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Short communication

Paeonidanins F–H: Three new dimeric monoterpene glycosides from *Paeonia lactiflora* and their anti-inflammatory activity

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ABSTRACT

Three new dimeric monoterpene glycosides, paeonidanins F–H (**1**–**3**) were isolated from the roots of *Paeonia lactiflora*. Their structures were elucidated on the basis of spectroscopic evidence and hydrolysis products. Compounds **1**–**3** showed inhibitory effects against nitric oxide (NO) and pro-inflammatory cytokine TNF-α release in LPS-induced RAW 246.7 macrophages.

1. Introduction

Substantial efforts have been put on the investigation of "cage-like" monoterpene glycosides in past decades due to their production of diversified structures and biological activities. Many "cage-like" monoterpene derivatives were isolated and reported from plants, such as from genus *Paeonia*. These compounds exhibited anticoagulant, anti-inflammatory, antihyperglycemic, analgesic, and antithrombotic activities (He et al., 2004; Tsuboi et al., 2004; Duan et al., 2009; Fu et al., 2013).

Paeonia lactiflora Pall. is a well-known ornamental plant with ornate flowers blooming in spring in mainland China. Its dried roots have been used in traditional Chinese medicine for a long time, with claims being made of its antispasmodic, anti-inflammatory, tonic, astringent, and analgesic properties (Baumgartner et al., 2010). Previous chemical investigations on this plant afforded a series of monoterpene derivatives (Wang et al., 2009; Fu et al., 2013; Zou et al., 2015). In our continuing effort to seek the interesting monoterpenes from genus *Paeonia*, a re-investigation on the roots of *P. lactiflora* led to the discovery of three new dimeric analogues, paeonidanins F–H.

Herein, we report the isolation and structure elucidation, and anti-inflammatory activity of these compounds.

2. Results and discussion

The EtOH extract of dried roots of *P. lactiflora* was subjected to silica gel column chromatography and prep-HPLC to obtain three new compounds (**1**–**3**). Their structures were elucidated on the basis of spectroscopic evidence and hydrolysis products. The inhibitory effects against nitric oxide (NO) and pro-inflammatory cytokine TNF-α release in LPS-induced RAW 246.7 macrophages of all compounds were also evaluated.

The molecular formula of compound **1** was found to be $C_{46}H_{54}O_{21}$ [$(M-H)^-$, *m/z* 941.3072, calcd for $C_{46}H_{53}O_{21}$, 941.3079] by HR-ESIMS. The ^1H, ^{13}C NMR (Table 1) and heteronuclear multiple quantum coherence (HMQC) spectra of **1** revealed that **1** contained two methyl groups (C-10 and C-10‴), four methylenes (C-3, C-7, C-3‴, and C-7‴), four oxymethylene (C-8, C-6′, C-8‴, and C-6‴), two methines (C-5 and C-5‴), ten oxymethines (C-9, C-2′–C-5′, C-2‴–C-5‴, and C-4‴), two anomeric carbons (C-1′ and C-1‴), ten aromatic carbons (C-2″–C-6″, and C-2⁗–C-6⁗), two quaternary aromatic carbons (C-1″, and C-1⁗), four quaternary oxygenated carbons (C-1, C-2, C-1‴, and C-2‴) and two quaternary carbons (C-6, and C-6‴), one carbonyl carbon (C-4), and three ester carbons (C-7″, C-7⁗, and C-9‴).

A detailed analysis of the ^1H–^1H correlated spectroscopy (COSY) spectrum of **1** allowed to elucidate the following six partial structures: C-5–C-7, C-1′–C-3′, C-2″–C-6″, C-5‴–C-7‴, C-1⁗–C-3⁗, and C-2⁗–C-6⁗. The heteronuclear multiple bond correlations (HMBC) 3H-10/C-1, C-2 and C-3; H-5/C-6, C-7 and C-8; H_b-7/C-1, C-5 and C-6; 2H-8/C-5, C-6 and C-9; and H-9/C-6 (Fig. 2) indicated that the partial structure of C-1–C-10 was the same as the

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Table 1
^{1}H spectral data of compounds **1** and **2** (500 MHz, in CD_3OD).

