

## A New Indole Glucoside and Other Constituents from the Sea Cucumber-Derived *Aspergillus fumigatus* M580 and Their Biological Activities

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**Abstract:** One new indole glucoside, 6-methoxyindole-3-carboxylic acid *O*- $\beta$ -D-glucopyranosyl ester (**1**) and ten known alkaloids, fumiquinazoline D (**2**), fumiquinazoline C (**3**), fumiquinazoline J (**4**), bisdethiobis(methylthio)gliotoxin (**5**), cyclo(L-prolyl-L-tryptophane) (**6**), tryprostatin B (**7**), 12,13-dihydroxy-fumitremorgin C (**8**), 6-methoxyspirotryprostatin B (**9**), cyclo(L-prolinyl-L-phenylalanine) (**10**), and cyclo(L-prolinyl-L-valine) (**11**) were isolated from marine-derived *Aspergillus fumigatus* M580. Compounds **2**, **3**, and **7** exhibited significant antimicrobial activity against Gram-positive *Enterococcus faecalis* with MIC values of 32, 32, and 64  $\mu$ g/mL, respectively. Compound **4** showed significant cytotoxic activities against Huh7 and HT-29 cancer cell lines with IC<sub>50</sub> values of  $9.7 \pm 0.9$  and  $10.3 \pm 0.9$   $\mu$ M, respectively. Compounds **3** and **10** showed the most  $\alpha$ -glucosidase inhibitory activity with inhibitory percentages of  $13.6 \pm 1.1$  and  $10.3 \pm 0.8$  % at the concentration of 100  $\mu$ g/mL, respectively.

**Keywords:** *Aspergillus fumigatus*; indole; alkaloid; antimicrobial; cytotoxic;  $\alpha$ -glucosidase. © 2022 ACG Publications. All rights reserved.

### 1. Animal and Fungal Sources

As part of our research program on the finding of bioactive compounds from fungal endophytes, we investigated chemical components and biological activities of an endophytic fungus *Aspergillus fumigatus* M580 associated with *Colochirus quadrangularis* Troschel, 1846. Herein, we reported the isolation, structural elucidation of one new and ten known alkaloids (Figure 1) and

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evaluation of their antimicrobial, cytotoxic, and  $\alpha$ -glucosidase inhibitory effects from *Aspergillus fumigatus* M580.

The sea cucumber *Colochirus quadrangularis* Troschel, 1846 was collected in Co To-Thanh Lan island, Vietnam on August 19, 2019, at 14 m depth at geographic coordinates 21°02'23"-107°45'40" and temperature at 28°C. Voucher specimen, 169h\_PDA and CT-2-3-4 was deposited at the Institute of Marine Biochemistry, VAST and Haiphong University of Medicine and Pharmacy, respectively.

The above-mentioned sea cucumber was collected in a 50 mL sterile falcon tube, preserved on ice, and processed within 24 h. The strain M580 was isolated from the acquired sea cucumber and identified as *Aspergillus fumigatus* M580 using 18S rRNA gene sequence analysis (GenBank accession no. MW015802). Strain M580 was activated and inoculated into 2.5 L of PDA medium, pH = 7 (30 g/L potato extract, 20 g/L dextrose, 5 g/L soluble starch, 30g/L instant ocean and distilled water). After 10 days of fermentation at 28 °C and 100 rpm agitation, the acquired fermentation (1 L) was used to inoculate 50 L fermentation in PDA media. The fermentation was incubated at 28 °C, 100 rpm agitation and harvested on the 14<sup>th</sup> day following previously reported method [1].

## 2. Previous Studies

Fungi have produced potential and valuable bioactive compounds. The secondary metabolites produced from *Aspergillus* species play an important role in medical, industrial, and agricultural importance [2]. In addition, these compounds exhibited antimicrobial, cytotoxic, and other activities. The chemical constituents from *Aspergillus fumigatus* have been reported [3-7].

