Highly efficient chemoselective construction of 2, 2-dimethyl-6-substituted-4-piperidone *via* multi-component tandem Mannich reaction in ionic liquids

Li-Chun Feng,[a] Ya-Wei Sun,[a] Wei-Jun Tang,[a] Li-Jin Xu,[a,*] Kim Hung Lam,[b] Zhongyuan Zhou,[b] Albert S. C. Chan[b]

[a] *Department of Chemistry, Renmin University of China, Beijing 100872, China. Email: xulj@chem.ruc.edu.cn;*

[b]*Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, the Hong Kong Polytechnic University, Hong Kong, China.*

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1. General Information

Unless otherwise noted, all experiments were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model Avance DMX 400 Spectrometer (^{1}H 400 MHz and ^{13}C 106.6 MHz, respectively). Chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks. (*S*)-2, 2'-dihydroxy-1, 1'-binaphthyl-3-carbaldehyde was prepared according to the reported method.[1] All other chemicals were used as received from Aldrich or Acros without further purification.

2. General procedure for the tandem Mannich reaction in ionic liquid

To a 10 mL sample vial charged with [bmim][PF_6] (1.0 mL) was added L-proline (0.2 mmol, 23 mg). To the mixture was bubbled in ammonia gas for 5 min. followed by the addition of aldehyde (1mmol) and acetone (10 mmol, 0.75 mL). The resulting mixture was allowed to stir at room temperature for 20 h. The excessive acetone was removed in vacuo and the residue was extracted with Et_2O (4 x 5mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo. Purification on a silica gel column (eluting with *n*-hexane and ethyl acetate) gave the pure product.

2, 2-dimethyl-6-phenyl-4-piperidone (2a) (known compound)[2]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41-7.39 (m, 2H), 7.36-7.33 (m, 2H), 7.29-7.26 (m, 1H), 4.20 (dd, *J* = 3.5, 11.0 Hz, 1H), 2.50-2.39 (m, 3H), 2.27-2.24 (m, 1H), 1.60 (br, 1H), 1.31 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.8, 143.1, 129.0, 128.0, 126.8, 56.3, 54.5, 54.2, 50.0, 32.4, 25.6; HR-ESI: calcd. for $C_{13}H_{18}NO$ ($M+H^+$): 204.1388; found: 204.1385.

2, 2-dimethyl-6-(4'-fluorophenyl)-4-piperidone (2b) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39-7.37 (m, 2H), 7.04-7.00 (m, 2H), 4.19 (dd, *J* = 3.0, 11.5 Hz, 1H), 2.47-2.34 (m, 3H), 2.27-2.24 (m, 1H), 1.50 (br, 1H), 1.31 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$): δ = 209.5, 162.4 (d, *J* = 250 Hz), 139.0 (d, *J* = 2.9 Hz), 128.4 (d, *J* = 8.1 Hz), 115.7 (d, *J* = 21.0 Hz), 55.6, 54.3, 54.1, 50.1, 32.4, 25.6; HR-ESI: calcd. for $C_{13}H_{17}NOF$ ($M+H^+$): 222.1294; found: 222.1261.

2, 2-dimethyl-6-(4'-chlorophenyl)-4-piperidone (2c) ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.32 (m, 2H), 7.29-7.27 (m, 2H), 4.15 (dd, *J* = 3.5, 11.0 Hz, 1H), 2.43-2.21 (m, 4H), 1.54 (br, 1H), 1.29 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.2, 141.8, 133.5, 129.0, 128.2, 55.6, 54.3, 54.1, 49.9, 32.3, 25.6; HR-ESI: calcd. for $C_{13}H_{17}NOCl$ ($M+H^+$): 238.0999; found: 238.0991.

2, 2-dimethyl-6-(4'-bromophenyl)-4-piperidone (2d) ^1H NMR (500 MHz, $CDCl_3$): δ = 7.47-7.45 (m, 2H), 7.30-7.26 (m, 2H), 4.17 (dd, *J* = 3.5, 11.0 Hz, 1H), 2.46-2.24 (m, 4H), 1.43 (br, 1H), 1.31 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.2, 142.3, 132.0, 128.6, 121.7, 55.7, 54.3, 54.2, 49.9, 32.4, 25.6; HR-ESI: calcd. for $C_{13}H_{17}NO^{79}Br$ ($M+H^+$): 282.0494; found: 282.0496; HR-ESI: calcd. for $C_{13}H_{17}NO^{81}Br$ ($M+H^+$): 284.0473; found: 284.0470.

2, 2-dimethyl-6-(4'-methoxyphenyl)-4-piperidone (2e) ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.30 (m, 2H), 6.87-6.85 (m, 2H), 4.14 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.77 (s, 3H), 2.43-2.22 (m, 4H), 1.62 (br, 1H), 1.29 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 159.3, 135.3, 127.9, 114.3, 55.7, 55.5, 54.4, 54.1, 50.1, 32.4, 25.6; HR-ESI: calcd. for $C_{14}H_{20}NO_2$ ($M+H^+$): 234.1494; found: 234.1521.

2, 2-dimethyl-6-(3'-nitrophenyl)-4-piperidone (2f) ^1H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 8.14-8.12 (m, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7,52 (t, *J* =8.0 Hz, 1H), 4.33 (dd, *J* = 3.5, 11.5 Hz, 1H), 2.52-2.27 (m, 4H), 1.59 (br, 1H), 1.34 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.5, 148.8, 145.4, 133.2, 129.9, 123.1, 121.9, 55.6, 54.3, 54.2, 49.7, 32.3, 25.7; HR-ESI: calcd. for $C_{13}H_{17}N_2O_3$($M+H^+$): 249.1239; found: 249.1261.

2, 2-dimethyl-6-(1'-naphthyl)-4-piperidone (2g) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 7.0 Hz, 1H), 7.57-7.48 (m, 3H), 5.04 (dd, *J* = 3.5, 12.0 Hz, 1H), 2.72-2.36 (m, 4H), 1.61 (br, 1H), 1.36 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 138.5, 134.2, 131.1, 129.3, 128.5, 126.6, 126.0, 125.9, 123.3, 123.0, 54.7, 54.4, 51.5, 48.9, 32.5, 25.6; HR-ESI: calcd. for $C_{17}H_{20}NO$ ($M+H^+$): 254.1545; found: 254.1543.

2, 2-dimethyl-6-(2'-pyridyl)-4-piperidone (2h) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.56-8.55 (m, 1H), 7.64 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.20-7.17 (m, 1H), 4.27 (dd, *J* = 4.5, 10.5 Hz, 1H), 2.56-2.32 (m, 4H), 2.19 (br, 1H), 1.34 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 160.4, 149.8, 137.3, 123.0, 122.1, 57.7, 55.0, 54.9, 48.6, 32.1, 25.6; HR-ESI: calcd. for $C_{12}H_{17}N_2O$ ($M+H^+$): 205.1341; found: 205.1339.

2, 2-dimethyl-6-(2'-furanyl)-4-piperidone (2i) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.36 (m, 1H), 6.32-6.31 (m, 1H), 6.20 (d, *J* = 4.0 Hz, 1H), 4.32 (dd, *J* = 6.5, 9.0 Hz, 1H), 2.57-2.28 (m, 4H), 1.91 (br, 1H), 1.30 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.8, 155.1, 142.4, 110.4, 106.0, 54.7, 54.3, 50.1, 46.4, 32,0, 25.4; HR-ESI: calcd. for $C_{11}H_{16}NO_2$ ($M+H^+$): 194.1181; found: 194.1190.

2, 2-dimethyl-6-(2'-ferrocenyl)-4-piperidone (2j) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.23 (s, 2H), 4.20 (s, 2H), 4.14 (s, 5H), 3.93 (d, *J* = 12.0 Hz, 1H), 2.59-2.24 (m, 4H), 1.62 (br, 1H), 1.30 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 91.8, 68.4, 68.1, 68.0, 66.6, 66.3, 54.7, 54.1, 51.1, 49.4, 32.4, 25.8; HR-ESI: calcd. for $C_{17}H_{22}NOFe$ ($M+H^+$): 312.1051; found: 312.1058.

2, 2-dimethyl-6-cyclohexyl-4-piperidone (2k) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.83-2.79 (m, 1H), 2.33-2.29 (m, 1H), 2.22-2.15 (m, 2H), 1.99-1.93 (m, 1H), 1.79-0.91 (m, 12H), 1.21 (s, 3H), 1.0 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ =

211.3, 56.7, 54.9, 53.9, 45.6, 43.6, 32.4, 29.9, 28.8, 26.7, 26.4, 26.3, 25.6; HR-ESI: calcd. for $C_{13}H_{24}NO$ ($M+H^+$): 210.1858; found: 210.1862.

2, 2-dimethyl-6-pentyl-4-piperidone (2k) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.13-3.07 (m, 1H), 2.38-1.97 (m, 4H), 1.54-1.23 (m, 9H), 1.28 (s, 3H), 1.09 (s, 3H), 0.91-0.86 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.3, 54.7, 54.4, 52.1, 48.2, 37.4, 32.1, 32.0, 25.7, 25.6, 22.8, 14.2; HR-ESI: calcd. for $C_{12}H_{24}NO$ ($M+H^+$): 198.1858; found:198.1858.

