A new antibiotic, designated mumiamicin, was isolated from the cultured broth of the rare actinomycete strain, *Mumia* sp. YSP-2-79, by Diaion HP-20, silica gel and ODS column chromatography, followed by HPLC purification. The chemical structure of mumiamicin was elucidated as a new furan fatty acid by nuclear magnetic resonance and mass spectrometry. Mumiamicin showed antimicrobial activity and antioxidative activity.

Key Words: antioxidative activity; furan fatty acid; marine actinomycete; mumiamicin; physicochemical screening

Introduction

Marine habitats and ecospheres differ substantially from those in terrestrial environments. Consequently, marine organisms are expected have evolved unique systems, including specialized metabolic pathways, for survival under their unique living conditions. In the past decades, many useful natural products, such as salinosporamide (Feling et al., 2003), abyssomicin (Bister et al., 2004) and thallusin (Matsuou et al., 2005), have been discovered from marine microorganisms. In particular, salinosporamide A, also known as marizomib, produced by marine actinobacteria belonging to the new genus *Salinispora*, is a proteasome inhibitor with promising anticaner activity against multiple myeloma and is now in Phase I/II clinical trials (Russo et al., 2015). The genome sequence of *S. tropica* CNB-440 (5.1 Mbp) revealed the majority of the 17 known secondary metabolite biosynthetic gene clusters, with a few clusters appearing to encode proteins previously identified in other actinobacteria. The biosynthetic gene clusters for secondary metabolites constitute approximately 10% of the whole genome, which is about twice as much as other actinomycetes (Udwary et al., 2007). It is expected that there are many untapped marine actinobacteria having the potential to produce unique chemicals, making them an invaluable resource for the discovery of novel, useful bioactive compounds.

Recently, it has become easy to acquire the UV and MS spectra of many single components from a microbial cultured broth. We have explored cultured broths of microorganisms for new compounds using physicochemical (PC) screening, an approach based simply on the physicochemical properties of compounds, using LC-UV/vis diode array detection (LC/DAD), liquid chromatography combined with mass spectrometry (LC/MS) and simple color-change reactions. New compounds, such as the spoxazomicins (Inahashi et al., 2011), trehangelins (Nakashima et al., 2013), mangromicins (Nakashima et al., 2014a, 2014b, 2015), iminimycins (Nakashima et al., 2016a, b), and sagamilactam (Kimura et al., 2016), were successfully discovered from metabolites of actinomycete strains by our PC screening.

In our course of PC screening, UV/vis and MS spectra-guided fractionation of a cultured broth of a marine actinomycete strain, *Mumia* sp. YSP-2-79, led to the discovery of a new compound, named mumiamicin (I), which consists of fatty acid and furan moieties (Fig. 1). Actinomycete strain YSP-2-79 was one of the strains isolated
from a sponge sample collected at Japan’s Kagoshima Prefecture. The present paper deals with taxonomic studies of the strain, as well as the isolation, physico-chemical properties, structure elucidation, and biological activities, of mumiamicin (I).

Materials and Methods

General experimental procedures. All solvents for HPLC were purchased from Wako Pure Chemical (Osaka, Japan) or Kanto Chemical (Tokyo, Japan). NMR spectra were obtained using XL-400 (Agilent Technologies, Santa Clara, CA, USA) with $^1$H NMR at 400 MHz and $^{13}$C NMR at 100 MHz in CDCl$_3$. Chemical shifts are expressed in ppm and are referenced to residual CDCl$_3$ (7.26 ppm) in the $^1$H NMR spectra and CDCl$_3$ (77.0 ppm) in the $^{13}$C NMR spectra. LC-ESI-MS spectra were obtained using an AB Sciex QSTAR Hybrid LC/MS/MS Systems (AB Sciex, Framingham, MA, USA). IR spectra (KBr) were obtained using a Horiba FT-710 Fourier transform IR spectrometer (Horiba, Kyoto, Japan). UV spectra were obtained with a Hitachi U-2810 spectrophotometer (Hitachi, Tokyo, Japan). Optical rotation was measured on a JASCO model DIP-1000 polarimeter (Jasco, Tokyo, Japan).

