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Activity of 1,4-Benzoquinones Against Formosan Subterranean Termites (*Coptotermes formosanus*)

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A large number of naturally occurring and synthetic benzoquinones were evaluated for activity against the Formosan subterranean termite, *Coptotermes formosanus*, with potential use in termite control. Among these bioactive naturally occurring benzoquinones are 2-methyl-5-isopropyl-1,4-benzoquinone, 2-methoxy-6-pentyl-1,4-benzoquinone, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone, 2,3-dimethoxy-5,6-dimethyl-1,4-benzoquinone, and 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone. All five of these compounds demonstrated 100% mortality against *C. formosanus* by day 11 at a concentration of 1% (wt/wt) or less. In general, benzoquinones with one or two hydrophobic groups on the 5 and/or 6 positions of the quinone ring along with one or two group(s) on the opposite side of the ring, at the 2 and/or 3 position, led to high rates of mortality against *C. formosanus*. Quantitative structure−activity relationship (QSAR) studies showed no correlation between lipophilicity (calculated log *P*) and mortality for the entire group of nonhalogenated benzoquinones. A correlation was observed between C-6 chain length and day 3 percent mortality for 2,3-dimethoxy-5-methyl-6-substituted aliphatic benzoquinones where short chain lengths resulted in higher mortality.

KEYWORDS: Benzoquinone; antitermite activity; termiticide

INTRODUCTION

The Formosan subterranean termite, *Coptotermes formosanus* Shiraki, an aggressive, invasive species, has caused billions of dollars in damage across the United States for the past 50 years. The diet of *C. formosanus* consists of anything that contains wood fiber (homes, buildings, and live trees), crops, and plants (*1*). The removal of chlordane and other pest control agents in the late 80s has led to a search for effective, environmentally friendly compounds with antitermite activities. A survey of the literature focusing on the search for biologically active compounds shows that naturally occurring quinones have been reported with a range of activity against insect, fungal, weed, and other agricultural pests (*2–13*). Several quinones have been reported as having activity against a number of termites including *Reticulitermes* and *Cryptotermes* species (*14–16*). To our knowledge, only five of these quinones (2-methylbenzoquinone, juglone, plumbagin, isodiospyrin, and microphyllone) are reported as having any significant activity against *C. formosanus* (*15, 17*). We have previously screened 1,4-naphthoquinones and 1,4-anthraquinones against *C. formosanus* (*18*). In this paper, we report the antitermite activity of selected naturally occurring and synthetic 1,4-benzoquinones.

METHODS AND MATERIALS

Termite Bioassays. Termites from four colonies of *C. formosanus* were obtained from field sites in New Orleans, Louisiana, from bucket traps and maintained on spruce (*Picea* spp.) slats (10 cm × 4 cm × 0.5 cm) under conditions of ca. 100% relative humidity and 26.6 °C. Termites were identified using keys for soldier identification from Scheffrahn and Su (*19*).

Benzoquinones were purchased from commercial sources (identified in section 2.2, Chemicals and Reagents) and dissolved in acetone. Briefly, 100 μL of an acetone solution was pipetted onto 2.5 cm diameter Whatman #1 filter paper. The solvent acetone was allowed to evaporate from the filter paper for several hours. Treated filter paper disks were placed in plastic Petri dishes (35 mm × 10 mm) and moistened with 100 μL water. Twenty *C. formosanus* workers (third instar or greater as determined by size) and a single soldier were placed on each treatment. Treatments were replicated four times with termites for each replicate originating from a different *C. formosanus* colony. Covered Petri dishes were maintained at ca. 100% relative humidity and 26.6 °C. Filter paper disks receiving water alone served as controls. It was previously determined that the filter paper treated with acetone solvent alone had no discernible effect on termite mortality or consumption. The initial primary screening for most compounds was

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Table 1. Primary Testing To Determine the Cumulative Percent Mortality of *C. formosanus* on Filter Paper Treated with Benzoquinones

