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Phytochemical Constituents of *Geranium eriostemon*

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Abstract – Phytochemical investigation of the MeOH extract of the aerial parts of *Geranium eriostemon* resulted in the isolation of one triterpene, three furofuran lignans, one syringic acid and four flavonoids. Their chemical structures were characterized by spectroscopic methods to be oleanolic acid (**1**), (−)-kobusin (**2**), (−)-eudesmin (**3**), (+)-magnolin (**4**), syringic acid (**5**), quercetin (**6**), juglanin (**7**), juglalin (**8**), and hyperin (**9**). All compounds (**1 - 9**) were isolated for the first time from this plant source and the compounds **2 - 4** were reported first from the genus *Geranium*. Compounds **4 - 6** exhibited moderate cytotoxicity against four human cancer cell lines *in vitro* using a SRB bioassay.
Keywords – *Geranium eriostemon*, Geraniaceae, Lignan, Cytotoxicity

Introduction

Geranium eriostemon FISCHER ex DC (Geraniaceae) is a perennial plant, which is widely distributed throughout northern parts of Korea. The aerial parts of *G. eriostemon* have long been used in traditional Korean medicine for the treatment of enteritis, dysentery and diarrhea (Lee, 2003). Tannins such as geraniin, dehydrogeraniin and furosin as well as flavonoids such as quercetin, kaempferol-7-rhamnoside and kaempferin (Bae, 2000) were reported from *G. eriostemon*. As a part of our continuing search for bioactive constituents from Korean natural sources, we investigated constituents of the aerial parts of *G. eriostemon*. As a result, we isolated one triterpene (**1**), three furofuran lignans (**2 - 4**), one syringic acid (**5**) and four flavonoids (**6 - 9**) from the MeOH extract of the aerial parts of *G. eristemon*. All the isolated compounds were tested for their cytotoxic activities against four human cancer cell lines *in vitro* using a SRB bioassay.

Experimental

General – Melting points were determined on a Gallenkamp melting point apparatus and uncorrected. Optical rotations were measured on a JASCO P-1020 Polarimeter. IR spectra were recorded on a Bruker IFS-66/S FT-IR spectrometer. UV spectra were recorded with a Schimadzu UV-1601 UV-Visible spectrophotometer. NMR spectra were recorded on a Varian UNITY INOVA 500 NMR spectrometer. EIMS and FABMS data were obtained on a JEOL JMS700 mass spectrometer, and LC-ESI/MS data on an Agilent 1100LC/ MSD trap SL LC/ MS. Preparative HPLC was performed using a Gilson 306 pump with a Shodex refractive index detector and Alltech Silica 5 μ column (250 × 22 mm) or Econosil® RP-18 10 μ column (250 × 22 mm). Silica gel 60 (Merck, 70~230 mesh and 230~400 mesh) was used for column chromatography. TLC was performed using Merck precoated Silica gel F_{254} plates and RP-18 F_{254s} plates. The packing material for molecular sieve column chromatography was Sephadex LH-20 (Pharmacia Co.). Low-pressure liquid chromatography was performed over Merck LiChroprep Lobar®-A Si 60 (240 × 10 mm) or LiChroprep Lobar®-A RP-18 (240 × 10 mm) columns with a FMI QSY-0 pump (ISCO).

Plant materials – The aerial parts of *G. eriostemon* were collected from Mt. Daeduk, Gangwon Province, Korea, in June 2008. A voucher specimen (SKKU-2008-6) of the plant was deposited in the herbarium of the College of Pharmacy, Sungkyunkwan University, Suwon, Korea.

Extraction and isolation – The aerial parts of *G. eriostemon* (2.7 kg) were extracted at room temperature with 80% MeOH three times and evaporated under reduced pressure to give a residue (275 g), which was dissolved in water (800 mL) and partitioned with solvent

