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Synthesis and Biological Evaluation of 3,5-Dimethoxystilbene Analogs

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ABSTRACT

In our continuing effort to discover natural product-based pest management agents, derivatives of 3,5-dimethoxystilbene were synthesized yielding 27 new and 6 known compounds. Compounds **11** and **12** showed strong *Aedes aegypti* larvicidal activity (LC_{50} 45.31 and 49.93 μM, respectively). Futhermore, **11** and **12** exhibited high effectiveness against larvae of pesticide-susceptible and pyrethroid-resistant strains of *Ae. aegypti*; activity against the adult mosquitoes was low. Compounds **6f**, **6g**, and **6i** at either 83.3 or 166.7 μg/ml reduced the mobility of second-stage juveniles (J2) of the root-knot nematode (*Meloidogyne incognita*) that hatched from eggs immersed in the test compounds for 7 days. However, there was little or no effect on J2 placed directly into these compounds, and none of the analogs suppressed *M. incognita* egg hatch. The compounds were tested for inhibition of some agriculturally important fungi; **6a**, **7a** and **7e** demonstrated strong inhibition of *Colletotrichum* species. Activity of the stilbenes against some human pathogens was also explored; **11**, **12,** and **16** showed moderate inhibitory activity against *Cryptococcus neoformans*, *Staphylococcus aureus*, methicillin-resistant *S. aureus* and *Mycobacterium intracellulare*. Except for **11** and **12**, which were active against mosquito larvae and some human pathogens, no single analog demonstrated activity in all the tests, indicating specific activities. Synthesis of the analogs and structure-activity relationships are discussed.

Keywords: 3,5-dimethoxystilbene analogs, *Aedes aegypti, Meloidogyne incognita*

INTRODUCTION

Stilbenes have been widely studied for their medicinal properties [1-3]. In contrast, while some are known as phytoalexins, studies on their pesticidal activity have been sparse. As part of our continuing effort exploring the biological activities of stilbenes, and with the objective to investigate their pesticidal properties, analogs of 3,5-dimethoxystilbene (*Suppl. Fig. 1*) were synthesized. This was triggered by a report on 3,5-dimethoxystilbene, isolated from *Lonchocarpus chiricanus*, as having potency equal to rotenone in an *Aedes aegypti* larvicidal assay [4]. *Ae. aegypti* is the primary vector for the transmission of dengue [5]. More than 500,000 people are hospitalized each year due to dengue and about 20,000 cases lead to severe complications resulting in death [6]. Dengue has become increasingly frequent in the U.S.A. [7], and this trend is also occurring worldwide [8]. *Ae. aegypti* is also the vector for yellow fever [9], chikungunya [10], and other tropical diseases which cause severe human health problems throughout the world. There are no effective vaccines or drugs for the control of these diseases, and controlling the mosquito vectors remains the major strategy for disease prevention [11]. It was therefore of interest to determine the activity of the synthesized analogs against *Ae. aegypti.*

A previous study that showed stilbenes having the 3,5-dimethoxystilbene core structure were toxic towards *Caenorhabditis elegans* adults [12] likewise incited determining the activity of the analogs against plant-parasitic nematodes. Plant-parasitic nematodes cause crop losses of approximately ten billion dollars each year in the United States and 125 billion globally [13]. Many of the conventional nematicides used to manage these plant pathogens

have been deregistered due to adverse effects on health and the environment. It is therefore necessary to develop efficacious, environmentally safe means of managing phytoparasitic nematodes, and that includes testing of novel compounds for nematotoxicity. The current study focused on the genus *Meloidogyne* (root-knot nematode), which is one of the most economically important nematodes attacking crop plants; species in this genus are found worldwide on numerous hosts [14]. Of specific interest is the southern root-knot nematode *Meloidogyne incognita* (Kofoid and White) Chitwood, a highly destructive species in this genus.

It was also of interest to test the activity of the analogs against some devastating fungal plant pathogens based on reports on the activity of stilbenes against *Colletotrichum*, *Botrytis*, *Fusarium*, and *Phomopsis* species [15], against fungi associated with esca of grapevine; *i.e.*, *Fomitiporia punctata*, *Libertella blepharis*, *Phaemoniella chlamydospora*, *Phaeoacremonium aleophilum*, and *Stereum hirsutum* [16], and against *Cladosporium cucumerinum*, *Plasmopara viticola* and *Pyricularia oryzae* [17]. Additionally, activity of the analogs against human and food pathogens and yeast was investigated, spurred by reports of strong activity of stilbenes against several pathogenic bacteria, the antimicrobial activity being similar to that of known antibiotics [18, 19].

We report the synthesis of 3,5-dimethoxystilbene analogs, most of which are novel, and their activities against *Ae. aegypti*, agricultural pests and human pathogens. We also discuss how pesticidal activity is affected by various substituents added to the core structure.

RESULTS AND DISCUSSION

As part of our on-going efforts to discover natural products and natural product-based pesticides, we synthesized analogs of 3,5-dimethoxystilbene, prompted by a report that this compound was as effective as rotenone against mosquito larvae, both having MIC = 3 ppm [4]. We prepared a series of *cis*- and *trans*- analogs of 3,5-dimethoxystilbene starting with the aldehydes and reacting with 3,5-dimethoxybenzyl-triphenylphosphonium to the corresponding styrenes (Schemes 1 – 4), yielding twenty-seven new and the six known (**3**, **6a**, **6n**, **7n**, **11**, and **17**) compounds (*Fig. 1*). The analogs were screened for activity against 1-day-old *Aedes aegypti* larvae. Of the 33 analogs, only **11** and **12** exhibited high larvidical activity, with LC_{50} values 45.31 and 49.93 μM, respectively (*Table 1*); **7f** was active only at 346.29 μM, and the rest of the compounds were inactive. Compounds **11** and **12** bear a prenyl substituent at C3′ in ring B, differing from **6n** and **7n** where the prenyl group is in an ether linkage at C4′. None of the other types of substituents (phosphate, methoxy, halogen, nitro, hydroxy) conferred larvicidal activity. Our results suggest that a prenyl group directly attached to the benzene ring at C3′ enhances larvicidal activity. It is noted that in the study of Ioset *et al*. [4], the prenylated stilbene derivatives tested for larvicidal activity had the prenyl group(s) in ring A; these derivatives were less larvicidal than 3,5-dimethoxystilbene. Compounds **11** and **12** were further investigated for their activity against larvae and adult pesticide-susceptible (Orlando (ORL)) and pyrethroid-resistant (Puerto Rico (PR)) strains of *Ae. aegypti* (*Tables 2 and 3*) Both compounds were highly effective against larvae of ORL and PR strains. Compound **11** showed a slightly better activity than **12**, and showed same

activity as permethrin at 0.1 µg/µL concentration, indicating a *trans*-configuration is preferable for larvicidal activity. Both compounds had low effectiveness against adult mosquitoes of both strains.

Based on a report that stilbenes having a 3,5-dimethoxy substitution in ring A are toxic towards the nematode *C. elegans* [12] the synthesized 3,5- dimethoxystilbene analogs were evaluated for activity against the plant-parasitic nematode *M. incognita*. None of the tested compounds suppressed hatch of *M. incognita* eggs. There was some suppressive effect on mobility in J2 that had hatched from eggs immersed in solutions of **6f**, **6g**, **6i**, and **7k** (*Table 4*). However, when J2 previously hatched in water were immersed directly into these same compounds or **6b**, only **6g** and **7k** had an effect on J2 mobility, and the suppression was temporary and occurred in only one of two trials. The assays indicated that the test compounds would not affect egg hatch or reliably inhibit J2 movement, and therefore may not have practical application. In comparison, 3,5-dihydroxy- 4-isopropylstilbene (DIS) (*Suppl. Fig. 1*) isolated from the culture filtrate of the bacterium *Photorhabdus luminescens* has been reported to inhibit egg hatch of *M. incognita* [37]. The total *M. incognita* egg hatch was significantly lower than in the solvent controls after treatment with 49.19 µM of DIS over a 5-day period followed by 5 days in water. DIS differs from **6f**, **6g**, **6i**, and **7k** in having OHs at C-3 and C-5 rather than OCH_3s. The meta-hydroxy group may be important for inhibition of *M. incognita* J2.

When evaluated for activity against some agriculturally important fungi (*Botrytis cinerea*, *Colletotrichum acutatum*, *C. fragariae*, *C. gloeosporioides*, and *Fusarium oxysporum*), none of the compounds inhibited *B. cinerea* or *F. oxysporum*. Compounds **6a**, **7a**,

and 7e had a strong inhibitory effect on *Colletotrichum* species (*Table 5*). The other analogs had either low activity or were not inhibitory. Sobolev et al., 2011 [15] tested a series of natural and synthetic stilbenoids against the same *Colletotrichum* species including 3,5-dimethoxystilbene as well as the analogs pterostilbene and 3,5,4-*O*-trimethylresveratrol (*Suppl. Fig. 1*), but none had activity against *Colletorichum* spp. While we found three analogs to be highly active, the structural features conferring activity for this set of compounds could not be deduced. Pterostilbene, a stilbene having 3,5-dimethoxy substitution, like **6a** and **7a**, has been reported to destroy cellular membranes by depolarization [38]. (*E*)-2-(4-fluorophenyl)-5-(4-(4-fluorostyryl)phenyl)-1,3,4-oxadiazole, a fluorine- containing stilbene, like **7e**, has likewise been reported to disturb mycelial cell membrane system [39]. These studies suggest that **6a**, **7a**, **and 7e** exert their effects through disruption of membrane function.

The activity of the analogs against some human pathogens was also explored. None of the compounds inhibited *Aspergillus fumigatus*, *Candida albicans*, *C. glabrata*, *C. krusei*, *Escherichia coli*, or *Pseudomonas aeruginosa*. Except for **11**, **12,** and **16**, none of the other analogs exhibited inhibitory activity towards *Cryptococcus neoformans*, *Mycobacterium intracellulare*, *Staphylococcus aureus* or methicillin- resistant *S. aureus*. Compounds **11**, **12,** and **16** showed moderate inhibition of *Cryptococcus neoformans* (IC_{50} = 13.63, 41.77, and 5.22 µM, respectively), *Mycobacterium intracellulare* (IC_{50} = 47.17, 50.40, and 33.98 µM, respectively), *Staphylococcus aureus* (IC_{50} = 13.11, 17.03, and 20.43 µg/mL, respectively), and methicillin-resistant *S. aureus* (IC_{50} = 9.10, 13.02, and 43.72 µM, respectively) (**Table 6**). 3,5-Dimethoxystilbene has been reported to inhibit *S. aureus* and methicillin-resistant *S.*

aureus, with a minimum inhibitory concentration >3121 μM [40]. In comparison, **11**, **12,** and **16** had MIC values 42 – 344 times less than that of 3,5-dimethoxystilbene (**Table 6**). This suggests that addition of OH at C-4′ enhances activity; none of the kinds of functional group addition at C-4′ resulted in an active analog. Our results indicate that 3,5-OCH_3 and 4′-OH, the common structural features of **11**, **12** and **16**, must be kept intact for activity. Absence of inhibitory effect of **17**, having 3,5-OH rather than 3,5-OCH_3 substituent, supports this structural requirement. Interestingly, (*E*)- and (*Z*)-3-(3,5-dimethoxy-4-methyl-styryl)-6-methoxybenzene-1,2-diol (DMMD; *Suppl. Fig. 1*) were reported to inhibit *S. aureus*, with MIC of 50-100 μg/disk [41]; this suggests that replacing 4′-OH with -OCH_3 reduces inhibitory activity. Addition of a prenyl moiety at C-3′ appears to further enhance inhibitory activity against *S. aureus* and methicillin-resistant *S. aureus*, as observed from the MICs of **11** and **16** (**Table 6**).

