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Two new polycyclic polyprenylated acylphloroglucinols derivatives from *Hypericum acmosepalum*

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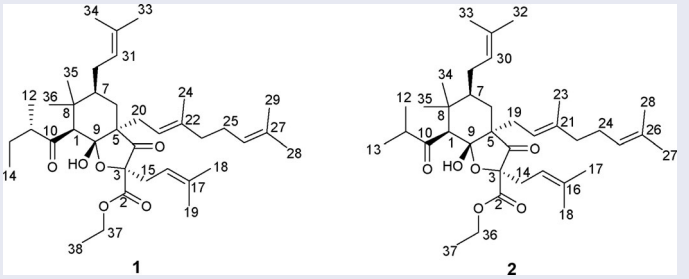
ABSTRACT

Polycyclic polyprenylated acylphloroglucinols (PPAPs) were mainly obtained from the plants of *Hypericum* genus of Guttiferae family, and possessed intriguing chemical structures and appealing biological activities. Two new PPAPs derivatives, hyperacmosin C (**1**) and hyperacmosin D (**2**) were isolated from *H. acmosepalum*. Their structures were established by NMR, HREIMS, and experimental electronic circular dichroism spectra. Besides, compound **1** showed significant hepatoprotective activity at 10 μM against paracetamol-induced HepG2 cell damage and compound **2** could moderately increase the relative glucose consumption.



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KEYWORDS
PPAPs; *Hypericum acmosepalum*; ECD; hepatoprotective activity; relative glucose consumption

1. Introduction

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are a group of structurally fascinating and synthetically challenging natural products, due to their highly oxygenated and various acylphloroglucinol-derived core structures that are decorated with prenyl substituents [1, 2]. More than 700 natural PPAPs have been isolated and there

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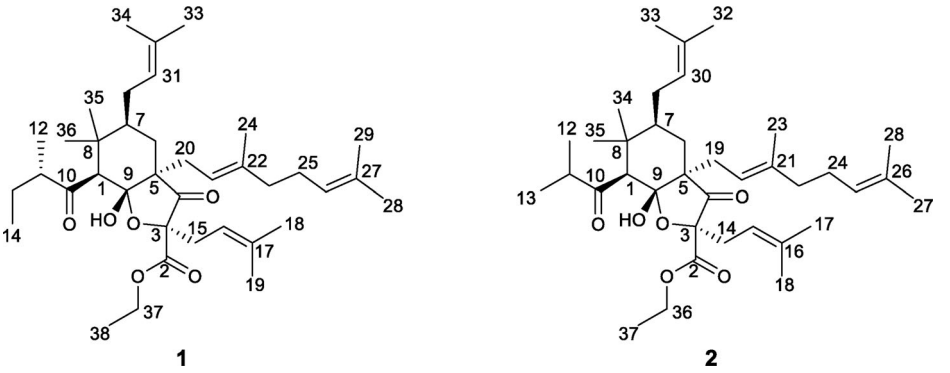

Figure 1. Structures of compounds **1** and **2**.

are many in-depth studies that have elucidated their biological activities and total synthesis in the past several years [3, 4]. PPAPs exhibit a broad range of biological activities, such as antidepressant, antimicrobial, anti-tumor, anti-inflammatory, anti-HIV, and antioxidant activities [5–11].

Hypericum acmosepalum, is distributed in Guangxi, Yunnan, Sichuan and Guizhou provinces in China. As a kind of traditional Chinese medicine, it has been used to treat hepatitis and relieve swelling and inflammation [12]. But the chemical constituents of *H. acmosepalum* are rarely reported [12–14].

2. Results and discussion

In the present study, we focused on the petroleum ether extract of the aerial parts of *H. acmosepalum* and succeeded in isolating and elucidating two new PPAPs derivatives (Figure 1), hyperacmosins C (**1**) and D (**2**). Their structures closely resembled that of hyperhexanone A, which was isolated from *H. sampsonii* with a novel 1,2-seco-bicyclo [3.3.1]-PPAP core that resulted from the cleavage of C-1/C-2 bonding via a Retro-Claisen condensation reaction [15]. In addition, hyperacmosin C (**1**) showed significant hepatoprotective activities against paracetamol-induced HepG2 cell damage and hyperacmosin D (**2**) could moderately increase the relative glucose consumption.

