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Antimicrobial *Piper* Metabolite and Related Compounds

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4,5-Dimethoxy-2,3-(methylenedioxy)-1-allylbenzene, a natural isolate of *Piper hispidum* and *Piper aduncum*, is found to have strong antimicrobial activity. This natural product and three other related compounds, 4-(5′-hydroxy-5′-nonanyl)-1,2-(methylenedioxy)benzene, 4-(5′-non-4′-enyl)-1,2-(methylenedioxy)benzene, and 6-methoxy-2,3-(methylenedioxy)-4-allylphenol, were synthesized from piperonal and screened for their biological activity. All four compounds showed high levels of antifungal and antibacterial activity on various fungi and bacteria. In vivo experiments with wheat powdery mildew pathogen *Erysiphe graminis* gave excellent disease control at 100 ppm for most of the test compounds.

Extracts of *Piper* species (Piperaceae) have reportedly found widespread application in medicinal practices and have also been used against insects (Atal et al., 1967; Asprey and Thornton, 1976; Escobar, 1972) in several parts of the world, although the active compounds have not been specifically defined. We have previously reported the isolation and characterization of 4,5-dimethoxy-2,3-(methylenedioxy)allylbenzene, pseudodillapiole, from the Jamaican *Piper aduncum* and *Piper hispidum* (Burke and Nair, 1986). Tumor inhibitory compounds and lignins with (methylenedioxy)phenyl substituents were isolated from *Piper novae-hollandiae* and *Piper cubeba*, respectively (Loden et al., 1969; Prabhu and Mulchandani, 1985). Synergistic activity of several (methylenedioxy)phenyl compounds with pyrethrum insecticides is also known (Devakumar et al., 1985; Indian Patent, 1969). The reported use of *Piper* plants as insect repellants (Escobar, 1972) and isolation of (methylenedioxy)phenyl propenoids from the Jamaican species of *Piper* prompted us to investigate the biological activity of compounds 4–7. The natural product and its chemically related compounds, 4–7, were prepared and investigated for antifungal, antibacterial, insecticidal, and herbicidal activities.

EXPERIMENTAL SECTION

Instrumentation. UV–visible and IR absorption spectra were recorded on Perkin-Elmer Lambda 5 and Perkin-Elmer 1420 spectrophotometers, respectively. NMR spectra were obtained on a Varian XL-300 (300 MHz for ^1H and 75 MHz for ^{13}C). Mass spectrometry was carried out by a VG analytical 7070E spectrometer. Melting points were determined on a Kofler hot stage and are uncorrected.

Materials Used. For *Xanthomonas campestris* bacteria, the enriched nutrient medium (ENM) used was made by mixing 0.5% glucose and 1.5% commercial nutrient agar. The Wantanabe broth used for bacterial suspension was made up with 0.1% L-glutamic acid, 0.5% L-methionine, 0.3% NH_4HPO_4, 0.2% KH_2PO_4, 0.1% $MgCl_2 \cdot 6H_2O$, 0.0001% $FeSO_4 \cdot 7H_2O$, 0.000 075% $MnSO_4 \cdot H_2O$, and 0.5% sucrose, and the pH was adjusted to 6.5–7.0. The *Agrobacterium tumefaciens* was assayed in Luria–Bertani (LB) medium containing 1% trylone, 0.5% yeast extract, 1% NaCl, and 1% NaOH. *Rhizobium japonicum* was assayed in yeast–mannitol medium containing 0.05% NaCl, 0.01% yeast extract, 0.02% K_2HPO_4, 1% mannitol, and 0.2% concentrated salt solution (the concentrated salts were 0.1 g of $MgSO_4 \cdot 7H_2O$, 0.02 g of $FeCl_3$, 0.04 g of $CaCl_2$, 0.83 mL of HCl, and 99.0 mL of H_2O), and the pH was adjusted to 7.2. The medium for yeast contained 1% yeast extract, 2% bactopeptone, 25% adenine (1 mg/mL) by volume, 2% uracil (1 mg/mL) by volume, 2% agar, and 4% glucose (50%) by volume. The V-8 medium for fungi consisted of V-8 juice (200 mL), $CaCO_3$ (3.0 g), and agar (15.0 g) per 1000 mL of medium, and the pH was adjusted to 7.2. All the cultures were incubated at 27 °C for 3–7 days.

