Kadsufolins A – D and Related Cytotoxic Lignans from *Kadsura oblongifolia*

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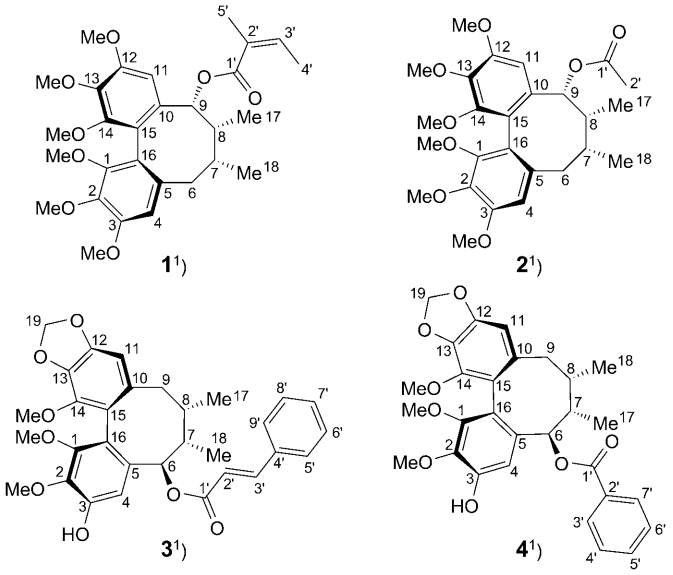
Kadsufolins A – D (**1** – **4**, resp.), four new dibenzocyclooctane-type lignans, were isolated from the roots and stems of *Kadsura oblongifolia*, together with eleven known lignans. Their structures and configurations were elucidated by spectroscopic methods including 2D-NMR techniques. The compounds were also evaluated for cytotoxic activity against human tumor cell lines A549 (lung carcinoma), DU145 (prostate carcinoma), KB (epidermoid carcinoma of the nasopharynx), and HCT-8 (ileocecal carcinoma). Kadsufolin A (**1**), kadsufolin D (**4**), angeloylbinankadsurin A, and heteroclitin B were found to show cytotoxic activities against A549, DU145, KB and HCT-8 with GI_{50} values of 5.1 – 20.0 μg/ml.

Introduction. – It is well-known that lignans, especially those of dibenzocyclooctane type, are principal bioactive constituents of the Schisandraceae medicinal plants, showing various beneficial activities such as antihepatotoxic, antilipid peroxidative, anti-HBV, anti-HIV, and antitumor-promoting effects, and cytotoxicity [1 – 7]. *Kadsura oblongifolia* MERR. (Schisandraceae) is a climbing plant distributed only in the southern of China. Its stems and roots have been used as a folk medicine for the treatment of cold, rheumatism, traumatic injury, stomachache [8], and cancers [9]. Several lignans [10] and flavonoids [11] have been recently isolated from the stems of *K. oblongifolia*; however, the bioactive constituents of this plant have never been reported. To elucidate the bioactive principles of this plant, phytochemical investigation on the stems and roots of *K. oblongifolia* was thus carried out, leading to the isolation of four new dibenzocyclooctane lignans, kadsufolins A – D (**1** – **4**, resp.), together with eleven known lignans, *i.e.*, kadsurarin, angeloylbinankadsurin A, schisantherin F, schisantherin K, heteroclitin B, kadsulignan L, kadsurin, angeloylbinankadsurin B, acetylbinankadsurin A, schizanrin F, and kadsulignan G. Here, we describe the isolation and structural elucidation of these compounds, as well as their cytotoxic activities against a panel of human tumor cell lines, including lung carcinoma (A549), prostate carcinoma (DU145), epidermoid carcinoma of the nasopharynx (KB), and ileocecal carcinoma (HCT-8).

Results and Discussion. – An EtOH extract of the stems and roots of *K. oblongifolia* was suspended in H_2O and partitioned with Et_2O. Repeated column chromatography (CC) of the Et_2O fraction, followed by preparative TLC, led to the



isolation of 15 lignans. The structures of the new compounds were determined by spectroscopic methods.

