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A Nitrogen-Containing 3-Alkyl-1,4-benzoquinone and a Gomphilactone Derivative from *Embelia ribes*

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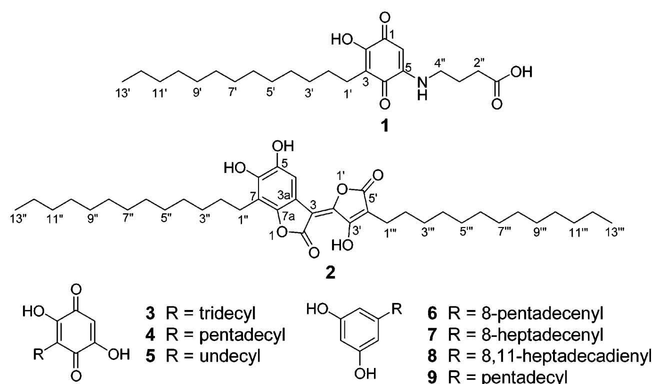
An unusual nitrogen-containing 3-alkyl-1,4-benzoquinone derivative, *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone (**1**), and a gomphilactone derivative, 5,6-dihydroxy-7-tridecyl-3-[4-tridecyl-3-hydroxy-5-oxo-2(5*H*)-furylidene]-2-oxo-3(2*H*)-benzofuran (**2**), together with 14 known compounds, as well as the common plant metabolites sitosterol and daucosterol, were isolated from the ethanolic extract of the roots of *Embelia ribes*. Their structures were elucidated by means of spectroscopic methods. Cytotoxicities of the purified compounds were tested.

Embelia ribes Burm. (Myrsinaceae) is one of several *Embelia* species used in traditional Chinese medicine. The roots, leafs, and fruits are separately used, and roots are used as an anti-inflammatory/analgesic medication and to improve general blood circulation.[1] The *Embelia* species collected in various parts of the world produce a rich and diverse range of secondary metabolites including 2,5-dihydroxy-3-alkyl-1,4-benzoquinones,[2] coumarins, flavonoids,[3,4] and triterpenoids,[5] and some of these compounds showed interesting bioactivities. There are, however, very few reports concerning the secondary metabolites isolated from the roots of *E. ribes*. Under a program to assess the chemical and biological diversity of several traditional Chinese medicines,[6,7] the roots of *E. ribes* were investigated, which resulted in the isolation and structural elucidation of an unusual 3-alkyl-1,4-benzoquinone derivative, coupled through a C−N bond with γ-aminobutyric acid (**1**), and a gomphilactone derivative (**2**), together with 14 known compounds.[8] By comparing with corresponding literature data, the known compounds were identified as 2,5-dihydroxy-3-tridecyl-1,4-benzoquinone (**3**),[9] 2,5-dihydroxyl-3-undecyl-1,4-benzoquinone (**4**),[10] 2,5-dihydroxyl-3-pentadecyl-1,4-benzoquinone (**5**),[9] 5-(8*Z*-pentadecenyl)-1,3-benzenediol (**6**),[11] 5-(8*Z*-heptadecenyl)-1,3-benzenediol (**7**),[12] 5-(8Z,11*Z*-heptadecadienyl)-1,3-benzenediol (**8**),[13] 5-pentadecyl-1,3-benzenediol (**9**),[12] 3-methoxy-5-pentylphenol,[14] 3,5-dimethoxy-4-hydroxy phenyl-1-*O*-β-D-glucopyranoside,[15] 2,6-dimethoxy-4-hydroxyphenyl-1-*O*-β-D-glucopyranoside,[16] (+)-catechin,[17] and (+)-lyoniresinol-3a-*O*-β-glucoside,[18] as well as sitosterol and daucosterol. We report herein the isolation and structural characterization of compounds **1** and **2**, as well as bioassay results of compounds **1**−**9**.



