

## Two New Lignans from *Lindera obtusiloba* Blume

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Two new furanolignans (**3**, **5**), together with three known lignans (**1**, **2**, **4**), were isolated from the stem of *Lindera obtusiloba* (Lauraceae). The structures of the compounds were determined as actifolin (**1**), pluviatilol (**2**), 5,6-dihydroxymatairesinol (**3**), (+)-syringaresinol (**4**), and (+)-9'-O-trans-feruloyl-5,5'-dimethoxyariciresinol (**5**) on the basis of physicochemical and spectroscopic evidences. Compounds **1**, **2**, **3**, and **5** showed cytotoxicity against a small panel of human tumor cell lines with ED<sub>50</sub> values of 3.40~19.27 µg/ml.

**Key words** : *Lindera obtusiloba*, Lauraceae, Cytotoxicity, Lignan, Actifolin, Pluviatilol

### INTRODUCTION

*Lindera obtusiloba* Blume (Lauraceae) which is widely distributed in Korea has been used as chinese medicine for the treatment of fever, abdominal pain, and extravasation (Yook, 1989). Phytosterols (Komae *et al.*, 1972) and obtusilactone derivatives have been isolated from this plant (Niwa *et al.*, 1975a, 1975b).

In a search for plant-derived bioactive compounds, the methanol extracts of *Lindera obtusiloba* Blume (Lauraceae) was investigated. The solvent fractionation and repeated column chromatographic separation of the MeOH extract resulted in the isolation of five lignans (**1-5**). The compounds exhibited cytotoxic activity against cultured human tumor cell lines. The present paper describes isolation, structural characterization and cytotoxicity of these compounds.

### MATERIALS AND METHODS

#### General experimental procedures

Melting points were measured on a Gallenkamp melting point apparatus (uncorr). <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker AMX 500 or Varian UNITY INOVA-500 spectrophotometer. IR spectra were measured on Nicolet model 205 FT-IR spectro-photometer. EIMS spectrum was obtained on a VG70-VSEQ mass spectro-

meter (VG Analytical, UK) and ESMS (electrospray mass) was measured on Quattro II mass spectrometer (Micro Mass, UK). TLC plates was used on precoated Si gel F<sub>254</sub> plates and RP-18 F<sub>254s</sub> plates (Merck). The open column

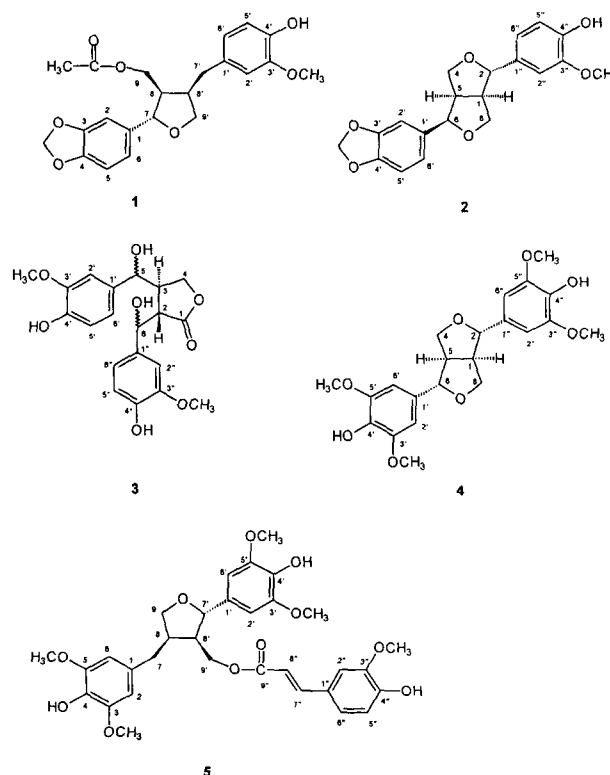


Fig. 1. Structures of compounds 1-5

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chromatographies were carried on Si gel 60 (Merck, 230~400 mesh) or Lichroprep RP-18 (Merck, 40~63  $\mu\text{m}$ ). prep. HPLC was JAI LC 908 model (Japan analytical instrument) equipped with refractive index detector and UV detector and JAIGEL 1H (20 $\times$ 900 mm) and 2H (20 $\times$ 900 mm) gel permeation column eluted with chloroform. Analytical grades of all other chemicals and solvents were used without further purification.

