Nitrogenous Compounds from the Antarctic Fungus *Pseudogymnoascus* sp. HSX2#-11

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Abstract: The species *Pseudogymnoascus* is known as a psychrophilic pathogenic fungus which is ubiquitously distributed in Antarctica. While the studies of its secondary metabolites are infrequent. Systematic research of the metabolites of the Antarctic fungus *Pseudogymnoascus* sp. HSX2#-11 led to the isolation of one new pyridine derivative, 4-(2-methoxycarbonyl-ethyl)-pyridine-2-carboxylic acid methyl ester (1), together with one pyrimidine, thymine (2), and eight diketopiperazines, cyclo-(dehydroAla-L-Val) (3), cyclo-(dehydroAla-L-Ile) (4), cyclo-(dehydroAla-L-Leu) (5), cyclo-(dehydroAla-L-Phe) (6), cyclo-(L-Val-L-Phe) (7), cyclo-(L-Leu-L-Phe) (8), cyclo-(L-Trp-L-Ile) (9) and cyclo-(L-Trp-L-Phe) (10). The structures of these compounds were established by extensive spectroscopic investigation, as well as by detailed comparison with literature data. This is the first report to discover pyridine, pyrimidine and diketopiperazines from the genus of *Pseudogymnoascus*.

Keywords: Antarctic fungus; *Pseudogymnoascus* sp.; secondary metabolites; nitrogenous compounds

1. Introduction

Nitrogenous compounds represent one of the most momentous family of secondary metabolites which are widely distributed in different biological sources [1]. They have been proved to exhibit various biological activities including cytotoxic, anti-inflammatory, antimicrobial activities and so on [1–4]. For example, pegaharine D, a β-carboline alkaloid isolated from the seeds of *Peganum harmala* exhibited strong antiviral activity against herpes simplex virus-2 [5]. For another example, asperversiamides A–C, a kind of cycloheptapeptide, showed potent inhibitory activity against *Mycobacterium marinum* [6]. Antarctica as the southernmost point of the earth, has the most hostile environment including cold, dry climate and low level of nutrition [7]. Microbes, especially fungi, have been proved to have the potential capacity to produce abundant novel compounds to adapt the extreme habitat. There were more and more bioactive natural products with novel structures have been discovered from Antarctic fungi [8–11]. The species *Pseudogymnoascus* is known as a psychrophilic pathogenic fungus with a ubiquitous distribution in Antarctica. While the rare research about its secondary metabolites suggested the potentials to discover interesting compounds [12]. *Pseudogymnoascus* sp. HSX2#-11, an Antarctic fungus derived from a soil sample of the Fields Peninsula, which can produce various compounds according to our previous study [13], was further investigated to search for new secondary metabolites. As a result, one new pyridine derivative, 4-(2-methoxycarbonyl-ethyl)-pyridine-2-carboxylic
acid methyl ester (1), together with one known pyrimidine, thymine (2) and eight known diketopiperazines (3–10) (Figure 1), were isolated and identified from the potato dextrose agar (PDA) culture broth fermentative extracts of this strain. This paper addresses the isolation, structure elucidation, and bioactivity evaluation of the isolated compounds.

Figure 1. Structures of compounds 1–10.