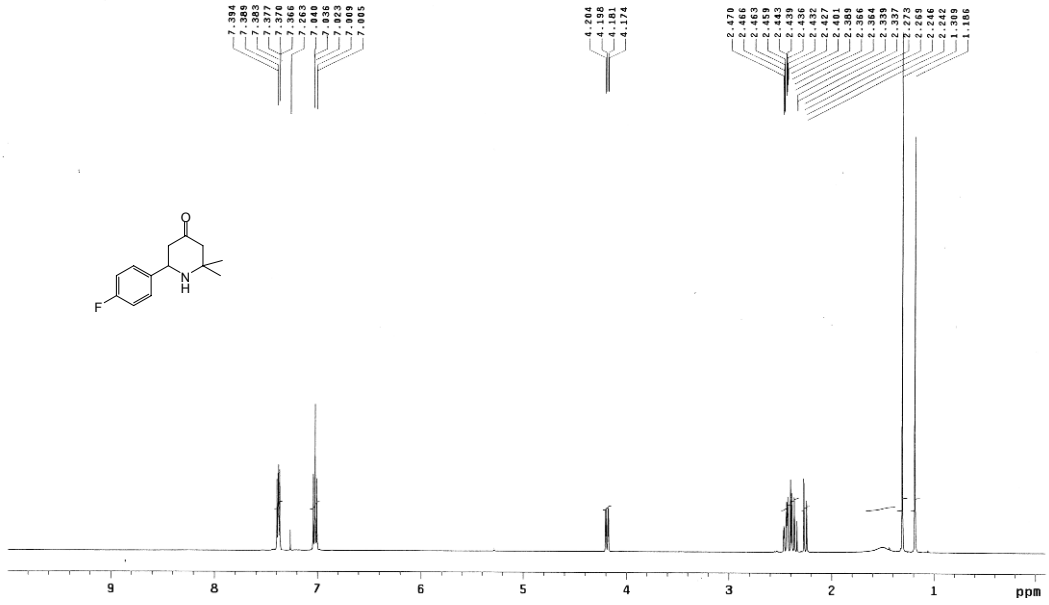
2, 2-dimethyl-6-(2'-hydroxyphenyl)-4-piperidone (2m) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19-7.09 (m, 1H), 6.88-6.86 (m, 1H), 6.79-6.78 (m, 1H), 6.74-6.71 (m, 1H), 4.26 (dd, *J* = 4.0, 12.5 Hz, 1H), 2.64-2.58 (m, 1H), 2.45-2.19 (m, 3H), 1.28 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.6, 157.2, 129.6, 127.4, 125.7, 119.8, 117.6, 56.1, 54.4, 53.6, 46.1, 32.2, 25.1; HR-ESI: calcd. for $C_{13}H_{18}NO_2$ ($M+H^+$): 220.1338; found: 220.1340.

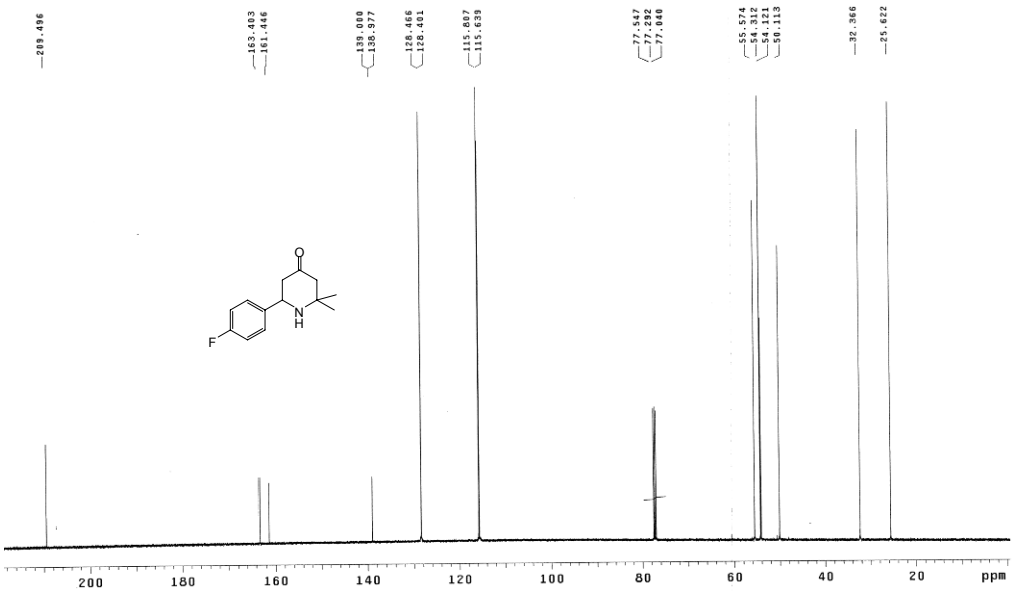
2, 2-dimethyl-6-(4'-hydroxyphenyl)-4-piperidone (2n) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26-7.17 (m, 2H), 6.73-6.68 (m, 2H), 4.16-4.13 (m, 1H), 2.56-2.25 (m, 4H), 1.32 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.3, 156.1, 134.0, 128.1, 116.0, 55.8, 54.5, 54.3, 49.5, 32.1, 25.5; HR-ESI: calcd. for $C_{13}H_{18}NO_2$ ($M+H^+$): 220.1338; found: 220.1332.

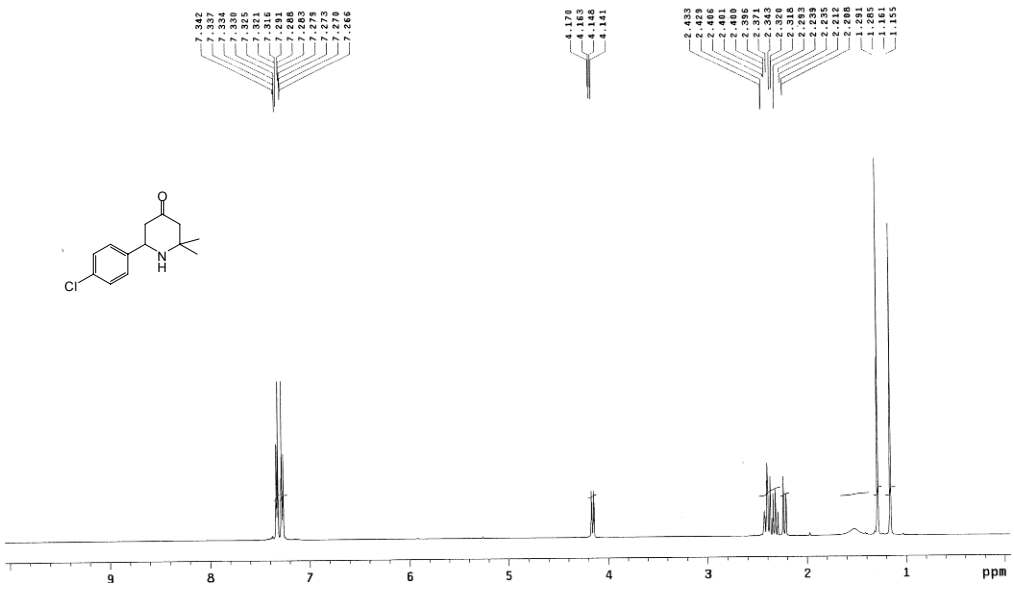
(*S*)-6-(2, 2'-dihydroxy-1, 1'-binaphthyl-3-yl)-2, 2-dimethylpiperidin-4-one (2o) ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.45-7.32 (m, 5H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 4.75 (dd, *J* = 4.0, 12.0 Hz, 1H), 3.01-2.96 (m, 1H), 2.54-2.36 (m, 2H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.8, 153.6, 151.5, 134.1, 133.8, 130.3, 129.5, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.0, 124.9, 124.8, 124.4, 123.7, 117.9, 114.8, 114.7, 56.2, 55.0, 53.4, 46.0, 31.7, 25.0; $[\alpha]^{20}_D$ = -

117 (c = 10 mg/mL, CH_2Cl_2); HR-ESI: calcd. for $C_{27}H_{25}NO_3$ ($M+H^+$): 412.1913; found: 412.1907.

