Synthesis of functionalised organochalcogenides and in vitro evaluation of their antioxidant activity

Synthesis of Functionalised Organochalcogenides and *in vitro* Evaluation of their Antioxidant Activity

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Dedicated to Professor Grzegorz Mlostoń on the occasion of his 70th birthday

The antioxidant properties and the cytotoxicity of differently substituted β-hydroxy- and β-amino dialkyl and alkyl-aryl tellurides, prepared through ring-opening reactions of epoxides and aziridines with selenium- or tellurium-centered nucleophiles, have been investigated on normal human dermal fibroblasts. Most of the studied compounds exhibited a low cytotoxicity and a number of them proved to be non-toxic, not showing any effect on cell viability even at the highest concentration used (100 μM). The obtained results showed a significant antioxidant potential of the selected organotellurium compounds, particularly evident under conditions of exogenously induced oxidative stress. The antioxidant activity of selenium-containing analogues of active tellurides has also been evaluated on cells, highlighting that the replacement of Se with Te brought about a significant increase in the peroxidase activity.

Keywords: tellurides; selenides; cytotoxicity; antioxidants; oxidative stress; GPx-like activity.

1. Introduction

A large number of human diseases, as neurodegenerative diseases (Alzheimer, Parkinson) and cancer are associated with changes in the intracellular redox state and in the presence of oxidative stress in the cells. This sharp increase in the intracellular concentration of reactive, oxidizing species, such as reactive oxygen species (ROS) is often combined with a loss of antioxidant defense and diminished antioxidant enzyme activity.

Glutathione peroxidase (EC 1.11.1.19, GPx) is a selenoenzyme that protects organisms against the damaging effect of ROS, catalysing the reduction of a variety of hydroperoxides (ROOH and H_2O_2)[1,2] using GSH as a reductant, thereby protecting mammalian cells from oxidative damage. This antioxidant property is of particular significance in living cells, because it decomposes hydrogen peroxide, phospholipid hydro-peroxide and other organic hydroxyl-peroxides, preventing the formation of reactive and toxic hydroxyl, and lipoperoxyl radicals.[3]

Therefore, there is a growing interest in the search for natural chemo preventative-products and antioxidants. Moreover, a wide range of agents mimicking these enzymes has been synthesized over the years and tested with mixed success in biological systems.[4] In this context, the synthesis and the development of new antioxidants, able to protect living cells against oxidative stress is highly sought after.

Chalcogen containing small molecules and enzymes play a crucial role in a wide range of biological functions and biochemistry mechanisms. Organoselenium derivatives have been attracting considerable interest because of their capability to mimic natural biologically active compounds and for their antioxidant,[5-9] antitumoral,[10,11] antiviral,[12] anti-inflammatory[13,14] activities.

Organic chalcogenides (especially selenides) have been also widely applied as synthetic mimics of glutathione peroxidase, but, while biological properties of a number of organoselenium derivatives have been described, a little is known about the biological and pharmacological effects of organotellurium compounds. Toxicity data of organotellurium derivatives are still scarce in the literature and, even if some data have indicated that a number of organotellurides are rather toxic,[14,15] some authors have described that organotellurium compounds are less toxic than their selenium derivatives.[16]

Over the past years, inorganic tellurium derivatives were applied for the development of innovative materials, such as fluorescent CdTe quantum dots as probes in biological detection,[17,18] nanoparticles and nanotubes, with potential applications in medicinal chemistry and electronic.[19,20]

Tellurium-containing organic molecules are readily oxidized from the divalent to the tetravalent state; consequently, tellurides can be studied as scavengers of reactive oxidizing agents such as hydrogen peroxide, hypochloride, and peroxyl radicals. Several authors have described that substitution of selenium by tellurium in a series of diarylchalcogenides results in a pronounced increase of the antioxidant activity.

In this *scenario*, the glutathione peroxidase-like activity,[21-23] the anticancer,[24] and the chemopreventive[25-27] of a number of organotellurium compounds have been reported. Examples of diaryl tellurides exhibiting protective effects on DNA damage in trout erythrocytes exposed to oxidative stress[23] have been described.

Furthermore, organotellurium compounds have been described as inhibitors of several enzymes such as thioredoxin reductase (Trx),[24,28] cathepsin, caspase[29] and carbonic anhydrase (CA).[30]

Telluro-xylofuranosides showed *in vivo* antioxidant activity in *C. elegans* by modulating the expression of superoxide dismutase (SOD-3), and increasing the protection against Mn-induced toxicity.[31] Tellurium-functionalized β-cyclodextrins, studied both for their glutathione peroxidase-like catalytic ability and thioredoxine reductase inhibitor activity, have been demonstrated to sensitize resistant breast cancer cells to TRAIL-induced apoptosis *in vitro* and *in vivo*.[28]

A comparative study on the bioactivation mechanisms and toxicity of chalcogen-containing unnatural amino acids showed that the *Te*-phenyl-L-tellurocysteine, being a stronger enzyme

modulator with respect to its sulfurated and selenated analogues, might represent an interesting prodrug for the treatment of cancer disease.[32]

Moreover, some tellurium containing compounds exhibited neuroprotective [33] and hepatoprotective [34] properties.

During the course of our studies in the synthesis and the reactivity of organochalcogenides, we developed convenient procedures for the preparation of a wide variety of novel functionalised oragnotellurium- and organoselenium-derivatives.[35,36] Particularly, the nucleophilic ring-opening-reaction of strained heterocycles with tellurium- and selenium-nucleophiles was exploited for the conversion of epoxides, aziridines, and thiiranes into the corresponding organochalcogenides bearing O-, N-, and S-containing moieties.[37-39] Notably, some of these compounds exhibited remarkable catalytic antioxidant properties, being capable to mimic the activity of the glutathione-peroxidase enzymatic complex.[40,41] Furthermore, a number of new chalcogen-containing carbonic anhydrase inhibitors[30,42,43] and activators[44] have been designed and synthesised by exploiting the above-mentioned procedures.

As a part of our growing interest in the study of selenium- and tellurium-containing organic systems, we report herein an evaluation of the antioxidant properties of a series of functionalized dialkyl- and aryl-alkyl tellurides and ditellurides and of some selenide and diselenide analogs, for comparison purpose.