The UV spectra with absorption maxima at 215–221, 250–255 (sh), 277–288 (sh) nm, and the corresponding NMR spectra (*Tables 1* and *2*) indicated that **1**–**4** were all dibenzocyclooctane lignans [12].

Kadsufolin A (**1**) was obtained as colorless needles. The molecular formula was determined as $C_{29}H_{38}O_8$ by HR-EI-MS (*m*/*z* 514.2566 (M^+)). The ^{1}H-NMR spectrum (*Table 1*) showed the signals due to two secondary Me groups at δ(H) 0.98 (*d*, *J* = 6.7, 3 H) and 1.11 (*d*, *J* = 6.4, 3 H), assignable to the *cis*-oriented Me(18) and Me(17)[1]) groups, respectively [13]. *Multiplet* at δ(H) 2.04–2.16 (*m*, 2 H), which exhibited HMBCs with Me(18) (δ(C) 14.6) and Me(17) (δ(C) 19.7) (*Fig. 1*), was assigned to H–C(7) and H–C(8). The HMBCs of the six MeO signals at δ(H) 3.48, 3.54, 3.82, 3.86, 3.87, and 3.91 (6*s*) with the C-atom signals at δ(C) 151.1 (C(1)), 151.7 (C(14)), 139.9 (C(2)), 141.0 (C(13)), 151.6 (C(3)), and 152.6 (C(12)), respectively, revealed that these six MeO groups were all connected to the aromatic rings.

The IR spectrum indicated the presence of an α,β-unsaturated ester with a band at 1710 cm^{-1}. The EI-MS peaks at *m*/*z* 414 ([$M - C_4H_7COOH$]$^+$), 83 ([C_4H_7CO]$^+$), and 55 ([C_4H_7]$^+$) suggested the presence of an unsaturated acyl moiety at C(9), as confirmed by ^{1}H-NMR signals at δ(H) 1.27 (*s*, 3 H), 1.88 (*d*, *J* = 7.3, 3 H), and 5.91 (*q*, *J* = 7.3, 1 H), along with the corresponding ^{13}C-NMR signals (*Table 2*) at δ(C) 166.8 (C=O), 140.5, 127.0, 20.4, and 15.6. The HMBCs of H–C(9) (δ(H) 5.78) with the C=O (δ(C) 166.8) and the ROESY cross-peak for H–C(9) and H–C(11) revealed that it was an α-oriented angeloyl group located at C(9) [14–16]. The distance extracted from the

[1]) Arbitrary numbering. For systematic names, see *Exper. Part*.

Table 1. *^{1}H-NMR Data* (400 MHz) *of* **1**–**4**. In $CDCl_3$ at 27°; δ in ppm, J in Hz.

