Supplementary Material (ESI) for Chemical Communications

Supporting information for

L-Proline amide-catalyzed Direct Nitroso Aldol Reactions of α-Branched Aldehydes: the Distinct Regioselectivity from that with L-Proline

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General Information. NMR spectra were recorded on a 300-MHz spectrometer (Bruker, Fallanden, Switzerland). IR spectra were recorded on a Nicolet MX-1 spectrometer and reported in terms of frequency of absorption (cm^{-1}). Optical rotations were measured on a Perkin-Elmer 341 Polarimeter at λ = 589 nm (c g/100ml). High-resolution mass spectra were recorded on Bruker BioTOF Q. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS, and OJ columns were purchased from Daicel Chemical Industries (Hong Kong, China). Purification of reaction products was carried out with flash column chromatography using silica gel 60 (E. Merck 230-400 mesh), silica gel 60 silanized (E. Merck) and Florisil® (Wako Pure Chemical or ACROS 60-100 mesh). Analytical thin layer chromatography (TLC) was performed on E. Merck precoated (0.25 mm) silica gel 60-F254 plates. Visualization was accomplished with UV light and phosphomolybdic acid solution in ethanol by heating. Toluene was used as dried through almina in solvent line purification system. Hexane and ethyl acetate for column chromatography were distilled before use.

Materials. Nitrosobenzene was purchased from Aldrich. Other aromatic nitroso compounds were synthesized by Coleman procedure [1]. Other starting materials were purchased from Aldrich or Tokyo Chemical Industry and used directly. (*S, R, R*)-pyrolidine-2-carboxylic acid (2'-hydroxyl-1',2'-diphenyl-ethyl)-amine (**3**) was synthesized according to reference [2].

Typical procedure for the direct enantioselective α-hydroxyamination reaction of aldehyde: (entry **1,** table **2)**

To a vial equipped with a magnetic stir bar and charged with catalyst **3** (0.2 mmol) was added anhydrous toluene (2 mL) and the suspension was cooled down to -40 °C. To the suspension was added nitrosobenzene (1.0 mmol) in one portion at –40 ^{o}C. To the resulting solution was then added the appropriate aldehyde (3.0 mmol) in one portion. The resulting reaction mixture was then stirred at -40 °C for 3 days until the reaction was determined to be complete (monitored by TLC). The reaction mixture was then transferred to an ethanol suspension of $NaBH_4$ at 0 °C. After 20 minutes, the reaction was treated with saturated aqueous $NaHCO_3$, extracted with dichloromethane (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was then purified by silica gel chromatography (eluent: hexane:ethyl acetate = 7:1) and fractions concentrated in vacuo to provide the title compounds. The enantioselectivity was determined by chiral HPLC analysis.

3-Benzo[1,3]dioxol-5-yl-2-(hydroxy-phenyl-amino)-2-methyl-propan-1-ol (entry 1, table 2). Yield: 74%; white solid, m.p. 130-131^{o}C, IR (KBr), 3460, 2979, 2925, 2891, 1488, 1442, 1242, 1073, 927, 817, 762, 701, 657 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.90 (s, 3H), 2.38 (d, *J*= 13.0 Hz, 1H), 3.17 (d, *J*= 13.0 Hz, 1H), 3.48 (d, *J*=11.3 Hz, 1H), 3.58 (d, *J*=11.3 Hz, 1H), 5.90 (s, 2H), 6.57-6.68 (m, 3H), 7.17-7.32 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.56, 38.54, 65.24, 66.82, 100.75, 107.82, 111.08, 123.72, 124.87, 125.88, 128.01, 130.99, 145.99, 147.25, 148.34. HRMS (M+Na) exact mass calcd for ($C17H19N_1Na_1O4$) requires *m/z* 324.1212, found *m/z* 324.1206. $[\alpha]_D$ = + 2.01 (c = 1.64, CH_3OH). Enantiomeric excess: 59%, determined by HPLC (Daicel Chiralpak OJ-H, *i*- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. major enantiomer, t_R 17.37 min and minor enantiomer, t_R 22.97 min.

3-Benzo[1,3]dioxol-5-yl-2-[(4-chloro-phenyl)-hydroxy-amino]-2-methyl-propan-1-ol (entry 2, table 2). Yield: 63%; white powder, m.p. 68-69 ^{o}C, IR (KBr), 3410, 2973, 2926, 2890, 1487, 1440, 1243, 1091, 1038, 1010, 928, 835, 818, 717, 668 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.89 (s, 3H), 2.39 (d, *J*=13.0 Hz, 1H), 3.13 (d, *J*=13.0 Hz, 1H), 3.48 (d, *J*=11.3 Hz, 1H), 3.57 (d, *J*=11.3 Hz, 1H), 5.91 (s, 2H), 6.58-6.70 (m, 3H), 7.22-7.29 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.42, 38.38, 65.16, 66.96, 100.80, 107.88, 110.95, 123.65, 126.06, 128.05, 130.56, 131.19, 146.07, 146.79, 147.29. HRMS (M+Na) exact mass calcd for ($C_{17}H_{18}Cl_1N_1Na_1O_4$) requires *m/z* 358.0822, found *m/z* 358.0817. $[\alpha]_D$= + 6.99 (c = 2.28, CH_3OH). Enantiomeric excess: 63%, determined by

HPLC (Daicel Chiralpak OJ-H, *i*- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. major enantiomer, t_R 15.10 min and Minor enantiomer, t_R 19.45 min.

3-Benzo[1,3]dioxol-5-yl-2-[(2-chloro-phenyl)-hydroxy-amino]-2-methyl-propan-1-ol (entry 3, table 2). Yield: 71%; white powder, m.p. 67-68 ^{o}C, IR (KBr), 3371, 2972, 2933, 2887, 1488, 1440, 1242, 1037, 929, 816, 763, 738, 678 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.03(s, 3H), 3.33 (d, *J*=11.9 Hz, 1H), 3.60(s, br, 3H), 5.90 (s, 2H), 6.59-7.72 (m, 7H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 15.46, 37.25, 64.52, 67.90, 100.62, 107.67, 110.96, 123.65, 127.12, 127.60, 128.35, 129,53, 130.32, 131.78, 145.22, 145.86, 147.05. HRMS (M+Na) exact mass calcd for ($C_{17}H_{18}Cl_1N_1Na_1O_4$) requires *m/z* 358.0822, found *m/z* 358.0817. $[\alpha]_D$= -5.25 (c = 1.58, CH_3OH) Enantiomeric excess: 59%, determined by HPLC (Daicel Chiralpak OJ-H, *i*- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 10.98 min and Minor enantiomer, t_R 19.13 min.

3-Benzo[1,3]dioxol-5-yl-2-[(2-bromo-phenyl)-hydroxy-amino]-2-methyl-propan-1-ol (entry 4, table 2). Yield: 76%; white powder, m.p. 86-87 ^{o}C, IR (KBr), 3428, 2972, 2931, 2887, 1488, 1440, 1243, 1037, 929, 815, 764, 733, 663 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.88(s, 3H), 3.36-3.60(s, br, 3H), 3.98(s, 1H), 5.89(s, 2H), 6.56-6.66(m, 3H), 7.12-7.72(m, 4H), ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 14.09, 37.72, 64.34, 68.10,100.69, 107.75, 111.03, 123.27, 123.72, 127.98, 128.27, 128.55, 130.36, 132.71, 145.97, 146.37, 147.15. HRMS (M+Na) exact mass calcd for ($C_{17}H_{18}Br_1N_1Na_1O_4$) requires *m/z* 402.0317, found *m/z* 402.0311. $[\alpha]_D$= -4.73 (c = 1.12, CH_3OH). Enantiomeric excess: 64%, determined by HPLC (Daicel Chiralpak OJ-H, *i*- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 11.25 min and Minor enantiomer, t_R 17.96 min.

3-Benzo[1,3]dioxol-5-yl-2-[(3-bromo-phenyl)-hydroxy-amino]-2-methyl-propan-1-ol (entry 5, table 2). Yield: 60%; white powder, m.p. 74-75 ^{o}C, IR (KBr), 3381, 2975, 2930, 2887, 1488, 1440, 1242, 1038, 928, 816, 786, 732, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.95 (s, 3H), 2.42 (d, *J*=13.0 Hz, 1H), 3.17 (d, *J*=13.0 Hz, 1H), 3.54 (d, *J*=11.3 Hz, 1H), 3.61 (d, *J*=11.3 Hz, 1H), 5.94 (s, 2H), 6.60-6.73 (m, 3H), 7.17-7.53 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.55, 38.34, 65.21, 67.13, 100.79, 107.79, 110.98, 121.72, 123.41, 123.68, 127.72, 128.76, 129.11, 130.53, 146.07, 147.29, 149.81. HRMS (M+Na) exact mass calcd for ($C_{17}H_{18}Br_1N_1Na_1O_4$) requires *m/z* 402.0317, found *m/z* 402.0311. $[\alpha]_D$= + 2.24 (c = 3.35, CH_3OH). Enantiomeric excess: 55%,

determined by HPLC (Daicel Chiralpak OJ-H, *i*- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 14.47 min and Minor enantiomer, t_R 27.85 min.

3-Benzo[1,3]dioxol-5-yl-2-[(4-bromo-phenyl)-hydroxy-amino]-2-methyl-propan-1-ol (entry 6, table 2). Yield: 61%; white powder, m.p. 80-81 ^{o}C, IR (KBr), 3353, 2973, 2929, 2889, 1488, 1243, 1039, 1007, 928, 832, 711, 661 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.93 (s, 3H), 2.41 (d, *J*= 13.0 Hz, 1H), 3.16 (d, *J*= 13.0 Hz, 1H), 3.52 (d, *J*= 11.3 Hz, 1H), 3.60 (d, *J*= 11.3 Hz, 1H), 5,94 (s, 2H), 6.60-6.73 (m, 3H), 7.20-7.47 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.42, 38.43, 65.10, 67.15, 100.82, 107.90, 110.99, 119.21, 123.69, 126.42, 130.54, 131.09, 146.11, 147.24, 147.33. HRMS (M+Na) exact mass calcd for ($C_{17}H_{18}Br_1N_1Na_1O_4$) requires *m/z* 402.0317, found *m/z* 402.0311. $[\alpha]_D$= + 6.36 (c = 1.65, CH_3OH). Enantiomeric excess: 61%, determined by HPLC (Daicel Chiralpak OJ-H, *i*- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 16.39 min and Minor enantiomer, t_R 21.53 min.

3-Benzo[1,3]dioxol-5-yl-2-(hydroxy-p-tolyl-amino)-2-methyl-propan-1-ol (entry 7, table 2). Yield: 66%; white powder, m.p. 158-160 ^{o}C, IR (KBr), 3530, 3293, 2983, 2920, 1501, 1486, 1440, 1243, 1035, 924, 833, 814, 786, 727, 686, 595 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.91 (s, 3H), 2.35 (s, 3H), 2.41 (d, *J*=12.9 Hz, 1H), 3.16 (d, *J*=12.9 Hz, 1H), 3.46 (d, *J*=11.3 Hz, 1H), 3.59 (d, *J*=11.3 Hz, 1H), 5.90 (s, 2H), 6.60-6.70 (m, 3H), 7.12-7.26 (m, 4H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.38, 20.83, 38.39, 65.12, 66.71, 100.67, 107.73, 111.04, 123.67, 124.73, 128.56, 130.99, 135.51, 145.53, 145.87, 147.15. HRMS (M+Na) exact mass calcd for ($C_{18}H_{21}N_1Na_1O_4$) requires *m/z* 338.1368, found *m/z* 338.1363. $[\alpha]_D$= + 8.67 (c = 1.13, CH_3OH). Enantiomeric excess: 59%, determined by HPLC (Daicel Chiralpak OJ-H, i- PrOH/hexane 10:90), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 14.33 min and Minor enantiomer, t_R 18.74 min.

