

Supplementary Information

Direct sequential C-H iodination/organoyl-thiolation for benzenoid A-ring modification of quinonoid deactivated systems: A new protocol for potent trypanocidal quinones

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General experimental details

Starting materials obtained from commercial suppliers were used as received unless otherwise stated. For reagents requiring purification standard laboratory techniques according to methods published by Perrin, Armarego, and Perrin (Pergamon Press, 1966) were employed. Catalytic reactions were run under dry nitrogen or argon; glassware, syringes and needles were either flame dried immediately prior to use or placed in an oven (200 °C) for at least 2 h and allowed to cool either in a desiccator or under nitrogen or argon; liquid reagents, solutions or solvents were added via syringe through rubber septa; solid reagents were added inside a glovebox. Flash column chromatography (FCC) was performed using silica gel (Aldrich 40-63 μm , 230-400 mesh). Thin layer chromatography (TLC) was performed using aluminium backed 60 F254 silica plates. Visualization was achieved by UV fluorescence. Proton nuclear magnetic resonance spectra (NMR) were recorded using Bruker DRX 400 or Bruker AVANCE 400. ^{13}C NMR spectra were recorded at 100 MHz as stated. Chemical shifts (δ) are given in parts per million (ppm). Peaks are described as singlets (s), doublets (d), double doublets (dd), triplets (t), double triplets (dt), and multiplets (m). ^1H and ^{13}C NMR spectra were referenced to the appropriate residual solvent peak or TMS peak. Coupling constants (J) were quoted to the nearest 0.5 Hz. All assignments of NMR spectra were based on 2D NMR data (HSQC and HMBC). Mass spectra were recorded using a Brüker Daltonics FT-ICRMS Apex 4e 7.0T FT-MS (ESI⁺ mode) and Shimadzu GCMS QP2010+ (EI⁺ mode). Infrared spectra were recorded on a Perkin Elmer Spectrum One FTIR spectrometer as thin films or solids compressed on a diamond plate. IR bands ($\bar{\nu}$, cm^{-1}) are described as strong (s), medium (m) and weak (w). Melting points were determined using Stuart SMP30 melting point apparatus and are uncorrected.

Mechanistic Studies:

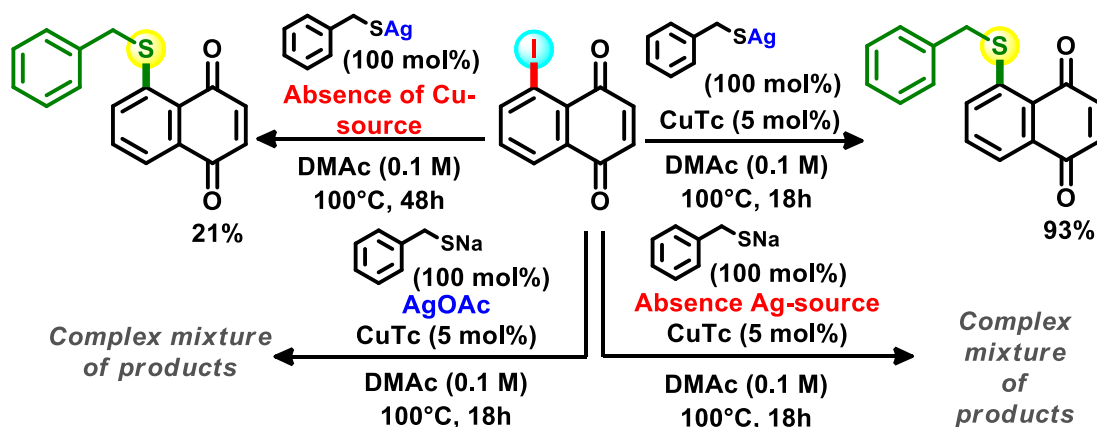
General procedure for the synthesis of Me₄NSCF₃:¹

The original procedure was used with minor modifications. 343 mg of elemental sulfur (10.7 mmol) was dissolved in 80 mL of THF at room temperature under inert atmosphere, followed by the addition of 1.9 mL of trifluoromethyltrimethylsilane (1.83 g, 12.9 mmol). The solution was subsequently cooled to -60 °C and 1.00 g of tetramethylammonium fluoride (10.7 mmol) was added under argon flow to the stirred mixture. The reaction was stirred for 13 h, while allowing it to warm to room temperature. An off-white to orange solid was subsequently filtered and washed with THF (30 mL) and diethyl ether (30 mL). The obtained solid was suspended in minimum amount of acetonitrile, filtered, washed with THF (30 mL) and diethyl ether (30 mL) and dried in vacuo. Me₄NSCF₃ was obtained (1.50 g, 80% yield) as a white powder. **m.p.** (°C) = 153.8-155.1, 194.2-194.9 (Et₂O/CH₃CN).

General procedure for the synthesis of sodium phenylmethanethiolate:²

The original procedure was used with minor modifications. A solution of phenylmethanethiol (4.84 g, 39.0 mmol) in 5.0 mL of Et₂O was added to a stirring suspension of sodium (0.45 g, 19.5 mmol) in 20 mL of Et₂O. Stirring was continued until sodium could no longer be seen. The white solid product was filtered and washed with hexane to remove phenylmethanethiol and dried under reduced pressure to give sodium phenylmethanethiolate (2.56 g, 90% yield) as a white powder. **m.p.** (°C) = 70.8-72.1 (EtOH).

Experiments in the presence and absence of Cu and Ag for preparing 4a:



Synthesis of substrates and known compounds:

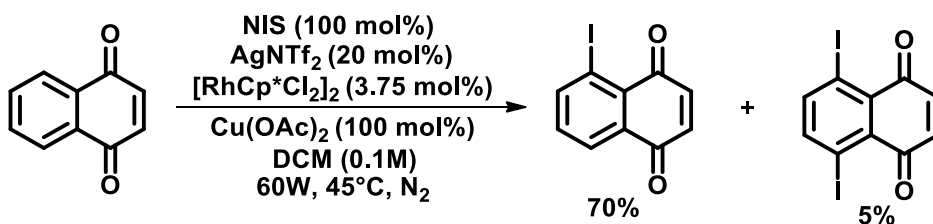
Compounds 1a-1g have already been described within Ref. 3

All commercially available naphthoquinones and further commercial chemicals were purchased from Sigma Aldrich, Alfa Aesar, Strem Chemicals and Santa Cruz Biotechnology. $[\text{RhCp}^*\text{Cl}_2]_2$ and copper 2-thiophene carboxylate (CuTc) were purchased from Sigma Aldrich.

General microwave procedure for the iodination reactions³:

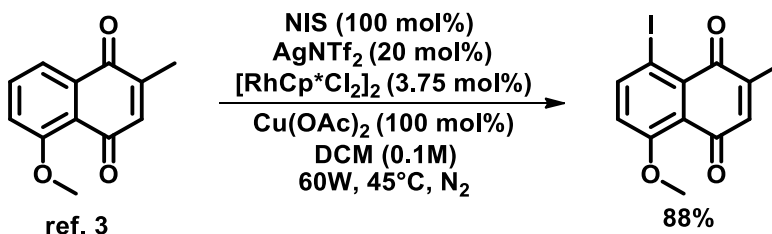
In a glovebox, an oven dried re-sealable reaction tube was charged with the corresponding naphthoquinone (0.10 mmol), $[\text{RhCp}^*\text{Cl}_2]_2$ (2.3 mg, 3.75 mol%), silver bis(trifluoromethanesulfonyl)imide (7.8 mg, 20 mol%), *N*-iodosuccinimide (22.5 mg, 100 mol%, 0.10 mmol) and anhydrous copper acetate (18.2 mg, 100 mol %, 0.10 mmol). The tube was removed from the glovebox and an inert atmosphere was maintained. Anhydrous CH_2Cl_2 (1.0 mL) was added via syringe and the tube was sealed. The mixture was irradiated in a CEM Discover microwave apparatus in open flask mode (60 W) and the nitrogen flow was adjusted to maintain a reaction temperature of 45 °C. After cooling, the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue was purified by FCC, under the conditions noted.

5-Iodo-1,4-naphthoquinone (**1a**) and 5,8-diiodo-1,4-naphthoquinone (**1f**)



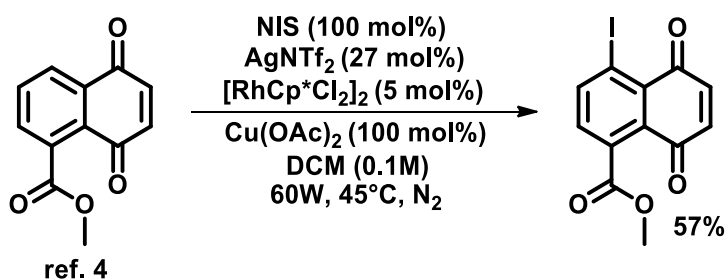
Purification by FCC (toluene) afforded iodinated product **1a** (19.9 mg, 0.70 mmol, 70% yield) as red crystals; ¹H NMR (400 MHz, CDCl₃) δ: 8.36 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 10.3 Hz, 1H), 6.94 (d, *J* = 10.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 183.6, 183.2, 148.2, 139.7, 137.1, 134.3, 133.7, 130.7, 127.6, 92.7. In addition to **1a**, bis-iodinated by-product **1f** (2.0 mg, 5% yield) was obtained as deep red crystals; ¹H NMR (400 MHz, CDCl₃) δ: 7.94 (s, 2H), 6.99 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 182.3, 147.7, 138.0, 133.0, 93.8.

8-Iodo-5-methoxy-2-methyl-1,4-naphthoquinone (**1b**)



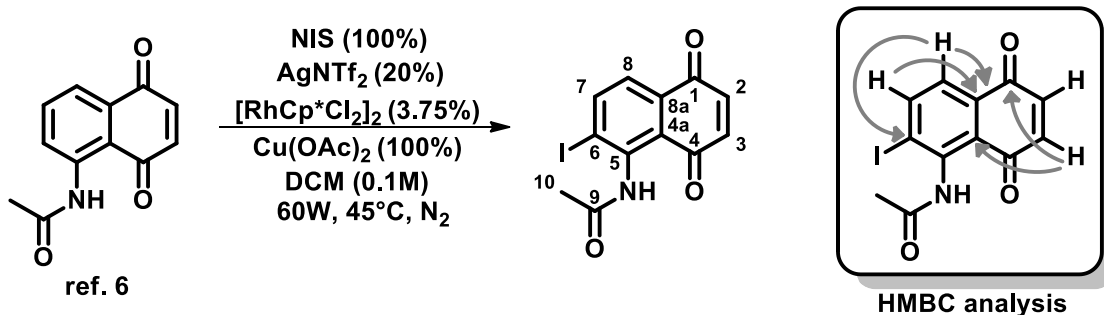
Purification by FCC (toluene/EtOAc 97:3) afforded iodinated product **1b** (28.9 mg, 0.88 mmol, 88% yield) as red crystals; ¹H NMR (400 MHz, CDCl₃) δ: 8.17 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 6.63 (s, 1H), 3.93 (s, 3H), 2.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 184.2, 182.9, 160.1, 148.4, 146.1, 136.4, 132.7, 122.3, 118.6, 81.8, 56.7, 16.3.

5-Iodo-8-methylcarboxylate-1,4-naphthoquinone (**1c**)



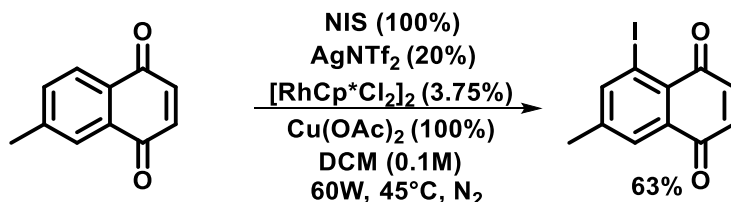
Purification by FCC (toluene) afforded iodinated product **1c** (19.5 mg, 0.57 mmol, 57% yield) as an orange powder; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.42 (d, $J = 8.2$ Hz, 1H), 7.27 (d, $J = 8.2$ Hz, 1H), 7.05 (d, $J = 10.3$ Hz, 1H), 6.95 (d, $J = 10.3$ Hz, 1H), 3.97 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 182.8, 182.4, 169.0, 148.0, 139.4, 137.2, 134.9, 131.9, 131.4, 131.0, 94.1, 53.2.

***N*-(2-Iodo-5,8-dioxo-5,8-dihydro-1-naphthalen-1-yl)acetamide (1d)**



Purification by FCC (toluene) afforded iodinated product **1d** (31.4 mg, 0.92 mmol, 92% yield) as a pale yellow solid; **m.p.** ($^{\circ}\text{C}$) = 203.8-204.9 (Petrol/ CH_2Cl_2); **IR** (solid, cm^{-1}) ν : 2991 (w), 1658 (s), 1223 (m), 780 (m); **HRMS** (EI^+): 340.9521 [M] $^+$. Calcd. for $[\text{C}_{12}\text{H}_8\text{INO}_3]$: 340.9549; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 9.29 (s, N-H), 8.30 (d, $J = 8.2$ Hz, C7-H), 7.69 (d, $J = 8.3$ Hz, C8-H), 6.96 (d, $J = 10.3$ Hz, C2-H), 6.90 (d, $J = 10.3$ Hz, C3-H), 2.28 (s, C10-H₃); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ : 186.55 (C4), 183.84 (C1), 168.68 (C9), 145.54 (C7), 140.29 (C5), 139.77 (C6-I), 139.48 (C3), 137.60 (C2), 132.52 (C8a), 125.56 (C8), 124.6 (C4a) 24.48 (C10).

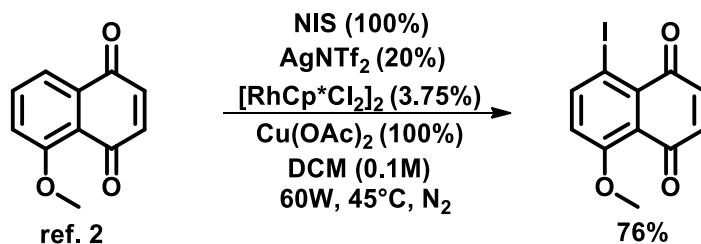
5-Iodo-7-methyl-1,4-naphthoquinone (1e)



Purification by FCC (toluene) afforded iodinated product **1e** (18.8 mg, 0.63 mmol, 63% yield) as a deep orange powder; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ : 8.17 (d, $J = 1.8$ Hz, 1H), 7.92 (d, $J = 1.8$ Hz, 1H), 6.97 (d, $J = 10.3$ Hz, 1H), 6.89 (d, $J = 10.3$ Hz, 1H), 2.42

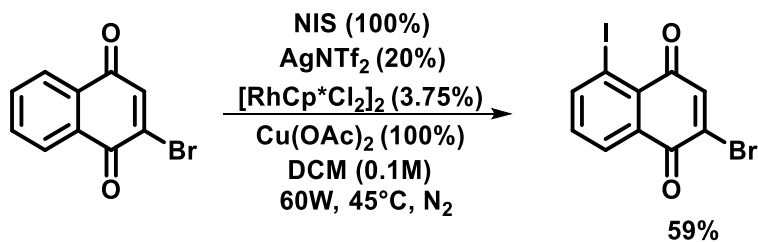
(s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 183.9, 182.9, 148.6, 145.1, 139.8, 136.9, 133.9, 128.4, 128.2, 93.0, 21.1.

5-Iodo-8-methoxy-1,4-naphthoquinone (**1g**)



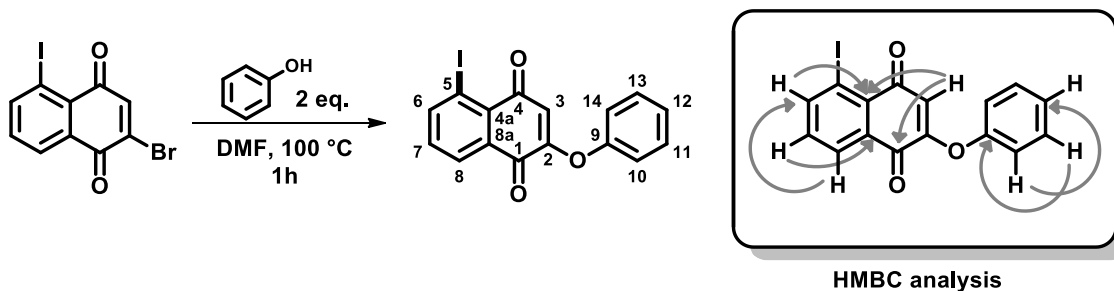
Purification by FCC (toluene) afforded iodinated product **1g** (23.9 mg, 0.76 mmol, 76% yield) as red crystals; ^1H NMR (400 MHz, CDCl_3) δ : 8.27 (d, $J = 9.0$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 1H), 6.91 (d, $J = 10.2$ Hz, 1H), 6.82 (d, $J = 10.2$ Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 183.6, 183.3, 160.4, 148.8, 139.2, 136.9, 132.4, 122.4, 118.8, 81.6, 56.7.

2-Bromo-5-iodo-1,4-naphthoquinone



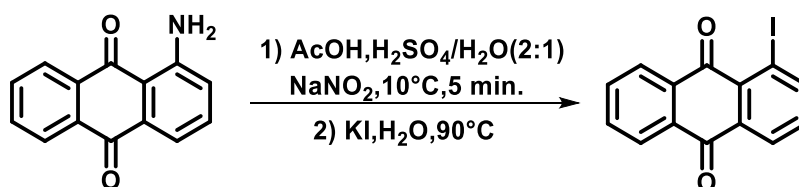
Purification by FCC (toluene) afforded 2-bromo-5-iodo-1,4-naphthoquinone (21.4 mg, 0.59 mmol, 59% yield) as orange crystals; ^1H NMR (400 MHz, CDCl_3) δ : 8.40 (d, $J = 7.2$ Hz, 1H), 8.25 (d, $J = 7.7$ Hz, 1H), 7.55 (s, 1H), 7.38 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 180.5, 177.0, 148.7, 141.2, 137.9, 133.8, 133.6, 130.5, 128.9, 93.3.

5-iodo-2-phenoxy-1,4-naphthoquinone (**1h**)



The product was obtained using a reported procedure, with minor modifications.⁸ To a solution of 2-bromo-5-iodo-1,4-naphthoquinone (72.4 mg, 0.20 mmol) in DMF (1.0 mL) was added phenol (37.6 mg, 0.40 mmol). The reaction was heated at 100 °C and kept under stirring for 1 h. The mixture was then washed with brine (10 mL) and extracted with CH₂Cl₂ (10 mL). The organic phase was dried with Na₂SO₄ and submitted to purification by FCC (toluene) affording product **1h** (48.1 mg, 0.13 mmol, 64% yield) as an orange solid; **m.p.** (°C) = 166.9-167.3 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2920 (w), 1648 (s), 1113 (s), 804 (s); **MS (EI⁺)**: 375.9 [M]⁺. Cald. for [C₁₆H₉IO₃]: 375.9; **¹H NMR (400 MHz, CDCl₃)** δ : 8.38 (dd, *J* = 7.7, 1.1 Hz, C6-H), 8.28 (dd, *J* = 7.7, 1.1 Hz, C8-H), 7.46 (t, *J* = 7.9 Hz, C7-H, C12-H), 7.38 – 7.30 (m, C11-H, C13-H), 7.13 (d, *J* = 7.7 Hz, C10-H, C14-H), 6.02 (s, C3-H). **¹³C NMR (100 MHz, CDCl₃)** δ : 183.2 (C4), 179.3 (C1), 159.3 (C2), 152.8 (C8a), 149.0 (C6), 148.2 (C9), 133.5 (C11), 130.7 (C7,C4a), 128.1 (C8), 127.5 (C12), 126.9 (C13), 121.2 (C10,C14), 114.7 (C3), 92.5 (C5).

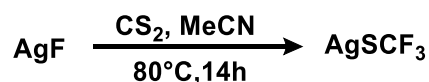
1-Iodoanthracene-9,10-dione (**1i**)⁹



To a solution of 1.00 g (2.99 mmol) of 1-aminoanthracene-9,10-dione in 30 mL of diluted H₂SO₄ (16 mL of concentrated H₂SO₄ and 8.0 mL of water), AcOH (20 mL) was gradually added. The solution was filtered to remove precipitated solids and 80 mL of water was added. The solution was cooled to 10 °C and diazotized with a solution of 600 mg of NaNO₂ in 1 mL of water. The diazonium solution was quickly poured into a

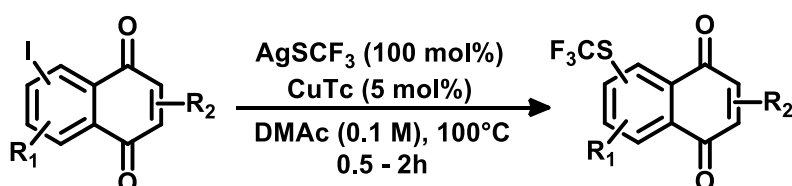
solution of 3.00 g of KI in 80 mL of water at 90 °C and vigorously stirred. The precipitate formed was filtered, washed with water and dried. Purification by FCC (toluene/EtOAc 3:1) afforded iodinated product **1i** (1.10 g, 3,30 mmol, 72% yield) as a deep orange solid; ¹H NMR (400 MHz, CDCl₃) δ: 8.41 (q, *J* = 7.8 Hz, 2H), 8.33 (d, *J* = 7.2 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.39 (t, *J* = 7.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 182.1, 181.7, 148.9, 136.1, 134.8, 134.2, 134.1, 134.0, 132.8, 132.5, 128.6, 128.0, 127.00, 93.4.

Synthesis of AgSCF₃¹⁰



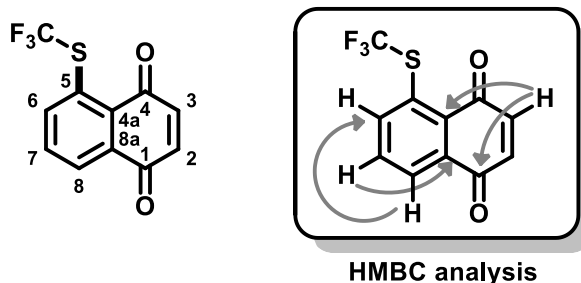
To an oven dried 30 mL Schlenk flask equipped with a stir bar 2.50 g (19,7 mmol) of dry AgF was added. The flask was evacuated and refilled with Argon (three times) until inert atmosphere was achieved. 15 mL of dry MeCN was injected into the flask followed by 2.5 mL of CS₂. The flask was then placed into a pre-heated at 80 °C oil bath with efficient stirring. After 14 h, the reaction mixture was black, and the mixture was allowed to cool to room temperature. MeCN and the excess of CS₂ were removed under reduced pressure with the aid of a rotary evaporator to produce a black residue, which was then dissolved in EtOAc and filtered through a pad of celite. The solvent was once again removed under reduced pressure and the resulting yellow solid was dissolved in a minimum amount of MeCN to produce a clear yellow solution. 30 mL of Et₂O was carefully layered on top of the yellow solution. The flask was placed in a freezer set to -10°C for 24 h to produce off-white crystals. The crystals were collected by filtration, dried under reduced pressure, affording AgSCF₃ (1.25 g, 5.98 mmol, 90%). **m.p.** (°C) = 224.8-225.9 (degrades) (Et₂O/CH₃CN).

General procedure for the trifluoromethylthiolation reactions:



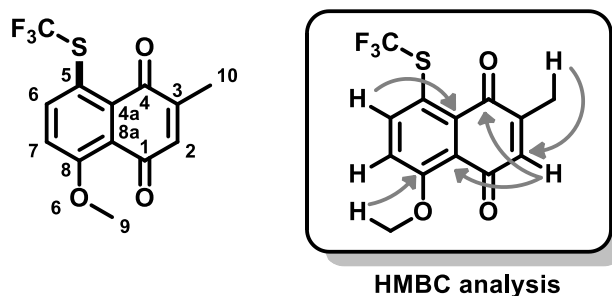
An oven dried re-sealable reaction tube was charged with the corresponding iodinated quinone (0.10 mmol), AgSCF₃ (20.8 mg, 0.10 mmol) and CuTc (0.8 mg, 5 mol%). Anhydrous DMAc (1.0 mL) was added and the tube was sealed. The mixture was heated at 100 °C for 0.5 – 2 h. After cooling and solvent removal by reduced pressure, the residue was purified by FCC, under the conditions noted.

5-((Trifluoromethyl)thio)-1,4-naphthoquinone (2a)



The product was obtained by the general trifluoromethylthiolation procedure, described above with a reaction time of 0.5 h. Purification by FCC (toluene) afforded product **2a** (25.8 mg, 0.10 mmol, 100% yield) as yellow crystals; **m.p.** (°C) = 116.3-117.1 (Petrol/CH₂Cl₂); **IR** (solid, cm⁻¹) *v*: 2923 (m), 1657 (s), 1107 (s), 776 (m); **HRMS** (ESI⁺): 259.0028 [M+H]⁺. Cald. for [C₁₁H₆F₃O₂S]⁺: 259.0035; **¹H NMR** (400 MHz, CDCl₃) *δ*: 8.07 (d, *J* = 7.6 Hz, C8-H), 7.97 (d, *J* = 8.2 Hz, C6-H), 7.76 (t, *J* = 8.0 Hz, C7-H), 7.03 (d, *J* = 10.3 Hz, C3-H), 6.99 (d, *J* = 10.3 Hz, C2-H). **¹³C NMR** (100 MHz, CDCl₃) *δ*: 185.6 (C4), 184.0 (C1), 139.1 (C3), 138.0 (C2), 134.0 (C7), 133.8 (C8a), 132.4 (q, *J* = 3.1 Hz, C6), 131.2 (C5), 128.5 (C4a), 128.1 (C-F₃), 125.8 (C8).

8-methoxy-2-methyl-5-((trifluoromethyl)thio)-1,4-naphthoquinone (2b)

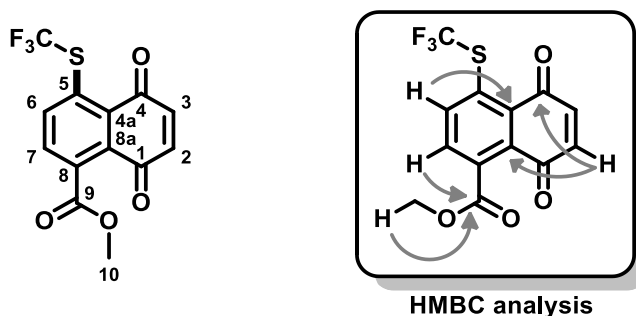


The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 0.5 h. Purification by FCC (toluene) afforded product **2b**

(28.7 mg, 0.95 mmol, 95% yield) as an orange powder; **m.p.** (°C) = 174.4-175.9 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 1645 (s), 1236 (m), 1092 (s), 810 (m); **HRMS (ESI⁺)**: 325.0124 [M+Na]⁺. Cald. for [C₁₃H₉F₃O₃SNa]⁺: 325.0117; **¹H NMR (400 MHz, CDCl₃)** δ : 7.90 (d, *J* = 9.3 Hz, C6-H), 7.35 (d, *J* = 9.3 Hz, C7-H), 6.75 (s, C2-H), 4.03 (s, C9-H₃), 2.16 (s, C10-H₃). **¹³C NMR (100 MHz, CDCl₃)** δ : 186.5 (C4), 183.4 (C1), 158.7 (C8), 145.5 (C3), 137.1 (C2), 133.9 (q, *J* = 3.1 Hz, C6), 131.4 (C4a), 128.2 (C-F₃), 124.4 (q, *J* = 2.2 Hz, C5), 121.2 (C8a), 118.6 (C7), 56.7 (C9), 15.7 (C10).

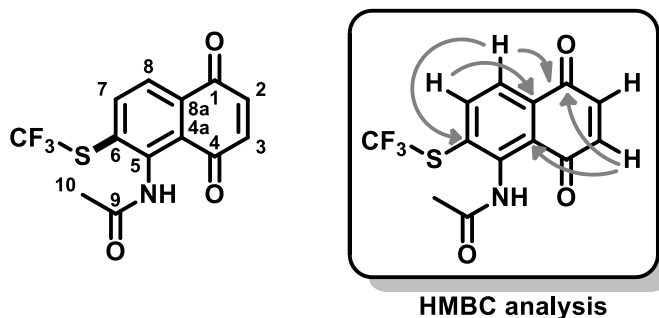
Methyl 1,4-dioxo-5-((trifluoromethyl)thio)-1,4-dihydronaphthalene-8-carboxylate

(2c)



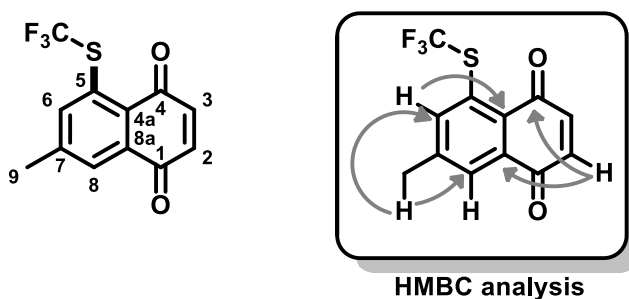
The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 0.5 h. Purification by FCC (toluene) afforded product **2c** (30.0 mg, 0.95 mmol, 95% yield) as a green-yellow solid; **m.p.** (°C) = 85.5-86.3 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2923 (w), 1648 (s), 1113 (s), 807 (s); **HRMS (ESI⁺)**: 338.9904 [M+Na]⁺. Cald. for [C₁₃H₇F₃O₄SNa]⁺: 338.9909; **¹H NMR (400 MHz, CDCl₃)** δ : 7.98 (d, *J* = 8.3 Hz, C6-H), 7.66 (d, *J* = 8.3 Hz, C7-H), 7.04 (d, *J* = 10.3 Hz, C3-H), 6.99 (d, *J* = 10.3 Hz, C2-H), 3.98 (s, C10-H₃). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.0 (C1), 183.1 (C4), 168.8 (C9), 138.6 (C3), 138.2 (C2), 136.2 (C4a), 133.0 (C8a), 132.4 (C7), 131.9 (q, *J* = 3.2 Hz, C6), 131.1 (C8), 128.6 (C5), 127.8 (C-F₃), 53.4 (C10).

N-(1,4-Dioxo-6-((trifluoromethyl)thio)-1,4-dihydronaphthalen-5-yl)acetamide (**2d**)



The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 2.0 h. Purification by FCC (toluene) afforded product **2d** (13.9 mg, 0.44 mmol, 44% yield) as yellow crystals; **m.p.** (°C) = 116.3-117.1 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 3309 (w), 1668 (s), 1651 (s), 1098 (s), 842 (s); **HRMS (ESI⁺)**: 338.0060 [M+Na]⁺. Calcd. for [C₁₃H₈F₃O₃NSNa]⁺: 338.0069; **¹H NMR (400 MHz, CDCl₃)** δ : 10.74 (s, N-H), 8.14 (d, *J* = 8.2 Hz, C7-H), 8.00 (d, *J* = 8.2 Hz, C8-H), 7.01 (d, *J* = 10.3 Hz, C2-H), 6.97 (d, *J* = 10.3 Hz, C3-H), 2.34 (s, C10-H₃). **¹³C NMR (100 MHz, CDCl₃)** δ : 187.9 (C4), 183.5 (C1), 170.2 (C9), 140.5 (q, *J* = 1.1 Hz, C7), 140.4 (C6), 139.9 (C3), 138.0 (C2), 133.4 (C8a), 130.1 (C5), 127.7 (C-F₃), 123.8 (C8), 121.7 (C4a), 24.2 (C10).

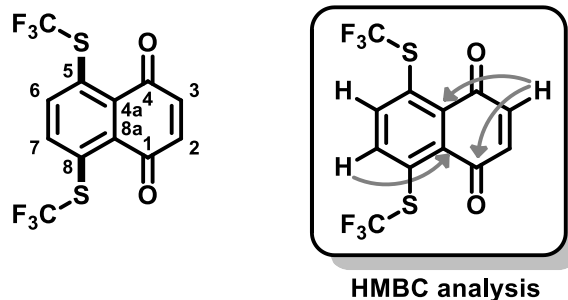
7-methyl-5-((trifluoromethyl)thio)-1,4-naphthoquinone (**2e**)



The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 1.0 h. Purification by FCC (toluene) afforded product **2e** (23.7 mg, 0.95 mmol, 95% yield) as yellow crystals; **m.p.** (°C) = 122.1-123.5 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 1645 (s), 1334 (m), 1107 (s), 842 (m); **¹H NMR (400 MHz, CDCl₃)** δ : 7.89 (s, C8-H), 7.76 (s, C6-H), 7.01 (d, *J* = 10.3 Hz, C3-H), 6.97 (d, *J* = 10.3 Hz, C2-H), 2.56 (s, C9-H₃). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.3 (C4),

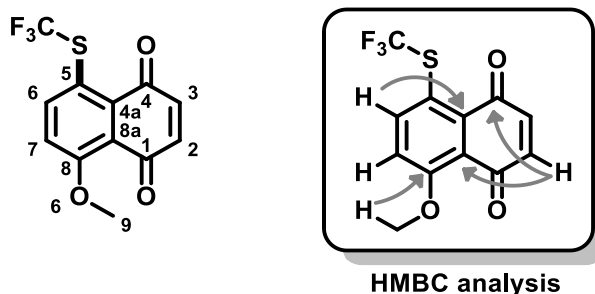
184.4 (C1), 145.6 (C7), 139.2 (C3), 137.8 (C2), 134.0 (q, $J = 2.3$ Hz, C5), 133.6 (C8a), 132.7 (q, $J = 3.4$ Hz, C6), 128.1 (C-F₃), 126.6 (C8), 126.3 (C4a), 22.4 (C9).

5,8-Bis((trifluoromethyl)thio)-1,4-naphthoquinone (2f)



The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 1.0 h. Purification by FCC (toluene) afforded product **2f** (28.3 mg, 0.79 mmol, 79% yield) as orange crystals; **m.p.** (°C) = 132.5-133.9 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 1645 (s), 1337 (w), 1069 (s), 750 (m); **HRMS (ESI⁺)**: 358.9626 [M+H]⁺. Cald. for [C₁₂H₅F₆O₂S₂]⁺: 358.9630; **¹H NMR (400 MHz, CDCl₃)** δ : 8.00 (s, C6-H, C7-H), 7.09 (s, C2-H, C3-H). **¹³C NMR (100 MHz, CDCl₃)** δ : 184.6 (C1, C4), 137.8 (C2, C3), 133.8 (q, $J = 2.2$ Hz, C5, C8), 131.7 (q, $J = 3.0$ Hz, C6, C7), 129.5 (C4a, C8a), 127.6 (C-F₃).

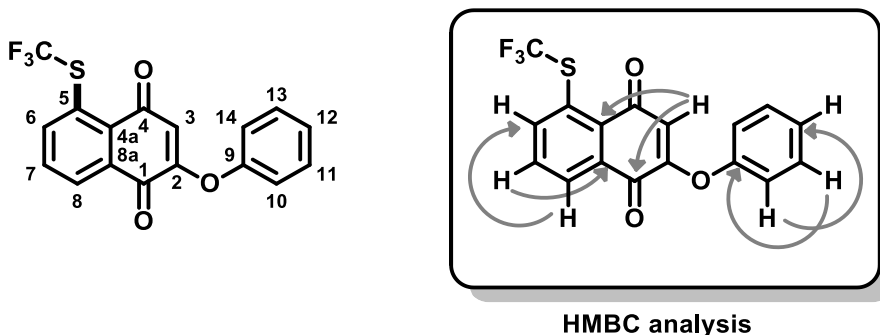
8-Methoxy-5-((trifluoromethyl)thio)-1,4-naphthoquinone (2g)



The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 0.5 h. Purification by FCC (toluene) afforded product **2g** (26.5 mg, 0.92 mmol, 92% yield) as an orange solid; **m.p.** (°C) = 142.3-143.9 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2926 (w), 1648 (s), 1113 (s), 807 (m); **HRMS (ESI⁺)**: 289.0134 [M+H]⁺. Cald. for [C₁₂H₈F₃O₃S]⁺: 289.0141; **¹H NMR (400 MHz, CDCl₃)** δ : 7.84 (d, $J = 9.3$ Hz, C6-H), 7.29 (d, $J = 9.3$ Hz, C7-H), 6.84 (d, $J = 10.2$ Hz,

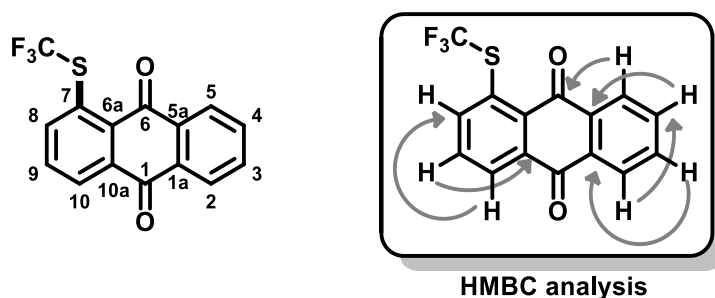
C2-H), 6.79 (d, $J = 10.2$ Hz, C3-H), 3.95 (s, C9-H₃). ¹³C NMR (100 MHz, CDCl₃) δ : 185.7 (C4), 183.4 (C1), 159.0 (C8), 139.9 (C3), 136.1 (C2), 134.3 (q, $J = 3.3$ Hz, C6), 131.3 (C5), 128.2 (C-F₃), 124.4 (C8a), 121.0 (C4a), 118.8 (C7), 56.8 (C9).

