

Coumarins from *Seseli hartvigii* RootsAlev Tosun^a, Masaki Baba^b and Toru Okuyama^{b*}^aAnkara University, Faculty of Pharmacy, Department of Pharmacognosy, 06100 Tandogan-Ankara, Turkey^bMeiji Pharmaceutical University, Department of Natural Medicine and Phytochemistry, 2-522-1, Noshio, Kiyose-shi, Tokyo 204-8588, Japan

okuyama@my-pharm.ac.jp

Received: January 19th, 2007; Accepted: March 6th, 2007This paper is dedicated to Professor Yoshinori Asakawa for his 65th Birthday.

Three angular-type pyranocoumarins, (–)-anomalin (**1**), (+)-(3'*R*,4'*R*)-3',4'-diseneciolyoxy-3', 4'-dihydroseselin (**2**), and (–)-(3'*R*,4'*R*)-3'-angeloyloxy-4'-acetoxy-3',4'-dihydroseselin (**3**), two linear-type furocoumarins, bergamottin (**4**) and isoimperatorin (**5**), and a simple coumarin, suberosin (**6**) have been isolated from the roots of *Seseli hartvigii* (Umbelliferae). The structures of these compounds were determined from spectral and physical information, and with reference to literature data.

Keywords: Umbelliferae, *Seseli hartvigii*, *S. resinosum*, *S. gummiferum* subsp. *corymbosum*, coumarins.

Umbelliferae is a widespread plant family represented by almost 455 genera and approximately 3750 species worldwide. The important characters of the family are aromatic herbage, typically umbellate inflorescences and schizocarp fruits. Some species of this family are economically important because of their use as condiments and ornamentals. The family contains many species used for their medicinal properties [1-3].

Seseli is a Greek name that was used by Hippocrates to refer to members of the Umbelliferae. In Turkey, the genus is represented by 12 taxa (11 species and 1 subspecies) [4-8].

Seseli species are used for the treatment of inflammation, swelling, rheumatism, pain and the common cold, in addition to having anthelmintic, carminative, stomachic and stimulant effects. *S. tortuosum*, known as French kummel, is reported to have cardiogenic, carminative and diuretic properties, and the leaves of *S. libanotis* are reported to regulate the stomach and intestine. On the other hand, the fruits of *S. tortuosum* are used as an

emmenagogue and antifatulent in Turkish folk medicine, and the leaves of *S. libanotis* are consumed as a vegetable in eastern Turkey [9-13]. However, only limited phytochemical and biological activity studies have been carried out on Turkish *Seseli* species.

In our previous study, together with osthol, five angular-type pyranocoumarins, (–)-(3'*S*, 4'*S*)-3'-acetoxy-4'-isovaleryloxy-3', 4'-dihydroseselin (corymbocoumarin), (–)-(3'*S*,4'*S*)-3'-acetoxy-4'-angeloyloxy-3', 4'-dihydroseselin, (+)-(3'*S*, 4'*S*)-3'-hydroxy-4'-angeloyloxy-3', 4'-dihydroseselin (d-laserpitin), (–)-(3'*S*,4'*S*)-3'-angeloyloxy-4'-hydroxy-3', 4'-dihydroseselin, and 3'-acetoxy-4'-isobutyloxy-3', 4'-dihydroseselin, were isolated from the aerial parts of *S. gummiferum* Pall. ex Sm. subsp. *corymbosum* (Boiss. & Heldr.) P. H. Davis [14,15], a perennial monocarpic plant that is endemic to southern Turkey. In that study, a new coumarin (corymbocoumarin) was isolated. In another previous study, the essential oils of *S. gummiferum* subsp. *corymbosum* and *S. gummiferum* subsp. *gummiferum* were compared by GC/MS [16].

We also previously isolated three angular-type pyranocoumarins, (+)-samidin [(+)-(3'S,4'S)-3'-seneciolyloxy-4'-acetoxy-3', 4'-dihydroseselin], (-)-anomalin [(-)-(3'R,4'R)-3',4'-diangeloyloxy-3', 4'-dihydroseselin], and calipteryxin [(-)-(3'R,4'R)-3'-angeloyloxy-4'-seneciolyloxy-3', 4'-dihydroseselin], and two linear type furocoumarins, isoimperatorin and deltoin, from the roots of *S. resinosum* Freyn et Sint., an endemic species growing at sea level in northern Turkey [17]. The essential oils present in the fruits of *S. resinosum* and *S. tortuosum* were also investigated by GC and GC/MS analysis in a comparative study. The main constituents of *S. resinosum* oil were β -pinene (37.5%), 4 α -hydroxygermacra-1(10)-5-diene (21.7%) and α -pinene (13.7%) [18].

