

1-1-2004

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SARACOĞLU, İCLAL; HARPUT, Ü. ŞEBNEM; and OGIHARA, YUKIO (2004) "Acylated Flavone Glycosides from *Veronica pectinata* var. *glandulosa* and *V. persica*," *Turkish Journal of Chemistry*. Vol. 28: No. 6, Article 10. Available at: <https://journals.tubitak.gov.tr/chem/vol28/iss6/10>

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Acylated Flavone Glycosides from *Veronica pectinata* var. *glandulosa* and *V. persica*

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Received 08.04.2004

This study deals with the isolation of a new acylated 5,6,7,3',4'-pentahydroxy-flavone glycoside (**1**) and 3 known allose-containing acylated flavone glycosides (**2-4**) as well as a known flavone aglycone (**5**) from the aerial parts of *Veronica pectinata* var. *glandulosa* and *V. persica*. The structures of the isolated compounds were determined to be 3'-hydroxy-4'-O-methylscutellarein-7-O-[2''-O- α -L-rhamnopyranosyl-3''-O-(6''''-O-acetyl- β -D-glucopyranosyl)]- β -D-glucopyranoside, named sarachoside (**1**), 4'-O-methylisoscuteallarein-7-O-2''-O-(6'''-O-acetyl- β -D-allopyranosyl)- β -D-glucopyranoside (**2**), isoscuteallarein-7-O-2''-O-(6'''-O-acetyl- β -D-allopyranosyl)- β -D-glucopyranoside (**3**), 3'-hydroxy-4'-O-methylisoscuteallarein-7-O-2''-O-(6'''-O-acetyl- β -D-allopyranosyl)- β -D-glucopyranoside (**4**) and 5,4'-dihydroxy-6,7,3'-trimethoxyflavone, named circilineol (**5**) by extensive 1-D and 2D-NMR spectroscopy. Sarachoside (**1**) exhibited potent radical scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical.

Key Words: *Veronica* species, Scrophulariaceae, acylated flavone glycosides, sarachoside, free radical scavenging activity, DPPH.

Introduction

In the flora of Turkey, the genus *Veronica* L. (Scrophulariaceae) is represented by 79 species, 26 of which are endemic¹. *Veronica* species are used as a diuretic, for wound healing and against rheumatic pain in Turkish folk medicine^{2,3}. Earlier investigations performed on *Veronica* species resulted in the isolation of mainly iridoid glucosides, especially benzoic and cinnamic acid esters of catalpol, and some phenylethanoid and flavonoid glycosides⁴⁻⁷. Previously, a large variety of flavone aglycones, such as luteolin, apigenin, chrysoeriol, scutellarein (6-hydroxyluteolin) and isoscuteallarein (8-hydroxyluteolin), were reported from

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Veronica species. Glycosidation of these aglycones was usually observed at the 7th or 5th position and the acylation of the sugars is another characteristic feature of some glycosides^{8–11}.

Our previous research on *Veronica* species showed that the water-soluble portions of the MeOH extracts suppress nitric oxide (NO) production in lipopolysaccharide-stimulated mouse peritoneal macrophages, while the chloroform-soluble portions of their MeOH extracts are cytotoxic against KB and B16 cells in microculture tetrazolium (MTT) assay¹². The present study describes the isolation and structure determination of 1 new and 3 known acylated flavone-7-*O*-glycosides (**1–4**) from the water-soluble portions, as well as a flavone aglycone (**5**) from the chloroform-soluble portion of the MeOH extracts of *Veronica pectinata* L. var. *glandulosa* Riek ex M.A. Fischer and *V. persica* L. (Scrophulariaceae). In addition, the free radical scavenging effect of compound **1** was assessed by the discoloration of methanol solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) spectroscopically.

