

SYNTHESIS OF GERANYLHYDROQUINONE DERIVATIVES WITH POTENCIAL CYTOTOXIC ACTIVITY

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Natural geranylhydroquinone **1** and geranyl-*p*-methoxyphenol **2** were prepared by 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, 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 were 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. IC_{50} values were in the μM range.

Keywords: synthesis; geranylhydroquinones; cytotoxic activity.

INTRODUCTION

Polyprenylated 1,4-benzoquinones and hydroquinones such as ubiquinones, plastoquinones, and tocopherols are widely found in plants and animals, in which they play important roles in electron transport, photosynthesis, and as antioxidants.¹ Prenyl benzoquinones have been also isolated from brown algae of the order Fucales,² sponges,³ alcyonaceans,⁴ gorgonaceans,⁵ and ascidians belonging to the genus *Aplidium*.⁶ These substances present a terpenoid portion ranging from one to nine isoprene units. Brown algae contain diprenyl-, triprenyl-, as well as tetraprenylquinones and hydroquinones,² where as sponges contain prenylated 1,4-benzoquinones and hydroquinones with linear and longer (up to nine isoprene units) terpenoid side chains.³ Ascidians of the genus *Aplidium* have previously yielded around a dozen prenylated quinones and related compounds.⁶ Studies on the relation structure activity (SAR) of a series of nonmethoxylated prenylated quinones, with side chains containing from one to eight isoprene units, 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.⁷ Another study of SAR investigating 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 in length showed specificity in the inhibitory effect for transformed JB6 P+ Cl41 cells.⁸ Due to these antecedents and as a continuation of our research, the current work describes the preparation and cytotoxic activity of prenyl benzoquinones and hydroquinones with two isoprene units, referred to as geranylhydroquinones derivatives (**1-5**). Two of these compounds, natural geranylhydroquinone **1** and geranyl-*p*-methoxyphenol **2**, were synthesized using the strategy of Electrophilic Aromatic Substitution (EAS) reactions, according to protocol reported elsewhere.⁹ All the compounds were evaluated *in vitro* against cultured human cancer cells in order to analyse the influence of molecular structure on the cytotoxic activity.

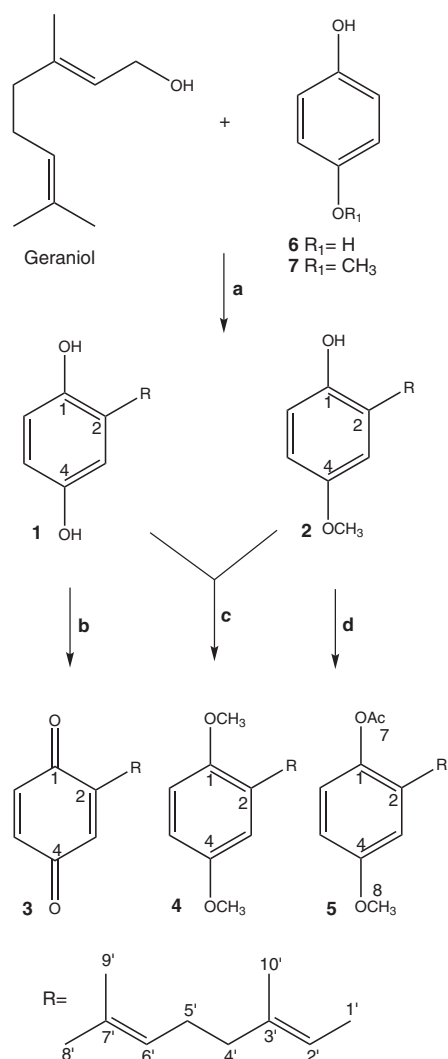
RESULTS AND DISCUSSION

Chemistry

The strategy of Electrophilic Aromatic Substitution (EAS) was used 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**), according to previously reported procedures.⁹ Chemical transformations of the coupling compounds **1** and **2** are summarized in Scheme 1. The structural determination of all the derivatives was accomplished mainly by IR, HRMS, ^1H , ^{13}C , DEPT-135, gs-2D HSQC and gs-2D HMBC NMR techniques (2D correlation were registered only for some compounds). The ^1H -NMR spectrum of **1** was compared with the spectral data reported for the isolated natural compound.¹⁰ This compound showed the existence of two hydroxyl groups at δ 4.75 and 4.46, and the presence of three aromatic hydrogens at δ 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 δ 3.30 (d, $J = 7.0$ Hz, 2H, H-1'). The signals at δ 116.6 (C-3), 113.7 (C-5), of three aromatic carbons and 26.4 ppm (C-1') in the ^{13}C -NMR spectrum corroborated the molecular structure. On the ^1H -NMR spectrum of geranyl-*p*-methoxyphenol **2**, the signals at δ 3.75 (s, 3H, H-8) of the methoxyl group, δ 3.33 (d, $J = 7.0$, 2H, H-1') of the point of coupling, δ 4.80 (s, 1H, OH) of the phenol and three aromatic hydrogens at δ 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 predominantly observed. On the ^{13}C -NMR spectrum, the presence of the methoxyl group at δ 55.7 (OCH₃) as well as the signals of three aromatic carbons at δ 116.4 (C-6), 115.7 (C-3), 112.1 (C-5), were also confirmed. (here the spectroscopic 2D NMR information of compound **2** was deleted). In addition, the configuration of the C2'-C3' double bond was compared with the chemical shifts of C-10' reported for similar compounds.¹¹