### Plant materials

*Lindera obtusiloba* was collected in Suwon, Kyunggi-Do, Korea, in September 1997. A voucher specimen (SKK-97-001) is deposited in College of Pharmacy, Sungkyunkwan University.

### Test for cytotoxicity

The screening test for cytotoxic activity was performed

using sulforhodamin B bioassay (SRB) (Skehan *et al.*, 1990). The cytotoxicities of the compounds measured against five human tumor cells, A549 (non small cell lung cancer), SK-OV-3 (ovarian cancer), SK-MEL-2 (skin cancer), XF498 (CNS cancer) and HCT15 (colon cancer).

### Extraction, separation, and purification

The dried and chopped stems of *Lindera obtusiloba* (5.8 kg) were extracted two times with MeOH for a week at room temperature. After this extraction, the residual material was successively extracted with MeOH for 5 hours at 50°C and followed by concentration *in vacuo*. The MeOH extract (200 g) was suspended in H<sub>2</sub>O and successively partitioned with n-hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc and BuOH. The concentrated extract (10 g) of CH<sub>2</sub>Cl<sub>2</sub> soluble portion was subjected to column chromatography over SiO<sub>2</sub> (350 g) eluting sequentially with hexane

**Table I.** NMR data of compounds **1, 2**, and **4** (CDCl<sub>3</sub>, <sup>1</sup>H: 500MHz, <sup>13</sup>C: 125MHz)

1		2		4			
<sup>1</sup> H	<sup>13</sup> C	<sup>1</sup> H	<sup>13</sup> C	<sup>1</sup> H	<sup>13</sup> C		
1	137.24	1	2.90 m	55.23	1	3.10 m	55.05
2	6.666.85	2	4.41 d (7.5)	88.34	2	4.73 d (4.5)	86.77
3	148.53	4	3.303.33 m	71.64	4	3.90 m	72.51
4	147.19		3.86 m			4.29 dd	
5	6.666.85	5	3.303.33 m	50.86		(9.0 7.0)	
6	6.666.85	6	4.85 d (6.0)	82.74	5	3.10 m	55.05
7	4.77 d (6.5)	8	3.85 dd	70.31	6	4.73 d (4.5)	86.77
8	2.52 m		(9.5, 6.5)		8	3.90m	72.51
9	4.17 dd		4.12 dd			4.29 dd	
	(11, 7.5)		(9.5, 1.0)			(9.0 7.0)	132.78
	4.35 dd	1'		132.98	1'		103.37
	(11.0, 7.0)	2'	6.806.91	109.27	2'	6.59 s	147.85
1'		3'		147.26	3'		134.97
2'	6.666.85	4'		146.04	4'		147.85
3'		5'	6.806.91	114.93	5'		103.37
4'		6'	6.806.91	119.34	6'	6.59 s	132.78
5'	6.666.85	1''		133.70	1''		103.37
6'	6.666.85	2''	6.806.91	107.10	2''	6.59 s	147.85
7'	2.52 m	3''		148.33	3''		134.97
	2.82 dd	4''		147.41	4''		147.85
	(13.5, 5.0)	5''	6.806.91	108.83	5''		103.37
8'	2.71 m	6''	6.806.91	119.90	6''	6.59 s	57.06
9'	3.73 dd	OCH <sub>2</sub> O	5.97 s	101.66	OMe	3.89 s	
	(9.0, 7.0)	OMe	3.91 s	56.64	OH	5.52 br.s	
	4.06 dd	OH	5.60 br.s				
	(9.0, 7.0)						
O=CMe	2.04 s						21.56
OCH <sub>2</sub> O	5.96 s						101.70
OMe	3.89 s						56.61
OH	5.50 br.s						
O=C							171.60

Values in parentheses are coupling constants in Hz.

