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Cytotoxic polycyclic polyprenylated acylphloroglucinol derivatives and xanthones from *Hypericum attenuatum*

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ABSTRACT

Two new polycyclic polyprenylated acylphloroglucinols, attenuatumione G (**1**) and attenuatumione H (**2**), together with five known compounds (**3**–**7**) have been isolated from the whole plant of *Hypericum attenuatum*. Their structures were elucidated by spectroscopic data including HRESIMS, 1D- and 2D-NMR. In biological assays, compound **2** showed moderate cytotoxic activities against Hep-G2 (IC_{50} 9.11 μM) and MCF-7 (IC_{50} 16.24 μM), compound **4** exhibited significant cytotoxic activity with IC_{50} value of 5.32 μM against Hep-G2, and both compounds **5** and **6** revealed significant nitric oxide production inhibitory activity with IC_{50} values of 5.52 and 8.46 μM, respectively.

1. Introduction

The genus *Hypericum* is distributed in wide areas from the semitropics to temperate zones in the northern hemisphere, various species of which have been commonly used as traditional remedies in several parts of the world (Avato, 2005; Yaylaci et al., 2013). Previous studies on *Hypericum* species have revealed the presence of several classes of bioactive constituents such as proanthocyanins, flavonoids, biflavonoids, xanthones, phenylpropanes and naphthodianthrones, as well as acylphloroglucinols and essential oil components (Crockett, 2010). Among of them, acylphloroglucinols and xanthones have engaged the attention of many scientists due to their wide variety of biological activities (Ciochina and Grossman, 2006; Demirkiran, 2007). *Hypericum attenuatum* Choisy is widespread in China and its whole plant is used as a folk medicine for haemostasia, analgesic and stimulation of lactation (Flora of China Editorial Committee of Chinese Academy of Sciences, 1990; Jiangsu New Medicine College, 1986). During our previous phytochemical investigation on this plant, we have reported the isolation of six polycyclic polyprenylated acylphloroglucinols (PPAPs) attenuatumiones A–F (Zhou et al., 2014). In a continuation of the search for bioactive compounds from *H. attenuatum*, we isolated two new PPAPs (**1** and **2**), and five known compounds, including one PPAP (**3**) and four xanthones (**4**–**7**). Here, we report their structure elucidation and biological activities.

2. Results and discussion

Compound **1** was isolated as a colorless oil. The molecular formula was assigned as $C_{35}H_{54}O_7$ on the basis of HRESIMS ion peak at *m/z* 587.3945 $[M+H]^+$ (calcd. for $C_{35}H_{55}O_7$, 587.3942). The UV spectrum showed two absorption maxima at 204 and 273 nm. The IR spectrum showed absorption bands for hydroxy (3434 cm^{-1}) and carbonyl (1730 cm^{-1}) groups. The ^{13}C NMR spectrum (Table 1) showed the signals for an unconjugated carbonyl (δ 204.3), and an enolised 1,3-dicarbonyl ether system (δ 193.7, 117.1 and 173.9), which indicated that **1** was a polyprenylated phloroglucinol derivative (Magadula et al., 2008). In ^1H-NMR spectrum, the following characteristic resonances are coincided with those of 17,18-dihydroxyfurohyperforin (Liu et al., 2014): δ_H 4.57 (1H, dd, J = 10.5 and 5.5 Hz), 3.25 (1H, d, J = 10.5 Hz), 2.66 (1H, dd, J = 13.0 and 11.0 Hz), 1.77 (1H, m), 1.38 and 1.22 (each 3H, s). Extensive analyses of NMR spectra of **1** led us to assume that **1** was a diastereromer of (1*S*,32*R*,5*S*,6*R*,7*R*)-6-((*R*)-3,4-di-hydroxy-4-methylpentyl)-2-(2-hydroxypropan-2-yl)-7-isobutyryl-6-methyl-5,9-bis(3-methylbut-2-en-1-yl)-4,5,6,7-tetrahydro-2*H*-32,7-methanocycloocta[*b*]furan-8,10(3H)-dione (Liu et al., 2014). In

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Table 1
^{1}H (500 MHz) and ^{13}C NMR (125 MHz) spectral data of compounds **1** and **2** (in $CDCl_3$).

