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Synthesis, Antioxidant Activity and Cytotoxicity of *N*-Functionalized Organotellurides

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ABSTRACT

The use of antioxidants is the most effective means to protect the organism against cellular damage caused by oxidative stress. In this context, organotellurides have been described as promising antioxidant agents for decades. Herein, a series of *N*-functionalized organotellurium compounds has been tested as antioxidant and presented remarkable activities by three different in vitro chemical assays. They were able to reduce DPPH$^{\cdot}$ radical with IC_{50} values ranging from 5.08 to 19.20 μg mL^{-1}, and some of them also reduced ABTS$^{\cdot+}$ radical and TPTZ-Fe^{3+} complex in ABTS$^{\cdot+}$ and FRAP assays, respectively. Initial structure-activity relationship discloses that the nature of *N*-substituent strongly influenced both activity and cytotoxicity of the studied compounds. Furthermore, radical scavenging activities of *N*-functionalized organotellurides have been compared with those of their selenilated congeners, demonstrating that the presence of tellurium atom has an essential role in antioxidant activity.

1. Introduction

For many years, tellurium was among the few elements in the Periodic Table virtually ignored in biology and medicinal chemistry fields.[1] Tellurium's low abundance (about 0.027 ppm) is an important point to be considered, which could instantiate the scarcity of tellurium species in nature and, consequently, the absence of natural biological functions.[2,3] Furthermore, pharmacological and toxicological properties of tellurium-containing substances still remain uncertain, demonstrating the need for more in-depth studies about these compounds.[4]

Syntheses and applications of organotellurium compounds have steadily increased in the last decades. These substances have shown promising and advantageous alternatives for numerous synthetic approaches, including carbon-carbon bond-forming reactions and a variety of functional group interconversions.[5–7] Additionally, organotellurium compounds have been described as promising pharmacological agents that possess anti-cancer, anti-inflammatory, antibacterial, antifungal, antiprotozoal and antioxidant activities.[8–13]Among these, the antioxidant potential is, certainly, the best studied pharmacological property.[14–17]

Organotellurium compounds are very attractive as antioxidant agents due to their ability of readily oxidizing from the divalent to tetravalent state, which often makes tellurides excellent scavengers for reactive oxygen or nitrogen species.[18] Antioxidants can protect the organism against cellular damage caused by oxidative stress, avoiding or retarding the progress of many chronic diseases as well as lipid peroxidation.[19] Moreover, among the methods employed to prevent the oxidative damage, the use of antioxidants is the most effective and convenient means, clearly justifying the efforts to find new substances with high antioxidant performances.

In this context, this work describes in vitro antioxidant activity and cytotoxicity of *N*-functionalized tellurides. The combination of nitrogenated organic functions (amines, oximes and hydrazones) with alkyl-aryl tellurides moieties afforded a new class of prominent antioxidants, which performances were strongly influenced by the nature of *N*-substituent.

2. Results and discussion

2.1. Synthesis of organotellurium compounds

A series of *N*-substituted organotellurides was designed in order to investigate some preliminary structure-activity relationships: a) substitution pattern on aromatic ring (meta or para); b) nitrogenated

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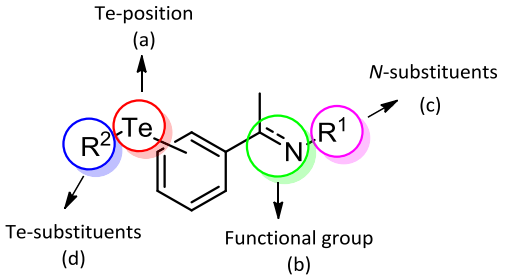


Fig. 1. Structural design of organotellurides for structure-activity insights.

functional group (primary and secondary amines, oximes and hydrazones); c) the nature of *N*-substituents; d) the nature of Te-substituents (Fig. 1).

N-Functionalized alkyl-aryl tellurides **LQ9-12**, **LQ26-29**, **LQ37** and **LQ47** and some selenium-containing analogues (**LQ17**, **LQ18** and **LQ20**) were synthesized as showed in Scheme 1.

The key starting materials arylchalcogen ketones (Y = Te, Se) were previously synthesized according to literature (See Supporting Information for details).[20,21] Primary and secondary Te/Se-amines (**LQ9-10**, **LQ17-18**, **LQ20** and **LQ26-29**) were conveniently prepared through microwave-assisted synthesis, in just 5 min and yields up to 89%.[17] Te-oximes **LQ10-11**, **LQ47** and Te-hydrazone **LQ37** were prepared in 63%–82% yields after 4 h, by refluxing an alcoholic solution of corresponding carbonyl compound with hydroxylamine hydrochloride or hydrazine dihydrochloride (Scheme 1). Whereas chalcogen amines **LQ9-10**, **LQ17-18**, **LQ20** and **LQ26-29** and oximes **LQ10-11** were obtained as bad smelling yellow liquids, telluro-hydrazone **LQ37** was obtained as an odorless yellow powder. Spectroscopic data (^{1}H, ^{13}C and ^{125}Te NMR, FTIR and GC–MS) of all synthesized compounds are available in Supporting Information.