2. Results

4-(2-Methoxycarbonyl-ethyl)-pyridine-2-carboxylic acid methyl ester (1) was obtained as a colorless oil. The molecular formula of C₁₁H₁₃O₄N was determined by high resolution electrospray ionization mass spectroscopy (HRESIMS) that displayed the [M + Na]⁺ peak at m/z 246.0742 (calcd for C₁₁H₁₃O₄NNa, 246.0737), indicating six degrees of unsaturation (Figure S8 from Supplementary Materials). The ¹H-NMR, ¹³C-NMR and heteronuclear single quantum coherence (HSQC) spectra (Figures S1, S2 and S6 in the Supplementary Materials) exhibited two methoxyls, (δH 3.66 (3H, s), δC 52.0; δH 3.98 (3H, s), δC 53.1), two methylenes, (δH 2.69 (2H, t, 7.5 Hz), δC 34.0; δH 3.03 (2H, t, 7.5 Hz), δC 30.1), three aromatic methines, (δH 7.37 (1H, br s), δC 127.4; δH 8.00 (1H, br s), δC 125.4; δH 8.66 (1H, br s), δC 149.6), two aromatic quaternary carbon signals (δC 147.6, δC 151.8), and two carbonyls (δC 165.4, δC 172.4) (Table 1). The five aromatic carbon signals combined with the molecular formula of C₁₁H₁₃O₄N indicated a pyridine substructure in 1. The splitting effects of ¹H-NMR were undesirable in CDCl₃ of the aromatic methines of 1. So the ¹H-NMR spectrum was measured again in DMSO-d₆. The coupling constants of 5.0 Hz (H-5/H-6), 1.7 Hz (H-3/H-5) and 0.8 Hz (H-3/H-6) revealed the ortho-position of H-5/H-6, meta-position of H-3/H-5 and para-position of H-3/H-6, respectively (Table 1). The ¹H-¹H chemical-shift correlation spectroscopy (COSY) cross peak of H-9/H-10, and key heteronuclear multiple-bond correlation (HMBC) correlations of H-9/C-3, H-9/C-5, H-10/C-4, H-10/C-11 and H-12/C-11 elucidated the methyl propionate substituent located at C-4 (Figure 2). The methyl formate group at C-2 was suggested by the key HMBC correlations from H-8 to C-7 and C-2, and H-3 to C-7 (Figure 2). Thus compound 1 was identified as 4-(2-methoxycarbonyl-ethyl)-pyridine-2-carboxylic acid methyl ester.
Table 1. NMR spectroscopic data (600/150 MHz) for compounds 1 and 4.

| No. | δC a Type | δH a Multiple (Hz) | δC b Type | δH b Multiple (Hz) | δC b Type | δH b Multiple (Hz) |
|-----|-----------|--------------------|-----------|-------------------|-----------|--------------------|
| 1   | -         | -                  | -         | -                 | -         | -                  |
| 2   | 147.6, C  | -                  | 147.5, C  | -                 | 134.7, C  | -                  |
| 3   | 125.4, CH | 8.00, br s         | 124.9, CH | 7.94, dd (1.7, 0.8)| 158.6, C  | -                  |
| 4   | 151.8, C  | -                  | 151.1, C  | -                 | 8.34, br s| -                  |
| 5   | 127.4, CH | 7.37, br s         | 127.2, CH | 7.52, dd (5.0, 0.8)| 59.6, CH  | 3.91, t (2.8)      |
| 6   | 149.6, CH | 8.66, br s         | 149.7, CH | 8.59, dd (5.0, 0.8)| 165.4, C  | -                  |
| 7   | 165.4, C  | -                  | 165.3, C  | -                 | 40.7, CH  | 1.85–1.80, m       |
| 8   | 53.1, CH3 | 3.98, s            | 52.4, CH3 | 3.87, s           | 24.1, CH2 | 1.41–1.33, m       |
| 9   | 30.1, CH2 | 3.03, t (7.5)      | 29.2, CH2 | 2.95, t (7.5)     | 11.7, CH3 | 0.85, t (7.4)      |
| 10  | 34.0, CH2 | 2.69, t (7.5)      | 33.2, CH2 | 2.73, t (7.5)     | 14.8, CH3 | 0.88, d (7.0)      |
| 11  | 172.4, C  | -                  | 172.3, C  | -                 | 98.8, CH2 | 5.17, br s         |
| 12  | 52.0, CH3 | 3.66, s            | 51.4, CH3 | 3.58, s           | -         | -                  |

* a measured in CDCl₃, b measured in DMSO-d₆.

Figure 2. COSY (red bold line) and key HMBC (blue arrows) correlations of 1 and 4.

