Synthesis and Activity of Substituted Anthraquinones against a Human Filarial Parasite, *Brugia malayi*

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Lymphatic filariasis (elephantiasis) is a global public health problem caused by the parasitic nematodes *Wuchereria bancrofti* and *Brugia malayi*. We have previously reported anthraquinones from daylily roots with potent activity against pathogenic trematode *Schistosoma mansoni*. Here we report the synthesis of novel anthraquinones **A**−**S** and their antifilrarial activity. Anthraquinones **A**−**S** were synthesized by a single-step Friedel−Crafts acylation reaction between phthalic anhydrides and substituted benzenes. The antifilarial properties of these synthetic anthraquinones were tested against microfilaria as well as adult male and female worms of *B. malayi*. The most active anthraquinone was **K**, which showed 100% mortality within 1, 5, and 3 days, respectively, against microfilaria and adult male and female worms at 5 ppm concentration. Albendazole, an oral drug currently used to treat parasitic infections, was used as a positive control. Methylated products of anthraquinones did not affect the microfilaria. Histological examination of treated adult female parasites showed most of the anthraquinones caused marked effects on intrauterine embryos.

Introduction

Lymphatic filariasis (elephantiasis) is a devastating disease caused by *Wuchereria bancrofti* and *Brugia malayi* spp. The World Health Organization estimates that 120 million people globally are affected by filariasis and at least 40 million are disabled both physically and psychosocially. Filariasis is one of the major public health problems with socioeconomic impacts in Africa, Asia, the Western Pacific, and the Americas.[1] About 90% of these infections are caused by *W. bancrofti*, and the remainder by *Brugia* spp. Humans are the only known host for *W. bancrofti*.[2]

Numerous quinones including dihydroxy- and trihydroxyanthraquinones are widely distributed in the plant kingdom and contribute to pigmentation in plants.[3] These compounds are believed to have medicinal values and are used in traditional medicine.[4] *Hemerocallis fulva* kwanza kaempfer (daylily) roots were reported to contain several anthraquinone derivatives, naphthaline glycosides, and flavones.[5] In our earlier studies, some of the anthraquinones isolated from daylily roots were found to be active against *Schistosoma mansoni*, one of the *Schistosoma* spp. parasites responsible for schistosomiasis.[5] Schistosomiasis is also a debilitating disease that afflicts 200 million people worldwide. We have assayed these active anthraquinones from daylily roots against the filarial parasite (*B. malayi*) and found them to be active.[5] Our investigation of daylily roots has revealed that the concentration of these active anthraquinones were too small to conduct further investigations. It is not economical to depend on the natural sources of these anthraquinones to explore their utility as prophylactic and/or therapeutic agents for parasitic diseases. We have therefore synthesized several of these bioactive anthraquinones to further evaluate their efficacy and toxicity in vivo to employ them as lead therapeutic drugs for filariasis and schistosomiasis.

Earlier methods of production of anthraquinones were by the catalytic oxidation of anthracene obtained from coal tar.[6,7] Anthraquinones have also been prepared by Diels−Alder cycloaddition and Friedel−Crafts acylation reactions using suitable reagents. The Diels−Alder reaction between 1,4-naphthaquinone and 1,3-diene followed by dehydrogenation of the resulting tricyclic adduct yielded anthraquinones.[8] However, production of 1,4-naphthaquinone and 1,3-dienes were complex and costly. The Friedel−Crafts acylation reaction is one of the most commonly used reactions in industrial production of compounds. The reaction is catalyzed by Lewis acids, such as $AlCl_3$, BF_3, $FeCl_3$, $TiCl_4$, and $Sc(OTf)_3$.[9−12] The mechanism involves the formation of an acylium ion intermediate that is generated by the reaction between carboxylic acid derivatives and acid catalysts.

Another method for the preparation of anthraquinones was the condensation of phthalic anhydride and benzene using an equimolar amount of HF and BF_3 as catalysts. The resulting *o*-benzoylbenzoic acid was then converted to the corresponding anthraquinone by heating it with concentrated sulfuric acid or by other means of cyclization. The drawbacks of this method included difficulties in purifying *o*-benzoylbenzoic acid from the crude reaction mixture, poor yields, and the formation of sulfonated products.[13] To avoid these disadvantages, the reaction was attempted under gaseous phase over a solid catalyst, such as silicoaluminate[14] or titanium oxide.[15] However, these processes required high temperature and expensive installations.

We have reported a one-pot synthesis of formononetin, an isoflavonoid that acts as a signal molecule for

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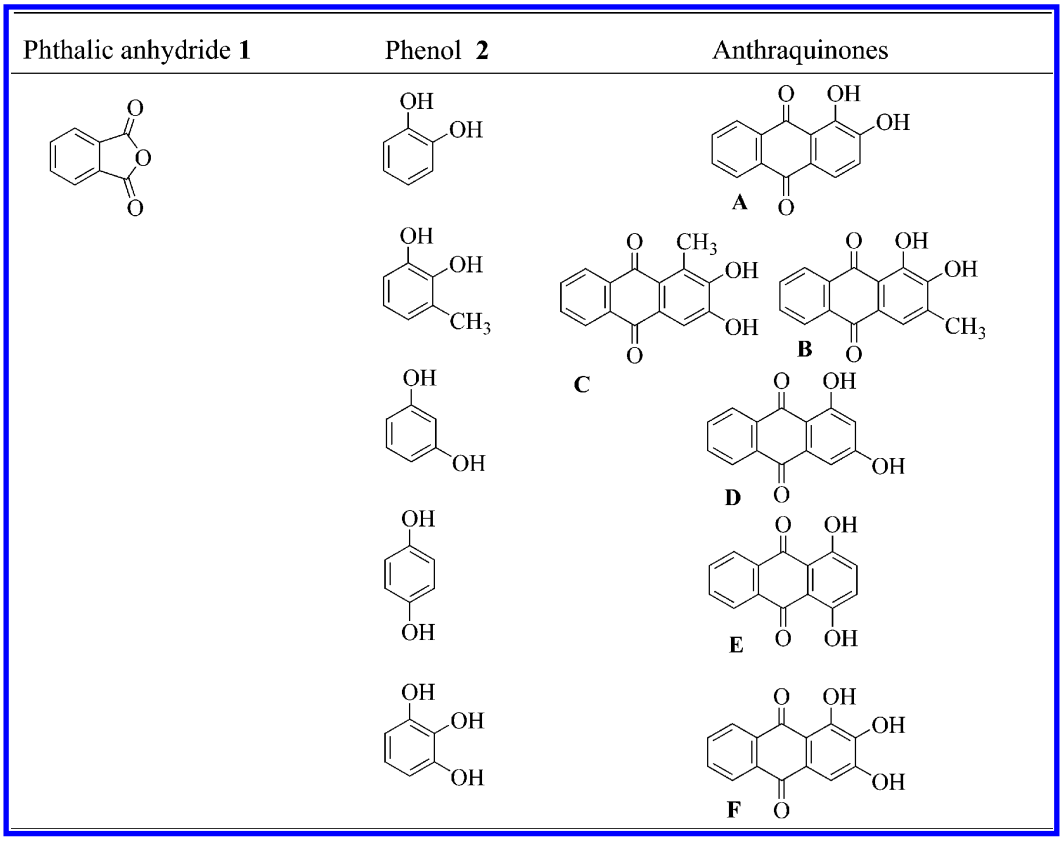

Figure 1. Products yielded from the Friedel–Crafts acylation of phthalic anhydride with phenols.

mycorrhiza-plant symbiosis, using Friedel–Crafts acylation.[15–17] Formononetin is being manufactured in multiton quantities using our method and sold as Mycoform and its potassium salt as Myconate. Therefore, we have attempted Friedel–Crafts acylation again to synthesize bioactive anthraquinone analogues economically by reacting phthalic anhydride with phenols in the presence of aluminum chloride and sodium chloride. In this paper, we report a series of novel anthraquinones produced by this method with significant activity against the human filarial parasite *B. malayi*.