Experimental

General Procedures: Optical rotations were measured on a JASCO DIP 140 digital spectrometer using a sodium lamp operating at 589 nm. The UV spectra (λ_{max}) were recorded on a Shimadzu UV-240 spectrometer. NMR measurements were performed on a JEOL JNM-A 500 spectrometer in methanol-*d*₄ and DMSO-*d*₆ with tetramethylsilane (TMS) as an internal standard. FAB-MS and HR-FAB-MS were recorded in an NBA matrix in the positive ion mode on a JEOL JMS-DX300 spectrometer. TLC plates using silica gel 60 F₂₅₄ and RP-18 F₂₅₄ were obtained from Merck (Darmstadt, Germany). Medium pressure liquid chromatography (MPLC) was performed on a lobar glass column packed with reversed-phase material (Merck, Lichroprep RP-18, 40–63 μ m). Polyamide C-200 was purchased from Wako (Osaka, Japan). DPPH was obtained from Aldrich Co. (Milwaukee, WI, USA). 3-*tert*-Butyl-4-hydroxyanisole (BHA) and *dl*- α -tocopherol were purchased from Nacalai Tesuque Co. (Kyoto, Japan).

Plant Material: *Veronica pectinata* L. var. *glandulosa* Riek ex M.A.Fischer and *V. persica* L. were collected in different provinces in Turkey. The identity of the plants was confirmed by Prof. Dr. Z. Aytaç (Faculty of Sciences, Gazi University, Ankara, Turkey). Voucher specimens are deposited in the Herbarium of the Faculty of Pharmacy, Hacettepe University (HUEF 99014 and 99015).

Extraction and Isolation: Air-dried aerial parts of *V. pectinata* var. *glandulosa* (80 g) and *V. persica* (220 g) were extracted with MeOH at 40 °C for 12 h (x 2, 2 L), separately. The extracts were evaporated under vacuum to give 13 g and 35 g of crude extracts, respectively. The MeOH extracts were dissolved in H₂O and H₂O-insoluble materials were removed by filtration. The filtrates were fractionated with CHCl₃ (x 4, 100 mL), and the water fractions were lyophilized to yield 10 g and 18 g dry weight. The water fractions of both plants were subjected to polyamide column chromatography separately, and eluted with H₂O, followed by increasing concentrations of MeOH to give 6 fractions: A₁-F₁ (Fr. A₁, 4.9 g; Fr. B₁, 0.45 g; Fr. C₁, 0.28 g; Fr. D₁, 0.27 g; Fr. E₁, 0.41 g; Fr. F₁, 0.65 g) for *V. pectinata* var. *glandulosa*, and A₂-F₂ (Fr. A₂, 12.2 g; Fr. B₂, 0.85 g; Fr. C₂, 2.23 g; Fr. D₂ 0.15 g; Fr. E₂, 0.59 g; Fr. F₂ 0.85 g) for *V. persica*. Fr. F₁ (45 mg) was chromatographed by medium pressure liquid chromatography (MPLC), eluting with increasing concentrations of MeOH (30→60%) to yield compound **1** (10 mg). Fr. F₂ (200 mg) was subjected to silica gel column chromatography, eluting with CHCl₃-MeOH-H₂O (95:5:0.5→80:20:2) and compounds **2** (15 mg), **3** (20 mg) and **4** (5 mg) were isolated. Frs. D₁, E₁, D₂, E₂, rich in phenylethanoid

glycosides, and Frs. A₁-C₁, A₂-C₂, rich in iridoid glucosides, were studied previously and 8 phenylethanoid glycosides, 4 of which were new^{6,7}, and 11 iridoid glucosides, 2 of which were new^{5,13}, were isolated. On the other hand, isolation studies were also performed on the CHCl₃ fraction (9 g) of *V. persica*. To remove chlorophylls and pigments, the CHCl₃ fraction was fractionated with hexane and MeOH. After repeated silica gel column chromatographies of the MeOH fraction, compound **5** (2 mg) was isolated.

DPPH Free Radical Scavenging Activity: MeOH solution (100 μL) of compound **1** at various concentrations was added to 1.5 x 10⁻⁵ M DPPH/MeOH solution. The reaction mixture was shaken vigorously and the absorbance of the remaining DPPH was measured at 520 nm after 30 min. The radical scavenging activity was determined by subtracting the absorbance from that of blank (100%) containing only DPPH and solvent. BHA and *dl*-α-tocopherol were used as standards and samples were prepared using the same dilution procedures^{6,14}.

