



Secondary metabolites from the cold-seep-derived fungus *Penicillium* sp. SCSIO 41425 and their free radical scavenging activity

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ABSTRACT

Objective: To study the chemical compositions from *Penicillium* sp. SCSIO 41425 and explore their DPPH radical scavenging activity.

Methods: Ethyl acetate extract of *Penicillium* sp. SCSIO 41425 was separated and purified by silica gel, Ostadecylsilane (ODS), semi-preparative HPLC, and thin layer chromatography, and their structures were determined by spectroscopic analysis and comparison with the reported literatures.

Results: A total of 18 compounds were isolated from *Penicillium* sp. SCSIO 41425, including one new compound, (2'*R*,3'*R*)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol (**1**) and seventeen known compounds (**2–18**). Their structures were elucidated by detailed NMR and ECD calculations. Compounds **4** and **5** exhibited potent DPPH radical scavenging activity, with EC₅₀ values of 8.42 and 6.62 µg/mL, which were stronger than the positive control ascorbic acid (EC₅₀, 11.22 µg/mL).

Conclusion: This study expands the natural product library of marine cold-seep-derived fungus and provides marine-derived drug source molecules for potent antioxidants.

1. Introduction

Marine derived microorganisms can produce secondary metabolites with rich structures and activities.^{1–3} Deep sea cold seeps are typical deep-sea chemical synthesis driven ecosystems, characterized by rich methane fluid emissions and unique sulfur redox reactions, which give rise to abundant cold spring microorganisms.^{4,5} Deep sea fungi play an important role in deep-sea microorganisms, producing a series of secondary metabolites with rich structures and activities, such as alkaloids, polyketides, peptides, etc. They have anti-inflammatory, anti-tumor and other biological activities.^{6–8} *Penicillium* sp., as the second most common species of marine fungi, are a rich source for discovering active compounds.^{6,9} The novel structures penoxahydrazones A–C and

penoxazolones A–B, isolated from the cold-seep-derived fungus *Penicillium oxalicum*, some of them exhibited inhibitory effects on some marine phytoplankton and marine-derived bacteria.¹⁰ Poloncosidins A–F, isolated from the deep-sea-derived fungus *Penicillium polonicum* CS-252, showed inhibitory activities against several human and aquatic pathogens.¹¹

In our study, eleven benzene derivatives (**1–11**), three polyketide compounds (**12–14**), two alkaloid compounds (**15–16**), one linear dipeptide derivative (**17**), and one fatty acid (**18**) (Fig. 1) were isolated from a cold-seep-derived fungus *Penicillium* sp. SCSIO 41425. Herein, the specifics of the isolation, structural elucidation, and antioxidant activity assessment of the isolated compounds were reported.

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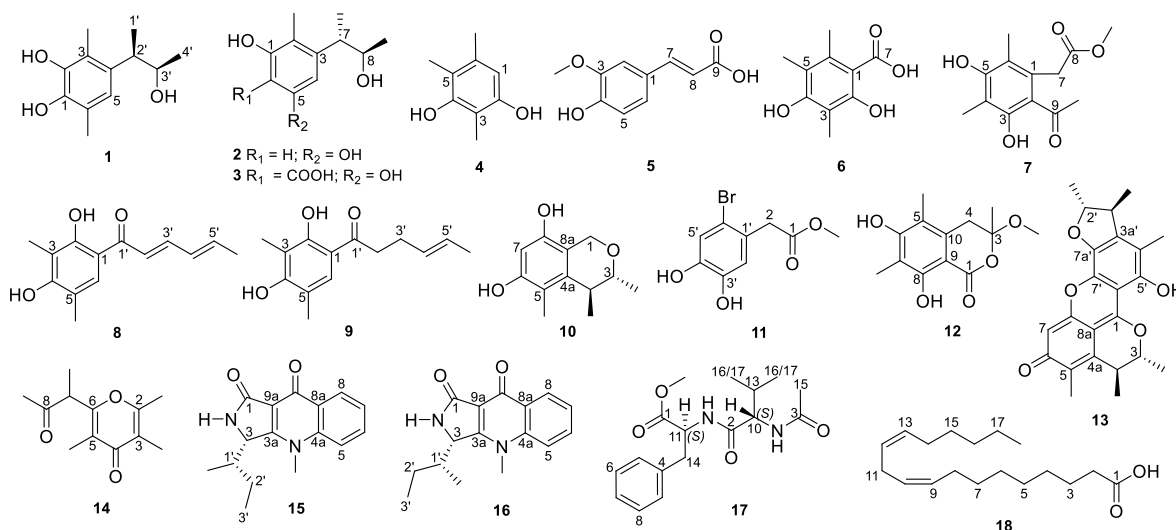