3. ^{1}H and ^{13}C NMR spectra of piperidones



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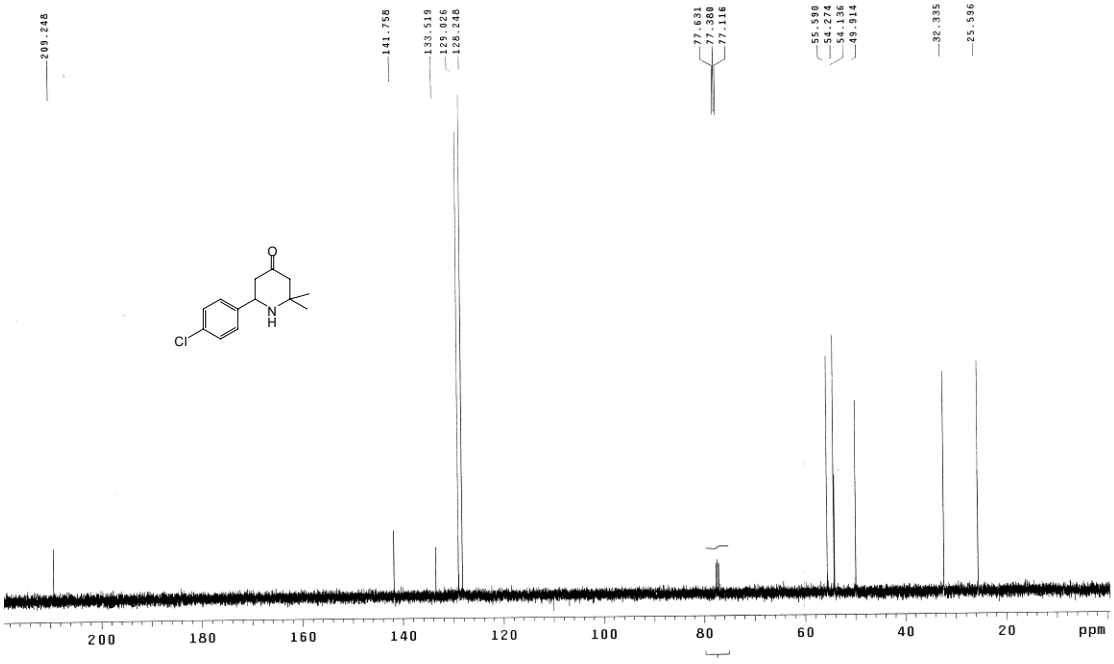
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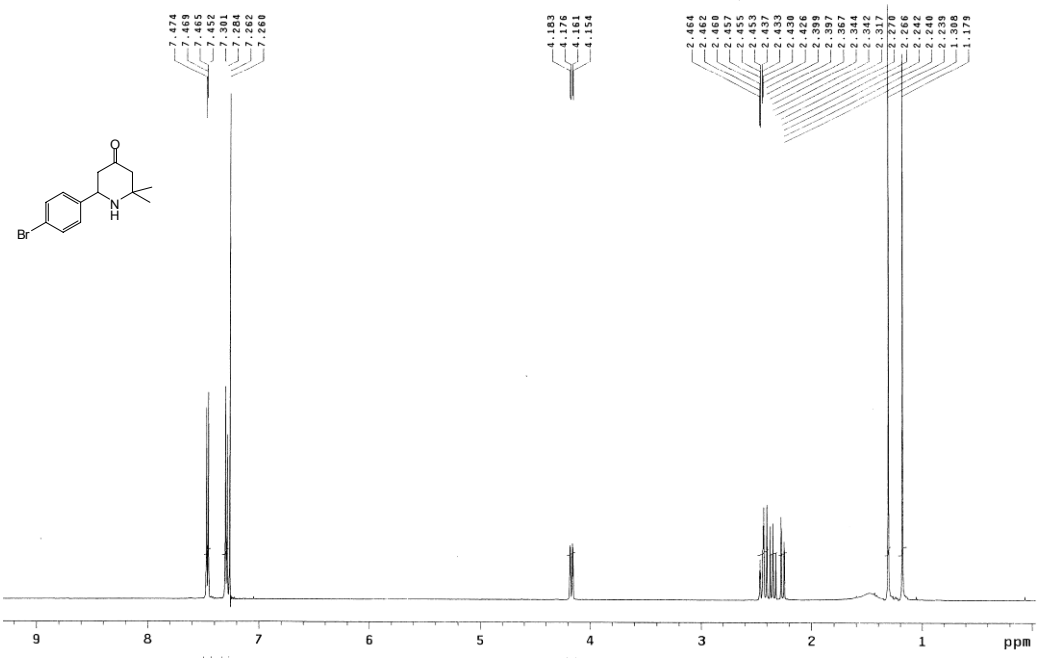
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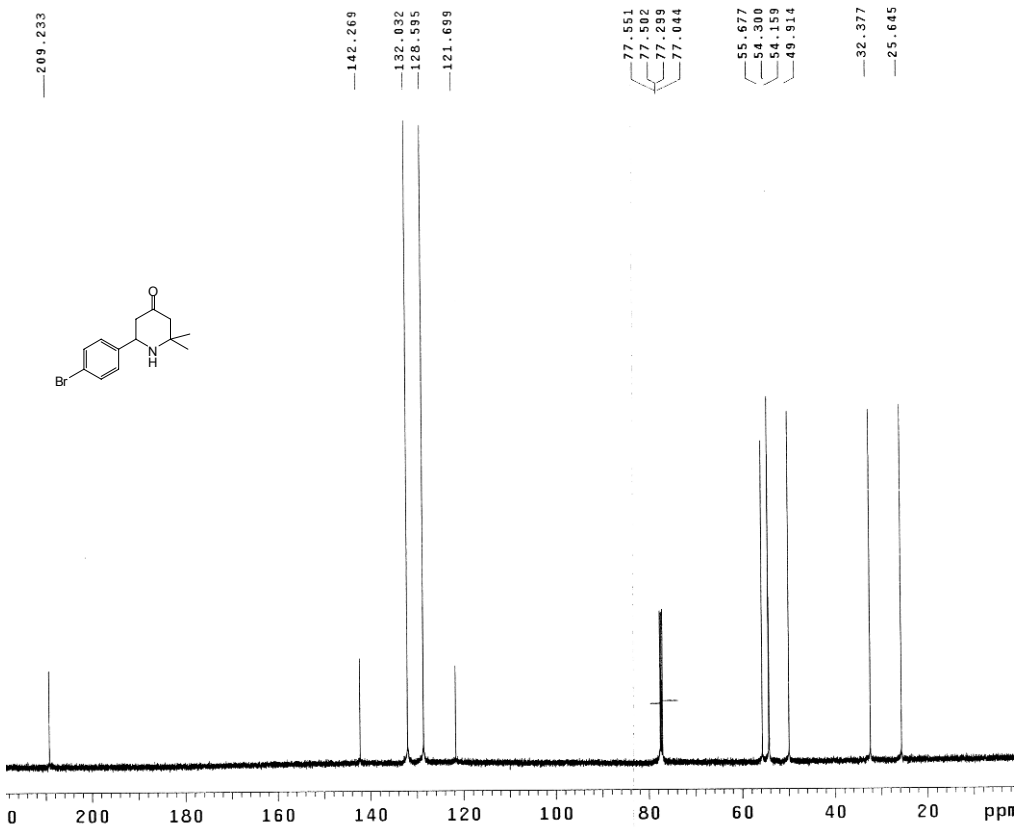
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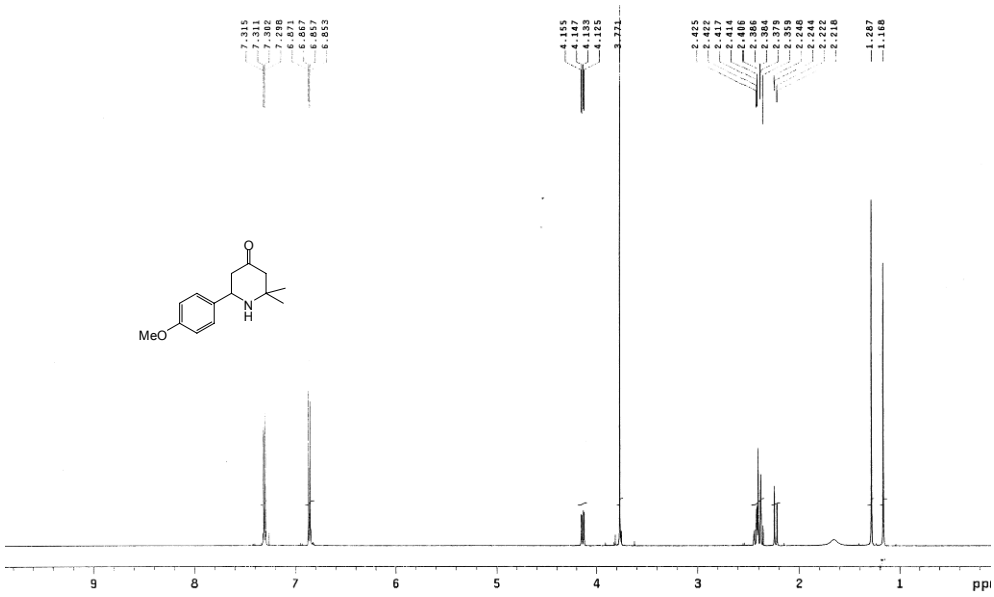
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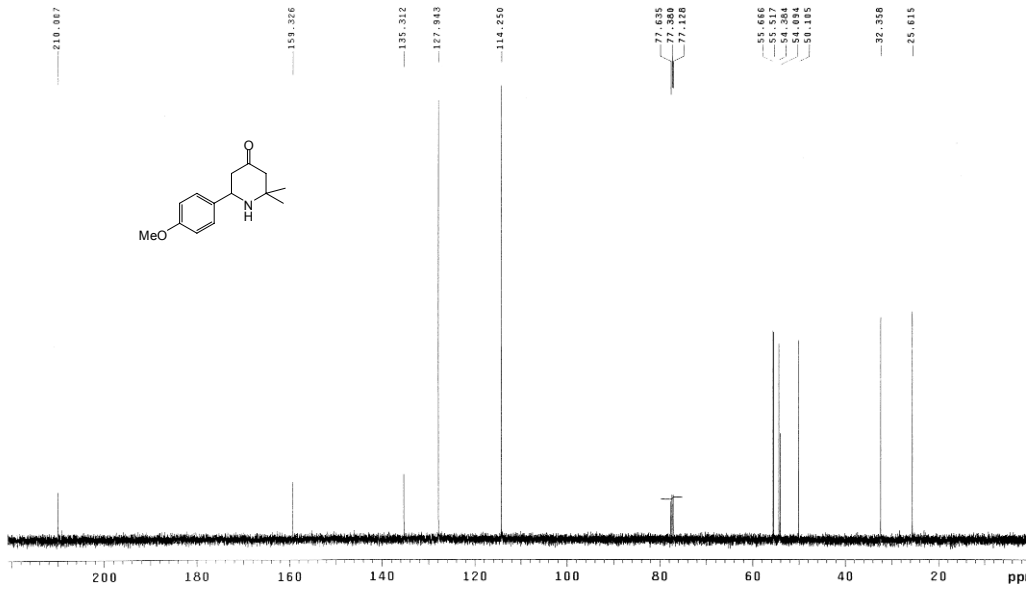
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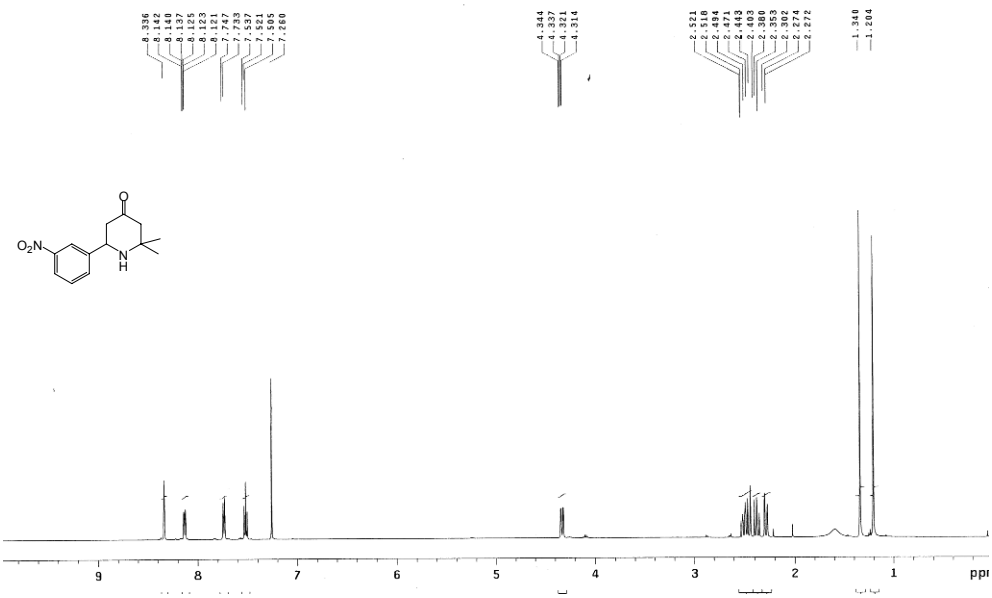
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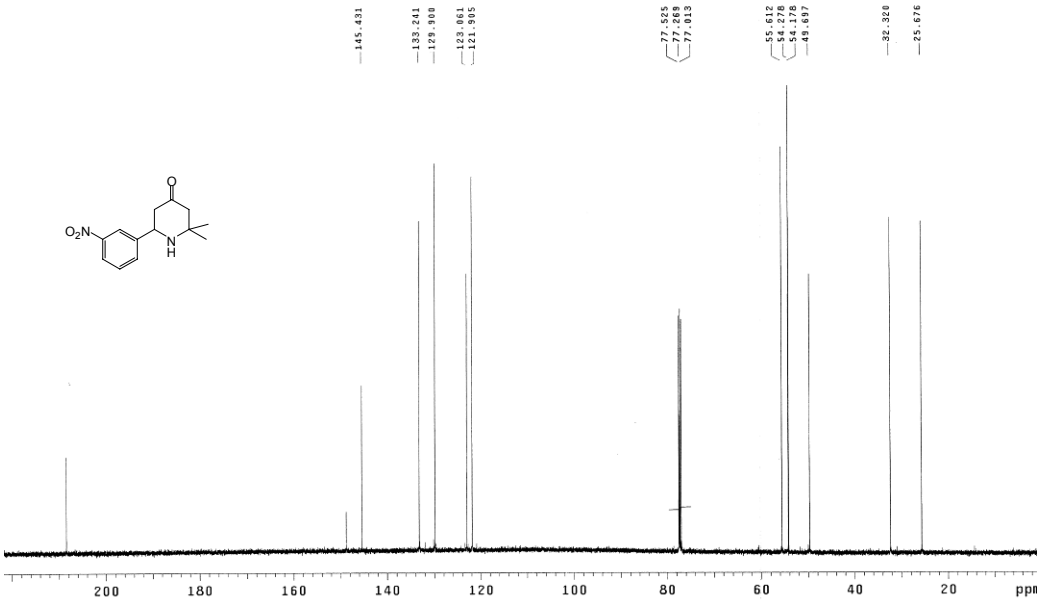
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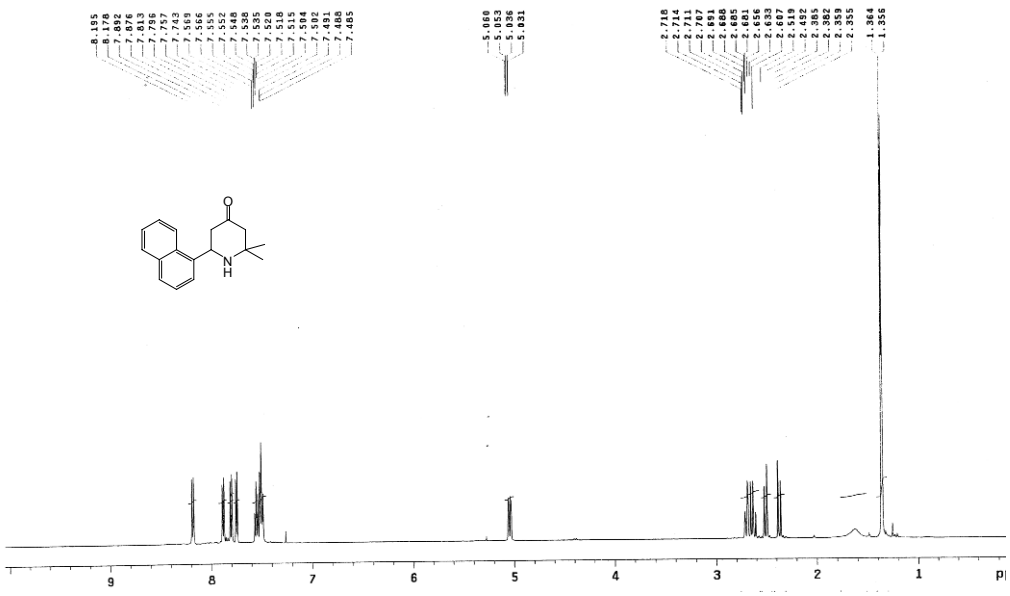
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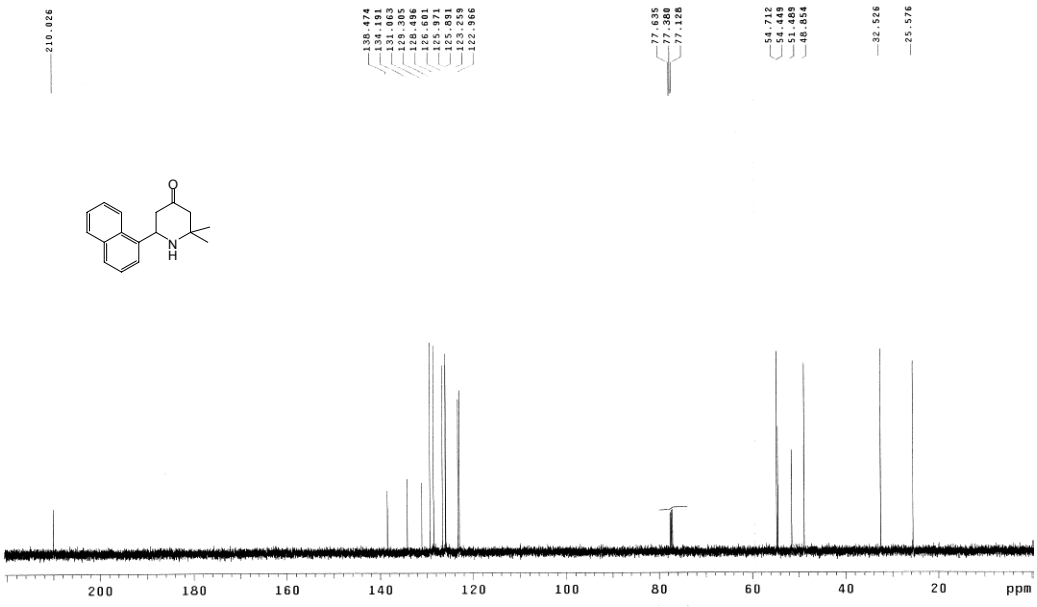
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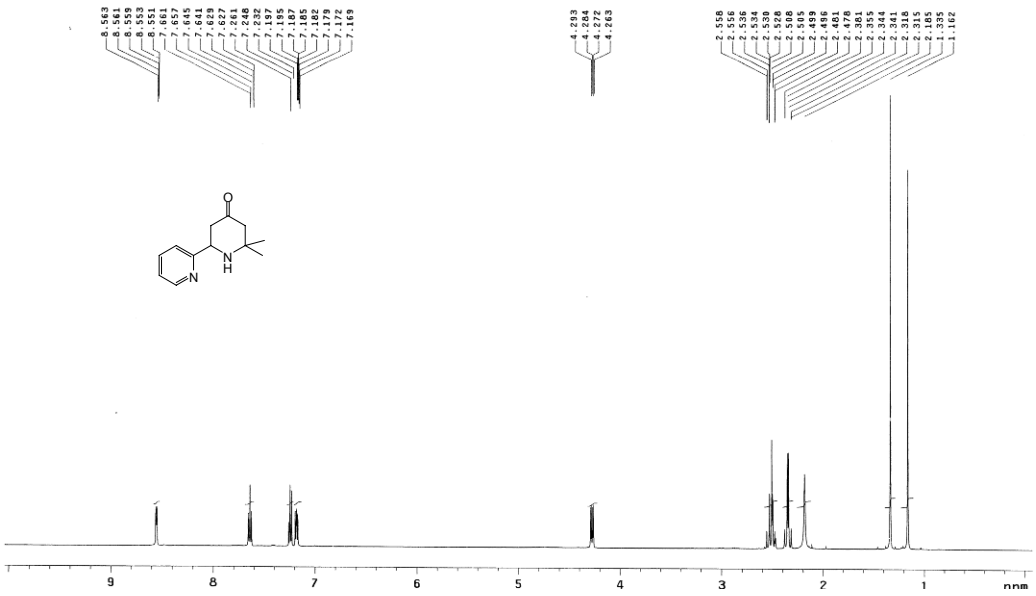
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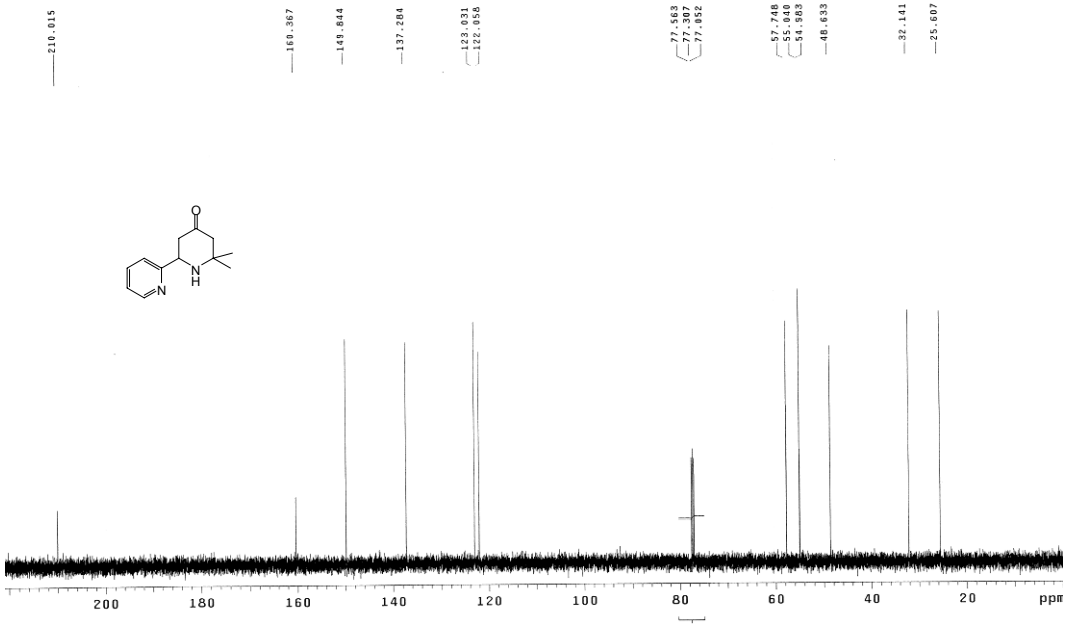
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20
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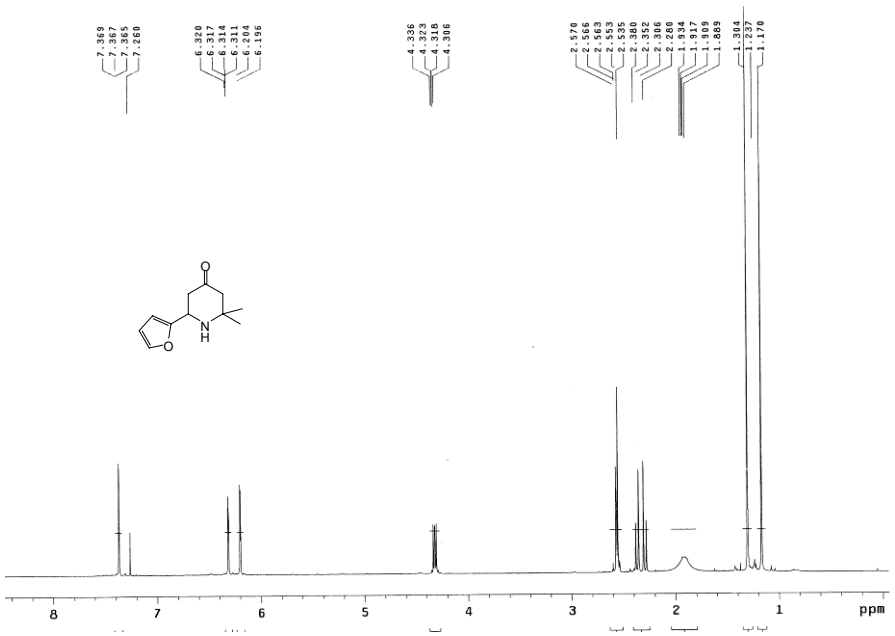
