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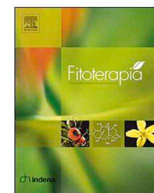
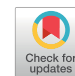


New quinoline alkaloid and bisabolane-type sesquiterpenoid derivatives from the deep-sea-derived fungus *Aspergillus* sp. SCSIO06786



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ABSTRACT

One new quinoline alkaloid (**1**), two new bisabolane-type sesquiterpene derivatives (**2** and **3**), and a new natural product (**4**) along with ten known compounds (**514**) were isolated from the deep sea-derived fungus *Aspergillus* sp. SCSIO06786 which cultured on solid rice medium. Three new structures were elucidated by analysis of 1D/2D NMR data and HR-ESI-MS. The absolute configurations of **2** and **3** were established by comparison of the experimental and reported ECD values. Compounds **11–13** exhibited moderate selective inhibitory activities against the tested pathogenic bacteria with MIC values among 3.13–12.5 μg/mL.

1. Introduction

With the advances in sampling techniques and the possibility to culture these organisms even in standard microbiological laboratories, deep sea fungi have recently received a wide attention as a new area for bioprospecting [1]. Although the conditions in deep-sea benthic environments are extreme, fungi in deep-sea benthic environments are abundant and diverse. Also, the rich fungi in deep-sea benthic environments increase the pool of fungi available for natural bioactive product screening and new drug discoveries [2]. Up to October 2016 nearly 300 new metabolites with cytotoxic [3], antimicrobial [4], antiviral [5], antioxidant [6], antifouling [7], and other bioactivities [8–10] have been identified from deep-sea fungi. *Aspergillus* and *Penicillium* belonging to Ascomycota are dominant in deep-sea benthic environments [2]. Besides, the *Aspergillus* species is one of the main source of new marine fungi-derived compounds in recent years [11]. As part of our ongoing efforts to search for bioactive secondary metabolites from deep-sea-derived fungi [12–15], the fungus *Aspergillus* sp. SCSIO06786 was studied. Three new compounds (**1–3**) and a new natural product (**4**) along with ten known compounds (**5–14**) (Fig. 1) were isolated from the rice solid culture extract of the fungus *Aspergillus* sp. SCSIO06786. Herein, we describe the isolation, structure elucidation and bioactivity evaluation of the fourteen compounds.

2. Experimental

2.1. General experimental procedures

HRESIMS data were recorded on a maXis Q-TOF mass spectrometer inpositive ion mode (Bruker, Fällanden, Switzerland). Optical rotations were measured using an MCP-500 polarimeter (Anton, Austria). ECD spectrum was measured with a Chirascan circular dichroism spectrometer (Applied Photophysics). UV spectra were recorded on a UV-2600 UV–Vis spectrophotometer (Shimadzu, Japan). 1D and 2D NMR spectra were measured on a Bruker Avance 500 MHz or 700 MHz NMR spectrometer (Fällanden, Switzerland) with TMS as an internal standard. HPLC was performed on Hitachi Primaide with YMC ODS SERIES column (YMC-Pack ODS-A, YMC Co. Ltd., Kyoto, 250 × 10 mm I.D., S-5 μm, 12 nm). Column chromatography (CC) was carried out on silica gel (200–300 mesh, Jiangyou Silica Gel Development Co., Yantai, China), YMC Gel ODS-A (12 nm, S-50 μm YMC, MA, USA) and Sephadex LH-20 (40–70 μm, Amersham Pharmacia Biotech AB, Uppsala, Sweden). Spots were detected under UV light by heating after spraying with the mixed solvent of saturated vanillin and 5% H_2SO_4 in H_2O or on TLC. The TLC plates with silica gel GF254 (0.4–0.5 mm, Qingdao Marine Chemical Factory, Qingdao, China) were used for analysis and preparative.

