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Antituberculosis Cycloartane Triterpenoids from *Radermachera boniana*

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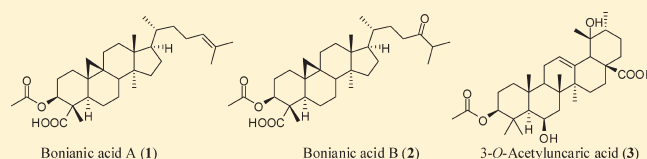
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S Supporting Information

ABSTRACT: Three new triterpenoids, bonianic acids A (1) and B (2) and 3-*O*-acetylluncaric acid (3), were isolated from the leaves and twigs of *Radermachera boniana*, together with six known compounds, ursolic acid (4), oleanolic acid (5), 3-epi-oleanolic acid (6), 3 α -*O*-acetyl- α -boswellic acid (7), ergosterol peroxide (8), and β -sitosterone (9). Ergosterol peroxide (8) and bonianic acids A (1) and B (2) exhibited significant activity against *Mycobacterium tuberculosis* H₃₇Rv strain.



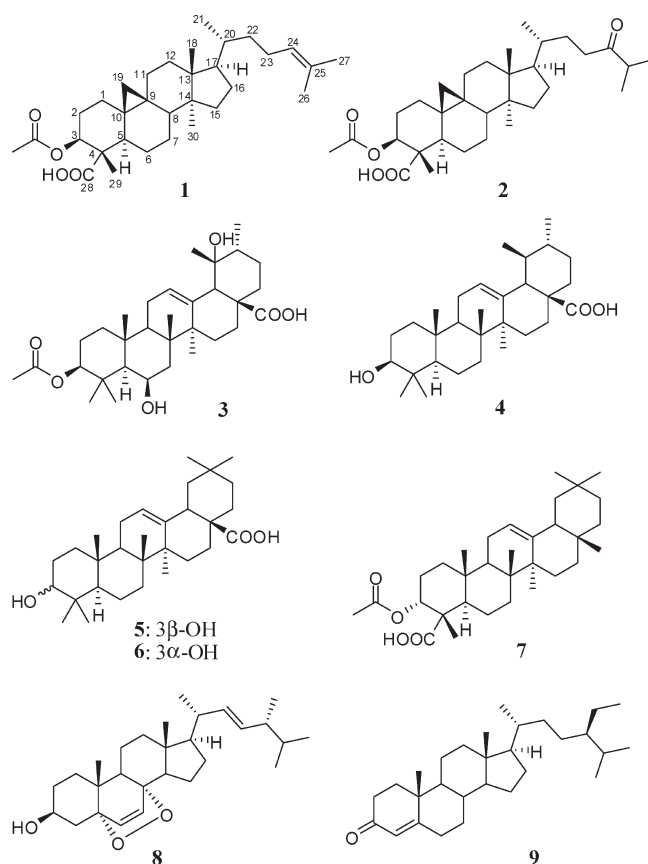
Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* that most often affects the lungs.¹ According to a 2009 estimate by the World Health Organization, 1.7 million deaths resulted from tuberculosis.² The number of new cases recorded each year continues to rise globally, especially in Africa, the Eastern Mediterranean region, and Southeast Asia. As part of our study in the search for new bioactive compounds from plants of Vietnam and Laos under the International Cooperative Biodiversity Groups (ICBG) Program,³ a plant extract (SV2933, *Radermachera boniana* Dop, Bignoniaceae) collected from the Cuc Phuong National Park was found to inhibit the growth of *M. tuberculosis* H₃₇Rv with an MIC value of 78 μ g/mL. Since a literature review showed that no chemical study of this plant had previously been reported, we selected this species for further studies. In this paper, we report the isolation and structural elucidation of three new triterpenoids (1–3), along with six known compounds, ursolic acid (4),⁴ oleanolic acid (5),⁵ 3-epi-oleanolic acid (6),⁶ 3 α -*O*-acetyl- α -boswellic acid (7),⁷ ergosterol peroxide (8),⁸ and β -sitosterone (9).⁹ Ergosterol peroxide (8) was the most active compound against the *M. tuberculosis* H₃₇Rv strain, followed by bonianic acids B (2) and A (1).

The dried and milled collected sample of the leaves and twigs of *R. boniana* (5.0 kg) was extracted with EtOAc at room temperature. The EtOAc-soluble product was purified by repeated open column chromatographies over silica gel to give compounds 1–9.

