Prenylated Phloroglucinol Derivatives from *Hypericum perforatum* var. *angustifolium*

Chika HASHIDA,[a] Naonobu TANAKA,[a] Yoshiki KASHIWADA,[a] Makoto OGAWA,[b] and Yoshihisa TAKAISHI*,[a]

[a] *Graduate School of Pharmaceutical Sciences, University of Tokushima; 1–78 Shomachi, Tokushima 770–8505, Japan: and* [b] *Tokushima Prefectural Museum; Bunka-no-mori Park Hachiman-cho, Tokushima 770–8070, Japan.*
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Two new prenylated phloroglucinol derivatives and 15 known compounds were isolated from the aerial parts of *Hypericum perforatum* var. *angustifolium*. Their structures were determined on the basis of spectroscopic evidence.

Key words *Hypericum perforatum* var. *angustifolium*; prenylated phloroglucinol; Clusiaceae

Hypericum perforatum (St. John's Wort, Clusiaceae) has been used for centuries in the treatment of burns, bruises, swelling, inflammation, and anxiety, as well as bacterial and viral infections. In addition, *H. perforatum* has become popular herbal medicine quickly in the world for the treatment of mood disorders, since its effectiveness in the therapy for mild to moderate depression with a smaller side effects profile than that of traditional antidepressant medications has been claimed in the United States. Numerous studies have proven the clinical efficacy of *H. perforatum* in both human and animal behavioral models of depression.[1)] This medicinal herb produces various types of secondary metabolites, including flavonoids, xanthones, naphthodianthrones, and prenylated phloroglucinols.[2)] Among others, hyperforin, a main component of *H. perforatum* being classified as phloroglucinol derivatives, is regarded as a potential leads for new medicinal agents because of its various biological activities (*e.g.* antibacterial, apoptotic properties, anti-tumor, anti-inflammatory, and anti-depressant).[3,4)]

We have been studying the chemical constituents of various *Hypericum* plants for the purpose of the search for biologically active secondary metabolites. We have so far reported anti-HIV agent, biyouyanagin A[5)] and xanthones[6,7)] from *H. chinense*, and prenylated benzophenones and xanthones from *H. scabrum*.[8,9)] In continuing this program, we have examined the aerial parts of *H. perforatum* var. *angustifolium*. Varieties of *H. perforatum* with "broad" (var. *perforatum*) and "narrow" (var. *angustifolium*) sized leaves have been recognized.[10)] *H. perforatum* var. *angustifolium* was reported to contain a larger quantity of hypericin, and to have a stronger antimicrobial effect than typical variety, *H. perforatum* var. *perforatum*.[11)] This paper deals with the isolation and characterization of ten prenylated phloroglucinol derivatives, including two new prenylated phloroglucinols named furoadhyperforin isomers A (**1**) and B (**2**), together with five xanthones and two flavonoids from this plant material.

The methanolic extracts of the air-dried aerial parts of *Hypericum perforatum* var. *angustifolium* were successively partitioned between *n*-hexane, EtOAc, BuOH, and H_2O. The *n*-hexane, the EtOAc, and the BuOH-soluble fractions were repeatedly subjected to column chromatography, respectively, to afford two new (**1**, **2**) and 15 known (**3**—**17**) compounds.

