Synthesis of new triarylpyrazole derivatives possessing terminal sulfonamide moiety and their inhibitory effects on PGE_2 and nitric oxide productions in LPS-induced RAW 264.7 macrophages

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Experimental

Synthesis of methyl benzoate

A solution of 3-methoxybenzoic (304 mg, 2.0 mmol) in methanol (5 ml) were heated under reflux until the acid was completely dissolved in methanol then few drops of concentrated sulphuric acid was added to the mixture and refluxed for 8 hr. The resulting mixture was cooled to room temperature, diluted with water and a saturated solution of sodium bicarbonate was added to the mixture to neutralize the benzoic acid, extracted with ethyl acetate, dried and evaporated to get the required ester (300 mg, 90.3%) as yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 9.0 Hz, 2H, Ar-H), 7.49 (t, *J* = 9.0 Hz, 1H, Ar-H), 7.37 (t, *J* = 9.0 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3 ester), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 132.8, 130.1, 129.5, 128.2 (Ar-C), 55.2 (OCH_3), 51.8 (OCH_3 ester).

Synthesis of 2-(2-bromopyridin-4-yl)-1-(3-methoxyphenyl)ethan-1-one

To a solution of methyl benzoate (775 mg, 5.0 mmol) and 2-bromo-4-picoline (0.5 mL, 5.6 mmol) in anhydrous THF (5 mL) in a cooled bath at -25 ℃, LiHMDS (3.7 mL, 1.0M solution in THF, 19.9 mmol) was slowly added to maintain the temperature at -25 ℃. The resulting mixture was stirred overnight at room temperature. The mixture was quenched with saturated aqueous NH_4Cl. Ethyl acetate was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x10 mL). The combined organic layer extracts were washed with brine and dried over anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel, hexane ethyl acetate 12:1 v/v then switching to hexane-ethyl acetate 10:1 v/v) to yield 2-(2-Bromopyridin-4-yl)-1-(3-methoxyphenyl) ethan-1-one (**17**) (1.0 g, 69.9 %) as light yellow solid; m.p.85-88 ℃; ^{1}H

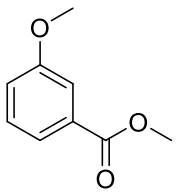
NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.52 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.56-7.48 (m, 1H, Ar-H), 7.40 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.15 (m, 2H, Ar-H), 4.25 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C=O), 150.0, 146.5, 137.3, 129.9, 129.2, 124.2, 121.0, 120.2, 112.8 (Ar-C), 55.5 (OCH_3), 44.0 (CH_2). LC-MS (m/z) calculated for $C_{14}H_{12}BrNO_2$: 306.16 found 307.20 $(M+1)^+$.

Synthesis of 2-bromo-4-(3-(3-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)pyridine

A solution of (1.16 g, 3.8 mmol) of 2-(2-bromopyridin-4-yl)-1-(3-methoxyphenyl)ethan-1-one in DMF-DMA (5.14 mL, 38.2 mmol) was refluxed for 18 h. The solution was cooled down and concentrated under reduced pressure. The residue was dissolved in 5 mL of anhydrous ethanol. Phenyl hydrazine (0.394 mL, 4 mmol) was added to the ethanolic solution and the mixture was stirred overnight at room temperature. Water (5 mL) was added to the reaction mixture and the organics were extracted with ethyl acetate (3 x 15 mL). The combined organic layer extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, hexane-ethyl acetate 100:1 v/v) to yield the title compound 2-bromo-4-(3-(3-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)pyridine (729 mg, 48 %) yellow solid ; mp 96-98 ℃; IR (KBr, Cm^{-1}): 3078, 2964, 1593, 1262; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.98 (s, 1H, ar-H), 7.38-7.37 (m, 1H, Ar-H), 7.31-7.23 (m, 5H, Ar-H), 7.00 (dd, *J* = 5.2, *J* = 1.2 Hz, 1H, Ar-H), 6.94-6.91 (m, 1H, Ar-H), 6.77-6.75 (m, 1H, Ar-H), 6.68-6.66 (m, 1H, Ar-H), 3.66 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.0, 143.6, 142.6, 140.7, 139.3, 130.3, 128.9, 127.9, 125.7, 125.1, 122.5, 120.9, 118.3, 115.5, 115.2 (Ar-C), 55.3 (OCH_3); LC-MS(m/z) calculated for $C_{21}H_{16}BrN_3O$ (m/z):406.05 found: 407.0 $(M + 1)^+$.

Synthesis of N^1-(4-(3-(3-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)pyridin-2-yl)ethane1,2-diamine and N^1-(4-(3-(3-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)pyridin-2-yl)propane-1,3-diamine

A mixture of 2-bromo-4-(3-(3-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)pyridine (17.09 g, 42.2 mmol) and Copper Iodide (0.95g, 5mmol) in 50 ml of ethylene diamine or 1,3-diaminopropane was heated at 100 degree for 24 h. The reaction mixture was treated with water (150 mL) and ethyl acetate (150 ml). The organic layer was collected and washed with additional water (100 mL) then dried over Na_2SO_4 and evaporated to get the required product as grayish white solid, which was dried and used in the next step without further purification.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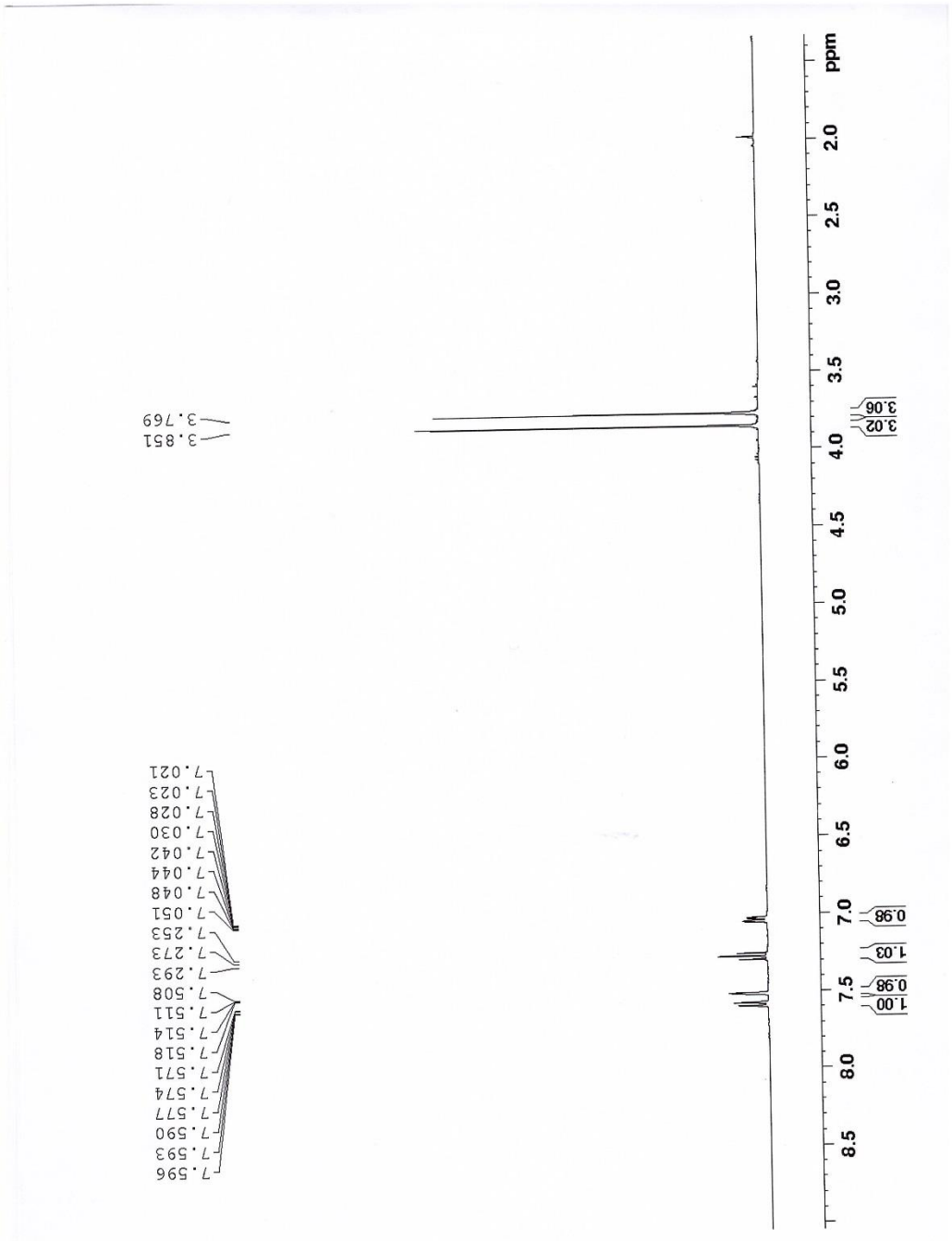
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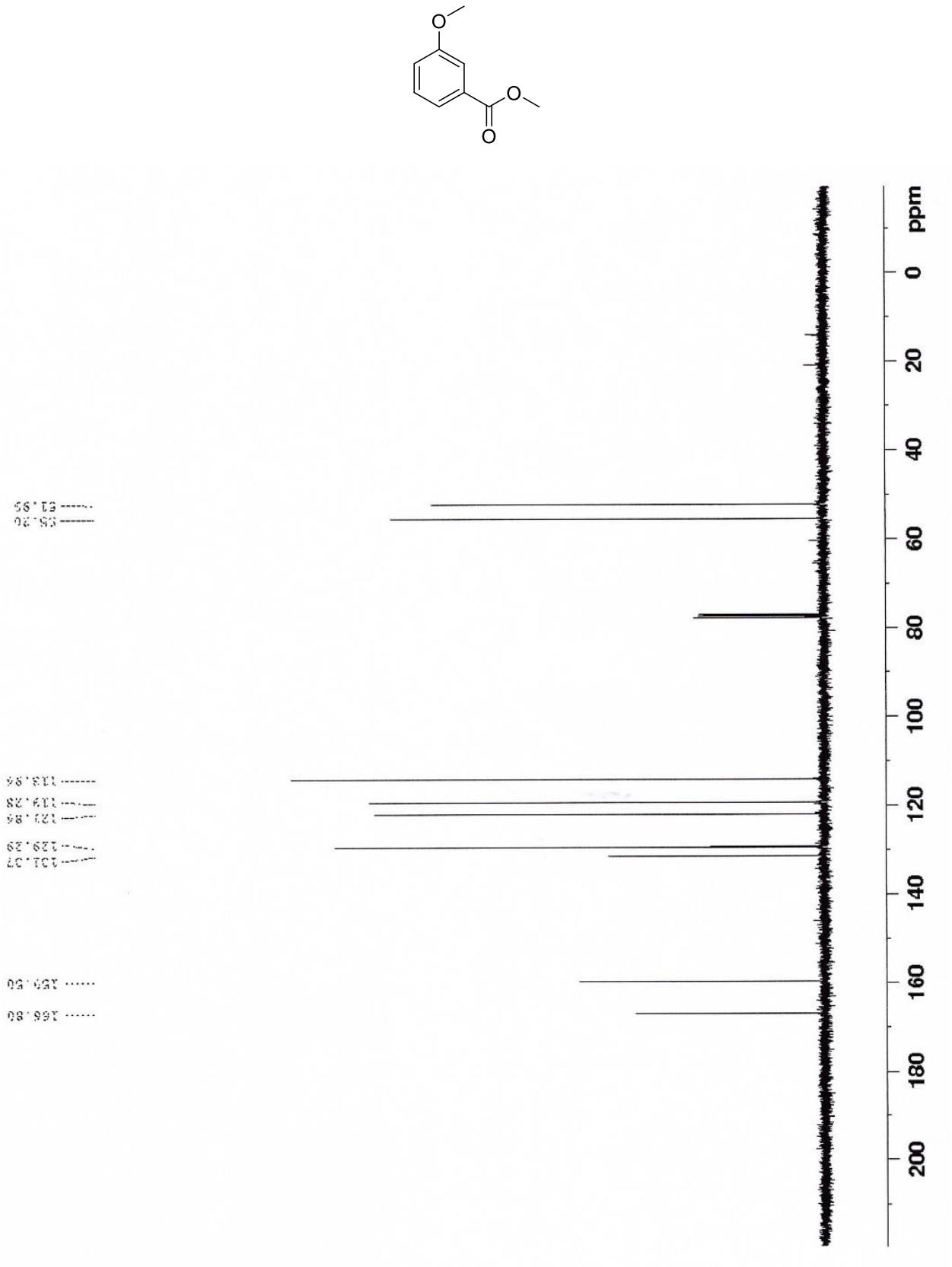
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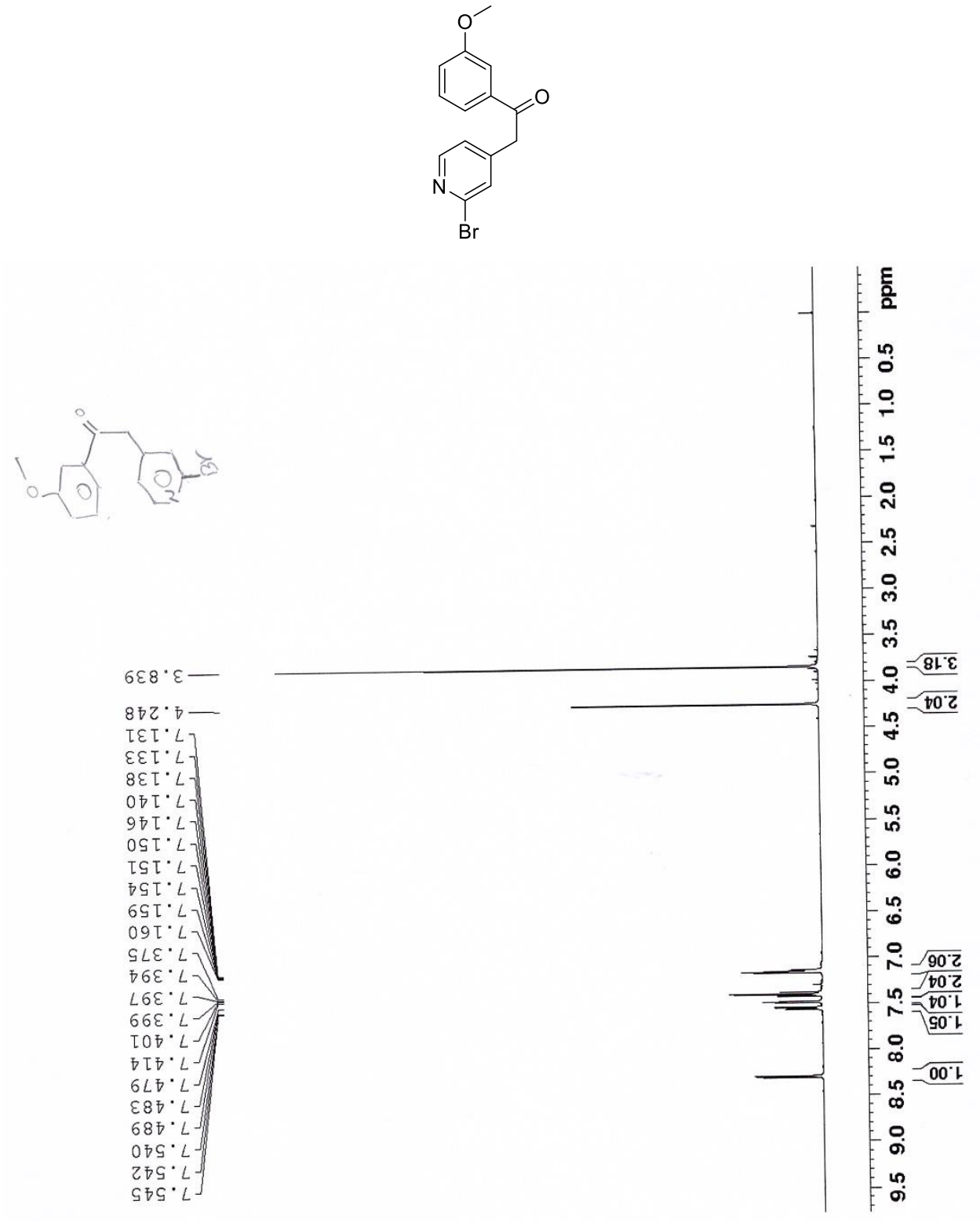
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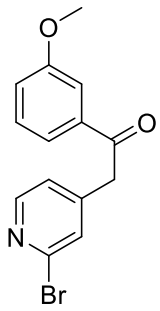
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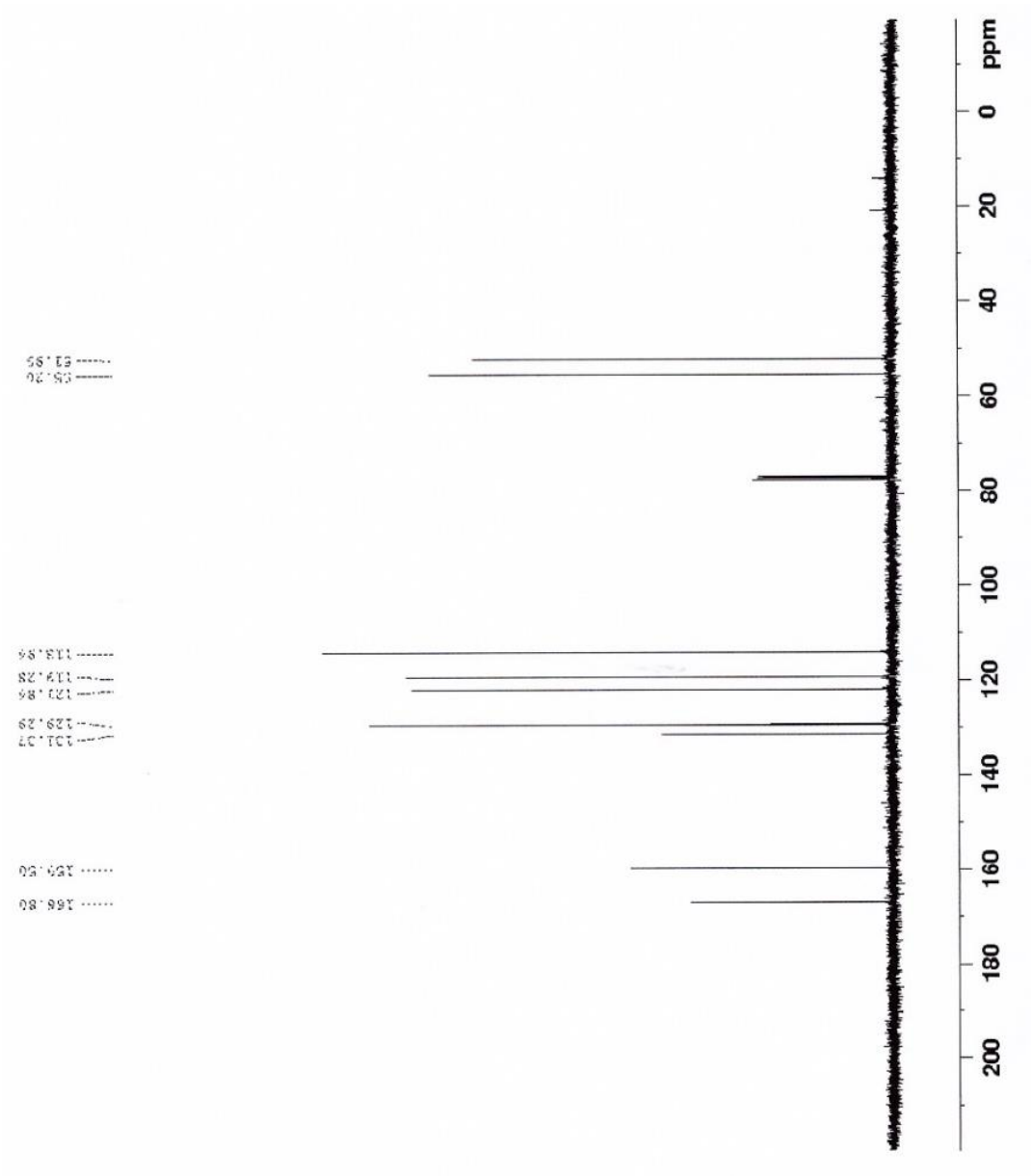
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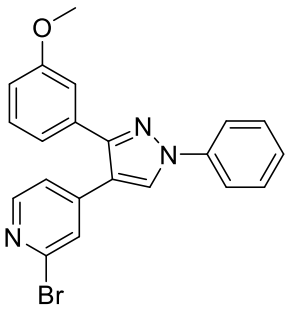
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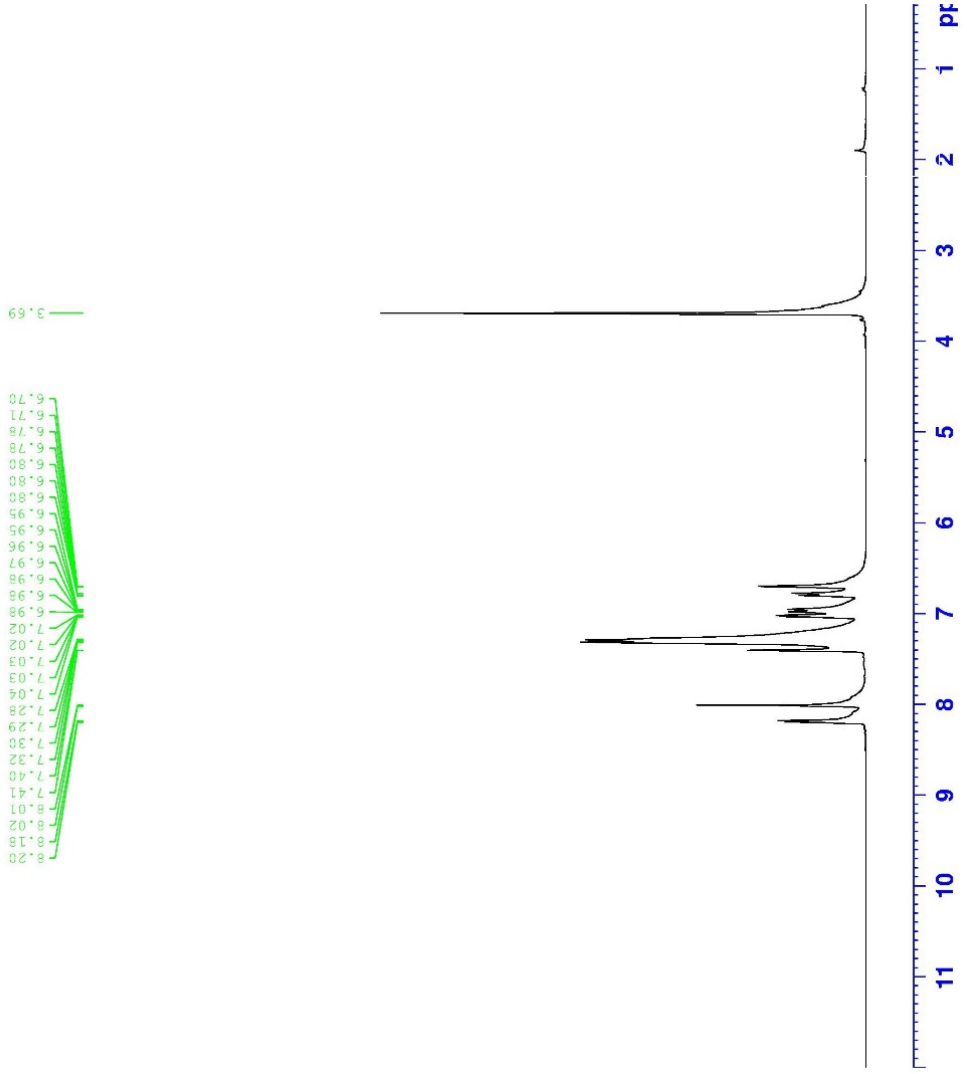
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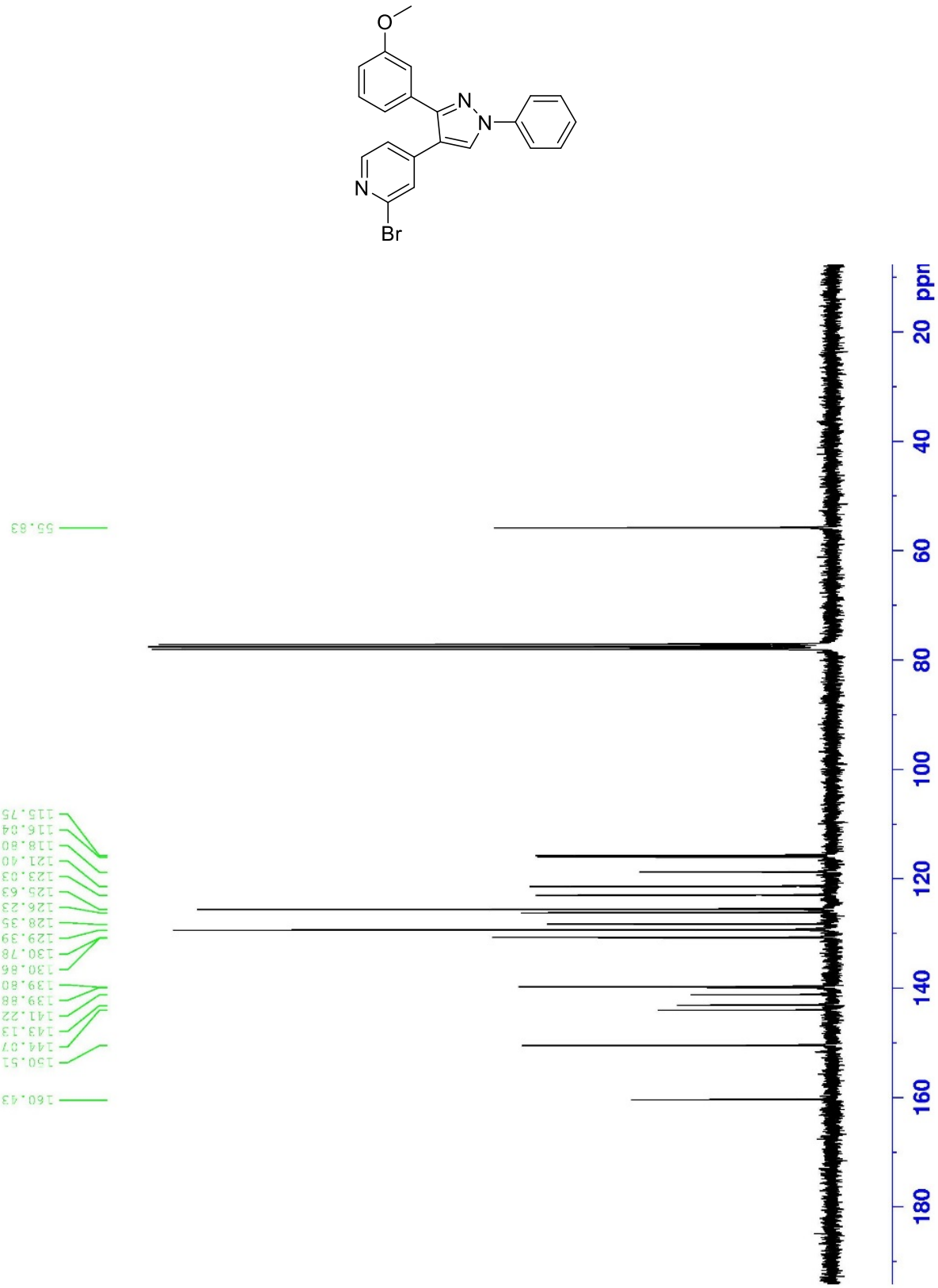
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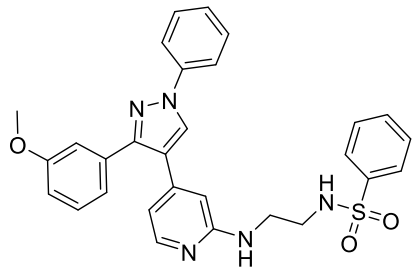
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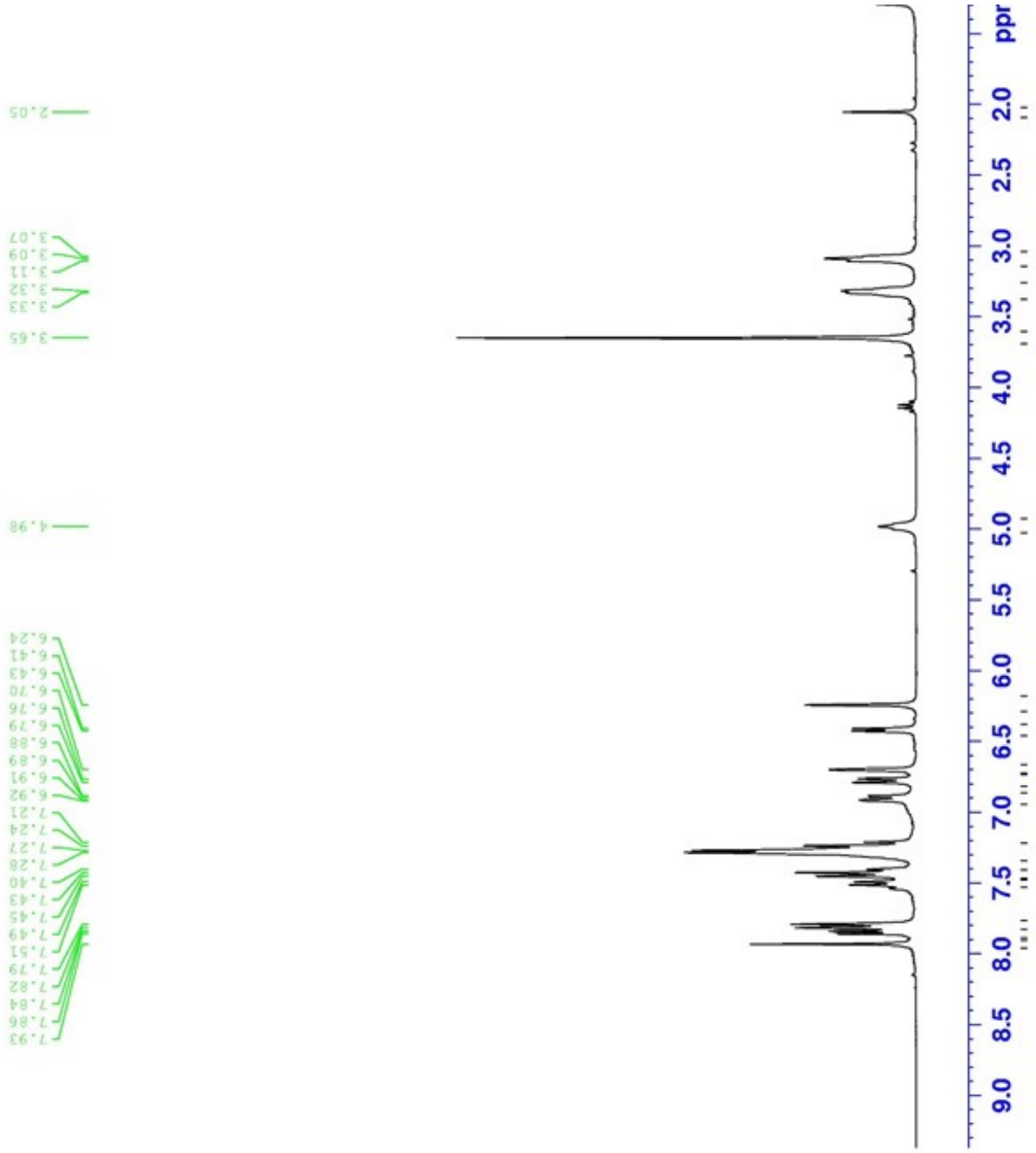
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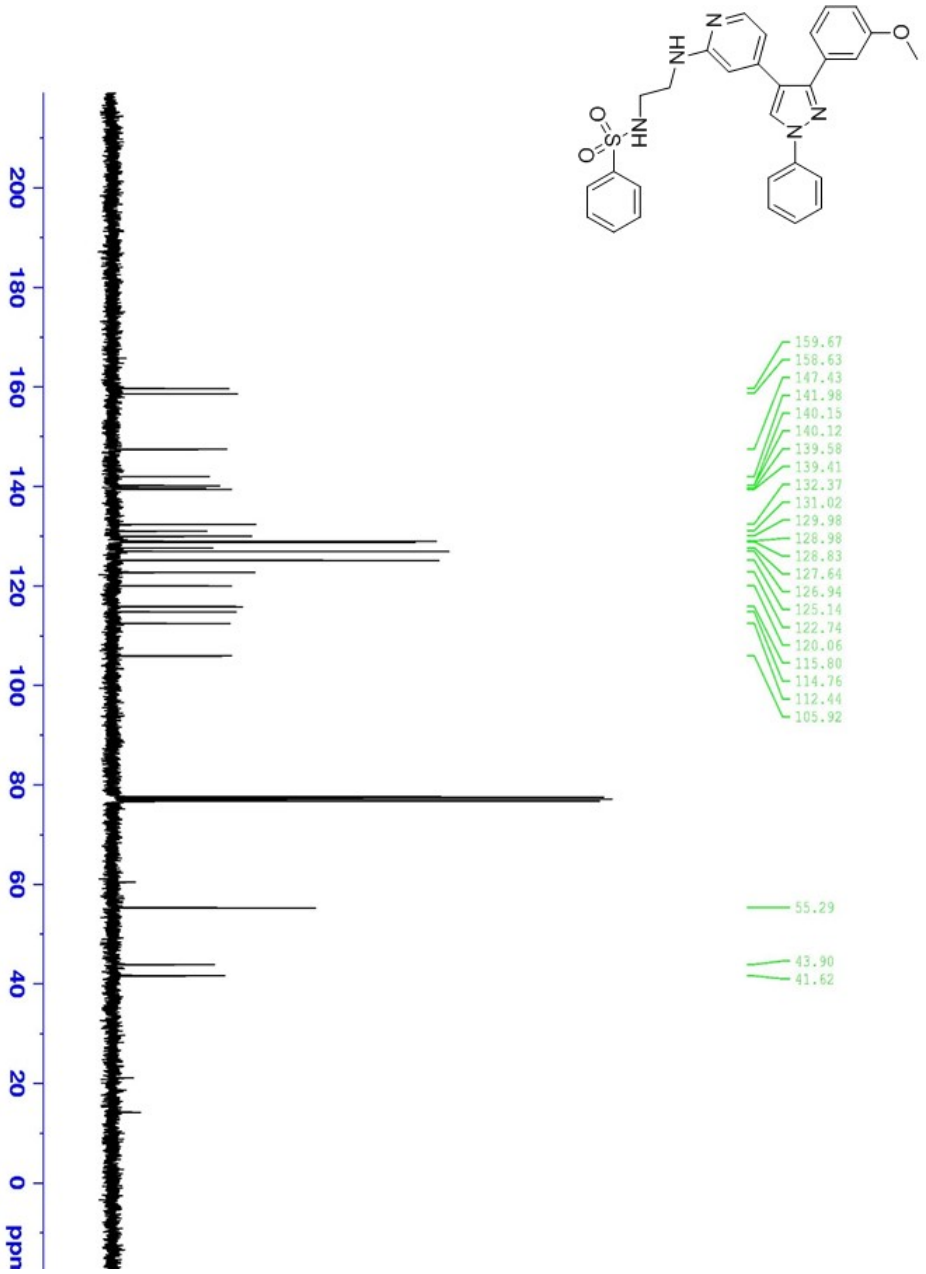
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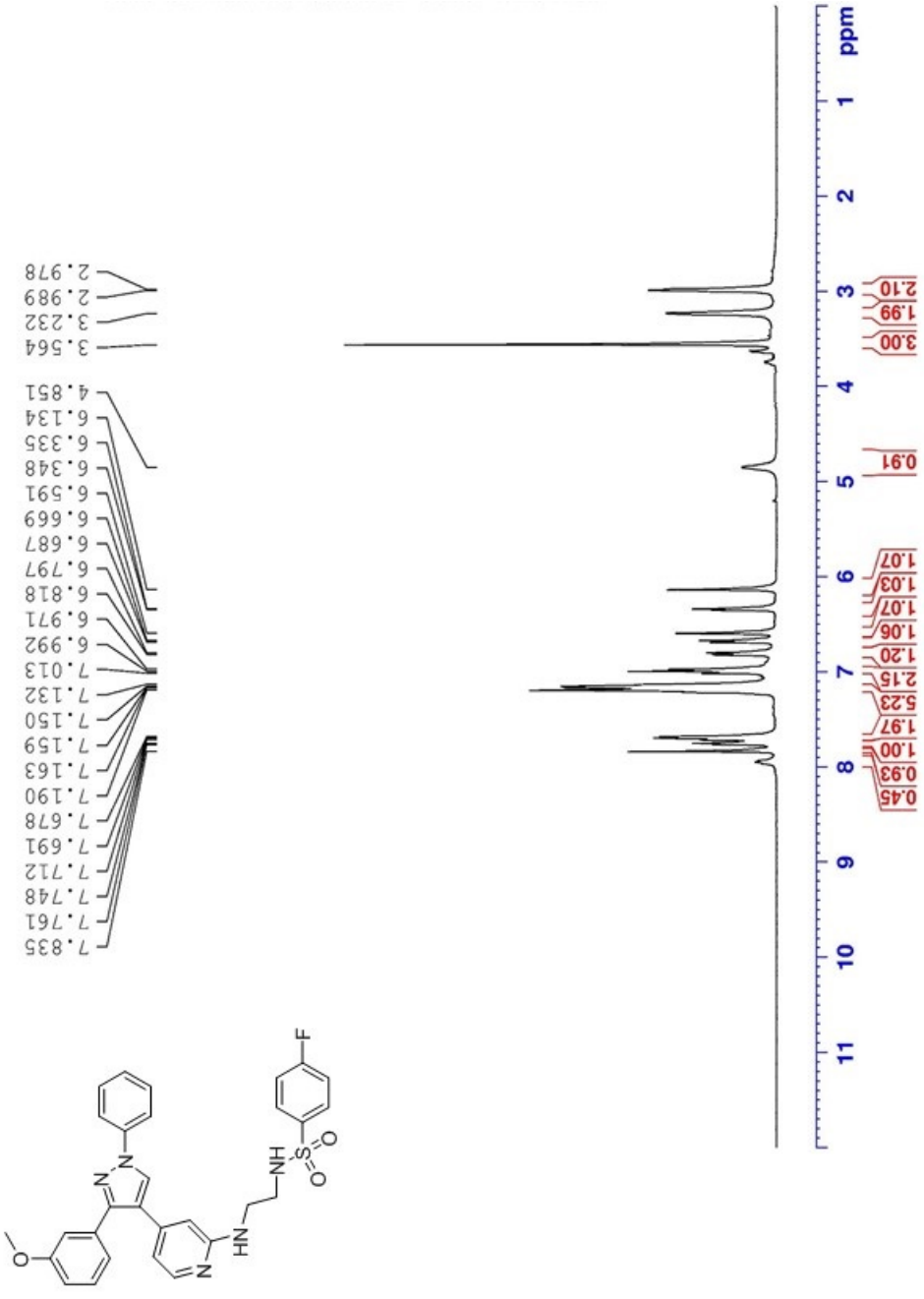
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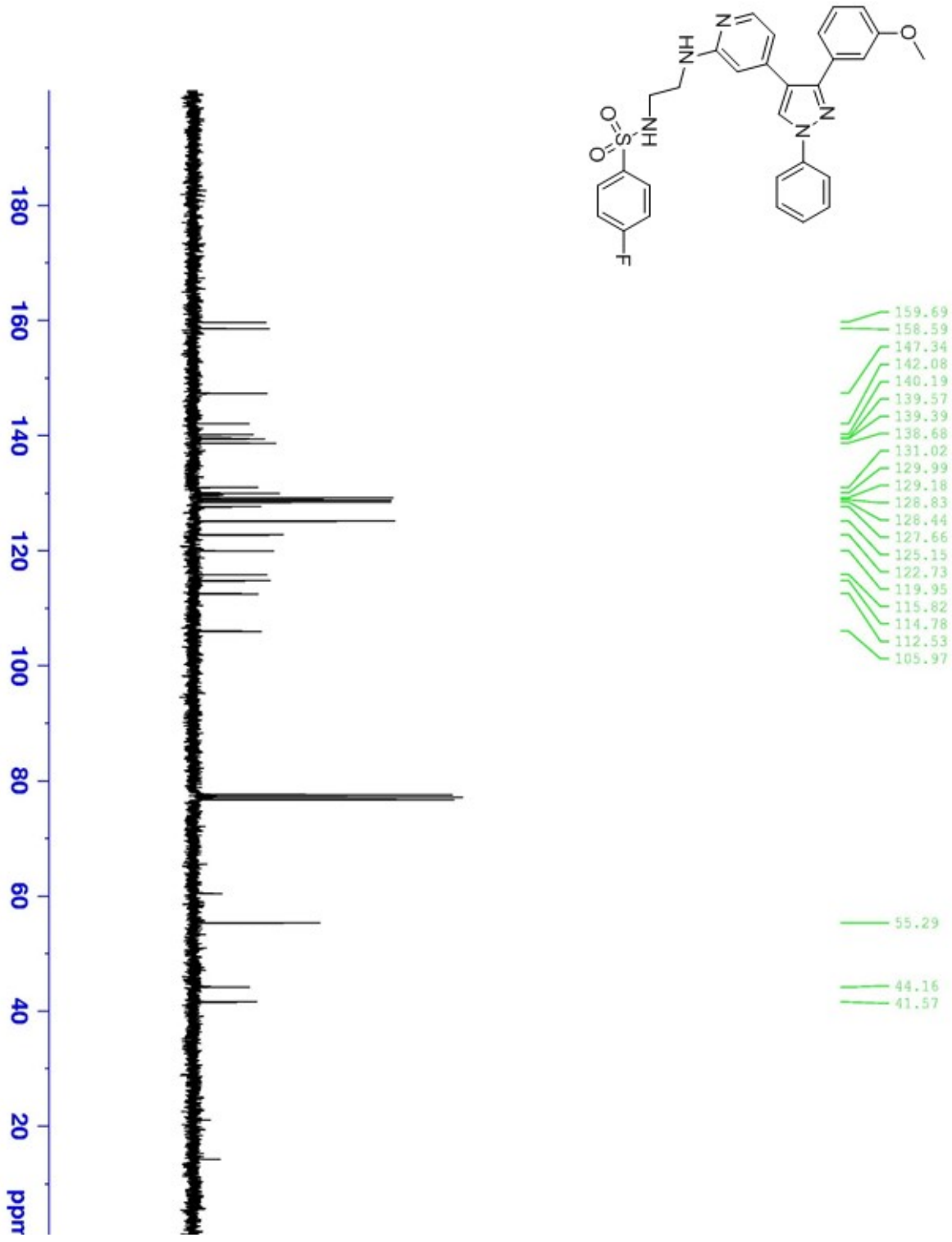
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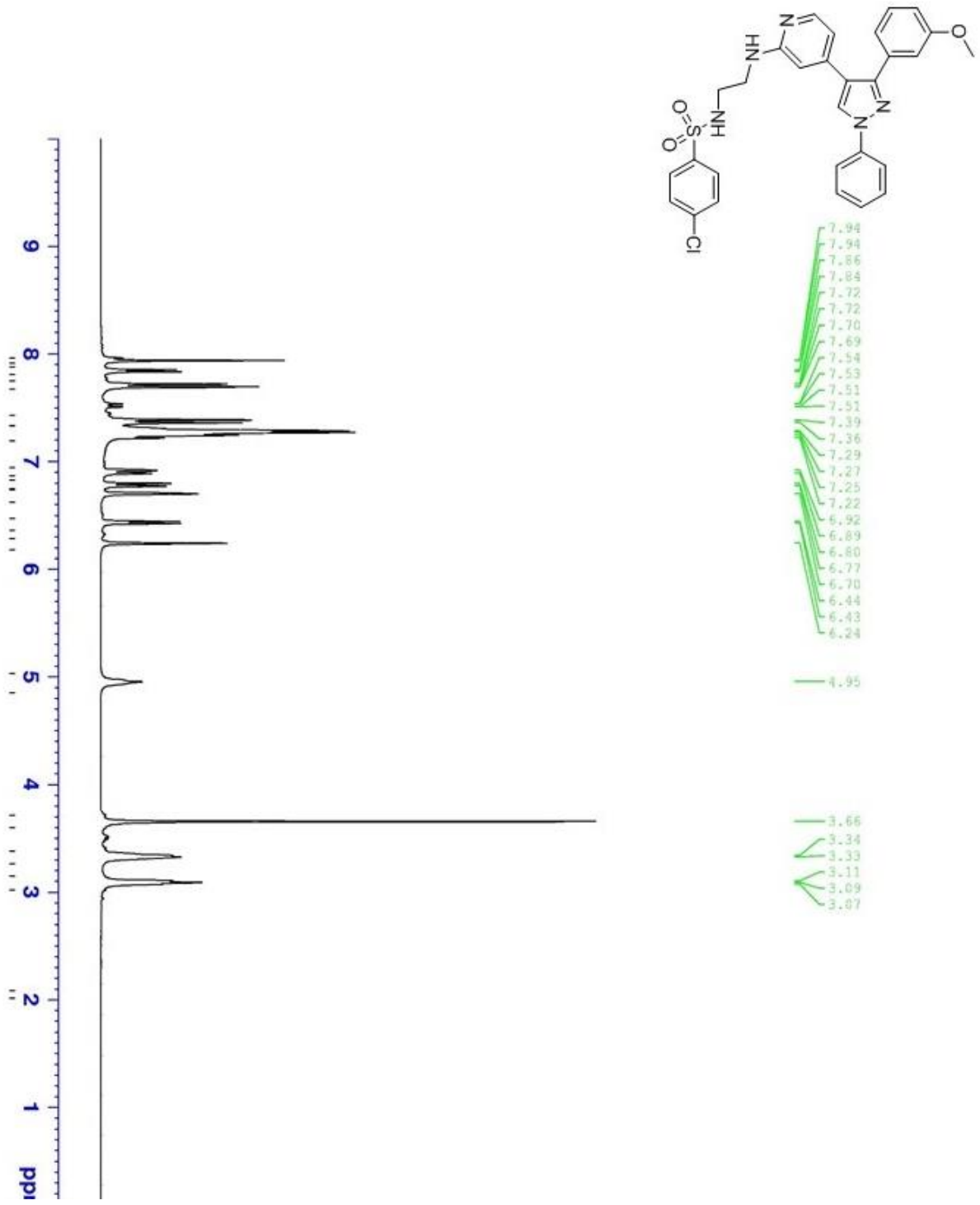
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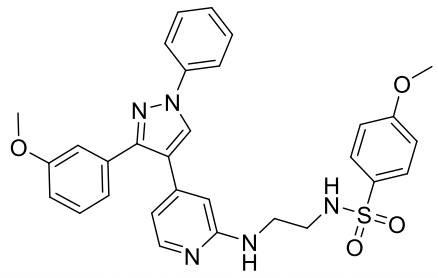

