Identification of a potential lead structure for designing new antimicrobials against *Staphylococcus epidermidis* resistant strains

André Luiz P. G. Lourenço[1], Paula A. Abreu[1], Bruno Leal[1], Luiz C. S. Pinheiro[2], Carlos R. Rodrigues[3], Alice M. R. Bernardino[2], Helena C. Castro[1].

[1]Universidade Federal Fluminense; Instituto de Biologia ,LABioMol,[2]Universidade Federal Fluminense; Instituto de Química, [3]Universidade Federal do Rio de Janeiro; Faculdade de Farmácia, Rio de Janeiro, Brazil.

Bacterial infections are a significant cause of morbidity and mortality among critically ill patients. The increase of antibiotic resistance in bacteria from human microbiota such as *Staphylococcus epidermidis*, - an important nosocomial pathogen that affects immunocompromised patients or those with indwelling devices, - increased the desire for new antibiotics. In this study we determined the antimicrobial activity of a series of 27 thieno[2,3-b]pyridines derivatives (**1, 2, 2a–2m, 3, 3a–3m**) against a drug-resistant clinical *S. epidermidis* strain and performed a structure-activity relationship analysis using molecular modeling. Our results showed that some stereoelectronic properties, calculated using Spartan`06 program, were correlated with the biological activity, as the high lipophilicity and LUMO energy, and the low molecular weight and polar surface area values. The addition of a tetrazole group, the occupation of the meta position in the phenyl ring by low or noncharged substituents were also important. In addition, we evaluated the *in silico* pharmacokinetics and toxicity parameters using Osiris Property Explorer program and Lipinski ‘‘rule of five,’’ which are tools to assess the relationship between structures and drug-like properties of active compounds. Our results showed that **3b** was the most potent compound of the series and presented lower theoretical toxicity risks and a better druglikeness and drug-score profile than chloramphenicol. All molecular modeling and biological results reinforced the promising profile of **3b** for further experimental investigation and development of new antibiotics.

Keywords: Antimicrobials, *Staphylococcus epidermidis*, Molecular modeling.