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Antioxidant xanthones and anthraquinones isolated from a marine-derived fungus *Aspergillus versicolor*

WU Ze-Hong[1, 2], LIU Dong[2], XU Ying[3], CHEN Jian-Liang[1*], LIN Wen-Han[2*]

[1] *The Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen 518033, China;*
[2] *State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, China;*
[3] *Shenzhen Key Laboratory of Marine Bioresource & Eco-environmental Science, Shenzhen Engineering Laboratory for Marine Algal Biotechnology, College of Life Science, Shenzhen University, Shenzhen 518060, China*

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[ABSTRACT] Chemical examination of an EtOAc extract of cultured *Aspergillus versicolor* fungus from deep-sea sediments resulted in the isolation of four xanthones, eight anthraquinones and five alkaloids, including a new xanthone, oxisterigmatocystin D (**1**) and a new alkaloid, aspergillusine A (**13**). High resolution electron impact mass spectrometry (HR-EI-MS), FT-IR spectroscopy, and NMR techniques were used to elucidate the structures of these compounds, and the absolute configuration of compound **1** was established by its NMR features and coupling constant. Furthermore, the biosynthesis pathway of these xanthones and anthraquinones were deduced, and their antioxidant activity and cytotoxicity in human cancer cell lines (HTC-8, Bel-7420, BGC-823, A549, and A2780) were evaluated. The trolox equivalent antioxidant capacity (TEAC) assay indicated most of the xanthones and anthraquinones possessing moderate antioxidant activities. The Nrf2-dependent luciferase reporter gene assay revealed that compounds **6**, **7**, **9**, and **12** potentially activated the expression of Nrf2-regulated gene. In addition, compounds **5** and **11** showed weak cytotoxicity on A_{549} with the IC_{50} values of 25.97 and 25.60 μmol·L^{-1}, respectively.

[KEY WORDS] *Aspergillus versicolor*; Xanthones; Anthraquinones; Antioxidant activity; Cytotoxicity

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Introduction

Over the past years, more than 180 *Aspergillus* strains have been isolated from a host of terrestrial ecological niches, and they provide a steady stream of diverse small molecules [1]. Aflatoxin pathway, as a main biosynthesis pathway in the genus of *Aspergillus* [2-3], can produce abundant of xanthones and anthraquinones, which always show antioxidant activity and cytotoxicity [4-5]. The fungal strain *Aspergillus versicolor*, a species of this genus, also has been proven to be a rich source of diverse secondary metabolites with novel structures and interesting bioactivities [6-8].

As part of our ongoing research on structurally novel and bioactive compounds, the EtOAc extract of a fungus strain *A. versicolor* A-21-2-7, which was obtained from the marine sediment samples, has been studied. Chemical investigation resulted in the isolation of a new xanthone, oxisterigmatocystin D (**1**) and a new alkaloid, aspergillusine A (**13**), along with another three known xanthones (**2**−**4**), eight known anthraquinones (**5**−**12**), and four known alkaloids (**14**−**17**) (Fig. **1**). Their structure elucidation and biological activities are described here in detail.

Results and Discussion

Compound identification and structure elucidation

Chromatographic separation of the EtOAc extract of *A. versicolor* cultured in solid rice medium, including semipreparative HPLC purification, resulted in the isolation of compounds **1**−**17**, two of which were new.

Compound **1** was obtained as a pale yellow needle-like crystal, with the molecular formula of $C_{19}H_{16}O_7$ based on HRESIMS, ^{1}H NMR and ^{13}C NMR data (12 degrees of unsaturation). The IR absorption bands showed the presence of

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[*Corresponding author] Tel/Fax: 86-10-82806188, E-mails: chenjianliang2014@163.com (CHEN Jian-Liang); whlin@bjmu.edu.cn. (LIN Wen-Han);
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hydroxyl (2 917 cm^{-1}) and carbonyl (1 649 cm^{-1}) groups. The NMR data exhibited 18 carbon signals, including two benzene rings, two methoxy groups, one methylene, two methines, and a keto carbonyl group (δ_C 180.9). Careful analysis of 1D NMR data (Table **1**) revealed that compound **1** had a similar sterigmatocystin skeleton as that of oxisterigmatocystin C (**2**) [9], which also could be confirmed by the COSY correlations of H-5/H-6/H-7 and H-1′/H-2′/H-3′/H-4′, and the HMBC correlations from H-2 to C-1/C-3/C-4/C-9a, H-6 to C-8a/C-10a, and OH-8 to C-7/C-8/C-8a, as shown in Fig. **2**. Furthermore, the methoxyl groups could be assigned at C-1 and C-4′, respectively, based on the HMBC correlations from 1-OMe (δ_H 3.90, s) to C-1 (δ_C 163.5) and from 4′-OMe (δ_H 3.37, s) to C-4′ (δ_C 107.0) (Fig. **2**). The ^{1}H and ^{13}C NMR data of compound **1** were almost identical to those of compound **2** except that they had different coupling patterns of H-2′, H-3′, and H-4′ (Table **1**). Thus, compound **1** was proposed as a diastereomer of compound **2**, with the absolute configurations of 1′*R*, 2′*S* and 4′*S* [9]. Thus, the structure of **1** was elucidated, and named as oxisterigmatocystin D.