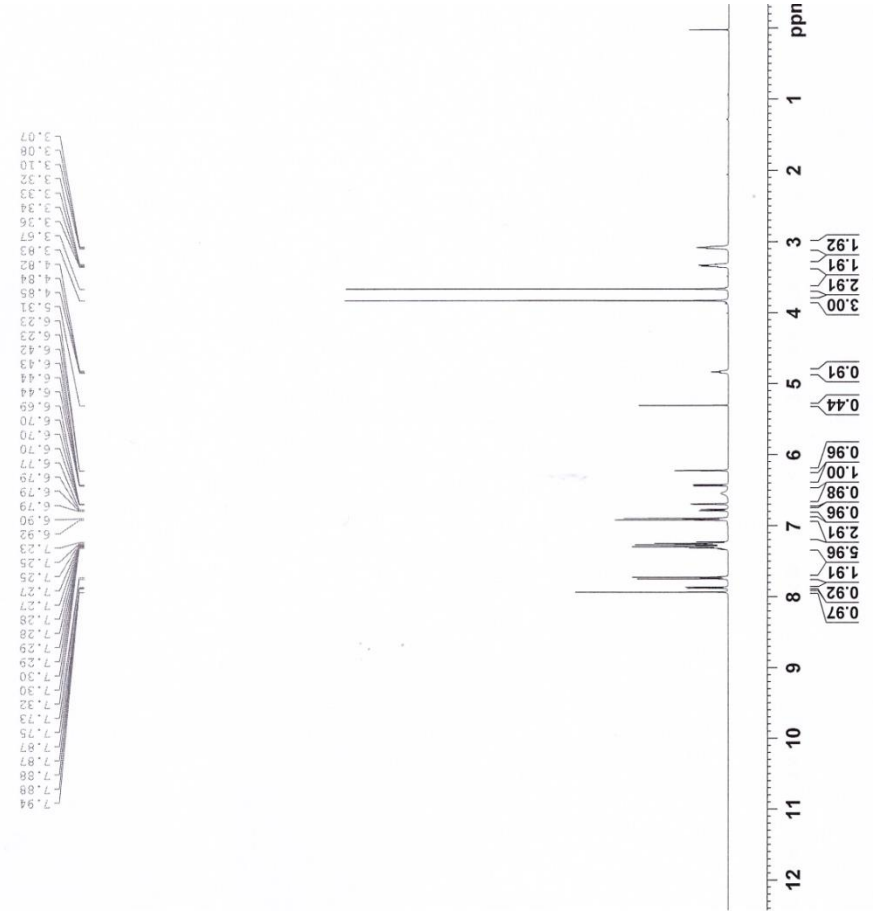

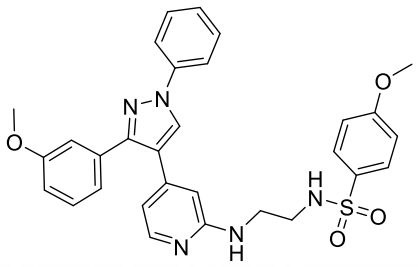
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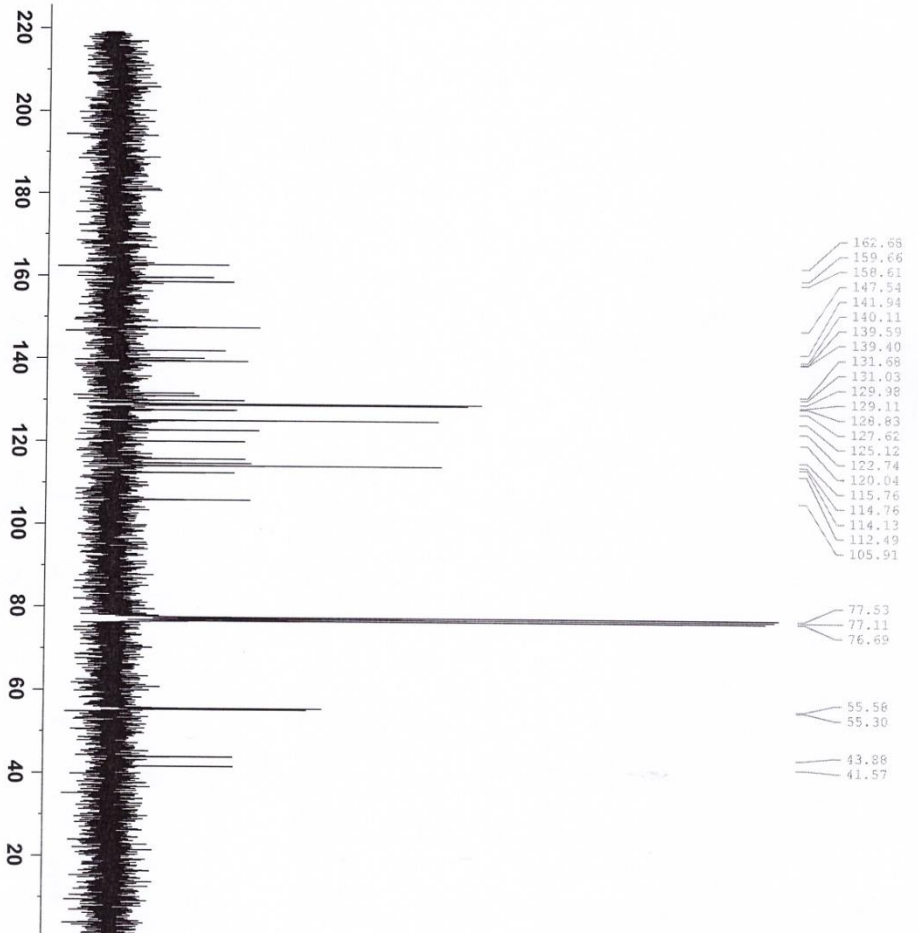
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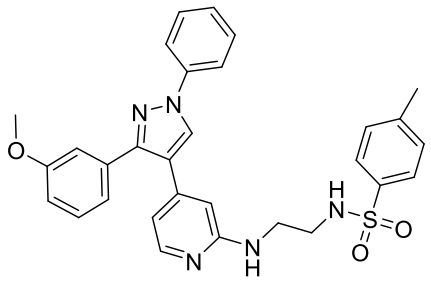
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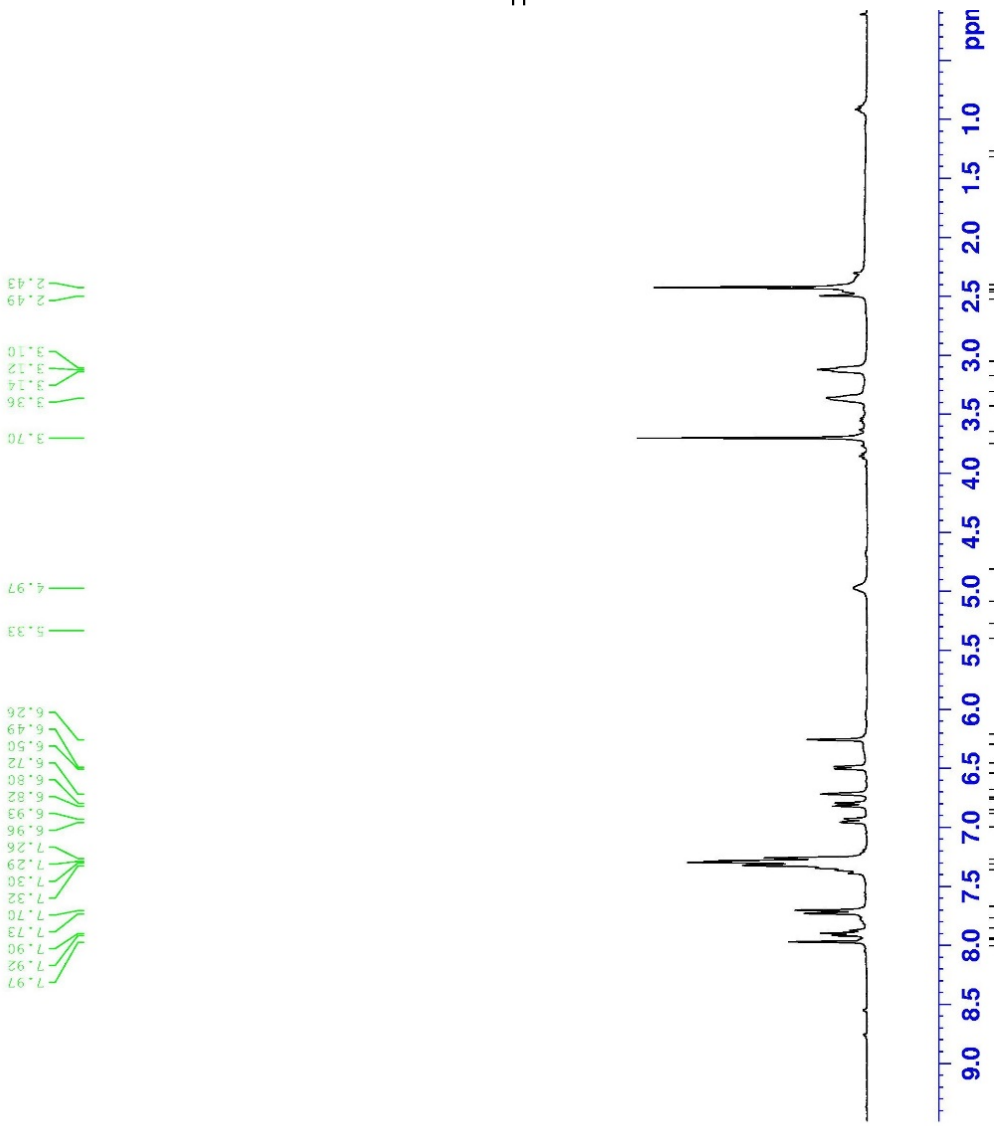
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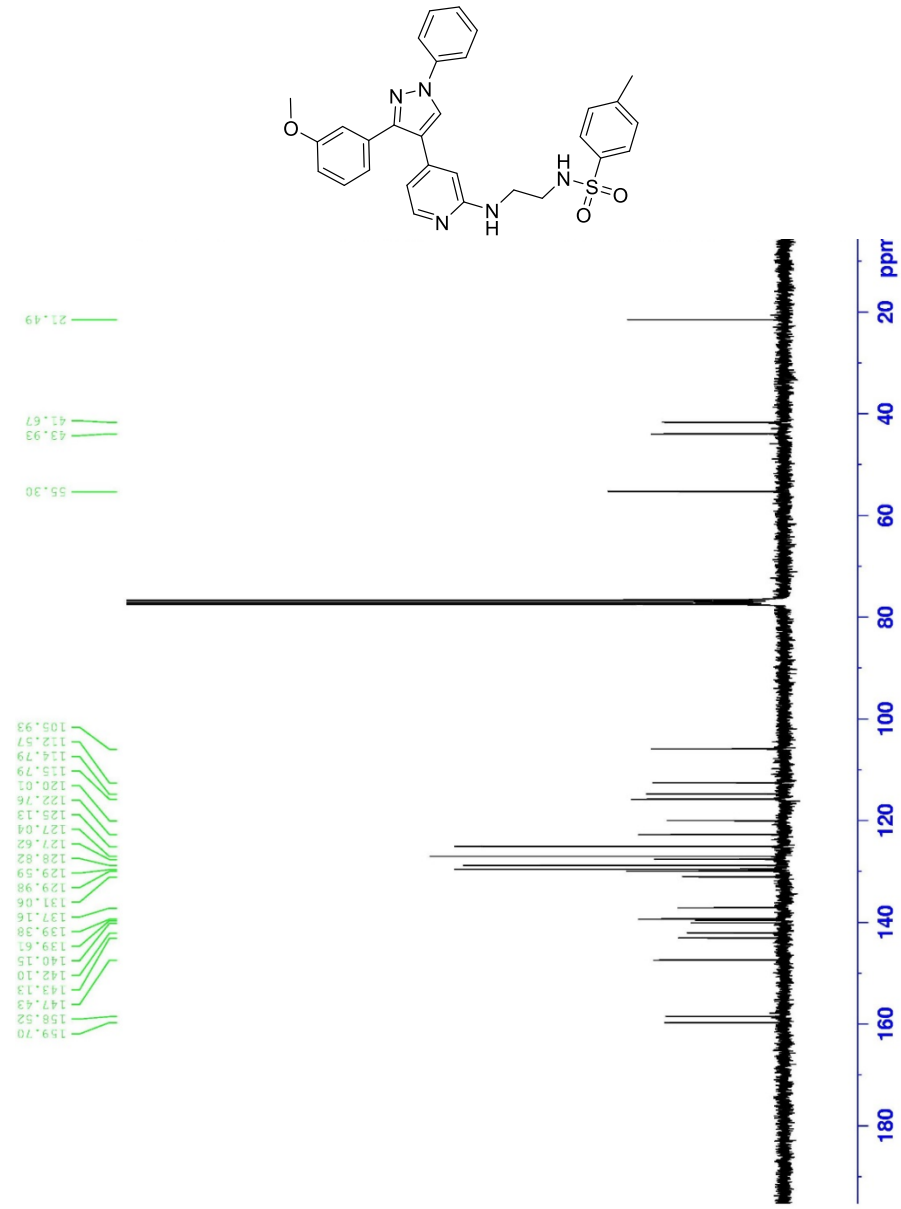
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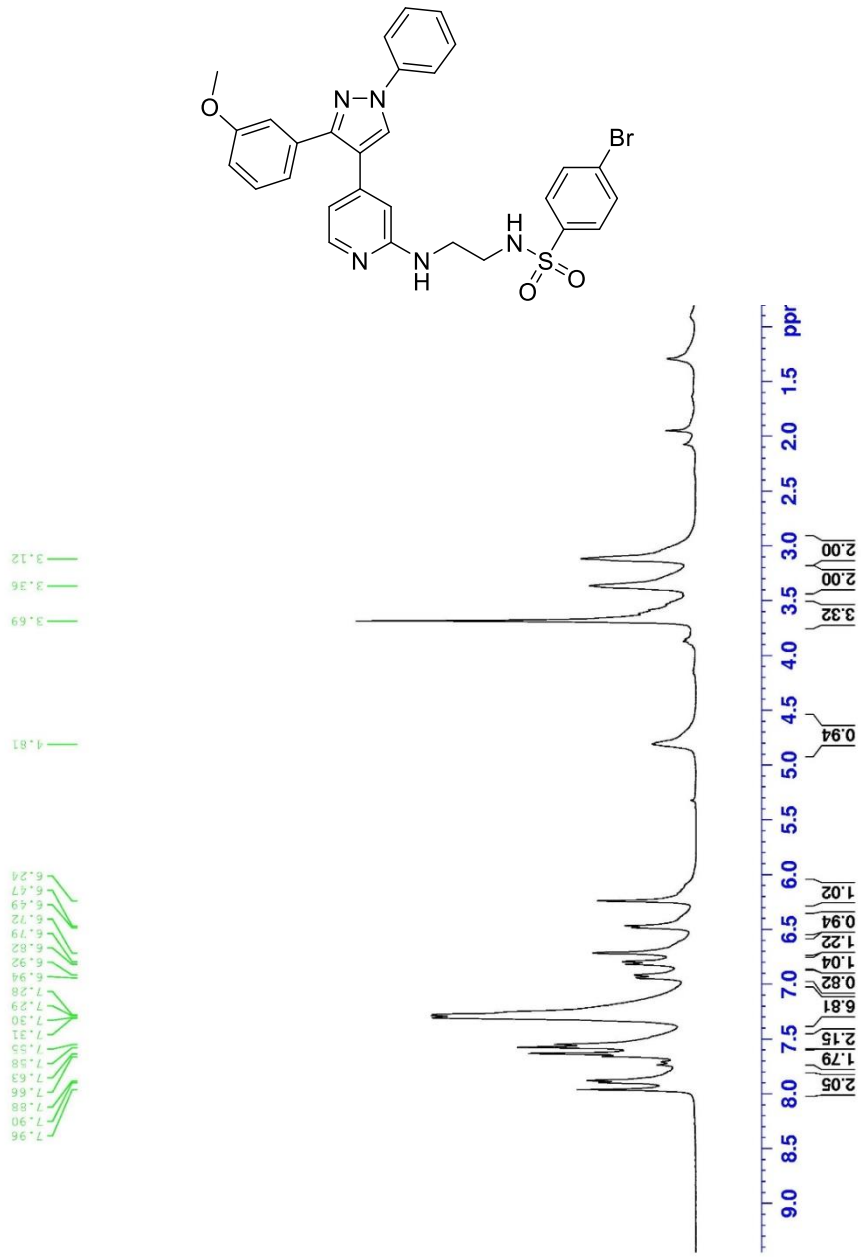
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2.05
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6.79
6.82
6.92
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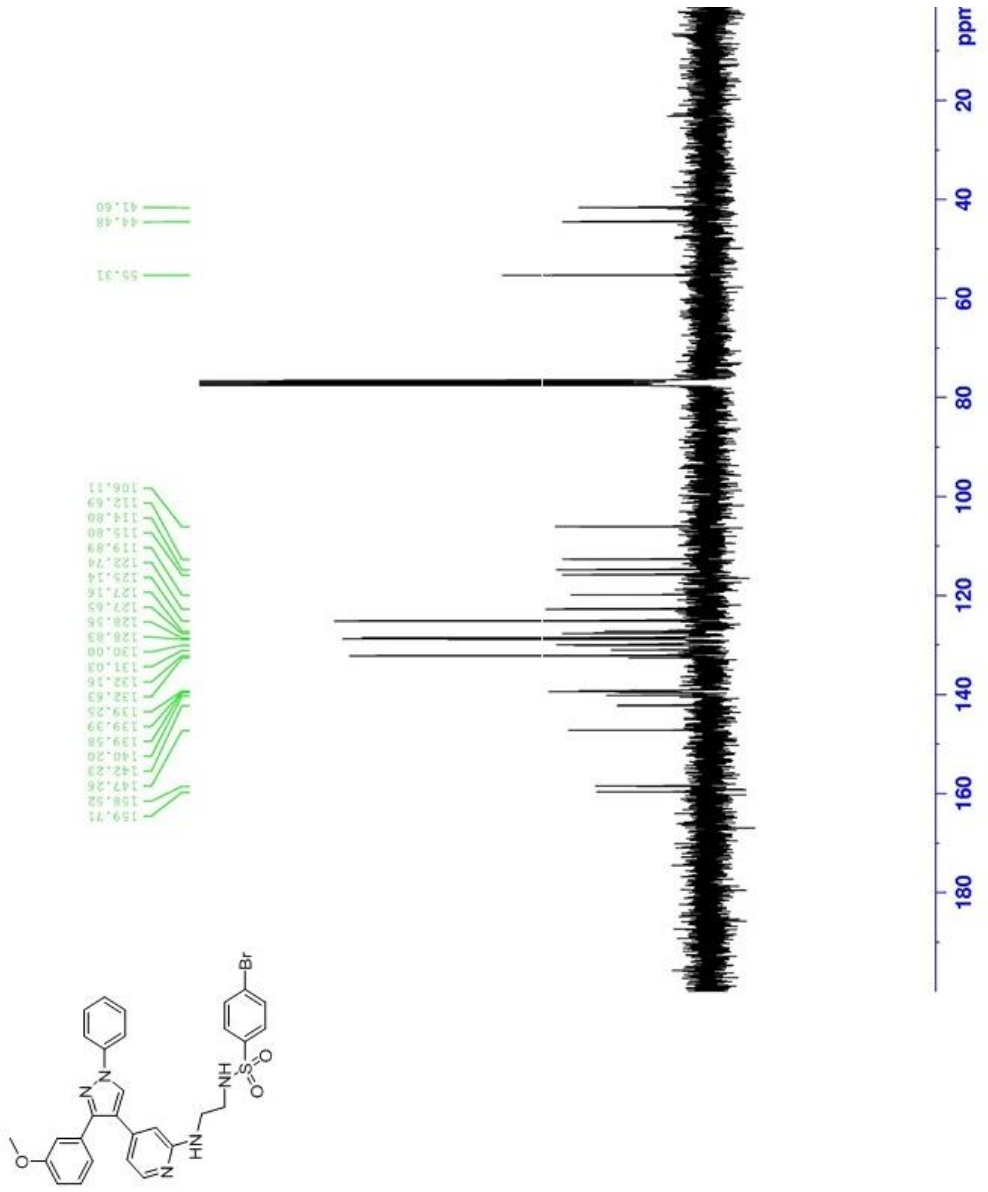
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147.26
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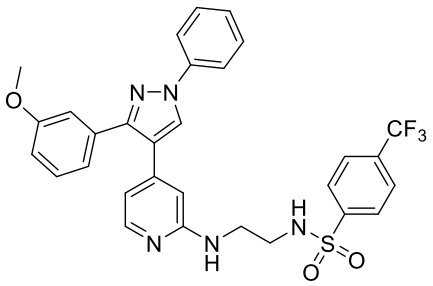
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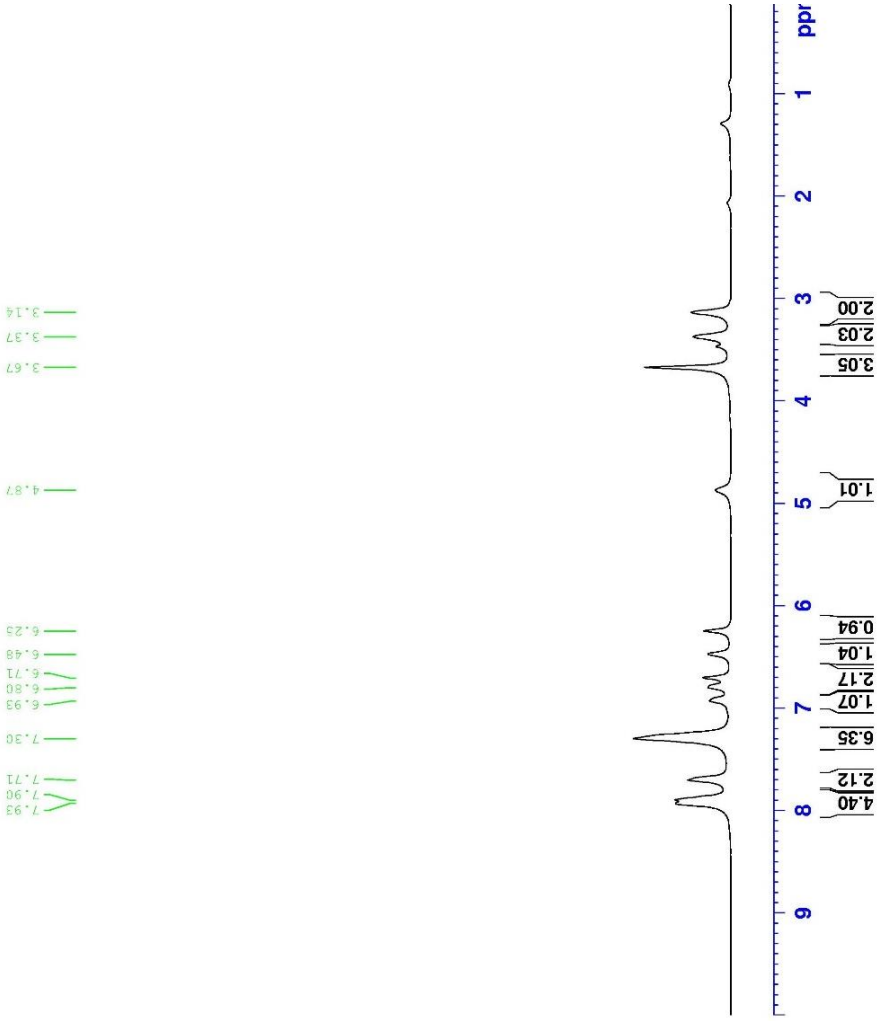
O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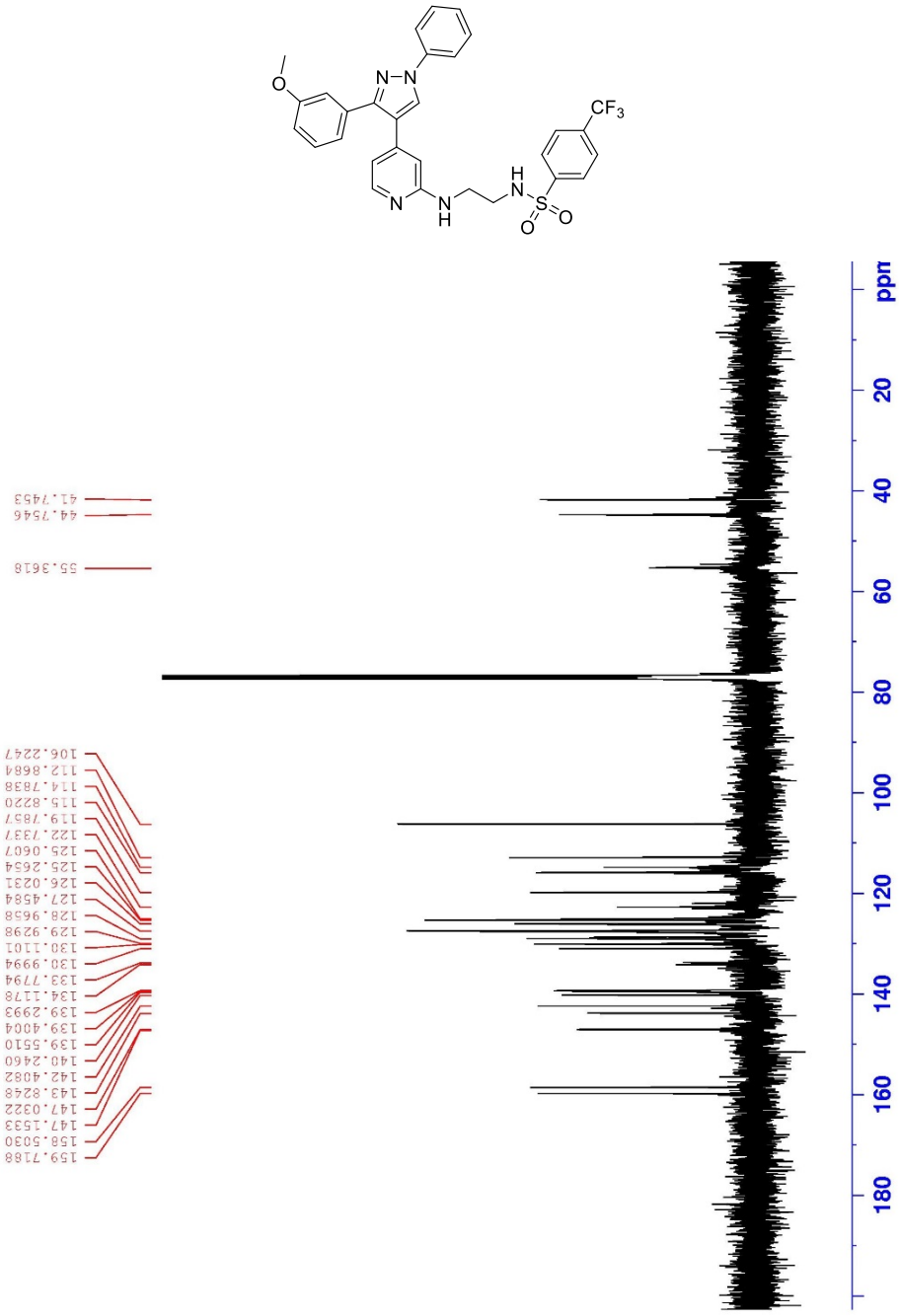
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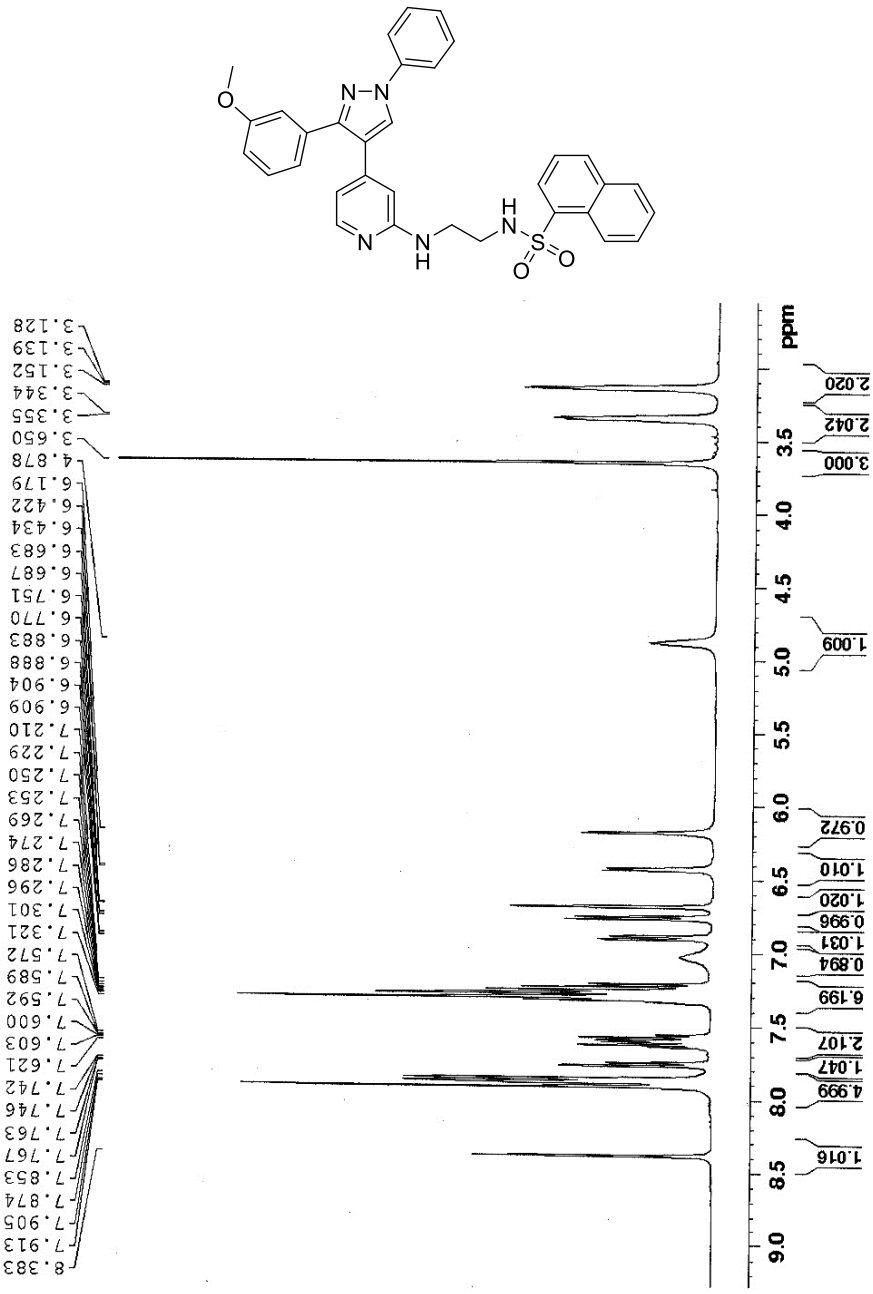

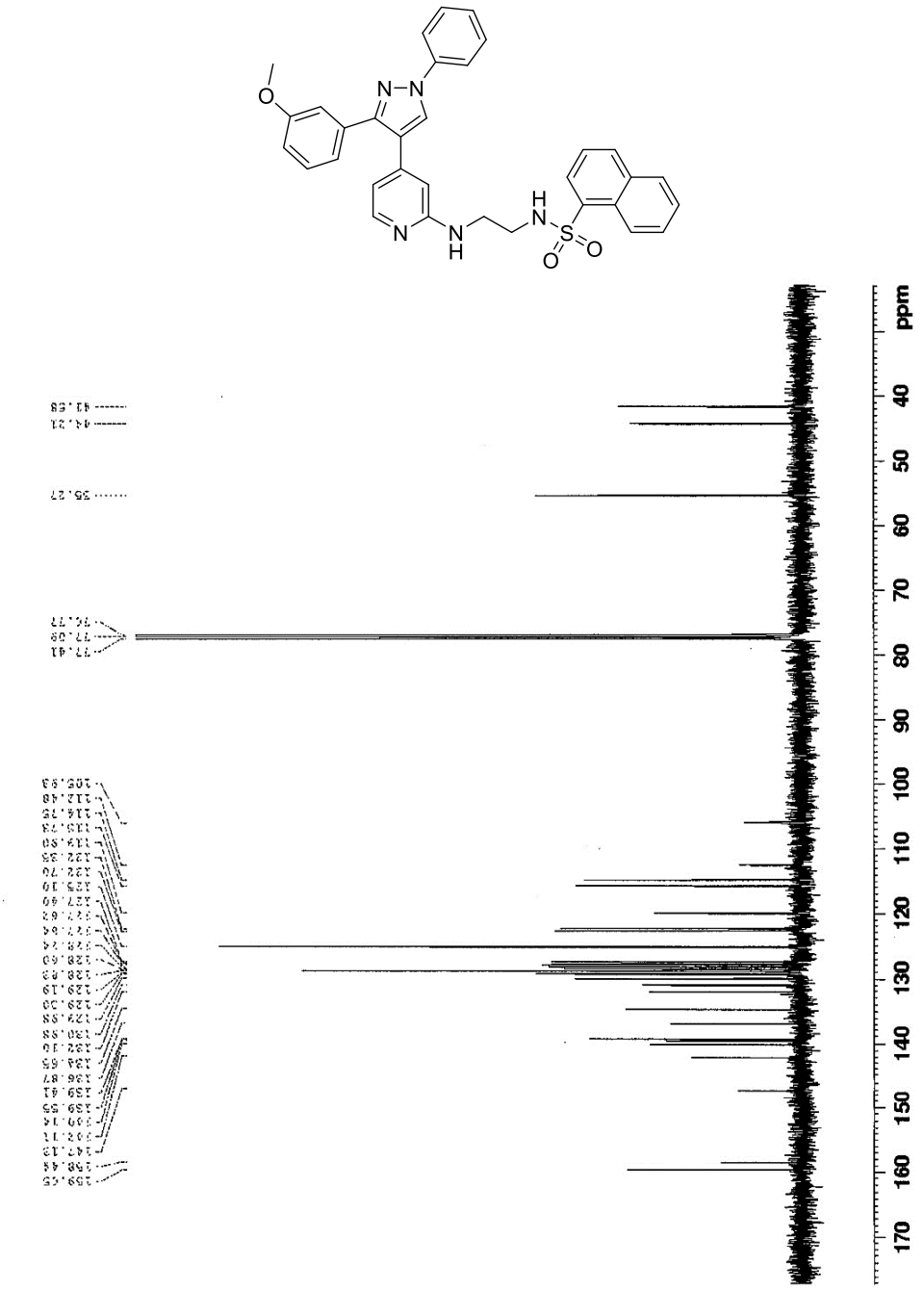
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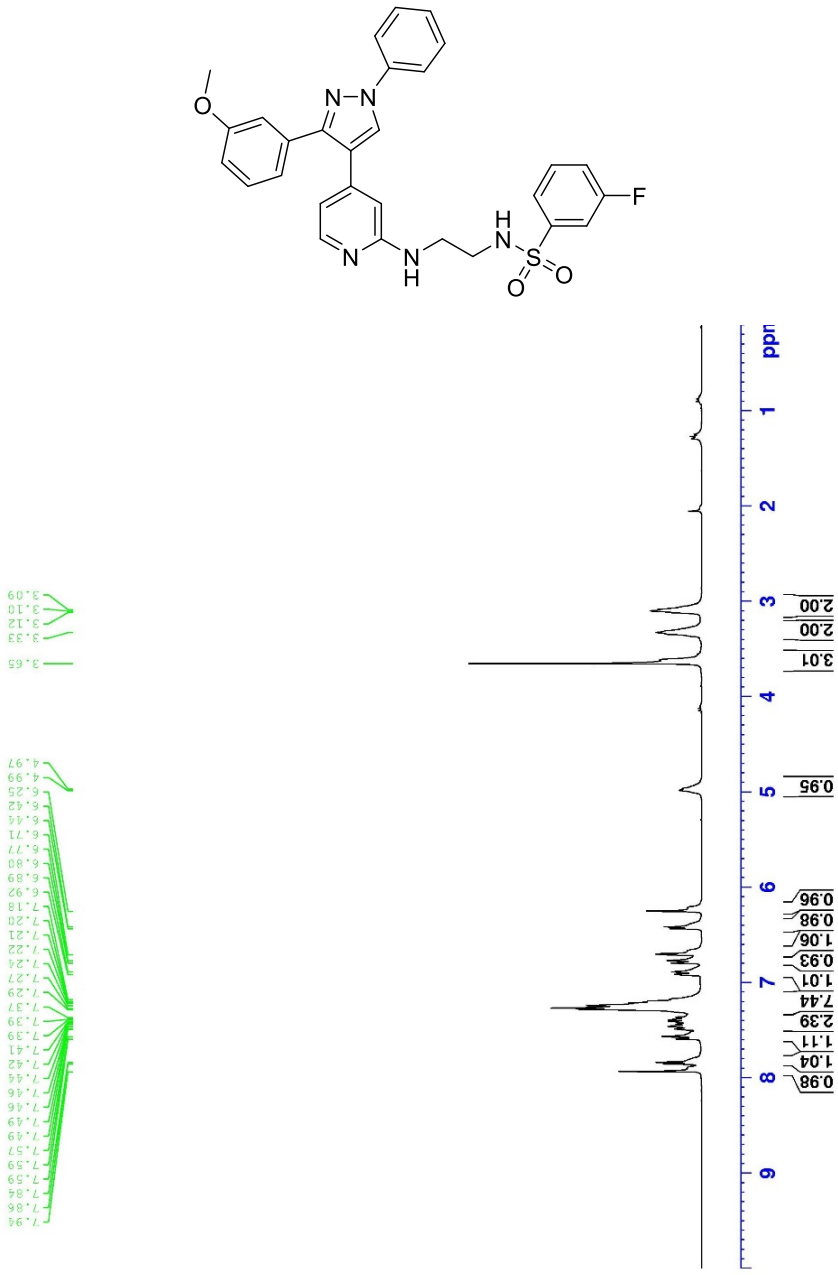