Physicochemical screening. A total of 26 actinomycete strains isolated from marine sediments and sponges collected in Japan were used for PC screening. These strains isolated from marine sediments and sponges collected in Japan were used for PC screening. These strains were incubated on a rotary shaker (280 rpm) for 6–14 days at 27°C. The 16S rRNA gene sequence was amplified by PCR and sequenced on a 3130 Genetic Analyzer (Applied Biosystems, Carlsbad, CA, USA) using a BigDye Terminator v.3.1 cycle sequencing kit (Applied Biosystems), according to the manufacturer’s instructions.

Biological activities.

Antimicrobial activity and cytotoxicity: Antimicrobial activities of I against six microorganisms, Bacillus subtilis ATCC 6633, Kocuria rhizophila ATCC 9341, Escherichia coli NIH, Xanthomonas campestris pv. oryzae KB 88, Candida albicans KF1, and Mucor racemosus IFO4581, were evaluated using the paper disk method (ø6 mm disk, Advantec, Co., Ltd., Tokyo, Japan). Media for microorganisms were as follows: nutrient agar (Sanko Junyaku, Co., Ltd., Tokyo, Japan) for the bacteria, and for the fungi, the medium was composed of 1.0% glucose, 0.5% yeast extract and 0.8% agar. A paper disk containing a sample (at a final concentration of 10 μg per disk) was placed on an agar plate with each microorganism. The bacteria, except for Xanthomonas campestris pv. oryzae KB 88, were incubated at 37°C for 24 h. Fungi and X. campestris pv. oryzae KB 88 were incubated at 27°C for 48 h. The cytotoxic activity of I against HeLa S3 and Jurkat cells were evaluated, according to previously reported techniques (Nakashima et al., 2016a).

Scavenging effects on hydroxyl radical (·OH) and singlet oxygen (1O$_2$): Both ·OH and 1O$_2$ scavenging assays were essentially identical to those previously described (Katsuda et al., 2015).

For the ·OH scavenging assay, a non-thermal atmospheric pressure plasma-jet device was used as an ·OH generator. The device was connected to a sinusoidal voltage power source with a voltage of 3 kV, and helium gas at a flow rate of 3 L/min was used as a feeding gas at atmospheric pressure. An aliquot (500 μL) of a reaction mixture comprising 1 mM of I and 300 mM 5,5-dimethyl-1-pyrrrole N-oxide (DMPO) (Labotec, Tokyo, Japan) dissolved in pure water was irradiated with the plasma jet for 30 s. DMSO (at a final concentration of 3.5 M) and pure water were used as positive and negative controls, respectively. 4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL) (Sigma-Aldrich, Saint Louis, MO, USA) (5 μM) was used as a standard sample to calculate the concentration of DMPO-OH, and the ESR spectrum of the manganese ion, which was equipped in the ESR cavity, was used as an internal standard. The measurement conditions for ESR (X-band ESR Spectrometer; JES-FA-100; JEOL, Tokyo, Japan) were: field sweep, 331.92–341.92 mT; field modulation frequency, 100 kHz; field modula-
For the $^{1}$O$_{2}$ scavenging assay, $^{1}$O$_{2}$ was generated by laser irradiation of rose bengal. An experimental laser device equipped with the second harmonic of Nd-YAG laser (wavelength: 532 nm) and a laser power meter (PAX Co. Ltd., Sendai, Japan) was used. Output power of the laser was set at 40 mW. When a semi-micro cuvette containing 200 μL of a reaction mixture comprising 2 mM of 1, 50 mM 2,2,5,5-tetramethyl-3-pyrroline-3-carboxamide (TPC) (Sigma-Aldrich, Saint Louis, MO, USA) and 10 μM rose bengal was set in the experimental device, the area of the mixture irradiated by the laser was approximately 5 × 5 mm, resulting in an irradiance of 160 mW/cm$^{2}$. The light path of the cuvette was 10 mm. Compound I was dissolved in 100 μL of pure water, and TPC and rose bengal were dissolved in 100 μL of phosphate buffer (pH 7.0). Positive control was 2.5 mM NaN$_{3}$ and negative control was pure water. After laser irradiation, the sample was transferred to a quartz cell and the ESR spectrum recorded on an X-band ESR Spectrometer (JES-FA-100). Measurement conditions for the ESR were: field sweep, 330.50–340.50 mT; field modulation frequency, 100 kHz; field modulation width, 0.05 mT; amplitude, 200; sweep time, 2 min; time constant, 0.03 s; microwave frequency, 9.420 GHz; microwave power, 4 mW. To calculate the spin concentration of the nitroxide radical generated through TPC oxidation by $^{1}$O$_{2}$, 20 μM TEMPOL was used as a standard and the ESR spectrum of the manganese ion, which was equipped in the ESR cavity, was used as an internal standard.

