Polyketides and Meroterpenes from the Marine-Derived Fungi *Aspergillus unguis* 158SC-067 and *A. flocculosus* 01NT-1.1.5 and Their Cytotoxic and Antioxidant Activities

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Abstract: Ten secondary metabolites, including a new grifolin analog, grifolin B (1); a new homovalenic acid derivative, 12-hydroxyhomovalenic acid (7); and a compound isolated from a natural source for the first time (9), along with seven known compounds, grifolin (2), averantin (3), 7-chloroaverantin (4), 1′-O-methylaverantin (5), 7-hydroxy-2-(2-hydroxypropyl)-5-pentylchromone (6), homovalenic acid (8), and bekeleylactone E (10), were isolated from two fungal strains. The structures of 1–10 were identified by detailed analysis and comparison of their spectroscopic data with literature values. Compounds 9 and 10 showed moderate cytotoxic activity against a panel of cancer cell lines (PC-3, HCT-15, MDA-MB-231, ACHN, NCI-H23, NUGC-3), with the GI50 values ranging from 1.1 µM to 3.6 µM, whereas 7 displayed a weak 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity without cytotoxicity against all tested cell lines.

Keywords: marine-derived fungi; *Aspergillus* sp.; polyketides; meroterpenes; antioxidant; cytotoxicity

1. Introduction

Marine habitats have been acknowledged as prolific sources of new chemical entities with various worthwhile pharmacological activities [1]. Over the past decade, more than 1000 new marine natural products have been reported annually [2]. Whereas the discovery of new compounds from tunicates, cnidarians, and sponges is diminishing, there is a remarkable increase in the number of new substances isolated from marine-derived bacteria and fungi [2]. According to the latest statistics, new natural products (NPs) reported from marine-derived fungi accounted for almost half (47%) of the total new marine NPs reported in 2019 [2].

*Aspergillus* is one of the most ubiquitous genera of filamentous fungi, and they are the major contributor to marine-derived fungal natural products [2,3]. A great number of secondary metabolites with structural diversity, such as polyketides, alkaloids, terpenes, steroids, and peptides, have been isolated from this genus, and many of them display potent biological activities [2].

As part of our ongoing program to investigate marine-derived fungi as an under-explored source of new natural products, we focused our attention on *Aspergillus unguis* 158SC-067 and *A. flocculosus* 01NT-1.1.5 strains, which showed good antimicrobial activity in the preliminary screening. Our previous studies on the EtOAc extract of *A. flocculosus* 01NT-1.1.5 grown on rice medium led to the isolation of fungal metabolites having antimicrobial properties and the suppression of RANKL-induced osteoclastogenesis activities [4,5]. To further study the secondary metabolites from marine-derived fungi, the...
“one strain many compounds” (OSMAC) strategy was applied by changing the culture medium from rice medium to Bennett’s broth medium. Interestingly, the $^1$H NMR spectra of the crude extracts from A. unguis 158SC-067 and A. flocculosus 01NT-1.1.5 grown in Bennett’s broth medium showed some unique peaks in aromatic and olefinic regions, which did not appear or were much smaller when cultured in the rice medium. Therefore, the extracts from two strains were chemically investigated. As a result, two new phenolic compounds were isolated from one strain, together with eight known compounds (2–6 and 8–10), isolated (Figure 1). Herein, we report the isolation, structure determination, and bioactivities of these compounds.

Figure 1. Structures of 1–10 isolated from Aspergillus unguis 158SC-067 and A. flocculosus 01NT-1.1.5.

