SECONDARY METABOLITES PRODUCED BY MARINE BACTERIRUM *MICROMONOSPORA* SP. (G068)

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ABSTRACT

Nine compounds (**1-9**) were isolated and characterized from the culture broth of the marine bacteria *Micromonospora* sp. (strain G068), which was isolated from sediment collected at Co To – Quang Ninh. Their structures were determined by spectroscopic analysis including MS, 1D NMR and 2D NMR, as well as by comparison with reported data in the literature. All compounds were evaluated for their antimicrobial activities against a panel of clinically significant microorganisms. Compounds **1**, **6**, and **9** selectively inhibited *Escherichia coli* with MIC values of 128, 128 and 64 μg/mL, respectively.

Keywords: Micromonospora sp., marine microorganisms, antibacteria, norharman, cyclic dipeptide.

1. INTRODUCTION

Marine microorganisms have been important targets to study in recent years because of their production of novel metabolites which represent various biological properties such as antiviral, antitumor or antimicrobial activities. These secondary metabolites serve as model systems in discovery of new drugs [1 - 4]. In the research for bioactive metabolites from marine bacteria, we examined the extract of the culture broth of the marine *Micromonospora* sp. (G068 strain). During our screening program, the EtOAc extract of this strain exhibited antimicrobial activity against a Gram negative (*Escherichia coli* - ATCC25922) bacteria strain, and a fungus strain (*Candida albicans* - ATCC1023). Herein, we describe the isolation and structural determination of nine compounds (**1-9**) from the extract of the culture broth of *Micromonospora* sp. (strain G068). Compounds norharman (**1**), valine (**6**), and 3-hydroxy-4-methoxybenzoic acid (**9**) selectively inhibited *E. coli* with MIC values of 128, 128 and 64 μg/mL, respectively, in comparison with the reference compound, streptomycin (MIC: 32 μg/mL).

2. MATERIALS AND METHODS

1.1 General experiment procedure

Optical rotations were recorded on a Polax-2L polarimeter in $CHCl_3$. ESIMS were recorded on an Agilent 1100 LC-MSD Trap spectrometer. NMR spectra were recorded on a Bruker 500.13 MHz spectrometer operating at 125.76 MHz for ^{13}C NMR, and at 500.13 MHz for ^{1}H NMR. ^{1}H chemical shifts were referenced to $CDCl_3$, DMSO-d_6 and CD_3OD at δ 7.27, 2.50 and 3.31 ppm, respectively, while the ^{13}C chemical shifts were referenced to the central peak of at δ 77.1 ($CDCl_3$), 39.5 (DMSO-d_6), and 49.0 (CD_3OD). For HMBC experiments the delay (1/2J) was 70 ms.

TLC silica gel Merk 60 F_{254} was used as Thin-layer chromatography. Column chromatography (CC) was carried out using silica gel 40-63 μm or Sephadex LH-20.

2.2. Bacteria isolation and fermentation

Strain G068 was isolated from a sediment sample collected by PONAR at a depth of 14 m, from the coast of Co To - Quảng Ninh in Vietnam in April 2014. On the basis of morphological and phylogenetic evidence, the actinomycete strain G068 was assigned to the genus *Micromonospora.*

An agar grown culture of G068 was inoculated into 1 L of a medium comprising starch, yeast extract, peptone, artificial sea salt and distilled water with a ratio of 10.0 g/4.0 g/2.0 g/30.0 g/1.0 L, respectively. After 7 days incubation at 28°C with agitation, the first stage was used to inoculate the production fermentation into 29 L of a culture medium (starch, yeast extract, peptone, $CaCO_3$, $FeSO_4$, KBr, artificial sea salt and distilled water with a ratio of 10.0 g/4.0 g/2.0 g/1.0 g/40 mg/100 mg/30.0 g/1.0 L, respectively). The fermentation was incubated at 28°C with agitation and harvested on the seventh day.

