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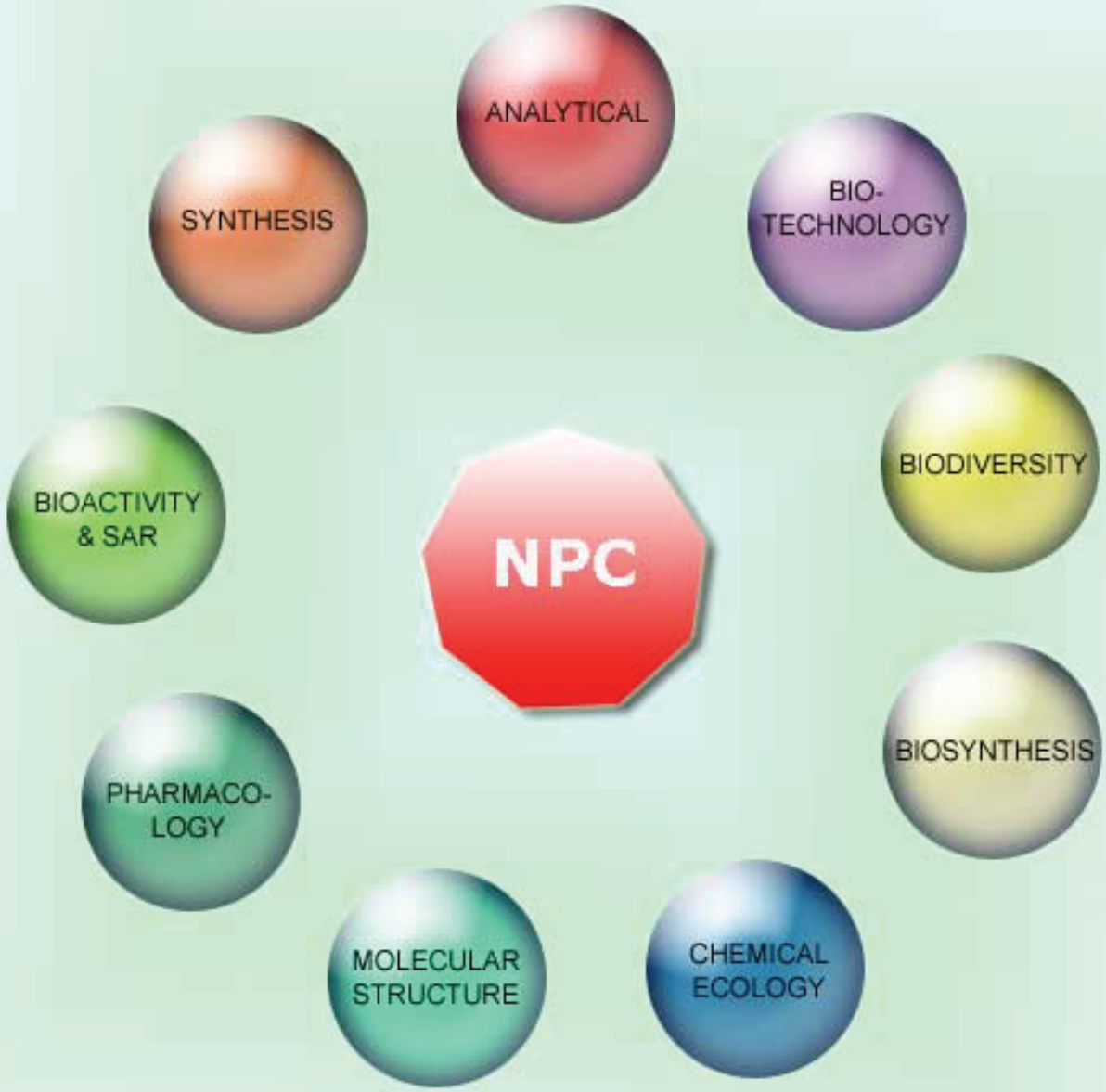

Volume 12. Issue 6. Pages 803-1006. 2017
ISSN 1934-578X (printed); ISSN 1555-9475 (online)
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NPC Natural Product Communications

2017
Vol. 12
No. 6
921 - 924

Isoprenylated Phenolics from Roots of *Artocarpus heterophyllus*

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Received: January 9th, 2017; Accepted: March 28th, 2017

