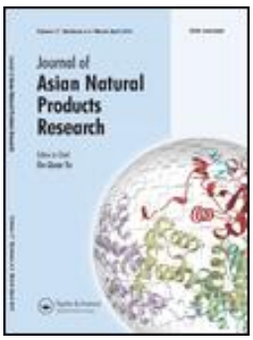

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Two new prenylated phloroglucinol derivatives from *Hypericum scabrum*

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ABSTRACT

Two new prenylated phloroglucinol derivatives (**1**–**2**), and a known compound furohyperforim isomer 2 (**3**), were isolated from the aerial parts of *Hypericum scabrum*. Their structures were elucidated by various spectroscopic methods, including MS, IR, UV, and NMR.

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Guttiferae; *Hypericum scabrum*; prenylated phloroglucinol derivatives; furohyperforim

1. Introduction

The plants of the genus *Hypericum* (family Guttiferae), such as St. John's wort, have been used as herbal medicine for the treatment of mild-to-moderate depression [1]. Unfortunately, it showed some side effects such as gastrointestinal irritations, allergic reactions, fatigue, restlessness, and acute neuropathy [2]. Thus, it is urgent for researchers to find the constituents of antidepressant activity so as to avoid adverse reaction of *H. perforatum*. Then, hyperforin and adhyperforin, which were isolated from *H. perforatum,* are thought to be accounted for some of the antidepressant activity of St. John's wort [3]. Although hyperforin and adhyperforin inhibit the synaptosomal uptake of some neurotransmitters, such as dopamine, serotonin, and norepinephrine *in vitro* [4], it is uncertain whether this mechanism is effective *in vivo* [5,6]. Thus, it is very important for researchers to find the source of polycyclic polyprenylated acylphloroglucinols (PPAPs) from the traditional medicine. *Hypericum scabrum*, which is mainly distributed in Xinjiang Uygur Autonomous Region, China, is used to treat some disorders, for example, rheumatism, heart disease, intestinal disease, and cystitis [7]. It has been some chemically investigated, which resulted in the isolation of many secondary metabolites, including phloroglucinols, xanthones, flavones, naphthodianthrones, and so on [8,9]. Our research team previously reported many phloroglucinols compounds, such as hyperscabrin A, hyperscabrin B, and hyperscabrin C [10], and another two polyprenylated acylphloroglucinols were isolated from *H. scabrum* [11]. Thus, in order to clarify its chemical constituents further and find more PPAPs, studies on the chemical constituents of *H. scabrum* resulted in the isolation of another two new prenylated phloroglucinol derivatives (Figure 1), which were reported by mistake in the literature [12].

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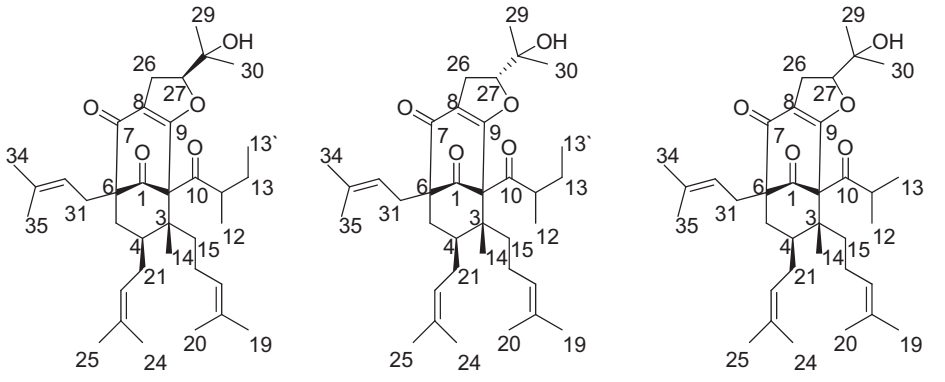


1 **2** **3**

Figure 1. Structures of compounds **1**, **2,** and **3**.