Hyperacmosin C (**1**) was obtained as a colorless viscous oil. The molecular formula was established as $C_{38}H_{60}O_6$ according to HREIMS *m/z* 635.4290 $[M+Na]^+$, containing nine degrees of unsaturation. The UV spectrum of **1** showed maximum absorption at 204 nm (log ε 4.46), while the IR spectrum exhibited absorption bands for hydroxy group (3386 cm^{-1}) and carbonyl group (1712 cm^{-1}). The ^1H NMR spectrum of **1** (Table 1) showed characteristic signals assignable to four olefinic protons (δ_H 5.00, m; 5.07, m; 5.14, m and 5.29, m), a methine proton (δ_H 3.16, s), an sec-butyl group (δ_H 0.86, t, $J=7.4$ Hz; 1.06, d, $J=6.8$ Hz; 1.25, m, 1.82, m; 2.58, m), an ethoxy group (δ_H 4.20, m; 1.25, t, $J=7.2$ Hz), and nine other singlet methyls [δ_H 0.94, 1.02, 1.55, 1.59, 1.61, 1.67(overlap), 1.69]. The ^{13}C NMR spectrum (Table 1) of **1** displayed 37 carbon resonances, including characteristic signals of one carbonyl (δ_C 211.2), one ester carbonyl (δ_C 170.3), and eight olefinic carbons (δ_C 116.6, 119.1, 123.4, 124.4, 131.4, 132.7, 136.5, 138.9). Furthermore, the signal of another carbonyl at δ_C 215.7

Table 1. ^{1}H and ^{13}C NMR spectral data for compounds **1** and **2** in $CDCl_3$.

	1		2	
Position	δ_H (J (Hz))[a]	δ_C[b]	δ_H (J (Hz))[c]	δ_C[d]
1	3.16 s	64.1	3.18 s	63.9
2		170.3		171.3
3		86.4		86.3
4		211.2		211.1
5		55.3		55.3
6	1.17–1.18 m 1.28–1.30 m	29.9	1.15–1.20 m 1.25–1.27 m	29.8
7	1.70–1.72 m	30.3	1.68–1.70 m	31.7
8		36.7		36.6
9		106.2		106.1
10		215.7		216.3
11	2.55–2.60 m	51.5	2.77 Sept (7.0)	44.8
12	1.06 d (6.8)	14.6	1.08 d (7.0) (overlap)	18.1
13	1.78–1.85 m 1.24–1.26 m	24.8	1.08 d (7.0) (overlap)	18.2
14	0.86 t (7.4)	11.7	2.98 dd (15.0,9.0) 2.34–2.40 m	35.9
15	2.99 dd (14.8,8.8) 2.37–2.42 m	36.0	5.11–5.15 m	116.6
16	5.10–5.15 m	116.6		136.5
17		136.5	1.66 s	26.0
18	1.67 s	26.0	1.54 s	18.2
19	1.55 s	18.2	2.63 dd (15.5,9.5) 2.36 dd (15.5,5.5)	28.2
20	2.65 dd (15.6,9.2) 2.34 dd (15.2,5.6)	28.2	5.26–5.30 m	119.1
21	5.26–5.32 m	119.1		139.0
22		138.9	1.96–2.00 m	40.3
23	1.95–2.00 m	40.3	1.68 s	16.5
24	1.69 s	16.5	2.03–2.07 m	26.8
25	2.00–2.05 m	27.0	5.03–5.08 m	124.3
26	5.05–5.09 m	124.4		131.5
27		131.4	1.66 s	25.8
28	1.67 s	25.8	1.61 s	17.8
29	1.61 s	17.8	2.07–2.11 m 1.50–1.52 m	27.7
30	2.05–2.10 m 1.54–1.56 m	27.7	4.97–5.02 m	123.4
31	4.98–5.02 m	123.4		132.7
32		132.7	1.66 s	26.1
33	1.67 s	26.1	1.58 s	18.0
34	1.59 s	18.0	0.93 s	26.9
35	0.94 s	26.9	1.01 s	23.2
36	1.02 s	23.3	4.20 dd (10.0,7.0) 4.16–4.24 m	62.7
37	4.18–4.22 m	62.8	1.24 t (7.0)	14.3
38	1.25 t (7.2)	14.1		

