

## Anti-inflammatory and antiproliferative diterpenoids from *Plectranthus scutellarioides*



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### ABSTRACT

Chemical investigation of the dichloromethane extract of the aerial parts of *Plectranthus scutellarioides* led to the isolation and characterization of 10 diterpenoids with an abietane skeleton and one cembrane-type diterpenoid. Among them, six have not yet been described in the literature. Their structures were established by 1D and 2D NMR, UV and IR spectroscopy, and HRESIMS. The relative configuration was determined by Gauge-Independent Atomic Orbital NMR chemical shift calculations supported by the advanced statistical method DP4 plus and further confirmed by electronic circular dichroism. The isolated constituents were evaluated for their *in vitro* NF- $\kappa$ B inhibitory activity, as well as for their cytotoxic effects in human multiple myeloma cancer stem cells and RPMI 8226 tumor cell line. Coleon O, coleon G, lanugone K and 6-acetylfredricone B showed the highest inhibitory effect against NF- $\kappa$ B, displaying IC<sub>50</sub> of 11.2, 11.0, 4.5 and 9.7  $\mu$ M, respectively. Coleon O exhibited also a significant activity towards human multiple myeloma cancer stem cells and RPMI 8226 cells with IC<sub>50</sub> of 9.2 and 8.4  $\mu$ M, respectively.

### 1. Introduction

The genus *Plectranthus* L'Hér. (Lamiaceae) comprises about 300 species distributed in Tropical Africa, Asia and Australia. Some species such as *Plectranthus amboinicus*, *P. laxiflorus* and *P. barbatus* are well documented for their ethnomedicinal uses (Brito et al., 2018; Lukhoba et al., 2006). Phytochemical studies on this genus report mainly the presence of diterpenoids with abietane or labdane skeletons. Monoterpenoids, sesquiterpenoids and phenolics have also been described in different species of *Plectranthus* (Lukhoba et al., 2006). However, very few phytochemical investigations were performed on *P. scutellarioides* (L.) R.Br. (syn. *Coleus pumilus* or *Coleus blumei*) (www.theplantlist.org, 2018). In spite of its traditional use for the treatment of various ailments (Bourdy and Walter, 1992; Roosita et al., 2008; Waruruai et al., 2011) only rosmarinic acid (Razzaque and Ellis, 1977), quercetin (Moektiwardoyo et al., 2011), five abietane diterpenes derivatives coleon O (Devriese et al., 1988), 2,16-diacetyl derivative of 2,6,11,12,14,16,17-heptahydroxy-5,8,11,13-abietatetraen-7-one (Ragasa et al., 2001) and spiroscutelones A-C (Ito et al., 2018) were identified in this plant. In addition to its ethnomedicinal use as a treatment against several inflammatory disorders, *P. scutellarioides* is used as hallucinogen in the region of Oaxaca, Mexico (Schultes, 1984).

However, as yet, no psychoactive constituent has been found.

In the present study, a bioactivity-guided isolation using a NF- $\kappa$ B assay was performed to support its traditional use as an anti-inflammatory plant and to gain knowledge on the phytochemical composition of this plant. Eleven terpenoids were isolated and characterized from the aerial parts of *P. scutellarioides*. Among these, six compounds (1–6) are undescribed phytochemicals (Fig. 1). The NF- $\kappa$ B inhibitory activity of the isolated compounds as well as their cytotoxic effects in human multiple myeloma cancer stem cells (MM-CSCs) and RPMI 8226 multiple myeloma plasma cells were determined.

### 2. Results and discussion

The crude dichloromethane extract of the aerial parts of *P. scutellarioides* was fractionated using flash chromatography. The resulting fractions were tested for their NF- $\kappa$ B inhibitory activity (Fig. S1). Fraction F11 and those possessing higher than 40% inhibition were purified by semi-preparative HPLC yielding six previously unreported (1–6) and five (7–11) known compounds.