E-DMMD also exhibited inhibition of *Cryptococcus neoformans*, MIC = 50-100 μg/disk [39]. *E*-DMMD and **16** differ in the functional groups attached in ring B. Similar to the observation on their activities against *S. aureus*, substitution of the 4′-OH with -OCH_3 appears to cause a reduction in activity against *C. neoformans*. Synthetic halostilbenes where the C-3/5 bears either F or Cl, namely, 3-fluoro-4,4′,5-trimethoxy-3′-hydroxy-*Z*-stilbene; 3-fluoro-4,4′,5-trimethoxy-3′-hy- droxy-*E*-stilbene; and 3-chloro-4,4′,5-trimethoxy-3′-hydroxy-*Z*-stilbene (*Suppl. Fig. 1*) showed relatively strong inhibition of *C. neoformans*, with MIC of 62 μl/mL [39]. Lack of inhibitory activity of analogs **6e**, **6f**, **6i**, **7e**, **7f**, and **7i**, bearing the halogen(s) in ring B, suggests that halogenation in ring B is not favorable. Studies on stilbenes against *Mycobacterium* species are scanty, and

most report absence of or insignificant activity. (*E*)-3-Hydroxy-5-methoxystilbene (*Suppl. Fig. 1*) was found to be effective in inhibiting the growth of *Mycobacterium bovis* with an MIC of 26 μg/mL [42]. This is the first report of stilbenes having activity against *M. intracellulare*. Thus, finding **11**, **12** and **16** as inhibitory, albeit moderately, is quite stimulating.

In summary, we have synthesized 33 analogs of 3,5-dimethoxystilbene, consisting of 27 new, unreported structures and 6 known compounds. The analogs were tested for activity against mosquito larvae and adults, root-knot nematode, crop pathogens, and microorganisms related to human diseases. No single compound exhibited activity in all the tests, indicating activity specificity. Of interest are **11** and **12**, which showed inhibition of mosquito larvae, *C. neoformans, S. aureus, methicillin-resistant S. aureus,* and *M. intracellulare*; notably, **11** showed activity against *Ae. aegytpi* larvae similar to that of perrmethrin; 3.08 μM of **11** and 2.5 μM of perrmethrin had 100% mortality. Compound **11** presents a scaffold that could be optimized to generate analogs with improved activity. Results obtained with the other analogs provide guidance for structure-activity optimization.

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MATERIALS AND METHODS

General Methods. All solvents were redistilled prior to use. All reactions were performed in a dry round-bottom flask and occurred under N_2 atmosphere. Reactions were monitored by thin-layer chromatography (TLC) using TLC Silica gel 60 F_{254} (Merck); the spots were visualized under UV light. Purification was performed by preparative TLC on silica gel GF plates (SORBTECH, scored, 20×20 cm, 500 μm) or flash chromatography using silica gel (40-60 μm; Sorbent Technologies). NMR spectra were recorded on a Bruker Avance DRX-500 MHz spectrometer in $CDCl_3$, DMSO-d_6 or Acetone-d_6. ESI MS spectra were collected using a JEOL AccuTOF JMS-T100LC mass spectrometer (JEOL USA, Inc., Peabody, MA). GC-MS spectra were obtained with a JEOL GCMate II spectrometer coupled with an Agilent 6890N gas chromatograph (Agilent Technologies, Santa Clara, CA).

Preparation and Synthesis of Stilbene Analogs. (*E*)-4-(3,5-Dimethoxysty- ryl)phenyl dihydrogen phosphate **(3)** was synthesized through reaction of pterostilbene (**1)** and dibenzylphosphite using 4-dimethylaminopyridine (DMAP) and N,N-Diisopropylethylamine (DIEA), followed by deprotection of the benzyl groups (*Scheme 1*), as previously reported [20]. Pterostilbene was synthesized according to published methods [21]. 3,5-Dimethoxybenzyl-triphenylphosphonium (**4b)** and 4-((*tert*-butyl-dimethyl-silyl)oxy)benzaldehyde **(13)** were synthesized following published procedures [22] and [23], respectively.

General Procedure for the Synthesis of Stilbene Analogs ***6a-6n*** *and* ***7a-7n***. *n*-Butyllithium (*n*-BuLi) (1.6 M in hexanes, 1.0 equiv) was added to a cold solution (-78 °C)

of phosphonium salt (1.0 equiv) in THF, and the resulting red solution was stirred under nitrogen for 2 h. A solution of aldehyde (1.0 equiv) in THF was added drop-wise over 30 min, and the mixture was stirred for 12 h at room temperature (*Scheme 2*). The resulting suspension was poured into water and extracted with dichloromethane multiple times. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After solvent removal under reduced pressure, the crude product was purified by preparative TLC or flash chromatography. The *cis* isomer eluted first followed by the *trans* isomer.

1,3-Dimethoxy-2-methyl-5-styrylbenzene (**6a**, **7a**). (3,5-Dimethoxy-4-methyl-benzyl)triphenylphosphonium **4a** (200 mg, 0.394 mmol) was reacted with benzaldehyde **5a** (42.3 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 97:3) to afford **6a** and 7**a**. Compound **6a** was obtained as a white solid: 22.4 mg (22.3%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.13 (s, Me-C(4)), 3.89 (s, MeO-C(3,5)), 6.72 (s, H-C(2,6)), 7.09 (t, J = 16.5 Hz, H-C(7,8)), 7.27 (t, J = 7.3 Hz, H-C(4')), 7.37 (t, J = 7.7 Hz, H-C(3',5')), 7.53 (d, J = 7.3 Hz, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 55.8 (MeO-C(3,5)), 102.0 (C(2,6)), 114.6 (C(4)), 126.4 (C(2',6')), 127.5 (C(7)), 127.9(C(8)), 128.7 (C(3',5')), 129.2 (C(4')), 135.7 (C(1')), 137.4 (C(1)), 158.5 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{19}O_2$ $[M+H]^+$, 255.1385; found, 255.1393. Compound **7a** ws a viscous liquid: 57.8 mg (57.7%). ^{1}H NMR (CDCl3, 500 MHz): δ 2.09 (s, Me-C(4)), 3.64 (s, MeO-C(3,5)), 6.46 (s, H-C(2,6)), 6.57 (d, J = 12.2 Hz, H-C(7)), 6.62 (d, J = 12.2 Hz, H-C(8)), 7.19-7.22 (m, H-C(4')), 7.25-7.29 (m, H-C(3',5')), 7.33 (d, J = 7.2 Hz, H-C(2,6)). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.2 (Me-C(4)), 55.5 (MeO-C(3,5)), 104.5 (C(2,6)), 113.7 (C(4)), 127.0 (C(7)), 128.2 (C(2',6')), 128.9 (C(3',5')), 129.8 (C(8)), 130.7 (C(4')), 135.1(C(1')), 137.7 (C(1)), 157.9

(C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{19}O_2$ $[M+H]^+$, 255.1385; found, 255.1377.

1,3-Dimethoxy-5-(3-methoxystyryl)-2-methylbenzene (**6b**, **7b**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 3-methoxybenzaldehyde **5b** (55.3 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 95:5) to afford **6b** and 7**b**. Compound **6b** was obained as a white solid: 34.9 mg (31.1%). ^{1}H NMR ($CDCl_3$): δ 2.16 (s, Me-C(4)), 3.87 (s, MeO-C(3')), 3.90 (s, MeO-C(3,5)), 6.73 (s, H-C(2,6)), 6.85 (ddd, *J* = 8.2, 2.5, 0.7 Hz, H-C(4')), 7.05-7.13 (overlap, H-C(7,8,2')), 7.14-7.15 (m, H-C(6')), 7.30 (t, *J* = 7.9 Hz, H-C(5')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.4 (Me-C(4)), 55.2 (MeO-C(3')), 55.8 (MeO-C(3,5)), 102.0 (C(2,6)), 111.6 (C(2')), 113.3 (C(4')), 114.7 (C(4)), 119.2 (C(6')), 127.8 (C(7)), 129.5 (C(8)), 129.6 (C(5')), 135.6 (C(1')), 138.8 (C(1)), 158.5 (C(3,5)), 159.9 (C(3')). Positive ion ESI-HRMS: calcd for $C_{18}H_{21}O_3$ $[M+H]^+$, 285.1490; found, 285.1496. Compound **7b** was a viscous liquid: 69.3 mg (61.8%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.10 (s, Me-C(4)), 3.66 (s, MeO-C(3,5)), 3.72 (s, MeO-C(3')), 6.49 (s, H-C(2,6)), 6.57 (d, *J* = 12.4 Hz, H-C(7)), 6.60 (d, *J* = 12.3 Hz, H-C (8)), 6.78 (ddd, *J* = 8.2, 2.5, 0.7 Hz, H-C (4')), 6.87-6.91 (m, H-C(2')), 6.93-6.95 (m, H-C(6')), 7.20 (t, *J* = 7.9 Hz, H-C(5')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.2 (Me-C(4)), 55.1 (MeO-C(3')), 55.5 (MeO-C(3,5)), 104.5 (C(2,6)), 113.0 (C(2')), 113.8 (C(4')), 114.0 (C(4)), 121.5 (C(6')), 129.2 (C(7)), 129.6 (C(8)), 130.9 (C(5')), 135.1 (C(1')), 139.0 (C(1)), 158.0 (C(3,5)), 159.5 (C(3')). Positive ion ESI-HRMS: calcd for $C_{18}H_{21}O_3$ $[M+H]^+$, 285.1490; found, 285.1495.

1,3-Dimethoxy-5-(4-methoxystyryl)-2-methylbenzene (**6c**, **7c**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 4-methoxybenzaldehyde **5c** (54.8 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 95:5) to afford **6c** and 7**c**. Compound

6c was obtained as a white solid: 25.3 mg (22.6 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.14 (s, Me-C(4)), 3.86 (s, MeO-C(4')), 3.91 (s, MeO-C(3,5)), 6.71 (s, H-C(2,6)), 6.93 (d, *J* = 8.7 Hz, H-C(3',5')), 6.97 (d, *J* = 16.0 Hz, H-C(7)), 7.05 (d, *J* = 16.0 Hz, H-C(8)), 7.48 (d, *J* = 8.7 Hz, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 55.3 (MeO-C(4')), 55.7 (MeO-C(3,5)), 101.8 (C(2,6)), 114.1 (C(3',5')), 127.2 (C(4)), 127.4 (C(7)), 127.6 (C(2',6')), 128.4 (C(8)), 130.2 (C(1')), 136.0 (C(1)), 158.4 (C(3,5)), 159.2 (C(4')). Positive ion ESI-HRMS: calcd for $C_{18}H_{21}O_3$ $[M+H]^+$, 285.1490; found, 285.1485. Compound **7c** was a viscous liquid: 41.5 mg (37.0 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.08 (s, Me-C(4)), 3.66 (s, MeO-C(3,5)), 3.79 (s, MeO-C(4')), 6.46-6.48 (overlap, H-C(2,6,7)), 6.52 (d, *J* = 12.3 Hz, H-C(8)), 6.77-6.80 (m, H-C(3',5')), 7.24-7.27 (m, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.1 (Me-C(4)), 55.2 (MeO-C(4')), 55.6 (MeO-C(3,5)), 104.3 (C(2,6)), 104.4 (C(4)), 113.5 (C(3',5')), 129.2 (C(7)), 129.3 (C(8)), 129.9 (C(1')), 130.3 (C(2',6')), 135.5(C(1)), 158.0 (C(3,5)), 158.7 (C(4')). Positive ion ESI-HRMS: calcd for $C_{18}H_{21}O_3$ $[M+H]^+$, 285.1490; found, 285.1502.