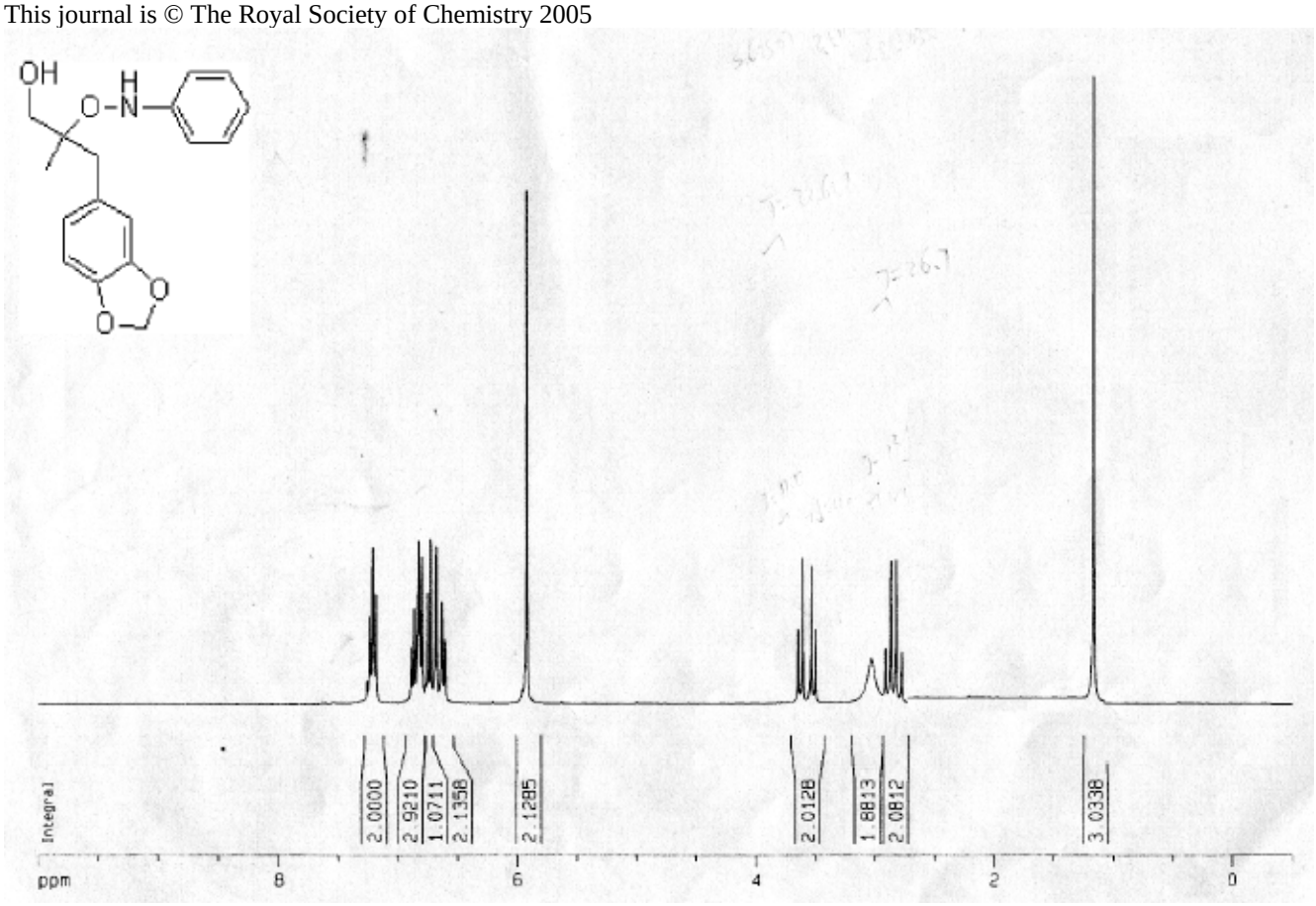
2-(Hydroxy-phenyl-amino)-2-methyl-butan-1-ol (entry 2, table 3). Yield: 53%; colourless oil, IR (film), 3323, 2940, 2881, 1595, 1486, 1377, 1044, 916, 770, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.80 (t, *J*= 7.5 Hz, 3H), 0.94 (s, 3H), 1.21-1.28 (m, 1H), 1.70-1.77 (m, 1H), 3.57 (d, *J*= 11.5 Hz, 1H), 3.69 (d, *J*= 11.5 Hz, 1H), 7.11-7.25 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 8.34, 16.58, 25.74, 65.55, 66.32, 124.58, 125.41, 127.63, 148.32. HRMS (M+Na) exact mass calcd for ($C_{11}H_{17}N_1Na_1O_2$) requires *m/z* 218.1157, found *m/z* 218.1151. $[\alpha]_D$= - 3.05 (c = 1.87, CH_3OH). Enantiomeric excess: 46%, determined by HPLC (Daicel Chiralpak AS-H, *i*- PrOH/hexane 5:95), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 9.98 min and Minor

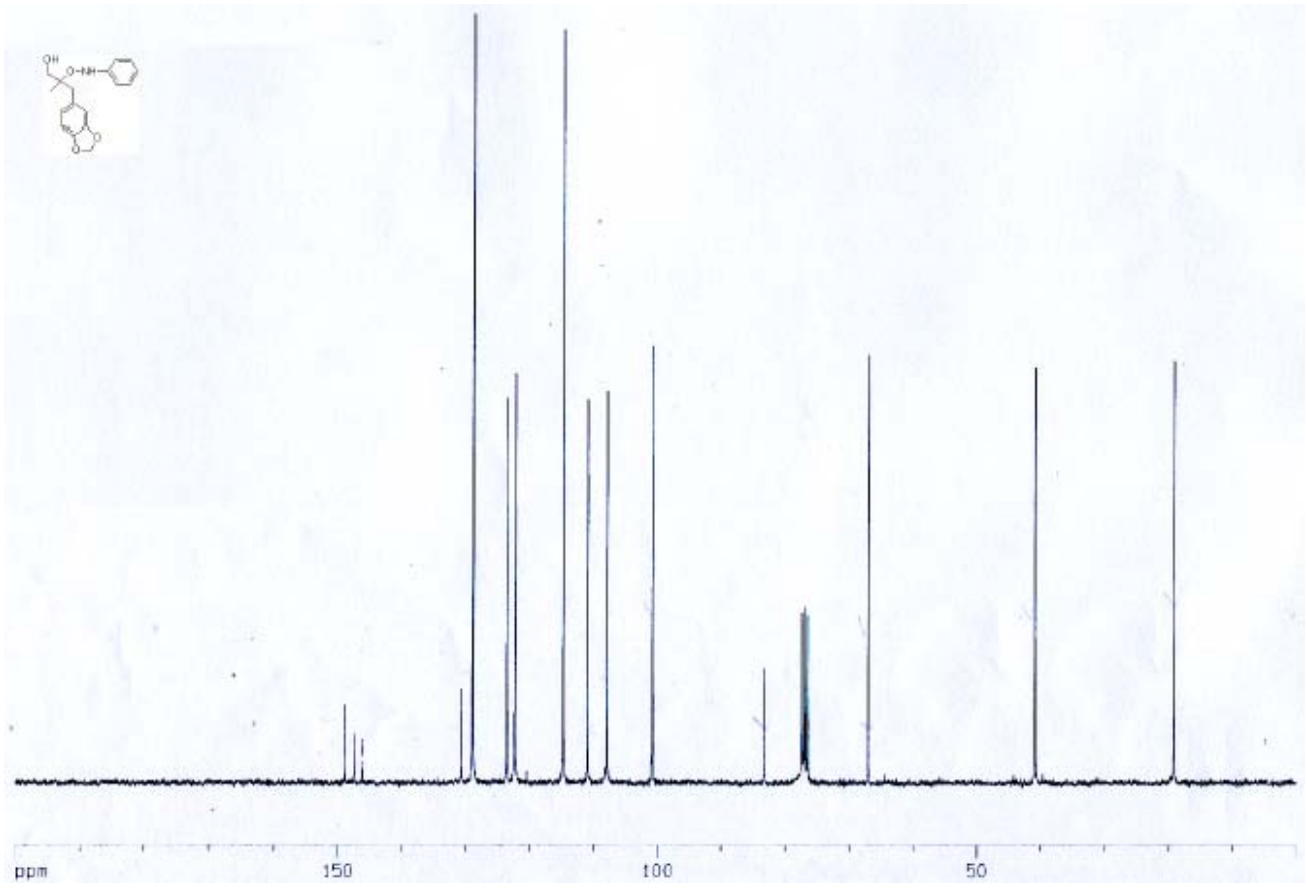
enantiomer, t_R 8.88 min.

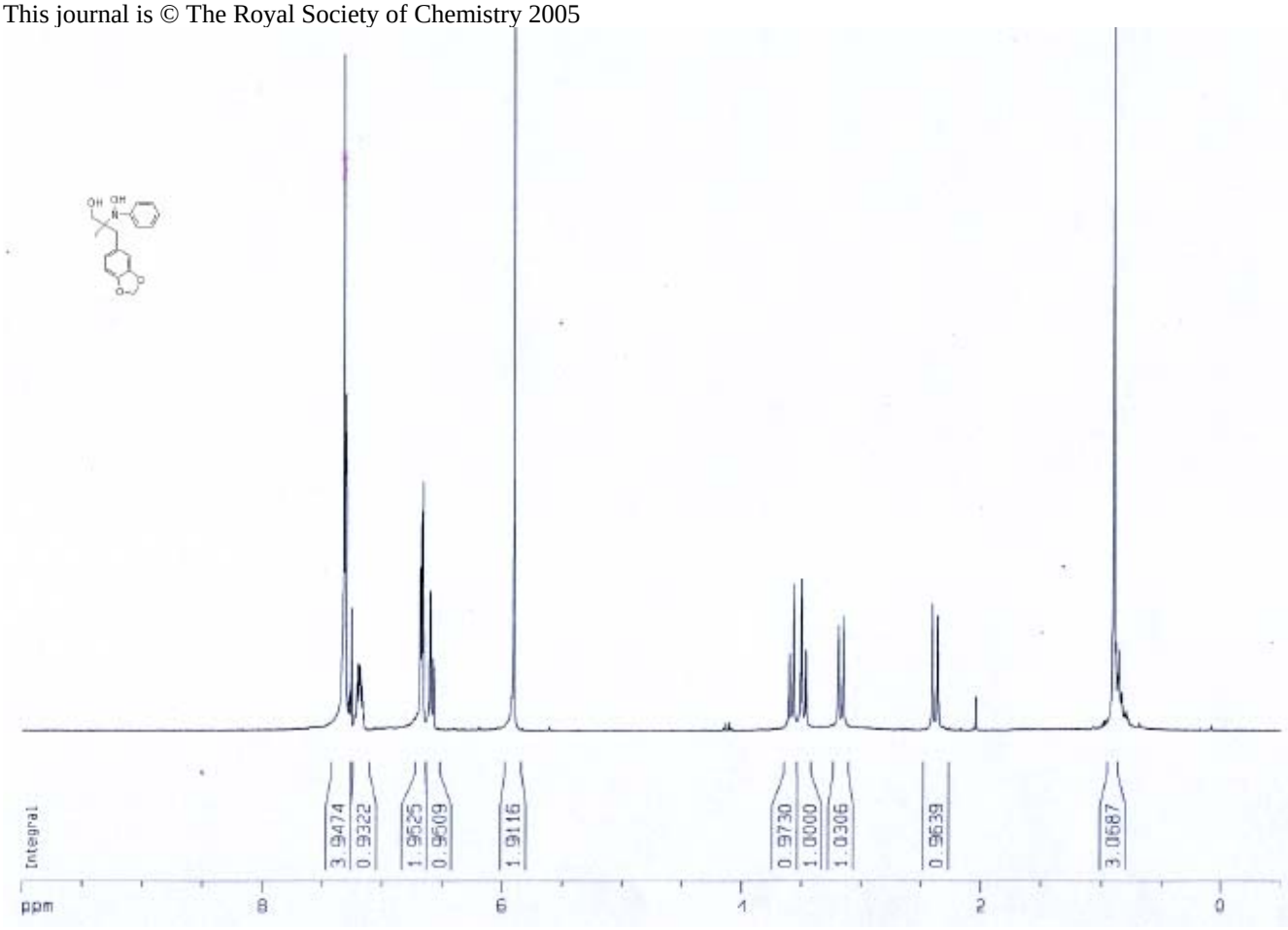
2-(Hydroxy-phenyl-amino)-2-methyl-pentan-1-ol (entry 3, table 3). Yield: 61%; colourless oil, IR (film), 3323, 2958, 2929, 2872, 1596, 1487, 1377, 1052, 1026, 770, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.82 (t, *J*=6.8 Hz, 3H), 0.95 (s, 3H), 1.13-1.30 (m, 4H), 3,57 (d, *J*=11.3 Hz, 1H), 3.67 (d, *J*=11.3 Hz, 1H), 7.12-7.54(m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 14.60, 17.19, 17.48, 35.52, 66.10, 66.19, 124.55, 125.44, 127.66, 148.31. HRMS (M+Na) exact mass calcd for ($C_{12}H_{19}N_1Na_1O_2$) requires *m/z* 232.1313, found *m/z* 232.1308. $[\alpha]_D$= - 5.69 (c = 3.35, CH_3OH). Enantiomeric excess: 46%, determined by HPLC (Daicel Chiralpak AS-H, *i*- PrOH/hexane 5:95), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 8.45 min and Minor enantiomer, t_R 7.98 min.

