Abstract

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Title of doctoral thesis: Synthesis of substituted nitrogen heterocycles as potential antitubercular agents

Tuberculosis (TB) is one of the most common causes of death in the world. It is an infectious disease caused by *Mycobactetrium tuberculosis* (M.tb.). Worldwide, it is estimated that only in 2017 TB caused 1.6 million deaths and 10 million new cases of TB have appeared. TB is treatable and curable disease, but multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains of TB have appeared and the treatment of these resistant strains of TB is very complicated. During the last several decades, only two new antitubercular drugs bedaquilin and delamanid have been introduced into the clinical practice. Thus the development of new antitubercular drug is still very important.

In our group, we developed new antitubercular compounds based on 3,5-dinitrobenzylsulphanyl tetrazole and oxa(thia)diazole, whose efficient concentrations reached tens of nM against drug susceptible and drug-resistant strains of *M. tb*.

In my work, I dealt with both structural types. At first, we prepared series of substituted 5-(3-amino-5-nitrophenyl)-1,3,4-oxadiazole-2-thiols and their *N*-substituted derivatives to demonstrate the necessity of the 3,5-dinitrophenyl moiety for high antitubercular activity. Furthermore, the series of 2-substituted 5-(3,5-dinitrophenyl)-*2H*-tetrazoles and 1-substituted 5-((3,5-dinitrophenyl)thio)-*1H*-tetrazoles were prepared as the analogues of the previously prepared 3,5-dinitrobenzylsulphanyl tetrazoles with a modified linker between the 3,5-dinitrophenyl group and tetrazole heterocycle. These compounds showed comparable or higher efficacy than the parent substances. In the next part of the work we prepared and studied antitubercular activity of a series of 1-substituted 5-(((5-(3,5-dinitrophenyl)-*2H*-tetrazol-2-yl)methyl)thio)-*1H*-tetrazoles and also the impact of the length of a linker between tetrazole cycles to antitubercular activity.

From 1-substituted 5-(((5-(3,5-dinitrophenyl)-*2H*-tetrazol-2-yl)methyl)thio)-*1H*-tetrazole derivatives was derived small series of 2-substituted 5-((5-(3,5-dinitrophenyl)-*2H*-tetrazol-2-yl)methylthio)-1,3,4-oxadiazoles and 2-(3,5-dinitrophenyl)-5-((1-substituted-*1H*-tetrazol-5-ylthio)methyl)-1,3,4-oxadiazoles, that have one oxadiazole cycle instead of tetrazole cycle. All these compounds again showed comparable or higher efficacy than commonly used antitubecular drugs.

Then we prepared a series of 5-substituted 2-(3,5-dinitrophenyl)-1,3,4-oxadiazoles, which did not contain a sulfur atom in the molecules. This change had no effect to antitubercular activity of the prepared substances. Finally, several water-soluble derivatives based on 2-substituted-5-(3,5-dinitrophenyl)-*2H*-tetrazole were prepared.

In addition to the *in vitro* antitubercular activity, *in vitro* antibacterial and antifungal activity was also determined. Moreover, antitubercular activities of the most active compounds from each series against seven clinically isolated MDR strains of *M. tb*. were evaluated and the effects on *in vitro* proliferation of selected mammalian cell lines were studied. These experiments demonstrated high selectivity of action of our compounds.