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An azole, an amide and a limonoid from *Vepris uguenensis* (Rutaceae)

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Abstract

The limonoid derivative, methyl uguenenoate, the azole, uguenenazole, and the amide, uguenenonamide, together with the known furoquinoline alkaloids flindersiamine and maculosidine, and syringaldehyde have been isolated from the root of the East African Rutaceae *Vepris uguenensis*. While methyl uguenenoate and the furoquinoline alkaloids displayed mild antimalarial activity, the azole and amide were completely inactive.

Keywords: *Vepris uguenensis*; Rutaceae; Limonoid; Azole; Amide; Furoquinoline alkaloid; Methyl uguenenoate; Uguenenzole; Uguenenonamide; Flindersiamine; Maculosidine; Antimalarial activity

1. Introduction

The genus *Vepris* Comm. ex A. Juss. comprises some 80 species of shrubs and trees, occurring primarily in tropical Africa, Zanzibar, Madagascar and the Mascarene Islands, and to a lesser extent in tropical Arabia and southwest India (Chaturvedula et al., 2003).

Ethnomedicinally, species of the genus *Vepris* are employed in the treatment of a diverse range of ailments, including pneumonia, lung diseases and kidney disorders (Hedberg et al., 1983), eye troubles, cardiac pains, coughs, colds and influenza (Chhabra et al., 1991; Gurib-Fakim et al., 1993), headache (Arnold and Gulumian, 1984), menorrhegia and infertility (Steenkamp, 2003), and as an aphrodisiac (Poitou et al., 1995), diuretic and antipyretic (Gomes et al., 1994), astringent and fortifier (Vera et al., 1990), tonic for angina and rheumatism (Gurib-Fakim et al., 1993), and both orally and externally as a treatment for malaria (Gessler et al., 1994, 1995). *Vepris uguenensis* Engl., the subject of the present study, is known is "chemchir" by the Pokot tribe of Kenya, who use it as an antimalarial (Cheplogoi, pers. comm.).

Fifteen *Vepris* species have previously been investigated: *V. ampody* H. Perr. (Kan-Fan et al., 1970), *V. bilocularis* (Wight et Arn.) Engl. (Govindachari and Sundararajan, 1961; Govindachari et al., 1964; Ganguly et al., 1966; Brader et al., 1996), *V. dainellii* (Pic. Serm.) Kokwaro (Dagne et al., 1988), *V. elliotii* (Radlk.) I. Verd. (Poitou et al., 1995), *V. fitoravina* H. Perr. (Koffi et al., 1987), *V. glomerata* (F. Hoff.) Engl. (Dagne et al., 1988), *V. heterophylla* R. Let. (Gomes et al., 1983, 1994; Moulis et al., 1994; Sidibe et al., 2001), *V. leandriana* H. Perr. (Rakotondraibe et al., 2001), *V. louisii* (Ayafor et al., 1980, 1981, 1982a, 1982b, 1982c; Ngadjui et al., 1982), *V. macrophylla* (Baker)

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I. Verd. (Koffi et al., 1987), *V. madagascarica* (Baill.) H. Perr. (Billet and Favre-Bonvin, 1973), *V. pilosa* (Baker) I. Verd. (Haensel and Cybulski, 1978), *V. punctata* (I. Verd.) W. Mziray (Chaturvedula et al., 2003), *V. sclerophylla* H. Perr. (Rasoanaivo et al., 1999) and *V. stolzii* I. Verd. (Khalid and Waterman, 1982). Although furoquinoline alkaloids are the most common isolates, acridone and quinol-2-one alkaloids, limonoids and triterpenoids have also been found (Dictionary of Natural Products on CD-ROM, 2007).

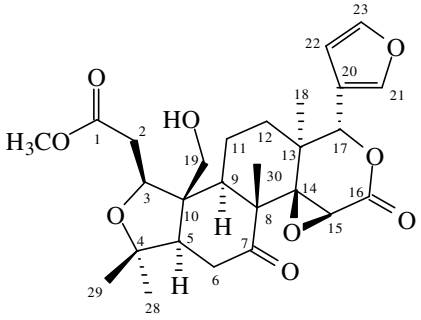
2. Results and discussion

A new limonoid derivative, methyl uguenenoate (**1**), a new azole, uguenenzole (**2**), a new amide, uguenenonamide (**3**) (Fig. 1), the known furoquinoline alkaloids flindersiamine (**4**) and maculosidine (**5**), and syringaldehyde (**6**), were isolated from the dichloromethane extract of the roots of *V. uguenensis*.

