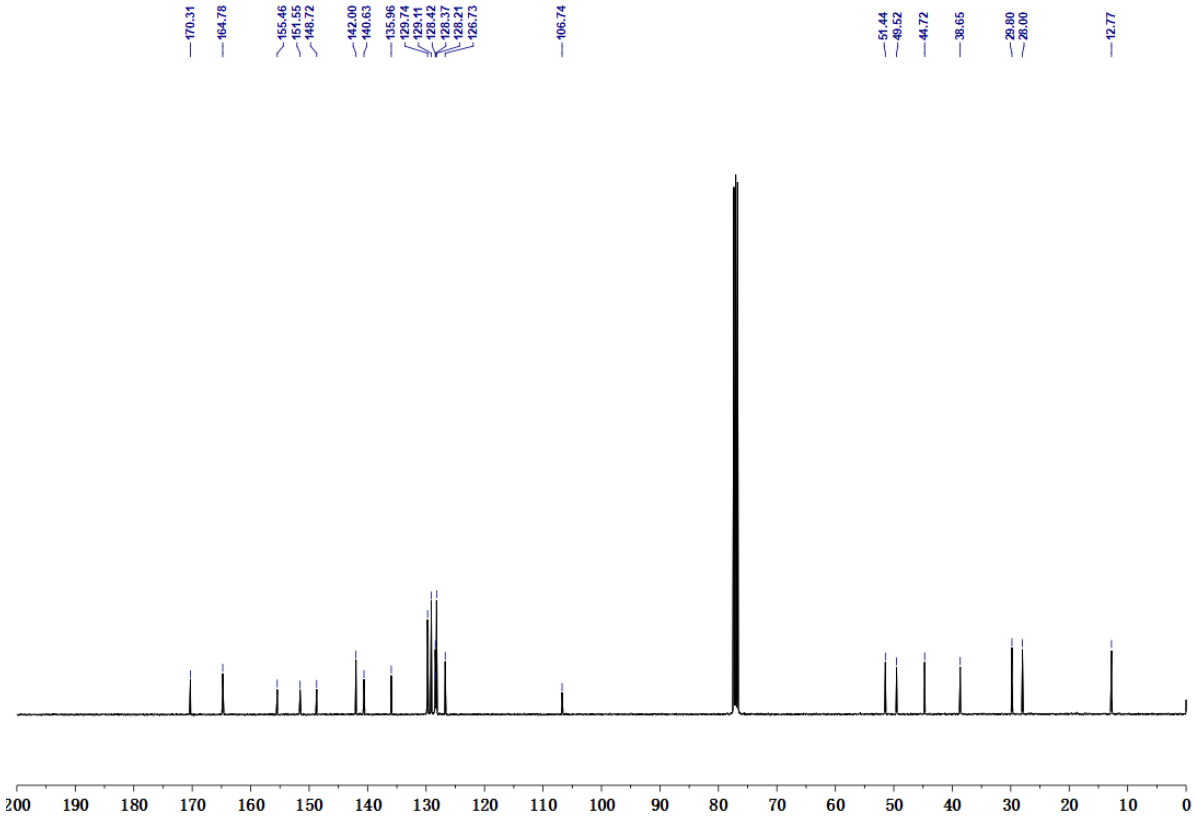
12.5 11.5 10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5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28.00
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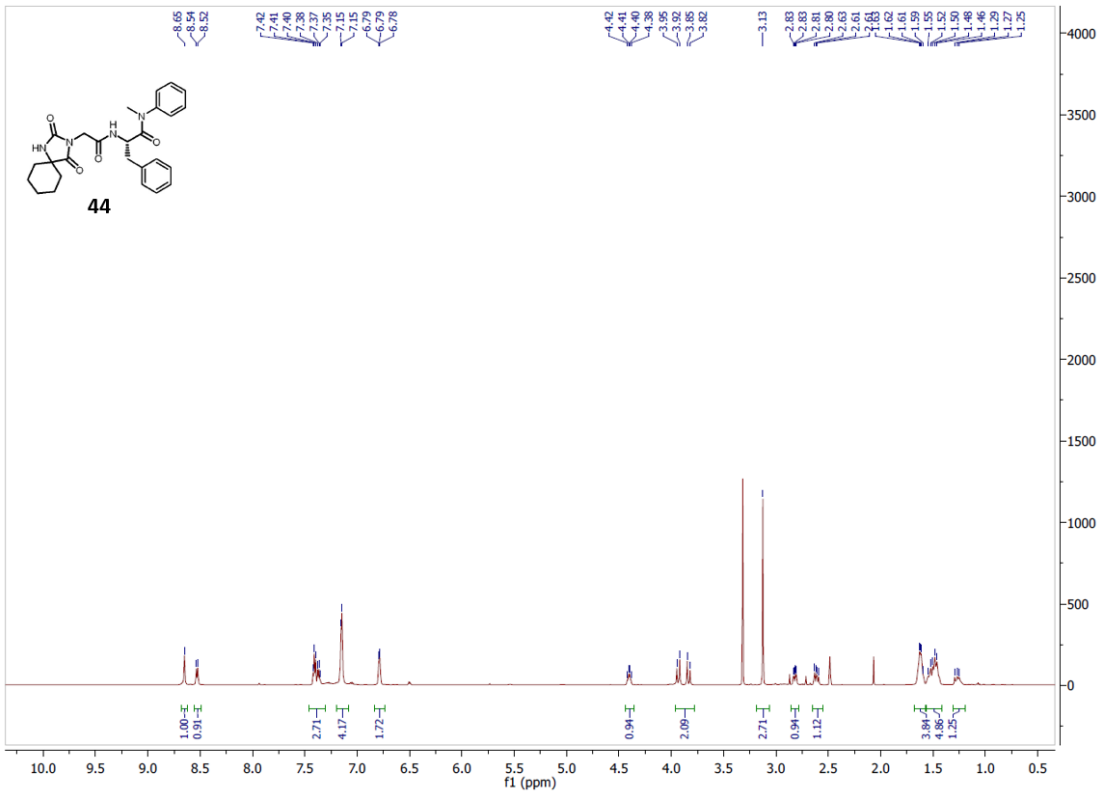
44
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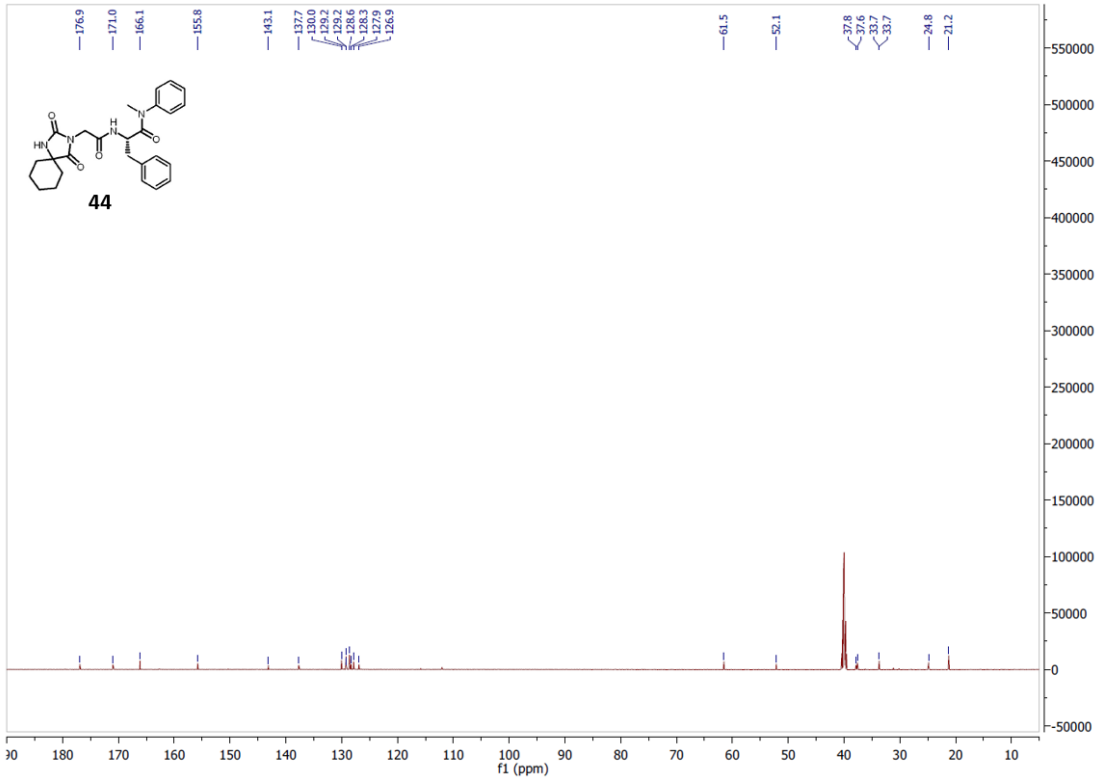
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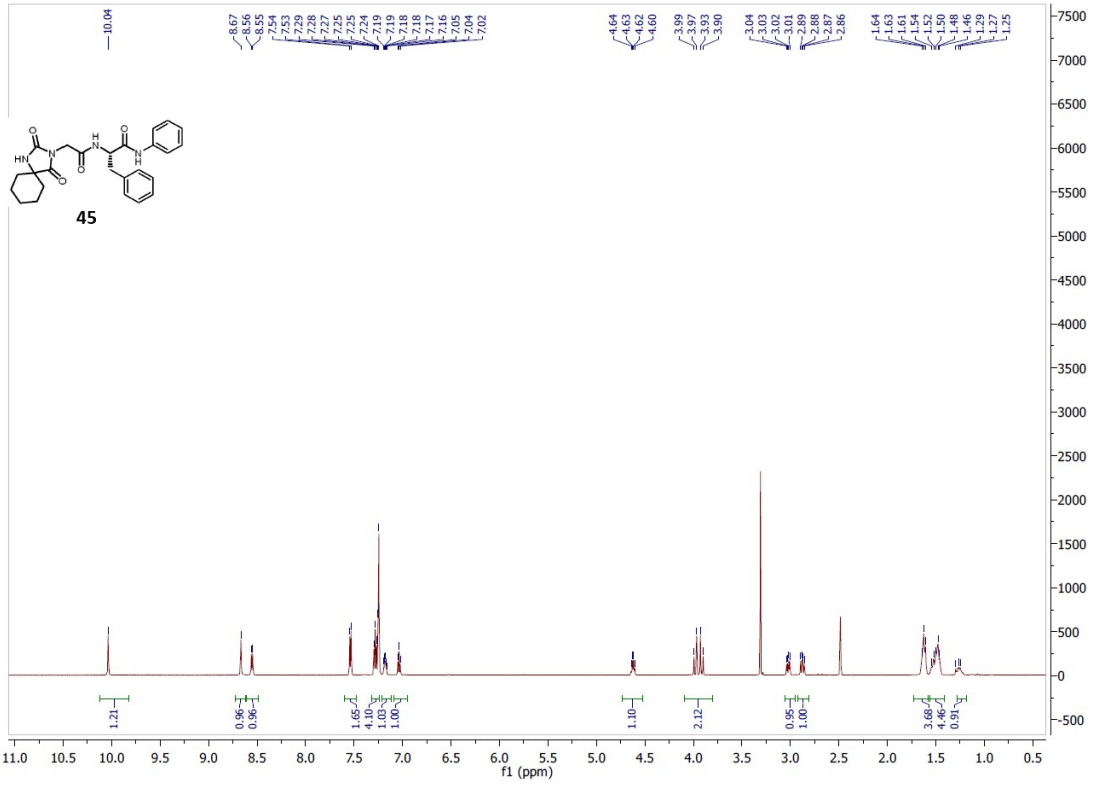
21.2
44
f1 (ppm)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0.91
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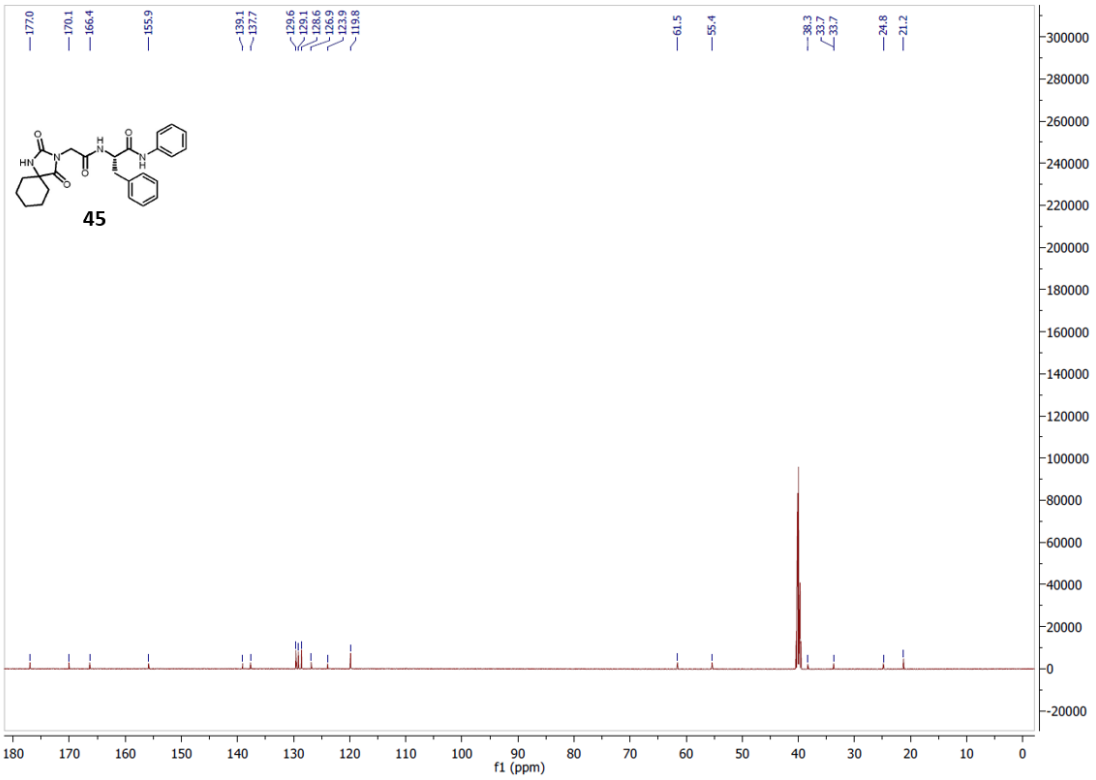
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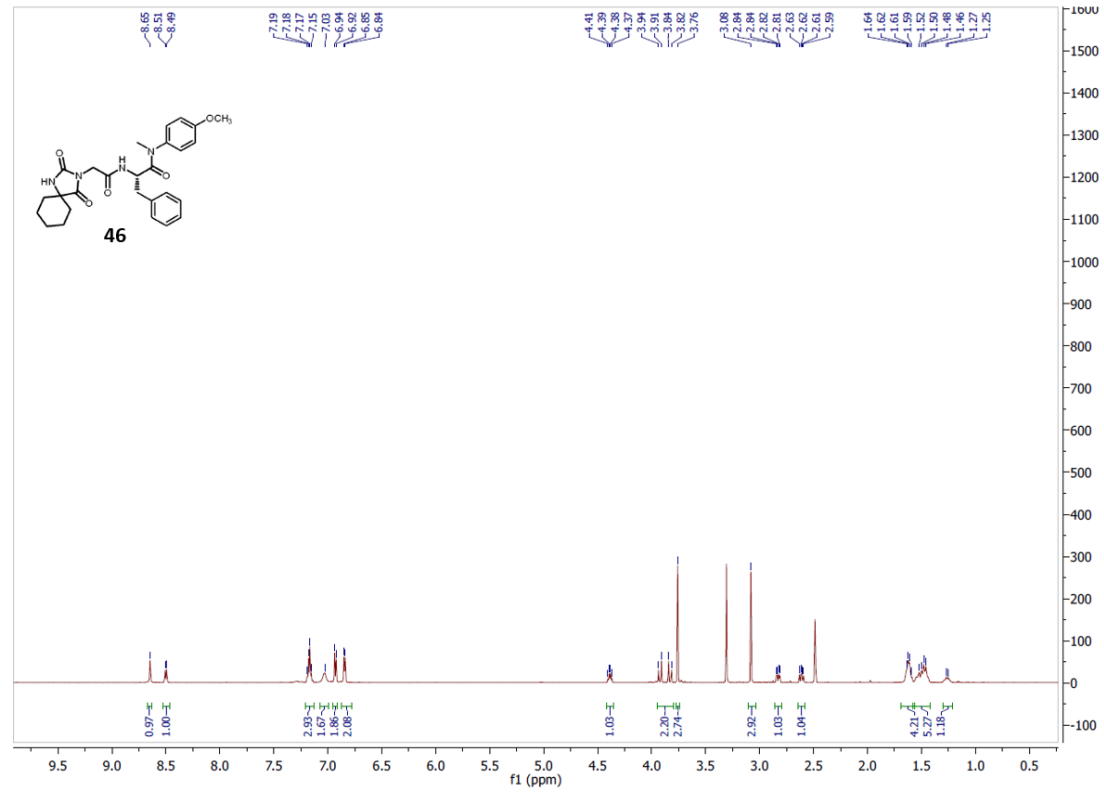
33.7
33.7
24.8
21.2
45
f1 (ppm)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OCH3
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1.04
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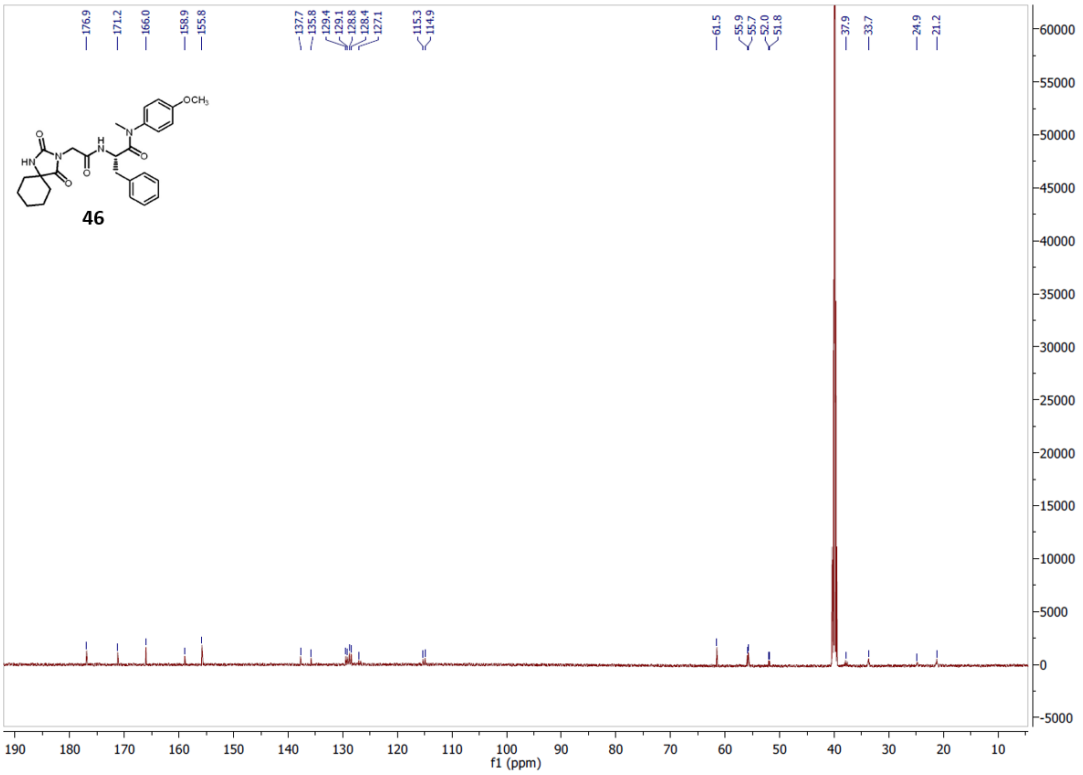
f1 (ppm)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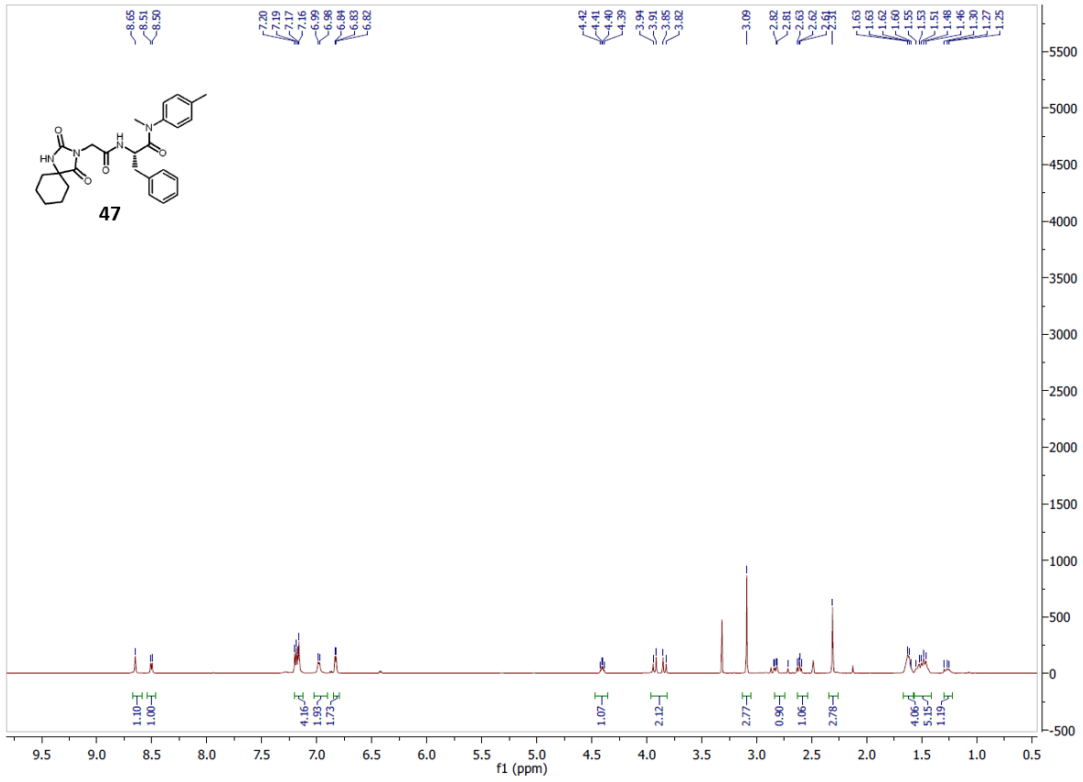
37.9
33.7
24.9
