Electronic Supplementary Information

Exploring synthetic avenues for the effective synthesis of selenium and tellurium containing multifunctional redox agents

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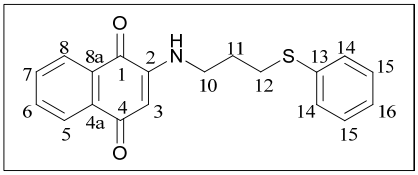
S1. Synthesis of individual compounds

Compound **7**[1], 4-(3-methyl-1,4-naphthoquinone-2-yl)butanoic acid **10**[2], 6-(1,4-naphthoquinone-2-ylamino)hexanoic acid (**16**)[3], 3-(3-methyl-1,4-naphthoquinone-2-ylthio)propanoic acid (**19**)[4,5], 1,4,7-tri(*tert*-butyloxycarbonyl)-1,4,7,10-tetra-azacyclododecane[6-8], 3-(3-methyl-1,4-naphthoquinone-2-ylthio)-1-(4,7,10-tri-*tert*-butyloxycarbonyl-1,4,7,10-tetraazacyclododecane-1-yl)propane-1-one **20**[1], 3-(3-methyl-1,4-naphthoquinone-2-ylthio)-1-(1,4,7,10-tetraazacyclododecane-1-yl)propane-1-one **21**[1], 2-(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-ylselanyl)acetaldehyde[9], 3-(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-ylthio)propanoic acid[9], compound **26**[9], compound **27**[9] compound **28**[9], compound **29**[9] were synthesized according the literature.

2-(3-(phenylthio)propylamino)-1,4-naphthoquinone (4)



3-(phenylthio)propane-1-amine (167.3 mg, 1.00 mmol) was dissolved in 10 ml EtOH and added dropwise to a solution of 1,4-naphthoquinone (158.2 mg,1.00 mmol) in 10 ml EtOH. The reaction was stirred for three days on air and in the dark. The precipitated solid was filtered off, washed thoroughly with EtOH and purified by silica gel column chromatography (CH_2Cl_2) to obtain a bright orange solid (88.4 mg, 0.27 mmol).

Yield: 27.3%.

$C_{19}H_{17}NO_2S$ (MW = 323.41 g/mol).

TLC: R_f = 0.25 (CH_2Cl_2).

Mp = 175-177°C.

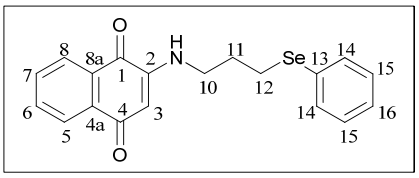
^{1}H NMR ($CDCl_3$): δ = 2.00 (quint, 2 H, H^{11}, $^3J_{HH}$ = 6.9), 3.01 (t, 2 H, H^{12}, $^3J_{HH}$ = 6.9), 3.34 (q, 2 H, H^{10}, $^3J_{HH}$ = 6.6), 5.73 (s, 1 H, H^3), 5.93 (br s, 1 H, NH), 7.20 (m, 1 H, H^{16}), 7.30 (m, 2 H, H^{15}), 7.37 (m, 2 H, H^{14}), 7.61 (dt, 2 H, H^6 or H^7, not assigned (n.a.), $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 7.73 (dt, 2 H, H^6 or H^7, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 8.04 (dd, 2 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0), 8.10 (dd, 2 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0).

^{13}C NMR ($CDCl_3$): δ = 27.4, 31.3, 41.1 ($C^{10,11,12}$, n.a.), 101.0 (C^3), 126.20, 126.26, 126.57, 131.98, 134.76 ($C^{5,6,7,8,16}$, n.a.), 129.10, 129.91 ($C^{14,15}$, n.a.), 130.49, 133.59, 135.35, ($C^{4a,8a,13}$, n.a.), 147.79 (C^2), 181.8, 182.9 ($C^{1,4}$, n.a.).

LC-MS: R_t, m/z (%) = not ionisable.

HRMS: $[M+H]^+$ calcd 324.1058, $[M+H]^+$ found 324.1062.

2-(3-(phenylselenyl)propylamino)-1,4-naphthoquinone (5)



The same procedure used for the preparation of **4** was applied in the reaction of 3-(phenylselenyl)propane-1-amine (428.3 mg, 2.00 mmol) with 1,4-naphthoquinone (316.3 mg, 2.00 mmol). After appropriate workup (silica gel column chromatography with CH_2Cl_2) a bright orange solid (150.3 mg, 0.41 mmol) was obtained.

Yield: 20.3%.

$C_{19}H_{17}NO_2Se$ (MW = 370.30 g/mol).

TLC: R_f = 0.25 (CH_2Cl_2).

Mp = 161°C.

^{1}H NMR ($CDCl_3$): δ = 2.01 (quint, 2 H, H^{11}, $^3J_{HH}$ = 6.9), 2.97 (t, 2 H, H^{12}, $^3J_{HH}$ = 6.9), 3.31 (q, 2 H, H^{10}, $^3J_{HH}$ = 6.3), 5.72 (s, 1 H, H^3), 5.89 (br s, 1 H, NH), 7.26 (m, 3 H, $H^{15,16}$), 7.52 (m, 2 H, H^{14}), 7.61 (dt, 2 H, H^6 or H^7, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 7.72 (dt, 2 H, H^6 or H^7, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 8.03 (dd, 2 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0), 8.10 (dd, 2 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0).

^{13}C NMR ($CDCl_3$): δ = 24.8, 28.3, 42.0 ($C^{10,11,12}$, n.a.), 101.0 (C^3), 126.1, 126.2, 127.3, 131.9, 134.7 ($C^{5,6,7,8,16}$, n.a.), 129.2, 133.0 ($C^{14,15}$, n.a.), 129.3, 130.4, 133.5 ($C^{4a,8a,13}$, n.a.), 147.7 (C^2, n.a.), 181.8, 182.8 ($C^{1,4}$, n.a.).

NMR data including COSY spectroscopy:

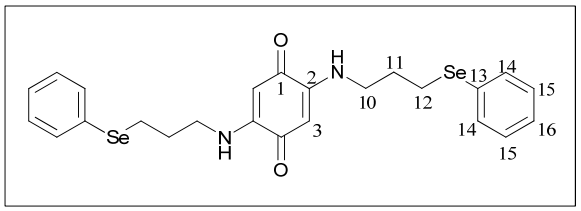
^{1}H NMR ($CDCl_3$): δ = 2.01 (quint, 2 H, H^{11}, $^3J_{HH}$ = 6.9), 2.97 (t, 2 H, H^{12}, $^3J_{HH}$ = 6.9), 3.31 (q, 2 H, H^{10}, $^3J_{HH}$ = 6.3), 5.72 (s, 1 H, H^3), 5.89 (br s, 1 H, NH), 7.26 (m, 3 H, $H^{15,16}$), 7.52 (m, 2 H, H^{14}), 7.61 (dt, 2 H, H^7, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 7.72 (dt, 2 H, H^6, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 8.03 (dd, 2 H, H^8, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0), 8.10 (dd, 2 H, H^5, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0).

^{13}C NMR ($CDCl_3$): δ = 24.8 (C^{12}), 28.3 (C^{11}), 42.0 (C^{10}), 101.0 (C^3), 126.1 (C^5), 126.2 (C^8), 127.3 (C^{16}), 129.2 (C^{15}), 129.3 (C^{13}), 130.4 (C^{8a}), 131.9 (C^7), 133.0 (C^{14}), 133.5 (C^{4a}), 134.7 (C^6), 147.7 (C^2), 181.8 (C^1), 182.8 (C^4).

LC-MS: R_t= 11.7 min, m/z (%) 372.1 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 372.0502, $[M+H]^+$ found 372.0402.

2,5-bis(3-(phenylselenyl)propylamino)-1,4-benzoquinone (6)



Following the procedure for the preparation of **4** and **5**, 3-(phenylselenyl)propane-1-amine (1.67 g, 3.14 mmol) was reacted with 1,4-benzoquinone (108.1 mg, 1.00 mmol). A red solid (183.8 mg, 0.35 mmol) was obtained.

Yield: 34.5%.

$C_{24}H_{26}N_2O_2Se_2$ (MW = 532.40 g/mol).

TLC: R_f = 0.21 (CH_2Cl_2).

Mp = 164-166°C.

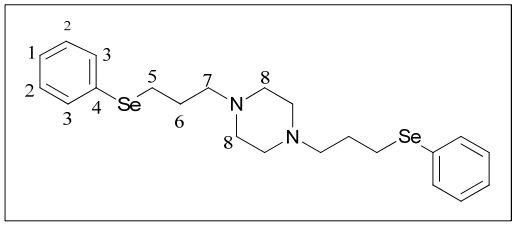
^{1}H NMR ($CDCl_3$): δ = 2.01 (quint, 4 H, H^{11}, $^3J_{HH}$ = 6.9), 2.93 (t, 4 H, H^{12}, $^3J_{HH}$ = 6.9), 3.28 (q, 4 H, H^{10}, $^3J_{HH}$ = 6.6), 5.29 (s, 2 H, H^3), 6.54 (br s, 2 H, NH), 7.27 (m, 6 H, $H^{15,16}$), 7.51 (m, 4 H, H^{14}).

^{13}C NMR ($CDCl_3$): δ = 24.9, 28.5, 42.0 ($C^{10,11,12}$, n.a.), 93.2 (C^3), 127.5 (C^{16}), 129.1 (C^{13}), 151.3 (C^2), 129.2, 133.1 ($C^{14,15}$, n.a.), 178.4 (C^1).

LC-MS: R_t, = 12.9 min, m/z (%) 535.0 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 535.0402, $[M+H]^+$ found 535.0285

1,4-bis(3-(phenylselenyl)propyl)piperazine (8)



Piperazine (2.7 mg, 0.73 mmol) was dissolved in 25 ml dry THF. A solution of 3-(phenylselenyl)propanal (310.3 mg, 1.46 mmol) in 18 ml THF was added dropwise at room temperature over a period of 10 min. After 15 min sodium triacetoxyborohydride (308.5 mg, 1.46 mmol) was added and the reaction was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and the crude product was purified by silica

gel column chromatography (CH_2Cl_2/MeOH 95:5) to yield a beige solid (109.6 mg, 0.22 mmol).

