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Isolation, Synthesis, and Structure−Activity Relationships of Bioactive Benzoquinones from *Miconia lepidota* from the Suriname Rainforest[1]

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Bioactivity-directed fractionation of an EtOAc extract from the leaves of *Miconia lepidota* afforded the two benzoquinones 2-methoxy-6-heptyl-1,4-benzoquinone (**1**) and 2-methoxy-6-pentyl-1,4-benzoquinone (primin) (**2**). This is the first reported isolation of **1**. Both quinones **1** and **2** exhibited activity toward mutant yeast strains based on *Saccharomyces cerevisiae*, indicative of their cytotoxicity and potential anticancer activity. A number of previously synthesized and new analogues were prepared and tested in the same strains. Compounds **1**, **2**, 2-methoxy-6-butyl-1,4-benzoquinone (**5**), and 2-methoxy-6-decyl-1,4-benzoquinone (**6**) were tested in two cytotoxicity assays. In the M109 tumor cell lines, quinones **1**, **2**, and **6** had an IC_{50} value of 10 μg/mL. In the A2780 cell line, compounds **1**, **2** and **5** had IC_{50} values of 7.9, 2.9, and 3.2 μg/mL, respectively.

In our continuing efforts to uncover bioactive constituents from Suriname flora as part of an International Cooperative Biodiversity Group (ICBG)[2] program we obtained a sample of the plant *Miconia lepidota* DC. (Melastomataceae). *Miconia* is the largest genus of Melastomataceae with about 1000 species widely distributed in the New World tropics and one species in West Africa. Various species of *Miconia* are common components of forest understory throughout the neotropics, often with many species occurring sympatrically (more than one species of a genus at the same locality). *M. lepidota* is widespread in northern South America, occurring in all of the Guianas, adjacent Brazil, Venezuela, and Colombia. An EtOAc extract of the leaves of this plant exhibited a positive response to our bioassay using mutant yeast strains, which have been shown to respond to known cytotoxic agents,[2] and this extract was thus selected for detailed examination.

Results and Discussion

The EtOAc extract was partitioned between hexane and MeOH−H_2O (80:20), and the aqueous layer was diluted with H_2O to MeOH−H_2O (60:40) and extracted with $CHCl_3$ to afford a bioactive $CHCl_3$ fraction. Repeated chromatography of this fraction on Si gel followed by reversed-phase chromatography on a C-18-bonded phase afforded the two bioactive compounds **1** and **2**.

The ^1H and ^{13}C NMR spectra of both **1** and **2** indicated clearly that they were simple alkylated benzoquinones, and this conclusion was supported by their mass spectra. Thus, the EIMS of **1** showed a molecular ion at *m/z* 236, with major fragment ions at *m/z* 179, 154, 153, 139, and 125, consistent with the formation of the fragments $C_{10}H_{11}O_3$, $C_8H_{10}O_3$, $C_8H_9O_3$, $C_7H_7O_3$, and $C_6H_5O_3$.[3] The EIMS of **2** showed a molecular ion at *m/z* 208 and contained the same fragment ions as **1**. Based on their ^1H and ^{13}C NMR data (Tables 2 and 3) and confirmed by COSY, HETCOR, and HMBC data, compounds **1** and **2** were assigned as the benzoquinones 2-methoxy-6-heptyl-1,4-benzoquinone and 2-methoxy-6-pentyl-1,4-benzoquinone (primin), respectively. These assignments were confirmed by comparison with literature data.[3]

Quinone **1** has previously been synthesized as part of a structure−activity relationship study of primin-type benzoquinones as cell-mediated allergens causing contact dermatitis[3] and has been identified as a minor component of *Primula obconica*,[4] but it has not previously been isolated as a homogeneous compound. Previous phytochemical studies of various *Miconia* spp. have resulted in the isolation of primin (**2**),[5] its quinol analogue miconidin,[5,6] and several triterpenes.[7] Insect antifeedant,[5] antimicrobial,[6,8] and antineoplastic[6,8] activities of primin and miconidin have also been evaluated.

