New Isoprenylated Flavones, Artochamins A−E, and Cytotoxic Principles from *Artocarpus chama*

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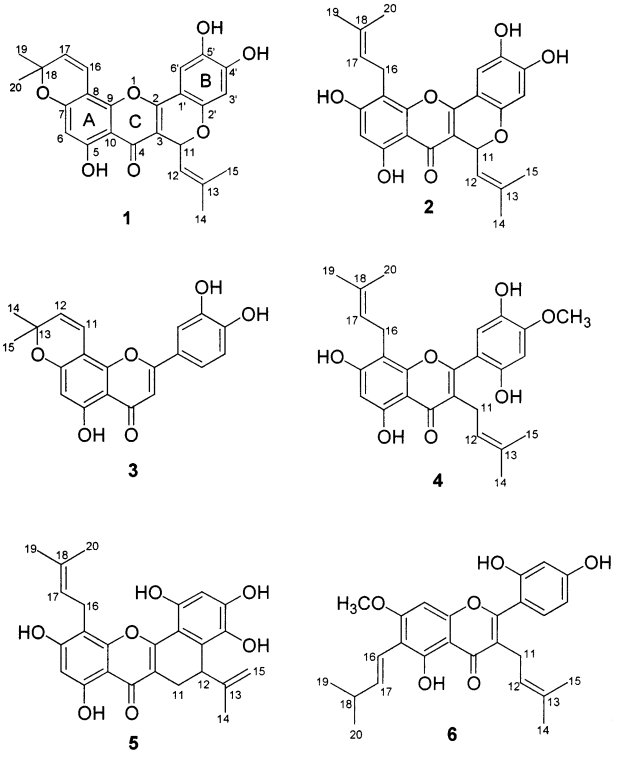
Five new isoprenylated flavones, artochamins A−E (**1**−**5**), together with eight known flavones (**6**−**13**), were isolated from the roots of *Artocarpus chama*. All structures were elucidated by spectroscopic methods. Artonin E (**12**) showed strong cytotoxicity against 1A9 (ovarian), significant activity against MCF-7 (breast adenocarcinoma), and moderate activity against HCT-8 (ileocecal) and MDA-MB-231 (breast adenocarcinoma) tumor cell lines. Artochamin C (**3**) was more potent against MCF-7, 1A9, HCT-8, and SK-MEL-2 (melanoma) than A549 (lung carcinoma), KB (epidermoid carcinoma of the nasopharynx), and its drug-resistant (KB-VIN) variant. Artocarpin (**6**) displayed weak but relatively broad inhibitory effects compared with **3** and **12**.

Artocarpus species (Moraceae) are evergreen trees distributed over tropical regions of Asia. Primarily known for their large edible fruits, some members also have important medicinal value, having been used as traditional folk medicines in Indonesia, Thailand, Taiwan, and Sri Lanka.[1−4] Previously, a series of prenylated flavonoids were isolated from *Artocarpus* species, some of which were found to inhibit mouse TNF-α release and arachidonate 5-lipoxygenase activity, show cytotoxic and antiplatelet activities, and exert antibacterial effects against cariogenic bacteria.[5] In our continuing research on cytotoxic phenolic compounds with isoprenoid groups from Moraceous plants,[6] we investigated the constituents of *Artocarpus chama* Buch.-Ham, which has not been studied with respect to its chemical constituents. The chloroform-soluble fraction from an ethanol extract of the roots of this plant exhibited cytotoxic activity against human lung carcinoma (A549) and breast adenocarcinoma (MCF-7) in vitro. Further fractionation of this extract resulted in the isolation of five new isoprenoid-substituted flavones, artochamins A−E (**1**−**5**), and eight known compounds, artocarpin (**6**),[7,8] cycloartocarpin A (**7**),[9] cudraflavone A (**8**),[10] artonin A (**9**),[11] artonin U (**10**),[12] cycloartobiloxanthone (**11**),[13] artonin E (**12**),[14] and 3′,4′,5,7-tetrahydroxy-8-(methylbut-2-enyl)flavone (**13**).[15] The new structures were established from spectroscopic data. In addition, 2D NMR experiments permitted the correct assignment of several carbon signals of **6**.

Compounds **1**, **2**, **7**, and **8** have a characteristic pyranoid unit, which is formed by oxidative cyclization of the allylic methylene of a C-3 prenyl chain with the C-2′ hydroxyl group. Compounds **3** and **13** contain 3′,4′-dihydroxy substitution in the B ring, although almost all flavonoids from *Artocarpus* genus have a 2′,4′-dioxygenated or 2′,4′,5′-trioxygenated pattern.[5] Compounds **5**, **9**, and **11** have a typical dihydrobenzoxanthone skeleton originating from a phenolic oxidation between an isoprenoid group at C-3 and the 6′-carbon of the B ring.

