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Fusasolpolyol A, An Unreported Polyhydroxy Compound Isolated from the *Sargassum thunbergii*-Derived Endophytic Fungus *Fusarium solani* 2024f-xx

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Abstract: *Fusarium solani* 2024f-xx, an endophytic fungus derived from the marine brown algae *Sargassum thunbergii*, was chemically studied. As a result, two polyhydroxy compounds, namely fusasolpolyol A (**1**) and (4*E*,8*E*,12*E*)-2,3,7,11-tetrahydroxy-2,4,6,8,10,12-hexamethyltetradeca-4,8,12-trienoic acid (**2**), as well as two known drimane-type sesquiterpenoids (**3** and **4**) were isolated and identified. The structures of the isolated compounds were ascertained by means of specific spectroscopic methods (mainly determined by HRESIMS and 1D/2D NMR data). Compound **1** was identified as a new compound. In the cytotoxic assays, compound **2** revealed moderate activity against the human gastric carcinoma cell MKN-45 and the human pancreatic cancer cell PATU8988T, with the respective IC_{50} values of 19.6 ± 1.2 μM and 26.3 ± 0.9 μM.

Keywords: *Fusarium solani*; endophytic fungus; secondary metabolites; polyhydroxy compound; cytotoxic activity.

1. Fungus

The target fungus *Fusarium solani* 2024f-xx was independently isolated from the marine brown algae *Sargassum thunbergii* that was collected in June 2024 from Jiangmen, Guangdong Province, China. This fungus was identified by the previously reported method via the comparison of the ITS rDNA gene sequence [1]. Analysis of the ITS rDNA sequence of the fungal strain 2024f-xx (GenBank accession No. PV276913) showed that this fungus shared a 99.24% identity with *Fusarium solani* strain MR29 (GenBank accession No. MW509863.1). The producing strain has been deposited at Fujian Medical University.

2. Previous Studies

Previous studies have shown that endophytic fungi are a treasure trove of active natural products [2−4]. Chemical research on endophytic fungi has yielded many natural compounds with various

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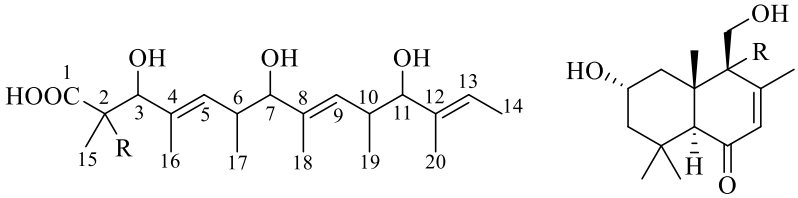
skeleton types, including chromones, lactones, steroids, terpenes, alkaloids, and peptides [5−7]. These compounds possess rich medicinal values [3−7]. The endophytic fungus *Fusarium solani* has been reported to be a producer of bioactive natural compounds. For example, fusarins G−L, six new fusarin derivatives with strong anti-inflammatory activities, were isolated from the fungus *F. solani* strain 7227 [8]. Seven new polyketides inhibiting cell proliferation were isolated from *Camellia chrysantha*-derived endophytic fungus *F. solani* [9]. Seven new antibacterial 7-desmethyl fusarin C derivatives were yielded from the medicinal plant *Chlorophora regia*-derived endophytic fungus *F. solani* JK10 [10]. The aforementioned examples indicate that endophytic fungi, especially *Fusarium* species, are nonnegligible sources of secondary metabolites [11].

3. Present Study

In this study, the *S. thunbergii*-derived endophytic fungus *F. solani* 2024f-xx was chemically investigated. This fungus was inoculated onto PDA plates and cultured at 28 ℃ for 5 days. Afterwards, the spores were picked out and transferred into 100 × 1 L Erlenmeyer flasks, each preloaded with sterilized 250 g of rice and 150 mL of distilled water. All the flasks were statically cultured for 35 days at room temperature. The culture materials were then extracted with EtOAc for three times to yield 125.5 g of extracts. Repeated silica gel chromatography was performed to obtain the pure compounds. Firstly, the extracts were fractionated into six fractions (Fr.1−Fr.6) by using CH_2Cl_2-MeOH elution (from 30:1 to 1:1, v/v) by silica gel chromatography column. Then, Fr.3 (2.5 g), eluted with CH_2Cl_2-MeOH 10:1, was separated by using C_{18} reversed-phase chromatography column (MeOH-H_2O elution, from 10% to 90%, v/v), yielding eight subfractions (Fr.3.1−Fr.3.8). Fr.3.5 was subjected to semi-preparative HPLC (58% MeOH-H_2O) to obtain compound **3** (6.8 mg, t_R = 9.8 min). In contrast, Fr.3.6 was separated by semi-preparative HPLC (55% MeOH-H_2O) to give compound **4** (10.5 mg, t_R = 11.9 min). Finally, Fr.4 (8.2 g), eluted with CH_2Cl_2-MeOH 5:1, was purified with silica gel chromatography column by using CH_2Cl_2-MeOH 10:1. As a result, compound **2** (4.5 mg) was obtained by subsequent semipreparative HPLC (45% MeOH-H_2O containing 0.05% TFA). In contrast, compound **1** (2.6 mg) was isolated by semi-preparative HPLC (55% MeOH-H_2O containing 0.05% TFA).