	1	**2**	**3**	**4**
H–C(4)	6.54 (*s*)	6.55 (*s*)	6.93 (*s*)	6.99 (*s*)
CH_2(6) or H–C(6)	2.56–2.68 (*m*, 2 H)	2.58–2.66 (*m*, 2 H)	5.60 (*s*, 1 H)	5.75 (*s*, 1 H)
H–C(7)	2.04–2.16 (*m*)	2.02–2.08 (*m*)	2.10–2.14 (*m*)	2.12–2.15 (*m*)
H–C(8)	2.04–2.16 (*m*)	2.02–2.08 (*m*)	2.00–2.10 (*m*)	2.17–2.19 (*m*)
H–C(9) or CH_2(9)	5.78 (*s*, 1 H)	5.70 (*s*, 1 H)	1.86–2.00 (*m*), 2.15–2.22 (*m*)	1.98–2.08 (*m*), 2.21–2.24 (*m*)
H–C(11)	6.58 (*s*)	6.51 (*s*)	6.49 (*s*)	6.50 (*s*)
Me(18)	1.11 (*d*, J = 6.4)	1.10 (*d*, J = 7.0)	0.78 (*d*, J = 6.7)	0.75 (*d*, J = 7.0)
Me(17)	0.98 (*d*, J = 6.7)	0.90 (*d*, J = 7.0)	1.00 (*d*, J = 7.0)	1.05 (*d*, J = 7.2)
MeO–C(1)	3.48 (*s*)	3.65 (*s*)	3.55 (*s*)	3.56 (*s*)
MeO–C(2)	3.82 (*s*)	3.85 (*s*)	3.92 (*s*)	3.87 (*s*)
MeO–C(3)	3.87 (*s*)	3.90 (*s*)	–	–
MeO–C(12)	3.91 (*s*)	3.89 (*s*)	–	–
MeO–C(13)	3.86 (*s*)	3.86 (*s*)	–	–
MeO–C(14)	3.54 (*s*)	3.52 (*s*)	3.78 (*s*)	3.78 (*s*)
CH_2(19)	–	–	5.97 (*s*)	5.97 (*s*)
HO–C(3)	–	–	5.80 (br. *s*)	5.77 (br. *s*)
AngO–C(9)	5.91 (*q*, J = 7.3, 1 H), 1.88 (*d*, J = 7.3, 3 H), 1.27 (*s*, 3 H)	–	–	–
AcO–C(9)	–	1.58 (*s*)	–	–
CinO–C(6)	–	–	7.63 (*d*, J = 16.0, 1 H), 6.45 (*d*, J = 16.0, 1 H), 7.48–7.52 (*m*, 2 H), 7.35–7.40 (*m*, 3 H)	–
BzO–C(6)	–	–	–	8.05 (*dd*, J = 8.2, 1.1, 2 H), 7.40–7.58 (*m*, 3 H)

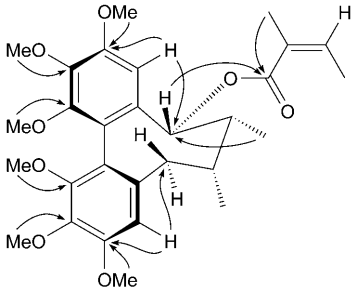


Fig. 1. *Key HMBC correlations* (H → C) *of* **1**

3D model was 2.4 Å from H–C(11) to H_β–C(9), which further confirmed the above deduction (*Fig. 2*).

The biphenyl unit in **1** was determined to have an (*S*)-configuration according to the CD spectrum with a negative *Cotton* effect at 252 nm and a positive *Cotton* effect at 216 nm [17]. The configuration was deduced by ROESY experiment (*Fig. 2*). The key

Table 2. *^{13}C-NMR Data* (100 MHz) *of* **1**–**4**. In $CDCl_3$ at 27°; δ in ppm.