2-Phenoxy-5-((trifluoromethyl)thio)-1,4-naphthoquinone (2h)



The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 0.5 h. Purification by FCC (toluene) afforded product **2h** (32.9 mg, 0.94 mmol, 94% yield) as a yellow solid; **m.p.** (°C) = 100.9-101.3 (Petrol/CH₂Cl₂); **IR** (solid, cm⁻¹) ν : 2923 (w), 1645 (s), 1113 (s), 854 (m); **HRMS** (ESI⁺): 373.0104 [M+Na]⁺. Cald. for [C₁₇H₉F₃O₃SNa]⁺: 373.0117; **¹H NMR** (400 MHz, CDCl₃) δ : 8.17 (d, $J = 8.2$ Hz, C8-H), 7.96 (d, $J = 8.2$ Hz, C6-H), 7.74 (t, $J = 8.2$ Hz, C7-H), 7.47 (t, $J = 7.9$ Hz, C11-H, C13-H), 7.33 (t, $J = 7.5$ Hz, C12-H), 7.13 (d, $J = 7.7$ Hz, C10-H, C14-H), 5.98 (s, C3-H). ¹³C NMR (100 MHz, CDCl₃) δ : 185.5 (C4), 178.8 (C1), 159.7 (C2), 152.5 (C5), 133.3 (C7), 132.8 (C8a), 132.4 (q, $J = 3.5$ Hz, C6), 130.5 (C11, C13), 127.8 (C4a), 126.8 (C12), 125.8 (C8), 120.9 (C10, C14), 113.4 (C-F₃).

1-((trifluoromethyl)thio)anthracene-9,10-dione (2i)



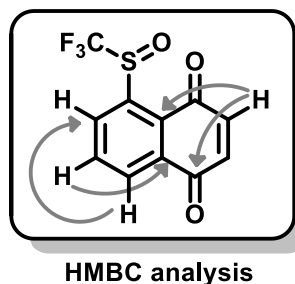
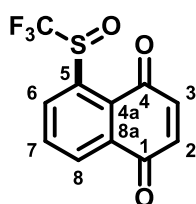
The product was obtained by the general trifluoromethylthiolation procedure described above with a reaction time of 0.5 h. Purification by FCC (toluene) afforded product **2i**

(28.3 mg, 0.92 mmol, 92% yield) as yellow crystals; **m.p.** (°C) = 174.7-175.1 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 1671 (w), 1274 (m), 1098 (s), 698 (s); **HRMS (ESI⁺)**: 331.0011 [M+Na]⁺. Cald. for [C₁₅H₇F₃O₂SNa]⁺: 331.0011; **¹H NMR (400 MHz, CDCl₃)** δ : 8.27 (d, J = 7.5 Hz, C2-H, C5-H, C10-H), 7.99 (d, J = 8.2 Hz, C8-H), 7.84 – 7.75 (m, C3-H, C4-H, C9-H). **¹³C NMR (100 MHz, CDCl₃)** δ : 184.1 (C6), 182.3 (C1), 135.0 (q, J = 2.6 Hz, C7), 134.8 (C3), 134.7 (C4), 134.1 (C9), 133.4 (C10a), 132.7 (C1a), 132.4 (q, J = 3.1 Hz, C8), 131.3 (C5a), 130.0 (C6a), 128.2 (C-F₃), 127.7 (C5), 127.4 (C2), 126.4 (C10).

General procedure for oxidation with MCPBA¹¹

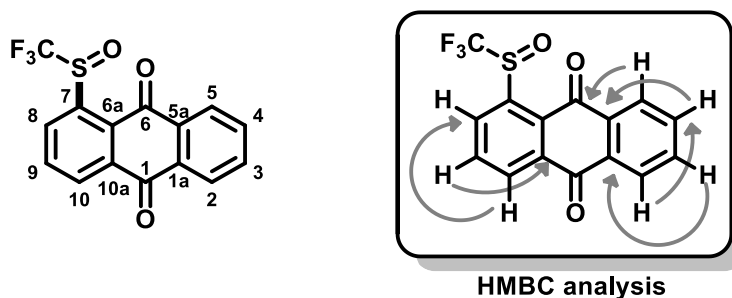
To a solution of the corresponding quinone (0.10 mmol) in CH₂Cl₂ (3.0 mL) was added MCPBA (25.8 mg, 0.15 mmol) at 0°C, under inert atmosphere. The reaction was allowed to warm to room temperature and kept under stirring for 18 h. The mixture was then washed with a saturated solution of NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (10 mL). The organic phase was dried with Na₂SO₄ and submitted to purification by FCC, under the conditions noted.

5-((Trifluoromethyl)sulfinyl)-1,4-naphthoquinone (3a)



Purification by FCC (toluene) afforded product **3a** (20.3 mg, 0.74 mmol, 74% yield) as yellow crystals; **m.p.** (°C) = 101.3-102.5 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2926 (w), 1657 (s), 1300 (m), 1072 (s); **HRMS (ESI⁺)**: 296.9802 [M+Na]⁺. Cald. for [C₁₁H₅F₃O₃SNa]⁺: 296.9804; **¹H NMR (400 MHz, CDCl₃)** δ : 8.60 (d, J = 7.9 Hz, C6-H), 8.35 (d, J = 7.7 Hz, C8-H), 8.08 (t, J = 7.8 Hz, C7-H), 7.09 (d, J = 10.3 Hz, C2-H), 7.05 (d, J = 10.3 Hz, C3-H). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.5 (C4), 183.4 (C1), 140.5 (q, J = 2.8 Hz, C5), 139.3 (C2), 138.2 (C3), 135.0 (C7), 133.2 (C8a), 131.0 (C6), 130.8 (C4a), 130.6 (C8), 123.6 (C-F₃).

1-((trifluoromethyl)sulfinyl)anthracene-9,10-dione (**3b**)

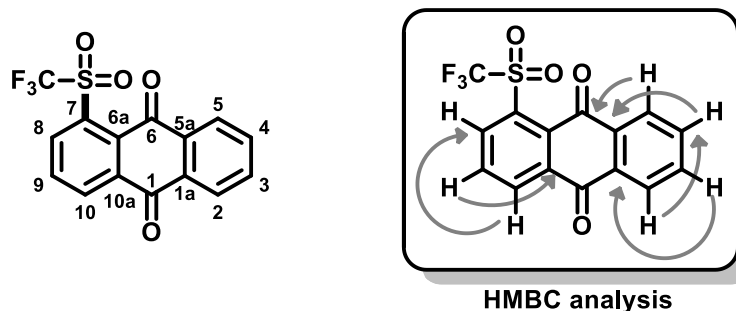


Purification by FCC (toluene) afforded product **3b** (22.7 mg, 0.70 mmol, 70% yield) as yellow crystals; **m.p.** (°C) = 217.9-218.1 (Petrol/CH₂Cl₂); **IR** (solid, cm⁻¹) ν : 2923 (w), 1657 (s), 1303 (m), 1072 (s); **HRMS** (ESI⁺): 346.9972 [M+Na]⁺. Cald. for [C₁₅H₇F₃O₃SNa]⁺: 346.9960; **¹H NMR** (400 MHz, CDCl₃) δ : 8.68 (d, *J* = 7.8 Hz, C8-H), 8.59 (d, *J* = 7.8 Hz, C10-H), 8.34 (dd, *J* = 7.2, 1.8 Hz, C2-H), 8.30 (dd, *J* = 7.2, 1.8 Hz, C5-H), 8.12 (t, *J* = 7.8 Hz, C9-H), 7.92 – 7.84 (m, C3-H, C4-H). **¹³C NMR** (100 MHz, CDCl₃) δ : 183.9 (C6), 181.7 (C1), 141.4 (q, *J* = 2.8 Hz, C7), 135.5 (C9), 135.1 (C4), 135.0 (C3), 133.0 (C10a), 132.5 (C6a), 132.4 (C5a), 131.4 (C10), 131.2 (C8), 127.9 (C2), 127.8 (C5), 127.1 (C1a), 123.7 (C-F₃).

General procedure for oxidation with RuCl₃.H₂O/NaIO₄¹²

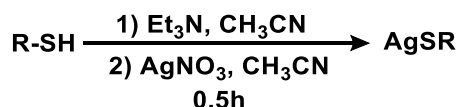
To a solution of the corresponding quinone (0.10 mmol) in H₂O/CH₃CN/CH₂Cl₂ (2:1:1, 4.0 mL) was added RuCl₃.H₂O (1.1 mg, 5 mol%). The mixture was kept under vigorous stirring, and NaIO₄ (63.9 mg, 0.30 mmol) was added. The mixture was allowed to stir for 1 h, washed with a saturated solution of NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (10 mL). The organic phase was dried with Na₂SO₄ and submitted to purification by FCC under the conditions noted.

1-((trifluoromethyl)sulfonyl)anthracene-9,10-dione (**3c**)



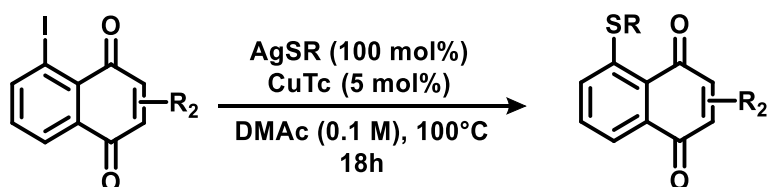
Purification by FCC (toluene) afforded product **3c** (31.3 mg, 0.92 mmol, 92% yield) as yellow crystals; **m.p.** (°C) = 214.9-216.0 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2923 (w), 1685 (m), 1190 (s), 704 (s); **HRMS (ESI⁺)**: 362.9913 [M+Na]⁺. Cald. for [C₁₅H₇F₃O₄SNa]⁺: 362.9909; **¹H NMR (400 MHz, CDCl₃)** δ : 8.77 (dd, *J* = 7.9, 1.0 Hz, C10-H), 8.73 (dd, *J* = 7.9, 1.0 Hz, C8-H), 8.37 – 8.31 (m, C2-H), 8.32 – 8.26 (m, C5-H), 8.06 (t, *J* = 7.9 Hz, C9-H), 7.93 – 7.81 (m, 2H). **¹³C NMR (100 MHz, CDCl₃)** δ : 181.2 (C6), 180.9 (C1), 138.5 (C8), 136.1 (C10a), 135.3 (C4), 135.1 (C3), 134.8 (C10), 134.7 (C6a), 134.1 (C9), 133.6 (C5a), 132.2 (C1a), 128.2 (C2), 127.5 (C5), 122.6 (C7), 119.1 (C-F₃).

General procedure for the synthesis of AgSR salts:¹³



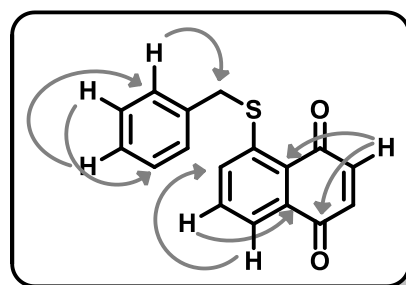
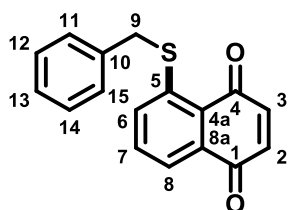
A 50 mL round bottom flask was charged with the corresponding thiol (2.00 mmol), EtN₃ (2.00 mmol, 279 μ L) and acetonitrile (5.0 mL). The mixture was stirred and a solution of AgNO₃ (339.7 mg, 2.00 mmol) in acetonitrile (10 mL) was added dropwise. The suspension was stirred for 30 min under vigorous stirring, and the resulting solid was filtered, washed with acetonitrile (30 mL) and dried under reduced pressure. Yields for all AgSR salts were quantitative.

General procedure for the thiolation reactions:



An oven dried re-sealable reaction tube was charged with the corresponding iodinated quinone (0.10 mmol), AgSR salt (0.10 mmol) and CuTc (0.8 mg, 5 mol %). Anhydrous DMAc (1.0 mL) was added and the tube was sealed. The mixture was heated at 100 °C for 18 h. After cooling and solvent removal by reduced pressure, the residue was purified by FCC, under the conditions noted.

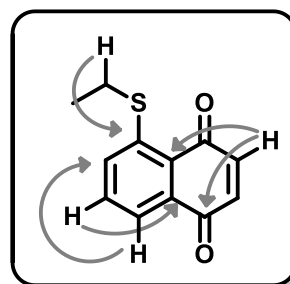
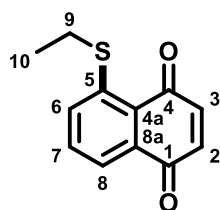
5-(Benzylthio)-1,4-naphthoquinone (4a)



HMBC analysis

The product was obtained by the general thiolation procedure described above. (Benzylthio)silver (23.1 mg, 0.10 mmol) was used. Purification by FCC (toluene) afforded product **4a** (26.0 mg, 0.93 mmol, 93% yield) as red crystals; **m.p.** (°C) = 183.9-185.1 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 3053 (w), 1648 (m), 1136 (s), 773 (s); **¹H NMR (400 MHz, CDCl₃)** δ : 7.88 (d, J = 7.3 Hz, C8-H), 7.66 (d, J = 8.0 Hz, C6-H), 7.59 (t, J = 7.8 Hz, C7-H), 7.45 (d, J = 7.3 Hz, C11-H, C15-H), 7.34 (t, J = 7.3 Hz, C10-H, C14-H), 7.31 – 7.26 (m, C13-H), 6.96 (d, J = 10.2 Hz, C3-H), 6.90 (d, J = 10.2 Hz, C2-H), 4.23 (s, C9-H₂). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.5 (C4), 185.1 (C1), 144.78 (C5), 139.9 (C3), 137.0 (C2), 135.6 (C10), 134.0 (C8a), 133.1 (C7), 130.2 (C6), 129.3 (C11, C15), 129.0 (C12, C14), 127.9 (C13), 127.5 (C4a), 123.2 (C8), 37.28 (C9).

5-(Ethylthio)-1,4-naphthoquinone (4b)

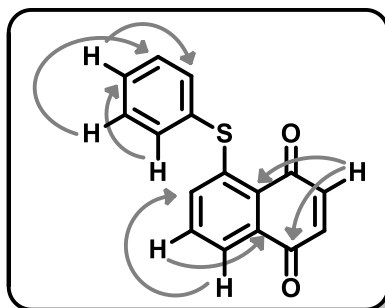
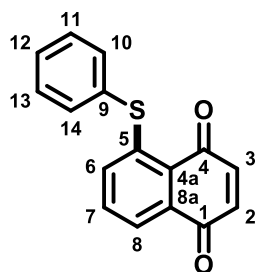


HMBC analysis

The product was obtained by the general thiolation procedure described above. (Ethylthio)silver (16.9 mg, 0.10 mmol) was used. Purification by FCC (toluene) afforded product **4b** (13.3 mg, 0.61 mmol, 61% yield) as a red solid; **m.p.** (°C) = 140.5-142.0 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2932 (m), 1648 (m), 1291 (s), 773 (s); **¹H NMR (400 MHz, CDCl₃)** δ : 7.87 (dd, J = 5.8, 2.6 Hz, C8-H), 7.66 – 7.58 (m, C6-H, C7-H), 6.96 (d, J = 10.2 Hz, C3-H), 6.90 (d, J = 10.2 Hz, C2-H), 3.01 (q, J = 7.4 Hz,

C9-H₂), 1.44 (t, $J = 7.4$ Hz, C10-H₃). ¹³C NMR (100 MHz, CDCl₃) δ : 185.5 (C4), 185.1 (C1), 145.1 (C5), 140.1 (C3), 136.9 (C2), 134.1 (C8a), 133.0 (C7), 129.9 (C6), 127.5 (C4a), 122.9 (C8), 26.0 (C9), 13.1 (C10).

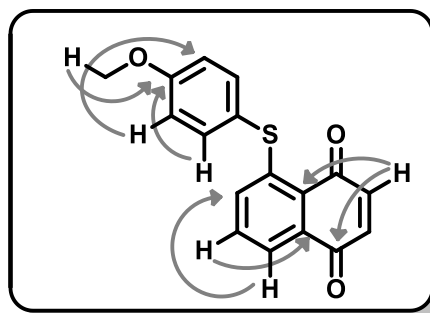
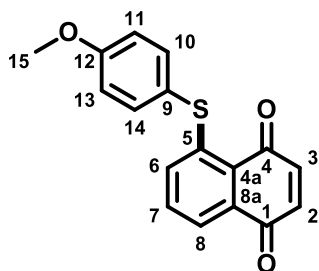
5-(Phenylthio)-1,4-naphthoquinone (4c)



HMBC analysis

The product was obtained by the general thiolation procedure described above. (Phenylthio)silver (21.7 mg, 0.10 mmol) was used. Purification by FCC (toluene) afforded product **4c** (25.8 mg, 0.97 mmol, 97% yield) as a red solid; **m.p.** (°C) = 157.3-158.0 (Petrol/CH₂Cl₂); **IR** (solid, cm⁻¹) ν : 2926 (m), 1636 (m), 1133 (s), 744 (s); **HRMS** (ESI⁺): 267.0470 [M+H]⁺. Cald. for [C₁₅H₁₁O₂S]⁺: 267.0474; **¹H NMR** (400 MHz, CDCl₃) δ : 7.84 (d, $J = 7.5$ Hz, C8-H), 7.60 (m, C10-H, C14-H), 7.54 – 7.44 (m, C11-H, C12-H, C13-H), 7.39 (t, $J = 7.9$ Hz, C7-H), 7.11 – 6.97 (m, C3-H, C6-H), 6.94 (d, $J = 10.3$ Hz, C2-H). ¹³C NMR (100 MHz, CDCl₃) δ : 185.5 (C4), 185.0 (C1), 146.0 (C5), 139.9 (C3), 137.3 (C2), 136.3 (C10, C14), 133.7 (C8a), 132.9 (C7), 131.9 (C6), 131.5 (C9), 130.3 (C11, C13), 130.1 (C12), 126.8 (C4a), 123.7 (C8).

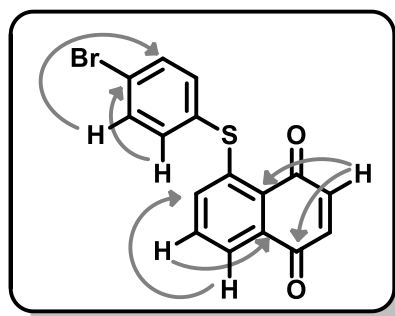
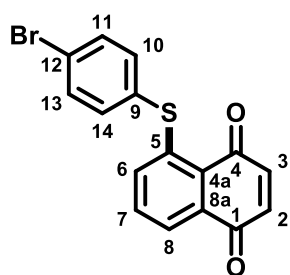
5-((*para*-Methoxyphenyl)thio)-1,4-naphthoquinone (4d)



HMBC analysis

The product was obtained by the general thiolation procedure described above. ((4-Methoxyphenyl)thio)silver (24.7 mg, 0.10 mmol) was used. Purification by FCC (toluene) afforded product **4d** (28.1 mg, 0.95 mmol, 95% yield) as a red solid; **m.p.** (°C) = 165.0-166.0 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2920 (w), 1651 (m), 1245 (s), 779 (s); **HRMS (ESI⁺)**: 319.0393 [M+Na]⁺. Calcd. for [C₁₇H₁₂O₃SNa]⁺: 319.0399; **¹H NMR (400 MHz, CDCl₃)** δ : 7.83 (d, *J* = 7.5 Hz, C8-H), 7.50 (d, *J* = 8.7 Hz, C10-H, C14-H), 7.39 (t, *J* = 7.9 Hz, C7-H), 7.08 – 6.97 (m, C3-H, C6-H, C11-H, C13-H), 6.93 (d, *J* = 10.3 Hz, C2-H), 3.87 (s, C15-H₃). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.5 (C4), 185.1 (C1), 161.3 (C12), 147.1 (C5), 139.9 (C3), 137.9 (C10, C14), 137.3 (C2), 133.7 (C8a), 132.8 (C7), 131.7 (C6), 126.6 (C4a), 123.5 (C8), 121.9 (C9), 115.9 (C11, C13), 55.7 (C15).

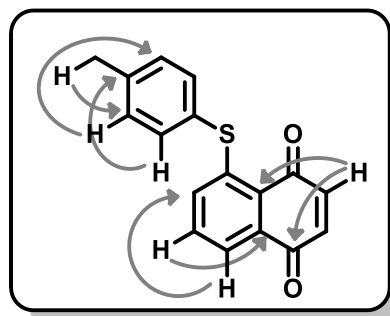
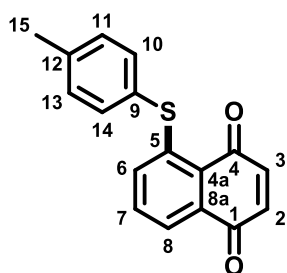
5-((*para*-Bromophenyl)thio)-1,4-naphthoquinone (**4e**)



HMBC analysis

The product was obtained by the general thiolation procedure described above. ((4-Bromophenyl)thio)silver (29.6 mg, 0.10 mmol) was used. Purification by FCC (toluene) afforded product **4e** (34.5 mg, 0.10 mmol, 100% yield) as a red solid; **m.p.** (°C) = 178.9-179.6 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 1645 (m), 1334 (m), 1265 (m), 779 (m); **HRMS (ESI⁺)**: 344.9595 [M+H]⁺. Calcd. for [C₁₆H₁₀BrO₂S]⁺: 344.9579; **¹H NMR (400 MHz, CDCl₃)** δ : 7.86 (d, *J* = 8.3 Hz, C8-H), 7.61 (d, *J* = 8.4 Hz, C10-H, C14-H), 7.47 – 7.41 (m, C7-H, C11-H, C13-H), 7.05 - 7.03 (m, C3-H, C6-H), 6.95 (d, *J* = 10.3 Hz, C2-H). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.5 (C4), 184.9 (C1), 145.1 (C5), 139.8 (C3), 137.8 (C11, C13), 137.4 (C2), 133.7 (C8a), 133.5 (C10, C14), 133.1 (C7), 131.7 (C6), 130.8 (C12), 126.9 (C4a), 124.9 (C9), 123.9 (C8).

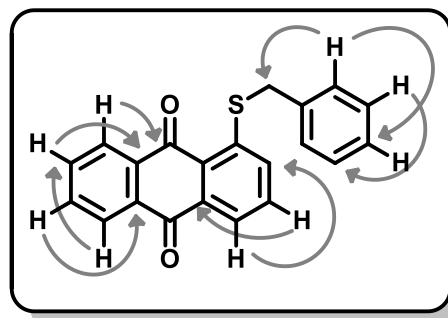
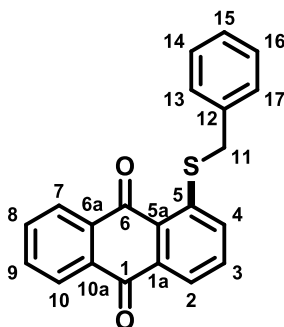
5-((*para*-Methylphenyl)thio)-1,4-naphthoquinone (**4f**)



HMBC analysis

The product was obtained by the general thiolation procedure described above. ((4-Methoxyphenyl)thio)silver (24.7 mg, 0.10 mmol,) was used. Purification by FCC (toluene) afforded product **4f** (27.7 mg, 0.99 mmol, 99% yield) as a red solid; **m.p.** (°C) = 162.4-163.1 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2909 (w), 1645 (m), 1334 (s), 782 (m); **HRMS (ESI⁺)**: 281.0626 [M+H]⁺. Cald. for [C₁₇H₁₃O₂S]⁺: 281.0631; **¹H NMR (400 MHz, CDCl₃)** δ : 7.83 (d, *J* = 8.2 Hz, C8-H), 7.47 (d, *J* = 8.0 Hz, C10-H, C14-H), 7.39 (t, *J* = 7.9 Hz, C7-H), 7.29 (d, *J* = 7.9 Hz, C11-H, C13-H), 7.10 – 6.96 (m, C3-H, C6-H), 6.93 (d, *J* = 10.3 Hz, C2-H), 2.43 (s, C15-H₃). **¹³C NMR (100 MHz, CDCl₃)** δ : 185.5 (C4), 185.1 (C1), 146.5 (C5), 140.4 (C12), 139.9 (C3), 137.3 (C2), 136.3 (C10, C14), 133.7 (C8a), 132.8 (C7), 131.8 (C6), 131.1 (C11, C13), 127.9 (C9), 126.7 (C4a), 123.6 (C8), 21.6 (C15).

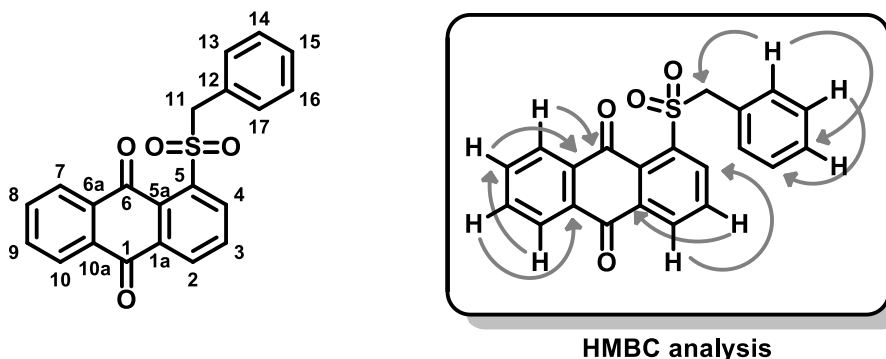
1-(benzylthio)anthracene-9,10-dione (**4g**)



HMBC analysis

The product was obtained by the general thiolation procedure described above. (Benzylthio)silver (23.1 mg, 0.10 mmol) was used. Purification by FCC (toluene) afforded product **4g** (30.0 mg, 0.91 mmol, 91% yield) as a light orange solid; **m.p.** (°C) = 250.7-251.1 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 2923 (m), 1668 (m), 1271 (m), 704 (s); **HRMS (ESI⁺)**: 331.0781 [M+H]⁺. Calcd. for [C₂₁H₁₅O₂S]⁺: 331.0787; **¹H NMR (400 MHz, CDCl₃)** δ : 8.31 (dd, J = 7.4, 1.4 Hz, C7-H), 8.27 (dd, J = 7.4, 1.4 Hz, C10-H), 8.13 (d, J = 7.8 Hz, C2-H), 7.82 – 7.71 (m, C8-H, C9-H, C15-H), 7.65 (t, J = 7.8 Hz, C3-H), 7.48 (d, J = 7.2 Hz, C13-H, C17-H), 7.35 (t, J = 7.3 Hz, C14-H, C16-H), 7.30 (d, J = 7.2 Hz, C4-H), 4.26 (s, C11-H₂). **¹³C NMR (100 MHz, CDCl₃)** δ : 183.8 (C6), 183.3 (C1), 145.5 (C5), 135.7 (C13), 135.3 (C1a), 134.7 (C10a), 134.6 (C9), 134.2 (C17), 133.9 (C8), 133.3 (C3), 132.8 (C6a), 130.3 (C15), 130.0 (C12), 129.4 (C14), 129.0 (C16), 128.9 (C5a), 127.8 (C7), 127.7 (C4), 127.1 (C10), 123.8 (C2), 37.7 (C11).

1-(benzylsulfonyl)anthracene-9,10-dione (**5**)



The product was obtained by the general procedure for oxidation with RuCl₃.H₂O/NaIO₄ described above. Purification by FCC (toluene) afforded product **5** (32.2 mg, 0.89 mmol, 89% yield) as a yellow solid; **m.p.** (°C) = 241.3-242.1 (Petrol/CH₂Cl₂); **IR (solid, cm⁻¹)** ν : 1680 (m), 1303 (s), 1110 (m), 692 (s); **HRMS (ESI⁺)**: 363.0680 [M+H]⁺. Calcd. for [C₂₁H₁₅O₄S]⁺: 363.0686; **¹H NMR (400 MHz, CDCl₃)** δ : 8.55 (d, J = 8.9 Hz, C10-H), 8.36 (d, J = 8.7 Hz, C7-H), 8.29 (d, J = 7.0 Hz, C2-H), 8.18 (d, J = 6.8 Hz, C4-H), 7.93 – 7.82 (m, C8-H, C9-H), 7.73 (t, J = 7.8 Hz, C3-H), 7.40 – 7.31 (m, C13-H, C17-H), 7.28 – 7.26 (m, C14-H, C15-H, C16-H), 5.27 (s, C11-H₂). **¹³C NMR (100 MHz, CDCl₃)** δ : 183.6 (C6), 182.0 (C1), 140.1 (C5), 138.1 (C8), 135.7 (C1a), 134.7 (C9), 134.6 (C10a), 134.3 (C6a), 133.3 (C3), 132.6 (C10), 132.4 (C5a), 131.3 (C13, C17), 129.1 (C15), 128.9 (C14, C16), 128.5 (C12), 128.0 (C7), 127.3 (C2), 62.6 (C11).

Trypanocidal and cytotoxicity assays

Direct effect on Trypanosoma cruzi

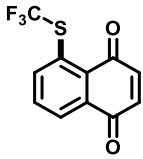
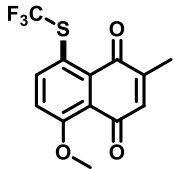
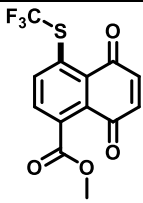
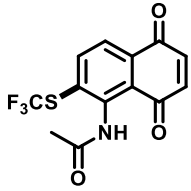
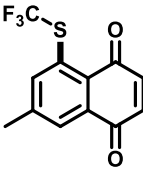
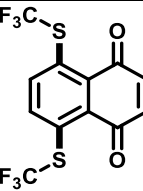
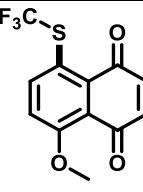
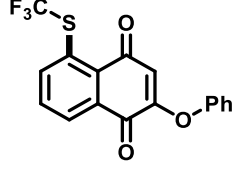
Bloodstream trypomastigotes (Y strain) were obtained at the peak of parasitaemia from infected albino mice, isolated by differential centrifugation and resuspended in RPMI medium (10^7 parasites/mL) in the presence of 10% of mouse blood. This suspension (100 μ L) was added in the same volume of each compound previously prepared at twice the desired final concentrations in 96-well microplates and incubated at 4 °C for 24 h. Alternatively, trypomastigotes were also resuspended in absence of mouse blood and incubated at 37 °C for 24 h. Parasites counts were performed in Neubauer chamber and the trypanocidal activity was expressed as $IC_{50}/24$ h, corresponding to the concentration that leads to lysis of 50% of the parasites. Stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.1%.

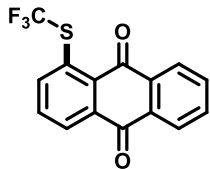
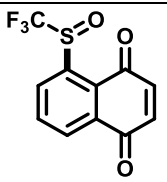
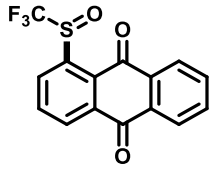
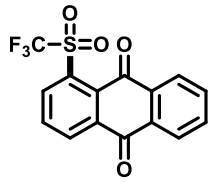
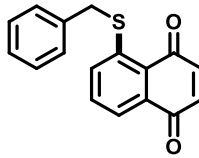
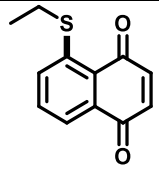
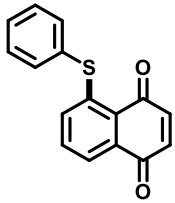
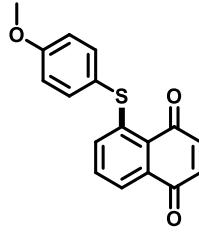
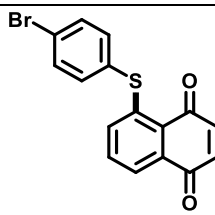
Cytotoxicity assays

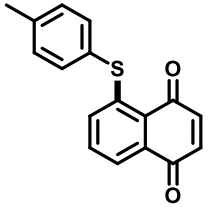
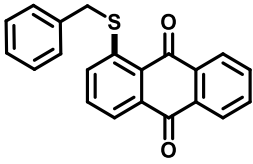
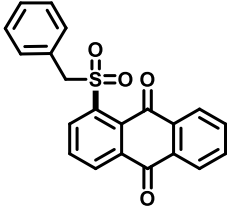
Swiss mice peritoneal macrophages were resuspended in RPMI, added to 24-well plates (10^5 cells/well) and maintained for 24 h at 37°C. The cultures were then washed with phosphate buffered saline (PBS, pH 7.2) and treated with the compounds in medium without phenol red (200 μ L/well) for 24 h at 37°C. After this period, 110 μ L of the medium was discarded and 10 μ L of PrestoBlue (Invitrogen) was added to complete the final volume of 100 μ L. Thus, the plate was incubated for 2 h and the measurement was performed at 560 and 590 nm, as recommended by the manufacturer. The results were expressed as the difference in the percentage of reduction between treated and untreated cells being the $LC_{50}/24$ h value, corresponds to the concentration that leads to damage of 50% of the mammalian cells.

All animal procedures were reviewed and approved by Fiocruz Committee of Ethics in Animal Research (LW16/13), according to resolution 196/96 of the National Health Council of Brazilian Ministry of Health.

Table S1. Activity of naphthoquinones on trypomastigote forms of *T. cruzi*.

Compounds	Structure	IC ₅₀ / 24 h ^a (μM)
2a		41.2 (± 3.5)
2b		>1000.0
2c		34.5 (± 6.3)
2d		32.7 (± 4.1)
2e		67.3 (± 5.5)
2f		240.1 (± 14.8)
2g		41.9 (± 5.8)
2h		54.4 (± 5.5)

2i		>1000.0
3a		67.3 (± 6.1)
3b		>1000.0
3c		>1000.0
4a		14.3 (± 0.9)
4b		31.3 (± 2.4)
4c		12.4 (± 2.2)
4d		7.6 (± 0.3)
4e		6.6 (± 0.8)

4f		2.5 (\pm 0.3)
4g		64.9 (\pm 5.9)
5		36.3 (\pm 2.2)
Benznidazole		103.6 \pm 0.6 ¹⁴

^aMean \pm SD of at least three independent experiments. ***Table 2 in the manuscript.**

Table S1.1. High active naphthoquinones selected to trypanocidal (in different conditions) and cytotoxicity assays. ***Table 3 in the manuscript.**

Compounds	IC ₅₀ / 24 h		LC ₅₀ / 24h	SI
	5% blood, 4 °C	0% blood, 37 °C	0% blood, 37 °C	
4a	14.3 (\pm 0.9)	1.1 (\pm 0.2)	10.5 (\pm 0.2)	9.5
4c	12.4 (\pm 2.2)	0.3 (\pm 0.04)	3.6 (\pm 0.7)	12.0
4d	7.6 (\pm 0.3)	1.3 (\pm 0.03)	3.3 (\pm 0.3)	2.5
4e	6.6 (\pm 0.8)	1.9 (\pm 0.03)	6.0 (\pm 1.0)	3.2
4f	2.5 (\pm 0.3)	0.3 (\pm 0.06)	3.7 (\pm 1.4)	12.3

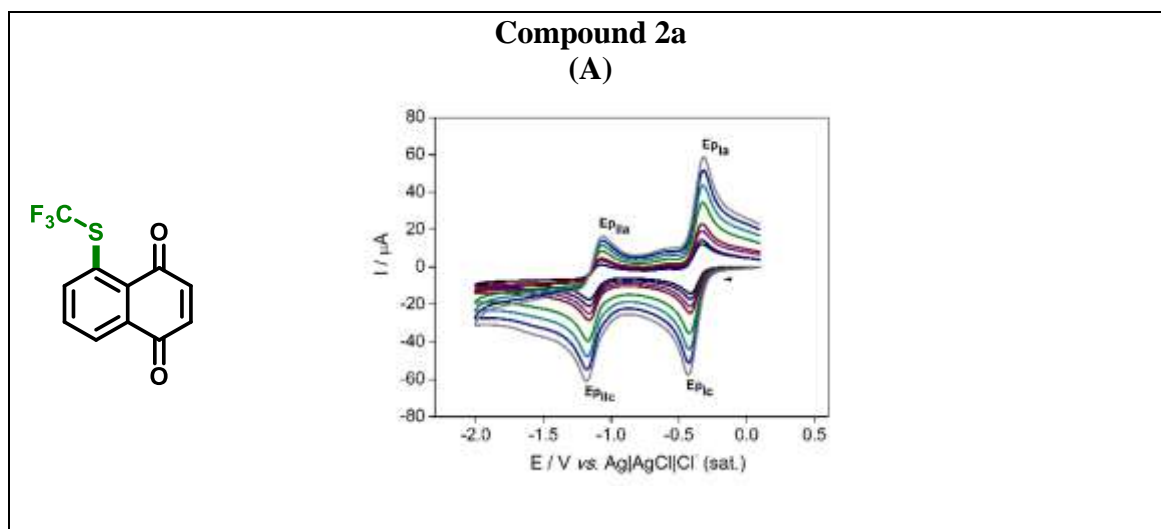
Electrochemical studies

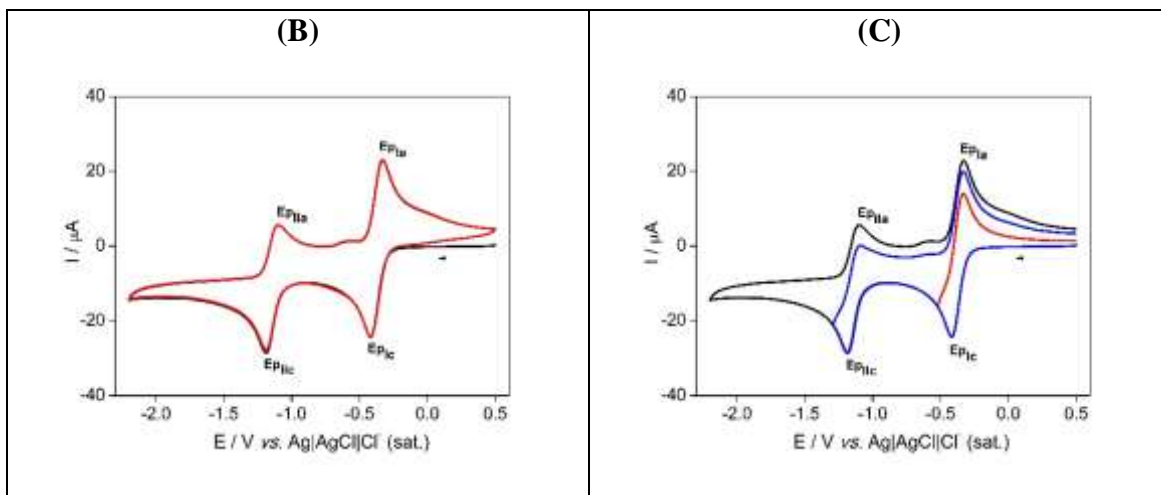
The last two decades have witnessed a growing interest in chalcogen containing agents with potential ‘redox modulating’ properties. Certain redox catalysts containing quinone- and chalcogen-bearing building blocks have shown considerable promise when assayed toward cancer cells and other biological targets. The search for selectivity toward redox therapeutic agents remains of expanding interest.¹⁵ Electrochemical

methods are extraordinarily powerful and useful in the characterization and design of redox-modulating agents.¹⁶ They provide thermodynamic and kinetic parameters of bioactive compounds, under different conditions, that may be related to their biological activity in living cells.