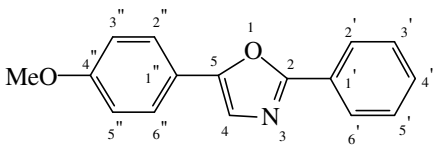
The HREIMS of methyl uguenenoate (**1**) showed a molecular ion peak at *m*/*z* 502.2203, corresponding to the molecular formula $C_{27}H_{34}O_9$ and indicating 11 double bond equivalents. Analysis of the 2D NMR spectra, and comparison with the literature values (Ng et al., 1987; Patra et al., 1988) for limonin showed that (1) also possessed the furan ring (δ_H 7.39 (1H, *s*), H-21; δ_H 6.30 (1H, *s*), H-22; δ_H 7.37 (1H, *s*), H-23; δ_C 141.1, 109.8, 143.1 (each CH), C-21, C-22, C-23; δ_C 120.3, C, C-20), 14β,15β-epoxy ring D lactone (δ_H 5.57 (1H, *s*), H-17; δ_H 3.91 (1H, *s*), H-15; δ_C 78.1 (CH), C-17; δ_C 167.5 (C), C-16; δ_C 55.4 (CH), C-15; δ_C 69.5 (C), C-14), C-7 ketone (δ_C 211.8 (C)), contracted ring A (δ_H 4.15 (1H, *m*), H-3; δ_C 74.7 (CH), C-3; δ_C 83.8 (C), C-4), and four quaternary methyl groups (δ_H 1.17, 1.10, 1.24, 1.39 (each 3H, *s*), 3H-18, 3H-28, 3H-29, 3H-30; δ_C 19.6, 24.2, 28.9, 16.9 (each CH_3), C-18, C-28, C-29, C-30) of the limonin skeleton. However, although the signals of the C-19 oxymethylene (δ_C 68.7 (CH_2)) and ester carbonyl (δ_C 173.6 (C)) carbons were still present in (**1**), they differed from the literature values; additionally, while (**1**), relative to limonin, lacked a double bond equivalent, it possessed both an additional carbon and additional oxygen atom, which appeared as the signals of a carbomethoxy group (δ_H 3.72 (3H, *s*); δ_C 52.3 (CH_3)). Methyl uguenenoate, with structure (**1**) in Fig. 1, is thus a new, albeit simple, derivative of limonin in which the ring A′ lactone has undergone cleavage to give the hydroxy-acid, followed by methylation.

The HREIMS of uguenenazole (**2**) showed a molecular ion peak at *m*/*z* 251.0948, corresponding to the molecular formula $C_{16}H_{13}NO_2$ and 11 double bond equivalents. Inspection of the ^1H, ^{13}C and 2D NMR spectra showed (**2**) to possess two aromatic rings, one monosubstituted (δ_H 8.08 (2H, *dd*, $J = 8.1$, 1.7 Hz), H-2′/6′; δ_H 7.46 (2H, *m*), (H-3′/5′); δ_H 7.44 (1H, *m*), (H-4′)) and the second *p*-methoxy disubstituted (δ_H 7.64 (2H, *d*, $J = 9.0$ Hz), H-2″/6″; δ_H 6.96 (2H, *d*, $J = 9.0$ Hz), (H-3″/5″); δ_H 3.84 (3H, *s*)). The remaining C_3HNO and three double bond equivalents were accounted for as a 2,5-disubstituted-1,3-oxazole ring, with a correlation in the NOESY spectrum between the signals of H-4 and H-2″/6″ placing the *p*-methoxy disubstituted ring at C-5. Uguenenazole, as the new 5-(4″-dimethoxyphenyl)-2-phenyl-1,3-oxazole) has structure (**2**) in Fig. 1.

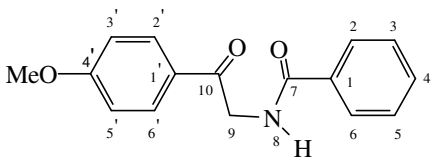
Balsoxine (5-(3,4-dimethoxyphenyl)-2-phenyl-1,3-oxazole), from *Amyris balsamifera* L. (Burke et al., 1979), and its 3,4-methylenedioxy analogue texamine, from *Amyris texana* P. Wilson (Dominguez et al., 1988), are the only compounds with the 2,5-diphenyl-1,3-oxazole ring skeleton to have been isolated to date from natural sources. Even 2,5-diaryl-1,3-oxazole compounds are uncommon, with a further 14 examples only reported in the literature. Apart



methyl uguenesonate (**1**)



unguenena zole (**2**)



unguenenonamide (**3**)

Fig. 1. Isolates from *Vepris uguenensis*.

from phorbazoles A–D, four chlorinated-2-pyrrole derivatives from a *Phorbas* species of marine sponge (Rudi et al., 1994), all of the others have come from species of the Rutaceae (Dictionary of Natural Products on CD-ROM, 2007).