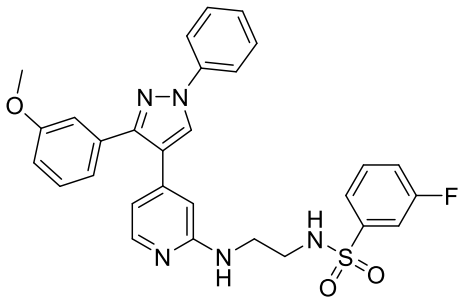
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N
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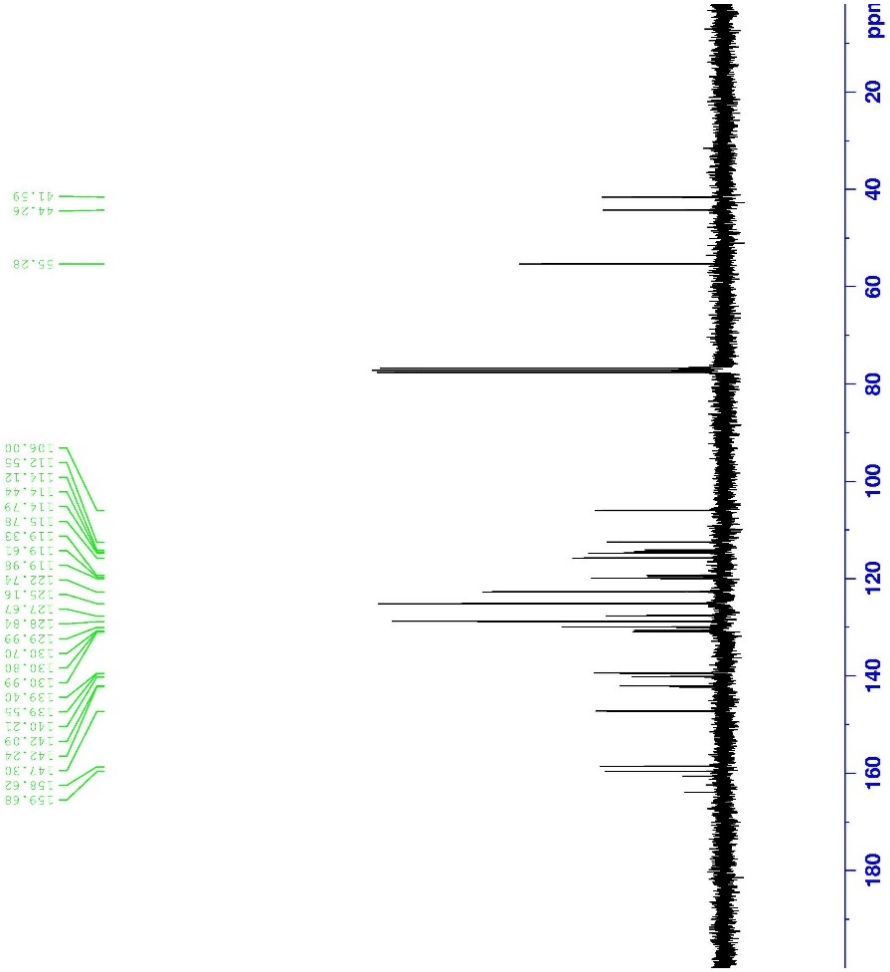
O
O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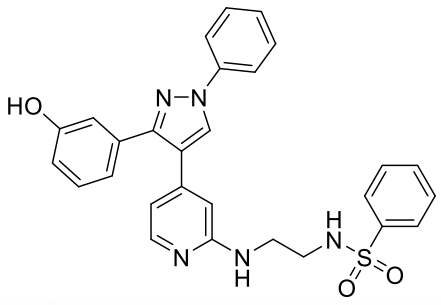
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H
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N
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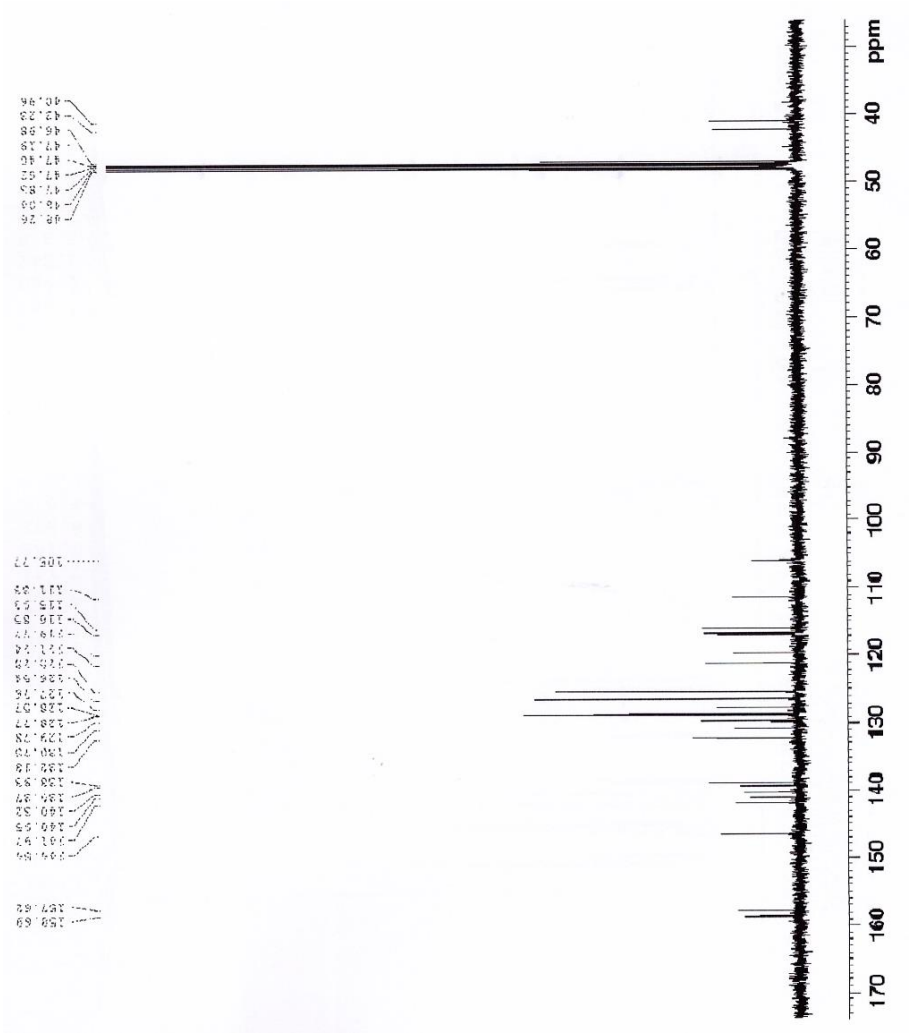
O
O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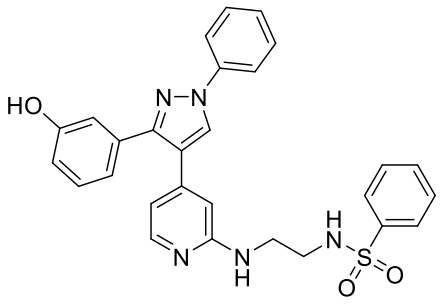
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H
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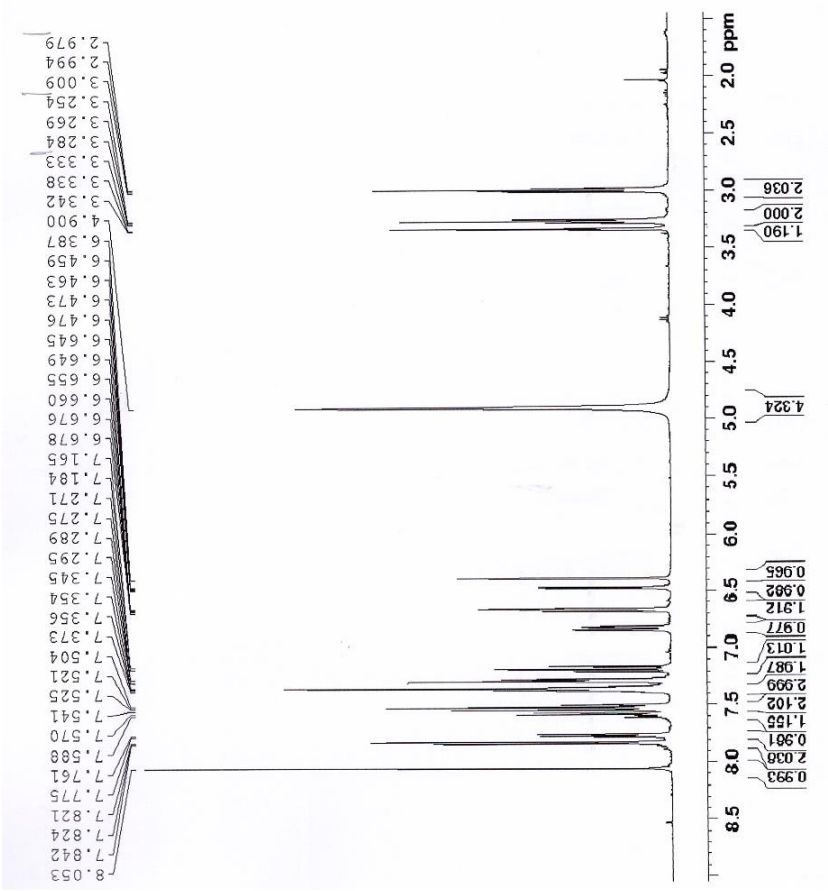
O
O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6.649
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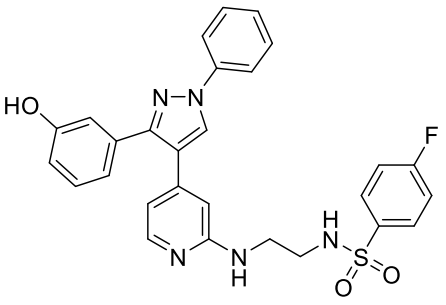
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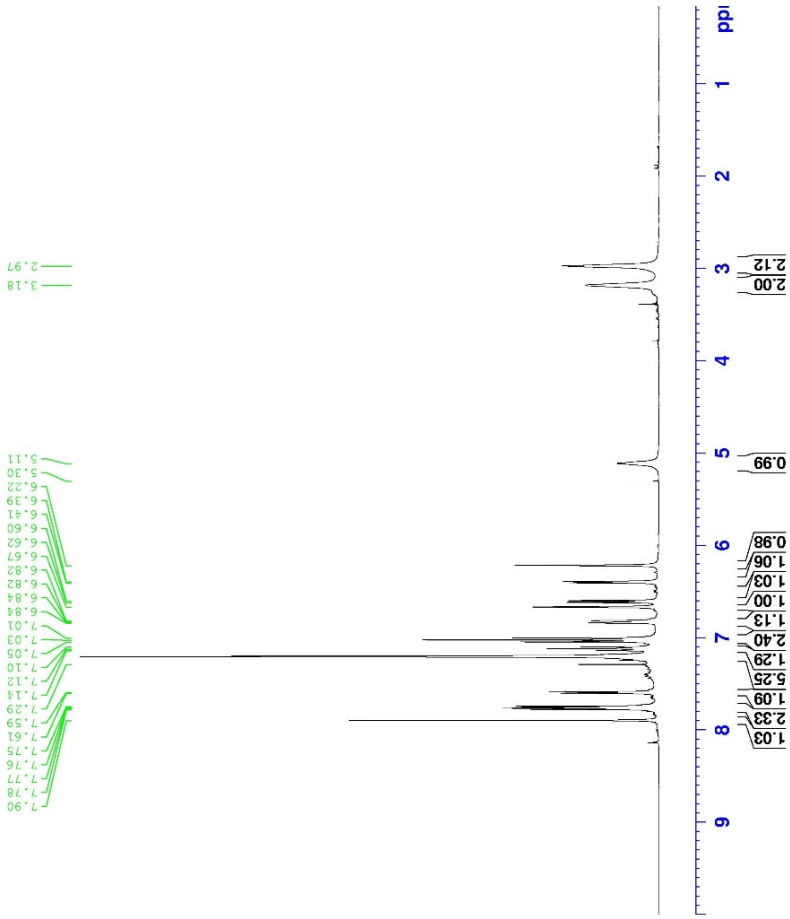
N
S
O
O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6.84
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7.75
7.76
7.77
7.78
7.90
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1.03
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1.29
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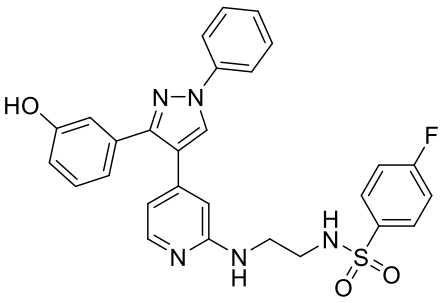
1.09
2.33
1.03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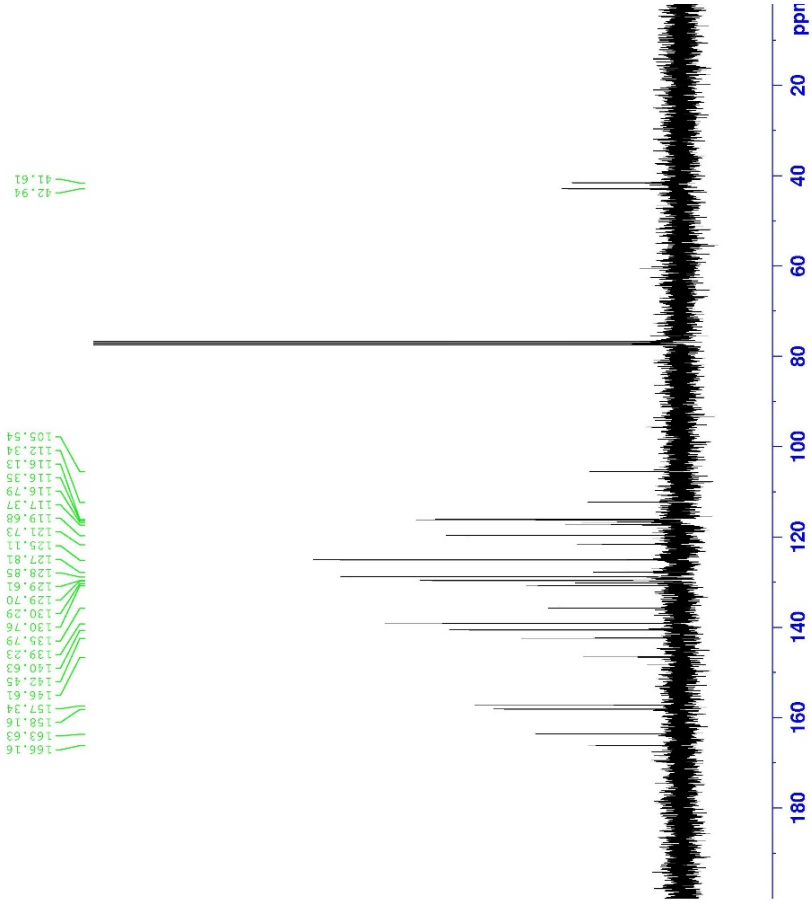
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117.37
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6.0
5.5
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3.0
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NH
S
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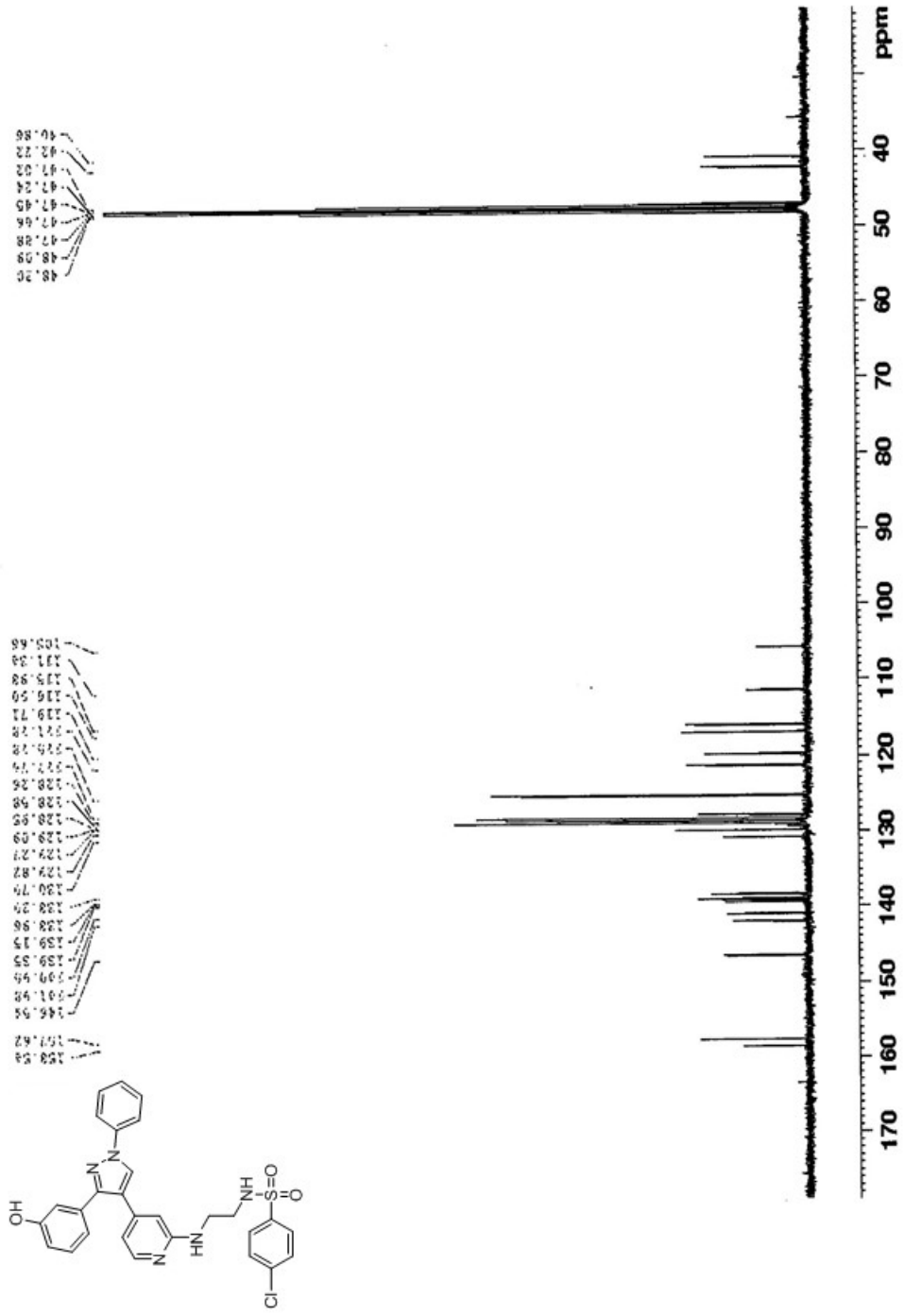
O
Cl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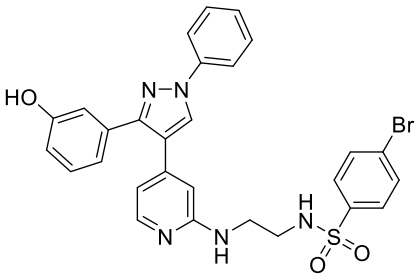
O
Cl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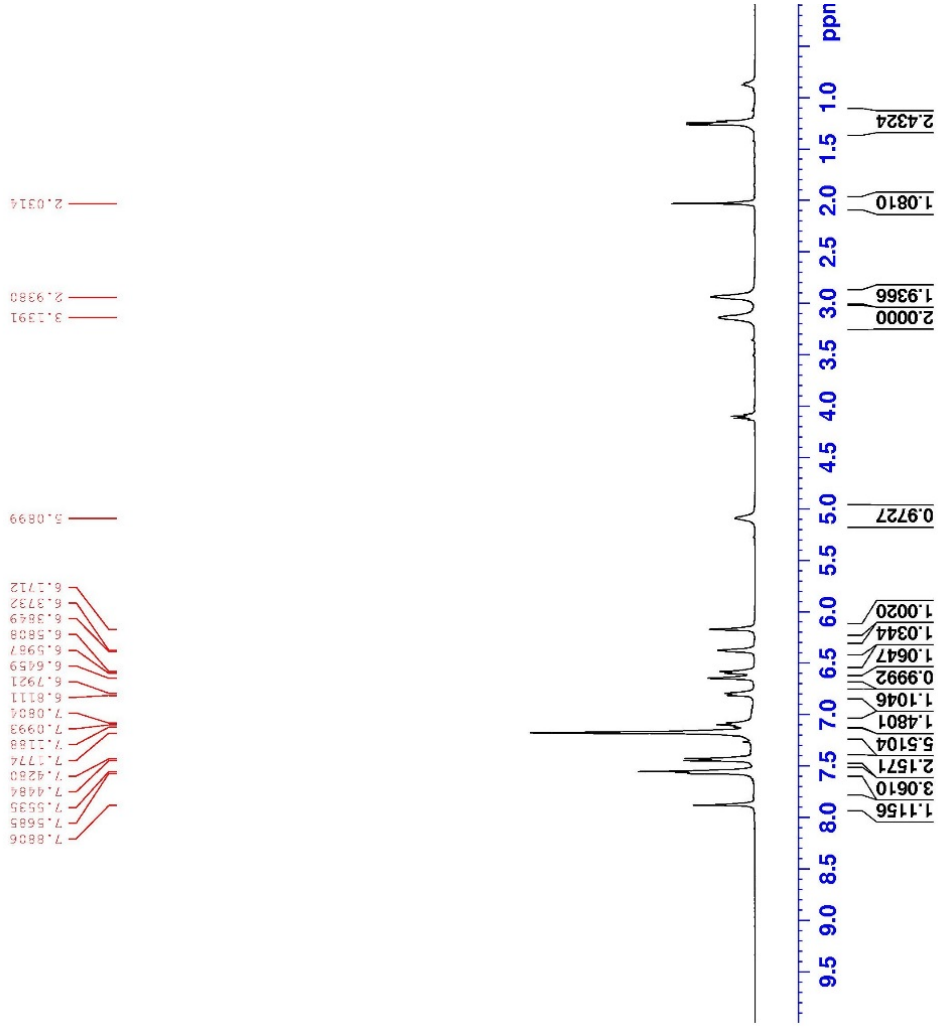
O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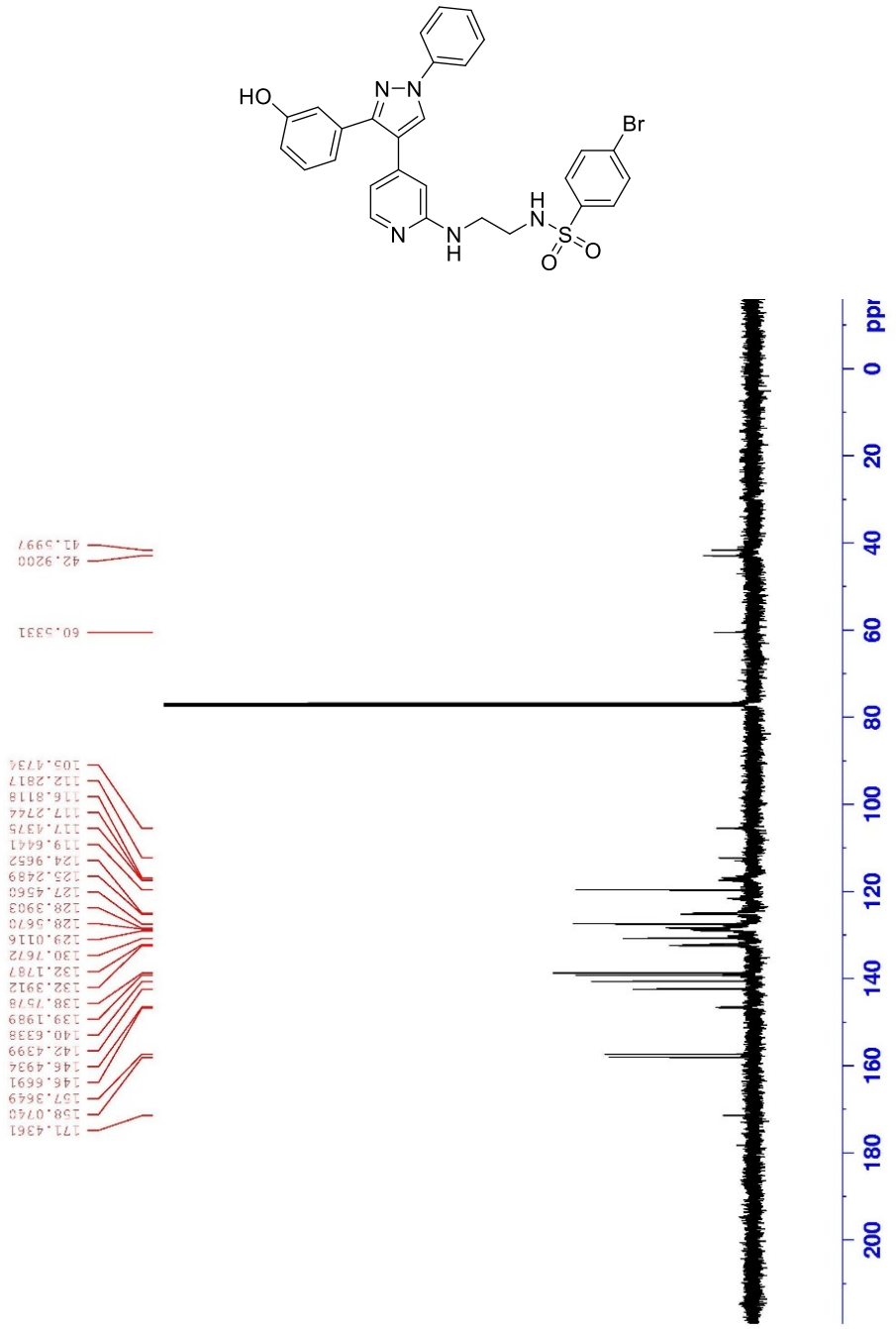
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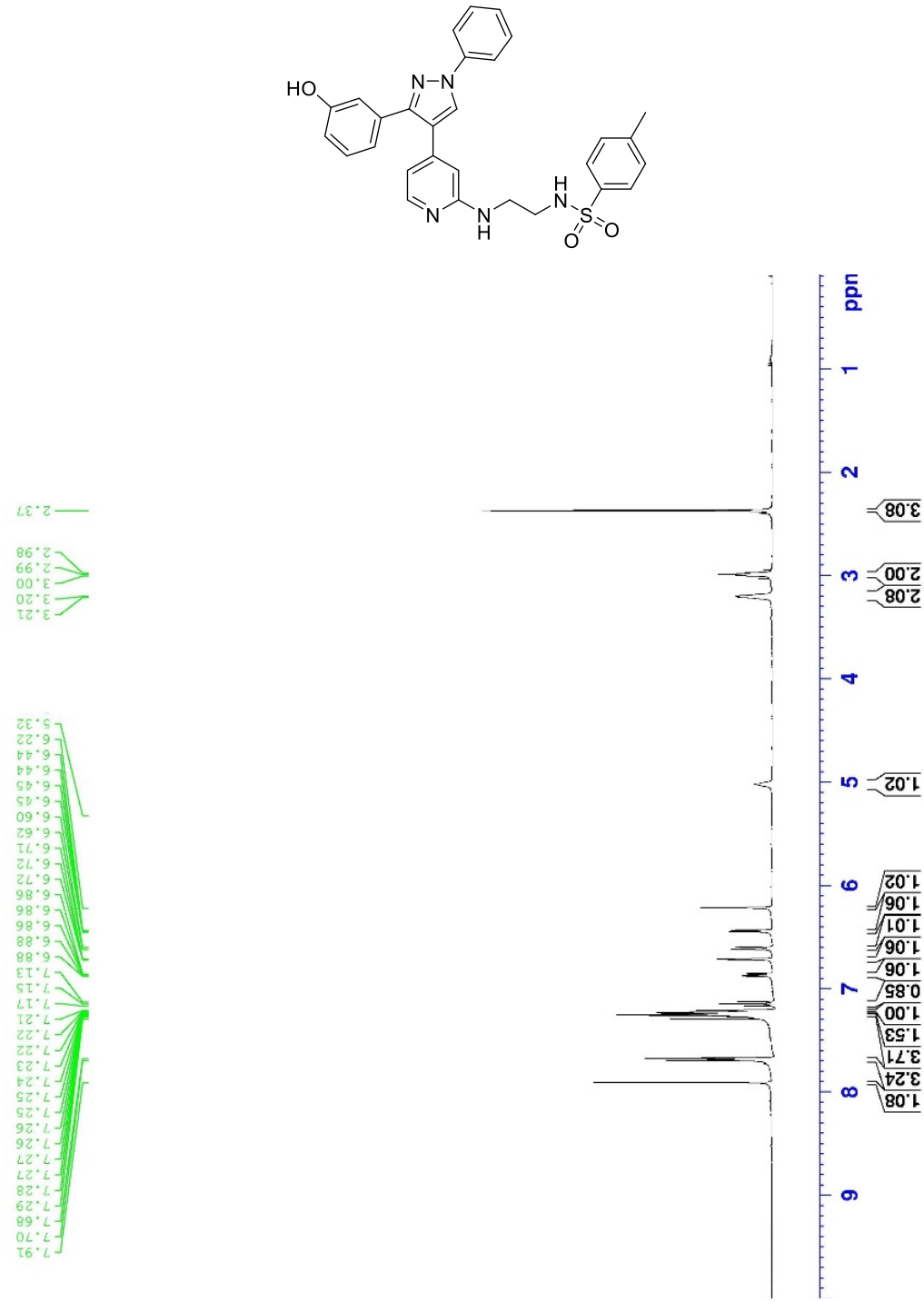
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H