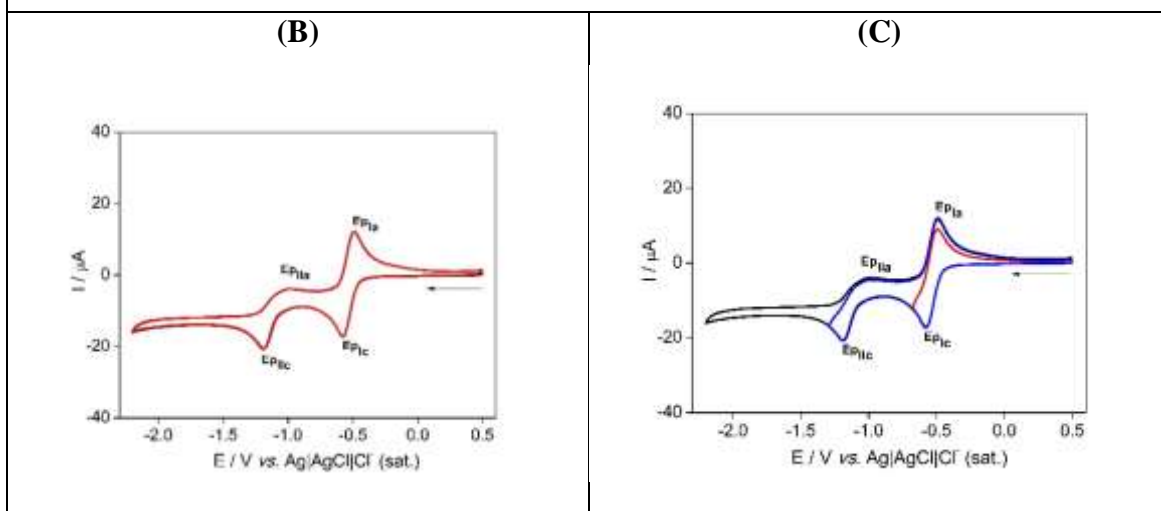
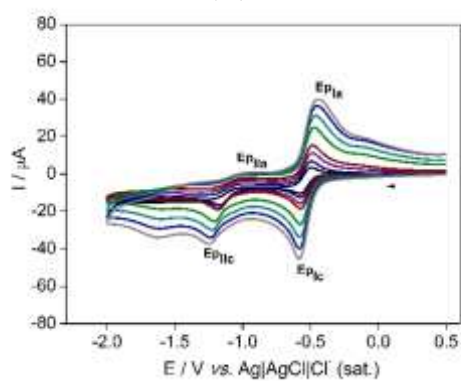
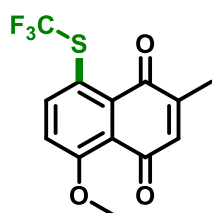
Cyclic voltammetry (CV) experiments were performed with a conventional three electrode cell in an Autolab PGSTAT-30 potentiostat (Echo Chemie, Utrecht, the Netherlands) coupled to a PC microcomputer, using GPES 4.9 software. The working electrode was a glassy carbon (GC) BAS (d = 3 mm), the counter electrode was a Pt wire and the reference electrode an Ag|AgCl|Cl⁻ (saturated), all contained in a one-compartment electrochemical cell with a volumetric capacity of 5 mL. The GC electrode was cleaned up by polishing with alumina on a polishing felt (BAS polishing kit). The solvent used in aprotic media studies was extra dry *N,N*-dimethylformamide (99.8%) acquired from Acros Organics. In CV experiments, the scan rate varied from 35 to 500 mV s⁻¹. Electrochemical reduction were performed in aprotic media (DMF + TBAPF₆ 0.1 mol L⁻¹) at room temperature (25 ± 2 °C). Each compound (1 × 10⁻³ mol L⁻¹) was added to the supporting electrolyte and the solution was deoxygenated with argon before the measurements by cyclic voltammetry, in different potential intervals.

Cyclic voltammograms of the thio-substituted naphthoquinones display the common quinone behaviour, represented by two redox systems ($E_{P_{Ic}}/E_{P_{Ia}}$ and $E_{P_{IIc}}/E_{P_{IIa}}$) (Figure S1), whose main electrochemical parameters are listed in Table S2.

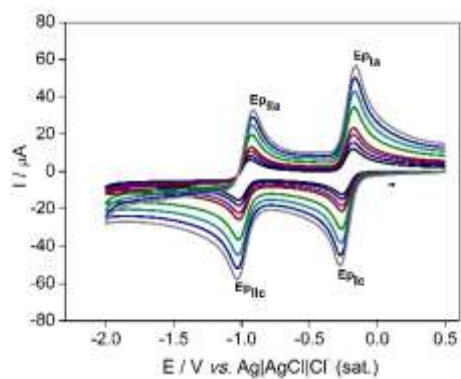
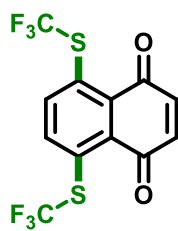




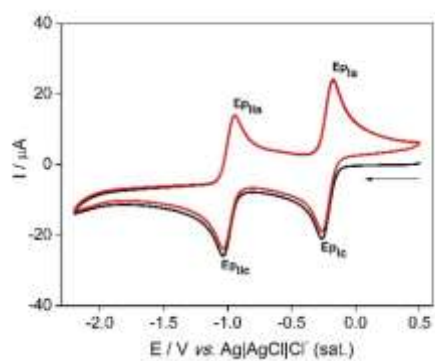
Compound 2b
(A)



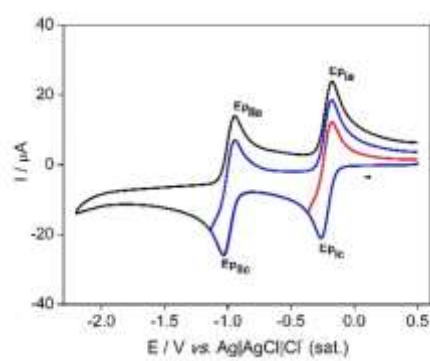
Compound 2f
(A)



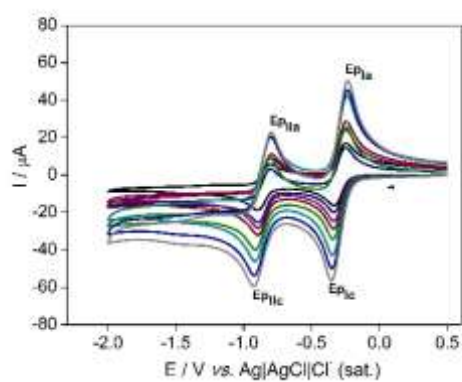
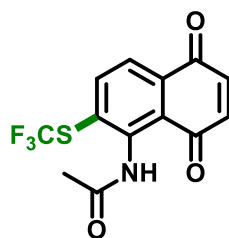
(B)



(C)



Compound 2d
(A)



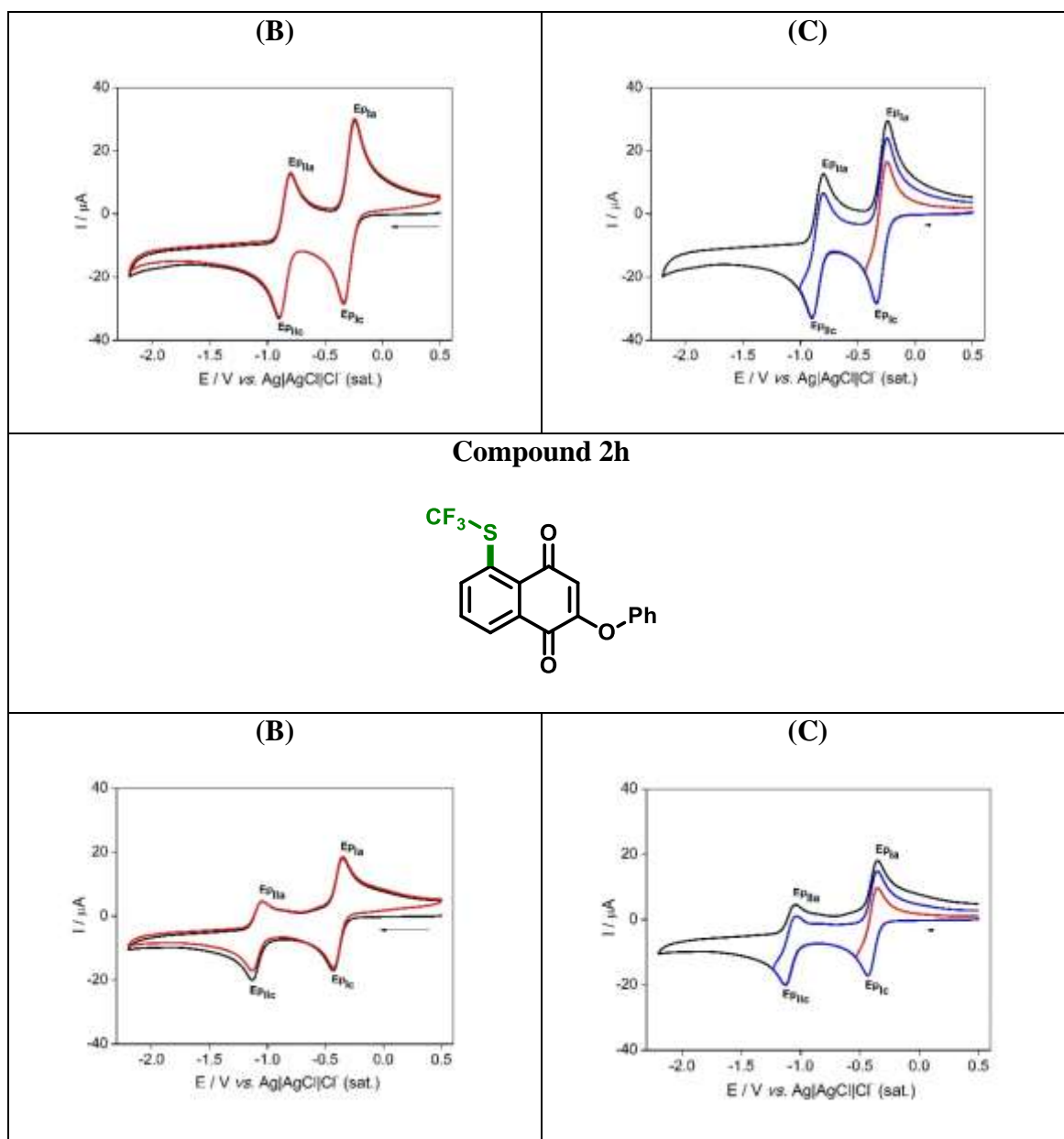
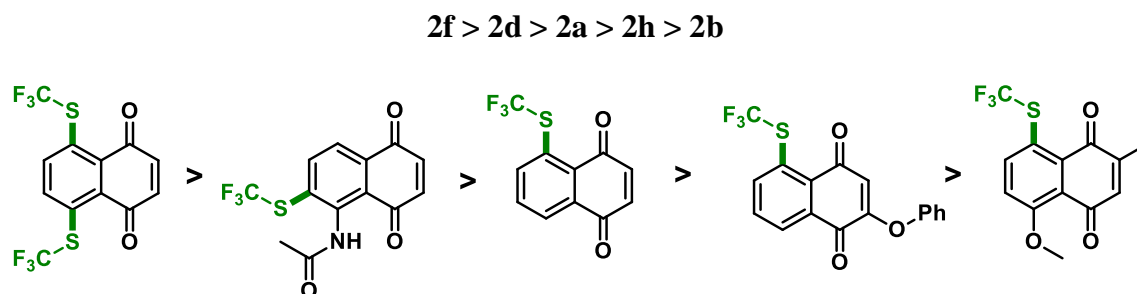


Figure S1. Cyclic voltammetry (CV) of **2a**, **2b**, **2f**, **2d** and **2h** (1 mM) in DMF + TBAPF₆ (0.1 M), glassy carbon electrode, $\nu = 100 \text{ mV s}^{-1}$. **(A)** Different scan rates of 35, 50, 75, 100, 200, 300, 400 and 500 mV s^{-1} . **(B)** Successive CVs (scan 1: black line and scan 2: red line). **(C)** Several inversion potentials in the CV of compounds. Arrows indicate cathodic direction

Table S2. Major electrochemical parameters of the sulphide naphthoquinones (c = 1mM), using cyclic voltammetry, in DMF/TBAPF₆, 0.1 M, v = 100 mV s⁻¹.

Compounds	E_{pIc} (V)	E_{pIIc} (V)	E_{pIa} (V)	E_{pIIa} (V)	$\Delta(E_{pIc} - E_{pIa})$ (mV)	$\Delta(E_{pIIc} - E_{pIIa})$ (mV)	$\Delta(E_{pIc} - E_{pIIc})$ (V)
2a	-0.421	-1.185	-0.326	-1.103	95	82	0.764
2b	-0.582	-1.196	-0.486	-1.036	96	160	0.614
2f	-0.262	-1.028	-0.178	-0.943	84	85	0.766
2d	-0.336	-0.897	-0.243	-0.803	93	94	0.561
2h	-0.440	-1.131	-0.356	-1.045	84	86	0.691

Considering the ease of the reduction related to E_{pIc} (Table 2), the compounds can be ranked as shown below. Less negative potentials indicate higher electrophilicity and facility to be reduced



There is an additive reduction-facilitating effect concerning the electron withdrawing substituents (2 x -SCF₃ and -SCF₃ and the acetamide), as shown by the potential values of E_{pIc} . The electrodonating groups (-OMe and -OPh), have an opposite effect. It is noticeable the hydrogen-bonding capacity of the acetamide group, which strongly facilitates the second electron uptake ($E_{pIIc} = -0.897$ V), at least 100 mV less negative than the others.

Crystallographic data collection and refinement

X-ray diffraction data collections on single crystals of **2a**, **2b**, **2e**, **2f**, **4d**, **4e**, **4g** and **5** were performed with an Oxford-Diffraction GEMINI-Ultra using Mo-K α radiations (0.71073 Å). Measurements were performed at 293 K as shown in Table S3.

Data integration and scaling of the reflections for all compounds were performed with the *CRYSTALIS* suite.¹⁷ Final unit cell parameters were based on the fitting of all reflections positions. Analytical absorption corrections and the space group identification were performed using *CRYSTALIS* suite. The structures of all compounds were solved by direct methods using the *SUPERFLIP* program.¹⁸ For each compound, the positions of all atoms could be unambiguously assigned on consecutive difference Fourier maps. Refinements were performed using *SHELXL*¹⁹ based on F^2 through full-matrix least square routine. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. All hydrogen atoms were located in difference maps and included as fixed contributions according to the riding model.²⁰ Values C–H = 0.93 Å and $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ for aromatic carbon atoms, C–H = 0.97 Å and $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{C})$ for methylene groups, C–H = 0.97 Å and $U_{\text{iso}}(\text{H}) = 1.5 U_{\text{eq}}(\text{C})$ for methyl groups and N–H = 0.97 Å and $U_{\text{iso}}(\text{H}) = 1.2 U_{\text{eq}}(\text{N})$ for amide nitrogen atom. For **2b** methyl groups directly bonded to aromatic rings has shown in difference maps two possible positions for hydrogen atoms, twisted 30° from each other. Trifluoromethyl group in **3b** is also disordered exhibiting the electronic maxima position twisted c.a. 18° from each other. The fluoride atoms were split in two distinct positions according to electronic maxima. Both positional disorders were treated splitting the occupancy between the sets of possible positions. Samples of compounds **2e** and **4d** used in the single X-ray diffraction experiments were found to be twinned. The integration of data used in the final structure refinement was performed considering two domains rotated by 180° around the [100] axes. The refinement was performed using all overlapping and non-overlapping reflections from both domains and the final twin volume ratio converged to c.a. 0.4 for **2e** and 0.1 for **4d**. Molecular graphics were obtained with ORTEP3²¹ in association with POV-Ray software.²² CCDC numbers concerning the crystal structures presented in this work are 1586321 (**2d**), 1586322 (**4d**), 1586323 (**2f**), 1586324 (**4e**), 1586325 (**2i**), 1586747 (**3a**), 1586748 (**3c**), 1586326 (**4g**), 1586327 (**5**), 1586328 (**2b**) and 1586329 (**2a**).

Table S3. Crystallographic data.

Compound	2a	2b	2d	2f	2i	3a
Formula	C ₁₁ H ₅ F ₃ O ₂ S	C ₁₃ H ₉ F ₃ O ₃	C ₁₃ H ₈ NO ₃ F ₃ S	C ₁₂ H ₄ F ₆ O ₂ S ₂	C ₁₅ H ₇ F ₃ O ₂ S	C ₁₁ H ₅ O ₃ F ₃ S
<i>F</i> _w	258.21	302.26	315.26	358.27	308.27	274.21
<i>T</i> / K	293(2)	293(2)	200(2)	200(2)	250(2)	220(2)
<i>λ</i> / Å	0.71073	1.5418	1.5418	1.5418	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic	Triclinic	Triclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>I</i> 2/ <i>a</i>	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$
<i>a</i> / Å	19.2151(6)	14.5769(4)	4.7875(4)	4.67670(10)	7.4794(7)	8.0423(4)
<i>b</i> / Å	7.8797(2)	11.1576(2)	10.5072(9)	19.3071(3)	7.9785(8)	8.0926(5)
<i>c</i> / Å	7.1525(2)	31.0437(7)	14.2488(15)	14.5648(2)	11.9788(10)	9.4378(6)
<i>α</i> / °	90	90	71.680(9)	90	95.823(8)	68.147(6)
<i>β</i> / °	97.718(3)	102.048(2)	88.646(8)	97.9490(10)	102.310(8)	84.221(5)
<i>γ</i> / °	90	90	76.869(7)	90	113.691(9)	72.377(5)
<i>V</i> / Å ³	1073.14(5)	1073.14(5)	661.76(11)	1302.47(4)	625.39(11)	543.30(6)
<i>Z</i>	4	16	2	4	2	2
<i>ρ</i> / kg m ⁻³	1.598	1.626	1.582	1.827	1.637	1.676
<i>μ</i> / mm ⁻¹	0.328	2.771	2.636	4.489	0.297	0.336
<i>F</i> (000)	520	2464	320	712	312	276
Crystal size / mm ³	0.60× 0.32× 0.16	0.36× 0.28× 0.11	0.56× 0.08× 0.05	0.49× 0.08× 0.05	0.86× 0.18× 0.10	0.48× 0.22× 0.10
Reflections collected	42253	33710	4295	11706	10141	8889
Reflection with <i>I</i> ≥ 2σ(<i>I</i>) [<i>R</i> _{int}]	1914 [0.036]	3705 [0.066]	3270 [0.207]	1984 [0.068]	1955 [0.034]	1820 [0.027]
Goodness-of-fit on <i>F</i> ² (<i>S</i>)	1.062	1.026	1.334	1.049	1.069	1.040
<i>R</i> ^a , <i>wR</i> ^b [<i>I</i> > 2σ(<i>I</i>)]	0.0658; 0.1866	0.0830; 0.2014	0.1180; 0.2534	0.0347; 0.0874	0.0393; 0.0892	0.0392; 0.0973
<i>R</i> ^a , <i>wR</i> ^b (all data)	0.0726; 0.1802	0.0933; 0.2103	0.1408; 0.2653	0.0420; 0.0937	0.0589; 0.1000	0.0503; 0.1055
Larg diff.peak and hole/e Å ⁻³)	0.424; -0.370	3.194; -1.219	0.958; -0.421	0.233; -0.334	0.228; -0.219	0.293; -0.261

^a $R = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}$. ^b $wR = \frac{[\sum (|F_o|^2 - |F_c|^2)^2 / \sum |F_o|^2]}{1/2}$

Table S3. Continuation.

Compound	3c	4d	4e	4g	5
Formula	C ₁₅ H ₇ O ₄ F ₃ S	C ₁₃ H ₈ NO ₃ F ₃ S	C ₁₆ H ₉ O ₂ SBr	C ₁₇ H ₁₂ O ₂ S	C ₂₁ H ₁₄ O ₄ S
<i>F</i> _w	340.27	315.26	345.20	280.33	362.38
<i>T</i> / K	200(2)	220(2)	250(2)	250(2)	250(2)
λ / Å	1.5418	1.5418	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic	Orthorhombic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>P</i> $\bar{1}$	<i>Pbca</i>
<i>a</i> / Å	12.2391(3)	9.0948(7)	7.8595(5)	7.2227(6)	14.1466(18)
<i>b</i> / Å	8.0497(2)	20.0144(16)	7.9836(5)	8.4064(7)	12.4232(17)
<i>c</i> / Å	13.6415(4)	7.8362(6)	12.2941(7)	12.3348(9)	18.979(2)
α / °	90	90	89.939(5)	75.046(7)	90
β / °	91.602(2)	106.353(9)	74.827(5)	76.516(7)	90
γ / °	90	90	68.477(6)	66.783(8)	90
<i>V</i> / Å ³	1343.45(6)	1368.69(19)	688.73(8)	657.64(10)	3335.6(7)
<i>Z</i>	4	4	2	2	8
ρ / kg m ⁻³	1.682	1.438	1.665	1.416	1.443
μ / mm ⁻¹	2.690	0.243	3.132	0.243	0.219
<i>F</i> (000)	688	616	344	292	1504
Crystal size / mm ³	0.43× 0.26× 0.13	0.39× 0.28× 0.03	0.44× 0.29× 0.11	0.55× 0.35× 0.04	0.66× 0.47× 0.11
Reflections collected	11565	4917	18417	7911	15833
Reflection with $I \geq 2\sigma(I)$ [<i>R</i> _{int}]	2051 [0.068]	3535 [0.101]	2223 [0.054]	2090 [0.035]	2303 [0.047]
Goodness-of-fit on <i>F</i> ² (<i>S</i>)	1.066	0.972	1.029	1.036	1.047
<i>R</i> ^a , <i>wR</i> ^b [<i>I</i> > 2σ(<i>I</i>)]	0.0660; 0.1733	0.0546; 0.1575	0.0426; 0.0846	0.0386; 0.0848	0.0445; 0.0958
<i>R</i> ^a , <i>wR</i> ^b (all data)	0.0743; 0.1861	0.0754; 0.1666	0.0711; 0.0889	0.0562; 0.0939	0.0791; 0.1137
Larg. diff. peak and hole / e Å ⁻³)	0.696; -0.439	0.376; -0.266	0.317; -0.521	0.228; -0.219	0.262; -0.346

$$^a R = \frac{\sum ||F_o| - |F_c||}{\sum |F_o|}, \quad ^b wR = \left[\frac{\sum (|F_o|^2 - |F_c|^2)^2}{\sum |F_o|^2} \right]^{1/2}$$

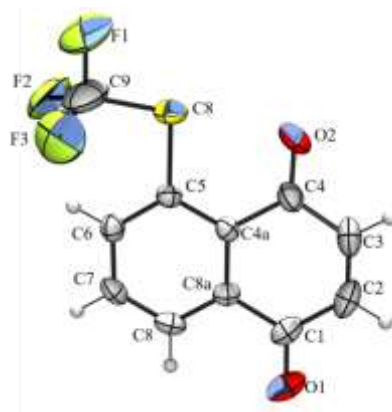


Figure S2. Representation of molecular structure of **2a** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 30% of probability.

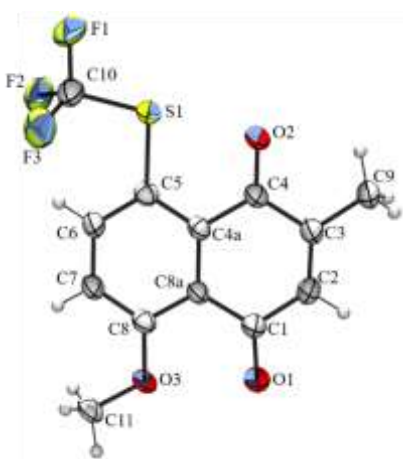


Figure S3. Representation of molecular structure of **2b** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

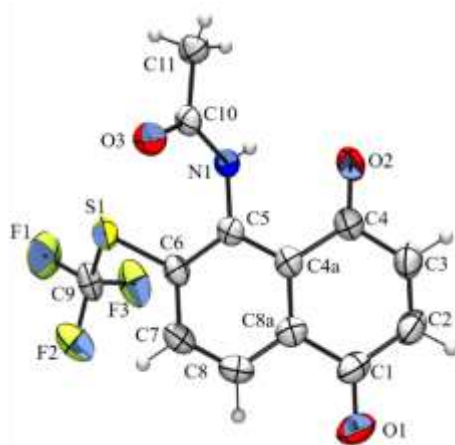


Figure S4. Representation of molecular structure of **2d** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

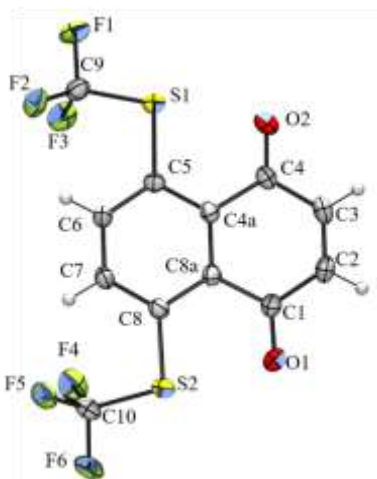


Figure S5. Representation of molecular structure of **2f** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

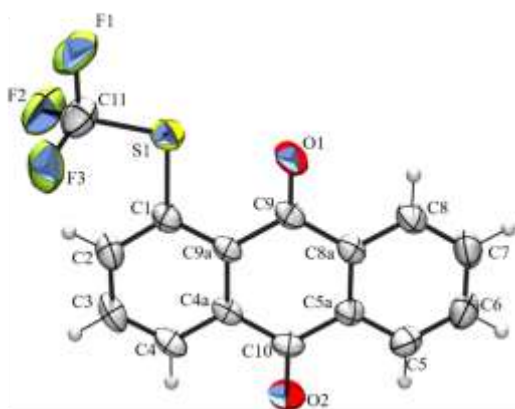


Figure S6. Representation of molecular structure of **2i** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

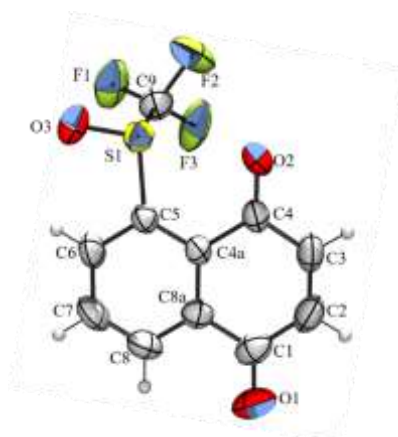


Figure S7. Representation of molecular structure of **3a** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.



Figure S8. Representation of molecular structure of **3c** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

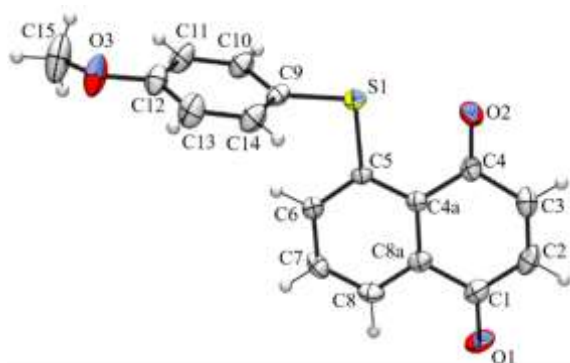


Figure S9. Representation of molecular structure of **4d** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.



Figure S10. Representation of molecular structure of **4e** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

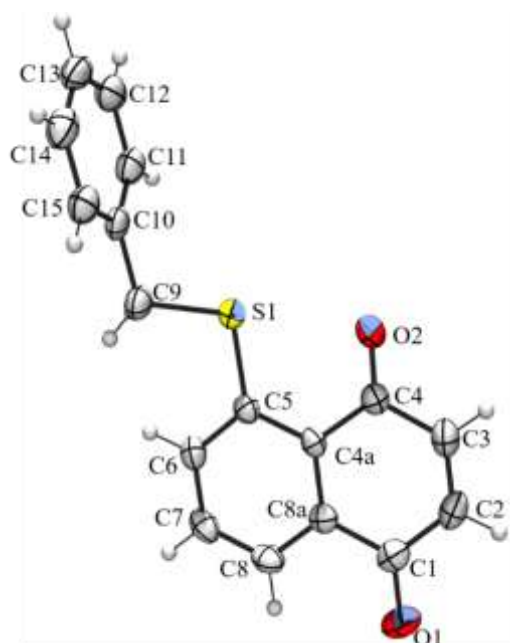


Figure S11. Representation of molecular structure of **4g** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

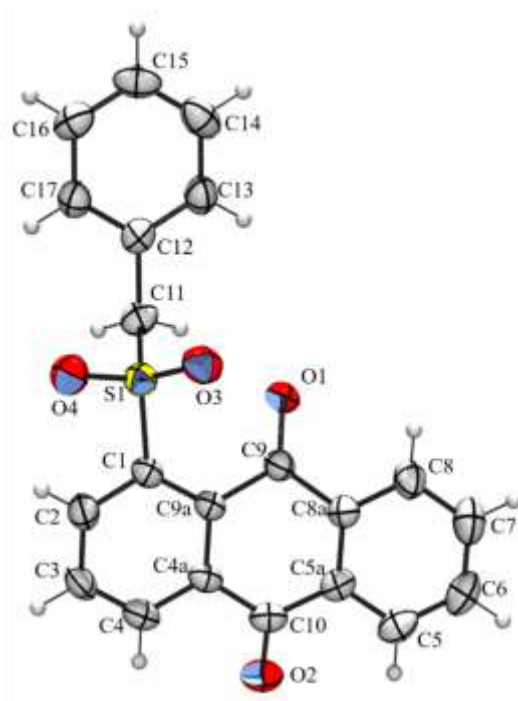


Figure S12. Representation of molecular structure of **5** obtained by single crystal X-ray experiments, with atomic labelling. Ellipsoids are presented at 50% of probability.

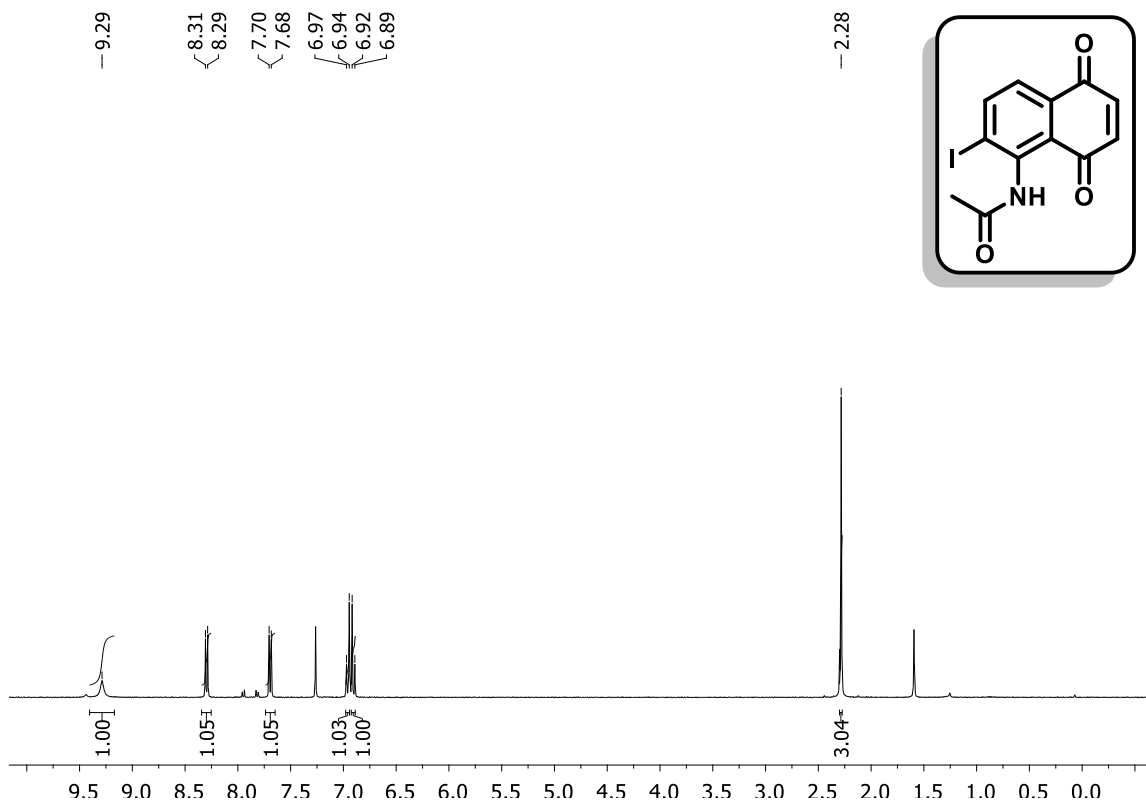


Figure S13. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **1d**.

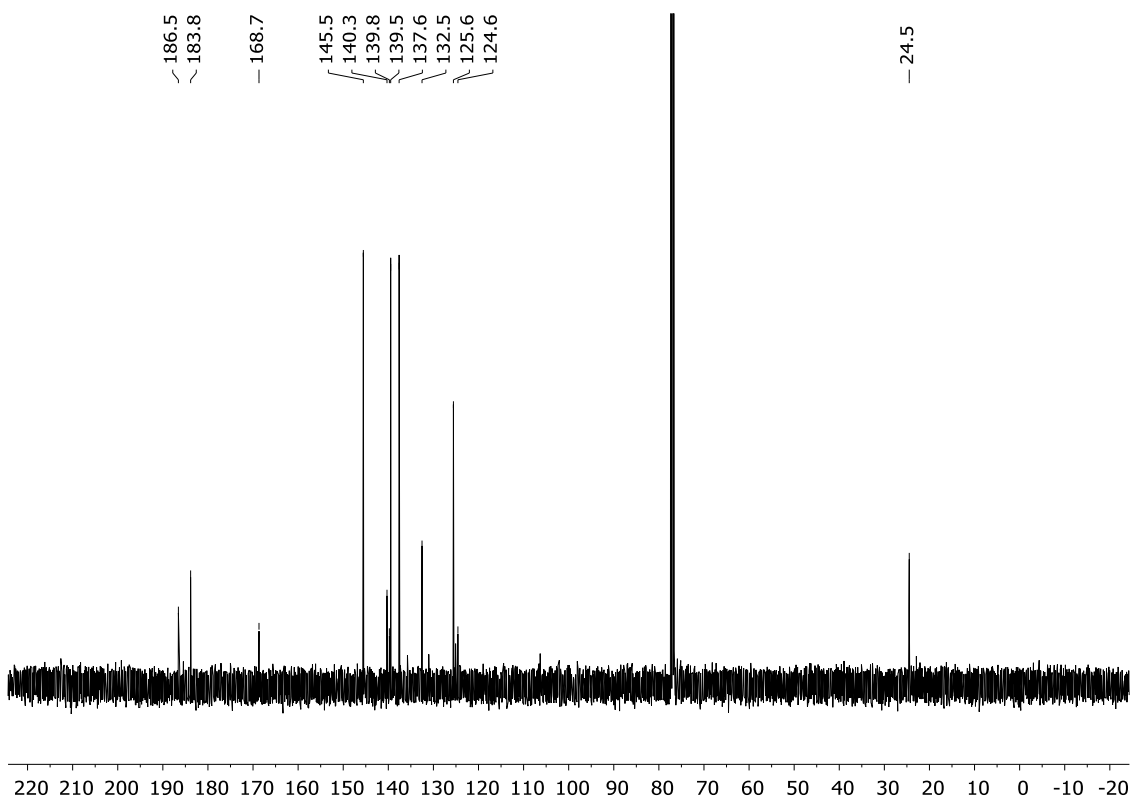


Figure S14. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound **1d**.

