TITLE: *IN VITRO* ACTIVITY OF (E)-2-(4-(TERT-BUTYL)BENZYLIDENE)-N-((1S.2R.4R)-2.3.3-TRIMETHYLBICYCLO[2.2.1]HEPTAN-2-YL) THIOSEMICARBAZONE AND COMBINED WITH ANTITUBERCULOSIS DRUGS AGAINST *Mycobacterium tuberculosis*

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ABSTRACT:

Tuberculosis (TB) ranks alongside with the Acquired immunodeficiency syndrome (AIDS) as a leading cause of death worldwide. The increase of AIDS cases, insufficient TB control, the emergence of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), especially in cases of co-infection with human immunodeficiency virus (HIV), are a major concern for the control of TB. Therefore, the search for new compounds or drugs combinations that inhibit the growth of *Mycobacterium tuberculosis* is an alternative to help the TB control. The Thiosemicarbazones, which showed chemical and biological properties, such as antibacterial, antiviral and antiprotozoal activity are compounds with great scientific interest due to their easy synthetic acquisition. In this sense, we aimed to evaluate the activity of (E)-2-(4-(tert-butyl)benzylidene)-N-((1S.2R.4R)-2.3.3-trimethylbicyclo[2.2.1]heptan-2-yl) thiosemicarbazone **(C-1)** and their effect in combination with anti-TB drugs against *M. tuberculosis*. The compound tested was synthetized and kindled provided by Chemical Laboratory of State University of Maringa. The minimal inhibitory concentration (MIC) and the anti-TB combinatory actions were conducted using **C-1** alone and combined with isoniazid (INH), ethambutol (EMB), streptomycin (SM) against *M. tuberculosis* H_{37}Rv (ATCC 27294) reference strain by *Resazurin Microtiter Assay Plate* (REMA) and checkerboard method, respectively. The fractional inhibitory concentration index (FICI) was calculated for each combination and FICI ≤ 0.5 was considered as synergism, FICI > 0.5 - 4 as no interaction or additive effect and FICI > 4 as antagonism. Also, the **C-1** cytotoxicity was determined on epithelial VERO cells (ATCC CCL 81) using the MTT colorimetric method (3- (4,5-dimethylthiazol-2-yl) 5-diphenyltetrazolium). The cytotoxic concentration (CC_{50}) was determined and the selectivity index (SI) obtained by the CC_{50}/MIC ratio. The compound **C-1** showed good activity against *M. tuberculosis* with MIC 3.9 µg/mL and no antagonistic effects were observed with the used anti-TB drugs (**C-1** x INH, **C-1** x EMB, **C-1** x SM). The **C-1** had good selectivity by the detected SI 21.36. Our study indicates that **C-1** takes place as a good candidate for additional studies to find new compounds against *M. tuberculosis*.

Keywords: *Mycobacterium tuberculosis*, camphene, REMA, synergism.

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