

## SYNTHESIS OF GERANYLHYDROQUINONES DERIVATIVES WITH POTENCIAL CYTOTOXIC ACTIVITY

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The natural geranylhydroquinone **1** and geranyl-*p*-methoxyphenol **2** were prepared by an Electrophilic Aromatic Substitution (EAS) reactions between geraniol and 1,4-hydroquinone or *p*-methoxyphenol respectively, using  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as a catalyst. Furthermore, the natural geranylquinone **3**, geranyl-1,4-dimethoxyquinone **4** and the new geranyl-4-methoxyphenyl acetate **5** were obtained by chemical transformations of **1** and **2**. The compounds have been evaluated for their *in vitro* cytotoxicity activities against cultured human cancer cells of PC-3 human prostate cancer, MCF-7 and MDA-MB-231 breast carcinoma and Dermal Human Fibroblasts DHF.  $\text{IC}_{50}$  values ranged in the  $\mu\text{M}$  level.

Keywords: synthesis; geranylhydroquinones; cytotoxic activity.

### INTRODUCTION

Polyprenylated 1,4-benzoquinones and hydroquinones such as ubiquinones, plastoquinones, and tocopherols are widespread in plants and animals, in which they play important roles in electron transport, photosynthesis, and as antioxidants.<sup>1</sup> Prenyl benzoquinones have been also isolated from brown algae of the order Fucales,<sup>2</sup> sponges,<sup>3</sup> alcyonaceans,<sup>4</sup> gorgonaceans,<sup>5</sup> and ascidians belonging to the genus *Aplidium*.<sup>6</sup> These substances present a terpenoid portion ranging from one to nine isoprene units. As Brown algae contain diprenyl-, triprenyl-, and tetraprenylquinones and hydroquinones,<sup>2</sup> where as sponges contain prenylated 1,4-benzoquinones and hydroquinones with linear and longer (up to nine isoprene units) terpenoid side chains.<sup>3</sup> Ascidians of the genus *Aplidium* have previously yielded about a dozen prenylated quinones and related compounds.<sup>6</sup> Studies on the relation structure activity (SAR) of a serie of nonmethoxylated prenylated quinones with side chains containing from one to eight isoprene units by using antimicrobial, brine shrimp lethality, and fish lethality assays have demonstrated that the optimum length of the side-chain corresponds to two isoprene units in the terpenoid part.<sup>7</sup> Another study of SAR in the cancer-preventive activity of a group of methoxylated prenylated quinones containing from one to four isoprene units reported that quinones having a side chain of 10 carbon atoms length showed specificity in the inhibitory effect for transformed JB6 P+ Cl41 cells.<sup>8</sup> Due to these antecedents and as continuation of our research we describe in this work the preparation and cytotoxic activity of prenyl benzoquinones and hydroquinones having two isoprene units, named geranylhydroquinones derivatives (**1-5**). Two of these compounds, the natural geranylhydroquinone **1** and geranyl-*p*-methoxyphenol **2** were synthesized using the strategy of Electrophilic Aromatic Substitution (EAS) reactions, according to protocol reported.<sup>9</sup> All the compounds were evaluated *in vitro* against cultured human cancer cells in order to analyse the influence of the molecular structure on the cytotoxic activity.