## 3. Present Study

The fermentation broth (50 L) of *Aspergillus fumigatus* M580 was harvested then extracted with ethyl acetate (5x40 L) to give ethyl acetate extract. The ethyl acetate extract was concentrated under reduced pressure and used for antimicrobial assays and isolation studies. The ethyl acetate extract showed antimicrobial activity against microorganisms, *Enterococcus faecalis* (ATCC29212), *Staphylococcus aureus* (ATCC25923), *Escherichia coli* (ATCC25922), and *Candida albicans* (ATCC10231) with MIC values of 16, 32, 32, and 16  $\mu$ g/mL, respectively. Using various chromatographic methods of ethyl acetate extract from *A. fumigatus* M580 revealed one new and ten known alkaloids.

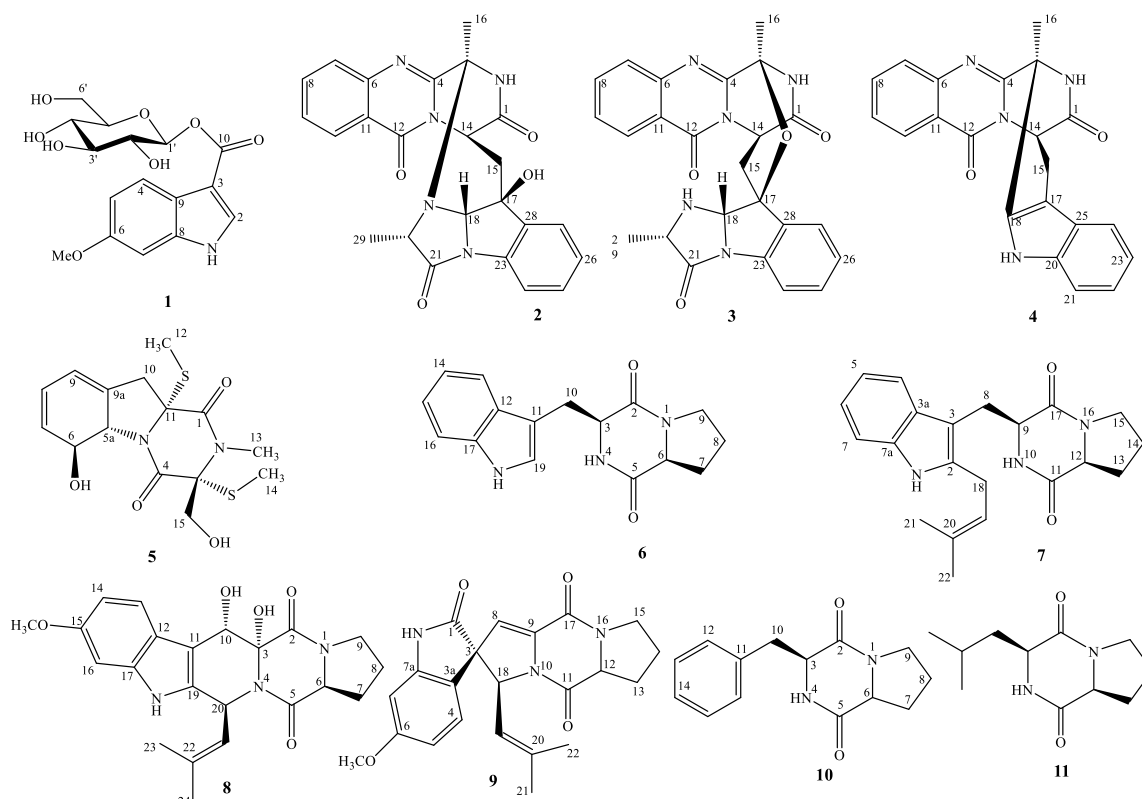
The ethyl acetate extract (15.0 g) was loaded on a silica gel column chromatography (CC) and eluted with a solvent system of *n*-hexane–acetone (40:1, 20:1, 10:1, 5:1, 1:1, v/v) to give five fractions, ML1A (1.1 g), ML1B (0.5 g), ML1C (1.3 g), ML1D (0.4 g), and ML1E (2.2 g), respectively. ML1C fraction was further chromatographed on an RP-18 CC using acetone–water (1:1, v/v) as the eluent solvent to give five fractions, ML1C1 (0.38 g), ML1C2 (0.32 g), ML1C3 (0.22 g), ML1C4 (0.03 g), and ML1C5 (0.1 g). The ML1C1 fraction was chromatographed on an HPLC system (J'sphere column, ODS H-80, 4  $\mu$ m, 250 mm length  $\times$  20 mm ID) eluting 15 % acetonitrile in water with a flow rate of 3 mL/min to yield compounds **1** (6.0 mg) and **5** (12.0 mg). The ML1C2 fraction was chromatographed on an HPLC system (J'sphere column, ODS H-80, 4  $\mu$ m, 250 mm length  $\times$  20 mm ID) eluting 25 % acetonitrile in water with a flow rate of 3 mL/min to yield compounds **6** (15.0 mg), **10** (20.0 mg), and **11** (10.0 mg). The ML1C3 fraction was chromatographed on an HPLC system (J'sphere column, ODS H-80, 4  $\mu$ m, 250 mm length  $\times$  20 mm ID) eluting 40 % acetonitrile in water with a flow rate of 3 mL/min to yield compounds **2** (18.0 mg) and **9** (5.0 mg). Finally, ML1C3 fraction was chromatographed on an HPLC system (J'sphere column, ODS H-80, 4  $\mu$ m, 250 mm length  $\times$  20 mm ID) eluting 45 % acetonitrile in water with a flow rate of 3 mL/min to yield compounds **3** (6.0 mg), **7** (6.0 mg), and **8** (8.0 mg).