2. Results and discussion

Compound **1** was isolated as a colorless oil, which showed a green spot on thin-layer chromatography (TLC) plates when sprayed with anisaldehyde–sulfuric acid reagent. The molecular formula, $C_{36}H_{54}O_5$, was determined by HRESI-MS at *m/z* 567.4024 $[M+H]^+$, corresponding to 10° of unsaturation. The IR spectrum showed absorption bands at 3436 and 1725 cm^{-1}, indicative of the presence of hydroxyl and carbonyl groups. The UV spectrum showed absorption maxima at 207 and 281 nm. The ^1H NMR spectrum of **1** ($CDCl_3$, Table 1) showed the presence of 11 methyl signals [δ_H 1.12 (3H, d, J = 6.8 Hz, H-12), 0.89 (3H, t, J = 7.6 Hz, H-13′), 1.13 (3H, s, H-14), 1.67 (3H, s, H-19), 1.54 (3H, s, H-20), 1.65 (9H, s, H-24, 34, 35), 1.57 (3H, s, H-25), 1.38 (3H, s, H-29), and 1.24 (3H, s, H-30)], three vinylic protons [δ_H 4.98 (1H, t, J = 8.0 Hz, H-17), 4.93 (1H, t, J = 6.8 Hz, H-22), and 5.00 (1H, dd, J = 14.4, 7.2 Hz, H-32)]. The ^{13}C NMR spectrum of **1** ($CDCl_3$, Table 1) revealed 36 carbon signals, which could be sorted by HSQC experiment into 12 quaternary carbons, including three carbonyls [δ_C 205.6 (C-1), 190.6 (C-7), and 208.2 (C-10)], six methines [δ_C 42.5 (C-4), 47.6 (C-11), 124.4 (C-17), 122.3 (C-22), 119.5 (C-32), and 93.9 (C-27)], and 11 methyls [δ_C 16.7 (C-12), 11.2 (C-13′), 14.3 (C-14), 25.6 (C-19), 17.7 (C-20), 25.9 (C-24), 17.9 (C-25), 26.7 (C-29), 25.4 (C-30), 25.9 (C-34), and 18.0 (C-35)]. Furthermore, the following characteristic spectral features are coincided with those of furohyperforim [12] [δ_H 2.98 (2H, dd, J = 10.4, 2.4 Hz, H-26), 4.75 (1H, t, J = 10.4 Hz, H-27), 1.24 (3H, s, H-30), and 1.38 (3H, s, H-29), δ_C 26.6 (C-26), 93.9 (C-27), 70.9 (C-28), 26.7 (C-29), and 25.4 (C-30)]. Additionally, the 1D-NMR data were similar to those of furohyperforim isomer 2 [13], except for the signals of C-11, C-12, and C-13. This fact indicated that **1** had 2-methylbutanoyl group at C-2 instead of a 2-methylpropanoyl group in furohyperforim isomer 2.

Meanwhile, the HMBC spectrum (Figure 2) of compound **1** showed long-range correlations between H-12 (δ_H 1.12) and C-10 (δ_C 208.2), C-11 (δ_C 47.6) and C-13 (δ_C 28.1); H-13′ (δ_H 0.89) and C-11 (δ_C 47.6) and C-13 (δ_C 28.1), indicating the presence of 2-methylbutanoyl group. The HMBC spectrum showed correlations of H-15 (δ_H 1.61) with the carbon signals C-3 (δ_C 47.7), C-4 (δ_C 42.5), C-14 (δ_C 14.3), C-16 (δ_C 24.4), and C-17 (δ_C 124.4);

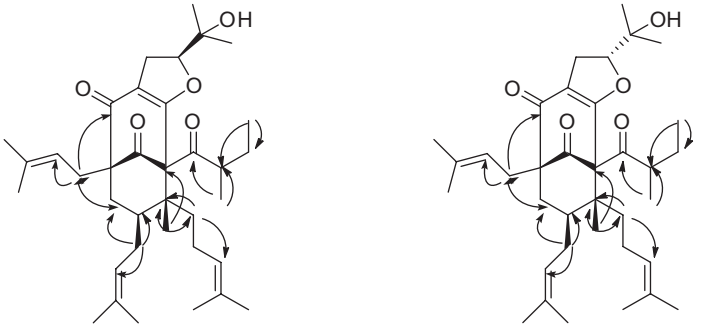
Table 1. ^{1}H and ^{13}C NMR spectral data of compounds **1**, **2,** and **3** in $CDCl_3$ (***δ*** in ppm, ***J*** in Hz).