**Table II.** NMR data of compounds **3** and reference compound **3a**

<b>3<sup>a)</sup></b>			<b>3a<sup>b)</sup></b>	
position	<sup>1</sup> H	<sup>13</sup> C	position	<sup>1</sup> H
1		177.61	1	
2	3.47 dd (9.0, 3.5)	54.02	2	2.66 dd (6.3, 3.0)
3	3.25 m	50.70	3	2.81 m
4 $\alpha$	4.07 dd (9.5, 5.0)	73.40	4	3.98 dd (9.0, 5.7)
4 $\beta$	4.35 dd, (9.5, 7.0)			4.38 dd (9.0, 7.8)
5	5.34 d (4.0)	84.08 <sup>c</sup>	5	2.26 dd (13.8, 7.8)
				2.46 dd (13.8, 7.8)
6	5.36 d (3.5)	85.29 <sup>c</sup>	6	5.29 br.s
1'		131.81	1'	
2'	6.80-6.94 m	108.48	2'	6.03 d (1.5)
3'		147.43	3'	
4'		146.05	4'	
5'	6.80-6.94 m	115.12	5'	
6'	6.80-6.94 m	118.72	6'	5.07 d (1.5)
1''		133.01	1''	
2''	6.80-6.94 m	108.82	2''	6.50 s
3''		147.64	3''	
4''		146.77	4''	
5''	6.80-6.94 m	115.42	5''	
6''	6.80-6.94 m	119.10	6''	6.50 s
OMe	3.91 s	56.72	OMe	3.84 s
			OCH <sub>2</sub> O	5.92 5.95 each s

Values in parentheses are coupling constants in Hz.

<sup>a)</sup> CDCl<sub>3</sub>, <sup>1</sup>H: 500MHz, <sup>13</sup>C: 125MHz

<sup>b)</sup> CDCl<sub>3</sub>, <sup>1</sup>H: 200MHz

<sup>c)</sup> Values can be interchanged.

/EtOAc (1 : 1, 1.2 L), hexane/EtOAc/MeOH (20 : 20 : 1, 1 L), hexane/EtOAc/MeOH (5 : 5 : 1, 1.5 L), EtOAc/MeOH (20 : 1, 2.7 L), EtOAc/MeOH (5 : 1, 1.5 L), and MeOH (1.5L). The eluates were grouped based on TLC pattern to yield fractions designated as LOM1~LOM7 : void volume (0.4 L), LOM1 (1 L), LOM2 (1 L), LOM3 (1.4 L), LOM4 (2.3 L), LOM5 (0.3 L), LOM6 (1.5 L), and LOM7 (1.5 L).

The LOM3 fraction (1.7 g) was chromatographed on silica gel column (250 g) with eluting solvents of hexane-EtOAc-MeOH (10 : 10 : 1) to give seven subfractions (LOM31~LOM37).

The LOM32 fraction (200 mg) was further subjected to silica gel column chromatography (40 g, hexane-EtOAc-MeOH (20 : 20 : 1)) and prep. HPLC to afford compound **1** (4 mg) and **2** (10 mg). The LOM33 fraction (400 mg) was rechromatographed over silica gel (n-hexane-EtOAc-MeOH = 10 : 10 : 1) to yield six subfractions (LOM331-LOM336). The LOM332 subfraction (51 mg) was purified by RP C-18 column chromatography (50% MeOH/H<sub>2</sub>O) and prep. HPLC to afford compound **3** (7 mg). The LOM335 subfraction (56 mg) was further purified by Sephadex LH-20 column chromatography (MeOH) and RP C-18 column chromatography (70%

MeOH/H<sub>2</sub>O) to afford compound **4** (20 mg). The LOM336 subfraction (15 mg) further purified with RP C-18 column chromatography (70% MeOH/H<sub>2</sub>O) and prep. HPLC to afford compound **5** (8 mg).

**Compound 1:** colorless oil; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 4.0 (c 0.02, CHCl<sub>3</sub>); EIMS (70 eV) m/z (rel. int.): 400 (M<sup>+</sup>, 100), 357 ([M-acetyl]<sup>+</sup>, 3), 340 (40), 217 (25), 203 (76), 190 (31), 176 (32), 164 (18), 149 (85), 137 (90); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): Table I; <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): Table I.

**Compound 2:** colorless gum; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 79.8 (c 0.16, MeOH); EIMS (70 eV) m/z (rel. int.): 356 ([M]<sup>+</sup>, 100), 205 (17), 203 (15), 163 (22), 161 (28), 151 (74), 149 (65), 137 (31), 135 (40), 131 (31), 124 (10), 122 (14); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): Table I; <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): Table I.

