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NOVEL ANTIPROLIFERATIVE FALCARINDIOL FURANOCOUMARIN ETHERS FROM THE ROOT OF *ANGELICA JAPONICA*

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Abstract: Four novel antiproliferative furanocoumarin ethers of falcariindiol, named japoangelols A (8.5), B (7.2), C (7.4), and D (8.4), were isolated from the root of *Angelica japonica* together with panaxynol (0.3), falcariindiol (3.2), (9Z)-1,9-heptadecadiene-4,6-diyne-3,8,11-triol (2.2), and 8-acetoxylfalcariinol (3.2). Structures were established from the spectroscopic evidence, and the inhibitory activities (ED₅₀, µg/ml, shown in the parentheses) were evaluated using the MTT assay. © 1997 Elsevier Science Ltd. All rights reserved.

After we found the acetylenic compound, panaxytriol, as an antiproliferative acetylenic compound in the steamed and dried ginseng root ("red ginseng"),¹ we systematically screened the 21 Umbelliferae plants² for the antiproliferative acetylenic compounds using the combination of the ELISA^{1,3} for panaxytriol and the MTT assay,⁴ and isolated falcariindiol from the root and fruit of *Anthriscus sylvestris*⁵ and falcariindiol and panaxynol from the root of *Heracleum moellendorfii*² as the antiproliferative constituents.

In the course of our continuing search for antiproliferative acetylenic compounds in the Umbelliferae plants, we found the MeOH extract of the root of *Angelica japonica* showed the antiproliferative activity (ED₅₀ 25 µg/ml) against human gastric adenocarcinoma cell (MK-1) *in vitro*, and the activity is localized only in the CHCl₃-soluble fraction. Subsequent bioassay-directed fractionation of the CHCl₃-soluble fraction (105.6 g from 5.5 kg dried root) of the MeOH extract using chromatography on silica gel and YMC-ODS, and the preparative HPLC on ODS has led to the isolation of four furanocoumarin ethers of falcariindiol, named japoangelols A (1, 28 mg), B (2, 38 mg), C (3, 43 mg), and D (4, 44 mg), in addition to five polyacetylenic compounds, panaxynol (57 mg), falcariindiol (5, 2.94 g), (9Z)-1,9-heptadecadiene-4,6-diyne-3,8,11-triol (25 mg), and 8-acetoxylfalcariinol (100 mg). Non-antiproliferative free furanocoumarins, byakangelicin (6, 93 mg) and oxypeucedanin hydrate (7, 23 mg) were also isolated.

Japoangelols A (1)⁶ and B (2)⁷ were obtained as yellow syrups with a molecular formula C₃₄H₄₀O₈. Both showed ¹H and ¹³C nmr signals almost identical to those of falcariindiol and byakangelicin suggesting them to be conjugates of the two. In the ¹H nmr spectrum of 1, the proton signals of the hydroxyl groups corresponding to C8"-OH of falcariindiol and C3'-OH of byakangelicin were not observed in spite that the

signals of the corresponding C3''-OH (δ 2.23) and C2'-OH (δ 3.08) were observed. The ^{13}C nmr signals of C3' appeared at δ 78.5, 7.0 ppm lower than that of free byakangelicin (δ 71.5), suggesting that faltarindiol is linked to the C3'-OH of byakangelicin. The down-field shift of the signal of the counterpart carbon (C8'') in the faltarindiol moiety was not observed, however, the C8''-H signal showed in the HMBC spectrum a clear cross peak with a carbon signal (C3') of the byakangelicin moiety (see Figure 1). From these spectroscopic evidence, the location of the linkage was concluded to be C8''-O-C3'. In the ^{13}C nmr spectrum of **2**, the signal of C3' appeared at δ 78.7, 7.2 ppm lower than that of free byakangelicin, and C3''-H and C3' showed a cross peak in the HMBC spectrum, indicating the location of the linkage is C3''-O-C3'.

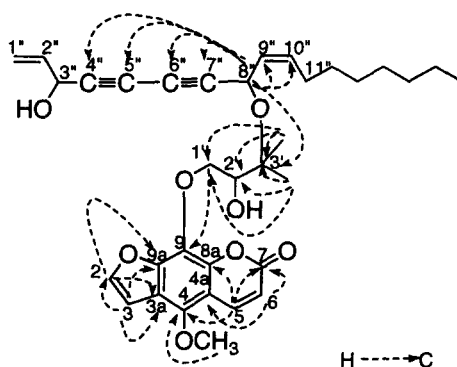


Figure 1: ^1H - ^{13}C Long-range Correlations in **1**

Japoangelols C (**3**)⁸ and D (**4**)⁹ were obtained as yellow syrups with a molecular formula $\text{C}_{33}\text{H}_{38}\text{O}_7$. Both showed the ^1H and ^{13}C nmr signals nearly identical to those of faltarindiol and oxypeucedanin hydrate. In the ^{13}C nmr spectrum of **3**, the signal of C3' appeared at δ 78.5, 6.8 ppm lower than that of free oxypeucedanin hydrate (δ 71.7), suggesting that faltarindiol is linked to the C3'-OH of oxypeucedanin hydrate. The location of the linkage of the two was concluded to be C8''-O-C3' by the HMBC experiment. In the same way, the location of the linkage of faltarindiol and oxypeucedanin hydrate in **4** was concluded to be C3''-O-C3'.