2.3. Extraction and isolation

Culture broth (30 L) of *Micromonospora sp.* G068 strain was extracted with EtOAc (5 × 15 L). The solvent was concentrated under reduced pressure to dryness. The EtOAc extract (3.9 g) was subjected to a silica gel column chromatography (CC) and eluted with CH_2Cl_2/MeOH mixture (0 to 100 % MeOH in CH_2Cl_2) to give 8 fractions. Fraction 1 (316 mg) was purified by silica gel CC, eluting with *n*-hexane/EtOAc gradient to obtain 4 subfractions (F1.1-F1.4). Subfraction F1.4 (14 mg) was purified by silica gel CC using *n*-hexane/acetone gradient to give compound **1** (5 mg). Fraction 2 (224 mg) was subjected to silica gel column using *n*-hexane/acetone gradient to yield compound **2** (4 mg). Fraction 3 (416 mg) was subjected to silica gel column chromatography (CC) and eluted with *n*-hexane/EtOAc mixture (0 to 100% EtOAc in *n*-hexane) to give 6 fractions (F3.1-F3.6). Subfraction F3.4 (54 mg) was separated by CC on silica gel column using *n*-hexane/EtOAc gradient to give compound **3** (6 mg). Subfraction F3.4 (122 mg) was processed by silica gel column, eluting with *n*-hexane/acetone gradient to obtain compound **4** (15 mg). Fraction 4 (194 mg) was purified by CC on silica gel column using *n*-hexane/EtOAc gradient to retrieve 7 subfractions (F4.1-F4.7). Subfraction F4.1 (46 mg) was purified on a silica gel CC (*n*-hexane/acetone gradient) and followed by CC on Sephadex LH-20 (MeOH) to furnish compounds **6** (8 mg). Subfraction F4.4 (54 mg) was purified by silica gel CC (CH_2Cl_2/EtOAc gradient) to yield compounds **7** (5 mg). Fraction 5 (188 mg) was subjected to silica gel CC (CH_2Cl_2/MeOH gradient) and further purified by CC on

Sephadex LH-20 (MeOH) to furnish compounds **5** (10 mg) and **8** (6 mg). Fraction 6 (200 mg) was subjected to silica gel CC (CH_2Cl_2/acetone gradient) and repeatedly chromatographed by Sephadex LH-20 CC (MeOH) to give compound **9** (8 mg).

Norharman (1): White amorphous solid, ESI-MS: *m/z* 169 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 7.23 (1H, td, *J*= 0.5; 8.0 Hz, H-6), 7.53 (1H, td, *J* = 0.5; 8.0 Hz, H-7), 7.60 (1H, dd, *J* = 0.5; 8.0 Hz, H-8), 8.09 (1H, dd, *J*= 0.5, 5.0 Hz, H-4), 8.22 (1H, dd, *J* = 0.5, 8.0 Hz, H-5), 8.31 (1H, d, *J* = 5.0 Hz, H-3), 8.90 (1H, d, *J*= 0.5 Hz, H-1); ^{13}C-NMR (125 MHz, CD_3OD): δ_C (ppm): 112.0 (C-8), 114.6 (C-4), 119.2 (C-6), 120.6 (C-4b), 121.7 (C-5), 127.4 (C-4a), 128.1 (C-7), 134.1 (C-1), 136.1 (C-8b), 137.9 (C-3), 140.7 (C-8a).

***(2S,4S*)-4-hydroxyproline (2):** White amorphous solid, mp. 248 ^{o}C; $[\alpha]_D^{25}$ -71.2 (c 0,12; H_2O); ESI-MS: *m/z* 132 $[M+H]^+$; ^{1}H-NMR (500 MHz, D_2O): δ_H (ppm): 2.03 (1H, m, H_a-3), 2.30 (1H, m, H_b-3); 3.22 (1H, m, H_a-5), 3.36 (1H, dd, *J* = 1.5, 12.5 Hz, H_b-5), 4.20 (1H, t, *J* = 7.0 Hz, H-2), 4,54 (1H, m, H-4). ^{13}C NMR (125 MHz, D_2O): δ_C (ppm): 37.6 (C-3), 53.1 (C-2), 59.9 (C-5), 70.2 (C-4), 174.6 (C=O).

L-Proline (3): White amorphous solid, ESI-MS: *m/z* 116 $[M+H]^+$, ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 1.99 (2H, m, CH_2-4), 2.14 (1H, m, H_a-3), 2.32 (1H, m, H_b-3); 3.27 (1H, m, H_a-5), 3.40 (1H, m, H_b-5), 4.00 (1H, m, H-2).