Results and Discussion

A single-step synthesis of anthraquinones **A**–**N** was accomplished by reacting selected phthalic anhydrides with substituted phenols in the presence of $AlCl_3$/NaCl (Figures 1 and 2). A comparison of the product yields resulting from the reaction between phthalic anhydride and various substrates was useful. For example, the reaction of phthalic anhydride with catechol yielded 50% of **A**, whereas with 3-methylcatechol the products were **B** and **C** in 60 and 15% yield, respectively. However, the reaction of phtahlic anhydride with 1,4-hydroquinone and pyrogallol afforded 80 and 75% of **E** and **F**, respectively, whereas reaction with resorcinol yielded 50% of **D** and 20% of 3′,6′-dihydroxyfluoran. The variation in yield was probably due to the acylation at the ortho and para positions to the hydroxyl groups in the substrates. There is no para position free in 1,4-hydroquinone, and hence, the acylation was exclusively ortho to the hydroxyl groups, resulting in a higher yield of product **E**. In the reaction between pyrogallol and phthalic anhydride, the acylium ion was substituted either ortho to the 1-hydroxyl or 3-hydroxyl group or para to 2-hydroxyl group to yield a single product **F**. However, with 3-methylcatechol, the possible substitution of the acylium ions was either ortho or para to hydroxyl groups or ortho to the methyl group and led to products **B** and **C** with different yields. When resorcinol was used as the substrate, the substitutions of the acylium ion could have taken place at positions 2, 4, and 6. However, the substitution did not take place at position 2, even with a high electron density, and yielded **D** due to steric hindrance. However, reacting an excess amount of resorcinol with phthlic anhydride gave another side product, 3′,6′-dihydroxyfluoran. Interestingly, catechol gave only product **A** due to substitutions at positions 3 and 6. It was clear that even if the acylium ion reacted at positions 4 or 5 in catechol, **A** would have been the only product due to ring closures at the 3 or 6 position.

We have also studied the Friedel–Crafts bisacylations to afford anthraquinones in the presence of various solvents using $AlCl_3$ as the Lewis acid (Figure 3). Although benzene, toluene, and nitrobenzene were reported as solvents of choice for acylation reaction,[18,19] we found that nitrobenzene was the only solvent among them to yield anthraquinones. The yield of anthraquinone with nitrobenzene as the solvent was extremely low and will not be economical. The reactivity and yield of products between $AlCl_3/C_6H_5NO_2$ and $AlCl_3$/NaCl melt were also compared. $AlCl_3/C_6H_5NO_2$ needed longer time (>4 h) and high temperatures (>215 °C) for the reaction to complete and gave yields below 10%. The poor yield at higher temperatures was probably due to the potential decomposition of substrates used. The reaction also was carried out with phthaloyl chloride **1a**, instead of

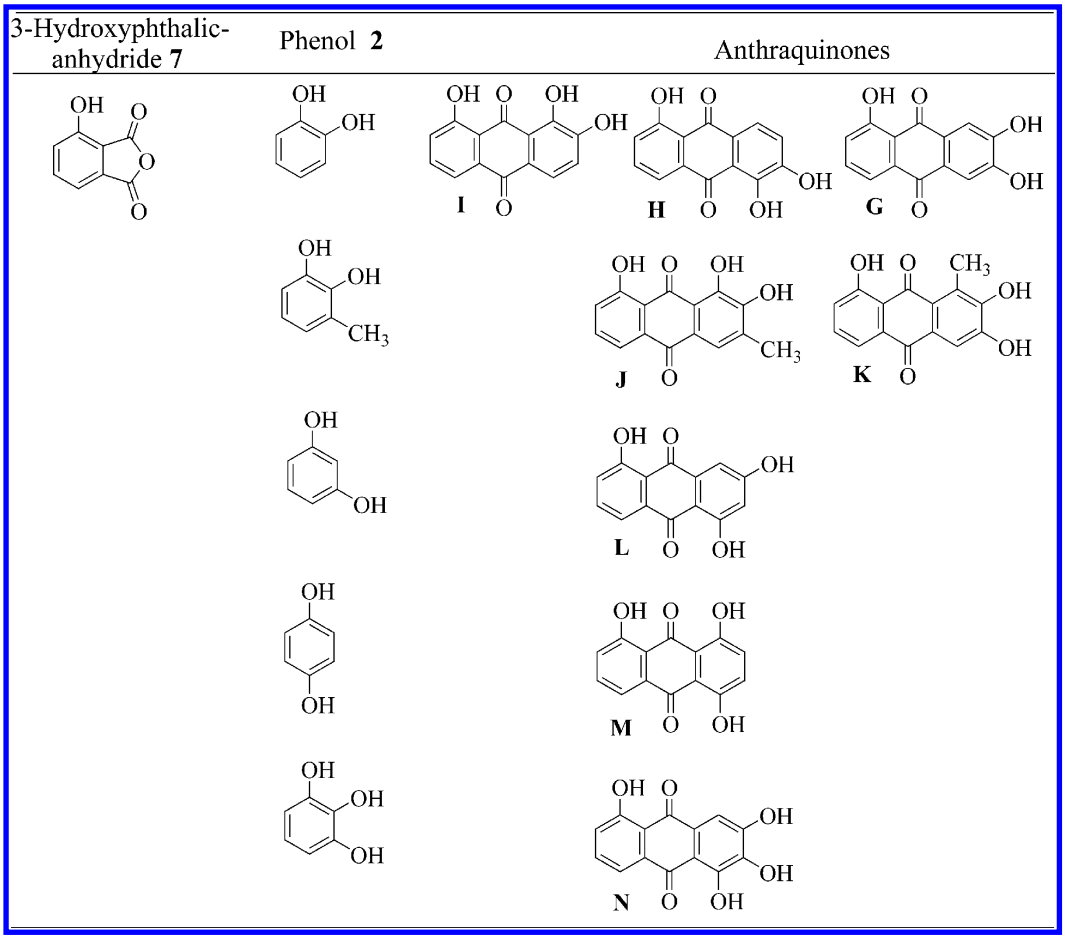

Figure 2. Products yielded from the Friedel−Crafts acylation of 3-hydroxyphthalic anhydride with phenols.

phthalic anhydride, to improve the yield, but this was not successful. Phthaloyl chloride **1a** was prepared by treating phthalic acid with an excess of thionyl chloride at 80 °C for 2 h. However, with the $AlCl_3$/NaCl melt at 165 °C, the reaction proceeded faster and gave a much higher yield (Figure 2).

Compound **J** was one of the bioactive anthraquinones isolated from daylily roots with significant activity against *S. mansoni*[5] and *B. malayi*. We have synthesized compound **J** and its analogues using 3-hydroxyphthalic anhydride with 3-methylcatechol as synthons. 3-Hydroxyphthalic anhydride is very expensive and its preparation by reacting maleic anhydride with 2-triethylsiloxyfuran followed by the aromatization of the resulting cyclic adduct was reported.[20] It was also prepared by using 3-aminophthalic anhydride[21] or 3,6-diiodophthalic anhydride[22] as synthons. However, all of these published methods resulted in very poor yields. A considerably higher yield of 3-hydroxyphthalic anhydride was reported[23] from 2-oxo-2,5-dihydrofuran, a commercially available and less expensive starting material for the production of 3-hydroxyphthalic anhydride. We have, therefore, synthesized 3-hydroxyphthalic anhydride by using the less expensive and commercially available 3-hydroxybutyrolactone as the starting material. The 3-hydroxybutyrolactone (**3**) was treated with acetic anhydride in the presence of a catalytic amount of concentrated sulfuric acid at 100 °C to yield 5-hydrofuran-2-one (**4**) at yields >90%. Compound **4** was then reacted with trimethylacetyl chloride in the presence of triethylamine at 0 °C to afford 2-furyl 2,2-dimethylpropionate (**5**). A mixture of **5** and maleic anhydride was then stirred at room temperature for 12 h to form a Diels−Alder cyclic adduct, **6** (1-(2,2-dimethylpropionyl)-4,10-dioxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione). The resulting product was then aromatized with concentrated sulfuric acid at −15 °C to afford 3-hydroxyphthalic anhydride (**7**) (Figure 4).

The reaction between 3-hydroxyphthalic anhydride and catechol afforded three products, 1,2,8-trihydroxy-, 1,2,5-trihydroxy- and 2,3,8-trihydroxyanthraquinones (**I**, **H**, and **G**), respectively. However, 3-methylcatechol gave only two products, 1,2,8-trihydroxy-3-methylanthraquinone (**J**) and 1-methyl-2,3,8-trihydroxyanthraquinone (**K**). In addition, the reactions of 3-hydroxyphthalic anhydride with resorcinol, 1,4-hydroquinone, and pyrogallol afforded 1,3,5-trihydroxy- (**L**), 1,4,8-trihydroxy- (**M**), and 1,2,3,5-tetrahydroxyanthraquinone (**N**), respectively. It is interesting to note that with an excess amount of resorcinol in the reaction mixture yielded a byproduct, 4,3′,6′-trihydroxyfluoran.