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to give hexane (10 g), CH_2Cl_2 (5 g), EtOAc (37 g), and BuOH (53 g) soluble portions. The hexane fraction (10 g) was separated over a silica gel column (hexane:EtOAc = 5 : 1 - 2 : 1) to yield seven fractions (H1 - H7). Fraction H4 (211 mg) was further separated over a silica Lobar A®-column ($CHCl_3$: MeOH = 50 : 1) and purified by recrystallization using $CHCl_3$ to give compound **1** (5 mg). Fraction H5 was separated over a Sephadex LH-20 column (CH_2Cl_2 : MeOH = 1 : 1), separated over a silica Lobar A®-column ($CHCl_3$: MeOH = 55 : 1) and purified with a RP-C_{18} silica gel redisep (70% MeOH) to give compound **2** (8 mg). The CH_2Cl_2 fraction (5 g) was separated over a silica gel column with a solvent system of CH_2Cl_2 : MeOH (20 : 1 - 1 : 1) as the eluant to yield eight fractions (M1 - M8). Fraction M2 (200 mg) was further separated over a Sephadex LH-20 column (CH_2Cl_2 : MeOH = 1 : 1) and purified with a silica gel prep. HPLC (hexane : $CHCl_3$: MeOH = 2.5 : 6 : 0.1, over 30 min at a flow rate of 2.0 mL/min, Alltech silica 5 μ column 250 × 10 mm, Shodex RI-101 refractive index detector) to give compounds **3** (13 mg) and **4** (4 mg), respectively. Similarly, EtOAc fraction (20.8 g) was separated over a silica gel column ($CHCl_3$: MeOH = 5 : 1 - 1 : 1) to yield six fractions (E1 - E6). Fraction E1 was separated over a silica gel column with a solvent system of $CHCl_3$: MeOH (20 : 1) as the eluant to give six fractions (E11 - E16). Fraction E14 was separated over a RP-C_{18} silica gel column (30% MeOH) and purified with a Sephadex LH-20 column (CH_2Cl_2 : MeOH = 1 : 1) to afford compound **5** (13 mg). Fraction E142 was purified by recrystallization using MeOH to give compound **6** (6 mg). In turn, fraction E16 (62 mg) was separated over a Sephadex LH-20 column (CH_2Cl_2 : MeOH = 1 : 1) and purified with a RP-C_{18} prep. HPLC (Econosil® RP-18 10 μ column, 250 × 22 mm; 55% MeOH) to yield compound **7** (5 mg). The Fraction E2 was separated over a silica gel column with a solvent system of $CHCl_3$: MeOH (15 : 1) as the eluant to give four fractions (E21 - E24). Fraction E23 was then separated over a RP-C_{18} silica gel column (50% MeOH) and purified with a Sephadex LH-20 column (80% MeOH) to afford compound **8** (6 mg). The fraction E4 was purified by recrystallization using MeOH to yield compound **9** (13 mg).

Oleanolic acid (**1**) – White powder, mp 296 - 298 °C; $[\alpha]_D^{25}$: +33.3° (*c* 0.175, $CHCl_3$); ES/MS *m/z* : 456, 438, 248, 207, 203, 189; IR ν_{max} ($CHCl_3$) : 3420, 2930, 1680 cm^{-1} ; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.76 (3H, s, H-29), 0.78 (3H, s, H-26), 0.91 (3H, s, H-25), 0.93 (3H, s, H-30), 1.00 (3H, s, H-24), 1.13 (3H, s, H-27), 1.23 (3H, s, H-23), 3.22 (1H, dd, *J* = 11.0, 4.5 Hz, H-3), 5.29 (1H, br. s, H-12); ^{13}C- NMR (125 MHz, $CDCl_3$): δ 15.5 (C-25), 15.8 (C-24), 17.3 (C-26), 18.5 (C-6), 23.2 (C-11), 23.6 (C-16), 23.8 (C-30), 26.1 (C-27), 27.4 (C-2), 27.9 (C-15), 28.3 (C-23), 30.9 (C-20), 32.7 (C-22), 32.9 (C-7), 33.3 (C-29), 34.0 (C-21), 37.3 (C-10), 38.6 (C-1), 39.0 (C-4), 39.5 (C-8), 41.3 (C-18), 41.9 (C-14), 46.1 (C-19), 46.7 (C-17), 47.9 (C-9), 55.5 (C-5), 79.3 (C-3), 122.9 (C-12), 143.8 (C-13), 182.7 (C-28).

