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Cytotoxic Apigenin Derivatives from *Chrysopogon aciculatis*

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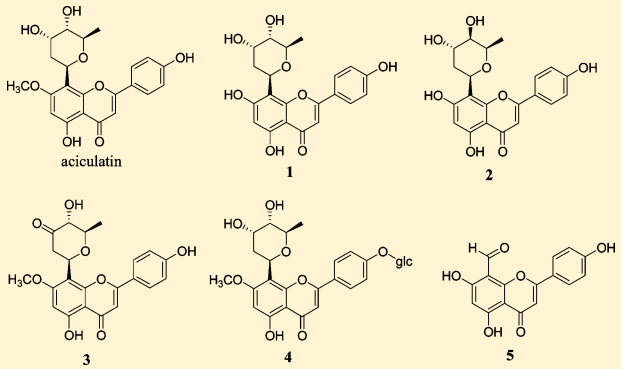
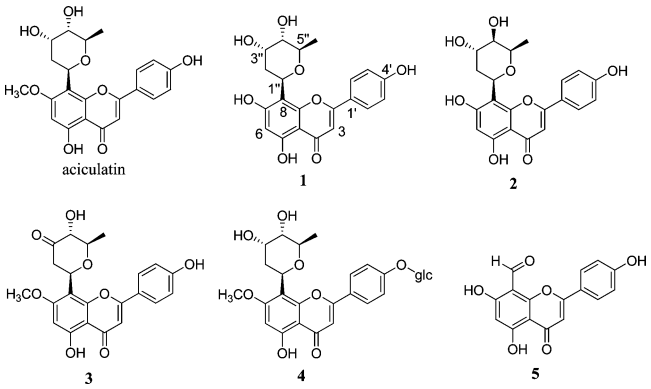
Supporting Information

ABSTRACT: Four new apigenin derivatives, 7-de-*O*-methylaciculatin (**1**), 8-*C*-*β*-D-boivinopyranosylapigenin (**2**), aciculatinone (**3**), and 4′-*O*-glucosylaciculatin (**4**), along with eight known compounds, apigenin-8-carbaldehyde (**5**), kaempferol, tricin, taxifolin, 6,7,4′-trihydroxyflavone, *trans*-oxyresveratrol, aciculatin, and luteolin-7-sulfate, were isolated from an ethanolic extract of *Chrysopogon aciculatis*. Their chemical structures were elucidated by spectroscopic methods. Among the known compounds, the natural occurrence of apigenin-8-carbaldehyde and luteolin-7-sulfate is demonstrated for the first time. Some of the isolates were evaluated for cytotoxic activity against human cancer cell lines including MCF-7, H460, HT-29, and CEM.



The whole grass of *Chrysopogon aciculatis* (Poaceae) has been used as pasturage in Taiwan. A DNA binding agent, aciculatin, was isolated from this plant in the previous study.[1] Recently, as part of our program on the discovery of potential cytotoxic principles from natural sources,[2−6] the EtOH extract of *C. aciculatis* was partitioned with H_2O and EtOAc, and the latter extract was found to show potent cytotoxicity against human tumor cells. Further investigation of *C. aciculatis* led to the isolation and characterization of four new apigenin derivatives (**1**−**4**) and eight known compounds. The structures of the known compounds were elucidated on the basis of spectroscopic methods or identified by comparison of their ^1H and ^{13}C NMR data with literature data. Some of the isolates were evaluated for their cytotoxic activities against human cancer cell lines including MCF-7, H460, HT-29, and CEM.



