Interiotherins C and D, Two New Lignans from *Kadsura interior* and Antitumor-Promoting Effects of Related Neolignans on Epstein−Barr Virus Activation

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Two new lignans, interiotherins C (**1**) and D (**2**), together with the known compounds interiorin (**3**), heteroclitin F (**4**), neokadsuranin (**5**), heteroclitin D (**6**), kadsurin (**7**), gomisin A (**8**), schisandrin C (**9**), interiotherin A (**10**), angeloylgomisin R (**11**), gomisin G (**12**), interiotherin B (**13**), and gomisin C (**14**), were isolated from the stems of *Kadsura interior*. The structures and stereochemistries of the new compounds were determined from mass, CD, and NMR spectral data. Fourteen neolignans were screened as potential antitumor promoters by examining their ability to inhibit Epstein−Barr virus early antigen (EBV-EA) activation (induced by 12-*O*-tetradecanoylphorbol-13-acetate) in Raji cells. Neokadsuranin (**5**) and schisandrin C (**9**) were the most potent compounds. These data suggest that some neolignans might be valuable antitumor promoters or chemopreventors.

The stems of *Kadsura interior* A. C. Smith (Schisandraceae), a plant indigenous to southern China, are the main botanical components of the Chinese medicinal herb Ji-Xue-Teng.[1,2] An extract of these plant stems is used to prepare the Chinese medicine Fufang Jixueteng Gao, which is prescribed to treat menstrual irregularities, blood deficiencies, and other feminine disorders.[3] In previous papers,[4,5] we reported that several dibenzocyclooctadiene lignans from *Kadsura* species showed significant inhibitory activity in vitro against HIV replication in H9 lymphocytes. Dibenzocyclooctadiene lignans are also known to have potent antioxidant activity[6,7] and, consequently, might also demonstrate antitumor-promoting activities. Fractionation of ethanolic extracts from the stem bark of *K. interior* collected during a different season from the prior study led to the isolation and identification of two new neolignans, interiotherins C (**1**) and D (**2**), along with the known compounds interiorin (**3**), heteroclitin F (**4**), and neokadsuranin (**5**). Previously, heteroclitin D (**6**), kadsurin (**7**), gomisin A (**8**), schisandrin C (**9**), interiotherin A (**10**), angeloylgomisin R (**11**), gomisin G (**12**), interiotherin B (**13**), and gomisin C (**14**) were isolated.[4,5] Neokadsuranin (**5**) and schisandrin C (**9**) showed potent inhibitory effects on EBV-EA activation. We report herein on the structural elucidation of **1** and **2** and the results of primary screening for the inhibitory effects of 14 dibenzocyclooctadiene neolignans (**1**−**14**) on EBV-EA activation.

Results and Discussion

Interiotherin C (**1**), obtained as colorless needles, has the molecular formula $C_{30}H_{36}O_{10}$ as determined by HREIMS (*m*/*z* 556.2307). The UV spectrum of **1** showed maximum absorption at 217, 260, and 285 nm, indicating that **1** is a dibenzocyclooctadiene lignan.[8] The IR spectrum showed the presence of both α,*β*-unsaturated and saturated ester (1708 and 1741 cm^{-1}) groups.

