Investigation of Leoligin Derivatives as NF-κB Inhibitory Agents.

Papaplioura Eleni [a], **Michael Schnürch** [b, *]

Vienna University of Technology (TU Wien), Getreidemarkt 9/163-OC, 1060 Wien, Austria;
**michael.schnuerch@tuwien.ac.at*

The natural compound leoligin [1] a furan-type lignan and a secondary metabolite found in the roots of edelweiss (*Leontopodium nivale* ssp. *alpinum*) was discovered as an interesting compound with anti-inflammmatory pharmacological activity profile [2-5]. Among other effects, it acts as a weak NF-κB inhibitor.

The transcription factor NF-κB is an essential mediator of inflammation; thus, the identification of compounds that interfere with the NF-κB signaling pathway is an important topic. The natural products leoligin and 5-methoxyleoligin have served as a starting point for the development of NF-κB inhibitors. Using our modular total synthesis method of leoligin, modifications at two positions were undertaken and the effects of these modifications on the biological activity were investigated. The first modification concerned the ester functionality, where it was found that variations in this position have a significant influence, with bulky esters lacking Michael-acceptor properties being favored. Additionally, the substituents on the aryl group in position 2 of the tetrahydrofuran scaffold can vary to some extent, where it was found that a 3,4-dimethoxy and a 4-fluoro substitution pattern show comparable inhibitory efficiency.

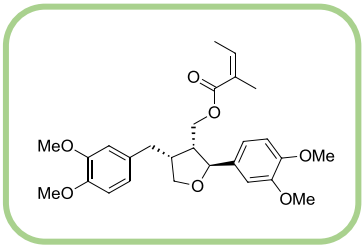

Figure 1. Leoligin, the major lignan isolated from *L. nivale ssp. alpimum*.

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