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Antiplasmodial and Cytotoxic Flavans and Diarylpropanes from the Stems of *Combretum griffithii*

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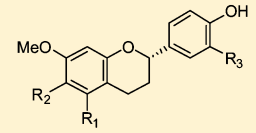
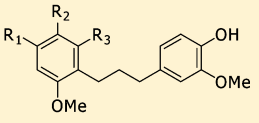
Supporting Information

ABSTRACT: Four new flavans, griffinoids A–D (**1**–**4**), and two new diarylpropanes, griffithanes E and F (**7** and **8**), together with two known flavans (**5** and **6**), four known diarylpropanes, and β-sitosterol, were isolated from the EtOAc extract of the stems of *Combretum griffithii*. Compounds **3**, **4**, **5**, and **9** exhibited weak antiplasmodial activity, with IC_{50} values of 15.74, 13.04, 9.66, and 14.45 μM, respectively. In addition, compounds **4**, **5**, and **8** also exhibited weak cytotoxicity toward one or more cancer cell lines including human epidermoid carcinoma, human breast cancer, and human small cell lung cancer cell lines.

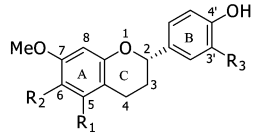


	R_1	R_2	R_3
1:	H	OMe	OMe
2:	H	OH	OMe
3:	H	OMe	OH
4:	H	OH	OH
5:	OMe	H	OMe

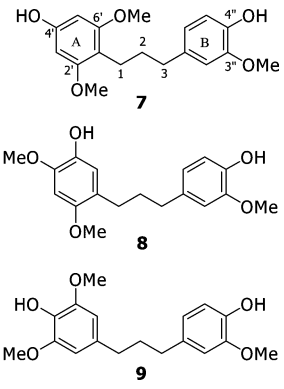


	R_1	R_2	R_3
7:	OH	H	OMe
8:	OMe	OH	H

Polyphenols[1] are important secondary metabolites of plants and comprise a variety of flavonoids that exhibit various biological properties.[2] For example, many flavonoids, such as those isolated from the roots of *Mutingia calabura* and the leaves of *Pithecellobium clypearia*, including flavans, showed cytotoxic activity against several cancer cell lines[3] as well as antiviral activities.[4] In addition, 1,3-diarylpropanes showed antioxidative and anti-inflammatory activities.[5] In our previous study of the stems of *Combretum griffithii* Van Heurck & Müll. Arg. (Combretaceae), diarylpropanes, griffithanes A, B, C, and D, and 1-(2-hydroxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane were isolated from the MeOH extract. Most of them showed cytotoxicity against several cancer cell lines, and the latter compound also showed antimycobacterial activity.[6] As part of our continuous investigation of the bioactive compounds from the EtOAc extract of the stems of *C. griffithii*, we report herein the isolation and structural elucidation of four new flavans (**1**–**4**), two new diarylpropanes (**7** and **8**), and seven known compounds, as well as the bioactivity evaluation of the isolated flavonoids. This is also the first report of the natural occurrence of (2*S*)-**5**.



1: R_1 = H; R_2 = OMe; R_3 = OMe
2: R_1 = H; R_2 = OH; R_3 = OMe
3: R_1 = H; R_2 = OMe; R_3 = OH
4: R_1 = H; R_2 = OH; R_3 = OH
5: R_1 = OMe; R_2 = H; R_3 = OH
6: R_1 = H; R_2 = H; R_3 = OMe



RESULTS AND DISCUSSION

An EtOAc extract of *C. griffithii* was purified by successive chromatographic procedures including silica gel CC and silica gel preparative TLC, as well as Sephadex LH-20 chromatography, to yield four new flavans (**1**–**4**), named griffinoids A–D, two new diarylpropanes, named griffithanes E and F (**7** and **8**), two known flavans, (2*S*)-3′,4′-dihydroxy-5,7-dimethoxyflavan (**5**)[7−9] and (2*S*)-4′-hydroxy-7,3′-dimethoxyflavan (**6**),[10] four known diarylpropanes, 1-(4-hydroxy-3,5-dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane (**9**),[11] 1-(2-hydroxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane, and griffithanes C and D,[6] and a common phytosterol, β-sitosterol.[12]

