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### Lignans from *Kadsura angustifolia*

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## LIGNANS FROM *KADSURA ANGUSTIFOLIA*

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A new dibenzocyclooctadiene lignan named angustifolin D (**1**) together with four known lignans: kadsulignan L (**2**), kadsulignan N (**3**), schisantherin P (**4**) and meso-dihydroguaiaretic acid (**5**) were isolated from the stems of *Kadsura angustifolia*. Their structures and stereochemistries were elucidated by spectral studies. Compounds **2** and **5** showed moderate platelet-activating factor (PAF) antagonistic activities with IC<sub>50</sub> values of  $2.6 \times 10^{-5}$  and  $4.1 \times 10^{-5}$  M, respectively.

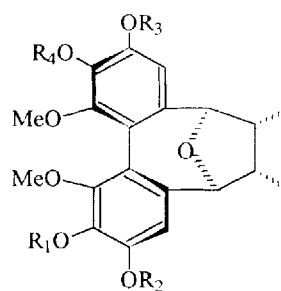
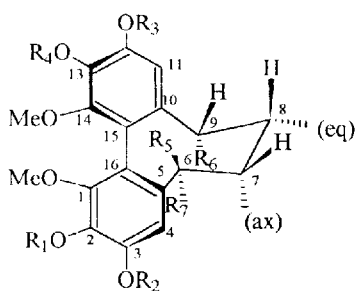
**Keywords:** Lignan; *Kadsura angustifolia*; Anti-PAF activities

Plants of Schisandraceae family are rich sources of dibenzocyclooctadiene lignans, which have been found to possess some beneficial pharmacological effects including antihepatitis, antitumor and anti-HIV activities [1-3]. In order to search for bioactive natural products, we have initiated chemical investigation on the stems of *Kadsura angustifolia* A.C. Smith in Schisandraceae family. This plant is an evergreen liana, indigenous to Yunnan province, China and used in local folk medicine to promote blood circulation

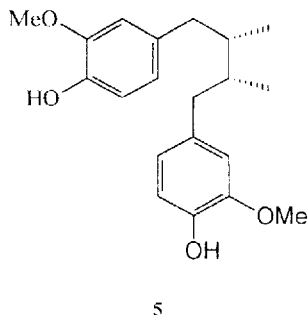
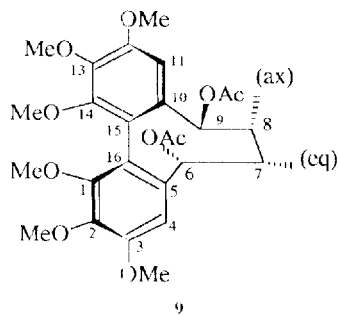
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and to treat fracture and irregular menstruation [4]. Literature survey failed to show any report on its chemical constituents. In our previous paper we reported the isolation and structure determination of three new dibenzocyclooctadiene lignans named angustifolin A–C [5]. Further investigation on the constituents of the same plant has led to the isolation of another new dibenzocyclooctadiene lignan named angustifolin D (**1**), along with four known lignans: kadsulignan L (**2**), kadsulignan N (**3**), schisantherin P (**4**) and meso-dihydroguaiaretic acid (**5**). This paper describes the isolation and structural elucidation of these lignans, and their platelet-activating factor (PAF) receptor binding bioassay results.



