SUPPLEMENTARY MATERIAL

Natural Products as Sources of New Fungicides (II): Antiphytopathogenic activity of 2,4-dihydroxyphenyl ethanone derivatives

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Abstract

A series of 17 simple 1-(2,4-dihydroxyphenyl) ethanones were synthesized, and their structures characterized by ^1H , ^{13}C NMR and ESI-MS. Their *in vitro* antifungal activities were evaluated against five phytopathogenic fungi including *Glomerella cingulate*, *Botrytis cinerea*, *Fusarium graminearum*, *Curvularia lunata* and *Fusarium oxysporum* f. sp. *vasinfectum* by the mycelial growth inhibition assay. Compounds **2g** and **2h** exhibited broad-spectrum inhibitory activity against the mycelial growth of the tested pathogens with IC_{50} values in the range of 16 - 36 $\mu\text{g/mL}$, and in particular being more active to *Glomerella cingulate*, with IC_{50} values of 16.50 and 19.25 $\mu\text{g/mL}$, respectively, than the other pathogens. Preliminary SAR indicated that an α,β -unsaturated ketone unit of the alkyl chain of the compounds is the structure requirement for fungicidal action. The results suggested that **2g** and **2h** may be promising leads in the development of new antifungal agents.

Keywords: acetophenones; benzophenones; phytopathogenic fungi; antifungal activity; structure-activity relationship

Experimental

General.

The melting points of the products were determined on an XT-4 apparatus (Beijing Tech Instrument Co., Beijing, China) and are uncorrected. ^1H and ^{13}C NMR spectra were taken on a Bruker Avance 500 MHz (500 MHz for ^1H and 125 MHz for ^{13}C , respectively) spectrometer in CD_3OD solution using tetramethylsilane (TMS) as an internal standard (δ given in ppm, J in Hz). MS spectra were taken on a Bruker Daltonics esquire 6000 (ESI-ION TRAP). Thin-layer chromatography (TLC) was performed with silica gel plates using silica gel 60 GF254 and column chromatography (CC) was carried out on silica gel (200-300 mesh) (Qingdao Haiyang Chemical Co. Ltd. Qingdao, Shandong province, China).

All the solvents were of analytical grade (Xilong Chemical Co. Ltd. Shantou, Guangdong, China), and different acyl chlorides and halides were commercial reagents (Aladdin Chemistry Co. Ltd. Shanghai, China).

Synthetic procedures

In an effort to define the structural elements essential to the antifungal activity, we have altered leading compound 1-(2,4-dihydroxyphenyl)ethanone at single sites assumed to be critical for function: the phenol group, and the acyl moieties.

Two different strategies were applied to obtain 2,4-dihydroxyphenyl ethanones and the series of acetophenones; the first one employed Fries-type rearrangement of appropriate phenol esters (Method A); the second one involved the reaction of resorcinol with appropriate acyl chlorides to yield ortho-acyl phenols in a single step (Method B).

General Synthetic Procedure for Compound **2a-f** by method A (Bharate et al. 2008). A mixture of 2,4-dihydroxytoluene (124 mg, 1 mmol), respective acid anhydride (1.2 mmol) and boron trifluoride-diethyl ether (5 mL) was refluxed at 90 °C for 2 hours. Reaction mixture was poured in crushed ice and stirred for 10 min and then extracted with ethyl acetate. Ethyl acetate layer was washed with brine solution and finally dried over anhydrous sodium sulphate. Solvent was removed under reduced pressure and crude product was purified by silica gel column chromatography (#200-300) using petroleum ether /EtOAc (15:1) as eluent to give target compounds.

