



Hypoxia-inducible factor-1 and nuclear factor- κ B inhibitory meroterpenoid analogues of bakuchiol, a constituent of the seeds of *Psoralea corylifolia*

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Abstract—Two new meroterpenoids, 12,13-dihydro-12,13-dihydroxybakuchiol (**2**) and (12'*S*)-bisbakuchiol C (**3**), were isolated from the seeds of *Psoralea corylifolia* L. (Fabaceae). The structures of **2** and **3** were elucidated by spectroscopic and chemical methods. Six meroterpenoids isolated from *P. corylifolia* and three semi-synthetic analogues were evaluated for HIF-1 and NF- κ B inhibition, and *O*-methyl and *O*-ethylbakuchiols (**6** and **7**) inhibited HIF-1 and NF- κ B activation without significantly decreasing the viability of the AGS and HeLa cells, respectively.

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Bakuchiol (**1**), a meroterpenoid isolated from the seeds of *Psoralea corylifolia* L. (Fabaceae), has been shown to exhibit the various biological properties including antidiabetic,^{1,2} antiinflammatory,³ antimicrobial,⁴ antioxidant,⁵ cytotoxic,⁶ and liver protective activities.^{7,8} In our search for biologically active agents of natural origin, a methanol extract of the seeds of *P. corylifolia* potently inhibited hypoxia-inducible factor-1 (HIF-1) activation induced by hypoxia (100% inhibition at 20 μ g/mL) in a HIF-1-mediated reporter gene assay in AGS human gastric cancer cells. HIF-1 controls a number of cellular events required for the adaptation of cancer cells to hypoxia. Therefore, HIF-1 inhibitors are considered as potential therapeutic agents for cancer.^{9,10} In a preliminary communication, we reported the initial phytochemical and biological investigation of this plant, with the isolation of bakuchiol (**1**) as a HIF-1 inhibitory constituent, as well as two novel dimeric meroterpenoids, bisbakuchiols A and B (**8** and **9**), which were

not active in the HIF-1 mediated reporter gene assay.¹¹ Here, we report the isolation of two new meroterpenes (**2** and **3**) and a known meroterpenoid, 12,13-dihydro-12,13-epoxybakuchiol (**4**),¹² and the preparation of bakuchiol analogues (**5**–**7**) (Fig. 1), in addition to the biological evaluation of these compounds obtained.

Compound **2** was obtained as yellow oil and shown to possess a molecular formula of C₁₈H₂₆O₃ by positive HRFABMS (*m/z* [M+Na]⁺, 313.1776). The ¹H and ¹³C NMR spectra of **2** were comparable to those of bakuchiol (**1**), suggesting that **2** is a modified bakuchiol and a meroterpenoid (Table 1). Thus, AA'XX'-type proton signals at δ_{H} 6.71 (2H, d, *J* = 8.8 Hz, H-3 and H-5) and 7.19 (2H, d, *J* = 8.8 Hz, H-2 and H-6), *trans* double bond signals at δ_{H} 6.04 (1H, d, *J* = 16.4 Hz, H-8) and 6.25 (1H, d, *J* = 16.4 Hz, H-7), vinyl group signals at δ_{H} 5.02 (overlap, H-18) and 5.91 (1H, m, H-17), and three methyl signals at δ_{H} 1.11 (3H, s, H-14), 1.15 (3H, s, H-15), and 1.20 (3H, s, H-16) were apparent. However, the absence of the proton signal of an olefinic methine (H-12) of bakuchiol (**1**) and the presence of signals at δ_{H} 3.21 (1H, dd, *J* = 2.0 and 10.8 Hz, H-12), δ_{C} 74.0 (s, C-13), and δ_{C} 80.6 (d, C-12) led to the inference that oxidative modification had occurred at the C-12 and C-13 double bond of bakuchiol

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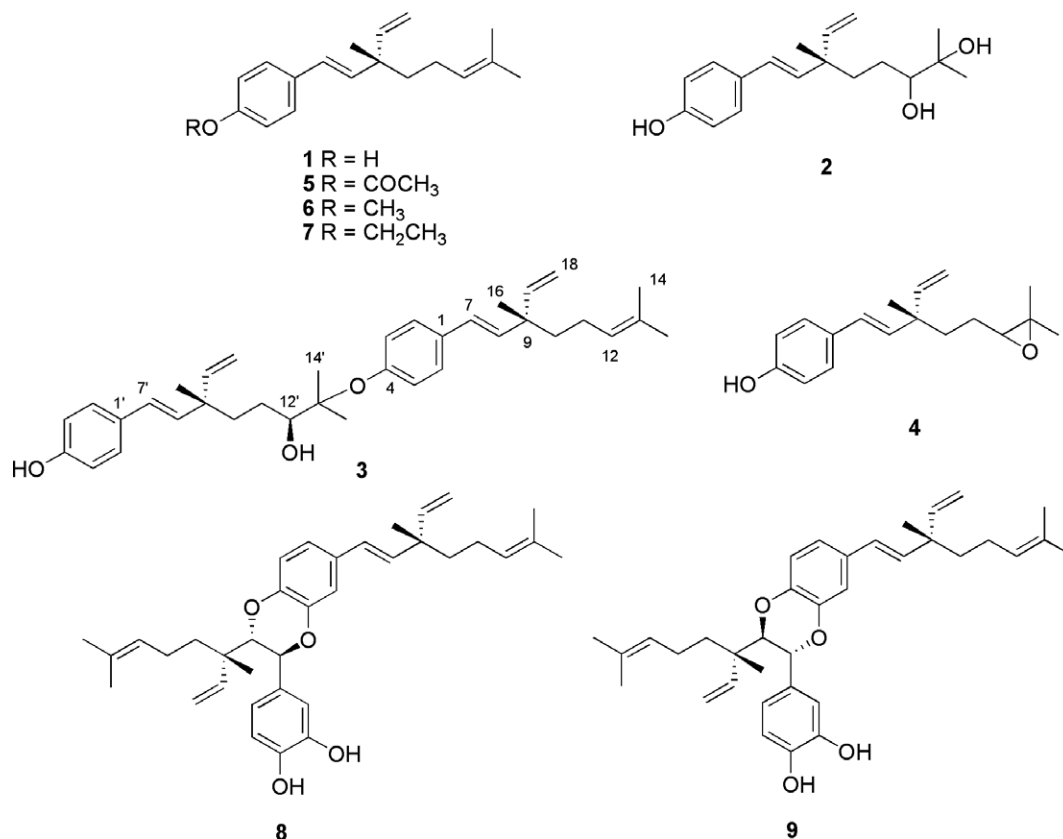