Yield: 30.2 %.

$C_{22}H_{30}N_2Se_2$ (MW = 480.41 g/mol).

TLC: R_f = 0.25 (CH_2Cl_2/MeOH 95:5).

Mp = 61-63°C.

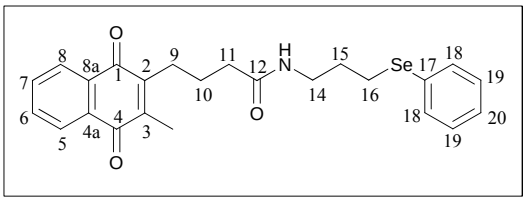
^{1}H NMR ($CDCl_3$): δ = 1.90 (quint, 4 H, H^6, $^3J_{HH}$ = 7.3), 2.45 (t, 12 H, H^5 or H^7, n.a., H^8, $^3J_{HH}$ = 7.3), 2.96 (t, 4 H, H^5 or H^7, n.a., $^3J_{HH}$ = 7.3), 7.27 (m, 6 H, $H^{1,2}$), 7.52 (m, 4 H, H^3).

^{13}C NMR ($CDCl_3$): δ = 25.6, 27.4 ($C^{5,6}$), 53.1 (C^8), 58.0 (C^7), 126.6 (C^1), 128.9, 132.4 ($C^{2,3}$, n.a.) 130.5 (C^4).

LC-MS: R_t = 7.4 min, m/z (%) 482.9 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 483.0817, $[M+H]^+$ found 483.0715.

4-(3-methyl-1,4-naphthoquinone-2-yl)-*N*-(3-(phenylselenyl)propyl)butanamide (11)



The method employed for the synthesis of **11** has been derived from the literature, where similar molecules have been recorded, yet without selenium.[10] Briefly, *N*-methylmorpholine (101.2 mg, 1.00 mmol) in 3 ml dry $CHCl_3$ was added to a solution of 4-(3-methyl-1,4-naphthoquinone-2-yl)butanoic acid[2] (**10**) (258.3 mg, 1.00 mmol) in 3 ml of dry $CHCl_3$ at 0

°C. After 15 min ethylchloroformate (108.5 mg, 1.00 mmol) in 3 ml dry $CHCl_3$ was added and after additional 30 min at 0 °C, 3-(phenylselenyl)propane-1-amine (214.2 mg, 1.00 mmol) in 3 ml dry $CHCl_3$ was added. The reaction mixture was stirred at 0 °C for 1 h and afterwards at room temperature overnight. The solvent was evaporated under reduced pressure and the crude product purified by silica gel column chromatography (CH_2Cl_2/MeOH 95:5). A yellowish brown solid (323.4 mg, 0.71 mmol) was obtained.

Yield: 71.2%.

$C_{24}H_{25}NO_3Se$ (MW = 454.42 g/mol).

TLC: R_f = 0.65 (CH_2Cl_2/MeOH 95:5).

Mp = 79-80°C.

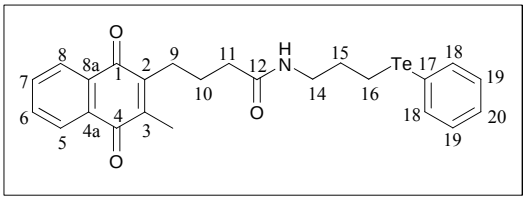
^{1}H NMR ($CDCl_3$): δ = 1.79 (quint, 2 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.9), 1.92 (quint, 2 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.3), 2.19 (s, 3 H, CH_3), 2.24 (t, 2 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.3), 2.64 (t, 2 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.9), 2.93 (t, 2 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.3), 3.37 (q, 2 H, H^{14}, $^3J_{HH}$ = 6.6), 5.93 (br s, 1 H, NH), 7.23 (m, 3 H, $H^{19,20}$), 7.48 (m, 2 H, H^{18}), 7.68 (m, 2 H, $H^{6,7}$), 8.05 (m, 2 H, $H^{5,8}$).

^{13}C NMR ($CDCl_3$): δ = 12.7 (CH_3), 24.2, 25.0, 26.3, 29.9, 36.0, 39.3 ($C^{9,10,11,14,15,16}$, n.a.), 126.2, 126.9, 129.1, 132.7, 133.3, 133.4 ($C^{5,6,7,8,18,19,20}$, n.a.), 129.9, 132.0, 132.1, 144.0, 146.2 ($C^{2,3,4a,8a,17}$, n.a.), 172.1 (C^{12}), 184.9, 185.1 ($C^{1,4}$, n.a.).

LC-MS: R_t = 9.9 min, m/z (%) 456.0 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 456.1077, $[M+H]^+$ found 456.1104.

4-(3-methyl-1,4-naphthoquinone-2-yl)-*N*-(3-(phenyltelluryl)propyl)butanamide (12)



Based on the preparation of **11**, 4-(3-methyl-1,4-naphthoquinone-2-yl)butanoic acid[2] (**10**) (258.3 mg, 1.00 mmol) was reacted with 3-(phenyltelluryl)propane-1-amine (262.8 mg, 1.00 mmol) using *N*-methylmorpholine (101.2 mg, 1 mmol) and ethylchloroformate (108.5 mg, 1.00 mmol) to result in a yellowish brown solid (201.8 mg, 0.40 mmol).

Yield: 40.1%.

$C_{24}H_{25}NO_3Te$ (MW = 503.06 g/mol).

TLC: R_f = 0.51 (CH_2Cl_2/MeOH 95:5).

Mp = 58°C.

^{1}H NMR ($CDCl_3$): δ = 1.79 (quint, 2 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.9), 2.01 (quint, 2 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 6.9), 2.20 (s, 3 H, CH_3), 2.22 (t, 2 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 6.9), 2.64 (t, 2 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.9), 2.89 (t, 2 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.6), 3.33 (q, 2 H, H^{14}, $^3J_{HH}$ = 6.6), 5.79 (br s, 1 H, NH), 7.18 (m, 2 H, H^{19}), 7.26 (m, 1 H, H^{20}), 7.69 (m, 2 H, $H^{6,7}$), 7.72 (m, 2 H, H^{18}), 8.07 (m, 2 H, $H^{5,8}$).

^{13}C NMR ($CDCl_3$): δ = 5.0 (C^{16}), 24.2, 26.3, 31.6, 36.1, 41.1 ($C^{9,10,11,14,15}$, n.a.), 12.7 (CH_3), 111.5 (C^{17}), 132.0, 132.1, 144.1, 146.2 ($C^{2,3,4a,8a}$, n.a.), 126.3, 127.7, 129.2, 133.4, 133.5, 138.5 ($C^{5,6,7,8,18,19,20}$, n.a.), 172.1 (C^{12}), 184.9, 185.1 ($C^{1,4}$, n.a.).

NMR data including COSY spectroscopy:

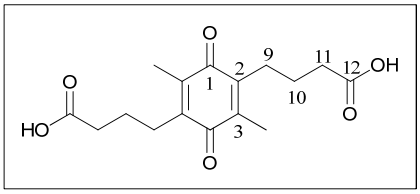
^{1}H NMR ($CDCl_3$): δ = 1.79 (quint, 2 H, H^{10}, $^{3}J_{HH}$ = 7.9), 2.01 (quint, 2 H, H^{15}, $^{3}J_{HH}$ = 6.9), 2.20 (s, 3 H, CH_3), 2.22 (t, 2 H, H^{11}, $^{3}J_{HH}$ = 6.9), 2.64 (t, 2 H, H^{9}, $^{3}J_{HH}$ = 7.9), 2.89 (t, 2 H, H^{16}, $^{3}J_{HH}$ = 7.6), 3.33 (q, 2 H, H^{14}, $^{3}J_{HH}$ = 6.6), 5.79 (br s, 1 H, NH), 7.18 (m, 2 H, H^{19}), 7.26 (m, 1 H, H^{20}), 7.69 (m, 2 H, $H^{6,7}$, thereof H^{6} in the low field and H^{7} in the high field of the signal), 7.72 (m, 2 H, H^{18}), 8.07 (m, 2 H, $H^{5,8}$, thereof H^{5} in the low field and H^{8} in the high field of the signal).

^{13}C NMR ($CDCl_3$): δ = 5.0 (C^{16}), 12.7 (CH_3), 24.2 (C^{10}), 26.3 (C^{9}), 31.6 (C^{15}), 36.1 (C^{11}), 41.1 (C^{14}), 111.5 (C^{17}), 126.3 ($C^{5,8}$), 127.7 (C^{20}), 129.2 (C^{19}), 132.0 (C^{8a}), 132.1 (C^{4a}), 133.4, 133.5 ($C^{6,7}$, n.a.), 138.5 (C^{18}), 144.1 (C^{3}), 146.2 (C^{2}), 172.1 (C^{12}), 184.9 (C^{1}), 185.1 (C^{4}).

LC-MS: R_t = 10.3 min, m/z (%) 506.0 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 506.0974, $[M+H]^+$ found 506.0834.

4,4'-(3,6-dimethyl-1,4-benzoquinone-2,5-diyl)dibutanoic acid (13)



2,5-dimethyl-1,4-benzoquinone (1.50 g, 10.02 mmol) and glutaric acid (14.53 g, 110.0 mmol) were mixed in 100 ml of 30 % aqueous CH_3CN and heated to 65°C. After all solids had dissolved, silver nitrate (1.25 g, 7.36 mmol) was added, followed by a solution of ammonium peroxodisulfate (6.53 g, 28.62 mmol) in 50 ml aqueous CH_3CN (dropwise over a period of 2 h). The reaction was heated for another 1 h at 65 °C before it was cooled and stirred overnight. 300 ml CH_2Cl_2 and 200 ml H_2O were added and under addition of NaCl phases

were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with H_2O (5 x 100 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the crude yellowish brown oil was purified by using silica gel column chromatography (CH_2Cl_2/MeOH 95:5) to yield a orange solid (679 mg, 2.20 mmol).