General Synthetic Procedure for Compound **2g-n** by method B (Magalhaes et al. 2005). To a three-necked flask (50 mL) equipped with a condenser, an addition funnel, an HCl trap and a stopper with nitrogen flow, AlCl_3 (1.5 mmol) and dry CH_2Cl_2 (5 mL) were added. The flask was

then cooled with ice bath, and a solution of acyl chloride (1.2 mmol) in CH_2Cl_2 (5 mL) slowly added via the addition funnel, until all the solid AlCl_3 had dissolved. A solution of phenol (1 mmol) in CH_2Cl_2 was then added drop wise through addition funnel, to avoid excessive evolution of gaseous HCl . The ice bath was then removed, and the mixture was refluxed for 2 hours, and then cooled to room temperature. The reaction was poured into a beaker containing ice (5 g) and concentrated HCl (5 mL), and stirred for 30 min. The organic layer was extracted with ethyl acetate (3 x 10 mL), washed with saturated NaHCO_3 , brine and dried over Na_2SO_4 and concentrated under vacuum. The concentrated mixture was purified by silica gel column chromatography (200-300 mesh) using petroleum ether/EtOAc (10:1 -15:1, v/v) as eluent to give title compounds.

Synthetic Procedure for Compound **3** (Witiak et al. 1988). To a solution of **2a** (152 mg, 1 mmol) in acetone (5 mL), K_2CO_3 (165 mg, 1.2 mmol) and MeI (0.3 mL, 5 mmol) were added, and the mixture was refluxed for 15 h. The mixture was filtered, then the solution was removed in vacuo, the residue was extracted by ethyl acetate. The organic layer was washed with H_2O and brine, the solution was dried (Na_2SO_4), and solvent was removed in vacuo. The crude material was purified by flash CC (petroleum ether and ethyl acetate 15:1) to give **3**.

Synthetic Procedure for Compound **4** (Wang et al. 2006). To a solution of **2a** (152 mg, 1 mmol) in MeOH (5 mL), this solution was chilled to 0°C , and sodium borotetrahydride (0.05 g, 1.2 mmol) was added portion-wise over 30 min. Upon completion by thin-layer chromatography (TLC) analysis the reaction was quenched by the slow addition of ice. The resulting mixture was slowly evaporated to remove the methanol. The resulting solution was taken up in 10 mL of ethyl acetate and washed with 1M HCl . The organic layer was then washed three times with water and once with brine. The organic layer was dried over sodium sulfate and concentrated in vacuo to give brown viscous oil. The crude material was purified by flash CC (petroleum ether and ethyl acetate 5:1) to give **4**.

Synthetic Procedure for Compound **5** (Musso et al. 2010). To a suspension of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (69 mg, 1 mmol) and AcONa (163 mg, 1.2 mmol) in MeOH (10 mL), **2a** (152 mg, 1 mmol) was added, and the mixture was refluxed for 6 h. After the addition of a second portion of $\text{NH}_2\text{OH}\cdot\text{HCl}$ (69 mg, 1 mmol) and AcONa (163 mg, 1.2 mmol), the mixture was refluxed for 8 h. The solvent was evaporated, and the crude material was dissolved in AcOEt . The organic phase was washed with H_2O , dried (Na_2SO_4), and the solvent was removed in vacuo. The crude material was purified by FCC (petroleum ether / AcOEt 10: 1) to give **5**.

Antifungal bioassay

The tested phytopathogenic fungi (*Botrytis cinerea*, *Curvularia lunata*, *Glomerella cingulate*, *Fusarium graminearum* Sehwa., and *Fusarium oxysporum* f. sp. *vasinfectum*) were provided by College of Science, Northwest A&F University. Cultures of the test fungi were maintained on potato dextrose agar (PDA) slants at 4 °C and were subcultured in Petri dishes prior to testing.