Sarachoside (1): Pale yellow, amorphous powder. $[\alpha]_D^{15}$ - 46.9°, *c* = 0.10; MeOH-H₂O (1:1); HR-FAB-MS: *m/z* 829.1515 [M+1]⁺ (calcd. for C₃₆H₄₄O₂₂: 829.1533); UV λ_{max} (MeOH) nm: 378, 344, 300, 210; ¹H and ¹³C NMR (Table 1).

4'-O-Methylisoscuteallarein-7-O-2''-O-(6'''-O-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside (2): Pale yellow, amorphous powder. UV λ_{max} (MeOH) nm: 276, 303, 325 (sh); ¹H NMR data were identical to those reported in the literature^{4,11,15}. ¹³C NMR (CD₃OD, 125 MHz): Aglycone; δ 166.35 (C-2), 104.36 (C-3), 184.57 (C-4), 154.18 (C-5), 101.85 (C-6), 152.14 (C-7), 129.71 (C-8), 145.42 (C-9), 107.80 (C-10), 124.59 (C-1'), 129.70 (C-2'/6'), 115.69 (C-3'/5'), 164.66 (C-4'), Glucose; δ 102.97 (C-1''), 84.10 (C-2''), 77.61 (C-3''), 70.85 (C-4''), 78.55 (C-5''), 62.34 (C-6''), Allose; 104.36 (C-1'''), 73.15 (C-2'''), 72.64 (C-3'''), 68.56 (C-4'''), 73.46 (C-5'''), 65.10 (C-6'''), 173.08 (C=OCH₃), 20.86 (COCH₃), 56.15 (OCH₃).

Isoscuteallarein-7-O-2''-O-(6'''-O-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside (2): Pale yellow, amorphous powder. UV λ_{max} (MeOH) nm: 276, 305, 325 (sh); ¹H NMR data were identical to those reported in the literature^{4,11,15}. ¹³C NMR (CD₃OD, 125 MHz): Aglycone; δ 162.96 (C-2), 103.76 (C-3), 184.52 (C-4), 152.00 (C-5), 101.78 (C-6), 154.09 (C-7), 129.82 (C-8), 145.35 (C-9), 107.75 (C-10), 123.21 (C-1'), 129.76 (C-2'/6'), 117.04 (C-3'/5'), 166.71 (C-4'), Glucose; δ 102.94 (C-1''), 83.98 (C-2''), 78.48 (C-3''), 70.80 (C-4''), 77.56 (C-5''), 62.28 (C-6''), Allose; 104.20 (C-1'''), 73.08 (C-2'''), 72.59 (C-3'''), 68.49 (C-4'''), 73.41 (C-5'''), 65.01 (C-6'''), 172.98 (C=OCH₃), 20.81 (COCH₃).

3'-Hydroxy-4'-O-methylisoscuteallarein-7-O-2''-O-(6'''-O-acetyl-β-D-allopyranosyl)-β-D-glucopyranoside (4): Pale yellow, amorphous powder. UV λ_{max} (MeOH) nm: 275, 300, 325 (sh); ¹H NMR data were identical to those reported in the literature^{4,11,15}. ¹³C NMR (CD₃OD, 125 MHz): Aglycone; δ 166.39 (C-2), 104.43 (C-3), 184.51 (C-4), 154.12 (C-5), 101.81 (C-6), 152.07 (C-7), 129.82 (C-8), 145.38 (C-9), 107.81 (C-10), 124.96 (C-1'), 114.18 (C-2'), 148.22 (C-3'), 152.87 (C-4'), 112.71 (C-5'), 120.52 (C-6'), Glucose; δ 102.97 (C-1''), 83.81 (C-2''), 78.51 (C-3''), 70.85 (C-4''), 77.58 (C-5''), 62.33 (C-6''), Allose; 104.15 (C-1'''), 73.10 (C-2'''), 72.64 (C-3'''), 68.51 (C-4'''), 73.42 (C-5'''), 65.05 (C-6'''), 173.31 (C=OCH₃), 20.90 (COCH₃), 56.55 (OCH₃).

Circilineol (5): Pale yellow, amorphous powder. UV, ¹H and ¹³C NMR data were identical to those reported in the literature¹⁶.

Table 1. ^{13}C and ^1H NMR spectral data for compound **1*** (in $\text{DMSO-}d_6$; ^{13}C : 125 MHz; ^1H : 500 MHz).