RESULTS AND DISCUSSION

The ethanolic extract of the whole grass *C. aciculatis* was successively partitioned between H_2O and EtOAc and then *n*-BuOH. The EtOAc-soluble material was sequentially chromatographed on silica gel, Sephadex LH-20, and C_{18}-OPN columns to give three new flavones, 7-de-*O*-methylaciculatin (**1**), 8-*C*-*β*-D-boivinopyranosylapigenin (**2**), and aciculatinone (**3**), and six known compounds, kaempferol,[7] tricin,[8] taxifolin,[9] 6,7,4′-trihydroxyflavone,[10] *trans*-oxyresveratrol,[11] and aciculatin.[1] The *n*-BuOH-soluble material was repeatedly separated on silica gel, Sephadex LH-20, and C_{18}-OPN columns to afford the new flavone 4′-*O*-glucosylaciculatin (**4**) and two known flavones, apigenin-8-carbaldehyde (**5**)[12] and luteolin-7-sulfate.[13] Luteolin-7-sulfate was previously synthesized by sulfation of luteolin[13] and was isolated from a natural source for the first time.

Compound **1** was obtained as a light yellow powder, and its molecular formula was deduced as $C_{21}H_{20}O_8$ from its HREIMS and NMR data. The IR spectrum of **1** showed the presence of hydroxy (3500 cm^{-1}) and carbonyl (1659 cm^{-1}) groups. Its ^1H and ^{13}C NMR spectra were similar to those of aciculatin,[1] an apigenin *C*-glycoside, except for the absence of one methoxy group (Table 1). The analysis of the aromatic regions in the ^1H and ^{13}C NMR spectra suggested compound **1** was a monosubstituted apigenin. The presence of a *β*-*C*-digitoxosyl

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds from *Chrysopogon aciculatis*[a]

	1[b]		2[b]		3[b]		4[c]		5[c]	
position	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
2		164.7		164.7		165.5		162.5		164.1
3	6.67 s	103.7	6.66 s	103.8	6.69 s	103.9	6.95 s	103.5	7.01 s	103.5
4		183.2		183.2		183.5		182.4		181.5
5		162.0		162.0		163.6		161.0		166.7
6	6.17 s	100.4	6.17 s	100.5	6.48 s	95.9	6.53 s	95.3	6.26 s	98.8
7		163.3		163.7		163.3		162.1		168.5
8		105.4		106.4		106.7		107.7		104.1
9		154.3		153.8		156.1		154.9		157.9
10		105.3		105.0		105.8		104.6		103.6
1′		123.0		123.2		123.4		124.3		120.7
2′, 6′	8.07 d (9.0)	129.5	8.02 d (9.0)	129.4	8.08 d (8.4)	129.6	8.16 d (8.4)	128.5	8.10 d (8.4)	129.0
3′, 5′	7.01 d (9.0)	116.9	7.00 d (9.0)	116.9	7.06 d (8.4)	116.9	7.19 d (8.4)	116.5	6.94 d (8.4)	116.0
4′		162.1		162.1		162.1		160.5		161.6
5-OH	12.95 s		12.94 s		13.41 s		13.24 s		14.01 br s	
7-OCH_3					3.97 s	57.0	3.89 s	56.6		
1″	5.77 dd (2.4, 11.4)	70.3	5.77 dd (2.4, 12.0)	70.3	5.40 dd (3.0, 12.0)	72.2	5.44 dd (2.0, 12.0)	64.9	10.38 s	188.3
2″	2.11 ddd (2.4, 11.4, 14.4)	38.9	1.84 td (2.4, 14.4)	33.9	2.51 dd (3.0, 13.8)	45.6	1.63 dd (2.4, 14.4)	36.6		
	2.20 ddd (2.4, 3.6, 14.4)		2.33 ddd (2.4, 12.0, 14.4)		3.55 dd (12.0, 13.8)		2.35 dt (2.4, 13.8)			
3″	4.18 br q (3.0)	68.0	4.12 br q (3.0)	68.2		207.0	3.95 br s	66.8		
4″	3.49 dd (3.0, 9.6)	73.6	3.52 d (3.6)	70.4	4.09 d (9.6)	79.9	3.24−3.34 m	73.2		
5″	4.01 dq (6.6, 9.6)	74.8	4.29 br q (6.6)	72.9	3.60 qd (6.0, 9.6)	80.3	3.75 qd (6.0, 9.6)	72.3		
6″	1.38 d (6.6)	18.7	1.31 d (6.6)	17.3	1.48 d (6.0)	19.7	1.20 d (6.0)	18.6		
1‴							5.05 d (7.8)	99.9		
2‴							3.24−3.34 m	76.5		
3‴							3.18 t (10.5)	69.6		
4‴							3.24−3.34 m	73.1		
5‴							3.40 m	77.1		
6‴							3.47 m	60.6		
							3.68 dd (1.8, 11.4)			

