

Gaboroquinones A and B and 4'-O-Demethylknipholone-4'-O- β -D-glucopyranoside, Phenylanthraquinones from the Roots of *Bulbine frutescens*

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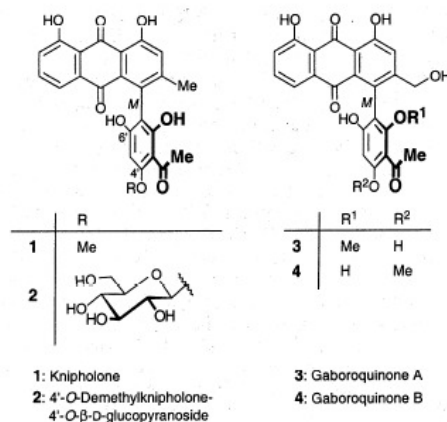
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The novel phenylanthraquinones 4'-O-demethylknipholone-4'-O- β -D-glucopyranoside (**2**) and gaboroquinones A (**3**) and B (**4**) were isolated from the African medicinal plant *Bulbine frutescens*. Biaryl **2** represents the first phenylanthraquinone glucoside, while **3** and **4** are the first side-chain-hydroxylated phenylanthraquinones. Their constitutions were determined by spectroscopic analysis, in particular by HMBC, HMQC, and ROESY NMR investigations, and by chemical transformations. The axial configurations were elucidated chemically, by deglucosylation of **2** and by side-chain deoxygenation of **3** and **4** to give the known phenylanthraquinones 4'-O-demethylknipholone (**5**), isknipholone (**6**), and knipholone (**1**), respectively, and chiroptically, by CD investigations. Compounds **2**, **3**, and **4** showed moderate to good antiparasmodial and antitrypanosomal activities in vitro.

Bulbine frutescens (L.) Wild (Asphodelaceae) is an ornamental herb that grows widely, e.g., in the city of Gaborone, Botswana. It is also used medicinally to enhance the healing of wounds.¹ As part of our continuing program to investigate secondary metabolites from marketed plants, we have reported the presence of anthraquinones, phenylanthraquinones, and isofuranonaphthoquinones in *B. capitata* and *B. abyssinica*.^{2–5} Phenylanthraquinones are a new class of antiparasmodial substances. The few that have been tested so far show activities comparable to or only slightly weaker than the commercial drug chloroquine.⁶ The co-occurring isofuranonaphthoquinones have been found to have antioxidant and also mild antiparasmodial properties.⁵ The first phenylanthraquinone, knipholone (**1**), was reported from *Kniphofia foliosa*⁷ in 1984 and has been found subsequently in other *Kniphofia*,⁸ *Bulbinella*,⁸ *Bulbine* (all Asphodelaceae),^{9–11} and *Senna* species (Fabaceae).¹² Recent reports have indicated that the genus *Bulbine* produces a greater diversity of phenylanthraquinones: eight knipholone-type phenylanthraquinones have been described so far, differing in the O-methylation pattern of the acetylphloroglucinol part and/or the oxidation state of the anthraquinone moiety.^{2–4,7,11,13,14} All of these constitutionally unsymmetric biaryls are optically active ($[\alpha]_D \neq 0^\circ$) and thus stereochemically stable. The antiparasmodial activity of the knipholones appears to be associated intrinsically with the complete molecular array of a phenylanthraquinone (including the stereogenic axis), since neither chrysophanol nor phloracetophenone possesses significant antiparasmodial activity.⁶ Structurally related, but simplified synthetic substances have also been tested and have been found to be devoid of activity (IC₅₀ values > 10 μ m).⁶ The absolute configuration of **1** as *M* was determined by quantum chemical CD calculations.¹⁵ Recently, a first,

atropo-enantioselective total synthesis was developed for knipholone and 6'-O-methylknipholone, which has the same stereo-orientation at the axis (although, for formal reasons, being *P*-configured).^{16,17} The present study on *B. frutescens* was undertaken in an attempt to search for more knipholone-type structures and to investigate their antiparasitic properties. Three such novel compounds have been isolated now (**2–4**), and this report describes their structural elucidation and antiprotozoal properties.



Results and Discussion

The roots of *B. frutescens* were successively extracted with CHCl₃ and MeOH. After evaporation of the solvent, the gummy organic extract was subjected to various fractionation and separation procedures to yield the known metabolite (*M*)-knipholone (**1**), along with the new compounds (*M*)-4'-O-demethylknipholone-4'-O- β -D-glucoside (**2**) and gaboroquinones A (**3**) and B (**4**).

Compound **2** was isolated as a red pigment. FABMS indicated a protonated molecular ion peak at *m/z* 583.1466

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