Compound **1** was obtained as a red, amorphous powder. The positive mode FABMS of **1** gave a quasi-molecular ion at m/z 408 $[M + H]^+$ and HRFABMS at m/z 408.2727 $[M + H]^+$, indicating the molecular formula $C_{23}H_{37}NO_5$ (calcd for $C_{23}H_{38}NO_5$ 408.2750). The IR spectrum of **1** showed absorption bands for hydroxyl and/or amino (3313 and 3271 cm^{-1}) and carbonyl (1703, 1639, and 1564 cm^{-1}) functional groups. The ^1H NMR spectrum displayed resonances similar to those of 2,5-disubstituted 3-alkyl-1,4-benzoquinone derivatives[2] at δ 5.31 (1H, s, H-6), 2.24 (2H, t, J = 7.0 Hz, H-1′), 1.33 (2H, m, H-2′), 1.22 (20H, m, from H_2-3′ to 12′, overlapped), and 0.84 (3H, t, J = 7.0 Hz, H_3-13′). In addition, the ^1H NMR spectrum showed resonances attributable to a γ-aminobutyric acid unit at δ 7.77 (1H, t, J = 6.0 Hz, exchangeable, *NH*), 3.13 (2H, dt, J = 6.0 and 7.0 Hz, H_2-4″, 2.26 (2H, t, J = 7.0 Hz, H-2″), and 1.73 (2H, quintet, J = 7.0 Hz, H-3″). Besides signals due to the 2,5-disubstituted 3-alkyl-1,4-benzoquinone moiety (Experimental Section), the ^{13}C NMR and DEPT spectra of **1** showed signals assignable to the γ-aminobutyric acid unit at δ 174.1 (C-1″), 30.8 (C-2″), 22.7 (C-3″), and 41.4 (C-4″). The presence of the γ-aminobutyric acid unit was further indicated by the $^1H-^1H$ COSY spectrum of **1**, which showed a coupling extension from the nitrogen proton through H_2-4″ and H_2-3″ to H_2-2″. In the HMBC spectrum of **1**, correlations (Figure 1) from H-6 to C-2 and C-4, from H_2-1′ to C-2, C-3, C-4, C-2′, and C-3′, from both H_2-2″ and H_2-3″ to C-1″ and C-4″, from H_2-2″ to C-3″, from H_2-3″ to C-2″, and from H_2-4″ to C-2″ and C-3″, together with the chemical shift values of these carbons, further confirmed the presence of the 5-disubstituted 2-hydroxyl-3-alkyl-1,4-benzoquinone and γ-aminobutyric acid moieties. HMBC correlations from H-4″ to C-5 and from the nitrogen proton to C-4 and C-6 indicated unequivocally the connection between the nitrogen and C-5. In consideration of the molecular composition, the alkyl was assigned as a tridecyl group. Therefore, the structure of **1** was determined as *N*-(3-carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone.

Compound **2** was obtained as a red, amorphous powder. The IR spectrum of **2** showed absorption bands for hydroxyl (3516 and 3323 cm^{-1}) and conjugated lactone carbonyl (1763, 1720, 1653, and 1624 cm^{-1}) groups. The UV spectrum of **2** confirmed the presence of the conjugated carbonyl and aromatic ring functional groups by showing absorption maxima at λ_{Max}^{MeOH} (log ϵ) 204 (1.40), 275 (0.58), 383 (0.44), and 456 (0.42) nm. The positive mode FABMS of **2** gave a quasi-molecular ion peak at m/z 627 $[M + H]^+$, and the molecular formula $C_{38}H_{58}O_7$ was established by the HRFABMS at m/z 627.4265 $[M + H]^+$. The ^1H NMR spectrum of **2** in $CDCl_3$ showed an aromatic singlet at δ 7.31 (1H, s, H-4) and three exchangeable hydroxy protons at δ 6.06 (1H,

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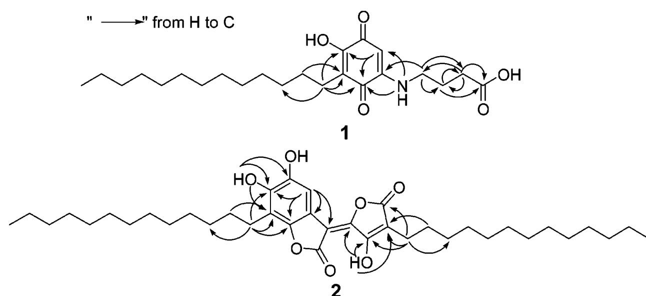