Compound **1** was obtained as a white solid and was assigned the molecular formula $C_{18}H_{20}O_5$ based on the HRESITOFMS data (observed m/z 339.1203 $[M + Na]^+$), indicating nine indices of hydrogen deficiency. The UV spectrum displayed absorption maxima at 205 and 235 nm due to an aromatic ring. The IR spectrum showed absorption bands corresponding to hydroxy (3408 cm^{-1}) and aromatic (1617 and 1513 cm^{-1}) groups. The ^1H and ^{13}C NMR data (Tables 1 and 2) and a DEPT experiment showed 18 carbon signals attributable to three methyl, two methylene, six methine including five aromatic carbons, and seven nonprotonated aromatic carbons. The ^1H NMR signals of an oxymethine proton at δ_H 4.86 (dd, *J*

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Table 1. ^{1}H NMR Spectroscopic Data (δ_H, ppm) for Compounds 1, 2, and 5 in Methanol-d_4 and Compounds 3 and 4 in $CDCl_3$

position	1	2	3	4	5
2	4.86 dd (10.4, 2.4)	4.84 dd (10.4, 2.4)	4.79 dd (10.0, 2.4)	4.76 dd (10.4, 2.4)	4.78 dd (10.4, 2.0)
3	2.14−1.94 m	2.12−1.97 m	2.09−1.97 m	2.04−1.94 m	2.14−2.06 m and 1.95−1.84 m
4ax	2.89 ddd (16.0, 11.2, 6.0)	2.89 ddd (16.0, 11.6, 6.4)	2.86 ddd (16.0, 11.2, 6.0)	2.79 ddd (16.0, 10.4, 6.4)	2.57 ddd (16.4, 10.8, 6.0)
4eq	2.67 ddd (16.0, 5.6, 2.8)	2.62 ddd (16.0, 5.2, 2.8)	2.65 ddd (16.0, 5.2, 2.8)	2.60 ddd (16.0, 4.8, 2.8)	2.66 ddd (16.4, 5.6, 2.8)
5	6.65 s	6.51 s	6.53 s	6.54 s	
6					6.07 d (2.4)
7					
8	6.44 s	6.41 s	6.41 s	6.37 s	6.02 d (2.4)
2′	6.98 d (1.6)	6.99 d (1.6)	6.87 d (2.0)	6.85 d (2.0)	6.83 d (1.6)
5′	6.77 d (8.2)	6.77 d (8.2)	6.79 d (8.0)	6.77 d (8.0)	6.74 d (8.4)
6′	6.84 dd (8.2, 1.6)	6.84 dd (8.2, 1.6)	6.75 dd (8.0, 2.0)	6.74 dd (8.0, 2.0)	6.70 dd (8.4, 1.6)
OCH_3-5					3.76 s
OCH_3-6	3.75 s		3.77 s		
OCH_3-7	3.75 s	3.77 s	3.75 s	3.74 s	3.71 s
OCH_3-3′	3.84 s	3.85 s			
OH-6		5.18 s[a]			
OH-4′	5.65 s[a]	5.62 s[a]			

[a]Peaks in $CDCl_3$.