1,3-Dimethoxy-2-methyl-5-(4-nitrostyryl)benzene (**6d**, **7d**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 4-nitrobenzaldehyde **5d** (60.8 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 95:5) to afford **6d** and 7**d**. Compound **6d** was obtained a a yellow solid: 19.0 mg (16.1 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.12 (s, Me-C(4)), 3.89 (s, MeO-C(3,5)), 6.73 (s, H-C(2,6)), 7.10 (d, *J* = 16.2 Hz, H-C(7)), 7.24 (d, *J* = 16.23 Hz, H-C(8)), 7.62-7.64 (m, H-C(2',6')), 8.20-8.23 (m, H-C(3',5')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.4 (Me-C(4)), 55.8 (MeO-C(3,5)), 102.4 (C(2,6)), 116.1 (C(4)), 124.1 (C(3',5')), 125.4(C(7)), 126.7 (C(2',6')), 133.9 (C(8)), 134.5 (C(1)), 143.9 (C(1')), 146.6 (C(4')), 158.5

(C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$, 300.1235; found, 300.1243. Compound **7d** as a yellow solid: 76.0 mg (64.4 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.07 (s, Me-C(4)), 3.63 (s, MeO-C(3,5)), 6.38 (s, H-C(2,6)), 6.57 (d, *J* = 12.2 Hz, H-C(7)), 6.77 (d, *J* = 12.2 Hz, H-C(8)), 7.43-7.45 (m, H-C(2',6')), 8.08-8.10 (m, H-C(3',5')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.2 (Me-C(4)), 55.6 (MeO-C(3,5)), 104.2 (C(2,6)), 114.8 (C(4)), 123.4 (C(3',5')), 127.4 (C(7)), 129.8 (C(2',6')), 134.1 (C(8)), 134.4 (C(1)), 144.5 (C(1')), 146.4 (C(4')), 158.2 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$, 300.1235; found, 300.1237.

5-(4-Fluorostyryl)-1,3-dimethoxy-2-methylbenzene (**6e**, **7e**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 4-fluorobenzaldehyde **5e** (49.9 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 98:2) to afford **6e** and 7**e**. Compound **6e** was obtained as white solid: 21.8 mg (20.3 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.14 (s, Me-C(4)), 3.89 (s, MeO-C(3,5)), 6.70 (s, H-C(2,6)), 6.99 (d, *J* = 16.3 Hz, H-C(7)), 7.03-7.08 (overlap, H-C(8,3',5')), 7.47-7.50 (m, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 55.7 (MeO-C(3,5)), 101.9 (C(2,6)), 114.6 (C(4)), 115.6 (d, *J* = 21.6 Hz, (C(2',6')), 126.7 (d, *J* = 0.8 Hz, C(7)), 127.9 (d, *J* = 7.9 Hz, C(3',5')), 129.0 (d, *J* = 2.4 Hz, C(8)), 133.6 (d, *J* = 3.3 Hz, (C(1')), 135.6 (C(1)), 158.5 (C(3,5)), 162.3 (d, *J* = 247.0 Hz, (C(4')). Positive ion ESI-HRMS: calcd for $C_{17}H_{18}FO_2$ $[M+H]^+$, 273.1290; found, 273.1303. Compound **7e** was a viscous liquid: 29.1 mg (27.1 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.14 (s, Me-C(4)), 3.89(s, MeO-C(3,5)), 6.70 (s, H-C(2,6)), 6.54 (d, *J* = 12.2 Hz, H-C(7)), 6.57 (d, *J* = 12.2 Hz, H-C(8)), 6.93-6.98 (m, H-C(3',5')), 7.28-7.30 (m, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.2 (Me-C(4)), 55.5 (MeO-C(3,5)), 104.3 (C(2,6)), 113.9 (C(4)), 115.0 (d, *J* = 21.4 Hz, (C(2',6')), 128.6 (C(7)), 130.7 (d, *J* = 7.8 Hz, C(3',5')), 130.8 (d, *J* = 1.2 Hz, C(8)), 133.5 (d, *J* = 3.5 Hz,

(C(1')), 134.9 (C(1)), 158.1 (C(3,5)), 161.8 (d, *J* = 246.6 Hz, (C(4')). Positive ion ESI-HRMS: calcd for $C_{17}H_{18}FO_2$ $[M+H]^+$, 273.1290; found, 273.1304.

5-(4-Chlorostyryl)-1,3-dimethoxy-2-methylbenzene (**6f**, **7f**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 4-chlorobenzaldehyde **5f** (56.3 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 98:2) to afford **6f** and 7**f**. Compound **6f** was a white solid: 41.2 mg (36.2 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.14 (s, Me-C(4)), 3.89 (s, MeO-C(3,5)), 6.70 (s, H-C(2,6)), 7.01 (d, *J* = 16.3 Hz, H-C(7)), 7.06 (d, *J* = 16.3 Hz, H-C(8)), 7.32-7.35 (m, H-C(3',5')), 7.43-7.45 (m, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.4 (Me-C(4)), 55.7 (MeO-C(3,5)), 102.0 (C(2,6)), 114.9 (C(4)), 126.5 (C(7)), 127.6 (C(3',5')), 128.8 (C(2',6')), 129.9 (C(8)), 133.0 (C(4')), 135.4 (C(1')), 135.9 (C(1)), 158.5 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{18}ClO_2$ $[M+H]^+$, 289.0995; found, 289.1025. Compound **7f** was a viscous liquid: 36.2 mg (32.0 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.08(s, Me-C(4)), 3.66 (s, MeO-C(3,5)), 6.42 (s, H-C(2,6)), 6.52 (d, *J* = 12.2 Hz, H-C(7)), 6.59 (d, *J* = 12.2 Hz, H-C(8)), 7.21-7.26 (m, H-C(2',3',5',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.2 (Me-C(4)), 55.5 (MeO-C(3,5)), 104.3 (C(2,6)), 114.0 (C(4)), 128.3 (C(3',5')), 128.4 (C(7)), 130.3 (C(2',6')), 131.4 (C(8)), 132.7 (C(4')), 134.8 (C(1')), 136.0 (C(1)), 158.1 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{18}ClO_2$ $[M+H]^+$, 289.0995; found, 289.0971.

5-(4-Bromostyryl)-1,3-dimethoxy-2-methylbenzene (**6g**, **7g**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 4-bromobenzaldehyde **5g** (73.7 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 98:2) to afford **6g** and 7**g**. Compound **6g** was obtained as white solid: 26.2 mg (19.9 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.13 (s, Me-C(4)), 3.88 (s, MeO-C(3,5)), 6.70 (s, H-C(2,6)), 6.99 (d, *J* = 16.2 Hz, H-C(7)), 7.07 (d, *J*

= 16.2 Hz, H-C(8)), 7.37 (d, *J* = 8.4 Hz, H-C(3',5')), 7.48 (d, *J* = 8.4 Hz, H-(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.4 (Me-C(4)), 55.8 (MeO-C(3,5)), 102.0 (C(2,6)), 114.9 (C(4)), 121.1 (C(4')), 126.6 (C(7)), 127.9 (C(3',5')), 130.0 (C(8)), 131.8 (C(2',6')), 135.3 (C(1')), 136.3 (C(1)), 158.5 (C(3,5)). Positive ion EI-HRMS: calcd for $C_{17}H_{18}BrO_2$ $[M]^+$, 332.0411; found, 332.0471. Compound **7g** was a viscous liquid: 41.8 mg (31.8 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.07(s, Me-C(4)), 3.65(s, MeO-C(3,5)), 6.41(s, H-C(2,6)), 6.49 (d, *J* = 12.2 Hz, H-C(7)), 6.60 (d, *J* = 12.1 Hz, H-C(8)), 7.17-7.20 (m, H-C(3',5')), 7.36-7.39 (m, H-(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.2 (Me-C(4)), 55.6 (MeO-C(3,5)), 104.3 (C(2,6)), 114.0 (C(4)), 120.8 (C(4')), 128.4 (C(7)), 130.7 (C(3',5')), 131.3 (C(2',6')), 131.5 (C(8)), 134.7 (C(1')), 136.4 (C(1)), 158.1 (C(3,5)). Positive ion EI-HRMS: calcd for $C_{17}H_{18}BrO_2$ $[M]^+$, 332.0411; found, 3320471.

1,3-Dimethoxy-2-methyl-5-(4-(trifluoromethyl)styryl)benzene (**6h**, **7h**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 4-(trifluoromethyl)ben- zaldehyde **5h** (72.3 mg, 0.394 mmol), then purified by preparative TLC (hexanes/acetone, 95:5) to afford **6h** and 7**h**. Compound **6h** was obtained as white solid: 49.4 mg (38.9 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.15 (s, Me-C(4)), 3.90 (s, MeO-C(3,5)), 6.73 (s, H-C(2,6)), 7.08 (d, *J* = 16.3 Hz, H-C(7)), 7.17 (d, *J* = 16.3 Hz, H-C(8)), 7.59~7.63 (overlap, H-C(2',3',5',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.4 (Me-C(4)), 55.7 (MeO-C(3,5)), 102.2 (C(2,6)), 115.4 (C(4)), 124.26 (q, *J* = 271.7 Hz, CF_3), 125.6 (q, *J* = 3.8 Hz, C(3',5')), 126.2 (C(7)), 126.5 (C(2',6')), 129.1 (q, *J* = 32.4 Hz, C(4')), 131.7 (C(8)), 135.0 (C(1)), 140.9 (q, *J* = 1.4 Hz, C(1')), 158.5 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{18}H_{18}F_3O_2$ $[M+H]^+$, 323.1258; found, 323.1278. Compound **7h** was a viscous liquid: 51.8 mg (40.7 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.08 (s,

Me-C(4)), 3.62 (s, MeO-C(3,5)), 6.38 (s, H-C(2,6)), 6.60 (d, *J* = 12.2 Hz, H-C(7)), 6.68 (d, *J* = 12.2 Hz, H-C(8)), 7.41 (d, *J* = 8.2 Hz, H-C(3',5')), 7.52 (d, *J* = 8.2 Hz, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.1 (Me-C(4)), 55.4 (MeO-C(3,5)), 104.4 (C(2,6)), 114.3 (C(4)), 124.2 (q, *J* = 271.8 Hz, CF_3), 125.1 (q, *J* = 3.8 Hz, C(3',5')), 128.2 (C(7)), 128.9 (q, *J* = 32.4 Hz, C(4')), 129.3 (C(2',6')), 132.7 (C(8)), 134.4 (C(1)), 141.4 (q, *J* = 1.3 Hz, C(1')), 158.1 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{18}H_{18}F_3O_2$ $[M+H]^+$, 323.1258; found, 323.1263.