Compounds **1** and **2** showed a hydroxyl and a carbonyl absorption bands in their IR spectrum. Their molecular formulae were decided as the same of $C_{36}H_{54}O_5$ on the basis of the HR-MS data. The ^{1}H- and ^{13}C-NMR spectra of **1** and **2** resembled each other, which indicated the presence of a 2-methylbutanoyl group, three isoprenyl groups, two carbonyl groups, one enol moiety, one oxygenated quaternary carbon, one oxygenated methine, three quaternary carbons, one methine, four methylenes, and three tertiary methyls (Table 1). From these data, **1** and **2** were assumed to be prenylated phloroglucinol derivatives having a 2-methylbutanoyl group in each case. Furthermore, the following characteristic spectral features are coincided with those of furohyperforins[12)]: δ_H 4.75 (1H, dd, J=10.4, 8.0 Hz), 2.99 (1H, dd, J=15.0, 10.4 Hz), 2.87 (1H, dd, J=15.0, 8.2 Hz), 1.28 and 1.22 (each 3H, s), δ_C 92.3, 71.9, 27.1, 24.8, and 23.5 in **1**; δ_H 4.82 (1H, dd, J=12.0, 8.0 Hz), 2.98 (1H, dd, J=14.7, 10.0 Hz), 2.96 (1H, dd, J=14.7, 8.0 Hz), 1.31 and 1.20 (each 3H, s), δ_C 93.0, 71.5, 27.2, 26.2, and 23.0 in **2**. The ^{13}C-NMR data of **1** was similar to those of hyperforin isomer 1[12)] except for the signals of C-2, C-10 to C-14. This fact indicated that **1** had a 2-methylbutanoyl group at C-2 instead of a 2-methylpropanoyl group in furohyperforin isomer 1. In contrast, **2** was regarded as a C-28 stereoisomer of **1** due to the small difference appeared in their chemical shifts of C-28 to C-31 (Table 1). The relative stereochemistry of **1** was decided as the same as that of furohyperforin isomer 1 based on the marked similarity of their ^{13}C-NMR data. However, the C-28 configuration of furohyperforin isomer 1 was not reported previously. The relative stereochemistry of C-28 in **1** and **2** were decided by comparison of the ^{1}H-NMR chemical shifts with those of garsubellins D and C, respectively, prenylated phloroglucinol derivatives isolated from *Garcinia subelliptica*,[13)] which have the same partial structure as **1** and **2**. Since the chemical shifts of H-28 for **1** and **2** (δ_H 4.75 in **1**; δ_H 4.82 in **2**) measured in $CDCl_3$ were similar, the orientations of H-28 in **1** and **2** could not be compared with those of garsubellins D and C. In contrast, those measured in C_6D_6 showed distinguishable chemical shifts (δ_H 4.20 in **1**; δ_H 4.02 in **2**), which were in good agreement with those of garsubellins D and C (measured in C_6D_6, δ_H 4.20 in garsubellin D; 4.01 in garsubellin C), respectively. These observations indicated that the orientations of H-28 in **1** and **2** were α and β, respectively. Consequently, the relative stereochemistries of **1** and **2** were established as shown in Fig. 1, and they were designated furoadhyperforin isomers A and B, respectively.

The structures of **3** and **4** were assigned as furohyperforin

* To whom correspondence should be addressed. e-mail: takaishi@ph.tokushima-u.ac.jp

Table 1. NMR Data for **1** and **2** (δ, Measured in $CDCl_3$)

Position	**1**		**2**	
	^{13}C	^{1}H	^{13}C	^{1}H
1	205.9	—	206.2	—
2	83.5	—	83.5	—
3	48.3	—	48.4	—
4	43.2	1.55 (1H, m)	42.7	1.65 (1H, m)
5	37.6	1.85, 1.46 (each 1H, m)	38.4	1.90, 1.44 (each 1H, m)
6	54.5	—	54.4	—
7	176.5	—	176.1	—
8	118.2	—	119.0	—
9	187.4	—	187.1	—
10	209.5	—	208.9	—
11	48.7	1.93 (1H, m)	48.8	1.89 (1H, m)
12	16.4	1.12 (3H, d, 6.4)	16.4	1.12 (3H, d, 6.4)
13	27.3	2.10 (2H, m)	27.3	2.10 (2H, m)
14	11.5	0.82 (3H, t, 6.4)	11.4	0.84 (3H, t, 7.4)
15	13.5	1.03 (3H, s)	13.8	1.04 (3H, s)
16	36.6	1.90, 1.46 (each 1H, m)	36.5	1.89, 1.48 (each 1H, m)
17	25.6	2.10, 1.90 (each 1H, m)	25.7	2.08, 1.86 (each 1H, m)
18	124.6	5.05 (1H, m)	124.5	5.07 (1H, m)
19	131.1	—	131.1	—
20	25.7	1.65 (3H, s)	25.8	1.65 (3H, s)
21	17.7	1.60 (3H, s)	17.9	1.61 (3H, s)
22	27.0	2.10, 1.70 (each 1H, m)	26.8	2.12, 1.81 (each 1H, m)
23	122.4	4.93 (1H, m)	122.3	4.97 (1H, m)
24	133.5	—	133.4	—
25	25.9	1.67 (3H, s)	24.7	1.71 (3H, s)
26	17.9	1.56 (3H, s)	18.1	1.58 (3H, s)
27	27.1	2.99 (1H, dd, 15.0, 10.4) 2.87 (1H, dd, 15.0, 8.2)	27.2	2.98 (1H, dd, 14.7, 10.0) 2.96 (1H, dd, 14.7, 8.0)
28	92.3	4.75 (1H, dd, 10.4, 8.0)	93.0	4.82 (1H, dd, 12.0, 8.0)
29	71.9	—	71.5	—
30	23.5	1.22 (3H, s)	23.0	1.20 (3H, s)
31	24.8	1.28 (3H, s)	26.2	1.31 (3H, s)
32	28.9	2.51 (1H, dd, 14.0, 6.4) 2.43 (1H, dd, 14.0, 7.8)	29.2	2.49 (2H, m) —
33	118.3	5.09 (1H, m)	120.0	5.04 (1H, m)
34	134.8	—	134.6	—
35	24.9	1.67 (3H, s)	25.6	1.71 (3H, s)
36	17.6	1.70 (3H, s)	17.6	1.71 (3H, s)