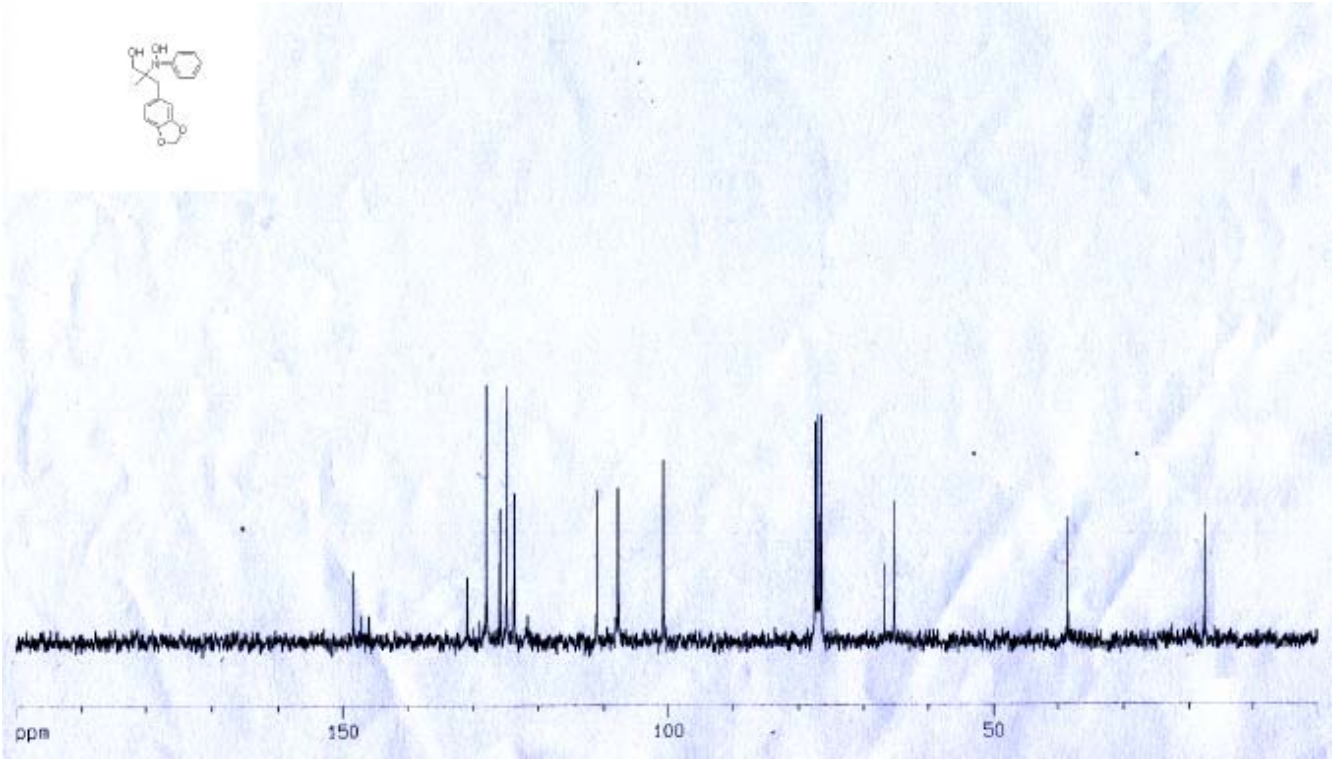
3-(4-tert-Butyl-phenyl)-2-(hydroxy-phenyl-amino)-2-methyl-propan-1-ol (entry 4, table 3). Yield: 69%; white powder, m.p. 163-165 ^oC, IR (KBr), 3448, 2956, 2923, 1486, 1363, 1201, 1054, 835, 769, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.93 (s, 3H), 1.28 (s, 9H), 2.47 (d, *J*=12.8 Hz, 1H), 3.21 (d, *J*=12.8 Hz, 1H) 3.52 (q, *J*=11.4 Hz, 1H), 3.57 (d, *J*=11.4 Hz, 1H), 6.29 (s, 1H), 7.06-7.36 (m, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.55, 31.33, 34.31, 38.32, 65.28, 66.90, 124.89, 125.84, 127.99, 130.40, 134.18, 148.36, 149.05. HRMS (M+Na) exact mass calcd for ($C_{20}H_{21}N_1Na_1O_2$) requires *m/z* 336.1939, found *m/z* 336.1934. $[\alpha]_D$= + 7.42 (c = 1.28, CH_3OH). Enantiomeric excess: 59%, determined by HPLC (Daicel Chiralpak AD, *i*- PrOH/hexane 5:95), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 10.87 min and Minor enantiomer, t_R 15.15 min.

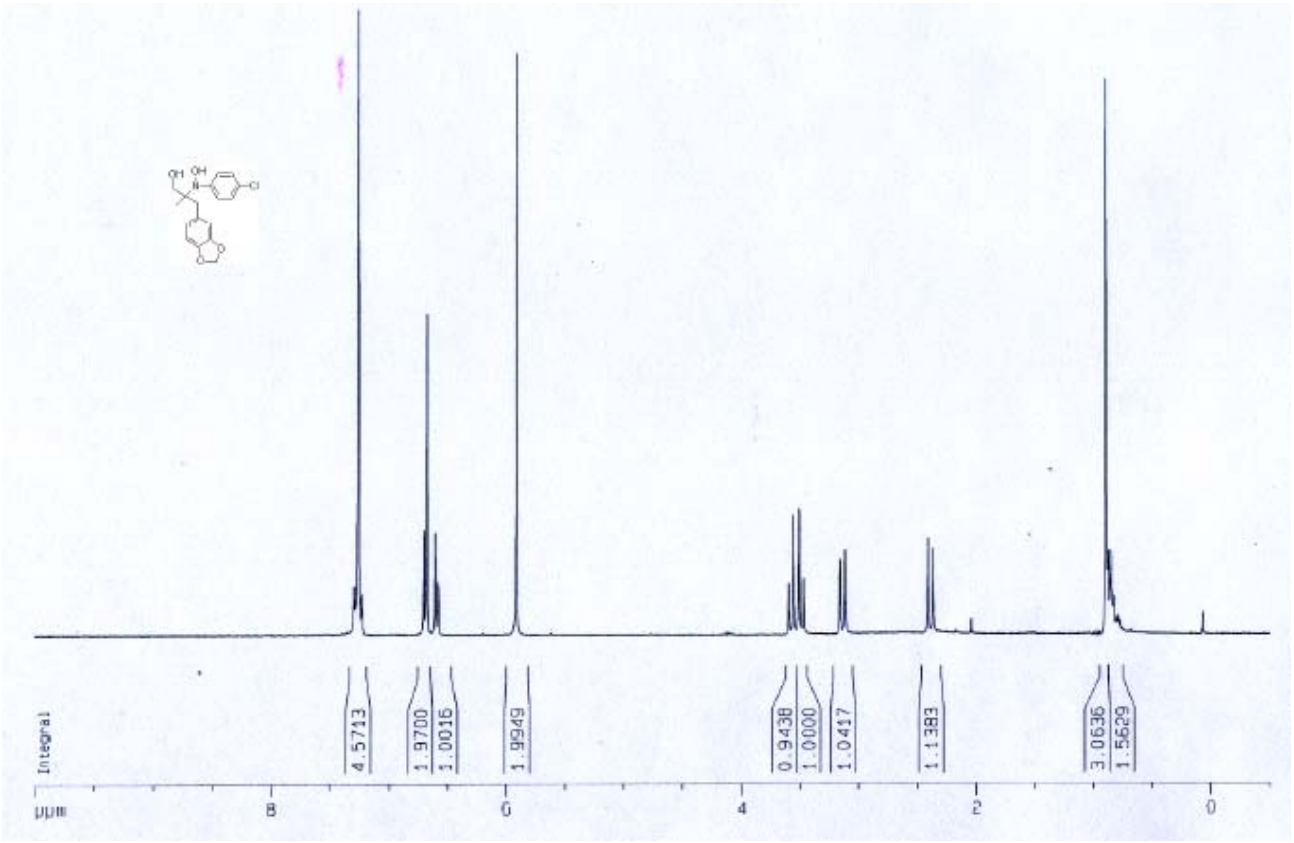
2-(Hydroxy-phenyl-amino)-3-(4-isopropyl-phenyl)-2-methyl-propan-1-ol (entry 5, table 3). yield: 71%; white powder, m.p. 126-127 ^oC, IR (KBr), 3447, 2956, 2423, 2869, 1487, 1471, 1052, 918, 837, 771, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.92 (s, 3H), 1.22 (d, *J*=6.2 Hz, 6H), 2.46 (d, *J*=12.8 Hz, 1H), 2.80-2.90 (m, 1H), 3.20 (d, *J*=12.8 Hz, 1H), 3.51 (d, *J*=11.4 Hz, 1H), 3.57 (d, *J*=11.4 Hz, 1H), 6.21 (s, 1H), 7.08-7.36 (m, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) 17.53, 23.96, 33.61, 38.44, 65.27, 66.89, 124.89, 125.85, 126.03, 127.99, 130.65, 134.55, 146.78, 148.38. HRMS (M+Na) exact mass calcd for ($C_{19}H_{25}N_1Na_1O_2$) requires *m/z* 322.1783, found *m/z* 322.1778. $[\alpha]_D$= + 4.41 (c = 1.86, CH_3OH). Enantiomeric excess: 46%, determined by HPLC (Daicel Chiralpak AD, *i*- PrOH/hexane 5:95), UV 254 nm, flow rate 1.0 ml/min. Major enantiomer, t_R 13.15 min and Minor enantiomer, t_R 17.15 min.

