Abstract

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Pathogens *Burkholderia pseudomallei* and *Legionella pneumophila* cause severe diseases like Legionnaire’s disease and melioidosis. While Legionnaire’s disease manifests as acute pneumonia, melioidosis has different clinical features and ends by multi-organ involvement and septic shock. Low sensibility of gram negative bacteria *B. pseudomallei* and *L. pneumophila* to antibiotics together with threatening resistance represent a great problem. For these pathogens their virulent factor macrophage infectivity potentiator (MIP) protein is a suitable target. MIP proteins are peptidyl/prolyl *cis/trans* isomerases, highly important factor of penetration and dissemination for *B. pseudomallei* and *L. pneumophila*. MIP protein belongs to FK506 binding protein (FKBPs) superfamily, which forms highly stable complex with its inhibitors tacrolimus and rapamycin. Due their immunosuppressive activity, these drugs are contraindicated for treatment of infection diseases. However inhibition of the protein proves that MIP protein is appropriate pharmacological target.
Recently it has been discovered that MIP protein inhibition is conserved to pipecolic acid part of rapamycin structure. Group of prof. Holzgrabe prepared library of MIP protein inhibitors based on pipecolic acid structure without immunosuppressive activity. The aim of my work was preparation of new analogues of potential inhibitors, namely pyrrole and phosphonamide analogues (Fig. 1).

In the first part of my work I prepared analogues of previously synthetized inhibitors with substitution of pipecolic acid by 1H-pyrrole-2-carboxylic acid. This synthesis was problematic due to low reactivity and stability of products, however I managed to prepare one analogue. In the second part I tried to prepare analogues with substitution of sulphonamide by phosphonamide group. Synthesis of these analogues was unsuccessful because of high hydrophilicity, complicated detection and separation of the products. Synthesis developed in my work could enable the preparation of new pyrrole analogues and to test their potential activity on MIP protein. Furthermore, results of phosphonamide synthesis can be utilized and eventually more lipophilic analogues can be prepared.