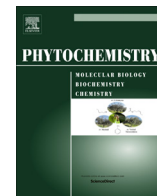




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## Cytotoxic sesquiterpenes from the endophytic fungus *Pseudolagarobasidium acaciicola*

Mario Wibowo<sup>a</sup>, Vilailak Prachyawarakorn<sup>b</sup>, Thammarat Aree<sup>c</sup>, Chulabhorn Mahidol<sup>a,b</sup>, Somsak Ruchirawat<sup>a,b,d</sup>, Prasat Kittakoop<sup>a,b,d,\*</sup>

<sup>a</sup> Chulabhorn Graduate Institute, Chemical Biology Program, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand

<sup>b</sup> Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand

<sup>c</sup> Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

<sup>d</sup> Center of Excellence on Environmental Health and Toxicology (EHT), CHE, Ministry of Education, Bangkok, Thailand

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## ABSTRACT

Twenty previously unknown compounds and two known metabolites, merulin A and merulin D, were isolated from the endophytic fungus *Pseudolagarobasidium acaciicola*, which was isolated from a mangrove tree, *Bruguiera gymnorrhiza*. Structures of the 20 compounds were elucidated by analysis of spectroscopic data. The absolute configuration of seven of these compounds was addressed by a single crystal X-ray analysis using CuK $\alpha$  radiation and an estimate of the Flack parameter. Three compounds also possessed a tricyclic ring system. Terpene endoperoxides isolated exhibited cytotoxic activity, while those without an endoperoxide moiety did not show activity. The endoperoxide moiety of sesquiterpenes has significant impact on cytotoxic activity, and thus is an important functionality for cytotoxicity. One terpene endoperoxide displayed potent cytotoxic activity (IC<sub>50</sub> 0.28  $\mu$ M), and selectively exhibited activity against the HL-60 cell line.

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## 1. Introduction

Endophytic fungi symbiotically live in plant tissues, and they are important sources of bioactive compounds (Kusari et al., 2013; Tan and Zou, 2001). Endophytic fungi from Thai medicinal plants were isolated, and chemical investigation of these fungi led to the isolation of several bioactive metabolites (Chomcheon et al., 2010, 2009; Senadeera et al., 2012). Recently, the isolation of novel tricyclic and spirobicyclic compounds (**1** and **2**) and (nor)sesquiterpene endoperoxides **3–6** was communicated, i.e. merulin or steperoxide (Fig. 1), from the endophytic fungus *Pseudolagarobasidium acaciicola*, which was isolated from a mangrove tree, *Bruguiera gymnorrhiza* (Wibowo et al., 2014). Unique structures of **1** and **2** were highlighted as novel natural products isolated in 2014 (Hill and Sutherland, 2014). Herein, the isolation and cytotoxic activity of twenty new compounds (**7–26**)

and two known sesquiterpenes **27** and **28** from the endophytic fungus *P. acaciicola* are reported.

## 2. Results and discussion

2.1. Structure elucidation of new fungal metabolites (**7–26**)

Isolation of a broth extract of the fungus *P. acaciicola* gave twenty new compounds (**7–26**), together with known metabolites, merulin A or steperoxide B (**27**) and merulin D (**28**) (Chokpaiboon et al., 2011, 2010; Li et al., 2011; Liu et al., 2010).

Acaciicolide A (**7**), C<sub>15</sub>H<sub>22</sub>O<sub>3</sub>, had an IR absorption 1716 cm<sup>-1</sup> of a carbonyl group. The <sup>1</sup>H NMR spectrum of **7** exhibited signals of three singlet methyls, five methylene groups, an olefinic proton, and an oxygenated methine, while <sup>13</sup>C NMR and DEPT spectra had fifteen signals attributable to three methyl, five methylene, two methine, and five quaternary carbons. The <sup>1</sup>H–<sup>1</sup>H COSY spectrum of **7** established partial structures of H<sub>2</sub>-1/H-2, H-4/H<sub>2</sub>-5, and H<sub>2</sub>-9/H<sub>2</sub>-10. Its HMBC spectrum also showed correlations from: H<sub>2</sub>-9 to C-7, C-8, and C-11; H<sub>2</sub>-10 to C-6, C-8, and C-11;

\* Corresponding author at: Chulabhorn Research Institute, Kamphaeng Phet 6 Road, Laksi, Bangkok 10210, Thailand.

