**Regioselective Synthesis and biological evaluation of Novel** **dispiropyrrolidine derivatives Via One-Pot Four-Component Reaction**

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**Table of contents**

**General Information S1**

**Copies of all NMR Spectra S2-S17**

##### **General Information**

**General.** Microwave irradiations were carried out in a Microwave Vials\* 0.2-0.5 mL of Biotage Initiator+ at 120oC, 300W. Reactions were monitored by TLC using 0.25 mm thick Merck plates, silica gel 60 F254. Products were purified by flash column chromatography on silica gel Merck (40-63) μ, 60.08 g/mol). NMR spectra were recorded with a Bruker DRX 400 MHz spectrometer in CDCl3. 13C spectra were recorded with 100MHz. The chemical shifts (δ) are given in parts per millions (ppm) relative to tetramethylsilane (TMS) for 1H and 13C nuclei. Conventional abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad. Coupling constants (J) are given in Hertz (Hz). Mass spectra were obtained on a GC/MS Saturn 2000 spectrometer. LC/MS were performed on 6410A Series electrospray ionization (ESI).

**1',1'',3''-trimethyl-5'-(4-nitrophenyl)-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone**, **(5c)**

Pale yellow solid; m.p.: 225–227 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.03 (m, 4H), 7.98 (dd, *J* = 12.0 Hz, 1H), 7.82-7.86 (m, 1H), 7.71-7.73 (m, 1H), 7.62-7.66 (m, 1H), 5.50 (s, 1H), 3.04 (s, 3H), 2.98 (d, *J* = 12.00 Hz, 1H), 2.76 (d, *J* = 12.00 Hz, 1H), 2.49 (s, 3H), 1.88 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 27.87, 28.84, 33.26, 37.72, 62.95, 63.83, 65.49, 67.78, 73.56, 76.75, 82.23, 122.71, 123.08, 123.36, 123.46, 128.95, 129.55, 132.03, 136.83, 137.08, 137.54, 137.85, 139.46, 140.64, 140.98, 142.87, 147.81, 149.93, 150.06, 150.47, 166.24, 166.36, 167.47, 168.74, 194.92, 196.76, 198.11, 201.72. Calculated MS (ESI) m/z: 476.13, found m/z: 477.21 [M + H+]. Anal. Calcd. For C24H20N4O7: C, 60.50; H, 4.23; N, 11.76. Found: C, 60.77; H, 4.56; N, 11.99.

**5'-([1,1'-biphenyl]-4-yl)-1',1'',3''-trimethyl-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5d)**

Pale yellow solid; m.p.: 209–211 °C. 1H-NMR(400 MHz, DMSO-*d6* ): *δ*H = 8.04-8.09 (m, 4H), 7.65-7.67 (m, 4H), 7.48 (t, *J* = 16.00 Hz, 2H), 7.36-7.41 (m, 1H), 7.31 (s, 2H), 4.81 (s, 1H), 3.19 (s, 3H), 2.94 (d, *J* = 12.00 Hz, 1H), 2.77 (d, *J* = 16.00 Hz, 1H), 2.46 (s, 3H), 1.96 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 28.06, 28.73, 33.22, 37.16, 38.69, 62.93, 73.14, 77.55, 119.06, 119.95, 123.0, 123.29, 127.24, 129.86, 130.42, 136.80, 137.02, 139.55, 141.0, 150.66, 155.66, 156.61, 167.73, 169.10, 198.41, 202.19. Calculated MS (ESI) m/z: 507.18, found m/z: 508.20 [M + H+]. Anal. Calcd. For C30H25N3O5: C, 70.99; H, 4.96; N, 8.28. Found: C, 71.35; H, 5.30; N, 8.55.

**1',1'',3''-trimethyl-5'-(o-tolyl)-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5e)**

Pale yellow solid; m.p.: 221–223 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.01-8.08 (m, 4H), 7.16-7.30 (m, 4H), 5.19 (s, 1H), 3.08 (s, 3H), 2.88 (d, *J* = 16.00 Hz, 1H), 2.74 (d, *J* = 16.00 Hz, 1H), 2.49 (s, 3H), 2.13 (s, 1H), 1.82 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 28.00, 28.72, 33.19, 37.74, 62.24, 68.97, 73.11, 117.63, 117.85, 123.08, 123.36, 123.72, 124.30, 124.41, 125.15, 136.87, 137.07, 139.55, 141.02, 146.60, 146.78, 147.76, 147.92, 150.60, 167.48, 168.75, 197.97, 201.91. Calculated MS (ESI) m/z: 445.16, found m/z: 446.20 [M + H+]. Anal. Calcd. For C25H23N3O5: C, 67.41; H, 5.20; N, 9.43. Found: C, 67.70; H, 5.44; N, 9.75.

**5'-(4-bromophenyl)-1',1'',3''-trimethyl-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5f)**

Yellow solid; m.p.: 240–242 °C. 1H-NMR(400 MHz, DMSO-*d6* ): *δ*H = 8.04-8.08 (m, 4H), 7.57 (d, *J* = 8.00 Hz, 2H), 7.20 (d, *J* = 12.00 Hz, 2H), 4.74 (s, 1H), 3.16 (s, 3H), 2.90 (d, *J* = 20.00 Hz, 1H), 2.74 (d, *J* = 16.00 Hz, 1H), 2.48 (s, 3H), 1.89 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 28.10, 28.71, 33.13, 62.47, 70.30, 73.17, 123.09, 123.35, 124.67, 128.85, 129.76, 130.37, 133.24, 136.80, 137.10, 139.58, 140.89, 149.71, 150.39, 167.97, 168.58, 198.09, 201.47. Calculated MS (ESI) m/z: 509.06, found m/z: 511.25 [M + H+]. Anal. Calcd. For C24H20BrN3O5: C, 56.48; H, 3.95; N, 8.23. Found: C, 56.63; H, 4.30; N, 8.55.

**5'-(2,3-difluorophenyl)-1',1'',3''-trimethyl-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5g)**

Pale yellow solid; m.p.: 232–234 °C. 1H-NMR(400 MHz, DMSO-*d6* ): *δ*H = 8.04-8.06 (m, 4H), 7.44-7.51 (m, 1H), 7.30-7.35 (m, 1H), 7.15 (t, *J* = 12.00 Hz, 1H), 5.16 (s, 1H), 3.13 (s, 3H), 2.93 (d, *J* = 12.00 Hz, 1H), 2.80 (d, *J* = 12.00 Hz, 1H), 2.50 (s, 3H), 1.92 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 27.90, 28.71, 33.23, 37.32, 63.02, 73.39, 77.82, 122.98, 123.27, 126.57, 127.61, 128.91, 134.19, 136.75, 137.0, 139.41, 139.55, 140.76, 140.94, 150.54, 167.76, 169.13, 198.46, 202.05. Calculated MS (ESI) m/z: 467.13, found m/z: 468.25 [M + H+]. Anal. Calcd. For C24H19F2N3O5: C, 61.67; H, 4.10; N, 8.99. Found: C, 61.98; H, 4.42; N, 9.36.

**5'-(3-chloro-4-methoxyphenyl)-1',1'',3''-trimethyl-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5h)**

Pale yellow solid; m.p.: 251–253 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.02-8.07 (m, 4H), 7.17-7.25 (m, 3H), 4.70 (s, 1H), 3.85 (s, 3H), 3.16 (s, 3H), 2.88 (d, *J* = 16.00 Hz, 1H), 2.74 (d, *J* = 16.00 Hz, 1H), 2.49 (s, 3H), 1.89 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 27.88, 28.74, 33.14, 37.38, 62.81, 73.36, 77.20, 122.10, 123.01, 123.29, 131.36, 134.54, 136.77, 137.01, 139.52, 140.93, 150.51, 167.63, 168.95, 198.28, 201.88. Calculated MS (ESI) m/z: 495.12, found m/z: 496.21 [M + H+]. Anal. Calcd. For C25H22ClN3O6: C, 60.55; H, 4.47; N, 8.47. Found: C, 60.87; H, 4.80; N, 8.78.