Compound 1 was obtained as a brownish oil, and its molecular formula C<sub>20</sub>H<sub>26</sub>O<sub>7</sub> was determined by HRESIMS from the ion *m/z* 379.1753 [M + H]<sup>+</sup>. The IR spectrum showed absorption bands

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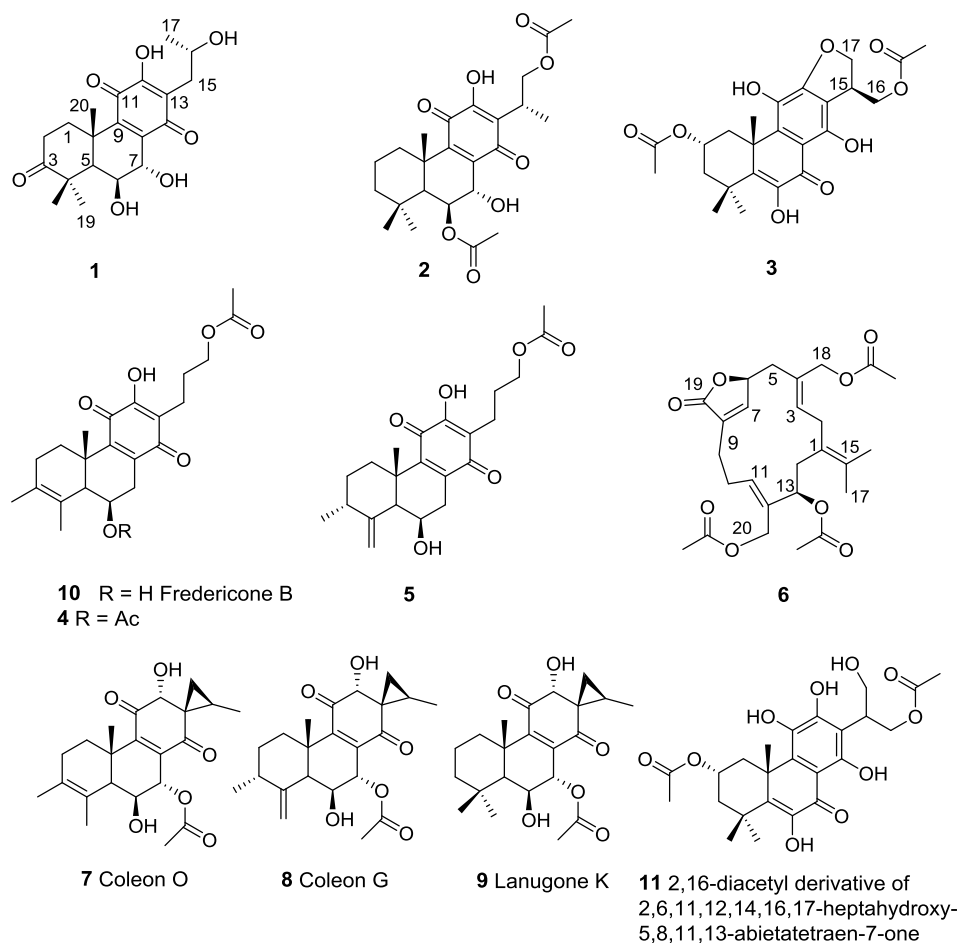


Fig. 1. Structures of the isolated compounds from *Plectranthus scutellarioides*.

