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RESEARCH ARTICLE

Cytotoxic isocoumarin derivatives from the mangrove endophytic fungus *Aspergillus* sp. HN15-5D

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Abstract Five isocoumarin derivatives including three new compounds, aspergisocoumrins A–C (**1**–**3**), together with two known analogues, 8-dihydroxyisocoumarin-3-carboxylic acid (**4**) and dichlorodiaportin (**5**) were obtained from the culture of the endophytic fungus *Aspergillus* sp. HN15-5D derived from the fresh leaves of the mangrove plant *Acanthus ilicifolius*. Their structures were elucidated using comprehensive spectroscopic methods. The double bond geometry of compounds **1** and **2** were assigned as *E* and *Z* on the basis of the distinct coupling constants, respectively. Compounds **1** and **2** showed cytotoxicity against MDA-MB-435 with IC_{50} values of 5.08 ± 0.88 and 4.98 ± 0.74 μM, respectively.

Keywords Isocoumarins · Cytotoxicity · *Aspergillus* sp. · Mangrove endophytic fungus

Introduction

Aspergillus species are ubiquitous in nature (Kwon-Chung and Sugui 2013; Volke-Sepulveda et al. 2016) and have been identified as a prolific fungal source of various structural compounds such as polyketones (Huang et al. 2010), alkaloids (Liao et al. 2015; Zhuang et al. 2011; Dai et al. 2001), terpenoids (Wei et al. 2010; Li et al. 2012; Sun et al. 2014; Prompanya et al. 2014), steroids (Liang et al. 2015), haloggenated compounds (Huang et al. 2012), peptides (Chaiyosang et al. 2016), glycosides (Zhuravleva et al. 2012) and fatty acids (Huang et al. 2011). Most of them were examined to exhibit extensive biological activities, mainly including antibacterial (Li et al. 2012; Sun et al. 2014; Prompanya et al. 2014), cytotoxic (Kito et al. 2008), radical scavenging (Abd El-Hady et al. 2015) and anticancer (Nguyen et al. 2013) activities.

In our ongoing research for novel compounds from *Aspergillus* species (Xiao et al. 2013; Liu et al. 2016; Huang et al. 2013), a strain of marine fungus *Aspergillus* sp. HN15-5D was isolated from the leaves of the mangrove plant *Acanthus ilicifolius*. The ethyl acetate extract of a fermentation broth of the fungus showed moderate cytotoxicity against the MDA-MB-435 human breast cancer cell line. Subsequent chemical investigation led to the isolation of three new isocoumarins, aspergisocoumrins A–C (**1**–**3**) and two known analogues (**4** and **5**) (Fig. 1). Compounds **1** and **2** displayed cytotoxicity against MDA-

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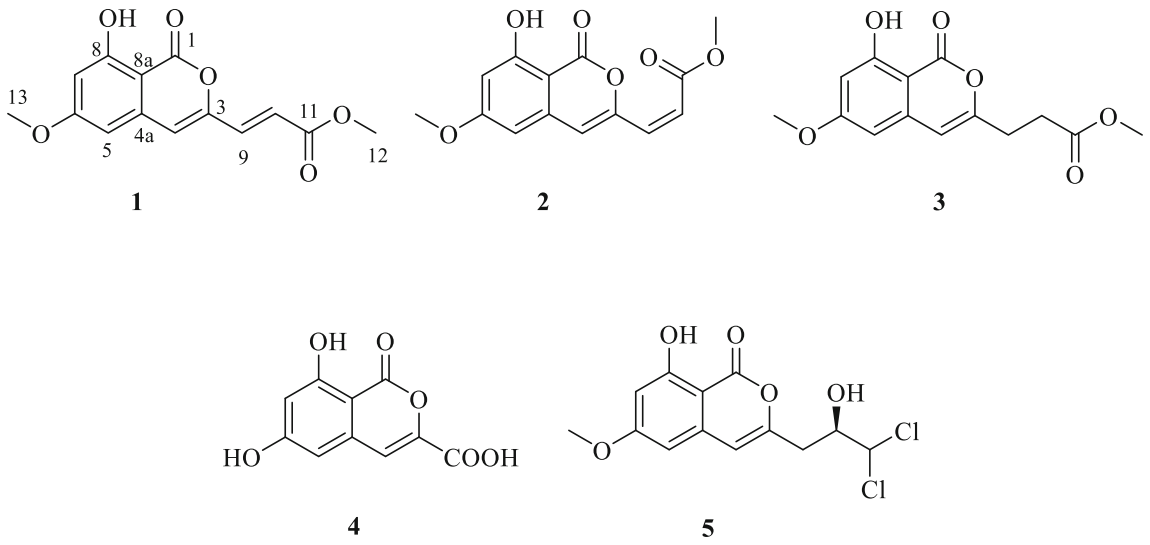

Fig. 1 Structures of the isolated compounds **1–5**

MB-435 with IC_{50} values of 5.08 ± 0.88 and 4.98 ± 0.74 μM, respectively. Herein, we reported the isolation, structure elucidation, cytotoxic and antibacterial activities of these isocoumarins.

