

## **Abstract**

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Title of diploma thesis: Inhibitory effect of SPA70 on hPXR activation

This work focuses on pregnane X receptor (PXR) and its antagonists. PXR is a ligand-activated nuclear receptor that plays a major role in detoxification of xenobiotics and protecting the organism from their toxic effects. Recent evidence also shows endogenous action of PXR in the metabolism of lipids, glucose and bile acids. However, PXR activation could be harmful, since induction of biotransformation enzymes by PXR agonists may result in reduced treatment efficacy, increased toxicity of drug metabolites and resistance to chemotherapeutic agents. Recent research has been intensively focused on PXR antagonists capable of abolishing these unfavourable effects. Recently discovered human PXR antagonist SPA70 has a promising potential for future usage. In this study, we investigated the inhibitory effect of SPA70 on activated PXR. To activate PXR we used agonists binding directly to PXR (rifampicin, hyperforin, SR12813) and also agonists activating PXR indirectly via cell signalling pathways (U0126, PD184352, PD0325901). Experiments were performed using luciferase reporter gene assay in HepG2 cell line. Based on our results, we confirmed that SPA70 antagonizes agonist-activated PXR. We also presume that SPA70 inhibits activation of PXR caused by indirectly acting agonists. These findings provide a new insight into SPA70 antagonism and suggest another possible future application for the antagonist.