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New antifungal tetrahydrofuran derivatives from a marine sponge-associated fungus *Aspergillus* sp. LS78

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ABSTRACT

Two new tetrahydrofuran derivatives named aspericacids A and B (**1** and **2**) were isolated from the metabolites produced by the sponge-associated *Aspergillus* sp. LS78. They represented an unusual type of tetrahydrofuran derivatives, possessing 2,5-disubstituted tetrahydrofuran ring coupled with a chain unsaturated fatty acid. The planar structures of **1** and **2** were determined by HRESIMS, 1D and 2D NMR spectroscopy. The absolute configuration of **1** was assigned using both experimental and computational electronic circular dichroism (ECD). In addition, aspericacid A (**1**) exhibited *in vitro* antifungal activity (MIC = 50 μg/mL), but **2** showed not significantly activity against any of the tested strains with the MIC values of 128 μg/mL.

1. Introduction

The increasing number of drug-resistant fungal pathogen strains has become resistant to commonly used antifungal drugs in recent years [1]. For some opportunistic human pathogens who caused superficial and systemic infections exemplified by *Candida albicans* and *Cryptococcus neoformans*, experimental data clearly indicated that it was resistant to conventional antifungal agents, and infections caused by it were difficult to cure with conventional antifungal drugs [2–4]. Hence, novel classes of antibiotics that can effectively resist drug-resistant fungi or adjuvants that could restore antibiotic sensitivity are urgently needed, which prevent our ability to control fungal infections from collapsing. The *Aspergillus* genus, a genus can produce diverse secondary metabolites, were renowned for its commercial and medical importance [5,6]. Some species can produce devastating toxins such as aflatoxins, but also many others in *Aspergillus* have been a pivotal sources of mass-produced industrial enzymes and lifesaving drugs like lovastatin [7]. Various types of novel bioactive metabolites have been reported from this genus, including polyketides [8–10], alkaloids [11–13], terpenes [14], steroids [15–17], halides [18], and peptides [12,19,20]. Excitingly, some metabolites among of them were potent and selective inhibitors for fungal protein synthesis such as aspirochlorines [21].

In our continuous investigations of new antifungal lead drugs produced by marine sponge-associated microbes [22], the ethyl acetate extract of the marine-associated *Aspergillus* sp. LS78 was revealed the presence of moderate antifungal activity against *C. albicans* and *C. neoformans*. A further chemical study on its secondary metabolites resulted in the identification of a pair of new tetrahydrofuran derivatives named aspericacids A and B (**1** and **2**). Herein, we described the isolation and structure elucidation, involving comparison of experimental and calculated electronic circular dichroism (ECD) spectra, along with the *in vitro* anti-fungal activity assessment of these compounds.

2. Experimental

2.1. General experimental procedures

Nuclear Magnetic Resonance (NMR) spectra were obtained on a Varian 600 MHz (Palo Alto, CA, USA) at room temperature, using solvent signal ($CDCl_3$: δ_H 7.26/δ_C 77.0) as reference. HRESIMS data were recorded using an Agilent Technologies 6224 Q − TOF LC/MS spectrometer, which equipped with an ESI-ion source (Agilent Technologies, Santa Clara, CA, USA). UV data were measured on a NADE Evolution 201 spectrophotometer (Thermo Fisher, Waltham, MA, USA). IR experiments were carried out on a Nicolet iS5 spectrometer (Thermo Fisher, Waltham, MA, USA). CD spectra were carried out on JASCO *J*-810 Circular Dichroism spectrometer (Jasco Inc., Tokyo, Japan). Sephadex LH20 (25–100 μm, Pharmacia, Uppsala, Sweden) and silica gel (200–300 mesh, Qingdao Marine Chemical Co. Ltd., Qingdao, China) were used for CC (column chromatography). Medium-pressure liquid chromatography (MPLC) was performed using

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ODS column on FLEXA Purification System (Agela Technologies, Tianjin, China). Semi-preparative HPLC was conducted on a Waters HPLC instrument (Waters 600, Milford, MA, USA) equipped with a Waters 2996 detector and combined with C_{18} column (YMC-Pack ODS-A, 250 × 10 mm, 5 μm, Tokyo, Japan).