[a]Recorded at 400 MHz.
[b]Recorded at 100 MHz.
[c]Recorded at 500 MHz.
[d]Recorded at 125 MHz.

was observed in the HMBC spectrum. Analysis of these data indicated the existence of two isoprenyls, a geranyl group, an ethoxyl acyl group, and an sec-butyl group linked to the carbonyl. The HMQC spectrum suggested the rest carbon resonances to be two methyls (δ_C 23.3, 26.9), two quaternary carbons (δ_C 36.7, 55.3), two tertiary carbons linked with an oxygen atom (δ_C 86.4, 106.2), one methine (δ_C 30.3), one methine linked with carboxyl (δ_C 64.1), and one methylene (δ_C 29.9).

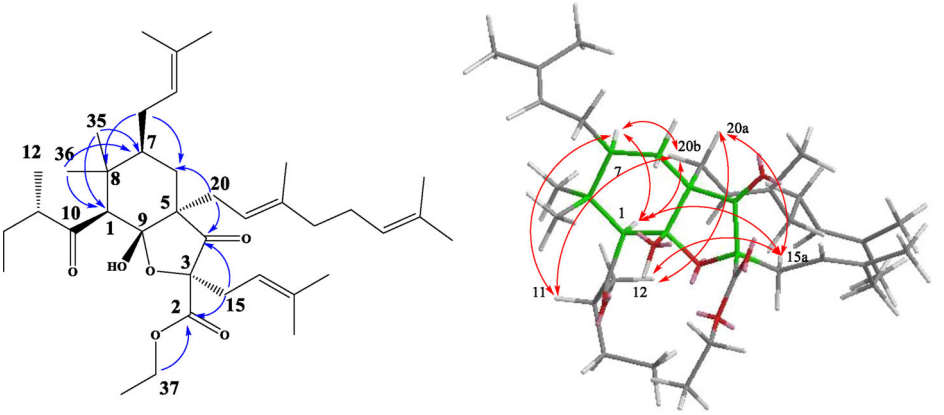

Figure 2. Selected key HMBC and ROESY correlations for **1**.

The cyclohexane ring was established by HMBC correlations (Figure 2) from the gem-dimethyl (Me-35 and Me-36) to C-1, C-7, and C-8; H-1 to C-8, C-9, and C-10; H-20 to C-4, C-5, C-6 and C-9; H-30 to C-6, C-7, and C-8. Meanwhile, the presence of the tetrahydrofuran ring between C-3 and the hemiketal carbon was elucidated based on the downfield shifted chemical shifts of C-3 and C-9 (δ_C 86.4, 106.2), as well as the degrees of unsaturation. An isoprenyl group and the ethoxyl acyl group were linked to C-3, supported by HMBC correlations from H-15 to C-2, C-3, and C-4; H-37 to C-2 and C-38; and H-38 to C-37. Thus, the aforementioned data suggested the planar structure of **1** to be a PPAP with an octahydrobenzofuran-3-one core scaffold containing an unusual hemiketal group.

The relative configuration of **1** was set up by careful analysis of its ROESY spectrum. The ROESY correlations (Figure 2) from H-1 to H-7, H-15 and H-20; H-20 to H-7 and H-15 indicated the relative configuration of C-1, C-3, C-5, and C-7. The orientation of the hydroxyl at C-9 could not be determined directly. However, owing to W-coupling of H-1 and C-3 in HMBC spectrum which is strictly depended on the specific conformation, only cis-fusion of the cyclohexane and the tetrahydrofuran rings could provide such a conformation with the five atoms of H-1, C-1, C-9, O-C-3, and C-3 in a plane and the four bonds between them to construct a "W" [15]. Therefore, the inexistence of W-coupling of H-1 and C-3 could be the proof of trans-fusion of the cyclohexane and the tetrahydrofuran rings.