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1.02
1.06
1.01
1.06
1.06
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1.00
1.53
3.71
3.24
1.08
2.37
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3.00
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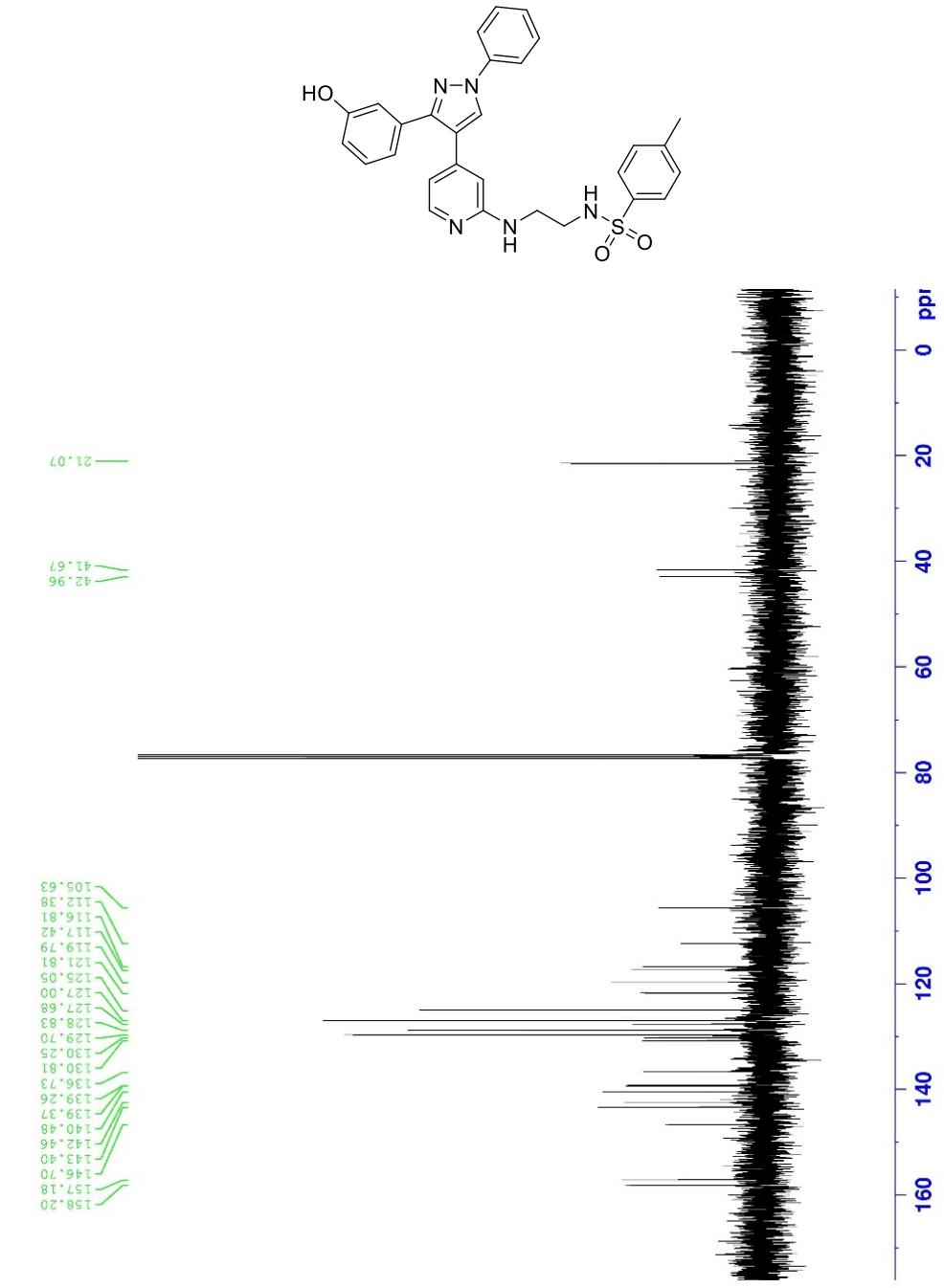
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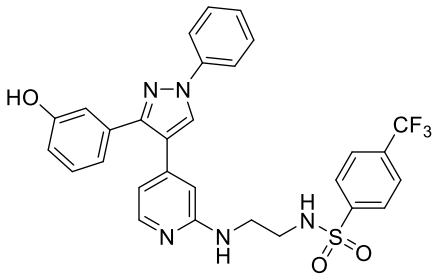
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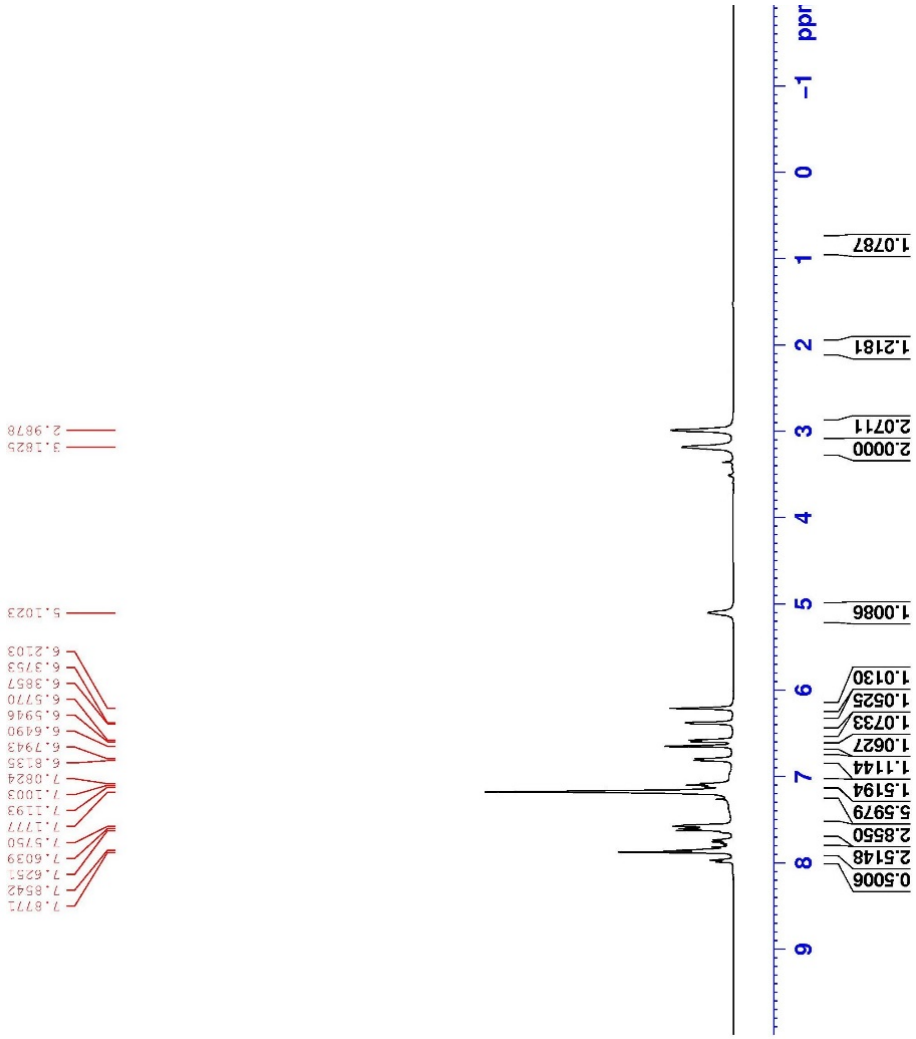
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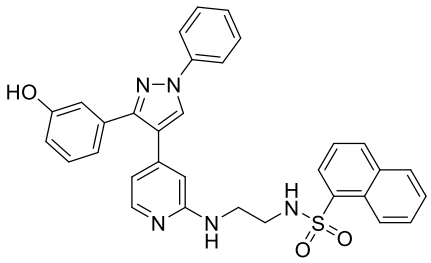
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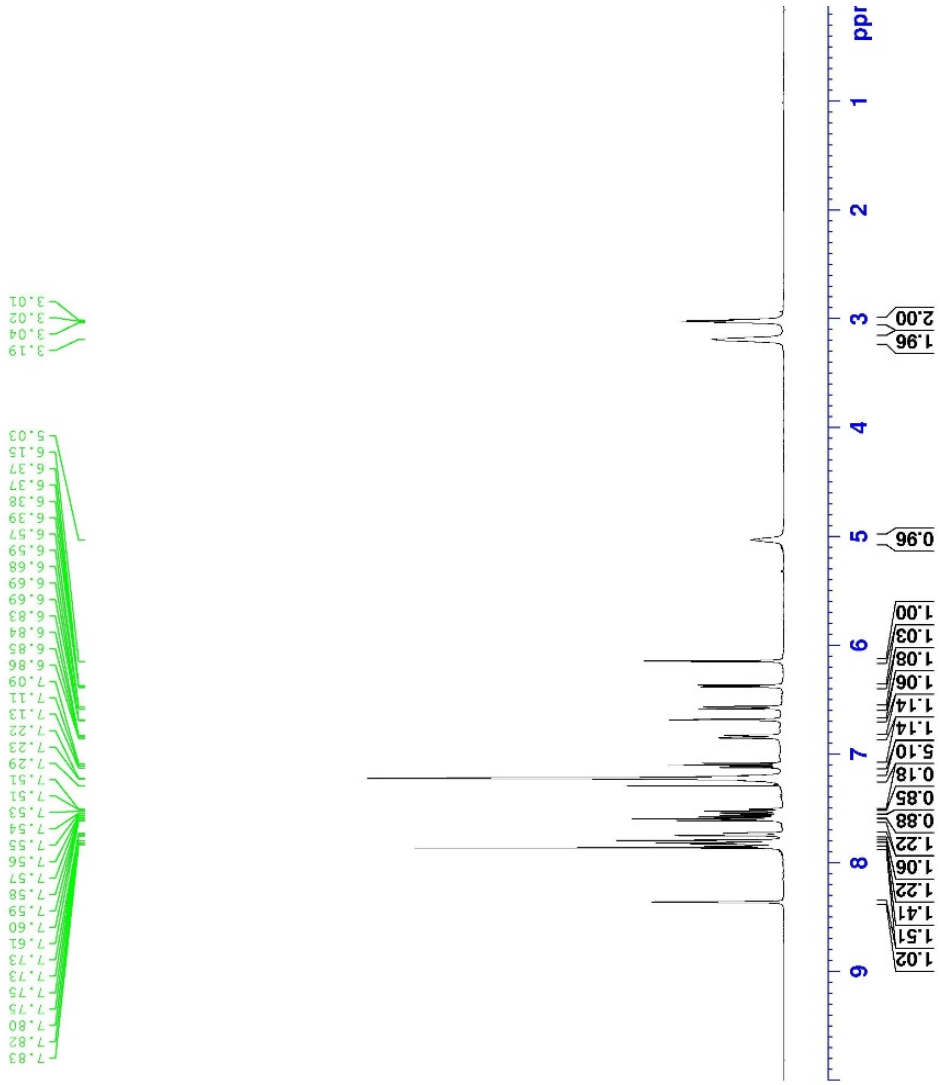
ppr
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1.14
1.14
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1.06
1.22
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3.01
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3.04
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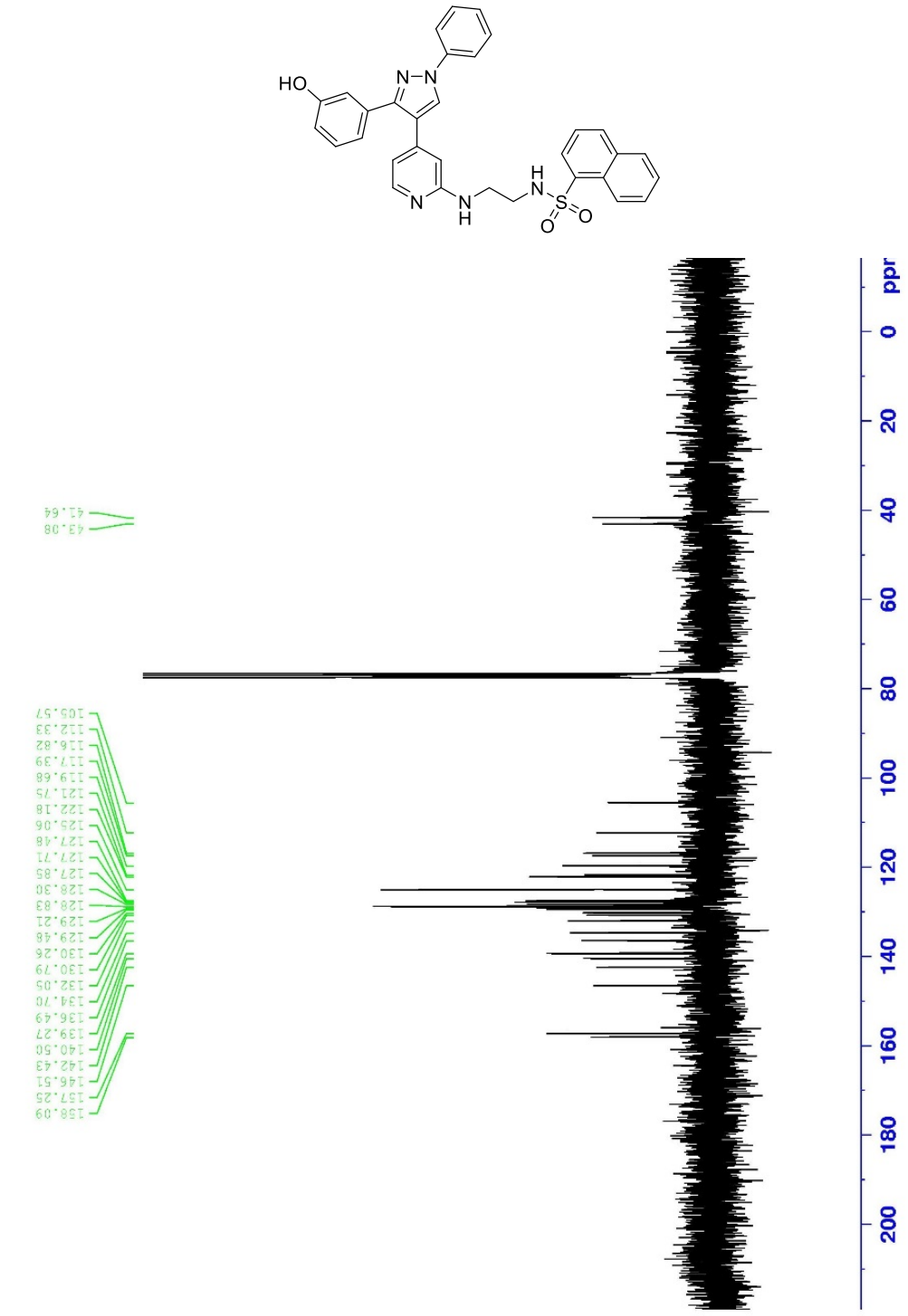
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ppr
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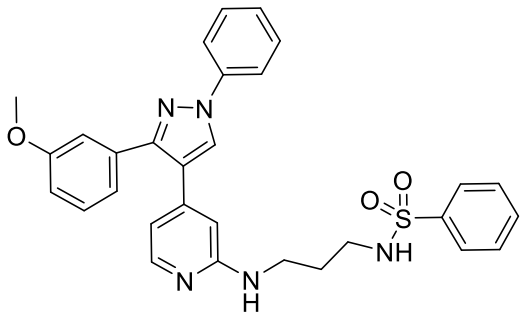
O
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O
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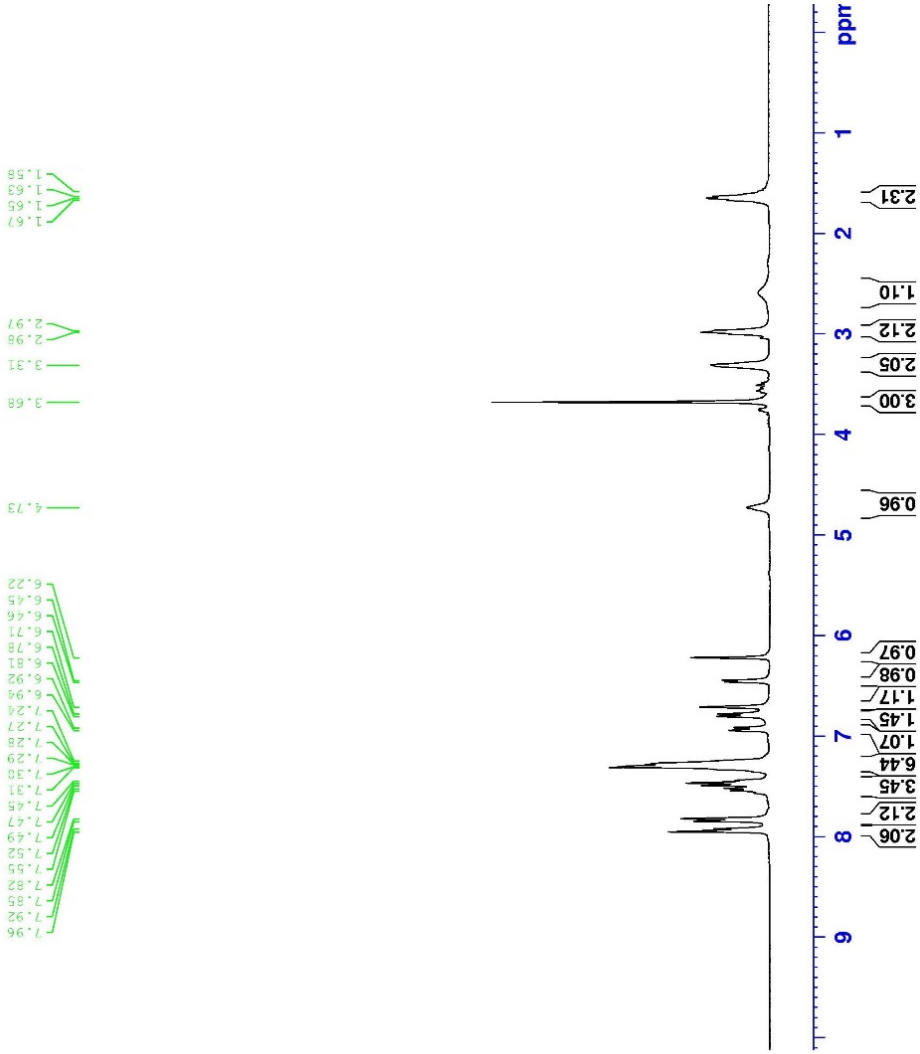
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1.67
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2.98
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6.92
6.94
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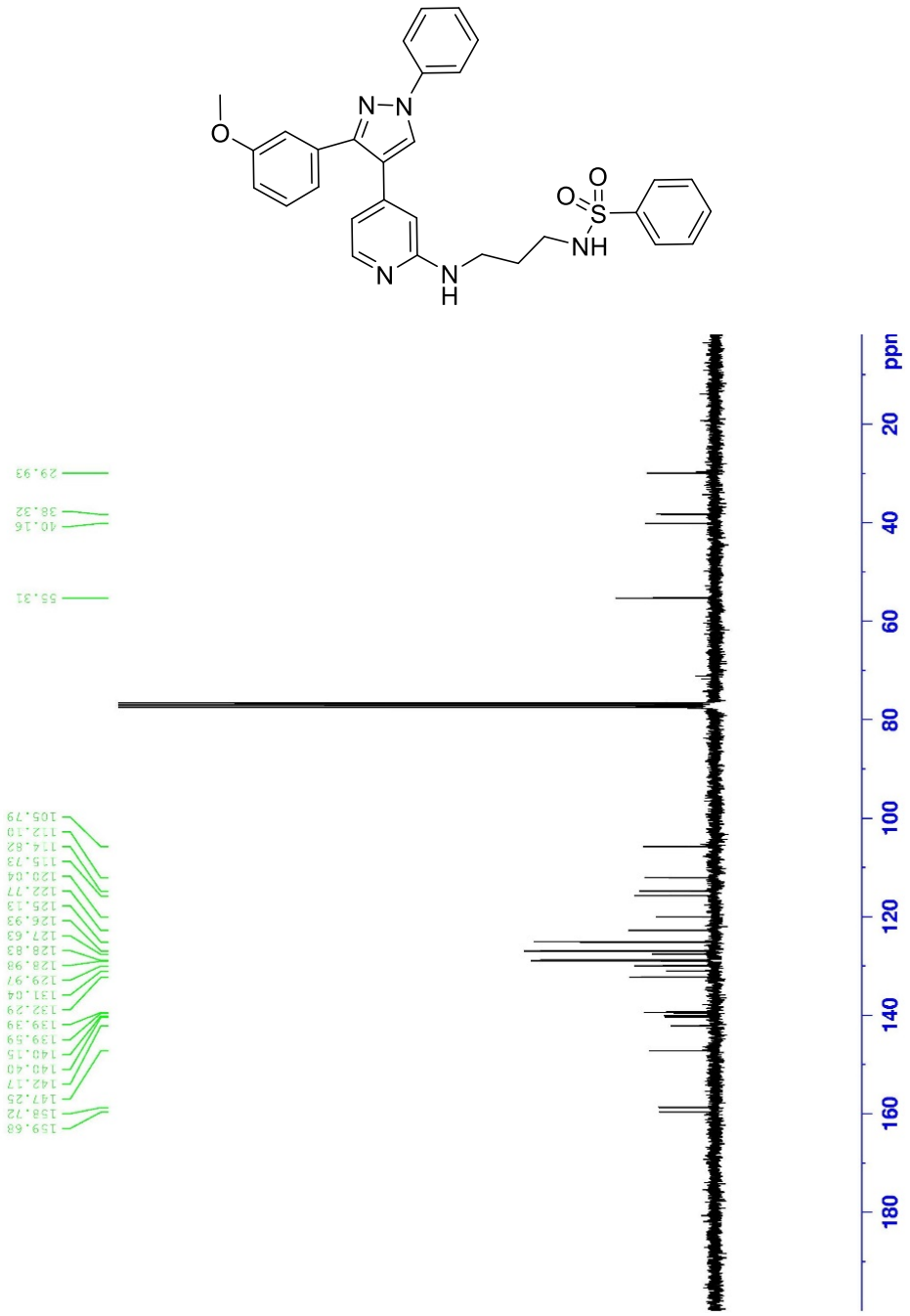
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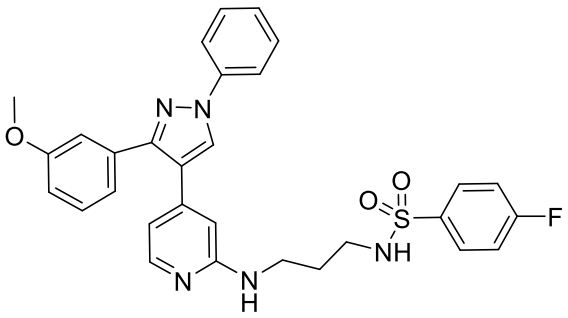
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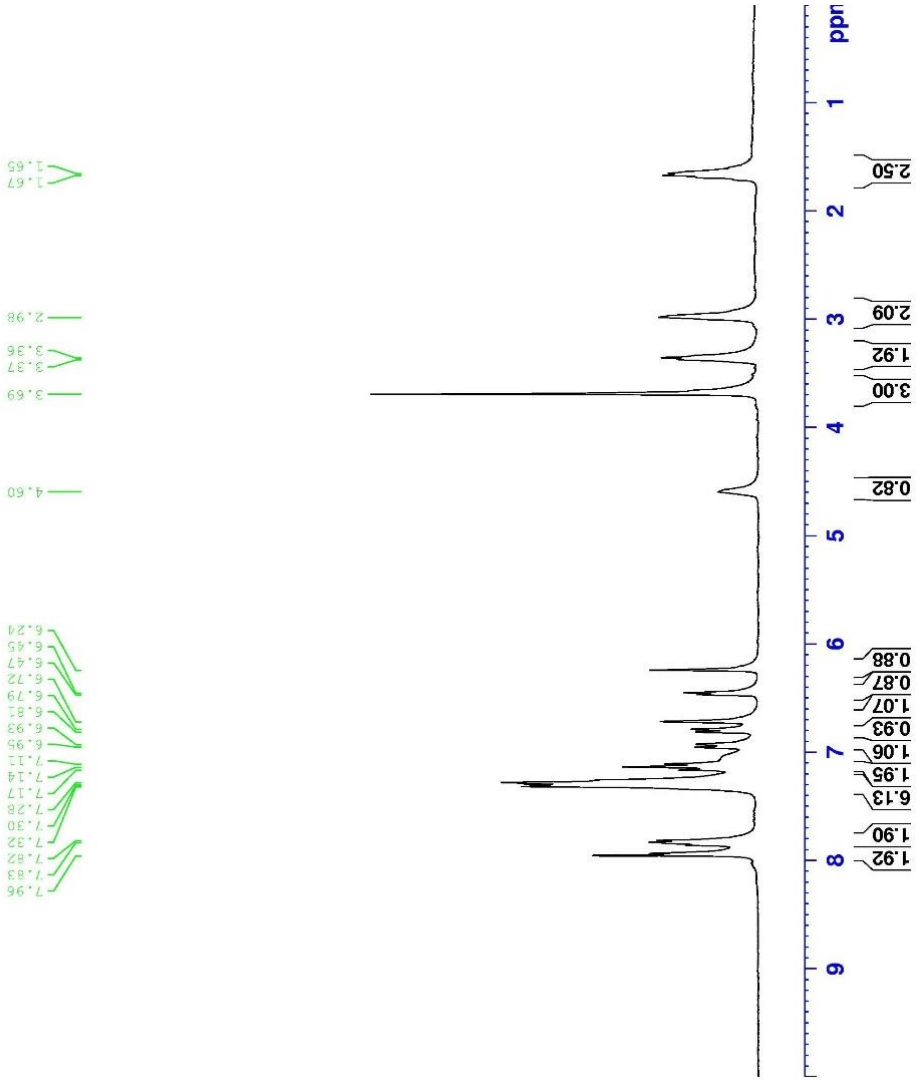
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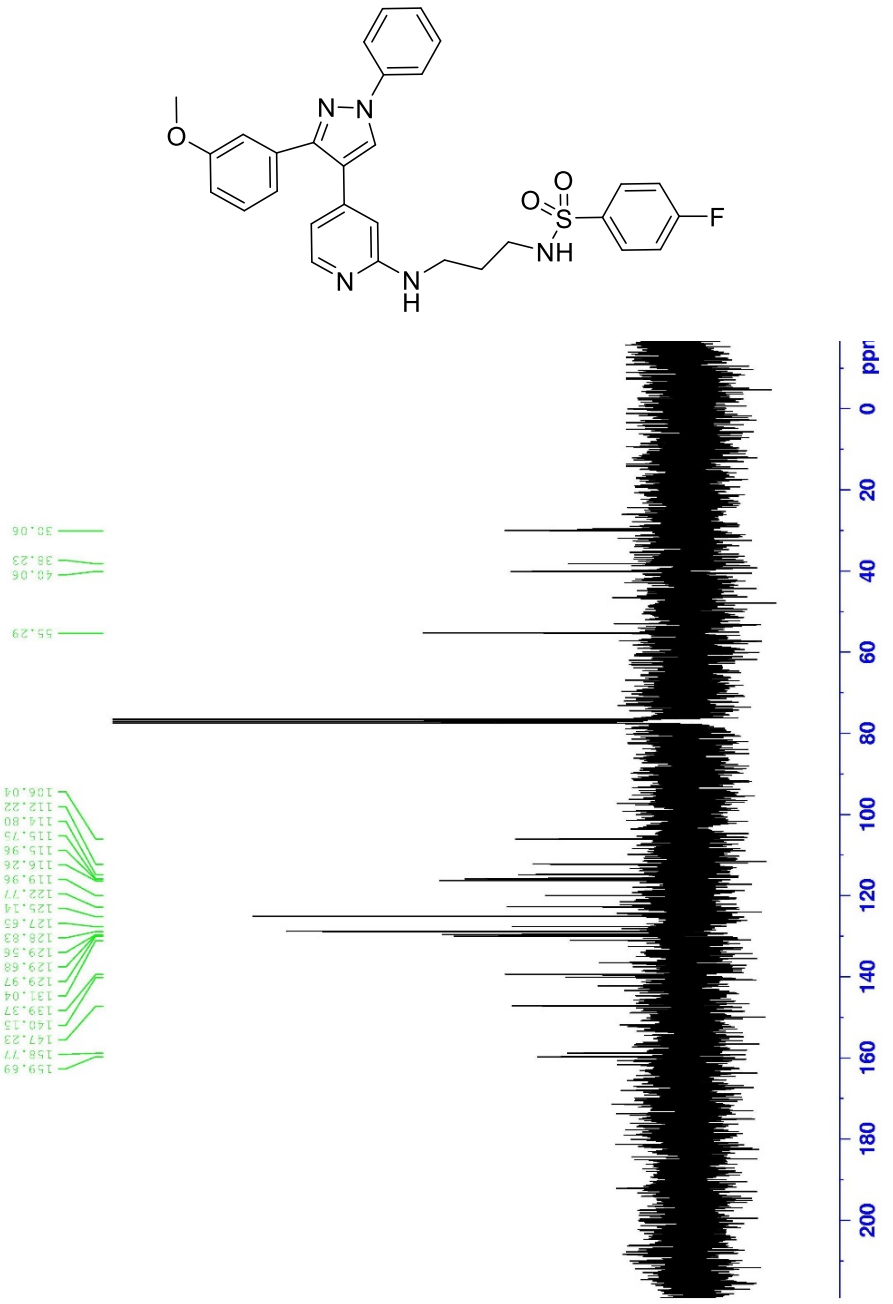
7.96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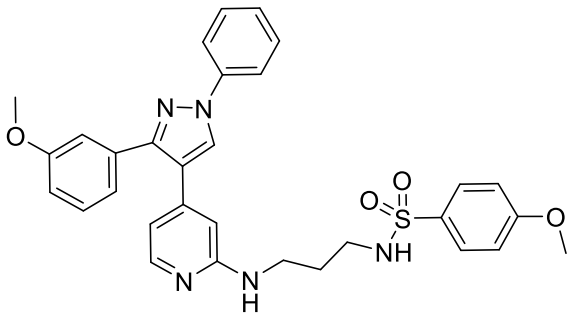
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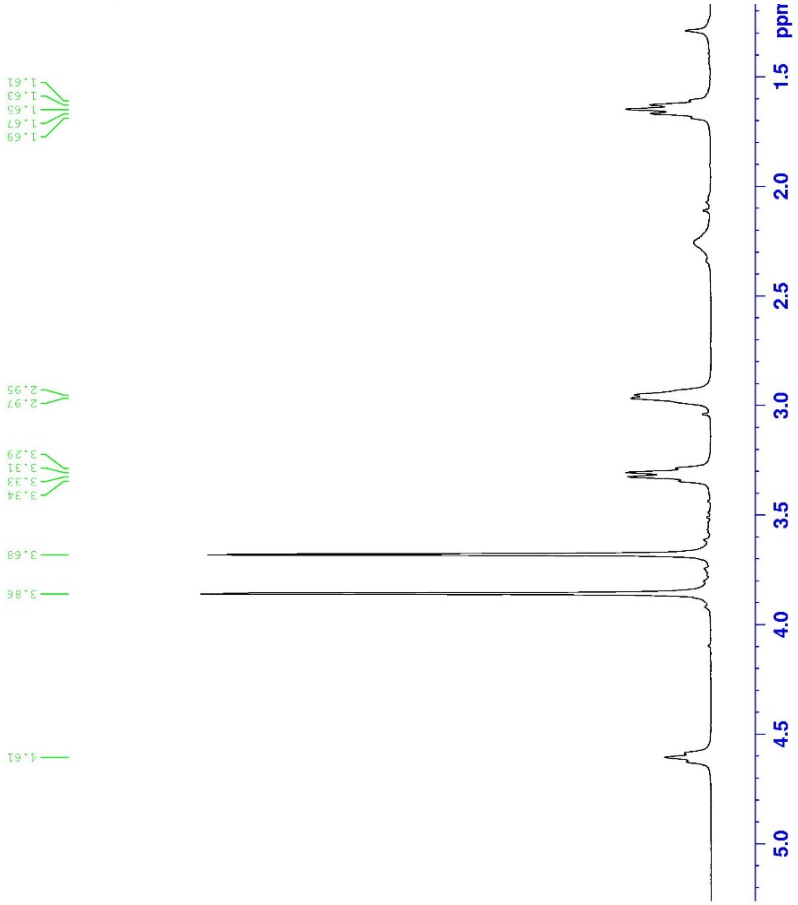
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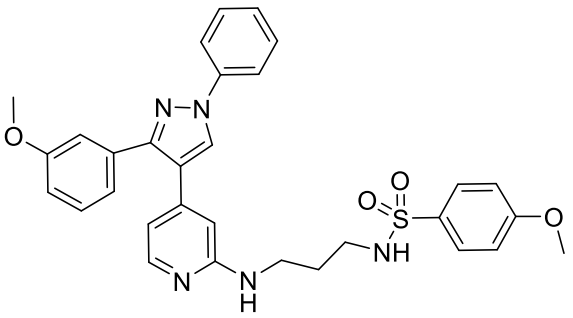

