

**TITLE:** A SYNTHETIC ALKALOID DERIVED FROM MARINE SPONGE: ANTIBACTERIAL AND ANTIBIOFILM ACTIVITIES, AND CITOTOXICITY

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**ABSTRACT:**

Healthcare-associated infections (HAI) are an important public health problem in the world that compromises the safety and quality of care of patients in health facilities. Among the microorganisms that cause HAI, highlight the bacteria *Klebsiella pneumoniae* and *Staphylococcus aureus*, both from ESKAPE group, and resistant to several antimicrobials. In this work, we evaluated the antibacterial and antibiofilm activity of a synthetic alkaloid (named Teoc-9a) derived from the marine sponge *Theonella* sp. against *K. pneumoniae* ATCC 43816 and *S. aureus* ATCC 29213. In addition, we also investigated the role of the outer membrane of *K. pneumoniae* as an intrinsic barrier to the performance of compound and its cytotoxicity in mammalian cells. The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) were determined as described by the Clinical and Laboratory Standards Institute (CLSI). The MIC and MBC against *S. aureus* were 0.98 and 7.8 µg/mL, respectively, and against *K. pneumoniae* there was no activity at highest concentration tested (125 µg/mL). Therefore, we repeated the assay against *K. pneumoniae* in presence of polymyxin B at sub-inhibitory concentration (0.49 µg/mL), and found a MIC value of 62.5 µg/mL, indicating that the compound did not would be acting on Gram-negative bacteria due to the presence of the outer membrane. The MIC values to amoxicillin and gentamicin used as positive control, to *S. aureus* and *K. pneumoniae* were, 0.24 and 0.49 µg/mL, respectively. The experiments in disruption established biofilms was performed using a microtiter dish biofilm formation assay, and the biofilm reduction percentages in treated groups were calculated by comparing absorbance values to untreated wells. The alkaloid was able to reduce 25% of the pre-formed *S. aureus* biofilm at 0.49 to 3.91 µg/mL concentrations, while it was not able to reduce pre-formed *K. pneumoniae* biofilm. The cytotoxicity evaluated in baby hamster kidney (BHK) cells, by colorimetric method using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT), revealed cytotoxic concentration 50 (CC50) of 33.61 µg/mL. The selectivity index, calculated by the ratio between CC50 and MIC, indicated that the compound is 37 times more toxic to bacteria than to cell. The findings for *S. aureus* are considered promising and further studies should be conducted to verify their antibacterial activity *in vivo*.

**Keywords:** alkaloid, antibacterial, biofilm, cytotoxicity, *Klebsiella pneumoniae*, *Staphylococcus aureus*

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