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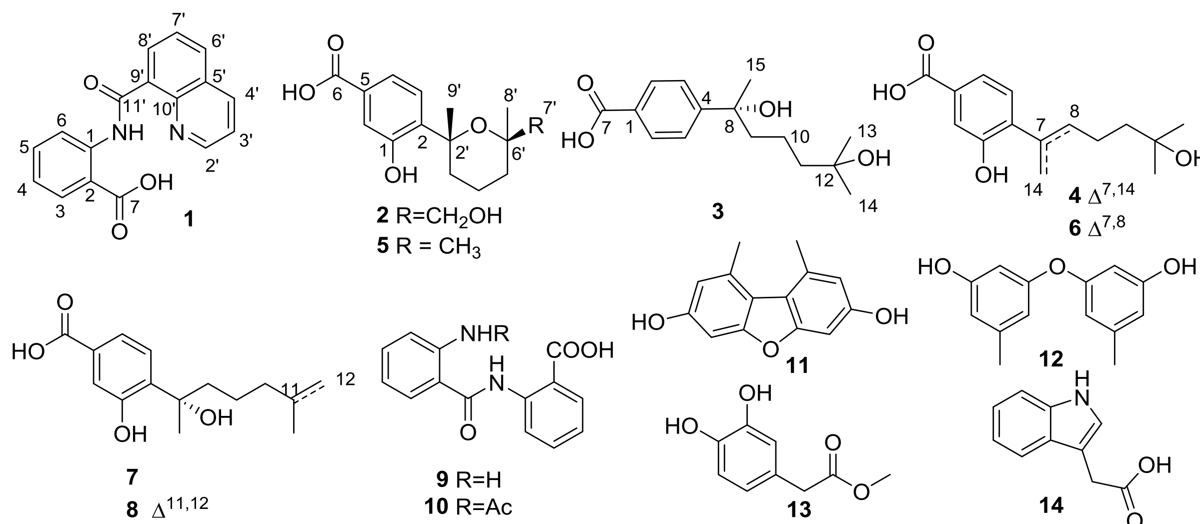

Fig. 1. Chemical structures of compounds **1**–**14**.

2.2. Fungal material

The strain SCSIO 06786 was isolated from the deep-sea sediment collected from Indian Ocean (94°37.377′E; 2°59.853′S; Deep 4762 m). The ITS sequences of SCSIO 06786 (523 base pairs, GenBank accession No. MN203718) has 99% sequence identity to that of *Aspergillus versicolor* strain TF4 (GenBank accession No. 625700). Then it was designated as a member of *Aspergillus* sp. and named *Aspergillus* sp. SCSIO 06786. The strain SCSIO 06786 was stored on MB agar (malt extract 15 g, agar 16 g, sea salt 10 g, water 1 L, pH 7.4–7.8) slants at 4 °C and deposited at Key Laboratory of Tropical Marine Bio-resources and Ecology, Chinese Academy of Science.

2.3. Fermentation and extraction

The mass fermentation of this fungus was carried out at 25 °C for 32 days using a rice medium in the 1 L flask (×45) and every flask containing rice 150 g, sea salt 2.25 g, and tap H_2O 150 mL. The flasks were cultivated statically at 25 °C under normal day night cycle. After 32 days, the cultures were soaked in EtOAc (500 mL/flask) and mashed into small pieces and sonicated for 20 min. The EtOAc solution was concentrated under reduced pressure to gain a crude extract. The crude extract was suspended in MeOH and then partitioned with an equal volume of petroleum ether to remove the oil. Finally, the MeOH solution was concentrated under reduced pressure to afford a brown extract (61.2 g).