	Compound **1**		Compound **2**		Compound **3**	
Position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1		205.6		205.7		205.6
2		73.9		74.6		74.0
3		47.7		47.2		47.5
4	1.65–1.69, m	42.5	1.52–1.56, m	44.2	1.65–1.69, m	42.2
5	1.82,dd (14.0, 3.2); 1.40–1.42, m	39.5	1.81,dd (13.2, 4.4); 1.35–1.39, m	39.5	1.83, dd (13.6, 4.0); 1.36–1.40, m	39.5
6		63.9		63.6		63.9
7		190.6		190.8		190.6
8		120.6		120.3		120.6
9		171.5		171.7		171.5
10		208.2		208.4		208.7
11	2.26–2.30, m	47.6	2.13–2.17, m	47.6	2.44–2.52, m	40.8
12	1.12, d (6.8)	16.7	1.16, d (6.4)	17.0	1.14, d (1.3)	21.0
13	2.02–2.08, m; 1.66–1.70, m	28.1	1.71–1.77, m; 1.25–1.29, m	27.9	1.15, d (1.3)	21.0
14	1.13, s	14.3	1.11, s	12.8	1.13, s	14.4
15	1.60–1.62, m	38.2	1.75–1.79, m; 1.42–1.44, m	39.2	1.64–1.68, m; 1.56–1.60, m	38.1
16	1.93–1.97, m	24.4	2.13–2.17, m; 1.98–2.03, m	24.8	1.98–2.03, m; 1.91–1.97, m	24.3
17	4.98, t (8.0)	124.4	5.00, t (8.0)	124.3	4.96–5.00, m	124.4
18		131.6		132.2		131.6
19	1.67, s	25.6	1.66, s	25.6	1.65, s	25.6
20	1.54, s	17.7	1.58, s	17.8	1.56, s	17.7
21	1.76–1.78, m; 1.46–1.48, m	26.5	2.06–2.10, m; 1.68–1.72, m	26.4	2.03–2.07, m; 1.68–1.73, m	28.1
22	4.93, t (6.8)	122.3	4.91, t (6.8)	122.3	4.93, t (8.0)	122.2
23		133.4		133.4		133.4
24	1.65, s	25.9	1.66, s	25.8	1.64, s	25.9
25	1.57, s	17.9	1.52, s	17.9	1.54, s	17.9
26	2.98, dd (10.4, 2.4)	26.6	3.06, dd (14.8, 10.4), 2.91, dd (14.8, 10.4)	26.7	2.98, d (10.4);	26.7
27	4.75, t (10.4)	93.9	4.62, t (10.4)	93.5	4.76, t (10.4)	93.2
28		70.9		71.0		71.0
29	1.38, s	26.7	1.33, s	27.0	1.37, s	26.0
30	1.24, s	25.4	1.24, s	25.1	1.24, s	25.3
31	2.42–2.44, m	29.2	2.42–2.44, m	29.1	2.42–2.44, m	29.2
32	5.00, dd (14.4,7.2)	119.5	5.00, dd (15.6,7.2)	119.5	4.98–5.01, m	119.5
33		134.1		134.2		134.2
34	1.65, s	25.9	1.66, s	25.9	1.67, s	26.0
35	1.65, s	18.0	1.66, s	18.1	1.64, s	18.0
13`	0.89, t (7.6)	11.2	0.88, t (7.6)	11.8		

Note: Measured in $CDCl_3$ at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, with assignments confirmed by HSQC and HMBC.

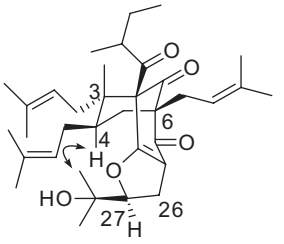
H-21 (δ_H 1.77) with the carbon signals C-3 (δ_C 47.7), C-4 (δ_C 42.5), C-5 (δ_C 39.5), and C-22 (δ_C 122.3); H-31 (δ_H 2.43) with the carbon signals C-1 (δ_C 205.6), C-5 (δ_C 39.5), C-6 (δ_C 63.9), C-7 (δ_C 190.5), and C-32 (δ_C 119.5); Me-14 (δ_H 1.13) with the carbon signals C-2 (δ_C 73.9), C-3 (δ_C 47.7), C-4 (δ_C 42.5), and C-15 (δ_C 38.2); indicating that two prenyl side chains were connected to C-4 and C-6, and a 4-methyl-3-pentenyl side chain was connected to C-3, respectively.

The relative configuration of **1**, except for the spatial configuration of C-27, was elucidated as the same as that of furohyperforim isomer 2 based on the marked similarity of their 1D-NMR data. In the NOESY experiment [14], H-4 showed cross-peaks to the Me-29 signal



1 **2**

Figure 2. Key HMBC correlations of compounds **1** and **2**.



1

Figure 3. Key NOESY correlations of compound **1**.

(Figure 3). Thus, the orientation of H-27 in **1** was *α*. Unluckily, the relative configuration of C-11 cannot be inferred from the NOESY experiment. Consequently, compound **1** was elucidated as shown in Figure 1 and named as furoadhyperforim isomer 2a.