The reaction of 3-hydroxyphthalic anhydride and catechol gave 30% of **G** and 10% of each **H** and **I**. Similarly, 3-methylcatechol and 3-hydroxyphthalic anhydride gave **J** and **K** in 30 and 15% yields, respectively. The reactions of 3-hydroxyphthalic anhydride with resorcinol, 1,4-hydroquinone, and pyrogallol afforded 35% of **L**, 55% of **M**, and 50% of **N**, respectively. However, an excess amount of resorcinol in the reaction led to 40% of **L** and 20% of 4,3′,6′-trihydroxyfluoran. The variations in the yield demonstrated the acylium ion substitution at ortho and para positions to the hydroxyl

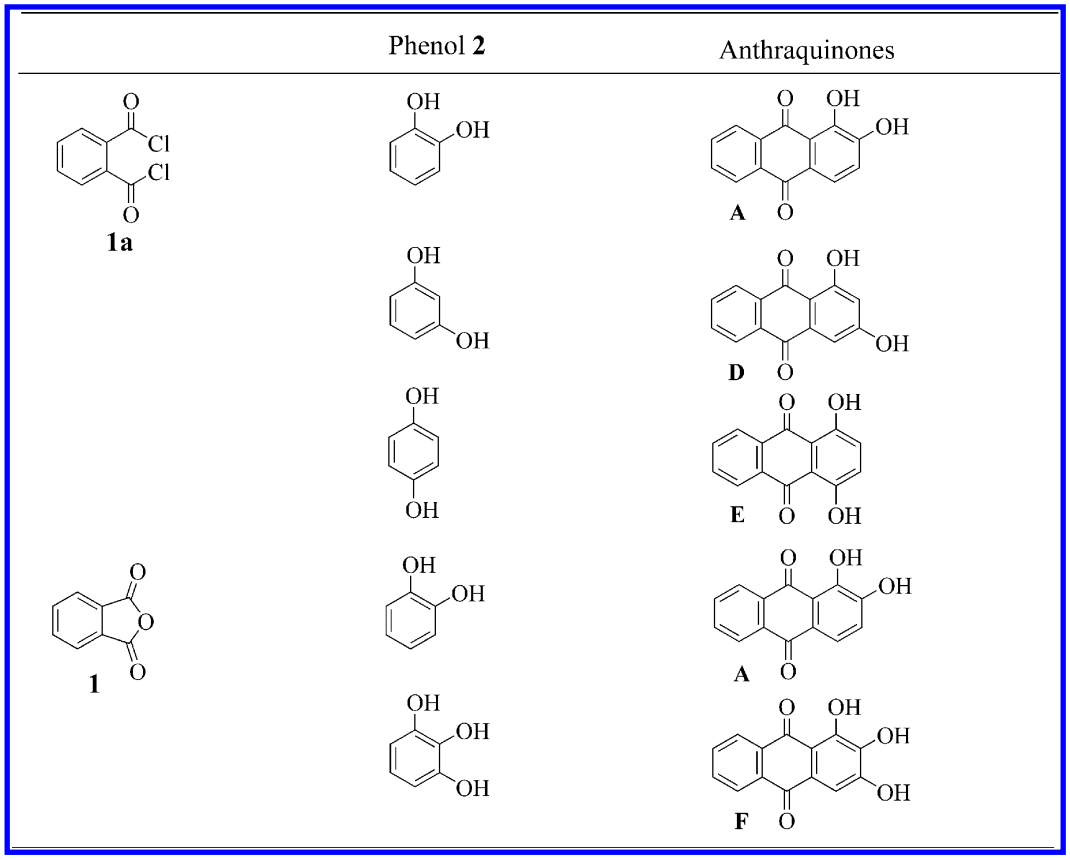

Figure 3. Products yielded from the Friedel–Crafts acylation acylations in the presence of $AlCl_3/C_6H_5NO_2$.

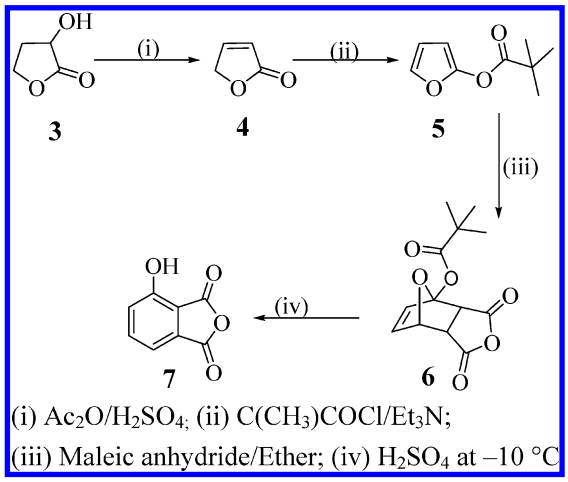

Figure 4. Synthetic scheme for the preparation of 3-hydroxyphthalic anhydride.

groups. There was no para position free in 1,4-hydroquinone. Therefore, the acylium ion substitution was favored only at ortho to the hydroxyl groups, which led to a single product, **M**. In pyrogallol, acylium ion was substituted ortho to the 1-hydroxyl or 3-hydroxyl group to afford product **N**. However, in 3-methylcatechol, the possible substitution of acylium ions was either at ortho and para to hydroxyl groups or ortho to methyl group, which led to products **J** and **K.** The reaction of phthalic anhydride with resorcinol indicated substitutions at positions 2, 4, and 6. Due to steric hindrance at position 2 (though it had a high electron density), the reaction was not favored at that position. Instead the reaction was favored at positions 4 and 6 to yield **L**.

Table 1. Comparison of ^{13}C NMR Chemical Shifts of C9 and C10 Carbons, Color, and Melting Points of Isomeric Anthraquinones Synthesized

anthraquinones	δ C9	δ C10	mp (°C)	color
B	189.87	182.17	224–225	dark orange
C	183.76	182.07	297–299[a]	yellow
G	187.69	181.05	302–304[a]	yellow
H	188.04	186.57	263–264	dark orange
I	192.59	180.07	234–235	dark orange
J	192.26	180.19	239–240	dark orange
K	191.05	182.14	304–305[a]	yellow

[a] Decomposition point.

The anthraquinones **B**, **C**, **G**, **H**, **I**, **J**, and **K** are positional isomers. The color and melting points of these isomers were also distinct (Table 1). In addition, they were readily distinguished by the C9 and C10 chemical shift in their ^{13}C NMR spectra. The hydrogen bonding of the carbonyl carbons to the OH group shifted their resonances by 4–10 ppm downfield. The chemical shift of the C9 carbonyl carbon will be around 182 ppm, if there is no hydrogen bonding. For example, in anthraquinone B, the C9 is hydrogen bonded to C1–OH and hence appeared at 189.87 ppm. However, in anthraquinone C both C9 and C10 are not hydrogen bonded to hydroxyl groups and appeared at 183.76 and 182.07 ppm, respectively (Table 1).