*6-Methoxyindole-3-carboxylic acid O- $\beta$ -D-glucopyranosyl ester (1)*: White amorphous powder;  $[\alpha]_D^{25}$  –66.8 (*c* 0.1, MeOH); HR-ESI-MS *m/z* 354.1165  $[M+H]^+$  (Calcd. for  $[C_{16}H_{20}NO_8]^+$ , 354.1183) on <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta_H$ : 7.97 (s, H-2), 7.96 (d, *J* = 7.5 Hz, H-4), 6.87 (dd, *J* = 2.0, 8.0 Hz, H-5), 6.99 (d, *J* = 2.0 Hz, H-7), 5.74 (d, *J* = 7.5 Hz, H-1'), 3.85 (s, OCH<sub>3</sub>), 3.55 (dd, *J* = 7.5, 9.0 Hz, H-2'),

3.54 (t,  $J = 9.0$  Hz, H-3'), 3.46 (t,  $J = 9.0$  Hz, H-4'), 3.47 (m, H-5'), 3.74 (dd,  $J = 5.5, 12.0$  Hz, H<sub>a</sub>-6'), and 3.88 (dd,  $J = 2.0, 12.0$  Hz, H<sub>b</sub>-6');  $^{13}\text{C}$  NMR (CD<sub>3</sub>OD)  $\delta_{\text{C}}$ : 133.2 (C-2), 107.6 (C-3), 122.6 (C-4), 112.8 (C-5), 158.4 (C-6), 96.1 (C-7), 139.0 (C-8), 121.5 (C-9), 165.7 (C-10), 95.8 (C-1'), 74.2 (C-2'), 78.3 (C-3'), 71.2 (C-4'), 78.8 (C-5'), 62.4 (C-6'), and 56.0 (OCH<sub>3</sub>).

**Biological Activity Assays:** All isolated compounds were evaluated for their antimicrobial activity against microorganisms, Gram-positive bacteria (*Enterococcus faecalis* and *Staphylococcus aureus*), Gram-negative bacteria (*Escherichia coli* and *Salmonella enterica*), and yeast (*Candida albicans*), using dilution turbidimetric broth method as the standard protocols published by the Clinical and Laboratory Standard Institute [8]. Compounds were also evaluated for cytotoxic activity [9] and  $\alpha$ -glucosidase inhibitory activity [10].

