Biflavones and Furanone Glucosides from *Zabelia tyaihyonii*

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Two new biflavones, (a*R*)-3′-methoxycupressuflavone (**1**) and (a*R*)-3′,3‴-dimethoxycupressuflavone (**2**), and two new furanone glucosides, zabeliosides A and B (**3** and **4**, resp.), along with two known biflavones, cupressuflavone (**5**) and amentoflavone (**6**), were isolated from the leaves of *Zabelia tyaihyonii*. The structures of the new compounds were elucidated by 1D- and 2D-NMR, HR-ESI-MS, and circular dichroism.

Introduction. – *Zabelia tyaihyonii* (T.H.CHUNG ex NAKAI) HISAUTI & H.HARA (formerly known as synonym of *Abelia tyaihyonii* T.H.CHUNG ex NAKAI (Caprifoliaceae)), a species endemic of Korea, is a deciduous shrub belonging to the family Linnaeaceae. It is distributed mainly in the central and northern parts of the Korean peninsula [1–3]. Previous phytochemical studies on the genus *Zabelia* resulted in the isolation of bisiridoid and secoiridoid glucosides [4][5]. However, to the best of our knowledge, no phytochemical investigation of *Z. tyaihyonii* has been reported. In this study, two new biflavones, (a*R*)-3′-methoxycupressuflavone (**1**) and (a*R*)-3′,3‴-dimethoxycupressuflavone (**2**), and two new furanone glucopyranosides, zabeliosides A and B (**3** and **4**, resp.), along with two known biflavones, cupressuflavone (**5**) and amentoflavone (**6**; *Fig. 1*), were isolated from the MeOH extract of the leaves of *Z. tyaihyonii*. Herein, we report the isolation and structure elucidation of the new compounds **1**–**4**.

Results and Discussion. – Compound **1** was obtained as yellow amorphous powder. The molecular formula, $C_{31}H_{20}O_{11}$, was deduced from HR-ESI-MS (*m*/*z* 591.0899 ($[M+Na]^+$; calc. 591.0898)). The IR spectrum showed the presence of OH (3291 cm^{-1}) and C=O (1647 cm^{-1}) groups. The ^{1}H- and ^{13}C-NMR spectra (*Table 1*) exhibited signals of two chelated OH groups (δ(H) 13.15 (*s*, HO–C(5)) and 13.12 (*s*, HO–C(5″))), two C=O groups (δ(C) 182.5 (C(4,4″))), one 1,4-disubstituted benzene ring (δ(H) 7.44 (*d*, *J* = 9.0, H–C(2‴,6‴)), 6.73 (*d*, *J* = 9.0, H–C(3‴,5‴)); δ(C) 161.5 (C(4‴)), 128.4 (C(2‴,6‴)), 121.7 (C(1‴)), 116.3 (C(3‴,5‴))), two 1,2,3,4,5-pentasubstituted benzene rings (δ(H) 6.33 (*s*, H–C(6)), 6.34 (*s*, H–C(6″)); δ(C) 164.2 (C(7,7″)), 161.3 (C(5,5″)), 155.2 (C(9,9″), 104.0 (C(10″)), 103.9 (C(10)), 99.5 (C(8,8″)), 99.4 (C(6,6″))), one 1,3,4-trisubstituted benzene ring (δ(H) 6.96 (*d*, *J* = 2.0, H–C(2′)), 6.74 (*d*, *J* = 8.5, H–C(5′)), 7.22 (*dd*, *J* = 8.5, 2.0, H–C(6′)); δ(C) 150.9 (C(4′)), 148.2 (C(3′)),