[a]Measured at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR. [b]Measured in acetone-d_6. [c]Measured in DMSO-d_6.

moiety was deduced by ^{1}H and ^{13}C NMR and NOE experiments. In the HMBC spectrum, cross-peaks of 5-OH/C5, C-6, C-10; H-6/C-5, C-7, C-8, C-10; and H-1″/C-7, C-8 indicated that the sugar moiety was attached to C-8 via a C−C linkage. A similar apigenin *C*-glycoside, torosaflavone A, has been isolated from *Drymaria diandra*[14,15] and *Cassia torosa*;[16] however, its sugar moiety was linked to C-6 instead of C-8. On the basis of the above NMR analysis, the structure of compound **1** was determined as 8-*C*-*β*-D-digitoxopyranosylapigenin and was named 7-de-*O*-methylaciculatin.

Compound **2** was obtained as light yellow prisms and gave the same molecular formula as **1** according to HREIMS. Its ^{1}H and ^{13}C NMR spectra were similar to those of **1** except for the signals arising from the 2,6-dideoxyhexosyl moiety. In the ^{1}H NMR spectrum, the anomeric proton H-1″ of the 2,6-dideoxyhexosyl moiety showed a signal at δ 5.77 (dd, J = 2.4, 12.0 Hz), in which the large coupling constant indicated the axial orientation of H-1″ and *β*-linkage of the sugar moiety to the flavone. Furthermore, the coupling pattern of H-3″ (br q, J = 3.0 Hz) suggested the equatorial orientation of H-3″. The relative configuration of the 2,6-deoxyhexopyranose moiety was determined by NOE experiments. The enhancement of H-1″ by irradiation of H-5″ indicated that H-5″ was in an axial position. The signals of H-3″, H-5″, and H-6″ were enhanced by irradiation of H-4″, which suggested that H-4″ was in an equatorial position. Thus, the 2,6-dideoxyhexosyl moiety was deduced to be boivinopyranose. Its linkage to C-8 was confirmed by the HMBC correlations of H-1″/C-7, C-8; 5-OH/C-5, C-6, C-10; and H-6/C-5, C-7, C-8, C-10. On the basis of the above evidence, the structure of compound **2** was assigned as 8-*C*-*β*-D-boivinopyranosylapigenin.

The molecular formula of **3** was deduced as $C_{22}H_{20}O_8$ by HREIMS. Its ^{1}H and ^{13}C NMR spectra showed a monosubstituted apigenin moiety like aciculatin and a sugar moiety that possessed a carbonyl carbon (δ_C 207.0). In the HMBC spectrum, the cross-peaks of 5-OH/C-5, C-6, C-10; H-6/C-5, C-7, C-8, C-10; and 7-OCH_3/C-7 revealed that the methoxy group was attached to C-7. Furthermore, the HMBC correlations of H-1″ (δ 5.40) to C-7, C-8, and C-9 indicated that the sugar moiety was attached to C-8 with a C−C linkage. The carbonyl signal at δ 207.0 exhibited HMBC correlations with H-2″, H-4″, and H-5″, suggesting the position of the carbonyl group at C-3″. Moreover, the coupling constant (J = 9.6 Hz) of H-4″ and H-5″ indicated that these two protons had *trans*-diaxial orientations. Thus, the structure was established as **3** and was named aciculatinone.