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 MnO_2 , being an alternative method to that reported.¹² The molecular structure was confirmed for the presence of the signals at δ 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 geranylhydroquinones derivatives: (a) dioxane/ BF_3Et_2O , N_2 , r.t.; (b) MnO_2/CH_2Cl_2 , r.t.; (c) $(CH_3)_2SO_4/K_2CO_3$, acetone, r.t.; (d) $Ac_2O/CH_2Cl_2/DMAP$, r.t.

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

The preparation of 1,4-dimethoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)benzene compound **4** was carried out by methylation reaction with $(CH_3)_2SO_4$ in relatively basic conditions of **1** or **2**, as an alternative method to that reported.¹³ 1H -NMR spectrum showed two singlets at δ 3.79 and 3.76, the signals corresponding to the methoxyl groups. These signals also were observed in the ^{13}C -NMR spectrum at δ 56.1 and 55.6.

To obtain 4-methoxy-2-((E)-3,7-dimethylocta-2,6-dienyl)phenyl acetate derivative **5**, geranyl-*p*-methoxyphenol **2** was acetylated with acetic anhydride using dimethylaminopyridine (DMAP) as a catalyst. The molecular structure was corroborated by the signals at δ 2.29 (s, 3H, H-7), 20.8 (C-7) and 169.9 (C=O) of the acetyl group, and their spectral data compared 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, der-

mal human fibroblasts (DHF), using *in vitro* analysis. A conventional colorimetric assay was set up to estimate the IC_{50} values representing the concentration of the drug, required for 50% inhibition *in vitro* after 72 h of continuous exposure to the test compounds. Four serial dilutions (from 12.5 to 100 μM) of 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, compounds **1** and **3** showed IC_{50} values with inhibitory activity in the μM range albeit lower than the positive control (Dunnione), where 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 obtaining compounds with potentially lower toxicity in normal human cells.

Table 1. Cytotoxicity (IC_{50} μM) 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 on a Nicolet Impact 420 spectrometer, and frequencies are reported in cm^{-1} . High resolution mass spectra were recorded on an 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 maximum loading time for the ICR cell was set to 250 ms. 1H , ^{13}C , DEPT-135, sel. 1D 1H NOESY, 2D HSQC and 2D HMBC spectra were recorded in $CDCl_3$ solutions and were referenced to the residual peaks of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm for 1H and ^{13}C , respectively, on a Bruker Avance 400 digital NMR spectrometer, operating at 400.1 MHz for 1H and 100.6 MHz for ^{13}C . Chemical shifts were reported at δ ppm and coupling constants (J) 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% H_2SO_4 in H_2O .

Chemistry

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

$BF_3 \cdot Et_2O$ (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, after which the completion of the reaction was verified by TLC. The mixture was poured onto crushed ice (about 30 g) and the organic layer extracted with EtOAc (3×30 mL). The combined organic phase

was washed with 5% NaHCO₃ (30 mL), then with water (2 × 20 mL) and dried over anhydrous Na₂SO₄, filtered and evaporated. The crude residue was redissolved in CH₂Cl₂ (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%), ¹H-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'). ¹³C-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⁻¹): 3385, 2966, 2920, 1654, 1500, 1450, 1193. HRMS: (M + 1) calcd. for C₁₆H₂₂O₂: 247.1620, found: 247.1623.

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

Colorless viscous oil, 0.1444 g (10%), ¹H-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, OCH₃); 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'). ¹³C-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 (OCH₃), 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⁻¹): 3418, 2965, 2916, 1609, 1279, 1043. HRMS: (M + 1) calcd. for C₁₇H₂₄O₂: 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), MnO₂ (0.05 g, 0.6 mmol) was added. The mixture was stirred at room temperature for 18 h. After filtration, the solution was evaporated to dryness to afford the crude reaction product, which yielded 117.8 mg (82% Yield) of compound **3**, after column chromatography (eluent dichloromethane), colorless viscous oil. ¹H-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'). ¹³C-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⁻¹): 2919, 1648, 1655, 1197. HRMS: (M + 1) calcd. for C₁₆H₂₀O₂: 245.1463, found: 245.1468.