In this paper, we describe the structure elucidation of **1**−**5**, the spectral revision of some carbon signals of **6**, and the cytotoxicity evaluation against a panel of human tumor cell lines, including human lung carcinoma (A549), breast adenocarcinoma (MCF-7 and MDA-MB-231), ovarian carcinoma (1A9), ileocecal carcinoma (HCT-8), kidney carcinoma (CAKI-1), melanoma (SK-MEL-2), glioblastoma (U-87-MG), prostate cancer (PC-3), epidermoid carcinoma of the nasopharynx (KB), and the KB-VIN subclone.



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Results and Discussion

The EtOH extract of the roots of *A. chama* was suspended in H_2O and partitioned successively with petroleum ether, $CHCl_3$, EtOAc, and *n*-BuOH. Repeated column chromatography of the $CHCl_3$ layer on Si gel and RP_{18} gel yielded artochamins A−E (**1**−**5**) and eight known isoprenylated flavones (**6**−**13**).

Artochamin A (**1**), orange prisms, gave a positive reaction with ferric chloride reagent, indicating the presence of a phenol. The HREIMS showed an $[M]^+$ peak at *m/z* 434.1397, consistent with a molecular formula of $C_{25}H_{22}O_7$. The IR spectrum showed absorptions for a hydroxyl moiety (3492 cm^{-1}), a carbonyl group conjugated with an aromatic ring and also hydrogen-bonded with a hydroxyl group (1655 cm^{-1}), and a benzene ring (1580, 1556, 1482 cm^{-1}). The UV spectrum resembled those of flavone derivatives.[16] The ^{13}C NMR spectrum revealed the presence of 25 carbons, including a carbonyl group (δ 179.6) and four methyl groups, corresponding to a diprenylated flavonoid. The ^1H NMR spectrum indicated a hydrogen-bonded hydroxyl group [δ 13.00 (1H, s)], two additional hydroxyl groups [δ 8.89 and 8.09 (each 1H, br s)], and a 2,2-dimethylpyran ring [δ 6.86 (1H, d, J = 10.0 Hz), 5.78 (1H, d, J = 10.0 Hz), and δ 1.47 (6H, s)]. It also exhibited signals for two vinyl methyl groups [δ 1.93 and 1.68 (each 3H, br s)] and two doublets [δ 6.14 (1H, d, J = 9.0 Hz) and 5.51 (1H, br d, J = 9.0 Hz)] on a substituted 2H-benzopyran ring system, which resulted from the oxidative cyclization between the allylic methylene of a C-3 prenyl chain with the C-2′ hydroxyl group of the B ring in the flavone.[16] Moreover, three aromatic singlets [δ 7.33, 6.46, and 6.15 (each 1H, s)] were observed. On the basis of HMQC and HMBC spectral analysis, all proton and carbon signals were fully assigned, and the positions of the substitution and cyclization on the flavone skeleton were determined. In the HMBC spectrum, the proton at δ 6.86 (1H, d, J = 10.0 Hz, H-16) was correlated with three quaternary carbons, C-7 (δ 160.3), C-8 (δ 102.6), and C-9 (δ 152.4), which indicated that the 2,2-dimethylpyran ring was fused to C-7 and C-8 in the A ring. The oxidative cyclization was confirmed by the long-range cross-peaks of H-11 (δ 6.14) with C-2 (δ 157.1), C-3 (δ 110.6), C-4 (δ 179.6), C-2′ (δ 152.6), C-12 (δ 122.4), and C-13 (δ 139.0). On the other hand, the following HMBC correlations (^2J and ^3J) were observed: the proton at δ 7.33 with C-2, C-2′, C-4′ (δ 152.8), and C-5′ (δ 141.8); the signal at δ 6.46 with C-1′ (δ 108.0), C-2′, and C-5′; and the singlet at δ 6.15 with C-8 and C-10 (δ 106.5). These results assigned the three aromatic singlets at δ 7.33, 6.46, and 6.15 to H-6′, H-3′, and H-6, respectively. Thus, the structure of artochamin A (**1**) was deduced as 2,3,8-trihydroxy-11,11-dimethyl-6-(2-methyl-1-propenyl)-6*H*,7*H*,11*H*-bis[1]benzopyrano[4,3-*b*:6′,5′-*e*]pyran-7-one.

