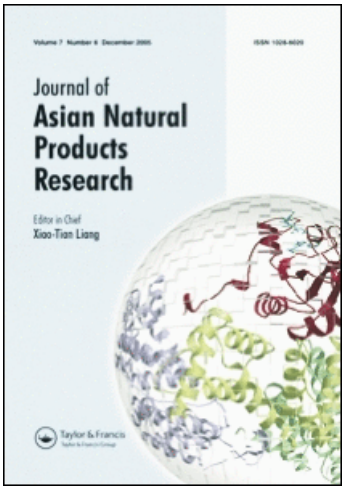

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Phenolic compounds with cell protective activity from the fruits of *Livistona chinensis*

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Two new depsidones, livistones A (**1**) and B (**2**), and a new benzofurane, livistone C (**3**), together with the 11 known compounds including three stilbenes (**4**–**6**), four steroids, three flavan-3-ols, and an alkaloid were isolated from the fruits of *Livistona chinensis*. The structures of the new compounds were determined by spectroscopic methods. Compounds **1**, **4**–**6** exhibited remarkable cell protective activities against H_2O_2-induced SH-SY5Y cell damage.

Keywords: *Livistona chinensis*; Palmae; depsidones; stilbenes; livistones A–C; cell protecting activity

1. Introduction

The genus *Livistona* is widely distributed over the tropical zone of Asia and Australia. There are three species of this genus growing in South China [1]. *Livistona chinensis* R. Brown (Palmae family) is an arbor, and its seeds have traditionally been used for analgesic, hemostatic, anti-esophageal cancer, and anti-leukemia purposes [2]. The aqueous extract of its fruits showed inhibition on angiogenesis and subcutaneous fibrosarcoma tumor growth [3], and the ethanol extract of the fruits was also demonstrated to inhibit protein kinase [4]. Earlier chemical investigations on this plant reported a number of flavonoids, steroids, amino acids, and vitamins [5–7]. In the present study, two new depsidones livistones A (**1**) and B (**2**), and a new benzofurane, livistone C (**3**) (Figure 1), together with the 11 known compounds *trans*-3,5,3′,5′-tetrahydroxy-4′-methoxy-stilbene (**4**), *cis*-3,5,3′,5′-tetrahydroxy-4′-methoxystilbene (**5**), 4-hydroxy-3′,5′-dimethoxystilbene (**6**), 5α,8α-epidioxy-22*E*-ergosta-6,22-dien-3β-ol, 5α,8α-epidioxy-22*E*-ergosta-6,9(11),22-trien-3β-ol, 24-ethylcholest-4-en-3-one, 6-hydroxy-stigmast-4-en-3-one, catechin, epicatechin, epiafzelechin, and terreusinone were isolated from the fruits of *L. chinensis*.

Accumulating evidence highlighted that the generation of reactive oxygen species and the associated oxidative stress have been implicated in the development of multiple disorders, such as neurodegenerative diseases [8], malaria [9], and inflammation [10]. The compounds **1**, **3**–**6** isolated from this plant material were tested for cell protecting activities against H_2O_2-induced SH-SY5Y cell damage, and all of them except livistone C (**3**) exhibited significant activities.

We present herein the isolation and structural elucidation of these new compounds, and the cell protective activities of some of the isolates.

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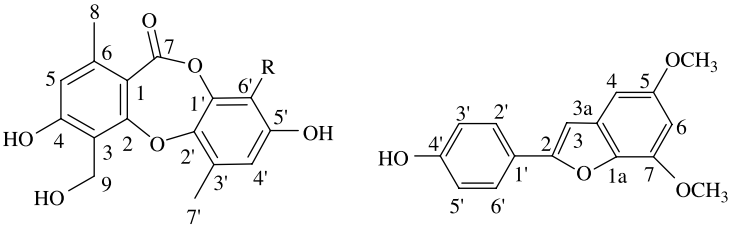

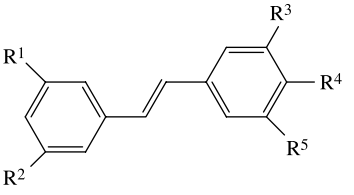

4 (*E*) $R^1 = R^2 = R^3 = R^5 = OH$ $R^4 = OCH_3$
5 (*Z*) $R^1 = R^2 = R^3 = R^5 = OH$ $R^4 = OCH_3$
6 (*E*) $R^1 = R^2 = OCH_3$ $R^4 = OH$ $R^3 = R^5 = H$

Figure 1. Structures of compounds **1**–**6**.

