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•Special topic•

Three new isocoumarin derivatives from the mangrove endophytic fungus *Penicillium* sp. YYSJ-3

QIU Pei[1], CAI Run-Lin[1], LI Lin[1], SHE Zhi-Gang[1, 2*]

[1] *School of Chemistry, Sun Yat-Sen University, Guangzhou 510275, China;*
[2] *South China Sea Bio-Resource Exploitation and Utilization Collaborative Innovation Center, Guangzhou 510006, China*

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[ABSTRACT] Three new isocoumarin derivatives, (*S*)-6,8-dihydroxy-5-(methoxymethyl)-3,7-dimethylisochroman-1-one (**1**), (*S*)-6,8-dihydroxy-3,5,7-trimethyl-isochroman-1-one (**2**) and (*R*)-2-chloro-3-(8-hydroxy-6-methoxy-1-oxo-1*H*-isochromen-3-yl) propyl acetate (**3**), along with four known compounds (**4**–**7**) were isolated from a mangrove endophytic fungus *Penicillium* sp. YYSJ-3. Their structures were established on the basis of the extensive spectroscopic data and HR-ESI-MS analysis. The absolute configurations of **1**–**3** were further determined by *X*-ray diffraction analysis and optical rotations. Compounds **3**, **6** and **7** showed promising inhibitory activity against *α*-glucosidase, which were stronger than that of the positive control 1-deoxynojirimycin (IC_{50} 141.2 μmol·L^{-1}).

[KEY WORDS] Isocoumarin derivatives; *Penicillium* sp.; Structure elucidation; *α*-Glucosidase inhibitory activity
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Introduction

Isocoumarin is a basic structure of some natural products and widely distributed in nature. Up to now, nearly 400 isocoumarin derivatives have been identified, including some dihydroisocoumarins and dimericisocoumarins [1]. The isocoumarin derivatives displayed the varieties of physiological and biological activities such as antibacterial [2], anti-inflammatory [3], anticancer [4-5], inhibiting protease [6] and other effects. As part of our ongoing investigation on new active natural products from mangrove endophytic fungi in the South China Sea [7-12], an endophytic fungus, *Penicillium* sp. YYSJ-3, collected from the stem of the mangrove plant *Heritiera littoralis* was carried out and three new isocoumarin derivatives (**1**–**3**), including (*S*)-6,8-dihydroxy-5-(methoxymethyl)-3,7-dimethylisochroman-1-one (**1**), (*S*)-6,8-dihydroxy-3,5,7-trimethylisochroman-1-one (**2**) and (*R*)-2-chloro-3-(8-hydroxy-6-methoxy-1-oxo-1*H*-isochromen-3-yl)propyl acetate (**3**), together with four known compounds, monaschromone (**4**) [13], cytosporone B (**5**) [14], dothior-elone C (**6**) [15] and cytosporone A (**7**) [14], were isolated. In the bioactivity assay, compounds **3**, **6** and **7** showed promising inhibitory activity against *α*-glucosidase with IC_{50} values of 100.6, 133.4 and 130.9 μmol·L^{-1}, respectively, which were stronger than that of the positive control 1-deoxynojirimycin (IC_{50} 141.2 μmol·L^{-1}). The absolute configuration of compound **1** was unambiguously established by *X*-ray diffraction analysis. This study further expanded the structural diversity of naturally occurring isocoumarin derivatives and the potential choice of *α*-glucosidase inhibitors.