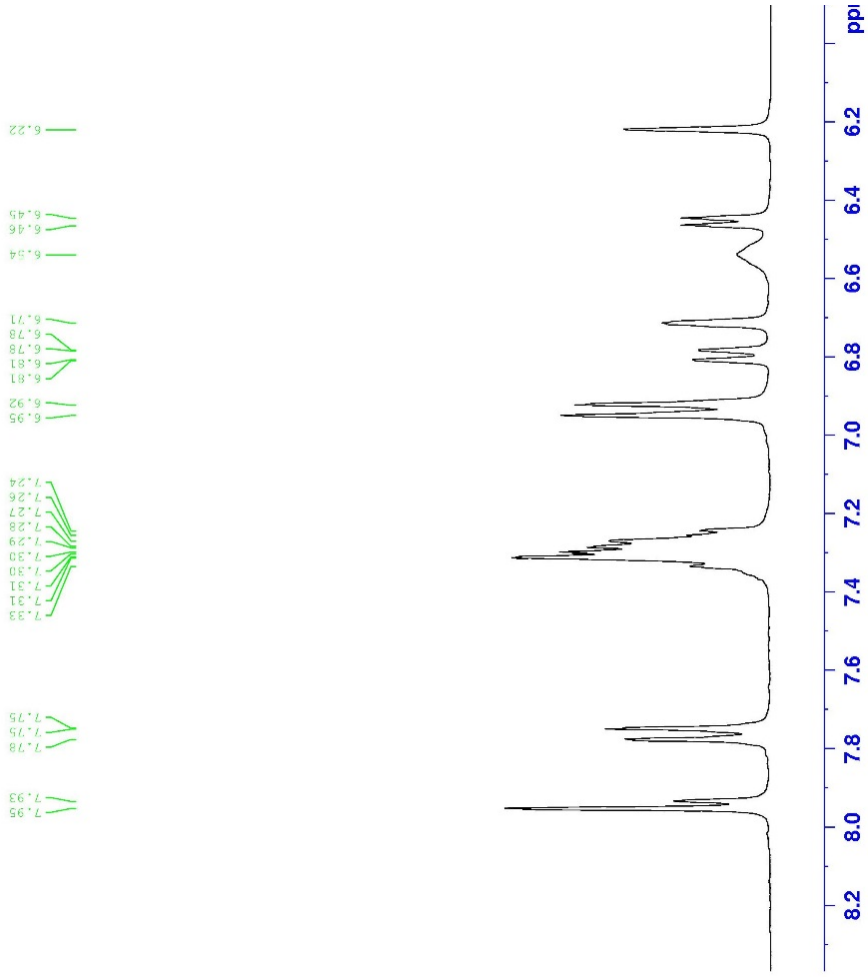
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7.28
7.29
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7.31
7.31
7.33
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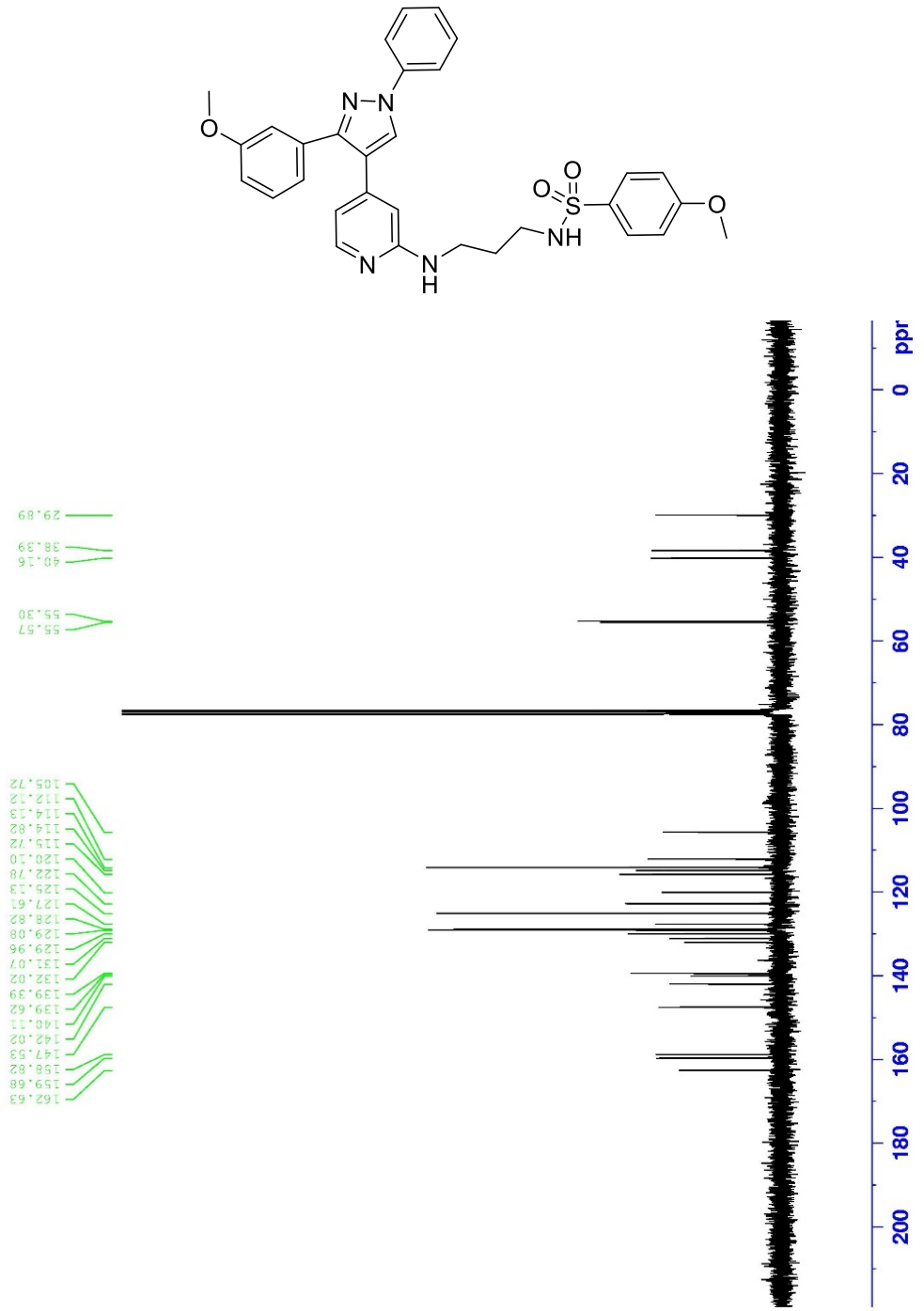
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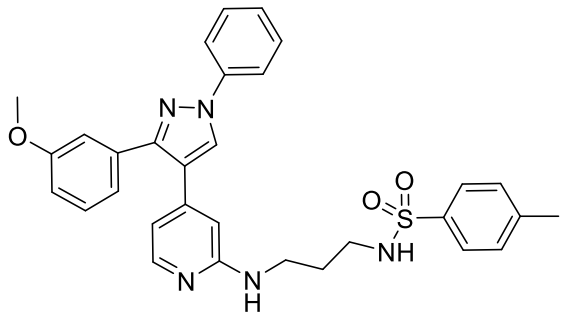
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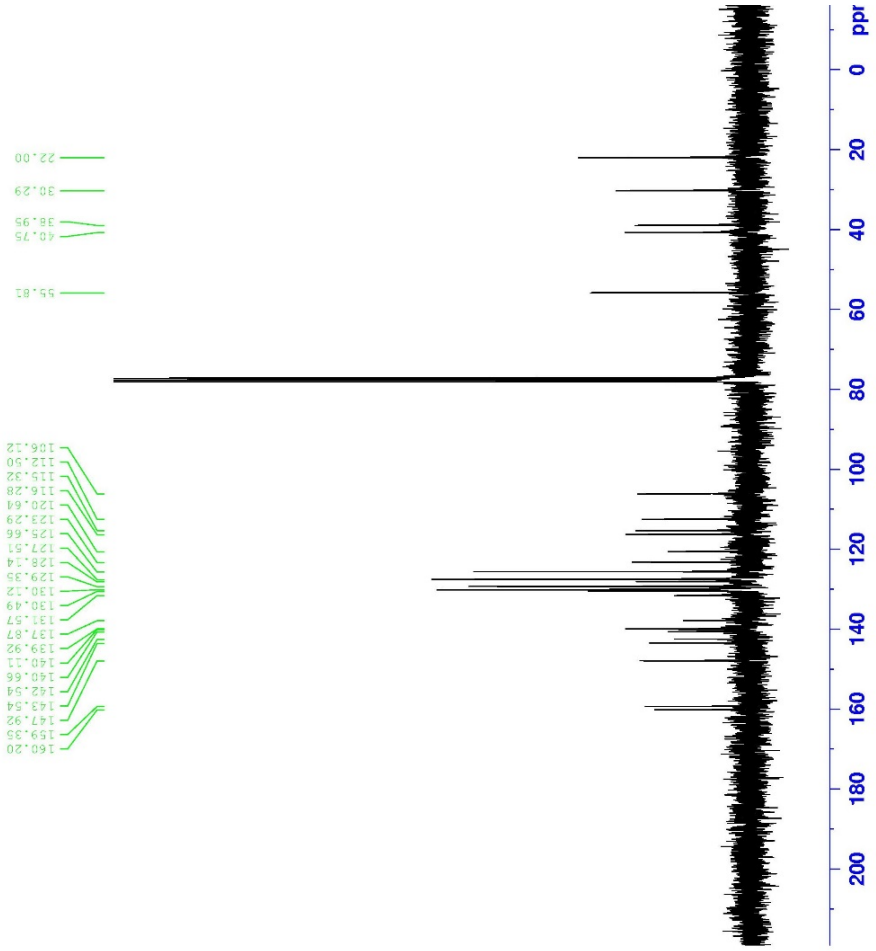
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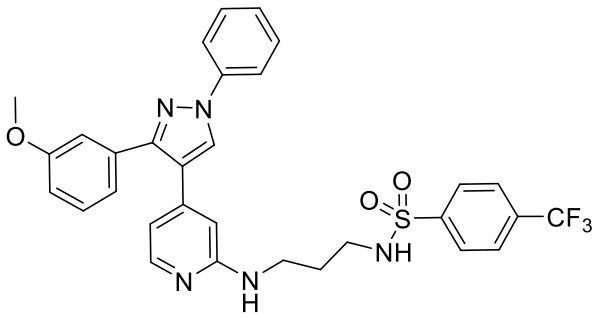
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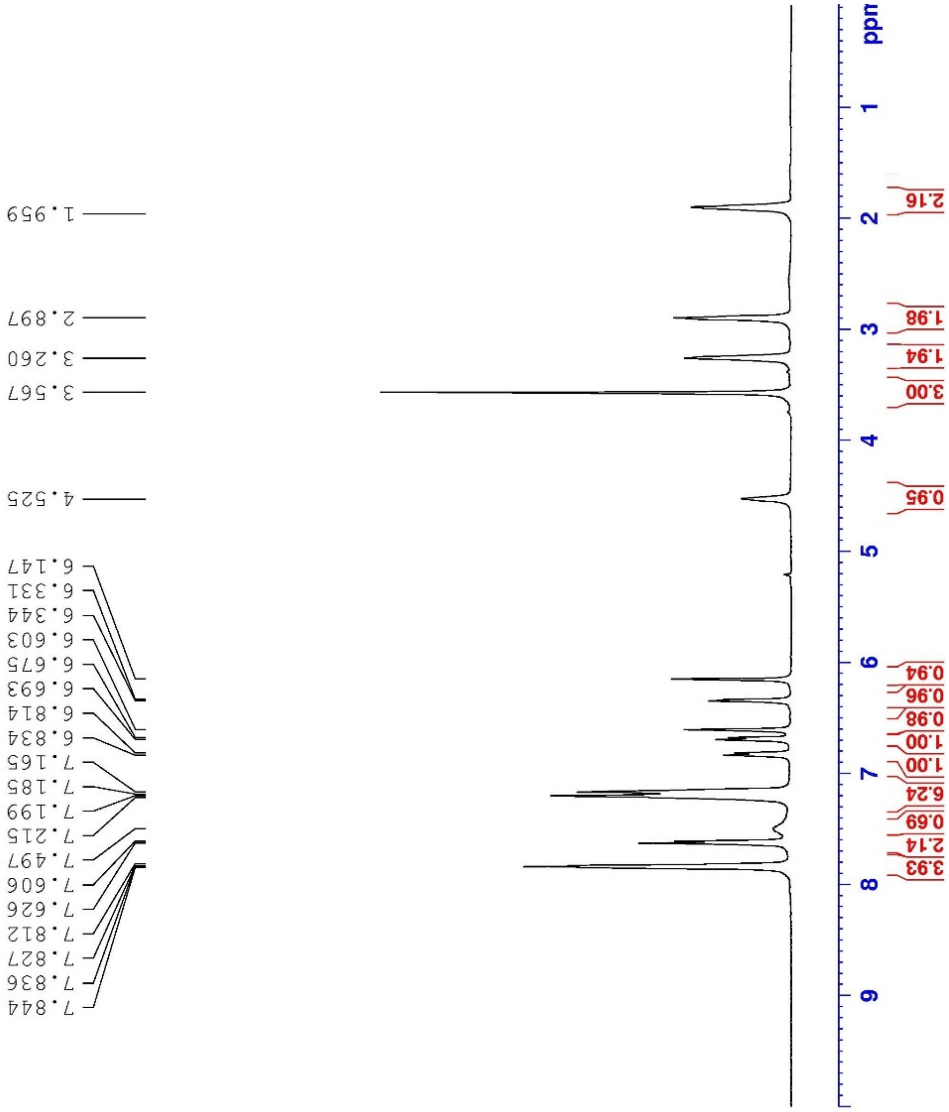
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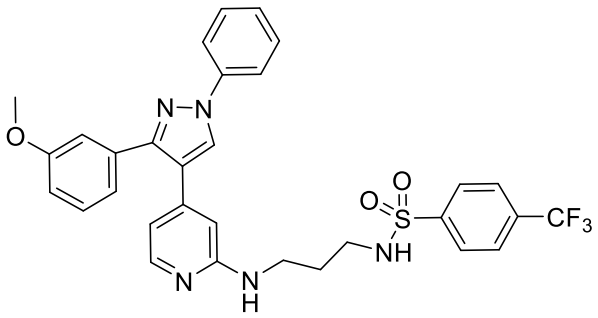
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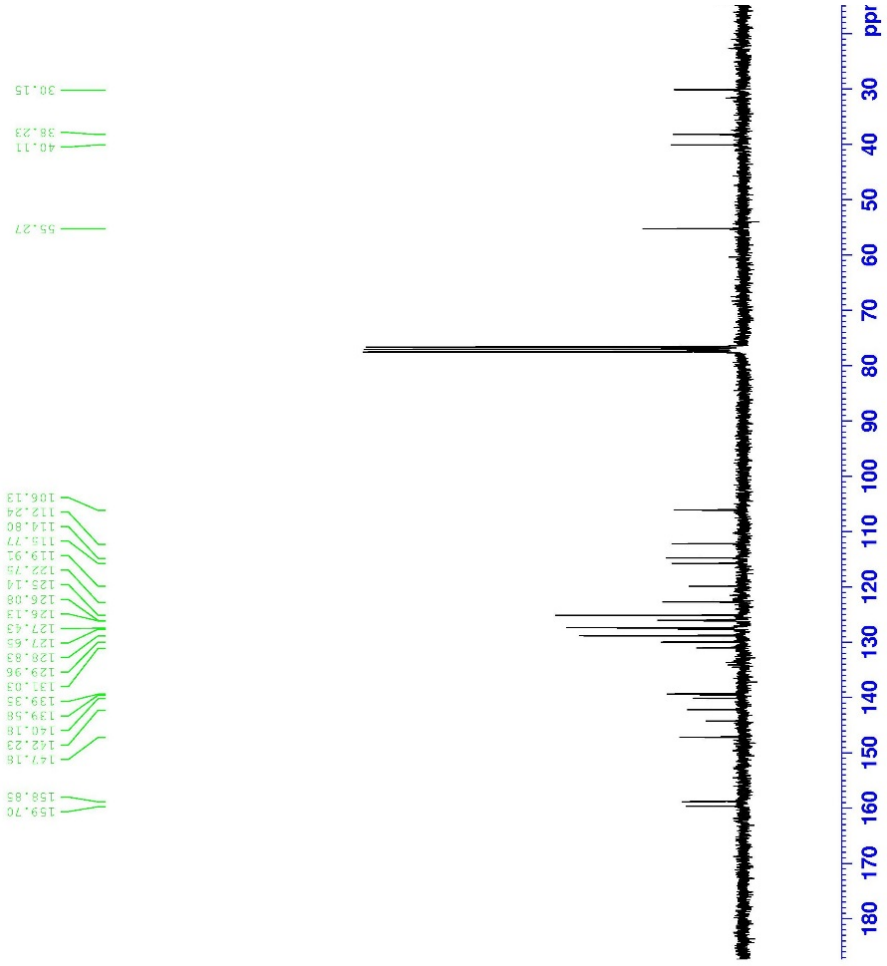
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128.83
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139.58
140.18
142.23
147.18
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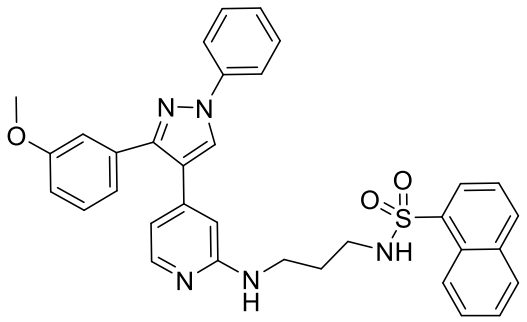
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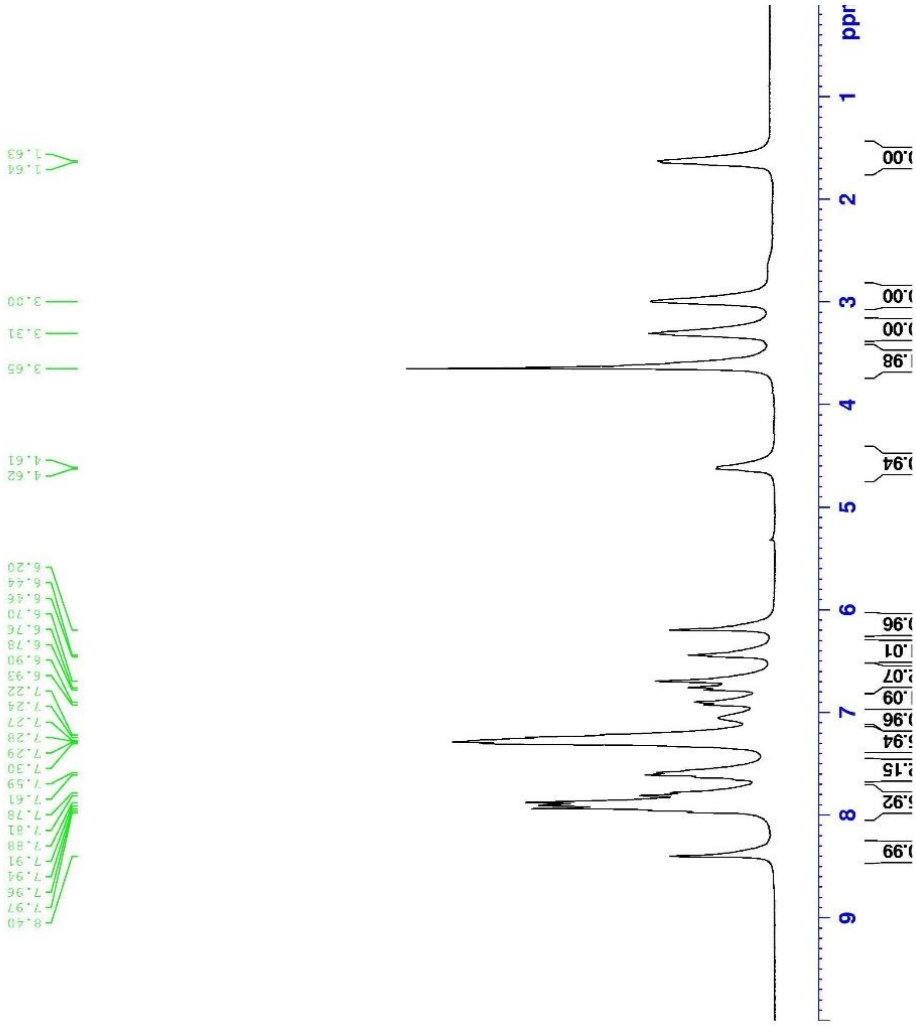
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7.91
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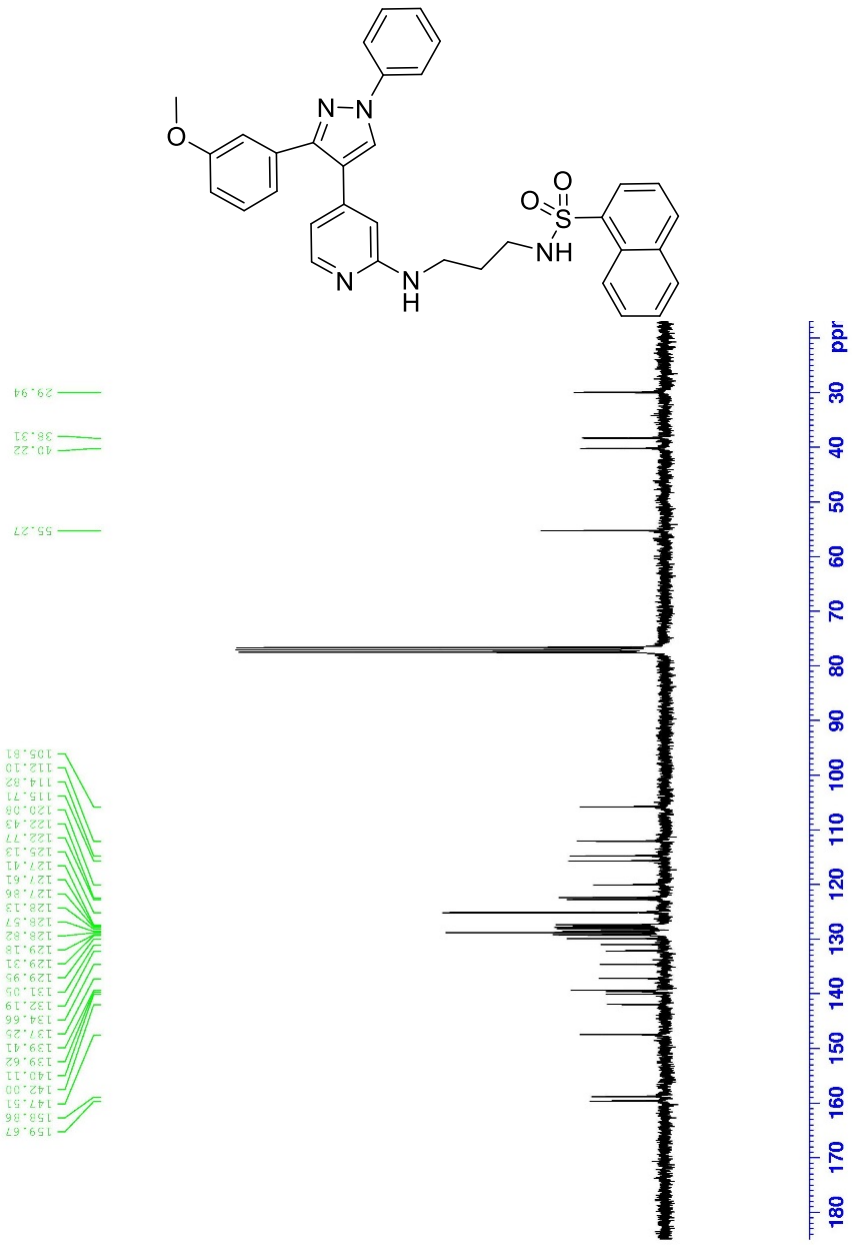
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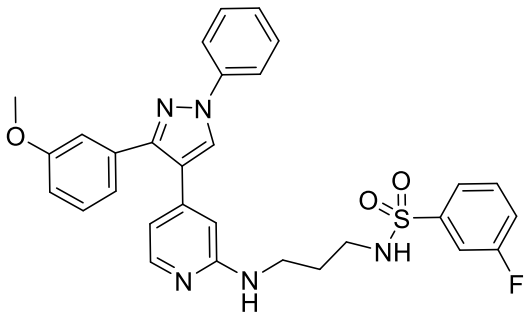
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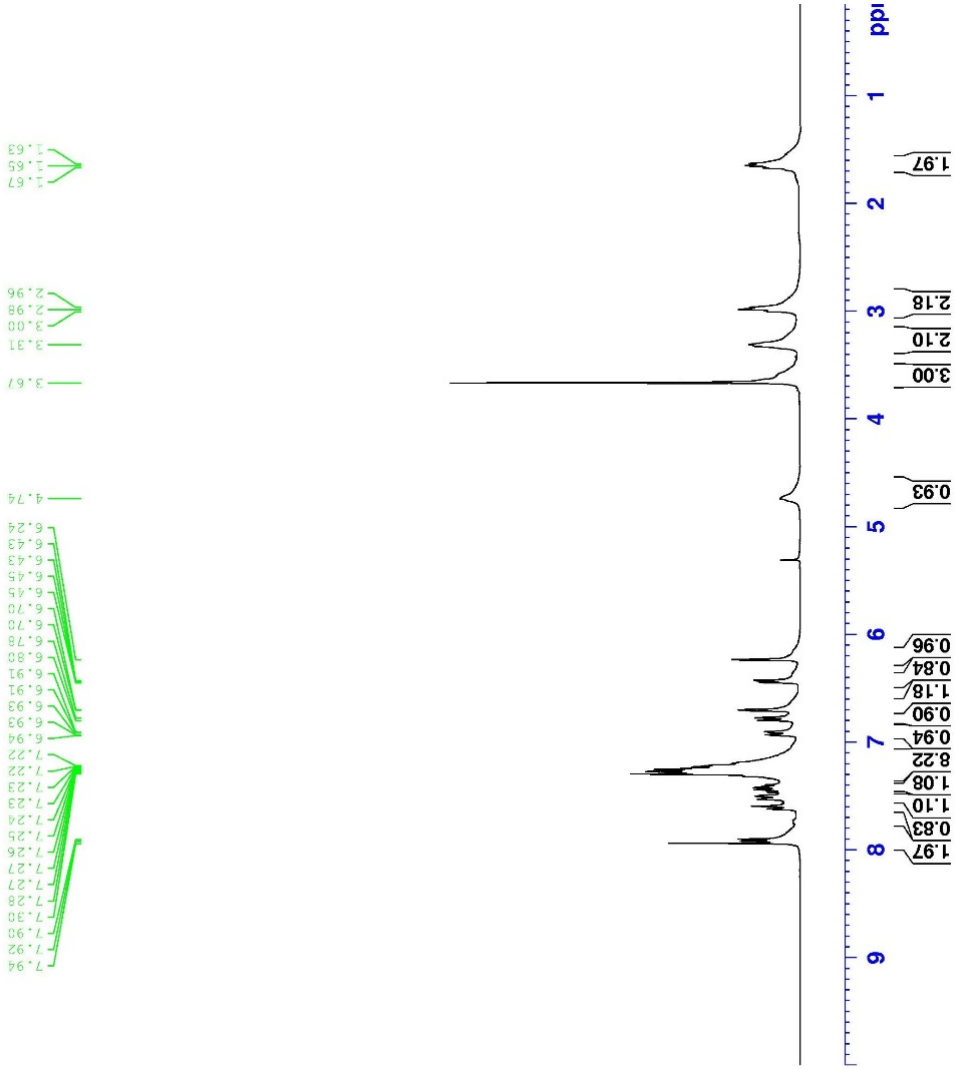
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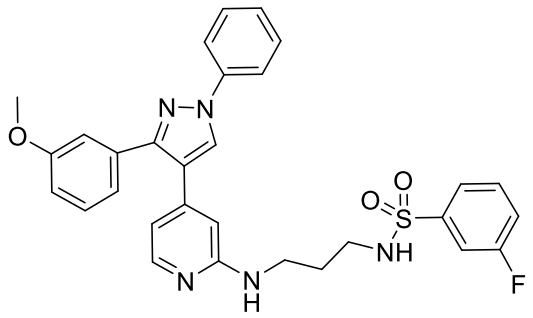
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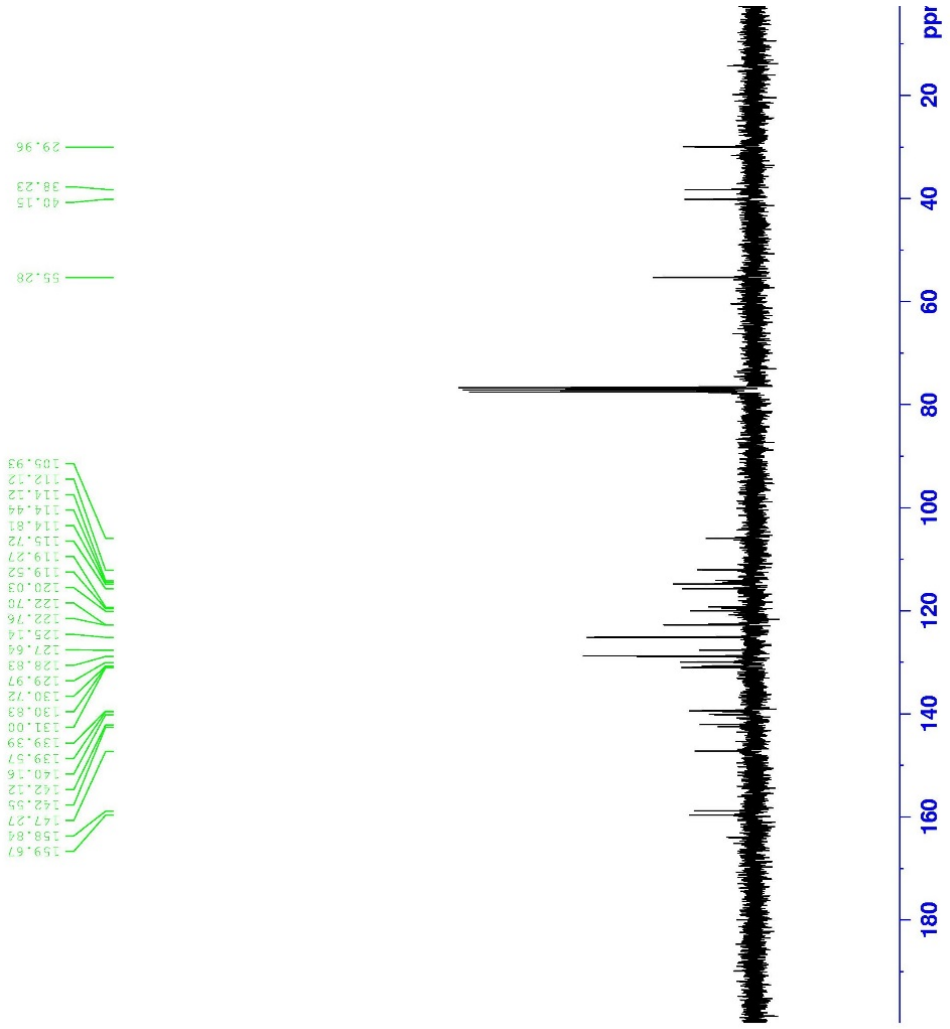
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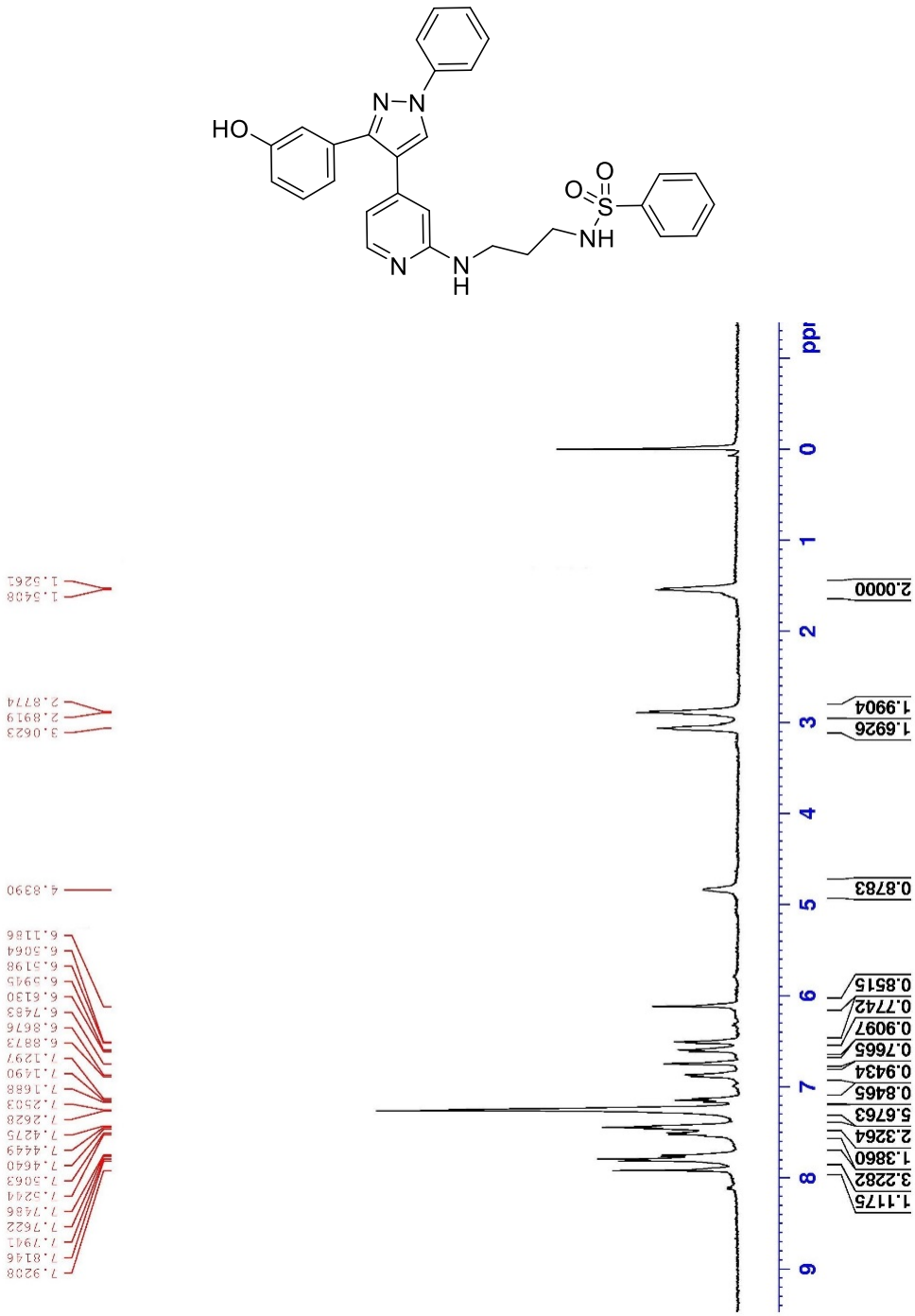
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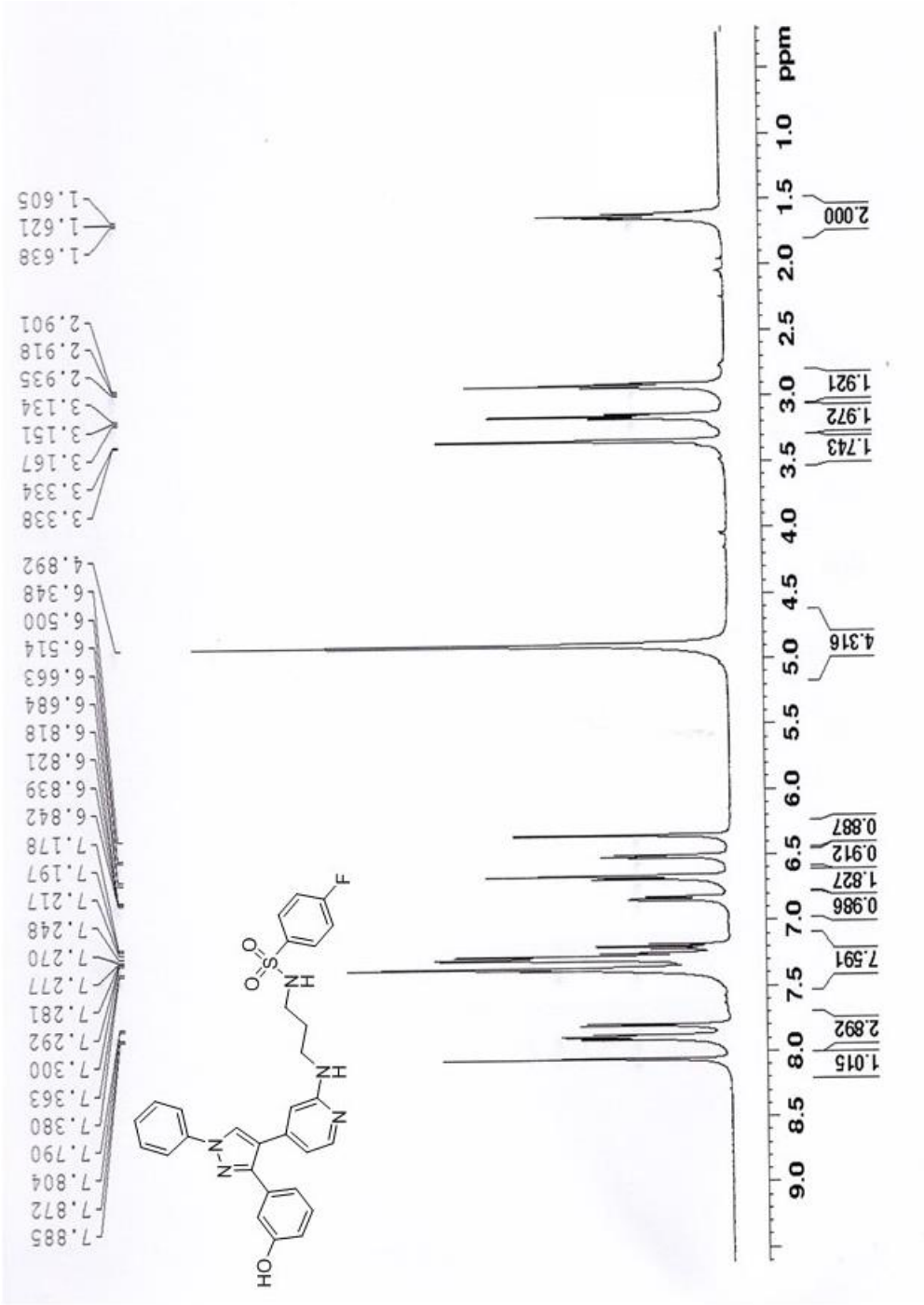
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6.500
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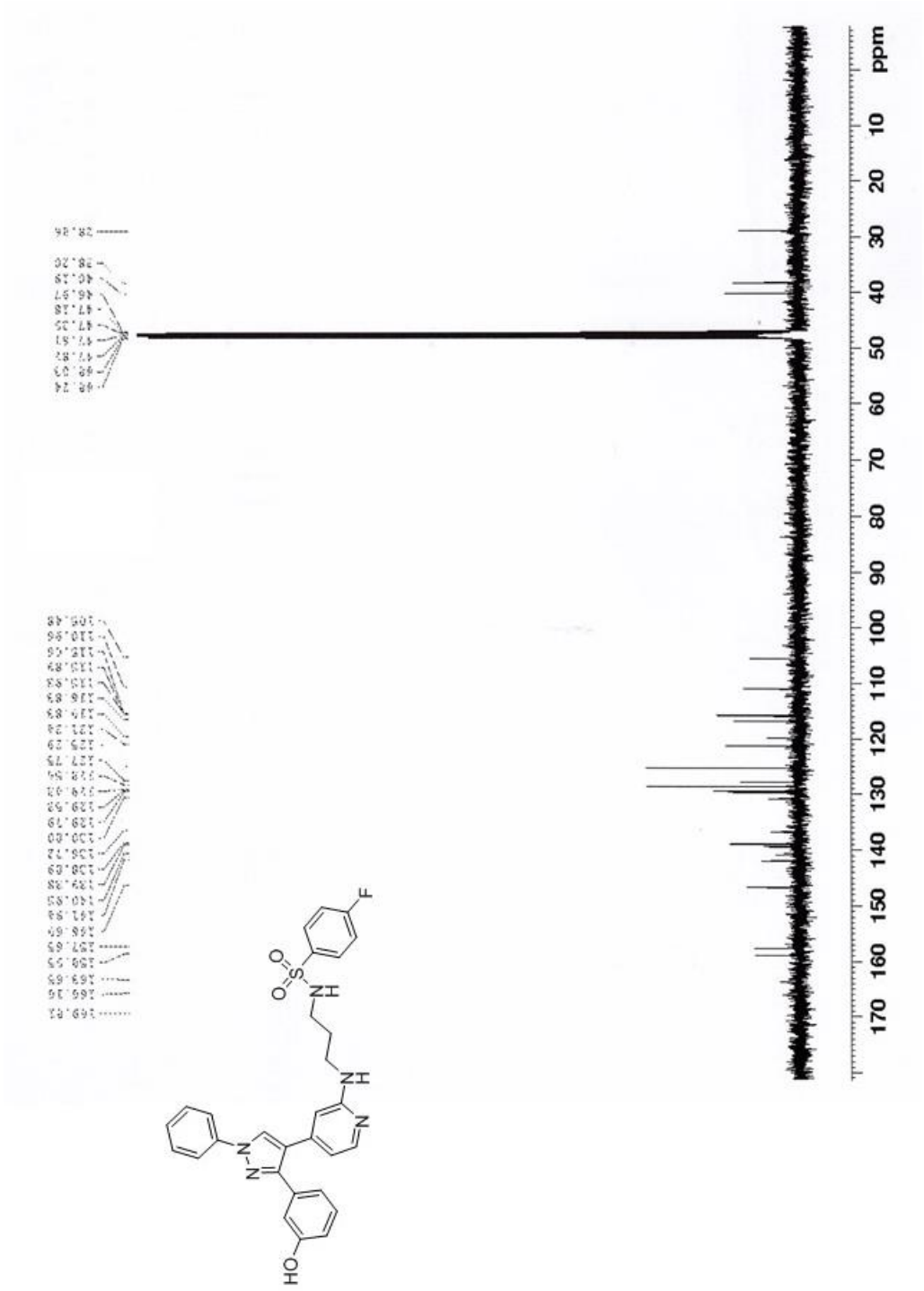
N
OH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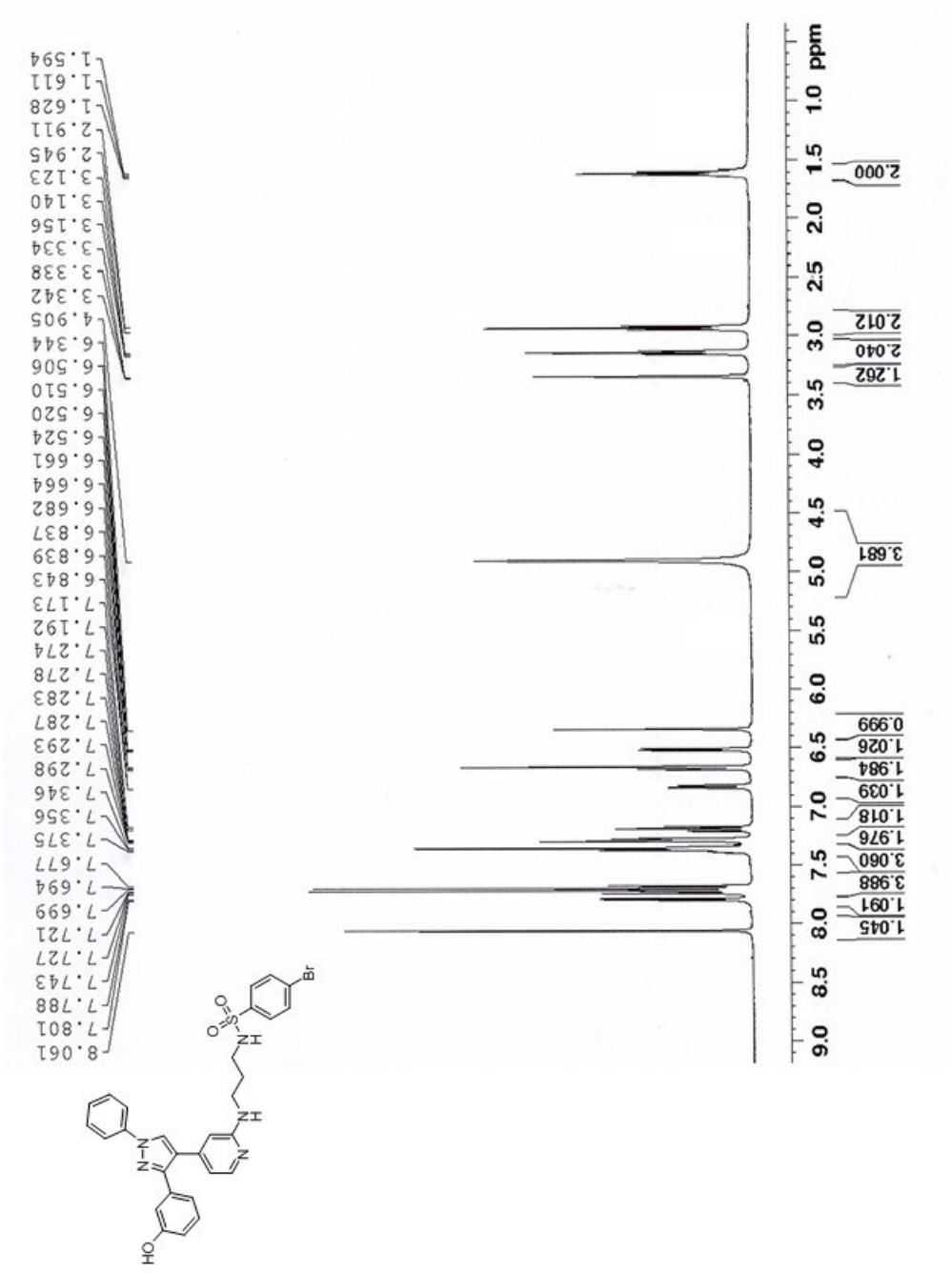
N
HO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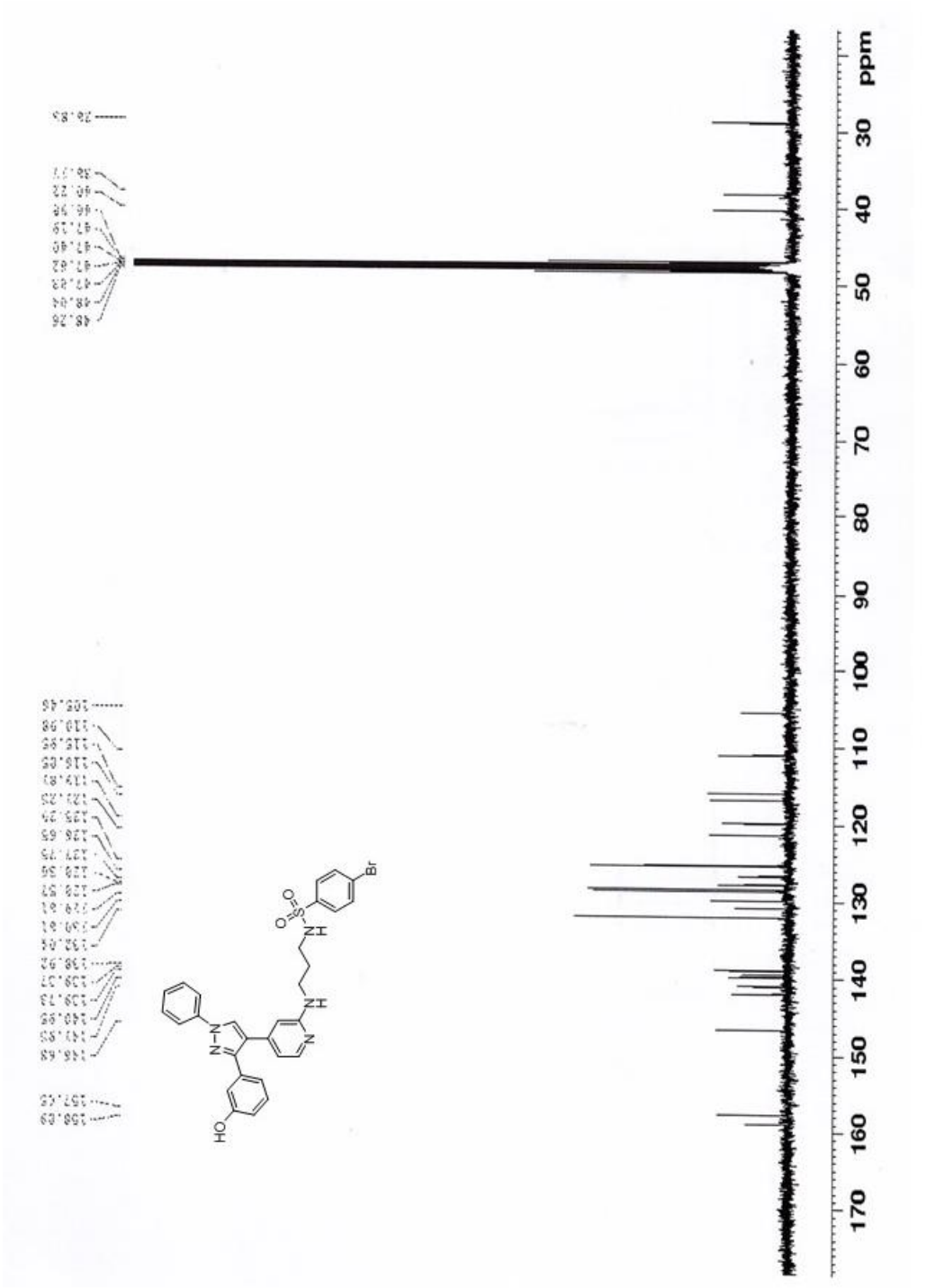
N
HO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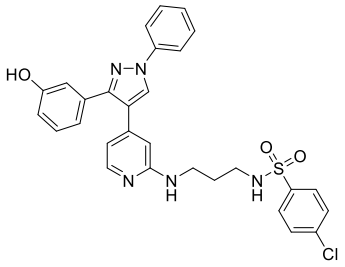
170
Br
HO