- |                     |  |                                       |                                     |          |                                      |   |
|---------------------|--|---------------------------------------|-------------------------------------|----------|--------------------------------------|---|
| <b>1</b> (dl-form). | R <sub>1</sub> ~R <sub>4</sub> = Me  | R <sub>5</sub> = R <sub>6</sub> = OAc | R <sub>7</sub> = H                  | <b>2</b> | R <sub>1</sub> = R <sub>2</sub> = Me | R <sub>3</sub> + R <sub>4</sub> = CH <sub>2</sub> |
| <b>4</b>            | R <sub>1</sub> + R <sub>2</sub> = R <sub>3</sub> + R <sub>4</sub> =CH <sub>2</sub> | R <sub>5</sub> = H                    | R <sub>6</sub> =R <sub>7</sub> = OH | <b>3</b> | R <sub>1</sub> ~R <sub>4</sub> = Me  |   |
| <b>6</b>            | R <sub>1</sub> + R <sub>2</sub> = R <sub>3</sub> + R <sub>4</sub> =CH <sub>2</sub> | R <sub>5</sub> =R <sub>6</sub> = OBen | R <sub>7</sub> = H                  |          |                                      |   |
| <b>7</b>            | R <sub>1</sub> + R <sub>2</sub> = R <sub>3</sub> + R <sub>4</sub> =CH <sub>2</sub> | R <sub>5</sub> = OBen                 | R <sub>6</sub> = OAc                |          |                                      |   |
| <b>8</b>            | R <sub>1</sub> + R <sub>2</sub> = R <sub>3</sub> + R <sub>4</sub> =CH <sub>2</sub> | R <sub>5</sub> = OBen                 | R <sub>6</sub> = OH                 |          |                                      |   |
|                     | R <sub>7</sub> = H   |                                       |                                     |          |                                      |   |



## RESULTS AND DISCUSSION

The ethanolic extract of the stems of *K. angustifolia* was fractionated into petroleum ether, ethyl acetate and *n*-butanol soluble fractions. The petroleum ether fraction was subjected to column chromatography on silica gel, followed by preparative TLC to yield **1**~**3** and **5**. The EtOAc fraction yielded **4** in the same way.

Angustifolin D (**1**), white amorphous powder,  $[\alpha]_D^{19}$  0 (*c* 0.21, MeOH), has the molecular formula  $C_{28}H_{36}O_{10}$  (HRMS). The UV spectrum showed maximum absorption at  $\lambda$  219 (log  $\epsilon$ , 4.64), 255 (log  $\epsilon$ , 4.17, sh) and 284 (log  $\epsilon$ , 3.30, sh) nm, indicating that **1** is a dibenzocyclooctadiene lignan [6]. The  $^1H$  NMR spectrum (Table I) showed signals for two aromatic protons ( $\delta$  6.69, 6.50 each 1H, s) and six methoxy groups ( $\delta$  3.62, 3.67, each 3H, s;  $\delta$  3.87, 3.90, each 6H, s) on two aromatic rings. Additionally, the signals at  $\delta$  0.90, 0.99 (each 3H, d,  $J=6.9$  Hz) in  $^1H$  NMR and  $\delta$  16.6 q, 29.7 q in  $^{13}C$  NMR (Table II) can be assigned to two adjacent methyls at C-7 and C-8 in *cis*-orientation, without any other geminal substituents at these two carbons [7]. The signals at  $\delta$  5.75 (1H, d,  $J=8.7$  Hz), and  $\delta$  5.83 (1H, d,  $J=4.8$  Hz) were assigned to two oxygen-bearing benzylic methines, suggesting two ester groups substituted at C-6 and C-9 respectively, similar to that of angustifolin A–C (**6**–**8**) [5]. The presence of two acetyl groups was deduced from NMR data ( $\delta_H$  1.57 s, 1.75 s;  $\delta_C$  20.7 q, 21.0 q, 170.0 s, 170.1 s) and EIMS data ( $m/z$  472 [ $M - CH_3COOH$ ] $^+$  and 412 [ $M - CH_3COOH \times 2$ ] $^+$ ). Angustifolin D showed no optical activity and no

TABLE I  $^1H$  NMR spectral data of compounds **1**–**4**\*

H	1	2	3	4
4	6.69s	6.43s	6.46s	6.90s
6	5.75d (8.7)	4.26d (6.9)	4.33d (6.9)	4.64d (0.8)
7	2.05m	2.58m	2.62m	2.10m
8	2.15m	2.02m	2.05m	2.00m
9	5.83d (4.8)	4.83s	4.94s	4.57s
11	6.50s	6.24s	6.32s	6.29s
Me-7	0.90d (6.9)	0.96d (6.8)	1.04d (7.0)	0.88d (7.3)
Me-8	0.99d (6.9)	0.96d (6.8)	1.04d (7.0)	1.17d (7.3)
OCH <sub>2</sub> O		5.86d (1)		5.98s (2H)
		5.80d (1)		5.94s (2H)
OMe	3.62s	3.39s	3.49s (6H)	3.85s
	3.67s	3.76s	3.83s (6H)	3.87s
	3.87s (6H)	3.82s	3.85s (6H)	
	3.90s (6H)	3.83s		
OAC	1.57s			
	1.75s			

\*  $J$  (Hz) in parentheses.

