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Sesquiterpene lactones from *Polydora serratuloides* and their quorum sensing inhibitory activity

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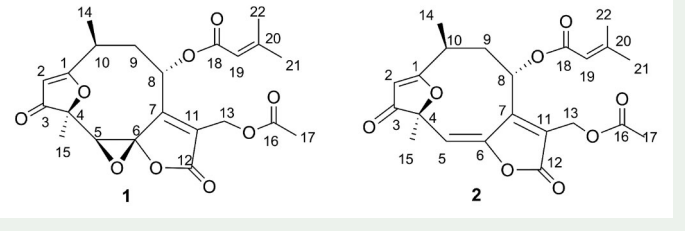
ABSTRACT

The leaves of *Polydora serratuloides*, with the synonym *Vernonia perrottetii* are widely used as purgative agents for gastrointestinal problems, and other members of Vernonieae have been used in African traditional medicine for decades. A new sesquiterpene lactone of the keto-hirsutinolide type, 13-acetoxy-1(4β),5(6)β-diepoxy-8α-(senecioyloxy)−3-oxo-1,7(11)-germacradiene-12,6-olide **1**, was isolated from the hexane extract of its leaves, in addition to the known 13-acetoxy-1,4β-epoxy-8α-(senecioyloxy)−3-oxo-1,5,7(11)-germacratriene-12,6-olide **2**. Three common flavonoids (apigenin **3**, luteolin **4** and velutin **5**) were also isolated. The antibacterial and quorum sensing inhibitory activities of compounds **1** and **2** and crudes extracts showed limited activity on *Bacillus subtilis* and *Staphylococcus aureus*, with no activity on Gram negative bacteria. However, quorum sensing (QSI) experiments indicated that **1** and **2**, and the four crude extracts had interesting inhibitory activity on the biosensor organism, *Chromobacterium violaceum* ATCC 12472 in the range of 0.33–5.25 mg mL^{-1}, with compound **1** being the most effective at 0.33 mg mL^{-1}.



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1. Introduction

Polydora serratuloides (DC.) H. Rob., with the synonym *Vernonia perrottetii* Sch. Bip. ex Walp. (Asteraceae) (Robinson 1999) is an annual herb that grows up to 60 cm high with leaves of 1–3 cm long. It is commonly found in abandoned fields in Northern

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Nigeria, where the leaves are widely used as purgative agents for gastrointestinal problems (Hutchinson and Dalziel 1963; Burkill 1985). Although not much information regarding the ethnobotany of *Polydora* occurs in the literature, species within the genus *Vernonia* have been used in traditional medicine for decades across Africa and South America. Some of these *Vernonia* species are synonyms for *Polydora* species (Robinson 1999; Robinson et al. 2016). The plant's activity is probably due to secondary metabolites such as sesquiterpene lactones (SLs) found in most *Vernonia* species. These compounds can be considered major biochemical markers within the genus (Seaman 1982), and since *Vernonia* is a synonym for most *Polydora* species, these sesquiterpene lactones are probably found in the *Polydora* as well.

Sesquiterpene lactones such as guaianolides (Bohlmann et al. 1978), glaucolides (Williams et al. 2005), hirsutinolides (Pillay et al. 2007) and eudesmanolides (Aliyu et al. 2015) were isolated from African species of *Vernonia*. Plant-derived sesquiterpene lactones contain interesting pharmacophores such as the α,β-unsaturated-γ-lactone group (Ghantous et al. 2010). A number of pharmacological activities including cytotoxicity (Buskuhl et al. 2010), anti-inflammatory (Walshe-Roussel et al. 2013), antibacterial (Duraipandiyan et al. 2012), and quorum sensing inhibitory activity (Amaya et al. 2012) have been attributed to the lactone moiety.