Determination of ED_{50} on Fungi. ED_{50} values for the fungi were calculated by determining inhibition of mycelial growth on solid nutrient medium (V-8 juice agar). A small plug of the desired fungus on solid nutrient agar was placed on solid nutrient agar previously incorporated with the compounds under investigation. The concentrations used were from 5 to 100 ppm. The inhibition of the mycelial growth was recorded at the end of 72 h.

Determination of ED_{50} on Bacteria and Yeast. Bacterial and yeast bioassay were carried out in their respective liquid nutrient mediums. The compound to be assayed was incor-

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porated with the desired bacteria or yeast, and the resultant mixture was shaken on a rotary shaker at 170 rpm (28 °C) for 2 days. The samples were examined visually or by measuring the absorbance at 640 nm on a UV–visible spectrophotometer. For a bacterial solution, at 640 nm, an OD value of 0.685 indicates 129×10^4 colony-forming units (CFU). Before inoculation, each bacteria or yeast in their respective liquid nutrient medium was diluted to approximately 104 CFU/mL. One-milliliter aliquots of this clear bacterial or yeast solution were used to inoculate the various concentrations of the compound being tested, and at the end of 2 days of shaking, activity was recorded by the turbidity of the solution. A clear solution indicated the inhibition for lower concentrations of the test compounds, and after the 2-day inoculation, aliquots were further diluted with the respective medium; 10 μL of these diluted solutions was applied on solid ENM medium, and the number of colony-forming units was counted.

Germination Inhibition. This was carried out by the previously reported procedure by Nair and Burke (1988).

3,4-(Methylenedioxy)phenol (1). Commercial piperonal (Aldrich) (60 g) was dissolved in CH_2Cl_2 (500 mL), *m*-chloroperoxybenzoic acid (MCPBA) (90 g) added in portions, and the resultant mixture left to stir at room temperature (18 h). The precipitate was filtered off and washed with CH_2Cl_2. The combined filtrate was then washed with cold saturated Na_2CO_3 solution, followed by H_2O dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting formate ester [^{1}H NMR ($CDCl_3$, 300 Hz): δ 5.99 (2 H, s, OCH_2O), 6.56 (1 H, d, J = 8 Hz, H-6), 6.65 (1 H, d, J = 2 Hz, H-2), 6.70 (1 H, d, J = 8 Hz, H-5), 8.25 (1 H, s, formate)] was dissolved in MeOH (250 mL) and the resultant mixed with a solution of 30 g of KOH in 200 mL of MeOH. The reaction mixture was left at room temperature for 15 h and evaporated to dryness and the residue dissolved in water (300 mL), acidified to neutral by dilute HCl (6 N), and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ followed by water, dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude product (57 g) was recrystallized from hexane (48 g) to yield colorless crystals: mp 64–65 °C; IR (KBr cm^{-1}) 3580, 1625; UV (MeOH; λ_{max}, nm (ε) 300.1 (2436), 234.2 (2269), 215.3 (2697); UV (KOH in methanol; λ_{max}, nm (ε)) 314.2 (2477), 242.6 (2781), 225.6 (2746); ^{1}H NMR ($CDCl_3$) δ 5.90 (2 H, s, OCH_2O) 6.15 (1 H, dd, J = 2.4, 8.0 Hz, H-6), 6.24 (1 H, d, J = 2.4 Hz, H-2), 6.34 (1 H, d, J = 8.0, Hz, H-5), 4.68 (1 H, br s, exchanged with D_2O, phenolic); HRMS (m/z; rel intens, % comp) 138.0316 (M^+, 100, $C_7H_6O_3$), 137.0238 (M^+ – H, 88.42, $C_7H_5O_3$).

