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## Short Communication

# 4-Quinolone Alkaloids Isolated from the Leaves of *Waltheria indica* (Malvaceae) and their Chemosystematic Significance

Juliane S Falcão<sup>1</sup>, Meriane P Carvalho Lima<sup>2</sup>, Anne Caroline C Gomes<sup>3</sup>, Pedro Correia<sup>4</sup>, Murilo M C Lima<sup>\*5</sup>

<sup>1</sup> Instituto de Pesquisa de Produtos Naturais, Universidade Federal do Rio de Janeiro, Rio de Janeiro-RJ, Brazil.

<sup>2,3,5</sup> Instituto Federal de Educação, Ciência e Tecnologia do Rio de Janeiro – Campus Realengo, Rio de Janeiro-RJ, Brazil.

<sup>4</sup> Faculdade de Educação, Universidade Nacional Timor Lorosa'e – Díli, Timor Leste.

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## ABSTRACT

The chemical investigation of the leaves of *Waltheria indica* (Malvaceae) afforded eight 4-quinolone alkaloids structurally related to the waltheriones: waltherione A (1), waltherione B (2), waltherione C (3), N-methyl-waltherione A (4), 5'-methoxy-waltherione A (5), N-methoxy-waltherione B (6), antidesmone (7) and 8-deoxy-antidesmone (8). Among these alkaloids, N-methoxy-waltherione A has not been described in the literature yet. The related compounds belong to an unusual class of 4-quinolones and have chemosystematic significance for the Hermannieae tribe of the Malvaceae family.

## INTRODUCTION

*Waltheria indica* L. (syn. *Waltheria americana*), a plant belonging to the Malvaceae family, is a shrub widespread in tropical and subtropical regions of the world, known as a weed of some plantations, but also occurs in small urban areas (Zongo et al., 2013). In traditional medicine of several countries, it is used against various ailments such as cancer (Jadulco et al., 2014), throat inflammation (Taveira de Jesus et al., 2009),

fungal infections (Creton et al., 2014), gingivitis (Garcia et al., 2010), conjunctivitis (Kokwaro, 2009), among others (Zongo et al., 2013). In many places of Brazil, *Waltheria indica* is commonly known as “vassourinha”, a portuguese term that means “small broom”.

The plant material for this work was collected in August 2014 at the urban area of Tombos city (Minas Gerais State, Brazil), by professors Murilo M C Lima and Eliane Carvalho, and authenticated

**\*Corresponding Author:** Murilo M C Lima

**Address:** Instituto Federal de Educação, Ciência e Tecnologia do Rio de Janeiro – Campus Realengo, Rio de Janeiro-RJ, Brazil.

**Email** ✉: [murilo.lima@ifrj.edu.br](mailto:murilo.lima@ifrj.edu.br)

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by botanic Cosme Correia dos Santos. A voucher specimen (HUEFS 72670) was deposited at the Herbarium of the Universidade Estadual de Feira de Santana for reference.

The previous chemical investigations with plants of genus *Waltheria* indicate high similarity with the chemical composition of *Melochia*, another genus of the Hermannieae tribe of Malvaceae family (Cretton et al. 2014; 2016; Jadulco et al., 2014; Erwin et al., 2014). Both genera are potential source of bioactive alkaloids, to date, cyclic peptides and an unusual class of 4-quinolone alkaloids, named as waltheriones (Hoelzel et al., 2005; Gressler et al., 2008; Lima et al., 2009; Cretton et al., 2014; 2016).