Results and Discussion

Compound **1** was obtained as a colorless crystal. Its molecular formula was deduced as $C_{13}H_{16}O_5$ based on the HR-ESI-MS at *m/z* 251.0927 ([M – H]$^-$, Calcd. for 251.0925), indicating six degrees of unsaturation. (Fig. 1) The broad band at 1709 and 3412 cm^{-1} detected in IR spectrum suggested the presence of carbonyl and hydroxyl functionalities, respectively. The ^{1}H NMR spectrum (Table 1) recorded in $CDCl_3$ of compound **1** displayed two chelating hydroxyl singlets at δ_H 11.66 (8-OH) and 8.49 (6-OH), an AB system of a methylene group at δ_H 4.65 (H_2-10a, d, J = 12.3 Hz) and 4.57 (H_2-10b, d, J = 12.3 Hz), an ABX system of a methylene group at δ_H 2.88 (H_2-4a, dd, J = 3.3, 16.2 Hz) and 2.67 (H_2-4b, dd, J = 11.6, 16.2 Hz), an oxygenated methine at δ_H 4.59 (H-3), a methoxyl at δ_H 3.47 (H_3-12), and two methyls including a doublet at δ_H 1.51 (H_3-9, J = 6.3 Hz). The ^{13}C NMR data (Table 1) revealed an ester carbonyl carbon at δ_C 170.6 (C-1)

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[*]**Corresponding author]** E-mail: cesshzhg@mail.sysu.edu.cn
These authors have no conflict of interest to declare.

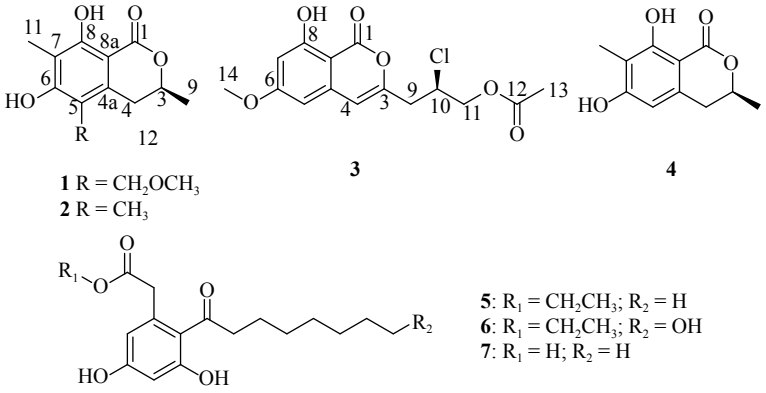

Fig. 1 Chemical structures of compounds 1–7

Table 1 ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data for 1 in $CDCl_3$

No.	1	
	δ_C	δ_H (mult, *J*, Hz)
1	170.6 C	
3	74.7 CH	4.59 (m)
4	31.5 CH_2	2.88 (dd, 16.2, 3.3)
		2.67 (dd, 16.2, 11.6)
4a	134.7 C	
5	110.2 C	
6	161.6 C	
7	111.6 C	
8	162.5 C	
8a	100.7 C	
9	21.0 CH_3	1.51 (d, 6.3)
10	69.4 CH_2	4.65 (d, 12.3)
		4.57 (d, 12.3)
11	7.6 CH_3	2.12 (s)
12	58.5 CH_3	3.47 (s)
6-OH		8.49 (s)
8-OH		11.66 (s)

as well as a fully substituted benzene ring based on the detected six sp^2 carbon signals. A $CH_2CH(O)CH_3$ fragment could be speculated by comprehensive analysis of 1D NMR spectra. This deduction was further evidenced by the ^{1}H-^{1}H COSY cross peaks of H_3-9/H-3/H_2-4b (Fig. 2).