No.	**1**		**2**	
1		204.3		209.8
2		83.0		77.1
3		48.5		48.9
4	1.68 m	42.1	1.69 m	44.8
5	2.04 dd (13.5, 4.0) 1.50 t (13.5)	38.1	1.94 dd (13.5, 3.0) 1.37 t (m)	39.9
6		59.8		63.7
7		173.9		165.9
8		117.1		113.9
9		193.7		195.1
10		209.6		208.9
11	1.97 m	42.3	2.42 m	40.6
12	0.99 d (6.5)	21.6	1.14 d (6.5)	22.1
13	1.09 d (6.5)	20.6	1.10 d (6.5)	21.7
14	1.06 s	15.0	1.07 s	12.8
15	2.04 dd (13.5, 4.0) 1.92 m	33.3	2.13 m 2.00 m	38.4
16	1.61 m 1.50 t (13.5)	27.5	2.00 m 1.56 m	25.6
17	3.25 d (10.5)	78.9	5.01 t (6.5)	124.8
18		73.1		131.5
19	1.19 s	26.4	1.66 s	25.9
20	1.13 s	23.7	1.60 s	18.0
21	2.17 dd (13.5, 3.5) 1.77 m	27.6	2.15 m	28.1
22	4.93 t (6.5)	122.2	4.91 t (6.5)	122.4
23		133.9		133.7
24	1.70 s	26.0	1.66 s	26.0
25	1.57 s	18.2	1.53 s	18.0
26	3.14 dd (14.0, 7.0) 3.03 dd (14.0, 7.0)	22.3	2.66 dd (17.0, 4.5) 2.55 dd (17.0, 6.5)	25.8
27	5.06 t (7.0)	121.2	3.80 t (5.0)	68.7
28		132.9		83.2
29	1.65 s	25.8	1.40 s	25.1
30	1.70 s	18.0	1.36 s	21.6
31	2.66 dd (13.0, 11.0) 1.77 m	30.4	2.13 m 1.86 dd (15.0, 5.0)	33.2
32	4.57 dd (10.5, 5.5)	90.5	3.38 d (9.0)	74.7
33		71.0		73.2
34	1.38 s	27.0	1.21 s	25.7
35	1.22 s	24.3	1.21 s	24.6

HMBC spectrum, the cross-peaks from H-15 (δ 2.04, dd, J = 13.5, 4.0 Hz; 1.92, m) to C-2, −3, and −14, and from H-17 (δ 3.25, d, J = 10.5 Hz) to C-15, −16, and −18 were observed. Therefore, compound **1** was determined to bear a 3,4-dihydroxyl-4-methylpentyl side chain (C-15 to C-20) at C-3. This deduction was also supported by the absence of a couple of olefinic carbon signals and the presence of a secondary alcohol [δ_H 3.25 (d, J = 10.5 Hz), δ_C 79.4]. The HMBC correlations from H-26 (δ 3.14, dd, J = 14.5 and 7.0 Hz; 3.03, dd, J = 14.5 and 7.0 Hz) to C-7, −8, and −9 indicated the location of one prenyl unit at C-8. The HMBC cross-peaks from H-31 (δ 2.66, dd, J = 13.0 and 11.0 Hz; 1.77, m) to C-1, −6, and −7, from Me-34 (δ 1.38, s) to C-32, and −33, from H-32 (δ 4.57, dd, J = 10.5 and 5.5 Hz) to C-34, −35, and from H-11 (δ 1.97, m) to C-2 and −10 confirmed that the cyclopentane-ring was fused at C-6 and C-7, and the 2-propanol group was at C-2. In addition, another prenyl unit (C21-C25) was believed to be attached to C-4, as disclosed by the HMBC correlations from H-21 (δ 2.17, dd, J = 13.5 and 3.5 Hz; 1.77, m) to C-4. The key ROESY correlation (Fig. 2) of the proton signal at δ_H 2.04 (H-5α) with δ_H 4.57 (H-32), together with the correlation between δ_H 1.50 (H-5β) and 1.06 (Me-14) indicated that the 2-hydroxypropyl group at C-32 and Me-14 were both β-oriented. The ROESY cross peak from δ 1.50 (H-5β) to δ 1.77 (H-31) confirmed the relative configuration at C-6. The α-orientation of H-4 was deduced from the chemical shifts of C-4 (δ 42.1) and the difference value of H-5β and H-5α ($\Delta\delta$ *ca.* 0.54 ppm) (Chen et al., 2010). The absolute configuration at