Fig. 1. Structures of compounds 1–18.

2. Materials and methods

2.1. General experimental procedures

The Chirascan circular dichroism spectrometer (Applied Photophysics, Leatherhead Surrey, UK) was used to perform ECD spectra, while optical rotations were calculated using an Anton Paar MPC500 (Anton, Graz, Austria) polarimeter. A Shimadzu UV-2600 PC spectrometer (Shimadzu, Beijing, China) was used to record the UV spectra. The IR spectra were detected by an IR Affinity-1 spectrometer (Shimadzu). Using a Bruker maXis Q-TOF mass spectrometer (Bruker BioSpin International AG, Fällanden, Switzerland), high-resolution electrospray ionization mass spectroscopy (HRESIMS) spectra were acquired. The NMR spectra were tested on a Quantum-I Plus 500 MHz (Q-one Instrument Co., Ltd, Wuhan, China) operating at 500 MHz for ¹H NMR and 125 MHz for ¹³C NMR, and were collected on a AVANCE III HD 700 MHz (Bruker Switzerland AG, Fällanden, Switzerland) operating at 700 MHz for ¹H NMR and 175 MHz for ¹³C NMR. Tetramethylsilane was used as an internal standard. ODS columns (ChromCore 120 C₁₈, 10 × 250 mm, 5 μm; COSMOSIL πNAP 10 × 250 mm; COSMOSIL 5C18-AR-II 10 × 250 mm) were used in semipreparative high-performance liquid chromatography (HPLC) which was performed on the Hitachi Primaide with a DAD detector (Hitachi, Tokyo, Japan). Silica gel (200–300 mesh) was used to perform the column chromatography and spots was detected on TLC (Qingdao Marine Chemical Factory, Qingdao, China) under 254 nm UV light, respectively. Tianjin Fuyu Chemical and Industry Factory, located in Tianjin, China, supplied all of the analytical-grade solvents that were used.

2.2. Fungal material

The strain *Penicillium* sp. SCSIO 41425 was isolated from a cold-seep sediment that was taken from the South China Sea in May 2022 at a depth of 1439 m. It was kept in storage at the Chinese Academy of Sciences (CAS) Key Laboratory of Tropical Marine Bioresources and Ecology, South China Sea Institute of Oceanology, CAS, Guangzhou, China. According to BLAST analysis of the ITS sequence (Supplementary Information), the strain was named *Penicillium* sp. SCSIO 41425 which revealed 90% of the strain's similarities to *Penicillium citrinum* (NR_121224.1). The sequence was finally added to GenBank and assigned the accession number PQ312694.

2.3. Fermentation and extraction

For 7 days, the fungus *Penicillium* sp. SCSIO 41425 was grown statically on MA media at 26 °C, then cut into small pieces and inoculated into the 1 L flask, which was incubated for 30 days using a rice medium (150 g rice, 3.2% sea salt, 150 mL H₂O) under static conditions. The entire fermented culture was extracted five times using Ethyl acetate (EtOAc) and eventually obtained the extract (317.7 g).

