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5-Deoxyflavones with Cytotoxic Activity from *Mimosa diplotricha*

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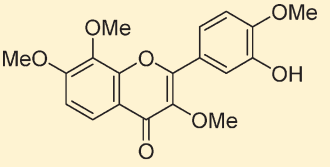
Supporting Information

ABSTRACT: Bioassay-guided isolation of *Mimosa diplotricha* led to the isolation of four new 5-deoxyflavones, diplotrins A−C (**1**−**3**) and diplotasin (**4**), together with 12 known flavonoids, flavonolignans, and triterpenoids. On the basis of spectroscopic evidence, compounds **1**−**4** were characterized as 2′,5′-dihydroxy-3,7,8,4′-tetramethoxyflavone (**1**), 3′-hydroxy-3,7,8,4′-tetramethoxyflavone (**2**), 2′-hydroxy-7,4′,5′-trimethoxyflavone (**3**), and 4-hydroxy-3,10,11-trimethoxyisochromeno[4,3-*b*]-chromen-7(5*H*)-one (**4**). The cytotoxic effects of these isolated compounds were evaluated against the A549, AGS, HT-29, and PC3 human cancer cell lines. Compounds **2** and 5″-methoxyhydnocarpin-D (**5**) showed the most potent antiproliferative activity.



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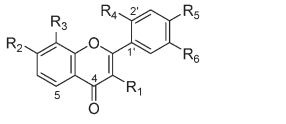
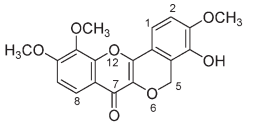
Mimosa diplotricha C. Wright [syn.: *Mimosa invisa* Mart. ex Colla (Leguminosae)], a subshrub with multibranched vines, is native to tropical America. This species has been introduced as a fertilizing plant by agricultural authorities in Taiwan and is naturalized in uncultivated land in central and southern regions.[1] The roots or the whole plant of *M. diplotricha* have been used as an analgesic, anticancer remedy, antidote, hemostatic agent, and tranquilizer in Formosan folk medicine.[2] A variety of chemical components, including alkaloids,[3,4] flavonoids,[5,6] 2-phenoxychromones,[6] diterpenoids,[7] and triterpenoids,[8] have been identified in *Mimosa* species, but these have received little biological study previously. The chemical constituents of *M. diplotricha* and their biological activities have not been reported. A preliminary biological screen revealed that an EtOH extract of *M. diplotricha* exhibited cytotoxic activity against various human tumor cell lines, prompting a more detailed investigation. Described herein are the isolation of four new 5-deoxyflavones (**1**−**4**) from *M. diplotricha* and their evaluation against four human cancer cell lines.



1 $R_1 = R_2 = R_3 = R_5 = OMe$, $R_4 = R_6 = OH$
2 $R_1 = R_2 = R_3 = R_5 = OMe$, $R_6 = OH$, $R_4 = H$
3 $R_2 = R_5 = R_6 = OMe$, $R_4 = OH$, $R_1 = R_3 = H$



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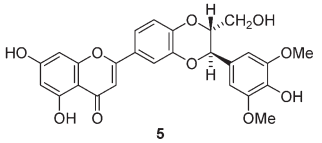

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The $CHCl_3$ and *n*-BuOH extracts of *M. diplotricha* were subjected individually to a combination of silica gel, Sephadex LH-20, and C_{18} chromatography, yielding 16 compounds. Of these compounds, 12 were known previously and were identified from their ^1H and ^{13}C NMR and MS data as 5″-methoxyhydnocarpin-D (**5**),[9] 7,3′,4′-trihydroxy-3,8-dimethoxyflavone,[10] 2′-hydroxy-3,7,8,4′,5′-pentamethoxyflavone,[11] hernancorizin,[12] 5,3′-di-*O*-methylluteolin,[13] betulinic acid, luteolin, quercetin, quercetin-3-*O*-xylopyranoside,[14] quercetin-3-*O*-arabinofuranoside,[14] myricetin-3-*O*-xylopyranoside,[14] and myricetin-3-*O*-arabinofuranoside.[14]