				percent mortality (mean ± SD)		
				days		
experiment[a]	IUPAC name	trivial name	concn (% wt/wt)	3	11	21
1	1,4 benzoquinone (**1**)	quinone	1	0 J	1.7 ± 2.9 IJ	5.0 ± 0.0 JK
	quinhydrone (**2**)		1	15.0 ± 13.2 F−J	43.3 ± 32.5 C−H	51.7 ± 45.4 B−J
	methyl-1,4-benzoquinone (**3**)	cresoquinone	1	1.7 ± 2.9 IJ	11.7 ± 7.6 G−J	20.0 ± 5.0 G−K
	2-methoxy-1,4-benzoquinone (**4**)		1	13.3 ± 2.9 E−J	21.7 ± 10.4 E−J	31.7 ± 15.3 E−K
	2,5-dimethyl-1,4-benzoquinone (**5**)	*p*-xyloquinone	1	31.7 ± 7.6 D−F	45.0 ± 10.0 C−G	45.0 ± 10.0 B−K
	2-methyl-5-isopropyl-1,4-benzoquinone (**6**)	thymoquinone	1	100.0 ± 0.0 A	100.0 ± 0.0 A	100.0 ± 0.0 A
	2-methoxy-5-methyl-1,4-benzoquinone (**7**)	coprinin	1	18.3 ± 2.9 E−I	56.7 ± 16.1 B−F	93.3 ± 5.8 AB
	2,5-dimethoxy-1,4-benzoquinone (**8**)		1	3.3 ± 2.9 IJ	6.7 ± 5.8 G−J	8.3 ± 2.9 H−K
	2,6-dimethoxy-1,4-benzoquinone (**9**)		1	0 J	3.3 ± 5.8 H−J	3.3 ± 5.8 K
	2,5-dihydroxy-3-undecyl-1,4-benzoquinone (**12**)	embelin	1	3.3 ± 5.8 IJ	18.3 ± 16.1 F−J	46.7 ± 2.9 B−K
	2,3-dimethoxy-5-(3-methyl-2-butenyl)-6-methyl-1,4-benzoquinone (**14**)	coenzyme Q1	1	70.0 ± 27.8 B	100.0 ± 0.0 A	100.0 ± 0.0 A
	2,3-dimethoxy-5-geranyl-6-methyl-1,4-benzoquinone (**15**)	coenzyme Q2	1	0 J	15.0 ± 13.2 F−J	25.0 ± 21.8 G−K
	2,3-dimethoxy-6-methyl-5-tetraisoprenoid-1,4-benzoquinone (**16**)	coenzyme Q4	1	1.7 ± 2.9 IJ	11.7 ± 7.6 F−J	15.0 ± 8.7 H−K
	2,3-dimethoxy-6-methyl-5-hexaisoprenoid-1,4-benzoquinone (**17**)	coenzyme Q6	1	1.7 ± 2.9 IJ	6.7 ± 2.9 G−J	18.3 ± 14.4 G−K
	2,3-dimethoxy-6-methyl-5-nonaisoprenoid-1,4-benzoquinone (**18**)	coenzyme Q9	1	15.0 ($N = 1$) E−J	15.0 ($N = 1$) E−J	15.0 ($N = 1$) H−K
	2,3-dimethoxy-6-methyl-5-decaisoprenoid-1,4-benzoquinone) (**19**)	coenzyme Q10	1	0 J	10.0 ± 10.0 G−J	10.0 ± 10.0 I−K
	2-*tert*-butyl-1,4-benzoquinone (**27**)		1	13.3 ± 7.6 E−J	18.3 ± 5.8 E−J	28.3 ± 2.9 E−K
	2-*tert*-butyl-5-methyl-1,4-benzoquinone (**28**)		1	5.0 ± 8.7 IJ	21.7 ± 20.8 E−J	26.7 ± 20.2 F−K
	2-(*p*-tolyl)-1,4-benzoquinone (**29**)		1	5.0 ± 8.7 IJ	16.7 ± 20.8 F−J	38.3 ± 35.5 E−K
	untreated			0 J	6.3 ± 7.5 G−J	6.3 ± 7.5 JK
2	2-methoxy-6-pentyl-1,4-benzoquinone (**10**)	primin	1	87.5 ± 3.5 B	100.0 ± 0.0 A	100.0 ± 0.0 A
	2,5-dihydroxy-3-tridecyl-1,4-benzoquinone (**13**)	rapanone	1	5.0 ± 5.0 C	76.7 ± 22.6 AB	81.7 ± 23.6 AB
	2,3-dimethoxy-5,6-dimethyl-1,4-benzoquinone (**20**)	aurantiogliocladin	1	100.0 ± 0.0 A	100.0 ± 0.0 A	100.0 ± 0.0 A
	untreated			13.3 ± 2.9 C	15.0 ± 0.0 C	15.0 ± 0.0 C
3	2-methoxy-5-phenyl-1,4-benzoquinone (**22**)		1	3.3 ± 2.9 C	6.7 ± 7.6 C	31.7 ± 2.8 B
	(4-methoxy-3,6-dioxo-cyclohexa-1,4-dienylmethyl)-triphenyl-phosponium,chloride (**23**)		1	13.3 ± 7.6 B	60.0 ± 21.8 B	98.3 ± 2.9 A
	2,3-dimethoxy-5-methyl-1,4-benzoquinone (**24**)		1	75.0 ± 43.3 A	81.7 ± 31.8 A	90.0 ± 17.3 A
	2,3-dimethoxy-5-methyl-6-decyl-1,4-benzoquinone (**25**)	decylubiquinone	1	13.3 ± 7.6 B	75.0 ± 22.9 B	100.0 ± 0.0 A
	2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone (**26**)	idebenone	1	0 C	0 C	38.3 ± 28.4 B
	untreated			0 C	0 C	0 C
4	2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**30**)		0.5	100 ± 0 A	100 ± 0 A	100 ± 0 A
	2,3-dichloro -5-6-dimethoxy-1,4-benzoquinone (**31**)		0.5	2.5 ± 2.9 B	8.8 ± 8.5 B	30.0 ± 47.1 B
	2,6-dibromo-3-chloro-5-methyl-1,4-benzoquinone (**32**)		0.5	2.5 ± 2.9 B	22.5 ± 38.4 B	31.3 ± 46.6 B
	untreated			1.3 ± 2.5 B	2.5 ± 2.9 B	2.5 ± 2.9 B
5	2,5-bis(4-methlyamino)-3,6-dichloro-1,4-benzoquinone (**33**)		1	8.8 ± 8.5 A	90.0 ± 8.2 A	100.0 ± 0 A
	2,6-dichloro-3,5-dimethoxy-1,4-benzoquinone (**34**)		1	0 B	0 C	2.5 ± 2.9 D
	2,5-bis(3-methoxanilino)-3,6-dichloro-1,4-benzoquinone (**35**)		1	0 B	1.3 ± 2.5 C	33.8 ± 39.4 CD
	2,5-bis(3-nitroanilino)-3,6-dichloro-1,4-benzoquinone (**36**)		1	6.3 ± 4.8 AB	75.0 ± 16.8 AB	90.0 ± 16.8 AB
	2,5-bis(4-methylanilino)-3,6-dichloro-1,4-benzoquinone (**37**)		1	1.3 ± 2.5 B	52.5 ± 32.8 B	88.8 ± 22.5 AB
	2,5-bis(4-methoxanilino)-3,6-dichloro-1,4-benzoquinone (**38**)		1	1.3 ± 2.5 B	3.8 ± 4.8 C	57.5 ± 32.3 BC
	2,5-bis(2-methoxanilino)-3,6-dichloro-1,4-benzoquinone (**39**)		1	0 B	0 C	2.5 ± 5.0 D
	2,5-bis(4-chloroanilino)-3,6-dichloro-1,4-benzoquinone (**40**)		1	10.0 ± 7.1 A	62.5 ± 33.0 AB	86.3 ± 12.5 AB
	2,5-dianolino-3,6-dichloro-1,4-benzoquinone (**41**)		1	0 B	40.0 ± 33.4 B	60.0 ± 36.7 BC
	untreated			0 B	0 C	12.5 ± 6.5 D
6	2,3,5-trimethyl-1,4-benzoquinone (**11**)		1	0 A	18.3 ± 23.1 A	36.7 ± 54.9 A
	untreated			0 A	1.3 ± 2.5 A	1.3 ± 2.5 A
7	2,5-dihydroxy-3-methyl-6-(14- nonadecenyl)-1,4-benzoquinone (**21**)	maesaquinone	2	0 A	6.7 ± 2.9 A	20.0 ± 5.0 A
	untreated			0 A	0 B	2.5 ± 5.0 B