Artochamin B (**2**), a yellow amorphous powder, had a molecular formula of $C_{25}H_{24}O_7$ established from its HREIMS and NMR data. The ^1H NMR spectrum provided evidence for a hydrogen-bonded hydroxyl group [δ 12.84 (1H, s)], an isoprenyl oxidative cyclization similar to that of **1** [δ 6.13 (1H, d, J = 9.4 Hz), 5.50 (1H, br d, J = 9.4 Hz), and 1.92, 1.66 (each 3H, br s)], and a γ,γ-dimethylallyl group [δ 5.33 (1H, br t, J = 7.2 Hz), 3.56, 3.40 (each 1H, br dd, J = 7.2, 14.6 Hz), and 1.84, 1.66 (each 3H, br s)]. It also showed three aromatic singlets at δ 7.30, 6.46, and 6.31. By comparing the NMR spectra of **2** and **1**, it could be inferred that **2** contained an isoprenyl side chain rather than the 2,2-dimethylpyran ring in **1**. The structure was further confirmed by the HMQC and HMBC spectral data. Thus, the structure of artochamin B (**2**) was concluded to be 2,3,8,10-tetrahydroxy-11-(3-methyl-2-butenyl)-6-(2-methyl-1-propenyl)-6*H*,7*H*-[1]benzopyrano[4,3-*b*][1]benzopyran-7-one.

Artochamin C (**3**), obtained as an amorphous powder, was assigned a molecular formula of $C_{20}H_{16}O_6$ on the basis of its HREIMS and NMR data. Its color test with ferric chloride reagent and IR and UV spectral data indicated **3** is a flavonoid. The ^1H NMR spectrum of **3** contained signals of three hydroxyl groups [δ 13.11 (1H, s) and 9.75 (2H, br s)], a 2,2-dimethylpyran ring [δ 6.84 (1H, d, J = 10.0 Hz), 5.83 (1H, d, J = 10.0 Hz), and 1.46 (6H, s)], two aromatic singlets [δ 6.75 and 6.23 (each 1H, s)], and a 3′,4′-dihydroxylated B ring [δ 7.48 (1H, br s), 7.47 (1H, br d, J = 8.6 Hz), and 6.92 (1H, d, J = 8.6 Hz)]. In the HMBC spectrum, the doublet at δ 6.84 (H-11) coupled with C-7 (δ 158.6) and C-9 (δ 151.2), and the proton at δ 5.83 (H-12) showed cross-peaks with C-8 (δ 100.9), which established the 2,2-dimethylpyran ring at C-7 and C-8. The signals at δ 6.75 and 6.23 were assigned to H-3 and H-6, respectively, on the basis of their long-range correlations with C-2 (δ 163.7), C-4 (δ 181.8), C-10 (δ 104.5), and C-1′ (δ 121.3) and with C-5 (δ 160.9), C-7, C-8, and C-10, respectively. The structure of the B ring was also verified from the HMBC spectral data. All proton and carbon signals were fully assigned by the HMQC and HMBC experiments. Consequently, the structure of artochamin C (**3**) was determined as 5-hydroxy-8,8-dimethyl-2-(3,4-dihydroxyphenyl)-4*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-4-one.

Artochamin D (**4**), $C_{26}H_{28}O_7$ (HRESIMS *m/z* 453.1926 [M + H]$^+$), was isolated as a yellow amorphous powder. Its UV spectral data were similar to those of C-3 isoprenylated flavones.[17] The ^1H NMR spectrum revealed the presence of four hydroxyl groups, two γ,γ-dimethylallyl side chains, three aromatic singlets, and a methoxy group. Comparison of its NMR spectra with those of artonin V[17] showed that one hydroxyl group in artonin V was methylated in **4**. The carbon signals of **4** were in agreement with those of artonin V, except for those of the B ring, suggesting that the methoxy group in **4** was possibly present in the B ring. This assumption was verified by the HMBC and NOESY experiments. The O-methyl protons at δ 3.76 were correlated with C-4′ (δ 152.7) in the HMBC spectrum and coupled only with H-3′ (δ 6.71) in the NOESY spectrum, indicating that the methoxy group was located at C-4′. Thus, artochamin D (**4**), 4′-*O*-methylartonin V, was elucidated as 5,7-dihydroxy-3,8-bis(3-methyl-2-butenyl)-2-(2,5-dihydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one.

