Synthesis of bis(indolyl)methanes using ammonium niobium oxalate (ANO) complex as an efficient and recyclable catalyst

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Contents

General Information: The reactions were monitored by TLC carried out on Merck silica gel (60 F_{254}) by using UV light as visualizant agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Baker silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 and 400 MHz on Bruker DPX spectrometers. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Hidrogen coupling patterns are described as singlet (s), doublet (d), triplet (t) and multiplet (m). Coupling constants (*J*) are reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 50 MHz and at 100 MHz on Bruker DPX 200 and 400 spectrometers. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$. The ultrasoun-rpomoted reactions were conduced using a Cole Parmer-ultrasonic processor Model CPX 130, with a maxim power of 130 W, operating at amplitude of 60% and a frequency of 20 kHz. The temperature of the reaction under US was monitored using an Incoterm digital infrared thermometer Model Infraterm (Brazil). Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. GC analysis were conducted on a RESTEC RTX-5MS capillary column (30 m, 0.25 mm id, 0.25 μm film thickness) using the products dissolved in ethyl acetate with the following conditions:Injected sample volume was 1.0 μL; He constant flow, 54.1 mL/min; initial inlet temperature, 100 °C ramped to 280 °C at 10 °C/min (held for 10 min) (total run time: 40.0 min). The yields of product **3a** (GC retention time of the separately synthesized compound **3a** was 37.9 min) given in Table 1 were detemined by GC analisys.

General Procedure for the Synthesis of *bis*(indolyl)methanes at Ultrassound:

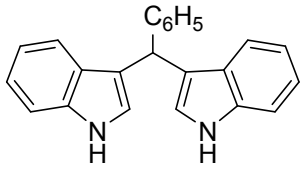
To a 3 mL vassel was added aldehyde **2a** (0.6 mmol), indole **1a** (1.0 mmol), glycerol (1 mL) and ANO (3 mol%), the reaction was carried out under ultrasound (20 KHz, 60% of sonic amplitude). The resulting solution was sonicated with an US probe for the time indicated in Table 3. After that, the reaction mixture was received in water (10 mL), extracted with ethyl acetate (3 x 5 mL), dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

General Procedure for the Synthesis of *bis*(indolyl)methanes at Ultrassound:

To a 3 mL vassel was added aldehyde **2a** (0.6 mmol), indole **1a** (1.0 mmol), H_2O (1 mL) and ANO (5 mol%), the reaction was put in a oil bath pre-heated at 50 °C. The resulting solution was stirred for the time indicated in Table 3. After that, the reaction mixture was received in water (10 mL), extracted with ethyl acetate (3 x 5 mL), dried over $MgSO_4$ and concentrated

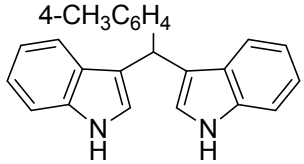
under vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent.

3,3'-(phenylmethylene)bis(1*H*-indole) **(3a)[1]**



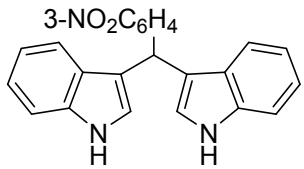
Yield: US 0.1643g (99%) Conv. 0.1594 (97%); dark red solid; mp 123-125°C (Lit. 124-125°C). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.57 (s, 2H); 7.37–7.08 (m, 11H); 6.96 (ddd, J = 7.9; 1.1 Hz, 2H); 6.47 (s, 2H); 5.83 (s, 1H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 144.0, 136.5, 128.6, 128.2, 127.0, 126.1, 123.6, 121.8, 119.8, 119.4, 119.1, 111.0, 40.1. MS (relative intensity) *m*/*z*: 322 (100), 245 (69), 204 (39), 176 (6), 122 (29), 117 (17), 90 (9), 77 (4), 63 (4).

3,3'-(p-tolylmethylene)*bis*(1*H*-indole) **(3b)[2]**



Yield: US 0.1546g (92%) Conv. 0.1546g (92%); white solid, mp 102-105°C (Lit. 103-104°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.59 (s, 2H); 7.35 (d, J = 7.70 Hz, 2H); 7.21-6.91 (m, 10H); 6,44 (s, 2H); 5.79 (s, 1H); 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 141.0, 136.5, 135.4, 128.8, 128.5, 127.0, 123.5, 121.7, 119.8, 119.6, 119.0, 111.0, 39.7, 21.0. MS (relative intensity) *m*/*z*: 336 (100), 245 (50), 218 (31), 207 (20), 189 (5), 160 (5), 117 (15), 90 (8), 63 (3).

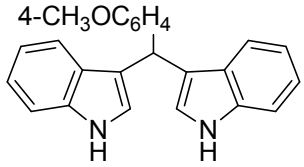
3,3'-[(3-nitrophenyl)methylene]*bis*(1*H*-indole) **(3c)[3]**



Yield: US 0.1504g (82%) Conv. 0.1633 (89%); Dark red solid; mp 92-93°C (Lit. 88-90°C). 1H NMR ($CDCl_3$, 200 MHz): δ 8.21 (t, J = 1.8 Hz, 1H); 8.07 (ddd, J = 8.13; 2.33; 1.03 Hz, 1H);

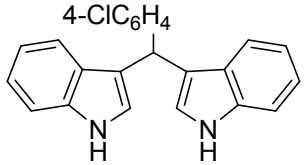
7.99 (br s, 2H); 7.69 (d, J= 7.6 Hz, 1H); 7.47-7.16 (m, 7H); 7.06-6.68 (m, 2H); 6.65 (d, J= 1.6 Hz, 2H); 5.99 (s, 1H). 13C NMR ($CDCl_3$ 50 MHz); δ (ppm): 148.3, 146.3, 136.6, 134.8, 129.0, 126.5, 123.7, 123.5, 122.2, 121.4, 119.4, 118.0, 111.3, 39.9. MS (relative intensity) *m*/*z*: 367 (99), 320 (15), 245 (100), 217 (18), 204 (26), 159 (9), 122 (17), 117 (7), 77 (3).

3,3'-[(4-methoxyphenyl)methylene]*bis*(1*H*-indole) (3d)[4]



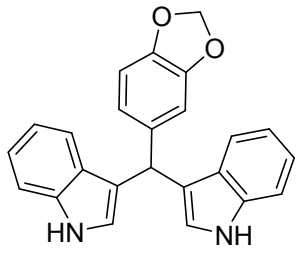
Yield: US 0.1584g (90%) Conv. 0.1742 (99%); Red solid; mp 194-197°C (Lit. 188-190°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.85 (br s, 2H); 7.39-6.57 (m, 14H); 5.81 (s, 1H); 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 157.8, 136.6, 136.2, 129.5, 127.0, 123.5, 121.8, 119.9, 119.1, 113.5, 111.0, 55.2, 39.3. MS (relative intensity) *m*/*z*: 352 (100), 281 (7), 245 (34), 207 (33), 191 (9), 165 (6), 117 (11), 90 (7), 63 (3).

3,3'-[(4-chlorophenyl)methylene]*bis*(1*H*-indole) (3e)[4]



Yield: US 0.1637g (92%) Conv. 0.1584g (89%); Red solid; mp 70-72°C (Lit. 74-75°C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.80 (s, 2H); 7.35-7.10 (m, 10H); 7.02-6.94 (m, 2H); 6.49 (s, 2H); 5.80 (s, 1H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 142.5, 136.6, 131.7, 130.0, 128.3, 126.8, 123.6, 122.0, 119.7, 119.2, 119.0, 111.1, 39.5. MS (relative intensity) *m*/*z*: 356 (100), 319 (7), 245 (66), 217 (14), 204 (27), 160 (9), 122 (25), 108 (2), 77 (3).

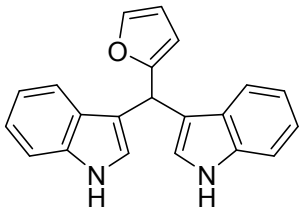
3,3'-(benzo[d][1,3]dioxol-5-ylmethylene)*bis*(1*H*-indole) (3f)[5]



Yield: US 0.1610g (88%) Conv. 0.1519g (83%); Dark red solid; mp 95-98°C (Lit 96-98°C). ^{1}H

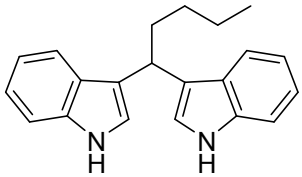
NMR ($CDCl_3$, 200 MHz): 7.89 (s, 2H); 7.41-7.33 (m, 2H); 7.29-7.12 (m, 4H); 7-04-6.90 (m, 2H); 6.90-6.68 (m, 3H); 6.61 (d, J= 1.5 Hz, 2H); 5.88 (s, 2H); 5.78 (s, 1H). NMR (CDCl3 50 MHz) δ (ppm): 147.4, 145.7, 138.1, 136.6, 127.0, 123.5, 121.9, 121.5, 119.8, 119.7, 119.2, 111.0, 109.3, 107.9, 100.7, 39.8. MS (relative intensity) *m*/*z*: 336 (100), 305 (4), 245 (48), 217 (11), 191 (13), 153 (8), 122 (4), 117 (5), 77(3), 63 (4).

