

ABSTRACT

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Title of diploma thesis: **LC-MS analysis of phase one biotransformation of K1277, a potential drug against Alzheimer's disease.**

Alzheimer's disease belongs to the most common neurodegenerative diseases that several millions of people all around the world suffer from. There are few symptomatic drugs, which are able to reduce signs and symptoms of this type of dementia, however none of them is able to completely stop it.

The diploma thesis is focused on a metabolomic study of compound K1277, synthesized as a combination of 6-chlortacrine and aminoacid tryptophan, which thanks to its properties belongs to promising potential drugs against Alzheimer's disease and which has not been published yet.

The aim of this diploma thesis was to perform *in vitro* metabolomic screening of the compound K1277 using human liver microsomes focusing on qualitative and quantitative analysis. As intermediate aims of the thesis, necessary conditions for sufficient biotransformation of compound K1277 were investigated, quantity of metabolised compound K1277, identifications of particular metabolites and proposition of their chemical structures were provided.

The studied compound and its metabolites were analysed by high performance liquid chromatography coupled with high resolution mass spectrometry (LC-MS/MS). An universal gradient elution method of fifteen minutes (using column Kinetex C18, 150 x 3 mm, 2,6 μm , 100 \AA) in a positive mode together with mass scans Full MS/AIF and Full MS/dd-MS² were used for analysis of the metabolites.

Within the diploma thesis was found that chemical compound K1277 provides metabolites during all studied incubation periods with human liver microsomes

in different intensity. Experiments with one and six hour period of incubation revealed only trace amount of the metabolites. Therefore, we focused on an experiment with incubation of twenty four hours and performed qualitative and quantitative analysis. The results of the diploma thesis present a summary of five metabolites of the compound K1277 and their suggested hypothetical chemical structures. In the quantitative part of the results, proportional decrease of compound K1277 metabolised after every incubation period with HLM was determined on each of the tested concentration level.