Further analysis of HMBC spectrum led to the establishment of the planar structure of **1** (Fig. 2). The HMBC correlations from H_2-4 to C-4a, C-5 and C-8a as well as H-3 to C-4a indicated that C-4 was linked to the benzene ring at C-4a (Fig. 2). The chemical shift of C-8a (δ_C 100.7) combined the correlations from the chelating hydroxyl group (8-OH) to C-7, C-8a and C-8 in the HMBC spectrum (Fig. 2), suggested the linkage of the carbonyl (C-1) at C-8a. Considering the requirement of degrees of unsaturation, an oxygen atom was deduced to connect C-1 and C-3 to construct an isocoumarin skeleton (Fig. 2). In addition, the detected HMBC cross peaks from H_2-10 to C-4a/C-5/C-6 and from H_3-11 to C-6/C-7/C-8 (Fig. 2) revealed that the methylene (H_2-10) and the methyl (H_3-11) was attached to C-5 and C-7, respectively. Finally, the location of a methoxyl group was assigned at C-10 based on the correlation from H_3-12 to C-10 (Fig. 2). Thus, the planar structure of **1** was established. Generally, the signals of exocyclic hydroxymethyl should not split in ^{1}H NMR spectrum recorded in $CDCl_3$, in which the phenolic hydroxyl group signals could not be detected either. However, since the hydroxyl group at C-6 formed an intramolecular hydrogen bond with the oxygen at hydroxymethyl group and a six-membered ring was formed, the 6-OH could be detected unambiguously in the NMR data and the 10-methylene was splitting into typical AB spin system signals [16]. The intramolecular hydrogen bond was confirmed clearly with the assistance of *X*-ray diffraction analysis (Fig. 3).

The absolute configuration of C-3 in **1** was established as *S* under the guidance of single-crystal *X*-ray (Fig. 3).

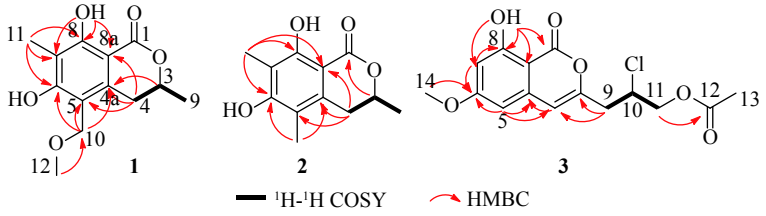

Fig. 2 The key 2D NMR correlations of compounds 1–3

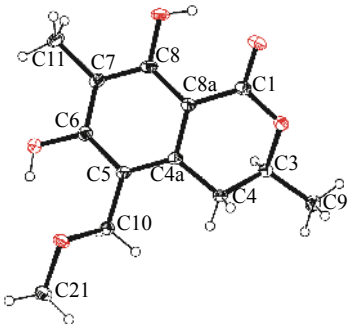

Fig. 3 Single-crystal *X*-ray structure of compound 1

Compound **2** was obtained as a white powder. Its molecular formula was deduced as $C_{12}H_{14}O_4$ based on the HR-ESI-MS at *m/z* 221.0818 ($[M - H]^-$, Calcd. for 221.0819), indicating six degrees of unsaturation. The ^1H NMR spectrum (Table 2) recorded in methanol-d_4 of **2** was closely resembled that of compound **1** with an isocoumarin core structure. However, a methoxyl group at δ_H 3.47 (H_3-12) and an AB system of a methylene group at δ_H 4.65 (H_2-10a, d, J = 12.3 Hz) and 4.57 (H_2-10b, d, J = 12.3 Hz) in **1** disappeared in the spectrum of **2** (Table 2). Instead, a methyl signal at δ_H 2.07 (H_3-10) was detected in the ^1H NMR spectrum of **2** (Table 2), which was not present in the spectrum of **1**. Additionally, the HMBC correlations from H_3-10 to C-4a, C-5 and C-6 (Fig. 2) indicated that the hydroxymethyl group in **1** was replaced by a methyl group in **2**. Hence, the planar structure of **2** was constructed. The absolute configuration of C-3 in **2** was established as *S* by comparing the optical rotations with **1** $[\alpha]_D^{20}$+6.7 (*c* 0.1, MeOH)) and **4** $[\alpha]_D^{25}$+34.4 (*c* 0.065, $CHCl_3$)) [13].

