

Acridone and furoquinoline alkaloids from *Teclea gerrardii* (Rutaceae: Toddalioideae) of southern Africa

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This paper is dedicated to the memory of the late Ms Sawsan Mekki El Amin.

Abstract

The combined hexane/CH₂Cl₂ extract of the stem bark of *Teclea gerrardii* (Rutaceae: Toddalioideae) has yielded two acridone alkaloids, 3-hydroxy-1-methoxy-*N*-methylacridone (tegerrardin A) (1) and 3-hydroxy-*N*-methyl-1-(γ,γ -dimethylallyloxy)acridone (tegerrardin B) (2), three known acridones (3–5), two known furoquinolines (6,7), and the acridone precursor tecleanone (8). Arborinine (3) and evoxine (6) displayed moderate antiparasmodial activity against the CQS D10 strain of *Plasmodium falciparum*, with IC₅₀ values of 12.3 and 24.5 μ M, respectively.

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1. Introduction

Teclea gerrardii I.Verd., the Flaky cherry-orange, is an aromatic shrub or tree (to 15 m) occurring in riverine thicket and dry forest along the eastern seaboard of southern Africa, in which region it is known from South Africa, Swaziland and southern Mozambique. As a genus of about 22 species, *Teclea* Del. is restricted to Africa and the Mascarenes (Victor, 2000) and has been assigned to the subtribe Amyridinae in the subfamily Toddalioideae of the Rutaceae (Engler, 1931). Continentally, *Teclea* is the

most widely distributed of the African Toddalioideae (Verdoorn, 1926) though with most taxa localised in the tropics, only three species are known from the Flora of Southern Africa (FSA) region. *T. gerrardii* is known to the Zulu as *umboza* or *umozane* and is employed in traditional medicine; bark decoctions are taken for chest complaints (Hutchings et al., 1996). Whilst South African material of *T. natalensis* has previously been the subject of phytochemical study (Tarus et al., 2005), *T. gerrardii* has not. Accordingly, the current investigation sought chemically to profile this medicinal plant and to interpret findings in view of earlier chemotaxonomic assessments of African Toddalioideae (Waterman, 1973; Waterman et al., 1978; Dagne et al., 1988).

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2. Results and discussion

In continuation of our studies on southern African rutaceae taxa (Naidoo et al., 2005; Tarus et al., 2005, 2006; Mbala, 2006), we report the isolation of two novel acridone alkaloids, together with three known acridones, two known furoquinolines, and an aminobenzophenone, from the combined hexane/CH₂Cl₂ extract of the stem bark of *T. gerrardii*.

An HREIMS of tegerrardin A **1** showed an [M]⁺ peak at *m/z* 255.0896, corresponding to the molecular formula C₁₅H₁₃NO₃. Inspection of the IR, ¹H and ¹³C NMR spectra of **1** showed it to possess a carbonyl carbon (δ_C 180.6(C); 1639 cm⁻¹, C=O stretch), an aromatic methoxy group (δ_H 3.86 s, 3H; δ_C 55.5 (CH₃)), an *N*-methyl group (δ_H 3.73 s, 3H; δ_C 34.0 (CH₃)), and six aromatic proton signals. A correlation in the HMBC spectrum between the C-9 carbonyl resonance and a ¹H doublet signal at δ_H 8.39 (*J* = 8.1 Hz) established this as H-8, with correlations in the COSY spectrum then permitting the assignment of ¹H multiplet resonances at δ_H 7.24 and 7.65, and a ¹H doublet signal at δ_H 7.43 (*J* = 8.6 Hz), to H-7, H-6 and H-5, respectively, of the unsubstituted A ring of an acridone alkaloid. These assignments were confirmed by a correlation in the NOESY spectrum between the latter signal and that of the *N*-methyl group, which also displayed a further correlation to the more upfield signal of a pair of *m*-coupled aromatic protons (δ_H 6.23, 6.24, each *d*, *J* = 2.2 Hz), which was assigned to H-4. A further correlation in the NOESY spectrum between the methoxy group resonance and that at δ_H 6.24, assigned to H-2, but not to that of H-4, placed this at C-1, and the remaining O and H atoms are accounted for by placing a hydroxy group at C-3. As 3-hydroxy-1-methoxy-*N*-methylacridone, tegerrardin A **1** is reported here for the first time from a natural source, although it has previously been synthesized (Hlubcek et al., 1970; Su and Chou, 1994), while the closely related 1-hydroxy-3-methoxy-*N*-methylacridone and 1,3-dimethoxy-*N*-methylacridone are widespread in the Rutaceae (Dictionary of Natural Products, 2006).