(–)-Kobusin (**2**) – Colorless gum; $[\alpha]_D^{25}$: −54.3° (*c* 0.42, $CHCl_3$); FAB-MS *m/z* : 371 $[M + H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.10 (2H, m, H-1/5), 3.88 (3H, s, -OCH_3), 3.89 (3H, s, OCH_3), 3.91 (2H, m, H-4a/8a), 4.27 (2H, dd, *J* = 9.0, 4.0 Hz, H-4b/8b), 4.76 (2H, dd, *J* = 10.5, 5.0 Hz, H-2/6), 5.97 (2H, s, -OCH_2O), 6.79-6.92 (6H, m, aromatic H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 54.4 (C-1), 54.6 (C-5), 56.1 (-OCH_3), 56.2 (-OCH_3), 71.9 (C-8), 72.0 (C-4), 86.0 (C-6), 86.1 (C-2), 101.3 (-OCH_2O-), 106.7 (C-2"), 108.4 (C-5"), 109.5 (C-2'), 111.3 (C-5'), 118.5 (C-6'), 119.6 (C-6"), 133.8 (C-1'), 135.3 (C-1"), 147.3 (C-4"), 148.2 (C-3"), 148.9 (C-4'), 149.4 (C-3')

(–)-Eudesmin (**3**) – Colorless gum; $[\alpha]_D^{25}$: −78.5° (*c* 0.41, $CHCl_3$); FAB-MS *m/z* : 387 $[M + H]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.12 (2H, m, H-1/5), 3.88 (6H, s, -OCH_3 × 2), 3.90 (6H, s, OCH_3 × 2), 3.91 (2H, m, H-4a/8a), 4.27 (2H, dd, *J* = 9.0, 4.0 Hz, H-4b/8b), 4.76 (2H, dd, *J* = 10.5, 5.0 Hz, H-2/6), 6.84 (2H, br. s, H-2'/2"), 6.88 (2H, dd, *J* = 8.0, 2.0 Hz, H-6'/6"), 6.91 (2H, d, *J* = 8.0 Hz, H-5'/5"); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 54.4 (C-1/5), 56.1 (-OCH_3 × 4), 71.9 (C-4/8), 86.0 (C-2/6), 109.5 (C-2'/2"), 111.3 (C-5'/5"), 118.5 (C-6'/6"), 133.8 (C-1'/1"), 148.9 (C-3'/3"), 149.4 (C-4'/4")

(+)-Magnolin (**4**) – Colorless gum; $[\alpha]_D^{25}$: +47.8° (*c* 0.1, MeOH); FAB-MS *m/z* : 417 $[M + H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ 3.15 (2H, m, H-1/5), 3.76 (3H, s, -OCH_3), 3.85 (6H, s, OCH_3 × 2), 3.87 (6H, s, OCH_3 × 2) 3.89 (2H, m, H-4a/8a), 4.28 (2H, m, H-4b/8b), 4.77 (2H, dd, *J* = 10.5, 5.0 Hz, H-2/6), 6.70 (2H, s, H-2", 6"), 6.94 (1H, br. s, H-2'), 6.97 (1H, dd, *J* = 8.0, 2.0 Hz, H-6'), 7.00 (1H, d, *J* = 8.0 Hz, H-5'); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 54.2 (C-1), 54.3 (C-5), 54.6 (-OCH_3), 55.3 (-OCH_3 × 2), 55.4 (-OCH_3), 59.9 (-OCH_3), 71.5 (C-8), 71.7 (C-4), 86.0 (C-6), 86.2 (C-2), 103.0 (C-2"/6"), 110.0 (C-2'), 111.7 (C-5'), 118.6 (C-6'), 134.1 (C-1'), 137.3 (C-1"), 137.7 (C-4"), 149.0 (C-3'), 149.5 (C-4'), 153.5 (C-3"/5")

Syringic acid (**5**) – Colorless gum; FAB-MS *m/z* : 199 $[M + H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ 3.82 (6H, s, -OCH_3 × 2), 7.06 (2H, s, H-2, 6); ^{13}C-NMR (125 MHz, CD_3OD): δ 51.1 (OCH_3 × 2), 108.9 (C-2, 6), 120.3 (C-1), 138.6 (C-4), 145.3 (C-3, 5), 167.8 (COOH)