2.2. Fungal material

The fungal strain in this work was obtained from the tissue of sponge *Haliclona* sp. collected at Lingshui, Hainan Province, China. Based on morphology, combined with the internal transcribed spacer region (ITS) sequencing (GenBank accession ID: EU645719, 99% similarity), the fungal strain LS78 was identified eventually as *Aspergillus* sp. Detailed procedure was that the DNA fragment of the fungal ITS regions was amplified using polymerase chain reaction (PCR) with the pair of primers ITS1 (5′-TCC GTA GGT GAA CCT GCG G-3′) and ITS4 (5′-TCC TCC GCT TAT TGA TAT GC-3′) in reaction system. Finally, the correct PCR product was verified by gel electrophoresis and then submitted to Sangon Biotech (Shanghai) Co., Ltd. for sequencing. A voucher specimen (No. LS78) was deposited with the PDB medium at Ningbo University, Ningbo, China.

2.3. Fermentation, extraction and isolation

The purified fungal strain *Aspergillus* sp. was initially cultured on potato dextrose agar (PDA, containing potato extract 8.0 g, dextrose 20 g, artificial sea salt 35 g, agar 20 g and distilled water 1 L) at 25 °C for 7 days. A single colony was inoculated into 250 mL Erlenmeyer flasks containing 100 mL PDB medium on a rotary shaker (180 rpm, 28 °C) for three days. Subsequently, the seed culture was equally transferred to 40 × 1000 mL flask containing rice medium (200 g of rice, 200 mL of water, and 35 g of sea salt). A large-up fermentation was processed under static condition for 35 days at 25 °C. Then, the whole broth of finished fermentation was extracted with EtOAc for three times and concentrated under reduced pressure to obtain a crude extract (15 g). The crude extract was divided into 4 fractions (Fr.1 − Fr.4) using chromatographed on a Sephadex LH-20 column eluting with CH_3OH and CH_2Cl_2 (1:1, *v*/v). Fraction 3 was subjected to vacuum liquid chromatography on silica gel column (6 × 15 cm, 200–300 mesh) using a gradient of mixed petroleum ether/EtOAc (form 20:1 to 0:1, v/v) to yield eight subfractions (Fr.3.A − Fr.3.H), and the resulting subfraction Fr.3.F was further performed on MPLC (40–100% MeOH/H_2O, flow rate 20 mL/min, 120 min) to obtain 6 fractions (Fr.3.F.1 − Fr.F.6). Further, Fr.3.F.6 was purified by semi-preparative HPLC with UV detection at 200 nm to yield **1** (2.0 mg) and **2** (1.3 mg).

Aspericacid A (**1**): Yellow wax; $[\alpha]_D^{25}$ + 7.00 (*c* 0.15, MeOH); ECD (*c* 11.82 × 10^{-4} M, MeOH) λ_{ext} (Δε) 233 (+6.78), 250 (+0.25), 29 (+2.93) nm; UV (MeOH) λ_{max} (log ε) 204.5 (3.60), 238 (3.47), 277.5 (3.47); IR (KBr) ν_{max} 3400, 2963, 2931, 2874, 1713, 1610, 1459, 1377, 1266, 1202, 1166, 1045, 1023, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Table 1; HRESIMS *m/z* $[M + NH_4]^+$ peak at 321.2069 (calculated for $C_{16}H_{30}NO_4$).

Aspericacid B (**2**): Pale yellow wax; $[\alpha]_D^{25}$–2.54 (*c* 0.37, MeOH); UV (MeOH) λ_{max} (log ε) 220.5 (4.58); IR (KBr) ν_{max} 3419, 2974, 2935, 2874, 1711, 1459, 1381, 1258, 1195, 1089, 1028, 955, 800, 754 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1. HRESIMS *m/z* $[M + H]^+$ peak at 285.2064 (calculated for $C_{16}H_{29}O_4$).