Compound 1 was obtained as a microcrystalline (mp 202–203 °C) material and was optically active, $[\alpha]_D^{25} +118$ (c 0.2, CHCl₃). In its positive HRESI mass spectrum, the pseudomolecular ion was observed at m/z 521.3615 $[M + Na]^+$, suggesting a molecular formula of C₃₂H₅₀O₄. The 1D NMR spectra (¹H and ¹³C) of 1 indicated the presence of an acetyl, six methyls (five singlets and one doublet), 11 methylenes, six methines (five sp³ and one sp²), one carboxylic carbon, and six quaternary carbons (five sp³ and one sp²). The chemical shifts of CH₂-19 (δ_C 29.6, δ_H 0.39 and 0.64, each dd, $J = 4.5$ Hz) were characteristic of a methylene function in a cyclopropane ring (Table 1).^{10ab} This observation suggested that 1 was a cycloartane triterpenoid. Analysis of the DEPT spectrum with the aid of 2D NMR determined the planar structure of 1 (Figure 1A), in which the methyl carbon C-28 was oxidized into a carboxylic group, which was established in turn by the presence of the HMBC correlation of the carboxylic carbonyl carbon at δ_C 180.5 (C-28) with H-3 at δ_H 5.23. The double bond was located between C-24 and C-25, as determined by the presence of the HMBC correlations of the proton at δ_H 5.10 (H-24) with two methyl carbons at δ_C 17.6 (C-26) and 25.7 (C-27). The cyclopropane ring formation involving C-9, C-10, and C-19 was determined by the presence of the HMBC cross-peaks of the protons at δ_H 0.39 and 0.64 (CH₂-19) to the carbons at δ_C 44.3 (C-5) and 47.5 (C-8). The acetoxy group was assigned at C-3 due to the presence of the HMBC correlations between

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H-3 and the carbonyl carbon of the acetyl group at δ_C 170.2. This was also supported by the downfield chemical shift of H-3 at δ_H 5.23.

The relative configuration of **1** was defined on the basis of analysis of ^1H – ^1H vicinal coupling constants and NOE interactions. H-3 displayed a *gauche* (5.0 Hz) and an *anti* (12.0 Hz) coupling constant, indicating its axial disposition on the A-ring. In addition, H-5 appeared as a doublet of doublets in the ^1H NMR spectrum with small (4.0 Hz) and large (12.5 Hz) coupling constants, suggesting its axial orientation. In the NOESY spectrum, the proton H_β of CH_2 -19 of the cyclopropane ring at δ_H 0.64 correlated with the protons at δ_H 1.22 (CH_3 -29) and 1.58 (H-8). The latter proton (H-8) showed a further cross-peak with the protons at δ_H 0.95 (CH_3 -18). This observation indicated that H-8, CH_2 -19, CH_3 -18, and CH_3 -29 were cofacial. In addition, CH_3 -30 at δ_H 0.90 exhibited a cross-peak with H_α of CH_2 -11 at δ_H 1.99 that suggested a boat conformation for the C-ring. The structure of **1** was finally established as drawn in Figure 1B. This new cycloartane was identified as 3β-O-acetylcycloart-24-en-28-oic acid and named bonianic acid A. Cycloartane triterpenoids bearing carboxylic functions are rare in nature.^{11a,b}

Compound **2** was obtained in microcrystalline form and was optically active, $[\alpha]_D^{25} + 68$ (c 0.4, CHCl_3). The negative HRESI mass spectrum exhibited the base peak at m/z 513.3595 $[\text{M} - \text{H}]^-$, suggesting a molecular formula of $\text{C}_{32}\text{H}_{50}\text{O}_5$. The ^1H and ^{13}C NMR spectroscopic data of **2** were similar to those of **1**, except for the presence of a carbonyl group at δ_C 215.5 and a methine function at δ_C 40.8 and δ_H 2.64 (CH -25) instead of the olefinic signals in **1**. 2D NMR analysis allowed the determination of a planar structure for **2**. The presence of a C-24 keto group was shown by the presence of the HMBC cross-peaks of the carbonyl at δ_C 215.5 (C-24) with two methyl groups CH_3 -26 and CH_3 -27 at δ_H 1.12, as well as with

the protons at δ_H 2.40 and 2.51 (CH_2 -23). The C-28 carboxylic carbon was confirmed by the ^3J -HMBC correlation with the proton at δ_H 5.22 (H-3). H-3 was further correlated to the carbon at δ_C 10.1 (C-29), the carbonyl of the acetyl group at δ_C 170.2, and the carbon at δ_C 44.2 (C-5), depicting the linkage of the acetate group to C-3.