3,3'-(furan-2-ylmethylene)*bis*(1*H*-indole) (3g)[6]



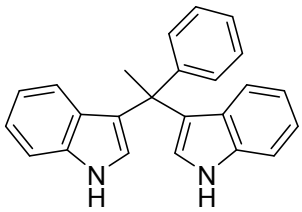
Yield: US 0.1373g (88%) Conv. 0.1498 (96%); Red Solid; mp 322-326 °C (Lit. 322-325 °C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.78 (s, 2H); 7.44 (d, *J* = 7.5 Hz, 2H); 7.30-6.97 (m, 7H); 6.70 (s, 2H); 6.26 (s, 1H); 6.02 (s, 1H); 5.89 (s, 1H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 157.0, 141.1, 136.4, 126.7, 123.1, 121.8, 119.6, 119.3, 117.0, 111.1, 110.1, 106.6, 34.0. MS (relative intensity) *m*/*z*: 312 (100), 283 (47), 256 (8), 192 (26), 167 (28), 141 (22), 117 (25), 89 (5), 63 (3).

3,3'-(pentane-1,1-diyl)*bis*(1*H*-indole) (3h)



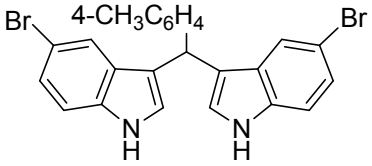
Yield: US 0.0528g (35%) Conv. 0.0906g (60%); Green oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.63-7.52 (m, 4H); 7.18 (dd, *J* = 8.1, 0.76 Hz, 2H); 7.13-7.08 (m, 2H); 7.03-6.99 (m, 2H); 6.78-6.77 (m, 2H); 4.42 (t, *J* = 7,4 Hz, 1H); 2.17 (q, *J* = 7.2 Hz, 2H); 1.37-1.34 (m, 4H); 0.86-0.83 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 136.4, 127.1, 121.4, 120.4, 119.6, 118.9, 111.1, 35.6, 33.9, 30.5, 22.8, 14.1. MS (relative intensity) *m*/*z*: 302 (16), 245 (100), 218 (14), 207 (4), 189 (2), 130 (3), 122 (14), 108 (3).

3,3'-(1-phenylethane-1,1-diyl)*bis*(1*H*-indole) (3i)[7]



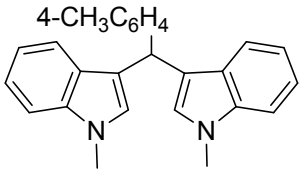
Yield: US 0.0336g (20%) Conv. 0.1142g (68%); Brown oil (188-191 °C (Lit. 188-190 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.76 (s, 2H); 7.38-7.06 (m, 11H); 6.94-6.86 (m, 2H); 6.51 (d, J = 2.3 Hz, 2H); 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 148.0, 137.0, 128.0, 127.7, 126.4, 125.7, 124.6, 123.4, 122.0, 121.4, 118.8, 111.1, 43.7, 28.7. MS (relative intensity) *m*/*z*: 336 (16), 321 (100), 259 (8), 217 (6), 160 (10), 129 (5), 115 (5), 77 (4).

3,3'-(p-tolylmethylene)*bis*(5-bromo-1*H*-indole) (3k)[8]



Yield: US 0.2209g (90%) Conv. 0.2430 (99%); white solid; mp 212-214°C (Lit, 214.5-214.7°C). ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.94 (s, 2H); 7.47-7.46 (d, J = 1.6, 2H); 7.25-7.05 (m, 8H); 6.58 (d, J = 1.6, 2H); 5.68 (s, 1H); 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 140.0, 135.9, 135.3, 129.1, 128.7, 128.3, 124.8, 124.7, 122.2, 119.2, 122.6, 39.4, 21.0. MS (relative intensity) *m*/*z*: 492 (30), 403 (20), 323 (6), 294 (13), 242 (12), 218 (23), 159 (15), 129 (15), 117 (3), 83 (50), 57 (100).

3,3'-(p-tolylmethylene)*bis*(1-methyl-1*H*-indole) (3i)[2]



Yield: US 0.1692g (93%) Conv. 0.1183g (65%); beige solid; mp 195-197 (Lit. 197-198°C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.38 (d, J= 7.9 Hz, 2H);7.30-7.14 (m, 6H); 7.09-6.94 (m, 4H); 6.52 (s, 2H); 5.84 (s, 1H); 3.66 (s, 6H); 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$ 50 MHz); δ (ppm): 141.4, 137.4, 135.3, 128.8, 128.5, 128.1, 127.5, 121.3, 120.0, 118.5, 118.4, 109.0, 39.6, 32.6, 21.1. MS (relative intensity) *m*/*z*: 364 (100), 273 (75), 257 (15), 233 (48), 218 (21), 182 (10), 136 (19), 131 (6), 115 (4), 77 (2).

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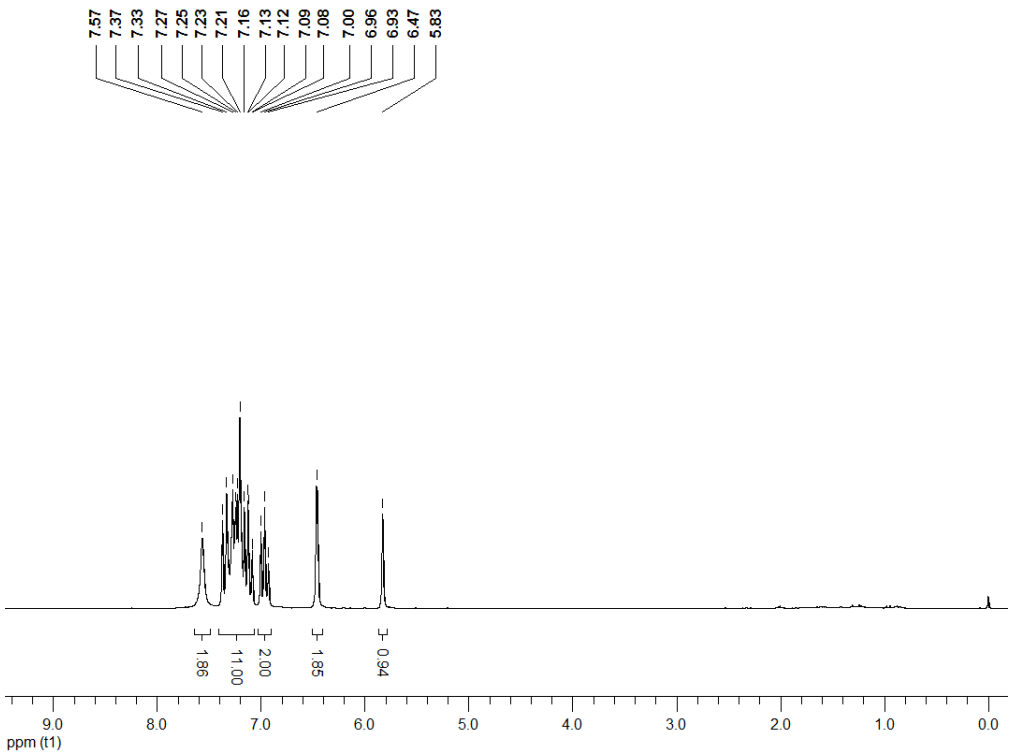
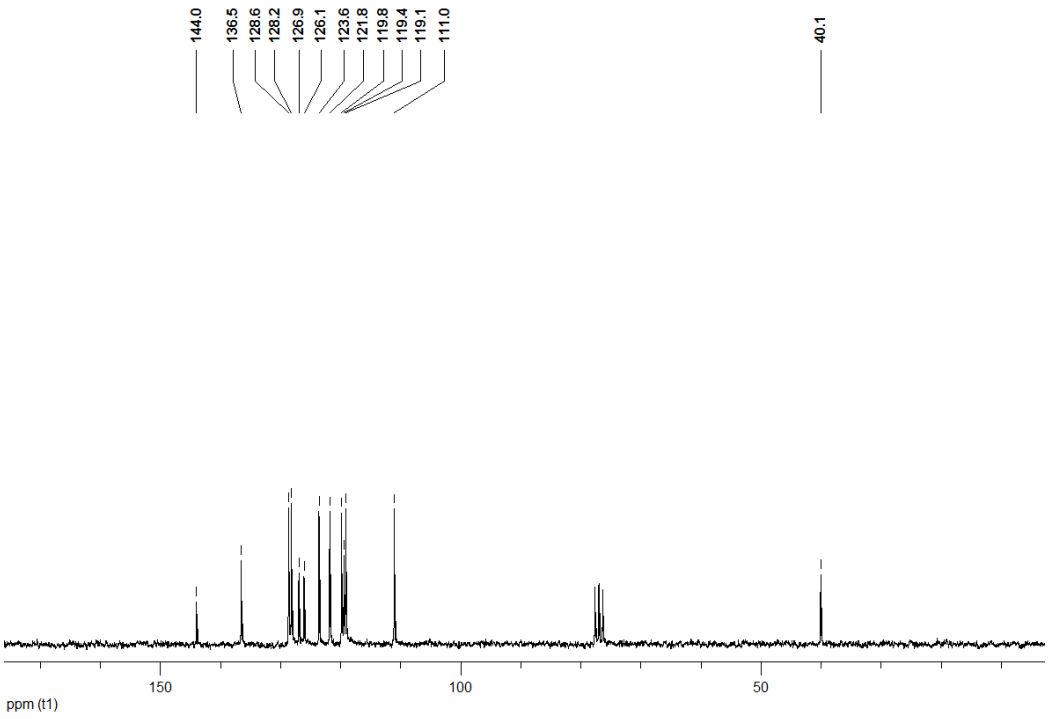
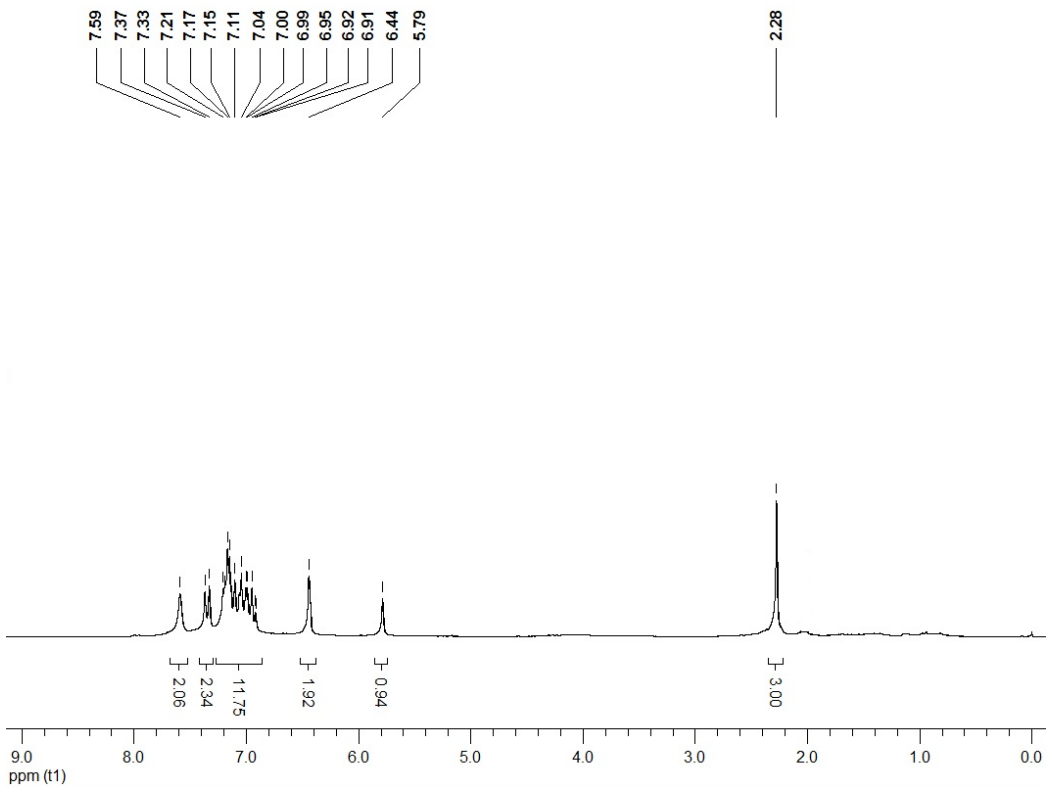


