Unusual Naphthoquinone Derivatives from the Twigs of *Avicennia marina*

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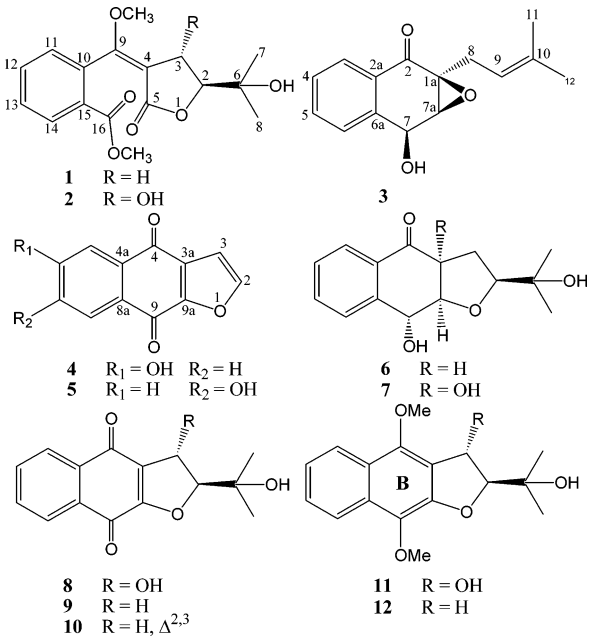
In a continuing search for novel bioactive compounds from marine mangrove plants, seven new naphthoquinone derivatives were isolated from *Avicennia marina*, namely, avicennone A (**1**), avicennone B (**2**), avicennone C (**3**), avicennone D (**4**), avicenone E (**5**), avicennone F (**6**), and avicennone G (**7**), along with the known compounds avicequinone A (**8**), stenocarpoquinone B (**9**), avicequinone C (**10**), avicenol A (**11**), and avicenol C (**12**). The chemical structures of **1**−**7** were elucidated by spectroscopic methods. Compounds **8**−**10**, and a mixture of **4** and **5**, which all contain a 4,9-dione group, showed strong antiproliferative and moderate cytotoxic activities, as well as antibacterial effects.

Avicennia marina (Forsk.) Vierh., belonging to the family Verbenaceae, is an evergreen mangrove tree widely distributed along tropical and subtropical coastlines. Previous studies on other plants of the genus *Avicennia* have shown the presence of naphthoquinone derivatives,[1,2] iridoid glycosides,[3−5] flavonoids,[6] and lignans.[7] In a continuing search for novel bioactive compounds from marine mangrove plants, we have investigated the chemical constituents of the twigs of *A. marina* collected from the coast of Xiamen in the south of mainland China. In this paper, we report the isolation of seven new naphthoquinone derivatives, avicennones A−G (**1**−**7**), as well as the known avicequinone A (**8**),[1,2] stenocarpoquinone B (**9**),[8] avicequinone C (**10**),[1,2] avicenol A (**11**),[1,2,9] and avicenol C (**12**).[1,2] The structures of compounds **1**−**7** were determined on the basis of 1D and 2D NMR spectroscopic analysis as well as from their UV, IR, and mass spectra. The antiproliferative, cytotoxic, and antibacterial activities of several of these compounds are presented.



Results and Discussion

Compound **1** was obtained as a yellow oil, and its molecular formula was assigned as $C_{17}H_{20}O_6$, by HRESIMS at *m*/*z* 343.1152 $[M + Na]^+$ (calcd 343.1157 for $C_{17}H_{20}NaO_6$). The IR spectrum revealed the presence of a hydroxyl group (3406 cm^{-1}), two carbonyl group (1736, 1714 cm^{-1}), and C═C double bond (1663 cm^{-1}) absorptions. The ^1H NMR data (Table 1) indicated four aromatic proton signals (δ_H 8.05, dd, $J = 7.8$, 1.3 Hz; δ_H 7.59, td, $J = 7.5$, 1.6 Hz; δ_H 7.52, td, $J = 7.5$, 1.6 Hz; δ_H 7.24, dd, $J = 7.8$, 1.3 Hz), two methoxyl signals (δ_H 3.47 s, δ_H 3.83, s), and one methine, one methylene, and two methyl signals. The ^{13}C NMR spectrum of **1** showed all 17 signals, as indicated by the molecular formula (Table 1). Next to the ^{13}C NMR signals corresponding with the ^1H NMR data, seven quaternary carbons were found. The close similarity of NMR data indicated compound **1** to be structurally related to avicenol C (**12**).[1] Differences between these two natural products were found for the ^{13}C NMR data of ring B of **1**. The ^{13}C NMR signals of C-4, C-8a, C-9, and C-9a showed significant upfield shifts of $\Delta\delta_C$ −32.3, 8.7, 19.1, and 23.0 ppm, respectively, in **12** as compared to those of **1** (C-9, C-15, C-16, C-5). In addition, C-3a of **12** showed a downfield shift $\Delta\delta_C$ +16.8 ppm as compared with **1** (C-4). As two additional oxygen atoms in **1** were indicated by the HRESIMS data, ring B of **12** was suggested to be cleaved by oxygenation, resulting in two carbonyl groups in **1**. The positions of the carbonyl groups were confirmed through HMBC correlations (Figure 1). A full assignment of all ^1H and ^{13}C NMR data of **1** was obtained from COSY, HMQC, and HMBC experiments. Therefore, the structure of **1** (avicennone A) was proposed as methyl 2-[(*E*)-[5-(1-hydroxy-1-methylethyl)-2-oxodihydrofuran-3(2*H*)-ylidene]-(methoxy)methyl]benzoate.