Diplotrin A (**1**) was obtained as yellow needles from MeOH. The molecular formula of **1** was consistent with $C_{19}H_{18}O_8$ from the HRESIMS at m/z 375.1066 $[M + H]^+$ and in agreement with the carbon and proton numbers as deduced from the ^{13}C and ^1H NMR spectra. The ^1H NMR spectrum of **1** exhibited a pair of aromatic doublets at δ 7.95 and 7.02 (each 1H, d, J = 9.0 Hz), characteristic of H-5 and H-6 in 5-dehydroxyflavone.[15] Two other aromatic proton singlets at δ 6.59 (H-3′) and 7.32 (H-6′) and four aromatic methoxy signals at δ 3.84, 3.91, 3.95, and 3.97 were also observed. The addition of the shift reagents, $AlCl_3$ and NaOAc, had no effect on the UV spectra, indicating no free hydroxy group at C-3 or C-5,[15] or at C-7 or C-4′, respectively. Examination of the ^{13}C NMR spectrum of **1** (Table 1) showed in addition 14 signals for aromatic carbons including eight oxygenated carbons, the presence of four methoxy groups in the range δ 56.0−61.8, and a carbonyl group at δ 173.4. These data suggested that **1** is a flavone with a 3,7,8,2′,4′,5′-hexahydroxy substitution pattern. From HMBC (Figure 1) and NOESY experiments, the locations of the methoxy substitutions were inferred to be at C-3, C-7, C-8, and C-4′. A HMBC experiment showed correlations from $-OCH_3$ (δ 3.95) and H-6 to C-8, from $-OCH_3$ (δ 3.97) and H-5 to C-7, and from $-OCH_3$ (δ 3.91), H-3′, and H-5′ to C-4′, suggesting the placement of methoxy groups at C-7, C-8, and C-4′. The fourth methoxy group was located at C-3 on the basis of the low-field shift of C-3 (δ_C 138.2) observed and a relevant HMBC correlation (δ_H 3.91/δ_C 138.2). The NOESY experiment performed on **1**

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds 1−3

	1[a]		2[b]		3[b]	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	150.2		157.6		163.6	
3	138.2		141.4		110.6	7.33 s
4	173.4		176.7		180.7	
5	121.0	7.95 (d, 9.0)	121.7	7.88 (d, 9.0)	127.3	8.01 (d, 9.0)
6	110.1	7.02 (d, 9.0)	111.9	7.23 (d, 9.0)	115.9	7.04 (dd, 9.0, 2.4)
7	156.6		158.3		166.2	
8	136.8		138.1		101.5	7.22 (d, 2.4)
9	150.0		150.9		159.7	
10	118.6		119.6		118.0	
1′	110.2		124.6		110.0	
2′	155.4		116.2	7.70 (d, 1.8)	154.6	
3′	102.2	6.59 s	147.7		102.0	6.58 s
4′	150.9		151.8		154.9	
5′	139.8		112.4	7.09 (d, 8.4)	144.1	
6′	113.5	7.32 s	122.3	7.75 (dd, 8.4, 1.8)	113.0	7.52 s
OCH_3-3	61.8	3.84 s	60.4	3.80 s		
OCH_3-7	56.5	3.97 s	57.1	4.00 s	56.6	3.96 s
OCH_3-8	61.6	3.95 s	62.0	3.98 s		
OCH_3-4′	56.0	3.91 s	56.4	3.95 s	57.6	3.87 s
OCH_3-5′					56.4	3.88 s

[a] Measured in $CDCl_3$. [b] Measured in MeOH-d_4.

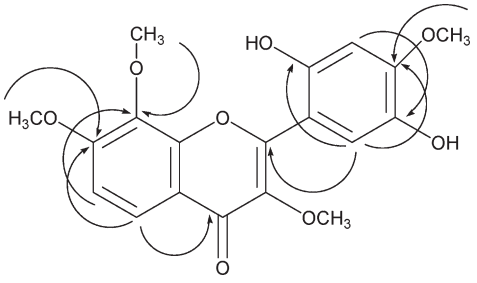

Figure 1. Key HMBC corrections of compound **1**.

showed interactions between the OCH_3-7 and H-6 signals and between those of OCH_3-4′ and H-3′, further supporting the above deductions. Therefore, compound **1** (diplotrin A) was deduced as 2′,5′-dihydroxy-3,7,8,4′-tetramethoxyflavone.