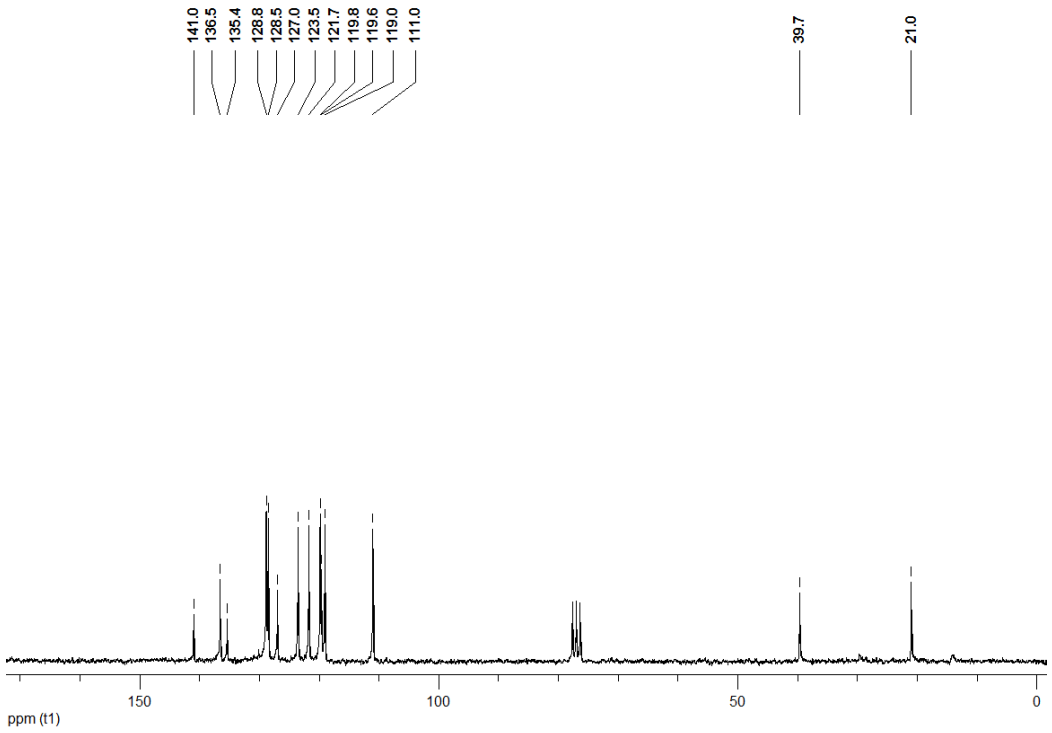
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(phenylmethylene)*bis*(1*H*-indole) (**3a**)



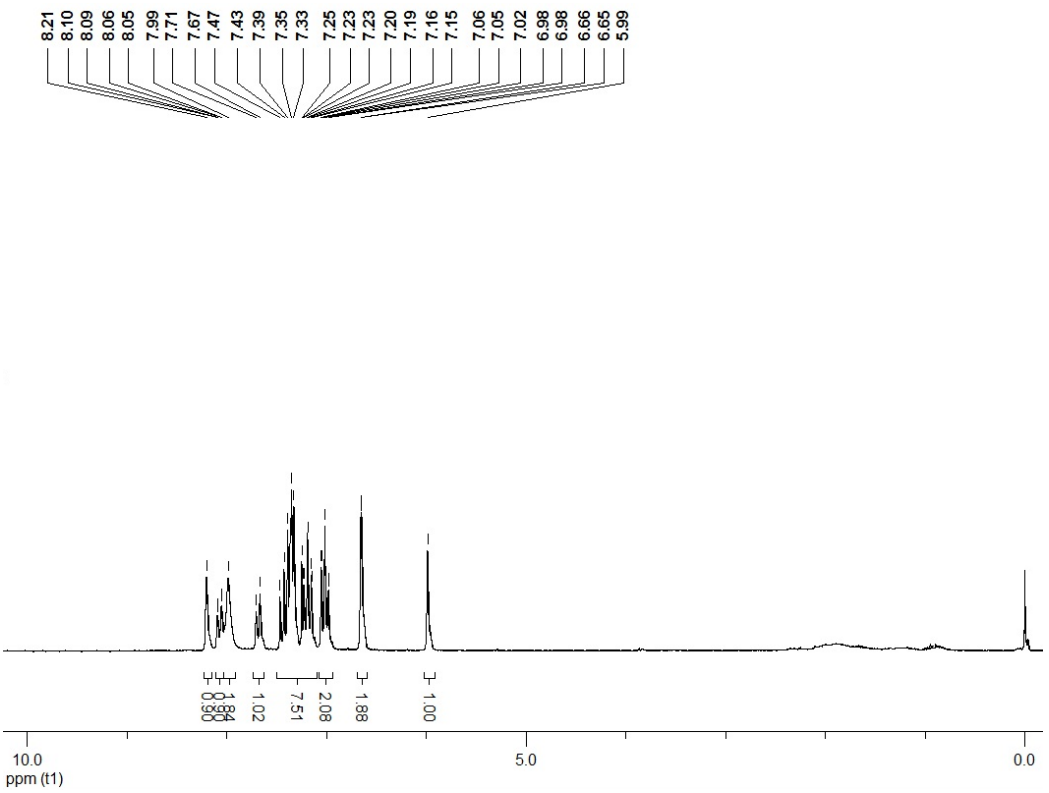
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(phenylmethylene)*bis*(1*H*-indole) (**3a**)



