

Design and evaluation against resistant *Mycobacterium tuberculosis* of novel thiophene-thiazolidine hybrid derivatives

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Keywords: (Thiophene, Thiazolidine, *Mycobacterium tuberculosis*)

ABSTRACT

Tuberculosis (TB) refers to an infectious disease caused primarily by the bacterium *Mycobacterium tuberculosis* (Mtb), which, although it primarily affects the lungs, can also affect other parts of the body such as bones, brain, and stomach. It is transmitted through the air after infected people sneeze, cough, or spit.[1–3] In Brazil, the disease affected 80,012 individuals in 2023, leading to 5,845 deaths recorded in the previous year. In 2022, there were 770 new cases of drug-resistant tuberculosis.[4] In addition, a recent study estimated that almost half of the affected families (48.1%) with an infected patient had costs above 20% of their annual family income – reaching 44.4% and 78.5% among patients with sensitive and resistant tuberculosis, respectively.[5] The current treatment offered by SUS includes Isoniazid for 6 (6H) or 9 months (9H), Rifampicin for 4 months (4R) and, more recently, starting in 2021, Rifapentine associated with Isoniazid for 3 months (3HP).[4] Recently, our research group published a review listing active multi-target compounds against TB [6], which encouraged the search for active compounds by analyzing our internal chemolibrary of compounds. Thus, in an initial screening, 36 compounds were evaluated against the resistant TB strain H37Ra, identifying the hit compound LQM495. After applying a virtual reverse docking protocol, it was suggested that this compound is a potential inhibitor of the enhanced intracellular survival protein (Eis), which was confirmed experimentally.[7] Thus, 47 novel thiophene-thiazolidine hybrid compounds were investigated, in which 4 derivatives showed promising activity against H37Ra and H37Rv strains (a strain resistant to rifampicin, isoniazid, and streptomycin). Among these, hit compound **LQM421** was the most promising, with minimum inhibitory concentration (MIC) values of 10 and 20 μM against MTb strains H37Ra and H37Rv, respectively (INH presented 0.2 and 0.6 μM , respectively, and RIF 0.03 μM for both strains). In addition, combination tests with the reference drugs isoniazid (INH), rifampicin (RIF), moxifloxacin (MOX), streptomycin (STR), and ethambutol (ETB) suggest that hit compound **LQM421** and the drugs act independently. Finally, these data suggest a new scaffold for the development of potential compounds against this serious disease, which are safe, low-cost and accessible, especially to individuals who are in a situation of socioeconomic vulnerability.