Compound **1** was isolated as a white amorphous powder. The molecule of **1** was determined to be C<sub>16</sub>H<sub>19</sub>NO<sub>8</sub> by a molecular ion peak at  $m/z$  354.1165 [M+H]<sup>+</sup> (Calcd. for [C<sub>16</sub>H<sub>20</sub>NO<sub>8</sub>]<sup>+</sup>, 354.1183) on HR-ESI-MS. The  $^1\text{H}$ -NMR spectrum of **1** showed three aromatic protons of an ABX aromatic spin system at  $\delta_{\text{H}}$  6.87 (1H, dd,  $J = 2.0, 8.0$  Hz), 6.99 (1H, d,  $J = 2.0$  Hz), and 7.96 (1H, d,  $J = 8.0$  Hz), one singlet aromatic proton at  $\delta_{\text{H}}$  7.97 (1H, s), one anomeric proton at  $\delta_{\text{H}}$  5.74 (1H, d,  $J = 7.5$  Hz), and one methoxy group at  $\delta_{\text{H}}$  3.85 (3H, s). The  $^{13}\text{C}$ -NMR and HSQC spectra of **1** exhibited resonances signals of 16 carbons classified into one carboxyl carbon ( $\delta_{\text{C}}$  165.7), four non-protonated carbons ( $\delta_{\text{C}}$  107.6, 121.5, 139.0, and 158.4), nine methines ( $\delta_{\text{C}}$  71.2, 74.2, 78.3, 78.8, 95.8, 96.1, 112.8, 122.6, and 133.2), one methylene ( $\delta_{\text{C}}$  62.4), and one methoxy carbon ( $\delta_{\text{C}}$  56.0). Analysis of  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data indicated the structure of **1** was similar to that of indole-3-carboxylic acid *O*- $\beta$ -D-Glucopyranosyl ester [11] except for the addition of methoxy group at C-6 of indole moiety. The position of methoxy group at C-6 of indole was determined by the HMBC correlations from H-4 ( $\delta_{\text{H}}$  7.96) to C-3 ( $\delta_{\text{C}}$

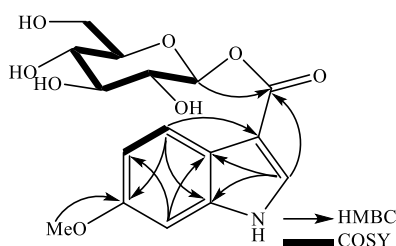


**Figure 1.** The chemical structures of compounds **1-11**

107.6)/C-6 ( $\delta_{\text{C}}$  158.4)/C-8 ( $\delta_{\text{C}}$  139.0)/C-9 ( $\delta_{\text{C}}$  121.5), from H-7 ( $\delta_{\text{H}}$  96.1) and C-5 ( $\delta_{\text{C}}$  112.8)/C-6 ( $\delta_{\text{C}}$  158.4)/C-8 ( $\delta_{\text{C}}$  139.0)/C-9 ( $\delta_{\text{C}}$  121.5) and from methoxy proton ( $\delta_{\text{H}}$  3.85) to C-6 ( $\delta_{\text{C}}$  158.4). The position of the carboxyl group at C-3 was determined by HMBC correlation between H-2 ( $\delta_{\text{H}}$  7.97) and carboxyl carbon ( $\delta_{\text{C}}$  165.7). The monosaccharide glucose occurs naturally in the form of D-

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glucose. The  $^{13}\text{C}$ -NMR chemical shifts for the monosaccharide for **1** are  $\delta_{\text{C}}$  95.8, 74.2, 78.3, 71.2, 78.8, and 62.4 and the multiplicity of the anomeric proton as [ $\delta_{\text{H}}$  5.74 (d,  $J = 7.5$  Hz)] is similar to that of  $\beta$ -glucopyranosyl. Furthermore, the monosaccharide was shown to be D-glucose using acid hydrolysis (identified as trimethylsilyl derivative by GC method) [12]. Therefore, the sugar moiety was determined to be  $\beta$ -D-glucopyranosyl. The position of the sugar moiety at C-10 was confirmed by HMBC correlations between H-2 ( $\delta_{\text{H}}$  7.97) and C-3 ( $\delta_{\text{C}}$  107.6)/C-10 ( $\delta_{\text{C}}$  165.7) and between glc H-1' ( $\delta_{\text{H}}$  5.74) and C-10 ( $\delta_{\text{C}}$  1665.7) (Figure 2). Consequently, the new structure of **1** was defined to be 6-methoxyindole-3-carboxylic acid *O*- $\beta$ -D-glucopyranosyl ester.



