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Novel 9, 10-dihydrophenanthrene derivatives from *Eria bambusifolia* with cytotoxicity aganist human cancer cells *in vitro*

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[ABSTRACT] The present study was designed to identify bioactive compounds similar to those isolated from *Dendrobium* genus from its relative specie *Eria bambusifolia*. Compounds **1**–**10** were isolated and purified using silica gel, MCI CHP-20 gel, Sephadex LH-20, and Lichroprep RP-18 chromatography methods. Their structures were elucidated by means of extensive spectroscopic analyses. The cytotoxicity of these compounds against five human cancer cell lines was tested. Erathrins A and B (**1** and **2**) were new compounds, and compound **1** represented a novel carbon framework having a phenanthrene-phenylpropane unit with a dioxane moiety. Moreover, compound **1** showed selective cytotoxic activity against HL-60 cells (IC_{50} = 14.50 μmol·L^{-1}). These results provided a basis for future development of these agents as anticancer lead compounds.

[KEY WORDS] *Eria bambusifolia*; 9, 10-Dihydrophenanthrene; Erathrins A and B; Cytotoxicity

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Introduction

Medical plant Dendrobium is highly prized and widely used as Chinese folk medicine for a long history. Five species of *Dendrobium* named as "Shi-Hu" have been documented in the Chinese Pharmacopoeia [1-3]. Phytochemical investigations on this genus have confirmed that the stilbenoids (including bibenzyls and phenanthrenes), the major constituents of this genus, have a broad spectrum of biological activities, including anticancer, anti-angiogenesis, immunomodulatory, free radical scavenging, platelet aggregation inhibitory, nitric oxide production-inhibitory, and anti-senescence activities [4-16].

Previous investigations on some close relative genera of *Dendrobium* have shown that similar stilbenoids usually found in *Dendrobium* also exist in those genera, such as *Eria* genus [17]. In our research with the aim of discovering new bioactive stilbenoids, *Eria bambusifolia*, abundant in the southeast China, was phytochemically explored. The samples of this plant were collected in Yunnan Province, People's Republic of China. From the EtOAc-extract, ten 9, 10-dihydrophenanthrene derivatives, including a novel dihydrophenanthrenoligan, erathrin A (**1**), and a new phenanthrofuran, erathrin B (**2**), were isolated (Fig. 1). Compound **1** represented a novel carbon framework, having a phenanthrene-phenylpropane unit with a dioxane moiety. Reported herein are the isolation, structural elucidation, and biological evaluation of these compounds.

Results and Discussion

The MeOH extract of the air-dried and powdered aerial parts of *E. bambusifolia* was partitioned between EtOAc and H_2O. The EtOAc extract was subjected to column chromatography on silica gel, MCI CHP-20 gel, Sephadex LH-20, and Lichroprep RP-18 columns to afford two new phenolic compounds, which were named as erathrins A and B (**1** and **2**), along with eight known analogues. The structures of the known compounds were determined by comparing spectroscopic data with literature values and identified as shanciol G (**3**) [18], shanciol (**4**) [19], shanciol E (**5**) [20], flavanthrin (**6**) [21], coelonin (**7**) [22], 4,7-dihydroxy-2-methoxy-9,10-dihydrophenanthene (**8**) [23], 7-hydroxy-2, 3, 4-trimethoxy-9, 10-dihydrophenanthrene (**9**) [24], and methoxy-9, 10-dihydropheanthrene-1, 2, 7-triol (**10**) [25], respectively (Fig. 1).

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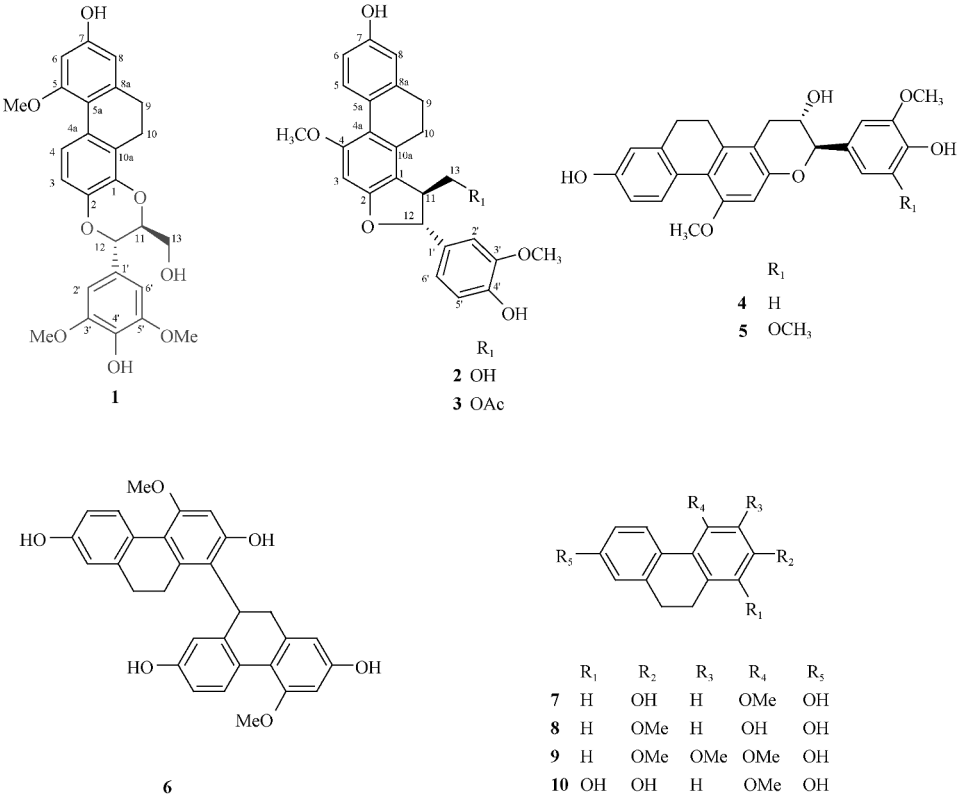