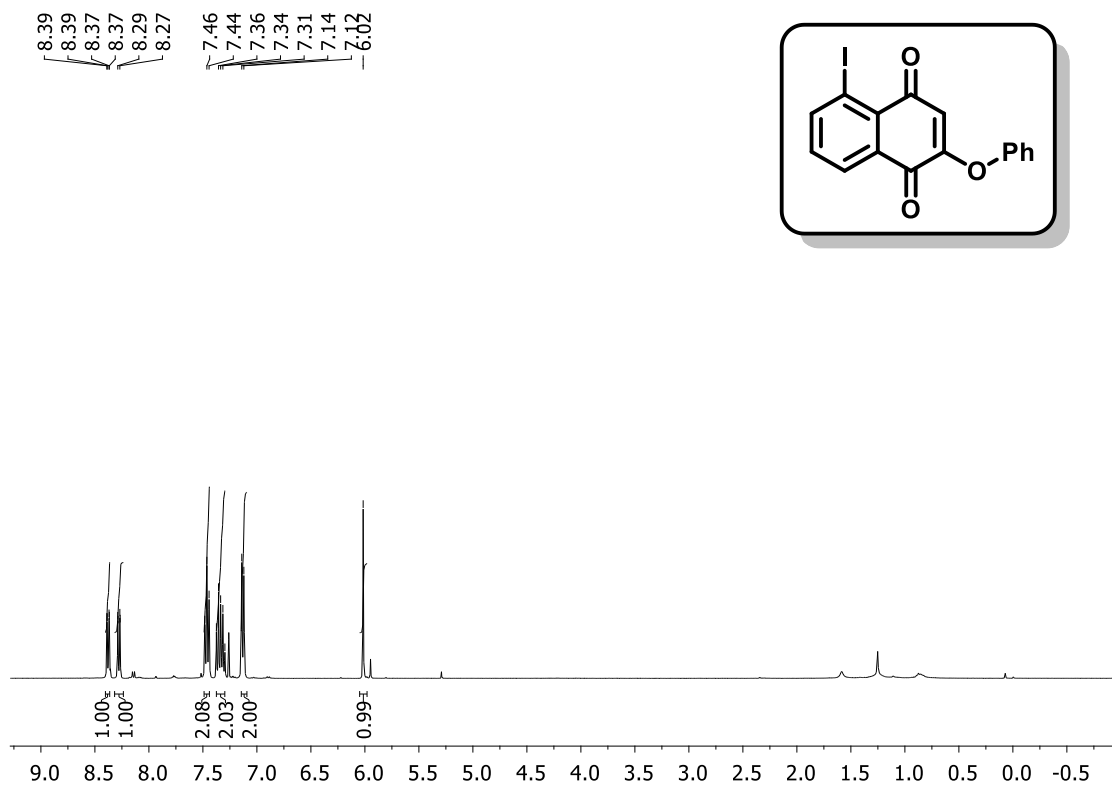


Figure S15. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **1h**.

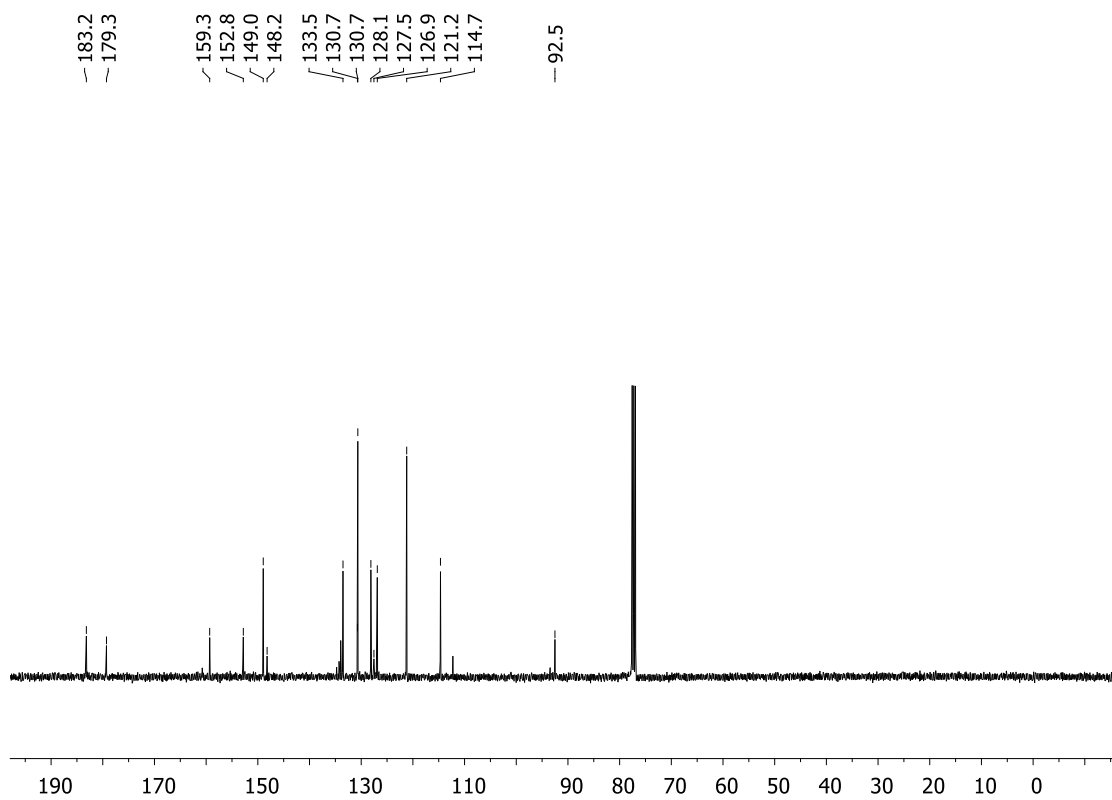


Figure S16. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **1h**.

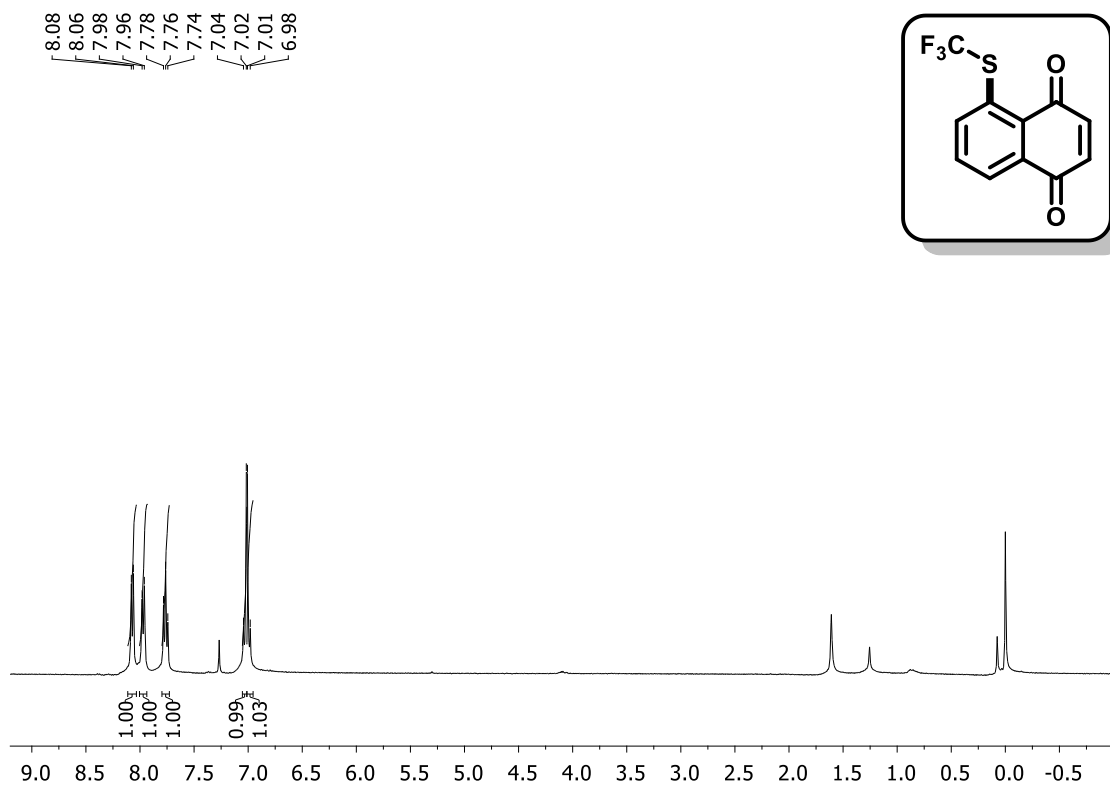


Figure S17. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 2a.

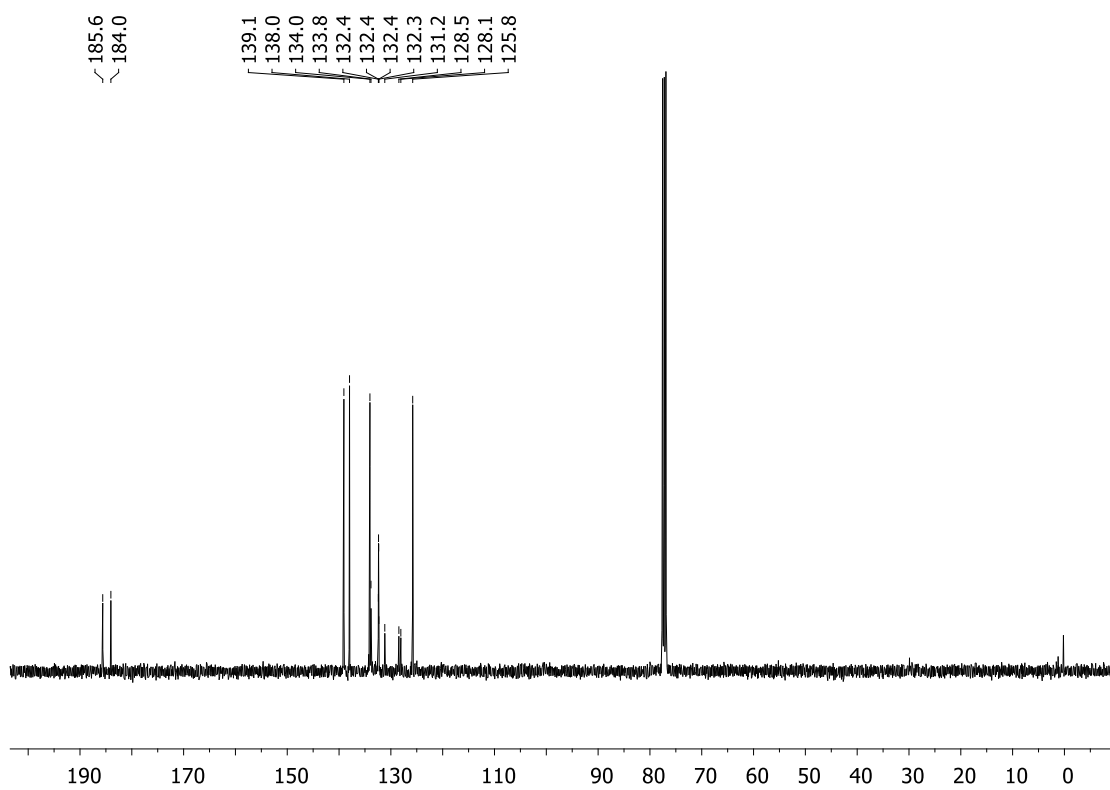
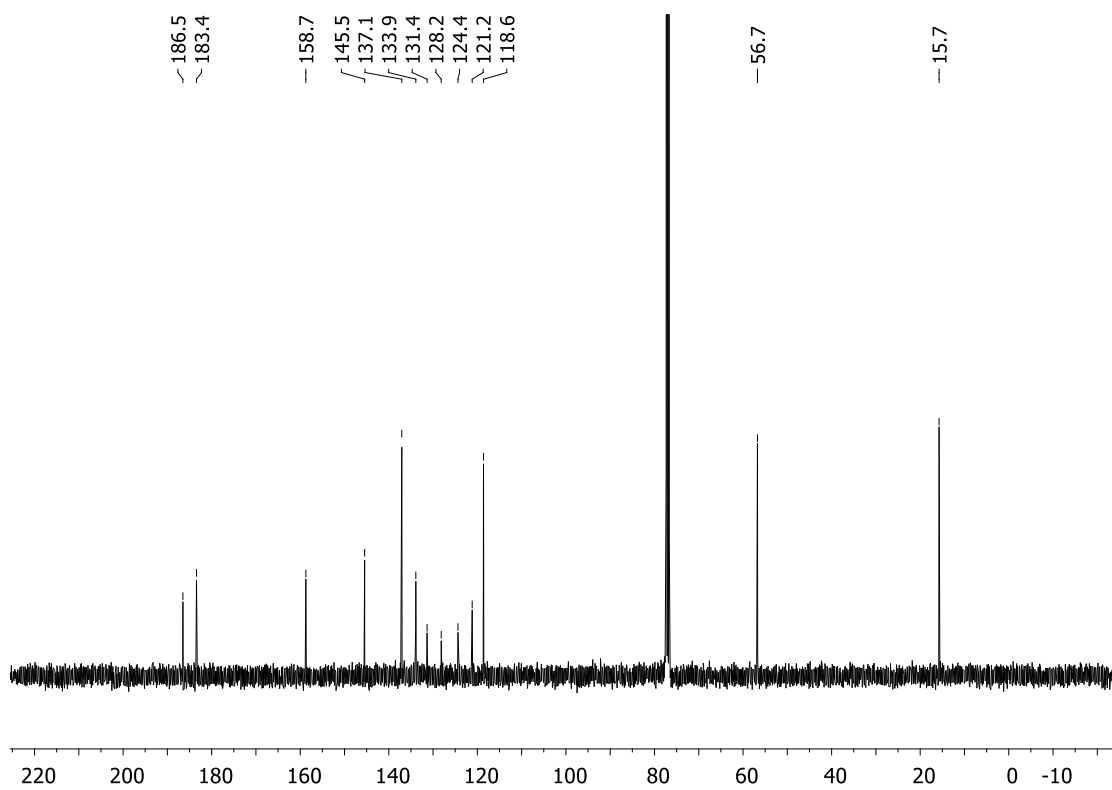
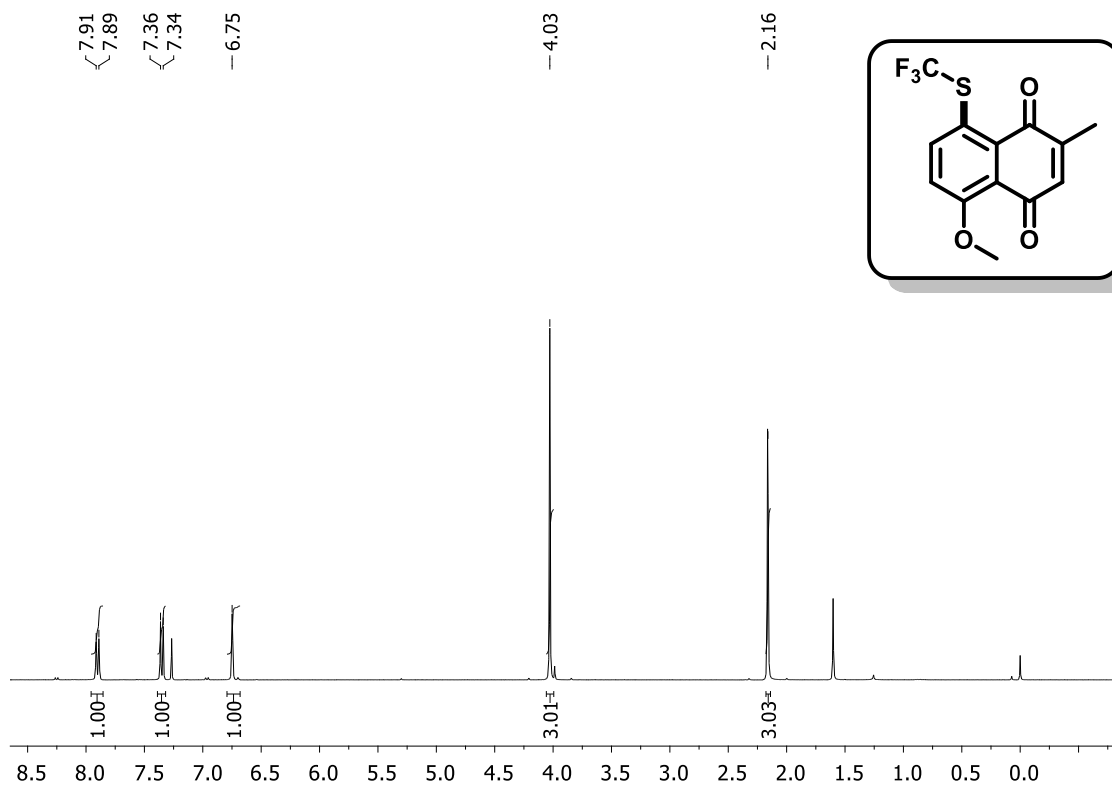


Figure S18. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound 2a.



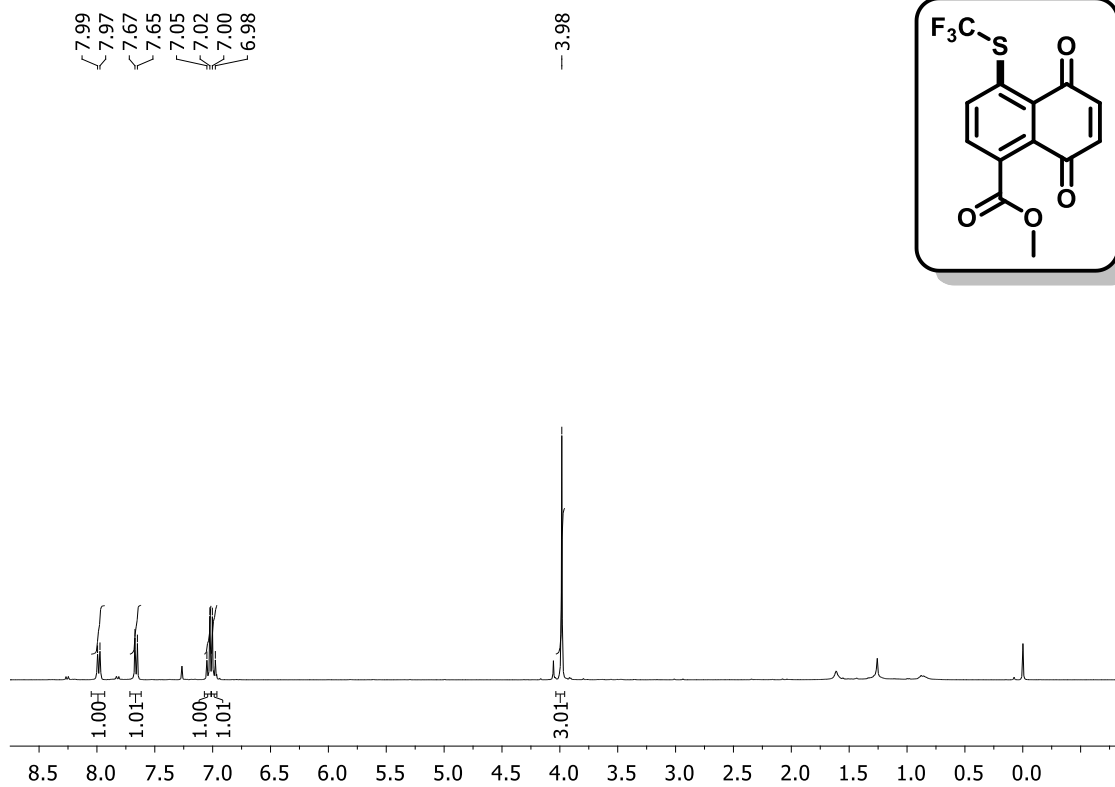


Figure S21. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **2c**.

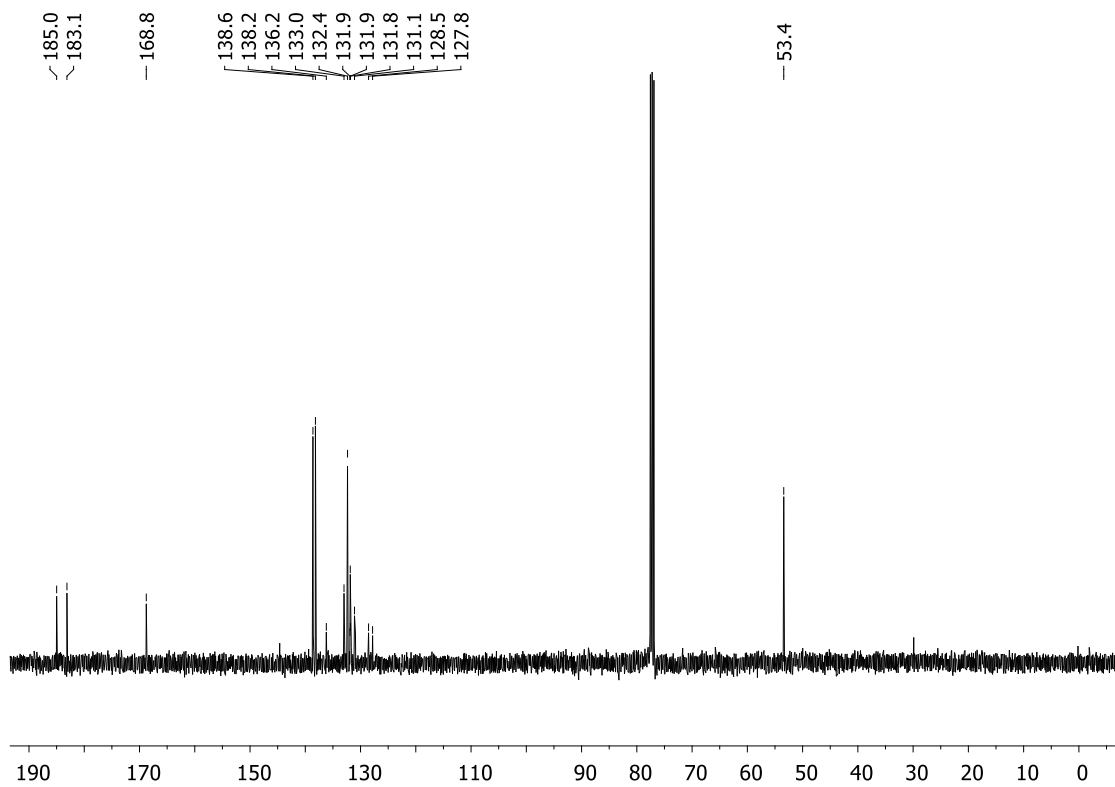


Figure S22. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound **2c**.

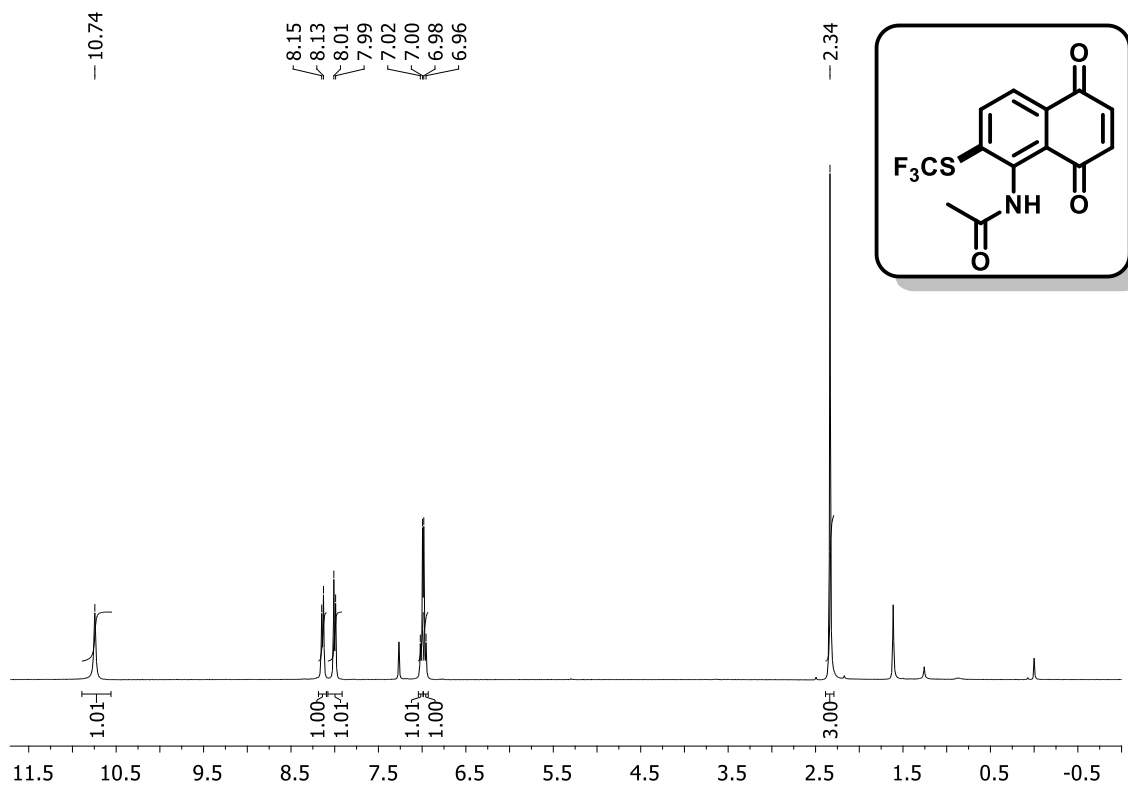


Figure S23. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **2d**.

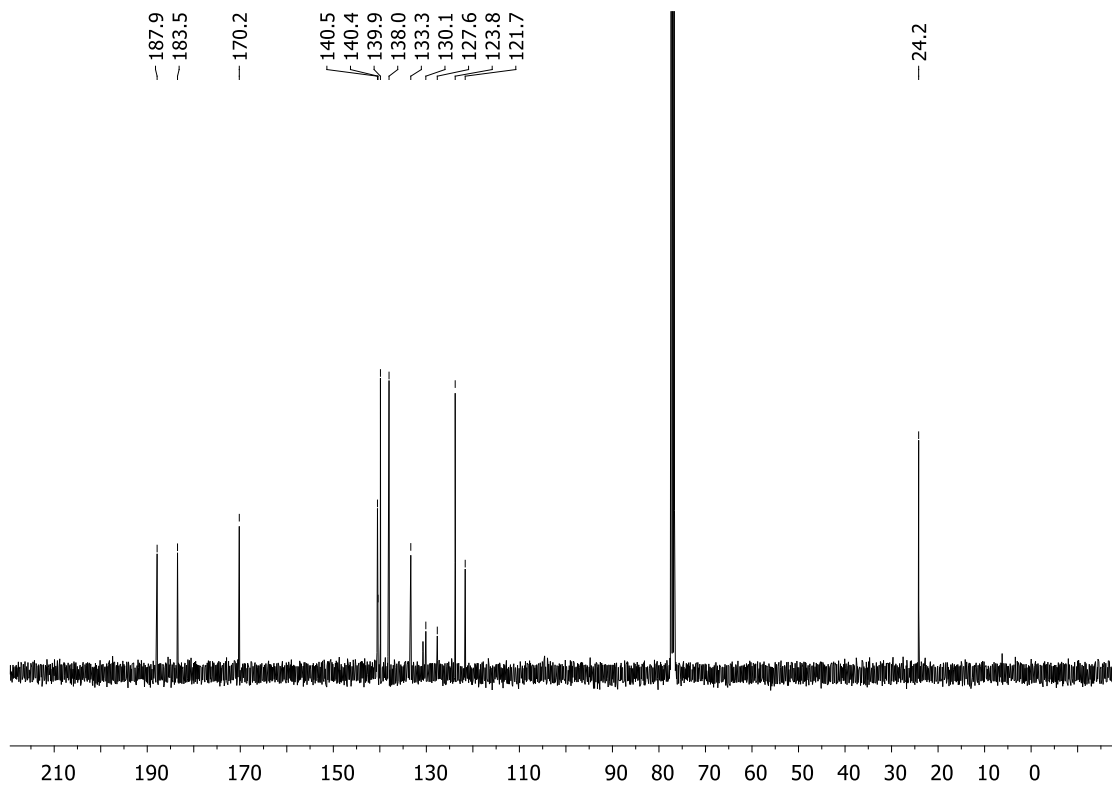


Figure S24. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound **2d**.

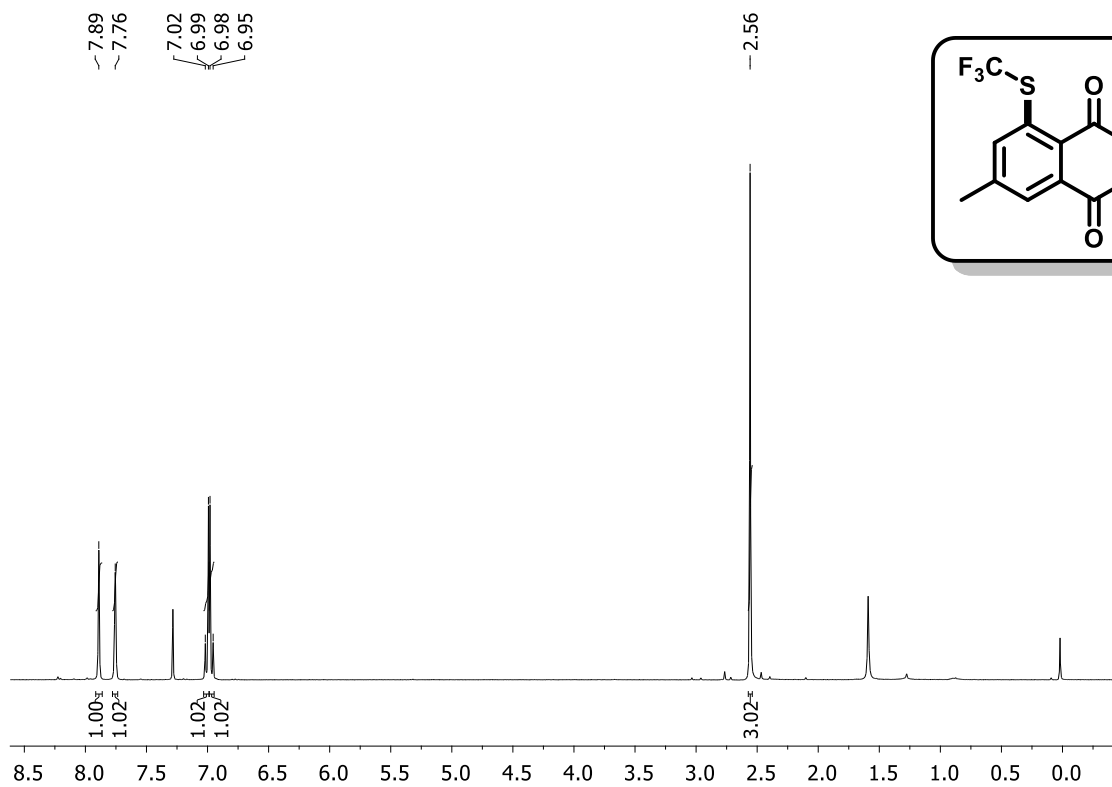


Figure S25. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **2e**.

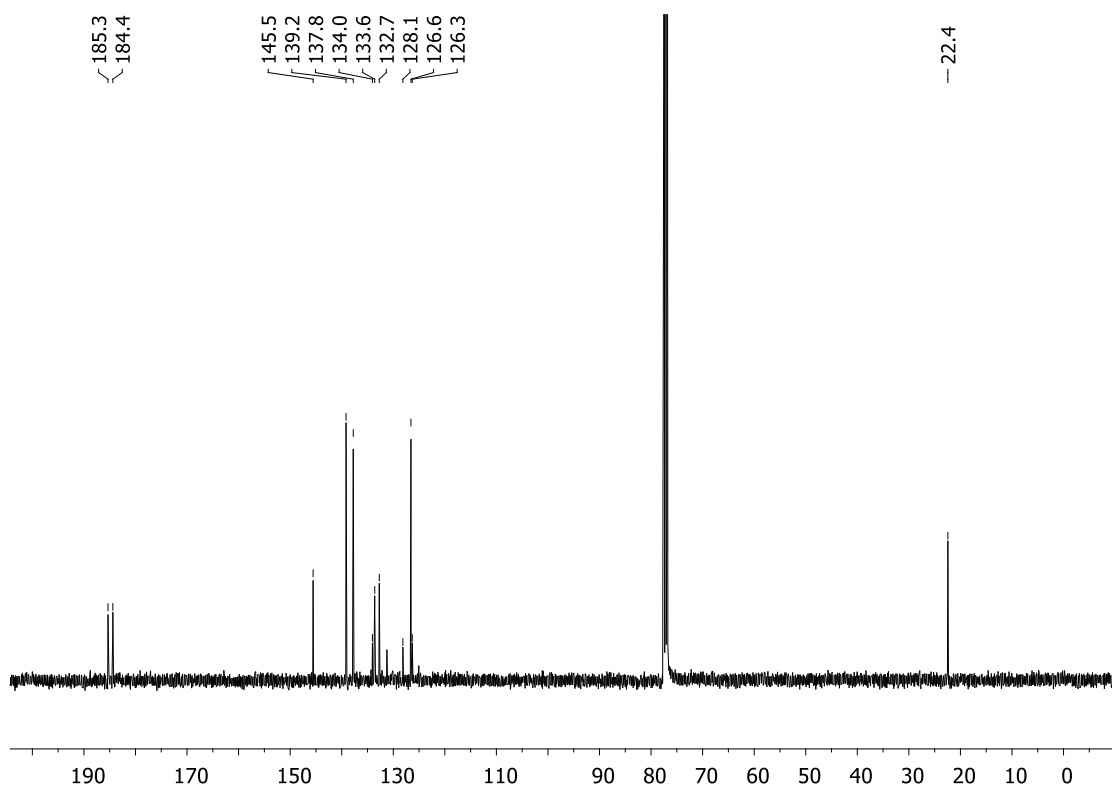


Figure S26. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **2e**.

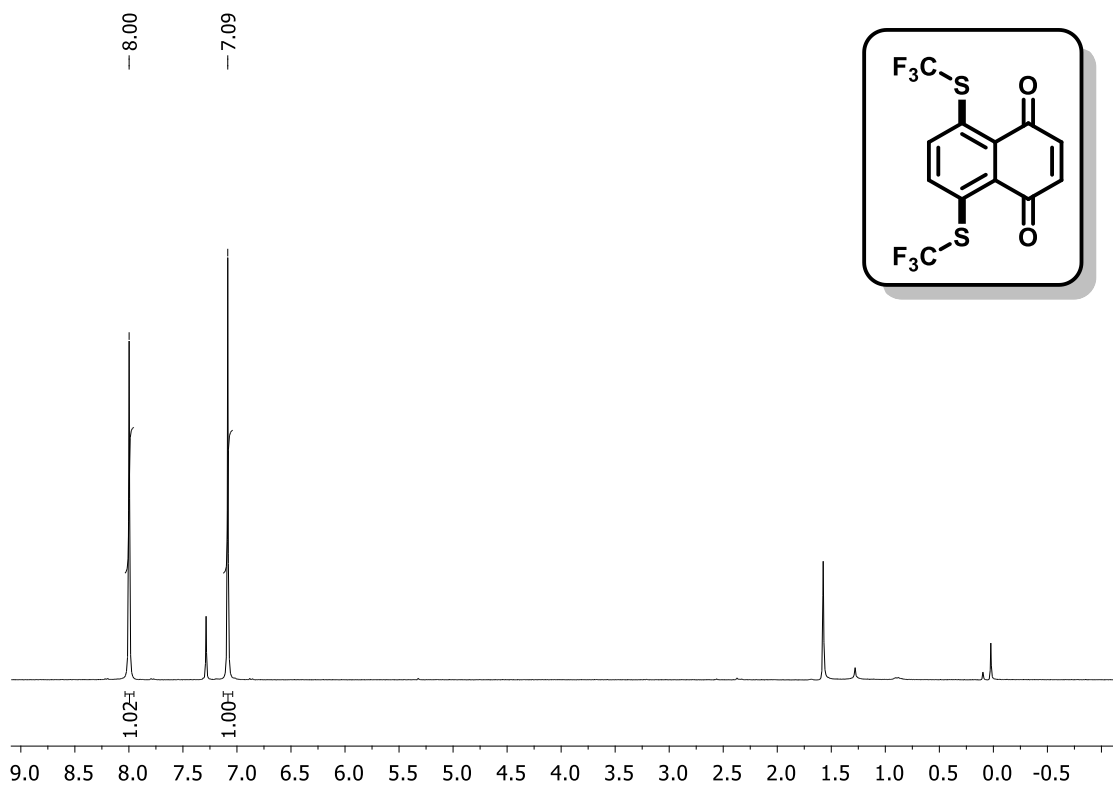


Figure S27. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **2f**.