Coupling constants given (J in Hz) in parentheses.

isomer 1 and its 27-epimer, respectively, by comparisons of their ^{1}H- and ^{13}C-NMR spectral data with those reported in the literature.[12,14—16] The stereochemistries at C-27 in **3** and **4**, however, had not been discussed so far. Therefore, the C-27 configurations of **3** and **4** were elucidated in the same way as **1** and **2**: the ^{1}H-NMR chemical shifts measured in C_6D_6 of **3** (δ_H 4.22) and **4** (δ_H 4.00) indicated the orientations of H-27 in **3** and **4** to be α and β, respectively. Accordingly, the relative stereochemistries of **3** and **4** were determined as shown in Fig. 1.

The following known compounds were identified by comparison of their spectral data with those in the literature: furohyperforin (**5**),[12] 33-deoxy-33-hydroperoxyfurohyperforin (**6**),[17] furohyperforin isomer 2 (**7**),[12] hyperibone J (**8**),[10] 8-hydroxyhyperforin 8,1-hemiacetal (**9**),[17] pyrano[7,28-*b*]hyperforin (**10**),[18] calycinoxanthone D (**11**),[19] 1,3,6-trihydroxy-5-methoxy xanthone (**12**),[20] 4′,5′-dihydro-1,6,7-trihydroxy-4′,4′,5′-trimethylfurano(2′,3′:3,4)xanthone (**13**),[21] deprenylatedrheediaxanthone (**14**),[22,23] paxanthone (**15**),[24] quercetin (**16**),[25] rutin (**17**).[26]

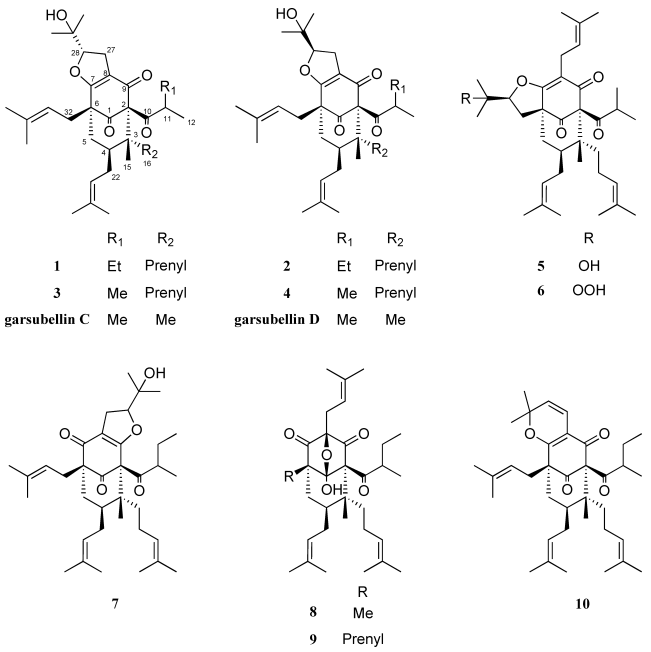

Fig. 1. Isolated Prenylated Phloroglucinol Derivatives (**1**—**10**), and Garsubellins C and D

