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


Institute of Exact Sciences, Department of Chemistry, Federal University of Minas Gerais, Belo Horizonte, MG, 31270-901, Brazil;
Oswald Cruz Institute, FIOCRUZ, Rio de Janeiro, RJ, 21045-900, Brazil
Federal University of Alagoas, Maceió, AL, 57072-970, Brazil

Corresponding authors: eufranio@ufmg.br

Contents

A) General experimental details S2
B) Mechanistic Studies S3
C) Synthesis of substrates and known compounds S4
D) General procedure for the trifluoromethylthiolation reactions S9
E) General procedure for oxidation with MCPBA S15
F) General procedure for oxidation with RuCl₃·H₂O/NaIO₄ S16
G) General procedure for the thiolation reactions S17
H) Trypanocidal and Cytotoxicity assays S23
I) Electrochemical studies S26
J) Crystallographic data collection and refinement S31
K) Copies of NMR spectra of novel compounds S39
L) Copies of HRMS of novel compounds S61
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 ($\delta$) 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). $^1$H 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 (v, 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. [RhCp*Cl₂]₂ and copper 2-thiophene carboxylate (CuTc) were purchased from Sigma Aldrich.

General microwave procedure for the iodination reactions:

In a glovebox, an oven dried re-sealable reaction tube was charged with the corresponding naphthoquinone (0.10 mmol), [RhCp*Cl₂]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 CH₂Cl₂ (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; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 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; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.94 (s, 2H), 6.99 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 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; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 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)

S5
Purification by FCC (toluene) afforded iodinated product 1c (19.5 mg, 0.57 mmol, 57% yield) as an orange powder; \( ^1H \text{ NMR} (400 \text{ MHz}, \text{CDCl}_3) \) \( \delta \): 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); \( ^{13}C \text{ NMR} (100 \text{ MHz}, \text{CDCl}_3) \) \( \delta \): 182.8, 182.4, 169.0, 148.0, 139.4, 137.2, 134.9, 131.9, 131.4, 131.0, 94.1, 53.2.

\[ \text{N-}(2\text{-Iodo-5,8-dioxo-5,8-dihydronaphthalen-1-yl)}\text{acetamide (1d)}} \]

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/\( \text{CH}_2\text{Cl}_2 \)); IR (solid, cm\(^{-1}\)) \( \nu \): 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; \( ^1H \text{ NMR} (400 \text{ MHz}, \text{CDCl}_3) \) \( \delta \): 9.29 (s, N-H), 8.30 (d, \( J = 8.2 \) Hz, C\(_7\)-H), 7.69 (d, \( J = 8.3 \) Hz, C\(_8\)-H), 6.96 (d, \( J = 10.3 \) Hz, C\(_2\)-H), 6.90 (d, \( J = 10.3 \) Hz, C\(_3\)-H), 2.28 (s, C\(_{10}\)-H); \( ^{13}C \text{ NMR} (100 \text{ MHz}, \text{CDCl}_3) \) \( \delta \): 186.55 (C\(_4\)), 183.84 (C\(_1\)), 168.68 (C\(_9\)), 145.54 (C\(_7\)), 140.29 (C\(_5\)), 139.77 (C\(_6\)), 139.48 (C\(_3\)), 137.60 (C\(_2\)), 132.52 (C\(_8\)), 125.56 (C\(_8\)), 124.6 (C\(_{4a}\)) 24.48 (C\(_{10}\)).

\[ \text{5-Iodo-7-methyl-1,4-naphthoquinone (1e)}} \]