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Compound **4** had the molecular formula $C_{28}H_{33}O_{13}$ as determined from its HRFABMS. Its ^{1}H and ^{13}C NMR spectra exhibited the typical resonances of a substituted apigenin moiety. The ^{13}C NMR spectrum showed signals similar to those of aciculatin except for six more signals, at δ 60.6, 69.6, 73.1, 76.5, 77.1, and 99.9, attributed to a glucose moiety. In the ^{1}H NMR spectrum, two anomeric protons appeared at δ_H 5.05 (1H, d, J = 7.8 Hz, H-1‴) and 5.44 (1H, dd, J = 2.0, 12.0 Hz, H-1″), which correlated, respectively, with carbons resonating at δ_C 99.9 (C-1‴) and 64.9 (C-1″) in the HMQC spectrum. The coupling constants of the anomeric protons indicated that each sugar moiety was connected to the flavone via a β-linkage. Enzymatic hydrolysis of **4** with β-glucosidase gave aciculatin and glucose, suggesting that glucose was attached to the flavone through a C−O bond. A positive optical rotation for the isolated glucose indicated that it was β-D-glucose. In the HMBC spectrum, the cross-peaks of 5-OH/C-5, C-6, C-10; H-6/C-5, C-7, C-8, C-10; and H-1″/C-7, C-8, C-9 revealed that the digitoxosyl moiety was attached to C-8 through a C−C linkage. On irradiation at δ_H 5.05 (H-1‴), an NOE enhancement was observed for the signal at δ_H 7.19 (H-3′ and H-5′), indicating that the β-*O*-D-glucosyl moiety was linked to C-4′ via an ether linkage. This linkage was further confirmed by the HMBC correlation of H-1‴ to C-4′. Thus, compound **4** was elucidated to be 8-*C*-β-D-digitoxopyranosyl-4′-*O*-β-D-glucopyranosylapigenin.

Compound **5** was obtained as light yellow prisms and gave the molecular formula $C_{16}H_{10}O_6$ according to HREIMS. The ^{1}H and ^{13}C NMR spectra showed a monosubstituted apigenin moiety and a formyl group (δ_H 10.38 and δ_C 188.3). The HMBC cross-peaks of H-1″/C-7, C-9 and H-6/C-5, C-7, C-8, C-10 indicated that the formyl group was attached to C-8. Thus, compound **5** was identified as apigenin-8-carbaldehyde, which was previously obtained by oxidation of vitexin with sodium periodate[12] and here isolated from nature for the first time.

Some of the isolates were evaluated for cytotoxic activity against human cancer cell lines (Table 2). Aciculatin, **1**, **2**, and **3** showed differential potency on different cancer cell lines. Noticeably, aciculatin and **1** indicated specificity of cytotoxicity on MCF-7 and CEM cell lines.

Table 2. Cytotoxicity of Isolated Compounds against Four Human Cell Lines

	cell line (IC_{50} values in μM)			
compound	MCF-7[a]	H460[b]	HT-29[c]	CEM[d]
aciculatin	3.16	46.94	25.98	2.65
1	6.35	18.25	25.29	4.42
2	74.98	11.96	10.00	2.58
3	18.36	18.06	11.59	13.33
4	>100	>100	>100	>100
doxorubicin	2.50	6.06	6.04	3.14

[a]MCF-7: human breast cancer cells. [b]H460: human lung cancer cells. [c]HT-29: human colon cancer cells. [d]CEM: human leukemia cells.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined on a Yanaco MP-I3 micro melting point apparatus and are uncorrected. Optical rotations were recorded with a JASCO DIP-370 digital polarimeter. UV spectra were measured on a Hitachi U-3310 spectrophotometer. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H, ^{13}C, and 2D NMR spectra were recorded on a Varian VNMRS 600 MHz spectrometer. EIMS and HRMS were obtained on Finnigan MAT GCQ and JEOL JMS-700 spectrometers, respectively. Silica gel 60 (Merck, 230−400 mesh), Sephadex LH-20 (Amersham Biosciences, Sweden), and Cosmosil C_{18}-OPN (Nacalai Tesque, Kyoto Japan) were used for purification. β-Glucosidase from almond (Nacalai Tesque, Kyoto Japan) was used for the hydrolysis of compound **4**.

