

Highly Efficient Synthesis of Thioesters in Water

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General experimental information

All reagents, unless otherwise stated, were used as received from commercial suppliers. THF was distilled twice from KOH. Thin layer chromatography (TLC) was performed on UV-active aluminum-backed plates of silica gel (TLC Silica gel 60 F₂₅₄). Flash chromatography was performed using silica gel (60 Å, 230-400 mesh) with reagent grade solvents. NMR spectra were recorded at 400 MHz (^1H NMR) and 100 MHz (^{13}C NMR) referenced to an internal standard (TMS) or residual solvent protons and signals are reported in ppm (δ). Low-resolution mass spectra (LRMS) were recorded on a Bell and Howell 21-490 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. FT-IR spectra were obtained on a Perkin-Elmer Spectrum 1000 with samples loaded as KBr discs.

General procedure for the preparation of thioamides. In a 100 ml round bottom flask, benzaldehyde derivatives (50 mmol), sulfur (70 mmol, 2.24 g), and morpholine (150 mmol, 13 ml) were mixed and heated gradually to 130 °C and the heating was continued for 5-6 h. After completion, the reaction mixture was cooled to 70 °C, poured in methanol (40 ml) and left in a refrigerator to complete the crystallization (about 2 h). Then the precipitated crystals were filtered, washed with ice-cold methanol (2×8 ml), and air dried to obtain pure thioamides as yellow solids in good to excellent yields (78-95 %).

General procedure for the synthesis of thioesters in DMF. In a round bottom flask, thioamide (1 mmol), alkyl halide (1 mmol), were dissolved in DMF (1.5 ml) with stirring and heated to 95 °C for 40 minutes. Then to the reaction mixture water (1.5 mmol, 0.27 ml) and DABCO (0.22 mmol, 25 mg) was added and heating was continued for 20 min at the same temperature. Then the reaction mixture was cooled, poured in water (20 ml), and extracted with EtOAc (2×10 ml). The solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 1:8 EtOAc-Hexane) to afford thioesters as white to pale yellow solids.

General procedure for the synthesis of thioesters in CS₂. In a round bottom flask, thioamide (1 mmol), alkyl halide (1 mmol), were dissolved in CS₂ (15 ml) with stirring and heated to reflux for 40 minutes. After removal the solvent under vacuum, the semi-solid residue was treated with a solution of DABCO (0.22 mmol, 25 mg) in EtOH (80 % w/v, 5 ml) and heated to 95 °C for 20 minutes. Then the reaction mixture was cooled, poured in water (10 ml), and extracted with EtOAc (2×10 ml). The solvent was removed under reduced pressure and the residue was chromatographed (silica gel, 1:8 EtOAc-Hexane) to give thioesters as white to pale yellow solids.

General procedure for the synthesis of thioesters in water. In a round bottom flask, thioamide (1 mmol), alkyl halide (1 mmol), NaI (0.1 mmol, 15 mg), DABCO (0.22 mmol, 25 mg) and hexadecyltrimethylammonium bromide (HTAB, 0.1 mmol, 36.5 mg) were suspended in water (0.5 ml) with vigorous stirring and heated to 95 °C for 50 minutes. Then the reaction mixture was cooled and thereafter an oily residue was left which slowly solidified. After that, the solid was filtered and washed with water

(2×10 ml). Finally the solid compound was recrystallized from MeOH (in the case of entry 6, Table 2 with MeOH-CHCl₃) to afford pure thioesters as white or pale yellow needles in good to excellent yields (80-96 %).

(3a): mp (MeOH): 93-94 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.19 (d, *J*= 8.8 Hz, 2H), 7.97 (d, d, *J*= 8.5 Hz, *J*= 1.3 Hz, 2H), 7.61 (t, *J*=7.5 Hz, 1H), 7.58 (d, *J*= 8.8, 2H), 7.48 (t, *J*= 7.5, 2H), 4.38 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 190.5, 147.1, 145.6, 136.3, 133.9, 129.9, 128.8, 127.4, 124.0, 32.6; Anal. Calcd. for C₁₄H₁₁NO₃S: C, 61.52; H, 4.06; N, 5.12; S, 11.73 Found: C, 61.48; H, 3.95; N, 5.23; 11.81.

(3b): mp (MeOH): 102-103 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.21 (d, *J*= 8.9 Hz, 2H), 7.86 (d, *J*= 8.2 Hz, 2H), 7.56 (d, *J*= 8.9 Hz, 2H), 7.27 (d, *J*= 8.2 Hz, 2H), 4.36 (s, 2H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 190.0, 147.1, 145.8, 144.9, 133.7, 130.1, 129.2, 127.5, 123.8, 32.4; Anal. Calcd. for C₁₅H₁₃NO₃S: C, 62.70; H, 4.56; N, 4.87; S, 11.16 Found: C, 62.53; H, 4.43; N, 5.01; S, 11.28.

(3c): mp (MeOH): 118-119 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.19 (d, *J*= 8.7 Hz, 2H), 7.91 (d, *J*= 8.6 Hz, 2H), 7.57 (d, *J*= 8.7 Hz, 2H), 7.45 (d, *J*= 8.6 Hz, 2H), 4.38 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 189.3, 147.2, 145.2, 140.3, 134.6, 129.9, 129.1, 128.7, 123.9, 32.6; Anal. Calcd. for C₁₄H₁₀ClNO₃S: C, 54.64; H, 3.28; N, 4.55; S, 10.42 Found: C, 54.45; H, 3.19; N, 4.71; S, 10.61.

(3d)¹: mp (MeOH): 54-56 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.90 (d, *J*= 9.0 Hz, 2H), 6.67 (d, *J*= 9.0 Hz, 2H), 3.06 (s, 6H), 2.45 (s, 3H).

(3e): mp (MeOH-CHCl₃): 106-108 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.91 (d, *J*= 9.0 Hz, 2H), 7.41 (d, *J*= 7.1 Hz, 2H), 7.33 (t, *J*= 7.3 Hz, 2H), 7.26 (t, *J*= 7.3 Hz, 1H), 6.71 (d, *J*= 9.0 Hz, 2H), 4.32 (s, 2H), 3.09 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 189.0, 153.6, 138.3, 129.4, 129.0, 128.6, 127.1, 126.4, 110.9, 40.2, 32.9; Anal. Calcd. for C₁₆H₁₇NOS: C, 70.81; H, 6.31; N, 5.16; S, 11.82 Found: C, 70.64; H, 6.12; N, 5.21; S, 11.94.

(3f): mp (MeOH): 74-76 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J*= 8.3 Hz, 2H), 7.71 (d, *J*= 8.3 Hz, 2H), 7.66 (d, *J*= 7.3 Hz, 2H), 7.51 (d, *J*= 7.4 Hz, 2H), 7.43-7.46 (m, 3H), 7.38 (t, *J*= 7.4 Hz, 2H), 7.31 (t, *J*= 7.2 Hz, 1H), 4.40 (s, 2H); ¹³C NMR (100

MHz, CDCl₃): δ 190.9, 146.2, 139.8, 137.6, 135.5, 129.1, 129.0, 128.9, 128.7, 128.4, 127.9, 127.4, 127.3, 33.4; Anal. Calcd. for C₂₀H₁₆OS: C, 78.91; H, 5.30; S, 10.53 Found: C, 78.77; H, 5.11; S, 10.76.

(3g): mp (MeOH): 150-151 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.20 (d, J = 8.7 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.71 (d, 8.5 Hz, 2H), 7.64 (d, J = 5.2 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.50 (t, J = 6.8, 2H), 7.44 (t, J = 7.3, 1H), 4.41 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 190.0, 147.1, 146.6, 145.6, 139.6, 134.9, 129.9, 129.0, 128.5, 128.0, 127.6, 127.3, 123.9, 32.6; Anal. Calcd. for C₂₀H₁₅NO₃S: C, 68.75; H, 4.33; N, 4.01; S, 9.18 Found: C, 68.61; H, 4.14; N, 4.11; S, 9.30.

(3h): mp (MeOH): 75-77 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.58 (s, 1H), 8.04 (d, d, J = 8.6 Hz, J = 1.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 8.3 Hz, 2H), 7.56-7.64 (m, 2H), 7.46 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.1 Hz, 1H), 4.42 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 191.3, 137.6, 135.8, 134.1, 132.5, 129.6, 129.1, 128.8, 128.7, 128.6, 127.8, 127.4, 127.0, 125.9, 123.2, 33.5; Anal. Calcd. for C₁₈H₁₄OS: C, 77.66; H, 5.07; S, 11.52 Found: C, 77.55; H, 5.01; S, 11.65.

(3i): mp (MeOH): 127-128 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.54 (s, 1H), 8.20 (d, J = 8.6 Hz, 2H), 7.99 (t, J = 9.6 Hz, 2H), 7.90 (t, J = 8.3 Hz, 2H), 7.57-7.65 (m, 4H), 4.43 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 190.3, 147.2, 145.6, 136.0, 133.6, 132.4, 129.9, 129.6, 129.1, 128.8, 128.7, 127.9, 127.1, 123.9, 123.0, 32.7; Anal. Calcd. for C₁₈H₁₃NO₃S: C, 66.86; H, 4.05; N, 4.33; S, 9.92 Found: C, 66.61; H, 3.98; N, 4.45; S, 10.02.

(3j): mp (MeOH): 62-64 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.56 (s, 1H) 8.02 (d, d, J = 8.6 Hz, J = 1.7 Hz, 1H), 8.97 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 8.3 Hz, 2H), 7.56-7.64 (m, 2H), 7.40 (t, J = 4.6 Hz, 2H), 7.04 (t, J = 8.7 Hz, 2H), 4.37 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 191.1, 163.3, 160.9, 135.8, 134.0, 130.7, 130.6, 129.6, 128.8, 128.6, 127.8, 127.0, 123.1, 115.7, 115.4, 32.7.

(3k): mp (MeOH): 100-102 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, J = 9.3 Hz, 2H), 7.91 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 4.37 (s, 2H), 2.97 (sep, J = 6.9 Hz, 1H), 1.28 (d, J = 7.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃):

δ 190.0, 155.6, 147.1, 145.8, 134.1, 129.8, 127.6, 126.9, 123.8, 34.3, 32.4, 32.6; Anal. Calcd. for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17 Found: C, 64.62; H, 5.32; N, 4.60; S, 10.29.

(3l): mp (MeOH): 104-106 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.6 Hz, 2H), 7.63 (d, d, J = 8.5 Hz, J = 1.9 Hz, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 8.5 Hz, 1H), 4.34 (s, 2H), 3.94 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 153.8, 149.0, 147.1, 145.8, 130.0, 129.2, 123.8, 122.0, 110.3, 109.4, 56.2, 56.0, 32.5; Anal. Calcd. for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20; S, 9.62 Found: C, 57.57; H, 4.41; N, 4.42; S, 9.75.

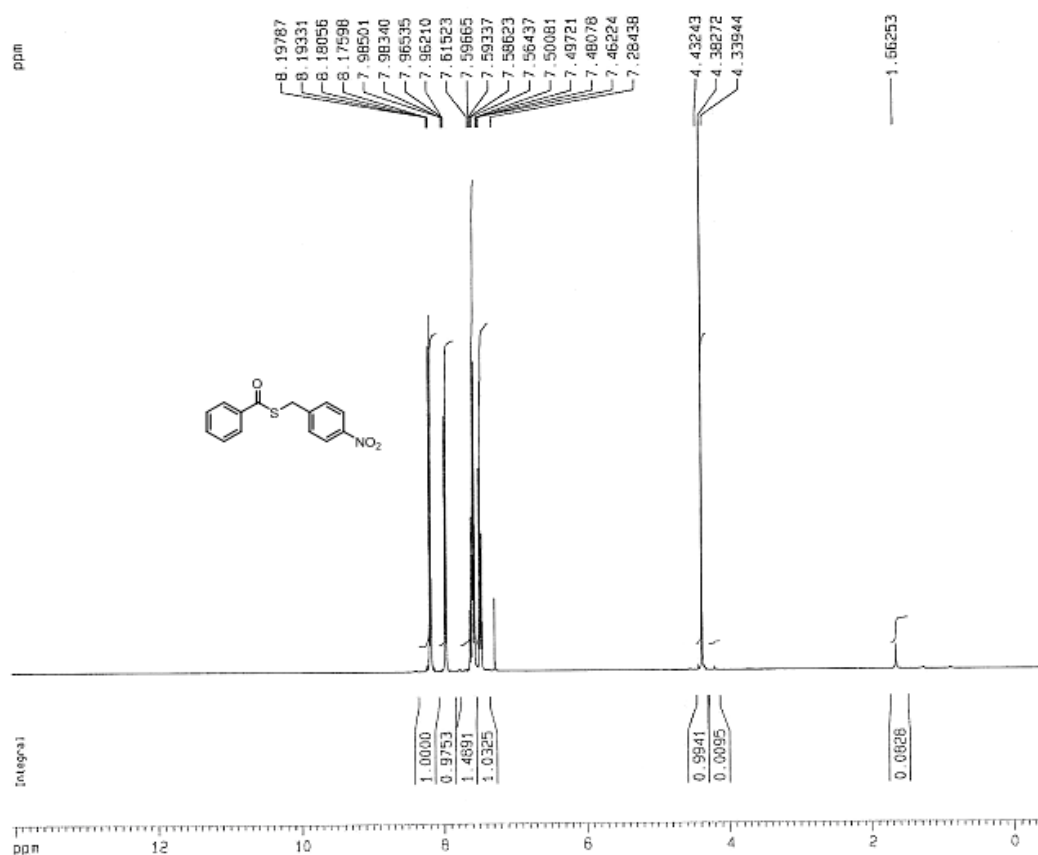
(3m)²: mp (MeOH): 60-61 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.6 Hz, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.78 (t, J = 7.1 Hz, 1H), 7.63 (t, J = 7.1 Hz, 1H), 2.49 (s, 3H).

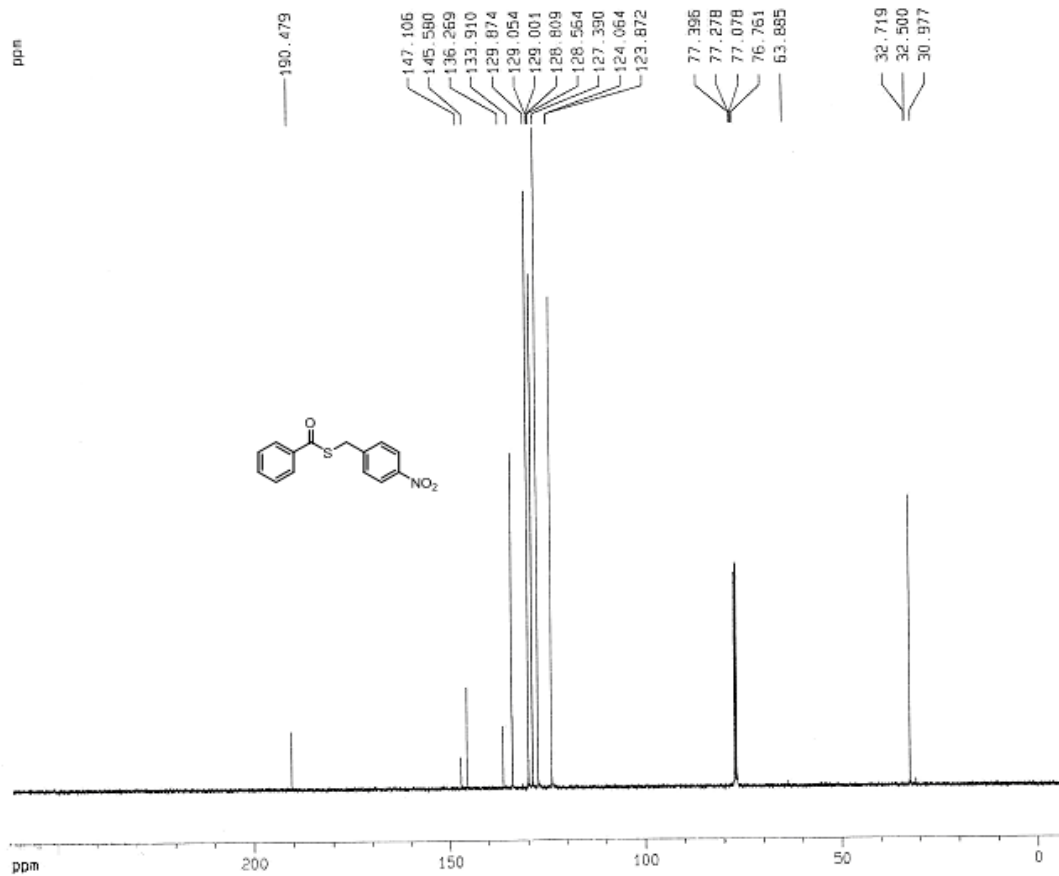
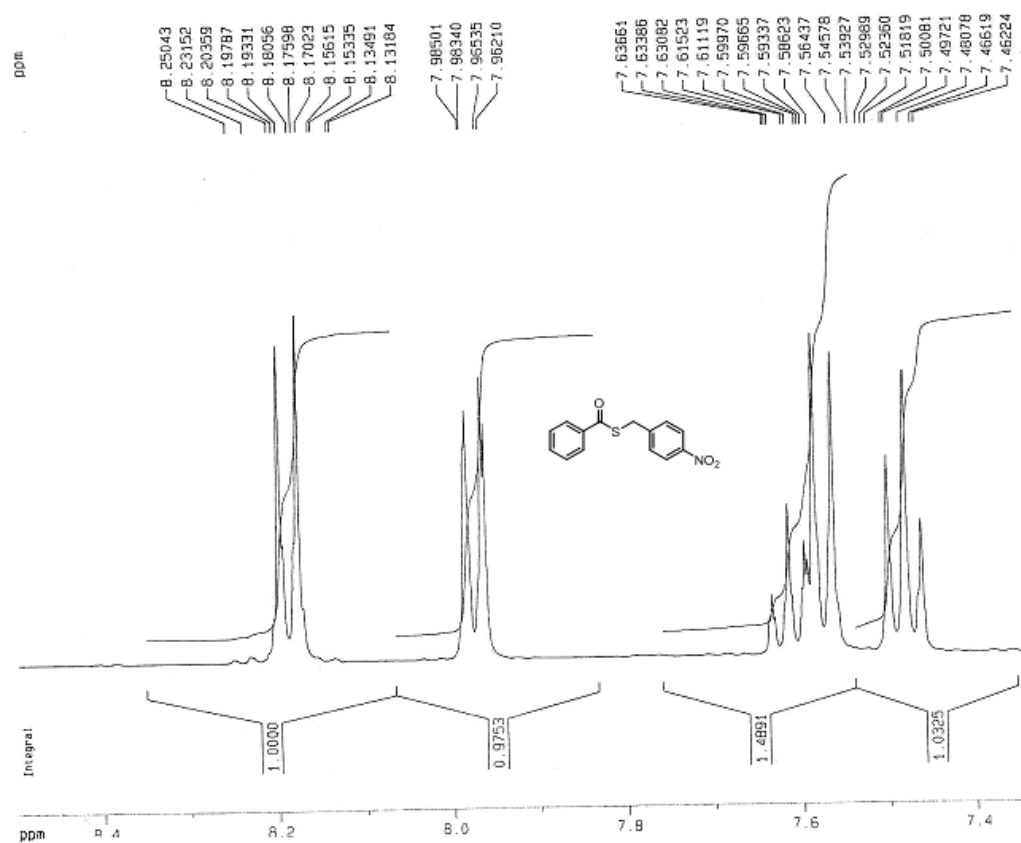
(3n): mp (MeOH): 140-142 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 10.3 Hz, 1H), 7.81 (t, d, J = 8.4 Hz, J = 1.3 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.42 (t, d, J = 5.4 Hz, J = 3.2 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 4.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 163.2, 160.8, 151.3, 147.0, 137.6, 130.8, 130.7, 130.4, 128.8, 127.7, 117.1, 115.6, 115.3, 32.6; Anal. Calcd. for $C_{17}H_{12}FNOS$: C, 68.67; H, 4.07; N, 4.71; S, 10.78 Found: C, 68.55; H, 4.14; N, 4.84; S, 10.89.