The *in vitro* antifungal activity of the test compounds was evaluated by the mycelial growth inhibitory rate method (Li et al. 2012). Briefly, the media (100 mL) incorporating test samples were inoculated at the center of agar discs of the test fungi (4 mm diameter). Three replicate plates for each fungus were incubated at 26 (±2) °C for all test fungi. Control plates containing media mixed with acetone (1 mL) were included. After incubation for 72 h, the mycelial growth of fungi (mm) in both treated (T) and control (C) Petri dishes was measured diametrically in three different directions (decussation method) till the fungal growth in the control dishes was almost complete. The percentage of growth inhibition (I) was calculated using the following formula.

$$I (\%) = [(C-T)/C] \times 100.$$

Statistical analysis

The experimental data of the antifungal activities were analysed using SPSS 13.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance is indicated as determined by one-way ANOVA followed by Dunnett's multiple comparison test, $P < 0.05$, using GraphPad Prism 6 program (GraphPad Software Inc., San Diego, CA, USA).

Analytical data

1-(2,4-Dihydroxyphenyl)ethanone (2a) White crystal, yield 83%, m.p. 146-147 °C. ^1H NMR (500 MHz, CD_3OD) δ 12.92 (s, OH), 7.63 (d, $J = 8.6$ Hz, 1 arom. H), 6.47 (dd, 1 arom. H), 6.32 (d, $J = 2.3$ Hz, 1 arom. H), 2.63 (s, 3H, CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 205.7, 165.3, 163.2, 132.8, 113.2, 108.1, 103.5, 27.0. Chemical Formula: $\text{C}_8\text{H}_8\text{O}_3$, ESI-MS: m/z $[\text{M}+\text{H}]^+$ 152.14.

1-(2,4-Dihydroxyphenyl)propan-1-one (2b) White crystal, yield 80%, m.p. 95-97 °C. ^1H NMR (500MHz, CD_3OD) δ 12.92 (s, OH), 7.64 (d, $J = 8.6$ Hz, 1 arom. H), 6.44 (dd, 1 arom. H), 6.32 (d, $J = 2.3$ Hz, 1 arom. H), 3.50 (q, 2H, CH_2), 1.22 (t, 3H, CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 205.1, 165.5, 163.1, 131.9, 113.1, 108.1, 103.9, 35.5, 8.5. Chemical Formula: $\text{C}_9\text{H}_{10}\text{O}_3$, ESI-MS: m/z $[\text{M}+\text{H}]^+$ 166.17.

1-(2,4-Dihydroxyphenyl)butan-1-one (2c) White crystal, yield 82%, m.p. 73-74 °C. ^1H NMR (500MHz, CD_3OD) δ 12.94 (s, OH), 7.65 (d, $J = 8.6$ Hz, 1 arom. H), 6.40 (dd, 1 arom. H), 6.39 (d,

$J = 2.3$ Hz, 1 arom. H), 2.89 – 2.84 (m, 2H, CH₂), 1.80 – 1.70 (m, 2H, CH₂), 1.00 (t, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 205.9, 165.1, 163.2, 132.7, 113.7, 108.2, 103.6, 40.0, 18.6, 13.9. Chemical Formula: C₁₀H₁₂O₃, ESI-MS: m/z [M+H]⁺ 180.20.

1-(2,4-Dihydroxyphenyl)-2-methylpropan-1-one (2d) White crystal, yield 65%, m.p. 67-69 °C. ¹H NMR (500MHz, CD₃OD) δ 12.95 (s, OH), 7.64 (d, $J = 8.6$ Hz, 1 arom. H), 6.41 (dd, 1 arom. H), 6.27 (d, $J = 2.3$ Hz, 1 arom. H), 3.63-3.40 (m, 1H, CH), 1.16 (d, $J = 12.8$ Hz, 6H, 2CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 210.2, 164.7, 162.9, 130.2, 112.1, 107.8, 103.36, 34.7, 19.9. Chemical Formula: C₁₀H₁₂O₃, ESI-MS: m/z [M+H]⁺ 180.21.