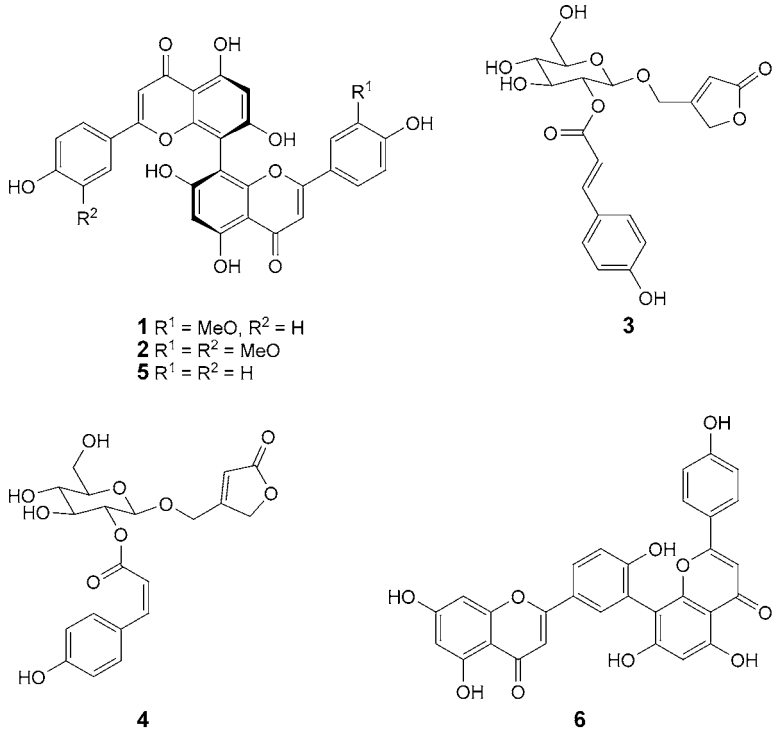


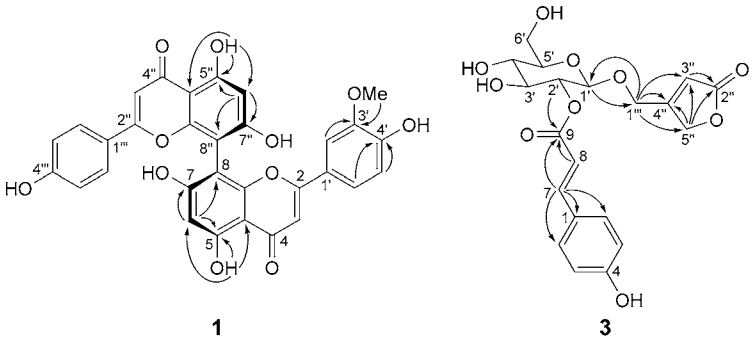
Fig. 1. *Structures of* **1**–**6** *isolated from* Z. tyaihyonii

121.9 (C(1′)), 120.6 (C(6′)), 116.2 (C(5′)), 109.3 (C(2′)), and one MeO group (δ(H) 3.62 (*s*); δ(C) 55.7)). The remaining two olefinic signals (δ(H) 6.83 (*s*, H–C(3)) and 6.74 (*s*, H–C(3″))) are characteristic of H–C(3,3″) of the flavone skeleton. The aforementioned data suggested that **1** could be a cupressuflavone derivative, a biflavonoid consisting of two flavone units linked through a C(8)–C(8″) bond, with a MeO group [6][7]. In the HMBC spectrum of **1** (*Fig. 2*), the correlations H–C(6)/C(5), H–C(6)/C(7), H–C(6)/C(8), HO–C(5)/C(5), H–C(6″)/C(5″), H–C(6″)/C(7″), H–C(6″)/C(8″), and HO–C(5″)/C(5″) further confirmed the formation of the C–C linkage of the two flavone units between C(8) and C(8″). The location of the MeO group at C(3′) was determined by the HMBCs between the MeO H-atoms at δ(H) 3.62 and C(3′) at δ(C) 148.2 (*Fig. 2*). The absolute configuration of **1** was elucidated on the basis of its optical rotation and circular dichroism (CD) data [7–10]. Compound **1** showed a negative optical rotation ($[\alpha]_D^{25} = -38.0$ ($c = 0.1$, MeOH)), a positive *Cotton* effect at 362 nm, and a negative *Cotton* effect at 326 nm, indicating that **1** has an axially chiral (a*R*)-8,8′-biflavone unit ((*M*)-configuration). Therefore, **1** was identified as (a*R*)-3′-methoxycupressuflavone.