The bioactivity profiles for **1** and **2** in our yeast-based bioassays are depicted in Table 1. Both compounds exhibited moderate activity. However, it was interesting to note that quinone **1**, having two additional carbon atoms in the side-chain, was significantly more active than its lower homologue, primin (**2**), in the Sc-7 yeast strain. Because of this apparent relationship between the length of the alkyl side chain and activity in the Sc-7 yeast assay, we prepared a number of additional 2-methoxy-6-alkyl-1,4-benzoquinones to determine whether the relationship was a general one. The previously reported quinones **1**−**7** were synthe-

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Table 1. Bioactivity Data of Alkyl Benzoquinones

compound	side chain	yeast strains[a] Sc-7	1138	1140	1353	cytotoxicity to M109 (IC_{50}, μg/mL)	A2780 (IC_{50}, μg/mL)
3	CH_3	530 ± 100	580 ± 100	630 ± 180	830 ± 110	NT	NT[b]
4	C_2H_5	220 ± 50	200 ± 30	140 ± 20	233 ± 20	NT	NT
5	C_4H_9	80 ± 25	220 ± 30	150 ± 20	210 ± 28	NT	3.2
2 (primin)	C_5H_{11}	48 ± 1	240 ± 40	170 ± 40	285 ± 40	10	2.9
1	C_7H_{15}	16 ± 10	120 ± 10	130 ± 10	220 ± 10	10	7.9
6	$C_{10}H_{21}$	3 ± 1	380 ± 180	380 ± 180	380 ± 180	10	NT
7	$C_{19}H_{39}$	>2000	>2000	>2000	>2000	NT	NT
8	CH_2Ph	180 ± 20	460 ± 80	420 ± 150	590 ± 80	NT	NT
9	$CH(OH)C_4H_9$	438 ± 121	536 ± 40	430 ± 50	577 ± 40	NT	NT
nystatin	NA[b]	NT[b]	14	13	14	NT	NT

[a] Yeast strain results are expressed as IC_{12} values (μg/mL), which is the concentration required to generate a kill-zone 12 mm in diameter in yeast supported on an agar-based gel. [b] NA = not applicable; NT = not tested.

Table 2. ^{1}H NMR Spectral Data for Compounds **7**−**9**[a,b]

proton	δ **7**	**8**	**9**
H-3	5.86, d, J = 2.5	5.86, d, J = 2.3	5.89, d, J = 2.5
H-5	6.47, dt, J = 2.5, 1.3	6.29, dt, J = 2.3, 1.6	6.69, dt, J = 2.5, 1.2
H_2−1′	2.41, dt, J = 7.9, 1.4	3.74, d, J = 1.4	4.69, m
H_2−2′	1.49, m		1.7, m
H_2−3′,4′			1.38, m
$(CH_2)_n$	1.24, m		
CH_3	0.87, t, J = 6.9		0.89, t, J = 7.3
Ar−H-3′		7.19, br d, J = 6.7	
Ar−H-4′		7.31, br t, J = 7.1	
Ar−H-5′		7.24, tt, J = 7.3, 1.4	
CH_3O	3.81, s	3.80, s	3.81, s

[a] In $CDCl_3$ [b] Coupling constants are reported from direct measurement of peak splittings and will thus vary slightly from their true values.

