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THREE NEW FLAVONOL GLYCOSIDES FROM THE AERIAL PARTS OF *TETRAGONIA TETRAGONOIDES*

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Abstract – Three new flavonol glycosides (**1**-**3**) and three known lignan amides (**4**-**6**) were isolated from the MeOH extract of the aerial parts of *Tetragonia tetragonoides*. The chemical structures of the new compounds (**1**-**3**) were determined to be 6-methoxykaemferol-3-*O*-*β*-D-glucosyl (1′″→2″)-*β*-D-glucopyranosyl-(6″″-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside (**1**), 6,4′-dimethoxy kaemferol-3-*O*-*β*-D-glucosyl (1′″→2″)-*β*-D-glucopyranosyl-(6″″-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside (**2**), 4′-methoxypatuletin-3-*O*-*β*-D-glucosyl (1′″→2″) -*β*-D-glucopyranosyl-(6″″-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside (**3**) on the basis of extensive spectroscopic analyses (FAB-MS/MS, 1D and 2D NMR experiments).

INTRODUCTION

Tetragonia tetragonoides (Aizoaceae) has been used in Korean traditional medicine for the treatment of stomach cancer and ulcers.[1] Polysaccharides,[2] cerebrosides,[3] and diterpenoids[4] have been isolated from this plant source and an anti-ulcerogenic effect of the isolated cerebrosides from this source was described.[3] In continuation of our study for bioactive components from Korean medicinal plants,[5,6] we investigated the constituents of the aerial parts of *T. tetragonoides.* The repeated column chromatographic separation of the ethyl acetate and BuOH fractions of the MeOH extract resulted in the isolation of three new flavonol glycosides (**1**-**3**), as well as three known lignan amides (**4**-**6**). The structures of the known lignan amides were determined to be *N-cis*-caffeoyltyramine (**4**),[7] cannabisin B (**5**),[8] and *N-trans*-caffeoyltyramine (**6**)[7,9] by comparing their spectroscopic data with those in the literatures. All compounds were isolated for the first time from the family Aizoaceae.