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6.311
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6.196
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4.318
4.306
2.570
2.566
2.563
2.553
2.535
2.380
2.352
2.306
2.280
1.934
1.917
1.908
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1.170
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H
O
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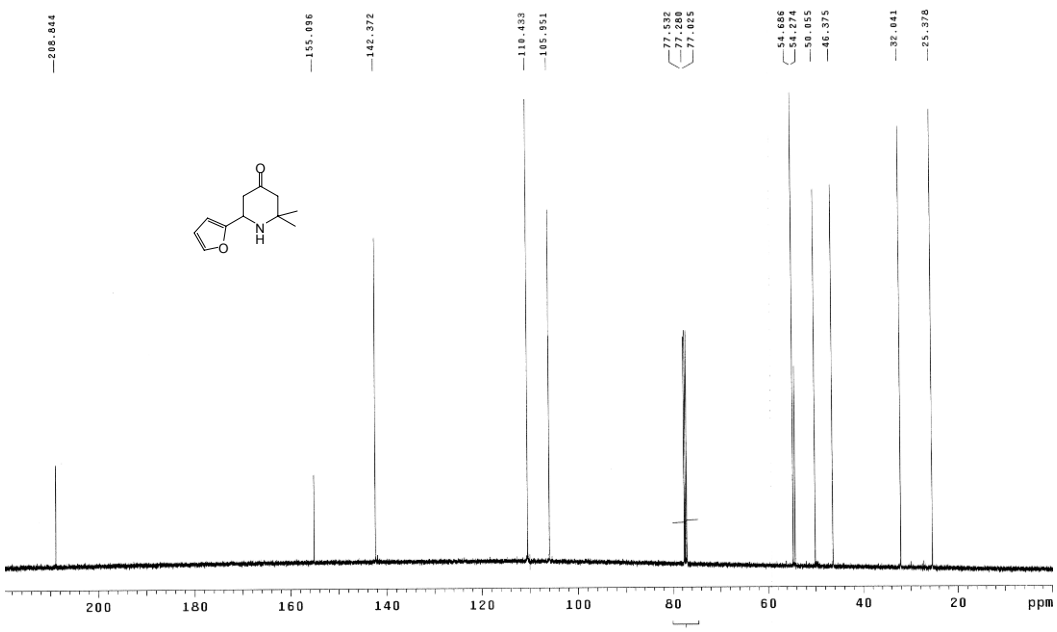
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142.372
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54.274
50.055
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25.378
O
N
H
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200
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20
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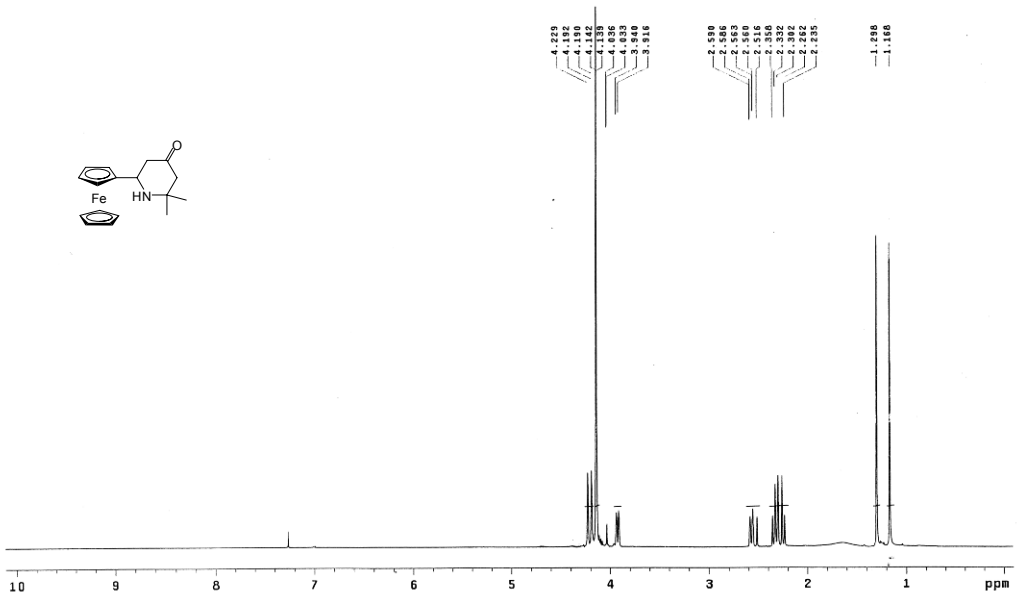
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4.182
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2.560
2.516
2.356
2.332
2.302
2.282
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1.168
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Fe
HN
10
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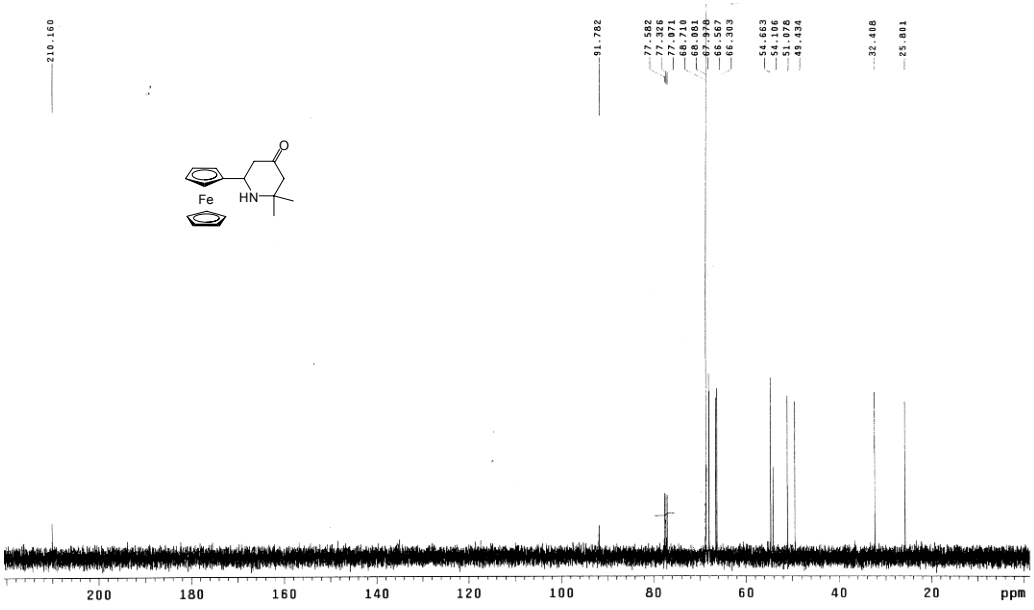
