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Sesquiterpene lactones from the extracts of two Balkan endemic *Laserpitium* species and their cytotoxic activity

Višnja Popović^{a,b,*}, Arne Heyerick^a, Silvana Petrović^b, Serge Van Calenbergh^c, Izet Karalić^c, Marjan Niketić^d, Dieter Deforce^a

^aLaboratory of Pharmacognosy and Phytochemistry, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium

^bUniversity of Belgrade – Faculty of Pharmacy, Department of Pharmacognosy, Vojvode Stepe 450, 11221 Belgrade, Serbia

^cLaboratory for Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, 9000 Ghent, Belgium

^dNatural History Museum, Njegoševa 51, 11000 Belgrade, Serbia

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ABSTRACT

Chloroform extracts of the underground parts of two Balkan endemic *Laserpitium* species, *Laserpitium zernyi* Hayek and *Laserpitium ochridanum* Micevski, were chemically investigated. Five unknown guaianolides from the class of slovanolides, of which four were additionally 2 β -esterified, as well as two lactones, previously identified in other *Laserpitium* species, were isolated from the *L. ochridanum* extract. From the *L. zernyi* extract one slovanolide derivative was isolated for the first time in the genus *Laserpitium*. In addition, the phenylpropanoid latifolone and six known sesquiterpene lactones, characterised as derivatives of slovanolide and silerolide, were isolated from the extracts of both species.

The cytotoxic activities of the total extracts and the isolated compounds were tested using MTT and SRB assays on the two human breast cancer cell lines, MCF 7/6 and MCF 7/AZ.

The extracts exerted cytotoxic activities with the IC₅₀ values ranging 65.21–348.25 μ g/mL. The *L. ochridanum* extract was most potent in the MTT test with IC₅₀ values of 65.21 and 66.09 μ g/mL in the MCF 7/AZ and MCF 7/6 cell lines, respectively. The highest cytotoxic activity exerted 2 β ,8 α -di-angeloyloxy-10 β -hydroxy-6 α H-guaian-3,(7-11)-dien-12,6-olide, a slovanolide derivative with an additional double bond in lactone ring, on highly invasive MCF 7/6 cell line, with IC₅₀ value 0.7 μ M in both assays tested. Generally, guaianolides with a higher number of ester moieties at the positions 2 β , 8 α , 10 β or 11 α exhibited IC₅₀ values in the micromolar range, while eudesmanolides and guaianolides with a lower number of esters did not induce significant cytotoxicity.

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1. Introduction

Plant-derived natural products still provide a source of new potential cancer chemotherapeutic agents as evidenced by clinical trials for cytotoxic activity of naturally occurring or synthetically modified molecules (Lee, 2010; Saklani and Kutty, 2008). Sesquiterpene lactones (SLs) are secondary plant metabolites that are gaining more and more attention in the view of their broad spectrum of pharmacological activities, such as anti-inflammatory, antitumour, cytotoxic, antibacterial, antihelminthic, uterus contracting, antimalarial, neurotoxic and allergic activity (Merfort,

2011). Structure activity relationship (SAR) studies indicate that specific features in the structure of SLs are responsible for antitumour and cytotoxic effects by the interference with specific signalling pathways. This made specific SLs such as artemisinin, thapsigargin and dimethyl-amino-parthenolide lead compounds in cancer clinical trials (Ghantous et al., 2010).

The genus *Laserpitium* L. (Apiaceae) comprises about 20 aromatic perennial species distributed from the Canary Islands in the West to Iran in the East (Hartvig, 1986). In the *Flora Europaea* ca. 14 species of the genus *Laserpitium* are noticed, most of which are European endemics limited to the mountainous areas of Central and Southern Europe (Tutin, 1968). *Laserpitium ochridanum* Micevski is a local endemic species at Mt. Galičica, Former Yugoslav Republic of Macedonia (FYROM) (Micevski, 2005). *Laserpitium zernyi* Hayek (Micevski, 2005) is an endemic plant in the mountainous regions of the Central Balkans (S.W. Serbia, W. FYROM, E. Albania, N.W. Greece) and previously it was treated as a subspecies of the closely related *L. siler* L. subsp. *zernyi* (Hayek) Tutin (Tutin, 1968).

* Corresponding author at: University of Belgrade – Faculty of Pharmacy, Department of Pharmacognosy, Vojvode Stepe 450, 11221 Belgrade, Serbia. Tel.: +381 11 39 51 319; fax: +381 11 39 72 840.

E-mail addresses: visnjap@pharmacy.bg.ac.rs (V. Popović), Arne.Heyerick@ugent.be (A. Heyerick), silvana.petrovic@pharmacy.bg.ac.rs (S. Petrović), Serge.VanCalenbergh@UGent.be (S. Van Calenbergh), Izet.Karalic@UGent.be (I. Karalić), mniketic@nhmbeo.rs (M. Niketić), Dieter.Deforce@UGent.be (D. Deforce).

The underground parts of some widely distributed *Laserpitium* species were used as the traditional herbal medicines in Europe. The roots and rhizomes of laserwort (*L. siler*) were used for the preparation of tonics for strengthening and refreshing with a bitter and sharp taste and for treating toothache. The underground parts of *L. latifolium* L. were used as emenagogue, diuretic, for treating gastrointestinal disorders, heart and liver dysfunctions, pulmonary tuberculosis, rheumatism and topically in pruritic dermatomycoses (Hegi, 1906; Kuprevič, 1974; Vereskovskii et al., 1992).

Chemical investigations into the composition of chloroform extracts of different plant parts of various *Laserpitium* species confirmed the presence of sesquiterpene lactones belonging almost exclusively to the class of guaianolides of the slovanolide type (Milosavljević et al., 1999).