Experimental

General Experimental Procedures NMR experiments were run on a

Bruker ARX-400 instrument, ^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz, using tetramethylsilane (TMS) as an internal standard. MS was obtained on a JEOL JMSD-300 instrument (FAB), and a Waters LCT Premier (ESI). Chromatography column: silica gel 60 (Merck, 63—210 μm), Sephadex LH-20 (Pharmacia), and Toyopearl HW-40 (TOSOH), DIAION® HP-20; HPLC: GPC (Shodex H-2001, 2002, $CHCl_3$; Asahipak, GS-310 2G, MeOH), silica gel HPLC (YMC-Pack SIL-06 SH-043-5-06, 250×20 mm). IR spectra were recorded on a 1720 Infrared fourier transform spectrometer (Perkin-Elmer). Optical rotations were measured with a JASCO DIP-370 digital polarimeter.

Plant Material *Hypericum perforatum* var. *angustifolium* was identified by Mr. Makoto Ogawa and collected in October 2004 in Tokushima Prefecture, Japan. Herbarium specimens were deposited in the botanical garden of the University of Tokushima (specimen number: UTP98009).

Extraction and Isolation The air-dried aerial parts of *H. perforatum* var. *angustifolium* (2.82 kg) were crushed and extracted with hot MeOH (16 l×3). The MeOH extracts were concentrated *in vacuo* to give a residue (233.1 g), which was partitioned successively between *n*-hexane, EtOAc, BuOH and H_2O to give *n*-hexane, EtOAc, BuOH-soluble fractions (58.8 g, 22.1 g, and 23.0 g, respectively).

The *n*-hexane-soluble fraction was separated on a silica gel column eluted with different solvents of increasing polarity (*n*-hexane–EtOAc; EtOAc–MeOH) to give 10 fractions (frs. 1—10). Fr. 2 (4.0 g) was separated on a Toyopearl column with $CHCl_3$–MeOH (2 : 1) to give three fractions (frs. 2.1—2.3). Fr. 2.3 was purified on a silica gel column ($CHCl_3$–*n*-hexane–EtOAc, 50 : 50 : 2) and a silica gel HPLC (*n*-hexane–EtOAc, 95 : 5) to give **8** (44 mg). Fr. 4 (58.0 g) was subjected to a Toyopearl column with $CHCl_3$–MeOH (2 : 1) and a silica gel column eluted with $CHCl_3$–*n*-hexane–EtOAc (50 : 50 : 2) to give three fractions (frs. 4.1—4.3). Fr. 4.1 was applied to a silica gel column (*n*-hexane–EtOAc, 95 : 5) to give five fractions (frs. 4.1.1—4.1.5). Fr. 4.1.1 was subjected to a silica gel column with *n*-hexane–EtOAc (5 : 1) to give five fractions (frs. 4.1.1.1—4.1.1.5). Fr. 4.1.1.2 was separated by preparative TLC with *n*-hexane–diethyl ether (9 : 1) to give **9** (39 mg). Fr. 4.1.1.3 was applied to a GPC on HPLC with MeOH and then purified by a silica gel HPLC with *n*-hexane–EtOAc (95 : 5) to give **10** (10 mg). Silica gel HPLC of Fr. 4.1.4 with *n*-hexane–EtOAc (6 : 1) yielded **7** (6 mg). Fr. 4.2 was subjected to silica gel HPLC with *n*-hexane–EtOAc (5 : 1) to give seven fractions (frs. 4.2.1—4.2.7), among which fr. 4.2.2 was shown to be a pure compound (**6**; 16 mg). Purification of fr. 4.2.4 by silica gel HPLC ($CHCl_3$–MeOH, 99 : 1) yielded **5** (8 mg).