2.4. Antifungal assay

Aspericacids A and B (**1** and **2**) were tested for their antifungal activities against *C. albicans* and *C. neoformans* based on the previously described method [23]. Briefly, the SDA medium were prepared, the two indicator strains (*C. neoformans* and *C. albicans*) were incubated at 30 °C for 16–20 h based on the growth appearance. All compounds were dissolved in dimethyl sulfoxide. The stock solution (12.8 mg/mL) was diluted with RPMI-1640 medium (Roswell Park Memorial Institute) with a serial 2-fold dilution to concentrations from 0.256 to 256 μg/mL in the 96-well plates. Each well was inoculated with 20 μL of homogeneous suspensions. Then the plates were incubation at 35 °C for 70 h. A culture supplemented with 8 μg/mL fluconazole was used as positive control. The culture containing DMSO (0.5%) was used as a negative control. The MIC (Minimal Inhibit Concentration) was assessed at the lowest concentration at which the test compound inhibits fungal growth.

Table 1
^1H (600 MHz) and ^{13}C NMR (150 MHz) data for **1** and **2** ($CDCl_3$, **δ** in ppm, ***J*** in Hz).

NO.	1		2	
	δ_C, type	δ_H(*J* in Hz)	δ_C, type	δ_H(*J* in Hz)
1	180.6, C	-	181.8, C	-
2	37.3, CH	2.45, m	37.7, CH	2.39, m
3a	41.1, CH_2	1.71, m;	41.0, CH_2	1.68, m;
3b	-	1.40, m	-	1.38, m
4	30.1, CH	2.50, m	30.3, CH	2.48, m
5	131.8, CH	5.22, d (9.6)	131.8, CH	5.20, d (9.6)
6	134.0, C	-	134.0, C	-
7	85.5, CH	4.31, t (7.0)	82.6, CH	4.33, t (7.6)
8a	30.5, CH_2	1.77, m	30.7, C	2.00, m;
8b	-	1.92, m;	-	1.74, m
9a	34.6, CH_2	2.21, m;	30.5, CH_2	2.12, m;
9b	-	1.74, m	-	1.52, m
10	88.8, C	-	86.3, C	-
11	213.8, C	-	72.3, CH	3.79, q (6.4)
12	24.7, CH_3	2.25, s	17.4, CH_3	1.15, d (6.7)
13	17.2, CH_3	1.16, d (6.9)	17.4, CH_3	1.15, d (6.7)
14	21.0, CH_3	0.96, d (6.6)	21.1, CH_3	0.97, d (6.6)
15	11.9, CH_3	1.63, s	12.2, CH_3	1.64, s
16	23.9, CH_3	1.38, s	23.1, CH_3	1.17, s

3. Results and discussion

Aspericacid A (**1**) was obtained as a yellow wax. The HRESIMS of **1** (**Fig. S9**) showed the $[M + NH_4]^+$ peak at *m/z* 300.1272, established the molecular formula as $C_{16}H_{26}O_4$ indicating four degrees of unsaturation. The IR spectrum revealed the presence of a carboxylic acid (1713 cm^{-1} and 3400 cm^{-1}). The ^1H NMR and HSQC spectrum of **1** (Table 1) indicated resonances attributable to one olefinic proton (δ_H 5.22,1H, d, J = 9.6 Hz, H-5), one oxymethine proton (δ_H 4.31, 1H, t, J = 7.0 Hz, H-7), two methine protons (δ_H 2.45, 1H, m, H-4; δ_H 2.50, 1H, m, H-2), three pairs of methylene protons [(δ_H 2.21, 1H, m, H-9a; δ_H 1.74, 1H, m, H-9b), (δ_H 1.77, 1H, m, H-8a; δ_H 1.92, 1H, m, H-8b) and (δ_H 1.71, 1H, m, H-3a; δ_H 1.40, 1H, m, H-3b)], two methyls with doublet (δ_H 1.16, 3H, d, J = 6.9 Hz, H_3-13; δ_H 0.96, 3H, d, J = 6.6 Hz, H_3-14) and three methyls with singlet (δ_H 2.25, 3H, s, H_3-12; δ_H 1.63, 3H, s, H_3-15; δ_H 1.38, 3H, s, H_3-16). Analysis of ^{13}C NMR and DEPT spectrum data of **1** classified the 16 carbons into five methyls, three methylenes, four methines as well as four nonprotonated carbons.

