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## Cytotoxic and allergenic sesquiterpene lactones from cushion bush (*Leucophyta brownii* Cass.)

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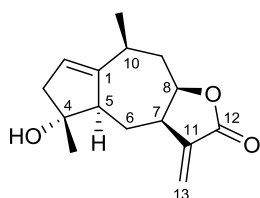
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## Cytotoxic and allergenic sesquiterpene lactones from cushion bush (*Leucophyta brownii* Cass.)

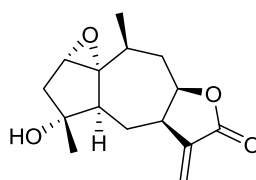
Hyldgaard MG<sup>1</sup>, Purup S<sup>2</sup>, Paulsen E<sup>3</sup>, Andersen KE<sup>3,4</sup>, Andersen F<sup>3,4</sup>, Fretté F<sup>1</sup>, Christensen LP<sup>1</sup>

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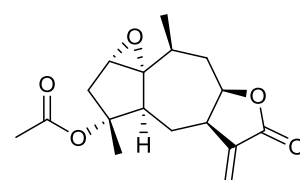
Cushion bush (*Leucophyta brownii* Cass., Asteraceae) has become a popular pot and outdoor container plant in some Nordic countries. Several cases of allergic contact dermatitis caused by cushion bush have been reported [1, 2]. Cushion bush is rich in sesquiterpene lactones containing an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone moiety that are known for their anti-inflammatory and cytotoxic activity due to reactions with sulfhydryl groups of functional proteins via a Michael-type reaction. This also makes this type of sesquiterpene lactones potential allergenic [1, 3]. Seven sesquiterpene lactones (**1–7**) containing an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone moiety were isolated from cushion bush and identified by LC-MS and 1D and 2D NMR spectroscopy as described previously [3]. Compounds **1–7** were investigated for their cytotoxic activity towards human breast cancer (MCF-7) and colon cancer (HT-29) cells as well as their allergenicity. Compounds **2, 3, 5** and **6** reduced proliferation of HT-29 and MCF-7 cells with IC<sub>50</sub> values < 10  $\mu$ M, whereas compounds **1, 4** and **7** showed less cytotoxicity with an IC<sub>50</sub> value of > 20  $\mu$ M for both cell lines. Six of seven sesquiterpene lactones elicited positive reactions in 4 of 11 patients. The sesquiterpene lactones **3** and **5–7**, were confirmed to be sensitizers, whereas leucophytalin A (**4**) and 4 $\alpha$ -hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide (**1**) were shown to be allergenic for the first time. No clear correlation between the cytotoxic activity and allergenicity of the tested compounds could be established. However, the present investigation confirmed a connection between type IV allergenicity and cytotoxicity of sesquiterpene lactones containing an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone moiety.



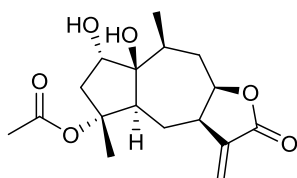
4 $\alpha$ -Hydroxy-5 $\alpha$ H,10 $\alpha$ H-1,11(13)-guaidien-8 $\beta$ ,12-olide (**1**)



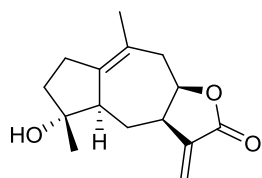
4 $\alpha$ -Hydroxy-1 $\alpha$ ,2 $\alpha$ -epoxy-5 $\alpha$ H,10 $\alpha$ H-11(13)-guaien-8 $\beta$ ,12-olide (**2**)



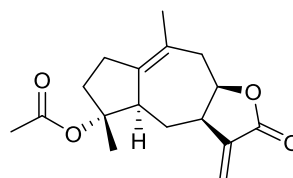
Calocephalin (**3**)



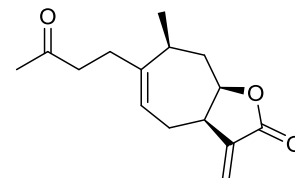
Leucophytalin A (**4**)



Pseudoivalin (**5**)



Pseudoivalin acetate (**6**)



Tomentosin (**7**)

**References:** 1. Paulsen et al. (2013) Contact Dermatitis 69: 303-310. 2. Paulsen et al. (2017) Contact Dermatitis 76: 280-286. 3. Hyldgaard MG et al. (2015) J. Nat. Prod. 78: 1877-1885.