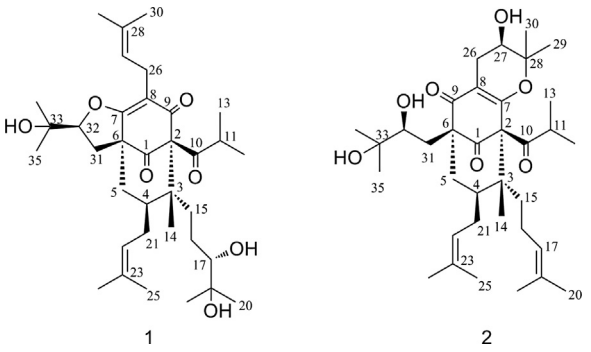

Fig. 1. Structures of compounds **1** and **2**.

C-17 was confirmed by the induced CD of the in situ formed $[Rh_2(OCOCF_3)_4]$ complex (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990). The Rh complex of compound **1** exhibited a positive *E* band correlating with the 17*S* configuration by applying the bulkiness rule (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990; Liu et al., 2010). Thus, the structure of **1** was assigned as shown in Fig. 1 and was named attenuatumione G.

Compound **2** was obtained as a colorless oil. The molecular formula was determined to be $C_{35}H_{54}O_7$ based on the HRESIMS data. Compound **2** showed the similar UV, IR, and NMR spectra with those of **1,** indicating that **2** was a PPAP. The spectroscopic analyses also revealed that compound **2** was structurally similar to the reported compound furohyperforin isomer 2 (Verotta et al., 1999). The major structural difference between **2** and furohyperforin isomer 2 was the replacement of a C-6 prenyl unit and 2-(2-hydroxypropyl)-2*H* dihydrofuran unit in furohyperforin

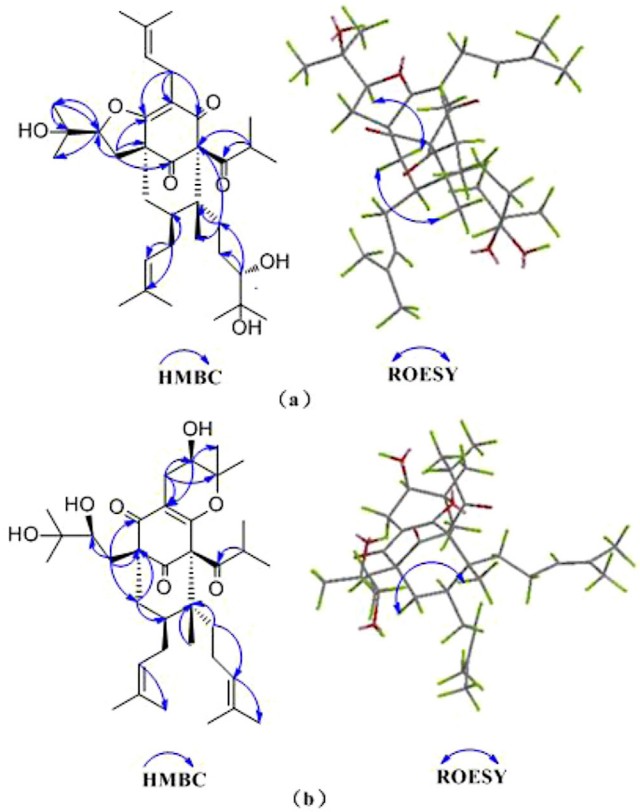

Fig. 2. Selected 2D NMR correlations of attenuatumione G (a) and attenuatumione H (b) (**1** and **2**).

isomer 2 with a 2,3-dihydroxy-3-methylbutyl unit and a 3-hydroxy-2,2-dimethyl-2*H*-dihydropyran ring in compound **2**.