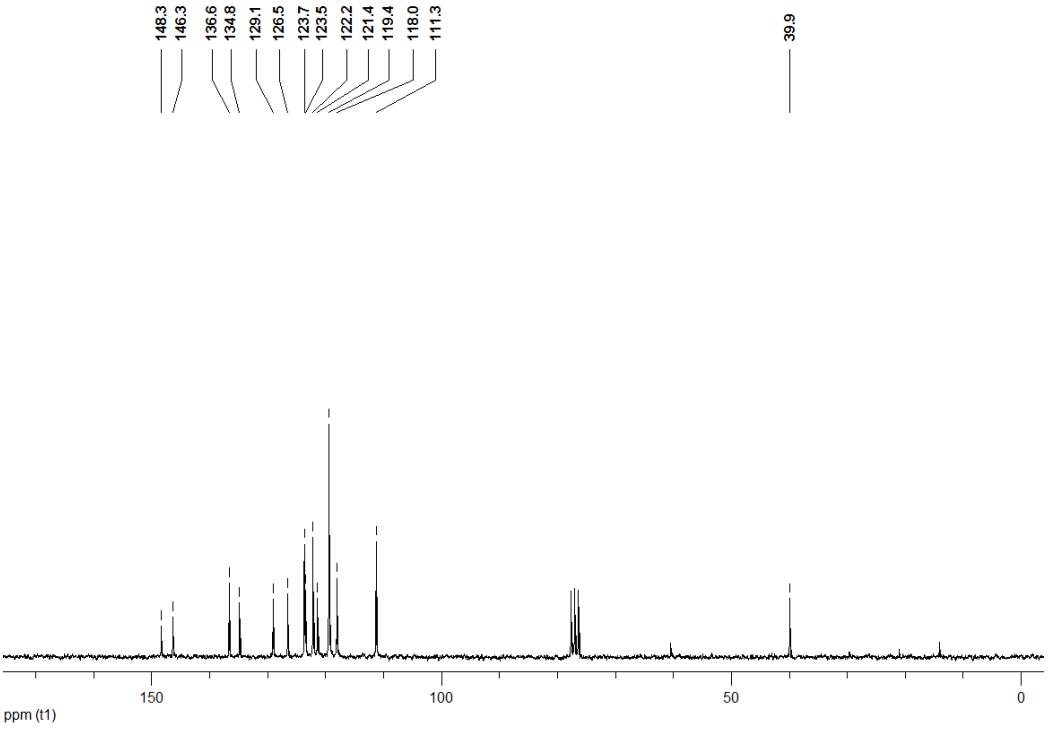
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(*p*-tolylmethylene)*bis*(1*H*-indole) (**3b**)



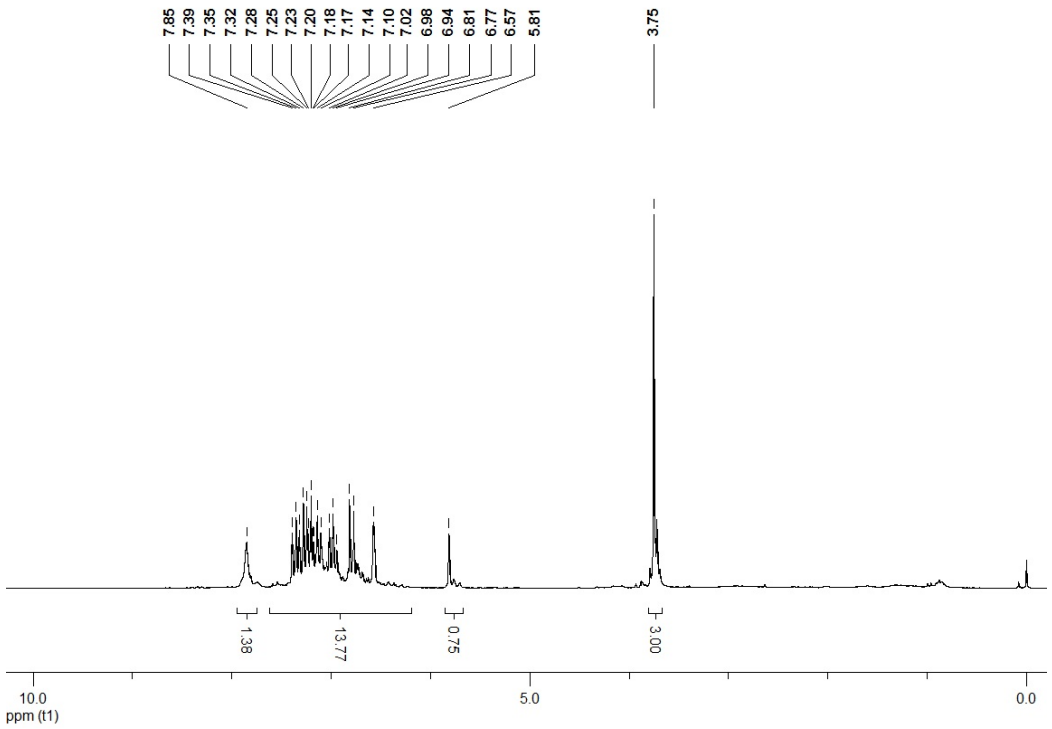
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(*p*-tolylmethylene)*bis*(1*H*-indole) (**3b**)



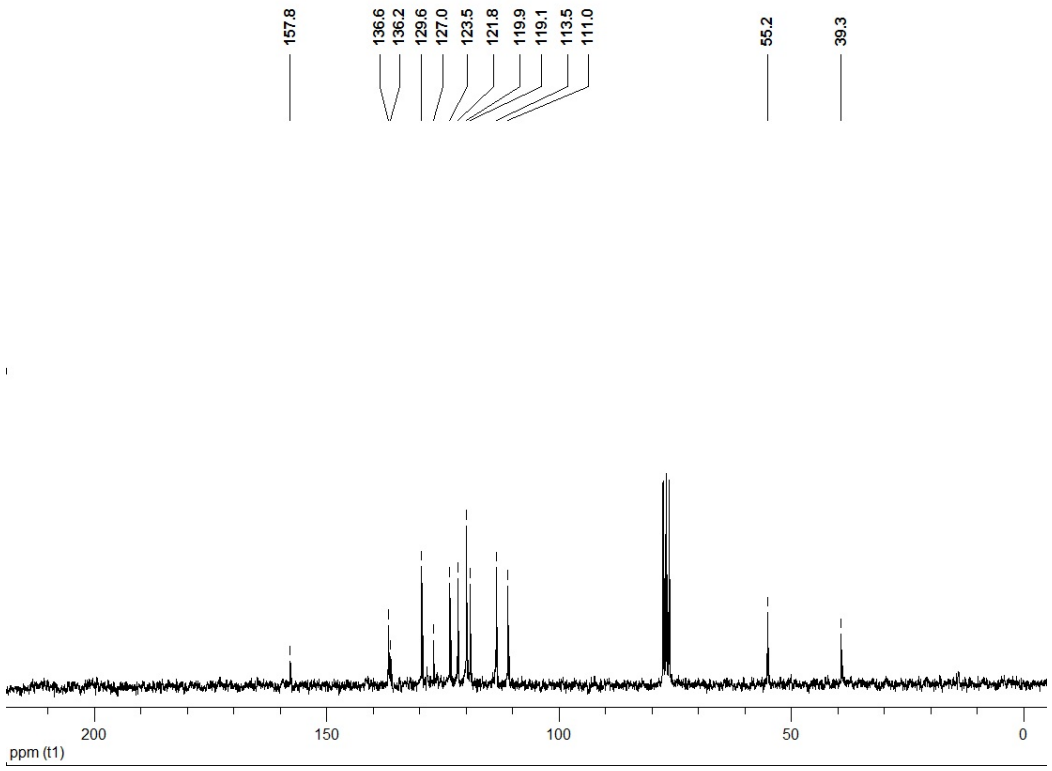
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-[(3-nitrophenyl)methylene]*bis*(1*H*-indole) (**3c**)



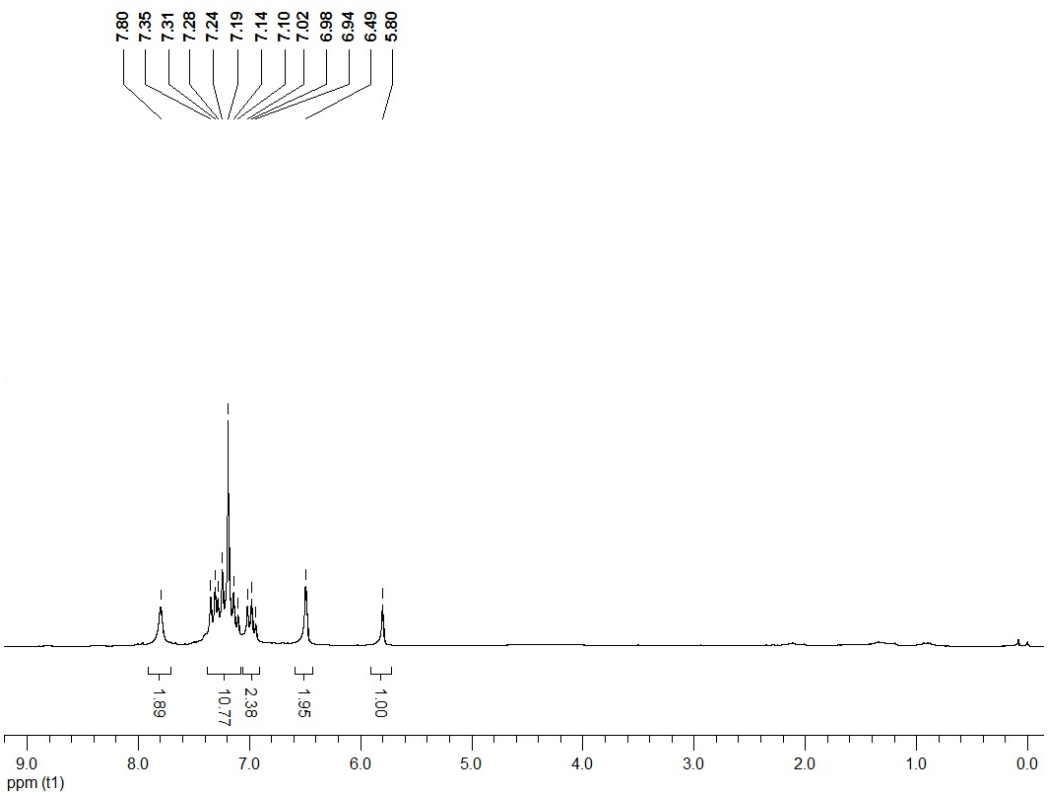
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-[(3-nitrophenyl)methylene]*bis*(1*H*-indole) (**3c**)