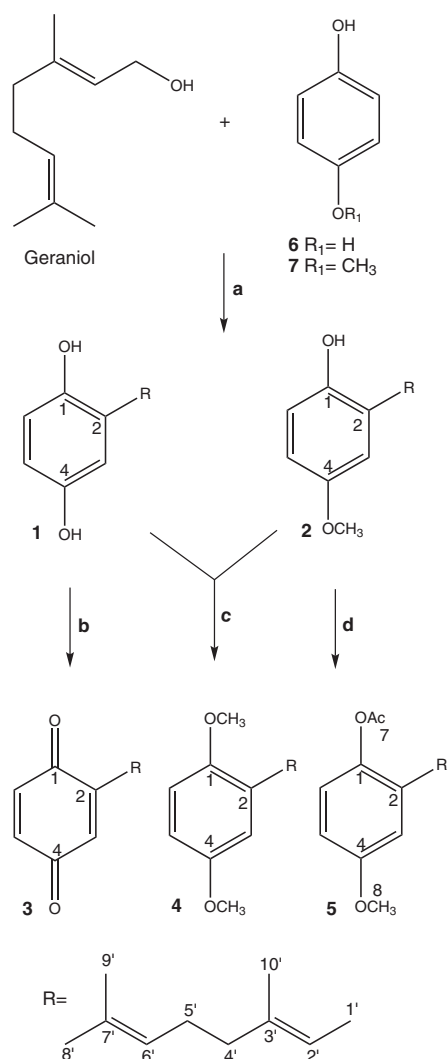
### RESULTS AND DISCUSSION

#### Chemistry

In the coupling reaction for preparation of 2-((E)-3,7-dimethylocta-2,6-dienyl)benzene-1,4-diol (**1**) and 4-methoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)phenol (**2**), the strategy of Electrophilic Aromatic Substitution (EAS) was used, according to previously reported procedure.<sup>9</sup> Chemical transformations of the compounds coupling **1** and **2** are summarized in Scheme 1. The structural determination of all the derivatives was mainly accomplished by IR, HRMS,  $^1\text{H}$ ,  $^{13}\text{C}$ , DEPT-135, gs-2D HSQC and gs-2D HMBC NMR techniques (2D correlation were registered only for some compounds).  $^1\text{H}$ -NMR spectrum of **1** was compared with the spectral data reported for the isolated natural compound.<sup>10</sup> This compound showed the existence of two hydroxyl groups at  $\delta$  4.75 and 4.46 and the presence of three aromatic hydrogens at  $\delta$  6.69 (d,  $J = 8.0$  Hz, 1H, H-6), 6.61 (d,  $J = 3.0$  Hz 1H, H-3), 6.58 (dd,  $J = 3.0$  and 8.0 Hz, 1H, H-5). In addition, the point of coupling was confirmed by the presence of the signal at  $\delta$  3.30 (d,  $J = 7.0$  Hz, 2H, H-1'). While in the  $^{13}\text{C}$ -NMR spectrum the signals at  $\delta$  116.6 (C-3), 113.7 (C-5), of three aromatic carbons and 26.4 ppm (C-1') corroborate the molecular structure.  $^1\text{H}$ -NMR spectrum of geranyl-*p*-methoxyphenol **2** the signals at  $\delta$  3.75 (s, 3H, H-8) of the methoxyl group,  $\delta$  3.33 (d,  $J = 7.0$ , 2H, H-1') of the point of coupling,  $\delta$  4.80 (s, 1H, OH) of the phenol and three aromatic hydrogens at  $\delta$  6.74 (d,  $J = 8.5$  Hz, 1H, H-6), 6.68 (d,  $J = 3.0$  Hz, 1H, H-3), 6.65 (dd,  $J = 8.5$  and 3.0 Hz, 1H, H-5) were mainly observed. In the  $^{13}\text{C}$ -NMR spectrum the presence of the methoxyl group at  $\delta$  55.7 (OCH<sub>3</sub>), the signals of three aromatic carbons at  $\delta$  116.4 (C-6), 115.7 (C-3), 112.1 (C-5), also were confirmed. (here the spectroscopic 2D NMR information of compound **2** were delete). In addition, the configuration of the C2'-C3' double bond was compared with the chemical shifts of C-10' reported for similar compounds.<sup>11</sup>

The 2-((E)-3,7-dimethylocta-2,6-dienyl)cyclohexa-2,5-diene-1,4-dione compound **3** was prepared by oxidation reaction of geranylhydroquinone **1** with  $\text{MnO}_2$ , being an alternative method to the reported.<sup>12</sup> The molecular structure was confirmed for the presence of the signals at  $\delta$  6.75 (d,  $J = 10.0$  Hz, 1H, H-6); 6.70 (dd,  $J = 2.0$  and 10.0 Hz, 1H,

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**Scheme 1.** Synthesis of geranylhydroquinone derivatives: (a) dioxane/ $\text{BF}_3\text{Et}_2\text{O}$ ,  $\text{N}_2$ , r.t.; (b)  $\text{MnO}_2/\text{CH}_2\text{Cl}_2$ , r.t.; (c)  $(\text{CH}_3)_2\text{SO}_4/\text{K}_2\text{CO}_3$ , acetone, r.t.; (d)  $\text{Ac}_2\text{O}/\text{CH}_2\text{Cl}_2/\text{DMAP}$ , r.t.

H-5); 6.52 (dd,  $J = 2.0$  and  $4.0$  Hz, 1H, H-3) of the quinonic hydrogens in the  $^1\text{H}$ -NMR spectrum and the existence of two carbonyl carbons at  $\delta$  187.9 (C-1), 187.6 (C-4) in the  $^{13}\text{C}$ -NMR spectrum.