Figure 1. Key HMBC correlations of compounds **1** and **2**.

brs, *OH*-6), 6.18 (1H, brs, *OH*-5), and 11.78 (1H, s, *OH*-3′) in the deshielded region and signals attributed to two saturated long chains attached respectively to two sp^2 hybrid carbons at δ 2.70 (2H, t, J = 7.5 Hz H$_2$-1″), 2.38 (2H, t, J = 7.5 Hz, H$_2$-1‴), 1.61 (2H, quintet, J = 7.5 Hz, H$_2$-2″), 1.59 (2H, quintet, J = 7.5 Hz, H$_2$-2‴), 1.35 (4H, m, H$_2$-3″ and H$_2$-3‴), 1.27 (36H, m, from H$_2$-4″ to H$_2$-12″ and from H$_2$-4‴ to H$_2$-12‴), and 0.88 and 0.87 (3H, t, J = 7.0 Hz each, H$_3$-13″ and H$_3$-13‴) in the shielded region. The ^{13}C NMR and DEPT spectra of **2** exhibited 12 sp^2 hybrid carbon resonances consisting of an aromatic methine and 11 quaternary carbons (two lactone carbonyls, δ 173.6 and 168.9 ppm; five oxygenated carbons, δ > 140 ppm) in the lower field region. In addition, two overlapping methyl carbons at δ 14.3 ppm, as well as partially overlapped methylene carbons assignable to two long side chains between δ 32.5 and 22.0 ppm (Experimental Section), were displayed in the higher field region. These spectroscopic data revealed that **2** possesses a highly conjugated and highly oxygenated structure with two saturated long side chains.

The structure of **2** was established by a comprehensive analysis of 2D NMR spectra, especially the HMBC spectrum, as well as high-resolution mass measurements of the abundant fragment ions in the EIMS of **2**. The ^{1}H−^{1}H COSY confirmed unambiguously the presence of two saturated side chains by showing coupling chain extensions from H$_2$-1″ and H$_2$-1‴ respectively through H$_2$-2″ and H$_2$-3″ and through H$_2$-2‴ and H$_2$-3‴ to the overlapped methylene protons, which in turn coupled with H$_3$-13″ and H$_3$-13‴. In the HMBC spectrum of **2**, two- and three-bond correlations (Figure 1) from H-4 to C-3, C-3a, C-5, C-6, and C-7a, from *OH*-6 to C-5, C-6, and C-7, and from H-1″ to C-6, C-7, and C-7a, together with the uncorrelated carbonyl carbon (C-2), as well as the chemical shifts of these carbons (Experimental Section) and the characteristic IR absorptions for conjugated lactone carbonyls at ν_{max} 1763 and 1720 cm^{-1}, revealed unambiguously the presence of a 7-alkyl-5,6-dihydroxy-2-oxo-3(2*H*)-benzofuryliden-3-yl in **2**. In addition, HMBC correlations from *OH*-3′ to C-2′, C-3′, and C-4′ and from H$_2$-1‴ to C-3′, C-4′, and C-5′ in combination with chemical shift values of these carbons (Experimental Section) indicated the presence of a 4-alkyl-3-hydroxy-5-oxo-2(5*H*)-furyliden-2-yl unit in **2**. To satisfy the 10 degrees of unsaturation of the molecule and the sp^2 hybrid nature quaternary nature of C-3 and C-2′, these two carbons have to be connected to form the 7-alkyl-5,6-dihydroxy-3-[4-alkyl-3-hydroxy-5-oxo-2(5*H*)-furylidene]-2-oxo-3(2*H*)-benzofuran structure. The high-resolution mass measurement of fragment ions suggested a cleavage pattern in the EIMS, as illustrated in Scheme 1. This indicated that both side chains are tridecyls. The configuration related to the orientation of the two lactone rings was evidenced by the absence of the NOE effect of H-4 in the NOE difference spectrum when the hydroxyl proton at C-3′ was irradiated. This is also supported by the deshielded chemical shift of the hydroxyl proton at C-3′ (δ 11.78), indicating hydrogen bond formation between the hydroxyl at C-3′ and the carbonyl oxygen at C-2. Therefore, the structure of **2** was determined as 7-tridecyl-5,6-dihydroxy-3-[4-tridecyl-3-hydroxy-5-oxo-2(5*H*)-furylidene]-2-oxo-3(2*H*)-benzofuran.