On the basis of spectral evidences described above, the structures of japoangelol A, B, C, and D are represented by formula **1**, **2**, **3**, and **4**, respectively.

The inhibitory activities (ED_{50} , $\mu\text{g/ml}$) against MK-1 cell growth of the acetylenic compounds isolated were as follows: panaxynol (0.3), faltarindiol (3.2), (9Z)-1,9-heptadecadiene-4,6-diyne-3,8,11-triol (2.2), 8-acetoxypalcarinol (3.2), japoangelols A (8.5), B (7.2), C (7.4), and D (8.4).

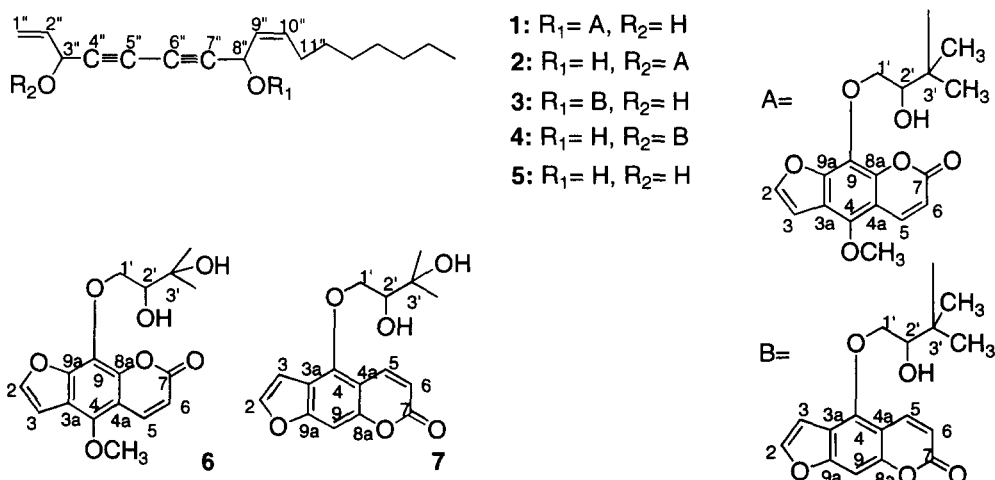


Figure 2

TABLE I. ^1H -NMR Data (δ , J in Hz) for Compounds 1-7 (CDCl_3 , 500 MHz)

	1	2	3	4	5	6	7
H-2	7.63 (br d, 2.5)	7.64 (d, 2.5)	7.60 (br d, 2.5)	7.61 (br d, 2.5)		7.64 (d, 2.5)	7.60 (br d, 2.5)
H-3	6.99 (br d, 2.5)	7.00 (d, 2.5)	7.01 (br dd, 1,2.5)	7.01 (br dd, 1,2.5)		7.01 (d, 2.5)	6.99 (dd, 1,2.5)
4-OMe	4.17 (s)	4.18 (s)				4.19 (s)	
H-5	8.11 (d, 10)	8.11 (d, 10)	8.23 (dd, 0.5,10)	8.23 (br d, 10)		8.12 (d, 10)	8.17 (d, 10)
H-6	6.27 (d, 10)	6.28 (d, 10)	6.30 (d, 10)	6.30 (d, 10)		6.29 (d, 10)	6.26 (d, 10)
H-9			7.14 (br s)	7.17 (br s)			7.15 (br s)
H-1'	4.23 (dd, 8,10)	4.27 (dd, 8,10)	4.42 (dd, 7.5,10)	4.42 (dd, 8,10)		4.28 (dd, 8,10)	4.44 (dd, 8,10)
	4.63 (dd, 3,10)	4.60 (dd, 3,10)	4.59 (dd, 3,10)	4.59 (dd, 3,10)		4.61 (dd, 3,10)	4.55 (dd, 3,10)
H-2'	3.99 (br d, 8)	3.99 (dd, 3, 8)	3.96 (m)	3.96 (m)		3.84 (dd, 3,8)	3.90 (dd, 3,8)
3'-Me	1.33 (s)	1.33 (s)	1.30 (s)	1.30 (s)		1.29 (s)	1.31 (s)
	1.38 (s)	1.38 (s)	1.40 (s)	1.40 (s)		1.33 (s)	1.36 (s)
H-1''	5.22 (ddd, 1,1,10)	5.16 (ddd, 1,1,10)	5.22 (ddd, 1,1.5,10)	5.22 (br d, 10)	5.25 (ddd, 1,1.5,10.5)		
	5.44 (br d, 17)	5.39 (ddd, 1,1.5,17)	5.42 (ddd, 1,1.5,17)	5.42 (br d, 17)	5.46 (ddd, 1,1.5,17)		
H-2''	5.92 (ddd, 5,10,17)	5.81 (ddd, 5,10,17)	5.82 (ddd, 5,10,17)	5.82 (ddd, 5,10,17)	5.93 (ddd, 5.5,10.5,17)		
H-3''	4.91 (br s)	4.93 (br d, 5)	4.87 (br d, 5)	4.87 (br d, 5)	4.93 (br d, 5.5)		
H-8''	5.17 (br d, 8)	5.18 (br d, 8)	5.20 (br d, 9)	5.20 (br d, 8)	5.20 (br d, 8)		
H-9''	5.41 (br dd, 8,10.5)	5.50 (dddd, 1,1.5,8,10.5)	5.51 (ddt, 9,10.5,1.5)	5.51 (ddt, 8,10.5,1.5)	5.51 (ddt, 8,10.5,1.5)		
H-10''	5.46 (br dt, 10.5,7.5)	5.59 (ddt, 1,10.5,7.5)	5.61 (ddt, 1,10.5,7.5)	5.61 (ddt, 1,10.5,7.5)	5.60 (ddt, 1.5,10.5,7.5)		
H-11''	2.07 (m)	2.10 (dq, 1.5,7.5)	2.11 (br q, 7.5)	2.11 (br q, 7.5)	2.11 (dq, 1.5,7.5)		
H-12''	1.36 (t-like, 7.5)	1.36 (t-like, 7.5)	1.36 (t-like, 7.5)	1.38 (t-like, 7.5)	1.38 (t-like, 7.5)		
H-13''	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)		
H-14''	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)		
H-15''	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)		
H-16''	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)	1.28 (m)		
H-17''	0.88 (t-like, 7)	0.88 (t-like, 7)	0.87 (t-like, 7)	0.87 (t-like, 7)	0.88 (t-like, 7)		