**Results**

**Selection of *Mumia* sp. YSP-2-79 by PC screening**

The 104 samples were prepared from 26 marine actinomycete strains using four different media for PC screening. As a result, a cultured broth of *Mumia* sp. YSP-2-79 cultured in soybean meal medium was selected for evaluation due to the following criteria: 1) many peaks were observed by LC/DAD analyses in a cultured broth, 2) HPLC peaks with characteristic physico-chemical features were deduced to be new compounds, 3) production of compounds was strongly dependent on the growth medium. Although many flavonoids were detected from the cultured broth, the strain YSP-2-79 produced a compound possessing characteristic physico-chemical properties, with the maximum absorption at 322 nm in the UV spectrum and the exact MS value at m/z 251.1649 ([M+H]$^+$, C$_{15}$H$_{23}$O$_{3}$) (Fig. 2), which was deduced as a new compound following database searches of the Dictionary of Natural Products (http://dnp.chemnetbase.com/) and inhouse databases.

**Taxonomy of the producing strain of mumiamicin (1)**

Strain YSP-2-79 was isolated from a sponge, *Paratetilla bacca* (Selenka), collected at offshore of Shimokoshikijima Island, Kagoshima Prefecture, Japan. The sample (~1 cm$^{3}$) was homogenized with a glass rod in 5 mL of sterile seawater. The resulting homogenate (50 μL) was spread on the artificial seawater agar plate containing 0.1% pyruvate, 0.05% catechin and the mixture of antibiotics (100 mg/L cycloheximide and 20 mg/L gryseofulvin). Colonies appeared after 2 weeks incubation at 25°C. The 16S rRNA gene sequence (803 bp) of the strain was analyzed using the EzTaxon-e database (http://eztaxon-e.ezbiocloud.net/) and showed 100% similarity with that of *Mumia flava* MUSC 201T (KC907394) (Lee et al., 2014). It was suggested that the strain YSP-2-79 belongs to the genus *Mumia*.

**Fermentation and isolation of mumiamicin (1)**

The strain *Mumia* sp. YSP-2-79 was grown and maintained in broth consisting of 1.0% dextrose and 1.0% yeast extract (adjusted to pH 7.0 before sterilization). A loop of frozen broth of strain YSP-2-79 was inoculated into 100 mL of the seed medium, consisting of 1.0% dextrose and 1.0% yeast extract (adjusted to pH 7.0 before sterilization) in a 500-mL Erlenmeyer flask. The flask was incubated on a rotary shaker (210 rpm) at 27°C for 7 days. A 2 mL portion of the seed culture was inoculated into 500 mL-Erlenmeyer flasks (total 100 flasks) each containing 100 mL of soybean meal medium, and fermentation was carried out on the rotary shaker (210 rpm) at 27°C for 11 days.
The isolation of 1 is summarized in Scheme 1. The whole cultured broth (10 L) was added to 10 L of EtOH, followed by centrifugation for 10 min at 3,000 rpm. The supernatant was added to 20 L of water and then passed through a column of Diaion HP-20 (100 i.d. × 250 mm; Mitsubishi Chemical Ltd, Tokyo, Japan). After washing with water, the fraction containing 1 was eluted with MeOH. The eluate was concentrated in vacuo followed by trituration with MeOH to yield a MeOH-soluble crude material (4.1 g). This material was applied on a silica gel open column eluted with n-hexane : CHCl₃ : MeOH (10:1:0, 1:1:0, 0:100:0, 0:1:1, and 0:0:1) (v/v), each 1.5 L, to give five fractions. The eluate fraction (0:100:0 fraction (566.1 mg)) was dissolved in a small amount of MeOH and purified by HPLC on an ODS column (14 I.d. × 250 mm; GL Sciences Inc., Tokyo, Japan) and eluted with a stepwise gradient of CHCl₃-MeOH (10:1:0, 1:1:0, 0:100:0, 0:1:1, and 0:0:1) (v/v), each 1.5 L, to give five fractions. The eluate fraction (0:100:0 fraction) was concentrated in vacuo to afford 566.1 mg. This material was applied on an ODS column (40 i.d. × 150 mm; Senshu Scientific, Tokyo, Japan) previously equilibrated with water. After washing with 50% MeOH aq, the fraction containing 1 was eluted with 70% MeOH aq and concentrated in vacuo. The eluate fraction (230.3 mg) was dissolved in a small amount of MeOH and purified by HPLC on an Inertsil ODS-4 column (14 i.d. × 250 mm; GL Sciences Inc., Tokyo, Japan) with 80% MeOH aq, 0.1% formic acid. The peak at retention time of 17.0 min was collected and dried in vacuo to yield 1 (7.8 mg).