Fusasolpolyol A ***(1)***: colorless oil; $[\alpha]^{20}_D$ +31.9 (*c* 0.05, MeOH); UV (MeOH) λ_{max} (log ε) 210 (4.05) nm; ^{1}H and ^{13}C NMR data, displayed in Table 1; HRESIMS *m/z* 353.2350 $[M - H]^-$ (calcd for $C_{20}H_{33}O_5^-$, 353.2328).

(4E,8E,12E)-2,3,7,11-tetrahydroxy-2,4,6,8,10,12-hexamethyltetradeca-4,8,12-trienoic acid ***(2)***: colorless oil; $[\alpha]^{20}_D$ +20.6 (*c* 0.08, MeOH); UV (MeOH) λ_{max} (log ε) 213 (3.96) nm; ^{1}H and ^{13}C NMR data, displayed in Table 1; HRESIMS *m/z* 369.4720 $[M - H]^-$ (calcd for $C_{20}H_{33}O_6^-$, 369.4724).



1 R = H
2 R = OH

3 R = H
4 R = OH

Figure 1. The structures of the obtained compounds **1**−**4**

Cytotoxic Assay: Compounds **1**−**4** were evaluated for their cytotoxic activities against six human cancer cell lines (the human lung cancer cell A549, the human hepatocellular carcinoma cell HepG2, the human colon cancer cell HCT-116, the human breast cancer cell MCF7, the human gastric carcinoma cell MKN-45, and the human pancreatic cancer cell PATU8988T) by the CCK-8 method. Seven

continuous concentrations (0, 3.125, 6.25, 12.5, 25, 50, and 100 μM) of compounds **1**−**4** were prepared. The IC_{50} values, which were calculated by the inhibition rates of different concentrations, were used to evaluate the cytotoxic abilities of the isolated compounds. Detailed methods were previously reported by Yuan et al. [12].

Compound **1** was obtained as a colorless oil and the molecular formula was determined to be $C_{20}H_{34}O_5$ based on HRESIMS data at *m/z* 353.2350 $[M - H]^-$, indicating four degrees of unsaturation. Its ^1H NMR data (Table 1) along with the HSQC spectrum displayed characteristic signals for three olefinic protons resonating at δ_H 5.35 (1H, q, *J* = 6.4 Hz, H-13), 5.18 (1H, d, *J* = 9.0 Hz, H-5), and 5.18 (1H, d, *J* = 9.0 Hz, H-9), three oxygenated methine groups including two chemical equivalent protons at δ_H 3.82 (1H, d, *J* = 9.5 Hz, H-3), 3.57 (1H, d, *J* = 7.6 Hz, H-7), and 3.57 (1H, d, *J* = 7.6 Hz, H-11), three methine groups including two chemical equivalence protons at δ_H 2.44 (1H, ddq, *J* = 9.0, 7.6, 6.6 Hz, H-6) and 2.44 (1H, ddq, *J* = 9.0, 7.6, 6.6 Hz, H-10) and 2.27 (1H, m, H-2), seven methyl groups at δ_H 1.56 (3H, d, *J* = 6.4 Hz, H_3-14), 1.54 (3H, s, H_3-18), 1.53 (3H, s, H_3-20), 1.51 (3H, s, H_3-16), 0.80 (3H, d, *J* = 7.0 Hz, H_3-15), 0.72 (3H, d, *J* = 6.6 Hz, H_3-19), and 0.71 (3H, d, *J* = 6.6 Hz, H_3-17). In the ^{13}C NMR (Table 1) and HSQC spectra, 20 carbon signals were observed, which were assigned to one ester carbonyl (δ_C 178.0, deduced from the HMBC correlations from H-3 and H_3-15 to C-1, shown in Figures S19 and S20), six sp^2 hybridized carbons (δ_C 138.0, 136.5, 135.4, 132.3, 130.8, and 120.2), three oxygenated aliphatic carbons (δ_C 81.4, 81.3, and 80.0), seven methyl groups (δ_C 18.1, 18.0, 14.9, 13.3, 12.0, 11.6, and 11.2), and other three aliphatic carbons (δ_C 43.9, 36.3, and 36.1). The abovementioned spectroscopic analyses indicated that compound **1** had four double bonds, further suggesting that compound **1** possessed a long chain skeleton according to the four degrees of unsaturation deduced by the molecular formula.