E-mail address: [prasat@cri.or.th](mailto:prasat@cri.or.th) (P. Kittakoop).

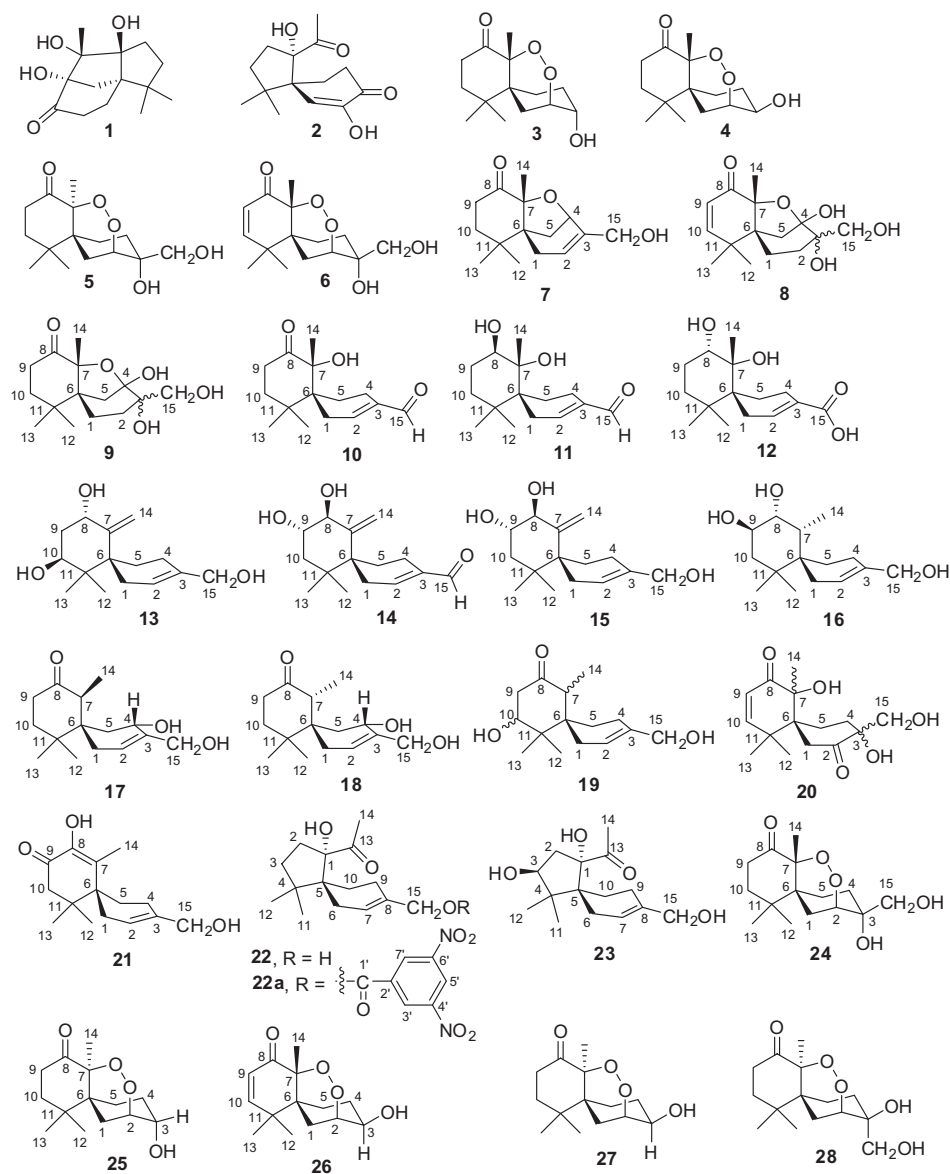


Fig. 1. Metabolites 1–28 isolated from the fungus *P. acaciicola*.