C-Atom	**1**	**2**	**3**	**4**
1	151.1 (*s*)	150.8 (*s*)	150.0 (*s*)	150.0 (*s*)
2	139.9 (*s*)	139.6 (*s*)	138.3 (*s*)	138.4 (*s*)
3	151.6 (*s*)	151.8 (*s*)	147.9 (*s*)	148.0 (*s*)
4	110.3 (*d*)	110.0 (*d*)	109.0 (*d*)	109.1 (*d*)
5	132.9 (*s*)	133.0 (*s*)	133.5 (*s*)	133.4 (*s*)
6	38.7 (*t*)	38.7 (*t*)	75.7 (*d*)	76.0 (*d*)
7	34.7 (*d*)	35.0 (*d*)	40.3 (*d*)	38.9 (*d*)
8	41.8 (*d*)	41.9 (*d*)	38.9 (*d*)	40.7 (*d*)
9	82.4 (*d*)	81.9 (*d*)	34.6 (*t*)	34.9 (*t*)
10	136.2 (*s*)	136.0 (*s*)	137.5 (*s*)	137.5 (*s*)
11	106.7 (*d*)	106.4 (*d*)	103.3 (*d*)	103.3 (*d*)
12	152.6 (*s*)	152.5 (*s*)	149.2 (*s*)	149.2 (*s*)
13	141.0 (*s*)	141.0 (*s*)	135.5 (*s*)	135.5 (*s*)
14	151.7 (*s*)	151.4 (*s*)	141.0 (*s*)	141.0 (*s*)
15	123.5 (*s*)	121.4 (*s*)	119.8 (*s*)	119.8 (*s*)
16	121.4 (*s*)	123.4 (*s*)	120.7 (*s*)	120.8 (*s*)
17	14.6 (*q*)	14.7 (*q*)	21.8 (*q*)	21.8 (*q*)
18	19.7 (*q*)	19.4 (*q*)	8.5 (*q*)	8.6 (*q*)
19	–	–	100.9 (*t*)	101.0 (*t*)
*Me*O–C(1)	60.1 (*q*)	60.2 (*q*)	60.1 (*q*)	60.0 (*q*)
*Me*O–C(2)	60.5 (*q*)	60.6 (*q*)	60.9 (*q*)	60.1 (*q*)
*Me*O–C(3)	56.0 (*q*)	55.8 (*q*)	–	–
*Me*O–C(12)	55.7 (*q*)	55.9 (*q*)	–	–
*Me*O–C(13)	60.8 (*q*)	60.8 (*q*)	–	–
*Me*O–C(14)	60.5 (*q*)	60.5 (*q*)	60.0 (*q*)	60.9 (*q*)
1′	166.8 (*s*)	170.1 (*s*)	165.5 (*s*)	165.1 (*s*)
2′	127.0 (*s*)	20.7 (*q*)	118.5 (*d*)	130.6 (*s*)
3′	140.5 (*d*)	–	144.6 (*d*)	129.5 (*d*)
4′	15.6 (*q*)	–	134.3 (*s*)	128.3 (*d*)
5′	20.4 (*q*)	–	128.0 (*d*)	132.8 (*d*)
6′	–	–	128.8 (*d*)	128.3 (*d*)
7′	–	–	130.1 (*d*)	129.5 (*d*)
8′	–	–	128.8 (*d*)	–
9′	–	–	128.0 (*d*)	–

ROESY cross-peaks for Me(18) with H–C(4), Me(18) with H–C(6), Me(17) with H–C(9), and Me(17) with Me(18) indicated a twist-boat-chair (TBC) conformation for the cyclooctane ring [18]. These ROESY interactions were supported by the related distances (all less than 3.5 Å) extracted from the 3D model with a TBC conformation (*Fig. 2*). Thus, **1** was identified as (5*R*,6*R*,7*R*)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*][8]annulen-5-yl (2*Z*)-2-methylbut-2-enoate.

Kadsufolin B (**2**) was obtained as colorless needles. The molecular formula was assigned as $C_{26}H_{34}O_8$ by HR-EI-MS (*m*/*z* 474.2259 (M^+)). The ^{1}H- and ^{13}C-NMR spectra (*Tables 1* and *2*) of **2** were quite similar to those of **1** except for the characteristic signals due to an AcO group, instead of the angeloyl group in **1**.

The EI-MS peaks at *m*/*z* 414 ([M – MeCOOH]$^+$) and 60 (MeCOOH]$^+$) suggested the presence of an AcO group, as confirmed by the ^{1}H-NMR signals at δ(H) 1.58 (*s*,

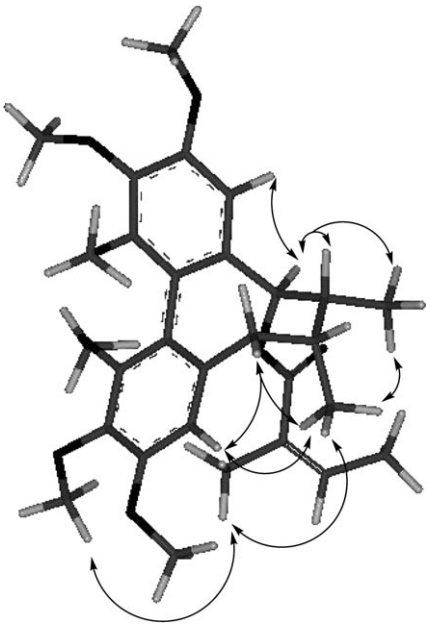


Fig. 2. *3D Structure and key ROESY correlations of* **1**

3 H), along with the corresponding ^{13}C-NMR signals (*Table 2*) at δ(C) 170.1 (C=O) and 20.7 (Me). The HMBCs of H–C(9) (δ(H) 5.70) with the C=O (δ(C) 170.1), and the ROESY cross-peak for H–C(9) and H–C(11) revealed that the AcO group was located at C(9) and α-oriented.

