Abstract

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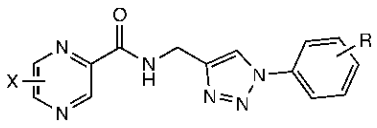
Title of diploma thesis: Design, synthesis, and biological evaluation of pyrazinamide derivatives containing 1,2,3-triazole linker II

Antimicrobial resistance is a serious problem, making it important to develop new antibiotics.This thesis focuses on the design and synthesis of pyrazinamide derivatives with a *1H*-1,2,3-triazole linker and their evaluation for antimicrobial activity. Taking inspiration from previous works, we synthesized a series of 20 compounds where pyrazinamide is linked to a phenyl side ring through the triazole heterocycle. The compounds vary in substitution at the pyrazine ring (H, 3-Cl, 5-Cl or 6-Cl) and the phenyl side ring (2-Cl, 2-OH, 4-Et, 4-OMe, 4-OH). The synthesis was done through a multi-step procedure, with the main triazole synthesis combining azides and alkynes in a reaction inspired by click chemistry, with yields ranging from 23 to 80%. All reported compounds are characterised by ^{1}H NMR, ^{13}C NMR, elemental analysis and melting points. Biological evaluation revealed promising inhibitory activity against *Mtb* H37Ra with three compounds: 5-chloro-*N*-((1-(4-hydroxyphenyl)-*1H*-1,2,3-triazol-4-yl)methyl)pyrazine-2-carboxamide (**19**) MIC = 15.625 µg/ml, 5-chloro-*N*-((1-(2-hydroxyphenyl)-*1H*-1,2,3-triazol-4-yl)methyl)pyrazine-2-carboxamide (**7**) MIC = 3.97 µg/mL and 5-chloro-*N*-((1-(2-chlorophenyl)-*1H*-1,2,3-triazol-4-yl)methyl)pyrazine-2-carboxamide (**3**) MIC = 1.98 µg/mL. Most compounds showed good inhibitory activity against *M. kansasii* with tyoical MIC values ranging from 62.5 to 1.98 µg/mL. Established structure activity relationship suggests an increase in antimycobacterial activity in the case of 5-Cl substitution on the pyrazine ring, combined with substitution in pos. 2 or 4. by an electronegative substituent. Antibacterial and antifungal screening showed no considerable activity.



R= 2-Cl , 2-OH , 4-Et , 4-OMe , 4-OH

x= H, 3-Cl , 5-Cl , 6-Cl