

# Lanostane-Type Triterpenes from the Mushroom *Astraeus pteridis* with Antituberculosis Activity

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Bioassay-guided fractionation of an EtOH extract of the truffle-mimicking mushroom *Astraeus pteridis* led to the isolation and identification of three new (3–5) and two known (1, 2) lanostane triterpenes and phenylalanine betaine (6). The structures of the isolates were elucidated on the basis of 1D and 2D NMR spectroscopic data, HRESIMS results, and X-ray crystallographic analysis. Compounds 5 and 1 showed moderate activity against *Mycobacterium tuberculosis* with MIC values of 34.0 and 58.0  $\mu\text{g/mL}$ , respectively.

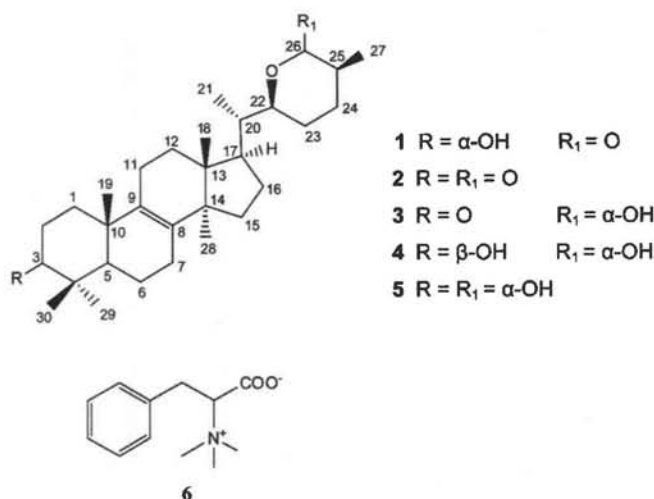
*Astraeus pteridis* (Shear) Zeller, which mimics a truffle in its early developmental stage, is an earth-star fungus in the *Astraeaceae* (phylum Basidiomycota, order Boletales). It is known only from western North America, occurring alone or in groups on the ground in forests of conifers, with which it forms symbiotic, mycorrhizal associations.<sup>1</sup> It is unpalatable because of its leathery texture and powdery spore mass.

The related *Astraeus hygrometricus* (Pers.) Morgan has been used traditionally in Chinese folk medicine as a hemostatic agent.<sup>2</sup> Several triterpenoids have been isolated from *A. hygrometricus*, but no biological activities have been investigated.<sup>3</sup> Recently heteroglycan-type polysaccharide and water-soluble glucan have been isolated from *A. hygrometricus*. The glucan showed strong splenocyte activation in a dose-dependent manner in vitro.<sup>4–6</sup>

In our search for new antituberculosis agents we have studied truffles and truffle-like fungi.<sup>7,8</sup> We report herein the isolation and structural elucidation of three new (3–5) and two known (1, 2) lanostane triterpenes plus phenylalanine betaine (6) and evaluate their inhibitory effects on *Mycobacterium tuberculosis*.

Fruit-bodies of *A. pteridis* were collected in Oregon, dried in a forced air dehydrator at 35 °C, and then ground and exhaustively extracted by maceration with 95% EtOH at room temperature. Bioassay-guided fractionation of the extract resulted in the isolation and identification of six compounds (1–6). Compounds 3, 4, and 5 were identified as new by analysis of their spectroscopic data.

Compound 3 was purified as colorless needles, and its molecular formula was assigned as  $\text{C}_{30}\text{H}_{48}\text{O}_3$  from the HRESIMS pseudo-molecular ion peak at  $m/z$  479.3501  $[\text{M} + \text{Na}]^+$ . The IR spectrum of 3 exhibited absorption bands of OH ( $3422\text{ cm}^{-1}$ ) and ketone ( $1715\text{ cm}^{-1}$ ) groups. The  $^1\text{H}$  NMR spectrum (Table 1) showed the presence of two secondary methyls ( $\delta_{\text{H}}$  0.99 and 1.14), five tertiary methyl singlets ( $\delta_{\text{H}}$  0.79, 0.94, 1.00, 1.03, and 1.13), and two oxymethines [ $\delta$  4.14 (1H, d,  $J = 11.4\text{ Hz}$ , H-22) and  $\delta$  4.81 (1H, s, H-26)]. The  $^{13}\text{C}$  NMR spectroscopic data (Table 1) revealed 30 carbon resonances, which were assigned by DEPT experiments to seven methyl, 10 methylene, six methane, and seven quaternary carbons. Three signals were characteristic for the oxygenated carbons, C-3 ( $\delta_{\text{C}}$  215.1), C-22 ( $\delta_{\text{C}}$  70.3), and C-26 ( $\delta_{\text{C}}$  97.0). The signal at  $\delta_{\text{C}}$  97.0 indicated a carbon atom bearing two oxygens,