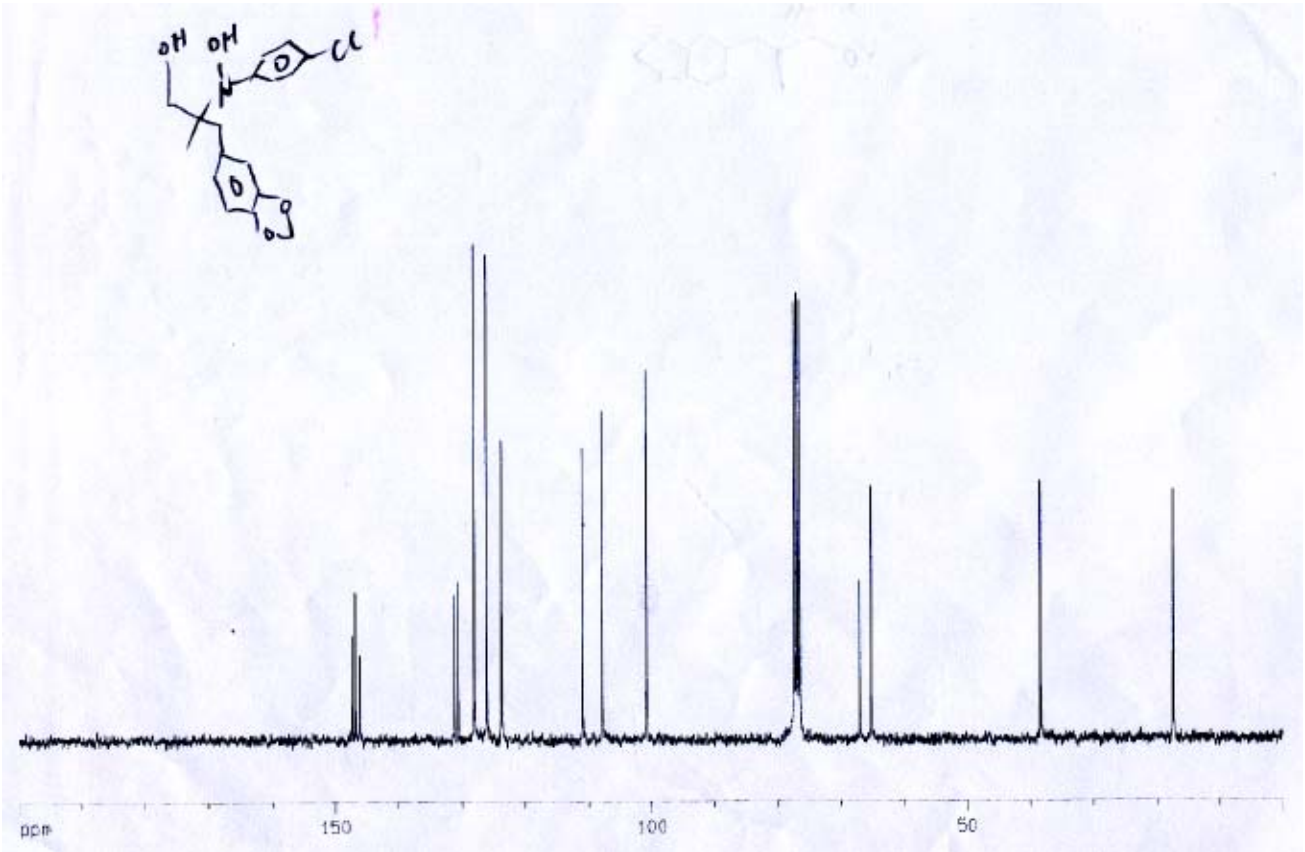


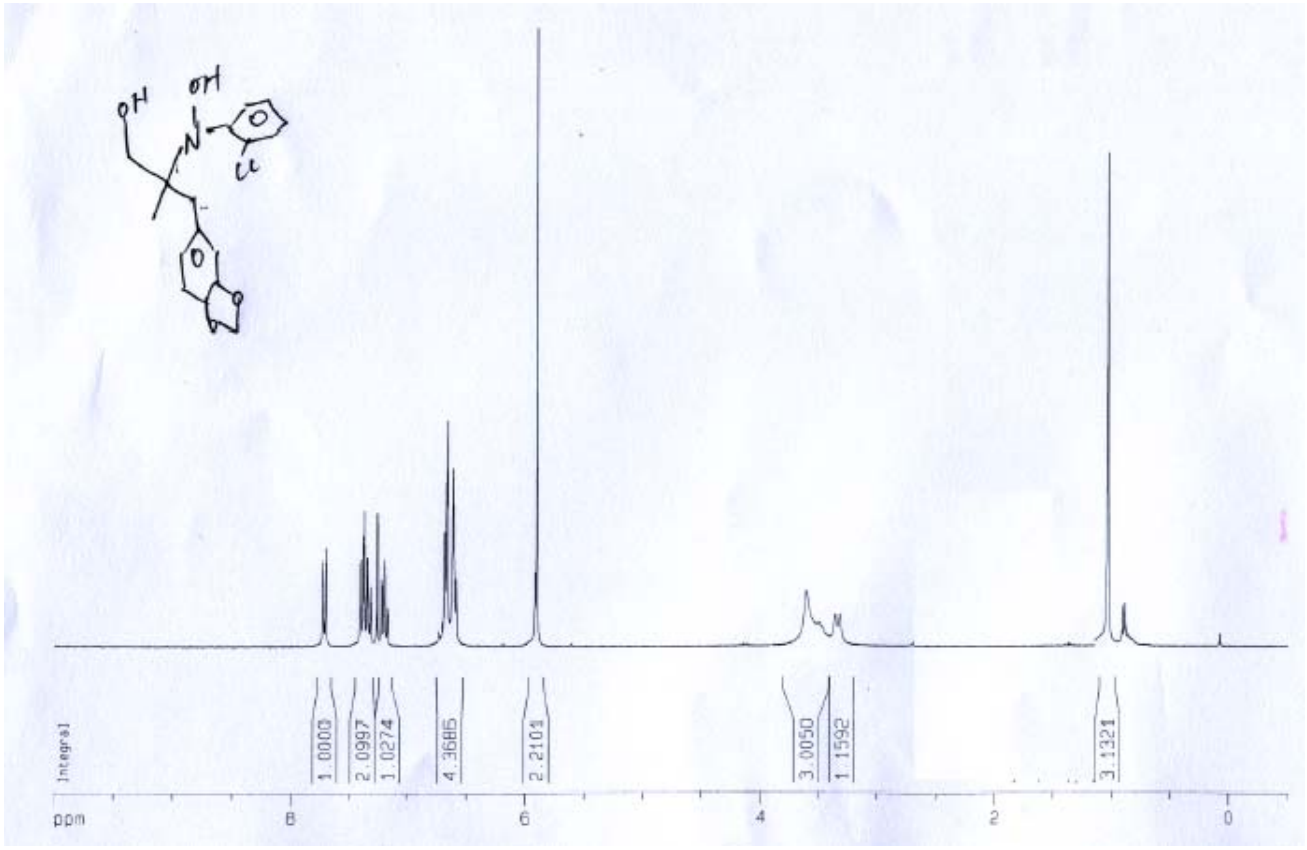


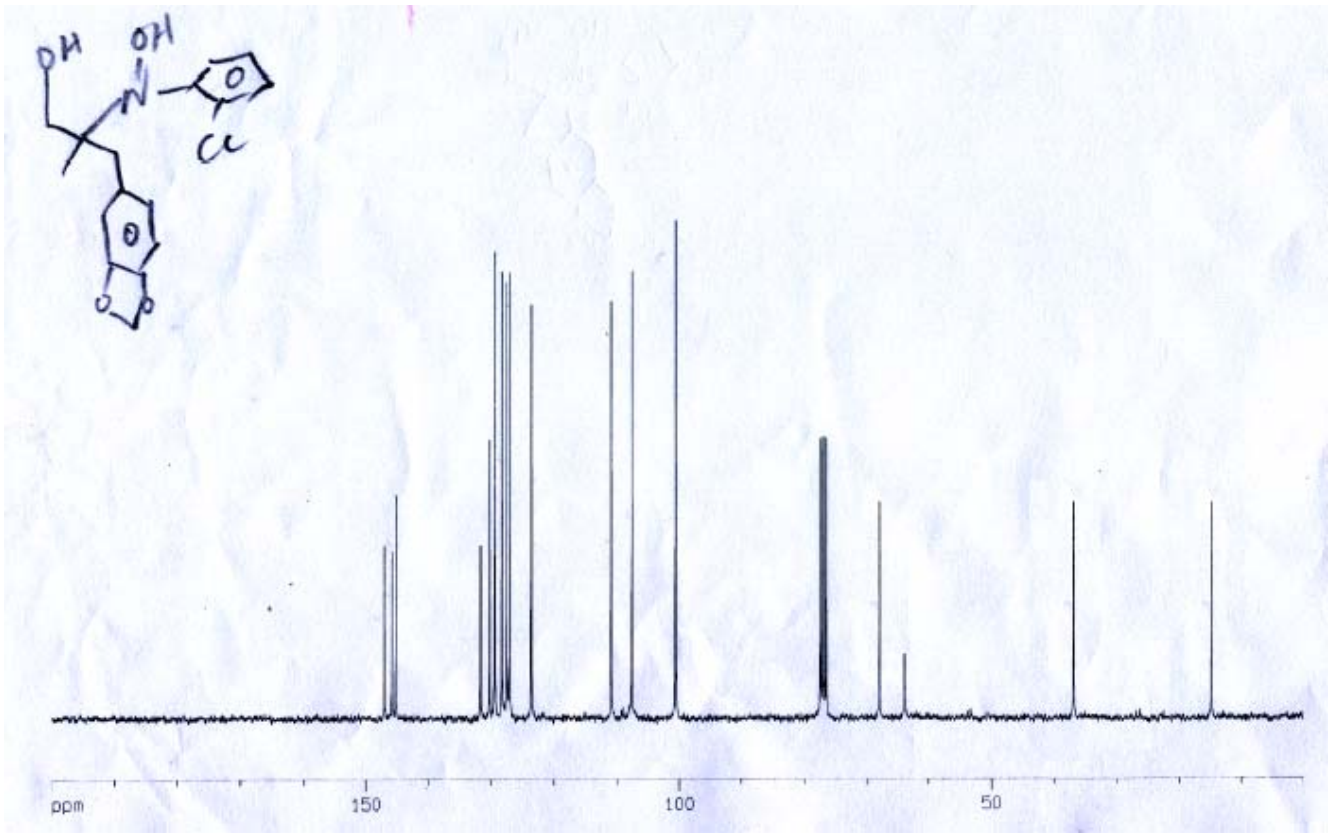


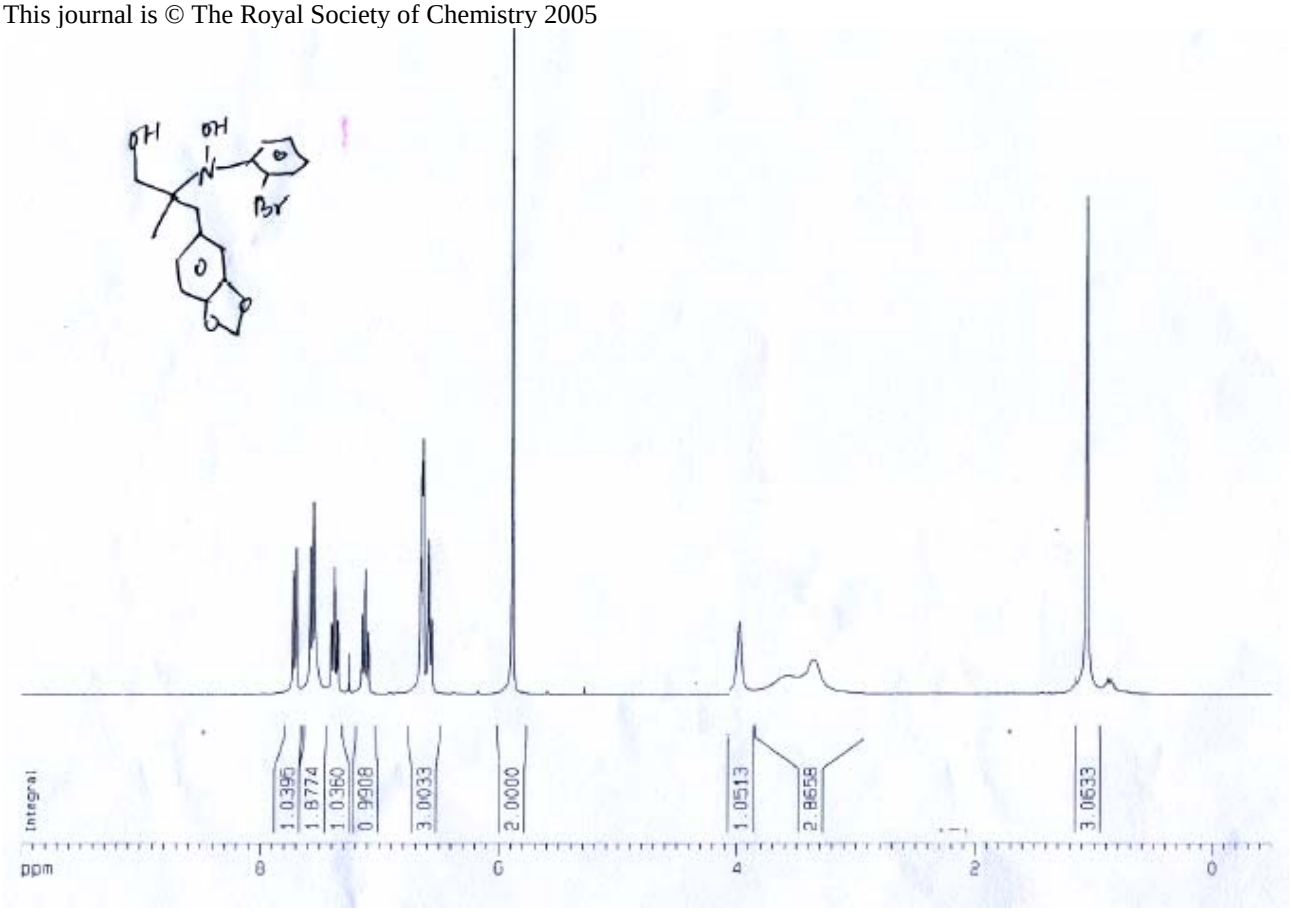