Given the three of four degrees of unsaturation were attributed to the vinyl group at δ_C 131.8 (C-5) and δ_C 134.0 (C-6), two carbonyl signals at δ_C 180.6 (C-1) and δ_C 213.8 (C-11), the presence of a single ring was inferred from the last degree of unsaturation. Then the existence of the 2,5-disubstituted tetrahydrofuran ring was further confirmed by the COSY correlations of H-7/H-8/H-9 in conjunction with the HMBC correlation of H-8b/C-10 (δ_C 88.8) as well as the observation of chemical shift at C-10 and C-7 (δ_C 85.5) (Fig. 2, **Figs. S4** and **S6**). Moreover, the HMBC correlations from H_3-12/H_3-16 to C-10 and from H_3-16 to C-11 allowed the assignment of both the acetyl at C-11 and the methyl at C-16 (δ_C 23.9) were tethered to C-10 in the tetrahydrofuran ring. A closer examination of the COSY spectrum constructed the 1,3-dimethyl-1,3-propanediyl by correlations of H-2/H_2-3/H_3-13 and H_2-3/H-4/ H_3-14. One end of the residue of 1,3-dimethyl-1,3-propanediyl

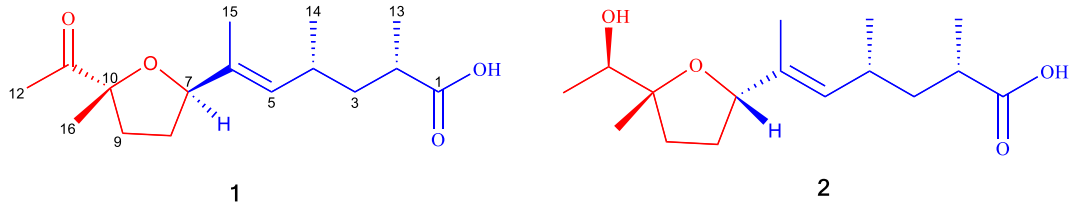

Fig. 1. Chemical structures of compounds **1** and **2.**

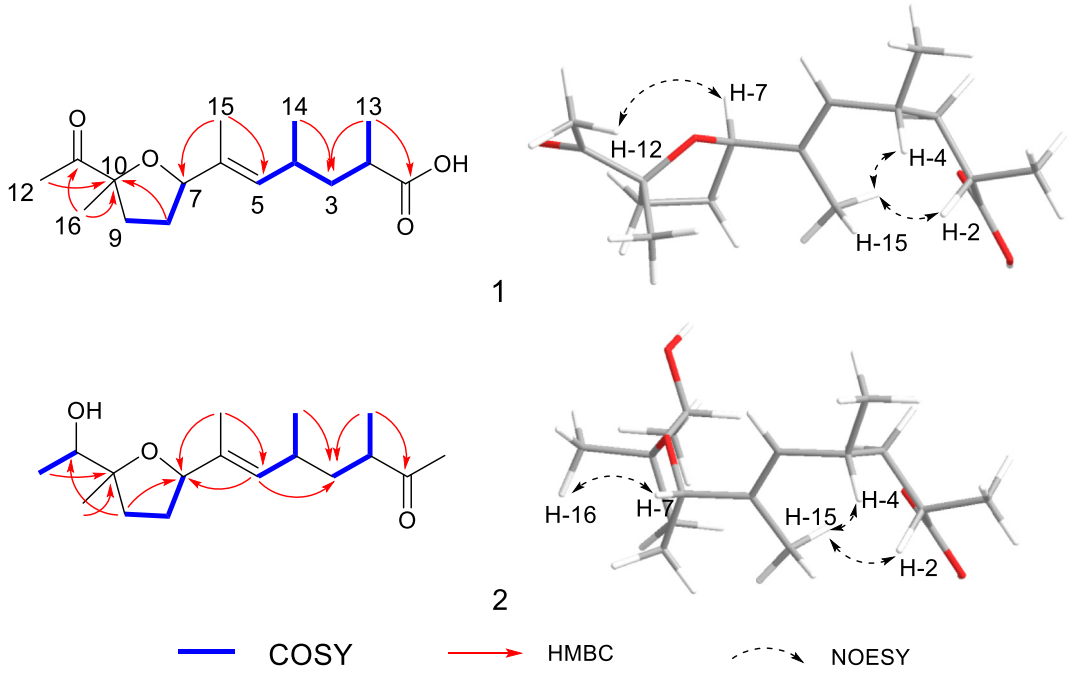

Fig. 2. Selected 2D NMR correlations for **1** and **2.**

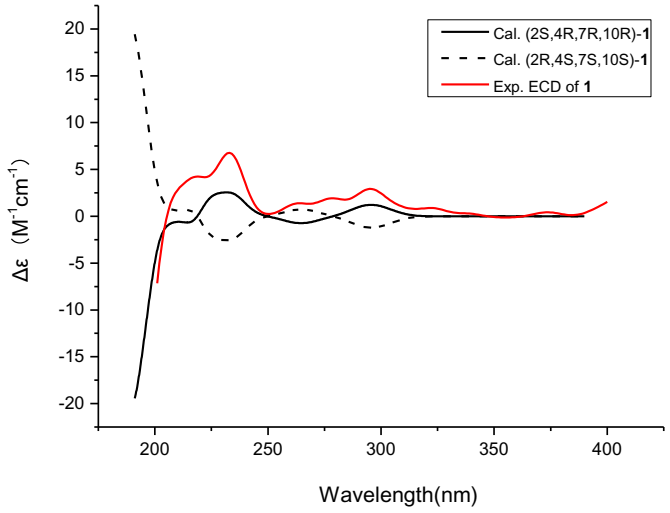

Fig. 3. Experimental ECD spectra in MeOH and the calculated ECD spectra of **1** at B3LYP-D3/def2-TZVP level.

was attached to a carboxylic acid at C-2 (δ_C 37.3) based on the HMBC correlation of H_3-13/C-1. The chain unsaturated fatty acid moiety on the side chain of tetrahydrofuran was further verified by the HMBC correlation of H_3-15/C-5 and COSY correlation of H-4/H-5. Subsequently, the crucial cross-peak of H_3-15/C-7 in the HMBC spectrum established unambiguously the linkage of the unsaturated fatty acid moiety to C-7 of the tetrahydrofuran ring (Fig. 2). Thus, the planar structure of aspericacid A (**1**) was elucidated as depicted in Fig. 1.