Purification by FCC (toluene) afforded iodinated product 1e (18.8 mg, 0.63 mmol, 63% yield) as a deep orange powder; \( ^1H \text{ NMR} (400 \text{ MHz}, \text{CDCl}_3) \) \( \delta \): 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; $^{1}$H 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; $^{1}$H 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. 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 CH$_2$Cl$_2$ (10 mL). The organic phase was dried with Na$_2$SO$_4$ 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/CH$_2$Cl$_2$); IR (solid, cm$^{-1}$): 2920 (w), 1648 (s), 1113 (s), 804 (s); MS (EI$^+$): 375.9 [M$^+$]. Calcd. for [C$_{16}$H$_9$IO$_3$]: 375.9; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.38 (dd, $J = 7.7, 1.1$ Hz, C$_6$-H), 8.28 (dd, $J = 7.7, 1.1$ Hz, C$_8$-H), 7.46 (t, $J = 7.9$ Hz, C$_7$-H, C$_{12}$-H), 7.38 – 7.30 (m, C$_{11}$-H, C$_{13}$-H), 7.13 (d, $J = 7.7$ Hz, C$_{10}$-H, C$_{14}$-H), 6.02 (s, C$_3$-H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 183.2 (C$_4$), 179.3 (C$_1$), 159.3 (C$_2$), 152.8 (C$_8$a), 149.0 (C$_6$), 148.2 (C$_9$), 133.5 (C$_{11}$), 130.7 (C$_7$), 128.1 (C$_8$), 127.5 (C$_{12}$), 126.9 (C$_{13}$), 121.2 (C$_{10}$,C$_{14}$), 114.7 (C$_3$), 92.5 (C$_5$).

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 H$_2$SO$_4$ (16 mL of concentrated H$_2$SO$_4$ 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 NaNO$_2$ 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 li (1.10 g, 3.30 mmol, 72% yield) as a deep orange solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 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). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 182.1, 181.7, 148.9, 136.1, 134.8, 134.2, 134.1, 134.0, 132.8, 132.5, 128.6, 128.0, 127.0, 93.4.

**Synthesis of AgSCF\(_3\)\(^{10}\)**

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 CS\(_2\). 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 CS\(_2\) 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 Et\(_2\)O 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 AgSCF\(_3\) (1.25 g, 5.98 mmol, 90%). m.p. (°C) = 224.8-225.9 (degrades) (Et\(_2\)O/CH\(_3\)CN).

**General procedure for the trifluoromethylthiolation reactions:**

\[ \text{AgSCF}_3 (100 \text{ mol\%}) + \text{CuTc (5 mol\%)} \rightarrow \text{F}_3\text{CS} \]
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) ν: 2923 (m), 1657 (s), 1107 (s), 776 (m); HRMS (ESI⁺): 259.0028 [M+H]+. Calcd. 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-H4). ^13C NMR (100 MHz, CDCl3) δ: 185.3 (C4),
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-,C₇-), 7.09 (s, C₂-,C₃-). **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-F₂).
C2-H), 6.79 (d, J = 10.2 Hz, C3-H), 3.95 (s, C9-H).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 an 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 [C₁₅H₁₁F₃O₂Na]⁺: 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 MCPBA

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-napthoquinone (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 [C₁₁H₅F₃O₃Na]⁺: 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]⁺. Calcd. for [C₁₅H₁₇F₃O₃SNa]⁺: 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/NaIO₄

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]⁺. Calcd. for [C₁₅H₁₇F₃O₄SNa]⁺: 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:**

![Diagram of the reaction (R-SH) → 1) Et₃N, CH₃CN 2) AgNO₃, CH₃CN → AgSR](attachment:image.png)

A 50 mL round bottom flask was charged with the corresponding thiol (2.00 mmol), EtN₃ (2.00 mmol, 279 µL) 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:**

![Diagram of the reaction (I) → AgSR (100 mol%), CuTc (5 mol%), DMAc (0.1 M), 100°C 18h → SR](attachment:image.png)

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.
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).