The preparation of 1,4-dimethoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)benzene compound **4** was carried out by reaction of methylation with  $(\text{CH}_3)_2\text{SO}_4$  in slightly basic conditions of **1** or **2**, like an alternative method to the reported.<sup>13</sup>  $^1\text{H}$ -NMR spectrum showed two singlets at  $\delta$  3.79 and 3.76, the signals corresponding to the methoxyl groups. These signals also were observed in the  $^{13}\text{C}$ -NMR spectrum at  $\delta$  56.1 and 55.6.

To obtain the 4-methoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)phenyl acetate derivative **5**, the geranyl-*p*-methoxyphenol **2** was acetylated with acetic anhydride and dimethylaminopyridine (DMAP) as catalyst. The molecular structure was corroborated for the signals at  $\delta$  2.29 (s, 3H, H-7), 20.8 (C-7) and 169.9 ( $\underline{\text{COCH}_3}$ ) of the acetyl group, in addition for comparison of their spectral data with geranyl-*p*-methoxyphenol **2**.

### Bioactivity

The cytotoxicity of the compounds was evaluated against three different cancer cell lines: PC-3 human prostate cancer, MCF-7 and

MDA-MB-231 breast carcinoma and one non-tumoral cell line, dermal human fibroblasts (DHF) by using *in vitro* analysis. A conventional colorimetric assay was set up to estimate the  $\text{IC}_{50}$  values which represents the concentration of a drug that is required for 50% inhibition *in vitro* after 72 h of continuous exposure to the test compounds. Four serial dilutions (from 12.5 to 100  $\mu\text{M}$ ) for each sample were evaluated in triplicate. The results obtained from these assays are shown in Table 1. The derivatives compounds **2**, **4** and **5** did not affect the bioactivity of the cells lines studied, however the compounds **1** and **3** showed  $\text{IC}_{50}$  values with inhibitory activity, ranged in the  $\mu\text{M}$  level but lower than the positive control (Dunnione), these values may be due to the presence of hydroquinone or quinone moiety. Moreover, compounds **1** and **3** displayed some selectivity for the cancer cells versus fibroblast cells, which could provide an approach to obtain compounds with potential less toxicity in normal human cells.

**Table 1.** Cytotoxicity ( $\text{IC}_{50}$   $\mu\text{M}$ ) of Geranylhydroquinones **1** and derivatives

Compound	PC-3	MCF-7	MDA-MB-231	DHF
1	93,18	86,54	84,23	>100
2	>100	>100	>100	>100
3	89,51	91,08	85,23	>100
4	>100	>100	>100	>100
5	>100	>100	>100	>100
Dunnione	26.51	14.56	22.13	27.03

## EXPERIMENTAL

### General

Unless otherwise stated, all chemical reagents purchased (Merck or Aldrich) were of the highest commercially available purity and were used without previous purification. IR spectra were recorded as thin films in a Nicolet Impact 420 spectrometer and frequencies are reported in  $\text{cm}^{-1}$ . High resolution mass spectra were recorded on a LTQ Orbitrap XL spectrometer by applying a voltage of 1.8 kV in the positive and 1.9 kV in the negative ionization mode. The spectra were recorded using full scan mode, covering a mass range from  $m/z$  100-1300. The resolution was set to 50,000 and the maximum loading time for the ICR cell was set to 250 ms.  $^1\text{H}$ ,  $^{13}\text{C}$ , DEPT-135, sel. 1D  $^1\text{H}$  NOESY, 2D HSQC and 2D HMBC spectra were recorded in  $\text{CDCl}_3$  solutions and are referenced to the residual peaks of  $\text{CHCl}_3$  at  $\delta$  7.26 ppm and  $\delta$  77.0 ppm for  $^1\text{H}$  and  $^{13}\text{C}$ , respectively, on a Bruker Avance 400 digital NMR spectrometer, operating at 400.1 MHz for  $^1\text{H}$  and 100.6 MHz for  $^{13}\text{C}$ . Chemical shifts are reported in  $\delta$  ppm and coupling constants ( $J$ ) are given in Hz. Silica gel (Merck 200-300 mesh) was used for C.C. and silica gel plates HF-254 for TLC. TLC spots were detected by heating after spraying with 25%  $\text{H}_2\text{SO}_4$  in  $\text{H}_2\text{O}$ .

