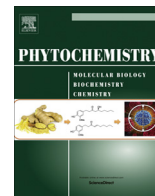




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Sesquiterpenes and other constituents of *Xylaria* sp. NC1214, a fungal endophyte of the moss *Hypnum* sp.

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ABSTRACT

Oxygenated guaiane-type sesquiterpenes, xylaguanols A–D (**1–4**), an iso-cadinane-type sesquiterpene isocadinanol A (**5**), and an α -pyrone 9-hydroxyxylarone (**6**), together with five known sesquiterpenes (**7–11**), and four known cytochalasins (**12–15**) were isolated from a culture broth of *Xylaria* sp. NC1214, a fungal endophyte of the moss *Hypnum* sp. The structures of all compounds were elucidated by the analysis of their spectroscopic data and relative configurations of **1–5** were determined with the help of NMR NOESY experiments. Cytochalasins C (**12**), D (**13**), and Q (**14**) were investigated for their cytotoxic activity against five tumor cell lines. Cytochalasin D showed significant cytotoxicity against all five cell lines, with IC_{50} s ranging from 0.22 to 1.44 μ M, whereas cytochalasins C and Q exhibited moderate, but selective cytotoxicity.

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1. Introduction

Endophytic fungi constitute rich sources of secondary metabolites with novel structures and biomedical potential (Schulz et al., 2002; Gunatilaka, 2006; Zhang et al., 2006). *Xylaria* species, often isolated as endophytes from decaying plant tissue, occur worldwide from arctic to tropical regions (Schüffler et al., 2007). Many *Xylaria* species are known to produce diverse secondary metabolites (Song et al., 2014), which include succinic acid derivatives (Klaiklay et al., 2012), cytochalasins (Espada et al., 1997), α -pyrones (Schüffler et al., 2007), terpenoids (Li et al., 2010; Wu et al., 2014; Yan et al., 2011), xanthenes (Davis and Pierens, 2006; Healy et al., 2004), cyclopeptides (Lin et al., 2001; Wu et al., 2011), and lactones (Jimenez-Romero et al., 2008). In an ongoing search for bioactive natural products from fungal endophytes, a cytotoxic EtOAc extract of *Xylaria* sp. NC1214, a fungal endophyte of the moss *Hypnum* sp., cultured in potato dextrose

broth (PDB) containing 0.25 mM CuSO₄ (Paranagama et al., 2007) was investigated. Fractionation of this extract resulted in the isolation of fifteen metabolites including four cytotoxic cytochalasins. Herein reported are the isolation and structure elucidation of four new oxygenated guaiane-type sesquiterpenes (**1–4**), a rare bicyclic sesquiterpene (**5**) and a new α -pyrone (**6**), as well as the known sesquiterpenes, *epi*-guaidiol A (**7**) (Xu et al., 2009), hydroheptelidic acid (**8**) (Calhoun et al., 1992), gliocladic acid (**9**) (Itoh et al., 1982), bullatantriol (**10**) (Sung et al., 1992), and 1 β ,4 β ,7 α -trihydroxyeudesmane (**11**) (Sung et al., 1992), and four known cytochalasins, cytochalasins C (**12**), D (**13**), Q (**14**), and R (**15**) (Edwards et al., 1989). Also reported herein is the cytotoxic activity of cytochalasins **12–14** against five sentinel cancer cell lines.

2. Results and discussion

Xylaguanols A (**1**) and B (**2**) (Fig. 1) were determined to have the same molecular formula, C₁₅H₂₈O₄, on the basis of their HRMS and ¹³C NMR spectroscopic data, indicating that they are sesquiterpenes. Comparison of their ¹H and ¹³C NMR spectroscopic data (Tables 1 and 2, respectively) with those reported for bicyclic sesquiterpenes (Wu et al., 2014) suggested that **1** and **2** are

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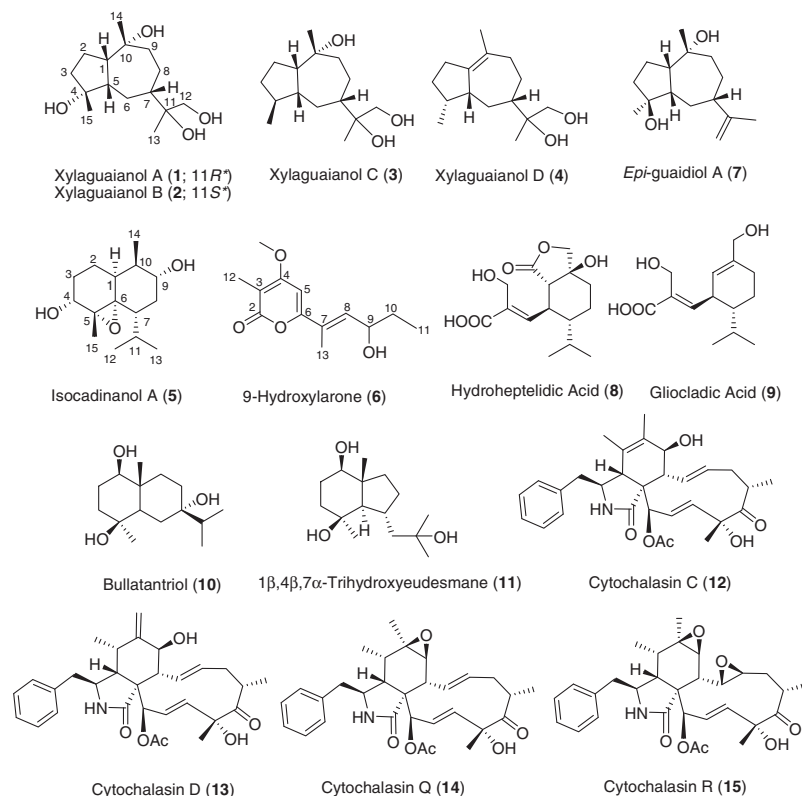


Fig. 1. Structures of metabolites 1–15.