Table 3. ^{13}C NMR Spectral Data for Compounds **1**−**9**[a]

carbon	δ compound **1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
C-1	182.1	182.2	182.4	182.2	182.3	182.4	182.2	182.0	182.4
C-2	158.8	158.9	159.0	158.9	159.3	158.7	158.8	158.9	158.4
C-3	107.1	107.0	107.4	107.1	107.2	107.0	107.0	107.3	107.0
C-4	187.7	187.8	187.7	187.8	188.1	187.8	187.8	187.6	187.1
C-5	132.8	132.0	133.5	132.2	133.1	132.9	132.9	133.9	131.9
C-6	147.6	147.7	144.1	148.7	148.1	147.4	147.7	146.7	148.1
CH_3O	56.4	56.4	56.4	55.9	56.4	55.8	56.4	56.5	56.4
C-1′	28.7	28.8		21.9	29.8	28.8	28.8	35.0	68.4
C-2′	27.7	27.5			28.5	27.8	27.7	136.4	35.9
C-3′	29.0	31.5			22.4	29.3	29.3	129.5	27.7
C-4′	29.2	22.4				29.6	29.4	128.9	22.2
C-5′	31.7					29.6		127.1	
C-6′	22.6					29.4			
C-7′						29.4			
C-8′						32.0	29.6		
C-9′						22.7			
(CH_2)							29.8[b]		
C-16′							29.4		
C-17′							32.1		
C-18′							22.8		
CH_3	14.1	13.9	15.4	11.5	13.9	14.1	14.1		13.6

[a] In $CDCl_3$. [b] Includes C-5′, C-6′, C-7′, C-9′ to C-15′.

sized by previously reported methods[3] (Figure 1) and were evaluated for bioactivity in the Sc-7 and other yeast strains. Two related benzoquinones, 2-methoxy-6-benzyl-1,4-benzoquinone (**8**) and 2-methoxy-5-(1-hydroxy)pentyl-1,4-benzoquinone (**9**), were also synthesized and tested in these

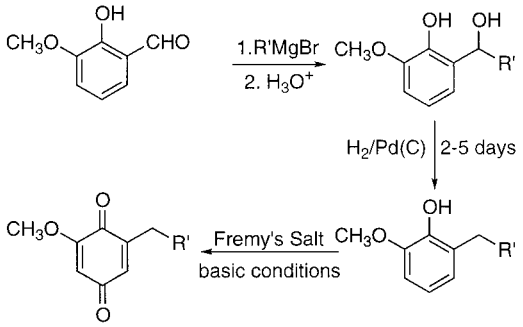


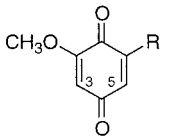
Figure 1. General procedure for the synthesis of substituted 2-methoxy-1,4-benzoquinones **1**, **2**, **4**, and **8**.

strains. Compound **8** was previously reported as a minor product of the oxidation of 2-benzyl phenol with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methanol.[9]

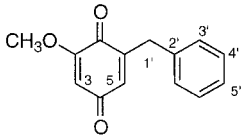
In the Sc-7 yeast assay, increasing the length of the 6-alkyl side chain results in increased potency up to the decyl side chain (**6**), but potency decreases when the significantly longer nonadecyl side chain is introduced (compound **7**). A similar trend has been noted in previous investigations of benzoquinones as cell allergens.[3]

The compounds were also evaluated in the three yeast strains 1138, 1140, and 1353, inasmuch as differential activity in these strains is a predictor of activity against the enzymes topoisomerase I and topoisomerase II.[2c] As it turned out, the benzoquinones evaluated were not particularly selective for any one of these three yeast strains, but they did show a similar increase in potency with increasing length of the alkyl side chain as they did with the Sc-7 assay. In this case, however, the greatest potency was observed with the seven-carbon side chain of compound **1**.

The four most potent compounds in the Sc-7 strain (compounds **1**, **2**, **5**, and **6**) were also subjected to cytotoxicity testing. In the M109 cell line compounds **1**, **2**, and **6** all had IC_{50} values of 10 μg/mL, and in the A2780 cell line compounds **1**, **2**, and **5** had IC_{50} values of 7.9, 2.9, and 3.2 μg/mL, respectively. Although these compounds are thus clearly cytotoxic, their potency is such that they are not being evaluated any further as anticancer compounds.



