Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 5091–5100

BIOORGANIC & MEDICINAL CHEMISTRY

Thioredoxin Reductase and Cancer Cell Growth Inhibition by Organotellurium Compounds that Could be Selectively Incorporated into Tumor Cells

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Received 3 December 2002; accepted 21 August 2003

Abstract—The thioredoxins are small ubiquitous redox proteins with the conserved redox catalytic sequence-Trp-Cys-Gly-Pro-Cys-Lys, where the Cys residues undergo reversible NADPH dependent reduction by selenocysteine containing flavoprotein thioredoxin reductases. Thioredoxin expression is increased in several human primary cancers including lung, colon, cervix, liver, pancreatic, colorectal and squamous cell cancer. The thioredoxin/thioredoxin reductase pathway therefore provides an attractive target for cancer drug development. Organotellurium steroid, lipid, amino acid, nucleic base, and polyamine inhibitors were synthesized on the basis that they might be selectively or differentially incorporated into tumor cells. Some of the newly prepared classes of tellurium-based inhibitors (lipid-like compounds **3b** and **3e**, amino acid derivative **5b**, nucleic base derivative **8b**, and polyamine derivatives **14a** and **14b**) inhibited **TrxR/Trx** and cancer cell growth in culture with IC_{50} values in the low micromolar range.

Introduction

Thioredoxins (**Trxs**) are small ubiquitous redox proteins with the conserved redox catalytic sequence -Trp-Cys-Gly-Pro-Cys-Lys where the Cys residues undergo reversible NADPH dependent reduction by selenocysteine containing flavoprotein thioredoxin reductases.[1,2] There are two mammalian **Trxs**. Human **Trx-1** is a 105 amino acid protein found in the cytoplasm and nucleus of cancer cells.[3,4] **Trx-1** is also secreted by cells and accumulates in growth media and in plasma.[5,6] The second thioredoxin, **Trx-2**, is found in the mitochondria, its functions are unknown but it may protect mitochondria against oxidative damage.[7] Through thiol disulfide exchange, reduced **Trx-1** is able to catalyze the selective reduction of protein Cys residues resulting in alterations in their enzymatic and DNA binding properties. **Trx-1** is a protooncogene and nuclear targeted **Trx-1** transforms mouse NIH 3T3 embryonic cells allowing them to form tumors in immunodeficient mice.[8] **Trx-1** transfection of MCF-7 human breast cancer and HT-29 colon cancer cells stimulates tumor growth.[9] **Trx-1** transfection of mouse WEHI7.2 lymphoma cells markedly inhibits both spontaneous and drug induced apoptosis.[10,11] Redox activity is essential for the biological effects of **Trx-1**.[12] Transfection of cancer cells with a redox inactive mutant **Trx-1** does not transform cells, inhibits cell growth, potentiates apoptosis[9,11] and blocks tumor formation by the cells in immunodeficient *scid* mice.[10] Proteins with activity dependent on reduction by **Trx-1** include the DNA binding transcription factors NF-kB, AP-1, HIF-1a and p53.[2,11,13,14] The binding of **Trx-1** also regulates the activity of enzymes such as apoptosis signal regulating kinase-1 (ASK1),[15] and protein kinases C a,d,e,z.[16]

Trx-1 protein levels are significantly elevated in several human primary cancers including gastric (50%), colon (55%), pancreas (41%), hepatoma (52%), lung (50%) and cervical cancer (75%).[3,17–22] Human primary gastric cancer shows a highly significant correlation between elevated increased **Trx-1** expression and increased proliferation and inhibited apoptosis.[3] Increased **Trx-1** expression is a late event in colon

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doi:10.1016/j.bmc.2003.08.021

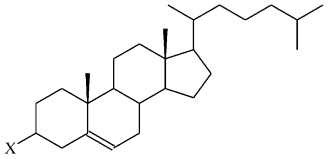
cancer, occurring in primary and metastatic disease but not in colon polyps, and is an independent prognostic factor for poor patient survival in colorectal cancer.[23]

The **Trx-1** redox system provides an attractive target for cancer drug development. Thioredoxin reductase (**TrxR**) is a selenocysteine containing flavoenzyme that catalyzes the reduction of oxidised thioredoxin. This enzyme could therefore be used for regulating the activity of the thioredoxin system. Previous studies of organotellurium inhibitors of thioredoxin (**Trx-1**) indicated that compounds with antioxidative capacity, especially peroxide-decomposing ability, were the most efficient.[24] The compounds investigated also inhibited the growth of human cancer cells in culture. However, the poor solubility of these materials in water was a restriction when administered to animals as antitumor agents. For enhancing hydrophilicity, it was decided to introduce sulfopropyl groups into this class of compounds. Water soluble organotellurium compounds of the diaryl telluride, alkyl aryl telluride and dialkyl telluride type, were found to be the most efficient tellurium based inhibitors of thioredoxin reductase ever tested.[25] Some of the compounds inhibited the enzyme at submicromolar levels. The compounds also inhibited the growth of MCF-7 and HT-29 human cancer cells in culture at the 5–10 μM level but their hydrophilicity seemed to restrict cellular uptake. For obtaining more useful compounds, we thought the next generation of organotellurium compounds must also possess an additional quality in addition to thioredoxin reductase inhibiting activity, the ability to localize tumor cells. Thus, various classes of compounds were synthesized on the basis that they might become selectively or differentially incorporated into tumor cells. Based on general knowledge about biodelivery, molecular mimicry of a known cellular constituent or metabolite can be employed for delivery of organotelluriums to the targeted tumor cell. As detailed in the following, tellurium containing steroids, lipids, amino acids, nucleic bases, and polyamines are candidates for such an approach. Provided their capacity to inhibit thioredoxin reductase is similar to that observed with compounds previously prepared, they could be expected to possess superior antitumor properties.

Results and Discussion

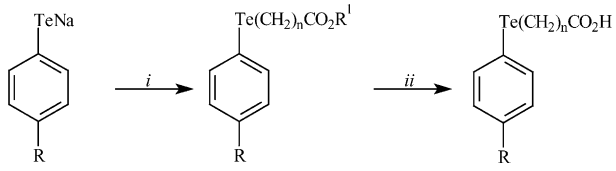
Preparation of organotellurium compounds

Organotelluriums conjugated to steroids and lipids. Receptor–LDL complexes are internalized by endocytosis. The LDL is degraded to cholesterol by lysosomes, and the receptor returns to the external cell wall. Malignant cells are expected to use cholesterol at a much higher rate than normal cells because of higher replication rates, and therefore to have correspondingly higher receptor turnover rates.[26] This provides a basis for cellular differentiation and the targeting of tumor cells with organotellurium compounds if the cholesteryl esters of the LDL core are replaced with tellurium containing material. The alkylation of tellurolates is one of the most versatile procedures for the synthesis of unsymmetrical diorganotellurium compounds.[27] The required lithium organyl tellurolates can be readily obtained by insertion of elemental tellurium into the carbon–lithium bond of organolithiums, while the corresponding sodium tellurolates can be prepared by reduction of ditellurides with $NaBH_4$. Nucleophilic substitution of bromide **1a** or tosylate **1b** with various lithium- or sodium- organotellurolates was used for the preparation of steroid derivatives **1c–1f**. The materials were found to oxidise quite rapidly to the corresponding oxides when exposed to air.