Yield: 22%.

$C_{16}H_{20}O_6$ (MW = 308.33 g/mol).

R_f = 0.11 (CH_2Cl_2/MeOH 95:5).

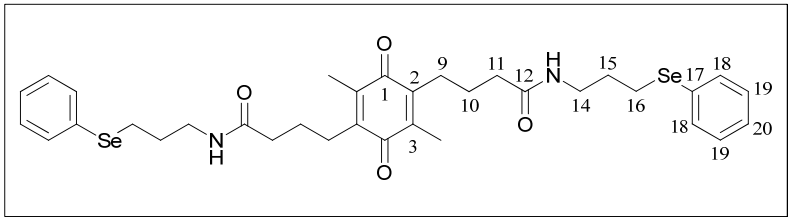
^{1}H NMR ($CDCl_3$): δ = 2.05 (m, 4 H, H^{10}), 2.08 (s, 6 H, CH_3), 2.35 (m, 4 H, H^9 or H^{11}, n.a.), 2.66 (m, 4 H, H^9 or H^{11}, n.a.).

^{1}H NMR (CD_3OD): δ = 0.18 (m, 4 H, H^{10}), 0.49 (s, 6 H, CH_3), 0.79 (m, 4 H, (m, 4 H, H^9 or H^{11}, n.a.), 1.00 (m, 4 H, H^9 or H^{11}, n.a.).

^{13}C NMR ($CDCl_3$): δ = 12.2 (CH_3), 24.9, 26.8, 34.6 ($C^{9,10,11}$, n.a.), 142.1, 142.7 ($C^{2,3}$, n.a.), 177.0 (C^{12}), 188.5 (C^1).

LC-MS: R_t = 6.5 min, m/z (%) 308.94 (100) $[M+H]^+$.

4,4'-(3,6-dimethyl-1,4-benzoquinone-2,5-diyl)bis(*N*-(3-(phenylselenyl)propyl)butanamide) (14):



Based on the preparation of **11**, 4,4'-(3,6-dimethyl-1,4-benzoquinone-2,5-diyl)dibutanoic acid (**13**) (102.8 mg, 0.33 mmol) was reacted with 3-(phenylselenyl)propane-1-amine (142.7 mg, 0.66 mmol) using *N*-methylmorpholine (67.5 mg, 0.66 mmol) and ethylchloroformate (72.3 mg, 0.66 mmol). The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH 98:2). A light yellow solid (109.2 mg, 0.16 mmol) was obtained.

Yield: 47.2%.

$C_{34}H_{42}N_2O_4Se_2$ (MW = 700.63 g/mol).

TLC: R_f = 0.24 (CH_2Cl_2/MeOH 98:2).

Mp = 114-116°C.

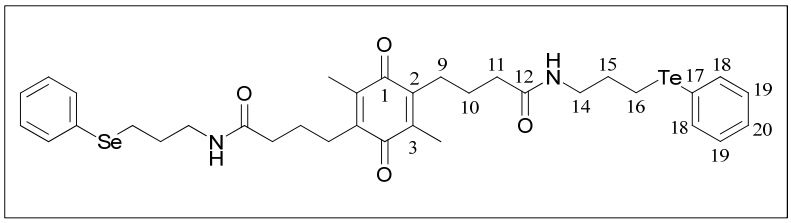
^{1}H NMR ($CDCl_3$): δ = 1.71 (quint, 4 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.9), 1.91 (quint, 4 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.3), 2.02 (s, 6 H, CH_3), 2.18 (t, 4 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.3), 2.48 (t, 4 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.9), 2.92 (t, 4 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.3), 3.36 (q, 4 H, H^{14}, $^3J_{HH}$ = 6.6), 5.84 (br s, 2 H, NH), 7.25 (m, 6 H, $H^{19,20}$), 7.48 (m, 4 H, H^{18}).

^{13}C NMR ($CDCl_3$): δ = 12.1 (CH_3), 24.3, 25.0, 25.9, 29.9, 36.1, 39.3 ($C^{9,10,11,14,15,16}$, n.a.), 127.0 (C^{20}), 129.1, 132.7 ($C^{18,19}$, n.a.), 129.9, 140.9, 143.5 ($C^{2,3,17}$, n.a.), 172.2 (C^{12}), 187.6 (C^1).

LC-MS: R_t = 10.5 min, m/z (%) 703.1 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 703.1553, $[M+H]^+$ found 703.1356

4,4'-(3,6-dimethyl-1,4-benzoquinone-2,5-diyl)bis(*N*-(3-(phenyltelluryl)propyl)butanamide) (15)



Based on the preparation of **14**, 4,4'-(3,6-dimethyl-1,4-benzoquinone-2,5-diyl)dibutanoic acid (**13**) (205.6 mg, 0.66 mmol) was reacted with 3-(phenyltelluryl)propane-1-amine (350.4 mg, 1.32 mmol) using *N*-methylmorpholine (134.9 mg, 1.32 mmol) and ethylchloroformate (144.7 mg, 1.32 mmol). After purification by silica gel column chromatography (CH_2Cl_2/MeOH 98:2) a yellowish brown solid (298.6 mg, 0.37 mmol) was obtained.

Yield: 56.1%.

$C_{34}H_{42}N_2O_4Te_2$ (MW = 797.91 g/mol).

TLC: R_f = 0.40 (CH_2Cl_2/MeOH 98:2).

Mp = 99-103°C

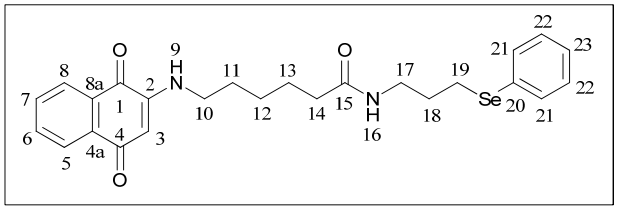
^{1}H NMR ($CDCl_3$): δ = 1.69 (quint, 4 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.9), 1.99 (quint, 4 H, H^{10} or H^{15}, n.a., $^3J_{HH}$ = 7.3), 2.00 (s, 6 H, CH_3), 2.15 (t, 4 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.3), 2.46 (t, 4 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.9), 2.86 (t, 4 H, H^9 or H^{11} or H^{16}, n.a., $^3J_{HH}$ = 7.6), 3.31 (q, 4 H, H^{14}, $^3J_{HH}$ = 6.3), 5.71 (br s, 2 H, NH), 7.18 (m, 4 H, H^{19}), 7.26 (m, 2 H, H^{20}), 7.71 (m, 4 H, H^{18}).

^{13}C NMR ($CDCl_3$): δ = 4.9 (C^{16}), 24.3, 25.9, 31.6, 36.0, 41.0 ($C^{9,10,11,14,15}$, n.a.), 12.1 (CH_3), 111.4 (C^{17}), 140.9, 143.5 ($C^{2,3}$, n.a.), 127.7 (C^{20}), 129.2, 138.5 ($C^{18,19}$, n.a.), 172.2 (C^{12}), 187.5 (C^1).

LC-MS: R_t = 11.0 min, m/z (%) 801.7 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 803.1347, $[M+H]^+$ found 803.1330.

6-(1,4-naphthoquinone-2-ylamino)-*N*-(3-(phenylselenyl)propyl)hexanamide (17)



As described earlier, 6-(1,4-naphthoquinone-2-ylamino)hexanoic acid (**16**) (278.3 mg, 1.00 mmol) and 3-(phenylselenyl)propane-1-amine (214.2 mg, 1.00 mmol) were reacted in presence of *N*-methylmorpholine (101.2 mg, 1.00 mmol) and ethylchloroformate (108.5 mg, 1.00 mmol). After appropriate workup (silica gel column chromatography with CH_2Cl_2), an orange-red solid (124.9 mg, 0.26 mmol) was obtained.

Yield: 25.8%.

$C_{25}H_{28}N_2O_3Se$ (MW = 483.46 g/mol).

TLC: R_f = 0.50 (CH_2Cl_2/MeOH 95:5).

Mp = 124-126°C.

^{1}H NMR ($CDCl_3$): δ = 1.41 (m, 2 H, H^{12}), 1.68 (m, 4 H, $H^{11,13}$), 1.90 (quint, 2 H, H^{18}, $^3J_{HH}$ = 6.9), 2.15 (t, 2 H, H^{14}, $^3J_{HH}$ = 7.3), 2.90 (t, 2 H, H^{19}, $^3J_{HH}$ = 7.3), 3.17 (q, 2 H, H^{10} or H^{17}, n.a., $^3J_{HH}$ = 6.3), 3.35 (m, 2 H, H^{10} or H^{17}, n.a.), 5.63 (br s, 1 H, NH), 5.70 (s, 1 H, H^3), 5.90 (br s,

1 H, NH), 7.24 (m, 3 H, $H^{22,23}$), 7.47 (m, 2 H, H^{21}), 7.60 (dt, 1 H, H^6 or H^7, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 7.71 (dt, 1 H, H^6 or H^7, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 8.03 (dd, 1 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0), 8.08 (dd, 1 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0).

^{13}C NMR ($CDCl_3$): δ = 25.08, 25.16, 26.6, 27.9, 29.9, 36.3, 39.2, 42.3 ($C^{10,11,12,13,14,17,18,19}$, n.a.), 100.7 ($C^3$), 126.1, 126.2, 127.0, 131.9, 134.7 ($C^{5,8,6,7,23}$, n.a.), 129.1, 132.7 ($C^{21,22}$, n.a.), 129.9, 130.5, 133.6 ($C^{4a,8a,20}$, n.a.), 147.9 (C^2), 172.5 (C^{15}), 181.9, 182.9 ($C^{1,4}$, n.a.).