L-Phenyl alanine (4): White amorphous solid, mp. 145 - 146 ^{o}C; ESI-MS: *m/z* 166 $[M+H]^+$; ^{1}H- NMR (500 MHz, CD_3OD): δ_H (ppm) 3.03 (1H, dd, *J* = 9.0, 14.0 Hz, H_a-3), 3.34 (1H, m, H_b-3), 3.85 (1H, m, H-2), 7.28-7.38 (5H, m, Ph-H). ^{13}C- NMR (125 MHz, CD_3OD): δ_C (ppm): 38.2 (C-3), 57.5 (C-2), 128.4 (C-4'), 129.9 (C-2', C-6'), 130.4 (C-3', C-5') , 137.2 (C-1'), 173.7 (COOH).

Cyclo-(Leu-Ile) (5): White amorphous solid, ESI-MS: *m/z* 227 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 0.89 - 0.95 (9H, m, 3 x CH_3), 0.98 (3H, d, *J* = 7.0 Hz, CH_3-4'), 1.22 (1H, m, H_a-2'), 1.43 (1H, m, H_b-2'), 1.65 (3H, m, H-2'' + CH_2-1''), 1.90 (1H, m, H-1'), 3.54 (1H, d, *J* = 3,0 Hz, H-5), 3.62 (1H, m, H-2). ^{13}C-NMR (125 MHz, CD_3OD): δ_C (ppm): 11.2 (C-3'), 15.0 (C-4'), 21.1 (C-3''), 22.2 (C-4''), 24.4 (C-2'), 24.5 (C-2''), 36.5 (C-1'), 40.8 (C-1''), 53.8 (C-5), 60.0 (C-2), 176.1 (C=O), 177.2 (C=O).

L-Valine (6): White amorphous solid, ESI-MS: *m/z* 118 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 0.94 (3H, d, *J*=7,0 Hz, CH_3), 0.99 (3H, *J* = 7,0 Hz, CH_3), 2.24 (1H, m, H-3), 3.57 (1H, m, H-2). ^{13}C-NMR (125 MHz, CD_3OD): δ_C (ppm): 16.7 (CH_3), 18.1 (CH_3), 29.2 (C-3), 60.5 (C-2), 174.3 (COOH).

L-Alanine (7): White amorphous solid, ESI-MS: *m/z* 90 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 1.35 (3H, d, *J*=7.0 Hz, CH_3), 3.65 (1H, q, *J* = 7.0 Hz, H-2). ^{13}C NMR (125 MHz, CD_3OD): δ_C (ppm): 16.3 (CH_3), 46.2 (C-2), 176.1 (COOH).

Acetovanillone (8): White amorphous solid, ESI-MS: *m/z* 167 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 2.21 (3H, s, $COCH_3$), 3.76 (3H, s, OCH_3), 7.12 (1H, d, *J* = 8.0 Hz, H-5), 7.22 (1H, dd, *J* = 1.0; 8.0 Hz, H-6); 7.52 (1H, br s, H-2).

3-hydroxy-4-methoxybenzoic acid (9): White amorphous solid, ESI-MS: *m/z* 169 $[M+H]^+$; ^{1}H-NMR (500 MHz, CD_3OD): δ_H (ppm): 3.76 (3H, s, OCH_3), 7.12 (1H, d, *J* = 8.5 Hz, H-5), 7.21 (1H, dd, *J* = 1.5, 8.5 Hz, H-6), 7.54 (1H, br s, H-2).

2. RESULTS AND DISCUSSION

Compound **1** was isolated as a white amorphous solid. The ESI mass spectrum of **1** presented a base peak at *m/z* 169 $[M+H]^+$. In the ^1H NMR spectrum, the presence of a 1,2-disubstituted benzene ring at [δ_H 7.23 (1H, td, *J* = 0.5; 8.0 Hz, H-6), 7.53 (1H, td, *J* = 0.5; 8.0 Hz, H-7), 7.60 (1H, dd, *J*= 0.5, 8.0 Hz, H-8), and 8.22 (1H, dd, *J*= 0.5, 8.0 Hz, H-5)], and three aromatic proton at δ_H 8.09 (1H, dd, *J*= 0.5, 5.0 Hz, H-4), 8.31 (1H, d, *J* = 5.0 Hz, H-3), 8.90 (1H, d, *J*= 0.5 Hz, H-1) was noted. Analyses of the ^{13}C-NMR and DEPT spectra with the aid of the HSQC of **1** indicated the presence of 11 carbons, including seven aromatic methines and four sp^2 quaternary cacbons at δ_C 120.6 (C-4b), 127.4 (C-4a), 136.1 (C-8b), 140.7 (C-8a). The chemical shifts of C-8a and C-8b suggested their linkage to nitrogen nitrogen atoms. Analysis of the ^1H-^1H COSY spectrum of **1** revealed two spin-spin coupling systems as follows H-5/H-6/H-7/H-8 and H-3/H-4. Analysis of the HMBC spectrum confirmed the 1,2-disubstituted benzene ring by cross-peaks of the quaternary carbon C-4b with H-5 and H-6, and those of C-8a with H-7 and H-8. Furthermore, HMBC correlation of the quaternary carbon C-8b with H-1 and H-4, and those of C-4a with H-1, H-5 and H-3 assigned connections of C-8a to C-4b, C-4a and C-8b (Figure 2). Analyses of 2D NMR spectra established the structure of **1** as 9H-pyrido[3,4-b]indole (Norharman). The NMR data of **1** were in agreement with those previously reported [6].