Compound **1** is the first naturally occurring nitrogen-containing 2,5-dihydroxy-3-alkyl-1,4-benzoquinone derivative. Compound **2** possesses a central moiety identical to that of the fungal metabolites gomphilactone[19] and bovilactone-4,4.[20] The biosynthesis of bovilactone-4,4 has been proposed by the feeding experiments with 4-hydroxy[1-^{13}C]benzoic acid, 3,4-dihydroxy[1-^{13}C]benzoic acid, and [1′-^{13}C]tyrosine.[21] A metabolite similar to **2** was also reported from the mangrove plant.[22] This indicated that a possible biogenesis (Scheme 2) similar to that of bovilactone-4,4 may occur in plants where the alkylation of the phenolic intermediates may take place, instead of the geranylgeranylation in fungi.

The EtOH extract of the roots of *E. ribes* showed moderate activity (IC$_{50}$ 36−48 μg/mL) in the preliminary cytotoxic assay against several human cancer cell lines. In the in vitro bioassay of the purified compounds, 2,5-dihydroxy-3-alkyl-1,4-benzoquinone derivatives (**3**−**5**) and 5-alkenyl-1,3-benzenediol derivatives (**4**−**9**) showed cytotoxic activities against several human cancer cell lines (Table 2), and other compounds were inactive. In addition, on the basis of the traditional usage of this plant,[1] protein tyrosine phosphatase 1B (PTP1B)[23] and thrombin[24] inhibitory activities of the purified compounds were also tested, but all compounds were inactive at a concentration of 50 μM.

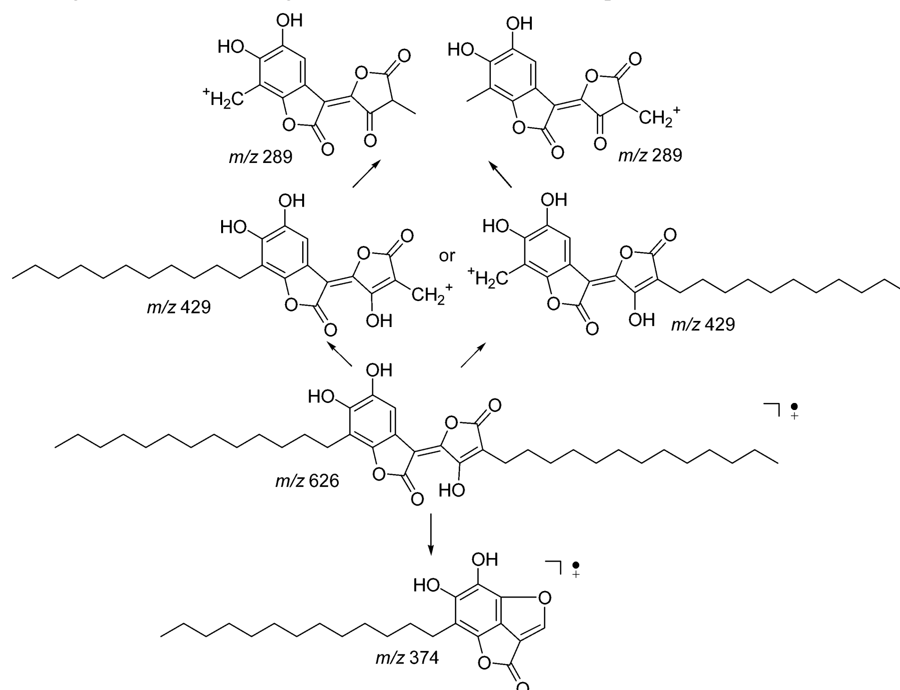
Experimental Section

General Experimental Procedures. Melting points were determined on an XT-4 micro melting point apparatus and are uncorrected. IR spectra were recorded as KBr disks on a Nicolet Impact 400 FT-IR spectrophotometer. 1D and 2D NMR spectra were obtained at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, on an Inova 500 MHz spectrometer in DMSO-d_6 or CDCl$_3$ with solvent peaks as references. EIMS, HREIMS, FABMS, and HRFABMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. Column chromatography was performed on silica gel (200−300 mesh) and Sephadex LH-20. TLC was carried out with glass precoated silica gel GF$_{254}$ plates. Spots were visualized under UV light or by spraying with 7% sulfuric acid in EtOH followed by heating.