We have also isolated the coumarin components of an endemic species collected from southern Turkey, *S. hartvigii* Parolly & Nordt. Several coumarins, isopteryxin [(-)-(3'R, 4'R)-3'-angeloyloxy- 4'-acetoxy-3', 4'-dihydroseselin], suberosin, and mexoticin were isolated from the aerial parts of the plant [19].

In addition to the studies described above, *Seseli* species have been examined with regard to coumarins, cinnamic acid derivatives, sesquiterpene lactones, phenyl propane type compounds and constituents of essential oils. Biological activity studies have also been performed for some *Seseli* species. Recently, antimicrobial, anti-inflammatory and analgesic activities have been reported for Turkish *Seseli* species [20, 21], and isolation studies and analysis of essential oils have also been carried out [14-23].

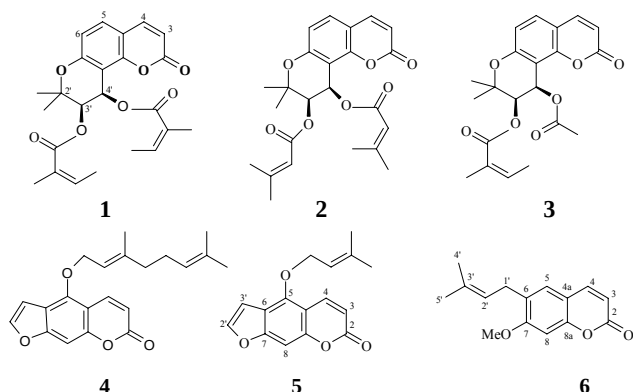


Figure 1: Coumarins isolated from the roots of *S. hartvigii*.

In the present study, the *n*-hexane extract of the roots of *S. hartvigii* was subjected to open column chromatography to obtain the coumarin-type

compounds that exist mostly in the nonpolar fractions. We isolated and characterized three angular-type pyranocoumarins, (-)-anomalin (**1**), (+)-(3'R,4'R)-3',4'-diseneciolyloxy-3', 4'-dihydroseselin (**2**), and (-)-(3'R,4'R)-3'-angeloyloxy-4'-acetoxy-3',4'-dihydroseselin (**3**), two linear-type furocoumarins, bergamottin (**4**) and isoimperatorin (**5**), and a simple coumarin, suberosin (**6**) (Figure 1).

In the ^1H NMR spectra, doublets in the range of δ 6.20-7.63 (each 1H, d, $J = 9.3$ -9.5 Hz) and 6.82-7.35 (each 1H, d, $J = 8.5$ -8.8 Hz) were assigned to the H-3, H-4 and H-6, and H-5 protons in the coumarin skeleton, respectively. A pair of doublets in the range δ 5.35-6.70 indicated that the structures were angular pyranocoumarins, with 3' and 4' protons (1H, d, $J = 4.9$ Hz). The seselin type angular pyranocoumarins (khellactone derivatives) were assigned the *cis* configuration on the basis of a coupling constant of 4.9 Hz between H-3' and H-4', and the small differences (δ 0.04-0.05) in the geminal dimethyl resonances, features which characterize this group of coumarins [24-26]. Optical rotation measurements and reference to values in the literature allowed the 3' and 4' configurations of the structures to be determined.

Interestingly, ester groups are present as side chains that can be observed in high field ^1H NMR spectra with angeloyl, seneciyl and acetoxyl group signals (Table 1).

Table 1: ^1H NMR spectral data for the angular-type pyranocoumarins obtained from *S. hartvigii* (**1-3**).^a

Position	1	2	3
3	6.21 (1H, d, $J=9.5$)	6.20 (1H, d, $J=9.3$)	6.24 (1H, d, $J=9.5$)
4	7.60 (1H; d, $J=9.5$)	7.59 (1H; d, $J=9.5$)	7.63 (1H; d, $J=9.5$)
5	7.36 (1H, d, $J=8.5$)	7.35 (1H, d, $J=8.6$)	7.39 (1H, d, $J=8.8$)
6	6.81 (1H; d, $J=8.5$)	6.80 (1H; d, $J=8.6$)	6.82 (1H; d, $J=8.6$)
3'	5.45 (1H, d, $J=4.9$)	5.35 (1H, d, $J=4.9$)	5.40 (1H, d, $J=4.9$)
4'	6.70 (1H, d, $J=4.9$)	6.62 (1H, d, $J=4.9$)	6.59 (1H, d, $J=4.9$)
Gem-Me	1.49 (3H, s) 1.45 (3H, s)	1.46 (3H, s) 1.42 (3H, s)	1.49 (3H, s) 1.44 (3H, s)
Acetoxyl	----	----	2.11 3H, s
Ester group	6.03 (1H, m) 6.13 (1H, m) 1.96 (6H, dd, $J=1.2$) 1.86 (6H, d, $J=1.2$)	5.66 (1H, s) 5.62 (1H, s) 2.19 (3H, s) 2.15 (3H, s)	6.14 (1H, qm, $J=5.8, 1.4$) 1.97 (3H, dd, $J=1.4, 5.8$) 1.88 (3H, t, $J=5.3, 1.4$)