The configuration of **2** was determined as the same in **1**. Thus, **2** was identified as (5*R*,6*R*,7*R*)-5,6,7,8-tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo[*a*,*c*][8]-annulen-5-yl acetate.

Kadsufolin C (**3**) was obtained as a white solid with the molecular formula $C_{31}H_{32}O_8$ as revealed by HR-EI-MS (*m*/*z* 532.2100 (M^+)). The IR spectrum with bands at 3443 (OH), 1711 (ester C=O), and 1634 and 1495 (aromatic) cm^{-1} indicated that **3** was a dibenzocyclooctane lignan with OH and ester groups.

Comparison of the ^{1}H- and ^{13}C-NMR spectra of **3** with those of **1** (*Tables 1* and *2*) indicated that three of the MeO groups connected to the aromatic rings in **1** were replaced by a OH and a O–CH_2–O group in **3**, and the angeloyloxy group connected to cyclooctane ring in **1** was replaced by a cinnamoyloxy group in **3**. The ^{1}H-NMR spectrum of **3** displayed a *singlet* at δ(H) 5.80 (br. *s*, 1 H), which showed HMBC correlations with C(2) (δ(C) 138.4), C(3) (δ(C) 147.9), and C(4) (δ(C) 109.1) and assigned to HO–C(3); and a signal at δ(H) 5.97 (*s*, 2 H), characteristic for a O–CH_2–O group (δ(C) 100.9) connecting C(12) (δ(C) 149.2) and C(13) (δ(C) 135.5) (HMBCs as indicated in *Fig. 2*). Other partial structures could be assembled by the HMBC experiment (*Fig. 3*), where three MeO groups (δ(H) 3.55, 3.78, 3.92 (3*s*)) were assigned to C(1) (δ(C) 150.0), C(14) (δ(C) 141.0) and C(2) (δ(C) 138.3), respectively. The ^{1}H-NMR spectrum also indicated the presence of a cinnamoyloxy group with H-atom signals at δ(H) 6.45, 7.63 (2*d*, J = 16.0, each 1 H) and aromatic H-atom signals at

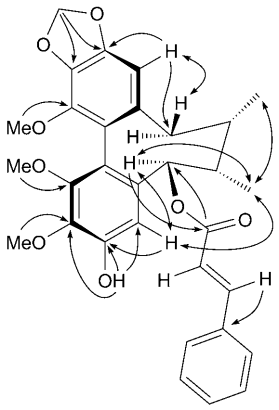


Fig. 3. *Key HMBC* (H → C) *and ROESY* (H ↔ C) *correlations of* **3**

δ(H) 7.35 – 7.40 (*m*, 3 H) and 7.48 – 7.52 (*m*, 2 H). The C-atom signals at δ(C) 118.5 (C(2′)), 144.6 (C(3′)), 128.0 (C(5′)), 128.8 (C(6′)), 130.1 (C(7′)), 128.8 (C(8′)), 128.0 (C(9′)), as well as a signal at δ(C) 134.3 (C(4′)), and a CO C-atom signal at δ(C) 165.5 (C(1′)) supported this deduction. Furthermore, the EI-MS peak at *m*/*z* 384 ($[M - C_6H_5C_2H_2COOH]^+$) confirmed the presence of a cinnamoyloxy group. The HMBC between H–C(6) (δ(H) 5.60) and δ(C) 165.5 (C(1′)), and the ROESY correlations between H–C(4) and H–C(6), and Me(18) and H–C(6) indicated that the cinnamoyloxy group was located at C(6) and β-oriented [16].