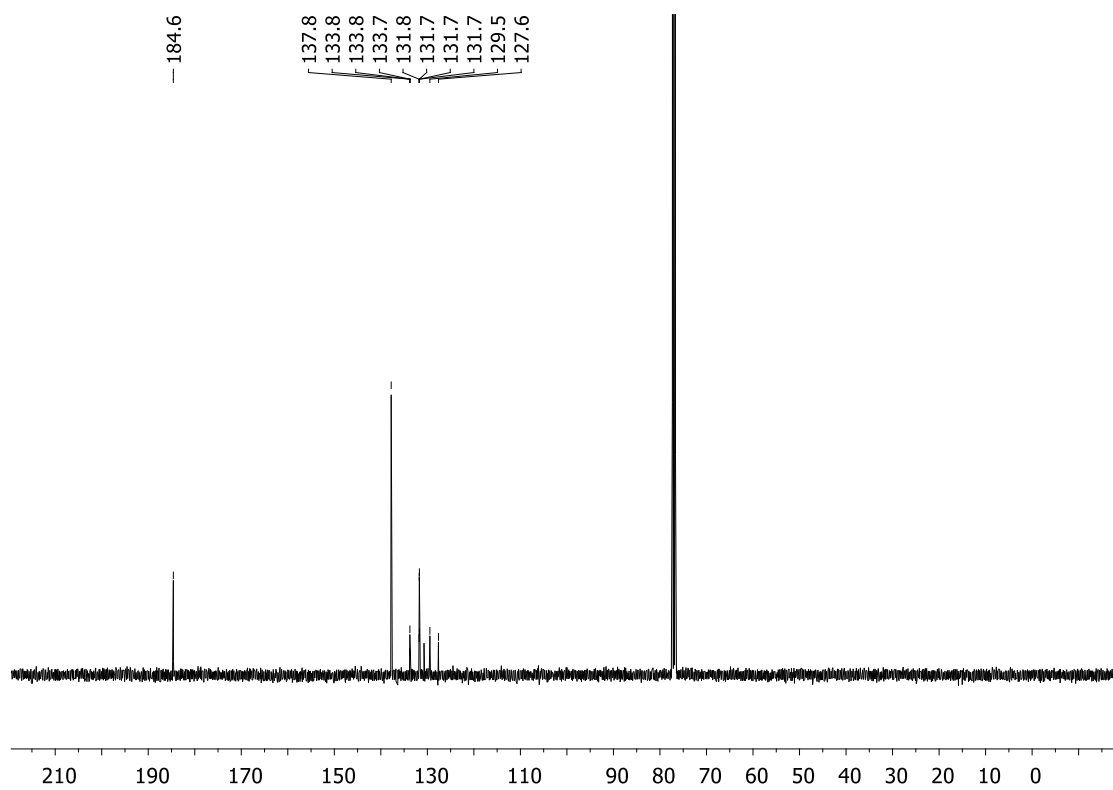


Figure S28. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **2f**.

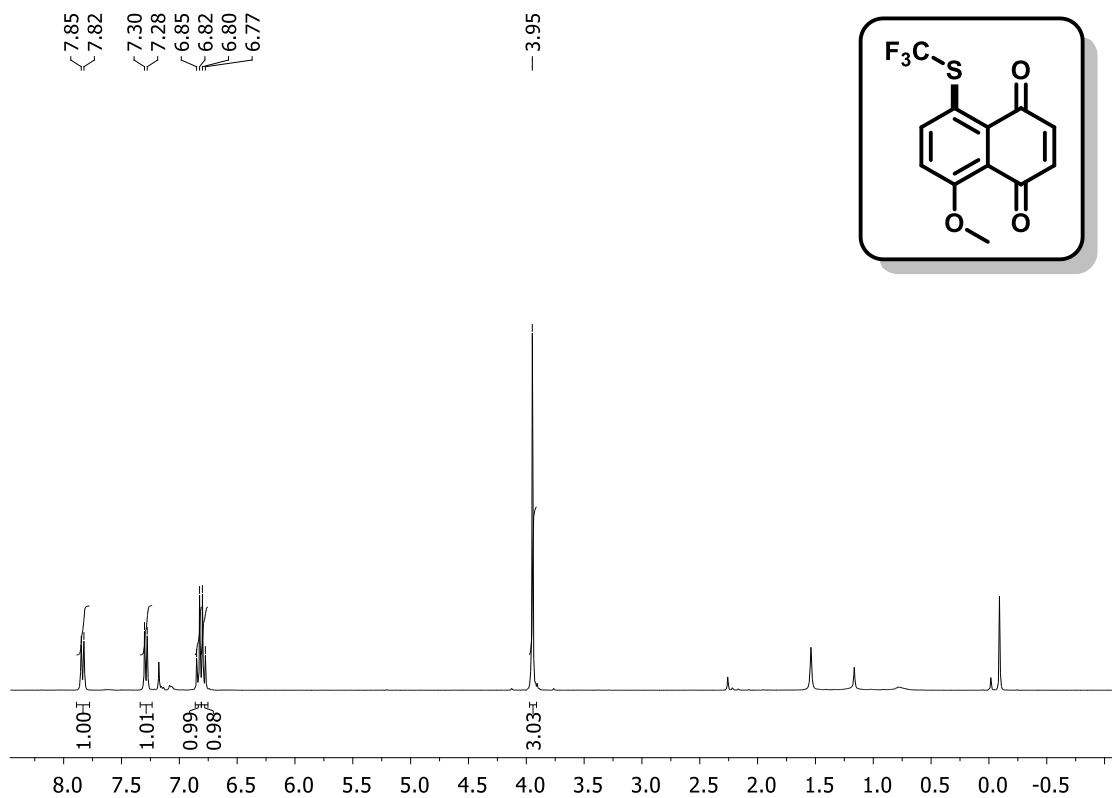


Figure S29. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **2g**.

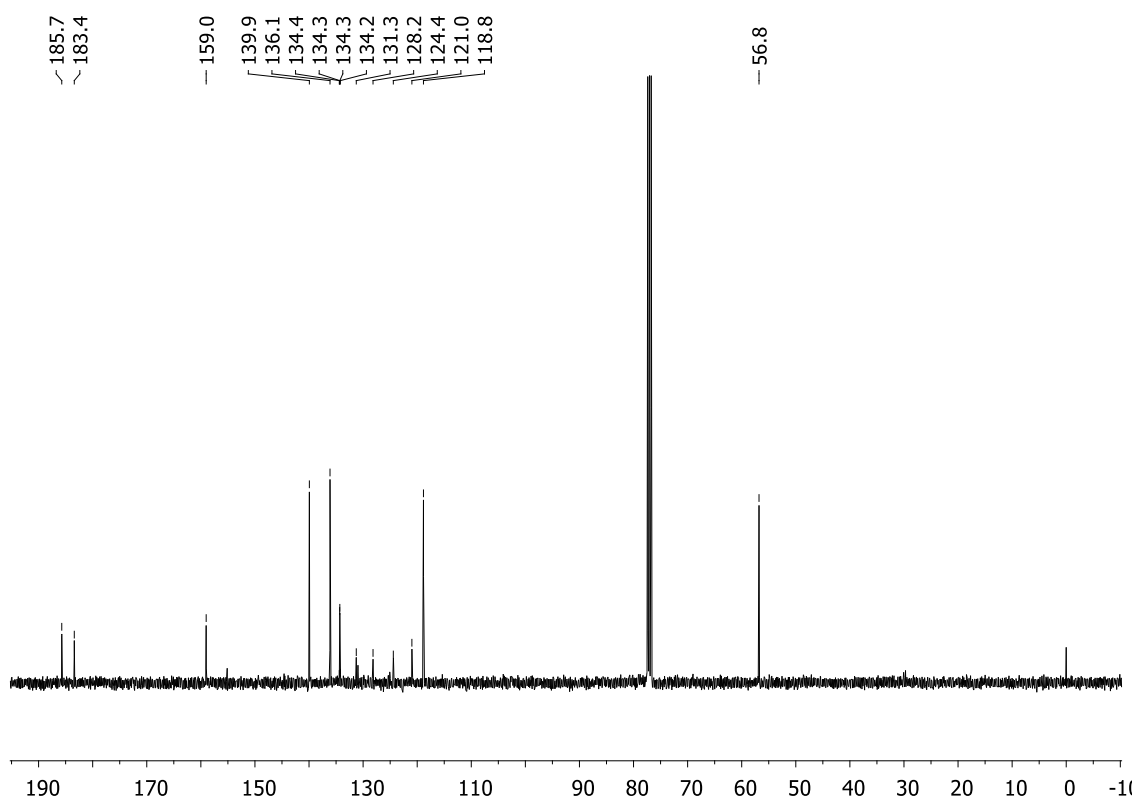


Figure S30. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound **2g**.

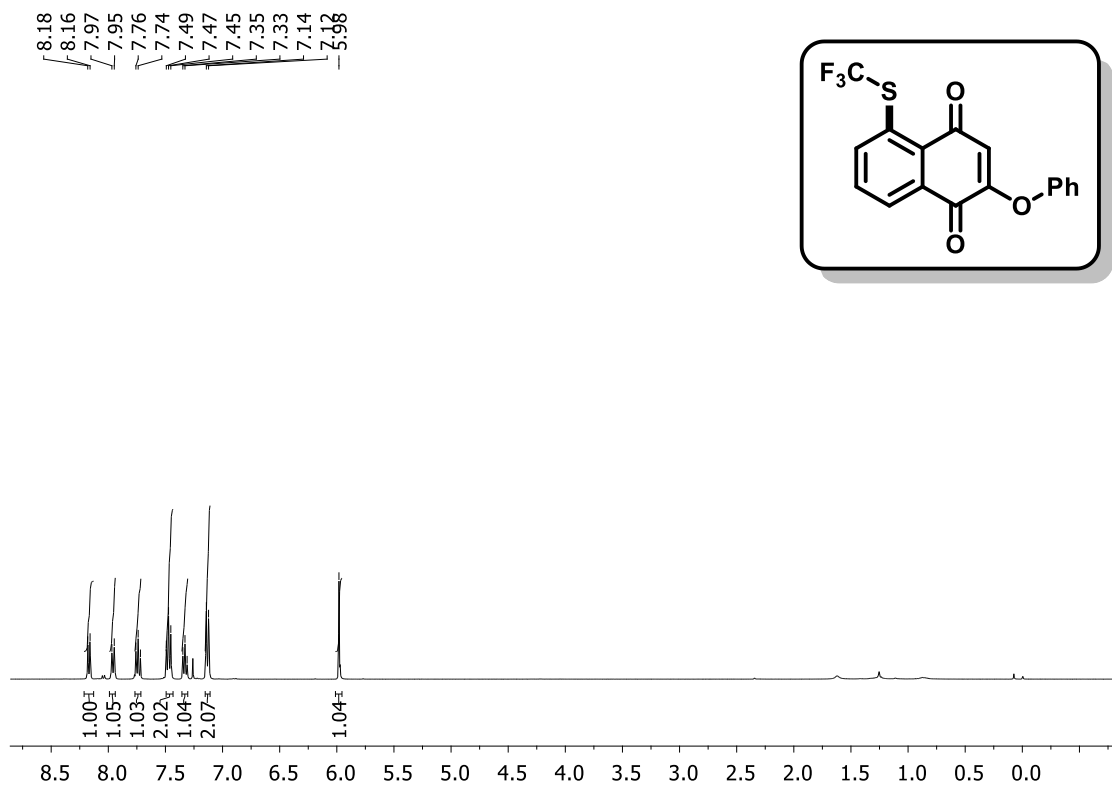


Figure S31. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **2h**.

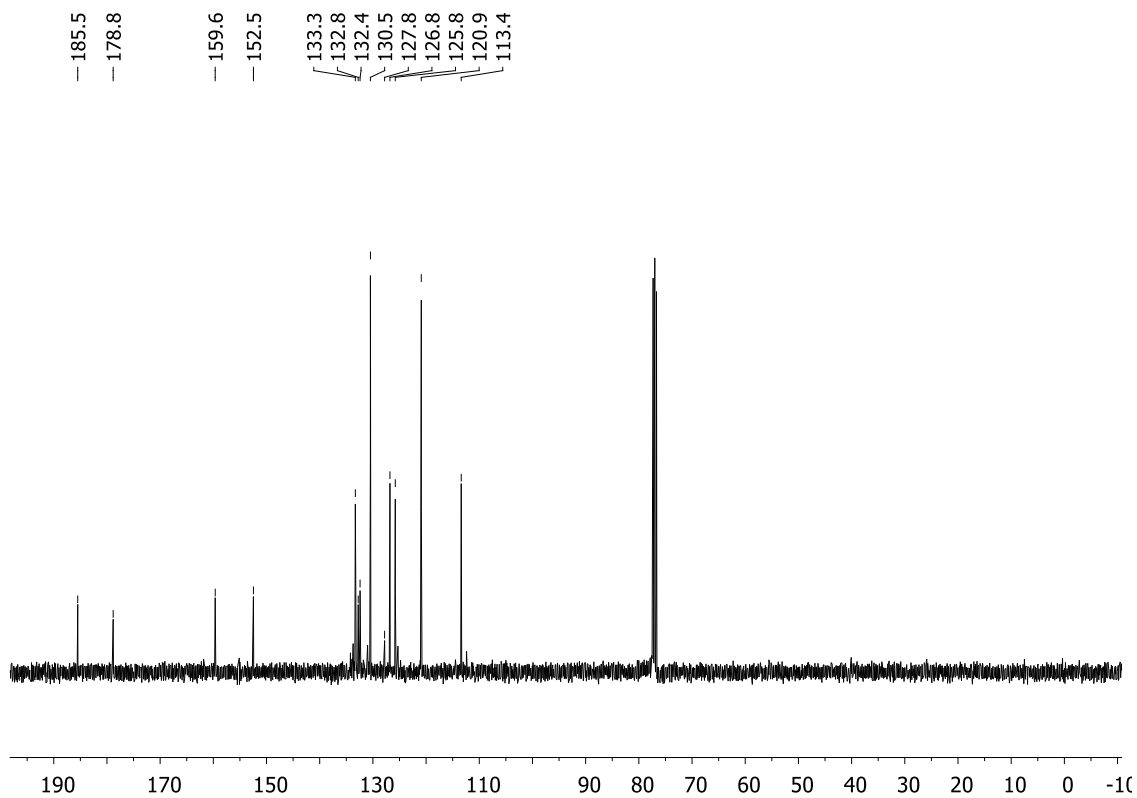


Figure S32. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **2h**.

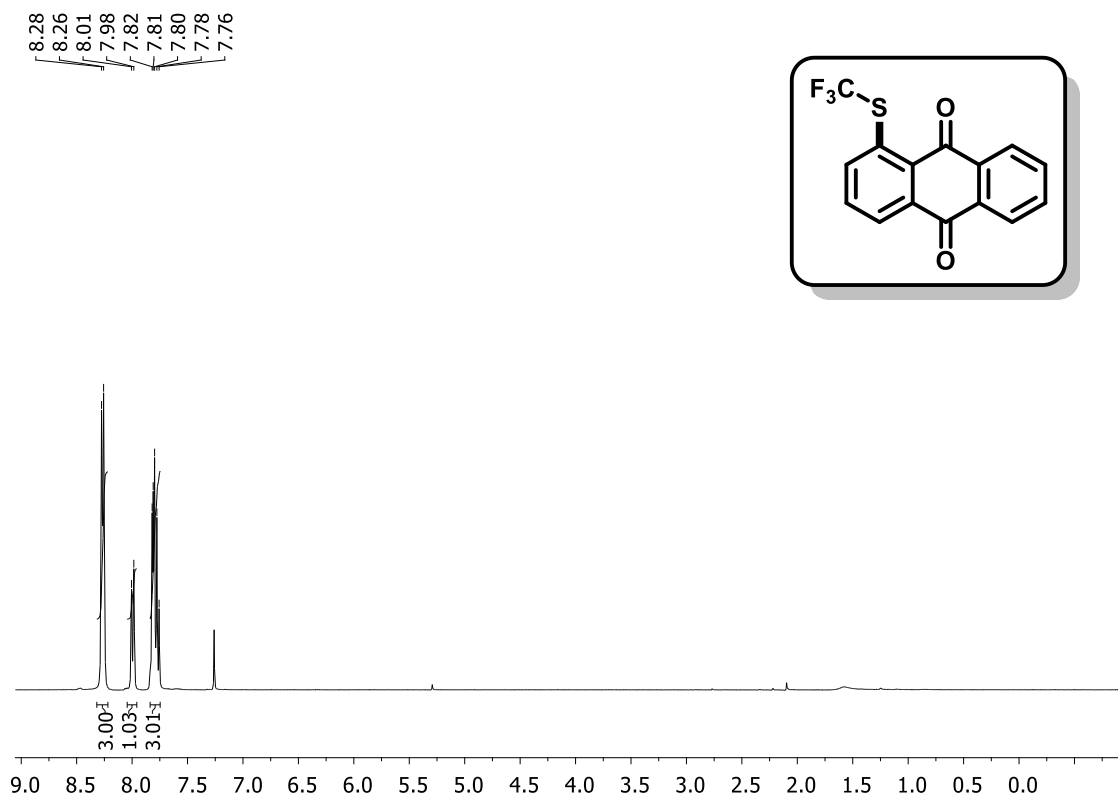


Figure S33. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **2i**.

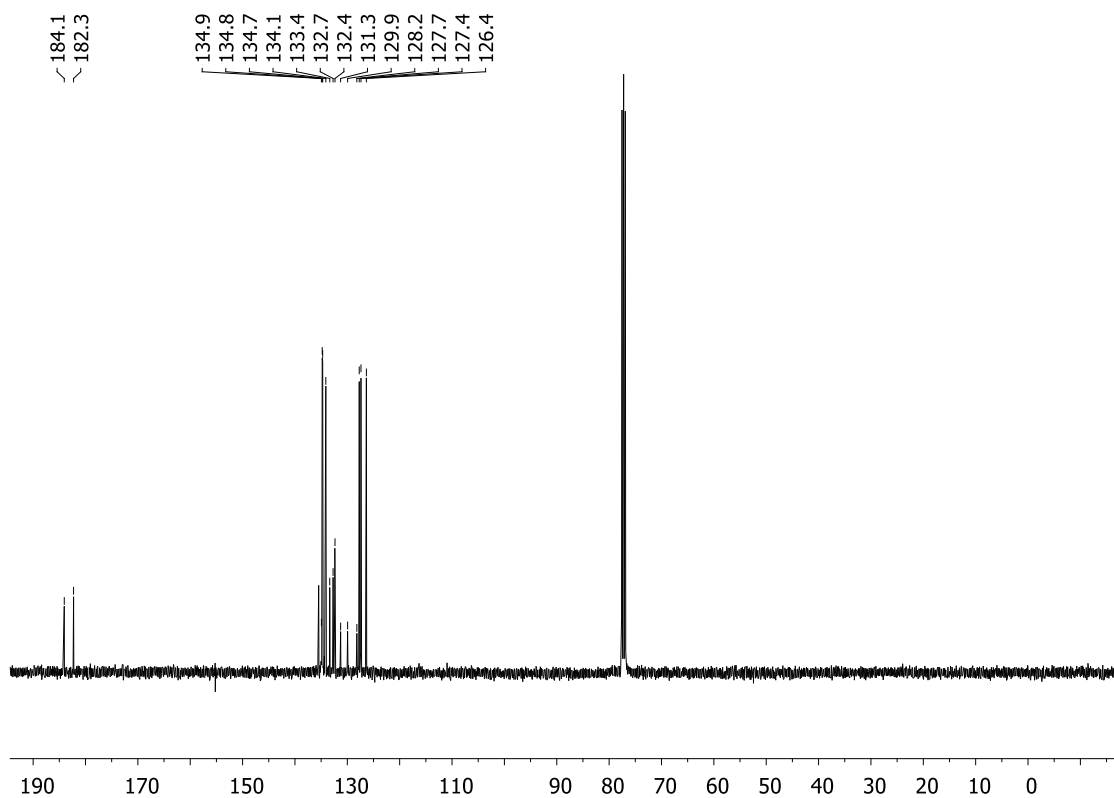


Figure S34. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **2i**.

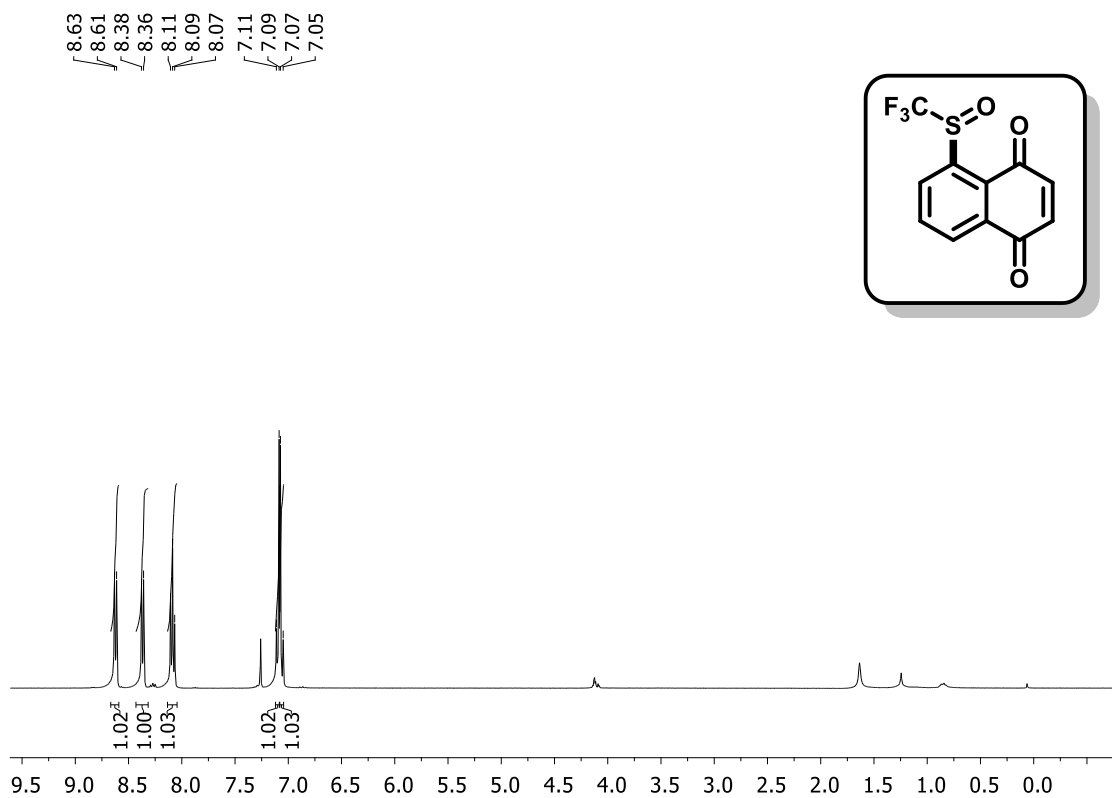


Figure S35. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **3a**.

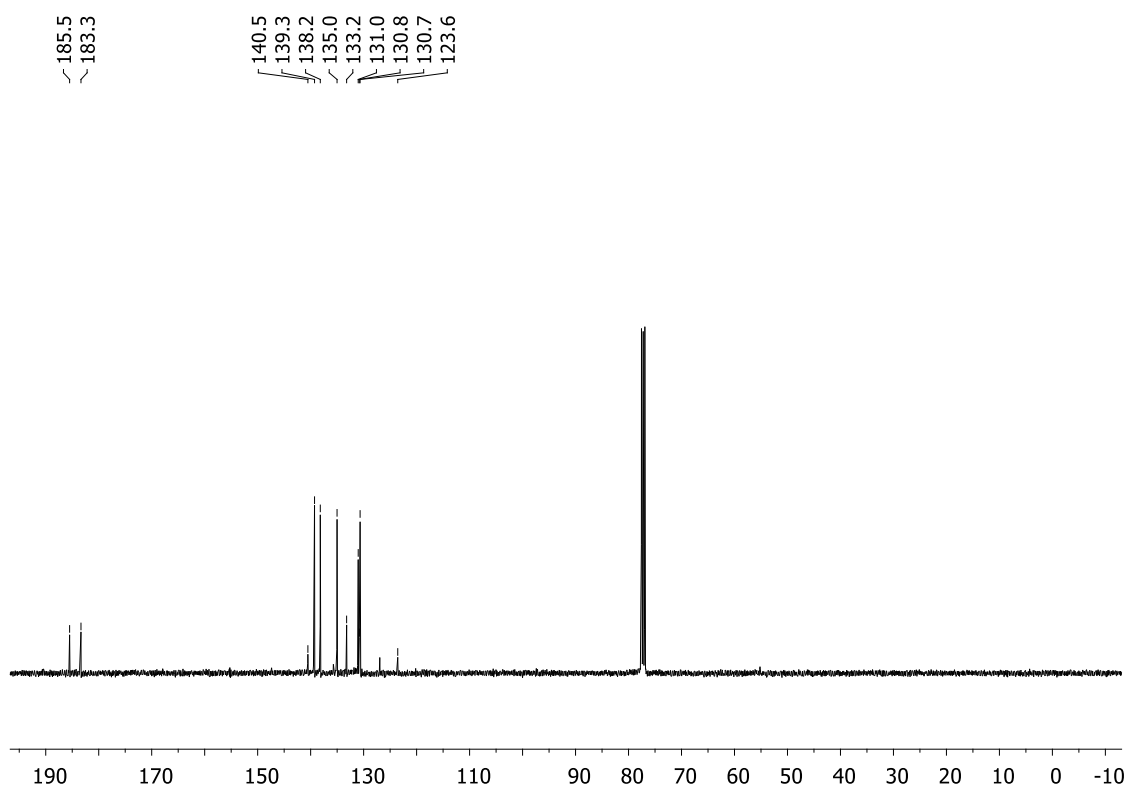


Figure S36. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **3a**.

8.69
8.67
8.60
8.58
8.35
8.35
8.34
8.33
8.31
8.31
8.29
8.29
8.14
8.12
8.10
7.91
7.89
7.89
7.88
7.88
7.87
7.87
7.86
7.85

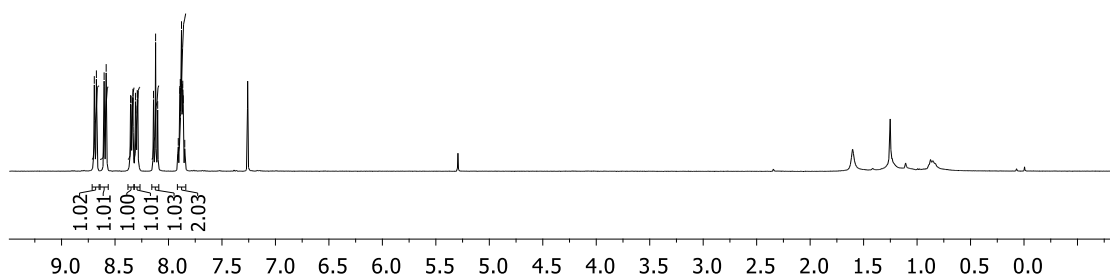
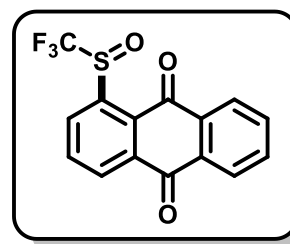


Figure S37. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **3b**.

183.9
181.7
141.4
135.5
135.1
135.0
133.0
132.5
132.4
131.4
131.2
127.9
127.8
127.1
123.7

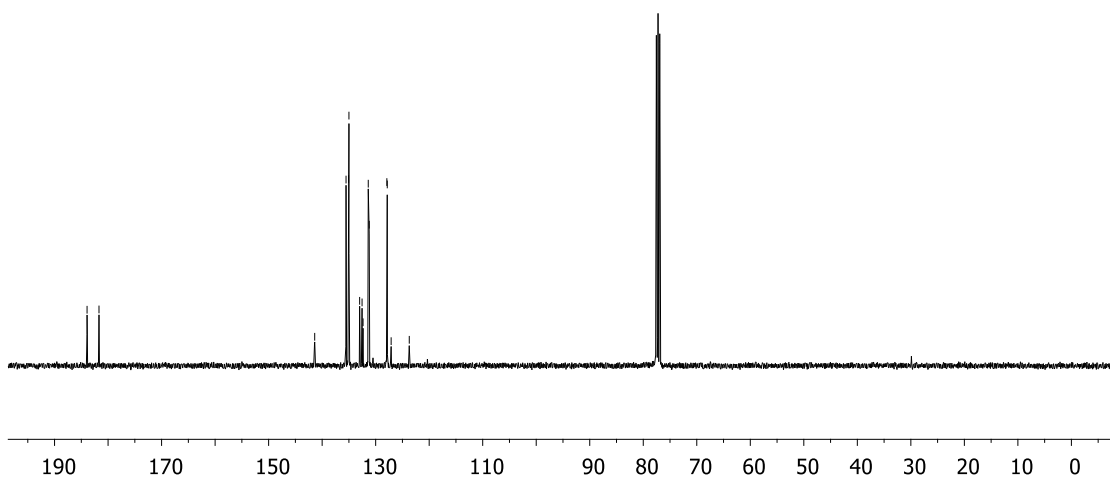


Figure S38. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **3b**.

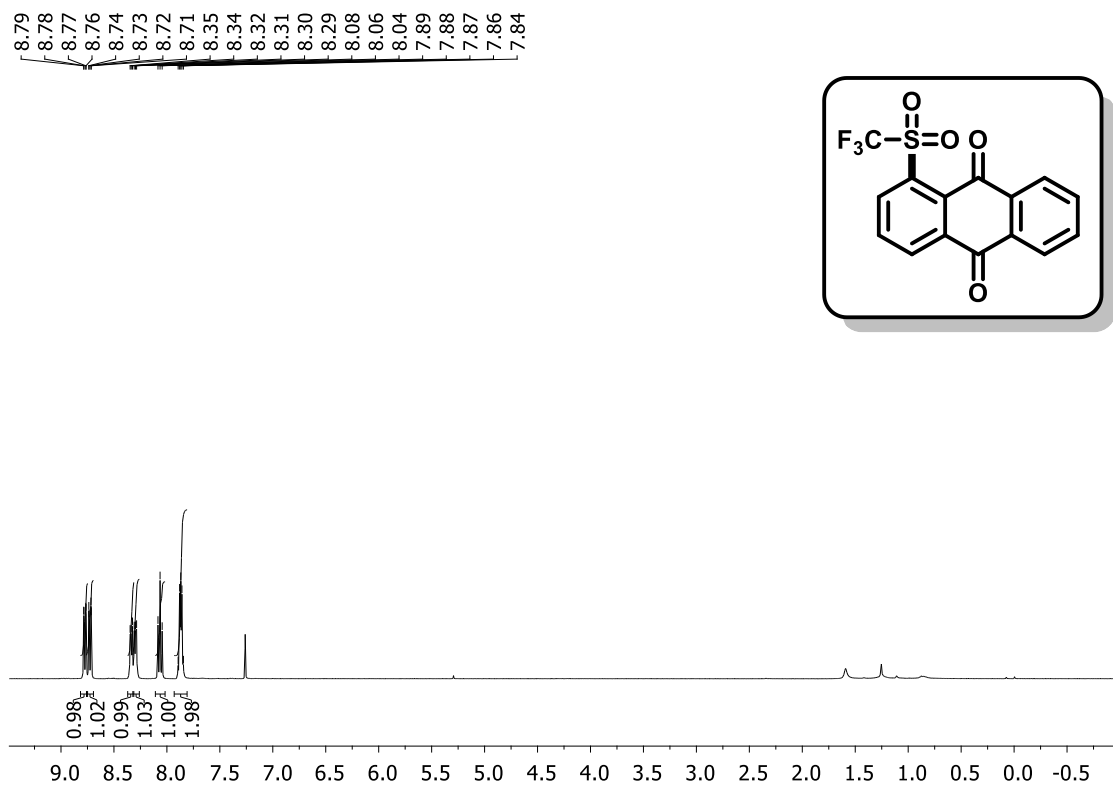


Figure S39. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **3c**.

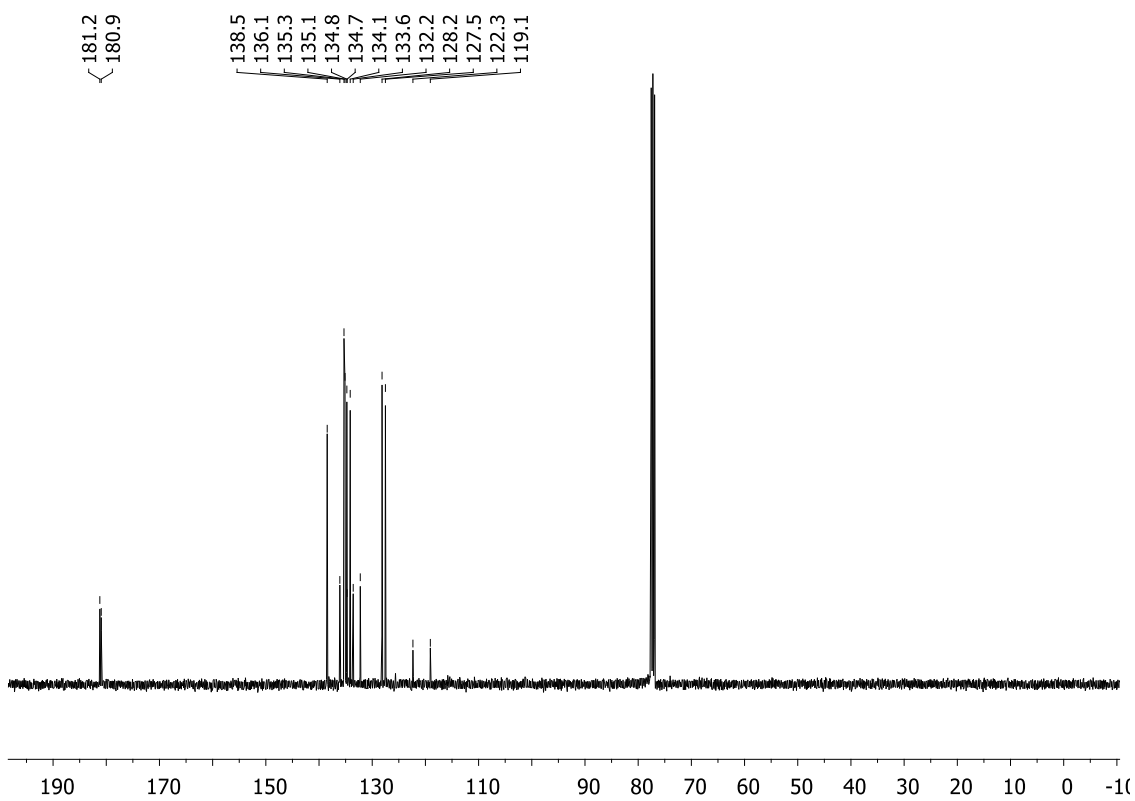


Figure S40. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **3c**.

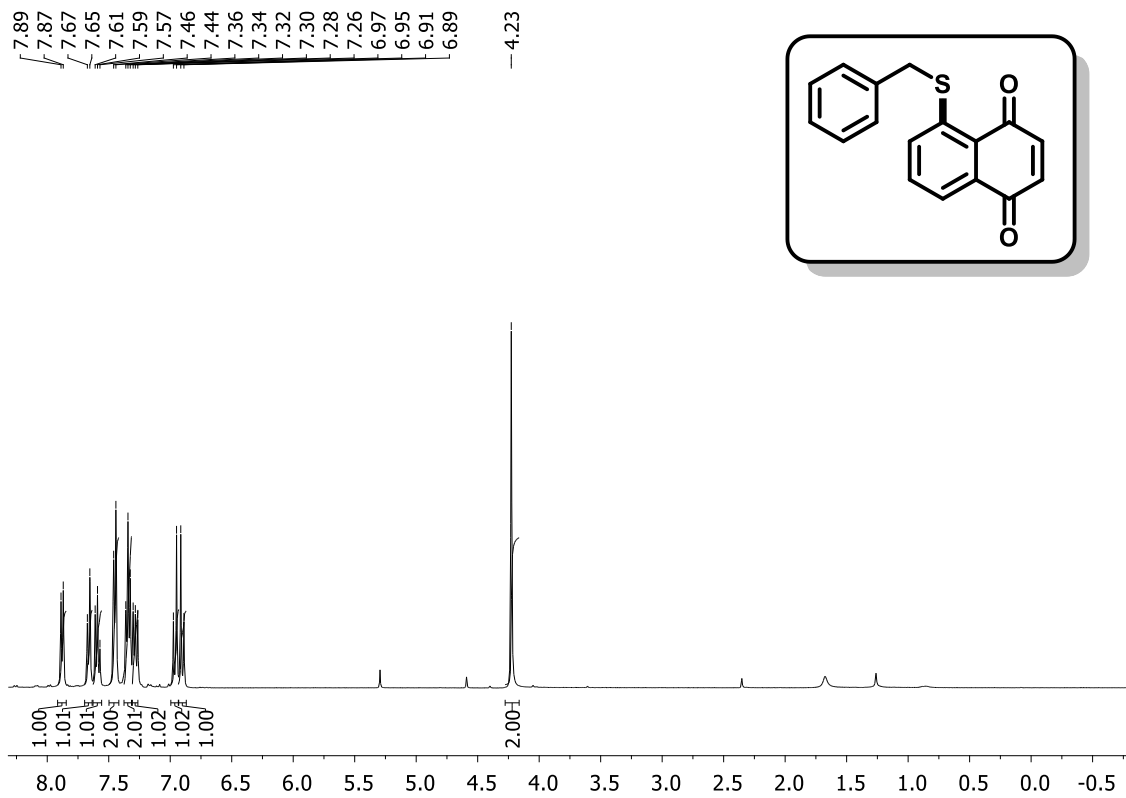


Figure S41. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4a.