Compound **3** was obtained as a pale yellow oil. Its molecular formula was deduced as $C_{15}H_{15}O_6Cl$ by the HR-ESI-MS ion at *m/z* 327.0630 $[M + H]^+$ (100%) and *m/z* 329.0601 $[M + H]^+$ (33%) with the ratio 3 : 1, indicating one chlorine atom in the structure. Detailed inspection of the 1D NMR spectra of **3** (Table 2) revealed that compound **3** possessed similar carbon skeleton with **2** and exhibited two olefinic carbons on C-3 and C-4. The HMBC correlations from H-4 to C-3/C-5, from H-5 to C-4/C-4a/C-6, from H-7 to C-6/C-8, and from 8-OH to C-1/C-7/C-8/C-8a (Fig. 2) suggested that two methyl groups at C-5 and C-7 were replaced by two protons. The HMBC correlation from H_3-14 to C-6 (Fig. 2) showed the replacement of the hydroxy group at C-6 with a methoxy group. In addition, the side chain at C-3 was different from **2** due to the HMBC correlations (Fig. 2) from H_2-9 to C-3/C-4 and the ^1H-^1H COSY correlations from H-10 (δ_H 4.47, 1H) to H-9 (δ_H 3.06 and 2.81, 2H) and H-11 (δ_H 4.34 and 4.32, 2H). The aforementioned structural features combined the chemical shift of C-10 (δ_C 54.8) confirmed the position of the chlorine atom at C-10. Moreover, the presence of a carbonyl group (δ_C 170.5) was observed in the ^{13}C NMR spectrum and location of the ester group at C-11 was further confirmed by an HMBC correlation from H_2-11 to C-12 (Fig. 2). According to

Table 2 ^1H and ^{13}C NMR data for compounds 2 (Methanol-d_4) and 3 ($CDCl_3$)

	2[a]		3[b]	
No.	δ_C	δ_H (mult, *J*, Hz)	δ_C	δ_H (mult, *J*, Hz)
1	172.7 C		167.1 C	
3	76.5 CH	4.58 (m)	152.2 C	
4	32.8 CH_2	3.02 (dd, 16.6, 3.4)	107.1 CH	6.32(s)
		2.63 (dd, 16.6, 11.6)		
4a	137.1 C		138.7 C	
5	114.3 C		102.1 CH	6.36 (s)
6	161.4 C		167.1 C	
7	110.4 C		101.0 CH	6.50 (s)
8	161.8 C		163.9 C	
8a	101.3 C		100.1 C	
9	21.0 CH_3	1.48 (d,6.3)	39.3 CH_2	3.06 (dd, 15.0, 4.4)
				2.81 (dd, 15.0, 9.3)
10	11.2 CH_3	2.07 (s)	54.8 CH	4.47 (m)
11	8.1 CH_3	2.07 (s)	66.9 CH_2	4.34 (dd, 11.6, 6.0)
				4.32 (dd, 11.6, 6.0)
12			170.5 C	
13			20.8 CH_3	2.12 (s)
14			55.9 CH_3	3.87 (s)
8-OH				10.99 (s)

[a] ^1H and ^{13}C NMR recorded at 500 MHz and 125 MHz; [b] ^1H and ^{13}C NMR recorded at 400 MHz and 100 MHz.

peniisocoumarin E ($[\alpha]_D^{25}$+69.2 (*c* 0.15, MeOH), a previously reported and characterized isocoumarin derivative with a 10*R*-configuration which was established by X-ray diffraction analysis [17], the absolute configuration of C-10 in **3** was determined as *R* by optical rotation value $[\alpha]_D^{20}$+43.4 (*c* 0.1, MeOH).

As far as we know, a number of isocoumarins exhibited significant inhibitory activity against *α*-glucosidase [18-20]. Compounds **1**–**7** were evaluated for their *α*-glucosidase inhibitory activity. As seen in Table 3, compounds **3, 6** and **7** showed promising inhibitory activity against *α*-glucosidase with IC_{50} values of 100.6, 133.4 and 130.9 μmol·L^{-1}, respectively, which were stronger than that of the positive control 1-deoxynojirimycin (IC_{50} 141.2 μmol·L^{-1}). Compounds **1** and **2** exhibited weak inhibitory activity against *α*-glucosidase.