[a] Twenty workers (≥third instar)/1 soldiers per rep. Four reps, four colonies. Means for a particular experiment within a column/treatment with the same letter are not significantly different; LSD, $P < 0.05$.

performed at a concentration of 1% (wt/wt), while compounds **30**−**32** were initially evaluated at 0.5% (wt/wt) due to availability and cost of the compounds, and compound **21** was evaluated at 2%.

Termite Bioassay Data Analysis. Daily termite mortality was evaluated for 3 weeks. Consumption was determined by subtracting post-treatment from pretreatment filter paper weights, which were dried for 24 h at 50% relative humidity. Cumulative daily mortality and consumption (mean and standard deviation) were calculated from the four replicates ($n = 20$) of each treatment. Treatments are compared using analysis of variance, and means were separated using a protected Fisher least-significant difference (LSD) test ($P < 0.05$; PROC GLM, SAS, Statistical Analysis Systems, Cary, NC). The LSD means separations test followed transformation to arcsine square root percent mortality. The actual percent mortality is reported in the tables.

Chemicals and Reagents. Solvents used in the preparation of stock solutions were purchased from Sigma-Aldrich (St. Louis, MO) and were all reagent grade. Benzoquinones are identified with respective numbers in **Table 1**. Benzoquinones **1** and **2** were purchased from Acros (Morris Plains, NJ). Benzoquinone **3** was purchased from Alfa Aesar (Ward Hill, MA). Benzoquinone **4** was purchased from TCI America (Portland, OR). Benzoquinones **5**, **6**, **7**−**10**, **13**−**19**, **21**−**26**, and **27**−**41** were purchased from Sigma-Aldrich. Benzoquinone **11** was purchased from