The relative configuration of **2** was determined by a ROESY experiment and the comparative analysis of the NMR data with its analogues. The chemical shifts of C-4 (δ 44.8) and the difference of H-5β and H-5α ($\Delta\delta$ *ca.* 0.57 ppm) indicated that H-4 was in α-orientation (Chen et al., 2010). The ROESY (Fig. 2) correlations of the signal at δ_H 1.37 (H-5β) with those at δ_H 1.07 (Me-14) and δ_H 1.86 (H-31) indicated the Me-14 and side chain at C-6 were both β-orientated. The ROESY cross peaks from δ_H 2.66 (H-26α) and 1.36 (Me-30) to δ_H 3.81 (H-27), from δ_H 2.55 (H-26β) and 2.42 (H-11) to δ_H 1.40 (Me-29) suggested that the side chain at C-2 was β-orientated, and H-27 was α-orientated, respectively. The absolute configuration at C-32 was confirmed by the induced CD of the in situ formed [$Rh_2(OCOCF_3)_4$] complex (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990). The Rh complex of **2** exhibited a positive *E* band correlating with the 32*S* configuration by applying the bulkiness rule (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990; Liu et al., 2010). Thus, the structure of **2** was established as shown in Fig. 1 and was named attenuatumione H.

Five known compounds were identified as (1*S*,32*R*,5*S*,6*R*,7*R*)-6-((*R*)-3,4-di-hydroxy-4-methylpentyl)-2-(2-hydroxypropan-2-yl)-7-isobutyryl-6-methyl-5,9-bis(3-methylbut-2-en-1-yl)-4,5,6,7-tetrahydro-2*H*-32,7-methanocycloocta[b]furan-8,10(3H)-dione (**3**) (Liu et al., 2014), 1,7-dihydroxyxanthone (**4**) (Iinuma et al., 1996), 2-deprenylrheediaxanthone B (**5**) (Rath et al., 1996), Jacareubin (**6**) (King et al., 1953) and isojacareubin (**7**) (Ishiguro et al., 1993), by comparison of their spectroscopic data with those reported.

Recently, polycyclic polyprenylated derivatives and xanthones with anti-inflammatory effects or cytotoxicity on different cancer cell lines are reported (Hashida et al., 2008; Li et al., 2015; Tanaka et al., 2009; Trinh et al., 2013; Xin et al., 2012). Therefore, the cytotoxic effects against three human cancer cell lines Hep-G2, U2OS and MCF-7 were carried out on all the isolates using the MTT cell viability assay. As indicated in Table 2, compound **2** showed moderate cytotoxic activities against Hep-G2 (IC_{50} 9.11 μM) and MCF-7 (IC_{50} 16.24 μM). And compound **4** exhibited significant cytotoxic activity against Hep-G2 (IC_{50} 5.32 μM). The inhibitory effects of all the compounds on the release of NO in lipopolysaccharide (LPS)-induced RAW264.7 cells were also evaluated. As a result, compounds **5** and **6** displayed potent nitric oxide production inhibitory activity with IC_{50} values of 5.52 and 8.46 μM, respectively.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a JASCO P-1020 polarimeter. CD spectra were obtained on a JASCO 810 spectropolarimeter. UV spectra were recorded with a Shimadzu UV-2450 spectropolarimeter. A Bruker Tensor 27 spectrometer (KBr discs) was used to acquire the IR spectra. NMR spectra were carried out in $CDCl_3$ and DMSO-d_6 at 303 K on Bruker AV-500 (^{1}H NMR, 500 MHz; ^{13}C NMR, 125 MHz) with TMS as the internal standard. ESIMS and HRESIMS data were obtained on an Agilent 1100 series LC/MSD Trap mass spectrometer (ESIMS) and an Agilent UPLCQ-TOF (6520B) (HRESIMS), respectively. Silica gel (200–400 mesh, Qingdao Marine Chemical Co., Ltd.), Sephadex LH-20 (Pharmacia), and ODS (40–63 μm, Fuji) were used for open column chromatography. Preparative HPLC was carried out using Agilent 1100 Series equipped with Shim-park RP-C_{18} column (5 μm, 200 × 20 mm i.d., Shimadzu) and 1100 Series Multiple Wavelength Detector.