1 a x = α-Br
b x = β-Tosyl
c x = α-TePh
d x = β-TePh
e x = β-Te-*n*-Bu
f x = β-Te-C_6H_4-*p*-NMe_2

Tellura fatty-acids have already found use in biomedical research. They were synthesized with γ-emitting tellurium isotopes for organ-imaging purposes in nuclear medicine and have been designed specifically for the investigation of cardiac disorders.[28] Scheme 1 outlines the preparation of some organotellurium fatty acid derivatives **3**. Alkylation of in situ generated sodium arenetellurolates with 1.1 equiv of alkyl ω-bromoalkanoates in EtOH resulted in the formation of compounds **2** in 76–94% yields. Basic hydrolysis (LiOH in $MeOH/H_2O$) afforded compounds **3** in similarly good yields.



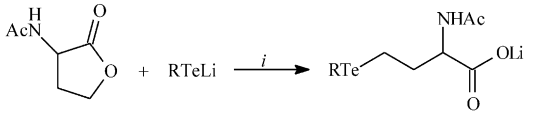
2a-f **3a-f**

Product	n	R	R^1
a	3	H	Et
b	4	H	Me
c	11	H	Me
d	4	NMe_2	Me
e	11	NMe_2	Me
f	3	OMe	Et

Scheme 1. Reagents and conditions: (i) $Br(CH_2)_nCO_2R^1$, EtOH, rt; (ii) LiOH, MeOH, H_2O, rt, 20 h, 1 N HCl.

Organotelluriums conjugated to amino acids. The accelerated rate of synthesis of proteins and amino acid metabolites exhibited by a malignant cell, coupled with the active transport mechanisms available for amino acid accumulation within cells,[29] provides a bioutilization process that may allow organotelluriums to enter tumor cells preferentially. Concerning tellurium analogues of naturally occurring amino acids, most synthetic work has been directed to the synthesis of tellluromethionine.[30–32] However, in non-degassed aqueous solution at pH 7.0, this material has only a half-life of ca. 30 min.[32] Therefore, for the evaluation of thioredoxin reductase inhibiting capacity, the corresponding *N*-acetyl derivative seems more attractive from a practical point of view ($t_{1/2}$ ca. 20 h). For preparation of compounds **5**, *N*-acetyl-α-aminobutyrolactone (**4**) was treated with 1.1 equiv of various lithium organotellurolates in THF in the presence of tetramethylethylenediamine (TMEDA). The desired lithium carboxylates **5a–c** were isolated in 82, 71 and 92% yield, respectively (Scheme 2). Attempts to remove the *N*-protecting group under various acidic conditions were unsuccessful (tellurium extrusion). Unfortunately, the enantioselective enzymatic deacylation of **5a** using aminoacylase-based procedures also failed.[32]

Organotelluriums conjugated to nucleic bases. As compared with normal cells, malignant cells show an increased rate of mitosis.[33] This would lead to enhanced uptake, accumulation and retention of nucleic acids, nucleosides and nucleotides. Concerning the preparation of tellurium containing pyrimidines and purines derivatives, there are only sporadic reports in the literature. In analogy with the preparation of other organochalcogen derivatives of pyrimidines,[33] the following route to arenetellurenylyluracils (**8**) was used (Scheme 3): Lithiation of 5-bromo-2,4-(bis-benzyloxy)pyrimidine (**6**), followed by addition of diphenyl ditelluride, bis(4-methoxyphenyl) ditelluride and bis(4-*N*,*N*-dimethylaminophenyl) ditelluride (1.5 equiv), respectively, afforded compounds **7a**, **7b** and **7c** in 72, 68 and 63% isolated yield. The protecting benzyl groups were then removed by exposure to trimethylsilyl iodide (2.4 equiv) in dry CH_2Cl_2 at room temperature to furnish the desired compounds **8a–c** in 70–78% yield.



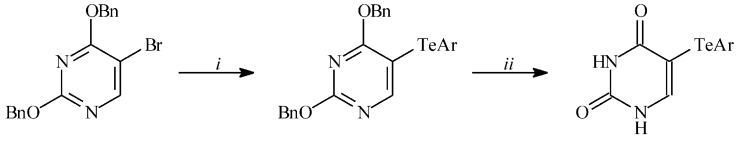
4 **5a** R = Ph; **b** R = C_6H_4-*p*-NMe_2; **c** R = *n*-Bu

Scheme 2. Reagents and conditions: (i) TMEDA, THF, 4 h, rt.

Organotelluriums conjugated to polyamines. Almost all cells contain substantial amounts of at least one of the polyamines putrescine, spermidine and spermine. Polyamines are required for the optimum growth and replication of various cell types and are present in higher concentrations in rapidly proliferating cells.[34] Polyamine depletion has growth inhibitory effects.[35] Metabolism studies with labelled polyamines in vivo has shown that they can be taken up from the circulation. It is also well established that tissues with a high demand for polyamines such as prostate, tumors or normal but rapidly dividing cells are accumulating polyamines in increasing amounts with a specific uptake system. Incorporation of tumoricidal agents into the polyamine scaffold has previously produced more active compounds than the parent chemotherapeutic agent.[36–39] On the basis of these observations we decided to prepare tellurium containing polyamines.

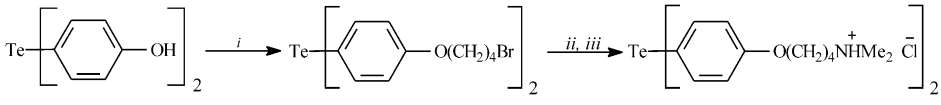
The hydrochloride **11** was prepared by the reaction sequence shown in Scheme 4. Bis-*O*-ω-bromoalkylation of bis(4-hydroxyphenyl)telluride (**9**) with an excess of 1,4-dibromobutane (2.5 equiv) in dry acetone in the presence of anhydrous K_2CO_3 furnished telluride **10** in 45% yield. Changing the solvent to DMF, acetonitrile or *t*-butanol and varying the base (NaOH, NaH or *t*-BuOK) did not cause any improvement in yield. Bisamination of **10** with an excess of 40% aqueous of $HNMe_2$ in EtOH, followed by addition of HCl furnished bis-hydrochloride **11** in excellent yield.