**5'-(4-chloro-2-methylphenyl)-1',1'',3''-trimethyl-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5i)**

Brown solid; m.p.: 220–222 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.03-8.08 (m, 4H), 7.26-7.33 (m, 3H), 5.14 (s, 1H), 3.09 (s, 3H), 2.88 (d, *J* = 16.00 Hz, 1H), 2.74 (d, *J* = 16.00 Hz, 1H), 2.58 (s, 3H), 2.13 (s, 3H), 1.81 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 18.5, 27.8, 28.6, 33.2, 37.3, 38.6, 62.9, 73.3, 78.1, 122.9, 123.28, 128.4, 129.0 135.3, 136.7, 138.1, 139.5, 140.9, 150.5, 167.5, 169.2, 199.5, 202.1. Calculated MS (ESI) m/z: 479.12, found m/z: 480.23 [M + H+]. Anal. Calcd. For C25H22ClN3O5: C, 62.57; H, 4.62; N, 8.76. Found: C, 62.90; H, 4.93; N, 8.99.

**5'-(4-(4-chlorophenoxy) phenyl)-1',1'',3''-trimethyl-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5j)**

Yellow solid; m.p.: 239–241 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.04-8.06 (m, 2H), 8.03 (m, 8H), 7.5 (d, *J* = 12.00 Hz, 2H), 4.92 (s, 1H), 3.20 (s, 3H), 2.93 (d, *J* = 12.00 Hz, 1H), 2.80 (d, *J* = 12.00 Hz, 1H), 2.50 (s, 3H), 1.92 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 27.87, 28.84, 33.26, 37.72, 62.95, 63.83, 65.49, 67.78, 73.56, 76.75, 82.23, 122.71, 123.08, 123.36, 123.46, 128.95, 129.55, 132.03, 136.83, 137.08, 137.54, 137.85, 139.46, 140.64, 140.98, 142.87, 147.81, 149.93, 150.06, 150.47, 166.24, 166.36, 167.47, 168.74, 194.92, 196.76, 198.11, 201.72. Calculated MS (ESI) m/z: 557.14, found m/z: 558.20 [M + H+]. Anal. Calcd. For C30H24ClN3O6: C, 64.58; H, 4.34; N, 7.53. Found: C, 64.90; H, 4.66; N, 7.80.

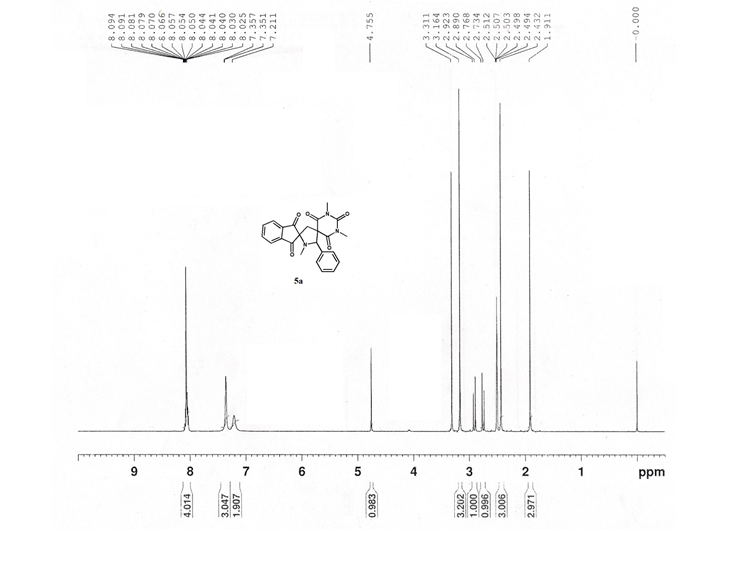
**4-(1',1'',3''-trimethyl-1,2'',3,4'',6''-pentaoxo-1,1'',3,3'',4'',6''-hexahydro-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidin]-5'-yl) benzonitrile, (5k)**

Pale yellow solid; m.p.: 219–221 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.04-8.08 (m, 4H), 7.98 (m, 4H), 4.92 (s, 1H), 3.04 (s, 3H), 2.98 (d, *J* = 12.00 Hz, 1H), 2.76 (d, *J* = 12.00 Hz, 1H), 2.49 (s, 3H), 1.88 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 29.7, 31.5, 37.3, 48.0, 52.9, 117.7, 118.2, 127.5, 127.9, 128.2, 128.6, 131.5, 131.7, 141.7, 150.2, 154.1, 155.3, 178.4, 197.7, 199.5, 202.1. Calculated MS (ESI) m/z: 456.14, found m/z: 457.21 [M + H+]. Anal. Calcd. For C25H20N4O5: C, 65.78; H, 4.42; N, 12.27. Found: C, 66.01; H, 4.62; N, 12.53.

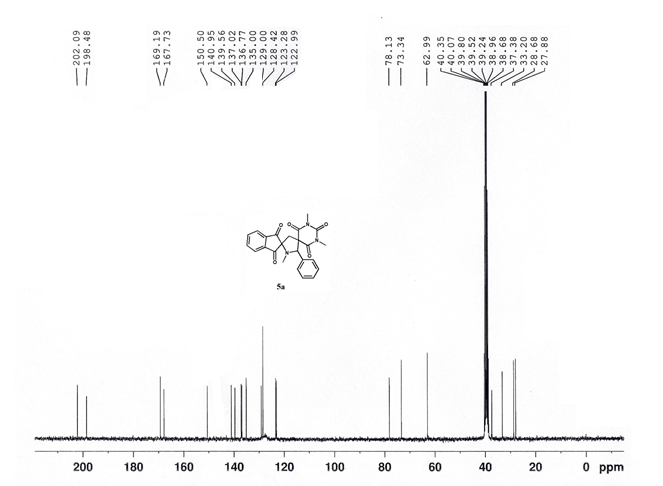
**1',1'',3''-trimethyl-5'-(pyridin-4-yl)-2''*H*-dispiro[indene-2,2'-pyrrolidine-4',5''-pyrimidine]-1,2'',3,4'',6''(1''*H*,3''*H*)-pentaone, (5l)**

Brown solid; m.p.: 260–262 °C. 1H-NMR (400 MHz, DMSO-*d6*): *δ*H = 8.04-8.08 (m, 4H), 7.57 (d, *J* = 8.00 Hz, 2H), 7.20 (d, *J* = 12.00 Hz, 2H), 4.74 (s, 1H), 3.16 (s, 3H), 2.90 (d, *J* = 20.00 Hz, 1H), 2.74 (d, *J* = 16.00 Hz, 1H), 2.48 (s, 3H), 1.89 (s, 3H). 13C NMR (100 MHz, DMSO-*d6*): *δ*C = 28.10, 28.71, 33.13, 62.47, 70.30, 73.17, 123.09, 123.35, 124.67, 128.85, 129.76, 130.37, 133.24, 136.80, 137.10, 139.58, 140.89, 149.71, 150.39, 167.97, 168.58, 198.09, 201.47. Calculated MS (ESI) m/z: 432.14, found m/z: 433.25 [M + H+]. Anal. Calcd. For C23H20N4O5: C, 63.88; H, 4.66; N, 12.96. Found: C, 64.15; H, 4.85; N, 13.21.