The CD spectrum of **3** showed a negative *Cotton* effect at 210 nm and positive *Cotton* effect at 250 nm, indicating that **3** had an (*R*)-biphenyl configuration [17]. The key ROESY cross-peaks between Me(18) and H–C(4), Me(18) and H–C(6), H–C(9) and H–C(11), and Me(18) and Me(17) indicated a TBC conformation of the cyclooctane ring (*Fig.* 3). Thus, **3** was determined as (5*R*,6*S*,7*S*)-5,6,7,8-tetrahydro-3-hydroxy-1,2,13-trimethoxy-6,7-dimethylbenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-*d*][1,3]-dioxol-5-yl (2*E*)-3-phenylprop-2-enoate.

Kadsufolin D (**4**) was obtained as white powder with the molecular formula $C_{29}H_{30}O_8$, according to HR-EI-MS (*m*/*z* 506.1939 (M^+)).

Comparison of the ^{1}H- and ^{13}C-NMR spectra of **4** with those of **3** (*Tables 1* and *2*) indicated that the cinnamoyloxy group in **3** was replaced by a benzoyloxy group in **4**. The EI-MS fragment-ion peak at *m*/*z* 384 ($[M - C_6H_5COOH]^+$) suggested the presence of a benzoyl (Bz) group in **4**. It was also evident from signals for a CO group at δ(C) 165.1 (C(1′)), a quaternary C-atom at δ(C) 130.6 (C(2′)), and aromatic CH groups at δ(C) 129.5 (C(3′), C(7′)), 128.3 (C(4′), C(6′)), and 132.8 (C(5′)), in addition to aromatic H-atom signals at δ(H) 8.05 (*dd*, *J* = 8.2, 1.1, H–C(3′), H–C(7′)) and 7.40 – 7.58 (*m*, H–C(4′), H–C(5′), H–C(6′)).

The configuration of **4** was determined as the same in **3**. Thus, **4** was determined as (5*R*,6*S*,7*S*)-5,6,7,8-tetrahydro-3-hydroxy-1,2,13-trimethoxy-6,7-dimethylbenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-*d*][1,3]dioxol-5-yl benzoate.

The known compounds were identified as kadsurarin [19], angeloylbinankadsurin A [20], schisantherin F [21], schisantherin K [22], heteroclitin B [23], kadsulignan L [24], kadsurin [19], angeloylbinankadsurin B [25], acetylbinankadsurin A [20],

schizanrin F [14], and kadsulignan G [26] by comparing their CD, UV, IR, and NMR data with those reported in the literature.

All isolates were screened in an *in vitro* cytotoxicity assay against a panel of human tumor cell lines including A549, DU145, KB, and HCT-8 according to a reported procedure [27]. The results are summarized in *Table 3*. Among them, kadsufolin D (**4**) was the most active compound, exhibiting strong cytotoxic activities against A549 and HCT-8 with GI_{50} values of 5.1 and 5.7 μg/ml, respectively. Kadsufolin A (**1**), heteroclitin B (**9**), and angeloylbinankadsurin A (**6**) showed cytotoxic activities against one or several cancer cell lines, with GI_{50} values in the range of 8.39 – 20.0 μg/ml (*Table 3*).

Table 3. *Cytotoxicity Data of the Active Compounds* (GI_{50} [μg/ml])

Compounds	Cell Lines			
	A549	DU145	KB	HCT-8
Kadsufolin A (**1**)	15.72 ± 0.7	10.55 ± 0.3	10.06 ± 0.3	20.00± 1.2
Kadsufolin D (**4**)	5.10 ± 0.4	–[a])	–	5.70 ± 0.4
Angeloylbinankadsurin A	> 20.00	> 20.00	14.62 ± 0.7	> 20.00
Heteroclitin B	8.61 ± 0.3	8.39 ± 0.6	8.92 ± 0.4	–
Paclitaxel[b])	0.003	0.003	0.002	0.21

[a]) –: Not tested. [b]) Positive control.

