Triterpene-Farnesyl Hydroquinone Conjugates from *Ganoderma sinense*

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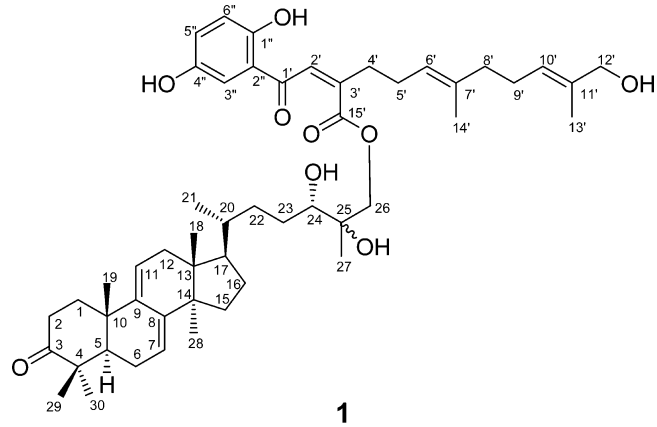
Three new lanostane-type triterpenoids having farnesyl hydroquinone moieties, named ganosinensins A−C (**1**−**3**), were isolated from the fruiting body of *Ganoderma sinense*, together with three known lanostane triterpenes, ganodermanontriol, ganoderiol A, and ganoderiol D. The structures of compounds **1**−**3** were determined by spectroscopic data interpretation.

Lanostane-type triterpenoids are known to be common secondary metabolites from *Ganoderma* species. In the past three decades, over 150 lanostane triterpenoids have been isolated and characterized from *Ganoderma* species,[1−3] and their biological activities include anti-HIV-1 protease,[4,5] anti-5α-reductase,[6] antihistamine,[7] anticomplement,[8] and anticholesterol effects,[9] as well as cytotoxicity to cancer cells.[10,11] In addition, some *Ganoderma* species have been reported to contain prenyl hydroquinones, such as ganoderma aldehyde and applanatins A and B from *G. applanatum* (Fr.) Pat,[12,13] ganomycins A and B from *G. pfeifferi* (Fr.) Bresadola,[14] and fornicins A−C from *G. fornicatum* (Fr.) Pat.[15] Among the *Ganoderma* species, *G. lucidum* Karst. and *G. sinense* Zhao, Xu et Zhang. are designated as important medicinal fungi referred to as "Lingzhi" (Ganoderma) in the Chinese Pharmacopoeia. Many chemical studies have been carried out on *G. lucidum,*[16,17] but few studies have been conducted on *G. sinense.*[18−20] In this study, we have investigated the chemical constituents of the fruiting bodies of *G. sinense* and isolated three new triterpenes, called ganosinensins A−C (**1**−**3**), in which ganoderma alcohols are esterified with farnesyl hydroquinone moieties. Three known lanostane triterpenes, ganodermanontriol,[21] ganoderiols A,[22] and ganoderiol D,[23] were also obtained. The triterpenes having a farnesyl hydroquinone moiety have been isolated for the first time. The structure elucidation of the new compounds **1**−**3** is described in this paper.

Repeated column chromatography of a chloroform extract of the fruiting bodies of *G. sinense* resulted in the isolation of three new triterpenoids (**1**−**3**) and three known compounds. The known compounds have previously been isolated from *G. lucidum* and were identified by comparing their spectroscopic data with those reported.