Analyses of ^1H – ^1H vicinal coupling constants and NOE interactions showed that this compound had the same relative configuration as **1**: H-3 had a *gauche* ($J = 4.5$ Hz) and a *trans*-diaxial ($J = 12.5$ Hz) coupling constant, indicating its axial disposition on the A-ring. Similarly, H-5 was a doublet of doublets ($J = 4.0$ and 12.5 Hz) in the ^1H NMR spectrum and had a NOE interaction with H-3. An axial orientation was thus assigned for H-5. Similar to **1**, a boat conformation of the C-ring was also observed for **2**, which was determined from the presence of the NOE interaction of the protons at δ_H 0.88 (CH_3 -30) with the proton at δ_H 1.99 (H_α of CH_2 -11). Compound **2** was thus 3β-O-acetylcycloart-24-one-28-oic acid and named bonianic acid B.

Compound **3**, a microcrystalline solid, was optically active, $[\alpha]_D^{30} + 34$ (c 0.5, CHCl_3). The base peak was observed at m/z 531.3693 for $[\text{M} + \text{H}]^+$ in its positive mass spectrum, suggesting a molecular formula of $\text{C}_{32}\text{H}_{50}\text{O}_6$. The ^1H NMR spectrum exhibited signals of eight methyl groups (seven singlets and one doublet). The ^{13}C NMR and DEPT spectra showed the presence of 32 carbons, including the presence of an acetyl group. The NMR signals of **3** resembled those of ursolic acid,¹² except for the additional signal of an acetyl group and the signal of H-3 shifted downfield at δ_H 4.45. Analyses of the 2D NMR allowed to assign the structure of **3** as shown. The acetyl group at C-3 was established from the presence of the HMBC correlation of the proton at δ_H 4.45 (H-3) with the carbonyl carbon at δ_C 171.0 of the acetyl group. The β-configuration of the C-3 substituent was determined from vicinal coupling constants of H-3, which exhibited a *gauche* ($J = 4.0$ Hz) and an *anti* ($J = 11.5$ Hz) coupling constant. Similarly, H-6 appeared as a broad singlet in the ^1H NMR spectrum, indicating its equatorial orientation. Comparison of the chemical shifts of C-19 of **3** (δ_C 73.2 in CDCl_3) and ursolic acid (δ_C 72.2 in CDCl_3 +pyridine- d_5)¹² suggested the α-orientation of the C-19 OH group for **3**. The compound was determined as 3β-O-acetyl-6β,19α-diol-12-ursen-28-oic acid and was named 3-O-acetylursolic acid.

The known compounds, ursolic acid (**4**),⁴ oleanolic acid (**5**),⁵ 3-epi-oleanolic acid (**6**),⁶ 3α-O-acetyl-α-boswellic acid (**7**),⁷ ergosterol peroxide (**8**),⁸ and β-sitosterone (**9**),⁹ were also isolated and characterized. Their NMR data were compared with reported data.

The fractions obtained from the first chromatography column were evaluated for their activity against *M. tuberculosis* H₃₇Rv. Subsequent separation of the active fractions led to the isolation of the pure compound ergosterol peroxide (**8**) with an MIC value of 3.5 μM, followed by the new triterpene bonianic acid B (**2**) (MIC value: 9.9 μM) (Table 2). It is important to note that ergosterol peroxide (**8**) had no toxicity against Vero cells at 200 μM, while bonianic acid B (**2**) exhibited weak cytotoxicity with an IC₅₀ value of 74.2 μM. Furthermore, the new compound bonianic acid A (**1**) demonstrated moderate anti-TB activity with an MIC value of 34.8 μM. The other compounds showed no or weak anti-TB activity. The activity and selectivity of ergosterol peroxide (**8**) are consistent with previous reports.^{13a,b}

Table 1. NMR Data for Compounds 1–3 (CDCl₃, ¹H: 500 MHz, ¹³C: 125 MHz)

