SHORT REPORT

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Eudesmane Sesquiterpenoids from *Salvia plebeia*

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Abstract: A new eudesmane sesquiterpenoid (**1**), named sapleudesone, together with four known analogs (**2**–**5**) were isolated from the aerial parts of *Salvia plebeia*. The structure of compound **1** was established by NMR and HRESIMS data, and the absolute configuration of **1** was determined by comparing the experimental ECD spectrum with the calculated ECD spectra. The known compounds were identified to be salplebeone A (**2**), linderolide I (**3**), chlorantene D (**4**), and chlomultin B (**5**), respectively, by comparing the NMR data and specific rotations with reported data. All five compounds were tested for the inhibitory effects against NO production in LPS-activated RAW 264.7 macrophages. As a result, compound **2** exhibited weak inhibitory effects with an IC_{50} value of 42.3 ± 1.4 μM.

Keywords: *Salvia plebeia*; eudesmane sesquiterpene; inhibitory effects; NO production.

1. Plant Source

The aerial parts of *Salvia plebeia* R. Br. were collected in October 2018 in Jiangsu Province, P. R. China, and were identified by Prof. Jianyong Zhu of Shanghai University of Traditional Chinese Medicine. The voucher specimen (accession number: Sapl201810) was deposited at Zhejiang University (HZU).

2. Previous Studies

S. plebeia R· Brown is a biennial herb widely distributed in China, especially in Shaanxi, Jiangsu, Fujian, Guizhou, Hunan, and Guangdong Provinces, it is used for the treatment of bruises, flu, sore throat, pediatric convulsion, and vomiting blood in Traditional Chinese Medicine [1]. Previous chemical investigations of this plant led to the isolation of sesquiterpenoids [2-6], diterpenoids [7,8], and flavonoids [9]. The eudesmane squiterpenoids are major metabolites of this plant, and several cases showed significant anti-inflammatory effects, such as salviplenoid and salviplenoid A [5, 10] .

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2. Present Study

The aerial parts of *S. plebeia* (1.0 kg) was extracted with 95% EtOH (4 × 2 L) at room temperature to give an extract (98 g). The extract was further suspended in water (1 L) and extracted with petroleum ether (4 × 0.5 L) and EtOAc (4 × 0.5 L), respectively. The EtOAc extract (57 g) was separated on silica gel chromatographic column (CC) gel (petroleum ether/ EtOAc, 10:1 to 1:1) to obtain six fractions (Fra.A− Fra.F). Fra. C was chromatographed over silica gel CC (petroleum ether/acetone, 20:1 to 1:1) to afford three subfractions (Fra.C1−Fra.C3). Fra.C1 was further purified by silica gel CC (petroleum ether/ EtOAc, 10:1 to 5:1) to yield **1**. Fra.C2 was purified by silica gel CC (petroleum ether/acetone, 20:1 to 10:1) to give **2**, **3**, and **5**. Fra. C3 was further purified by ODS C18 silica gel CC with MeOH/H_2O (60:40 to 90:10) as mobile phase to give **4**.