8
7
6
5
4
3
2
1
ppm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Fe
HN
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20
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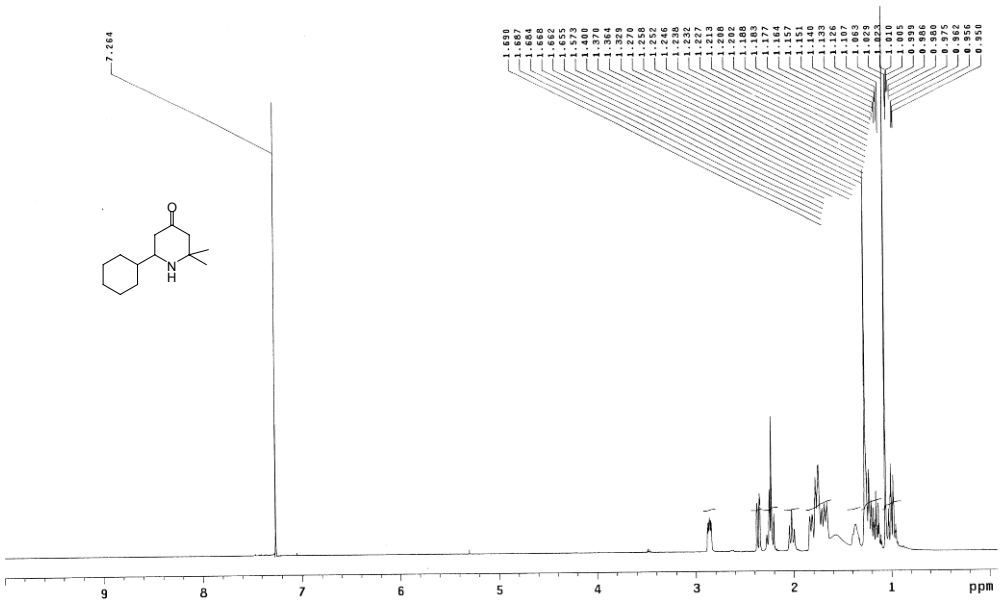
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1.573
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1.270
1.258
1.252
1.246
1.238
1.232
1.227
1.223
1.208
1.202
1.188
1.183
1.177
1.164
1.157
1.151
1.140
1.133
1.126
1.107
1.063
1.029
1.023
1.010
1.005
0.999
0.986
0.980
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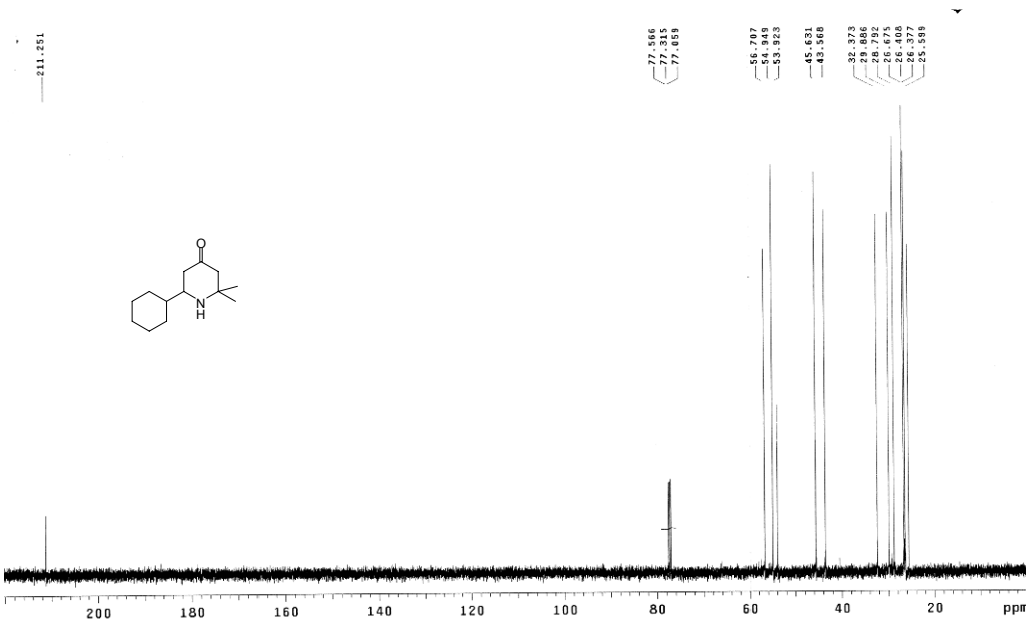
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77.315
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45.631
43.568
32.373
29.886
28.792
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25.599
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N
H
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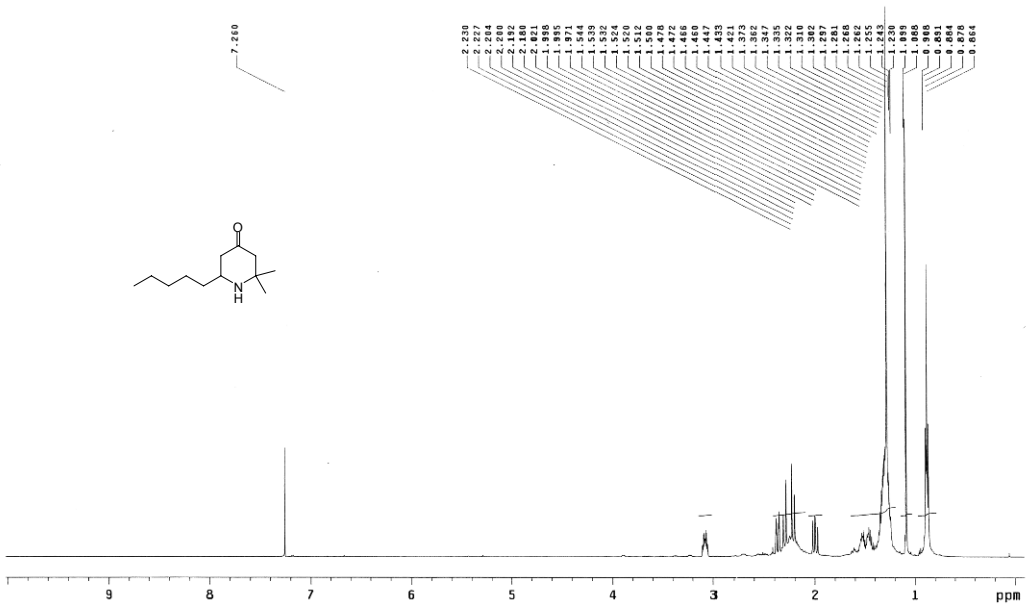
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2.230
2.227
2.204
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2.182
2.180
2.021
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1.935
1.971
1.544
1.539
1.532
1.524