1-(2,4-Dihydroxyphenyl)pentan-1-one (2e) White crystal, yield 60%, m.p. 63-64 °C. ¹H NMR (500MHz, CD₃OD) δ 12.95 (s, OH), 7.67 (d, $J = 8.6$ Hz, 1 arom. H), 6.49 (dd, 1 arom. H), 6.30 (d, $J = 2.3$ Hz, 1 arom. H), 3.01 – 2.89 (m, 2H, CH₂), 1.75 – 1.35 (m, 4H, 2CH₂), 0.99 – 0.87 (m, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 205.4, 163.2, 162.8, 131.97, 112.5, 110.9, 106.8, 37.1, 26.9, 21.4, 13.3. Chemical Formula: C₁₁H₁₄O₃, ESI-MS: m/z [M+H]⁺ 194.22.

1-(2,4-Dihydroxyphenyl)-2,2-dimethylpropan-1-one (2f) White crystal, yield 56%, m.p. 83-84 °C. ¹H NMR (500MHz, CD₃OD) δ 12.96 (s, OH), 7.90 (dd, 1 arom. H), 6.48 (d, $J = 2.3$ Hz, 1 arom. H), 1.41 (s, 9H, 3CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 210.6, 164.6, 161.1, 130.8, 111.5, 105.9, 103.4, 43.8, 28.3. Chemical Formula: C₁₁H₁₄O₃, ESI-MS: m/z [M+H]⁺ 194.22

1-(2,4-Dihydroxyphenyl)prop-2-en-1-one (2g) White crystal, yield 56%, m.p. 103-104 °C. ¹H NMR (500MHz, CD₃OD) δ 12.92 (s, OH), 7.83 (d, $J = 8.6$ Hz, 1 arom. H), 6.79 (dd, 1H, CH=CH₂), 6.43 (m, 1 arom. H), 6.41 – 6.36 (m, 1H, CH=CH₂), 6.36 (s, 1 arom. H), 5.77 (dd, 1H, CH=CH₂). ¹³C NMR (125 MHz, CD₃OD) δ 196.9, 164.1, 163.7, 131.6, 131.5, 124.7, 113.6, 108.0, 103.5. Chemical Formula: C₉H₈O₃, ESI-MS: m/z [M+H]⁺ 164.15

1-(2,4-Dihydroxyphenyl)-2-methylprop-2-en-1-one (2h) White crystal, yield 62%, m.p. 63-64 °C. ¹H NMR (500MHz, CD₃OD) δ 12.92 (s, OH), 7.86 (d, $J = 8.6$ Hz, 1 arom. H), 6.45 (dd, 1 arom. H), 6.38 (d, $J = 2.3$ Hz, 1 arom. H), 6.27 – 6.22 (m, 1H, CH=CH₂), 5.50 – 5.46 (m, 1H, CH=CH₂), 1.87 (t, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 205.7, 164.8, 163.2, 140.5, 131.7, 123.8, 113.5, 107.4, 102.7, 17.1. Chemical Formula: C₁₀H₁₀O₃, ESI-MS: m/z [M+H]⁺ 178.18

2-Chloro-1-(2,4-dihydroxyphenyl)ethanone (2i) White crystal, yield 65%, m.p. 134-136 °C. ¹H NMR (500MHz, CD₃OD) δ 12.90 (s, OH), 7.61 (d, $J = 8.6$ Hz, 1 arom. H), 6.45 (dd, 1 arom. H), 6.30 (d, $J = 2.3$ Hz, 1 arom. H), 4.79 (s, 2H, CH₂Cl). ¹³C NMR (125 MHz, CD₃OD) δ 205.6, 167.8, 164.3, 133.1, 111.0, 107.7, 105.1, 49.8. Chemical Formula: C₈H₇ClO₃, ESI-MS: m/z [M+H]⁺ 186.59

(2,4-Dihydroxyphenyl) cyclopropylethanone (**2j**) White crystal, yield 65%, m.p. 95-96 °C. ¹H NMR (500MHz, CD₃OD) δ 12.96 (s, OH), 6.34 (dd, 1 arom. H), 6.27 (d, *J* = 2.3 Hz, 1 arom. H), 2.83 (p, 1H, CH), 1.27 – 0.82 (m, 4H, 2 CH₂). ¹³C NMR (125 MHz, CD₃OD) δ 206.8, 165.5, 164.1, 132.6, 113.8, 109.2, 103.9, 21.8, 11.5. Chemical Formula: C₁₀H₁₀O₃, ESI-MS: *m/z* [M+H]⁺ 178.18