**Compound 3:** colorless gum; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 0.4 (c 0.1, CHCl<sub>3</sub>); ESMS m/z (rel. int.): 413 ([M+Na], 12), 290 (100); EIMS (70 eV) m/z (rel. int.): 373 (19), 372 (83), 287 (11), 259 (17), 191 (13), 163 (33), 151 (100), 137 (42), 131 (68); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): Table II; <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): Table II.

**Compound 4:** colorless needle (from EtOH); mp. 180 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 4.8 (c 0.32, CHCl<sub>3</sub>); EIMS (70 eV) m/z (rel. int.): 418 (M<sup>+</sup>, 100), 387 (6), 235 (10), 210 (17), 193

**Table III.** NMR data of compound **5** and reference compounds (**5a** and **5b**)

<b>5<sup>a)</sup></b>			<b>5a<sup>b)</sup></b>		<b>5b<sup>b)</sup></b>	
position	<sup>1</sup> H	<sup>13</sup> C	position	<sup>1</sup> H	position	<sup>1</sup> H
1		131.81				
2	6.42 s	106.02	2	6.41 s	2	6.70 s
3		147.79				
4		134.26				
5		147.79			5	6.86 d (7.8)
6	6.42 s	106.02	6	6.41, s	6	6.71 d (7.8)
7a	2.56 dd (13.5, 11.0)	34.56	7	2.56 dd (13.1, 11.2)	7	2.58 dd (13.7, 10.7)
7b	2.90 dd (13.5, 5.5)			2.92 dd (13.1, 10.7)		2.90 dd (13.7, 4.9)
8	2.77 m	43.48	8	2.75 m	8	2.77 m
9 $\beta$	3.78 t (8.5)	73.48	9	3.79 dd (8.8, 7.4)	9	3.79 dd (8.8, 8.6)
9 $\alpha$	4.10 dd (8.5, 7.0)			4.12 dd (8.8, 6.2)		4.12 dd (8.8, 6.3)
1'		133.98				
2'	6.60 s	103.39	2'	6.59 s	2'	6.60 s
3'		147.79				
4'		134.86				
5'		147.79				
6'	6.60 s	103.39	6'	6.59 s	6'	6.60 s
7'	4.82 d (7.0)	84.45	7'	4.82 d (6.3)	7'	4.83 d (6.3)
8'	2.66 m	49.86	8'	2.66 m	8'	2.66 m
9'a	4.34 dd (11.0, 7.5)	63.48	9'	4.33 dd (11.2, 7.3)	9'	4.34 dd (11.3, 7.3)
9'b	4.54 dd (11.0, 6.5)			4.52 dd (11.2, 7.2)		4.52 dd (11.3 7.2)
1''		127.42				
2''	6.99 d (3.0)	110.19	2''	7.00 s	2''	7.00 s
3''		147.51				
4''		148.90				
5''	6.93 d (8.0)	115.47	5''	6.92 d (7.8)	5''	6.93 d (7.8)
6''	7.05 dd (8.0, 3.0)	123.67	6''	7.06 d (7.8)	6''	7.06 d (7.8)
7''	7.51 d (16.0)	146.08	7''	7.00 d (15.8)	7''	7.51 d (15.8)
8''	6.23 d (16.0)	115.47	8''	6.22 d (15.8)	8''	6.23 d (15.8)
9''		167.69				
3, 5, 3', 5'-OMe	3.88 s	57.04	3, 3', 5, 5'-OMe	3.87, 3.88 s	3,3',5'- OMe	3.88 s
3''-OMe	3.95 s	56.72	3''-OMe	3.95 s	3''-OMe	3.96 s
4,4'-OH	5.405.45 br.s		4,4'-OH	5.40, 5.45 br.s	4,4'-OH	5.47, 5.51 br.s
4''-OH	5.88 br.s		4''-OH	5.88 br.s	4''-OH	5.90 br.s

Values in parentheses are coupling constants in Hz.

<sup>a)</sup>CDCl<sub>3</sub>, <sup>1</sup>H: 500 MHz, <sup>13</sup>C: 125 MHz.

<sup>b)</sup>CDCl<sub>3</sub>, <sup>1</sup>H: 400 MHz, <sup>13</sup>C: 100 MHz.

