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Two new polycyclic polyprenylated acylphloroglucinols from *Hypericum curvisepalum* N. Robson

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ABSTRACT

Phytochemical investigation of the whole plant of *Hypericum curvisepalum* led to the isolation of nine polycyclic polyprenylated acylphloroglucinols (**1**–**9**). Among them, curvisepalumiones A (**1**) and B (**2**) are two new compounds and their structures were elucidated based on extensive spectroscopic data analysis combined with $Rh_2(OCOCF_3)_4$-induced electronic circular dichroism experiment. Cytotoxic assay showed that all the tested compounds except for **1** was moderately cytotoxic against human hepatocarcinoma cell line SMMC-7721 cell line, while compounds **3** and **4** also exhibited cytotoxicity toward MGC-803 cells. In addition, compound **2** exhibited weak inhibitory activity against *Bacillus subtilis*.

1. Introduction

Hypericum, the largest genus within the plant family Hypericaceae, comprises nearly 500 species throughout the world (Robson, 2012) and many of them have been commonly used as traditional remedies (Avato, 2005; Yaylaci et al., 2013). Investigations of the constituents from the genus *Hypericum* have revealed a large number of biologically active and structurally interesting metabolites. Especially, the polycyclic polyprenylated acylphloroglucinols (PPAPs) have attracted much attention for their fascinating chemical structures and promising bioactivities including antibacterial, anticancer, antidepressant, anti-inflammatory, anti-HIV, anti-neurodegenerative, antioxidant, antiulcer, and antimalarial activities (Verotta, 2002). *H. curvisepalum* N. Robson is distributed in southwest of China (Flora of China Editorial Committee of Chinese Academy of Sciences, 1990). To our knowledge, only two PPAPs have been reported from this plant to date (Sun et al., 2021). As a part of our ongoing search for bioactive compounds from *Hypericum* spp., the whole plant of *H. curvisepalum* was phytochemically studied, resulting in the isolation of nine PPAPs including two new ones (**1** and **2**). Herein, the isolation and structural elucidation of the new compounds and their biological activities are described.

2. Results and discussion

Curvisepalumione A (**1**) was obtained as colorless oil. Its molecular formula, $C_{36}H_{56}O_7$, was determined based on the HRESIMS ion at *m/z* 601.4102 $[M+H]^+$ (calcd. for $C_{36}H_{57}O_7$, 601.4104). The UV spectrum showed an absorption maximum at 271 nm. The IR spectrum exhibited absorption bands due to hydroxy (3414 cm^{-1}) and carbonyl (1724 cm^{-1}) groups. In the ^1H NMR spectrum, signals assignable to an isopropyl group (δ_H 1.10, 1.03, and 2.01), two olefinic protons (δ_H 5.10 and 4.96), and nine methyl singlets were clearly observed. The ^{13}C NMR (Table 1) and HSQC spectra displayed 36 resonances including those for an enolized 1,3-diketo functionality (δ_C 193.0, 116.9, and 173.1), two unconjugated carbonyl groups (δ_C 209.8 and 204.7), three quaternary carbons (δ_C 49.0, 59.6, and 82.9), a methine carbon (δ_C 41.3), and a methylene (δ_C 38.1) carbon. These spectroscopic findings suggested that **1** was a PPAP and structurally resembled known compound

