Abstract:

Cancer is the second major cause of death after heart-attack in the world. In recent years, research has focused on tyrosine kinase inhibitors (TKIs) as part of targeted chemotherapeutic treatment. Vandetanib is a TKI affecting epidermal growth factor receptor (EGFR), rearrangement during transfection (RET) and vascular endothelial growth factor receptor 2 (VEGFR2). It is primary used for treatment of medullary thyroid cancer. Vandetanib is biotransformed by cytochromes P450 and flavin monooxygenases in human organism. Cytochromes P450 (CYPs) oxidaze vandetanib to only one metabolite, N-desmethyl vandetanib, which exhibits similar efficiency as parental molecule. NADPH is the major cofactor of reaction cycle of CYPs.

This bachelor thesis studies the effect of various types of cofactors and pH on oxidation of vandetanib by selected human recombinant cytochromes P450, namely CYP2C8 coexpressed with cyt b_5, CYP2D6, CYP3A4 and CYP3A4 coexpressed with cyt b_5. Here, we investigate the effect of cofactors NADPH, NADH and their mixture in a 1:1 ratio on the amount of N-desmethyl vandetanib formed during the biotransformation of vandetanib. The effect of pH on the oxidation of vandetanib by CYP 3A4 and CYP 3A4 + b_5 was also analysed. We analysed the amount of the metabolite formed at the pH range 7 to 8.5 and we try to find if the pH optimum of vandetanib biotransformation by selected CYPs is located in this pH range.

The results found in this thesis demonstrate that the most effective cofactor for CYP 2C8 + b_5, 2D6 and 3A4 + b_5 is NADPH. Other types of cofactors were also able to oxidize vandetanib to its metabolite, but not as effective as NADPH. However, the highest amount of N-desmethyl vandetanib was generated by CYP3A4 in the presence of NADPH-NADH mixture. Stimulation of CYP3A4 by cytochrome b_5 resulted in an increase in formation of N-desmethyl vandetanib. Throughout the examination of pH effect, the trend of increasing biotransformation efficiency with increasing pH was observed. No pH optimum of vandetanib oxidation was found in chosen pH range (7 to 8.5).

Key words: biotransformation, cytochromes P450, carcinogenesis, thyroid cancer, vandetanib