Abstract

Recently, biologically targeted treatment by another name targeted molecular therapies have begun to be used in the treatment of cancers bearing specific molecular genetic or morphological traits. Vandetanib is an oral anticancer drug that belongs to a group of tyrosine kinases inhibitors. These inhibitors block signal pathway receptors, thereby inhibit growth, stimulate cell death and reduce the spread of cancer. Vandetanib was approved in April 2011 by the US FDA for a treatment of progressive or symptomatic medullary thyroid cancer. It is used in patients with metastatic or inoperable locally advanced cancer.

The metabolism of vandetanib was studied in this thesis. Specifically, the kinetics of vandetanib oxidation to *N*-desmethylvandetanib by human recombinant cytochromes P450 3A4 expressed in the membrane of *E. coli* (Bactosomes). The effect of the presence of cytochrome b_5 and the effect of the level of NADPH: cytochrome P450 reductase activity on the activity of cytochrome P450 3A4 were studied.

The demethylated metabolite of vandetanib, *N*-desmethylvandetanib, was identified and separated by high performance liquid chromatography (HPLC). Enzyme kinetics studies indicate that vandetanib oxidation is affected by both, the level of NADPH:CYP reductase activity and the presence of cyt b_5. Systems with a higher reductase level show higher oxidation activity than systems with a lower reductase level. Likewise, the presence of cyt b_5, which increases the stimulation of vandetanib oxidation, has a positive effect on vandetanib oxidation activity. Vandetanib oxidation kinetics catalyzed by systems without cyt b_5 (CYP3A4LR006, CYP3A4R044 and CYP3A4046) exhibit sigmoidal concentration dependence, which indicates the possibility of binding two vandetanib molecules into the active site of the enzyme.

Key words: cytochrome P450, tyrosine kinase inhibitors, cancer illnesses, vandetanib, *N*-desmethylvandetanib

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