2. Results and Discussion

Compound 1 was isolated as a brown solid, and its molecular formula was deduced as C$_{19}$H$_{26}$O$_{4}$ by HRESIMS data (m/z 341.1728 [M + Na]$^+$, calculated for C$_{19}$H$_{26}$O$_{4}$Na 341.1724), requiring seven degrees of unsaturation. The $^1$H NMR spectrum revealed signals of two aromatic protons at $\delta_H$ 6.12 (2H, s, H-4 and H-6); two olefinic protons at $\delta_H$ 5.21 (t, $J$ = 7.0, H-2') and 5.12 (t, $J$ = 7.0, H-2'); ten methylene protons at $\delta_H$ 3.24 (d, $J$ = 7.1, H$_2$-1'), 2.26 (m, H$_2$-9'), 2.20 (m, H$_2$-8'), 2.07 (dd, $J$ = 7.3, 14.6, H$_2$-5'), and 1.96 (t, $J$ = 7.4, H$_2$-4'); and three methyl groups at $\delta_H$ 2.13 (s, H$_3$-7), 1.74 (s, H$_3$-12'), and 1.57 (s, H$_3$-11') (Table 1). The $^{13}$C NMR spectrum, in combination with the gHSQC NMR spectrum, displayed nineteen resonances belonging to a carboxyl carbon at $\delta_C$ 177.9 (C-10'); six non-protonated sp$^2$ carbons at $\delta_C$ 156.9 (C-1 and C-3), 137.2 (C-5), 134.2 (C-7'), and 113.3 (C-2); four protonated sp$^2$ carbons at $\delta_C$ 126.0 (C-6'), 125.2 (C-2'), and 108.5 (C-4 and C-6); five sp$^3$ methylene carbons at $\delta_C$ 40.7 (C-4'), 35.9 (C-8'), 34.2 (C-9'), 27.5 (C-5'), and 22.9 (C-1'); and three methyls at $\delta_C$ 21.3 (C-7), 16.2 (C-12'), and 16.0 (C-11'). One carboxyl and ten sp$^2$ carbons were accounted for six out of seven degrees of unsaturation, indicating that 1 possesses a monocyclic skeleton.
The 1H and 13C NMR spectra were recorded in CD3OD at 600 MHz and 150 MHz, respectively.

The gross structure of 1 was identified by a detailed analysis of 1H-1H COSY and HMBC data. The structure of a symmetrical 1,2,3,5-tetrasubstituted benzene ring was identified by the HMBC cross peaks from H-4 to C-2, C-3, and C-6, and from H-6 to C-2, C-4, and C-5 (Figure 2). A methyl group attached to C-5 of the benzene ring was confirmed by the HMBC correlations from H3-7 to C-4, C-5, and C-6, and those of H-4/C-7 and H-5/C-6. The side chain was determined as a 4,8-dimethyldeca-4,8-dienoic acid by the COSY correlations from H-2' to H-2, H2-4'/H2-5', H2-5'/H-6', and H2-8'/H2-9'; as well as the HMBC cross peaks from H3-12' to C-2', C-3', C-4'; from H3-11' to C-6', C-7', C-8'; and from H2-8' to C-6' and C-10'. The side chain connected to the ring at C-2 was supported by the HMBC cross peaks from H2-1' to C-1, C-2, and C-3.

The NOESY correlations from H-2' to H2-4', H3-12' to H2-5', and no observed correlation from H-2' to H3-12' confirmed the geometry of C7 as E. Similarly, C7' was deduced as E' as shown in Figure 2. Thus, 1 is a new derivative of the co-isolated compound, grifolin (2) [6], and named grifolin B (Figure 1).

Compound 7 was isolated as a yellowish powder with a molecular formula of C13H16O4 based on its HRESIMS data (m/z 259.0945 [M + Na]+, calculated for C13H16O4Na 259.0946), requiring six degrees of unsaturation. The 1H NMR spectrum revealed the presence of thirteen signals, which were classified into two pairs of magnetically symmetrical protons at δH 7.18 (d, J = 8.5, H-4 and H-8) and 6.86 (d, J = 8.6, H-5 and H-7); an olefinic proton at δH 5.71 (td, J = 1.2, 6.3, H-10); two oxygenated sp3 methylenes at δH 4.60 (d, J = 6.3, H2-9) and 3.98 (s, H2-12); a sp3 methylene at δH 3.52 (s, H2-2); and a methyl group at δH 1.74 (s, H3-13). The 13C and gHSQC NMR spectra revealed the presence of thirteen carbon signals belonging to a carboxyl carbon at δC 176.0 (C-1); three non-protonated sp2 carbons