2.4. Isolation and purification

The brown extract was subjected to silica gel CC, which was eluted with CH_2Cl_2 and MeOH mixed solvent in a step gradient (100:0–5:1, *v*/v) and separated into seven fractions (Fr-1–Fr-7). Fr-2 (1.0 g) was applied to a Sephadex LH-20 column eluted with MeOH and reversed-phase C-18 MPLC with MeOH/H_2O (10:90–100:0, v/v) to gain four sub-fractions (Fr-2-1–Fr-2-4). Fr-2-2 was further purified with semi-preparative HPLC (45% CH_3CN/H_2O with 0.5‰ TFA (trifluoroacetic acid), 2 mL/min) to afford **10** (8.3 mg, t_R = 14.5 min). Fr-2-3 was further separated with semi-preparative HPLC (34% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min) to yield **14** (8.5 mg, t_R = 10.6 min), **1** (3.4 mg, t_R = 13.4 min) and **12** (160.4 mg, t_R = 25.0 min). Fr-2-4 was further purified with semi-preparative HPLC (34% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min) to gain **11** (7.2 mg, t_R = 13 min) and **9** (3.9 mg, t_R = 15.5 min). Fr-3 (1.4 g) was subjected to a Sephadex LH-20 column eluted with MeOH and reversed-phase C-18 MPLC with MeOH/H_2O (10:90–100:0, *v*/v) and further purified with semi-preparative HPLC (55% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min) to obtain **7** (25.9 mg, t_R = 11.0 min) and **8** (15.4 mg, t_R = 9.4 min). Fr-4 (1.5 g) was subjected to a Sephadex LH-20 column eluted with MeOH, and reversed-phase C-18 MPLC with MeOH/H_2O (10:90–100:0, v/v) to get two sub-fractions (Fr-4-1–Fr-4-2). Fr-4-1 was further purified with semi-preparative HPLC (34% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min) to obtain **6** (28.2 mg, t_R = 17.0 min). Compound **2** (2.3 mg, t_R = 28 min) was obtained from Fr-4-2 with semi-preparative HPLC (28% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min). Fr-5 (5.0 g) was subjected to a Sephadex LH-20 column eluted with MeOH to get three sub-fractions (Fr-5-1–Fr-5-3). Fr-5-1 was applied to reversed-phase C-18 MPLC with MeOH/H_2O (10:90–100:0, *v*/v) to gain two sub-fractions (Fr-5-1a and Fr-5-1b). Fr-5-1a was subjected by semi-preparative HPLC (9% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min) to afford **13** (10.8 mg, t_R = 12.0 min). Fr-5-1b was purified by semi-preparative HPLC (13% CH_3CN/H_2O, 2 mL/min) to obtain **3** (7.4 mg, t_R = 18.5 min). Compound **4** (4.3 mg, t_R = 33 min) and **5** (7.7 mg, t_R = 38 min) was gained from Fr-5-2 with semi-preparative HPLC (29% CH_3CN/H_2O with 0.5‰ TFA, 2 mL/min).

*2.4.1. 2-(Quinoline-8-carboxamido)benzoic acid (**1**)*

Pale yellow solid; UV(MeOH) λ_{max}(logε) 305 (3.92), 216 (4.56) nm; ^{1}H NMR (CD_3OD, 700 MHz) and ^{13}C NMR (CD_3OD, 175 MHz), Table 1; HRESIMS *m/z* 293.0926 [M + H]$^+$ (calcd for $C_{17}H_{13}N_2O_3$, 293.0921).

*2.4.2. 3-Hydroxy-4-((2S,6S)-6-(hydroxymethyl)-2,6-dimethyltetrahydro-2H-pyran-2-yl)benzoic acid (**2**)*

Colorless oil; $[\alpha]_D^{20}$ + 5.7(*c* 0.1, $CHCl_3$); ECD (0.71 mM, MeOH) λ_{max} ($\Delta\varepsilon$) 248 (−0.82), 213 (−5.26) nm; UV(MeOH)λ_{max}(log ε) 296 (3.24), 241 (3.65), 209 (4.16) nm; ^{1}H NMR (CD_3OD, 500 MHz) and ^{13}C NMR (CD_3OD, 125 MHz), Table 1; HRESIMS *m/z* 279.1242 [M–H]$^-$ (calcd for $C_{15}H_{19}O_5$, 279.1238) and 559.2550 [2 M–H]$^-$ (calcd for $C_{30}H_{39}O_5$, 559.2549).

*2.4.3. (−)-Austrosene(**3**)*

Colorless oil; $[\alpha]_D^{20}$ −4.6 (*c* 0.1, MeOH); ECD (0.75 mM, MeOH) λ_{max} ($\Delta\varepsilon$) 234 (−1.03), 200 (−4.21) nm; UV(MeOH)λ_{max}(log ε) 237 (2.99), 200 (3.23) nm; ^{1}H NMR (CD_3OD, 700 MHz) and ^{13}C NMR (CD_3OD, 175 MHz), Table 1; HRESIMS *m/z* 265.1453 [M–H]$^-$ (calcd for $C_{15}H_{21}O_4$, 265.1445).

