Supporting Material for:

A Focused Library of Protein Tyrosine Phosphatase Inhibitors

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General Methods. NMR spectra were recorded on Bruker Avance-300 or Avance-400 instruments. Spectra were calibrated using TMS (δ = 0.00 ppm) for ^{1}H NMR, $CDCl_3$ (δ = 77.0 ppm), acetone-d_6 (δ = 29.5 ppm) or DMSO-d_6 for ^{13}C NMR. Mass spectra were recorded using fast atom bombardment or electrospray ionization methods. Methylene chloride and methanol were obtained from a dry solvent dispensing system. HPLC analyses were performed on a Rainin HPLC system with C_{18} columns and UV detection. All other reagents were used as received. Full characterization for compound **1** and **8** have been previously reported.[1]

General Procedure for the Synthesis of 6a-e, **h**, **j**, **l**, **m**, **o.** The representative phenol (1.40 mmol), 4-chloronitrobenzene (1.70 mmol), K_2CO_3 (2.80 mmol) and 4 mL of DMSO were combined in a 5 mL microwave reaction vessel. The mixture was heated using microwave irradiation at a temperature of 195 °C for 10 minutes. The reaction was then diluted with EtOAc and the organic phase was washed with water and brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography.

Compound 6a. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (5:95 EtOAc/hexane) to obtain **6a** (0.346 g, 1.19 mmol, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 9.4 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.40 (m, 1H), 7.50 (m, 2 H), 7.71 (m, 2 H), 7.81 (d, J = 8.8 Hz, 2 H), 8.31 (d, J = 9.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.2, 120.8, 126.0, 127.0, 127.6, 129.0, 138.5, 140.0, 142.7, 154.2, 163.3; HRMS-FAB ($M + Na^+$) calcd for $C_{18}H_{13}NNaO_3$ 314.0793, found 314.0781.

Compound 6b. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (1:9 EtOAc/hexane) to obtain **6b** (0.384

g, 1.22 mmol, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 9.2 Hz, 2 H), 7.14 (d, J = 8.5 Hz, 2 H), 7.73 (d, J = 8.6 Hz, 2 H), 8.27 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.3, 120.2, 121.2, 126.0, 129.4 (d, J_{CF} = 306 Hz), 138.7, 143.4, 157.6, 161.8; HRMS-FAB (M + Na^+) calcd for $C_{13}H_8F_3NNaO_3S$ 338.0075, found 338.0091.

Compound 6c. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (1:9 EtOAc/hexane) to obtain **6c** (0.279 g, 1.15 mmol, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, J = 7.4 Hz, 3 H), 2.70 (q, J = 7.9 Hz, 2 H), 6.99 (d, J = 9.3 Hz, 2 H), 7.02 (d, J = 8.3 Hz, 2 H), 7.27 (d, J = 8.3 Hz, 2 H) 8.18 (d, J = 9.7 Hz, 2 H); proton coupled ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0 (q, J_{CH} = 123.5 Hz), 28.7 (t, J_{CH} = 126.4 Hz), 117.2 (dd, J_{CH} = 164.4, 4.9 Hz), 120.9 (dd, J_{CH} = 160.7, 4.9 Hz), 126.3 (dd, J_{CH} = 167.2, 4.9 Hz), 130.0 (dd, J_{CH} = 164.7, 4.9 Hz), 141.9, 142.8, 152.8, 164.2; HRMS-FAB (M + Na^+) calcd for $C_{14}H_{13}NNaO_3$ 266.0793, found 266.0781.

Compound 6d. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (5:95 EtOAc/hexane) to obtain **6d** (0.381 g, 1.27 mmol, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (m, 3 H), 1.35 (m, 6 H), 1.65 (m, 2 H), 2.65 (t, J = 7.5 Hz, 2 H), 7.01 (m, 4 H), 7.25 (d, J = 8.6 Hz, 2 H), 8.21 (d, J = 9.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.6, 29.1, 31.6, 31.8, 35.4, 116.7, 120.4, 125.8, 130.1, 140.3, 142.4, 152.4, 163.8; HRMS-FAB (M + Na^+) calcd for $C_{18}H_{21}NNaO_3$ 322.1419, found 322.1423.

Compound 6e. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (1:9 EtOAc/hexane) to obtain **6e** (0.285 g, 1.09 mmol, 78%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 6.99 (d, J =

9.2 Hz, 2 H), 7.02 (d, J = 8.7 Hz, 2 H), 7.32 (d, J = 9.2 Hz, 2 H), 8.18 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 116.9, 121.2, 126.0, 128.6, 135.4, 142.6, 152.2, 163.4; HRMS-FAB (M + Na^+) calcd for $C_{13}H_{11}NNaO_3S$ 284.0357, found 284.0362.

Compound 6h. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (5:95 EtOAc/hexane) to obtain **6h** (0.353 g, 1.30 mmol, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3 H), 1.40 (tq, J = 7.8, 7.3 Hz, 2 H), 1.64 (m, 2 H), 2.66 (t, J = 7.8 Hz, 2 H), 7.00 (m, 4 H), 7.25 (d, J = 8.4 Hz, 2 H), 8.18 (d, J = 9.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.4, 33.7, 35.0, 116.8, 120.4, 125.9, 130.1, 140.3, 142.4, 152.4, 163.8; HRMS-FAB (M + Na^+) calcd for $C_{16}H_{17}NNaO_3$ 294.1106, found 294.1099.

Compound 6j. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (1:9 EtOAc/hexane) to obtain **6j** (0.267 g, 1.15 mmol, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (m, 1 H), 6.90 (m, 1 H), 6.98 (m, 1 H) 7.07 (d, J = 8.6 Hz, 2 H), 7.40 (ddd, J = 8.6, 7.7, 6.5 Hz, 1 H), 8.24 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.8 (d, J_{CF} = 261 Hz), 118.3, 124.2 (d, J_{CF} = 115 Hz), 126.1, 129.4 (d, J_{CF} = 218 Hz), 143.6, 155.7, 162.1; HRMS-FAB (M + Na^+) calcd for $C_{12}H_8FNNaO_3$ 256.0386, found 256.0393.

Compound 6l. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (5:95 EtOAc/hexane) to obtain **6l** (0.320 g, 1.25 mmol, 89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 6 H), 2.99 (septet, J = 7.5 Hz, 1 H), 7.11 (d, J = 9.1 Hz, 4 H), 7.39 (d, J = 8.2 Hz, 2 H), 8.26 (d, J = 9.1

Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 34.0, 117.2, 120.8, 126.3, 128.6, 142.8, 146.6, 152.9, 164.1; HRMS-FAB ($M + Na^+$) calcd for $C_{15}H_{15}NNaO_3$ 280.0950, found 280.0941.

Compound 6m. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (1:9 EtOAc/hexane) to obtain **6m** (0.320 g, 1.27 mmol, 91%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (m, 4 H), 7.22 (ddd, J = 6.0, 5.1, 4.7 Hz, 1 H), 8.21 (d, J = 9.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.5, 112.4, 116.3 (dd, J_{CF} = 165, 5 Hz), 124.4 (dd, J_{CF} = 143, 10 Hz), 126.5 (dd, J_{CF} = 168, 5 Hz), 140.5, 154.9, 160.2, 163.0; HRMS-FAB ($M + Na^+$) calcd for $C_{12}H_7F_2NNaO_3$ 274.0292, found 274.0305.

Compound 6o. This compound was prepared according to the general procedure. The crude product was purified by column chromatography (1:9 EtOAc/hexane) to obtain **6o** (0.249 g, 1.04 mmol, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 8.6 Hz, 4 H), 7.74 (d, J = 8.6 Hz, 2 H), 8.29 (d, J = 9.2 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.8, 118.6, 119.4, 120.4, 126.6, 135.0, 144.4, 159.4, 161.3; HRMS-FAB ($M + Na^+$) calcd for $C_{13}H_8N_2NaO_3$ 263.0433, found 263.0430.

General Procedure for the Synthesis of 7a-e, **h**, **j**, **l**, **m**, **o.** The nitro diaryl ether was dissolved in EtOH (10 mL) and a catalytic amount of $Pd(OH)_2/C$ corresponding to 10 wt % of the substrate was added. This mixture was stirred under 1 atm of H_2 (balloon) at RT for approximately 2 hrs until TLC analysis indicated complete disappearance of the starting material. The mixture was filtered through a pad of celite using a fritted glass funnel. The solvent was removed at reduced pressure and the crude product was purified by column chromatography.

Compound 7a. According to the general procedure **6a** (0.346 g, 1.19 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7a** (0.292 g, 1.12 mmol, 94%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 9.4 Hz, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 7.40 (m, 1H), 7.50 (m, 2 H), 7.71 (m, 2 H), 7.81 (d, J = 8.8, 2 H), 8.31 (d, J = 9.4, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.3, 117.5, 121.3, 126.9, 127.0, 128.3, 128.9, 135.2, 140.7, 143.0, 148.5, 158.6; HRMS-FAB (M + H^+) calcd for $C_{18}H_{16}NO$ 262.1232, found 262.1241.

Compound 7b. According to the general procedure **6b** (0.384 g, 1.22 mmol) was reduced and the product was purified by column chromatography (1:3 EtOAc/hexane) to obtain **7b** (0.316 g, 1.11 mmol, 91%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 1H), 6.71 (d, J = 9.2 Hz, 2 H), 6.93 (d, J = 8.4 Hz, 2 H), 6.96 (d, J = 9.5 Hz, 2 H), 7.58 (d, J = 9.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.0, 117.4, 121.8, 129.7 (d, J_{CF} = 306 Hz), 138.3, 143.7, 147.0, 161.8; HRMS-FAB (M + H^+) calcd for $C_{13}H_{11}F_3NOS$ 286.0513, found 286.0503.

Compound 7c. According to the general procedure **6c** (0.279 g, 1.15 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7c** (0.218 g, 1.02 mmol, 89%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, J = 7.3 Hz, 3 H), 2.68 (q, J = 7.5 Hz, 2 H), 3.58 (s, 2 H), 6.71 (d, J = 8.7 Hz, 2 H), 6.95 (m, 4 H), 7.19 (d, J = 8.7 Hz, 2 H); proton coupled ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4 (q, J_{CH} = 1201 Hz), 28.6 (t, J_{CH} = 125 Hz), 116.7 (dd, J_{CH} = 158, 5 Hz), 117.9 (dd, J_{CH} = 160, 5 Hz), 121.4 (dd, J_{CH} = 151, 5 Hz), 129.4 (d, J_{CH} = 153 Hz), 138.5 (m), 143.0 (t, J_{CH} = 8 Hz), 149.4 (m), 157.2 (m); HRMS-FAB (M + H^+) calcd for $C_{14}H_{16}NO$ 214.1232, found 214.1345.

Compound 7d. According to the general procedure **6d** (0.381 g, 1.27 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7d** (0.329 g, 1.22 mmol, 96%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (m, 3 H), 1.37 (m, 6 H), 1.63 (m, 2 H), 2.62 (t, *J* = 7.6 Hz, 2 H), 3.59 (s, 2 H), 6.69 (d, *J* = 8.9 Hz, 2 H), 6.92 (d, *J* = 8.2 Hz, 4 H), 7.14 (d, *J* = 8.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 29.1, 31.7, 31.8, 35.2, 116.3, 117.3, 120.9, 129.4, 136.8, 142.5, 149.1, 156.7; HRMS-FAB (M + H^+) calcd for $C_{18}H_{24}NO$ 270.1858, found 270.1867.

Compound 7e. According to the general procedure **6e** (0.285 g, 1.09 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7e** (0.230 g, 0.99 mmol, 91%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (d, *J* = 1.2 Hz, 3 H), 3.58 (s, 2 H), 6.69 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.23 (d, *J* = 8.9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 116.3, 118.0, 121.0, 129.5, 130.7, 142.8, 148.6, 157.2; HRMS-FAB (M + H^+) calcd for $C_{13}H_{14}NOS$ 232.0796, found 232.0805.

Compound 7h. According to the general procedure **6h** (0.353 g, 1.30 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7h** (0.301 g, 1.25 mmol, 96%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, *J* = 7.7 Hz, 3 H), 1.42 (tq, *J* = 7.7, 7.3 Hz, 2 H), 1.65 (septet, *J* = 7.7 Hz, 2 H), 2.63 (t, *J* = 7.3 Hz, 2 H), 3.59 (s, 2 H), 6.70 (d, *J* = 9.0 Hz, 2 H), 6.93 (d, *J* = 8.6 Hz, 4 H), 7.15 (d, *J* = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.4, 33.9, 34.9, 116.3, 117.3, 120.9, 129.4, 136.7, 142.6, 149.1, 156.8; HRMS-FAB (M + H^+) calcd for $C_{16}H_{20}NO$ 242.1545, found 242.1561.

Compound 7j. According to the general procedure **6j** (0.267 g, 1.15 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7j** (0.210 g, 1.03 mmol, 90%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 2 H), 6.72, (m, 5 H), 6.92 (d, J = 8.6 Hz, 2 H), 7.24 (q, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 106.6 (dd, J_{CF} = 316, 25 Hz), 112.6, 116.3, 121.5, 130.3 (d, J_{CF} = 10 Hz), 145.5 (d, J_{CF} = 316 Hz), 161.2 (d, J_{CF} = 98 Hz), 165.2; HRMS-FAB ($M + H^+$) calcd for $C_{12}H_{11}FNO$ 204.0825, found 204.0836.

Compound 7l. According to the general procedure **6l** (0.320 g, 1.25 mmol) was reduced and the product was purified by column chromatography (15:85 EtOAc/hexane) to obtain **7l** (0.257 g, 1.13 mmol, 91%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, J = 7.0 Hz, 6 H), 2.91 (septet, J = 7.0 Hz, 1 H), 6.75 (d, J = 8.9 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 4 H), 7.18 (d, J = 8.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 33.8, 116.5, 117.7, 121.3, 127.5, 142.6, 143.1, 149.6, 157.1; HRMS-FAB ($M + Na^+$) calcd for $C_{15}H_{18}NNaO$ 250.1208, found 250.1203.

Compound 7m. According to the general procedure **6m** (0.320 g, 1.27 mmol) was reduced and the product was purified by column chromatography (2:8 EtOAc/hexane) to obtain **7m** (0.262 g, 1.18 mmol, 93%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.7 (m, 2 H), 6.8 (m, 3 H), 6.93 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 105.2, 111.4, 115.6 (d, J_{CF} = 6 Hz), 117.1 (dd, J_{CF} = 225, 6 Hz), 119.2 (dd, J_{CF} = 228, 5 Hz), 121.3 (dd, J_{CF} = 88, 10 Hz), 143.0 (t, J_{CF} = 8 Hz), 153.9, 158.1; HRMS-FAB ($M + H^+$) calcd for $C_{12}H_{10}F_2NO$ 222.0731, found 222.0719.

Compound 7o. According to the general procedure **6o** (0.249 g, 1.04 mmol) was reduced and the product was purified by column chromatography (1:3 EtOAc/hexane) to obtain **7o** (0.183 g, 0.87 mmol, 84%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 2 H), 6.71 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 9.3 Hz, 2 H), 6.93 (d, J = 9.3 Hz, 2 H), 7.54 (d, J = 9.0 Hz,

2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.7, 116.3, 116.9, 119.2, 121.8, 134.1, 144.2, 146.2, 162.9; HRMS-FAB ($M + H^+$) calcd for $C_{13}H_{11}N_2O$ 211.0871, found 211.0885.

General Procedure for the Synthesis of 9a-o and 10. To a solution of compound **8** (0.040 g, 0.063 mmol) in benzene (3 mL) was added $SOCl_2$ (0.5 mL). The mixture was heated at reflux for 3 h under a N_2 atmosphere. The solvent and excess reagent was removed at reduced pressure and the crude material was dried under vacuum. The resulting yellow solid was dissolved in either CH_2Cl_2 or THF, cooled to 0 °C, and the aniline derivative (0.082 mmol) was added to the acid chloride of **8**. The reaction progress was monitored by TLC until completion, which required approximately 1 h. The solvent was removed at reduced pressure and the crude material was purified by column chromatography.

Compound 9a. According to the general procedure the acid chloride derivative of **8** was reacted with **7a** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9a** (0.045 g, 0.052 mmol, 82%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.36 (s, 2 H), 5.57 (s, 2 H), 6.80 (m, 2 H), 7.09 (d, J = 7.8 Hz, 4 H), 7.32 (m, 5 H), 7.70 (m, 8 H), 7.87 (m, 3 H), 8.37 (d, J = 9.6 Hz, 2 H), 8.43 (d, J = 9.0 Hz, 2 H), 9.90 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 67.6, 69.2, 92.0 (q, J_{CF} = 35 Hz), 115.4 (two overlapping resonances), 116.2, 118.2, 119.3, 120.6, 120.7, 121.7, 123.0, 127.1 (d, J_{CF} = 155 Hz), 129.5, 130.8, 130.9, 135.2, 136.2, 136.3, 136.8, 138.6, 151.2, 159.4, 161.2, 163.1, 163.2, 163.3, 166.8; HRMS-FAB ($M + Na^+$) calcd for $C_{42}H_{26}F_9N_3NaO_8S$ 926.1195, found 926.1172.

Compound 9b. According to the general procedure the acid chloride derivative of **8** was reacted with **7b** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9b** (0.043 g, 0.048 mmol, 76%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ

5.38 (s, 2 H), 5.58 (s, 2 H), 6.80 (m, 2 H), 7.10 (d, J = 8.7 Hz, 2 H), 7.14 (d, J = 8.2 Hz, 2 H), 7.22 (d, J = 9.8 Hz, 2 H), 7.29 (d, J = 9.3 Hz, 2 H), 8.38 (d, J = 9.8 Hz, 2 H), 8.43 (d, J = 9.3 Hz, 2 H), 9.9 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 67.6, 69.2, 92.0 (q, J_{CF} = 35 Hz), 115.4 (two overlapping resonances), 116.2, 118.2, 119.3, 120.6, 120.7 121.7, 123.0, 127.1 (d, J_{CF} = 155 Hz), 129.5, 130.8, 130.9, 135.2, 136.2, 136.3, 136.8, 138.6, 151.2, 159.4, 161.2, 163.1, 163.2, 163.3, 166.8; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{26}F_9N_3NaO_8S$ 926.1195, found 926.1172.

Compound 9c. According to the general procedure the acid chloride derivative of **8** was reacted with **7c** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9c** (0.041 g, 0.049 mmol, 78%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.22 (t, J = 7.6 Hz, 3 H), 2.64 (q, J = 7.6 Hz, 2 H), 5.33 (s, 2 H), 5.55 (s, 2 H), 6.80 (m, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 6.98 (d, J = 9.0 Hz, 2 H), 7.23 (m, 6 H), 7.70 (m, 2 H), 7.80 (d, J = 8.9 Hz, 2 H), 7.88 (s, 1 H), 8.37 (d, J = 9.0 Hz, 2 H), 8.43 (d, J = 9.0 Hz, 2 H), 9.77 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 15.4, 27.8, 67.6, 69.2, 92.1 (q, J_{CF} = 33 Hz), 115.4 (two overlapping resonances), 118.4, 118.9, 119.3, 120.6, 120.7, 121.5, 121.6, 123.0, 126.7, 126.9, 128.9, 129.1, 129.5, 130.8, 130.9, 134.7, 136.3, 136.7, 139.0, 153.6, 155.6, 159.4, 163.1, 163.2, 163.3, 166.7; HRMS-FAB (M + Na^+) calcd for $C_{43}H_{31}F_6N_3NaO_8$ 854.1913, found 854.1931.

Compound 9d. According to the general procedure the acid chloride derivative of **8** was reacted with **7d** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9d** (0.045 g, 0.051 mmol, 81%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.91 (t, J = 5.1 Hz, 3 H), 1.34 (m, 6 H), 1.63 (m, 2 H), 2.61 (t, J = 5.7 Hz, 2 H), 5.35 (s, 2 H), 5.56 (s, 2 H), 6.80 (m, 2 H), 6.94 (d, J = 8.9 Hz, 2 H), 6.99 (d, J = 7.9 Hz, 2 H), 7.23 (m, 4 H), 7.28 (d, J = 8.9 Hz, 2 H), 7.72 (m, 2 H), 7.81 (d, J = 9.9 Hz, 2 H), 7.89 (s, 1 H), 8.38 (d, J = 8.9 Hz, 2 H), 8.43 (d, J = 9.9 Hz, 2 H), 9.75 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 13.9, 22.8,

28.8, 29.5, 32.0, 35.3, 68.0, 69.7, 92.5 (q, J_{CF} = 24 Hz), 115.8 (two overlapping resonances), 118.7, 119.3, 121.0, 121.1, 122.0, 122.9, 127.3, 129.3, 129.8, 130.0, 131.2, 131.3, 135.1, 135.6, 136.7, 137.1, 138.1, 154.1, 156.0, 159.8, 163.5, 163.6, 163.7, 167.1; HRMS-FAB (M + Na^+) calcd for $C_{47}H_{39}F_6N_3NaO_8$ 910.2539, found 910.2565.

Compound 10. According to the general procedure the acid chloride derivative of **8** was reacted with 3-benzyloxyaniline and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **10** (0.039 g, 0.047 mmol, 75%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.10 (s, 2 H), 5.36 (s, 2 H), 5.55 (s, 2 H), 6.79 (m, 3 H), 7.27 (m, 8 H), 7.48 (m, 2 H), 7.70 (m, 3 H), 7.86 (s, 1 H), 8.36 (d, J = 8.9 Hz, 2 H), 8.41 (d, J = 8.9 Hz, 2 H), 9.68 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 67.6, 69.2, 69.5, 92.0 (q, J_{CF} = 34 Hz), 106.8, 110.2, 112.4, 115.4 (two overlapping resonances), 120.6, 120.7, 126.9, 127.6, 127.7, 128.4, 129.0, 129.5, 130.8, 130.9, 135.0, 136.5, 136.8, 137.4, 140.4, 159.3, 159.4, 163.1, 163.2, 163.3, 166.8; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{29}F_6N_3NaO_8$ 840.1757, found 840.1786.

Compound 9e. According to the general procedure the acid chloride derivative of **8** was reacted with **7e** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9e** (0.043 g, 0.050 mmol, 80%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.49 (s, 3 H), 5.37 (s, 2 H), 5.56 (s, 2 H), 6.81 (m, 2 H), 6.97 (d, J = 9.1 Hz, 2 H), 7.00 (d, J = 9.1 Hz, 2 H), 7.28 (m, 6 H), 7.78 (m, 5 H), 8.36 (d, J = 9.0 Hz, 2 H), 8.42 (d, J = 9.0 Hz, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 15.8, 67.6, 69.2, 91.9 (q, J_{CF} = 34 Hz), 115.4 (two overlapping resonances), 119.2, 119.3, 120.6, 120.7, 121.6, 123.0, 126.9, 128.8, 129.0, 129.3, 130.8, 130.9, 132.4, 135.1, 135.2, 136.4, 136.7, 153.1, 155.7, 159.4, 163.1, 163.2, 163.3, 166.6; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{29}F_6N_3NaO_8S$ 872.1477, found 872.1498.

Compound 9f. According to the general procedure the acid chloride derivative of **8** was reacted with 4-(4-fluorophenoxy)aniline and the product was purified by column chromatography (5:95 EtOAc/hexane) to obtain **9f** (0.036 g, 0.044 mmol, 70%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.36 (s, 2 H), 5.56 (s, 2 H), 6.81 (m, 2 H), 7.05 (m, 4 H), 7.15 (d, J = 8.4 Hz, 2 H), 7.21 (t, J = 9 Hz, 2 H), 7.28 (d, J = 9.0 Hz, 2 H), 7.73 (m, 2 H), 7.81 (d, J = 8.9 Hz, 2 H), 7.89 (s, 1 H), 8.37 (d, J = 8.9 Hz, 2 H), 8.42 (d, J = 8.9 Hz, 2 H), 9.75 (s, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 67.6, 69.2, 91.9 (q, J_{CF} = 34 Hz), 115.4 (two overlapping resonances), 116.2 (d, J_{CF} = 24 Hz), 118.9, 119.7, 120.0 (d, J_{CF} = 8 Hz), 120.7 (q, J_{CF} = 9 Hz), 121.6, 122.5, 126.9, 129.0, 129.5, 130.8, 130.9, 135.0, 135.1, 136.4, 136.8, 153.5, 153.7, 153.8, 157.4, 159.4, 159.8, 163.1, 163.2, 163.3, 166.7; HRMS-FAB (M + Na^+) calcd for $C_{41}H_{26}F_7N_3NaO_8$ 844.1506, found 844.1530.

Compound 9g. According to the general procedure the acid chloride derivative of **8** was reacted with 4-(4-methylphenoxy)aniline and the product was purified by column chromatography (5:95 EtOAc/hexane) to obtain **9g** (0.038 g, 0.046 mmol, 73%) as a white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 2.32 (s, 3 H), 5.36 (s, 2 H), 5.56 (s, 2 H), 6.81 (m 2 H), 6.91 (d, J = 8.5 Hz, 2 H), 6.98 (d, J = 9.0 Hz, 2 H), 7.21 (t, J = 7.1 Hz, 4 H), 7.28 (d, J = 9.0 Hz, 2 H), 7.72 (m, 2 H), 7.81 (d, J = 8.9 Hz, 2 H), 7.89 (s, 1 H), 8.38 (d, J = 9.0 Hz, 2 H), 8.42 (d, J = 9.0 Hz, 2 H), 9.75 (s, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.2, 68.1, 69.7, 92.4 (q, J_{CF} = 8 Hz), 115.8 (two overlapping resonances), 118.8, 119.2, 121.0, 121.1, 122.0, 127.3, 129.3, 129.8, 130.6, 131.2, 131.3, 132.9, 135.1, 135.5, 136.7, 137.1, 154.1, 155.8, 159.8, 163.5, 163.6, 163.7, 167.1; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{29}F_6N_3NaO_8$ 840.1757, found 840.1771.

Compound 9h. According to the general procedure the acid chloride derivative of **8** was reacted with **7h** and the product was purified by column chromatography (35:65 EtOAc/hexane)

to obtain **9h** (0.044 g, 0.051 mmol, 82%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.33 (m, 2 H), 1.60 (m, 2 H), 2.61 (t, J = 7.6 Hz, 2 H), 5.37 (s, 2 H), 5.57 (s, 2 H), 6.81 (m, 2 H), 6.93 (d, J = 8.7 Hz, 2 H), 7.00 (d, J = 8.1 Hz, 2 H), 7.22 (m, 4 H), 7.29 (d, J = 8.8 Hz, 2 H), 7.76 (m, 4 H), 7.89 (s, 1 H), 8.38 (d, J = 8.7 Hz, 2 H), 8.43 (d, J = 9.4 Hz, 2 H), 9.74 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 13.3, 22.0, 33.8, 34.5, 67.6, 69.2, 91.9 (q, J_{CF} = 33 Hz), 115.4 (two overlapping resonances), 118.3, 118.9, 120.6, 120.7, 121.4, 121.5, 126.9, 129.0, 129.4, 129.6, 130.8, 130.9, 134.8, 135.1, 136.4, 136.7, 137.6, 153.6, 155.6, 159.4, 163.1, 163.2, 163.3, 166.6; HRMS-FAB (M + Na^+) calcd for $C_{45}H_{35}F_6N_3NaO_8$ 882.2226, found 882.2245.

Compound 9i. According to the general procedure the acid chloride derivative of **8** was reacted with 4-(3,4-dichlorophenoxy)aniline and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9i** (0.043 g, 0.049 mmol, 78%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.26 (s, 2 H), 5.38 (s, 2 H), 6.80 (m, 2 H), 7.01 (m, 1 H), 7.13 (m, 2 H), 7.27 (m, 4 H), 7.56 (m, 2 H), 7.76 (m, 2 H), 7.90 (m, 3 H), 8.42 (m, 4 H, 9.81 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 68.0, 69.6**,** 92.3 (q, J_{CF} = 34 Hz), 115.7, 115.8, 118.2, 119.9, 120.5, 121.0, 122.0, 127.3, 129.4, 129.9, 131.2, 131.3, 131.7, 132.2, 132.9, 135.6, 136.5, 136.7, 137.2, 152.1, 158.1, 159.8, 163.5, 163.7, 167.1; LRMS-FAB (M + Na^+) calcd for $C_{41}H_{25}Cl_2F_6N_3NaO_8$ 894.1, found 894.1.

Compound 9j. According to the general procedure the acid chloride derivative of **8** was reacted with **7j** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9j** (0.040 g, 0.049 mmol, 79%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 5.37 (s, 2 H), 5.56 (s, 2 H), 6.80 (m, 2 H), 7.03 (m, 5 H), 7.23 (m, 5 H), 7.79 (m, 5 H), 8.36 (d, J = 8.8 Hz, 2 H), 8.41 (d, J = 9.0 Hz, 2 H), 9.74 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 67.6,

69.2, 91.9 (q, J_{CF} = 33 Hz), 115.4 (two overlapping resonances), 116.0 (two overlapping resonances), 116.4, 118.9, 119.9, 120.0, 120.6, 120.7, 121.6, 126.9, 129.0, 130.4 (d, J_{CF} = 122 Hz), 130.8, 130.9, 135.0, 135.1, 136.4, 136.8, 153.8, 153.5, 159.4, 163.1, 163.2, 163.3, 166.7; HRMS-FAB (M + Na^+) calcd for $C_{41}H_{26}F_7N_3NaO_8$ 844.1506, found 844.1530.

Compound 9k. According to the general procedure the acid chloride derivative of **8** was reacted with 4-(2-methylphenoxy)aniline and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9k** (0.039 g, 0.048 mmol, 76%) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.24 (s, 3 H), 5.36 (s, 2 H), 5.56 (s, 2 H), 6.81 (m, 2 H), 6.89 (m, 5 H), 7.25 (m, 5 H), 7.78 (m, 5 H), 8.37 (d, J = 9.0 Hz, 2 H), 8.41 (d, J = 9.0 Hz, 2 H), 9.72 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 15.4, 67.6, 69.2, 91.9 (q, J_{CF} = 27 Hz), 115.4 (two overlapping resonances), 117.6, 119.1, 120.6, 120.7, 121.6, 123.9, 126.9, 127.3, 128.9, 129.3, 129.4, 130.8, 130.9, 131.4, 134.3, 135.1, 136.4, 136.7, 154.0, 154.9, 159.4, 163.1, 163.2, 163.3, 166.6; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{29}F_6N_3NaO_8$ 840.1757, found 840.1775.

Compound 9l. According to the general procedure the acid chloride derivative of **8** was reacted with **7l** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9l** (0.044 g, 0.053 mmol, 84%) as a white solid. ^{1}H NMR (300 MHz acetone-d_6) δ 1.24 (d, J = 5.2 Hz, 6 H), 2.06 (m, 1 H), 5.36 (s, 2 H), 5.56 (s, 2 H), 6.80 (m, 2 H), 6.94 (d, J = 6.4 Hz, 2 H), 6.99 (d, J = 6.7 Hz, 2 H), 7.25 (m, 6 H), 7.76 (m, 5 H), 8.37 (d, J = 6.7 Hz, 2 H), 8.42 (d, J = 6.7 Hz, 2 H), 9.72 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 23.6, 33.3, 67.6, 69.3, 92.0 (q, J_{CF} = 27 Hz), 115.4 (two overlapping resonances), 118.3, 119.0, 120.6, 120.7, 121.6, 126.9, 127.6, 128.5, 129.0, 129.4, 130.8, 130.9, 134.8, 135.1, 136.4, 136.7, 143.6, 153.6, 155.6, 159.4, 163.1, 163.2, 163.3, 166.6; HRMS-FAB (M + Na^+) calcd for $C_{44}H_{33}F_6N_3NaO_8$ 868.2070, found 868.2093.

Compound 9m. According to the general procedure the acid chloride derivative of **8** was reacted with **7m** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9m** (0.042 g, 0.050 mmol, 79%) as a white solid. ^{1}H NMR (300 MHz acetone-d_6) δ 5.36 (s, 2 H), 5.56 (s, 2 H), 6.82 (m, 2 H), 6.99 (d, J = 9.0 Hz, 3 H), 7.24 (m, 6 H), 7.80 (m, 5 H), 8.37 (d, J = 9.0 Hz, 2 H), 8.42 (d, J = 9.0 Hz, 2 H), 9.76 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 67.6, 69.2, 92.0 (q, J_{CF} = 26 Hz), 105.3 (q, J_{CF} = 26 Hz), 111.6 (d, J_{CF} = 17 Hz), 115.4 (two overlapping resonances), 117.1, 119.3, 120.7 (d, J_{CF} = 7 Hz), 121.6, 122.8, 123.0, 127.9 (d, J_{CF} = 153 Hz), 129.5, 130.8, 130.9, 135.0 (d, J_{CF} = 18 Hz), 136.3, 136.7, 140.4 (d, J_{CF} = 4 Hz), 152.4 (d, J_{CF} = 11 Hz), 153.7, 156.5 (dd, J_{CF} = 95, 11 Hz), 159.4, 160.1, 163.1, 163.2, 163.3, 166.7; HRMS-FAB (M + Na^+) calcd for $C_{41}H_{25}F_8N_3NaO_8$ 862.1412, found 862.1432.

Compound 9n. According to the general procedure the acid chloride derivative of **8** was reacted with 4-(4-methoxyphenoxy)aniline and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9n** (0.040 g, 0.048 mmol, 77%) as a white solid. ^{1}H NMR (300 MHz acetone-d_6) δ 3.80 (s, 3 H), 5.36 (s, 2 H), 5.55 (s, 2 H), 6.82 (m, 4 H), 7.01 (m, 2 H), 7.20 (m, 6 H), 7.72 (m, 4 H), 7.88 (s, 1 H), 8.36 (d, J = 9.7 Hz, 2 H), 8.41 (d, J = 9.7 Hz, 2 H), 9.7 (s, 1 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 55.2, 67.6, 69.2, 91.9 (q, J_{CF} = 35 Hz), 113.2, 115.4 (two overlapping resonances), 116.5, 120.6, 120.7, 121.0, 121.4, 125.2, 126.9, 128.5, 128.9, 129.4, 130.8, 130.9, 133.8, 135.1, 136.4, 136.7, 144.7, 151.9, 154.7, 163.1, 163.2, 163.3, 166.5; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{29}F_6N_3NaO_9$ 856.1706, found 856.1735.

Compound 9o. According to the general procedure the acid chloride derivative of **8** was reacted with **7o** and the product was purified by column chromatography (35:65 EtOAc/hexane) to obtain **9o** (0.039 g, 0.047 mmol, 75%) as a white solid. ^{1}H NMR (300 MHz acetone-d_6) δ

5.36 (s, 2 H), 5.56 (s, 2 H), 6.80 (m, 4 H), 6.99 (m, 3 H), 7.25 (m, 5 H), 7.79 (m, 5 H), 8.37 (d, J = 9.8 Hz, 2 H), 8.42 (d, J = 9.4 Hz, 2 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 68.0, 69.6, 92.4 (q, J_{CF} = 33 Hz), 115.6, 115.8 (two overlapping resonances), 119.1, 119.7, 121.0, 121.1, 122.0, 123.4, 124.1, 127.3, 128.9, 129.8, 129.9, 131.2, 131.3, 135.3, 135.5, 136.7, 137.1, 140.3, 153.6, 158.2, 159.8, 163.5, 163.6, 163.7, 167.1; HRMS-FAB (M + Na^+) calcd for $C_{42}H_{26}F_6N_4NaO_8$ 851.1553, found 851.1579.

General Procedure for the Synthesis of 2a-d: 4, 4'-[[2-[[(4-(4-Trifluoromethylthio)phenoxy phenyl)amino]carbonyl]-1, 4-phenylene]bis(methyleneoxy)]bis[α-oxobenzeneacetic acid] (2a). A solution of 0.25 M NaOH (2 mL) was added to compound **9a** (0.045 g, 0.052 mmol) and the mixture was stirred at 25 °C for 1 h. The solution was washed with Et_2O and then acidified with 0.5 M HCl to pH 2. The resulting precipitate was centrifuged, the aqueous phase was separated from the solid, and the solid was dried under vacuum to obtain **2a** (28.1 mg, 39.0 μmol, 75 %) as a white solid. A portion of the crude material was purified by reverse phase HPLC using a C-18 column eluted with 50% acetonitrile in water with 0.1% TFA. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.33 (s, 2 H), 5.45 (s, 2 H), 7.05 (m, 3 H), 7.09 (m, 5 H), 7.35 (m, 5 H), 7.65 (m, 7 H), 7.87 (d, J = 8.5 Hz, 2 H), 7.93 (d, J = 9.2 Hz, 2 H), 10.61 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 68.0, 69.5, 115.8, 115.9, 118.6, 120.1, 122.1, 126.9, 127.6, 127.8, 128.7, 129.4, 129.6, 129.9, 132.4, 132.5, 134.7, 135.4, 135.6, 136.8 (two overlapping resonances), 140.0, 152.3, 157.6, 163.9, 167.1; LRMS-ESI (M + H^+) calcd for $C_{43}H_{32}NO_{10}$ 722, found 722.

4, 4'-[[2-[[(4-(4-Trifluoromethylthio)phenoxyphenyl)amino]carbonyl]-1, 4-phenylene]bis (methyleneoxy)]bis[α-oxobenzeneacetic acid] (2b). According to the general procedure **9b** (0.043 g, 0.048 mmol) was hydrolyzed to obtain **2b** (25.4 mg, 34.1 μmol, 71 %) as a white solid.

A portion of the crude material was purified by reverse phase HPLC using a C-18 column eluted with 55% acetonitrile in water with 0.1% TFA. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.33 (s, 2 H), 5.47 (s, 2 H), 7.12 (m, 8 H), 7.72 (m, 7 H), 7.85 (d, J = 8.9 Hz, 2 H), 7.90 (d, J = 8.9 Hz, 2 H), 10.64 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 68.0, 69.5, 115.1, 115.8 (two overlapping resonances), 118.5, 121.2, 122.2, 125.6, 127.8 (d, J_{CF} = 143 Hz), 129.7, 129.9, 131.8, 132.1, 132.5, 134.7, 136.5, 136.7, 136.9, 139.0, 150.7, 161.2, 162.2, 163.8, 167.2, 188.3; LRMS-ESI (M + H$^+$) calcd for $C_{38}H_{27}F_3NO_{10}S$ 746, found 746.

4, 4'-[[2-[[(4-(4-Ethyl)phenoxyphenyl)amino]carbonyl]-1, 4-phenylene]bis(methylene oxy)]bis[α-oxobenzeneacetic acid] (2c). According to the general procedure **9c** (0.041 g, 0.049 mmol) was hydrolyzed to obtain **2c** (23.1 mg, 34.3 μmol, 70 %) as a white solid. A portion of the crude material was purified by reverse phase HPLC using a C-18 column eluted with 55% acetonitrile in water with 0.1% TFA. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.20 (t, J = 6.5 Hz, 3 H), 2.26 (d, J = 7.0 Hz, 2 H), 5.32 (s, 2 H), 5.44 (s, 2 H), 7.02 (m, 5 H), 7.16 (m, 3 H), 7.25 (d, J = 8.7 Hz, 2 H), 7.78 (m, 5 H), 8.01 (d, J = 8.7 Hz, 2 H), 8.07 (d, J = 9.5 Hz, 2 H), 10.57 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.2, 27.9, 67.9, 69.5, 115.1 (two overlapping resonances), 115.8 (two overlapping resonances), 118.5, 119.4, 122.1, 123.8, 125.9, 127.7, 129.6 129.8, 131.9, 132.3, 134.7, 135.1, 136.8, 139.0, 153.1, 155.6, 163.7, 167.0, 167.7, 188.8; LRMS-ESI (M + H$^+$) calcd for $C_{39}H_{32}NO_{10}$ 674, found 674.

4, 4'-[[2-[[(4-(4-n-Hexyl)phenoxyphenyl)amino]carbonyl]-1, 4-phenylene]bis (methyleneoxy)]bis [a-oxobenzeneacetic acid] (2d). According to the general procedure **9d** (0.045 g, 0.051 mmol) was hydrolyzed to obtain **2d** (29.4 mg, 40.3 μmol, 79 %) as a white solid. A portion of the crude material was purified by reverse phase HPLC using a C-18 column eluted with 60% acetonitrile in water with 0.1% TFA. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.86 (m, 3 H),

1.28 (m, 8 H), 1.54 (m, 2 H), 5.33 (s, 2 H), 5.43 (s, 2 H), 6.87 (d, J = 8.3 Hz, 2 H), 6.97 (d, J = 8.6 Hz, 2 H), 7.05 (m, 1 H), 7.16 (m, 4 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.67 (m 3 H), 7.75 (s, 1 H), 8.24 (d, J = 8.6 Hz, 2 H), 8.30 (d, J = 8.8 Hz, 2 H), 10.5 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.4, 22.5, 28.8, 31.5, 31.6, 34.8, 68.0, 69.5, 115.0, 115.1, 115.8, 118.4, 119.4, 122.1, 125.8, 127.7, 129.5, 129.8, 130.1, 131.9, 132.4 (two overlapping resonances), 134.7, 135.1, 136.8, 137.6, 153.1, 155.6, 163.7, 167.1, 167.4, 167.7, 188.8; LRMS-ESI (M + H^+) calcd for $C_{43}H_{40}NO_{10}$ 730, found 730.

General Procedure for the Synthesis of compounds 2e-o and 3: Compound 3. A solution of 0.25 M NaOH (2 mL) was added to compound **10** (0.039 g, 0.047 mmol) and the mixture was stirred at 25 °C for 1 h. The solution was washed with Et_2O and then acidified with 0.5 M HCl to pH 2. The resulting precipitate was centrifuged, the aqueous phase was separated from the solid, and the solid was dried under vacuum to obtain **3** (22.3 mg, 33.8 μmol, 72 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.06 (s, 2 H), 5.33 (s, 2 H), 5.43 (s, 2 H), 6.75 (m, 1 H), 7.13 (d, J = 9.0 Hz, 2 H), 7.24 (m, 3 H), 7.40 (m, 7 H), 7.70 (m, 3 H), 7.86 (d, J = 8.9 Hz, 2 H), 7.92 (d, J = 8.9 Hz, 2 H), 10.5 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{38}H_{30}NO_{10}$ 660, found 660.

Compound 2e. According to the general procedure **9e** (0.043 g, 0.050 mmol) was hydrolyzed to obtain **2e** (28.0 mg, 40.5 μmol, 81 %) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.47 (s, 3 H), 5.32 (s, 2 H), 5.43 (s, 2 H), 6.96 (m, 2 H), 6.96 (m, 3 H), 7.25 (m, 5 H), 7.72 (m, 5 H), 7.86 (m, 4 H) 10.56 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{38}H_{30}NO_{10}S$ 692, found 692.

Compound 2f. According to the general procedure **9f** (0.036 g, 0.044 mmol) was hydrolyzed to obtain **2f** (18.7 mg, 28.2 μmol, 64 %) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.32 (s, 2 H), 5.43 (s, 2 H), 7.01 (m, 3 H), 7.12 (d, J = 8.9 Hz, 2 H), 7.21 (m, 5 H), 7.69 (m, 5 H), 7.84 (d, J = 8.9 Hz, 2 H), 7.90 (d, J = 8.9 Hz, 2 H), 10.5 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{37}H_{27}FNO_{10}$ 664, found 664.

Compound 2g. According to the general procedure **9g** (0.038 g, 0.046 mmol) was hydrolyzed to obtain **2g** (17.6 mg, 27.0 μmol, 58 %) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3 H), 5.32 (s, 2 H), 5.43 (s, 2 H), 6.87 (d, J = 8.3 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.14 (m, 4 H), 7.25 (d, J = 8.8 Hz, 2 H), 7.67 (m, 5 H), 7.85 (d, J = 8.7 Hz, 2 H), 7.92 (d, J = 8.7 Hz, 2 H), 10.5 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{38}H_{30}NO_{10}$ 660, found 660.

Compound 2h. According to the general procedure **9h** (0.044 g, 0.051 mmol) was hydrolyzed to obtain **2h** (21.8 mg, 31.1 μmol, 61 %) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (t, J = 7.1 Hz, 3 H), 1.28 (m, 2 H), 1.52 (m, 2 H), 2.54 (m, 2 H), 5.33 (s, 2 H), 5.44 (s, 2 H), 6.87 (d, J = 7.9 Hz, 2 H), 6.96 (d, J = 8.6 Hz, 2 H), 7.15 (m, 3 H), 7.25 (m, 3 H), 7.45 (s, 1 H), 7.68 (m, 4 H), 7.84 (d, J = 8.6 Hz, 2 H), 7.90 (d, J = 8.2 Hz, 2 H), 10.61 (s, 1 H); LRMS (M + H^+) calcd for $C_{41}H_{36}NO_{10}$ 702, found 702.

Compound 2i. According to the general procedure **9i** (0.043 g, 0.049 mmol) was hydrolyzed to obtain **2i** (21.0 mg, 29.4 μmol, 60 %) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.26 (s, 2 H), 5.38 (s, 2 H), 6.98 (m, 2 H), 7.11 (m, 3 H), 7.23 (m, 1 H), 7.63 (m, 4 H), 7.75 (m, 8 H), 10.61 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{37}H_{26}Cl_2NO_{10}$ 714, found 714.