The synthesis of tellurium containing spermidine analogues **14** from N^1,N^{10}-bis-phthalimidyl spermidine **12**[40] is outlined in Scheme 5. The most commonly used procedure



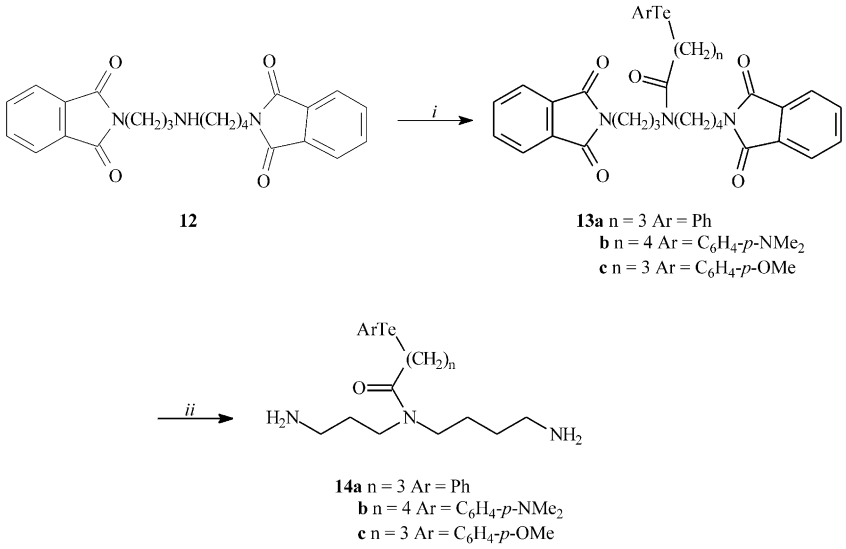
6 **7a** Ar = Ph; **b** Ar = C_6H_4-*p*-NMe_2; **c** Ar = C_6H_4-*p*-OMe **8a** Ar = Ph; **b** Ar = C_6H_4-*p*-NMe_2; **c** Ar = C_6H_4-*p*-OMe

Scheme 3. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C; (ii) ArTeTeAr, −78 °C, 2 h; (iii) trimethylsilyl iodide, CH_2Cl_2.



9 **10** **11**

Scheme 4. Reagents and conditions: (i) K_2CO_3, 1.4-dibromobutane, acetone, 20 h, reflux; (ii) 40% aq $HNMe_2$, THF, 8 h, rt; (iii) 1 M HCl, rt, 2 h.



Scheme 5. Reagents and conditions: (i) *N*-carbethoxyphthalimide, CH_2Cl_2, rt, 2 h; (ii) in situ prepared $ArTe(CH_2)_nCOOCOO$-*i*-Bu, CH_2Cl_2, 20 h; (iii) N_2H_4, EtOH, 20 h, rt, 2 h.

for amide formation from carboxylic acids and amines involves in situ formation of acid chloride followed by addition of the amine. However, due to partial extrusion of tellurium, this methodology proved to be unsuitable in our case. Instead, spermidine derivatives **13** were obtained via treatment of acids **3a**, **3d** and **3f**, respectively, with *i*-butyl chloroformate and then protected spermidine **12**. Final removal of phthaloyl groups using hydrazine in ethanol afforded compounds **14a–c**.

TrxR and cancer cell growth inhibition

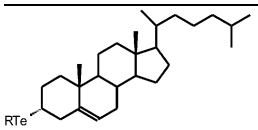
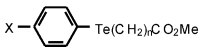
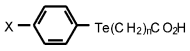
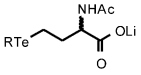
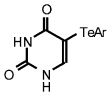
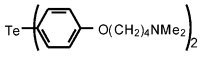
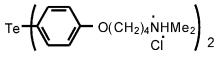
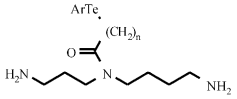
TrxR activity was measured as the increase in absorbance at 405 nm which occurs as post reaction dithionitrobenzoic acid (DTNB) is reduced by thiols produced in an incubation containing **Trx**, **TrxR**, NADPH, insulin and the inhibitor (Table 1: **TrxR**/**Trx**-activity). This assay reflects the combined effects of the inhibition of **Trx** and **TrxR**. For most of the inhibitors tested, **TrxR** activity was also measured in incubations of DTNB, **TrxR**, NADPH and inhibitor and measured as the initial increase in absorbance at 405 nm (Table 1: **TrxR**-activity). This assay reflects the inhibition of **TrxR** only. With some exceptions (vide infra), the IC_{50} values (concentrations required to inhibit thionitrobenzoate formation by 50%) obtained using the two methods were similar.

For most of the compounds, the effect on growth of MCF-7 breast cancer cells in culture was also studied. Inhibition data expressed as IC_{50} values (concentration required to inhibit cell growth by 50% of that observed in a control incubation) are shown in Table 1.

Organotellurium steroid compounds (cholesterol derivatives **1c–1f**) turned out to be poor inhibitors ($IC_{50} > 25\,\mu M$) in the **TrxR/Trx** and **TrxR** assays. Their cell-killing capacity was therefore not assessed. The observed reactivity of these materials towards air may in part explain their poor performance. Some of the organotellurium derivatives of fatty acids (**2**) or esters (**3**) proved to be slightly more effective inhibitors. 5-Phenyltellurenylvaleric acid (**3b**) inhibited **TrxR/Trx** with an IC_{50} value of 14.6 μM and MCF-7 cell growth with an IC_{50} value of 5.6 μM. The more lipid-like compound **3e** inhibited **TrxR** with an IC_{50} value of 1.0 μM, but its cell-killing properties were not impressive ($IC_{50} = 16.4\,\mu M$). Based on the few examples where the effect of a tellurium containing carboxylic acid (**3**) and the corresponding methyl ester (**2**) could be made, it seems that the acid is the more efficient inhibitor. Among the three tellurium derivatives of amino acids (**5**) tested, the aryltelluro derivative **5b**, carrying an electron donating dimethylamino group, turned out to be an excellent inhibitor of **TrxR** ($IC_{50} = 0.42\,\mu M$). Again, the good enzyme inhibiting capacity was not quite reflected in the ability to kill MCF-7 cells ($IC_{50} = 10.6\,\mu M$). Among tellurium-containing uracils (**8**) prepared, the aryltelluro derivative **8b**, carrying a strongly electron donating aryl substituent, turned out to be a good inhibitor of **TrxR** ($IC_{50} = 2.6\,\mu M$). Compound **8c** was a similarly good inhibitor in the combined **TrxR/Trx** assay ($IC_{50} = 2.1\,\mu M$). However, none of the uracils prepared showed any notable capacity to inhibit growth of cancer cells ($IC_{50} > 14\,\mu M$). The tellurium containing diamine derivative **11**, as a free base or as a bis-hydrochloride, was a poor inhibitor of **TrxR/Trx**. In contrast, spermidine derivatives **14a** and **14b** were some of the best organotellurium inhibitors of **TrxR** ever reported ($IC_{50} = 1.8$ and 0.2 μM). For **14a**, the inhibiting effect was also largely reflected in the cell-growth assay ($IC_{50} = 3.8\,\mu M$).

