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# Xylarianins A-D from the endophytic fungus *Xylaria* sp. SYPF 8246 as natural inhibitors of human carboxylesterase 2

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ABSTRACT

Eighteen secondary metabolites were isolated from the fermentation broth of the endophytic fungus *Xylaria* sp. SYPF 8246, including four new compounds, xylarianins A-D (**1**–**4**), three new natural products, 6-methoxycarbonyl-2′-methyl-3,5,4′,6′-tetramethoxy-diphenyl ether (**5**), 2-chlor-6-methoxycarbonyl-2′-rnethyl-3,5,4′,6′-tetramethoxy-diphenyl ether (**6**), and 2-chlor-4′-hydroxy-6-methoxy carbonyl-2′-methyl-3,5,6′-trimethoxy-diphenyl ether (**7**), and eleven known compounds (**8**–**18**). Their structural elucidations were conducted by using 1D and 2D NMR, HRESIMS, and $Rh_2(OCOCF_3)_4$-induced electronic circular dichroism (ECD) spectra analyses. The integrated $^1H$ and $^{13}C$ NMR data of three new natural products **5**–**7** were reported for the first time. All the isolated compounds were assayed for their inhibitory activities against human carboxylesterase 2 (hCE 2). Compounds **1**, **5**–**9**, and **18** displayed significant inhibitory activities against hCE 2 with $IC_{50}$ values of 10.43 ± 0.51, 6.69 ± 0.85, 12.36 ± 1.27, 18.25 ± 1.78, 29.78 ± 0.48, 18.86 ± 1.87, and 20.72 ± 1.51 μM, respectively. The interactions between compounds **1** and **5** with hCE 2 were anaylzed by molecular docking.

## 1. Introduction

Endophytic fungi are regarded as key resources for discovering bioactive metabolites [1,2], such as cytochalasins, diphenyl ethers, xanthones, isocoumarines, indole diterpenoids, and depsipeptides, that can be used in medicinal and agricultural fields [1]. Some of bioactive secondary metabolites from fungi have been used in clinic [3–5], including penicillin, cyclosporine A, FK-506, and vancomycin, therefore, endophytic fungi have received more attentions from biosynthetic chemists and pharmacists. Recently, some bioactive indole diterpenoids that displayed antimicrobial activity and agonistic effect against human pregnane X receptor have been isolated from the endophytic fungus *Drechmeria* sp. in our laboratory [6,7]. As part of our continuous research for discovering bioactive secondary metabolites from plants and fungi [8–12], the investigation of the fermentation broth of the endophytic fungus *Xylaria* sp. SYPF 8246 led to the isolation of seventeen metabolites (Fig. 1), including four new compounds, xylarianins A-D (**1**–**4**), and three new natural products, 6-methoxycarbonyl-2′-methyl-3,5,4′,6′-tetramethoxy-diphenyl ether (**5**), 2-chlor-6-methoxycarbonyl-2′-methyl-3,5,4′,6′-tetramethoxy-diphenyl ether (**6**), and 2-chlor-4′-hydroxy-6-methoxycarbonyl-2′-methyl-3,5,6′-trimethoxy-diphenyl ether (**7**), as well as eleven known compounds (**8**–**18**). Their structural elucidations were conducted by using HRESIMS, 1D and 2D NMR, and $Rh_2(OCOCF_3)_4$-induced electronic circular dichroism (ECD) spectra analyses. All the isolated compounds were assayed for their inhibitory activities against human carboxylesterase 2 (hCE 2).

## 2. Results and discussion

Compound **1** was obtained as an amorphous powder, and had the molecular formula of $C_{18}H_{20}O_7$ on the basis of the quasi-molecular ion peak at *m/z* 371.1107 $[M+Na]^+$ (calcd. for $C_{18}H_{20}NaO_7$, 371.1101) in the HRESIMS spectrum. The $^1H$ NMR data (Table 1) of **1** displayed signals of four aromatic protons at $\delta_H$ 6.37 (1H, d, $J$ = 2.6 Hz, H-5′), 6.28 (1H, d, $J$ = 2.6 Hz, H-3′), 6.21 (1H, d, $J$ = 2.0 Hz, H-4), and 5.59 (1H, d, $J$ = 2.0 Hz, H-2), signals of four methoxy groups at $\delta_H$ 3.84 (3H,