Materials and methods

General experimental procedures

Melting points were measured on a Fisher-Johns hot-stage apparatus. UV data were obtained on a Shimadzu UV-240 spectrophotometer. IR spectra were recorded in KBr on a Nicolet 5DX-FTIR. Optical rotations were determined on an Anton Paar MCP 300 (Anton Paar) polarimeter at 25 °C. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 (500 and 125 MHz) NMR spectrometer, using $CDCl_3$ as solvent and TMS as an internal standard. All chemical shifts (δ) are given in ppm, and coupling constants (J) are given in Hertz (Hz). ESIMS data were recorded on a Micro mass Q-TOF spectrometer and HRESIMS recorded on a Thermofisher LTQ Orbitrp Elite LC–MS spectrometer. Column chromatography (CC) was performed using silica gel (200–300 mesh, Qingdao Marine Chemical Factory) and Sephadex LH-20 (Amersham Pharmacia Biotech AB).

Fungal material

The fungal HN15-5D was isolated from fresh leaves of *A. ilicifolius* collected in April 2009 from Dongzhaigang Mangrove National Nature Reserve in Hainan Island, China. The fungus was identified as *Aspergillus* sp. by the morphologic traits and molecular identification. It had 99% sequence identity to that of *Aspergillus* sp. (KP881422.1). The sequence data had been submitted to GenBank (Accession Number KX711974). A voucher strain has been deposited at Sun Yat-sen University, China.

Extraction and isolation

The fungus *Aspergillus* sp. HN15-5D was grown on autoclaved rice solid-substrate medium (thirty 500 mL Erlenmeyer flasks, each containing 50 g of rice and 50 mL 3‰ of saline water) at room temperature for 30 days. After incubation, the mycelia and solid rice medium were extracted with $CH_3COOCH_2CH_3$ three times. Then, the extract was evaporated under reduced pressure to yield 8.7 g, the residue was divided into five fractions (Fr. 1–Fr. 5) by a silica gel column (40 × 6 cm), eluting with a gradient of petroleum ether to ethyl acetate, containing 1.8, 1.0, 2.1, 1.2 and 2.6 g of material, respectively. Fr. 3 (2.1 g) was purified on a silica gel column (30 × 3 cm) eluted by gradient mixtures of petroleum ether/EtOAc to yield five subfractions (Fr. 3-1–Fr. 3-5). Fr. 3-2 (450 mg) was re-chromatographed on silica gel column (20 × 4 cm) with a gradient of petroleum ether and EtOAc from 100:0 to 50:50 v/v to obtain **1** (10.4 mg), **2** (1.2 mg) and **3**(0.92 mg), respectively. Fr. 3-3 (650 mg) was applied to column chromatography (CC) on silica gel (20 × 6 cm column) eluting with a gradient of petroleum ether/EtOAc from 80:20 to 20:80 v/v affording **5** (5.8 mg). Fr. 3-5 (1.2 g) was eluted with $CHCl_3$-MeOH (1:1, v/v) on Sephadex LH-20 CC (110 × 3 cm) to give **4** (13 mg).

Aspergisocoumrin A (**1**) : white soild; m.p. 81.2–82.2 °C; UV (MeOH) λ_{max} (log ε): 215 (4.15), 267

Table 1 ^{1}H and ^{13}C NMR Data ($CDCl_3$, 500/125 MHz, δ ppm, J in Hz) of compounds **1–3**