Organotellurium inhibitor **8c** performed much better in the combined **TrxR**/**Trx**-assay than in the **TrxR**-assay. This may indicate inhibition of **Trx** rather than **TrxR**. Some of the inhibitors investigated (compounds **3e**, **5b**, **8b**, **14a** and **14b**) turned out to be significantly poorer inhibitors in the combined **TrxR**/**Trx**-assay than in the **TrxR**-assay. This unusual result is difficult to rationalize but it could indicate some interaction of the organotellurium inhibitor with **Trx** outside the active-site cysteine residue.

Table 1. Inhibition of thioredoxin reductase and cancer cell growth by organotellurium compounds

Structure	Compd	Inhibition		
		TrxR/Trx[a] IC_{50} (μM)	TrxR[b] IC_{50} (μM)	MCF-7[c] IC_{50} (μM)
	**1c** R = α-TePh	34.6	> 50	—
	d R = β-TePh	26.6	> 50	—
	e R = α-Te-*n*-Bu	34.6	> 50	—
	f R = β-C_6H_4-*p*-NMe_2	> 25	—	—
	**2b** X = H *n* = 4	19.9	—	—
	2c X = H *n* = 11			
	2d X = NMe_2 *n* = 4	24.5	—	—
	2e X = NMe_2 *n* = 11	> 25	—	—
	**3b** X = H *n* = 4	14.6	—	5.6
	3c X = H *n* = 11	> 50	> 50	—
	3d X = NMe_2 *n* = 4	17.4	—	> 50
	3e X = NMe_2 *n* = 11	9.4	1	16.4
	**5a** R = Ph	10.8	13.8	7.8
	b R = C_6H_4-*p*-NMe_2	> 20	0.42	10.6
	c R = *n*-Bu	5.8	9.8	> 50
	**8a** Ar = Ph	20.6	—	—
	b Ar = C_6H_4-*p*-NMe_2	12.6	2.6	> 50
	c Ar = C_6H_4-*p*-OMe	2.1	22.4	14.2
	**11** (free base)	31.6	—	—
	**11**	26.7	—	—
	**14a** Ar = Ph *n* = 3	8.8	1.8	3.8
	b Ar = C_6H_4-*p*-NMe_2			
	n = 4	10	0.2	10.8
	c Ar = C_6H_4-*p*-OMe			
	n = 3	> 20	10.6	10.4

[a]Inhibition of thioredoxin reductase in the presence of thioredoxin and insulin.
[b]Inhibition of thioredoxin reductase.
[c]Inhibition of growth of MCF-7 breast cancer cells in culture.

Among the amino acid, nitrogen base and polyamine classes of tellurium containing inhibitors, it seems that the compounds carrying a strongly electron donating substituent in the aryltelluro moiety (dimethylamino group) show better inhibition characteristics than the corresponding phenyltelluro derivatives (compounds **5b**/**5a**, **8b**/**8a**, and **14b**/**14a**). This could indicate that the nucleophilicity/one-electron donating capacity of tellurium in the compounds tested could be critical for their **TrxR** and cell growth inhibiting capacity. Whether this is an antioxidative effect, (such as peroxide decomposition via nucleophilic attack on organic hydroperoxides or chain-breaking donating activity via one-electron donation to peroxyl radicals) or if it involves nucleophilic attack elsewhere (e.g., on some electrophilic disulfide bonds) is difficult to say.

In conclusion, some of the newly prepared classes of tellurium-based inhibitors with a potential to be selectively incorporated into tumor cells (amino acid, nitrogen base and polyamine compounds) show promising inhibition of **TrxR** and growth of MCF-7 cells in culture (IC_{50} values in the low micromolar range). These structures will be subject to further elaboration and carried on to in vivo testing.

Experimental

TrxR/Trx-assay

Thioredoxin reductase/thioredoxin-dependent insulin reducing activity was measured in an incubation with a final volume of 60 μL containing 100 mM HEPES buffer, pH 7.2, 5 mM EDTA (HE buffer), 1 mM NADPH, 1.0 μM human placental thioredoxin reductase, 0.8 μM thioredoxin, 2.5 mg/mL bovine insulin and inhibitor. Incubations were for 30 min at 37 °C in flat-bottom 96-well microtiter plates. The reaction was stopped by the addition of 50 μL of 6 M guanidine-HCl, 50 mM Tris, pH 8.0, and 10 mM DTNB, and the absorbance measured at 405 nM.

TrxR-assay

Assays of TrxR were carried out in flat-bottom 96-well microtiter plates. TrxR activity was measured in a final

incubation volume of 60 μL containing HE buffer, 10 mM DTNB, 1.0 μM TrxR and 1 mM NADPH and inhibitor. Compounds were diluted in HE buffer and added to the wells as 20-μL aliquots, and TrxR was then added, also as 20-μL aliquots in HE buffer. To ensure uniform coverage of the bottom of the well the plate was spun briefly at 3000 g. To start the reaction, NADPH and DTNB were added as a 20 μL aliquot in HE buffer and the plate was moved to the plate reader which had been preheated to 37 °C. The optical density at 412 nm was measured every 10 s and initial linear reaction rates measured.

Growth inhibition assay

Compound cytotoxicity was measured using modifications of the MTT assay as described by Mosmann[41] and Carmichael.[42] Human MCF-7 breast cancer cells were seeded at 3000 cells/well into 96-well plates in Dulbecco's minimum essential medium (DMEM) supplemented with 10% fetal bovine serum (FBS). After 16 h at 37 °C and 5.5% CO_2 in air, drugs were added to the wells at concentrations ranging from 0.1 to 20 μM. The cells were further incubated for 72 h after which 40 μL per well of a 2.5-μg/μL solution MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) solution was added and an additional 3 h, 37 °C, 5.5% CO_2 in air, incubation was performed. At the end of the incubation, the untransformed MTT was removed form each well by aspiration and 150 μL per well of DMSO (dimethyl sulfoxide) was added. The plate was shaken to ensure full solubilization of the formazan dye followed by dual optical density readings of 595 and 655 nm using a multiwell microplate spectrophotometer (Molecular Device Corp., Menlo Park, CA, USA). Cytoviability of control cells was considered to be 100%. For the treated cells viability was expressed as a percentage of control cells. All determinations were carried out in triplicate.

