Short Lecture SL13

Synthetic Lignans Targeting Cardiovascular Diseases: Structure Motifs and Biological Activity

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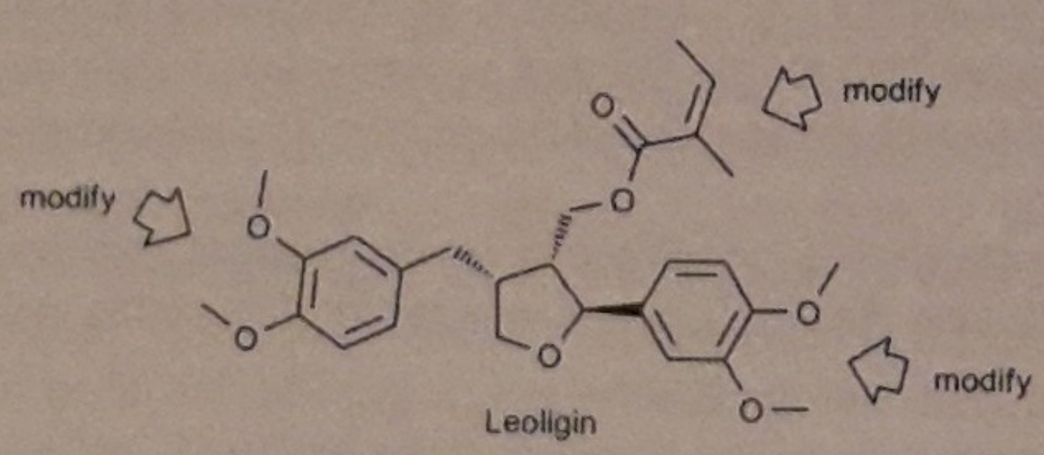
Intimal hyperplasia is a condition mainly characterized by the infiltration of smooth muscle cells (SMCs) and their excessive proliferation at the inside of blood vessels. This inflammatory response is a key factor in the development of atherosclerosis, and hence thrombus formation, possibly with ensuing myocardial infarction or stroke. Compounded by damage to endothelial cells (ECs), this vessel-occluding over-response is frequently encountered in the wake of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI, stenting), leading to eventual restenosis.[1] A useful drug would therefore potently inhibit SMC proliferation and thus prevent intimal hyperplasia, but ideally not interfere with ECs.

Leoligin (see Figure), a furan-type lignan isolated from the roots of *Leontopodium alpinum*,[2] had previously been shown to prevent intimal hyperplasia in *in vitro* human saphenous vein organ cultures as well as *in vivo* mouse models by inhibiting SMCs. Unfortunately, this natural product also inhibited ECs, but was not toxic to these cells.[3]

We thus set out to prepare synthetic analog compounds of leoligin in order to understand the structure-activity relationships involved, and also with the aim of developing lignans which were more potent and SMC/EC-selective.



This contribution discusses our approach of iterative structural motif variation driven by results of phenotype-based SMC and EC inhibition assays, providing lead structures and molecular probes suited to a translational research phase of the project.

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References:

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