Compound 2j. According to the general procedure **9j** (0.040 g, 0.049 mmol) was hydrolyzed to obtain **2j** (23.7 mg, 35.8 μmol, 73 %) as a white solid. ^{1}H NMR (300 MHz,

DMSO-d_6) δ 5.37 (s, 2 H), 5.57 (s, 2 H), 7.03 (m, 3 H), 7.20 (m, 5 H), 7.80 (m, 7 H), 8.01 (d, J = 8.6 Hz, 2 H), 8.06 (d, J = 8.6 Hz, 2 H), 9.71 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{37}H_{27}FNO_{10}$ 664, found 664.

Compound 2k. According to the general procedure **9k** (0.039 g, 0.048 mmol) was hydrolyzed to obtain **2k** (25.6 mg, 38.8 μmol, 81 %) as a white solid. ^{1}H NMR (300 MHz DMSO-d_6) δ 1.24 (s, 3 H), 5.34 (s, 2 H), 5.44 (s, 2 H), 6.94 (d, J = 2.8 Hz, 1 H), 6.97 (d, J = 2.9 Hz, 1 H), 7.11 (m, 3 H), 7.24 (m, 3 H), 7.63 (m, 4 H), 7.75 (m, 3 H), 7.85 (d, J = 8.8 Hz, 2 H), 7.93 (d, J = 8.8 Hz, 2 H), 10.6 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{38}H_{30}NO_{10}$ 660, found 660.

Compound 2l. According to the general procedure **9l** (0.044 g, 0.053 mmol) was hydrolyzed to obtain **2l** (30.6 mg, 44.5 μmol, 84 %) as a yellow solid. ^{1}H NMR (300 MHz DMSO-d_6) δ 1.19 (d, J = 6.9 Hz, 6 H), 2.87 (m, 1 H), 5.33 (s, 2 H), 5.44 (s, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 7.13 (d, J = 8.8 Hz, 2 H), 7.23 (m, 5 H), 7.70 (m, 4 H), 7.85 (d, J = 8.7 Hz, 2 H), 7.91 (d, J = 8.7 Hz, 2 H), 10.5 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{40}H_{34}NO_{10}$ 688, found 688.

Compound 2m. According to the general procedure **9m** (0.042 g, 0.050 mmol) was hydrolyzed to obtain **2m** (25.9 mg, 38.0 μmol, 76 %) as a yellow solid. ^{1}H NMR (300 MHz DMSO-d_6) δ 5.32 (s, 2 H), 5.43 (s, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.18 (m, 5 H), 7.45 (m, 2 H), 7.67 (m, 5 H), 7.83 (d, J = 8.9 Hz, 2 H), 8.10 (d, J = 9.0 Hz, 2 H), 10.6 (s, 1 H); LRMS-ESI (M + H^+) calcd for $C_{37}H_{26}F_2NO_{10}$ 682, found 682.

Compound 2n. According to the general procedure **9n** (0.040 g, 0.048 mmol) was hydrolyzed to obtain **2n** (23.3 mg, 34.6 μmol, 72 %) as a white solid. ^{1}H NMR (300 MHz

DMSO-d_6) δ 2.19 (s, 3 H), 5.33 (s, 2 H), 5.43 (s, 2 H), 6.85 (m, 3 H), 7.18 (m, 7 H), 7.68 (m, 5 H), 7.85 (d, J = 8.9 Hz, 2 H), 7.91 (d, J = 8.8 Hz, 2 H), 10.5 (s, 1 H); LRMS-ESI ($M + H^+$) calcd for $C_{38}H_{30}NO_{11}$ 676, found 676.

Compound 2o. According to the general procedure **9o** (0.039 g, 0.047 mmol) was hydrolyzed to obtain **2o** (23.9 mg, 35.7 μmol, 76 %) as a yellow solid. ^{1}H NMR (300 MHz DMSO-d_6) δ 5.31 (s, 2 H), 5.43 (s, 2 H), 6.77 (m, 2 H), 6.84 (m, 2 H), 7.08 (m, 4 H), 7.21 (m, 2 H), 7.38 (m, 2 H), 7.81 (m, 7 H), 10.6 (s, 1 H); LRMS-ESI ($M + H^+$) calcd for $C_{38}H_{27}N_2O_{10}$ 671, found 671.

Modeling Studies. The inhibitor **2a** was modeled into the active site of PTP1B using the X-ray structure of PTP1B (PDB code 1QXK) as the starting point. Modelling studies were performed using Autodock Vina. A ligand file was prepared using Autodock Tools and the bonds of **2a** were set as rotatable, with the exception of the amide bond, which was set as nonrotatable. A gridmap that encompassed the proposed binding site on PTP1B was calculated. Using the Lamarckian Genetic Algorithm in Autodoc Vina and a linear free energy model of molecular dynamics terms, the global minimum of the binding potential was determined.

Cloning, Expression and Purification of HePTP. Wild-type HePTP (residues 44–339) was subcloned into a derivative of the pET28a bacterial expression vector (Novagen) containing an *N*-terminal expression and hexahistidine purification tag (MGSDKIHHHHHH). HePTP was expressed and purified as described.[2] Briefly, following overnight expression at 18 °C, the protein was purified by immobilized metal affinity chromatography (HisTrap HP column, GE healthcare) followed by size exclusion chromatography (Superdex75 26/60, GE Healthcare).

Monomeric HePTP in protein stabilization buffer (10 mM Tris pH 7.8, 100 mM NaCl, 0.5 mM TCEP) was pooled, concentrated, frozen in liquid nitrogen, and stored at −80 °C until needed.

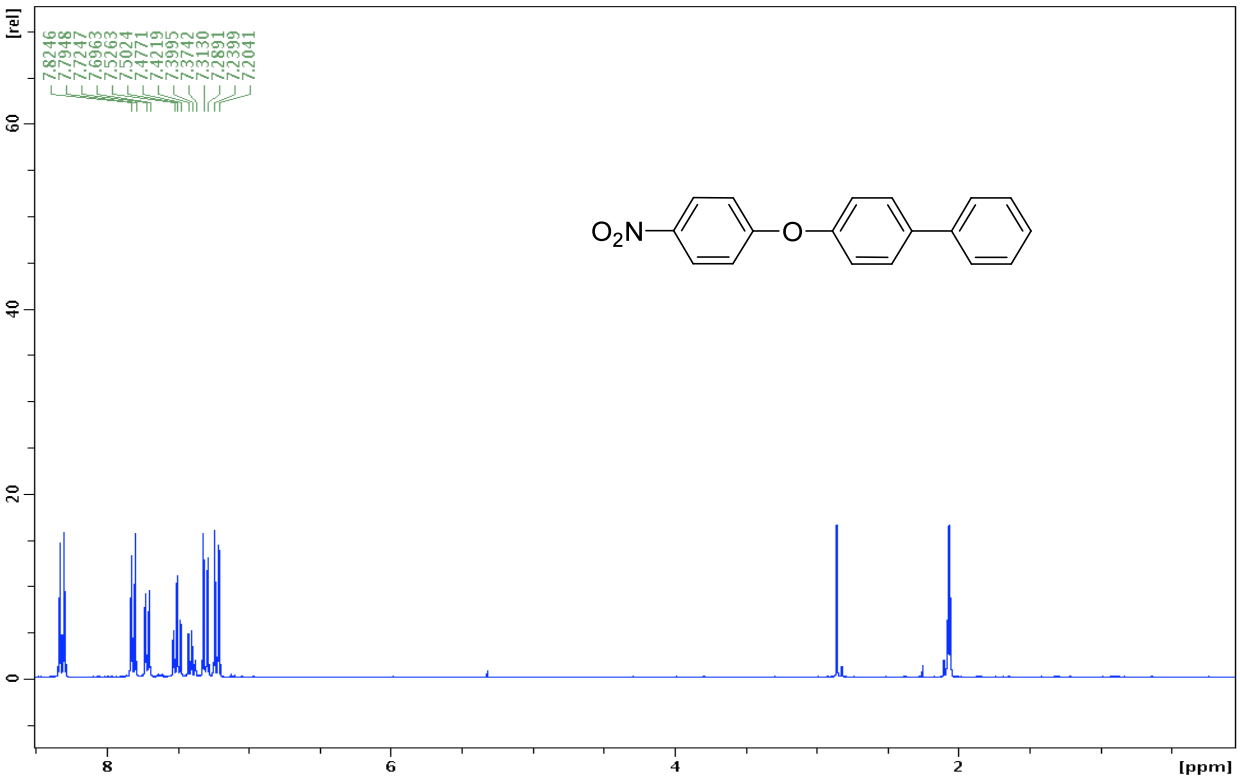

Figure S1. [1]HNMR spectrum of compound **6a**.

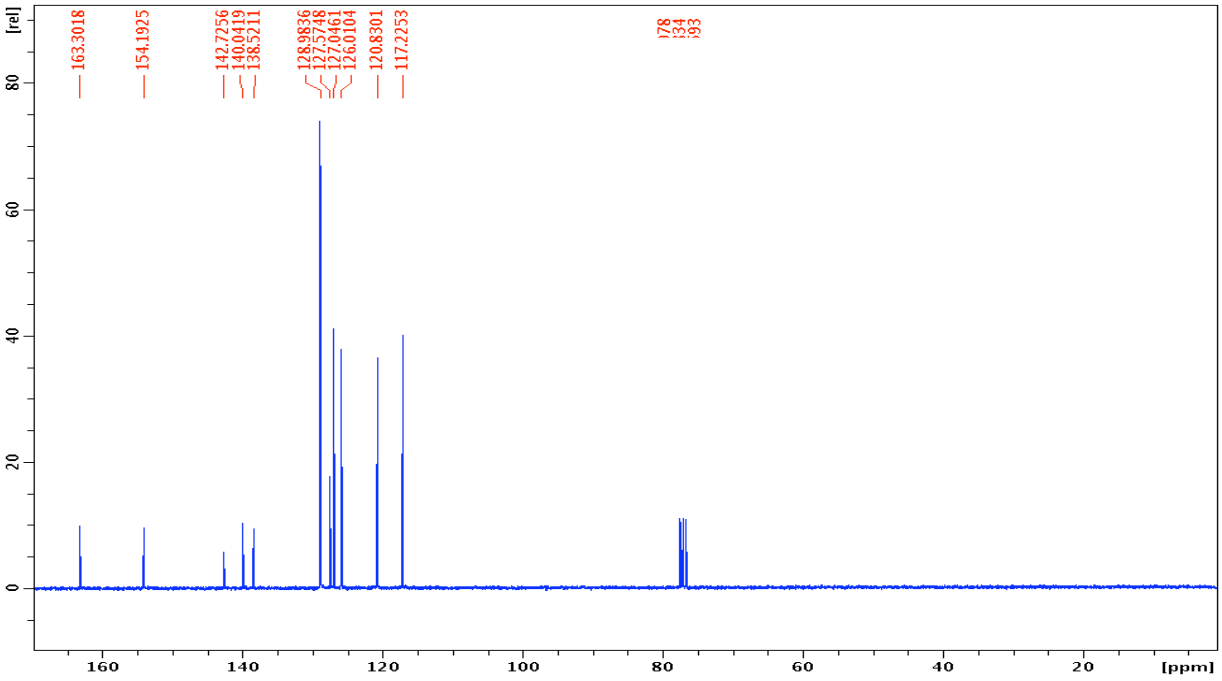

Figure S2. [13]CNMR spectrum of compound **6a**.

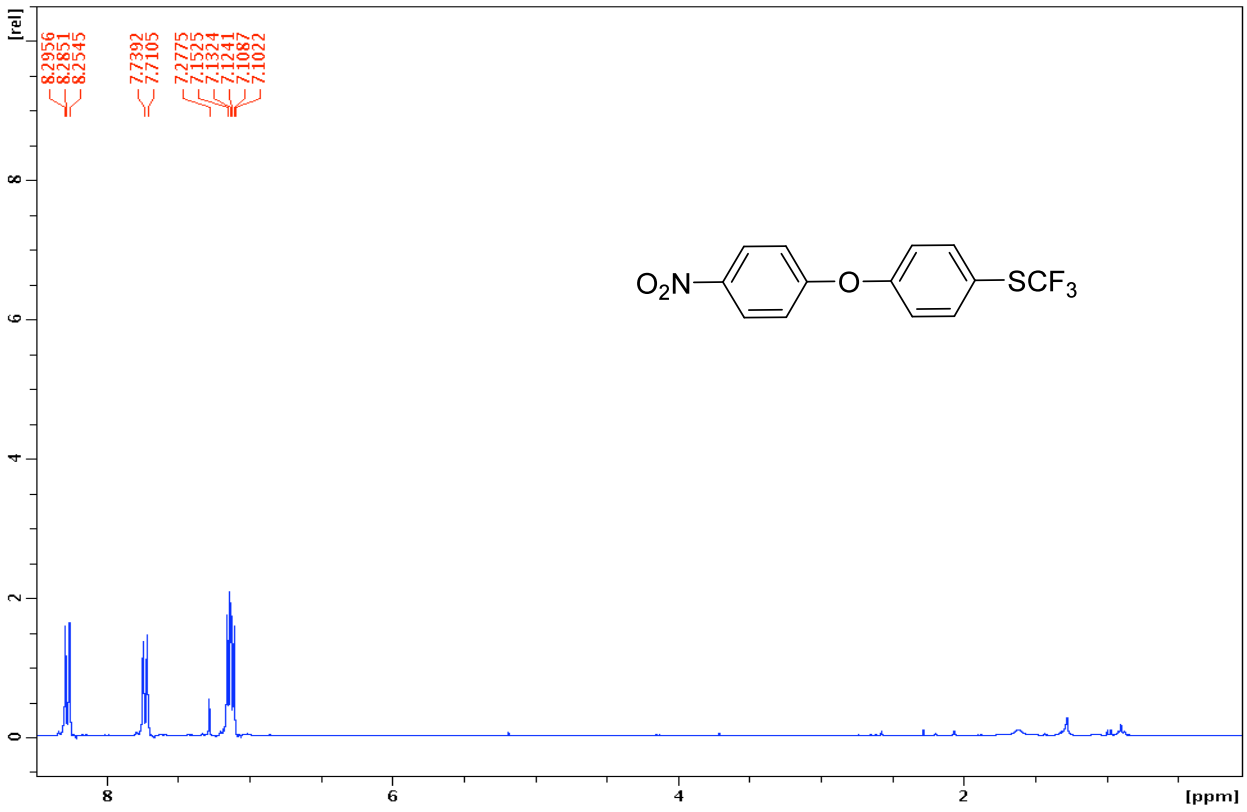

Figure S3. [1]HNMR spectrum of compound **6b**.

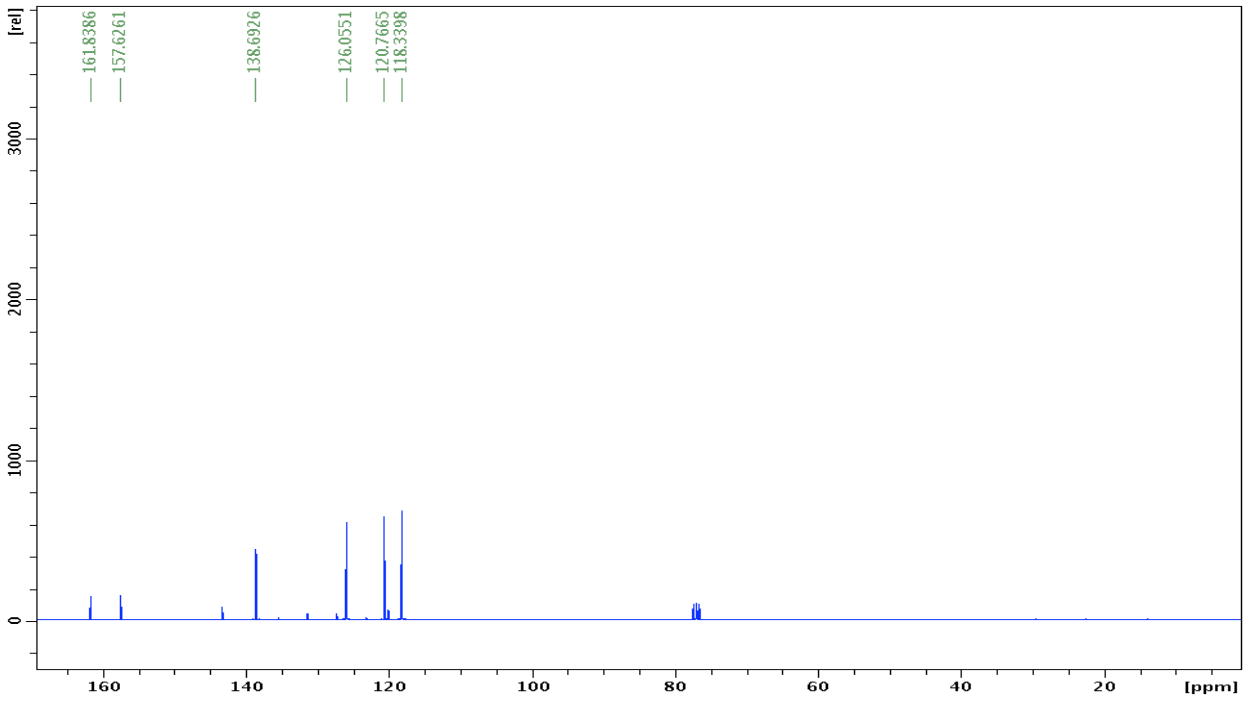

Figure S4. [13]CNMR spectrum of compound **6b**.

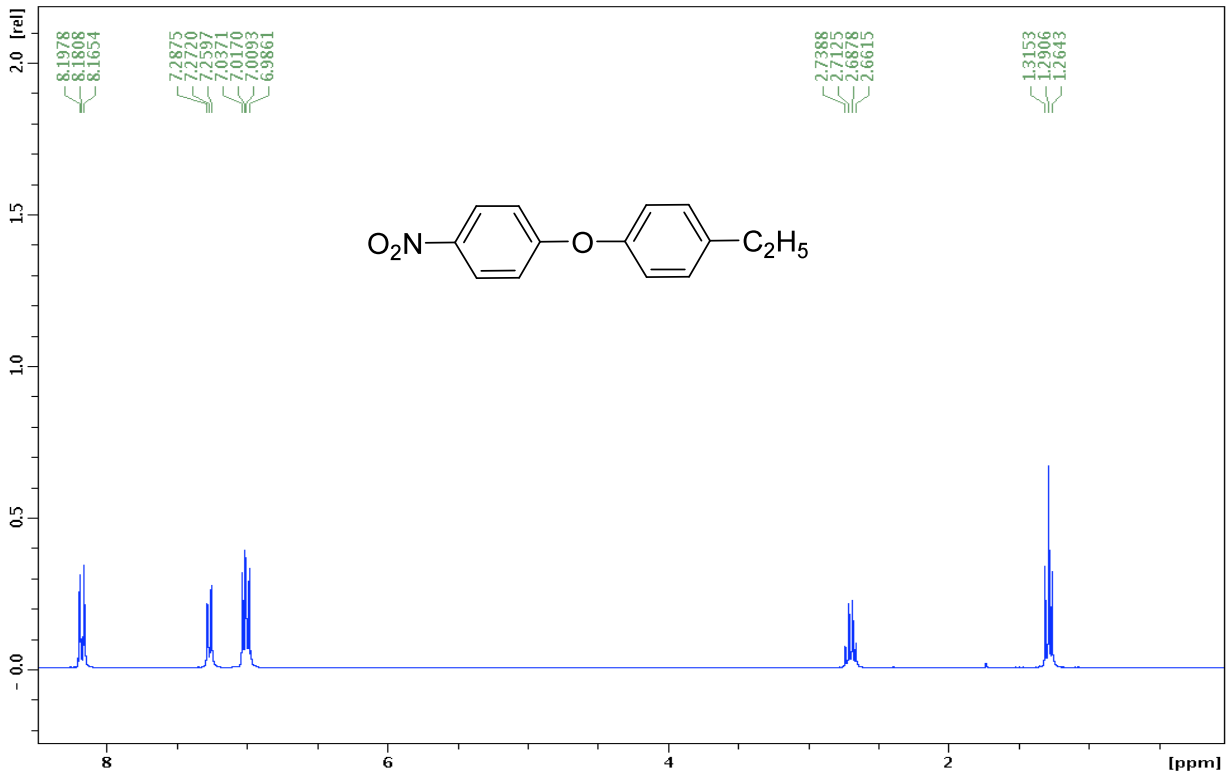

Figure S5. [1]HNMR spectrum of compound **6c**.

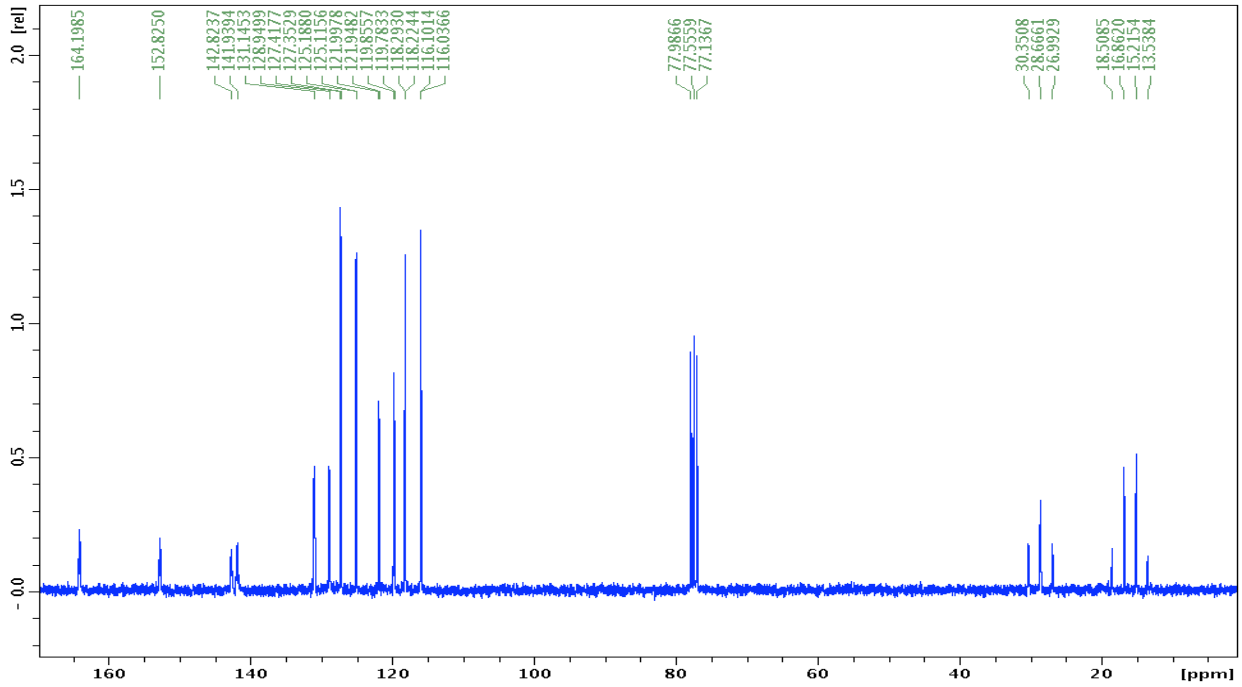

Figure S6. [13]CNMR proton-coupled spectrum of compound **6c**.

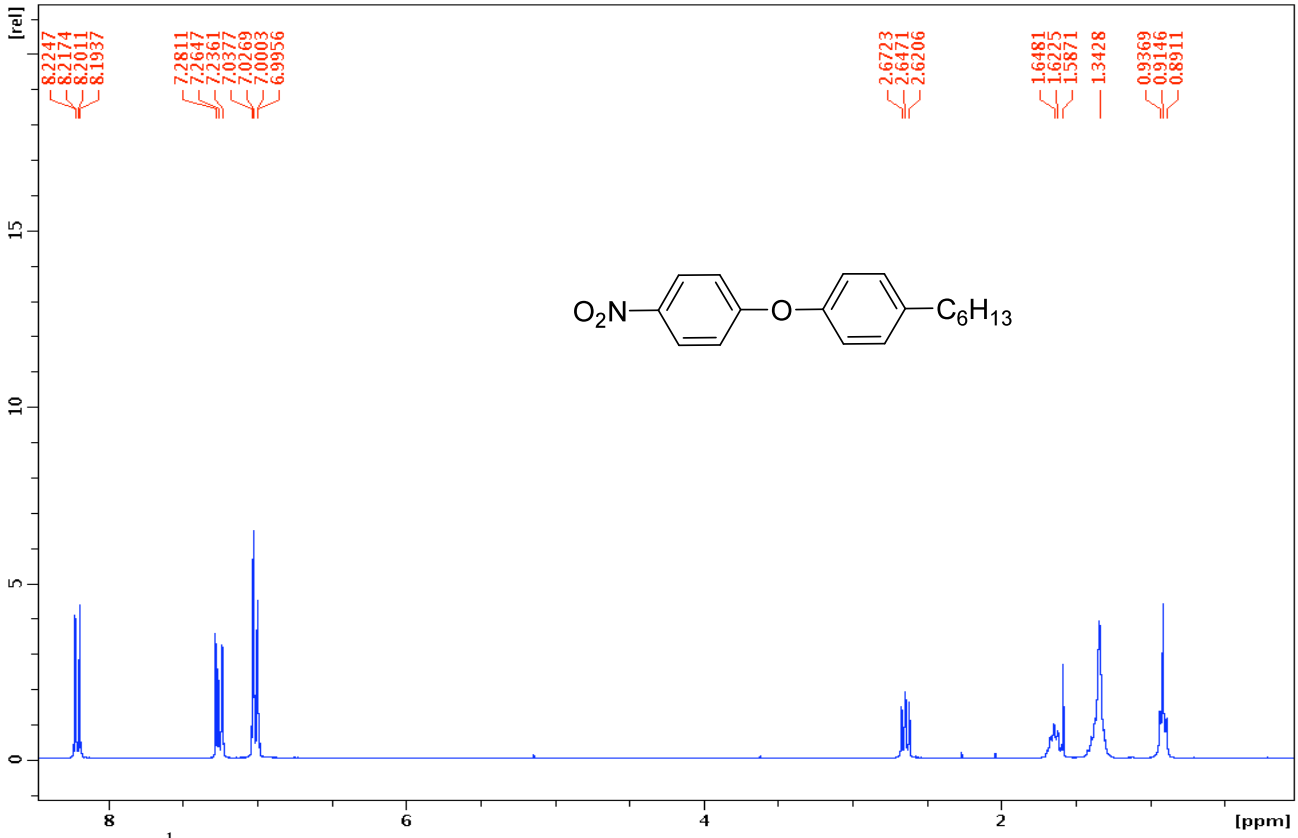

Figure S7. [1]HNMR spectrum of compound **6d**.

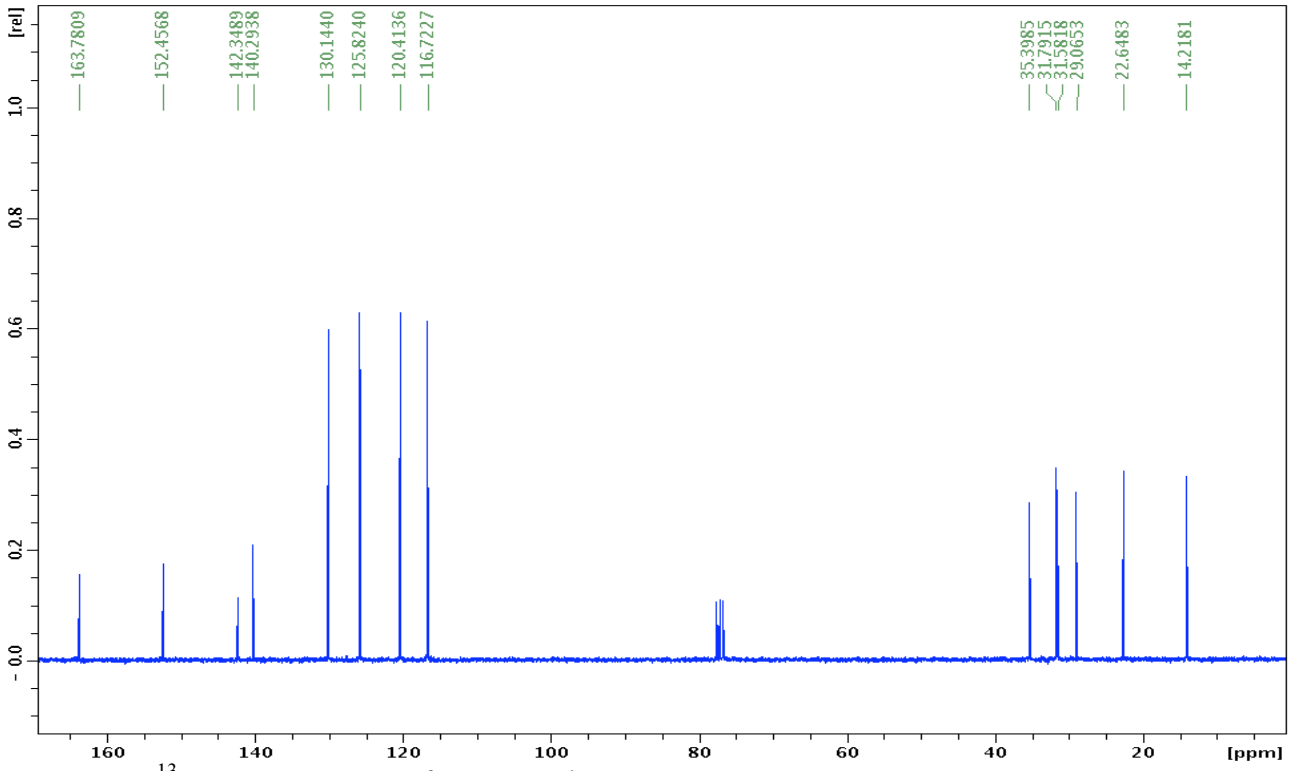

Figure S8. [13]CNMR spectrum of compound **6d**.

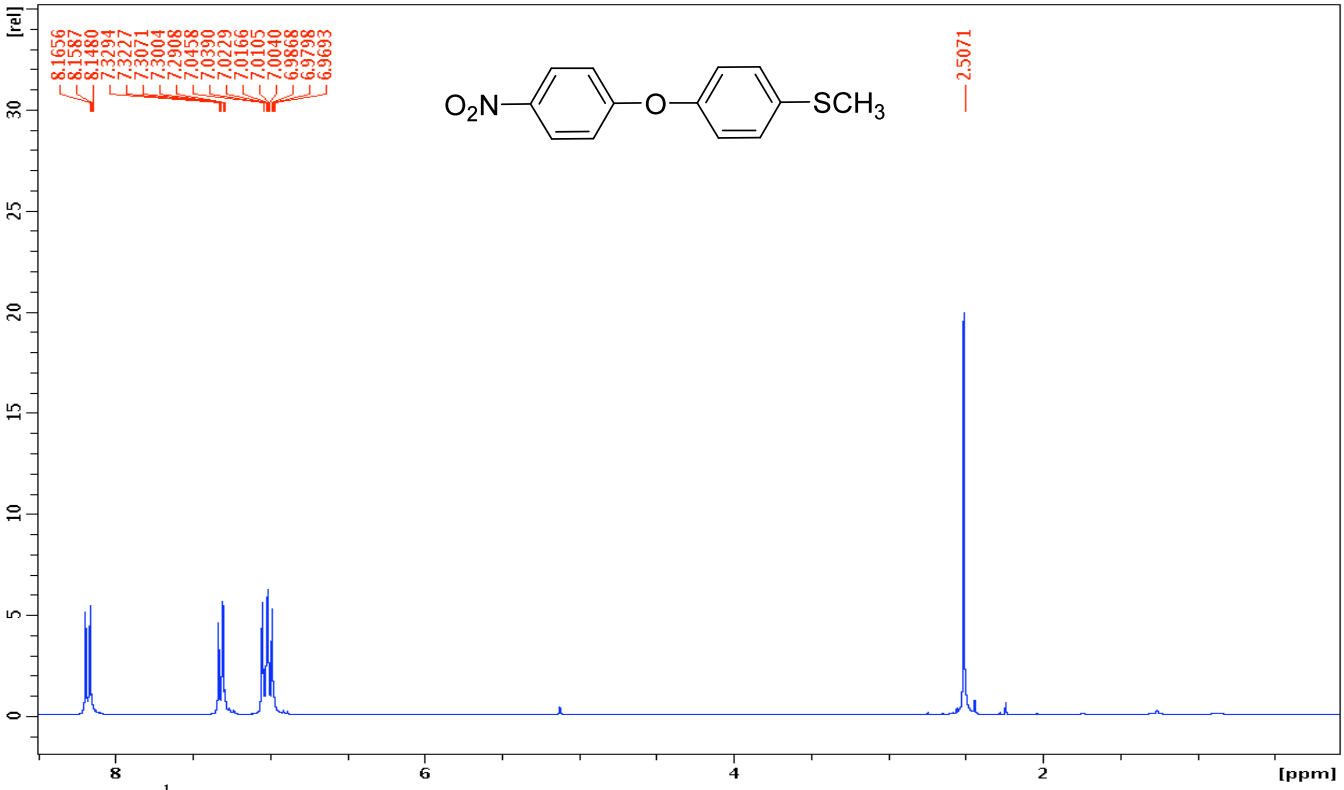

Figure S9. [1]HNMR spectrum of compound **6e**.

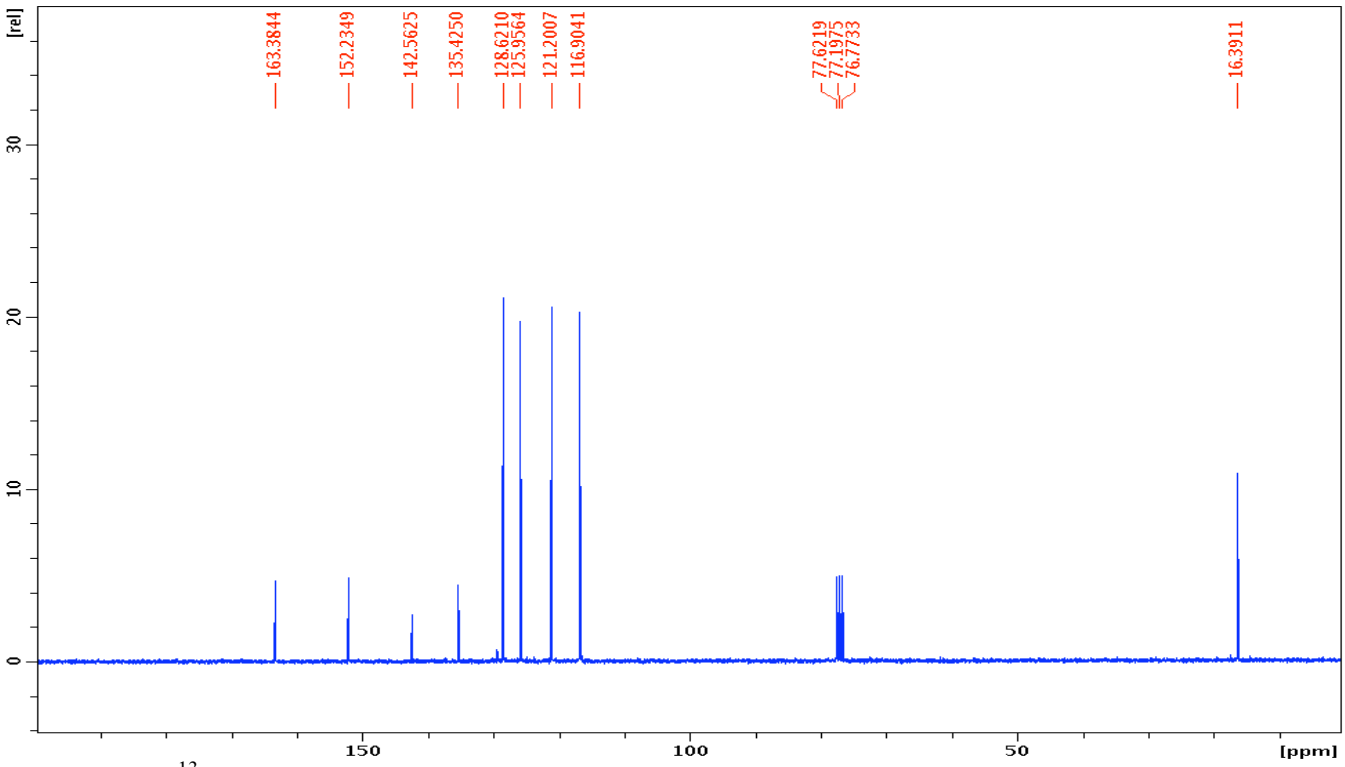

Figure S10. [13]CNMR spectrum of compound **6e**.

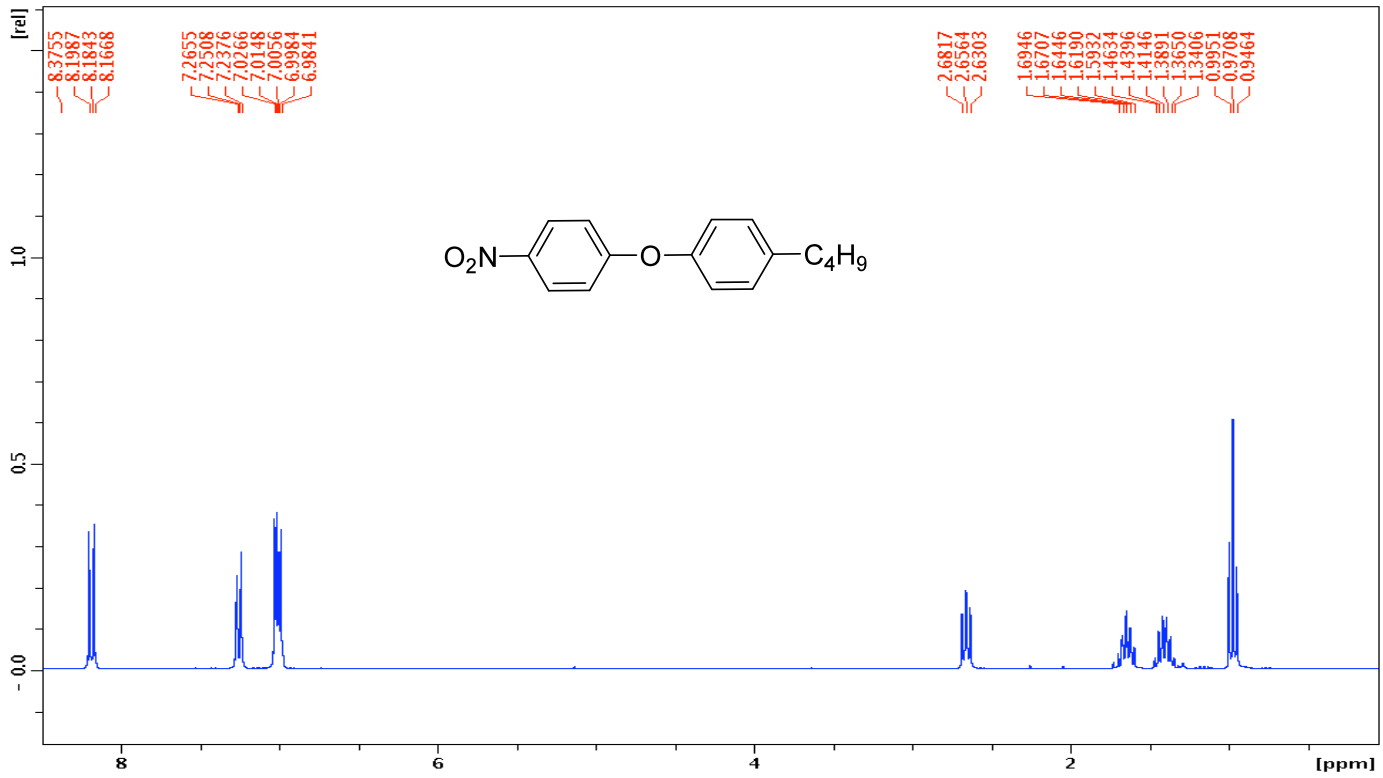

Figure S11. [1]HNMR spectrum of compound **6h**.

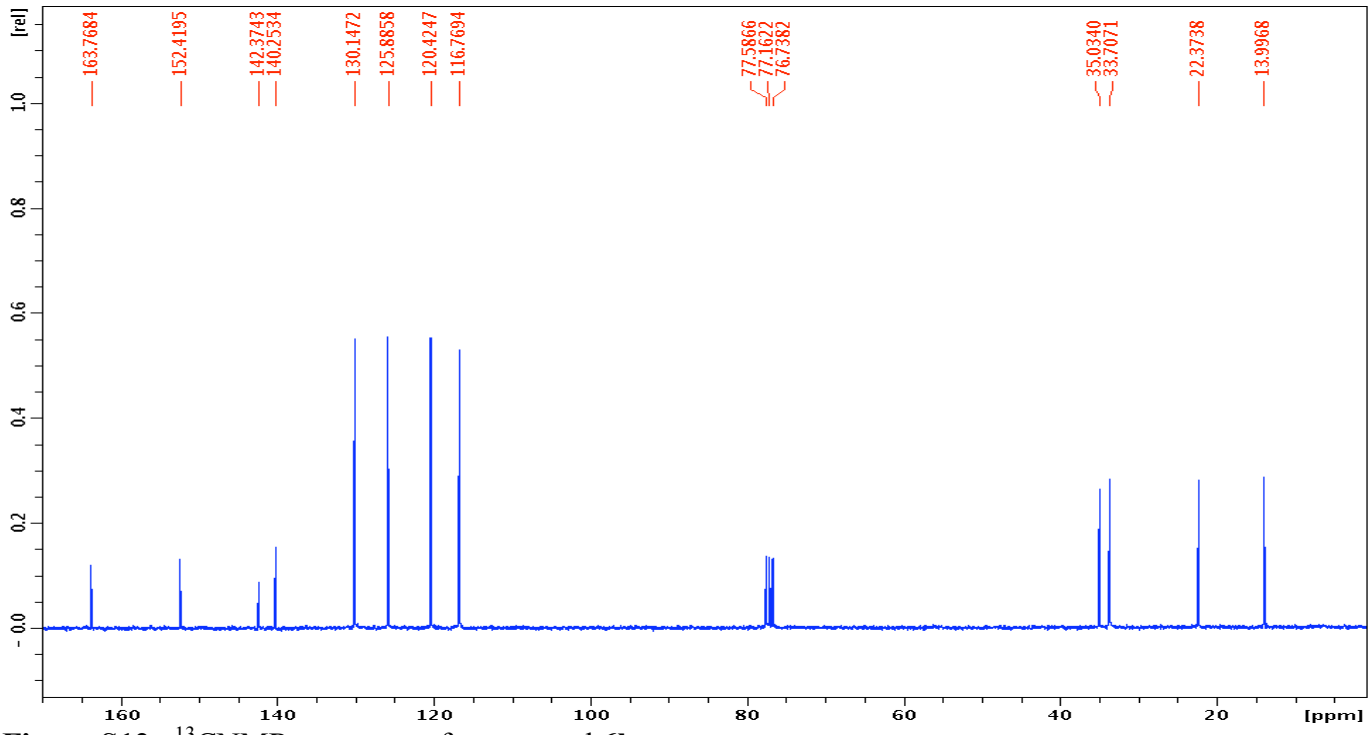

Figure S12. [13]CNMR spectrum of compound **6h**.

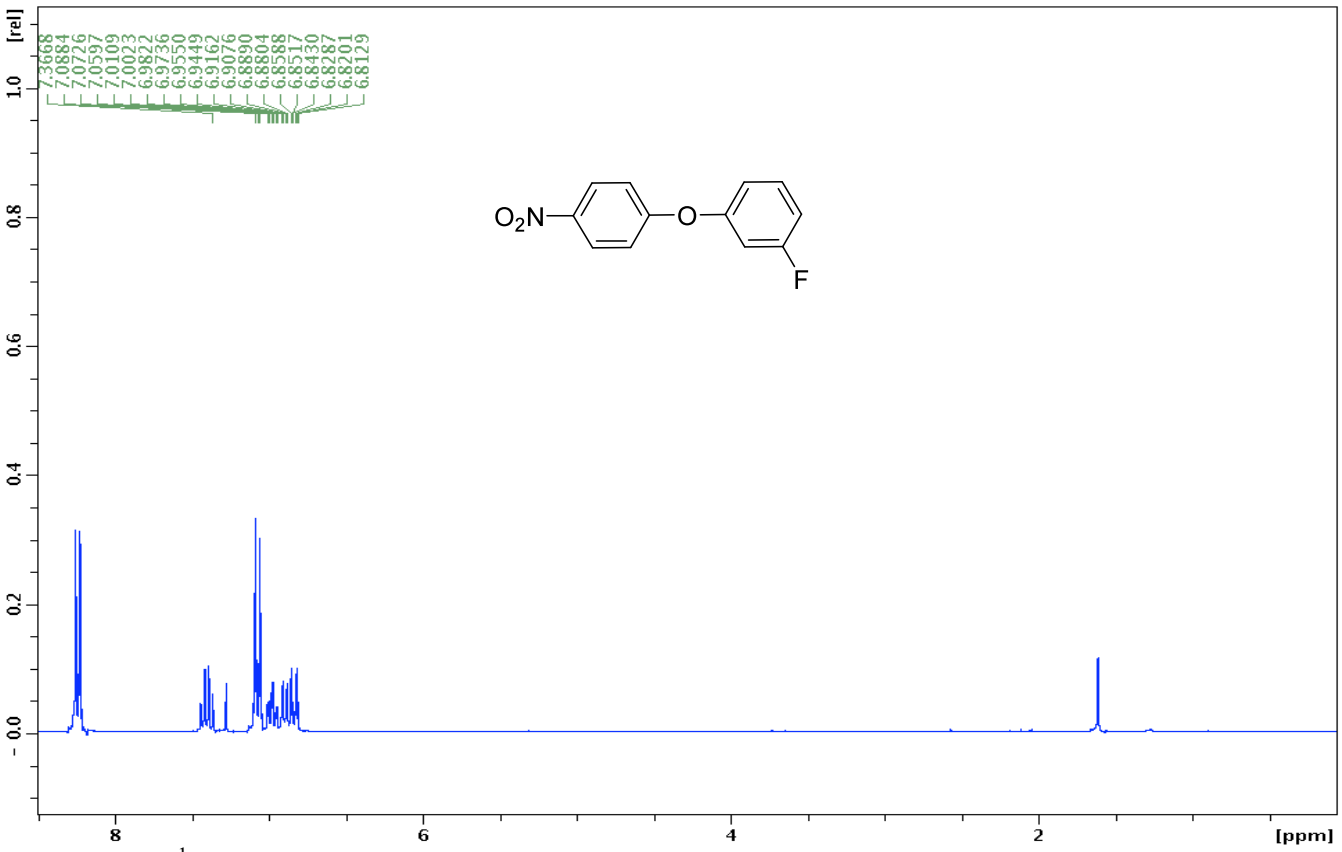

Figure S13. ^{1}HNMR spectrum of compound **6j**.