Compound **2** was obtained as a yellow oil, and its molecular formula was deduced as $C_{17}H_{20}O_7$, from HRESIMS at *m*/*z* 359.1114 $[M + Na]^+$ (calcd 359.1107 for $C_{17}H_{20}NaO_7$). The IR, ^1H NMR, and ^{13}C NMR data of **2** indicated a close resemblance to analogous data for compound **1** (Table 1). The only difference was an oxygenated methine replacing the C-3 methylene. The location of the hydroxy group at C-3 was confirmed by HMBC correlations between H-3 (δ_H 5.13) and C-2 (δ_C 92.5), C-4 (δ_C 107.0), and C-6 (δ_C 71.5). A *trans*-orientation of the 2-isopropanol moiety and the 3-hydroxy substituent was proposed from the coupling constants ($^3J_{2-H,3-H} = 2.0$ Hz) of the AB-type doublets. Accordingly, the structure of **2** (avicenone B) was established as methyl 2-[(*E*)-[4α-hydroxy-5*β*-(1-hydroxy-1-methylethyl)-2-oxodihydrofuran-3(2*H*)-ylidene](methoxy)methyl]benzoate.

Compound **3** was obtained as a colorless oil, and its molecular formula was assigned as $C_{15}H_{16}O_3$ by HRESIMS at *m*/*z* 267.0977 $[M + Na]^+$ (calcd 267.0997 for $C_{15}H_{16}NaO_3$). The IR spectrum

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Table 1. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR Spectroscopic Data (δ in ppm, J value in Hz) of Compounds **1** and **2**

	1[a]			**2**[b]		
position	δ_C		δ_H	δ_C		δ_H
2	82.1	CH	4.25 dd 8.4, 6.4	92.5	CH	4.01 d 2.0
3	27.0	CH_2	3.00 dd 16.5, 8.4 2.88 dd 16.5, 6.4	69.1	CH	5.13 d 2.0
4	101.8	C		107.0	C	
5	170.3	C		172.5	C	
6	71.6	C		71.5	C	
7	23.5	CH_3	1.17 s	24.9	CH_3	1.17 s
8	25.6	CH_3	1.25 s	25.7	CH_3	1.22 s
9	164.6	C		172.3	C	
10	130.1	C		133.78	C	
11	130.3	CH	7.24 dd 7.8, 1.3	131.06	CH	7.33 brd 6.7
12	129.7	CH	7.52 td 7.5, 1.6	133.85	CH	7.69 td 7.5, 1.3
13	132.5	CH	7.59 td 7.5, 1.6	131.10	CH	7.60 td 7.7, 1.4
14	130.4	CH	8.05 dd 7.8, 1.3	131.30	CH	8.06 dd 7.7, 1.3
15	132.8	C		131.10	C	
16	166.1	C		167.7	C	
OMe-9	56.3	CH_3	3.47 s	57.4	CH_3	3.58 s
OMe-16	52.3	CH_3	3.83 s	52.8	CH_3	3.83 s

[a] In $CDCl_3$. [b] In CD_3OD.

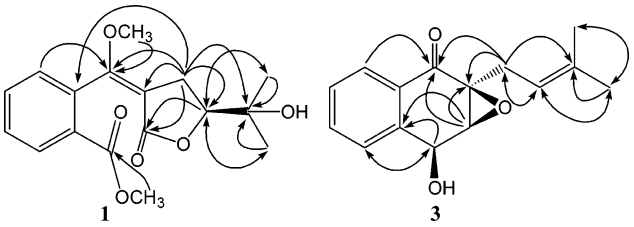

Figure 1. Relevant HMBC correlations of compounds **1** and **3**.