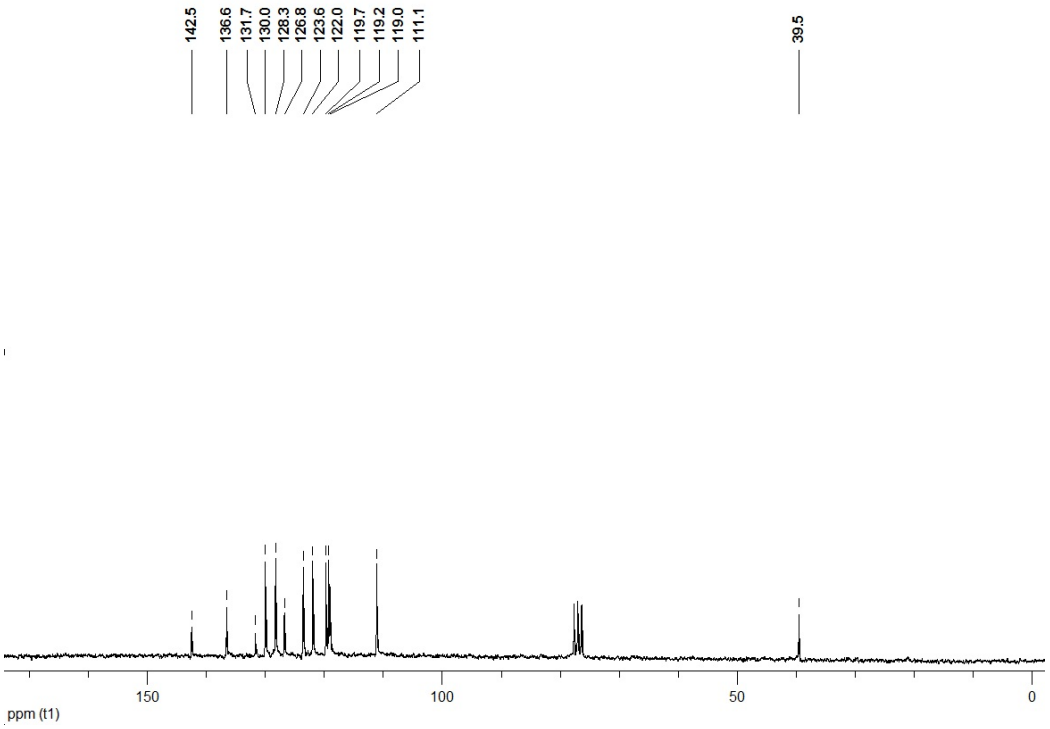
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-[(4-methoxyphenyl)methylene]*bis*(1*H*-indole) (**3d**)



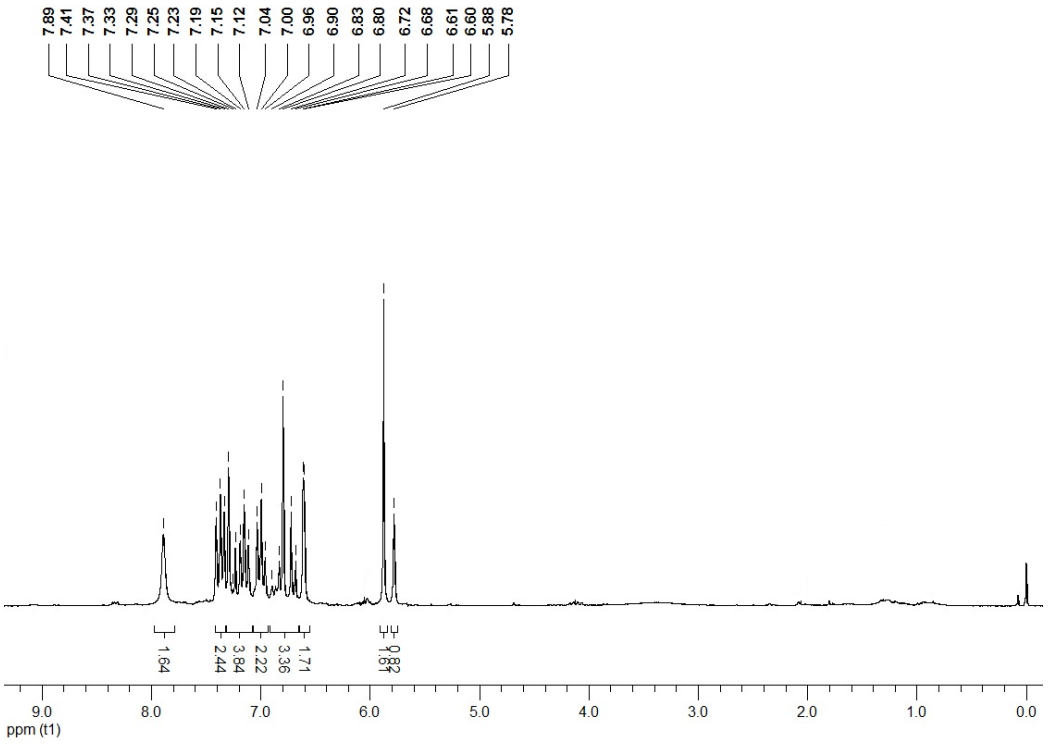
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-[(4-methoxyphenyl)methylene]*bis*(1*H*-indole) (**3d**)



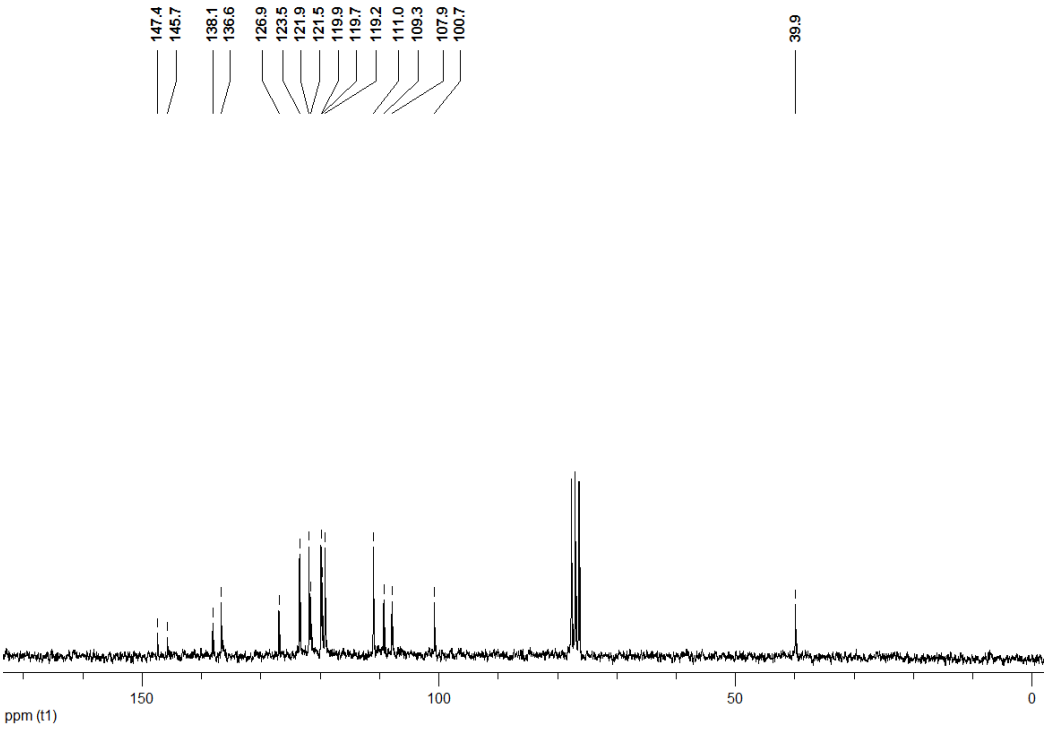
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-[(4-chlorophenyl)methylene]*bis*(1*H*-indole) (**3e**)



