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# Cytotoxic lanostane triterpenoids from the fruiting bodies of *Piptoporus betulinus*

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ABSTRACT

Chemical investigation of a bioactive methanolic extract of the fruiting bodies of *Piptoporus betulinus* led to the isolation of five previously undescribed lanostane triterpenoids named piptolinic acids A–E, as well as five known lanostane triterpenoids. Their structures were elucidated on the basis of 1D and 2D NMR spectroscopic and HRESIMS analysis. Piptolinic acid A with an unusual moiety (3-hydroxy-4-methoxycarbonyl-3-methylbutyryloxy) at C-3 exhibited comparable cytotoxic activity against human promyelocytic leukemia cell line HL-60 ($IC_{50}$ = 1.77 μM) and human acute monocytic leukemia cell line THP-1 ($IC_{50}$ = 8.21 μM) to those of positive control, fluorouracil ($IC_{50}$ = 6.38 and 4.41 μM, respectively).
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## 1. Introduction

*Piptoporus betulinus* (Bull.: Fr.) Karst. (Polyporaceae), commonly known as the birch polypore, is an annual wood-rotting fungus on birch trunks and branches. It is mainly distributed in the Northern regions of Europe, North America, and Asia (Pleszczyńska et al., 2016). *P. betulinus* is an edible mushroom when the fruiting bodies are young, but it was more often used as folk medicine for various medicinal purposes. For example, the fruiting bodies of *P. betulinus* were used to treat various types of cancer in some European countries (Grienke et al., 2014). Pharmacological studies also revealed that the extracts of *P. betulinus* showed various biological activities including anti-proliferation, anti-microbial and anti-inflammation (Cyranka et al., 2011). Previous phytochemical investigation of this fungus has reported some triterpenoids, a hydroquinone and an alkaloid, which exhibited anti-inflammatory, MMP inhibitory, and anti-microbial activities, respectively (Kamo et al., 2003; Wangun et al., 2004; Kawagishi et al., 2002; Schlegel et al., 2000). However, to date, the chemical constituents of the fruiting bodies of *P. betulinus* from China have not been investigated. Moreover, our preliminary experiments revealed that the methanolic extract of *P. betulinus* showed potential cytotoxic activities against several human cancer cell lines, which motivated us to discover cytotoxic compounds from this species. Here we report the isolation and identification of five previously undescribed lanostane triterpenoids named piptolinic acids A–E (**1**–**5**) (Fig. 1), along with five known lanostane triterpenoids (**6**–**10**), and their cytotoxicity evaluation against HL-60 and THP-1 human leukemia cell lines.

## 2. Results and discussion

Compound **1**, a colorless amorphous solid, showed a molecular formula of $C_{39}H_{60}O_8$ with 10 degrees of unsaturation as determined by HRESIMS at *m/z* 655.4212 $[M-H]^-$ (calcd for $C_{39}H_{59}O_8$, 655.4210). In the $^1H$ NMR spectrum (Table 1), six tertiary methyl signals ($\delta_H$ 0.59, 0.90, 1.02, 1.03, 1.05, and 1.35, each 3H, s), two secondary methyl signals [$\delta_H$ 0.96 (d, $J$ = 6.0 Hz), 1.25 (d, $J$ = 7.0 Hz)], two olefinic proton signals ($\delta_H$ 5.60, 5.75), a terminal double bond signals ($\delta_H$ 4.92, 4.88, each 1H, s), two oxygenated methine protons [$\delta_H$ 3.54 (d, $J$ = 5.2 Hz), 4.70 (brs)], as well as two methoxyl signals ($\delta_H$ 3.33, 3.63, each 3H, s), were observed. The $^{13}C$ NMR (Table 1)

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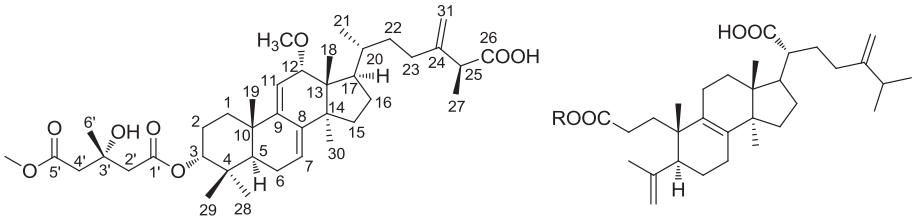
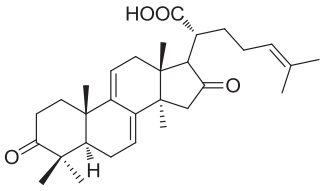