Ganosinensin A (**1**) was obtained as a yellow, amorphous powder. The molecular formula of **1** was determined as $C_{51}H_{72}O_9$ by HRFABMS (*m/z* 827.5102 $[M - H]^-$, calcd for $C_{51}H_{71}O_9$, 827.5098). The IR spectrum showed the presence of carbonyl (1700 cm^{-1}) and aryl (1000, 1050, and 1120 cm^{-1}) groups. The UV spectrum showed the presence of a conjugated system (λ_{max} 246, 254 nm). The ^1H NMR spectrum exhibited eight methyl singlets, one methyl doublet, and one hydroxyl group having an intramolecular hydrogen bond (δ_H 11.43). The ^{13}C NMR spectrum exhibited 51 carbon signals that were assigned by a DEPT experiment as nine methyls, 14 methylenes (including two oxymethylenes at δ_C 68.6 and 69.6), 12 methines (including an oxymethine at δ_C 77.2), and 16 nonprotonated carbons, including a quaternary carbon substituted by oxygen at δ_C 73.9, a carboxylic carbon at δ_C 168.3, and two carbonyl carbons at δ_C 195.3 and 216.9. The ^1H and ^{13}C NMR signals for the aliphatic part of the structure of compound **1** resembled those of triterpenes. Detailed analysis of the 2D NMR spectra of **1** established that the triterpene moiety in the structure of **1** corresponded to ganodermanontriol.[21] On the basis of $^1H-^1H$ COSY and HMQC spectroscopic evidence, the presence of a farnesyl group in the structure of **1** was suggested, and this was confirmed by HMBC correlations between the allylic methyl groups and the corresponding methylene and methine carbons (Figure 1a). The characteristic ABX-type signals for the aromatic protons in the ^1H NMR spectrum indicated the presence of a 1,2,4-trisubstituted phenyl ring.[24,25] The linkage sites of the triterpene, farnesyl, and phenyl moieties were determined by HMBC, in which H-3″ at δ_H 7.11 (d, $J = 1.5$ Hz) was correlated with the carbonyl C-1′ carbon of the farnesyl moiety at δ_C 195.3. The HMBC correlations



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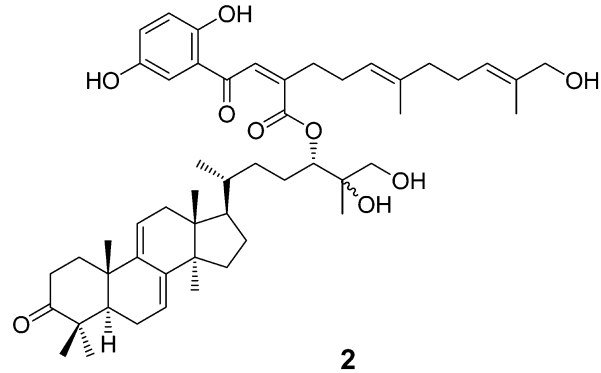

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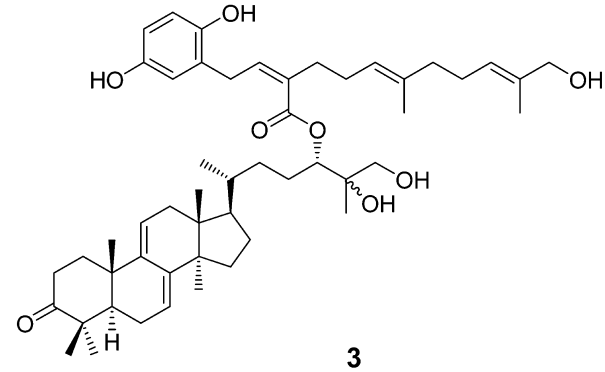

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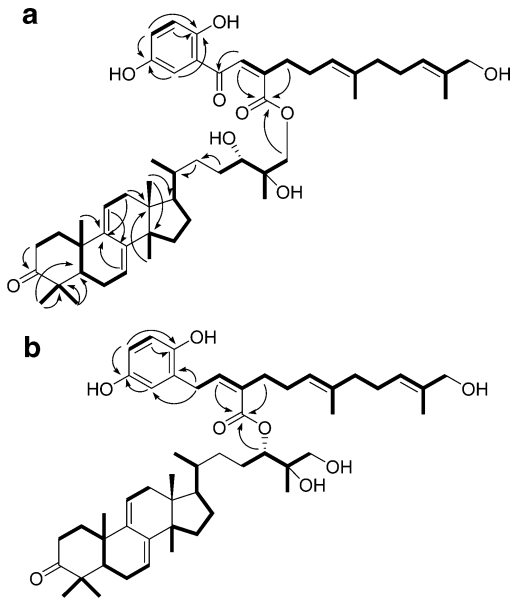

Figure 1. (a) Selected 2D correlations for ganosinensin A (**1**). ^{1}H−^{1}H COSY: bold lines; HMBC: arrows (selected). (b) Selected 2D correlations for ganosinensin C (**3**). ^{1}H−^{1}H COSY: bold lines; HMBC: arrows (selected).