Table 2. ^{13}C NMR Spectroscopic Data (δ_C, ppm) for Compounds 1, 2, and 5 in Methanol-d_4 and Compounds 3 and 4 in $CDCl_3$[a]

position	1	2	3	4	5
2	77.7 d	77.6 d	77.7 d	77.7 d	77.5 d
3	29.9 t	30.0 t	29.7 t	29.7 t	29.2 t
4	24.3 t	24.2 t	24.7 t	24.6 t	18.8 t
5	113.2 d	114.8 d	112.4 d	114.5 d	158.4 s
6	143.1 s	139.7 s	142.9 s	139.2 s	90.5 d
7	148.5 s	146.7 s	148.2 s	145.9 s	159.4 s
8	101.1 d	100.4 d	101.0 d	100.4 d	93.3 d
9	149.4 s	148.2 s	149.0 s	148.3 s	156.3 s
10	112.8 s	113.1 s	112.4 s	113.3 s	103.1 s
1′	133.5 s	133.7 s	133.7 s	133.8 s	133.5 s
2′	109.6 d	109.6 d	113.2 d	113.4 d	113.0 d
3′	147.5 s	147.5 s	144.4 s	144.4 s	144.8 s
4′	145.8 d	145.8 d	144.1 s	144.1 s	144.6 s
5′	114.6 s	114.6 s	115.0 d	115.0 d	114.7 d
6′	118.6 d	118.6 d	118.2 d	118.2 d	117.3 d
OCH_3-5					54.4 q
OCH_3-6	55.9 q		56.5 q		
OCH_3-7	55.0 q	55.0 q	55.8 q	55.8 q	54.2 q
OCH_3-8					
OCH_3-3′	55.0 q	55.0 q			

[a]Multiplicities were deduced from DEPT and/or HSQC experiments.

= 10.4, 2.4 Hz, H-2) and two methylene groups at δ_H 2.89 (ddd, J = 16.0, 11.2, 6.0 Hz, H-4$_{ax}$), 2.67 (ddd, J = 16.0, 5.6, 2.8 Hz, H-4$_{eq}$), and 2.14−1.94 (m, H$_2$-3), as well as the COSY correlations from H$_2$-3 to H-2 and H-4, were characteristic of the C ring of a flavan skeleton. In addition, the ^{1}H NMR data revealed signals for five aromatic protons and three methoxy groups. Ring A showed two singlet resonances for two aromatic protons at δ_H 6.65 (s, H-5) and 6.44 (s, H-8), indicating the presence of a 1,2,4,5-tetrasubstituted ring system. The HMBC correlations of methoxy protons at δ_H 3.75 (s, 6H) to C-6 (δ_C 143.1) and C-7 (δ_C 148.5) as well as the NOESY correlations of the methoxy protons to H-5 and H-8 confirmed that ring A contained methoxy groups at C-6 and C-7 (Figure 1). Ring B showed resonances for two doublets and a doublet of doublets

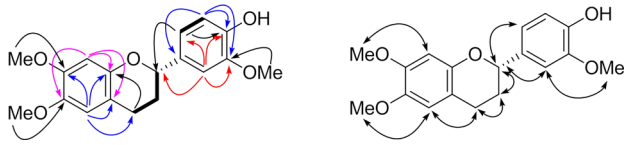

Figure 1. Key HMBC (arrows) and COSY (bold lines) correlations (left) and NOESY correlations (right) for 1.

for three aromatic protons at δ_H 6.98 (d, J = 1.6 Hz, H-2′), 6.77 (d, J = 8.2 Hz, H-5′), and 6.84 (dd, J = 8.2 and 1.6 Hz, H-6′), indicating the presence of a 1,2,4-trisubstituted benzene ring. The HMBC spectrum (Figure 1) showed correlations of H-2′ and H-6′ to C-2, confirming the connectivity of ring B to ring C at C-2. The HMBC correlations of methoxy protons at δ_H 3.84 to C-3′; H-2′ to C-1′, C-3′, C-4′, and C-6′; H-5′ to C-1′, C-3′, and C-4′; and H-6′ to C-2′ and C-4′, and the NOESY correlation of the methoxy protons with H-2′, together with the low-field resonances for C-3′ (δ_C 147.5) and C-4′ (δ_C 145.8) in the ^{13}C NMR spectrum indicated that the methoxy and hydroxy groups were located at C-3′ and C-4′, respectively. Compound 1 exhibited a negative specific rotation [−37.0 (c 0.20, $CHCl_3$)], indicative of its 2S absolute configuration.[8,10] Thus, compound 1 was identified as a new flavan, (2S)-4′-hydroxy-6,7,3′-trimethoxyflavan and was named griffinoid A.