6-Methoxy-2,3-(methylenedioxy)benzaldehyde (2). Compound 1 (47 g) in dry acetone (500 mL), K_2CO_3 (100 g), and dimethyl sulfate (70 mL) was refluxed overnight. The white solid was filtered off and the filtrate concentrated, diluted with water, and extracted with EtOAc. The EtOAc layer was washed with $NaHCO_3$ solution and water and dried over anhydrous $MgSO_4$. Removal of solvent afforded a straw-colored liquid: TLC, one spot; IR (liquid film, cm^{-1}) 1624; UV (MeOH; λ_{max}, nm (ε)) 296 (2875), 236 (2937), 217 (3027); ^{1}H NMR ($CDCl_3$) δ 3.74 (3 H, s, OCH_3), 5.91 (2 H, s, OCH_2O), 6.31 (1 H, dd, J = 2.5, 8.5 Hz, H-5), 6.49 (1 H, d, J = 2.5, Hz, H-1), 6.70 (1 H, d, J = 8.5 Hz, H-4); HRMS (m/z; rel intens, % comp) 152.0473 (M^+, 100, $C_8H_8O_3$), 137.0238 (M^+ – CH_3, 88.42, $C_7H_5O_3$). This methyl ether (40 g) in absolute THF (300 mL) at –10 °C under argon gas was stirred with butyllithium in hexane (100 mL, 1.1 mol) for $2^1/_2$ h. After the addition of BuLi, the temperature of the reaction mixture was slowly raised to room temperature. Formation of the anion was confirmed by quenching an aliquot of the reaction mixture with D_2O and observing the ^{1}H NMR (disappearance of the doublet signal at 6.49 ppm). The anion thus formed was stirred with dry DMF (20 mL) in THF (100 mL), at 0 °C (10 min) followed by refluxing (2 h). The reaction mixture was then acidified with HCl (6 N) and extracted with ether ($1^1/_2$ L). Drying over anhydrous $MgSO_4$ and evaporation of the solvent afforded a pale yellow crystalline compound: 30 g; mp 124 °C; IR (KBr, cm^{-1}) 1620, 1695; UV (MeOH; λ_{max}, nm (ε)) 211 (7811), 217.9 (7788), 268 (4536), 294.6 (2177): ^{1}H NMR ($CDCl_3$) δ 3.81 (3 H, s, OCH_3), 6.07 (2 H, s, OCH_2O), 6.33 (1 H, d, J = 7 Hz, H-5), 6.88 (1 H, d, J = 7 Hz, H-4), 10.31 (1 H, s, aldehyde); HRMS (m/z; rel intens, % comp) 180.0401 (M^+, 100, $C_9H_8O_4$), 165.0189 (M^+ – CH_3, 35, $C_8H_5O_4$), 137.0238 (M^+ – CH_3, CO, 45, $C_7H_5O_3$).

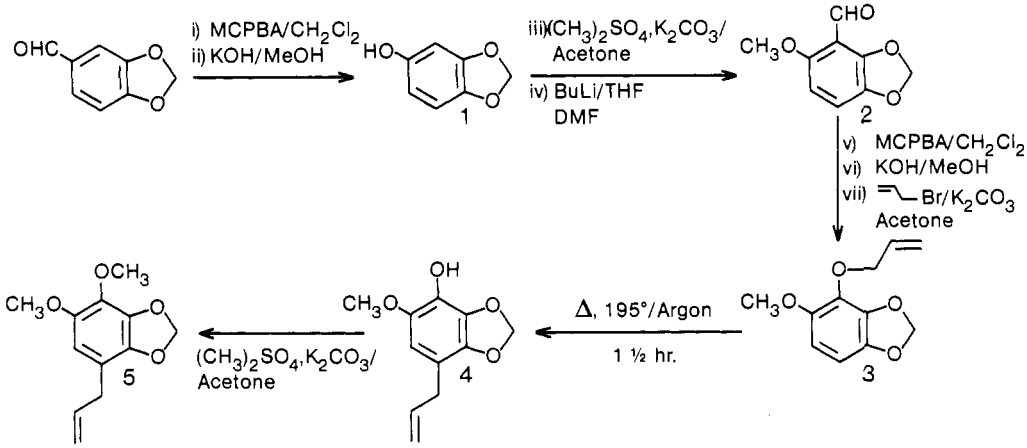
6-Methoxy-2,3-(methylenedioxy)phenyl 1-Allyl Ether (3). Aldehyde 2 (20 g) was stirred with *m*-chloroperoxybenzoic acid (23 g) in CH_2Cl_2 (500 mL) for 18 h. The precipitate was filtered off, the filtrate was washed with Na_2CO_3 solution and evaporated to dryness [^{1}H NMR δ 3.80 (3 H, s, OCH_3), 5.95 (1 H, d, J = 6 Hz, C-5), 6.01 (2 H, s, OCH_2O), 6.35 (1 H, d, J = 6 Hz, C-4), 8.19 (1 H, s, formate ester)]. The formate ester was treated with 5% KOH in MeOH at room temperature (2 h), and the resulting low-melting solid (12 g) was recrystallized from hexane: mp 89–90 °C; IR (KBr, cm^{-1}) 3530; UV (MeOH; λ_{max}, nm (ε)) 214 (8846), 292 (2160); UV (base; λ_{max}, nm (ε)) 230 (9360), 311 (2184); ^{1}H NMR ($CDCl_3$) δ 3.92 (3 H, s, OCH_3), 5.90 (2 H, s, OCH_2), 6.33, 6.42 (each 1 H, d, J = 8.5 Hz, H-4, H-5); HRMS (m/z; rel intens, % comp) 168.0422 (M^+, 100, $C_8H_8O_4$), 153.0187 (M^+ – CH_3, 100, $C_7H_5O_4$). This phenol (6 g), K_2CO_3 (40 g), and dry acetone (250 mL) were stirred (10 min), allyl bromide (8 mL) was added, and the mixture was refluxed (18 h). The resulting product on purification produced a colorless liquid (3): 8 g; IR (liquid film, cm^{-1}) 1620; UV (MeOH; λ_{max}, nm (ε)) 215 (9606), 288.6 (2002), no base shift; ^{1}H NMR ($CDCl_3$) δ 3.80 (3 H, s, OCH_3), 4.70 (2 H, d, J = 6 Hz, CH_2), 5.31 (2 H, dd, J = 13, 6 Hz, CH=CH_2), 5.90 (2 H, s, OCH_2O), 6.03 (1 H, m, CH_2=CH), 6.32 (1 H, d, J = 8.7 Hz, C-5), 6.46 (1 H, d, J = 8.7 Hz, C-6); HRMS (m/z; rel intens, % comp) 208.0735 (M^+, 100, $C_{11}H_{12}O_4$), 193.0500 (M^+ – CH_3,22; $C_{10}H_9O_4$), 168.0344 (M^+ – CH_2CH=CH_2, 78, $C_8H_7O_4$).

