TITLE: MINIMUM INHIBITORY CONCENTRATION OF (-)-CAMPHENE THIOSEMICARBAZONES DERIVATIVES IN ACID ENVIRONMENT AGAINST *Mycobacterium tuberculosis*

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ABSTRACT: Tuberculosis (TB) is an infectious disease mainly caused by *Mycobacterium tuberculosis,* which is a curable disease if the patients are properly treated. However, the routinely used anti-TB first line drugs such as rifampicin (RIF), isoniazid (INH), ethambutol (EMB), streptomycin (STR), and pyrazinamide (PZA) have become therapeutically ineffective due to the increased occurrence of resistant bacillus. With the global emergence of resistant TB, mainly in certain regions of the world, an urgent need for development of new anti-TB drugs arose. In addition, it is important to investigate alternative drugs with action in acid pH, once the bacillus stays inside macrophage environment during the infection and the disease. The PZA is a pro-drug, which has activity against the *M. tuberculosis* inside the macrophage where the pH is acid. Despite of the remarkable PZA *in vivo* activity, some isolates have been resistant to this drug. Thus, the objective of this study was to determine the minimum inhibitory concentration (MIC) of (-)-camphene thiosemicarbazones derivatives, at acid pH, and compare the previously obtained MIC at neutral pH in *M. tuberculosis* $H_{37}Rv$ (ATCC 27294). The MIC was performed three times on different days by modified REMA (Resazurin microtiter assay plate) by using neutral (7.0) and acid (6.0) pH Middlebrook 7H9 added of OADC Enrichment medium in 96 wells microplates. The 15 (-)-camphene thiosemicarbazones derivatives were studied using concentrations ranging from 250 to 0.976 µg/mL. PZA was used as drug control for each assay. In the previously determined MICs at neutral pH, nine derivatives showed MIC > 250 µg/mL, two 62.5 µg/mL and four 15.6 µg/mL. In acid pH, seven derivatives showed MIC > 250 µg/mL, one 31.25 µg/mL, two 15.6 µg/mL and five 7.8 µg/mL. Of 15 (-)-camphene thiosemicarbazones derivatives, three (20 %) showed decrease of three, four or five fold MIC value compared to neutral pH. The other 80 % derivatives did not have technically significant difference in MICs values compared to those at neutral pH. We observed that these three (-)-camphene thiosemicarbazones derivatives had their action against the bacillus improved in acid pH, similarly to PZA. Additional studies are being carried out to elucidate the improvement of the anti-*M. tuberculosis* activity.

Keywords: Tuberculosis, acid pH, REMA, camphene

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