Position	1		2		3	
	δ_C, type	δ_H, (J in Hz)	δ_C, type	δ_H, (J in Hz)	δ_C, type	δ_H, (J in Hz)
1	165.0, C		165.0, C		166.3, C	
3	149.9, C		149.4, C		155.7, C	
4	112.1, CH	6.58, s	110.7, CH	7.01, s	104.9, CH	6.25,s
4a	137.9, C		138.3, C		139.2,C	
5	103.8, CH	6.47, d (2.3)	103.3, CH	6.45, d (2.2)	101.6, CH	6.32, d (2.1)
6	167.0, C		166.9, C		167.0, C	
7	102.3, CH	6.56, d (2.3)	102.1, CH	6.53, d (2.2)	100.7, CH	6.47, d (2.1)
8	164.1, C		163.8, C		163.8, C	
8a	100.9, C		100.7, C		100.1, C	
9	134.7, CH	7.21, d (15.5)	129.4, CH	6.36, d (12.8)	28.7, CH_2	2.84, t (7.3)
10	122.0, CH	6.65, d (15.5)	123.5, CH	6.10, d (12.8)	31.2, CH_2	2.72, t (7.3)
11	166.7, C		166.7, C		172.5, C	
12	52.2, CH_3	3.82, s	52.4, CH_3	3.86, s	52.1, CH_3	3.70, s
13	56.0, CH_3	3.89, s	55.9, CH_3	3.87, s	55.8, CH_3	3.86, s
8-OH		11.01, s		11.01, s		11.05, s

(3.78), 339 (3.71) nm; IR (KBr) υ_{max} 3433, 2920, 1633, 1458, 1261, 1163, 1061, 802 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; ESIMS *m/z* 275 $[M–H]^-$; HRESIMS *m/z* 275.05580 $[M–H]^-$ (calcd for $C_{14}H_{11}O_6$, 275.05611).

Aspergisocoumrin B (**2**): yellow soild; m.p. 98.7–99.7 °C; UV (MeOH) λ_{max} (log ε): 249 (4.14), 274 (3.78), 332 (3.71) nm; IR (KBr) υ_{max} 3420, 2950 1639, 1720, 1693, 1642, 1579, 1443, 1383, 1235, 1196, 1158, 874 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; ESIMS *m/z* 275$[M–H]^-$; HRESIMS *m/z* 275.05585 $[M–H]^-$ (calcd for $C_{14}H_{11}O_6$, 275.05611).

Aspergisocoumrin C (**3**): white soild; m.p. 95.1–96.1 °C; UV (MeOH) λ_{max} (log ε): 244 (4.20), 277(3.79), 323(3.75); IR (KBr) υ_{max} 3400,2150,1640,1560, 1420, 1110, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; ESIMS *m/z* 277 $[M–H]^-$; HRESIMS *m/z* 277.07184 $[M–H]^-$ (calcd for $C_{14}H_{13}O_6$, 277.07176).

Dichlorodiaportin (**5**): brownish solid; [α] +15 (c 0.02 $CHCl_3$).

Biological activity

Cytotoxicity assay

Cytotoxic activities were evaluated by the MTS assay as described previously (Chen et al. 2016a, b). Five cells lines, MDA-MB-435 (breast cancer cells), HepG2 (liver cancer cells), HCT116 (colon cancer cells), H460 (lung carcinoma cells), and MCF10A (immortalized non-cancer breast epithelial cells) were used.

Antibacterial activity

Antibacterial activities were evaluated by the conventional broth dilution assay as described previously (Chen et al. 2016a, b). Five bacterial strains, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Bacillus subtilis* were used. All experiments were performed in three replicates and with ciprofloxacin and gentamicin as the positive control.

Results

Aspergisocoumrin A (**1**) was obtained as white solid. Its molecular formula was deduced as $C_{14}H_{12}O_6$ on the basis of HRESIMS analysis at *m/z* 275.05580 $[M–H]^-$ (calcd for $C_{14}H_{11}O_6$, 275.05611), implying nine degrees of unsaturation. The IR absorption bands at υ_{max} 3420 and 1720 cm^{-1} revealed the presence of hydroxy and carbonyl groups. In the ^{1}H NMR spectrum (Table 1), the signals for one chelated hydroxyl (δ_H 11.01, s), two olefinic protons [δ_H 7.21 (d, J = 15.5 Hz, H-9); 6.65 (d, J = 15.5 Hz, H-10)], one singlet olefinic proton (δ_H 6.58, s, H-4), two meta-coupled aromatic protons [δ_H 6.47 (d, J = 2.3 Hz, H-5); 6.56 (d, J = 2.3 Hz, H-7)], and two methoxyl groups (δ_H 3.89, s, H_3-13; 3.82, s, H_3-12) were observed. ^{13}C NMR spectra of **1** showed the resonances of two carbonyl (δ_C 165.0, 166.7), six aromatic, four olefinic, and two methoxyl carbons (Table 1). Overall