Thirteen compounds were isolated from *Artocarpus heterophyllus,* including one new di-isoprenylated stilbene, (±)-artoheterin A (**1**), and twelve known isoprenylated phenolics, artocarbene (**2**), 3',5',2,4-tetrahydroxy-4'-(3-methyl-2-butenyl) stilbene (**3**), cudrastilbene (**4**), 3-(3-methyl-2-butenyl) luteolin (**5**), 5,7,2',4'-tetrahydroxy-6-(3-methyl-2-butenyl) flavone (**6**), 6-(3-methyl-2-butenyl) apigenin (**7**), artochamin B (**8**), 5'-hydroxycudraflavone A (**9**), artonins A and B (**10**-**11**), heterophyllin (**12**), and 8-(3-methyl-2-butenyl)-6,7-dihydroxycoumarin (**13**). The structures of these compounds were identified by spectroscopic methods. All isolated compounds were screened for their inhibitory abilities against cathepsin K (CatK). Of them, compounds **1**-**4** and **8**-**13** were found to have suppression capabilities against CatK with IC_{50} values ranging from 1.9 to 73.7 μM.

Keywords: Moraceae, *Artocarpus heterophyllus*, Cathepsin K inhibitory activity, Artoheterin A, Isoprenylated phenolics, Stilbene.

Artocarpus heterophyllus (Moraceae), an evergreen arbor tree, is mainly distributed in tropical and subtropical regions of Asia, including Southern China. In China, *A. heterophyllus* is popularly cultivated for its edible fruits, while its root has been used as a folk medicine for subduing swelling and detoxicating [1]. Previous phytochemical studies on *A. heterophyllus* have displayed the occurrence of a variety of flavonoids and 2-arylbenzofurons with cytotoxicity [2], tyrosinase inhibitory [3], anti-inflammatory [4], antioxidant [5], and anti-respiratory burst activities [6]. Cathepsin K (CatK) is the most important enzyme for osteoclast-mediated bone resorption and inhibition of CatK is generally regarded as an effective approach for the treatment of osteoporosis [7]. Recently, we reported a variety of isoprenylated flavonoids with CatK inhibitory activities from *A. styracifolius* [8]. As a part of our continuing research on *Artocarpus* plants, the investigation on chemical constituents with CatK inhibitory activities from *A. heterophyllus* were performed. Herein, we described the isolation, structural elucidation, and CatK inhibitory capabilities of one new di-isoprenylated stilbene, artoheterin A (**1**), as well as twelve known isoprenylated phenolics, artocarbene (**2**), 3',5',2,4-tetrahydroxy-4'-(3-methyl-2-butenyl) stilbene (**3**), cudrastilbene (**4**), 3-(3-methyl-2-butenyl) luteolin (**5**), 5,7,2',4'-tetrahydroxy-6-(3-methyl-2-butenyl) flavone (**6**), 6-(3-methyl-2-butenyl) apigenin (**7**), artochamin B (**8**), 5'-hydroxycudraflavone A (**9**), artonins A and B (**10**-**11**), heterophyllin (**12**), and 8-(3-methyl-2-butenyl)-6,7-dihydroxycoumarin (**13**) (Figure 1).

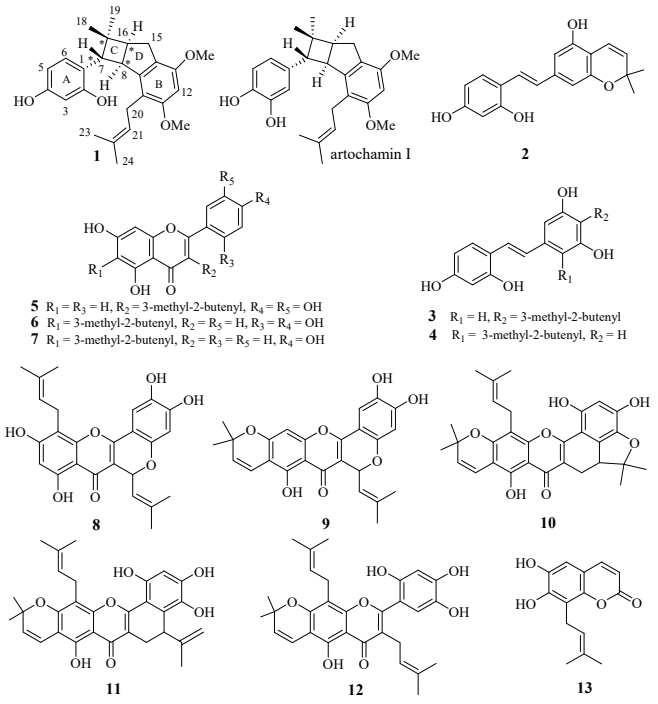

Figure 1: Structures of compounds **1**-**13**. An asterisk designates relative configuration for the specific chiral carbon.

