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Short communication

Bioactive secondary metabolites from the marine-associated fungus *Aspergillus terreus*

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ABSTRACT

Three new compounds, including a prenylated tryptophan derivative, luteoride E (**1**), a butenolide derivative, versicolactone G (**2**), and a linear aliphatic alcohol, (3*E*,7*E*)-4,8-dimethyl-undecane-3,7-diene-1,11-diol (**3**), together with nine known compounds (**4**–**12**), were isolated and identified from a coral-associated fungus *Aspergillus terreus*. Their structures were elucidated by HRESIMS, one- and two-dimensional NMR analysis, and the absolute configuration of **2** was determined by comparison of its electronic circular dichroism (ECD) spectrum with the literature. Structurally, compound **1** featured an unusual (*E*)-oxime group, which occurred rarely in natural products. Compounds **1**–**3** were evaluated for the α-glucosidase inhibitory activity, and compound **2** showed potent inhibitory potency with IC_{50} value of 104.8 ± 9.5 μM, which was lower than the positive control acarbose (IC_{50} = 154.7 ± 8.1 μM). Additionally, all the isolated compounds were evaluated for the anti-inflammatory activity against NO production, and compounds **1**–**3**, **5**–**7**, and **10** showed significant inhibitory potency with IC_{50} values ranging from 5.48 to 29.34 μM.

1. Introduction

With times moving rapidly, some new techniques and methods, such as synthetic biology [1], heterologous expression of gene clusters [2], OSMAC (One Strain/Many Compounds) [3], co-culture [3], etc., were successfully applied to explore the chemical space of terrestrial fungi, thus searching for new bioactive natural products from terrestrial fungi is becoming increasingly difficult. On the contrary, the ocean, which covers over 70% of the Earth's surface, is a neglected and insufficiently explored natural resource [4]. In recent years, the chemical investigations on marine organisms are increasing, of which many findings showed that marine-associated fungi are a prolific and promising resource of structurally novel and pharmaceutically active metabolites [5,6], including alkaloids, polyketides, terpenes, lignans, steroids, cyclic peptides, etc., with the surprising potentials for medicinal chemistry development, clinical trials and marketing.

Secondary metabolites that are produced by the *Aspergillus* species have attracted much attention from scientific community, because of their architecturally complex frameworks with multiple chiral centers and temping biological profiles. Representative examples included asperflavipine A [7], aspergilasines A–D [8], asperterpenes A and B [9], spiroaspertrione A [10], aspermerodione [11], and aspergillines A–E [12]. As part of our program to discover novel bioactive chemicals from marine-associated fungi [13–15], we performed a chemical investigation on a coral-associated fungus *Aspergillus terreus*, leading to the isolation and identification of three new compounds, including a prenylated tryptophan derivative, luteoride E (**1**), a butenolide derivative, versicolactone G (**2**), and a linear aliphatic alcohol, (3*E*,7*E*)-4,8-dimethyl-undecane-3,7-diene-1,11-diol (**3**), together with nine known compounds, which were identified as asterrelenin (**4**) [16], methyl 3,4,5-trimethoxy-2-(2-(nicotinamido)benzamido)benzoate (**5**) [17], 14α-hydroxyergosta-4,7,22-triene-3,6-dione (**6**) [18], territrem A (**7**) [19], territrem B (**8**) [20], territrem C (**9**) [20], lovastatin (**10**) [21], monacolin L acid methyl ester (**11**) [22], and monacolin L (**12**) [22] by detailed comparison of their NMR data and specific rotations with the literature. Remarkably, compound **1** featured an unusual (*E*)-oxime group, which occurred rarely in natural products. Herein, the details of the isolation, structural elucidation, and bioactivity evaluations of these compounds (Fig. 1) are described.

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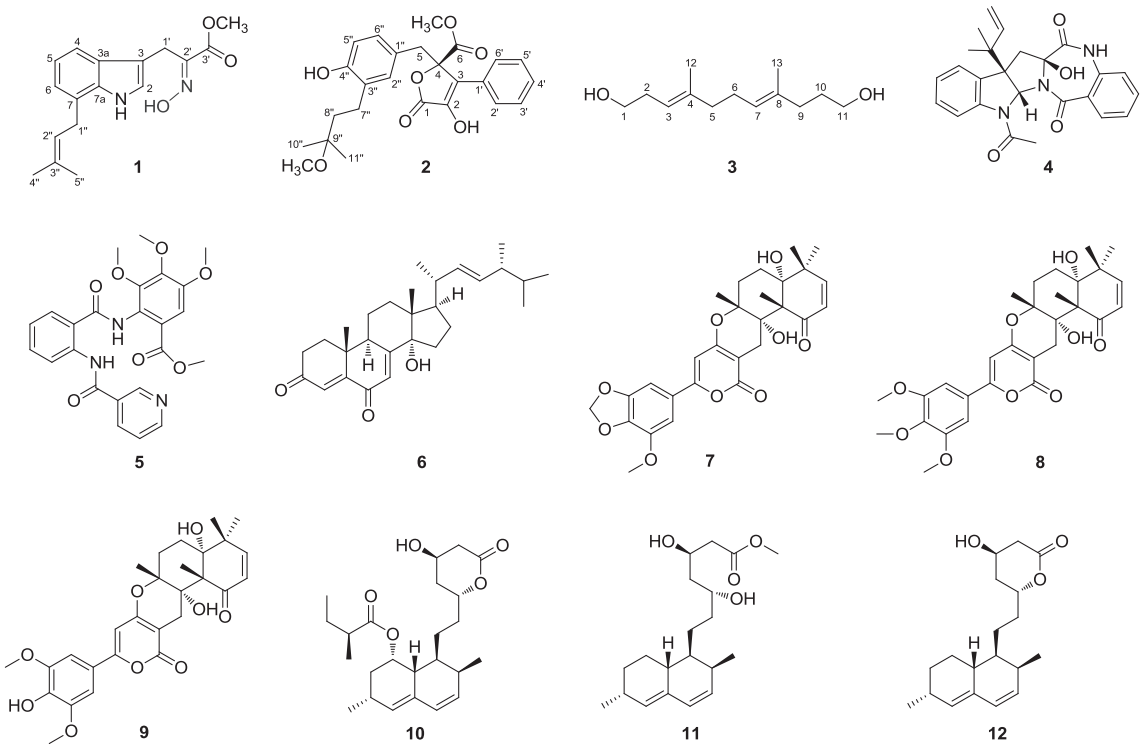

Fig. 1. Structures of compounds **1–12**.

