

# 1 Summary

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CYP3A4 is an important enzyme involved in elimination of majority of metabolized xenobiotics. It plays a major role in the detoxification system of the human body, therefore it is responsible for many drug-drug interactions (DDIs). DDI present a complication of current pharmacotherapy, in the extreme they can lead in failure of therapy or in life-threatening toxic effects.

DDIs are caused by changes in enzymatic activity of CYP3A4, which is highly variable among individuals. An important mechanism of modulating CYP3A4 activity is the regulation of inducible transcription by nuclear receptors, especially PXR, CAR and GR. The structure of *CYP3A4* promoter and mechanisms of transcriptional regulation has been studied intensively for many years, but the research of relationship of nuclear receptors and transcriptional cofactors in CYP3A4 transactivation is still incomplete.

Present work contributes to elucidation of some questions concerning the effects of azole antimycotics on CYP3A4 transcription via PXR, potency of valproic acid to activate PXR and CAR or determinants of CYP3A4 expression via GR in placental cells. The experiments were performed with up-to-date molecular biology methods and using *in vitro* models of the primary human hepatocytes and hepatoma cell lines.

To the aims of the doctoral thesis:

1. The effects of selected azole antimycotics on CYP3A4 gene expression via PXR. Elucidation of nature of observed effects in the molecular level (**Chyba! Nenalezen zdroj odkazů.**).

We tested effects of selected azole antimycotics (clotrimazole, ketoconazole, itraconazole, fluconazole, oxiconazole, econazole and miconazole) on CYP3A4 gene expression via PXR in primary culture of human hepatocytes and cell lines HepG2, LS174T and CV-1. Using real time RT-PCR, gene reporter assay, one hybrid assay and two hybrid assay we investigated potency of each azole to transactivate CYP3A4 promoter not only in monotherapy but also in co-treatment

with rifampicin, the known CYP3A4 inductor via PXR. We noted significant differences among azoles, identified a potent inductor oxiconazole and illustrated nature of CHibí !!!