such as a cyclic hemiacetal type. The above data suggested a lanostane-type triterpene with a structure similar to astrahygrone (2),<sup>3</sup> with an OH at C-26 instead of a carbonyl function. The location of the keto group at C-3 was confirmed by the HMBC correlations of H<sub>3</sub>-30 ( $\delta_{\text{H}}$  1.00)/H<sub>3</sub>-29 ( $\delta_{\text{H}}$  1.13) with C-3 ( $\delta_{\text{C}}$  215.1) and of H-2 ( $\delta_{\text{H}}$  2.32) with C-3 ( $\delta_{\text{C}}$  215.1) (Figure 1). The six-membered hemiacetal ring of 3 was supported by HMBC correlations (H-26/C-22, C-25, C-27; H<sub>3</sub>-27/C-24, C-25, C-26) (Figure 1). The relative configuration of 3 was established by NOESY experiment. The absence of NOESY correlations between H-22 and H<sub>3</sub>-27 indicated a  $\beta$ -orientation of H<sub>3</sub>-27, while the relative configuration of the OH group at C-26 was assigned as  $\alpha$  on the basis of a NOESY correlation between H-26 ( $\delta_{\text{H}}$  4.81) and H<sub>3</sub>-27 ( $\delta_{\text{H}}$  0.99) (Figure 1). X-ray crystallographic data confirmed the structure of 3 (Figure 2) to be a new lanostane-type triterpenoid, and it was named astrapteridone.

The molecular formula of compound 4 was deduced as  $\text{C}_{30}\text{H}_{50}\text{O}_3$  from its HRESIMS ion peak at  $m/z$  481.3638  $[\text{M} + \text{Na}]^+$ , two mass units larger than that of 3 and suggesting replacement of the carbonyl group of 3 by an OH in 4. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data of 4 were similar to those of 3 (Table 1) except for the absence of the carbonyl group at C-3 and the presence of an OH instead ( $\delta_{\text{C}}$  78.5). This was confirmed by the lack of carbonyl absorption in the IR spectrum. The location of the OH group at C-3 was confirmed by HMBC correlations of H<sub>3</sub>-29 ( $\delta_{\text{H}}$  1.24) and H<sub>3</sub>-30 ( $\delta_{\text{H}}$  1.08) with C-3 ( $\delta_{\text{C}}$  78.5) and H-3 ( $\delta_{\text{H}}$  3.46) with C-29 ( $\delta_{\text{C}}$  29.0) and C-30 ( $\delta_{\text{C}}$  16.7). Comparison of spectroscopic data

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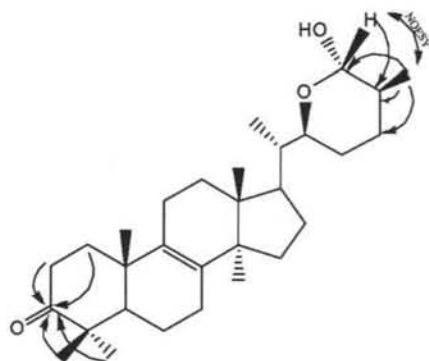
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**Table 1.**  $^1\text{H}$  (600 MHz) and  $^{13}\text{C}$  NMR (150 MHz) Spectroscopic Data of Compounds 3–5<sup>a</sup>