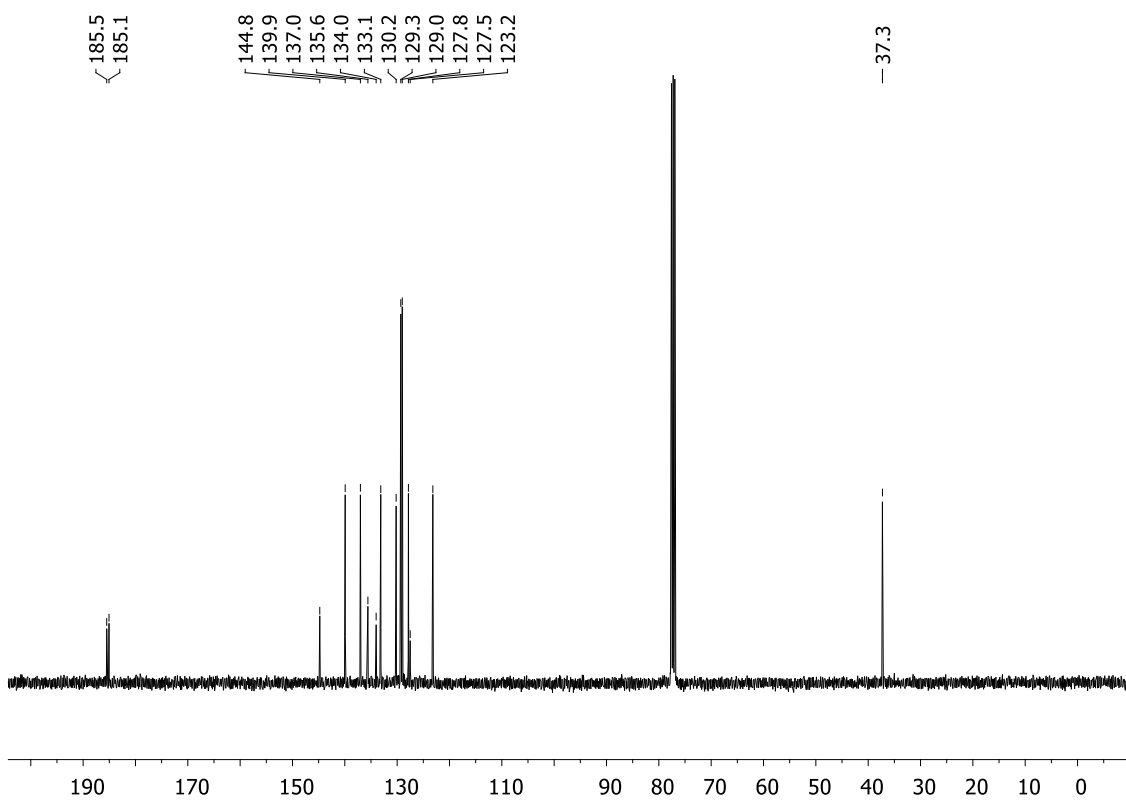
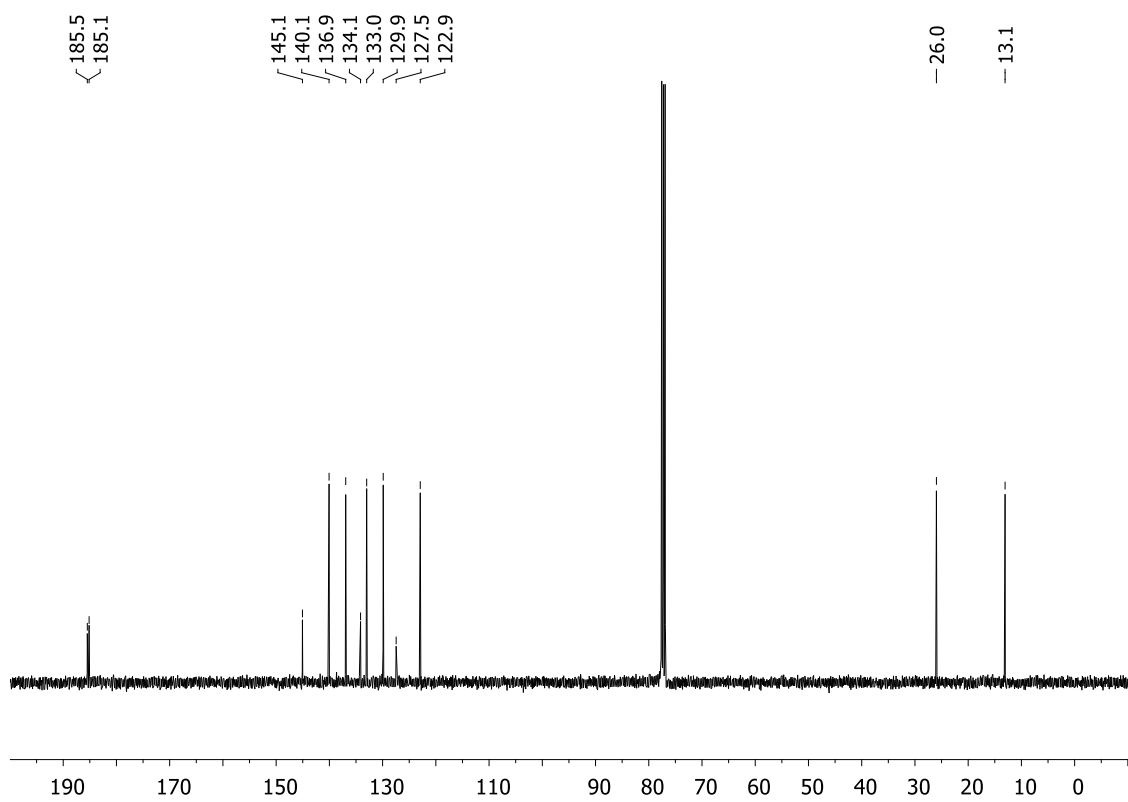
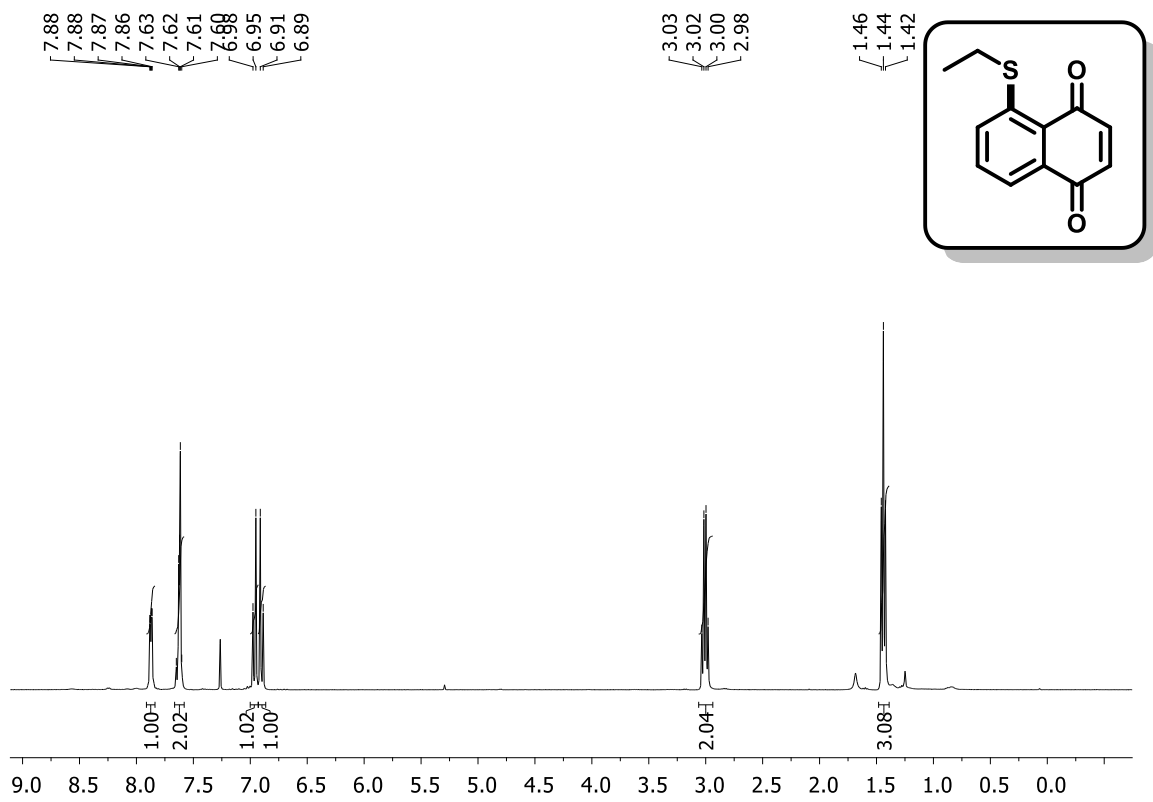


Figure S42. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound 4a.



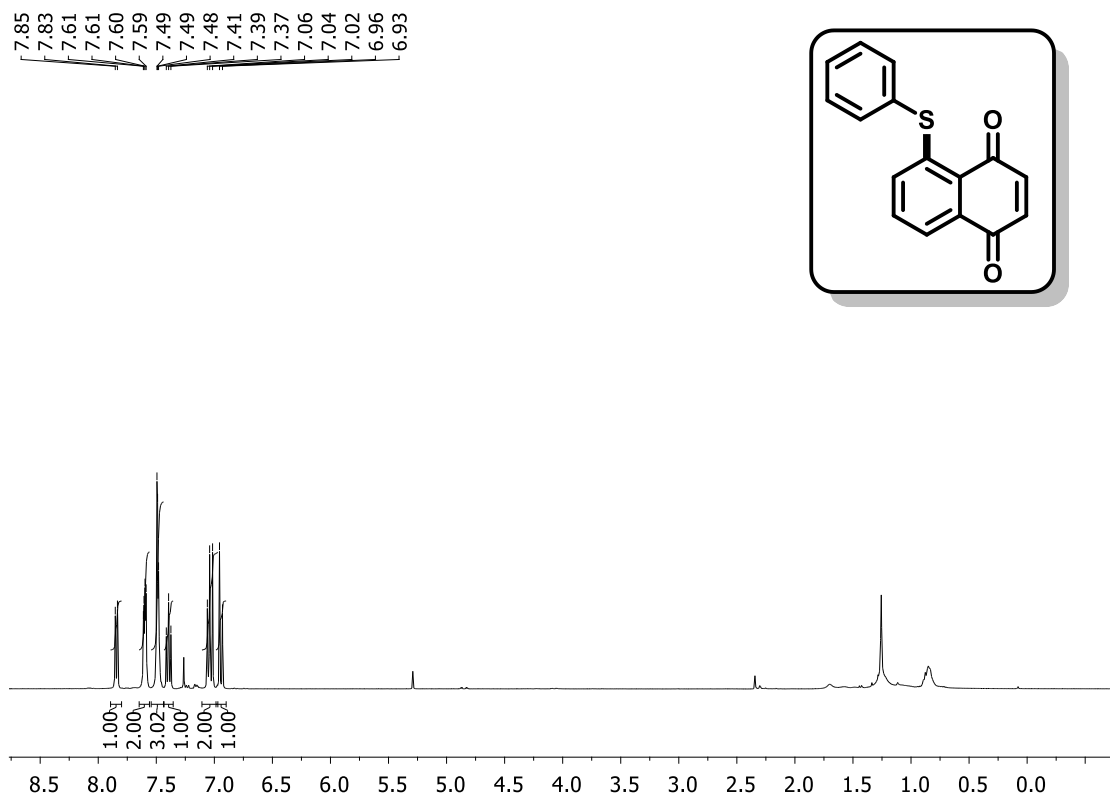


Figure S45. ¹H NMR spectrum (400 MHz, CDCl₃) of compound 4c.

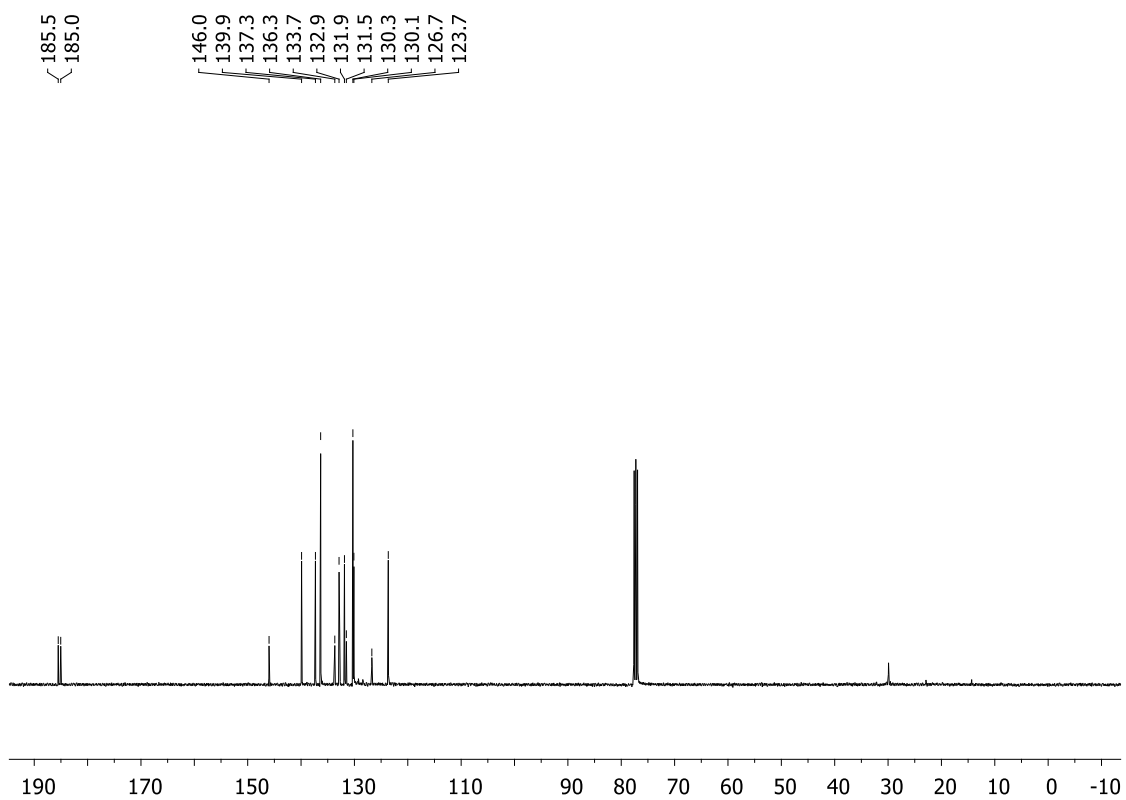


Figure S46. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound 4c.

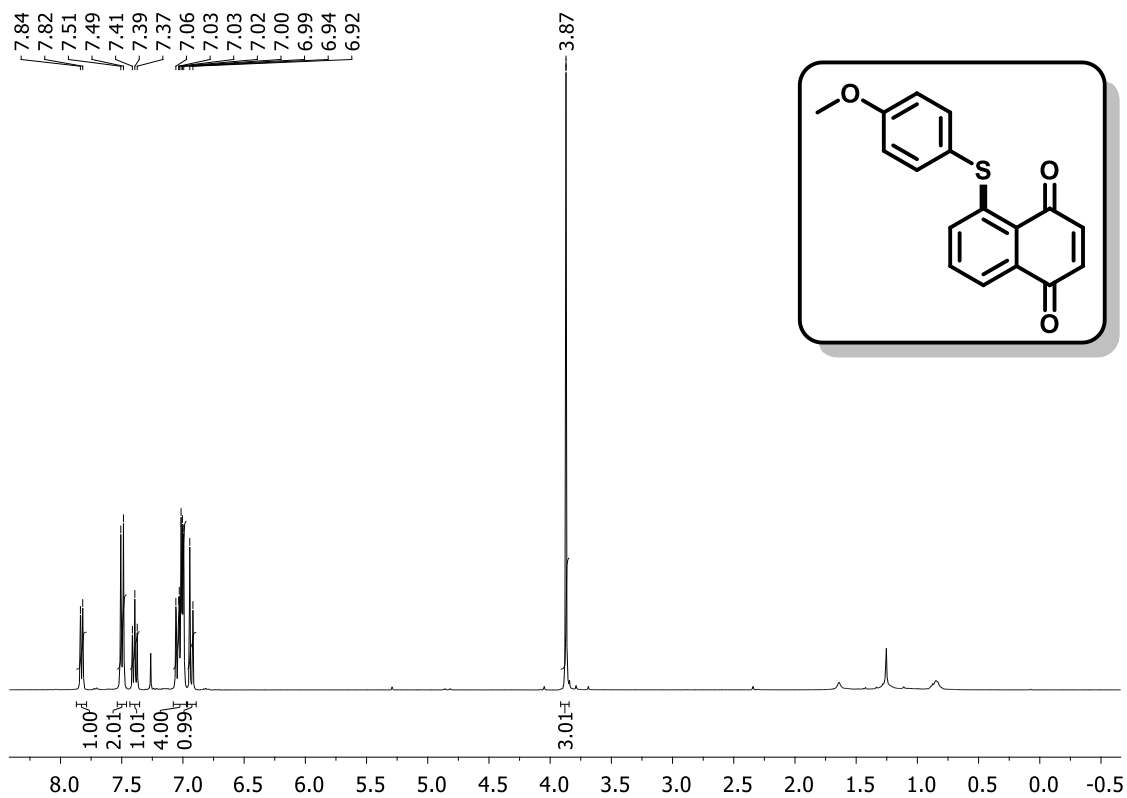


Figure S47. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **4d**.

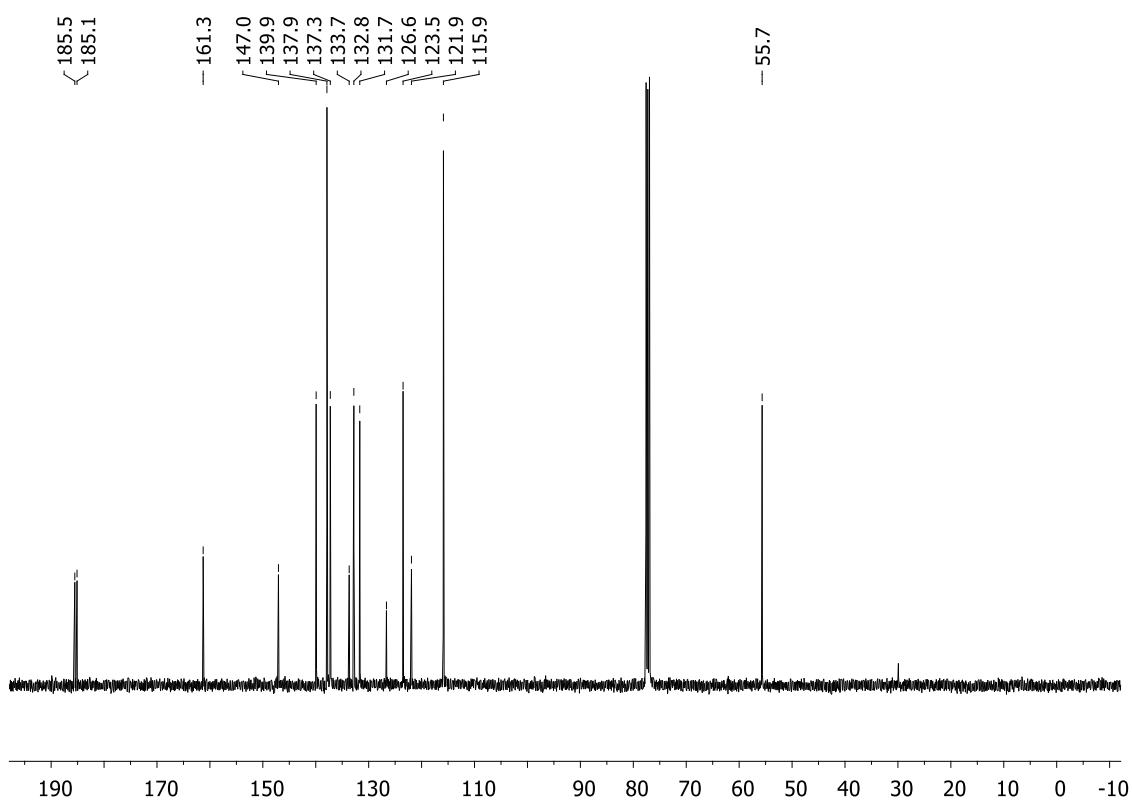


Figure S48. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **4d**.

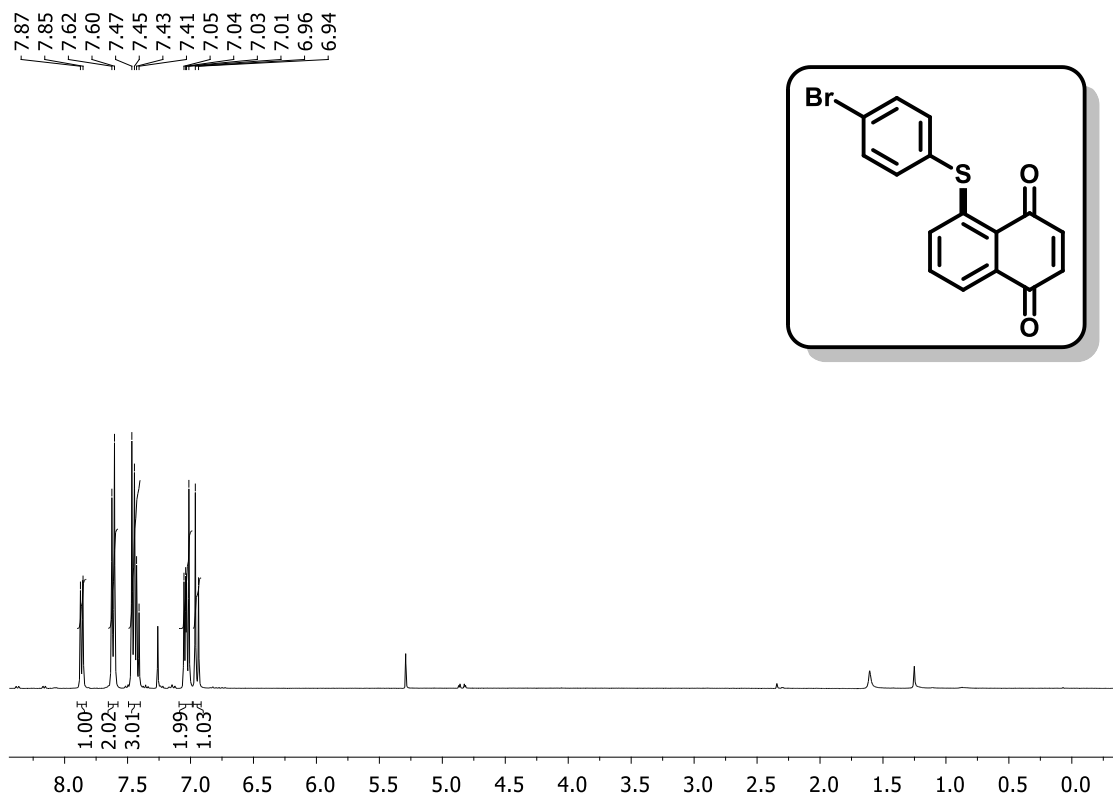


Figure S49. ^1H NMR spectrum (400 MHz, CDCl_3) of compound **4e**.

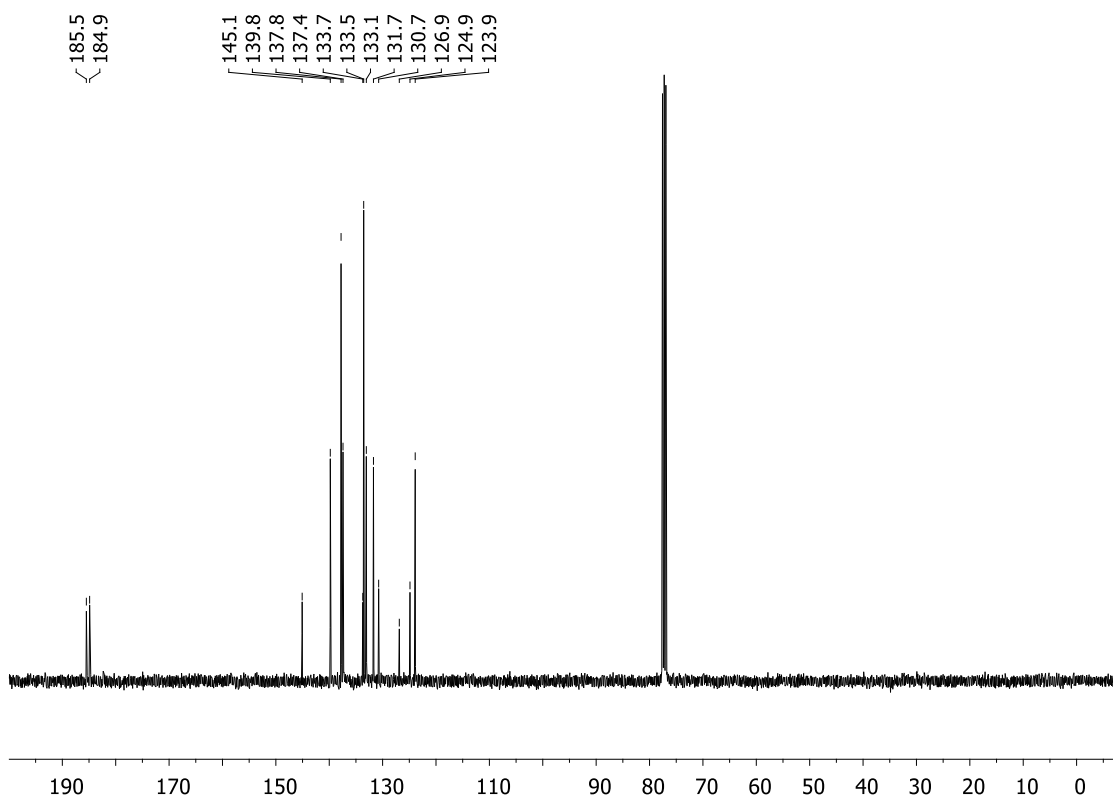


Figure S50. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound **4e**.

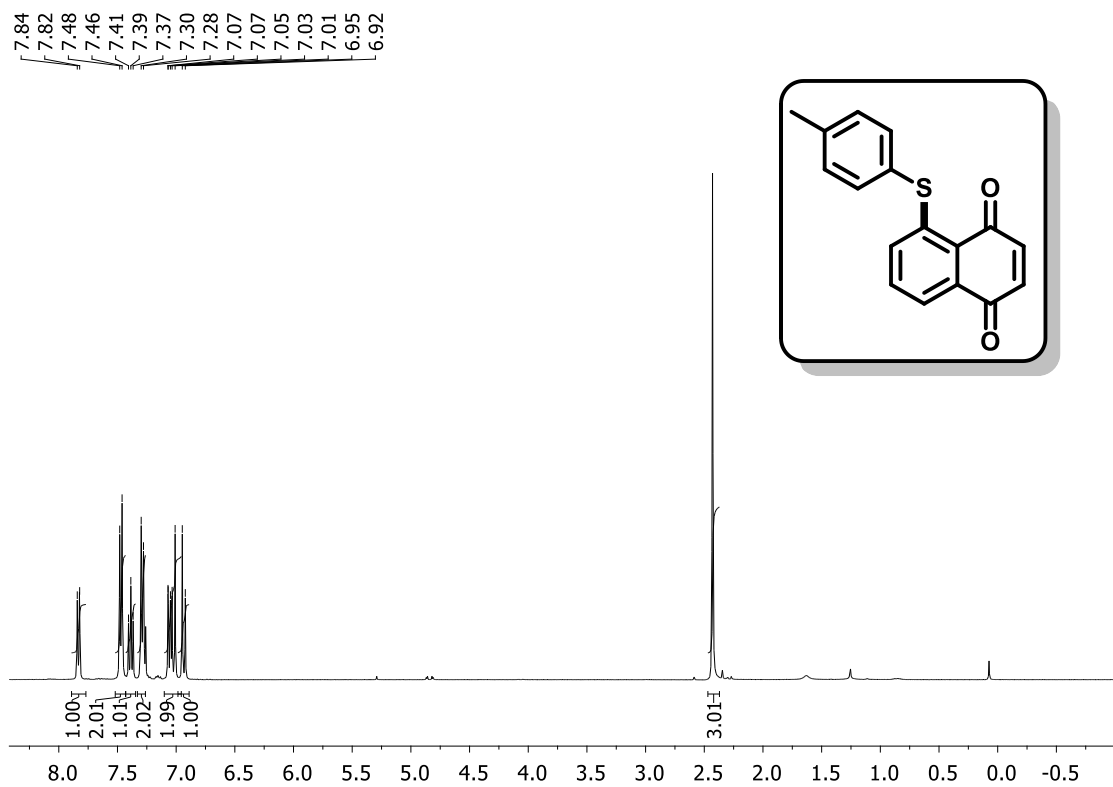


Figure S51. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **4f**.

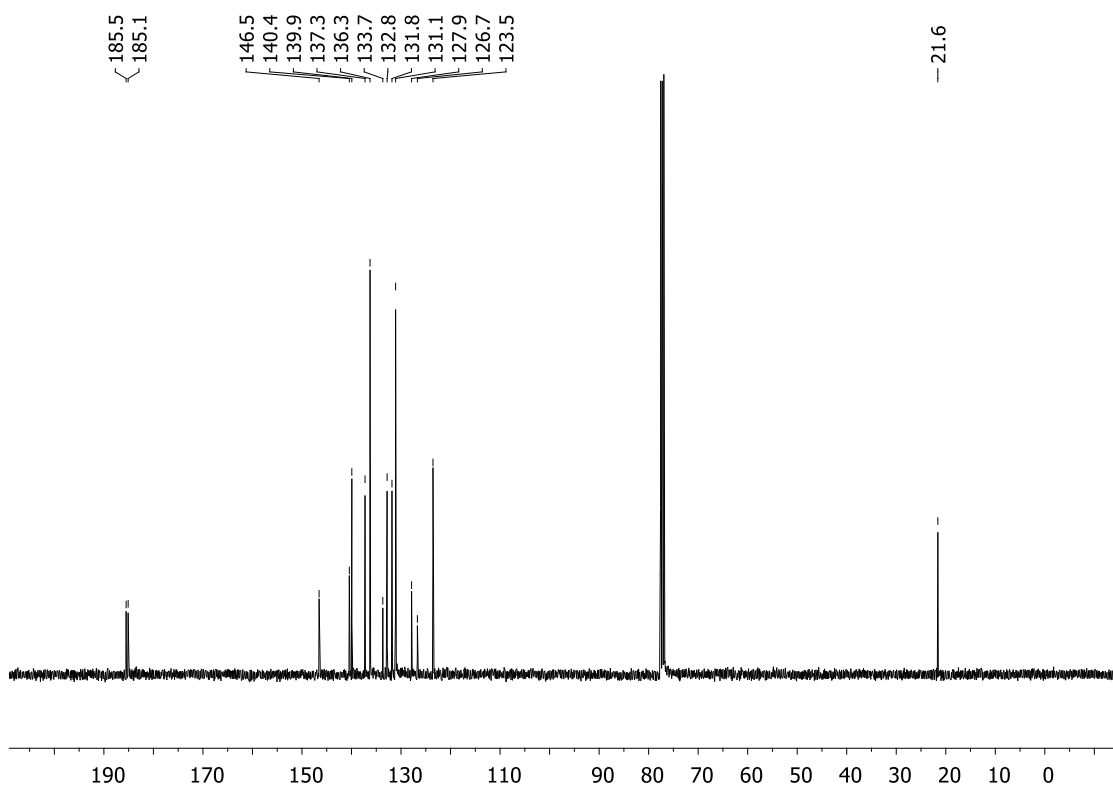


Figure S52. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound **4f**.

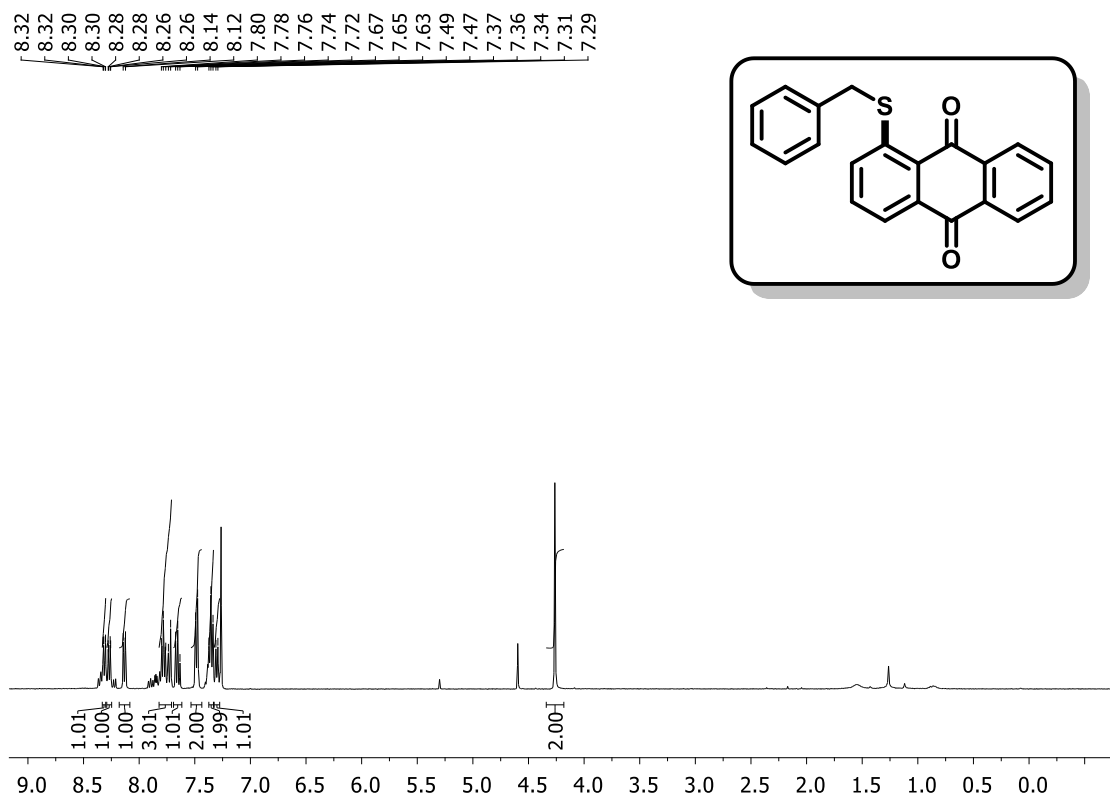


Figure S53. ¹H NMR spectrum (400 MHz, CDCl₃) of compound **4g**.

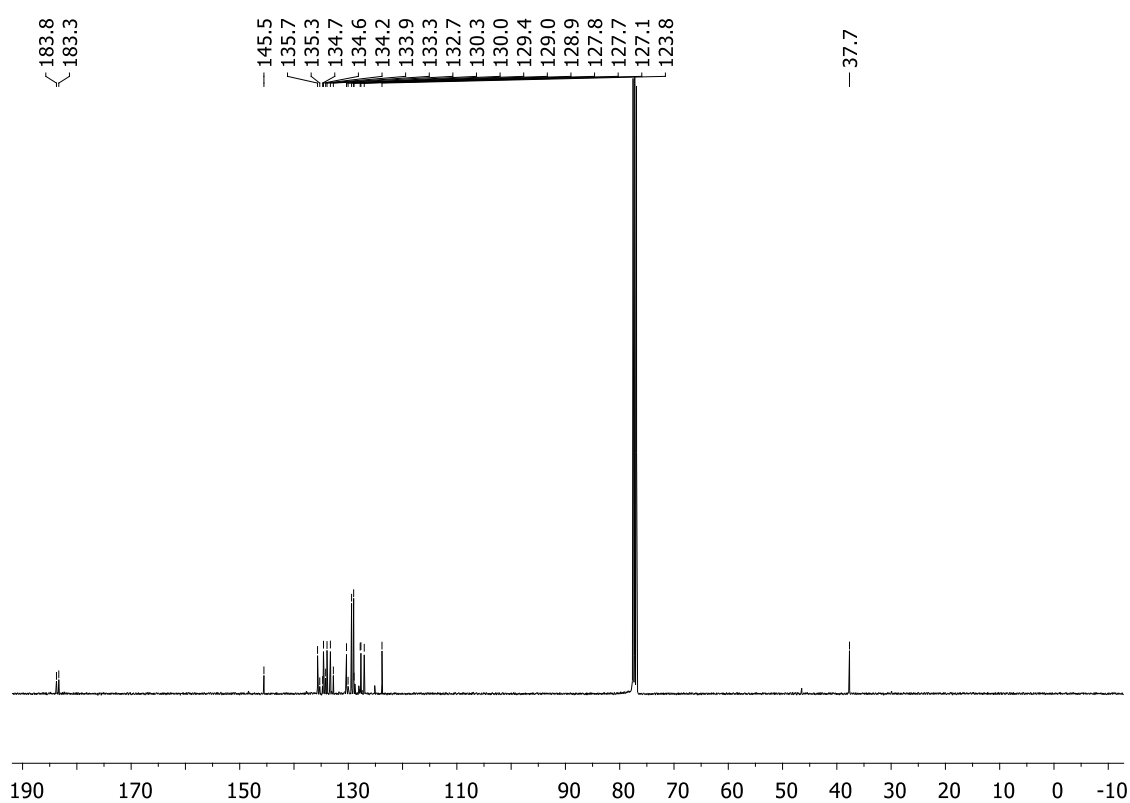


Figure S54. ¹³C NMR spectrum (100 MHz, CDCl₃) of compound **4g**.