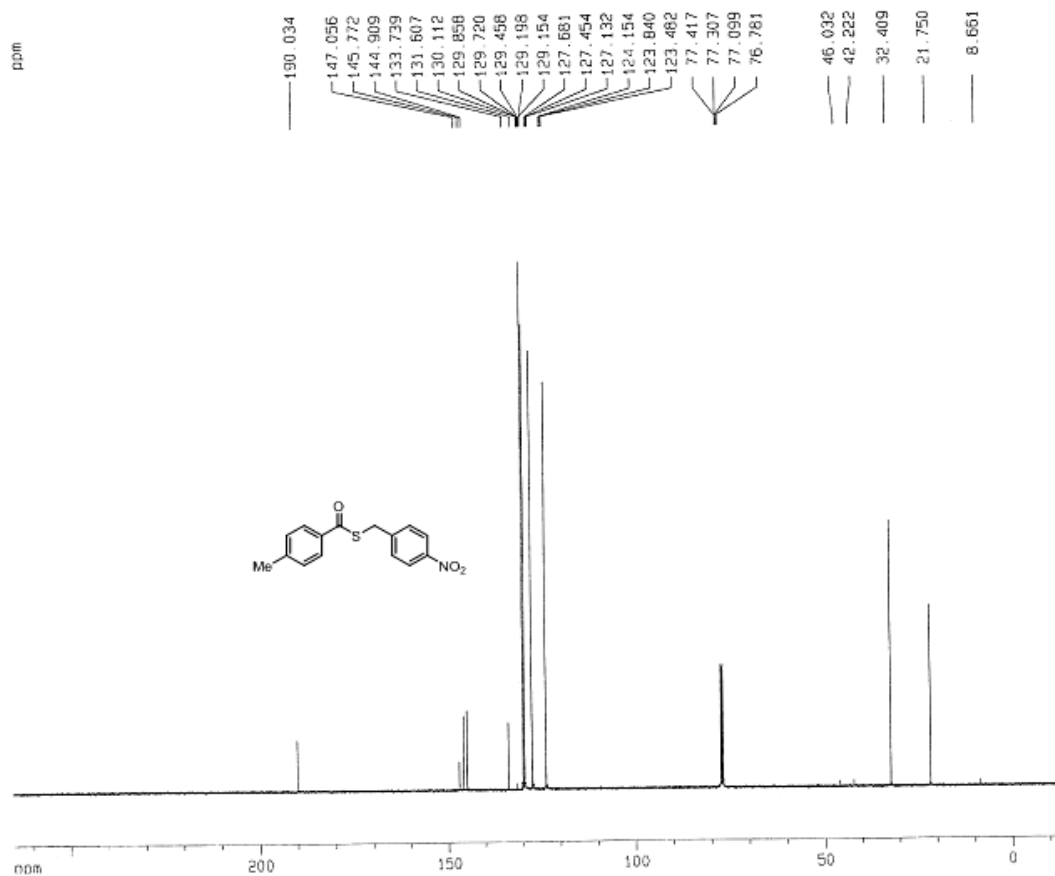
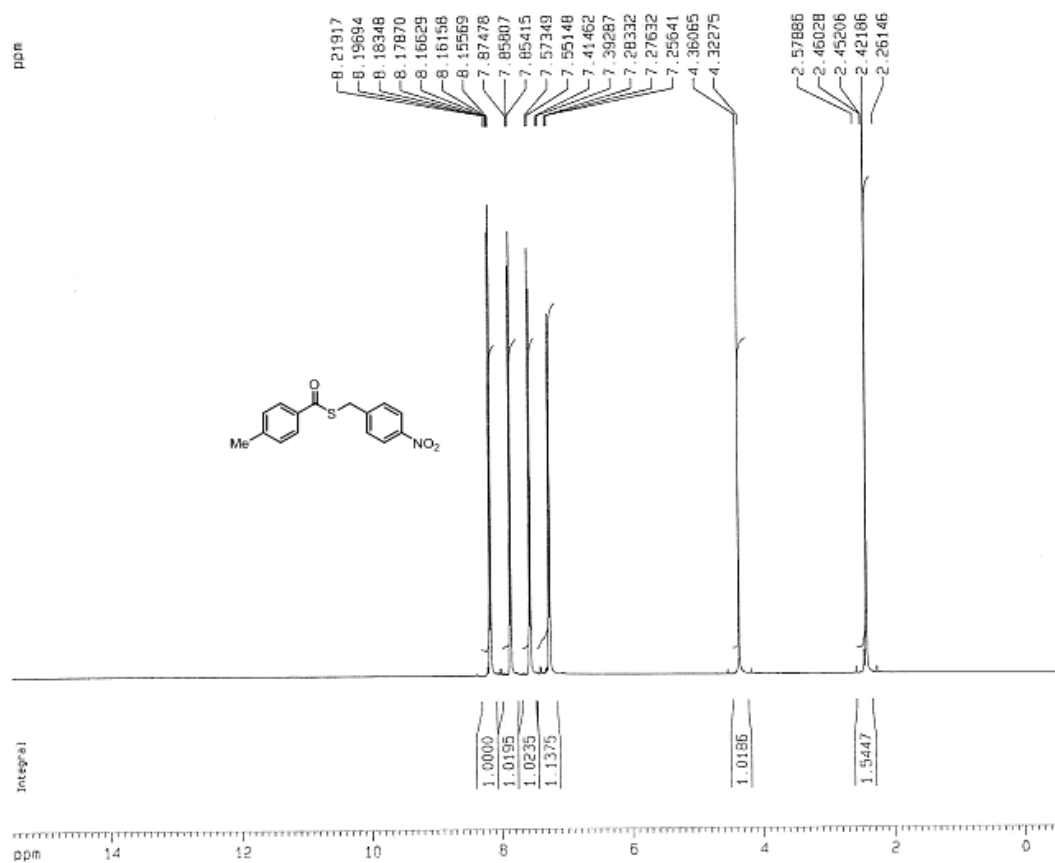
(3o): mp (MeOH): 114-115 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.0, 1H), 7.80 (t, d, J = 8.4 Hz, 1.4 Hz, 1H), 7.66 (t, d, J = 7.0 Hz, J = 1.1 Hz, 1H), 7.45 (d, J = 7.0 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.27 (t, J = 7.0 Hz, 1H), 4.35 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 151.5, 147.1, 137.6, 137.5, 130.4, 130.2, 129.6, 129.1, 128.8, 128.6, 127.7, 127.2, 117.1, 33.4; Anal. Calcd. for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01; S, 11.48 Found: C, 72.91; H, 4.56; N, 5.09; S, 11.57.

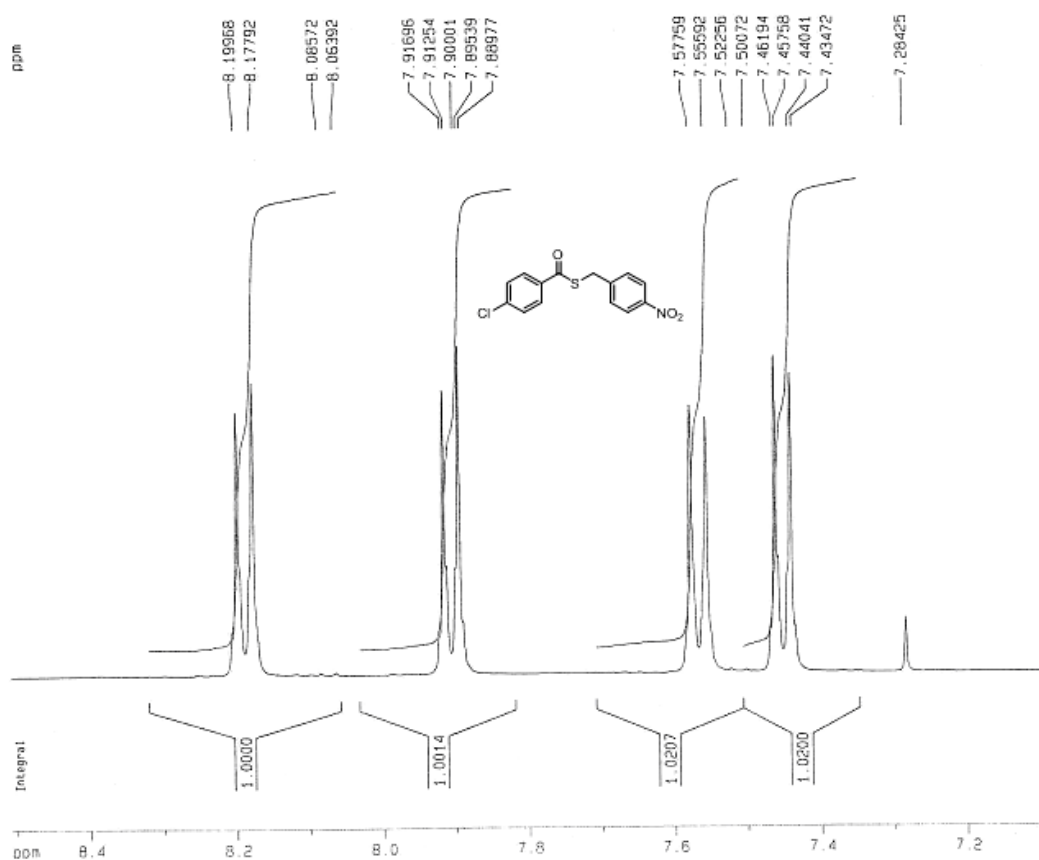
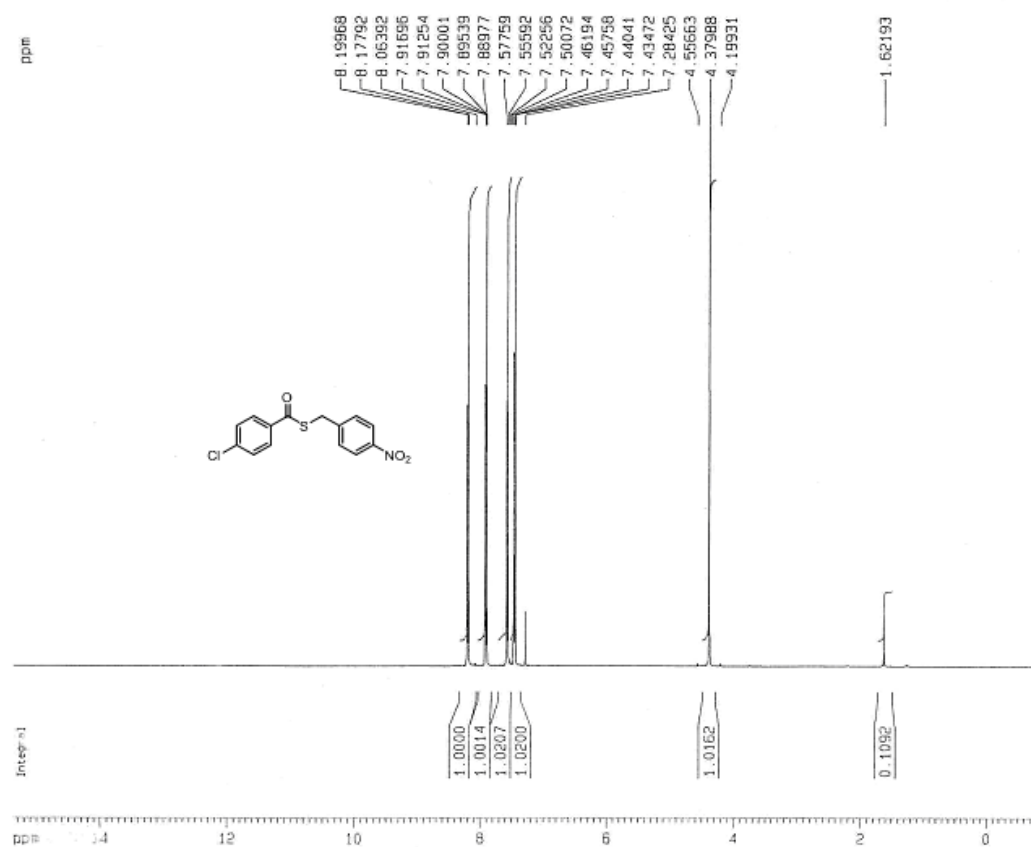
(3p): mp (MeOH): 84-86 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 3.06 (s, 6H), 3.05 (t, J = 8.0 Hz, 2H), 1.73 (sep, J = 6.4 Hz, 1H), 1.54-1.59 (m, 2H), 0.95 (d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9,

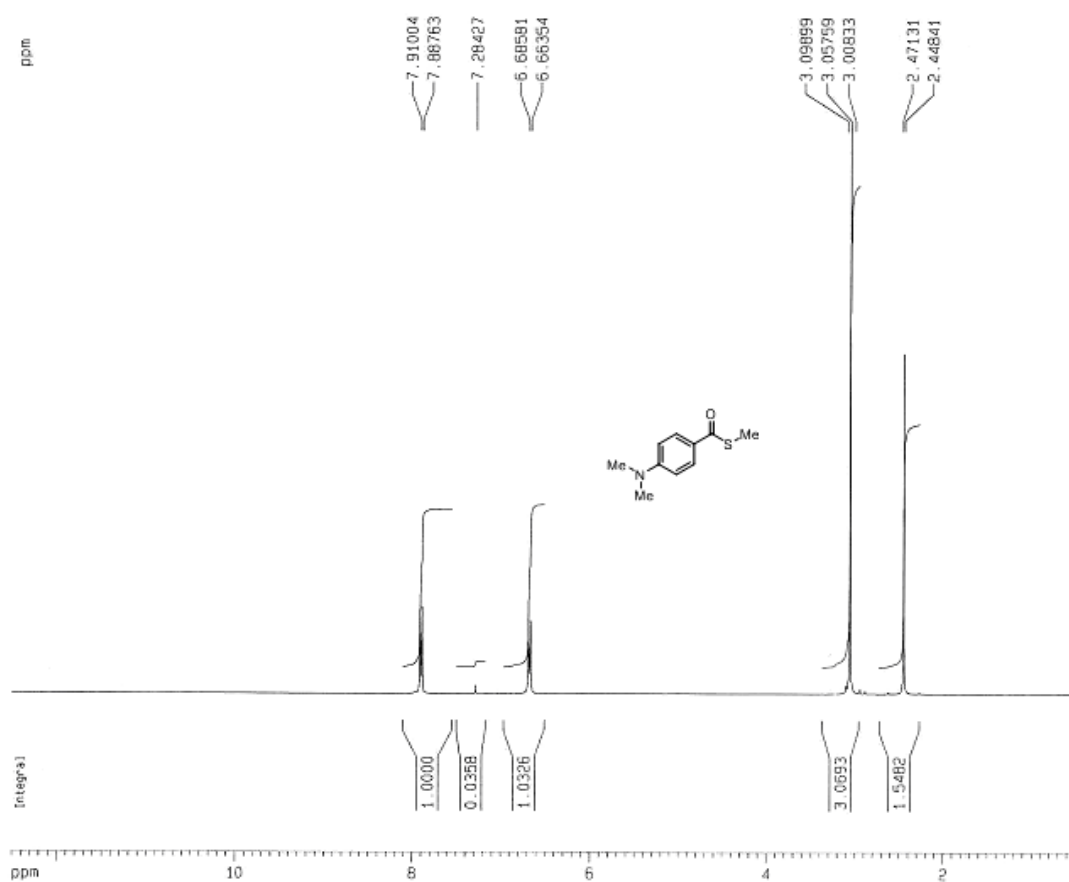
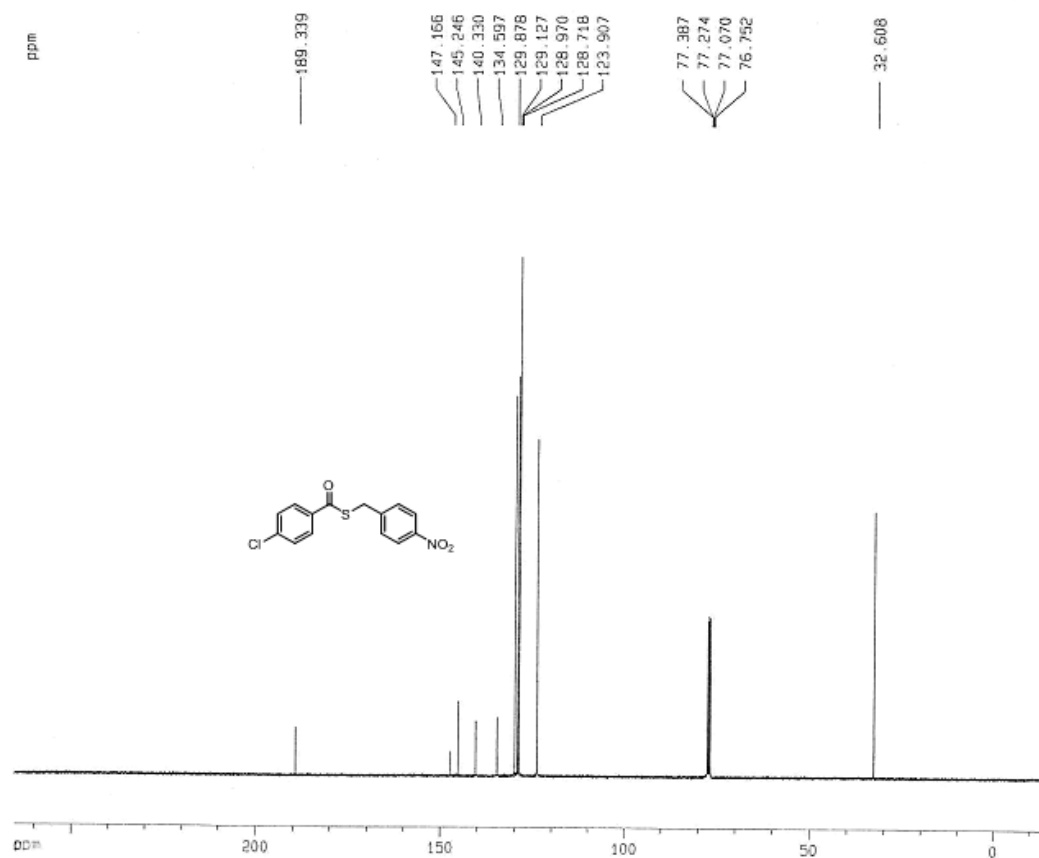
153.6, 129.2, 124.9, 110.6, 40.0, 38.8, 27.7, 26.7, 22.3; Anal. Calcd. for $C_{14}H_{21}NOS$:
C, 66.89; H, 8.42; N, 5.57; S, 12.76 Found: C, 68.65; H, 8.56; N, 5.79; S, 12.83.