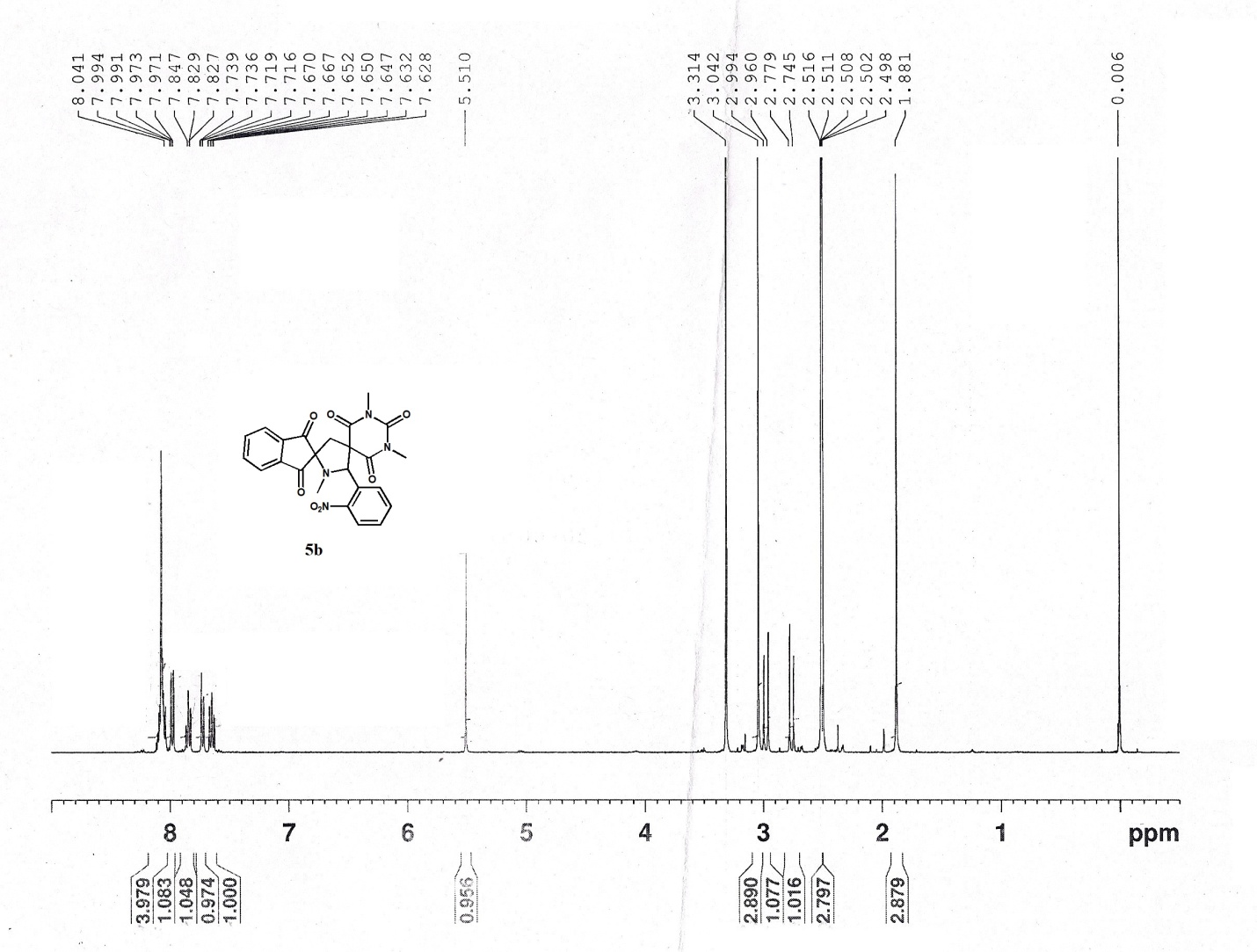
1H NMR spectrum of 5a



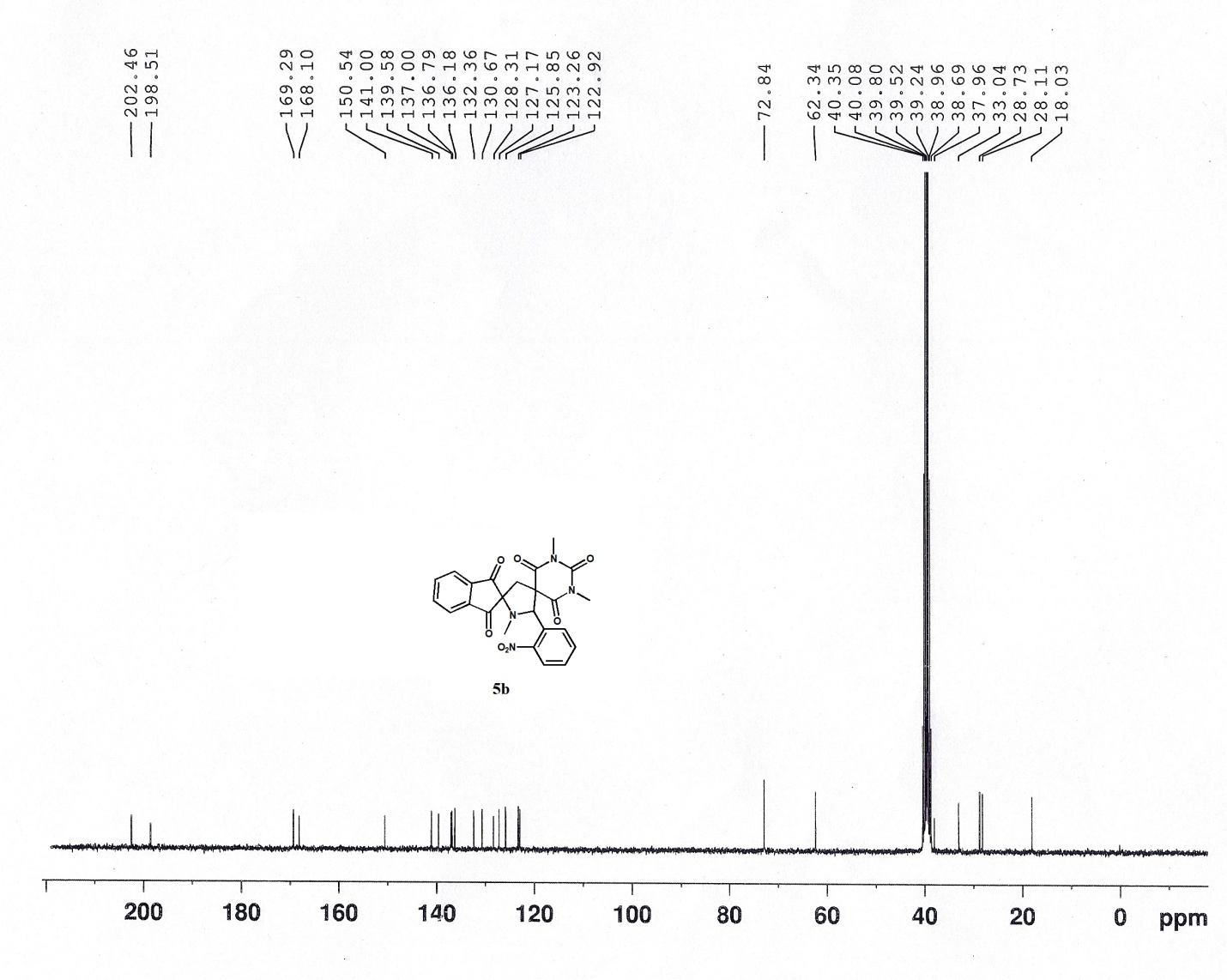
13C NMR spectrum of 5a



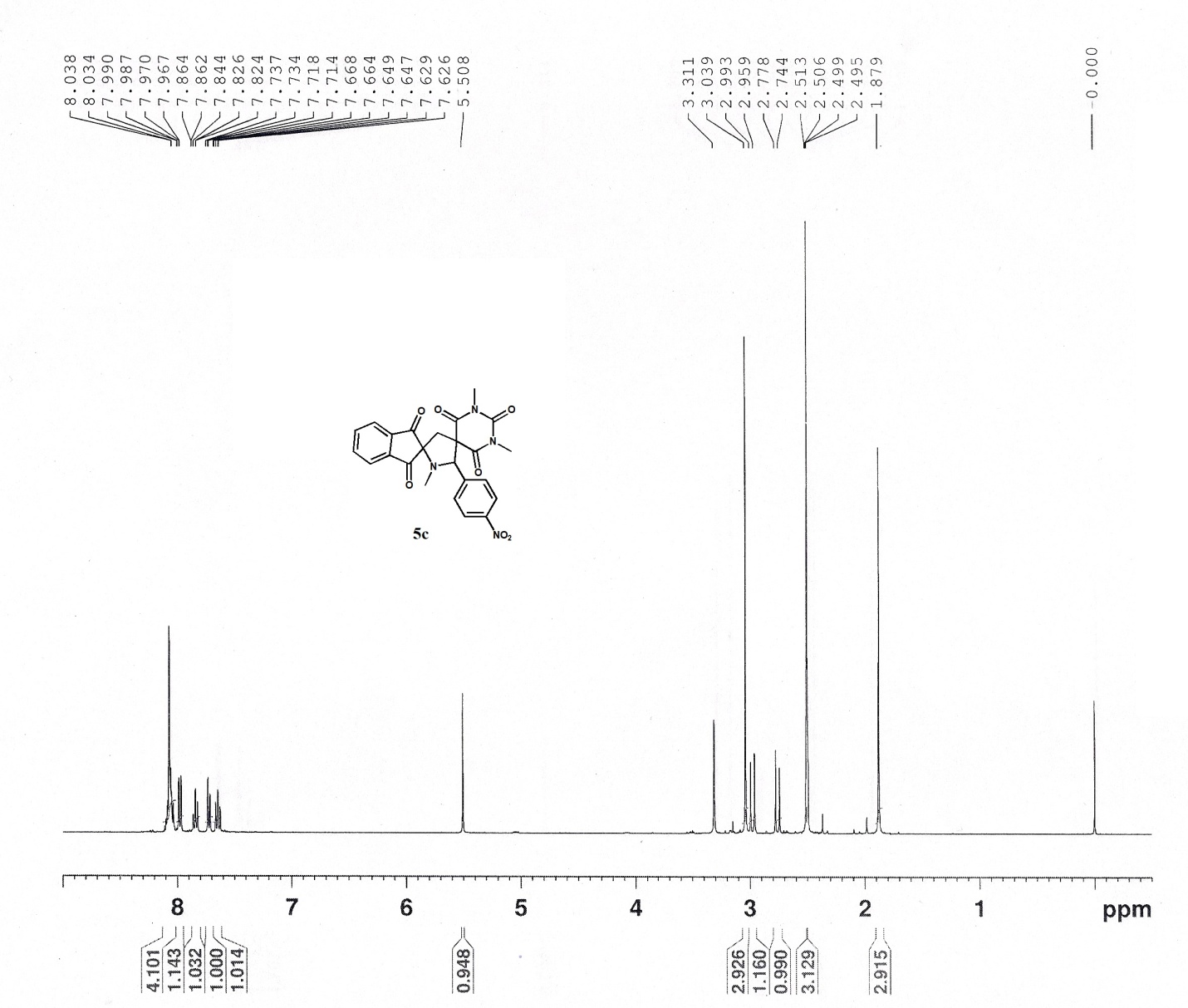