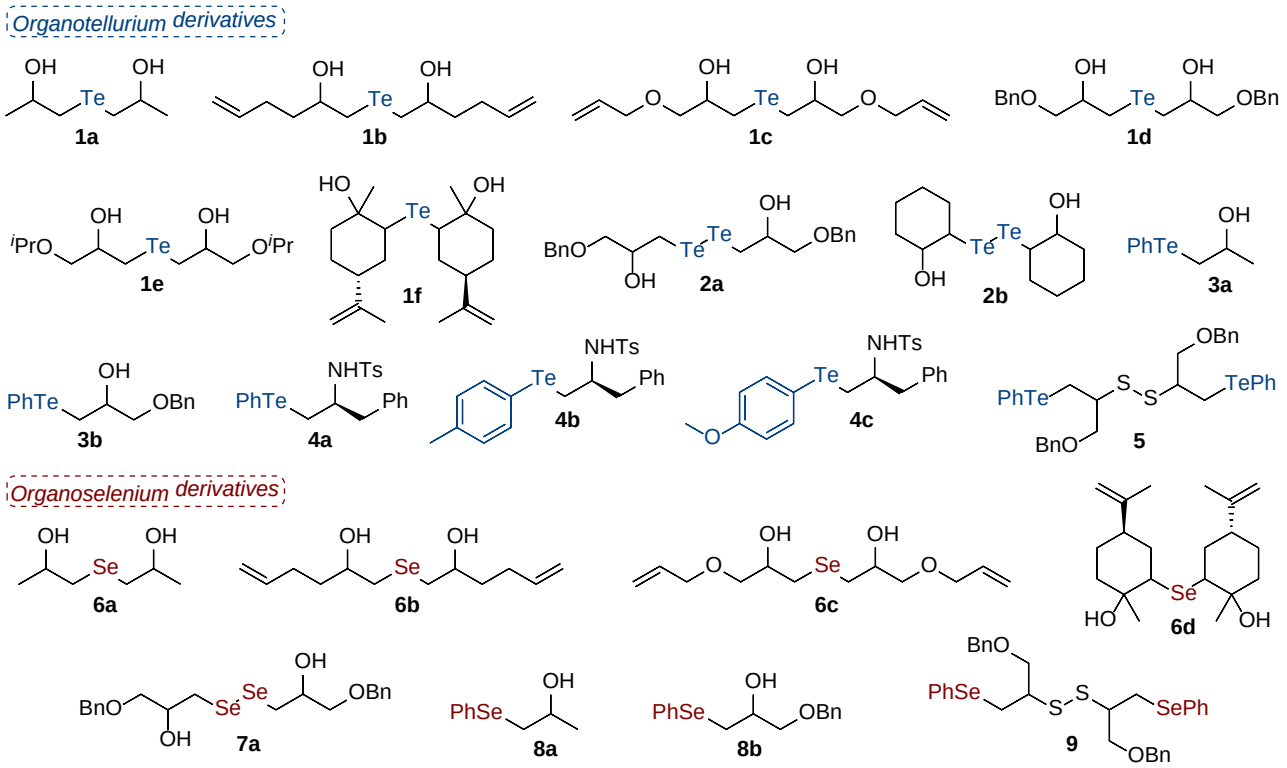


Figure 1. Organotellurium and organoselenium compounds studied in this work.

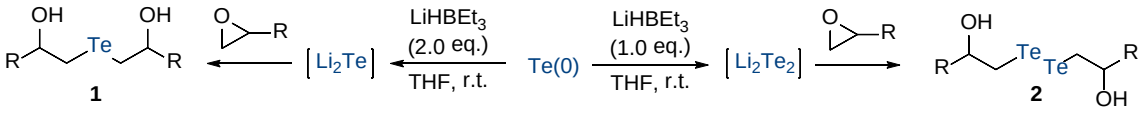
In order to investigate the activity of differently substituted and functionalised chalcogen-containing organic derivatives, the series of organotellurium- and organoselenium-compounds reported in the Figure 1, including a number of previously reported derivatives,[5,30,38,45]

characterised by a broad skeletal diversity, was conceived and synthesised following the ring-opening procedures described below. In particular, we focused our attention on homologous series of hydroxy- or amino-functionalised dialkyl and alkyl-aryl tellurides bearing variously substituted alkyl chains. The ditelluride **2a**, structurally related to the telluride **1d**, was also prepared in order to compare their activites. Furthermore, to evaluate the specific effect of the chalcogen atom, the selenium-containing isosteres of selected organotellurides were also prepared (see Figure 1). Preliminary evaluation of their thiol-peroxidase-like properties according to the dithiothreitol (DTT) oxidation test[41,46] confirmed that chalcogen derivatives show good GPx-like properties and that, as already reported, the replacement of Se with Te brought a relevant increase in the peroxidase activity. Therefore, we investigated more in details the ability of the aforementioned products to protect cells from oxidative stress; before performing these experiments, we checked the cytotoxicity of these organochalcogen derivatives. Both cytotoxicity and antioxidant activity of the products have been evaluated in normal fibroblast cells of human origin. The antioxidant activity was evaluated by the measurement of intracellular ROS using 2',7'–dichlorofluorescein diacetate (DCFH-DA) fluorescence assay.

2. Results and discussion

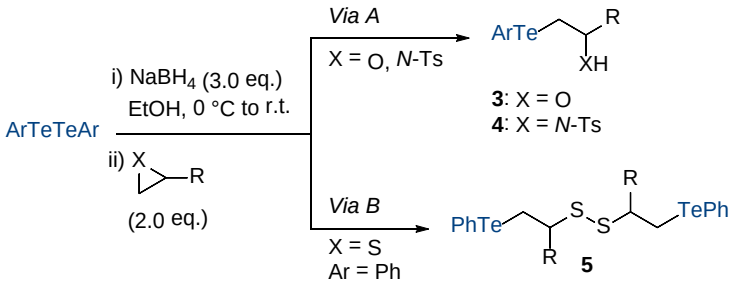
2.1. Chemistry

Symmetrical β-hydroxy alkyl tellurides **1a**-**f** were achieved through the ring opening reaction of the corresponding epoxides with Li_2Te, *in situ* generated from elemental tellurium and $LiHBEt_3$ (Scheme 1, left).[45] A related procedure enabled the synthesis of ditellurides **2a**,**b** by exploiting the reactivity of Li_2Te_2 (Scheme 1, right).[45]

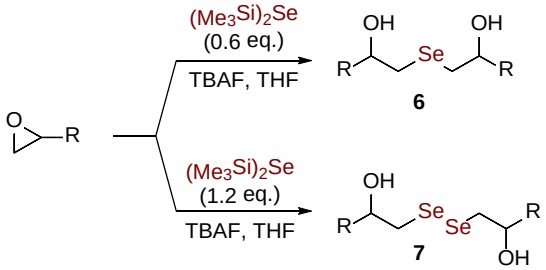


Scheme 1. Synthesis of β-hydroxy- tellurides **1** and ditellurides **2** from epoxides. R: see Figure 1.

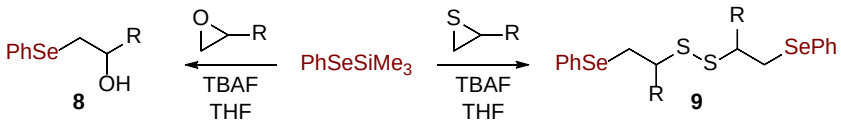
Unsymmetrical aryl-alkyl tellurides **3** and **4,** bearing hydroxy and amino functionalities were obtained through ring-opening reaction of the corresponding epoxides and aziridines with suitable aryl tellurolates, *in situ* formed by reduction of diaryl ditellurides (Scheme 2).[45,47,48] A similar approach was employed for the synthesis of the disulfide **5**, arising from the ring-opening of the corresponding thiirane and subsequent dimerization of the thiol intermediate.[45]
Symmetrical β-hydroxy selenides **6** and diselenides **7** were synthesised through the TBAF-induced ring-opening reaction of epoxides with $(Me_3Si)_2Se$ [bis(trimethylsilyl)selenide or HMDSS]. A simple tuning of the reaction stoichiometry enabled the selective formation of selenides **6** and diselenides **7** (Scheme 3). Similarly, a fluoride ion-induced silicon-mediated procedure was employed for the preparation of β-phenylseleno alcohols **8** and disulfide **9** from (phenylseleno)trimethylsilane and epoxides or thiiranes (Scheme 4).[49]



Scheme 2. *Via A*: synthesis of hydroxy- and amino-substituted aryl-alkyl tellurides **3** and **4**; *Via B*: synthesis of tellurium containing disulfide **5**. R, Ar: see Figure 1.