Compound **2** was obtained as yellow amorphous powder and had the molecular formula $C_{32}H_{22}O_{12}$, as determined by HR-ESI-MS (*m*/*z* 621.0999 ($[M+Na]^+$; calc. 621.1003)). The ^{1}H- and ^{13}C-NMR spectra of **2** (*Table 2*) were similar to those of **1**,

Table 1. *^{1}H- and ^{13}C-NMR Data* (500 and 125 MHz, resp.; in (D_6)DMSO) *of* **1**. δ in ppm, J in Hz.

Position	δ(H)	δ(C)	Position	δ(H)	δ(C)
2	–	163.7	2″	–	163.9
3	6.83 (*s*)	103.0	3″	6.74 (*s*)	103.1
4	–	182.5	4″	–	182.5
5	–	161.3	5″	–	161.3
6	6.33 (*s*)	99.4	6″	6.34 (*s*)	99.4
7	–	164.2	7″	–	164.2
8	–	99.5	8″	–	99.5
9	–	155.2	9″	–	155.2
10	–	103.9	10″	–	104.0
1′	–	121.9	1‴	–	121.7
2′	6.96 (*d*, J = 2.0)	109.3	2‴	7.44 (*d*, J = 9.0)	128.4
3′	–	148.2	3‴	6.73 (*d*, J = 9.0)	116.3
4′	–	150.9	4‴	–	161.5
5′	6.74 (*d*, J = 8.5)	116.2	5‴	6.73 (*d*, J = 9.0)	116.3
6′	7.22 (*dd*, J = 8.5, 2.0)	120.6	6‴	7.44 (*d*, J = 9.0)	128.4
3-MeO	3.62 (*s*)	55.7	5″-OH	13.12 (*s*)	–
5-OH	13.15 (*s*)	–			



1 **3**

Fig. 2. *Key HMBCs of* **1** *and* **3**

except for the presence of an additional MeO group. However, the ^{1}H- and ^{13}C-NMR data of **2** revealed a symmetrical structure with each half of the molecule, $C_{16}H_{11}O_6$, consisting of a 1,3,4-trisubstituted benzene ring, a 1,2,3,4,5-pentasubstituted benzene ring, an olefinic group, and a MeO group. The location of the MeO groups at C(3′,3‴) was confirmed by the HMB correlation of the H-atoms of the MeO groups with C(3′,3‴). The C(8)–C(8″) linkage of two flavones was further confirmed by the HMBC cross-peaks H–C(6,6″)/C(5,5″), H–C(6,6″)/C(7,7″), H–C(6,6″)/C(8,8″), and HO–C(5,5″)/C(5,5″). The absolute configuration of **2** was determined to be same as that of **1** on the basis of similar optical rotation ($[\alpha]_D^{25} = -37.8$ (c = 0.1, MeOH)) and CD data, *i.e.*, a positive *Cotton* effect at 362 nm and a negative *Cotton* effect at 326 nm. Therefore, **2** was identified as (a*R*)-3′,3‴-dimethoxycupressuflavone.

Table 2. *^{1}H- and ^{13}C-NMR Data* (500 and 125 MHz, resp.; in (D_6)DMSO) *of* **2**. δ in ppm, J in Hz.

Position	δ(H)	δ(C)
2,2″	–	163.7
3,3″	6.88 (*s*)	103.1
4,4″	–	182.5
5,5″	–	161.3
6,6″	6.42 (*s*)	99.4
7,7″	–	164.0
8,8″	–	99.3
9,9″	–	155.2
10,10′	–	104.0
1′,1‴	–	121.9
2′,2‴	7.01 (*d*, $J = 2.0$)	109.3
3′,3‴	–	148.2
4′,4‴	–	151.0
5′,5‴	6.77 (*d*, $J = 8.5$)	116.2
6′,6‴	7.28 (*dd*, $J = 8.5, 2.0$)	120.6
3′,3‴-MeO	3.63 (*s*)	55.7