Position	1 δ_H	2 δ_H		1 δ_H	2 δ_H
3a	2.51 d (18.0)	2.50 d (18.0)	3‴ a	2.01 d (12.0)	2.01 d (12.0)
3b	2.94 d (18.0)	2.93 d (18.0)	3‴ b	2.80 d (12.0)	2.79 d (12.0)
5	2.84 d (5.0)	2.85 d (4.5)	4‴	4.24 d (5.0)	4.23 d (5.0)
7a	1.88 d (12.0)	1.86 d (12.0)	5‴	2.92 m	2.91 m
7b	2.92 dd (12.0, 5.0)	2.91 dd (12.0, 4.5)	7‴a	2.05 d (15.0)	2.03 d (14.0)
8a	4.71 d (12.5)	4.71 d (12.0)	7‴b	2.39 dd (15.0 5.0)	2.38 dd (14.0 5.0)
8b	4.81 d (12.5)	4.81 d (12.0)	8‴a	4.66 d (12.0)	3.95 s 2H
9	5.32 s	5.32 s	8‴b	4.80 d (12.0)	
10	1.41 s 3H	1.40 s 3H	10‴	1.52 s 3H	1.51 s 3H
1′	4.57 d (7.5)	4.55 d (7.0)	1⁗	4.22 d (7.5)	4.20 d (7.0)
2′	3.15 dd (9.0, 7.5)	3.16 dd (9.0, 7.0)	2⁗	3.12 dd (9.0, 7.5)	3.13 dd (9.0, 7.0)
3′	3.32 dd (9.0, 7.5)	3.33 dd (9.0, 7.0)	3⁗	3.24 dd (9.0, 7.5)	3.22 dd (9.0, 7.5)
4′	3.14 m	3.12 m	4⁗	3.20 m	3.19 m
5′	3.22 m	3.20 m	5⁗	3.22 m	3.21 m
6′a	3.61 dd (12.0, 6.0)	3.61 dd (12.0, 6.0)	6⁗a	3.68 dd (12.0, 6.0)	3.68 dd (12.0, 6.0)
6′b	3.89 dd (12.0, 2.0)	3.89 dd (12.0, 2.0)	6⁗b	3.78 dd (12.0, 2.0)	3.78 dd (12.0, 2.0)
2″,6″	8.01 d (7.5) 2H	8.02 d (7.5) 2H	2⁗⁗,6⁗⁗	8.06 d (7.5) 2H	
3″,5″	7.49 t (7.5) 2H	7.49 t (7.5) 2H	3⁗⁗,5⁗⁗	7.47 t (7.5) 2H	
4″	7.58 t (7.5)	7.57 t (7.5)	4⁗⁗	7.60 t (7.5)	

corresponding section of paeonidanin (Okasaka et al., 2008). The HMBC signals between 3H-10‴/C-1‴, C-2‴ and C-3‴; H-5‴/C-4‴, C-6‴ and C-9‴; 2H-8‴/C-5‴and C-9‴; and H-4‴/C-3‴, C-5‴ and C-7‴(Fig. 2) indicated the presence of partial structure of albiflorin (Yen et al., 2007). The ^{1}H and ^{13}C NMR data as well as acid hydrolysis and GC comparison with an authentic sample indicated the presence of a D-glucose moiety. The β-configuration of the glycosidic linkage was determined from the coupling constant of the anomeric proton. Sugar-aglycone linkages were determined by HMBC data analysis.

The signals at δ_C 131.2 (C-1″), 130.6 (C-2″, C-6″), 129.6 (C-3″, C-5″), 134.2 (C-4″) and 167.7 (C-7″), and 131.2 (C-1⁗), 130.6 (C-2⁗, C-6⁗), 129.6 (C-3⁗, C-5⁗), 134.2 (C-4⁗) and 167.8 (C-7⁗) disclosed the presence of two sets of benzoyl units. The connections between the benzoyl moiety and aglycone were confirmed by HMBC correlations H_2-8/C-7″ and H_2-8‴/C-7⁗.