Quorum sensing (QS) mechanisms are critical to bacterial virulence and development of antibiotic resistance; hence its inhibition has become a novel strategy to control bacterial resistance (Cámara et al. 2002). Secondary metabolites from plants have been reported as effective inhibitors of QS (Nazzaro et al. 2013). The sesquiterpene lactones goyazensolides (Amaya et al. 2012), 6-gingerol (Kim et al. 2015) and natural stilbenoids (Sheng et al. 2015) have all exhibited potent QS inhibitory activities. In addition, blumeoidolides A and B from *V. blumeoides* demonstrated good QS inhibitory potential (Aliyu et al. 2016). We herein report on the isolation and structure elucidation of a new sesquiterpene lactone **1**, together with a known related sesquiterpenoid **2**, and three known flavonoids. The QS inhibitory potential of the two hirsutinolides **1** and **2** and the crude extracts are also reported.

2. Results and discussion

2.1. Chemical constituents

A novel sesquiterpene lactone **1** of the germacranolide type was isolated from the hexane extract of the leaves of *P. serratuloides*. In addition, a known sesquiterpene lactone 13-acetoxy-1,4β-epoxy-8α-(senecioyloxy)−3-oxo-1,5,7(11)-germacratriene-12,6-olide **2** (Bohlmann et al. 1983) was isolated from the same extract. Three known flavonoids, apigenin **3** (Wawer and Zielinska 2001), luteolin **4** (Li et al. 2008), and velutin **5** (Kang et al. 2011) were also isolated from the ethyl acetate (**3-4**) and hexane (**5**) extracts of the leaf (Figure 1).

The sesquiterpene lactone **2**, was previously isolated from *V. poskeana* (Bohlmann et al. 1983). The structures of the known compounds were determined from their ^{1}H and ^{13}C NMR spectra together with 2D NMR spectra and confirmed by comparing the NMR data with those contained in the literature (Bohlmann et al. 1983; Wawer and Zielinska 2001; Li et al. 2008; Kang et al. 2011). Some assignments for the ^{1}H NMR

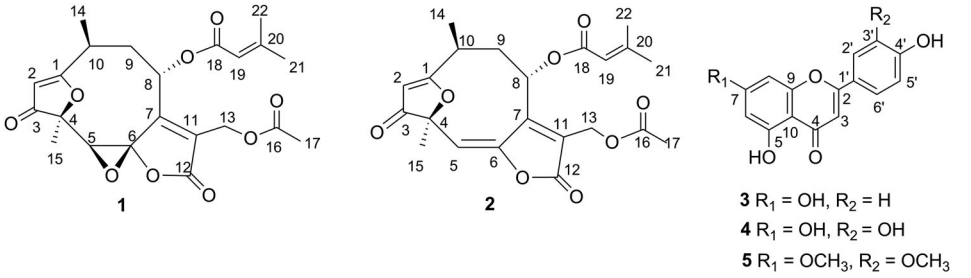

Figure 1. Structures of compounds **1-5** isolated from the leaves of *Polydora serratuloides*.

data for compound **2** contained in Bohlmann et al. (1983) were revised based on HMBC correlations and ^{13}C NMR data provided, and is reported in Table S1 (Supplementary material). Germacranolides are the largest class of sesquiterpene lactones reported from *Vernonia* with hirsutinolides being the most frequently reported skeletal type.

2.2. Structural elucidation of the new compound

Compound **1** was isolated as a brown crystalline solid with a melting point of 95–96 °C and molecular formula of $C_{22}H_{24}O_9$ as established by the EI-MS showing a molecular ion peak at 455.2 $[M+Na]^+$ calculated for $C_{22}H_{24}O_9Na$. Absorption bands at 1781 and 1713 cm^{-1} for the ester carbonyl and ketone group, respectively were observed. The ^1H and ^{13}C NMR spectra (Table S1, Supplementary material) showed resonances typical of the hirsutinolide type sesquiterpenoid similar to 13-acetoxy-1,4β-epoxy-8α-(senecioyloxy)−3-oxo-1,5,7(11)-germacratriene-12,6-olide **2** (Bohlmann et al. 1983), with characteristic resonances for the olefinic methine protons at δ_H 5.69 (1H, s, H-19) and 5.44 (1H, s, H-2), the methine protons, H-8 at δ_H 6.14 (1H, d, $J = 8.3$ Hz) and H-10 at δ_H 2.94 (1H, m), the geminal methylene protons at δ_H 4.81 and 4.96 (each 1H, d, $J = 13.4$ Hz, H-13a, H-13b) and five methyl resonances at δ_H 1.25 (3H, d, $J = 6.9$ Hz, H-14), 1.60 (3H, s, H-15), 1.91 (3H, s, H-21), 2.07 (3H, s, H-17), and 2.14 (3H, s, H-22).

