Supplementary information

Multicomponent reactions for the synthesis of multifunctional redox agents with biological activity against cancer cells

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Synthesis of compounds

Chemical reagents were purchased from Sigma-Aldrich-Fluka (Darmstadt, Germany) and used without further purification unless stated otherwise. 3-(Phenylselanyl)propanoic acid **1a**[1], 3-(3-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-ylthio)propanoic acid **1b**[2], 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin **1d**[3], 2-(phenylselanyl)acetaldehyde **2b**[4], 3-(phenyltellanyl)propan-1-amine[5], 3-(phenylselanyl)propan-1-amine[5], 3-(phenylthio)propan-1-amine[6], 1,2-bis(2,2-diethoxyethyl)diselane[4] and benzyl 6-isocyanohexanoate **3e**[4] were synthesised according to the literature.

General Procedure for the preparation of chalcogen containing isonitrile building blocks 3b-3d

A mixture of 1 g of appropriate amine, 1.0-1.2 equivalents of formic acid and 1.5-2.0 equivalents of acetic anhydride were mixed and heated for 2h. The progress of the reaction was monitored by TLC, and after starting material had disappeared, the solvent was evaporated from the reaction mixture to give the crude *N*-formyl compound, essentially as an oily product which could be purified by chromatography on silica gel, usually with dichloromethane: methanol (10: 1). The *N*-formyl compound (6.05 g, 50.0 mmol) and diisopropylamine (DIPA, 19 mL, 0.14 mol) were dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. $POCl_3$ (5.0 mL, 55 mmol) was slowly added and stirring was continued at 0 °C for another 30 min. Sodium carbonate (10 g) in H_2O (50 mL) was added at room temperature in a rate so that the temperature was maintained at 25 - 35 °C. The mixture was stirred for 90 min at room temperature. H_2O and CH_2Cl_2 (25 mL each) were added. The organic layer was separated, washed with H_2O (three times 25 mL), dried over $MgSO_4$ and purified by chromatography on silica gel, in general with petrol ether: ethyl acetate (8: 1) as eluent.

General Procedure for the preparation of α-acyloxy amide via the three-component Passerini reaction

As a general procedure, a mixture of aldehyde (1 mmol), carboxylic acid (1.2 mmol) and isonitrile (1.5 mmol) in 5 ml solvent were stirred at room temperature overnight. Upon completion (monitored by TLC), 10 ml CH_2Cl_2 were added to dissolve the sticky product. The water layer was washed three times with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4 and concentrated to yield a sticky product which was purified by chromatography on silica gel, usually with petrol ether: ethyl acetate (4: 1) as eluent. Figure 1 and Table 1 provide details of the individual reactions.

General Procedure for the preparation of α-aminoacyl amide via the four-component Ugi reaction

As a general procedure, a mixture of aldehyde (1 mmol), amine (1 mmol), carboxylic acid (1.2 mmol), and isonitrile (1.5 mmol) in 5 ml solvent were stirred at room temperature overnight. Upon completion (monitored by TLC), 10 ml CH_2Cl_2 were added to dissolve the sticky product. The water layer was washed three times with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4 and concentrated to yield a sticky product which was purified by chromatography on silica gel, usually with petrol ether: ethyl acetate (5: 2). Figure 1 and Table 1 provide details of the individual reactions.

Synthesis of building blocks

Several building blocks could be synthesised according to literature methods. Some building blocks, however, have not been reported to date and were synthesised as follows.

Compound **2c** was synthesised via 2-(2,2-diethoxyethylselanyl)-3-methylnaphthalene-1,4-dione. The latter was synthesised from 1,2-bis(2,2-diethoxyethyl)diselane (237 µl, 0.6 mmol) dissolved in a 1:1 mixture of water and ethylacetate (50 ml) along with the phase transfer catalyst (PTC) tricarpylmethylammonium chloride (200 mg, 0.45 mmol) under nitrogen. $NaBH_4$ (76 mg, 2 mmol) was added and the mixture was stirred until the solution turned colorless. Acetaldehyde solution (2-3 ml) was added and the reaction stirred for a further 5 min. A solution of 3-bromo-2-methyl-1,4-naphthoquinone (250 mg, 1 mmol) in ethylacetate (5 ml) was added and the reaction mixture stirred at room temperature for 10 min under nitrogen and for a further 30 min on air. The orange coloured reaction mixture was diluted with 50 ml of water and extracted with diethylether. The combined organic extracts were dried over Na_2SO_4 and solvent was evaporated under

reduced pressure. TLC, R_f = 0.75 (petroleum ether: ethyl acetate 9:1) 2-(2,2-diethoxyethylselanyl)-3-methylnaphthalene-1,4-dione was purified by column chromatography on silica gel with petrol ether: ethyl acetate = 10:1. It was obtained as a yellow solid. Yield = 94 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.02-7.98 (m, 2H), 7.63-7.58 (m, 2H), 4.72-4.70 (t, 2H), 3.63-3.56 (m, 2H), 3.48-2.42 (m, 2H), 3.28 (d, CH_2Se, 2H), 2.30 (s, 3H), 1.08-1.05 (t, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 181.6 (s), 181.4 (s), 148.0 (s), 146.8 (s), 133.5 (d), 133.2 (d), 132.9 (s), 131.9 (s), 126.9 (d), 126.6 (d), 102.8 (d), 62.2 (t, 2C), 30.9 (t), 17.3 (q), 15.2 (q, 2C) ppm.

Compound **2c** was then synthesised in a two-phase system consisting of a solution of 2-(2,2-diethoxyethylselanyl)-3-methylnaphthalene-1,4-dione (386 µl, 1 mmol) in 500 ml of ether and 500 ml of 1 M HCl. The reaction mixture was vigorously stirred for 24 h. TLC, R_f = 0.55 (petrol ether : ethyl acetate 9:1). After separation of the phases, the aqueous layer was re-extracted with ether (2x) and the organic layers were washed with water (2x) and brine (1x). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. **2c** was purified by column chromatography on silica gel with petrol ether: ethyl acetate = 7:1. The compound was obtained as a yellow solid. Yield = 90 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.02-7.98 (m, 2H), 7.63–7.58 (m, 2H), 3.28 (d, 2H), 2.30 (s, 3H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 181.9 (d), 181.6 (s), 181.2 (s), 148.0 (s), 146.8 (s), 133.5 (d), 133.2 (d), 132.9 (s), 131.9 (s), 126.9 (d), 126.6 (d), 30.9 (t), 17.3 (q) ppm. LC-MS (ESI): *m*/*z* calc. 293.980, R_t = 7.01 min, *m*/*z* found 295.79 $[M+H]^+$, HRMS: [M+H] calc. 294.9873 [M+H] found 294.9868.

Compound **3b** was synthesised in a two-step reaction starting from 3-(phenyltellanyl)propan-1-amine (1 g, 3.77 mmol), formic acid (5.5 ml, 4.5 mmol) and acetic anhydride (8.10 ml, 7.54 mmol) following the general procedure for isonitrile synthesis described above. TLC, R_f = 0.41 (petroleum ether : ethyl acetate 10:1). The *N*-(3-(phenyltellanyl)propyl)formamide intermediate was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 91 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.06 (s, 1H), 7.67-7.65 (m, 2H), 7.24-7.21 (m, 1H), 7.17-7.12 (m, 2H), 5.38 (br s, 1H), 3.31-3.19 (m, 2H), 2.81-2.77 (m, 2H), 1.97-1.88 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 161.37 (d), 138.37 (d, 2C), 129.14 (d, 2C), 127.66 (d), 111.24 (s), 39.62 (t), 31.36 (t), 4.60 (t) ppm. HRMS: [M+H] calc. 291.9981 [M+H] found 291.9976.