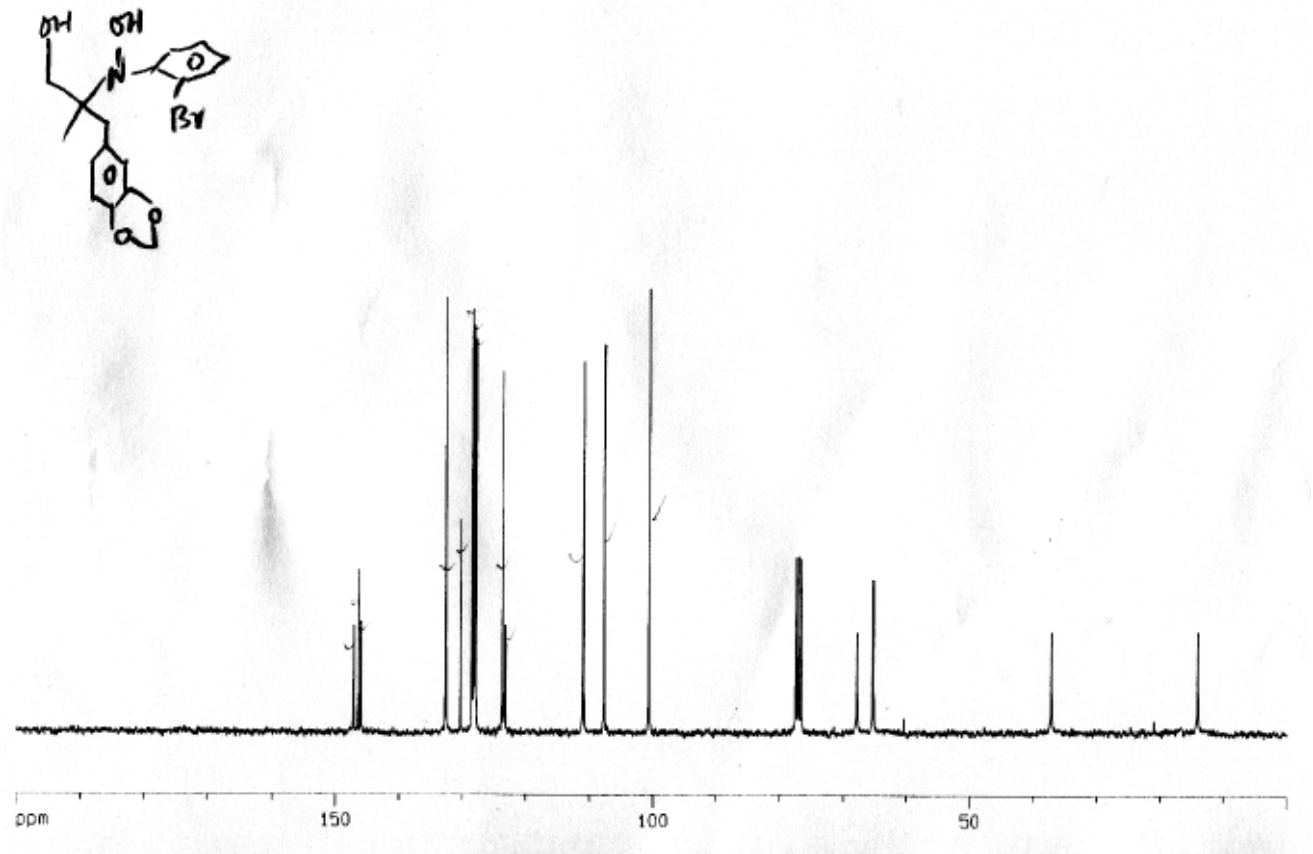


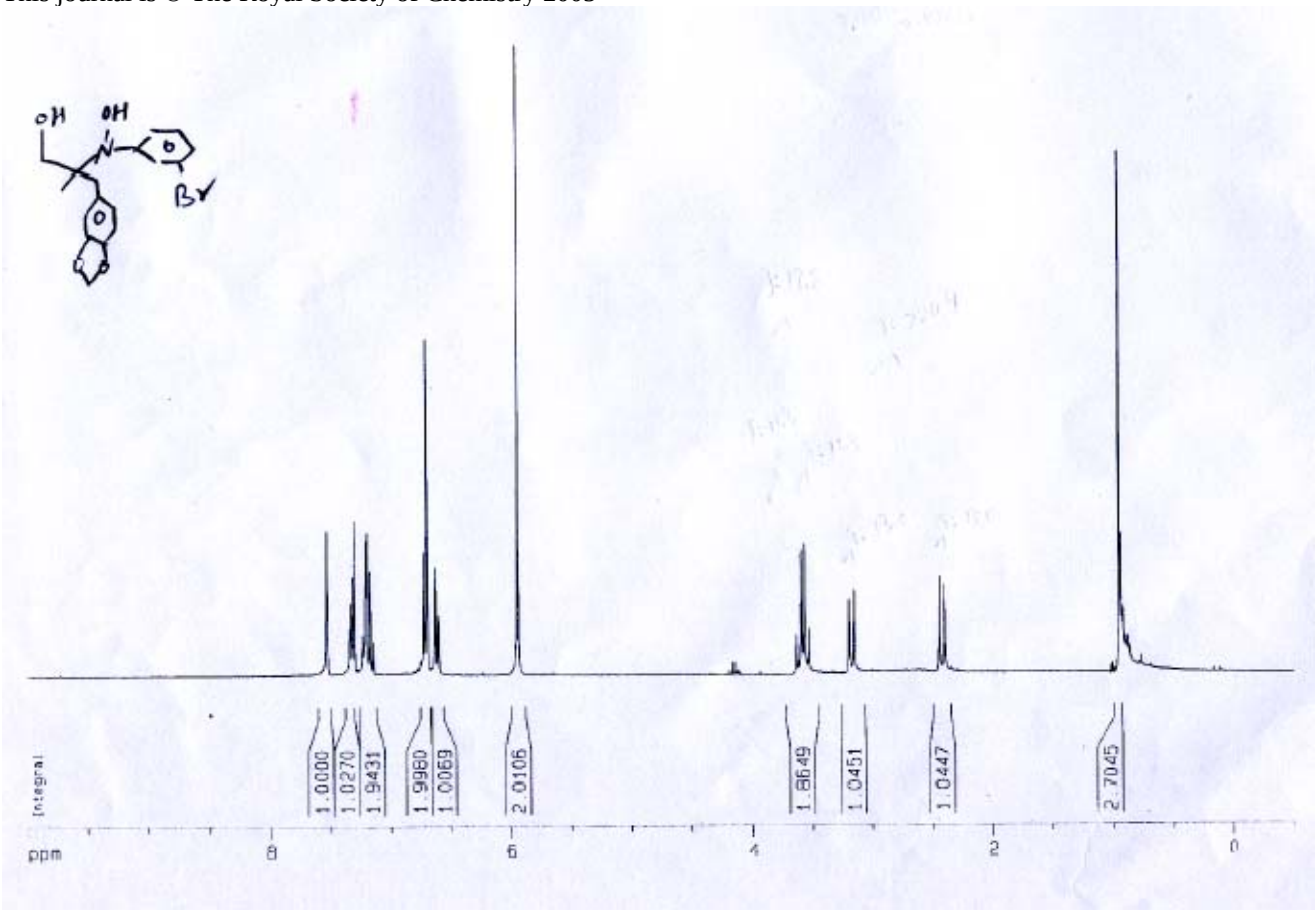


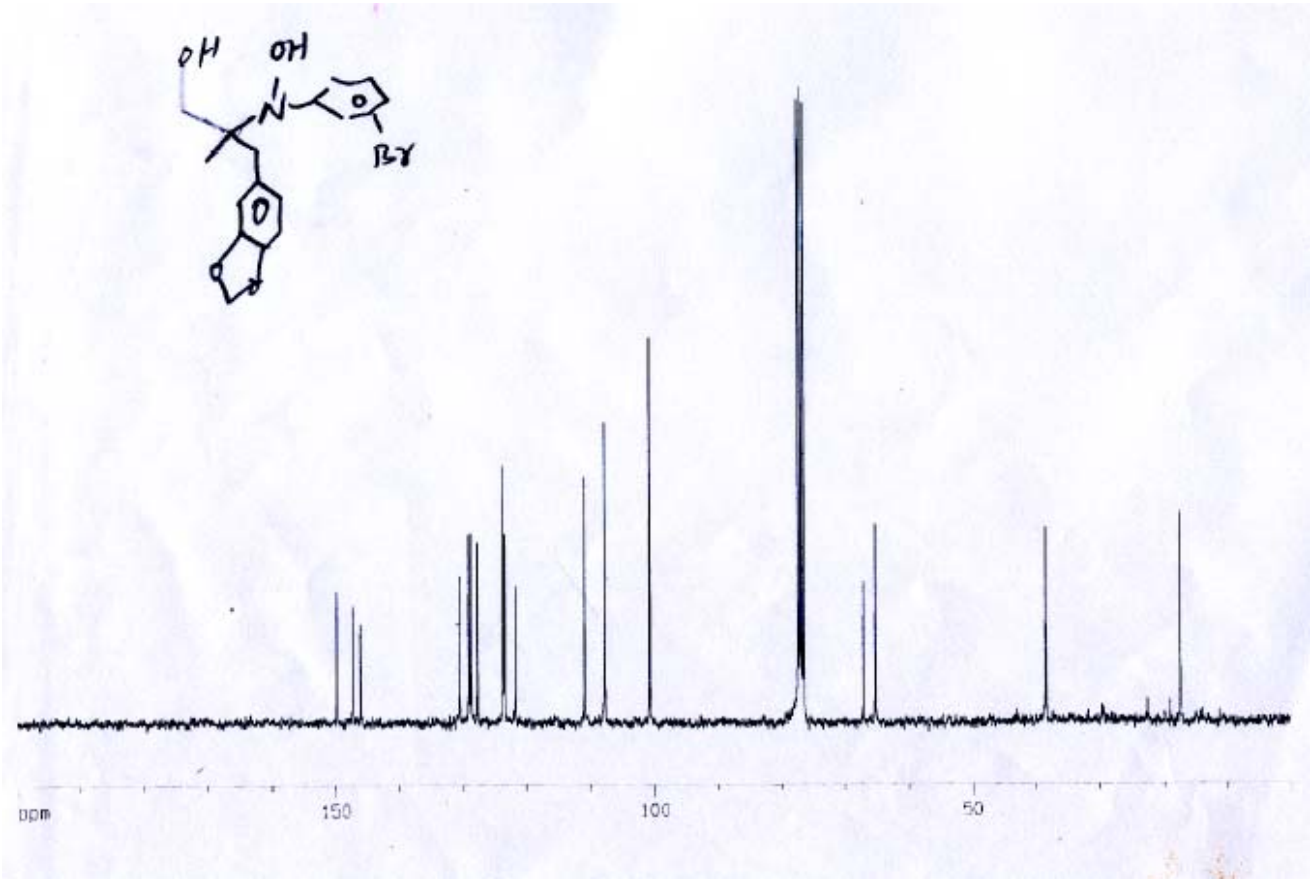


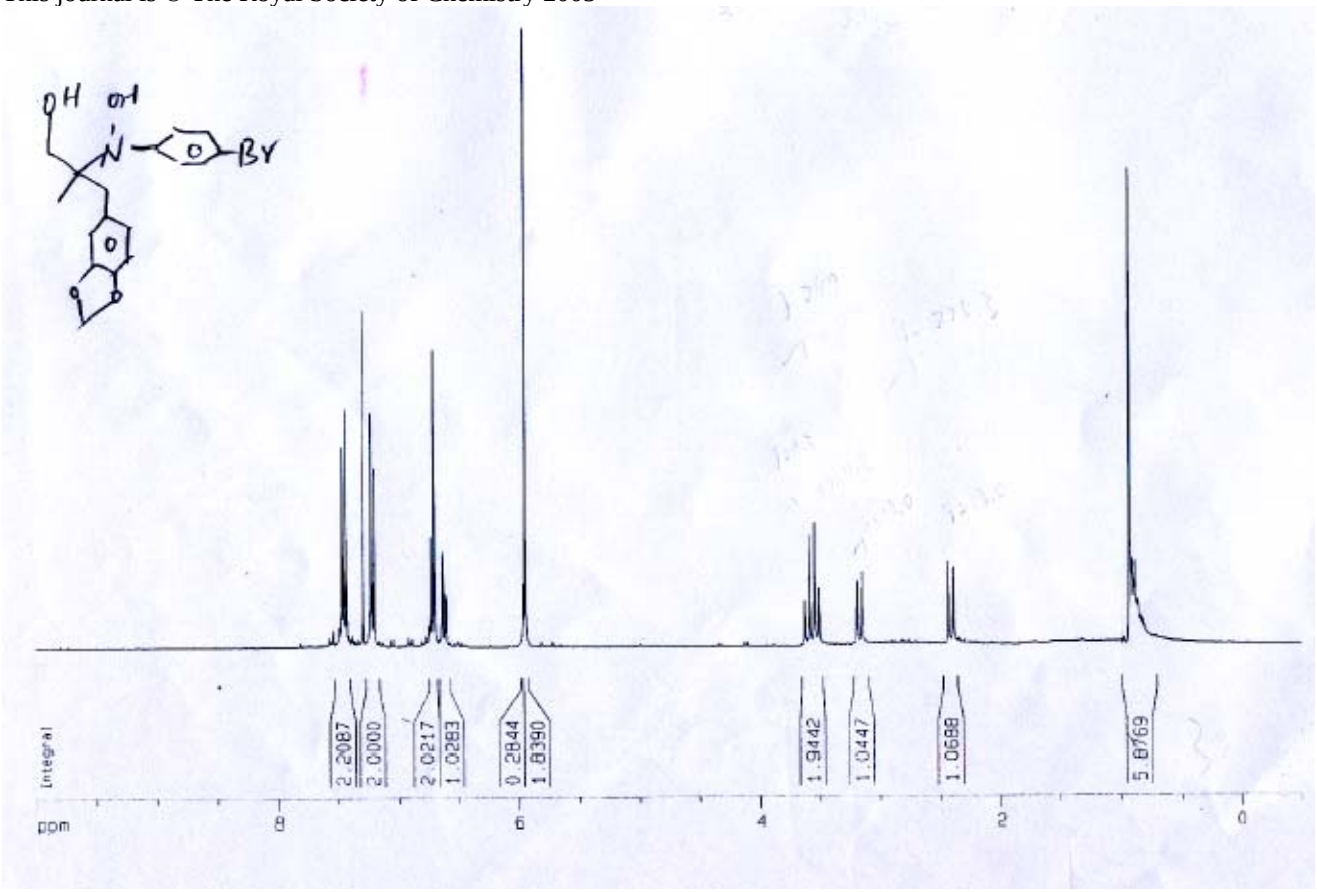