revealed carbonyl (1685 cm^{-1}) and aromatic (1603, 1457 cm^{-1}) functionalities. The ^{1}H NMR spectrum indicated an *ortho*-substituted benzene ring (δ_H 7.93, 7.60, 7.44, 7.42), as well as signals of an isopropenyl group at δ_H 2.92, 2.62 (CH_2), 5.12 (C=CH), 1.67 (Me), and 1.72 (Me). In addition, two vicinal oxygenated methines at δ_H 5.21 and 3.81 were detected. All three moieties were confirmed by COSY correlations. The ^{13}C NMR spectroscopic data showed additional signals for one carbonyl at δ_C 194.2 and one quaternary carbon at δ 60.5. The NMR data indicated **3** to be very similar to 7,7a-dihydro-3,6,7-trihydroxy-1a-(3-methylbut-2-enyl)-naphtho[2,3-*b*]oxiren-2(1a*H*)-one, but lacking the aromatic hydroxyl substituent.[10] Because of a hydrogen bond between the hydroxyl at C-3 and the carbonyl at C-2, and a γ-gauche effect between the hydroxyl at C-6 and H-7, the ^{13}C NMR signal of C-2 was shifted downfield by $\Delta\delta_C$ +6.6 ppm and that of C-7 was shifted upfield by $\Delta\delta_C$ −5.8 ppm in the known compound as compared to **3**. All NMR data of **3** were assigned by COSY, HMQC, and HMBC experiments. The relative stereochemistry of **3** was determined by a NOESY experiment, in which NOE correlations between H-7a and H-7, H-8, H-9, Me-11, and Me-12 and between H-7 and H-6 indicated that the C-1a isopropenyl group and the oxirane proton H-7a and proton H-7 are *cis* configured (Figure 2).

The absolute stereochemistry of **3** was established by analysis of the CD spectrum and molecular modeling using both MM2 and MOPAC protocols. The CD spectrum of **3** showed a positive Cotton effect at 251 nm and a negative Cotton effect at 331 nm. The interpretation of a $\pi \rightarrow \pi^*$ transition at +251 nm by the helicity rule allowed a determination of the conformation of the α,β-unsaturated ketone, and with that, the octant rule could be applied to the negative Cotton effect of the $n \rightarrow \pi^*$ transition at 331 nm (Figure 3).[11,12] Thus, **3** was determined to be (1a*S*,7*S*,7a*S*)-7,7a-dihydro-7-hydroxy-1a-(3-methylbut-2-enyl)naphtho[2,3-*b*]oxiren-2(1a*H*)-one and has been named avicennone C.

Compounds **4** and **5** could be obtained only as a mixture (5:3 according to ^{1}H NMR data) that was chromatographically inseparable. The identical molecular formula of **4** and **5** was established as $C_{12}H_6O_4$ by HRESIMS at *m*/*z* 213.0195 [M − H]$^-$ (calcd

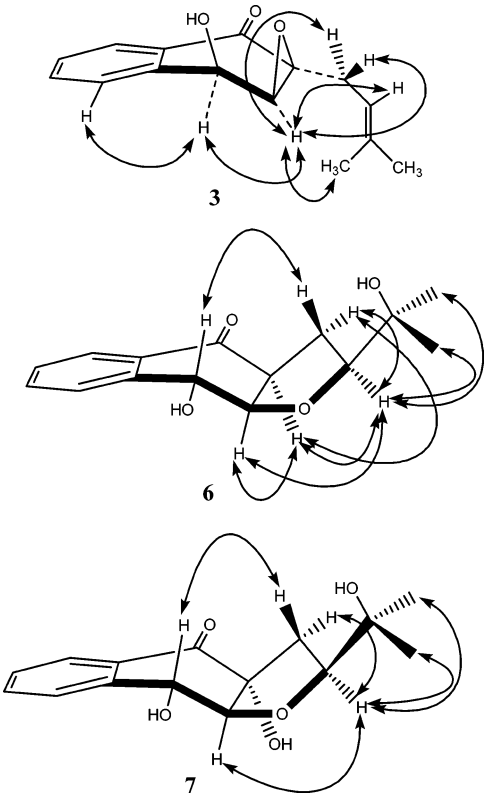

Figure 2. Relevant NOE correlations (NOESY data) of **3**, **6**, and **7**.