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

Potassium carbonate (0.1 g, 0.7 mmol) and dimethyl sulphate (0.12 g, 0.9 mmol) were added to geranylhydroquinone **1** (0.1139 g, 0.46 mmol) dissolved in acetone (30 mL). The mixture was stirred at room temperature for 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 then dried over anhydrous Na₂SO₄. 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. ¹H-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, OCH₃); 3.76 (s, 3H, OCH₃); 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'). ¹³C-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⁻¹): 2925, 2853, 1590, 1463, 1052. HRMS: (M + 1) calcd. for C₁₈H₂₆O₂: 275.1933, found: 275.1937.

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

Acetic anhydride (1.4 g, 1.3 mL, 13 mmol) and dimethylamino-pyridine (DMAP, 0.02 g, 0.16 mmol) were added to geranyl-4-methoxyphenol **2** (0.1306 g, 0.5 mmol) dissolved in dichloromethane (20 mL). The mixture was stirred at room temperature for 2 h. The organic phase was washed with water and subsequently dried over anhydrous Na₂SO₄. The solution was evaporated to dryness to afford the crude reaction product, yielding 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. ¹H-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'). ¹³C-NMR: 169.9 (COCH₃), 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⁻¹): 2924, 1762, 1496, 1195, 1041. HRMS: (M + 1) calcd. for C₁₉H₂₆O₃: 303.1882, found: 303.1885.

Bioactivity: cell growth inhibition assay

The colorimetric assay using sulforhodamine B (SRB) following adaptation of the method described by Skehan *et al.*,¹⁴ was used. Cells were seeded onto 96-well microtiter plates, at 5 × 10³ cells per well in aliquots of 100 μL of DMEM/F-12 medium, and were allowed to attach to the plate surface by growing in drug-free medium for 18 h. Subsequently, compounds samples were added in aliquots (dissolved in EtOH/H₂O) to achieve a final concentration of 12.5, 25, 50 and 100 μM. The same ethanol/H₂O solution was used as a negative control. Moreover, dunnione was used as a positive control although this compound did not show structural similarity with the analysed compounds. After 72 h exposure, *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 was 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 % viability vs. Ctrl + SD, n = four independent experiments in triplicate.

CONCLUSIONS

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

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

SUPPLEMENTARY MATERIAL

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

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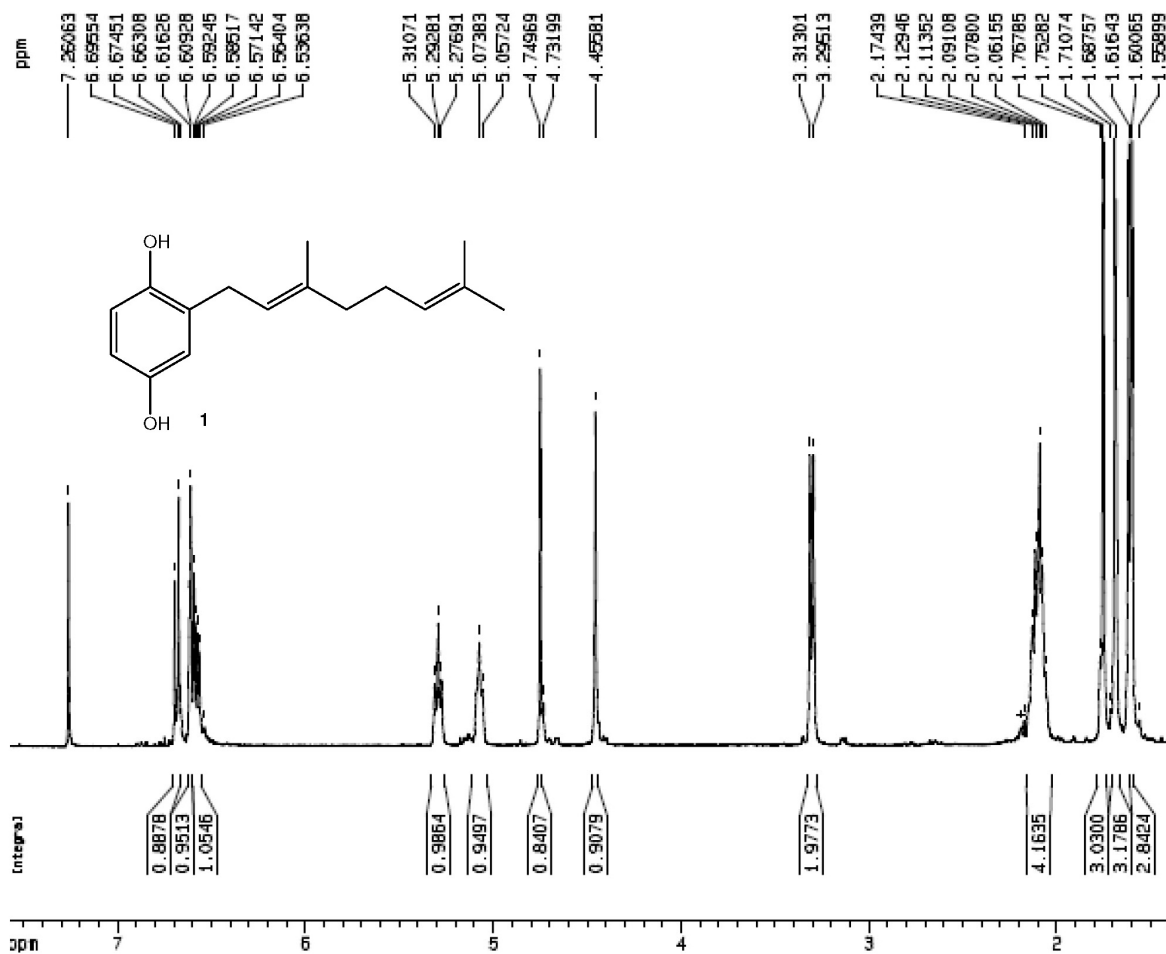