Cyclo-(dehydroAla-l-Ile) (4) was obtained as a white powder. The HRESIMS spectrum of 4 led to the molecular formula of C₉H₁₄O₂N₂ (m/z 205.0975, calcd for C₉H₁₄O₂N₂Na 205.0948), indicating 4 degrees of unsaturation (Figure S16 in the Supplementary Materials). The ¹H-NMR, ¹³C-NMR and HSQC spectra (Figures S11, S12 and S14 in the Supplementary Materials) exhibited two methyls, (1H, m), δC 59.6), one aromatic quaternary carbon signals (δC 158.6, 𝛿C 165.4) (Table 1). The two NH signals (δH 8.34, (1H, br s), δH 10.53, (1H, s)) combined with two carbonyls indicated the diketopiperazine structure of 4. The ¹H-¹H COSY correlations of H-5/H-7, H-7/H-10, H-7/H-8 and H-8/H-9 revealed the substitute group of 1-methyl-propyl. And the group was located at C-5 determined by the ¹H-¹H COSY cross peak of H-5 and N-4, and the HMBC correlation from H-10 to C-5. The dehydro-methyl substitue was located at C-2 by the HMBC signal from H-11 to C-2. Thus the planar structure of 4 was confirmed as cyclo-(dehydroAla-l-Ile) which was first isolated from marine bacteria Claviceps purpurea in 1994, while its detailed NMR data were not reported [14]. The absolute configuration of 4 was proposed to be same as 3 and 5 according to biogenetic perspective and their similar specific optical rotation (OR) data ([α]₂⁰D −19.3 (c 0.18, CH₃OH) of 4 vs [α]₂⁰D −10.5 (c 0.18, CH₃OH) of 3 and [α]₂⁰D −78.1 (c 0.18, CH₃OH) of 5, Table 2).

The structures of 2, 3, 5–10 were determined thymine [15], cyclo-(dehydroAla-l-Val) [16,17], cyclo-(dehydroAla-l-Leu) [18], cyclo-(dehydroAla-l-Phe) [19], cyclo-(l-Val-l-Phe) [20], cyclo-(l-Leu-l-Phe) [20], cyclo-(l-Trp-l-Ile) [21] and cyclo-(l-Trp-l-Phe) [22], respectively, by comparing their NMR and specific OR data (Table 2) with those in the literature.
Table 2. Specific OR of diketopiperazines 3–10 in CH$_3$OH.

| Compounds | Natural $[\alpha]_D^{20}$ | Literature $[\alpha]_D^{26}$ |
|-----------|--------------------------|-----------------------------|
| 3         | −10.5 (c 0.18)           | 95.7 (c 0.4) [17]           |
| 4         | −19.3 (c 0.18)           |                             |
| 5         | −78.1 (c 0.18)           | −163 (0.01) [18]            |
| 6         | −41.3 (c 0.18)           | −40.0 (1.08) * [19]         |
| 7         | −25.3 (c 0.18)           | −11.4 (1.0) * [20]          |
| 8         | +18.9 (c 0.14)           | +30.0 (0.3) [20]            |
| 9         | −16.5 (c 0.18)           | −31.5 (0.065) [21]          |
| 10        | −144.2 (c 0.14)          | −254.9 (1.0) [22]           |

*measured in DMSO.

All the isolated compounds were evaluated for their antibacterial activities against a panel of bacteria, including four pathogenic bacteria, E. coli, S. aureus, P. aeruginosa and B. subtilis, and nine marine fouling bacteria, P. fulva, A. hydrophila, A. salmonicida, V. anguillarum, V. harveyi, P. halotolerans, P. angustum, E. cloacae and E. hormaechei, and cytotoxic activities against five human cancer cell lines A549, PANc-1, HCT116, HepG2 and MDA-MB-231. Unfortunately, none of the tested compounds showed any activity.

3. Materials and Methods

3.1. General Experimental Procedures

Optical rotations were measured on a JASCO P-1020 digital polarimeter (JASCO, Tokyo, Japan). UV spectra were recorded using an Implen GmbH NanoPhotometer N50 Touch (Implen, Munich, Germany). NMR spectra were recorded on a Bruker AVANCE NEO (Bruker, Fällanden, Switzerland) at 600 MHz for $^1$H and 150 MHz for $^{13}$C in CDCl$_3$ or DMSO-$d_6$. Chemical shifts $\delta$ were recorded in ppm, using TMS as internal standard. HRESIMS spectra were measured on a Thermo Scientific LTQ Orbitrap XL spectrometer (Thermo Fisher Scientific, Bremen, Germany). HPLC separation was performed using a Hitachi Primeraide Organizer Semi-HPLC system (Hitachi High Technologies, Tokyo, Japan) coupled with a Hitachi Primeraide 1430 photodiodearray detector (Hitachi High Technologies). A Kromasil C$_{18}$ semi-preparative HPLC column (250 × 10 mm, 5 µm) (Eka Nobel, Bohus, Sweden) was used. Silica gel (200–300 mesh; Qingdao Marine Chemical Group Co., Qingdao, China) and Sephadex LH-20 (Amersham Biosciences Inc., Piscataway, NJ, USA) were used for column chromatography. Precoated silica gel GF254 plates (Yantai Zifu Chemical Group Co., Yantai, China).