(±)-Artoheterin A **(1),** a brownish red amorphous powder, has a positive reaction with ferric chloride reagent, proving the presence of the phenolic moiety. Its molecular formula was determined to be $C_{26}H_{32}O_4$ by HR-ESI-MS at *m/z* 407.2220 ($[M-H]^-$, calcd for $C_{26}H_{31}O_4$, 407.2228). The IR spectrum of **1** showed absorptions for hydroxyl group (3404 cm^{-1}), aliphatic chain (2930 and 2857 cm^{-1}), and aromatic ring (1601, 1455 and 1377 cm^{-1}). The ^1H NMR spectrum (Table 1) of **1** exhibited signals for an aromatic ABX spin system (ring A) at δ 7.25 (1H, d, *J* = 8.0 Hz, H-6), 6.38 (1H, br. s, H-3), and 6.39 (1H, overlap, H-5), a 3-methyl-2-butenyl (isoprenyl) group at δ 4.94 (1H, t, *J* = 6.1 Hz, H-21), 3.05 (1H, m, H_a-20), 3.03 (1H, m, H_b-20), 1.50 (3H, s, H-24), and 1.44 (3H, s, H-23), an aromatic proton (ring B) at δ 6.45 (1H, s, H-12), four tertiary methyl groups (two oxygenated) at δ 3.82 (3H, s, MeO-13), 3.78 (3H, s, MeO-11), 1.07 (3H, s, H_3-18), and 0.74 (3H, s, H_3-19),

Table 1: ^{1}H and ^{13}C NMR data of compound **1** and artochamin I [9] in acetone-d_6.

Position	**1**[a]		artochamin I[b]	
	δ_H (m, *J* in Hz)	δ_C	δ_H (m, *J* in Hz)	δ_C
1		120.2		134.2
2		158.6	6.75 (d, 1.8)	116.3
3	6.38 (br. s)	103.0		145.8
4		157.2		144.4
5	6.39 (overlap)	106.9	6.76 (d, 8.0)	115.8
6	7.25 (d, 8.0)	129.2	6.58 (dd, 1.8, 8.0)	120.2
7	3.31 (d, 5.8)	51.4	2.77 (d, 5.7)	58.9
8	4.07 (br. t, 6.4)	44.0	3.94 (t, 5.7)	45.9
9		150.5		150.2
10		118.0		118.4
11		161.3		158.9
12	6.45 (s)	94.8	6.45 (s)	95.4
13		155.4		155.6
14		124.7		125.0
15	2.90 (overlap)	30.8	3.00 (dd, 1.8, 17.0)	30.9
	2.86 (overlap)		2.84 (dd, 9.7, 17.0)	
16	2.70 (m)	45.1	2.71 (m)	45.6
17		39.1		39.3
18	1.07 (s)	26.1	0.97 (s)	26.4
19	0.74 (s)	27.6	0.71 (s)	27.7
20	3.05 (m)	26.6	2.97 (dd, overlap)	26.8
	3.02 (m)		2.86 (dd, 5.7, 14.5)	
21	4.94 (t, 6.1)	124.6	4.88 (br. t, 5.7)	124.7
22		130.4		131.0
23	1.44 (s)	17.8	1.39 (br. s)	18.0
24	1.50 (s)	25.8	1.48 (br. s)	26.0
HO-2	7.99 (br. s)		7.71 (br. s)*	
HO-4	7.99 (br. s)		7.68 (br. s)*	
MeO-11	3.78 (s)	56.3	3.76 (s)	56.7
MeO-13	3.82 (s)	55.5	3.81 (s)	55.9

[a] Bruker Avance 600 spectrometer; chemical shifts (ppm) referred to $(CD_3)_2CO$ (δ_H 2.04; δ_C 206.0).
[b] Bruker DRX 500 spectrometer; chemical shifts (ppm) referred to $(CD_3)_2CO$ (δ_H 2.04; δ_C 206.0).
* The assignment may be interchanged.