NMR data including COSY spectroscopy:

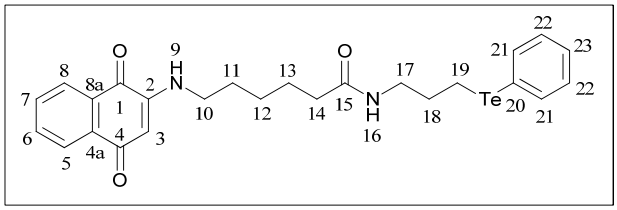
^{1}H NMR ($CDCl_3$): δ = 1.41 (m, 2 H, H^{12}), 1.68 (m, 4 H, $H^{11,13}$), 1.90 (quint, 2 H, H^{18}, $^3J_{HH}$ = 6.9), 2.15 (t, 2 H, H^{14}, $^3J_{HH}$ = 7.3), 2.90 (t, 2 H, H^{19}, $^3J_{HH}$ = 7.3), 3.17 (q, 2 H, H^{10}, $^3J_{HH}$ = 6.3), 3.35 (m, 2 H, H^{17}), 5.63 (br s, 1 H, NH, H^{16}), 5.70 (s, 1 H, H^3), 5.90 (br s, 1 H, NH, H^9), 7.24 (m, 3 H, $H^{22,23}$), 7.47 (m, 2 H, H^{21}), 7.60 (dt, 1 H, H^7, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 7.71 (dt, 1 H, H^6, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 8.03 (dd, 1 H, H^8, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0), 8.08 (dd, 1 H, H^5, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 1.0).

^{13}C NMR ($CDCl_3$): δ = 25.08 (C^{19}), 25.16 (C^{13}), 26.6 (C^{12}), 27.9 (C^{11}), 29.9 (C^{18}), 36.3 (C^{14}), 39.2 (C^{17}), 42.3 (C^{10}), 100.7 (C^3), 126.1 (C^5), 126.2 (C^8), 127.0 (C^{23}), 129.1 (C^{22}), 129.9 (C^{20}), 130.5 (C^{8a}), 131.9 (C^7), 132.7 (C^{21}), 133.6 (C^{4a}), 134.7 (C^6), 147.9 (C^2), 172.2 (C^{15}), 181.9 (C^1), 182.9 (C^4).

LC-MS: R_t = 8.8 min, m/z (%) 484.9 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 485.1343, $[M+H]^+$ found 485.1320.

6-(1,4-naphthoquinone-2-ylamino)-*N*-(3-(phenyltelluryl)propyl)hexanamide (18)



Similar to the preparation of **17**, 6-(1,4-naphthoquinone-2-ylamino)hexanoic acid (**16**) (191.5 mg, 0.67 mmol) and 3-(phenyltelluryl)propane-1-amine (175.0 mg, 0.67 mmol) were reacted in presence of *N*-methylmorpholine (67.4 mg, 0.67 mmol) and ethylchloroformate (72.3 mg, 0.67 mmol). After appropriate workup, an orange-red solid (250.3 mg, 0.47 mmol) was obtained.

Yield: 70.6%.

$C_{25}H_{28}N_2O_3Te$ (MW = 532.10 g/mol).

TLC: R_f = 0.36 (CH_2Cl_2/MeOH 95:5).

Mp = 105-107°C.

^{1}H NMR ($CDCl_3$): δ = 1.40 (m, 2 H, H^{12}), 1.67 (m, 4 H, $H^{11,13}$), 1.99 (m, 2 H, H^{18}), 2.13 (t, 2 H, H^{14}, $^3J_{HH}$ = 7.6), 2.86 (t, 2 H, H^{19}, $^3J_{HH}$ = 7.6), 3.17 (m, 2 H, H^{10} or H^{17}, n.a.), 3.31 (m, 2 H, H^{10} or H^{17}, n.a.), 5.55 (br s, 1 H, NH), 5.70 (s, 1 H, H^3), 5.90 (br s, 1 H, NH), 7.19 (m, 2 H, H^{22}), 7.27 (m, 1 H, H^{23}), 7.60 (dt, 1 H, H^6 or H^7, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 7.71 (m, 3 H, H^6 or H^7, H^{21}), 8.03 (dd, 1 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3), 8.08 (dd, 1 H, H^5 or H^8, n.a., $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.3).

^{13}C NMR ($CDCl_3$): δ = 5.0 (C^{19}), 25.1, 26.6, 27.9, 31.6, 36.3, 41.0, 42.3 ($C^{10,11,12,13,14,17,18}$, n.a.), 100.7 (C^3), 111.5 (C^{20}), 126.1, 126.2, 127.7, 131.9, 134.7 ($C^{5,8,6,7,23}$, n.a.) 129.2, 138.5 $C^{21,22}$, n.a.), 130.5, 133.6 ($C^{4a,8a}$, n.a.), 147.9 (C^2), 172.5 (C^{15}), 181.8, 182.9 ($C^{1,4}$, n.a.).

NMR data including COSY spectroscopy:

^{1}H NMR ($CDCl_3$): δ = 1.40 (m, 2 H, H^{12}), 1.67 (m, 4 H, $H^{11,13}$), 1.99 (m, 2 H, H^{18}), 2.13 (t, 2 H, H^{14}, $^{3}J_{HH}$ = 7.6), 2.86 (t, 2 H, H^{19}, $^{3}J_{HH}$ = 7.6), 3.17 (m, 2 H, H^{10}), 3.31 (m, 2 H, H^{17}), 5.55 (br s, 1 H, NH, H^{16}), 5.70 (s, 1 H, H^{3}), 5.90 (br s, 1 H, NH, H^{9}), 7.19 (m, 2 H, H^{22}), 7.27 (m, 1 H, H^{23}), 7.60 (dt, 1 H, H^{7}, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.3), 7.71 (m, 3 H, $H^{6,21}$), 8.03 (dd, 1 H, H^{8}, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.3), 8.08 (dd, 1 H, H^{5}, $^{3}J_{HH}$ = 7.6, $^{4}J_{HH}$ = 1.3).

^{13}C NMR ($CDCl_3$): δ = 5.0 (C^{19}), 25.1 (C^{13}), 26.6 (C^{12}), 27.9 (C^{11}), 31.6 (C^{18}), 36.3 (C^{14}), 41.0 (C^{17}), 42.3 (C^{10}), 100.7 (C^{3}), 111.5 (C^{20}), 126.1 (C^{5}), 126.2 (C^{8}), 127.7 C^{23}), 129.2 (C^{22}), 130.5 (C^{8a}), 131.9 (C^{7}), 133.6 (C^{4a}), 134.7 (C^{6}), 138.5 (C^{21}), 147.9 (C^{2}), 172.5 (C^{15}), 181.8 (C^{1}), 182.9 (C^{4}).

LC-MS: R_t = 12.4 min, m/z (%) 535.2 (100) $[M+H]^+$.

HRMS: $[M+H]^+$ calcd 535.1240, $[M+H]^+$ found 535.1223.

S2. SK-Mel-5 and HL-60 cell culture studies

SK-Mel-5 (human melanoma) and HL-60 (human leukemia) cell lines were cultured at 37°C in RPMI 1640 medium containing 10% FCS gold and 100U/mL penicillin and 100 µg/mL streptomycin. Cell viability was determined using a variation of the standard Methylthiazolyldiphenyltetrazolium bromide (MTT) assay.[11-13] To test the pro- or antioxidative properties of compounds, SK-Mel-5 cells were placed in wells of a 96-well plate (4 x 10^4 cells per well) and grown for 20 h to reach confluency. The medium was removed and cells were incubated with new medium containing the test compounds (5 to 200 µM). They were then incubated at 37°C for 24 h in the absence and presence of 1 mM H_2O_2. At

this point, the medium was removed and the MTT assay carried out. HL-60 cells were treated accordingly, yet an initial cell density of 9 x 10^4 cells per well was used.

S3. Activity assay against ***Plasmodium falciparum***

Cultivation of *Plasmodium falciparum* and drug sensitivity tests. *P. falciparum* (3D7-Netherlands strain) was grown in continuous culture as described by Trager and Jensen[14] with slight modifications. Unless otherwise stated, parasites were maintained at 1 to 10% parasitemia and 3.3% hematocrit in an RPMI 1640 culture medium supplemented with A+ erythrocytes, 0.5% lipid-rich bovine serum albumin (Albumax), 9 mM (0.16%) glucose, 0.2 mM hypoxanthine, 2.1 mM L-glutamine, and 22 µg/ml gentamicin. All incubations were carried out at 37°C in 3% O_2, 3% CO_2, and 94% N_2. Synchronization of parasites in culture to ring stages was carried out by treatment with 5% (w/v) sorbitol.[15]

Isotopic drug sensitivity assays by means of the semi-automated microdilution technique[16] were employed to investigate the susceptibility of the malaria parasites to the various compounds. The method depends on the incorporation of radioactive ^{3}H-hypoxanthine which is taken up by the parasite as a precursor of purine deoxynucleotides for DNA synthesis and was performed according to the modifications of Fivelman and colleagues.[17] In 96 well microtitre plates (Nunc®), a two-fold serial dilution of the starting concentration of each drug to be tested was carried out. Parasites were incubated at a parasitemia of 0.25% (>70% ring forms) and 1.25% hematocrit in hypoxanthine free medium. After 48 hours, 0.5 µCi ^{3}H-hypoxanthine was added into each well and the plates were incubated for another 24 h. The cells of each well were harvested on a glass fibre filter (Perkin-Elmer, Rodgau-Jügesheim,

Germany), washed and dried. Their radioactivity in counts per minute was considered to be proportional to the respective growth of *P. falciparum* in the well.