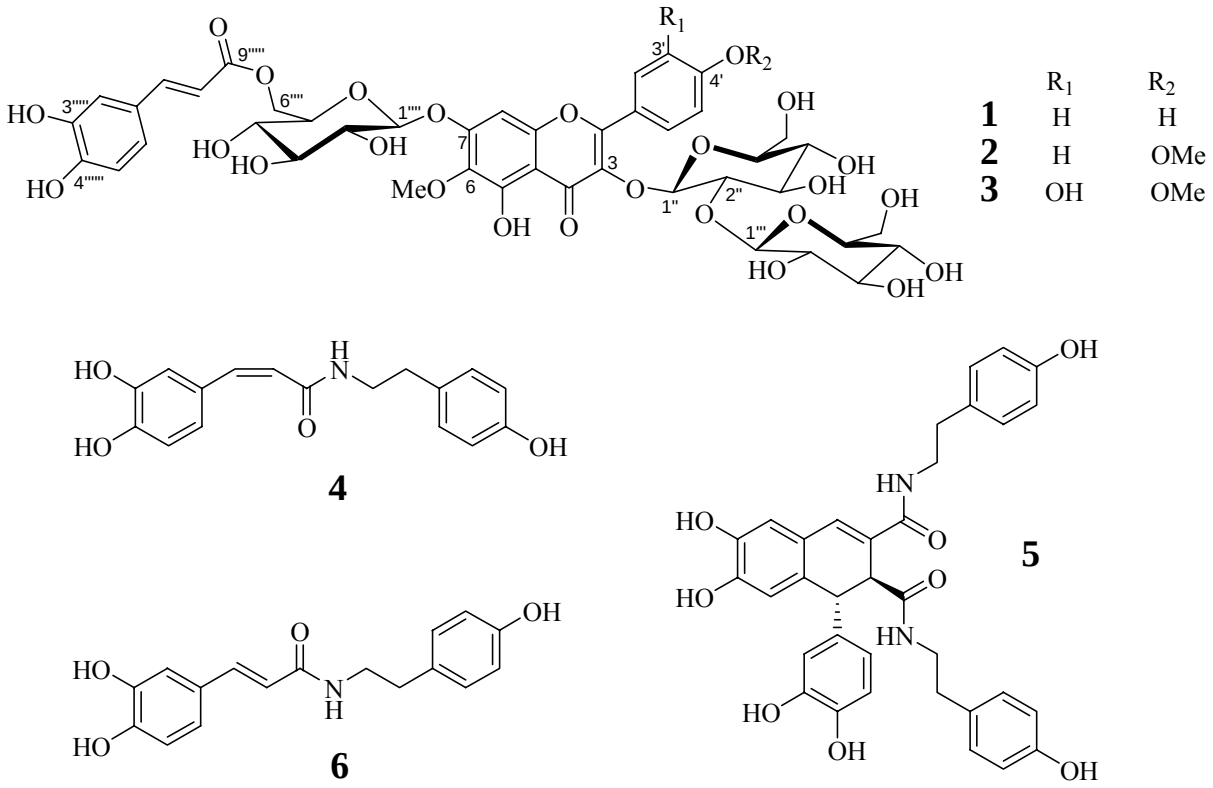

Figure 1. The structures of the isolated compounds (**1**–**6**) from *T. tetragonoides*

RESULTS AND DISCUSSION

Compound **1** was obtained as a yellowish gum. Its molecular formula $C_{43}H_{48}O_{25}$ was deduced by HR FAB-MS [m/z 965.2534 $[M+H]^+$, (calcd. 965.2563)]. The one singlet signal at δ 7.00 (1H, s, H-8), two doublet signals at δ 8.05 (2H, d, J = 9.5 Hz, H-2′, 6′), and 6.88 (2H, d, J = 9.5 Hz, H-3′, 5′), a methoxy signal at δ 3.75 (3H, s, OMe) and a hydroxyl signal at δ 12.67 in the ^{1}H-NMR spectrum were assumed to be protons of the A ring and the B ring of 6-methoxykaemferol type flavonol derivative,[10] respectively. The sixteen signals at δ 177.8 (C-4), 160.1 (C-4′), 156.3 (C-7), 156.2 (C-5), 152.2 (C-9), 148.4 (C-2), 132.8 (C-3), 132.3 (C-6), 131.0 (C-2′, 6′), 121.0 (C-1′), 115.3 (C-3′, 5′), 106.1 (C-10), 93.8 (C-8) and 60.3 (OMe) in the ^{13}C-NMR spectrum suggested that **1** was 6-methoxykaemferol flavonol derivative.[10] The olefinic signals at δ 7.44 (1H, d, J = 16.0 Hz, H-8′′′′′), 6.99 (1H, d, J = 2.0 Hz, H-2′′′′′), 6.89 (1H, dd, J = 8.5, 2.0 Hz, H-6′′′′′), 6.68 (1H, d, J = 8.5 Hz, H-5′′′′′) and 6.24 (1H, d, J = 16.0 Hz, H-7′′′′′) in the ^{1}H-NMR spectrum indicated the presence of a caffeoic acid moiety.[11] Three anomeric protons of sugars were shown in the ^{1}H-NMR spectrum at δ 5.71 (1H, d, J = 7.0 Hz, H-1″), 5.22 (1H, d, J = 7.0 Hz, H-1′′′′) and 4.61 (1H, d, J = 8.0 Hz, H-1′′′).[12,13] The correlations of δ 5.71 (H-1″) with δ 132.8 (C-3), δ 5.22 (H-1′′′′) with δ 156.3 (C-7), δ 4.61 (H-1′′′) with δ 82.4 (C-2″) in the HMBC spectrum of **1**