of H-26 (δ_H 4.03 and 4.41) with C-15′ (δ_C 168.3) suggested that the ganodermanontriol unit and the 2-(2-(2,5-dihydroxyphenyl)-2-oxoethylidene)-11-hydroxy-6,10-dimethylundeca-5,9-dienoic acid unit (called oxoganomycin A unit) are conjugated through an ester linkage (C-26 to C-15′). The configurations of the olefin of **1** were determined on the basis of NOESY data, in which H-2′, H-4′, H-6′, H-8′, H-10′, and H-12′ showed NOE correlations, each with its neighboring proton(s). These findings suggested that the configurations of the C-2′−3′, C-6′−7′, and C-10′−11′ double bonds are *Z*, *E*, and *E*, respectively. Accordingly, ganosinensin A was determined to be **1** as shown.

The molecular formula of ganosinensin B (**2**) was determined as $C_{51}H_{72}O_9$ by HRFABMS (*m*/*z* 827.5094 [M − H]$^-$ calcd for $C_{51}H_{71}O_9$, 827.5098). The ^{1}H NMR spectrum was very similar to that of compound **1** except for the H-24 and H-26 signals (Table 1). In the HMBC spectrum, the correlation of H-24 (δ_H 4.85) with C-15′ (δ_C 169.0) suggested that the oxoganomycin A unit was esterified with ganodermanontriol through a C-24 and C-15′ linkage in this structure. The configuration of **2** was determined by the same method as that for **1**. Accordingly, the structure of ganosinensin B was assigned as shown in **2**.

Hydrolysis of **1**- and **2**-rich fractions under either alkaline or acidic conditions was attempted to confirm the configuration of the triterpene moiety and to obtain the farnesyl hydroquinone unit. The farnesyl hydroquinone moiety could not be obtained due to its instability under these conditions, but the triterpene unit was easily recovered. The structure of this product was confirmed to be

Table 1. ^{1}H NMR Data (500 MHz) of **1**−**3** (in $CDCl_3$)

position	**1** δ_H	**2** δ_H	**3** δ_H
1	2.25 m	2.27 m	2.26 m
	1.75 dt, *J* = 14.5, 5.5 Hz	1.75 dt, *J* = 14.5, 5.5 Hz	1.75 m
2	2.34 m	2.36 m	2.35 m
	2.77 dt, *J* = 14.5, 9.0 Hz	2.77 dt, *J* = 14.5, 9.0 Hz	2.78 dt, *J* = 14.5, 9.0 Hz
5	1.55 dd, *J* = 11.5, 4.0 Hz	1.53 dd, *J* = 11.5, 4.0 Hz	1.53 m
6	2.05 m	2.05 m	2.05 m
	2.31 m	2.24 m	2.22 m
7	5.38 d, *J* = 6.5 Hz	5.39 d, *J* = 5.5 Hz	5.38 d, *J* = 4.5 Hz
11	5.50 d, *J* = 6.5 Hz	5.49 d, *J* = 6.5 Hz	5.49 d, *J* = 4.5 Hz
12	2.10 m	2.10 m	2.09 m
	2.18 m	2.21 m	2.19 m
15	1.34 m	1.32 m	1.35 m
	1.97 m	1.92 m	1.92 m
16	1.38 m	1.36 m	1.38 m
	1.61 m	1.62 m	1.61 m
17	1.57 m	1.57 m	1.57 m
18	0.58 s	0.57 s	0.58 s
19	1.19 s	1.19 s	1.19 s
20	1.75 m	1.75 m	1.75 m
21	0.89 d, *J* = 6.5 Hz	0.88 d, *J* = 6.5 Hz	0.90 d, *J* = 6.5 Hz
22	1.06 m	1.48 m	1.48 m
	1.76 m	1.61 m	1.61 m
23	1.14 m	1.31 m	1.32 m
	1.62 m	1.93 m	1.93 m
24	3.34 d, *J* = 9.0 Hz	4.87 d, *J* = 8.5 Hz	5.01 d, *J* = 8.5 Hz
26	4.03 d, *J* = 11.5 Hz	3.24 d, *J* = 12.5 Hz	3.34 d, *J* = 11.5 Hz
	4.41 d, *J* = 11.5 Hz	3.61 d, *J* = 12.5 Hz	3.52 d, *J* = 11.5 Hz
27	1.12 s	0.98 s	1.14 s
28	0.87 s	0.86 s	0.86 s
29	1.13 s	1.13 s	1.13 s
30	1.09 s	1.08 s	1.09 s
1′			3.62 d, *J* = 8.5 Hz
2′	6.72 s	6.73 s	5.97 t, *J* = 8.5 Hz
4′	2.51 t, *J* = 7.0 Hz	2.51 t, *J* = 6.5 Hz	2.26 m
5′	2.30 m	2.33 m	2.09 m
6′	5.17 t, *J* = 7.0 Hz	5.18 t, *J* = 7.0 Hz	4.99 t, *J* = 7.0 Hz
8′	2.08 m	2.09 m	1.91 m
9′	2.14 m	2.17 m	2.14 m
10′	5.42 t, *J* = 7.0 Hz	5.42 t, *J* = 6.5 Hz	5.30 t, *J* = 7.0 Hz
12′	3.99 s	4.00 s	3.99 s
13′	1.63 s	1.63 s	1.63 s
14′	1.63 s	1.64 s	1.52 s
3″	7.11 d, *J* = 1.5 Hz	7.10 d, *J* = 1.5 Hz	6.62 d, *J* = 1.5 Hz
5″	6.87 dd, *J* = 9.0, 1.5 Hz	6.87 dd, *J* = 9.0, 1.5 Hz	6.59 dd, *J* = 9.0, 1.5 Hz
6″	7.06 d, *J* = 9.0 Hz	7.05 d, *J* = 9.0 Hz	6.68 d, *J* = 9.0 Hz
1″-OH	11.43 s	11.41 s	