2.2. Antioxidant activity

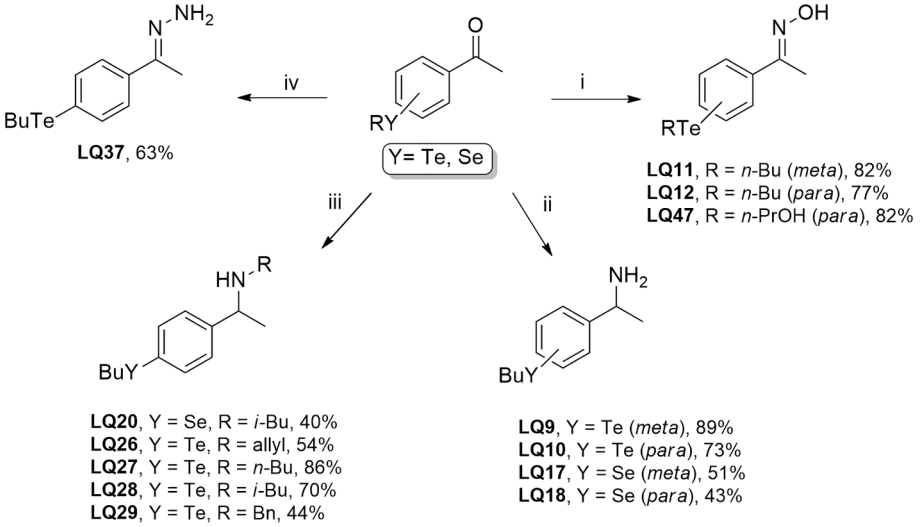
In vitro antioxidant activity of organotellurated substances **LQ9-12**, **LQ26-29**, **LQ37** and **LQ47** were preliminarily studied by the DPPH$^{\cdot}$ (2,2-diphenyl-1-picryl-hydrazyl radical) scavenging assay (Table 1). This method is based on an electron transfer reaction and hydrogen atom abstraction, reflecting the capacity of tested substance to reduce DPPH$^{\cdot}$ to corresponding $DPPH_2$. The results were expressed in concentration of antioxidant required to scavenge 50% of DPPH$^{\cdot}$ radical (IC_{50}, Table 1). Quercetin was used as standard antioxidant.[22,23]

Table 1
Antioxidant activity of *N*-functionalized organotellurides by DPPH$^{\cdot}$ scavenging assay.

Entry	Substance	IC_{50} ± SD (μg mL^{-1})
1	**LQ9**	19.22 ± 2.17
2	**LQ10**	12.07 ± 1.68
3	**LQ11**	5.12 ± 0.71
4	**LQ12**	7.79 ± 0.33
5	**LQ26**	> 100
6	**LQ27**	8.63 ± 0.06
7	**LQ28**	12.49 ± 0.17
8	**LQ29**	11.41 ± 0.09
9	**LQ37**	5.08 ± 0.87
10	**LQ47**	13.06 ± 1.84
11	Quercetin	2.54 ± 0.05

The majority of screened organotellurium compounds exhibited high antioxidant activity, presenting exciting results as radical scavengers (Table 1). The most active substances were tellurium-containing oximes **LQ11** and **LQ12** (Table 1, entries 3 and 4, respectively) and hydrazone **LQ37** (Table 1, entry 9), with relatively close performance to standard quercetin (Table 1, entry 11). Primary telluro-amines **LQ9** and **LQ10**, although less active than oximes, also exhibit prominent antioxidant performances (Table 1, entries 1 and 2, respectively). It was not possible to establish a direct relationship between tellurium atom position on aromatic ring – *meta* or *para* – and nitrogenated functional group – primary amine or oxime – since *p*-Te-substituted amine (**LQ10**) and *m*-Te-substituted oxime (**LQ12**) were the most active substances in each class.