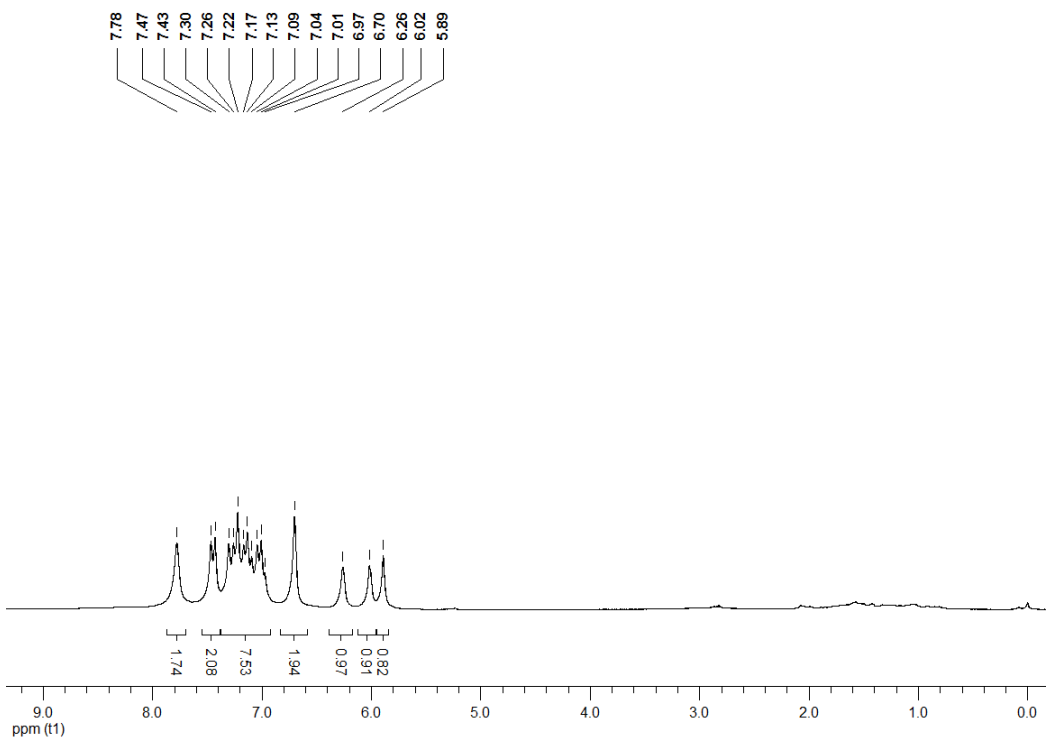
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-[(4-chlorophenyl)methylene]*bis*(1*H*-indole) (**3e**)



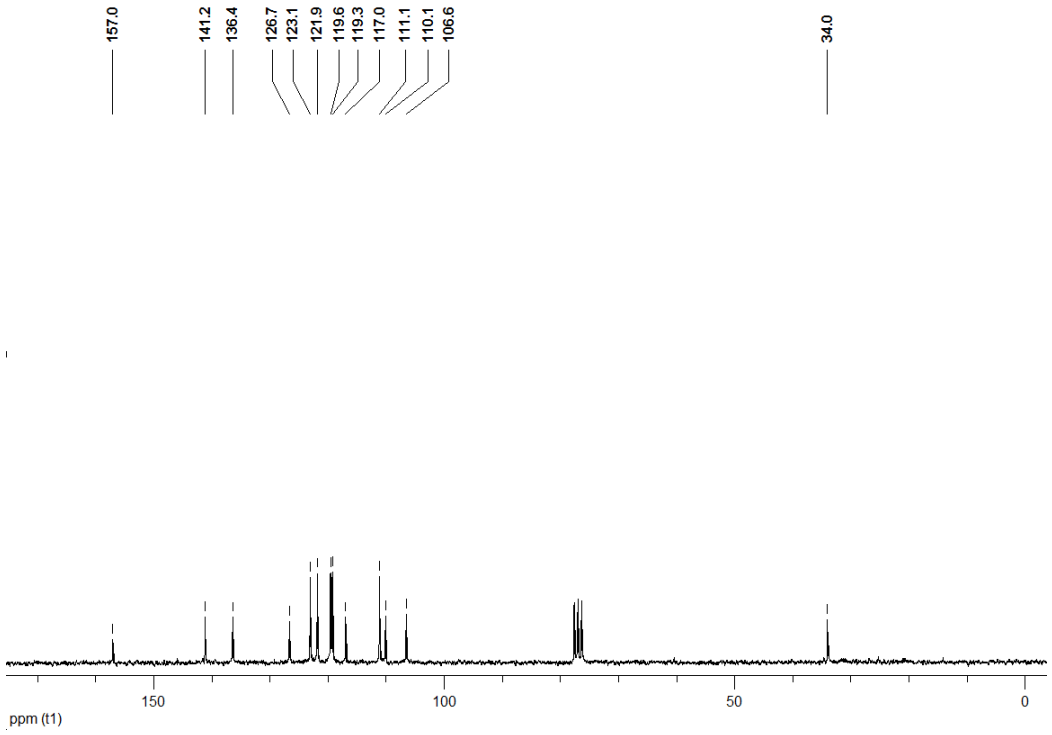
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(benzo[d][1,3]dioxol-5-ylmethylene)*bis*(1*H*-indole) (**3f**)



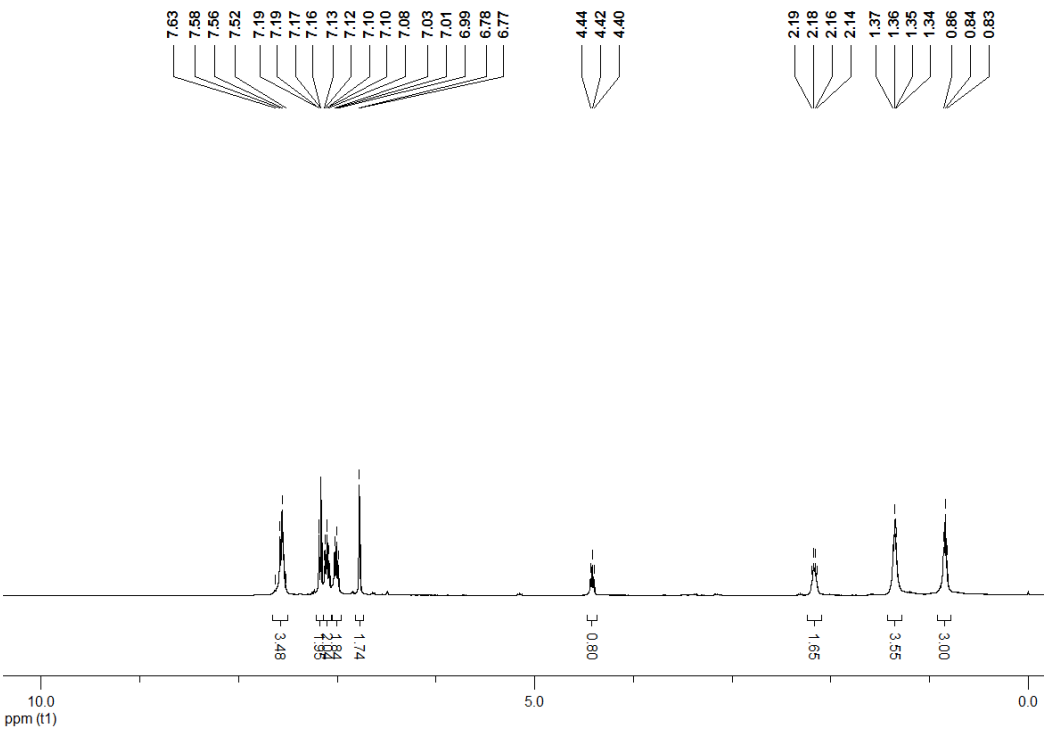
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(benzo[d][1,3]dioxol-5-ylmethylene)*bis*(1*H*-indole) (**3f**)