| position | 3 <sup>b</sup>      |  | 4 <sup>c</sup>      |  | 5 <sup>c</sup>      |  |
|----------|---------------------|--|---------------------|--|---------------------|--|
|          | $\delta_{\text{C}}$ | $\delta_{\text{H}}$ , multi, (J in Hz) | $\delta_{\text{C}}$ | $\delta_{\text{H}}$ , multi, (J in Hz) | $\delta_{\text{C}}$ | $\delta_{\text{H}}$ , multi, (J in Hz) |
| 1        | 36.5                | 1.60, m                                | 36.5                | 1.24, m, 1.72, m                       | 30.2                | 1.50, m, 2.03, m                       |
| 2        | 34.9                | 2.32, m, 2.37, m                       | 28.2                | 1.47, m, 1.88, m                       | 26.8                | 1.82, m, 2.03, m                       |
| 3        | 215.1               |  | 78.5                | 3.46, br, s                            | 75.4                | 3.63, br, s                            |
| 4        | 47.7                |  | 39.9                |  | 38.5                |  |
| 5        | 51.8                | 1.48, m                                | 51.3                | 1.20, m                                | 44.9                | 1.94, m                                |
| 6        | 20.0                | 1.39, m                                | 19.1                | 1.72, m                                | 18.9                | 1.72, m                                |
| 7        | 28.3                | 1.48, m                                | 29.1                | 1.88, m                                | 28.2                | 1.44, m                                |
| 8        | 134.2               |  | 134.8               |  | 134.5               |  |
| 9        | 135.7               |  | 135.5               |  | 135.5               |  |
| 10       | 37.4                |  | 37.7                |  | 37.7                |  |
| 11       | 21.7                | 1.85, m                                | 21.7                | 2.03, m                                | 21.7                | 2.03, m                                |
| 12       | 27.0                | 2.00, m                                | 27.2                | 2.02, m                                | 27.2                | 2.03, m                                |
| 13       | 45.0                |  | 44.9                |  | 44.9                |  |
| 14       | 50.7                |  | 50.4                |  | 50.4                |  |
| 15       | 31.9                | 1.70, m                                | 31.8                | 1.72, m                                | 31.8                | 1.72, m                                |
| 16       | 31.8                | 1.70, m                                | 31.5                | 1.72, m                                | 31.5                | 1.72, m                                |
| 17       | 47.3                | 2.20, m                                | 47.3                | 2.17, m                                | 47.3                | 2.14, m                                |
| 18       | 16.4                | 0.79, s                                | 16.3                | 0.80, s                                | 16.2                | 0.80, s                                |
| 19       | 19.0                | 0.94, s                                | 19.8                | 1.07, s                                | 19.7                | 1.07, s                                |
| 20       | 41.9                | 1.41, m                                | 42.0                | 1.47, m                                | 42.0                | 1.47, m                                |
| 21       | 13.8                | 1.14, d (6.6)                          | 13.8                | 1.16, d (6.6)                          | 13.8                | 1.14, d (6.6)                          |
| 22       | 70.3                | 4.14, d (11.4)                         | 69.8                | 4.44, d (12.0)                         | 69.8                | 4.42, d (11.4)                         |
| 23       | 23.8                | 1.30, m                                | 24.0                | 1.12, m, 1.47, m                       | 24.0                | 1.12, m, 1.47, m                       |
| 24       | 24.7                | 1.30, m                                | 25.1                | 1.12, m, 1.47, m                       | 25.1                | 1.12, m, 1.47, m                       |
| 25       | 32.4                | 1.80, m                                | 33.1                | 1.98, m                                | 33.1                | 1.98, m                                |
| 26       | 97.0                | 4.81, s                                | 96.6                | 5.28, s                                | 96.6                | 5.27, s                                |
| 27       | 16.9                | 0.99, d (6.6)                          | 17.1                | 1.13, d (7.2)                          | 17.1                | 1.12, d (6.6)                          |
| 28       | 25.2                | 1.03, s                                | 24.9                | 0.80, s                                | 24.8                | 0.80, s                                |
| 29       | 26.7                | 1.13, s                                | 29.0                | 1.24, s                                | 29.3                | 1.22, s                                |
| 30       | 21.7                | 1.00, s                                | 16.7                | 1.08, s                                | 22.9                | 0.92, s                                |