2. Experiment

2.1. General

Optical rotations, UV, and FT-IR data were recorded on a PerkinElmer 341 instrument, a Varian Cary 50 instrument, and a Bruker Vertex 70 instrument with KBr pellets, respectively. ECD data were measured with a JASCO-810 CD spectrometer instrument. The high-resolution electrospray ionization mass spectra (HRESIMS) were recorded by using a positive ion mode on a Thermo Fisher LC-LTQ-Orbitrap XL instrument. One- and two-dimensional NMR data were recorded on a Bruker AM-400 instrument, with the reference of ^{1}H and ^{13}C NMR chemical shifts of the solvent peaks for methanol-d_4 (δ_H 3.31 and δ_C 49.0) and $CDCl_3$ (δ_H 7.24 and δ_C 77.23). Semi-preparative HPLC purifications were carried out by using an Agilent 1100 instrument with a Zorbax SB-C_{18} (9.4 mm × 250 mm) column. Column chromatography (CC) was carried out by using silica gel (200–300 mesh, Qingdao Marine Chemical, Inc., Qingdao, People's Republic of China), Lichroprep RP-C_{18} gel (40–63 μm, Merck, Darmstadt, Germany), and Sephadex LH-20 (GE Healthcare Bio-Sciences AB, Sweden). Silica gel 60 F_{254} and RP-C_{18} F_{254} plates were used for the TLC (thin-layer chromatography) detection, and spots were visualized by spraying heated silica gel plates with 10% H_2SO_4 in EtOH.

2.2. Fungal material

The strain *Aspergillus terreus* was separated from the coral *Sarcophyton subviride*, which was collected from the coast of Xisha Island in the South China Sea, in October 2016. For identification, this strain was cultured on potato dextrose agar (PDA) at 28 °C for a week in an incubator. The strain was identified based on its morphology analysis and ITS (Internal Transcribed Spacer) sequencing data of the rDNA. The ITS sequence data of this strain has been deposited at the GenBank (accession number MF972904). The fungal sample was deposited in the culture collection of Tongji Medical College, Huazhong University of Science and Technology.

2.3. Fermentation, extraction, and purification

The strain *Aspergillus terreus* was incubated on potato dextrose agar (PDA) medium at 28 °C for a week to prepare the seed cultures, which was then transferred into 300 × 500 mL Erlenmeyer flasks, each containing 200 g cooked rice. 28 days later, 300 mL EtOAc was added to each flask to stop the growth of cells, and followed by ultrasonic extraction with 95% aqueous EtOH at room temperature. Afterwards, the solvent was removed under reduced pressure to yield a total residue, which was then suspended in water and partitioned repeatedly with EtOAc (6 × 15 L). The EtOAc extract (1.5 kg) was chromatographed on silica gel CC using an increasing gradient of petroleum ether–ethyl acetate–MeOH (10:1:0, 7:1:0, 5:1:0, 3:1:0, 1:1:0, 2:2:1, 1:1:1) to afford seven fractions (A–G).

Fraction B (55 g) was chromatographed on silica gel CC (petroleum ether–ethyl acetate, 8:1–0:1, v/v) to yield three main fractions (B1–B3). Repeated purification of fraction B2 (4.6 g) using Sephadex LH-20 eluted with CH_2Cl_2–MeOH (1:1, v/v), RP-C_{18} column (MeOH–H_2O, from 30:70 to 100:0, v/v), and semi-preparative HPLC (isopropanol-*n*-hexane, 10:90, v/v, 2.0 mL/min) afforded compound **6** (t_R 12.2 min, 4.4 mg).

Fraction C (75 g) was subjected to an RP-C_{18} column eluted with MeOH–H_2O (from 20:80 to 100:0, v/v) to yield five fractions (C1–C5). Fraction C3 (2.3 g) was chromatographed on Sephadex LH-20 eluted with CH_2Cl_2–MeOH (1:1, v/v) to yield two fractions (C3.1–C3.2). Fraction C3.2 was further purified via repeated silica gel CC (stepwise petroleum ether–ethyl acetate, 4:1–1:1) to furnish three additional fractions (C3.2.1–C3.2.3). Purification of fraction C3.2.1 by using semi-preparative HPLC eluted with MeOH–H_2O (70:30, v/v, 3.0 mL/min) afforded compound **1** (t_R 27.2 min, 3.9 mg). Compound **2** (t_R 20.6 min, 4.5 mg) was purified by semi-preparative HPLC (MeOH–H_2O, 68:32, v/v, 3.0 mL/min) from fraction C3.2.2.

Fraction D (198 g) was separated by RP-C_{18} column with MeOH–H_2O (from 20:80 to 100:0, v/v) as eluent to yield five fractions (D1–D5) based on TLC analysis. Fraction D1 (45 g) was consecutively separated through Sephadex LH-20 eluted with CH_2Cl_2–MeOH (1:1, v/v) and silica gel CC