On account of the key NOE correlation of H_3-12/H-7 (Fig. 2), the C-1 to C-6 chain and the Me-16 were located in the same face of the tetrahydrofuran ring. The *E*-configuration was appointed to the vinyl group between C-5 and C-6 based on the NOE correlation between H-5 and H-7. Then on the observation of NOE correlations of H-2/H_3-15 and H-4/H_3-15, the relative configuration of **1** was established as (2*S*,*4*R*,*7*R*,*10*R**). To elucidate the absolute configuration of in **1**, the ECD curve of **1** was recorded and compared with its stereoisomer calculated by the time-dependent density functional theory method (TDDFT) at the B3LYP/def2-TZVP level. In general, conformational analyses were carried out *via* random searching in the Sybyl-X2.0 using the MMFF94S force field with an energy cutoff of 6.0 kcal/mol [24]. The results showed nine lowest energy conformers for **1**. Subsequently, the conformers were re-optimized using DFT at the B3LYP-D3/6-31G(d) level in MeOH using the polarizable conductor calculation model (SMD) by the GAUSSIAN 09 program [25]. The energies, oscillator strengths, and rotational strengths (velocity) of the first 30 electronic excitations were calculated using the TDDFT methodology at the B3LYP-D3/def2-TZVP level in MeOH. The ECD spectra were simulated by the overlapping Gaussian function (half the bandwidth at 1/e peak height, sigma = 0.30 for all) [26]. The Boltzmann-averaged computed ECD spectrum of the **(**2*S*,4*R*,7*R*,10*R*)-**1** well matched with that experimental spectrum of **1** (Fig. 3). Thus, the absolute configuration for **1** was identified as 2*S*,4*R*,7*R*,10*R*.