Artochamin E (**5**), a yellow amorphous powder, $C_{25}H_{24}O_7$ (HRESIMS *m/z* 437.1596 [M + H]$^+$), was also shown to be a flavone derivative on the basis of its color test and UV and IR spectra. The ^1H NMR spectrum indicated five hydroxyl groups [δ 13.22 (1H, s), 9.29 (2H, br s), and 8.29, 7.15 (each 1H, br s)], two aromatic singlets [δ 6.56 and 6.31 (each 1H, s)], and a γ,γ-dimethylallyl group [δ 5.29 (1H, br t, J = 7.5 Hz), 3.67, 3.44 (each 1H, br dd, J = 7.5, 14.7 Hz), and 1.76, 1.61 (each 3H, br s)]. Moreover, signals of an isoprenyl group [δ 4.65, 4.32 (each 1H, br s) and 1.78 (3H, s)] and an ABX system [δ 4.00 (1H, br d, J = 6.5 Hz), 3.42 (1H, dd, J = 1.5, 16.0 Hz), and 2.45 (1H, dd, J = 6.5, 16.0 Hz)] were also observed, proposing that a C−C linkage had formed between the isoprenyl moiety and the B ring.[11,13] This hypothesis was supported by certain carbon signals in the ^{13}C NMR spectrum [δ 22.6 (C-11), 38.5 (C-12), 145.7 (C-13), 22.3 (C-14), and 112.2 (C-15)] and the long-range cross-peaks in the HMBC spectrum [the protons at δ 3.42 and 2.45 (H-11a, b) with C-2 (δ 162.0), C-3 (δ 111.5), C-4 (δ 181.8), and C-6′ (δ 130.1), and another broad

Table 1. ^{13}C NMR Data for Compounds **1**−**5** (100 or 125 MHz, δ in ppm)

carbon	**1**[a]	**2**[a]	**3**[b]	**4**[a]	**5**[a]	**6**[a]
2	157.1	156.7	163.7	162.5	162.0	162.8
3	110.6	109.9	102.9	121.4	111.5	122.3
4	179.6	179.4	181.8	183.6	181.8	183.7
5	163.2	161.0	160.9	161.2	161.2	160.2
6	100.7	99.4	99.2	99.2	99.5	110.1
7	160.3	161.9	158.6	162.1	162.0	164.2
8	102.6	107.5	100.9	107.1	107.6	90.9
9	152.4	155.2	151.2	156.8	155.7	157.8
10	106.5	105.6	104.5	105.6	105.4	105.9
1′	108.0	107.9	121.3	113.8	107.4	113.2
2′	152.6	152.1	113.2	149.5	151.7	157.5
3′	105.8	105.4	145.6	101.4	103.9	104.1
4′	152.8	152.3	149.7	152.7	151.1	161.8
5′	141.8	141.4	116.1	139.6	137.0	108.4
6′	110.3	110.0	119.0	118.1	130.1	132.7
11	70.3	69.9	114.1	25.0	22.6	25.0
12	122.4	122.2	128.1	123.1	38.5	122.9
13	139.0	138.4	78.1	132.3	145.7	132.6
14	26.2	25.9	27.7	26.2	22.3	26.2
15	19.0	18.6	27.7	18.0	112.2	18.0
16	115.7	22.3		22.4	22.7	117.4
17	129.1	123.4		123.5	123.9	142.5
18	79.2	132.1		132.0	132.6	34.3
19	28.6	25.9		26.2	26.2	23.5
20	28.6	18.1		18.0	18.3	23.5
OCH_3				56.8		57.0

[a] In acetone-d_6. [b]In DMSO-d_6.

doublet at δ 4.00 (H-12) with C-3, C-1′ (δ 107.4), C-5′ (δ 137.0), C-6′, and C-13 (δ 145.7)]. In addition, in the HMBC spectrum of **5**, the broad double doublet at δ 3.67 (H-16a) was correlated with C-7 (δ 162.0), C-8 (δ 107.6), and C-9 (δ 155.7), which determined the isoprenyl side chain at C-8 in the A ring. Two singlets at δ 6.56 and 6.31 were also established as H-3′ and H-6 by the HMBC spectrum. From these data together with those of the HMQC and HMBC spectra, the structure of artochamin E (**5**) was determined as 5,6-dihydro-1,3,4,8,10-pentahydroxy-5-(1-methylethenyl)-11-(3-methyl-2-butenyl)-7*H*-benzo[*c*]xanthen-7-one.