2. Results and discussion

Livistone A (**1**), a white amorphous powder, had a molecular formula of $C_{16}H_{14}O_6$ as determined by HR-ESI-MS at *m/z* 325.0683 $[M + Na]^+$ with 10 degrees of unsaturation. The ESI-MS ions at *m/z* 325.1 $[M + Na]^+$ and 627.1 $[2M + Na]^+$ in positive mode, and at *m/z* 301.0 $[M - H]^-$ in negative mode further supported this assignment. Its IR absorptions implied the presence of hydroxyl (3406 cm^{-1}), carbonyl (1680 cm^{-1}), and aromatic (1608 and 1496 cm^{-1}) functionalities. In the ^1H NMR spectrum (Table 1), two aromatic methyls at δ 2.45 and 2.37 (each 3H, s) and an oxymethylene at δ 5.01 (2H, s), were easily identified. Sixteen carbons in the molecule were resolved as two methyls (δ 20.8 and 16.7), one oxymethylene (δ 55.1), three sp^2 methines (δ 115.9, 114.4, and 105.4), and 10 sp^2 quaternary carbons (one ester carbonyl and nine aromatic ones) in the ^{13}C NMR spectrum (with DEPT experiments; Table 1). The aforementioned data suggested that compound **1** likely possessed a scaffold of depsidones [11].

Detailed analysis of the 2D-NMR (HSQC, HMBC, and ROESY) spectra further confirmed a depsidone feature for compound **1**, and finally allowed to establish its structure. In the HMBC spectrum (Figure 2(a)), the correlations from H_3-8 to C-1, C-5, and C-6 indicated that Me-8 was attached to C-6; the correlations from H-5 to C-1 and C-7 suggested that the ester carbonyl was linked to C-1; the correlations of H-5/C-3 and C-4, and H-9/C-2, C-3, and C-4 revealed that a hydroxyl and the oxymethylene groups were attached to C-4 and C-3, respectively. A partial structure (Figure 2(a), part A) possessing a pentasubstituted benzene ring of **1** was thus defined. Two overlapped proton resonances at δ 6.53 correlating with two carbon signals at δ 114.4 and 105.4 in the HSQC spectrum was assignable to the two methine protons of the other benzene ring. In addition, the HMBC correlations of H_3-7′/C-2′, C-3′ and C-4′, H-4′/C-2′, C-5′ and C-6′, and H-6′/C-1′ and C-2′ were indicative of the presence of a partial structure of tetrasubstituted benzene ring (Figure 2(a), part B) for **1**. Moreover, the

Table 1. ^{1}H and ^{13}C NMR spectral data of compounds **1**–**3**[a].