The ^1H NMR spectrum of **1** was similar to that of acetylschisantherin L,[9] showing signals due to two secondary methyl groups (*δ* 0.94 and 1.03, 3H each, d, $J = 7.0$ Hz), assignable to CH_3-7 and CH_3-8 groups, respectively; one methylenedioxy moiety (*δ* 5.95, 2H, s); four methoxy groups (*δ* 3.58, 3.78, 3.88, 3.90, 3H, each, s) on two aromatic rings; an acetyl group (*δ*1.59, 3H, s); and an angeloyl group (*δ* 1.50, 3H, br s, *δ* 1.86, 3H, dq, $J = 7.0$, 1.0 Hz, 5.98, 1H, q, $J = 7.0$ Hz). Multiplet signals (*δ* 2.12 and 2.22, 1H each, m), which exhibited $^1H-^1H$ correlation with the two secondary methyls (*δ* 0.94 and 1.03), respectively, were assigned to H-7 and H-8. Doublets at *δ* 5.84 (1H, d, $J = 7.5$ Hz), which was correlated with the signal at *δ* 2.12, and at *δ* 5.73 (1H, d, $J = 3.5$ Hz), which was correlated with the multiplet at *δ* 2.22, were assigned to the benzylic oxymethines (H-6α and H-9*β*, respectively). The latter signal (*δ* 5.73, H-9*β*) was also correlated with the aromatic signal at *δ* 6.44 (H-11), possibly by a long-range coupling, which has also been observed in other similar compounds.[7] The coupling constants of H-6α and H-9*β* are consistent with their stereochemical assignments. Comparing the ^1H NMR spectrum of **1** with that of acetylschisantherin L revealed that **1** has one fewer methylenedioxy moiety and two more methoxy groups than acetylschisantherin L, which indicated that one methylenedioxy moiety was replaced by two methoxy groups on the aromatic ring. In the NOESY spectrum of **1** (Figure 2), CH_3O-14 (*δ* 3.78) was established by correlations with the C-12, 13 methylenedioxy group (*δ* 5.95), the α-methyl (*δ* 1.50) of the C-6*β* angeloyl group, and the CH_3O-1 (*δ* 3.58). The CH_3O-2 group (*δ* 3.88) displayed cross-peaks with both CH_3O-1 (*δ* 3.58) and the acetoxy methyl signal (*δ* 1.59), indicating that the acetyl group was located at C-9. The substituent positions and stereochemical assignments in the cyclooctane ring were strengthened by the correlations of the aromatic H-4 (*δ* 6.71) with CH_3O-3 (*δ* 3.90), H-6α (*δ* 5.84), and CH_3-7 (*δ*

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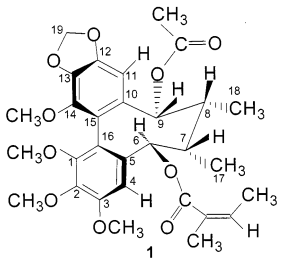

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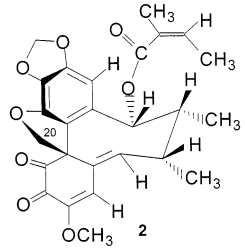

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Figure 1. Structures of **1** and **2**.

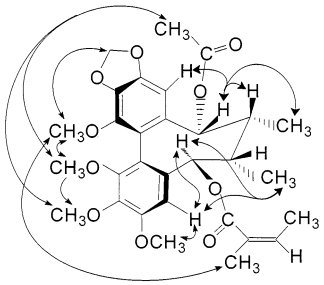

Figure 2. Key NOE correlations of **1**.

0.94) [which was also correlated with H-6α (δ 5.84)] and of H-11 (δ 6.44) with H-9β (δ 5.73) [which was further correlated with H-8β (δ 2.22) and CH_3-8 (δ 1.03)].

Interiotherin C (**1**) and acetylschisantherin L have similar CD spectra with a positive Cotton effect at 235 nm and a negative Cotton effect at 255 nm, indicating that both compounds possess an *S*-biphenyl configuration.[9] The absolute structure of interiotherin C was thus elucidated as **1**.

Interiotherin D (**2**), obtained as yellow prisms, had the molecular formula $C_{26}H_{26}O_8$ as determined by HREIMS (*m*/*z* 466.1628). Its CD spectral features together with a characteristic AB quartet signal at δ 4.84, 4.40 in the ^{1}H NMR spectrum and a quaternary carbon at δ 66.7 (s) in the ^{13}C NMR spectrum suggested that compound **2** is a dibenzocyclooctadiene lignan with a spirobenzofuranoid skeleton.[10] The ^{1}H NMR spectrum showed the presence of two secondary methyl groups (δ 1.02, 1.04, 3H each, d, J = 6.0 Hz), assignable to CH_3-7 and CH_3-8 groups, respectively; one methylenedioxy moiety (δ 6.02, 2H, AB, J = 17.0, 1.5 Hz); one methoxy group (δ 3.80, 3H, s) on an aromatic ring; and an angeloyl group (δ 1.63, 3H, m, δ 1.78, 3H, m). Multiplet signals (δ 3.03 and 1.88, 1H each, m) that were correlated (^{1}H−^{1}H) with the two secondary methyls were assigned to H-7 and H-8, respectively. The doublet at δ 5.82 (1H, d, J = 2.5 Hz), which correlated with the multiplet at δ 1.88, was assigned to the benzylic oxymethine (H-9β), and the doublet at δ 5.83 (1H, d, J = 6.5 Hz), which correlated with the multiplet signal at δ 3.03, was assigned to the H-6 olefinic proton. The aromatic methylenedioxy moiety was located at C-12 and C-13, and the angeloyl group was assigned as C-9α. The ^{1}H NMR spectral patterns were similar to those of heteroclitin E.[11] However, the hydroxyl and one methoxy group in the latter

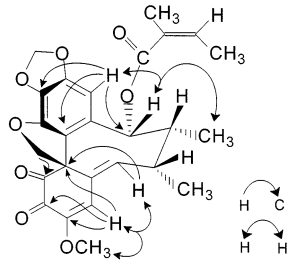

Figure 3. Long-range HETCOR and NOE correlations of **2**.