1H NMR spectrum of 5b



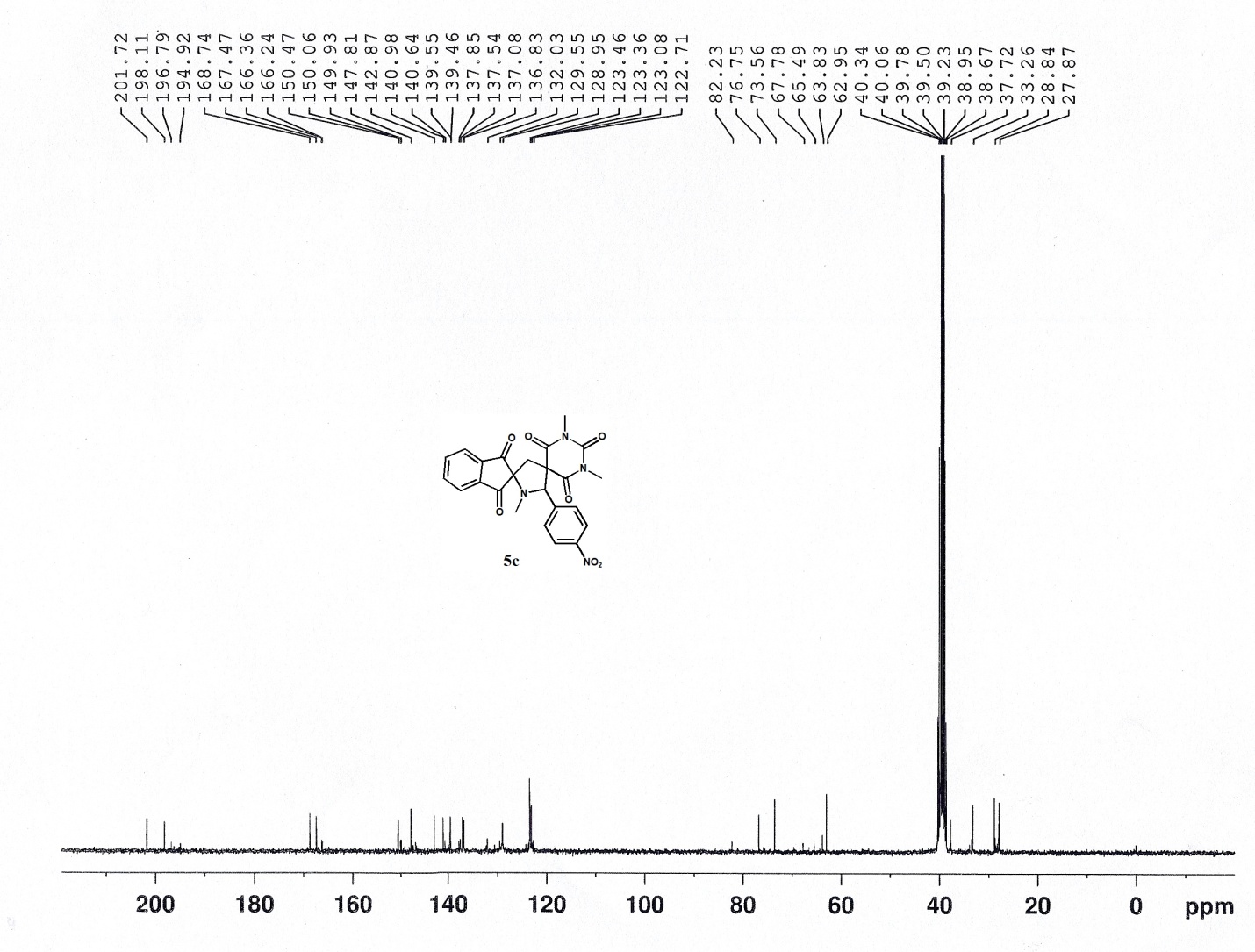
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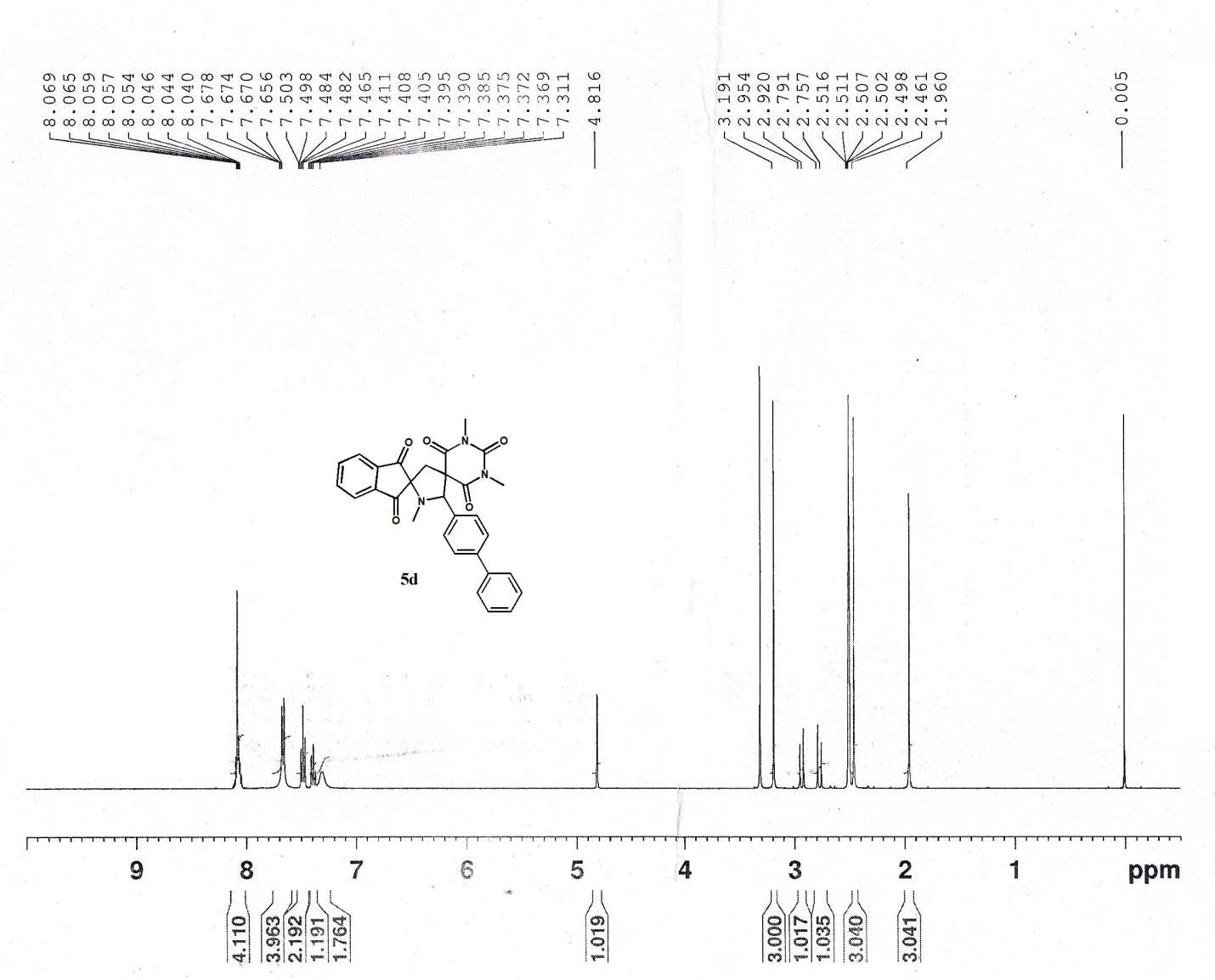
1H NMR spectrum of 5c