Above information suggested that compound **1** was a dimer comprising a paeonidanin unit and an albiflorin unit. The HMBC correlations from H-9 to C-6⁗ indicated that C-6⁗ of paeonidanin was connected to C-9 of albiflorin through an oxygen atom.

The configurations of the stereogenic centers in the monoterpene units were assigned by comparison to the spectra of related compounds (Okasaka et al., 2008; Yen et al., 2007) and were confirmed by the ROESY spectrum. The ROESY spectrum also showed cross-correlations between the pairs of protons H-9/H-8, H-1⁗/H-7‴α, H-7‴α/H-8‴α, H-7‴α/H-5‴, H-8‴α/H-5‴, and H-6⁗/H-3. Thus, the structure of **1** was determined as shown in Fig. 1, and named paeonidanin F.

The molecular formula of compound **2** was found to be $C_{39}H_{50}O_{20}$ [$(M-H)^-$, *m/z* 837.2813, calcd for $C_{39}H_{49}O_{20}$, 837.2817] by HR-ESIMS. Comparison of the NMR data for **2** and **1** revealed that the compounds are similar, except for the absence of signals for benzoyl moiety connected with C-8‴ in **1**. This was confirmed by the C-8‴ appeared comparatively upfield at δ 59.9. Therefore, the structure of **2** was determined as shown in Fig. 1, and named paeonidanin G.

The molecular formula of compound **3** was found to be $C_{53}H_{58}O_{22}$ [$(M-H)^-$, *m/z* 1045.3349, calcd for $C_{53}H_{57}O_{22}$, 1045.3342] by HR-ESIMS. The ^{13}C NMR data suggested that compound **3** was a dimer comprising paeonidanin and paeoniflorin structural moieties. The ^{1}H and ^{13}C NMR spectra showed a striking resemblance to those of paeonidanin E (Duan et al., 2009), with common signals of two monoterpene systems and benzoyl moieties. Comparison of the NMR data for **3** and paeonidanin E revealed that the compounds are similar, except for the appearance of signals for benzoyl moiety connected with C-6′ in **3**. This was confirmed by the HMBC correlation H-6′/C-7⁗, and the C-6′ appeared comparatively downfield at δ 65.1. Therefore, the structure of **3** was determined as shown in Fig. 1, and named paeonidanin H.

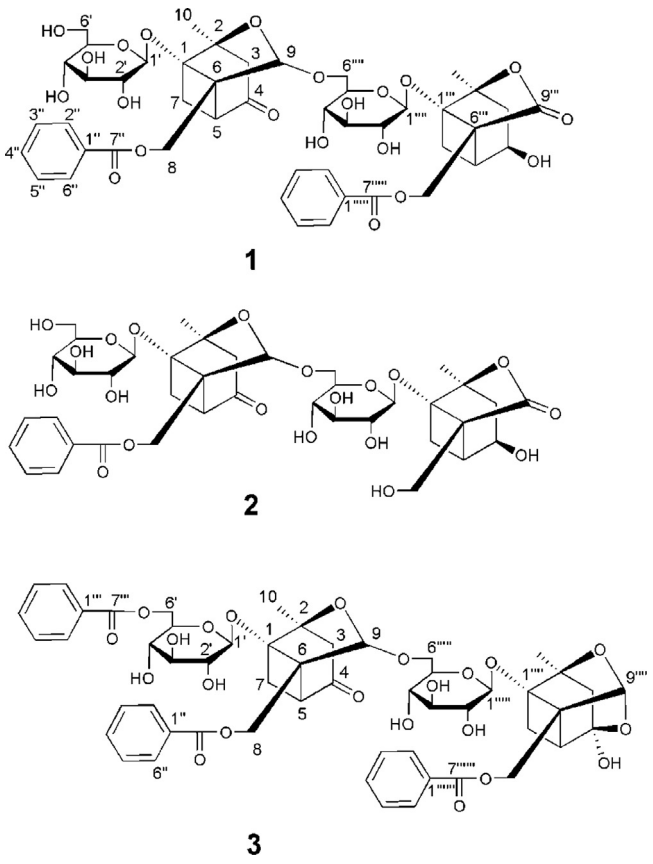

Fig. 1. The structures of compounds **1–3**.