| Compound | Position | δH (Mult, J in Hz) | δC, Type | Position | δH (Mult, J in Hz) | δC, Type |
|----------|----------|-------------------|---------|----------|-------------------|---------|
| 1        | 1, 3     | 156.9, C          | 1       | 7        | 176.0, C          |         |
|          | 2        | 113.3, C          | 2       | 3        | 3.52, s           | 41.1, CH2 |
|          | 4, 6     | 6.12, s           | 3       | 5        | 108.5, CH         | 572.2   |
|          | 7        | 2.13, s           | 5, 7    | 6        | 7.18, d (8.5)     | 131.3, CH |
|          | 1'       | 3.24, d (7.1)     | 6       | 7        | 4.60, d (6.3)     | 65.6, CH2 |
|          | 2'       | 5.21, t (7.0)     | 9       | 3        | 5.12, t (7.0)     | 140.8, C |
|          | 3'       | 134.2, C          | 10      | 4        | 1.96, t (7.4)     | 121.1, CH |
|          | 5'       | 2.07, dd (7.3, 14.6) | 12 | 6        | 1.74, t (7.0)     | 67.8, CH2 |
|          | 7'       | 134.6, C          | 13      | 6        | 5.12, t (7.0)     | 14.0, CH3 |
|          | 8'       | 2.20, m           | 369.5, CH2 | 7       | 1.74, s           |         |
|          | 9'       | 2.26, m           | 34.2, CH2 | 8       | 1.74, s           |         |
|          | 10'      | 177.9, C          |         | 9       | 1.57, s           |         |
|          | 11'      | 1.57, s           |         | 10      | 16.0, CH3         |         |
|          | 12'      | 1.74, s           |         |          | 16.2, CH3         |         |

Table 1. 1H and 13C NMR spectroscopic data for 1 and 7.
at δC 159.2 (C-6), 140.8 (C-11), and 128.2 (C-3); two pairs of magnetically symmetrical carbons at δC 131.3 (C-4 and C-8) and 115.7 (C-5 and C-7); a protonated sp² carbon at δC 121.1 (C-10); two oxygenated sp³ methylene carbons at δC 67.8 (C-12) and 65.6 (C-9); a sp³ methylene at δC 41.1 (C-2); and a methyl at δC 14.0 (C-13).

The structure of a symmetrical 1,4-disubstituted benzene ring was determined by the COSY correlations from H-4 to H-5 and from H-7 to H-8, and the HMBC correlations from H-4 to C-6 and C-8, from H-5 to C-3 and C-7, from H-7 to C-3 and C-5, and from H-8 to C-4 and C-6 (Figure 2). A carboxy methyl group attached to the benzene ring at C-3 was supported by the HMBC correlations from H₂-9 to C-1, C-3, C-4, and C-8. The HMBC correlation from H₂-9 to C-6 supported that a prenyl unit was attached to C-4 via an ether linkage. The fact that CH₂-12 bears a hydroxy group was evidenced by the chemical shift values of H₂-12 (δH 3.98) and C-12 (δC 67.8) as well as the molecular formula. The geometry of the double bond between C-10 and C-11 was determined as 10E by the strong NOESY correlation from H₁₀ to H₂-12 (Figure S14). Thus, 7 is a new derivative of the co-isolated compound, homovalencic acid (8) [7], and named 12-hydroxyhomovalencic acid.

