TITLE: New benzofuroxan compound as a promising candidate for tuberculosis treatment: activity against resistant clinical isolates and *in vivo* infection.

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ABSTRACT:

The recommended treatment for Tuberculosis (TB) has become obsolete in view of the various resistance mechanisms developed by *Mycobacterium tuberculosis* (*M. tb*). Therefore, the search for new compounds that are active against resistant isolates and with strong inhibitory action associated with low toxicity has been intense. The benzofuroxan compound called TB 13 is a potential drug candidate for the treatment of TB since, as a preliminary result, it has already presented a minimum inhibitory concentration value (MIC90) of 0.70 μM against a standard strain of *M. tb* $H_{37}Rv$ and a selectivity index (SI) value greater than 58 against macrophage cells (J774A.1) and lung fibroblasts (MRC-5) in 24h. Further investigating its potential, benzofuroxan was evaluated for its inhibitory capacity against 5 clinical isolates of *M. tb* with different resistance profiles using the *in vitro* methodology of REMA – microdilution technique in a 96-well plate that uses rezasurin as a developer after 7 days of incubation – in addition to being evaluated *in vivo* after infection of Balb/C mice with *M. tb* $H_{37}Rv$ that received treatment by gavage of a suspension at 200 mg/kg for 4 weeks. The results obtained showed that TB 13 was able to inhibit mono and pre-extensively resistant isolates at concentrations that varied between 0.27 and 0.52 μg/mL and was able to promote an *in vivo* inhibition of 1.45 $\log_{10}$ compared to the untreated group, equating to the effect presented by rifampicin, administered under the same conditions, which showed an inhibition of mycobacterial growth of 1.23 $\log_{10}$. Furthermore, even after completion of treatment (3 months), a decrease in mycobacterial concentration in the lungs of mice was observed when compared to the untreated group. These results converge with the expectations of the potential of a new drug candidate and, therefore, are quite encouraging. The evaluation of the mechanism of action, in the next stage of the work, will promote a better understanding of this new and promising compound.

Keywords: benzofuroxan, tuberculosis, drug discovery.

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