ABSTRACT

Vandetanib is an oral anticancer drug, acting as tyrosinkinase inhibitor of a number of cell receptors. It targets to cell receptors, which are responsible for a development and proliferation of medullary thyroid cancer. This drug was approved by FDA (US Food and Drug Administration) for a treatment of late-stage (metastatic) or a progressive medullary thyroid cancer at patients who are ineligible for a surgery. Recent studies indicate that one of problems with the vandetanib therapy is its biotransformation in human organism.

This thesis investigates metabolism of vandetanib. Human and rat hepatic microsomes as well as rat and human cytochromes P450 (CYPs) and flavin monooxygenases expressed in Supersomes™ were used for this study. During experiments rat hepatic microsomes isolated from both the uninduced rats and animals in which indiviual CYPs expression was increased by CYP inducers were used. The metabolites formed from vandetanib were separated by HPLC and identified by mass spectrometry. The formed metabolites were identified as N-desmethylvandetanib and vandetanib N-oxide. Vandetanib N-oxide was generated by all tested microsomes. The highest amount of N-desmethylvandetanib was produced by microsomes of rats pretreated with pregnenolon carbonitrile (PCN that is an inducer of CYP3A). This metabolite was also generated in a low amount by microsomes of rats induced by phenobarbital (an inducer of CYP2B/C) and in microsomes of control (untreated) rats. From all tested human recombinant cytochromes P450, only CYP3A4 was able to produce N-desmethylvandetanib. Of the tested rat recombinant CYPs, only CYP2C11 was able to generate this metabolite. If CYP3A4 was expressed in Supersomes™ together with cytochrome b_5, a significant increased amount of N-desmethylvandetanib was detected. In the case of the flavin monooxygenase 1 (FMO1), this enzyme produced the highest amount of vandetanib N-oxide. Flavin monooxygenase 3 (FMO3) was much less efective in oxidation of vandetanib to this metabolite than FMO1, whereas FMO5 was ineffective in this reaction.

Keywords: tyrosine kinase inhibitors, xenobiotics, vandetanib, N-desmethylvandetanib, vandetanib N-oxide, cytochrome P450