1.520
1.512
1.500
1.478
1.472
1.466
1.460
1.447
1.433
1.421
1.373
1.362
1.347
1.335
1.322
1.310
1.302
1.297
1.281
1.268
1.262
1.255
1.243
1.230
1.099
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0.891
0.884
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1
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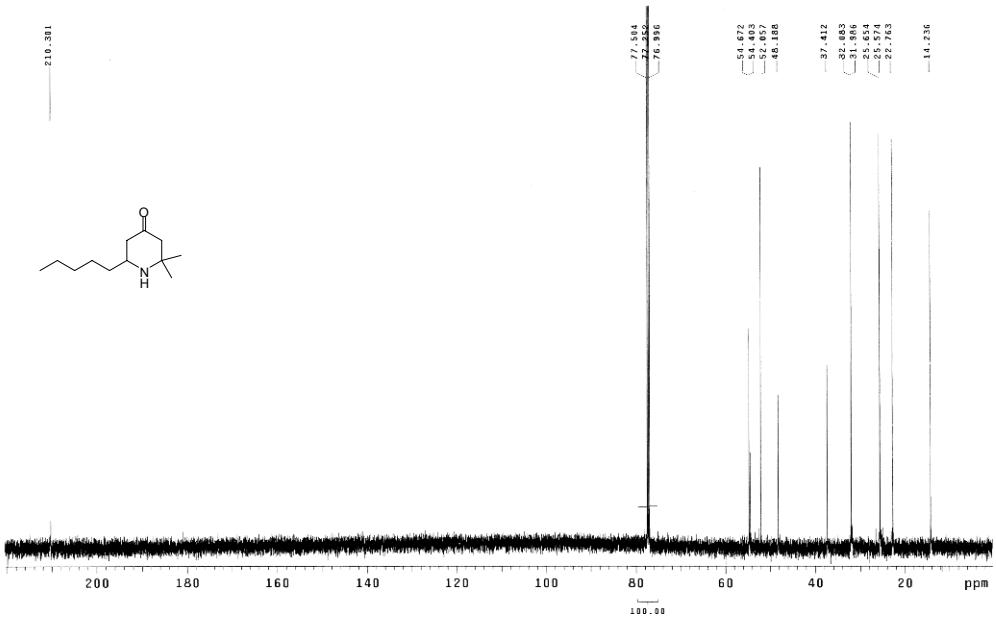
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77.252
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32.083
31.966
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22.763
14.236
200
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100
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60
40
20
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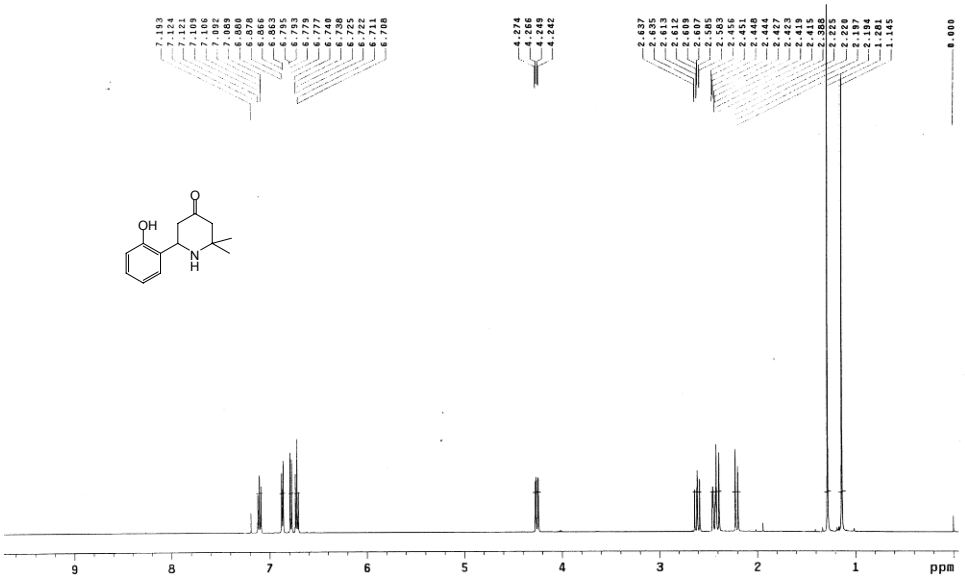
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6.777
6.740
6.738
6.725
6.722
6.711
6.708
4.274
4.266
4.249
4.242
2.637
2.635
2.613
2.612
2.609
2.607
2.585
2.583
2.456
2.451
2.446
2.444
2.427
2.423
2.419
2.415
2.388
2.225
2.220
2.197
2.194
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OH
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H
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4
3