The HREIMS of uguenenonamide (**3**) showed a molecular ion peak at *m/z* 269.1045, corresponding to the molecular formula $C_{16}H_{15}NO_3$ and 10 double bond equivalents. Like (**2**), (**3**) also has two aromatic rings, one monosubstituted (δ_H 7.86 (2H, *dd*, $J = 7.5$, 1.7 Hz), H-2/6; δ_H 7.45 (2H, *dd*, $J = 7.5$, 7.5 Hz, H-3/5); δ_H 7.51 (1H, *m*, H-4)) and the second *p*-methoxy disubstituted (δ_H 8.00 (2H, *d*, $J = 8.0$ Hz), H-2′/6′; δ_H 6.97 (2H, *d*, $J = 8.0$ Hz), H-3'/5'; δ_H 3.90 (3H, *s*)). Also visible in the spectra of this compound were the signals of an amide carbonyl group (δ_H 7.32 (1H, *br s*), 3364 cm^{-1}, N–H; δ_C 167.4 (C)), a ketone carbonyl group (δ_C 192.6 (C)), and an isolated methylene carbon (δ_H 4.89 (2H, *s*); δ_C 46.5 (CH_2)). The downfield position of the signals of both H-2/6 and H-2′/6′ suggested that both aromatic rings had a benzylic carbonyl group, while correlations in the NOESY spectrum between the ^1H resonances of the methylene protons and H-2′/6′ on one hand, and between those of the amide proton and H-2/6 on the other, confirmed the structure as that of (**3**) in Fig. 1.

Surprisingly, the *N*-benzoylmethylbenzamide skeleton that characterizes uguenenonamide (**3**) has been reported only once previously, in the form of muricatisine from *Oxytropis muricata* (Pall.) DC. and *O. puberula* Boriss (Demeuov et al., 1999), two Asian members of the Fabaceae. This is the first report of both an azole such as (**2**) and its amide (**3**) precursor simultaneously being found, which is surprising as construction of the azole ring by Robinson–Gabriel dehydration of 2-acylaminoketones is a standard laboratory procedure (cf. e.g. Brain and Paul, 1999; Nicolaou et al., 2004).

The known compounds were identified as flindersiamine (**4**) (Chaturvedula et al., 2003), maculosidine (**5**) (Sekiba, 1973), and syringaldehyde (**6**) (Moodley, 2001) by comparison of their physical properties and spectral data with literature values.

As species of the Rutaceae (Watt and Breyer-Brandwijk, 1962; Kokwaro, 1976; Neuwinger, 2000) and Meliaceae (MacKinnon et al., 1997) are frequently cited as antimalarials or febrifuges in African traditional medicine, and the antiplasmodial activity of a variety of both limonoids (Khalid et al., 1986; MacKinnon et al., 1997) and furoquinoline alkaloids (Basco et al., 1994) has previously been demonstrated, all six compounds were tested against the 3D7 (chloroquine susceptible, CQS) and FCM29 (chloroquine resistant, CQR) strains of *Plasmodium falciparum*. While compounds (**2**–**4**) were found to be completely inactive against both strains, (**1**), (**5**) and (**6**) displayed mild activity, with IC_{50} values of 10.4 ± 4.4, 29.2 ± 3.2, and 13.0 ± 11.5 μg ml^{-1}, and 13.8 ± 1.0, 40.4 ± 3.6, and 21.4 ± 8.2 μg ml^{-1}, against the CQS and CQR strains, respectively. No statistically significant difference between the activity against CQS and CQR strains was observed, except that of maculosidine (**5**), which was more active against the CQS 3D7 strain.

3. Experimental

3.1. General

Melting points were determined on a Kofler micro-hot stage melting point apparatus and are uncorrected. NMR spectra were recorded at room temperature on a 400 MHz Varian UNITY-INOVA spectrometer. ^1H NMR spectra were referenced against the C*H*Cl_3 signal at δ_H 7.27, and ^{13}C NMR spectra against the corresponding signal at δ_C 77.0. Coupling constants are given in Hz. Optical rotations were measured at room temperature in chloroform using a Perkin–Elmer 241 polarimeter with a 10 cm flow tube. IR spectra were recorded on a Nicolet Impact 400D Fourier-transform infrared (FT-IR) spectrometer, using NaCl windows with $CHCl_3$ as solvent against an air background. UV spectra were obtained on a Varian DMS 300 UV–visible spectrometer. HREIMS were taken on a Micromass VG 70 SEQ instrument.