Quercetin (**6**) – Yellow gum; FAB-MS *m/z* : 303 [M +

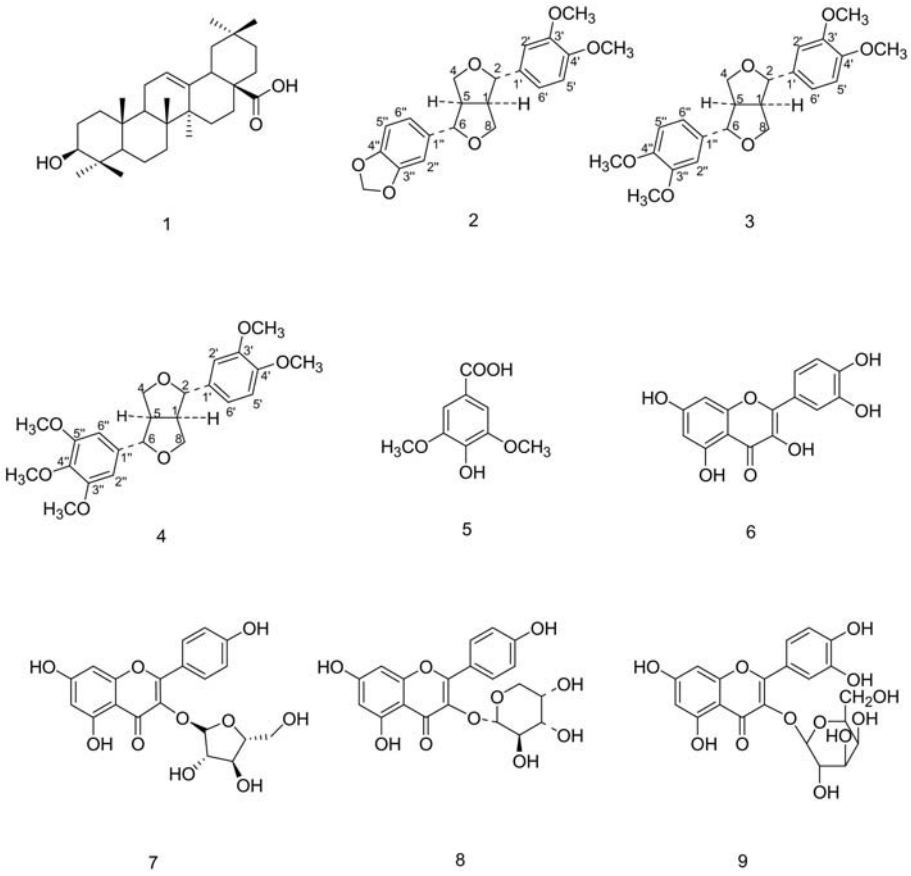

Fig. 1. The structures of **1** - **9** isolated from *G. eriostemon.*

H]$^+$; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 6.18 (1H, d, *J* = 2.0 Hz, H-6), 6.40 (1H, d, *J* = 2.0 Hz, H-8), 6.88, (1H, d, *J* = 8.5 Hz, H-5'), 7.54 (1H, dd, *J* = 8.5, 2.5 Hz, H-6'), 7.67 (1H, d, *J* = 2.5 Hz, H-2'); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 93.5 (C-8), 98.2 (C-6), 103.0 (C-10), 115.2 (C-2'), 115.5 (C-5'), 120.1 (C-6'), 122.0 (C-1'), 135.7 (C-3), 145.0 (C-3'), 146.8 (C-2), 147.5 (C-4'), 156.2 (C-9), 160.6 (C-5), 163.8 (C-7), 175.6 (C-4).

Juglanin (**7**) – Yellow gum; FAB-MS *m/z* : 419 [M + H]$^+$; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 5.63 (1H, br. s, H-1"), 6.19 (1H, d, *J* = 2.0 Hz, H-6), 6.42 (1H, d, *J* = 2.0 Hz, H-8), 6.89, (2H, d, *J* = 8.0 Hz, H-3', 5'), 8.02 (2H, d, *J* = 8.0 Hz, H-2', 6'), 10.38 (1H, br. s, OH), 10.51 (1H, br. s, OH), 12.62 (1H, br. s, 5-OH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 60.8 (C-5"), 77.1 (C-3"), 82.1 (C-2"), 86.3 (C-4"), 93.6 (C-8), 98.8 (C-6), 108.0 (C-1"), 103.9 (C-10), 115.4 (C-3', 5'), 120.7 (C-1'), 130.8 (C-2', 6'), 133.4 (C-3), 156.3 (C-2), 156.7 (C-9), 159.9 (C-4'), 161.2 (C-5), 164.2 (C-7), 177.6 (C-4)