Compound 2 was obtained as colorless needles. The molecular formula of 2, $C_{17}H_{18}O_5$, was established by the HRESITOFMS data (observed m/z 325.1046 [M + Na]$^+$), suggesting nine indices of hydrogen deficiency. The UV and IR spectra were similar to those of 1, and hydroxy and aromatic groups were apparent. The ^{1}H and ^{13}C NMR spectral data (Tables 1 and 2) and a DEPT experiment showed 17 carbon signals, indicating one less methyl carbon than 1. The ^{1}H and ^{13}C NMR data for 2 were similar to those for 1, except for replacement of the C-6 methoxy group in 1 with a hydroxy group in 2. This substitution was confirmed by the HMBC correlations of the hydroxy proton to C-5, C-6, and C-7. The 2S absolute configuration was again confirmed by the negative specific rotation [−30.8 (c 0.27, $CHCl_3$)]. Thus, compound 2 was identified as the new flavan (2S)-6,4′-dihydroxy-7,3′-dimethoxyflavan and was named griffinoid B.

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Compound **3** was obtained as a white solid and showed the same molecular formula ($C_{17}H_{18}O_5$) as compound **2** from the HRESITOFMS data (observed m/z 325.1046 $[M + Na]^+$) as well as similar UV and IR data. The ^1H and ^{13}C NMR data for **3** (Tables 1 and 2) revealed a flavan skeleton similar to **2** with interchange between hydroxy and methoxy groups at C-6 and C-3′. The location of the C-6 methoxy group was confirmed by the NOESY correlations between the methoxy protons at δ_H 3.77 and H-5. The 2*S* absolute configuration was confirmed by the negative specific rotation [−27.4 (*c* 0.37, $CHCl_3$)]. Thus, compound **3** was identified as (2*S*)-3′,4′-dihydroxy-6,7-dimethoxyflavan, which was a new isomer of **2** and was named griffinoid C.

Compound **4** was obtained as a white solid, and the deduced molecular formula was $C_{16}H_{16}O_5$ based on the HRESITOFMS data (observed m/z 311.0890 $[M + Na]^+$). The ^1H and ^{13}C NMR data (Tables 1 and 2) and a DEPT experiment were similar to those of **3**, except for replacement of the C-6 methoxy group in **3** with a hydroxy group in **4**. Thus, **4** is the 6-de-*O*-methyl derivative of **3**. The 2*S* absolute configuration was again confirmed by the negative specific rotation [−33.2 (*c* 0.52, $CHCl_3$)]. On the basis of the above data, compound **4** was identified as the new flavan (2*S*)-6,3′,4′-trihydroxy-7-methoxyflavan and was named griffinoid D.

Compound **5** was identified as (2*S*)-3′,4′-dihydroxy-5,7-dimethoxyflavan via ^1H and ^{13}C NMR data and its negative specific rotation [−53.0 (*c* 0.36, $CHCl_3$)]. Racemic **5** has previously been isolated form *Iryanthera coriaceae*[7] and *Mariscus psilostachys*.[8] The 2*R* and 2*S* enantiomers have been reported as synthetic products in a U.S. patent.[9] This is also the first report of the natural occurrence of (2*S*)-**5**.

Compound **7** was obtained as a white solid and exhibited a molecular formula of $C_{18}H_{22}O_5$, as determined by the HRESITOFMS data (observed m/z 341.1359 $[M + Na]^+$), indicating eight indices of hydrogen deficiency. The presence of aromatic rings was confirmed by the UV (λ_{max} 205 and 280 nm) and IR (1601 and 1514 cm^{-1}) spectra. The IR spectrum also showed a hydroxy absorption band (3384 cm^{-1}). The ^1H and ^{13}C NMR data (Table 3) and a DEPT experiment indicated that **7** and griffithane A[6] were regiometric isomers. A methoxy group at C-5′ of griffithane A was found at C-6′ in **7**. This was supported by HMBC correlations from OCH_3-6′ (δ_H 3.74) to C-6′ (δ_C 158.9). Thus, compound **7** was identified as the new diarylpropane 1-(4-hydroxy-2,6-dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane and was named griffithane E.