21.2
OCH3
46
f1 (ppm)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4.06
5.15
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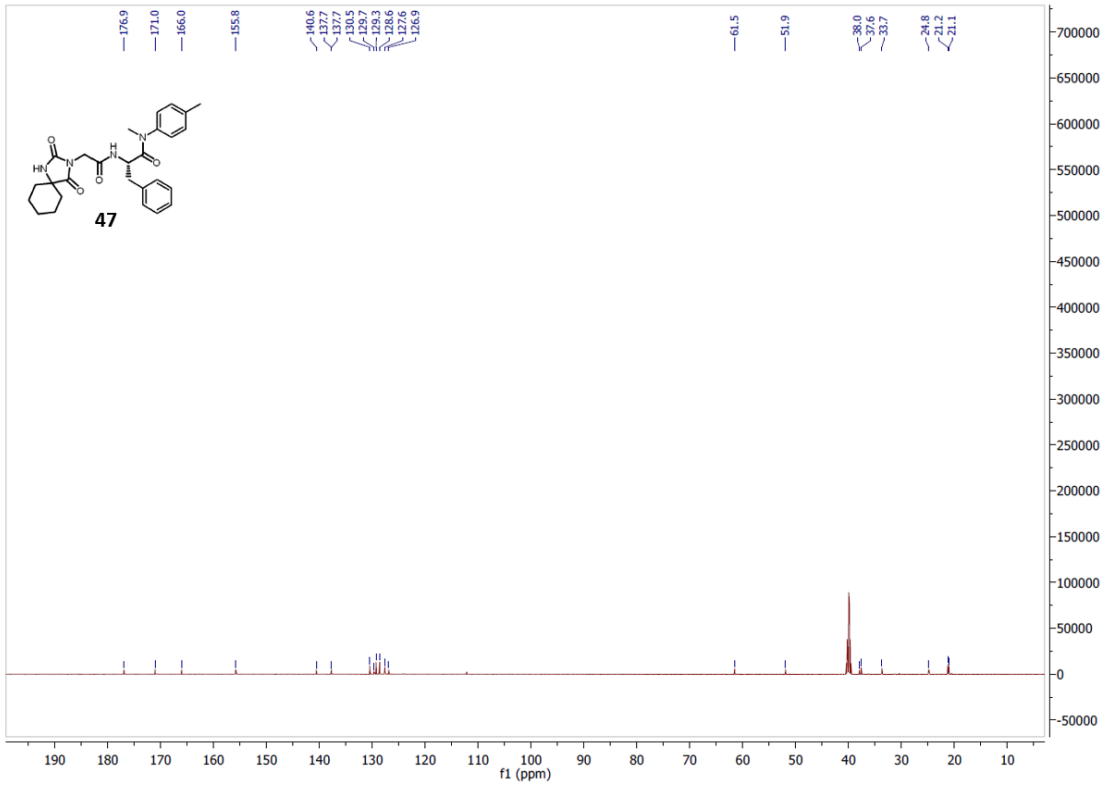
f1 (ppm)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127.6
126.9
61.5
51.9
38.0
37.6
33.7
24.8
21.2
21.1
f1 (ppm)

47


7.32
7.26
7.25
7.24
7.23
7.03
7.02
7.00
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6.97
6.96
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4.59
4.58
4.16
4.13
4.07
4.04
3.13
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2.98
2.97
2.96
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2.76
2.75
2.73
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1.82
1.80
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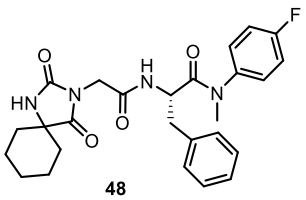
1.39



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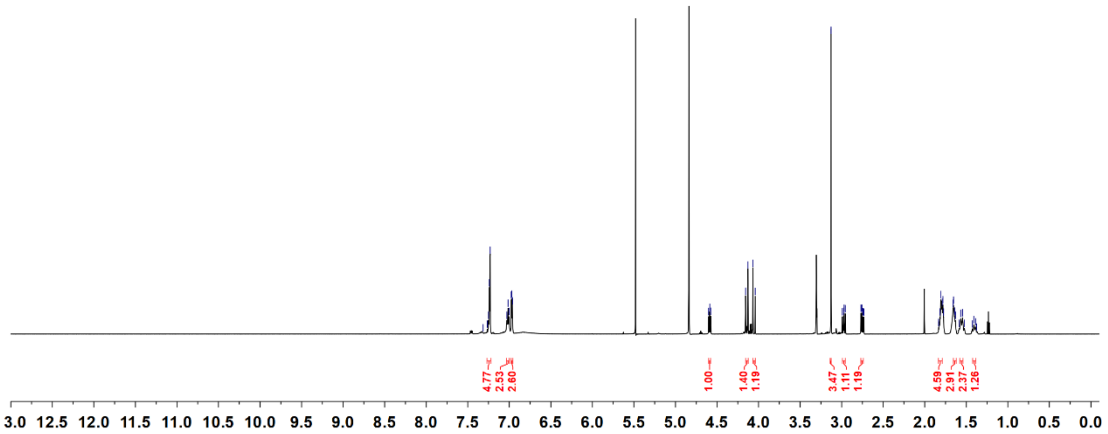
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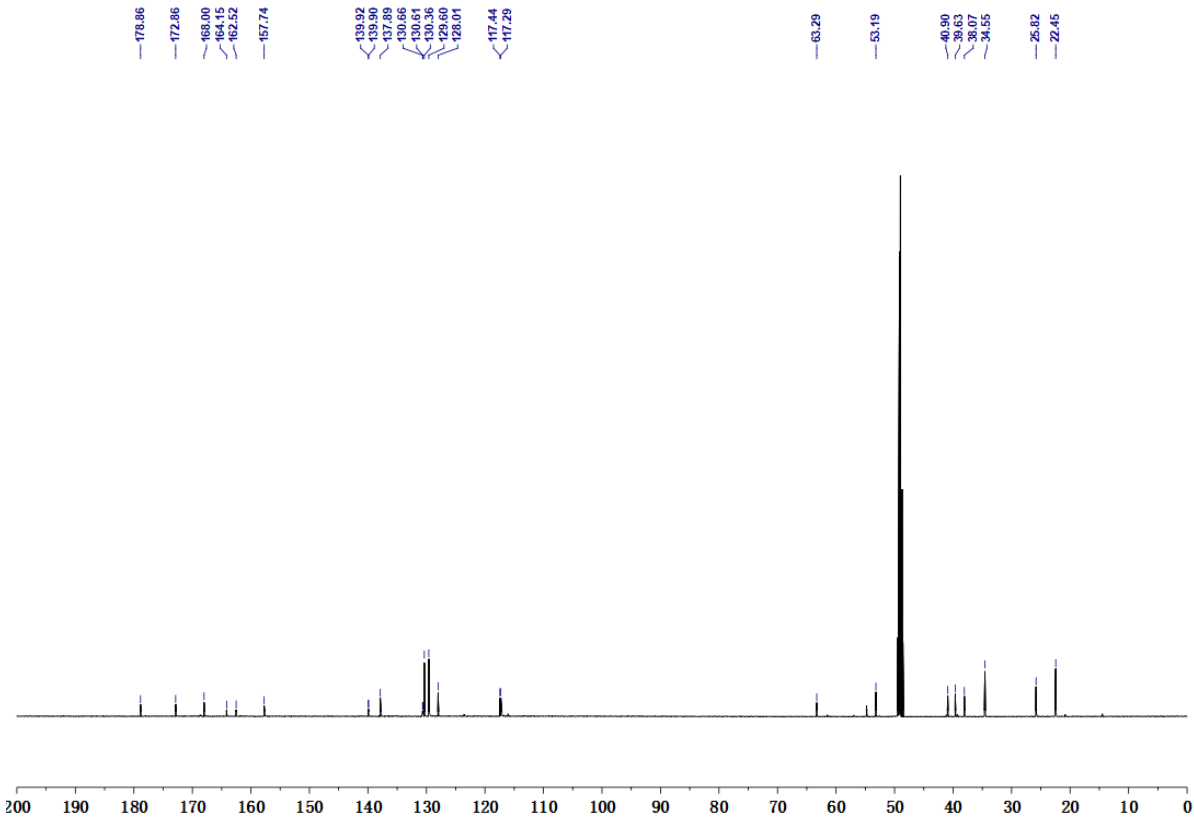
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130.36