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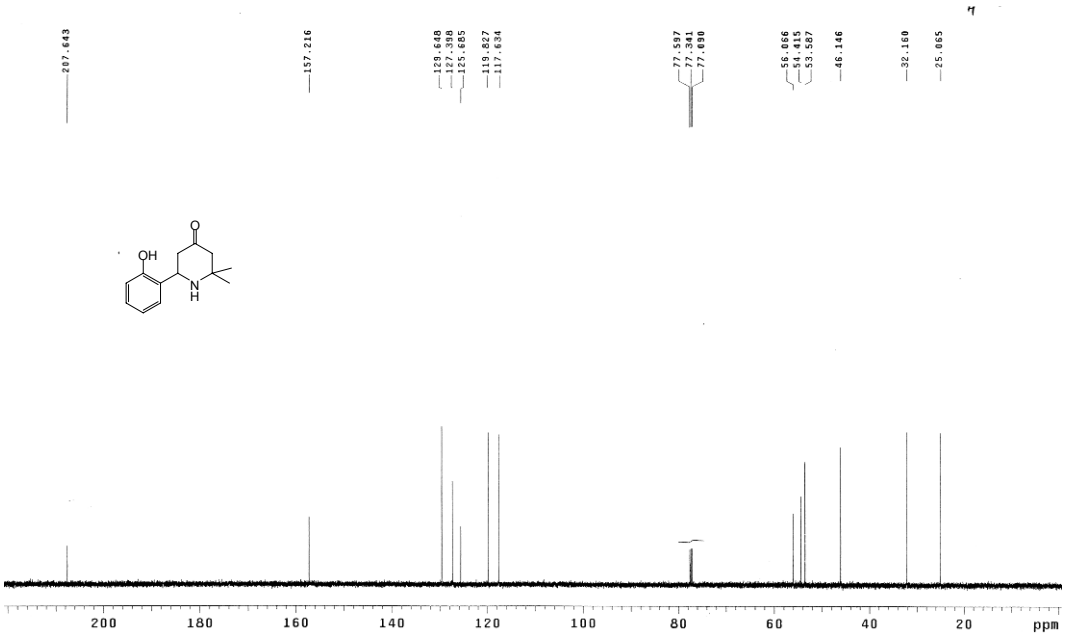
1
ppm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119.827
117.634
77.587
77.341
77.090
56.066
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53.587
46.146
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25.065
OH
N
H
O
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180
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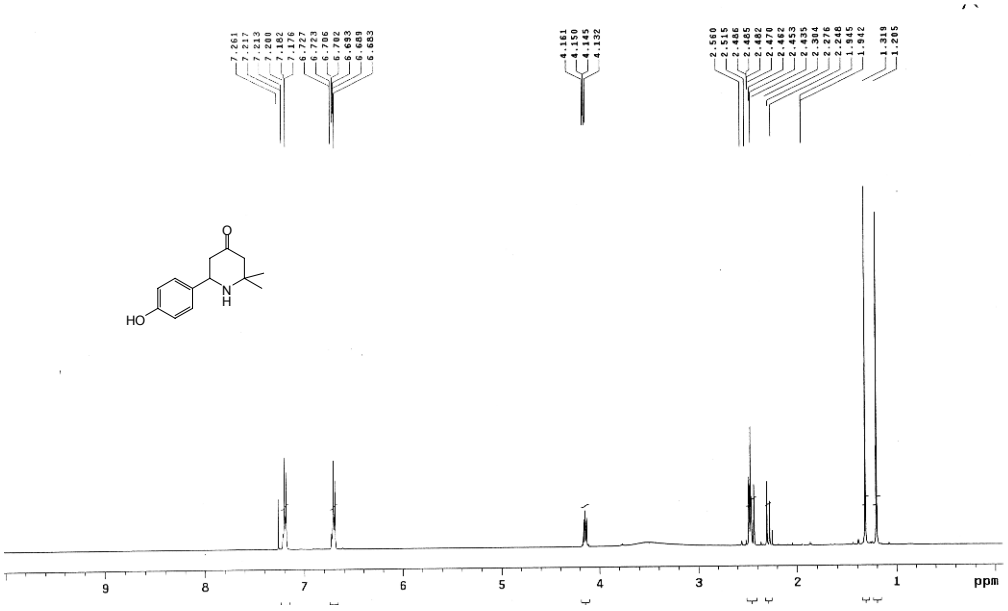
140
120
100
80
60
40
20
ppm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7.213
7.200
7.182
7.176
7.127
6.723
6.706
6.702
6.693
6.688
6.683
4.161
4.150
4.145
4.132
2.580
2.515
2.496
2.485
2.482
2.470
2.462
2.455
2.435
2.304
2.276
2.248
1.945
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1.295
O
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H
HO
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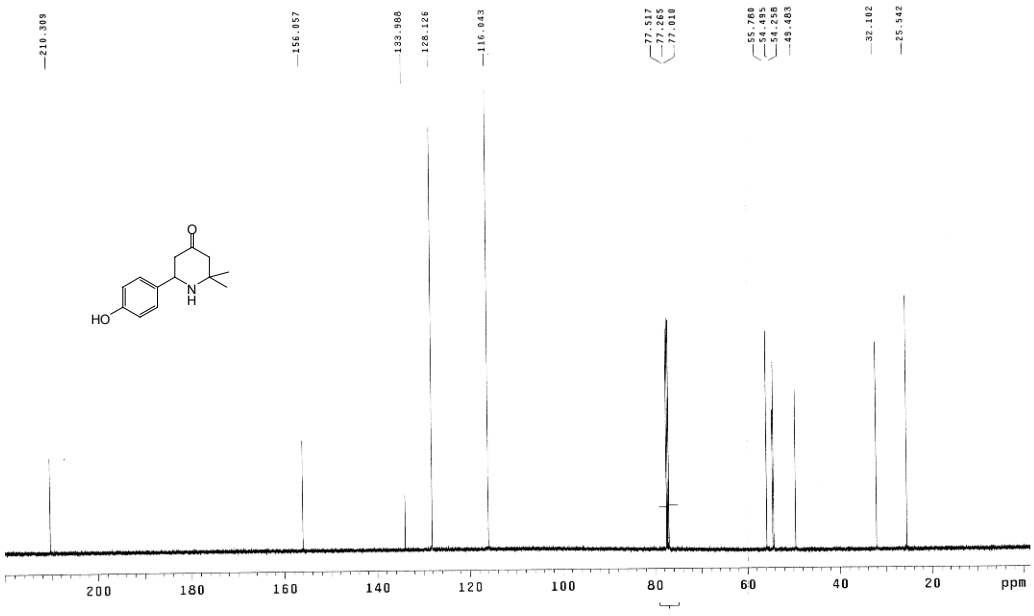
5
4
3
2
1
ppm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77.517
77.265
77.010
55.708
54.495
54.258
49.483
32.102
25.542
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N
H
HO
200
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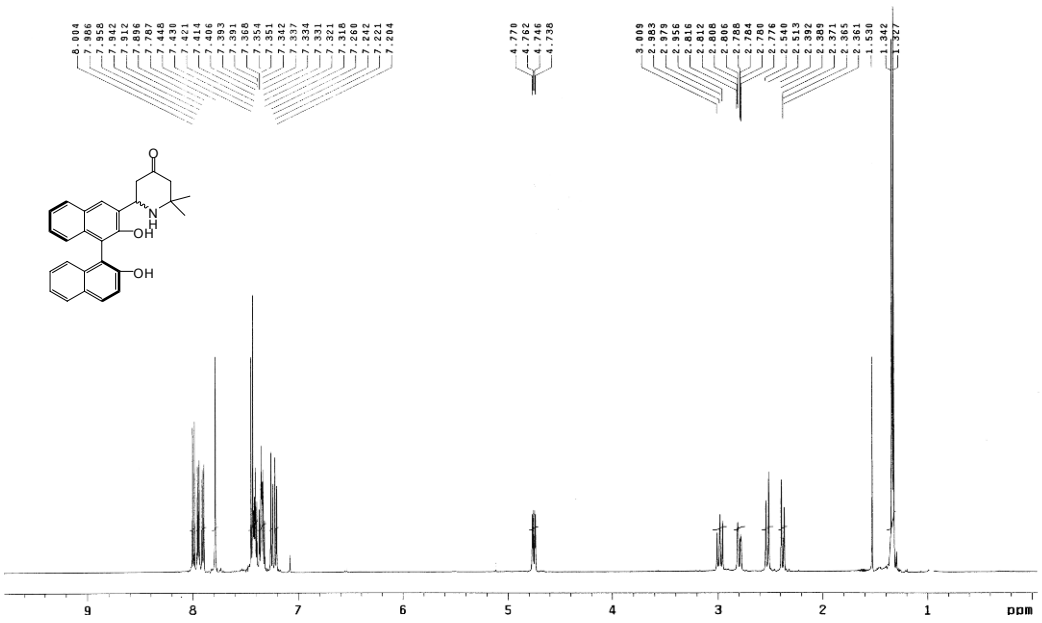
160
140
120
100
80
60