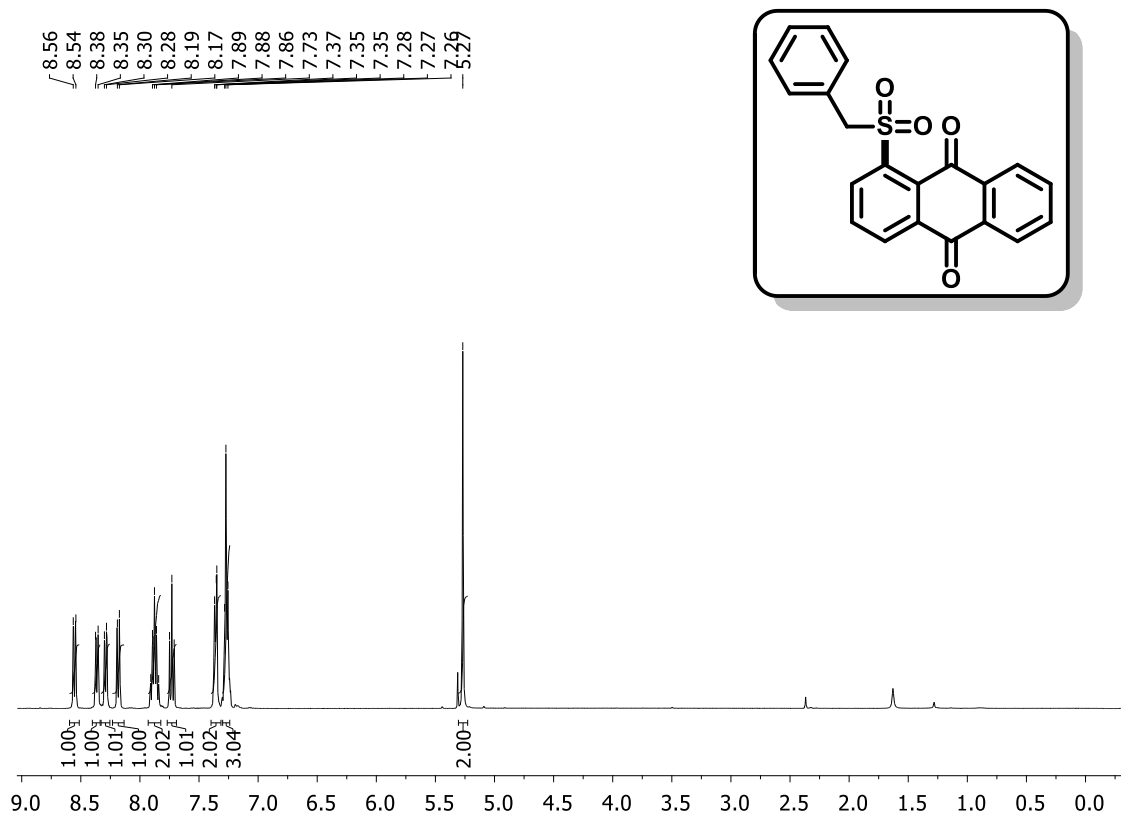


Figure S55. ^1H NMR spectrum (400 MHz, CDCl_3) of compound 5.

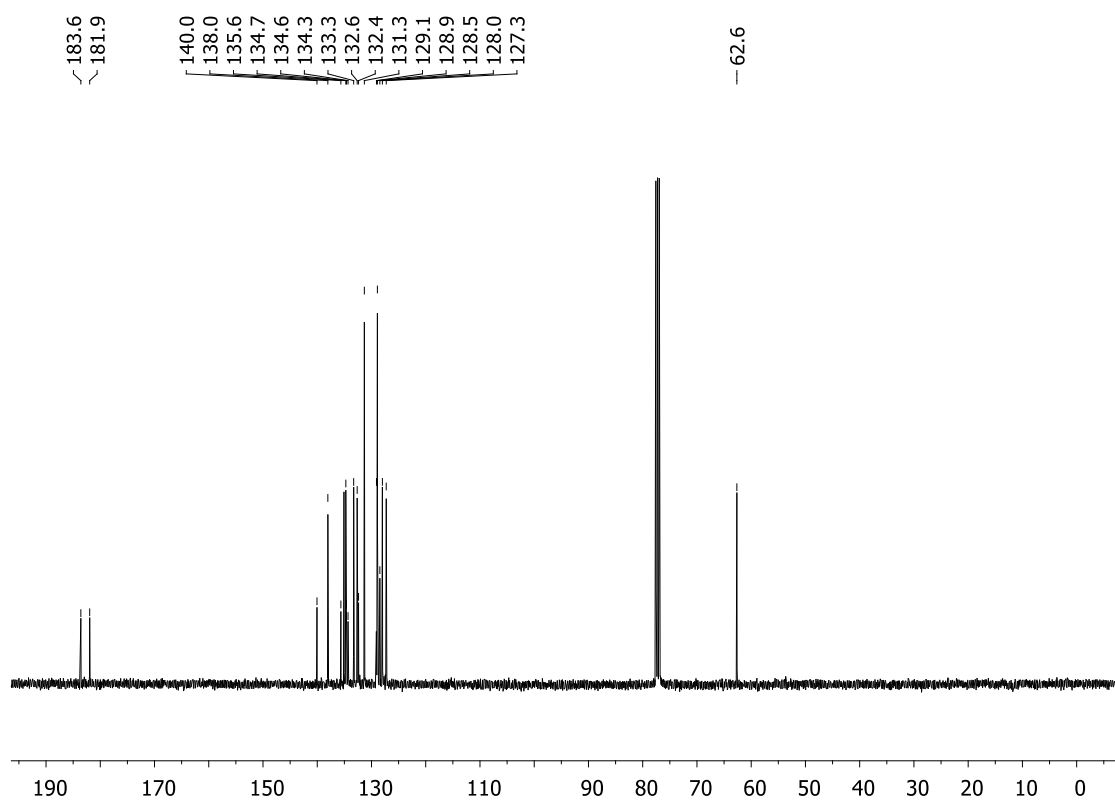


Figure S56. ^{13}C NMR spectrum (100 MHz, CDCl_3) of compound 5.

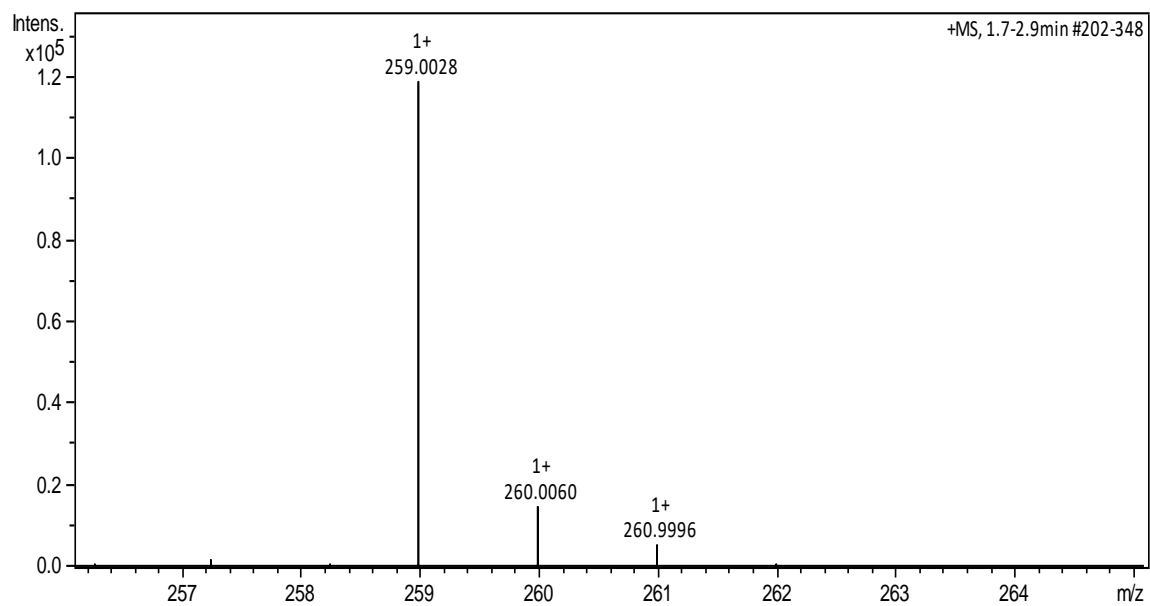
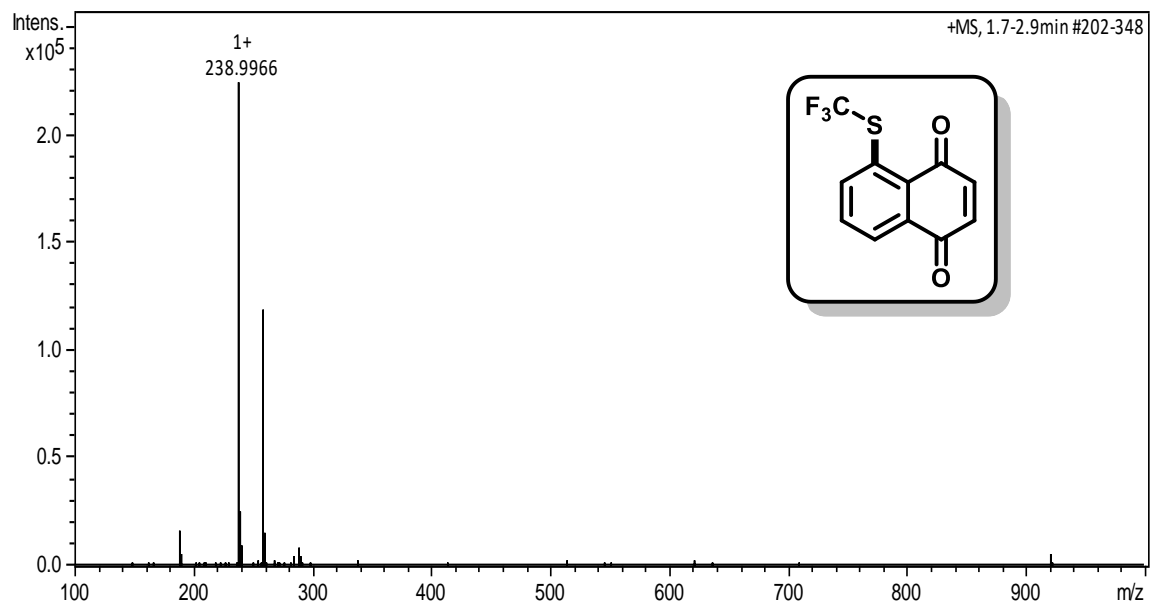


Figure S57. HRMS (ESI⁺) of compound **2a**.

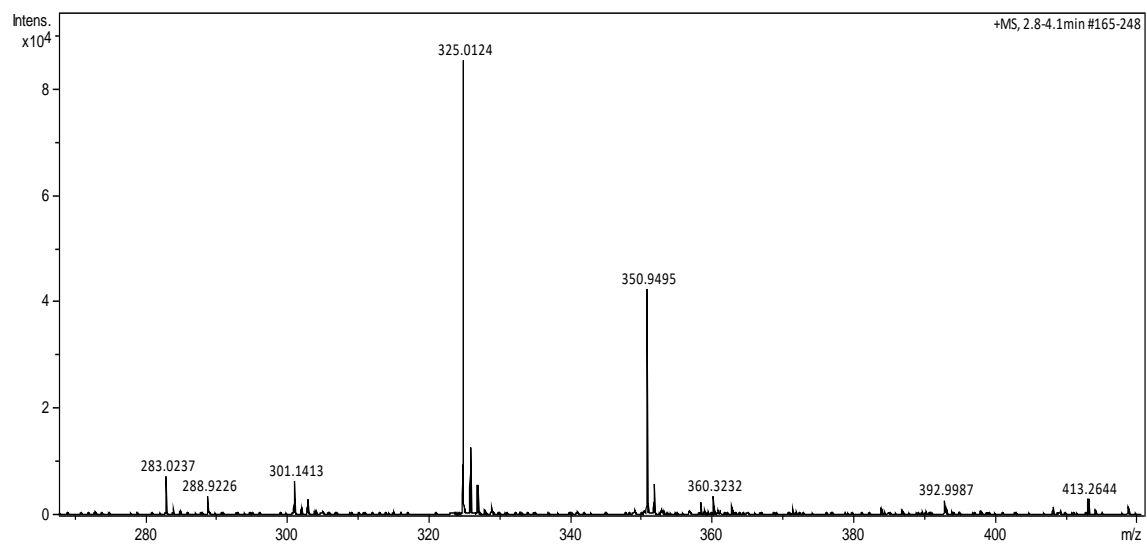
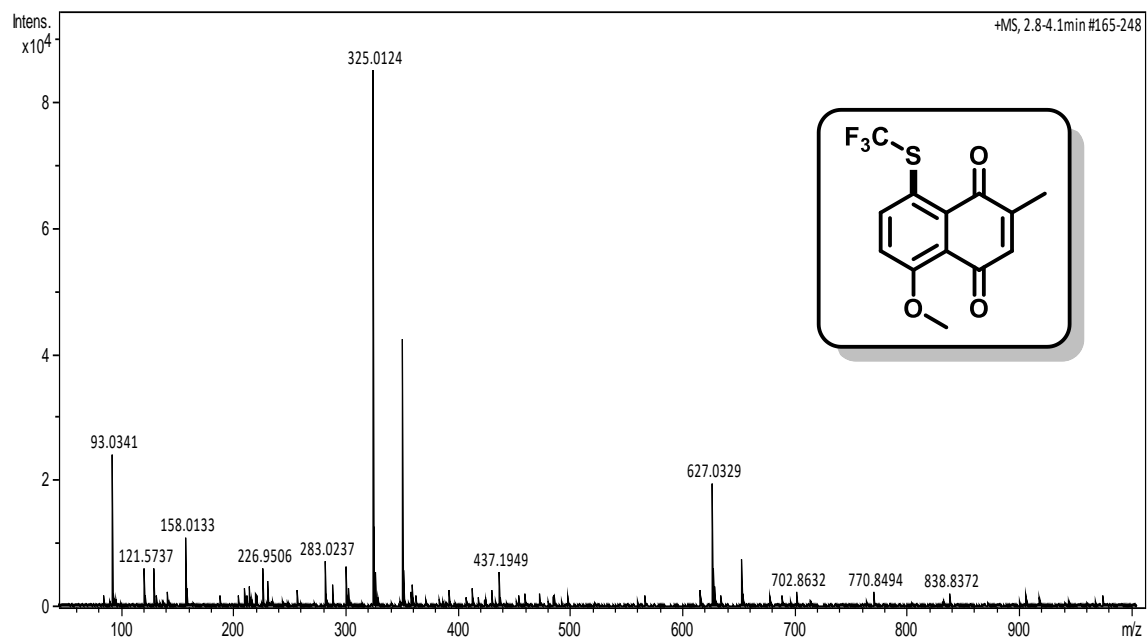


Figure S58. HRMS (ESI⁺) of compound **2b**.

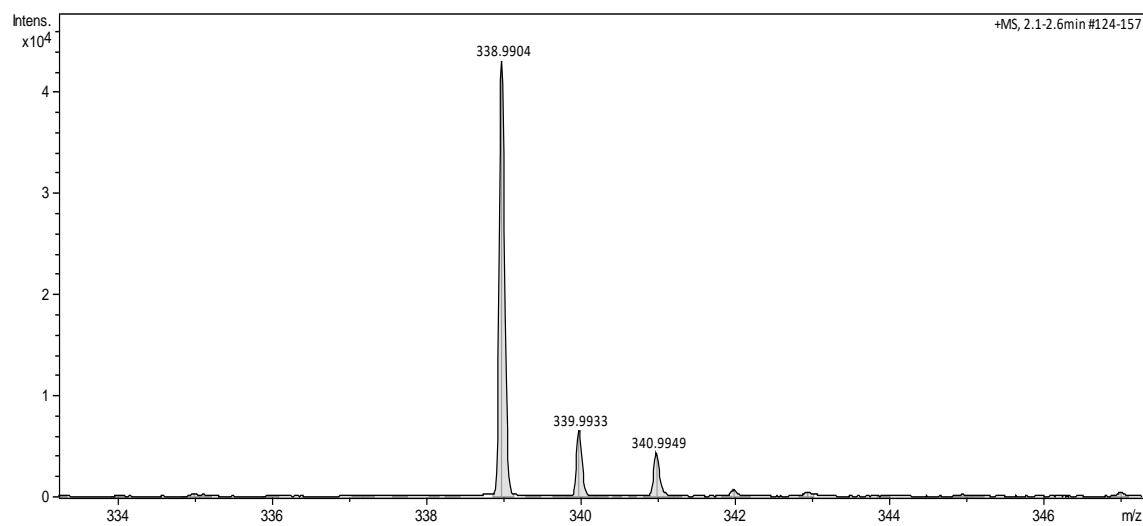
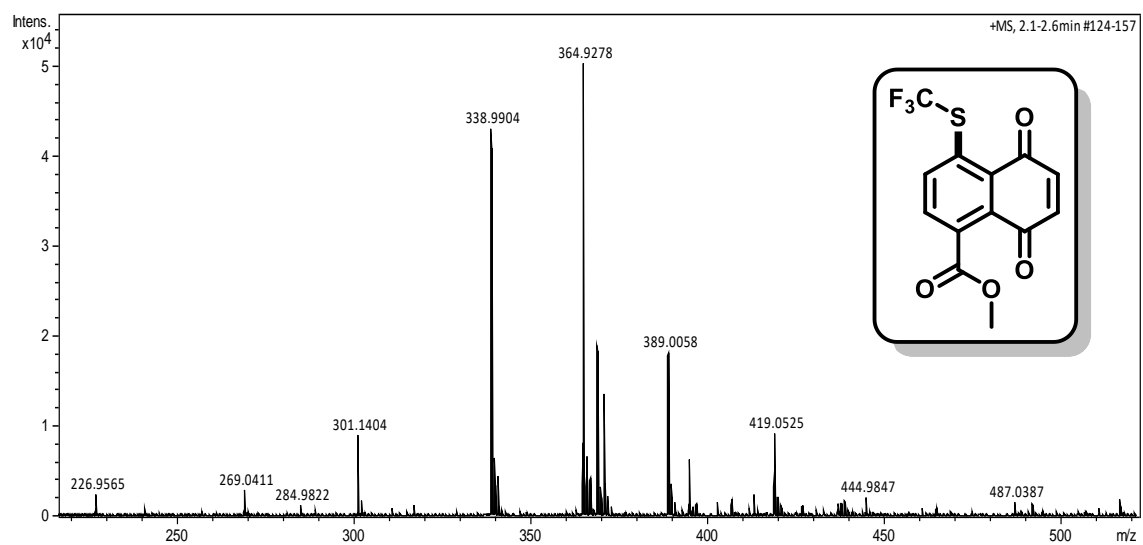


Figure S59. HRMS (ESI⁺) of compound **2c**.

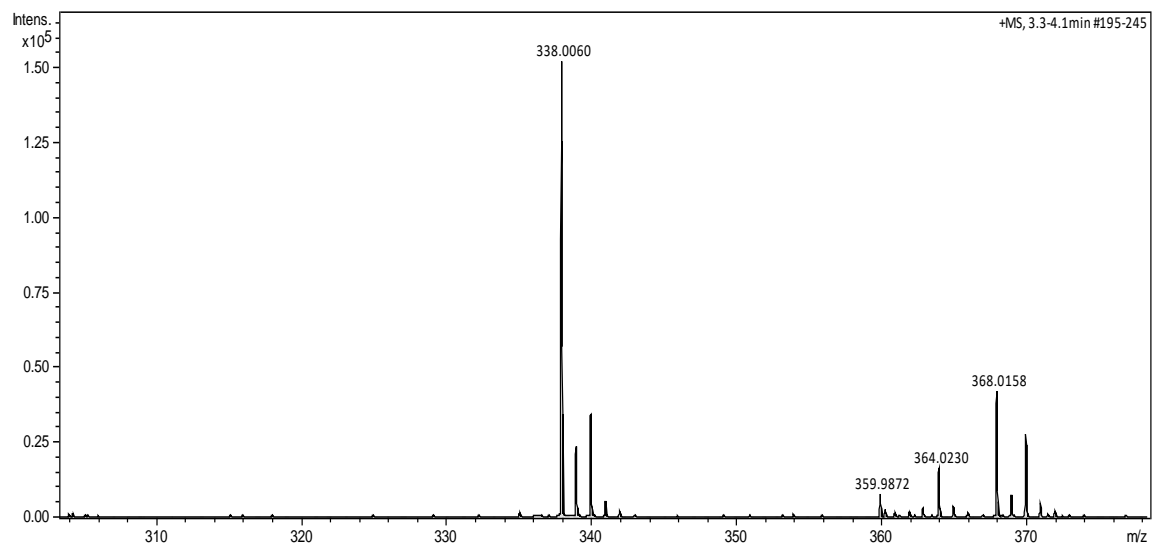
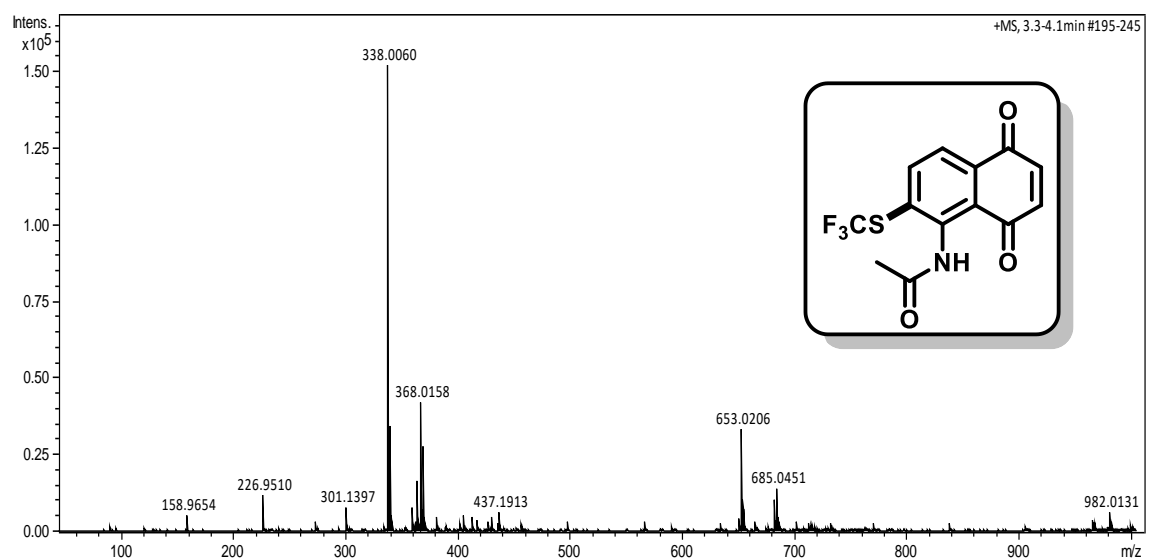


Figure S60. HRMS (ESI⁺) of compound **2d**.

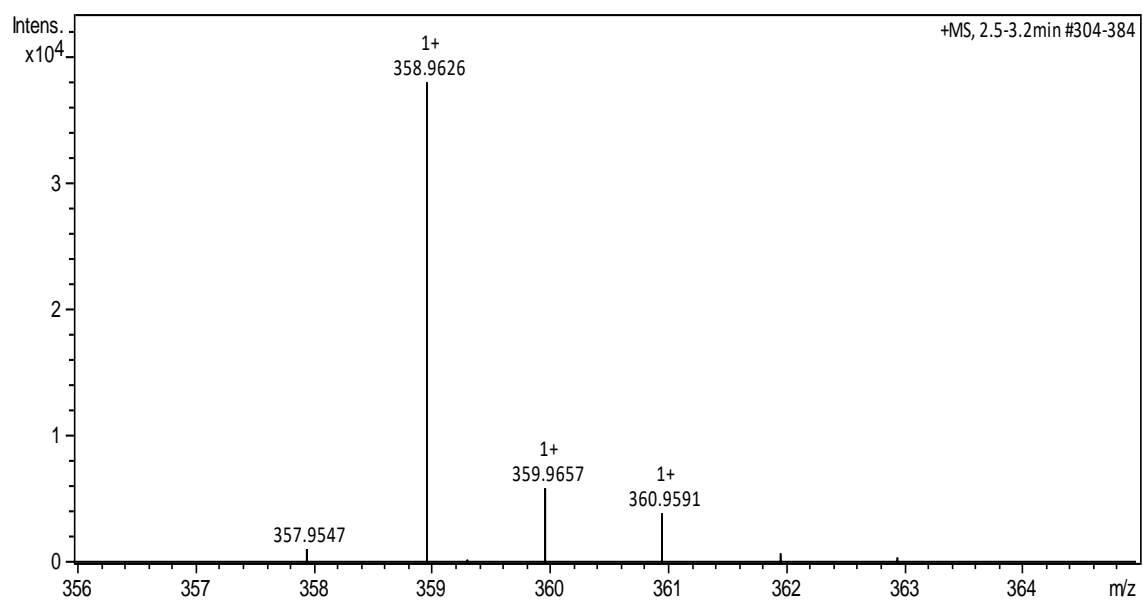
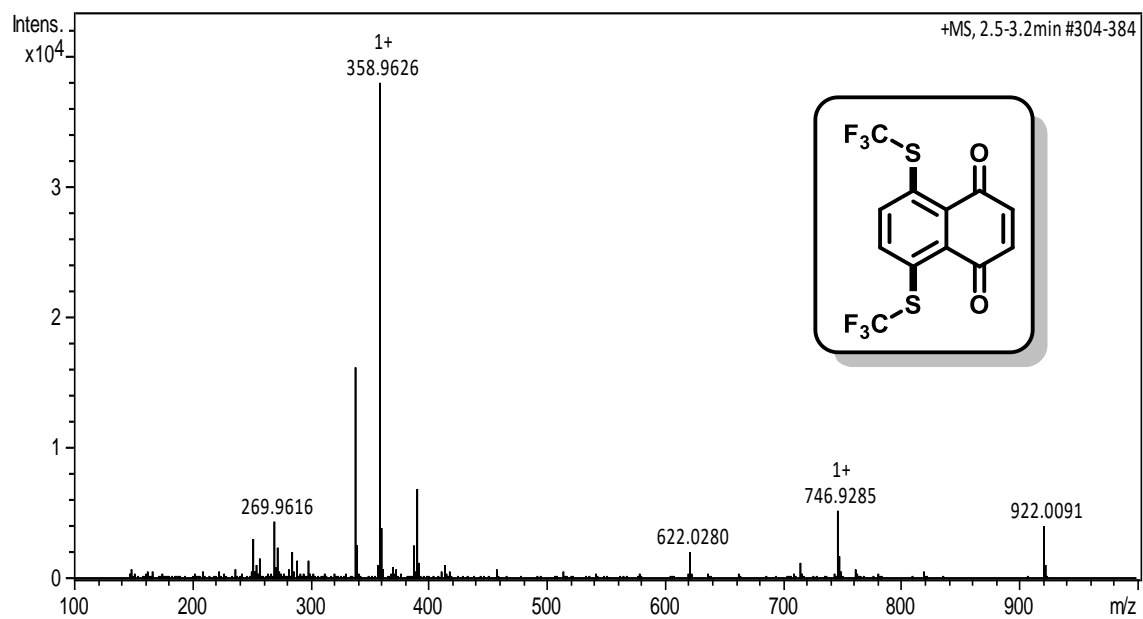


Figure S61. HRMS (ESI⁺) of compound **2f**.

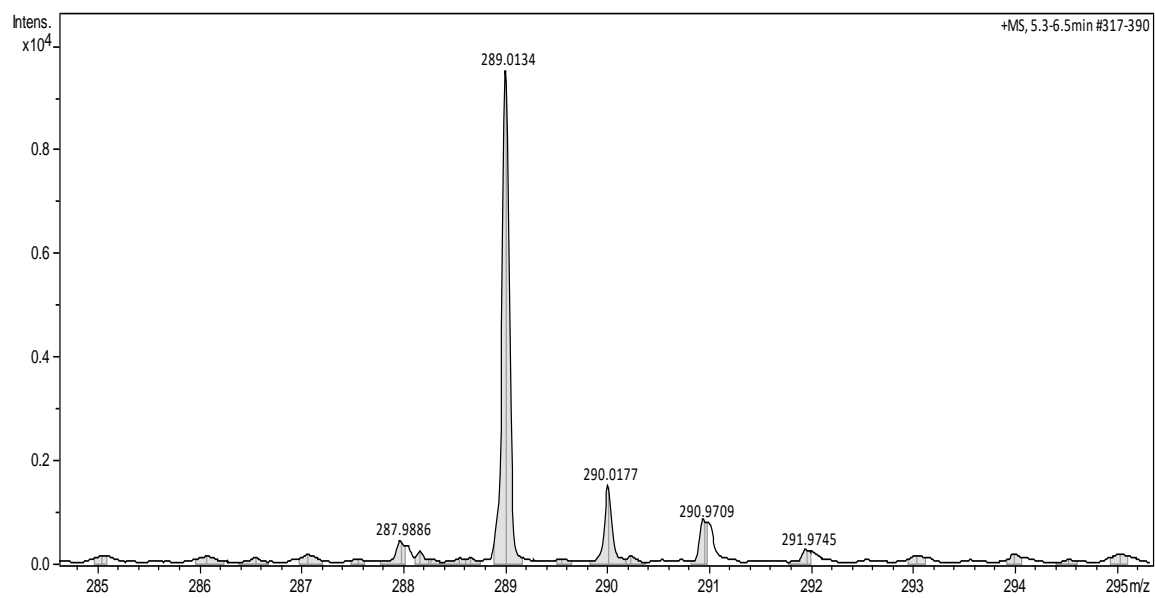
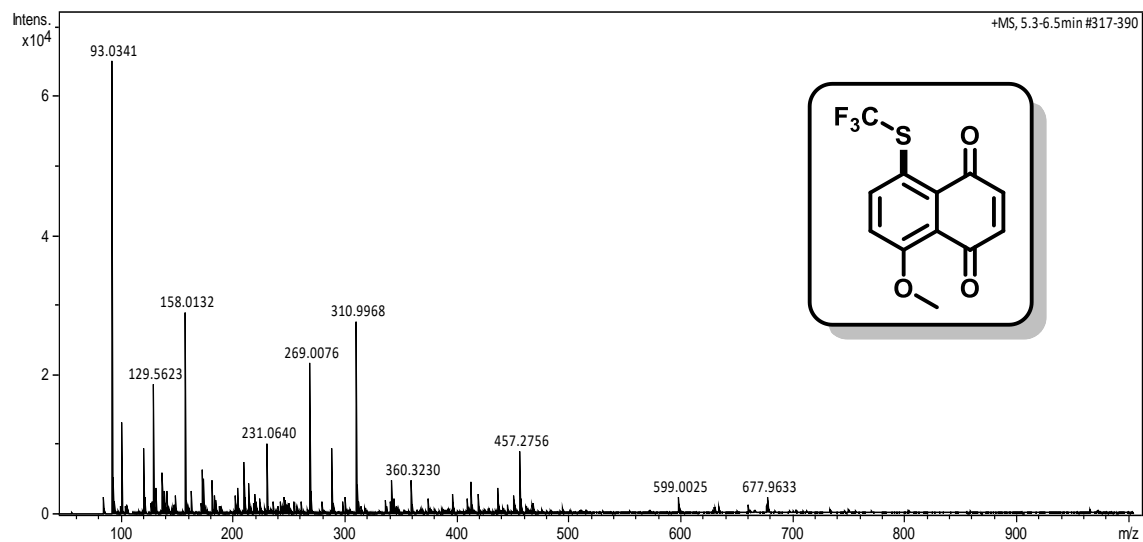


Figure S62. HRMS (ESI⁺) of compound **2g**.

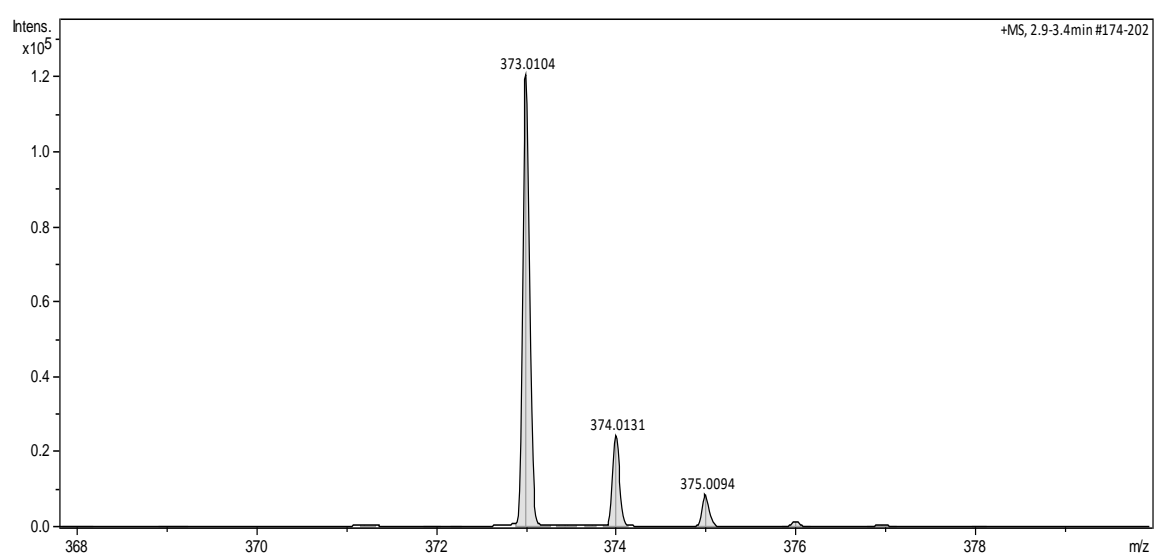
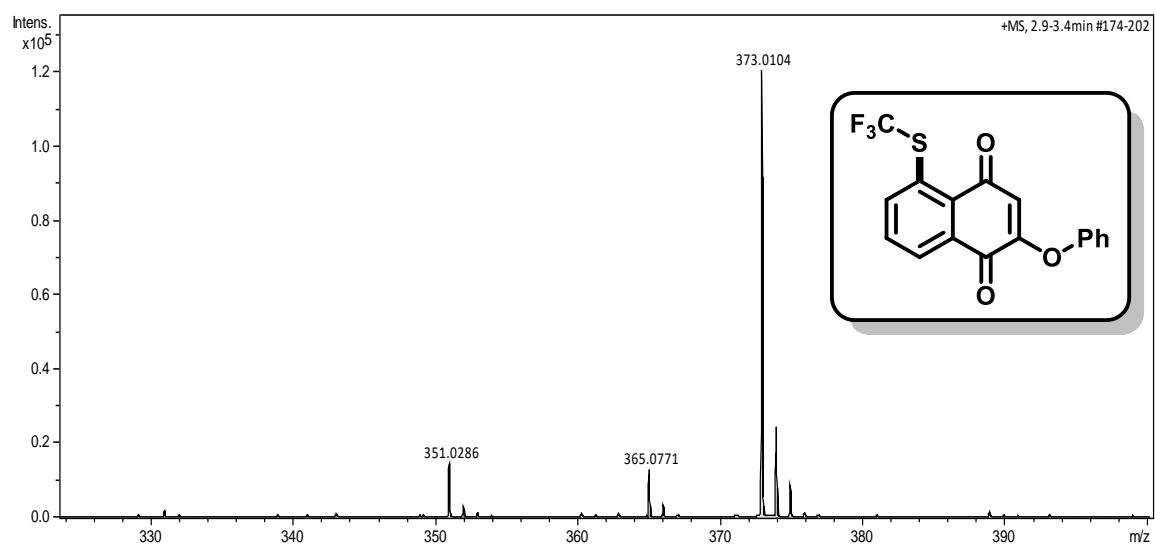


Figure S63. HRMS (ESI⁺) of compound **2h**.

