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SECONDARY METABOLITES OF THE ENDOPHYTIC FUNGI *Penicillium polonicum* AND THEIR MONOAMINE OXIDASE INHIBITORY ACTIVITY

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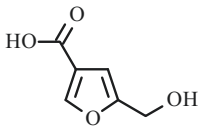
Plant endophytic fungi are well known as common sources of bioactive secondary metabolites [1, 2]. *Penicillium polonicum* is a species of the genus *Penicillium*, which produces a variety of bioactive natural products such as antibiotics, antifungal, anticancer, and a potential chemotherapeutic agent [3–5]. Monoamine oxidase inhibitors (MAOIs) are chemicals that inhibit the activity of the monoamine oxidase enzyme family. They have a long history of use as medications prescribed for the treatment of depression [6]. They are also used in the treatment of Parkinson′s disease and several other disorders.

Endophytic fungi (SMH-3) was isolated from stems of the Chinese medicinal plant *Desmodium elegans* identified as *Penicillium polonicum* based on both morphology on PDA and analysis of the DNA sequences of the ITS1-5.8S-ITS2 ribosomal RNA gene region. A GenBank search for DNA sequence similarity revealed that ITS1-5.8S-ITS2 of SMH-3 was 99% homologous to that of *Penicillium polonicum* reference strain (GenBank accession No. JF731260).

In investigations of new MAO inhibitors, we found that the extract of strain SMH-3 showed relatively high monoamine oxidase inhibitory activity. The isolation led to six compounds that were identified as flufuran (**1**) [7], deacetylfructigenine A (**2**) [8], fructigenine B (**3**) [8], *N*-(4-hydroxy-2-methoxyphenyl)acetamide (**4**) [9], ergosterol (**5**) [10], and ergosterol peroxide (**6**) [11], and their structures were identified based on MS and NMR spectral data by comparing their ^{1}H NMR and ^{13}C NMR data with those reported in the literature.



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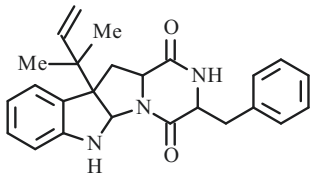

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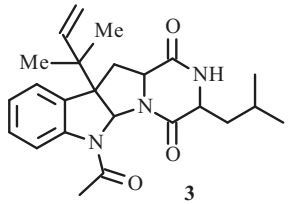

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Compound **1** showed relatively high anti-monoamine oxidase activity with IC_{50} of 16.2 ± 0.9 μM; the IC_{50} of iproniazid A as standard was 0.95 ± 0.1 μM; compounds **2–6** showed weak inhibitory activity against MAO (Table 1).

Extraction and Isolation of the Metabolites. The strain SMH-3 was inoculated into 10 Erlenmeyer flasks (500 mL) for 7 days, each containing 250 mL potato-dextrose broth (PDB). Then the cultures were transferred into 50 L fermenters, which were cultured in 50 LPDB media at 28°C for 20 days. The fermented broth (50 L) was extracted with EtOAc (50 L × 2) to afford the crude extract (3.1 g). The crude extract was subjected to macroporous resin column chromatography and eluted with a gradient of aqueous EtOH (20%, 40%, 60%, 80%, 100%) to give six fractions (A–F). Fractions A and C were subjected to HPLC separation (Waters-510 pump, Waters 2487 Dual λ absorbance detector, YMC-Pack ODS-A column, 250 × 10 mm, 5 μm). Fraction A was eluted with MeOH–water (25:75, flow rate 2 mL/min, 254 nm) to yield compounds **1** (13 mg, t_R = 9 min) and **4** (6 mg, t_R = 21 min). Fraction C was eluted with MeOH–H_2O (74:26, flow rate 2 mL/min, 254 nm) to yield compounds **2** (8.1 mg, t_R = 17 min) and **3** (9 mg, t_R = 15 min). Fraction F was subjected to silica gel column chromatography (GF254, 200–300 mesh) eluting with petroleum ether–acetone (5:1) to give compounds **5** (8 mg) and **6** (12 mg).

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TABLE 1. The Inhibitory Activity of Compounds **1–6** against MAO (IC_{50} ± S.D, μM)

Compound	Inhibition rate at 100 μg/mL, %	IC_{50} value, μM	Compound	Inhibition rate at 100 μg/mL, %	IC_{50} value, μM
Crude extract	51.6 ± 2.4	121 ± 3.5	**4**	13.8 ± 2.1	NULL
1	80.4 ± 1	16.9 ± 0.9	**5**	5.7 ± 3.7	NULL
2	8.5 ± 1.7	NULL	**6**	11.6 ± 4.3	NULL
3	8.9 ± 3.2	NULL	Iproziazid*		0.95 ± 0.1

*Iproziazid is a positive control.

Bioassay Procedures for MAO Inhibition. The procedure for testing MAO inhibiting activity was the same as that reported in our pervious paper [12].

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