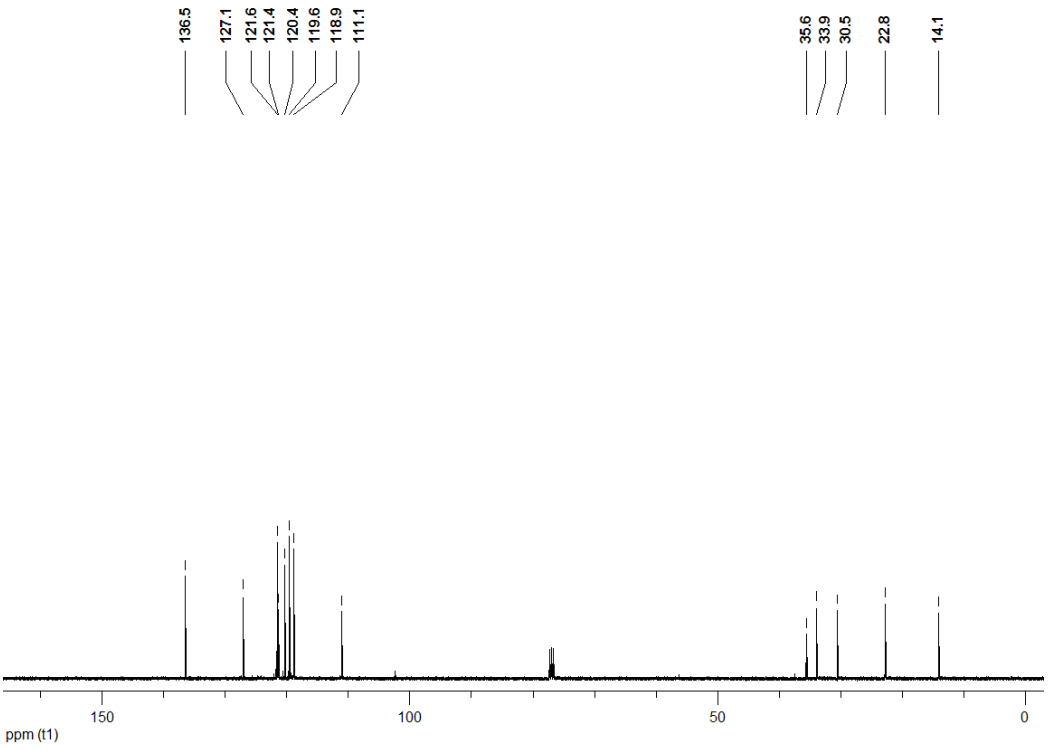
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(furan-2-ylmethylene)*bis*(1*H*-indole) (**3g**)



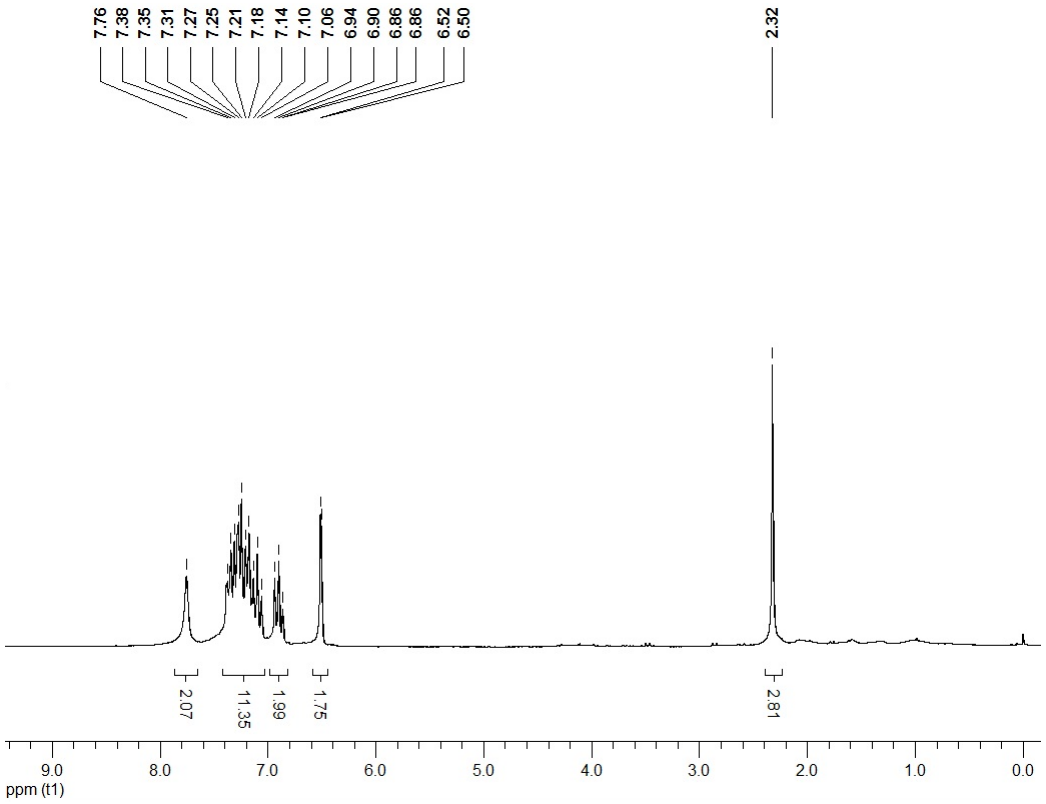
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(furan-2-ylmethylene)*bis*(1*H*-indole) (**3g**)



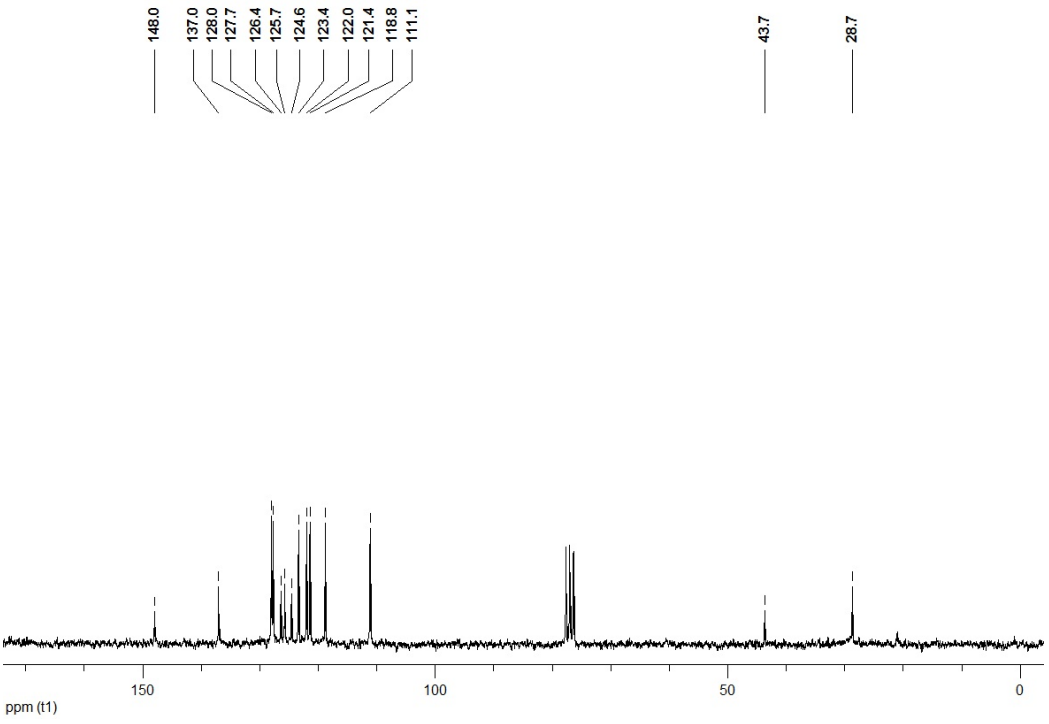
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3,3'-(pentane-1,1-diyl)*bis*(1*H*-indole) (**3h**)



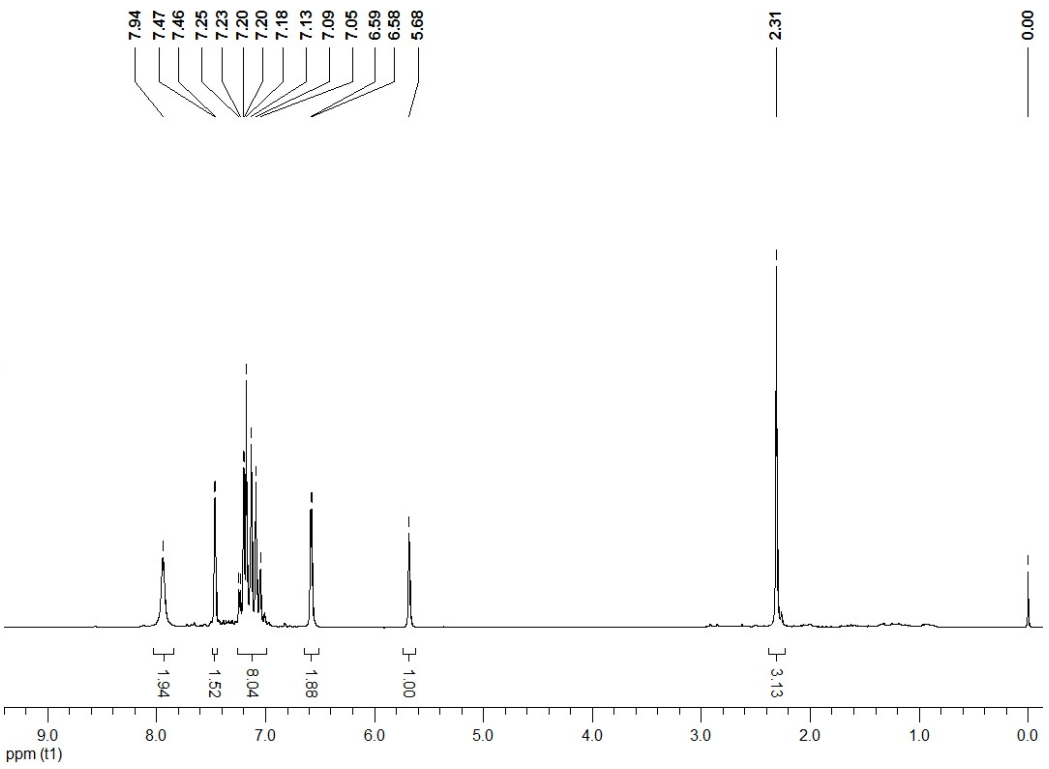
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of 3,3'-(pentane-1,1-diyl)*bis*(1*H*-indole) (**3h**)



