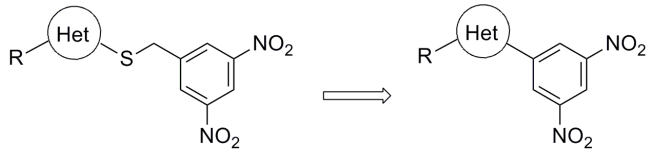
ABSTRACT

Charles University
Faculty of Pharmacy in Hradec Králové
Department of Inorganic and Organic Chemistry

Candidate: Pavel Sychra
Supervisor: prof. PharmDr. Alexandr Hrabálek, CSc.
Title of diploma thesis: **Five-members N-heterocycles as potential antituberculotics**

Tuberculosis is widespread infectious disease predominantly caused by *Mycobacterium tuberculosis*. According to World Health Organization, 10.4 million new cases of tuberculosis and 1.8 million deaths from tuberculosis were registered worldwide only in 2015.

In the previous work of our group it was found that 2,5- and 1,5-disubstituted tetrazoles and 2,5-disubstituted oxadiazoles bearing 3,5-dinitrobenzylsulfanyl fragment exhibited outstanding antimycobacterial activities. The aim of this work was to modify these lead structures by removing the methylsulfanyl linker and to prepare a series of 3,5-dinitrophenyl tetrazole and oxadiazole derivatives.



Het = tetrazole, 1,3,4-oxadiazole

Figure 1: General formula of the compounds studied in this work

Firstly, we prepared a series of 2- and 1-benzyl-5-(3,5-dinitrophenyl)-1*H*-tetrazoles by the reaction of 5-(3,5-dinitrophenyl)-1*H*-tetrazole with diversely substituted benzyl halide. In another part, we dealt with the preparation of tetrazole derivatives containing saturated nitrogen heterocycle. At first, it was necessary to prepare alkylating agents, which have been subsequently used for alkylation of saturated nitrogen heterocycles. Furthermore, several water-soluble analogs of compounds with saturated nitrogen heterocycle and high antimycobacterial activity were prepared.

The next task was to prepare a series of 3,5-dinitrophenyl oxadiazole derivatives. Two pathways were used. The first method was the reaction of acid chloride with 5-(3,5-dinitrophenyl)-1*H*-tetrazole, but the products were not isolated. Target oxadiazoles were obtained by the reaction of hydrazide with 3,5-dinitrobenzoylchloride and by the subsequent closure of oxadiazole ring.

Seventeen of twenty prepared structures were evaluated for their antimycobacterial activities and some of them for their effects on mammalian cell viability. Some of these compounds showed comparable or higher antimycobacterial activity than standard antitubercular drug isoniazid.