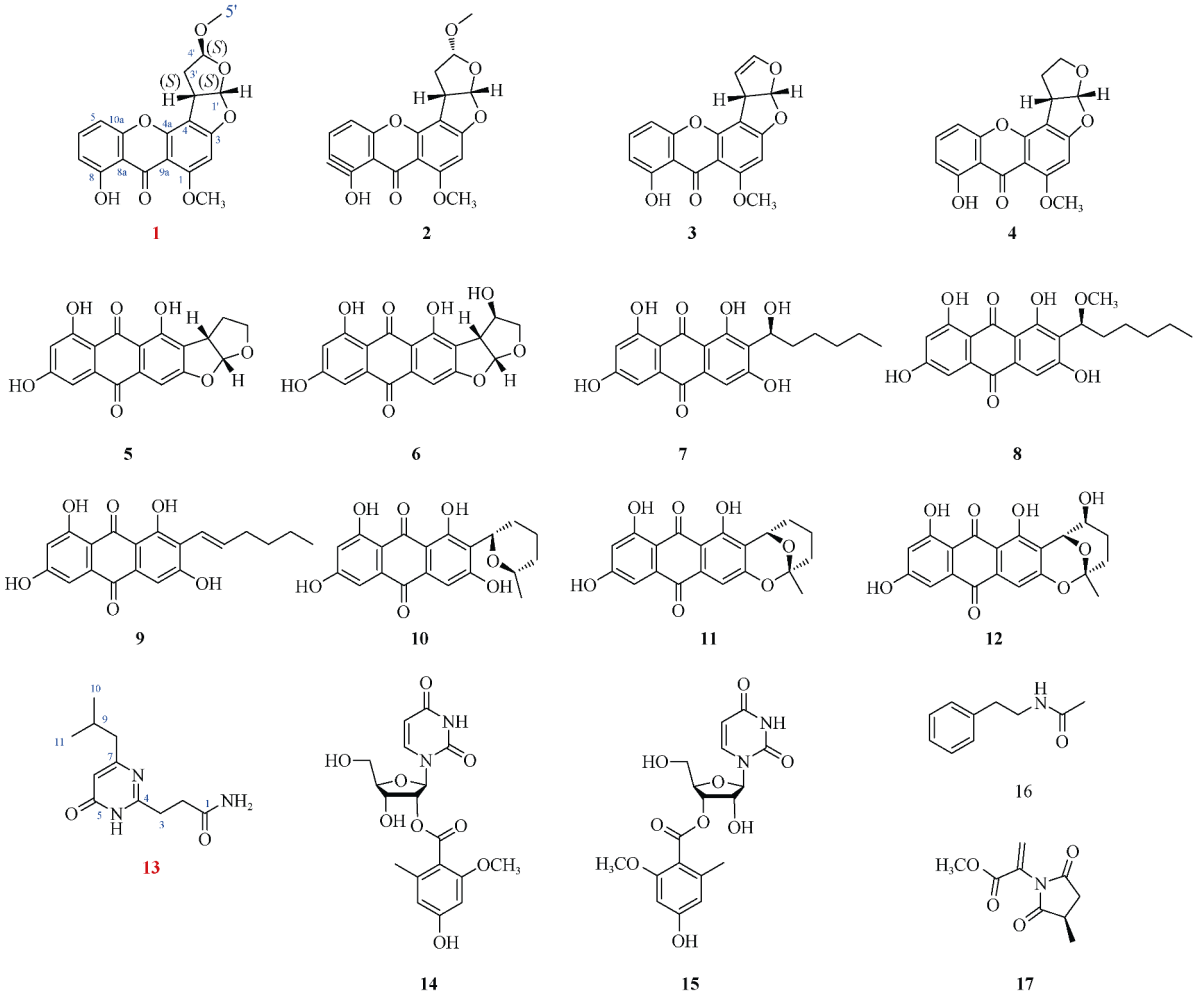

Fig. 1 Structures of compounds 1–17

Aspergillusine A (**13**), isolated as a colorless needle-like crystal, was assigned the molecular formula of $C_{11}H_{17}N_3O_2$ by the HRESIMS data (*m/z* 224.138 5 $[M + H]^+$) with 5 degrees of unsaturation. The IR absorptions at 3 404 cm^{-1} and 1 652 cm^{-1} suggested the presence of amino group (-NH) and carbonyl group. The 1D NMR and HSQC (Table 2) spectra provided the resonances for 11 carbon signals, including two methyl (δ_C, 22.3; δ_H 0.84, d), three methylene (δ_H 2.79, t; 2.41, t; 2.24, d), one methine (δ_H 1.90, m), one tri-substituted double bond (δ_H 7.00, s), two quaternary carbons, and an amide carbonyl group (δ_C 174.2). The ^{1}H-^{1}H COSY correlations between H_2-2 and H_2-3, H-9 and H_2-8/H_3-10/H_3-11, together with the HMBC correlations from H-6 to C-5/C-7, from H_2-8 to C-6/C-7, from H_2-3 to C-4, from H_2-2 to C-1, and from NH_2 to C-1 indicated the structure units and the basic skeleton of compound **13** (Fig. 2). The lower field location of NH group (δ_H 12.05, s) in ^{1}H NMR indicated the NH was nearby with the carbonyl. All the information mentioned above showed that the structure of **13** probably contained a pyrimidine ring, which could be further certified by the chemical shifts of C-4, C-5 and C-7 in ^{13}C-APT spectrum (Table 2), and the linkage of the two residues was also assigned (Fig. 2). Thus, the structure of **13** was determined (Fig. 1).

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