Aspericacid B (**2**), a pale yellow wax, had a molecular formula of $C_{16}H_{28}O_4$, determined by HR-ESI-MS ([M + H]$^+$ peak at *m/z* 285.2064) (**Fig. S19**). The ^{1}H and ^{13}C NMR data of **2** resembled those of

1, the appearance of an additional oxymethine (δ_C 72.3/δ_H 3.79) and the absence of a carbonyl unit (δ_C 213.8) indicated that compound **2** contained an oxymethine group at C-11 instead of ketonic carbonyl group, which was confirmed by correlations of H-9/C-11, from H_3-12 and H_3-16 to C-10 in HMBC experiment of **2** as shown in Fig. 2. According to the aforementioned information, the planar structure of **2** was established. The relative positions of the unsaturated fatty acid chain and Me-16 were located in the opposite of the tetrahydrofuran ring in compound **2**, based on the NOE correlation of H_3-16/H-7. Its relative configuration for the stereogenic centers at C-2/C-4 was assigned to be the same as those of **1**, on the basis of the NOE correlations of H_3-15/H-4 and H_3-15/H-2 (**Fig. S17**). In addition, the chemical shift (δ_C 72.3) of C-11 revealed an *erythro* configuration according to the described rule that the ^{13}C NMR shift for the hydroxymethine carbon was δ_C 74.0 for a *threo* relationship, and δ_C 72.0 for an erythro configuration normally [27]. In light of the biosynthetic origin, the stereogenic centers of **2** were tentatively proposed to be 2*S*,4*R*,7*R*,10*R*,11*R* (Fig. 3).

Biosynthetically, aspericacids A and B (**1** and **2**) are presumably to be derived from polyketide pathway. In the sight of the side chain unsaturated fatty acid, the precursors of compounds **1** and **2** would be likely derived from acetyl CoA and malonyl CoA [28]. Moreover, the tetrahydrofuran core was created with the help of a series of reactions exemplify with decarboxylation, epoxidation step at olefin, and ring-opening of the epoxide with water followed by a cyclization [29,30].

The biological activities of aspericacids A and B (**1** and **2**) were initially assessed by *in vitro* antifungal assays against selected pathogenic fungal strains. The bioassay results showed that **1** possessed moderate inhibitory activities with MIC value of 50 μg/mL against both *C. albicans* and *C. neoformans*, while compound **2** displayed slightly weak activity (MIC = 128 μg/mL).

In summary, chemical investigation of sponge-derived fungus *Aspergillus* sp. has resulted in the purification and characterization of two new compounds, aspericacids A and B (**1** and **2**). Structurally, they represented a rare type of tetrahydrofuran derivatives, possessing 2,5-disubstituted tetrahydrofuran ring coupled with a chain unsaturated fatty acid unit, and the absolute stereochemistry was firstly determined using ECD experiment. Biogenetically, **1** and **2** are presumably to be derived from the polyketide pathway. In addition, compound **1** exhibited moderate inhibitory activity (50 μg/mL) against both strains tested, while compound **2** displayed weak activity. Collectively, this study further enlarged the structurally diversity of occurring tetrahydrofuran derivatives.

Declaration of Competing Interest

The authors 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.fitote.2020.104677.