TABLE II  $^{13}\text{C}$  NMR spectral data of compounds 1–3

C	1	2	3
1	151.7s	154.7s	152.3s
2	141.6s	142.2s	141.4s
3	152.0s	135.5s	153.2s
4	110.6d	106.9d	106.8d
5	131.0s	140.5s	137.2s
6	79.9d	90.3d	90.5d
7	38.0d	37.1d	37.7d
8	39.8d	52.3d	52.4d
9	81.1d	89.8d	90.3d
10	134.2s	140.3s	140.5s
11	106.5d	99.6d	103.7d
12	152.8s	136.3s	154.8s
13	141.4s	148.1s	140.7s
14	152.3s	150.9s	151.4s
15	122.1s	118.5s	118.2s
16	123.6s	118.3s	119.9s
7-Me	16.6q	13.2q	13.6q
8-Me	29.7q	13.8q	14.1q
OMe	56.1q	55.6q	55.8q
	56.1q	59.6q	56.0q
	60.3q	60.6q	60.2q
	60.4q	60.7q	60.9q
	60.6q		61.0q
	60.9q		61.2q
OCH <sub>2</sub> O		100.6q	
OAc	170.1s		
	170.0s		
	21.0q		
	20.7q		

Cotton curve over 200 nm, leading to a conclusion that it is a racemate of **1** (S-biphenyl configuration) or **9** (R-biphenyl configuration). The  $J$  value (4.8 Hz) between H-8 and H-9 and the correlations between H-4 and H-6, and H-11 and H-9 in 2D-NOESY spectrum (Fig. 1) showed that two acetyl groups are in  $6\beta$  and  $9\alpha$  positions as to the S-biphenyl isomer **1**. On the basis of the results mentioned above, angustifolin D was thus determined as dl-form of **1** or **9**. The correlated peaks between H-4 and Me-7; H-4 and H-6 $\alpha$ ; Me-8 and H-9; and H-9 and H-11 in NOESY spectrum indicated that the cyclooctadiene ring was in a twist-boat–chair conformation.

The structures of kadsulignan L (**2**), kadsulignan N (**3**), schisantherin P (**4**) and meso-dihydroguaiaretic acid (**5**) were determined by various spectral studies. All known lignans **2–5** were first discovered to occur in *K. angustifolia*. Since lignans are known to possess significant PAF antagonistic activity [8], **2**, **3** and **5**, along with angustifolin B (**7**) and C (**8**) isolated previously were tested for inhibition of binding of  $^3\text{H}$ -PAF to

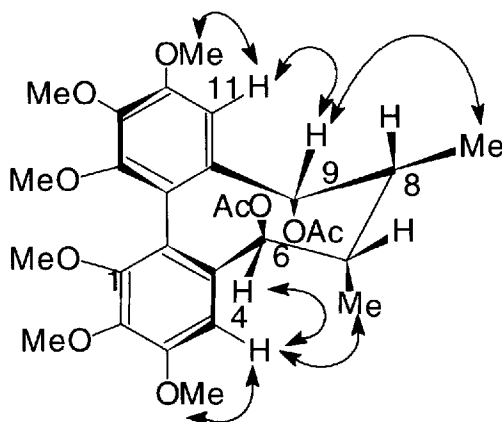


FIGURE 1 NOE correlations of angustifolin D (1).

rabbit platelets. Among these compounds, **2** and **5** demonstrated moderate inhibitory activities with 61% inhibition at 20  $\mu\text{g/ml}$  ( $\text{IC}_{50}$   $2.6 \times 10^{-5}$  M) for **2** and 56% inhibition at 20  $\mu\text{g/ml}$  ( $\text{IC}_{50}$   $4.1 \times 10^{-5}$  M) for **5** respectively, whereas **3**, **7** and **8** showed no PAF antagonistic activity (negative).