Compound **8** was obtained as a red-brown, viscous oil. The molecular formula was assigned as $C_{18}H_{22}O_5$, the same as **7** due to the HRESITOFMS data (observed m/z 319.1540 $[M + H]^+$). The UV and IR spectra were also similar to those of **7**. The ^1H and ^{13}C NMR data (Table 3) and DEPT experiment of **8** were compatible with those of **7**, except for the proton spin patterns of ring A. Ring A of **8** showed two singlets at δ_H 6.73 (s, H-6′) and 6.48 (s, H-3′), indicating that ring A was a 1,2,4,5-tetrasubstituted benzene moiety. This was supported by correlations from H-3′ to C-1′, C-2′, C-4′, and C-5′ and from H-6′ to C-2′, C-4′, and C-5′. The methoxy protons at δ_H 3.77 and 3.87 correlated to C-2′ and C-4′, indicating that the two methoxy groups were located at C-2′ and C-4′. Thus, compound **8** was identified as 1-(5-hydroxy-2,4-dimethoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane, an isomer of **7**, and was named griffithane F.

Table 3. ^1H and ^{13}C NMR Spectroscopic Data (ppm) for Compounds 7 and 8 in $CDCl_3$[a]

	7		8	
position	δ_H	δ_C	δ_H	δ_C
1	2.57 t (8.0)	22.4 t	2.56 t (8.0)	29.1 t
2	1.74 quint (8.0)	31.2 t	1.74 quint (8.0)	31.9 t
3	2.62 t (8.0)	35.5 t	2.58 t (8.0)	35.2 t
1′		111.3 s		123.5 s
2′		158.9 s		150.9 s
3′	6.06 brs	91.9 d	6.48 s	97.0 d
4′		154.9 s		144.6 s
5′	6.06 brs	91.9 d		139.2 s
6′		158.9 s	6.73 s	115.8 d
1″		135.5 s		134.6 s
2″	6.70 brs	111.1 d	6.68 brs	111.0 d
3″		146.2 s		146.3 s
4″		143.3 s		143.5 s
5″	6.82 d (8.0)	114.0 d	6.82 d (8.0)	114.1 d
6″	6.69 brd (8.0)	120.9 d	6.68 brd (6.4)	120.9 d
OCH_3-2′	3.74 s	55.6 q	3.77 s	56.6 q
OCH_3-4′			3.87 s	56.2 q
OCH_3-6′	3.74 s	55.6 q		
OCH_3-3″	3.86 s	55.8 q	3.86 s	55.8 q
OH-4′	5.10 s			
OH-4″	5.50 s			

[a]Multiplicities were deduced from DEPT and/or HSQC experiments. Values in parentheses are coupling constants in Hz.

The EtOAc extract was found to exhibit cytotoxicity against the KB cancer cell line (IC_{50} 14.58 μg/mL), antimycobacterial activity against *Mycobacterium tuberculosis* (MIC 12.5 μg/mL), and antimalarial activity against *Plasmodium falciparum* (IC_{50} 3.52 μg/mL). All isolated compounds were evaluated for biological activities, and the results are summarized in Table 4.