Artocarpin (**6**), a yellow amorphous powder, possessed a molecular formula of $C_{26}H_{28}O_6$ on the basis of EIMS and NMR data. Most spectral data of **6** were in agreement with those of artocarpin except for the ^{13}C NMR data for C-2, C-5, C-6, C-9, and C-1′, which were assigned respectively to the signals at δ 160.2, 157.8, 113.3, 162.8, and 110.2 in a previous report.[8] According to the HMBC experiment of **6**, such assignments were obviously incorrect because of the following correlations: H_2-11 (δ 3.12) and H-6′ (δ 7.22) with C-2 (δ 162.8); OH-5 (δ 13.97) with C-5 (δ 160.2) and C-6 (δ 110.1); H-8 (δ 6.56) with C-9 (δ 157.8); and H-5′ (δ 6.53) with C-1′ (δ 113.2). Therefore, the signals of C-2, C-5, C-6, C-9, and C-1′ were revised. From the analysis of its HMQC, HMBC, and NOESY spectra, the structure of artocarpin (**6**) was further confirmed to be 5-hydroxy-7-methoxy-3-(3-methyl-2-butenyl)-6-(3-methyl-1-butenyl)-2-(2,4-dihydroxyphenyl)-4*H*-1-benzopyran-4-one.

Compounds **3**, **6**, **7**, **9**, **11**, and **12** were screened for in vitro cytotoxicity against a panel of human tumor cell lines. The results are shown in Table 2. Compound **3** exhibited significant activity against MCF-7, 1A9, HCT-8, and SK-MEL-2 cell lines with ED_{50} values of 2.0−2.3 μg/mL, moderate activity against A549, KB, and KB-VIN cell lines with ED_{50} values of 3.0−3.4 μg/mL, and insignificant activity against CAKI-1, U-87-MG, PC-3, and MDA-MB-231 cell lines with ED_{50} values > 4.0 μg/mL. Compound **6** displayed weak inhibitory effects against A549, MCF-7, 1A9, HCT-8, U-87-MG, MDA-MB-231, KB, and KB-VIN tumor cells, with ED_{50} values of 3.2−3.8 μg/mL, and was

Table 2. Cytotoxicity (ED_{50} in μg/mL) of Isoprenylated Flavones against Human Tumor Cell Lines

cell line	**3**	**6**	**7**[a]	**9**[a]	**11**[a]	**12**
A549	3.0	3.3	6.6	6.1	7.2	8.5
MCF-7	2.2	3.3	6.0	6.7	7.7	2.2
1A9	2.0	3.4	NT[b]	NT[b]	NT[b]	<1.25
HCT-8	2.3	3.8	NT[b]	NT[b]	NT[b]	3.3
CAKI-1	5.3	4.9	NT[b]	NT[b]	NT[b]	9.7
SK-MEL-2	2.3	5.4	NT[b]	NT[b]	NT[b]	4.3
U-87-MG	7.2	3.7	NT[b]	NT[b]	NT[b]	6.4
PC-3	4.2	4.1	NT[b]	NT[b]	NT[b]	6.9
MDA-MB-231	6.2	3.8	NT[b]	NT[b]	NT[b]	3.0
KB	3.4	3.2	NT[b]	NT[b]	NT[b]	6.5
KB-VIN	3.4	3.6	NT[b]	NT[b]	NT[b]	>10

[a] ED_{50} values of **7**, **9**, and **11** against A549 and MCF-7 cell growth were >4 μg/mL, not considered to be significant and not further evaluated. [b]NT = not tested.

inactive against CAKI-1, SK-MEL-2, and PC-3 cell lines. Compound **12** exerted strong cytotoxicity against 1A9 (ED_{50} < 1.25 μg/mL), significant activity against MCF-7 (ED_{50} = 2.2 μg/mL), and lower activity against HCT-8 and MDA-MB-231 (ED_{50} values = 3.3 and 3.0 μg/mL, respectively) tumor cell lines. Compounds **7**, **9**, and **11** were not cytotoxic against A549 and MCF-7 cell lines (ED_{50} values = 6.0−7.7 μg/mL) and were not tested further.

Compounds **6** and **12** have two sets of hydrophobic (isoprenoid groups at C-3 or A ring) and hydrophilic groups (hydroxyl groups) at different sites; this structure−activity correlation is similar to SAR conclusions reported previously.[6,18] In compounds **7**, **9**, and **11**, the cyclization between the isoprenyl group at C-3 and the B ring possibly decreased their cytotoxicity. However, further investigation is necessary to fully elucidate the structural determinants for cytotoxic activity.