confirmed the connections of three D-glucoses at C-3, C-7 and C-2″, respectively. The correlations of δ 4.39 (1H, dd, *J* = 12.0, 1.5 Hz, H-6‴a) and δ 4.24 (1H, dd, *J* = 12.0, 5.0 Hz, H-6‴b) with δ 166.5 (C-9‴″) in the HMBC spectrum of **1** confirmed the attachment of caffeoic acid moiety at H-6‴″ (Figure 2). The fragmentation pattern of the FAB MS/MS spectrum {965 $[M + H]^+$, 803 $[M + H – \text{caffeoic acid}]^+$, 641 $[M + H – \text{Glc} – \text{caffeoic acid}]^+$, and 317 $[\text{aglycone} + H]^+$} reconfirmed the connectivities of three D-glucoses and the caffeoic acid group (Figure 3). The enzymatic hydrolysis of **1** with cellulase[14] afforded 6-methoxykaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranoside (**1a**),[15] which was identified by ^{1}H- and ^{13}C- NMR and MS data. Therefore, the structure of **1** was determined to be 6-methoxykaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranosyl-(6‴″-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside.

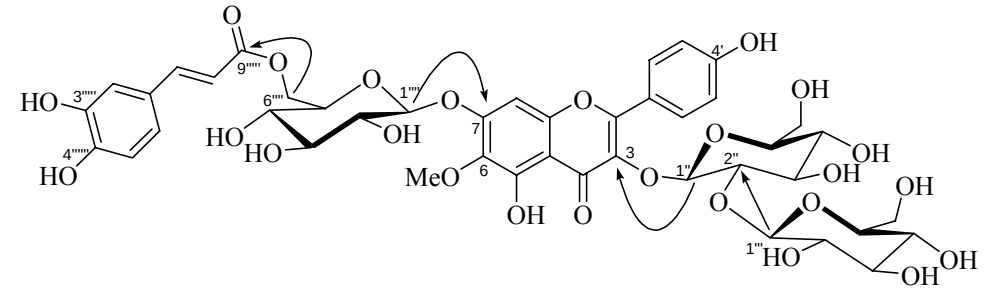

Figure 2. Key HMBC of **1** (^{1}H→^{13}C)

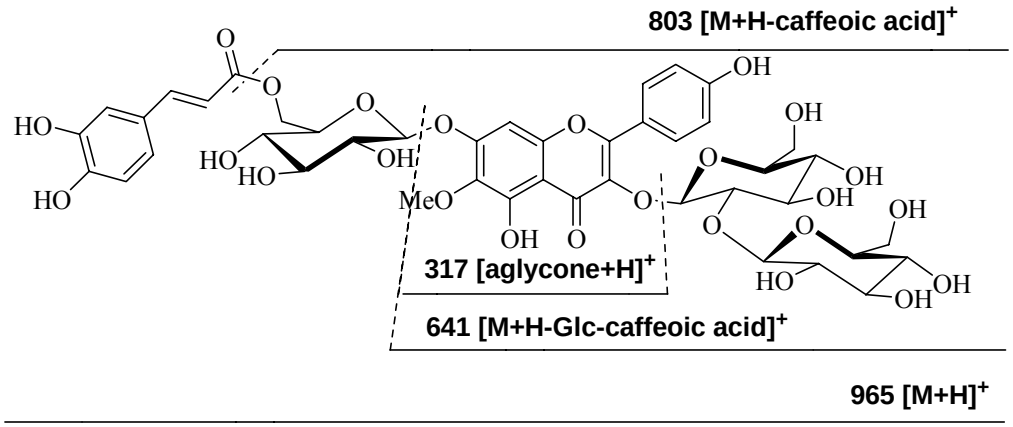

Figure 3. FAB MS/MS fragmentation pattern of **1**

Compound **2** was obtained as a yellowish gum. Its molecular formula $C_{44}H_{50}O_{25}$ was deduced by HR FAB-MS [m/z 979.2693 $[M+H]^+$, (calcd. 979.2719). The ^{1}H- and ^{13}C-NMR spectra of **2** were very similar to those of **1**, except for an additional methoxy group (^{1}H-NMR: δ 3.76 (s); ^{13}C-NMR: δ 55.1) in **2**. The correlation of the methoxy signal at δ 3.76 (3H, s) with δ 160.5 (C-4′) in the HMBC spectrum

confirmed the connectivity of the methoxy group at C-4′. The HMBC spectrum and the FAB MS/MS fragmentation pattern recomfirmed the connectivities of the structure of **2**. Thus, the structure of **2** was determined to be 6,4′-dimethoxykaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranosyl-(6‴-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside.