S4. Activity assay against ***Trichophyton rubrum***

Activity against ***Trichophyton rubrum*** was measured in a plate assay. Briefly, agar plates containing streptomycin (40 ug/ml), penicillin (40 Units/ml) and cycloheximide (500 ug/ml) were prepared. The plates were placed on top of an 'injection mask', which formally divides the plate into eight equally-sized sectors and contains an inner and outer ring. Small amounts of ***Trichophyton rubrum*** samples obtained from patients were transferred onto the plate with a diluting loop, and positioned at the intersections of the sectors with the *outer* ring. The agar plate was stored in an incubator at 26°C for 6-10 days, during which time the dermatophytes grew to a size of around 1 cm in diameter. In order to test the ability of compounds to slow down or inhibit the further growth of the dermatophyte, cellulose plates soaked in compound (10 µl per plate) were added at the intersections of the sectors with the *inner* ring. The agar plates were returned to the incubator and the distance between the dermatophyte and the compound-containing plates was measured after 0, 2, 4, 6, 8 and 10 days. Incubations with DMSO as well as empty cellulose plates were used as negative controls, ketoconazol served as positive control and benchmark.

S5. 58-cell line screening at the National Cancer Institute (NCI)

The 58 cancer cell line screen for was performed at the National Cancer Institute (NCI) at the NIH (US). These single-dose tests (at 10 µM) were performed for cell lines clustered in cells

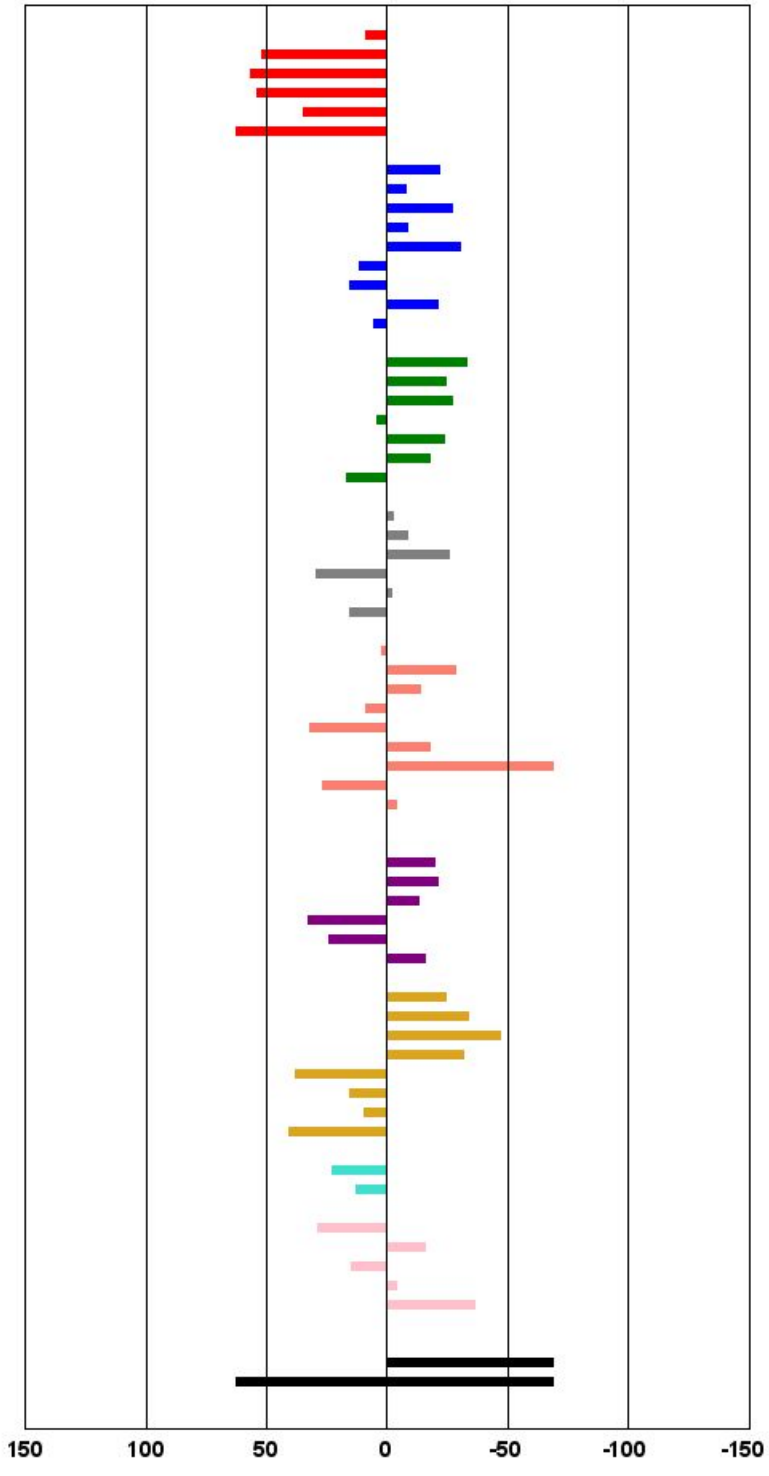
representing leukaemia, non-small cell lung cancer, colon cancer, cancer of the central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer.[18,19] All tests follow a standard protocol for cytotoxicity screens, details of which can be obtained from the NCI website at http://dtp.nci.nih.gov. Based on the results obtained as part of the single-dose testing, compounds with a particular activity were then selected for five-dose tests (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} M) and LC_{50} determination.

Developmental Therapeutics Program

One Dose Mean Graph

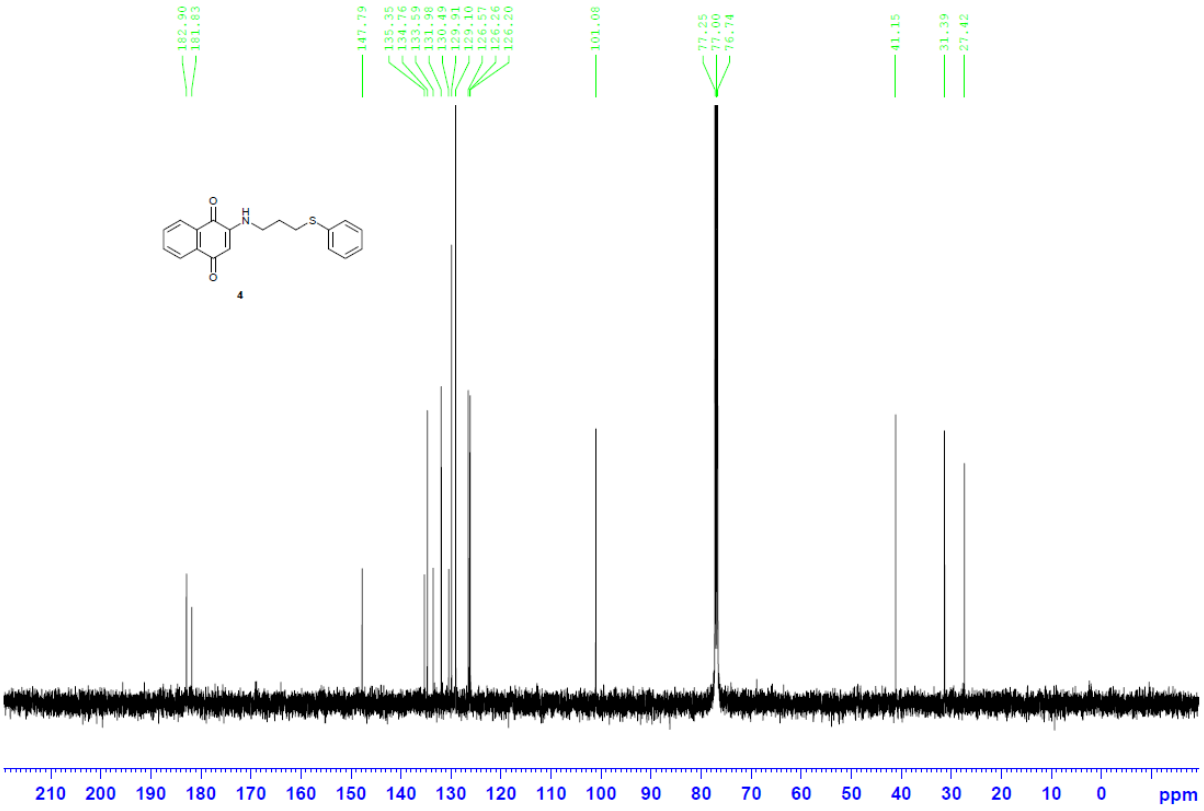
NSC: 748896 / 1	Conc: 1.00E-5 Molar	Test Date: Oct 20, 2008
Experiment ID: 0810OS74		Report Date: Mar 11, 2009