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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**	
	δ_H (δ in ppm, J in Hz)	δ_C	δ_H (δ in ppm, J in Hz)	δ_C
1		204.7		204.6
2		82.9		83.3
3		49.0		48.4
4	1.72 m	41.3	1.63 m	43.7
5	2.08 m	38.1	2.03 m	38.1
	1.54 t (12.5)		1.50 t (13.0)	
6		59.6		59.6
7		173.1		173.3
8		116.9		116.9
9		193.0		193.0
10		209.8		209.7
11	2.01 m	42.3	1.98 m	42.2
12	1.10 d (6.0)	21.6	1.08 d (6.5)	21.5
13	1.03 d (6.0)	20.6	0.99 d (6.5)	20.6
14	1.10 s	15.7	1.04 s	13.5
15	2.14 m	34.1	2.03 m	34.0
	1.87 m		1.80 m	
16	2.03 m	27.3	1.80 m	28.4
	1.47 m		1.27 m	
17	3.36 d (9.0)	77.2	3.35 d (10.0)	76.8
18		77.6		77.7
19	1.10 s	20.8	1.10 s	20.9
20	1.14 s	19.7	1.14 s	19.8
21	2.18 m	27.1	2.25 m	27.1
	1.77 m		1.77 m	
22	4.96 t (5.5)	122.3	4.94 t (5.5)	122.4
23		133.6		133.6
24	1.72 s	26.1	1.65 s	26.1
25	1.59 s	18.2	1.57 s	18.1
26	3.16 dd (14.0, 7.0)	22.3	3.16 dd (14.0, 7.0)	22.3
	3.05 dd (14.0, 7.0)		3.01 dd (14.0, 7.0)	
27	5.10 t (7.0)	121.4	5.07 t (7.0)	121.3
28		132.7		132.7
29	1.68s	25.8	1.69 s	25.8
30	1.72 s	18.0	1.69 s	18.0
31	2.66 dd (12.5, 11.5)	30.4	2.66 dd (12.0, 11.5)	30.3
	1.80 m		1.80 m	
32	4.57 q (5.5)	90.2	4.55 q (5.5)	90.3
33		71.0		71.0
34	1.41 s	27.1	1.38 s	27.2
35	1.24 s	24.2	1.21 s	24.2
OCH3	3.23 s	49.2	3.20 s	49.2

furohyperforin (Verotta et al., 1999). The marked difference was that the side chain attached to C-3 was a 3-methoxy-3-methyl-2-butanol moiety in **1** rather than the prenyl group in furohyperforin. This deduction was corroborated by HMBC interactions (Figure 2) from H_2-15 (δ_H 2.14 and 1.87) to C-2 (δ_C 82.9) and C-3 (δ_C 49.0), and from H_2-16 (δ_H 2.03 and 1.47) to C-15 (δ_C 34.1), and from H-17 (δ_H 3.36) to C-15 (δ_C 34.1), C-16 (δ_C 27.3), C-18 (δ_C 77.6) and C-20 (δ_C 19.7). The relative configuration of **1** was determined based upon analysis of ROESY data. Specifically, the cross-peaks of H-5α (δ_H 2.08) with H-32 (δ_H 4.57), and of H-5β (δ_H 1.54) with H_3-14 (δ_H 1.10) indicated that the Me-14 and H-32 adopted β and α orientations, respectively. To clarify the absolute configuration of C-17, $Rh_2(OCOCF_3)_4$-induced ECD experiments were performed (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990), which exhibited a negative E band correlating with the 17*R* configuration by applying the bulkiness rule (Figure 3. Accordingly, the structure of **1** was assigned (Figure 1).

Curvisepalumione B (**2**) had the same molecular formula as **1** according to its sodium adduct ion at *m/z* 623.3921 ($[M + Na]^+$, calcd. for $C_{36}H_{56}NaO_7$, 623.3924) in the HRESIMS spectrum. A comparison of the NMR data of **2** with those of **1** suggested that the two compounds were a pair of C-17 epimers. The 17*S* configuration of **2** was determined by the positive E band of the in situ [$Rh_2(OCOCF_3)_4$] complex-induced ECD spectrum (Frelek and Szczepek, 1999; Gerards and Snatzke, 1990).

Seven known compounds were identified as oxepahyperforin (**3**) (Verotta et al., 2000), furoadhyperforin (**4**) (Verotta et al., 1999), uralodin A (**5**) (Guo et al., 2008), uralione H (**6**) (Zhou et al., 2016), uralodin B (**7**) (Chen et al., 2010), hypercohin E (**8**) and hypercohin F (**9**) (Liu et al., 2013) by comparison of their spectroscopic data with those reported in the literatures.