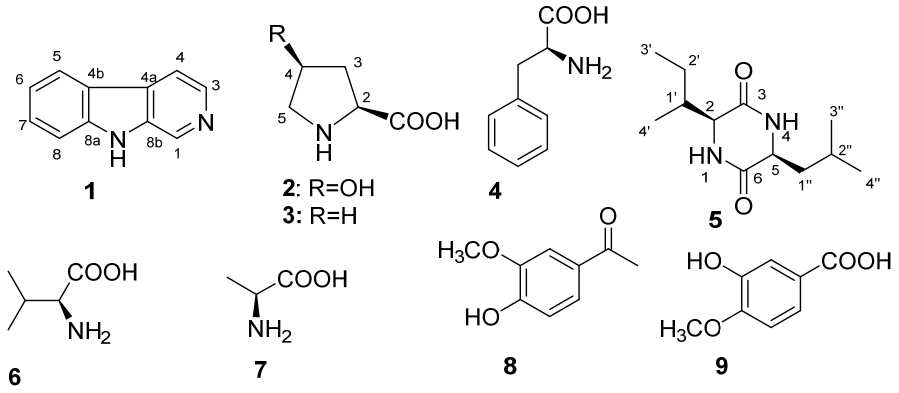

Figure 1. Isolated compounds from marine bacteria *Micromonospora* sp. (G068 strain).

Compound **2** was obtained as a white amorphous solid, and optically, $[\alpha]_D^{30}$ -71.2 (*c* 0.01, H_2O). The ESI mass spectrum of **2** showed a pseudomolecular ion peak at *m/z* 132 $[M+H]^+$. 1D-NMR spectrum of **4** showed signals of two methine, two methylenes groups and a carboxyl group (δ_C 174.6). The chemical shifts of CH-4 (δ_C 70,2, δ_H 4.54), CH_2-5 (δ_C 59.9, δ_H 3.22, 3.36) and CH-2 (δ_C 53.1, δ_H 4.20) suggesting their linkages to oxygen and nitrogen atoms. The hydroxyl group was linked to C-4 as suggested by HMBC correlation of C-4 (δ_C 70.2) with H_b-3 (δ_H 2.30) and H_a-5 (δ_H 3.22). Complete analyses of the NMR spectra and comparison of optical activity with the literature [7] indicated the structure of **4** as (*2S,4S*)-4-hydroxyproline.

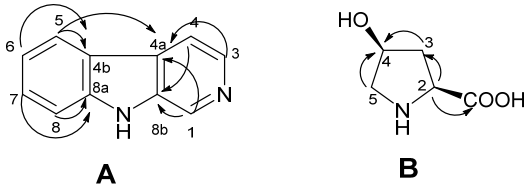

Figure 2. Selected HMBC correlations of **1** (**A**) and **2** (**B**).

Compound **3** was obtained as a white amorphous solid. The ESI mass spectrum of **2** showed a pseudomolecular ion peak at *m/z* 116 $[M+H]^+$. The NMR data of compound **3** showed similar spectroscopic features as compound **2**. The differences between these two compounds were the presence of a methylene group instead of the oxymethine group. Comparison of NMR data of **3** with those reported for L-proline [8] revealed that they were identical.