The previously described compounds were identified as grifolin (2) [6], averantin (3) [8], 7-chloroaverantin (4) [8], 1′-O-methylaverantin (5) [8], 7-hydroxy-2-(2-hydroxypropyl)-5-pentylchromone (6) [9], homovalencic acid (8) [7], (5R,6S,16R,3E)-5,6-dihydroxy-16-methyloxacyclohexadec-3-en-2-one (9) [10], and bekeleylactone E (10) [11] by comparison of their spectroscopic data and the signs of optical rotation with those reported in the literature. It is noteworthy that 9 was isolated for the first time from natural source in this study, and its spectroscopic data were identical to those reported for a synthetic analog by Stierle et al. (Figures S15–S18) [10].

Since some of the previously reported compounds isolated in this work have been shown to possess cytotoxic activity [8,12], 1, 7, 9, and 10 were evaluated for their cytotoxicity against six cancer cell lines, HCT-15 (colon), NUGC-3 (stomach), NCI-H23 (lung) ACHN (renal), PC-3 (prostate), and MDA-MB-231 (breast), which are the most common cancer types in Korea. However, only 9 and 10 showed moderate cytotoxic activity against all of the tested cell lines, with GI₅₀ values ranging from 1.1 µM to 3.6 µM (Table 2). Additionally, 1 and 7 were screened for their DPPH radical scavenging activity. Compound 1 showed a weak DPPH radical scavenging activity with an IC₅₀ value of 86.4 µM, whereas 7 showed neither cytotoxic nor DPPH radical scavenging activity.

**Table 2. Growth Inhibition (GI₅₀, µM) of 9 and 10 against human cancer cell lines.**

| Cell Lines | 9 | 10 | Adr. |
|------------|---|----|------|
| PC-3       | 2.7 | 3.6 | 0.17 |
| HCT-15     | 3.0 | 2.8 | 0.12 |
| MDA-MB-231 | 2.4 | 3.1 | 0.16 |
| ACHN       | 3.4 | 3.1 | 0.16 |
| NCI-H23    | 1.1 | 1.2 | 0.13 |
| NUGC-3     | 2.7 | 2.6 | 0.16 |

Adr. Adriamycin as a positive control. GI₅₀ values are the concentration corresponding to 50% growth inhibition.

3. Materials and Methods

3.1. General Experimental Procedures

High-resolution ESIMS data were measured with a hybrid ion-trap time-of-flight mass spectrometer (Shimadzu LC/MS-IT-TOF, Kyoto, Japan). IR spectra were obtained on a JASCO FT/IR-4100 spectrophotometer (JASCO Corporation, Tokyo, Japan). The 1D and 2D NMR spectra were recorded by a Bruker 600 MHz spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany). HPLC was performed using a semi-preparative ODS column (YMC-Triart C18, 250 × 10 mm i.d., 5 µm) and an analytical ODS column (YMC-Triart C18, 250 × 4.6 mm i.d., 5 µm) (YMC Corporation, Kyoto, Japan). UV spectra were measured with a Shimadzu UV-1650PC spectrophotometer in 1 mm quartz cells (Shimadzu Corporation, Kyoto, Japan). All the reagents were purchased from Sigma-Aldrich (Merck...
KGaA, Darmstadt, Germany), and the organic solvents and water were distilled prior to use. Cancer cell lines were obtained from Japanese Cancer Research Resources Bank (JCRB) (NUGC-3, gastric adenocarcinoma, JCRB Cell Bank/Cat. # JCRB0822, and American Type Culture Collection (ATCC) (PC-3, prostate adenocarcinoma, ATCC/Cat. # CRL-1435; MDA-MB-231, breast adenocarcinoma, ATCC/Cat. # HTB-26; ACHN, renal adenocarcinoma, ATCC/Cat. # CRL-1611; NCI-H23, lung adenocarcinoma, ATCC/Cat. # CRL-5800; HCT-15, colorectal adenocarcinoma, ATCC/Cat. # CCL-225).