ganodermanontriol by comparison of ESI-MS, ^{1}H NMR, and ^{13}C NMR data with those of an authentic sample.[21]

Ganosinensin C (**3**) was obtained as a yellow, amorphous powder. The molecular formula of **3** was determined as $C_{51}H_{74}O_8$ by HRFABMS (*m/z* 813.5333 [M − H]$^-$, calcd for $C_{51}H_{71}O_9$, 813.5305). The ^{1}H NMR spectrum was similar to that of compound **2** except for some of the signals for a partial farnesyl hydroquinone moiety (Table 1). The absence of a carbonyl signal (δ_C 195.5) and a conjugated carbonyl absorption (1640 cm^{-1}) in the ^{13}C NMR and IR spectra of **3**, compared to those of **2**, and the difference in molecular formula suggested that a farnesyl acid is present in **3**, instead of an oxofarnesyl acid as in **2**. This was further confirmed from the HMBC spectrum, in which three olefinic protons at δ_H 6.59 (H-5″), 6.62 (H-3″), and 6.68 (H-6″) showed long-range correlations with C-1″ (δ_C 128.0) and C-4″ (δ_C 151.2), while the signal at δ_H 6.62 (H-3″) showed long-range correlations with a carbon signal at δ_C 31.8 (C-1′), indicating an α-methylene hydroquinone moiety as a partial structure (Figure 1b).[25] The configuration of **3** was determined by the same method as that for **1**. The structure of the farnesyl hydroquinone moiety matched that of ganomycin A. Accordingly, ganosinensin C (**3**) was determined to be an ester of ganomycin A with ganodermanontriol.

Since these triterpene-farnesyl hydroquinone conjugates were detected in the methanol extract obtained under mild conditions, they must be natural products rather than artifacts formed through extraction processes. However, we cannot exclude a possibility of transesterification between **1** and **2**.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. UV spectra were measured with a UV-2200 UV−vis recording spectrophotometer (Shimadzu Co., Kyoto, Japan). IR spectra were measured with a JASCO FT/IR-230 infrared spectrometer. NMR spectra were measured with a Varian Unity 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) NMR spectrometer. TMS was used as an internal standard, and *J* values were reported in hertz. HRFABMS were measured on a JEOL JMS-AX505HAD apparatus with a resolution of 5000 and with *m*-nitrobenzyl alcohol as matrix. Preparative HPLC was performed on a Tosoh CCPM- II system (Tosoh Co., Tokyo, Japan) equipped with a UV 8020 detector and a Cholester Waters HPLC column (20 × 250 mm). Column chromatography was carried out on BW-820MH silica gel (Fuji Silica Chemical Co. Aichi, Japan) or Wakogel 50C18 (38−63 μm, Wako Pure Chemical Industries, Ltd.).