References

[1] M.C. Fisher, N.J. Hawkins, D. Sanglard, S.J. Gurr, Worldwide emergence of resistance to antifungal drugs challenges human health and food security, Science 360 (2018) 739–742.
[2] C. Tsui, E.F. Kong, M.A. Jabra-Rizk, Pathogenesis of *Candida albicans* biofilm, Pathog. Dis. 74 (2016) ftw018.
[3] M. Selvaraj, P. Pandurangan, N. Ramasami, S.B. Rajendran, S.N. Sangilimuthu, P. Perumal, Rajendran. Highly potential antifungal activity of quantum-sized silver nanoparticles against *Candida albicans*, Appl. Biochem. Biotechnol. 173 (2014) 55−−56.
[4] M. Cogliati, A. Prigitano, M.C. Esposto, L. Romanò, A. Grancini, A.M. Tortorano, Epidemiological trends of *cryptococcosis* in Italy: molecular typing and susceptibility pattern of *Cryptococcus neoformans* isolates collected during a 20-year period, Med. Mycol. 56 (2018) 963–971.
[5] H.W. Zhang, X.L. Bai, M. Zhang, J.W. Chen, H. Wang, Bioactive natural products from endophytic microbes, Nat. Prod. J. 8 (2018) 86–108.
[6] X.L. Zhang, Z. Li, J.T. Gao, Chemistry and biology of secondary metabolites from *Aspergillus* genus, Nat. Prod. J. 8 (2018) 275–304.
[7] J.F. Sanchez, A.D. Somoza, N.P. Keller, C.C.C. Wang, Advances in *Aspergillus* secondary metabolite research in the post-genomic era, Nat. Prod. Rep. 29 (2012) 351–371.
[8] L.H. Zhang, B.M. Feng, Y.Q. Zhao, Y. Sun, B. Liu, F. Liu, G. Chen, J. Bai, H.M. Hua, H.F. Wang, Y.H. Pei, Polyketide butenolide, diphenyl ether, and benzophenone derivatives from the fungus *Aspergillus flavipes* PJ03-11, Bioorg. Med. Chem. Lett. 26 (2016) 346–350.
[9] X.W. Du, D. Liu, J. Huang, C.J. Zhang, P. Peter, W.H. Lin, Polyketide derivatives from the sponge associated fungus *Aspergillus europaeus* with antioxidant and NO inhibitory activities, Fitoterapia 130 (2018) 190–197.
[10] G.P. Yin, Y.R. Wu, M.H. Yang, T.X. Li, X.B. Wang, M.M. Zhou, J.L. Lei, L.Y. Kong, Four dimeric aromatic polyketides with new carbon skeletons from the fungus *Aspergillus* sp, Org. Lett. 19 (2017) 4058–4061.
[11] J.R. Gubiani, M.C.S. Oliveira, R.A.R. Neponuceno, M.J. Camargo, W.S. Garcez, A.R. Biz, M.A. Soares, A.R. Araujo, V.S. Bolzani, H.C.F. Lisboa, T.A.N. Ribeiro, J.M. Oliveria, T.P. Banzato, L.G. Vasconcelos, C.A. Lima, G.B. Longato, J.M. Batista, H.L. Teles, Cytotoxic prenylated indole alkaloid produced by the endophytic fungus *Aspergillus terreus* P63, Phytochem. Lett. 32 (2019) 162–167.
[12] X.W. Luo, C.M. Chen, H.M. Tao, X.P. Lin, B. Yang, X.F. Zhou, Y.H. Liu, Structurally diverse diketopiperazine alkaloids from the marine-derived fungus *Aspergillus versicolor* SCSIO 41016, Org. Chem. Front. 6 (2019) 736–740.
[13] M.H. Chen, R.Z. Wang, W.L. Zhao, L.Y. Yu, C.H. Zhang, S.S. Chang, Y. Li, T. Zhang, J.G. Xing, M.L. Gan, F. Feng, S.Y. Si, Isocoumarindole A, a chlorinated isocoumarin and indole alkaloid hybrid metabolite from an endolichenic fungus *Aspergillus* sp, Org. Lett. 21 (2019) 1530–1533.
[14] H.J. Lacey, C.L.M. Gilchrist, A. Crombie, J.A. Kalaitzis, D. Vuong, P.J. Rutledge, P. Turner, J.I. Pitt, E. Lacey, Y.H. Chooi, A.M. Piggott, Nanangenines: drimane sesquiterpenoids as the dominant metabolite cohort of a novel Australian fungus, *Aspergillus nanangensis*, Beilstein J. Org. Chem. 15 (2019) 2631–2643.
[15] S. Limbadri, X.W. Luo, X.P. Lin, S.G. Liao, J.F. Wang, X.F. Zhou, B. Yang, Y.H. Liu, Bioactive novel indole alkaloids and steroids from deep sea-derived fungus *Aspergillus fumigatus* SCSIO 41012, Molecules 23 (2018) 2379.
[16] C.P. Xing, J. Wu, J.M. Xia, S.Q. Fan, X.W. Yang, Steroids and anthraquinones from the deep sea-derived fungus *Aspergillus nidulans* MCCC 3A00050, Biochem. Syst. Ecol. 83 (2019) 103–105.
[17] Z.M. Liu, Z.T. Dong, P. Qiu, Q.L. Wang, J.J. Yan, Y.J. Lu, P.A. Wasu, K. Hong, Z.G. She, Two new bioactive steroids from a mangrove-derived fungus *Aspergillus* sp, Steroids 140 (2018) 32–38.
[18] L.A. Azeez, S. Muid, B.M. Hasnul, Identification of volatile secondary metabolites from an endophytic microfungus *Aspergillus nomius* KUB105, Malays. J. Anal. Sci. 20 (2016) 751 − 759.
[19] C. Luz, F. Saladino, F.B. Luciano, J. Manes, G. Meca, In vitro antifungal activity of bioactive peptides produced by *Lactobacillus plantarum* against *Aspergillus parasiticus* and *Penicillium expansum*, Lwt-Food Sci. Tech. 81 (2017) 128–135.
[20] X. Ma, X.H. Nong, Z. Ren, J. Wang, X. Liang, L. Wang, S.H. Qi, Antiviral peptides from marine gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501, Tetrahedron Lett. 58 (2017) 1151–1155.
[21] P. Klausmeyer, T.G. McCloud, K.D. Tucker, J.H. Cardellina, R.H. Shoemaker, Aspirochlorine class compounds from *Aspergillus flavus* inhibit azole-resistant *Candida albicans*, J. Nat. Prod. 68 (2005) 1300–1302.
[22] L.J. Ding, T. Li, X.J. Liao, S. He, S.H. Xu, Asperitaconic acids A–C, antibacterial itaconic acid derivatives produced by a marine-derived fungus of the genus *Aspergillus*, J. Antibiot. 71 (2018) 902–904.
[23] A. Samie, T. Tambani, E. Harshfield, E. Green, J.N. Ramalivhana, P.O. Bessong, Antifungal activities of selected Venda medicinal plants against *Candida albicans*, *Candida krusei* and *Cryptococcus neoformans* isolated from south African AIDS patients, Afr. J. Biotechnol. 9 (2010) 2965–2976.
[24] Sybyl Software, Version X 2.0, Tripos Associates Inc, St. Louis, MO, 2013.
[25] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, O. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision C.01, Gaussian, Inc., Wallingford, CT, 2010.