1 R = C_7H_{15} **5** R = C_3H_7
2 R = C_5H_{11} **6** R = $C_{10}H_{21}$
3 R = CH_3 **7** R = $C_{19}H_{39}$
4 R = C_2H_5 **9** R = $CH(OH)C_4H_9$



8

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler hot stage apparatus equipped with a microscope and are uncorrected. All NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C spectra on a Varian Unity 400 instrument or at 500 MHz for ^{1}H and 125 MHz for ^{13}C spectra on a JEOL Eclipse instrument. MS were obtained on a VG7070E-HF, a VG Quattro, or a Hewlett-Packard HP-5890-5970-GC/MSD instrument. Gel filtration chromatography used Sephadex LH-20 (25−100 μM), and column chromatography employed Si gel 60 (230−400 mesh) for normal-phase chromatography and Varian 5g ODS SPE cartridges and Whatman LRP-2 column packing for reversed-phase chromatography.

Yeast Bioassay. The Sc-7[2a] and 1138/1140/1353[2c] yeast bioassays were performed as previously reported. Samples were prepared and incubated for 48 h for the 1138, 1140, and 1353 strains, or 72 h for the Sc-7 strain. The zones of inhibition were measured, and IC_{12} values and standard deviations were obtained from the results of three individual experiments.

Cytotoxicity Bioassay. In vitro antitumor cytotoxicity assays were performed at Bristol-Myers Squibb using the Madison Lung Carcinoma (M109)[10] murine cell line as previously reported.[11]

Plant Material. The leaves of *M. lepidota* were collected in Suriname by a team from Missouri Botanical Gardens and given the collector's number Evans 1848. The collection was made in the Para district in northern Suriname in low-elevation wet forest along the road from Zanderij to Kraka, 4.4 km from its intersection with Zanderij Highway, 0.5 km before the bridge over Sabakoe Creek, at an elevation of 25 m. Identification of the plant was carried out by Suzanne Renner. Voucher specimens are deposited in the National Herbarium of Suriname, Paramaribo, Suriname, and the Missouri Botanical Garden, St. Louis, MO. Extracts for screening were prepared with EtOAc and MeOH by Bedrijf Geneesiddelen Voorziening, Suriname, and sent for bioassay and isolation work to Virginia Polytechnic Institute and State University; the EtOAc extract was designated E 940138.

Bioactivity-Guided Fractionation and Isolation. The EtOAc extract E 940138 (6.7 g) was found to be bioactive in our Sc-7 yeast assay and was partitioned between hexane and 80% MeOH in H_2O. The hexane fraction (4.57 g) was found to be weakly active and subsequently was found to contain minor quantities of the bioactive compounds isolated from the more active aqueous MeOH fraction and was therefore not further investigated. Water was added to the bioactive 80% MeOH in H_2O fraction to give a 60% MeOH in H_2O solution, which was thoroughly extracted with $CHCl_3$ to yield 1.03 g of the bioactive $CHCl_3$ fraction. The remaining aqueous MeOH fraction was found to be inactive and was not further investigated. The $CHCl_3$ fraction was subjected to column chromatography (CC) on Si gel, eluting with $CHCl_3$, 2% *i*-PrOH in $CHCl_3$, and 50% $CHCl_3$ in MeOH. The bioactive fractions of the 2% *i*-PrOH in $CHCl_3$ eluates were combined (428 mg) and submitted to CC on Si gel using a solvent gradient from 1 to 2.5% of *i*-PrOH in hexane with the bioactive fraction (369 mg) eluting with 1% *i*-PrOH in hexane. The bioactive fraction was then subjected to RP-CC on LRP-2 and eluted with 50−100% MeOH in H_2O to give quinones **1** (158 mg) and **2** (34.2 mg).