C/H	DEPT	δ_C (ppm)	δ_H (ppm)	J (Hz)
Aglycone				
2	C	163.84		
3	CH	102.89	6.79 s	
4	C	182.12		
5	C	146.78		
6	C	130.75		
7	C	150.87		
8	CH	93.70	6.98 s	
9	C	148.89		
10	C	105.58		
1'	C	123.01		
2'	CH	112.86	7.44 d	(2.3)
3'	C	146.78		
4'	C	151.10		
5'	CH	112.01	7.12 d	(8.7)
6'	CH	118.60	7.55 dd	(8.7/2.3)
Glucose-1				
1''	CH	97.27	5.49 d	(7.3)
2''	CH	76.53	3.81 d	(9.4)
3''	CH	86.63	3.73 t	(9.4)
4''	CH	68.14	3.44 [†]	
5''	CH	76.85	3.25 t	(9.8)
6''	CH ₂	60.89	3.44 dd	(12.0/6.0)
			3.78 dd	(12.0/2.0)
Rhamnose				
1'''	CH	101.03	5.21 d	(1.5)
2'''	CH	70.20	3.85 [†]	
3'''	CH	70.20	3.37 m	
4'''	CH	71.97	3.18 t	(9.8)
5'''	CH	68.89	3.64 dd	(9.5/6.1)
6'''	CH ₃	17.78	1.04 d	(6.1)
Glucose-2				
1''''	CH	103.01	4.42 d	(7.6)
2''''	CH	73.33	3.13 t	(9.8)
3''''	CH	76.53	3.22 t	(9.2)
4''''	CH	69.93	3.13 t	(9.8)
5''''	CH	72.91	3.85 [†]	
6''''	CH ₂	62.89	4.10 dd	(11.9/6.7)
			4.32 brd	(9.8)
OCH ₃	CH ₃	55.71	3.88 s	
OCOCH ₃	CH ₃	20.38	1.94 s	
OCOCH ₃	C	170.04		

*The ^{13}C and ^1H assignments were based on 2D NMR (DQF-COSY, HMQC and HMBC) experiments.

[†]Signal patterns are unclear due to overlapping.

Results and Discussion

The methanol extracts of the aerial parts of *V. pectinata* var. *glandulosa* and *V. persica* were suspended in water and partitioned with chloroform. The water fractions of the extracts were subjected to polyamide column chromatography to afford 6 main fractions. Repeated column chromatographies of the flavonoid fractions, eluted with methanol from the polyamide columns, resulted in the isolation of 4 compounds (**1-4**) in pure form. Compound **1** was isolated as a pale yellow, amorphous powder, with negative optical rotation $[\alpha]_D^{15} - 46.9^\circ$, $c=0.10$; MeOH-H₂O (1:1)] from *V. pectinata* var. *glandulosa*. It was the main component of the flavonoid fraction of the polyamide column and no other flavonoids were detected by TLC in this plant. Its UV spectrum showed λ_{max} at 378, 344, 300 and 210 nm, indicating its polyphenolic nature. The HR-FAB-MS of **1** exhibited a pseudomolecular ion $[M+1]^+$ at m/z 829.1515 compatible with the molecular formula C₃₆H₄₄O₂₂ (calcd. for C₃₆H₄₄O₂₂: 829.1533). This was in good agreement with the presence of 3 methyl, 2 methylene, 20 methine and 11 quaternary carbon resonances in its ¹³C NMR and DEPT spectra (Table 1). Its ¹H NMR spectrum displayed 5 aromatic protons δ 7.12 (d, J=8.7 Hz), 7.44 (d, J=2.3 Hz), 7.55 (dd, J=8.7/2.3 Hz), 6.79 (s) and 6.98 (s), which constitute the presence of 1 ABX system and 2 non-correlated aromatic protons, respectively. This suggested that **1** might be a 5,6,7,3',4' or 5,7,8,3',4' penta-substituted flavone derivative. Since the signal at δ 102.89 was assigned to the C-3 position in the flavone aglycone according to its ³J_{HC} and ²J_{HC} correlations in the HMBC spectrum and the published data for flavone glycosides, the signal at δ 93.70 was attributed to the A-ring. The difference between the 5,6,7 (scutellarein-type) and 5,7,8 (isoscutellarein-type) trioxygenation patterns on the basis of A-ring methine resonance has been previously reported^{4,17}. According to this finding, the presence of an aromatic methine carbon signal (δ 93.70) in the range 90.0-96.0 ppm indicates a non-substituted C-8. These data showed that **1** was not an isoscutellarein but a scutellarein derivative flavone glycoside. Furthermore, the correlation observed between the methoxy proton signal (δ 3.88 s) and C-4' of the benzoyl group (δ 151.10) in the HMBC spectrum led us to determine aglycone moiety as 3'-hydroxy-4'-O-methylscutellarein (Figure 1).