1			2		3	
position	δ _C	δ _H m (J, Hz)	δ _C	δ _H m (J, Hz)	δ _C	δ _H m (J, Hz)
1	31.1, CH ₂	1.30, m 1.74, ddd (3.5, 13.5, 13.5)	31.0, CH ₂	1.30, m 1.76, m	40.3, CH ₂	1.08, m 1.60, m
2	26.0, CH ₂	1.61, m 1.95, m	26.0, CH ₂	1.60, m 1.95, m	23.8, CH ₂	1.65, m 1.74, m
3	77.3, CH	5.23, dd (5.0, 12.0)	76.9, CH	5.22, d (4.5, 12.0)	80.9, CH	4.45, dd (4.0, 11.5)
4	52.9, C		52.9, C		38.6, C	
5	44.3, CH	2.10, dd (4.0, 12.5)	44.2, CH	2.12, dd (4.0, 12.5)	55.7, CH	0.87, m
6	22.7, CH ₂	0.98, m 1.26, m	22.7, CH ₂	0.97, m 1.24, m	68.6, CH	4.54, br s
7	25.3, CH ₂	1.17, m 1.32, m	25.3	1.17, m 1.32, m	40.7, CH ₂	1.49, br d (14.5)
8	47.5, CH	1.58, m	47.4, CH	1.58, m	39.1, C	
9	20.3, C		20.2, C		47.4, CH	1.69, m
10	24.9, C		25.0, C		36.4, C	
11	26.5, CH ₂	1.17, m 1.99, m	26.4, CH ₂	1.17, m 1.99, m	23.6, CH ₂	2.05, m
12	32.8, CH ₂	1.64, m	32.7, CH ₂	1.62, m	129.5, CH	5.38, t (3.5)
13	45.3, C		45.3, C		137.1, C	
14	48.8, C		48.8, C		41.8, C	
15	35.4, CH ₂	1.28, m	35.3, CH ₂	1.29, m	28.1, CH ₂	1.04, m 1.74, m
16	28.1, CH ₂	1.29, m 1.90, m	28.0, CH ₂	1.31, m 1.91, m	25.5, CH ₂	1.60, m 2.51, ddd (4.5, 13.5, 13.5)
17	52.2, CH	1.59, m	52.2, CH	1.59, m	47.7, C	
18	17.9, CH ₃	0.95, s	17.9, CH ₃	0.94, s	52.9, CH	2.54, s
19	29.6, CH ₂	0.39, d (4.5) 0.64, d (4.5)	29.6, CH ₂	0.42, d (4.5) 0.67, d (4.5)	73.2, C	
20	35.9, CH	1.39, m	35.7, CH	1.38, m	41.1, CH	1.39, m
21	18.3, CH ₃	0.88, d (6.5)	18.1, CH ₃	0.88, d (6.5)	26.0, CH ₂	1.31, m 1.71, m
22	36.3, CH ₂	1.04, m 1.44, m	30.1, CH ₂	1.25, m 1.77, m	37.3, CH ₂	1.65, m 1.81, m
23	25.0, CH ₂	1.88, m 2.06, m	37.5, CH ₂	2.40, ddd (6.0, 9.5, 16.5) 2.51, ddd (5.0, 10.0, 16.5)	27.9, CH ₃	0.96, s
24	125.2, CH	5.10, dd (7.0, 7.0)	215.5, C		18.3, CH ₃	1.26, s
25	130.9, C		40.8, CH	2.64, sept (7.0)	17.0, CH ₃	1.33, s
26	17.6, CH ₃	1.60, s	18.3, CH ₃	1.12, d (7.0)	17.9, CH ₃	1.05, s
27	25.7, CH ₃	1.68, s	18.4, CH ₃	1.12, d (7.0)	24.4, CH ₃	1.22, s
28	180.5, C		181.0, C		183.8, C	
29	10.1, CH ₃	1.22, s	10.1, CH ₃	1.21, s	27.4, CH ₃	1.22, s
30	19.2, CH ₃	0.90, s	19.2, CH ₃	0.88, s	16.1, CH ₃	0.94, d (6.5)
31	170.2, C		170.2, C		171.0, C	
32	21.1, CH ₃	1.99, s	21.1, CH ₃	1.99, s	21.3, CH ₃	2.06, s

EXPERIMENTAL SECTION

General Experimental Procedures. See the Supporting Information.

Plant Material. See the Supporting Information.

Extraction and Isolation. The dried and ground mixture of the twigs and leaves (5.0 kg) of *R. boniana* was extracted with EtOAc three times at room temperature. The EtOAc extract was concentrated under reduced pressure, and the residue (254 g) was purified by silica gel column chromatography (600 g), eluted with a solvent gradient of

n-hexane/EtOAc (4 L) and then EtOAc/MeOH (3 L), to yield 15 fractions. Fraction 3 (16.12 g) was purified by column chromatography over silica gel (150 g), eluted with *n*-hexane/acetone (2–40% of acetone in *n*-hexane, 1.5 L) to afford 9 (14 mg). Fraction 4 (11.91 g) was separated on a silica gel column (150 g) eluting with a gradient of *n*-hexane/EtOAc (5–30% of EtOAc in *n*-hexane, 2.1 L) to give five subfractions. Subfraction 3 (0.7 g) was separated by silica gel column chromatography (20 g), eluted with a mixture of *n*-hexane/EtOAc (5–30% of EtOAc in *n*-hexane, 280 mL), followed by recrystallization