All isolates were evaluated for inhibitory activity against LPS-induced nitric oxide (NO) and TNF-α production in RAW

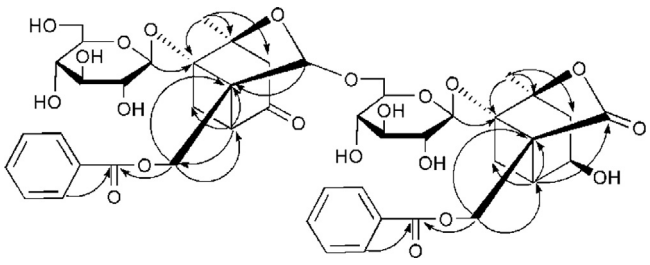

Fig. 2. Selected HMBC correlations of compound **1**.

246.7 macrophages. Compounds **1**–**3** significantly suppressed NO production. Curcumin was used as positive control. The IC_{50} values of compounds **1**–**3** and curcumin were 22.7, 19.4, 29.1 and 12.5 μM, respectively. However, those compounds showed weak inhibitory effects against TNF-α production with the inhibition ratios of 27%, 22%, and 19.5% at 50 μM, respectively. No cytotoxicity was observed in compounds **1**–**3** treated cells (cell viability >90%).

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a JASCO P-1020 digital polarimeter (Jasco, Tokyo, Japan). Spots were visualized by spraying 10% H_2SO_4–EtOH followed by heating. IR spectra were obtained on a Bruker IFS-55 plus spectrometer (Bruker, Ettlingen, German). UV spectra were recorded on a SHIMADZU UV-2201 UV–vis recording spectrophotometer (Shimadzu, Kyoto, Japan). NMR spectra were recorded on an Inova 500 spectrometer with TMS as an internal standard, operating at 500 MHz for ^{1}Hand 125 MHz for ^{13}C (Bruker, Waltham, MA, USA). HR-ESIMS data were obtained on a Bruker-Daltonics APES-III 7.0 TESLA FTMS spectrometer (Bruker, Billerica, MA, USA). GC was obtained on a SHIMADZU GC-14D. Precoated silica gel GF254 plates (Qingdao Haiyang Chemical Co., Qingdao, China) were employed for thin layer chromatography. Column chromatography was performed with silica gel (Merck, Darmstadt, Germany) and C18 silica gel (150–200 mesh, Merck). High performance liquid chromatography (HPLC) separation was carried out on an octadecylsilanized column (YMC-pack ODS-A, 250 × 10 mm, i.d. 5 μm, YMC, Kyoto, Japan) with a photo-diode array detector (Waters, Millford, MA, USA).

3.2. Plant material

The roots of *P. lactiflora* were collected in Chengdu, Sichuan Province, China, in May 2014, and identified by author (Qiang Fu). A voucher specimen (PL 201403) is maintained in the herbarium of Faculty of Biotechnology Industry, Chengdu University.

3.3. Extraction and isolation

The dried roots of *P. lactiflora* (2.6 kg) were refluxed two times with EtOH, each for 2 h. After concentrated *in vacuo*, the residue (321 g) was suspended in water, and partitioned with ethyl acetate and *n*-butanol successively. The *n*-butanol-soluble fraction (105 g) was further chromatographed over a silica gel column chromatography using $CHCl_3$–MeOH (100:1 → 10:90) as an eluent to give fractions 1–5. Fraction 1 (5.3 g) was subjected to ODS open column chromatography (MeOH–H_2O, 10:90 → 95:5) to afford sub-fractions 1–6 (0.3, 0.8, 0.1, 0.4, 1.7 and 0.6 g, respectively). Sub-fraction 2 (0.8 g) was separated by prep-HPLC (MeOH–H_2O, 50:50, UV detection at 230 nm, 2.0 ml/min) to yield compound **2** (29 mg, t_R 24.7 min). Sub-fraction 5 (1.7 g) was subjected to prep-HPLC (MeOH–H_2O, 48:52, UV detection at 230 nm, 2.0 ml/min) to afford compounds **1** (37 mg, t_R 18.0 min). Fraction 5 (6.7 g) was subjected to C_{18} silica gel chromatography (MeOH–H_2O, 10:90 → 95:5) to afford sub-fractions 1–4 (2.2, 0.7, 0.8 and 0.9 g, respectively). Sub-fraction 2 (0.7 g) was separated by prep-HPLC (MeOH–H_2O, 47:53, UV detection at 230 nm, 2.0 ml/min), affording compound **3** (33 mg, t_R 25.1 min).