2.4. Isolation and purification

Using a step gradient elution of petroleum ether (PE)-dichloromethane (DCM) (v:v 1:0, 1:1, 0:1), DCM-methyl alcohol (CH₃OH) (v:v 100:1, 100:3, 20:1, 10:1, 5:1, 2:1, 0:1), yielded twelve fractions (Frs. 1–12) based on TLC characteristics. Fr. 2 was separated by semipreparative HPLC (80% CH₃OH/H₂O, 2.5 mL/min) to obtain compound 18 (7.2 mg, t_R 8.5 min). Fr. 3 to Fr. 6 were merged and was divided into 16 subfractions (Frs. 3-1–3-16) by ODS silica gel eluting with CH₃OH/H₂O (5%–100%). Fr. 3-6 was separated by semipreparative HPLC (35% CH₃OH/H₂O, 2.5 mL/min; 43% CH₃OH/H₂O, 0.04% formic acid, 2.5 mL/min) to obtain compound 4 (31.9 mg, t_R 17.0 min) and compound 5 (2.2 mg, t_R 12.5 min). Fr. 3-7 was separated by semipreparative HPLC (55% CH₃OH/H₂O, 2.5 mL/min) to obtain compound 12 (16.1 mg, t_R 20.5 min). Fr. 3-9 was divided into 14 subfractions (Frs. 3-9-1–3-9-14) by ODS silica gel eluting with CH₃OH/H₂O (10%–100%). Compound 13 (10.4 mg, t_R 13.8 min) was purified from Fr. 3-9-10 by semipreparative HPLC (76% CH₃OH/H₂O, 3.0 mL/min). Fr. 3-11 was separated by semipreparative HPLC (70% CH₃OH/H₂O, 3.0 mL/min) to obtain compound 8 (9.6 mg, t_R 24.3 min) and 9 (5.1 mg, t_R 27.8 min). Fr. 7 to Fr. 9 were merged and was divided into 13 subfractions (Frs. 7-1–7-13) by ODS silica gel eluting with CH₃OH/H₂O (20%–100%). Fr. 7-4 was separated into five components (Frs. 7-4-1–7-4-5) by semipreparative HPLC (40% CH₃OH/H₂O, 3.0 mL/min). Compound 1 (5.1 mg, t_R 19.4 min) was purified from Fr. 7-4-1 by semipreparative HPLC (38% CH₃OH/H₂O, 2.5 mL/min). Compound 14 (2.7 mg, t_R 32.7 min) was purified from Fr. 7-4-2 by semipreparative HPLC (33% CH₃OH/H₂O, 2.5 mL/min). Fr. 7-4-3 was separated by semipreparative HPLC (35% CH₃CN/H₂O, 0.04% formic acid, 3.0 mL/min) to obtain compound 7 (6.1 mg, t_R 9.4 min). Compound 6 (6.4 mg, t_R 31.2 min) and compound 10 (3.1 mg, t_R 33.6 min) were purified from Fr. 7-4-5 by semipreparative HPLC (30% CH₃OH/H₂O, 3.0 mL/min). Fr. 7-5 to Fr. 7-6 were merged once more and divided into 10 subfractions (Frs. 7-5-1–7-5-10) by ODS silica gel eluting with CH₃OH/H₂O (5%–100%). Compound 17 (5.5 mg, t_R 36.2 min) was purified from

Table 1¹H NMR (500 MHz) and ¹³C NMR (125 MHz) data for compound **1** in DMSO-*d*₆.

Position	δ_{H} (ppm), <i>J</i> (Hz)	δ_{C} (ppm)
1	—	153.2
2	—	153.0
3	—	113.6
4	—	140.3
5	6.28, s	105.1
6	—	108.3
1'	1.04, d, (7.0)	15.2
2'	2.93, m	41.1
3'	3.66, m	69.1
4'	0.93, d, (6.2)	19.1
3-CH ₃	1.94, s	11.5
6-CH ₃	2.02, s	9.1