Table 1

¹H NMR (400 MHz) spectroscopic data for compounds 1–4 (acetone-*d*₆, δ in ppm, *J* in Hz).

Position	1	2	3	4
1	2.86 m	2.90 m	2.05 m	–
2 α	1.50 m	1.53 m	1.50 m	2.31 m
2 β	1.71 m	1.70 m	1.64 m	2.16 m
3 α	1.63 m	1.67 m	1.66 m	1.35 m
3 β	1.91 m	1.93 m	1.21 m	1.64 m
4	–	–	1.97 m	2.08 m
5	2.17 m	2.24 m	1.88 m	2.38 m
6 α	2.17 m	2.13 m	1.77 m	0.81 m
6 β	1.12 m	1.20 m	0.90 m	1.76 m
7	1.95 m	1.99 m	1.89 m	1.67 m
8 α	2.12 m	2.08 m	1.82 m	1.13 m
8 β	1.45 m	1.44 m	1.14 m	2.05 m
9 α	1.85 m	1.70 m	1.88 m	2.08 m
9 β	1.72 m	1.53 m	1.37 m	2.08 m
12a	3.28–3.33 m	3.17–3.22 m	3.29–3.36 m	3.35–3.40 m
12b	3.59–3.65 m	3.41–3.50 m	3.40–3.50 m	3.47–3.52 m
13	1.25 s	1.23 s	0.98 s	1.00 s
14	1.08 s	1.07 s	1.10 s	1.63 d (1.2)
15	1.18 s	1.20 s	0.93 d (6.8)	0.88 d (7.2)
12-OH	3.50–3.56 m			3.54–3.60 m
13-OH				3.12 s
14-OH			3.03 s	
15-OH	3.18 s	3.19 s		

tetrahydroxy derivatives of guaiane-type sesquiterpenes. The ¹³C and DEPT NMR spectra of xylaguaianol A (1) (Table 2) indicated fifteen carbons consisting of three primary, six secondary (of which one was oxygenated; δ_C 68.8), three tertiary, and three oxygenated quaternary carbons (δ_C 75.3, 77.6 and 81.9). The analysis of the ¹H NMR and HSQC data (Table 1) established that 1 possessed three tertiary methyl groups (δ_H 1.08 s, δ_C 33.3; δ_H 1.18 s, δ_C 24.5; δ_H 1.25 s, δ_C 26.6), six methylene groups of which one is oxygenated (δ_H 3.28–3.33 m and 3.59–3.65 m, δ_C 68.8), and three methine

Table 2

¹³C NMR (100 MHz) spectroscopic data for compounds 1–4 (acetone-*d*₆, δ in ppm).

Position	1	2	3	4
1	55.0, CH	54.9, CH	56.6, CH	142.0, C
2	26.2, CH ₂	26.3, CH ₂	26.8, CH ₂	30.9, CH ₂
3	38.9, CH ₂	39.0, CH ₂	31.7, CH ₂	33.7, CH ₂
4	81.9, C	81.8, C	40.0, CH	39.9, CH
5	49.3, CH	49.3, CH	47.9, CH	47.3, CH
6	36.0, CH ₂	36.3, CH ₂	22.3, CH ₂	29.6, CH ₂
7	33.4, CH	32.2, CH	44.9, CH	50.3, CH
8	25.9, CH ₂	25.8, CH ₂	25.0, CH ₂	27.6, CH ₂
9	29.7 ^a , CH ₂	28.9 ^a , CH ₂	34.3, CH ₂	35.8, CH ₂
10	75.3, C	75.2, C	74.0, C	129.7, C
11	77.6, C	77.6, C	75.9, C	75.2, C
12	68.8, CH ₂	70.2, CH ₂	69.2, CH ₂	69.0, CH ₂
13	26.6, CH ₃	23.8, CH ₃	19.3, CH ₃	21.0, CH ₃
14	33.3, CH ₃	33.2, CH ₃	31.9, CH ₃	22.5, CH ₃
15	24.5, CH ₃	24.6, CH ₃	16.8, CH ₃	15.6, CH ₃

^a Overlapping with signals due to the solvent.

groups (δ_H 1.95 m, δ_C 33.4; δ_H 2.17 m, δ_C 49.3; δ_H 2.86 m, δ_C 55.0). Detailed analysis of ¹H–¹H COSY and HMBC spectra (Fig. 2) confirmed that 1 contained a guaiane-type sesquiterpene skeleton bearing four hydroxyl groups. Careful inspection of the HMBC spectrum suggested the presence of long-range correlations of H-15 to C-4 (δ_C 81.9), H-14 to C-10 (δ_C 75.3), H-13 to C-11 (δ_C 77.6), and H-13 to C-12 (δ_C 68.8) confirming that these four hydroxyls were attached to C-4, C-10, C-11 and C-12. These data indicated that 1 had the same overall skeletal structure as that of 4 β -hydroxyylaranol recently encountered in an endophytic fungus of a mangrove plant (Zeng et al., 2015). However, comparison of their $[\alpha]_D$ and NMR data suggested that they are not identical but may be stereoisomers. The relative configuration of 1 was assigned by the NOESY experiment combined with MM2 energy-minimized three-dimensional molecular modeling. The NOE corre-

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