2-Methoxy-6-heptyl-1,4-benzoquinone (**1**): yellow crystals; ^{13}C NMR, see Table 3; EIMS *m*/*z* (rel int) 236 (M^+, 55), 193 (15), 179 (39), 166 (18), 153 (100), 139 (17), 125 (40), 108 (19), 95 (8), 81 (8), 69 (45), and 53 (18).[3]

2-Methoxy-6-pentyl-1,4-benzoquinone (primin) (**2**): yellow crystals; ^{13}C NMR, see Table 3; EIMS *m*/*z* (rel int) 208 (M^+, 40), 179 (37), 153 (100), 139 (16), 124 (54), 109 (36), 95 (16), 91 (11), 81 (17), 69 (78), and 53 (20).[3]

General Procedures for the Synthesis of Alkyl and Benzyl Benzoquinones. Selected 2-methoxy-6-alkyl-1,4-benzoquinones were synthesized in a manner similar to that reported by Konig et al.[3] Alkyl and benzyl Grignard reagents were prepared by the slow addition of 0.009 mol of alkyl or benzyl bromide in 8 mL of THF to 0.629 g (0.026 mol) of magnesium turnings in a vented 20-mL vial with vigorous shaking until the addition was complete. *o*-Vanillin (0.5 g, 0.003 mol) in 8 mL of THF was slowly added with vigorous shaking at 0 °C until either the addition was complete or until the yellow color (indicative of unreacted *o*-vanillin) persisted. The vial was allowed to stand at room temperature overnight. The reaction was worked up with 100 mL of 10% HCl in H_2O, extracted with 200 mL of Et_2O, and the Et_2O layer dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude addition product as an oil. This crude product was purified with 25% EtOAc in hexane over Si gel; if necessary further purification was performed using a reversed-phase 5g Varian C18 SPE with a gradient of 70−100% MeOH in H_2O.

The addition product obtained as described above was hydrogenated with an equal weight of 5% Pd/C in 50 mL of MeOH over a period of 2−5 days at atmospheric pressure and room temperature. The reaction was monitored by TLC until it was complete or 5 days had passed. The reaction mixture was filtered over Celite, and the Celite was washed with additional MeOH. The combined MeOH solution was evaporated under reduced pressure to yield a homogeneous product in most cases; if further purification was necessary, it was carried out by preparative TLC on Si gel with 25% EtOAc in hexane.

The deoxy product thus obtained (50−100 mg) was oxidized to the benzoquinone by oxidation with 0.5 g of Fremy's salt in either 100 mL aqueous 5% Na_2CO_3 or 20 mL pH 9 phosphate buffer in 80 mL H_2O with vigorous stirring overnight. The resulting solution was extracted twice with 100 mL of $CHCl_3$ and the $CHCl_3$ layer dried over Na_2SO_4, filtered, and solvent removed under reduced pressure. The crude product was then purified by Si gel preparative TLC with 25% EtOAc in hexane and/or recrystallization with hexane−$CHCl_3$ or hexane−EtOAc. Compound **3** was synthesized by direct reduction of *o*-vanillin with hydrogen over 5% Pd/C, followed by oxidation with Fremy's salt.[3]

2-Methoxy-6-heptyl-1,4-benzoquinone (**1**): yellow solid, mp 64−66 °C (from hexane−$CHCl_3$); lit. 63 °C;[3] overall yield 6%; ^{13}C NMR, see Table 3; *anal.* C 70.92%, H 8.56%, calcd for $C_{14}H_{20}O_3$, C 71.16%, H 8.53%.

2-Methoxy-6-pentyl-1,4-benzoquinone (primin) (**2**): yellow solid, mp 62−64 °C (from hexane−$CHCl_3$); lit. 62−63 °C;[3] overall yield 8%; ^{13}C NMR, see Table 3; *anal.* C 68.99%, H 7.74%, calcd for $C_{12}H_{16}O_3$, C 69.21%, H 7.74%.

