Abstract

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Title of Thesis: Study of Novel FXR Ligands

Human farnesoid X receptor (FXR) is ligand-activated transcription factor that belongs to the nuclear receptor superfamily. FXR binds to its response element (FXRE) as monomer or heterodimer with retinoid X receptor (RXR) resulting to activation of transcription of target genes. FXR positively or negatively regulates a wide range of target genes involved in maintaining the homeostasis of bile acids, cholesterol, lipid and glucose metabolism. Furthermore, FXR transcriptionally regulates genes involved in regulation of the immune response, in the development of inflammation and maintaining the intestinal barrier function and genes controlling coagulation and remodeling of the vessel wall. The interest of current scientific studies is to find the new ligands of FXR, which would be suitable for therapeutic use. Besides the natural bile acids, the first medicinal product containing semi-synthetic FXR ligand, obeticholic acid (6-ECDCA) as active substance was registered last year for the treatment of primary biliary cholangitis. In this experimental rigorosum thesis we focused on testing of the potential ligands of FXR from group of steroid compounds that belongs to the steroid hormones, neuroactive steroids, the compounds derived from bile acids and other using the human hepatoma cell line HepG2. In preliminary experiments, effects of tested compounds on cell viability was tested by MTT assay, however, no meaningful negative effect on cell viability was observed. To demonstrate the interactions of studied steroids with the human FXR, the molecular biological method gene reporter assay was used. Based on our results, we assume that the substance similar to the natural bile acids 12-oxo-5β-cholan-24-oic acid and the compound 5β-androstane-3β-ol are ligands-agonists of the human FXR. In addition, 12-oxo-5β-cholan-24-oic acid appears to be more potent agonist than the natural bile acid chenodeoxycholic acid (CDCA). These results could provide useful insights to development of new drugs targeting to FXR receptor.