Compound **3** was obtained as a yellowish gum. Its molecular formula $C_{44}H_{50}O_{26}$ was deduced by HR FAB-MS [m/z 995.2654 $[M+H]^+$, (calcd. 995.2669)]. The five signals at δ 7.64 (1H, s, H-2′), 7.52 (1H, d, *J* = 8.0 Hz, H-6′), 6.82 (1H, m, H-5′), 6.66 (1H, s, H-8) and 3.91 (3H, s, OMe) in the ^{1}H-NMR spectrum and the sixteen signals at δ 180.2 (C-4), 159.0 (C-2), 157.7 (C-7), 154.0 (C-5), 153.2 (C-9), 149.2 (C-4′), 147.4 (C-3′), 135.2 (C-3), 131.0 (C-6), 123.2 (C-6′), 123.8 (C-1′), 117.8 (C-2′), 116.5 (C-5′), 108.1 (C-10), 95.4 (C-8) and 61.5 (OMe) in the ^{13}C-NMR spectrum suggested that **3** was patuletin type flavonol derivative.[16] The ^{1}H-NMR spectrum indicated the presence of a caffeoic acid moiety[11] and three anomeric protons of D-glucose[12,13] (Table 1). On the basis of correlations of the methoxy signal at δ 3.76 (3H, s) with the signal at δ 149.2 (C-4′) in the HMBC spectrum confirmed the connections of two methoxy groups (Table 1). The HMBC spectrum and the FAB MS/MS fragmentation pattern confirmed the connectivities of the structure of **3**. Thus, the structure of **3** was determined to be 4′-methoxypatuletin-3-*O*-*β*-D-glucosyl(1‴→2″)-*β*-D-glucopyranosyl-(6‴-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside.

EXPERIMENTAL DETAILS

General. FAB MS spectrum was recorded on JEOL JMS-700 mass spectrometer (JEOL Ltd. Japan), FAB source was Xe atom beam, and MS/MS was B/E linked scan. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian 500 MHz spectrometer for ^{1}H, and 125 MHz for ^{13}C, respectively. ^{1}H-^{1}H COSY, HMQC and HMBC spectra were obtained with the usual pulse sequences and data processing was performed with standard software. TLC and column chromatography were carried out on pre-coated silica gel F_{254} plates and RP C-18 F_{254s} plates (Merck), Sephadex LH-20 (Pharmacia) and LiChroprep® Lobar-A Si 60 and RP C-18 (Merck). The semi-preparative HPLC was carried out on a gemini RP C-18 column (10 μm, 22 x 250 mm, Phenomenex Co., USA) using on a Knauer pump model K-1001 with a RI detector (Knauer model K-2401).

Plant material. The aerial parts of *Tetragonia tetragonoides* was collected at Jeju island, South Korea in June 2003. A voucher speciemen of the plants (SKKU-03-2003) was deposited at the College of Pharmacy, Sungkyunkwan University, Korea.

