Abstract

The main task of the thesis was a design and synthesis of new potential antimycobacterial active molecules. Presently, the appearance of MDR-TB strains is alarming and the development of new therapeutical agents is necessary. The work is divided into two parts; first one is related to aminopolysaccharide chitosan and its connection with appropriate antimycobacterial drugs or dyes, second part is concerned with modifications of current antituberculotics.

Due to the structure and physico-chemical properties, chitosan has been found as an interesting drug carrier in biomedicinal chemistry. It is used in drug delivery system with control release of the drug in the target cells or tissues. The component of the first part of the thesis was to review molecular modelling of chitosan, especially its usage as a prodrug or carrier in a field of antibacterial, antitumor and antioxidant activity. Derivatives of chitosan linked with the first or second line antituberculotics were prepared for the purpose of decreasing hepatotoxicity of used drugs. Their antimycobacterial activity against *M. tbc.*, *M. avium* and *M. kansasii* was 125 μg/mL for all strains. Unexpectedly, *O*-carboxymethyl chitosan as an intermediate showed better MIC against *M. tbc.* and *M. avium*. It means that biological activity of chitosan derivatives is based on the inhibitory effect of linked antituberculotics and the degree of deacetylation of chitosan. All tested derivatives did not exhibit cytotoxic effect on PBMC and Hep G2 cells. Chitosan was able to reduce cytotoxicity of antimycobacterial drugs.

Chitosan has been found as a convenient carrier for photoantimicrobial activity in wound healing treatment. Nanofibres of chitosan with rose bengal were prepared, but finally, they had not a sufficient quality for following usage.

Fluorescent labelled chitosan was used for uptake studies by flow cytometer assay. Phagocytosis of chitosan was observed on macrophages and monocytes which are hosts for mycobacteria during a long-time treatment and latent TB.

The aim of the second part of the thesis was a connection of two active molecules by an easily released methine bridge. In first series, PAS, CPX, NFX, PZA were linked with fluorinated hydrazones of benzoic acid. They have shown higher activity against MDR-TB (0.5 μg/mL) than isoniazid and exhibited no decomposition at neutral pH and also in rat plasma more than 48 hours which could improve the bioavailability to target site.

Second series of hydrazones included isoniazid connected with electron acceptor substituted anilines through the methine bridge showed similar biological activity as the parent compound

INH. Lipophility of these derivatives is higher than INH, it signifies more effective transport of the molecule through cellular membranes.