Synthesis and biological evaluation of new piperazine-based amino-alcohol-quinolines as promising antimycobacterial drugs

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Abstract: Worldwide, *Mycobacterium tuberculosis* (*M. tb*) is responsible for 10.6 million infections and 1.6 million deaths. In Europe and North America, the incidence of non-tuberculous mycobacteria (NTM) infections exceeds that of *M. tb*. NTM are ubiquitous and opportunistic for immunocompromised people and/or with chronic respiratory diseases. Among NTM with pulmonary pathogenicity, *Mycobacterium abscessus* is the most difficult to treat and *Mycobacterium avium complex* (MAC) is the most common, causing 80% of NTM infections. Current NTM treatments require a combination of antibiotics which can cause many side effects over a long period. For example, MAC infections should be treated with at least three drugs (macrolides, rifamycin and ethambutol) for 12 to 24 months. These drugs are not very effective with a success rate of 52 to 60%, as they were initially designed for *M. tb* infection treatment. In addition, they can occur many side effects, including hepatotoxicity, urine coloration, ocular disorders, … Thus, it is urgent to develop new molecules that are safer, more NTM specific and, if possible, with a novel mechanism of action. Quinoline-based pharmacophore is found in two compounds active against MAC, bedaquiline (BQ) and mefloquine (MQ). Interestingly, they target ATP synthase, an enzyme essential for mycobacteria. However, BQ and MQ can induce side effects on the liver and central nervous system, respectively. In order to reduce the toxicity of MQ, quinoline core has been pharmacomodulated. Herein, we present (i) the synthesis of piperazine-based amino-alcohol-quinolines active against NTM, (ii) their *in silico* physicochemical and pharmacokinetic properties and, (iii) their *in vitro* antimycobacterial evaluation.

Keywords: non-tuberculous mycobacteria; amino-alcohol-quinolines; heterocyclic synthesis; antimycobacterial evaluation