Table 1. ^{13}C NMR Data of Compounds **1** and **2** ($CDCl_3$)

carbon	**1**	**2**
1	151.5 s	189.2 s
2	141.2 s	175.8 s
3	151.8 s	151.0 s
4	110.4 d	126.1 d
5	131.3 s	150.6 s
6	80.7 d	140.7 d
7	38.7 d	30.5 d
8	38.7 d	43.9 d
9	80.7 d	79.2 d
10	133.1 s	130.6 s
11	102.2 d	101.9 d
12	148.6 s	129.5 s
13	135.9 s	132.9 s
14	141.7 s	142.8 s
15	121.1 s	118.8 s
16	121.1 s	66.7 s
17	15.6 q	19.5 q
18	19.9 q	11.0 q
19	101.0 t	102.3 t
20		79.9 t
CH_3O	56.0 q, 59.3 q	55.7 q
	60.2 q, 60.6 q	
Ang C=O	166.7 s	167.1 s
α-CH_3	20.7 q	20.3 q
β-CH_3	15.6 q	15.6 q
α-C	127.8 s	127.7 s
β-C	138.6 d	137.5 d
Ac C=O	170.0 s	
CH_3	20.7 q	

compound were replaced by an olefinic proton and a carbonyl group in **2**. A long-range HETCOR experiment showed that the olefinic H-6 was correlated with C-16 and the aromatic H-4 was correlated with C-2 and C-3 (Figure 3). In the NOESY spectrum of **2** (Figure 3), H-4 showed cross-peaks with CH_3O-3, as well as with H-6. These data indicated that the two carbonyl groups can be assigned to C-1 and C-2 and the methoxy group can be assigned to C-3. Molecular mechanics calculations indicated a distance of 2.41 Å between H-6 and H-4, which is consistent with the observed cross-peak between H-6 and H-4 in the NOESY spectrum. The NOESY spectrum also showed H-9 was correlated with H-11 and CH_3-8, suggesting that H-9 was β-oriented. The coupling constants of the olefinic H-6 and H-9β were 6.5 and 2.5 Hz, respectively, which indicated that H-7 and H-8 had β-orientations. The ^{1}H−^{1}H COSY and HETCOR spectra were used to assign all proton resonances, and long-range HETCOR for all carbon resonances as listed in Table 1. Figure 3 summarizes the latter correlations. The structure of **2** was assigned as shown and is compatible with all ^{1}H and ^{13}C NMR data.

The primary screening used a short-term in vitro assay on EBV-EA activation. Table 2 lists the inhibitory effects of **1**−**14** on the EBV-EA activation induced by TPA and the associated viability of Raji cells. In this assay, all compounds showed inhibitory effects on EBV-EA activation without cytotoxicity on Raji cells. As shown in Table 2, neokadsuranin (**5**) and schisandrin C (**9**) showed potent

Table 2. Relative Ratio[a] of EBV-EA Activation with Respect to Positive Control (100%) in the Presence of the Lignans **1**−**14**

	concentration (mol ratio/TPA)[b]			
compound	1000	500	100	10
1	16.0 ± 0.6 (60)	59.0 ± 1.6	78.9 ± 2.2	100 ± 0.5
2	11.5 ± 0.5 (60)	55.8 ± 1.7	75.0 ± 2.3	94.8 ± 0.4
3	13.5 ± 0.6 (60)	52.0 ± 1.1	77.4 ± 1.9	100 ± 0.4
4	16.5 ± 0.6 (60)	58.9 ± 1.0	82.4 ± 1.9	100 ± 0.2
5	4.7 ± 0.4 (70)	51.6 ± 1.1	72.9 ± 2.3	92.6 ± 0.4
6	9.4 ± 0.5 (70)	54.7 ± 1.2	76.2 ± 2.4	100 ± 0.5
7	15.0 ± 0.7 (60)	58.3 ± 1.3	79.9 ± 2.0	100 ± 0.3
8	7.1 ± 0.4 (70)	52.5 ± 1.4	78.3 ± 2.4	96.6 ± 0.4
9	2.6 ± 0.2 (70)	50.7 ± 1.1	73.6 ± 2.1	92.1 ± 0.4
10	18.3 ± 1.0 (60)	60.1 ± 1.5	85.7 ± 2.0	100 ± 0.2
11	10.6 ± 0.4 (60)	55.6 ± 1.6	79.0 ± 2.1	100 ± 0.4
12	18.9 ± 0.6 (60)	59.2 ± 1.2	81.4 ± 1.8	100 ± 0.3
13	11.6 ± 0.4 (60)	57.2 ± 1.5	80.3 ± 2.0	100 ± 0.2
14	19.7 ± 0.5 (60)	60.2 ± 1.2	87.4 ± 1.5	100 ± 0.6