3.2. Fungal Materials

The fungus Pseudogymnoascus sp. HSX2#-11 was isolated from a soil sample of the Fields Peninsula at Chinese 35th Antarctic expedition in 2019. The strain was deposited in the State Key Laboratory of Microbial Technology, Institute of Microbial Technology, Shandong University, Qingdao, China, with the GenBank (NCBI) accession number MT367223.

3.3. Extraction and Isolation

The fungal strain Pseudogymnoascus sp. HSX2#-11 was fermented in a PDA liquid medium in 200 Erlenmeyer flasks (300 mL in each 1000 mL flask) at 16 °C for 45 days. The culture (60 L) was filtered to separate the broth from the mycelia. Then the mycelia were extracted three times with EtOAc (3 × 4000 mL) and then repeated extracted with CH$_2$Cl$_2$–MeOH (v/v, 1:1) three times (3 × 4000 mL). The broth was extracted repeatedly with EtOAc (3 × 60 L) to get the EtOAc layer. All the extracts were combined and were evaporated to dryness under reduced pressure to afford a residue (71.5 g). The residue was subjected to vacuum liquid chromatography (VLC) on silica gel using step gradient elution with EtOAc–petroleum ether (PE) (0–100%) and then with MeOH–EtOAc (0–100%) to afford eight fractions (Fr.1–Fr.8). Fr.3 was first subjected to gradient elution of octadecylsilyl silica gel (ODS) column chromatography (CC) with MeOH in H$_2$O (10–100%), and then...
purified by using semi-preparative HPLC on an ODS column (Kromasil C$_{18}$, 250 × 10 mm, 5 µm, 2 mL/min) eluted with 45% MeOH–H$_2$O to give compounds 7 (5.5 mg), 8 (6.4 mg), 9 (3.5 mg) and 10 (4.4 mg). Fr.4 was isolated by CC on Sephadex LH-20 eluted with CH$_2$Cl$_2$–MeOH (v/v, 1:1) to afford two fractions (Fr.4.1, Fr.4.2). Fr.4.1 was first subjected to silica gel CC eluting with EtOAc–PE (0–50%), and then purified with HPLC eluted with 10% MeOH–H$_2$O to give compound 2 (3.1 mg). Fr.7 was separated on CC on Sephadex LH-20 eluted with CH$_2$Cl$_2$–MeOH (v/v, 1:1) to afford three fractions (Fr.7.1–Fr.7.3). Fr.7.2 was first subjected on HPLC eluted with 50% MeOH–H$_2$O, and then purified with HPLC eluted with 20% MeOH–H$_2$O to afford 3 (2.5 mg). Fr.7.3 was first isolated by HPLC eluted with 50% MeOH–H$_2$O, and then purified with HPLC eluted with 30% MeOH–H$_2$O to obtain 1 (2.1 mg), 4 (2.8 mg) and 5 (2.9 mg). Fr.8 was subjected to HPLC with 55% MeOH–H$_2$O to gain 6 (7.6 mg).

4-(2-Methoxycarbonylethyl)-pyridine-2-carboxylic acid methyl ester (1): colorless oil; UV (MeOH) $\lambda_{\text{max}}$ (log ε): 200 (4.70), 264 (4.11); $^1$H- and $^{13}$C-NMR data, see Table 1; HRESIMS $m/z$ 246.0742 [M + Na]$^+$ (calcd for C$_{11}$H$_{13}$O$_2$Na, 246.0737).

Cyclo-(dehydroAla-Ile) (4): white powder; [α]$_{D}^{20}$ $-19.3$ (c 0.18, MeOH); UV (MeOH) $\lambda_{\text{max}}$ (log ε): 247 (4.30), 288 (4.01); $^1$H- and $^{13}$C-NMR data, see Table 1; HRESIMS $m/z$ 205.0975 [M + Na]$^+$ (calcd for C$_9$H$_{14}$O$_2$N$_2$Na, 205.0948).