The ^{13}C NMR spectrum showed the olefinic oxygenated carbon resonance C-1 at δ_C 195.3, C-2 at 99.2 and the ketone (C-3) at 201.8. Three other carbonyl resonances at δ_C 165.6 (C-12 lactone), 170.1 (C-16 ester) and 165.4 (C-18 ester), and two other olefinic carbon resonances at δ_C 157.5 (C-7) and 133.6 (C-11) were also observed, similar to compound **2**, as was the oxygenated C-4 carbon resonance bearing the methyl group at δ_C 83.1. However, a notable difference in comparison to compound **2** was the absence of the olefinic proton resonance of H-5 at δ_H 5.87, which was replaced by δ_H 3.64 (an oxygenated methine resonance) and two deshielded oxygenated carbon resonances at δ_C 66.4 and 90.2 instead of the olefinic carbon resonances at δ_C 117.1 and 146.5 seen in **2**. This was an indication that the double bond at C-5 in **2** was replaced by an epoxide at C-5/6 in **1**. The carbon resonance at δ_C 66.4 was typical for epoxides with δ_C 90.2 being more deshielded, due to the oxygen from the lactone ring.

The structure was confirmed by HMBC correlations from H-15 to C-5, and H-5 to C-4 and C-6. Other relevant HMBC correlations were H-2 to C-4; H-14 to C-1 and C-10; H-8 to C-18; and H-13a/b to C-7, C-11 and C-16, confirming the positions of the double

bond at C-1 and the 14-methyl-8α-senecioyloxy and 13-acetoxy groups (Figure S6, Supplementary material). The stereochemistry at the chiral centres of C-4, C-10 and C8, was assigned in comparison with the known related compound **2**, since the methyl groups at C-4 and C-10 and the senecioyloxy group at C-8 had very similar proton resonances to that of compound **2**. The H-15 resonance was then used to assign the stereochemistry of H-5 as alpha, since a NOESY correlation was observed between H-5 and H-15. The epoxide at C-5 and C-6 was thus assigned as beta. Compound **1** was thus identified as 13-acetoxy-1(4β),5(6)β-diepoxy-8α-(senecioyloxy)−3-oxo-1,7(11)-germacradiene-12,6-olide. This is the first report of sesquiterpene lactones from *P. serratuloides*.

13-Acetoxy-1(4β),5(6)β-diepoxy-8α-(senecioyloxy)−3-oxo-1,7(11)-germacradiene-12,6-olide (1): brown crystalline solid, mp 95-96 °C, IR (KBr) ν_{max} 2927, 1781 (C=O), 1737 (C=O), 1713 (C=O), 1645, 1603, 1453, 1375, 1236, 1213, 1136 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.14 (d, $J = 8.3$, H-8), 5.69 (s, H-19), 5.44 (s, H-2), 4.96 (d, $J = 13.4$, H-13b), 4.81 (d, $J = 13.4$, H-13a), 3.64 (s, H-5), 2.94 (m, H-10), 2.71 (ddd, $J = 6.0$, 8.3, 14.4, H-9α), 2.14 (s, H-22), 2.07 (s, H-17), 1.91 (s, H-21), 1.76 (dd, $J = 11.9$, 14.4, H-9β), 1.60 (s, H-15), 1.25 (d, $J = 6.9$, H-14). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 201.8 (C-3), 195.3 (C-1), 170.1 (C-16), 165.6 (C-12), 165.4 (C-18), 159.2 (C-20), 157.5 (C-7), 133.6 (C-11), 114.7 (C-19), 99.2 (C-2), 90.2 (C-6), 83.1 (C-4), 66.7 (C-8), 66.4 (C-5), 54.9 (C-13a), 42.0 (C-9α), 30.7 (C-10), 27.6 (C-21), 20.6 (C-17), 20.5 (C-22), 17.3 (C-15), 16.4 (C-14). EI-MS: *m/z* 455.2 $[M + Na]^+$ calculated for $C_{22}H_{24}O_9Na$.