To study the structure–activity relationship, methyl and methoxy derivatives of the anthraquinones synthesized were prepared (Figure 5). Methylation of anthraquinones **B** and **J** with diazomethane in ether at room temperature afforded 1-hydroxy-2-methoxy-3-methylanthraquinone (**O**) and 1,8-dihydroxy-2-methoxy-3-methylanthraquinone (**Q**), respectively. Similarly, methylation of anthraquinone **K** with CH_2N_2 yielded a

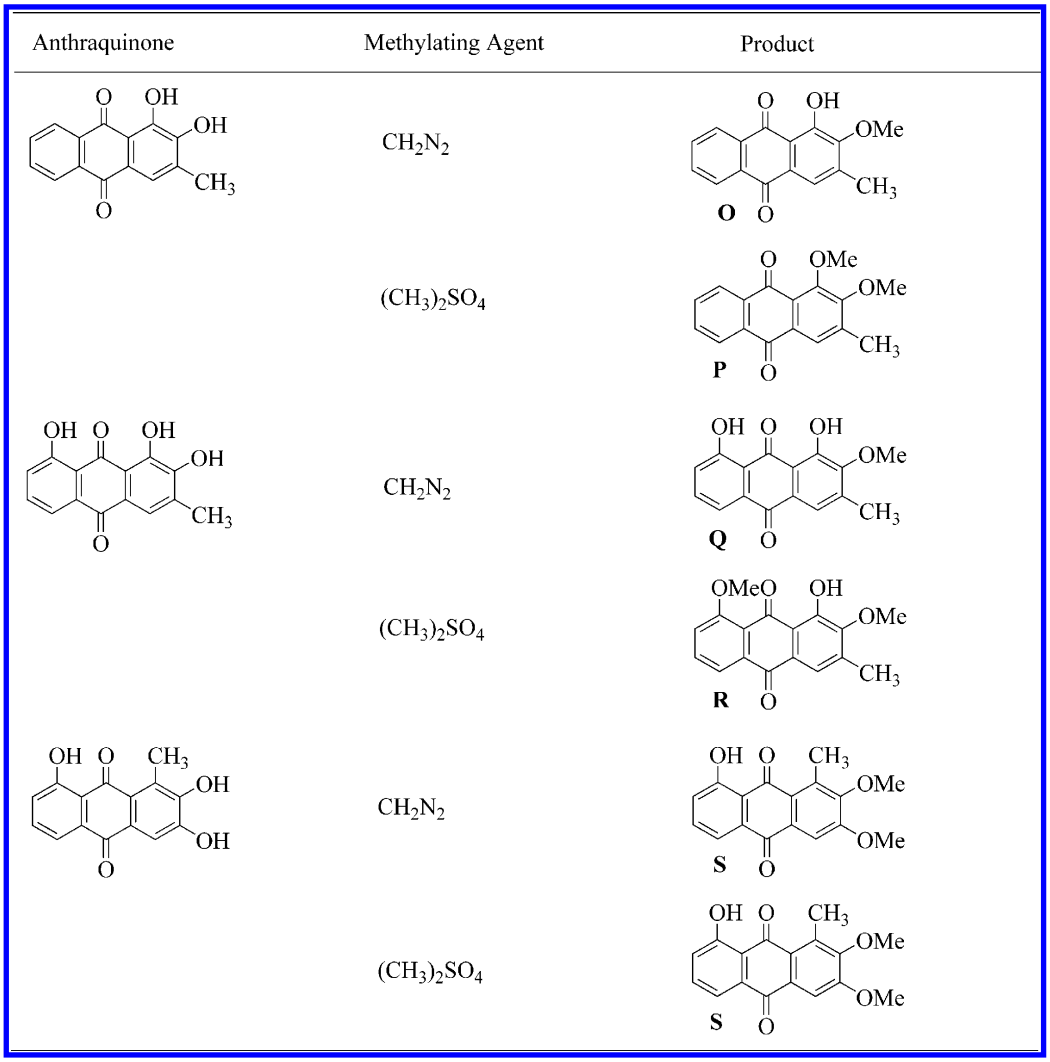

Figure 5. Methylated products of anthraquinones.

dimethylated product, 1-methyl-2,3-dimethoxy-8-hydroxyanthraquinone (**S**). However, methylation of anthraquinones **B**, **J**, and **K** with dimethyl sulfate/K_2CO_3 in acetone at room temperature afforded 1,2-dimethoxy-3-methylanthraquinone (**P**), 1,2-dimethoxy-8-hydroxy-3-methylanthraquinone (**R**), and 1-methyl-2,3-dimethoxy-8-hydroxyanthraquinone (**S**), respectively.

Although *W. bancrofti* is the cause of most human lymphatic filariasis, there is no animal model for this parasite, and thus no ready source of adult worms for drug testing. Because *Brugia malayi* is also a human filarial parasite and adult female worms can be produced in hamsters in sufficient quantities for drug testing, the US NIH provides a filaria repository service for *B. malayi*. The WHO has mandated a search for macrofilaricides, new drugs that are effective specifically against the adult female and male filaria.

The antiparasitic effects of anthraquinones **A**, **B**, **D**, **E**, **F**, **J**, **Q**, and **R**, selected randomly, were tested using adult female *B. malayi* worms. The measurements were mortality and inhibition of motility. The assay was conducted in RPMI medium containing penicillin/streptomycin and the initial concentration of anthraquinones tested was 50 ppm (90−95 μM based on the MW of the anthraquinones). The results showed that anthraquinones **B** and **R** were the most active against *B. malayi* with 100% mortality in 24 h. Compound **J** also showed significant activity and displayed 100% mortality in 48 h. Other anthraquinones tested gave 100% mortality between 3 and 10 days. The controls, treated with 2% DMSO solvent (2−3% of DMSO is a standard for this assay), showed no mortality or inhibition of motility to adult male and female worms, even after 17 days. The assay was repeated with the most active anthraquinones **B**, **F**, **J**, and **R** at lower concentrations (Table 2). The dose−response study was for concentrations ranging from 50 to 3.12 ppm, and 100% mortality of the adult female worms was observed for compound **B** at 3.125 ppm in 6 days, compound **F** at 3.125 ppm in 5 days, compound **J** at 6.25 ppm in 5 days, and compound **R** at 6.25 ppm in 8 days (Table 2).

Table 2. Dose−Response of Active Anthraquinones, B, F, J, and Q against *B. malayi* Female Adult Worms

	100% mortality of *B. malayi* (days)			
concn (ppm)	B	F	J	Q
50	1	2	2	1
25	3	4	3	2
12.5	4	4	4	4
6.25	5	5	5	8
3.125	6	5	no mortality	no mortality
RPMI	no mortality	no mortality	no mortality	no mortality
RPMI + 2% DMSO	no mortality	no mortality	no mortality	no mortality

Table 3. Antifilarial Activity of Anthraquinones against *B. malayi* Female and Male Adult Worms and Microfilaria at 5 ppm

	100% mortality (days)		
anthraquinones	female *B. malayi*	male *B. malayi*	microfilaria[a]
A	5	NT[b]	3
B	5	6	3
C	7	NT	3
D	NM[b]	NT	NM
E	10	NT	NM
F	5	NT	3
G	5	NT	3
H	9	NT	3
I	14	NT	3
J	5	5	3
K	3	5	1
L	7	NT	3
M	9	NT	5
N	5	6	3
O	NM	NT	NM
P	11	NT	NM
Q	NM	NT	NM
R	7	NT	NM
S	9	NT	NM
albendazole	16	9	NM
RPMI + 2.5% DMSO	NM	NM	NM
RPMI alone	NM	NM	NM

[a] Results in the first 5 days. [b] NT, not tested; NM, no mortality.

On the basis of the activity from the preliminary dose−response study of the selected anthraquinones (Table 2), all anthraquinones were then assayed at 5 ppm (18−19 μM based on the MW of the anthraquinones), and the results are shown in Table 3. It was found that the anthraquinone **K** was the most active among all the compounds tested, with 100% mortality in 3 days. However, its structural isomer **J** and analogues **B** and **C**, with no OH group at C8 position, showed 100% mortality in 5 days. Anthraquinones **P**, **R**, and **S** were less active and killed the worms in 11, 7, and 9 days, respectively. The dimethylated derivatives of **B**, **J**, and **K** and the monomethylated derivatives **O** and **Q** did not show mortality during the assay period. Anthraquinones **G** and **N** and their respective analogues **A** and **F** also showed 100% mortality in 5 days, but the structural isomers of **G**, compounds **H** and **I**, were less active and killed the worms in 9 and 14 days, respectively. In assays with anthraquinones **E**, **L**, and **M**, 100% mortality was observed in 10, 7, and 9 days, respectively. Anthraquinone **D** and the media controls (RPMI 1640 with and without 2.5% DMSO) did not show any mortality during the assay period of 20 days. The positive control, albendazole, an oral drug used to treat a variety of parasitic infections, killed the female adult worms in 16 days at 5 ppm.

Due to the scarcity of male adult *B. malayi* worms, we have assayed only a limited number of anthraquinones at 5 ppm. The anthraquinones **B**, **J**, **K**, and **N** were selected to assay with the male adult *B. malayi* worms, since they were the most active against the female adult worms. The assays revealed 100% mortality for anthraquinones **B** and **N** in 6 days. Compounds **J** and **K** showed 100% mortality in 5 days, whereas the positive control, albendazole, showed 100% mortality in 9 days. The media controls, with and without DMSO, did not show any mortality during the assay period of 14 days (Table 3).