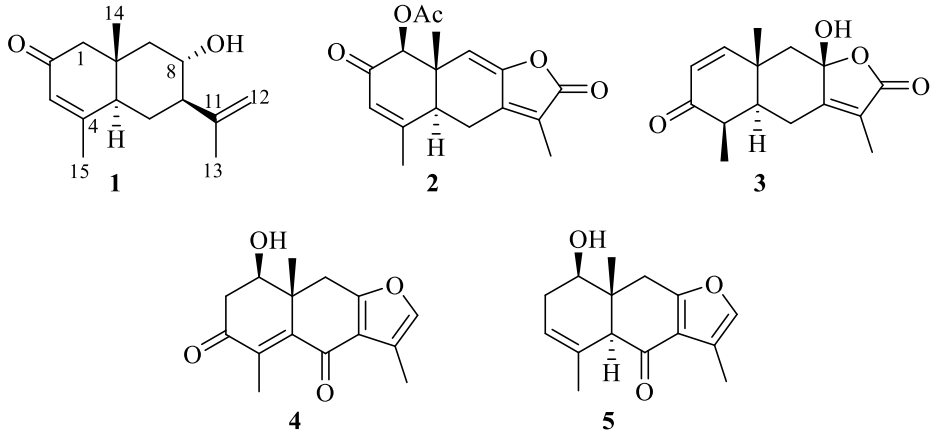

Figure 1. Structures of compounds **1**–**5**

*Sapleudesone (**1**):* Colorless oil; $[\alpha]^{25}_D$ −178 (*c* 0.1, MeOH); ECD (*c* 1.1 × 10^{-3} M, MeOH) λ_{max} ($\Delta\varepsilon$) 329 (−1.55), 286 (−0.81), 241 (+11.2) nm; HRESIMS *m/z* 235.1695 $[M + H]^+$ (calcd for $C_{15}H_{23}O_2$, 235.1698). ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 5.79 (1H, s, H-3), 4.79 (1H, s, H-12b), 4.78 (1H, s, H-12a), 3.62 (1H, m, H-8), 2.50 (1H, m, H-5), 2.29 (1H, d, *J* =15.0 Hz, H-1b), 2.09 (1H, d, *J* =15.0 Hz, H-1a), 2.03 (1H, m, H-7), 1.87 (3H, s, H-15), 1.81 (1H, d, *J* =13.0, 3.4 Hz, H-6b), 1.75 (3H, s, H-13), 1.70 (1H, dd, *J* =12.3, 4.6 Hz, H-9a), 1.45 (1H, d, *J* =13.0 Hz, H-6a), 1.34 (1H, dd, *J* =12.3, 11.0 Hz, H-9b), 0.84 (3H, s, H-14). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 197.2 (C-2), 162.2 (C-4), 146.9 (C-11), 125.3 (CH-3), 110.9 (CH_2-12), 65.4 (CH-8), 53.5 (C-7), 53.2 (CH_2-1), 47.9 (CH_2-9), 45.8 (CH-5), 37.8 (CH-10), 27.9 (CH_2-6), 21.0 (CH_3-15), 19.3 (CH_3-13), 16.9 (CH_3-14).

The molecular formula of compound **1** was established as $C_{15}H_{22}O_2$ by HRESIMS data (*m/z* 235.1695 $[M + H]^+$, calcd *m/z* 235.1698), suggesting 5 indices of hydrogen deficiency. The ^{1}H NMR spectrum displayed signals for two olefinic methyls (δ_H 1.87, 1.75), a tertiary methyl (δ_H 0.84), three olefinic protons (δ_H 5.79, 4.79, 4.78), an oxygenated proton (δ_H 3.62). The ^{13}C NMR spectrum exhibited 15 carbon resonances, including four olefinic carbons for two double bonds (δ_C 162.2, 146.9, 125.3, 110.9), a carbonyl carbon for a ketone (δ_C 197.2), and an oxygenated methine (δ_C 65.4). Detailed analyses of the 2D NMR data established an eudesmane sesquiterpene skeleton for compound **1** (Figure 2). Especially, the HMBC correlations from H_3-15 (δ_H 1.87) to C-3 (δ_C 125.3), C-4 (δ_C 162.2), and H_2-1 (δ_H 2.29, 2.09) to C-2 (δ_C 197.2) assigned an α,β-unsaturated ketone moiety residing at C-2, C-3, and C-4. Additional HMBC correlations from H_3-13 (δ_H 1.75) and the exomethylene protons H_2-12 (δ_H 4.79, 4.78) to C-7 (δ_C 53.5) and C-11 (δ_C 146.9) located an isopropenyl group at C-7 (δ_C 53.5). The ^{1}H-^{1}H COSY correlations from H-7 (δ_H 2.03) to H_2-9 (δ_H 1.70, 1.34) via the the oxygenated proton H-8 at δ_H 3.62 positioned a hydroxyl group at C-8 (δ_C 65.4).

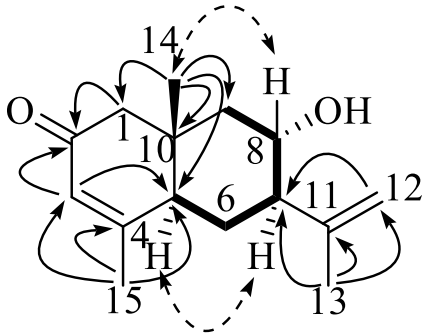

Figure 2. ^{1}H-^{1}H COSY (▬), HMBC (⟶), and NOE (◂- -▸) correlations of **1**.