p-Substituted primary amine **LQ10** presented remarkable antioxidant activity, thus encouraging the investigation of the influence of *N*-substitution using alkyl groups with varying bulk and flexibility. For this purpose, secondary telluro-amines **LQ26-29** were conveniently achieved through microwave-assisted synthesis.[17] Surprisingly, branched aliphatic chain (*i*-butyl) or benzyl group in *N*-position (**LQ28** and **LQ29**, Table 1, entries 7 and 8, respectively) did not result in any activity improvements when compared to the unsubstituted co-partner **LQ10** (Table 1, entry 2). In fact, the insertion of *N*-allyl group in **LQ26** led to total loss of activity (IC_{50} > 100 μg mL^{-1}, Table 1, entry 5). On the other hand, *N*-substitution with a straight aliphatic chain (*n*-butyl) furnished **LQ27**, a telluro-amine endowed with high antioxidant activity (Table 1, entry 6). Based on these findings, it is possible to reason that the nature of *N*-substituent strongly influenced the antioxidant



Scheme 1. Reagents and conditions: i. $NH_2OH{\cdot}HCl$, $NaOH/H_2O$, EtOH, reflux, N_2, 3 h; ii. $AcONH_4$, $NaBH_3CN$, EtOH, microwaves, 80 °C, 5 min. iii. RNH_2, $NaBH_3CN$, AcOH, EtOH, microwaves, 80 °C, 5 min. iv. $NH_2NH_2.2HCl$, $AcONa/H_2O$, EtOH, 4 h.

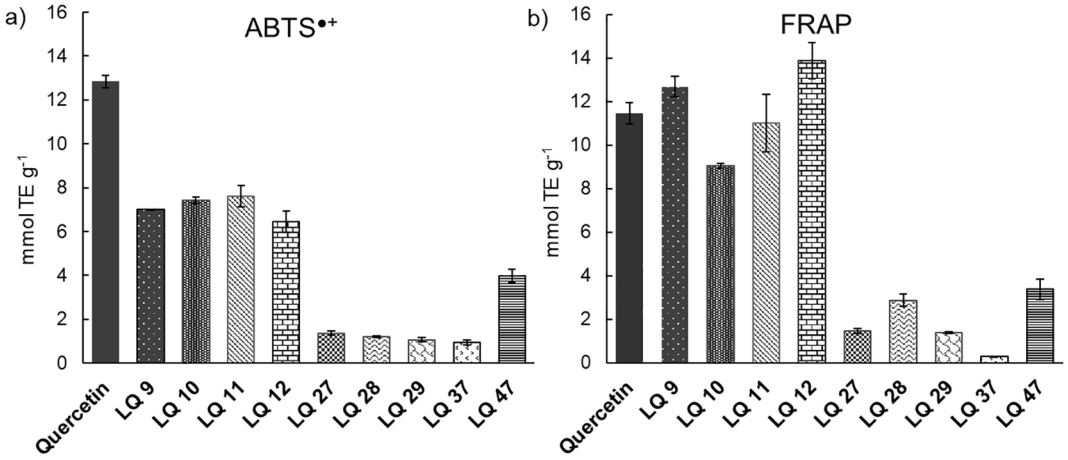


Fig. 2. Antioxidant activity of N-functionalized organotellurides by ABTS$^{\cdot+}$ and FRAP assays. Results are expressed in trolox equivalent antioxidant capacity (TEAC).

profile of the studied compounds.

Despite the highly satisfactory results obtained in DPPH$^{\cdot}$ assay, organotellurium compounds were also investigated about their radical scavenging activity according to ABTS$^{\cdot+}$ (2,2-azinobis-3-ethylbenzothiazoline-6-sulfonic acid, Fig. 2a) and FRAP (ferric reducing antioxidant power) assays (Fig. 2b).

The most active substances were primary Te-amines **LQ9-10** and Te-oximes **LQ11-12**, with activities similar to quercetin (Fig. 2). The insertion of substituents at *N*-position led to a strong decrease of activity in both ABTS$^{\cdot+}$ and FRAP assays, as it was clearly observed for substances **LQ27-29**.

p-Substituted Te-oxime **LQ12** exhibited remarkable reducing antioxidant capacity in FRAP assay, with better performance than quercetin (Fig. 2b). The replacement of Te-substituent (*n*-Bu with *n*-PrOH group) led to a decrease in antioxidant power, evidenced by profile of the congener oxime **LQ47**.

In general, TEAC values of screened substances in FRAP assay (Fig. 2b) were higher than those obtained by ABTS$^{\cdot+}$ assay (Fig. 2a). Thus, it could be estimated that the mechanism of antioxidant activity of these organotellurium compounds is probably based on hydrogen-transfer, since reactions in FRAP assay generally involve donation of a hydrogen atom, whereas the reactions with ABTS$^{\cdot+}$ involve an electron transfer process.[24] Furthermore, these results are in agreement with the high performance observed in DPPH$^{\cdot}$ assay, which mechanism also involve a hydrogen radical transfer. However, additional studies are needed to elucidate the detailed mechanism of action of these substances.