Experimental Section

General Experimental Procedures. Melting points were measured on an XT-4 micro-melting point apparatus and are uncorrected. Optical rotations were run on a Perkin-Elmer polarimeter 341. UV spectra were obtained from a Shimadzu UV-2401PC spectrophotometer. IR spectral data were recorded on a Nicolet Avatar 360 spectrometer with KBr pellets. NMR spectra were obtained on Bruker DRX-300, 400, and 500 instruments. Chemical shifts were reported with respect to acetone-d_6 (δ_H 2.04, δ_C 206.0 ppm) and DMSO-d_6 (δ_H 2.50, δ_C 39.5 ppm). EIMS were recorded on Agilent 5973N and HP 5989A mass spectrometers. HREIMS and HRESIMS data were obtained on Concept 1H series and AB QSTAR Pulsar mass spectrometers. Column chromatography was performed on silica gel (200−300 mesh, Yantai, People's Republic of China), silica gel H (10−40 μm, Yantai, People's Republic of China), and Lichroprep RP_{18} gel (40−63 μm, Merck, Darmstadt, Germany). TLC analysis was run on GF_{254} precoated silica gel plates (10−40 μm, Yantai, People's Republic of China).

Plant Material. The roots of *A. chama* Buch.-Ham were collected in Xishuangbanna, Yunnan, People's Republic of China, in July 1998, and air-dried. The identity of the plant material was verified by Professor Han-Dong Sun (Kunming Institute of Botany), and a voucher specimen (TCM 98-07 Hou) was deposited in the Herbarium of the Department of Pharmacognosy, School of Pharmacy, Fudan University.

Extraction and Isolation. The dried and powdered roots (5.4 kg) were extracted with EtOH under reflux three times and filtered. The filtrate was evaporated in vacuo to give a residue (642 g), a portion of which (564 g) was suspended in H_2O and partitioned successively with petroleum ether, $CHCl_3$, EtOAc, and *n*-BuOH. Because the $CHCl_3$ extract showed more potent cytotoxicity against A549 and MCF-7 cell lines in vitro than the others, this extract (223 g) was subjected to column

chromatography on Si gel eluted with petroleum ether−acetone (6:1, 4:1, 3:1, 2:1, and 1:1) and acetone to yield fractions 1−10. Fraction 1 (10 g) was chromatographed over Si gel (petroleum ether−ether, 4:1) to give five fractions. The second fraction was eluted with C_6H_6−ether (20:1) on Si gel, followed by RP_{18} (MeOH−H_2O, 85:15) to provide **8** (3 mg). The fourth fraction was separated over Si gel (C_6H_6−EtOAc, 20:1) to yield **7** (28 mg). Fraction 3 (15 g) was purified by column chromatography over Si gel (petroleum ether−EtOAc, 4:1) to afford two fractions. The first was fractionated on Si gel developed with C_6H_6−ether (20:1), petroleum ether−acetone (6:1), and petroleum ether−2-propanol (24:1) to afford **6** (20 mg). The second fraction was eluted with C_6H_6−ether (24:1) and petroleum ether−EtOAc (4:1) over Si gel, followed by passage over RP_{18} (MeOH−H_2O, 6:4) to give **9** (39 mg). Further separation of the second fraction over Si gel ($CHCl_3$−ether, 30:1, and petroleum ether−acetone, 6:1) and RP_{18} (MeOH−H_2O, 6:4) yielded **10** (6 mg) and **1** (39 mg). Fraction 4 (15 g) was purified by column chromatography over Si gel (petroleum ether−ether, 4:1) to provide **11** (186 mg). Fraction 5 (32 g) was isolated over Si gel ($CHCl_3$−ether, 6:1, and C_6H_6−MeOH, 15:1) to give **3** (33 mg) and **12** (15 mg). Fraction 7 (10 g) was fractioned over Si gel (C_6H_6−EtOAc, 6:1) to afford four fractions. The second fraction was repeatedly chromatographed over Si gel (petroleum ether−2-propanol, 15:1), followed by RP_{18} (MeOH−H_2O, 4:1 and 6:4) to yield **2** (15 mg). The third fraction was subjected to column chromatography on Si gel ($CHCl_3$−ether, 6:1, petroleum ether−2-propanol, 10:1, and C_6H_6−EtOAc, 4:1) to provide **4** (40 mg). Fraction 10 (4.5 g) was separated over Si gel (petroleum ether−2-propanol, 15:1) to give two fractions. The first fraction was purified over Si gel (petroleum ether−EtOAc, 4:1) to yield **13** (35 mg). The second fraction was eluted with $CHCl_3$−ether (9:1) and petroleum ether−acetone (4:1) over Si gel to provide **5** (30 mg).