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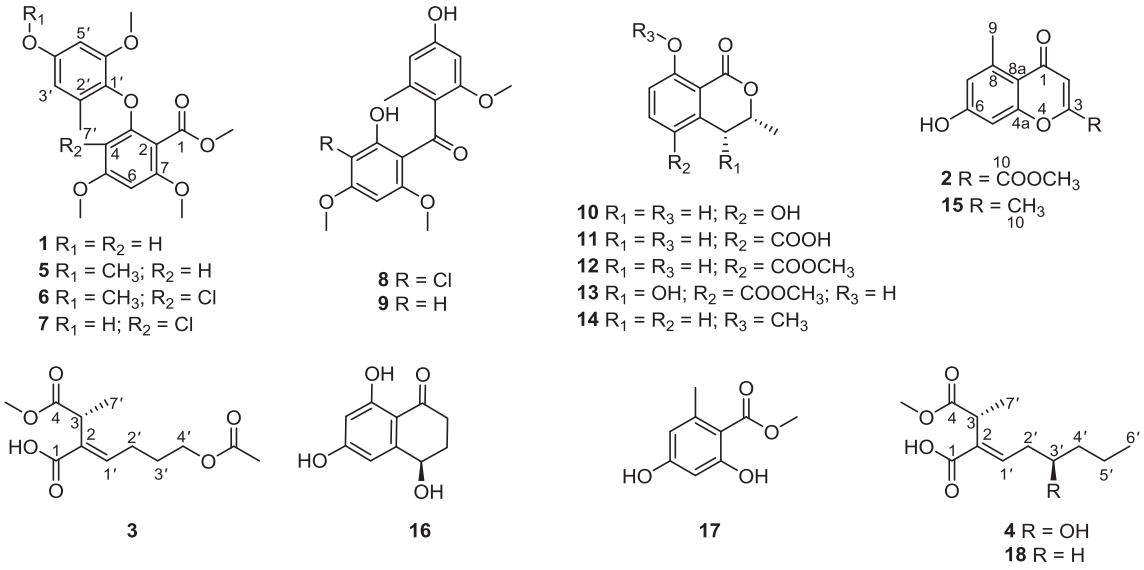


**Fig. 1.** Secondary metabolites isolated from *Xylaria* sp. SYPF 8246.

s, $OCH_3$-7), 3.81 (3H, s, $OCH_3$-5), 3.69 (3H, s, $OCH_3$-6′), and 3.63 (3H, s, $OCH_3$-3), and the signal of a methyl group at $\delta_H$ 2.04 (1H, s, $CH_3$-7′). The $^{13}C$ NMR data (Table 1) of **1** showed 18 carbon signals, including an ester carbonyl carbon at $\delta_C$ 169.2, twelve aromatic carbons at $\delta_C$ 164.2, 160.4, 159.2, 156.7, 154.5, 135.2, 134.1, 109.8, 106.9, 99.6, 92.9, and 92.3, four methoxy carbons at $\delta_C$ 56.6, 56.4, 55.9, and 52.8, and a methyl carbon at 16.2, which indicated that **1** was a derivative of the diphenyl ethers [13,14]. Comparison of NMR data of **1** and 6-methoxycarbonyl-2′-methyl-3,5,4′,6′-tetramethoxy-diphenyl ether (**5**) [15] indicated that **1** lacked a methoxy moiety than **5**. The locations of four methoxy moieties in **1** were established through an HMBC spectrum showing correlations of $OCH_3$-3 with C-3, $OCH_3$-5 with C-5, $OCH_3$-7 with C-7, and $OCH_3$-6′ with C-6′ (Fig. 2) in conjunction with NOESY correlations of $OCH_3$-5 with H-4, $OCH_3$-3 with H-2/H-4, and $OCH_3$-6′ with H-5′ (Fig. 3). Therefore, the structure of **1** was showed in Fig. 1, and it was named as xylarianin A.

Compound **2** was assigned the molecular formula $C_{12}H_{10}O_5$ according to positive HRESIMS *m/z* 235.0602 $[M + H]^+$ (calcd. for $C_{12}H_{11}O_5$, 235.0606), indicating 8 degrees of unsaturation. The $^1H$ NMR data (Table 1) of **1** displayed the presence of two aromatic protons at $\delta_H$ 6.76 (1H, d, $J$ = 2.0 Hz, H-8), and 6.71 (1H, d, $J$ = 2.0 Hz, H-6), an olefinic proton at $\delta_H$ 6.84 (1H, s, H-3), a methoxy at $\delta_H$ 3.98 (3H, s, $OCH_3$-10), and a methyl at $\delta_H$ 2.73 (3H, s, $CH_3$-9). The $^{13}C$ NMR data (Table 1) of **2** showed 12 carbon resonances, including a carbonyl carbon at $\delta_C$ 181.5, an ester carbonyl carbon at $\delta_C$ 162.4, six aromatic carbons at $\delta_C$ 164.3, 161.2, 144.3, 119.1, 117.0, and 102.2, one methoxy carbon at $\delta_C$ 54.0, and a methyl carbon at 23.2. The $^1H$ and $^{13}C$ NMR data of **2** were closely resembling to those of 2,5-dimethyl-7-hydroxychromone (**15**) [16], except for that the chemical shift value of C-10 was deshielded from $\delta_C$ 14.5 in **15** to $\delta_C$ 162.4 in **2**, and signals of a methoxy moiety [$\delta_H$ 3.98 and $\delta_C$ 54.0] were present in **2**, requiring that their difference was at C-10. The above-mentioned deduction was confirmed by long-range correlations of $OCH_3$-10 with C-10, and H-3 with C-2/C-10 in the HMBC spectrum (Fig. 2). Accordingly, the structure of **2** was showed in Fig. 1, and it was named as xylarianin B.