In order to verify the influence of chalcogen atom in biological activity, the antioxidant properties of some selenium-containing analogues (**LQ17**, **LQ18** and **LQ20**, Scheme 1) were evaluated by DPPH$^{\cdot}$ scavenging assay (data not shown). Curiously, no activity was observed for selenium-containing analogues under our assay's conditions. Whereas Te-substituted compounds presented high antioxidant potential, the selenium analogues had no significant activity (IC_{50} > 100 μg mL^{-1}). As reported for other classes of chalcogen-containing compounds,[25,26] the replacement of tellurium with selenium led to a dramatic decrease in antioxidant activity. These outcomes indicated that antioxidant activity is remarkably influenced by the presence of tellurium atom on the chemical structure.

Considering potential therapeutic applications, additional studies about toxicity were necessary. Thus, having confirmed the great antioxidant potential of the studied organotellurium compounds, these substances were tested for cytotoxicity on L929 normal fibroblast cell lines (Fig. 3).

For Te-amines and oximes **LQ9-12**, weak cytotoxic effects were observed only at the lowest concentration tested (1.9 μg mL^{-1}, Fig. 3). The cell viability drastically decreased after treatment with higher concentrations (3.9 μg mL^{-1}, 7.8 μg mL^{-1} and 15.6 μg mL^{-1}, Fig. 3), indicating that, despite the great antioxidant potential, organotellurated substances **LQ9-12** displayed strong cytotoxic effects leading to cellular damage.

Unlike observed in antioxidant activity evaluation, the *N*-substitution pattern had a positive effect in cytotoxicity assays, being secondary Te-amines **LQ27-29** less cytotoxic at higher concentrations than unsubstituted co-partner **LQ10** (Fig. 3).

The nature of Te-substituents also influenced the cytotoxicity of synthesized substances. Unlike Te-oxime **LQ12** (R = *p*-TeBu) that displayed accentuated toxicity, the congener **LQ47** (R = *p*-TePrOH) showed weak cell damage effects in all tested concentrations (Fig. 3).

The least cytotoxic substance was Te-hydrazone **LQ37**, with low cytotoxicity on fibroblasts cell lines in all concentrations (Fig. 3). Since **LQ37** has presented high antioxidant activity in DPPH$^{\cdot}$ assay (IC_{50} = 5.08 ± 0.87 μg mL^{-1}), these findings indicate that this substance is a promising antioxidant agent for further biological studies.

3. Conclusions

In summary, a series of *N*-functionalized organotellurides has been synthesized and evaluated as novel antioxidants. The results showed that the nature of nitrogenated organic functions, as well as the kind of the tellurium moiety, are important factors that influenced both antioxidant activity and cytotoxicity of studied compounds. Furthermore, the selenium-containing analogues showed no significant activity, proving that the presence of tellurium atom is essential to the antioxidant character.

Although all screened substances had displayed remarkable in vitro activities, most of them presented accentuated toxicity on L929 fibroblasts cell lines. Nevertheless, the combination of hydrazone organic function with butyltellurium moiety provided the substance **LQ37**, which presented high activity and low cytotoxicity. These results indicate that this organotelluride is a promising antioxidant agent for further pharmacological studies and provides useful criteria for design of good synthetic tellurium-containing antioxidants. Furthermore, this work can contribute with cytotoxicity data for organotellurium compounds as antioxidant agents, as this is not an usual analysis available in the current literature.