TABLE II. ^{13}C -NMR Data (δ) for Compounds 1-7 (CDCl_3 , 125 MHz)

	1	2	3	4	5	6	7
2	145.2	145.3	145.1	145.2		145.2	145.2
3	105.1	105.1	104.9	104.8		105.3	104.7
3a	114.8	114.7	114.1	114.4		114.6	114.3
4	144.6	144.7	148.7	148.7		144.9	148.6
4-OMe	60.8	60.8				60.8	
4a	107.6	107.6	107.3	107.6		107.6	107.3
5	139.4	139.5	139.4	139.4		139.4	139.0
6	112.9	112.9	112.8	113.0		112.9	113.0
7	160.3	160.3	161.3	161.3		160.1	161.0
8a	144.0	144.0	152.6	152.6		144.0	152.6
9	127.2	127.2	94.5	94.7		126.9	94.8
9a	150.3	150.3	158.1	158.1		150.2	158.1
1'	75.7	75.6	74.2	74.2		76.1	74.5
2'	76.0	76.0	76.3	76.2		76.1	76.6
3'	78.5	78.7	78.5	78.7		71.5	71.7
3'-Me	22.1	22.1	22.2	21.9		25.1	26.6
	23.5	22.8	23.0	22.6		26.7	26.6
1''	117.1	116.6	117.2	117.0	117.2		
2''	136.0	135.7	135.9	135.4	135.9		
3''	63.4	63.3	63.4	63.4	63.4		
4''	77.9	79.0	78.4	78.3	78.3		
5''	70.5	70.0	70.2	70.5	70.2		
6''	68.5	69.0	68.9	68.6	68.7		
7''	80.6	79.4	79.9	80.0	79.9		
8''	59.0	58.6	59.0	58.6	58.5		
9''	127.7	127.9	127.4	127.7	127.7		
10''	132.3	134.4	132.8	134.6	134.5		
11''	27.9	27.6	27.9	27.7	27.6		
12''	29.2	29.3	29.2	29.2	29.2		
13''	29.2	29.1	29.1	29.1	29.1		
14''	29.1	29.1	29.1	29.1	29.1		
15''	31.8	31.8	31.7	31.8	31.7		
16''	22.6	22.6	22.6	22.6	22.6		
17''	14.1	14.0	14.0	14.0	14.0		

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6. $[\alpha]_{\text{D}}^{29} + 111.8^\circ$ ($c = 0.50$, CHCl_3). $\text{C}_{34}\text{H}_{40}\text{O}_8$ $[(\text{M}+\text{Na})^+ m/z 599.2635$, calcd. 599.2621].
7. $[\alpha]_{\text{D}}^{29} + 138.4^\circ$ ($c = 0.17$, CHCl_3). $\text{C}_{34}\text{H}_{40}\text{O}_8$ $[(\text{M}+\text{Na})^+ m/z 599.2635$, calcd. 599.2621].
8. $[\alpha]_{\text{D}}^{29} + 117.5^\circ$ ($c = 0.19$, CHCl_3). $\text{C}_{33}\text{H}_{38}\text{O}_7$ $[(\text{M})^+ m/z 546.2633$, calcd. 546.2617].
9. $[\alpha]_{\text{D}}^{29} + 219.4^\circ$ ($c = 0.16$, CHCl_3). $\text{C}_{33}\text{H}_{38}\text{O}_7$ $[(\text{M}+\text{Na})^+ m/z 569.2502$, calcd. 569.2515].