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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 falcarindiol, 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), falcarindiol (3.2), (9Z)-1,9-heptadecadiene-4,6-diyne-3,8,11-triol (2.2), and 8-acetoxyfalcarinol (3.2). Structures were established from the spectroscopic evidence, and the inhibitory activities (ED_{50}, μg/ml, shown in the parentheses) were evaluated using the MTT assay.

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 plants[2] for the antiproliferative acetylenic compounds using the combination of the ELISA[1,3] for panaxytriol and the MTT assay,[4] and isolated falcarindiol from the root and fruit of *Anthriscus sylvestris*[5] and falcarindiol 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 (ED_{50} 25 μg/ml) against human gastric adenocarcinoma cell (MK-1) *in vitro*, and the activity is localized only in the $CHCl_3$-soluble fraction. Subsequent bioassay-directed fractionation of the $CHCl_3$-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 falcarindiol, 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), falcarindiol (**5**, 2.94 g), (9Z)-1,9-heptadecadiene-4,6-diyne-3,8,11-triol (25 mg), and 8-acetoxyfalcarinol (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 $C_{34}H_{40}O_8$. Both showed ^1H and ^{13}C nmr signals almost identical to those of falcarindiol 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 falcarindiol and C3'-OH of byakangelicin were not observed in spite that the

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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 falcarindiol is linked to the C3'-OH of byakangelicin. The down-field shift of the signal of the counterpart carbon (C8") in the falcarindiol 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'.

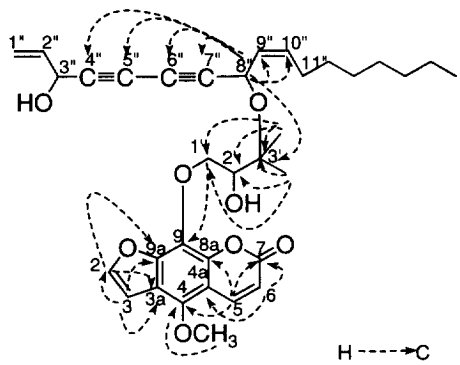

Figure 1: ^{1}H-^{13}C Long-range Correlations in **1**

Japoangelols C (**3**)[8] and D (**4**)[9] were obtained as yellow syrups with a molecular formula $C_{33}H_{38}O_7$. Both showed the ^{1}H and ^{13}C nmr signals nearly identical to those of falcarindiol 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 falcarindiol 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 falcarindiol 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}, μg/ml) against MK-1 cell growth of the acetylenic compounds isolated were as follows: panaxynol (0.3), falcarindiol (3.2), (9Z)-1,9-heptadecadiene-4,6-diyne-3,8,11-triol (2.2), 8-acetoxyfalcarinol (3.2), japoangelols A (8.5), B (7.2), C (7.4), and D (8.4).

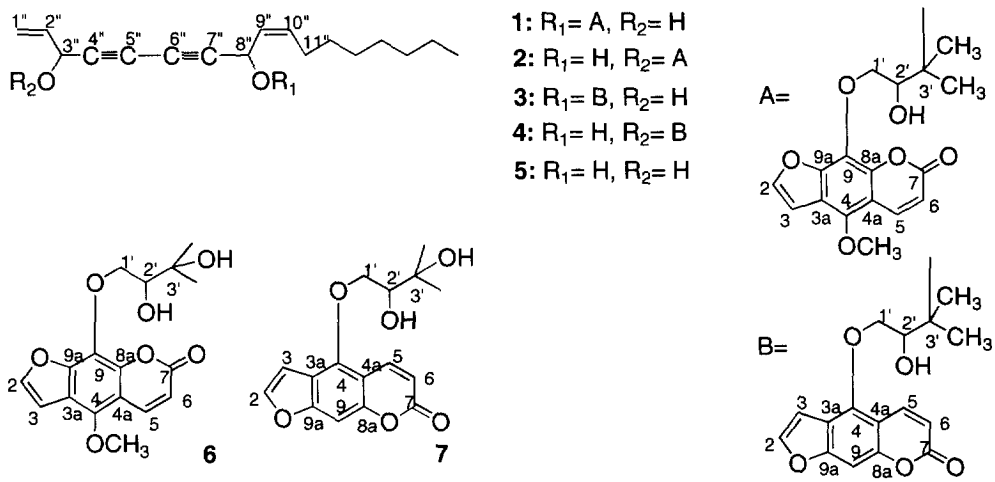

Figure 2

TABLE I. ^{1}H-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		

References and Notes

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5. Ikeda, R.; Nagao, T.; Okabe, H.; Nakano, Y.; Matsunaga, H.; Katano, M.; Mori, M., *Chem. Pharm. Bull., submitted.*
6. $[\alpha]_D^{29}$ +111.8° (*c*= 0.50, $CHCl_3$). $C_{34}H_{40}O_8$ [$(M+Na)^+$ *m/z* 599.2635, calcd. 599.2621].
7. $[\alpha]_D^{29}$ +138.4° (*c*= 0.17, $CHCl_3$). $C_{34}H_{40}O_8$ [$(M+Na)^+$ *m/z* 599.2635, calcd. 599.2621].
8. $[\alpha]_D^{29}$ +117.5° (*c*= 0.19, $CHCl_3$). $C_{33}H_{38}O_7$ [$(M)^+$ *m/z* 546.2633, calcd. 546.2617].
9. $[\alpha]_D^{29}$ +219.4° (*c*= 0.16, $CHCl_3$). $C_{33}H_{38}O_7$ [$(M+Na)^+$ *m/z* 569.2502, calcd. 569.2515].