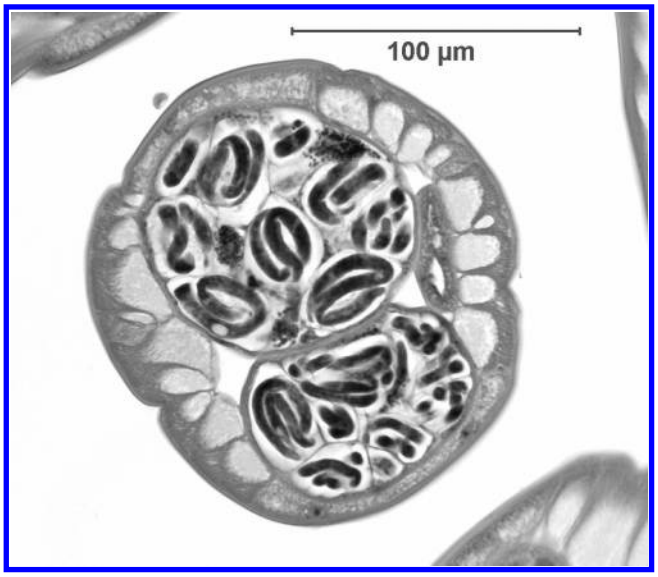

Figure 6. Cross section of H & E stained normal control adult female *B. malayi*. Normal duplicate intrauterine structures contain many well-formed microfilaria larvae that have not yet been released from the uterus. Magnification 320×. Calibration mark indicates 100 μm in Figures 6−9.

Assays with microfilaria of *B. malayi* showed 100% mortality for anthraquinone **K** in 24 h, whereas its isomer **J** and analogues **B** and **C** demonstrated mortality in 3 days. Anthraquinones **A**, **F**, **G**, **H**, **I**, **L**, and **N** showed 100% mortality in 3 days and **M** in 5 days. It should be noted that the control with 2.5% DMSO, the mono- and dimethyl derivatives (O to S), and albendazole gave 100% mortality in the range of 7−10 days (Table 3). The mortality of microfilaria reported in Table 3 was at 5 days. It appears that 2.5% of DMSO, a nonlethal concentration to the adults, in the medium showed some toxicity to microfilaria. The control RPMI 1640 alone (without DMSO) did not show mortality during the assay period of 14 days.

The morphological changes observed in adult filaria killed by each compound appeared similar. In female worms, the normal bipartite uterus contains microfilaria in different stages of development (Figure 6). In male worms, nuclei are generally well structured and the cuticle is clearly demarcated from an underlying hypodermal region (Figure 7). In killed parasites, the normal cuticle and hypodermal architecture of each worm have become distorted (Figure 8). Nuclei of intrauterine larvae have become disorganized and demonstrated early degeneration (Figure 9).

Our results indicate that the anthraquinones studied are potential antifilarial therapeutic candidates. The Friedel−Crafts synthesis of these active anthraquinones is cost-effective and, if developed, should be affordable in countries where filariasis is prevalent. The toxicity and pharmacology of the most active anthraquinone analogue should be determined for its development as an antifilarial therapeutic agent.

Experimental Section

Phthalic anhydride and 3-hydroxyphthalic anhydride (initial supply), catechol, 3-methlylcatechol, resorcinol, 1,4-hydroquinone, phyrogallol, anhydrous $AlCl_3$, and NaCl were purchased from Sigma-Aldrich. ^1H and ^{13}C NMR were recorded (DMSO-d_6 or $CDCl_3$) at 500 MHz on a Varian VRX instrument.

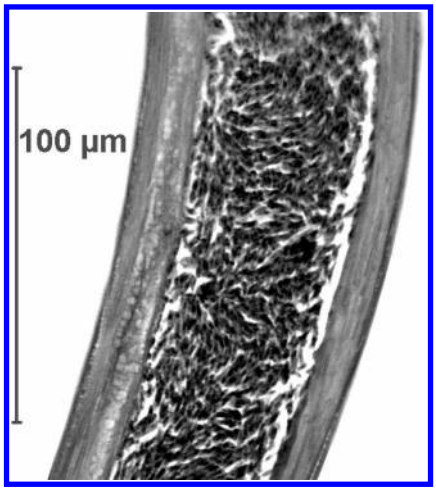

Figure 7. Longitudinal section of normal adult male *B. malayi*. Section demonstrates well-organized nuclei deep in the cuticle. Magnification 320×.

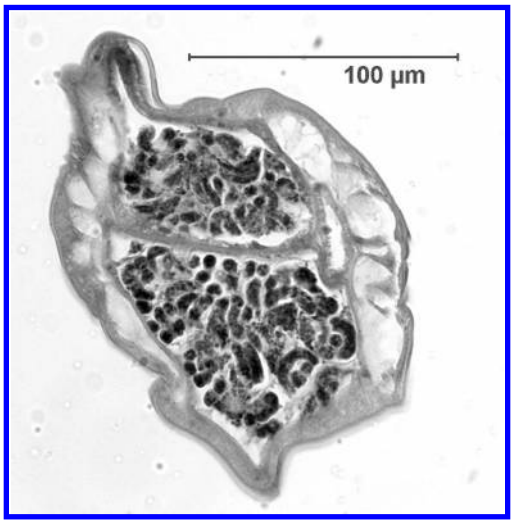

Figure 8. Cross sectional morphology of adult female *B. malayi* that has been killed by 5 ppm compound **B**. Note disruption of the stable cuticle and hypodermal regions, along with disorganization of the intrauterine microfilariae. Magnification 320×.

DMSO-d_6 and $CDCl_3$ was purchased from Cambridge Isotope Laboratories, Inc., Andover, MA. UV−vis spectra were recorded in CH_3OH using a Shimatzu (UV-260) spectrophotometer. Silica gel (32−63 μm) was obtained from Fischer Scientific, PA. A collection of microfilaria and male and female adult *B. malayi* worms were obtained through an NIH subcontract from Dr. John McCall, University of Georgia, in order to test the efficacy of anthraquinones as antifilarial agents.

5-Hydrofuran-2-one (4). 3-Hydroxybutyrolactone (**3**) (10 mmol, 0.779 mL) and acetic anhydride (10 mmol, 0.95 mL) were mixed in a round bottom flask, and 2 drops of concentrated H_2SO_4 was added at 0 °C. The pale yellow solution became dark yellow. The reaction mixture was stirred for 15 min. DMAP was added to neutralize H_2SO_4, and the mixture was heated (100 °C) for 3 h in an oil bath. The reaction mixture was distilled at atmospheric pressure to remove acetic acid, followed by vacuum distillation to yield the desired product **4** (90% yield). ^{1}H NMR ($CDCl_3$): δ 4.83 (m, 2H), 6.06 (m, 1H), 7.56 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 72.11, 121.00, 153.22, 173.76.

2-Furyl 2,2-dimethylpropionate (5). A solution of triethylamine (6 mmol, 0.83 mL) in acetonitrile (5 mL) was added dropwise to a solution of 5-hydrofuran-2-one (5 mmol, 0.35 mL) and trimethylacetyl chloride (6 mmol, 0.74 mL) in acetonitrile (20 mL) and the mixture stirred at 60 °C for 4 h. The precipitate formed, triethylamine hydrochloride, was filtered off. The filtrate was washed with 10% sodium carbonate, dried over $MgSO_4$, and distilled to remove acetonitrile. The resulting product was further distilled under vacuum to yield product **5** (80%).

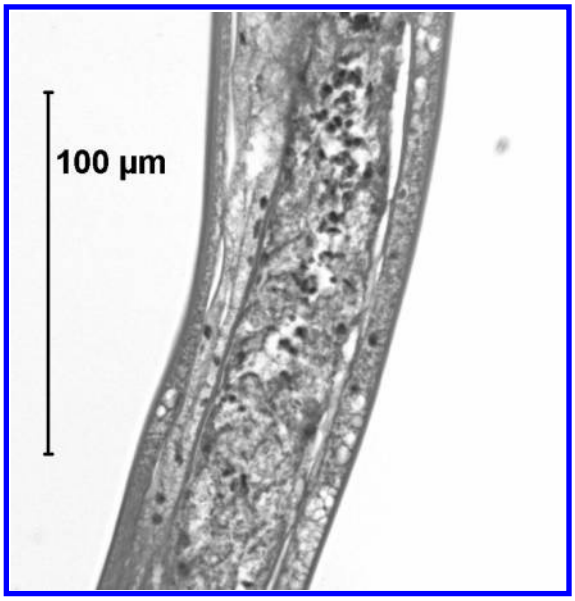

Figure 9. Longitudinal section of adult male *B. malayi* killed by 5 ppm compound **B**. Note marked loss of cellularity in hypodermal and deeper structures. Magnification 320×.