HO
N
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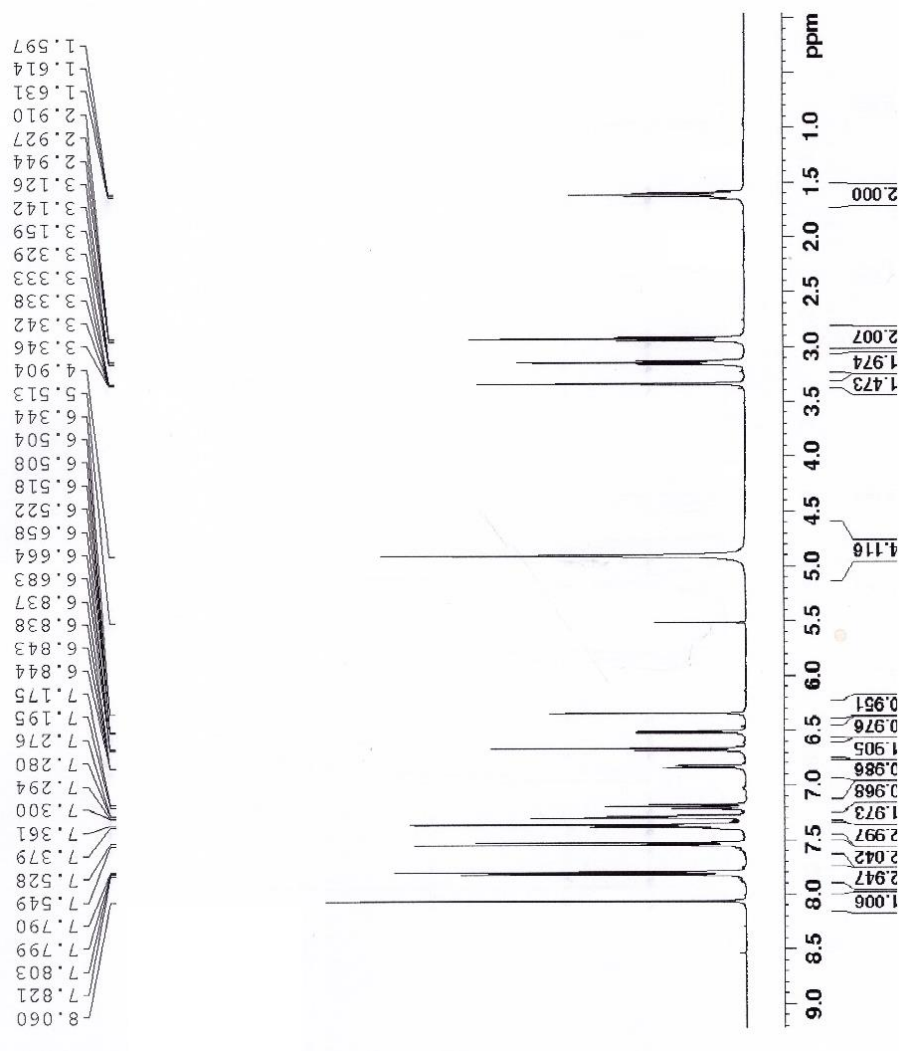
N
H
N
H
O
S
O
Cl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3.342
3.346
4.904
5.513
6.344
6.504
6.508
6.518
6.522
6.658
6.664
6.683
6.837
6.838
6.843
6.844
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7.195
7.276
7.280
7.294
7.300
7.361
7.379
7.528
7.549
7.790
7.799
7.803
7.821
8.060
ppm
9.0
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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
2.000
2.007
1.974
1.473
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0.986
0.968
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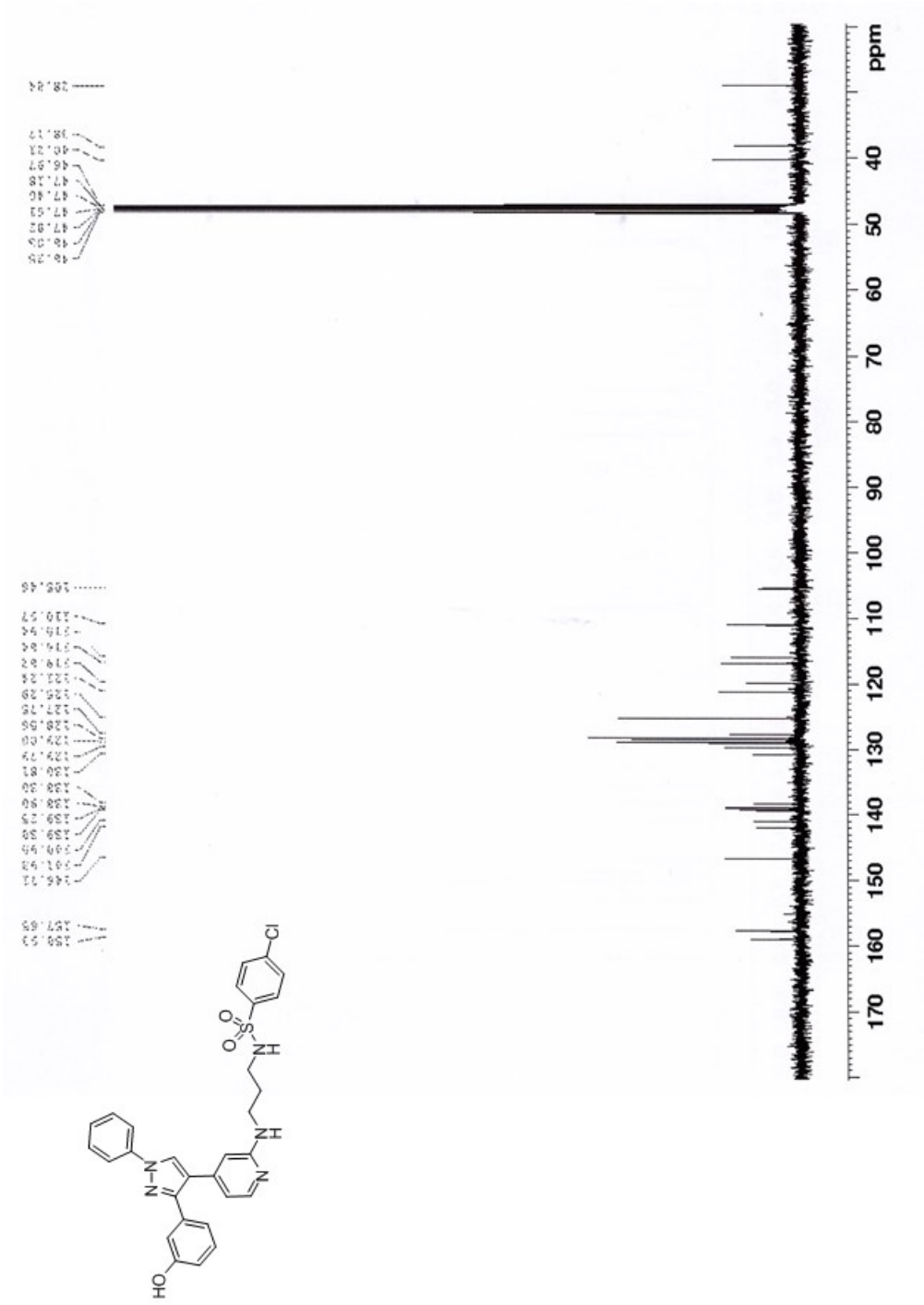
2.997
2.042
2.947
1.006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150
140
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120
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100
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80
70
60
50
40
Cl
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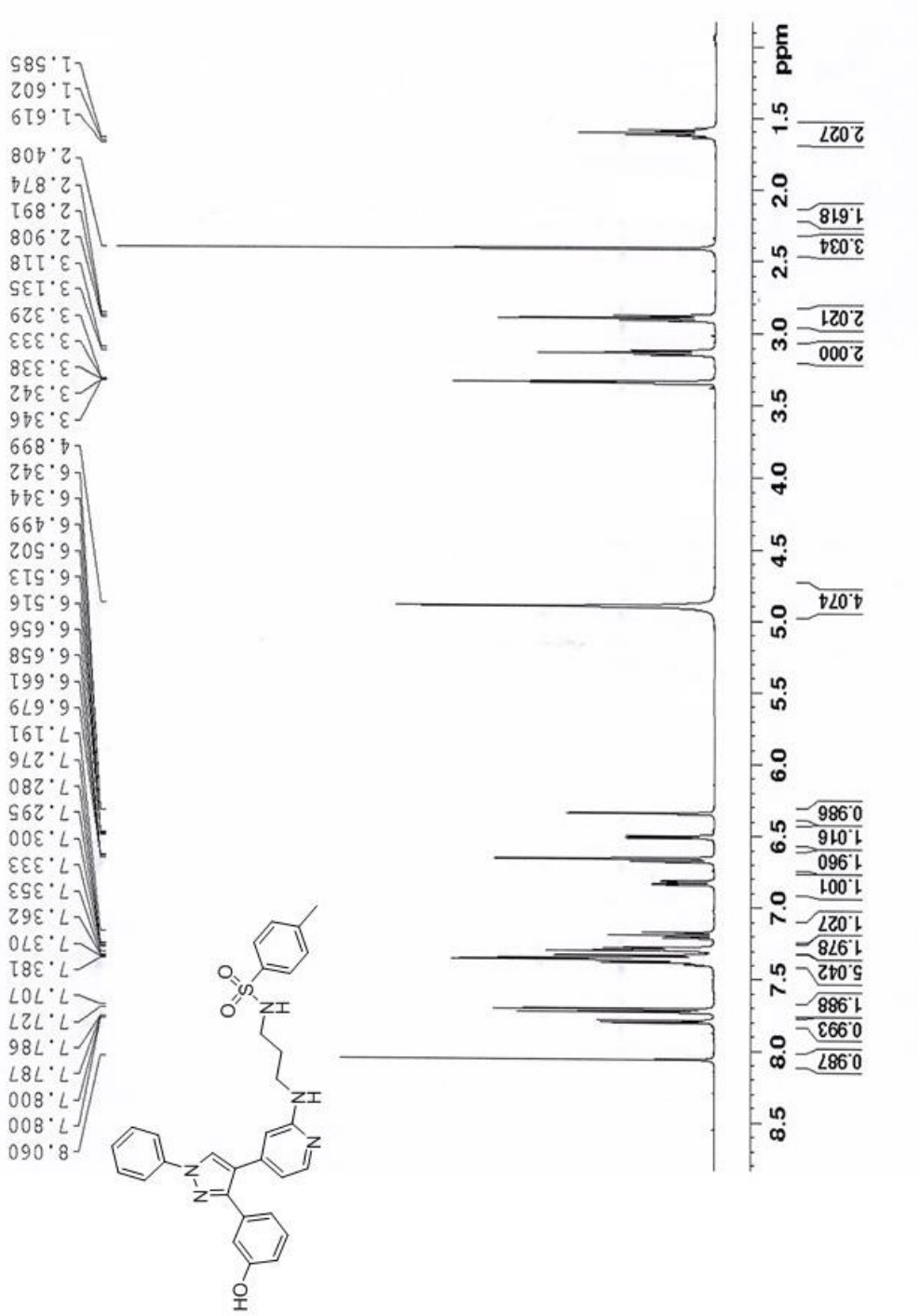
S
O
N
H
N
H
N
N
HO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7.0
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8.0
8.5
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3.034
2.021
2.000
4.074
0.986
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1.978
5.042
1.988
0.993
0.987
1.585
1.602
1.619
2.408
2.874
2.891
2.908
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3.329
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3.338
3.342
3.346
4.899
6.342
6.344
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6.502
6.513
6.516
6.656
6.658
6.661
6.679
7.191
7.276
7.280
7.295
7.300
7.333
7.353
7.362
7.370
7.381
7.707
7.727
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8.060
HO
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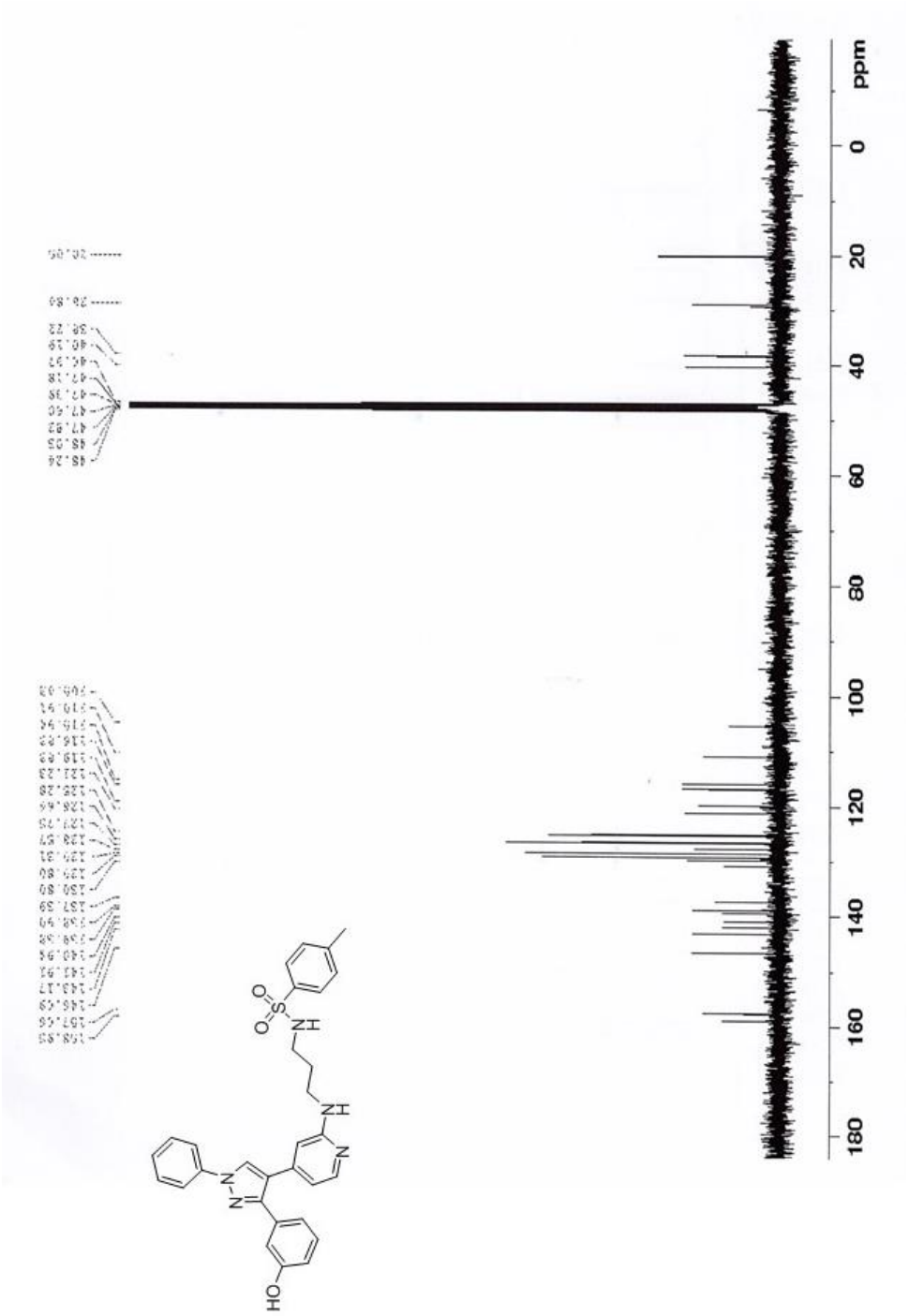
N
H
N
S
O
O
H
N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120
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180
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N
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N
H
S
O
O
N
H