Compound **3** was obtained as brown syrup with the molecular formula $C_{20}H_{22}O_{10}$ from HR-ESI-MS data (*m*/*z* 445.1105 ($[M + Na]^+$; calc. 445.1105)). The IR spectrum showed the presence of OH (3336 cm^{-1}) and C=O (1647 cm^{-1}) groups. The ^{1}H- and ^{13}C-NMR data of **3** (*Table 3*) exhibited resonances for a (2*E*)-*p*-coumaroyl group (δ(H) 7.59 (*d*, $J = 16.0$, H–C(8)), 7.56 (*d*, $J = 8.5$, H–C(2,6)), 6.80 (*d*, $J = 8.5$, H–C(3,5)), 6.40 (*d*, $J = 16.0$, H–C(7)); δ(C) 166.2 (C(9)), 160.4 (C(4)), 145.6 (C(7)), 130.8 (C(2,6)), 125.5 (C(1)), 116.3 (C(3,5)), 114.5 (C(8))), a (2,5-dihydro-5-oxofuran-3-yl)methoxy group (δ(H) 5.90 (*s*, H–C(3″)), 4.83 (br. *s*, CH_2(5″)), 4.68 – 4.69 (*m*, 1 H of CH_2(1‴)), 4.54 – 4.55 (*m*, 1 H of CH_2(1‴)); δ(C) 173.5 (C(2″)), 169.2 (C(4″)), 114.5 (C(3″)), 71.7 (C(5″)), 64.6 (C(1‴))) [11], and a glucose moiety (δ(H) 4.56 (*d*, $J = 8.0$, H–C(1′)); δ(C) 100.5 (C(1′)), 77.6 (C(4′)), 74.4 (C(3′)), 73.9 (C(2′)), 70.5 (C(5′)), 61.2 (C(6′))). Acid hydrolysis of **3** yielded β-D-glucose by GC/MS analysis. The coupling constant $J = 8.0$ of the anomeric H-atom indicated the β-configuration of the glucose moiety. In the HMBC spectrum of **3** (*Fig. 2*), the anomeric H-atom (δ(H) 4.56) correlated with C(1‴) (δ(C) 64.6), indicating the attachment of the (2,5-dihydro-5-oxofuran-3-yl)methoxy moiety at C(1′). Moreover, the HMB correlation of H–C(2′) (δ(H) 4.70) and C(9) (δ(C) 166.2) corroborated that the (2*E*)-*p*-coumaroyloxy group was located at C(2′) (*Fig. 2*). Therefore, **3** was determined to be (2,5-dihydro-5-oxofuran-3-yl)methyl 2-*O*-[(2*E*)-*p*-coumaroyl]-β-D-glucopyranoside, and it was named zabelioside A.

Compound **4** was obtained as brown syrup. The molecular formula, $C_{20}H_{22}O_{10}$, was deduced from HR-ESI-MS data (*m*/*z* 445.1103 ($[M + Na]^+$; calc. 445.1105)). The ^{1}H- and ^{13}C-NMR data of **4** (*Table 3*) were quite similar to those of **3**, except for the presence of a (2*Z*)-*p*-coumaroyl moiety instead of a (2*E*)-*p*-coumaroyl moiety. This was supported by the coupling constant ($J = 12.5$) and characteristic chemical shifts for H–C(7) and H–C(8) (δ(H) 5.78 and 6.89, resp.) of **4**. Acid hydrolysis of **4** gave β-D-glucose and the coupling constant ($J = 8.0$) of the anomeric H-atom indicated the

Table 3. *^{1}H- and ^{13}C-NMR Data* (500 and 125 MHz, resp.; in (D_6)DMSO) *of* **3** *and* **4**. δ in ppm, J in Hz.