Figure 1. Structures of compounds 1–9.

(1).¹² Based on these observations and by comparison of its spectroscopic data with those of bakuchiol (1),¹² compound 2 was suggested to be a 12,13-dihydroxylated bakuchiol, confirmed by HMQC and HMBC NMR experiments. Therefore, the structure of the new compound 2 was determined to be 12,13-dihydro-12,13-dihydroxybakuchiol.¹³ Mosher's methodology was applied to determine the absolute stereochemistry of the C-12 position according to established procedures.^{14–16} However, after several attempts, Mosher's esters of 2 could not be prepared, so the absolute configuration of the C-12 position remains unknown.

Compound 3 was obtained as yellow oil and shown to possess a molecular formula of C₃₆H₄₈O₃ by positive HRFABMS (*m/z* [M+Na]⁺, 551.3498). The ¹H and ¹³C NMR spectra of 3 exhibited two characteristic sets of signals corresponding to bakuchiol (1) and compound 2, respectively (Table 1). Briefly, two sets of AA'XX'-type proton signals at δ_{H} 6.91 (2H, d, *J* = 8.4 Hz, H-3 and H-5) and 7.28 (2H, d, *J* = 8.4 Hz, H-2 and H-6); 6.78 (2H, d, *J* = 8.4 Hz, H-3' and H-5') and 7.24 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), proton signals of two *trans* double bonds at δ_{H} 6.13 (1H, d, *J* = 16.0 Hz, H-8) and 6.30 (1H, d, *J* = 16.0 Hz, H-7); 6.06 (1H, d, *J* = 16.0 Hz, H-8') and 6.28 (1H, d, *J* = 16.0 Hz, H-7'), proton signals of two vinyl groups at δ_{H} 5.90 (1H, dd, *J* = 10.4 and 17.2 Hz, H-17) and 5.04 (overlap, H-18); 5.89 (1H, dd, *J* = 10.4 and 17.2 Hz, H-17') and 5.04 (overlap, H-18') were observed

in the ¹H NMR spectrum of 3. In the aliphatic region, an oxygenated methine signal at δ_{H} 3.61 (1H, dd, *J* = 1.6 and 9.2 Hz, H-12') and six methyl signals at δ_{H} 1.20 (3H, s, H-15'), 1.21 (3H, s, H-14'), 1.22 (6H, s, H-16 and H-16'), 1.60 (3H, s, H-14), and 1.69 (3H, s, H-15) were apparent. Therefore, it was inferred that compound 3 is a dimeric meroterpene, in which bakuchiol (1) and compound 2 are connected by ether linkage, which was supported by mass fragmentations (Fig. 2). This inference was supported by 2D NMR experiments and was consistent with the molecular formula obtained. The connectivity between the two meroterpene units was determined by the analysis of ¹³C NMR data. Thus, the downfield shift of the C-13' (α carbon) signal of 3 and the upfield shifts of the C-12', 14', and 15' (β carbons) compared to the corresponding ¹³C NMR data of 2 clearly indicated the linkage of the two units (C-4–C-13').¹⁷ The absolute configurations of the C-12' and C-9 (C-9') positions were clarified by Mosher's methodology and biogenetic consideration, respectively. Mosher's esters (3s and 3r) indicated the *S* configuration at C-12', because of the positive values ($\Delta\delta_{\text{S-R}}$) obtained for H-14' and H-15' and the negative differences for H-10' and H-11' (Fig. 2).¹⁸ Based on biogenetic consideration (given the occurrence of 9*S*-bakuchiol only from nature),^{12,19} the stereochemistry of the stereogenic centers at C-9 and C-9' could be assumed. Accordingly, the structure of the new dimeric meroterpene, (12'*S*)-bisbakuchiol C (3), was elucidated.²⁰ To the best of our knowledge, (12'*S*)-bisbakuchiol C (3) is the first example

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