5-(3,4-Dichlorostyryl)-1,3-dimethoxy-2-methylbenzene (**6i**, **7i**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 3,4-dichlorobenzaldehyde **5i** (70.4 mg, 0.394 mmol), then purified by preparative TLC (hexanes/acetone, 95:5) to afford **6i** and 7**i**. Compound **6i** was a white solid: 43.0 mg (33.7 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.12 (s, Me-C(4)), 3.88 (s, MeO-C(3,5)), 6.68 (s, H-C(2,6)), 6.94 (d, *J* = 16.2 Hz, H-C(7)), 7.06 (d, *J* = 16.2 Hz, H-C(8)), 7.32 (dd, *J* = 8.3, 2.0 Hz, H-C(6')), 7.41 (d, *J* = 8.3 Hz, H-C(5')), 7.59 (d, *J* = 1.9 Hz, H-C(2')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.4 (Me-C(4)), 55.8 (MeO-C(3,5)), 102.1 (C(2,6)), 115.3 (C(4)), 125.3 (C(6')), 125.5 (C(7)), 127.9 (C(8)), 130.5 (C(2')), 130.9 (C(5')), 131.1 (C(4')), 132.8 (C(3')), 134.9 (C(1')), 137.6 (C(1)), 158.5 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{17}Cl_2O_2$ $[M+H]^+$, 323.0606; found, 323.0543. Compound **7i** was a viscous liquid: 46.8 mg (36.7 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.08 (s, Me-C(4)), 3.67 (s, MeO-C(3,5)), 6.43 (s, H-C(2,6)), 6.44 (d, *J* = 12.2 Hz, H-C(7)), 6.62 (d, *J* = 12.2 Hz, H-C(8)), 7.13 (dd, *J* = 8.3, 1.6 Hz, H-C(6')), 7.30 (d, *J* = 8.3 Hz, H-C(5')), 7.44 (d, *J* = 1.8 Hz, H-C(2')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.2 (Me-C(4)), 55.6 (MeO-C(3,5)), 104.3 (C(2,6)), 114.5 (C(4)), 127.0 (C(6')), 128.4 (C(7')), 130.0 (C(8')), 130.7 (C(2',5')), 132.1 (C(4')), 132.5 (C(3')), 134.2 (C(1')), 137.6 (C(1)), 158.1 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{17}H_{17}Cl_2O_2$ $[M+H]^+$, 323.0605;

found, 323.0601.

5-(2,4-Dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene (**6j**, **7j**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 2,4-dimethoxybenzaldehyde **5j** (66.8 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 90:10) to afford **6j** and **7j**. Compound **6j** was obtained as white solid: 31.2 mg (25.2 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.13 (s, Me-C(4)), 3.84 (s, MeO-C(4')), 3.89 (s, MeO-C(3,5)), 3.89 (s, MeO-C(2')), 6.50 (d, *J* = 2.4 Hz, H-C(3')), 6.54 (dd, *J* = 8.5, 2.4 Hz, H-C(5')), 6.72 (s, H-C(2,6)), 7.01 (d, *J* = 16.4 Hz, H-C(7)), 7.35 (d, *J* = 16.4 Hz, H-C(8)), 7.52 (d, *J* = 8.5 Hz, H-C(6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 55.4 (MeO-C(4')), 55.5 (MeO-C(2')), 55.8 (MeO-C(3,5)), 98.5 (C(3')), 101.9 (C(2,6)), 105.0 (C(5')), 113.8 (C(1')), 119.6 (C(4)), 122.5 (C(8)), 127.3 (C(7)), 127.7 (C(6')), 136.7 (C(1)), 158.0 (C(2')), 158.4 (C(3,5)), 160.5 (C(4')). Positive ion ESI-HRMS: calcd for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1596; found, 315.1601. Compound **7j** was obatained as a white solid: 46.0 mg (37.1 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.07 (s, Me-C(4)), 3.65 (s, MeO-C(3,5)), 3.79 (s, MeO-C(4')), 3.83 (s, MeO-C(2')), 6.35 (dd, *J* = 8.5, 2.4 Hz, H-C(5')), 6.48 (d, *J* = 2.4 Hz, H-C(3')), 6.49 (s, H-C(2,6)), 6.52 (d, *J* = 12.1 Hz, H-C(7)), 6.61 (d, *J* = 12.1 Hz, H-C(8)), 7.22 (d, *J* = 8.5 Hz, H-C(6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.1 (Me-C(4)), 55.4 (MeO-C(4')), 55.5 (MeO-C(2')), 55.5 (MeO-C(3,5)), 98.2 (C(3')), 104.2 (C(5')), 104.4 (C(2,6)), 113.3 (C(1')), 119.0 (C(4)), 124.8 (C(8)), 129.5 (C(7)), 130.8 (C(6')), 135.6 (C(1)), 157.8 (C(3,5)), 158.3 (C(2')), 160.3 (C(4')). Positive ion ESI-HRMS: calcd for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1596; found, 315.1600.

5-(3,4-Dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene (**6k**, **7k**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 3,4-dimethoxybenzaldehyde **5k** (66.2 mg, 0.394 mmol),

then purified by preparative TLC (hexanes/ethyl acetate, 80:20) to afford **6k** and 7**k**. Compound **6k** was obtained as white solid: 48.3 mg (38.9 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.11 (s, Me-C(4)), 3.88 (s, MeO-C(3,5)), 3.90 (s, MeO-C(3')), 3.95 (s, MeO-C(4')), 6.69 (s, H-C(2,6)), 6.86 (d, *J* = 8.2 Hz, H-C(5')), 6.95 (d, *J* = 16.2 Hz, H-C(7)), 7.02 (d, *J* = 16.2 Hz, H-C(8)), 7.06 (dd, *J* = 8.3, 1.9 Hz, H-C(6')), 7.08 (d, *J* = 1.7 Hz, H-C(2')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.3 (Me-C(4)), 55.7 (MeO-C(3,5)), 55.8 (MeO-C(3')), 55.9 (MeO-C(4')), 101.8 (C(2,6)), 108.7 (C(2')), 111.3 (C(5')), 114.2 (C(4)), 119.8 (C(6')), 127.4 (C(8)), 127.6 (C(7)), 130.5 (C(1')), 135.9 (C(1)), 148.9 (C(4')), 149.1 (C(3')), 158.4 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1596; found, 315.1595. Compound **7k** was obtained as white solid: 60.2 mg (48.6 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (s, Me-C(4)), 3.66 (s, MeO-C(3,5)), 3.67 (s, MeO-C(3')), 3.85 (s, MeO-C(4')), 6.49 (s, H-C(2,6)), 6.50 (s, H-C(7,8)), 6.76 (d, *J* = 8.2 Hz, H-C(5')), 6.85 (d, *J* = 1.9 Hz, H-C(2')), 6.87 (dd, *J* = 8.2, 2.0 Hz, H-C(6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ8.1 (Me-C(4)), 55.6 (MeO-C(3,5)), 55.6 (MeO-C(3')), 55.8 (MeO-C(4')), 104.3 (C(2,6)), 110.8 (C(2')), 111.9 (C(5')), 113.5 (C(4)), 121.9 (C(6')), 129.4 (C(8)), 129.5 (C(7)), 130.1 (C(1')), 135.5 (C(1)), 148.1 (C(4')), 148.4 (C(3')), 158.0 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1596; found, 315.1602.

5-(3,5-Dimethoxystyryl)-1,3-dimethoxy-2-methylbenzene (**6l**, **7l**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 3,5-dimethoxybenzaldehyde **5l** (65.5 mg, 0.394 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 90:10) to afford **6l** and 7**l**. Compound **6l** as a white solid: 26.0 mg (20.9 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.13 (s, Me-C(4)), 3.84 (s, MeO-C(3,5)), 3.89 (s, MeO-C(3',5')), 6.41 (t, *J* = 2.2 Hz, H-C(4')), 6.70 (d, *J* = 2.2 Hz,

H-C(2',6')), 6.71 (s, H-C(2,6)), 7.01 (d, *J* = 16.2 Hz, H-C(7)), 7.08 (d, *J* = 16.2 Hz, H-C(8)). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 55.4 (MeO-C(3,5)), 55.7 (MeO-C(3',5')), 100.0 (C(4')), 102.0 (C(2',6')), 104.5 (C(2,6)), 114.7 (C(4)), 127.8 (C(7)), 129.7 (C(8)), 135.5 (C(1)), 139.4 (C(1')), 158.4 (C(3,5)), 161.0 (C(3',5')). Positive ion ESI-HRMS: calcd for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1596; found, 315.1595. Compound **7l** was a white solid: 46.0 mg (37.1 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.07 (s, Me-C(4)), 3.66 (s, MeO-C(3,5)), 3.69 (s, MeO-C(3',5')), 6.34 (t, *J* = 2.3 Hz, H-C(4')), 6.49 (d, *J* = 2.4 Hz, H-C(2,6,2',6')), 6.53 (d, *J* = 12.3 Hz, H-C(7)), 6.56 (d, *J* = 12.2 Hz, H-C(8)). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.1 (Me-C(4)), 55.2 (MeO-C(3,5)), 55.5 (MeO-C(3',5')), 99.7 (C(4')), 104.5 (C(2',6')), 106.7 (C(2,6)), 113.8 (C(4)), 129.7 (C(7)), 131.0 (C(8)), 135.0 (C(1)), 139.5 (C(1')), 157.9 (C(3,5)), 160.6 (C(3',5')). Positive ion ESI-HRMS: calcd for $C_{19}H_{23}O_4$ $[M+H]^+$, 315.1596; found, 315.1599.

5-(2,6-Dimethoxy-4-methylstyryl)-1,3-dimethoxy-2-methylbenzene (**6m**, **7m**). Compound **4a** (200 mg, 0.394 mmol) was reacted with 2,6-dimethoxy-4- methylbenzaldehyde **5m** (73.2 mg, 0.394 mmol), then purified by preparative TLC (hexanes/acetone, 90:10) to afford **6m** and 7**m**. Compound **6m** was obtained as white solid: 20.5 mg (15.8 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.12 (s, Me-C(4)), 2.38 (s, Me-C(4')), 3.89 (s, MeO-C(3,5)), 3.90 (s, MeO-C(2',6')), 6.43 (s, H-C(2,6)), 6.72 (s, H-C(3',5')), 7.38 (d, *J* = 16.6 Hz, H-C(7)), 7.51 (d, *J* = 16.6 Hz, H-C(8)). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 22.2 (Me-C(4')), 55.8 (MeO-C(3,5)), 55.8 (MeO-C(2',6')), 101.9 (C(2,6)), 105.0 (C(3',5')), 112.1 (C(1')), 113.5 (C(4)), 119.2 (C(7)), 132.0 (C(8)), 137.9 (C(1)), 138.4 (C(4')), 158.3 (C(3,5)), 158.4 (C(2',6')). Positive ion ESI-HRMS: calcd for $C_{20}H_{25}O_4$ $[M+H]^+$, 329.17528; found, 329.17524.

Compound **7m** was a white solid: 73.5 mg (56.8 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.05 (s, Me-C(4)), 2.36 (s, Me-C(4')), 3.59 (s, MeO-C(3,5)), 3.65 (s, MeO-C(2',6')), 6.38 (s, H-C(2,6)), 6.40 (s, H-C(3',5')), 6.42 (d, *J* = 12.0 Hz, H-C(7)), 6.67 (d, *J* = 12.0 Hz, H-C(8)). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.1 (Me-C(4)), 22.1 (Me-C(4')), 55.3 (MeO-C(3,5)), 55.6 (MeO-C(2',6')), 103.6 (C(2,6)), 104.8 (C(3',5')), 112.8 (C(1')), 113.1 (C(4)), 121.0 (C(7)), 132.0 (C(8)), 136.7 (C(1)), 138.8 (C(4')), 157.5 (C(3,5)), 157.6 (C(2',6')). Positive ion ESI-HRMS: calcd for $C_{20}H_{25}O_4$ $[M+H]^+$, 329.1752; found, 329.1768.