Figure 1S. ¹H NMR (400 MHz, CDCl₃) of compounds 1

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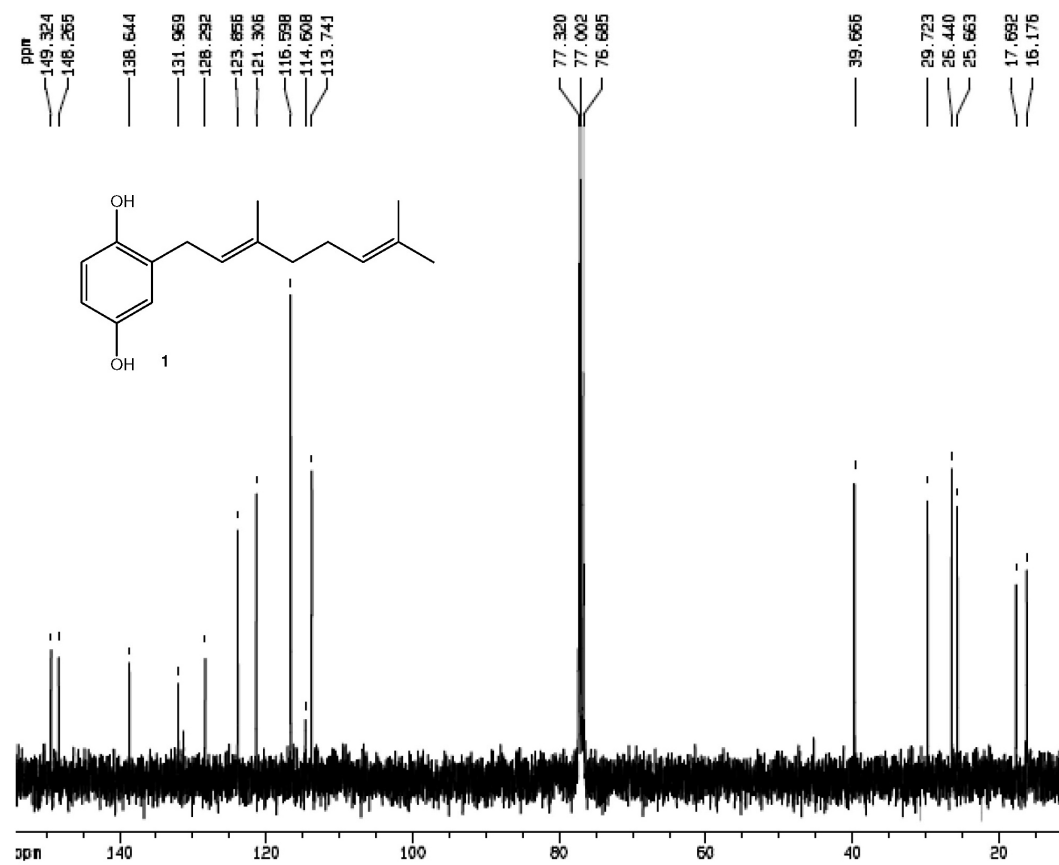