Table 4. Antiplasmodial and Cytotoxic Activities of Compounds 1−9

		cytotoxicity IC_{50} (μM)		
compound	antimalarial IC_{50} (μM)	KB[a]	MCF-7[b]	NCI-H187[c]
1	inactive	105.86	inactive	125.40
2	inactive	69.0	90.07	76.48
3	15.74	43.07	74.95	51.37
4	13.04	24.59	110.13	72.04
5	9.66	31.82	49.15	10.41
6	inactive	97.88	88.39	60.25
7	inactive	49.31	64.17	96.05
8	inactive	24.63	23.12	34.65
9	14.45	45.95	71.96	42.09
dihydroartemisinine[d]	0.001 42			
doxorubicine[d]		0.38	15.88	0.12

[a]Human epidermoid carcinoma of the mouth. [b]Human breast cancer. [c]Human small cell lung cancer. [d]Positive control substances.

Compounds **3**, **4**, **5**, and **9** exhibited antiplasmodial activity against *P. falciparum* with IC_{50} values of 15.74, 13.04, 9.66, and 14.45 μM, respectively. It appeared that hydroxy groups at C-3′ and C-4′ in flavans **3**, **4**, and **5** played an important role for antiplasmodial activity. The data in Table 4 showed that all compounds exhibited weak cytotoxicity against most of the cancer cell lines tested. In particular, **4** displayed cytotoxicity

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against the KB cell line (IC_{50} 24.59 μM), while **5** exhibited cytotoxicity against the NCI-H187 and KB cell lines with IC_{50} values of 10.41 and 31.82 μM, respectively. In addition, **8** showed cytotoxicity against KB and MCF7 cells with IC_{50} values of 24.63 and 23.12 μM, respectively. All compounds were inactive for antimycobacterial activity at 50 μg/mL.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. UV spectra were measured on an Agilent 8453 UV−visible spectrophotometer. Optical rotations were obtained using a JASCO DIP-1000 digital polarimeter. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer. HRESITOFMS data were obtained using a Micromass Q-TOF-Z spectrometer. Column chromatography (CC) was carried out on silica gel 60 (230−400 mesh) and Sephadex LH-20. Preparative TLC was carried out on silica gel PF_{254}.

Plant Material. Stems of *C. griffithii* were collected in July 2011 from Ubonratana District, Khon Kaen Province, Thailand, and were identified by James F. Maxwell from the Department of Biology, Chiang Mai University. A voucher specimen (SRITUBTIM 61) was deposited at the Udon Thani Rajabhat University Herbarium, Thailand.

Extraction and Isolation. Air-dried stems of *C. griffithii* (5.2 kg) were ground and extracted successively at room temperature with EtOAc (3 × 5 L) to produce the crude EtOAc extract (60.5 g).

The EtOAc extract (60.0 g) was separated initially by silica gel CC and eluted with a gradient system of EtOAc−hexanes (200 mL/fraction) to yield six fractions (A−F). Fraction B (17.41 g) was subjected to silica gel CC using EtOAc−hexanes (10−50%, 150 mL/fraction) as the eluent to furnish five subfractions (B1−B5). Subfraction B1 (0.24 g) was purified by silica gel CC using EtOAc−CH_2Cl_2 (0−20%, 30 mL/fraction) as the eluent to yield **6** as colorless needles (EtOAc, 11.3 mg). Subfraction B2 (0.29 g) was rechromatographed on silica gel using EtOAc−hexanes (10−30%, 30 mL/fraction) as an eluent and was further purified by silica gel CC using EtOAc−hexanes (20%, 25 mL/fraction) as the eluent to afford β-sitosterol as needles (EtOAc, 70.6 mg) and **1** as a white solid (26.2 mg). Subfraction B4 was purified by preparative TLC and developed five times with 15% EtOAc−CH_2Cl_2 (R_f = 0.65) to afford **2** as colorless needles (EtOAc, 27.9 mg).