213.0193 for $C_{12}H_5O_4$). The IR spectrum indicated the presence of hydroxy groups (3358 broad cm^{-1}) and signals of a naphthoquinone nucleus (1664 and 1594 cm^{-1}). The UV spectrum also suggested a naphthoquinone skeleton by absorption bands at λ_{max} 409, 333, 293, and 254 nm. The set of stronger signals of compound **4** in the ^{1}H NMR spectrum indicated three aromatic protons (δ_H 8.03, 7.47, 7.11) of an AMX system and two AB-type olefinic protons (δ_H 7.94, d, J = 1.9 Hz, δ_H 6.98, d, J = 1.9 Hz) of a furan ring (Table 2). In the ^{13}C NMR spectrum, two sets of signals, each representing 12 carbons, could be distinguished. The NMR data of the mixture of compounds **4** and **5** indicated them to be analogues of avicequinone B, carrying a hydroxy substituent on the aromatic ring.[1,13] HMBC correlations revealed this substitution to be located at C-6 in **4** and at C-7 in **5**. Thus, **4** was determined to be 6-hydroxynaphtho[2,3-*b*]furan-4,9-dione and **5** as 7-hydroxynaphtho[2,3-*b*]furan-4,9-dione, and these compounds have been named

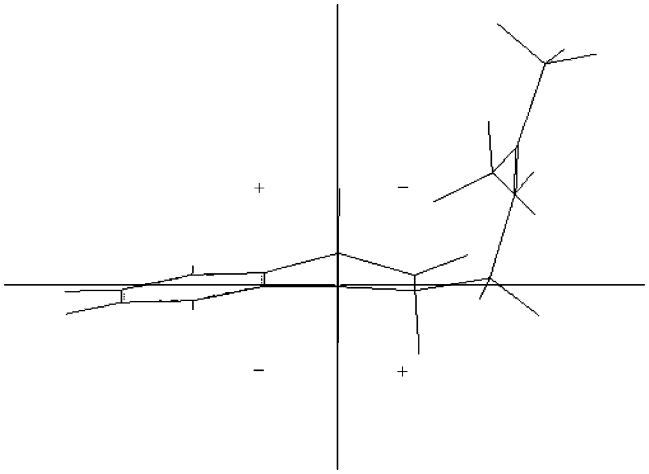

Figure 3. Stereostructure of compound **3** as deduced by molecular modeling and CD data.

avicennone D and avicennone E, respectively. We assume compounds **4** and **5** are new natural products. While they are listed in the *Dictionary of Natural Products*, they could not be found in the cited references.[13−16] The related methoxy derivatives of **4** and **5** were also referred to in the literature as being inseparable.[13]

Compound **6** was isolated as a colorless oil, and its molecular formula, $C_{15}H_{18}O_4$,was deduced from the HRESIMS at *m*/*z* 285.1115 $[M + Na]^+$ (calcd 285.1103 for $C_{15}H_{18}NaO_4$). The IR spectrum revealed hydroxy (3400 cm^{-1}), carbonyl (1683 cm^{-1}), and aromatic (1600, 1457 cm^{-1}) functionalities and the UV spectral characteristic absorptions of a dihydronaphthoquinone nucleus (λ_{max} at 249 and 285 nm).[17] The ^1H NMR spectrum exhibited four aromatic protons (δ_H 7.90, 7.61, 7.61, 7.42), one methylene (δ_H 2.05, 2.40), four methines (δ_H 4.92, 4.41, 3.92, 3.38), and two methyls (δ_H 1.06, 1.23) (Table 2). Thus, **6** was suggested to have the same planar structure as the known (2*R**,3a*R**,9*R**,9a*R**)-9-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3,3a,4,9,9a-hexahydronaphtho[2,3-*b*]furan-4-one.[18] However, the relative stereochemistry of these two structures varied, as evidenced by significant differences in their ^{13}C NMR chemical shift data, especially for C-2, C-9, C-9a, C-10, CH_3-11, and CH_3-12 (e.g., $\Delta\delta_C$ +12 ppm for C-2 and −5.5 ppm for C-10). NOE correlations were found between H-9 and H-3β, between H-9a and H-3a and H-2, and between H-2 and H-3a, H-3α, H-9a, CH_3-11, and CH_3-12. Thus, together with the vicinal couplings of $J_{H-3a,H-9a} = 7.5$ Hz (11.6 Hz in ref 10) and $J_{H-9,H-9a} = 6.5$ Hz (9.0 Hz in ref 10), H-2, H-3a, and H-9a were suggested to be located in an α-orientation and H-9 to be located in a β-orientation in **6** vs H-2, H-3a, and H-9 in a β-orientation and H-9a in an α-orientation in the known stereoisomer (Figure 2). Thus, **6** was established as (2*S**,3a*S**,9*R**,9a*R**)-9-hydroxy-2-(1-hydroxy-1-methylethyl)-2,3,3a,4,9,9a-hexahydronaphtho[2,3-*b*]-furan-4-one and was named avicennone F.