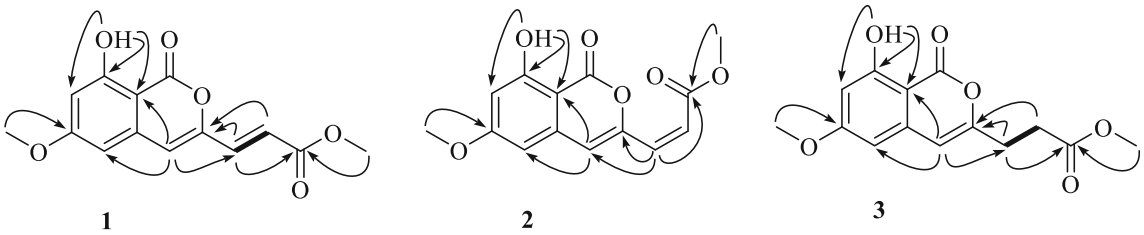

Fig. 2 Selected ^{1}H–^{1}H COSY (bold line) and HMBC (arrow) correlations of compounds **1**–**3**

inspection of the ^{1}H and ^{13}C NMR spectra (Table 1) indicated that compound **1** shared isocoumarin skeleton. The HMBC correlations from H_3-12, H-9 and H-10 to C-11, together with the ^{1}H–^{1}H COSY correlation of H-9 and H-10 indicated a fragment of –CH = CH–$COOCH_3$, which was connected to C-3 supported by the HMBC correlations of H-9 and H-10 with C-3, and H-4 with C-9 (Fig. 2). The HMBC correlation of H_3-13 to C-6 revealed that another methoxyl group was attached to C-6. The geometry of the 1,3-diene (C-4–C-11) was established by 1D NOESY difference spectra. The resonances of H-9 (δ_H 7.21) was enhanced after irradiation of H-4 (δ_H 6.58) using the optimized 800 ms mixing time, which suggested the *s-trans* configuration of the 1,3-diene. Furthermore, The double bond $\Delta^{9,10}$ geometry of **1** were determined as *E* in the light of the coupling constant $J_{9,10}$ = 15.5 Hz. Therefore, structure of **1** was elucidated as methyl (*E*)-3-(8-hydroxy-6-methoxy-1-oxo-1H-Isochromen-3-yl) acrylate, named as aspergisocoumrin A (Figs. 1, 2).

Aspergisocoumrin B (**2**) was obtained as yellow solid. Its molecular formula was established as $C_{14}H_{12}O_6$ on the basis of the HRESIMS negative ion at *m/z* 275.05585 $[M–H]^-$ (calcd for $C_{14}H_{11}O_6$, 275.05611), which was the same as **1**. The ^{1}H and ^{13}C NMR data (Table 1) of **2** were similar to those of **1**, except for the different chemical shifts of H-4, H-9, H-10 and C-4, C-9, and C-10 and the coupling constant of double bond $\Delta^{9,10}$ that changed from 15.5 Hz to 12.8 Hz, indicating that the double bond geometry may change *Z* correspondingly. 1D NOE correlations of H-4/H-9 and H-9/H-10 suggested the same *s-trans* configuration of 1,3-diene (C-4–C-11) and the *Z* geometry of $\Delta^{9,10}$, respectively. In order to further confirm the geometry of **2**, the quantum chemical calculation of the NMR of the two feasible geometrical isomers (**2a** and **2b**) were carried out at rwb97xd/6-31 g (Table S1; Fig. S1). The calculated chemical shifts and the couple constants of **2a** showed a more excellent fit to the experiment data than those of **2b** (Table S2). Thus, the structure of **2** was established as shown and named aspergisocoumrin B.

Aspergisocoumrin C (**3**) was obtained as white solid. Its molecular formula was established as $C_{14}H_{14}O_6$ on the basis of HRESIMS analysis at *m/z* 277.07184 $[M–H]^-$ (calcd for $C_{14}H_{13}O_6$, 277.07176). The ^{1}H and ^{13}C NMR data (Table 1) of **3** were quite similar to those of aspergisocoumrin A (**1**), indicating that **3** also shared the same isocoumarin skeleton as **1**. The main differences were that two additional methylene protons [δ_H 2.84 (t, *J* = 7.3 Hz, H-9); 2.72 (t, *J* = 7.3 Hz, H-10)] were observed, whereas two olefinic protons [δ_H 7.21 (d, *J* = 15.5 Hz, H-9); 6.65 (d, *J* = 15.5 Hz, H-10)] were absent in the ^{1}H NMR spectrum of **3**. At the same time, olefinic carbons C-9 and C-10 (δ_C 134.7, 122.0) in **1** were replaced by two sp^3 hybridized methylenes (δ_C 28.7.0 and 31.2) in **3**, respectively. The HMBC correlations from H_3-12, H_2-9 and H_2-10 to C-11 (δ_C 172.5), together with the ^{1}H-^{1}H COSY correlation of H_2-9 and H_2-10 further established a moiety of –CH_2–CH_2–$COOCH_3$, which was linked to C-3 (δ_C 155.7) in the light of the HMBC correlations from H-9 and H-10 to C-3, and H-4 to C-9. Therefore, compound **3** was identified as methyl 3-(8-hydroxy-6-methoxy-1-oxo-1H-isochromen-3-yl) propanoate.