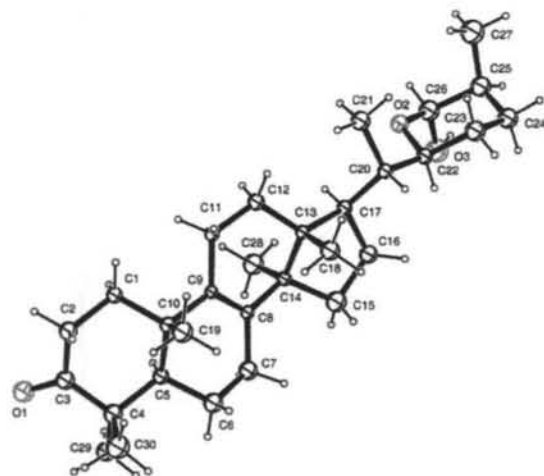
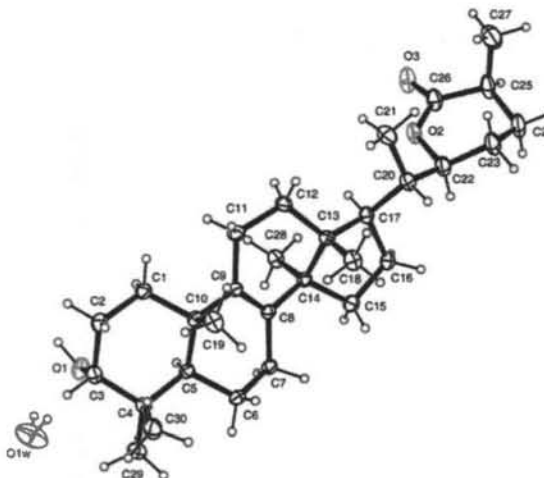
<sup>a</sup> Assignments confirmed by DEPT-135, HMQC, COSY, NOESY, and HMBC experiments. <sup>b</sup> In  $\text{C}_6\text{D}_6$ . <sup>c</sup> In  $\text{C}_5\text{D}_5\text{N}$ .

**Figure 1.** Key HMBC (→) and NOESY (↔) correlations of 3.

of 4 with literature values of astrahyrol, perenniporiol, and 15-deacetoxy-7,11-dihydropenniporiol indicated that the OH group at C-3 was in a  $\beta$ -orientation.<sup>3,9,10</sup> This was confirmed on the basis of a NOESY correlation of H-3 ( $\delta_{\text{H}}$  3.46) and H<sub>3</sub>-29 ( $\delta_{\text{H}}$  1.24). Compound 4 was named astrapteridiol, a new lanostane-type triterpene.

Compound 5 was isolated as a white, amorphous solid and showed a pseudomolecular ion peak at  $m/z$  481.3644 [ $\text{M} + \text{Na}$ ]<sup>+</sup> in the HRESIMS, corresponding to the molecular formula  $\text{C}_{30}\text{H}_{50}\text{O}_3$ . The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (Table 1) of 5 were similar to 4 except for low-frequency chemical shifts of C-2 (−1.4 ppm), C-3 (−3.1 ppm), and C-4 (−1.4 ppm) as well as a high-frequency shift of H-3 (+0.17 ppm), suggesting an  $\alpha$ -orientation of the OH group at C-3,<sup>3</sup> which was confirmed by NOESY correlation between H-3 ( $\delta_{\text{H}}$  3.63) and H<sub>3</sub>-30 ( $\delta_{\text{H}}$  0.92). Consequently, compound 5 was named 3-epi-astrapteridiol, a new lanostane-type triterpene.