6-Methoxy-2,3-(methylenedioxy)-4-allylphenol (4). Compound 3 (3.5 g) was heated under argon at 195 °C ($1^1/_2$ h), cooled, dissolved in ether (200 mL), and extracted with 2 N NaOH (250 mL). The NaOH portion was back-washed once with ether, acidified with 6 N HCl, and extracted with ether (3 × 250 mL). The ether layer was washed with $NaHCO_3$, followed by water, dried over anhydrous $MgSO_4$, and evaporated to dryness. The resulting product (4), recrystallized from hexane (2.7 g), was a low-melting solid: mp 52–53 °C; IR (KBr, cm^{-1}) 1625, 3500; UV (MeOH; λ_{max}, nm (ε)) 212 (9627), 295 (1782); UV (base; λ_{max}, nm (ε)) 219 (11 291); 312 (2377); ^{1}H NMR ($CDCl_3$) δ 3.27 (2 H, d, J = 6 Hz, benzylic CH_2), 3.82 (3 H, s, OCH_3), 5.06 (2 H, m, CH=CH_2), 5.34 (1 H, br s, exchanged with D_2O, phenol), 5.90 (2 H, s, OCH_2O), 5.94 (1 H, m, CH_2=CH), 6.15 (1 H, s, C-6); HRMS (m/z; rel intens, % comp) 208.0735 (M^+, 100, $C_{11}H_{12}O_4$). This is the normethyl homologue of compound 5.

4,5-Dimethoxy-2,3-(methylenedioxy)-1-allylbenzene (5). Allylphenol 4 (1 g) was methylated with dimethyl sulfate and K_2CO_3 in acetone. Usual workup afforded a colorless liquid: 1 g; IR (liquid film, cm^{-1}) 1610, 1630; UV (MeOH; λ_{max}, nm (ε)) 216 (10 113), 220 (10 189), 289 (2077), no base shift; ^{1}H NMR ($CDCl_3$) δ 3.24 (2 H, d, J = 6 Hz, benzylic CH_2), 3.76 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 5.05 (2 H, unresolved d, CH=CH_2), 5.87 (2 H, s, OCH_2O), 5.93 (1 H, m, CH_2=CH), 6.14 (1 H, s, C-6); ^{13}C NMR ($CDCl_3$ ppm) 58.08 and 56.33 (both q, OCH_3), 100.71 (t, OCH_2O), 32.97 (t, benzylic CH_2), 115.43 (t, CH=CH_2), 135.0 (d, CH=CH_2), 104.90 (d, C-6), 113.30 (s, C-1), 146.82 (s, C-12), 140.37 (s, C-5), 137.19 (s, C-3), 131.97 (s, C-4); HRMS (m/z; rel intens, % comp) 222.0892 (M^+, 100, $C_{12}H_{14}O_4$), 207.0657 (M^+ – CH_3, 36, $C_{11}H_{11}O_4$), 195.0576 (M^+ – C_2H_3, 6, $C_{10}H_{11}O_4$).