Compound **2** was isolated as a colorless oil, which showed a green spot on TLC plates when sprayed with anisaldehyde–sulfuric acid reagent. The molecular formula, $C_{36}H_{54}O_5$, was determined by HRESI-MS at *m/z* 567.4022 $[M+H]^+$, corresponding to 10° of unsaturation. The IR spectrum showed absorption bands at 3438 and 1722 cm^{-1}, indicative of the presence of hydroxyl and carbonyl groups. The UV spectrum showed absorption maxima at 207 and 281 nm. The ^1H NMR spectrum of **2** ($CDCl_3$, Table 1) showed the presence of 11 methyl signals [δ_H 1.16 (3H, d, J = 6.4 Hz, H-12), 0.88 (3H, t, J = 7.6 Hz, H-13′), 1.11(3H, s, H-14), 1.58 (3H, s, H-20), 1.66 (12H, s, H-19, 24, 34, 35), 1.52 (3H, s, H-25), 1.33 (3H, s, H-29), and 1.24 (3H, s, H-30)], three vinylic protons [δ_H 5.00 (1H, t, J = 8.0 Hz, H-17), 4.91 (1H, t, J = 6.8 Hz, H-22), and 5.00 (1H, dd, J = 15.6, 7.2 Hz, H-32)]. The ^{13}C NMR spectrum of **1** ($CDCl_3$, Table 1) revealed 36 carbon signals, which could be sorted by HSQC experiment into 12 quaternary carbons, including three carbonyls [δ_C 205.7 (C-1), 190.8 (C-7), and 208.4 (C-10)], six methines [δ_C 44.2 (C-4), 47.6 (C-11), 124.3 (C-17), 122.3 (C-22), 119.5 (C-32), and 93.5 (C-27)], and 11 methyls [δ_C 17.0 (C-12), 11.8 (C-13′), 12.8 (C-14), 25.6 (C-19), 17.8 (C-20), 25.8 (C-24), 17.9 (C-25), 27.0 (C-29), 25.1 (C-30), 25.9 (C-34), and 18.1 (C-35)]. The IR, UV, and NMR spectra of compound **2** (Table 1) were similar with those of compounds **1** and **3**, which indicated **2** had 2-methylbutanoyl group

at C-2 instead of a 2-methylpropanoyl group in furohyperforim isomer **2**. Meanwhile, the HMBC spectrum (Figure 2) of compound **2** showed long-range correlations between H-12 (δ_H 1.16) and C-10 (δ_C 208.4), C-11 (δ_C 47.6) and C-13 (δ_C 27.9); H-13′ (δ_H 0.88) and C-11 (δ_C 47.6), and C-13 (δ_C 27.9), indicating the presence of 2-methylbutanoyl group. The HMBC spectrum showed correlations of H-15 (δ_H 1.77) with the carbon signals C-3 (δ_C 47.2), C-4 (δ_C 44.2), C-14 (δ_C 12.8), C-16 (δ_C 24.8), and C-17 (δ_C 124.3); H-21 (δ_H 1.77) with the carbon signals C-3 (δ_C 47.2), C-4 (δ_C 44.2), C-5 (δ_C 39.5), and C-22 (δ_C 122.3); H-31 (δ_H 2.43) with the carbon signals C-1 (δ_C 205.7), C-5 (δ_C 39.5), C-6 (δ_C 63.6), C-7 (δ_C 190.8), and C-32 (δ_C 119.5); Me-14 (δ_H 1.11) with the carbon signals C-2 (δ_C 74.6), C-3 (δ_C 47.2), C-4 (δ_C 44.2), and C-15 (δ_C 39.2); indicating that two prenyl side chains were connected to C-4 and C-6, and a 4-methyl-3-pentenyl side chain was connected to C-3, respectively. Thus, compounds **2** and **1** were epimers at C-27.

The relative configuration of **2**, except for the spatial configuration of C-27, was elucidated as the same as that of furohyperforim isomer 2 based on the marked similarity of their 1D-NMR data. In the NOESY experiment, H-4 showed no cross-peaks to the Me-29 or Me-30 signal. Meanwhile, the relative configuration of C-11 cannot be inferred from the NOESY experiment. Fortunately, there is a rule to distinguish spatial configuration of C-27 by ^{1}H NMR [12], and the chemical shifts of H-27 for **2** and **1** (δ_H 4.62 in **2**; δ_H 4.75 in **1**) measured in $CDCl_3$ were similar with the fact reported by Chika Hashida. Thus, the orientation of H-27 in **2** may be β. Consequently, the relative stereochemistry of C-27 in **1** and **2** were elucidated as shown in Figure 1 and named as furoadhyperforim isomer 2a and furoadhyperforim isomer 2b, respectively.

The known compounds were identified as furohyperforim isomer 2 (**3**) by comparison of its spectral data with those reported in the literature [13].

