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Communication

Microindolinone A, a Novel 4,5,6,7-Tetrahydroindole, from the Deep-Sea-Derived Actinomycete *Microbacterium* sp. MCCC 1A11207

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Abstract: A novel indole, microindolinone A (**1**), was isolated from a deep-sea-derived actinomycete *Microbacterium* sp. MCCC 1A11207, together with 18 known compounds (**2**–**19**). By detailed analysis of the ^{1}H, ^{13}C, HSQC, COSY, HMBC, HRESIMS, and CD data, the absolute configuration of **1** was elucidated as 5*R*-hydroxy-4,5,6,7-tetrahydroindole-4-one. Noteworthily, **1** is the second example of a saturated indole isolated from nature.

Keywords: deep-sea; actinomycete; *Microbacterium* sp.; indole

1. Introduction

Actinomycetes are Gram-positive bacteria known for their ability to produce structurally novel secondary metabolites with various biological activities [1]. The best-known compound is salinosporamide A [2, 3]. Very recently, the representative examples included pyrazolofluostatins and aminorifamycins isolated from marine *Micromonospora* species [4, 5].

The genus *Microbacterium* of the *Microbacteriaceae* family was first proposed by Orla-Jensen in 1919. Up to now, there are 97 species reported from diverse habitats including land, ocean, air, and blood *etc*. However, only four compounds were obtained from this genus [6, 7]. In our current research for structurally novel secondary metabolites from deep-sea-derived microorganisms [8-10], the actinomycete *Microbacterium amylolyticum* MCCC 1A11207, isolated from southwestern Indian Ocean sediment, was subjected to a systematic chemical examination. Consequently, one new and 18 known compounds were obtained. Herein, we report the isolation, structural elucidation, and bioactivities of these compounds.

2. Results and Discussion

Microbacterium sp. MCCC 1A11207 was cultured in a 50 L fermentor containing 30 L A3 medium for 10 d. Then the fermentation broth was centrifuged and extracted to provide the crude extract (17 g). By repeated column chromatography (CC) over silica gel, ODS, and Sephadex LH20, 19 compounds were obtained (Figure 1).

2.1. Structure Elucidation

Microindolinone A (**1**) was isolated as colorless oil. The molecular formula was established as $C_8H_9NO_2$ on the basis of a quasi-molecular ion peak at *m*/*z* 174.0525 $[M + Na]^+$ in its HRESIMS, requiring five degrees of unsaturation. The ^{1}H-NMR spectrum (Figure S1) exhibited two exchangeable protons at δ_H 11.3 (1H, brs, 1-NH) and 4.98 (1H, d, *J* = 3.8 Hz, 5-OH), one oxygenated sp^3 (δ_H 4.05, ddd, *J* = 11.6, 4.5, 3.8 Hz, H-5) and two sp^2 [(δ_H 6.74, dd, *J* = 2.9, 2.4 Hz, H-2) and (δ_H 6.25,

dd, J = 2.9, 2.2 Hz, H-3)] methines, together with two methylenes. The ^{13}C (APT)-NMR spectrum (Figure S2) showed 8 resonance signals involving three quaternary carbons at δ_C 194.1 (C-4), 143.4 (C-7a) and 118.4 (C-3a), three methines (δ_C 120.3/C-2, 105.2/C-3, and 72.6/C-5), and two methylenes at δ_C 33.0 (C-6) and 21.3 (C-7). In the ^{1}H–^{1}H COSY spectrum (Figure S4), two fragments of NH-1/C-2/C-3 and OH-5/C-5/C-6/C-7 was determined on the basis of COSY correlations of NH-1(δ_H 11.3)/H-2 (δ_H 6.74)/H-3 (δ_H 6.25), and 5-OH (δ_H 4.98)/H-5 (δ_H 4.05)/H$_2$-6 (δ_H 1.87, m; 2.20, m)/H$_2$-7 (δ_H 2.83, m). The two fragments can be connected by a α,β-unsaturation ketone unit on the basis of HMBC cross-peaks (Figure S5) from H-2 to C-3/C-3a, H-3 to C-7a, OH-5 to C-4/C-5/C-6, H$_2$-7 to C-3a/C-5/C-6/C-7a (Figure 2), which established the planar structure of **1** as 5-hydroxy-4,5,6,7-tetrahydroindole-4-one.