40
20
ppm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7.896
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7.414
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7.393
7.391
7.366
7.354
7.351
7.342
7.337
7.334
7.331
7.321
7.316
7.260
7.242
7.221
7.204
4.770
4.762
4.746
4.738
3.009
2.983
2.979
2.956
2.818
2.812
2.806
2.788
2.784
2.780
2.776
2.646
2.513
2.392
2.389
2.371
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2.361
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1.342
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OH
OH
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8
7
6
5
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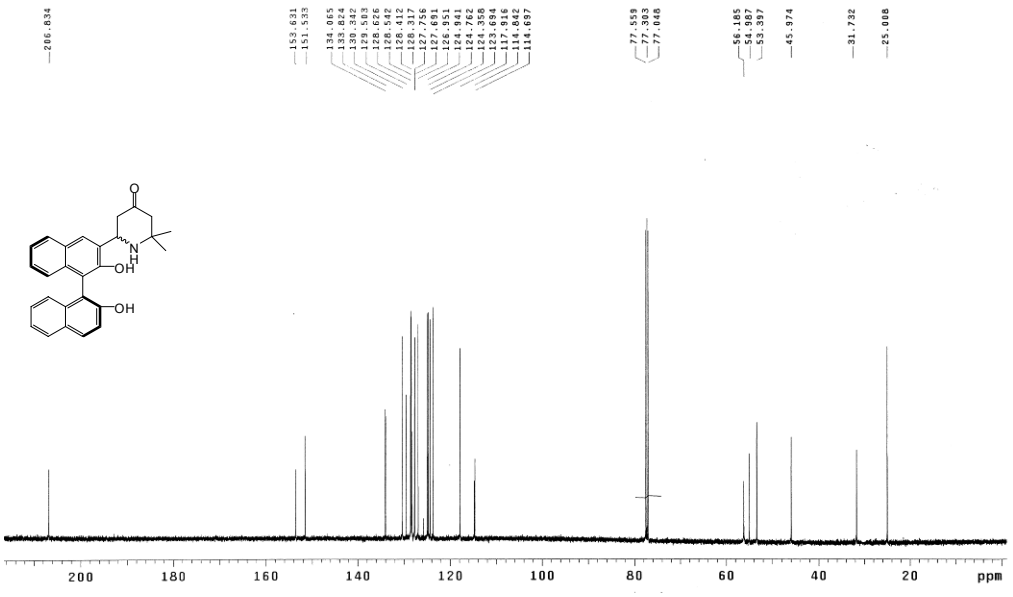
3
2
1
ppm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127.691
126.951
124.761
124.762
124.356
123.694
117.916
114.842
114.697
77.559
77.303
77.048
56.185
54.987
53.397
45.974
31.732
25.008
OH
OH
200
180
160
140
120
100
80
60
40
20
ppm

4. Reference

1. J. Chin, D. C. Kim, H.-J. Kim, F. B. Panosyan and K. M. Kim, *Org. Lett.*, 2004, **6**, 2591.
2. (a) F. A. Davis, B. Chao and A. Rao, *Org. Lett.*, 2001, **3**, 3169. (b) M. Balasubramanian and N. Padma, *Tetrahedron* 1963, **19**, 2135.