Scheme 3. Synthesis of β-hydroxy- selenides **6** and diselenides **7** through ring-opening reactions of epoxides with $(Me_3Si)_2$. R: see Figure 1.



Scheme 4. Synthesis of β-hydroxy aryl-alkyl selenides **8** and selenium-containing disulfide **9**. R: see Figure 1.

2.2. Thiol-peroxidase antioxidant properties

As preliminary assay, the thiol-peroxidase-like properties of the synthesised chalcogen-containing derivatives were evaluated according to the dithiothreitol (DTT) oxidation test[41,46], which is a ^{1}H NMR-based technique. The activity of these molecules in catalyzing the reaction between H_2O_2 and dithiothreitol was tested, monitoring the oxidation of the thiol substrate in CD_3OD: after the addition of H_2O_2 the signals relative to the reduced form of dithiothreitol decrease their integral, while the signals referred to the oxidized form increase. The parameter that defines the activity of the compounds is T_{50} that is the time required to lower of 50% the concentration of reduced DTT in the reported conditions. Results of this investigation are summarised in Table S1 (see Supplementary Information); thiol-peroxidase-like properties of selected compounds are reported in Table 1.

Table 1. Thiol-peroxidase-like properties of selected organochalcogenides studied in this work[a]

Te-compounds	T_{50} (DTT test)[b]	Se-compounds	T_{50} (DTT test)[b]
1a	<60	**6a**	2760 (±268)
3b	92 (±10)	**8b**	328 (±34)
5	516 (±53)	**9**	4870 (±387)

[a]The thiol-peroxidase-like activity has been measured by the DTT oxidation test. [b]T_{50} is the time required, in seconds, to halve the initial thiol concentration after the addition of H_2O_2; data in parenthesis are the experimental error. DTT oxidation was monitored by the mean of ^{1}H NMR spectroscopy. T_{50} for PhSeSePh (commonly used reference compound) was found to be 796 (±84) seconds. 1% mol of organotellurium compounds **1**-**5** were used; 10% mol of organoselenium compounds **6**-**9** were used.

As reported in Table 1, and as we already observed,[41] organotellurium compounds behaved as more effective catalysts with respect to their selenium-containing analogues, promoting complete DTT oxidation within few minutes from the initiation of the reaction (addition of H_2O_2). These findings are in line with results previously reported by other authors on the catalytic antioxidant properties of different classes of organoselenium and organotellurium compounds.[50,51] Most of the tellurides exhibited better thiol-peroxidase-like properties with respect to the reference compound diphenyldiselenide (796 seconds)[52,53]. On the other hand, related selenium-containing structures generally showed poorer catalytic antioxidant properties when compared with their tellurated analogues and with diphenyl diselenide. Furthermore, organotellurium compounds were used at the concentration of 1% in the DTT oxidation test, while the selenium-containing analogues, as well as the reference diphenyl diselenide, were used at the concentration of 10%. As a first conclusion, evaluation of the catalytic activity of this set of organotellurides and of some selenium analogues in this preliminary test confirmed that chalcogen derivatives show good GPx-like properties. Moreover, as already reported, the replacement of Se with Te brought a relevant increase in the peroxidase activity (Table 1).

2.3. Cytotoxicity on primary cultures of human dermal fibroblasts

The obtained results prompted us to investigate more in detail the ability of our products to protect cells from oxidative stress; before performing these experiments, we evaluated the cytotoxicity of the organochalcogen derivatives. In fact, information about the toxicity of selenides and even more of tellurides are scarce, and in some cases the results contradict each other. One hypothesis is that the ability to oxidize thiol groups of biological molecules can be involved both in their pharmacological properties and in their toxicological effects.[54]

Therefore, cytotoxicity of these derivatives was assayed on primary cultures of human dermal fibroblasts upon 72 h incubation with different concentrations (1-100 μM) of the studied compounds and using the MTS test. In this assay, the intensity of the reaction product, a brown formazan, is quantified with a spectrophotometer and is proportional to the number of living cells. The viability is expressed as percentage of control, i.e. untreated cells. Some representative photomicrographs of the fibroblast cultures are reported (Figure 2). On the left, normal healthy

cells can be seen; with increasing toxicity, the cells appear shrinked and damaged on a higher extent.

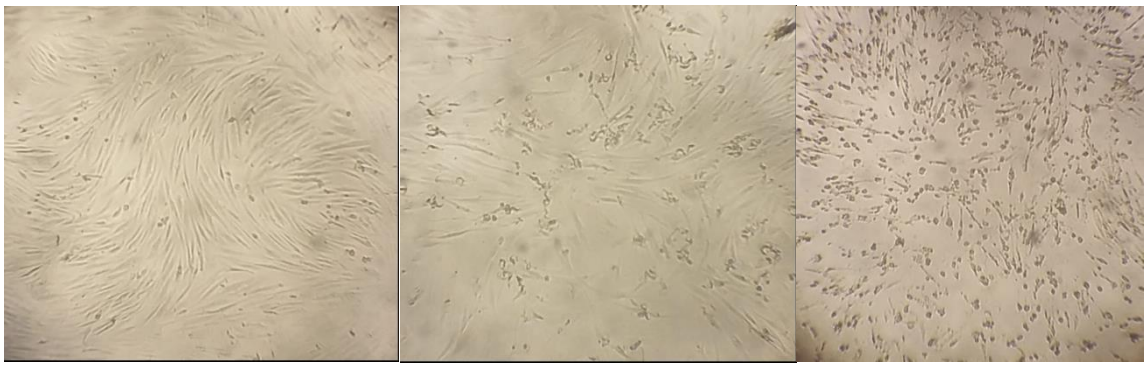


Figure 2. Photomicrographs of living fibroblast cultures in a healthy state (left panel), middle-grade cytotoxicity (medium panel), and strong cytotoxicity (right panel).

We verified that several compounds exhibited low cytotoxicity expressed as IC_{50}, as reported in Table 1. In particular, some selenated derivatives and a couple of tellurated compounds did not show any effect on cell viability even at the highest concentration used (100 μM). Compounds **4a**, **4b** and **4c** were not tested because they were not soluble enough. The active GPx-like tellurated compounds **1a** and **1c** showed to be the less toxic compounds within the series; therefore, we selected these compounds and their two non-toxic selenated analogues **6a** and **6c**, for the antioxidant activity tests on cells.