1,3-Dimethoxy-5-(4-((3-methylbut-2-en-1-yl)oxy)styryl)benzene (**6n**, **7n**). (3,5-Dimethoxybenzyl)triphenylphosphonium **4b** (379.5 mg, 0.769 mmol) was reacted with 4-((3-methylbut-2-en-1-yl)oxy)benzaldehyde **5n** (154.0 mg, 0.769 mmol), then purified by preparative TLC (hexanes/ethyl acetate, 97:3) to afford **6n** and 7**n**. Compound **6n** was a white solid: 56.4 mg (22.6 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.76 (s, H-C(5")), 1.81 (s, H-C(4")), 3.83 (s, MeO-C(3,5)), 4.53 (d, *J* = 6.7 Hz, H-C(1")), 5.49-5.53 (m, H-C(2")), 6.38 (t, *J* = 2.2 Hz, H-C(4)), 6.65 (d, *J* = 2.2 Hz, H-C(2,6)), 6.89-6.92 (overlap, H-C(7,3',5')), 7.04 (d, *J* = 16.2 Hz, H-C(8)), 7.44 (d, *J* = 8.7 Hz, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.2 (C(5")), 25.8 (C(4")), 55.3 (MeO-C(3,5)), 64.8 (C(1")), 99.6 (C(4)), 104.3 (C(2,6)), 114.9 (C(3',5')), 119.6(C(2")), 126.5 (C(7)), 127.8 (C(2',6')), 128.8 (C(8)), 129.8 (C(1')), 138.3 (C(3")), 139.7 (C(1)), 158.7 (C(4')), 161.0 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{21}H_{25}O_3$ $[M+H]^+$, 325.1803; found, 325.1842. Compound **7n** was a viscous liquid: 163.2 mg (65.4 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.65 (s, H-C(5")), 1.71 (s, H-C(4")), 3.58 (s, MeO-C(3,5)), 4.40 (d, *J* = 6.7 Hz, H-C(1")), 5.38-5.40 (m, H-C(2")), 6.24 (t, *J* = 2.0 Hz, H-C(4)), 6.34-6.37 (overlap, H-C(2,6,7)), 6.44 (d, *J* = 12.3 Hz, H-C(8)), 6.70 (d, *J* = 8.6 Hz,

H-C(3',5')), 7.13 (d, J = 8.7 Hz, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 18.1 (C(5")), 25.7 (C(4")), 55.1 (MeO-C(3,5)), 64.6 (C(1")), 99.6 (C(4)), 106.5 (C(2,6)), 114.2 (C(3',5')), 119.6 (C(2")), 128.5 (C(7)), 129.4 (C(8)), 130.1 (C(1')), 130.1 (C(2',6')), 138.0 (C(3")), 139.4 (C(1)), 158.0 (C(4')), 160.5 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{21}H_{25}O_3$ $[M+H]^+$, 325.1803; found, 325.1804.

4-(3,5-Dimethoxystyryl)-2-(3-methylbut-2-en-1-yl)phenol (**11**, **12**). Compound **4b** (453.9 mg, 0.92 mmol) was reacted with 4-((*tert*-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde **9** (280 mg, 0.92 mmol), then purified by flash chromatography (hexanes/ethyl acetate, 97:3) to afford 270 mg (66.9 % yield) of a mixture of *cis* and *trans* stilbenes **10** (*Scheme 3*). Due to difficulty encountered in separating the two isomers, deprotection of TBS group was performed without isolation of the isomers. To a solution of **10** (270 mg, 0.61 mmol) in anhydrous THF was added tetrabutylammnonium fluoride (TBAF) (800 μL, 0.80 mmol). The solution was stirred for 45 min, poured into water, extracted with dichloromethane and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by preparative TLC (hexanes/ethyl acetate, 80:20) to afford to afford **11** and **12**. Compound **11** was obtained as a viscous liquid: 84.7 mg (42.4 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.80 (s, H-C(5")), 1.81 (s, H-C(4")), 3.39 (d, J = 7.2 Hz, H-C(1")), 3.83 (s, MeO-C(3,5)), 5.31 (brs, OH), 5.33-5.37 (m, H-C(2")), 6.39 (t, J = 2.2 Hz, H-C(4)), 6.66 (d, J = 2.2 Hz, H-C(2,6)), 6.80 (d, J = 8.0 Hz, H-C(5')), 6.89 (d, J = 16.2 Hz, H-C(7)), 7.02 (d, J = 16.2 Hz, H-C(8)), 7.26-7.29 (overlap, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.9 (C(5")), 25.8 (C(4")), 29.8 (C(1")), 55.4 (MeO-C(3,5)), 99.6 (C(4)), 104.3 (C(2,6)), 116.0 (C(5')), 121.6 (C(2")), 125.8 (C(6')), 126.3

(C(7)), 127.1 (C(2')), 128.4 (C(3')), 129.0 (C(8)), 130.0 (C(1')), 134.9 (C(3")), 139.8 (C(1)), 154.3 (C(4')), 160.9 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{21}H_{25}O_3$ $[M+H]^+$, 325.1803; found, 325.1800. Compound **12** was a viscous liquid: 35.8 mg (17.9 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.72 (s, H-C(5")), 1.74 (s, H-C(4")), 3.26 (d, *J* = 7.2 Hz, H-C(1")), 3.68 (s, MeO-C(3,5)), 5.21-5.25 (m, H-C(2")), 5.27 (s, OH), 6.34 (t, *J* = 2.3 Hz, H-C(4)), 6.44 (d, *J* = 12.2 Hz, H-C(7)), 6.47 (d, *J* = 2.2 Hz, H-C(2,6)), 6.51 (d, *J* = 12.2 Hz, H-C(8)), 6.66 (d, *J* = 8.1 Hz, H-C(5')), 7.03-7.05 (overlap, H-C(2',6')). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 17.8 (C(5")), 25.7 (C(4")), 29.3 (C(1")), 55.2 (MeO-C(3,5)), 99.7 (C(4)), 106.6 (C(2,6)), 115.3 (C(5')), 121.6 (C(2")), 126.6 (C(6')), 128.2 (C(7)), 128.5 (C(2')), 129.6 (C(3')), 130.4 (C(8)), 130.8 (C(1')), 134.4 (C(3")), 139.6 (C(1)), 153.4 (C(4')), 160.5 (C(3,5)). Positive ion ESI-HRMS: calcd for $C_{21}H_{25}O_3$ $[M+H]^+$, 325.1803; found, 325.1802.

(E)-4-(3,5-dimethoxy-4-methylstyryl)phenol (**16**). Compound **4a** (326.5 mg, 0.643 mmol) was reacted with 4-((*tert*-butyldimethylsilyl)oxy)benzaldehyde **13** (152.0 mg, 0.643 mmol), then purified by flash chromatography (hexanes/ethyl acetate, 97:3) to afford 185.7 mg (75.0 % yield) of a mixture of *cis* and *trans* stilbenes **14** (*Scheme 4*). To a solution of **14** (185.7 mg, 0.483 mmol) in THF was added TBAF (628 μl, 0.628 mmol). The solution was stirred for 45 min, poured into water, and extracted with dichloromethane. The solvent was removed under reduced pressure, and the crude product was purified by preparative TLCs (hexanes/ethyl acetate, 80:20) to afford (*E*)-4-(3,5-dimethoxy-4-methylstyryl)phenol **16** as a light-yellow solid (98.2 mg, 75.2 %). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.11 (s, Me-C(4)), 3.88 (s, MeO-C(3,5)), 5.11 (brs, OH), 6.68 (s, H-C(2,6)), 6.83 (dd, *J* = 8.6, 2.0 Hz, H-C(3',5')), 6.93 (d, *J* = 16.2 Hz, H-C(7)), 7.01 (d, *J* = 16.2 Hz, H-C(8)), 7.41 (d, *J* = 8.5 Hz, H-C(2',6')).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 8.3 (Me-C(4)), 55.8 (MeO-C(3,5)), 101.8 (C(2,6)), 114.2 (C(4)), 115.6 (C(3',5')), 127.2 (C(7)), 127.4 (C(8)), 127.8 (C(2',6')), 130.3 (C(1')), 136.0 (C(1)), 155.2 (C(4')), 158.4 (C(3,5)). Negative ion ESI-HRMS: calcd for $C_{17}H_{17}O_3$ $[M–H]^-$, 269.1177; found, 269.1197.

(E)-5-(4-hydroxystyryl)-2-methylbenzene-1,3-diol (**17**). To a cold solution (-20 °C) of **16** (30 mg, 0.111 mmol) in anhydrous CH_2Cl_2 was added, dropwise, BBr_3 (153 mg, 0.611 mmol) (*Scheme 4*). The mixture was allowed to warm to room temperature, and was stirred for 10 h. The reaction was quenched by ice-water, and extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by preparative TLC (hexanes/ethyl acetate, 60:40) to afford (*E*)-5-(4-hydroxystyryl)-2-methylbenzene-1,3-diol **17** (9.0 mg, 33.5 %) as a white solid. ^{1}H NMR (Acetone-d_6, 500 MHz): δ 2.09 (s, Me-C(4)), 6.60 (s, H-C(2,6)), 6.83 (d, *J* = 8.6 Hz, H-C(3',5')), 6.83 (d, *J* = 16.3 Hz, H-C(7)), 6.92 (d, *J* = 16.3 Hz, H-C(8)), 7.38 (d, *J* = 8.6 Hz, H-C(2',6')), 8.09 (s, OH-C(3,5)), 8.46 (s, OH-C(4')). ^{13}C NMR (Acetone-d_6, 125 MHz): δ 7.8 (Me-C(4)), 104.6 (C(2,6)), 110.2 (C(4)), 115.5 (C(3',5')), 126.1 (C(7)), 127.1 (C(8)), 127.6 (C(2',6')), 129.2 (C(1')), 136.1 (C(1)), 156.4 (C(3,5)), 157.1(C(4')). Positive ion ESI-HRMS: calcd for $C_{15}H_{15}O_3$ $[M+H]^+$, 243.1021; found, 243.1028.

4-((Tert-butyldimethylsilyl)oxy)-3-(3-methylbut-2-en-1-yl)benzaldehyde (**9**). To a solution of 4-hydroxy-3-(3-methylbut-2-en-1-yl)benzaldehyde **8** (200 mg, 1.0 mmol), was added imidazole (96.3 mg, 1.4 mmol) in DMF (10 ml) and tertbutyldimethylsilyl chloride (202 mg, 1.3 mmol). The solution was left stirring for 20 h at room temperature, and then the mixture was poured into water and extracted with ethyl acetate. The organic phase was

combined and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/ethyl acetate, 95:5) to give **9** (283.2 mg, 90.3%) as a viscous liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.29 (s, Me-Si), 1.02 (s, $(CH_3)_3$C-Si), 1.70 (s, H-C(5')), 1.77 (s, H-C(4')), 3.34 (d, *J* = 7.2 Hz, H-C(1')), 5.29-5.33 (m, H-C(2')), 6.88 (d, *J* = 8.3 Hz, H-C(5)), 7.62 (dd, *J* = 8.3, 2.2 Hz, H-C(6)), 7.67 (d, *J* = 2.1 Hz, H-C(2)), 9.85 (s, CHO). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.1 (Me-Si), 17.9 (C(5')), 18.3 (C(4')), 25.7 ($(CH_3)_3$), 25.8 (C(1')), 28.4 (C-Si), 118.4 (C(5)), 121.5 (C(2')), 129.5 (C(6)), 130.1 (C(3')), 131.4 (C(1)), 133.3 (C(2)), 133.6 (C(3)), 159.3 (C(4)), 191.2 (CHO). Positive ion ESI-HRMS: calcd for $C_{18}H_{29}O_2Si$ $[M+H]^+$, 305.1936; found, 305.1895.