### Chemistry

#### General procedure for the Electrophilic Aromatic Substitution (EAS), synthesis of compounds **1**, **2**

$\text{BF}_3\text{Et}_2\text{O}$  (0.2300 g, 1.6 mmol) was gradually added at room temperature to a solution of 1,4-hydroquinone (0.6012 g, 5.5 mmol) or *p*-methoxyphenol (0.8749 g, 7.06 mmol) and geraniol (0.8 g, 5.5 mmol) in freshly distilled 1,4-dioxane (20 mL). The mixture was stirred at room temperature under a nitrogen atmosphere for 24 h, when the completion of the reaction was verified by TLC. The mixture was poured onto crushed ice (about 30 g) and the organic layer was extracted with EtOAc ( $3 \times 30$  mL). The combined organic phase

was washed with 5% NaHCO<sub>3</sub> (30 mL), then with water (2 × 20 mL) and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated. The crude residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and chromatographed on silica gel with petroleum ether/EtOAc mixtures of increasing polarity (19.8:0.2→13.0:7.0) for **1** and (19.8:0.2→14.4:5.6) for **2**.

#### 2-((E)-3,7-dimethylocta-2,6-dienyl)benzene-1,4-diol (**1**)

Colorless viscous oil, 0.3726 g (28%), <sup>1</sup>H-NMR: 6.69 (d, *J* = 8.0 Hz, 1H, H-6); 6.61 (d, *J* = 3.0 Hz 1H, H-3); 6.58 (dd, *J* = 3.0 and 8.0 Hz, 1H, H-5); 5.29 (t, *J* = 7.0 Hz, 1H, H-2'); 5.07 (t, *J* = 5.0 Hz, 1H, H-6'); 4.75 (s, 1H, OH); 4.46 (s, 1H, OH); 3.30 (d, *J* = 7.0 Hz, 2H, H-1'); 2.09 (m, 4H, H-5' and H-4'); 1.75 (s, 3H, H-10'); 1.69 (s, 3H, H-8'); 1.60 (s, 3H, H-9'). <sup>13</sup>C-NMR: 149.3 (C-1), 148.3 (C-4), 138.6 (C-3'), 132.0 (C-7'), 128.3 (C-2), 123.9 (C-6'), 121.3 (C-2'), 116.6 (C-3), 116.6 (C-6), 113.7 (C-5), 39.7 (C-4'), 29.7 (C-5'), 26.4 (C-1'), 25.7 (C-8'), 17.7 (C-9'), 16.2 (C-10'). IR (cm<sup>-1</sup>): 3385, 2966, 2920, 1654, 1500, 1450, 1193. HRMS: (M + 1) calcd. for C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>: 247.1620, found: 247.1623.

#### 4-methoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)phenol (**2**)

Colorless viscous oil, 0.1444 g (10%), <sup>1</sup>H-NMR: 6.74 (d, *J* = 8.5 Hz, 1H, H-6); 6.68 (d, *J* = 3.0 Hz, 1H, H-3); 6.65 (dd, *J* = 8.5 and 3.0 Hz, 1H, H-5); 5.31 (t, *J* = 7.0 Hz, 1H, H-2'); 5.07 (t, *J* = 6.0 Hz, 1H, H-6'); 4.80 (s, 1H, OH); 3.75 (s, 3H, OCH<sub>3</sub>); 3.33 (d, *J* = 7.0, 2H, H-1'); 2.08 (m, 4H, H-5' and H-4'); 1.76 (s, 3H, H-10'); 1.68 (s, 3H, H-8'); 1.60 (s, 3H, H-9'). <sup>13</sup>C-NMR: 153.7 (C-4), 148.3 (C-1), 138.6 (C-3'), 132.0 (C-7'), 128.1 (C-2), 123.8 (C-6'), 121.4 (C-2'), 116.4 (C-6), 115.7 (C-3), 112.1 (C-5), 55.7 (OCH<sub>3</sub>), 39.7 (C-4'), 29.9 (C-5'), 26.5 (C-1'), 25.6 (C-8'), 17.7 (C-9'), 16.2 (C-10'). IR (cm<sup>-1</sup>): 3418, 2965, 2916, 1609, 1279, 1043. HRMS: (M + 1) calcd. for C<sub>17</sub>H<sub>24</sub>O<sub>2</sub>: 261.1776, found: 261.1779.