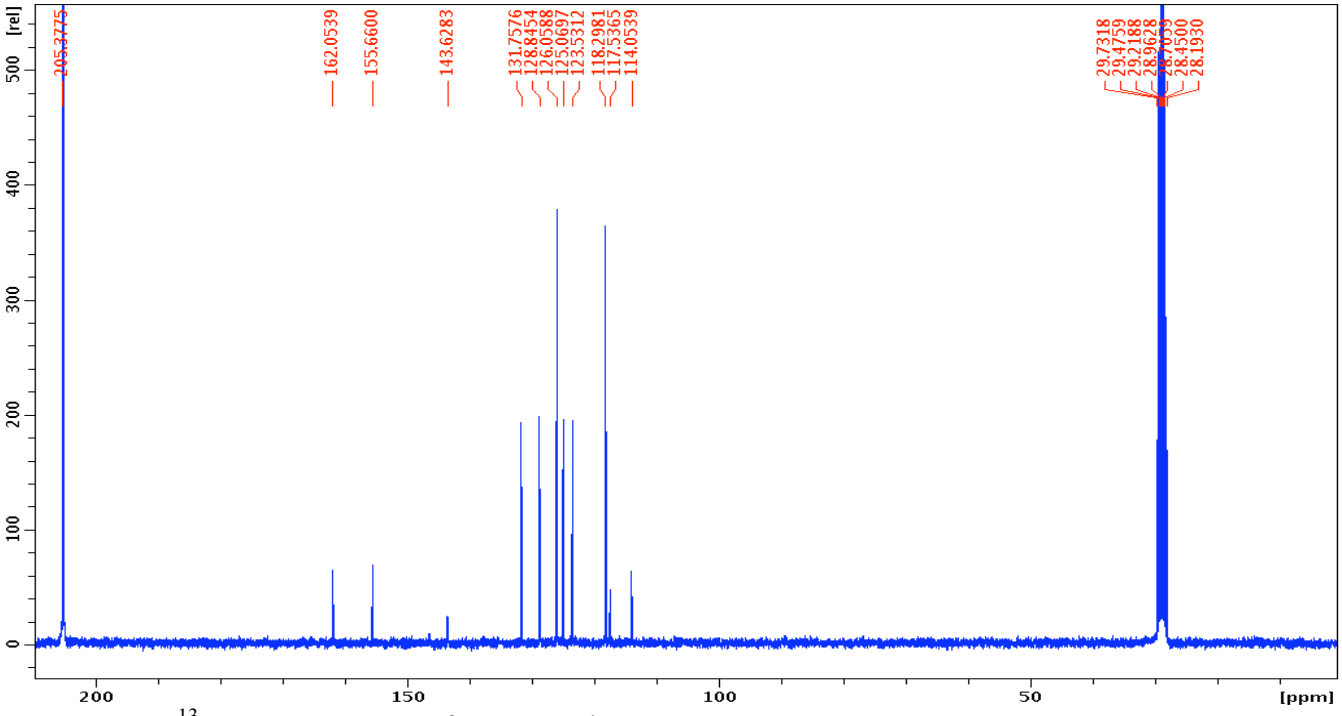

Figure S14. ^{13}CNMR spectrum of compound **6j**.

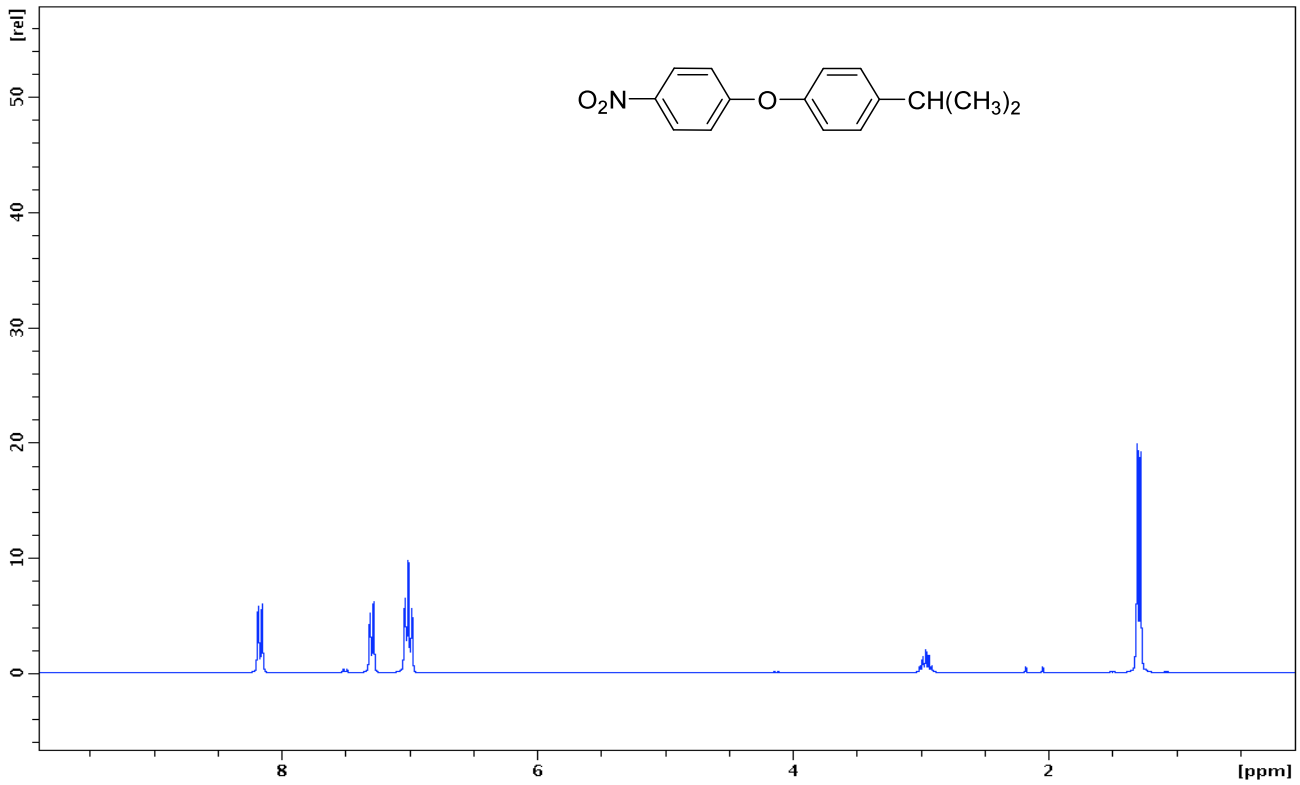

Figure S15. ^{1}HNMR spectrum of compound **6l**.

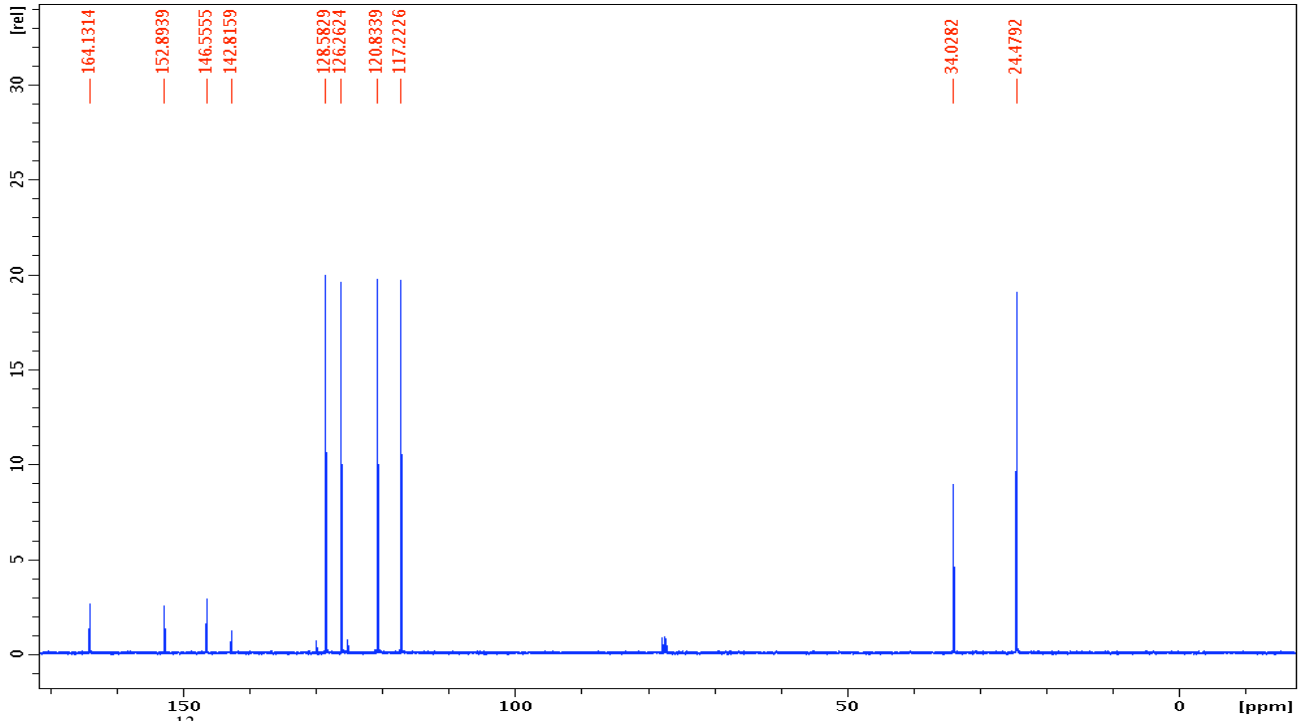

Figure S16. ^{13}CNMR spectrum of compound **6l**.

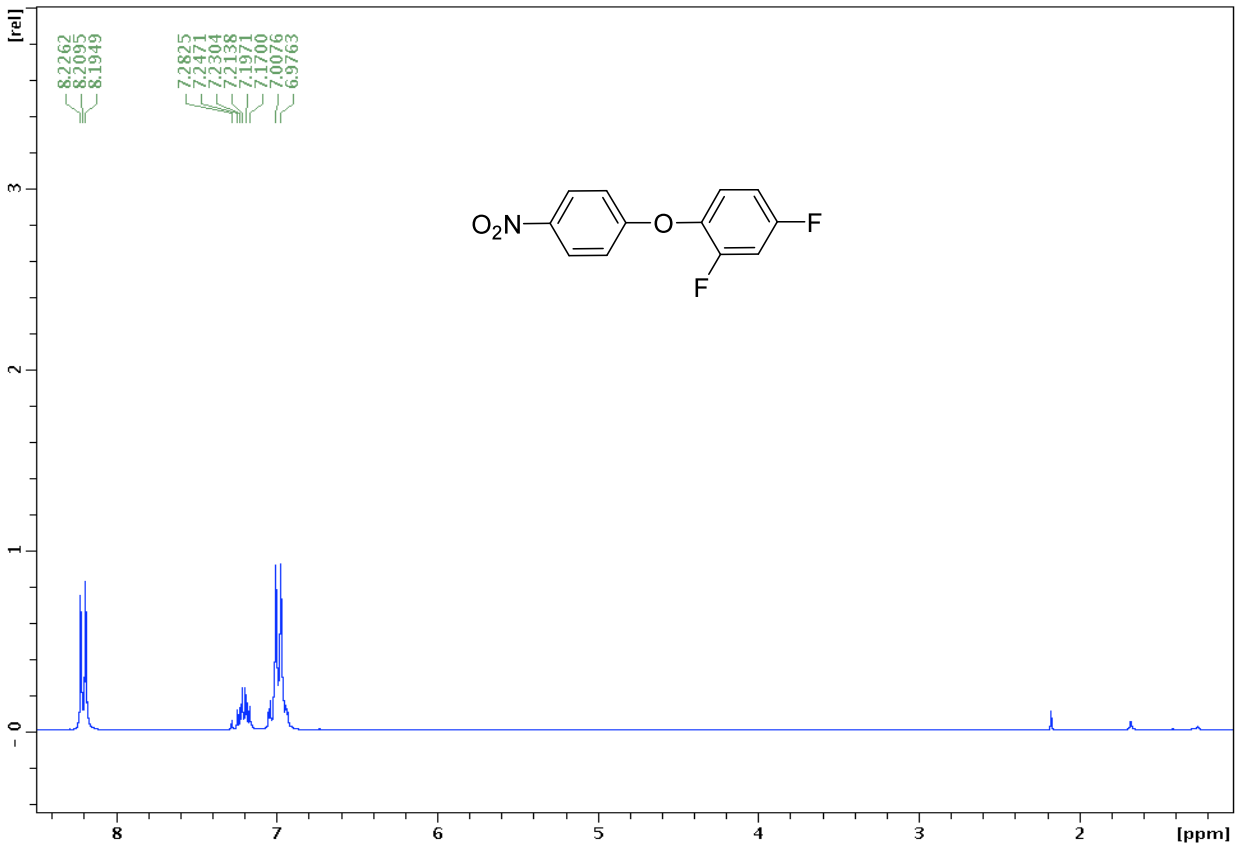

Figure S17. [1]HNMR spectrum of compound **6m**.

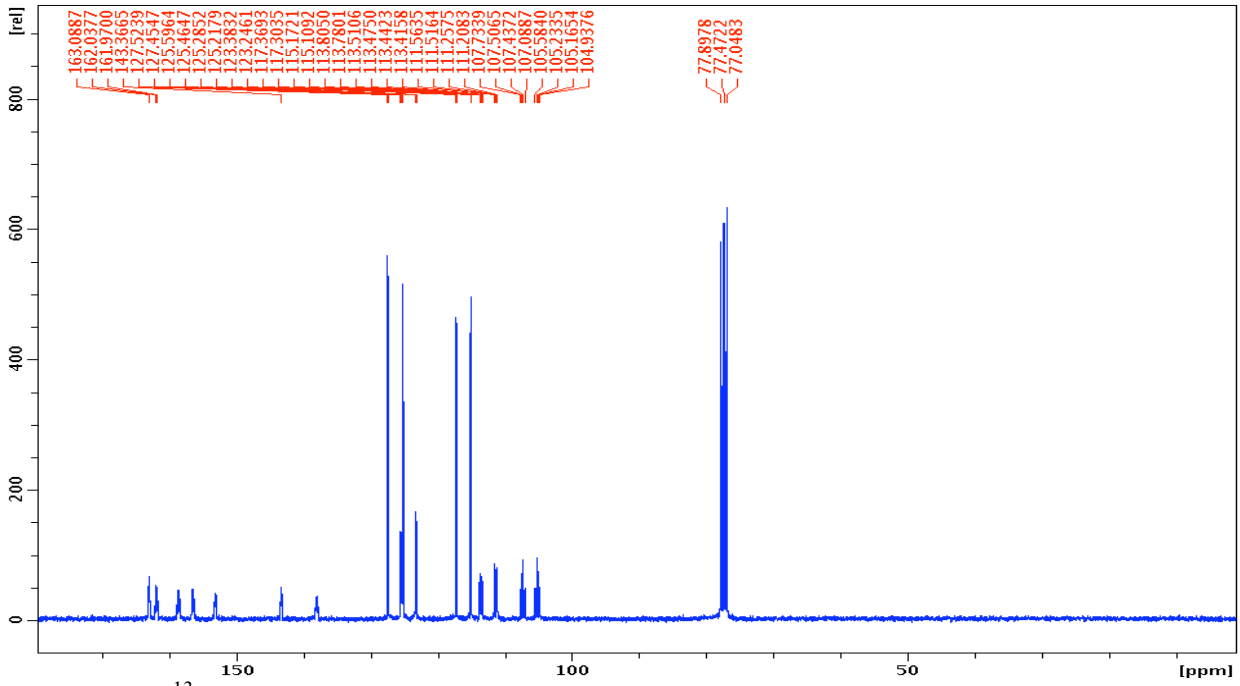

Figure S18. [13]CNMR spectrum of compound **6m**.

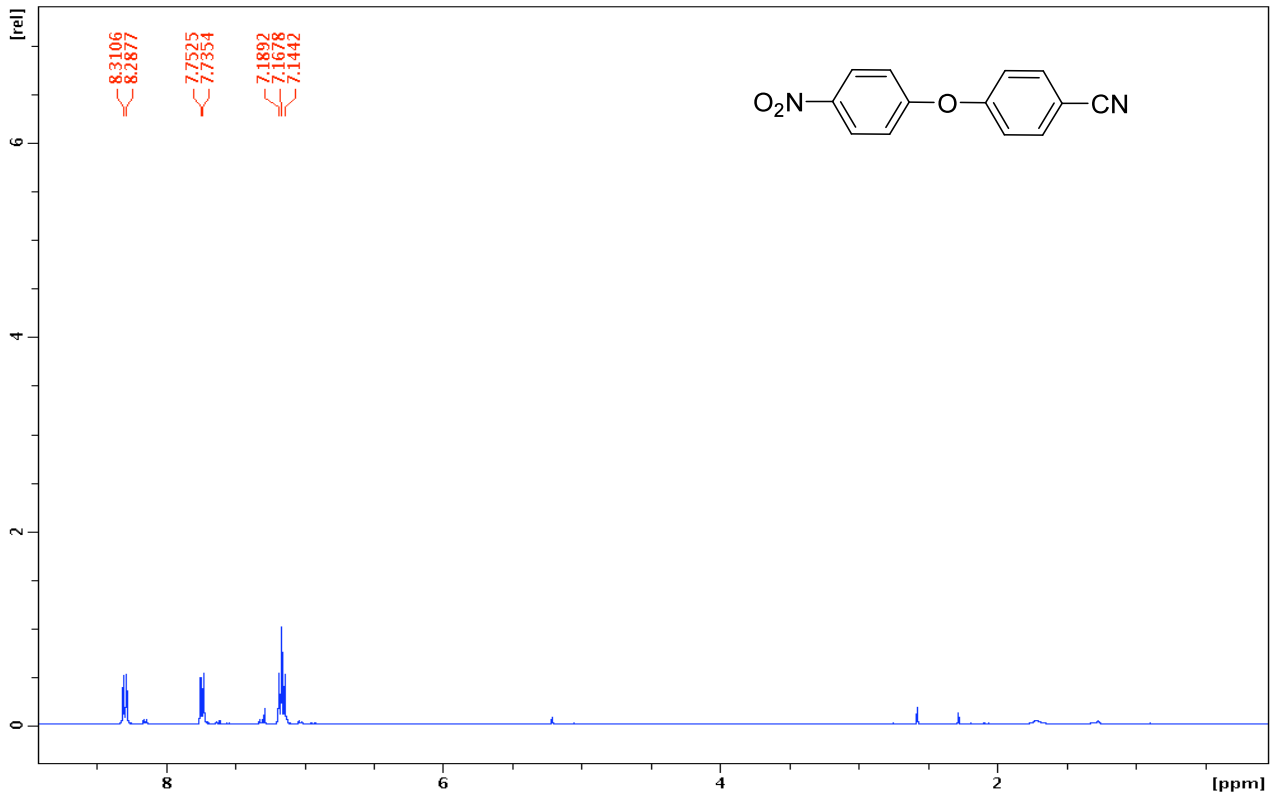

Figure S19. [1]HNMR spectrum of compound **6o**.

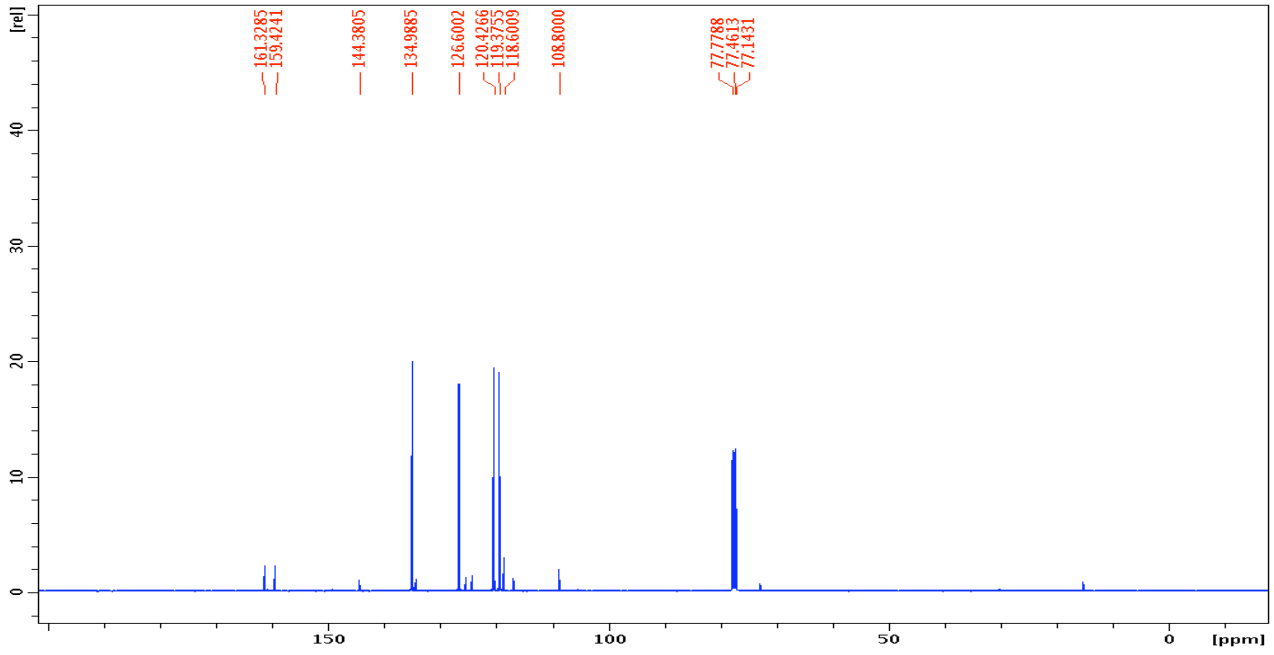

Figure S20. [13]CNMR spectrum of compound **6o**.

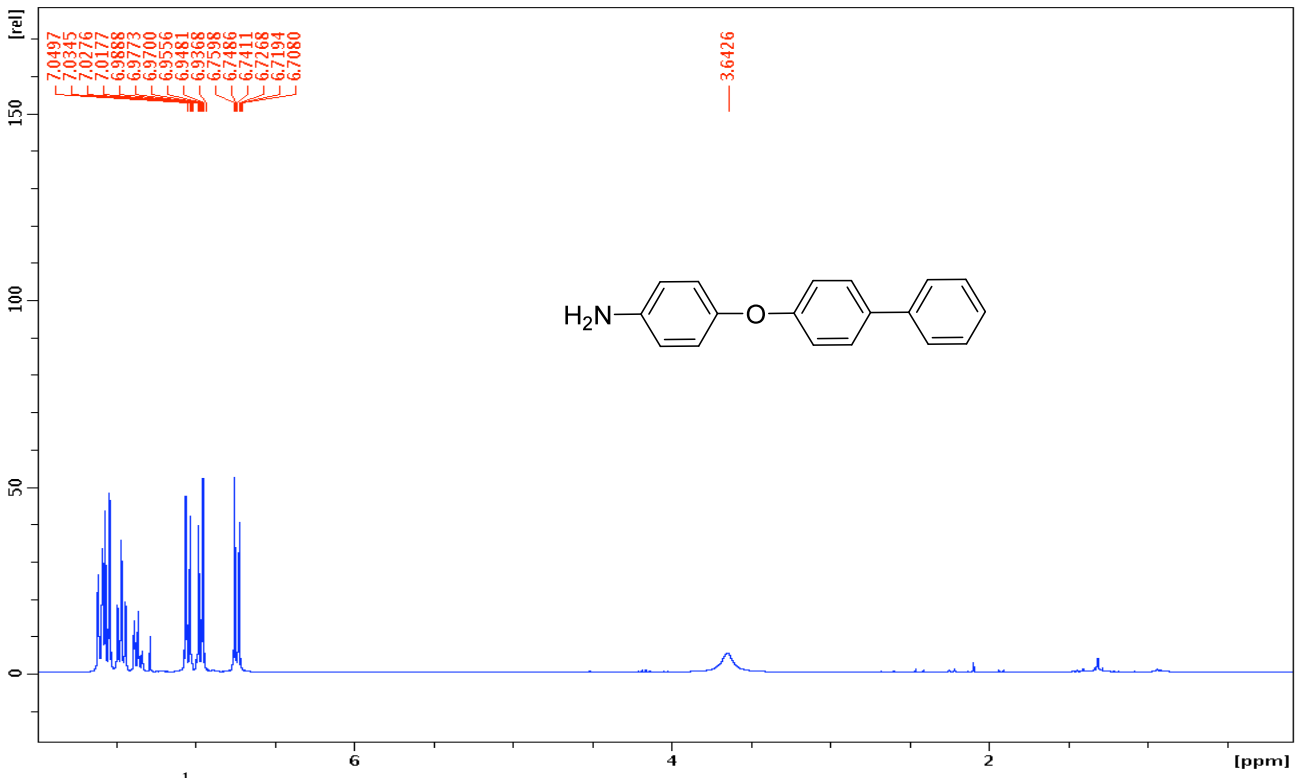

Figure S21. [1]HNMR spectrum of compound **7a**.

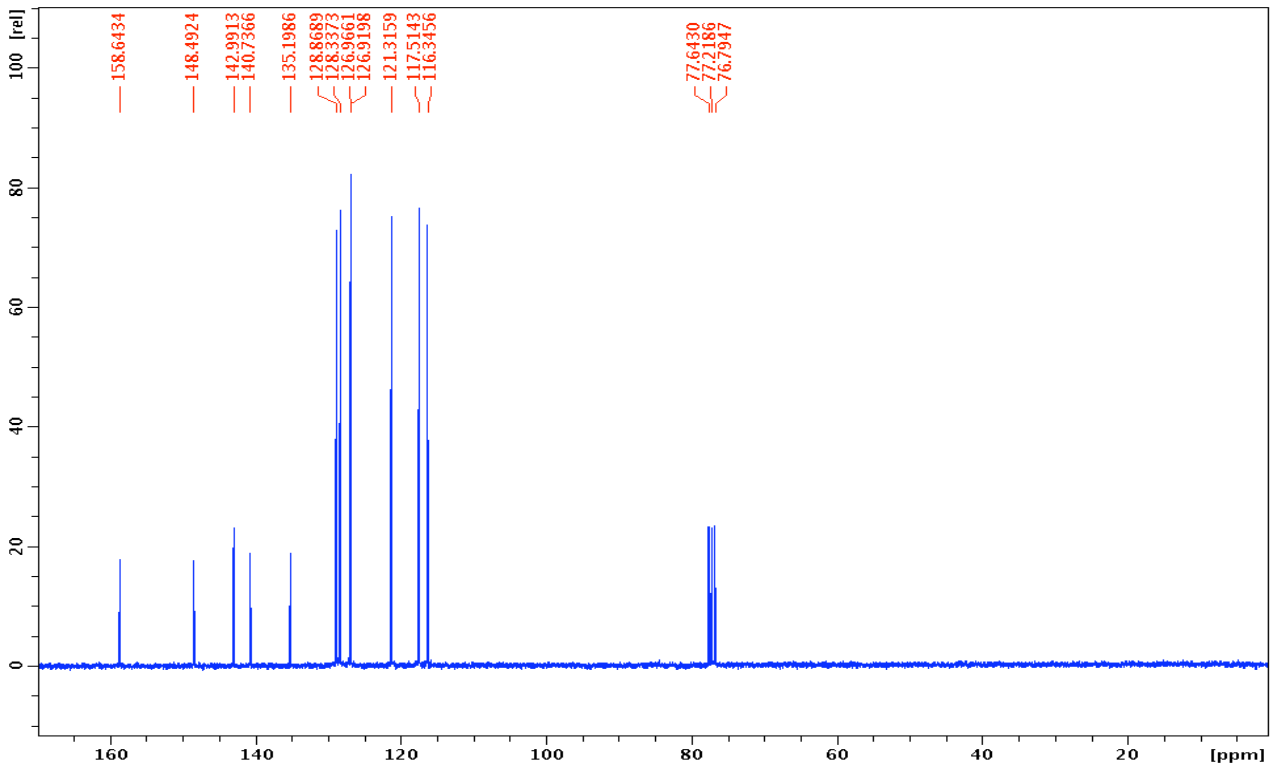

Figure S22. [13]CNMR spectrum of compound **7a**.

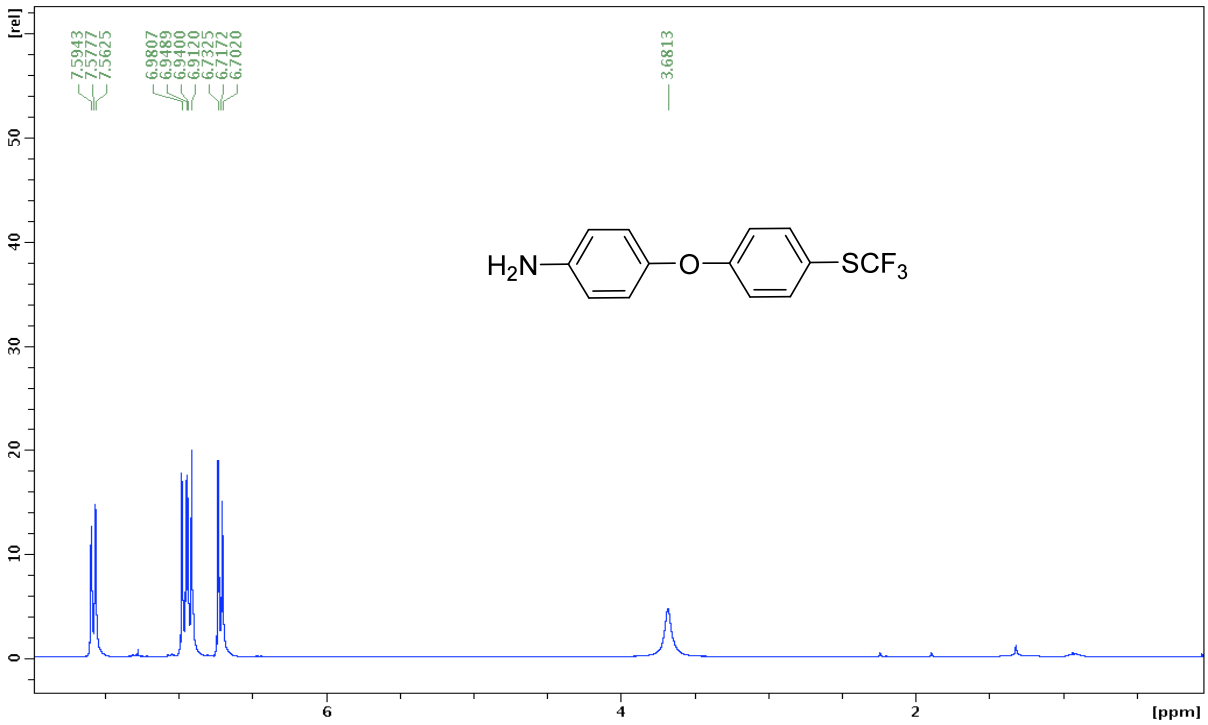

Figure S23. [1]HNMR spectrum of compound **7b**.

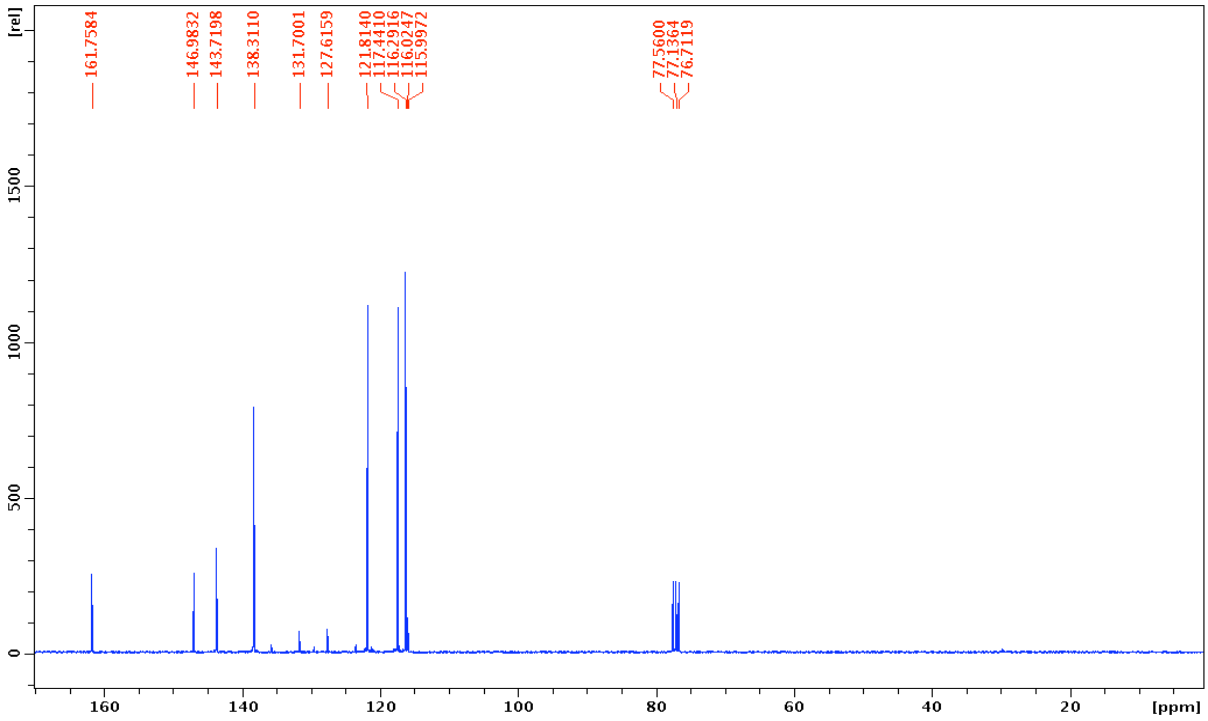

Figure S24. [13]CNMR spectrum of compound **7b**.

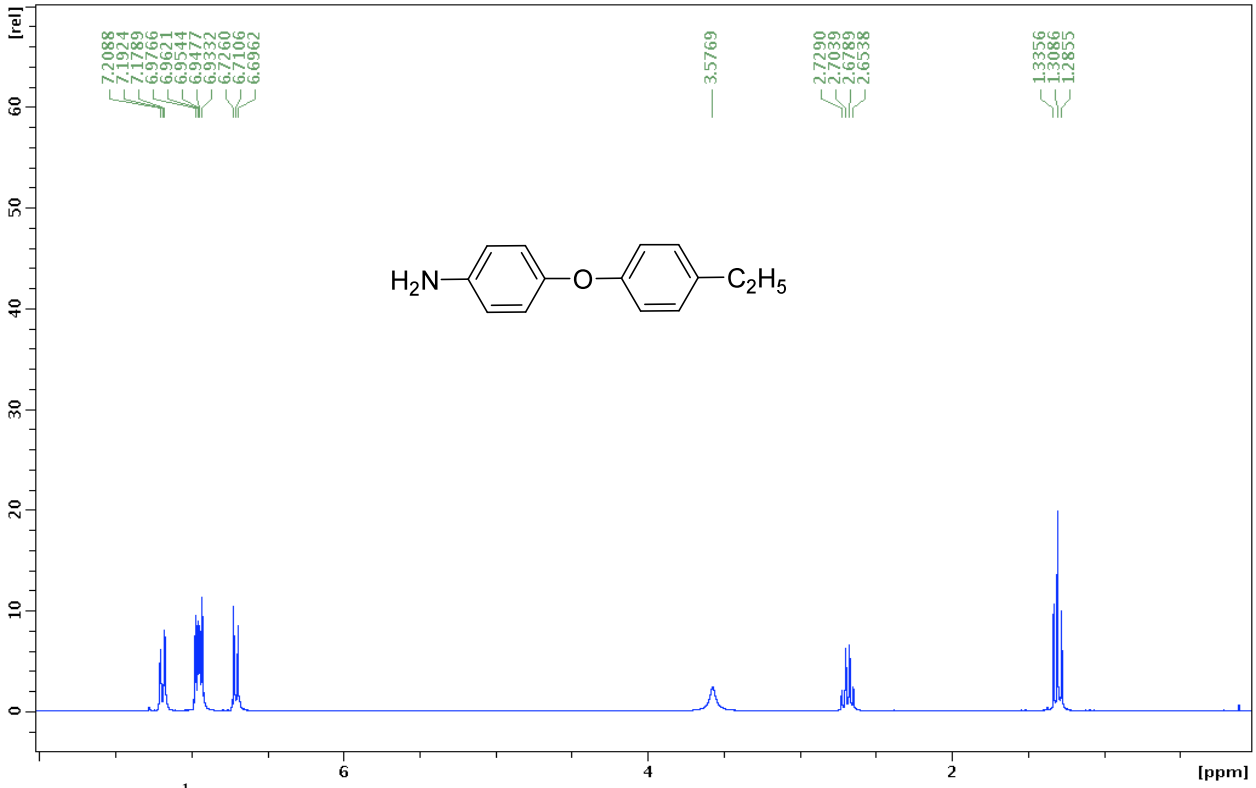

Figure S25. ^{1}HNMR spectrum of compound **7c**.

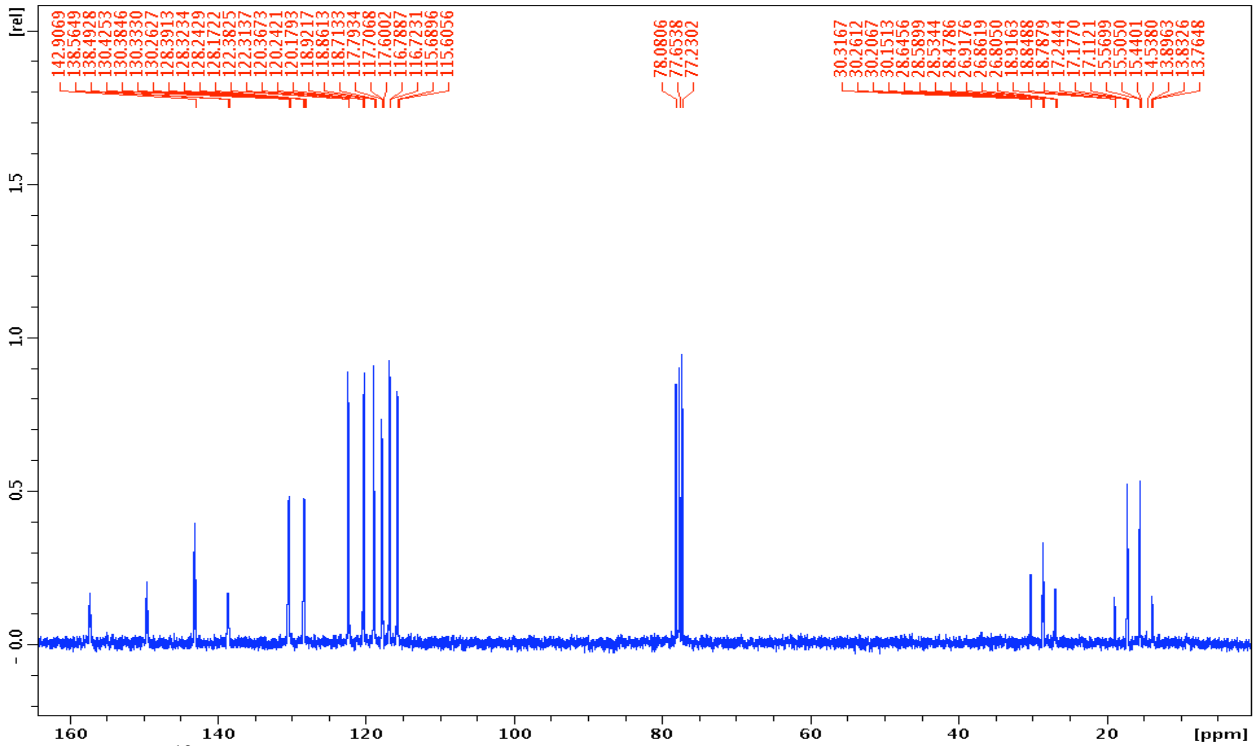

Figure S26. ^{13}CNMR proton-coupled spectrum of compound **7c**.

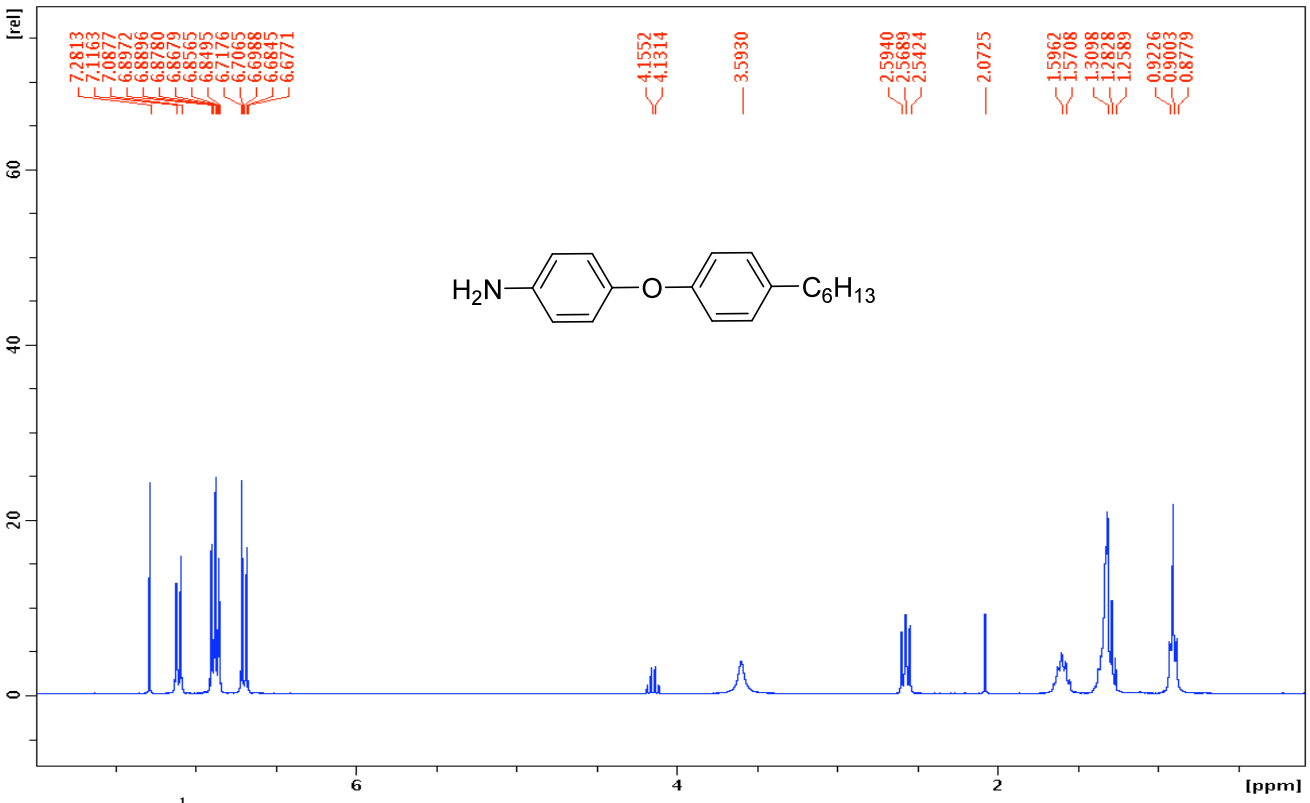

Figure S27. [1]HNMR spectrum of compound **7d**.