Table 2. IC_{50} values (μM) of the chalcogen compounds[a]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
1a	**>100**	**4b**	**ND**
1b	**100 ***	**4c**	**ND**
1c	**>100**	**5**	**11.6**
1d	**20.7**	**6a**	**>100**
1e	**80.7**	**6b**	**76.2**
1f	**22.9**	**6c**	**>100**
2a	**31.9**	**6d**	**67.3**
2b	**49.3**	**7a**	**2.4**
3a	**8.5**	**8a**	**>100**
3b	**19.8**	**8b**	**>100**
4a	**ND**	**9**	**>100**

[a]IC_{50} values (μM) were calculated for all the analyzed compounds in the MTS test upon 72 h exposure to concentrations ranging from 1 to 100 μM. *For compound **1b** the IC_{50} was not attainable with the concentrations tested: the 100 μM concentration corresponded to IC_{43}. ND: the analysis was not possible because of low solubility.

2.4 Basal and induced ROS production in primary cultures of human dermal fibroblasts

The effect of the non-toxic GPx-like tellurated compounds **1a** and **1c** and of their selenated analogues **6a** and **6c** on basal and induced ROS production was evaluated by measurement of ROS production using 2',7'–dichlorofluorescein diacetate (DCFH-DA) assay on primary cultures of human dermal fibroblasts. The antioxidant activity of the four selected compounds was assessed both on the basal levels of ROS, and on the induction of ROS production by H_2O_2. As regard the basal levels, untreated samples showed a progressive increase in ROS production over time (Figure 3A). When analyzing basal ROS production, cell samples pre-treated for 48 h with the studied compounds showed a pronounced concentration-dependent pro-oxidant effect, particularly evident for compound **1c**, which exhibited an FR > 200 at 50 nM concentration ($\mathbf{T_{120}}$) (Figure 3B and C). Pro-oxidant activities of selenium compounds have been described and attributed to the ability of these derivatives to oxidize directly thiol groups[55] or through interaction with glutaredoxin and thioredoxin systems.[56] It has to be noted that this cellular increase in ROS was not associated to cell death, as indicated by the MTS test results showing no reduction in cell viability up to 100 μM concentration (see above, par. 2.3). The reference antioxidant compound *N*-acetyl-cysteine (NAC) was effective in reducing ROS production under basal conditions (Figure 3B and C).

The same test was performed after exposing cells to H_2O_2, which induced a strong increase in ROS production (57-fold increase in exposed cells compared to non-exposed at T_{120}, see Figures 3A and 4A). This effect was also progressive over time as shown in Figure 4A. In this second assay, upon 48 h treatment with the studied compounds, a protective effect towards H_2O_2 action was found for all the compounds at all the tested concentrations. However, at higher concentrations the protective effect tended to be reduced or lost, except for compound **1a**, which was equally effective at all the three tested concentrations (Figures 4B and 4C). The most effective compounds resulted **1a** and **6a** (more than 50% reduction at 5 nM concentration at T_{120}). At higher concentrations, 10 nM in the case of compound **6a** and 50 nM for compound **6c**, the reduction of oxidative stress was less than 20% at T_{120}. Therefore, compound **6a** was not further tested at 50 nM.

Figures 4B and 4C show that for all the compounds the protection from oxidative stress was more evident at 120 min than immediately after the addition of the hydrogen peroxide (T_0). The results for the other tested time points are reported in Table S2 (Supplementary Information), and indicate an antioxidant activity that starts immediately after the addition of H_2O_2 (T_0), reaches a high value after only 30 min and remains high up to 120 min with small variations in the intermediate times. In the case of compound **1c**, the antioxidant effect is not detectable at T_0, either at 10 or at 50 nM (Figure 4B), possibly due to its higher pro-oxidant activity in basal conditions (Figures 3B and 3C).

The antioxidant activity of the reference compound NAC (5 mM) was higher than the tested compounds (about 70% reduction).