	Compound **1**		Compound **2**		Compound **3**	
Position	δ(C)	δ(H), (*J*) [Hz]	δ(C)	δ(H), (*J*) [Hz]	δ(C)	δ(H), (*J*) [Hz]
1	113.1		113.6			
2	161.0		161.5		157.3	
3	116.2		116.5		100.3	6.95 (s, 1H)
4	161.5		161.7		94.8	6.64 (d, $J = 2.2$, 1H)
5	115.9	6.64 (s, 1H)	116.0	6.66 (s, 1H)	157.6	
6	144.3		144.7		97.0	6.45 (d, $J = 2.2$, 1H)
7 (1a)	163.6		164.2		139.3	
8 (3a)	20.8	2.37 (s, 3H)	21.0	2.36 (s, 3H)	131.5	
9	55.1	5.01 (s, 2H)	55.2	4.99 (s, 2H)		
1′	145.3		144.2		122.4	
2′	142.7		143.3		126.8	7.73 (d, $J = 8.7$, 1H)
3′	132.1		128.1		116.2	6.94 (d, $J = 8.7$, 1H)
4′	114.4	6.53 (brs, 1H)	113.6	6.55 (s, 1H)	158.7	
5′	155.2		153.4		116.2	6.94 (d, $J = 8.7$, 1H)
6′	105.4	6.53 (brs, 1H)	114.7		126.8	7.73 (d, $J = 8.7$, 1H)
7′	16.7	2.45 (s, 3H)	16.6	2.37 (s, 3H)		
8′			9.2	2.11 (s, 3H)		
OCH_3					5-OCH_3: δ(C) 55.6, δ(H) 3.79 7-OCH_3: δ(C) 55.9, δ(H) 3.96	

[a] Data were measured in CD_3COCD_3 at 400 MHz (^{1}H) and 100 MHz (^{13}C).

ROESY correlations (Figure 2(b)) between Me-8 and H-5, and between Me-7′ and H-4′, confirmed the above assignment. The aforementioned functionalities accounted for nine degrees of unsaturation, the remaining one degree of unsaturation required the presence of an additional ring in **1**. Analysis of the IR and ^{13}C NMR (Table 1) spectral data suggested that two structural parts A and B were probably linked via an ester between C-7 and C-1′, and an ether bridge between C-2 and C-2′ to furnish a characteristic feature of depsidones. A long-range ROESY correlation (Figure 2(b)) observed between H_2-9 and Me-7′ supported the above structural arrangement. The structure of **1** was thus established as depicted.

Livistone B (**2**), obtained as white amorphous powder, showed a molecular formula of $C_{17}H_{16}O_6$ as determined by HR-ESI-MS ion at *m/z* 315.0875 $[M - H]^-$. The ^{1}H and ^{13}C NMR (Table 1) spectra were very similar to those of **1**, and the only difference implied that one proton at C-4′ or C-6′ was most likely replaced by a methyl group (δ_H 2.11, 3H, s). The methyl group was readily located at C-6′ by the HMBC correlations from Me-8′ to C-1′, C-5′, and C-6′. The structure of **2** was thus established as depicted.

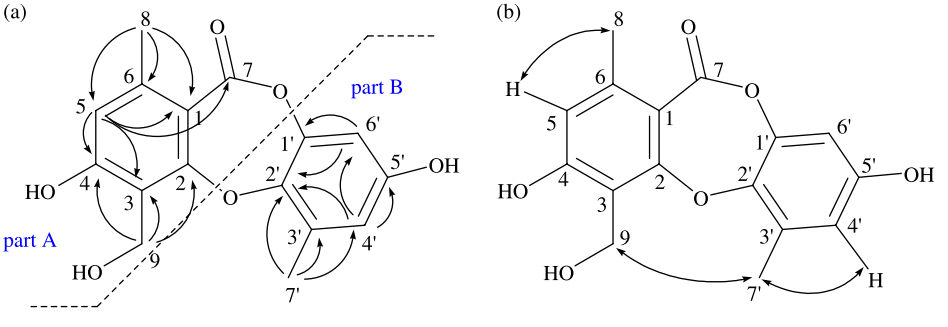

Figure 2. (a) Selected HMBC (H ⟶ C) correlations of **1**. (b) Key ROESY (↔) correlations of **1**.