The waltheriones are structurally characterized by a 4-quinolone moiety with a methyl group in C-2 and methoxy group in C-3, divided into open-chain (e.g. alkaloids 7 and 8) and cyclized compounds (e.g. alkaloids 1-6). Among the open-chain waltheriones are included the alkaloid named antidesmone (7) and its analogues, which are chemosystematic markers of Antidesmeae tribe of the Euphorbiaceae family (Brigmann et al., 2000; Buske et al., 2002), although antidesmone has been reported in *Waltheria douradinha* (Gressler et al., 2008), *Melochia chamaedrys* (Dias et al., 2007b) and *Waltheria indica* (Cretton et al., 2014). More recently the new open-chain waltheriones E-Q, such as the cyclized waltheriones A and C were reported in *Waltheria indica* (Cretton et al., 2014; 2015; 2016). In earlier studies, only flavonoids and four cyclic peptide alkaloids, named adoutines X, Y, Y1 and Z, have been isolated and identified from *W. indica* (Maheswara et al., 2006; Pais et al., 1963, 1968; Ragasa et al., 1997).

The cyclized waltheriones contain a benzo-fused oxabicyclo [3.2.1] octene moiety, where the epoxide bridge of the bicycle can be between the

carbons C-13 and C-10, as occurs in waltheriones A (1) and B (2), unlike waltherione C (3), which presents this epoxide bridge between the carbons C-13 and C-9. The precursor of the cyclized waltheriones is the alkaloid melochinone, reported from *Melochia tomentosa*, which presents a 7-membered ring fused to the quinolinone system replacing the oxabicyclo [3.2.1] moiety (Erwin et al., 2014).

Among the cyclized waltheriones, the alkaloid waltherione A (1) was first described in *Waltheria douradinha* (Hoelzel et al., 2005), and further reported in *Waltheria brachypetala* (Lima et al., 2009), *Waltheria brachypetala* (Lima et al., 2009), *Melochia chamaedrys* (Dias et al., 2007a), *Melochia odorata* (Emille et al., 2007; Jadulco et al., 2014) and *Waltheria indica* (Cretton et al., 2015); whereas waltherione B (2) was only reported in *Waltheria douradinha* (Gressler et al., 2008), and the waltherione C (3) was reported in *Melochia odorata* (Jadulco et al., 2014), *Melochia umbellata* (Erwin et al., 2014) and *Waltheria indica* (Cretton et al., 2015).

## 2. MATERIAL AND METHODS

### 2.1. Extraction and isolation

The dried ground powdered leaves (500g) of *Waltheria indica* were exhaustively extracted by static maceration with MeOH (4 x 6L, 72 hours each, at room temperature). The resulting methanolic extract was filtered and concentrated in rotary evaporator under vacuum to obtain the crude methanolic extract of leaves (85g). This extract was suspended in MeOH:H<sub>2</sub>O (1:3) and successively partitioned with hexane and CH<sub>2</sub>Cl<sub>2</sub> to provide the hexane and CH<sub>2</sub>Cl<sub>2</sub> phase from leaves, WIH (3g) and WID (1,1 g) respectively.

The hexane (WIH) and CH<sub>2</sub>Cl<sub>2</sub> (WID) phases of leaves were submitted to silica gel (70-230 mesh)



chromatographic column (CC) (45 x 3,5 cm to WIH and 35 x 2,5 cm to WID) eluted with solvents mixture in gradient mode using CH<sub>2</sub>Cl<sub>2</sub> and MeOH in different ratios (10:0; 97:3; 95:5; 9:1; 85:15; 8:2; 7:3; 6:4, 1:1) followed by MeOH, obtaining 10 fractions to WIH and 25 fractions to WID. All of these were later evaluated on TLC using Dragendorff reagent, fractions which present positive spots with this reagent on TLC were selected for further purifications. The fraction WIH-1 eluted in CH<sub>2</sub>Cl<sub>2</sub>:MeOH (95:5) was submitted to successive silica gel (70-230 mesh) CC (25 x 2,5 cm) using isocratic elution with CH<sub>2</sub>Cl<sub>2</sub>:MeOH (95:5) to afford the alkaloids 7 (10 mg) and 8 (2,5 mg). The fraction WIH-2 eluted in CH<sub>2</sub>Cl<sub>2</sub>:MeOH (9:1) was submitted to silica gel (70-230 mesh) CC (25 x 2,5 cm) using isocratic elution with CH<sub>2</sub>Cl<sub>2</sub>:MeOH (95:5) to afford the alkaloids 1 (25 mg) and the mixture of the alkaloids 2 and 6, further purified by successive silica gel silica gel (70-230 mesh) CC (15 x 1,5 cm) using isocratic elution with CH<sub>2</sub>Cl<sub>2</sub>:MeOH (9:1) obtaining 10 mg and 15 mg, respectively.