[a] Values represent relative percentage to the positive control value (100%). Data are expressed as mean ± SD. Values in parentheses are viability percentages of Raji cells. [b] Mol ratio/TPA (20 ng = 32 pmol/mL).

inhibitory effects. Because inhibitory effects on EBV-EA activation correlate well with antitumor-promoting activity in vivo,[12] these data suggest that neokadsuranin (**5**) and schisandrin C (**9**) may be antitumor promoters.

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler or Fluka 51 micromelting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets on a 360 FT-IR Nicolet spectrophotometer. The UV spectra were measured on a Shimadzu UV-260 spectrophotometer in absolute MeOH. Optical rotations were measured with a PE-514 spectropolarimeter. The CD spectra were measured with a JASCO-715 spectropolarimeter. Mass spectra were determined on a Varian MAT-711 mass spectrometer for EIMS and HP 5989A mass spectrometer for HRMS. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-300 spectrometer with TMS as internal standard and $CDCl_3$ as solvent unless otherwise specified. Analytical TLC was performed on silica gel plates (Yantai Institute of Chemical Technology) with petroleum ether−EtOAc (4:1). Silica gel H (200−300 mesh, Qing Dao) was used for CC. Spots on the plate were observed under UV light and visualized by spraying with 10% H_2SO_4, followed by heating.

Plant Material. The stem bark of *Kadsura interior* A. C. Smith was collected in Feng-Qing County, Yunnan Province, People's Republic of China, in November 1995. A voucher specimen is deposited in the Herbarium of Materia Medica, Department of Pharmacognosy, School of Pharmacy, Fudan University, Shanghai, People's Republic of China.

Extraction and Isolation. The stem bark (8.5 kg) of *K. interior* was air-dried, ground, and extracted several times with 95% ethanol at room temperature. The alcoholic extract was evaporated in vacuo to yield a semisolid (1550 g). Water (1500 mL) was added to the residue, and a water steam distillation was performed to give the volatile oil (28 g). The remaining solution was extracted eight times with diethyl ether. This ether solution was concentrated to yield 150 g of residue. The residue was chromatographed on silica gel (1500 g), employing petroleum ether containing increasing amounts of ethyl acetate as eluent. Fractions 47−54 eluted with petroleum ether−EtOAc (90:10) gave **5** (55 mg). Fractions 61 and 62 eluted with petroleum ether−EtOAc (80:20) gave **1** (529 mg). Fractions 65 and 70−72 eluted with petroleum ether−EtOAc (80:20) were subjected to repeated column chromatography with the same solvent to yield **4** (33 mg) and **3** (715 mg), respectively. Fractions 66−69 eluted with petroleum ether−EtOAc (80:20) were separated in the same manner to yield **3** (606 mg) and **2** (71 mg). Compounds **6**−**14** were previously isolated from the same plant, which was collected in a different season.[5]