Hyperacmocin D (**2**) was also obtained as a colorless viscous oil. HREIMS *m/z* 621.4126 $[M+Na]^+$, showed its molecular formula as $C_{37}H_{58}O_6$, containing nine degrees of unsaturation. The UV spectrum of **2** showed maximum absorption at 204 nm (log ε 3.84), while the IR spectrum exhibited absorption bands for hydroxy group (3397 cm^{-1}) and carbonyl groups (1758 and 1715 cm^{-1}). Nine singlet methyls (δ_H 0.93, 1.01, 1.54, 1.58, 1.61, 1.66, overlap, 1.68) and four olefinic protons (δ_H 5.00, 5.06, 5.13, and 5.28) were observed in the ^1H NMR spectrum. The ^{13}C NMR spectrum displayed 36 carbon resonances, including one carbonyl signal (δ_C 211.1), one ester carbonyl (δ_C 171.3) and eight olefinic carbons (δ_C 116.6, 119.1, 123.4, 124.3, 131.5, 132.7, 136.5, 139.0), and another carbonyl at δ_C 216.3 was observed in the HMBC spectrum. Key HMBC correlations from the gem-dimethyl (Me-34 and Me-

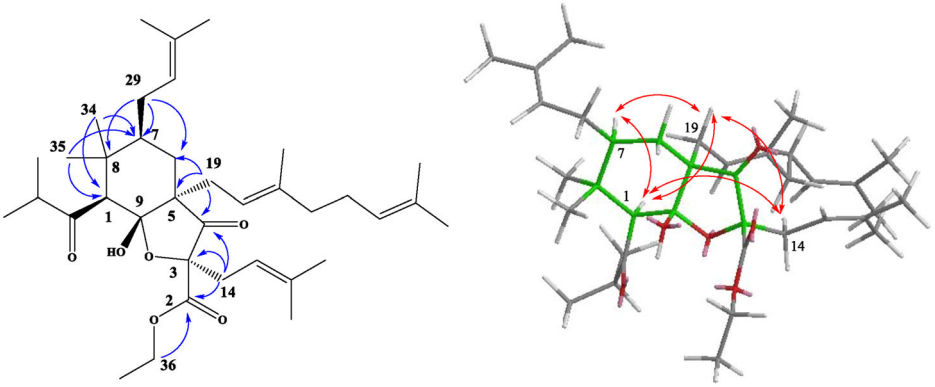

Figure 3. Selected key HMBC and ROESY correlations for **2**.

35) to C-1, C-7, and C-8; H-1 to C-8, C-9, and C-10; H-19 to C-4, C-5 and C-6; H-29 to C-6, C-7, and C-8; H-14 to C-2, C-3, and C-4; H-36 to C-2 and C-37, H-37 to C-36 were observed as shown in Figure 3. These data indicated compounds **1** and **2** shared similar planar structure.

The ROESY correlations (Figure 3) from H-1 to H-7, H-14, and H-19, as well as H-19 to H-7 and H-14 indicated the relative configuration of C-1, C-3, C-5, and C-7. Moreover, the inexistence of W-coupling of H-1 and C-3 could prove trans-fusion of the cyclohexane and the tetrahydrofuran rings in compound **2**.