The fraction WID-8 eluted in CH<sub>2</sub>Cl<sub>2</sub>:MeOH (9:1) presented positive spots on TLC with Dragendorff reagent, thus it was submitted to successive silica gel (70-230 mesh) CC (25 x 1,5 cm) eluted with solvents mixture in gradient mode using CH<sub>2</sub>Cl<sub>2</sub>:MeOH in different ratios (10:0; 97:3; 95:5; 9:1; 85:15; 8:2; 7:3; 6:4, 1:1) followed by MeOH. This procedure afforded the alkaloids 3 (15 mg), eluted in CH<sub>2</sub>Cl<sub>2</sub>:MeOH (97:3), alkaloid 4 (10 mg), eluted in CH<sub>2</sub>Cl<sub>2</sub>:MeOH (95:5) and alkaloid 5 (6 mg), eluted in CH<sub>2</sub>Cl<sub>2</sub>:MeOH (9:1).

## 2.2. Structural elucidation

The structure of the isolated compounds (fig.1.) were unequivocally determined by analysis and comparison of their data [<sup>1</sup>H-and-<sup>13</sup>C-NMR (1D and 2D), MS and specific rotation] with respective literature values: waltherione A (1) (Hoelzel et al., 2005), waltherione B (2) (Gressler et al., 2008), waltherione C (3) (Jadulco et al., 2014), N-methyl-waltherione A (4) (Hoelzel et al., 2005), 5'-methoxy-waltherione A (5) (Jang et al., 2015), antidesmone (7) (Bringmann et al., 2000) and 8-deoxoantidesmone (8) (Cretton et al., 2014).

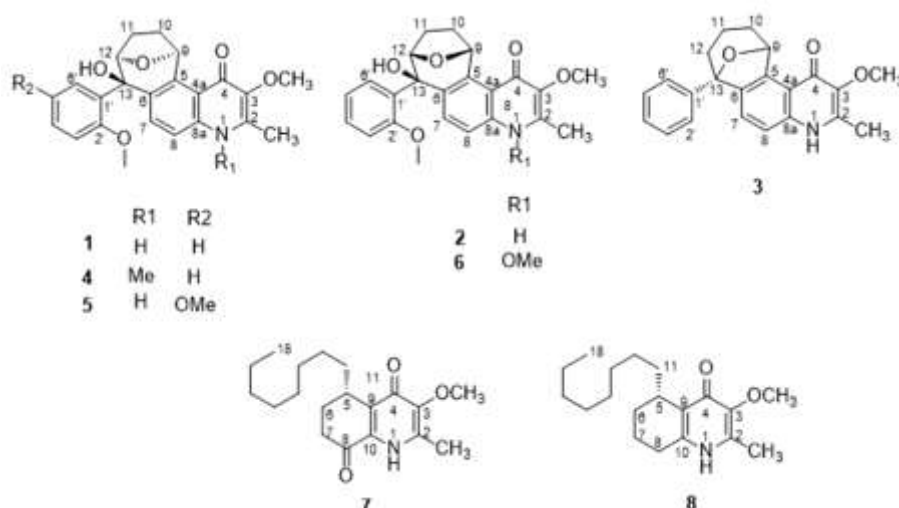


Fig.1. 4-quinolone alkaloids isolated from *Waltheria indica*

The alkaloid 6, was obtained as an off-white solid. High-resolution electrospray ionization mass spectrometry (HRESIMS) of compound 6 showed

a *pseudo* molecular ion peak at  $m/z$  424.1756 [ $M + H$ ]<sup>+</sup> (calc. for C<sub>24</sub>H<sub>25</sub>NO<sub>6</sub>, 424.1760). The <sup>1</sup>H NMR spectrum revealed the presence of