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-H9), 1.44 (t, J = 7.4 Hz, C10-H10). $^{13}$C 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)

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]$^+$. Calcd. for [C15H11O2S]$^+$: 267.0474; $^1$H 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). $^{13}$C 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)
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-H). 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,C₁₀), 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)

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)

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⁺]. Calcd 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-H). 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)
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]⁺. Cald. 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]⁺. Cald. for [C₂₁H₁₅O₂S]⁺: 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 µL) 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 µL/well) for 24 h at 37°C. After this period, 110 µL of the medium was discarded and 10 µL of PrestoBlue (Invitrogen) was added to complete the final volume of 100 µL. Thus, the place 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 napththoquinones on trypomastigote forms of *T. cruzi*.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Structure</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;/ 24 h (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td><img src="image" alt="Structure of 2a" /></td>
<td>41.2 (± 3.5)</td>
</tr>
<tr>
<td>2b</td>
<td><img src="image" alt="Structure of 2b" /></td>
<td>&gt;1000.0</td>
</tr>
<tr>
<td>2c</td>
<td><img src="image" alt="Structure of 2c" /></td>
<td>34.5 (± 6.3)</td>
</tr>
<tr>
<td>2d</td>
<td><img src="image" alt="Structure of 2d" /></td>
<td>32.7 (± 4.1)</td>
</tr>
<tr>
<td>2e</td>
<td><img src="image" alt="Structure of 2e" /></td>
<td>67.3 (± 5.5)</td>
</tr>
<tr>
<td>2f</td>
<td><img src="image" alt="Structure of 2f" /></td>
<td>240.1 (± 14.8)</td>
</tr>
<tr>
<td>2g</td>
<td><img src="image" alt="Structure of 2g" /></td>
<td>41.9 (± 5.8)</td>
</tr>
<tr>
<td>2h</td>
<td><img src="image" alt="Structure of 2h" /></td>
<td>54.4 (± 5.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>2i</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>&gt;1000.0</td>
</tr>
<tr>
<td>3a</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>67.3 (± 6.1)</td>
</tr>
<tr>
<td>3b</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>&gt;1000.0</td>
</tr>
<tr>
<td>3c</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>&gt;1000.0</td>
</tr>
<tr>
<td>4a</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>14.3 (± 0.9)</td>
</tr>
<tr>
<td>4b</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>31.3 (± 2.4)</td>
</tr>
<tr>
<td>4c</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>12.4 (± 2.2)</td>
</tr>
<tr>
<td>4d</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>7.6 (± 0.3)</td>
</tr>
<tr>
<td>4e</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>6.6 (± 0.8)</td>
</tr>
</tbody>
</table>
Table S1.1. High active naphthoquinones selected to trypanocidal (in different conditions) and cytotoxicity assays. *Table 3 in the manuscript.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC_{50}/ 24 h</th>
<th>LC_{50}/ 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5% blood, 4 °C</td>
<td>0% blood, 37 °C</td>
</tr>
<tr>
<td>4a</td>
<td>14.3 (± 0.9)</td>
<td>1.1 (± 0.2)</td>
</tr>
<tr>
<td>4c</td>
<td>12.4 (± 2.2)</td>
<td>0.3 (± 0.04)</td>
</tr>
<tr>
<td>4d</td>
<td>7.6 (± 0.3)</td>
<td>1.3 (± 0.03)</td>
</tr>
<tr>
<td>4e</td>
<td>6.6 (± 0.8)</td>
<td>1.9 (± 0.03)</td>
</tr>
<tr>
<td>4f</td>
<td>2.5 (± 0.3)</td>
<td>0.3 (± 0.06)</td>
</tr>
</tbody>
</table>

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. Electrochemical
methods are extraordinarily powerful and useful in the characterization and design of redox-modulating agents.\textsuperscript{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\textsuperscript{−} (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\textsuperscript{−1}. Electrochemical reduction were performed in aprotic media (DMF + TBAPF\textsubscript{6} 0.1 mol L\textsuperscript{−1}) at room temperature (25 ± 2 °C). Each compound (1 x 10\textsuperscript{−3} mol L\textsuperscript{−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 ($E_{\text{p}Ic}/E_{\text{p}Ia}$ and $E_{\text{p}IIc}/E_{\text{p}IIa}$) (Figure S1), whose main electrochemical parameters are listed in Table S2.
Compound 2b