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7.178
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3.346
3.342
3.338
3.333
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ppm
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5.5
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2.025
HO
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N
H
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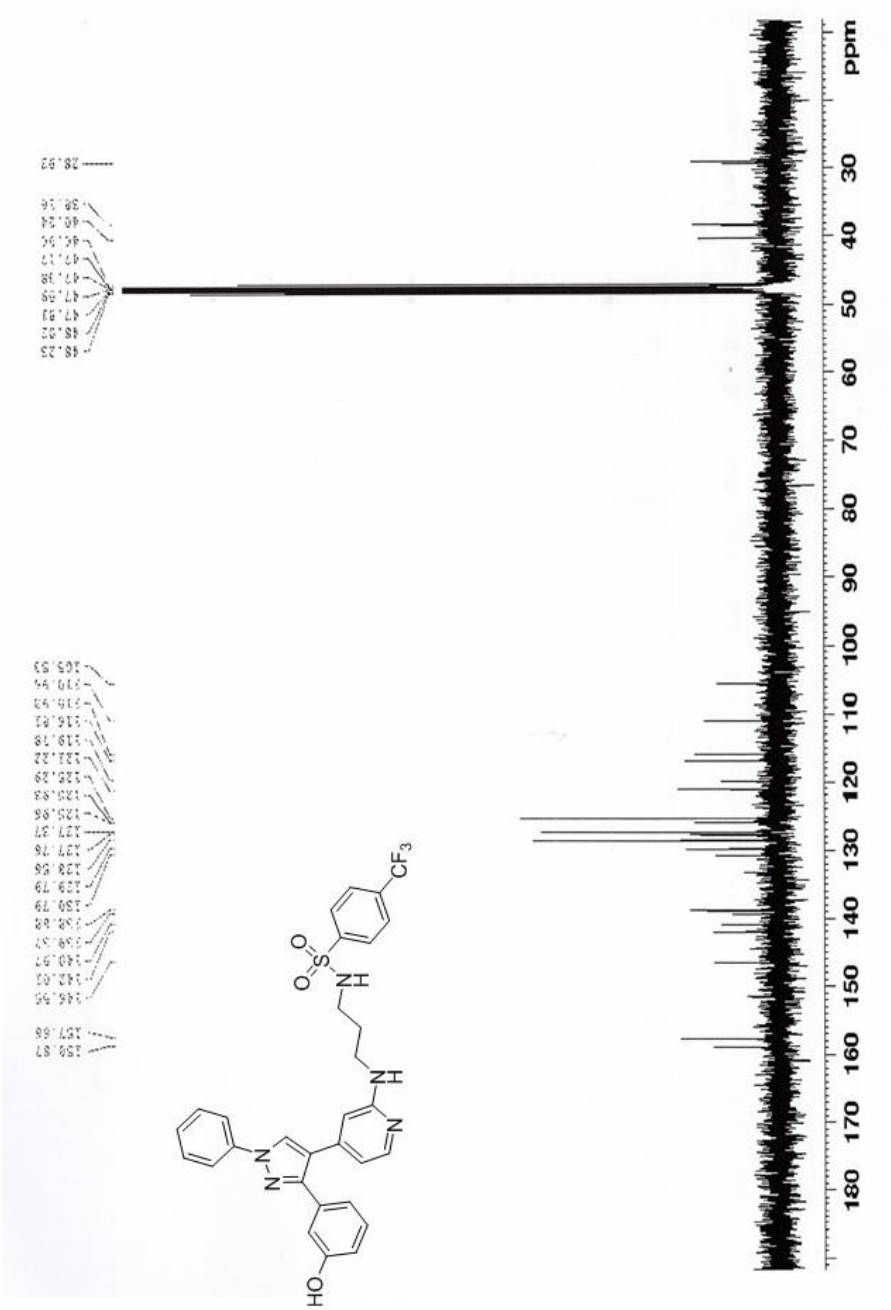
S
O
N
H
CF3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100
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120
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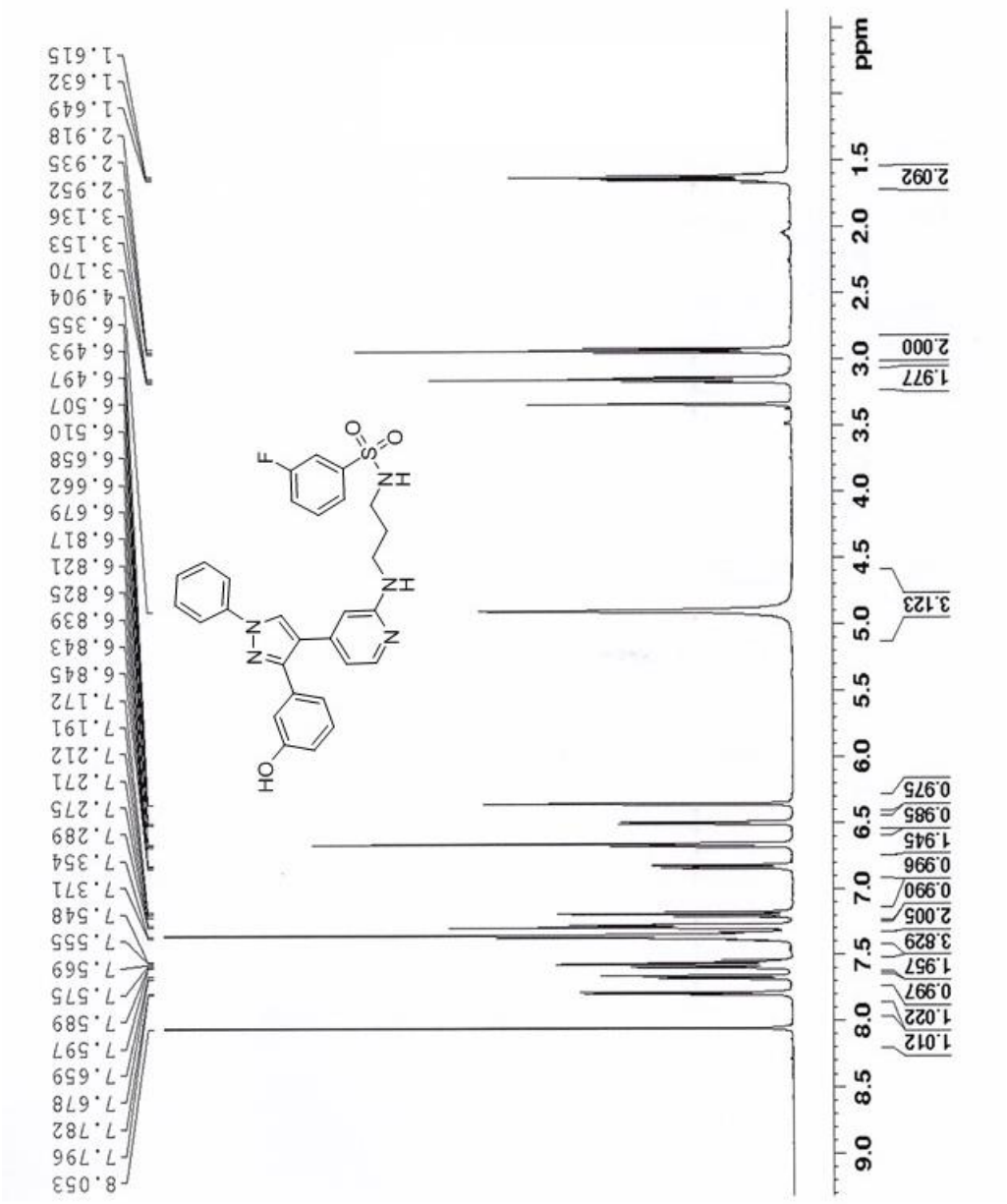
140
150
160
170
180
CF3
HO
N
H
O
S