(2,4-Dihydroxyphenyl)(4-nitrophenyl)methanone (**2k**) White crystal, yield 56%, m.p. 222-223 °C. ¹H NMR (500MHz, CD₃OD) δ 12.96 (s, OH), 8.33 – 8.25 (m, 2 arom. H), 7.96 – 7.86 (m, 2 arom. H), 7.44 (d, *J* = 8.6 Hz, 1 arom. H), 6.36 (dd, 1 arom. H), 6.33 (d, *J* = 2.3 Hz, 1 arom. H). ¹³C NMR (125 MHz, CD₃OD) δ 204.3, 167.4, 165.4, 151.8, 142.8, 132.6, 131.1, 123.1, 115.0, 107.2, 102.5. Chemical Formula: C₁₃H₉NO₅, ESI-MS: *m/z* [M+H]⁺ 259.21

(2,4-Dihydroxyphenyl)(4-chlorophenyl)methanone (**2l**) White crystal, yield 56%, m.p. 160-162 °C. ¹H NMR (500MHz, CD₃OD) δ 12.95 (s, OH), 7.87 – 7.78 (m, 2 arom. H), 7.58 – 7.51 (m, 2 arom. H), 7.44 (d, *J* = 8.6 Hz, 1 arom. H), 6.36 (dd, 1 arom. H), 6.33 (d, *J* = 2.3 Hz, 1 arom. H). ¹³C NMR (125 MHz, CD₃OD) δ 204.3, 167.2, 164.9, 140.1, 134.2, 131.7, 130.1, 129.2, 116.4, 108.5, 103.9. Chemical Formula: C₁₃H₉ClO₃, ESI-MS: *m/z* [M+H]⁺ 248.66

(2,4-Dihydroxyphenyl)(4-methoxyphenyl)methanone (**2m**) White crystal, yield 55%, m.p. 140-142 °C. ¹H NMR (500MHz, CD₃OD) δ 12.96 (s, OH), 7.77 – 7.68 (m, 2 arom. H), 7.44 (d, *J* = 8.6 Hz, 1 arom. H), 7.05 – 6.97 (m, 2 arom. H), 6.36 (dd, 1 arom. H), 6.33 (d, *J* = 2.3 Hz, 1 arom. H), 3.79 (s, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 205.5, 167.8, 165.2, 164.9, 134.5, 132.6, 129.3, 118.4, 113.2, 109.5, 104.9, 59.1. Chemical Formula: C₁₄H₁₂O₄, ESI-MS: *m/z* [M+H]⁺ 244.24

(2,4-Dihydroxyphenyl)(phenyl)methanone (**2n**) White crystal, yield 55%, m.p. 142-143 °C. ¹H NMR (500MHz, CD₃OD) δ 12.90 (s, OH), 7.72 – 7.68 (m, 2 arom. H), 7.66 – 7.57 (m, 1 arom. H), 7.55 – 7.47 (m, 2 arom. H), 7.44 (d, *J* = 8.6 Hz, 1 arom. H), 6.36 (dd, 1 arom. H), 6.33 (d, *J* = 2.3 Hz, 1 arom. H). ¹³C NMR (125 MHz, CD₃OD) δ 199.8, 164.5, 164.3, 136.3, 132.6, 132.5, 130.1, 128.6, 116.4, 108.2, 104.0. Chemical Formula: C₁₃H₁₀O₃, ESI-MS: *m/z* [M+H]⁺ 214.21

1-(2-Hydroxy-4-methoxyphenyl)ethanone (**3**) White crystal, yield 56%, m.p. 52-53 °C. ¹H NMR (500MHz, CD₃OD) δ 12.94 (s, OH), 7.48 (d, *J* = 8.6 Hz, 1 arom. H), 6.57 (dd, 1 arom. H), 6.52 (d, *J* = 2.3 Hz, 1 arom. H), 3.92 (s, 3H, CH₃), 2.52 (s, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 205.8, 165.3, 163.2, 132.8, 113.2, 108.1, 103.5, 57.1, 27.0. Chemical Formula: C₉H₁₀O₃, ESI-MS: *m/z* [M+H]⁺ 166.17.