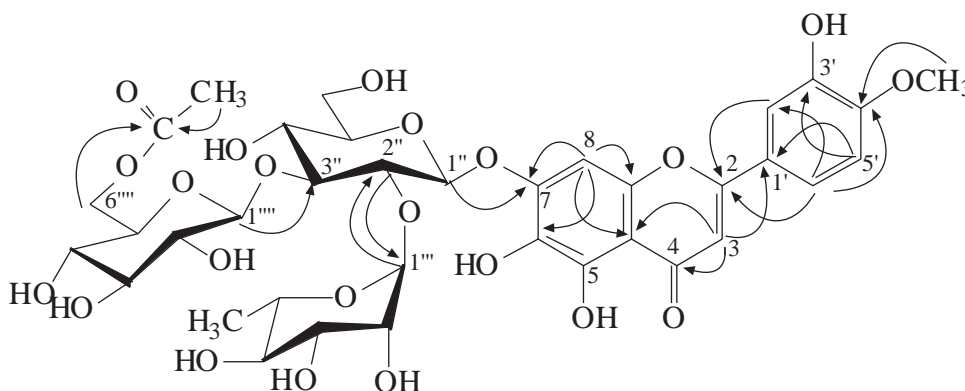


Figure 1. Significant HMBC correlations for compound **1**. Arrows point from H to C.

On the other hand, the presence of 3 proton signals represented by 3 doublets at δ 4.42 (J=7.6 Hz), 5.21 (J=1.5 Hz) and 5.49 (J=7.3 Hz), characteristic for the anomeric protons of 2 β -glucopyranosyl and 1 α -rhamnopyranosyl moieties, indicated its triglycosidic structure. The secondary-methyl signal at δ 1.04 (d, J=6.1 Hz) supported the presence of a rhamnose unit. The sugar moiety was further confirmed by the DEPT spectrum, which revealed the presence of 18 C signals, of which 3 represent anomeric carbon signals

at δ 97.27, 101.03 and 103.01, 12 methine carbon signals, 2 oxymethylene carbons at δ 60.89 and 62.89, and 1 methyl carbon at δ 17.78. All protons of the 3 sugar units were assigned unambiguously from the COSY spectrum and HMQC experiment in which all proton resonances were correlated with those of corresponding carbons in each sugar unit. These results led us to determine the assignments of the interglycosidic linkages by comparison of the observed carbon chemical shifts with those of corresponding sugars, taking into account the known effects of glycosidation. The absence of any ^{13}C NMR glycosidation shift for the rhamnopyranosyl, and the second glucopyranosyl residues suggested that these sugars are terminal. The inter-glycosidic linkage in **1** was confirmed by the HMBC correlations observed between the following protons and carbons: H-1''' of the rhamnose (δ 5.21 d) and C-2'' of the central glucose (δ 76.53), and H-1'''' of the terminal glucose (δ 4.42 d) and C-3''' of the central glucose (δ 86.63) (Figure 1). The presence of 2 carbon signals at δ 20.38 (CH_3) and 170.04 (C=O) as well as a sharp singlet in the ^1H NMR spectrum at δ 1.94 (s, 3H) indicated the presence of an acetyl group. Downfield shifts of H₂-6'''' (δ 4.10 dd and 4.32 d) and an upfield shift of C-5'''' (δ 72.91) signals indicated the bonding site of the acetyl function. Additionally, HMBC correlations between the acetyl carbonyl group (δ 170.04) and 2 protons of C-6'''' showed that the acetyl group was located at C-6'''' of the terminal glucose. The attachment of the sugar moiety to the aglycone was determined from the long-range correlation between H-1'' of the inner glucose (δ 5.49 d) and C-7 of the aglycone (δ 150.87). ^1H and ^{13}C NMR spectral data of each sugar unit and the deshielding effect of the connections were further confirmed by a comparison of its spectral data with literature values for flavonoid triglycosides^{18,19}. From these results, compound **1** was identified as 3'-hydroxy-4'-O-methylscutellarein-7-O-[2''-O- α -L-rhamnopyranosyl-3'''-O-(6''''-O-acetyl- β -D-glucopyranosyl)]- β -D-glucopyranoside. To the best of our knowledge this compound was isolated from natural sources for the first time in this study and the trivial name sarachoside was proposed.