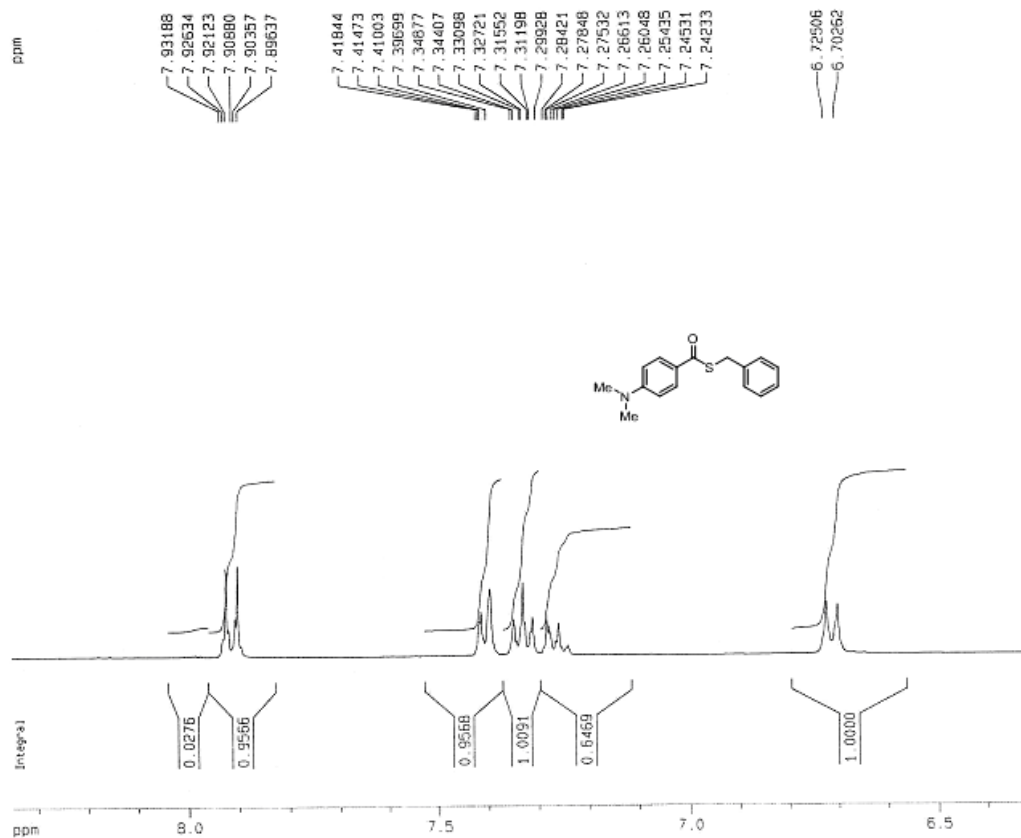
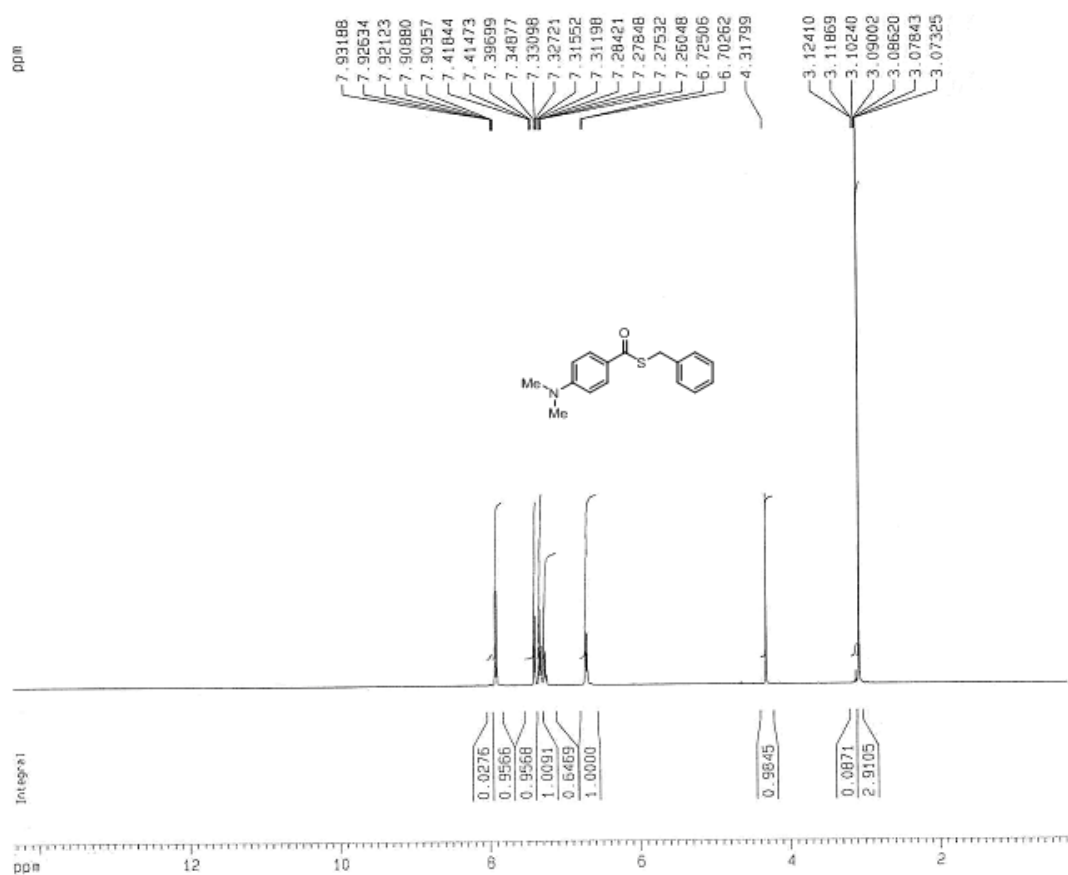


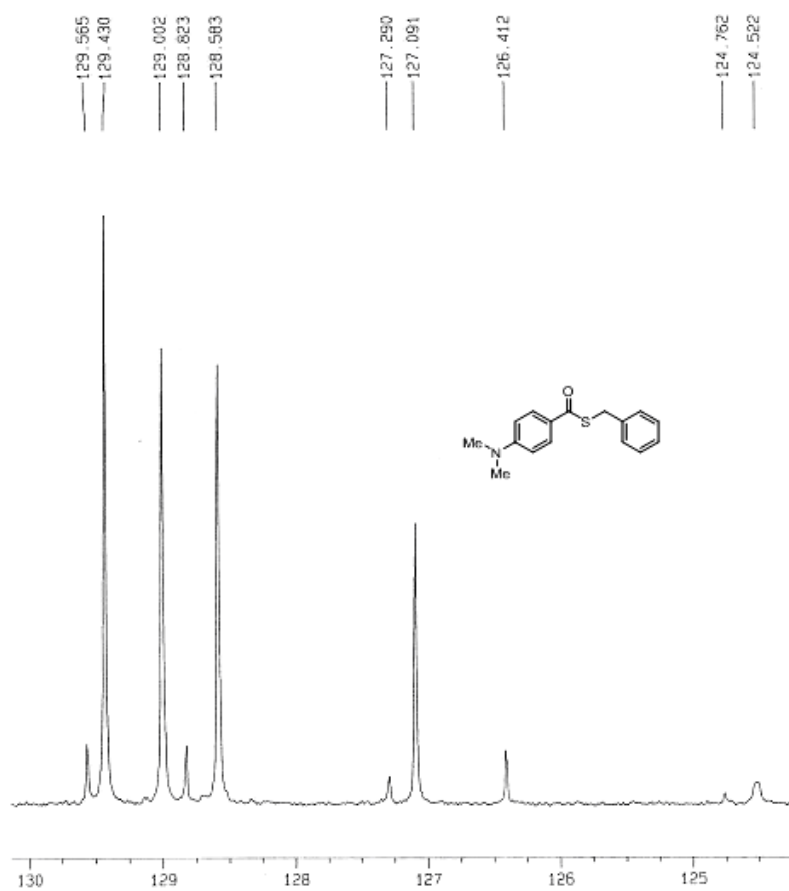
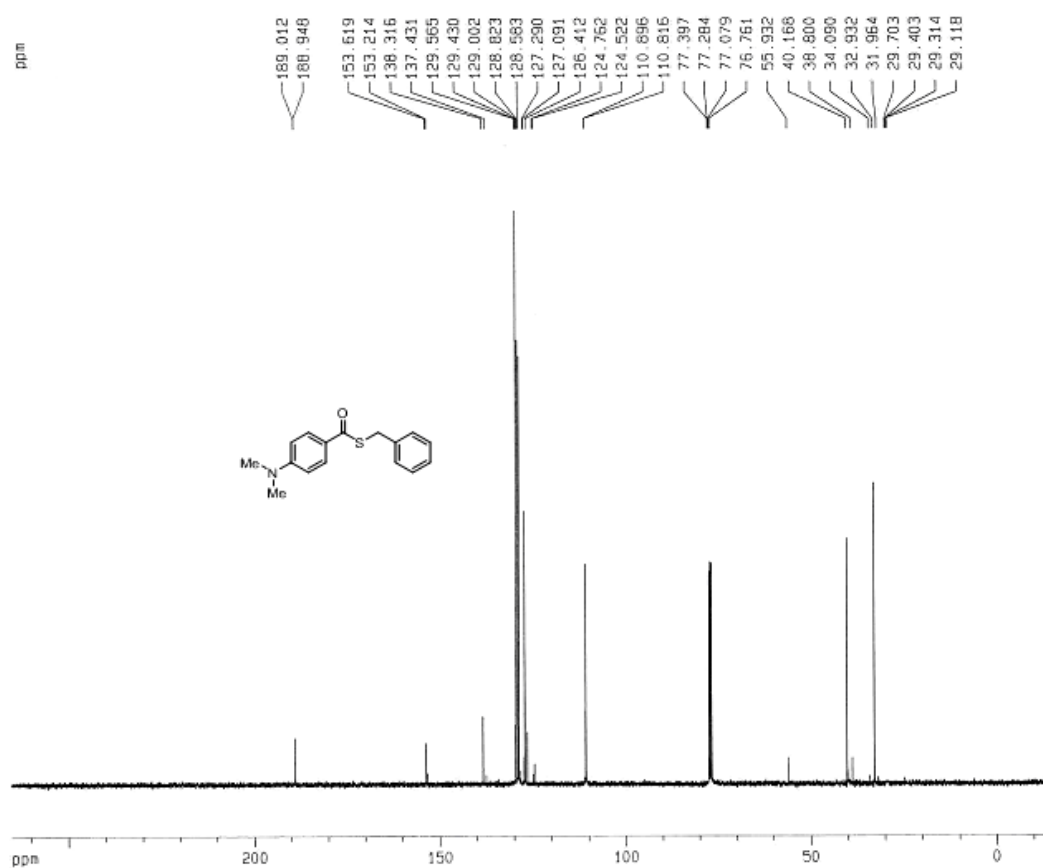


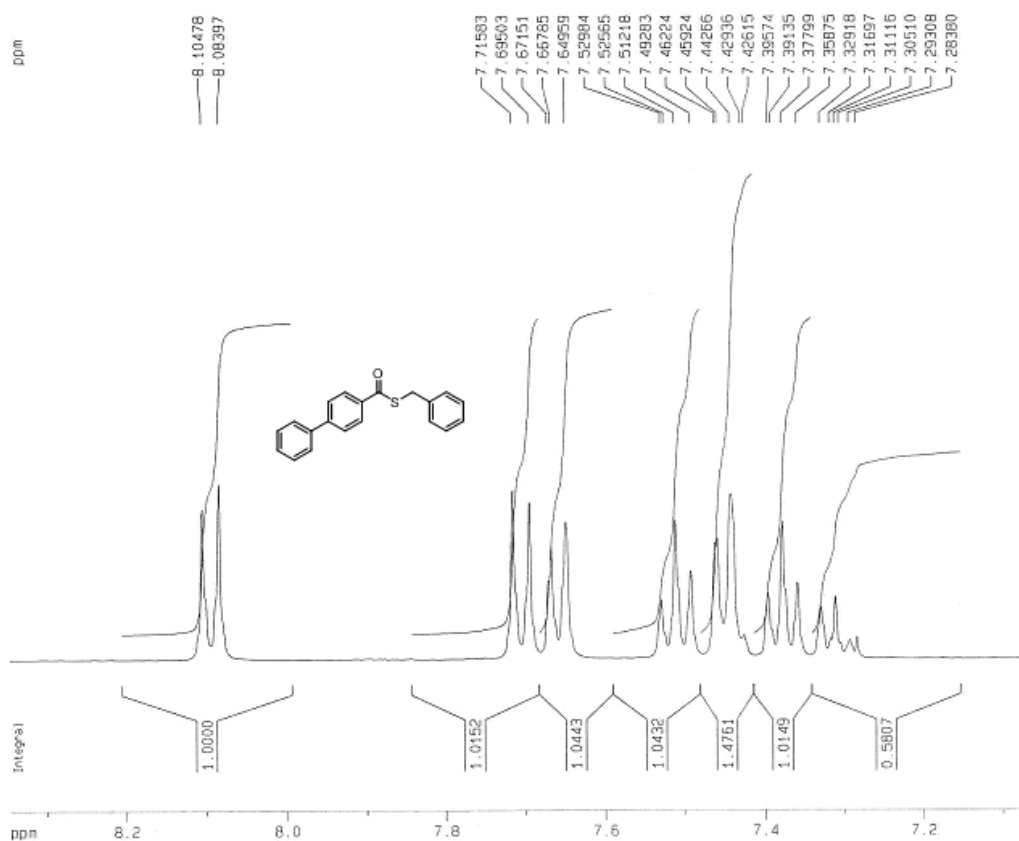
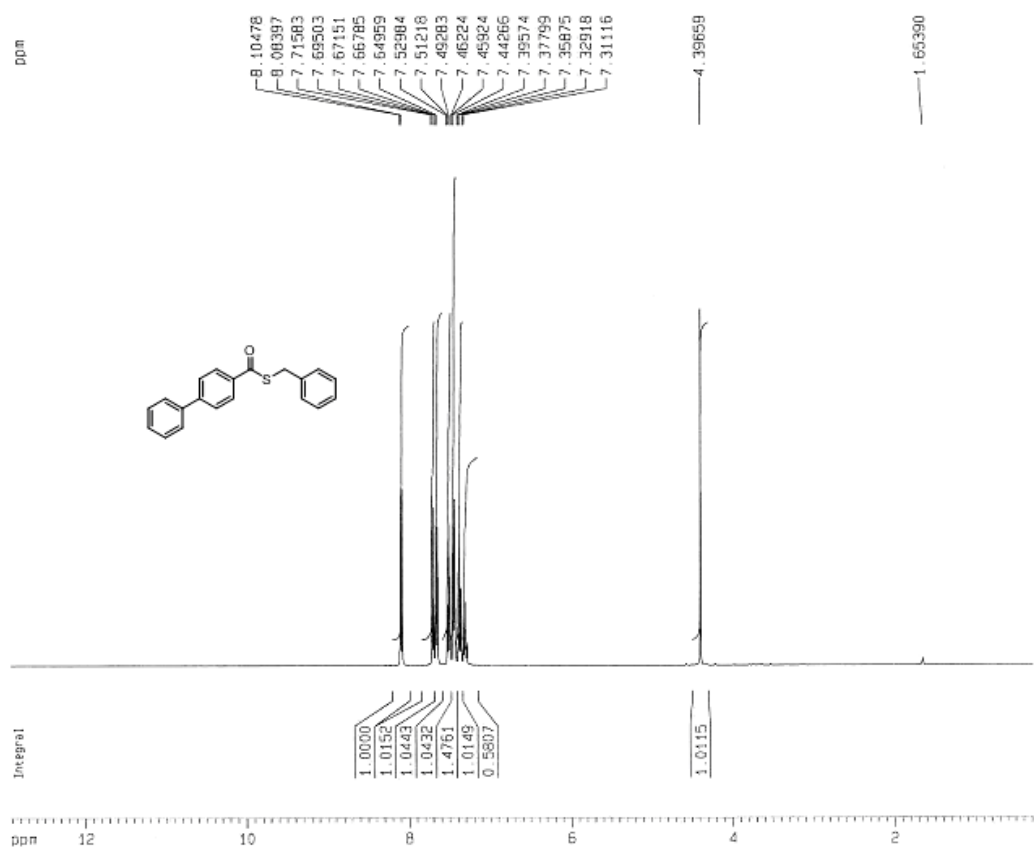


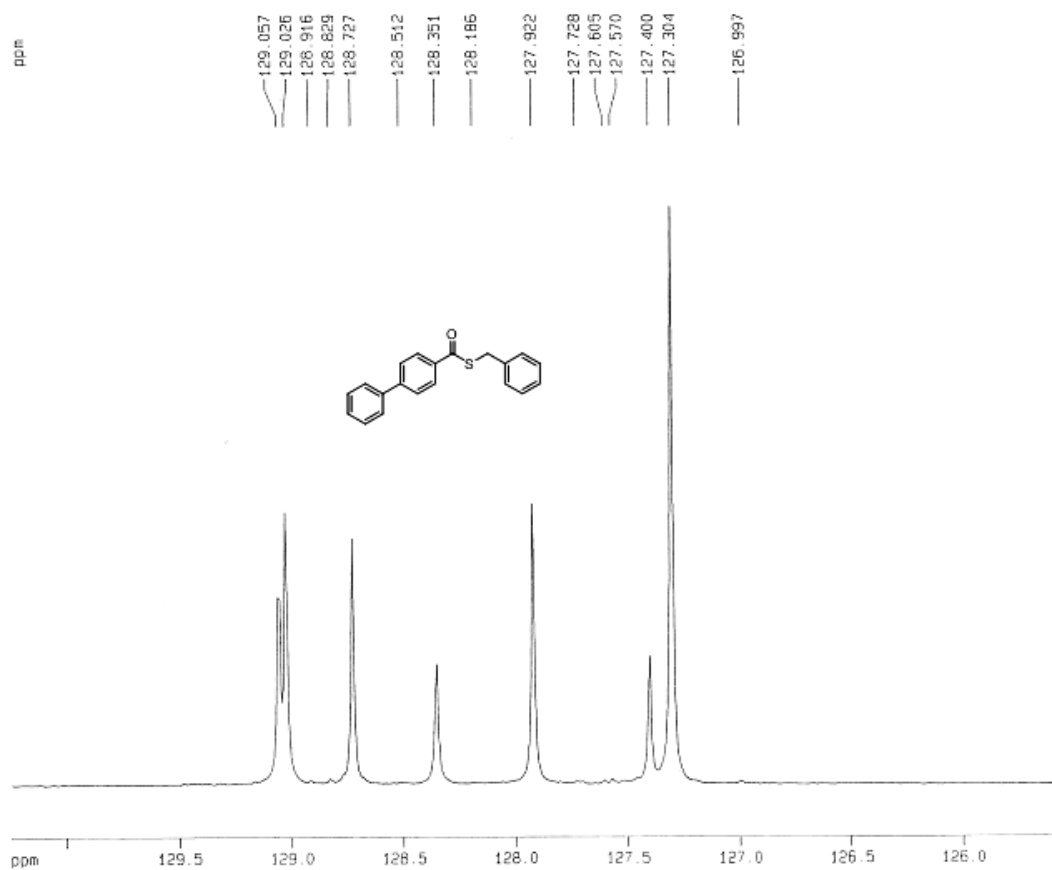
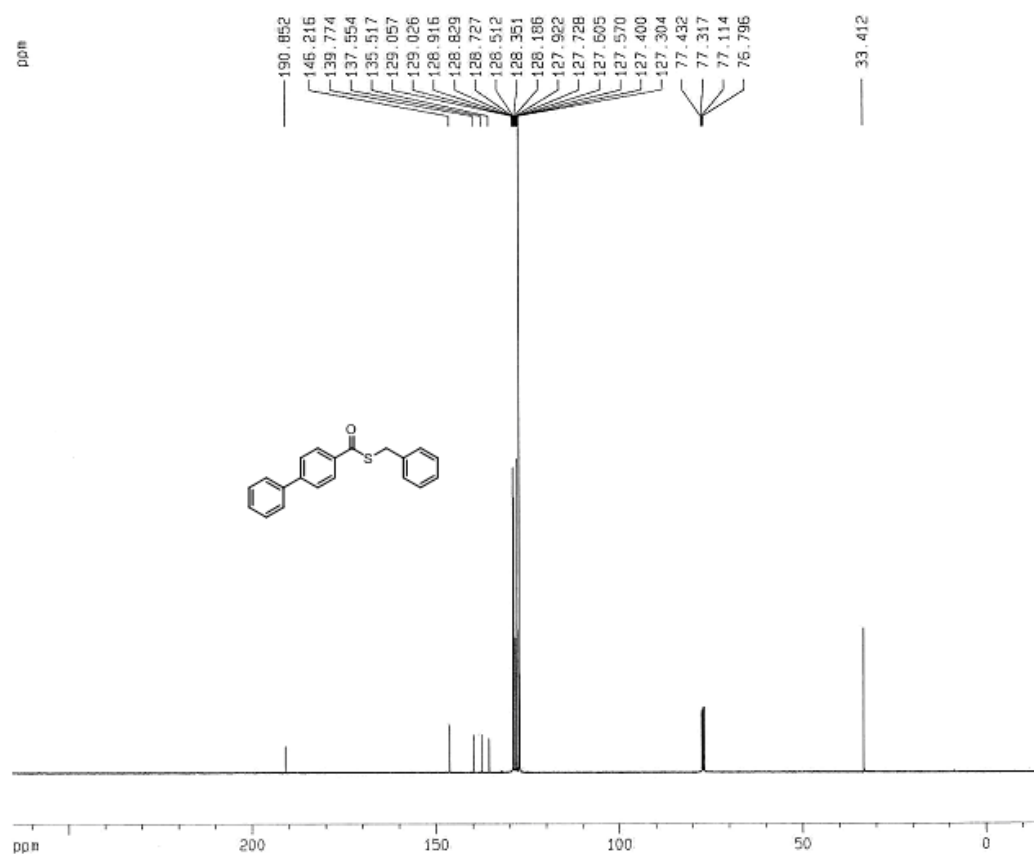