(3,5-Dimethoxy-4-methylbenzyl)triphenylphosphonium Bromide (**4a**). To a solution of 5-(bromomethyl)-1,3-dimethoxy-2-methylbenzene (500 mg, 1.938 mmol) in toluene (10 ml) was added triphenylphosphine (565.4 mg, 2.134 mmol). The solution was heated at reflux for 6 h. The resulting precipitate was collected and recrystallized from ethanol as a white solid (930.0 mg, 94.5%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.89 (s, Me-C(4)), 3.39 (s, MeO-C(3,5)), 5.12 (d, *J* = 15.4 Hz, CH_2-C(1)), 6.22 (s, H-C(2,6)), 7.67-7.76 (m, H-C(2',3',5',6',2",3",5",6",2"',3"',5"',6"')), 7.89 (t, *J* = 7.3 Hz, H-C(4',4",4"')). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 8.5 (d, *J* = 1.3 Hz, Me-C(4)), 29.4 (d, *J* = 46.8 Hz, CH_2), 55.8 (MeO-C(3,5)), 107.0 (d, *J* = 5.7 Hz, C(2,6)), 113.4 (d, *J* = 4.3 Hz, C(4)), 118.4 (d, *J* = 85.5 Hz, C(4',4",4"')), 126.5 (d, *J* = 8.7 Hz, C(1)), 130.5 (d, *J* = 12.4 Hz, C(3',5',3",5",3"',5"')), 134.6 (d, *J* = 9.8 Hz, C(2',6',2",6",2"',6"')), 135.5 (d, *J* = 2.9 Hz, C(1',1",1"')), 157.9 (d, *J* = 3.5 Hz, C(3,5)). Positive ion ESI-HRMS: calcd for $C_{28}H_{28}O_2P$ $[M–Br]^+$, 427.1826; found, 427.1913.

***Aedes aegypti* larvicidal assay.** All of the analogs were screened for activity against *Ae. aegypti* larvae following a bioassay system described in Ali et al., 2014 [24]. *Ae. aegypti* larvae used in these studies were from a laboratory colony maintained at the Mosquito and Fly Research Unit at the Center for Medical, Agricultural and Veterinary Entomology, USDA-ARS, Gainesville, Florida. For larval bioassays, the eggs were hatched and the larvae were maintained at a temperature of 27 ± 2˚C and 60 ± 10 % RH with a photoperiod regimen of 12:12 h (L: D). Five 1-d-old *Ae. aegypti* larvae were added in a droplet of water to each well of 24-well plates (BD Labware, Franklin Lakes, NJ) by use of a disposable 22.5 cm Pasteur pipette. Fifty microliters of larval diet (2% slurry of 3:2 beef liver powder (Now Foods, Bloomingdale, Illinois) and Brewer's yeast (Lewis Laboratories Ltd., Westport, CT) was added to each well by using a Finnpipette stepper (Thermo Fisher, Vantaa, Finland). All chemicals tested were diluted in dimethyl sulfoxide (DMSO). Eleven microliters of the test chemical was added to the labeled wells, while 11 µL of DMSO was added to control treatments. After the treatment application, the plates were swirled in clockwise and counterclockwise motions and front and back and side to side five times to ensure even mixing of the chemicals. Larval mortality was recorded 24-h post treatment. Larvae that showed no movement in the well after manual disturbance of the water were recorded as dead. Three dosages, 100, 50 and 25 ppm, were used in the screening bioassay to determine the larvicidal activity and each treatment was replicated twice. A series of 4 dosages ranging between 50 and 6.25 ppm was used to determine the dose-response of **11** and **12**, which showed high activity in the screening bioassay. Each treatment was replicated 10 times.

Statistical Analyses. LC_{50} values for larvicidal data were calculated by using SAS, Proc

Probit [25]. Control mortality was corrected by using Abbott's formula [16].

Testing for activity against larvae and adult pyrethroid-resistant and susceptible strains of *Aedes aeypti*. Further tests were performed on **11** and **12** to determine their effect on larvae and adult mosquitoes. The compounds were tested in the standard bioassays using the Orlando (ORL), pesticide-susceptible strain and the Puerto Rico (PR), pyrethroid-resistant strain of *Ae. aegypti*. The Orlando strain has been in continuous colony since 1952 with no pesticide exposure while the resistant PR strain was colonized from egg papers collected near San Juan, PR in June, 2012. The PR strain is available as a resistant reference strain through BEIResources/CDC [27]. Mortality was determined in the larval assays at four different concentrations (1, 0.5, 0.25, and 0.1µg/µl) and three concentrations for adults (6.25%, 3.125% and 1.56%). Mortality was recorded 24 hours post application and in all assays a negative solvent and a positive control using permethrin were utilized, tests were done I triplicate (**Tables 2 and 3**). Assays were conducted according to published procedures [28].

Testing for activity against *Meloidogyne incognita*. Two types of assays were used to investigate activity against *M. incognita*: A) eggs were immersed in solutions of the test compounds, and B) second-stage juveniles (J2) previously hatched from eggs immersed in the test solutions. These assays were conducted with procedures similar to those in Meyer et al. [29]. *Meloidogyne incognita* race 1 (originally isolated in 2013 from a field in Maryland) was grown in the greenhouse on pepper (*Capsicum annuum* L.) cultivar PA-136. Egg masses were hand-picked from plant roots, rinsed three times with sterile distilled water, and agitated in 0.6% sodium hypochlorite for 3½ min to separate and surface-sterilize eggs. The eggs were rinsed in sterile distilled water and stored overnight at 4°C prior to use in egg

immersion assays. To collect J2 for direct immersion into the test compounds, sterilized eggs were placed into a hatching chamber comprised of a Spectra/Mesh Nylon Filter (openings 25 µm in diameter; Spectrum Laboratories Inc., Rancho Dominguez, CA) in an autoclaved dish. J2 that passed through the filter within 3 d were used immediately for assays.

The assays were conducted in 96-well polystyrene plates. For the assays with immersed eggs, each well received ca. 50 eggs in 35 µl sterile deionized water (SDW). For assays with previously hatched J2, a suspension of ca. 50 J2 in 35 µL SDW was placed into each well. Each well then received 165 µl of treatment or control. The solvent used to dissolve the test chemicals was a 1:1:1 mixture referred to herein as CTD: comprised of equal parts Cremophor® EL Castor Oil (BASF Corporation, Vandalia, IL), Tween 80® (Sigma-Aldrich, St. Louis, MO), and dimethyl sulfoxide (DMSO; Sigma-Aldrich). A high and low rate of each compound was tested. After addition to the nematode suspensions in the wells, the low and high rates were 83.3 µg/mL and 166.7 µg/mL of each test compound, respectively, dissolved in 0.5% and 1.0% of each of the three combined solvents. Controls were CTD equivalent to the low and high rates, and SDW. Because of the large number of treatments, the test compounds were divided into two groups for the egg immersion assays. The compounds tested in egg immersion Assay 1 were **3**, **6a**, **6e**, **6f**, **6g**, **6n**, **7a**, **7c**, , **7e, 7f**, **7n**, **11**, **12**, **16**, and **17**. The compounds tested in egg immersion Assay 2 were **6b**, **6h**, **6i**, **6j**, **6k**, **6l**, **7b**, **7g**, **7h**, **7i**, **7j**, **7k**, **7l**, and **7m**. Test compounds used for assays with previously hatched J2 were selected based on results with the egg assays. The five compounds tested were **6b, 6f**, **6g**, **6i**, and **7k**, high and low rates. Assays were then repeated with **6g** and **7k**,

high rates.

Each polystyrene culture plate was covered with a plastic adhesive sheet (Excel Scientific, Inc., Victorville CA) and incubated at 25°C. Ten wells (water controls) or five wells (all other treatments) were used per treatment in each assay. In the egg immersion assays, total numbers of hatched J2, and numbers of mobile and immobile J2, were counted after 2 d and 7 d incubation in the test compounds. In the first assay with previously hatched J2, the numbers of mobile and immobile J2 were counted after 1 and 2 d incubation, the treatments removed and replaced with a SDW rinse, and 2 d later the mobile vs. immobile J2 counted again. In the assays with **6g** and **7k**, high rates, counts were made on Days 1, 2, 4 and 6, without a SDW rinse.

Statistical methods. Data from the *M. incognita* assays were analyzed with the statistical package JMP 11.2.0 (SAS Institute, Cary, NC). Differences among numbers of hatched J2 in each treatment, and among percentage of mobile J2 per treatment (number mobile J2/total J2 × 100), were determined by ANOVA, and means were compared using Tukey Kramer's adjustment for multiple comparisons ($P \leq 0.05$). For percent mobile J2 on Day 2 in egg immersion Assays 1 and 2, and Day 4 with the five compounds in the J2 immersion assay, data were $\log_{10}(x+1)$-transformed prior to analysis. Data presented are non-transformed means.

Assay against plant-pathogenic fungi. The analogs were tested for activity against *Botrytis cinerea* Pers.:Fr, *Colletotrichum acutatum* Simmonds, *C. fragariae* Brooks, *C. gloeosporioides* (Penz.) Penz. & Sacc. in Penz., and *Fusarium oxysporum* Schlechtend:Fr using a direct bioautography method as previously described [30, 31]. Technicial grade

commercial fungicide standards benomyl, cyprodinil, azoxystrobin, and captan were used at 0.9 to 1.61 µg/µl concentrations in 95% ethanol. After sample application, each TLC plate was subsequently sprayed with a spore suspension (3.0 x 10^5 spores/ml) of the fungus of interest and incubated in a moisture chamber for 4 days at 26°C with a 12 h photoperiod. Clear zones of fungal growth inhibition on the TLC plate indicated the presence of antifungal constituents in each extract or pure compound. The test compounds were prepared at 2 mM solution in 95% ethanol, and 4 µl were spotted on the plates (2 µl of the positive controls).