4-(1-Hydroxyethyl)benzene-1,3-diol (**4**) Yellow oil, yield 90%, ¹H NMR (500MHz, CD₃OD) δ 12.95 (s, OH), 7.50 (d, *J* = 8.6 Hz, 1 arom. H), 6.34 (dd, 1 arom. H), 6.24 (d, *J* = 2.3 Hz, 1 arom. H)

H), 4.71 (q, 1H, CH), 1.60 (d, $J = 8.6$ Hz, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 159.5, 157.2, 130.8, 123.4, 108.2, 102.6, 65.7, 22.6. Chemical Formula: C₈H₁₀O₃, ESI-MS: m/z [M+H]⁺154.16

1-(2,4-Dihydroxyphenyl)ethanone oxime (5) White crystal, yield 56%, m.p. 209-210 °C. ¹H NMR (500MHz, CD₃OD) δ 12.94 (s, OH), 7.52 (d, $J = 2.3$ Hz, 1 arom. H), 7.14 (d, $J = 8.6$ Hz, 1 arom. H), 6.38 (dd, 1 arom. H), 3.80 (s, 3H, CH₃). ¹³C NMR (125 MHz, CD₃OD) δ 1622, 160.4, 158.7, 131.4, 109.4, 107.5, 101.9, 12.9. Chemical Formula: C₈H₉NO₃, ESI-MS: m/z [M+H]⁺167.16.

Table S1 Growth Inhibition [%] of five plant pathogenic fungi by Compounds **1-5** (conc. 100 μ g/mL)

Compd.	<i>Glomerella cingulate</i>	<i>Botrytis cinerea</i>	<i>FusaHum graminearum</i> Sehwa.	<i>Curvularia lunata</i>	<i>Fusarium oxysporum</i> f. sp. <i>vasinfectum</i>
1	15.52 $\pm$ 0.44	18.33 $\pm$ 0.14	11.26 $\pm$ 1.66	10.64 $\pm$ 0.96	9.92 $\pm$ 1.33
2a	35.47 $\pm$ 2.89	63.36 $\pm$ 0.48	34.35 $\pm$ 1.60	28.56 $\pm$ 2.00	44.52 $\pm$ 1.73
2b	32.50 $\pm$ 2.31	58.34 $\pm$ 0.42	27.00 $\pm$ 1.46	28.44 $\pm$ 2.20	38.25 $\pm$ 3.71
2c	35.25 $\pm$ 3.08	57.35 $\pm$ 0.20	26.55 $\pm$ 1.63	34.65 $\pm$ 1.61	45.25 $\pm$ 3.12
2d	32.60 $\pm$ 2.41	60.35 $\pm$ 0.64	25.04 $\pm$ 0.88	48.55 $\pm$ 1.30	45.56 $\pm$ 1.19
2e	68.75 $\pm$ 0.84	74.52 $\pm$ 1.04	65.50 $\pm$ 1.94	76.83 $\pm$ 2.72	52.72 $\pm$ 2.32
2f	35.05 $\pm$ 0.69	50.82 $\pm$ 2.39	24.20 $\pm$ 2.84	32.05 $\pm$ 1.47	26.50 $\pm$ 1.69
2g	95.45 $\pm$ 2.80	97.52 $\pm$ 0.85	98.65 $\pm$.055	92.03 $\pm$ 1.02	98.21 $\pm$ 0.61
2h	98.70 $\pm$ 0.75	95.65 $\pm$ 1.30	95.52 $\pm$ 1.30	96.15 $\pm$ 3.03	97.85 $\pm$ 0.46
2i	56.56 $\pm$ 1.35	78.60 $\pm$ 2.76	63.35 $\pm$ 2.07	57.40 $\pm$ 2.70	65.52 $\pm$ 3.52
2j	50.03 $\pm$ 1.73	56.32 $\pm$ 1.15	58.85 $\pm$ 2.29	57.26 $\pm$ 0.76	56.45 $\pm$ 1.62
2k	25.05 $\pm$ 0.39	36.03 $\pm$ 1.48	15.05 $\pm$ 0.35	21.15 $\pm$ 1.59	23.42 $\pm$ 1.42
2l	22.45 $\pm$ 0.36	18.50 $\pm$ 0.83	22.45 $\pm$ 2.17	18.60 $\pm$ 0.79	9.85 $\pm$ 3.44
2m	27.25 $\pm$ 0.35	57.23 $\pm$ 1.22	25.72 $\pm$ 2.79	27.35 $\pm$ 2.27	26.00 $\pm$ 2.68
2n	12.25 $\pm$ 0.20	10.00 $\pm$ 1.74	7.71 $\pm$ 1.32	7.25 $\pm$ 1.83	-
3	30.93 $\pm$ 0.24	59.45 $\pm$ 1.92	25.95 $\pm$ 3.03	32.65 $\pm$ 1.65	37.05 $\pm$ 1.25
4	55.33 $\pm$ 0.63	73.35 $\pm$ 2.19	50.35 $\pm$ 1.48	43.25 $\pm$ 2.88	38.45 $\pm$ 1.83
5	54.50 $\pm$ 0.30	75.45 $\pm$ 2.23	64.22 $\pm$ 0.57	53.37 $\pm$ 1.27	64.55 $\pm$ 0.82
Thiabendazole	77.35 $\pm$ 0.35	100.00 $\pm$ 0.00	100.00 $\pm$ 0.00	60.25 $\pm$ 1.25	100.00 $\pm$ 0.00