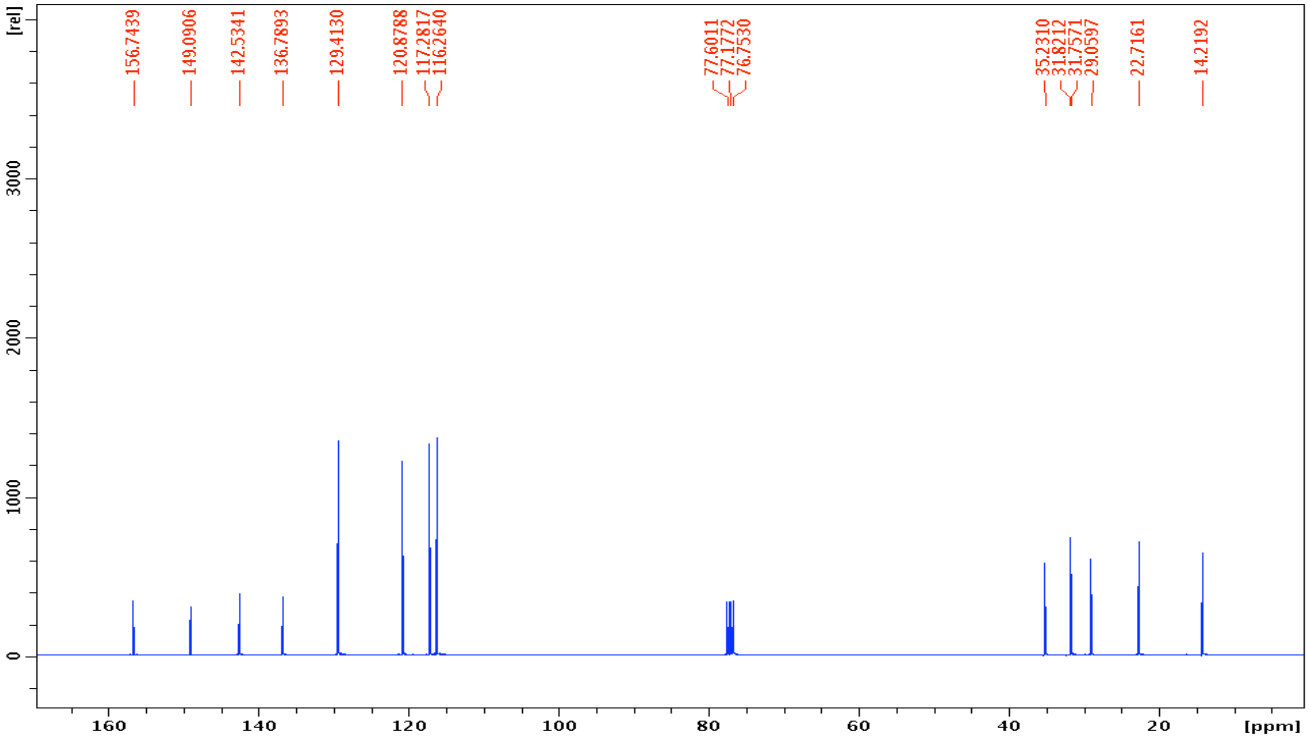

Figure S28. [13]CNMR spectrum of compound **7d**.

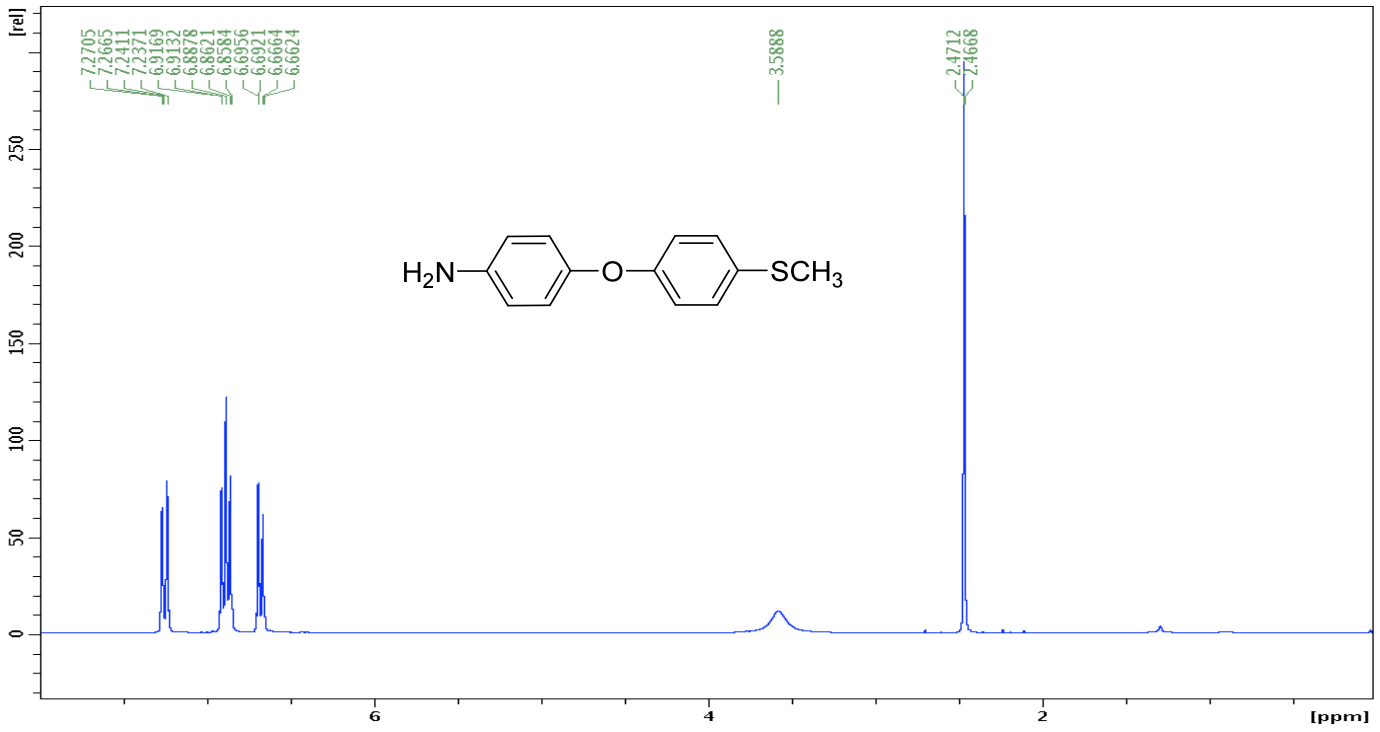

Figure S29. [1]HNMR spectrum of compound **7e**.

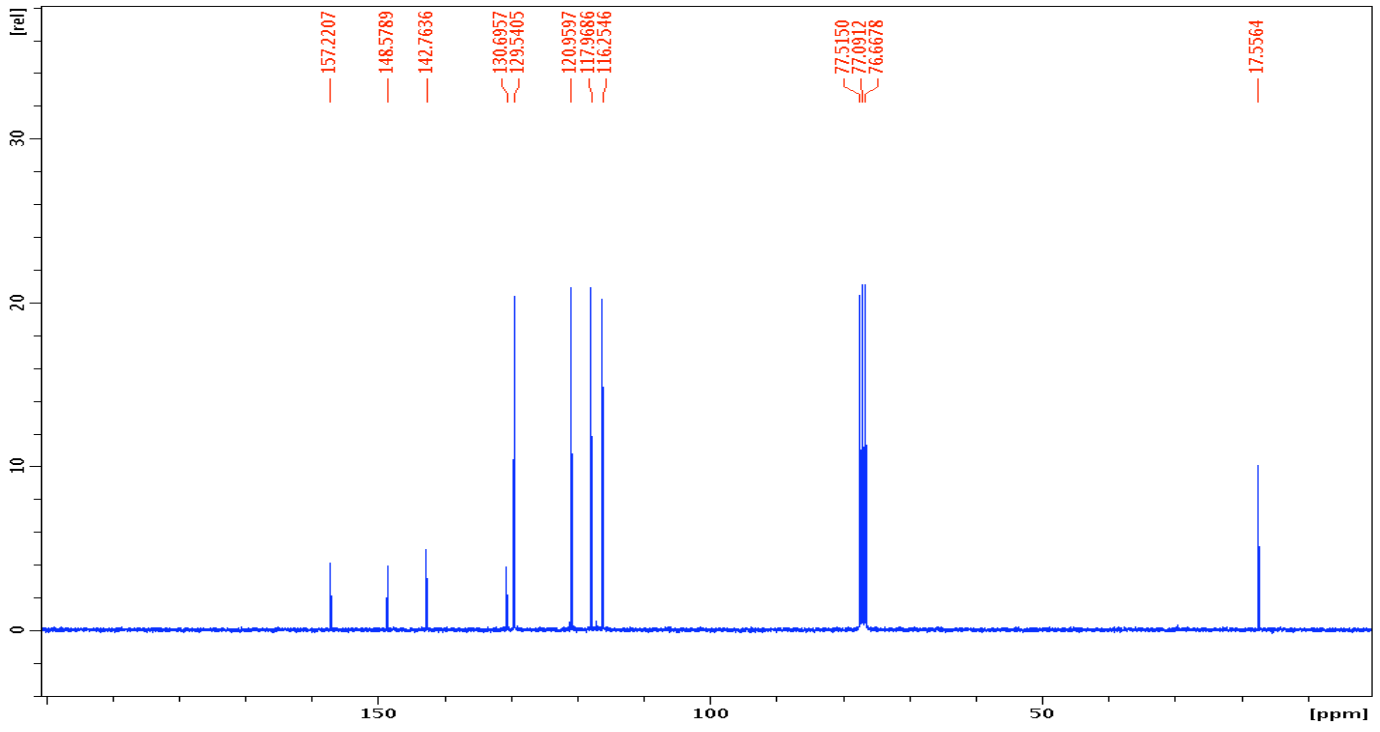

Figure S30. [13]CNMR spectrum of compound **7e**.

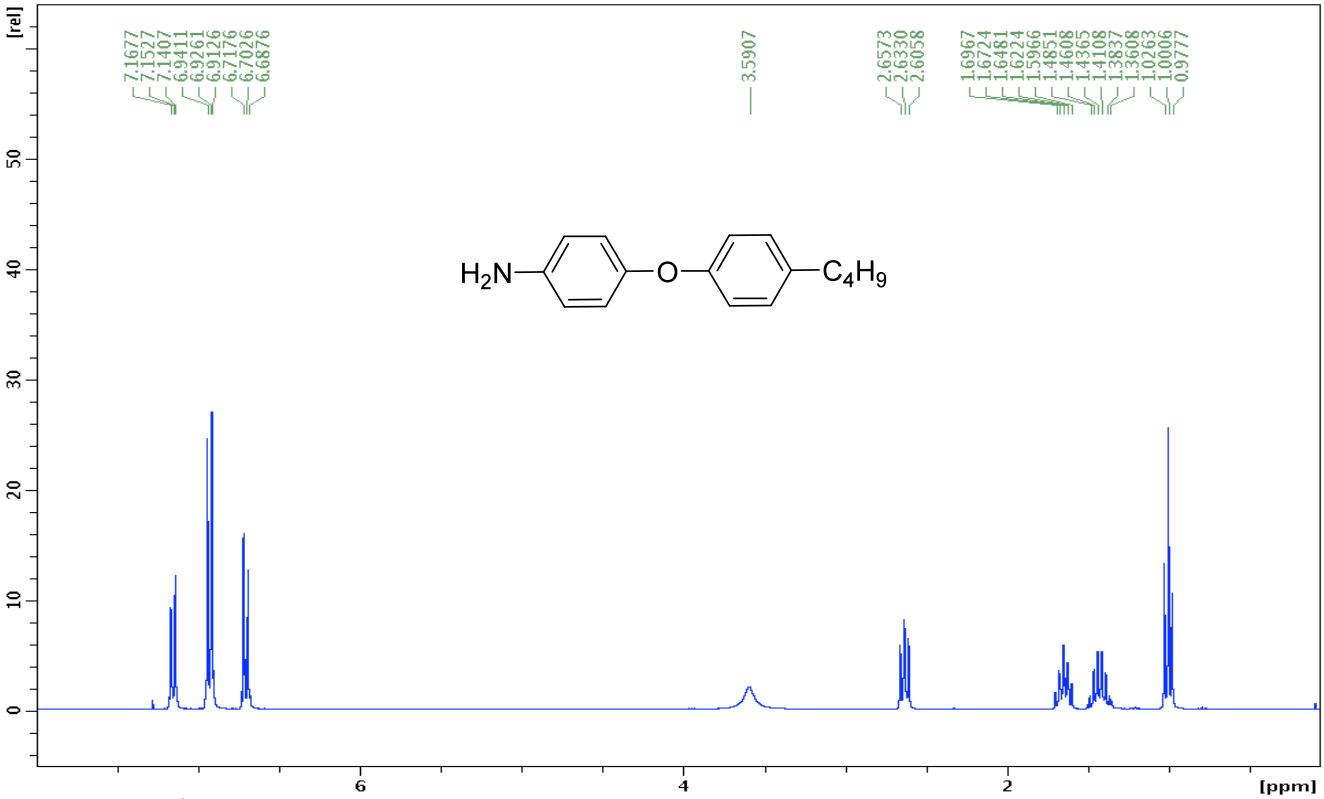

Figure S31. [1]HNMR spectrum of compound **7h**.

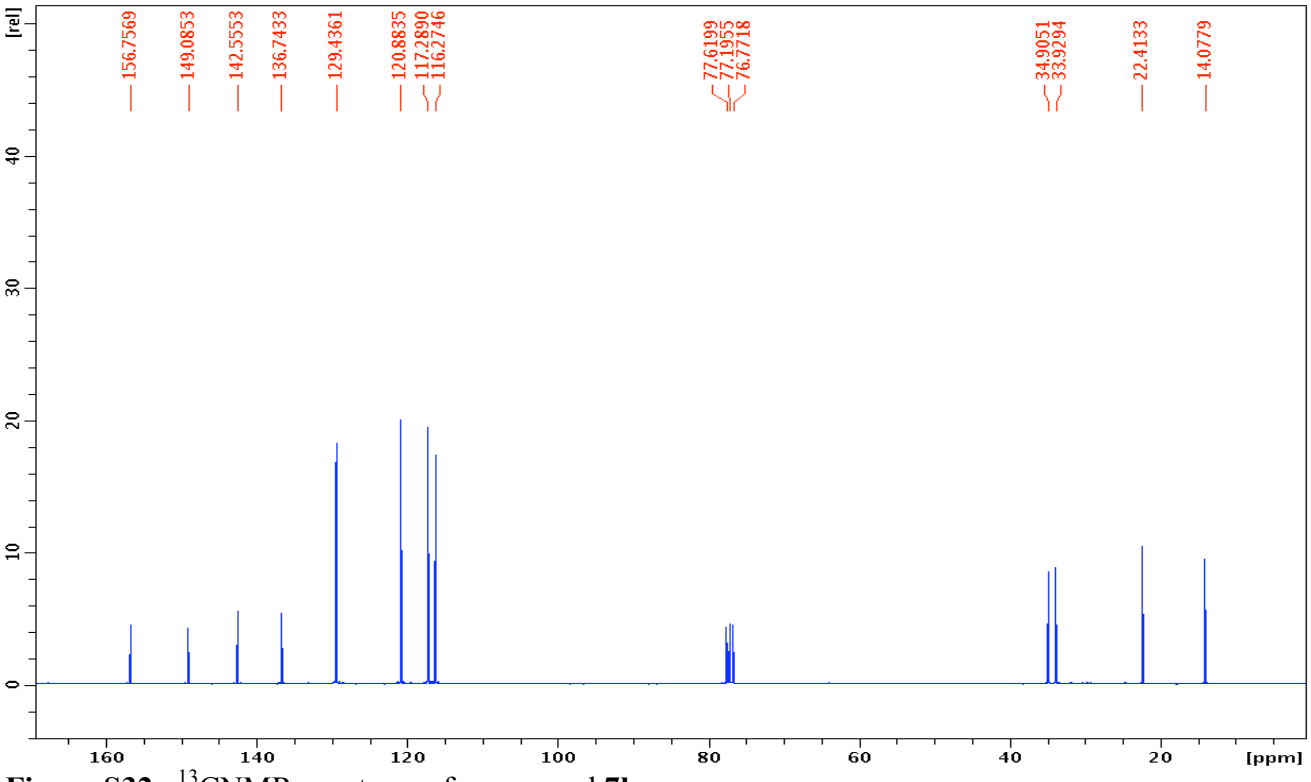

Figure S32. [13]CNMR spectrum of compound **7h**.

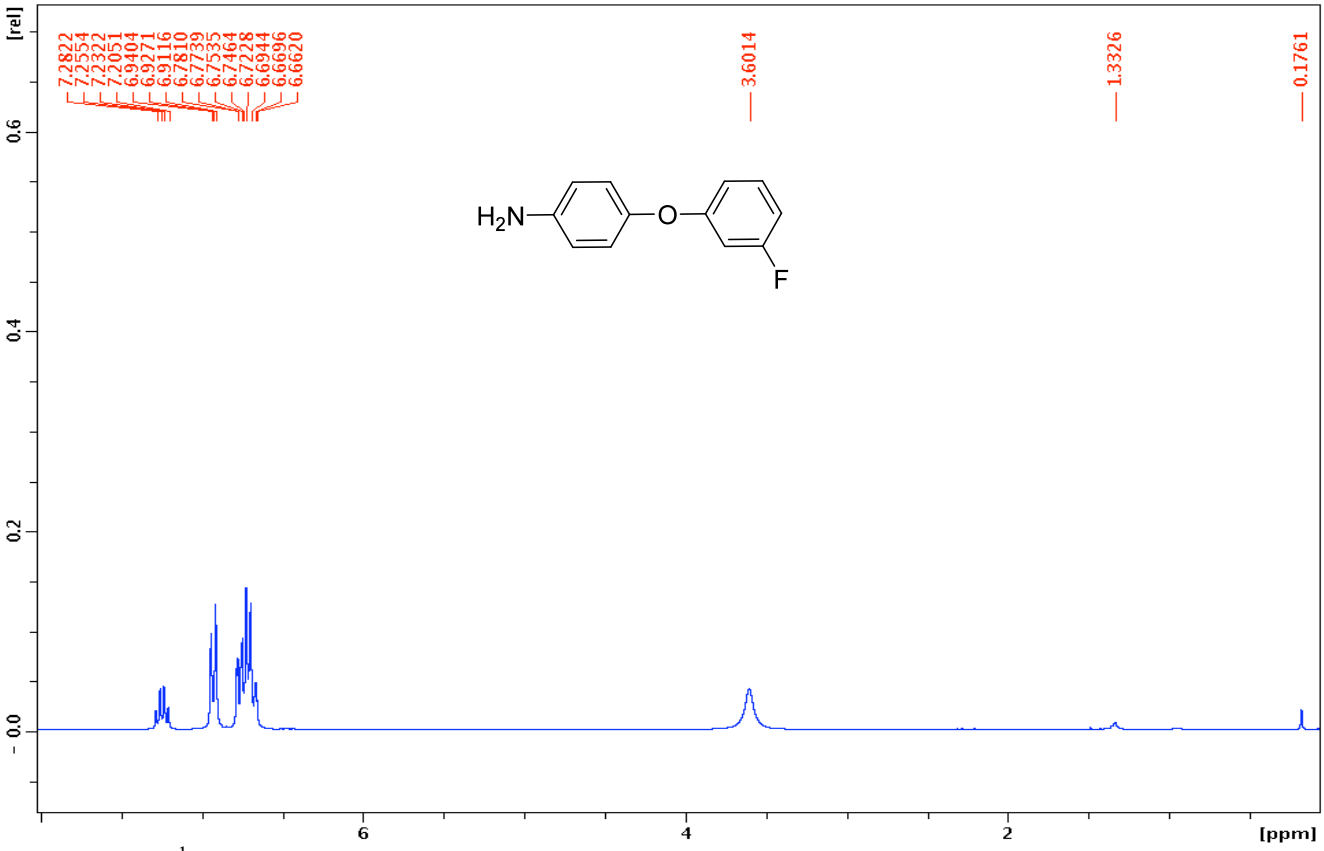

Figure S33. [1]HNMR spectrum of compound **7j**.

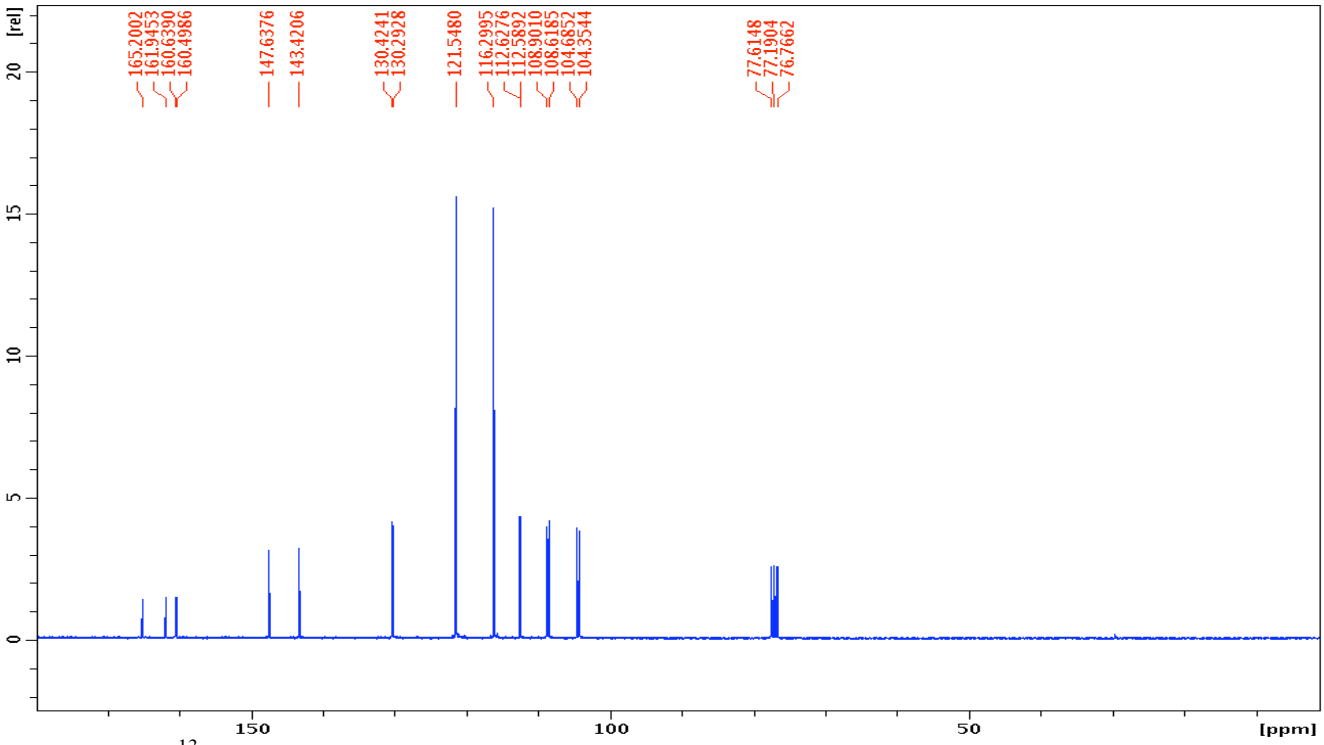

Figure S34. [13]CNMR spectrum of compound **7j**.

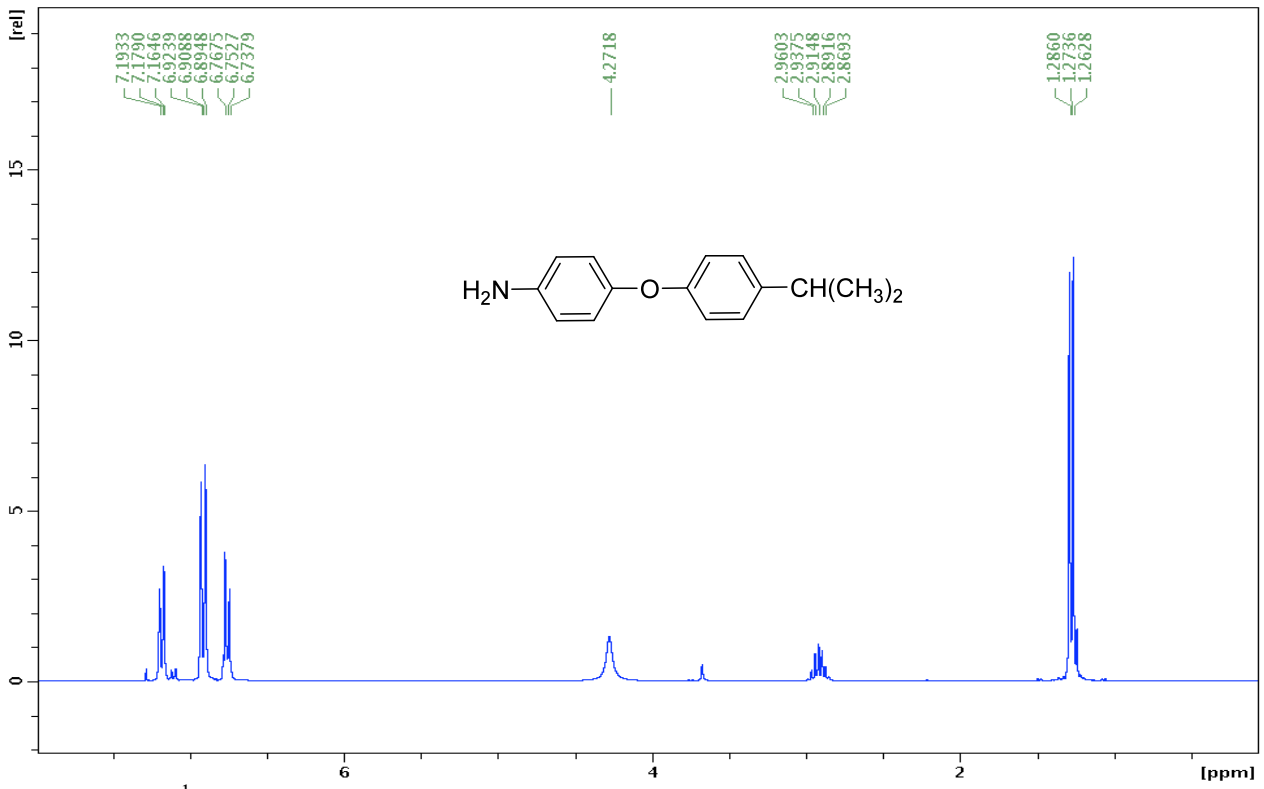

Figure S35. [1]HNMR spectrum of compound **7l**.

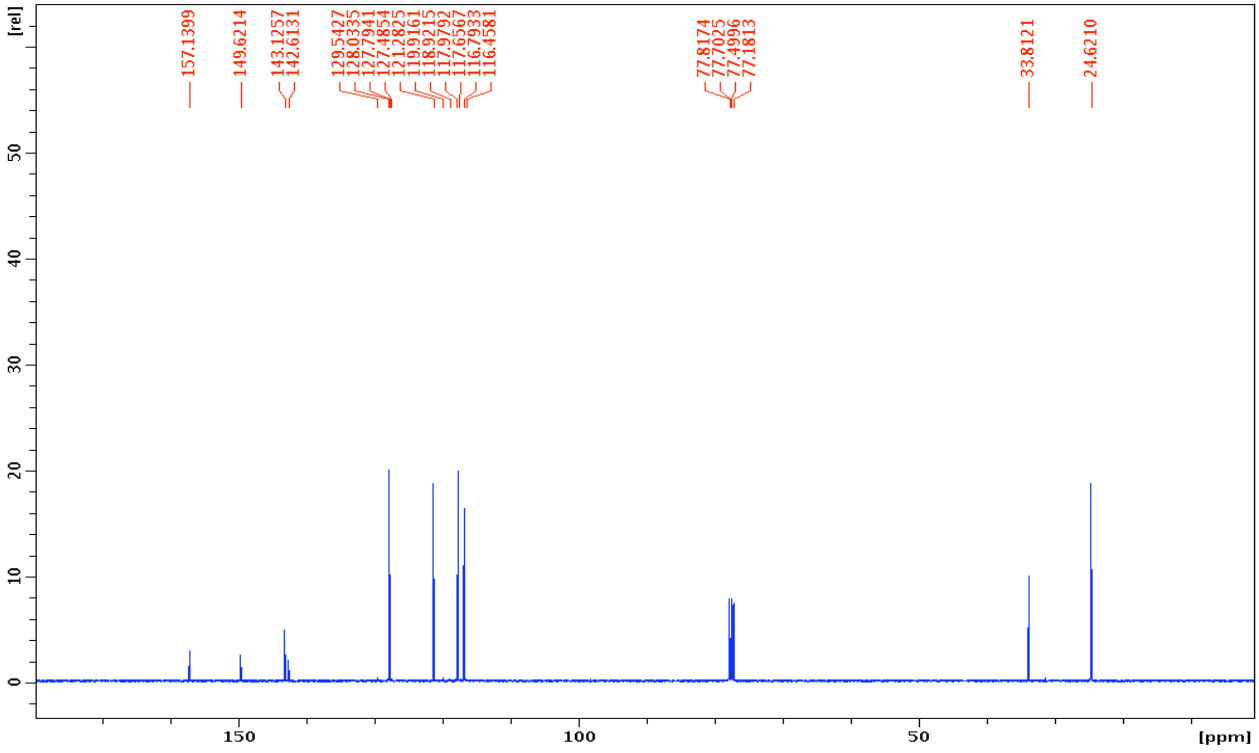

Figure S36. [13]CNMR spectrum of compound **7l**.

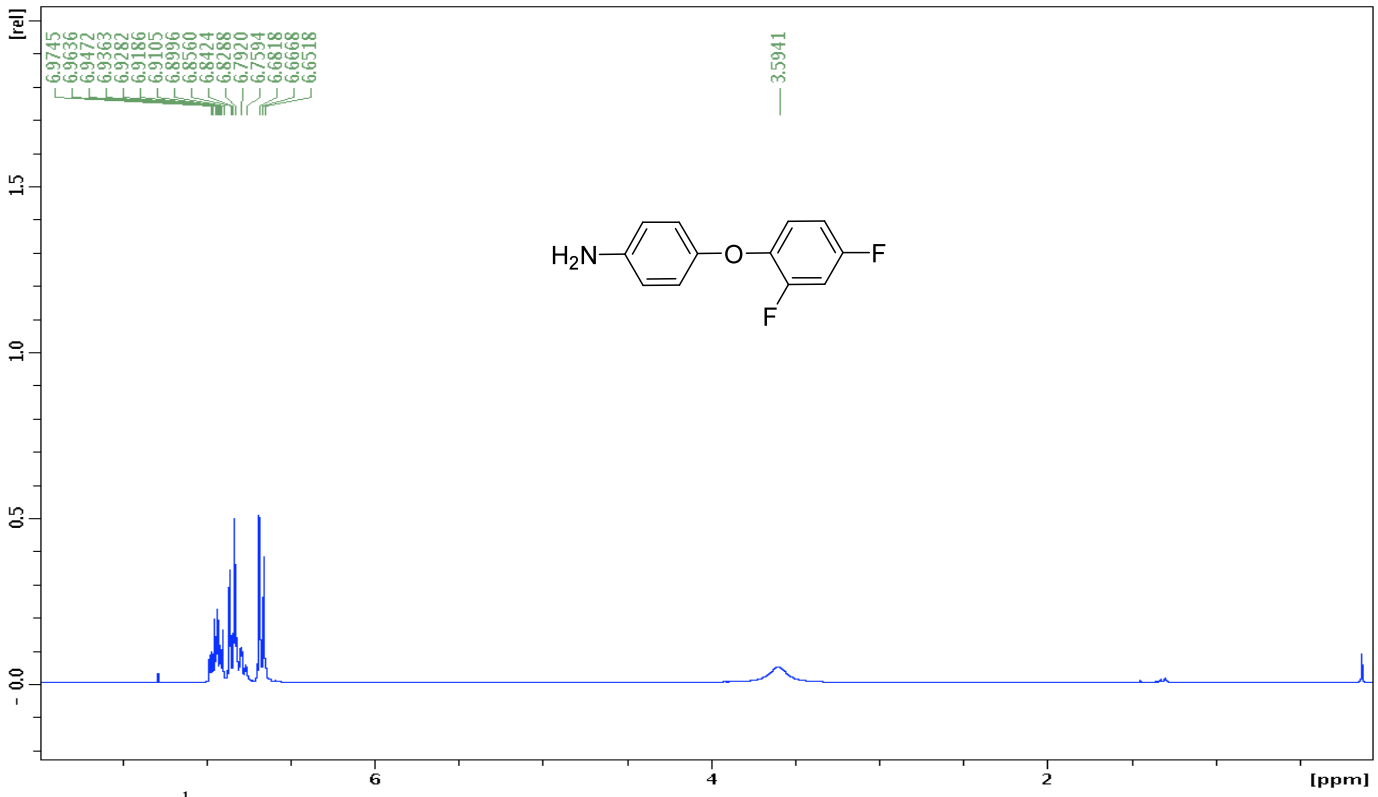

Figure S37. [1]HNMR spectrum of compound **7m**.

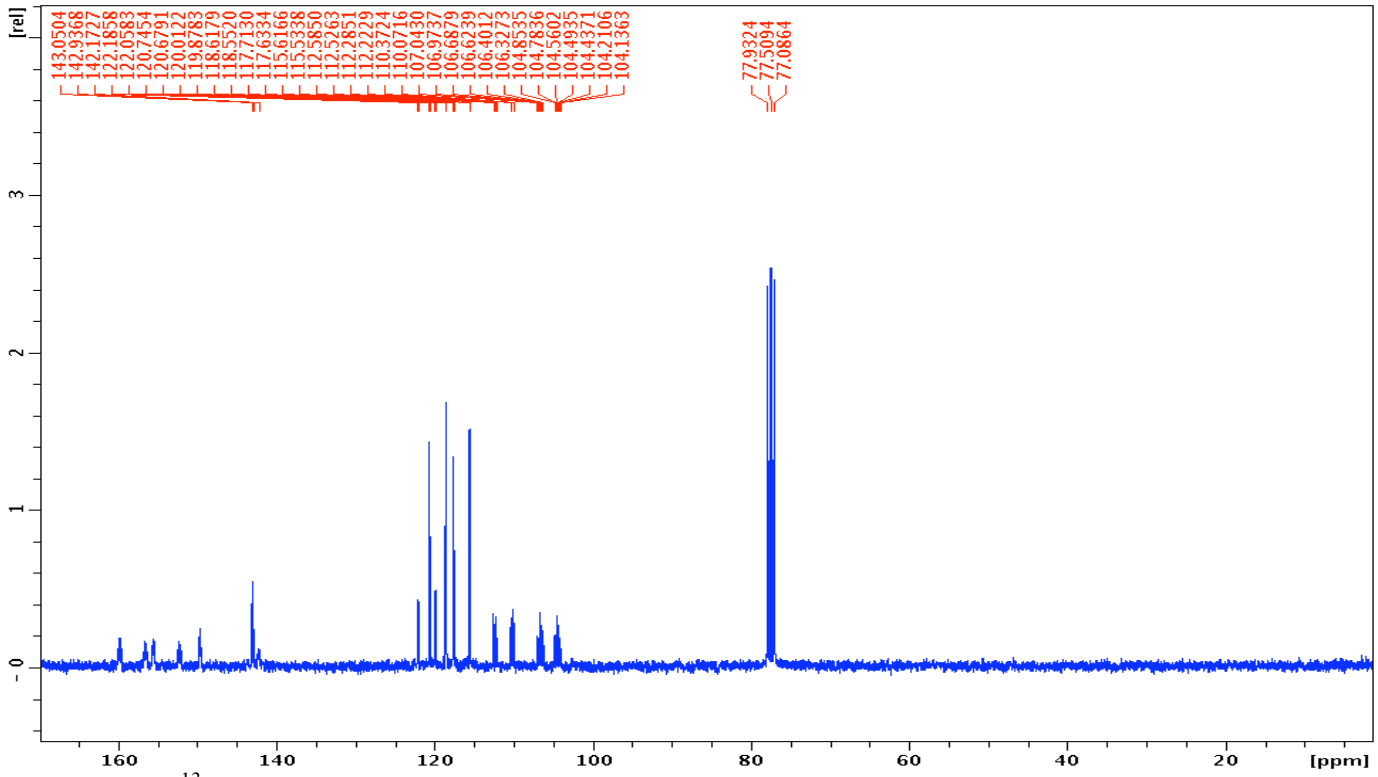

Figure S38. [13]CNMR spectrum of compound **7m**.

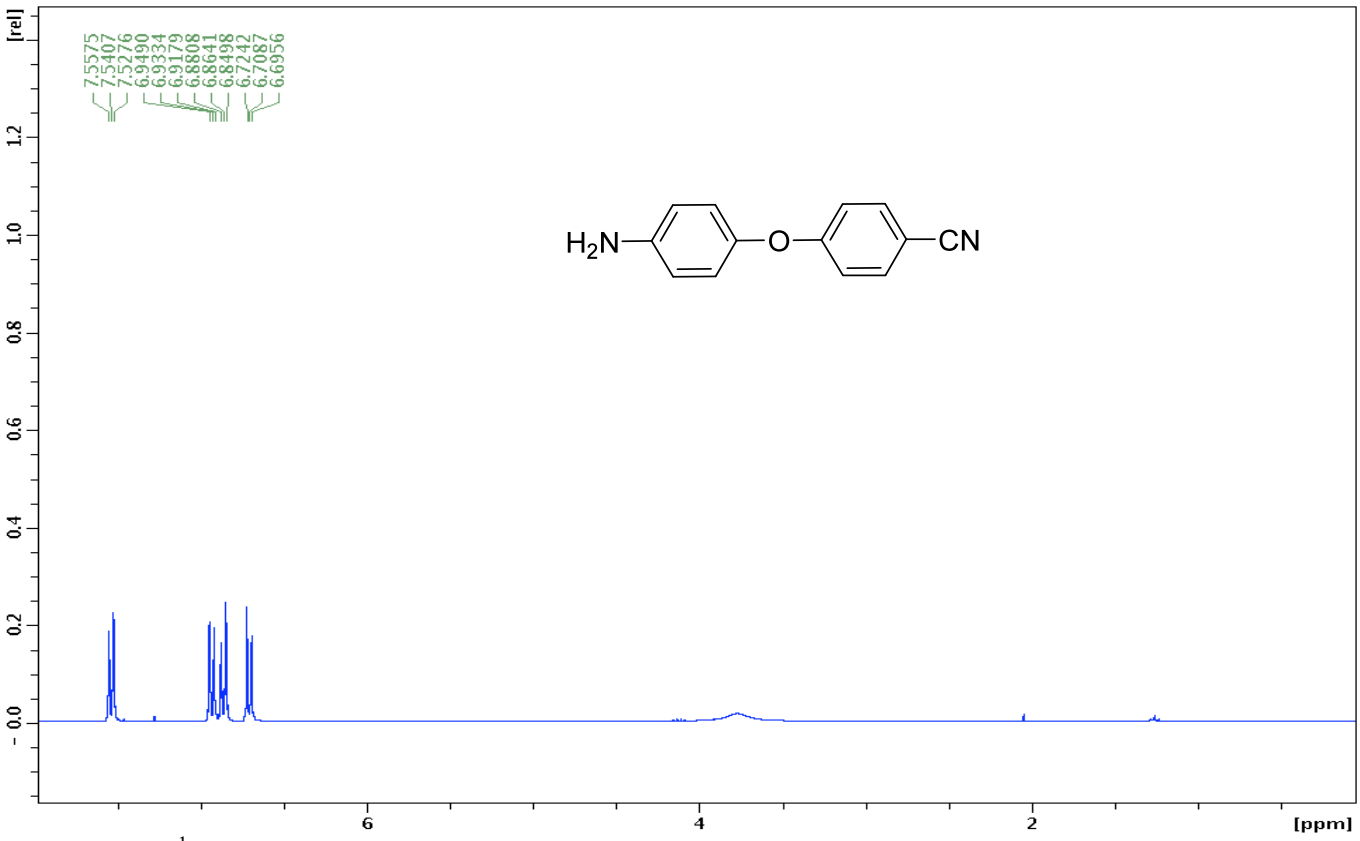

Figure S39. [1]HNMR spectrum of compound **7o**.

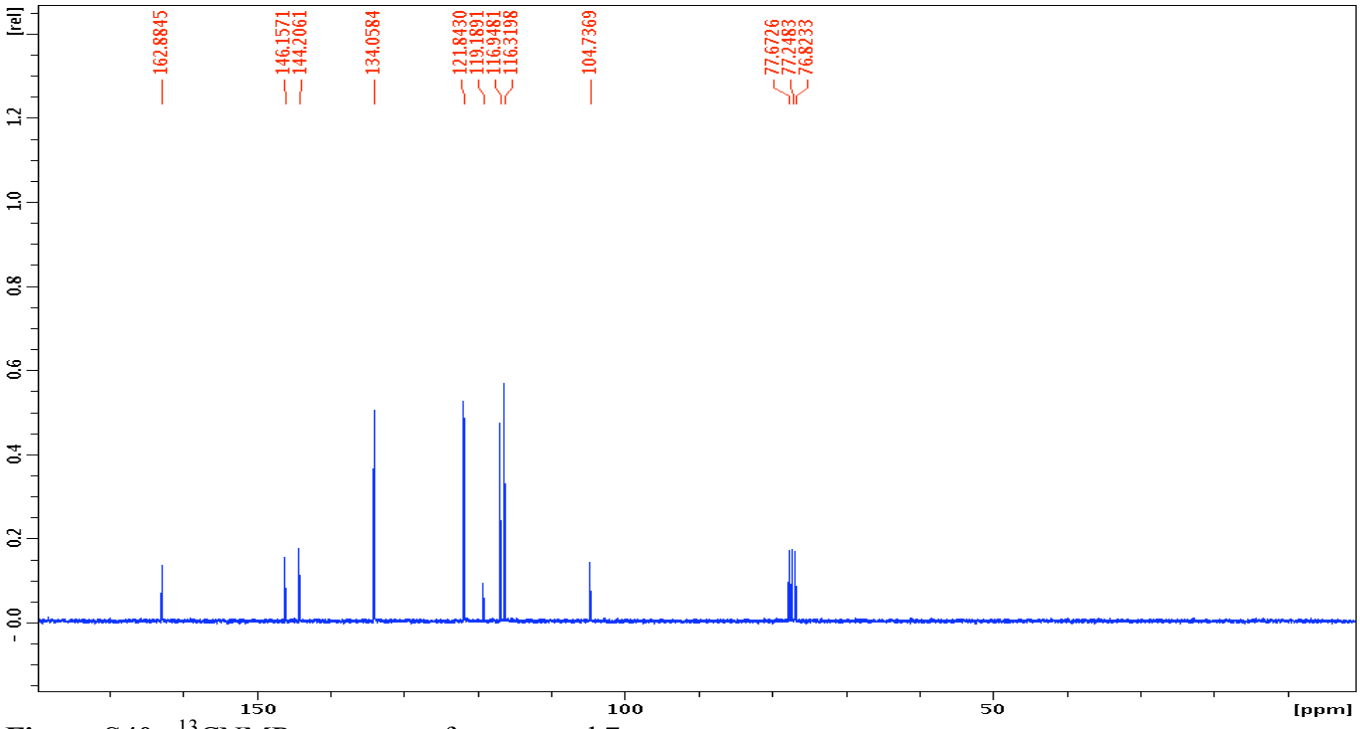

Figure S40. [13]CNMR spectrum of compound **7o**.

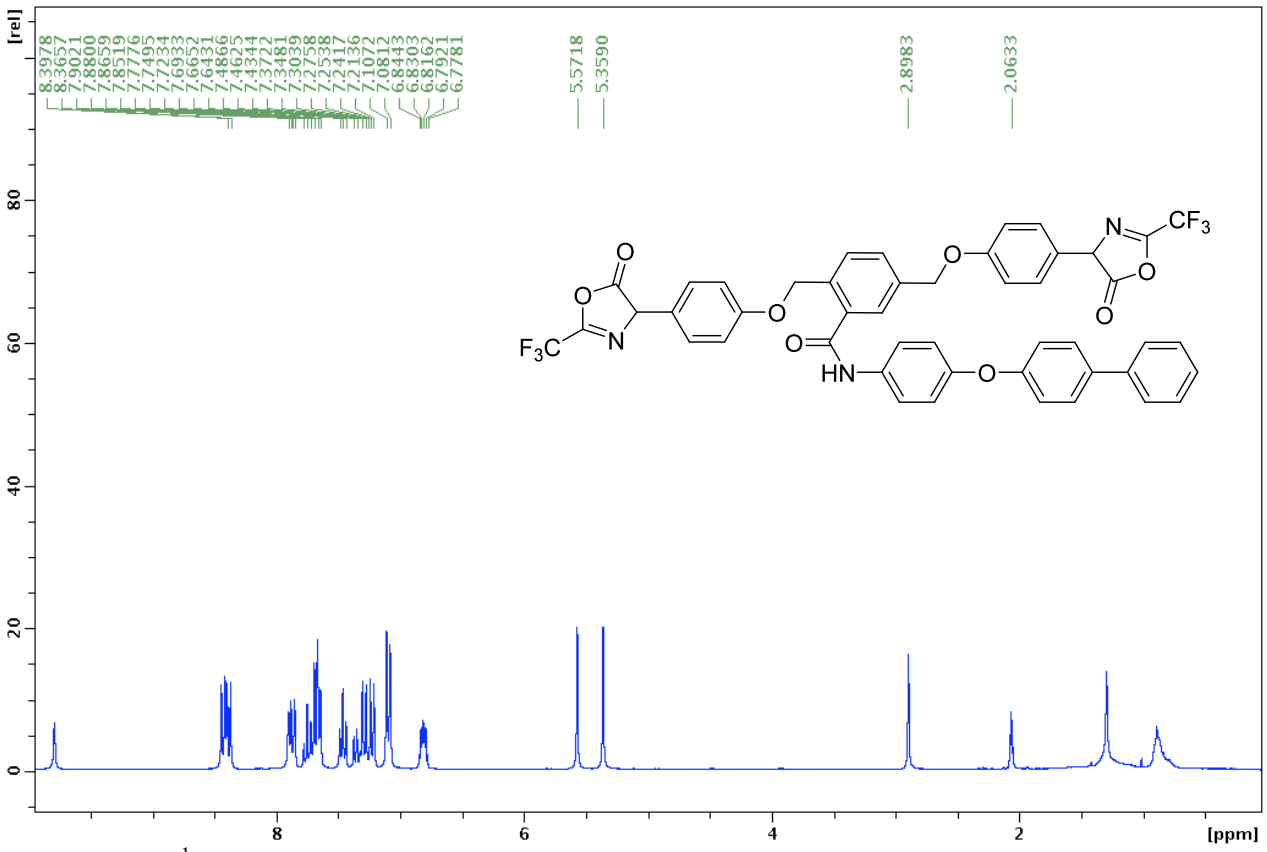

Figure S41. [1]HNMR spectrum of compound **9a**.