Livistone C (**3**), obtained as white amorphous powder, had a molecular formula of $C_{16}H_{14}O_4$ as determined by HR-EI-MS ion at *m/z* 270.0880 $[M]^+$. The IR spectrum of compound **3** also showed the presence of hydroxyl (3427 cm^{-1}) and aromatic rings (1612 and 1483 cm^{-1}). Except for the resonances of two methoxyls at δ_H 3.96 and 3.79 (each 3H, s), the ^1H NMR spectrum (Table 1) also showed the resonances for a 1,4-disubstituted benzene ring (δ_H 7.73 and 6.94, each 2H, d, $J = 8.7$ Hz) and a 1,2,3,5-tetrasubstituted benzene ring (δ_H 6.64 and 6.45, each 1H, d, $J = 2.2$ Hz). Further analysis of the ^{13}C NMR data (Table 1) suggested that compound **3** featured a 2-arylbenzofuran scaffold [12]. This was verified by HMBC spectrum (Figure 3), in which, two methoxyls were readily located at C-5 and C-7 by the correlations of their corresponding protons to C-5 and C-7, respectively. The structure of **3** was thus elucidated to be 5,7-dimethoxyl-2-(4-hydroxyphenyl)benzofuran.

Eleven known compounds were identified on the basis of the spectroscopic data (^1H, ^{13}C NMR, and EI-MS) as *trans*-3,5,3′,5′-tetrahydroxy-4′-methoxystilbene (**4**) [13], *cis*-3,5,3′,5′-tetrahydroxy-4′-methoxystilbene (**5**) [13], 4-hydroxy-3′,5′-dimethoxystilbene (**6**) [14], 5α,8α-epidioxy-22*E*-ergosta-6,22-dien-3β-ol [15], 5α,8α-epidioxy-22*E*-ergosta-6,9(11),22-trien-3β-ol [15], 24-ethylcholest-4-en-3-one [16], 6-hydroxystigmast-4-en-3-one [16], catechin [17], epicatechin [17], epiafzelechin [18], and terreusinone [19].

In this study, the cell survival activities of compounds **1**, **3**–**6** were evaluated according to the reported protocol [20] with minor modifications (see Experimental section), and resveratrol was used as positive control. After 100 μM H_2O_2 exposure, cell viability as determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction was markedly decreased to 66.26% ($*p < 0.005$ vs. control). However, on respective pretreatment with compounds **1**, **3**–**6** at 1 and 10 μM, compounds **1**, **4**–**6** significantly attenuated the H_2O_2-induced SH-SY5Y cell damage ($^{\#\#}p < 0.005$ vs. H_2O_2 group) at 1 μM, and especially compound **1** showed remarkable activity at 1 and 10 μM (stronger than the positive control resveratrol) in a dose-dependent manner, while compound **6** implied cytotoxicity at 10 μM (Figure 4).

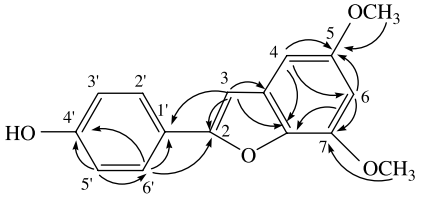

Figure 3. Selected HMBC (H ⟶ C) correlations of compound **3**.

In conclusion, depsidones, a group of secondary metabolites were usually found in lichens, and recently, a depsidone excelsione was also isolated from the extract of a fungal endophyte obtained from a New Zealand endemic tree *Knightia excelsa* [11]. With respect to the excelsione, compounds **1** and **2** were different in the substitution patterns of the eastern hemisphere. Compounds **1**, **4**–**6** showed stronger cell protective activity than that of the positive control resveratrol at the concentration of 1 μM; especially, compound **1** showed remarkable activity at 1 and 10 μM in a dose-dependent manner.

3. Experimental

3.1 General experimental procedures

The UV spectra were recorded on a Shimadzu UV-2550 spectrophotometer. The IR spectra were recorded on a Perkin-Elmer 577 spectrometer with KBr disks. The NMR spectra were measured on a Bruker AM-400 spectrometer. EI-MS and HR-EI-MS (70 eV) were carried out on a Finnigan MAT 95 mass spectrometer, and ESI-MS and HR-ESI-MS were made on a Esquire 3000plus LC-MS and a Waters Q-Tof Ultima Global mass spectrometers, respectively. Semipreparative HPLC was performed on a Waters 515 pump equipped with a Waters 2487 detector (254 nm) and a YMC-Pack ODS-A column (250 × 10 mm, S-5 μm, 12 nm). Silica gel H