Physico-chemical properties of mumiamicin (1)

The physico-chemical properties of 1 are summarized in Table 1. The compound is readily soluble in MeOH and CHCl₃ and less soluble in H₂O. Compound 1 showed absorption maxima at 205 and 322 nm in UV spectrum. The IR absorption at 2923, 2854 and 1581 cm⁻¹ suggested the presence of an aliphatic chain and carbonyl groups.

Structure elucidation of mumiamicin (1)

Compound 1 was obtained as a white powder and determined to have the molecular formula of C₁₅H₂₂O₃ by HR-ESI-MS with [M+H]+ ion at m/z 251.1649 (calculated value for C₁₅H₂₃O₃, 251.1641) using NMR spectral data.

The ¹H and ¹³C NMR spectral data of 1 are shown in Table 2. The ¹H NMR data indicated the presence of six methylene protons, three sp² methine protons and two methyl protons. The ¹³C NMR spectrum showed the resonances of fifteen carbons, which were classified into six olefinic and aromatic carbons, one carbonyl carbon at δ 172.6, six sp² methylene carbons, and two methyl carbons by HSQC spectra.

The ¹H-¹H COSY spectra revealed the presence of three partial structures (a) C-2/C-3 (b) C-8/C-11, (c) C-12/C-14 as shown in Fig. 3. Analysis of HMBC data confirmed the presence of a 3-methyl-furan ring connected to 1-propenoic acid at the C-4 position, including partial structure (a), based on correlations from H-2 to C-1 and C-4; from H-3 to C-1, C-2, C-4 and C-5; from H₂-12 to C-13; from H₂-11 to C-10 and C-12; from H₂-10 to C-11 and C-12; from H₂-9 to C-7 and C-10; from H₂-11 to C-7 and C-10; from H₂-12 to C-13; from H₂-13 to C-14; and from H₂-14 to C-12 and C-13. The geometry of an α,β-unsaturated carboxyl group was determined to be E by a large coupling constant (15.2 Hz) between H-2 and H-3. The chemical shift of carboxylic acid (12 ppm) was observed in DMSO-d₆ (Fig. S6).

In addition, the carboxylic acid was reacted with trimethylsilyldiazomethane (TMSCHN₂) to give the methyl ester product of mumiamicin (Figs. S7, S8, and S9). Finally, the furan ring was absolutely formed by the remaining three degrees of unsaturation. This is strongly supported by the comparison of ¹³C chemical shifts between 1 and a known furan fatty acid, 3′-methyl-5′-pentyl-furylaryllic acid, isolated from a plant (Kimura et al., 2010). Overall, the structure of 1 proved to be a new furan fatty acid (Fig. 1), and it was named mumiamicin.

Table 1. Physico-chemical properties of mumiamicin (1).

| Mumiamicin (1) |                  |
|---------------|-----------------|
| Appearance    | White powder    |
| Molecular formula | C₁₅H₂₂O₃     |
| Molecular weight | 250             |
| ESI-MS (m/z) |                  |
| Calc.         | 251.1641 (for C₁₅H₂₃O₃) |
| Found         | 251.1649 [M+H]+ |
| UV λmax, MeOH (nm) | 205 (1083), 322 (2218) |
| IR ν(KBr) cm⁻¹ | 2923, 2854, 1581, 1411, 1257, 964 |
| Soluble       | MeOH, CHCl₃     |
| Insoluble     | H₂O             |