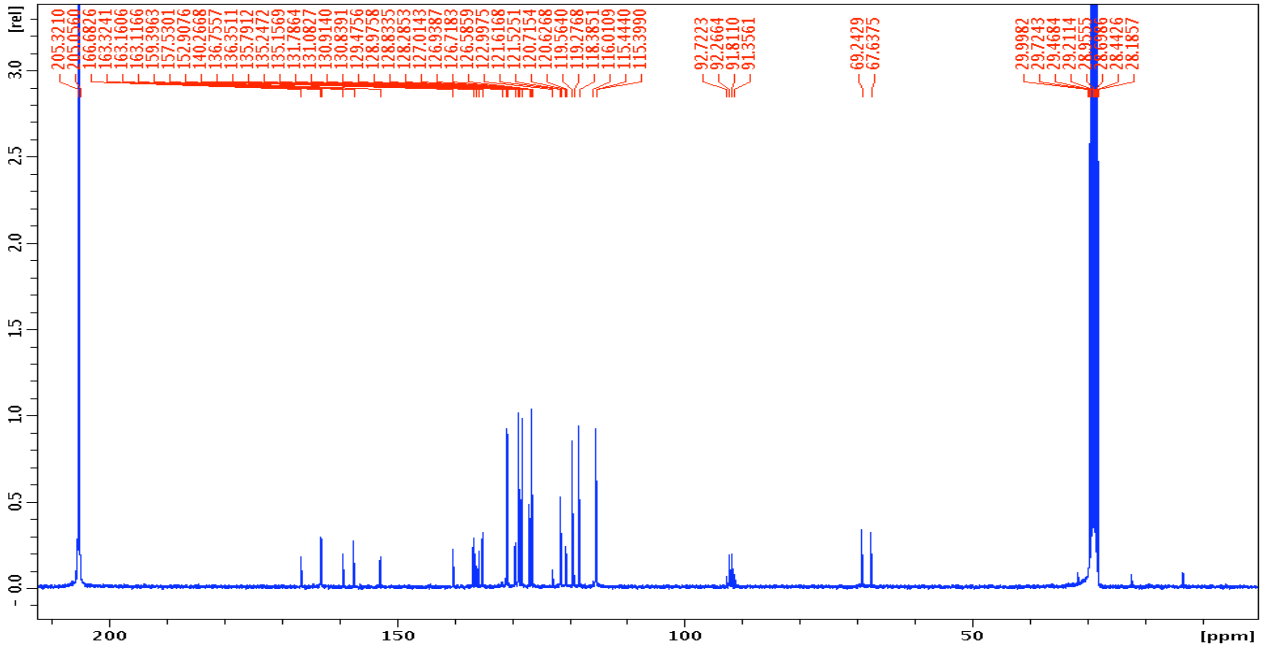

Figure S42. [13]CNMR spectrum of compound **9a**.

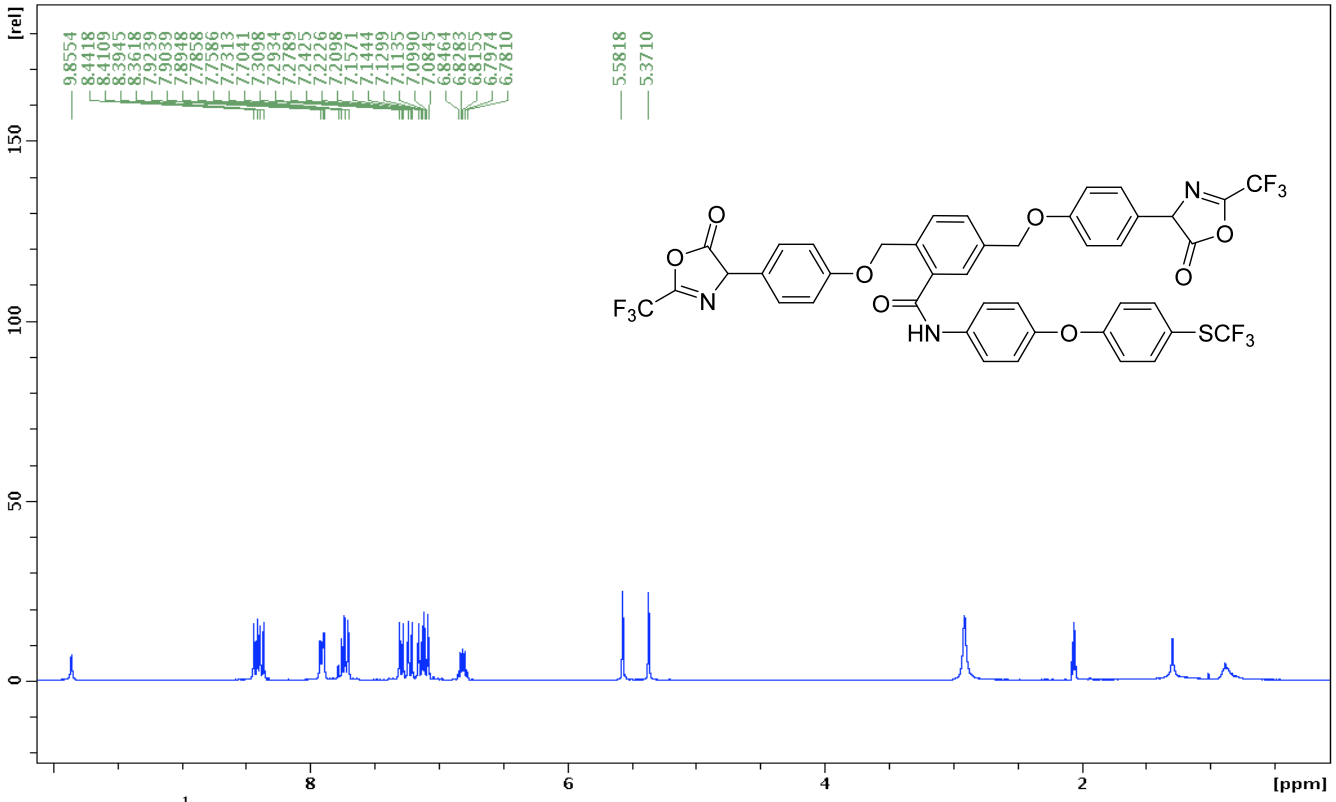

Figure S43. ^{1}HNMR spectrum of compound **9b**.

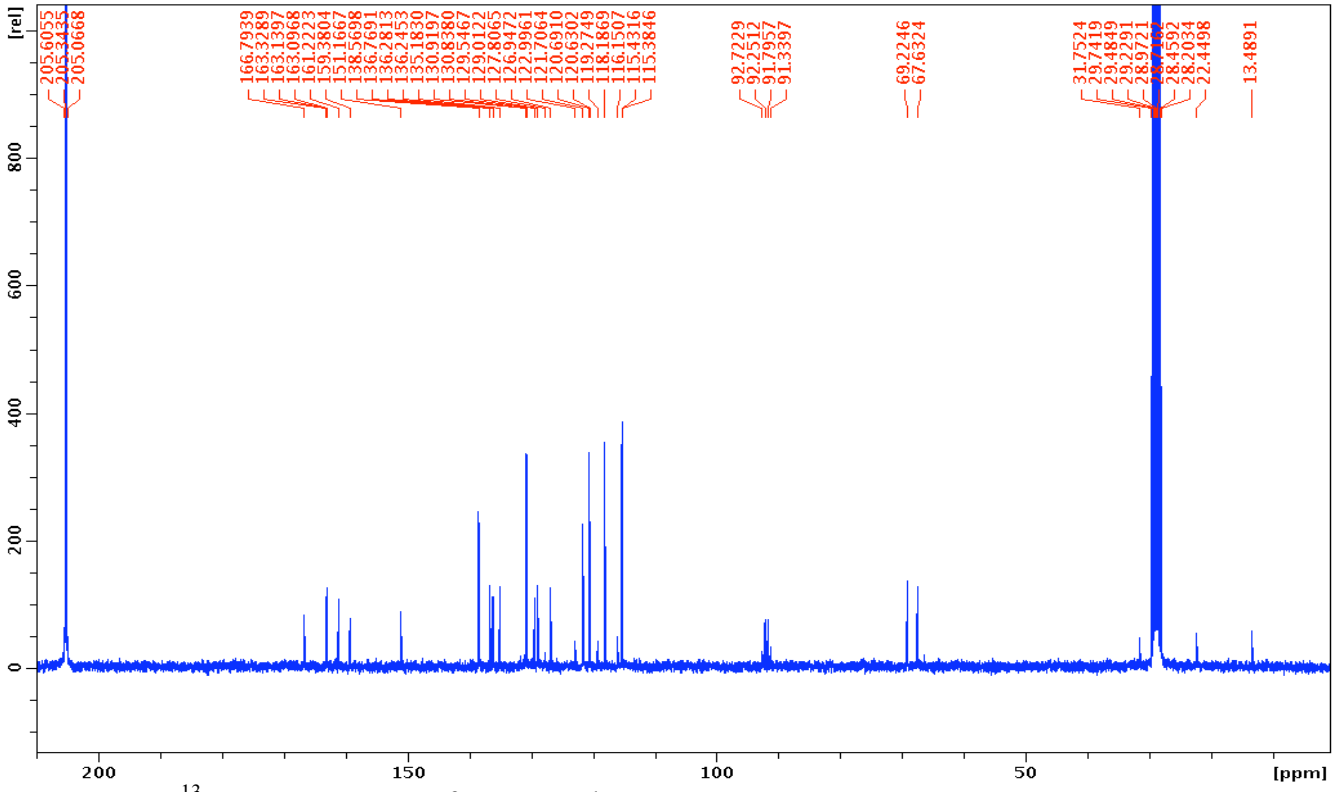

Figure S44. ^{13}CNMR spectrum of compound **9b**.

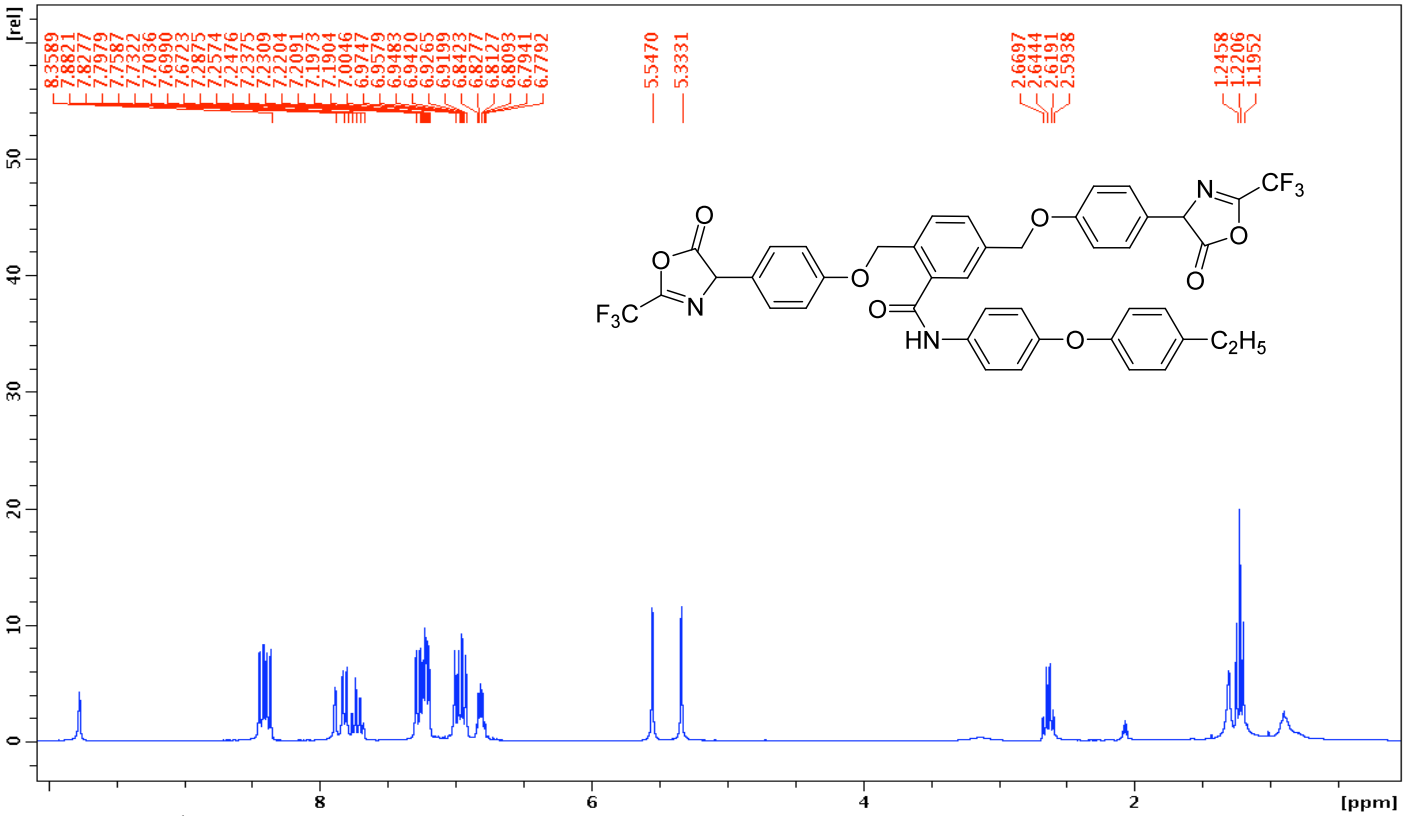

Figure S45. [1]HNMR spectrum of compound **9c**.

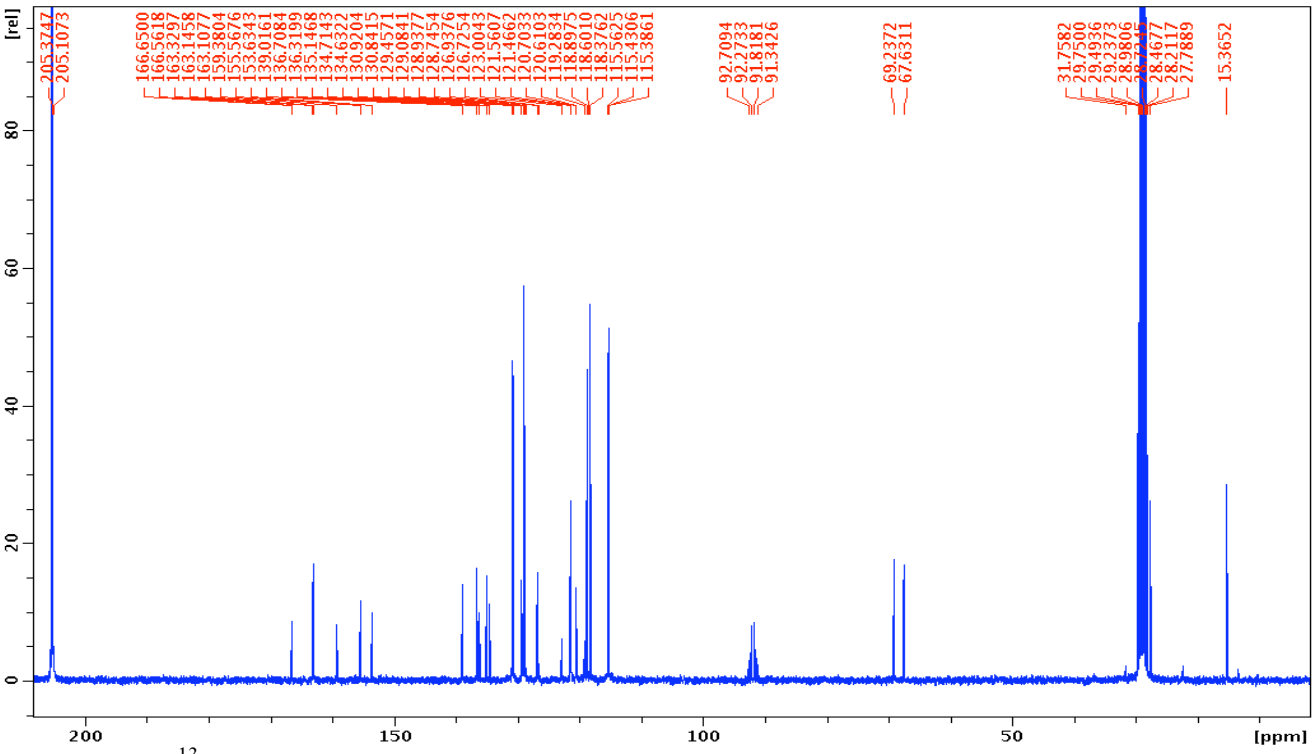

Figure S46. [13]CNMR spectrum of compound **9c**.

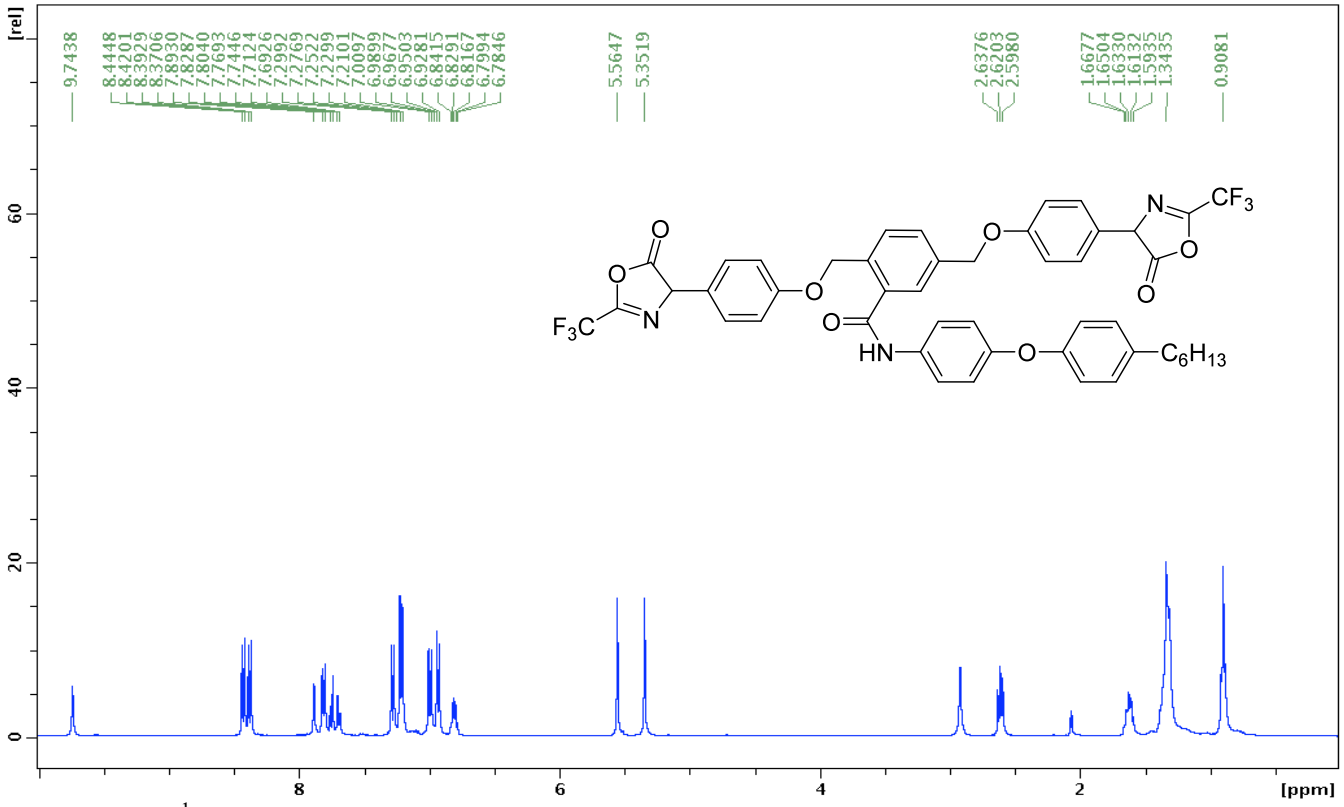

Figure S47. [1]HNMR spectrum of compound **9d**.

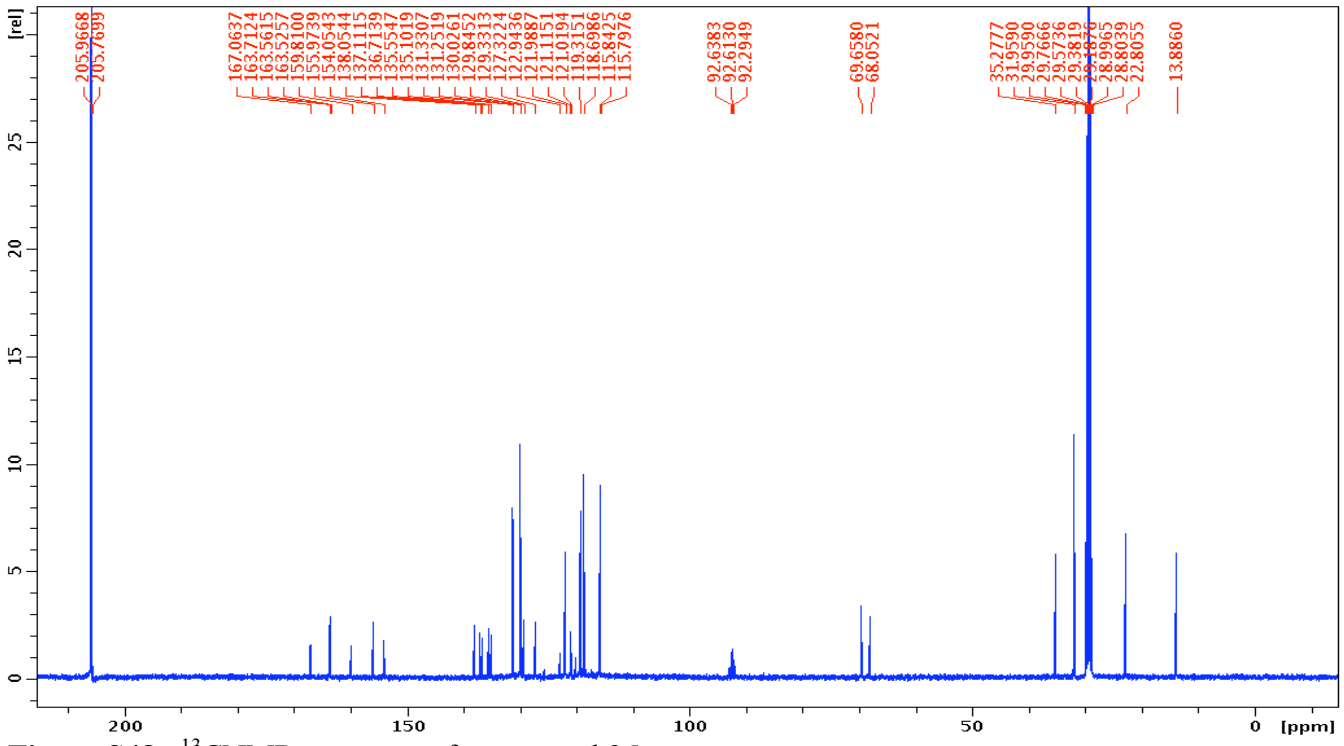

Figure S48. [13]CNMR spectrum of compound **9d**.

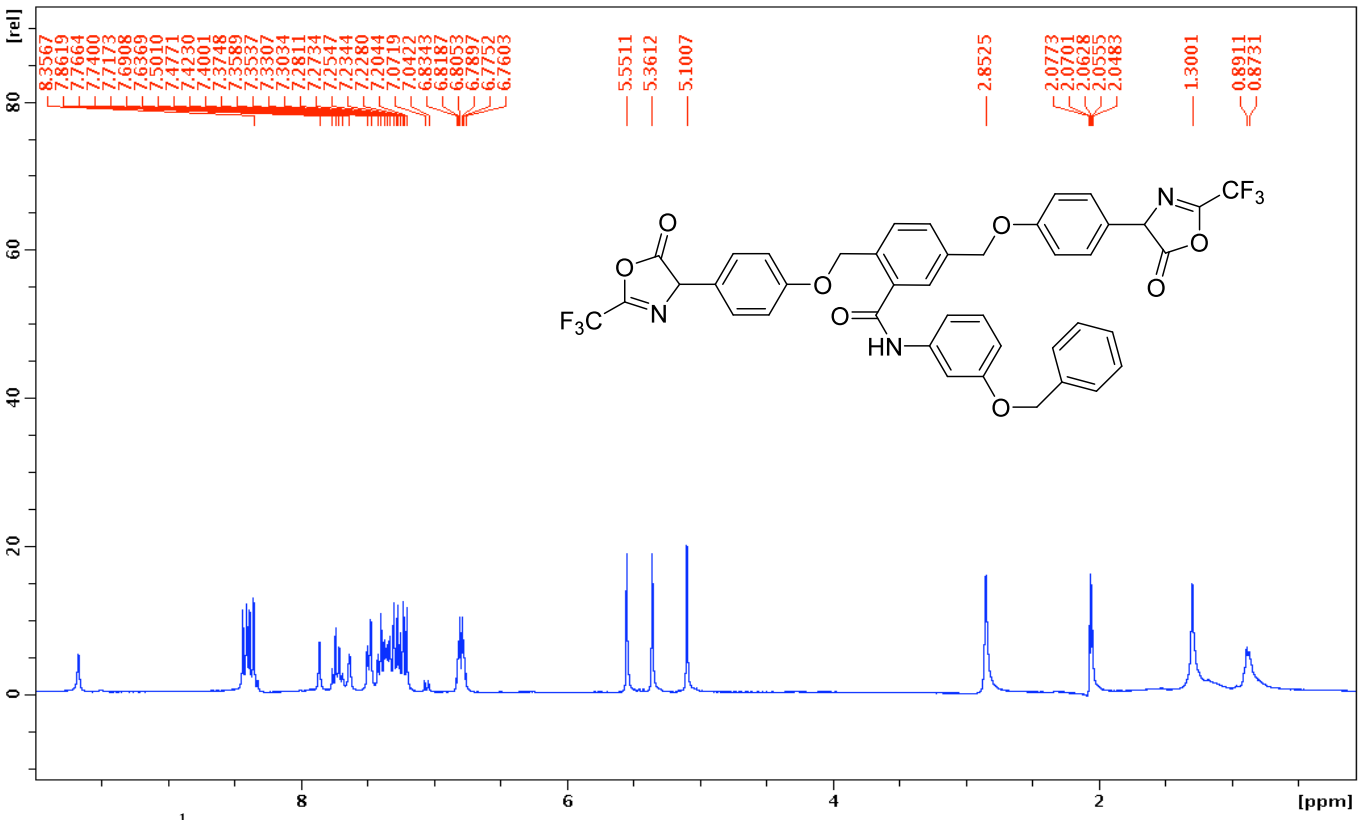

Figure S49. [1]HNMR spectrum of compound **10**.

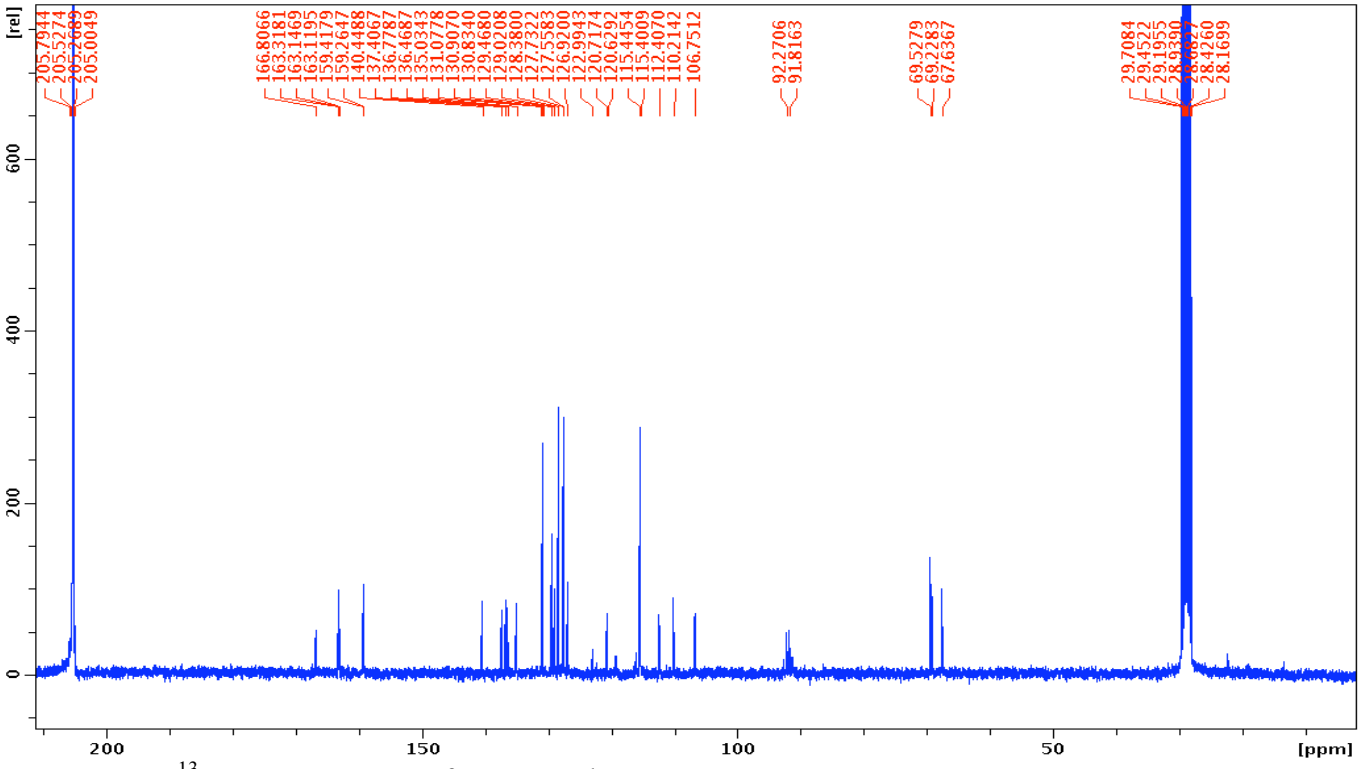

Figure S50. [13]CNMR spectrum of compound **10**.

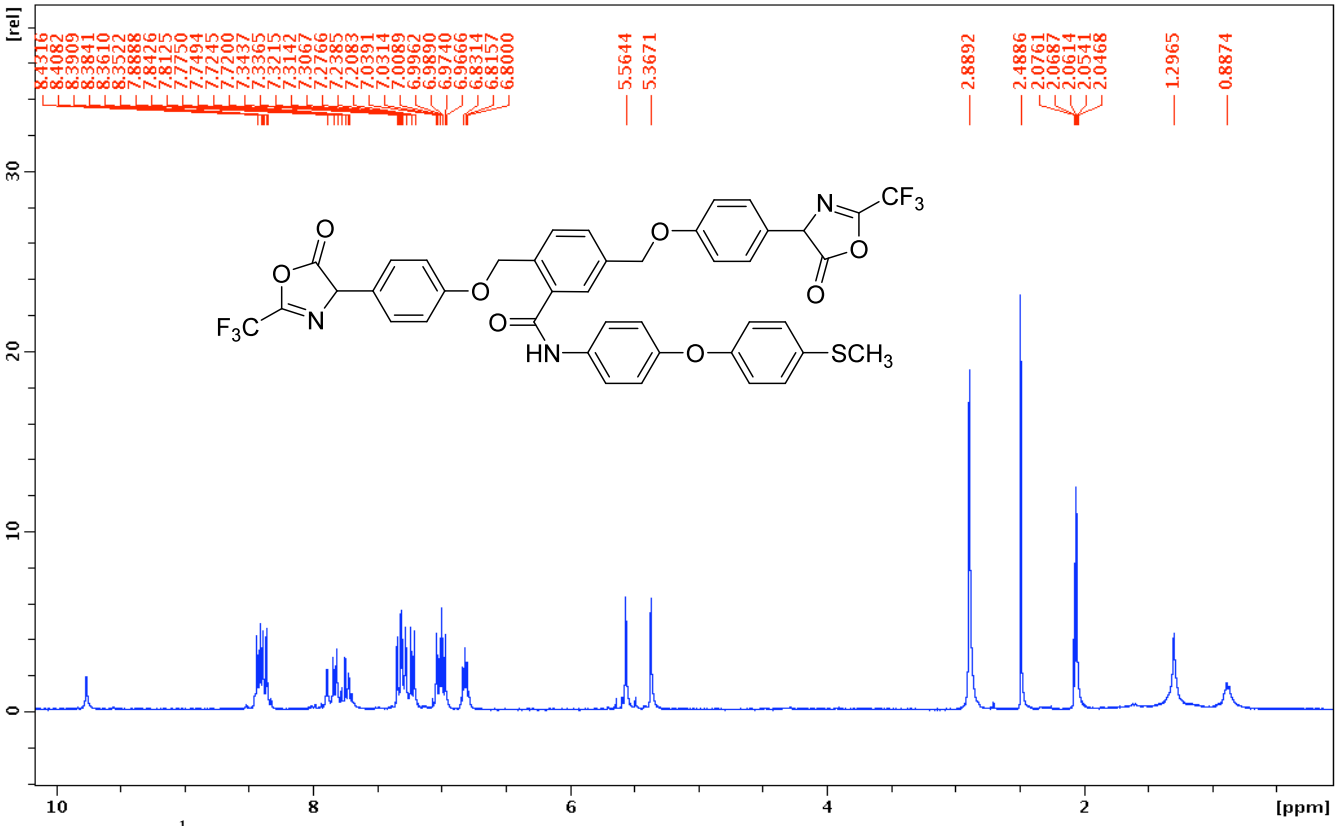

Figure S51. [1]HNMR spectrum of compound **9e**.

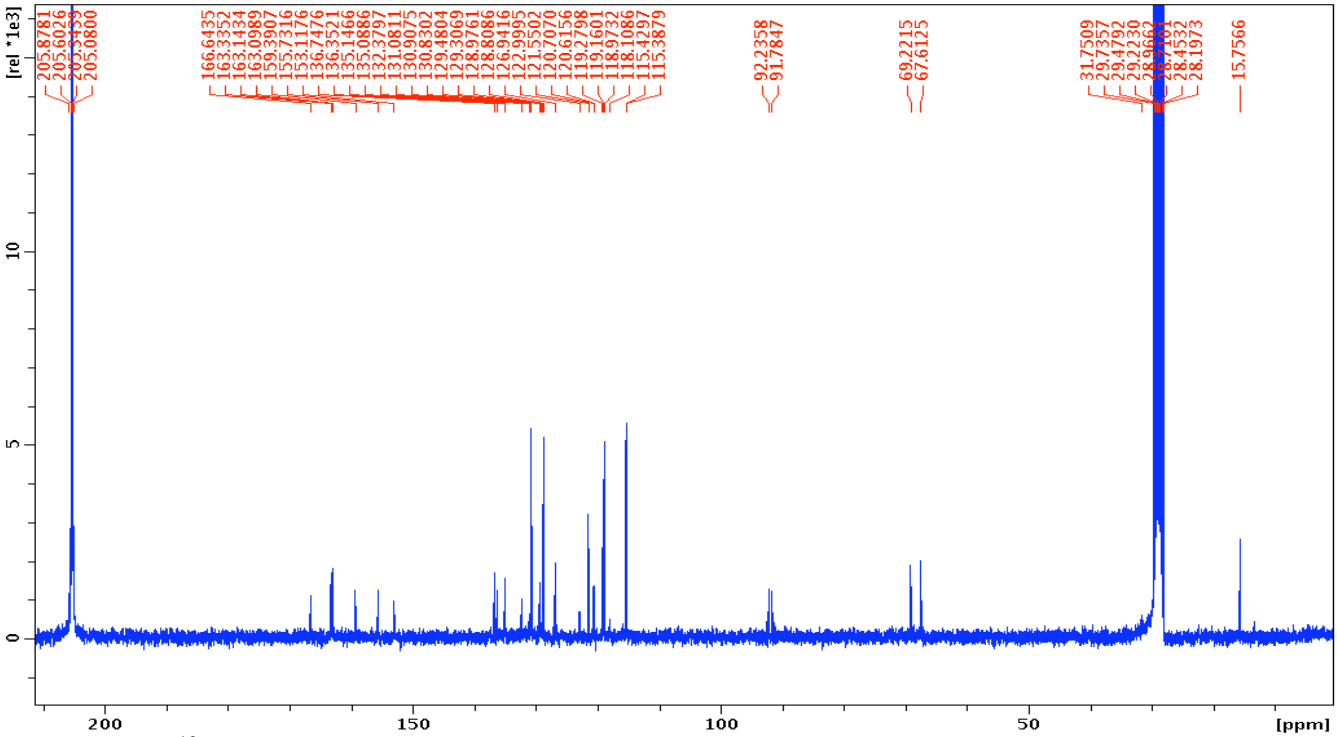

Figure S52. [13]CNMR spectrum of compound **9e**.

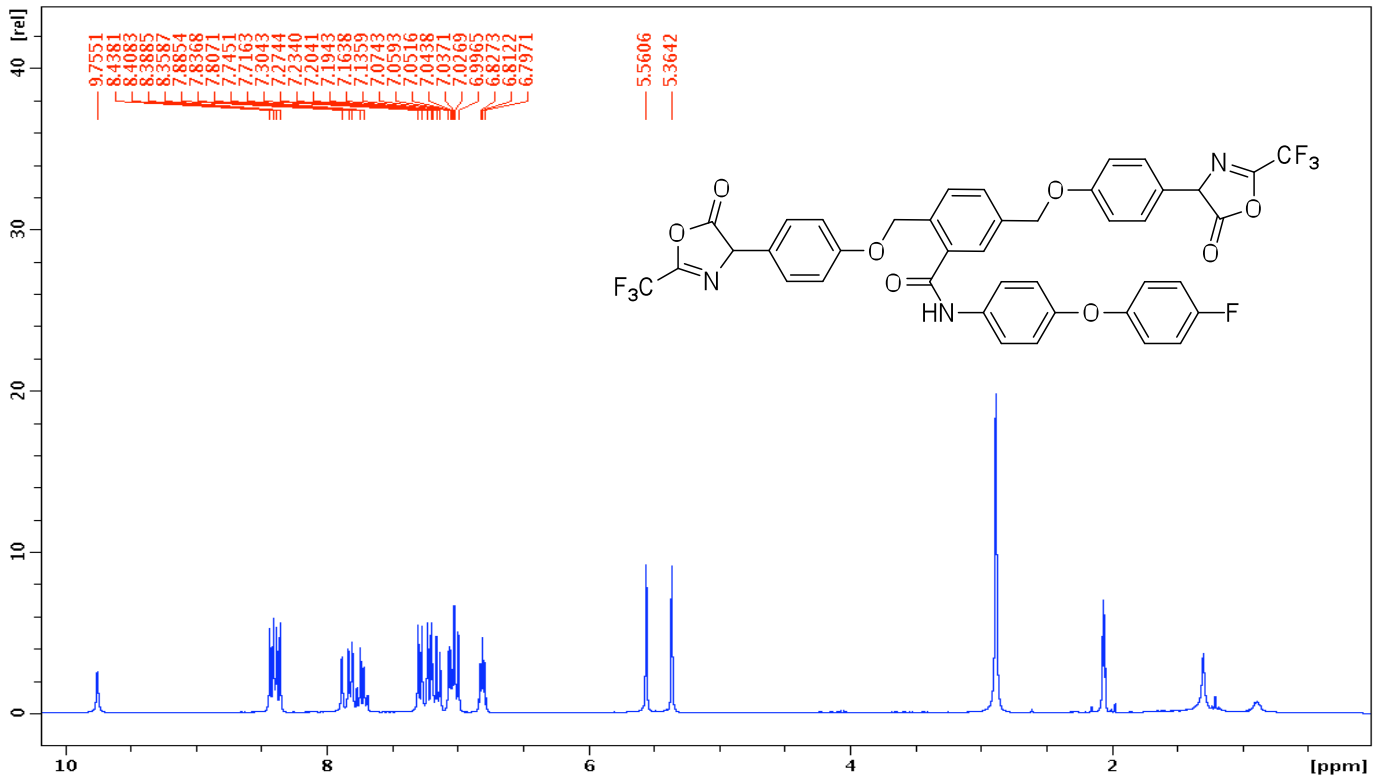

Figure S53. [1]HNMR spectrum of compound **9f**.

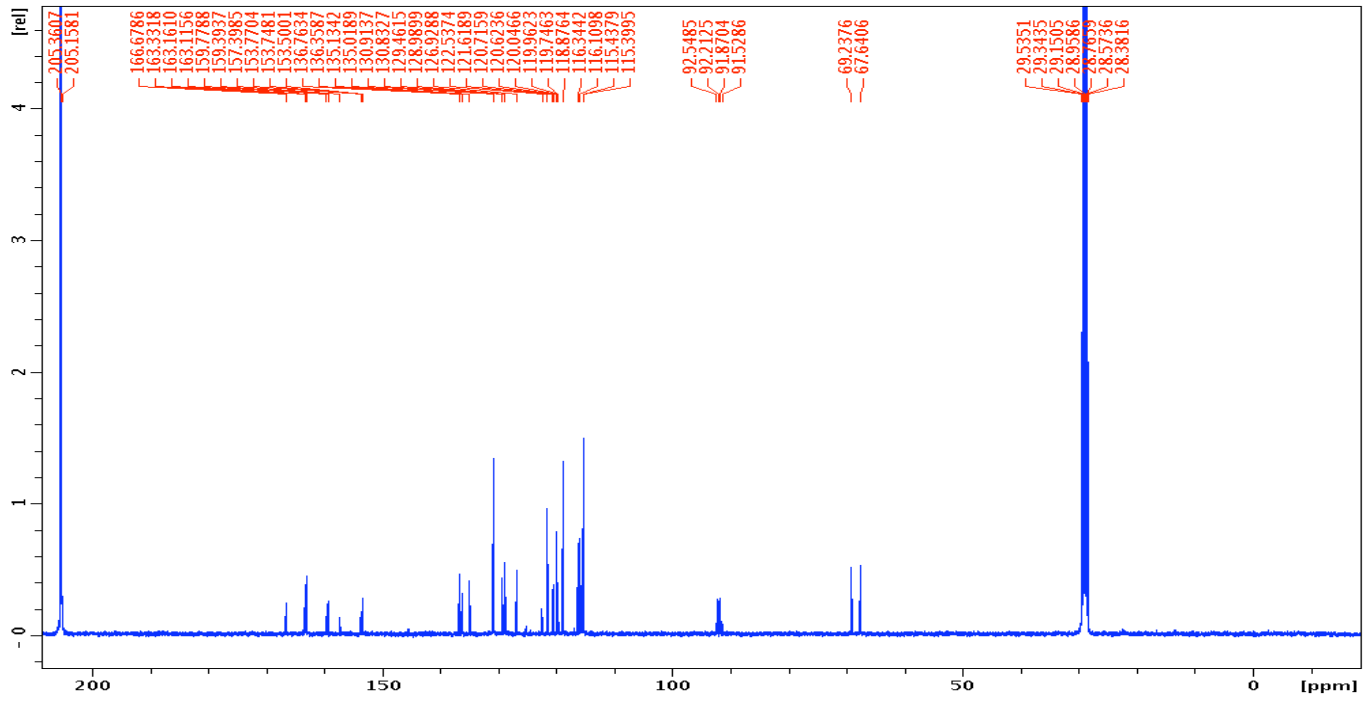

Figure S54. [13]CNMR spectrum of compound **9f**.