All data represent the mean $\pm$ S.D. of at least three independent experiments performed in triplicates.

References

- Bharate, SB, Rodge A, Joshi RK, Kaur J, Srinivasan S, Senthil Kumar S, Kulkarni-Almeida A, Balachandran S, Balakrishnan A, and Vishwakarma RA. 2008. Discovery of diacylphloroglucinols as a new class of GPR40 (FFAR1) agonists. *Bioorg Med Chem Lett.* 18: 6357-6361.
- Magalhaes AF, Magalhaes EG, Trazzi G, and Moraes VRdS. 2005. Synthetic model of a new deoxybenzoin derivative from *Deguelia hatschbachii* A.M.G. Azevedo. *Ecletica Quim.* 30:

43-49.

- Witiak, DT, Kim SK, Tehim AK, Sternitzke KD, McCreery RL, Kim SU, Feller DR, Romstedt KJ, Kamanna VS, and Newman HAI. 1988. Synthetic aci-reductones 3,4-Dihydroxy-2H-1-benzopyran-2-ones and their cis- and trans-4a,5,6,7,8,8a-hexahydro diastereomers. Antiaggregatory, antilipidemic, and redox properties compared to the 4-substituted 2-hydroxytetronic acids. J Med Chem. 31: 1437-1445.
- Wang C, Liu J, Ji Y, Zhao J, Li L, and Zhang H. 2006. Total synthesis of ($\pm$)-paeonilide. Org Lett. 8: 2479-2481.
- Musso L, Dallavalle S, Merlini L, and Farina G. 2010. Synthesis and antifungal activity of 2-hydroxy-4,5-methylenedioxyaryl ketones as analogues of kakuol. Chem Biodivers. 7: 887-897.
- Li XJ, Zhang Q, Zhang AL, and Gao JM. 2012. Metabolites from *Aspergillus fumigatus*, an endophytic fungus associated with *Melia azedarach*, and their antifungal, antifeedant, and toxic activities. J Agric Food Chem. 60: 3424-3431.