Diplotrin B (**2**) was obtained as a light yellow, amorphous powder. The ^{1}H and ^{13}C NMR spectra of **2** resembled those of **1** except for the presence of ABX-type aromatic signals [(δ 7.70 (d, J = 1.8 Hz, H-2′), 7.09 (d, J = 8.4 Hz, H-5′), 7.75 (dd, J = 8.4, 1.8 Hz, H-6′)] instead of having two singlet aromatic signals on the B-ring. The HRESIMS of **2** revealed a protonated molecular ion at m/z 359.1120 $[M + H]^+$, consistent with the molecular formula $C_{19}H_{18}O_7$ and in agreement with the presence of one less hydroxy group in ring B than in compound **1**. A NOESY experiment on **2** showed an interaction between the OCH_3-4′ and H-5′ resonances. Accordingly, compound **2** (diplotrin B) was deduced as 3′-hydroxy-3,7,8,4′-tetramethoxyflavone.

Diplotrin C (**3**) was obtained as a light yellow, amorphous powder. The ESIMS exhibited a $[M + H]^+$ ion at m/z 329 and, together with the ^{13}C NMR data, suggested a molecular formula of $C_{18}H_{16}O_6$. The ^{13}C NMR spectrum of **3** (Table 1) showed 14 signals for the aromatic carbons of a flavone, including six oxygenated carbons, together with resonances for three methoxy groups and a carbonyl group. The ^{1}H NMR spectrum exhibited an aromatic ABC-type pattern [δ 8.01 (d, J = 9.0 Hz, H-5), 7.04 (dd, J = 9.0, 2.4 Hz, H-6), and 7.22 (d, J = 2.4 Hz, H-8)], a characteristic low-field H-5 signal, and a HMBC correlation between H-5 and δ_C 180.7, indicating the molecule of **3** to be a 5-dehydroxyflavone substituted at C-7. Two singlets, at δ 6.58 and δ 7.52, were assignable to the two *para*-position aromatic protons, H-3′ and H-6′, suggesting a 1,2,4,5-substituted B-ring system. The other aromatic singlet at δ 7.33 was placed at C-3. The positions of three methoxy groups and one hydroxy group were established by HMBC and NOESY experiments. A HMBC experiment showed correlations of δ 3.96 (OCH_3-7), H-5/δ 166.2 (C-7), δ 3.87 ($-OCH_3$), H-3′, H-6′/δ 154.9, δ 3.88 ($-OCH_3$), H-3′, H-6′/δ 144.1, and H-3′, H-6′/δ 154.6, indicating the placements of a methoxy group at C7 and two methoxy groups and one hydroxy group on the B -ring. Key NOESY correlations of δ 6.58 (H-3′)/δ 3.87 and δ 7.52 (H-6′)/δ 3.88 were observed, but not for δ 7.33 (H-3), implying the presence of OCH_3-4′, OCH_3-5′, and OH-2′ groups. On the basis of the above data, compound **3** was deduced as 2′-hydroxy-7,4′,5′-trimethoxyflavone.

The HRESIMS of **4** showed a pseudomolecular ion at m/z 357.0956 $[M + H]^+$, in agreement with a molecular formula of $C_{19}H_{16}O_7$, and indicating 12 degrees of unsaturation. The ^{1}H NMR spectrum exhibited two pairs of aromatic doublets at δ 8.00/7.00 (J = 9.0 Hz, H-8/9) and δ 7.42/6.90 (J = 8.4 Hz, H-1/2) and three aromatic methoxy groups at δ 3.95, 3.98, and 4.03. In addition, the appearance of a downfield methylene proton as a singlet at δ 5.34, consistent with an ether oxygen, and an aromatic moiety placed vicinal to the methylene carbon were characteristic of a peltogynoid derivative.[16] The ^{13}C NMR spectrum of **4** (see Experimental Section) showed 14 signals for aromatic carbons, of which seven are oxygenated, three methoxy groups in the range δ 56.2−61.6, and a carbonyl group at δ 171.4. Another distinctive feature was the observation of an oxygenated methylene carbon at δ 63.2. Diagnostic HMBC corrections were