3.2. Plant material

The whole plant was purchased from Bozhou, Anhui Province, China, in November 2011, and authenticated as *Hypericum attenuatum* Choisy by Professor Mian Zhang, Department of Natural Medicinal Chemistry, China Pharmaceutical University. A voucher specimen (No. HA-201112) has been deposited in the Department of Natural Medicinal Chemistry, China Pharmaceutical University.

3.3. Extraction and isolation

The air-dried plant materials (8.5 kg) were powdered and extracted with 95% aqueous EtOH (3 × 20 L) under reflux. Extracts were combined and dried under vacuum in a rotary evaporator. The resulting crude extract (ca. 633 g) was suspended in H_2O (2 L) and successively partitioned with petroleum ether (3 × 2 L) and CH_2Cl_2 (3 × 2 L). The petroleum ether extract (181.5 g) was fractionated using a silica gel column, eluted with a gradient of petroleum ether–acetone (1:0 to 0:1) to afford four fractions (A–D). Fraction C (33 g) was chromatographed over a silica gel column using a gradient of petroleum ether–acetone (10:1–0:1) to yield five fractions (CI–CV). Fraction CII (7.8 g) was further seperated by MPLC (MeOH–H_2O, 50:50 to 100:0) to get six fractions (CII1–CII6). Fraction CII4 (2.1 g) was reseperated by passage over a LH-20 column ($CHCl_3$–MeOH, 1:1) to give four fractions (CII4a–CII4d). CII4b (1.6 g) was further fractionated by MPLC (MeOH–H_2O, 70:30 to 100:0) to afford six fractions

Table 2
Cytotoxicities and nitric oxide production in LPS-stimulated RAW264.7 of the isolates from *H. attenuatum*.[a,b]

Compounds	Cytotoxicities			Effects of inhibiting NO production
	Hep-G2	U2OS	MCF-7	
1	>50	>50	>50	>50
2	9.11 ± 1.40	>50	16.24 ± 1.48	>50
3	>50	>50	>50	–
4	5.32 ± 2.79	>50	36.97 ± 0.52	–
5	>50	>50	>50	5.52
6	>50	>50	>50	8.46
7	>50	>50	>50	14.15
cis-platinum[c]	6.62 ± 1.57	6.19 ± 0.85	9.69 ± 0.64	
N-monomethyl-L-arginine[c]				39.00 ± 2.81

[a] Results are expressed as IC_{50} values in μM.
[b] Compounds with IC_{50} >50 μM are not shown.
[c] Positive controls.

(CII4bA–CII4bF). Fraction CII4bA (206 mg) was subjected to a LH-20 column ($CHCl_3$–MeOH, 1:1) and further purified by preparative HPLC (CH3CN–H_2O 55:45) to give **1** (6.5 mg) and **3** (3.9 mg). Fraction CII3 (684 mg) was separated with a LH-20 column ($CHCl_3$–MeOH, 1:1) and further isolated by preparative HPLC (MeOH–H_2O 70:30) to afford **4** (4.9 mg), **5** (22.0 mg), **6** (5.8 mg) and **7** (4.9 mg). Fraction CIV (4.0 g) was applied to MPLC (MeOH–H_2O, 50:50 to 100:0) to get four fractions (CIV1–CIV4). Fraction CIV3 (994 mg) was reseperated by passage over a LH-20 column ($CHCl_3$–MeOH, 1:1) to afford five fractions (CIV3a–CIV3e). Fraction CIV3c (359 mg) was subjected to MPLC (MeOH–H_2O, 60:40 to 100:0) and further isolated by preparative HPLC (CH_3CN–H_2O 70:30) to give **2** (3.0 mg).