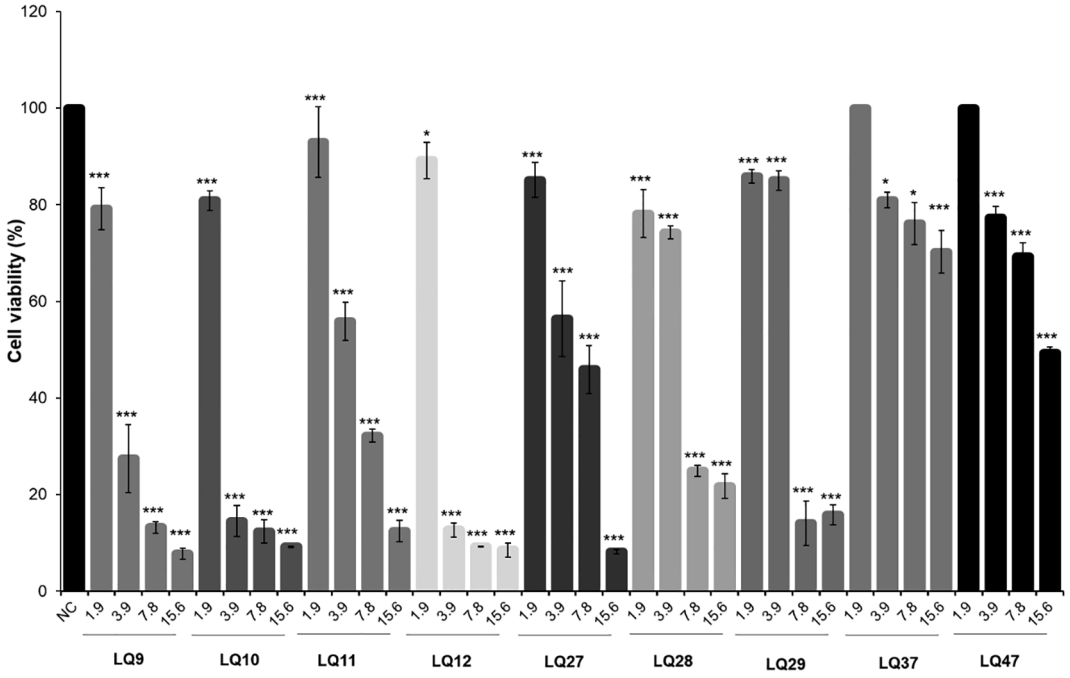


Fig. 3. Mean values of cell viability obtained on L929 fibroblast cell lines after 24 h of treatment with different concentrations of organotellurium compounds by neutral red assay. NC: negative control. Results are expressed as mean ± S.E.M. for three independent experiments. $^{*}(p < 0.05)$ and $^{***}(p < 0.001)$ indicate significant difference from NC according to the Tukey's test.

4. Experimental section

4.1. Chemical

*General procedure for synthesis of telluroamines **LQ9-10** and **LQ26-29***[17]

To a microwave reactor flask equipped with magnetic stirring bar, the appropriate amine source (6 equiv.), AcOH (15 equiv.), $NaBH_3CN$ (1.2 equiv.) were added to a solution of chalcogen-acetophenone of interest (100 mg) in ethanol (1 mL). The reaction medium was assisted by microwave irradiation at 80° C for 5 min. Then, the solvent was removed under reduced pressure, the crude residue dissolved in distilled water (5 mL) and the pH adjusted to 10 with NaOH (1 mol L^{-1}). The product was extracted with dichloromethane (3 × 10 mL), the combined organic layers dried over with anhydrous $MgSO_4$ and concentrated under reduced pressure. The products were purified via chromatographic column using ethyl acetate:ethanol (9:1) as solvent system.

*1-(3-(Butyltellanyl)phenyl)ethanamine **(LQ9)***. Pale yellow oil. Yield: 89%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.93 (t, J = 7.4 Hz, 3H), 1.25–1.53 (m, 2H), 1.40 (d, J = 6.5 Hz, 3H), 1.72–1.90 (m, 2H), 2.95 (t, J = 7.5 Hz, 2H), 4.08 (q, J = 6.5 Hz, 1H), 7.08–7.26 (m, 2H), 7.56 (d, J = 7.3 Hz, 1H), 7.68 (s, 1H), 9.50 (sl, N$\underline{H}_2$). ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 8.4, 13.4, 25.0, 25.5, 33.9, 51.1, 112.1, 124.9, 129.1, 136.5, 148.4.

*1-(4-(Butyltellanyl)phenyl)ethanamine **(LQ10)***. Pale orange oil. Yield: 73%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.90 (t, J = 7.3 Hz, 3H), 1.23–1.49 (m, 3H), 1.36 (d, J = 6.6 Hz, 3H), 1.67 (sl, N$\underline{H}_2$), 1.77 (m, 3H), 2.88 (t, J = 7.8 Hz, 2H), 4.08 (q, J = 6.6 Hz, 1H), 7.15–7.19 (dd, J_A = 8.2 Hz and J_B = 1.9 Hz, 2H), 7.65–7.69 (dd, J_A = 8.2 Hz e J_B = 1.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 8.4, 13.4, 25.0, 25.6, 33.9, 51.0, 109.5, 126.6, 128.5, 147.2. FTIR (cm^{-1}): 3343, 3280, 2963, 2915, 2874, 1569, 1481, 1003, 817. GC–MS (70 eV), *m/z* (relative abudance): 307 (M^+, 84), 292 (82), 249 (8), 235 (63), 206 (2), 120 (51), 104 (100), 91 (14), 77 (44), 65 (4), 44 (78), 41 (39).