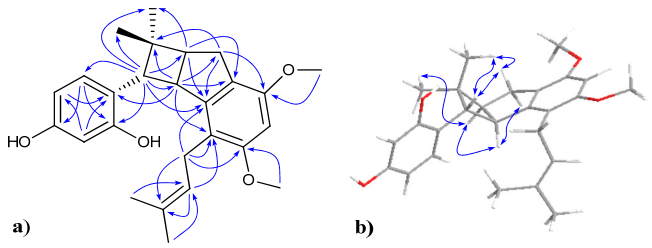

Figure 2: **a**) Key HMBC (H→C) correlations of **1**; **b**) Key NOESY (H↔H) correlations of **1**.

a methylene groups at δ 2.90 (1H, overlap, H_a-15) and 2.86 (1H, overlap, H_b-15), as well as three aliphatic methines at δ 3.31 (1H, d, *J* = 5.8 Hz, H-7), 4.07 (1H, br. t, *J* = 6.4 Hz, H-8), and 2.70 (1H, m, H-16). These ^{1}H NMR data was highly similar to those of the known compound, artochamin I [9]. A comparison of the ^{1}H NMR data (Table 1) of **1** with artochamin I showed that the main difference is the chemical shift dislocations of the three protons from ring A, indicating they share the same ring B, C, and D, but had different substitution on ring A. This was supported by the ^{13}C NMR data of **1** also similar to that of artochamin I, except for the carbons from ring A and C-7 (Table 1). The interpretation of the DEPT, HSQC, and HMBC spectra of **1** allow us to determine the substitution pattern of ring A as 2′,4′-dihydroxy substitution (Table 1, Figure 2). For the relative configuration of **1**, the NOESY cross peaks of H-8 with H-16, H_a-15, and H_3-19 and H-7 with H_3-18 and H_b-15 indicated a *cis* arrangement between H-8 and H-16. In addition, the optical rotation value of **1** was zero, suggesting **1** was obtained as a racemate. The existence of enantiomers was further supported by a follow-up chiral HPLC analysis, which displayed a pair of chromatographic peak with an intensity ratio of ca. 1:1. Thus, the structure of **1** was established as shown (Figure 1) and **1** was named (±)-artoheterin A.

By comparison of their ^{1}H, ^{13}C NMR and ESI-MS spectral data with those reported in literatures, the other twelve known isoprenylated compounds (**2-13**) were identified as artocarbene (**2**) [10], 3',5',2,4-tetrahydroxy-4'-(3-methyl-2-butenyl) stilbene (**3**) [11], cudrastilbene (**4**) [12], 3-(3-methyl-2-butenyl) luteolin (**5**) [13], 5,7,2',4'-tetrahydroxy-6-(3-methyl-2-butenyl) flavone (**6**) [14], 6-(3-methyl-2-butenyl) apigenin (**7**) [15], artochamin B (**8**) [16], 5'-hydroxycudraflavone A (**9**) [17], artonins A and B (**10-11**) [18], heterophyllin (**12**) [19], and 8-(3-methyl-2-butenyl)-6,7-dihydroxycoumarin (**13**) [20].

The inhibitory effects of all isolated compounds on CatK were evaluated by a fluorescence colorimetric assay described previously [8]. The results are summarized in Table 2. Compounds **1-4**, and **8-13** showed inhibitory capacities to CatK with the IC_{50} values ranging from 1.9 to 73.7 μM. The other compounds showed no activities up to a highest concentration of 100 μM.

Table 2: Inhibitory activities of **1-13** on cathepsin K.

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
1	73.7	**8**	1.9
2	9.6	**9**	2.0
3	10.9	**10**	1.9
4	24.6	**11**	9.0
5	ND	**12**	48.4
6	ND	**13**	13.2
7	ND	E64[b]	0.003

a ND, not detectable. b Positive control.