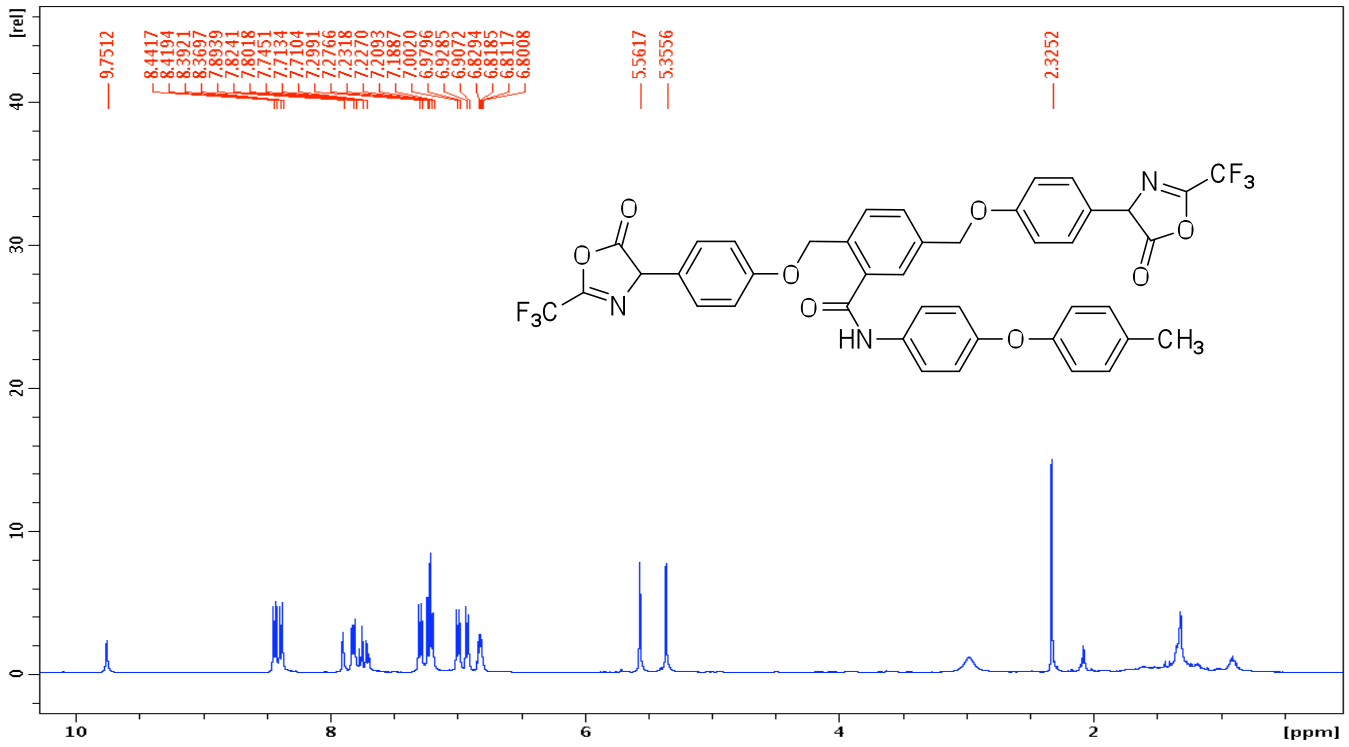

Figure S55. [1]HNMR spectrum of compound **9g**.

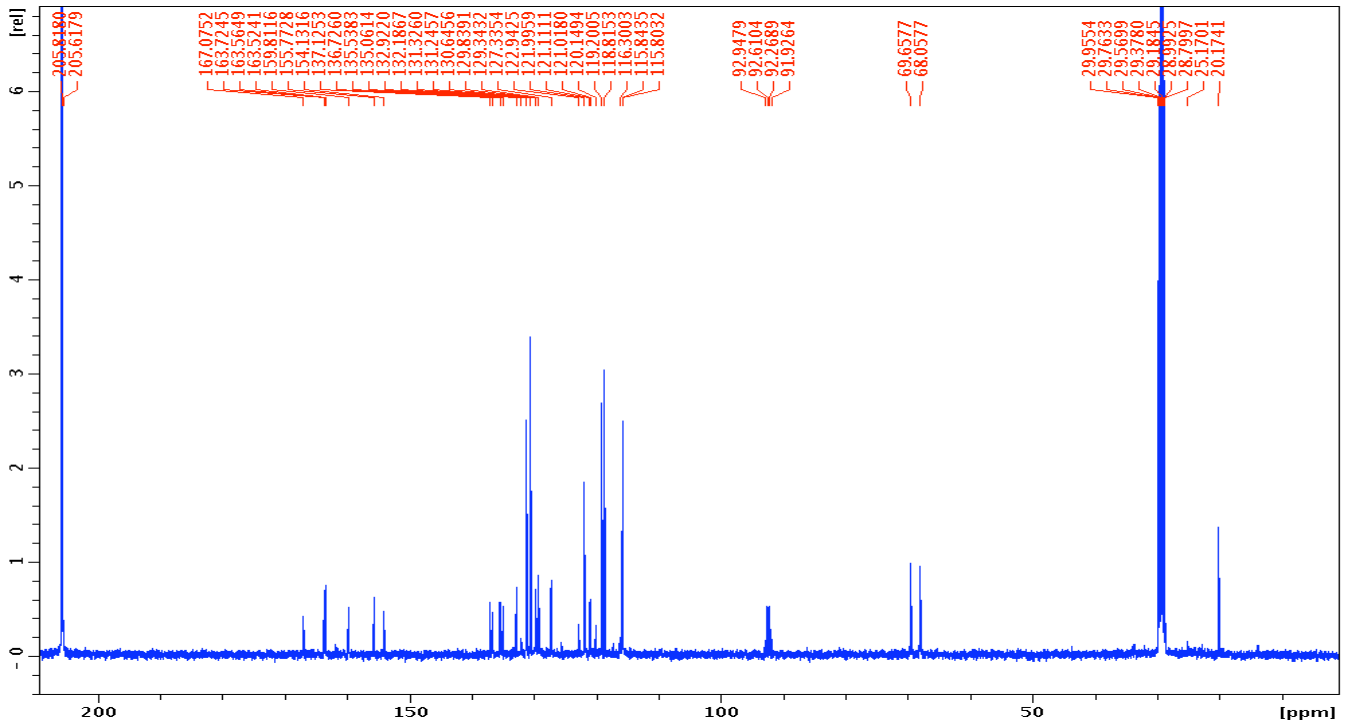

Figure S56. [13]CNMR spectrum of compound **9g**.

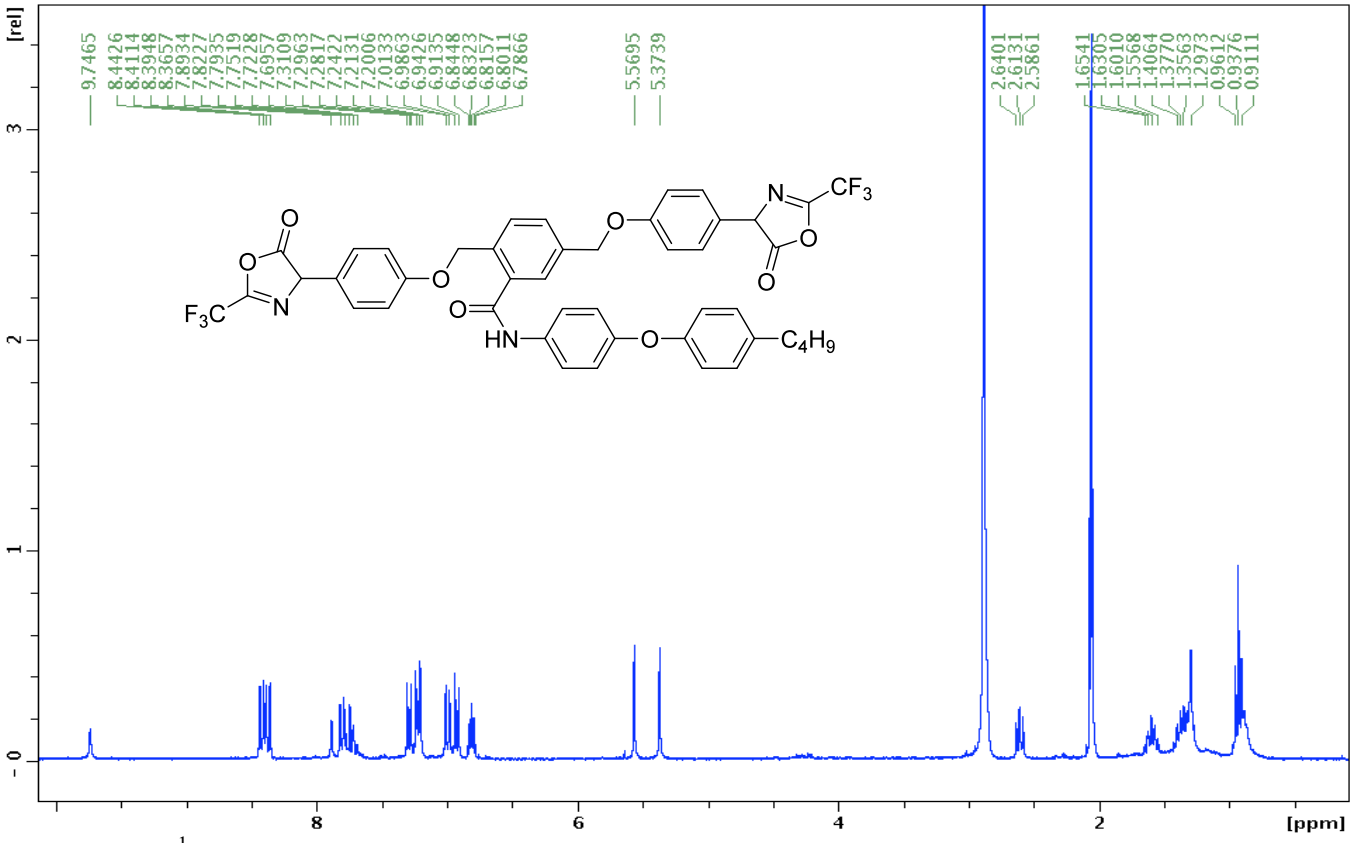

Figure S57. [1]HNMR spectrum of compound **9h**.

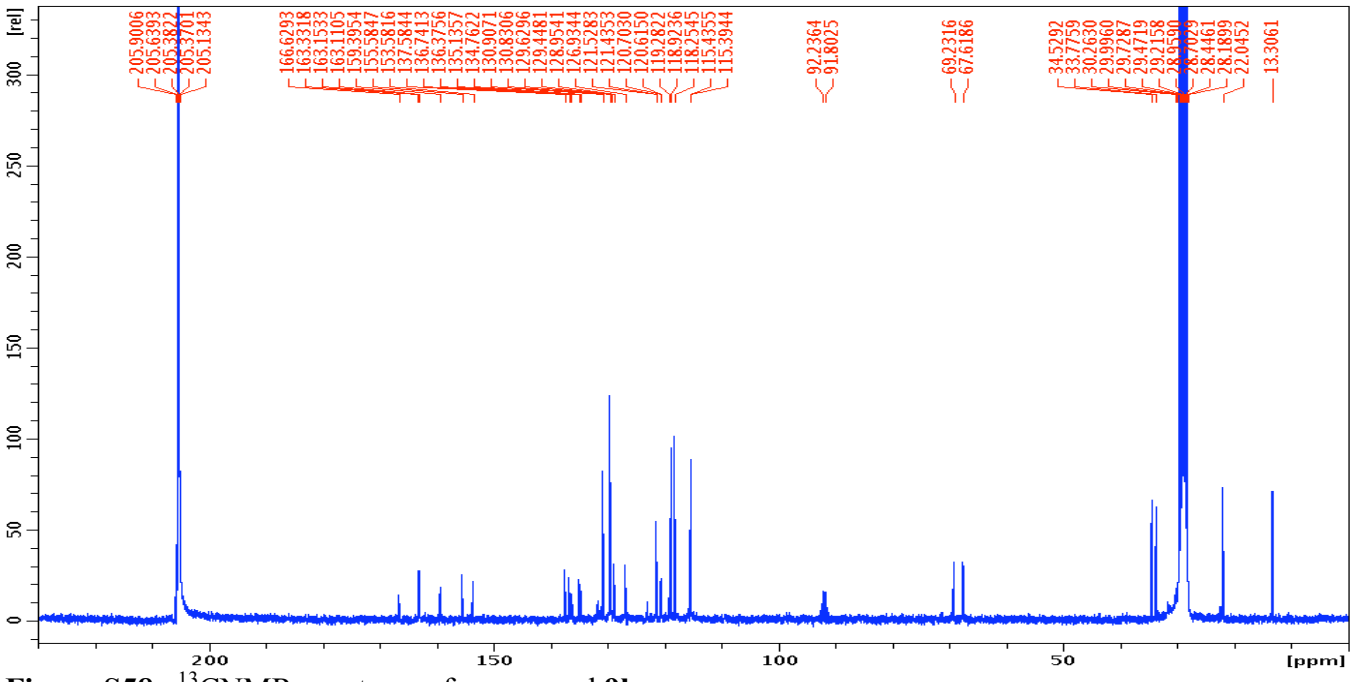

Figure S58. [13]CNMR spectrum of compound **9h**.

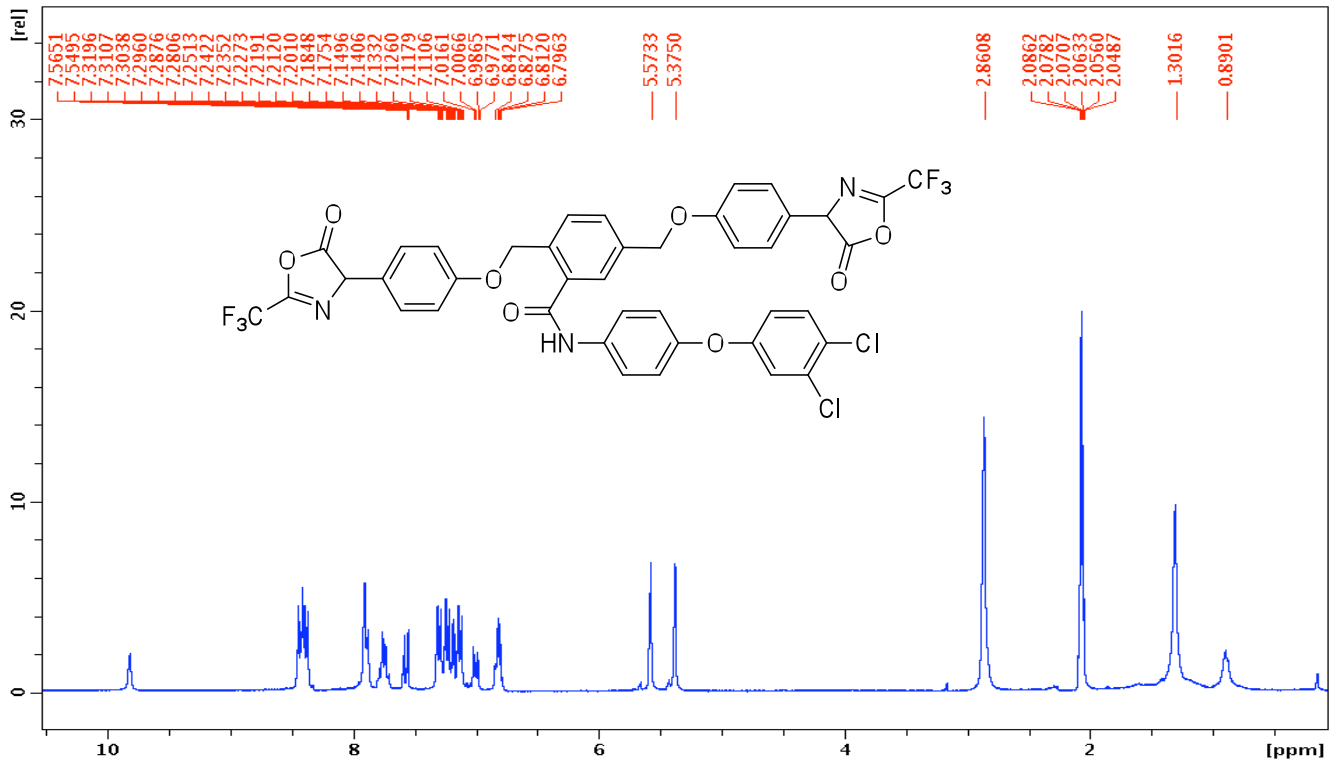

Figure S59. [1]HNMR spectrum of compound **9i**.

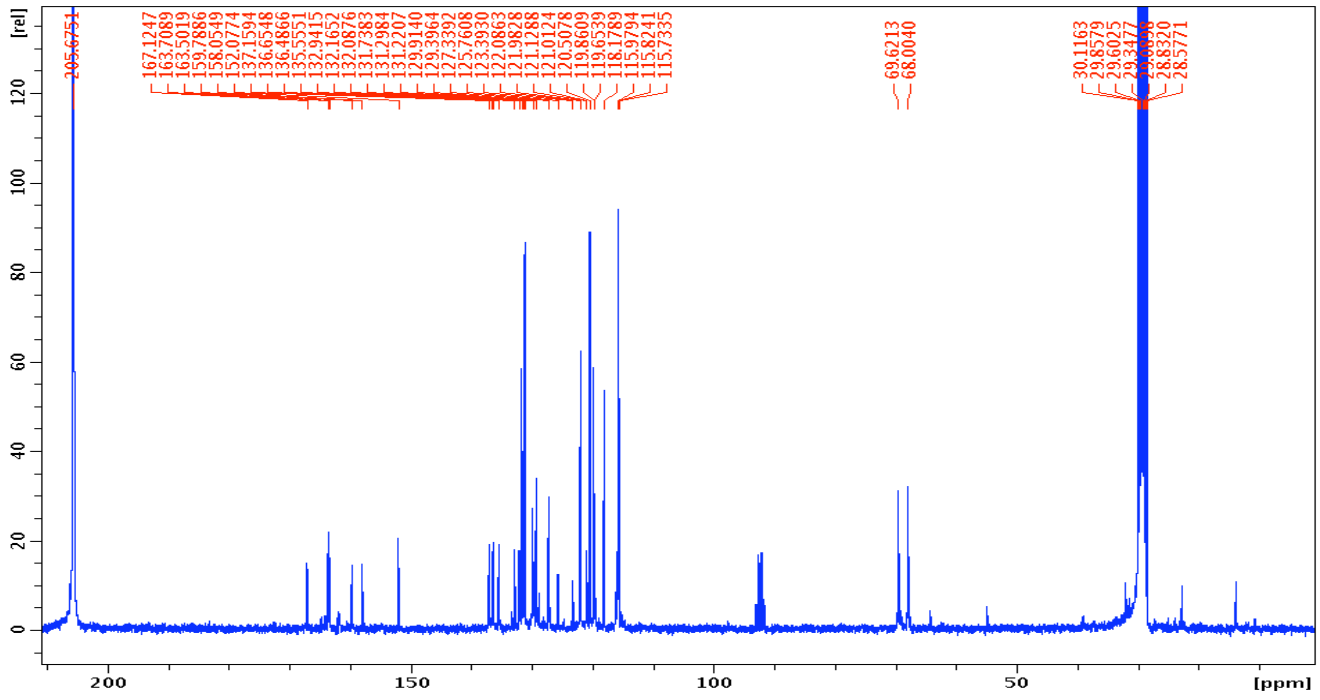

Figure S60. [13]CNMR spectrum of compound **9i**.

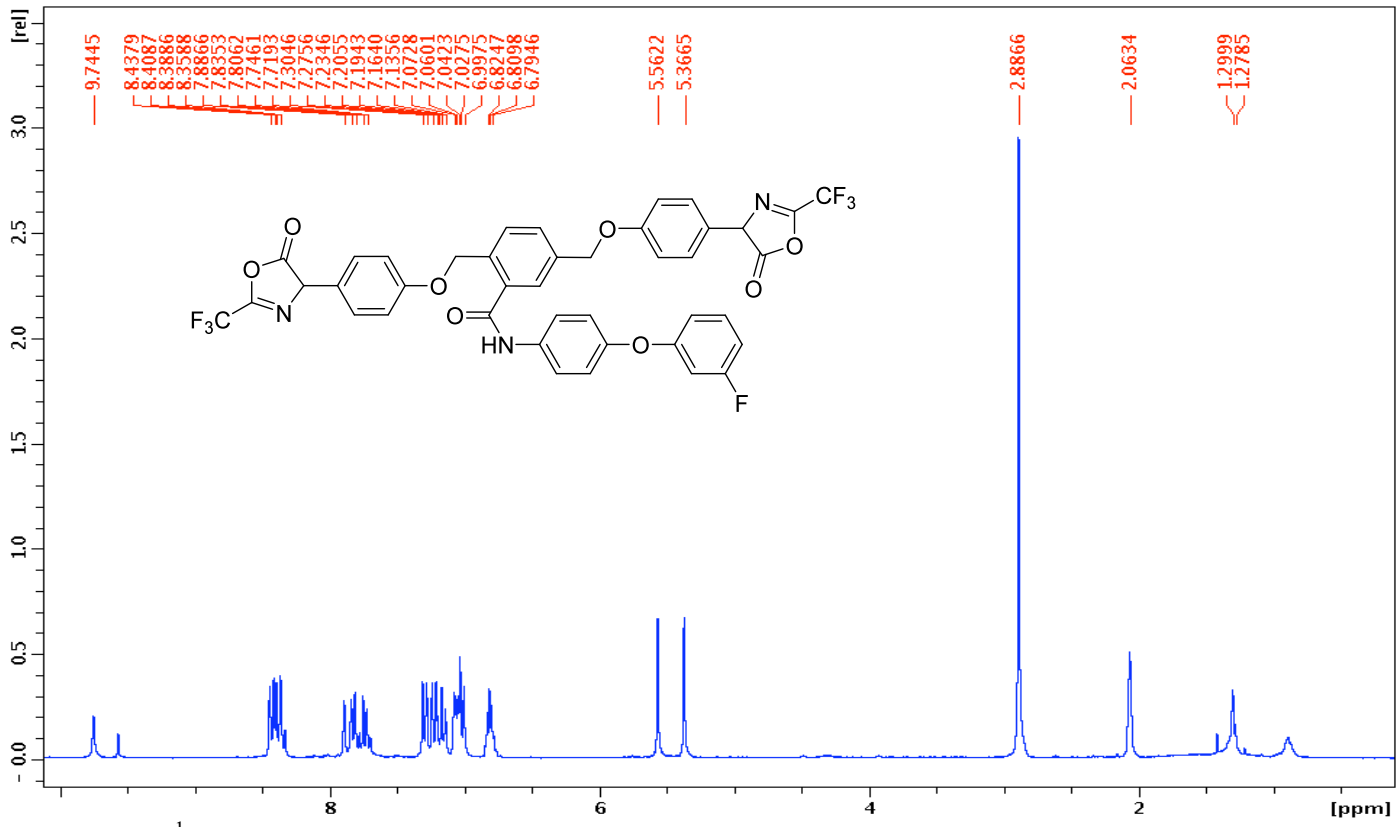

Figure S61. [1]HNMR spectrum of compound **9j**.

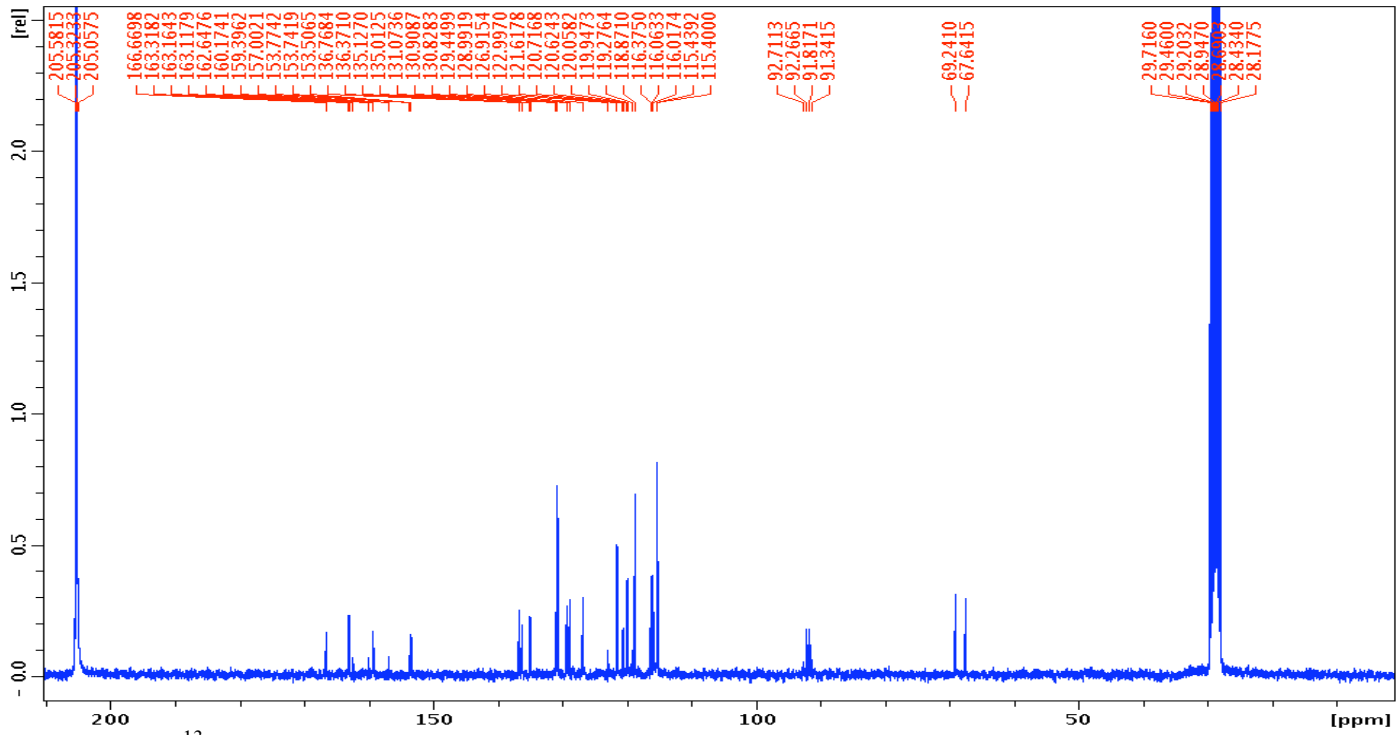

Figure S62. [13]CNMR spectrum of compound **9j**.

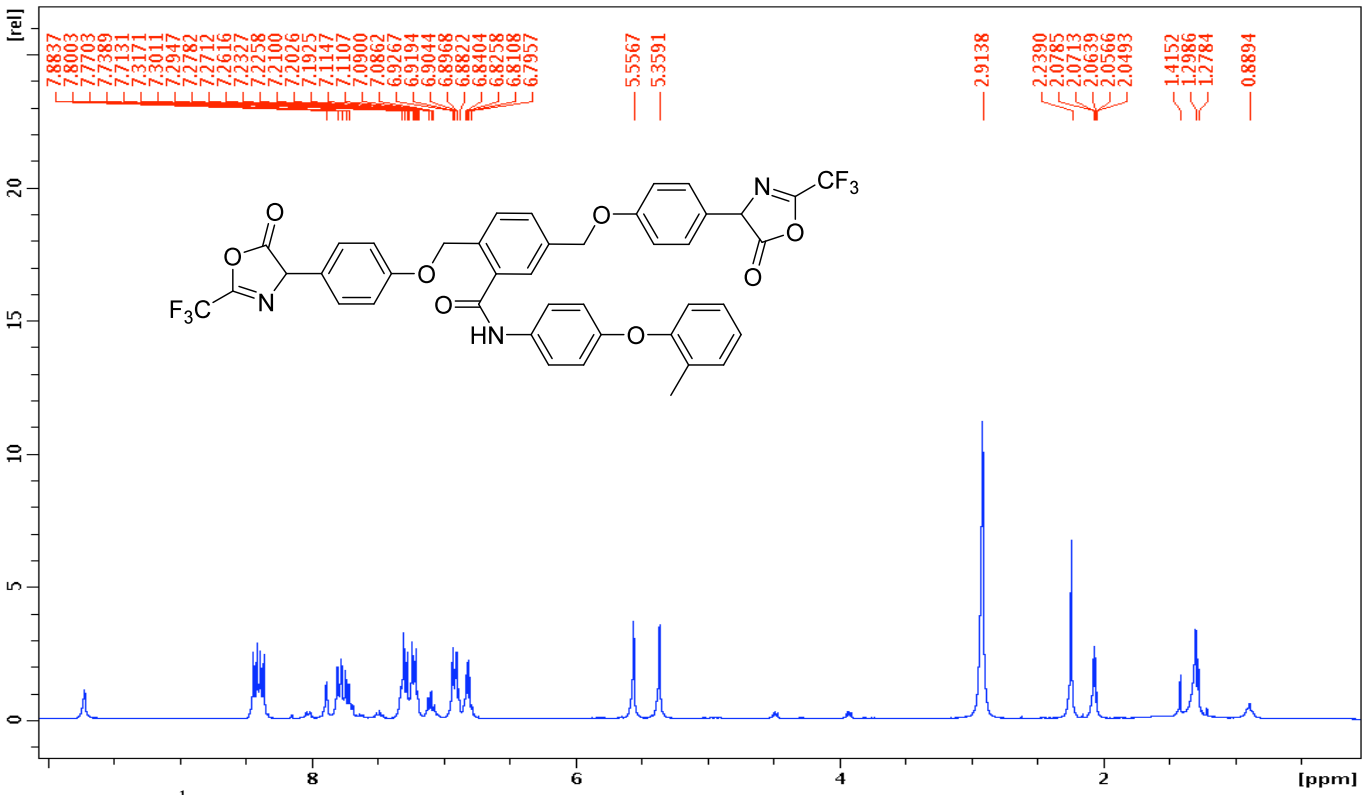

Figure S63. [1]HNMR spectrum of compound **9k**.

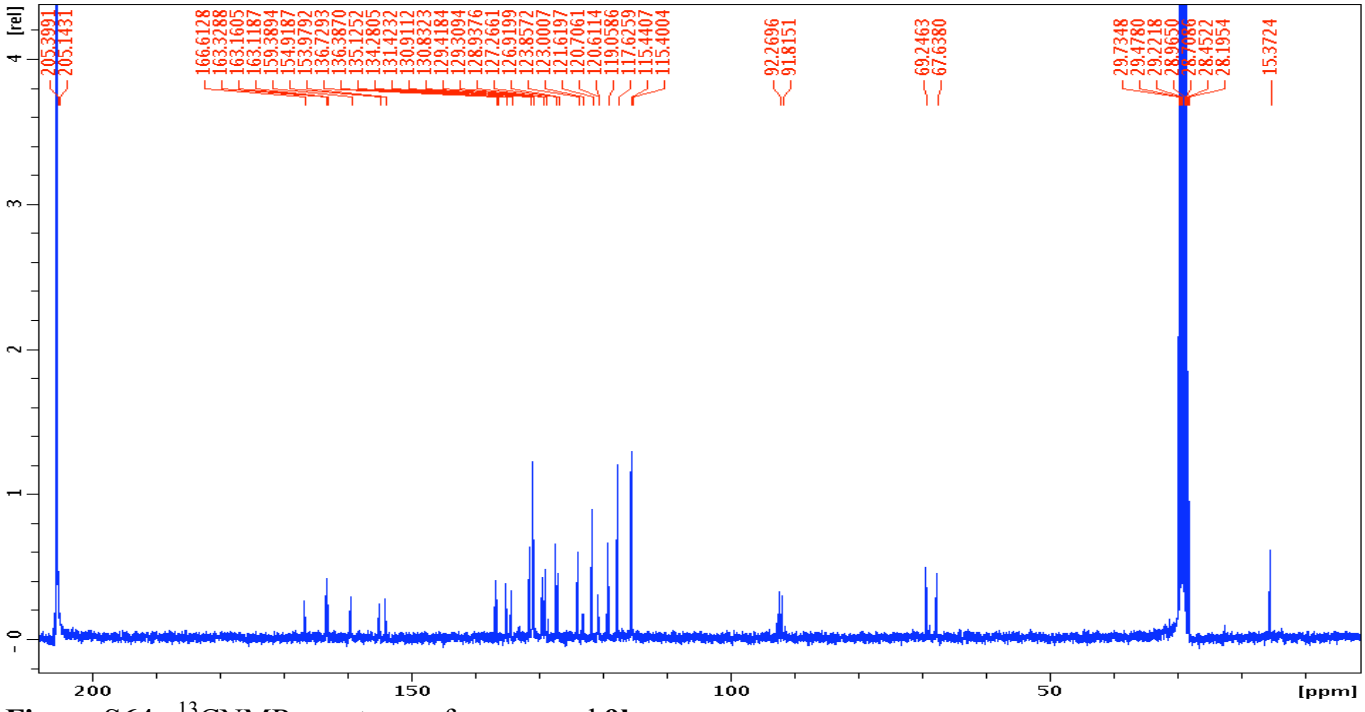

Figure S64. [13]CNMR spectrum of compound **9k**.

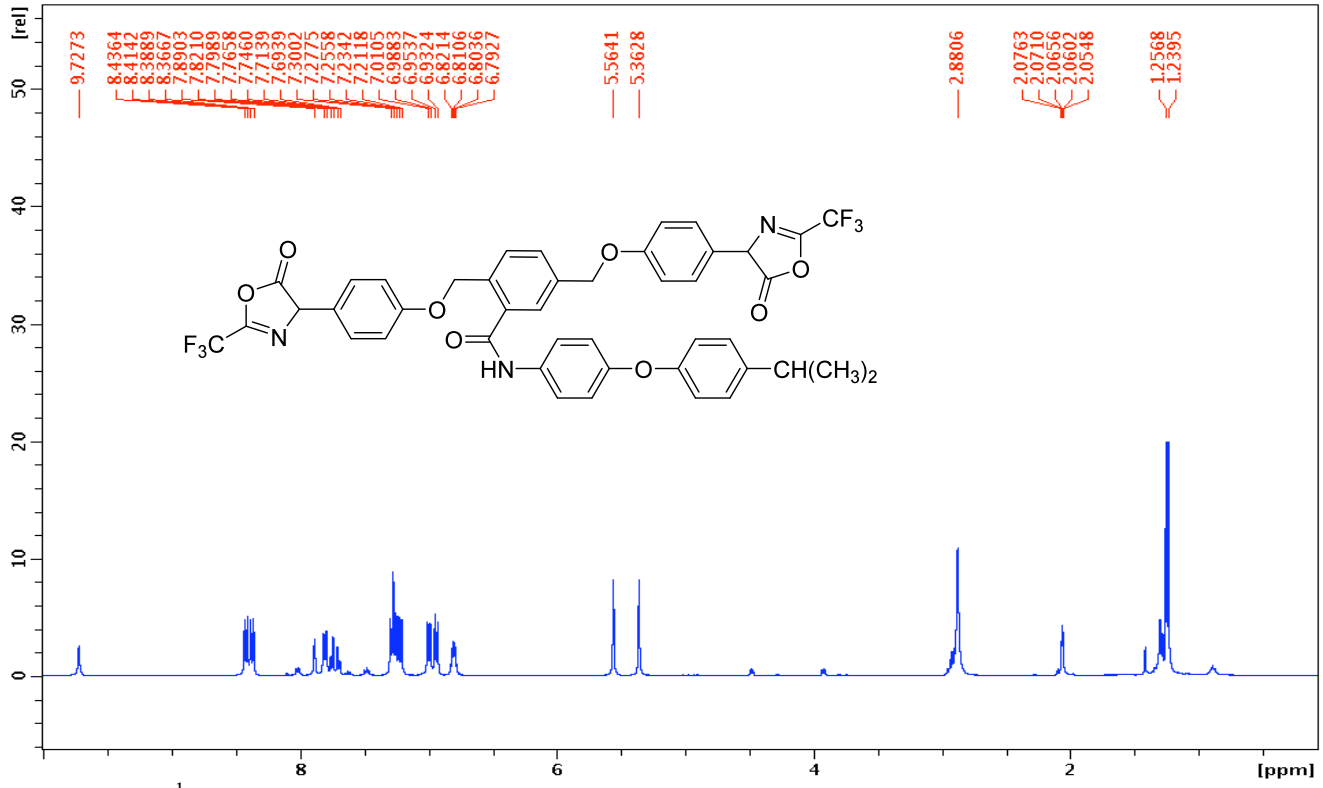

Figure S65. [1]HNMR spectrum of compound **9l**.

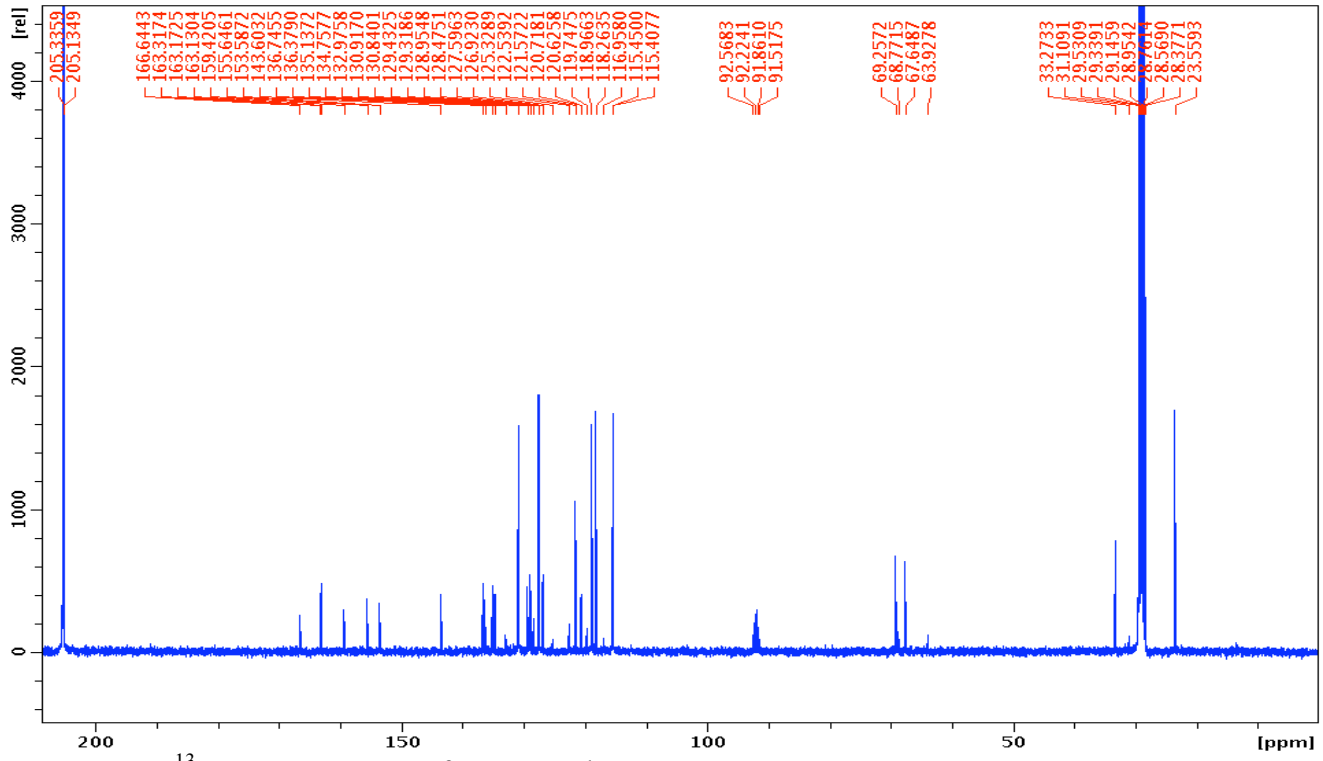

Figure S66. [13]CNMR spectrum of compound **9l**.

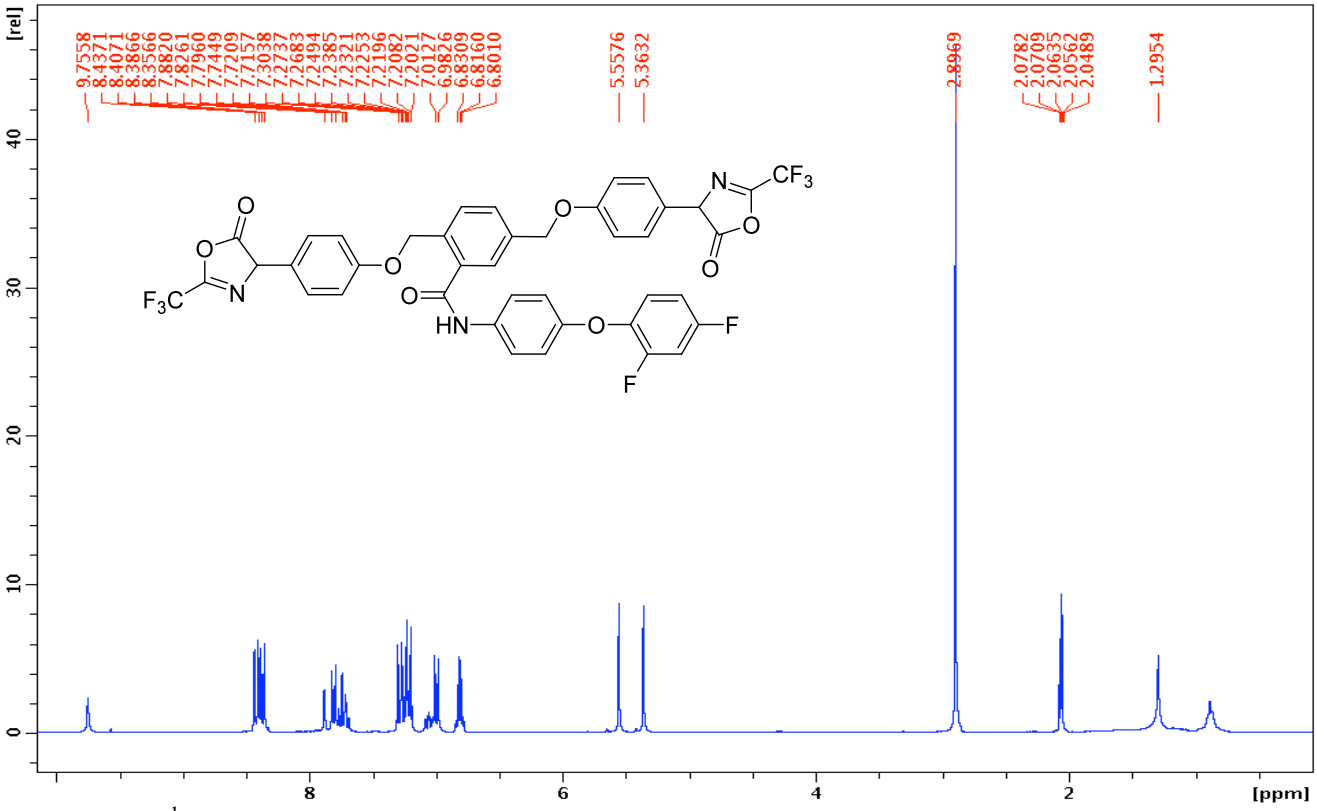

Figure S67. [1]HNMR spectrum of compound **9m**.

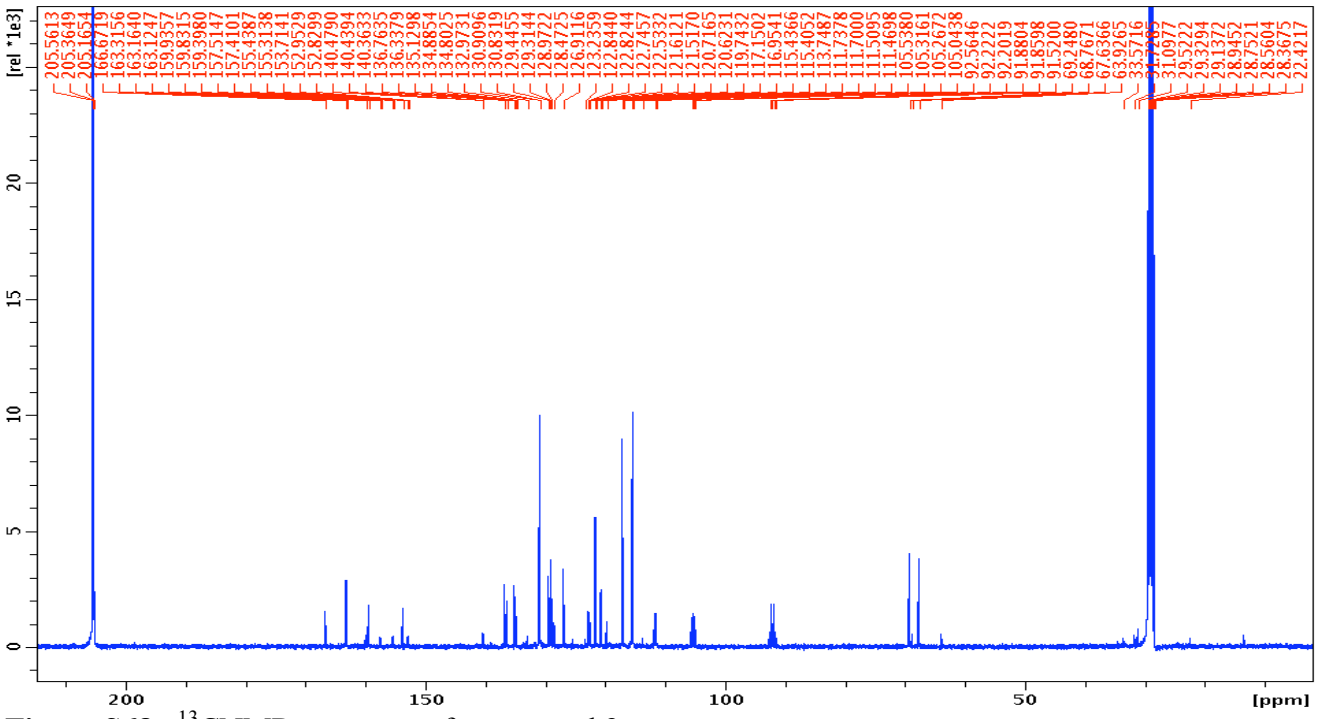

Figure S68. [13]CNMR spectrum of compound **9m**.

