ABSTRACT

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Title of rigorous thesis: Interaction studies of MEK inhibitors and Cytochrome P450 3A4

Objective of our work was to introduce a new method for detection of CYP3A4 inhibition effect of potentially therapeutical compounds. CYP3A4 is the main biotransformation enzyme of 50% current drugs in clinical use and its inhibition may lead to the plasma levels increase of other coadministered drugs which may result in various drug-drug interactions and potentially life threatening adverse effects. Potential of a drug candidate to cause severe pharmacokinetic interactions may be a reason of the clinical trials suspension or withdrawal of a medicinal product from the market and therefore it is essential to determine pharmacokinetic profile of drug candidates at early stages of the development.

In addition, we focused on study of interaction potential of MEK1/2 inhibitors PD0325901, PD184352 and U0126 known to inhibit Ras/Raf/MEK/ERK pathway playing an important role in the oncogenesis of various malignancies. Due to the fact that some of these MEK1/2 inhibitors have already entered clinical trials it is absolutely crucial to study their interaction potential with other commonly used drugs in order to be able to introduce these compounds succesfully into clinical use.

The method we introduced using comercially available kit P450-Glo™ CYP3A4 Assay (Luciferin-PPXE) Promega has proven to be very practical and useful tool for detection of the interaction potential of selected MEK1/2 inhibitors in terms of possible CYP3A4 inhibition and potential of influencing other drugs metabolism. Moreover, our results have shown mainly that level of CYP3A4 inhibition differs across the studied MEK 1/2 inhibitors and only U0126 exhibited significant CYP3A4 inhibition effect. In case of other MEK1/2 inhibitors we observed only weak or no CYP3A4 inhibition potential and thus they represent compounds with more favourable pharmacokinetic profile in terms of CYP3A4 interaction potential.