This compound (1 mg, 3.43 mmol) was reacted with DIPA (19 mL, 9.6 mmol), $POCl_3$ (0.40 mL, 3.77 mmol) and Na_2CO_3 (0.60 g) following the procedure described for isonitrile above. TLC, R_f = 0.63 (petroleum ether : ethyl acetate 8:1). Compound **3b** was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 62 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.76-7.74 (m, 2H), 7.34-7.30 (m, 1H), 7.27-7.22 (m, 2H), 3.49-3.45 (m, 2H), 2.97-1.98 (t, *J* = 7.18, 14.67 Hz, 2H), 2.13-2.05 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79Hz): 156.73 (s), 138.68 (d, 2C), 129.43 (d, 2C), 128.11 (d), 110.69 (s), 43.25 (t), 31.00 (t), 3.64 (t) ppm. LC-MS (ESI): *m*/*z* calc. 272.8, R_t = 1.33 min, *m*/*z* found 274.1 $[M+H]^+$, HRMS: [M+H+O] calc. 291.9981, [M+H+O] found 291.9976. Isotope pattern of Te: *m/z* (relative abundance %) 281.9954 (1.0), 283.9944 (8.0), 285.9942 (14.5), 286.9958 (21.0), 287.9946 (55.5), 289.9958 (93.5), 291.9976 (100), 293.0009 (11.0), 294.0043 (5.0).

The selenium and sulfur analogues (**3c** and **3d**, respectively) were synthesised following the same procedure. Compound **3c** was obtained as yellow oil. TLC, R_f = 0.66 (petroleum ether : ethyl acetate 8:1).Yield = 82 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.51-7.49 (m, 2H), 7.30-7.28 (m, 3H), 3.48-3.46 (m, 2H), 2.95-2.90 (m, 2H), 1.98-1.90 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 156.65 (s), 134.68 (s), 130.00 (d, 2C), 129.10 (d, 2C), 127.76 (d), 40.74 (t), 29.94 (t), 19.20 (t) ppm. LC-MS (ESI), *m*/*z* calc. 224.16, R_t = 1.65 min, *m*/*z* found 225.18 $[M+H]^+$, HRMS: [M+H] calc. 226.0134, [M+H] found 226.0129.

Compound **3d** was obtained as a yellow oil. TLC, R_f = 0.69 (petroleum ether : ethyl acetate 8:1). Yield = 77 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.30-7.28 (m, 2H), 7.25-7.22 (m, 2H), 7.17-7.13 (m, 1H), 3.44-3.41 (m, 2H), 2.98-2.95 (t, *J* = 6.83, 13.66 Hz, 2H), 1.89-1.83 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 156.65 (s), 134.68 (s), 129.45 (d, 2C), 128.76 (d, 2C), 126.22 (d), 39.74 (t), 29.94 (t), 28.01 (t) ppm. LC-MS (ESI): *m*/*z* calc. 177.26, R_t = 15.26 min, *m*/*z* found 178.15 $[M+H]^+$, HRMS: [M+H] calc. 178.0690, [M+H] found 178.0685.

Compound **5** was synthesised from **2b** (200 µl, 1 mmol), **1b** (331.6 mg, 1.2 mmol) and *tert*-butyl isocyanide **3a** (124.6 µl, 1.5 mmol) following the general procedure described for the Passerini reaction above. TLC, R_f = 0.67 (petroleum ether : ethyl acetate 5:1). It was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 68 %. ^{1}H-NMR ($CDCl_3$, 500

MHz): 8.03-7.98 (m, 2H), 7.66-7.62 (m, 2H), 7.45-7.52 (m, 2H), 7.18-7.12 (m, 3H), 5.98 (br s, 1H), 5.25-5.22 (dd, *J* = 5.1, 7.0 Hz, 1H), 3.38-3.34 (m, 1H), 2.49-2.43 (m, 1H), 2.27 (s, 3H), 1.29 (s, 9H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79Hz): 182.0 (s), 181.2 (s), 167.0 (s), 147.5 (s), 145.4 (s), 133.8 (d), 133.5 (d), 132.9 (d, 2C), 132.7 (s), 131.9 (s), 129.6 (s), 129.2 (d, 2C), 127.3 (d), 126.8 (d), 126.7 (d), 73.9 (d), 51.7 (s), 35.3 (t), 29.0 (t), 28.9 (t), 28.6 (q, 3C), 15.4 (q) ppm. LC-MS (ESI) *m*/*z* calc. 559.09, R_t = 14.33 min, *m*/*z* found 560.08 $[M+H]^+$, HRMS: [M+H] calc. 560.1009, [M+H] found 560.1004, [M+Na] calc. 582.0829 [M+Na] found 582.0824. Isotope pattern of Se: *m*/*z* (relative abundance %) 554.1064 (2.0), 556.1031 (20.0), 558.1012 (48.0), 560.1004 (100.0), 561.1038 (31.0), 562.1006 (21.0), 563.1040 (6.0).

Compound **6** was synthesised from **2c** (293 µl, 1 mmol), **1b** (331.6 mg, 1.2 mmol) and *tert*-butyl isocyanide **3a** (124.6 µl, 1.5 mmol) following the general procedure described for the Passerini reaction above. TLC, R_f = 0.57 (petroleum ether : ethyl acetate 2.5:1). It was purified by column chromatography on silica gel with petrol ether: ethyl acetate = 3:1. The compound was obtained as a yellow oil. Yield = 76 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.01-7.96 (m, 4H), 7.65-7.58 (m, 4H), 6.01 (br s, 1H), 5.37-5.35 (dd, *J* = 5.2, 7.1 Hz, 1H), 3.69-3.65 (dd, *J* = 5.2, 13.2 Hz, 1H), 3.46-3.42 (dd, *J* = 6.6, 13.2 Hz, 1H), 3.31-3.28 (t, *J* = 6.6, 13.2 Hz, 2H), 2.69-2.66 (m, 2H), 2.30 (s, 3H), 2.24 (s, 3H), 1.28 (s, 9H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 182.1 (s), 181.7 (s), 181.3 (s), 181.2 (s), 170.1 (s), 166.8 (s), 148.7 (s), 147.4 (s), 145.6 (s), 145.5 (s), 133.8 (d), 133.7 (d), 133.5 (d), 133.4 (d), 132.7 (s, 2C), 132.0 (s), 131.8 (s), 126.9 (d), 126.8 (d), 126.7 (d), 126.6 (d), 74.4 (d), 51.7 (s), 35.6 (t), 29.1 (t), 28.9 (t), 28.6 (q, 3C), 17.4 (q), 15.3 (q) ppm. LC-MS (ESI): *m*/*z* calc. 653.09, R_t = 14.68 min, *m*/*z* found 654.20 $[M+H]^+$, HRMS: [M+H] calc. 654.1064, [M+H] found 654.1059, [M+Na] calc. 676.0884 [M+Na] found 676.0879. Isotope pattern of Se: *m*/*z* (relative abundance %) 648.1119 (2.0), 650.1086 (20.0), 652.1067 (47.0), 654.1079 (100.0), 655.1093 (35.0), 656.1061 (18.0), 657.1095 (7.0).

Compound **7** was synthesised from **2c** (293 µl, 1 mmol), **1a** (275.9 mg, 1.2 mmol) and benzyl 6-isocyanohexanoate **3e** (346.9 µl, 1.5 mmol) following the general procedure described for the Passerini reaction above. TLC, R_f = 0.43 (petroleum ether : ethyl acetate 2.5:1). It was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 79 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.02-7.97 (m, 2H), 7.65-7.61 (m, 2H), 7.45-7.41 (m, 2H), 7.29-7.21 (m, 5H), 7.17-7.12 (m, 3H), 6.41 (br s, 1H), 5.37-5.33 (dd, *J* = 4.4, 5.8 Hz, 1H), 5.03 (s, 2H),

3.31-3.23 (m, 2H), 3.19-3.15 (t, *J* = 6.2, 13.0 Hz, 2H), 3.01-2.95 (m, 2H), 2.66-2.64 (t, *J* = 7.1, 14.0 Hz, 2H), 2.46-2.40 (m, 2H), 2.30 (s, 3H), 1.61-1.55 (m, 2H), 1.50-1.44 (m, 2H), 1.30-1.24 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79Hz): 182.3 (s), 181.5 (s), 173.5 (s), 170.2 (s), 168.2 (s), 148.3 (s), 145.5 (s), 136.3 (s), 134.1 (d), 133.7 (d), 133.1 (d, 2C), 132.9 (s), 132.2 (s), 129.8 (s), 129.4 (d, 2C), 128.8 (d, 2C), 128.4 (d), 128.3 (d, 2C), 127.6 (d), 127.5 (d), 126.9 (d), 73.9 (d), 66.4 (t), 39.5 (t), 35.4 (t), 34.2 (t), 32.5 (t), 29.1 (t), 26.5 (t), 24.6 (t), 22.5 (t), 15.7 (q). HRMS: [M+H] calc. 756.0978, [M+H] found 756.0973. Isotope pattern of Se: *m*/*z* (relative abundance %) 746.1060 (1.5), 749.1034 (5.0), 750.1008 (20.0), 752.1000 (40.0), 756.0973 (100.0), 757.1007 (41.0), 759.1009 (15.0), 760.0977 (7.0).