Extraction and isolation. Dried and chopped aerial parts of *T. tetragonoides* (2 kg) were extracted with MeOH three times at r.T. The MeOH extract (180 g) was suspended in distilled water (1.6 L) and then successsively partitioned with *n*-hexane, CH_2Cl_2, EtOAc and BuOH, followed by evaporation to afford 19 g, 9 g, 5 g and 26 g fraction, respectively. The EtOAc fraction (5 g) was chromatographed over a silica gel column using a solvent of EtOAc:MeOH:H_2O (10:1:0.1) to give five fractions (E1 ~ E5). The E1 fraction (1.3 g) was subjected to silica gel column chromatography eluted with $CHCl_3$:EtOAc:MeOH (4:2:1) to give two fractions (E1-1 and E1-2). The E1-1 fraction (0.7 g) was subjected to silica gel column chromatography eluted with $CHCl_3$:EtOAc:MeOH (14:1:1) and purified with RP C-18 preparative HPLC (10 % MeOH, flow rate 2.0 mL/min) to afford **4** (15 mg). The E2 fraction (0.2 g) was subjected to Sephadex LH-20 column chromatography (CH_2Cl_2:MeOH = 1:1) and RP C-18 HPLC (40 % MeOH) to afford **5** (15 mg). The BuOH fraction (26 g) was chromatographed over silica gel-flash column eluting with EtOAc:MeOH:H_2O (9:3:1) to give five fractions (B1 ~ B5). The B1 fraction (2 g) was subjected to silica gel column chromatography eluted with $CHCl_3$:MeOH:H_2O (9:3:0.1) to give four fractions (B1-1 ~ B1-4). The B1-2 fraction (0.6 g) was subjected to silica gel column chromatography eluted with $CHCl_3$:MeOH (13:2) and purified with preparative HPLC ($CHCl_3$:MeOH = 7:1, flow rate 2.0 mL/min) to afford **6** (9 mg). The B4 fraction (3 g) was chromatographed over a silica gel-flash column eluting with $CHCl_3$:MeOH:H_2O (8:4:0.1) to give three subfractions (B4-1 ~ B4-3). The B4-1 fraction (2 g) was subjected to a silica gel column eluted with $CHCl_3$:MeOH:H_2O (9:5:1) and purified with preparative RP C-18 HPLC (45 % MeOH, flow rate 2.0 mL/min and 30 % MeOH, flow rate 2.0 mL/min) to afford **1** (29 mg). The B4-2 fraction (0.3 g) was subjected to RP C-18 silica gel column chromatography eluted with 50 % MeOH to give two subfractions (B4-2-1 and B4-2-2). The B4-2-2 fraction (150 mg) was purified with preparative HPLC ($CHCl_3$:MeOH:H_2O (8:4:0.1), flow rate 2.0 mL/min) to afford **2** (25 mg), and **3** (6 mg).

Enzymatic hydrolysis[14] **of 1. 1** (10 mg) and cellulase (45 mg, Sigma-aldrich) in 10 mL of 0.2 M NaOAc/HOAc buffer solution (pH 5) was stirred at 37 ^{o}C for 2 days. After 10 mL of H_2O was added, the reaction mixture was extracted with BuOH (10 mL). The BuOH extract (8 mg) was purified with preparative RP C-18 HPLC (50 % MeOH, flow rate 2.0 mL/min, UV detected at 254nm) to afford **1a** (5 mg). **1a** was identified to be 6-methoxykaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranoside by ^{1}H- and ^{13}C-NMR and MS data.

6-Methoxykaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranoside (1a). FAB-MS (m/z) : 641 $[M+H]^+$, 316 $[aglycone]^+$; ^{1}H-NMR (DMSO-d_6, 500MHz): δ 7.96 (2H, d, J = 8.5 Hz, H-2′, 6′), 6.86 (2H, d, J = 8.5 Hz, H-3′, 5′), 5.80 (1H, s, H-8), 5.69 (1H, d, J = 7.0 Hz, H-1″), 4.60 (1H, d, J = 7.5 Hz, H-1‴),

3.67 (3H, s, OMe); ^{13}C- NMR (DMSO-d_6, 125MHz): δ 178.2 (C-4), 160.3 (C-4′), 156.3 (C-7), 156.2 (C-5), 152.2 (C-9), 148.4 (C-2), 132.8 (C-3), 132.3 (C-6), 131.6 (2C-2′,6′), 121.7 (C-1′), 116.0 (2C-3′,5′), 106.7 (C-10), 104.1 (C-1‴), 99.7 (C-1″), 94.4 (C-8), 83.9 (C-2″), 60.5 (OMe).