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Experimental Part

General. M.p.: *XT-4* Micro-melting point apparatus; uncorrected. Column chromatography (CC): silica gel (SiO_2; 200 – 300 and 300 – 400 mesh; *Qingdao Marine Chemical Factory*, Qingdao, P. R. China). Anal. and prep. TLC: silica-gel plates (*Yantai Institute of Chemical Technology*), with petroleum ether (PE)/acetone 5 : 1 or 3 : 1; visualization under UV light, and by spraying with 10% H_2SO_4, followed by heating. Optical rotations: *JASCO P-1020* polarimeter at r.t. UV Spectra: *Shimadzu UV-260* spectrophotometer in abs. MeOH. CD Spectra: *JASCO J-715* spectropolarimeter at r.t. IR Spectra: *Avatar 360 FT-IR ESP* spectrometer in CH_2Cl_2 or KBr. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-400* spectrometer in $CDCl_3$. MS: *Agilent 5973N* (for EI-MS) and *Waters Micromass GCT* mass spectrometers (for HR-EI-MS).

Computer Modeling (see *Fig. 2*). The modeling was performed with the SYBYL (v. 7.0) software on a *Silicon Graphics* workstation. The structure was simulated annealing and optimized subsequently with the *Tripos* force-field energy-minimizing program.

Plant Material. The stems and roots of *Kadsura oblongifolia* were collected in Xian-You County, Fujian Province, P. R. China, in July 2007. A voucher specimen (DFC-XY070701) is deposited with the Herbarium of Materia Medica, Department of Pharmacognosy, School of Pharmacy, Fudan University, Shanghai, P. R. China.

Extraction and Isolation. The air-dried and ground stems and roots (8.7 kg) of *K. oblongifolia* were extracted exhaustively with 95% aq. EtOH at r.t. The EtOH extract was concentrated *in vacuo* to yield a semi-solid (0.69 kg), which was suspended in H_2O (1000 ml) and extracted with Et_2O (7 × 2000 ml). The combined org. phase was concentrated to yield a residue (198 g), which was subjected to CC (SiO_2 (200–300 mesh, 2 kg, 10 × 120 cm); eluted successively with PE/acetone 20:1, 10:1, 8:1, 7:1, 5:1, 4:1, 2:1, 1:1, and acetone) to afford nine fractions, *Frs. 1–9*. *Fr. 2*, eluted with PE/acetone 10:1, was subjected to CC (SiO_2; PE/acetone 30:1, 20:1, 15:1, 10:1) to afford **1** (20 mg), kadsurin (300 mg), and heteroclitin B (10 mg). *Fr. 3*, eluted with PE/acetone 8:1, was subjected to CC (SiO_2; PE/acetone 20:1, 15:1, 10:1, 5:1) to yield **2** (5 mg), schisantherin F (50 mg), and then purified with prep. TLC (PE/acetone 5:1) to afford schisantherin K (3 mg). *Fr. 4*, eluted with PE/acetone 7:1, was subjected to CC (SiO_2; PE/acetone 20:1, 15:1, 10:1, 5:1) to yield angeloylbinankadsurin A (30 mg), and then purified with prep. TLC (PE/acetone 5:1 and 3:1) to afford **3** (3 mg), **4** (3 mg), and kadsulignan L (4 mg). *Fr. 5*, eluted with PE/acetone 5:1, was subjected to CC (SiO_2; PE/acetone 10:1, 8:1, 6:1, 4:1, 2:1) to yield kadsurarin (60 mg), angeloylbinankadsurin B (50 mg), and acetylbinankadsurin A (6 mg). *Fr. 6*, eluted with PE/acetone 4:1, was subjected to CC (SiO_2; PE/acetone 10:1, 8:1, 6:1, 4:1, 2:1) to yield schizanrin F (40 mg) and kadsulignan G (5 mg).

Kadsufolin A (=*(5*R,*6*R,*7*R*)-5,6,7,8-Tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo-[*a*,*c*]-[8]annulen-5-yl (2*Z*)-2-Methylbut-2-enoate*; **1**). Colorless needles (PE/acetone). M.p. 107–108°. $[\alpha]_D^{25} = -10.0$ ($c = 1.4$, MeOH). UV (MeOH): 216 (4.64), 252 (sh, 4.09), 287 (sh, 3.31). CD ($c = 3 \times 10^{-4}$ g/ml, MeOH): 216 (+45), 252 (−24). IR (KBr): 1710, 1595, 1491, 1406, 1332. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 431 (5.5), 414 (24.3), 83 (90.2), 55 (100). HR-EI-MS: 514.2566 (M^+, $C_{29}H_{38}O_8^+$; calc. 514.2567).