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63.29
53.19
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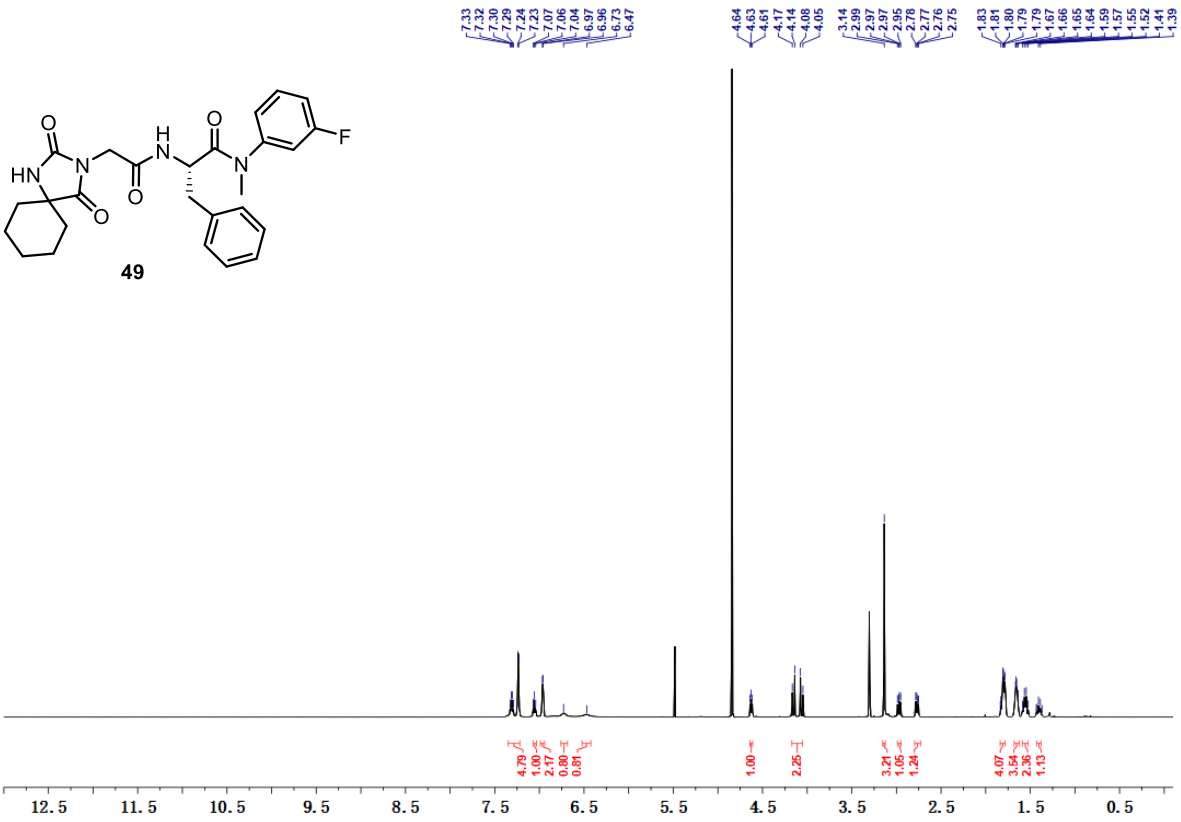
39.63
38.07
34.55
25.82
22.45

49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6.47
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4.63
4.61
4.17
4.14
4.08
4.05
3.14
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2.97
2.97
2.95
2.78
2.77
2.76
2.75
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1.66
1.65
1.64
1.59
1.57
1.55
1.52
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1.39
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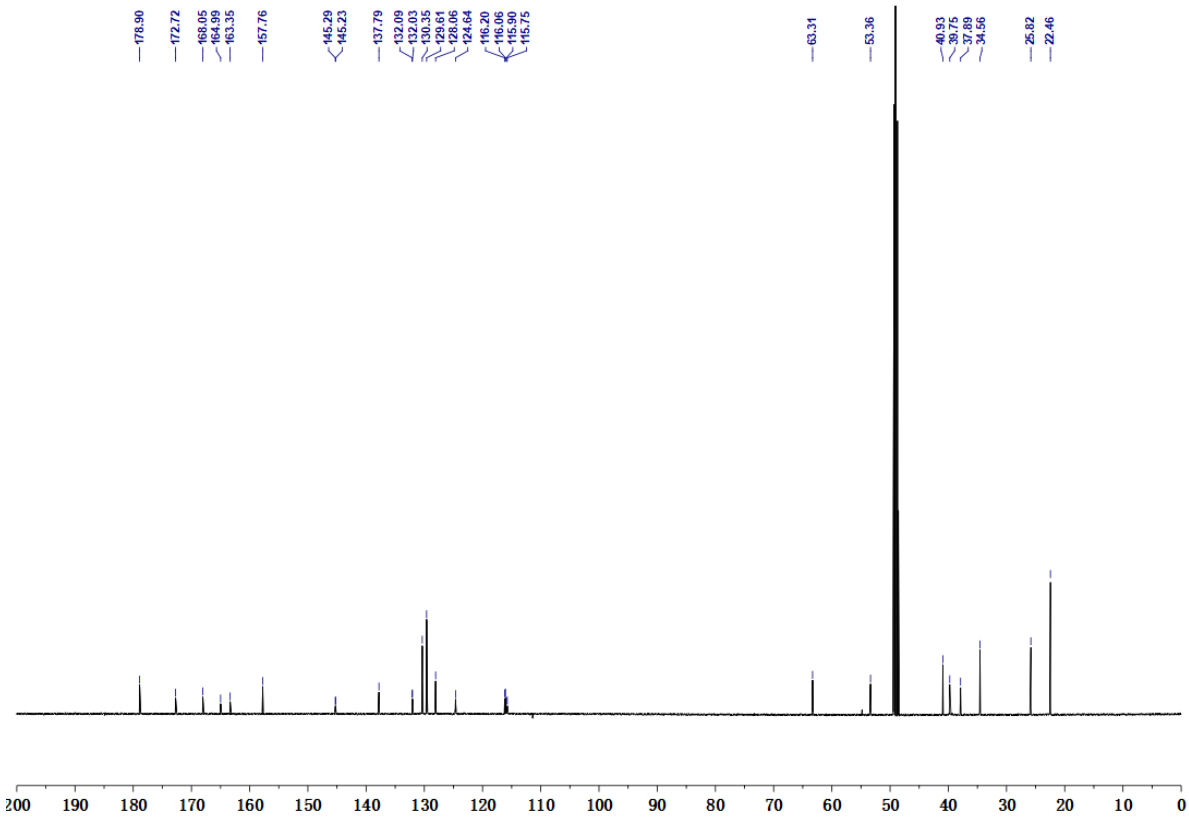
1.13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145.23
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132.09
132.03
130.35
129.61
128.06
124.64
116.20
116.06
115.90
115.75
63.31
53.36
40.93
39.75
37.89
34.56
25.82
22.46
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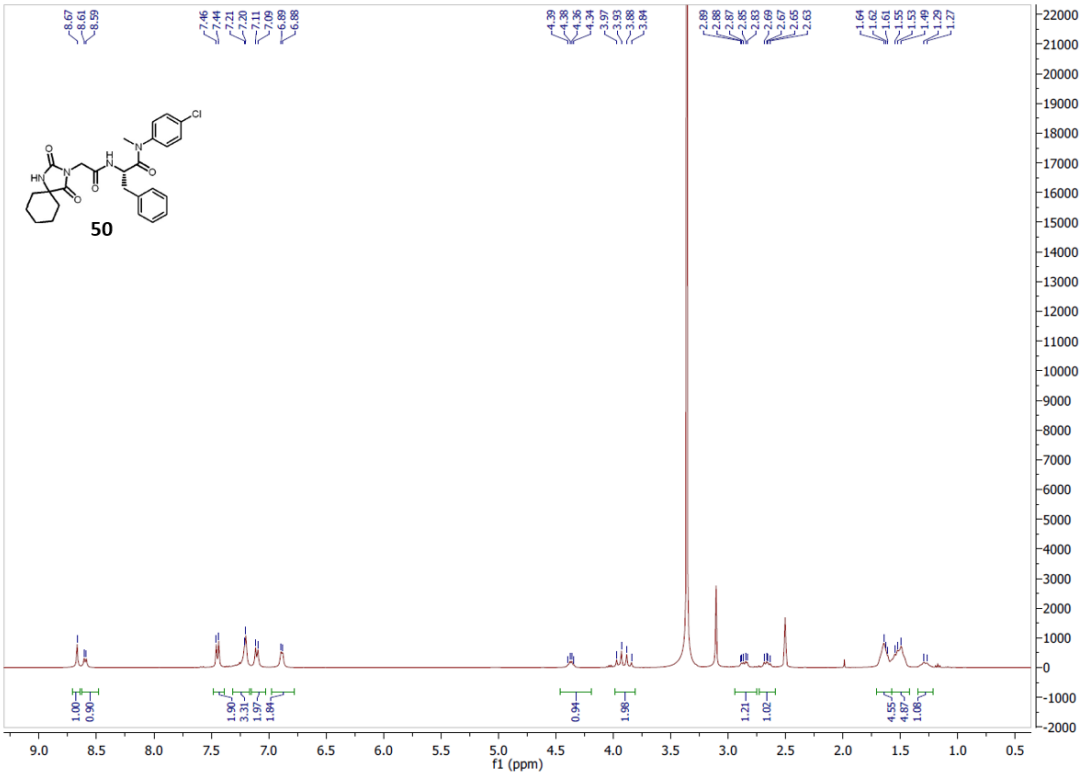
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4.38
4.36
4.34
3.97
3.93
3.88
3.84
2.89
2.88
2.87