The analysis of the $^1H-^1H$ COSY and HMBC spectra constructed the planar structure of **1**. Analysis of the $^1H-^1H$ COSY spectrum of **1** enabled the establishment of three independent spin-spin systems in the core structure, namely H-2/H-3/H_3-15, H-5/H-6/H-7/H_3-17, H-9/H-10/H-11/H_3-19, and H-13/H_3-14 (Figure 2). According to the HMBC correlations from H_3-14 to C-12, from H_3-20 to C-11/C-12/C-13, from H-11 to C-13, from H_3-19 to C-9/C-10/C-11, from H-9 to C-7/C-11, from H_3-18 to C-7/C-8/C-9, from H_3-17 to C-5/C-6/C-7, from H-5 to C-3/C-7, from H_3-16 to C-3/C-4/C-5, and from H_3-15 to C-1/C-2/C-3, the planar structure of **1** was elucidated as a long chain polyhydroxy compound, which was similar to that of pestalpolyol B [13]. The NOE correlations of H-3/H-5, H-5/H-7, H-7/H-9, H-9/H-11, and H-11/H-13 supported the *E*-configuration of the double bond C-4−C-5, C-8−C-9, and C-12−C-13. Due to the lack of key NOE correlations, the relative configurations of **1** could not be determined by the NOESY spectrum. Since compound **1** had a long chain skeleton, the stereochemistry of **1** was unsolved. Compound **1** was named as fusasolpolyol A.

Compound **2**, named as (4*E*,8*E*,12*E*)-2,3,7,11-tetrahydroxy-2,4,6,8,10,12-hexamethyltetradeca-4,8,12-trienoic acid, was isolated as a colorless oil. Its molecular formula was determined as $C_{20}H_{34}O_6$ by HRESIMS spectrum (*m/z* 369.4720 $[M - H]^-$, calcd for $C_{20}H_{33}O_6^-$, 369.4724), suggesting four degrees of unsaturation. The ^1H NMR data of **1** along with the HSQC spectrum demonstrated three olefinic protons resonating at δ_H 5.35 (1H, q, *J* = 6.5 Hz, H-13), 5.18 (1H, d, *J* = 9.1 Hz, H-5), and 5.18 (1H, d, *J* = 9.1 Hz, H-9), three oxygenated methine protons at δ_H 4.01 (1H, s, H-3), 3.57 (1H, d, *J* = 7.5 Hz, H-7), and 3.57 (1H, d, *J* = 7.5 Hz, H-11), two chemical equivalent methine protons at δ_H 2.46 (1H, ddq, *J* = 9.1, 7.5, and 6.7 Hz, H-6) and 2.46 (1H, ddq, *J* = 9.1, 7.5, and 6.7 Hz, H-10), seven methyl groups at δ_H 1.62 (3H, s, H_3-16), 1.56 (3H, d, *J* = 6.5 Hz, H_3-14), 1.54 (3H, s, H_3-18), 1.53 (3H, s, H_3-20), 1.06 (3H, s, H_3-15), 0.73 (3H, d, *J* = 6.7 Hz, H_3-17), and 0.72 (3H, d, *J* = 6.7 Hz, H_3-19) (Table 1). The ^{13}C NMR spectrum (Table 1), together with the HSQC spectrum of **1**, clearly displayed 20 carbon resonances that could be classified into one ester carbonyl (δ_C 178.0), six sp^2 hybridized carbons (δ_C 138.0, 136.6, 134.6, 133.7, 130.8, and 120.2), four oxygenated aliphatic carbons (δ_C 81.5, 81.2, 81.0, and 77.5), seven methyl groups (δ_C 23.2, 18.1, 18.0, 13.3, 13.1, 12.0, and 11.6), and the other two aliphatic carbons (δ_C 36.3 and 36.1). Compound **2** was a hydroxylated product of **1** at C-2, which was confirmed by HMBC correlations from H_3-15 to C-2 (Figure 2). It should be pointed out that compound **2** is commercially produced and sold with a CAS Registry Number of 1246086-02-1. Initially, compound **2** was considered as a new natural product. However, compound **2** also might be an artificial product of **1**, which might be formed during the isolation process.