Compound **8** was synthesised from **2c** (293 µl, 1 mmol), 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldisulfanyl)propanoic acid **1c** (370.8 mg, 1.2 mmol) and *tert*-butyl isocyanide **3a** (124.6 µl, 1.5 mmol) following the general procedure described for the Passerini reaction above. TLC, R_f = 0.45 (petroleum ether : ethyl acetate 3:1). It was purified by column chromatography on silica gel with petrol ether: ethyl acetate = 3:1. The compound was obtained as a yellow oil. Yield = 54 %. This compound consists of two optical isomers, which could not be separated by simple column chromatography. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.02-7.99 (m, 2H), 7.65-7.60 (m, 2H), 6.54-6.47 (br s, 1H), 5.41-5.11 (m, 1H), 4.45-4.25 (m, 1H), 3.70-3.68 (m, 1H), 3.52-3.47 (m, 2H), 3.13-2.90 (m, 2H), 2.29 (s, 3H), 1.38 (s, 9H), 1.28 (s, 18H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79Hz): 181.6 (s), 181.3 (s), 170.1 (s), 169.8 (s), 148.6 (s), 148.5 (s), 133.6 (d), 132.8 (s), 131.9 (s), 127.0 (d), 126.8 (d), 126.7 (d), 80.7 (s), 75.1 (d), 53.9 (d), 53.8 (s), 48.8 (s), 41.1 (t), 29.8 (q, 3C), 29.7 (s), 29.1 (t), 28.6 (q, 3C), 28.3 (s), 28.2 (q, 3C), 17.5 (q) ppm. LC-MS (ESI): *m*/*z* calc. 686.16, R_t = 15.87 min, *m*/*z* found 687.02 $[M+H]^+$, HRMS: [M+H] calc. 687.1676, [M+H] found 687.1671, [M+Na] calc. 709.1496 [M+Na] found 709.1491. Isotope pattern of Se: *m*/*z* (relative abundance %) 681.1731 (4.0), 683.1698 (19.0), 685.1679 (48.0), 687.1671 (100.0), 688.1705 (33.0), 689.1673 (18.0), 690.1707 (7.0).

Compound **9** was synthesised from **2c** (293 µl, 1 mmol), 5-(4-carboxyphenyl)-10,15,20-triphenylporphyrin (TPPA), **1d** (789.0 mg, 1.2 mmol) and *tert*-butyl isocyanide **3a** (124.6 µl, 1.5 mmol) following the general procedure described for Passerini reaction above. TLC, R_f = 0.45 (petroleum ether : ethyl acetate 4:1). It was purified by column chromatography on silica gel with petrol ether: ethyl acetate = 5:2. The compound was obtained as a purple solid. Yield = 86 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.90-8.88 (d, *J* = 5.27 Hz, 2H), 8.85 (s, 3H),

8.73-8.72 (d, *J* = 4.52 Hz, 2H), 8.82-8.20 (m, 8H), 8.14-8.13 (m, 2H), 8.07-8.05 (m, 1H), 7.94-7.92 (m, 1H), 7.78-7.73 (m, 8H), 7.57-7.54 (m, 1H), 7.41-7.38 (m, 1H), 6.28 (s, 1H), 5.85-5.83 (q, *J* = 4.35, 6.40, 10.92 Hz, 1H), 4.03-3.83 (m, 3H), 2.44 (s, 3H), 1.47 (s, 9H), -2.8 (s, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 181.89 (s), 181.57 (s), 167.44 (s), 149.60 (s), 148.19 (s), 145.72 (s), 142.25 (s, 8C), 135.03 (d, 2C), 134.79 (d, 10C), 133.87 (d), 133.59 (d), 132.95 (s), 132.05 (s), 128.18 (s), 128.07 (d, 2C), 128.03 (d, 2C), 127.22 (d), 126.99 (d, 8C), 126.96 (d, 2C), 126.91 (d, 2C), 120.99 (s), 120.70 (s, 4C), 118.17 (s), 75.37 (d), 60.61 (s), 52.08 (s), 29.36 (t), 29.03 (q, 3C), 17.99 (q) ppm. LC-MS (ESI): *m*/*z* calc. 1035.00, R_t = 18.27 min, *m*/*z* found 1035.91 $[M+H]^+$, HRMS: [M+H] calc. 1036.2977, [M+H] found 1036.2972. Isotope pattern of Se: *m*/*z* (relative abundance %) 1030.3031 (3.0), 1032.2999 (19.0), 1034.2980 (49.0), 1036.2972 (100.0), 1037.3005 (69.5), 1038.3039 (24.0), 1039.3007 (13.0).

Compound **10** was synthesised from formaldehyde **2a** (75 µl, 1 mmol), **1b** (331.26 mg, 1.2 mmol) and (3-isocyanopropyl)(phenyl)tellane **3b** (412.5 µl, 1.5 mmol) following the general procedure described for the Passerini reaction above. TLC, R_f = 0.63 (petroleum ether : ethyl acetate 4:1). It was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 96 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.02-7.97 (m, 2H), 7.65-7.62 (m, 2H), 7.61-7.58 (m, 2H), 7.18-7.15 (m, 1H), 7.11-7.07 (m, 2H), 6.47 (br s, 1H), 4.50 (s, 2H), 3.35-3.28 (m, 4H), 2.79-2.73 (m, 4H), 2.27 (s, 3H), 1.97-1.91 (m, *J* = 6.90, 14.29, 21.44, 28.59 Hz, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 182.04 (s), 181.40 (s), 169.96 (s), 166.81 (s), 148.25 (s), 145.18 (s), 138.33 (d, 2C), 133.86 (d), 133.52 (d), 132.54 (s), 131.92 (s), 129.19 (d, 2C), 127.69 (d), 126.79 (d), 126.67 (d), 111.35 (s), 63.14 (t), 40.82 (t), 35.29 (t), 31.39 (t), 29.22 (t), 15.43 (q), 4.64 (t) ppm. LC-MS (ESI): *m*/*z* calc. 579.1, R_t = 1.60 min, *m*/*z* found 580.0 $[M+H]^+$, HRMS: [M+H] calc. 582.0594, [M+H] found 582.0588, [M+H+O] calc. 598.0543, [M+H+O] found 598.0538. Isotope pattern of Te: *m*/*z* (relative abundance %) 590.0506 (8.0), 593.0520 (23.0), 594.0508 (58.0), 596 (93.0), 598.0538 [M+H] (100.0), 599.0571 (29.0), 600.0496 (6.0).

