Title: EVALUATION OF ANTIMICROBIAL ACTIVITY OF NAPHTHOQUINONES AGAINST *Mycobacterium tuberculosis*

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Abstract:

Tuberculosis (TB) is an infectious disease caused mainly by *Mycobacterium tuberculosis*, despite being curable, is still a problem of global public health. Among the obstacles to TB control, is the increase in cases of patients infected by resistant strains, the long duration of treatment and its toxic effects. This reinforces the need to develop new drugs that increase the therapeutic arsenal available for the treatment of TB. The aim of this study was to evaluate the antimycobacterial activity of six naphthoquinones compounds. It was determined the minimum inhibitory concentration (200 µg/mL to 0.4 µg/mL) of the molecules by the microdilution method Resazurin Microtiter Assay (REMA) and the minimum concentration capable of inhibiting 90% of bacterial growth (IC90) of three *M. tuberculosis* strains: a pan susceptible H37Rv (ATCC 27294); a isoniazid monoresistant (INHr), with mutation in the *kat*G gene codon 315 Ser-Tir (ATCC 35822); and a rifampin monoresistant (RMPr), with mutation in the *rpo*B gene codon 526 His-Tir (ATCC 35338).. From six naphthoquinones, five were active against the H37Rv strain (IC90 between 10 and 89 µg/mL); six were active against INHr (IC90 between 10 and 44 µg/mL) and RIFr (IC90 between 0.9 and 95 µg/mL). The most active molecule against the H37Rv strain was also the most active for the INHr, with IC90 of 10 µg/mL, and contains cloro as substituent, while the unique molecule to have a benzene ring as a substituent, had the lowest IC90 for the RMPr strain, of 0.9 µg/mL. These differences in antimycobacterial activity of naphthoquinones seem to be related to the radicals in 3-*meta* position. The results demonstrate the potential of these molecules, particularly with the cloro substituent for sensitive and INHr strains, and with a benzene ring for RMPr strains, and could be a scaffold for new drugs for TB treatment. The next step is to elucidate the mechanisms of action of these compounds.

Key-words: Antimicrobials, drug resistance, *Mycobacterium tuberculosis*

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