The ¹H and ¹³C NMR spectra of tegerrardin B **2** were similar to those of **1** (δ_C 180.8 (C), C-9; δ_H 8.39, *d*, *J* = 8.1 Hz, H-8; δ_H 7.27, *m*, H-7; δ_H 7.71, *m*, H-6; δ_H 7.43, *d*, *J* = 8.8 Hz, H-5; δ_H 3.77 s, 3H, δ_C 34.1 (CH₃), *N*-methyl; δ_H 6.34, *d*, *J* = 2.2 Hz, H-4; δ_H 6.33, *d*, *J* = 2.2 Hz, H-2). However, the methoxy group proton and carbon resonances observed in the NMR spectra of **2** have disappeared, having been replaced by the signals of a γ,γ -dimethylallyloxy (prenyloxy) substituent (δ_H 4.61, 2H, *d*, *J* = 6.6 Hz, 2H-1'; δ_H 5.50, 1H, *m*, H-2'; δ_H 1.76, 3H, *s*, 3H-4'; δ_H 1.81, 3H, *s*, 3H-5'; δ_C 65.2, CH₂, C-1'; 118.8, CH, C-2'; 142.3, C, C-3'; 18.3, CH₃, C-4'; 25.9, CH₃, C-5'), which was placed at C-1, as before, on the basis of correlations in the NOESY spectrum between 2H-2' and H-2, but not between 2H-2' and H-4. As 3-hydroxy-*N*-methyl-1-(γ,γ -dimethylallyloxy)acridone, tegerrardin B **2** is reported here, for the first time, from either natural or

synthetic sources, although the 3-prenyloxy isomer vebilocine has previously been isolated from *Vepris bilocularis* (Wight et Arn.) Engl. (Brader et al., 1996).

The known compounds were identified as arborinine **3** (Chakravarti et al., 1953; Bergenthal et al., 1979), evoxanthine **4** (Hughes and Neill, 1949; Rasoanaivo et al., 1999), 1,3-dimethoxy-*N*-methylacridone **5** (Reisch et al., 1991), evoxine **6** (Moulis et al., 1981; Ali et al., 2001), 4,8-dimethoxy-7-(γ,γ -dimethylallyloxy)furo[2,3-*b*]furoquinoline **7** (Bessonova et al., 1974; Al-Rehaily et al., 2003) and tecleanone **8** (Casey and Malhotra, 1975; Waterman, 1975) by comparison of their physical properties and spectral data with the literature values.

As rutaceae taxa often feature as antimalarials or febrifuges in African traditional medicine (Watt and Breyer-Brandwijk, 1962; Kokwaro, 1976; Neuwinger, 2000), and the significant antiplasmodial activity of a variety of both furoquinoline and acridone alkaloids has earlier been demonstrated (Nkunya, 1992; Basco et al., 1994; Weniger et al., 2001), compounds **1–8** were tested against the CQS D10 strain of *P. falciparum*. While compounds **2** and **8** were found to be completely inactive, compounds **1**, **3** and **4–7** displayed mild activity, with IC₅₀ values of 12.3, 95.3, 70.6, 46.8, 24.5 and 132.4 μ M, respectively, against a value of 57.5 nM for CQ as positive control. At 12.3 μ M, the activity of arborinine **3** compares reasonably with values of 2.5, 5.3 and 11.1 μ M recently reported for three acridones from *Swinglea glutinosa* Merr. against a Nigerian CQS strain (Weniger et al., 2001), while the 24.5 μ M of evoxine **6** makes it more active than haplopine, at 38.8 μ M the most active of five furoquinolines tested against the Honduran CQS strain HB3 (Basco et al., 1994).

Although numerous studies on the cytotoxicity of acridones against a variety of cell lines have been carried out (Su et al., 1992; Su and Chou, 1994; Kawai et al., 1999; Teng et al., 2005), Weniger et al. (2001) remains, to our knowledge, the only investigation to date in which antiplasmodial activity and cytotoxicity were simultaneously established. Selectivity indices for the four compounds evaluated were 0.3 and 0.5 for those compounds with a methoxy group at C-4, compared to 9.0 and 7.7 for those without. As some 65% of the more than 150 acridone alkaloids identified to date (Dictionary of Natural Products, 2006) fall into this category, there is scope for much future study.

In contrast, the furoquinoline alkaloids have been much less investigated, with only one cytotoxicity study (Chen et al., 2003) to date. No inferences can thus currently be made about this group of compounds.

Whereas Dagne et al. (1988) recognized two groups within the genus *Teclea*, defined by the production of either acridone or furoquinoline alkaloids, both the current report on *T. gerrardii* and earlier ones on *T. natalensis* (Pegel and Wright, 1969; Tarus et al., 2005) indicate that at least the southern African representatives produce both alkaloid classes. As all of the constituent classes isolated in the present investigation have previously been recorded from the genus *Teclea* (Dagne et al., 1988), only minor

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