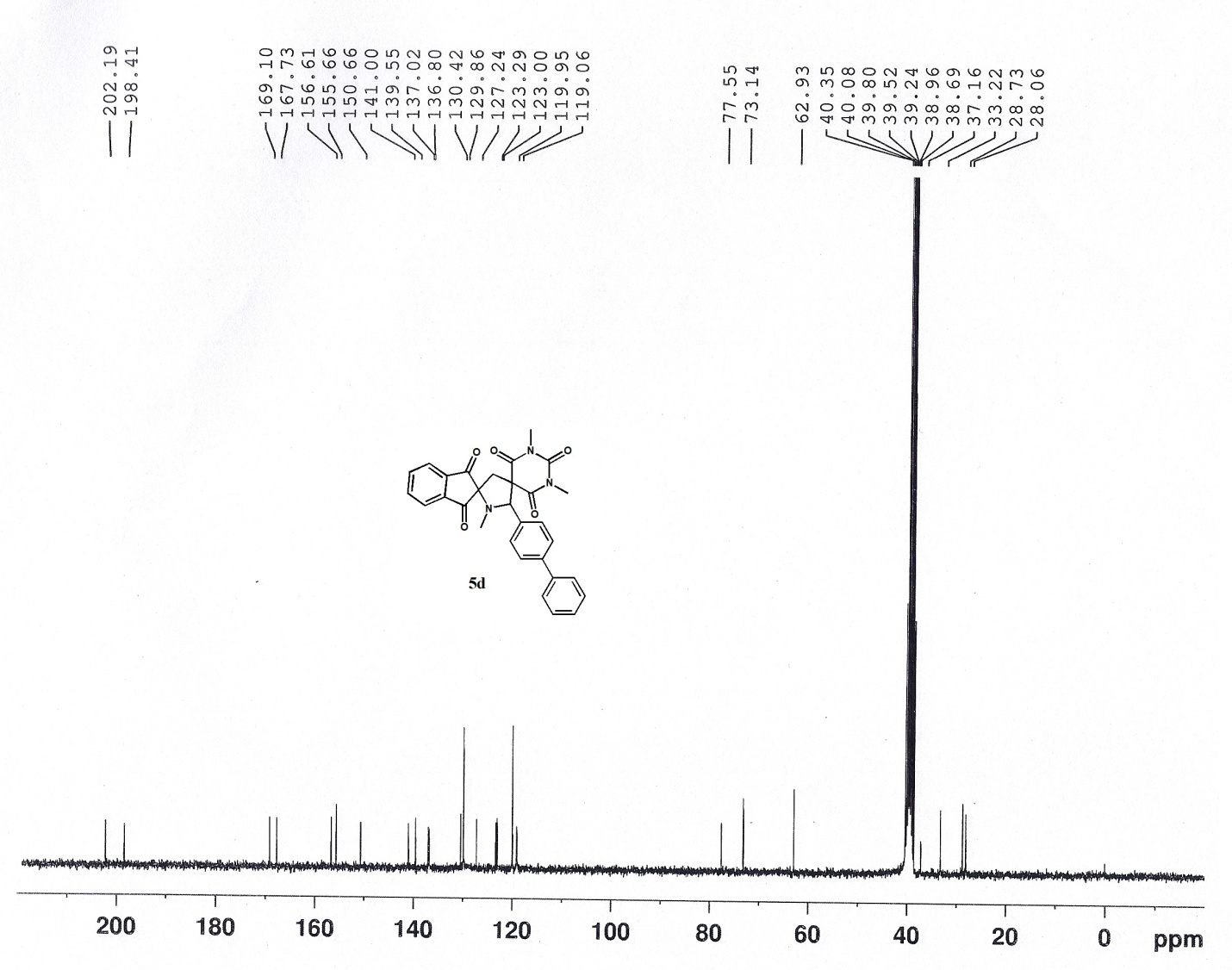
13C NMR spectrum of 5c



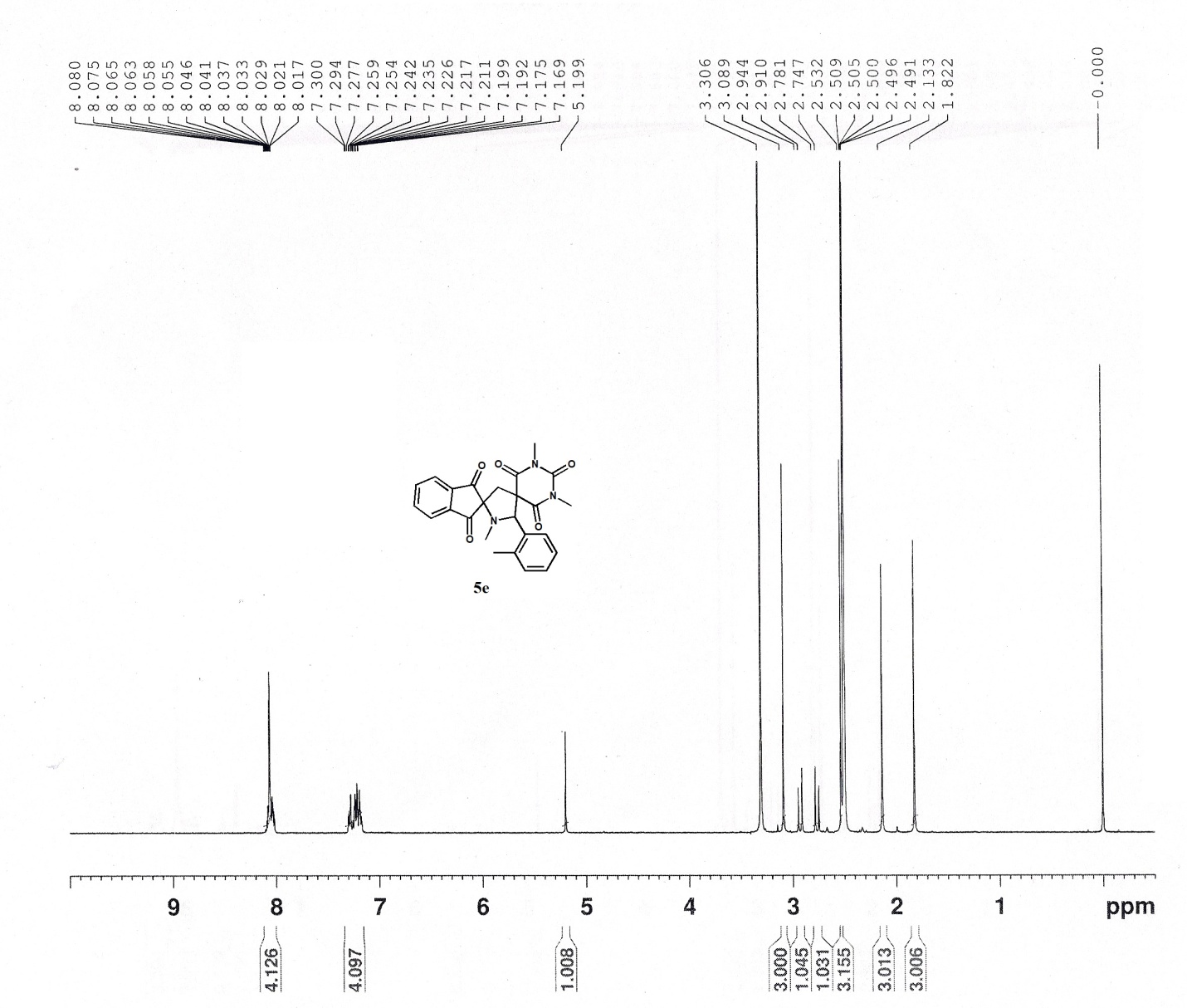
1H NMR spectrum of 5d



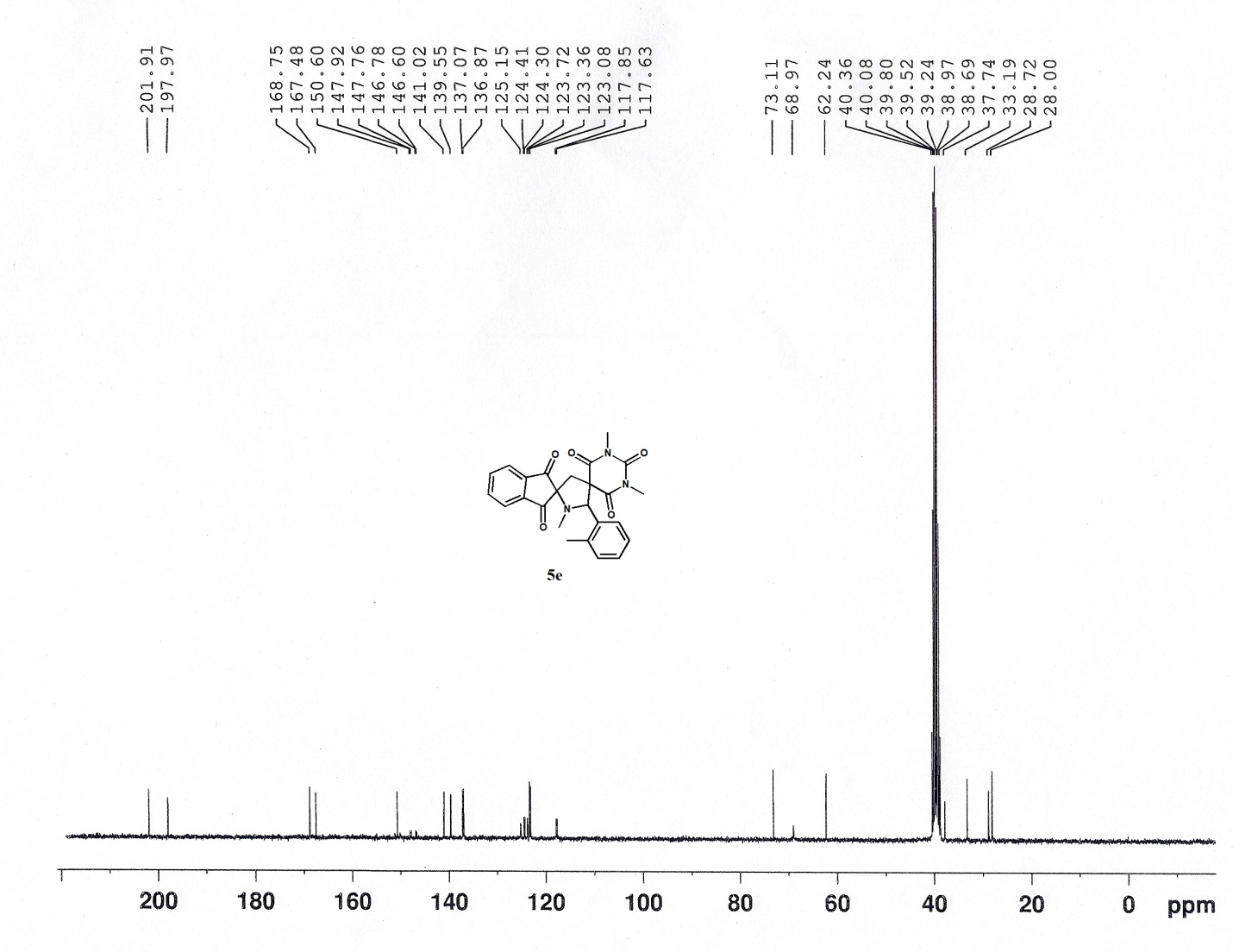
