Electrochemistry meets enzymes: Investigation of the biotransformation pathway of C-1311 based on electrochemical simulation in comparison to in vitro methods

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The knowledge of the metabolic pathways and the biotransformation of new drugs in the human body is one of the major challenges in pharmaceutical research. It is crucial for elucidation of degradation routes of the new biologically active compounds, especially in the area of possible toxicity. Conventional in vitro drug metabolism studies are based on incubating drug candidate with e.g. hepatocytes or, most importantly, liver cell microsomes and isolating and detecting the metabolic products. Microsomes contain a high enzyme concentration of the cytochrome P450 (CYP) superfamily, which catalyses the majority of oxidative metabolism reactions. As a purely instrumental alternative to mimic drug oxidation reactions occurring in the human body the electrochemical simulation has been developed. Electrochemistry (EC) is recently gaining more attention as a tool in rapid, on-line single compound screening. Potential oxidative metabolites are generated in an electrochemical cell and are subsequently identified by on-line mass spectrometry (EC/MS). C-1311 (5-diethylaminoethylamino-8-hydroxyimidazoacridinone, SymadexTM) is representative antitumor imidazoacridinone derivative developed in our laboratory. It exhibits high cytotoxic activity against a broad spectrum cell lines in vitro and of transplantable animal tumors. The previous studies on molecular mechanisms of its biochemical action showed that the metabolic activation by intracellular enzymes might be necessary for the following interactions of this agent with cell proteins and DNA. Next, we showed that compound was metabolized by enzymes originating from rat and human liver microsomes (RLMs and HLMs). In the presented work C-1311 was chosen as model drug to investigate oxidative metabolism using electrochemistry (the ROXYTM EC System, Antec, USA) coupled to mass spectrometry. The results obtained by EC were then compared with conventional in vitro studies with RLMs as well as HLMs. Electrochemical conversion of C-1311 into phase I metabolites was successfully achieved. Comparing MS results from liver cell microsome incubations to MS results from electrochemical studies we were able to demonstrate that two main metabolic products of C-1311 (side chain degradation products) were detected both in the conventional microsomal approach and in the electrochemical simulation. Thus, it can be noted that EC is very well-suited for the simulation of the oxidative metabolism of imidazoacridinone derivative. In summary, our study clearly confirms that EC/MS method is a feasible alternative to microsomal studies. It can be a versatile and user friendly tool in drug discovery and development when applied complementary to established in vitro or in vivo approaches.

Biography
Agnieszka Potęga obtained her PhD in 2011 in Chemical Sciences (Biotechnology) at the Gdańsk University of Technology (Poland) where she is currently working in the Department of Pharmaceutical Technology and Biochemistry. Her area of research interests are studies on the role of activation and detoxification metabolism in the mechanisms of action and biological outcome of potential anticancer agents and mechanisms of inhibition of drug-metabolising enzymes activity. In particular, her academic work is focused on generation conditions and identification of reactive intermediates from model antitumor acridinone derivatives. 
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