Fr. 7-5-2 by semipreparative HPLC (65% CH₃OH/H₂O, 0.04 % formic acid, 2.8 mL/min). Fr. 10 was separated by semipreparative HPLC (85% CH₃OH/H₂O, 3.0 mL/min) to offer four subfractions (Frs. 10-1–10-4). Compound **2** (10.0 mg, *t*_R 14.2 min) and compound **11** (3.8 mg, *t*_R 13.4 min) were purified from Fr. 10-1 by semipreparative HPLC (45% CH₃OH/H₂O, 2.5 mL/min). Fr. 10-3 was separated by semipreparative HPLC (50% CH₃OH/H₂O, 2.2 mL/min) to obtain compound **3** (8.5 mg, *t*_R 9.2 min). Compound **15** (15.6 mg, *t*_R 10.5 min) and compound **16** (11.5 mg, *t*_R 12.0 min) were purified from Fr. 10-4 by semipreparative HPLC (68% CH₃OH/H₂O, 3.0 mL/min).

(2'*R*,3'*R*)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol (**1**): Red brown oil; [α]_D²⁵ −9.7 (c 0.1, CH₃OH); UV (CH₃OH): λ_{max} (log ϵ): 206 (4.52); ECD (0.48 mM, CH₃OH) λ_{max} 201 (−6.81), 216 (−1.05), 232 (−2.93), 264 (+0.29); IR (film) ν_{max} 3348, 1645, 1634, 1101 cm^{−1}; ¹H and ¹³C NMR data see Table 1; HRESIMS *m/z* 211.1330 [M+H]⁺ (calcd. for C₁₂H₁₈O₃⁺, 211.1329).

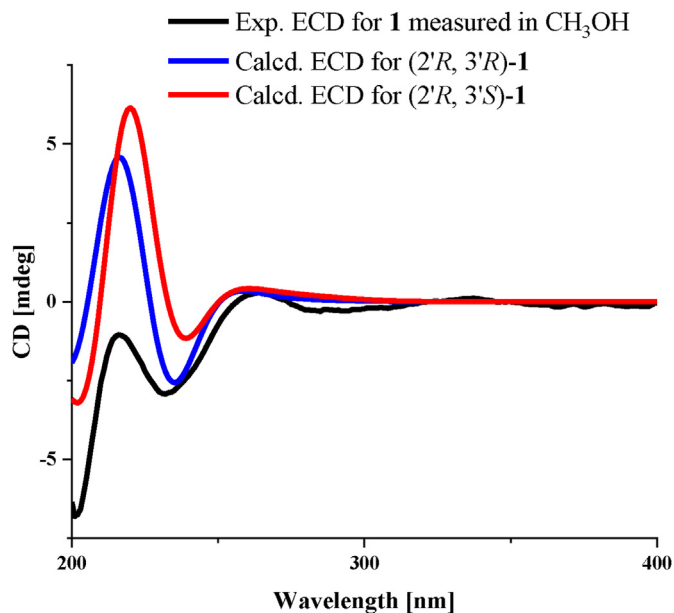
2.5. Computational methods

Optimized the four conformational structures of compound **1** using MM2 molecular force field in ChemBio3D Ultra 14.0, and conducted random conformational searches for optimized structures using MMFF molecular force field in Spartan'14 software. Selected reasonable conformations beyond 5% Boltzmann distribution from the results. Then, Gaussian 09W software density functional DFT was used for further optimization at the B3LYP/6-31+G (d) level. The optimized stable conformation was subjected to energy calculation at the B3LYP/6-311+G (d, p) level, and the calculated results were weighted averaged using the Boltzmann distribution. Next, Gaussian View 6.0 software was used to adjust the half width parameter (0.3–0.4 eV) and exported the ECD curve data. Ultimately, ECD spectra were drawn using Origin 2021 software.^{12,13}