(A)
Figure S1. Cyclic voltammetry (CV) of 2a, 2b, 2f, 2d and 2h (1 mM) in DMF + TBAPF₆ (0.1 M), glassy carbon electrode, v = 100 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.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>(E_{p_{lc}}) (V)</th>
<th>(E_{p_{la}}) (V)</th>
<th>(E_{p_{la}}) (V)</th>
<th>(\Delta(E_{p_{lc}} - E_{p_{la}})) (mV)</th>
<th>(\Delta(E_{p_{lc}} - E_{p_{la}})) (mV)</th>
<th>(\Delta(E_{p_{lc}} - E_{p_{la}})) (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>-0.421</td>
<td>-1.185</td>
<td>-0.326</td>
<td>95</td>
<td>82</td>
<td>0.764</td>
</tr>
<tr>
<td>2b</td>
<td>-0.582</td>
<td>-1.196</td>
<td>-0.486</td>
<td>96</td>
<td>160</td>
<td>0.614</td>
</tr>
<tr>
<td>2f</td>
<td>-0.262</td>
<td>-1.028</td>
<td>-0.178</td>
<td>84</td>
<td>85</td>
<td>0.766</td>
</tr>
<tr>
<td>2d</td>
<td>-0.336</td>
<td>-0.897</td>
<td>-0.243</td>
<td>93</td>
<td>94</td>
<td>0.561</td>
</tr>
<tr>
<td>2h</td>
<td>-0.440</td>
<td>-1.131</td>
<td>-0.356</td>
<td>84</td>
<td>86</td>
<td>0.691</td>
</tr>
</tbody>
</table>

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

\(2f > 2d > 2a > 2h > 2b\)

