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Letter to the Editor

Antimicrobial metabolites from *Streptomyces* sp. strain PDH23 derived from marine sponge *Rhabdastrella globostellata*

Sir,

Sponge-associated bacterial community has shown great potential as a source of biologically active constituents. The marine sponge *Rhabdastrella globostellata* has been known to display potent anti-cancer effects (Hirashima et al. 2010; Li et al., 2010, Aoki et al., 2007). Pandey et al. (2014) revealed that 18 of 127 microorganisms isolated from *R. globostellata* exhibited acetylcholinesterase inhibitory activity. However, the antimicrobial activity of *R. globostellata* associated bacteria has not been reported so far. In our search for antibacterial agents from marine organisms, the strain of *Streptomyces* sp. PDH23 isolated from *R. globostellata*, which was collected at depth of 10 m in Da Nang sea, Vietnam, was found to exhibit remarkable antimicrobial activity against *Bacillus cereus* (ATCC14579) and *Candida albicans* (ATCC1023) (see supplemental data). The cultured broth of PDH23 strain (50 L) was extracted with ethyl acetate (30 L x 3 times), the organic layers were combined and concentrated to obtain crude extract. A half of the extract was fractionated in a silica gel column eluted with a gradient of 0-100% methanol in dichloromethane to afford eight fractions F1-8. The fraction F1 was chromatographed on a silica gel column eluted with n-hexane:acetone (3:1, v/v) to give four subfrations F1.1-1.4. Compound **2** (*p*-hydroxybenzaldehyde, 5.8 mg) and **3** (indole-3-carboxaldehyde, 6.2 mg) were respectively isolated from the subfractions F1.2 and F1.4 by a silica gel column using dichloromethane:ethyl acetate (20:1, v/v). Cyclo(D-Pro-D-Val)(**4**) (22 mg) was purified from F2 through a Sephadex LH-20 column eluted with methanol:water (1:1, v/v). Fraction F5 was passed through a silica gel column to afford four subfractions F5.1-5.4. Compound **1** (11.6 mg) was isolated from F5.3 by silica gel column chromatography using dichloromethane:methanol (3:1, v/v) and **5** (uracil, 6.5 mg) was purified from F5.4 by a Sephadex LH-20 eluted with methanol:water (1:1, v/v) (Figure 1).

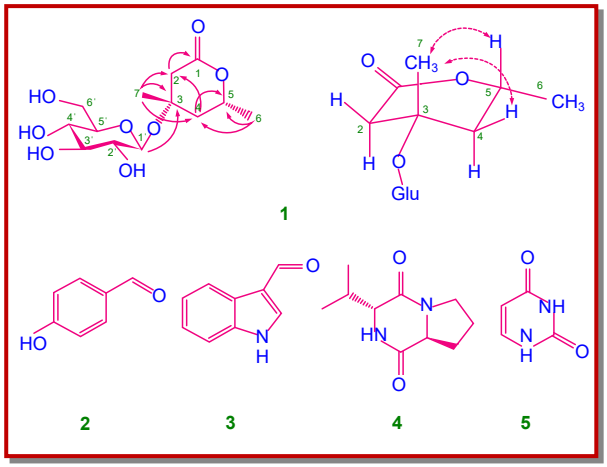

Figure 1: Structure of the compounds **1-5** and key HMBC (→) and NOESY (<--->) correlations of **1**

Compound **1** was obtained as a colorless solid. Its HR-ESI-MS revealed an ion peaks at *m/z* 307.1385 $[M + H]^+$, which confirmed the molecular formula of $C_{13}H_{22}O_8$ of **1**. The ^{1}H-NMR spectrum of 1 showed the presence of two methyl groups at δ_H 1.40 (3H, br d, J = 6.5 Hz, H-6) and 1.46 (3H, br s, H-7), an anomeric signal at δ_H 4.48 (1H, d, J = 8.0, H-1′) characteristic for a β-glycosyl unit. The ^{13}C NMR and DEPT spectra of **1** showed the presence of 13 signals including a carboxylic, an oxygenated quaternary carbon, six oxygenated methine and three methylene groups. Six signals at δ_C 98.5 (C-1'), 74.9 (C-2'), 77.8 (C-3'), 72.0 (C-4'), 78.0 (C-5'), and 63.3 (C-6') were assigned to a glucose moiety. Acid hydrolysis follwed by HPLC analysis allowed to determined the glucosidic unit as β-D-glucopyranoside (Thai et al., 2017). According to the mass spectral data which indicated three double bond equivalents (DBE) in the structure of **1**, the remaining ^{13}C signals should be cyclized since 2 DBEs were attributed to a carboxylic group and a glucopyranoside ring. The HMBC correlations showed the coupling from H-2 (δ_H 2.78 and 2.86) to C-1 (δ_C 175.1) and C-3 (δ_C 76.6); from H-7 (δ_H 1.46) to C-2 (δ_C 42.6) C-3 and C-4 (δ_C 45.1); from H-6 (δ_H 1.40) to C-4 and C-5 (δ_C 74.9). The correlation from the anomeric proton H-1' (δ_H 4.48) to C-3 suggested that the glucosidic moiety attached to C-3. Thus compound **1** was elucidated to be 3-methyl-5-hexanolide 3-O-β-D-glucopyranoside. The relative configuration of **1** was determined based on the proton coupling constants and NOESY experiments. The coupling constant between H-5 and H-4a and H-4b were 11.5 and 3.5 Hz, corresponding to di-axial and axial-equatorial relationship, respectively (Breitmaier, 2002). Thus the proton H-5 was in axial orientation. The obvious coupling between H-5 and H-7 suggested that H-7 was in axial position.

The antimicrobial activity of the isolated compounds was evaluated.

Table I

Antimicrobial activity of the isolated compounds

Compounds	MIC (µg/mL)	
	Candida albicans	*Bacillus cereus*
Compound 1	256	512
Compound 2	1024	512
Both	128 (**1**) + 32 (**2**)	128 (**1**) + 64 (**2**)
Nystatin	8.0	-
Chloramphenicol	-	2.5

The antimicrobial activity of the isolated compounds was evaluated against *Candida albicans* and *Bacillus cereus* (Teh et al., 2013). Compound **1** showed moderate effect with MIC values of 256 µg/mL and 512 µg/mL, respectively (Table I). Interestingly, the growths of the microorganism were completely inhibited when treated with the combination of **1** (128 µg/mL) and **2** (32 µg/mL for *C. albicans* and 64 µg/mL for *B. cereus*).

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Conflict of Interest: Nil

Vu Thi Thu Huyen[1,2], Le Thi Hong Minh[2], Vu Thi Quyen[2], Nguyen Mai Anh[2], Nguyen Thi Kim Cuc[2], Nguyen Thi Luyen[3], Nguyen Tien Dat[3]

[1]Graduate University of Science and Technology, VAST, 18 Hoang Quoc Viet, CauGiay, Hanoi, Vietnam; [2]Institute of Marine Biochemistry, Vietnam Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, CauGiay, Hanoi, Vietnam; [3]Center for Research and Technology Transfer, VAST, 18 Hoang Quoc Viet, CauGiay, Hanoi, Vietnam.

Corresponding author:

email: ngtiend@imbc.vast.vn

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Supplementary File