Compounds **2-4** were also isolated as pale yellow amorphous powders from the flavonoid fraction of *V. persica*, and their ^1H and ^{13}C NMR spectra as well as UV characteristics resembled those of **1**. In contrast with **1**, the absence of an aromatic methine carbon signal in the range 90.0-96.0 ppm indicated that C-8 should be substituted. Since C-6 carbon signals of compounds **2-4** were observed at δ 101.85, 101.78 and 101.81 respectively, their aglycones were determined as isoscutellarein derivatives. Previously, 4'-O-methylisoscutellarein-7-O-2''-O-(6''''-O-acetyl- β -D-allopyranosyl)- β -D-glucopyranoside was reported from *V. filiformis* and its spectral data were superimposable with those of **2** for both the aglycone and acylated sugar moieties⁴. Furthermore, it was found that the structures of compounds **3** and **4** were the same as those of isoscutellarein-7-O-2''-O-(6''''-O-acetyl- β -D-allopyranosyl)- β -D-glucopyranoside and 3'-hydroxy-4'-O-methylisoscutellarein-7-O-2''-O-(6''''-O-acetyl- β -D-allopyranosyl)- β -D-glucopyranoside isolated from *Stachys recta*, respectively. Therefore, the structures of **2-4** were determined as shown in Figure 2 by a comparison of their 1D and 2D NMR spectral data with those reported in the literature^{4,11,15}.

Sarachoside (**1**) was the major component of the water soluble fraction of *V. pectinata* var. *glandulosa* and exhibited potent radical scavenging activity comparable to that of 3-*tert*-butyl-4-hydroxy-anisole (BHA) and *dl*- α -tocopherol (Table 2). The radical scavenging effects of antioxidants on DPPH radicals might be due to their hydrogen donating ability¹⁴. Sarachoside (**1**) has an *ortho*-dihydroxy group that has been recognized to function as an electron or hydrogen donor²⁰. The DPPH radical scavenging activity of sarachoside (**1**) may be mostly related to the 4-oxo and 5,6-dihydroxy group in its structure.