Compound **7** was isolated as a colorless oil, and its molecular formula $C_{15}H_{18}O_5$ was determined by HRESIMS at *m*/*z* 301.1059 $[M + Na]^+$ (calcd 301.1052 for $C_{15}H_{18}NaO_5$). Once again, the IR and UV spectra suggested a dihydronaphthoquinone skeleton. The ^1H NMR spectrum indicated four aromatic protons (δ_H 7.85, 7.67, 7.63, and 7.47), one methylene (δ_H 1.89, 1.99), three methines (δ_H 4.77, 4.18, 4.13), and two methyls at δ_H 1.03, 1.15 (Table 2). Like the ^1H NMR spectrum, the ^{13}C NMR spectrum was very similar to that of compound **6**. However, the H-3a methine signal was replaced by a resonance for an additional oxygenated quaternary carbon. By MS and HMBC NMR analysis, an additional hydroxy group could be located at C-3a in **7**. The relative stereochemistry of **7** was determined by NOE correlations and coupling constants. NOE correlations between H-9 and H-3β and between H-2 and H-3α, H-9a, CH_3-11, and CH_3-12, combined with the vicinal proton coupling constant of $J_{9,9a} = 5.6$ Hz, suggested that H-2, OH-3a, and H-9a are located in an α-orientation and H-9 is located in a β-orientation (Figure 2). Thus, the chemical structure of **7** (avicennone G) was established as (2*S**,3a*R**,9*R**,9a*R**)-3a,9-dihydroxy-2-(1-hydroxy-1-methylethyl)-2,3,3a,4,9,9a-hexahydronaphtho-[2,3-*b*]furan-4-one.

In the course of biological activity testing, compounds **1**, **9**−**12**, and a mixture of compounds **4** and **5** were tested for antiproliferative activities against L-929 (mouse fibroblasts) and K562 (human chronic myeloid leukemia) and for cytotoxic activities against the HeLa (human cervix carcinoma) cell line (Table 3). Due to limited availability, compounds **2**, **3**, **6**, and **7** were not subjected to bioassay. Compounds **9**, **10**, and **4**/**5** showed strong antiproliferative activities while being less cytotoxic, whereas **1**, **11**, and **12** were only weakly active. Interestingly, all of the active compounds contain the *p*-dione of the naphthoquinone core as a structural element. The importance of the α,β-unsaturated quinone system for cytotoxicity within this class of compounds was also demonstrated in an earlier study with related compounds from *Ekmanianthe longiflora* against nine human cancer cell lines and one murine cell line.[18] In a previous study that focused on chemopreventive activities, the naphthoquinones **8**−**10**, together with **11** and **12**, were found in an assay using Raji cells to be only weakly cytotoxic.[2] The microbroth dilution method was used to screen compounds **1**, **8**−**12**, and **4**/**5** for antimicrobial activity against several bacteria and a yeast (Table 4). Again, all compounds containing the 4,9-dione group showed significant activity, whereas the others were inactive. This is the first report on antimicrobial activities within this class of compounds.

Experimental Section

General Experimental Procedures. Optical rotation was recorded on a Propol digital automatic polarimeter (Dr. Wolfgang Kernchen GmBh, Seelze, Germany); UV spectra, on Varian UV−visible Cary spectrophotometer (Varian, Palo Alto, CA); CD spectra, on a J-810-150s spectropolarimeter (JASCO, Groβ Umstadt, Germany); and IR spectra, on an IFS55 spectrometer (Bruker, Karlsruhe, Germany). ^1H, ^{13}C, and 2D NMR spectra were obtained on DPX-300 and DPX-500 (Bruker) instruments as indicated; ESIMS data were obtained on a triple quadrupole mass spectrometer (Quattro; VG Biotech, Cheshire, UK). Column chromatography was performed on silica gel 60M (230−400 mesh, Macherey-Nagel, Düren, Germany) and Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden). TLC analysis was performed on silica gel plates (Sil G/UV_{254}, 0.20 mm, Macherey-Nagel), with spots being detected by UV radiation and staining with anisaldehyde/H_2SO_4 (1%/5% in methanol).

Plant Material. The twigs of *A. marina* were collected in Xiamen, People's Republic of China, in June 2002 and were authenticated by Prof. Peng Lin, Xiamen University, Xiamen, People's Republic of China. A voucher specimen of the plant is deposited in the State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing, People's Republic of China (MXM005). The twigs were air-dried and milled.

