ABSTRACT

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Drugs currently used for the treatment of tuberculosis are the result of studies carried out 50 or 60 years ago. With the constantly growing bacterial resistance to these pharmaceuticals grows also the importance of research for new antimycobacterially active compounds. The marine environment undoubtedly holds an enormous potential for discovering new leads for the development of antitubercular agents. One of these leads is a spirocyclic compound called aerothionin (**1**), which was found to be active against multidrug-resistant strains of *Mycobacterium tuberculosis*, as well as three non-tuberculosis mycobacteria (**Figure 1**). In addition, several spirocyclic structures (not only from marine origin) were discovered to affect on the *M. tuberculosis* in recent years, making this structure segment attractive for antitubercular research.

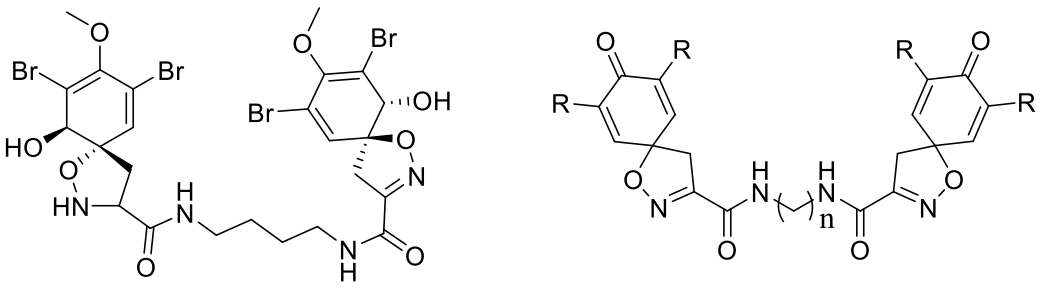

Figure 1: Aerothionin (**1**) and general structure of the products.

Following these promising results, the present thesis project is based on the development of bromotyrosine derivatives similar to aerothionin with the aim to optimize their biological

activity as well as their synthesis by removing some of the functional groups. Starting from L-tyrosine, through four step synthesis, 7,9-dibromo-8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxylic acid (**MS-4**) and 8-oxo-1-oxa-2-azaspiro[4.5]deca-2,6,9-triene-3-carboxylic acid **(MS-11)** were prepared and subsequently subjected to coupling reactions in order to achieve the desired products.

MS-4 and **MS-11** were obtained without significant complications, however, the amide coupling turned out to be quite problematic. More than ten synthesis approaches were tried for the syntheses of diamides, but only two of them proved to be successful, resulting in three final products (and one intermediate) that differ in the substitution of the aromatic ring. These products were tested for their antimycobacterial activity *in vitro*, using *Mycobacterium marinum* as a test organism. Compound **MS-20** showed the best results, when during first 48 hours performed better than rifampicin control treatment and decreased relative luminiscence under 1 % of the initial value before 24 h, when administered together with rifampicin.