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observed between H-8 (δ 8.00) and C-7 (δ 171.4), C-10 (δ 156.1), and C-11a (δ 149.1), between H-9 (δ 7.00) and C-11 (δ 136.6) and C-7a (δ 119.2), between OCH_3-11 (δ 4.03) and C-11, and between OCH_3-10 (δ 3.98) and C-10 of the aromatic ring A. Other HMBC correlations were observed for H-5 (δ 5.34) with C-6a (δ 135.8), C-4 (δ 140.7), and C-12b (δ 118.5); H-1 (δ 7.42) with C-3 (δ 149.2), C-4a (δ 118.1), and C-12a (δ 147.7); H-2 (δ 6.90) with C-4 (δ 140.7) and C-12b (δ 118.5); and OCH_3-3 (δ 3.95) with C-3. On the basis of the above evidence, compound **4** (diplotasin) was deduced as 4-hydroxy-3,10,11-trimethoxyisochromeno-[4,3-*b*]-chromen-7(5*H*)-one.

Thirteen of the compounds isolated were evaluated for their antiproliferative activity against the A549, AGS, HT-29, and PC3 human tumor cell lines. Compounds **2** and **5** exhibited antiproliferative activity against one or more tumor cell lines. Compound **2** was the most effective, with GI_{50} values of 2.7, 1.7, 7.5, and 20.8 μM, respectively. The GI_{50} data for **5** were, in turn, 20.3, 24.8, 4.1, and 2.3 μM. The GI_{50} values against the four human cancer cell lines of the remaining compounds were all >10 μM.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. UV spectra were measured on a Hitachi U-3200 spectrophotometer in MeOH. IR spectra were obtained on a Nicolet Avatar 320 IR spectrometer. ^{1}H, ^{13}C, and 2D NMR spectra were measured with a Varian INOVA-500 spectrometer with deuterated solvents used as internal standards. ESIMS and HRESIMS were recorded on Finnigan LCQ and Shimadzu LCMS-IT-TOF spectrometers, respectively. Column chromatography was performed on Sephadex LH-20 (Pharmacia) or silica gel 60 (70−230 or 230−400 mesh, Merck; or 12−26 μm, Eurochrom, Knauer). Silica gel 60F $_{254}$ (Merck, Darmstadt, Germany) was used for TLC (0.25 mm). The semipreparative HPLC system consisted of a chromatographic pump (LC-8A, Shimadzu, Kyoto, Japan) and a UV−visible detector (SPD-10A vp, Shimadzu, Kyoto, Japan). A Cosmosil 5C18-AR-II column (20 × 250 mm; particle size 5 μm; Nacalai tesque, Kyoto, Japan) was used for separation.

Plant Material. The whole plant of *Mimosa diplotricha* was collected from Taitung County, Taiwan, in May 2009, and identified by Dr. Cheng-Jen Chou, Research Fellow, National Research Institute of Chinese Medicine, Taipei, Taiwan. A voucher specimen (NHP01474) is deposited in the Herbarium of National Research Institute of Chinese Medicine, Taipei, Taiwan.