It is well-known that PPAPs isolated from the genus *Hypericum*, such as *H. scabrum* (Matsuhisa et al., 2002), *H. ascyron* (Niwa et al., 2019), *H. perforatum* (Lou et al., 2020), and *H. elodeoides* (Qiu et al., 2021), possess cytotoxicity or antibacterial activities. Owing to insufficient amounts of three compounds (**5**, **6**, and **9**), the cytotoxic effects of the other six isolates (**1**–**4**, **7**, and **8**) against two human cancer cell lines SMMC-7721 and MGC-803, as well as their antibacterial activity against three bacterial strains including *Bacillus subtilis*, methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant *Pseudomonas aeruginosa* (MDRPA), were evaluated. As showed in Table 2, all tested

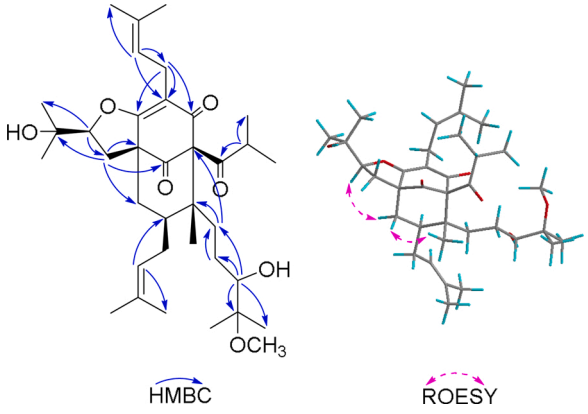

Fig. 2. Selected 2D NMR correlations of compound **1**.

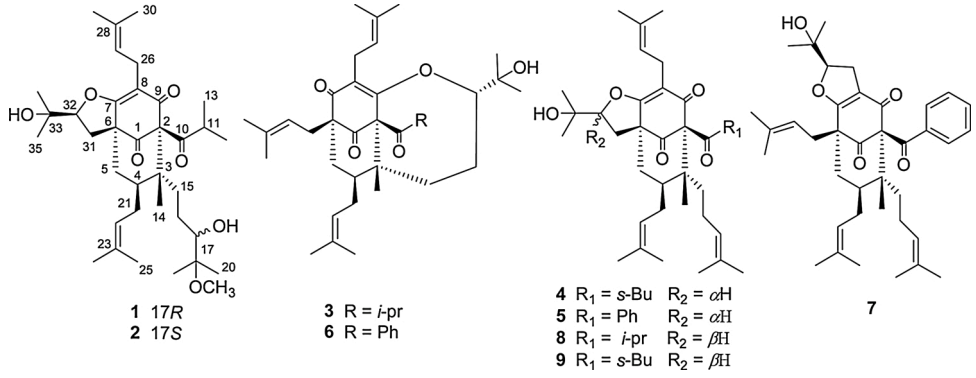

Fig. 1. Structures of compounds **1**–**9**.

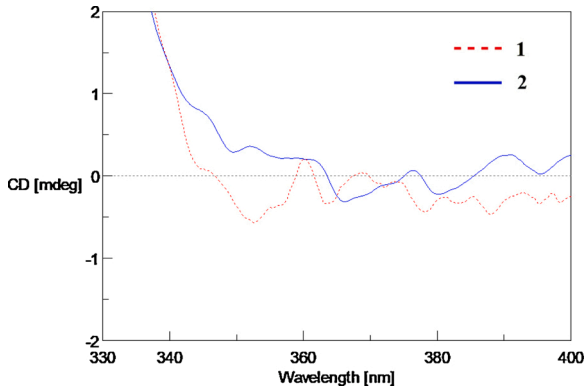

Fig. 3. [$Rh_2(OCOCF_3)_4$]-induced ECD spectra of compounds **1** and **2** in CH_2Cl_2.

Table 2
Cytotoxic and antimicrobial activities of the isolates from *H. curvisepalum* [a,b].

Compounds	Cytotoxicities[a]		Antimicrobial activities [b]		
	SMMC-7721	MGC-803	*B. subtilis*	MRSA	MDPRA
1	>160	>160	>320	>320	>320
2	70.30 ± 0.02	>160	320	>320	>320
3	24.41 ± 0.01	120.70 ± 0.01	>320	>320	>320
4	18.71 ± 0.02	99.57 ± 0.01	>320	>320	>320
7	45.79 ± 0.01	>160	>320	>320	>320
8	33.10 ± 0.01	>160	>320	>320	>320
5-Fu[c]	76.28 ± 0.01	124.20 ± 0.02	–	–	–
Paclitaxel[c]	9.18 ± 0.03	2.00 ± 0.01	–	–	–
Amoxicillin[c]	–	–	80	40	>320
Piperacillin[c]	–	–	–	–	160