1-(2,2-Dimethylpropionyl)-4,10-dioxatricyclo[5.2.1.0^{2,6}]-dec-8-ene-3,5-dione (6). 2-Furyl 2,2-dimethylpropionate (5 mmol, 840 mg) and maleic anhydride (5 mmol, 0.490 g) were dissolved in ether (1 mL/mmol of **5**) and stirred overnight. The precipitate, product **6**, was filtered off and crystallized from chloroform (75% yield). ^{1}H NMR (DMSO): δ 1.32(s, 9H), 3.39 (d, 1H, J = 7.0) 3.78 (d, 1H, J = 7.0) 5.33 (d, 1H, J = 2.0) 6.70 (m, 2H). ^{13}C NMR (DMSO): 176.68, 169.43, 166.10, 138.16, 137.33, 111.76, 52.87, 52.84, 48.92, 48.15, 48.09, 39.33, 27.10.

3-Hydroxyphthalic Anhydride (7). Compound **6** (1 mmol, 266 mg) was added in small portions to 98% H_2SO_4 (2 mL) at −15 °C. The cream-colored mixture was stirred for 5 min and then poured over crushed ice. The precipitated product was filtered off, washed with ice-cold water, and dried in a desiccator to afford product 7 (73%). ^{1}H NMR (CD_3OD): δ 7.40 (d, 1H, J = 8.1) 7.62 (d, 1H, J = 6.9), 7.85 (t, 1H, J = 7.8).

General Method for the Preparation of Anthraquinones. A mixture of anhydrous $AlCl_3$ (5 mmol, 0.667 g) and prebaked NaCl (2.5 mmol, 0.145 g) was heated (110 °C) in an oil bath till molten. A homogeneous mixture of phthalic anhydrides (1 mmol) and substituted phenols (1 mmol) separately were reacted with the $AlCl_3$/NaCl melt. The temperature was slowly increased and maintained at 165 °C for 4 h. The reaction mixture was cooled to 0 °C, 10 mL of 10% HCl was added, and the mixture was stirred for 15 min at 0 °C and refluxed at 100 °C for 30 min. The reaction mixture was cooled to room temperature and extracted with diethyl ether. The resulting product was purified by cellulose column using chloroform and ethyl acetate as the mobile phase.

General Method for the Preparation of Monomethylated Anthraquinones. Diazomethane was made by reacting *N*-nitroso-*N*-methylurea with KOH in ether. The anthraquinones (0.1 mmol) were dissolved separately in 2 mL of dry ether and cooled in an ice bath, and the diazomethane in ether was added in excess. The reaction mixture was allowed to stand for several hours, the solvent was evaporated under reduced pressure, and the resulting product was purified by silica MPLC using 30% ethyl acetate in hexane as the mobile phase.

General Method for the Preparation of Dimethylated Anthraquinones. The anthraquinone (0.1 mmol) was stirred with dry acetone (2 mL) and K_2CO_3 (0.1 mmol, 0.014 g). The

reaction mixture was cooled in an ice bath. Dimethyl sulfate (0.2 mmol) was added and allowed to stir for several hours at room temperature. The solvent was evaporated under vacuum, and the residue was dissolved in water and extracted with ethyl acetate. The resulting residue was purified by silica MPLC using 20% ethyl acetate in hexane as the mobile phase.

1,2-Dihydroxyanthraquinone (A). Yield: 55%. Mp: 173−174 °C. UV λ_{max} (CH_3OH) (log ϵ): 205 (4.47), 246 (4.6), 275 (4.4), 431 (3.7) nm. ^{1}H NMR (DMSO): δ 7.27 (d, 1H, J = 8.5, H3), 7.70 (d, 1H, J = 8.5, H4), 7.95 (m, 2H, H6, H7), 8.23 (m, 2H, H5, H8). ^{13}C NMR (DMSO): δ 190.25 (C-9), 182.03 (C-10), 154.2 (C-1), 152.28 (C-2), 136.57 (C-10a), 135.51 (C-8a), 135.04 (C-6), 134.16 (C-7), 128.59 (C-5), 127.95 (C-8), 125.26 (C-9a), 122.70 (C-3), 122.31 (C-4a), 117.73 (C-4). FABMS: *m/z* 241 (25), 240 (10), 232 (8), 209 (4). HRFAB: *m/z* 241.0502 [MH^+].

1,2-Dihydroxy-3-methylanthraquinone (B). Yield: 50%. Mp: 224−225 °C. UV λ_{max} (CH_3OH) (log ϵ): 206 (4.46), 245 (4.36), 270 (4.39), 280 (4.39), 417 (3.57) nm. ^{1}H NMR (DMSO): δ 2.32 (s, 3H, 3-CH_3), 7.61 (s, 1H, H4), 7.94 (m, 2H, H6, H7), 8.21 (m, 2H, H5, H8). ^{13}C NMR (DMSO): δ 189.87 (C-9), 182.17 (C-10), 151.61 (C-1), 151.11 (C-2), 135.48 (C-3), 134.99 (C-10a), 134.29 (C-8a), 133.48 (C-6), 128.18 (C-5), 127.82 (C-8), 124.57 (C-10), 124.02 (C-4a), 115.96 (C-4), 17.90 (C-11). FABMS: *m/z* 255 (15), 254 (7), 232 (19), 209 (4). HRFAB: *m/z* 255.0655 [MH^+].

1-Methyl-2,3-dihydroxyanthraquinone (C). Yield: 30%. Mp: 297−299 °C (dec). UV λ_{max} (CH_3OH) (log ϵ): 255 (3.89), 364 (3.48) nm. ^{1}H NMR (DMSO): δ 2.63 (s, 3H, 1-CH_3), 7.61 (s, 1H, H4), 7.85 (m, 2H, H6, H7), 8.10 (m, 2H, H5, H8). ^{13}C NMR (DMSO): δ 183.76 (C-9), 182.07 (C-10), 149.64 (C-2), 149.39 (C-3), 134.65 (C-1), 133.89 (C-10a), 132.24 (C-8a), 128.00 (C-6), 127.48 (C-7), 126.55 (C-5), 125.74 (C-8), 124.90 (C-9a), 111.12 (C-4a), 110.96 (C-4), 13.61 (C-11). FABMS: *m/z* 255 (90), 254 (37), 232 (20), 209 (3). HRFAB: *m/z* 255.0658 [MH^+].

1,3-Dihydroxyanthraquinone (D). Yield: 60%. Mp: 207−208 °C. UV λ_{max} (CH_3OH) (log ϵ): 211 (4.18), 282 (3.89), 311 (3.69), 410 (3.41) nm. ^{1}H NMR (DMSO): δ 5.73 (s, 1H, H2), 6.59 (s, 1H, H4), 7.72 (t, 1H, J = 7.5, H6), 7.83 (t, 1H, J = 7.5, H7), 8.07 (d, 1H, J = 7.5, H8), 8.13 (d, 1H, J = 8.0, H7). FABMS: *m/z* 241 (12), 240 (3), 232 (16), 209 (7). HRFAB: *m/z* 241.0500 [MH^+].

1,4-Dihydroxyanthraquinone (E). Yield: 80%. Mp: 195−196 °C. UV λ_{max} (CH_3OH) (log ϵ): 206 (4.51), 223, (4.54) 248 (4.64), 278 (4.20), 479 (4.02) nm. ^{1}H NMR (DMSO): δ 7.47 (s, 2H, H2, H3), 8.01 (m, 2H, H6, H7), 8.30 (m, 2H, H5, H8). ^{13}C NMR (DMSO): δ 1187.40 (C-9, C-10), 157.40 (C-1, C-4), 135.77 (C-10a, 8a), 133.61 (C-6, C-7), 133.04 (C-5, C-8), 127.38 (C-4a, C-9a), 113.40 (C-2, C-3). FABMS: *m/z* 241 (16), 240 (10), 232 (12), 209 (6). HRFAB: *m/z* 241.0500 [MH^+].