### Synthesis of geranylhydroquinones derivatives (**3-5**)

#### 2-((E)-3,7-dimethylocta-2,6-dienyl)cyclohexa-2,5-diene-1,4-dione (**3**)

The geranylhydroquinone **1** (0.1444 g, 0.59 mmol) dissolved in dichloromethane (20 mL), MnO<sub>2</sub> (0.05 g, 0.6 mmol) was added. The mixture was stirred at room temperature during 18 h. After filtration, the solution was evaporated to dryness to afford the crude reaction product, which gave 117.8 mg (82% Yield) of compound **3**, after column chromatography (eluent dichloromethane), colorless viscous oil. <sup>1</sup>H-NMR: 6.75 (d, *J* = 10.0 Hz, 1H, H-6); 6.70 (dd, *J* = 2.0 and 10.0 Hz, 1H, H-5); 6.52 (dd, *J* = 2.0 and 4.0 Hz, 1H, H-3); 5.14 (t, *J* = 7.0 Hz, 1H, H-2'); 5.07 (t, *J* = 5.0 Hz, 1H, H-6'); 3.12 (d, *J* = 7.0, 2H, H-1'); 2.07 (m, 4H, H-5' and H-4'); 1.68 (s, 3H, H-10'); 1.62 (s, 3H, H-8'); 1.59 (s, 3H, H-9'). <sup>13</sup>C-NMR: 187.9 (C-1), 187.6 (C-4), 148.5 (C-2), 140.1 (C-3'), 136.7 (C-5), 136.3 (C-6), 132.3 (C-3), 131.8 (C-7'), 123.9 (C-6'), 117.7 (C-2'), 39.6 (C-4'), 27.3 (C-5'), 26.4 (C-1'), 25.7 (C-8'), 17.7 (C-9'), 16.1 (C-10'). IR (cm<sup>-1</sup>): 2919, 1648, 1655, 1197. HRMS: (M + 1) calcd. for C<sub>16</sub>H<sub>20</sub>O<sub>2</sub>: 245.1463, found: 245.1468.

#### 1,4-dimethoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)benzene (**4**)

To geranylhydroquinone **1** (0.1139 g, 0.46 mmol) dissolved in acetone (30 mL), potassium carbonate (0.1 g, 0.7 mmol) and dimethyl sulphate (0.12 g, 0.9 mmol) were added. The mixture was stirred at room temperature during 24 h. After filtration, the solution was evaporated to dryness. Dilution with diethyl ether was followed by washing with NaOH solution (5%) and the organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated to dryness to afford the crude reaction product, obtaining 54.4 mg (44 % Yield) of compound **4** after column chromatography (eluent to hexane/ethyl

acetate, 19.8:0.2→18.0:2.0), colorless viscous oil. <sup>1</sup>H-NMR: 6.77 (d, *J* = 8.8 Hz, 1H, H-6); 6.74 (d, *J* = 3.0 Hz, 1H, H-3); 6.68 (dd, *J* = 3.0 and 8.8 Hz, 1H, H-5); 5.31 (t, *J* = 7.0 Hz, 1H, H-2'); 5.11 (bt, *J* = 5.0 Hz, 1H, H-6'); 3.79 (s, 3H, OCH<sub>3</sub>); 3.76 (s, 3H, OCH<sub>3</sub>); 3.31 (d, *J* = 7.0 Hz, 2H, H-1'); 2.08 (m, 4H, H-5' and H-4'); 1.74 (s, 3H, H-10'); 1.70 (s, 3H, H-8'); 1.68 (s, 3H, H-9'). <sup>13</sup>C-NMR: 153.6 (C-4), 151.7 (C-1), 136.4 (C-3'), 131.5 (C-2), 131.4 (C-7'), 124.3 (C-6'), 122.1 (C-2'), 116.0 (C-3), 111.2 (C-6), 110.5 (C-5), 56.1 (C-7), 55.6 (C-8), 39.8 (C-4'), 28.2 (C-5'), 26.7 (C-1'), 25.7 (C-8'), 17.7 (C-9'), 16.1 (C-10'). IR (cm<sup>-1</sup>): 2925, 2853, 1590, 1463, 1052. HRMS: (M + 1) calcd. for C<sub>18</sub>H<sub>26</sub>O<sub>2</sub>: 275.1933, found: 275.1937.