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 \(E_{p_{lc}}\). 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 (\(E_{p_{lc}} = -0.897\) 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-Kα 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 **CRYSALIS** suite.\textsuperscript{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 **CRYSALIS** suite. The structures of all compounds were solved by direct methods using the **SUPERFLIP** program.\textsuperscript{18} For each compound, the positions of all atoms could be unambiguously assigned on consecutive difference Fourier maps. Refinements were performed using **SHELXL**\textsuperscript{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.\textsuperscript{20} Values C–H = 0.93 Å and $U_{iso}(H) = 1.2 \times U_{eq}(C)$ for aromatic carbon atoms, C–H = 0.97 Å and $U_{iso}(H) = 1.2 \times U_{eq}(C)$ for methylene groups, C–H = 0.97 Å and $U_{iso}(H) = 1.5 \times U_{eq}(C)$ for methyl groups and N–H = 0.97 Å and $U_{iso}(H) = 1.2 \times U_{eq}(N)$ 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 **ORTEP3**\textsuperscript{21} in association with **POV-Ray** software.\textsuperscript{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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>2a</th>
<th>2b</th>
<th>2d</th>
<th>2f</th>
<th>2i</th>
<th>3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C₁₁H₂₃F₅O₂S</td>
<td>C₁₁H₂₃F₅O₂</td>
<td>C₁₃H₂₃NO₃F₃S</td>
<td>C₁₂H₂₃F₅O₂S₂</td>
<td>C₁₃H₂₃F₅O₂S</td>
<td>C₁₁H₂₃O₃F₃S</td>
</tr>
<tr>
<td>F₀</td>
<td>258.21</td>
<td>302.26</td>
<td>315.26</td>
<td>358.27</td>
<td>308.27</td>
<td>274.21</td>
</tr>
<tr>
<td>T / K</td>
<td>293(2)</td>
<td>293(2)</td>
<td>200(2)</td>
<td>200(2)</td>
<td>250(2)</td>
<td>220(2)</td>
</tr>
<tr>
<td>λ / Å</td>
<td>0.71073</td>
<td>1.5418</td>
<td>1.5418</td>
<td>1.5418</td>
<td>0.71073</td>
<td>0.71073</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁/c</td>
<td>l2/a</td>
<td>P̅1</td>
<td>P2₁/c</td>
<td>P̅1</td>
<td>P̅1</td>
</tr>
<tr>
<td>a / Å</td>
<td>19.2151(6)</td>
<td>14.5769(4)</td>
<td>10.5072(9)</td>
<td>19.3071(3)</td>
<td>11.9788(10)</td>
<td>8.0423(4)</td>
</tr>
<tr>
<td>b / Å</td>
<td>7.8797(2)</td>
<td>11.1576(2)</td>
<td>10.5072(9)</td>
<td>19.3071(3)</td>
<td>7.9785(8)</td>
<td>7.9785(8)</td>
</tr>
<tr>
<td>c / Å</td>
<td>7.1525(2)</td>
<td>31.0437(7)</td>
<td>14.2488(15)</td>
<td>14.5648(2)</td>
<td>11.9788(10)</td>
<td>9.4378(6)</td>
</tr>
<tr>
<td>α / °</td>
<td>90</td>
<td>90</td>
<td>71.680(9)</td>
<td>90</td>
<td>95.823(8)</td>
<td>68.147(6)</td>
</tr>
<tr>
<td>β / °</td>
<td>97.718(3)</td>
<td>102.048(2)</td>
<td>88.646(8)</td>
<td>97.9490(10)</td>
<td>102.310(8)</td>
<td>84.221(5)</td>
</tr>
<tr>
<td>γ / °</td>
<td>90</td>
<td>90</td>
<td>76.869(7)</td>
<td>90</td>
<td>113.691(9)</td>
<td>72.377(5)</td>
</tr>
<tr>
<td>V / Å³</td>
<td>1073.14(5)</td>
<td>1073.14(5)</td>
<td>661.76(11)</td>
<td>1302.47(4)</td>
<td>625.39(11)</td>
<td>543.30(6)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ρ / kg m⁻³</td>
<td>1.598</td>
<td>1.626</td>
<td>1.582</td>
<td>1.827</td>
<td>1.637</td>
<td>1.676</td>
</tr>
<tr>
<td>μ / mm⁻¹</td>
<td>0.328</td>
<td>2.771</td>
<td>2.636</td>
<td>4.489</td>
<td>0.297</td>
<td>0.336</td>
</tr>
<tr>
<td>F(000)</td>
<td>520</td>
<td>2464</td>
<td>320</td>
<td>712</td>
<td>312</td>
<td>276</td>
</tr>
<tr>
<td>Crystal size / mm³</td>
<td>0.60×0.32×0.16</td>
<td>0.36×0.28×0.11</td>
<td>0.56×0.08×0.05</td>
<td>0.49×0.08×0.05</td>
<td>0.86×0.18×0.10</td>
<td>0.48×0.22×0.10</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>42253</td>
<td>33710</td>
<td>4295</td>
<td>11706</td>
<td>10141</td>
<td>8889</td>
</tr>
<tr>
<td>Reflection with I ≥ 2σ(I) [Rint]</td>
<td>1914 [0.036]</td>
<td>3705 [0.066]</td>
<td>3270 [0.066]</td>
<td>1984 [0.068]</td>
<td>1955 [0.034]</td>
<td>1820 [0.027]</td>
</tr>
<tr>
<td>Goodness-of-fit on F²(S)</td>
<td>1.062</td>
<td>1.026</td>
<td>1.334</td>
<td>1.049</td>
<td>1.069</td>
<td>1.040</td>
</tr>
<tr>
<td>R₁, wR² [I &gt; 2σ(I)]</td>
<td>0.0658; 0.1866</td>
<td>0.0830; 0.2014</td>
<td>0.1180; 0.2534</td>
<td>0.0347; 0.0874</td>
<td>0.0393; 0.0892</td>
<td>0.0392; 0.0973</td>
</tr>
<tr>
<td>R₁, wR² (all data)</td>
<td>0.0726; 0.1802</td>
<td>0.0933; 0.2103</td>
<td>0.1408; 0.2653</td>
<td>0.0420; 0.0937</td>
<td>0.0589; 0.1000</td>
<td>0.0503; 0.1055</td>
</tr>
<tr>
<td>Larg diff.peak and hole/e Å⁻³</td>
<td>0.424; −0.370</td>
<td>3.194; −1.219</td>
<td>0.958; −0.421</td>
<td>0.233; −0.334</td>
<td>0.228; −0.219</td>
<td>0.293; −0.261</td>
</tr>
</tbody>
</table>