*N-(1-(4-(Butyltellanyl)phenyl)ethyl)prop-2-en-1-amine **(LQ26)***. Yellow oil. Yield: 54%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.89 (t, J = 7.2 Hz, 3H), 1.35 (d, J = 6.6 Hz, 3H), 1.25–1.48 (m, 1H), 1.78 (quint, J = 7.7 Hz, 3H), 2.90 (t, J = 7.7 Hz, 2H), 3.09 (d, J = 6.0 Hz, 2H), 3.78 (q, J = 6.6 Hz, 1H), 5.05–5.16 (m, 2H), 5.78–5.98 (m, 1H), 7.13–7.17 (dd, J_A = 8.2 Hz and J_B = 2.0 Hz, 2H), 7.64–7.68 (dd, J_A = 8.2 Hz e J_B = 2.0 Hz, 2H), 7.70 (sl, N$\underline{H}$). ^{13}C NMR (50 MHz, $CDCl_3$): 8.4, 13.4, 24.1, 25.0, 33.9, 50.1, 57.2, 116.0, 127.6, 128.5, 136.6, 138.4, 144.8. FTIR (cm^{-1}): 3391, 3074, 2936, 2798, 1638, 1176, 989, 929. GC–MS (70 eV), *m/z* (relative abundance): 347 (M^+, 26), 330 (100), 289 (11), 275 (86), 271 (58), 232 (22), 205 (6), 146 (60), 117 (34), 104 (90), 77 (36), 56 (20), 51 (10).

*N-(1-(4-(Butyltellanyl)phenyl)ethyl)butan-1-amine **(LQ27)***. Pale orange oil. Yield: 70%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS), δ (ppm): 0.91 (m, 6H), 1.35 (d, J = 6.6 Hz, 3H), 1.41 (m, 6H), 1.81 (quint, J = 7.6 Hz, 2H), 2.47 (m, 2H), 2.92 (t, J = 7.5 Hz, 2H), 3.74 (q, J = 6.6 Hz, 1H), 7.17 (dd, J_A = 8.1 Hz and J_B = 1.7 Hz, 2H), 7.69 (dd, J_A = 8.1 Hz and J_B = 1.7 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 8.4, 13.4, 14.0, 20.5, 24.3, 25.0, 32.4, 33.9, 47.6, 58.1, 109.5, 127.5, 138.4, 145.5. FTIR (cm^{-1}): 3315, 3191, 2950, 2929, 2860, 1466, 1121, 1003, 817. GC–MS (70 eV), *m/z* (relative abundance): 363 (M^+, 21), 348 (96), 291 (100), 243 (13), 162 (7), 104 (42), 78 (10), 57 (8), 41 (8).

*N-(1-(4-(Butyltellanyl)phenyl)ethyl)-2-methylpropan-1-amine **(LQ28)***. Pale yellow oil. Yield: 86%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.88 (d, J = 6.6 Hz, 6H), 0.89 (t, J = 7.2 Hz, 3H), 1.37 (m, 2H), 1.44 (d, J = 6.7 Hz, 3H), 1.78 (quint, J = 7.5 Hz, 3H), 2.32 (m, 2H), 2.90 (t, J = 7.5 Hz, 2H), 3.84 (q, J = 6.7 Hz, 1H), 4.85 (sl, N$\underline{H}$), 7.20 (dd, J_A = 8.1 Hz and J_B = 1.6 Hz, 2H), 7.67 (dd, J_A = 8.1 Hz and J_B = 1.6 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 8.4, 13.4, 20.5, 20.7, 23.1, 25.0, 27.7, 33.9, 55.1, 58.5, 110.8, 127.8, 138.3, 142.5. FTIR (cm^{-1}): 3315, 2963, 2915, 2874, 1459, 1121, 1010, 824. GC–MS (70 eV), *m/z* (relative abundance): 363 (M^+, 12), 346 (28), 291 (100), 234 (18), 207 (7), 105 (81), 78 (22), 41 (21).

N-Benzyl-1-(4-(butyltellanyl)phenyl)ethanamine ***(LQ29)***. Pale orange oil. Yield: 44%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.89 (t, J = 7.2 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H), 1.37–1.48 (m, 2H), 1.61 (sl, NH), 1.79 (quint, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 3.61 (d, J = 4.8 Hz, 2H), 3.77 (q, J = 6.6 Hz, 1H), 7.06–7.22 (dd, J_A = 8.1 Hz and J_B = 1.9 Hz, 2H), 7.24–7.40 (m, 5H), 7.58–7.78 (dd, J_A = 8.1 Hz and J_B = 1.9 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 8.4, 13.4, 24.4, 25.0, 33.9, 51.6, 57.2, 109.7, 126.9, 127.6, 128.1, 128.3, 138.4, 140.5, 145.1. FTIR (cm^{-1}): 3032, 2963, 2922, 2839, 1622, 1452, 996, 707. GC–MS (70 eV), *m/z* (relative abundance): 397 (M^+, 21), 382 (40), 325 (13), 291 (3), 234 (2), 196 (5), 104 (11), 91 (100), 65 (5), 41 (3).