Preparation of organotellurium compounds

Di-*n*-butyl ditelluride,[43] diphenyl ditelluride,[44] bis(4-hydroxyphenyl) telluride (**9**),[45] bis(4-methoxyphenyl) ditelluride,[44] bis(4-dimethylaminophenyl) ditelluride,[44] N^1,N^{10}-bis-phthaloylimidyl spermidine,[40] and 5-bromo-2,4-bis-(benzyloxy)pyrimidine[33] were synthesised according to literature methods. All other chemicals were purchased commercially and used without further purification, unless otherwise stated. THF and ether were distilled under nitrogen from sodium benzophenone and were used directly from the still. CH_2Cl_2 was dried by distillation from calcium hydride under nitrogen. ^{1}H NMR spectra were recorded at 400 MHz. Mass spectra were recorded by direct inlet on a Finnigan MAT GCQ, using +ve EI, or on a Finnigan Thermoquest AQA (ESI 10 eV, probe temperature 300 °C). High resolution mass spectra were recorded by nanospray inlet on a Quattro LCZ or Bruker Reflex III MALDI-TOF. M^+ and $(M+H)^+$ ions are given for ^{130}Te.

3-α-Phenyltellurenylcholest-5-ene (1c). A solution of the lithium salt of benzenetellurolate was prepared from elemental tellurium (0.236 g, 1.85 mmol) in dry THF and PhLi (1.09 mL, 1.85 mmol, 1.7 M in hexane) under a N_2-atmosphere according to literature procedure.[29] A solution of 3-β-tosylcholest-5-ene (1 g, 1.85 mol) in dry THF (5 mL) was added to the tellurolate solution, and the resultant reaction mixture was heated at reflux for 6 h. After cooling to rt, the solution was concentrated and the residue dissolved in $CHCl_3$ (50 mL × 3). The combined $CHCl_3$ extracts were filtered through anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The orange viscous oil was purified by flash chromatography on silica gel using pentane as the eluent to yield a light yellow viscous oil which was crystallised from EtOH to furnish the title compound (0.62 g, 58%) as a pale yellow solid: mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 3H), 0.87 (d, J = 6.4 Hz, 6H), 0.92 (d, J = 6.4 Hz, 3H), 1.01 (s, 3H), 1.64–2.14 (m, 26H), 2.40 (d, J = 14.5 Hz, 1H), 2.92 (d, J = 14.5 Hz, 1H), 4.07 (bs, 1H), 5.34 (d, J = 4.9 Hz, 1H), 7.20–7.35 (m, 3H), 7.74 (dd, J = 8.1, 1.5 Hz, 2H); MS m/z (relative intensity) 576 (M^+, 5), 572 (6), 410 (5), 369 (100), 255 (23).

Compounds **1d–f** were synthesised from the corresponding tellurolate and the corresponding 3-tosylcholest-5-ene according to the procedure for **1c**.

3-β-Phenyltellurenylcholest-5-ene (1d). Pale yellow solid (57%): mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 3H), 0.86 (d, J = 6.2 Hz, 6H), 0.92 (d, J = 6.2 Hz, 3H), 1.02 (s, 3H), 1.09–2.10 (m, 26H), 2.41 (d, J = 14.7 Hz, 1H), 2.91 (d, J = 14.7 Hz, 1H), 4.03 (bs, 1H), 5.33 (d, J = 4.8 Hz, 1H), 7.18–7.35 (m, 3H), 7.75 (dd, J = 8.0, 1.6 Hz, 2H); MS m/z (relative intensity) 576 (M^+, 8), 412 (15), 369 (100), 255 (27).

3-β-*n*-Butyltellurenylcholest-5-ene (1e). Yellow amorphous solid (50%); ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 3H), 0.86 (d, J = 6.4 Hz, 6H), 0.90 (m, 6H), 0.99 (s, 3H), 1.03–2.08 (m, 30H), 2.41 (td, J = 14.3, 2.1 Hz, 1H), 2.57 (dt, J = 7.2, 1.7 Hz, 2H), 2.84 (d, J = 14.3 Hz, 1H), 3.72 (bs, 1H), 5.33 (d, J = 5.3 Hz, 1H); MS m/z (relative intensity) 556 (M^+, 5), 554 (6), 369 (100), 255 (17).

3-β-(4-*N*,*N*-Dimethylaminophenyltellurenyl)cholest-5-ene (1f). Further purification by flash chromatography (pentane/CH_2Cl_2, 3:2) afforded the title compound (40%) as a pale yellow solid: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (s, 3H), 0.87 (d, J = 1.9 Hz, 3H), 0.872 (d, J = 1.9 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 1.00 (s, 3H), 1.34–2.04 (m, 26H), 2.35 (d, J = 14.5 Hz, 1H), 2.84 (d, J = 14.5 Hz, 1H), 2.95 (bs, 6H), 3.86 (bs, 1H); 5.33 (d, J = 5.3 Hz, 1H), 6.56 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H). MS m/z (relative intensity) 620 (M^+, 19), 505 (16), 449 (18), 167 (93).

Ethyl 4-phenyltellurenylbutyrate (2a). $NaBH_4$ (0.405 g, 10.7 mmol) was added to a well stirred suspension of diphenyl ditelluride (2.0 g, 4.89 mmol) in abs. EtOH (20 mL) at ambient temperature under N_2-atmosphere. After 20 min stirring, the orange colour had faded, and a solution of ethyl 4-bromobutyrate (2.0 g, 10.25 mmol) in abs EtOH (5 mL) was added dropwise. The reaction mixture was stirred for a further 6 h at the same

temperature, poured into H_2O and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give an orange oil. Purification by flash chromatography on silica gel (gradient elution with pentane: CH_2Cl_2 and CH_2Cl_2) furnished the title compound (2.95 g, 94%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3H), 2.08 (quint, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.89 (t, J = 7.2 Hz, 2H), 4.09 (q, J = 7.2 Hz, 2H), 7.22 (m, 3H), 7.71 (dd, J = 8.2, 1.4 Hz, 2H).

Compounds **2b–f** were synthesised from the corresponding ester according to the procedure for **2a**. In the preparation of **2d** and **2e**, bis(4-dimethylaminophenyl) ditelluride, and for **2f**, bis(4-methoxyphenyl) ditelluride, replaced diphenyl ditelluride.