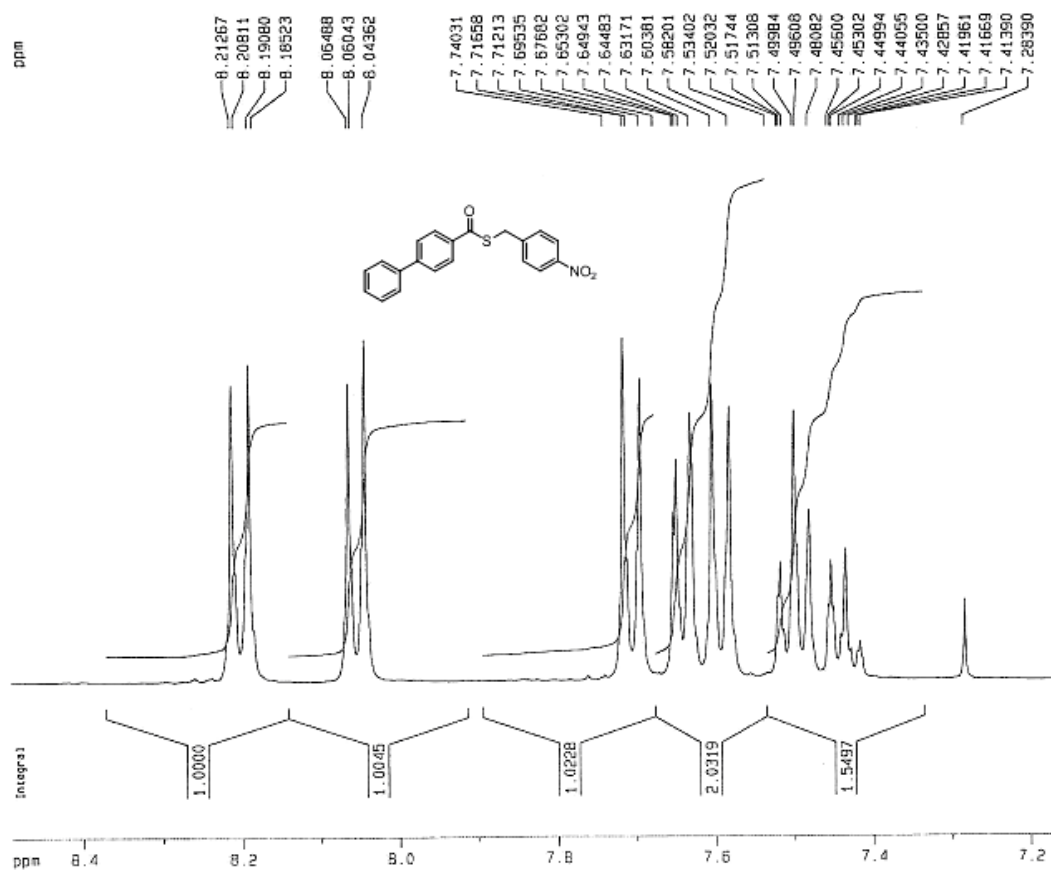
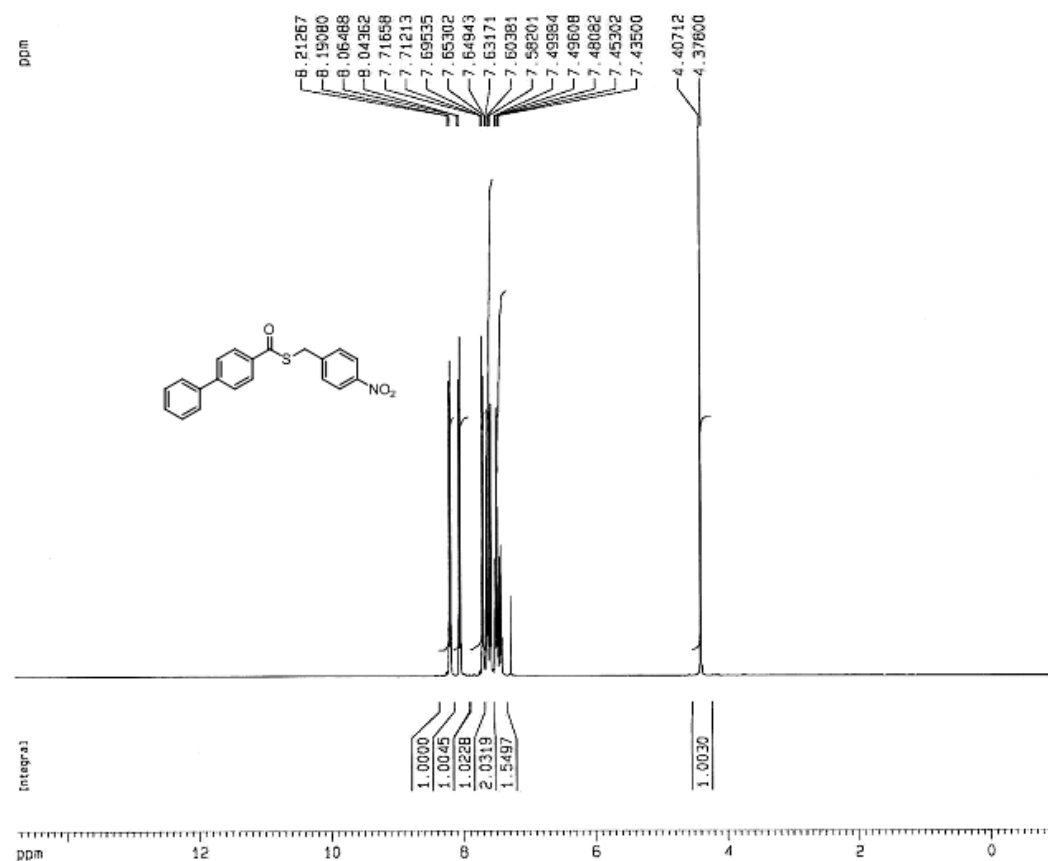


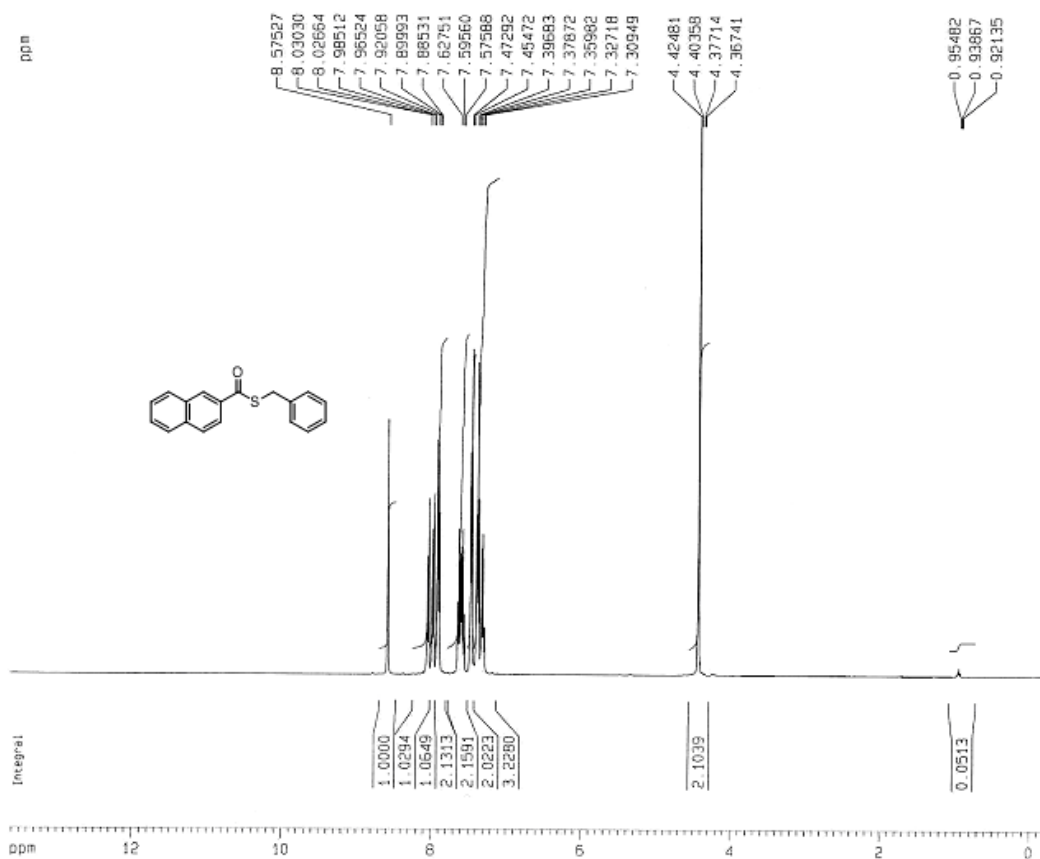
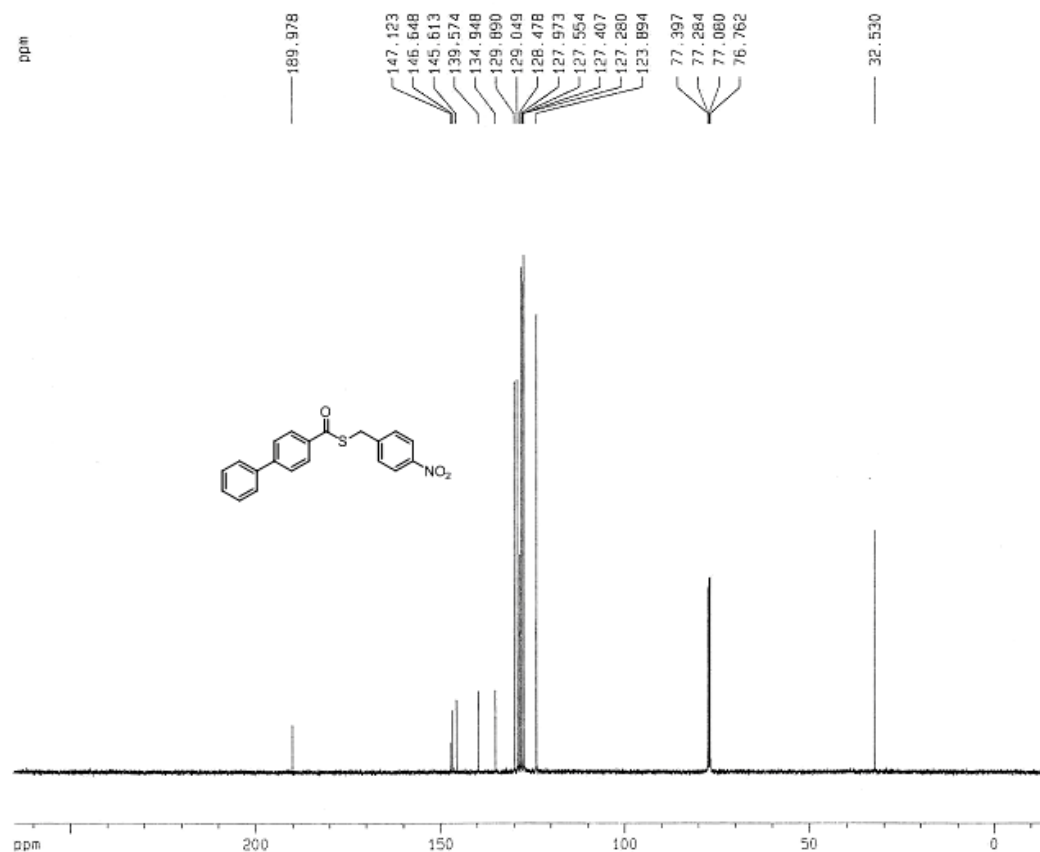


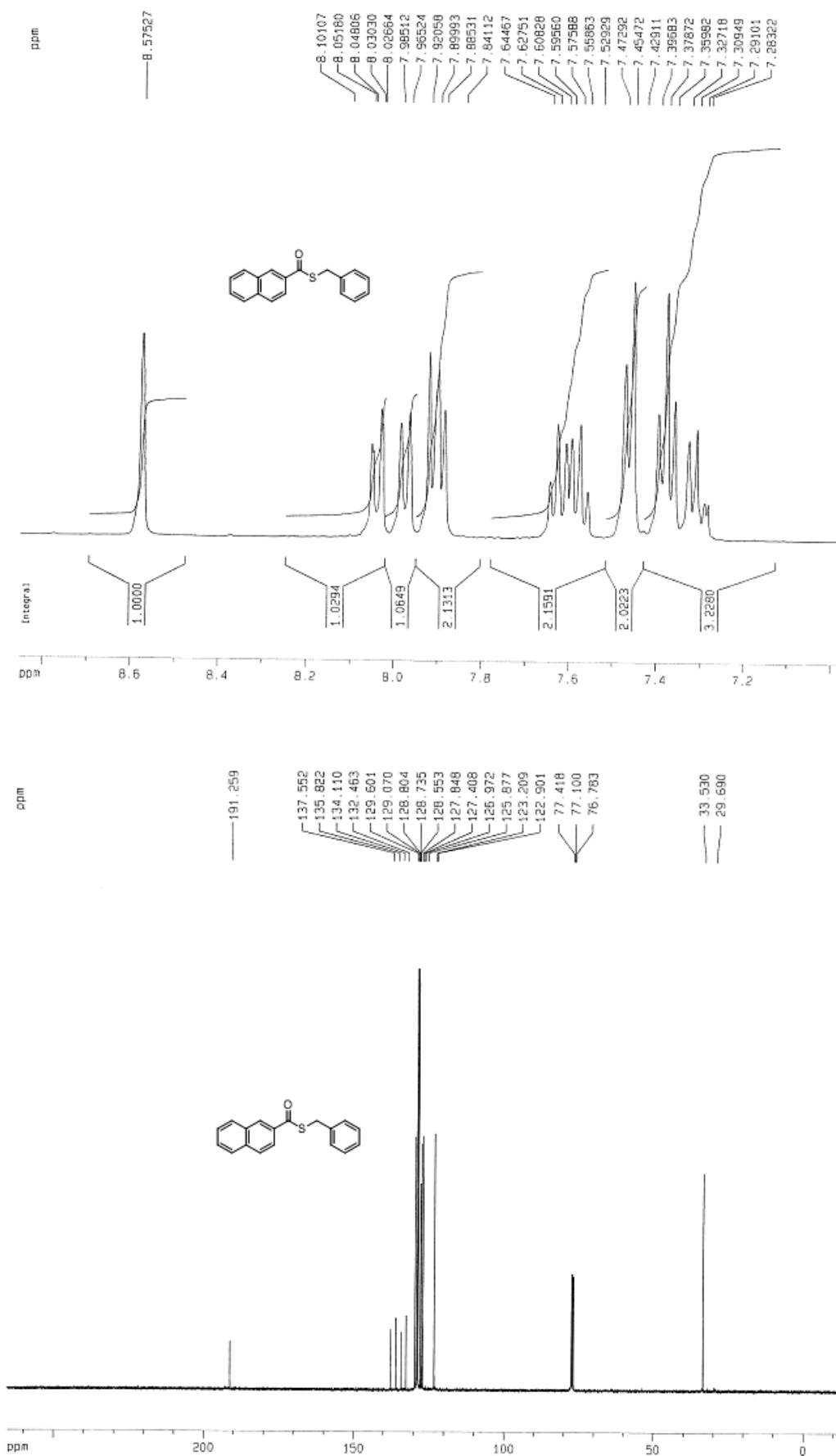


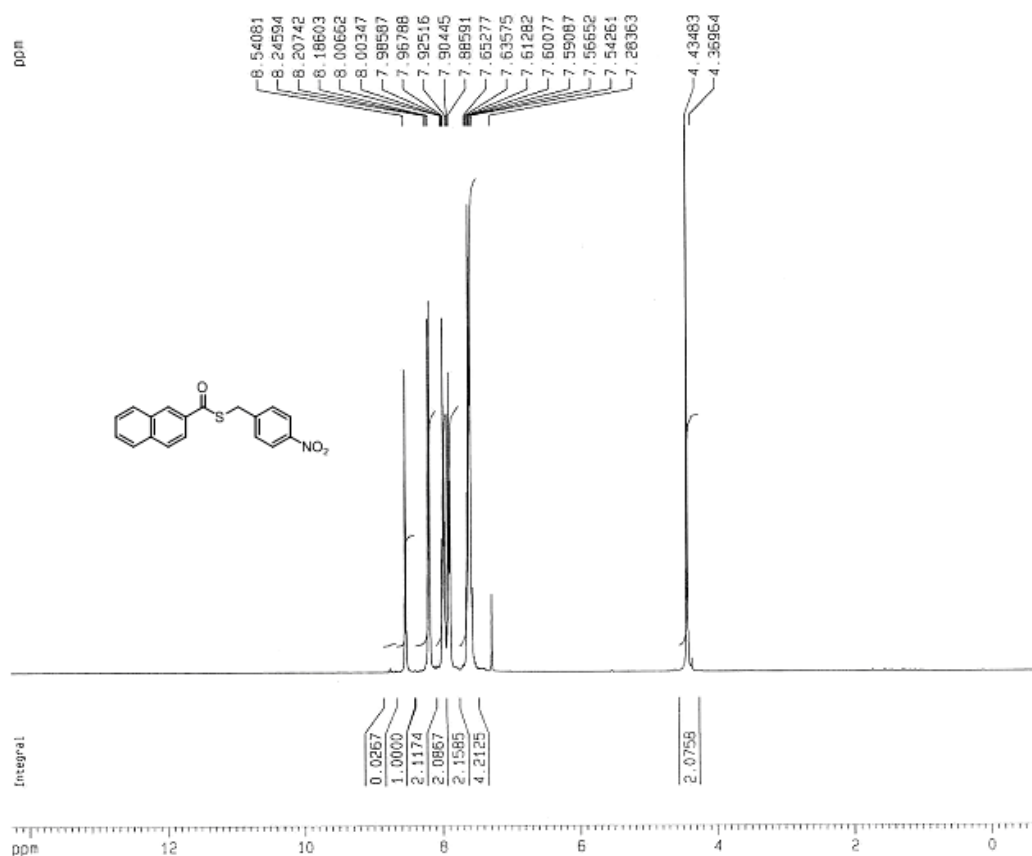
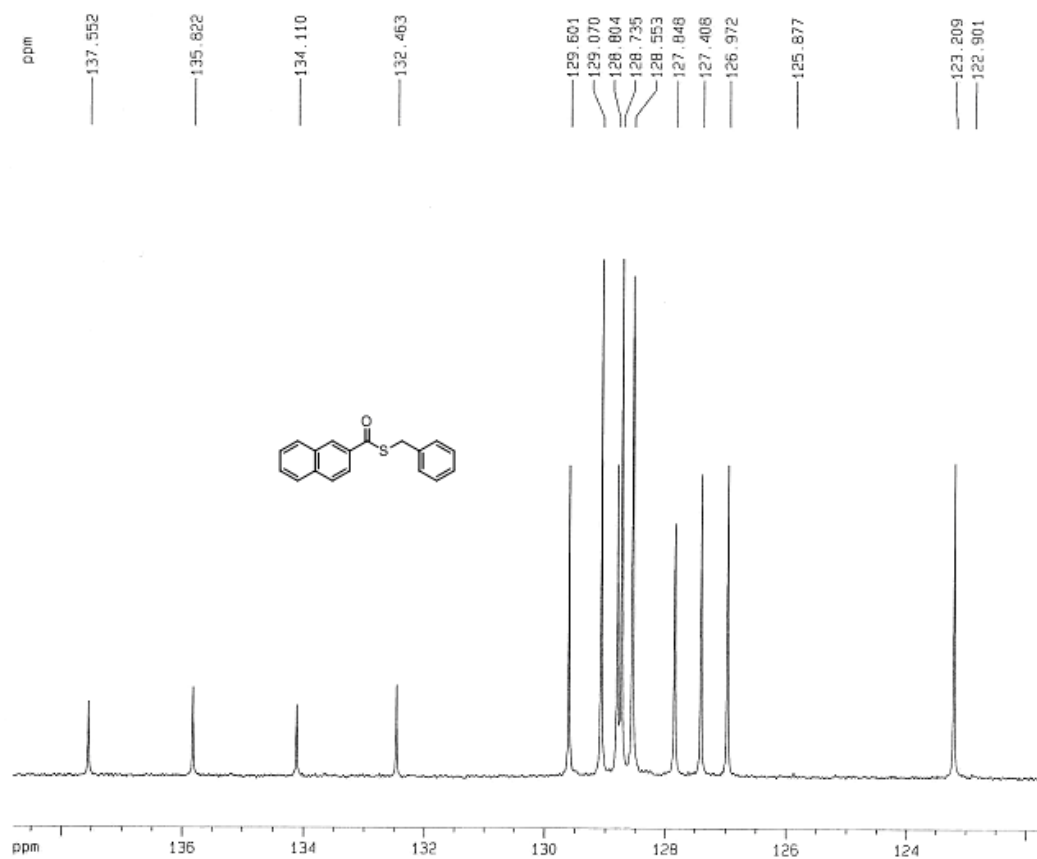