Fraction C (9.01 g) was chromatographed over silica gel using MeOH−CH_2Cl_2 (5−30%, 150 mL/fraction) as eluent to give six subfractions (C1−C6). Subfraction C3 (41 mg) was recrystallized from EtOAc to afford an additional 10.2 mg of **2**. Subfraction C4 (1.21 g) was purified by silica gel CC using EtOAc−hexanes (20%, 70 mL/fraction) as the eluent to yield 1-(2-hydroxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane as a colorless viscous oil (314.8 mg). Subfraction C5 (0.30 g) was subjected to silica gel CC using MeOH−CH_2Cl_2 (5%, 30 mL/fraction) as the eluent to yield **5** as a red-brown, viscous oil (23.2 mg). Subfraction C6 (0.82 g) was separated by silica gel CC using EtOAc−hexanes (50%, 50 mL/fraction) as the eluent to yield **3** (9.45 mg) and **4** (20.9 mg) as white solids.

Fraction D (8.05 g) was subjected to silica gel CC using EtOAc−hexanes (40%, 150 mL/fraction) as the eluent to give five subfractions (D1−D5). Subfraction D1 (1.08 g) was separated by silica gel CC using MeOH−CH_2Cl_2 (5%, 75 mL/fraction) as the eluent and further purified by Sephadex LH-20 CC using MeOH (25 mL/fraction) as the solvent to yield griffithane C as a white solid (10.0 mg) and an additional amount of **2** (15.0 mg). Subfraction D3 (0.16 g) was purified by silica gel CC using MeOH−CH_2Cl_2 (10%, 20 mL/fraction) as the eluent to afford griffithane D as orange needles (MeOH, 65.3 mg). Subfraction D5 (0.76 g) was separated by silica gel CC using MeOH−CH_2Cl_2 (10%, 50 mL/fraction) as an eluent and was further purified by preparative TLC and developed six times with 10% MeOH−CH_2Cl_2 (R_f = 0.65) to yield **7** as a white solid (49.9 mg).

Fraction E (5.56 g) was subjected to silica gel CC using EtOAc−hexanes (25−60%, 150 mL/fraction) as the eluent to give seven subfractions (E1−E7). Preparative TLC of E3 (93 mg) and developing four times with 40% EtOAc−hexanes (R_f = 0.58) yielded **8** (10.3 mg) as a red-brown, viscous oil, and preparative TLC of E5 (165 mg) and developing four times with 10% MeOH−CH_2Cl_2 (R_f = 0.60) yielded **9** (14.1 mg). Subfraction E6 (51 mg) was purified by preparative TLC and developed four times with 12% MeOH−CH_2Cl_2 (R_f = 0.50) to afford an additional amount of 1-(2-hydroxy-4-methoxyphenyl)-3-(4-hydroxy-3-methoxyphenyl)propane (15.6 mg).

*Griffinoid A (**1**):* white, amorphous solid; mp 117−119 °C; $[\alpha]^{20}_D$ −37.0 (*c* 0.20, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 205 (4.57), 235 (3.87), 288 (3.71) nm; IR (film) ν_{max} 3408, 2927, 2852, 1617, 1513, 1453, 1266, 1225, 1194, 1123 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) data, see Table 1; ^{13}C NMR (methanol-d_4, 100 MHz) data, see Table 2; HRESITOFMS *m/z* 339.1203 $[M + Na]^+$ (calcd for $C_{18}H_{20}O_5$ + Na, 339.1208).

*Griffinoid B (**2**):* colorless needles (EtOAc); mp 162−164 °C; $[\alpha]^{20}_D$ −30.8 (*c* 0.27, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 204 (4.72), 233 (3.94), 288 (3.76) nm; IR (film) ν_{max} 3387, 2923, 2848, 1609, 1512, 1451, 1267, 1072, 1028, 853, 817 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) data, see Table 1; ^{13}C NMR (methanol-d_4, 100 MHz) data, see Table 2; HRESITOFMS *m/z* 325.1046 $[M + Na]^+$ (calcd for $C_{17}H_{18}O_5$ + Na, 325.1052).