*2.4.4. 3-hydroxy-4-(5-hydroxy-5-methyl-1-methylenehexyyl)-benzoic acid (**4**)*

Yellow oil; UV(MeOH) λ_{max}(log ε) 298 (3.66), 249 (3.98), 201

Table 1
^1H NMR and ^{13}C NMR data for compounds **1–4** in CD_3OD.

NO.	**1**[a]		**2**[b]		NO.	**3**[a]		**4**[a]	
	δ_C	δ_H	δ_C	δ_H		δ_C	δ_H	δ_C	δ_H
1	141.0 C		157.2 C		1	129.8 C		131.7 C	
2	121.5 C		138.7 C		2	130.5 CH	7.97, d, 9.1	136.1 C	
3	132.4 CH	8.08, brd, 7.0	126.4 CH	7.26, d, 11.9	3	126.3 CH	7.55, d, 8.4	131.0 CH	7.18, d, 7.7
4	124.8 CH	7.24, t, 7.7	121.9 CH	7.46, dd, 11.9, 2.8	4	155.4 C		121.8 CH	7.47, dd, 7.7, 1.4
5	134.4 CH	7.62, brt, 7.0	132.2 C		5	126.3 CH	7.55, d, 8.4	155.5	
6	124.0 CH	8.69, d, 8.4	119.6 CH	7.39, d, 2.8	6	130.5 CH	7.97, d, 9.1	117.4 CH	7.45, d, 1.4
7	170.4 C		169.9 C		7	169.9 C		149.7	
2'	151.0 CH	9.07, brs	79.5 C		8	75.4 C		37.6 CH_2	2.56, t, 6.3
3'	123.0 CH	7.66, dd, 8.4, 3.5	35.3 CH_2	2.22, m 1.81–1.92, m	9	45.8 CH_2	1.74-1.83, m	23.9 CH_2	1.40–1.45, m
4'	139.6 CH	8.50, d, 8.4	16.9 CH_2	1.85–1.95, m 1.74–1.81, m	10	19.9 CH_2	1.34–1.44, m 1.14–1.21, m	44.3 CH_2	1.45–1.49, m
5'	130.2 C		31.3 CH_2	1.81–1.92, m 1.44, ddd, 17.5, 10.5, 4.2	11	45.1 CH_2	1.34–1.44, m	71.4 C	
6'	134.0 CH	8.19, d, 8.4	77.9 C		12	71.4 C		29.1 CH_3	1.12, s
7'	127.8 CH	7.77, t, 7.7	68.8 CH_2	3.35, overlap 3.24, d, 10.5	13	29.2 CH_3	1.09, s	29.1 CH_3	1.12, s
8'	134.4 CH	8.67, d, 7.0	25.7 CH_3	1.32, s	14	29.1 CH_3	1.10, s	115.3 CH_2	5.19, d, 1.4 5.07, d, 2.1
9'	131.0 C		28.9 CH_3	1.61, s	15	30.2 CH_3	1.54, s	169.9 C	
10'	145.8 C								
11'	166.9 C								

[a] Measured at 700, 175 MHz NMR.
[b] Measured at 500, 125 MHz NMR.

(4.50) nm; ^1H NMR (CD_3OD, 700 MHz) and ^{13}C NMR (CD_3OD, 175 MHz), Table 1; HRESIMS *m/z* 263.1271 $[M–H]^-$ (calcd for $C_{15}H_{19}O_4$, 263.1289).

2.5. Antibacterial activity assay

All compounds (**1–14**) were tested for antibacterial activities against five pathogenic bacteria using the method of agar filter paper diffusion. Compounds which had inhibition zone were evaluated in 96-well plates using a modification of the broth microdilution method [16]. Ampicillin and gentamicin were used as positive control for gram-positive and gram-negative bacteria, respectively.