Extraction and Isolation. The pulverized plant material (2.5 kg) was percolated in methanol (10 L) at room temperature for two weeks. The methanol extracts were concentrated and yielded 112.0 g of a crude extract. This crude extract was partitioned in H_2O−EtOAc to yield 9.4 g of a dried EtOAc extract and an aqueous residue. The EtOAc extract was subjected to silica gel column chromatography (6 × 50 cm; gradient mixtures, $CHCl_3$−MeOH from 50:1 to 1:1). The eluents were pooled to form 23 major fractions on the basis of TLC analysis. Fraction 6 (3.51 g) was subjected to silica gel column chromatography (3 × 50 cm; gradient mixtures, $CHCl_3$−MeOH from 100:1 to 1:1) to give fractions A−G. Fraction B (320 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, $CHCl_3$) and further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 6:1) to yield **3** (6.5 mg). Fraction F (161 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, MeOH), then further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 3:1) to give **9** (31.0 mg). Fraction 7 (508 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, MeOH), to afford fractions A−E.

Table 2. ^{1}H NMR (300 MHz, δ in ppm) and ^{13}C NMR (75 MHz, δ in ppm) Spectroscopic Data of Compounds **4**−**7**

	4[b]		**5**[b]		**6**[a]		**7**[b]	
no.	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	150.3 CH	7.94 d 1.9	150.8 CH	7.97 d 1.9	86.1 CH	3.92 dd 9.5, 6.4	86.8 CH	4.13 dd 10.6, 5.4
3	109.2 CH	6.98 d 1.9	109.4 CH	6.98 d 1.9	30.2 CH_2	β 2.05 m α 2.40 m	40.2 CH_2	β 1.89 dd 13.0, 10.6 α 1.99 dd 13.0, 5.4
3a	131.3 C		132.1 C		48.3 CH	3.38 m	83.4 C	
4	182.2 C		181.2 C		197.4 C		200.3 C	
4a	137.2 C		126.7 C		131.4 C		132.5 C	
5	114.4 CH	7.47 d 2.6	130.7 CH	8.01 d 8.4	127.4 CH	7.90 brd 7.6	128.2 CH	7.85 d 7.5
6	164.8 C		121.1 CH	7.09 dd 8.4, 2.5	128.7 CH	7.42 m	129.6 CH	7.47 td 7.8, 2.0
7	121.2 CH	7.11 dd 8.5, 2.6	164.8 C		134.3 CH	7.61 m	135.4 CH	7.67 td 7.8, 2.0
8	130.5 CH	8.03 d 8.5	114.2 CH	7.49 d 2.5	127.0 CH	7.61 m	128.7 CH	7.63 brd 7.8
8a	135.8 C		136.3 C		143.0 C		144.2 C	
9	174.5 C		174.8 C		68.1 CH	4.92 d 6.5	71.1 CH	4.77 d 5.6
9a	154.5 C		154.1 C		81.3 CH	4.41 dd 6.5, 7.5	90.6 CH	4.18 d 5.6
10					70.7 C		71.3 C	
11					24.1 CH_3	1.06 s	25.6 CH_3	1.03 s
12					24.3 CH_3	1.23 s	26.6 CH_3	1.15 s

[a] In $CDCl_3$. [b] In CD_3OD.

Table 3. Antiproliferative (GI_{50}) and Cytotoxic (CC_{50}) Activities of Compounds **1** and **9**−**12** and a Mixture of **4** and **5**

compound	L-929 (GI_{50})[a]	K562 (GI_{50})[a]	HeLa (CC_{50})[a]
1	>10	>10	>10
9	1.2	0.2	4.3
10	0.8	1.1	3.2
11	>10	>10	>10
12	>10	>10	>10
4/5	4.4	7.5	13.1
paclitaxel	0.1	0.01	0.01

[a] In μg/mL.

Table 4. Antimicrobial Activities of Compounds **8**−**10** and a Mixture of **4** and **5**

	MIC (μg/mL)[a,b]				
organism	**8**	**9**	**10**	**4/5**	control
Candida albicans BMSY 212	12.5	12.5	12.5	12.5	<0.05[d]
Mycobacterium smegmatis SG 987	12.5	12.5	6.25	6.25	0.4[c]
Mycobacterium aurum SB 66	12.5	12.5	6.25	6.25	<0.05[c]
Mycobacterium vaccae IMET 10670	12.5	6.25	6.25	6.25	0.2[c]
Mycobacterium fortuitum B	12.5	25.0	12.5	12.5	0.2[c]
Staphylococcus aureus 134/93 MRSA	6.25	12.5	6.25	12.5	12.5[c]
*Enterococcus faecalis*1528 VRE	50.0	25.0	50.0	50.0	0.8[c]

[a] The data for the minimal inhibitory concentration (MIC) represent the mean of three independent experiments. [b] MIC determined by a microbroth dilution method according to the National Committee for Clinical Laboratory Standards. [c] Ciprofloxacin. [d] Amphotericin B.