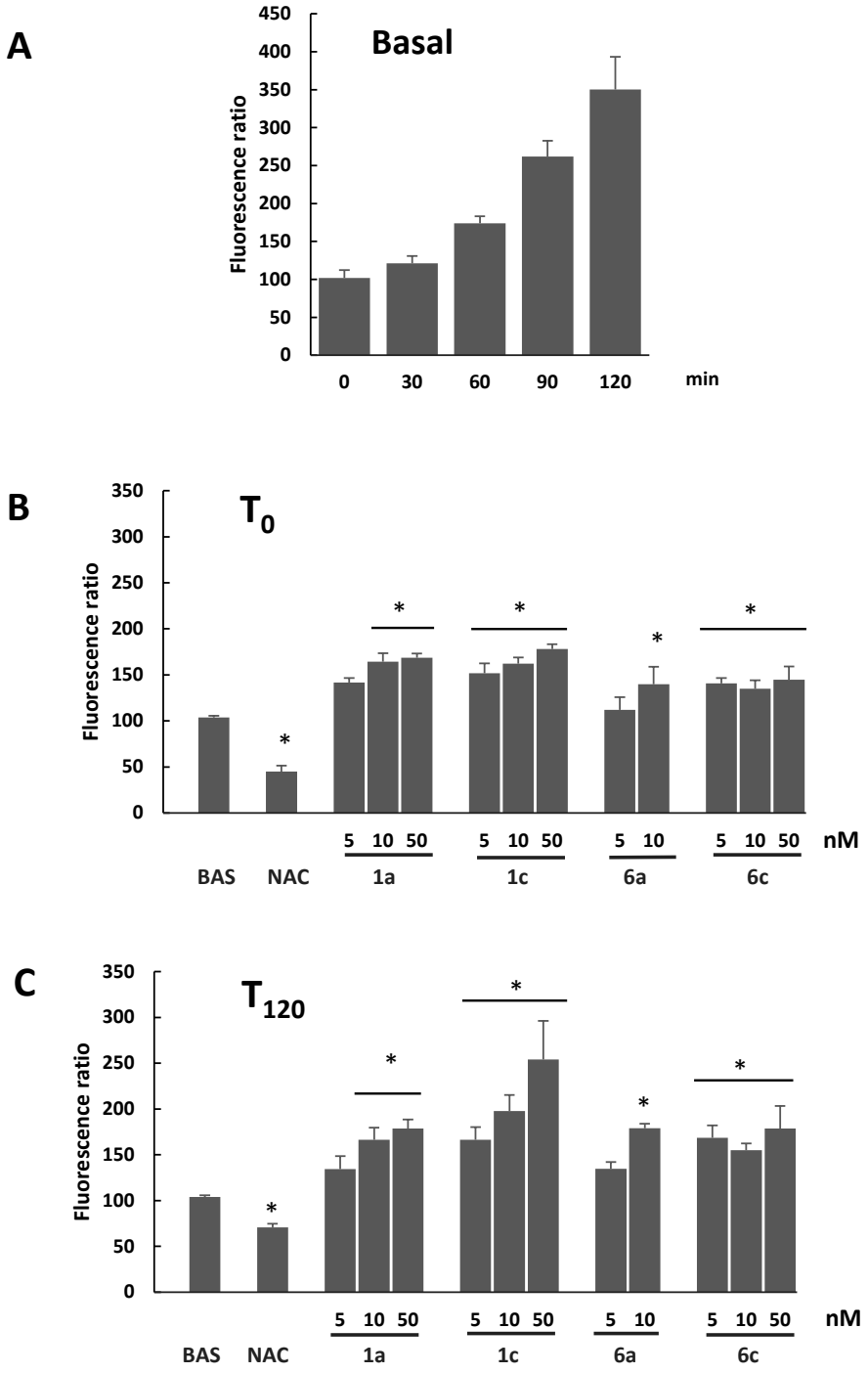


Figure 3. A: Basal fluorescence ratio values of Normal Human Dermal Fibroblasts (NHDF) over time (untreated samples). Data are reported as percentage of time 0. B and C: NHDF treated for 48 h with two or three concentrations of the compounds in study under basal conditions: only two reading times were reported: T_0 and T_{120} respectively (see Materials and Methods section). Data are reported as percentage of the untreated basal control (BAS) at the corresponding time. NAC=5 mM N-acetyl-cysteine. *p<0.05, statistically significant difference from the untreated control (BAS).

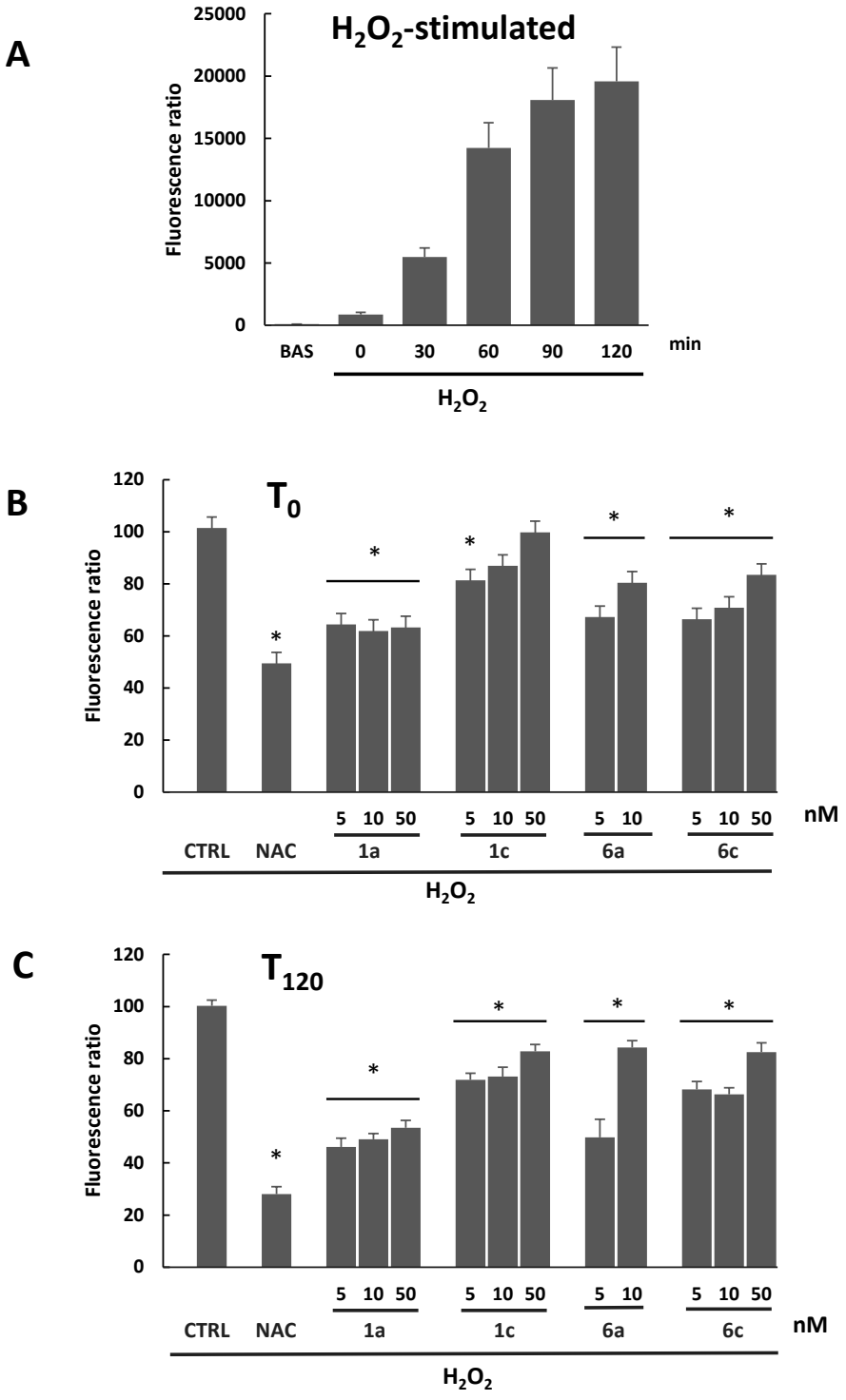


Figure 4. A: Temporal increase in oxidative stress levels induced by 500 μM H_2O_2 in Normal Human Dermal Fibroblasts (NHDF). B and C: NHDF pre-treated for 48h with two or three concentrations of the compounds in study and exposed to H_2O_2: only two reading times were reported: $\mathbf{T_0}$ and $\mathbf{T_{120}}$ respectively (see Materials and Methods section). BAS: untreated basal control; CTRL: untreated control, H_2O_2-stimulated; NAC = 5 mM *N*-acetyl-cysteine. *p<0.05, statistically significant difference from CTRL. Data are reported as percentage of BAS (A) and of CTRL (B, C).

In summary, the organocalchogen compounds exert a significant antioxidant activity (p<0.05), presumably due to their GPX-like activity[5,41]. On the other hand, an effect on gene expression

cannot be excluded, considering the long-term exposure to the studied compounds: modulation of the Nrf-2 antioxidant transcription factor has been recently reported for some selenium compounds[57]. The antioxidant effect was best detected when the concentration of ROS increased extensively within the cell, as it happens following H_2O_2 exposure, and was persistent up to 2 h. Apparently, the behavior of the organo-tellurium and of the organo-selenium compounds was similar under the present experimental conditions. However, the organo-tellurium compound **1a** resulted to be the most promising of the group, being endowed with very low toxicity, low ROS production under basal conditions, and good ability to counteract exogenous oxidative stress at all the tested concentrations.

Conclusions

As a continuation of our studies on the antioxidant properties of organochalcogenides, a series of chalcogen-containing organic compounds were synthesized. In detail, we obtained homologous series of hydroxy- or amino-functionalised dialkyl and alkyl-aryl tellurides bearing variously substituted alkyl chains, and some selenium-containing isosteres, to evaluate the specific effect of the chalcogen atom.