(28), 181 (69), 167 (57); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): Table I; <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): Table I

**Compound 5:** yellow gum; [ $\alpha$ ]<sub>D</sub><sup>20</sup> + 4.0 (c 0.12, MeOH); EIMS (70 eV) m/z (rel. int.): 596 (M<sup>+</sup>, 37), 402 (63), 315 (94), 235 (68), 194 (30), 181 (63), 167 (100); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): Table III; <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): Table III

## RESULTS AND DISCUSSION

Three known compounds, actifolin (**1**) (Tanaka *et al.*, 1989), pluviatilol (**2**) (Corrie *et al.*, 1970), and (+)-syringaresinol (**4**) (Deyama *et al.*, 1987) were identified by comparison of physicochemical data and spectral evidences (MS, <sup>1</sup>H- and <sup>13</sup>C-NMR, and <sup>1</sup>H-<sup>1</sup>H COSY) with those reported in the literatures. Actifolin (**1**) has been isolated from *Actinodaphne longifolia* (Tanaka *et al.*, 1989), and Pluviatilol (**2**) from *Xanthoxylum pluviatile* (Corrie *et al.*, 1970). However, **1** and **2** have not been

**Table IV.** Cytotoxicity of compounds **1-5**

cancer cell line compounds	ED <sub>50</sub> values <sup>a</sup>				
	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
<b>1</b>	12.16	16.38	12.80	14.33	10.86
<b>2</b>	19.27	21.84	14.91	18.04	15.27
<b>3</b>	16.39	9.86	3.40	15.36	5.62
<b>4</b>	>30.0	>30.0	>30.0	>30.0	>30.0
<b>5</b>	12.43	10.37	12.68	9.86	11.70

<sup>a</sup>ED<sub>50</sub> value of compound against each cancer cell line, which was defined as a concentration (μg/ml) that caused 50% inhibition of cell growth *in vitro*.

previously isolated from *Lindera* genus.

Compound **3** was obtained as colorless gum and afforded a quasimolecular ion [M+Na]<sup>+</sup> at *m/z* 413 in electrospray mass (ESMS). The ESMS and NMR data suggested the molecular formula to be C<sub>20</sub>H<sub>22</sub>O<sub>8</sub>. Six aromatic protons at δ 6.80–6.94 and two aromatic methoxyl groups at δ 3.91 in the <sup>1</sup>H-NMR spectrum showed a typical pattern of two 3-methoxy-4-hydroxy phenyl groups, which is a usual aromatic moiety in lignan. In the <sup>13</sup>C-NMR spectrum, besides two 3-methoxy-4-hydroxy phenyl groups, 6 carbon signals at δ 177.1 (carbonyl), 73.40, 84.08, 85.29 (oxygenated carbons), and δ 50.70, 54.02 (methine carbons) were also observed. In the <sup>1</sup>H-<sup>1</sup>H COSY spectrum, H-2 (δ 3.47) was correlated to H-3 (δ 3.25) and H-6 (δ 5.36), and H-3 signal (δ 3.25) was correlated to H-2 (δ 3.47), H-4 (δ 4.07 and δ 4.35) and H-5 (δ 5.34). Based on the evidences mentioned above, the structure of **3** was speculated to be 5,6-dihydroxymatairesinol. The *trans* junction of γ-lactone group is certain when the coupling constant (*J*<sub>2,3</sub>=9.0 Hz), the cross peak between H-2/H-4β (δ 4.35) in NOESY spectrum and reported data of lignans with the *trans* junction of γ-lactone ring were considered (Taufout *et al.*, 1984, Tanoguchi *et al.*, 1991). The skeleton of C<sub>2</sub>-C<sub>3</sub>-C<sub>6</sub> was determined to be the same to that of 5'-methoxypodorhizol (**3a**) (Tanoguchi *et al.*, 1991), by comparison of the coupling constants observed in the <sup>1</sup>H-NMR spectrum (Table II). Compared with chemical shifts of H-2 (δ 2.66), H-3 (δ 2.81) and H-5 (δ 2.26 and 2.46) of the reference compound **3a**, the downfield shifts of H-2 (δ 3.47), H-3 (δ 3.25) and H-5 (δ 5.34) of the compound **3** can be ascribed to the presence of OH group at C-5. But, the stereochemistry of OH groups at C-6 could not be determined by comparison of the <sup>1</sup>H-NMR data of 5'-methoxypodorhizol (Tanoguchi *et al.*, 1991) and 5-hydroxymatairesinol (Nishibe *et al.*, 1980). Thus, the structure of **3** was determined to be 5,6-dihydroxymatairesinol.

