ABSTRACT IN ENGLISH LANGUAGE

Charles University, Faculty of Pharmacy in Hradec Králové,

Department of Pharmacology and Toxicology

Candidate: Mgr. Alžbeta Štefela

Supervisor: Prof. PharmDr. Petr Pávek, PhD.

Title of the doctoral thesis: Novel bile acid derivatives as promising therapeutic approach

Bile acids (BAs) are amphipathic steroidal molecules that are ~~traditionally~~ known to facilitate intestinal digestion and absorption of lipids and fat-soluble substances. On top, the recent findings have revealed that they represent important signaling agents involved in the orchestration of lipid, glucose and energy metabolism and immune response. BAs exhibit these roles by activating intracellular nuclear receptors such as farnesoid X (FXR), pregnane X (PXR) vitamin D receptors. Furthermore, BAs act as endocrine signaling molecules and activate numerous biological cascades via a membrane G-protein-coupled receptor, termed TGR5. Therefore, the extensive modulation of BA scaffold underwent to identify compounds with specific targeting of above-mentioned receptors as a promising therapeutic approach for the treatment of various liver and metabolic disorders including cholestasis, biliary cirrhosis, nonalcoholic steatohepatitis or diabetes.

The principal aim of this doctoral thesis was to investigate the structure activity relationship (SAR) between bile acid-derived ligands and receptors involved in bile acid signaling. To address this goal, we used ~~a~~ complex approach combining *in vitro* and cell-free assays with molecular docking. Selected derivatives were then investigated in different cellular models as well as *in vivo* in mice. We demonstrated that acetyl derivatives of deoxycholic and cholic acid are PXR ligands. In the next study, we described 3β-isoobeticholic acid as a low-affinity FXR ligand, which readily epimerases to obeticholic acid in hepatic cells and therefore become a strong FXR agonist in cellular and animal models. In addition, we determined 3,7-dehydroobeticholic acid as a potent TGR5 ligand with minimal activity toward FXR. Then, we introduced a novel bile acid derivative

with unique, first-in-class, combined FXR antagonistic and TGR5 agonistic activity. The compound had no off-target activation and represented the most efficient TGR5 agonist among steroidal compounds described, so far.

The second aim of this doctoral thesis was to evaluate anti-inflammatory capacity of ursodeoxycholic acid derivatives in human THP-1-derived macrophages. We showed that a derivative termed UDCA-18:1LPE suppressed a release of inflammatory cytokines by the inhibiting the recruitment of adaptor proteins into lipid rafts which led to an attenuated activation of p38, JNK, and NF-κB signaling pathways. These results highlighted the previously observed protection by UDCA-18:1LPE *in vivo*.

In conclusion, the studies elaborated in this dissertation contributed to the understanding of SAR between compounds derived from bile acids and their receptors with the description of the downstream signaling and effects.