

Macroline, akuammiline, sarpagine, and ajmaline alkaloids from *Alstonia macrophylla*



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ARTICLE INFO

Article history:

Received 7 August 2013

Received in revised form 4 November 2013

Available online 13 December 2013

Keywords:

Alstonia macrophylla

Apocynaceae

Indole alkaloids

NMR

X-ray crystallography

Reversal of multidrug-resistance

ABSTRACT

A total of seventeen alkaloids, comprising six macroline (including alstofoline A, a macroline indole incorporating a butyrolactone ring-*E*), two ajmaline, one sarpagine, and eight akuammiline alkaloids, were isolated from the stem-bark and leaf extracts of the Malayan *Alstonia macrophylla*. The structure and relative configurations of these alkaloids were established using NMR, MS and in several instances, confirmed by X-ray diffraction analysis. Six of these alkaloids were effective in reversing multidrug-resistance (MDR) in vincristine-resistant KB cells.

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Introduction

Plants of the genus *Alstonia* (Apocynaceae), which are shrubs or trees, are distributed over tropical parts of Central America, Africa, and Asia (Whitmore, 1973; Markgraf, 1974; Sidiyasa, 1998) and are usually rich in alkaloids. A prominent feature of the *Alstonia* alkaloids is the preponderance of the macroline unit, which abounds in the alkaloids found in plants of the genus (Kam, 1999; Kam and Choo, 2006). About six species occur in Peninsular Malaysia and several of these (local name *Pulai*) are used in traditional medicine, for example, in the treatment of malaria and dysentery (Burkill, 1966; Perry and Metzger, 1980). In Peninsular Malaysia, these plants are mainly found in secondary and primary forest from sea level to about 3000 m altitude, as well as in swampy areas (Whitmore, 1973; Sidiyasa, 1998; Middleton, 2011). Recently the structure and absolute configurations of a number of new bisindoles isolated from a sample of *A. macrophylla* Wall collected from the western coast of Peninsular Malaya (Perak) were disclosed (Lim et al., 2011, 2012, 2013). In addition, a potentially useful method for the determination of the configuration at C-20 in *E-seco* macroline-macroline bisindoles, such as perhentinine, *seco*-macralstonine, and perhentidines A–C, was also reported. This was based on comparison of the NMR chemical shifts of the bisindoles and their acetate derivatives, in addition to X-ray determination of

the absolute configuration of perhentinine and macralstonine (Lim et al., 2012). Reported herein are the isolation and structure determination of 17 new indole alkaloids (Fig. 1) from the leaf and stem-bark extracts of this plant.

Results and discussion

Compound **1** was a minor alkaloid isolated from the leaf extract of *A. macrophylla*. It was obtained as a light yellowish oil, with $[\alpha]_D^{25} -104$ (*c* 0.36, CHCl₃). The UV spectrum showed two absorption bands (227 and 285 nm) characteristic of an indole chromophore. The IR spectrum showed a sharp band at 1769 cm⁻¹ due to a lactone function. The EIMS of compound **1** had a molecular ion at *m/z* 296, and high resolution measurements yielded the molecular formula C₁₈H₂₀N₂O₂. Other notable fragment peaks observed at *m/z* 197, 182, 181, 170, and 144, are typical of macroline derivatives (Mayerl and Hesse, 1978), while the mass fragment at *m/z* 281 can be attributed to loss of a CH₃. The ¹³C NMR spectrum (Table 1) displayed a total of 18 carbon resonances, corresponding to two methyl, three methylene, eight methine and five quaternary carbons. The presence of the lactone functionality, and an oxymethylene carbon, was supported by the observed carbon signals at δ 181.0 and δ 70.7, respectively. The ¹H NMR spectrum (Table 2) showed the presence of an unsubstituted indole moiety (δ 7.11–7.49), two methyl groups corresponding to N1-Me at δ 3.64 and N4-Me at δ 2.42, and two downfield resonances at δ 4.42 (H-17 β , *t*, *J* = 8 Hz) and 4.52 (H-17 α , *dd*, *J* = 11, 8 Hz) due to the geminal