*Griffinoid C (**3**):* white, amorphous solid; mp 170−172 °C; $[\alpha]^{20}_D$ −27.4 (*c* 0.37, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 204 (4.75), 289 (3.82) nm; IR (film) ν_{max} 3385, 2931, 2847, 1614, 1512, 1445, 1267, 1193, 1119, 1071, 893, 866, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) data, see Table 2; HRESITOFMS *m/z* 325.1046 $[M + Na]^+$ (calcd for $C_{17}H_{18}O_5$ + Na, 325.1052).

*Griffinoid D (**4**):* white, amorphous solid; mp 133−135 °C; $[\alpha]^{20}_D$ −33.2 (*c* 0.52, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 204 (4.86), 289 (3.93) nm; IR (film) ν_{max} 3376, 2925, 2848, 1608, 1511, 1444, 1268, 1233, 1191, 1162, 1115, 1070, 894, 876, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) data, see Table 2; HRESITOFMS *m/z* 311.0890 $[M + Na]^+$ (calcd for $C_{16}H_{16}O_5$ + Na, 311.0895).

*Griffinoid E (**5**):* red-brown, viscous oil; $[\alpha]^{21}_D$ −53 (*c* 0.36, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 205 (5.47), 281 (4.32) nm; IR (film) ν_{max} 3387, 2923, 2848, 1609, 1512, 1451, 1372, 1276, 1197, 1119, 1028, 853, 817 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz) data, see Table 1; ^{13}C NMR (methanol-d_4, 100 MHz) data, see Table 2; HRESITOFMS *m/z* 303.1227 $[M + H]^+$ (calcd for $C_{17}H_{18}O_5$ + H, 303.1232).

*Griffithane E (**7**):* white solid; mp 98 −100 °C; UV (MeOH) λ_{max} (log ε) 205 (4.83), 280 (3.66) nm; IR (film) ν_{max} 3384, 2986, 2840, 1601, 1514, 1469, 1269, 1194, 1151, 1123, 1033, 995, 815, 791 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$, 400 and 100 MHz) data, see Table 3; HRESITOFMS *m/z* 341.1359 $[M + Na]^+$ (calcd for $C_{18}H_{22}O_5$ + Na, 341.1365).

*Griffithane F (**8**):* red-brown, viscous oil; UV (MeOH) λ_{max} (log ε) 203 (5.99), 232 (4.28), 289 (4.11) nm; IR (film) ν_{max} 3384, 3002, 2936, 2840, 1599, 1514, 1469, 1428, 1268, 1192, 1148, 1122, 1031, 994, 814, 791 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$, 400 and 100 MHz) data, see Table 3; HRESITOFMS *m/z* 319.1540 $[M + H]^+$ (calcd for $C_{18}H_{22}O_5$ + H, 319.1545).

Antimalarial Assay. Antimalarial activity was evaluated in vitro against the parasite *Plasmodium falciparum* (K1, multidrug-resistant strain) using the method of Trager and Jensen.[13] The in vitro antimalarial activity was quantified using the microculture radioisotope technique based on the method described by Desjardins et al.[14] The inhibitory concentration (IC_{50}) represents the concentration that caused a 50% reduction in parasite growth as indicated by the in vitro uptake of $[^3H]$-hypoxanthine by *P. falciparum*. The standard compound dihydroartemisinin exhibited an IC_{50} value of 1.42 nM, and the maximum final concentration of tested sample for antimalarial activity was 10 μg/mL.

Antimycobacterial Assay. Antimycobacterial activity was assessed against *Mycobacterium tuberculosis* H37Ra using the microplate Alamar Blue assay (MABA).[15] The standard drug isoniazid

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showed MIC values of 0.68 μM, and the highest test concentration for anti-TB was 50 μg/mL.

Cytotoxicity Assay. Cytotoxicity assays using human epidermoid carcinoma (KB), human breast cancer (MCF7), and human small cell lung cancer (NCI-H187) cell lines were performed employing the colorimetric method described by Skehan and co-workers.[16] The reference substance was doxorubicin (Table 4), and the maximum final concentration of tested sample for cytotoxicity against cancer cell lines was 50 μg/mL.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for **1**−**5**, **7**, and **8** are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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