3. Experimental

3.1. General experimental procedures

UV spectra were collected in absolute MeOH on a JASCO V-650 spectrophotometer (JASCO Inc, Tokyo, Japan). The IR spectra were obtained on Nicolet 5700 IR spectrometer (Thermo Nicolet Inc, Waltham, MA, USA). Optical rotations were measured with a JASCO P-2000 polarimeter (JASCO Inc, Tokyo, Japan). ^{1}H-NMR, ^{13}C NMR, and 2D-NMR spectra were recorded on Varian Inova-500 spectrophotometer (Varian Inc, Palo Alto, CA, USA). ESI-MS was performed with Angilent 1100 LC/MSD (Agilent Technologies Ltd, Santa Clara, CA, USA). Silica gel (200–300 mesh, Qingdao Marine Chemistry Company, Qingdao, China) and silica gel H were used for column chromatography (CC) and silica gel GF-254 (Qingdao Marine Chemistry Company, Qingdao, China) was used for TLC. Additionally, Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Uppsala, Sweden), YMC-Pack ODS-A column (250 × 20 mm, 5 μm, kyoto, Japan), and ODS (40–60 mm, Alltech, Deerfield, IL, USA) were used.

3.2. Plant material

The aerial parts of *Hypericum scabrum* were obtained from the Wusun Mountain, Xinjiang Uygur Autonomous Region, China, in August 2010. The plant was identified by associate

Prof. Lin Ma, Institute of Materia Medica, Chinese Academy of Medicinal Sciences and Peking Union Medical College. A voucher specimen (No. ID-S-2370) was deposited in the Institute of Materia Medica, Chinese Academy of Medical Sciences.

3.3. Extraction and isolation

The air-dried aerial parts of *H. scabrum* (80.0 kg) were extracted three times by 95% EtOH under reflux. The obtained EtOH extracts were concentrated under reduced pressure below 45 °C and give a residue (11.0 kg), which was partitioned with petroleum ether (PE), EtOAc, and *n*-BuOH successively. The PE fraction (1.2 kg) was subjected to flash CC over silica gel (200–300 mesh) eluting with PE–EtOAc (100:1–4:1) and provided fractions A_1–A_{60}. Fractions A_{44}–A_{48} (50.78 g) were subjected to CC with CH_2Cl_2–Et_2O (40:1) affording fractions B_1–B_{13}. Fractions B_1–B_5 (15 g) were subjected to flash CC, eluting with PE–EtOAc (5:1), and give 13 fractions C_1–C_{13}. Fractions C_{10}–C_{11} (4.0 g) were chromatographed on a silica gel H, eluting with PE–EtOAc (4:1) and CH_2Cl_2–Et_2O (4:1), and gave 16 fractions D_1–D_{16}. Fractions D_7–D_9 (680 mg) were separated by preparative HPLC purification with MeOH–H_2O (90:10) (YMC, 250 × 20 nm, S-5 μm; 210 nm; 5 ml/mim), leading to the isolation of compounds **1** (23 mg, 41.0 min) and 2 (7 mg, 48.0 min). Fractions D_{10}–D_{11} (400 mg) were separated by preparative HPLC purification with MeOH–H_2O (90:10) (YMC, 250 × 20 nm, S-5 μm; 210 nm; 5 ml/mim), leading to the isolation of compound **3** (25 mg, 46.0 min).

3.3.1. Furoadhyperforim isomer 2a (1)

Colorless oil: $[\alpha]_D^{20}$ +65.5 (0.08, CH_3OH); UV (CH_3OH) λ_{max} (logε) nm: 207 (4.83), 282 (4.73); IR (Microscope Transmission) υ_{max}: 3436, 2970, 2927, 1725,1615 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectral data, see Table 1; ESI-MS: *m/z* 589.3 $[M+Na]^+$; (+)-HR ESI MS: *m/z* 567.4024 $[M+H]^+$ (calcd for $C_{36}H_{55}O_5$, 567.4044).

3.3.2. Furoadhyperforim isomer 2b (2)

Colorless oil: $[\alpha]_D^{20}$ +23.6 (0.06, CH_3OH); UV (CH_3OH) λ_{max} (logε) nm: 207 (4.12), 280 (3.74); IR (Microscope Transmission) υ_{max}: 3438, 2966, 2928, 1722, 1640, 1617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}C NMR ($CDCl_3$, 100 MHz) spectral data, see Table 1; ESI-MS: *m/z* 589.3 $[M+Na]^+$; (+)-HR ESI MS: *m/z* 567.4022 $[M+H]^+$ (calcd for $C_{36}H_{55}O_5$, 567.4044).

Disclosure statement

No potential conflict of interest was reported by the authors.

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