



Two new bioactive iridoids from *Rothmannia wittii*



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ABSTRACT

The first reported study of the isolation and identification of compounds from the bark and fruit of *Rothmannia wittii* yielded two new iridoids, 6 β -hydroxy-10-*O*-acetylgenipin (**1**) and 10-*O*-acetylmacrophyllide (**2**) together with six known iridoids; 6 β -hydroxygenipin (**3**), genipin (**4**), garjasmine (**5**), cerbinol (**6**), and mixture of β -gardiol (**7**) and α -gardiol (**8**); benzoic acid (**9**); vanillic acid (**10**); and stigmasterol (**11**). Their structures were elucidated by spectroscopic methods. Iridoid **1** showed antimycobacterial activity against *Mycobacterium tuberculosis* with a MIC value of 12.50 μ g/mL. Iridoid **2** showed cytotoxicity against the NCI-H187 cancer cell line with an IC₅₀ value of 6.82 μ g/mL. In addition, **2** and **5** exhibited weak cytotoxic activity against KB and MCF-7 cell lines, while **4** was active against the NCI-H187 cancer cell line.

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1. Introduction

Rothmannia wittii (Craib) Bremek. (RUBIACEAE) is a tree of 4–10 m in height and found in deciduous dipterocarp and mixed deciduous forest of Thailand. It is a Thai traditional medicinal plant and called “Muk Mo” in Thai. It has been used for venereal disease treatment and as an anti-fever agent [1]. However, the phytochemical study of the bark and fruit of this plant has not been reported. We report herein the first isolation and identification of the chemical constituents from the bark and fruits of *R. wittii*.

2. Results and discussion

The *n*-hexane and EtOAc extracts obtained from the bark and the MeOH extract from the fresh fruits of *R. wittii* were separated on silica gel column chromatography to yield two new iridoids, 6 β -hydroxy-10-*O*-acetylgenipin (**1**) and 10-*O*-acetylmacrophyllide (**2**), and nine known compounds. Their structures were identified using physical and spectroscopic data (¹H NMR, ¹³C NMR and 2D NMR) as well as comparing the data with those reported for the known compounds in the literature to be 6 β -hydroxygenipin (**3**) [2], genipin (**4**) [3,4], garjasmine

(**5**) [5], cerbinol (**6**) [6], β -gardiol (**7**), α -gardiol (**8**) [5], benzoic acid (**9**), vanillic acid (**10**) [7] and stigmasterol (**11**) [8] as shown in Fig. 1.

Compound **1** was obtained as a colourless viscous liquid. The molecular formula (C₁₃H₁₆O₇) was deduced from the HR-ESI-TOF-MS, *m/z* 307.0798 [M + Na]⁺ (calcd for C₁₃H₁₆O₇ + Na, 307.0794), indicating 6 degrees of unsaturation. The UV spectrum showed absorption maximum at 239 nm which correspond to those of iridoids, genipin [9] and 10-acetylgenipin skeletons [10]. The IR spectrum showed the presence of hydroxyl (3379 cm⁻¹), ester (1730 cm⁻¹), α,β -unsaturated ester (1676 cm⁻¹), and alkene (1629 cm⁻¹) functionality. The ¹H NMR spectrum of **1** showed resonances for two olefinic protons at δ 7.56 (1H, s, H-3) and 5.83 (1H, brs, H-7), oxygenated methylene protons at δ 4.75 (2H, m, H-10), two oxygenated methine protons at δ 4.72 (1H, d, *J* = 8.4 Hz, H-1) and 4.53 (1H, m, H-6), two methine protons at δ 2.95 (1H, m, H-5) and 2.78 (1H, m, H-9), methoxy protons at δ 3.75 (3H, s, OMe-11) and acetyl protons at δ 2.09 (3H, s, MeCOO-10). The ¹³C NMR and HMQC spectra showed resonances for alkene carbons at δ 155.0 (C-3), 142.4 (C-8), 132.4 (C-7) and 109.9 (C-4), oxygenated carbons at δ 98.3 (C-1) and 82.8 (C-6), methine carbons at δ 48.9 (C-9) and 46.8 (C-5), an oxygenated methylene carbon at δ 63.3 (C-10), carbonyl carbon at δ 170.8 (C-11) and a methoxy group at δ 52.1 which agreed well with those of the related iridoid, 6 β -hydroxygenipin [2]. The HMBC spectrum of **1** displayed correlations of H-1 with C-5 and C-8; H-3 with C-1, C-4, C-5 and the carbonyl (C-11); H-5 with C-1, C-3, C-4, C-6, C-9 and the carbonyl (C-11); H-6 with C-8; H-7 with C-5, C-6, C-8, C-9, and C-10; H-9 with C-1, C-5, C-6, C-7 and C-8; H-10 with C-7, C-8, C-9 and the carbonyl of acetate group (COO-10); OMe with C-11; and methyl protons of