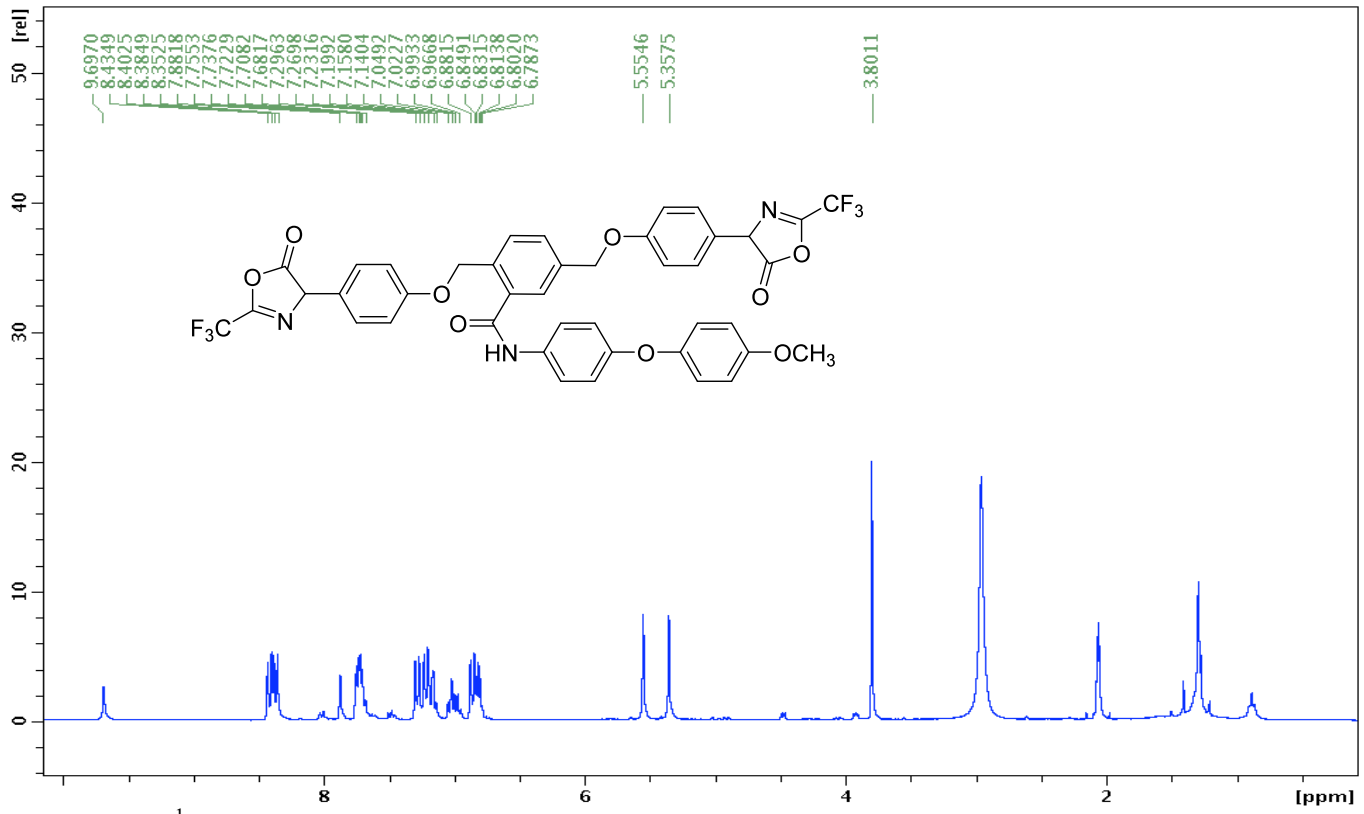

Figure S69. [1]HNMR spectrum of compound **9n**.

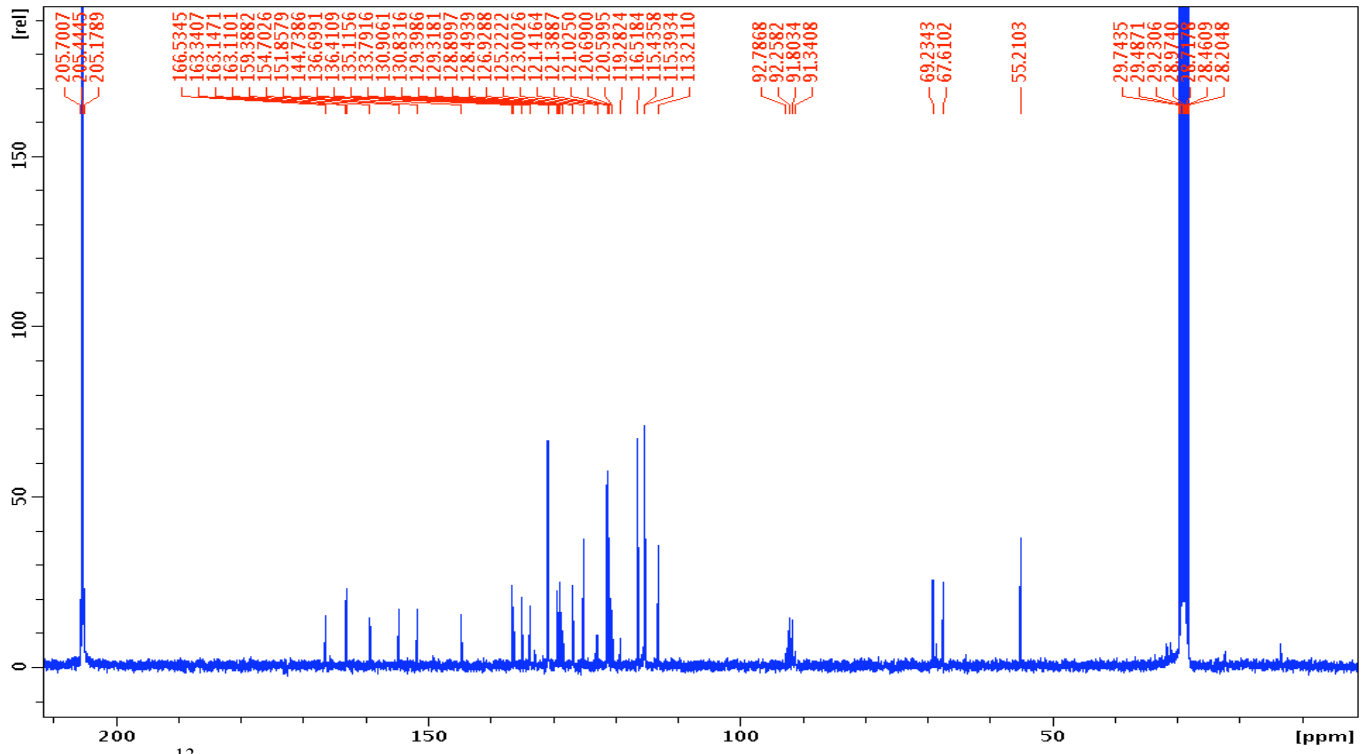

Figure S70. [13]CNMR spectrum of compound **9n**.

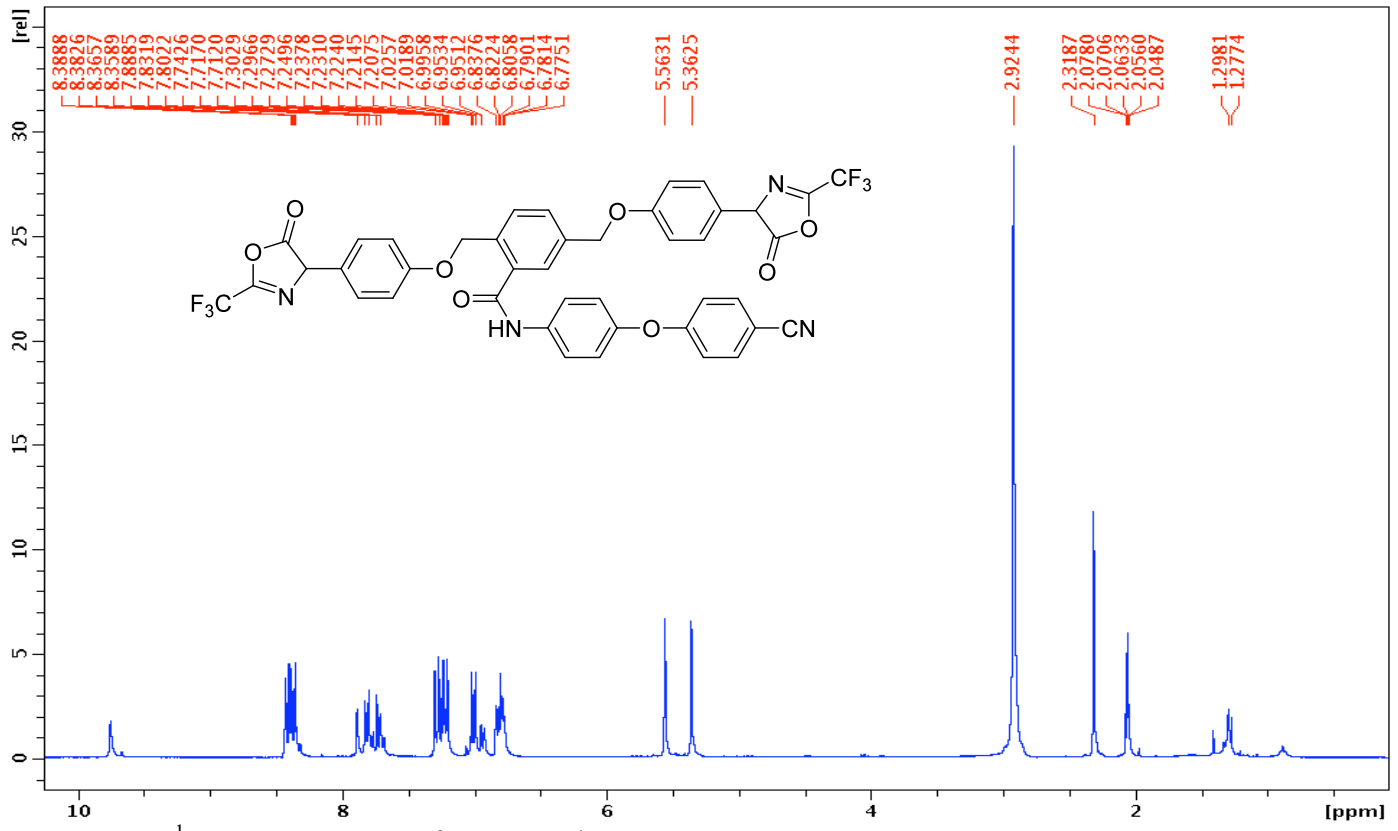

Figure S71. [1]HNMR spectrum of compound **9o.**

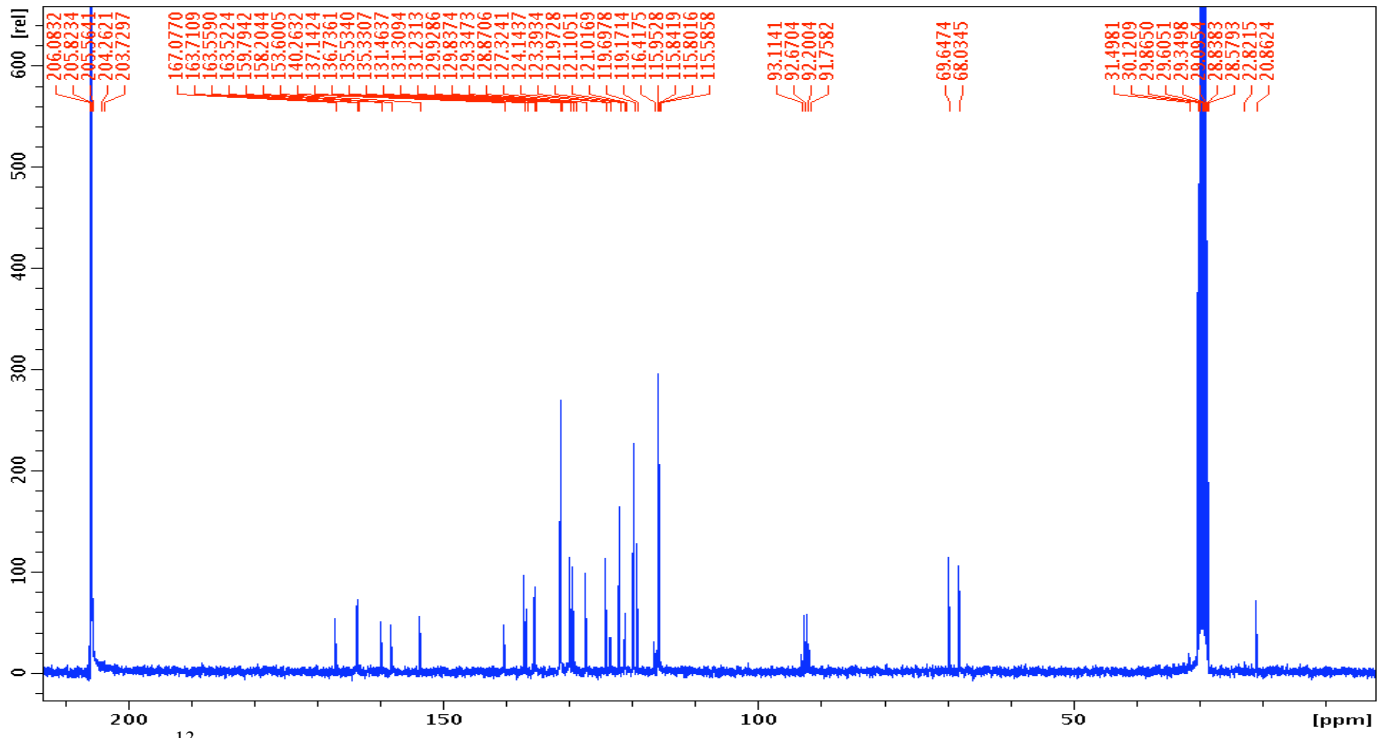

Figure S72. [13]CNMR spectrum of compound **9o.**

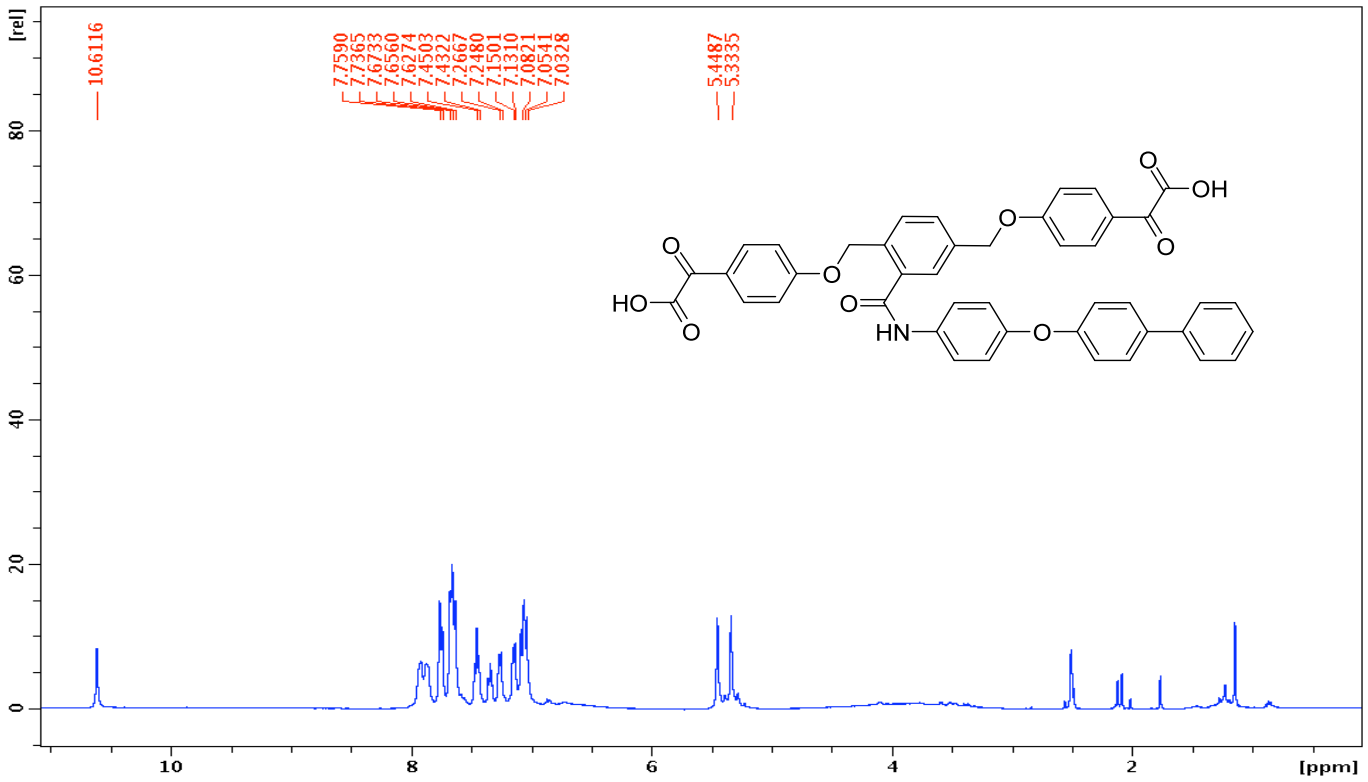

Figure S73. [1]HNMR spectrum of HPLC purified compound **2a**.

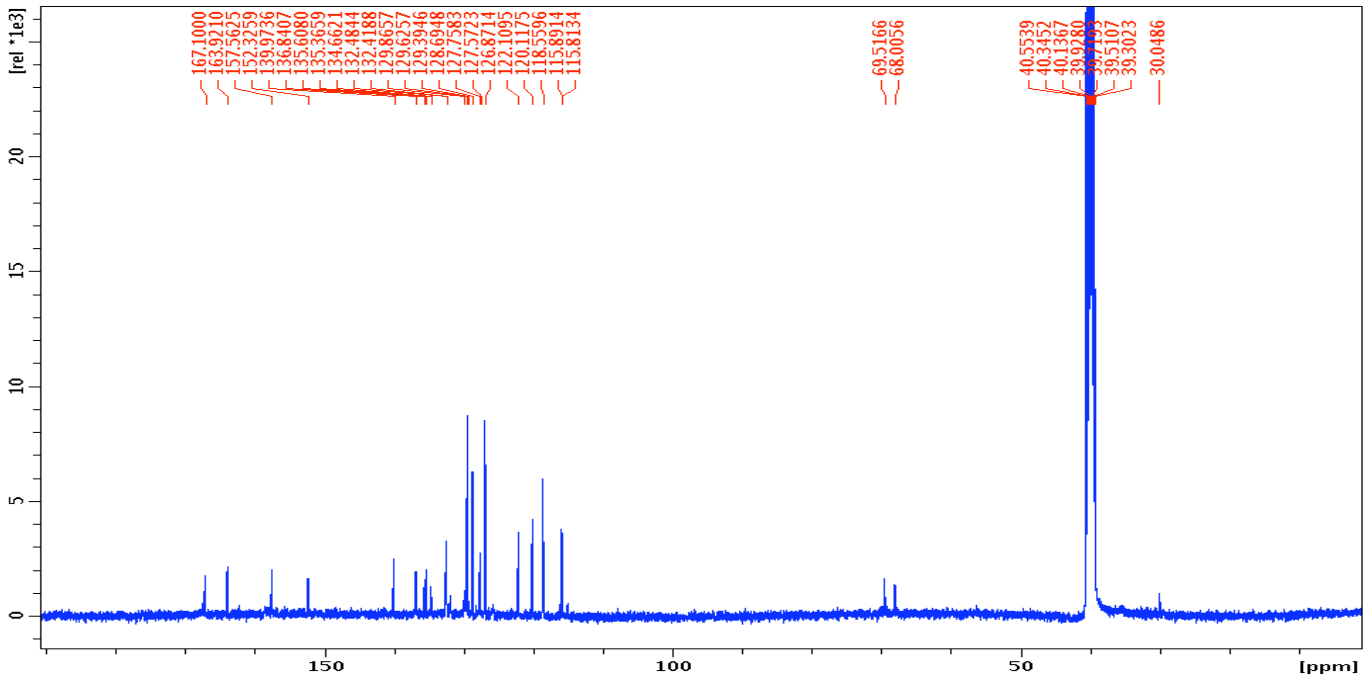

Figure S74. [13]CNMR spectrum of HPLC purified compound **2a**.

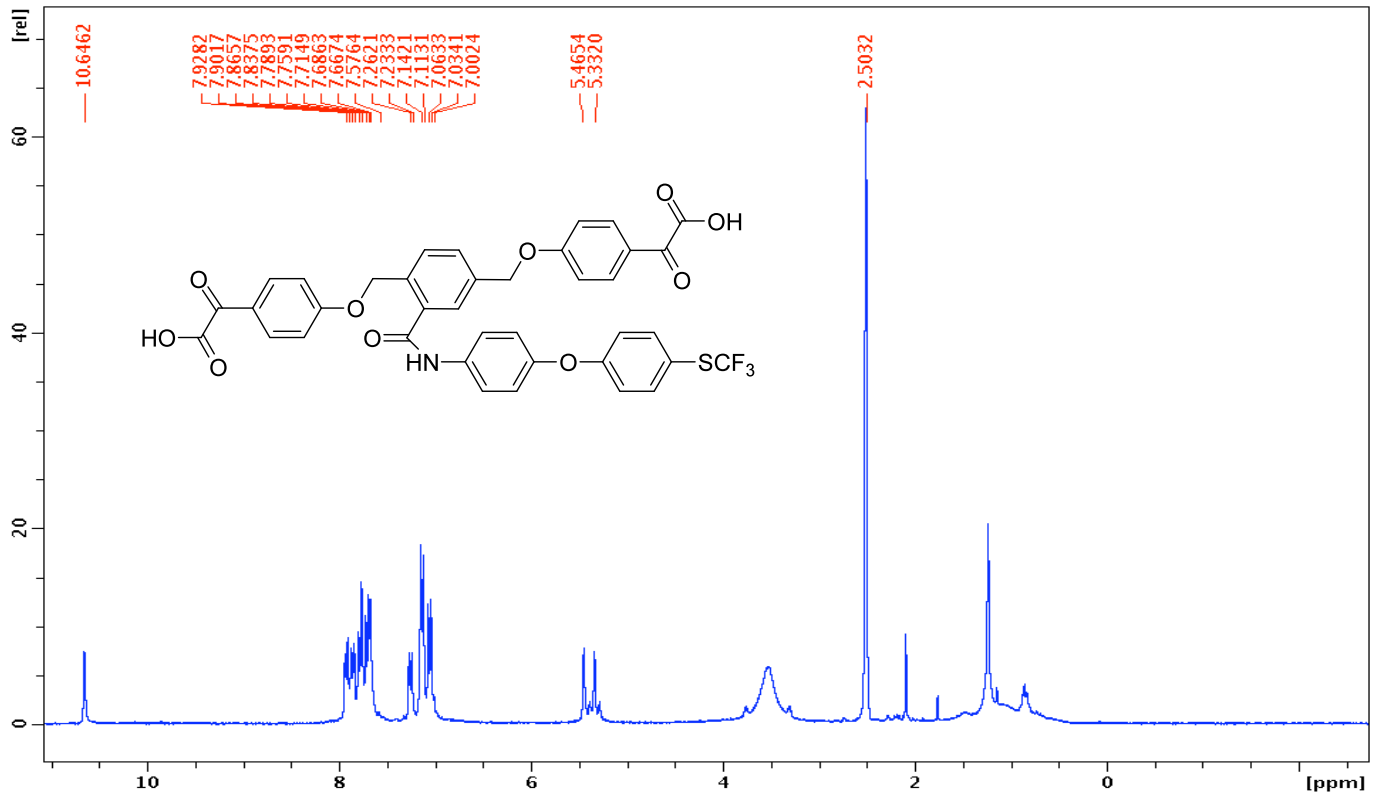

Figure S75. [1]HNMR spectrum of HPLC purified compound **2b**.

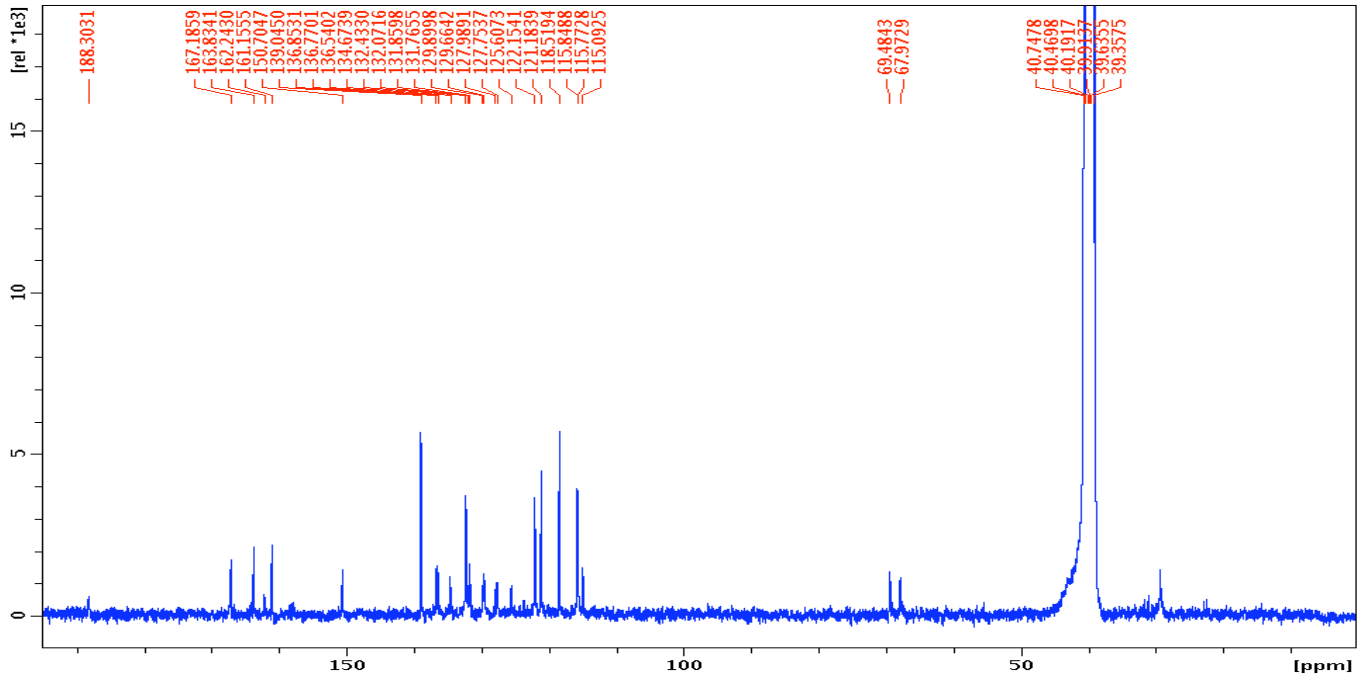

Figure S76. [13]CNMR spectrum of HPLC purified compound **2b**.

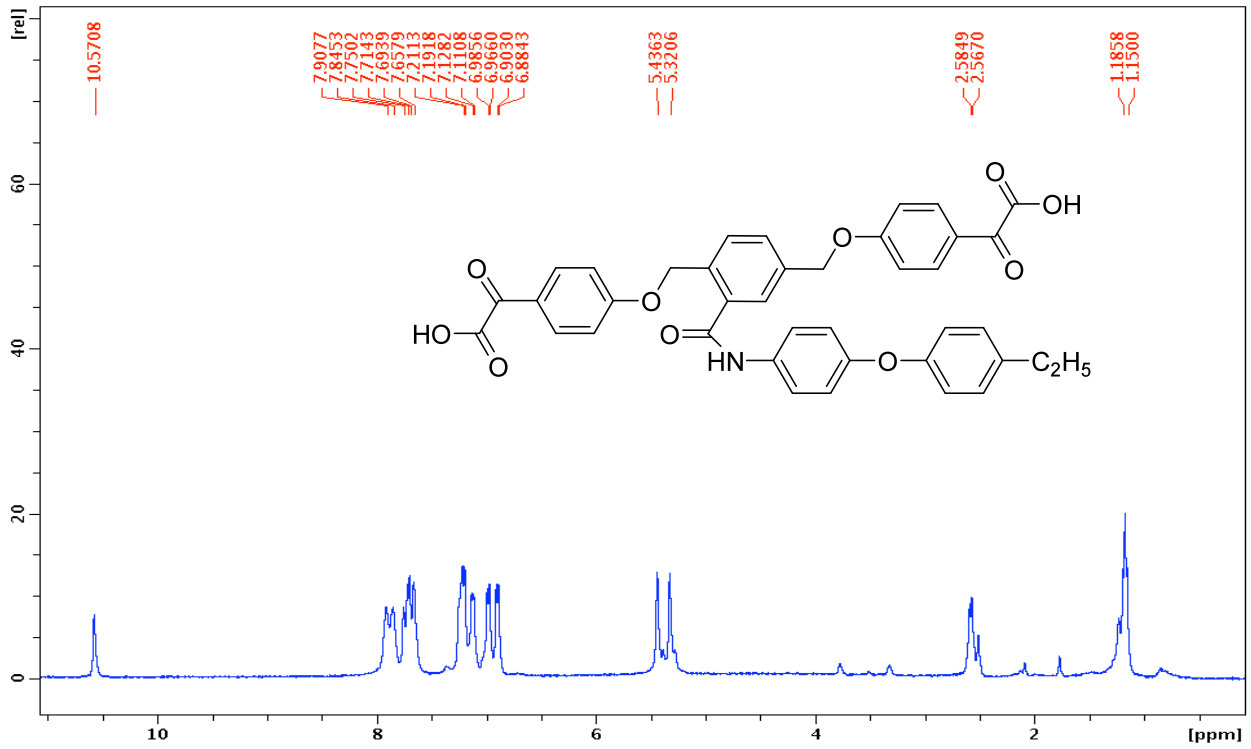

Figure S77. [1]HNMR spectrum of HPLC purified compound **2c**.

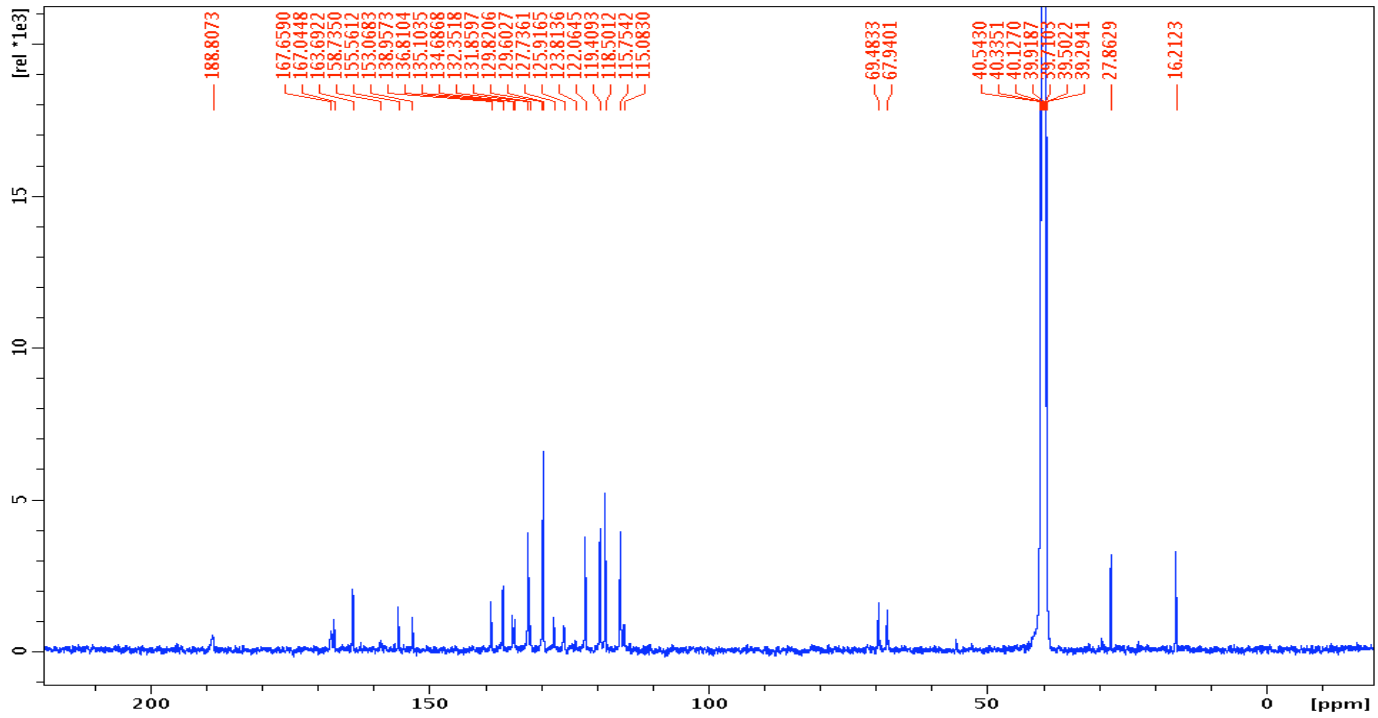

Figure S78. [13]CNMR spectrum of HPLC purified compound **2c**.

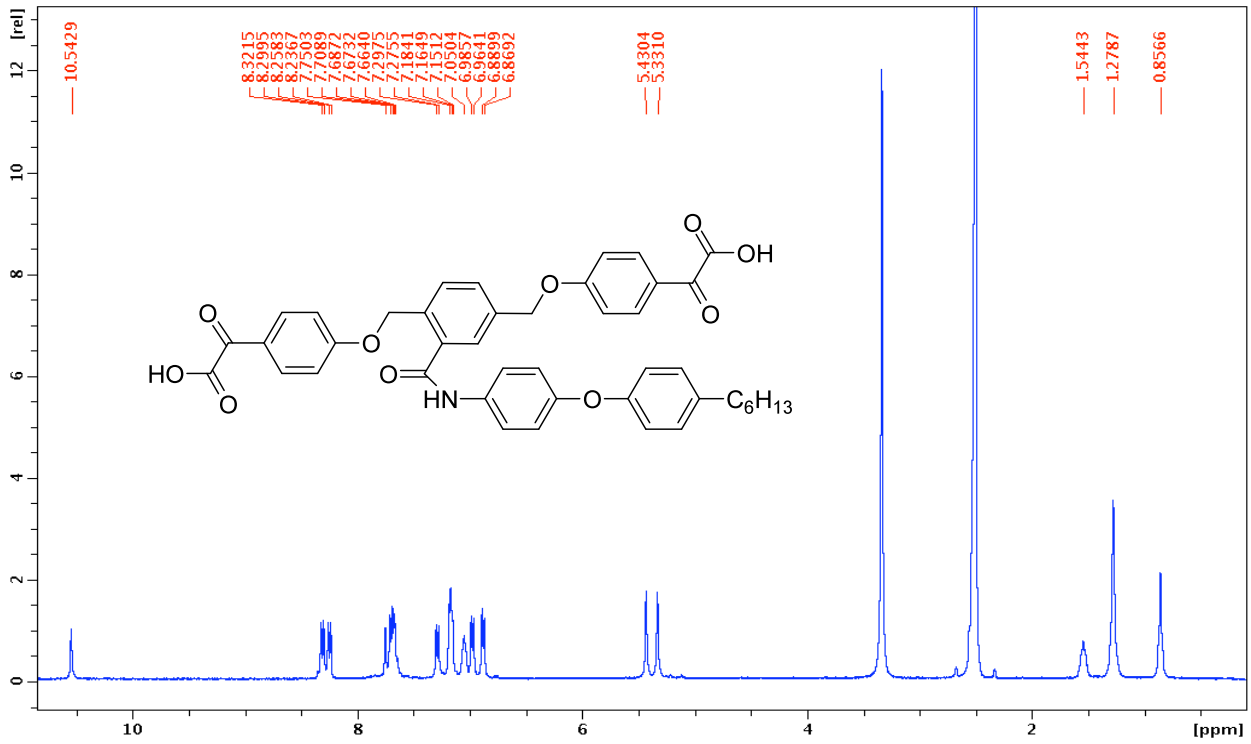

Figure S79. [1]HNMR spectrum of HPLC purified compound **2d**.

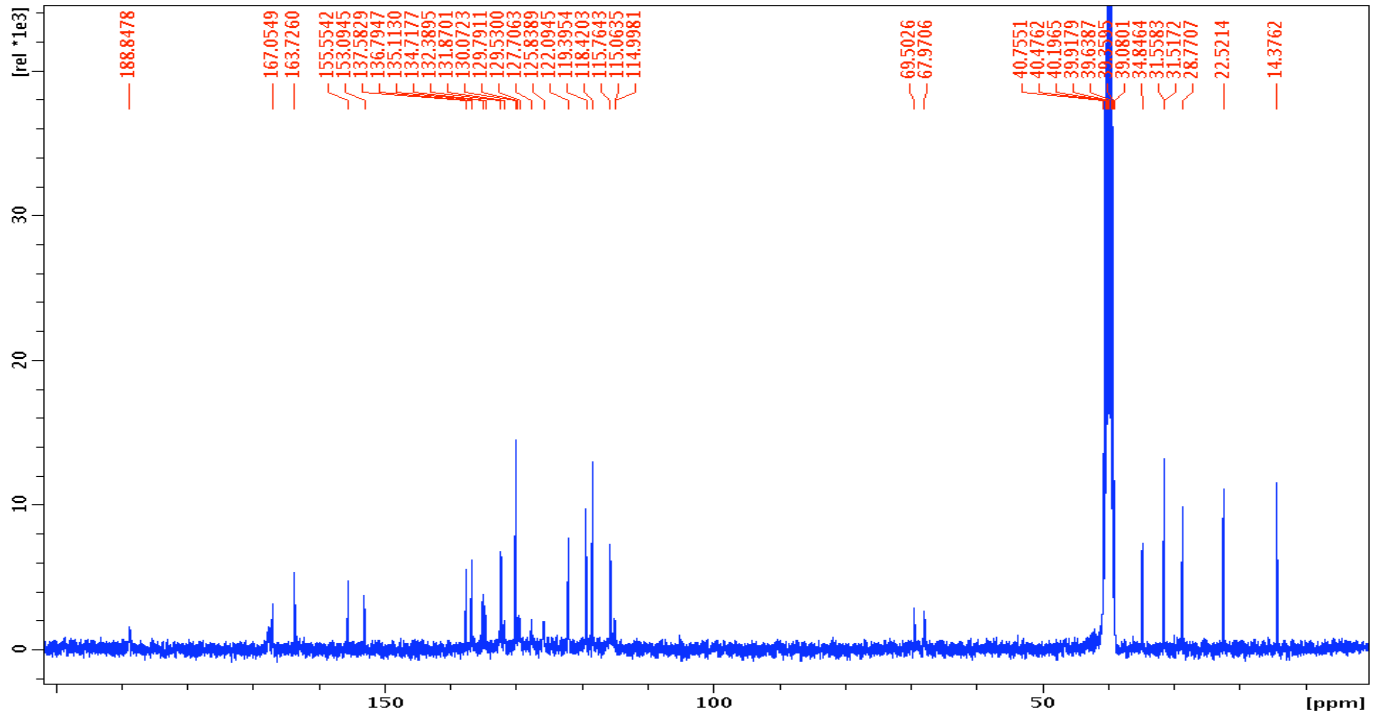

Figure S80. [13]CNMR spectrum of HPLC purified compound **2d**.

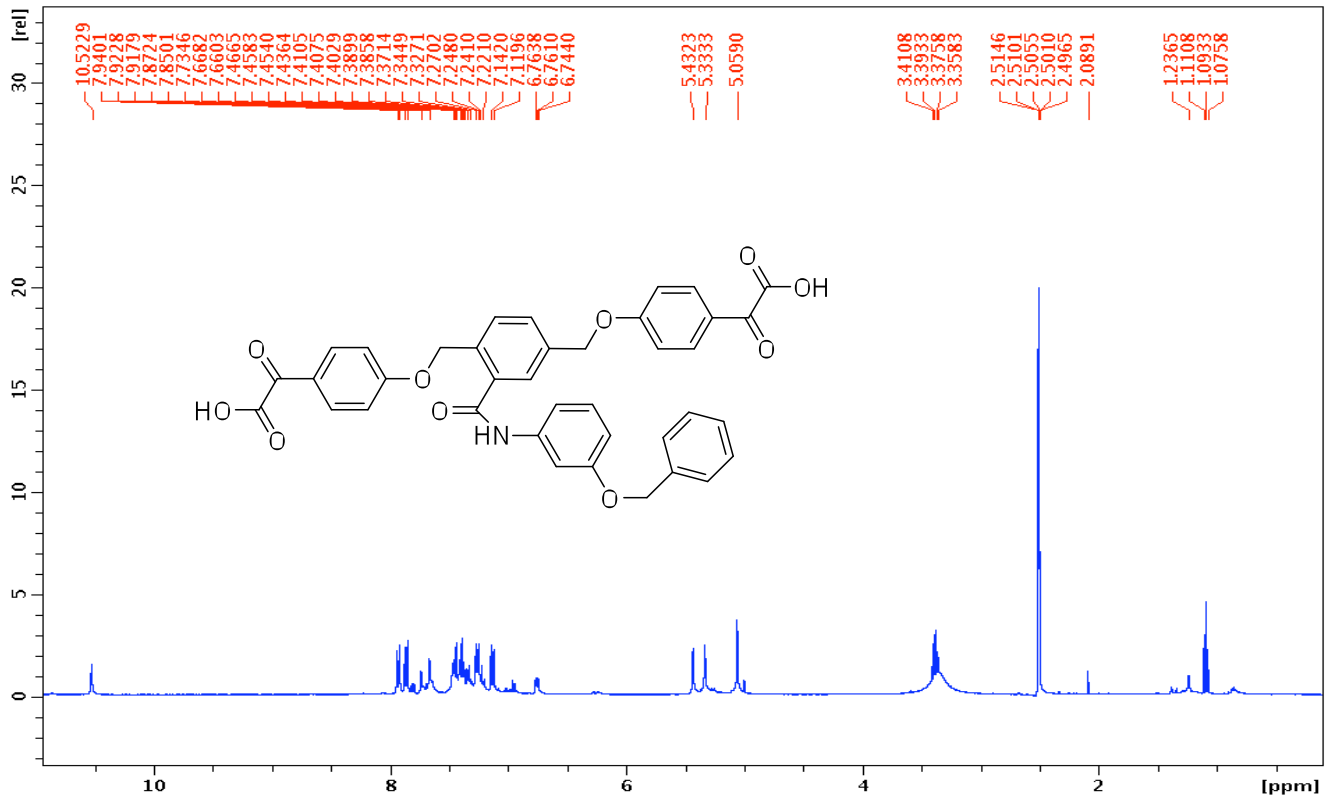

Figure S81. [1]HNMR spectrum of crude compound **3**.

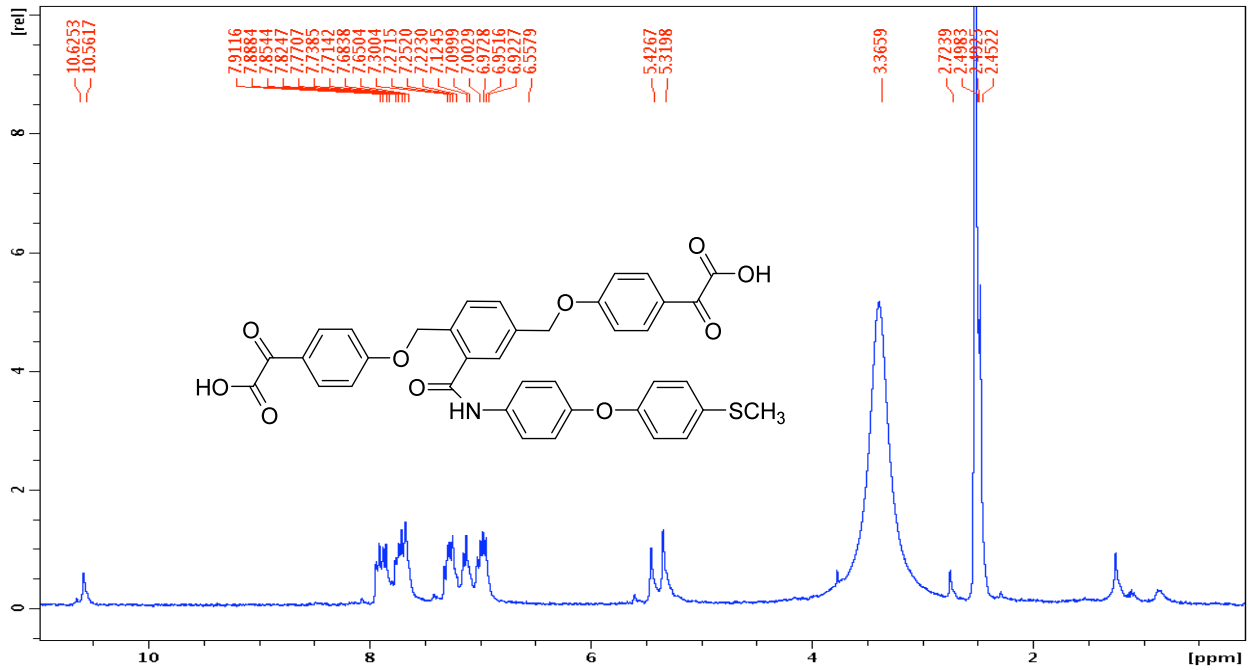

Figure S82. [1]HNMR spectrum of crude compound **2e**.