Compound **11** was synthesised from formaldehyde **2a** (75 µl, 1 mmol), 4-methoxybenzenamine **4** (123.07 mg, 1 mmol), **1b** (275.9 mg, 1.2 mmol) and (3-isocyanopropyl)(phenyl)tellane **3b** (412.5 µl, 1.5 mmol) following the general procedure described for the Ugi reaction above. TLC, R_f = 0.54 (petroleum ether : ethyl acetate 5:2). It was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 81 %. ^{1}H-NMR ($CDCl_3$, 500

MHz): 8.00-7.98 (m, 1H), 7.93-7.92 (m, 1H), 7.64-7.60 (m, 5H), 7.12-7.09 (m, 2H), 7.03-7.01 (m, 2H), 6.71-6.69 (m, 2H), 6.39 (br s, 1H), 4.11 (s, 2H), 3.65 (s, 3H), 3.29-3.24 (m, 4H), 2.80-2.77 (t, *J* = 7.43, 15.04 Hz, 2H), 2.44-2.41 (t, *J* = 6.49, 12.98 Hz, 2H), 2.23 (s, 3H), 1.96-1.90 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 182.14 (s), 181.21 (s), 172.12 (s), 170.80 (s), 168.72 (s), 159.32 (s), 147.03 (s), 146.43 (s), 138.43 (d, 2C), 134.93 (s), 133.64 (d), 133.33 (d), 132.74 (s), 131.98 (s), 129.23 (d, 2C), 128.67 (d), 127.69 (d, 2C), 126.74 (d), 126.55 (d), 114.99 (d, 2C) , 55.43 (q), 54.45 (t), 41.18 (t), 35.05 (t), 31.56 (t), 30.03 (t), 15.33 (q), 4.80 (t) ppm. LC-MS (ESI): *m*/*z* calc. 684.27, R_t = 1.63 min, *m*/*z* found 685.00 $[M+H]^+$, HRMS: [M+H] calc. 687.1172, [M+H] found 687.1167, [M+H+O] calc. 703.1121, [M+H+O] found 703.1116. Isotope pattern of Te: *m*/*z* (relative abundance %) 695.1084 (8.0), 698.1098 (24.0), 699.1087 (57.0), 702 (94.0), 703.1116 [M+H] (100.0), 704.1150 (36.0), 705.1183 (6.0).

Compound **12** was synthesised from formaldehyde **2a** (75 µl, 1 mmol), 4-methoxybenzenamine **4** (123.07 mg, 1 mmol), **1b** (331.26 mg, 1.2 mmol) and (3-isocyanopropyl)(phenyl)selane **3c** (377.5 µl, 1.5 mmol) following the general procedure described for Ugi reaction above. TLC, R_f = 0.52 (petroleum ether : ethyl acetate 4:1). It was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 94 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.00-7.98 (m, 1H), 7.93-7.91 (m, 2H), 7.64-7.59 (m, 2H), 7.39-7.37 (m, 2H), 7.17-7.13 (m, 2H), 7.04-7.02 (m, 2H), 6.71-6.68 (m, 2H), 6.48-6.46 (m, 1H), 4.12 (s, 2H), 3.65 (s, 3H), 3.32-3.26 (m, 4H), 2.84-2.81 (t, *J* = 7.30, 14.59 Hz, 2H), 2.44-2.42 (t, *J* = 6.78, 13.37 Hz, 2H), 2.23 (s, 3H), 1.87-1.81 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 182.09 (s), 181.16 (s), 172.08 (s), 168.69 (s), 159.28 (s), 155.16 (s), 153.19 (s), 146.98 (s), 146.39 (s), 134.91 (s), 133.59 (d), 133.29 (d), 132.55 (d), 131.93 (s), 129.06 (d, 2C), 128.64 (d, 2C), 126.86 (d), 126.69 (d), 126.50 (d), 114.95 (d, 2C), 114.30 (d) , 55.39 (q), 54.39 (t), 39.29 (t), 35.02 (t), 29.98 (t), 29.87 (t), 24.81 (t), 15.29 (q) ppm. LC-MS (ESI): *m*/*z* calc. 573, R_t = 14.76 min, *m*/*z* found 574.15 $[M+H]^+$, HRMS: [M+H] calc. 637.1275, [M+H] found 637.1270, [M+Na] calc. 659.1094, [M+Na] found 659.1089. Isotope pattern of Se: *m*/*z* (relative abundance %) 631.1329 (2.0), 633.1297 (20.0), 635.1278 (49.0), 637.1270 (100.0), 638.1303 (36.0), 639.1272 (19.0), 640.1305 (9.0).

Compound **13** was synthesised from formaldehyde **2a** (75 µl, 1 mmol), 4-methoxybenzenamine **4** (123.07 mg, 1 mmol), **1b** (331.26 mg, 1.2 mmol) and (3-isocyanopropyl)(phenyl)sulfane **3d** (265.5 µl, 1.5 mmol) following the general procedure

described for the Ugi reaction above. TLC, R_f = 0.51 (petroleum ether : ethyl acetate 4:1). It was purified by column chromatography on silica gel with petrol ether : ethyl acetate = 5:1. The compound was obtained as a yellow oil. Yield = 88 %. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.06-7.96 (m, 2H), 7.67-7.64 (m, 2H), 7.29-7.26 (m, 2H), 7.24-7.21 (m, 2H), 7.14-7.07 (m, 3H), 6.77-6.73 (m, 2H), 6.56 (br s, 1H), 4.18 (s, 2H), 3.71 (s, 3H), 3.41-3.36 (t, *J*= 5.86, 12.48 Hz, 2H), 3.34-3.30 (t, *J* = 6.28, 10.47 Hz, 2H), 2.93-2.90 (t, *J* = 6.43, 12.28 Hz, 2H), 2.50-2.46 (t, *J* = 6.87, 11.00 Hz, 2H), 2.28 (s, 3H), 1.88-1.82 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 125.79 Hz): 182.14 (s), 181.20 (s), 172.15 (s), 168.77 (s), 159.32 (s), 147.06 (s), 146.40 (s), 136.12 (s), 134.92 (s), 133.62 (d), 133.32 (d), 132.73 (s), 131.96 (s), 129.20 (d, 2C), 128.92 (d, 2C), 128.64 (d, 2C), 126.72 (d), 126.53 (d), 126.02 (d), 114.99 (d, 2C), 55.41 (q), 54.48 (t), 38.45 (t), 35.04 (t), 31.07 (t), 30.02 (t), 28.84 (t), 15.29 (q) ppm. LC-MS (ESI): *m*/*z* calc. 588.73, R_t = 1.85 min, *m*/*z* found 589.85 $[M+H]^+$, HRMS: [M+H] calc. 589.1830, [M+H] found 589.1825, [M+Na] calc. 611.1650, [M+Na] found 611.1645. Isotope pattern of S: *m*/*z* (relative abundance %) 589.1825 (100.0), 590.1859 (37.0), 591.1783 (10.0), 593.1850 (0.6).

In vitro activity assays

Thiobarbituric acid (TBA), 2,6-di-*tert*-butyl-4-methylphenol (BHT), vitamin C, ebselen and hydrogen peroxide (H_2O_2 35% in water) were purchased from Acros Organic (Germany). Sodium dodecyl sulphate (SDS) and glycine were purchased from Roth (Germany). Arachidonic acid was obtained from Sigma-Aldrich (Germany), thiophenol (PhSH) and $FeCl_3 \cdot 6H_2O$ from Fluka (Germany). All solvents were dried before use and Millipore Direct-Q® 3 UV water was used. Spectra were recorded on a CARY 50*Bio* UV-Visible spectrophotometer (Varian).

Thiophenol oxidation assay (PhSH assay)

The GPx-like catalytic activity of the compounds was measured by monitoring the formation of PhSSPh formed during thiophenol oxidation in presence of H_2O_2.[7,8] To 890 µL methanolic solution of PhSH (1 mM) containing Et_3N (0,05 mM) was added 10 µL of compound (100 µM) in DMSO. The reaction was initiated by adding 100 µL H_2O_2 (2 mM) and monitored at 305 nm for 30 min at 25 °C. The negative control included compounds in the presence of

H_2O_2 and compounds in the presence of PhSH. Ebselen was used as positive control and benchmark compound in this assay.

Thiobarbituric acid radical scavenging assay (TBA assay)

The TBA assay was carried out according to the method of Asakawa.[9] It was performed by measuring at 532 nm the formation of the adduct between malonaldehyde (MA) and TBA (MA-TBA). MA is produced by lipid oxidation. Briefly, 1.5 mL aqueous solution of TBA/SDS, 1.5 mL glycine-hydrochloric acid buffer (pH 2.5), 0.1 mL ethanolic solution of BHT, 0.1 mL aqueous solution of $FeCl_3 \cdot 6H_2O$, 0.1 mL of sample in DMSO (0.3 mM) and 10 µL arachidonic acid in DMSO (0.5 mM) were mixed in a glass vial and heated in a water bath for 15 min. A pink colour developed. After cooling, 1 mL of acetic acid and 2 mL of $CHCl_3$ were added, the mixture was centrifuged and the absorbance of the supernatant was measured using a spectrophotometer at 532 nm. Vitamin C was used as positive control and benchmark antioxidant in this assay.

