NATURAL COMPOUNDS AS LEAD STRUCTURES FOR FOCUSSED COMPOUND LIBRARY DESIGN TOWARDS ANTI-INFLAMMATORY AND CNS ACTIVITIES

Marko D. Mihovilovic

Institute of Applied Synthetic Chemistry, Vienna University of Technology
Getreidemarkt 9/163-OC, A-1060 Vienna, Austria
marko.mihovilovic@tuwien.ac.at

Natural compounds still represent a rich source of hit structures for medicinal chemistry exploitation. Their unique properties as small molecules including evolved interaction with large biomolecular receptors, metabolic stability, as well as mobility and distribution in various tissues make them highly interesting starting points for hit-to-lead development. This contribution will feature case studies regarding rapid compound assembly within the pharmacological areas stated.

Piperine, the pungent alkaloid of black pepper, and several of its derivatives are modulators of γ-amino butyric acid type A (GABAA) receptors. Concomitantly, this natural product has also been reported to activate transient receptor potential vanilloid type 1 (TRPV1) receptors. We have developed synthetic strategies towards as diversity oriented compound library probing the receptor selectivity for these two particular targets (in particularly highlighting a Heck cross-coupling reaction of conjugated dien-amides). [1]

Inflammatory events associated with cardiovascular conditions after stent- or by-pass surgery lead to decreased efficiency of these interventions on a mid- to long-term timeline. Leolignin (a tetrahydrofuran-type neolignan isolated from *Leontopodium alpinum*) was found to control this inflammatory reaction by preventing migration of vascular small muscle cells (VSMCs) into the neointima via inhibition of cell proliferation. We will present the stereoselective total synthesis based on a modular metal-assisted modification strategy to enable rapid development of focused compound libraries. Synthetic analogs displayed significant increase in efficacy in combination with a favorable improvement of anti-proliferative activity towards VSMCs versus endothelial cells.

1. Schöffmann, A.; Wimmer, L.; Goldmann, D.; Khom, S.; Hintersteiner, J.; Baburin, I.; Schwarz, T.; Hintersteininger, M.; Pakfeifer, P.; Oufir, M.; Hamburger, M.; Erker, T.; Ecker, G.F.; Mihovilovic, M.D.; Hering, S. *J. Med Chem.* **2014**, *57*, 5602-5619.