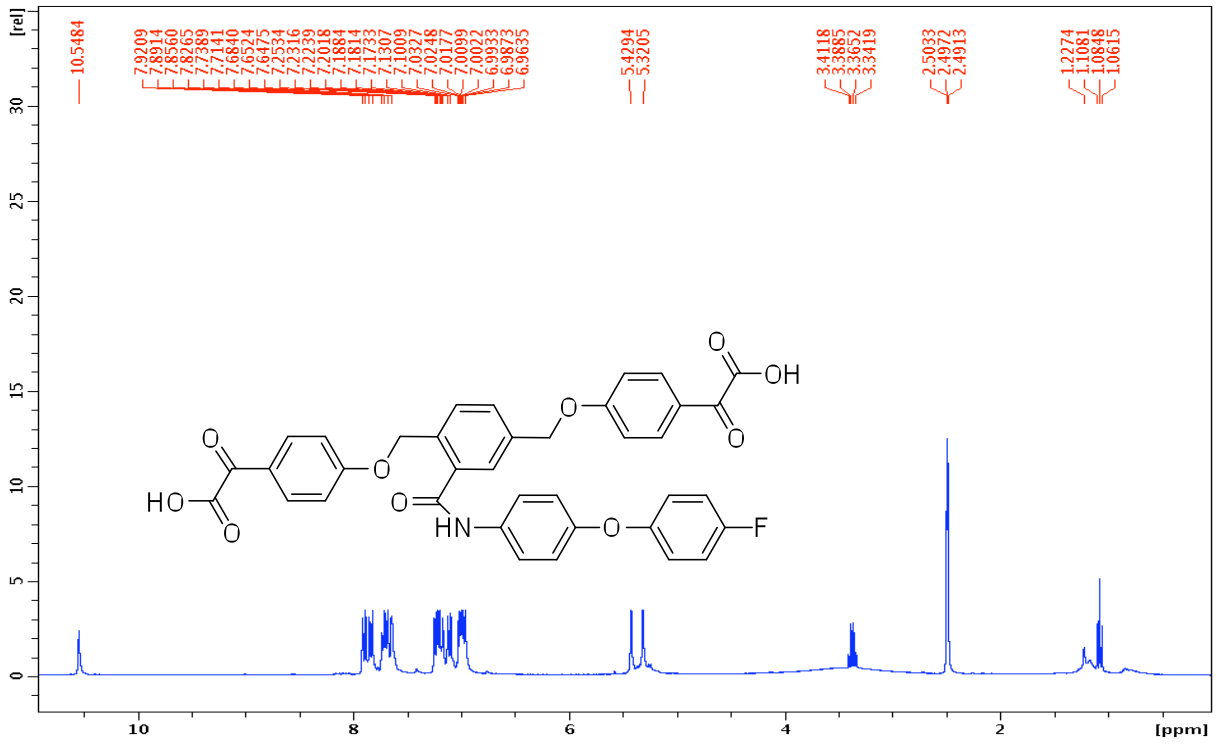

Figure S83. [1]HNMR spectrum of crude compound **2f**.

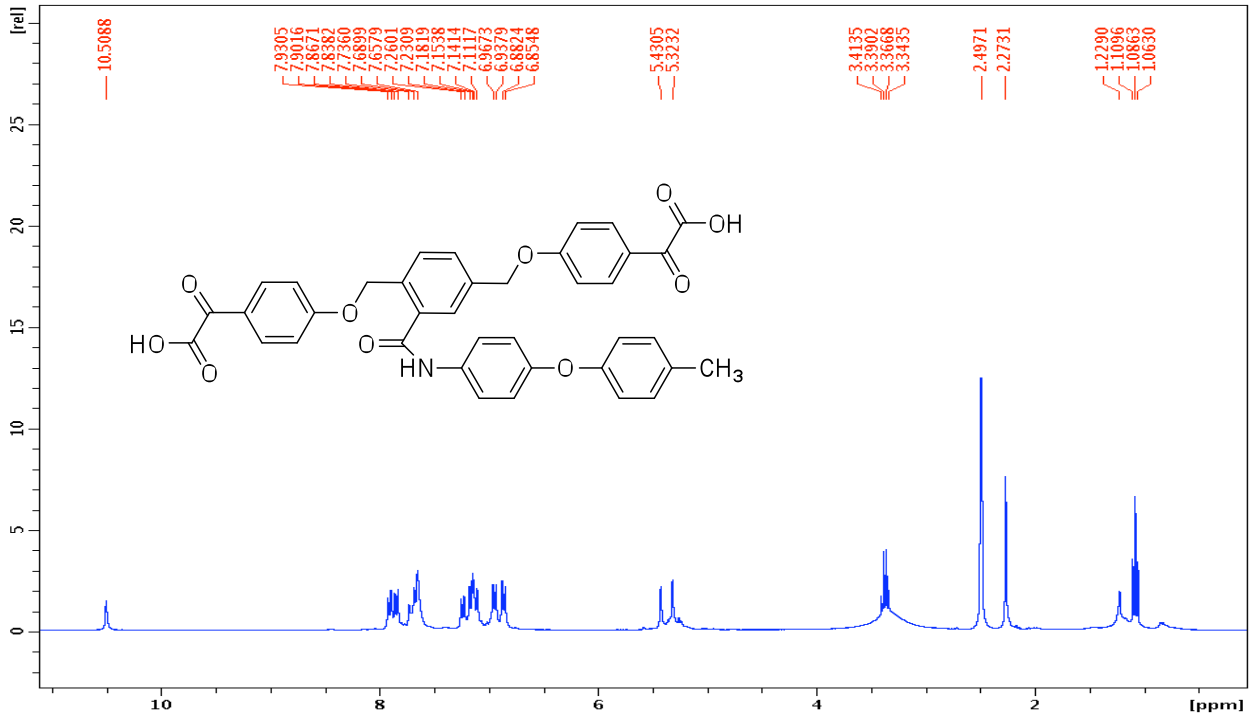

Figure S84. [1]HNMR spectrum of crude compound **2g**.

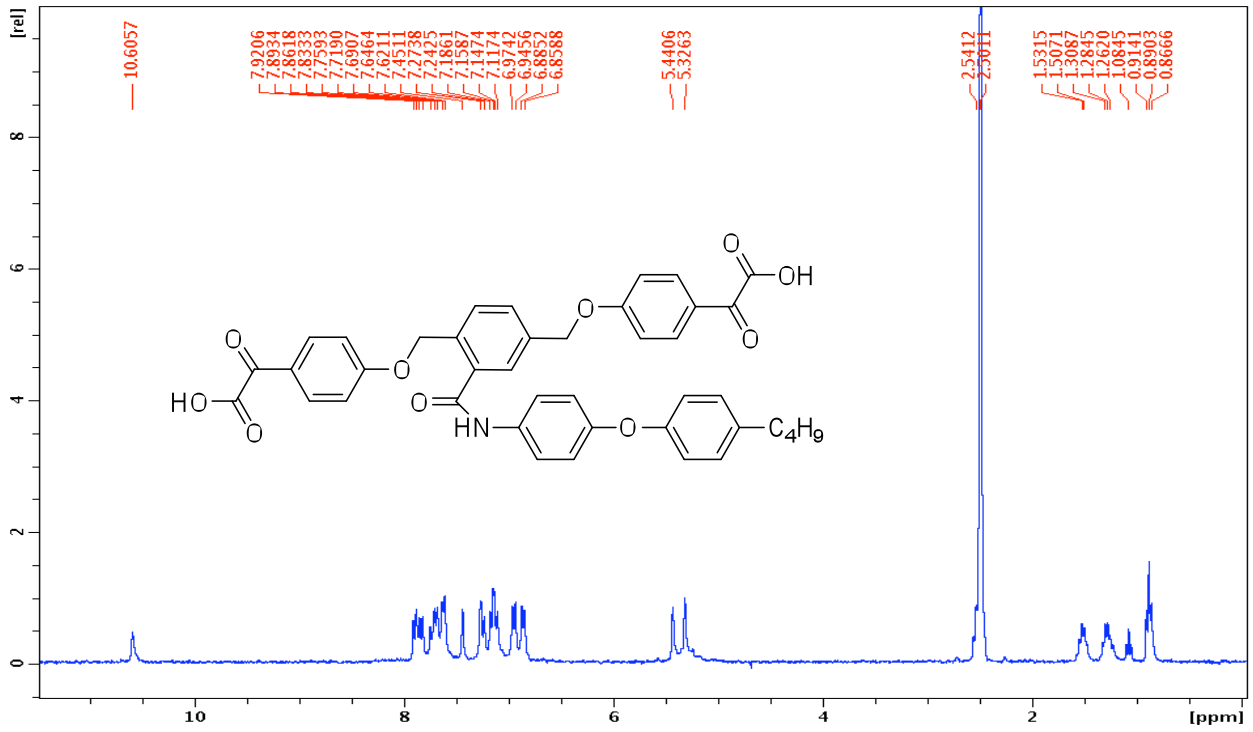

Figure S85. [1]HNMR spectrum of crude compound **2h**.

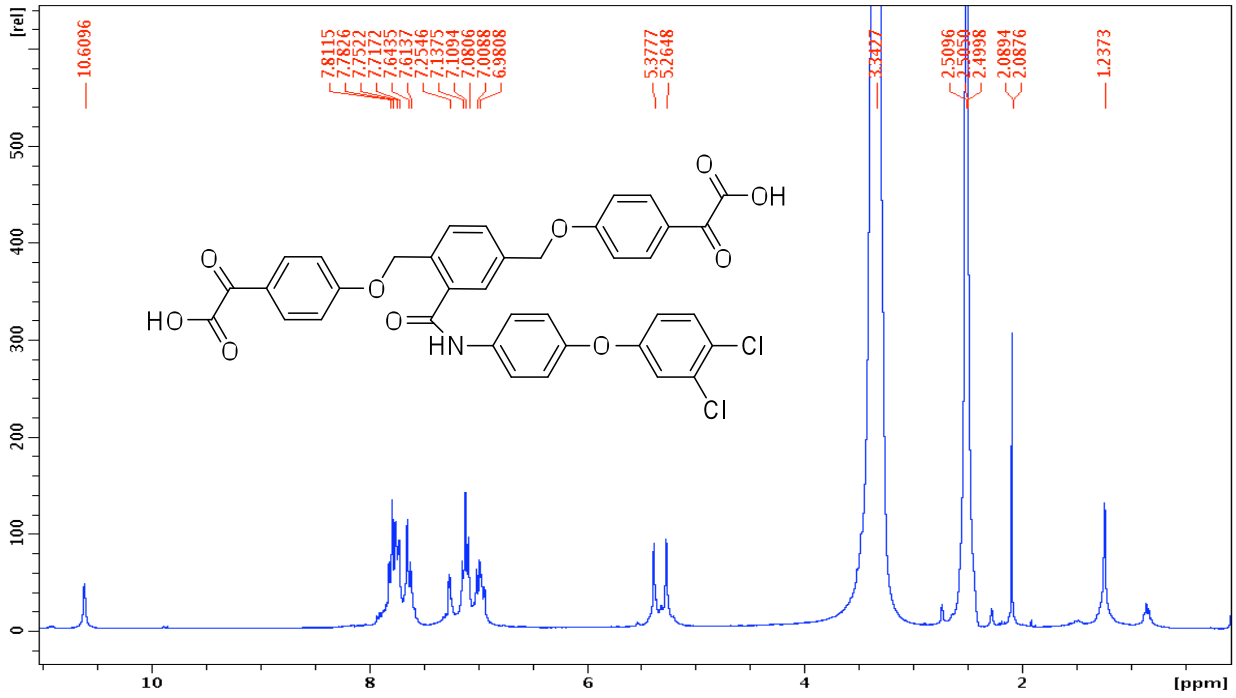

Figure S86. [1]HNMR spectrum of crude compound **2i**.

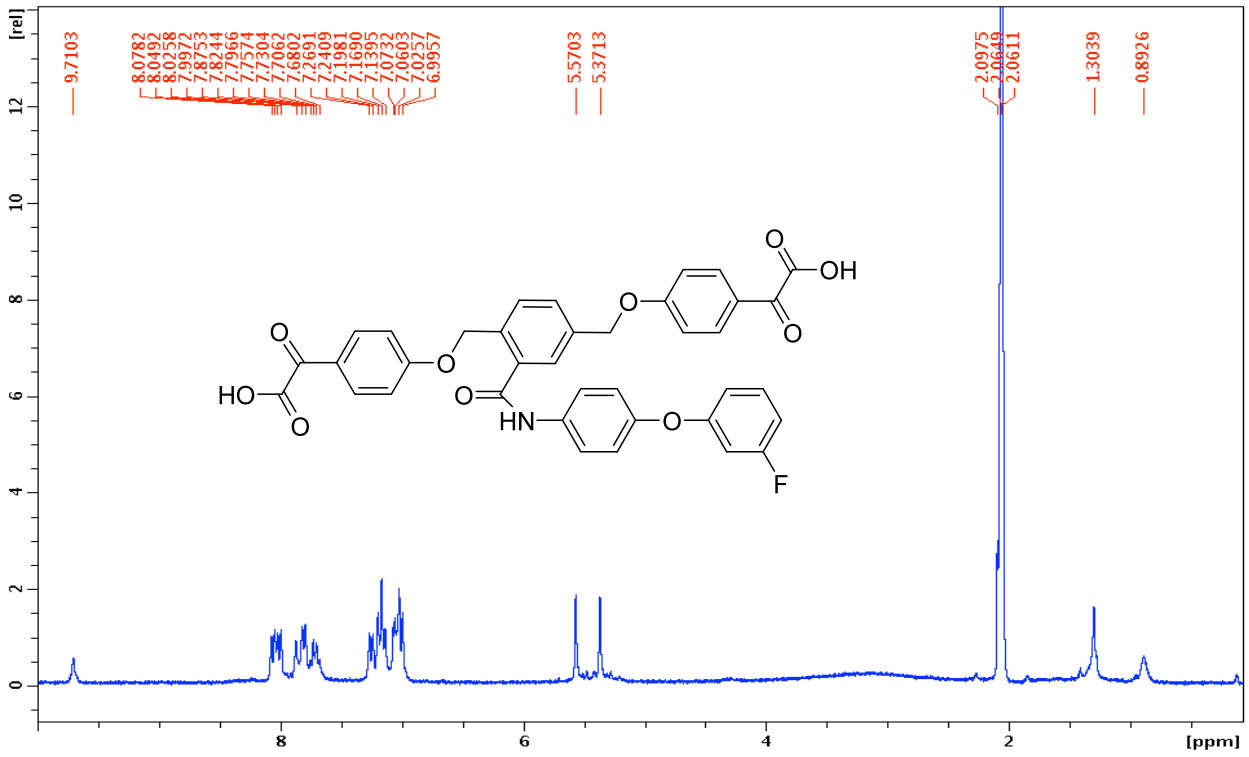

Figure S87. [1]HNMR spectrum of crude compound **2j**.

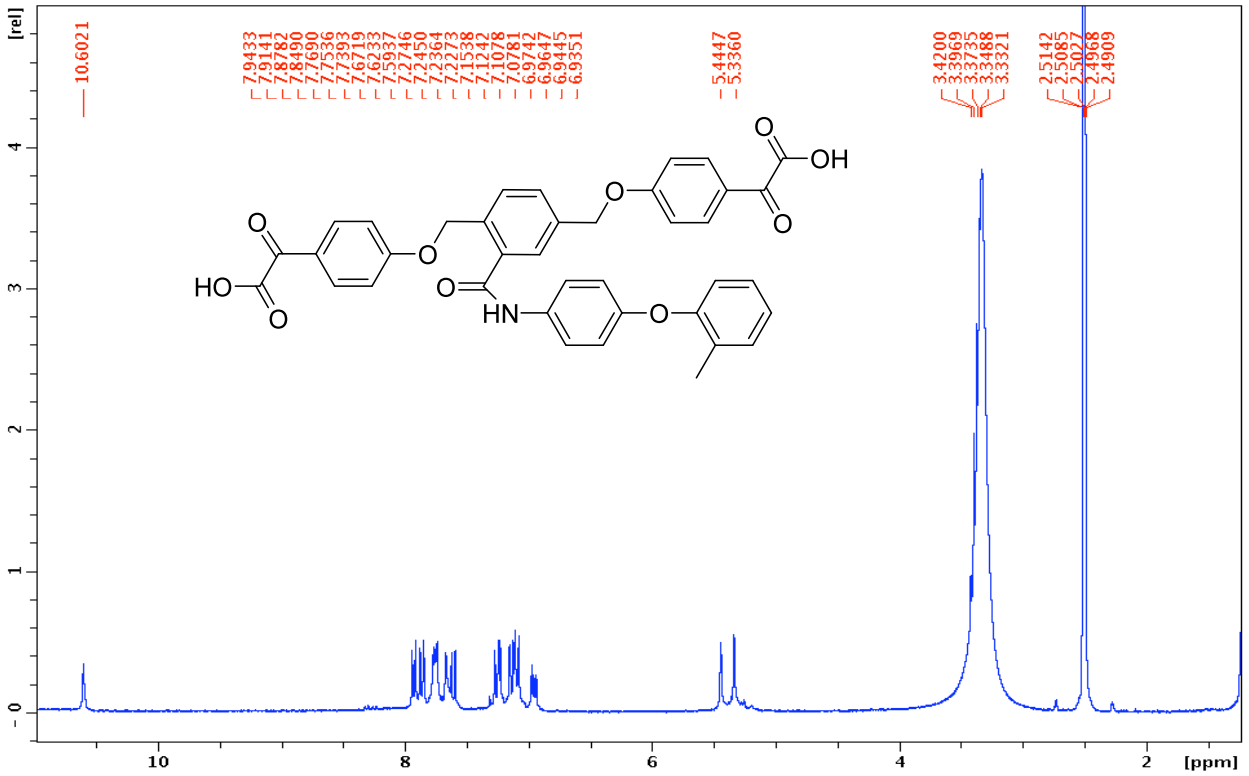

Figure S88. [1]HNMR spectrum of crude compound **2k**.

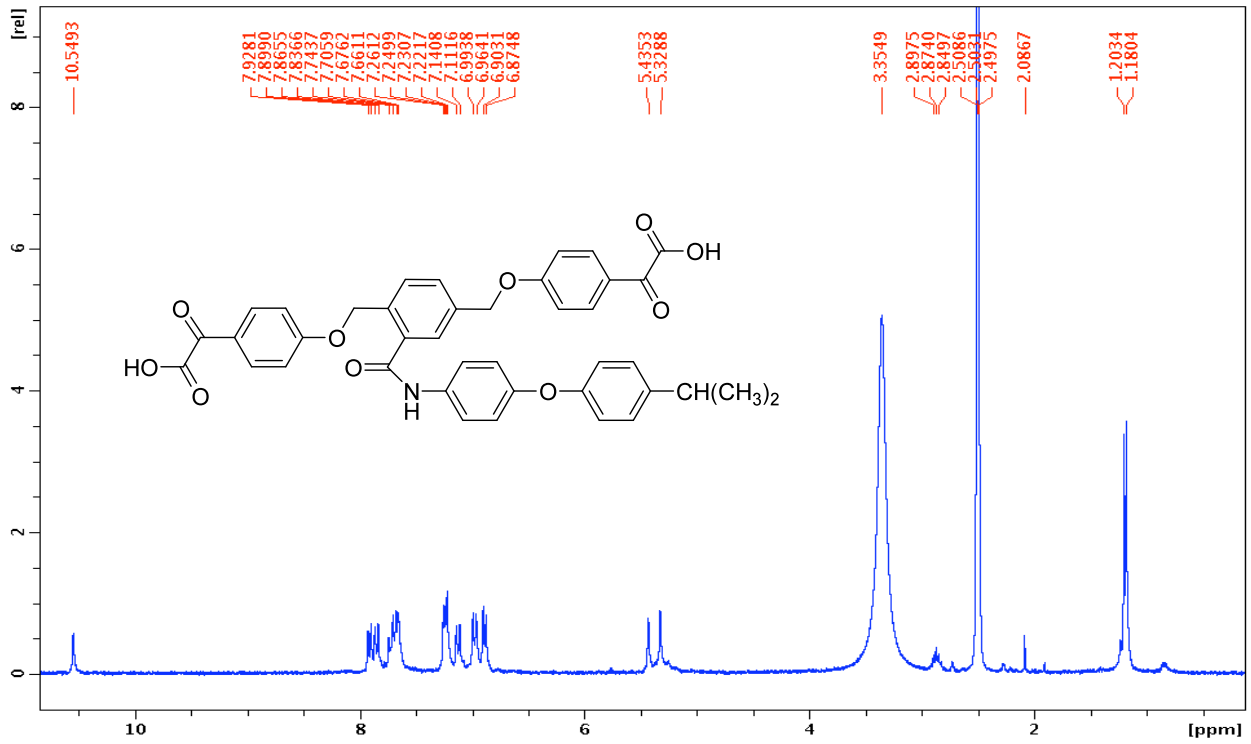

Figure S89. [1]HNMR spectrum of crude compound **2l**.

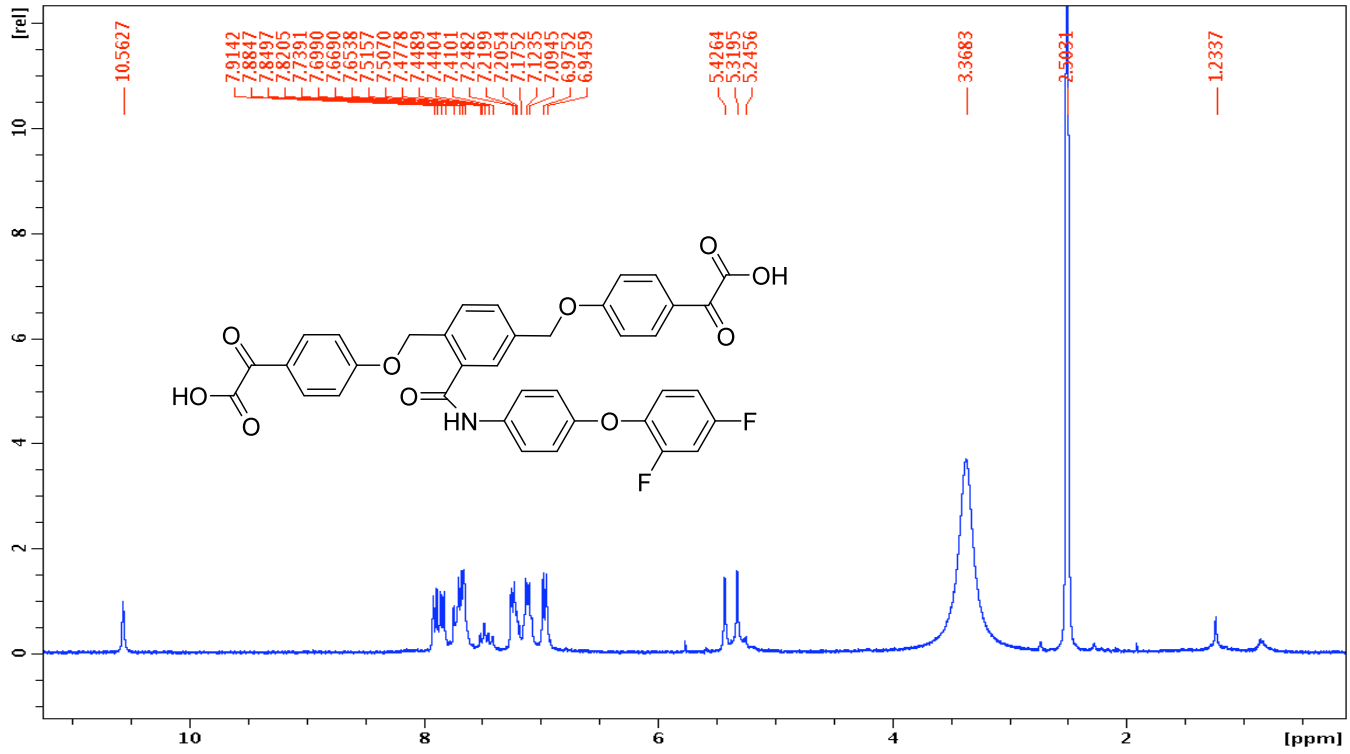

Figure S90. [1]HNMR spectrum of crude compound **2m**.

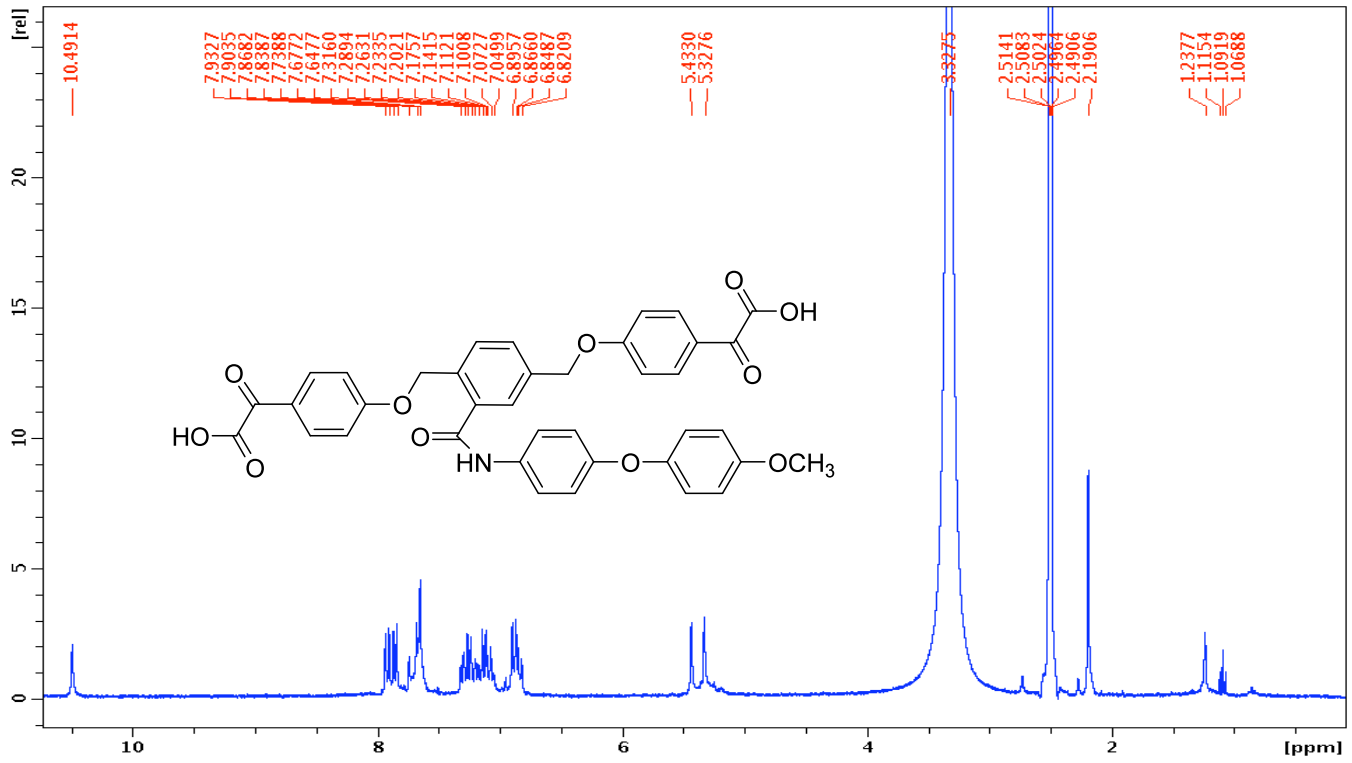

Figure S91. [1]HNMR spectrum of crude compound **2n.**

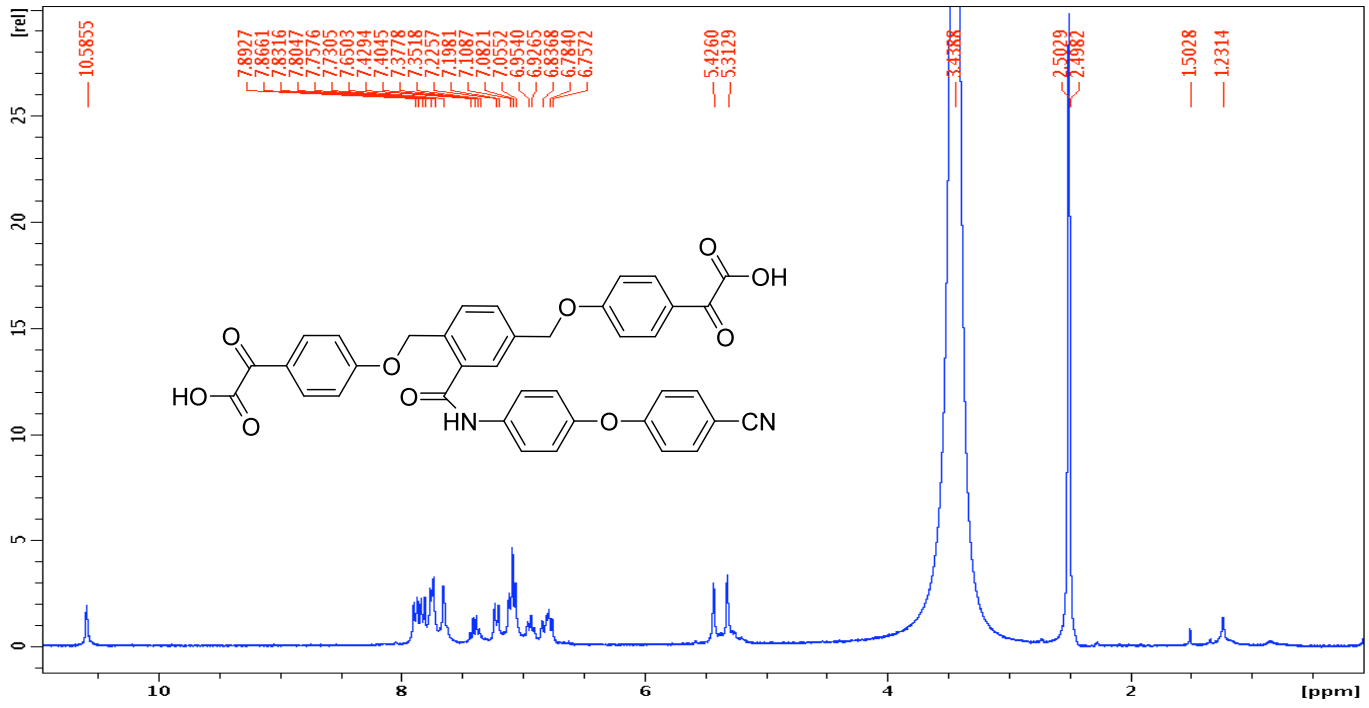

Figure S92. [1]HNMR spectrum of crude compound **2o.**

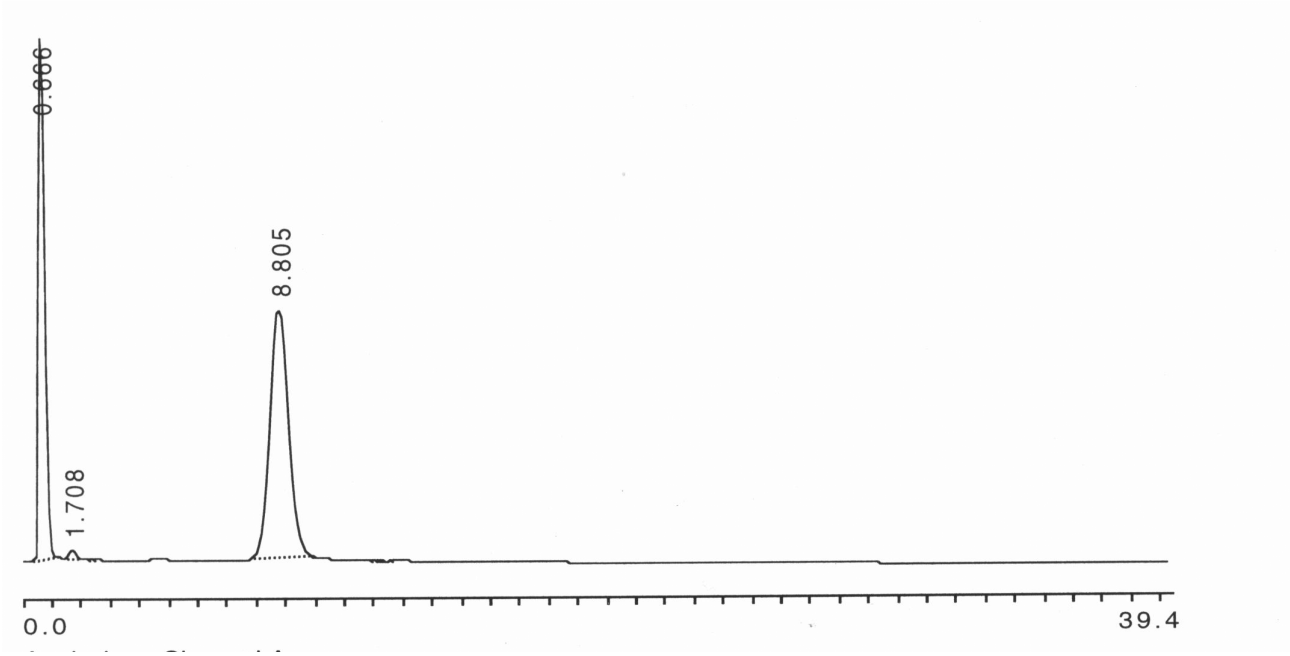

Figure S93. HPLC trace of compound **2a** using a reverse phase C-18 analytical column eluted with 50% CH_3CN in water with a total of 0.1% TFA at flow rate of 1 mL/min. Detection was performed at 254 nm.

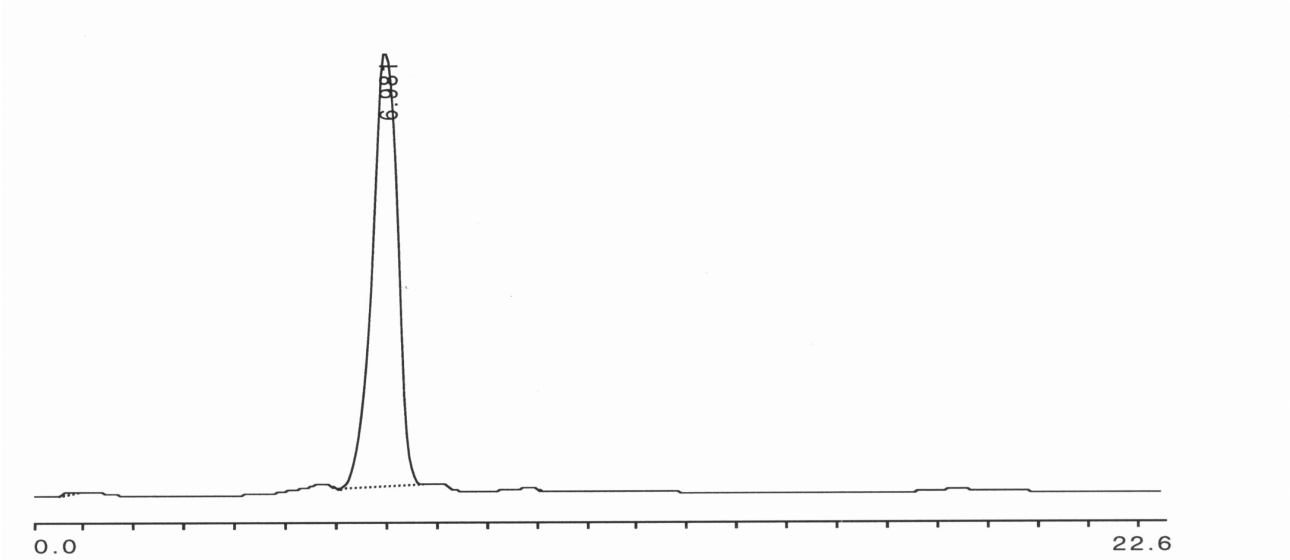

Figure S94. HPLC trace of compound **2b** using a reverse phase C-18 analytical column eluted with 55% CH_3CN in water with a total of 0.1% TFA at flow rate of 1 mL/min. Detection was performed at 254 nm.

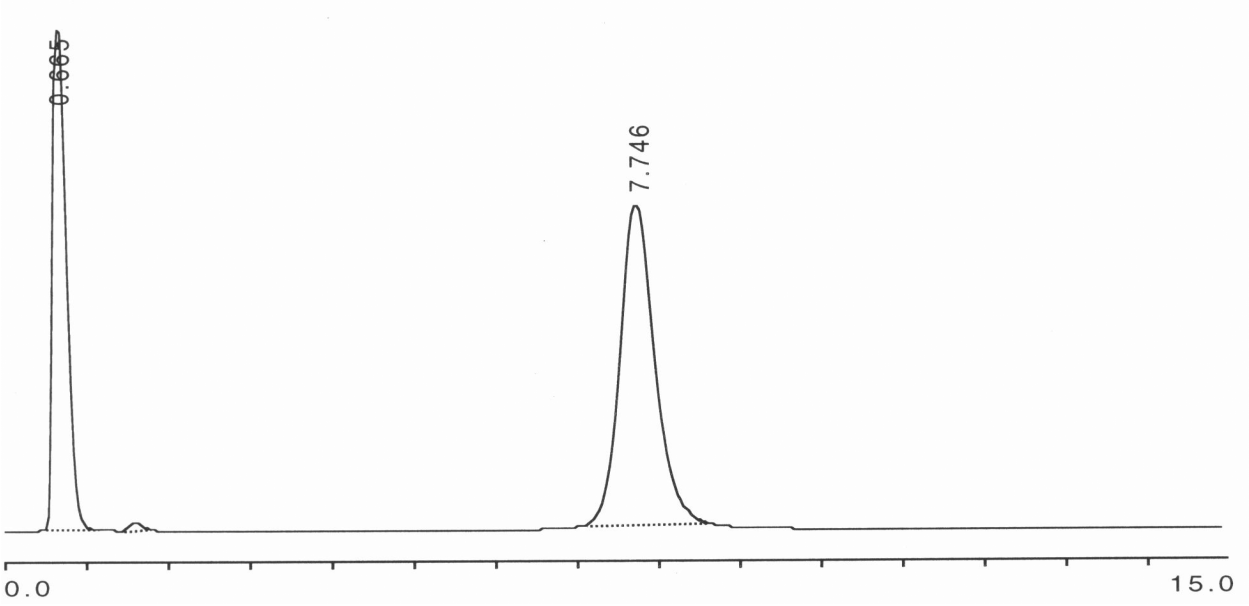

Figure S95. HPLC trace of compound **2c** using a reverse phase C-18 analytical column eluted with 55% CH_3CN in water with a total of 0.1% TFA at flow rate of 1 mL/min. Detection was performed at 254 nm.

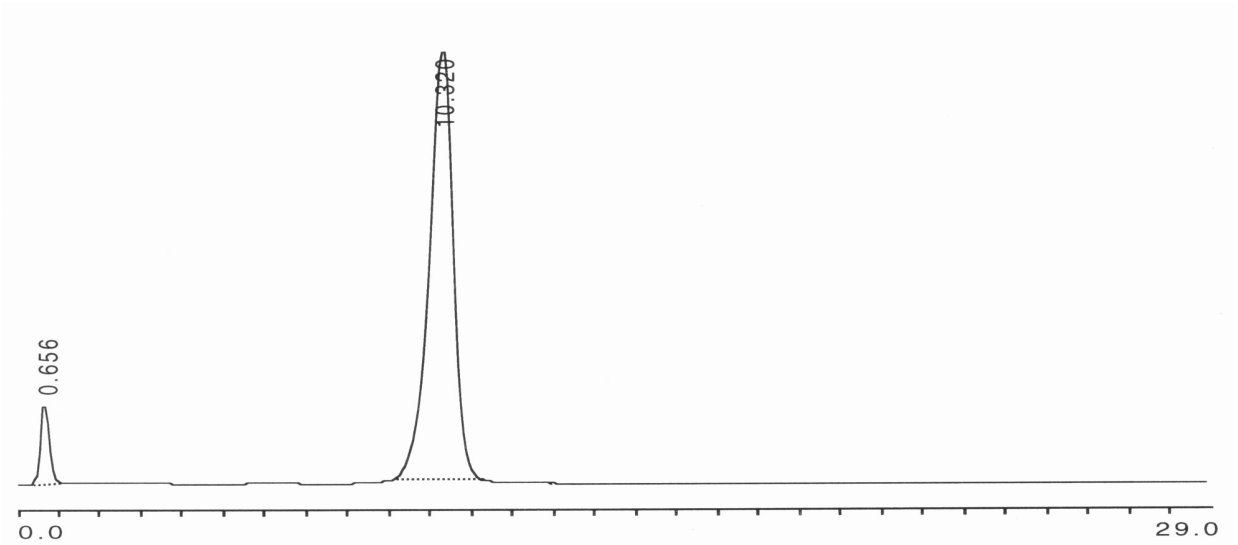

Figure S96. HPLC trace of compound **2d** using a reverse phase C-18 analytical column eluted with 60% CH_3CN in water with a total of 0.1% TFA at flow rate of 1 mL/min. Detection was performed at 254 nm.

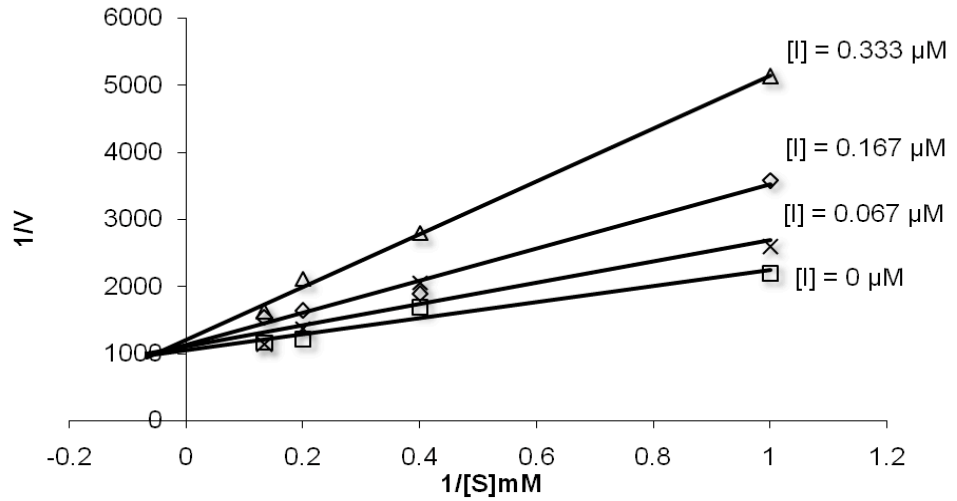

Figure S97. Inhibition of YopH by compound **2b**. The activity of YopH was measured at pH 7.0 as described in the Experimental Section in the presence of the following concentrations of **2b**: (□) 0 µM; (×) 0.067 µM; (◊) 0.167 µM; (Δ) 0.333 µM. Substrate concentrations used in the assays were 1.0, 2.5, 5.0 and 7.5 mM.

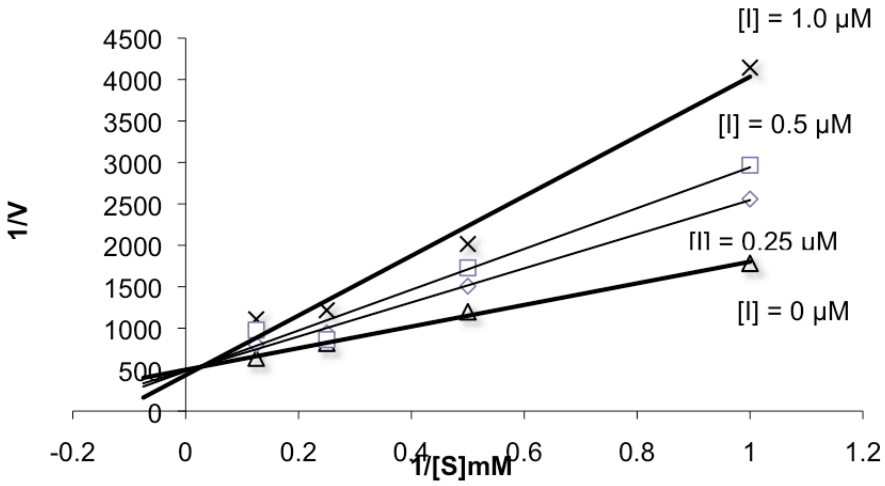

Figure S98. Inhibition of PTP1B by compound **2a**. The activity of PTP1B was measured at pH 7.0 as described in the Experimental Section in the presence of the following concentrations of **2a**: (Δ) 0 µM; (◊) 0.25 µM; (□) 0.50 µM; (×) 1.0 µM. Substrate concentrations used in the assays were 1.0, 2.0, 4.0 and 8.0 mM.

References and Notes

(1) Chen, Y. T.; Seto, C. T. Parallel synthesis of a library of bidentate protein tyrosine phosphatase inhibitors based on the α-ketoacid motif. *Biorg. Med. Chem.* **2004**, *12*, 3289-3298.

(2) Critton, D.A., Tortajada, A., Stetson, G., Peti, W., Page, R. Structural basis of substrate recognition by Hematopoietic Tyrosine Phosphatase (HePTP). *Biochemistry* **2008**, *47*, 13336-13345.