attributable to hydroxy ( $3349$  and  $2931\text{ cm}^{-1}$ ) and ketone ( $1703\text{ cm}^{-1}$ ) groups. Analysis of the 1D NMR data (Tables 1 and 2), HSQC and HMBC spectra of **1** revealed 20 carbon signals corresponding to four methyls C-17 to C-20 ( $\delta_{\text{C}}$  23.3, 22.9, 29.1 and 21.8, respectively), three methylenes C-1, C-2 and C-15 ( $\delta_{\text{C}}$  37.1, 34.7 and 33.3, respectively), four methines C-5 to C-7 and C-16 ( $\delta_{\text{C}}$  48.5, 69.4, 67.1 and 67.8, respectively), and nine quaternary carbons, C-3, C-4 and C-8 to C-14 ( $\delta_{\text{C}}$  220.4, 48.0, 141.4, 147.4, 38.8, 184.7, 156.0, 118.5 and 188.9, respectively). Considering these data and the diterpenoid fredericone B (**10**) isolated from the same plant, compound **1** could be assigned as an abietane quinone diterpenoid with the skeleton abieta-8,12-dien-3,11,14-trione. Cross peaks between H-15/H-16 and H-16/H-17 in a COSY experiment, and key HMBC correlations between H-15 ( $\delta_{\text{H}}$  2.55 and 2.67) and C-16, C-17, C-12, C-13 and C-14 allowed positioning a 2-hydroxypropyl sidechain in C-13 (Fig. 2). The chemical shift of the two methines C-6 and C-7 ( $\delta_{\text{C}}$  69.4 and 67.1, respectively) indicated the presence of two hydroxy groups in these positions. The ROESY correlations from H-5 to Me-19, H-1 $\alpha$ , and H-2 $\alpha$  below the plane of the molecule and from Me-20 to H-1 $\beta$  and Me-18 above the plane of the molecule allowed positioning these protons in  $\alpha$  and  $\beta$  orientation, respectively (Fig. 3). The ROESY correlation from H-6 to Me-18 and Me-19 as well as the small coupling constant between H-6 and H-5 (1.5 Hz) and H-6 and H-7 (2.8 Hz) indicated that H-6 is in a pseudo-equatorial position and thus in an  $\alpha$ -orientation. The lack of correlation between H-7 and H-5 indicated that H-7 is  $\beta$ -oriented and thus that the hydroxy group attached to C-7 is  $\alpha$ -oriented (Fig. 3). Moreover, the NMR data regarding those positions are in good agreement with the ones from lanugone K (**9**) (Schmid et al., 1982). The relative configuration at C-16 was assigned by calculation of the Smith and Goodman DP4 probability

(Smith and Goodman, 2010). Comparison of the experimental and theoretical chemical shifts indicated a 16S\* configuration with a 95.8% probability (see supporting information). The absolute configuration of **1** was established by comparison of experimental and calculated ECD spectra. A good agreement was observed between both experimental and theoretical ECD spectra (Fig. 4). Compound **1** was thus identified as the 13-isopropenyl derivative of (5R,10S)-6S,7S,12-trihydroxy-8,12-abietadien-3,11,14-trione and named scutellarioidone A.

The HRESIMS of compound **2** exhibited an ion at  $m/z$  449.2170 [ $M + H$ ]<sup>+</sup> (calcd for  $\text{C}_{24}\text{H}_{33}\text{O}_8$ , 449.2170), corresponding to the molecular formula  $\text{C}_{24}\text{H}_{32}\text{O}_8$ . Data provided by  $^1\text{H}$  and  $^{13}\text{C}$  NMR were compared to those of lophanthoidin B (Yunlong et al., 1989) and the difference between the two compounds was an acetoxy group in C-6 for **2** instead of C-7 in lophanthoidin B. This was confirmed by the HMBC correlation from H-6 ( $\delta_{\text{H}}$  5.48) and the methyl protons at  $\delta_{\text{H}}$  2.02 to the carbonyl ester carbon at  $\delta_{\text{C}}$  171.9. The ROESY correlations from H-5 to H-1 $\alpha$ , H-3 $\alpha$  and Me-19, and from H-6 to Me-19 allowed positioning all these protons in  $\alpha$ -orientation. The stereochemistry in C-15 was not previously determined. Therefore, a comparison of the experimental  $^{13}\text{C}$  NMR chemical shifts was performed. According to the DP4 probability, a 15S\* configuration was established (85.4%). The absolute configuration was assigned by comparison of experimental ECD spectrum with calculated ECD spectra (Fig. 4). Compound **2** was thus identified as the 13-propyl acetate derivative of (5R,10S)-6S-acetoxy,7S,12-dihydroxy-8,12-abietadien-11,14-dione and named scutellarioidone B.

The NMR data of compound **3** were very similar to those of compound **11**. The molecular weight deduced from the HRESIMS ion at  $m/z$  461.1808 [ $M + H$ ]<sup>+</sup> (calcd for  $\text{C}_{24}\text{H}_{29}\text{O}_9$ , 461.1806) indicated a difference of 18 Da. This could be explained by an additional cyclisation in

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