

Abstract:

Vandetanib is anticancer drug used mainly for targeted therapy of medullary thyroid carcinoma. It acts as inhibitor of tyrosine kinase and shows selectivity for vascular endothelial growth factor 2 (VEGFR-2) and epidermal growth factor (EGFR). It also inhibits rearranged during transfection (RET) tyrosine kinase activity. Vandetanib is metabolized by cytochromes P450 (CYPs) and flavin-containing monooxygenases (FMOs) in organism of humans as well as experimental animals. CYPs oxidize vandetanib to N-desmethylvandetanib. FMOs are responsible for the formation of vandetanib N-oxide.

This bachelor thesis studies effect of pH on vandetanib oxidation by CYPs a FMOs present in rat hepatic microsomes induced by different agents.

Collected data show that in majority of series, optimal pH levels for oxidation of vandetanib by CYPs and FMOs are similar to a large extend. The highest amount of N-desmethylvandetanib was observed mostly at the pH 8,5. Vandetanib N-oxide was also produced in the highest quantity at the same level of pH in majority of series.

Results suggest that N-desmethylvandetanib is formed at levels of pH which do not fit in interval of pH for optimal CYP activity. This finding is apparently due to a fact that presence of vandetanib in its neutral form, which is effectively oxidized by CYP, increases at higher pH levels. In majority of series maximum amount of vandetanib N-oxid was observed at levels of pH that fit in interval for optimal FMO activity.

Keywords: vandetanib, cytochromes P450, flavin-containing monooxygenases