Plant Material. The whole grass *C. aciculatis* was collected in Taipei, Taiwan, in August 2006, and was authenticated by Professor Ching-Hsiang Hsieh, Department of Plant Industry, National Pingtung University of Science and Technology (NPUST). A voucher specimen (No.70652) was deposited in PPI Herbarium of NPUST.

Extraction and Isolation. The whole herb *C. aciculatis* (5.5 kg) was heated under reflux with 95% EtOH (40 L) for one hour. After filtration, the EtOH solution was concentrated *in vacuo* to provide a dark brown EtOH extract (462 g). The EtOH extract was partitioned with H_2O/EtOAc (1:1) to give EtOAc and H_2O layers. The EtOAc layer was concentrated to afford an EtOAc extract (80.8 g). The H_2O layer was further partitioned with *n*-BuOH to give *n*-BuOH and H_2O layers. The *n*-BuOH layer was concentrated to yield an *n*-BuOH extract (48.4 g). The EtOAc extract was chromatographed on a silica gel column (11 × 60 cm) eluted with a stepwise gradient system of *n*-hexane/EtOAc (15:1; 10:1; 5:1; 1:1; 1:2; 0:1) to give six fractions (I−VI). Fraction IV (eluted with *n*-hexane/EtOAc, 1:1) was rechromatographed on a Sephadex LH-20 column eluted with MeOH to afford kaempferol (2.6 mg). Fraction V (eluted with *n*-hexane/EtOAc, 1:2) was subjected to a Sephadex LH-20 column eluted with MeOH to provide three subfractions (Va−Vc). Fraction Va was chromatographed on silica gel with $CHCl_3$/MeOH (20:1) as the eluent and Sephadex LH-20 with MeOH to give **3** (18.2 mg). Fraction Vb was subjected to Sephadex LH-20 and silica gel columns eluted with MeOH and $CHCl_3$/MeOH (10:1), respectively, to afford tricin (2.8 mg) and taxifolin (8.1 mg). Fraction Vc was purified by a Sephadex LH-20 column eluted with MeOH and a silica gel column eluted with $CHCl_3$/MeOH (7:1) to yield 6,7,4′-trihydroxyflavone (1.3 mg) and *trans*-oxyresveratrol (3.8 mg). Fraction VI (eluted with EtOAc) was further separated on a Sephadex LH-20 column eluted with MeOH to afford aciculatin (652.0 mg) and a subfraction, VIa. Fraction VIa was subjected to a silica gel column eluted with $CHCl_3$/MeOH (10:1) and a C_{18}-OPN column eluted with H_2O/MeOH (7:3) to give **1** (67.8 mg) and **2** (44.9 mg). The *n*-BuOH extract was separated with a Sephadex LH-20 column eluted with MeOH to give five fractions (VII−XI). Fraction VIII was chromatographed on a C_{18}-OPN column eluted with H_2O/MeOH (7:3) to afford **4** (1.72 g) and **5** (2.5 mg). Luteolin-7-sulfate (9.0 mg) was obtained from fraction XI through a Sephadex LH-20 column eluted with MeOH.

7-De-O-methylaciculatin (8-*C*-β-D-digitoxopyranosylapigenin, 1): light yellow powder, mp 188−190 °C (3:1 CH_3OH/H_2O); $[\alpha]_D$ +79 (*c* 0.54, MeOH); UV (MeOH) λ_{max} (log ε) 331 (4.31), 271 (4.31), 213 (4.55) nm; IR (KBr) ν_{max} 3500, 1659, 1611, 1576, 1544, 1449, 1354, 1243, 1176 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 400 $[M]^+$ (14), 382 (21), 307 (87), 284 (31), 270 (100), 256 (60), 189 (36); HREIMS *m*/*z* $[M]^+$ 400.1161 (calcd for $C_{21}H_{20}O_8$, 400.1164).