Plant Material. *Ganoderma sinense* Zhao, Xu et Zhang was purchased at Mei-Lingzhi in Hehuachi crude drug market for medicinal herbs (Chengdu, China) on August 2007 and identified by Dr. De-Yuan Chen, Guiyang College of Traditional Chinese Medicine, Guiyang, China. A voucher specimen (TMPW No. 25617) is deposited at the Museum of Materia Medica, University of Toyama, Japan.

Extraction and Isolation. Dried and chopped *G. sinense* (2.5 kg) was extracted with $CHCl_3$ (each 10 L) by refluxing for 9 h (3 h × 3 times) to give 61 g of a crude extract. The crude extract (60 g) was applied to a silica gel column (6 × 60 cm) and eluted with hexane−acetone (9:1; Fr. 1, 18.3 g), hexane−acetone (7:3; Fr. 2, 16.7 g), and $CHCl_3$−MeOH (1:2; Fr. 3, 16.2 g). Fr. 2 was subjected to silica gel column chromatography with a $CHCl_3$−MeOH gradient solvent system (100:0 → 0:100) to yield six fractions. Fr. 2-2 was crystallized from MeOH to afford ganoderiol A (40 mg). Fr. 2-4 was crystallized from hexane to yield ganodermanontriol (1.2 g). Fr. 2-6 was subjected to ODS column chromatography with a H_2O−MeOH gradient solvent system to provide **1**-rich (2-6-2a, 800 mg) and **2**-rich fractions (2-6-2b, 1 g). Further separation by preparative HPLC (Cholester column; MeOH−0.1% TFA/H_2O, 5 mL/min) of Fr. 2-6-2a and Fr. 2-6-2b (H_2O−MeOH, 15:85) gave compounds **1** (40 mg) and **2** (50 mg). Fr. 3 was subjected to silica gel column chromatography with a $CHCl_3$−MeOH gradient solvent system (100:0 → 0:100) to give nine fractions. Then, Fr. 3-6 was combined and subjected to ODS column chromatography with a H_2O−MeOH gradient solvent system to provide three fractions. Further separation by preparative HPLC (cholester column; MeOH−0.1% TFA/H_2O, 5 mL/min) of Fr. 3-6-2 (MeOH−H_2O, 85:15) gave compound **3** (40 mg), and that of Fr. 3-6-1 (H_2O−MeOH, 30:70) yielded ganoderiol D (30 mg).

Table 2. ^{13}C NMR Data (500 MHz) of **1**−**3** (in $CDCl_3$)

position	**1** δ_C	**2** δ_C	**3** δ_C
1	36.7	36.6	36.6
2	34.9	34.8	34.8
3	216.9	217.0	217.0
4	47.5	47.5	47.5
5	50.7	50.8	50.8
6	23.7	23.6	23.6
7	119.4	119.4	119.4
8	142.7	142.8	142.7
9	144.3	144.4	144.4
10	37.2	37.2	37.1
11	117.2	117.3	117.2
12	37.7	37.7	37.7
13	43.8	43.7	43.7
14	50.3	50.3	50.2
15	27.8	27.8	27.8
16	31.5	31.5	31.4
17	50.9	50.8	50.7
18	15.8	15.7	15.7
19	22.1	22.0	22.0
20	36.5	36.4	36.5
21	18.7	18.5	18.5
22	33.5	33.1	33.1
23	29.8	25.8	25.7
24	77.2	78.8	76.8
25	73.9	73.6	73.5
26	69.6	66.5	68.7
27	20.3	18.1	18.3
28	25.4	25.3	25.3
29	22.5	22.5	22.4
30	25.5	25.4	25.4
1′	195.3	195.5	31.8
2′	126.6	127.8	140.6
3′	146.3	145.2	133.3
4′	34.6	34.5	35.9
5′	25.5	25.6	28.5
6′	122.1	122.1	124.6
7′	136.6	136.9	136.7
8′	39.1	39.0	38.9
9′	25.5	25.6	27.3
10′	125.3	125.5	126.8
11′	134.4	134.5	135.8
12′	68.6	68.7	69.0
13′	13.9	13.8	13.7
14′	16.3	16.2	16.2
15′	168.3	169.0	172.3
1″	157.0	157.1	128.0
2″	114.9	112.7	149.3
3″	117.2	117.3	114.8
4″	148.1	148.2	151.2
5″	126.1	126.0	116.9
6″	119.8	119.8	117.8