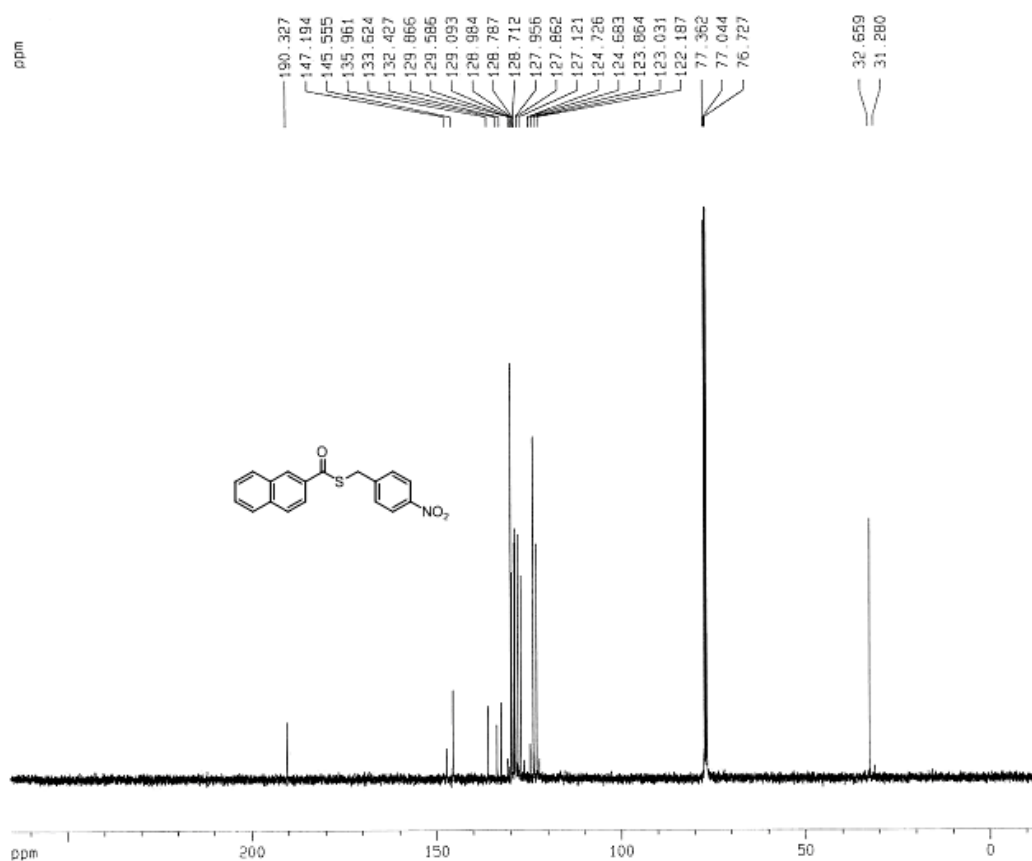
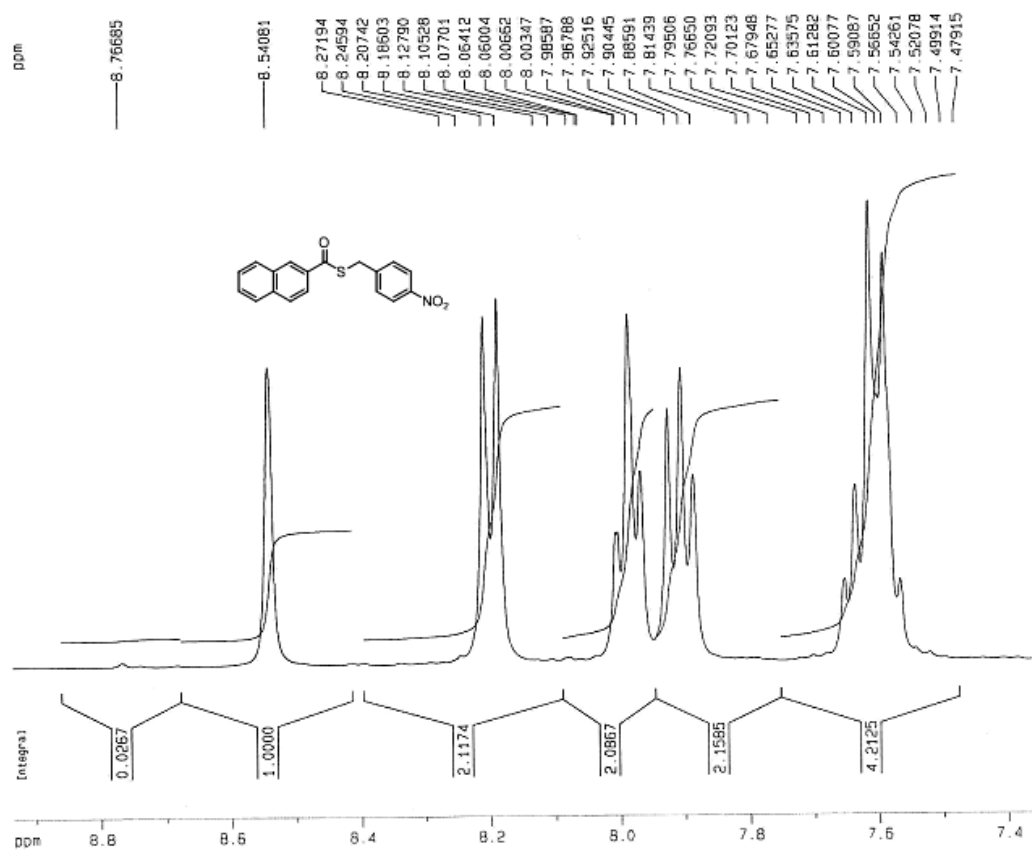


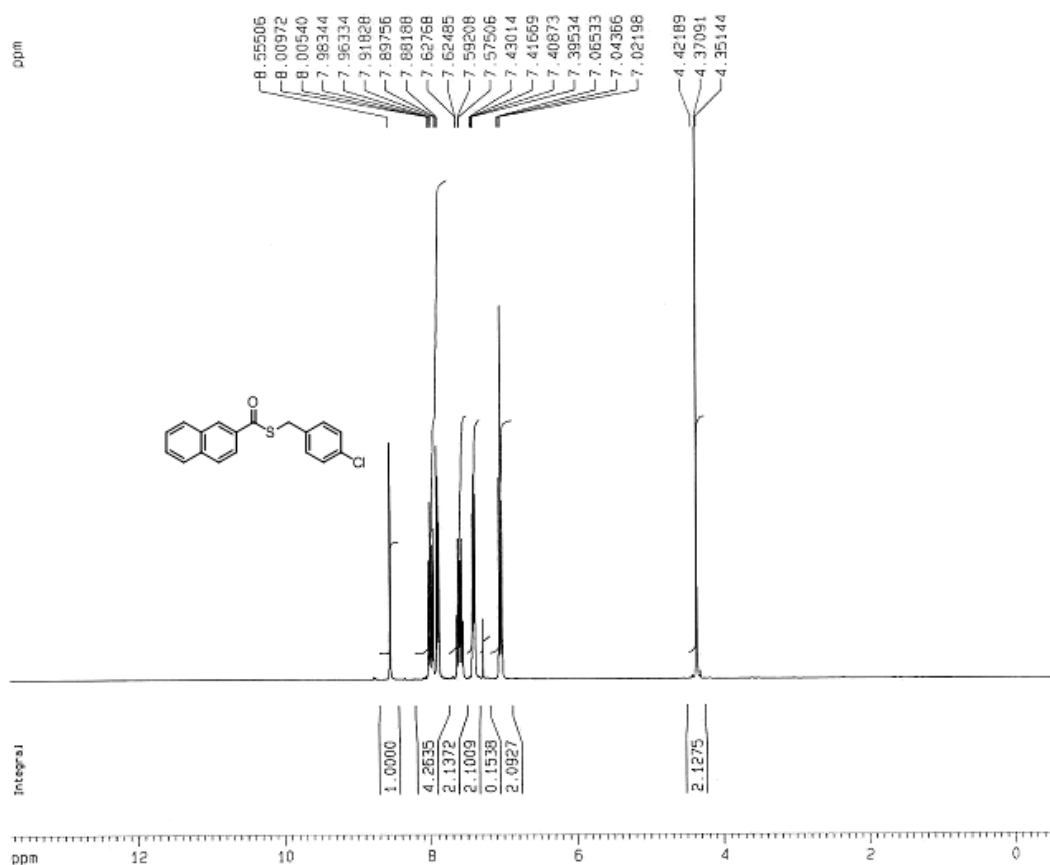
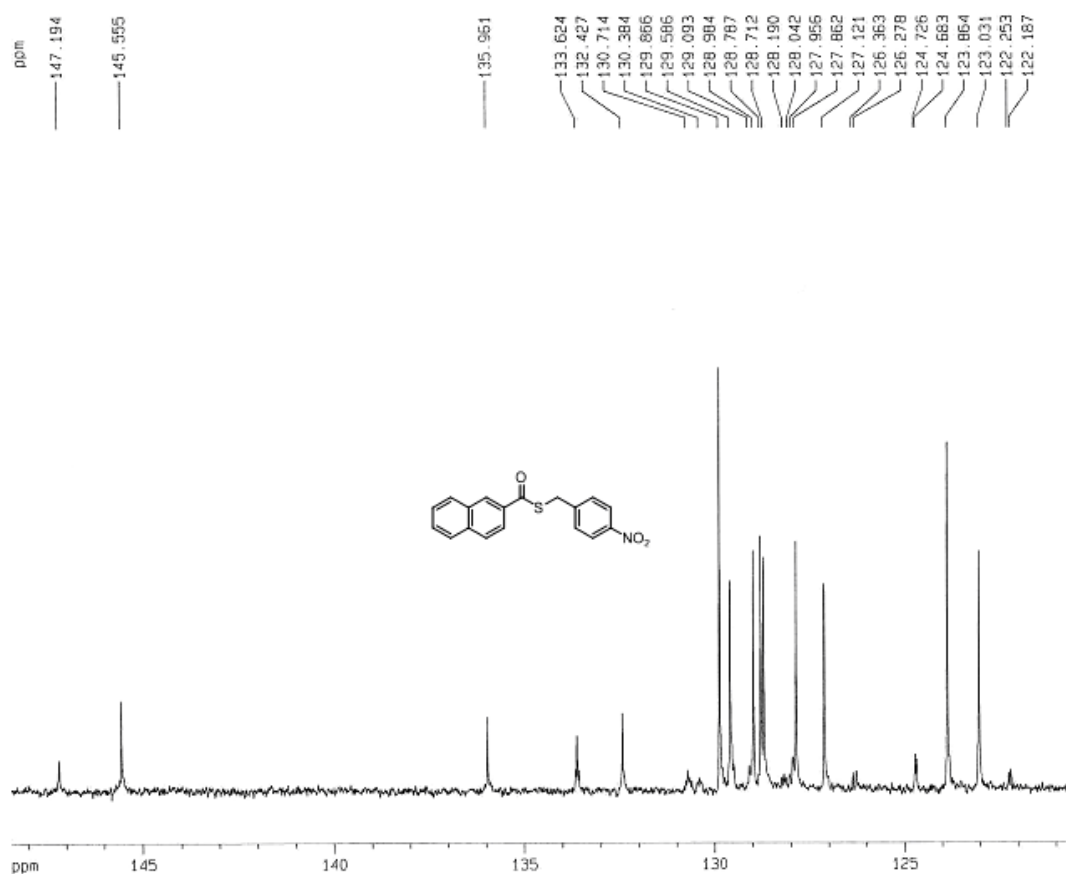


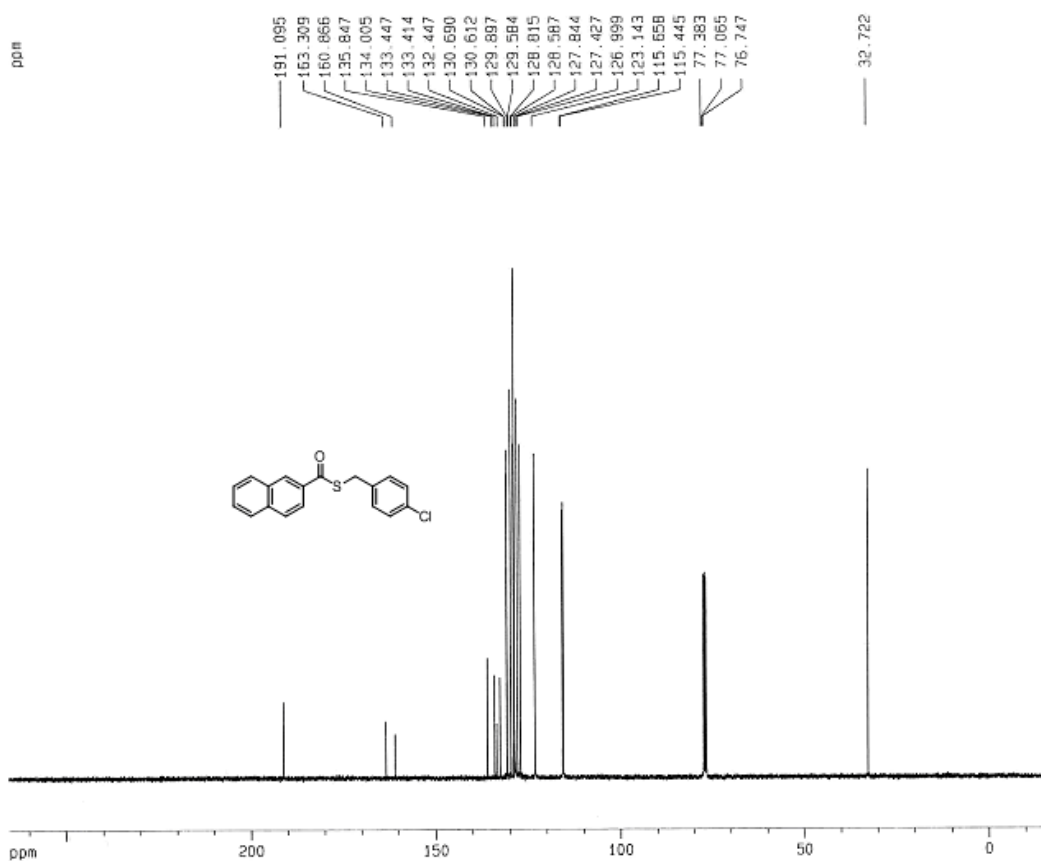
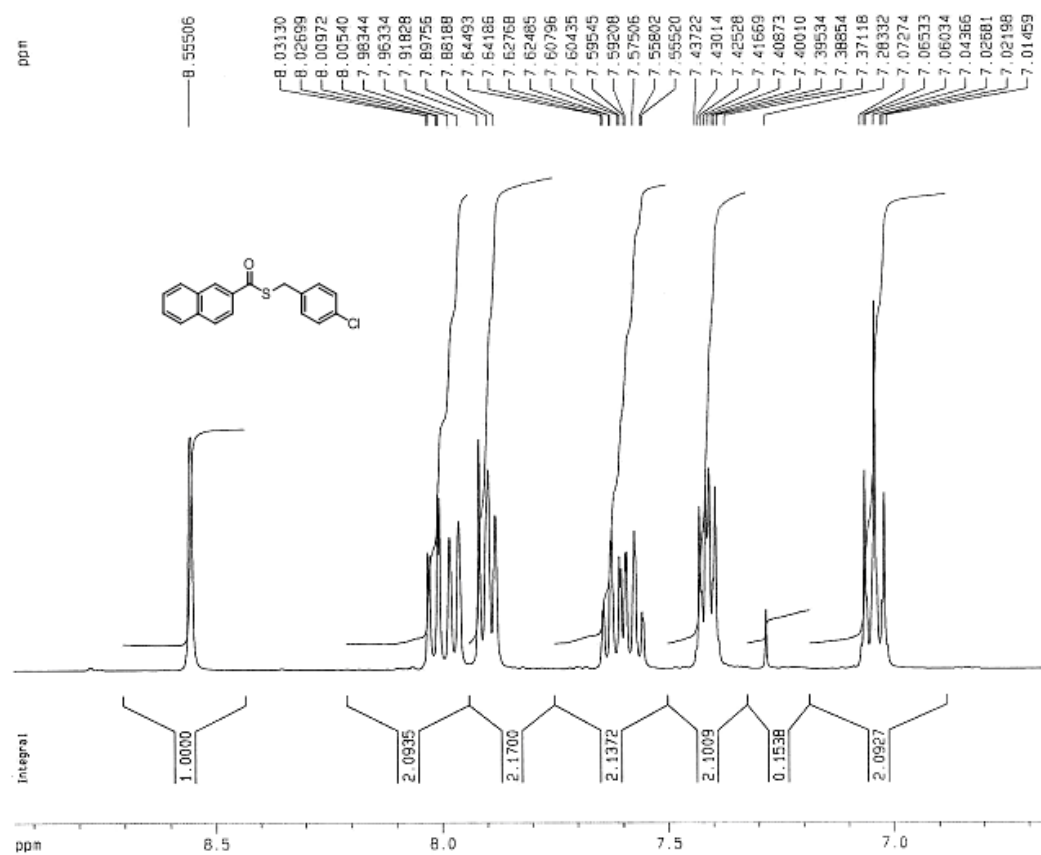