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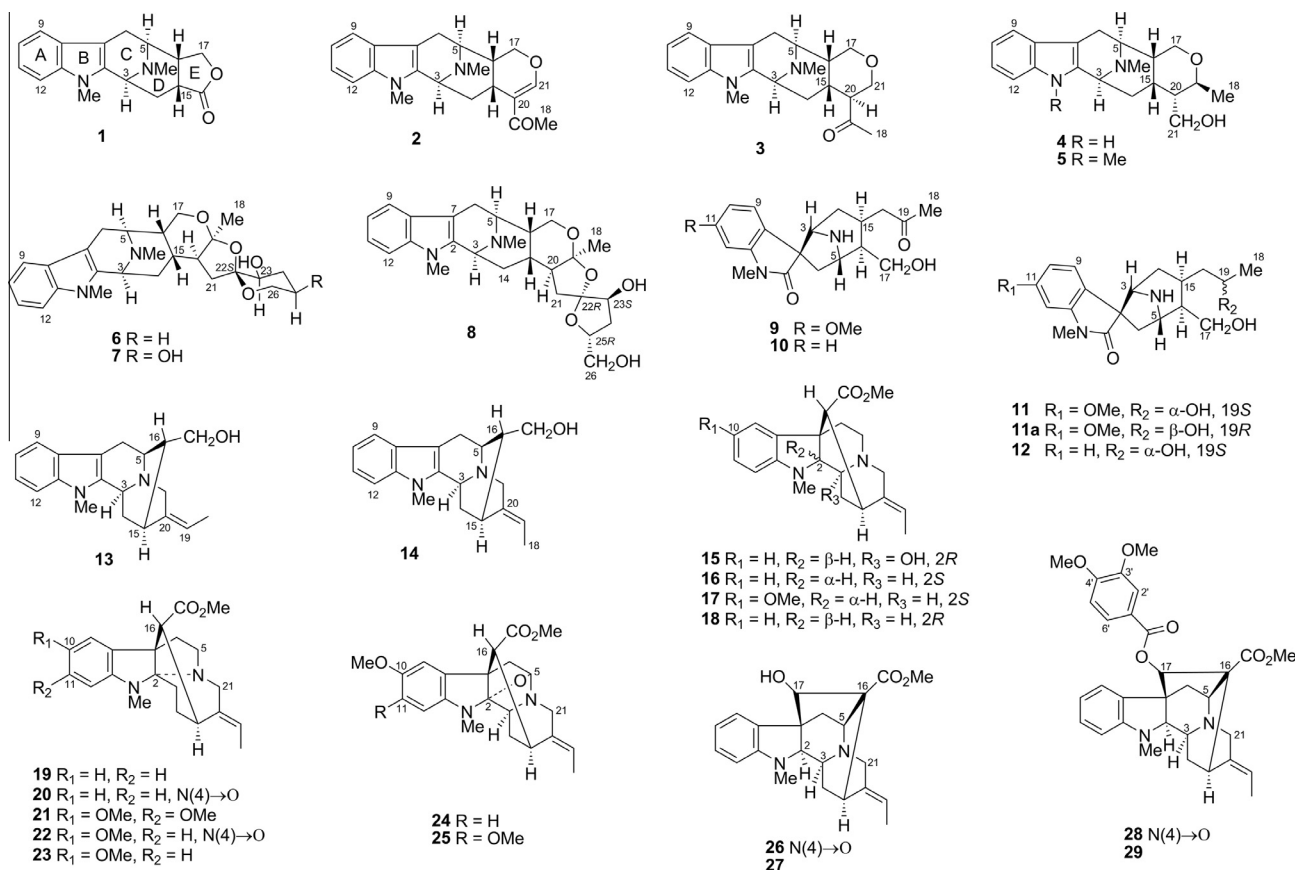


Fig. 1. Structures of compounds 1–29.