The isolated isocoumarins **1, 2**, **4**, and **5** were evaluated for their cytotoxicity using MDA-MB-435 (breast cancer), HepG2 (liver cancer), HCT116 (colon cancer), H460 (lung carcinoma), and MCF10A (immortalized non-cancer breast epithelial) human cell lines with epirubicin as the positive control (Table 2). Compound **1** showed selective cytotoxicity against MDA-MB-435, HepG2, H460, and MCF10A with IC_{50} values of 5.08 ± 0.88, 43.70 ± 1.26, 21.53 ± 1.37, and 11.34 ± 0.58 μM, respectively. Compound **2** exhibited selective cytotoxicity against MDA-MB-435 and MCF10A with IC_{50} values of 4.98 ± 0.74 and 21.40 ± 1.71 μM, respectively. The other compounds displayed no cytotoxicity against all five cell lines at 50 μM.

The isolated compounds were tested for their anti-bacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Bacillus subtilis*. Among the isolated compounds, only chlorinated compound **5** showed antibacterial activities against *S. aureus* and *B. subtilis* with the MIC values of 25 μg/mL, respectively. Compounds **1**, **2**, and **4** did not show antibacterial activity against the bacterial strains at 100 μg/mL.

Table 2 The cytotoxicity data of compounds **1**, **2**, **4** and **5** (IC_{50} μM)

Compounds	MDA-MB-435	HepG2	HCT116	H460	MCF10A
1	5.08 ± 0.88	43.70 ± 1.26	> 50	21.53 ± 1.37	11.34 ± 0.58
2	4.98 ± 0.74	> 50	> 50	> 50	21.40 ± 1.71
4	> 50	> 50	> 50	> 50	> 50
5	> 50	> 50	> 50	> 50	> 50
epirubicin	0.26 ± 0.06	0.32 ± 0.01	0.37 ± 0.05	0.12 ± 0.01	0.13 ± 0.01

The cytotoxicity of compound **3** was not tested due to the limited amounts

MDA-MB-435 breast cancer cells, *HepG2* liver cancer cells, *HCT116* colon cancer cells, *H460* lung carcinoma cells, *MCF10A* immortalized non-cancer breast epithelial cells

Discussion

The endophytic fungus *Aspergillus* sp. HN15-5D was isolated from the fresh leaves of the mangrove plant *Acanthus ilicifolius* in Dongzhaigang Mangrove National Nature Reserve of Hainan Island, China. The fungus was cultured on a rice-based medium and then extracted with ethyl acetate (EtOAc). The extract was subjected to silica gel column chromatography (CC) using gradient elution and were further purified by silica gel CC and Sephadex LH-20 CC to give compounds **1–5.** The structures of 6,8-dihydroxyisocoumarin-3-carboxylic acid (**4**) (Le et al. 2013), and dichlorodiaportin (**5**) (Larsen and Breinholt 1999) were assigned by comparison of their spectroscopic data with literature.

Structurally, compounds **1–5** belong to isocoumarins that have been widely derived from plants, insects, lichens, fungi, and bacteria (Saeed 2016; Hill 1986; Ellestad et al. 1978). Isocoumarins are a significant group of natural products with diverse chemical structures and pharmacological activities, such as irciniastatins A and B with cytotoxicity (Pettit et al. 2004), halorosellins A and B with antimalarial activity (Chinworrungsee et al. 2002), *O*-methylmellein with phytotoxicity (Glauser et al. 2009), peyroisocoumarins A–D with antioxidant activity (Zhao et al. 2016), machilusmarin with neuroprotective activity (Cheng et al. 2013), (-)-eurotiumides B and D with antifouling activity (Chen et al. 2014), and oospolactone with antifungal activity (Nozawa et al. 1981). The cytotoxicity of aspergisocoumrins A and B (**1** and **2**) suggested them become potential compounds of antitumor drugs.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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