Kadsufolin B (=*(5*R,*6*R,*7*R*)-5,6,7,8-Tetrahydro-1,2,3,10,11,12-hexamethoxy-6,7-dimethyldibenzo-[*a*,*c*]-[8]annulen-5-yl Acetate*; **2**). Colorless needles (PE/acetone). M.p. 104–105°. $[\alpha]_D^{25} = -89.0$ (c = 1.0, MeOH). UV (MeOH): 215 (4.73), 250 (sh, 4.20), 286 (sh, 3.31). CD ($c = 3 \times 10^{-4}$ g/ml, MeOH): 210 (+36), 250 (−26). IR (CH_2Cl_2): 1736, 1596, 1490, 1456, 1239, 1103, 734. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 474 (61, M^+), 414 (100), 415 (29), 181 (20), 60 (15). HR-EI-MS: 474.2259 (M^+, $C_{26}H_{34}O_8^+$; calc. 474.2254).

Kadsufolin C (=*(5*R,*6*S,*7*S*)-5,6,7,8-Tetrahydro-3-hydroxy-1,2,13-trimethoxy-6,7-dimethylbenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-*d*][1,3]dioxol-5-yl (2*E*)-3-Phenylprop-2-enoate*; **3**). White solid. M.p. 90–92°. $[\alpha]_D^{25} = +33.5$ ($c = 0.3$, MeOH). UV (MeOH): 216 (4.69), 250 (sh, 4.28), 277 (sh, 4.32). CD ($c = 3 \times 10^{-4}$ g/ml, MeOH): 210 (−12), 250 (+10). IR (KBr): 3443, 2931, 1711, 1634, 1495, 1417, 1333, 993, 767. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 532 (16, M^+), 384 (100), 148 (67), 147 (84), 131 (95), 103 (79), 77 (50). HR-EI-MS: 532.2100 (M^+, $C_{31}H_{32}O_8^+$; calc. 532.2097).

Kadsufolin D (=*(5*R,*6*S,*7*S*)-5,6,7,8-Tetrahydro-3-hydroxy-1,2,13-trimethoxy-6,7-dimethylbenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-*d*][1,3]dioxol-5-yl Benzoate*; **4**). White powder. M.p. 91–93°. $[\alpha]_D^{25} = +42.7$ ($c = 0.3$, MeOH). UV (MeOH): 221 (4.77), 255 (sh, 4.15), 280 (sh, 3.70). CD ($c = 3 \times 10^{-4}$ g/ml, MeOH): 235 (−14), 252 (+49). IR (KBr): 3426, 2955, 1717, 1620, 1584, 1494, 1418, 1326, 935, 712. ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*, resp. EI-MS: 506 (29, M^+), 384 (21), 122 (4), 105 (100), 77 (39). HR-EI-MS: 506.1939 (M^+, $C_{29}H_{30}O_8^+$; calc. 506.1941).

Cytotoxicity Assay. Drug stock solns. were prepared in DMSO and stored at −70°. Upon dilution into culture medium, the final DMSO concentration was ≤1% (*v*/*v*) DMSO, a concentration without effect on cell replication. The human tumor cell line panel consisted of lung carcinoma (A549), prostate carcinoma (DU145), epidermoid carcinoma of the nasopharynx (KB), and ileocecal carcinoma (HCT-8). Cell culture and other procedures were the same as those reported in [27]. In brief, tumor cells were incubated at 37° for 72 h in the presence of various concentrations (≤20 μg/ml) of compounds from DMSO-diluted stock solns. The GI_{50} values, the compound concentrations resulting in 50% growth inhibition, were obtained from dose–response data. Each test was performed three times, and then the mean and standard deviation were calculated.

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