Assays againt human-associated microorganisms. All organisms were obtained from the American Type Culture Collection (Manassas, VA) and included the fungi *Candida albicans* ATCC 90028, *C. glabrata* ATCC 90030, *C. krusei* ATCC 625), *Cryptococcus neoformans* ATCC 90113, and *Aspergillus fumigatus* ATCC 204305, and the bacteria *Staphylococcus aureus* ATCC 29213, methicillin-resistant *S. aureus* ATCC 33591 (MRSA), *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, and *Mycobacterium intracellulare* ATCC 23068. All organisms were tested using modified versions of the CLSI (formerly NCCLS) methods. For all organisms excluding *M. intracellulare* and *A. fumigatus*, optical density is used to monitor growth [32], [33]. Medium supplemented with 5% Alamar Blue™ (BioSource International, Camarillo, CA) was utilized for growth detection of *M. intracellulare* [34], [35] and *A. fumigatus* [36]. Samples (dissolved in DMSO) were serially-diluted in 20% DMSO/saline and transferred (10µL) in duplicate to 96 well flat-bottom microplates. Inocula were prepared by correcting the OD630 of microbe suspensions in incubation broth [RPMI 1640/0.2% dextrose/0.03% glutamine/MOPS @ pH 6.0 (Cellgro) for *Candida* spp., Sabouraud Dextrose for *C. neoformans*, cation-adjusted

Mueller-Hinton (Difco) @ pH 7.3 for *Staphylococcus* spp., *E. coli*, and *P. aeruginosa*, 5% Alamar Blue™ (BioSource International, Camarillo, CA) in Middlebrook 7H9 broth with OADC enrichment, pH = 7.0 for *M. intracellulare*, and 5% Alamar Blue™/RPMI 1640 broth (0.2% dextrose, 0.03% glutamine, buffered with 0.165M MOPS at pH 7.0) for *A. fumigatus* to afford an assay volume of 200 µl and final target inocula of: *Candida* spp. and *C. neoformans*.: 1.5 X 10^3, *M. intracellulare*: 2.0 x 10^6, *Staphylococcus* spp., *E. coli, P. aeruginosa*: 5.0 X 10^5 CFU/ml, and *A. fumigatus*: 2.7 x10^4 CFU/ml. Final sample test concentrations were 1/100th the DMSO stock concentration. Drug controls [Ciprofloxacin (ICN Biomedicals, Ohio) for bacteria and Amphotericin B (ICN Biomedicals, Ohio) for fungi] were included in each assay. All organisms were read at either 530 nm using the Biotek Powerwave XS plate reader (Bio-Tek Instruments, Vermont) or 544ex/590em, (*M. intracellulare, A. fumigatus*) using the Polarstar Galaxy Plate Reader (BMG LabTechnologies, Germany) prior to and after incubation: *Candida* spp. at 35°C for 46-50 h, *Staphylococcus* spp., *E. coli*, and *P. aeruginosa* at 35°C for 16-20 h, *C. neoformans* at 35°C for 70-74 h, *A. fumigatus* at 35°C for 46-50 h, and *M. intracellulare* at 37°C and 10% CO2 for 70-74 h. IC_{50} values (concentrations that afford 50% inhibition relative to controls) were calculated using XLfit 4.2 software (IDBS, Alameda, CA) using fit model 201. Toxicity of **6a, 7a, 7c, 7e, 11,** and **12** are provided in Supplemental Table 1. Lipinski parameters for **6a, 7a, 7c, 11, 12** and **16** are provided in Supplemental Table 2.

DISCLAIMER

Mention of trade names or commercial products in this paper is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the U.S. Department of Agriculture. The authors declare no competing financial interest.

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Table 1. Toxicity of compounds **11** and **12** against 1-d-old larvae of *Aedes aegypti*.

Compound	LD_{50} (95% CI)[a]	LD_{90} (95% CI)	χ^2	df
11	14.7 (12.6 ± 17.01)[#]	34.7 (28.3 ± 46.7)	72.4	38
12	16.2 (14.0 ± 18.7)[#]	37.9 (30.84 ± 51.1)	74.7	38

[a] LD_{50} and LD_{90} values are given in ppm (95% confidence interval).

[#]14.7 ppm of **11** = 45.31 µM; 16.2 ppm of **12** = 49.93 µM.

Table 2. Activity of compounds **11** and **12** against larvae of ORL and PR strains of *Aedes aegypti*.

		Concentration (µg/µL)			
	Compound	1.0	0.5	0.25	0.1[#]
ORL strain[a]	**11**	100*	100	100	100
	12	93.3 ± 11.5	93.3 ± 11.5	93.3 ± 11.5	66.7 ± 23.1
	Permethrin				100
PR strain[b]	**11**	100	100	100	93.3 ± 11.5
	12	93.3 ± 11.5	93.3 ± 11.5	73.3 ± 11.5	73.3 ± 11.5
	Permethrin				93.3 ± 11.5

*Values are percent mortality ± SD for mosquito larvae after 24 hours, (n=3).

[a] ORL = Orlando, nonpesticide-resistant strain. DMSO-treated wells = 0% mortality.

[b] PR = Puerto Rico, pesticide-resistant strain. DMSO-treated wells = 6.7 ± 11.5 % mortality.

[#] 0.1 µl/µL Cpd **11** and **12** = 3.08 µM; 0.1 µl/µL permethrin = 2.55 µM.

Table 3. Activity of Compounds **11** and **12** against adult ORL and PR strains of *Aedes aegypti*.

		Concentration (%)[#]		
	Compound	6.25	3.125	1.56
ORL strain[a]	**11**	24.2 ± 10.1*	3.3 ± 5.8	1.56%
	12	20 ± 10	3.3 ± 5.8	3.3 ± 5.8
	Untreated	0		
	Acetone	3.3 ± 5.8		
	Permethrin	100		
PR strain[b]	**11**	30 ± 26.5	23.3 ± 20.8	10 ± 10
	12	33.3 ± 30.6	12.1 ± 21	20 ± 20
	Untreated	3.3 ± 5.8		
	Acetone	6.7 ± 2.9		
	Permethrin	85 ± 10		

*Values are percent mortality for adult mosquitoes after 24 hours, (n=3).

[a] ORL = Orlando, pesticide-susceptible strain.

[b] PR = Puerto Rico, permetrhin-resistant strain.

[#]6.25, 3.125, and 1.56% **11** or **12** = 192.65, 96.32, 48.08 mM, respectively; 6.25% permethrin = 159.72 mM.

Table 4. Activity of Compounds **6f, 6g, 6i, and 7k** against *Meloidogyne incognita* second-stage juveniles (J2) previously hatched from eggs immersed in treatment solutions.*

Treatment[1]	Percent mobile J2[2] Assay 1	Percent mobile J2[2] Assay 2
Day 2		
Water	87.8% a[3]	97.2% a
CTD low	82.0% a	100.0% a
CTD high	75.1% a	100.0% a
Compound **6i** low	NT[4]	71.0% c
Compound **6i** high	NT	100.0% a
Compound **7k** low	NT	92.5% ab
Compound **7k** high	NT	72.2% bc
Day 7		
Water	94.0% a	96.1% a
CTD low	89.8% abcd	96.7% a
CTD high	90.2% abcd	94.1% ab
Compound **6f** low	93.9% a	NT
Compound **6f** high	71.3% f	NT
Compound **6g** low	89.2% abcd	NT
Compound **6g** high	74.6% ef	NT
Compound **6i** low	NT	87.2% b
Compound **6i** high	NT	93.2% ab

*Mobile and immobile J2 were counted after 2 and 7 days of incubation.

[1] The solvent, CTD, was a mixture of equal parts Cremophor® EL Castor Oil, Tween 80®, and dimethylsulfoxide (DMSO). The low rate of each compound was 83.3µg/ml dissolved in 0.5% of each of the combined solvents; the high rate was 166.7 µg/ml test compound dissolved in 1.0%. Thus, the concentration of **6f** low = 214.64 µM, high = 429.54 µM; **6g** low = 250.87 µM, high = 502.05 µM; **6i** low = 258.65 µM, high = 517.62 µM; **7k** low = 265.16 µM, high= 530.64 µM.

[2] Percent mobile J2 = (number of mobile J2/total hatched J2) × 100.

[3] Means are comparable within a column for each day; significance letters are not comparable between columns or between days.

[4] NT = not tested in that assay.

Table 5. Activity of Compounds **6a**, **7a** and **7e** against *Colletotrichum* species.*

	C. acutatum	*C. fragariae*	*C. gloeosporioides*
Compound[a]	4 µL	4 µL	4 µL
6a	5	5	5.5
7a	8	6.5	7
7e	6	6	6
Standard[a]	2 µL	2 µL	2 µL
Azoxystrobin	15	17.5	17.5
Benomyl	17	20	20
Captan	11.5	18.5	18.5
Cyprodinil	18	21.5	21.5

*Values are zones of inhibition (mm), average of 2 assays.

[a] Concentration of compounds and standards is 2 mM. Thus, there is 2.03 µg in of **6a** and **7a** in 4 µl, 2.17 µg of **7e** 4 µl, 1.61 µg of Azoxystrobin in 2 µl, 1.16 µg of Benomyl in 2 µl, 1.20 µg of Captan in 2 µl, and 0.90 µg of Cyprodinil in 2 µl.

Table 6. Activity of Compounds **11**, **12**, and **16** against human pathogens.

	Cryptococcus neoformans		*Staphylococus aureus*		MRSA*		*Mycobacterium intracellulare*	
Compound	IC_{50}**	MIC**	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC
11	13.63	30.84	13.11	30.84	9.10	15.42	47.17	61.68
12	41.77	61.68	17.03	30.84	13.02	30.84	50.40	61.68
16	5.22	9.25	20.43	74.04	43.72	74.04	33.98	74.04
Amphotericin B	0.698	1.353	--	--	--	--	--	--
Ciprofloxacin	--	--	0.383	1.509	0.356	1.509	0.815	1.509

*MRSA: Methicillin-resistant *Staphylococus aureus*.

**Unit: μM

Figure Captions

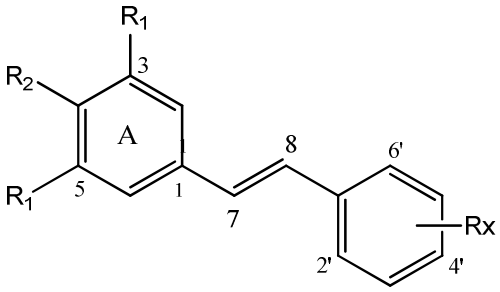
Figure 1. Structures of synthesized stilbenes.

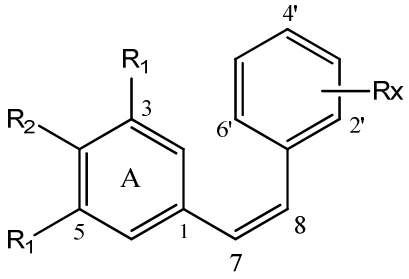
Scheme 1. Conditions: (a) DMAP, DIEA, CH_3CN, dibenzyl phosphonate, CCl_4; (b) $BrSi(CH_3)_3$, CH_2Cl_2.

Scheme 2. Conditions: (a) *n*-Buli, THF.

Scheme 3. Conditions: (a) TBDMSCl, Imidazole, DMF; (b) *n*-Buli, THF; (c) TBAF, THF.

Scheme 4. Conditions: (a) *n*-Buli, THF; (b) TBAF, THF; (c) BBr_3, CH_2Cl_2.