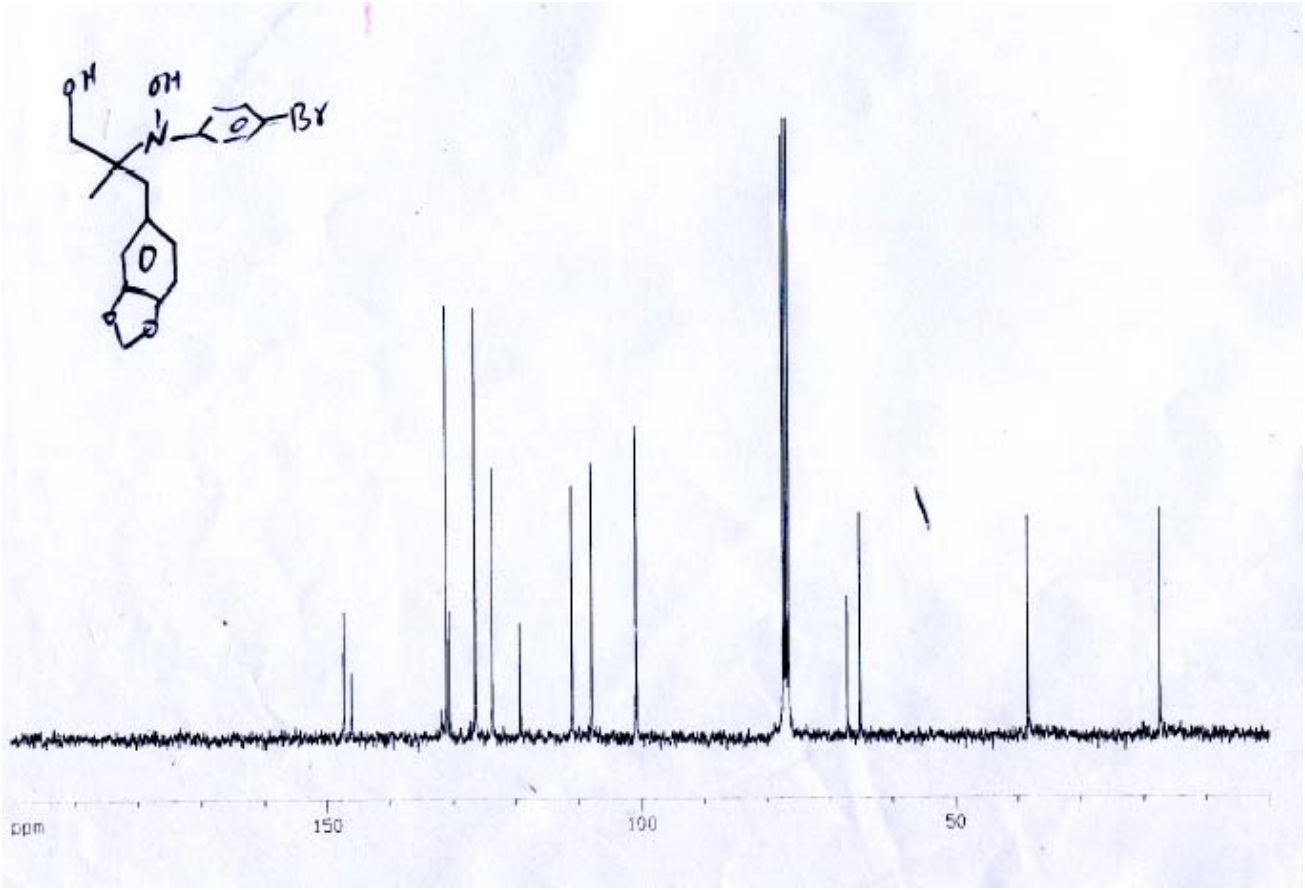


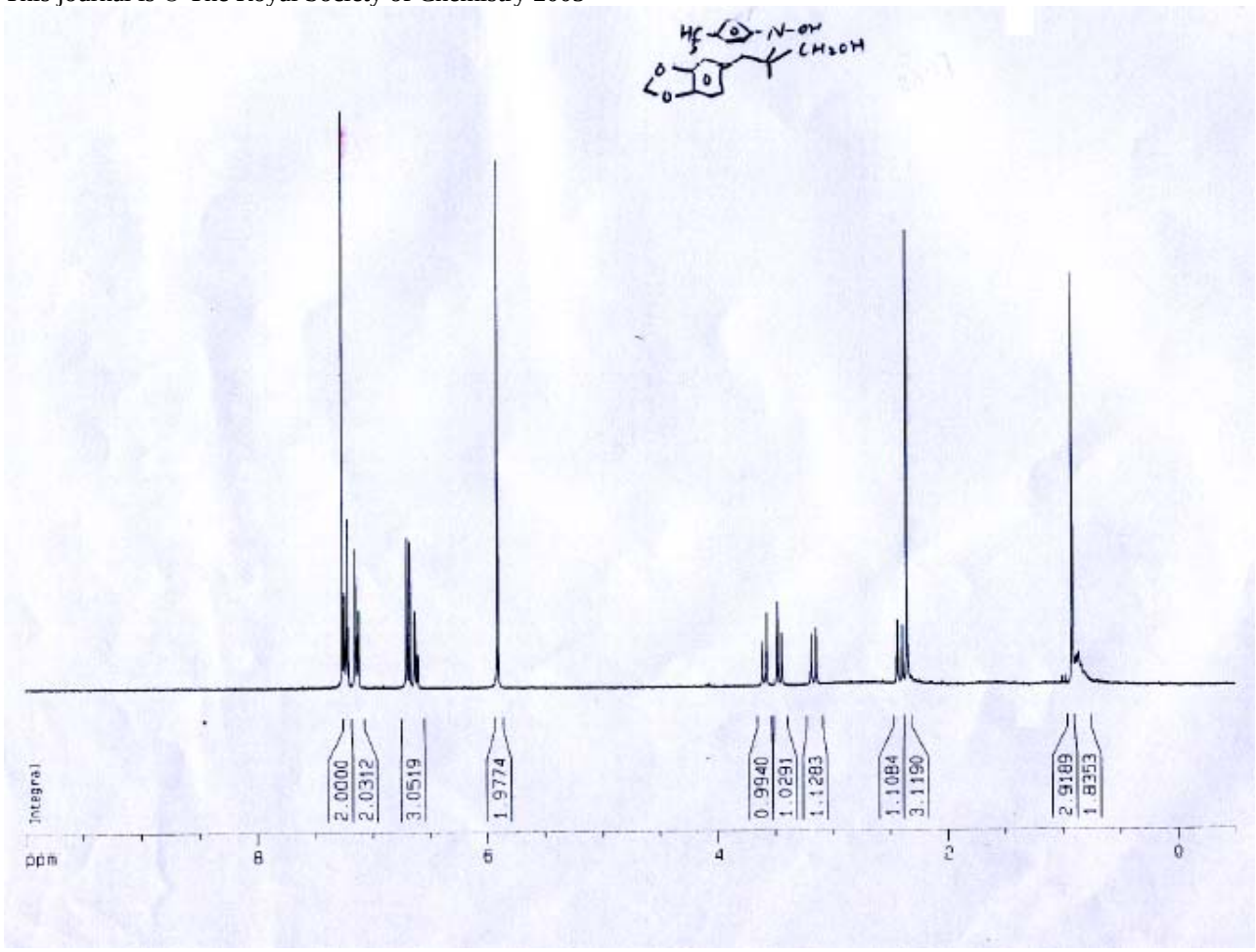


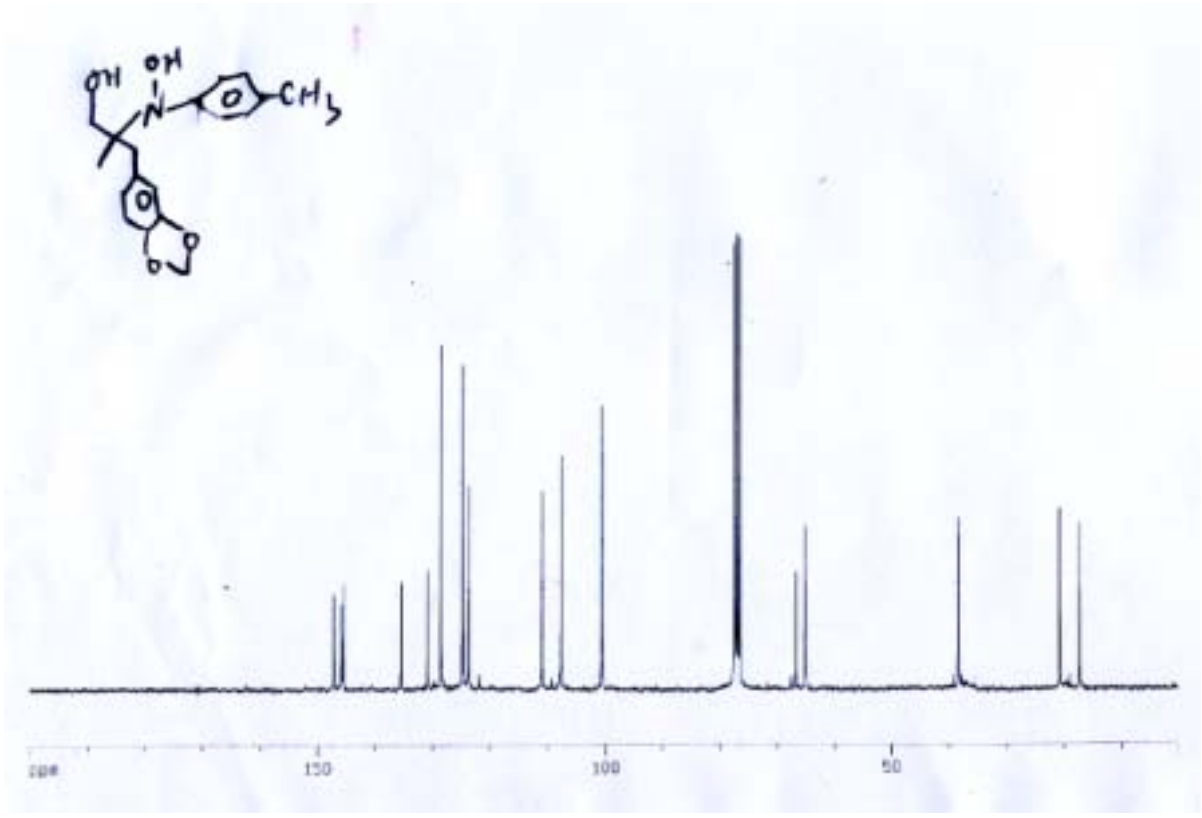


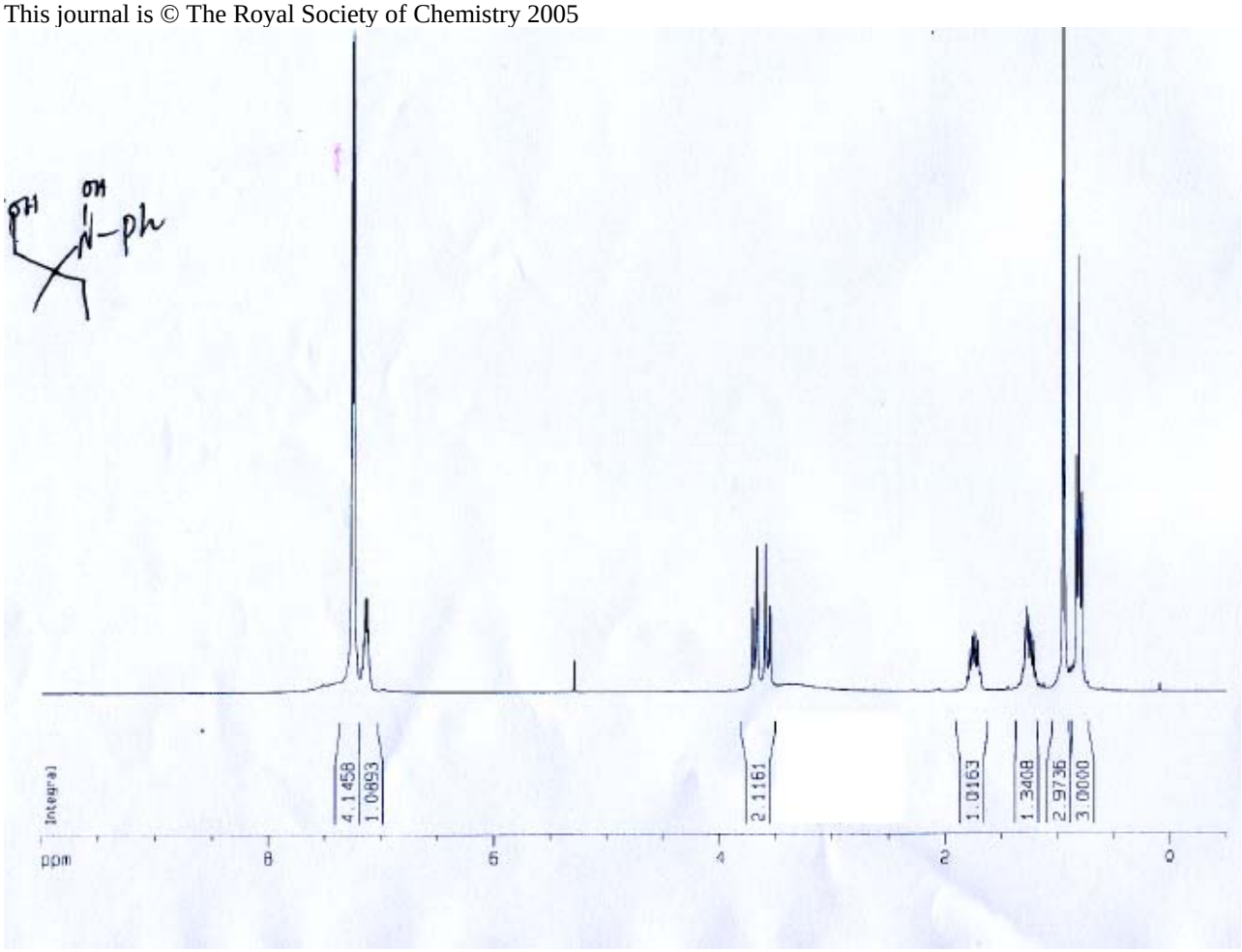