Compound **5** was obtained as a yellow gum, [α]<sub>D</sub> +4.0 (c 0.12, MeOH). Its molecular formula was established as C<sub>32</sub>H<sub>36</sub>O<sub>11</sub> by EIMS (*m/z* 596, M<sup>+</sup>) and NMR spectral data. The EIMS spectrum showed the presence of the feruloyl group at *m/z* 402. The <sup>1</sup>H-NMR spectra exhibited the presence of the *trans*-feruloyl moiety at δ

3.95 (3H, s), 6.23 (1H, d, *J*=16.0 Hz), 6.93 (1H, d, *J*=8.0 Hz), 6.99 (1H, d, *J*=3.0 Hz), 7.05 (1H, dd, *J*=8.0, 3.0 Hz), and 7.51 (1H, d, *J*=16.0 Hz). The <sup>13</sup>C-NMR spectrum showed the same moiety at 56.72, 167.69, 146.08, 115.47, 110.19, 115.47, 123.67, 127.42, 147.51, and 148.90. In addition, <sup>1</sup>H- and <sup>13</sup>C-NMR spectra exhibited the typical pattern of two 3,5-di-methoxy-4-hydroxy phenyl groups, which is also a usual aromatic moiety in lignan; in the <sup>1</sup>H-NMR spectrum showed the moiety at δ 3.88 (12H, s), 6.42 (2H, s) and 6.60 (2H, s), and the <sup>13</sup>C-NMR spectrum at 57.04, 103.39, 106.02, 131.81, 133.98, 134.26, 134.86, and 147.79. The <sup>1</sup>H-<sup>1</sup>H COSY spectrum exhibited the correlations of H-7' signal (δ 4.82) to H-8' (δ 2.66), H-8' signal to H-9' (δ 4.34 and 4.54) and H-8 (δ 2.77), and H-8 signal to H-7 (δ 2.56 and 2.90) and H-9 (δ 3.78 and 4.10). Compared with the chemical shifts of H-9' signals (δ 3.7–4.1) of 9'-hydroxyl-7',9'-epoxylignan (Kinjo *et al.*, 1991, Macrae *et al.*, 1985, Subbaraju *et al.*, 1991), the downfield shift of H-9' signals (δ 4.34 and 4.54) of compound **5** suggested the esterification at C-9'. The gross structure of **5** was, therefore, assigned as 9'-O-*trans*-feruloyl-5,5'-dimethoxylariciresinol. The NMR data of **5** were similar with those of (-)-9'-O-*trans*-feruloyl-5,5'-dimethoxylariciresinol (**5a**) (Hsiao *et al.*, 1995), except for the coupling constants of H-7b (*J*=13.5, 5.5 Hz for compound **5**, *J*=13.1, 10.7 Hz for **5a**) and [α]<sub>D</sub> values [+4.0 (c 0.12, MeOH) for **5**, -27.7 (c 0.007, MeOH) for **5a**].

The stereochemistry of H-7β, H-8α and H-8 were also confirmed in NOESY spectrum, which showed the cross peaks between H-7'/H-9 (δ 3.78), H-9'a and H-9'b, H-8'/H-8 and H-9α (δ 4.10), and H-8/H-9α (δ 4.10). From the above evidences, the comparisons of NMR data and [α]<sub>D</sub> values of (-)-9'-O-*trans*-feruloyl-5,5'-dimethoxylariciresinol (**5a**), (+)-9'-O-*trans*-feruloyl-5'-methoxylariciresinol (**5b**) (Hsiao *et al.*, 1995) and (+)-5,5'-dimethoxylariciresinol (Kinjo *et al.*, 1991), the whole structure of **5** was determined as (+)-9'-O-*trans*-feruloyl-5,5'-dimethoxylariciresinol.

As shown in Table IV, compounds **1**, **2**, **3**, and **5** showed weak cytotoxicity against five human tumor cells, A549 (non small cell lung cancer), SK-OV-3 (ovarian cancer), SK-MEL-2 (skin cancer), XF498 (CNS cancer) and

HCT15 (colon cancer).

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