Figure 2S. ¹³C NMR (100 MHz, CDCl₃) of compounds 1

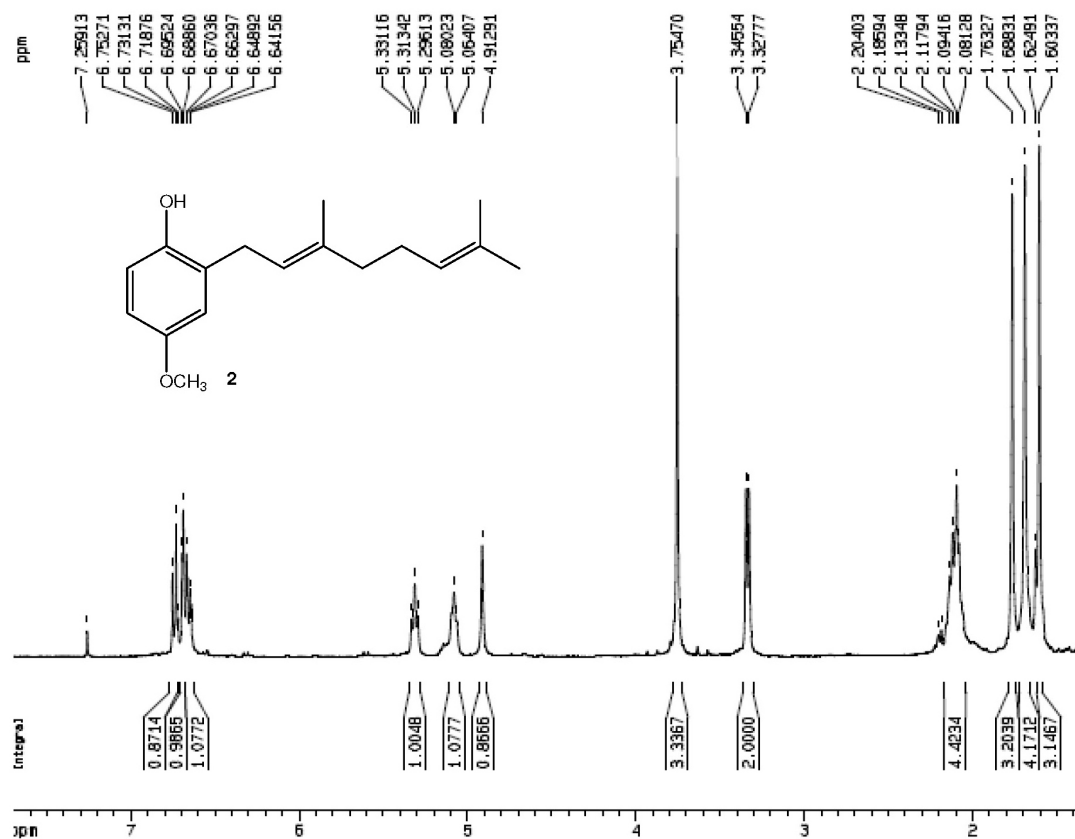