Experimental

General: IR spectrum was executed on Shimadzu Iraffinity-1 FTIR spectrometer with KBr disc (Shimadzu Co., Kyoto, Japan). Optical rotation was determined on a JASCO P-1020 polarimeter (JASCO International Corp., Ltd, Tokyo, Japan) at room temperature. NMR spectra were recorded on a Bruker Avance 600 spectrometer (Bruker Biospin, Rheinstetten, Germany) using acetone-d_6 and/or acetone-d_6 + D_2O as solvent. HR-ESI-MS analyses were implemented on an AB SCIEX Triple TOF^{TM} 5600+ mass spectrometer (AB SCIEX Co., Framingham, MA USA). Column chromatography (CC) was performed on HP-20 (75–150 μm, Mitsubishi Chemical Co., Tokyo, Japan), ODS gel (75-150 μm, YMC Co., Kyoto, Japan), MCI GEL CHP20P (75-150 μm, Mitsubishi Chemical Co., Tokyo, Japan) and Sephadex LH-20 (25-100 μm, GE Healthcare Bio-Sciences, Amersham, Sweden). Pre-coated TLC plates with silica gel GF_{254} (10-40 μm; Yantai Jiang You silicone Development Co., Ltd., Yantai, China) were used to detect the purity of the isolates achieved by coating with 10% H_2SO_4 in EtOH, followed by heating. Preparative HPLC was executed on a LC3000 liquid chromatograph (Beijing Tong Heng Innovation Technology Co., Ltd, Beijing, China) armed with an ODS column (5 μm, 250 mm × 30 mm i.d., Sepax Technologies,

Inc.). Chiral HPLC analysis was performed on a Phenomenex Lux Cellulose-2 column (5 μM, 4.6 × 250 mm) using acetonitrile-H_2O (4:1, v/v), at 1.2 mL/min.

Plant material: The roots of *A. heterophyllus* were collected from Nanning city, Guangxi Zhuang Autonomous Region, China, in March 2013 and identified by Lv Shihong, associate researcher of Guangxi Institute of Botany, Chinese Academy of Sciences. The voucher specimen (TCM20130101) was deposited in the Herbarium of the Department of Pharmacognosy, Research Center of Natural Resources of Chinese Medicinal Materials and Ethnic Medicine, Jiangxi University of Traditional Chinese Medicine.

Extraction and isolation: The air-dried and powdered roots of *A. heterophyllus* (17.0 kg) were extracted with 95% EtOH three times (140 L for each extraction) at room temperature. The filtrate was evaporated *in vacuo* to produce a residue (1.5 kg), which was suspended in H_2O, and then partitioned successively with petroleum ether (PE), $CHCl_3$, EtOAc, and *n*-BuOH to obtain the PE-soluble, $CHCl_3$-soluble, EtOAc-soluble and *n*-BuOH-soluble portions, respectively. The $CHCl_3$-soluble (574.0 g) was fractionated by HP-20 macroporous resin column chromatography (CC) eluted successively with a gradient of EtOH/H_2O (0%→100%) to give eleven fractions (Fr. H1-H11). Fr. H6 (57.3 g) was subjected to CC over ODS eluted by EtOH/H_2O (40%→100%) to yield six subfractions (Fr. H6O1-H6O6). Fr. H6O3 (13.7 g) was separated by CC over MCI CHP-20P resin eluted with EtOH/H_2O (50%→100%) to obtain seven subfractions Fr. H6O3M1-H6O3M7. Fr. H6O3M2 (1.3 g) was further fractioned by CC on Sephadex LH-20 gel eluted with MeOH to give five subfractions Fr. H6O3M2L1-H6O3M2L5. Fr. H6O3M4 (1.5 g) was further fractioned by CC on Sephadex LH-20 gel eluted with MeOH to give seven subfractions Fr. H6O3M4L1-H6O3M4L7. Fr. H6O4 (2.9 g) was separated by CC over MCI CHP-20P resin eluted with EtOH/H_2O (70%→100%) to obtain three subfractions Fr. H6O4M1–H6O4M3. Fr. H6O4M3 (674.0 mg) was further fractioned by CC on Sephadex LH-20 gel eluted with MeOH to give three subfractions Fr. H6O4M3L1-H6O4M3L3. Fr. H5 (10.0 g) was fractioned by CC on Sephadex LH-20 gel eluted with MeOH to yield ten subfractions (Fr. H5L1-H5L10). Fr. H5L5 (1.5 g) was subjected to CC over ODS eluted by MeOH/H_2O (40%→100%) to obtain three subfractions Fr. H5L5O1-H5L5O3. Fr. H5L6 (1.2 g) was separated by CC over MCI CHP-20P resin eluted with MeOH/H_2O (40%→100%) to obtain two subfractions Fr. H5L6M1-H5L6M2. Fr. H6O3M2L2 (148.0 mg) was further purification by preparative HPLC eluting with acetonitrile-H_2O (4:6, v/v) to yield **5** (6.0 mg, t_R 33 min). In the same way, **4** (7.1 mg, MeOH-H_2O (3:7, v/v), t_R 45 min) and **3** (284.5 mg, MeOH-H_2O (2:3, v/v), t_R 55 min), **6** (11.0 mg, acetonitrile-H_2O (4:6, v/v), t_R 58 min), **7** (2.8 mg, acetonitrile-H_2O (1:1, v/v), t_R 30 min), **8** (15.6 mg, acetonitrile-H_2O (6:4, v/v), t_R 30 min), **9** (15.1 mg, acetonitrile-H_2O (5:5, v/v), t_R 38 min), **11** (22.0 mg, acetonitrile-H_2O (7:3, v/v), t_R 25 min), **12** (3.0 mg, acetonitrile-H_2O (3:2, v/v), t_R 20 min), **10** (3.0 mg, acetonitrile-H_2O (4:1, v/v), t_R 30 min), and **1** (2.0 mg, acetonitrile-H_2O (4:1, v/v), t_R 20 min) were obtained from subfractions H5L5O3, H5L6M2, H6O3M2L3, H6O3M4L4, H6O3M4L7, H6O3M7, H6O3M6, H6O4M3L2, H6O4M3L4 and H6O6, respectively. **13** (4.0 mg) and **2** (6.9 mg) were obtained by preparative thin layer chromatography developed with $CHCl_3$-MeOH (10:1, v/v) from H5L3 and H5L6M2, respectively.