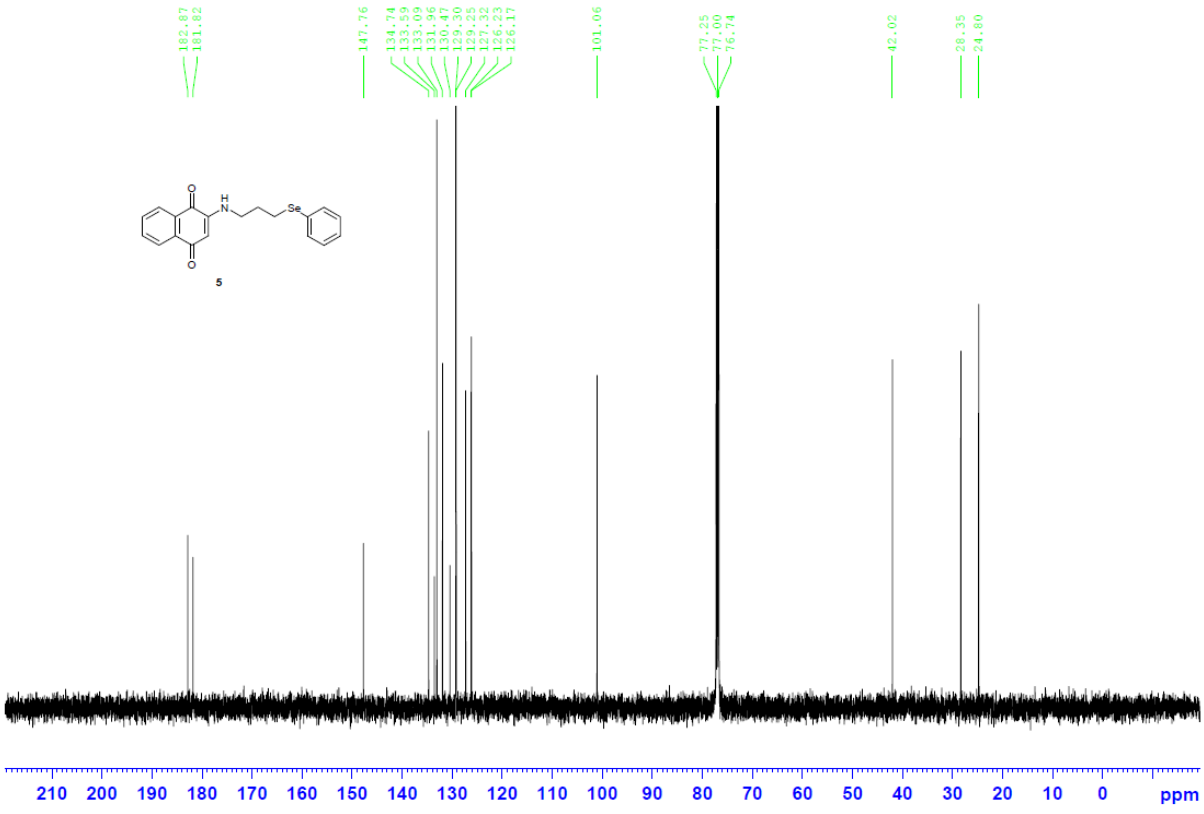
Panel/Cell Line	Growth Percent
Leukemia	
CCRF-CEM	-15.28
HL-60(TB)	28.14
K-562	32.72
MOLT-4	29.70
RPMI-8226	10.47
SR	38.33
Non-Small Cell Lung Cancer	
A549/ATCC	-45.43
EKVX	-31.93
HOP-62	-51.04
HOP-92	-32.45
NCI-H226	-54.59
NCI-H23	-12.86
NCI-H322M	-8.86
NCI-H460	-45.33
NCI-H522	-18.47
Colon Cancer	
COLO 205	-56.98
HCC-2998	-48.70
HCT-116	-50.99
HCT-15	-20.11
HT29	-47.54
KM12	-41.64
SW-620	-7.07
CNS Cancer	
SF-268	-26.67
SF-295	-32.51
SF-539	-49.68
SNB-19	5.42
SNB-75	-25.97
U251	-8.56
Melanoma	
LOX IMVI	-22.09
MALME-3M	-52.31
M14	-37.60
MDA-MB-435	-15.52
SK-MEL-2	8.28
SK-MEL-28	-42.01
SK-MEL-5	-92.89
UACC-257	2.91
UACC-62	-27.73
Ovarian Cancer	
IGROV1	-23.98
OVCAR-3	-43.81
OVCAR-4	-44.76
OVCAR-5	-36.95
OVCAR-8	8.94
NCI/ADR-RES	-0.19
SK-OV-3	-39.61
Renal Cancer	
786-0	-48.49
A498	-57.66
ACHN	-71.19
CAKI-1	-55.78
RXF 393	13.75
SN12C	-8.47
TK-10	-14.76
UO-31	16.87
Prostate Cancer	
PC-3	-0.99
DU-145	-11.55
Breast Cancer	
MCF7	4.88
MDA-MB-231/ATCC	-39.76
HS 578T	-9.34
BT-549	-27.72
T-47D	-60.51
Mean	-24.03
Delta	68.86
Range	131.22

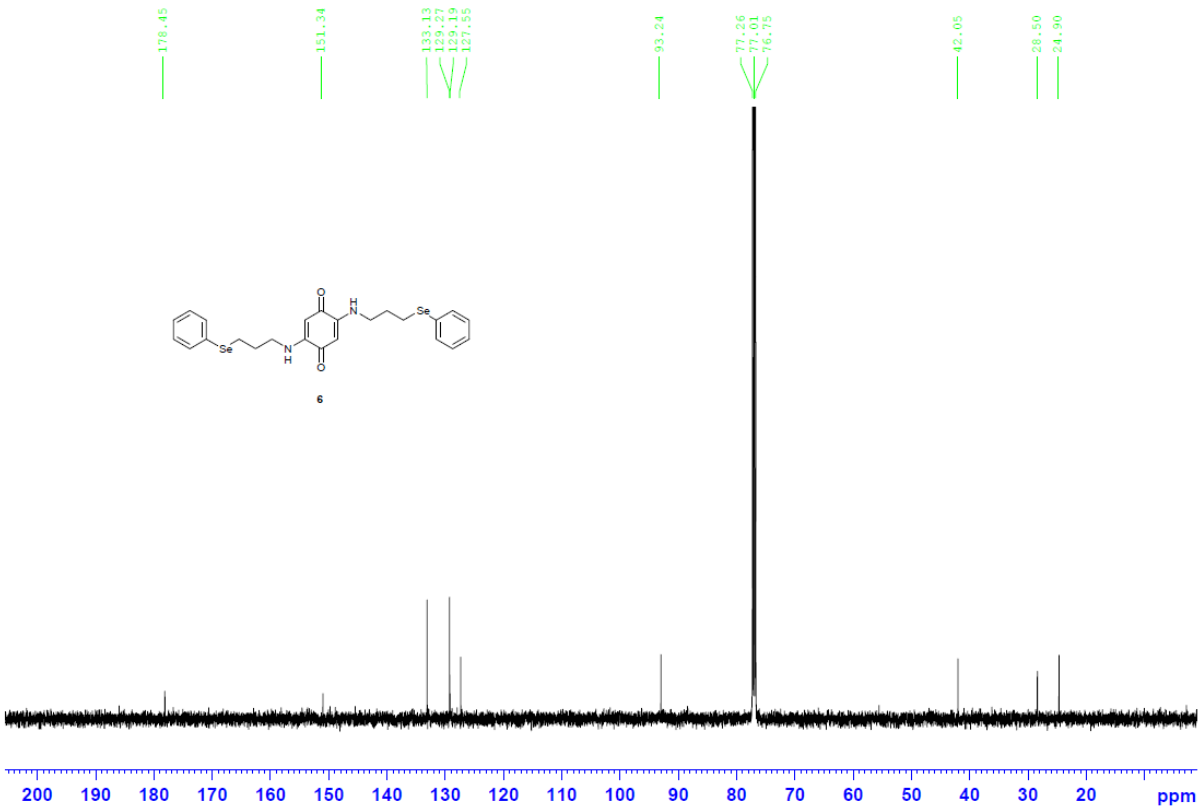


Summary of results obtained for **18** in the one-dose screen. Details are provided in the text.

S6. ^{13}C NMR spectra of novel compounds



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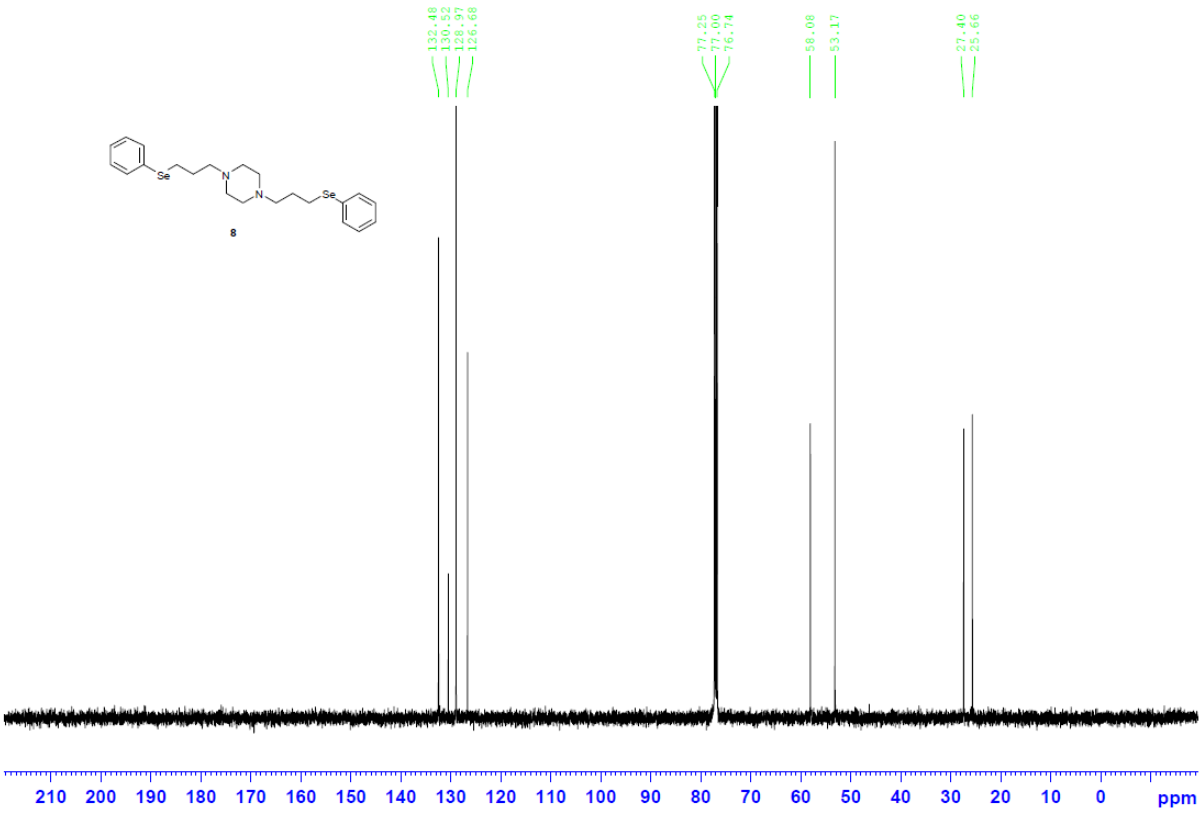
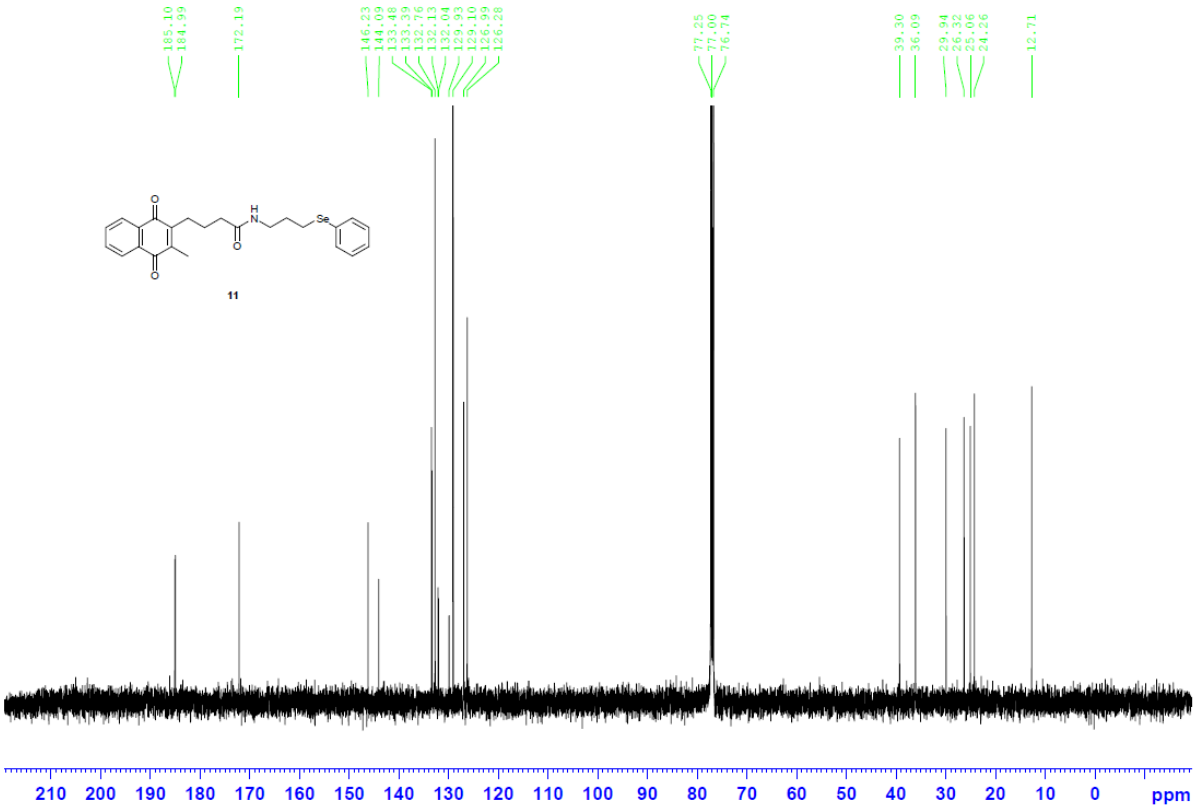
151.34
133.13
129.27
129.19
127.55
93.24
77.26
77.01
76.75
42.05
28.50
24.90
O
N
H
Se
N
H
Se
O
6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