In this study, chloroform extracts of the underground parts of two hitherto uninvestigated *Laserpitium* species were subjected to flash chromatography partition, followed by preparative HPLC separation. From the extract of *L. ochridanum* five unknown derivatives of slovanolide (1–5), four of them being 2 β -esterified, together with a slovanolide derivative previously isolated from *L. marginatum* L. (6), and the eudesmanolide isosilerolide (7), previously isolated from extracts of *L. siler* (Milosavljević et al., 1999), were isolated and chemically identified (Fig. 1). A guaianolide (8) previously isolated from *Seseli vayredanum* L. (Barrero et al., 1994) was for the first time isolated in the genus *Laserpitium*, more specifically from *L. zernyi*.

In addition, six SLs previously isolated from the underground parts of *L. siler* and *L. garganicum* (Ten.) Bertol., were isolated from the extracts of the underground parts of both *L. zernyi* and *L.*

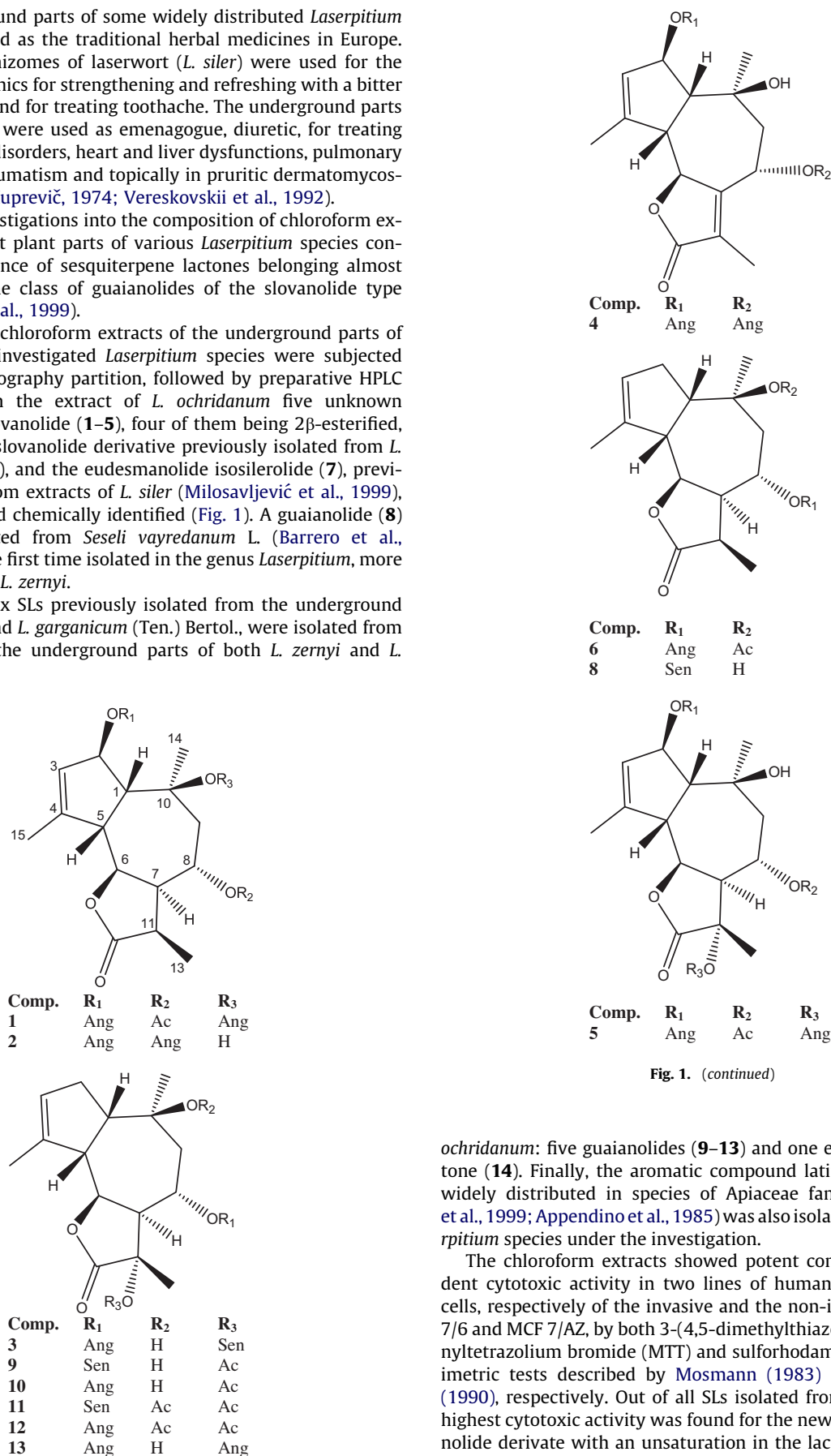


Fig. 1. Structures of compounds 1–15.

Fig. 1. (continued)

ochridanum: five guaianolides (9–13) and one eudesmanolide lactone (14). Finally, the aromatic compound latifolone (15) that is widely distributed in species of Apiaceae family (Milosavljević et al., 1999; Appendino et al., 1985) was also isolated from both *Laserpitium* species under the investigation.

The chloroform extracts showed potent concentration-dependent cytotoxic activity in two lines of human breast carcinoma cells, respectively of the invasive and the non-invasive type: MCF 7/6 and MCF 7/AZ, by both 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and sulforhodamine B (SRB), colorimetric tests described by Mosmann (1983) and Skehan et al. (1990), respectively. Out of all SLs isolated from the extracts the highest cytotoxic activity was found for the newly identified slovanolide derivative with an unsaturation in the lactone ring. The IC₅₀ values of the guaianolides were inversely related with the number of esterifications and molecular weight, whereas the cytotoxic

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