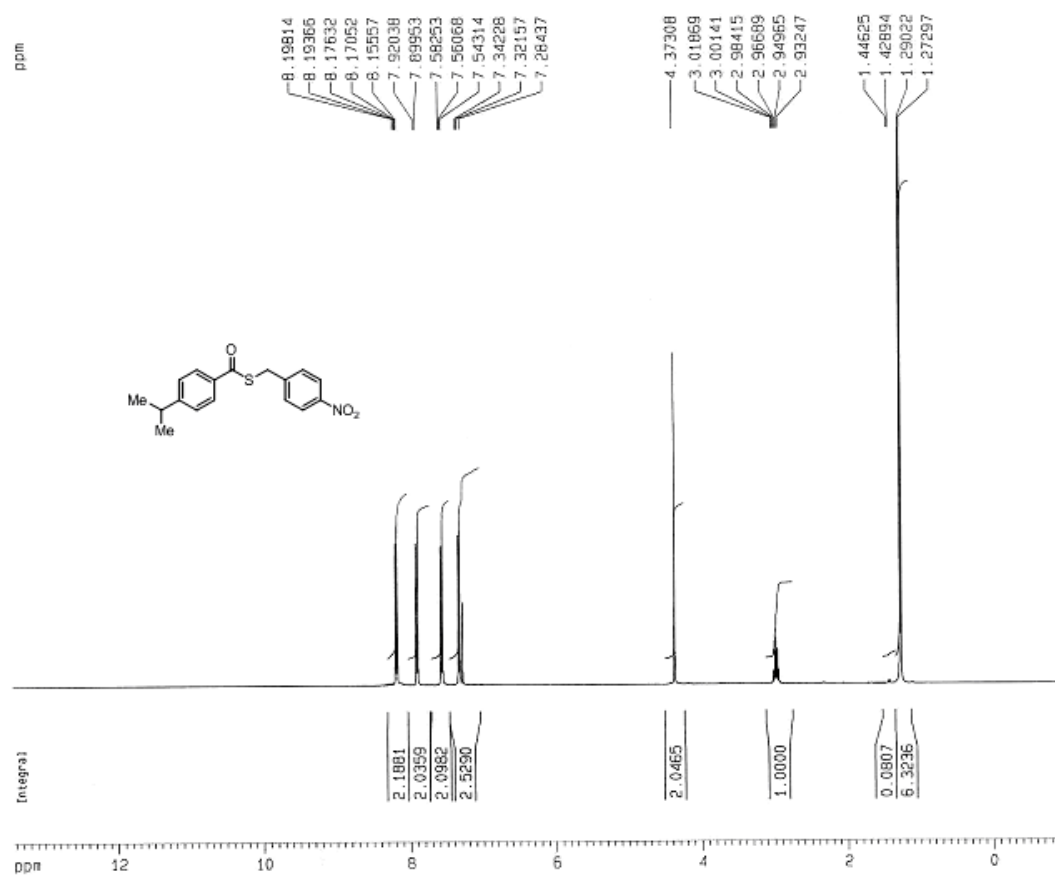
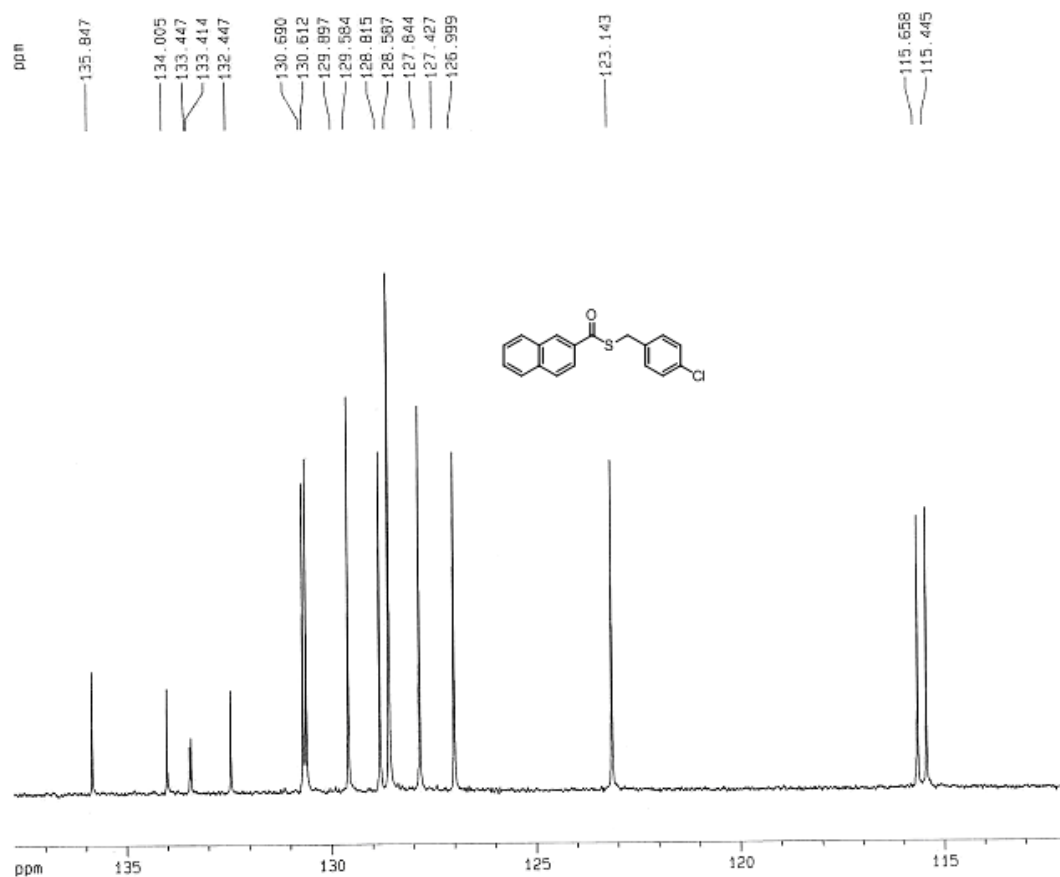


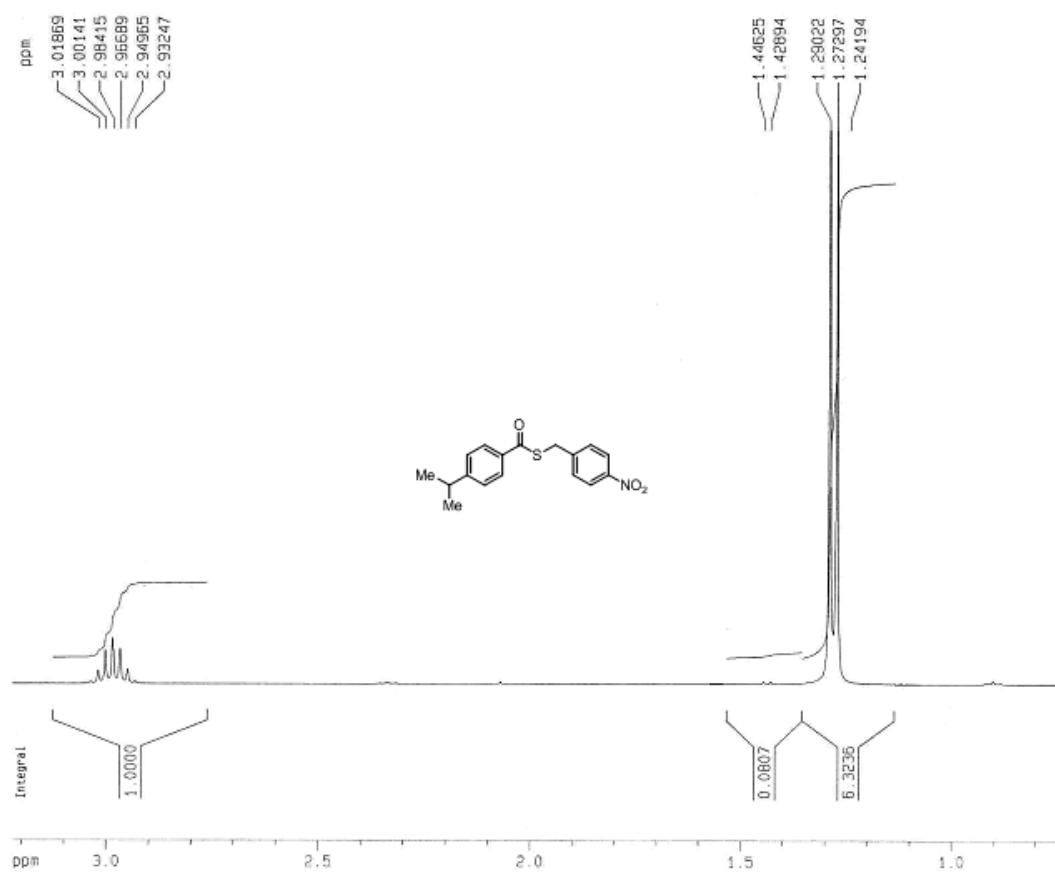
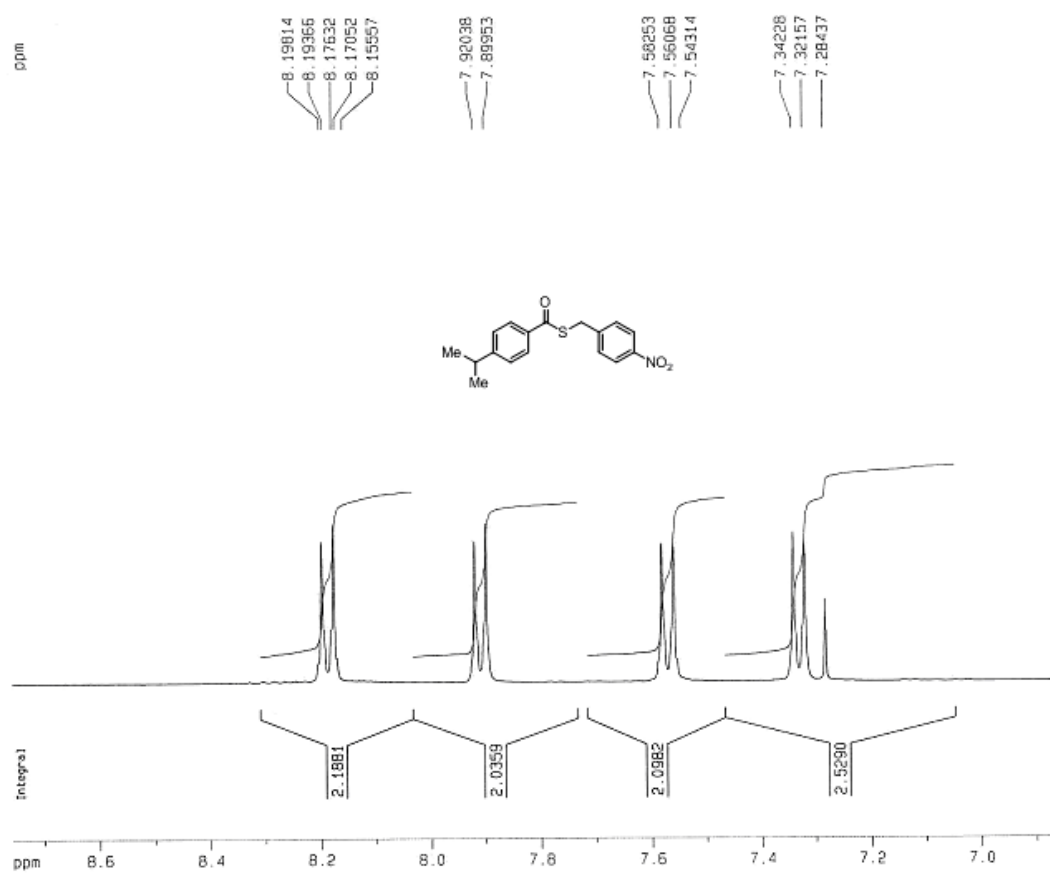


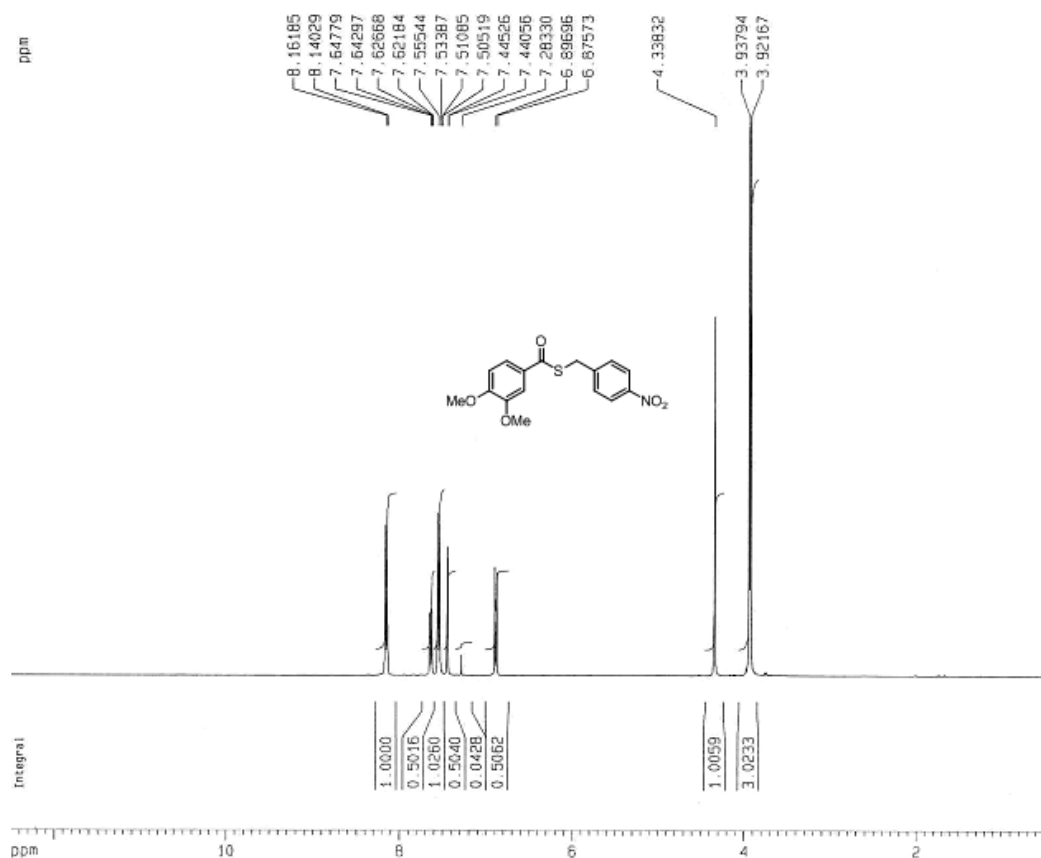
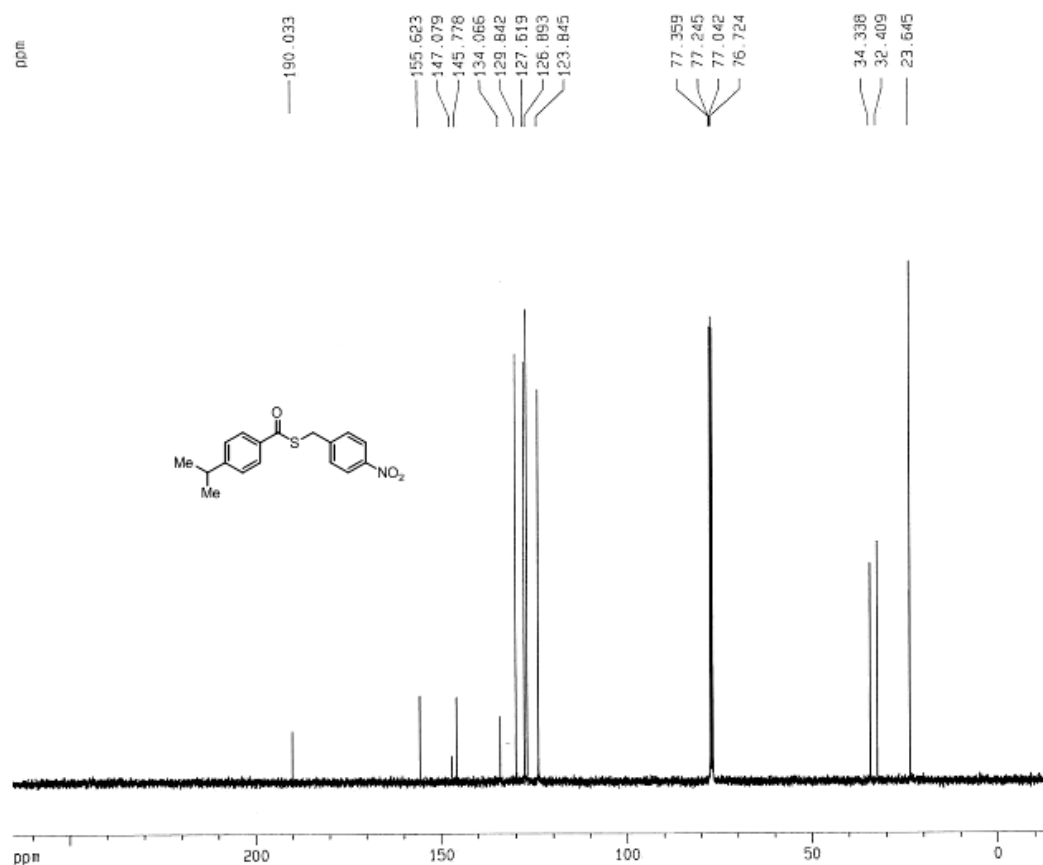


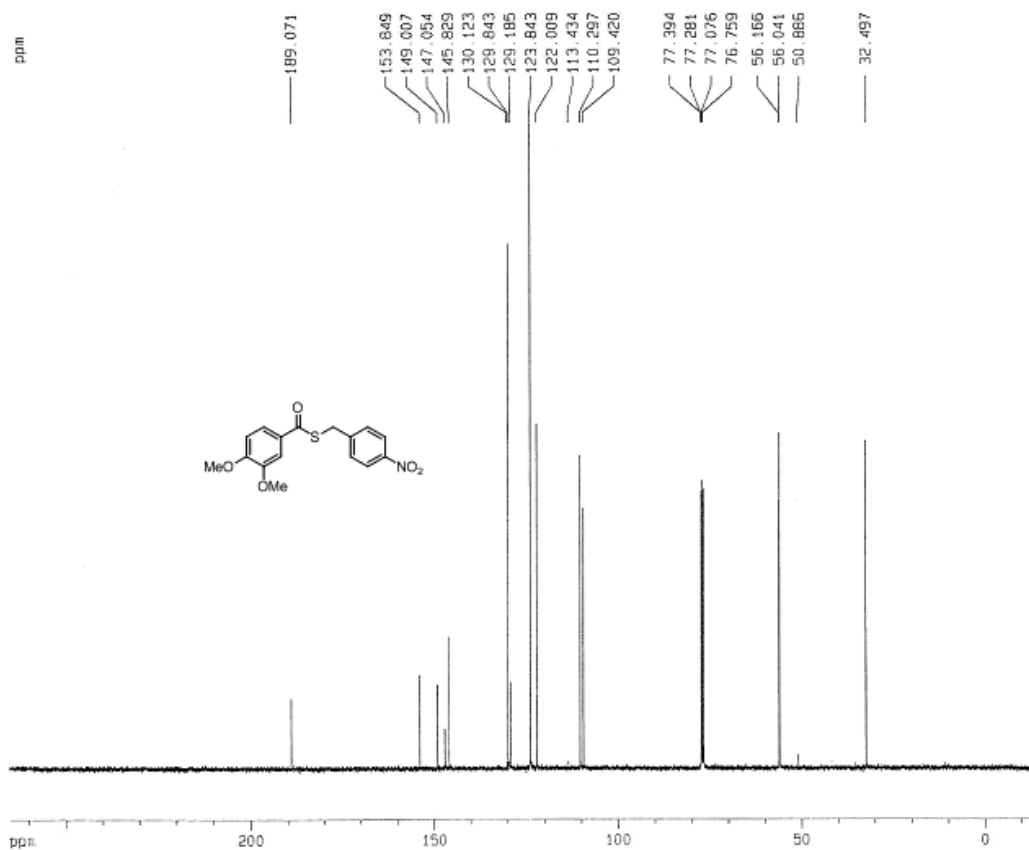
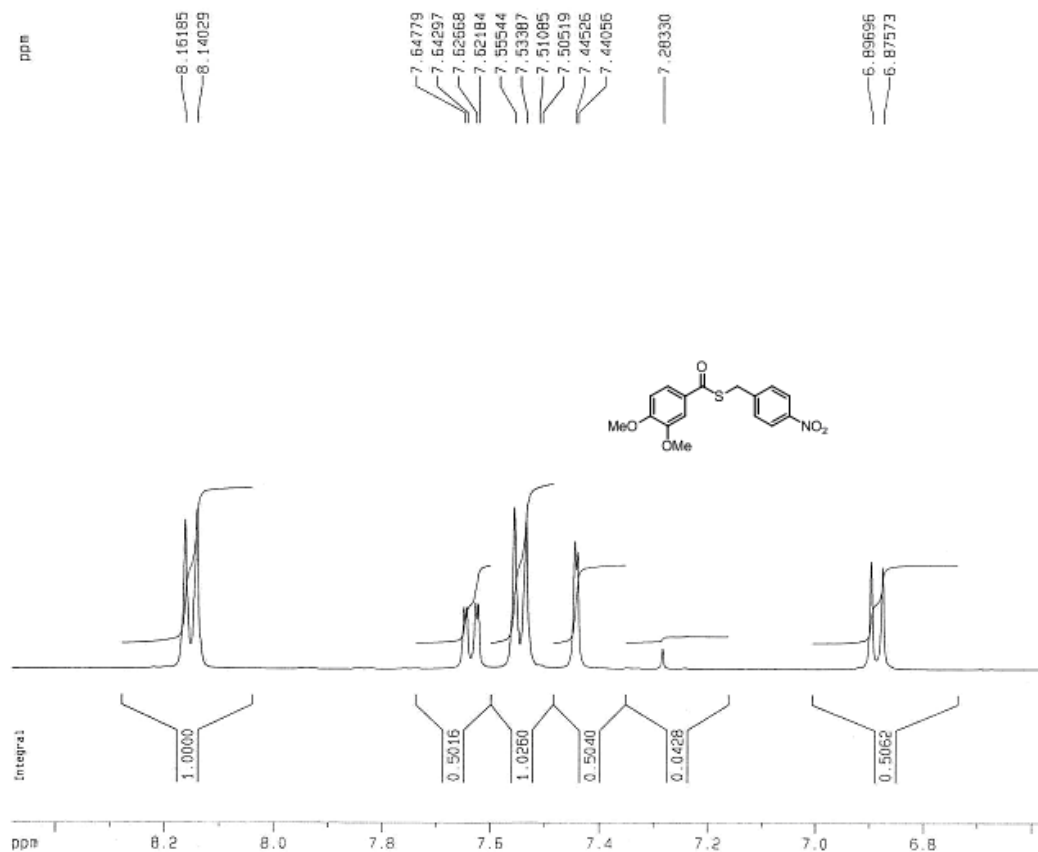