Plant Material. The roots of *E. ribes* (2.5 kg) were collected at Dayao Mountain, Guangxi Province, China, in August 2002. The plant was identified by Mr. Guang-Ri Long (Guangxi Forest Administration, Guangxi 545005, China). A voucher specimen (no. YG01092) was deposited at the Herbarium of the Department of Medicinal Plants, Institute of Materia Medica, Beijing, China.

Extraction and Isolation. The air-dried roots of *E. ribes* (2.5 kg) were extracted with 90% EtOH (3 × 5.0 L) at room temperature for 3 × 48 h. The extract was evaporated to dryness under reduced pressure to yield a dark brown residue (206.0 g). The residue was suspended in H$_2$O (600 mL) and then partitioned successively with petroleum ether (60−90 °C) (3 × 600 mL) and EtOAc (4 × 500 mL). The EtOAc fraction (36.3 g) was subjected to normal-phase silica gel (400 g) column chromatography eluting with a gradient of increasing MeOH (0−100%) in CHC1$_3$. The CHCl$_3$-eluted fraction (1.32 g) was chromatographed over Sephadex LH-20 (50 g) with petroleum ether−CHCl$_3$−MeOH (5:5:1) as eluent to give three subfractions. The second subfration (0.86 g) was further separated by reversed-phase HPLC using 92% MeOH in H$_2$O as the mobile phase to yield **3** (221 mg), **4** (62 mg), and **5** (138 mg). The CHCl$_3$−MeOH (50:1) eluted fraction (4.33 g) was chromatographed over Sephadex LH-20 (200 g) with petroleum ether−CHCl$_3$−MeOH (5:5:1) as eluent to give five subfractions. The second subfraction (1.56 g) was recrystallized from EtOAc to produce sitosterol (912 mg). The third subfraction (0.18 g) was further chromatographed over silica gel (30 g) eluting with petroleum ether−(Me)$_2$CO (2:1) to yield **2** (36 mg). The fourth subfraction (0.69 g) was separated by reversed-phase HPLC with 80% MeOH in H$_2$O as the mobile phase to yield **6** (73 mg), **7** (19 mg), **8** (42 mg), **9** (21 mg), and 3-methoxy-5-pentylphenol (9 mg). The CHCl$_3$−MeOH (10:1) eluted fraction (4.2 g) was separated into four subfractions by chromatography over Sephadex LH-20 (200 g) with petroleum ether−CHCl$_3$−MeOH (5:5:1) as eluent. The fourth subfraction (0.11 g) was rechromatographed over silica gel eluting with CHCl$_3$−MeOH (10:1) to give **1** (12 mg). The aqueous phase of the extract was subjected to column chromatography over macroporous resin (HPD-100, dry weight 350 g) eluting with H$_2$O, 30% EtOH, and EtOH, successively, to give three corre-

Scheme 1. Proposed Cleavage Patterns of the Fragment Ions in the EIMS of Compound **2**



Scheme 2. Proposed Biosynthetic Pathway of Compound **2**

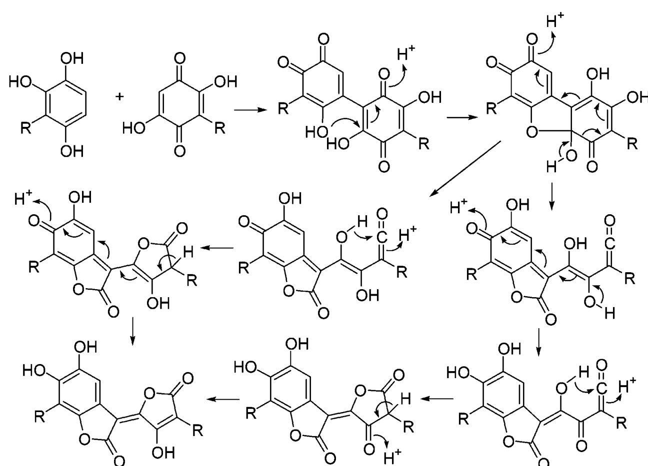


Table 1. Cytotoxicity of Compounds **3**−**9**[a]