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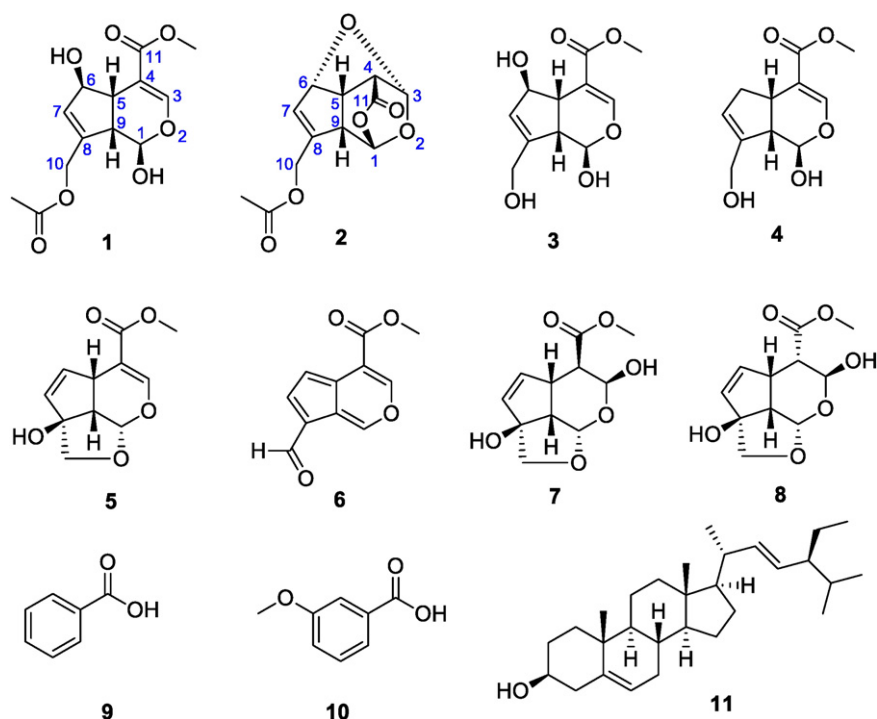


Fig. 1. Structures of isolated compounds 1–11.

acetate group (MeCOO-10) with the carbonyl carbon (COO-10) confirming the structure of **1** (Fig. 2).

The relative configuration of **1** was assigned from the NOESY and coupling constant. The NOESY spectrum showed correlations of H-1 with H-9 and 10; H-5 with H-9; and H-7 with H-6 and 10. The NOESY correlation between H-5 and H-9 revealed their *syn* relationship. Further, the absence of a NOESY correlations between H-5 and H-6 indicated the opposite (*anti*) orientation of these protons. The large coupling constant of H-1 with H-9 (8.4 Hz) indicating a *trans* disposition between these protons [2]. Moreover, the ^{13}C NMR chemical shift of the resonance associated with C-6 (δ_{C} 82.8) was comparable to an analogue, scandoside (δ_{C} 82.4) with a 6β -hydroxy orientation [11]. Hence, by analogy the configurations at C-1 and C-6 were tentatively assigned as 1*R* and 6*R*, respectively. On the basis of the above data, **1** was deduced as a new iridoid, 6β -hydroxy-10-*O*-acetylgenipin.