Compound 6 was obtained as a pale yellow solid and showed a molecular ion peak [ $\text{M} + \text{H}$ ]<sup>+</sup> at  $m/z$  208.1294 in the HRESIMS, corresponding to the molecular formula  $\text{C}_{12}\text{H}_{17}\text{NO}_2$  and suggesting five degrees of unsaturation. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data of 6 agreed

**Figure 2.** ORTEP drawing of 3.**Figure 3.** ORTEP drawing of 1.

well with those reported for *N,N,N*-trimethylphenylalanine.<sup>11,12</sup> The absolute configuration of 6 was determined from a circular dichroism (CD) spectrum that showed a positive Cotton effect at 231 nm, indicating *S*-configuration. The CD spectrum was comparable to that reported for L-phenylalanine betaine.<sup>10</sup> Phenylalanine betaine has been reported previously from only one natural source, latex and bark of *Antiaris africana* (Moraceae).<sup>13</sup>

The spectroscopic data of 1 and 2 matched those reported for 3-epi-astrahyrol and astrahygrone, respectively.<sup>3</sup> An X-ray crystallographic analysis (Figure 3) was performed to confirm the structure of compound 1. This is the first report of the occurrence of 1 and 2 in *A. pteridis*.

Compounds 1–6 were evaluated for their activity against *M. tuberculosis*. Compounds 5, 1, and 2 showed moderate activity, with MIC values of 34.0, 58.0, and 64.0  $\mu\text{g}/\text{mL}$ , respectively, while 3, 4, and 6 were inactive (MIC of > 64  $\mu\text{g}/\text{mL}$ ). None of the isolated compounds were cytotoxic to Vero cells (African green monkey kidney fibroblasts) up to 100  $\mu\text{g}/\text{mL}$ .

## Experimental Section

**General Experimental Procedures.** Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Optical rotations were recorded on a Rudolph Research Analytical Autopol IV automatic polarimeter model 589-546. The CD spectrum was measured with a JASCO J-715 spectrometer. IR spectra were recorded on a Bruker Tensor 27 instrument.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained on a 600 MHz Varian spectrometer, with a 3 mm inverse probe using residual solvent signal as internal standard. The mass spectrometric analysis was performed on an Agilent Series 1100 SL mass spectrometer

equipped with an ESI source. X-ray crystallographic data of compounds **1** and **3** were collected at  $T = 110$  K with Mo K $\alpha$  radiation on a Nonius Kappa CCD diffractometer.

**Fungal Material.** *Astraeus pteridis* was collected by Adrian Beyerle (collection AB 1228) in Oregon, Linn County, Willamette National Forest, on October 7, 2000. The fungus was identified by Dr. James Trappe, and a voucher specimen (OSC 80838) was deposited in the Mycological Herbarium, Department of Botany and Plant Pathology, Oregon State University.

**Extraction and Isolation.** The fruit-bodies of *A. pteridis* were dried for 24 h in a forced air dehydrator at 35 °C. Powdered material (14 g) was exhaustively extracted by maceration with 95% EtOH at room temperature and concentrated under reduced pressure to yield 880 mg of residue. The crude extract was divided into MeOH-soluble and -insoluble fractions. The MeOH-soluble fraction (700 mg) was subjected to silica gel (20 g, 5–25  $\mu$ m) vacuum liquid chromatography (VLC) and eluted with hexanes, CHCl<sub>3</sub>, and CHCl<sub>3</sub>–CH<sub>3</sub>OH (90:10–0:100) to yield six fractions (A–F). Fractions C and D were combined (303 mg) and subjected to another silica gel VLC using gradient elution with hexanes–CHCl<sub>3</sub> (50:50 to 0:100) followed by CHCl<sub>3</sub>–MeOH (95:5 to 90:10) to yield 13 fractions. Fractions 3–5 were combined (170 mg) and passed over a silica gel column (10 g, 40  $\mu$ m) eluted with hexanes–CHCl<sub>3</sub>–EtOAc (3:3:1) to yield **1** (6 mg), **2** (5 mg), **3** (4 mg), **4** (9 mg), and **5** (20 mg). Crystallization of **1** and **3** was performed by using an acetone–MeOH mixture. Fraction E (146 mg) was subjected to a reversed-phase C<sub>18</sub> silica gel column (10 g) using MeOH–H<sub>2</sub>O (95:5) as a mobile phase to afford **6** (15 mg).

**3-Epi-astrahygroly (1):** colorless needles (acetone–MeOH); mp 189–190 °C;  $[\alpha]_D^{27} + 77.0$  (c 0.26, acetone); IR (neat)  $\nu_{\max}$  3495, 2935, 2875, 1732, 1456, 1380, 1185 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR (identical to those reported);<sup>3</sup> HRESIMS  $m/z$  457.3654 (calcd for C<sub>30</sub>H<sub>49</sub>O<sub>5</sub>, [M + H]<sup>+</sup>, 457.3682).