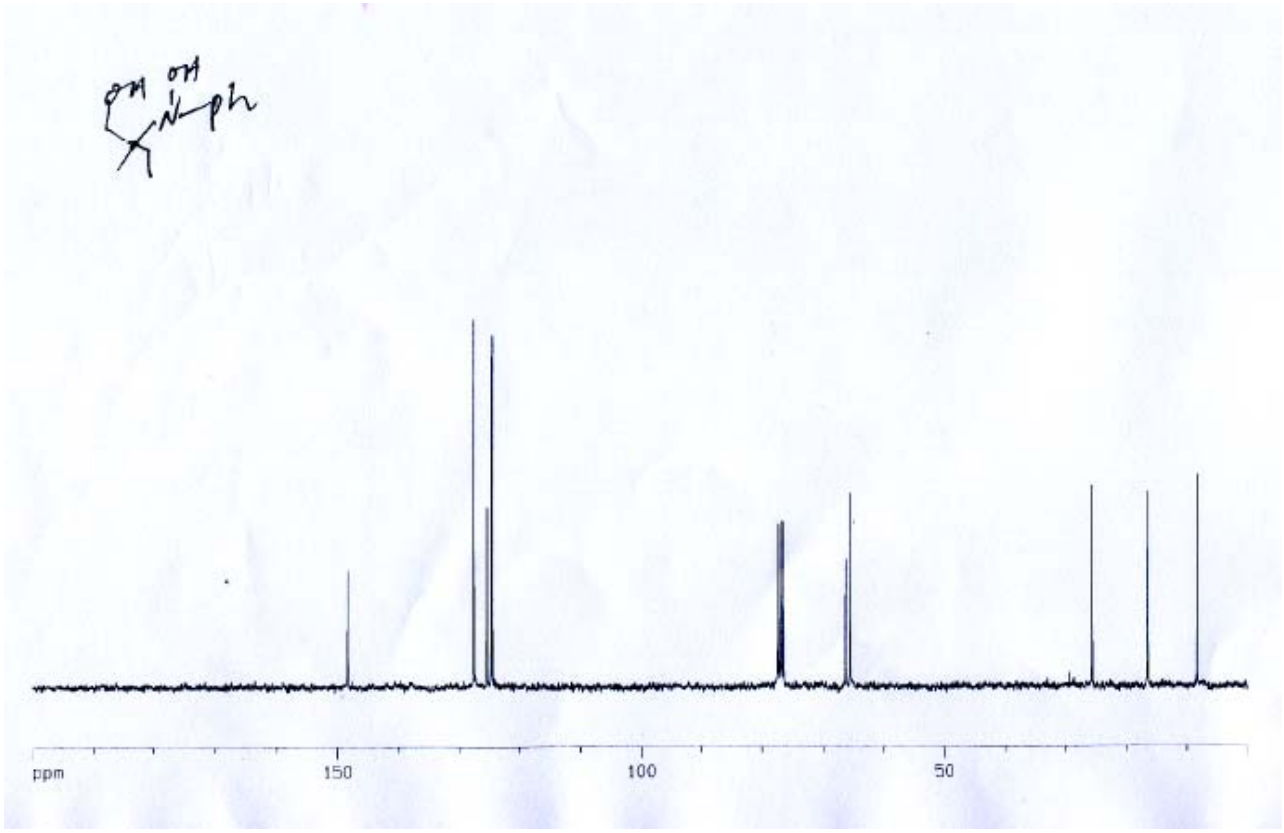


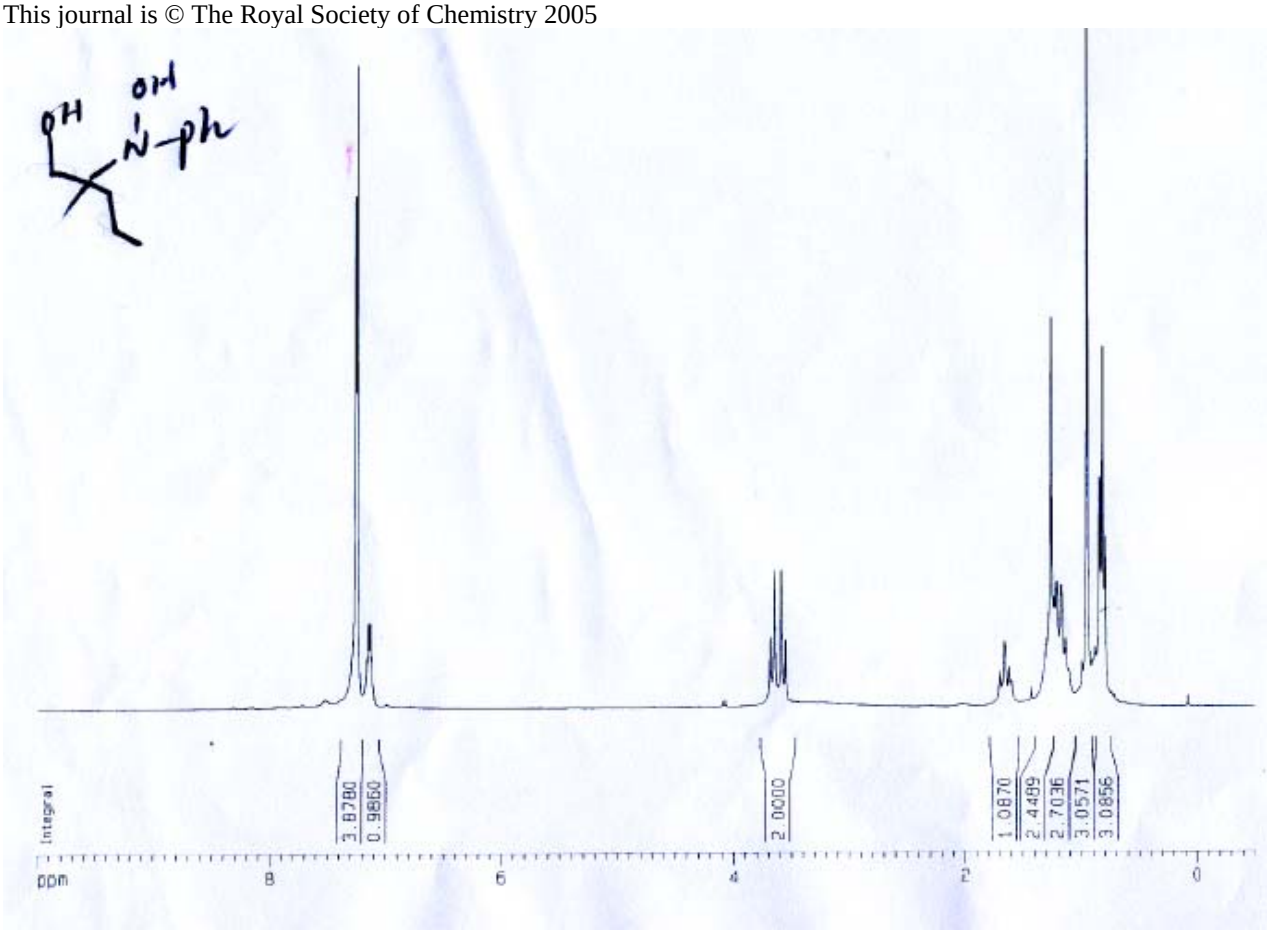


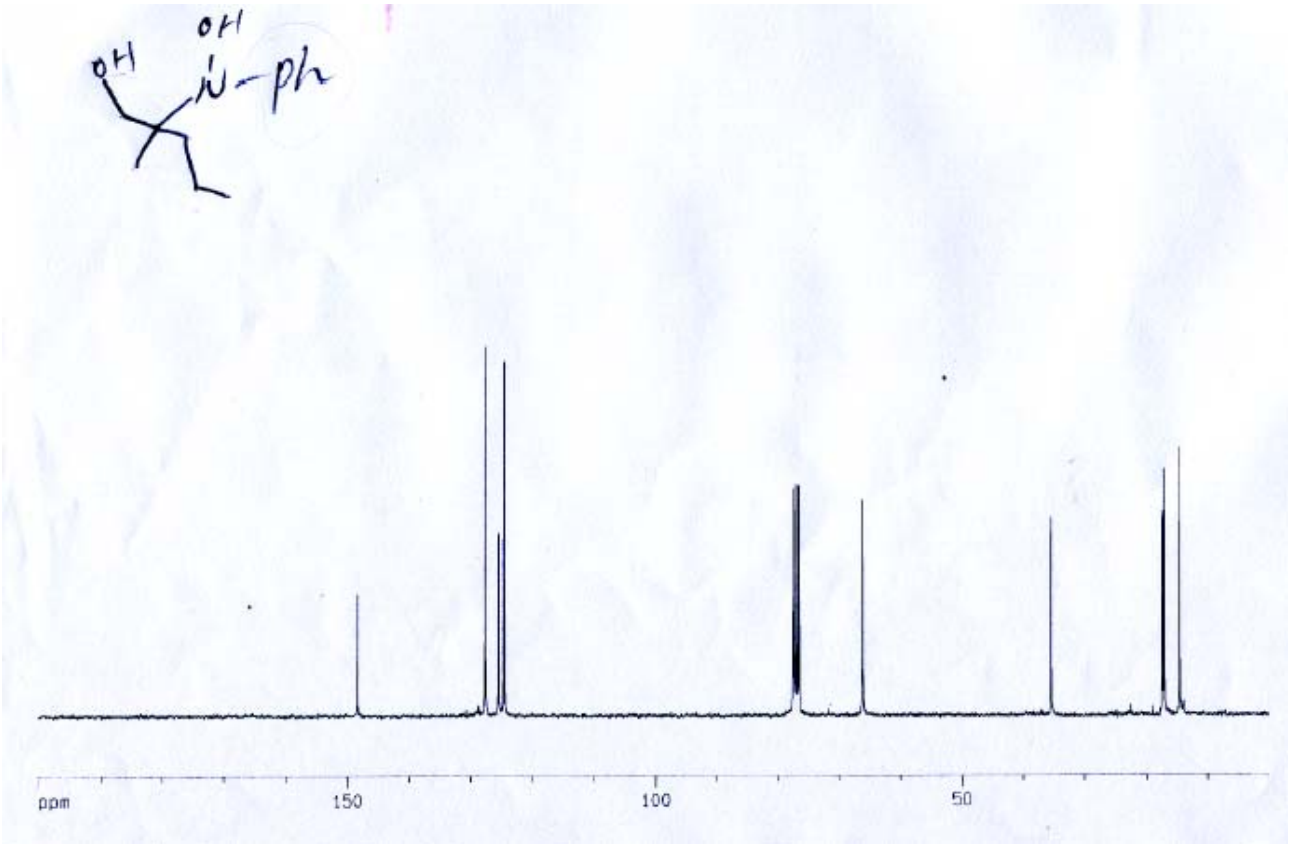


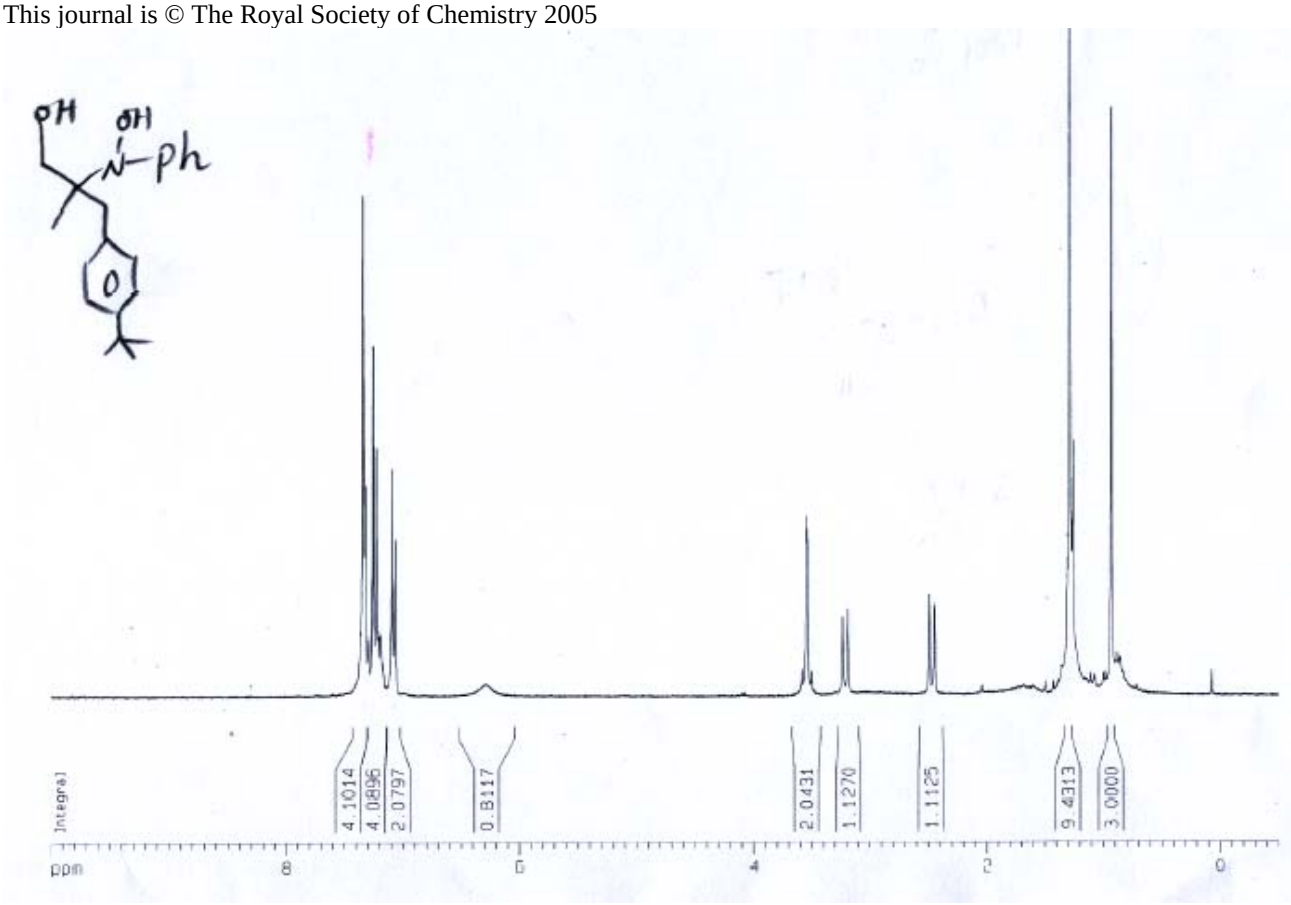