Fr. 4.3 was applied to silica gel HPLC with *n*-hexane–EtOAc (4 : 1) to give **1** (13 mg), **2** (9 mg), and **4** (42 mg), together with 9 fractions (frs. 4.3.1—4.3.9). **3** (6 mg) was isolated from fr. 4.3.7 by silica gel HPLC ($CHCl_3$–MeOH, 99 : 1).

Fr. 9 was separated on a Sephadex LH-20 column (MeOH) to give three fractions (frs. 9.1—9.3). Fr. 9.3 was loaded on a silica gel column with $CHCl_3$–acetone (95 : 5) to give three fractions (frs. 9.3.1—9.3.3). Fr. 9.3.3 was subjected to a Sephadex LH-20 column with MeOH to give three fractions (frs. 9.3.3.1—9.3.3.3). Fr. 9.3.3.1 was separated on a silica gel column with $CHCl_3$–acetone (95 : 5) to give three fractions (frs. 9.3.3.1.1—9.3.3.1.3). Fr. 9.3.3.1.1 was purified by a GPC on HPLC with $CHCl_3$ to give **14** (1 mg). Crystallization of fr. 9.3.3.1.2 from acetone gave **13** (3 mg). Fr. 9.3.3.2 was loaded on a silica gel column ($CHCl_3$–acetone, 95 : 5), and crystallized from acetone to give **12** (5 mg).

The EtOAc-soluble fraction (21.0 g) was subjected to a silica gel column eluted with different solvents of increasing polarity (*n*-hexane–EtOAc–MeOH) to give ten fractions (frs. 11—20). Fr. 12 was separated on a silica gel column with $CHCl_3$–MeOH (8 : 2) to give five fractions (frs. 12.1—12.5). Fr. 12.2 was applied to a Toyopearl column with $CHCl_3$–MeOH (1 : 2), and a Sephadex LH-20 (MeOH) to give **15** (4 mg). Fr. 12.3 was purificated on a Toyopearl column with $CHCl_3$–MeOH (1 : 2) and a GPC column with MeOH to give **11** (11 mg). Fraction 12.4 was separated on a Toyopearl column with $CHCl_3$–MeOH (1 : 2) and a GPC column with MeOH to give **16** (38 mg).

The BuOH-soluble fraction (20.0 g) was subjected to an Amberlite XAD-2 (H_2O–MeOH) to give five fractions (frs. 21—25). Fr. 24 was purified on a Sephadex LH-20 column with MeOH–H_2O (6 : 4) to give **17** (598 mg).

Furoadhyperforin Isomer A (**1**): Colorless gum; $[\alpha]_D$ +33.8° (c=0.9 $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 3432, 2971, 2931, 1725, 1623, 1454; HR-FAB-MS: m/z 567.4036 $[M+H]^+$ (Calcd for $C_{36}H_{55}O_5$, 567.4050). ^{1}H- and ^{13}C-NMR ($CDCl_3$): see Table 1.

Furoadhyperforin Isomer B (**2**): Colorless gum; $[\alpha]_D$ +13.8° (c=1.5 $CHCl_3$); IR (KBr) ν_{max} cm^{-1} 3428, 2975, 2931, 1725, 1619, 1452; HR-ESI-MS: m/z 589.3829 $[M+Na]^+$ (Calcd for $C_{36}H_{54}O_5Na$, 589.3869). ^{1}H- and ^{13}C-NMR ($CDCl_3$): see Table 1.