Table 1. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data of compounds **1** and **2** (measured in DMSO-d_6)

No	1		2	
	δ_H (*J* in Hz)	**δ_C, type**	**δ_H (*J* in Hz)**	**δ_C, type**
1		178.0[a] C		178.0 C
2	2.27 m	43.9 CH		77.5 C
3	3.82 d (9.5)	80.0 CH	4.01 s	81.0 CH
4		135.4 C		134.6 C
5	5.18 d (9.0)	132.3 CH	5.18 d (9.1)	133.7 CH
6	2.44 ddq (9.0, 7.6, 6.6)	36.1 CH	2.46 ddq (9.1, 7.5, 6.7)	36.3 CH
7	3.57 d (7.6)	81.4 CH	3.57 d (7.5)	81.5 CH
8		136.5 C		136.6 C
9	5.18 d (9.0)	130.8 CH	5.18 d (9.1)	130.8 CH
10	2.44 ddq (9.0, 7.6, 6.6)	36.3 CH	2.46 ddq (9.1, 7.5, 6.7)	36.1 CH
11	3.57 d (7.6)	81.3 CH	3.57 d (7.5)	81.2 CH
12		138.0 C		138.0 C
13	5.35 q (6.4)	120.2 CH	5.35 q (6.5)	120.2 CH
14	1.56 d (6.4)	13.3 CH_3	1.56 d (6.5)	13.3 CH_3
15	0.80 d (7.0)	14.9 CH_3	1.06 s	23.2 CH_3
16	1.51 s	11.2 CH_3	1.62 s	13.1 CH_3
17	0.71 d (6.6)	18.0 CH_3	0.73 d (6.7)	18.1 CH_3
18	1.54 s	12.0 CH_3	1.54 s	12.0 CH_3
19	0.72 d (6.6)	18.1 CH_3	0.72 d (6.7)	18.0 CH_3
20	1.53 s	11.6 CH_3	1.53 s	11.6 CH_3

[a] deduced from HMBC correlations

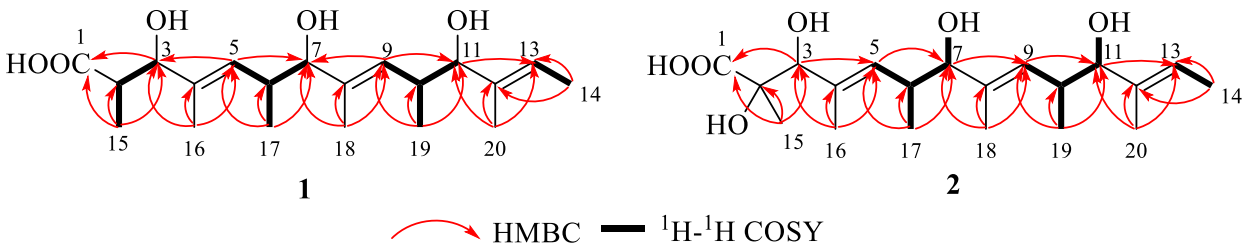


Figure 2. Key ^{1}H-^{1}H COSY and HMBC correlations of **1** and **2**

Compounds **1**–**4** were measured for their cytotoxic effects against six human cancer cell lines (A549, HepG2, HCT-116, MCF7, MKN-45, and PATU8988T cells). The results were shown in Table 2. Doxorubicin was selected as the positive control. Compound **2**, as a polyhydroxy compound, was found to have proliferation inhibition activities against MKN-45 and PATU8988T cells, suggesting that **2** possessed moderate activity against MKN-45 and PATU8988T cells, with IC_{50} values of 19.6 ± 1.2 μM and 26.3 ± 0.9 μM, respectively. The IC_{50} values of the positive control doxorubicin were 4.5 ± 0.1 μM (for the MKN-45 cell) and 1.9 ± 0.3 μM (for the PATU8988T cell), respectively. Compared with compound **1**, compound **2** exhibited higher activity, suggesting that the OH group at C-2 may enhance the cytotoxic activity. Compounds **3** and **4** were inactive against the test cell lines (The IC_{50} values were close to or higher than 50 μM).

Table 2. Cytotoxic results of the isolated compounds against six cancer cell lines (IC_{50}, μM, mean ± SD)

Compounds	A549	HepG2	HCT-116	MCF7	MKN-45	PATU8988T
1	> 50	> 50	> 50	> 50	> 50	38.6 ± 0.3
2	> 50	> 50	> 50	> 50	19.6 ± 1.2	26.3 ± 0.9
3	> 50	> 50	> 50	46.9 ± 1.2	> 50	> 50
4	> 50	> 50	> 50	> 50	40.8 ± 2.3	> 50
Doxorubicin	1.2 ± 0.1	1.9 ± 0.2	2.3 ± 0.2	3.1 ± 0.3	4.5 ± 0.1	1.9 ± 0.3

In conclusion, this study reported a new polyhydroxy compound **1** from the endophytic fungus *F. solani* 2024f-xx. The newly isolated compound **2** displayed considerable cytotoxic activity against the human gastric carcinoma MKN-45 cell and the human pancreatic cancer PATU8988T cell. This study added the structural diversity of natural products and provided a new lead compound for the development of antineoplastic drugs.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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