13C NMR spectrum of 5d



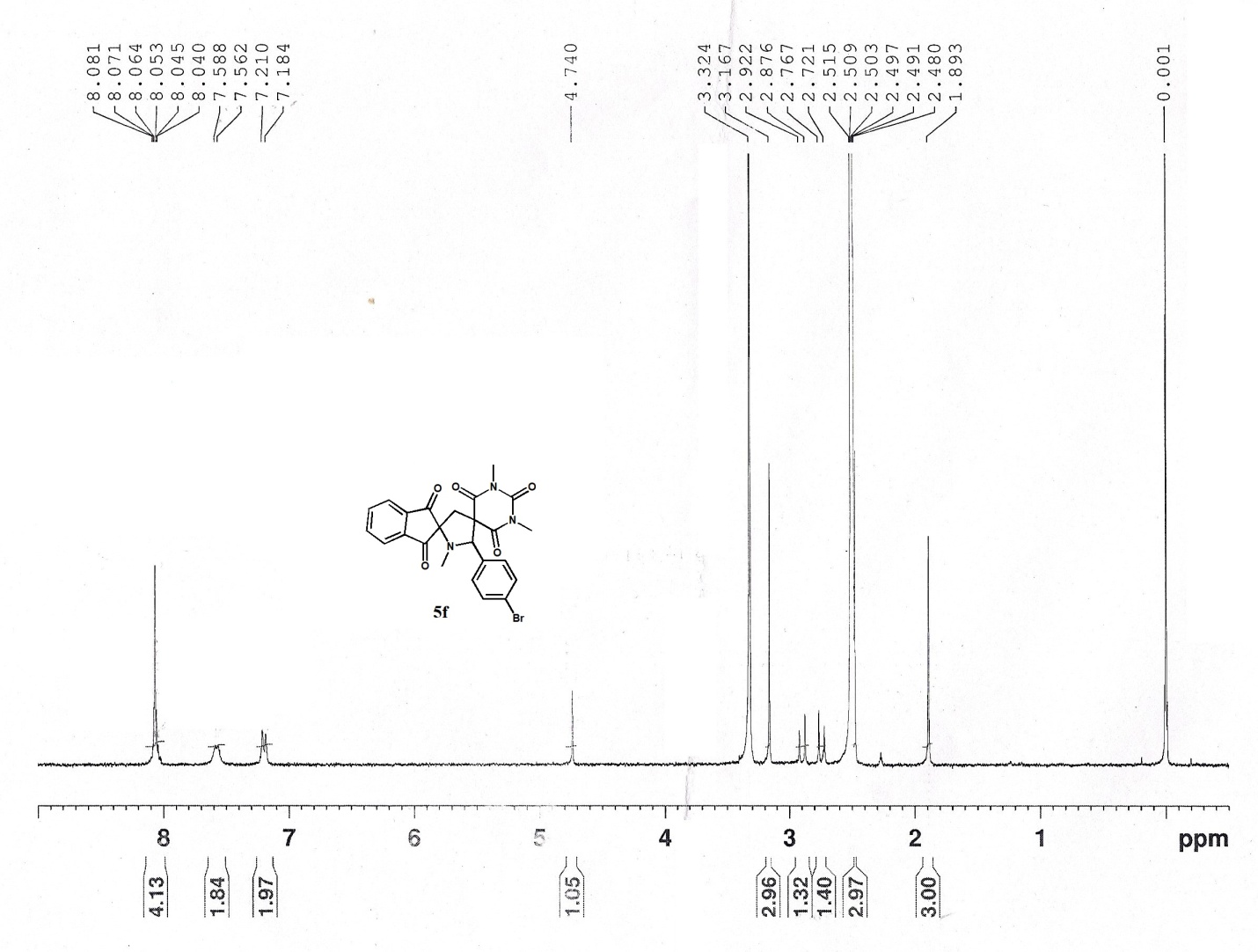
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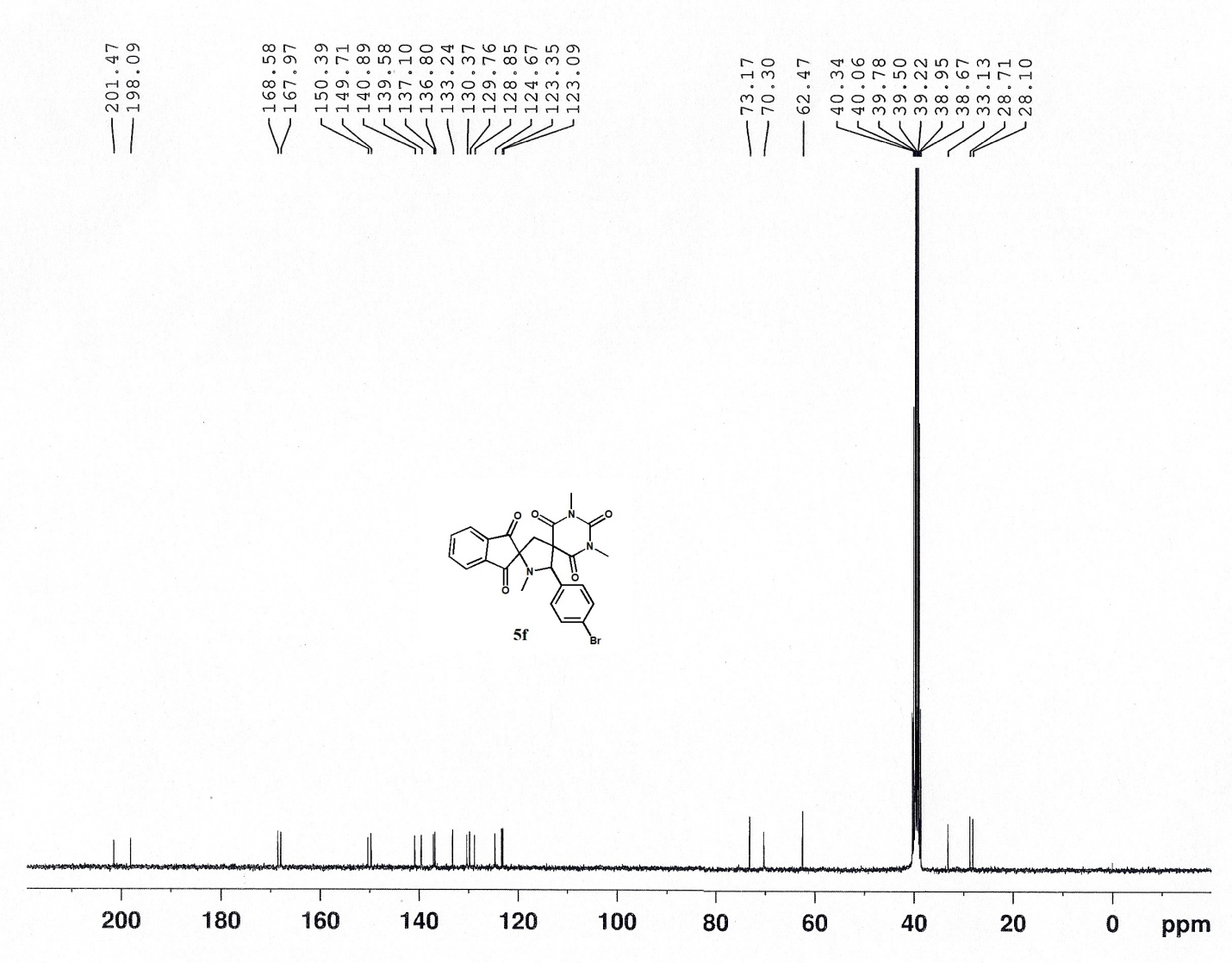
13C NMR spectrum of 5e