#### 4-methoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)phenyl acetate (**5**)

To geranyl-4-methoxyphenol **2** (0.1306 g, 0.5 mmol) dissolved in dichloromethane (20 mL), acetic anhydride (1.4 g, 1.3 mL, 13 mmol) and dimethylaminopyridine (DMAP, 0.02 g, 0.16 mmol) were added. The mixture was stirred at room temperature during 2 h. The organic phase was washed with water and after it was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was evaporated to dryness to afford the crude reaction product, achieving 31.7 mg (22% Yield) of compound **5** after column chromatography (eluent to hexane/ethyl acetate, 19.8:0.2→18.0:2.0), colorless viscous oil. <sup>1</sup>H-NMR: 6.93 (d, *J* = 8.7 Hz, 1H, H-6); 6.76 (d, *J* = 2.7 Hz, 1H, H-3); 6.73 (dd, *J* = 8.7 and 2.7 Hz, 1H, H-5); 5.24 (t, *J* = 7.0 Hz, 1H, H-2'); 5.10 (bt, *J* = 6.0 Hz, 1H, H-6'); 3.78 (s, 3H, H-8); 3.20 (d, *J* = 7.0, 2H, H-1'); 2.29 (s, 3H, H-7); 2.08 (m, 4H, H-5' and H-4'); 1.68 (s, 6H, H-8' and H-10'); 1.60 (s, 3H, H-9'). <sup>13</sup>C-NMR: 169.9 (COCH<sub>3</sub>), 157.4 (C-4), 142.5 (C-1), 137.2 (C-3'), 134.5 (C-2), 131.6 (C-7'), 124.1 (C-6'), 122.7 (C-6), 121.2 (C-2'), 115.4 (C-3), 111.5 (C-5), 55.5 (C-8), 39.6 (C-4'), 28.7 (C-5'), 26.6 (C-1'), 25.6 (C-8'), 20.8 (C-7), 17.7 (C-9'), 16.1 (C-10'). IR (cm<sup>-1</sup>): 2924, 1762, 1496, 1195, 1041. HRMS: (M + 1) calcd. for C<sub>19</sub>H<sub>26</sub>O<sub>3</sub>: 303.1882, found: 303.1885.

### Bioactivity: cell growth inhibition assay

The colorimetric assay using sulforhodamine B (SRB) following an adaptation of the described method for Skehan *et al.*<sup>14</sup> was used. Cells were seeded in 96-well microtiter plates, at 5 × 10<sup>3</sup> cells per well in aliquots of 100 μL of DMEM/F-12 medium, and they were allowed to attach to the plate surface by growing in drug-free medium for 18 h. Afterward, compounds samples were added in aliquots (dissolved in EtOH/H<sub>2</sub>O) to achieve a final concentration of 12.5, 25, 50 and 100 μM. The same solution ethanol/H<sub>2</sub>O was used as negative control. Moreover as positive control we used dunnione, however this compound did not show structural similarity with the analysed compounds. After 72 h exposure, the *in vitro* cytotoxicity was measured by the SRB dye assay. Cells were fixed by adding cold 50% (wt/vol) trichloroacetic acid (TCA, 25 μL) and incubating for 60 min at 4 °C. Plates were washed with deionized water and dried; SRB solution (0.1% wt/vol in 1% acetic acid, 50 μL) was added to each microtiter well and incubated for 30 min at room temperature. Unbound SRB is removed by washing with 1% acetic acid. Plates were air-dried and bound stain was solubilized with Tris base (100 μL, 10 mM). Optical densities were read on an automated spectrophotometer plate reader at a single wavelength of 540 nm. Values shown are the % viability vs. Ctrl + SD, n=four independent experiments in triplicate.

### CONCLUSIONS

In summary, we have prepared the natural geranylhydroquinone **1** and geranyl-4-methoxyphenol **2**. These compounds were obtained by Electrophilic Aromatic Substitution (EAS) coupling reactions between geraniol with 1,4-hydroquinone and 4-methoxyphenol. Fur-

thermore, the natural geranylquinone **3** and the geranylhydroquinone derivatives (**4-5**) were obtained by chemical transformations of the compounds coupling **1** and **2**. The compounds **1** and **3** showed cytotoxic activity against prostate cancer cell line PC-3, breast cancer cell lines MCF-7 and MDA-MB231. However the cytotoxicity is lower than the positive control (dunnione). Moreover, these compounds showed some selectivity for the cancer cells versus fibroblast cells. The increased cytotoxicity induced by compounds **1** and **3** on cell lines are due to the presence of hydroquinone or quinone moiety on the structure of these compounds versus the compounds **2**, **4** and **5**.

#### SUPPLEMENTARY MATERIAL

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of compounds **1-5** are available free of charge at <http://quimicanova.s bq.org.br> as a PDF file.

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