Position	**3**		**4**	
	δ(H)	δ(C)	δ(H)	δ(C)
1	–	125.5	–	125.8
2,6	7.56 (*d*, J = 8.5)	130.8	7.66 (*d*, J = 9.0)	133.1
3,5	6.80 (*d*, J = 8.5)	116.3	6.75 (*d*, J = 9.0)	115.4
4	–	160.4	–	159.4
7	6.40 (*d*, J = 16.0)	145.6	5.78 (*d*, J = 12.5)	144.1
8	7.59 (*d*, J = 16.0)	114.5	6.89 (*d*, J = 12.5)	115.6
9	–	166.2	–	165.5
1′	4.56 (*d*, J = 8.0)	100.5	4.55 (*d*, J = 8.0)	100.3
2′	4.70 (*dd*, J = 9.0, 8.0)	73.9	4.68 (*dd*, J = 9.0, 8.0)	73.8
3′	3.49 – 3.50 (*m*)	74.4	3.45 – 3.46 (*m*)	74.3
4′	3.24 – 3.25 (*m*)	77.6	3.20 – 3.21 (*m*)	77.6
5′	3.27 – 3.28 (*m*)	70.5	3.21 – 3.22 (*m*)	70.6
6′	3.70 (*dd*, J = 12.0, 2.0, H_a), 3.50 (*dd*, J = 12.0, 6.0, H_b)	61.2	3.70 (*dd*, J = 12.0, 2.0, H_a), 3.50 (*dd*, J = 12.0, 6.0, H_b)	61.2
2″	–	173.5	–	173.5
3″	5.90 (*s*)	114.5	5.91 (*s*)	114.5
4″	–	169.2	–	169.1
5″	4.83 (br. *s*)	71.7	4.83 (br. *s*)	71.6
1‴	4.68 – 4.69 (*m*), 4.54 – 4.55 (*m*)	64.6	4.66 – 4.67 (*m*), 4.55 – 4.56 (*m*)	64.5

β-configuration of the glucose moiety. The locations of the (2,5-dihydro-5-oxofuran-3-yl)methoxy and (2*Z*)-*p*-coumaroyloxy groups were assigned at C(1′) and C(2′), respectively, by the observed HMB correlations. Therefore, **4** was determined to be (2,5-dihydro-5-oxofuran-3-yl)methyl 2-*O*-[(2*Z*)-*p*-coumaroyl]-β-D-glucopyranoside, and it was named zabelioside B.

The two known compounds were identified as cupressuflavone (**5**) [12 – 14] and amentoflavone (**6**) [15][16] by comparison of their physicochemical and spectroscopic data with those reported in the literature.

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Experimental Part

General. Thin layer chromatography (TLC): silica gel *60 F_{254}* aluminum plates (SiO_2; *Merck*); visualized by UV light at 254 nm and by spraying with 10% aq. H_2SO_4, followed by heating. Column chromatograpy (CC): SiO_2 (70 – 230 mesh; *Merck*). Prep. HPLC: *Waters* HPLC system; *YMC J'sphere ODS-H80* column (150 × 20 mm i.d., 4 μm); *Waters 525* pump; *Waters 2996* detector. Optical rotations: *Jasco DIP-1000* polarimeter. CD Spectra: *Jasco J-715* spectropolarimeter; λ_{max} ($\Delta\varepsilon$) in nm. IR Spectra: *Jasco 4100 FT-IR* spectrophotometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker AMX-500* spectrometer (500 and 125 MHz, resp.); in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, J in Hz. GC/MS: *Agilent 6890/5973i* apparatus; in *m*/*z*. HR-ESI-MS: *Waters QTOF Micromass* spectrometer; in *m*/*z*.

Plant Material. Leaves of *Z. tyaihyonii* were collected from Yeongwol, Gangwon-do, Korea, in June 2012. A voucher specimen (NIBRVP0000366697) was authenticated by *S.-Y. K.* and deposited with the Herbarium of the National Institute of Biological Resources, Korea.

Extraction and Isolation. Dried and powdered leaves of *Z. tyaihyonii* (150 g) were extracted with MeOH (3 × 3 l, overnight) at r.t., and the soln. was evaporated *in vacuo*. The residue was suspended in H_2O (1 l) and partitioned successively with hexane, CH_2Cl_2, and AcOEt (each 3 × 1 l). The AcOEt-soluble fraction (1.2 g) was subjected to CC (SiO_2; hexane/CH_2Cl_2, CH_2Cl_2, and CH_2Cl_2/MeOH, gradient system) to afford six fractions, *Frs. 1–6*. *Fr. 3* (206 mg) was purified by prep. HPLC (MeCN/H_2O 30:70 to 80:20; flow rate, 6 ml min^{-1}) to give **1** (7.1 mg) and **2** (6.4 mg). *Fr. 4* (240 mg) was further purified by prep. HPLC (MeCN/H_2O 40:60 to 100:0; flow rate, 6 ml min^{-1}) to give **3** (13.7 mg), **4** (7.3 mg), **5** (5.4 mg), and **6** (2.3 mg).