3.3.1. Paeonidanin F (*1*)

White, amorphous powder; $[\alpha]_D^{25}$ −61.7 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε), 230 (4.20) nm; IR (KBr) ν_{max} (cm^{-1}): 3439, 2632, 1712, 1382, 1270 and 1071; ^{1}H and ^{13}C NMR spectral data, see Tables 1 and 2.

3.3.2. Paeonidanin G (*2*)

White, amorphous powder, $[\alpha]_D^{25}$ −65.2 (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ε) 229 (4.20) nm IR (KBr) ν_{max} (cm^{-1}): 3442, 2630, 1709, 1380, 1270 and 1072; ^{1}H and ^{13}C NMR spectral data, see Tables 1 and 2.

3.3.3. Paeonidanin H (*3*)

White, amorphous powder, $[\alpha]_D^{25}$ −64.6 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 228 (3.90) nm IR (KBr) ν_{max} (cm^{-1}): 3440, 2632, 1706, 1382, 1272 and 1072; ^{1}H and ^{13}C NMR spectral data, see Table 3.

3.4. Acid hydrolysis

Each compound (5 mg) was heated in 0.5 ml of 2 M HCl at 95 °C for 10 h in a sealed tube. After filtration of the reaction mixture, the filtrate was evaporated under vacuum. After addition of H_2O, the acidic solution was evaporated again to remove HCl. This procedure was repeated until a neutral solution was obtained, which was finally evaporated and dried in vacuo to furnish a monosaccharide residue. The sugar components obtained after acid hydrolysis of **1**–**3** were analyzed by GC analysis of the methyl

Table 2
^{13}C spectral data of compounds **1** and **2** (125 MHz, in CD_3OD)

Position	1 δ_C	2 δ_C	Position	1 δ_C	2 δ_C	Position	1 δ_C	2 δ_C	Position	1 δ_C	2 δ_C
1	88.6	88.6	1′	99.9	100.0	1‴	93.2	93.2	1⁗	100.1	100.2
2	87.4	87.5	2′	75.2	75.2	2‴	86.7	86.8	2⁗	74.8	74.8
3	49.8	49.8	3′	78.1	78.1	3‴	41.6	41.5	3⁗	78.1	78.2
4	208.4	208.4	4′	71.8	71.8	4‴	68.4	68.3	4⁗	71.6	71.6
5	47.9	48.0	5′	77.8	77.8	5‴	41.5	41.6	5⁗	76.7	76.7
6	65.1	65.2	6′	62.8	62.8	6‴	56.7	57.0	6⁗	69.5	69.4
7	27.5	27.6	1″	131.2	131.2	7‴	28.4	28.5	1⁗′	131.2	
8	63.6	63.7	2″,6″	130.6	130.7	8‴	62.0	59.9	2⁗′,6⁗′	130.6	
9	107.5	107.4	3″,5″	129.6	129.6	9‴	178.0	178.1	3⁗′,5⁗′	129.6	
10	20.7	20.8	4″	134.2	134.2	10‴	20.4	20.4	4⁗′	134.2	
			7″	167.7	167.6				7⁗′	167.8	

Table 3
^{1}H and ^{13}C spectral data of compound **3** (500 MHz, in CD_3OD)