The absolute configuration of **2** was elucidated by electronic circular dichroism (ECD) calculation using time-dependent density functional theory (TD-DFT). A pair of enantiomers, (1*S*, 3*R*, 5*R*, 7*R*, 9*S*)-**2**a and (1*R*, 3*S*, 5*S*, 7*S*, 9*R*)-**2**b were calculated for ECD spectra based on the known relative configuration of **2**. The ECD spectrum of **2** was in sufficient agreement with **2**b (Figure 4) and similar to **1** (Figure 5). On account of them, the absolute configurations of compounds **1** and **2** were both determined as 1*R*, 3*S*, 5*S*, 7*S*, 9*R*. As for the ambiguous absolute configuration at C-11 of **1**, we can still make inferences from its ROESY spectrum (Figure 2). The correlations from H-11 to H-7 and H-20b; H-12 to H-15a and H-20a indicated the sequence of substituents at C-11. Therefore, the absolute configuration of C-11 was established as 11*S*. Eventually, the six stereogenic centers of **1** were elucidated as 1*R*, 3*S*, 5*S*, 7*S*, 9*R*, and 11*S*.

Compounds **1** and **2** were both evaluated for their hepatoprotective effects against paracetamol-induced HepG2 cell damage with the MTT assay (bicyclol is used as positive control group) and their effects on glucose consumption by the hexokinase (HK) method (insulin is used as positive control group) [16]. Compound **1** showed significant hepatoprotective activities at 10 μM (Table 2), and compound **2** moderately increased relative glucose consumption (Figure 6).

3. Experimental

3.1. General experiment procedures

Optical rotations were measured on a JASCO P-2000 polarimeter (JASCO Inc. Tokyo, Japan) using methanol as the solvent. The UV spectra were determined with

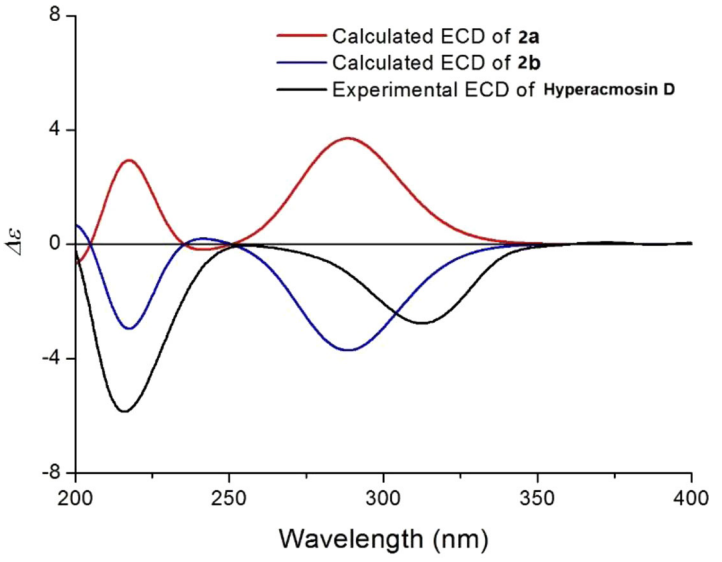

Figure 4. Calculated and experimental ECD spectra of **2**.

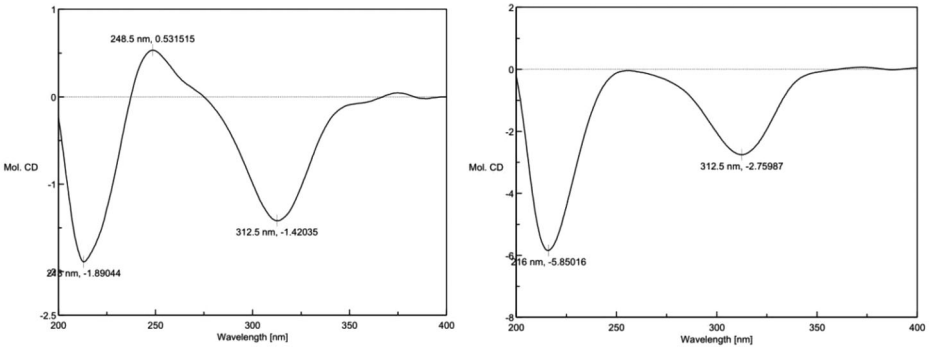

Figure 5. ECD spectra of compounds **1** and **2**.