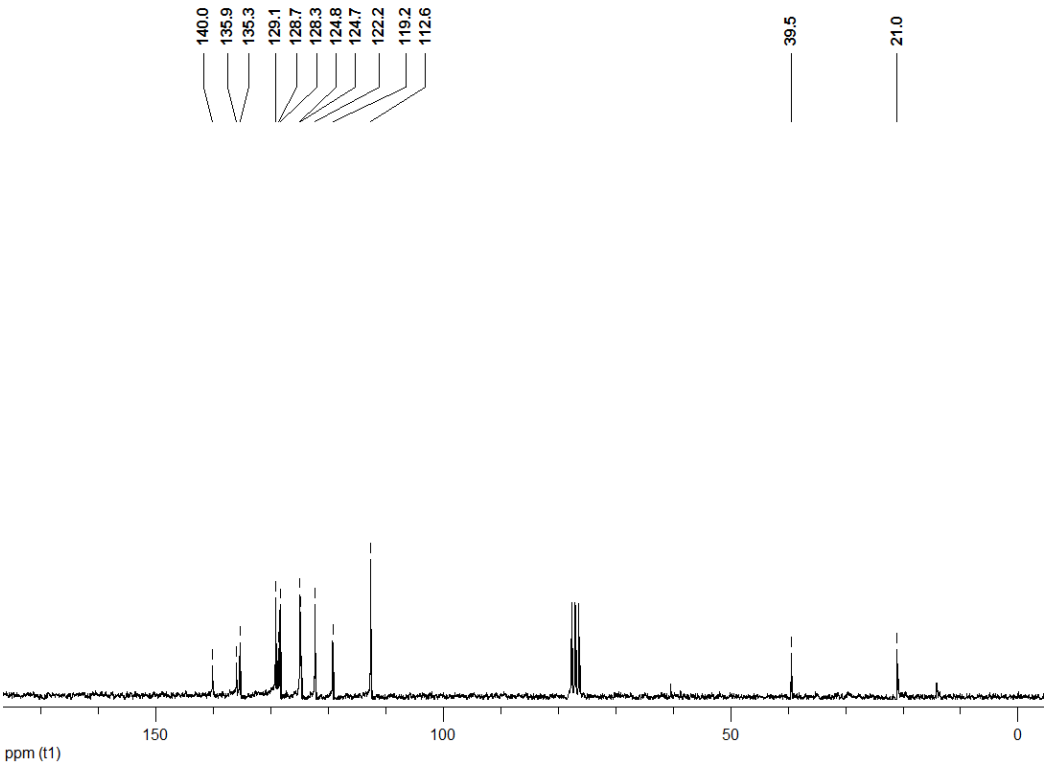
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(1-phenylethane-1,1-diyl)*bis*(1*H*-indole) (**3i**)



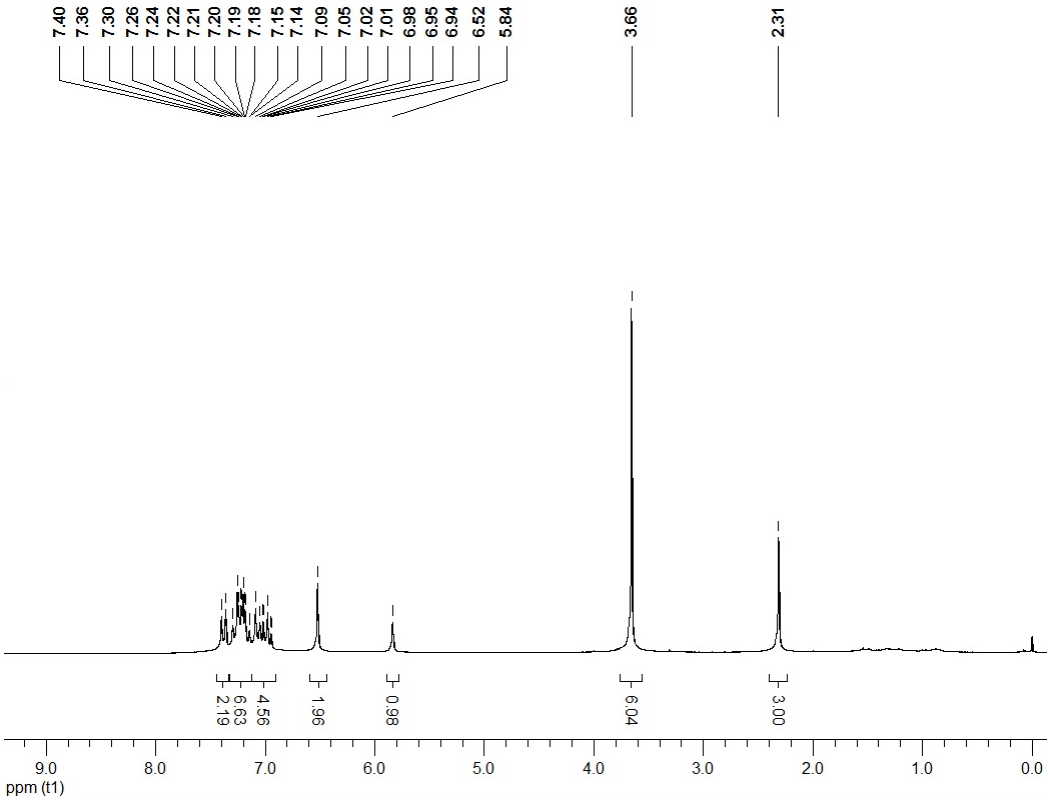
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(1-phenylethane-1,1-diyl)*bis*(1*H*-indole) (**3i**)



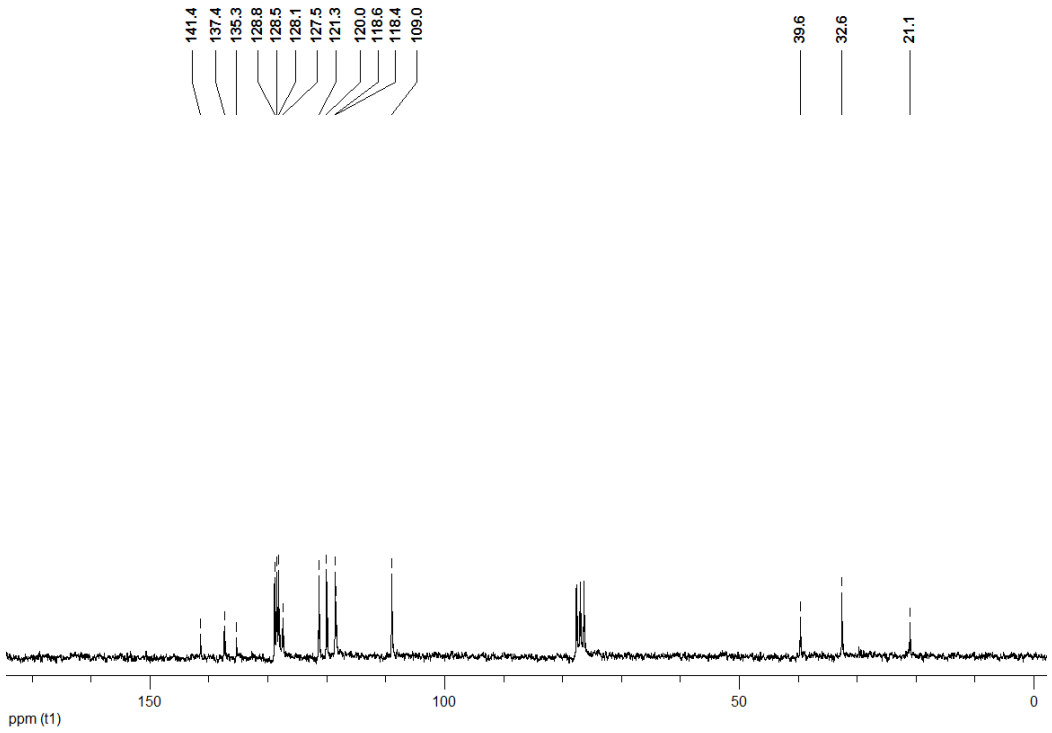
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(*p*-tolylmethylene)*bis*(5-bromo-1*H*-indole) (**3j**)



^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(p-tolylmethylene)*bis*(5-bromo-1*H*-indole) (**3j**)



^{1}H NMR (200 MHz, $CDCl_3$) spectrum of 3,3'-(*p*-tolylmethylene)*bis*(1-methyl-1*H*-indole) (**3k**)



^{13}C NMR (50 MHz, $CDCl_3$) spectrum of 3,3'-(*p*-tolylmethylene)*bis*(1-methyl-1*H*-indole) (**3k**)

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