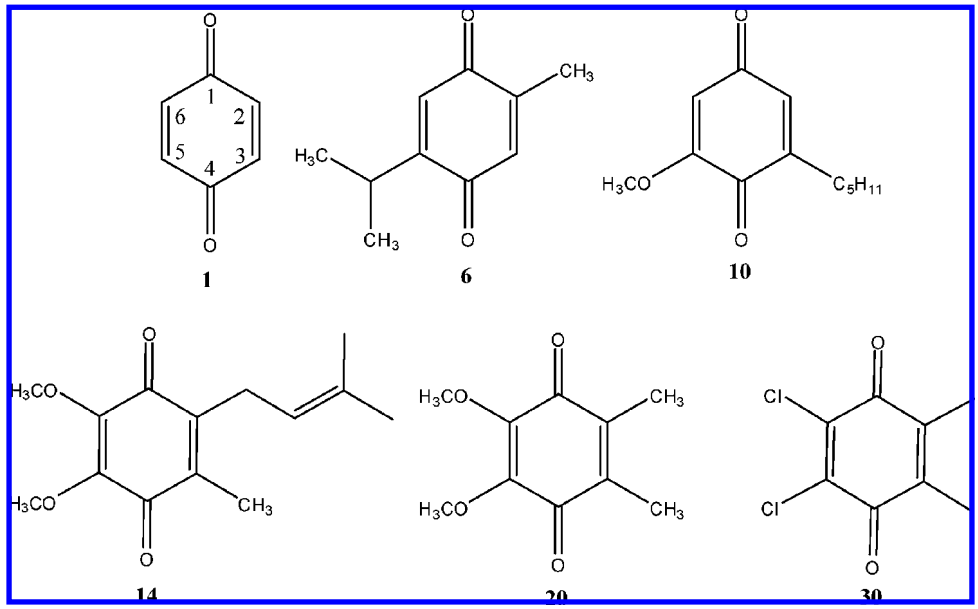

Figure 1. Chemical structures for 1,4-benzoquinone (**1**) and compounds subjected to secondary testing; 2-methyl-5-isopropyl-1,4-benzoquinone (**6**), 2-methoxy-6-pentyl-1,4-benzoquinone (**10**), 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone (**14**), 2,3-dimethoxy-5,6-dimethyl-1,4-benzoquinone (**20**), and 2,3-dichloro-5,6-dimethyl-1,4-benzoquinone (**30**).

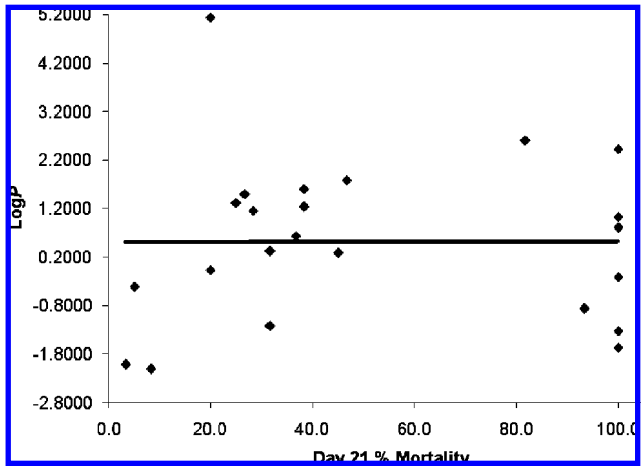

Figure 2. Crippen calculated log *P* values vs day 21 percent mortality against *C. formosanus* for nonhalogenated benzoquinones **1**, **3**−**15**, **20**−**22**, and **24**−**29** overlaid with a linear regression line, which includes all data points.

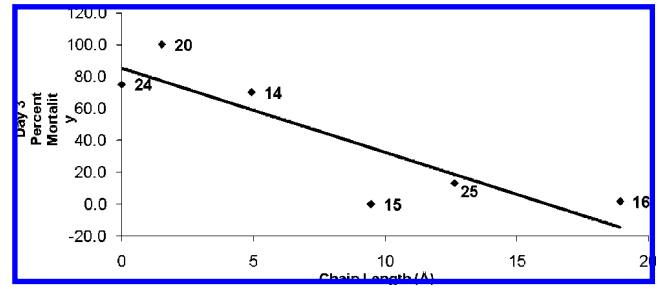

Figure 3. Calculated chain length (Å) for 2,3-dimethoxy-5-methyl-6-substituted aliphatic benzoquinones (**14**−**16**, **20**, and **24**−**25**) vs day 3 percent mortality against *C. formosanus* overlaid with a linear regression line including all data points.

ICN Biomedicals (Costa Mesa, CA). Benzoquinone **12** was purchased from Indofine Chemical Co., Inc. (Hillsborough, NJ). Benzoquinone **20** was purchased from Apin Chemicals, Ltd. (Abingdon, Oxon, United Kingdom). Benzoquinone purities were all 90% or higher, as reported by the manufacturer.