General procedure for synthesis of telluro-oximes ***LQ11-12, LQ47*** *and telluro-hydrazone* ***LQ37***

In a round-bottom flask equipped with magnetic stirring bar and reflux condenser were added the telluro-acetophenone of interest (0.4 mmol, 113 mg) and ethanol (1 mL). Then, for the synthesis of oximes, hydroxylamine hydrochloride (1.2 mmol, 83 mg) and sodium hydroxide (8.2 mmol, 325 mg) dissolved in distilled water (0.2 mL) were subsequently added. For the synthesis of tellurohydrazone, hydrazine dihydrochloride (1.2 mmol, 126 mg) and sodium acetate (8.2 mmol, 627 mg) dissolved in distilled water (0.4 mL) were employed. The reaction was maintained under reflux and inert atmosphere until total consumption of the starting material (ca. 2 h). The solvent was removed under reduced pressure, the crude mixture dissolved in distilled water (10 mL), extracted with dichloromethane (3 × 5 mL), washed with saturated NaCl solution (5 mL), dried over with anhydrous $MgSO_4$ and concentrated.

(E)-1-(3-(Butyltellanyl)phenyl)ethanone oxime ***(LQ11)***. Pale yellow oil. Yield: 82%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.89 (t, J = 7.2 Hz, 3H), 1.40 (sext, J = 7.3 Hz, 2H), 1.79 (quint, J = 7.6 Hz, 2H), 2.28 (s, 3H), 2.93 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.95 (s, 1H), 9.24 (sl, NOH). ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 8.7, 12.3, 13.4, 25.0, 33.9, 112.1, 125.2, 129.0, 135.6, 137.3, 138.8, 155.5.

(E)-1-(4-(Butyltellanyl)phenyl)ethanone oxime ***(LQ12)***. Orange oil. Yield: 77%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.90 (t, J = 7.4 Hz, 3H), 1.39 (sext, J = 7.7 Hz, 2H), 1.79 (quint, J = 7.6 Hz, 2H), 2.27 (s, 3H), 2.92 (t, J = 7.6 Hz, 2H), 7.43 (dd, J_A = 8.3 Hz and J_B = 1.7 Hz, 2H), 7.69 (dd, J_A = 8.3 Hz and J_B = 1.7 Hz, 2H), 9.50 (sl, NOH). ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 8.6, 12.2, 13.4, 25.0, 33.8, 113.7, 126.5, 128.5, 137.7, 155.6. FTIR (cm^{-1}): 3275, 3059, 2957, 2870, 1582, 1464, 1404, 1366, 1292, 1246, 1181, 1163, 995, 926, 787, 692, 646, 496. GC–MS (70 eV), *m/z* (relative abundance): 321 (M^+, 39), 305 (25), 301 (15), 265 (21), 247 (47), 233 (6), 206 (10), 175 (3), 146 (8), 130 (5), 118 (100), 104 (36), 91 (15), 77 (68), 57 (30), 41 (38).

(E)-1-(4-((3-Hydroxypropyl)tellanyl)phenyl)ethanone oxime ***(LQ47)***. Yellow solid. Yield: 82%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 2.04–2.08 (m, 2H), 2.26 (s, 3H), 2.98 (t, J = 7.6 Hz, 2H), 3.70 (t, J = 6.1 Hz, 2H), 7.44–7.45 (dd, J_A = 1.8 Hz and J_B = 8.3 Hz, 2H), 7.70–7.72 (dd, J_A = 1.8 Hz and J_B = 8.3 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 4.3, 11.9, 34.2, 63.9, 113.4, 126.6, 135.8, 138.0, 155.7.

(E)-(1-(4-(Butyltellanyl)phenyl)ethylidene)hydrazine ***(LQ37)***. Yellow solid. Yield: 63%. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 0.91 (t, J = 7.2 Hz, 3H), 1.41 (sext, J = 7.4 Hz, 2H), 1.81 (quint, J = 7.4 Hz, 2H), 2.29 (s, 3H), 2.94 (t, J = 7.8 Hz, 2H), 7.73 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$), δ (ppm): 8.6, 13.4, 14.8, 25.1, 33.9, 114.6, 127.1, 137.4, 137.6, 157.7. FTIR (cm^{-1}): 3047, 2957, 2924, 2870, 2854, 1601, 1583, 1489, 1391, 1360, 1192, 1167, 1080, 1005, 820, 593.

4.2. Antioxidant activity assays

The antioxidant activities of organotellurium compounds **LQ9-12**, **LQ26-29**, **LQ37** and **LQ47** (Scheme 1) were evaluated by the following in vitro chemical assays: radical scavenging activity (DPPH$^{\cdot}$ and ABTS$^{\cdot+}$) and FRAP. The standard antioxidant quercetin was used as reference.