3.2. Plant material

The roots of *V. uguenensis* (157 g) were collected in the Barwessa Division, Baringo District, Kenya in July 2004. The plant was identified by Mr. Ezekiel Cheboi of the Department of Natural Resources, Egerton University, Kenya. A voucher specimen (PKC 02, NH) has been retained at the Natal Herbarium, Durban.

3.3. Extraction and isolation of compounds

Air-dried, ground roots were left to stand in CH_2Cl_2 at room temperature for 5 days. The extract was decanted and concentrated to yield a crude extract (8.20 g) which was separated using column chromatography over silica gel (Merck 9385) with a hexane/EtOAc step gradient (100:0–50:50). Further purification using the given solvent systems yielded the following: hexane/EtOAc (75:25) yielded methyl uguenesonate (**1**) (13.9 mg), CH_2Cl_2/EtOAc (95/5) yielded uguenenzole (**2**) (15.9 mg), CH_2Cl_2 (100) yielded uguenenonamide (**3**) (3.6 mg) and maculosidine (**5**) (5.9 mg), hexane/EtOAc (85/15) yielded flindersiamine (**4**) (41.7 mg), and CH_2Cl_2/MeOH (99/1) yielded syringaldehyde (**6**) (5.2 mg).

3.3.1. Methyl uguenenoate (*1*)

White crystals; m.p. 118–119 °C; ν_{max} (NaCl) cm^{-1} 3405, 2927, 1737, 1702, 1436, 1366, 1271, 1106, 1030; HREIMS (70 eV) 502.2206 (calc. for $C_{27}H_{34}O_9$ 502.2203); EIMS (70 eV): *m/z* (rel. int.): 502 [M^+], 487 (2), 471 (2), 445 (9), 379 (100), 361 (6), 321 (4), 259 (13), 201 (10), 161 (6), 103 (17), 95 (11), 43 (18); $[\alpha]_D^{25}$ +82.3 ($c = 0.13$, $CHCl_3$); ^1H

NMR spectral data (400 MHz, $CDCl_3$) δ_H 7.39 (1H, *s*, H-21), 7.37 (1H, *s*, H-23), 6.30 (1H, *s*, H-22), 5.57 (1H, *s*, H-17), 4.15 (1H, *m*, H-3), 3.99 (1H, *m*, H-19b), 3.91 (1H, *s*, H-15), 3.73 (1H, *m*, H-19a), 3.72 (3H, *s*, CO_2CH_3), 2.97 (1H, *br s*, H-9), 2.61 (1H, *m*, H-2b), 2.57 (1H, *m* H-6α), 2.50 (1H, *m*, H-2a), 2.45 (1H, *m*, H-6β), 2.28 (1H, *m*, H-11α), 2.18 (1H, *m*, H-5), 1.75 (1H, *m*, H-12α), 1.70 (1H, *m*, H-11β), 1.50 (1H, *m*, H-12β), 1.39 (3H, *s*, 3H-30), 1.24 (3H, *s*, 3H-29), 1.17 (3H, *s*, 3H-18), 1.10 (3H, *s*, 3H-28); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) δ_C 211.8 (C, C-7), 173.6 (C, C-1), 167.5 (C, C-16), 143.1 (CH, C-23), 141.1 (CH, C-21), 120.3 (C, C-20), 109.8 (CH, C-22), 83.8 (C, C-4), 78.1 (CH, C-17), 74.7 (CH, C-3), 69.5 (C, C-14), 68.7 (CH_2, C-19), 55.4 (CH, C-15), 52.3 (CH_3, CO_2CH_3), 48.3 (C, C-8), 39.5 (CH_2, C-6), 39.3 (C-13), 36.9 (CH_2, C-2), 35.6 (CH, C-9), 28.9 (CH_3, C-29), 27.8 (CH_2, C-12), 24.2 (CH_3, C-28), 19.6 (CH_3, C-18), 18.5 (CH_2, C-11), 16.9 (CH_3, C-30).