^aChemical shifts in δ ppm relative to TMS; coupling constant (J) in Hz (400 MHz in CDCl_3).

The ^{13}C NMR spectra of these compounds supported them being pyranocoumarins (Table 2), because they exhibited signals consistent with a coumarin skeleton (eight aromatic carbons and one ester carbonyl),

Table 2: ^{13}C NMR spectral data for the angular-type pyranocoumarins obtained from *S. hartvigii* (1-3).^a

Position	1	2	3
2	159.50 s	159.64 s	159.55 s
3	113.13 d	112.98 d	113.0 d
4	142.96 d	142.97 d	143.09 d
5	129.00 d	128.83 d	129.00 d
6	114.23d	114.20 d	114.14 d
7	156.47 s	156.51 s	156.37 s
8	107.46 s	107.46 s	106.79 s
4a	112.35 s	112.35 s	112.33 s
8a	153.85 s	153.79 s	153.63 s
2'	77.43 s	77.32 s	76.68 s
3'	70.18 d	69.41 d	69.74 d
4'	60.19 d	59.80 d	60.90 d
Gem-Me	25.51 q	25.19 q	24.99 q
	22.62 q	22.68 q	22.87 q
Acetoxyl	----	----	169.41 s
			20.66 q
Ester group	166.23 s	164.90 s	166.06 s
	165.98 s	164.80 s	139.43 s
	139.61 s	157.91 s	126.71 d
	138.22 s	157.23 s	20.50 q
	127.21 d	115.16 d	15.79 q
	126.85 d	115.10 d	
	20.45 q	27.51 q	
	20.51 q	27.45 q	
	15.90 q	20.44 q	
	15.70 q	20.40 q	

^aChemical shifts in δ ppm relative to TMS (400 MHz in CDCl_3).

along with a geminal methyl group and a heteroatom ring consisting of one quaternary carbon (δ approx. 77 ppm) and two methines (with shifts of about 70 and 60 ppm).

In the ^1H NMR spectra of the furocoumarins, two characteristic pairs of doublets at δ 6.27-8.16 (each 1H, d, $J = 9.8$ Hz) were assignable to H-3 and H-4 on a coumarin nucleus, and two pairs of doublets in the range δ 6.96-7.60 (each 1H, d, $J = 2.2$ -2.4 Hz) indicated H-3' and H-2' on a furan ring, and a singlet at δ 7.15 (H-8) evidenced 5 substituted furocoumarins. The high field signals show that the compounds have hydrocarbon parts. The structures of the compounds were determined by further spectral analysis and by reference to literature data on furocoumarins (Table 3).

Coumarins are some of the most common secondary metabolites in the Umbelliferae family, and constitute a major class of *O*-heterocyclic natural products. They are known to have many biological activities, with anticoagulant, dermal photosensitizing, antibacterial, analgesic and hypothermal effects [27]. Various coumarins and furocoumarins have been reported to have anti-inflammatory activity [10, 28]. Moreover, naturally occurring pyranocoumarins have interesting cytotoxic and anti-tumor activities [29-31]. Some major plant-derived angular dihydropyranocoumarins have calcium antagonistic activity [32].

Table 3: ^1H NMR and ^{13}C NMR spectral data for the linear-type furocoumarins obtained from *S. hartvigii* (4 and 5).^a