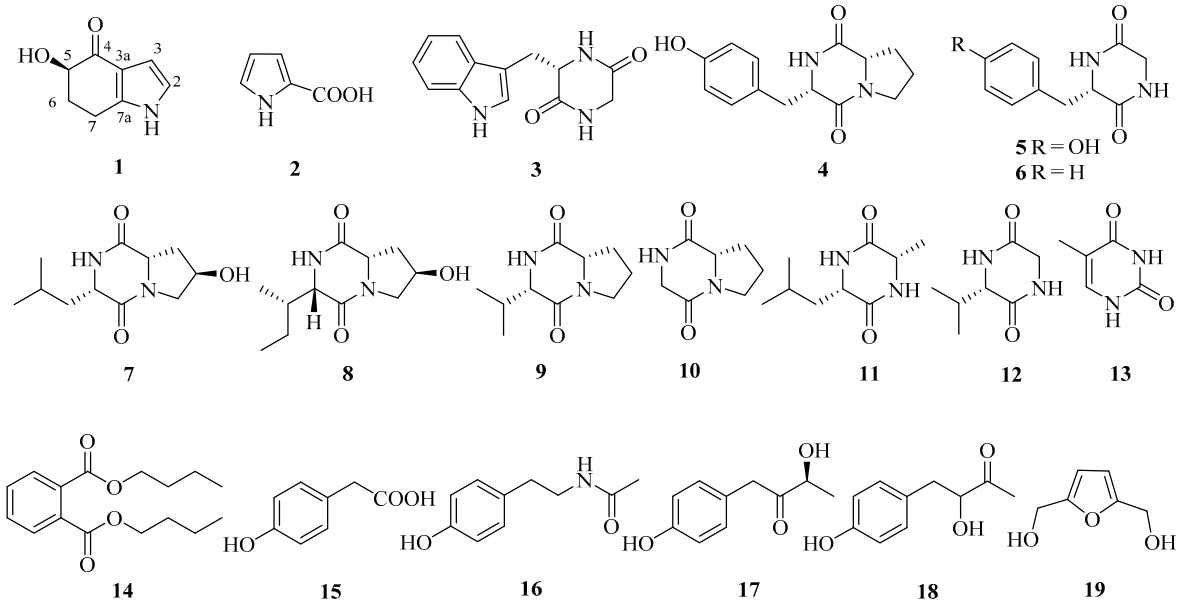

Figure 1. Compounds isolated from *Microbacterium amylolyticum* MCCC 1A11207.

The large coupling constant of H-5 and H-6a ($J_{H\text{-}5/H\text{-}6a}$ = 11.6 Hz) indicated H-5 as axial-orientation. In the CD spectrum, the negative Cotton effect ($\Delta\varepsilon_{296}$ −0.35) induced by n-π^* electronic transition revealed the *R*-orientation of the 5-hydroxyl group on the basis of the octant rule (Figure 3) [11, 12]. Therefore, the absolute configuration of **1** was determined as 5*R*-hydroxy-4,5,6,7-tetrahydroindole-4-one, and named microindolinone A. Surprisingly, although indoles occur broadly in nature [13-15], the saturated ones were seldom discovered. As a matter of fact, the only one reported was 6,7-dihydroxy-4,5,6,7-tetrahydroindole-4-one from *Nocardia* sp., a soil-derived actinomycete [16]. And microindolinone A (**1**) was the second example. Noteworthily, for the first time, the absolute configuration of such saturated indole was determined.

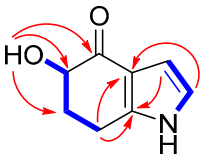

Figure 2. Key ^{1}H–^{1}H COSY (bold) and HMBC (arrow) correlations of **1**.

By comparing the ^{1}H-, ^{13}C-NMR, MS, and OR data with those reported in the literature, 18 known compounds were identified as pyrrole-2-carboxylic acid (**2**) [17], cyclo(L-Trp-Gly) (**3**) [18], cyclo-L-Tyr-L-Pro (**4**) [19], cyclo(L-Trp-Gly) (**5**) [20], cyclo(L-Phe-Gly) (**6**) [21], cyclo[L-(4-hydroxyprolinyl)-L-leucine] (**7**) [22, 23], cyclo[L-(4-hydroxyprolinyl)-L-isoleucine] (**8**) [24], cyclo-(L-Pro-L-Val) (**9**) [25], cyclo-(L-Pro-Gly) (**10**) [25], cyclo-(L-Leu-L-Ala) (**11**) [26], cyclo-(L-Val-Gly) (**12**) [27], 5-methyluracil (**13**) [26], dibutyl phthalate (**14**) [28], 4-hydroxyphenylacetic acid (**15**) [29], *N*-(4-hydroxyphenyl)-acetamide (**16**) [30], (*S*)-3-hydroxy-4-(4-hydroxyphenyl)butan-2-one (**17**) [31], 3-