4-(5′-Hydroxy-5′-nonanyl)-1,2-(methylenedioxy)benzene (6). Piperonoic acid methyl ester (40 g) in THF (250 mL) was reacted at –10 °C under argon gas with butyllithium in hexane (100 mL, 1.1 mol) for $2^1/_2$ h. The reaction mixture was diluted with crushed ice and brine and extracted with ethyl acetate. The removal of ethyl acetate gave a dark yellow liquid that was further purified by deactivated silica column with hexane as the eluant. The product was a colorless viscous liquid: 50 g; IR (liquid film, cm^{-1}) 1610, 3550; UV (MeOH; λ_{max}, nm (ε)) 223 (8133), 256 (7512); ^{1}H NMR ($CDCl_3$) δ 0.87 (6 H, t, J = 3 Hz, CH_3 × 2), 1.25 (8 H, m, CH_2 × 4), 1.66 (4 H, t, J = 3 Hz, CH_2 × 2), 5.94 (2 H, s, OCH_2O), 6.86 (1 H, d, J = 6 Hz, C-5), 6.80 (1 H, d, J = 2 Hz, C-2), 6.77 (1 H, d, J = 6 Hz, C-6); ^{13}C NMR ($CDCl_3$, ppm) 14.02 (q, 3 CH_3), 23.09, 25.62, 42.84 (all t, CH_2), 100.79 (t, OCH_2O), 100.28, 118.31 × 2 (all d), 77.4 (s, ArCO), 107.59, 140.83, 145.72, 147.48 (all s); HRMS (m/z;

Scheme I



rel intens, % comp) 264.169 99 (M, 5, $C_{16}H_{24}O_3$), 246.1602 ($M^+ - H_2O$, 100, $C_{16}H_{22}O_2$), 247.1698 ($M^+ - OH$, 22, $C_{16}H_{23}O_2$).

4-(5′-Non-4′-enyl)-1,2-(methylenedioxy)benzene (7). Compound **6** on heating converted to **7**. An attempted vacuum distillation of **6** at 145–146 °C (0.3 mmHg) produced only compound **7** as a colorless liquid: IR (liquid film, cm^{-1}) 1610, 2900; UV (MeOH; λ_{max}, nm (ϵ)) 212 (7889), 223 (8245), 256 (7303), 294 (4408); ^1H NMR ($CDCl_3$) δ 0.84 (3 H, t, J = 3 Hz, CH_3), 0.94 (3 H, t, J = 3 Hz, CH_3), 1.29 (6 H, m, $CH_2 \times 3$), 2.16 (2 H, q, J = 6 Hz, CH_2), 2.40 (2 H, m, CH_2), 5.92 (2 H, s, OCH_2O), 6.78 (1 H, m, C=CH), 6.87 (1 H, d, J = 6 Hz, C-5), 6.80 (1 H, d, J = 2 Hz, C-2), 6.75 (1 H, d, J = 6 Hz, C-6); ^{13}C NMR ($CDCl_3$, ppm) 14.0 (q, $CH_3 \times 2$), 22.66 (t, CH_2), 23.33 (t, CH_2), 30.00 (t, CH_2), 30.6 (t, CH_2), 31.33 (t, CH_2), 100.60 (t, OCH_2O), 107.30 (d), 108.31 (d), 119.6 (d), 128.33 (d), 138.33 (s), 140.00 (s), 146.33 (s), 138.00 (s); HRMS (m/z; rel intens, % comp) 246.1619 (M^+, 100, $C_{16}H_{22}O_2$).

RESULTS AND DISCUSSION

The synthesis of compound **4**, pseudodillapiole, and its normethoxy analogue were (Scheme I) high-yielding and similar to previously reported synthesis of pentasubstituted benzenes (Dallacker, 1969). Formylation reaction of the methyl ether of **1** afforded compound **2** in 72% yield. The double Claisen rearrangement of allyl ether **3** was clean and near-quantitative. The one-pot synthesis of compound **6** was in 55% yield (Scheme II). Compound **6** dehydrated rapidly to its corresponding alkene, **7**, on silica column or by vacuum distillation (Scheme II).

