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Title: Synthesis and Biological Evaluation of Natural Products and Derivatives as potential Anti-Inflammatory Agents and $GABA_A$ Receptor Modulators

The focus of this dissertation lies at the interface of organic and medicinal chemistry. With natural products Magnolol and Honokiol as starting point rational design of a compound library was achieved. Based on the known biological activity of the parent compounds, effects of non-natural derivatives on nuclear transcription factors (PPAR-, RXR-, LXR- and LXR-) were investigated as a potential anti-inflammatory treatment. Compounds were also investigated with regard to their ability to modulate GABAA receptors. Initially efforts were made to rapidly access novel derivatives. In a second round of compound design a hypothesis-driven approach based on the pharmacological data obtained from first-generation compounds was followed.

Eventually, this approach led to the discovery of subtype-selective GABAA receptor modulators, a success en route to developing drugs with improved side-effect profiles. Moreover, compounds selectively acting on RXR- receptors were identified as well. The second part of this work deals with the total synthesis of natural products Notoincisol A and B, which contain anunique polyenyne structure. Polyenyne-containing natural products, e.g. Falcarindiol, Falcarinol, Oploxynes or Oenanthotoxine, represent an important compound class due to their manifold biological activities. Notoincisol A and B were recently isolated from Notopterygium incisum and shown to possess potential anti-inflammatory activity via the interaction with peroxisome proliferator activated protein gamma (PPAR-). The total synthesis of Notoincisol A containing two stereogenic centers was accomplished.

Proof of the absolute configuration of the natural product was achieved by means of chemical synthesis. For medicinal chemistry purposes the remaining stereoisomers were synthesized and pharmacological evaluation of their anti-inflammatory potential is currently underway. In the synthesis of Notoincisol B great advances toward the target molecule could be made. However, attempts to finalize the total synthesis were yet unsuccessful. Several alternative strategies were outlined to achieve the target structure. Furthermore, Falcarindiol was synthesized for the purposes of an in-depth pharmacological characterization of the compound as GABAA receptor modulator.