The biological activities of mumiamicin (1)

Compound 1 showed weak antimicrobial activities against B. subtilis ATCC 6633, K. rhizophila ATCC 9341, and E. coli NIHJ, with inhibition zones of 9, 9 and 7 mm at 10 μg per 6 mm paper disk, respectively. Compound 1 showed no activity against X. campestris pv. oryzae KB 88, C. albicans KFI and M. racemosus IFO4581, nor against HeLa S3 and Jurkat cells, even at 10 μM.
Table 2. $^1$H and $^{13}$C NMR spectroscopic data of mumiamicin (1) in CDCl$_3$.

| Position | $\delta$ (ppm) | mult. | $\delta$ (ppm), int., mult., $J$ in Hz | HMBC |
|----------|----------------|-------|--------------------------------------|-------|
| 1        | 172.6          | C     |                                      |       |
| 2        | 110.7          | CH    | 6.14, 1H, d, 15.2                    | C-1, C-4 |
| 3        | 131.0          | CH    | 7.50, 1H, d, 15.2                    | C-1, C-2, C-4, C-5 |
| 4        | 145.5          | C     |                                      |       |
| 5        | 128.7          | C     |                                      |       |
| 6        | 110.8          | CH    | 5.97, 1H, s                          | C-4, C-5, C-5-Me, C-7 |
| 7        | 160.0          | C     |                                      |       |
| 8        | 28.2           | CH$_2$| 2.60, 2H, t, 7.4                     | C-6, C-7, C-9, C-10 |
| 9        | 27.7           | CH$_2$| 1.64, 2H, m                          | C-7, C-10 |
| 10       | 29.0           | CH$_2$| 1.32, 2H, m                          | C-11, C-12 |
| 11       | 29.1           | CH$_2$| 1.25, 2H, m                          | C-10, C-12 |
| 12       | 22.6           | CH$_2$| 1.28, 2H, m                          | C-13 |
| 13       | 31.7           | CH$_2$| 1.27, 2H, m                          | C-14 |
| 14       | 14.1           | CH$_3$| 0.90, 3H, t, 6.8                     | C-12, C-13 |
| 5-Me     | 10.4           | CH$_3$| 2.12, 3H, s                          | C-4, C-5, C-6 |

ESR analyses revealed that compound 1 has $\cdot$OH and $^{1}$O$_2$ scavenging activity. The spin concentrations of DMPO-$\cdot$OH (a spin adduct of $\cdot$OH and DMPO) and the nitroxide radical (derived from TPC oxidation by $^{1}$O$_2$) were reduced by 1. As shown in Fig. 4, the scavenging activity of 1 mM of 1 against $\cdot$OH and that of 2 mM of 1 against $^{1}$O$_2$ exceeded that of 3.5 M DMSO and of 2.5 mM NaN$_3$ used as each positive control, respectively.

Discussion

Several furan fatty acids have been isolated as secondary metabolites from various organisms, including plants (Kimura et al., 2010), fungi (Ma et al., 2016) and fish (Hammann et al., 2015). They have displayed various biological activities, such as antioxidative (Teixeira et al., 2013) and anti-inflammatory (Wakimoto et al., 2011) prop-
erties. To the best of our knowledge, mumiamicin (1) obtained from *Mumia* sp. YSP-2-79 is the first report of a furan fatty acid from actinomycetes. Additionally, this is the first report about secondary metabolites from the genus *Mumia*. A similar compound with a shorter aliphatic chain than 1 was only reported as a plant metabolite, and was devoid of any biological activity (Kimura et al., 2010).

Compound 1 showed scavenging activity against not only ·OH but 1O2. Since the former is a free radical but the latter is not, it is expected that the antioxidative activity of compound 1 would go beyond mere radical scavenging as is the case with a unique marine carotenoid, fucoxanthin (Sachindra et al., 2007). Thus, we are proceeding with further examination of the antioxidative profile of 1. In addition, continuing refinement and exploitation of our unique PC screening has an exciting potential for discovering yet more novel compounds from marine-dwelling microorganisms.

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Supplementary Materials

Supplementary figures and procedure are available in our J-STAGE site (http://www.jstage.jst.go.jp/browse/gam).

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