[26] P.J. Stephens, N. Harada, ECD cotton effect approximated by the Gaussian curve and other methods, Chirality 22 (2010) 229–233.
[27] Y.S. Che, J.B. Gloer, J.A. Scott, D. Malloch, Communiols A-D: new mono- and bis-tetrahydrofuran derivatives from the coprophilous fungus *Podospora communis*, Tetrahedron Lett. 45 (2004) 6891–6894.
[28] E. Liddle, A. Scott, L.C. Han, D. Ivison, T.J. Simpson, C.L. Willis, R.J. Cox, In vitro kinetic study of the squalestatin tetraketide synthase dehydratase reveals the stereochemical course of a fungal highly reducing polyketide synthase, Chem. Commun. 53 (2017) 1727–1730.
[29] T. Asai, S. Morita, N. Shirata, T. Taniguchi, K. Monde, H. Sakurai, T. Ozeki, Y. Oshima, Structural diversity of new C_{13}-Polyketides produced by chaetomium mollipilium cultivated in the presence of a NAD^+-dependent histone deacetylase inhibitor, Org. Lett. 14 (2012) 5456–5459.
[30] D.C. Braddock, A hypothesis concerning the biosynthesis of the obtusallene family of marine natural products via electrophilic bromination, Org. Lett. 8 (2006) 6055–6058.