132.48
130.52
128.97
126.68
77.25
77.00
76.74
58.08
53.17
27.40
25.66
Se
N
N
Se
8
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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126.28
77.25
77.00
76.74
39.30
36.09
29.94
26.32
25.06
24.26
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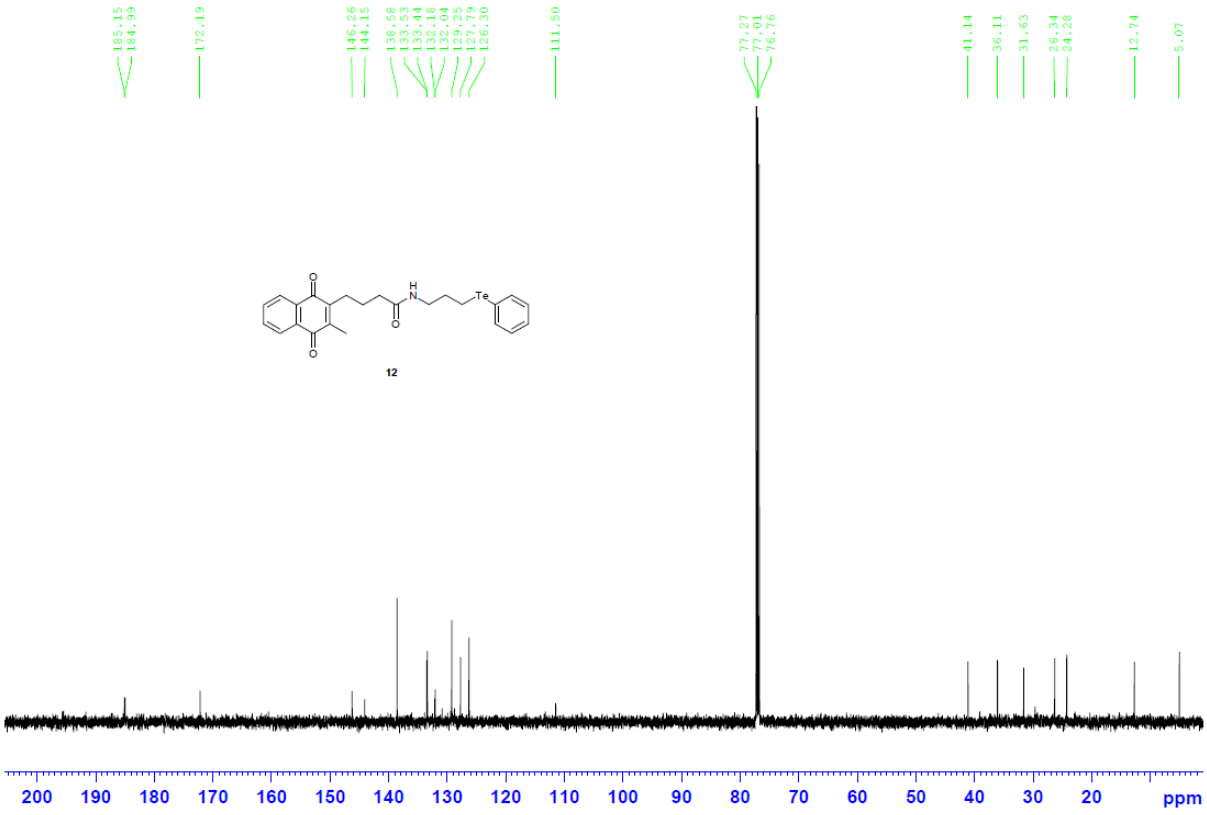
O
O
H
N
O
Se
11
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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111.50
77.27
77.01
76.76
41.14
36.11
31.63
26.34
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O
Te
12
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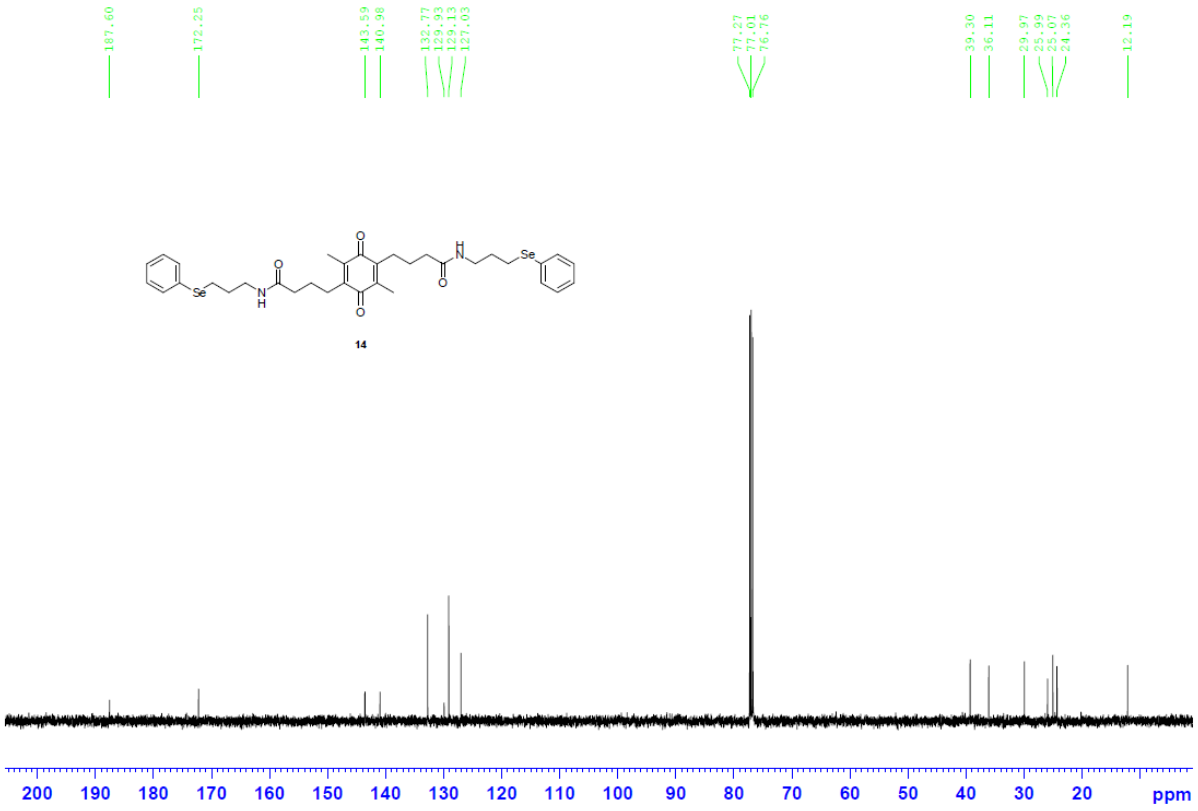
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140.98
132.77
129.93
129.13
127.03
77.27
77.01
76.76
39.30
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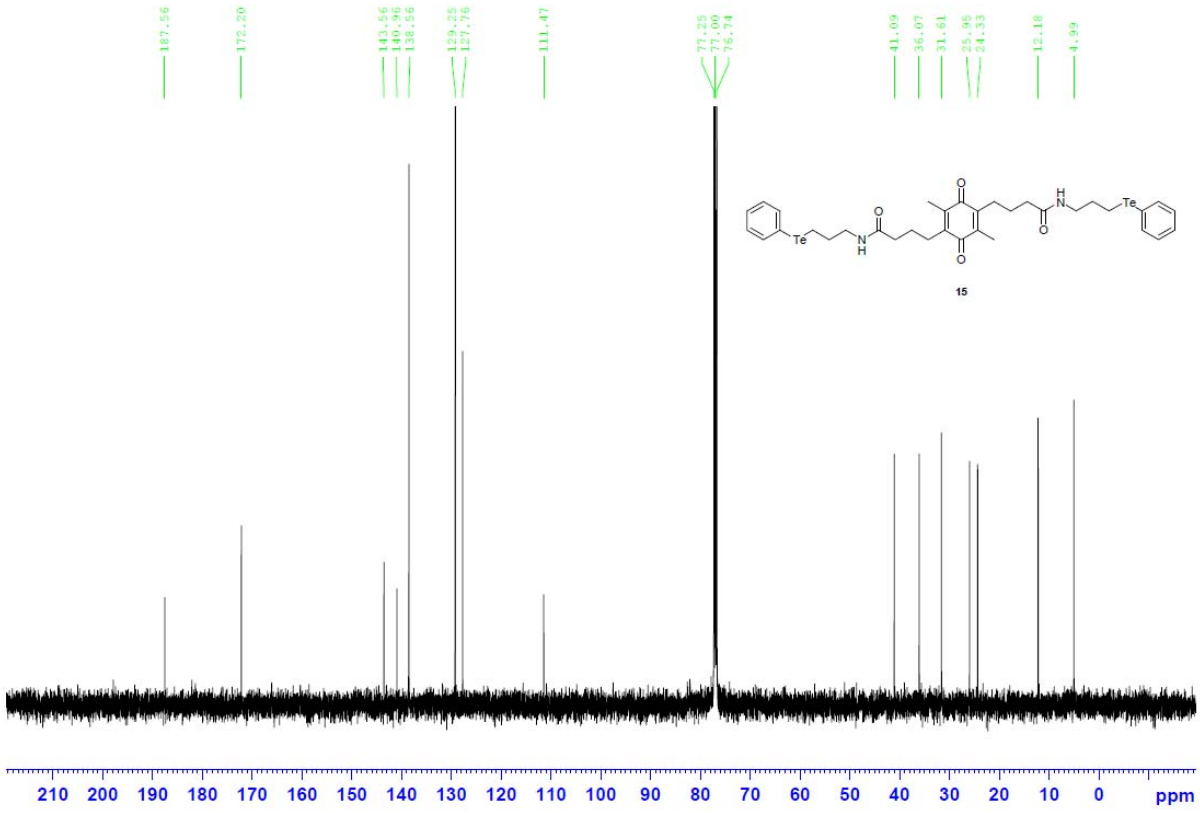
29.97
25.99