Juglalin (**8**) – Yellow gum; FAB-MS *m/z* : 419 [M + H]$^+$; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 5.35 (1H, br. s, H-1"), 6.15 (1H, d, *J* = 2.0 Hz, H-6), 6.42 (1H, d, *J* = 2.0 Hz, H-8), 6.89 (2H, d, *J* = 8.0 Hz, H-3', 5'), 8.02 (2H, d, *J* = 8.0 Hz, H-2', 6'), 10.19 (1H, br. s, OH), 12.62 (1H, br. s, 5-OH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 64.8 (C-5"), 66.7 (C-4"), 71.4 (C-2"), 72.2 (C-3"), 94.3 (C-8), 99.4 (C-6), 101.9 (C-1"), 104.6 (C-10), 115.9 (C-3', 5'), 121.3 (C-1'), 131.7 (C-2', 6'), 134.2 (C-3), 156.9 (C-2), 157.0 (C-9), 160.7 (C-4'), 161.9 (C-5), 164.9 (C-7), 178.2 (C-4)

Hyperin (**9**) – Yellow gum; FAB-MS *m/z* : 449 [M + H]$^+$; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 5.38 (1H, br. s, H-1"), 6.20 (1H, d, *J* = 2.0 Hz, H-6), 6.40 (1H, d, *J* = 2.0 Hz, H-8), 6.83 (1H, d, *J* = 8.0 Hz, H-5'), 7.53 (1H, d, *J* = 2.0 Hz, H-2'), 7.67 (1H, dd, *J* = 8.0, 2.0 Hz, H-6'), 12.63 (1H, br. s, 5-OH); ^{13}C-NMR (125 MHz, DMSO-d_6): δ 60.8 (C-6"), 68.6 (C-4"), 71.9 (C-2"), 73.9 (C-3"), 76.5 (C-5"), 94.1 (C-8), 99.3 (C-6), 102.5 (C-1"), 104.3 (C-10), 115.9 (C-2'), 116.6 (C-5'), 121.7 (C-1'), 122.7 (C-6'), 134.2 (C-3), 145.5 (C-3'), 149.2 (C-4'), 156.9 (C-2, 9), 162.0 (C-5), 164.5 (C-7), 178.2 (C-4)

Test for cytotoxicity *in vitro* – Sulforhodamin B bioassay (SRB) was used as for cytotoxicity screening (Skehan *et al.,* 1990). The *in vitro* cytotoxicity of each compound against four cultured human tumor cells was

assessed at the Korean Research Institute of Chemical Technology. The cell lines used were A549 (non small cell lung adenocarcinoma), SK-OV-3 (ovarian cancer cells), SK-MEL-2 (skin melanoma), and HCT-15 (colon cancer cells). Doxorubicin was used as a positive control. The cytotoxicities of doxorubicin against A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines were IC_{50} 0.0011, 0.0204, 0.0012, and 0.1080 μM, respectively.

Results and Discussion

Compounds **1**, and **5 - 9** were identified by comparing the ^{1}H-, ^{13}C-NMR, and MS spectral data with the literature values to be oleanolic acid (**1**) (Kim *et al*., 2005), syringic acid (**5**) (Wettasinghe *et al*., 2001), quercetin (**6**) (Lee *et al*., 2004), juglanin (**7**) (Jung *et al*., 2002), juglalin (**8**) (Begum *et al*., 2006), and hyperin (**9**) (Lee *et al*., 2002). The following describes the structural elucidation of compounds **2**, **3** and **4**, which were for the first time isolated from the genus *Geranium*.