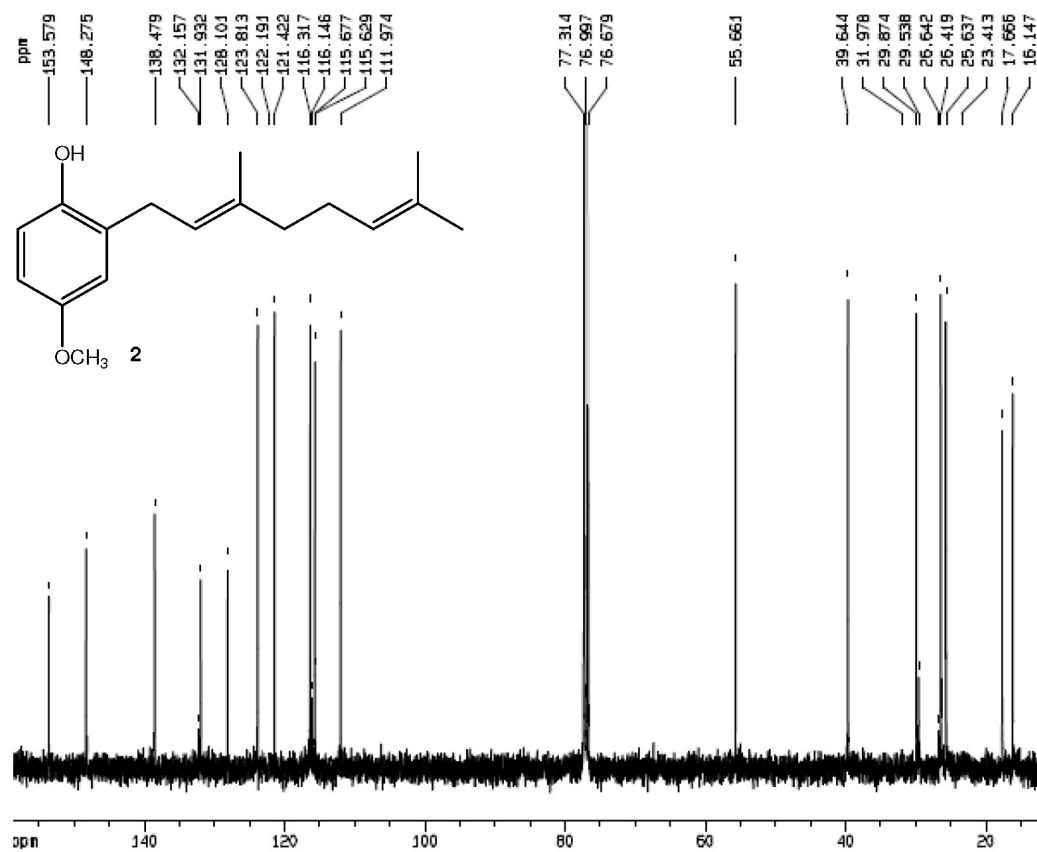
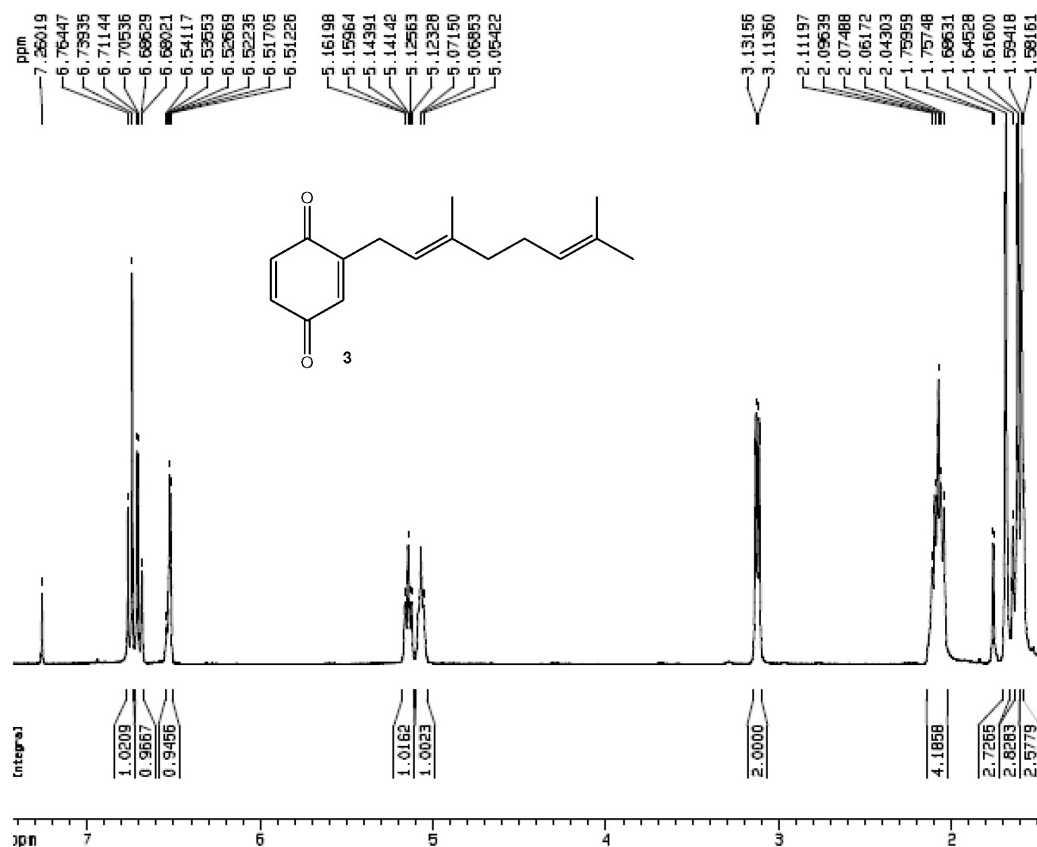