### 3.4. Antimicrobial and Cytotoxic Activity Assays

The antibacterial activities were evaluated by the conventional broth dilution assay [23]. Four pathogenic bacteria, _Escherichia coli_, _Staphylococcus aureus_, _P. aeruginosa_ and _Bacillus subtilis_, and nine marine fouling bacteria, _P. fulva_, _Aeromonas hydrophila_, _A. salmoni-cida_, _Vibrio anguillarum_, _V. harveyi_, _Photobacterium halotolerans_, _P. angustum_, _Enterobacter cloacae_ and _E. horneaehei_, were used, and cipofloxacin was used as a positive control.

The cytotoxicities against human breast cancer (MDA-MB-231, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, L-15), colorectal cancer (HCT116, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, L-15), together with one pyrimidine, thymine (2), and eight diketopiperazines 3–10, were isolated from the Antarctic fungus _Pseudogymnoascus_ sp. HSX2#-11. All the isolated compounds showed no antibacterial or cytotoxic activities. More bioactivity evaluating models should be needed to find the effects of these secondary metabolites. This is the first time to find pyridine, pyrimidine and diketopiperazines from the genus of _Pseudogymnoascus_. Our chemical investigation of the Antarctic fungus _Pseudogymnoascus_ sp. HSX2#-11 enriches the chemical diversity of this fungal species.

### 4. Conclusions

In summary, one new pyridine derivative, 4-(2-methoxycarbonyl-ethyl)-pyridine-2-carboxylic acid methyl ester (1), together with one pyrimidine, thymine (2), and eight diketopiperazines 3–10, were isolated from the Antarctic fungus _Pseudogymnoascus_ sp. HSX2#-11. All the isolated compounds showed no antibacterial or cytotoxic activities. More bioactivity evaluating models should be needed to find the effects of these secondary metabolites. This is the first time to find pyridine, pyrimidine and diketopiperazines from the genus of _Pseudogymnoascus_. Our chemical investigation of the Antarctic fungus _Pseudogymnoascus_ sp. HSX2#-11 enriches the chemical diversity of this fungal species.

### Supplementary Materials:

The following are available online, NMR and HRESIMS spectra of the isolated compounds 1–10: Figure S1: $^1$H NMR spectrum of compound 1 (CDCl$_3$); Figure S2: $^{13}$C NMR spectrum of compound 1 (CDCl$_3$); Figure S3: $^1$H NMR spectrum of compound 1 (DMSO-d$_6$); Figure S4: $^{13}$C NMR spectrum of compound 1 (DMSO-d$_6$); Figure S5: COSY spectrum of compound 1 (CDCl$_3$); Figure S6: HSQC spectrum of compound 1 (CDCl$_3$); Figure S7: HMBC spectrum of compound 1 (CDCl$_3$); Figure S8: HRESIMS spectrum of compound 1; Figure S9: $^1$H NMR spectrum of compound 2 (DMSO-d$_6$); Figure S10: $^1$H NMR spectrum of compound 3 (DMSO-d$_6$); Figure S11: $^1$H NMR spectrum of compound 4 (DMSO-d$_6$); Figure S12: $^{13}$C NMR spectrum of compound 4 (DMSO-d$_6$); Figure S13: COSY spectrum of compound 4 (DMSO-d$_6$); Figure S14: HSQC spectrum of compound 4 (DMSO-d$_6$); Figure S15: HMBC spectrum of compound 4 (DMSO-d$_6$); Figure S16: HRESIMS spectrum of compound 4; Figure S17: $^1$H NMR spectrum of compound 5 (DMSO-d$_6$); Figure S18: $^1$H NMR spectrum of compound 6 (DMSO-d$_6$);
Figure S19: $^1$H NMR spectrum of compound 7 (DMSO-$d_6$); Figure S20: $^1$H NMR spectrum of compound 8 (DMSO-$d_6$); Figure S21: $^1$H NMR spectrum of compound 9 (DMSO-$d_6$); Figure S22: $^1$H NMR spectrum of compound 10 (DMSO-$d_6$).

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Sample Availability: Samples of the compounds 1–10 are available from the authors.

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