## EXPERIMENTAL SECTION

### General Experimental Procedures

IR spectra were recorded as KBr pellets on a Perkin-Elmer 599B spectrophotometer. UV spectra were measured on a Shimadzu UV-3000 spectrophotometer in absolute MeOH. MS were determined on Finnigan-450 and Varian Mat-711 mass spectrometers. NMR spectra were measured on a Bruker AM-400 with TMS as internal standard and  $\text{CDCl}_3$  as solvent. 2D-NOESY spectra were performed on a DRX500 spectrometer. Optical rotations were recorded with a Jasco Dip-181 spectropolarimeter. 200–300 mesh silica gel was used for CC and silica gel GF<sub>254</sub> for TLC (Qingdao Marine Chemical Factory).

### Plant Material

The stems of *K. angustifolia* A.C. Smith were collected in April 1993 in Xichou county of Yunnan province, China and identified by Prof. Quan-an Wu of Kunming Institute of Botany, Chinese Academy of Sciences, where a voucher specimen (No. 9304016) is deposited.

### Extraction and Isolation

The dried powdered stems of *K. angustifolia* (5.2 kg) were extracted with 95% EtOH at room temperature. The EtOH extract was evaporated in vacuum to yield a dark brown residue. H<sub>2</sub>O (2500 ml) was added to the residue, and the resulting solution was extracted with petroleum ether, EtOAc and *n*-BuOH successively. The petroleum ether extract was concentrated to give a brown mass (130 g), which was applied to a silica gel column, eluting with petroleum ether containing increasing amounts of Me<sub>2</sub>CO. The fractions obtained from petroleum-ether-acetone (10:1) elution were combined and subjected to repeated CC and preparative TLC to yield angustifolin D (**1**, 20 mg), kadsulignan L (**2**, 2.5 g), kadsulignan N (**3**, 2.8 g) and meso-dihydroguaiaretic acid (**5**, 515 mg). Similarly, the EtOAc extract (100 g) was subjected to a silica gel column, eluting with petroleum ether containing increasing amounts of Me<sub>2</sub>CO. The petroleum-ether-acetone (10:1) fractions were further purified by repeated CC to yield schisantherin P (**4**, 40 mg).

Angustifolin D (**1**) was obtained as white amorphous powder from petroleum ether, 20 mg,  $[\alpha]_D^{19}$  0 (*c* 0.21, MeOH); CD (*c* 0.018, MeOH): no Cotton curve over 200 nm; UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 219 (4.64), 255 (4.17, sh), 284 (3.30, sh) nm; IR  $\nu_{\max}$ : 1732, 1597, 1493, 1460 cm<sup>-1</sup>; EIMS  $m/z$  [M]<sup>+</sup> 532 (60), 472 (4), 412 (6), 373 (9), 342 (4), 279 (2), 233 (2), 83 (100); HRMS found  $m/z$  532.2307, calcd. for C<sub>28</sub>H<sub>36</sub>O<sub>10</sub> (532.2308); <sup>1</sup>H NMR data, see Table I; <sup>13</sup>C NMR data, see Table II.

Kadsulignan L (**2**) was obtained as prisms from Me<sub>2</sub>CO, 2.5 g, m.p. 151–153°C,  $[\alpha]_D^{24}$  +22.55 (*c* 0.70, MeOH); UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 203 sh (4.17), 227.5 (4.42), 289 (4.09) nm; IR  $\nu_{\max}$ : 1600, 1570, 1500, 1480 cm<sup>-1</sup>; EIMS  $m/z$ : [M]<sup>+</sup> 414 (100), 399 (7), 383 (13), 356 (12), 249 (15), 233 (17); <sup>1</sup>H NMR data, see Table I; <sup>13</sup>C NMR data, see Table II.