3 R_1=OMe, R_2=H, R_x=4'-OPO_3H_2

6a R_1=OMe, R_2=Me, R_x= H

6b R_1=OMe, R_2=Me, R_x= 3'-OMe

6c R_1=OMe, R_2=Me, R_x= 4'-OMe

6d R_1=OMe, R_2=Me, R_x= 4'-NO_2

6e R_1=OMe, R_2=Me, R_x= 4'-F

6f R_1=OMe, R_2=Me, R_x= 4'-Cl

6g R_1=OMe, R_2=Me, R_x= 4'-Br

6h R_1=OMe, R_2=Me, R_x= 4'-CF_3

6i R_1=OMe, R_2=Me, R_x= 3',4'-di-Cl

6j R_1=OMe, R_2=Me, R_x= 2',4'-di-OMe

6k R_1=OMe, R_2=Me, R_x= 3',4'-di-OMe

6l R_1=OMe, R_2=Me, R_x= 3',5'-di-OMe

6m R_1=OMe, R_2=Me, R_x= 2',6'-di-OMe, 4'-Me

6n R_1=OMe, R_2=H, R_x=4'-$OCH_2CH=C(CH_3)_2$

11 R_1=OMe, R_2=H, R_x=3'-$CH_2CH=C(CH_3)_2$, 4'-OH

16 R_1=OMe, R_2=Me, R_x= 4'-OH

17 R_1=OH, R_2=Me, R_x= 4'-OH

7a R_1=OMe, R_2=Me, R_x= H

7b R_1=OMe, R_2=Me, R_x= 3'-OMe

7c R_1=OMe, R_2=Me, R_x= 4'-OMe

7d R_1=OMe, R_2=Me, R_x= 4'-NO_2

7e R_1=OMe, R_2=Me, R_x= 4'-F

7f R_1=OMe, R_2=Me, R_x= 4'-Cl

7g R_1=OMe, R_2=Me, R_x= 4'-Br

7h R_1=OMe, R_2=Me, R_x= 4'-CF_3

7i R_1=OMe, R_2=Me, R_x= 3',4'-di-Cl

7j R_1=OMe, R_2=Me, R_x= 2',4'-di-OMe

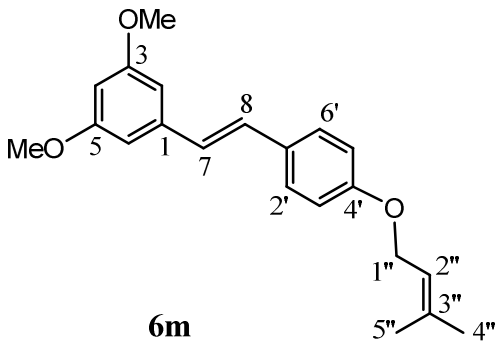
7k R_1=OMe, R_2=Me, R_x= 3',4'-di-OMe

7l R_1=OMe, R_2=Me, R_x= 3',5'-di-OMe

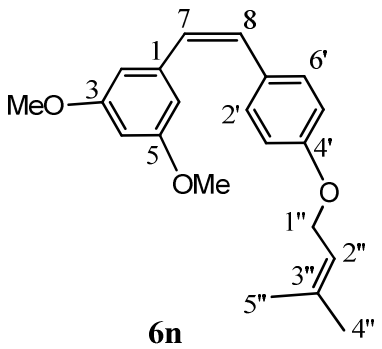
7m R_1=OMe, R_2=Me, R_x= 2',6'-di-OMe, 4'-Me

7n R_1=OMe, R_2=H, R_x=4'-$OCH_2CH=C(CH_3)_2$

12 R_1=OMe, R_2=H, R_x=3'-$CH_2CH=C(CH_3)_2$, 4'-OH

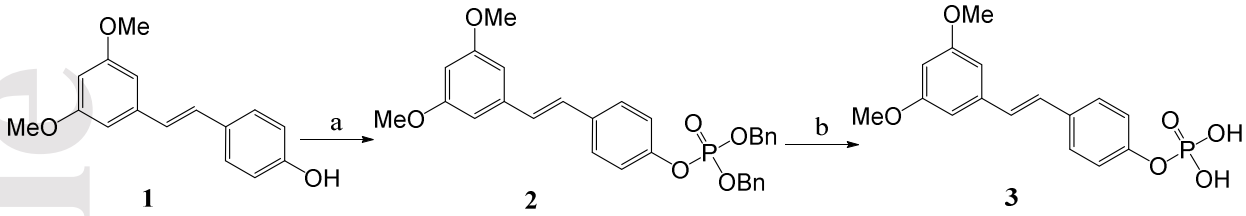


6m

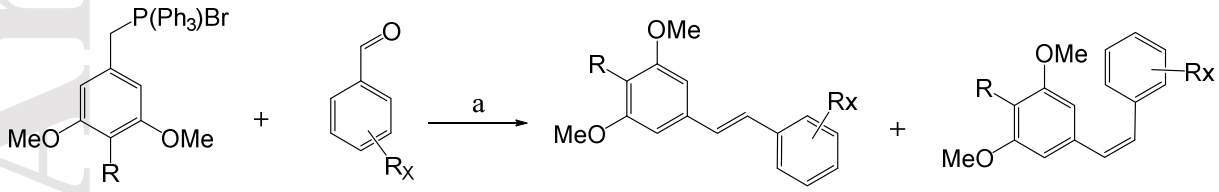


6n

Figure 1



Scheme 1

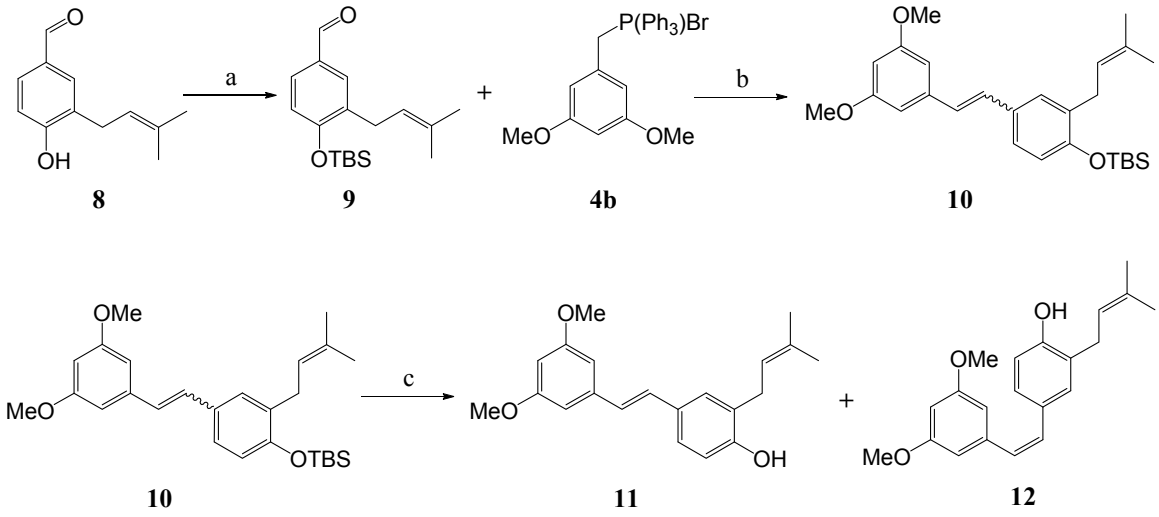


4a: R=Me
4b: R=H

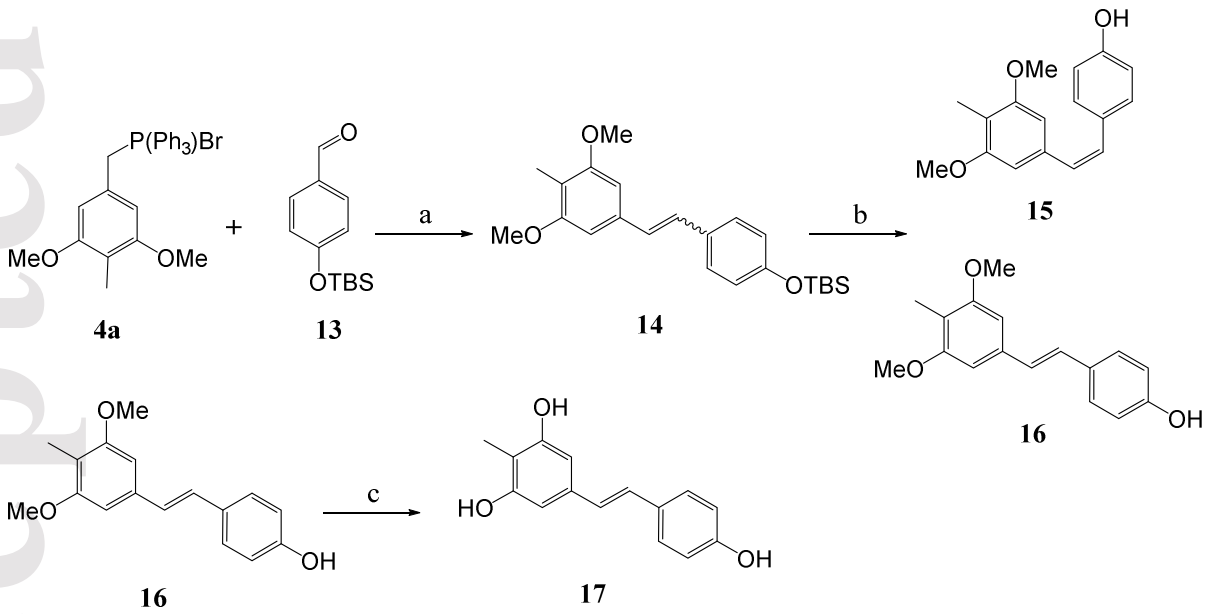
5a: R_x= H
5b: R_x= 3-OMe
5c: R_x= 4-OMe
5d: R_x= 4-NO_2
5e: R_x= 4-F
5f: R_x= 4-Cl
5g: R_x= 4-Br
5h: R_x= 4-CF_3
5i: R_x= 3,4-di-Cl
5j: R_x= 2,4-di-OMe
5k: R_x= 3,4-di-OMe
5l: R_x= 3,5-di-OMe
5m: R_x= 2,6-di-OMe, 4-Me
5n: R_x= 4-$OCH_2CH=C(CH_3)_2$

6a,7**a**: R=Me, R_x= H
6b,7**b**: R=Me, R_x= 3'-OMe
6c,7**c**: R=Me, R_x= 4'-OMe
6d,7**d**: R=Me, R_x= 4'-NO_2
6e,7**e**: R=Me, R_x= 4'-F
6f,7**f**: R=Me, R_x= 4'-Cl
6g,7**g**: R=Me, R_x= 4'-Br
6h,7**h**: R=Me, R_x= 4'-CF_3
6i,7**i**: R=Me, R_x= 3',4'-di-Cl
6j,7**j**: R=Me, R_x= 2',4'-di-OMe
6k,7**k**: R=Me, R_x= 3',4'-di-OMe
6l,7**l**: R=Me, R_x= 3',5'-di-OMe
6m,7**m**: R=Me, R_x= 2',6'-di-OMe, 4'-Me
6n,7**n**: R=H, R_x=4'-$OCH_2CH=C(CH_3)_2$

Scheme 2

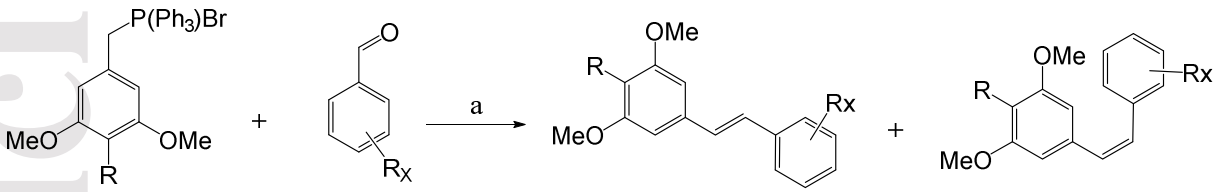


Scheme 3



Scheme 4

Graphical Illustration



R = H or Me

R_x = H; 3-OMe; 4-OMe; 4-NO_2; 4-F; 4-Cl; 4-Br; 4-CF_3; 3,4-di-Cl; 2,4-di-OMe; 3,4-d-OMe; 3,5-di-OMe; 2,6-di-OMe, 4-Me; 4-$OCH_2CH{=}C(CH_3)_2$