	IC$_{50}$ value (μM)[b]				
compound	A549	A2780	Bel7402	BGC-823	HCT-8
3	1.58	1.82	1.46	1.89	1.52
4	1.42	1.86	1.51	1.83	1.44
5	1.47	1.79	1.66	1.69	1.49
6	1.76	1.85	1.86	1.80	1.80
7	0.46	1.06	1.07	1.43	0.78
8	1.42	1.57	1.91	1.79	1.54
9	1.43	1.31	1.93	1.74	1.48
topotecan[c]	3.5	1.2	1.4	3.8	1.2

[a] Compounds **1**, **2**, and other known compounds were inactive against all cell lines tested (IC$_{50}$ > 10 μg/mL). [b] For cell lines used, see Experimental Section. [c] Positive control.

sponding fractions. The fraction (4.6 g) eluted by 30% EtOH was rechromatographed over silica gel (120 g) eluting with a gradient of increasing MeOH (5−100%) in $CHCl_3$. The $CHCl_3$−MeOH (10:1) eluted fraction (0.22 g) was crystallized in a mixed solvent of CH_3Cl−MeOH (1:1) to give daucosterol (96 mg). The $CHCl_3$−MeOH (6:1) eluted fraction (0.51 g) was separated by chromatography over Sephadex LH-20 (200 g) with $CHCl_3$−MeOH (2:1) as eluent to yield three subfractions. The second subfraction (0.27 g) was further isolated by reversed-phase HPLC with 30% MeOH in H_2O as mobile phase to afford 2,6-dimethoxy-4-hydroxyphenyl-1-*O*-*β*-D-glucopyranoside (26 mg) and (+)-lyoniresinol-3a-*O*-*β*-glucoside (39 mg). The third subfraction was crystallized from Me_2CO to give (+)-catechin (6 mg).

***N*-(3-Carboxylpropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone (1):** red, amorphous powder; λ_{Max}^{MeOH} (log ϵ) 207 (1.74), 317 (1.32), 500 (0.09) nm; IR (KBr) ν_{max} 3313, 3271, 2956, 2918, 2848, 1703, 1639, 1564, 1506, 1460, 1381, 1221 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.10 (1H, brs, *COOH*), 10.49 (1H, brs, *OH*), 7.77 (1H, t, J = 6.0 Hz, *NH*), 5.31 (1H, s, H-6), 3.13 (2H, dt, J = 6.0 and 7.0 Hz, H-4″), 2.26 (2H, t, J = 7.0 Hz, H$_2$-2″), 2.24 (2H, t, J = 7.0 Hz, H-1′), 1.73 (2H, quintet, J = 7.0 Hz, H$_2$-3″), 1.33 (2H, m, H-2′), 1.22 (20H, m, from H$_2$-3′ to 12′, overlapped), 0.84 (3H, t, J = 7.0 Hz, H$_3$-13′); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 182.4 (C-1), 178.4 (C-4), 174.1 (C-1″), 156.6 (C-2), 149.2 (C-5), 115.4 (C-3), 91.7 (C-6), 41.4 (C-4″), 31.3 (C-12′), 30.8 (C-2″), 28.7−29.0 (from C-3′ to C10′, overlapped), 27.6 (C-2′), 22.7 (C-3′), 22.1 (C-1′), 22.0 (C-11′), 13.9 (C-13′); FABMS (positive) *m/z* 408 [M + H]$^{+,}$ 390, 380, 365, 295, 238, 222, 194, 176, 162, 146, 134, 118; HRFABMS *m/z* 408.2727 [M + H]$^+$ (calcd for $C_{23}H_{38}NO_5$, 408.2750).