3. Results and discussion

Compound **1** possessed the elemental composition $C_{17}H_{12}N_2O_3$ as established by its ^{13}C NMR data and a quasi-molecular iron peak at *m/z* 293.0926 in the HR-ESI-MS spectrum. Its ^1H NMR data displayed ten aromatic protons whose chemical shifts among 7.2–9.5 ppm as shown in Table 1. Its ^{13}C NMR showed ten sp^2 methines, five sp^2 non-protonated carbons and two conjugated carbonyls (δ_C 170.4, C-7; 166.9, C-11′). The cross peaks of H-3 (δ_H 8.08, brd, J = 7.0 Hz)/H-4 (δ_H 7.24, t, J = 7.7 Hz)/H-5 (δ_H 7.62, brt, J = 7.0 Hz)/H-6 (δ_H 8.69, d, J = 8.4 Hz), of H-2′ (δ_H 9.07, brs)/H-3′ (δ_H 7.66, dd, J = 8.4, 3.5 Hz)/H-4′(δ_H 8.50, d, J = 8.4 Hz), and of H-6′ (δ_H 8.19, d, J = 8.4 Hz)/H-7′ (δ_H 7.77, d, J = 7.7 Hz)/H-8′ (δ_H 8.67, d, J = 7.0 Hz) in the COSY suggested three connected structural fragments. Chemical shift of H-2′ and coupling constant between H-2′ and H-3′ indicated the presence of carbon-nitrogen double bonds in **1** [17]. Combining with correlations of H-4′ to C-6′ and C-10′, and H-6′ to C-4′ and C-10′ in the HMBC spectrum suggested that **1** was quinoline alkaloid derivative. The NMR data of **1** closely resembled those of the synthetic *N*-(2-formylphenyl)quinoline-8-carboxamide [17] with an obvious difference that the aldehyde group in *N*-(2-formylphenyl)quinoline-8-carboxamide was oxidized to a carboxyl group in **1**. The speculation above has been confirmed by the HMBC spectrum of **1** (Fig. 2). Thereby, the structure of **1** was established to 2-(quinoline-8-carboxamido)benzoic acid.

Compound **2** was obtained as a colorless oil. Its molecular formula was established as $C_{15}H_{20}O_5$ by the HR-ESI-MS $[M–H]^+$ peak at *m/z* 279.1242 (calculated for $C_{15}H_{19}O_5$, 279.1238) indicating six degrees of unsaturation. Its ^1H NMR data (Table 1) showed three aromatic protons (δ_H 7.46, dd, J = 11.9, 2.8 Hz, H-4; 7.39, d, J = 2.8 Hz, H-6; 7.26, d, J = 11.9 Hz, H-3), one oxygenated methylene (δ_H 3.35, overlap, H-7′a; 3.24, d, J = 10.5 Hz, H-7′b), two methyls (δ_H 1.61, s, H_3–9′; 1.32, s, H_3–8′) and six protons whose chemical shifts among 1.2–2.5 ppm. Correspondingly, the ^{13}C NMR (DEPT) (Table 1) data exhibited fifteen carbon signals, including three sp^2 methines, four sp^3 methylene, two methyls (δ_C 28.9, C-9′ and 25.7, C-8′), two sp^3 oxygenated non-protonated carbons (δ_C 79.5, C-2′ and 77.9, C-6′), three sp^2 non-protonated carbons and one conjugated carboxyl (δ_C 169.9, C-7). Its NMR data are very similar to **5**, except a methyl in **5** was replaced by an oxygenated methylene in **2**. The change was verified by the HMBC of H_2–7′ to C-5′ (δ_C 31.3), C-6′ and C-8′. The planar structure of compound **2** was confirmed by its COSY and HMBC spectra (Fig. 2). The NOESY showed the key correlation of H_3–8′ to H-4 (Fig. 3), which indicated that H_3–9′ and H_2–7′ were on the same side of the pyran ring. The ECD curves of **2** and **5** were nearly same (Fig. 4), thus the absolute configuration of C-2′ in **2** was established to be *R*. Therefore, compound **2** was established to be 3-hydroxy-4-((2*R*,6*R*)-6-(hydroxymethyl)-2,6-dimethyltetrahydro-2*H*-pyran-2-yl) benzoic acid and named 7′-oxygenated sydowic acid.