Experimental

General experimental procedures

Optical rotations were obtained on an MCP300 (Anton

Table 3 The *α*-glucosidase inhibitory effect of compounds 1–7

Compound	*α*-Glucosidase inhibitory	
	% Inhibition	IC_{50}
1	58.0	309.6
2	63.6	237.4
3	97.5	100.6
4	< 50	–[a]
5	< 500	–[a]
6	89.9	133.4
7	88.7	130.9
1-Deoxynojirimycin[b]	78.6	141.2

[a]means no test; [b]a positive control

Paar, Shanghai, China). UV spectra were measured with a UV-Vis-NIR spectrophotometer (Perkin Elmer, Waltham, UK). IR spectra were recorded on a Bruker Vector spectrophotometer 22. Melting points were tested on a Fisher-Johns hot-stage apparatus which were uncorrected. The NMR spectra were recorded on Bruker Avance spectrometer (Bruker, Beijing, China). HR-ESI-MS spectra were detected on an Ion Mobility-Q-TOF High-Resolution LC-MS (Synapt G2-Si, Waters). Column chromatography (CC) was performed on silica gel (200–300 mesh, Marine Chemical Factory, Qingdao, China) and sephadex LH-20 (Amersham Pharmacia, Piscataway, NJ, USA).

Fungal materials

The fungus was isolated from the stem of the mangrove plant *Heritiera littoralis*, which were collected in 2018 from the Zhuhai Mangrove Nature Reserve in Guangdong Province, China. The fungal strain was identified as *Penicillium* sp. (compared to No. JN676120.1) by rDNA and ITS region sequencing. The ITS sequence data have been deposited at GenBank with accession No. MN900843. The fungus specimen has been deposited in our laboratory.

Fermentation, extraction and isolation

The fungus was cultured in eighty 1 L Erlenmeyer flasks (each containing 80 g of rice and 100 mL of 0.3% saline water) for 30 days at 25 ºC. After fermentation, the mycelia and solid rice medium were extracted with methanol three times and concentrated to yield a residual gum of 8.7 g under reduced pressure. The residue was subjected to a silica gel column (90 cm × 10 cm) using gradient elution with petroleum ether–EtOAc from 100 : 0 to 0 : 100 (*V/V*) to afford ten fractions (Fr. 1–Fr. 10). Fr. 3 (711 mg) was further eluted by silica gel CC using CH_2Cl_2/MeOH (from 99 : 1 to 90 : 10) to obtain Fr. 3.1–Fr. 3.5. Fr.3.2 (23 mg) was purified by Sephadex LH-20 CC using CH_2Cl_2/MeOH (1 : 1) to obtain compounds **1** (2.1 mg) and **3** (3.2 mg). Fr. 4 (455 mg) was applied to Sephadex LH-20 CC using MeOH to obtain Fr. 4.1–Fr. 4.6. Fr. 4.1 (202 mg) was further purified by silica gel CC by CH_2Cl_2/MeOH (95 : 1) to obtain compound **2** (2.9 mg). Fr. 4.2 was applied to Sephadex LH-20 using MeOH to obtain compound **4** (4.0 mg). Fr. 5 (407 mg) was eluted by silica gel CC using CH_2Cl_2/MeOH (40 : 1) to obtained **5** (13.1 mg) and **6** (5.9 mg). Fr. 6 (872 mg) was applied to Sephadex LH-20 CC using MeOH to obtain Fr. 6.1–Fr. 6.3. Fr. 6.1 (121 mg) was further purified by silica gel CC by CH_2Cl_2/MeOH (30 : 1) to obtain compound **7** (3.0 mg).