characteristic signals of the cyclized waltherriones, such as two oximethine hydrogens of the epoxide bridge, between C-10 and C-13, at  $\delta$  4.52 (*d*,  $J = 7.6$ ; H-10) and  $\delta$  6.59 (*d*,  $J = 8.4$  Hz, H-13), along with the diastereotopic methylene hydrogens at  $\delta$  1.85 (*m*, H-11a),  $\delta$  2.10 (*m*, H-11b),  $\delta$  1.5-1.63 (*m*, H-12a) and  $\delta$  1.5-1.63 (*m*, H-12b). These connectivities were confirmed by homonuclear COSY ( $^1\text{H} \times ^1\text{H}$ ) and heteronuclear HSQC ( $^1\text{H} \times ^{13}\text{C}$ ) correlations. The characteristic C-2 methyl and C-3 methoxy signals of the 4-quinolone moiety were verified at  $\delta$  2.33 (*s*) and 3.76 (*s*), respectively, while the hydrogens *ortho* coupling of the benzo-fused oxabicyclo were verified at  $\delta$  7.18 (*d*,  $J = 8.0$  Hz, H-8) and  $\delta$  7.29 (*d*,  $J = 8.0$  Hz, H-7). In addition, the  $^1\text{H}$  NMR spectrum indicated the presence of *ortho* disubstituted benzene spin system through the four hydrogens signals at  $\delta$  6.24 (*dd*, H-6'),  $\delta$  6.88 (*m*, H-5'),  $\delta$  7.27 (*t*, H-4') and  $\delta$  6.96 (*d*, H-3'). These correlations were confirmed by homonuclear COSY ( $^1\text{H} \times ^1\text{H}$ ) spectrum. The heteronuclear HMBC ( $^1\text{H} \times ^{13}\text{C}$ ) correlation between H-6' and C-9 ( $\delta$  71.36), as well as between methoxyl group at  $\delta$  3.76 (3H, C3-OMe) and  $\delta$  3.76 (C2'-OMe) and C2' ( $\delta$  152.54), confirm the substitution pattern of the *ortho* disubstituted aromatic ring attached to the oxabicyclo moiety. An additional signal at  $\delta$  4.01 (*s*, 3H) which presents heteronuclear HSQC correlation with C at  $\delta$  65.12 was characterized as a *N*-methoxy group. The  $^{13}\text{C}$  NMR spectrum revealed the presence of 24 carbons, highlighting the carbonyl group of 4-quinolone moiety at  $\delta$  173.38 and the oxygenated carbons C-10 ( $\delta$  85.2), C-13 ( $\delta$  73.90) of the oxabicyclo moiety. The  $^1\text{H}$ ,  $^{13}\text{C}$ , COSY, HSQC and HMBC NMR data and specific rotation of alkaloid 6 were very similar with literature values for waltherrione B (1) (Gressler et al., 2008) (see table 1), however, 6 presented an additional signal of methoxyl group, which was unequivocally attached to the nitrohen, as confirmed by  $^1\text{H}$  and  $^{13}\text{C}$  NMR and HRESMS.

Therefore, the structure of the alkaloid 6 was elucidated as *N*-methoxy-waltherrione B. It is reported for the first time in this study.

$^1\text{H}$  NMR of alkaloid 6 (400 MHz, DMSO- $d_6$ ):  $\delta$ : 7.29 (1H, *d*,  $J = 8.0$  Hz, H-8), 7.27 (1H, overlapped, H-4'), 7.24 (1H, overlapped, H-6'), 7.18 (1H, *d*,  $J = 8.0$  Hz, H-7), 6.96 (1H, *d*,  $J = 8.4$  Hz, H-3'), 6.88 (1H, *t*, H-5'), 6.59 (1H, *d*,  $J = 8.4$  Hz, H-13), 5.14 (1H, *s*, 9-OH), 4.52 (1H, *d*,  $J = 7.6$  Hz, H-10), 4.01 (3H, *N*-OCH<sub>3</sub>), 3.76 (3H, *s*, 3-OCH<sub>3</sub>), 3.53 (3H, *s*, 2'-OCH<sub>3</sub>), 2.33 (3H, *s*, 2-CH<sub>3</sub>), 2.10 (1H, *m*, H-11b), 1.85 (1H, *m*, H-11a), 1.63–1.50 (2H, *m*, H-12a/H-12b).