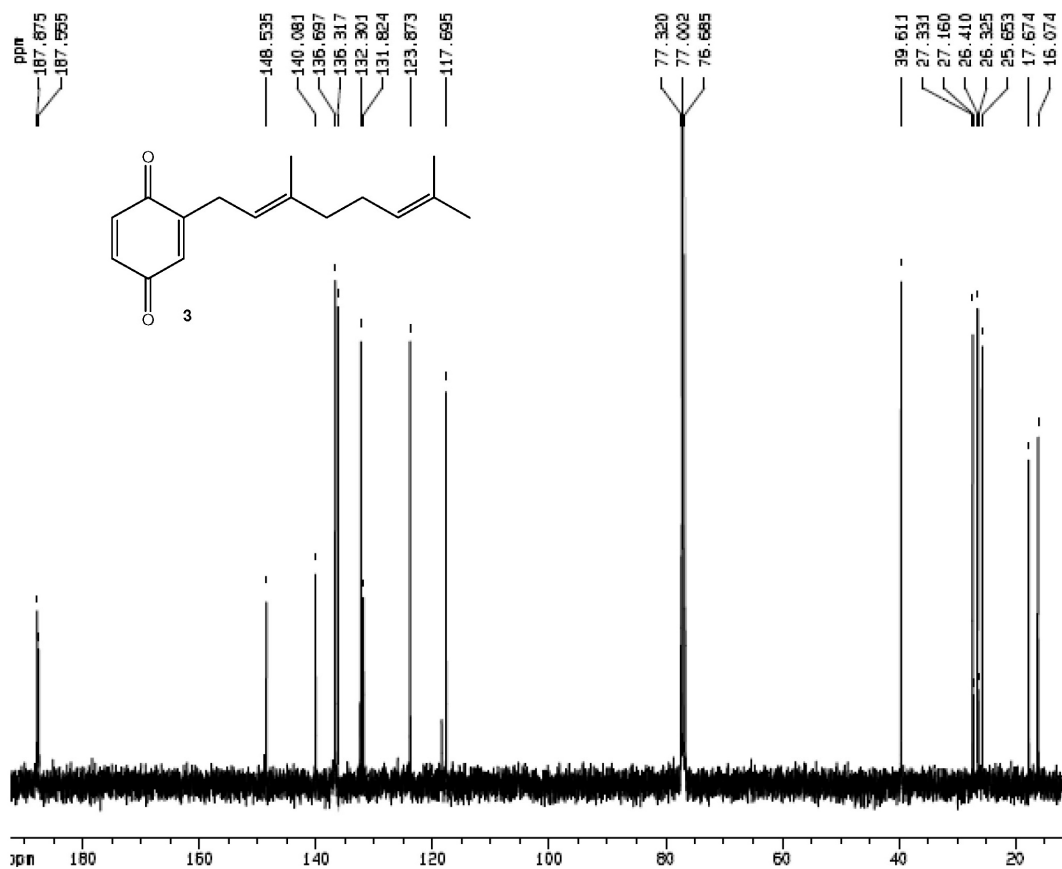
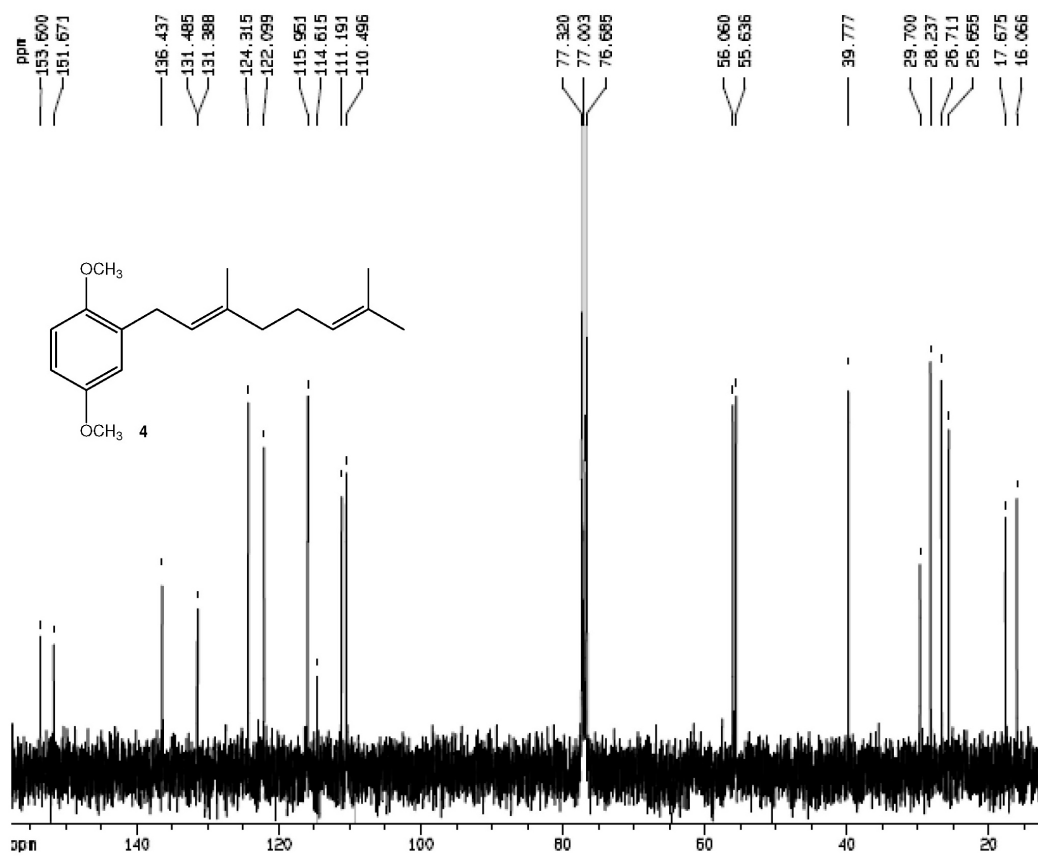