1,2,3-Trihydroxy anthraquinone (F). Yield: 75%. Mp: 282−284 °C. UV λ_{max} (CH_3OH) (log ϵ): 207 (4.59), 243 (4.39), 283 (4.49), 410 (3.71) nm. ^{1}H NMR (DMSO): δ 7.29 (s, 1H, H4), 7.91 (m, 2H, H6, H7), 8.18 (m, 2H, H5, H8): ^{13}C NMR (DMSO): δ 187.63 (C-9), 181.67 (C-10), 152.72 (C-1), 152.48 (C-2), 139.65 (C-3), 135.22 (C-10a), 134.79 (C-8a), 133.94 (C-6), 133.77 (C-7), 127.30 (C-8), 126.94 (C-5), 125.37 (C-9a), 111.03 (C-4a), 109.52 (C-4). FABMS: *m/z* 257 (11), 256 (6), 232 (7), 209 (3). HRFAB: *m/z* 257.0449 [MH^+].

2,3,8-Trihydroxyanthraquinone (G). Yield: 30%. Mp: 302−304 °C (dec). ^{1}H NMR (DMSO): δ 7.28 (dd, 1H, J = 8.0, 1.0, H7), 7.47 (s, 1H, H2), 7.51 (s, 1H, H1), 7.61 (dd, 1H, J = 7.5, 1.0, H5), 7.71 (t, 1H, J = 8.0, H6). ^{13}C NMR (DMSO): δ 187.69 (C-9), 181.05 (C-10), 161.32 (C-8), 152.45 (C-2), 151.71 (C-3), 136.63 (C-6), 133.46 (C-10a), 127.14 (C-8a), 126.15 (C-9a), 123.66 (C-7), 118.72 (C-5), 115.78 (C-4a), 113.21 (C-1), 112.66 (C-4). FABMS: *m/z* 257 (4), 256 (3), 246 (6), 232 (10), 209 (5). HRFAB: *m/z* 257.0449 [MH^+].

1,2,5-Trihydroxyanthraquinone (H). Yield: 10%. Mp: 263−264 °C. UV λ_{max}(CH_3OH) (log ϵ): 255 (4.56), 288 (4.35), 444 (4.08) nm. ^{1}H NMR (DMSO): δ 7.28 (d, 1H, J = 8.5, H2), 7.41 (dd, 1H, J = 8.5, 1.5, H7), 7.54 (d, 1H, J = 8.5, H3), 7.79 (dd, 1H, J = 7.5, 1.5, H5), 7.83 (t, 1H, J = 8, H6). ^{13}C NMR (DMSO): δ 188.04 (C-9), 186.57 (C-10), 161.70 (C-5), 153.61 (C-1), 151.14 (C-2), 136.66 (C-7), 133.14 (C-8a), 124.63 (C-6), 123.16 (C-4a), 121.48 (C-9a), 120.74 (C-4), 118.83 (C-8), 116.20 (C-3), 115.92 (C-10a). FABMS: *m/z* 257 (11), 256 (6), 246 (5), 232 (7), 209 (3). HRFAB: *m/z* 257.0449 [MH^+].

1,2,8-Trihydroxyanthraquinone (I). Yield: 10%. Mp: 234−235 °C. UV λ_{max} (CH_3OH) (log ϵ): 288 (4.90), 347 (4.29) nm. ^{1}H NMR (DMSO): δ 7.26 (d, 1H, J = 8.5, H3), 7.57 (dd, 1H, J = 8.5, 1, H5), 7.68 (d, 1H, J = 8, H4), 7.21 (dd, 1H, J = 7.5, 1, H7), 7.83 (t, 1H, J = 8, H6). ^{13}C NMR (DMSO): δ 192.59 (C-9), 180.07 (C-10), 161.34 (C-8), 152.93 (C-1), 150.57 (C-2), 137.49 (C-6), 133.83 (C-10a), 123.78 (C-7), 123.73 (C-8a), 121.42 (C-4a), 120.98 (C-4), 119.04 (C-5), 116.18 (C-3), 116.09 (C-9a). FABMS: *m/z* 257 (40), 256 (18), 246 (4), 232 (19), 209 (8). HRFAB: *m/z* 257.0449 [MH^+].

1,2,8-Trihydroxy-3-methylanthraquinone (J). Yield: 30%. Mp: 239−240 °C. UV λ_{max} (CH_3OH) (log ϵ): 256 (4.01), 427 (3.69) nm. ^{1}H NMR (DMSO): δ 2.24 (s, 3H, 3-CH_3), 7.32 (d, 1H, J = 8.5 Hz, H7), 7.54 (1H, s, H4), 7.67 (d, 1H, J = 7.5 Hz, H5), 7.74 (t, 1H, J = 7.5, H6). ^{13}C NMR (DMSO): δ 16.45 (C-11), 114.35 (C-9a), 115.94 (C-8a), 119.05 (C-5), 122.87 (C-4), 123.11 (C-4a), 123.73 (C-7), 132.32 (C-3), 132.75 (C-10a), 137.40 (C-6), 149.38 (C-1), 150.27 (C-2), 161.26 (C-8), 180.19 (C-10), 192.26 (C-9). FABMS: *m/z* 271 (7), 270 (2), 232 (24), 214 (5). HRFAB: *m/z* 271.0606 [MH^+].

1-Methyl-2,3,8-trihydroxy anthraquinone (K). Yield: 15%. Mp: 304−305 °C (dec). UV λ_{max} (CH_3OH) (log ϵ): 288 (4.90), 347 (4.29); ^{1}H NMR (DMSO): δ 2.65 (s, 3H, 1-CH_3), 7.19 (d, 1H, J = 8.5 Hz, H7), 7.60 (s, 1H, H4), 7.63 (d, 1H, J = 7.5 Hz, H5), 7.73 (t, 1H, J = 8, H6). ^{13}C NMR (DMSO): δ 13.93 (C-11), 112.18 (C-4), 117.43 (C-9a), 118.65 (C-5), 124.51 (C-4a), 124.83 (C-7), 128.42 (C-8a), 129.39 (C-3), 133.39 (C-10a), 136.63 (C-6), 150.38 (C-2), 150.90 (C-1), 162.10 (C-8), 182.14 (C-10), 191.05 (C-9). FABMS: *m/z* 271 (15), 256 (7), 232 (30), 214 (4). HRFAB: *m/z* 271.0606 [MH^+].

1,3,5-Trihydroxyanthraquinone (L). Yield: 35%. Mp: 284−286 °C (dec). UV λ_{max} (CH_3OH) (log ϵ): 268 (4.70), 426 (4.43) nm. ^{1}H NMR (DMSO): δ 6.58 (d, 1H, 2.5 Hz, H2), 7.14 (d, 1H, 2.5 Hz, H4), 7.33 (dd, 1H, J = 8.5, 1 Hz, H6), 7.68 (dd, 1H, J = 7.5 Hz, 1 Hz, H8), 7.78 (t, 1H, J = 8.0, H7). ^{13}C NMR (DMSO): δ 108.07 (C-2), 108.37 (C-4), 109.23 (C-9a), 115.67 (C-10a), 118.68 (C-8), 124.0 (C-6), 133.2 (C-4a), 134.64 (C-8a), 137.33 (C-7), 161.65 (C-3), 164.87 (C-1), 165.49 (C-5) 185.09 (C-10), 187.34 (C-9). FABMS: *m/z* 257 (20), 256 (7), 246 (4), 232 (21), 209 (4). HRFAB: *m/z* 257.0451 [MH^+].

1,4,8-Trihydroxyanthraquinone (M). Yield: 55%. Mp: 254−256 °C (dec). UV λ_{max} (CH_3OH) (log ϵ): 283 (3.44), 488 (3.45) 573 (2.75) nm. ^{1}H NMR (DMSO): δ 7.41 (dd, 1H, J = 8.0, 1.5 Hz, H7), 7.45 (d, 2H, H2, H3), 7.80 (dd, 1H, J = 7.5, 1.0 Hz, H6), 7.84 (t, 1H, J = 8.0, H6). FABMS: *m/z* 257 (10), 256 (8), 246 (4), 232 (16), 209 (4). HRFAB: *m/z* 257.0449 [MH^+].

