2-(Quinolin-4yloxy)acetamides are active against Drug-susceptible and Drug-resistant *Mycobacterium tuberculosis* strains

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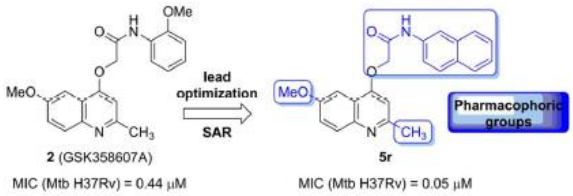
Palavras Chave: *4-quinoloxyacetamides, drug-susceptible, tuberculosis*

Abstract

Chemical modifications of lead compounds were carried out, potent antitubercular agents with MIC as low as 0.05 µM.



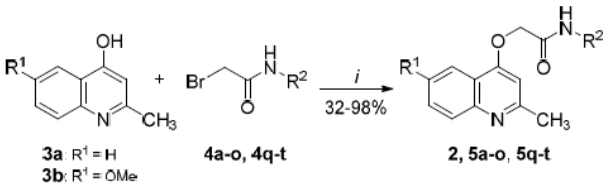
Introdução

Tuberculosis (TB) is an infectious disease caused mainly by *Mycobacterium tuberculosis* and is one of the most devastating public heath public problems worldwide. Approximately 9.6 million new cases claiming 1.5 million lives were report in 2014.[1] Furthermore, MDR-TB and XDR-TB treatments are limited and recommended medicines are often not available revealing an urgent need for new anti-TB alternatives.[2]

In this study, we synthetized a series of 2-(quinolin-4uloxy)acetamides for further evaluation of MICs using drug-susceptible and drug-resistant Mtb strains. Moreover, a preliminary structure-activity relationship (SAR) study was also presented.

Resultados e Discussão

The syntheses of 2-(quinolin-4uloxy)acetamides **2**, **5a-o** and **5q-t** were conducted in two synthetic steps[3]. First, the 2-bromo-*N*-arylacetamides **4a-o** and **4q-t** were prepared by the acylation reaction of substituted anilines or 1(2)-naphthylamine using bromoacetyl chloride in the presence of 4-dimethyl aminopyridine (DMAP) as a catalyst. Subsequently, 2-(quinolin-4-yloxy)acetamides **2**, **5a-o**, and **5q-t** were synthesized by the O-alkylation reaction of 4-hydroxyquinolines **3a-b** with 2-bromo-N-arylacetamides **4a-o** and **4q-t** in the presence of potassium carbonate using *N*,*N*-dimethylformamide (DMF) as the solvent (**Scheme 1**).



Scheme 1. Reaction conditions: i) DMF, K_2CO_3, 25 °C, 16 h.

The synthesized compounds were evaluated in a whole-cell assay against *M. tuberculosis* strain H37Rv conducted by the Resazurin Assay method using isoniazid (INH) as the standard drug. The most active molecules against *M. tuberculosis* H37Rv were tested against a panel of clinically isolated drug-resistant strains and in a macrophage-infected model. In addition, thermodynamic solubility, metabolic stability in human liver S9 fraction, cytochrome P450 inhibition, and cardio toxicity risk were also evaluated.[3]

The simplicity, easily accessible reactants and reagents, reasonably good yields (32–98%), and high purity make this synthetic method attractive.

Further, the synthesized compounds were active against drug-resistant strains and were devoid of apparent toxicity to Vero and HaCat cells (IC_{50}s ≥ 20 µM). In addition, the 2-(quinolin-4-yloxy)acetamides showed intracellular activity against the bacilli in infected macrophages with action similar to rifampin. Finally, the most potent compounds exhibited low to moderate metabolic stabilities, low risks of drug−drug interactions based on CYP450 inhibition studies with no signs of cardiac toxicity in zebrafish (*Danio rerio*) at 5 µM.

Conclusões

These data indicate that this class of compounds may furnish candidates for future development to, hopefully, provide drug alternatives for tuberculosis treatment.

Agradecimentos

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[1]WHO, Global tuberculosis report **2015**; [2]Hoffner, S. Lancet. **2012**, *380*, 1367−1369; [3]Pissinate K. *et al.* **2016**, DOI:10.1021/acsmedchemlett.5b00324.