a JASCO V-650 spectrophotometer (JASCO Inc.). The IR spectra were obtained using a Nicolet 5700 IR spectrometer (Thermo Nicolet, Waltham, MA, USA). The ECD spectra were obtained using a JASCO J-810 spectrometer (JASCO Inc.). The theoretical calculations of compounds 1 and 2 were performed using Gaussian 09. The theoretical calculations of ECD was performed using TD-DFT at APFD/6-31G(d) level in methanol with a PCM model. The NMR spectra were recorded on a Varian Inova-500 spectrometer (Varian Inc., Palo Alto, CA, USA), a Mecury-400 spectrometer (Varian Inc.) and a SYS-600 spectrometer (Varian Inc.) with trimethylsilane as an internal standard and $CDCl_3$ as the solvent. HR-ESI-MS were performed on an Agilent 1100 LC/MSD Trap-SL mass spectrometer (Agilent Technologies Ltd, Santa Clara, CA, USA). Silica gel (100–200 mesh and 200–300 mesh), silica gel H (Qingdao Haiyang Chemistry Company, Qingdao, China), MCI gel CHP20P ($35-75\,\mu$m, Mitsubishi Chemical Corp., Tokyo, Japan) were used for column chromatography and silica gel GF-254 (Qingdao Haiyang Chemistry Company) was used for TLC. HPLC experiments were carried out on a preparative YMC-Pack ODS-A column

Table 2. Hepatoprotective effects of **1** and **2** (10 μM) against paracetamol-induced HepG2 cell damage.[a]

Compound	OD value	Cell viability (% of normal)	Inhibition (% of control)
Normal	1.294 ± 0.082	100.00	–
Control	0.634 ± 0.046[b]	48.98	–
Bicyclol	0.735 ± 0.078[c]	56.83	15.30
Hyperacmosin C (**1**)	0.729 ± 0.078[d]	56.31	14.39
Hyperacmosin D (**2**)	0.713 ± 0.099	55.10	11.97

[a]Results were expressed as the mean ± SD ($n = 3$; for normal and control, $n = 6$); bicyclol was used as the positive control (10 μM).
[b]$P < 0.001$, compared with normal group.
[c]$P < 0.05$, compared with control group.
[d]$P < 0.01$, compared with control group.

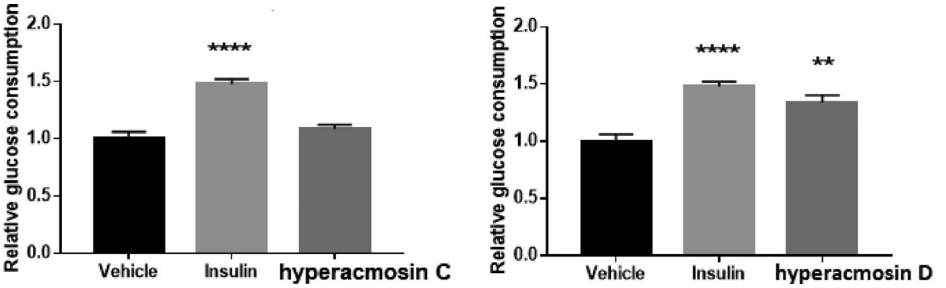

Figure 6. The relative glucose consumption of compounds **1** and **2**.

(250 × 10 mm, 5 μm; YMC, Tokyo, Japan). The absorbance of the relative glucose consumption were measured on enzyme-labeled instrument (SpectraMax M5, Molecular Devices, USA) and the absorbance of the hepatoprotective activities were measured on enzyme-labeled instrument (MQX-200, BioTek, USA). Glucose Assay Kit was purchased from Weirikang Biological, Wenzhou, China. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma-Aldrich (Saint Louis, MO, USA).

3.2. Plant material

The air-dried aerial parts of *Hypericum acmosepalum* were collected from Wenshan, Yunnan Province, China, in July 2016. The plant was identified by associate Prof. Lin Ma. A voucher specimen (No. ID-S-2764) was deposited in the herbarium of the Institute of Materia Medica, Chinese Academy of Medical Sciences.