Figure 3S. ¹H NMR (400 MHz, CDCl₃) of compounds 2

Figure 4S. ¹³C NMR (100 MHz, CDCl₃) of compounds 2Figure 5S. ¹H NMR (400 MHz, CDCl₃) of compounds 3

Figure 6S. ¹³C NMR (100 MHz, CDCl₃) of compounds 3Figure 7S. ¹H NMR (400 MHz, CDCl₃) of compounds 4

Figure 8S. ¹³C NMR (100 MHz, CDCl₃) of compounds 4Figure 9S. ¹H NMR (400 MHz, CDCl₃) of compounds 5

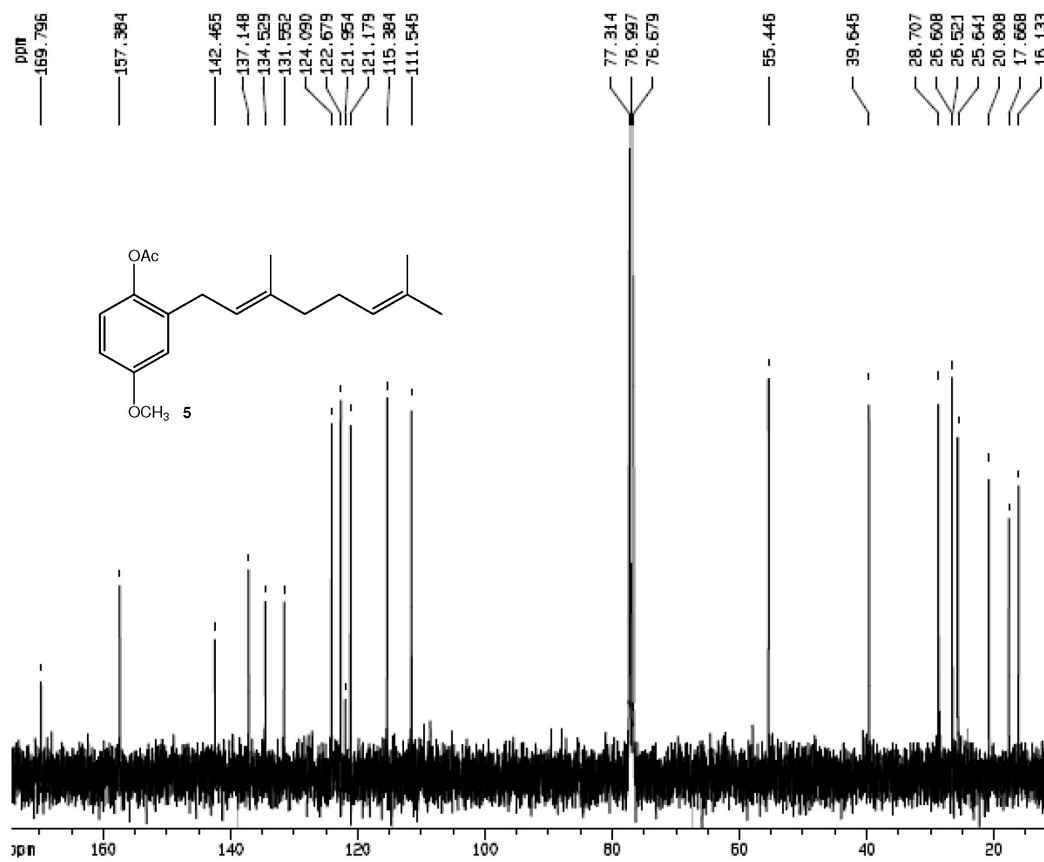


Figure 10S. ^{13}C NMR (100 MHz, CDCl_3) of compounds 5