Extraction and Isolation. (a) Solvent extraction: The aerial parts of *M. diplotricha* (12 kg) were extracted with ethanol (60 L × 3) under reflux and concentrated to give a dark green extract (1.2 kg). The extract was suspended in H_2O and partitioned successively with $CHCl_3$ and *n*-BuOH (each 2 L × 3) to yield $CHCl_3$, *n*-BuOH, and H_2O extracts. These extracts were examined for their cytotoxicity against four human cancer cell lines. The $CHCl_3$ extract displayed cytotoxic activity against the A549, AGS, HT-29, and PC3 cancer lines, with GI_{50} values of 21.1, 16.5, 23.0, and 12.5 μg/mL, respectively, while the *n*-BuOH extract was less active. (b) Workup of the $CHCl_3$ extract: The $CHCl_3$ extract (134 g) was subjected to column chromatography on silica gel (8 × 100 cm), with step gradient mixtures of EtOAc and *n*-hexane (0:1, 1:9, 2:8, 4:6, 6:4, 2:8, and 1:0), to yield 11 fractions (Fr.C1−C11). Fr.C5 (6.85 g) was chromatographed on a Sephadex LH-20 column (4.8 × 80 cm) with acetone elution, to give five subfractions (Fr.C5-1−C5-6). Purification of Fr.C5−5 (1.23 g) by Sephadex LH-20 column chromatography (EtOAc) gave betulinic acid (80.2 mg). Fr.C8 (4.59 g) was chromatographed on a Sephadex LH-20 column (4.8 × 80 cm) with EtOAc elution to also give five subfractions (Fr.C8-1−C8-5). Purification of Fr.C8-2 (2.3 g) by Sephadex LH-20 column chromatography (MeOH) gave **2** (9.2 mg) and pentamethoxyflavone (75.0 mg). Fr.C8-3 (6.8 g) was chromatographed over a Sephadex LH-20 column (4.8 × 100 cm; acetone) and by semipreparative HPLC (solvent: 60%MeOH/H_2O, flow rate: 15 mL/min) to yield **1** (11.7 mg) and **2** (63.5 mg). A solid precipitate that separated from Fr.C8-4 was recrystallized with MeOH to give hernancorizin (6.4 mg). The filtrate of Fr.C8-4 (250 mg) was chromatographed over Sephadex LH-20 (MeOH) to give **1** (46.9 mg) and **4** (1.7 mg). Fr.C9 (3.23 g) was chromatographed over Sephadex LH-20 (4.8 × 80 cm), using EtOAc elution, to yield four fractions (Fr.C9-1−C9-4). Two solid precipitates separated individually from Fr.C9-2 and Fr.C9-4 and were recrystallized with MeOH to give **3** (2.1 mg) and **5** (3.2 mg). The filtrate of Fr.C9-4 (250 mg) was chromatographed over a Sephadex LH-20 column (MeOH) to give luteolin (34.6 mg). Further purification of Fr.C9-3 (78.7 mg) by semipreparative HPLC (solvent: 60% MeOH/H_2O, flow rate: 15 mL/min) gave 7,3′,4′-trihydroxy-3,8-dimethoxyflavone (14.0 mg). Fr.C10 (1.10 g) was chromatographed over Sephadex LH-20, by elution with 5% $CHCl_3$/MeOH, to afford five subfractions, and 5,3′-di-*O*-methylluteolin (2.9 mg) was obtained from the fifth subfraction. (c) Workup of the *n*-BuOH extract: The *n*-BuOH extract (73 g) was subjected to column chromatography over Sephadex LH-20 (8 × 100 cm) eluted with MeOH and yielded eight fractions (Fr.B1−B8). Purification of Fr.B6 (5.58 g) over a Sephadex LH-20 column (MeOH) gave quercetin-3-*O*-xylopyranoside (34.0 mg), quercetin-3-*O*-arabinofuranoside (49.6 mg), myricetin-3-*O*-xylopyranoside (16.8 mg), and myricetin-3-*O*-arabinofuranoside (12.4 mg). In the same way, luteolin (46.4 mg) and quercetin (69.1 mg) were obtained from Fr.B7 (790.5 mg) and Fr.B8 (595.4 mg), respectively.

*Diplotrin A (**1**):* yellow crystals from MeOH, mp 113 °C; UV (MeOH) λ_{max} (log ε) 226 (4.30), 242 (4.33), 298 (4.08), 338 (3.99) nm; +NaOMe 236 (4.47), 293 (4.19) nm; IR ν_{max} (KBr) 3233, 1602, 1513, 1454, 1380, 1288, 1205, 1171, 1086 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 1; ESIMS *m*/*z* 375 $[M + H]^+$; HRESIMS *m*/*z* 375.1066 $[M + H]^+$ (calcd for $C_{19}H_{19}O_8$, 375.1080).

*Diplotrin B (**2**):* yellow crystals from MeOH, mp 159 °C; UV (MeOH) λ_{max} (log ε) 250 (4.35), 263 (4.17), 308 (4.11), 347 (4.30) nm; +NaOMe 256 (4.35), 310 (4.10), 385 (4.02) nm; IR (KBr) ν_{max} 3430, 1638, 1601, 1515, 1438, 1385, 1291, 1132, 1087 cm^{-1}; ^{1}H NMR and ^{13}C NMR data, see Table 1; ESIMS *m*/*z* 359 $[M + H]^+$; HRESIMS *m*/*z* 359.1120 $[M + H]^+$ (calcd for $C_{19}H_{19}O_7$, 359.1131).