Spectroscopic data of new compounds

Compound **1**: colorless crystal; mp 177.8–179.9 °C; $[\alpha]_D^{20}$ + 6.7 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 224 (4.06), 272 (3.76) nm; IR (KBr) ν_{max} 3412, 1709, 1624, 1301, 1205, 1132, 800 cm^{-1}; HR-ESI-MS *m/z* 251.0927 $[M - H]^-$ (Calcd. for $C_{13}H_{15}O_5$: 251.0925); ^1H and ^{13}C NMR data: see Table 1.

Compound **2**: white powder; $[\alpha]_D^{20}$+ 26.5 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 217 (4.42), 274 (4.18) nm; IR (KBr) ν_{max} 3390, 1635, 1375, 1301, 1213, 1130, 794 cm^{-1}; HR-ESI-MS *m/z* 221.0818 $[M - H]^-$ (Calcd. for $C_{12}H_{13}O_4$: 221.0819); ^1H and ^{13}C NMR data: see Table 2.

Compound **3**: pale yellow oil; $[\alpha]_D^{20}$+ 43.4 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε): 245 (3.37), 331 (3.63) nm; IR (KBr) ν_{max} 3377, 1681, 1620, 1381, 1232, 1163, 1028, 848, 798 cm^{-1}; HR-ESI-MS *m/z* 327.0630 $[M + H]^-$ (Calcd. for $C_{15}H_{16}O_6Cl$: 327.0630); ^1H and ^{13}C NMR data: see Table 2.

X-ray crystallographic data

The crystallographic data for compound **1** has been deposited in the Cambridge Crystallographic Data Centre (CCDC number: 1992433)

Crystal data of **1**: $C_{13}H_{16}O_5$, *Mr* = 252.26, orthorhombic, *a* = 4.0197(11) Å, *b* = 14.3385(3) Å, *c* = 20.3754(5) Å, α = 90°, β = 90°, γ = 90°, *V* = 1174.37(5) $Å^3$; space group *P212121*, flack 0.14(12), *Z* = 4, *Dc* = 1.427 $g \cdot cm^{-3}$, μ = 0.919 mm^{-1} and *F*(000) = 536; Crystal dimensions: 0.10 × 0.04 × 0.04 mm^3. Independent reflections: 2897 (R_{int} = 0.0154). The final R_1 was 0.0324, wR_2 = 0.1216 [$l > 2\sigma$ (*I*)]. The goodness of fit on F^2 was 1.088.

α-Glucosidase inhibitory activity assay

The *α*-glucosidase inhibitory activity was assayed according to the reported method [21]. The *α*-glucosidase inhibitory activity was tested with 100 mm PBS (KH_2PO_4-K_2HPO_4, pH 7.0) buffer solution each in the 96-well plated. Compounds **1**–**7** and 1-deoxynojirimycin (positive control) were dissolved in DMSO. The enzyme solutions (2.0 $U \cdot mL^{-1}$) and the substrate (*p*-nitrophenyl glycoside, 5 $mmol \cdot L^{-1}$) which dissolved in PBS buffer solution (100 $mmol \cdot L^{-1}$) were prepared. The test was conducted in a 200 μL reaction system containing 10 μL enzyme stock solutions, 176 μL PBS buffers and 4 μL of DMSO or testing materials. After 5 min incubation at 37 °C, 10 μL of the substrate was added to start the enzymatic reaction and incubated for 15 min at 37 °C. The Absorbance which measured by a BIO-RAD (iMark) microplate reader at 405 nm was used to calculate the inhibitory activity according to the equation:

$$\eta(\%) = [1 - A_{405}t/A_{405}c] \times 100\% \quad (1)$$

η (%) is the percentage of inhibition; $A_{405}t$ is the absorbance of the testing materials ($A_{405end} - A_{405initial}$), and $A_{405}c$ is the absorbance of the blank ($A_{405endblank} - A_{405initialblank}$). All assays were repeated three times. 1-deoxynojirimycin was used as positive control.

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