Fig. 1 Structures of compounds 1–10

Compound **1** was obtained as a colorless oil which gave the $[M + Na]^+$ ion peak at *m/z* 489.152 2 in HR-ESI-MS (Calcd. 489.152 5), indicating the molecular formula of $C_{26}H_{26}O_8$ and 14 degrees of unsaturation. Absorption bands at 3 431, 1 614, 1 464, and 820 cm^{-1} in the IR spectrum accounted for the presence of hydroxyl and phenyl groups. In the ^{13}C NMR and DEPT spectra, 26 carbon signals were observed, including three methoxyls (δ_C 56.7, 2C; δ_C 55.7, 1C), 18 aromatic carbons (six of them were methines), two oxidized methines (δ_C 79.3; δ_C 77.3), an oxidized methenes (δ_C 61.9), and two methenes (δ_C 30.7; δ_C 21.8). With the analysis of the ^1H NMR (Table 1), compound **1** was presumed to have a 9, 10-dihydrophenanthrene moiety and a symmetrically substituted phenyl ring.

HMBC correlations from H-10 to C-1, H-3, and H-4 to C-2, OMe to C-5, HO-7 to C-6, C-7, and C-8, along with two spin systems (CHCH H-3/H-4, CH_2CH_2 H-9/H-10) established by ^1H-^1H COSY and HSQC spectra, gave the partial structure of **1a** (Fig. 2). The HMBC spectrum showed that H-12 correlated with C-1′, C-2′ and C-6′; H-OMe correlated with C-3′ and C-5′; and H-4′-OH correlated with C-3′, C-4′ and C-5′. These evidences, coupling with the proton spin system deduced from the ^1H-^1H COSY correlations (-CHO-CHO-CH_2OH H-12/H-11/H-13), suggested the partial structure of phenylpropane unit **1b** (Fig. 2). The deshielded doublet at δ_H 4.98 (1H, d, J = 7.8 Hz, H-12), typical of a benzylic methine substituted by an oxygen, and the multiplet at δ_H 4.10 (1H, dd, J = 7.8, 3.5 Hz, H-11) which were coupled to each other implied the existence of a 1, 4-dioxane between the 9, 10-dihydrophenanthrene moiety and the phenyl ring [26-28]. HMBC correlations from H-12 to C-2 verified the positions of C-12 and C-11 in the 1,4-dioxane ring.

The configurations of the chiral centers were determined to be *trans* from the coupling constant ($J_{11,12}$ = 7.8 Hz) and the NOE correlations between H-13 and /H-2′ (Fig. 2). Therefore, erathrin A was established as the structure of compound **1**.

Compound **2** was obtained as colorless oil. The HR-ESI-MS gave a quasi-molecular ion peak at *m/z* 443.147 0 ($[M + Na]^+$), corresponding to the molecular formula of $C_{25}H_{24}O_6$. The 1D-NMR spectrum data (Table 1) indicated that compound **2** was a dihydrophenanthrofuran, very similar to pleionesin C [29]. In ^1H NMR spectrum, δ_H 6.97 (1H, d, J = 1.8 Hz), δ_H 6.83 (1H, dd, J = 8.1, 1.8 Hz), and δ_H 6.78 (1H, d, J = 8.1 Hz) suggested the existence of a 1, 3, 4-trisubstituented phenyl group. 2D-NMR spectra verified the above assumption and revealed that the differences between **2** and pleionesin C were the substituents at C-13 and C-5′. HMBC correlations verified that the dihydrophenanthrene moiety in compound **2** was the same as that in pleionesin C. In compound **2**, hydroxyl group connected to C-13, instead of acetyl group in pleionesin C, which was supported by peaks in HMBC between H-11/H-12 and C-13. Furthermore, the HMBC correlation peak between H-OMe and C-3′ suggested the linkage of OMe group at C-3′; and peaks between H-2′/H-5′ and C-4′ indicated the connection of OH to C-4′ in compound **2**.