Furohyperforin Isomer 1 (**3**): Colorless oil; $[\alpha]_D$: +49.7° (c=0.67 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ_H 5.08 (1H, m, H-32), 5.06 (1H, m, H-17), 4.93 (1H, m, H-22), 4.74 (1H, dd, J=10.6, 8.4 Hz, H-27), 2.99 (1H, dd, J=15.0, 10.4 Hz, H-26a), 2.87 (1H, dd, J=15.0, 8.4 Hz, H-26b), 2.52 (1H, dd, J=14.6, 6.6 Hz, H-31a), 2.43 (1H, dd, J=14.6, 7.8 Hz, H-31b), 2.17 (1H, m, H-11, H-21a), 2.09 (1H, m, H-16a), 1.89 (1H, m, H-5a), 1.88 (1H, m, H-16b), 1.80 (1H, m, H-15a), 1.75 (1H, m, H-21b), 1.69 (3H, s, H_3-34), 1.67 (3H, s, H_3-24, H_3-35), 1.65 (3H, s, H_3-19), 1.60 (3H, s, H_3-20), 1.58 (1H, m, H-4), 1.56 (3H, s, H_3-25), 1.46 (1H, m, H-5b), 1.39 (1H, m, H-15a), 1.28 (3H, s, H_3-30), 1.22 (3H, s, H_3-29), 1.13 (3H, d, J=6.4 Hz, H_3-12), 1.06 (3H, d, J=6.4 Hz, H_3-13), 1.02 (3H, s, H_3-14); ^{13}C-NMR ($CDCl_3$): δ_C 206.0 (C-1), 83.6 (C-2), 48.2 (C-3), 43.1 (C-4), 37.7 (C-5), 54.6 (C-6), 176.6 (C-7), 118.2 (C-8), 187.3 (C-9), 209.6 (C-10), 42.1 (C-11), 20.3 (C-12), 21.3 (C-13), 13.5 (C-14), 36.5 (C-15), 24.8 (C-16), 124.6 (C-17), 131.1 (C-18), 25.6 (C-19), 17.6 (C-20), 27.0 (C-21), 122.4 (C-22), 133.5 (C-23), 25.7 (C-24), 17.7 (C-25), 27.3 (C-26), 92.3 (C-27), 71.9 (C-28), 23.6 (C-29), 24.8 (C-30), 28.9 (C-31), 118.2 (C-32), 134.8 (C-33), 25.9 (C-34), 17.9 (C-35).

27-Epifurohyperforin Isomer 1 (**4**): Colorless oil; $[\alpha]_D$: +14.5° (c=0.3 $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ_H 5.04 (1H, m, H-17), 4.98 (1H, m, H-22), 4.96 (1H, m, H-32), 4.80 (1H, dd, J=9.6, 8.8 Hz, H-27), 2.99 (1H, dd, J=18.9, 9.6 Hz, H-26a), 2.94 (1H, dd, J=18.9, 8.4 Hz, H-26b), 2.51 (1H, m, H-31a), 2.47 (1H, m, H-31b), 2.11 (1H, m, H-21a), 2.10 (1H, m, H-11), 2.08 (1H, m, H-16a), 1.92 (1H, dd, J=13.6, 4.0 Hz, H-5a), 1.88 (1H, m, H-15a, H-16b), 1.78 (1H, m, H-21b), 1.71 (3H, s, H_3-24), 1.70 (3H, s, H_3-34, H_3-35), 1.64 (1H, m, H-4), 1.64 (3H, m, H_3-19), 1.59 (3H, s, H_3-20), 1.57 (3H, s, H_3-25), 1.53 (1H, m, H-15b), 1.45 (1H, m, H-5b), 1.30 (3H, s, H_3-30), 1.18 (3H, s, H_3-29), 1.13 (3H, d, J=6.4 Hz, H_3-12), 1.05 (3H, d, J=6.4 Hz, H_3-13), 1.02 (3H, s, H_3-14); ^{13}C-NMR ($CDCl_3$): δ_C 206.3 (C-1), 83.7 (C-2), 48.3 (C-3), 42.5 (C-4), 38.4 (C-5), 54.4 (C-6), 176.1 (C-7), 119.0 (C-8), 186.9 (C-9), 209.4 (C-10), 42.2 (C-11), 20.4 (C-12), 21.4 (C-13), 13.8 (C-14), 36.4 (C-15), 24.6 (C-16), 124.5 (C-17), 131.0 (C-18), 25.5 (C-19), 17.5 (C-20), 27.3 (C-21), 122.3 (C-22), 133.4 (C-23), 25.8 (C-24), 18.1 (C-25), 26.8 (C-26), 93.0 (C-27), 71.5 (C-28), 23.0 (C-29), 26.3 (C-30), 29.2 (C-31), 119.9 (C-32), 134.6 (C-33), 25.7 (C-34), 17.8 (C-35).

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