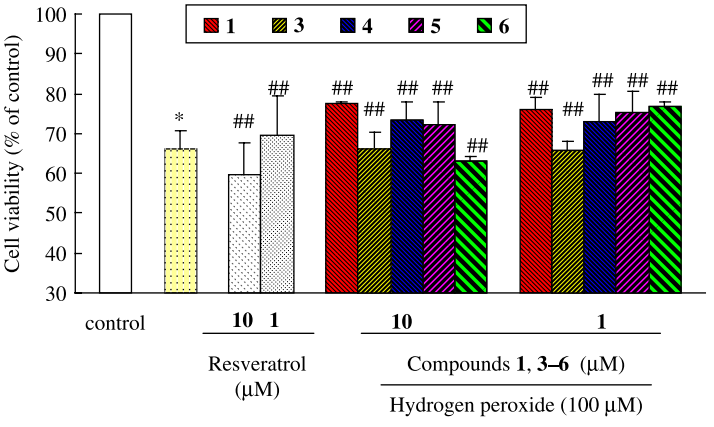

Figure 4. Effects of compounds **1**, **3**–**6** on cell viability (*$p < 0.005$ vs. control; ##$p < 0.005$ vs. H_2O_2 group).

(Qingdao Haiyang Chemical Co. Ltd, Qingdao, China); C_{18} reversed-phase silica gel (150–200 mesh, Merck, Darmstadt, Germany); MCI gel (CHP20P, 75–150 μm, Mitsubishi Chemical Industries Ltd, Tokyo, Japan); and Sephadex LH-20 gel (Amersham Biosciences, Arlington, IL, USA) were used for column chromatography (CC). Precoated silica gel GF_{254} plates (Qingdao Haiyang Chemical Co. Ltd) were used for TLC. All solvents used were of analytical grade (Shanghai Chemical Reagents Co., Ltd, Shanghai, China).

3.2 *Plant material*

The fruits of *L. chinensis*, collected from Hainan Province of China, were identified by Prof. Shi-Man Huang. A voucher specimen has been deposited in Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Accession No. LC-2004-1Y).

3.3 *Extraction and isolation*

The powder of the dried fruits of *L. chinensis* (5.0 kg) was extracted three times with 95% EtOH at room temperature. Evaporation of the solvent under reduced pressure provided 400 g of ethanolic extract, which was then partitioned between water and EtOAc to give 70 g of EtOAc-soluble fraction. EtOAc-soluble fraction was chromatographed over an MCI gel column (MeOH–H_2O 30:70 → 90:10, v/v) to give five fractions A–E. Fraction A was subjected to CC (SiO_2; $CHCl_3$–MeOH 10:1 to 5:1, v/v) in gradient to obtain three fractions A1–A3. Fraction A1 was chromatographed over a column of Sephadex LH-20 eluted with MeOH to give two subfractions A1a and A1b. A1a was purified by semipreparative HPLC (flow rate: 3 ml/min) with a mobile phase of MeOH–H_2O (35:55, v/v) to afford epicatechin (20 mg) and epiafzelechin (10 mg). Purification of A1b by semipreparative HPLC (flow rate: 3 ml/min; MeOH–H_2O 45:55, v/v) gave catechin (20 mg). Fraction B was separated over a silica gel column eluted with petroleum ether–acetone (5:1 to 0:1, v/v) to give compounds **4** (25 mg) and **5** (5 mg). Fraction D was subjected to CC (Sephadex LH-20; MeOH) to give three subfractions D1–D3. Fraction D1 was subjected to CC (SiO_2; $CHCl_3$–MeOH 50:1 to 10:1, v/v) to afford terreusinone (10 mg). Purification of fraction D3 over CC (SiO_2; $CHCl_3$–MeOH 20:1 to 5:1, v/v) gave two compounds **1** (8 mg) and **2** (3 mg). Fraction F was subjected to CC (SiO_2; petroleum ether–EtOAc 5:1 to 1:1, v/v) to give five subfractions F1–F5. Fractions F2 and F3 were, respectively, purified on a column of reversed-phase silica gel (MeOH–H_2O 75:25, v/v) to afford