The NOESY correlations of H_3-14 (δ_H 0.84) with H-8 (δ_H 3.62) and between H-5 (δ_H 2.50) and H-7 (δ_H 2.03) determined the same orientation of H_3-14 and H-8, while H-5 and H-7 were in opposite face relative to H_3-14 (Figure 2). The absolute configuration of **1** was determined by comparison of its experimental and calculated electronic circular dichroism (ECD) spectra (Figure 3). The experimental ECD spectrum showed positive Cotton effect at 241 nm, which was similar to the Cotton effect of the calculated ECD spectrum of **1a** (5*R*, 7*R*, 8*S*, 10*S*-**1**) at 241 nm, allowing the assignment of the absolute configuration of **1** to be 5*R*, 7*R*, 8*S*, and 10*S*. Compound **1** was given the trivial name sapleudesone.

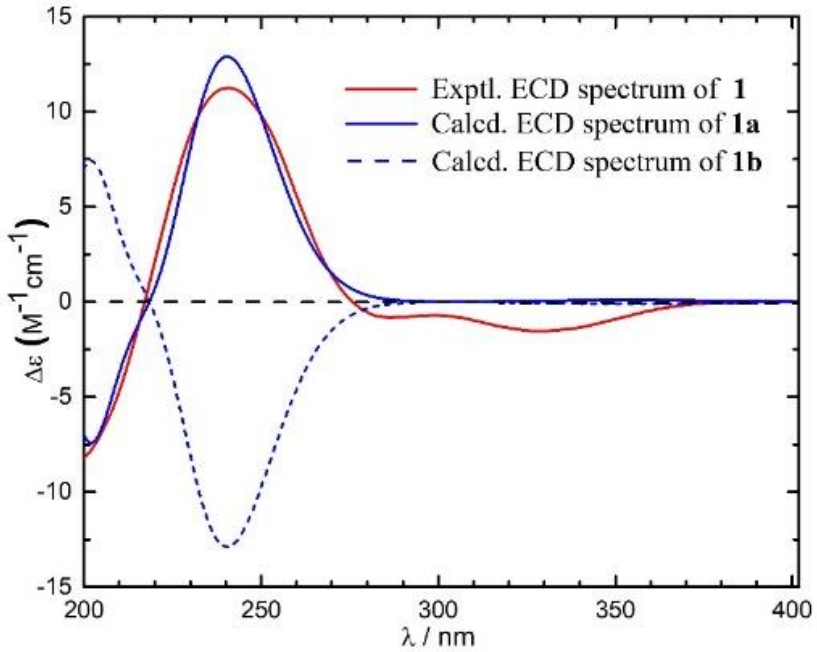

Figure 3. Experimental and calculated ECD spectra (200–400 nm) of compounds **1**, **1a** (5*R*, 7*R*, 8*S*, 10*S*), and **1b** (5*S*, 7*S*, 8*R*, 10*R*).

The known compounds were identified to be salplebeone A (**2**) [6], linderolide I (**3**) [11], curcolonol (**4**) [12], chlomultin B (**5**) [13], respectively, by comparisons of the NMR data and optical rotations with reported data.

Compounds **1**–**5** were tested for the inhibitory effects against NO production in LPS-activated RAW 264.7 macrophages following the procedures in the literature [14-16]. As results, only compound **2** exhibited weak inhibition rate of 63.2% at the initial concentration of 50 μM and had an IC_{50} value of 42.3 ± 1.4 μM, other compounds showed inhibition rate less than 30% at 50 μM, and the positive control quercetin possessed an IC_{50} value of 17.5 ± 1.1 μM.

Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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References

[1] Y. Q. Chen, D. Z. Cheng, G. F. Wu, P. S. Cheng and P. Z. Zhu (1977). In Chinese Flora (Zhongguo Zhiwu Zhi); Science Press: Beijing, **66**, 168-172.
[2] C. G. Zhang, M. R. Jin, G. X. Chou and Q. S. Yang (2017). Plebeins A–F, sesquiterpenoids and diterpenoids from *Salvia plebeian*, *Phytochem. Lett.* **19**, 254-258.
[3] H. J. Jang, H. M. Oh, J. T. Hwang, M. H. Kim, S. Lee, K. Jung, Y. H. Kim, S. W. Lee and M. C. Rho (2016). Eudesmane-type sesquiterpenoids from *Salvia plebeia* inhibit IL-6-induced STAT3 activation, *Phytochemistry* **130**, 335-342.
[4] Y. Dai, L. Liu, G. Xie, Y. Chen, X. Qin, Q. Wang, J. Li and M. Qin (2014). Four new eudesmane-type sesquiterpenes from the basal leaves of *Salvia plebeia* R. Br, *Fitoterapia* **94**, 142-147.
[5] H. J. Jang, S. Lee, S. J. Lee, H. J. Lim, K. Jung, Y. H. Kim, S. W. Lee and M. C. Rho (2017). Anti-inflammatory activity of eudesmane-type sesquiterpenoids from *Salvia plebeia*, *J. Nat. Prod.* **80**, 2666-2676.
[6] L. F. Ma, P. F. Wang, J. D. Wang, X. M. Tong, W. G. Shan, H. Zhang and Z. J. Zhan (2017). New eudesmane sesquiterpenoids from *Salvia plebeia* R. Br, *Chem. Biodivers.* **14**, e1700127.
[7] J. Xu, M. Wang, X. Sun, Q. Ren, X. Cao, S. Li, G. Su, M. Tuerhong, D. Lee, Y. Ohizumi, M. Bartlam and Y. Guo (2016). Bioactive terpenoids from *Salvia plebeia*: Structures, NO Inhibitory activities, and interactions with iNOS, *J. Nat. Prod.* **79**, 2924-2932.
[8] B. B. Zhang, B. Q. He, J. B. Sun, B. Zeng, X.-J. Shi, Y. Zhou, Y. Niu, S. Q. Nie, F. Feng, Y. Liang and F. H. Wu (2015). Diterpenoids from *Saliva plebeia* R. Br. and their antioxidant and anti-inflammatory activities, *Molecules* **20**, 14879-14888.
[9] Y. Oshima, Y. Kawakami, Y. Kiso, H. Hikino, L. L. Yang and K. Y. Yen (1984). Liver protective drugs. 13. Antihepatotoxic principles of *Salvia plebeia* herbs, *Shoyakugaku Zasshi* **38**, 201-202.
[10] Y. H. Zou, L. Zhao, Y. K. Xu, J. M. Bao, X. Liu, J. S. Zhang, W. Li, A. Ahmed, S. Yin and G.H. Tang (2018). Anti-inflammatory sesquiterpenoids from the traditional Chinese medicine *Salvia plebeia*: regulates pro-inflammatory mediators through inhibition of NF-κB and Erk1/2 signaling pathways in LPS-induced Raw264.7 cells, *J. Ethnopharmacol.* **210**, 95-106.
[11] Q. Liu, J. H. Ahn, S. B. Kim, C. Lee, B. Y. Hwang and M. K. Lee (2013). Sesquiterpene lactones from the roots of *Lindera strychnifolia*, *Phytochemistry* **87**, 112-118.
[12] C. Li, D. Zhang and Y. Luo (2005). Studies on the chemical constituents from the roots of *Chloranthus henryi*, *Acta. Pharm. Sin.* **40**, 525-528.
[13] S. Zhang, Z. S. Su, S. P. Yang and J. M. Yue (2010). Four sesquiterpenoids from *Chloranthus multistachys*, *J. Asian Nat. Prod.* **12**, 522-528.
[14] Z. Cheng, W. Xu, Y. Wang, S. Bai, L. Liu, Z. Luo, W. Yuan and Q. Li (2019). Two new meroterpenoids and two new monoterpenoids from the deep sea-derived fungus *Penicillium* sp. YPGA11, *Fitoterapia* **133**, 120-124.
[15] L. Li, W. Du and W. Wang (2019). Evaluation of the antioxidative and anti-inflammatory effects of the extract of *Ribes mandshuricum* (Maxim.) Kom. leaves, *Rec. Nat. Prod.* **13**, 141-155.
[16] M. Zhao, G. Chen, T. Lin and Y. Lu (2020). A new labdane diterpene from the aerial parts of *Chloranthus serratus*, *Rec. Nat. Prod.* **14**, 378-382.