H	4	5	C	4	5
3	6.27 (1H, d, $J=9.8$)	6.27 (1H, d, $J=9.8$)	2	161.01 s	161.05 s
4	8.16 (1H, d, $J=9.8$)	8.16 (1H, d, $J=9.8$)	3	112.48 d	112.49 d
5	-----	-----	4	139.38 d	139.64 d
8	7.15 (1H, s)	7.16 (1H, s)	4a	107.46 s	107.48 s
2'	7.59 (1H, d, $J=2.4$)	7.60 (1H, d, $J=2.2$)	5	148.79 s	148.77 s
3'	6.96 (1H, dd, $J=2.4, 1.0$)	6.96 (1H, dd, $J=2.2, 1.0$)	6	114.12 s	114.14 s
1''	4.95 (2H, d, $J=6.8$)	4.92 (2H, d, $J=7.1$)	7	157.91 s	157.92 s
2''	5.54 (1H, t, $J=6.8$)	5.54 (1H, t, $J=1.2$)	8	94.17 d	94.21 d
4''	2.09 (2H, m)	1.70 (3H, s)	8a	152.47 s	152.48 s
5''	2.09 (2H, m)	1.80 (3H, s)	2'	144.68 d	144.70 d
6''	5.07 (1H, tq)	-----	3'	104.96 d	104.95 d
8''	1.68 (3H, brs)	-----	1''	69.78 t	69.79 t
9''	1.60 (3H, brs)	-----	2''	118.77 d	118.99 d
10''	1.69 (3H, brs)	-----	3''	142.83 s	139.38 s
			4''	39.58 t	25.94 q
			5''	26.35 t	18.37 q
			6''	123.37 d	-----
			7''	131.86 s	-----
			8''	25.78 q	-----
			9''	16.82 q	-----
			10''	17.84 q	-----

^aChemical shifts in δ ppm relative to TMS; coupling constant (J) in Hz (400 MHz in CDCl_3).

It is obvious that the Turkish *Seseli* species are very rich sources of angular-type pyranocoumarins, as well as other types of coumarins. The coumarins isolated from *S. hartvigii*, as well as those isolated from *S. resinosum* and *S. gummiferum* subsp. *corymbosum*, will be investigated for possible biological activities in future studies. To the best of our knowledge, this is the first published chemical analysis of the roots of *S. hartvigii*.

Experimental

General: Chromatographic separations were carried out on silica gel using open column chromatography (0.063-0.200 mm, 70-230 mesh Merck 7734). HPLC purifications were carried out on a packed column of Senshu-Pak silica (4251-N, 250 mm x 10 mm, TOSOH UV-8010, 320 nm). TLC (silica gel 60 F₂₅₄, Merck 5554) was performed under UV at 366 nm and 254 nm, by spraying with sulfuric acid in methanol. Melting points were measured by using a YANACO Micro Melting Point Apparatus. Optical rotations were obtained by using a Horiba High Sensitivity Polarimeter (SEPA-300). NMR spectra were recorded on JEOL JNM-EX 270 and 400 FT-NMR

spectrometers. Chemical shifts are expressed as δ units, relative to TMS ($\delta=0$) as an internal standard. EIMS spectra were recorded on a JEOL-JMS DX 302 MS spectrometer operating at 70 eV in the electron impact mode. All compounds were kept in a vacuum oven at 76 mm Hg and 40°C overnight before the measurements.

Plant material: Aerial and underground parts of *Seseli hartvigii* were collected in August 2002 (during the plant's flowering period) from Antalya-Saklikent in the Bakirlar Mountains of Turkey (2300-2500 m above sea level). A voucher specimen has been deposited at the Herbarium of the Faculty of Pharmacy of Ankara University (AEF 21915). The species was identified by Prof. H. Duman (Gazi University, Department of Biology, Faculty of Letters and Sciences).

Isolation and identification of coumarins: Air-dried and powdered roots of *S. hartvigii* (450 g) were successively extracted with *n*-hexane, AcOEt, and MeOH for 8 h under reflux. The extracts were evaporated *in vacuo* to give crude *n*-hexane (25 g), AcOEt (7.5 g), and MeOH (42 g) extracts, respectively. The *n*-hexane extract was further separated into fifteen fractions by chromatography using a silica gel column eluted, in order of increasing polarity, with *n*-hexane, *n*-hexane:AcOEt, AcOEt and finally MeOH. Fraction 3 was purified by re-chromatography with a *n*-hexane:AcOEt mixture, re-crystallization, and again re-chromatography using a SEP-PAK® small column (Cardiges-Waters) combination with PTFE filter (0.45 μ , EKIRODISC 25 CR) to give bergamottin (**4**) (347.4 mg). (–)-Anomalin (**1**) was isolated from fractions 7 and 8, and prep-HPLC (*n*-hexane:AcOEt, 9:1) was used for the purification of compound **1** (20 mg). (+)-(3'*R*, 4'*R*)-3', 4'-diseneciyoxy-3', 4'-dihydroseselin (**2**) was obtained by re-chromatography of the same fraction as that used to yield compound **1**, by using a silica gel column eluted with a *n*-hexane-AcOEt gradient system (80 mg). Suberosin (**6**) was also obtained from the same fraction by prep-HPLC (13 mg). Fraction 4 was subjected to prep-HPLC using elution with a *n*-hexane:AcOEt gradient system to give isoimperatorin (**5**). (–)-(3'*R*, 4'*R*)-3'-Angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin (**3**) was obtained from fraction 11 (21.5 mg) via re-chromatography and prep-HPLC.