1,2,3,5-Tetrahydroxyanthraquinone (N). Yield: 50%. Mp: 278−279 °C (dec). ^{1}H NMR (DMSO): δ 7.32 (s, 1H, H4), 7.35 (dd, 1H, J = 7.0, 1.5 Hz, H6), 7.73 (dd, 1H, J = 7.5 Hz, 1.5 Hz, H8), 7.88 (t, 1H, J = 8.0, H6). ^{13}C NMR (DMSO): δ 108.89 (C-4), 110.33 (C-9a), 115.67 (C-10a), 118.62 (C-8), 124.02 (C-4a), 124.17 (C-6), 133.29 (C-8a), 136.74 (C-8), 139.69 (C-3), 151.87 (C-2), 152.06 (C-1), 161.56 (C-5), 186.20 (C-10), 186.83 (C-9). FABMS: *m/z* 273 (20), 272 (10), 232 (10), 209 (4). HRFAB: *m/z* 273.0398 [MH^+].

1-Hydroxy-2-methoxy-3-methylanthraquinone (O). Yield: 80%. Mp: 154−155 °C. UV λ_{max} (CH_3OH) (log ϵ): 261 (4.69), 337 (3.92) nm. ^{1}H NMR ($CDCl_3$): δ 8.27 (m, 2H, H5, H8), 7.79 (m, 2H, H6, H7) 7.67 (s, 1H, H4), 4.02 (s, 3H, OCH_3), 2.39 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$): δ δ 17.03 (3-CH_3), 60.64 (2-OCH_3), 115.91 (C-4), 122.55 (C-4a), 127.02 (C-9a), 127.61 (C-8), 127.85 (C-5), 133.58 (C-7), 133.93 (C-6), 134.17 (C-8a), 134.85 (C-10a), 140.22 (C-3), 152.14 (C-2), 155.84 (C-1), 182.30 (C-10), 188.99 (C-9). FABMS: *m/z* 269 (8), 268 (2), 241 (2). HRFAB: *m/z* 269.0813 [MH^+].

1,2-Dimethoxy-3-methylanthraquinone (P). Yield: 75%. Mp: 127−128 °C. UV λ_{max} (CH_3OH) (log ϵ): 263 (4.50), 409 (3.82) nm. ^{1}H NMR ($CDCl_3$): δ 8.26 (m, 2H, H5, H8), 7.77 (m, 2H, H6, H7) 7.99 (s, 1H, H4), 4.06 (s, 3H, 2-OCH_3), 3.99 (s,

3H, 1-OCH_3) 2.41 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$): δ 17.03 (3-CH_3), 61.00 (2-OCH_3), 61.54 (3-OCH_3), 125.85 (C-4), 126.19 (C-4a), 126.89 (C-8), 127.33 (C-5), 129.98 (C-9a), 132.98 (C-7), 133.67 (C-6), 134.22 (C-8a), 135.21 (C-10a), 139.42 (C-3), 153.74 (C-1), 158.33 (C-2), 182.74 (C-10), 183.05 (C-9). FABMS: *m/z* 283 (100), 282 (40), 232 (22). HRFAB: *m/z* 283.0970 [MH^+].

1,8-Dihydroxy-2-methoxy-3-methylanthraquinone (Q). Yield: 75%. Mp: 173−174 °C. ^1H NMR ($CDCl_3$): δ 7.82 (dd, 1H, J = 7.5, 1 Hz, H5), 7.68 (t, 1H, J = 8.0, H6) 7.30 (dd, 1H, J = 8.0, 1 Hz, H7), 7.25 (s, 1H, H4), 4.04 (s, 3H, OCH_3), 2.39 (s, 3H, 3-CH_3). FABMS: *m/z* 285 (8), 284 (4), 273 (4), 232 (16), 209 (2). HRFAB: *m/z* 285.0761 [MH^+].

1-Hydroxy-2,8-dimethoxy-3-methylanthraquinone (R). Yield: 80%. Mp: 283−284 °C. UV λ_{max} (CH_3OH) (log ϵ): 276 (3.90), 385 (3.32) nm. ^1H NMR ($CDCl_3$): δ 7.77 (s, 1H, H4), 7.61 (dd, 1H, J = 8.4, 0.9, H5) 7.58 (t, 1H, J = 7.8, H6), 7.27 (dd, 1H, J = 8.1, 1.2, H7), 4.05 (s, 3H, 2-OCH_3), 3.87 (s, 3H, 1-OCH_3), 2.76 (s, 3H, 3-CH_3). FABMS: *m/z* 299 (12), 298 (4), 273 (10), 246 (8), 232 (16), 209 (8). HRFAB: *m/z* 299.0920 [MH^+].

1-Methyl-2,3-dimethoxy-8-hydroxyanthraquinone (S). Yield: 75%. Mp: 197−198 °C. ^1H NMR ($CDCl_3$): δ 7.77 (s, 1H, H4), 7.58 (dd, 1H, J = 7.5, 1 Hz, H5) 7.60 (t, 1H, J = 8.0, H6), 7.27 (dd, 1H, J = 8.5, 1.0, H7), 4.05 (s, 3H, 3-OCH_3), 3.87 (s, 3H, 2-OCH_3), 2.77 (s, 3H, 1-CH_3). ^{13}C NMR ($CDCl_3$): δ 14.71 (1-CH_3), 56.43 (3-OCH_3), 60.88 (2-OCH_3), 108.90 (C-4), 117.38 (C-8a), 118.98 (C-5), 124.77 (C-7), 125.91, 132.61 (C-10a), 133.02 (C-4a), 135.83 (C-6), 137.23 (C-1), 152.69 (C-2), 157.32 (C-3), 162.55 (C-9), 182.82 (C-10), 190.58 (C-9). FABMS: *m/z* 299 (10), 298 (4), 273 (8), 232 (16), 209 (4). HRFAB: *m/z* 299.0920 [MH^+].

HPLC Analysis of Anthraquinones. The purity of the anthraquinones was evaluated by HPLC (Waters Corp.) analysis. All samples (10 μL injection volume) were filtered (0.22 μm) and analyzed on a C-18 Xterra column (20 × 3 mm id, 5 μm, Waters Corp.) at 25° C. Peaks were detected at 254 nm using a PDA detector (Waters Corp., Milford, MA) and analyzed by using the Millenium 2010 chromatography manager, version 3.05.01 (Waters Corp.). Anthraquinones were dissolved in HPLC-grade methanol, and aliquots of 10 μL were injected using an autosampler (Waters Corp.). For isocratic conditions, the mobile phase employed was a mixture of A (30% water, 0.1% TFA) and B (70% methanol). The flow rate was 1 mL/min for compounds **B**, **J**, **K**, and **N** and 0.5 mL/min for compounds **A**, **C**, **D**, **E**, and **F**. For gradient analysis, the mobile phase consisted of solvents A (0.1% TFA in Water) and B (100% methanol) under linear gradient conditions from 99% solvent A to 2% solvent B in 20 min at a flow rate of 1 mL/min. Between injections, the column was equilibrated for 10 min. The HPLC chromatograms under isocratic and gradient conditions are included in the Supporting Information (S3−S11).

Antifilarial Assay with Adult *B. malayi*. Live adult male and female *B. malayi* were obtained from John McCall, University of Georgia, Athens, GA. (NIH Subcontract). Adult worms were transferred to 6-well plates (3 worms, male or female, per well) containing fresh RPMI 1640 culture medium supplemented with L-glutamine and penicillin/streptomycin. Anthraquinones were dissolved separately in 100% DMSO (4 mg/ml) and diluted with RPMI media to obtain a final concentration of 5 ppm. Duplicate control groups received 2.5% DMSO or no DMSO. Every 48 h, the medium from each well was removed and replaced with fresh RPMI with or without drug in DMSO. The movement and mortality of the filaria were monitored every 24 h for 20 days. All *B. malayi* worms in the control wells were fully motile throughout the study and the worms treated with anthraquinones were dead. The results are summarized in Table 3. Dead adult parasites were formalin fixed, embedded in paraffin, sectioned, and stained with hemotoxylin and eosin (H & E) to examine morphology. The morphology of typical adult female *B. malayi* is shown in Figures 6 and 8, and adult male *B. malayi* in Figures 7 and 9.

Antifilaria Assay with *B. malayi* Microfilaria. Approximately 1000 *B. malayi* microfilaria (microscopic larva) per well were added into a 96-well plate containing 200 μL of fresh RPMI 1640 culture medium supplemented with l-glutamine and pencillin/streptomycin. DMSO solutions of anthraquinones were added to the media to achieve a final concentration of 5 ppm as described for adult assay, and microfilaria mortality and motility were observed for every 24 h for 10 days. The results are shown in Table 3.

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Supporting Information Available: Melting points, HRMS data, HPLC chromatograms, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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