hydrogens of an oxymethylene corresponding to C-17. The COSY and HSQC data disclosed partial structures that are characteristic of a macroline-type skeleton, such as NCHCH₂ and NCHCH₂-CHCHCH₂O, corresponding to the N-4-C-5-C-6 and N-4-C-3-C-14-C-15-C-16-C-17-O fragments, respectively. The NMR spectroscopic data were suggestive of a macroline derivative, such as alstonerine (**2**). (Ratnayake et al., 1987; Ghedira et al., 1988; Kam et al., 1999), except for the absence of the typical α,β unsaturated ketone group and the associated vinyl-H, in the ring E of compound **1**. In addition, both H-17 signals in **1** were shifted downfield to δ_H 4.42 and 4.52, when compared to those in alstonerine (**2**) (δ_H 4.16 and 4.40), as well as other typical macroline alkaloids (Kam et al., 2004a; Kam and Choo, 2004a). Furthermore, the observed coupling constants for the H-17 resonances in the case of **1** differed significantly when compared to those in **2** (**1**: H-17β, t, *J* = 8 Hz; H-17α, dd, *J* = 11 and 8 Hz; **2**: H-17β, ddd, *J* = 11, 4, 2 Hz; H-17α, t, *J* = 11 Hz), indicating changes in ring E of **1** (*J*₁₇₋₁₇ = 8 Hz) compared to normal macrolines with a six-membered ring E (*J*₁₇₋₁₇ = 11 Hz) as exemplified by alstonerine (**2**). The presence of a lactone functionality as a part of ring E (a butyrolactone moiety) was deduced from the observed three-bond correlations from H-14α, H-14β, and H-17α, to the lactone carbonyl C-18 in the HMBC spectrum (Fig. 2). The relative configurations at the various stereogenic centers of **1** were established by NOESY, and were similar to those in other macroline alkaloids. Alstofoline A (**1**) is the first example of a macroline indole alkaloid incorporating a γ-butyrolactone moiety in ring E.

Compound **3** was isolated in small amounts as a light yellowish oil, with [α]_D -31 (c 0.11, CHCl₃). The IR spectrum showed a band at 1710 cm⁻¹ due to a ketone function. The presence of a ketone function was confirmed by the observed resonance at δ 208.6 in the ¹³C NMR spectrum. The ESIMS of **3** showed an [M+H]⁺ ion at

m/z 339, which analyzed for C₂₁H₂₆N₂O₂. The UV spectrum showed absorption maxima at 228 and 286 nm, which are characteristic of an indole chromophore.

The ¹H and ¹³C NMR spectroscopic data (Tables 1 and 2) showed the presence of an unsubstituted indole moiety (δ_H 7.09–7.50, δ_C 108.7–120.9), two N-methyl signals (N4-Me, δ_C 41.8, δ_H 2.29; N1-Me, δ_C 29.1, δ_H 3.61), a methyl ketone function (δ_C 208.6; δ_C 28.4, δ_H 2.12), an oxymethylene, characteristic of C-17 in macroline alkaloids (δ_C 68.6, δ_H 3.72, and 3.95), and another oxymethylene signal at δ_C 64.3 (δ_H 3.86 and 4.18). The NMR signals, assigned with the aid of COSY and HSQC, indicated that **3** is a macroline-type alkaloid. The NMR spectroscopic data resembled those of alstonerine (**2**), which was also isolated from the extract of this plant, except for the absence of signals associated with the trisubstituted C-20–C-21 double bond, such as the olefinic carbon resonances at C-20 (δ 126.5) and C-21 (δ 157.4), and the signal due to the vinylic H-21 in the ¹H NMR spectrum (δ 7.52). These resonances have in **3** been replaced by a methine at C-20 (δ_C 51.9, δ_H 1.97, m) and a methylene at C-21 (δ_C 64.3; δ_H 3.86, dd, *J* = 12.5, 3 Hz, δ_H 4.18, d, *J* = 12.5 Hz), consistent with saturation of the C-20–C-21 double bond in **3**. Less substantial changes were observed for the signals of carbons β to both carbons (C-20, C-21) in the ¹³C NMR spectrum. The configuration at C-20 can be deduced from the observed NOEs, viz., H-20/H-14β, H-18, H-21α; H-21α/H-14α, H-20, H-21β, which indicated the orientation of H-20 is α. Compound **3** is, therefore, the 20,21-dihydro derivative of alstonerine (**2**), which, while previously encountered as an intermediate compound in synthesis (Zhang and Cook, 1990), is here encountered as an optically active natural product for the first time.

Macrocarpine D (**4**) was obtained as a light yellowish oil, with [α]_D -43 (c 0.89, CHCl₃). It was isolated from the stem-bark extract of *A. macrophylla*, as well as *A. angustifolia* (Tan, 2011). The IR spectrum indicated the presence of hydroxyl and secondary amine

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