**X-ray Crystallography of 1.** A colorless crystal was obtained from acetone–MeOH (1:1), orthorhombic space group  $P2_12_12_1$ ,  $a = 7.4151(10)$  Å,  $b = 18.256(3)$  Å,  $c = 19.817(4)$  Å,  $V = 2682.6$  (8) Å<sup>3</sup>,  $Z = 4$ ,  $R = 0.046$  ( $F^2 > 2\sigma$ ),  $R_w = 0.110$  (all  $F^2$ ) for 4241 unique data having  $2\theta < 61^\circ$  and 323 refined parameters.

**Astrahygrone (2):** white, amorphous solid;  $[\alpha]_D^{27} + 65.0$  (c 0.48, acetone); IR (neat)  $\nu_{\max}$  2918, 2845, 1714, 1422, 1363, 1224, 1093 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR (identical to those reported);<sup>3</sup> HRESIMS  $m/z$  455.3509 (calcd for C<sub>30</sub>H<sub>47</sub>O<sub>5</sub>, [M + H]<sup>+</sup>, 455.3525).

**Astrapteridone (3):** colorless needles (acetone–MeOH); mp 159–160 °C;  $[\alpha]_D^{27} + 59.5$  (c 0.32, acetone); IR (neat)  $\nu_{\max}$  3422, 2925, 1715, 1456, 1373 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data see Table 1; HRESIMS  $m/z$  479.3501 (calcd for C<sub>30</sub>H<sub>48</sub>O<sub>5</sub>Na, [M + Na]<sup>+</sup>, 479.3501).

**X-ray Crystallography of 3.** A colorless crystal was obtained from acetone–MeOH (1:1), monoclinic space group  $P2_1$ ,  $a = 15.921(2)$  Å,  $b = 10.663(2)$  Å,  $c = 16.822(2)$  Å,  $\beta = 113.384(7)^\circ$ ,  $V = 2621.2$  (7) Å<sup>3</sup>,  $Z = 4$ ,  $R = 0.144$  ( $F^2 > 2\sigma$ ),  $R_w = 0.394$  (all  $F^2$ ) for 3830 unique data having  $2\theta < 46^\circ$  and 265 refined parameters.

**Astrapteridiol (4):** white, amorphous solid;  $[\alpha]_D^{27} + 32.6$  (c 0.40, acetone); IR (neat)  $\nu_{\max}$  3389, 2927, 2869, 1456, 1369, 1022 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data see Table 1; HRESIMS  $m/z$  481.3638 (calcd for C<sub>30</sub>H<sub>50</sub>O<sub>5</sub>Na, [M + Na]<sup>+</sup>, 481.3657).

**3-Epi-astrapteridiol (5):** white, amorphous solid;  $[\alpha]_D^{27} + 75.1$  (c 0.44, acetone); IR (neat)  $\nu_{\max}$  3403, 2926, 2871, 1458, 1375, 981 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data see Table 1; HRESIMS  $m/z$  481.3644 (calcd for C<sub>30</sub>H<sub>50</sub>O<sub>5</sub>Na, [M + Na]<sup>+</sup>, 481.3657).

Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

**In Vitro Antituberculosis Activity.** The antituberculosis activity was determined against *M. tuberculosis* H<sub>37</sub>Rv (ATCC27294) in the microplate Alamar Blue assay.<sup>14</sup> The minimum inhibitory concentration (MIC) was defined as the lowest concentration affecting a reduction in fluorescence of 90% relative to controls. Rifampin was included as positive quality control compound for each test. The assay was performed at the Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago.

**Cytotoxicity Assay.** Cytotoxicity against Vero cells (African green monkey fibroblasts) (ATCC CCL-81) was determined by the Promega Cell Titer 96 nonradioactive cell proliferation assay.<sup>15</sup> The IC<sub>50</sub> was defined as the reciprocal dilution resulting in 50% inhibition of Vero cells. The assay was performed at the Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago.

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**Supporting Information Available:** X-ray experimental data for **1** and **3**. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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