2.85
2.83
2.69
2.67
2.65
2.63
1.64
1.62
1.61
1.55
1.53
1.49
1.29
1.27
50
1.00
0.90
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1.98
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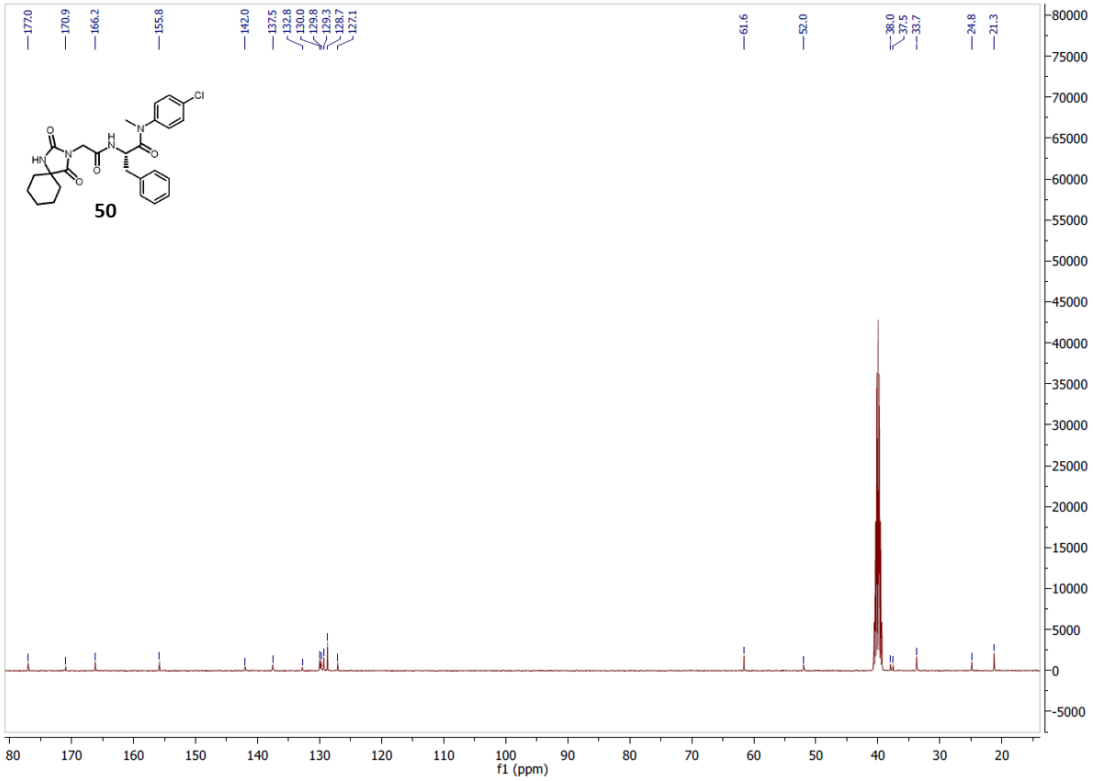
f1 (ppm)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129.8
129.3
128.7
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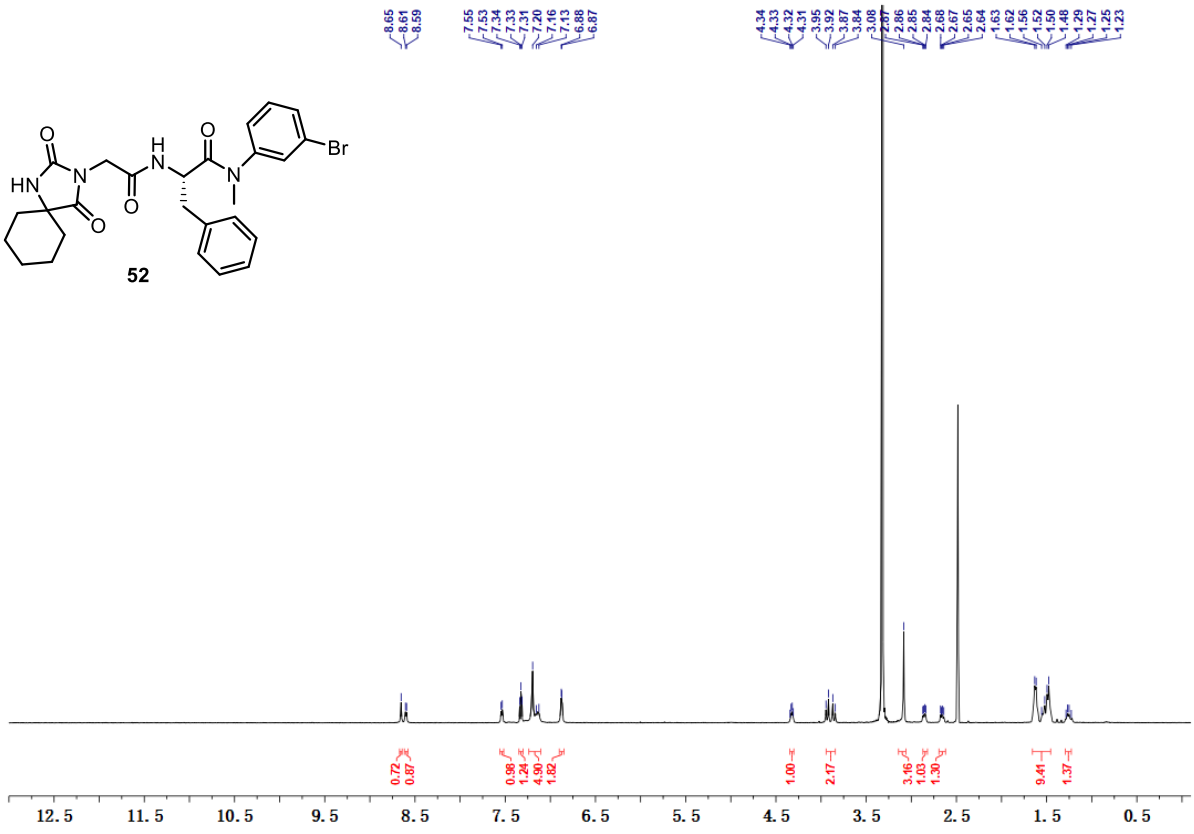
61.6
52.0
38.0
37.5
33.7
24.8
21.3
Cl
50
f1 (ppm)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7.16
7.13
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6.87
4.34
4.33
4.32
4.31
3.95
3.92
3.87
3.84
3.08
2.87
2.86
2.85
2.84
2.68
2.67
2.65
2.64
1.63
1.62
1.56
1.52
1.50
1.48
1.29
1.27
1.25
1.23
Br
52
0.72
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0.98
1.24
4.90
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1.00
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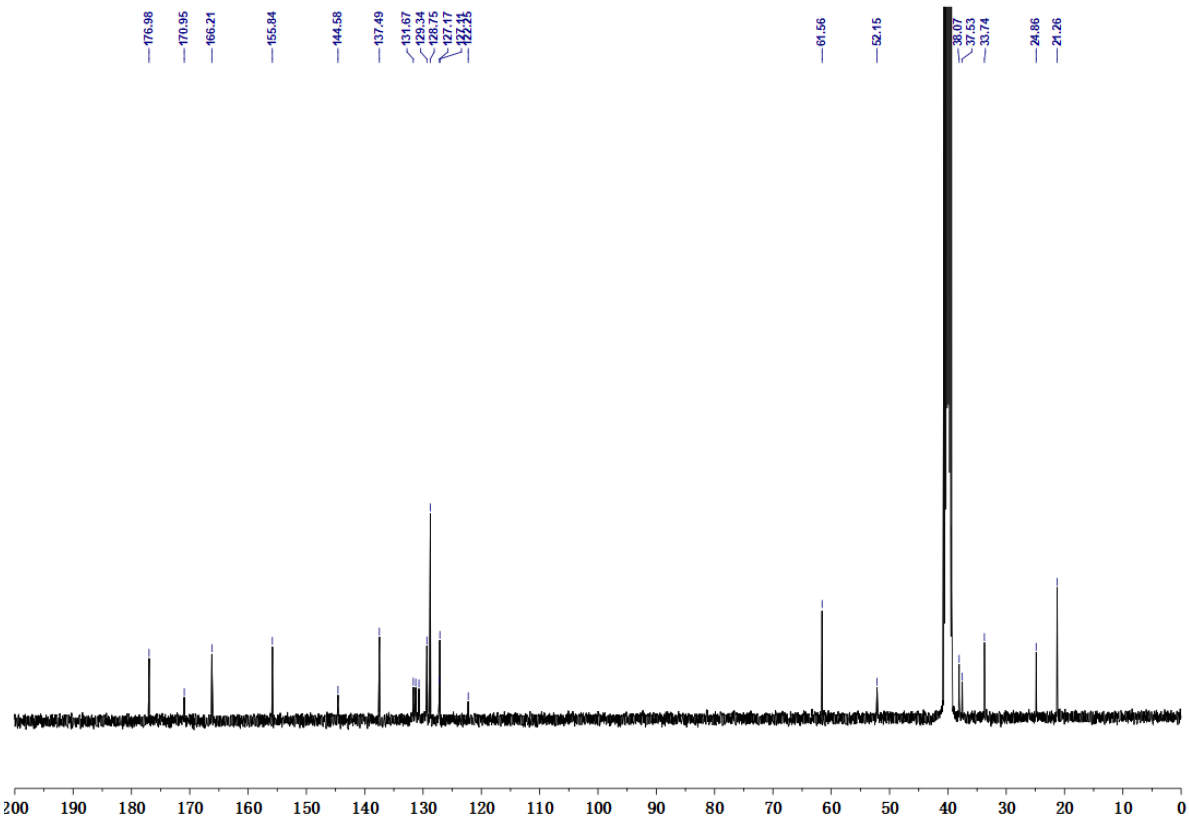
3.46
1.03
1.30
9.41
1.37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128.75
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38.07