"-" : no test.
[a] Results are expressed as IC_{50} values in μM. Compounds with IC_{50} > 160 μM are not shown.
[b] Results are expressed as MIC values in μM. Compounds with IC_{50} > 320 μM are not shown.
[c] Positive controls.

compounds except **1** manifested cytotoxicity against SMMC-7721 cells with IC_{50} values ranging from 18.71 to 70.30 μM, whereas **3** and **4** also exhibited cytotoxicity against MGC-803 cells (IC_{50} 120.7 and 99.57 μM, respectively). Furthermore, compound **2** was found to inhibit *B. subtilis* with MIC value of 320 μM.

3. Experimental

3.1. General

Optical rotations were obtained using a Rudolf AUTOPOL IV polarimeter. The UV spectra were recorded on a Shimadzu UV-2700 spectrophotometer. A Thermo Scientific Nicolet iN10 Microscope was used to measure the IR spectra. NMR spectra were acquired in $CDCl_3$ at 303 K on a Bruker AVANCE III-500 NMR spectrometer with TMS as internal standard. A Bruker SolariX 7T FTICRMS was adopted to obtain HRESIMS data. Preparative HPLC was carried out on a Shimadzu HPLC system consisted of a LC-6AD pump and a Shimadzu SPD-20A detector, coupled with a Shim-park RP-C_{18} column (5 μm, 200 × 20 mm i.d., Shimadzu). Silica gel (200–400 mesh, Qingdao Marine Chemical Co., Ltd.), ODS (40–63 μm, Fuji), and Sephadex LH-20 (Pharmacia) were used for open column chromatography.

3.2. Plant material

The whole plants of *Hypericum curvisepalum* N. Robson were collected during its flowering stage in Yunnan Province, People's Republic of China, in May 2019, and identified by the author (Teng, L-P). Voucher specimens (No. TLM-201903) were deposited in Xinjiang Production & Construction Corps Key Laboratory of Protection and Utilization of Biological Resources in Tarim Basin, Tarim University.

3.3. Extraction and isolation

The air-dried whole plant of *H. curvisepalum* (10 kg) were powdered and extracted with MeOH (3 × 30 L) under reflux. The extract was evaporated to obtained a residue under reduced pressure. The residue (1648 g) was subjected to a silica gel column, eluted with petroleum ether (to get Fr. A), ethyl acetate (to give Fr. B) and MeOH (to afford Fr. C). The ethyl acetate extract (Fr. B, 422 g) was treated by passage over another silica gel column eluted with a gradient of petroleum ether–ethyl acetate (1:0 to 0:1) to give five fractions (Fr. B1–B5). Fr. A and B1 were merged for containing similar chemical compositions by HPLC analysis, and dissolved in MeOH then filter out the residue to afford fraction D. Fr. D (103 g) was reseperated by MPLC (MeOH - H_2O, 70:30 to 100:0) to give three fractions (D1–D3). Fr. D3 (59 g) was further separated by a silica gel column using a gradient of n-hexane - Acetone (25:1 to 5:1) to yield four fractions (D3a–D3d). Fr. D3b (11 g) was subjected to a silica gel column, eluted with a gradient of methylene dichloride–ethyl acetate (80:1 to 30:1) to give sixteen fractions (D3b1–D3b16). Fr. D3b6 (2.1 g) was further seperated by a LH-20 column and eluted with MeOH to afford five fractions (D3b6a –D3b6e). Fr. D3b6c (1.8 g) was subjected to preparative HPLC (85 % MeOH in H_2O, 10 mL/min) to afford eight fractions (D3b6c1–D3b6c8). Fr. D3b6c1 (676 mg) was seperated by preparative HPLC (85 % MeOH in H_2O, 10 mL/min) to afford **1** (1.5 mg) and **2** (1.8 mg). Fr. D3b5 (635 mg) was seperated by preparative HPLC (90 % MeOH in H_2O, 10 mL/min) to produce **3** (37.8 mg), **4** (262.1 mg), **5** (21.4 mg), and **6** (12.3 mg). Fr. D3b7 (623 mg) was reseperated by preparative HPLC (90 % MeOH in H_2O, 10 mL/min) to obtain **7** (36.5 mg). Fr. D3b4 (268 mg) was further purified by preparative HPLC (85 % MeOH in H_2O, 10 mL/min) to yield **8** (61.5 mg) and **9** (22.7 mg).