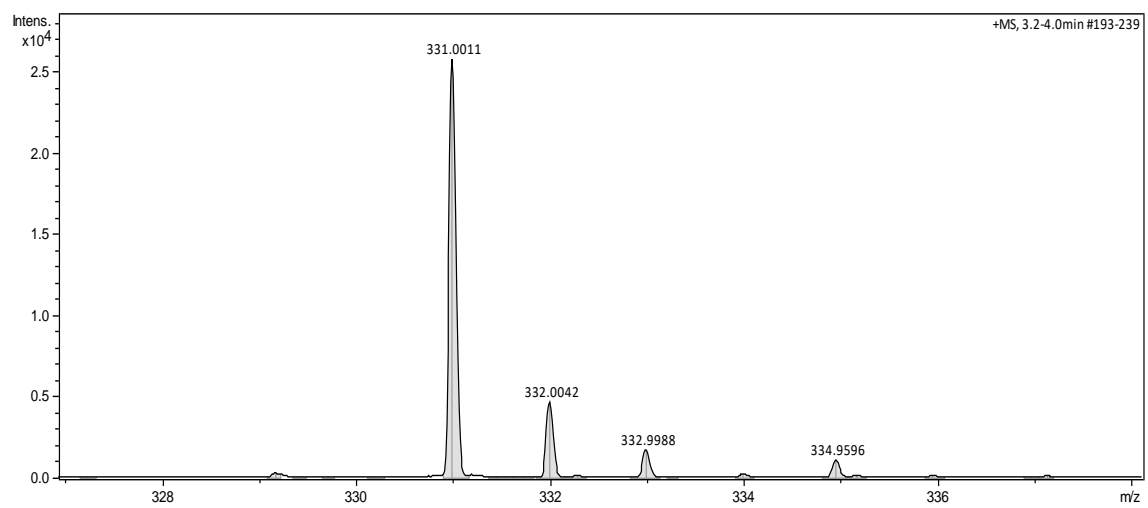
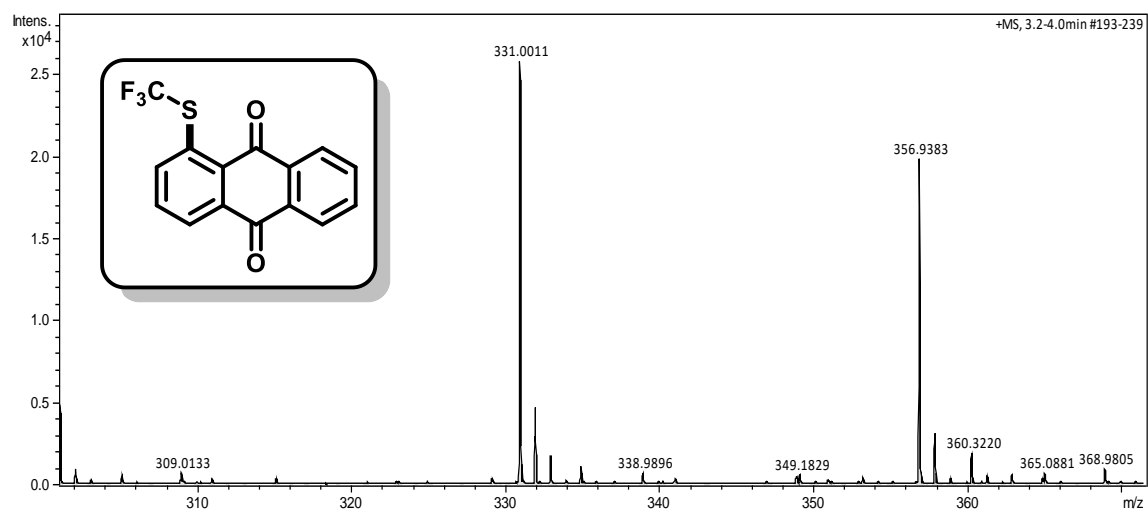


Figure S64. HRMS (ESI⁺) of compound **2i**.

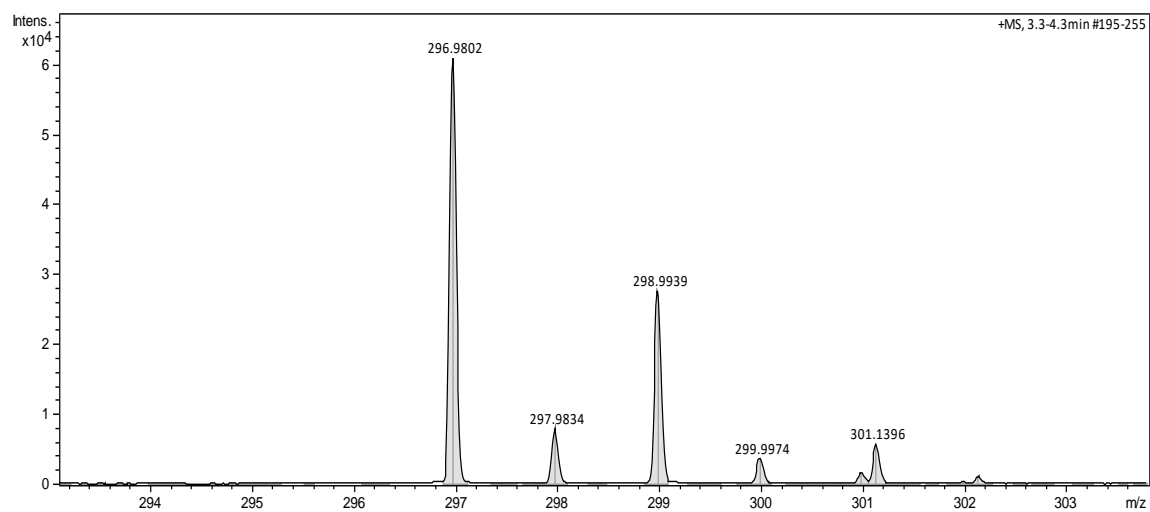
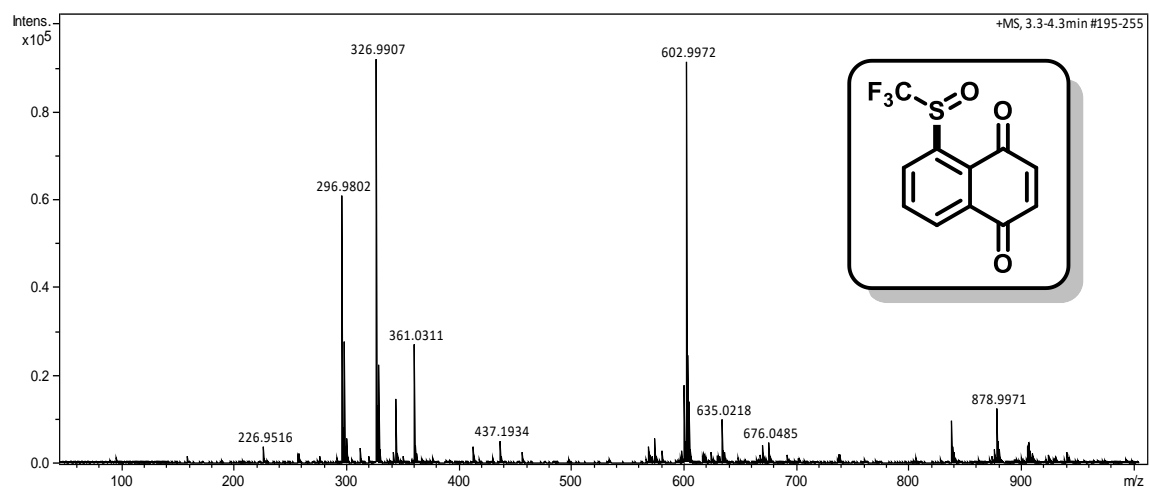


Figure S65. HRMS (ESI⁺) of compound **3a**.

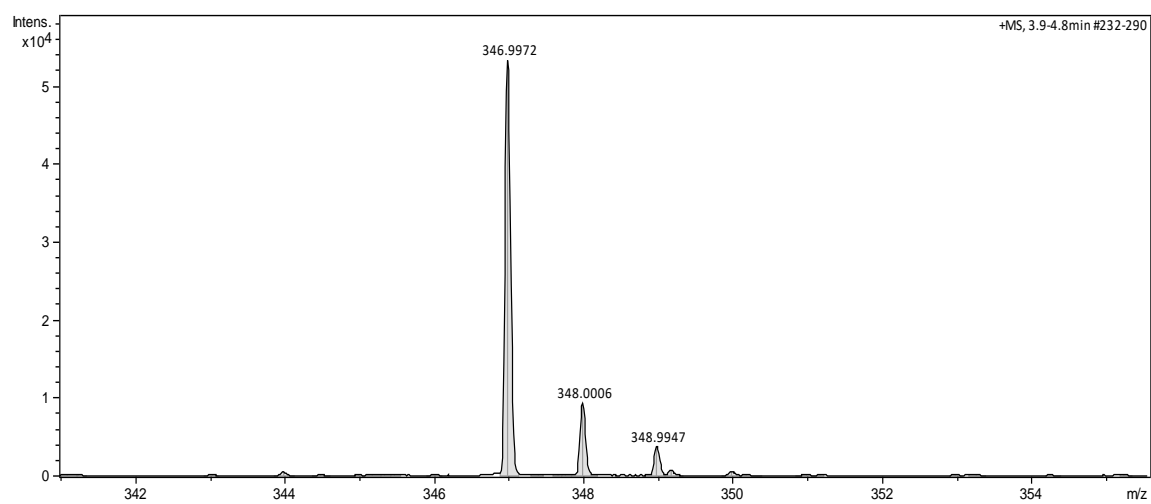
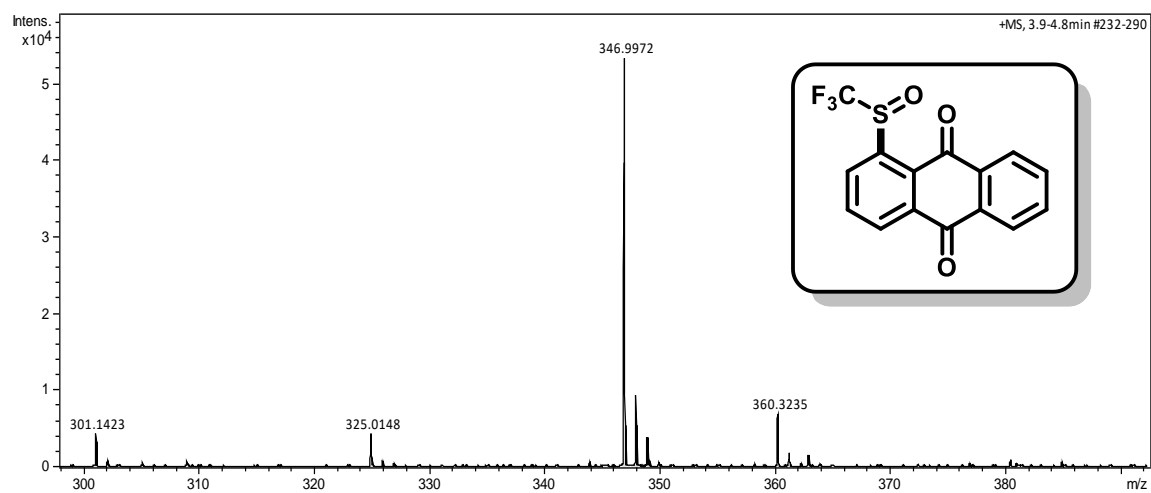


Figure S66. HRMS (ESI⁺) of compound **3b**.

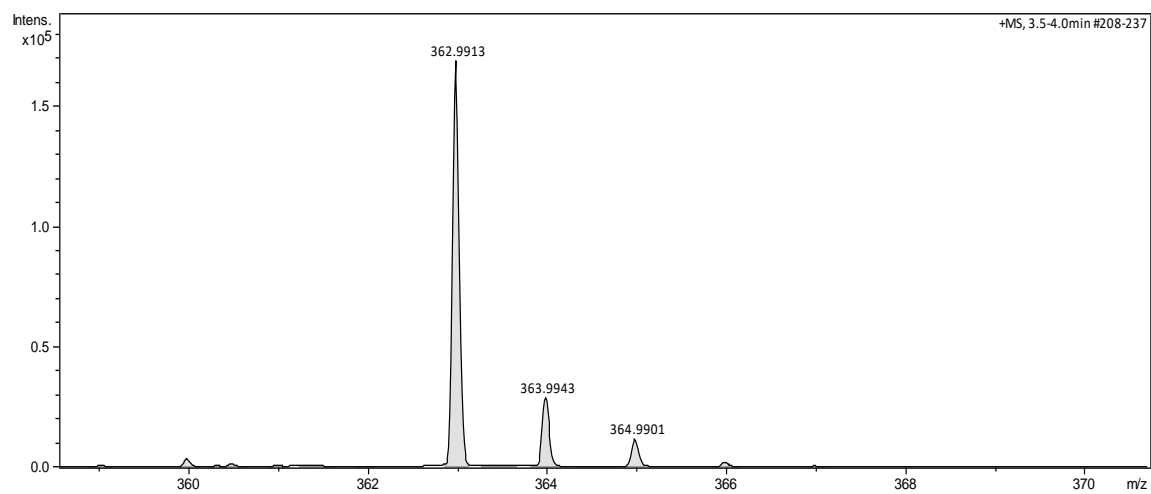
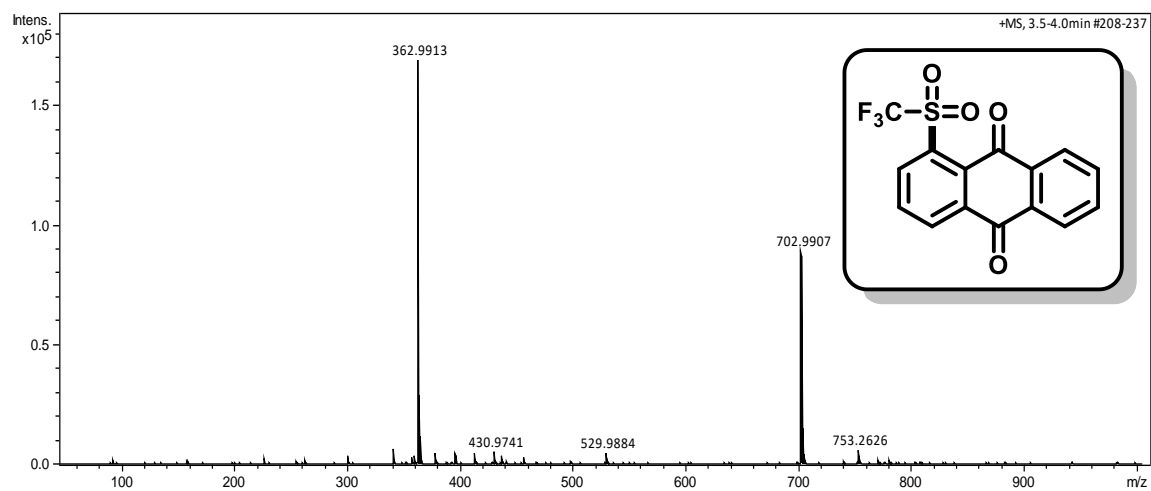


Figure S67. HRMS (ESI⁺) of compound **3c**.

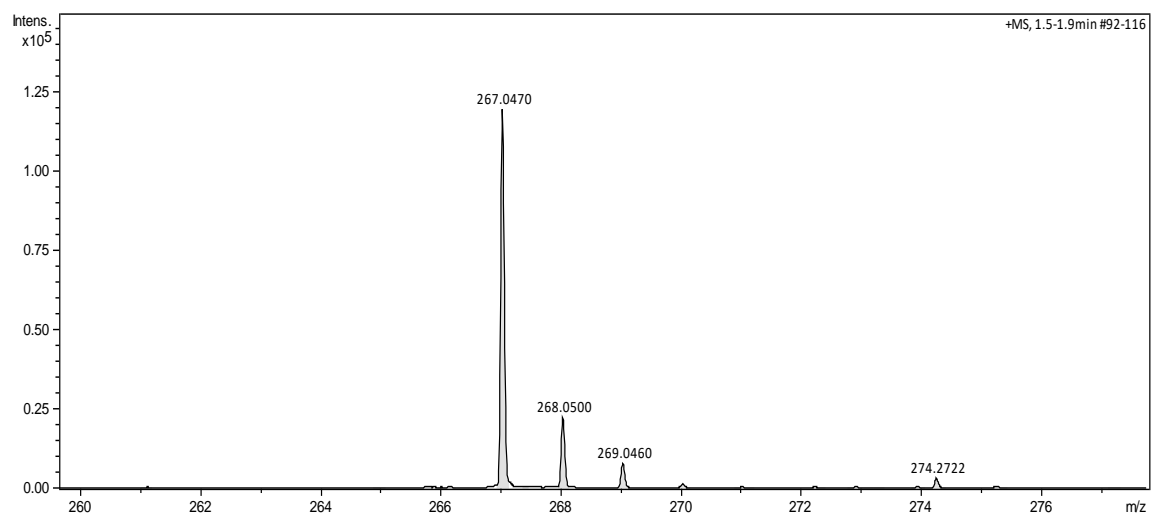
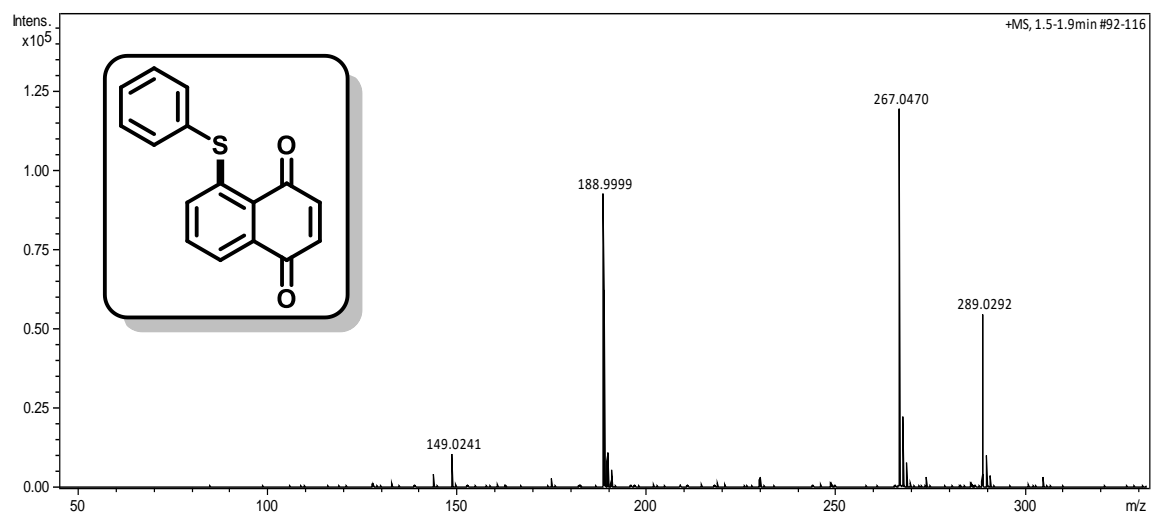


Figure S68. HRMS (ESI⁺) of compound **4c**.

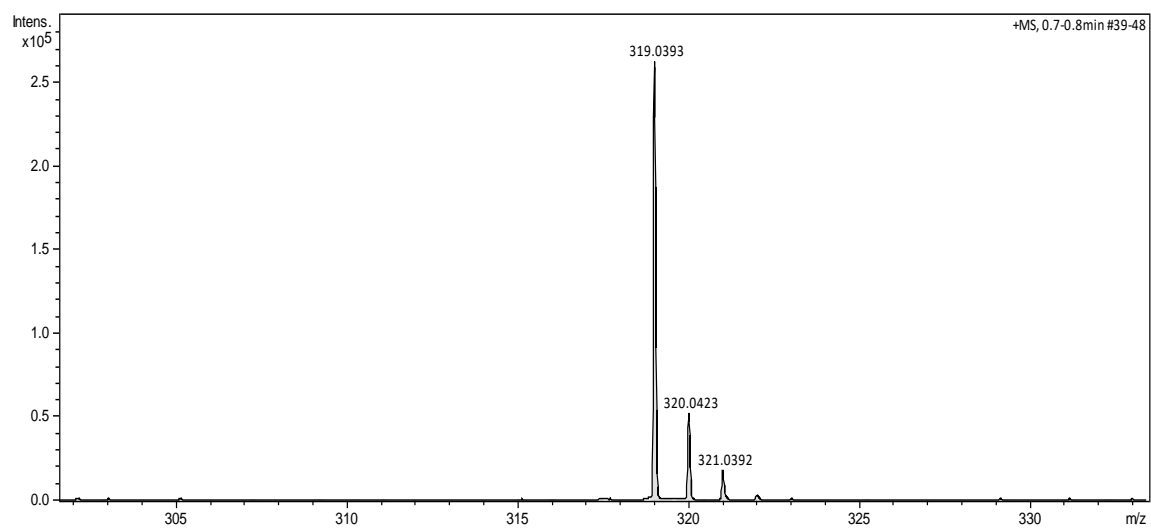
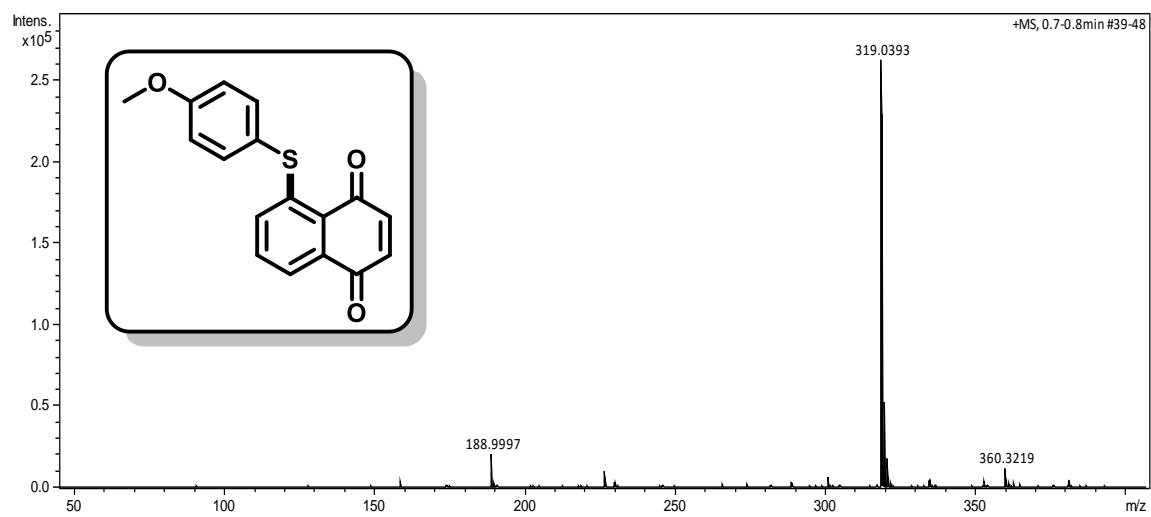


Figure S69. HRMS (ESI⁺) of compound **4d**.

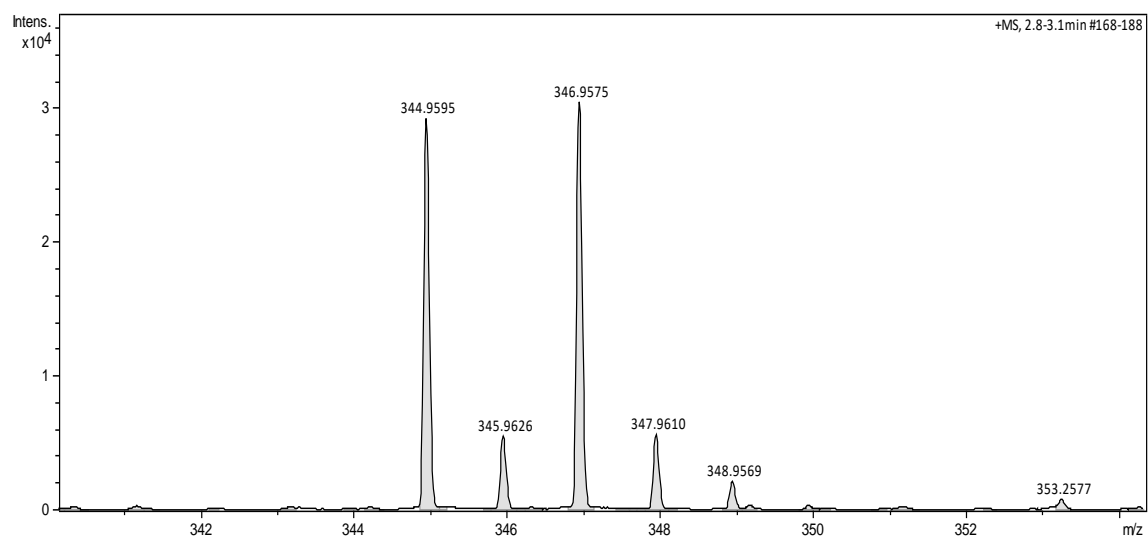
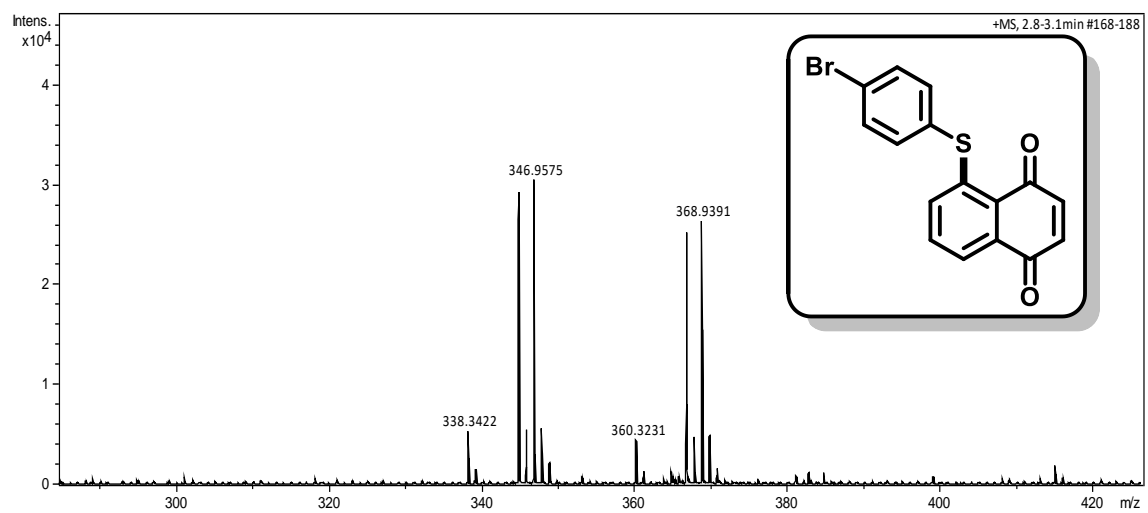


Figure S70. HRMS (ESI⁺) of compound **4e**.

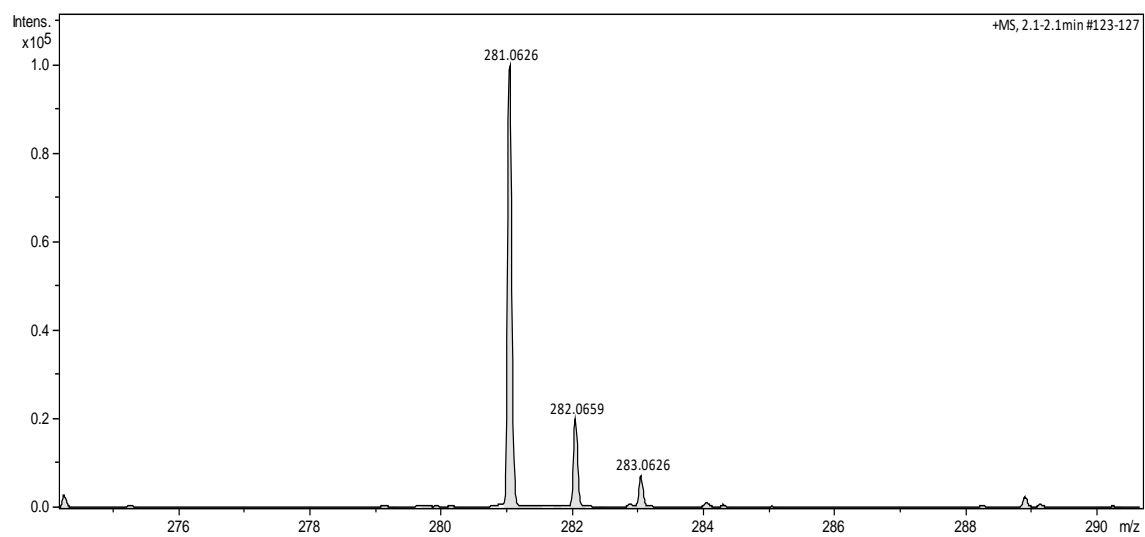
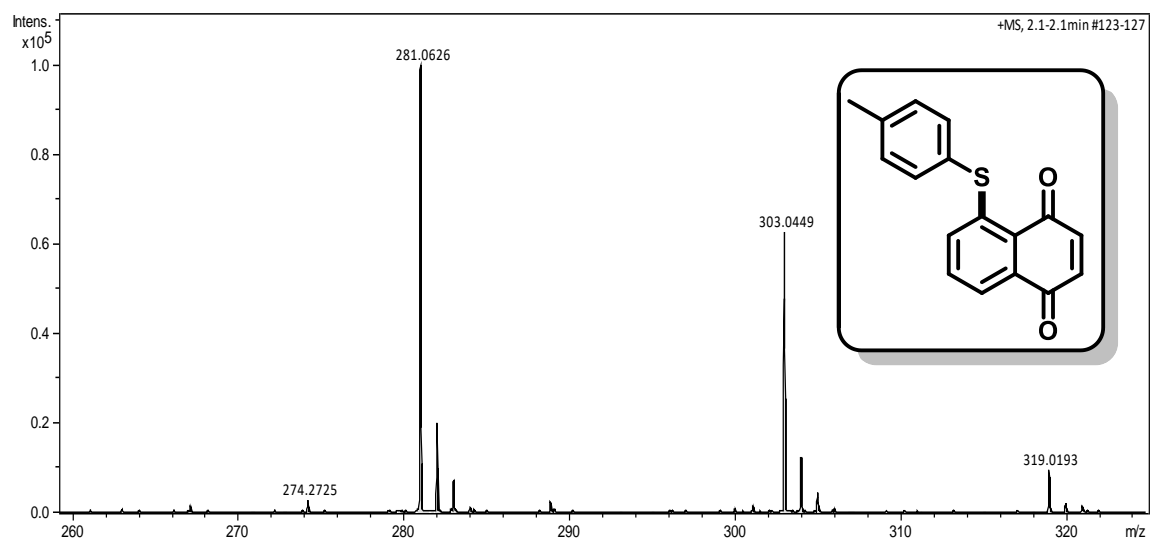


Figure S71. HRMS (ESI⁺) of compound **4f**.

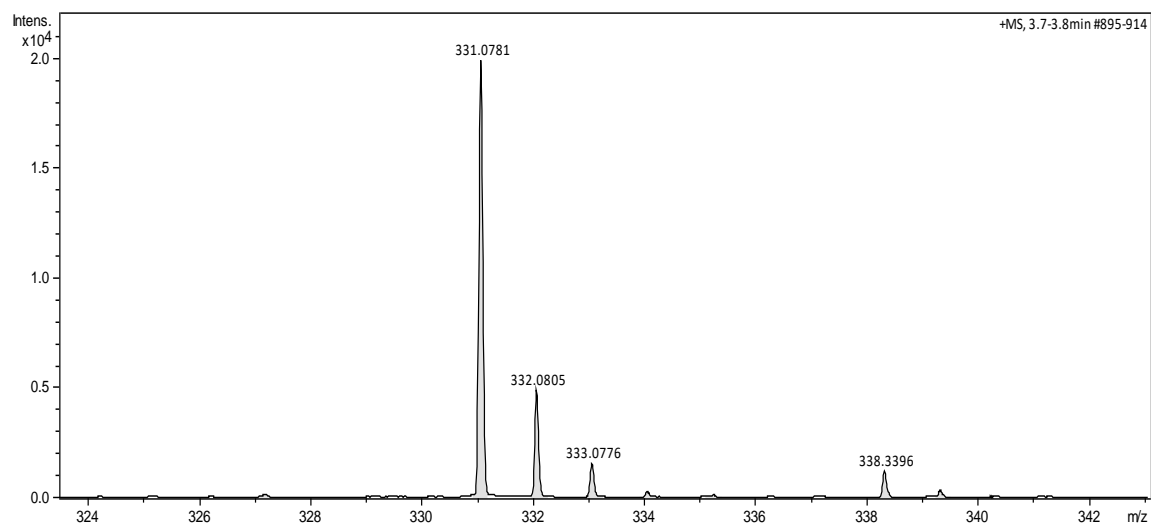
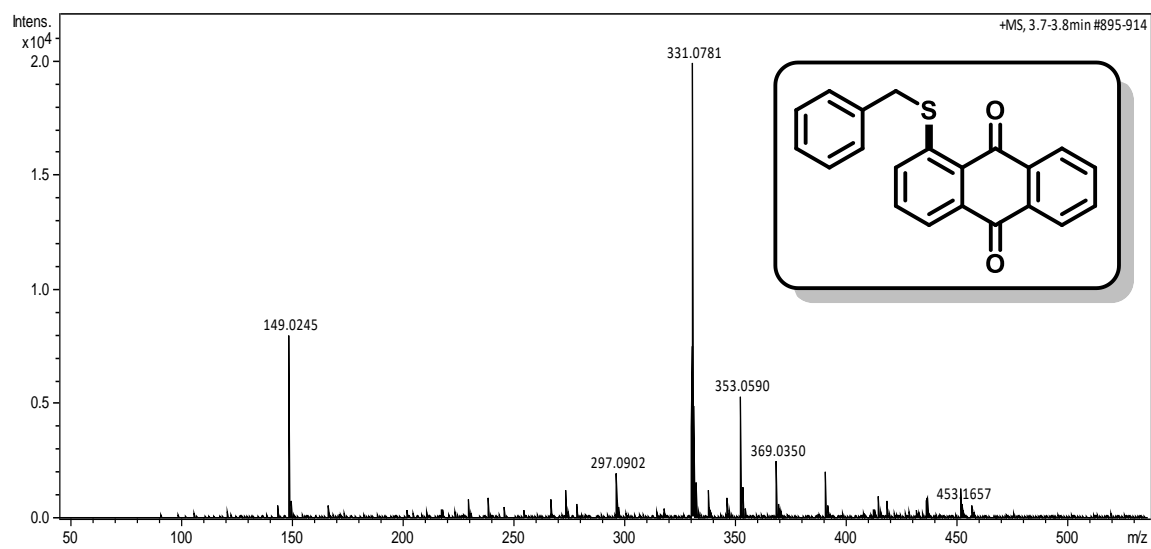


Figure S72. HRMS (ESI⁺) of compound **4g**.

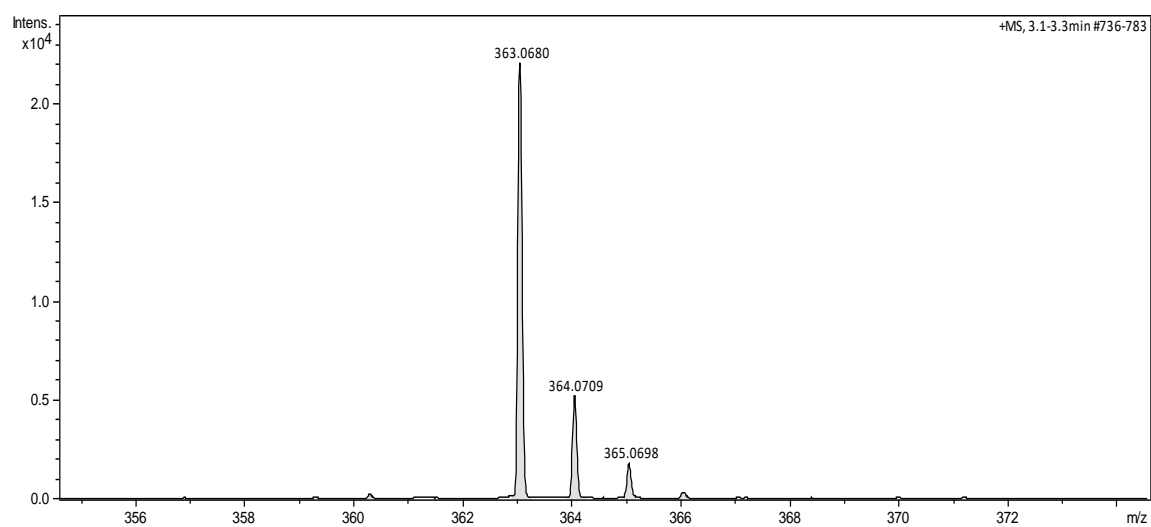
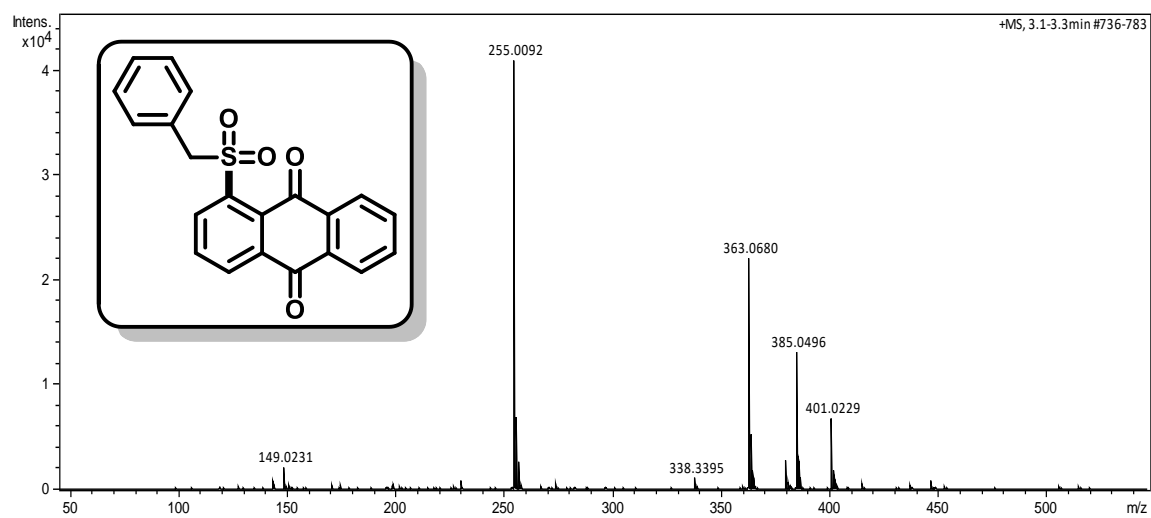


Figure S73. HRMS (ESI⁺) of compound **5**.

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