3.3. Extraction and isolation

The dried and powdered aerial parts of *H. acmosepalum* (17.0 kg) were extracted by 95% ethanol (170 L × 3 times) under reflux. The crude extract was suspended in H_2O and partitioned with petroleum ether (10 L × 4 times). The petroleum ether extract (500.0 g) was subjected to a silica gel column (petroleum ether: ethyl acetate 1:0–0:1) to yield eleven fractions (Fr. 1–11). Fr. 1 (254.0 g) was separated on a MCI gel column (75%–95% EtOH) to yield six fractions (Fr. 1.1–Fr. 1.6). Fr.1.1 (94.0 g) was subjected to a silica gel column, eluting with petroleum ether–ethyl acetate

(1:0–9:1–4:1–2:1–0:1, V/V) to yield 20 fractions (Fr. 1.1.1–Fr. 1.1.20). Then Fr.1.1.7 (247.0 mg) was further purified by semipreparative HPLC (CH_3OH–H_2O, 95:5, v/v, detected at 254 nm, 3 ml/min) to give compound **1** (6.0 mg, t_R = 35.3 min) and compound **2** (14 .0 mg, t_R = 28.9 min).

3.3.1. Hyperacmosin C (1)

Colorless oil; $[\alpha]_D^{25}$ −12.30 (c 0.26 MeOH); UV: (MeOH) λ_{max} (log ε) 204 (4.46) nm; ECD (MeOH) $\Delta\varepsilon_{248.5\,nm}$ +0.53, $\Delta\varepsilon_{312.5\,nm}$ −1.42; IR (KBr) ν_{max} 3386, 2961, 2919, 1712, 1454, 1377 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 635.4290 $[M+Na]^+$ (calcd for $C_{38}H_{60}O_6Na$, 635.4293).

3.3.2. Hyperacmosin D (2)

Colorless oil; $[\alpha]_D^{25}$ −25.45 (c 0.22 MeOH); UV: (MeOH) λ_{max} (log ε) 204 (3.84) nm; ECD (MeOH) $\Delta\varepsilon_{312.5\,nm}$ −2.76; IR (KBr) ν_{max} 3397, 2969, 2925, 1758, 1715, 1448, 1380 cm^{-1}; ^1H and ^{13}C NMR spectral data, see Table 1; HRESIMS: *m/z* 621.4126 $[M+Na]^+$ (calcd for $C_{37}H_{58}O_6Na$, 621.4117).

3.4. Hepatoprotection bioassays (in vitro)

The hepatoprotective effects of compounds **1** and **2** were determined by a (MTT) colorimetric assay in HepG2 cells. Each cell suspension of 2×10^4 cells in 200 µl of RPMI 1640 containing fetal calf serum (10%), penicillin (100 U/ml), and streptomycin (100 µg/ml) was placed in a 96-well microplate and pre-cultured for 24 h at 37 °C under 5% CO_2 atmosphere. Fresh medium (100 µl) containing bicyclol and test samples was added, respectively, and the cells were cultured for 1 h. The cultured cells were exposed to 8 mM paracetamol for 24 h. Then, 100 µl 0.5 mg/ml MTT was added to each well after the withdrawal of the culture medium and incubated for an additional 4 h. The resulting formazan was dissolved in 150 µl DMSO after aspiration of the culture medium. The optical density (OD) of the formazan solution was measured on a microplate reader at 570 nm. Percent inhibition was calculated as: Inhibition (%) = [OD (sample) – OD (control)]/[OD (normal) – OD (control)] × 100%.

3.5. Glucose consumption bioassays

HepG2 cells (50,000 cells/well) were placed in a 96-well plate and incubated for 24 h. 0.03 μM insulin and 0.1 μM samples were added with the medium containing low-level glucose, respectively. After the cells were incubated for 24 h, the supernatant was detected for glucose consumption, and CCK8 was added to detect cell viability. The standard curve (0, 0.8125, 1.625, 3.25, 6.5, 13 mM) was established with Glucose Assay Kit (hexokinase method) as well. The relative glucose consumption was calculated according to the standard curve and the cell viability.

Disclosure statement

No potential conflict of interest was reported by the authors.

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