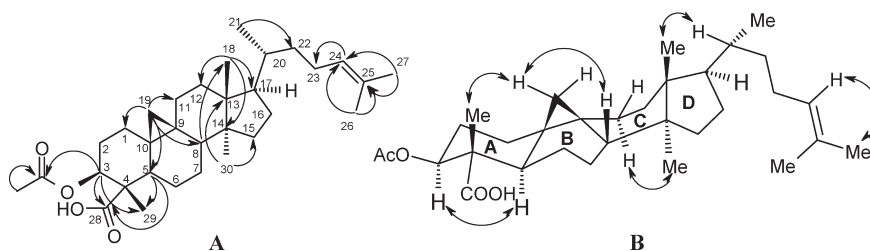


Figure 1. Key HMBC (A) and NOE (B) cross-peaks for 1.

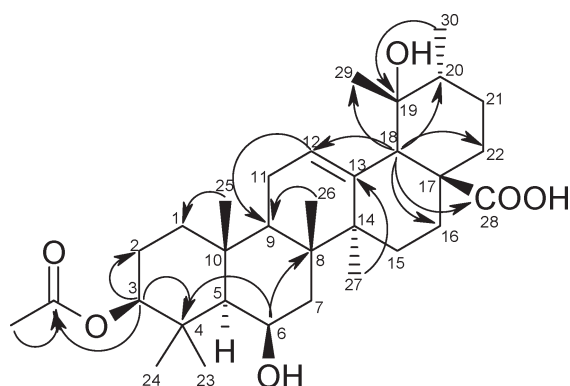


Figure 2. Selected HMBC correlations for 3.

Table 2. Anti-TB Activities of Compounds 1–9

compd	MIC (μM)	compd	MIC (μM)
1	34.8	6	>200
2	9.9	7	94.8
3	75.5	8	3.5
4	94.8	9	39.5
5	96.5	rifampin	0.14

from EtOAc to yield 1 (15 mg) and 7 (50 mg). Fraction 6 (12.36 g) was subjected to column chromatography on silica gel (150 g), eluted with a mixture of CH_2Cl_2 /acetone (5–30% of acetone in CH_2Cl_2 , 2.4 L), then crystallized from MeOH to afford 2 (13 mg), 3 (7 mg), 5 (100 mg), and 6 (20 mg). Crystallization of fraction 7 (7.0 g) from EtOAc yielded 4 (1.5 g). Fractions 8 and 9 were recombined (13.17 g) and separated on a silica gel column (150 g), eluted with a mixture of *n*-hexane/EtOAc (5–70% of EtOAc in *n*-hexane, 310 mL), to yield five subfractions. Subfraction 3 (2.0 g) was purified by column chromatography on silica gel (10–100% of EtOAc in *n*-hexane, 460 mL), followed by crystallization from a mixture of *n*-hexane/EtOAc (8:2) to give 8 (10 mg).

Bonianic acid A (1): microcrystals, mp 202–203 °C (EtOAc); $[\alpha]_D^{25} + 118$ (c 0.2, CHCl_3); IR ν_{max} 3456, 2941, 2875, 1738, 1693, 1465, 1378, 1241, 1025, 998 cm^{-1} ; HRESIMS (positive mode) m/z 521.3615 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{32}\text{H}_{50}\text{NaO}_4$, 521.3607); NMR data see Table 1.

Bonianic acid B (2): microcrystals, mp 193–194 °C (MeOH); $[\alpha]_D^{25} + 68$ (c 0.4, CHCl_3); IR ν_{max} 3498, 2933, 2869, 1727, 1628, 1469, 1377, 1264, 1030, 997 cm^{-1} ; HRESIMS (negative mode) m/z 513.3595 $[\text{M} - \text{H}]^-$ (calcd for $\text{C}_{32}\text{H}_{49}\text{O}_5$, 513.3580); NMR data see Table 1.

3-O-Acetyluncaric acid (3): microcrystals, mp 203–204 °C (MeOH); $[\alpha]_D^{30} + 34$ (c 0.5, CHCl_3); IR ν_{max} 3430, 2932, 1733, 1690, 1467, 1372, 1246, 1029, 893 cm^{-1} ; HRESIMS (positive mode) m/z 531.3693 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{32}\text{H}_{51}\text{O}_6$, 531.3686); NMR data see Table 1.

Bioassays. The details for the anti-TB bioassays are described in the Supporting Information.^{14a,b}

■ ASSOCIATED CONTENT

S Supporting Information. 1D and 2D NMR spectra of 1–3. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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