Keto hirsutinolides with a 3-oxo-1-desoxy-1,2-dehydro hirsutinolide-13-*O*-acetate moiety have previously been isolated from *V. poskeana* (Bohlmann et al. 1983), *V. jugalis* (Tsichritzis et al. 1991) and *V. staehelinoides* (Pillay et al. 2007).

The hirsutinolides **1–2** are biogenetically related to the glaucolides. However, Tully et al. (1987) have argued that the hirsutinolides are artefacts of isolation during column chromatography on silica gel. It was also demonstrated that *trans* annular cyclization of glaucolides on silica under acidic conditions yielded **2** (Tully et al. 1987). However, Pillay et al. (2007) have shown the hirsutinolides to exhibit characteristic TLC profiles before being subject to purification by column chromatography, supporting their existence as natural products. It is quite possible that due to the conformation of the germacrene skeleton, biosynthetic transformations are responsible for glaucolides being transformed into hirsutinolides **1–2** (Minnaard et al. 1999).

2.3. Antibacterial activity

2.3.1. Disc diffusion assay

Of the four crude extracts tested, only the DCM extract showed good antibacterial activity against *Bacillus subtilis* and the two *S. aureus* strains (Table S2, Supplementary material). The lactone **1** also showed good activity against *Bacillus subtilis* with **2** having weaker activity against the same strain.

2.3.2. Quorum sensing inhibitory activity

All four crude extracts and hirsutinolides **1** and **2** demonstrated QSI potential based on the violacein inhibition assay. Anomalously, no growth inhibition was observed with **2** at concentrations $\geq$5.25 mg mL^{-1}. Compound **2** had the most effective QSI,

with ≥75% at 0.33 mg mL^{-1}. Compound **1** demonstrated QSI ≥80% at 1.31 mg mL^{-1}. All tested samples demonstrated QSI ranging from 66-96% at 1.31 mg mL^{-1} (Figure S28, Supplementary material). There was a statistically significant difference ($p \leq 0.001$) in the mean values among the treatment groups based on concentration. However, no statistically significant differences ($p = 0.109$) were observed between the crude extracts or compounds **1** and **2** (Figure S28, Supplementary material). The effective QS inhibition of the hirsutinolide **2** surpassed the results of drimane sesquiterpenoids from Chilean flora, both in concentration and potency (Cárcamo et al. 2014). This is an indication of the potential for **2** to have therapeutic significance.

3. Conclusion

Keto-hirsutinolides were isolated from the leaves of *P. serratuloides* and their structures elucidated using spectroscopic information including 2D-NMR. This is the first report of 13-acetoxy-1(4β),5(6)β-diepoxy-8α-(senecioyloxy)−3-oxo-1,7(11)-germacradiene-12, 6-olide (**1**) and the first report of sesquiterepene lactones from *P. serratuloides*. The crude extracts and sesquiterpenoids **1** and **2** have limited antimicrobial activity against selected Gram-positive bacteria belonging to the genera *Bacillus* and *Staphylococcus*, with no antimicrobial activity against recalcitrant Gram-negative bacteria. Both keto-hirsutinolides (**1** and **2**) and four *P. serratuloides* crude extracts demonstrated QSI activity in the range of 0.33–5.25 mg mL^{-1}, with **2** being the most effective at 0.33 mg mL^{-1}, suggesting a potential candidate for the development of antibiotics.

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Disclosure statement

No potential conflict of interest was reported by the authors and they have no financial interest or benefit from the direct applications of this research.

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