H<sub>3</sub>-12 and H<sub>3</sub>-13 to C-6, C-10, and C-11; and H<sub>3</sub>-14 to C-6, C-7, and C-8, establishing a partial structure of a six-membered ring with a C-8 ketone and a geminal dimethyl group at C-11. The presence of a cyclohexene spiro-attached to a six-membered ring was evident from the HMBC correlations of: H<sub>2</sub>-1 to C-5, C-6, C-7, and C-11; H-2 to C-4, C-6, and C-15; H-4 to C-2, C-6, C-7, and C-15; and H<sub>2</sub>-5 to C-1, C-6, C-7, and C-11. A hydroxymethyl group in **7** was positioned at C-3 based on the HMBC correlation from H<sub>2</sub>-15 to C-2, C-3, and C-4. The <sup>13</sup>C resonances of C-4 ( $\delta_c$  70.6) and C-7 ( $\delta_c$  88.8) indicated that both C-4 and C-7 were attached to an oxygen atom. A molecular formula, C<sub>15</sub>H<sub>22</sub>O<sub>3</sub>, and the HMBC correlation from H-4 to C-7 suggested that C-4 was linked, through an ether bond, to C-7. The structure of **7** was finally confirmed by a single crystal X-ray analysis using CuK $\alpha$  radiation together with determining the Flack parameter (Parsons et al., 2013), which also established the absolute configuration of 4*R*, 6*R*, and 7*R* in **7** (ORTEP plot in Fig. 2). Acaciicolide A (**7**) was identified as (5*aR*,9*aR*)-3-(hydroxymethyl)-6,6,9*a*-trimethyl-6,7,8,9*a*-tetrahydro-2*H*-2,5*a*-methanobenzo[*b*]oxepin-9(5*H*)-one, and the assignment of <sup>1</sup>H and <sup>13</sup>C resonances in **7** is shown in Table 1.

Acaciicolide B (**8**), C<sub>15</sub>H<sub>22</sub>O<sub>5</sub>, had similar <sup>1</sup>H and <sup>13</sup>C NMR spectra (Table 1) to those of **7**. Analysis of spectroscopic data indicated that H<sub>2</sub>-9/H<sub>2</sub>-10 in **7** was replaced by a double bond in **8** and that an olefinic H-2 in **7** was reduced to methylene in **8**. The <sup>13</sup>C resonance of C-8 ketone was upfield shifted from  $\delta_c$  212.2 in **7** to  $\delta_c$  202.2 in **8**, supporting the presence of an  $\alpha,\beta$ -unsaturated ketone in **8**. The molecular formula from MS data indicated that **8** had two additional oxygen atoms, as compared to **7**. The <sup>13</sup>C resonance ( $\delta_c$  100.1) of C-4 in **8** implied that C-4 was a hemiketal group, while the C-3 resonance ( $\delta_c$  72.3) in **8** suggested that C-3 was attached to an oxygen atom. Based on these data, the structure of **8** was established. Acaciicolide B (**8**) should have the same biosynthetic origin as that of **7**; therefore, it is assumed that both **7** and **8** have the same configuration at C-4 and C-7. However, the C-3 configuration in **8** could not be determined upon available data. Acaciicolide B (**8**) was identified as (5*aR*)-2,3-dihydroxy-3-(hydroxymethyl)-6,6,9*a*-trimethyl-4,5,6,9*a*-tetrahydro-2*H*-2,5*a*-methanobenzo[*b*]oxepin-9(3*H*)-one.

Acaciicolide C (**9**), C<sub>15</sub>H<sub>24</sub>O<sub>5</sub>, had comparable <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data (Table 1) to those of **8**. Careful analysis of

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