Abstract

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Title of Diploma Thesis: Synthesis of substituted oxadiazoles with potential antimycobacterial activity

Tuberculosis is an infectious disease caused by mycobacteria *Mycobacterium tuberculosis*, which is one of the top ten causes of death worldwide. According to the World Health Organization, 10.4 million new cases were reported in 2016 and 1.7 million people died of this disease (including 0.4 million people with HIV). Treatment of tuberculosis caused by drug-susceptible strains of M. tuberculosis is very successful, with up to 82% of patients cured. However, a major problem is the therapy of patients with drug resistant strains of M. tuberculosis. Multidrug-resistant tuberculosis (MDR-TB) is a TB that cannot be cured by isoniazid (INH) or rifampicin (RIF), the two most effective first-line antituberculotics. In this case, TB is treated with second-line antituberculotics, which should be administered for up to two years. However, according to statistics, only 32.2% of patients with MDR-TB are successfully cured in the European Union. Therefore, it is important to look for and develop new drugs that act on MDR-TB and can help reduce the time and cost of treatment.

In the previous work at the Department of Organic and Bioorganic Chemistry it was found that 2,5-disubstituted 1,3,4-oxadiazoles bearing a 3,5-dinitrobenzylsulfanyl group and their reverse analogs carrying a 3,5-dinitrophenyl group directly attached to the heterocycle, exhibited significant and selective antimycobacterial activity. These compounds showed in vitro antimycobacterial activity in the MIC (minimal inhibitory concentration) range of 0.03-0.06 μM.

Previous studies of the structure-antimycobacterial activity relationships of the 1,3,4-oxadiazoles have shown that the heterocycle can significantly affect the efficacy of the compounds. The 1,3,4-oxadiazoles showed significantly higher efficacy than the 1,5- and 2,5-disubstituted tetrazoles or the non-heterocyclic substances. The aim of this work was to prepare a series of substances by bioisosteric exchange of 1,3,4-oxadiazole for 1,2,4-oxadiazole and see how the arrangement of heteroatoms in the heterocycle affects antimycobacterial activity.

First, a series of 3-aryl-5-((3,5-dinitrobenzyl)sulfanyl) -1,2,4-oxadiazoles was prepared. Two methods of preparing 1,2,4-oxadiazole were used. The first method was based on the reaction of the corresponding nitrile with *N*,*N*-diisopropylethylamine and subsequent closure of the 1,2,4-oxadiazole ring with 1,1'-thiocarbonyldiimidazole. All target oxadiazoles in a yield of 70-87% were prepared by this method. Subsequent alkylation of the prepared 3-aryl-1,2,4-oxadiazoles-5-thiols resulted in the synthesis of the final compounds in a yield of 31-98%. The second method was the reaction of 4-chlorobenzamidoxime with ethyl chloroformate, followed by cyclization to 1,2,4-oxadiazol-5-one and replacement of the carbonyl group of the 1,2,4-oxadiazole with a thiocarbonyl group by reaction with Lawesson's reagent. However, the last reaction was not carried out and 3-chlorophenyl-1,2,4-oxadiazole-5-thiol was not prepared by this method.

Subsequently, a series of 5-alkylsulfanyl-3-(3,5-dinitrophenyl)-1,2,4-oxadiazoles, i.e. reverse analogs, was prepared. For the synthesis of 3-(3,5-dinitrophenyl)-1,2,4-oxadiazole-5-thiol, the same procedure was used as for the preparation of 3-aryl-1,2,4-oxadiazole-5-thiols. The yield of reverse 1,2,4-oxadiazole-5-thiol was 44%. By alkylation of this thiol, 2 final compounds were prepared. Because of the low yields of the sequential reaction method, the „one pot“ method was used, which was more advantageous for reverse analogs.

Of the five structures prepared, four compounds were tested for their antimycobacterial activity and two for their cytotoxicity and antifungal and

antibacterial activity. The substances exhibited relatively similar or higher antimycobacterial activity than the standard first-line antitubercular drug isoniazid, but significantly lower activity than equally substituted 1,3,4-oxadiazole derivatives.