Position	3		Position	3	
	δ_H	δ_C		δ_H	δ_C
1		88.6	1‴		131.3
2		87.4	2‴,6‴	7.92 d (7.5) 2H	130.6
3a	2.50 d (18.0)	49.8	3‴,5‴	7.41 t (7.5) 2H	129.7
3b	2.94 d (18.0)		4‴	7.52 t (7.5)	134.6
4		208.5	7‴		168.0
5	2.85 d (5.0)	48.0	1⁗		89.2
6		65.1	2⁗		87.4
7a	1.87 d (12.0)	27.5	3⁗a	1.75 d (12.0)	44.5
7b	2.92 dd (12.0, 5.0)		3⁗b	2.52 d (12.0)	
8a	4.70 d (12.5)	63.6	4⁗		106.5
8b	4.82 d (12.5)		5⁗	2.40 d (7.5)	43.7
9	5.30 s	107.5	6⁗		72.2
10	1.40 s 3H	20.7	7⁗a	1.92 d (12.0)	22.8
1′	4.56 d (7.5)	100.1	7⁗b	2.43 dd (12.0, 7.5)	
2′	3.22 dd (9.0, 7.5)	74.9	8⁗a	4.56 d (12.0)	61.7
3′	3.37 dd (9.0, 7.5)	77.8	8⁗b	4.66 d (12.0)	
4′	3.35 m	72.1	9⁗	5.37 s	102.3
5′	3.58 m	75.2	10⁗	1.28 s 3H	19.5
6′a	4.50 dd (12.0, 6.0)	65.1	1⁗	4.22 d (7.5)	100.0
6′b	4.64 dd (12.0, 2.0)		2⁗	3.13 dd (9.0, 7.5)	74.8
1″		131.2	3⁗	3.26 dd (9.0, 7.5)	78.1
2″,6″	8.01 d (7.5) 2H	130.8	4⁗	3.20 m	71.6
3″,5″	7.49 t (7.5) 2H	129.6	5⁗	3.24 m	76.8
4″	7.58 t (7.5)	134.2	6⁗a	3.69 dd (12.0, 6.0)	69.4
7″		167.7	6⁗b	3.80 dd (12.0, 2.0)	
			1⁗⁗		131.2
			2⁗⁗,6⁗⁗	8.05 d (7.5) 2H	130.8
			3⁗⁗,5⁗⁗	7.49 t (7.5) 2H	129.9
			4⁗⁗	7.62 t (7.5)	134.6
			7⁗⁗		168.0

sugar peracetates. The monosaccharide residue was dissolved in anhydrous pyridine (100 ml), 0.1 M L-cysteinemethyl ester hydrochloride (200 ml) was added, and the resultant was warmed at 60 °C for 2 h. The trimethylsilylation reagent HMDS–TMCS (hexamethyldisilazane–trimethylchlorosilane–pyridine, 2:1:10; Acros Organics, Geel, Belgium) was added and warmed at 60 °C for 30 min. To the mixture, the thiazolidine derivatives were analyzed by GC for sugar identification. Separations were carried out on a DB-5 column (30 m × 0.25 mm × 0.25 mm). Highly pure N_2 was employed as carrier gas (1.0 ml/min flow rate), and the flame ionization detector detector operated at 280 °C (column initial temperature was maintained at 100 °C for 2 min and then raised to 280 °C at the rate of 10 °C/min). The retention time of the D-glucose derivative was 12.30 min.

3.5. Assay for inhibitory activity against LPS-induced NO production

Tested compounds were separately dissolved in DMSO, and diluted with phosphate buffered saline (PBS) to a final concentration of 10 mM. Such solution was then diluted to various test concentrations. RAW 264.7 macrophages were seeded in 24-well plates (1×10^5 cells/well), with cells co-incubated with the test compounds and lipopolysaccharide (LPS, 1 μg/ml) for 24 h. The amount of NO was assessed by determining the nitrite concentration in the cultured RAW 264.7 macrophage supernatants with Griess reagent. Aliquots of supernatants (100 μl) were incubated, in sequence, with 50 μl 1% sulphanilamide and 50 μl 0.1% naphthylethylenediamine in 2.5% H_3PO_4 solution. Absorbances at 570 nm were read using a microtiter plate reader.

3.6. Assay for inhibitory activity against LPS-induced TNF-α production

RAW 264.7 macrophages were seeded in 96 well plates (1×10^5 cells/well). Cells were co-incubated with drugs and lipopolysaccharide (LPS, 1 μg/ml) for 24 h. TNF-α production levels were determined using a commercially available TNF-α ELISA kit (BioLegend, Inc., CA) according to the protocol provided by the manufacturers.

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