SYNTHETIC LIGNANS TARGETING CARDIOVASCULAR DISEASES

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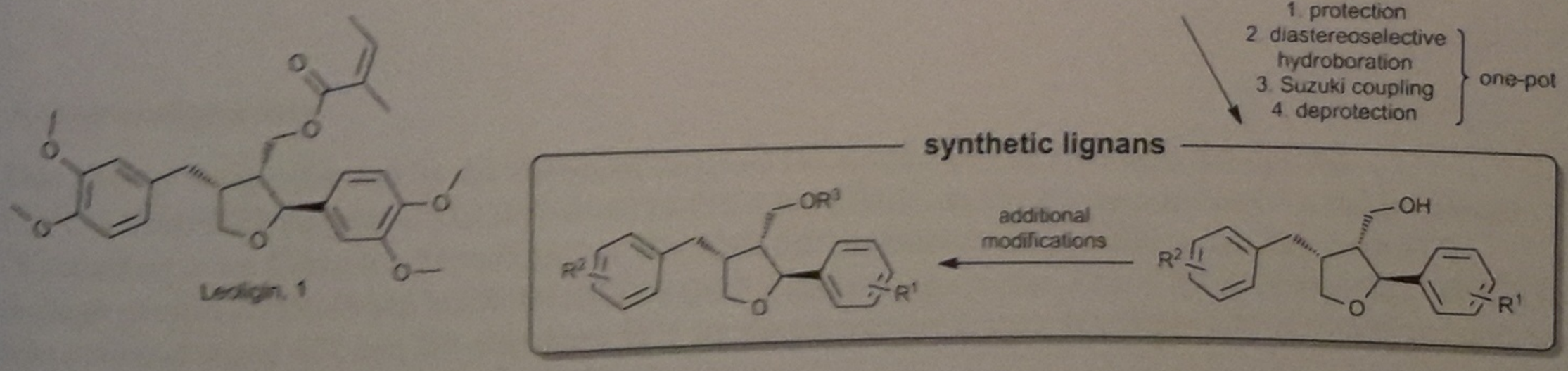
Intimal hyperplasia is a condition mainly characterized by the infiltration of smooth muscle cells (SMCs) and their excessive proliferation at the inside of blood vessels. This inflammatory response is a key factor in the development of atherosclerosis and hence thrombus formation, possibly with ensuing 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 **1**, a furan-type lignan isolated from the roots of *Leontopodium alpinum*,[2] had previously been shown to inhibit intimal hyperplasia in *in vitro* human saphenous vein organ cultures as well as *in vivo* mouse models.[3] Our aims were to prepare a library of analog compounds of this natural product using a modular synthetic route and study their inhibition profiles:



With such synthetic analogs we were able to increase the SMC inhibitory activity up to 15-fold compared to leoligin itself. Additionally, our most active analogs did not show inhibition activity on ECs, unlike the natural hit compound or other compounds which are currently used clinically, e. g. in drug-eluting stents.

We therefore conclude that the synthetic lignans we prepared are both useful probes to investigate the causative factors of graft disease and stent-related complications, as well as potential treatments for intimal hyperplasia and its detrimental consequences on the cardiovascular system.

References

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