compounds **3** (35 mg) and **6** (5 mg). Fraction H was chromatographed over a silica gel column (petroleum ether–EtOAc 25:1 to 10:1, v/v) to obtain two subfractions H1 and H2. Fraction H1 was separated over CC (SiO_2; petroleum ether–acetone 25:1 to 10:1, v/v) to yield 24-ethylcholest-4-en-3-one (90 mg) and 6-hydroxystigmast-4-en-3-one (30 mg). Fraction H2 was subjected to CC (Sephadex LH-20; MeOH) to give 5α,8α-epidioxy-22*E*-ergosta-6,22-dien-3β-ol (26 mg) and 5α,8α-epidioxy-22*E*-ergosta-6,9(11),22-trien-3β-ol (5 mg).

3.4 Cell protecting evaluation

The human neuroblastoma SH-SY5Y (The cell line SH-SY5Y is a third-generation neuroblastoma cloned from SH-SY5, which was cloned from SH-SY, the latter was cloned from SK-N-SH.) cells were maintained in MEM/F12 medium supplemented with 10% fetal calf serum, 100 U/ml penicillin, and 60 μg/ml streptomycin in a humid atmosphere of 5% CO_2 and 95% air at 37°C. SH-SY5Y cells were plated at a density of 1×10^5 cells per well in 96-well plates. Then, cells were pretreated with various concentrations (1 and 10 μM) of compounds for 2 h, followed by exposure to 100 μM of H_2O_2 in the presence of the same concentrations of compounds for another 24 h. To produce oxidative stress, H_2O_2 was freshly prepared from 30% stock solution prior to each experiment. The control cells were added with the same medium without H_2O_2 and compounds. Cell survival was evaluated by MTT reduction. Briefly, after 24 h exposure, 10 μl of MTT (5 mg/ml in PBS) were added to each well and the cells were incubated at 37°C for 3 h. The supernatants were aspirated carefully and 100 μl of dimethyl sulfoxide were added to each well to dissolve the precipitate and the absorbance at 490 nm was measured with a microplate reader (Bio-Tek Model ELX800). Two independent experiments were carried out in triplicate. All data were expressed as percentage of control value. Statistical comparison was made by using one-way ANOVA and followed by Duncan's test. The data were expressed as means + SEM; $^{*}p < 0.005$ vs. control; $^{\#\#}p < 0.005$ vs. H_2O_2 group.

3.4.1 Livistone A (**1**)

Obtained as white amorphous powder. UV (MeOH) λ_{max} (log ε): 269 (3.94) and 200 (4.63) nm. IR (KBr): 3406, 1680, 1608, and 1496 cm^{-1}. ^1H and ^{13}C NMR spectral data: see Table 1. Positive-ion ESI-MS *m/z*: 325.1 $[M + Na]^+$ and 627.1 $[2M + Na]^+$. Negative-ion ESI-MS *m/z*: 301.0 $[M - H]^-$. HR-ESI-MS *m/z*: 325.0683 $[M + Na]^+$ (calcd for $C_{16}H_{14}O_6Na$, 325.0688).

3.4.2 Livistone B (**2**)

Obtained as white amorphous powder. UV (MeOH) λ_{max} (log ε): 267 (3.95) and 200 (4.60) nm. IR (KBr): 3410, 1683, 1601, and 1501 cm^{-1}. ^1H and ^{13}C NMR spectral data: see Table 1. Positive-ion ESI-MS *m/z*: 339.1 $[M + Na]^+$ and 655.1 $[2M + Na]^+$. Negative-ion ESI-MS *m/z*: 315.0 $[M - H]^-$. HR-ESI-MS *m/z*: 315.0875 $[M - H]^-$ (calcd for $C_{17}H_{15}O_6$, 315.0869).