Acid Hydrolysis of **3** *and* **4** *and Determination of Sugar Components*. Compounds **3** and **4** (3.0 mg) were dissolved in 1N HCl (1 ml) and heated at 80° for 3 h. The solvent was removed under reduced pressure, and each mixture was suspended in H_2O and partitioned with AcOEt (3 × 3 ml). The aq. layer was evaporated *in vacuo*, and the residue (sugar portion) was dissolved in anh. pyridine (0.1 ml), and L-cysteine methyl ester hydrochloride (0.06M, 0.1 ml) was added. After heating the mixture at 60° for 2 h, $NaBH_4$ (2.0 mg) was added, and the mixture was stirred for 1 h at r.t. Trimethylsilylimidazole soln. (0.1 ml) was added, and the mixture was then heated at 60° for 2 h. The dried product was partitioned with hexane and H_2O, and the hexane layer was then analyzed by GC/MS on a *DB 5 MS* column (0.25 mm × 30 m, 0.25 μm; detector, FID; column temp., 250°; injector temp., 280°; detector temp., 280°; carrier gas, He (1 ml min^{-1})). The hydrolysates of **3** and **4** showed peaks at t_R 17.77 min, identical to that of authentic β-D-glucose.

*(a*R*)-3′-Methoxycupressuflavone* (*=5,5′,7,7′-Tetrahydroxy-2-(4-hydroxy-3-methoxyphenyl)-2′-(4-hydroxyphenyl)-[8,8′-bi-4*H*-1-benzopyran]-4,4′-dione*; **1**). Yellow amorphous powder. $[\alpha]_D^{25} = -38.0$ (c = 0.1, MeOH). CD (MeOH): 267 (+2.87), 326 (−7.73), 362 (+3.02). UV (MeOH): 337 (3.89), 287 (3.98), 229 (4.17). IR: 3291, 2939, 1647, 1581, 1508, 1488, 1397, 1244, 1186. ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-ESI-MS: 591.0899 ($[M+Na]^+$, $C_{31}H_{20}NaO_{11}^+$; calc. 591.0898).

*(a*R*)-3′,3‴-Dimethoxycupressuflavone* (*=5,5′,7,7′-Tetrahydroxy-2,2′-bis(4-hydroxy-3-methoxyphenyl)-[8,8′-bi-4*H*-1-benzopyran]-4,4′-dione*; **2**). Yellow amorphous powder. $[\alpha]_D^{25} = -37.8$ (c = 0.1, MeOH). CD (MeOH): 267 (+1.62), 326 (−4.94), 362 (+1.40). UV (MeOH): 347 (3.87), 285 (3.97), 237 (4.18). IR: 3305, 2939, 1679, 1542, 1508, 1417, 1022. ^{1}H- and ^{13}C-NMR: see *Table 2*. HR-ESI-MS: 621.0999 ($[M+Na]^+$, $C_{32}H_{22}NaO_{12}^+$; calc. 621.1003).

Zabelioside A (*=(2,5-Dihydro-5-oxofuran-3-yl)methyl 2-*O*-((2*E*)-*p*-Coumaroyl)-β-*D*-glucopyranoside*; **3**). Brown syrup. $[\alpha]_D^{25} = -56.0$ (c = 0.1, MeOH). UV (MeOH): 314 (3.75). IR: 3336, 1647, 1397, 1019. ^{1}H- and ^{13}C-NMR: see *Table 3*. HR-ESI-MS: 445.1105 ($[M+Na]^+$, $C_{20}H_{22}NaO_{10}^+$; calc. 445.1105).

Zabelioside B (*=(2,5-Dihydro-5-oxofuran-3-yl)methyl 2-*O*-((2*Z*)-*p*-Coumaroyl)-β-*D*-glucopyranoside*; **4**). Brown syrup. $[\alpha]_D^{25} = -48.0$ (c = 0.1, MeOH). UV (MeOH): 309 (3.74). IR: 3292, 1711, 1629, 1362, 1024. ^{1}H- and ^{13}C-NMR: see *Table 3*. HR-ESI-MS: 445.1103 ($[M+Na]^+$, $C_{20}H_{22}NaO_{10}^+$; calc. 445.1105).

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