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hydroxy-4-(4-dihydroxyphenyl)-2-butanone (**18**) [32], and (5-hydroxymethyl-furan-2-yl)-methanol (**19**) [33]. Surprisingly, these 19 compounds were all firstly isolated from *Microbacterium* species.

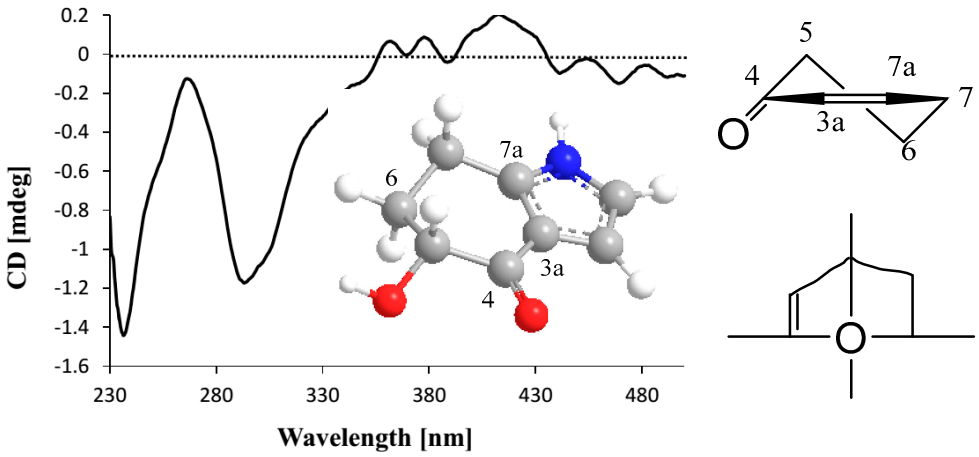

Figure 3. The CD spectrum and octant projection of compound **1**.

Table 1. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectroscopic data for **1** in DMSO-d_6.

Position	δ_C	δ_H
1		11.3, brs
2	120.3 d	6.74, dd (2.9, 2.4)
3	105.2 d	6.25, dd (2.9, 2.2)
3a	118.4 s	
4	194.1 s	
5	72.6 d	4.05, ddd (11.6, 4.5, 3.8)
6	33.0 t	1.87 m; 2.20 m
7	21.3 t	2.83 m
7a	143.4 s	
5-OH		4.98, d (3.8)

2.2. *Anti-proliferative activity of **1** against RBL-2H3 cells*

Microindolinone A (**1**) was tested for anti-proliferative activity against RBL-2H3 cells. Fortunately, it didn't show significant cytotoxicity even under the highest concentration of 20 μg/mL (Table 2).

Table 2. Anti-proliferative activity of **1** againstRBL-2H3 cells (n = 3, means ± SD).

Concentrations (μg/mL)	Cell viability (%)
20	91 ± 10
10	93 ± 1.4
5	90 ± 10
2.5	93 ± 12
1.25	94 ± 12
0.625	99 ± 14

2.3. *Anti-allergic Activity of **1***

Microindolinone A (**1**) was further subjected to anti-allergic bioactivity on IgE mediated rat mast RBL-2H3 cells. However, it didn't show any positive effects under the concentration of 20 μg/mL. While the positive control, loratadine, exhibited significant inhibition rate of 37 % (Table 3).

Table 3. The Anti-allergic Activity of **1** against RBL-2H3 cells (n = 3, means ± SD).

Compound	Concentration (μg/mL)	Inhibition rate (%)
1	20	−1.4 ± 0.8
Loratadine	20	37 ± 5.3

3. Materials and Methods

3.1. *General Experimental Procedures*

HRESIMS spectra were obtained from Xevo G2 Q-TOF mass spectrometer (Waters). Optical rotations were obtained from a Rudolph IV Autopol automatic polarimeter. NMR spectra were recorded on a Bruker 400 MHz spectrometer. Materials for column chromatography were silica gel (Qingdao Marine Chemistry Co. Ltd. China), ODS (50 μm, Daiso, Japan), and Sephadex LH-20 (Amersham Pharmacia Biotech AB, Uppsala, Sweden). Precoated silica gel plates (Qingdao Marine Chemistry Co. Ltd. China) were used for TLC analysis.