An evaluation of their thiol-peroxidase-like properties according the dithiothreitol (DTT) oxidation test was preliminarly performed, confirming that, as already reported, replacement of Se with Te brought a relevant increase in the peroxidase activity. Based on these results, we investigated the ability of the products to protect cells from oxidative stress in normal fibroblast cells of human origin, checking first their cytotoxicity in the same cell line.

Several compounds exhibited a low cytotoxicity. The active GPx-like tellurated compounds **1a** and **1c** did not show any effect on cell viability even at the highest concentration used (100 μM) and were selected with their non-toxic selenated analogues **6a** and **6c**, for the antioxidant activity tests on cells.

The results obtained showed a significant antioxidant potential of the studied compounds. This activity was evident under conditions of exogenously induced oxidative stress, whereas under basal conditions, a pro-oxidant activity was detected for all the compounds. It has to be noticed that this pro-oxidant activity did not compromise cell viability, as shown by the cytotoxicity data: for example, compound **1c** was non-toxic up to 100 μM, whereas its pro-oxidant activity was detected at 5-50 nM concentration. Furthermore, considering that the H_2O_2-induced level of ROS was about two hundred times higher than the basal level at 2 h, the extent of the pro-oxidant activity was much lower compared to the antioxidant one. Compounds **1a** and **6a** exhibited the highest antioxidant activity; for both compounds, 5 nM concentration was both antioxidant under oxidative stress and devoid of significant pro-oxidant activity in basal conditions. Such a low concentration is not difficult to attain in vivo. Thus, in a translational perspective these are the best candidate compounds and concentrations for future in vivo experiments.

Future studies will have to verify whether the observed protective effects are associated with the ability of these molecules to penetrate within the cells through passive diffusion or other mechanisms, and which are the cellular and molecular mechanism involved in the observed effects.

3. Experimental part

3.1. General

All dried reactions were carried out in an oven-dried glassware under inert atmosphere (N_2). Solvents were dried using a solvent purification system (Pure-Solv™). All commercial materials were purchased from various commercial sources and used as received, without further purification. Flash column chromatography purifications were performed with Silica gel 60 (230-400 mesh). Thin layer chromatography was performed with TLC plates Silica gel 60 F254, which was visualised under UV light, or by staining with an ethanolic acid solution of p-anisaldehyde followed by heating. Mass spectra were recorded by Electrospray Ionization (ESI). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Varian Mercury 400, Bruker 400 Ultrashield, and Varian Gemini 200 spectrometers operating at 400 MHz and 200 MHz (for ^{1}H), 100 MHz and 50 MHz (for ^{13}C). ^{77}Se NMR and ^{125}Te spectra were recorded using a Bruker 400 Ultrashield spectrometer, operating at 76 MHz and 126 MHz, respectively. NMR signals were referenced to nondeuterated residual solvent signals (7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C). Diphenyl diselenide $(PhSe)_2$ was used as an external reference for ^{77}Se NMR (δ = 461 ppm). Diphenyl ditelluride $(PhTe)_2$ was used as an external reference for ^{125}Te NMR (δ = 420 ppm). Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz), rounded to the nearest 0.1 Hz. ^{1}H NMR data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, ap d = apparent doublet, m = multiplet, dd = doublet of doublet, bs = broad singlet, bd = broad doublet, ecc.), coupling constant (J), and assignment.

4.1.2. General procedure for the synthesis of β*-hydroxy tellurides* **1**

Li_2Te was generated according to a literature reported procedure [58] from 1 mL of a 1 M THF solution of $LiEt_3BH$ (1.0 mmol, 2.0 eq.) and elemental tellurium powder (63 mg, 0.5 mmol, 1.0 eq.). The chalky-white suspension of Li_2Te in THF was *in situ* treated with the epoxide (1.0 mmol, 2.0 eq.) and the reaction was stirred for 12 h at ambient temperature. Afterwards, the mixture was diluted with Et_2O (10 mL), filtered through a short pad of celite, washed with sat. aq. NH_4Cl and then with H_2O (2 x 5 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography to afford β-hydroxy tellurides **1a**-**f**. Spectroscopic data of compounds **1a**,**c**-**f** matched those previously reported.[45]

4.1.3. Synthesis of 1,1'-tellurobis(hex-5-en-2-ol) **1b**

According to the general procedure, 2-(but-3-en-1-yl)oxirane (49 mg, 0.5 mmol) gave after flash column chromatography (petroleum ether:EtOAc 1:1) **1b** (42 mg, 53%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 1.58-1.66 (8H, m, C**H$_2$**CH_2CH=CH_2), 2.09-2.24 (8H, m, C**H$_2$**CH=CH_2), 2.73-2.78 (8H, m, C**H$_a$**H_bTe partially overlapped with O**H**), 2.93 (4H, dd, J = 5.1, 3.8 Hz, CH_a**H$_b$**Te), 3.68-3.73 (4H, m, C**H**OH), 4.96-5.07 (8H, m, CH=C**H$_2$**), 5.76-5.87 (4H, m, C**H**=CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 15.3 (CH_2Te), 30.9, 30.9, 37.9, 71.7 (CHOH), 71.9 (CHOH), 115.7, 138.7. **MS** (ESI): 350.8 [M+Na]$^{+}$.

4.1.4. General procedure for the synthesis of β*-phenyltelluro alcohols* **3** *and* β*-aryltelluro amines* **4**

$NaBH_4$ (0.75 mmol, 3.0 eq.) was portionwise added to a solution of diaryl ditelluride (0.25 mmol, 1.0 eq.) in EtOH (2 mL) at 0 °C under inert atmosphere (N_2). After 30 min, the epoxide or the

aziridine (0.45 mmol, 1.8 eq.) was slowly added and the reaction mixture was stirred at room temperature until complete consumption of the starting material was observed by TLC. The reaction was quenched by addition of saturated aq. NH_4Cl (2 mL) and diluted with Et_2O (5 mL), The layers were separated and the organic layer was washed with H_2O (3 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by flash chromatography to afford β-phenylelluro-alcohols **3** or β-arylelluro-amines **4**.

4.1.5. Synthesis of 1-(phenyltellanyl)propan-2-ol **3a** [59]

Following the general procedure, diphenyl ditelluride (51 mg, 0.125 mmol) and 2-methyloxirane (14 mg, 0.23 mmol) gave after flash chromatography (petroleum ether/EtOAc 3:1) **3a** (55 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* (ppm): 1.32 (3H, d, *J* = 6.1 Hz), 2.47 (1H, bs, OH), 2.99 (1H, dd, *J* = 7.4, 12.2 Hz, C**H$_a$**H$_b$Te), 3.14 (1H, dd, *J* = 4.7, 12.2 Hz, CH$_a$**H$_b$**Te), 3.89-4.01 (1H, m, C**H**OH), 7.19-7.24 (2H, m), 7.28-7.32 (1H, m), 7.75-7.78 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* (ppm): 22.1, 24.4, 68.1, 111.9, 128.4, 129.9, 139.1.