37.53
33.74
24.86
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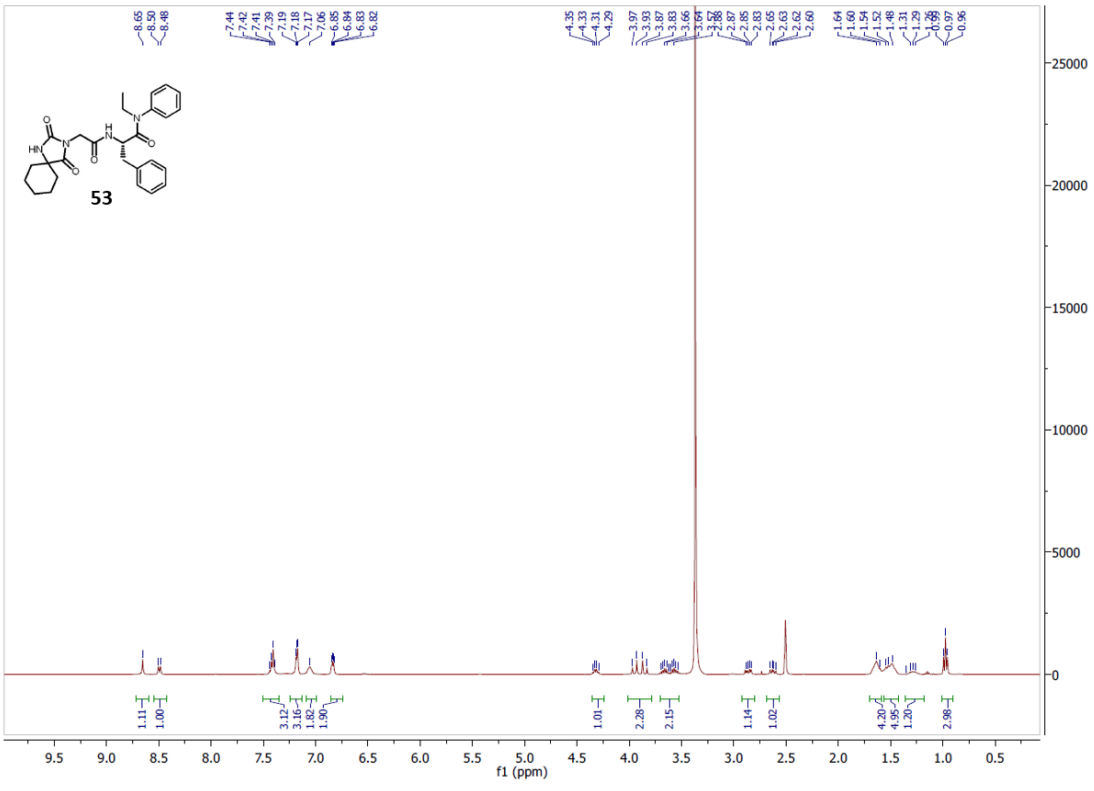
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0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7.44
7.42
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7.19
7.18
7.17
7.06
6.85
6.84
6.83
6.82
4.35
4.33
4.31
4.29
3.97
3.93
3.87
3.83
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3.64
2.88
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2.85
2.83
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2.63
2.62
2.60
1.64
1.60
1.54
1.52
1.48
1.31
1.29
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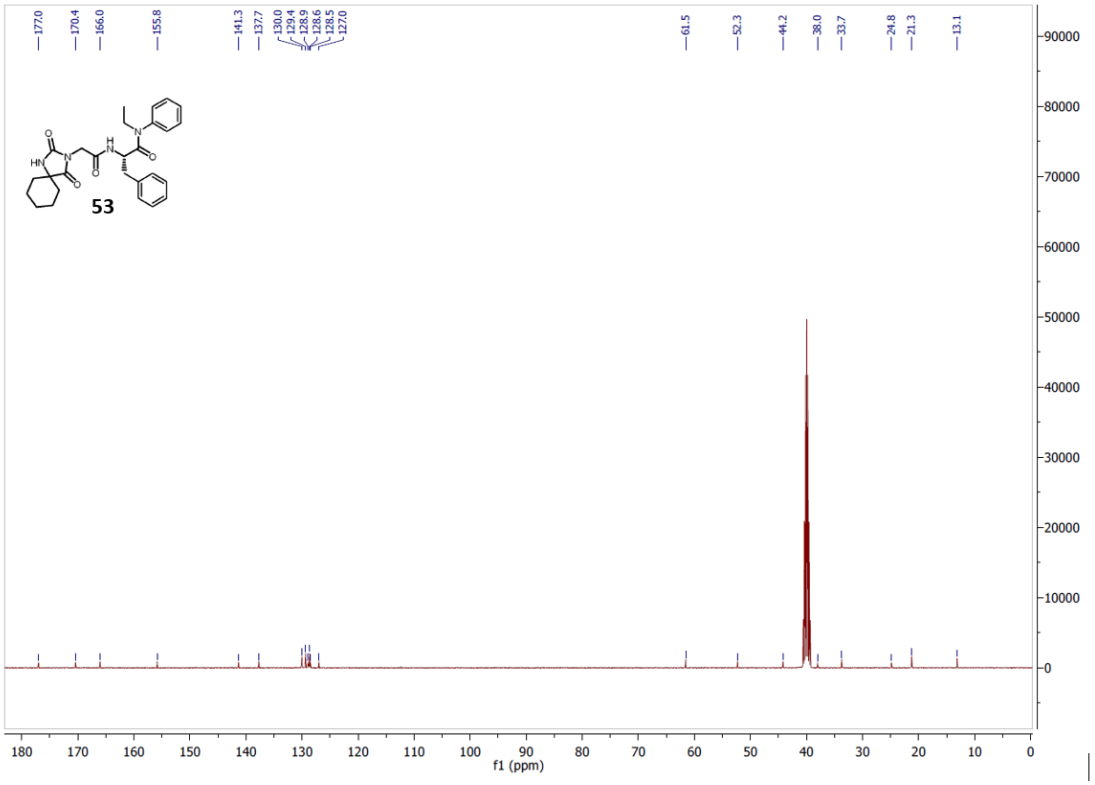
0.97
0.96
1.11
1.00
3.12
3.16
1.82
1.90
1.01
2.28
2.15
1.14
1.02
4.20
4.95
1.20
2.98
25000
20000
15000
10000
5000
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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130.0
129.4
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128.6
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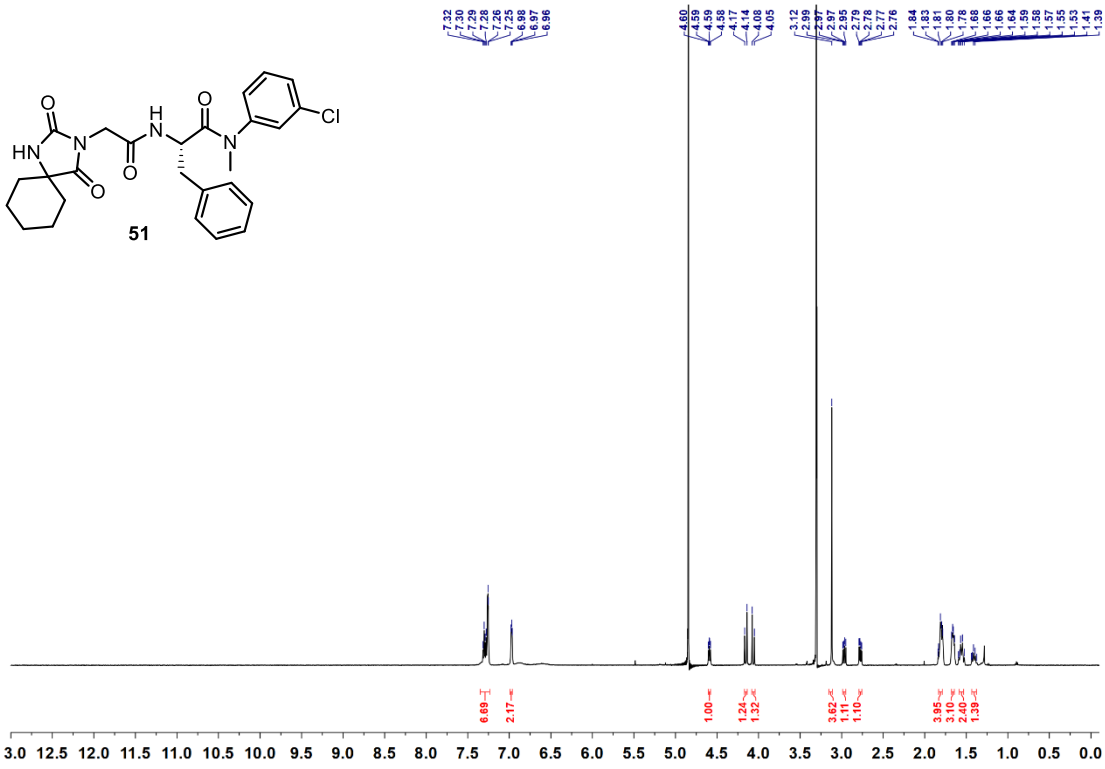