*3.3.1. Attenuatumione G (**1**)*

colorless oil; [α]25 D + 40.5 (*c* 0.19, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 203 (4.02), 273 (3.93) nm; CD ($c = 3.0 \times 10^{-4}$, MeOH) λ_{max} nm (Δε) 377 (+2.2), 359 (+0.2), 336 (+4.9), 303 (−30.1), 275 (+57.4); IR (KBr) ν_{max} cm^{-1} 3433, 2974, 2928, 1730, 1623, 1450, 1376, 1237, 1213, 1169, 1067, 855, 810, 683, 638, 583, 525; ^{13}C and ^{1}H NMR data, see Table 1; HRESIMS *m/z* 587.3945 $[M+H]^+$ (calcd. for $C_{35}H_{55}O_7$, 587.3942).

*3.3.2. Attenuatumione H (**2**)*

Colorless oil; [α]25 D + 34.6 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 203 (3.95), 272 (3.95) nm; CD ($c = 3.0 \times 10^{-4}$, MeOH) λ_{max} nm (Δε) 391 (+13.4), 386 (+10.1), 377 (+16.6), 347 (+3.5), 335 (+5.1), 299 (−73.5), 271 (+137.8); IR (KBr) ν_{max} cm^{-1} 3449, 2978, 2932, 2877, 1732, 1608, 1448, 1387, 1721, 1223, 1171, 1128, 1099, 1078, 991, 932, 891, 836, 759, 667, 608, 508; ^{13}C and ^{1}H NMR data, see Table 1; HRESIMS *m/z* 587.3940 $[M+H]^+$ (calcd. for $C_{35}H_{55}O_7$, 587.3942).

*3.4. Absolute configuration of C-17 in **1**,**3**, and C-33 in **2***

The in situ formed $[Rh_2(OCOCF_3)_4]$ complex method was used according to the published procedure (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990). Compound **1** (**2** or **3**, 0.3 mg) was dissolved in dried solution of the dirhodium trifluoroacetate $[Rh_2(OCOCF_3)_4]$ complex (1.0 mg) in CH_2Cl_2 (1 mL). After mixing, the first CD spectrum was recorded immediately, and the time evolution was monitored until stationary (about 10 min). The inherent CD spectrum was subtracted. The sign of the *E* band at around 350 nm in the induced CD data was correlated to the absolute configuration of the secondary alcohol (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990).

3.5. Cytotoxicity assay

The human tumor cell lines used were Hep-G2, U2OS, and MCF-7, which were obtained from the Cell Bank of Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China). All the cells were cultured in RPMI-1640 medium (GIBCO Invitrogen Corp., Carlsbad, CA) supplemented with 10% foetal bovine serum (Sijiqing, Hangzhou, China), 100 U/mL penicillin and 100 μg/mL streptomycin at 37 °C in a humidified atmosphere with 5% CO_2. Cells were gathered and seeded in 96-well plates at a density of 5×10^3 cells per well in 200 μL medium for 24 h at 37 °C. Each tumor cell line was exposed to the test compound at various concentrations in triplicate for 48 h, with *cis*-platinum (Sigma–Aldrich Company, USA) as a positive control. After the incubation, 20 μL of MTT solution (5 mg/mL) was added and cultured for 4 h. Then the supernatant was discarded and DMSO was added (150 μL/well). Absorbance was determined at 570 nm by a Universal Microplate Reader (SpectramaxPlus 384; Molecular Devices, Sunnyvale, CA).

3.6. NO production bioassay

The protocol for the NO production bioassays was provided in a previously published paper (Yang et al., 2011). *N*-monomethyl-L-arginine was used as a positive control, and all experiments were performed in three independent replicates.

Appendix A. Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **1**, **2** and their selected 2D NMR and HRESIMS spectra are available as Supporting Information.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phytol.2016.02.004.

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