2-Methoxy-6-methyl-1,4-benzoquinone (**3**): tan-yellow solid, mp 144−145 °C (from hexane−$CHCl_3$); lit. 150 °C;[3] overall yield 20%; ^{13}C NMR, see Table 3; *anal.* C 60.49%, H 5.36%, calcd for $C_8H_8O_3 \cdot {}^1/_3H_2O$, C 60.76%, H 5.52%.

2-Methoxy-6-ethyl-1,4-benzoquinone (**4**): bright yellow solid, mp 109−111 °C (from hexane−$CHCl_3$); lit. 106 °C;[3] overall yield 24%; ^{13}C NMR, see Table 3; *anal.* C 64.82%, H 6.21%, calcd for $C_9H_{10}O_3$, C 65.05%, H 6.07%.

2-Methoxy-6-butyl-1,4-benzoquinone (**5**): bright yellow solid, mp 52−54 °C (from hexane−$CHCl_3$); lit. 55 °C;[3] overall yield 19%; ^{13}C NMR, see Table 3; *anal.* C 67.74%, H 7.19%, calcd for $C_{11}H_{14}O_3$, C 68.02%, H 7.26%.

2-Methoxy-6-decyl-1,4-benzoquinone (**6**): tan-yellow solid, mp 62−63 °C (from hexane−EtOAc); lit. 60−61 °C;[3] overall yield 17%; ^{13}C NMR, see Table 3; EIMS *m*/*z* 278 (M^+, 48), 193 (13), 179 (27), 166 (17), 154 (98), 153 (100), 139 (14), 124 (19), 109 (10), 69 (43); HREIMS *m*/*z* 278.1884 (calcd for $C_{17}H_{26}O_3$, 278.1881). *anal.* C 71.98%, H 9.33%, calcd for $C_{17}H_{26}O_3 \cdot {}^1/_3H_2O$, C 71.80%, H 9.45%.

2-Methoxy-6-nonadecyl-1,4-benzoquinone (**7**): tan-yellow waxy solid, mp 86−87 °C (from EtOH); lit. 93.5 °C (from EtOH);[12] overall yield 10%; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; EIMS *m*/*z* 404 (M^+, 75), 193 (6), 179 (12), 166 (11), 154 (100), 153 (99), 139 (13), 124 (15), 109 (12), 69 (37), lit. 404 (11), 154 (100), 153 (92);[13] HREIMS *m*/*z* 404.3297 (calcd for $C_{26}H_{44}O_3$, 404.3290).

2-Methoxy-6-benzyl-1,4-benzoquinone (**8**): bright yellow solid, mp 128−130 °C (from hexane−$CHCl_3$); overall yield 7%; ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; EIMS *m*/*z* (rel

int) 228 (M^+, 80), 213 (70), 196 (50), 185 (20), 168 (22), 157 (28), 143 (44), 129 (36), 128 (28), 115 (90), and 69 (100); *anal.* C 73.37%, H 5.32%, calcd for $C_{14}H_{12}O_3$, C 73.67%, H 5.30%.

2-Methoxy-5-(1-hydroxypentyl)-1,4-benzoquinone (9). 2-Methoxy-5-(1-hydroxypentyl)phenol was partially hydrogenated by the same procedure described above, followed by oxidation with Fremy's salt, to give 2-methoxy-5-(1-hydroxypentyl)-1,4-benzoquinone in an overall yield of 21%: yellow-tan solid; mp 94−95 °C (from hexane−$CHCl_3$); ^{1}H NMR, see Table 2; ^{13}C NMR, see Table 3; EIMS *m/z* (rel int) 224 (M^+, 5), 196 (8), 195 (7), 182 (30), 168 (98), 167 (100), 159 (15), 158 (22), 140 (42), 139 (78), 125 (36), 122 (22) and 69 (62); *anal.* C 64.02%, H 7.18%, calcd for $C_{12}H_{16}O_4$, C 64.27%, H 7.19%.

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