5,6-Dihydroxy-7-tridecyl-3-[4-tridecyl-3-hydroxy-5-oxo-2(5*H*)-furylidene]benzo-2-oxo-3(2*H*)-furan (2): red, amorphous powder; λ_{Max}^{MeOH} (log ϵ) 204 (1.40), 275 (0.58), 383 (0.44), 456 (0.42) nm; IR (KBr) ν_{max} 3516, 3323, 2956, 2922, 2852, 1763, 1720, 1653, 1624, 1606, 1464, 1410, 1460, 1319, 1200, 1119, 1024 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.78 (1H, br s ,*OH*-3′), 6.18 (1H, brs, *OH*-5), 6.06 (1H, brs, *OH*-6), 7.31 (1H, s, H-4), 2.70 (2H, t, J = 7.5 Hz, H$_2$-1″), 2.38 (2H, t, J = 7.5 Hz, H$_2$-1‴), 1.60 (4H, m, H$_2$-2″ and H$_2$-2‴), 1.25−1.34 (40H, m, 20 × CH$_2$, from H$_2$-3″ to H$_2$-2″, and from H-3‴ to H$_2$-12‴), 0.87 (6H, t, J = 7.0 Hz, H-13″ and H-13‴); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (C-2), 112.3 (C-3a), 107.7 (C-3), 108.7 (C-4), 140.9 (C-5), 147.0 (C-6), 114.6 (C-7), 148.3 (C-7a), 150.0 (C-2′), 162.4 (C-3′), 108.5 (C-4′), 168.9 (C-5′), 23.9 (C-1″), 22.1 (C-1‴), 29.0 (C-2″), 27.7 (C-2‴), 29.5∼29.9 (from C-3″ to C10″, and from C-3‴ to C10‴, overlapped), 32.2 (C-11″ and C-11‴), 22.9 (C-12″ and C-12‴), 14.4 (C-13″ and C-13‴); FABMS (positive) *m/z* 627 [M + H]$^+$; EIMS *m/z* (%) 626 (50) [M]$^+$, 429 (5), 374 (18), 289 (30), 205 (18), 57(28); HRFABMS *m/z* 627.4265 [M + H]$^+$ (calcd for $C_{38}H_{59}O_7$, 627.4261); HREIMS *m/z* (%) 626.4205 [M]$^+$ (calcd for $C_{38}H_{58}O_7$, 626.4183), 429.1884 [M − $C_{12}H_{29}$]$^+$ (calcd for $C_{24}H_{29}O_7$, 429.1913), 374.2094 [M − $C_{16}H_{28}O_2$]$^+$ (calcd for $C_{22}H_{30}O_5$, 374.2093), 289.0354 [M − $C_{24}H_{49}$]$^+$ (calcd for $C_{14}H_9O_7$, 289.0348).

Cells and Culture Conditions. Human lung adenocarcinoma (A549), human hepatoma (Bel7402), human stomach cancer (BGC-823), human colon cancer (HCT-8), and human ovarian cancer (A2780)

cell lines were obtained from American Type Culture Collection (ATCC, Rockville, MD). Cells were maintained in RRMI1640 supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin, and 100 μg/mL streptomycin. Cultures were incubated at 37 °C in a humidified 5% CO_2 atmosphere.

Cell Proliferation Assay. A549, Bel7402, BGC-823, HCT-8, and A2780 cells were seeded in 96-well microtiter plates at 1200 cells/well. After 24 h, the compounds were added to the cells. After 96 h of drug treatment, cell viability was determined by measuring the metabolic conversion of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) into purple formazan crystals by active cells.[25,26] MTT assay results were read using a MK 3 Wellscan (Labsystem Drogon) plate reader at 570 nm. All compounds were tested at five concentrations and were dissolved in 100% DMSO to give a final DMSO concentration of 0.1% in each well. Each concentration of the compounds was tested in three parallel wells. IC_{50} values were calculated using Microsoft Excel software.

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Supporting Information Available: MS, IR, and 1D and 2D NMR spectra of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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