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Title: In vitro and In silico Analysis of β-lactam Derivatives as Antimycobacterial Agents

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Abstract: Background: Tuberculosis is a worldwide public health threat, according to the World Health Organization, 10.8 million people acquired the infection and 1.8 million deaths occurred due to the disease in 2015. Currently, β-lactam derivatives have emerged as antituberculosis agents.

Objective: β-lactam derivatives were synthesized and tested in vitro against M. tuberculosis (pan-susceptible and resistant strains) and macrophage cell line J77A.1.

Methods: Three series of β-lactam derivatives were synthetized following the Staudinger reaction of an aromatic imine and an acid chloride. The antimycobacterial activity was carried out by the microplate Alamar blue assay and cytotoxicity was assessed by the trypan blue exclusion assay on macrophage cell line J774A.1. The software AutoDock Vina was used to perform molecular docking studies of the synthesized drugs on the active site of the crystal structures of β -lactamase and transpeptidase from M. tuberculosis.

Results: 7 β-lactam derivatives were effective against M. tuberculosis, including resistant strains. β-5 was the most active compound against the five strains (MIC= 3.125-6.25 µg/mL) with low cytotoxicity. In silico analysis indicated the probable binding sites of the synthesized derivatives on β-lactamase and transpeptidase.

Conclusion: β-lactam derivatives were effective on resistant M. tuberculosis strains with a low cytotoxicity; therefore these compounds could be used for development new antitubercular agents.

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