6-Methoxykaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranosyl-(6‴-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside (1). Yellowish gum ; HR FAB-MS (m/z): 965.2534 $[M+H]^+$ ($C_{43}H_{49}O_{25}$, calcd. 965.2563); FAB MS/MS (m/z): 965 $[M+H]^+$, 803 [M+H-caffeoic acid]$^+$, 641 [M+H-Glc-caffeoic acid]$^+$ and 317 [aglycone+H]$^+$; see Figure 2; ^{1}H-NMR (DMSO-d_6, 500 MHz): see Table 1; ^{13}C-NMR (DMSO-d_6, 125 MHz): see Table 1; ^{1}H - ^{1}H COSY (DMSO-d_6, 500 MHz); HSQC (DMSO-d_6, 500 MHz); HMBC (DMSO-d_6, 500 MHz): see Figure 3; ROESY (DMSO-d_6, 500 MHz).

6,4′-Dimethoxy kaemferol-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranosyl-(6‴-(*E*)-caffeoyl) -7-*O*-*β*-D-glucopyranoside (2). Yellowish gum; UV (MeOH) λmax (nm): 233, 273, 297 (sh), 330; HR FAB-MS (m/z): $[M+H]^+$ 979.2693 ($C_{44}H_{51}O_{25}$, calcd. 979.2719); FAB MS/MS (m/z): 979 $[M+H]^+$, 817 [M+H-caffeoic acid]$^+$, 655 [M+H-Glc-caffeoic acid]$^+$; ^{1}H-NMR (CD_3OD, 500 MHz): see Table 1; ^{13}C-NMR (CD_3OD, 125 MHz): see Table 1; ^{1}H - ^{1}H COSY (CD_3OD, 500 MHz); HMQC (CD_3OD, 500 MHz); HMBC (CD_3OD, 500 MHz).

4′-Methoxypatuletin-3-*O*-*β*-D-glucosyl (1‴→2″)-*β*-D-glucopyranosyl-(6‴-(*E*)-caffeoyl)-7-*O*-*β*-D-glucopyranoside (3). Yellowish gum; UV (MeOH) λmax (nm): 233 (sh), 258, 270, 331; HR FAB-MS (m/z): $[M+H]^+$ 995.2654 ($C_{44}H_{51}O_{26}$, calcd. 995.2669); FAB MS/MS (m/z): 995 $[M+H]^+$, 833 [M+H-caffeoic acid]$^+$, 671 [M+H-Glc-caffeoic acid]$^+$; ^{1}H-NMR (CD_3OD, 500 MHz): see Table 1; ^{13}C-NMR (CD_3OD, 125 MHz): see Table 1; ^{1}H - ^{1}H COSY (CD_3OD, 500 MHz); HMQC (CD_3OD, 500 MHz); HMBC (CD_3OD, 500 MHz).

Table 1. ^{1}H- and ^{13}C-NMR chemical shifts of **1**–**3**

Position	**1**		**2**		**3**	
	δ_H (multi, J = Hz)	δ_C	δ_H (multi, J = Hz)	δ_C	δ_H (multi, J = Hz)	δ_C
2		148.4		148.0		159.0
3		132.8		133.9		135.2
4		177.8		178.9		180.2
5	12.67 (OH)	156.2		156.5		154.0
6		132.3		132.9		131.0
7		156.3		158.0		157.7