3.4.3 Livistone C (**3**)

Obtained as white amorphous powder. UV (MeOH) λ_{max} (log ε): 302 (4.55) and 213 (4.54) nm; IR (KBr): 3427, 1612, and 1483 cm^{-1}. ^1H and ^{13}C NMR spectral data: see Table 1. Positive-ion ESI-MS *m/z*: 271.0 $[M + H]^+$ and 562.9 $[2M + Na]^+$. Negative-ion ESI-MS *m/z*: 268.9 $[M - H]^-$. HR-EI-MS *m/z*: 270.0880 $[M]^+$ (calcd for $C_{16}H_{14}O_4$, 270.0892).

Acknowledgements

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References

[1] S.J. Pei, S.Y. Cheng, and S.J. Tong, *Flora Reipublicae Popularis Sinicae* (Science Press, Beijing, 1991), Vol. 13, p. 25.

[2] An Editorial Committee of the Administration Bureau of Traditional Chinese Medicine, *Chinese Materia Medica* (Zhonghua Benchao) (Shanghai Science & Technology Press, Shanghai, 1999), Vol. 8, p. 459.

[3] M. Sartippour, C.H. Liu, Z.M. Shao, V.L. Go, D. Heber, and M. Nguyen, *Oncol. Rep.* **8**, 1355 (2001).

[4] W.C. Huang, R.M. Hsu, L.M. Chi, Y.L. Leu, Y.S. Chang, and J.S. Yu, *Cancer Lett.* **248**, 137 (2007).

[5] Z.P. Liu, J.G. Cui, H.X. Liu, C.S. Huang, and Z.G. Zhong, *Guihaia* **27**, 140 (2007).

[6] Z.P. Liu, J.G. Cui, C.S. Huang, and Z.G. Zhong, *Chin. Tradit. Herb. Drugs* **38**, 178 (2007).

[7] V. Mala and M.U. Dahot, *Sci. Int.* (Lahore) **6**, 231 (1994).

[8] A. Reynolds, C. Laurie, R.L. Mosley, and H.E. Gendelman, *Int. Rev. Neurobiol.* **82**, 297 (2007).

[9] A. Pabón, J. Carmona, L.C. Burgos, and S. Blair, *Clin. Biochem.* **36**, 71 (2003).

[10] J.A. Martinez, *J. Physiol. Biochem.* **62**, 303 (2006).

[11] G. Lang, A.L.J. Cole, J.W. Blunt, W.T. Robinson, and M.H.G. Munro, *J. Nat. Prod.* **70**, 310 (2007).

[12] R. Dupont and P. Cotelle, *Tetrahedron* **57**, 5585 (2001).

[13] M.I. Fernández, J.R. Pedro, and E. Seoane, *Phytochemistry* **22**, 2819 (1983).

[14] F. Orsini, L. Verotta, M. Lecchi, R. Restano, G. Curia, E. Redaelli, and E. Wanke, *J. Nat. Prod.* **67**, 421 (2004).

[15] M. Kobori, M. Yoshida, M. Ohnishi-Kameyama, T. Takei, and H. Shinmoto, *Biol. Pharm. Bull.* **29**, 755 (2006).

[16] P. Georges, M. Sylvestre, H. Ruegger, and P. Bourgeois, *Steroids* **71**, 647 (2006).

[17] T. Yokozawa, Y. Kashiwada, M. Hattori, and H.Y. Chung, *Biol. Pharm. Bull.* **25**, 748 (2002).

[18] S.B. Wan and T.H. Chan, *Tetrahedron* **60**, 8207 (2004).

[19] S.M. Lee, X.F. Li, H.L. Jiang, J.G. Cheng, S. Seong, H.D. Choi, and B.W. Son, *Tetrahedron Lett.* **44**, 7707 (2003).

[20] R. Wang, X.Q. Xiao, and X.C. Tang, *Neuroreport* **12**, 2629 (2001).