**Figure 2.** The key HMBC and COSY correlations of compound **1**

The known compounds were determined as fumiquinazoline D (**2**) [4], fumiquinazoline C (**3**) [4], fumiquinazoline J (**4**) [13], bisdethiobis(methylthio)gliotoxin (**5**) [4], cyclo(L-prolyl-L-tryptophane) (**6**) [14], tryprostatin B (**7**) [15, 16], 12,13-dihydroxy-fumitremorgin C (**8**) [3], 6-methoxyspirotryprostatin B (**9**) [17], cyclo(L-prolinyl-L-phenylalanine) (**10**) [18], and cyclo(L-prolinyl-L-valine) (**11**) [19] (Figure 1) by comparing their NMR data with those reported in literature.

**Table 1.** Antimicrobial activity of ethyl acetate extract and compounds from *A. fumigatus*

Compounds	MIC ( $\mu\text{g/mL}$ )				
	Gram (+)		Gram (-)		Yeast
	<i>E. faecalis</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>S. enterica</i>	<i>C. albicans</i>
<b>EtOAc ext.</b>	16	32	32	-	16
<b>1</b>	-	-	-	-	-
<b>2</b>	32	-	-	256	128
<b>3</b>	32	-	-	256	64
<b>4</b>	128	64	-	-	128
<b>5</b>	256	-	-	-	128
<b>6</b>	-	-	-	-	-
<b>7</b>	64	-	-	256	128
<b>8</b>	256	-	-	-	256
<b>9</b>	256	-	-	-	128
<b>10</b>	-	-	-	-	-
<b>11</b>	-	-	-	-	-
<b>Streptomycin</b>	256	256	32	128	-
<b>Cyclohexamide</b>	-	-	-	-	32

(-) compound did not exhibit antimicrobial activity (MIC >256  $\mu\text{g/mL}$ )

All isolated compounds were evaluated for their antimicrobial activity against microorganisms, Gram-positive bacteria (*Enterococcus faecalis* ATCC29212 and *Staphylococcus aureus* ATCC25923), Gram-negative bacteria (*Escherichia coli* ATCC25922 and *Salmonella enterica* ATCC13076), and yeast (*Candida albicans* ATCC10231), using dilution turbidimetric broth method as the standard protocols published by the Clinical and Laboratory Standard Institute [8], (Table 1). Streptomycin, an antimicrobial reagent, was used as a positive control. Streptomycin inhibits Gram-positive bacteria (*E. faecalis* and *S. aureus*), Gram-negative bacteria (*E. coli* and *S. enterica*) with MIC values of 256, 256, 32, and 128  $\mu\text{g/mL}$ , respectively. Compounds **2**, **3**, and **7** showed significant antimicrobial activity on Gram-positive *E. faecalis* with MIC values of 32, 32, and 64  $\mu\text{g/mL}$ , respectively (Table 1). Compound **3** showed significant antimicrobial activity on yeast *C.*

*albicans* with MIC value of 64  $\mu\text{g/mL}$ . Compounds **2**, **4**, **5**, **7**, and **9** showed antimicrobial activity on yeast *C. albicans* with all MIC values of 128  $\mu\text{g/mL}$ . However, all compounds did not inhibit the growth of other tested strains (MIC > 256  $\mu\text{g/mL}$ ). The results suggested compounds **3** and **7** could be potential antimicrobial agents.

All compounds were also evaluated for cytotoxic activity against two human cancer cell lines, Huh7 (human hepatocarcinoma) and HT-29 (colon carcinoma) (Table S1). Compared to ellipticine, compound **4** showed significant cytotoxic activities against Huh7 and HT-29 cancer cell lines with  $\text{IC}_{50}$  values ranging from  $9.7 \pm 0.9$  and  $10.3 \pm 0.9$   $\mu\text{M}$ . Compounds **2** and **3** showed weak cytotoxic activity on all tested human cancer cell lines with  $\text{IC}_{50}$  values ranging from 60.9 to 70.9  $\mu\text{M}$ . Remaining compounds did not show cytotoxic activities.

All compounds **1-11** were evaluated for their  $\alpha$ -glucosidase inhibitory activity [10]. As the results, compounds **3** and **10** showed the most  $\alpha$ -glucosidase inhibitory activity with inhibitory percentages of  $13.6 \pm 1.1$  and  $10.3 \pm 0.8$  % at the concentration of 100  $\mu\text{g/mL}$ , respectively (Figure S26). Acarbose, an antidiabetic drug that was used as a positive control, exhibited inhibitory percentage of  $88.4 \pm 1.7$  %.

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## Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/records-of-natural-products>

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