DPPH$^{\cdot}$ assay

The methanolic solution of DPPH$^{\cdot}$ (100 µL, 130 µmol L^{-1}) were added to the methanolic solution of samples (100 µL) at different concentrations. After 30 min at room temperature, protected from the light, the absorbance was measured in a microplate spectrophotometer (Bio Tek, PowerWave XS microplate spectrophotometer) at 517 nm. The percentage of inhibition of DPPH$^{\cdot}$ was calculated using the following equation:

$$\text{DPPH·scavenging ability}(\%) = \frac{\text{Abs}_{nc} - \text{Abs}_{s}}{\text{Abs}_{nc}} \times 100$$

Abs_{nc} is the absorbance of the negative control (100 µL of methanol mixed in 100 µL of DPPH$^{\cdot}$ and maintained under the same conditions as samples) at 517 nm and Abs_s is the absorbance of the samples at 517 nm. IC_{50} values were estimated by linear regression.[27] The assays were performed in triplicate.

ABTS$^{\cdot+}$ assay

The ABTS$^{\cdot+}$ was generated with ABTS (5 mL, 7 mmol L^{-1}) and potassium persulfate (0.88 mL, 140 mmol L^{-1}) solutions. After 16 h, at room temperature and protected from the light, the ABTS$^{\cdot+}$ solution was dissolved in ethanol until obtained the absorbance of 0.70 ± 0.05 at 734 nm. Then, the sample solution (7 µL) in different concentrations was added to ABTS$^{\cdot+}$ solution (200 µL). After 6 min, the absorbance was measured in a microplate spectrophotometer (Bio Tek, PowerWave XS microplate spectrophotometer) at 734 nm. Ethanol solutions of Trolox (20–600 µmol L^{-1}) were used for the calibration curve and the results were expressed as mmol TE g^{-1}. All assays were performed in triplicate.[28]

Ferric reducing antioxidant power (FRAP)

FRAP reagent solution was prepared by mixing 0.3 mM sodium acetate buffer pH 3.6, 20 mM $FeCl_3$ and 10 mM tripyridyltriazine 10:1:1 (v/v/v). An aliquot of 30 µL of different samples concentrations was added to 180 µL of FRAP reagent. The mixture was incubated at 37 °C for 40 min protected from light. The absorbance of the resulting solutions was measured at 593 nm in a microplate spectrophotometer (Bio Tek, PowerWave XS microplate spectrophotometer). Ethanol trolox solutions (100–1000 µmol L^{-1}) were used for the calibration curve and the results were expressed as mmol TE g^{-1}. All assays were performed in triplicate.[29]

4.3. Cytotoxicity assay

The cytotoxicity of *N*-functionalized organotellurium compounds on L929 cell lines (NCTC clone 929 [L cell, L929, derivative of Strain L] (ATCC® CCL1™, Manassas, USA) was evaluated by neutral red assay.[24] L929 cell lines were maintained and cultured in Dulbecco's modified Eagle's medium (DMEM, Life Technologies/Gibco Laboratories, Grand Island, NY, USA) supplemented with 2 mM L-glutamine, 10% fetal bovine serum (FBS, Life Technologies/Gibco Laboratories, Grand Island, NY, USA), penicillin (50 U/mL) and streptomycin (50 µg/mL) at 37 °C in a 5% CO_2 atmosphere.

A suspension of L929 fibroblasts (2.5 × 10^5 cells ml^{-1}) was plated on 96-well sterile microplates and maintained at 37 °C in a 5% CO_2 atmosphere. After 24 h, the cells were treated with different samples concentrations (1.95–15.625 µg mL^{-1}) for 24 h, under the same conditions previously mentioned. After the treatment, the plate was

washed twice with phosphate buffered saline (PBS, 100 µL), and neutral red (Interlab, São Paulo, Br) in DMEM (200 µL, 40 µg mL^{-1}) was added. After 3 h, the plate was washed with fixative solution (200 µL, 1% calcium chloride and 2% formaldehyde in PBS). Then, the supernatant was discarded and 200 µL of a solution of 50% ethanol and 1% acetic acid were added. Absorbance was measured after 15 min at 540 nm on a microplate spectrophotometer (Bio Tek, PowerWave XS microplate spectrophotometer). The samples were aseptically dissolved in DMSO and diluted in DMEM, with a final maximum DMSO concentration of 1.5%. The percentage of viable cells was calculated in relation to the negative control.[30]

4.4. Statistical analysis

The statistical differences between samples was evaluated by one-way analysis of variance (ANOVA) followed by the Tukey test using Prism 5.0 Software. Values of $p < 0.5$ were considered statistically significant.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmc.2018.12.017.

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