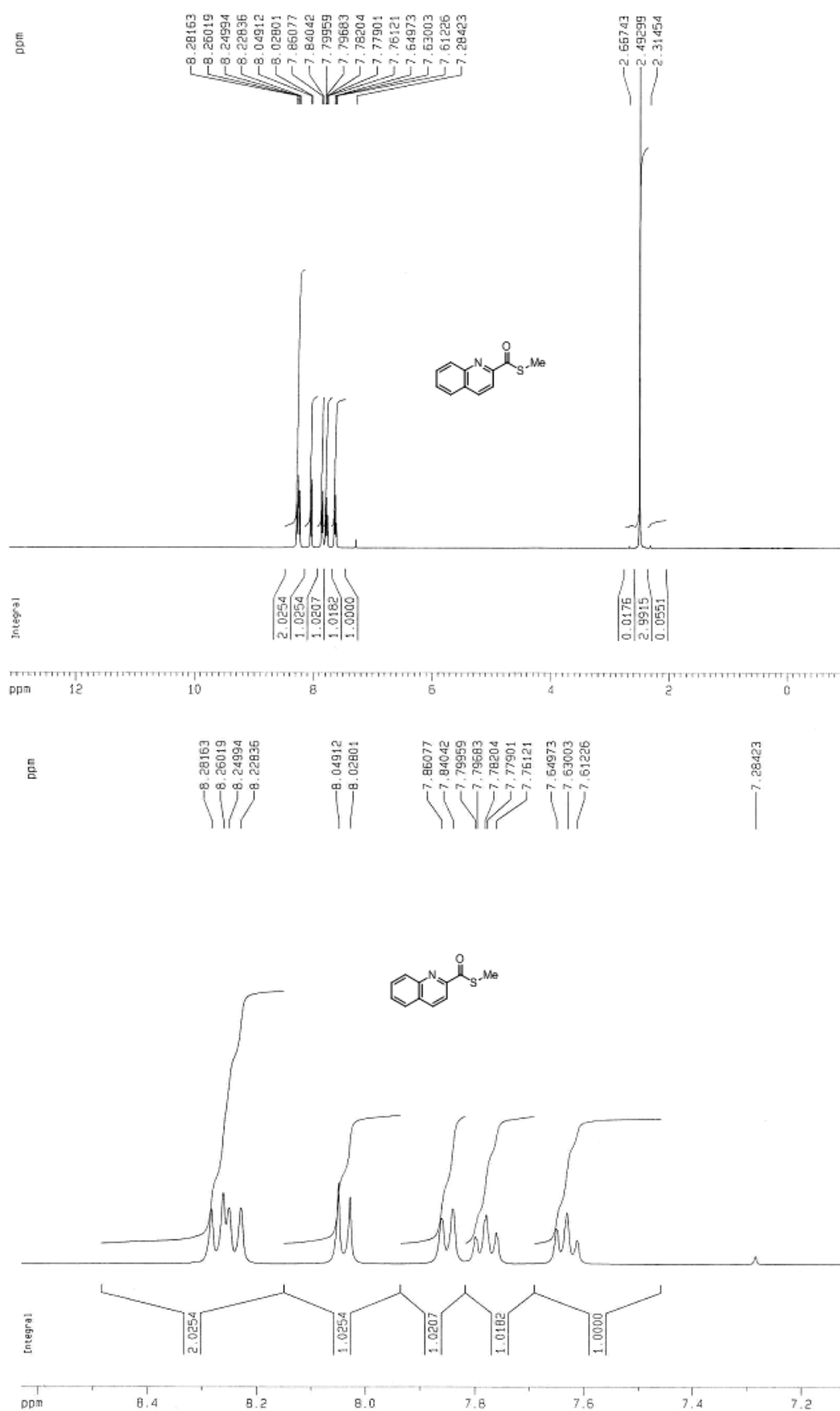


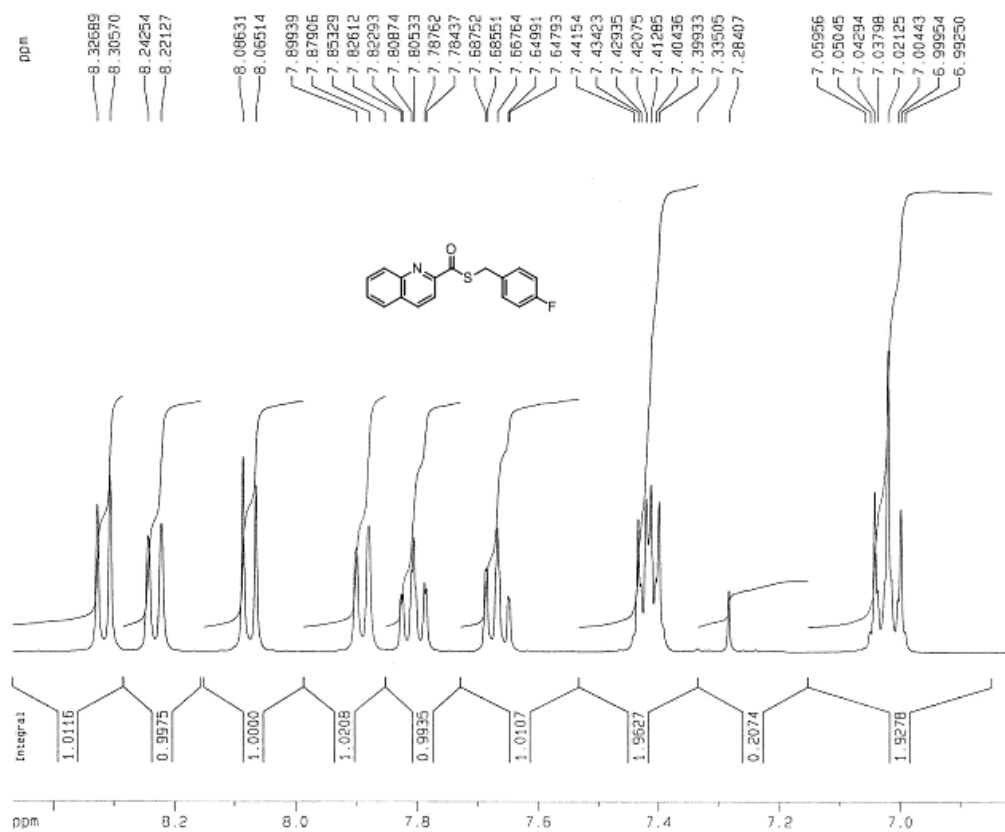
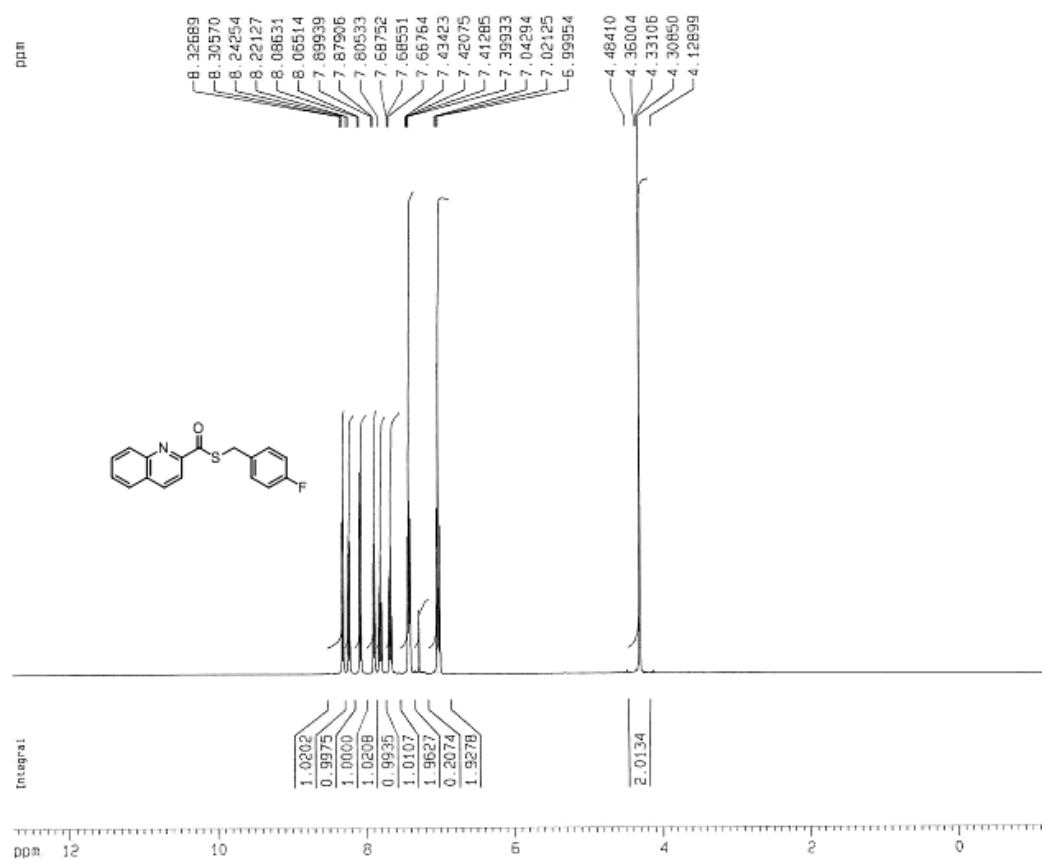


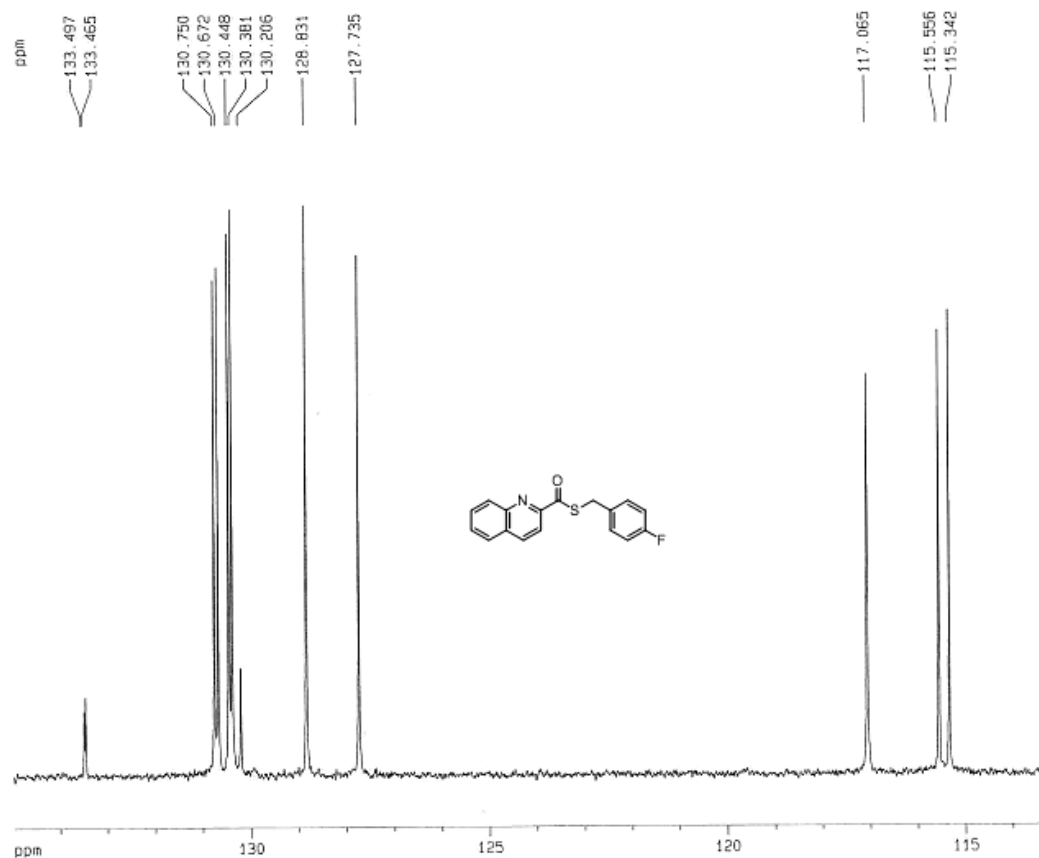
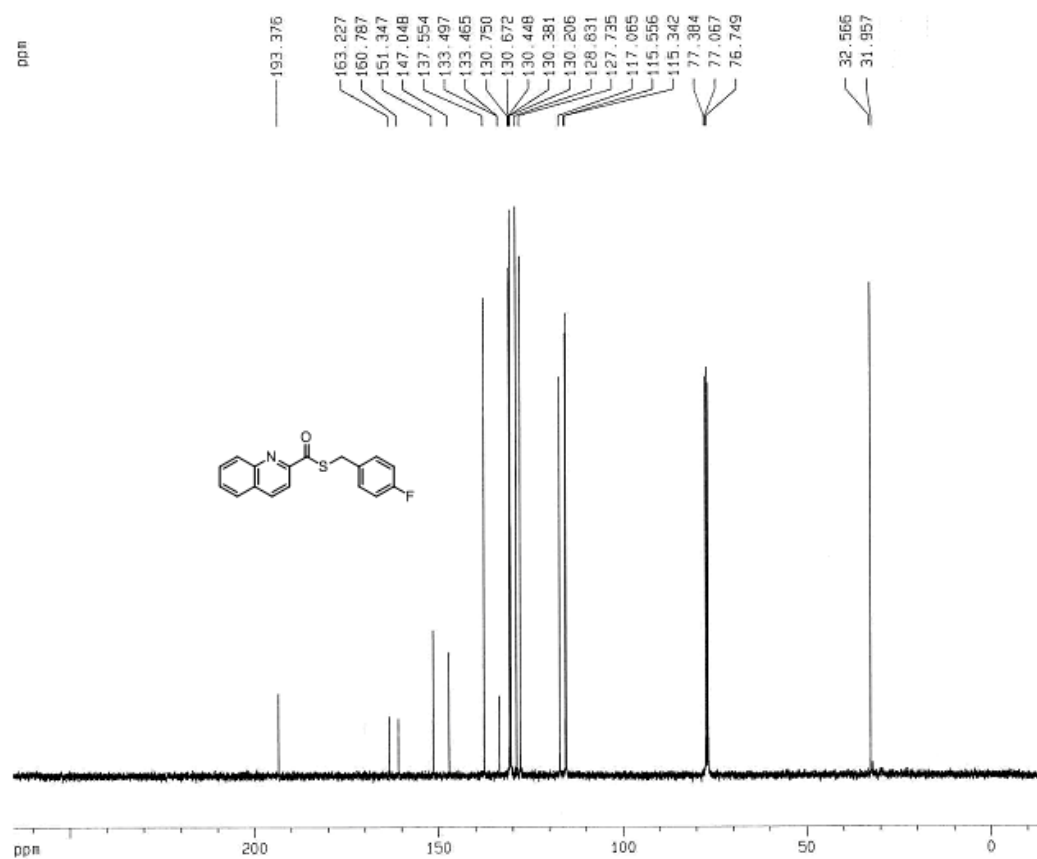