Compound **4** was isolated as a white amorphous solid. In its positive ESI mass spectrum, the pseudo-molecular ion was observed at *m/z* 166 $[M+H]^+$. The ^{1}H-NMR spectrum of **3** indicated the presence of five aromatic protons at δ_H 7.28-7.38, and three protons in the aliphatic region. The ^{13}C-NMR and DEPT spectra of **3** showed the presence of 9 carbon atoms, including one carbonyl groups at δ_C 173.7, one sp^3 methine at δ_C 57.5 (C-2), one methylene at δ_C 38.2 (C-3), one quaternary carbon at δ_C 137.2 (C-1'), and five aromatic methines at δ_C 128.4 (C-4'), 129.9 (C-2', C-6') and 130.4 (C-3', C-5'). The chemical shifts of CH-2 (δ_H 3.85, δ_C 57.5), indicated their bonding to nitrogen atom. Comparison of the ^{1}H-NMR spectrum and TLC of **4** with L-phenyl alanine which was available in our laboratory revealed their similarity. Thus, **4** was determined as L-phenyl alanine [9, 10].

Compound **5** was isolated as a white amorphous solid. The ESI-MS indicated the pseudomolecular ion peak at *m/z* 227 $[M+H]^+$. The ^{1}H-NMR spectrum of **5** displayed signals of 4 methyl groups at δ_H 0.89-0.95 (9H, m, 3 x CH_3), 0.98 (3H, d, *J*=7.0 Hz, CH_3-4') and signals of ten aliphatic protons ranging from 1.54 to 4.28 ppm. Analysis of the ^{13}C NMR and DEPT spectra of **5** revealed the presence of 12 carbons, including four methyl groups at δ_C 11.2 (C-3'), 15.0 (C-4'), 21.1 (C-3''), 22.2 (C-4''), four methines at 24.5 (C-2''), 36.5 (C-1'), 53.8 (C-5), 60.0 (C-2), two methylenes at δ_C 24.4 (C-2'), 40.8 (C-1''), and two carbonyl at δ_C 176.1 (C=O) and 177.2 (C=O). The chemical shifts of CH-2 and CH-5 suggested their linkage to nitrogen atoms. Complete analysis of NMR spectra and comparison with the reported data allowed determining the structure of **5** to be Cyclo-(Leu-Ile) [11].

The ^{1}H spectrum of the compound **6** displayed two doublets at δ_H 0.94 (3H, d, *J* = 7,0 Hz, CH_3-4) and 0.99 (3H, *J* = 7,0 Hz, CH_3-5) indicating the presence of two methyl groups. Moreover, the signals at δ_H 2.24 (1H, m, H-3) and δ_H 3.57 (1H, m, H-2) allowed to propose the structure of **6** as L-valine. The NMR data of **6** were in agreement with those reported in the literature [12].

By analysis of the NMR spectra, compounds **7, 8** and **9** were determined to be L-alanine [12], acetovanillone [13] and 3-hydroxy-4-methoxybenzoic acid [14], respectively. Their NMR data were identical with those reported in the literature.

All the isolates were evaluated for their antibacterial activity against *Escherichia coli* (ATCC25922), *Pseudomonas aeruginosa* (ATCC27853), *Salmonella enterica* (ATCC12228), *Enterococcus faecalis* (ATCC13124), *Staphylococcus aureus* (ATCC25923) and *Bacillus cereus* (ATCC13245), and antifungal activity against *Candida albicans* (ATCC1023). Compounds **1**, **6**, and **9** selectively inhibited *E. coli* with MIC values of 128, 128 and 64 µg/mL, respectively, in comparison with the reference compound, streptomycin (MIC: 32 µg/mL).

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TÓM TẮT

CÁC HỢP CHẤT THỨ CẤP TỪ CHỦNG VI SINH VẬT BIỂN *MICROMONOSPORA* SP. (G068)

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Chín hợp chất thứ cấp (**1-9**) được phân lập từ chủng vi sinh vật biển *Micromonospora* sp. (G068), phân lập từ mẫu trầm tích tại vùng biển Cô Tô – Quảng Ninh. Cấu trúc của các chất được xác định bằng các phương pháp phổ MS, 1D-NMR và 2D-NMR. Kết quả thử hoạt tính kháng vi sinh vật kiểm định cho thấy hợp chất **1**, **6** và **9** thể hiện hoạt tính chọn lọc đối với chủng vi sinh vật Gram (-) *Escherichia coli* với giá trị MIC lần lượt là 128, 128 và 64 μg/mL.

Từ khóa: Micromonospora sp, vi sinh vật biển, norharman, dipeptit vòng.