The HR-ESI-MS and NMR data of compound **3** were almost identical to those of (+)-austrosene [18], while the only difference was the opposite specific rotation value. A small negative specific rotation value of **3** ($[\alpha]_D^{20}$ = −4.6, CH3OH) was obtained compared to (*S*)-austrosene ($[\alpha]_D^{20}$ = +19.0, CH_3OH), suggesting racemate were existence with 8*R* configuration excess. The ECD values of **3** were similar with the calculated ECD values of *R*-curcutetraol [19], which also suggested 8*R* configuration in **3** was excess. Unfortunately, we failed to separate them by our available chiral columns (Fig. S2, Phenomenex Lux Cellulose-2 and Daicel Chiralpak IC columns). Thus, **3** was reported as racemate with new 8*R* configuration excess, and named as (−)-austrosene.

Compound **4** was isolated as a yellow oil. The ^{13}C NMR data and a deprotonated molecule peak at *m/z* 263.1271 in the HRESIMS spectrum. Its ^1H NMR and ^{13}C NMR data (Table 1) displayed similarity to those of 7-deoxy-7,14-didehydro-12-hydroxysydonic acid [20]. The

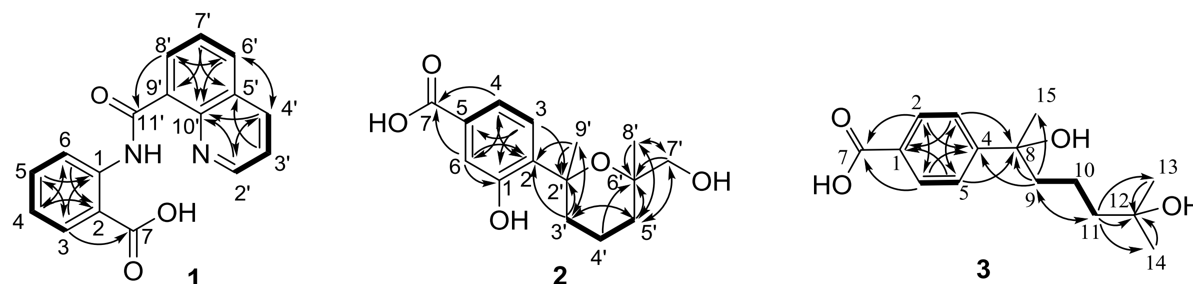

Fig. 2. COSY and key HMBC correlations of compounds **1–3**.

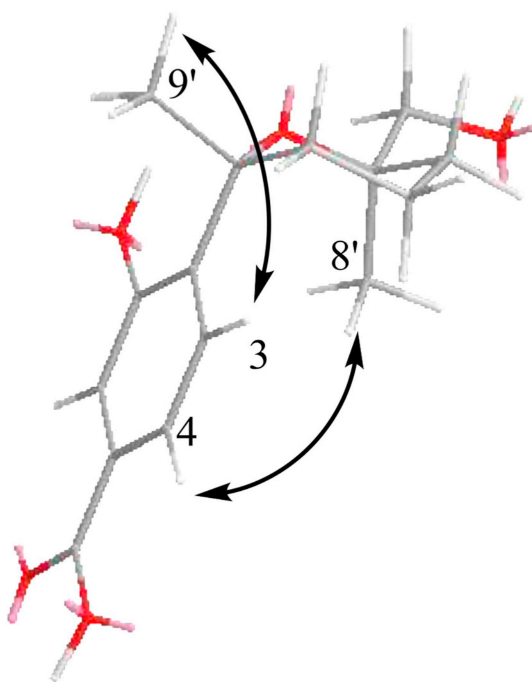

Fig. 3. Key NOESY correlations of compound **2**.