Molecular Modeling. All molecular minimizations were performed using CS Chem3D Ultra v 7.0.0 (CambridgeSoft, Cambridge, MA) after converting 2D molecular structures drawn using ChemDraw Ultra v 7.0 (CambridgeSoft). The molecular structures of the selected benzoquinones were completely optimized into the lowest energy conformers using MOPAC (*20*) with the semiempirical AM1 Hamiltonian (*21*).

Log *P* Estimations. All Crippen log *P* estimations were calculated from the optimized three-dimensional (3D) molecular structures using the Chem3D Ultra software package (*22, 23*). A select number of nonhalogenated benzoquinones (**1**, **3**−**15**, **20**, **22**, and **24**−**29**) were chosen for this particular analysis. Certain nonhalogenated benzoquinones were omitted from this study due to various reasons including their existence as salts (**2**, **23**) or the impracticality of using longer chain isomers, which are highly lipophilic, inactive, and would unnecessarily distort the graph (**16**−**19**) (**Figure 2**).

Chain Length Calculations. All chain length calculations were determined from the optimized 3D molecular structures using the Chem3D Ultra software package. Measurements were made from the center of the C-6 carbon to the center of the most distant carbon in the aliphatic chain. All measurements are reported in angstroms (Å) (**Figure 3**). Only nonhalogenated 2,3-dimethoxy-5-methyl-6-substituted aliphatic benzoquinones (**14**−**16**, **20**, and **24**−**25**) were used in this study. A few benzoquinones fitting this category (**17**−**19** and **26**) were intentionally omitted.

RESULTS AND DISCUSSION

Termiticidal Activity of Substituted Benzoquinones Against *Coptotermes formosanus*. The daily termite mortality against *C. formosanus* of 41 substituted benzoquinones was determined for 3 weeks, and the results are reported in **Table 1**. Twelve of the benzoquinones evaluated at day 3 demonstrated termite mortality significantly higher than that of the untreated control with the most active of those compounds being **6**, **20**, and **30** with percent mortalities of 100%. Compounds **10**, **24**, and **14** were also quite active with percent mortalities of 87.5 ± 3.5, 75.0 ± 43.3, and 70.0 ± 27.8. Sixteen of those compounds evaluated at day 11 demonstrated termite mortality significantly higher than that of the untreated control with the most active of those compounds being **6**, **10**, **14**, **20**, and **30** with percent mortalities of 100%. Lastly, 19 of those compounds evaluated at day 21 demonstrated termite mortality significantly higher

Table 2. Secondary Testing To Determine the Cumulative Percent Mortality of *C. formosanus* on Filter Paper Treated with Benzoquinones (**6**, **10**, **14**, **20**, and **30**)