(–)-(3 *R*,4 *R*)-3',4'-Diangeloyloxy-3',4'-dihydroseselin, [(–)-anomalin] (1**)**

Colorless needles.

MP: 171-172°C.

$[\alpha]_D^{20}$: –42.66° (*c* 1.00, CHCl₃).

¹H NMR: Table 1.

¹³C NMR: Table 2.

MS (EI, 70 eV): C₂₄H₂₆O₇ 426, *m/z* (%): 426 (2.27), 328 (11.80), 327 (58.18), 326 (28.80), 311 (41.04), 244 (19.13), 243 (16.91), 230 (12.75), 229 (91.43), 227 (24.25), 213 (15.26), 83 (M⁺, 100.00), 55 (52.61).

(+)-(3 *R*,4 *R*)-3',4'-Diseneciyoxy-3',4'-dihydroseselin (2**)**

White crystals.

MP: 105.0-108.0°C.

$[\alpha]_D$: +19.66° (*c* 1.00, CHCl₃).

¹H NMR: Table 1.

¹³C NMR: Table 2.

MS (EI, 70 eV): C₂₄H₂₆O₇ 426, *m/z* (%): 426 (2.41), 326 (29.39), 311 (27.73), 244 (15.18), 229 (51.70), 83 (M⁺, 100.00), 55 (12.16).

(–)-(3 *R*,4 *R*)-3'-Angeloyloxy-4'-acetoxy-3',4'-dihydroseselin (3**)**

White crystals.

MP: 133-135°C.

$[\alpha]_D$: –43.80° (*c* 1.00, CHCl₃)

¹H NMR: Table 1.

¹³C NMR: Table 2.

MS (EI, 70 eV): C₂₁H₂₂O₇ 386, *m/z* (%): 386 (21.80), 311 (13.01), 286 (13.09), 245 (19.57), 244 (46.64), 243 (13.92), 230 (14.20), 229 (M⁺, 100.00), 227 (14.65), 191 (16.53), 83 (68.13), 55 (17.55).

5[(3',7'-Dimethyl-2',6'-octadienyl)oxy]psoralen, (bergamottin) (4**)**

White crystalline substance

MP: 53-54°C.

¹H NMR: Table 3.

¹³C NMR: Table 3.

MS (EI, 70 eV): C₂₁H₂₂O₄ 338, *m/z* (%): 338 (0.26), 202 (M⁺, 100.00), 137 (12.81), 95 (2.95), 81 (13.61), 69 (24.93).

5-(3'-Methyl-2'-butenoxy)psoralen, (isoimperatorin) (5**)**

Colorless needles.

MP: 107.0-108.0°C.

¹H NMR: Table 3.

¹³C NMR: Table 3.

MS (EI, 70 eV): C₁₆H₁₄O₄ 270, *m/z* (%): 270 (1.39), 203 (11.93), 202 (M⁺, 100.00), 174 (16.46), 69 (29.95), 41 (8.86).

6-(3'-Methyl-2'-butenyl)-7-methoxycoumarin (suberosin) (6)

Amorphous powder.

¹H NMR: 6.23 (1H, d, *J* = 9.3 Hz, H-3), 7.62 (1H, d, *J* = 9.5 Hz, H-4), 7.18 (1H, s, H-5), 6.78 (1H, s, H-8), 3.31 (2H, m, H-1'), 5.28 (1H, m, H-2'), 1.77 (3H, s, H-4'), 1.71 (3H, s, H-5'), 3.90 (3H, s, OCH₃).

¹³C NMR: 160.44 (C-2), 112.66 (C-3), 143.43 (C-4), 111.80 (C-4a), 121.23 (C-5), 133.49 (C-6), 161.31 (C-7), 98.46 (C-8), 154.27 (C-8a), 27.91 (C-1'), 127.26 (C-2'), 127.37 (C-3'), 17.90 (C-4'), 25.92 (C-5'), 55.91 (-OCH₃).

MS (EI, 70 eV): C₁₅H₁₆O₃ 244, *m/z* (%): 244 (72.82), 229 (M⁺, 100.00), 189 (12.64), 131 (5.71)

Acknowledgments - The authors wish to thank TUBITAK (Scientific and Technical Research Council of the Turkish Republic) for supporting this study by means of a post-doctoral scholarship (no. 2219).

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