3.2. Fungal Material, Fermentation and Isolation of Secondary Metabolites

3.2.1. Fungal Material, Fermentation, and Isolation of 1–6 from Aspergillus unguis 158SC-067

The strain Aspergillus unguis 158SC-067 was isolated from a seawater sample collected at the depth of 30 m near the Socheongcho Ocean Research Station, Korea, in August 2015. The fungus was identified as Aspergillus unguis on the basis of DNA amplification and ITS gene sequencing (GenBank accession number MZ489151). The strain was deposited in the Microbial Culture Collection, KIOST, with the name of Aspergillus sp. 158SC-067 under the curatorship of Hee Jae Shin.

The seed and mass cultures were conducted in Bennett’s medium (1% glucose, 0.2% tryptone, 0.1% yeast extract, 0.1% beef extract, 0.5% glycerol, natural sea salts 3.2%, and agar 1.7% for agar medium). At first, the fungus was grown on Bennett’s agar medium in a Petri dish under static condition for 7 days. Agar plugs were cut into small pieces and aseptically transferred into a 500 mL conical flask containing 300 mL of Bennett’s broth medium and placed on a rotary shaker (140 rpm) at 28 °C for 7 days for the seed culture. An aliquot (0.1% v/v) from the seed culture was inoculated into 2.0 L flasks, each containing 1.0 L of the medium, and cultured under the same conditions as described for the seed culture for 14 days. In total, 20 flasks were prepared for the mass production.

After cultivation, the culture broth and mycelium were separated by filtration. The broth was extracted with EtOAc (20 L, twice). The EtOAc layer was evaporated under reduced pressure at 37 °C to yield a broth extract (1.0 g). The extract was separated into 10 fractions (fractions 1b–10b) by vacuum liquid chromatography on an ODS column using a stepwise elution with 100 mL each of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90% MeOH in H2O and 100% MeOH. Compound 1 (3.0 mg) was isolated from fraction 7b by a semipreparative HPLC (YMC-PackODS-A, 250 × 10 mm i.d., 5 µm, flow rate 2.0 mL/min) with an isocratic elution of 60% MeOH in H2O for 40.0 min.

The mycelium was extracted with EtOAc (3.0 L, three times) and the EtOAc solution was evaporated under reduced pressure to yield a mycelium extract (2.0 g). The extract was fractionated into 15 fractions (fractions 1m–15m) by the same procedure described for the broth extract. Compounds 2 (1.0 mg, tR = 54 min), 3 (10.0 mg tR = 64 min), and 4 (1.0 mg, tR = 92 min) were purified from fraction 9m by a semipreparative HPLC (YMC-PackODS-A, 250 × 10 mm i.d., 5 µm, flow rate 2.0 mL/min) with an isocratic elution of 80% MeOH in H2O. Fraction 10m was subjected to a semipreparative HPLC (YMC-PackODS-A, 250 × 10 mm i.d., 5 µm, flow rate 2.0 mL/min) with an isocratic elution of 90% MeOH in H2O to obtain compound 5 (2.0 mg, tR = 70 min). Compound 6 (1.5 mg) was isolated from fraction 7m by an analytical HPLC (YMC-PackODS-A, 250 × 4.6 mm i.d., 5 µm, flow rate 0.8 mL/min) with an isocratic elution of 60% MeOH in H2O for 38 min.

3.2.2. Fungal Material, Fermentation, and Isolation of 7–10 from Aspergillus flocculosus 01NT-1.1.5

Aspergillus flocculosus 01NT-1.1.5 was isolated from a Stylissa sp. sponge as previously described [4]. Based on NMR-guided isolation, the 1H NMR spectrum of the crude extract from the culture broth of A. flocculosus 01NT-1.1.5 showed some interesting peaks in olefinic and aromatic regions. Therefore, the broth extract was selected for further study. The culture broth was extracted with EtOAc, and the organic extract was fractionated into 15 fractions as described previously [13]. Compound 7 (10.0 mg) was purified from fraction 8 by a semipreparative HPLC (YMC-PackODS-A, 250 × 10 mm i.d., 5 µm, flow
rate 2.5 mL/min) with an isocratic elution of 25% MeCN in H₂O for 28.0 min. Compound 8 (10.0 mg) was isolated from fraction 10 by an analytical HPLC (YMC-PackODS-A, 250 × 4.6 mm i.d., 5 µm, flow rate 1.0 mL/min) with an isocratic elution of 50% MeCN in H₂O for 15 min. Fraction 12 was subjected to an analytical HPLC (YMC-PackODS-A, 250 × 4.6 mm i.d., 5 µm, flow rate 1.0 mL/min) with an isocratic elution of 50% MeCN in H₂O to yield 9 (3.0 mg, t<sub>R</sub> = 20.0 min) and 10 (3.0 mg, t<sub>R</sub> = 27 min).