4.1.6. Synthesis of 1-(benzyloxy)-3-(phenyltellanyl)propan-2-ol **3b** [47]

Following the general procedure, diphenyl ditelluride (51 mg, 0.125 mmol) and benzyl glycidyl ether (38 mg, 0.23 mmol) gave after flash chromatography (petroleum ether/EtOAc 3:1) **3b** (73 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* (ppm): 2.86 (1H, bd, *J* = 13.3 Hz, OH), 3.08-3.16 (2H, m, CH_2Te), 3.53 (1H, dd, *J* = 6.2, 9.5 Hz, C**H$_a$**H$_b$O), 3.61 (1H, dd, *J* = 3.9, 9.5 Hz, CH$_a$**H$_b$**O), 3.99-4.09 (1H, m, C**H**OH), 4.53 (2H, ap s, CH_2Ph), 7.20-7.24 (2H, m), 7.28-7.41 (6H, m), 7.77-7.79 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* (ppm): 14.5, 71.1, 74.0, 74.7, 112.5, 128.38, 128.43, 128.5, 129.1, 129.9, 138.5, 139.0.

4.1.7. Synthesis of (S)-4-methyl-N-(1-phenyl-3-(phenyltellanyl)propan-2-yl)benzenesulfonamide **4a**

Following the general procedure, diphenyl ditelluride (51 mg, 0.125 mmol) and (*S*)-2-benzyl-1-tosylaziridine (65 mg, 0.23 mmol) gave after flash chromatography (petroleum ether/Et_2O 3:1) **4a** (105 mg, 93%).[30] **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* (ppm): 2.38 (3H, s, CH_3), 2.74 (1H, dd, *J* = 6.8, 13.8 Hz), 2.84-2.89 (2H, m), 3.12 (1H, dd, *J* = 4.3, 12.4 Hz), 3.51-3.59 (1H, m, C**H**NH), 4.78 (1H, d, *J* = 7.5 Hz, NH), 6.90-6.92 (2H, m), 7.10-7.22 (7H, m), 7.29-7.33 (1H, m), 7.45 (2H, ap d, *J* = 8.3 Hz), 7.65-7.67 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* (ppm): 16.1 (CH_2Te), 21.5, 42.0, 55.3, 111.1 (TeC), 126.7, 127.0, 128.0, 128.6, 129.2, 129.4, 129.5, 136.5, 137.0, 138.6, 143.1. **^{125}Te NMR** (126 MHz, $CDCl_3$) *δ* (ppm): 386.4.

4.1.8. Synthesis of (S)-4-methyl-N-(1-phenyl-3-(p-tolyltellanyl)propan-2-yl)benzenesulfonamide **4b**

Following the general procedure, 1,2-di-*p*-tolylditellane (55 mg, 0.125 mmol) and (*S*)-2-benzyl-1-tosylaziridine (65 mg, 0.23 mmol) gave after flash chromatography (petroleum ether/EtOAc 5:1) **4b** (101 mg, 87%).[30] **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* (ppm): 2.36 (3H, s, CH_3), 2.39 (3H, s, CH_3), 2.74 (1H, dd, *J* = 6.8, 13.8 Hz), 2.79-2.88 (3H, m), 3.08 (1H, dd, *J* = 4.3, 12.4 Hz), 3.47-3.57 (1H, m, C**H**NH), 4.72 (1H, d, *J* = 7.5 Hz, NH), 6.90-6.92 (2H, m), 7.02 (2H, d, *J* = 8.0 Hz), 7.11 (2H, d, *J* = 8.3 Hz), 7.12-7.17 (3H, m), 7.44 (2H, d, *J* = 8.3 Hz), 7.56 (2H, d, *J* = 8.0 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* (ppm): 16.2 (CH_2Te), 21.2, 21.5, 41.7, 55.3, 106.9 (TeC), 126.7, 127.0, 128.6, 129.2, 129.5, 130.3, 136.6, 137.0, 138.1, 139.0, 143.1. **^{125}Te NMR** (126 MHz, $CDCl_3$) *δ* (ppm): 371.3.

4.1.9. Synthesis of (S)-N-(1-((4-methoxyphenyl)tellanyl)-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide **4c**

Following the general procedure, 1,2-bis(4-methoxyphenyl)ditellane (30 mg, 0.063 mmol) and (*S*)-2-benzyl-1-tosylaziridine (32 mg, 0.113 mmol) gave after flash chromatography (petroleum ether/EtOAc 5:1) **4c** (54 mg, 91%).[30] **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 2.39 (3H, s, CH_3); 2.74-2.76 (2H, m); 2.79 (1H, dd, *J* = 6.5, 13.8 Hz); 3.05 (1H, dd, *J* = 4.3, 12.4 Hz); 3.47-3.55 (1H, m, C**H**NH); 3.82 (3H, s, OCH_3); 4.75 (1H, d, *J* = 8 Hz, NH); 6.76 (2H, ap.d, *J* = 8.8 Hz); 6.79-6.91 (2H, m); 7.11-7.17 (5H, m); 7.43 (2H, d, *J* = 8.3 Hz); 7.62 (2H, ap.d, *J* = 8.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 16.4 (CH_2Te); 21.5; 41.8; 55.18; 55.23; 100.0 (TeC); 115.4; 126.7; 127.0; 128.6; 129.2; 129.5; 136.6; 137.0; 141.1; 143.1. **^{125}Te NMR** (126 MHz, $CDCl_3$) δ (ppm): 369.51.

4.1.10. Synthesis of 1,2-bis(1-(benzyloxy)-3-(phenyltellanyl)propan-2-yl)disulfane **5**

$NaBH_4$ (19 mg, 0.5 mmol, 3.0 eq.) was portionwise added to a solution of diphenyl ditelluride (68 mg, 0.17 mmol, 1.0 eq.) in EtOH (2 mL) at 0 °C under inert atmosphere (N_2). After 30 min, the thiirane (60 mg, 0.33 mmol, 2.0 eq.) was slowly added at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred for additional 12 h. Afterwards, 4 mL of H_2O were added and the organic phase was extracted with Et_2O (2 x 5 mL), washed with brine (1 x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude material by flash chromatography yielded β-phenyltellurodisulfides **5** (96 mg, 76%). Spectroscopic data matched those previously reported.[46]

4.1.11. General procedure for the synthesis of β*-hydroxy selenides* **6**

A solution of epoxide (1 mmol, 1.0 eq.) and bis(trimethylsilyl)selenide (HMDSS) (0.6 mmol, 0.6 eq.) in dry THF (3 mL), was treated under inert atmosphere with TBAF (0.24 mL of 1M THF solution, 0.24 mmol). After stirring for 4 h, the solution was diluted with diethyl ether, washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified on silica gel to yield β-hydroxy selenides **6a**-**d**. Spectroscopic data of compounds **6b**-**d** matched those previously reported.[49]

4.1.12. Synthesis of 1,1'-selenobis(propan-2-ol) **6a**

Following the general procedure, $(Me_3Si)_2Se$ (54 mg, 0.24 mmol) and 2-methyloxirane (23 mg, 0.4 mmol) gave after flash chromatography (petroleum ether/EtOAc 1:1) **6a** (30 mg, 76%, mixture of diastereoisomers). **^{1}H NMR** (400 MHz, $CDCl_3$) δ (ppm): 1.24 (12H, d, *J* = 6.2 Hz), 2.55-2.62 (4H, m, CH_2Se) 2.75-2.80 (4H, m, CH_2Se), 3.26 (4H, bs, OH), 3.86-3.93 (4H, m, C**H**OH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ (ppm): 23.35, 23.42, 35.4, 35.6, 67.3, 66.7. **^{77}Se NMR** (76 MHz, $CDCl_3$) δ (ppm): 58.0, 65.2. Spectroscopic data referred to an equimolar mixture of diastereoisomers.