In the meanwhile, MMFF was used to calculate the ¹³C NMR chemical shift in Spartan'14 software, selecting conformers of **1** with a Boltzmann population of greater than 5%. The Gaussian 09W software density functional DFT was used to re-optimize the conformers at the B3LYP/6-31G (d) level. GIAO was used to compute the chemical shifts of the NMR data at the PCM/mPW1PW91/6-311G (d, p) level in dimethylsulfoxide. The Boltzmann distribution theory was used to average the simulated spectra of the conformers in order to obtain the final spectra. The DP4+ probability analysis was carried out using shielding constants. The Excel spreadsheet, which was freely accessible at sarotti-NMR.weebly.com, was used to perform the DP4+ computations.¹²

2.6. Antioxidant activity assay

The effect of compounds on DPPH radicals was estimated referring to the previous methods.^{14,15} Generally, the compounds were dissolved in DPPH methanol solution to get a final concentration of 2.5–250 μ g/mL. The mixture was thoroughly shaken before being allowed to stand at room temperature in the dark for 30 mins, measured the OD₅₁₇ values

Fig. 2. Experimental and calculated ECD spectrum of **1**.

using the PerkinElmer Enspire Multi-mode micro-orifice detector and enzyme labeling instrument (PerkinElmer, Waltham, MA, USA). This experiment used ascorbic acid as a positive control. Then, used the formula to calculate the free radical scavenging rate *K* (%) based on the obtained OD₅₁₇ value, and determined the EC₅₀ value using Origin 2021.

3. Results and discussion

Compound **1** was obtained as a red brown oil and was determined to have the molecular formula C₁₂H₁₈O₃ from the HRESIMS data at *m/z* 211.1330 [M+H]⁺. The 1D NMR data of **1** (Table 1) showed signals of five unsaturated carbon signals (δ_{C} 153.2, 153.0, 113.6, 140.3, 108.3), one aromatic methine ($\delta_{\text{H/C}}$ 6.28/105.1), one oxygen-containing saturated methine ($\delta_{\text{H/C}}$ 3.66/69.1), one saturated methine ($\delta_{\text{H/C}}$ 2.93/41.1), and four methyls ($\delta_{\text{H/C}}$ 1.94/11.5, 2.02/9.1, 1.04/15.2, and 0.93/19.1). The NMR data of **1** was carefully analyzed and found to be comparable to 4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol with its planar structure.¹⁶ By calculating the CD, the measured curve of compound **1** was fitted with the theoretical curves of (2'*R*,3'*R*)-**1**, (2'*R*,3'*S*)-**1**, (2'*S*,3'*R*)-**1**, and (2'*S*,3'*S*)-**1**. The results showed that the trend of the curve of (2'*R*,3'*R*)-**1** and (2'*R*,3'*S*)-**1** were basically consistent with the measured curve (Fig. 2). This resulted in two unassigned chiral centers (CH-2' and CH-3') with two probable diastereoisomers, 3'*R* and 3'*S*. The PCM solvent continuum model with dimethylsulfoxide as a solvent was then studied using the gauge independent atomic orbital (GIAO) strategy at the mPW1PW91/6-311G (d, p) level of theory. With a 99.77% confidence level, the DP4+ probability analysis revealed that the configuration (2'*R*,3'*R*)-**1** was the most likely stereoisomer. Therefore, it was confirmed that the compound **1** was a new configuration compound, and the final structure of **1** was determined to be (2'*R*,3'*R*)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol.

The structures of the seventeen known compounds were identified as phenol A (**2**)^{17,18}, phenol A acid (**3**)^{17,19}, 2,4-dihydroxy-3,5,6-trimethylbenzene (**4**)²⁰, ferulic acid (**5**)²¹, 2,4-dihydroxy-3,5,6-trimethylbenzoic acid (**6**)²², methyl 2-(2-acetyl-3,5-dihydroxy-4,6-dimethylphenyl)acetate (**7**)²³, sorbicillin (**8**)^{24,25}, 2',3'-dihydrosorbicillin (**9**)^{24,26}, decarboxydhidrocitrinin (**10**)²⁷, methyl 2-(6-bromo-3,4-dihydroxyphenyl)acetate (**11**)²⁸, stoloniferol A (**12**)²⁹, penicitrinone A (**13**)²⁷, 2,3,5-trimethyl-6-(3-oxobutan-2-yl)-4*H*-pyran-4-one (**14**)³⁰, quinolactacin A2 (**15**)³¹, quinolactacin A1 (**16**)³¹, *N*-acetyl-L-valyl-L-phenylalanine methyl ester (**17**)³² and α -linoleic acid (**18**)^{33–35} by contrasting the spectroscopic

Table 2

DPPH radical scavenging activity assay.