3.3.2. Uguenenazole (**2**)

White crystals; m.p. 133–135 °C; (NaCl) cm^{-1} 3334, 2927, 2857, 1690, 1607, 1507, 1466, 1260, 1177, 1030; HREIMS: 251.0948 (calc. for $C_{16}H_{13}O_2N$ 251.0946); EIMS: *m/z* (rel. int.): 251 [M^+], 236 (17), 220 (28), 214 (8), 208 (5), 196 (7), 181 (6), 153 (11), 152 (100), 149 (9), 136 (8), 135 (87), 132 (8), 129 (4), 125 (4), 122 (3), 121 (30), 111 (4), 109 (4), 107 (9), 106 (5), 105 (51), 92 (13), 89 (4), 83 (4), 81 (6), 78(7), 77 (59), 76 (6), 75 (4), 74 (5), 71 (5), 69 (4), 65 (6), 64 (9), 63 (11), 57 (9), 55 (7), 51 (20), 50 (8), 43 (8), 41 (6), 40 (8); UV λ_{max} ($CHCl_3$) nm (log ε) 315 (4.51); ^1H NMR spectral data (400 MHz, $CDCl_3$) δ_H 8.08 (2H, *dd*, *J* = 8.1, 1.7 Hz, H-2′/6′), 7.64 (2H, *d*, *J* = 9.0 Hz, H-2″/6″), δ_H 7.46 (2H, *m*, H-3′/5′), 7.44 (1H, *m*, H-4′), 7.30 (1H, *s*, H-4), 6.96 (2H, *d*, *J* = 9.0 Hz, H-3″/5″), δ_H 3.84 (3H, *s*, –OCH_3); ^{13}C NMR spectral data (100 MHz, $CDCl_3$) 160.6 (C, C-2), 159.8 (C, C-4″), 151.3 (C, C-5), 130.1 (CH, C-4′), 128.8 (CH, C-3′/5′), 127.6 (C, C-1′), 126.1 (CH, C-2′/6′), 125.7 (CH, C-2″/6″), 121.9 (CH, C-4), 120.9 (C, C-1″), 114.4 (CH, C-3″/5″), 55.4 (CH_3, –OCH_3).

3.3.3. Uguenenonamide (**3**)

White crystals; m.p. 106–108 °C; ν_{max} (NaCl) cm^{-1}: 3364, 2927, 2857, 1684, 1631, 1602, 1578, 1525, 1436, 1248, 1030; HREIMS: 269.1045 (calc. for $C_{16}H_{15}O_3N$ 269.1051); EIMS: *m/z* (rel. int.): 269 [M^+], 258 (8), 182 (5), 149 (6), 136 (9), 135 (100), 107 (3), 105 (14), 92 (5), 77 (17), 57 (4), 51 (4), 43 (4), 41 (3); UV λ_{max} ($CHCl_3$) nm (log ε) 290 (4.53); ^1H NMR spectral data (400 MHz, $CDCl_3$) δ_H 8.00 (2H, *d*, *J* = 8.0, H-2′/6′), 7.86 (2H, *dd*, *J* = 7.5, 1.7 Hz, H-2/6), 7.51 (1H, *m*, H-4), 7.45 (2H, *dd*, *J* = 7.5, 7.5 Hz, H-3/5), 7.32 (1H, *br s*, N–*H*), 6.97 (2H, *d*, *J* = 8.0 Hz, H-3′/5′), 4.89 (2H, *s*, 2H-9), 3.90 (3H, *s*, –OCH_3), ^{13}C NMR spectral data (100 MHz, $CDCl_3$) 192.6 (C, C-10), 167.4 (C, C-7), 164.4 (C, C-4′), 134.0 (C, C-1), 131.7 (CH, C-4), 130.3 (CH, C-2′/6′), 128.6 (CH, C-3/5), 127.3 (C, C-1′), 127.1 (CH, C-2/6), 114.2 (CH, C-3′/5′), 55.6 (CH_3, –OCH_3), 46.5 (CH_2, C-9).

3.4. In vitro antimalarial testing

The chloroquine-sensitive 3D7 and chloroquine-resistant FCM29 strains of *P. falciparum* were maintained in continuous culture (Trager and Jensen, 1976) and used to assess the antiplasmodial activity of compounds isolated from *V. uguenensis*. The *in vitro* antiplasmodial testing was performed by use of the isotopic method as described elsewhere (Desjardins et al., 1979; Rason et al., 2007). Samples were tested in 96-well plates in triplicate at final concentrations of 64, 16, 8, 4, 2, and 0.5 μg ml^{-1}. We considered as inactive molecules with IC50 values >64 μg ml^{-1}. Student's *t*-test was used for statistical comparison between mean IC50s. Difference was significant for *P* values under 0.05.

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