Compound **3** was isolated as a colorless oil. HRESIMS spectrum of **3** displayed the $[M+Na]^+$ peak at *m/z* 281.0998 (calcd. for $C_{12}H_{18}NaO_6$, 281.0996), indicating that its molecular formula was $C_{12}H_{18}O_6$. Compared with 2-hexylidene-3-methyl succinic acid 4-methyl ester (**18**) [17], the chemical shift value of C-4′ was deshielded from $\delta_C$ 31.5 in **18** to $\delta_C$ 63.7 in **3**, signals of C-5′ ($\delta_C$ 22.4) and C-6′ ($\delta_C$ 13.9) in **18** were absent, and signals of an acetoxy moiety [$\delta_H$ 2.06; $\delta_C$ 171.3 and 21.1] were present in **3**, which suggested **3** had an acetoxy moiety at C-4′ rather than an ethyl group at C-4′. In the HMBC spectrum of **3**, correlations of H-4′ with OAc-4′ confirmed this deduction (Fig. 2). The configuration of C-3 in **3** was established as *R* according to optical rotation − 32.8 similar to that of **18** [17]. Thus, the structure of **3** was showed in Fig. 1, and it was named as xylarianin C.

Compound **4** had a molecular formula of $C_{12}H_{20}O_5$ established by HRESIMS (*m/z* 267.1204 $[M+Na]^+$, calcd. for $C_{12}H_{20}NaO_5$, 267.1203) and $^{13}C$ NMR spectra. The $^1H$ and $^{13}C$ NMR data of **4** were similar to those of 2-hexylidene-3-methyl succinic acid 4-methyl ester (**18**) [17], except for that the chemical shift value of C-3′ was deshielded from $\delta_C$ 28.1 in **18** to $\delta_C$ 70.4 in **4**, which indicating the location of a hydroxy group at C-3′. This deduction was confirmed by HMBC correlations of H-1′ with C-3′, H-2′a/H-2′b with C-3′, and H-3′ with C-5′. The absolute configuration of **4** was established as 3*R*,3′*R* according to a negative Cotton effect at 341 ($\Delta\varepsilon$ = −1.01) nm in the $Rh_2(OCOCF_3)_4$-induced ECD spectrum [18], the similar NMR data of C-3 in **3** and **18**, and the biosynthesis background of these analogues [17]. Accordingly, the structure of **4** was showed in Fig. 1, and it was named as xylarianin D.

In addition, the fermentation broth of the endophytic fungus *Xylaria* sp. SYPF 8246 was investigated, and led to the isolation of three new natural products, 6-methoxycarbonyl-2′-methyl- 3,5,4′,6′-tetramethoxy-diphenyl ether (**5**) [15], 2-chlor-6-methoxycarbonyl-2′-methyl- 3,5,4′,6′-tetramethoxy-diphenyl ether [**6**, same as methyl 4,6-dimethoxy-2-(2,4-dimethoxy-6-methyl-henoxy)-benzoate] [19], and 2-chlor-4′-hydroxy-6-methoxycarbonyl-2′-methyl-3,5,6′-trimethoxy-diphenyl ether (**7**) [19], together with eleven known compounds, grisephenone A (**8**) [20], 5,9,11-trimethoxy-3,13-dihydroxy benzophenone (**9**) [20], (*R*)-5-hydroxymellein (**10**) [21], (*R*)-5-carbonyl mullein (**11**) [22], (*R*)-5-methoxycarbonyl mullein (**12**) [23], xylarellein (**13**) [24], (3*R*)-mellein methyl ether (**14**) [25], 2,5-dimethyl-7-hydroxychromone (**15**) [16], (*R*)-4,6,8-trihydroxy-3,4-dihydro-1(2*H*)-naphthalenone (**16**) [26], methyl orsellinate (**17**) [27], and 2-hexylidene-3-methyl succinic acid 4-methyl ester (**18**) [17]. The integrated $^1H$ and $^{13}C$ NMR data (Table 2) of **5–7** were reported for the first time.

Human carboxylesterases (hCE 1 and hCE 2) are the important enzymes that hydrolyze chemicals with functional groups, such as a carboxylic acid ester and amide, and they are known to play vital roles in drug metabolism and insecticide detoxication [28]. hCE 1 is abundantly expressed in the liver, whereas hCE 2 is predominately expressed in the gastrointestinal tract. hCE 2 is a major mediator in the gastrointestinal tract to reduce drug toxicity and enhance drug bioavailability in drug metabolism [28], and it has attracted more attentions. Therefore, all the isolated compounds were assayed for their inhibitory activities against

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