Ganosinensin A (ganodermanontriol 26-*O*-{(2*Z*,5*E*,9*E*)-2-[2-(2,5-dihydroxyphenyl)-2-oxo-ethylidene]-11-hydroxy-6,10-dimethylundeca-5,9-dienate}, 1): yellow, amorphous powder; $[\alpha]^{23}_D$ +19.1 (*c* 0.46, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 246 (4.3), 254 (4.2), 380 (3.4) nm; IR (KBr) ν_{max} 3450, 2930, 2850, 1720, 1700, 1650, 1460, 1380, 1300, 1230, 1180, 1110, 1070, and 1000 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; HRFABMS, *m/z* 827.5102 [M − H]$^-$ (calcd for $C_{51}H_{71}O_9$, 827.5104).

Ganosinensin B (ganodermanontriol 24-*O*-{(2*Z*,5*E*,9*E*)-2-[2-(2,5-dihydroxyphenyl)-2-oxo-ethylidene]-11-hydroxy-6,10-dimethylundeca-5,9-dienate}, 2): yellow, amorphous powder; $[\alpha]^{23}_D$ +22.1 (*c* 0.63, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 246 (4.4), 254 (4.3), 377 (3.5) nm; IR (KBr) ν_{max} 3450, 2930, 2850, 1720, 1700, 1640, 1480, 1460, 1370, 1300, 1230, 1190, 1120, 1050, and 1000 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; HRFABMS, *m/z* 827.5094 [M − H]$^-$ (calcd for $C_{51}H_{71}O_9$, 827.5104)

Ganosinensin C (ganodermanontriol 24-*O*-{(2*Z*,5*E*,9*E*)-2-[2-(2,5-dihydroxyphenyl)ethylidene]-11-hydroxy-6,10-dimethylundeca-5,9-

dien-ate}, 3): yellow, amorphous powder; $[\alpha]^{23}_{D}$ +30.1 (*c* 0.72, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ϵ) 246 (4.4), 254 (4.3), 295 (3.6) nm; IR (KBr) ν_{max} 3400, 2930, 2880, 1700, 1460, 1380, 1230, 1210, 1180, 1110, 1070, and 1000 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) data, see Tables 1 and 2; HRFABMS, *m/z* 813.5333 $[M - H]^-$ (calcd for $C_{51}H_{71}O_9$, 813.5311).

Hydrolysis of Compounds 1 and 2. $NaHCO_3$ (320 mg) was added to a 100 mL flask containing compound **1** or **2** (ca. 200 mg) dissolved in 35 mL of EtOH and 12 mL of H_2O. The mixture was refluxed for 45 min, and then the solution was adjusted to pH 6 with 1 N HCl. After evaporating the EtOH, the solution was chromatographed on a column of ODS with a H_2O−MeOH gradient solvent system to yield ganodermanontriol (20 mg, H_2O−MeOH, 20:80).[21]

HPLC Analysis. Dried and chopped *G. sinense* (1 g) was extracted with methanol (20 mL) at room temperature for 15 min to give a crude extract. The extract was filtered through a 0.45 μm Millipore filter and applied to HPLC (column: Toso TSKgel ODS-80Ts column (4.6 i.d. × 150 mm, mobile phase: 1% AcOH/H_2O−CH_3CN; 0 min 20:80; 60 min 0:100, detecting wavelength: 246 nm). On the HPLC chromatogram, three obvious peaks at retention times of 42.1 (**3**), 47.4 (**1**), and 50.3 (**2**) min were observed and confirmed to be compounds **1**−**3**.

Supporting Information Available: ^1H NMR spectra of the new compounds and HPLC profile of a methanol extract of *G. sinense*. This material is available free of charge via the Internet at http://pubs.acs.org.

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