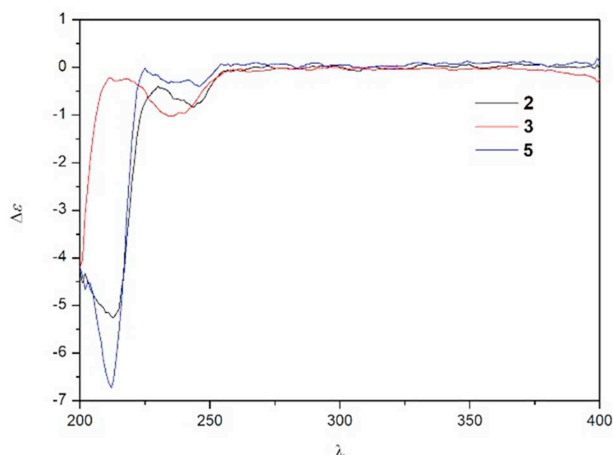

Fig. 4. Experimental ECD curves of compounds **2**, **3** and **5**.

obvious differences were the present of two methyls (δ_H 1.12, s; δ_C 29.1, CH_3–12 and CH_3–13) and one oxygenated quaternary carbon (δ_C 71.4, C-11) in **4** instead of an oxygenated methylene and a sp^3 methine in 7-deoxy-7,14-didehydro-12-hydroxysydonic acid. Thus, the structure of **4** was speculated as shown, which was verified by its HMBC spectrum (Fig. 2). Compound **4** was named 3-hydroxy-4-(5-hydroxy-5-methyl-1-methylenehexyyl)-benzoic acid (CAS No. 1083201-27-7) and can be found through a SciFinder search, but no reference or chemical-physical data are indicated. Here, its NMR data was reported for the first time.

Table 2
The MIC values (μg/mL) of compounds with antibacterial activities.

Compounds	*S. aureus*	MRSA	*E. faecalis*	*A. baumannii*
11	6.25	3.13	6.25	–
12	12.5	12.5	12.5	3.13
13	–	12.5	–	–
Ampicillin	1.25	0.08	0.31	–
Gentamicin	–	–	–	0.63

In addition, the ten known compounds (**5–14**) (Fig. 1) were identified as (*R*)-(+)-sydowic acid (**5**) [21], engyodontiumone I (**6**) [22], sydonic acid (**7**) [23], (*S*)-(+)-11-dehydrosydonic acid (**8**) [24], methyl 2-[(2-aminobenzoyl)amino]benzoate (**9**) [25], methyl-*N*-(2-acetaminobenzoyl) anthranilic acid (**10**) [26], 3,5-dimethoxytoluene (**11**) [27], 3,3′-dihydroxy-5,5′-dimethyldiphenyl ether (**12**) [28], 3,4-dihydroxyphenylacetic acid methyl ester (**13**) [29], indole-3-acetic acid (**14**) [30], respectively, by comparison of their physical and spectroscopic data with those in the literature. The possible biogenetic pathway of compounds **1**, **9** and **10** was deduced, and these compounds might derive from the anthranilates which were subjected with methylation, oxidation, intermolecular or intramolecular dehydration, and acetylation (Fig. S1).

Compounds **1–14** were evaluated their antibacterial activities against *Acinetobacter baumannii* (ATCC 19606), *Escherichia coli* (ATCC 25922), *Enterococcus faecalis* (ATCC 29212), *Klebsiella pneumonia* (ATCC 13883), *Staphyloccocus aureus* (ATCC 29213), and methicillin-resistant *Staphyloccocus aureus* (MRSA). Compounds **11** and **12** with 50 μg/disc showed inhibition zones against *S. aureus*, MRSA and *E. faecalis*. Compound **12** with 50 μg/disc also displayed an inhibition zone against *A. baumannii*. Compound **13** with 50 μg/disc showed an inhibition zone against MRSA (Fig. S28). Further, their minimum inhibitory concentrations (MIC) were tested and the results were shown in Table 2.

In conclusion, three new secondary metabolites including one alkaloid and two sesquiterpene derivatives and a new natural product along with ten known compounds were isolated from cultures of the deep sea-derived fungus *Aspergillus* sp. SCSIO06786. Their structures were elucidated by extensive spectroscopic methods. The possible biogenetic pathway of compounds **1**, **9** and **10** was discussed. All compounds were evaluated their antibacterial activities, compounds **11–13** exhibited moderate selective inhibitory activities against the tested pathogenic bacteria with MIC values among 3.13–12.5 μg/mL.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fitote.2019.104406.

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