8-*C*-β-D-Boivinopyranosylapigenin (2): light yellow prisms, mp 205−207 °C (3:1 CH_3OH/H_2O); $[\alpha]_D$ +85 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 333 (4.31), 271 (4.29), 212 (4.54) nm; IR (KBr) ν_{max} 3400, 1659, 1611, 1580, 1544, 1449, 1354, 1239, 1176 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 400 $[M]^+$ (5), 382 (15), 307 (100), 284 (36), 270 (85), 256 (39), 189 (50); HREIMS *m*/*z* $[M]^+$ 400.1165 (calcd for $C_{21}H_{20}O_8$, 400.1172).

Aciculatinone (3): light yellow prisms, mp 146−148 °C (3:1 CH_3OH/H_2O); $[\alpha]_D$ +62 (*c* 0.27, MeOH); UV (MeOH) λ_{max} (log ε) 335 (4.31), 268 (4.15), 214 (4.36) nm; IR (KBr) ν_{max} 3500, 1718, 1651, 1603, 1500, 1455, 1362, 1243, 1180 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 412 $[M]^+$ (42), 367 (15), 325 (23), 296 (42), 295 (45), 117 (90), 58 (100); HREIMS *m*/*z* $[M]^+$ 412.1152 (calcd for $C_{22}H_{20}O_8$, 412.1146).

4′-*O*-Glucosylaciculatin (4): light yellow prisms, mp 173−175 °C (2:1 CH_3OH/H_2O); $[\alpha]_D$ −10 (*c* 0.20, MeOH); UV (MeOH) λ_{max} (log ε) 315 (4.21), 271 (4.29), 214 (4.48) nm; IR (KBr) ν_{max} 3500, 1659, 1603, 1497, 1437, 1378, 1239, 1073 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; FABMS *m*/*z* 577 $[M + H]^+$ (10), 460 (10), 338 (21), 307 (60), 289 (40), 154 (100); HRFABMS *m*/*z* $[M + H]^+$ 577.1937 (calcd for $C_{28}H_{33}O_{13}$, 577.1938).

Apigenin-8-carbaldehyde (5): light brown prisms, mp 273−275 °C (2:1 CH_3OH/H_2O); UV (MeOH) λ_{max} (log ε) 333 (3.96), 251 (4.00), 231 (4.00) nm; IR (KBr) ν_{max} 3450, 1667, 1611, 1564, 1508, 1441, 1374, 1287, 1243, 1180 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; EIMS *m*/*z* 298 $[M]^+$ (100), 270 (6), 178 (23), 118 (19); HREIMS *m*/*z* $[M]^+$ 298.0471 (calcd for $C_{16}H_{10}O_6$, 298.0477).

Enzymatic Hydrolysis of 4. Compound **4** (20 mg) and β-glucosidase (10 mg) were dissolved in H_2O (15 mL), and the solution was allowed to stand at 37 °C for 24 h. After addition of H_2O (10 mL), the reaction mixture was extracted with EtOAc. The EtOAc extract was concentrated *in vacuo* to give aciculatin (10 mg), which showed NMR spectral data identical with those of the authentic sample. The aqueous layer was concentrated and then chromatographed on a silica gel column eluted with CH_3CN/H_2O (8:1) to afford D-glucose (4 mg), which showed a specific rotation of +21.1 (*c* 0.54, H_2O). Its NMR data were essentially identical with those reported in the literature,[17] and the retention factor (R_f = 0.24) in TLC was the same as that of the authentic sugar with CH_3CN/H_2O (6:1) as the solvent system.

Cytotoxic Assay. Four human cancer cell lines, MCF-7 (breast cancer), H-460 (lung cancer), HT-29 (colon cancer), and CEM (leukemia), were obtained from the Bioresources Collection and Research Center (BCRC), Hsin-Chu, Taiwan. Some of the isolates were evaluated for cytotoxic activity using a previously described protocol.[18] Doxorubicin was used as a positive control.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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