*Diplotrin C (**3**):* yellow powder from MeOH, mp 170 °C; UV (MeOH) λ_{max} (log ε) 234 (4.19), 249 (4.22), 302 (4.12), 361 (4.24) nm; +NaOMe 232 (4.58), 258 (4.28), 305 (4.28), 422 (4.29) nm; IR (KBr) ν_{max} 3380, 1625, 1561, 1405, 1218, 1168, 1093 cm^{-1}; ^{1}H NMR and ^{13}C NMR, see Table 1; ESIMS *m*/*z* 329 $[M + H]^+$; HRESIMS *m*/*z* 329.1003 $[M + H]^+$ (calcd for $C_{18}H_{17}O_6$, 329.1025).

*Diplotasin (**4**):* light yellow, amorphous powder; UV (MeOH) λ_{max} (log ε) 252 (3.77), 311 (3.61), 343 (3.63) nm; IR (KBr) ν_{max} 3389, 1619, 1601, 1438, 1383, 1286, 1097, 1067 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 9.0 Hz, H-8), 7.00 (1H, d, *J* = 9.0 Hz, H-9), 6.90 (1H, d, *J* = 8.4 Hz, H-2), 7.42 (1H, d, *J* = 8.4 Hz, H-1), 5.34 (2H, s, H-5), 3. 95 (s, OCH_3-3), 3.98 (s, OCH_3-10), 4.03 (s, OCH_3-11); ^{13}C NMR (150 MHz, $CDCl_3$) δ 114.4 (C-1), 109.7 (C-2), 149.2 (C-3), 140.7 (C-4), 118.1 (C-4a), 63.2 (C-5), 135.8 (C-6a), 171.4 (C-7), 119.2 (C-7a), 121.4 (C-8), 109.6 (C-9), 156.1 (C-10), 136.6 (C-11), 149.1 (C-11a), 147.7 (C-12a), 118.5 (C-12b), 56.2 (OCH_3-3), 56.5 (OCH_3-10), 61.6 (OCH_3-11); ESIMS *m*/*z* 357 $[M + H]^+$; HRESIMS *m*/*z* 357.0956 $[M + H]^+$ (calcd for $C_{19}H_{17}O_7$, 357.0974).

Cell Lines and Reagents. Human A549 lung carcinoma cells (BCRC 60074), human AGS gastric adenocarcinoma cells (BCRC 60102), human HT-29 colorectal adenocarcinoma cells (BCRC 67003), and human PC3 prostate carcinoma cells (BCRC 60122) were obtained from the Bioresources Collection and Research Center (BCRC), Hsin-Chu, Taiwan. All cell lines were maintained in RPMI 1640 medium supplied with 10% fetal bovine serum, nonessential amino acid, 100 units/mL penicillin, and 100 units/mL streptomycin. Cell culture reagents were obtained from Invitrogen (Rockville, MD). Sulforhodamine B (SRB), trichloroacetic acid (TCA), and other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO).

Cell Proliferation Assay. The SRB assay was performed with cells seeded in 96-well plates and cultured overnight. Then, six wells of each cell line were fixed in situ with 10% TCA to represent a measurement at the time of drug addition (T_0). In addition, test compounds were added to the cells and incubated for an additional 48 h. The assay was terminated by adding 10% TCA. After rinsing the plates with PBS and air-drying, 0.4% SRB solution (weight per volume in 1% acetic acid) was added to each well, and the plates were incubated for 10 min at room temperature. Unbound dye was removed with 1% acetic acid, and the plates were air-dried. Bound SRB was subsequently solved with 10 mM Tris base. Cell proliferation was determined by measuring the optical density at 515 nm using a M5 microplate reader (Molecular Devices, Sunnyvale, CA). From the absorbance measurement of cells at time zero (T_0), cells in control cultures (C), and cells in the presence of tested compound (T_x), the percentage of growth was calculated at each ATMA concentration. Percentages of growth inhibition and of cells killed were calculated using the formula $100 - [(T_x - T_0)/(C - T_0)] \times 100$ and $100 - (T_x - T) \times 100$, respectively. The GI_{50} values were determined at the drug concentrations resulting in 50% growth inhibition. Doxorubicin was used as positive control, with GI_{50} values of 0.27, 0.01, 0.12, and 0.09 μM against the A549, AGS, HT-29, and PC3 cancer cells, respectively.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra of compounds **1**−**4** are available free of charge via the Internet at http://pubs.acs.org.

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