ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové

Department of Organic and Bioorganic Chemistry

Author: Simona Antalová

Supervisor: doc. PharmDr. Mgr. Martin Krátký, Ph.D.

Title of diploma thesis: Synthesis and evaluation of InhA inhibitors as potential antitubercular drugs

Tuberculosis is an infectious disease that belongs to one of the top 10 causes of death worldwide. The most common cause of the disease are *Mycobacterium tuberculosis* complex strains. Antimicrobial therapy of the disease is nowadays complicated by alarming increase of strains resistant to standardly used antitubercular treatment. This is the reason of growing interest and significance in research of new potential antitubercular agents. One of the possible approaches is systematic modification of compounds with a known antimycobacterial activity, one of such compounds being triclosan. This substance acts as an uncompetitive inhibitor of enoyl-acyl-carrier protein reductase (InhA), an enzyme participating in the mycobacterial fatty acid biosynthesis pathway. It does not require activation by the mycobacterial KatG enzyme, thereby avoiding the most frequent mechanism of resistance to the frontline drug isoniazid targeting InhA too. The aim of the study was to synthesise ad evaluate new potential antitubercular drugs based on the structure of triclosan.

In this study we prepared eight compounds derived from triclosan, five of them were esters of carboxylic acids, three of sulfonic acids. Most of the derivatives showed a comparable activity to triclosan against *Mycobacterium tuberculosis* strain (MIC values after 14/21 days of incubation being of 32/64 μmol $L^{-1}$, for triclosan 32/32 μmol $L^{-1}$). Derivatives with the best results among all tested strains were (*E*)-5-chloro-2-(2,4-dichlorophenoxy)phenyl 4-(4-methoxyphenyl)-4-oxobut-2-enoate and 5-chloro-2-(2,4-dichlorophenoxy)phenyl 4-acetamidobenzoate, with comparatively higher activities than isoniazid for atypical strains. In general, esters of carboxylic acids proved to be superior to sulfonates, where aromatic core showed to be disadvantageous.