Artochamin A (1): orange prisms (petroleum ether−acetone, 15:1); mp 238−240 °C; $[\alpha]^{20}_D$ 0° (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ϵ) 227 (4.41), 270 (4.39), 282 (sh) (4.34), 407 (4.17) nm; IR (KBr) ν_{max} 3492, 2977, 2913, 1655, 1580, 1556, 1482, 1340, 1305, 1265, 1221, 1179 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 13.00 (1H, s, OH-5), 8.89 (1H, br s, OH), 8.09 (1H, br s, OH), 7.33 (1H, s, H-6′), 6.86 (1H, d, J = 10.0 Hz, H-16), 6.46 (1H, s, H-3′), 6.15 (1H, s, H-6), 6.14 (1H, d, J = 9.0 Hz, H-11), 5.78 (1H, d, J = 10.0 Hz, H-17), 5.51 (1H, br d, J = 9.0, H-12), 1.93 (3H, br s, H_3-15), 1.68 (3H, br s, H_3-14), 1.47 (6H, s, H_3-19, 20); ^{13}C NMR data, see Table 1; EIMS *m/z* 434 $[M]^+$ (38), 419 (100), 401 (10), 391 (2), 379 (45), 363 (17), 337 (2), 321 (3), 217 (3), 203 (13), 182 (7), 153 (4); HREIMS *m/z* 434.1397 $[M]^+$ (calcd for $C_{25}H_{22}O_7$, 434.1366).

Artochamin B (2): yellow amorphous powder; $[\alpha]^{20}_D$ +29° (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ϵ) 201 (3.68), 219 (4.15), 272 (4.11), 400 (3.98) nm; IR (KBr) ν_{max} 3419, 2923, 1652, 1580, 1558, 1506, 1455, 1384, 1254 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 12.84 (1H, s, OH-5), 7.30 (1H, s, H-6′), 6.46 (1H, s, H-3′), 6.31 (1H, s, H-6), 6.13 (1H, d, J = 9.4 Hz, H-11), 5.50 (1H, br d, J = 9.4 Hz, H-12), 5.33 (1H, br t, J = 7.2 Hz, H-17), 3.56 (1H, br dd, J = 7.2, 14.6 Hz, H-16a), 3.40 (1H, br dd, J = 7.2, 14.6 Hz, H-16b), 1.92 (3H, br s, H_3-15), 1.84 (3H, br s, H_3-20), 1.66 (6H, br s, H_3-14, 19); ^{13}C NMR data, see Table 1; EIMS: *m/z* 436 $[M]^+$ (46), 421 (65), 393 (3), 381 (100), 363 (4), 337 (5), 325 (7), 205 (11), 183 (5), 165 (9), 153 (8); HREIMS *m/z* 436.1529 $[M]^+$ (calcd for $C_{25}H_{24}O_7$, 436.1522).

Artochamin C (3): yellow amorphous powder; UV (MeOH) λ_{max} (log ϵ) 236 (4.42), 272 (4.37), 344 (4.17) nm; IR (KBr) ν_{max} 3472, 2920, 1654, 1593, 1560, 1490, 1450, 1342, 1278 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 13.11 (1H, s, OH-5), 9.75 (2H, br s, OH-3′, 4′), 7.48 (1H, br s, H-2′), 7.47 (1H, br d, J = 8.6 Hz, H-6′), 6.92 (1H, d, J = 8.6 Hz, H-5′), 6.84 (1H, d, J = 10.0 Hz, H-11), 6.75 (1H, s, H-3), 6.23 (1H, s, H-6), 5.83 (1H, d, J = 10.0 Hz, H-12), 1.46 (6H, s, H_3-14, 15); ^{13}C NMR data, see Table 1; EIMS *m/z* 352 $[M]^+$ (23), 337 (100), 323 (1), 309 (1), 217 (0.6), 203 (30), 169 (7), 134 (6); HREIMS *m/z* 352.0919 $[M]^+$ (calcd for $C_{20}H_{16}O_6$, 352.0947).

Artochamin D (4): yellow amorphous powder; UV (MeOH) λ_{max} (log ϵ) 202 (3.88), 219 (4.21), 269 (4.29), 303 (3.75), 336 (3.79) nm; IR (KBr) ν_{max} 3380, 3054, 2973, 2916, 2854, 1643, 1599, 1546, 1513, 1472, 1411, 1358, 1265 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 13.08 (1H, s, OH-5), 8.63 (3H, br s, OH-2′, 5′, 7), 6.91 (1H, s, H-6′), 6.71 (1H, s, H-3′), 6.32 (1H, s, H-6), 5.18 (1H, br t, J = 7.3 Hz, H-17), 5.10 (1H, br t, J = 7.0 Hz, H-12), 3.76 (3H, s, OMe-4′), 3.34 (2H, br d, J = 7.3 Hz, H_2-16), 3.05 (2H, br d, J = 7.0 Hz, H_2-11), 1.59 (3H, br s, H_3-19), 1.57 (6H, br s, H_3-14, 20), 1.42 (3H, br s, H_3-15); ^{13}C NMR data, see Table 1; EIMS *m/z* 452 $[M]^+$ (76), 437 (4), 421 (52), 409 (100), 395 (7), 379 (9), 365 (36), 353 (35), 338 (8), 323 (13), 310 (8), 297 (5), 281 (4), 219 (6), 205 (6), 165 (23), 69 (25), 41 (35); HRESIMS *m/z* 453.1926 $[M + H]^+$ (calcd for $C_{26}H_{29}O_7$, 453.1913).