\( a R = \frac{\sum|F_o| - |F_c|}{\sum|F_o|} \)

\( wR = \left(\sum|F_o|^2 - |F_c|^2\right)^2/\sum|F_o|^2\)^{1/2}
<table>
<thead>
<tr>
<th>Compound</th>
<th>3c</th>
<th>4d</th>
<th>4e</th>
<th>4g</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{15}H_{20}O_{3}S</td>
<td>C_{16}H_{12}NO_{4}F_{3}S</td>
<td>C_{16}H_{10}O_{2}SBr</td>
<td>C_{17}H_{12}O_{2}S</td>
<td>C_{21}H_{14}O_{4}S</td>
</tr>
<tr>
<td>( F_w )</td>
<td>340.27</td>
<td>315.26</td>
<td>345.20</td>
<td>280.33</td>
<td>362.38</td>
</tr>
<tr>
<td>( T / K )</td>
<td>200(2)</td>
<td>220(2)</td>
<td>250(2)</td>
<td>250(2)</td>
<td>250(2)</td>
</tr>
<tr>
<td>( \lambda / \text{Å} )</td>
<td>1.5418</td>
<td>1.5418</td>
<td>0.71073</td>
<td>0.71073</td>
<td>0.71073</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
<td>Triclinic</td>
<td>Triclinic</td>
<td>Triclinic</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>( P2_1/c )</td>
<td>( P\bar{1} )</td>
<td>( P\bar{1} )</td>
<td>( P\bar{1} )</td>
<td>( Pbc\bar{a} )</td>
</tr>
<tr>
<td>( a / \text{Å} )</td>
<td>12.2391(3)</td>
<td>9.0948(7)</td>
<td>7.8595(5)</td>
<td>7.2227(6)</td>
<td>14.1466(18)</td>
</tr>
<tr>
<td>( b / \text{Å} )</td>
<td>8.0497(2)</td>
<td>20.0144(16)</td>
<td>7.9836(5)</td>
<td>8.4064(7)</td>
<td>12.4232(17)</td>
</tr>
<tr>
<td>( c / \text{Å} )</td>
<td>13.6415(4)</td>
<td>7.8362(6)</td>
<td>12.2941(7)</td>
<td>12.3348(9)</td>
<td>18.979(2)</td>
</tr>
<tr>
<td>( \alpha /^\circ )</td>
<td>90</td>
<td>90</td>
<td>89.939(5)</td>
<td>75.046(7)</td>
<td>90</td>
</tr>
<tr>
<td>( \beta /^\circ )</td>
<td>91.602(2)</td>
<td>106.353(9)</td>
<td>74.827(5)</td>
<td>76.516(7)</td>
<td>90</td>
</tr>
<tr>
<td>( \gamma /^\circ )</td>
<td>90</td>
<td>90</td>
<td>68.477(6)</td>
<td>66.783(8)</td>
<td>90</td>
</tr>
<tr>
<td>( V / \text{Å}^3 )</td>
<td>1343.45(6)</td>
<td>1368.69(19)</td>
<td>688.73(8)</td>
<td>657.64(10)</td>
<td>3335.6(7)</td>
</tr>
<tr>
<td>( Z )</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>( \rho / \text{kg m}^{-3} )</td>
<td>1.682</td>
<td>1.438</td>
<td>1.665</td>
<td>1.416</td>
<td>1.443</td>
</tr>
<tr>
<td>( \mu / \text{mm}^{-1} )</td>
<td>2.690</td>
<td>0.243</td>
<td>3.132</td>
<td>0.243</td>
<td>0.219</td>
</tr>
<tr>
<td>( F(000) )</td>
<td>688</td>
<td>616</td>
<td>344</td>
<td>292</td>
<td>1504</td>
</tr>
<tr>
<td>Crystal size / \text{mm}^3</td>
<td>0.43×0.26×</td>
<td>0.39×0.28×</td>
<td>0.44×0.29×</td>
<td>0.55×0.35×</td>
<td>0.66×0.47×</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>11565</td>
<td>4917</td>
<td>18417</td>
<td>7911</td>
<td>15833</td>
</tr>
<tr>
<td>Reflection with ( I \geq 2\sigma(I) ) [( R_{	ext{int}} )]</td>
<td>2051 [0.068]</td>
<td>3535 [0.101]</td>
<td>2223 [0.054]</td>
<td>2090 [0.035]</td>
<td>2303 [0.047]</td>
</tr>
<tr>
<td>Goodness-of-fit on ( F^2 (S) )</td>
<td>1.066</td>
<td>0.972</td>
<td>1.029</td>
<td>1.036</td>
<td>1.047</td>
</tr>
<tr>
<td>( R^1, wR^b ) [( I &gt; 2\sigma(I) )]</td>
<td>0.0660; 0.1733</td>
<td>0.0546; 0.1575</td>
<td>0.0426; 0.0846</td>
<td>0.0386; 0.0848</td>
<td>0.0445; 0.0958</td>
</tr>
<tr>
<td>( R^1, wR^b ) (all data)</td>
<td>0.0743; 0.1861</td>
<td>0.0754; 0.1666</td>
<td>0.0711; 0.0889</td>
<td>0.0562; 0.0939</td>
<td>0.0791; 0.1137</td>
</tr>
<tr>
<td>Larg. diff. peak and hole / ( e \text{ Å}^{-3} )</td>
<td>0.696; −0.439</td>
<td>0.376; −0.266</td>
<td>0.317; −0.521</td>
<td>0.228; −0.219</td>
<td>0.262; −0.346</td>
</tr>
</tbody>
</table>