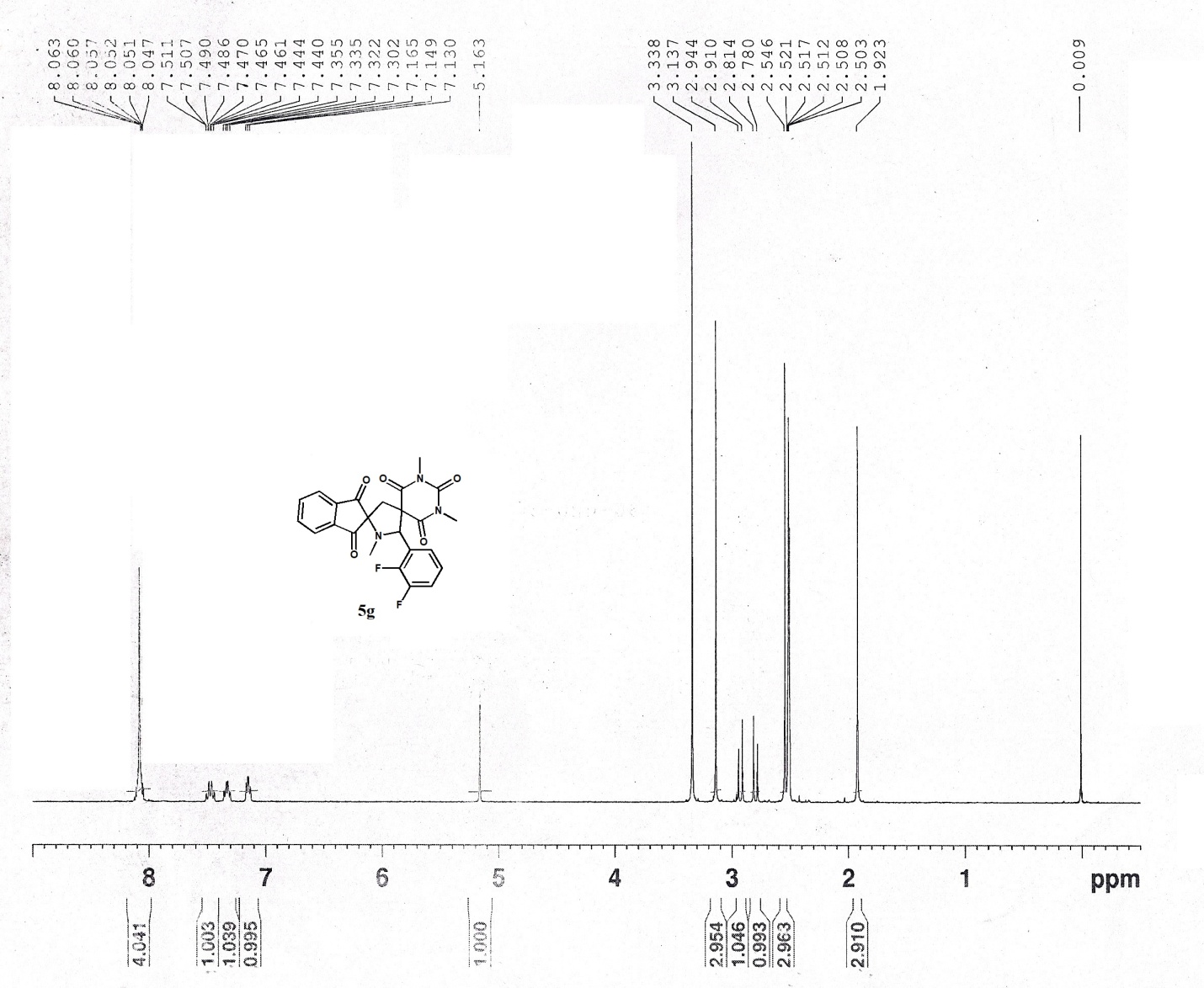
1H NMR spectrum of 5f



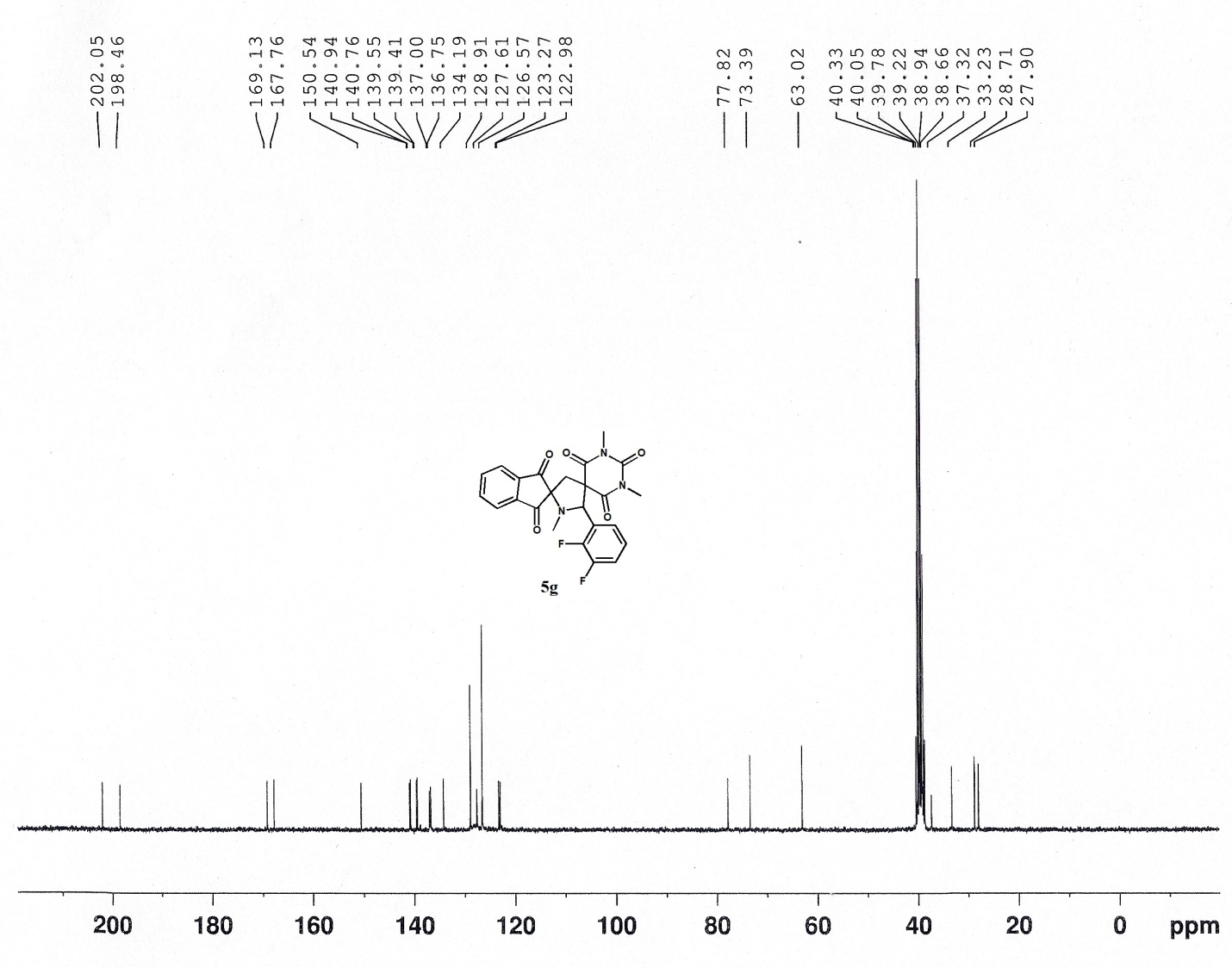
13C NMR spectrum of 5f