3.2. *Bacterial Material*

The strain MCCC 1A11207 was isolated from a deep-sea sediment of the southwestern Indian Ocean (−1603 m) in 2014. The 16S rRNA gene sequence of MCCC 1A11207 was compared with those of species with validly published names from the GenBank database via the BLAST program with the highest similarity (98.03%) to *Microbacterium amylolyticum* N5^T. Therefore, it was identified to be *Microbacterium* sp. MCCC 1A11207. The actinomycete was deposited in the Marine Culture Collection of China with the accession number of MCCC 1A11207.

3.3. *Cultivation and Extraction.*

The strain was cultured on 2216E medium at 28 °C for 3 d and the colony were inoculated to 250 mL Erlenmeyer flasks containing 50 mL A3 medium compositing with 15 g bacterial peptone, 5 g soybean peptone, 15 g soluble starch, 30 g marine salt, and 1 L tap water, and then was cultured in a rotary shaker with 180 rpm at 28 °C for 3 d as the spores medium. The large-scale fermentation was performed by a 50 L fermentor containing 30 L of the A3 medium with the 5% seed culture, and the fermentation continued at 28 °C with 180 rpm for 10 d. Then the fermentation broth was centrifuged (16000 rpm) to get supernatant and mycelium. The supernatant was extracted with EtOAc for three times, and then concentrated under reduced pressure to obtain the crude extract A. The mycelium was extracted with MeOH twice. After removing of the MeOH, the residue was re-extracted with EtOAc for three times to get extract B under reduced vacuum. The extracts A and B were combined to provide the crude extract.

3.4. *Isolation and Purification*

The crude extract (17 g) was subjected to column chromatography (CC) on ODS, eluting with a gradient of MeOH-H_2O (5:95→100:0) to obtain 4 fractions (Fr.1–Fr.4). Fraction Fr.2 (92 mg) was first subjected to Sephadex LH-20 CC eluting with MeOH, and then by silica gel CC with $CHCl_3$-MeOH (100:1) to obtain **2** (6.8 mg). Fraction Fr.3 (283 mg) was separated by CC over Sephadex LH-20 (MeOH) to get five subfractions (Fr.3.1–Fr.3.5). Subfraction Fr.3.1 was purified by CC on silica gel eluting with petroleum ether (PE)-acetone (2:1) to get **14** (11.3 mg). Compounds **12** (9.2 mg) and **19** (2.3 mg) were isolated from subfraction Fr.3.2 with CC over silica gel ($CHCl_3$-MeOH, 20:1), while **5** (2.1 mg) and **13** (23.0 mg) were obtained from subfraction Fr.3.5 ($CHCl_3$-MeOH, 6:1). Compound **10** (38.0 mg) was isolated from Fr.3.3 using recrystallization in MeOH. Subfraction Fr.3.4 was subjected to CC over silica gel eluting with PE-acetone (3:1) to get **1** (1.1 mg). Fraction Fr.4 (380 mg) was fractionated by CC on Sephadex LH-20 (MeOH) to obtain five subfractions (Fr.4.1–Fr.4.5). Subfraction Fr.4.1 was subjected to CC over silica gel (PE-acetone, 2:1) to get two fractions (Fr.4.1.1 and Fr.4.1.2). Subfraction Fr.4.1.1 was purified by CC over silica gel (PE: acetone, 2:1) to get **11** (1.8 mg). Fr.4.1.2 was subjected

to MPLC using gradient MeOH-H_2O (5→30%) to get **7** (8.0 mg), **8** (3.8 mg), and **9** (8.7 mg). Fr.4.2 was purified by CC over silica gel ($CHCl_3$-MeOH, 6:1) to provide **16** (38.2 mg). Fr.4.3 was subjected to CC on silica gel ($CHCl_3$-MeOH, 20:1) to get two fractions (Fr.4.3.1 and Fr.4.3.2). Subfraction Fr.4.3.1 was further purified by Prep. TLC (PE-EtOAc, 1:1) to get **17** (1.2 mg) and **18** (1.4 mg), while compounds **4** (12.1 mg) and **6** (9.8 mg) were isolated from Fr.4.3.2 by CC over silica gel (PE-EtOAc, 1:1). Fr.4.4 and Fr.4.5 were purified by CC on silica gel eluting with PE-EtOAc (1:1) and PE-EtOAc (2:1) to get **15** (8.6 mg) and **3** (2.3 mg), respectively.