**Grifolin B (1):** brown solid, UV (MeOH) λ<sub>max</sub> (log ε) 204 (4.15), 228 (3.73), 277 (3.12) nm; IR ν<sub>max</sub> 3678, 2987, 1706, 1452, 1058 cm<sup>−1</sup>; HRESIMS m/z 341.1728 [M + Na]<sup>+</sup>, calculated for C<sub>19</sub>H<sub>26</sub>O<sub>4</sub>Na 341.1724; ¹H NMR (CD<sub>3</sub>OD, 600 MHz) and ¹³C NMR (CD<sub>3</sub>OD, 150 MHz), see Table 1.

**12-Hydroxyhomovalenic acid (7):** yellowish powder, UV (MeOH) λ<sub>max</sub> (log ε) 203 (4.23), 227 (3.81), 276 (3.15) nm; IR ν<sub>max</sub> 3373, 2925, 1705, 1509, 1224, 1176 cm<sup>−1</sup>; HRESIMS m/z 259.0945 [M + Na]<sup>+</sup>, calculated for C<sub>13</sub>H<sub>16</sub>O<sub>4</sub>Na; ¹H NMR (CD<sub>3</sub>OD, 600 MHz) and ¹³C NMR (CD<sub>3</sub>OD, 150 MHz), see Table 1.

### 3.3. Cytotoxicity Test by SRB Assay

Cytotoxicity Test by SRB Assay has been described previously [14].

### 3.4. DPPH Radical Scavenging Assay

DPPH radical scavenging assay was performed according to the previously described method with minor modification [3,15]. The samples and a positive control, ascorbic acid, were dissolved in DMSO with final concentrations of 6.25, 12.5, 25, 50, 100, and 200 µg/mL. DPPH was dissolved in anhydrous ethanol (EtOH) with a concentration of 0.04 mg/mL. Tested samples (50 µL) were added to 50 µL of fresh DPPH, then kept in room temperature in the dark for 30 min. The optical density (OD) was measured by an AMR-100 microplate reader (Hangzhou Allsheng Instruments, Hangzhou, China) at 517 nm. The EtOH and DMSO were used as a blank and negative control, respectively. The IC<sub>50</sub> values were determined by the software of GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA) [3].

### 4. Conclusions

In summary, on the basis of the OSMAC strategy, ten secondary metabolites, including two new phenolic derivatives (1 and 7), and a substance isolated from a natural source for the first time (9), together with seven known compounds (2–6, 8, and 10), were isolated from two fungal strains of the genus Aspergillus. Compounds 9 and 10 showed moderate cytotoxic activity, while 1 exhibited a weak DPPH radical scavenging activity without cytotoxicity. To the best of our knowledge, the known compounds (2–6) were isolated from A. unguis for the first time. Moreover, we also found that A. flocculosus 01NT-1.1.5 produces various chemical constituents in different culture media [4,13]. This study expanded the chemical and biological diversity of natural products isolated from marine-derived fungi. The results indicate that marine-derived fungi, particularly the Aspergillus genus, could be a promising source to search for bioactive natural products with unique structures for discovery of new anti-cancer drugs.

**Supplementary Materials:** The followings are available online at https://www.mdpi.com/article/10.3390/md19080415/s1, Figures S1–S18: the analyzed data of MS, 1D and 2D NMR spectra of compounds 1, 7, and 9.

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