Fraction B (85 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, $CHCl_3$) to provide **10** (28.5 mg) and **12** (25.4 mg). Fraction E (76 mg) was further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 6:1) to give **4** and **5** (9.0 mg). Fraction 9 (629 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, MeOH) and further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 5: 4) to yield **1** (24.4 mg). Fraction 11 (873 mg) was subjected to silica gel column chromatography (3 × 30 cm; petroleum ether−EtOAc, 2:1−1:1−1:2) to give fractions A−C. Fraction C (80.4 mg) was further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 3:2) to give **8** (4.6 mg) and **11** (43.5 mg). Fraction 12 (279 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, MeOH) and further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 1:1) to yield **6** (3.8 mg). Fraction 13 (377 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, MeOH) and further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 2:3) to yield **2** (12.7 mg). Fraction 15 (288 mg) was subjected to Sephadex LH-20 column chromatography (3.5 × 120 cm, MeOH) to give fractions A−E. Fraction B (81.0 mg) was further purified by silica gel column chromatography (1.5 × 30 cm; petroleum ether−EtOAc, 1:2) to give **7** (4.5 mg).

Avicennone A (1): yellow oil; $[\alpha]_D^{20}$ +17.8 (*c* 1.60, MeOH); UV (MeOH) λ_{max} (log ϵ) 251 (4.08), 234 (4.12), 212 (4.09) nm, (MeOH + HCl) λ_{max} (log ϵ) 251 (4.08), 233 (4.13), 212 (4.12) nm, (MeOH + NaOH) λ_{max} (log ϵ) 252 (3.99), 236 (4.08), 213 (3.84) nm; IR (film) ν_{max} 3406, 2951, 2359, 1736, 1714, 1663, 1596, 1439, 1266, 1194, 1159, 1084, 1045, 1021, 968, 803, 772, 759, 714 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS *m/z* 343.2 $[M + Na]^+$, 662.9 $[2M + Na]^+$, 321.4 $[M + H]^+$, 319.3 $[M - H]^-$; HRESIMS *m/z* 343.1152 $[M + Na]^+$ (calcd for $C_{17}H_{20}NaO_6$, 343.1157).

Avicennone B (2): yellow oil; $[\alpha]_D^{20}$ −4.0 (*c* 0.80, MeOH); UV (MeOH) λ_{max} (log ϵ) 288 (4.47), 252 (4.14), 210 (4.24) nm, (MeOH + HCl) λ_{max} (log ϵ) 253 (3.77), 227 (3.85), 212 (3.94) nm, (MeOH + NaOH) λ_{max} (log ϵ) 253 (3.79), 236 (3.84), 213 (3.62) nm; IR (film) ν_{max} 3389, 2950, 2360, 2341, 1728, 1646, 1455, 1296, 1194, 1074, 767 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS *m/z* 337.4 $[M + H]^+$, 359.2 $[M + Na]^+$, 694.9 $[2M + Na]^+$, 690.2 $[2M + NH_4]^+$, 710.7 $[2M + K]^+$, 335.3 $[M - H]^-$; HRESIMS *m/z* 359.1114 $[M + Na]^+$ (calcd for $C_{17}H_{20}NaO_7$, 359.1107).

Avicennone C (3): colorless oil; $[\alpha]_D^{20}$ −157.5 (*c* 0.56, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 285 (3.16), 251 (3.99), 203 (4.45) nm, (MeOH + HCl) λ_{max} (log ϵ) 288 (3.03), 251 (3.94), 203 (4.42) nm, (MeOH + NaOH) λ_{max} (log ϵ) 287 (3.44), 250 (4.02), 206 (3.77) nm; CD (*c* 4.62 × 10^{-5} mol/L, MeOH) θ_{251} 22812, θ_{331} −23634; IR (film) ν_{max} 2919, 2360, 2341, 1685, 1603, 1457, 1292, 1194, 1035, 791, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, dd, *J* = 7.8, 1.3 Hz, H-3), 7.60 (1H, td, *J* = 7.4, 1.4 Hz, H-4), 7.44 (1H, td, *J* = 7.8, 1.3 Hz, H-5), 7.42 (1H, dd, *J* = 7.7, 1.3 Hz, H-6), 5.21 (1H, d, *J* = 2.1 Hz, H-7), 5.12 (1H, m, H-9), 3.81 (1H, d, *J* = 2.1 Hz, H-7a), 2.92 (1H, dd, *J* = 15.4, 7.9 Hz, H-8), 2.62 (1H, dd, *J* = 15.4, 6.8 Hz, H-8), 1.67 (3H, s, Me-11), 1.72 (3H, s, Me-12); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2 (C-2), 139.5 (C-6a), 136.2 (C-10), 134.2 (C-5), 129.7[a] (C-2a), 129.7[a] (C-6), 129.5 (C-4), 127.7 (C-3), 116.6 (C-9), 67.0 (C-7), 60.5 (C-1a), 59.9 (C-7a), 26.7 (C-8), 25.8 (Me-12), 18.1 (Me-11) ([a]signal overlap detected by HMBC correlations); ESIMS *m/z* 245.1 $[M + H]^+$, 267.1 $[M + Na]^+$, 265.1 $[(M + Na) - H]^-$; HRESIMS *m/z* 267.0997 $[M + Na]^+$ (calcd for $C_{15}H_{16}NaO_3$, 267.0977).