Compounds	1	2	3	4	5	7	10	13	Ascorbic acid
EC ₅₀ (μg/mL)	41.37	41.07	32.59	8.42	6.62	55.95	19.74	53.83	11.22

data with those documented in the literature.

Free radicals mediate the occurrence and development of many diseases *in vivo*, such as cancer, diabetes, etc.^{36,37} In order to investigate the free radical scavenging activity of the isolated compounds, the DPPH radical scavenging activity of the isolated compounds was tested using a 96 well plate method. The results in Table 2 indicated that compounds 4 (EC₅₀, 8.42 μg/mL) and 5 (EC₅₀, 6.62 μg/mL) demonstrated potent radical scavenging capacity, which were superior to the positive control (ascorbic acid, EC₅₀, 11.22 μg/mL). In addition, compounds 1–3 and 10 also exhibited strong DPPH scavenging activity. Comparing the activities of compounds 1, 2, and 3, it could be observed that their activities were stronger when a carboxyl group was attached to the benzene ring than when a hydroxyl group was attached, indicating that attaching a carboxyl group to the benzene ring could enhance free radical scavenging activity. Comparing the activities of compounds 5 and 7, it was found that their activities decreased when the carboxyl group on the chain was esterified. The above analysis indicated that carboxyl groups had a significant impact on the resistance of compounds to free radicals. It was speculated that this was due to the reaction between carboxyl groups (•COOH) and free radicals (•OH), which enhanced their free radical scavenging ability. Research had shown that excessive production of free radicals in the body was considered a trigger for various damages in biological species and a deactivator of enzymes, leading to the occurrence of many diseases.³⁸ Therefore, compounds 4 and 5 had good potential in anti-tumor and other diseases, which may develop into tiny therapeutic molecules derived from marine cold-seep.

4. Conclusion

A new benzene derivative, (2′R,3′R)-4-(3-hydroxybutan-2-yl)-3,6-dimethylbenzene-1,2-diol (1), together with seventeen known compounds (2–18) were isolated from the secondary metabolites of rice fermentation by *Penicillium* sp. SCSIO 41425, a fungus derived from deep-sea cold-seep. Compound 1 was a new compound reported for its configuration for the first time, and compound 17 was a linear dipeptide isolated from a deep-sea cold-seep strain for the first time, which had good antibacterial activity of its similar chemicals.^{39,40} Compounds 4 (EC₅₀, 8.42 μg/mL) and 5 (EC₅₀, 6.62 μg/mL) had strong free radical scavenging ability, which were stronger than the positive control (ascorbic acid, EC₅₀, 11.22 μg/mL), which had the potential to become potent antioxidants. In summary, the active and diverse compounds isolated in this study further expand the pool of active natural products from marine cold-seep.

CRediT authorship contribution statement

Yi Chen: Writing – original draft, Investigation, Data curation. **Ying Liu:** Investigation, Data curation. **Jianglian She:** Data curation. **Mengjing Cong:** Investigation. **Junfeng Wang:** Data curation. **Lalith Jayasinghe:** Data curation. **Yonghong Liu:** Project administration. **Xuefeng Zhou:** Writing – review & editing, Project administration, Funding acquisition.

Conflicts of interest

These authors have no conflict of interest to declare.

Declaration of competing interest

The authors declare the following financial interests/personal

relationships which may be considered as potential competing interests: Zhou xuefeng reports financial support was provided by The Special Project for Marine Economic Development of the Department of Natural Resources of Guangdong Province, and the International Partnership Program of Chinese Academy of Sciences. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhip.2024.10.002>.

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