33.7
24.8
21.3
13.1
53
f1 (ppm)


51
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4.59
4.58
4.17
4.14
4.08
4.05
3.12
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2.97
2.97
2.95
2.79
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2.77
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1.83
1.81
1.80
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1.68
1.66
1.66
1.64
1.59
1.58
1.57
1.55
1.53
1.41
1.39
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1.10
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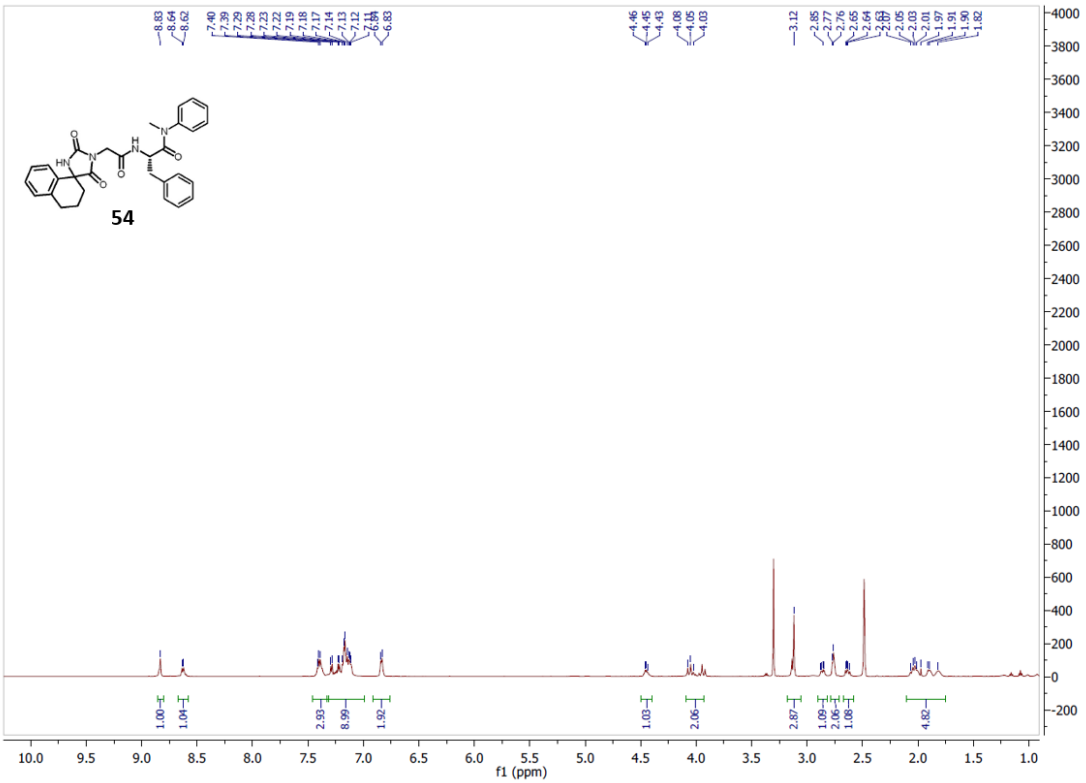
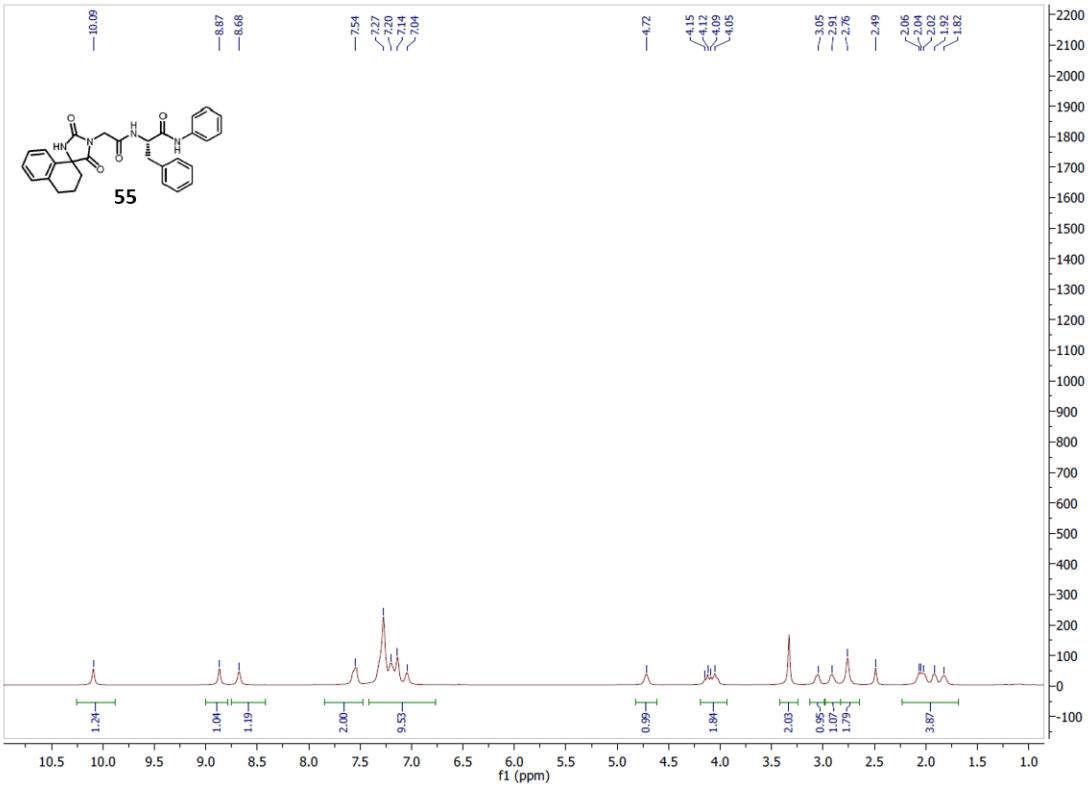
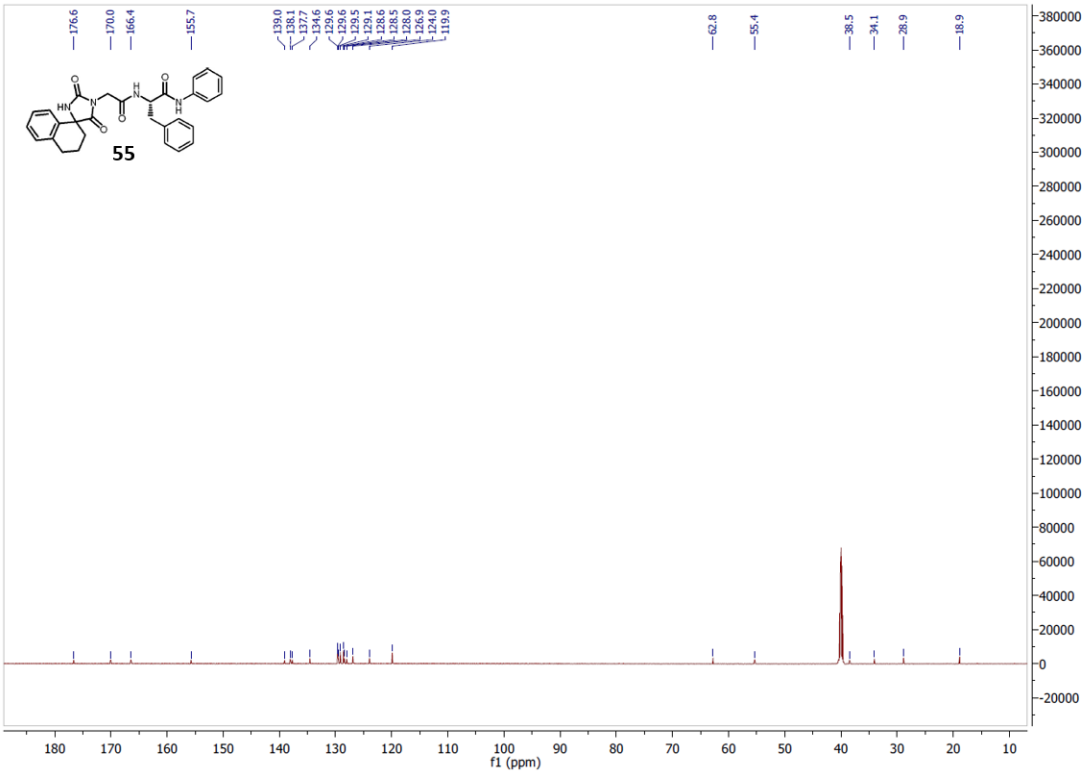
2.40
1.39


54
f1 (ppm)


55
f1 (ppm)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129.1
128.6
128.5
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124.0
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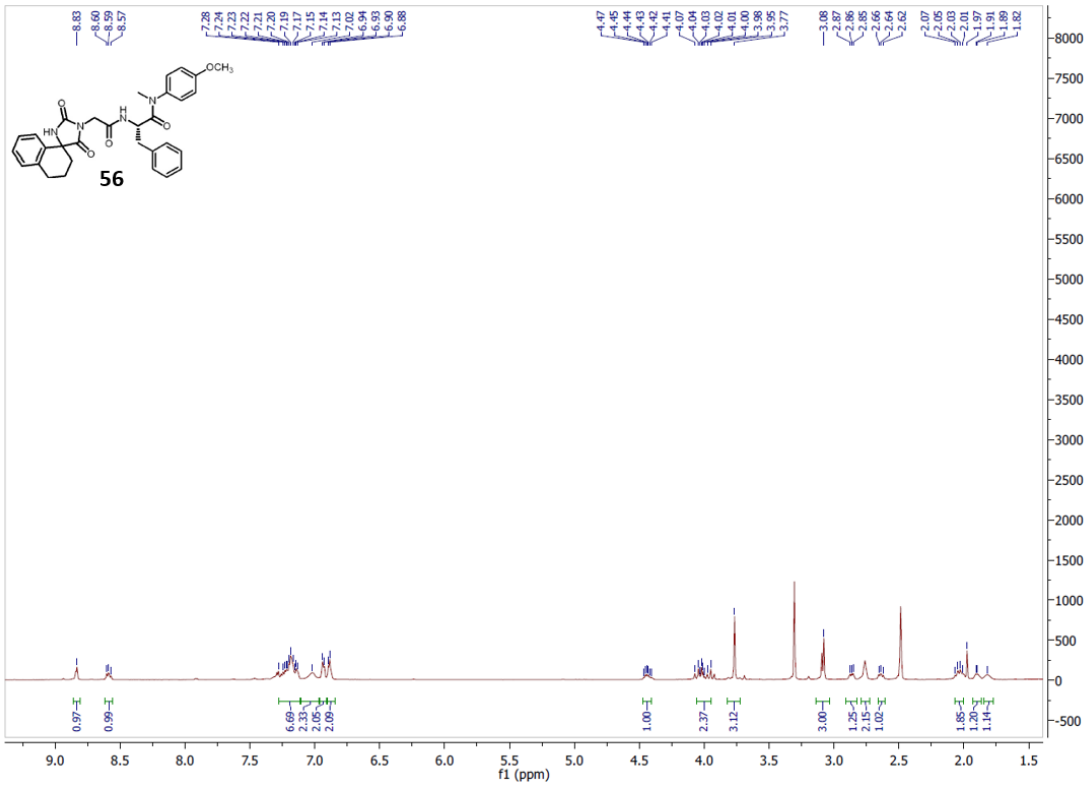
55.4
38.5
34.1
28.9
18.9
55
f1 (ppm)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7.15
7.14
7.13
7.02