25.07
24.36
12.19
14
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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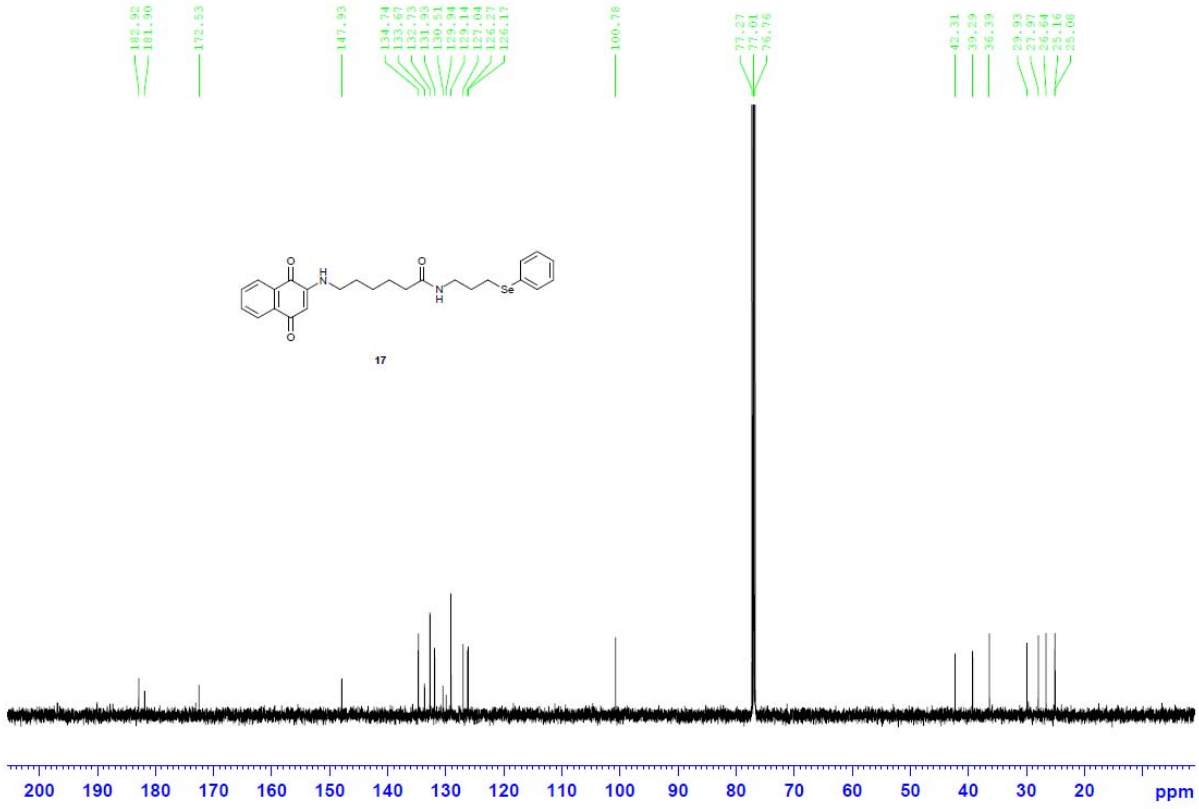
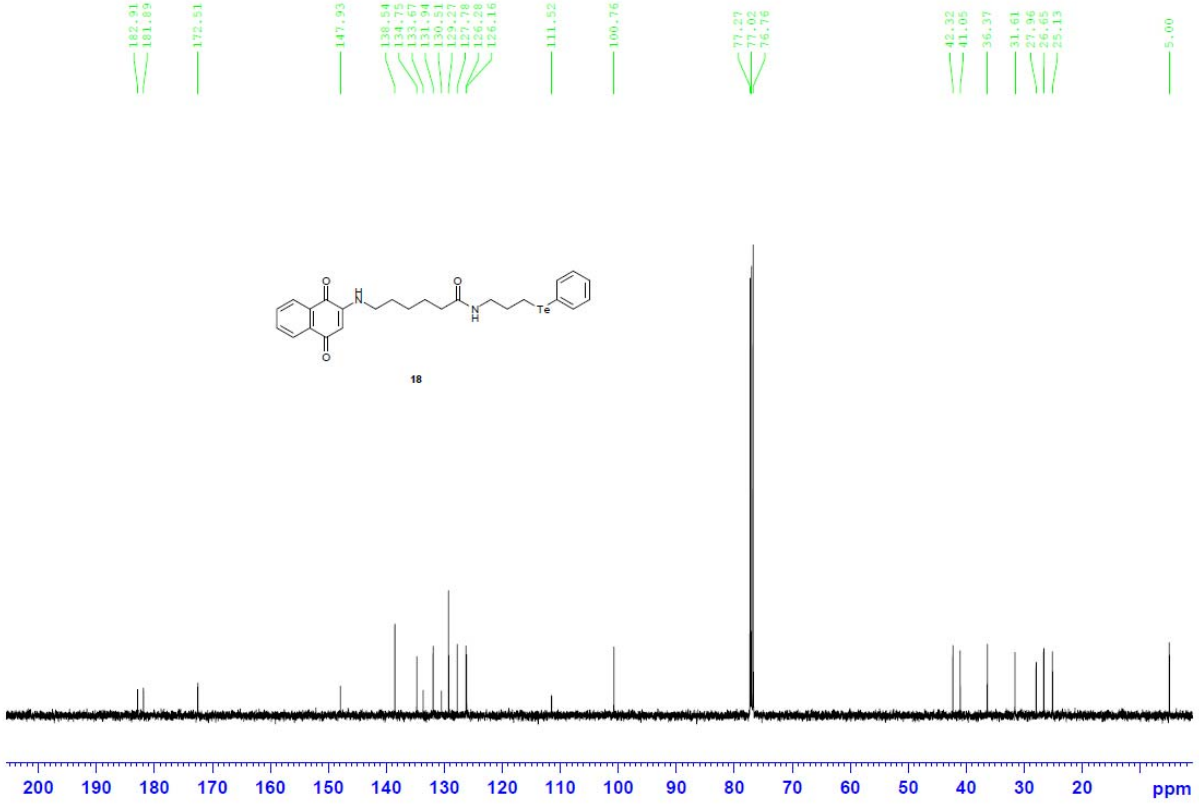
172.20
143.56
140.96
138.56
129.25
127.76
111.47
77.25
77.00
76.74
41.09
36.07
31.61
25.95
24.33
12.18
4.99
15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


182.92
181.90
172.53
147.93
134.74
133.67
132.73
131.93
130.51
129.94
129.14
127.04
126.27
126.17
100.78
77.27
77.01
76.76
42.31
39.29
36.39
29.93
27.97
26.64
25.16
25.06
Se
17
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


182.91
181.89
172.51
147.93
138.54
134.75
133.67
131.94
130.51
129.27
127.78
126.28
126.16
111.52
100.76
77.27
77.02
76.76
42.32
41.05
36.37
31.61
27.96
26.65
25.13
5.00
Te
18
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

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