Microindolinone A (**1**): Colorless oil; $[\alpha]_D^{25}$ +2.5 (c 0.11, MeOH); CD ($CHCl_3$) λ_{max} ($\Delta\varepsilon$) 237 (−0.42), 268 (−0.04), 296 (−0.35); ^{1}H- and ^{13}C-NMR data, see Table 1; HRESIMS (positive) *m*/*z* 174.0525, calcd. for $C_8H_9NO_3Na^+$ 174.0531.

3.5. *Anti-proliferative Assay*

According to previously reported protocols [34], the cytotoxic test was carried out using the MTT assay on RBL-2H3 cells. In brief, RBL-2H3 cells were seeded into 96-well cell culture plates. Then six different concentrations of **1**, ranging from 0.625 to 20 μg/mL, was added. After 24 h, the cells were treated with 20 μL of MTT solution. Cell viability was examined using a MTT assay kit according to the manufacturer's instructions (Promega, Madison, USA). Relative cytotoxicity was quantified by measuring the absorbance at 570 nm. And the cell viability was calculated using the following equation: Cell viability (%) = [(As – Av)/(Ac−Av) × 100%, where As is the absorbance of the sample, Av is the absorbance of the vehicle, and Ac is the absorbance of the control

3.6. *Anti-allergic Test*

The anti-allergic activity, indexed by the β-hexosaminidase release, was measured for the efficiency of the RBL-2H3 cell degranulation inhibition rate using IgE-mediated mast cell allergic reaction [8, 35]. In short, RBL-2H3 cells were seeded into 96-well cell culture plates (1×10^5 cells/well) to incubate with DNP-specific IgE overnight. IgE-sensitized RBL-2H3 cells were pre-treated with compound **1** (20 μg/mL) for 1 h and stimulated with DNP-BSA (500 ng/mL). The negative control group was added to 200 μL PBS buffer. The β-hexosaminidase activity was quantified by measuring the fluorescence intensity of the hydrolyzed substrate in a fluorometer. The degranulation efficiency was calculated using the following formula: Degranulation efficiency (%) = Fsup / (Fsup + Flys) ×100%, where Fsup is the fluorescence value of the supernatant and Flys is the fluorescence value of cell lysates. And the inhibition rate was calculated based on the following formula: Inhibition rate (%) = (Positive – Sample)/ (Positive – Negative) ×100%, where Positive is the degranulation efficiency of the DNP-BSA stimulated group, Sample is the degranulation efficiency of the sample group, and Negative is the degranulation efficiency of the vehicle group.

3.7. *Statistical Analysis*

Anti-proliferative and anti-allergic experiments were conducted three times. Results are presented as means ± SD. One-way analysis of variance (one-way ANOVA) comparison tests of SPSS statistics 17.0 software was used to evaluate the statistical significances of the differences between experimental groups. Differences were considered statistically significant for $P < 0.05$ using Duncan's multiple range tests between groups.

4. Conclusions

From the deep-sea-derived rare actinomycete *Microbacterium* sp. MCCC 1A11207, 19 secondary metabolites were isolated and identified. The new compound, microindolinone A (**1**), was determined as (5*R*)-4,5,6,7-tetrahydroindole-4-one. It was the second example of the tetrahydroindole found in nature. And for the first time, its absolute configuration was determined. Although **1** didn't exhibit anti-proliferative or anti-allergic effect, it might have some other bioactivities, for example, to inhibit the production of several pro-inflammatory cytokines such as TNF-α, IL-β, IL-6, IL-8, *etc*.

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Author Contributions: X.-W. Yang designed the project; S. Niu, T.-T. Zhou, and C.-L. Xie performed experiments; G.-Y. Zhang isolated and identified the actinomycete; S. Niu and X.-W. Yang analyzed the data and wrote the paper, while critical revision of the publication was performed by all authors.

Conflicts of Interest: The authors declare no conflict of interest.

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