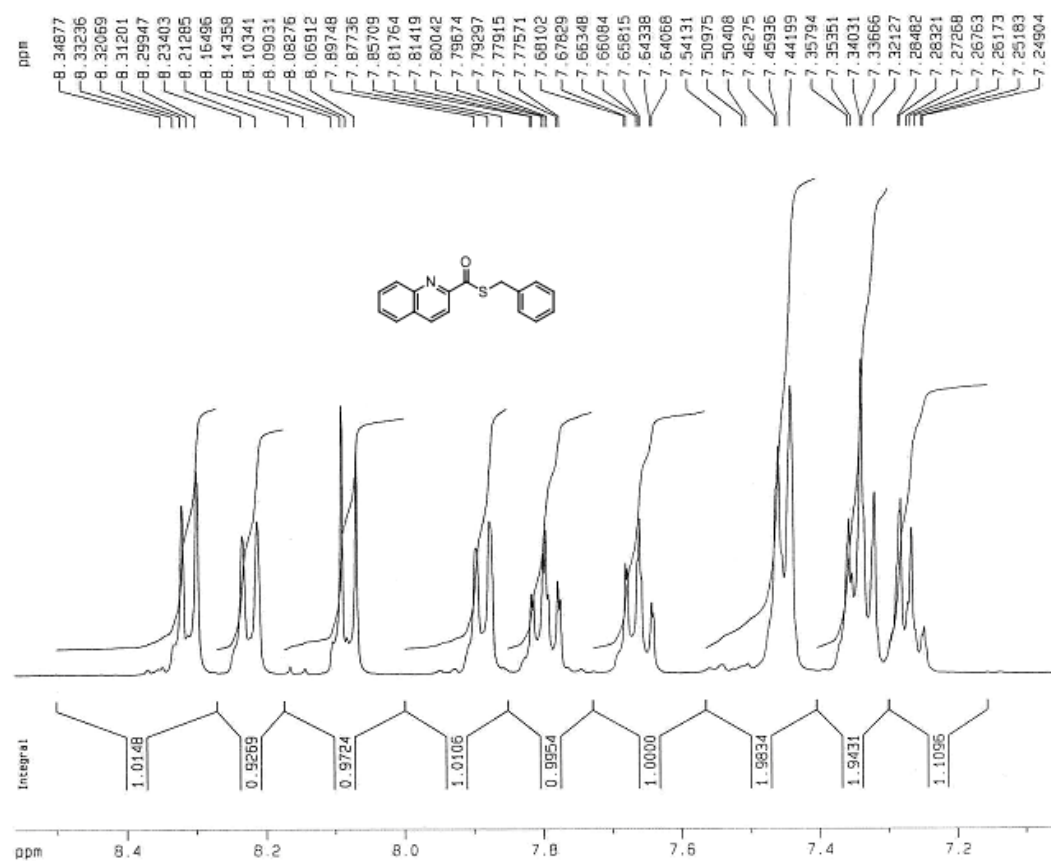
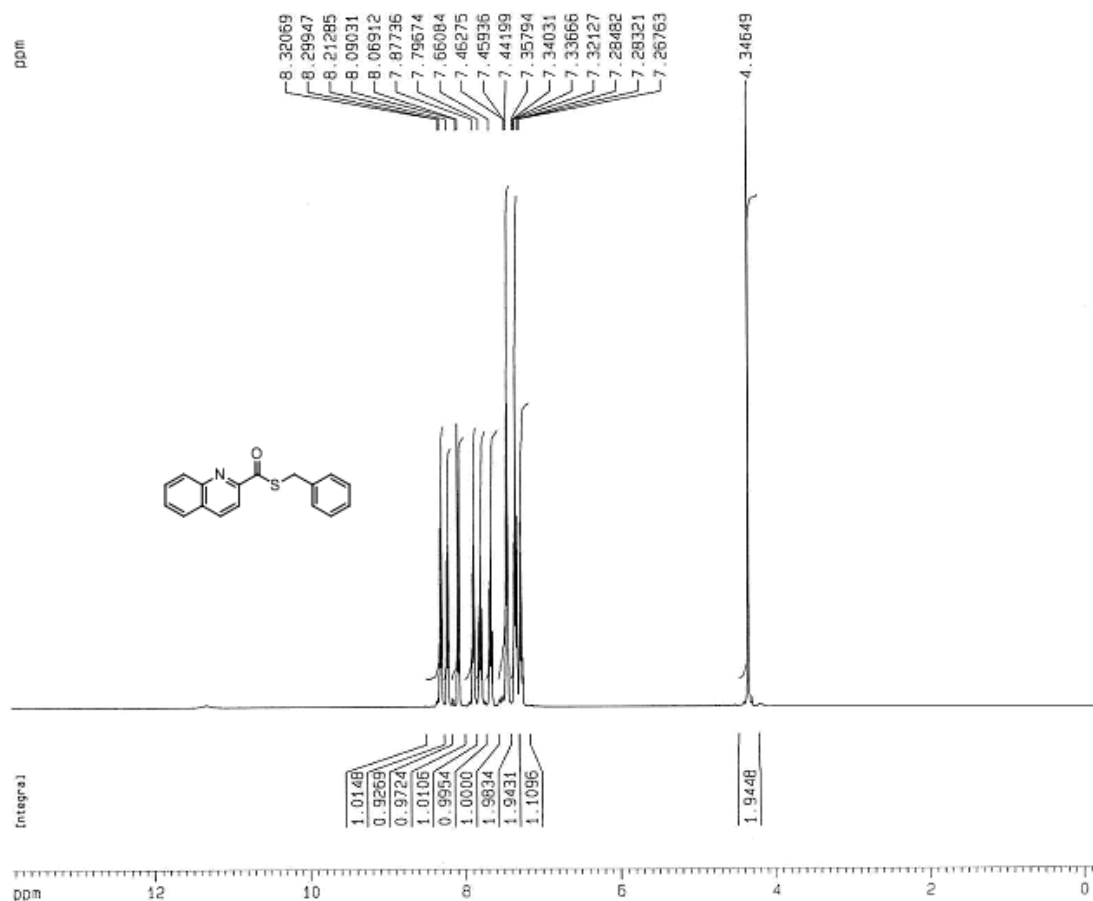


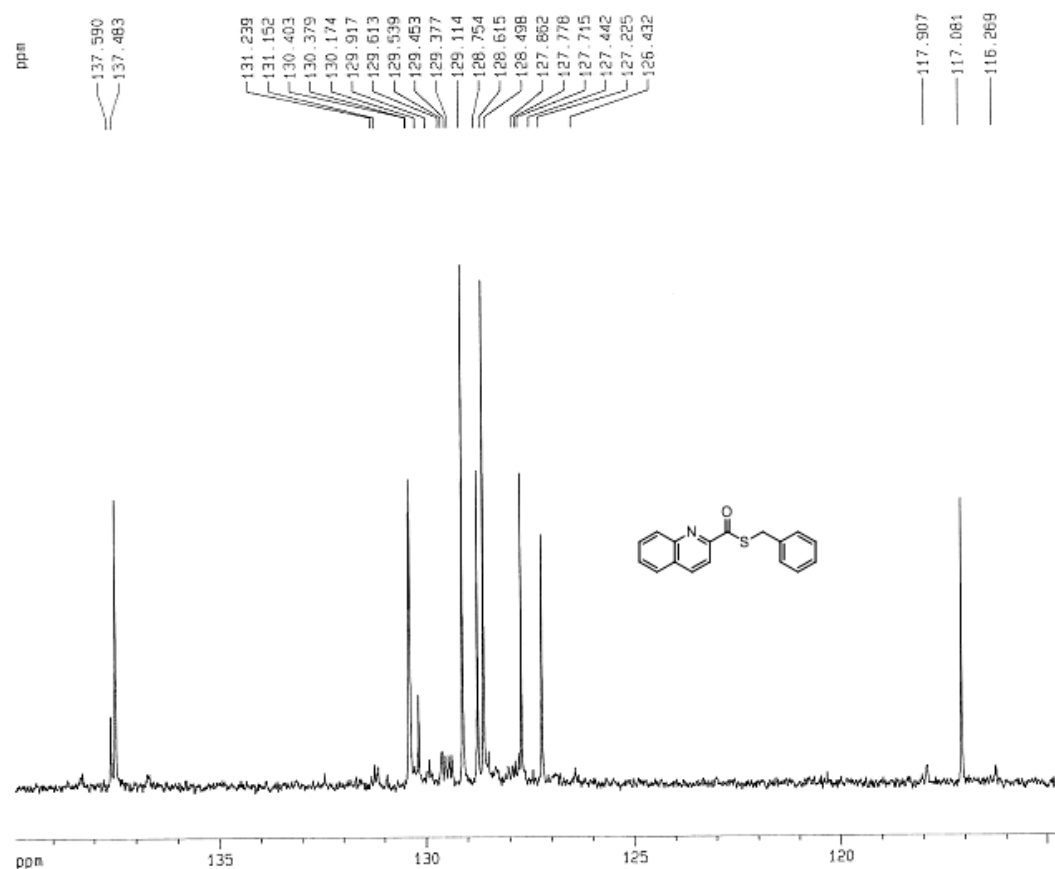
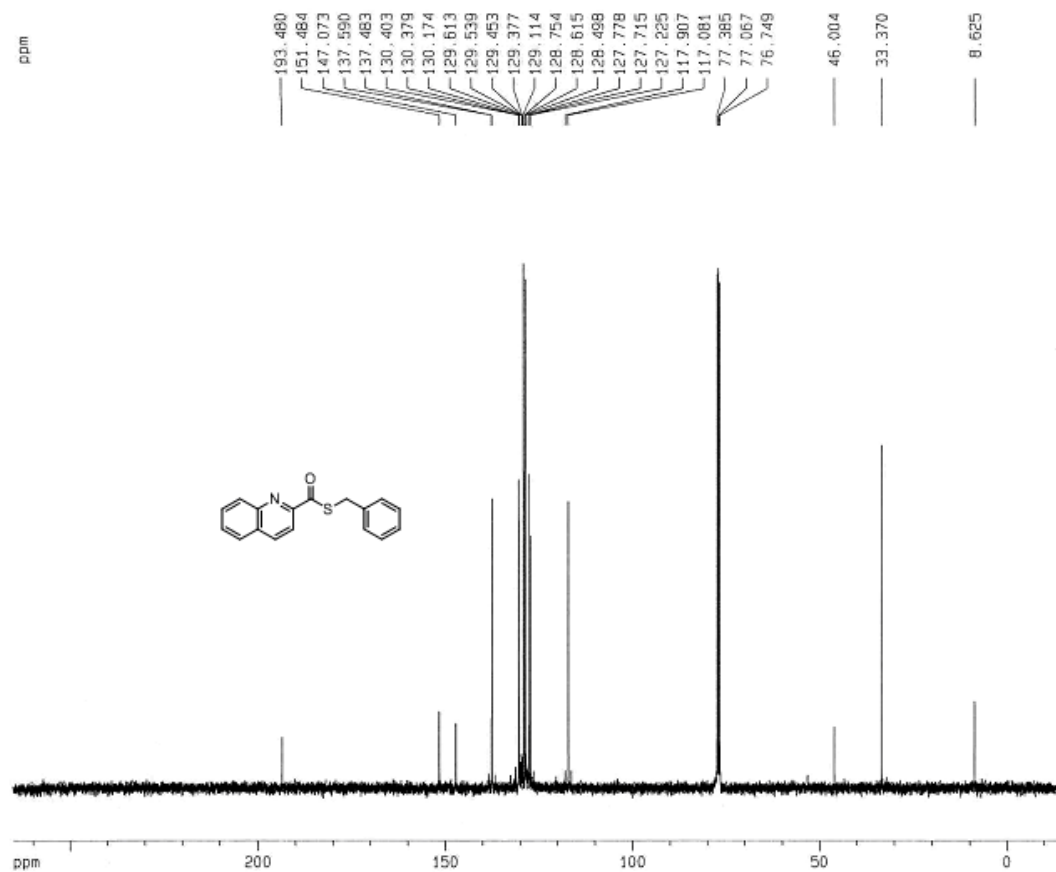


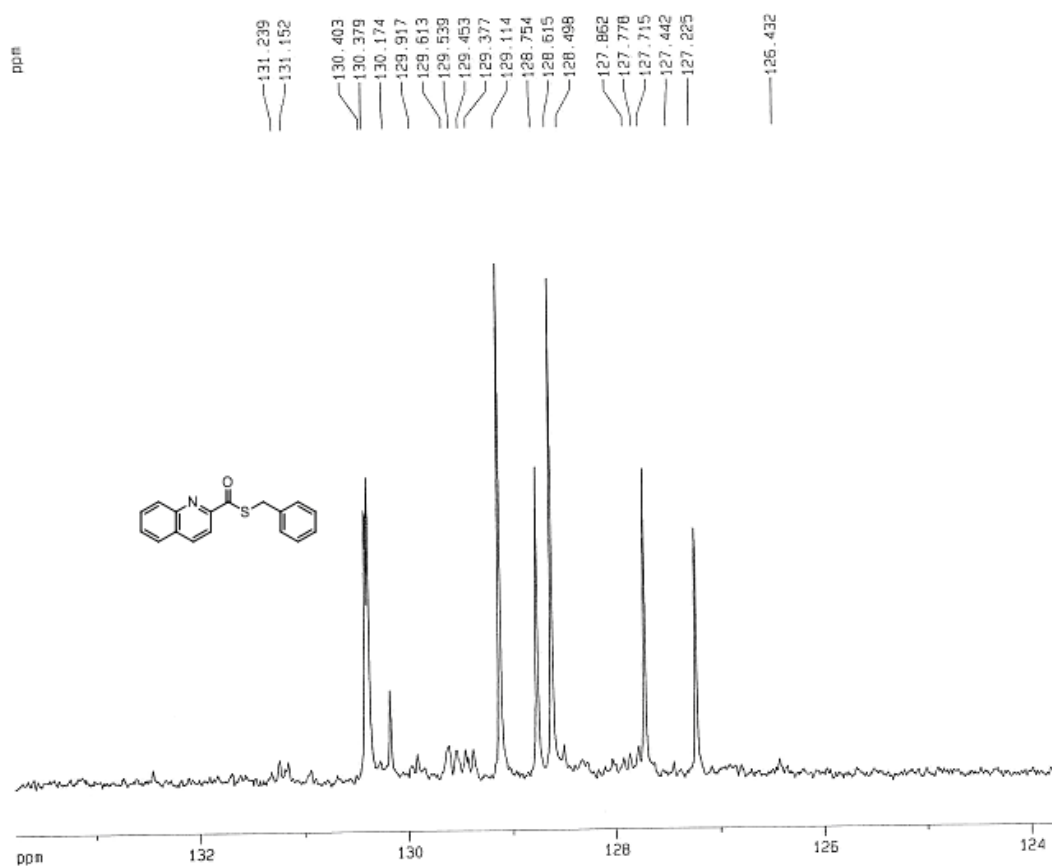


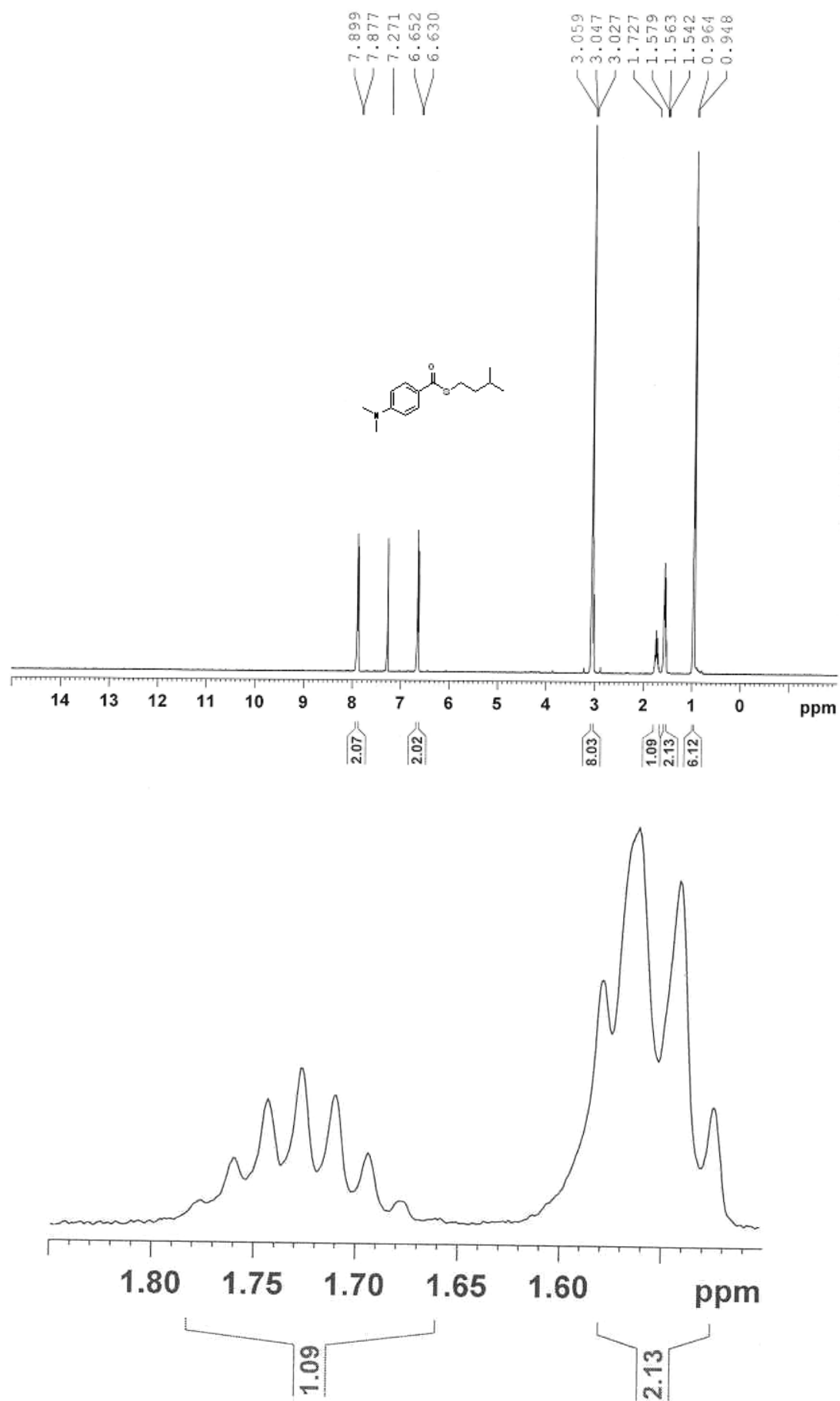


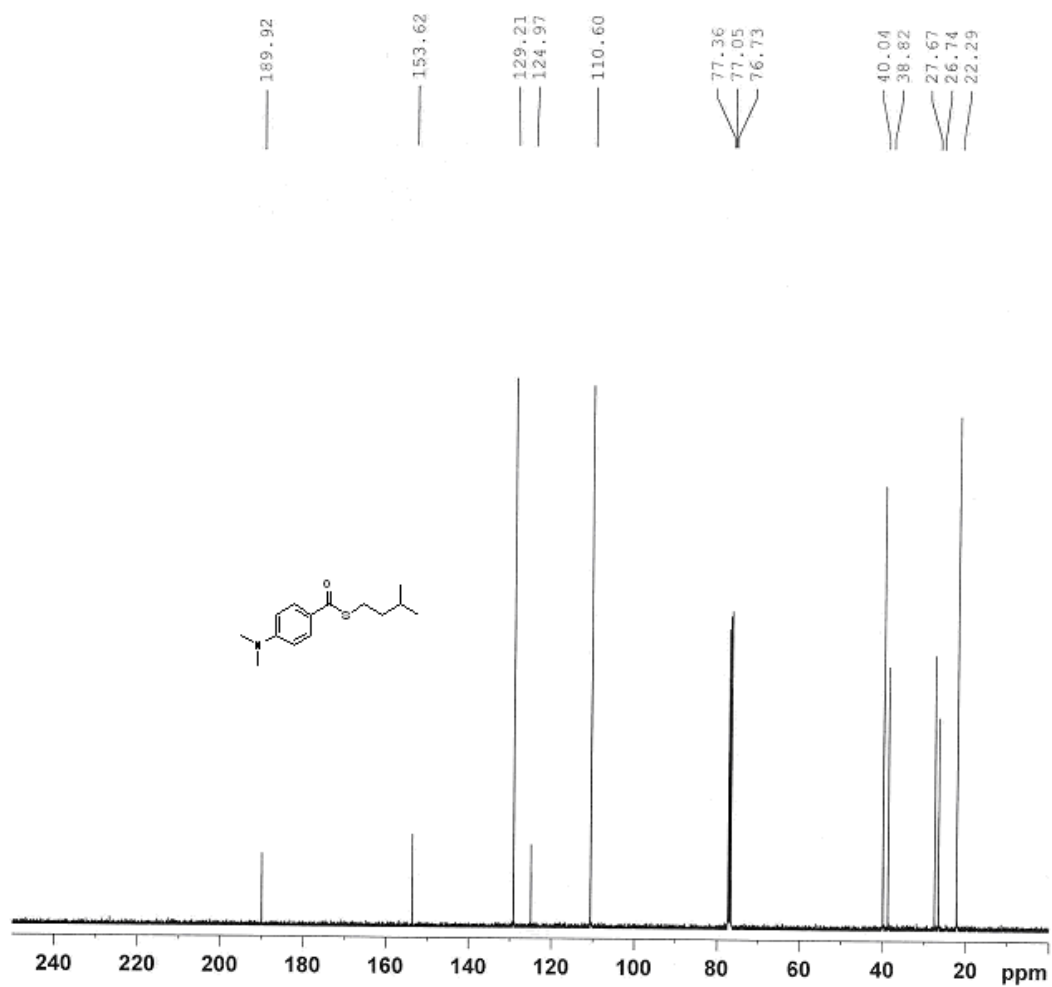












References for the known compounds

1. M. Barbero, S. Cadamuro, I. Degani, R. Fochi, A. Gatti, V. Regondi, *Synthesis* 1998, 300.
2. V. Mamane, E. Aubert, Y. Fort, *J. Org. Chem.* 2007, **72**, 7294.