**1**



**2** R = H
**3** R = $OCH_3$



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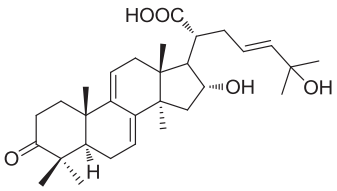
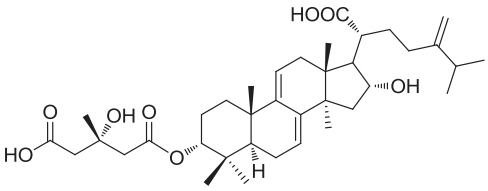


**5**



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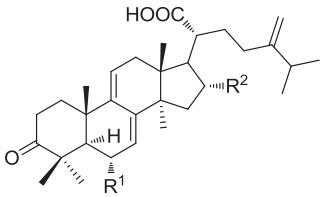
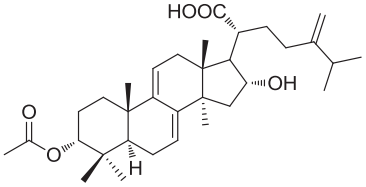


**7** $R^1$ = H, $R^2$ = H
**8** $R^1$ = H, $R^2$ = OH
**9** $R^1$ = OH, $R^2$ = OH



**10**

**Fig. 1.** Structures of compounds **1**–**10**.

spectrum showed 39 carbon signals, which were attributed to 10 methyl, 10 methylene, eight methine (including two $sp^2$ ones), and 11 quaternary carbons (three of which are characteristic of carbonyl) by HSQC spectra. Aforementioned data suggested that compound **1** is a 24-methyl-lanostane type triterpenoid. Comparison of the NMR data of **1** with those of polyporenic acid A (King et al., 1984) revealed that they had a similar structure. The differences between them are that C-3 of compound **1** is substituted by a functional group other than a hydroxyl group, and the presence of two double bonds except terminal double bond and two methoxyl groups in **1** while only a double bond except terminal double bond and no methoxyl group of polyporenic acid A. A 3-hydroxy-4-methoxycarbonyl-3-methylbutyryloxy moiety was assigned to C-3 on the basis of the HMBC correlations (Fig. 2) from H-3 to C-1′ ($\delta_C$ 170.9), from $H_3$-6′ to C-2′ ($\delta_C$ 45.0), C-3′ ($\delta_C$ 69.3) and C-4′ ($\delta_C$ 44.5), from H-2′ to C-1′, from H-4′ to C-5′ ($\delta_C$ 171.6), and from a methoxyl proton signal ($\delta_H$ 3.63) to C-5′. Two double bonds ($\Delta^{7,\,9(11)}$ conjugated diene system) were assigned by the $^1$H-$^1$H COSY correlations of H-6/H-7, H-11/H-12, and the HMBC correlations from H-7 and $H_3$-19 to C-9 ($\delta_C$ 148.6), and from H-11 and $H_3$-30 to C-8 ($\delta_C$ 142.8). A methoxyl group was attached to C-12 by the HMBC correlation from methoxyl signal ($\delta_H$ 3.33) to C-12 ($\delta_C$ 82.5). The planar structure of compound **1** was thus established. The relative configurations of compound **1** were determined by the NOESY experiment and coupling constant. First, H-3 was determined as a β-orientation based on its broad singlet-like signal ($\delta_H$ 4.70, brs). The NOESY correlations from H-12 to $H_3$-18 and $H_3$-21, indicated that the 12-MeO took an α-orientation. As the absolute configurations of polyporenic acid A had been assigned unambiguously by the single-crystal X-ray diffraction method, compound **1** shared the same skeleton with polyporenic acid A and its absolute configurations except moiety at C-3 were thus tentatively determined as depicted.

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