\[ a = \Sigma||F_o||−|F_c||/\Sigma|F_o|, \quad b = wR = [\Sigma(|F_o|^2−|F_c|^2)^2/\Sigma|F_o|^2]^{1/2}. \]
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. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 1d.

Figure S14. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 1d.
Figure S15. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 1h.

Figure S16. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 1h.
Figure S17. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2a.

Figure S18. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2a.
Figure S19. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2b.

Figure S20. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2b.
Figure S21. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2c.

Figure S22. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2c.
Figure S23. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2d.

Figure S24. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2d.
Figure S25. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2e.

Figure S26. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2e.
Figure S27. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2f.

Figure S28. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2f.
Figure S29. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2g.

Figure S30. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2g.
Figure S31. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2h.

Figure S32. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2h.
Figure S33. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 2i.

Figure S34. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 2i.
Figure S35. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 3a.

Figure S36. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 3a.
Figure S37. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 3b.

Figure S38. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 3b.
Figure S39. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 3c.

Figure S40. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 3c.
Figure S41. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4a.

Figure S42. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4a.
Figure S43. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4b.

Figure S44. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4b.
Figure S45. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4c.

Figure S46. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4c.
Figure S47. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4d.

Figure S48. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4d.
Figure S49. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4e.

Figure S50. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4e.
Figure S51. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4f.

Figure S52. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4f.
Figure S53. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4g.

Figure S54. $^{13}$C NMR spectrum (100 MHz, CDCl$_3$) of compound 4g.
Figure S55. $^1$H 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.