Artochamin E (5): yellow amorphous powder; $[\alpha]^{20}_D$ 0° (*c* 0.25, MeOH); UV (MeOH) λ_{max} (log ϵ) 196 (4.02), 220 (4.30), 255 (4.32), 280 (sh) (4.06), 315 (4.23) nm; IR (KBr) ν_{max} 3405, 2956, 2916, 2847, 1651, 1613, 1553, 1505, 1441, 1365, 1282, 1184 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 13.22 (1H, s, OH-5), 9.29 (2H, br s, OH), 8.29 (1H, br s, OH-2′), 7.15 (1H, br s, OH), 6.56 (1H, s, H-3′), 6.31 (1H, s, H-6), 5.29 (1H, br t, J = 7.5 Hz, H-17), 4.65 (1H, br s, H-15a), 4.32 (1H, br s, H-15b), 4.00 (1H, br d, J = 6.5 Hz, H-12), 3.67 (1H, br dd, J = 7.5, 14.7 Hz, H-16a), 3.44 (1H, br dd, J = 7.5, 14.7 Hz, H-16b), 3.42 (1H, dd, J = 1.5, 16.0 Hz, H-11a), 2.45 (1H, dd, J = 6.5, 16.0 Hz, H-11b), 1.78 (3H, s, H_3-14), 1.76 (3H, br s, H_3-20), 1.61 (3H, br s, H_3-19); ^{13}C NMR data, see Table 1; EIMS: *m/z* 436 $[M]^+$ (27), 421 (21), 393 (5), 380 (100), 365 (24), 337 (67), 327 (12), 309 (23), 297 (5), 281 (6), 165 (16); HRESIMS *m/z* 437.1596 $[M + H]^+$ (calcd for $C_{25}H_{25}O_7$, 437.1600).

Artocarpin (6): yellow amorphous powder; ^1H NMR (acetone-d_6, 500 MHz) δ 13.97 (1H, s, OH-5), 8.84 (2H, s, OH-2′, 4′), 7.22 (1H, d, J = 8.4 Hz, H-6′), 6.72 (1H, dd, J = 7.0, 16.4 Hz, H-17), 6.60 (1H, br d, J = 16.4 Hz, H-16), 6.57 (1H, d, J = 1.7 Hz, H-3′), 6.56 (1H, s, H-8), 6.53 (1H, dd, J = 1.7, 8.4 Hz, H-5′), 5.12 (1H, br t, J = 7.0 Hz, H-12), 3.96 (3H, s, OMe-7), 3.12 (2H, br d, J = 7.0 Hz, H_2-11), 2.43 (1H, br dq, J = 6.7, 7.0 Hz, H-18), 1.57 (3H, br s, H_3-14), 1.43 (3H, br s, H_3-15), 1.08 (6H, d, J = 6.7 Hz, H_3-19, 20); EIMS *m/z* 436 $[M]^+$ (8), 421 (1), 393 (16), 368 (5), 337 (17), 236 (19), 97 (73), 83 (94), 69 (100).

Growth Inhibition Assay. Drug stock solutions were prepared in DMSO and stored at −70 °C. Upon dilution into culture medium, the final DMSO concentration was ≤1% DMSO (v/v), a concentration without effect on cell replication. The human tumor cell line panel consisted of ovarian carcinoma (1A9), ileocecal carcinoma (HCT-8), renal cancer (CAKI-1), melanoma (SK-MEL-2), glioblastoma (U-87-MG), prostate cancer (PC-3), lung carcinoma (A549), breast adenocarcinoma (MCF-7 and MDA-MB-231), epidermoid carcinoma of the nasopharynx (KB), and its subclone (KB-VIN). Cell culture and other procedures were the same as those reported previously.[19]

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Supporting Information Available: 1D NMR and HRMS spectra of **1**−**5** (spectra 1−15), tables of HMQC and HMBC data for **1**−**6** (Tables 1−4), key NOESY correlations of **4** and **6** (Figures 1 and 2), and structures of the known compounds **7**−**13** (Figure 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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