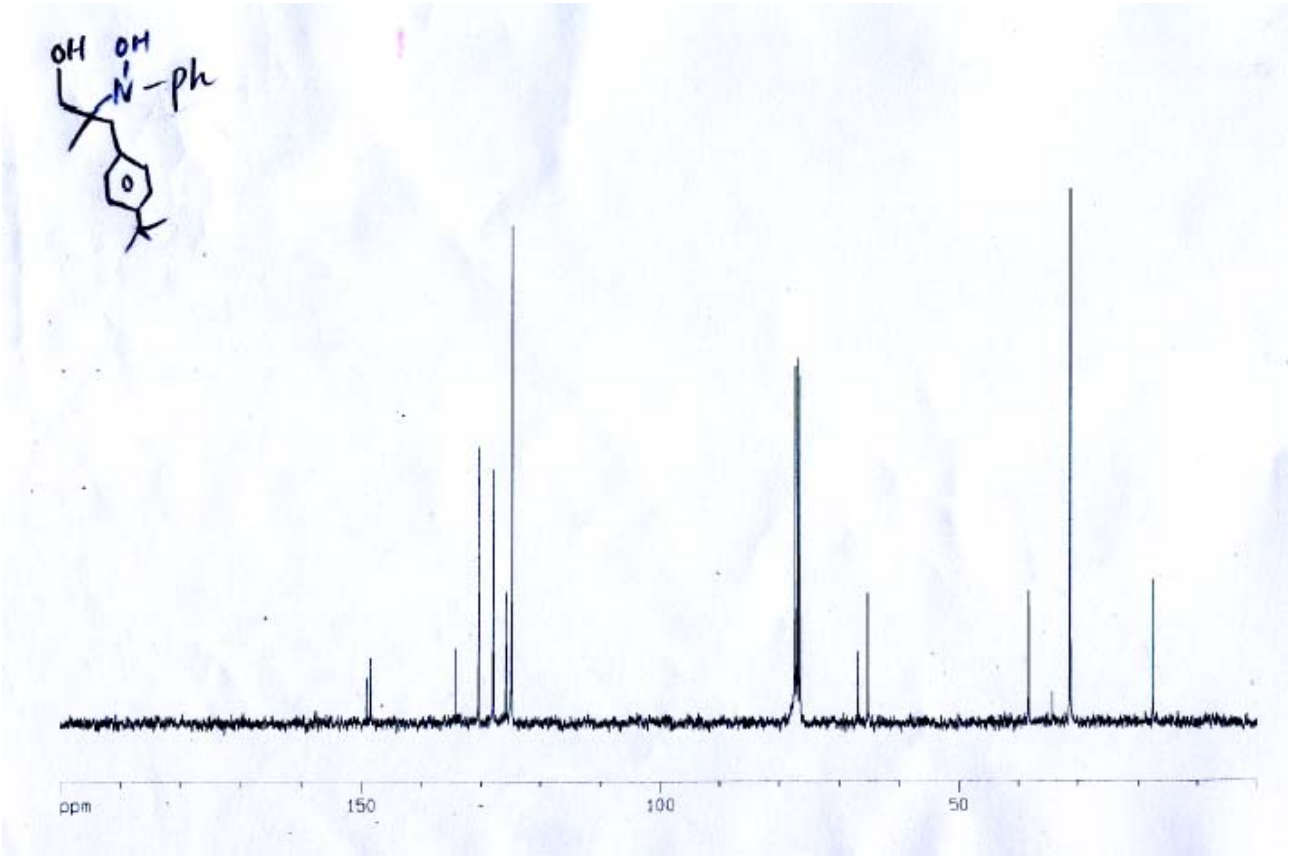


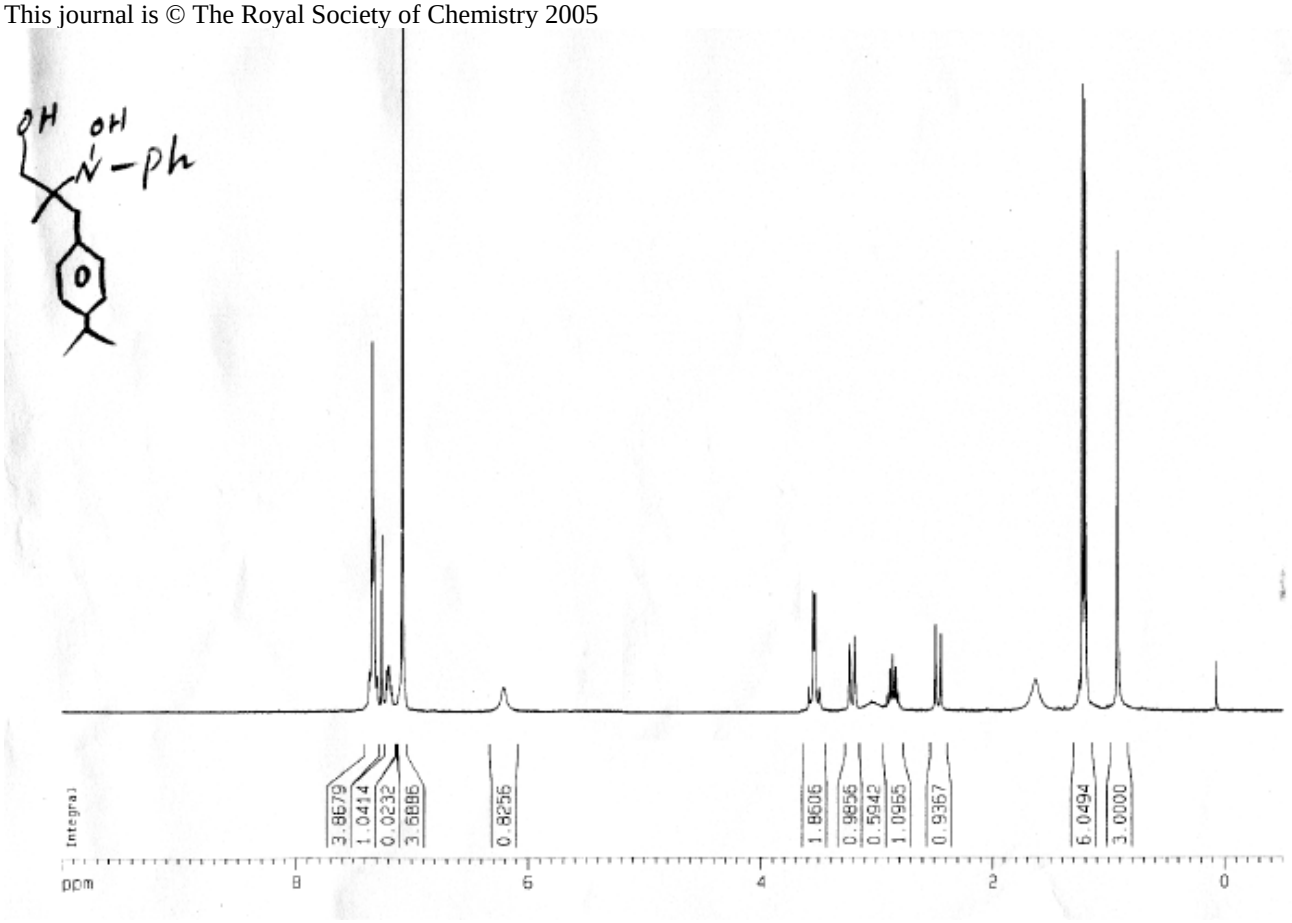


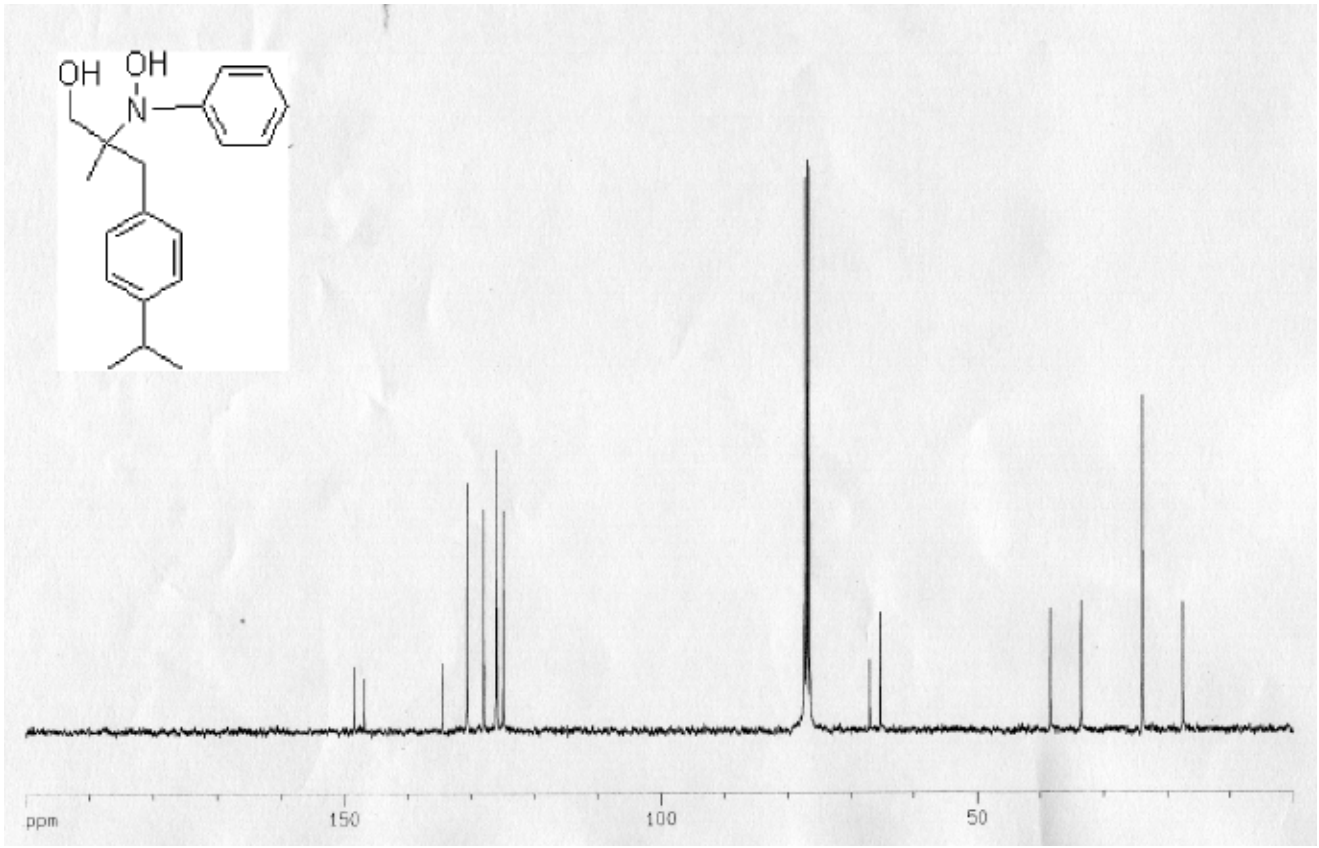












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