		percent mortality (mean ± SD)[a]					
		days					
compound	concn (% wt/wt)	6	9	11	13	17	21
6	0.5	1.7 ± 2.9 A	6.7 ± 7.6 A	6.7 ± 7.6 A	10.0 ± 8.7 A	11.7 ± 11.6 A	18.3 ± 11.6 A
	0.1	0 A	1.7 ± 2.9 A	1.7 ± 2.9 A	6.7 ± 7.6 A	8.3 ± 10.4 A	8.3 ± 10.4 A
	0.05	0 A	0 A	0 A	6.7 ± 2.9 A	6.7 ± 2.9 A	8.3 ± 2.9 A
	0.01	0 A	3.3 ± 2.9 A	3.3 ± 2.9 A	5.0 ± 5.0 A	5.0 ± 5.0 A	11.7 ± 7.6 A
	0.001	0 A	1.7 ± 2.9 A	1.7 ± 2.9 A	1.7 ± 2.9 A	5.0 ± 5.0 A	5.0 ± 5.0 A
untreated		0 A	1.3 ± 2.5 A	1.3 ± 2.5 A	1.3 ± 2.5 A	1.3 ± 2.5 A	1.3 ± 2.5 A
10	0.5	56.7 ± 37.9 A	80.0 ± 30.4 A	91.7 ± 14.4 A	96.7 ± 5.8 A	100.0 ± 0.0 A	100.0 ± 0.0 A
	0.1	21.7 ± 16.1 B	21.7 ± 16.1 B	28.3 ± 27.5 B	36.7 ± 41.9 B	40.0 ± 39.7 B	50.0 ± 45.8 B
	0.05	3.3 ± 5.8 B	3.3 ± 5.8 B	3.3 ± 5.8 C	5.0 ± 5.0 B	8.3 ± 7.6 BC	25.0 ± 21.8 B
	0.01	0 B	0 B	0 C	5.0 ± 5.0 B	10.0 ± 5.0 BC	21.7 ± 2.9 B
	0.001	0 B	0 B	0 C	0 B	1.7 ± 2.9 C	8.3 ± 10.4 B
untreated		1.3 ± 2.5 B	1.3 ± 2.5 B	1.3 ± 2.5 C	2.5 ± 2.9 B	2.5 ± 2.9 BC	5.0 ± 4.1 B
14	0.5	3.3 ± 2.9 A	3.3 ± 2.9 A	3.3 ± 2.9 A	5.0 ± 5.0 A	8.3 ± 10.4 A	10.0 ± 13.2 A
	0.1	0 A	0 A	0 A	0 A	8.3 ± 2.9 A	8.3 ± 2.9 A
	0.05	0 A	0 A	0 A	0 A	5.0 ± 5.0 A	5.0 ± 5.0 A
	0.01	5.0 ± 5.0 A	5.0 ± 5.0 A	5.0 ± 5.0 A	5.0 ± 5.0 A	5.0 ± 5.0 A	5.0 ± 5.0 A
	0.001	3.3 ± 2.9 A	3.3 ± 2.9 A	3.3 ± 2.9 A	3.3 ± 2.9 A	3.3 ± 2.9 A	3.3 ± 2.9 A
untreated		0 A	0 A	0 A	1.3 ± 2.5 A	1.3 ± 2.5 A	2.5 ± 5.0 A
20	0.5	0 A	0 A	0 A	0 C	0 C	0 C
	0.1	0 A	0 A	0 A	0 C	0 C	0 C
	0.05	0 A	0 A	0 A	0 C	0 C	5.0 ± 5.0 C
	0.01	0 A	0 A	0 A	0 C	0 C	1.7 ± 2.9 C
	0.001	0 A	0 A	0 A	0 C	0 C	0 C
untreated		0 A	0 A	0 A	0 C	0 C	0 C
30	0.5	100 ± 0 A	100 ± 0 A	100 ± 0 A	100 ± 0 A	100 ± 0 A	100 ± 0 A
	0.1	1.3 ± 2.5 B	26.3 ± 34.2 B	30.4 ± 39.3 B	41.3 ± 42.5 B	60.0 ± 39.2 B	68.8 ± 40.5 A
	0.05	0 B	1.3 ± 2.5 B	3.4 ± 4.3 B	5.0 ± 5.8 B	5.0 ± 5.8 B	5.0 ± 5.8 B
	0.01	3.8 ± 4.8 B	3.8 ± 4.8 B	3.8 ± 4.8 B	7.5 ± 6.5 B	10.0 ± 9.1 B	10.0 ± 9.1 B
	0.001	1.3 ± 2.5 B	2.5 ± 2.9 B	6.8 ± 10.7 B	26.3 ± 49.2 B	26.3 ± 49.2 B	27.5 ± 48.4 B
untreated		1.3 ± 2.5 B	1.3 ± 2.5 B	1.3 ± 2.5 B	2.5 ± 2.9 B	2.5 ± 2.9 B	2.5 ± 2.9 B

[a] Twenty workers (≥third instar)/1 soldiers per rep. Four reps, four colonies. Means for a particular experiment within a column/treatment with the same letter are not significantly different; LSD, $P < 0.05$.

than that of the untreated control with the most active of those compounds being **6**, **10**, **14**, **20**, **25**, **30**, and **33** with percent mortalities of 100%.

The 1,4-benzoquinone **1** and its analogues with only one [methyl-1,4-benzoquinone (**3**)], two [2,5-dimethyl-1,4-benzoquinone (**5**)], or three [2,3,5-trimethyl-1,4-benzoquinone (**11**)] methyl group(s) displayed no significant termiticidal activity, the same is also true if the substituents are only methoxy groups [2-methoxy-1,4-benzoquinone (**4**), 2,5-dimethoxy-1,4-benzoquinone (**8**), and 2,6-dimethoxy-1,4-benzoquinone (**9**)]. Interestingly, the activity increased dramatically when there were one or two electron-donating group(s) on one side of the ring (2 and/or 3 position) and one or two hydrophobic groups on the opposite side of the ring (5 and/or 6 position). Hydrophobic groups might include methyl or a longer alkyl chain (although length may become critical), short alkenyl (**14**), but not polyenes (**15**−**18**), methyl triphenylphosphonium chloride (**23**), or phenyl (**22**). Electron-donating groups might include alkoxy, chloro (**30**), and secondary alkyl (**6**) but not hydroxy (**12**, **13**, and **21**). Benzoquinones containing none or only one of those two features exhibited much reduced activity or no activity. Benzoquinones substituted with hydroxyl group on any position of the ring showed decreased activity or no activity (**12**, **13**, and **21**). Introducing *t*-butyl group to the quinone ring resulted in complete loss of activity (**27**, **28**); this may be due to a steric hindrance factor.

Because of the high level of day 11 mortality observed for compounds **6**, **10**, **14**, **20**, and **30** (**Figure 1**), secondary dose−response testing was performed to better understand the activity of these compounds. All of these compounds were evaluated for termiticidal activity at concentrations of 0.5, 0.1, 0.05, 0.01, and 0.001 (% wt/wt) (**Table 2**). The least active of these benzoquinones were **6**, **14**, and **20**, which all demonstrated no activity significant above the untreated control. Compound **10** demonstrated 100% mortality by day 17 at a concentration of 0.5 (% wt/wt), while 100% mortality was not obtained at any point out to 21 days, at lower concentrations. Compound **30** demonstrated 100% mortality by day **6** at a concentration of 0.5 (% wt/wt), while 100% mortality was also not obtained at any point out to 21 days at lower concentrations.