Methyl 5-phenyltellurenylvaleroate (2b). Yellow viscous oil (82%); ^{1}H NMR ($CDCl_3$) δ 1.72 (quint, J = 7.3 Hz, 2H), 1.84 (quint, J = 7.3 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 3.64 (s, 3H), 7.23 (m, 3H), 7.71 (dd, J = 8.2, 1.6 Hz, 2H); MS m/z 322.7 $(M+H)^+$.

Methyl 12-phenyltellurenyldodecanoate (2c). Yellow viscous oil (94%); ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 14H), 1.62 (quint, J = 7.4 Hz, 2H), 1.78 (quint, J = 7.4 Hz, 2H), 2.34 (t, J = 7.4 Hz, 2H), 2.89 (t, J = 7.4 Hz, 2H), 3.64 (s, 3H), 7.20 (m, 3H), 7.69 (dd, J = 8.0, 1.6 Hz, 2H); MS m/z (relative intensity) 420 (M^+, 39), 418 (39), 181 (50), 163 (100).

Methyl 5-(4-*N*,*N*-dimethylaminophenyltellurenyl)valeroate (2d). Orange viscous oil (89%); ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 4H), 2.28 (t, J = 7.3 Hz, 2H), 2.75 (t, J = 7.3 Hz, 2H), 2.93 (s, 6H), 3.63 (s, 3H), 6.55 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H); MS m/z (relative intensity) 365 (M^+, 38), 363 (34), 250 (52), 248 (50), 116 (100).

Methyl 12-(4-*N*,*N*-dimethylaminophenyltellurenyl)dodecanoate (2e). Orange viscous oil (76%); ^{1}H NMR ($CDCl_3$) δ 1.23 (m, 14H), 1.63 (m, 4H), 2.28 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 2.93 (s,6H), 3.64 (s, 3H), 6.55 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H); MS m/z (relative intensity) 463 (M^+, 36), 361 (35), 250 (67), 248 (66), 121 (100).

Ethyl 4-(4-methoxyphenyltellurenyl)butyrate (2f). Yellow oil (92%); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 2.05 (quint, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 3.79 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H).

4-Phenyltellurenylbutyric acid (3a). A solution of $LiOH.H_2O$ (1.05 g, 25 mmol) in H_2O (10 mL) was added dropwise to a well stirred solution of **2a** (2.0 g, 6.26 mmol) in THF (15 mL). After 24 h stirring at rt under N_2-atmosphere, THF was removed under reduced pressure, H_2O (50 mL) and ether (50 mL) were added to the light yellow solution, which was acidified under cooling to pH 6 with pre-cooled 5% HCl. The organic phase was separated and the aqueous phase was extracted with ether (50 mL × 3). The combined ether extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated to furnish the title compound (1.72 g, 93%) as a yellow semi solid: mp 35–37 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (quint, J = 7.1 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 7.24 (m, 3H), 7.72 (dd, J = 8.1, 1.6 Hz, 2H); MS m/z (relative intensity) 294 (M^+, 14), 284 (39), 207 (29), 154 (87), 87 (100).

Compounds **3b–f** were synthesised according to the procedure for **3a**.

5-Phenyltellurenylvaleric acid (3b). Yellow viscous oil (92%); ^{1}H NMR ($CDCl_3$) δ 1.72 (quint, J = 7.3 Hz, 2H), 1.84 (quint, J = 7.3 Hz, 2H), 2.35 (t, J = 7.3 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H), 7.23 (m, 3H), 7.71 (dd, J = 8.2, 1.2 Hz, 2H); HRMS calcd for $(C_{11}H_{15}O_2Te)^+$ m/z 308.0057 found m/z 308.0061.

12-Phenyltellurenyldodecanoic acid (3c). Yellow viscous oil (90%); ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 14H), 1.62 (quint, J = 7.3 Hz, 2H), 1.78 (quint, J = 7.3 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 2.89 (t, J = 7.3 Hz, 2H), 7.22 (m, 3H), 7.70 (dd, J = 8.1 Hz, 2H); MS m/z (relative intensity) 406 (M^+, 79), 404 (81), 284 (13), 282 (15), 208 (49), 206 (43), 163 (100).

5-(4-*N*,*N*-Dimethylaminophenyltellurenyl)valeric acid (3d). Orange viscous oil (94%); ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 4H), 2.33 (t, J = 7.1 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 2.95 (s, 6H), 6.57 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H); MS m/z (relative intensity) 351 (M^+, 48), 349 (41), 250 (46), 248 (41), 121 (100).

12 - (4 - *N*,*N* - Dimethylaminophenyltellurenyl)dodecanoic acid (3e). Yellow viscous oil (87%); ^{1}H NMR ($CDCl_3$) δ 1.24 (m, 14H), 1.62 (quint, J = 7.5 Hz, 2H), 1.66 (quint, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.95 (s, 6H), 6.58 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.9 Hz, 2H); HRMS calcd for $(C_{20}H_{34}O_2Te)^+$ m/z 450.1653 found m/z 450.1635.

4-(4-Methoxyphenyltellurenyl) butyric acid (3f). Yellow oil (21%); ^{1}H NMR ($CDCl_3$) δ 2.08 (quint, J = 7.2 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 3.81 (s, 3H), 6.78 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H).

***N*-Acetyl-2-amino-4-phenyltellurenylbutyric acid lithium salt (5a).** To PhTeLi, prepared in dry THF from elemental tellurium (0.41 g, 3.22 mmol) and PhLi (1.89 mL, 3.13 mmol, 1.7 M in hexane) according to a literature procedure,[44] was added a solution of **4** (0.4 g, 2.8 mmol) and TMEDA (0.47 mL, 3.12 mmol) in THF (10 mL). After 4 h of stirring at rt, the solvent was evaporated and the residue washed successively with ether (30 mL) and CH_2Cl_2 (30 mL). Flash chromatography on silica gel using CH_2Cl_2/MeOH (3:1 and then 2:1) as eluent furnished the title compound (0.81 g, 82%) as a pale yellow solid: mp 129–131 °C; ^{1}H NMR (CD_3OD) δ 1.95 (s, 3H), 2.06–2.36 (m, 2H), 2.82–2.95 (m, 2H), 4.36

(q, $J = 7.0$ Hz, 1H), 7.14–7.26 (m, 3H), 7.70 (dd, $J = 8.1$, 1.5 Hz, 2H); MS m/z (relative intensity) 350 (M^+, 4), 282 (45), 207 (25), 154 (100).

Compounds **5b** and **5c** were synthesised from the corresponding tellurolate according to the procedure for **5a**.