Curvisepalumione A (**1**): colorless oil; [α]25 D +50.0 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) 271 (3.91) nm; CD ($c = 1.0 \times 10^{-3}$, MeOH) λ_{max} nm (Δε) 230 (+ 70.3), 251 (– 23.9), 275 (+ 81.3), 303 (– 30.9), 333 (+ 1.5); IR (KBr) ν_{max} cm^{-1} 3414, 2975, 2933, 1724, 1613, 1382, 1221, 1076, 852; ^1H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 601.4102 $[M+H]^+$ (calcd for $C_{36}H_{57}O_7$, 601.4105).

Curvisepalumione B (**2**): colorless oil; [α]25 D +78.8 (*c* 0.17, MeOH); UV (MeOH) λ_{max} (log ε) 272 (4.06) nm; CD ($c = 1.0 \times 10^{-3}$, MeOH) λ_{max} nm (Δε) 228 (+ 35.3), 250 (– 9.9), 275 (+ 38.6), 305 (– 12.5), 329 (+ 2.1); IR (KBr) ν_{max} cm^{-1} 3420, 2976, 2933, 1728, 1619, 1447, 1379, 1217, 1154, 1072, 857; ^1H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 623.3921 $[M + Na]^+$ (calcd for $C_{36}H_{56}O_7Na$, 623.3917).

3.4. Absolute configuration of C-17 in 1 and 2

The in situ formed [$Rh_2(OCOCF_3)_4$] complex method was used according to the published procedure (Gerards and Snatzke, 1990; Frelek and Szczepek, 1999). The dirhodium trifluoroacetate [$Rh_2(OCOCF_3)_4$] complex (1.0 mg) was dissolved in CH_2Cl_2 (400 μL). After mixing with compounds **1** or **2** (0.5 mg each), the first ECD spectrum was recorded immediately, and the time evolution was monitored until stationary (about 10 min). The inherent ECD spectrum was subtracted. The absolute configuration of the tertiary alcohol in the tested compounds could be deduced from the E band observed at around 350 nm in the induced ECD spectrum.

3.5. Cytotoxicity assay

Two selected human hepatoma carcinoma cell lines SMMC-7721 and human gastric cancer cell MGC-803 were seeded in 96-well plates at 37 °C for 24 h with a density of 1×10^5 cells per well. After that, cells were treated with various concentrations of test compounds and incubated at

37 °C for 24 h. And then, 100 μL fresh RPMI1640 medium (Keygen Biotechnology, China) and 10 μL CCK8 (Beyotime Biotechnology, China) were added in 96 well plates incubated for another 4 h. The absorbance (450 nm) was recorded by a microplate reader (UH5300, Hitachi, Japan). The experiments were repeated three times. 5-Flurouacil (5-Fu, HPLC $\geq$ 98 %, Shanghai Yuanye Bio-Technology Company, China) and paclitaxel (HPLC $\geq$ 98 %, Shanghai Yuanye Bio-Technology Company, China) as a positive control.

3.6. Antibacterial assay

B. subtilis (MTCC619), along with two resistant strains methicillin-resistant *S. aureus* (MRSA), and multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) were used as target strains. Briefly, compounds of initial concentration 320 μM were serially diluted twofold with LB medium. The inoculate bacteria suspension were diluted 10 times with LB broth to obtain a working suspension 1×10^6 CFU/mL. And then, 10 μL of the working suspension was added to each well. The concentrations of tested compounds ranged from 320 to 2.5 μM. Amoxicillin and piperacillin were used as positive controls and medium without compounds were used as growth control. The microplates were incubated at 37 $\pm$ 2 ℃ for 24 h and MICs were determined.

Declaration of Competing Interest

There was no conflict of interest in all the authors.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2022.01.015.

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