8	7.00 (s)	93.8	6.68 (s)	94.3	6.66 (s)	95.4
9		152.2		152.8		153.2
10		106.1		103.6		108.1
1′		121.0		122.7		123.8
2′	8.05 (d, 9.5 Hz)	131.0	7.99 (d, 9.5 Hz)	131.2	7.64 (s)	117.8
3′	6.88 (d, 9.5 Hz)	115.3	6.87 (d, 9.5 Hz)	115.1		147.4
4′		160.1		160.5		149.2
5′	6.88 (d, 9.5 Hz)	115.3	6.87 (d, 9.5 Hz)	115.1	6.82 (m)	116.5
6′	8.05 (d, 9.5 Hz)	131.0	7.99 (d, 9.5 Hz)	131.2	7.52 (d, 8.0 Hz)	123.2
3-OGlc						
1″	5.71 (d, 7.0 Hz)	97.8	5.41 (d, 7.5 Hz)	99.9	5.32 (d, 8.0 Hz)	101.3
2″	3.46 (m)	82.4	3.80-3.20 (m)	81.5	3.86-3.17 (m)	83.1
3″	3.17 (m)	76.6	3.80-3.20 (m)	76.8	3.86-3.17 (m)	78.0
4″	3.15 (m)	69.6	3.80-3.20 (m)	70.6	3.86-3.17 (m)	71.8
5″	3.47 (m)	76.6	3.80-3.20 (m)	76.8	3.86-3.17 (m)	78.0
6″a	3.57 (m)	60.8	3.80-3.20 (m)	61.5	3.86-3.17 (m)	62.3
6″b	3.49 (m)		3.80-3.20 (m)		3.86-3.17 (m)	
2″-OGlc						
1‴	4.61 (d, 8.0 Hz)	104.1	4.76 (d, 7.5 Hz)	103.6	4.76 (d, 7.0 Hz)	105.2
2‴	3.08 (m)	74.4	3.80-3.20 (m)	74.5	3.86-3.17 (m)	75.7
3‴	3.09 (m)	77.5	3.80-3.20 (m)	77.1	3.86-3.17 (m)	78.3
4‴	3.09 (m)	69.5	3.80-3.20 (m)	70.1	3.86-3.17 (m)	71.0
5‴	3.12 (m)	77.0	3.80-3.20 (m)	77.0	3.86-3.17 (m)	77.9
6‴a	3.48 (m)	60.5	3.80-3.20 (m)	61.2	3.86-3.17 (m)	62.2
6‴b	3.25 (m)		3.80-3.20 (m)		3.86-3.17 (m)	
7-OGlc						
1⁗	5.22 (d, 7.0 Hz)	100.1	5.15 (d, 7.5 Hz)	100.7	5.14 (d, 7.5 Hz)	101.9
2⁗	3.37 (m)	69.2	3.80-3.20 (m)	69.9	3.86-3.17 (m)	70.9
3⁗	3.35 (m)	73.1	3.80-3.20 (m)	73.5	3.86-3.17 (m)	74.6
4⁗	3.34 (m)	76.3	3.80-3.20 (m)	76.6	3.86-3.17 (m)	77.8
5⁗	3.79 (m)	73.9	3.85 (br.t)	75.0	3.86-3.17 (m)	75.7
6⁗a	4.39 (dd, 12.0, 1.5 Hz)	62.9	4.71 (dd, 12.0, 2.5 Hz)	63.4	4.67 (dd, 12.0, 2.5 Hz)	64.6
6⁗b	4.24 (dd, 12.0, 5.0 Hz)		4.29 (dd, 12.0, 7.0 Hz)		4.30 (dd, 12.0, 7.5 Hz)	
Caffeoic acid moiety						
1⁗′		125.3		126.3		127.4
2⁗′	6.99 (d, 2.0 Hz)	115.2	6.89 (d, 1.5 Hz)	113.7	6.88 (br.s)	114.8
3⁗′		145.4		146.2		145.9
4⁗′		151.2		152.1		150.4
5⁗′	6.68 (d, 8.5 Hz)	115.8	6.69 (d, 8.5 Hz)	115.4	6.66 (m)	116.2
6⁗′	6.89 (dd, 8.5, 2.0 Hz)	120.8	6.86 (dd, 8.5, 1.5 Hz)	121.2	6.83 (m)	122.6

7‴″	6.24 (d, 16.0 Hz)	113.6	6.22 (d, 15.5 Hz)	110.2	6.23 (d, 16.0 Hz)	111.3
8‴″	7.44 (d, 16.0 Hz)	145.5	7.51 (d, 15.5 Hz)	149.3	7.51 (d, 16.0 Hz)	150.1
9‴″		166.5		167.7		168.9
OMe	3.75 (s)	60.3	3.91 (s)	60.4	3.91	61.5
			3.76 (s)	55.1	3.76 (s)	56.2

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