Evaluation for inhibitory capability against CatK: The inhibitory abilities of compounds **1**-**13** against CatK were performed on a fluorometer microplate reader based on the specific reaction of CatK with its substrate Z-GPR-AMC, as described previously [8], with some modifications. In brief, the compounds were diluted with the buffer (pH 6.8, 400 mM NaH_2PO_4-Na_2HPO_4 buffer, 8 mM Dithiothreitol, and 4 mM EDTA), and mixed with CatK (diluted in 0.1% Brij35) for 5-10 min at 25°C. Then, substrate Z-GPR-AMC was added to start the reaction. The final concentration of substrate Z-GPR-AMC was 20 μM in the assay mixture, Cat K was 14 nM. After incubation for 120 min at 37°C, the produced fluorescence was monitored on a SPECTROstar Omega fluorescent plate reader, emission at 460 nm after excitation at 355 nm. E64 (*N*-[*N*-(L-3-*Trans*-carboxirane-2-carbonyl)-L-leucyl]-agmatine), a general cysteine protease inhibitor, was used as the positive control to ensure the validity of the *in vitro* screening system.

Artoheterin A (1)

Brownish red amorphous powder.

IR (KBr): 3404, 2930, 2857, 1601, 1455, 1377, 1319, 1204, 1121, 1018.

UV λ_{max} (MeOH) nm (log ε): 284 (4.01), 331(3.75)

^1H and ^{13}C NMR: Table 1.

HR-ESI-MS: *m/z* $[M-H]^-$ calcd for $C_{26}H_{31}O_4$: 407.2228; found: 407.2220 and *m/z* $[M+H]^+$ calcd for $C_{26}H_{33}O_4$: 409.2373; found: 409.2375.

Supplementary data: ^1H and ^{13}C NMR, DEPT 135, HSQC, HMBC, UV, IR, and HR-ESI-MS (positive and negative ion modes) of **1**.

Acknowledgments - This study was supported by National Natural Science Foundation of China (No. 81160509; 81360475), Young Scientist Development Program of Jiangxi Province (No. 20142BCB23024), Jiangxi Provincial Natural Science Fund Project (20151BAB205074), Subject of Jiangxi Education Department (No. GJJ14614), and by State Scholarship Fund (No. 201508360057) from China Scholarship Council. Our sincere thanks go to Miss Sarah Grafton, Mississippi College, USA, for proofreading of the manuscript.

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Accounts/Reviews

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