Interiotherin C (1): colorless needles (MeOH); mp 179−181 °C; $[\alpha]_D$ +127.66° (*c* 1.175, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 217 (5.90), 260 (sh, 4.90), 285 (sh, 4.60) nm; CD (*c* 0.012, MeOH) [θ] (nm) 57 917 (200, tr), 98 673 (207, pk), 85 802 (211 tr), 152 299 (230, pk), 0 (244), 7508 (255 tr), 72 932 (295, pk); IR (KBr) ν_{max} 1741, 1708, 1593, 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, d, J = 7.0 Hz, H-17), 1.03 (3H, d, J = 7.0 Hz, H-18), 1.50 (3H, br s, angeloyl α-CH_3), 1.59 (3H, s, Ac-9), 1.86 (3H, dq, J = 7.0, 1.0 Hz, angeloyl β-CH_3), 2.12 (1H, m, H-7), 2.22 (1H, m, H-8), 3.58 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.73 (1H, d, J = 3.5 Hz, H-9), 5.84 (1H, d, J = 7.5 Hz, H-6), 5.95 (2H, s, OCH_2O), 5.98 (1H, q, J = 7.0 Hz, angeloyl β-H), 6.44 (1H, s, H-11), 6.71 (1H, s, H-4); ^{13}C NMR data, see Table 1; EIMS (70 eV) *m*/*z* 556 [M$^+$] (100), 496 (5), 456 (22), 413 (20), 396 (30), 357 (45), 329 (18); HREIMS *m*/*z* 556.2307 (calcd for $C_{30}H_{36}O_{10}$, 556.2308).

Interiotherin D (2): yellow prisms (MeOH); mp 148−151 °C; $[\alpha]_D$ −271.19° (*c* 1.180, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 214 (5.73), 240 (sh, 5.30), 379 (sh, 4.68) nm; CD (*c* 0.017, MeOH) [θ] (nm) 29 188 (204), −62 184 (226), 62 184 (230), 98 987 (264), −16 751 (315), 34 889 (400); IR (KBr) ν_{max} 1719, 1679, 1646, 1580, 1481 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, d, J = 5.5 Hz, H-17), 1.04 (3H, d, J = 6.0 Hz, H-18), 1.63 (3H, m, angeloyl β-CH_3), 1.78 (3H, m, angeloyl α-CH_3), 1.88 (1H, m, H-8), 3.03 (1H, m, H-7), 3.80 (3H, s, OCH_3), 4.40, 4.84 (2H, AB, J = 2.5, 9.0 Hz, H-20), 5.73 (1H, m, angeloyl β-H), 5.82 (1H, d, J = 2.5 Hz, H-9), 5.83 (1H, d, J = 6.5 Hz, H-6), 6.02 (2H, AB, J = 1.5, 17.0 Hz, OCH_2O), 6.50 (1H, s, H-11), 6.67 (1H, s, H-4); ^{13}C NMR data, see Table 1; EIMS (70 eV) *m*/*z* 466 [M$^+$] (18), 438 (18), 366 (6), 355 (30), 137 (15), 83 (100); HREIMS *m*/*z* 466.1628 (calcd for $C_{26}H_{26}O_8$, 466.1628).

In Vitro EBV-EA Activation Experiments. Cell culture reagents, *n*-butyric acid, and other reagents were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). TPA was obtained from Sigma Chemicals Co. (St. Louis, MO). EBV-EA positive serum from a patient with nasopharyngeal carcinoma (NPC), used for an immunofluorescence test, was a gift from Prof. H. Hattori, Department of Otorhinolaryngology, Kobe University.

EBV genome carrying lymphoblastoid cells (Raji cells derived from Burkitt's lymphoma) were cultured in RPMI-1640 medium (Nissui, Tokyo, Japan) under the conditions described previously.[13] Spontaneous activation of EBV-EA in our subline of Raji cells was less than 0.1%.

The inhibition of EBV-EA activation was assayed using Raji cells (virus nonproducer type), EBV genome-carrying human lymphoblastoid cells, which were cultivated in 10% fetal bovine serum (FBS) RPMI 1640 medium. The indicator cells (Raji, 1 × 10^6/mL) were incubated at 37 °C for 48 h in 1 mL of medium containing *n*-butyric acid (4 mM, inducer), TPA (32 pM), and various amounts of the test compounds dissolved in 5 μL of DMSO. Smears were made from the cell suspension. The EBV-EA inducing cells were stained with high-titer EBV-EA-positive serum from NPC patients and detected by an indirect immunofluorescence technique.[14] In each assay, 500 cells were counted, and the number of stained cells (positive cells) was recorded. Triplicate assays were performed for each data point. The EBV-EA inhibitory activity of the test compound was expressed by comparison with that of the positive control experiment (100%), which was carried out with *n*-butyric acid (4 mM) plus TPA (32 pM). In the experiments, the EBV-EA induction was ordinarily around 35%, and this value was taken as the positive control (100%). Four mM *n*-butyric acid alone induced 0.1% EA-positive cells. The viability of treated Raji cells was assayed by the trypan-blue staining method.

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Supporting Information Available: A structural diagram showing the long-range HETCOR correlations of **1** is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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