Seed germination bioassays for all test compounds were carried out on cress, lettuce, corn, and soybean seed (Nair and Burke, 1988). At the 250 μg/mL concentrations studied, it was evident that none of the compounds had any effect on the seed germination. Preliminary antifungal assay for compounds **4–7** was carried out on a TLC plate with use of *Cladosporium herbarum* (Nair and Burke, 1988; Homans and Fuchs, 1970). Compounds **4–6** showed total inhibition at 5-μg level, and **7**, at 20 μg. The growths of *C. herbarum* (saprophyte), *Helminthosporm carbonum* (maze pathogen), *Alternaria brassicicoli* (cabbage pathogen), *Pyrenochaeta terrestris* (onion pathogen), and *Alternaria chrysanthemi* (chrysanthemum sp. pathogen) were inhibited by all compounds in the nutrient agar medium at low concentrations (Table I). At 50 ppm all compounds except **7** totally inhibited the growth of *C. herbarum* and *H. carbonum*. At the end of 7 days, compound **7** was less active on all fungi studied. At concentrations of more than 20 ppm, compounds **4–6** totally inhibited growth of all fungi assayed. All compounds showed total kill at 50 ppm. The bacterial and yeast bioassay showed varying activity for compounds **4–7** (Table I). The yeast were unaffected by the 500 ppm concentration level of all test compounds. *A. tumefaciens* and *R. japonicum* suffered growth retardation at concentra-

Scheme II

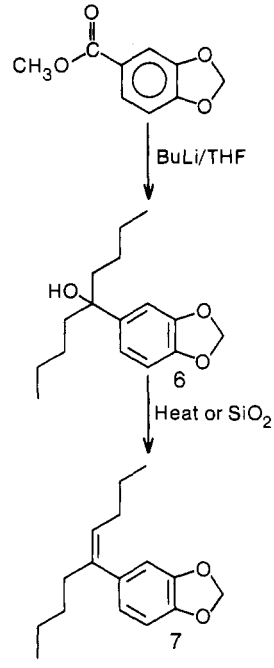


Table I. In Vivo Activity of Compounds 4–7 on Bacteria, Yeast, and Fungi

organism	ED_{50} concn of compd, ppm			
	4	**5**	**6**	**7**
Bacteria				
Xanthomonas compestris	10	10	20	50
Xanthomonas carotae	10	10	20	50
Agrobacterium tumefaciens	>200	>200	>200	>200
Rhizobium japoniam	>500	>500	>500	>500
Yeast				
Saccharomyces cerevisiae	>500	>500	>500	>500
Saccharomyces cerevisiae (lab strain)	>500	>500	>500	>500
Fungi				
Cladosporium herbarum	16	16	15	25
Helminthosporm carbonum	18	16	9	20
Alternaria brassicicoli	8	8	8	8
Pyrenochaeta terrestris	10	10	20	20
Alternaria chrysanthemi	10	10	20	20

Table II. In Vivo Disease Control of Compounds 4–7 on Some Selected Plant Pathogens

organism	% disease control of compd at 100 ppm			
	4	5	6	7
Psenotoperonospora cubensis (cucumber downy mildew)	0	0	0	0
Piricularia oryzae (rice blast)	0	0	0	0
Pellicularia filamantosa (rice sheath blast)	0	0	0	0
Phytophthora inbestans (tomato late blight)	0	0	0	0
Puccinia recondita (wheat leaf rust)	0	0	0	0
Erysiphe graminis (wheat powdery mildew)	75	95	95	50

tions greater than 200 ppm. *X. campestris* pv. *campestris* (cabbage pathogen) and pv. carotae (carrot pathogen) were affected by low concentrations of compounds **4** and **5**.

Preliminary fungicidal activity on various plant pathogens indicated strong disease control specifically on wheat powdery mildew for all the compounds studied (Table II). Further evidence of selectivity is shown by the fact that neither compound proved effective against other plant pathogens studied (Table II). They were also inactive as a herbicide or as an insecticide. For example, all compounds were ineffective against pigweed, green foxtail, signal grass, cress, and lettuce on pre- and postemergence. The insecticidal activity was performed on southern armyworm, mexican bean beetle, southern corn root worm, green peak aphid, two-spotted spider mite, and southern root knot nematode, and all were unaffected by the test compounds.

Activity on microbes but lack of effect on plants by these compounds show a distinct advantage of their use as antimicrobials, specifically as antifungal agents. Their greater activity against *Xanthomonas* bacteria suggests that these compounds are potential control agents for the dreaded canker disease caused by *Xanthomonas sp.* on citrus trees. In addition, the synergism demonstrated by (methylenedioxy)phenyl-type compounds, e.g., dillapiole, with pyrethrins (Devakumar et al., 1985) may be an additional quality for these antimicrobials to use in association with insecticides.

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