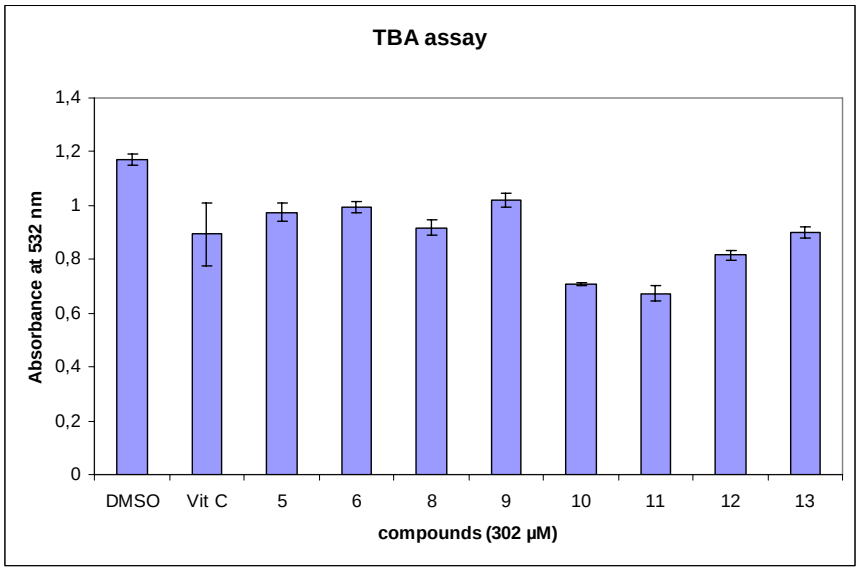


Figure S1: Results obtained in the radical scavenging TBA assay indicative of antioxidant activity. In this assay, only the tellurium compounds **10** and **11** show any significant activity, which is even superior to the one of ascorbic acid. In contrast, most of the other (selenium) compounds are not active. These results confirm that tellurides (and some) selenides can scavenge oxygen-based radicals - likely by forming telluroxides and selenoxides, respectively. Indeed, sensitivity of the tellurium compounds **10** and **11** towards oxidation has also been observed in the HRMS experiments. In cell culture, this

apparent 'antioxidant' reactivity is dominated by the catalytic activity demonstrated in the PhSH assay.

Cell culture studies

L-929 cell culture studies

Cell line L-929 was obtained from DSMZ (Braunschweig, Germany) and grown at 37°C and at 10 % CO_2 in DME medium (high glucose; GIBCO) supplemented with 10 % fetal calf serum (Lonza). As part of the cytotoxicity assay, MTT [3-(4,5-dimethylthiazol-2-yl)2,5-diphenyltetrazolium bromide] (Sigma) was used to measure the metabolic activity of cells which are capable of reducing it by dehydrogenases to a violet formazan product. 60 µL of serial dilutions of the test compounds were added to 120 µL aliquots of a cell suspension (50,000/mL) in 96-well microplates. Solvent controls were incubated under identical conditions. After 5 days 20 µL MTT in phosphate buffered saline (PBS) were added to a final concentration of 0.5 mg/mL. After 2 h the precipitate of formazan crystals was centrifuged, and the supernatant discarded. The precipitate was washed with 100 µL PBS and dissolved in 100 µL isopropanol containing 0.4 % hydrochloric acid. The resulting colour was measured at 590 nm using an ELISA plate reader. All experiments were carried out in two parallel experiments. The percentage of viability at a certain compound concentration was calculated as the mean with respect to the controls set to 100 %.

A-431 and PC-3 cell culture studies

The A-431 cell line has been derived from a human epidermoid solid cancer (ATCC number CRL-1555). These cells are highly malignant with a hypertriploid karyotype. The MTT cytotoxicity assay was performed as described for L-929 cells, with the following modifications: Adherent cells, grown to confluency in microtiter wells, were incubated for 22 h in DME medium (supplemented with 5 % NCS) with serial dilutions of test compounds (final volume 150 µl). The MTT reagent was then added to wells for 3.5 h prior to aspiration of medium and solubilisation of formazan crystals was achieved using isopropanol/HCl. PC-3 cells were cultured according to standard procedure.[10]

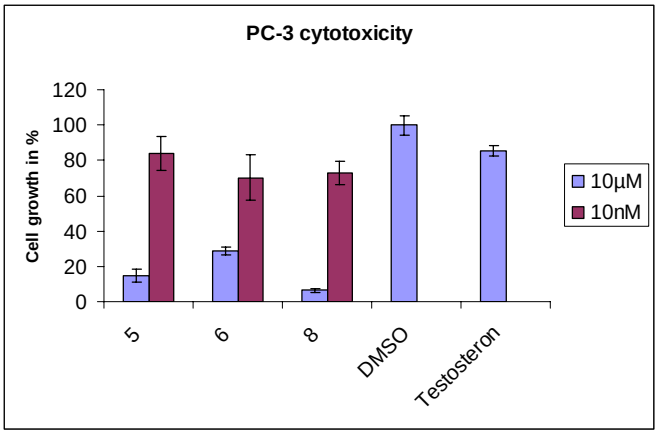


Figure S2: PC-3 cytotoxicity assay (using testosteron as a control).

Lipophilicity:

Compound	Retention time 75% MeOH	Log*K*	LogP_{ow}
Thiourea	0.728	-----	----
Acetanilide	0.811	-0.94	1
Benzene	0.941	-0.53	2.1
Toluene	1.508	0.03	2.7
Thymol	1.285	-0.12	3.3
Naphthalene	1.894	0.20	3.6
Phenanthrene	3.615	0.60	4.5
5	0.931	-0.55	1.94
6	0.929	-0.56	1.92
7	1.880	0.20	3.6
8	0.942	-0.53	1.99
9	0.840	-0.81	1.40
10	0.928	-0.56	1.92
11	0.938	-0.54	1.97
12	3.297	0.55	4.23
13	2.940	0.48	4.20

Table S1: Retention times, log*K* and log*P*ow values for compounds and several reference standards. In essence, these values point towards a lipophilicity which is in compliance with Lipinski's rule requiring a logP_{ow} value of below 5 (and above -0.4).

58 cancer cell line screen:

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 leukemia, non-small cell lung cancer, colon cancer, cancer of the central nervous system, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. Compounds **6** and **8** were selected for 5-dose testing. 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