Compound **2** was obtained as a white amorphous solid. The molecular formula $\text{C}_{12}\text{H}_{12}\text{O}_6$ was deduced from the molecular ion peak at m/z 275.0535 $[\text{M} + \text{Na}]^+$ by the HR-ESI-TOF-MS (calcd for $\text{C}_{12}\text{H}_{12}\text{O}_6 + \text{Na}$, 275.0532), indicating 7° of unsaturation. The IR spectrum showed the presence of lactone (1768 cm^{-1}), ester (1737 cm^{-1}) and alkene (1645 cm^{-1}) functionality. The ^1H NMR spectrum of **2** showed resonances for an olefinic proton at δ 6.16 (1H, brs, H-7), three oxygenated methine protons at δ 5.83 (1H, s, H-1), 5.50 (1H, d, $J = 3.6\text{ Hz}$, H-3) and 4.97 (1H, dd, $J = 2.2, 4.4\text{ Hz}$, H-6), three methine protons at δ 3.37 (1H,

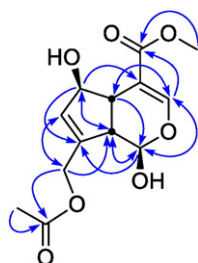


Fig. 2. Selected HMBC correlations of **1**.

m, H-5), 3.24 (1H, d, $J = 8.0\text{ Hz}$, H-9) and 3.21 (1H, dd, $J = 3.6, 5.2\text{ Hz}$, H-4), two methylene protons at δ 4.79 and 4.67 (2H, d, $J = 14.1\text{ Hz}$, H-10a and H-10b), and acetyl protons at δ 2.08 (3H, s, CH_3). ^{13}C NMR and HMQC spectra showed resonances for alkene carbons at δ 144.2 (C-8) and 133.9 (C-7); two ketal carbons at δ 102.0 (C-3) and 98.3 (C-1); an oxygenated methine carbon at δ 86.4 (C-6); three methine carbons at δ 53.4 (C-9), 48.3 (C-4) and 43.2 (C-5); an oxygenated methylene carbon at δ 62.2 (C-10); lactone carbonyl at δ 171.4 (C-11). These resonances agreed well with those of the related case-like iridoid, macrophyllide [12] except for an additional acetate group at C-10. The COSY experiments showed correlations of H-1 with H-9; H-4 with H-3 and H-5; H-5 with H-4, H-6 and H-9; H-6 with H-7; H-7 with H-10 (allylic coupling) (Fig. 3).

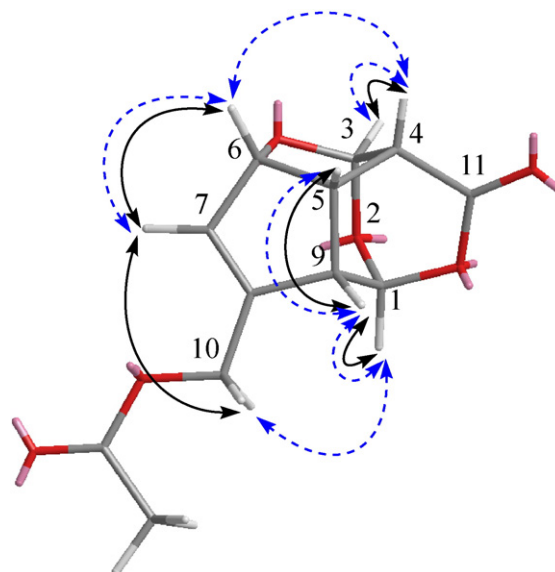


Fig. 3. COSY (arrow line) and NOESY (arrow dashed line) correlations of **2**.

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