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6.93
6.90
6.88
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4.45
4.44
4.43
4.42
4.41
4.07
4.04
4.03
4.02
4.01
4.00
3.98
3.95
3.77
3.08
2.87
2.86
2.85
2.66
2.64
2.62
2.07
2.05
2.03
2.01
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1.91
1.89
1.82
OCH3
56
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0.99
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2.05
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1.00
2.37
3.12
3.00
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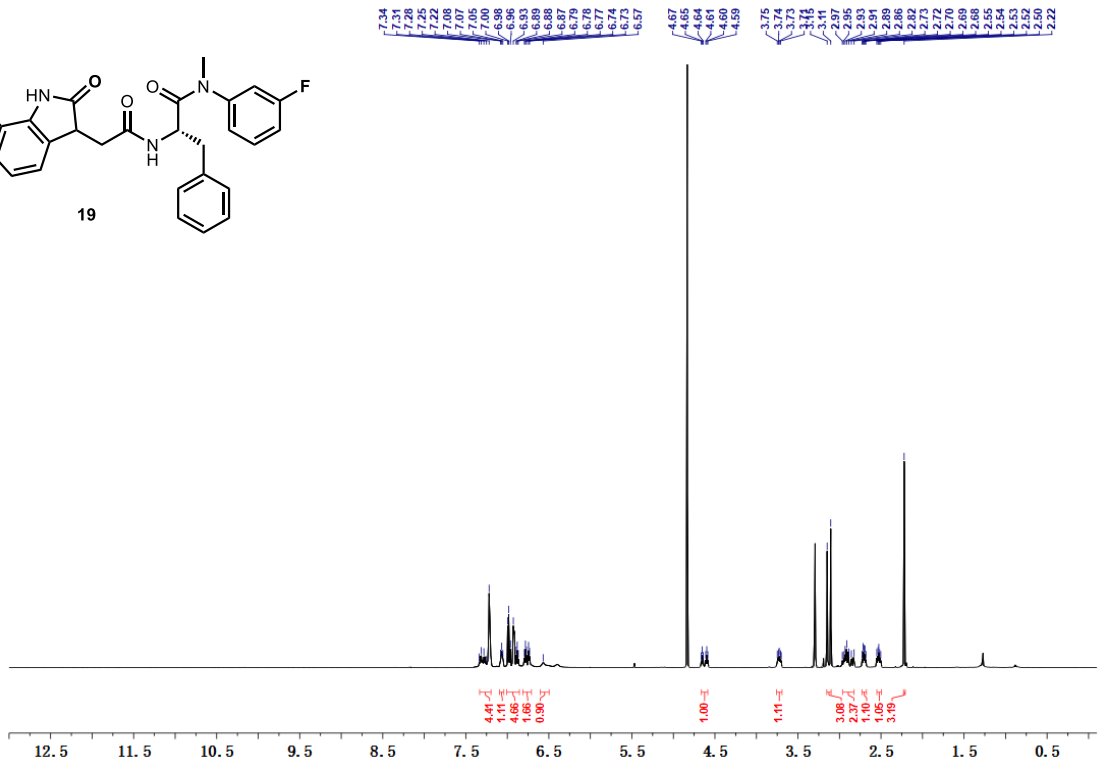
1.85
1.20
1.14
f1 (ppm)

HN
O
O
N
F
N
H

19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1.11
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1.10
1.15
3.19
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11.5
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1.5
0.5

HN
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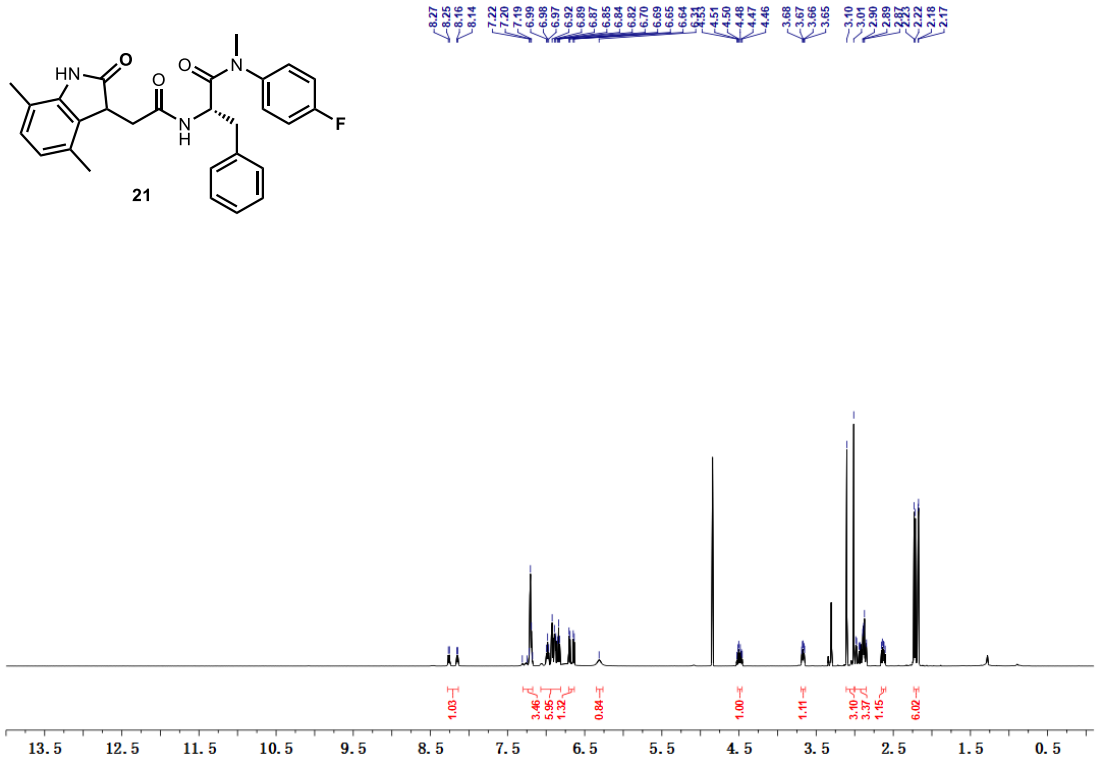
O
N
F
N
H

21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6.84
6.82
6.70