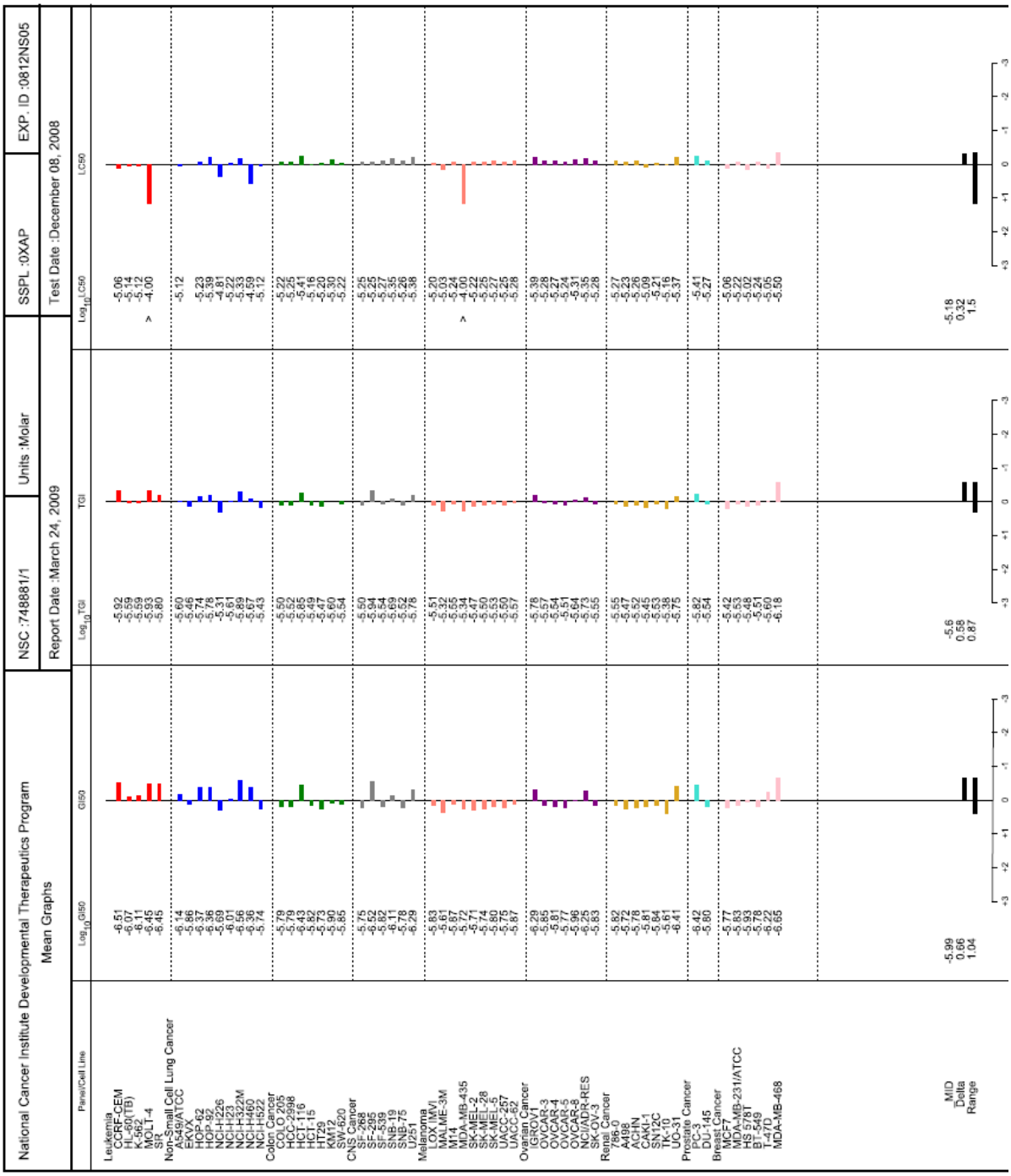


Table S2: LC_{50} values obtained for **6** in different cancer cell lines.

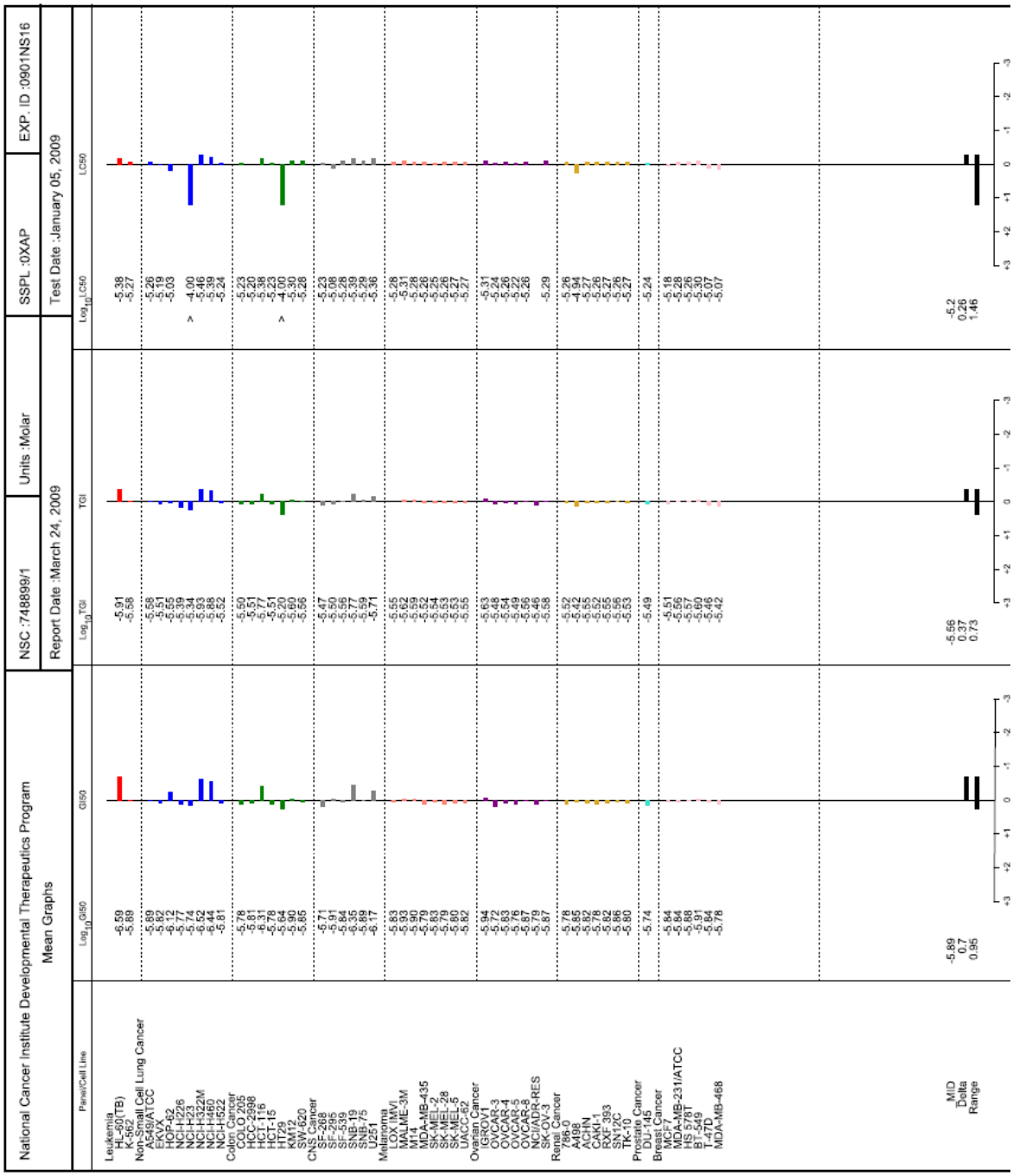
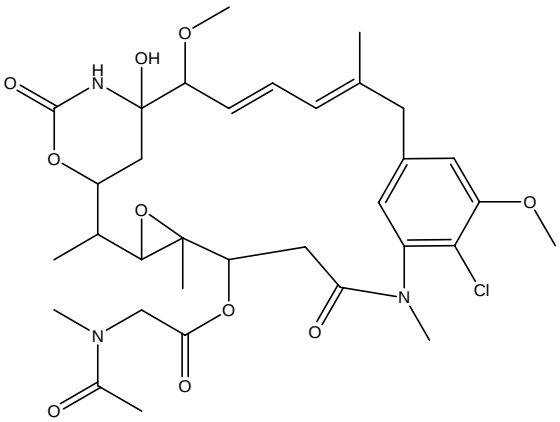


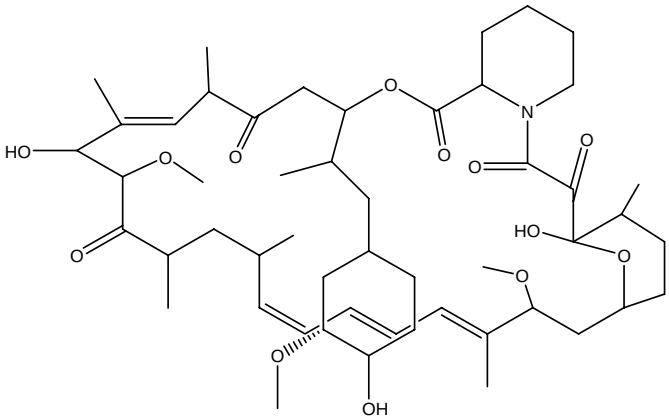
Table S3: LC_{50} values obtained for **8** in different cancer cell lines.