Antifeedant Activity of Substituted Benzoquinones Against *Coptotermes formosanus.* At the conclusion of the termite mortality study, the filter paper consumed by the termites was compared to that consumed by the untreated control, and 15 benzoquinones showed significant reduced feeding at 1% (**Table 3**). 2-Methyl-5-isopropyl-1,4-benzoquinone (**6**) and 2-methoxy-5-methyl-1,4-benzoquinone (**7**) consumed 0.0 and 4.2 mg of filter paper, respectively, as compared to 85.0 mg for untreated control. Among the other highly active compounds were 2-methoxy-1,4-benzoquinone (**4**), (4-methoxy-3,6-dioxo-cyclohexa-1,4-dienylmethyl)-triphenyl-phosponium,chloride (**23**), 2,3-dimethoxy-5-methyl-1,4-benzoquinone (**24**), and 2,5-bis(4-methylamino)-3,6-dichloro-1,4-benzoquinone (**33**) with consumption values all less than 10 mg and significant above the untreated controls.

Secondary dose−response consumption testing was also performed on a few of the more active compounds from the mortality study (**Table 4**). As was observed previously in the mortality study, the least active of these benzoquinones were **6** and **14**, and now **30**, which all demonstrated no activity

Table 3. Primary Testing To Determine the Filter Paper Consumed by *C. formosanus* When Treated with Benzoquinones for 21 Days

experiment[a]	compound	concn (% wt/wt)	consumption (mg, mean ± SD)
1	**1**	1	80.7 ± 3.8 A−E
	2	1	30.0 ± 11.2 C−O
	3	1	22.5 ± 27.1 E−O
	4	1	6.5 ± 1.7 K−O
	5	1	13.6 ± 15.8 H−O
	6	1	0 O
	7	1	4.2 ± 3.0 L−O
	8	1	107.0 ± 3.2 A
	9	1	75.9 ± 9.6 A−G
	12	1	10.7 ± 5.0 J−O
	14	1	16.9 ± 8.1 G−O
	15	1	56.1 ± 2.6 A−O
	16	1	74.6 ± 11.7 A−G
	17	1	97.3 ± 33.8 AB
	18	1	63.9 (N = 1) A−L
	19	1	49.6 ± 32.7 A−O
	27	1	60.4 ± 14.1 A−N
	28	1	68.3 ± 11.4 A−J
	29	1	43.2 ± 12.8 B−O
	untreated		85.0 ± 15.1 A−D
2	**10**	1	0.1 ± 0.0 A
	13	1	0.3 ± 0.1 A
	20	1	0.1 ± 0.1 A
	untreated		15.9 ± 10.4 A
3	**22**	1	35.8 ± 8.7 A
	23	1	5.3 ± 0.7 C
	24	1	7.2 ± 3.4 C
	25	1	19.3 ± 4.4 B
	26	1	37.9 ± 5.4 A
	Untreated		42.4 ± 4.3 A
4	**30**	0.5	3.2 ± 1.2 A
	31	0.5	19.3 ± 12.0 A
	32	0.5	26.1 ± 10.0 A
	untreated		23.6 ± 13.6 A
5	**33**	1	7.8 ± 5.1 C
	34	1	37.8 ± 7.8 A
	35	1	34.9 ± 6.5 A
	36	1	18.3 ± 13.5 BC
	37	1	19.1 ± 5.0 BC
	38	1	39.8 ± 3.9 A
	39	1	40.1 ± 3.3 A
	40	1	22.7 ± 7.1 B
	41	1	36.3 ± 7.1 A
	untreated		44.0 ± 1.1 A
6	**11**	1	55.4 ± 26.5 A
	untreated		54.4 ± 20.7 A
7	**21**	2	95.7 ± 31.4 A
	untreated		78.2 ± 26.7 A

[a] Twenty workers (≥third instar)/1 soldiers per rep. Four reps, four colonies. Means for a particular experiment within a column/treatment with the same letter are not significantly different; LSD, $P < 0.05$.

significant above untreated control. Compounds **10** and **20** did, however, demonstrate significant activity at a concentration of 0.5% (wt/wt), with the latter remaining significantly active at 0.05%.