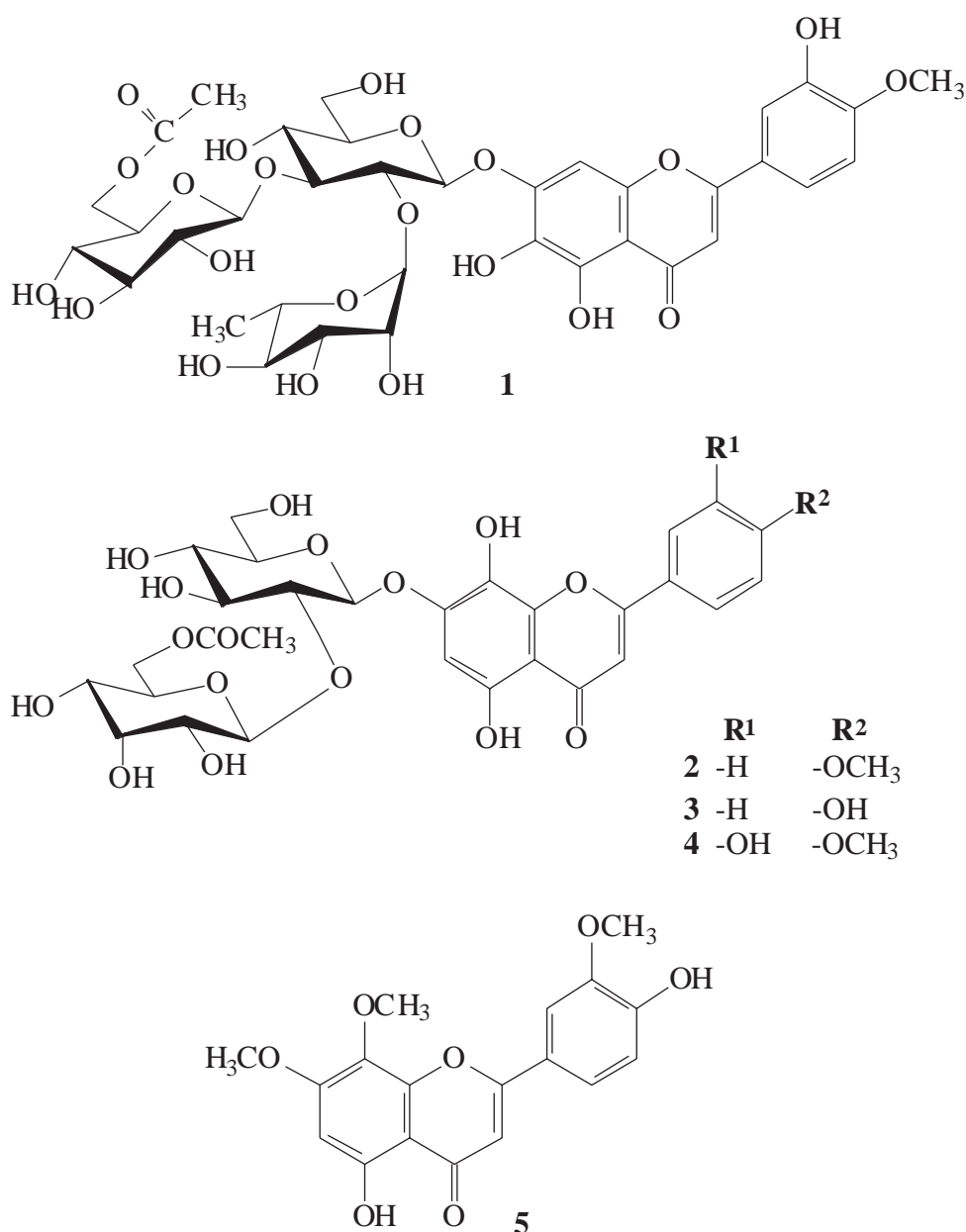


Figure 2. Structures of the isolated compounds (1-5).

Table 2. Free radical scavenging activity of compound 1, BHA[†] and *dl*- α -tocopherol on DPPH radical (1.5×10^{-5})*.

	1×10^{-6} M	1×10^{-5} M	5×10^{-5} M	1×10^{-4} M	2×10^{-4} M
Sarachoside (1)	5.3	32	83	82	85
<i>dl</i> - α -tocopherol	13	82	85	89	95
BHA	14	63	80	88	94

[†]BHA: 3-*tert*-butyl-4-hydroxy-anisole

*Each value is the average of duplicate determinations. Inhibitory ratio of each compound is expressed as follows: inhibition % = $10 \times [(Abs_{blank} - Abs_{sample}) / Abs_{blank}]$. Blank: in the absence of sample.

On the other hand, since the chloroform fraction of *V. persica* showed potent cytotoxicity, isolation studies also were performed on this fraction²¹. After repeated column chromatographies, compound **5** was isolated from the most active fraction. A comparison of its NMR data and MS results with previously reported data led us to determine its structure as 5,4'-dihydroxy-6,7,3'-trimethoxyflavone (circilineol), which had a scutellarein-type structure (Figure 2)¹⁶. However, circilineol (**5**) did not show strong enough activity to be the compound responsible for the cytotoxicity of the chloroform fraction.

The distribution of the acylated flavone glycosides in *Veronica* species may be useful from the view point of the chemotaxonomy of the genus *Veronica*¹¹. Our continuing studies will be of assistance in clarifying the chemotaxonomical classification of this genus.

Acknowledgments

The authors are grateful to Ms. S. Kato (Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan) for recording the NMR spectra.

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