$^{13}\text{C}$  NMR of alkaloid 6: (100 MHz, DMSO- $d_6$ )  $\delta$ : 173.38 (C-4), 152.54 (C-2'), 140.76 (C-8a), 140.05 (C-2), 138.20 (C-3), 131.32 (C-5, C-7, C-1'), 129.67 (C-6, C-6'), 128.71 (C-4'), 119.79 (C-5'), 119.23 (C-4a), 115.96 (C-8), 112.27 (C-3'), 85.20 (C-10), 73.94 (C-13), 71.36 (C-9), 58.87 (3-OCH<sub>3</sub>), 55.97 (2'-OCH<sub>3</sub>), 31.81 (C-12), 23.54 (C-11), 14.01 (2-CH<sub>3</sub>), 65.12 (*N*-OCH<sub>3</sub>).

### 3. RESULTS AND DISCUSSION

The family of 4-quinolone alkaloids named as waltherriones, which includes the alkaloids antidesmone (7), chamaedrone (Dias et al., 2007b), melochinone and melovinone (Kapadia et al., 1975;1978), has representative compounds in both genera *Waltheria* and *Melochia* of the Malvaceae family. However, to the best of our knowledge, very few chemical studies have been performed on plants of these genera, thus, it is not possible to draw conclusions about which of the waltherriones are more representative in *Waltheria* and *Melochia* genera. On the other hand, all studies with different species of these genera, raised after the report of isolation of waltherrione A (1) (Hoelzel et al., 2005), cited the isolation of new waltherriones or the re-isolation of waltherriones previously reported in the literature.



Among the waltheriones reported in this work, the waltheriones A (1), C (2) and antidesmone (7) were previously reported in species of both genera *Waltheria* and *Melochia* (Hoelzel et al., 2005; Dias et al., 2007b; Emille et al., 2008; Jadulco et al., 2014; Erwin et al., 2014; Cretton et al., 2014; 2015; 2016). The alkaloids waltherione B (2), *N*-methyl-waltherione A (4) and 8-deoxoantidesmone (8) were only reported in *Waltheria douradinha* (Gressler et al., 2008), *Waltheria brachypetala* (Lima et al., 2009) and *Waltheria indica* (Cretton et al., 2014), respectively. Since antidesmone and 8-deoxoantidesmone are chemical markers of Antidesmeae tribe of the Euphorbiaceae family, we suggest possible relationship among *Waltheria*, *Melochia* and species of the Antidesmeae tribe of the Euphorbiaceae family.

The alkaloid 5'-methoxy-waltherione A (5) is being reported for the first time to both *Waltheria* and *Melochia* genera, however it is not a new alkaloid, since the alkaloid 5 was isolated from *Triumfetta grandidens* earlier, along with the known alkaloid waltherione A (Jang et al., 2015). This fact has notable chemosystematic significance, since the genus *Triumfetta* belongs to the subfamily Tilioideae of the Malvaceae family. From this work, we suggest possible relationship among the genus *Triumfetta* with *Waltheria* and *Melochia* genera, as well as the possibility of other species of genus *Triumfetta* to contain waltherione type 4-quinolone alkaloids. The alkaloid 5 was named as waltherione E by Jang et al. 2015, however other structurally different waltherione alkaloid isolated from *Waltheria indica* was previously designated with this name (Cretton et al., 2014), thus, we named the alkaloid 5 as 5'-methoxy-waltherione A (Cretton et al., 2014).

To the best led of our knowledge, the alkaloid *N*-methoxy-waltherione B (6) is being reported for the first time in the literature.

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