ppm
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4.0
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2.0
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3.829
2.005
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0.985
0.975
3.123
2.000
1.977
2.092
8.053
7.796
7.782
7.678
7.659
7.597
7.589
7.575
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7.555
7.548
7.371
7.354
7.289
7.275
7.271
7.212
7.191
7.172
6.845
6.843
6.839
6.825
6.821
6.817
6.679
6.662
6.658
6.510
6.507
6.497
6.493
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3.153
3.136
2.952
2.935
2.918
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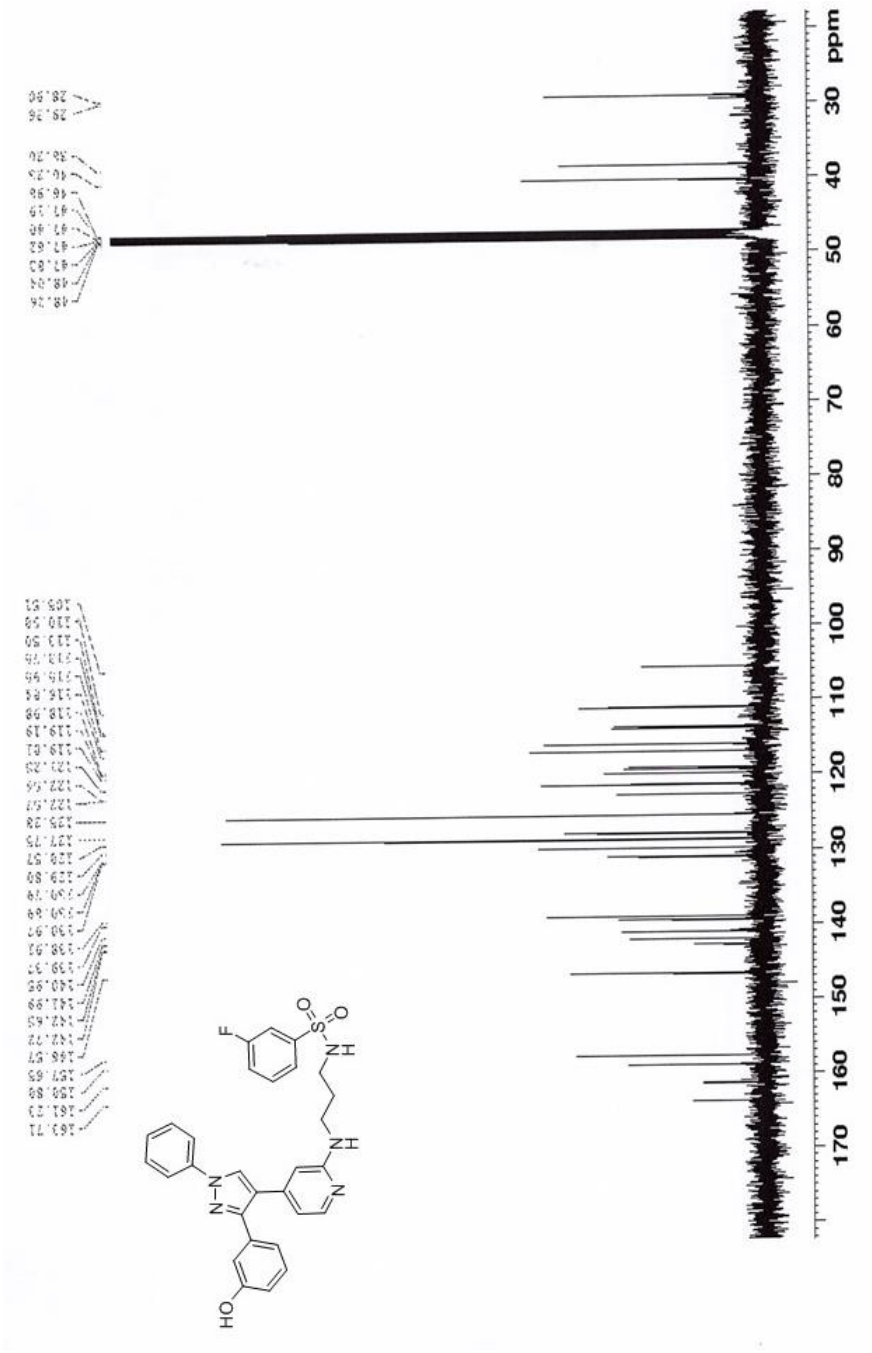
1.632
1.615


ppm
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60
70
80
90
100
110
120
130
140
150
160
170
F
S
O
O
NH
NH
N
N
N
HO