Molecular Modeling Studies on Substituted Benzoquinones. A preliminary quantitative structure−activity relationship (QSAR) study to evaluate the effect of lipophilia/aqueous solubility of nonhalogenated benzoquinones was conducted (**Figure 2**). Lipophilia is usually expressed through the logarithm of the octonal−water partition coefficient (log P). Minimized 3D molecular structures were subjected to Crippen (*22, 23*) log P estimations using Chem3D Ultra. All nonhalogenated benzoquinones were included in this study; however, some have been omitted from **Figure 2** due to reasons including their existence as salts (**2**, **23**) or the impracticality of using longer chain isomers, which are highly lipophilic, inactive, and would incorrectly distort the graph (**16**−**19**). For example, for the series

Table 4. Secondary Testing To Determine the Filter Paper Consumed by *C. formosanus* When Treated with Benzoquinones **6**, **10**, **14**, **20**, and **30** for 21 Days[a]

compound	concn (% wt/wt)	consumption (mg, mean ± SD)
6	0.5	93.1 ± 22.6 A
	0.1	83.5 ± 28.3 A
	0.05	74.0 ± 5.6 A
	0.01	75.4 ± 6.9 A
	0.001	80.6 ± 25.9 A
untreated		54.4 ± 20.7 A
10	0.5	4.9 ± 4.4 C
	0.1	26.8 ± 17.8 BC
	0.05	42.2 ± 2.5 AB
	0.01	48.4 ± 14.1 AB
	0.001	48.8 ± 14.7 AB
untreated		44.6 ± 0.0 AB
14	0.5	95.8 ± 15.9 A
	0.1	101.6 ± 14.7 A
	0.05	98.1 ± 16.2 A
	0.01	77.3 ± 69.9 A
	0.001	98.5 ± 25.8 A
untreated		78.2 ± 26.7 A
20	0.5	52.4 ± 22.9 C
	0.1	107.7 ± 17.2 AB
	0.05	48.6 ± 1.6 C
	0.01	86.6 ± 36.1 BC
	0.001	136.2 ± 4.2 A
untreated		113.2 ± 11.9 AB
30	0.5	3.2 ± 1.2 A
	0.1	13.1 ± 13.8 A
	0.05	18.3 ± 12.2 A
	0.01	25.0 ± 14.1 A
	0.001	17.5 ± 8.2 A
untreated		23.6 ± 13.6 A

[a] Twenty workers (≥third instar)/1 soldiers per rep. Four reps, four colonies. Means for a particular experiment within a column/treatment with the same letter are not significantly different; LSD, $P < 0.05$.

of coenzymes Q1−Q10 (**14**−**19**), only compounds **14** and **15** were included in the graph. These two compounds alone represent the trend observed as additional isoprene units are added. As we move from a single isoprene substituent at C-6 in **14** to two isoprene units in **15** at C-6, the day 21 percent mortality decreases to a level equivalent to the untreated control. As expected, compounds **16**−**19** are also equivalent to the untreated control while their log P values continue to increase. **Figure 2** indicates no relationship between calculated log P values for the entire group of nonhalogenated benzoquinones and day 21 percent mortality, as is evidenced by the overlaid linear regression line, which includes all data points. Day 21 percent mortality does not appear to be influenced by log P values for this large group of nonhalogenated benzoquinones. This result is not surprising, although lipophilicity is generally an important factor to the biological activity, it is not always the case for quinines. Schultz et al. observed no correlation between naphthoquinones against *Tetrahymena pyriformis* and lipophilicity (*24*), whereas there was a good correlation between a set of 2-hydroxy-3-alkyl-naphthoquinones and their log P (*25*).

Another QSAR study was conducted to examine the relationship between C-6 chain length and day 3 percent mortality for a select group of benzoquinones, namely, nonhalogenated 2,3-dimethoxy-5-methyl-6-substituted aliphatic benzoquinones (**14**−**16**, **20**, **24**, and **25**). The chain length calculations were reported in Ångstroms (**Figure 3**). There clearly appears to be a relationship between chain length and day 3 percent mortality as evidenced by the lower chain length compounds having the highest level of activity (**Figure 3**). It should be noted that compounds **17**−**19** and **26** were intentionally omitted from **Figure 3**, although they were included in this study. Inclusion

of these compounds would not change the observed relationship between calculated chain length (Å) and day 3 percent mortality; however, it would unnecessarily stretch out the curve. This is primarily because once the compounds reach a certain chain length with near 0% inhibition, an additional chain length is also inactive and therefore continues the same trend. These compounds support the same relationship between day 3 percent mortality and chain length observed for this entire group of nonhalogenated 2,3-dimethoxy-5-methyl-6-substituted aliphatic benzoquinones as a whole. They only served to further exaggerate the curve if included in **Figure 3**.

In conclusion, some of the tested benzoquinones do have effective activity against *C. formosanus*. A positive outcome of having multiple types of pesticides available to fight termites is that it eliminates or slows down the establishment of pesticide resistant forms of termites. This is a critical factor, especially in view of recent studies indicating that different colonies have different susceptibilities to current pesticides (*26*). The fact that some of these quinones come from natural sources may present useful alternatives to conventional, synthetic termiticides currently in the market. These quinones might be extracted from a number of natural sources or are synthesized using well-established procedures.

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