Avicennone D (4): yellow, amorphous powder; UV (MeOH) λ_{max} (log ϵ) 409 (3.14), 333 (4.48), 293 (3.90), 254 (3.82) nm, (MeOH + HCl) λ_{max} (log ϵ) 410 (2.85), 339 (3.15), 301 (3.45), 264 (3.96) nm, (MeOH + NaOH) λ_{max} (log ϵ) 515 (3.17), 355 (3.02), 298 (3.90), 227 (3.96) nm; IR (film) ν_{max} 3358, 1664, 1594, 1561, 1474, 1454, 1427, 1355, 1278, 1242, 1201, 1159, 1081, 990, 923, 880, 848, 807, 769, 742 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 2; ESIMS *m/z* 215.0 $[M + H]^+$, 237.1 $[M + Na]^+$, 450.8 $[2M + Na]^+$, 232.2 $[M + NH_4]^+$, 213.1 $[M - H]^-$, 427.2 $[2M - H]^-$; HRESIMS *m/z* 213.0195 $[M - H]^-$ (calcd for $C_{12}H_5O_4$, 213.0193).

Avicennone E (5): ^{1}H and ^{13}C NMR, see Table 2; other spectroscopic data were identical with **4**.

Avicennone F (6): colorless oil; $[\alpha]_D^{20}$ +20.5 (*c* 0.40, MeOH); UV (MeOH) λ_{max} (log ϵ) 248 (3.69), 206 (4.05) nm, (MeOH + HCl) λ_{max} (log ϵ) 285 (3.06), 249 (3.74), 203 (4.17) nm, (MeOH + NaOH) λ_{max} (log ϵ) 249 (3.74) nm; IR (film) ν_{max} 3400, 2923, 2360, 2341, 1683, 1600, 1457, 1375, 1299, 1158, 1045, 791 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; ESIMS *m*/*z* 285.3 $[M + Na]^+$, 547.5 $[2M + Na]^+$, 280.3 $[M + NH_4]^+$, 261.2 $[M - H]^-$; HRESIMS *m*/*z* 285.1115 $[M + Na]^+$ (calcd for $C_{15}H_{18}NaO_4$, 285.1103).

Avicennone G (7): colorless oil; $[\alpha]_D^{20}$ +21.8 (*c* 0.45, MeOH); UV (MeOH) λ_{max} (log ϵ) 285 (3.09), 249 (3.85), 204 (4.25) nm, (MeOH + HCl) λ_{max} (log ϵ) 289 (3.00), 248 (3.84), 203 (4.26) nm, (MeOH + NaOH) λ_{max} (log ϵ) 290 (3.28), 248 (3.88), 213 (3.95) nm; IR (film) ν_{max} 3364, 2927, 2360, 2341, 1684, 1601, 1457, 1374, 1304, 1258, 1232, 1127, 1085, 1044, 902, 745 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; ESIMS *m*/*z* 279.2 $[M + H]^+$, 301.3 $[M + Na]^+$, 579.1 $[2M + Na]^+$, 296.2 $[M + NH_4]^+$, 277.5 $[M - H]^-$; HRESIMS *m*/*z* 301.1059 $[M + Na]^+$ (calcd for $C_{15}H_{18}NaO_5$, 301.1052).

Biological Testing. Pure compounds **1** and **9**−**12** and a mixture of **4** and **5** were assayed against L-929 mouse fibroblasts (DSM ACC 2) and K562 human chronic myeloid leukemia cells (DSM ACC 10) for their antiproliferative effects (GI_{50}) and against HeLa human cervix carcinoma cells (DSM ACC 57) for their cytotoxic (CC_{50}) effects as previously described.[19] Inhibitory concentrations are provided as 50% inhibition of cell growth (GI_{50}; the concentration needed to reduce the growth of treated cells to half that of untreated cells) or 50% cytotoxic concentration (CC_{50}; the concentration that kills 50% of treated cells). Compounds **1** and **8**−**12** and a mixture of **4** and **5** were tested for their antimicrobial effects against a series of microorganisms by a microbroth dilution method, according to the National Committee for Clinical Laboratory Standards guidelines.[20,21]

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Supporting Information Available: Physico-chemical characterization data (UV, IR, 1D and 2D NMR, and MS) of compounds **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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