Kadsulignan N (**3**) was obtained as needles from MeOH, 2.8 g, m.p. 110–112°C,  $[\alpha]_D^{25}$  0 (*c* 0.50, MeOH), UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 204.5 sh (4.33), 255 (4.50), 285 (4.24) nm; IR  $\nu_{\max}$ : 1595, 1570, 1500, 1450 cm<sup>-1</sup>; EIMS  $m/z$  [M]<sup>+</sup> 430 (100), 415 (18), 399 (32), 360 (26), 356 (22), 249 (35); <sup>1</sup>H NMR data, see Table I; <sup>13</sup>C NMR data, see Table II.

Schisantherin P (**4**) was obtained as white amorphous powder from petroleum ether, 40 mg,  $[\alpha]_D^{25}$  +7.71 (*c* 0.30, MeOH), CD  $\Delta\epsilon$  (nm) in MeOH (*c* 0.00825): -12.84 (252.5), +8.25 (232), +11.00 (227), -4.48 (205); IR  $\nu_{\max}$ : 3442, 1619, 1500, 1477, 715 cm<sup>-1</sup>; EIMS  $m/z$  [M]<sup>+</sup> 416 (98), 398 (100), 380 (4), 360 (52), 328 (51), 313 (55), 233 (52), 180 (40); <sup>1</sup>H NMR data, see Table I.

Meso-dihydroguaiaretic acid (**5**) was obtained as colorless needles from MeOH, 515 mg, m.p. 85–86°C,  $[\alpha]_D^{25}$  0 (*c* 0.58, MeOH), UV (MeOH)  $\lambda_{\max}$  (log  $\epsilon$ ) 206 (4.64), 229 (4.14), 282 (3.82), 286 (3.77) nm; EIMS  $m/z$  [M]<sup>+</sup> 330 (55), 165 (8), 137 (100), 122 (23); <sup>1</sup>H NMR data, 6.84 (2H, d, *J* = 8 Hz), 6.67 (2H, dd, *J* = 8.0, 1.7 Hz), 6.63 (2H, d, *J* = 1.7 Hz), 5.62 (2H, br s, OH × 2), 3.84 (6H, s, OMe × 2), 2.74 (2H, dd, *J* = 13.5, 5.0 Hz, arom.-CH<sub>2</sub>), 2.30 (2H, dd, *J* = 13.5, 9.2 Hz, arom.-CH<sub>2</sub>), 1.76 (2H, m, CH × 2), 0.86 (6H, d, *J* = 6.7 Hz, Me × 2); <sup>13</sup>C NMR data, 16.15 (q, CH<sub>3</sub>), 38.85 (t, CH<sub>2</sub>), 39.11 (d, CH), 55.80 (q, OCH<sub>3</sub>), 111.54 (d, C-2), 114.00 (d, C-5), 121.68 (d, C-6), 133.71 (s, C-1), 143.58 (s, C-4), 146.33 (s, C-3).

### PAF Receptor Binding Assay

Binding of <sup>3</sup>H-PAF to rabbit platelets was carried out according to the method of Valone with some modifications. The reaction mixture consisted of 200  $\mu$ l of <sup>3</sup>H-PAF (0.6 nM, 60,000 dpm) with or without unlabeled PAF (500 fold of hot form), and 25  $\mu$ l of sample or control solution. The reaction mixture was incubated at room temperature for 1 h. The free and bound ligands were separated by filtration technique using Whatman GF/C glass fiber filters. The difference between total radioactivities of bound <sup>3</sup>H-PAF in the absence and presence of excess unlabeled PAF is defined as a specific binding of the radiolabeled ligand. In a set of experiments, <sup>3</sup>H-PAF (0.6 nM) is incubated with different concentrations of PAF receptor antagonist and the effect of the antagonist on the specific binding is expressed as percentage inhibition of the control. The IC<sub>50</sub> value was defined as the final concentration of the inhibitor required to block 50% of the specific <sup>3</sup>H-PAF binding to rabbit platelet receptors.

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