COMPARE analysis:[11]

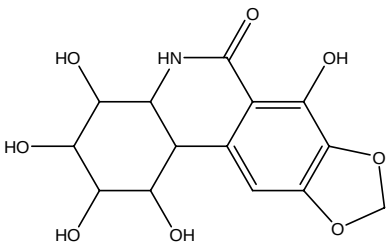
A COMPARE analysis for compounds **5**, **6** and **8** was performed using the NCI software. Based on the specific activities of a given compound in the 58 cell line screen, this programme searches the NCI databank for compounds with a similar activity profile. The resulting correlations can be quite useful. For instance, compounds with a high correlation for each other may act via a similar biochemical mode of action. In contrast, if only modest correlations are found for a new compound, this substance may act via a distinct, maybe even novel mechanism. Such aspects are discussed below for the more active compounds **6** and **8**. It should be pointed out, however, that the COMPARE analysis only provides indications for possible modes of action, but cannot replace a more detailed, in depth biochemical investigation at the cellular level.



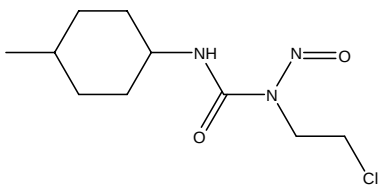
Maytansine (**A**)
R= 0.368



Rapamycin (**B**)
R= 0.361

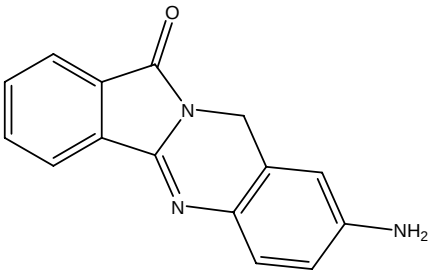


Pancratistatin (**C**)
R= 0.358

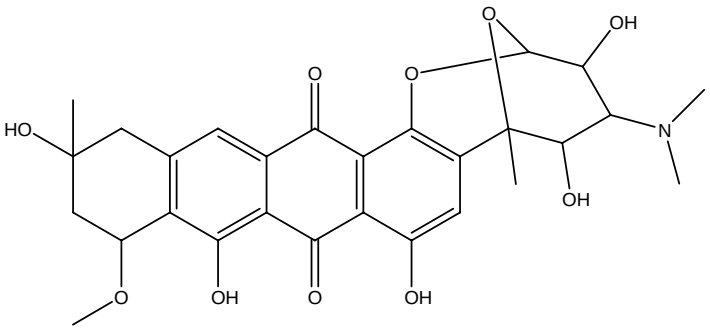


Methyl-CCNU (**D**)
R=0.341

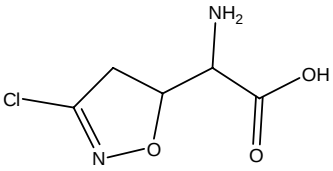
Figure S3: COMPARE analysis for compound **5**. Correlation factors R are provided. Please note that compound **5** was not particularly active in the various cell line based assays.



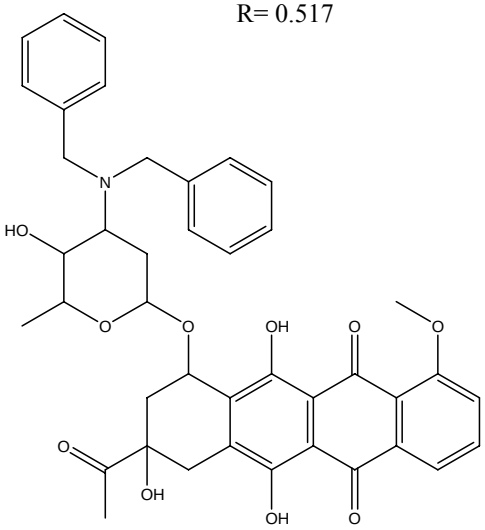
Batracylin (**E**)
R= 0.529



Menogaril (**F**)
R= 0.517

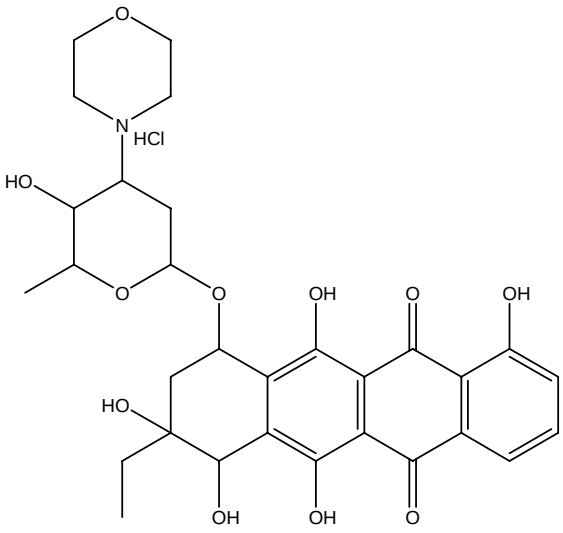


Acivicin (**G**)
R= 0.503

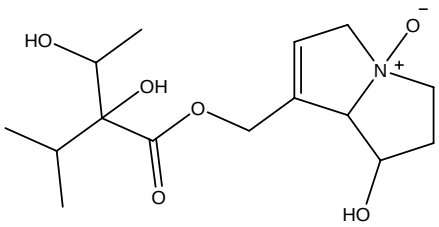


N,N-Dibenzyldaunomycin (**H**)
R= 0.501

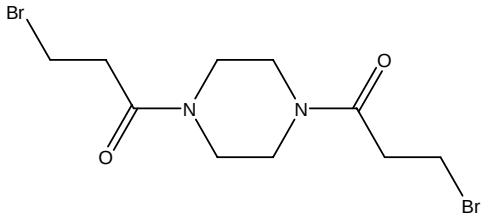
Figure S4: COMPARE analysis for compound **6**. Correlation factors R are provided. Compound **6** was among the most active of the compounds tested. Although the correlation is modest, it indicates that certain anthracycline-based redox agents exhibit a similar pattern of activity. Menogaril (**F**) and daunomycin are used in the treatment of prostate cancer and leukemia, respectively. Please note that the mode of action of these redox agents is complex and does not exclusively rely on redox reactions.



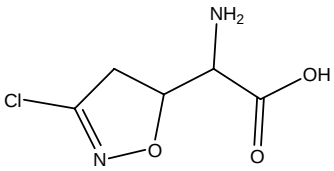
MX2 HCl (**I**)
R= 0.471



Indicine N-oxide (**J**)
R= 0.469



Pipobroman (**K**)
R= 0.452



Acivicin (**L**)
R= 0.441

Figure S5: COMPARE analysis for compound **8**. Correlation factors R are provided. Similar to compound **6**, compound **8** was among the most active compounds tested in this study, and its pattern of activity also correlates with anthracycline-based redox agents, in this case MX2 HCl (**I**).

Te-Isotope pattern:

Tellurium naturally occurs as a mixture of different isotopes, which gives rise to characteristic isotope patterns in the HRMS spectra of Te compounds. Tellurium has eight stable isotopes: ^{120}Te (0.09 % natural abundance), ^{122}Te (2.55 %), ^{123}Te (0.89 %), ^{124}Te (4.74 %), ^{125}Te (7.07 %), ^{126}Te (8.84 %), ^{128}Te (31.74 %), ^{130}Te (34.08 %). The resulting isotope patterns assist in the identification and characterisation of the tellurium compounds. Similar considerations apply to selenium and, to a lesser degree, also to sulfur compounds. The following figures show the Te isotope patterns found in the relevant parts of the HRMS spectra. Further information regarding the Te and Se isotope patterns, including percentage abundances, are provided as part of the individual synthetic procedures (see above).