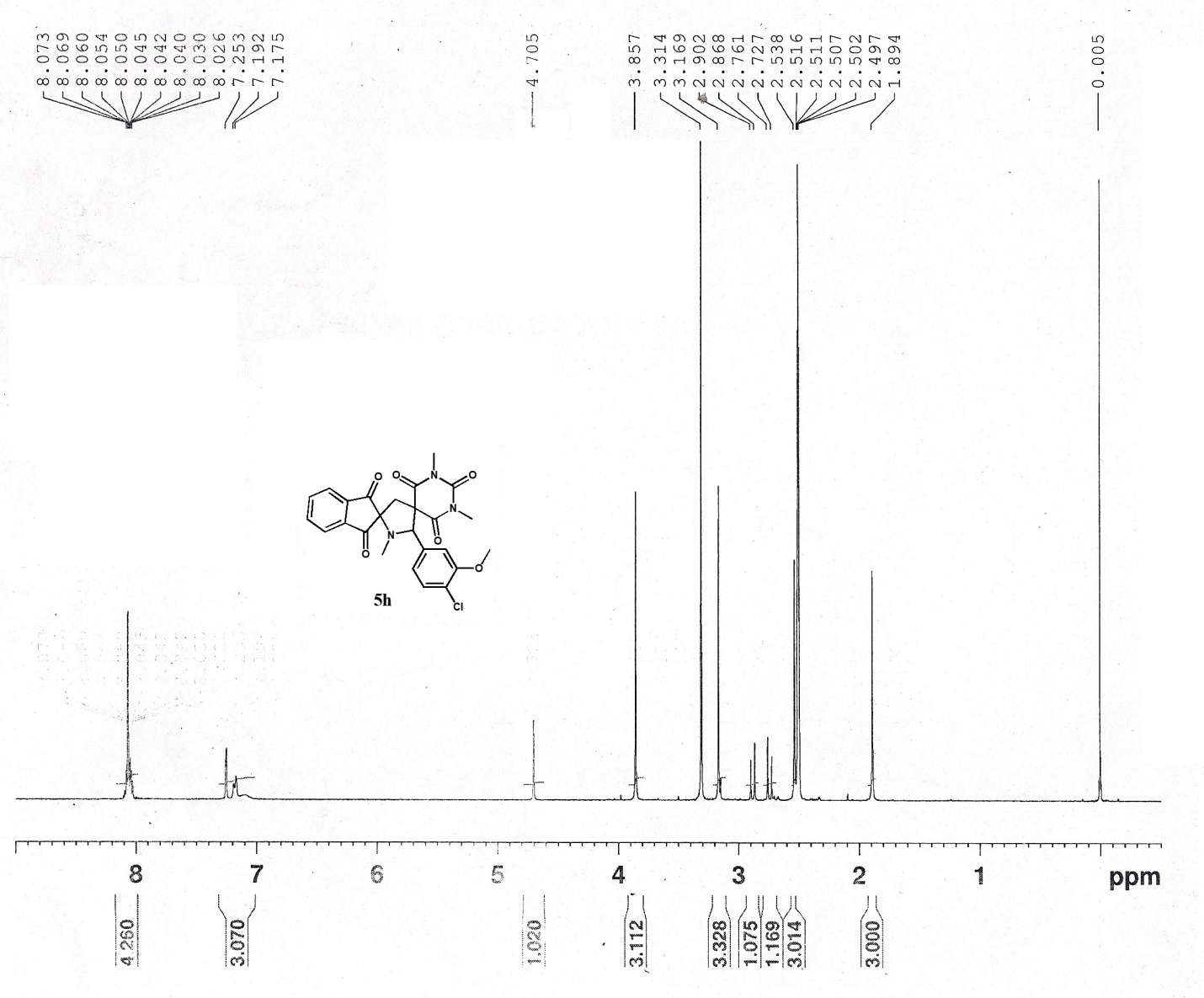
1H NMR spectrum of 5g



13C NMR spectrum of 5g



1H NMR spectrum of 5h



13C NMR spectrum of 5h