Compound **2** was obtained as a colorless gum with a negative optical rotation ($[\alpha]_D^{25}$: −54.3° in $CHCl_3$). From the EI-MS (*m/z* 370 $[M]^+$), ^{1}H-, and ^{13}C-NMR spectral data, the molecular formula of **2** was deduced to be $C_{21}H_{21}O_6$. The ^{1}H-NMR spectrum showed two methine protons at δ 3.10 (2H, m, H-1 and H-5), two methoxy protons at 3.88 (3H, s) and 3.89 (3H, s), two oxymethylene protons at 3.91 (2H, m, H-4a and H-8a), and 4.27 (2H, dd, J = 9.0, 4.0 Hz, H-4b and H-8b), two oxymethine protons at δ 4.76 (2H, dd, J = 10.5, 5.0 Hz, H-2 and H-6), dioxymethylene protons at δ 5.97 (2H, s), and six aromatic protons at δ 6.79-6.92 (6H, m). The ^{13}C-NMR spectra demonstrated the presence of 21 carbon signals, consisting of four trisubstituted carbons at δ 54.4, 54.6, 86.0, and 86.1, two methoxy carbons at δ 56.1, and 56.2, two oxymethylene carbons at δ 71.9, and 72.0, one dioxymethylene carbon at δ 101.3, and two aromatic rings at δ 106.7, 108.4, 109.5, 111.3, 118.5, 119.6, 133.8, 135.3, 147.3, 148.2, 148.9, and 149.4. The above mentioned ^{1}H- and ^{13}C-NMR spectra showed the presence of a 2,6-diaryl-3,7-dioxabicyclo[3,3,0]octane lignan with two methoxy groups and one dioxymethylene group (Pelter *et al.*, 1976). All (+)-sesamin type lignans have been reported to possess absolute configuration *R* form at the bridge carbons 1 and 5 (Freudenberg and Sidhu *et al*., 1961; Seo *et al.*, 2008). Since the specific rotation value of the compound **2** was negative (−54.3°), the compound was to be (−)-sesamin type and absolute configuration at the bridge carbons 1 and 5 to be *S* from. In comparison of the above mentioned data with published data (Gibbons *et al*., 1997; Seo *et al.*, 2008), the structure of **2** was determined to be (−)-kobusin.

Compound **3** was obtained as a colorless gum with a negative optical rotation ($[\alpha]_D^{25}$: −78.5° in $CHCl_3$). From the EI-MS (*m/z* 386 $[M]^+$) and ^{1}H- and ^{13}C-NMR spectral data, the molecular formula of **3** was deduced to be $C_{22}H_{26}O_6$. The NMR spectra of **3** were very similar to those of **2**, but the major difference was in ^{1}H-NMR spectrum of **3**; Instead of dioxymethylene proton signal at δ_H 5.97 in **2**, two additional methoxy proton signals at δ_H 3.88 were shown in **3**. Based on further comparison of the above data with published data (Latip *et al*., 1999), the structure of **3** was identified as (−)-eudesmin.

Compound **4** was obtained as a colorless gum with a positive optical rotation ($[\alpha]_D^{25}$: 47.8° in MeOH). From the EI-MS (*m/z* 416 $[M]^+$) and ^{1}H- and ^{13}C-NMR spectral

Table 1. Cytotoxic activities of compounds (**1 - 9**) isolated from *G. eriostemon*

Compound	IC_{50} (μM)[a]			
	A549	SK-OV-3	SK-MEL-2	HCT-15
1	20.34	62.72	95.25	29.26
2	68.28	> 100.0	> 100.0	> 100.0
3	57.81	> 100.0	103.22	92.14
4	39.52	24.38	24.03	19.82
5	35.29	24.84	22.63	20.45
6	29.64	24.71	19.33	17.37
7	> 100.0	> 100.0	> 100.0	> 100.0
8	> 100.0	> 100.0	> 100.0	> 100.0
9	> 100.0	> 100.0	> 100.0	> 100.0
Doxorubicin	0.0011	0.0204	0.0012	0.01080

[a]IC_{50} value of compounds against each cancer cell line, which was defined as the concentration (μM) that caused 50% inhibition of cell growth *in vitro*.

data, the molecular formula of **4** was deduced to be $C_{23}H_{23}O_7$. The NMR spectra of **4** were very similar to those of **3**, but the major difference was in ^{1}H-NMR spectrum of **4**; 5 aromatic proton signals at δ_H 6.70 (H-2", 6"), 6.94 (H-2', 5'), and 7.00 (H-6') were shown in **4**, whereas 6 aromatic proton signals at δ_H 6.84 (H-2'/2"), 6.88 (H-6'/6"), and 6.91 (H-5'/5") appeared in **3**. Furthermore, one more methoxy carbon signal was shown in the ^{13}C-NMR spectrum of **4**. Based on further comparison of the above data with published data (Miyazawa *et al*., 1993), the structure of **4** was identified as (+)-magnolin.

The isolated compounds (**1** - **9**) were tested *in vitro* for cytotoxicity against the A549, SK-OV-3, SK-MEL-2, and HCT15 human tumor cells using the SRB assay. Compounds **4** - **6** exhibited moderate cytotoxicity against the A549, SK-OV-3, SK-MEL-2, and HCT-15 cell lines as shown in Table 1.

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