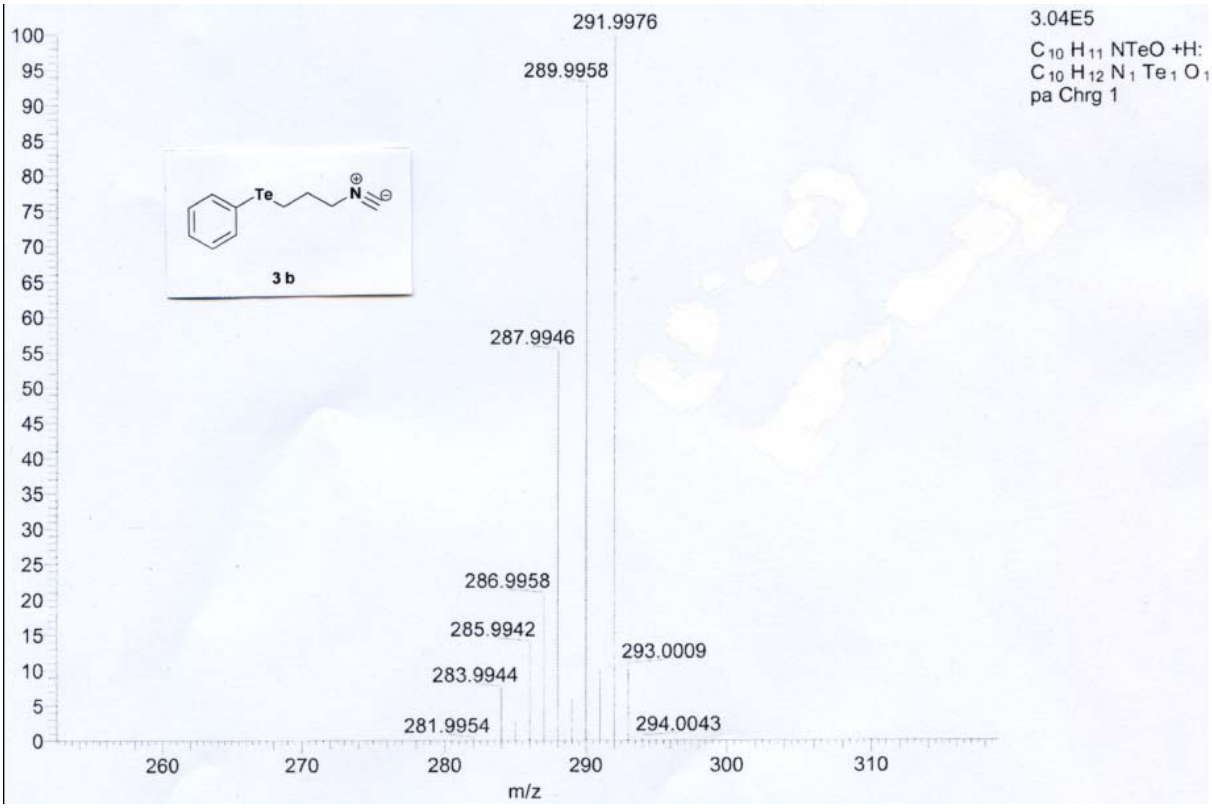


Figure S6: Te-isotope pattern for the building block compound **3b**. Please note that the spectrum shows the [M+H+O] form of the compound, *i.e.* the telluroxide form.

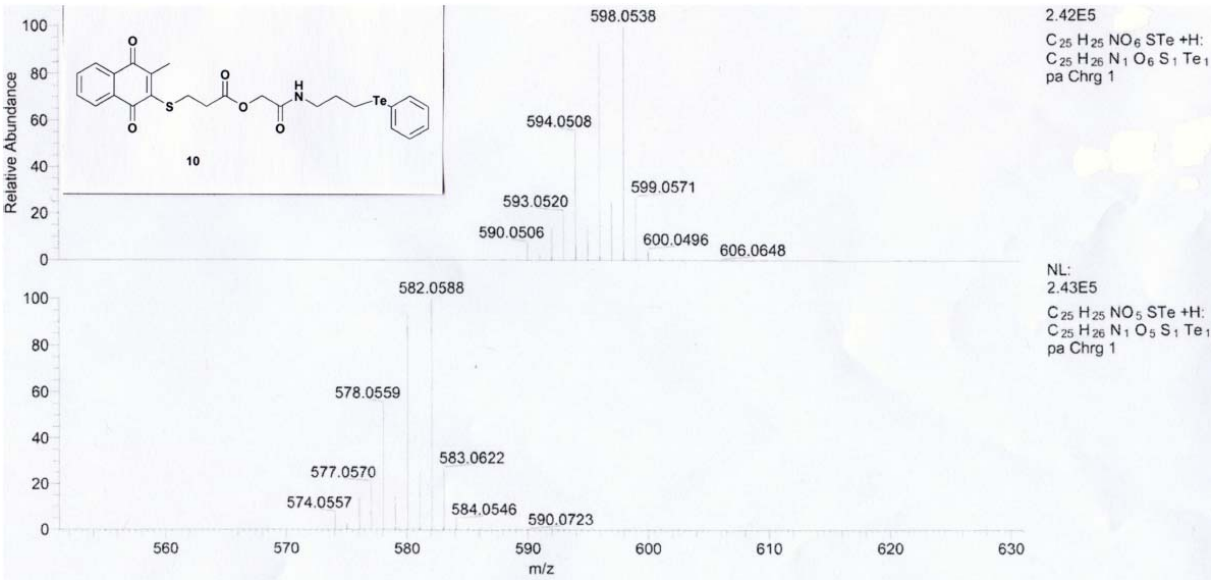


Figure S7: Te-isotope pattern for compound **10**. Please note that upper spectrum shows the [M+H+O] form of the compound, *i.e.* the telluroxide form, while the lower part shows the signals for [M+H].

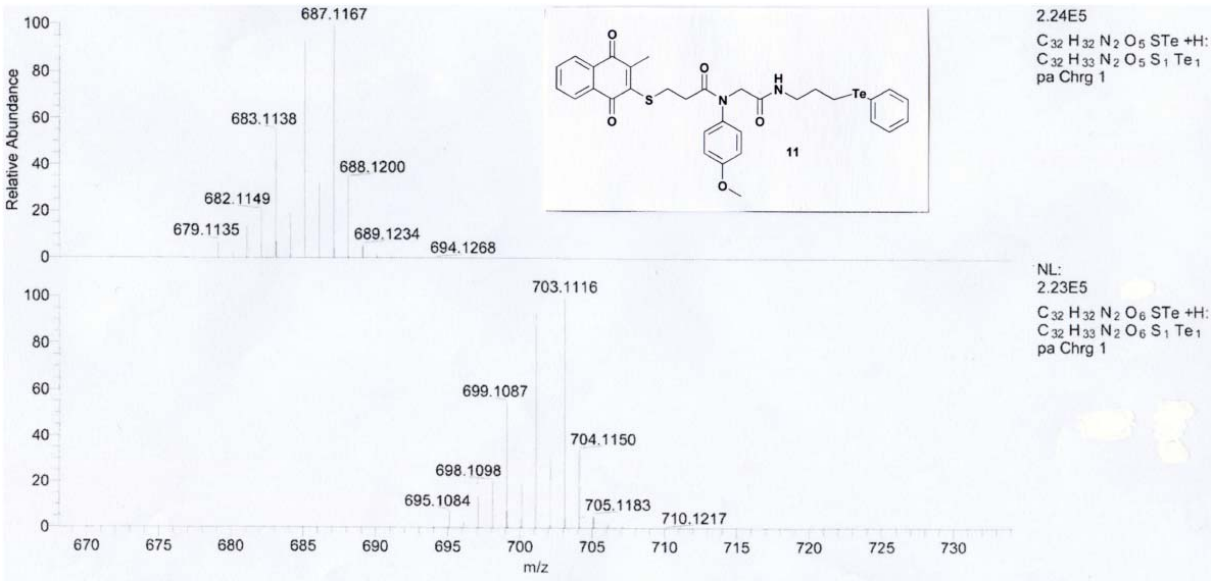


Figure S8: Te-isotope pattern for compound **11**. Please note that upper spectrum shows the [M+H] form of the compound, while the lower part shows the signals for [M+H+O], *i.e.* the telluroxide form.

References:

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