4.1.13. Synthesis of 3,3'-diselanediylbis(1-(benzyloxy)propan-2-ol) **7a**

A solution of benzyl glycidyl ether (0.5 mmol, 1.0 eq.) and bis(trimethylsilyl)selenide (HMDSS) (0.8 mmol, 1.6 eq.) in dry THF (3 mL), was treated under inert atmosphere with TBAF (0.32 mL of a 1M THF solution, 0.32 mmol). After stirring for 4 h, the solution was diluted with diethyl ether, washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum and the crude material was purified on silica gel (petroleum ether/ethyl acetate 2:1) to yield diselenide **7a** (104 mg, 85%). Spectroscopic data matched those previously reported. [49]

4.1.14. General procedure for the synthesis of β-phenyltelluro alcohols **8**

A solution of epoxide (1 mmol, 1.0 eq.) and phenylseleno(trimethylsilane ($PhSeSiMe_3$) (1.2 mmol, 1.2 eq.) in dry THF (3 mL), was treated under inert atmosphere (N_2) with TBAF (0.24 mL of 1M THF solution, 0.24 mmol). After stirring for 4 h, the solution was diluted with diethyl ether, washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified on silica gel to yield β-phenylseleno alcohols **8a,b**. Spectroscopic data of compounds **8a** [59] and **8b** [47,60] matched those previously reported in the literature.

4.1.15. Synthesis of 1-(phenylselanyl)propan-2-ol **8a**

Following the general procedure, phenylseleno(trimethylsilane) (110 mg, 0.48 mmol) and 2-methyloxirane (23 mg, 0.4 mmol) gave after flash chromatography (petroleum ether/EtOAc 3:1) **8a** (81 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* (ppm): 1.29 (3H, d, *J* = 6.2 Hz), 2.59 (1H, bs, OH), 2.91 (1H, dd, *J* = 8.2, 12.7 Hz, C**H$_a$**H$_b$Te), 3.14 (1H, dd, *J* = 4.1, 12.7 Hz, CH$_a$**H$_b$**Te), 3.85-3.92 (1H, m, C**H**OH), 7.27-7.31 (3H, m), 7.53-7.57 (2H, m). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* (ppm): 23.0, 39.0, 66.7, 127.9, 129.8, 130.0, 133.6.

4.2 Biological tests

4.2.1 Cell cultures

Neonatal Human Dermal Fibroblasts are a primary cell line derived from neonatal human dermal tissue (NHDFs Clonetics, Lonza). They were maintained in Dulbecco's modified Eagle's medium (DMEM, Lonza) supplemented with 10% FBS (Gibco, NY), 100 units/mL of penicillin G, 0.1 mg/ml streptomycin and 2mM glutamine (PAN-Biotech GmbH, Germany), at 37 °C in a humidified incubator containing 5% CO_2.

4.2.2 MTS test

For viability assay, NHDFs cells were seeded into 96-well plates (3000 cells per well) and grown for 72 h in the presence of the different chalcogen compounds at three different dilutions prepared from 10 mM stock solutions in DMSO: 1, 10 and 100 μM. Each experimental point was assayed in triplicate. Control cultures were treated with 1% DMSO: the obtained values were not different from those obtained in DMEM only. The Cell Titer 96 Non-Radioactive Cell Proliferation Assay Kit (Promega) was used. The assay is based on the bioreduction of MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium: inner salt] into formazan by NADH and NADPH produced by dehydrogenase enzymes only in active and viable cells. The reagent was added to each well and 96-well plates were incubated at 37 °C in humidified 5% CO2 atmosphere until color development had occurred (1–2 h). The formation of a purple formazan product was then measured spectrophotometrically at 490 nm. The measured absorbance value is a function of the amount of formazan produced and is proportional to the number of viable cells. Two independent experiments were performed and data are expressed as the percentage of live cells as a function of the concentration of the compound; on the basis of the toxicity of the compound in study, sigmoid curves are obtained on which the IC_{50} values are calculated.

4.2.3 DCF spectrofluorimetric test

DCFH-DA (2',7'-dichlorofluorescein diacetate) is the most used probe for the detection of intracellular oxidative stress. It is a non-fluorescent dihydro-derivative of fluorescein which is able to freely cross cell membranes, and is deacetylated in the intracellular environment to 2',7'-dichlorodihydrofluorescein (DCFH), still non-fluorescent, which however is not able to cross cell membranes and in the presence of intracellular reactive oxygen species (ROS) it is oxidized to the fluorescent compound 2', 7'-dichlorofluorescein (DCF). Fluorescence was measured in a plate reader (excitation 485 nm/emission 535 nm) [61]. The results were expressed as fluorescence ratios (see below).

Fetal human dermal fibroblasts, NHDFs, were trypsinized, detached and seeded in 96-well black plates ($2.0x10^4$ cell / well respectively) in complete DMEM medium, and exposed to the compounds under study at concentrations in the range 5-50 nM for 48 hours at 37°C in a humidified atmosphere with 5% CO_2. In parallel, a group of 4 wells was used for the measurement of autofluorescence (negative control), and 4 wells for the treatment with 2 mM N-acetylcysteine (NAC), used in the test as a reference antioxidant compound. After this period, the medium was replaced with 200 µL of a 2% serum solution in PBS and 2 µL of a 100x solution of DCFH-DA were added to each well, with the exception of those used for the measurement of autofluorescence, to obtain a final concentration of 20 µM DCFH-DA. The fluorimetric reading was conducted with a VictorTM X3 plate reader (PerkinElmer), set at 37°C, excitation wavelength 485 nm and emission at 535 nm. After reading in basal conditions, a 100x aqueous solution of H_2O_2 was added to each well, to obtain a final concentration of 500 µM. The fluorimetric reading was resumed under the same conditions, performing regular scans of each well, for a total of 25 readings per well, every 30 minutes up to 2 hours after the addition of the pro-oxidant stimulus. As regards the measurement of oxidative stress as a function of time under basal conditions and after exposure to H_2O_2, fluorescence ratios between the average fluorescence intensity of the cells stained with DCHF-DA and the average fluorescence intensity of the unstained cells representing the negative control or autofluorescence were reported. Graphs of the obtained values were obtained by means of GraphPad Prism 5 program, in the form of frequency histograms as a function of the time of exposure to the oxidizing agent

Statistical analysis

All calculations were performed with the Excel program and the average ± standard error is shown in the graph. The statistical analysis was performed by applying the Student *t* test followed by the analysis of variance with Bonferroni for the comparison of the samples with each other. A value of $p < 0.05$ was considered significant.

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