***N*-Acetyl-2-amino-4-(*p*-*N*,*N*-dimethylaminophenyltellurenyl)butyric acid lithium salt (5b).** Yellow solid (92%): mp 131 °C (dec); ^{1}H NMR (DMSO-d_6) δ 1.80 (s, 3H), 1.88–1.97 (m, 1H), 2.01–2.08 (m, 1H), 2.61–2.69 (m, 2H), 2.87 (s, 6H), 3.99 (q, $J = 7.0$ Hz, 1H), 6.56 (d, $J = 8.9$ Hz, 2H), 7.47 (d, $J = 8.9$ Hz, 2H), 7.57 (d, $J = 7.6$ Hz, 1H); MS m/z 401.0 $(M + H)^+$.

***N*-Acetyl-2-amino-4-*n*-butyltellurenylbutyric acid lithium salt (5c).** Yellow solid (72%): mp 176–178 °C; ^{1}H NMR (DMSO-d_6) δ 0.86 (t, $J = 7.2$ Hz, 3H), 1.31 (quint, $J = 7.2$ Hz, 2H), 1.63 (quint, $J = 7.2$ Hz, 2H), 1.82 (s, 3H), 1.93–2.11 (m, 2H), 2.46–2.59 (m, 4H), 3.98 (q, $J = 7.2$ Hz, 1H), 7.63 (d, $J = 7.6$ Hz, 1H); MS m/z (relative intensity) 330 (M^+, 2), 284 (43), 256 (19), 207 (34), 154 (100).

5-(Phenyltellurenyl)-2,4-bis(benzyloxy)pyrimidine (7a). To a well stirred solution of 5-bromo-2,4-bis(benzyloxy)pyrimidine (**6**, 0.50 g, 1.35 mmol) in THF (20 mL) at −78 °C was added dropwise *n*-BuLi (0.593 mL, 1.48 mmol, 2.5 M in hexane) under an argon atmosphere. The light yellow solution was stirred for 15 min and a pre-cooled solution of diphenyl ditelluride (0.83 g, 2.02 mmol) in THF (5 mL) was slowly added. After 2 h stirring at this temperature, the reaction was quenched with glacial acetic acid (0.3 mL) and the dark red solution was allowed to warm to rt. The solution was concentrated, H_2O (50 mL) and CH_2Cl_2 (50 mL) were added and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (50 mL), the combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and filtered. The solvent was evaporated to dryness in vacuo, and the dark red residue was subjected to flash chromatography on silica gel using gradient elution (pentane/CH_2Cl_2 1:1 and then CH_2Cl_2) to give a yellow viscous oil which on recrystallisation from EtOH furnished the title compound (0.48 g, 72%) as white needles: mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 2H), 5.49 (s, 2H), 7.20–7.46 (m, 13H), 7.77 (dd, $J = 8.3$, 1.4 Hz, 2H), 8.20 (s, 1H).

Compounds **7b** and **7c** were synthesised from the corresponding ditelluride according to the procedure for **7a**.

5-(4-*N*,*N*-Dimethylaminophenyltellurenyl)-2,4-bis(benzyloxy)pyrimidine (7b). Pale yellow solid (63%): mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 2.97 (s, 6H), 5.35 (s, 2H), 5.44 (s, 2H), 6.58 (d, $J = 8.9$ Hz, 2H), 7.31–7.41 (m, 10H), 7.70 (d, $J = 8.9$ Hz, 2H), 7.88 (s, 1H).

5-(4-Methoxyphenyltellurenyl)-2,4-bis(benzyloxy)pyrimidine (7c). White needles (68%): mp 118–120 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 5.36 (s, 2H), 5.44 (s, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 7.32–7.41 (m, 10H), 7.73 (d, $J = 8.8$ Hz, 2H), 7.99 (s, 1H).

5-(Phenyltellurenyl)uracil (8a). To a solution of **7a** (0.3 g, 0.605 mmol) in CH_2Cl_2 (10 mL) was added trimethylsilyl iodide (0.22 mL, 1.57 mmol) at rt under an argon atmosphere. The orange solution was stirred for an additional 2 h, then MeOH (2 mL) was added and the mixture stirred for a further 1 h. The precipitate was filtered and the yellow solid recrystallised from EtOH to furnish the title compound (0.145 g, 76%) as a light yellow solid: mp 175 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.21–7.31 (m, 3H), 7.44 (s, 1H), 7.63 (d, $J = 8.2$ Hz, 2H), 11.99 (bs, 2H); MS m/z (relative intensity) 318 (M^+, 31), 316 (32), 188 (100).

Compounds **8b** and **8c** were synthesised according to the procedure for **8a**.

5-(4-*N*,*N*-Dimethylaminophenyltellurenyl)uracil (8b). Yellow solid (77%): mp 168 °C (dec); ^{1}H NMR (DMSO-d_6) δ 2.90 (s, 6H), 6.63 (d, $J = 8.9$ Hz, 2H), 6.73 (dt, $J = 4.2$ Hz, 1H), 7.57 (d, $J = 8.9$ Hz, 2H), 10.80 (bs, 1H), 11.24 (bs, 1H); HRMS calcd for $(C_{12}H_{14}N_3O_2Te)^+$ m/z 362.0149 found m/z 362.0197.

5-(4-Methoxyphenyltellurenyl)uracil (8c). Yellow solid (79%): mp >280 °C; ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H), 6.65 (d, $J = 8.8$ Hz, 2H), 7.05 (s, 1H), 7.57 (d, $J = 8.8$ Hz, 2H), 10.91 (bs, 1H), 11.27 (bs, 1H); MS m/z (relative intensity) 348 (M^+, 25), 346 (23), 255 (35), 237 (43), 218 (95), 214 (100).

Bis[4-(4-bromobutoxy)phenyl] telluride (10). 1,4-Dibromobutane (1.52 mL, 12.8 mmol) was added to a well stirred suspension of bis(4-hydroxyphenyl)telluride (**9**, 1.0 g, 3.18 mmol) and anhydrous K_2CO_3 (1.76 g, 12.74 mmol) in dry acetone at rt under a N_2-atmosphere. After 20 h stirring at reflux (TLC monitoring), the mixture was cooled, and concentrated under reduced pressure. H_2O (100 mL) and CH_2Cl_2 (100 mL) were added, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (50 mL × 2). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated to give a yellow solid. Purification by flash chromatography (pentane/CH_2Cl_2, 3:2) and subsequent recrystallisation from EtOH afforded the title compound (0.87 g, 47%) as a white solid: mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.89–2.09 (m, 8H), 3.47 (t, $J = 6.5$ Hz, 4H), 3.96 (t, $J = 6.5$ Hz, 4H), 6.74 (d, $J = 8.8$ Hz, 4H), 7.61 (d, $J = 8.8$ Hz, 4H).

