NATURAL COMPOUND INSPIRED DEVELOPMENT OF NEW LEADS WITH ANTI-INFLAMMATORY AND CNS ACTIVITIES

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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 on the identification of particular pharmacophores responsible for receptor selectivity in combination with rapid compound assembly in various pharmacological areas.

Piperine, the pungent alkaloid of black pepper, and several of its derivatives are modulators of γ-amino butyric acid type A ($GABA_A$) 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). Key structural features for favorable interaction with each of the pharmacological targets will be outlined.

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. The identification of natural compounds controlling this inflammatory reaction by preventing migration of vascular small muscle cells (VSMCs) into the neointima via control of cell proliferation offers an interesting approach to alleviate this problem. We will present the total synthesis of leolignin, a neolignan isolated from *Leontopodium alpinum* (a famous Austrian flower found in Alpine regions). The approach is based on a highly modular metal-assisted modification strategy enabling rapid development of focused compound libraries. This enabled preparation of synthetic analogs with significant increase in efficacy in combination with a favorable improvement of anti-proliferative activity towards VSMCs versus endothelial cells.