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6.64
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5.95
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1.00
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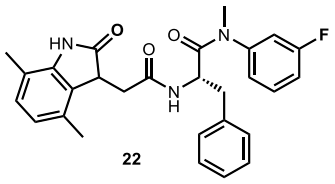
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O
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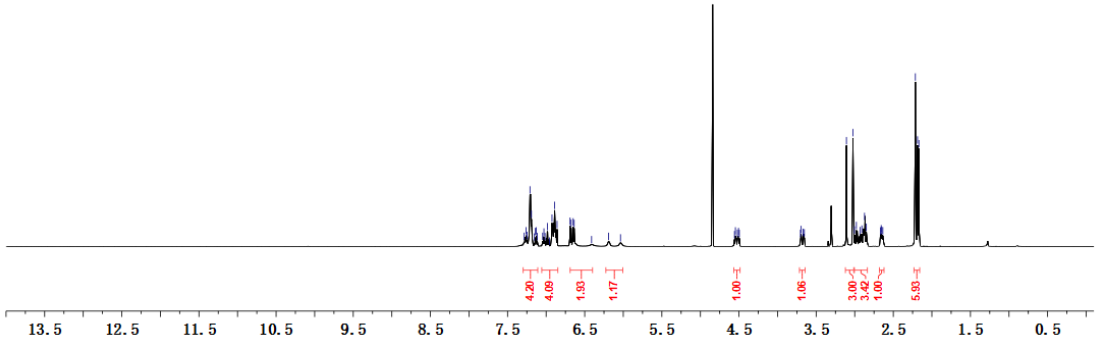
F

22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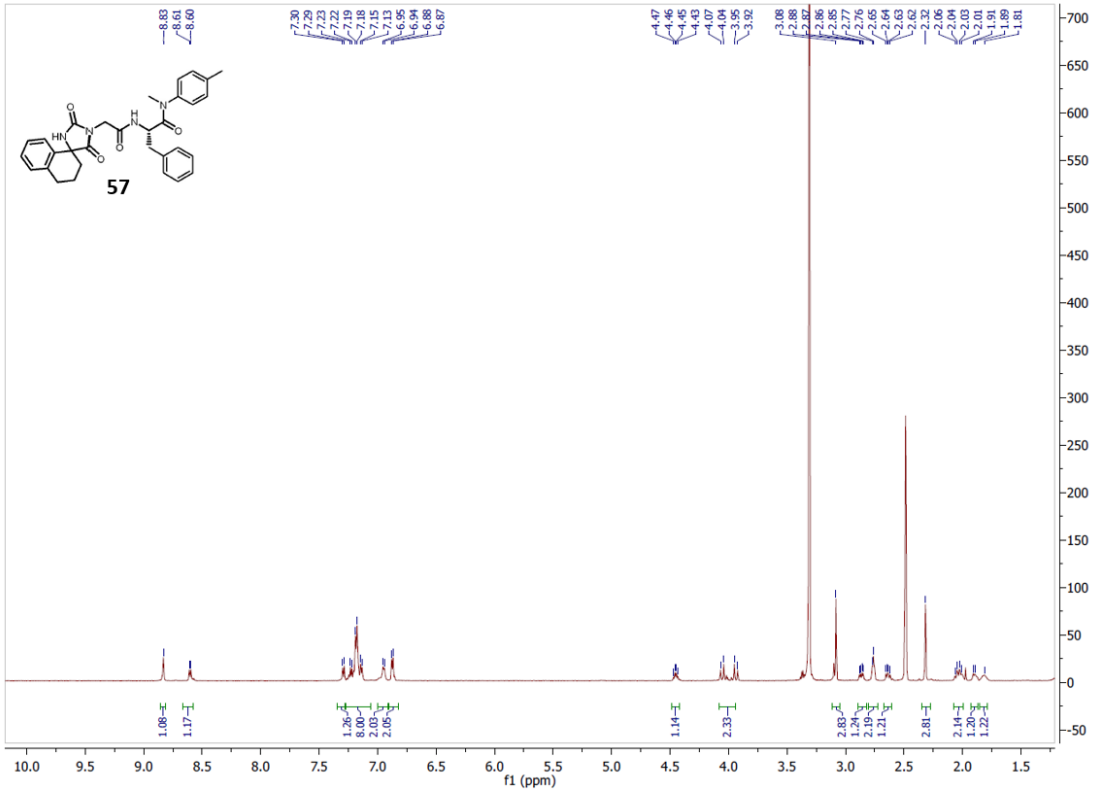
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N
H
O
N
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8.00
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2.05
1.14
2.33
2.83
1.24
2.19
1.21
2.81
2.14
1.20
1.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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3.5
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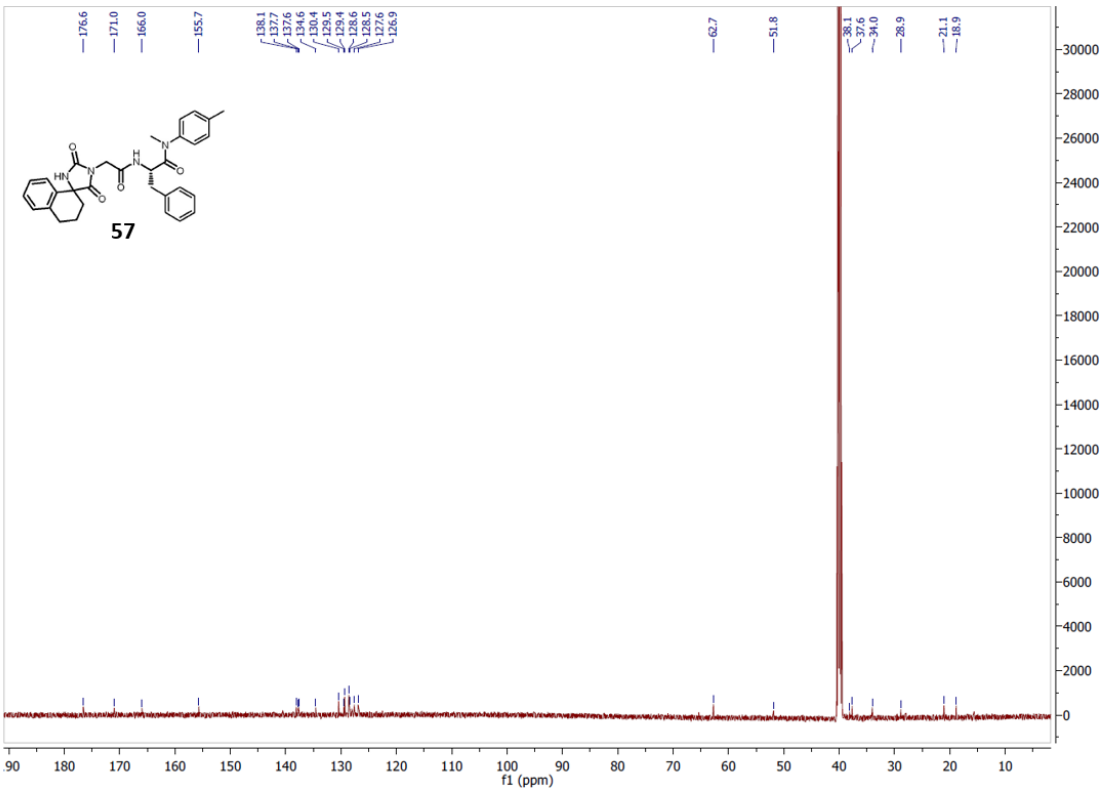
2.5
2.0
1.5
f1 (ppm)

57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128.5
127.6
126.9
62.7
51.8
38.1
37.6
34.0
28.9
21.1
18.9
57
f1 (ppm)