Bis[4-(4-dimethylaminobutoxy)phenyl] telluride bishydrochloride (11). A solution of dimethylamine (1.61 mL 40% aq, 12.84 mmol) was added dropwise to a stirred solution of **10** (0.50 g, 0.856 mmol) in THF (20 mL) at ambient temperature under a N_2-atmosphere. After 8 h stirring, the solution was concentrated and the solid residue was dissolved in ether (50 mL) and 2 N NaOH (15 mL). The organic layer was separated and the aqueous phase was extracted with ether (30 mL × 2). The combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. After filtration and removal of the solvent, the solid residue was recrystallised from EtOH to furnish bis[4-(4-dimethylaminobutoxy)phenyl] telluride (0.41 g, 93%) as a white

solid; ^{1}H NMR ($CDCl_3$) δ 1.62 (m, 4H), 1.79 (m, 4H), 2.22 (s, 12H), 2.30 (t, J = 7.4 Hz, 4H), 3.94 (t, J = 6.4 Hz, 4H), 6.74 (d, J = 8.8 Hz, 4H), 7.60 (d, J = 8.8 Hz, 4H). Bis[4-(4-dimethylaminobutoxy)phenyl] telluride (0.10 g, 0.292 mmol) and an ether solution of HCl (1 M, 0.69 mL) in ether (10 mL) were stirred at rt for 2 h under a N_2-atmosphere. The precipitate was filtered off and washed with ether to afford the title compound (0.165 g, 96%) as a white solid.

N^1,N^{10}-Diphthaloyl-N^5-(3-phenyltellurenylpropylcarbonyl)spermidine (13a). A stirred solution of **3a** (0.30 g, 1.03 mmol) in dry CH_2Cl_2 (30 mL) was treated with freshly distilled triethylamine and cooled to 0 °C. To this mixture *i*-butylchloroformate (0.146 mL, 1.13 mmol) was added and the mixture stirred at rt for 2 h. A solution of **12** (0.50 g, 1.234 mmol) in CH_2Cl_2 (10 mL) was added and stirring continued at ambient temperature for 20 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed successively with 2% aqueous Na_2CO_3 (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The resulting orange viscous oil was purified by flash chromatography using CH_2Cl_2/EtOAc (4:1) as eluent to afford the title compound (0.6 g, 74%) as a pale yellow viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.48–1.71 (m, 4H), 1.86–1.96 (m, 2H), 2.04–2.13 (m, 2H), 2.38 (q, J = 7.4 Hz, 4H), 2.86–2.98 (m, 2H), 3.22–3.41(m, 2H), 3.68 (q, J = 6.6 Hz, 4H), 7.17–7.24 (m, 3H), 7.65–7.74 (m, 6H), 7.79–7.87 (m, 4H).

Compounds **13b** and **13c** were synthesised from **3d** and **3f**, respectively, according to the procedure for **13a**.

N^1,N^{10}-Diphthaloyl-N^5-[4-(4-*N*,*N*-dimethylaminophenyl)-tellurenylbutylcarbonyl]spermidine (13b). Yellow viscous oil (79%); ^{1}H NMR ($CDCl_3$) δ 1.50–1.80 (m, 8H), 1.86–1.97 (m, 2H), 2.18–2.27 (m, 2H), 2.73 (quint, J = 7.6 Hz, 2H), 2.91 (s, 6H), 3.25–3.39 (m, 4H), 3.67 (q, J = 7.3 Hz, 4H), 6.54 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.66–7.72 (m, 4H), 7.79–7.84 (m, 4H).

N^1,N^{10}-Diphthaloyl-N^5-[3-(4-methoxyphenyl)tellurenylpropylcarbonyl]spermidine (13c). Yellow viscous oil (83%); ^{1}H NMR ($CDCl_3$) δ 1.56 (quint, J = 7.3 Hz, 2H), 1.65 (quint, J = 7.3 Hz, 2H), 1.90 (quint, J = 7.3 Hz, 2H), 2.03 (quint, J = 7.0 Hz, 2H), 2.34 (quint, J = 7.1 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.84 (t, J = 7.3 Hz, 2H), 3.23–3.38 (m, 4H), 3.63–3.70 (m, 2H), 3.75 (s, 3H), 6.72 (d, J = 8.9 Hz, 2H), 7.61 (dd, J = 4.8, 8.5 Hz, 2H), 7.66–7.70 (m, 4H), 7.78–7.83 (m, 4H).

***N*-(3-Aminopropyl)-*N*-(4-aminobutyl)-4-phenyltellurenylbutanoic amide (14a).** A solution of hydrazine hydrate (0.207 g, 4.15 mmol) in EtOH was added to a solution of **13a** (0.6 g, 1.037 mmol) in EtOH (10 mL) at rt under a N_2-atmosphere. After 20 h stirring, the solvent was evaporated and EtOH was added. This process was repeated twice. Then MeOH was added (10 mL), the resulting white precipitate was filtered off and the filtrate was concentrated to furnish the title compound (0.32 g, 72%) as a pale yellow solid: mp 210 °C (dec); ^{1}H NMR (CD_3OD) δ 1.60–1.71 (m, 6H), 2.07 (m, 2H), 2.46–2.56 (m, 2H), 2.96 (t, J = 6.8 Hz, 2H), 3.28–3.54 (m, 8H), 7.15–7.27 (m, 3H), 7.70 (dd, J = 8.1 Hz, 2H); HRMS calc for $(C_{17}H_{30}N_3OTe)^+$ m/z 422.1452 found m/z 422.1458.

Compounds **14b** and **14c** were synthesised according to the procedure for **14a** with subsequent purification by chromatography (Sigmacell Type 20, ACN/H_2O 2:1).

***N*-(3-Aminopropyl)-*N*-(4-aminobutyl)-4-(4-*N*,*N*-dimethylaminophenyl)tellurenylpentanoic amide (14b).** Yellow viscous oil (23%); ^{1}H NMR (CD_3OD) δ 1.60–2.16 (m, 10H), 2.46 (m, 2H), 2.91–3.06 (m, 4H), 3.30 (s, 6H), 3.35–3.51 (m, 6H), 7.61 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H); MS m/z 479.4 $(M+H)^+$.

***N*-(3-Aminopropyl)-*N*-(4-aminobutyl)-3-(4-methoxyphenyl)tellurenylbutanoic amide (14c).** Yellow viscous oil (67%); ^{1}H NMR (DMSO-d_6) δ 1.60–2.16 (m, 10H), 2.46 (m, 2H), 2.91–3.06 (m, 4H), 3.30 (s, 6H), 3.35–3.51 (m, 6H), 7.61 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H); MS m/z 452.4 $(M+H)^+$.

Acknowledgements

Financial support from Cancerfonden and the NIH (CA 77204 and CA 17094) is gratefully acknowledged.

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