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Structure-Activity Relationship Studies of Staphylococcus aureus DNA Gyrase B Inhibitors as Antibacterial Agents Employing Random Forest Models

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ABSTRACT

Infections by *Staphylococcus aureus* are a serious healthcare problem, with a high alert for resistant strains. The World Health Organization characterized the methicillin-resistant *S. aureus* in the high priority group for the development of new antibiotics. Following this need, inhibition of DNA gyrase presents itself as an interesting drug target, due to the lack of homologs in mammalian, and it could be a way to overcome the resistance problem. In this study, classification structure-activity relationship models based on the random forest algorithm were employed to classify antibacterial compounds acting as DNA gyrase inhibitors. The models were generated and validated for the classification of antibacterial activity (external MCC = 0.775), DNA gyrase inhibition (external MCC = 0.577), and a consensus of these two endpoints (external MCC = 0.577). The structural interpretation highlighted the relevance of heterocycle substituents. This information may provide understanding in the structure-activity relationship of this compounds class, providing insights for further developments.

KEYWORDS

Antibacterial Agents, Classification Models, DNA Gyrase B Inhibitors, Ligand-Based Drug Design (LBDD), Machine Learning, QSAR, Random Forest, SAR

1. INTRODUCTION

Antimicrobial resistance is a frightening problem spread around the world. It is responsible for the increase of the death risk, specifically in hospitalized patients due to multidrug-resistant (MDR) bacteria (Giske et al., 2008; Maragakis et al., 2008; Nelson et al., 2017). The number of new MDR strains increased as a result of the combination of different factors, such as the indiscriminate use of antibiotics (Fleming-Dutra et al., 2016; Centers for Disease Control and Prevention (U.S.), 2019). During the COVID-19 pandemic, despite the rareness of bacterial co-infections, most patients were treated with antibiotics (Calderón-Parra et al., 2021). Additionally, agriculture and livestock play

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an important role in this problem (Boeckel et al., 2015; Manyi-Loh et al., 2018; Van Boeckel et al., 2019). Annually, the global human death estimative is 700,000 and in 2050 will expect to reach 10 million (Ghosh et al., 2019). Besides this unfavorable scenario, pharmaceutical companies' lack of new antibiotics could represent a major risk to humankind leading to a new "pre-antibiotic era" (Gajdács, 2019).

To help overcoming this need, in 2017, the World Health Organization (WHO) set the priorities to antibacterial development. This priority list classified pathogens into three classes according to their urgency: critical priority, high priority (where the methicillin-resistant *Staphylococcus aureus* [MRSA] is included), and medium priority (World Health Organization, 2017). For the development of new antibacterial drugs, it is desired a high selectivity against the pathogen to avoid toxicity in the host. The simplest way to achieve this property is to use essential targets in the bacteria metabolism that is absent in the human organism. Following these guidelines are the *S. aureus* DNA gyrase, an essential enzyme for genetic material replication and has no direct counterpart in mammalian cells. This enzyme is responsible for introducing negative supercoils into DNA in advance of the replication fork. The DNA gyrase displays the biological activity as heterotetrameric structures containing two substructures A (GyrA) and B (GyrB) for DNA gyrase, where GyrB is responsible for ATP hydrolysis and provides the energy required for the reaction catalyzed by GyrA. The other two substructures are for topoisomerase IV (Collin et al., 2011; Gross et al., 2003).

Recently, drug design companies have been successful in showing DNA gyrase inhibition through the use of different chemical scaffolds such as Schiff bases (Salem, Ragab, El-Khalafawy, et al., 2020), quinoxalines (Ammar et al., 2020), coumarin-thiazolyl esters (Liu et al., 2020), and others (Kolarič et al., 2021; Salem, Ragab, Askar, et al., 2020; Werner et al., 2015). In 2020, a series of N-thiadiazole-4-hydroxy-2-quinolone-3-carboxamides was synthesized and tested against *S. aureus* and several other gram-positive species (Xue et al., 2020). One of the most active compounds showed, beyond the DNA gyrase B inhibition, antibacterial activity, and a viable pharmacokinetic profile, being metabolically stable as well as orally active. Following these results, this work aimed to understand and predict the DNA gyrase inhibition and the bactericidal activity of this moiety derivatives, using classification Random Forest (RF) models for these two endpoints.

2. MATERIAL AND METHODS

2.1. Dataset Compounds

Thirty-seven compounds with inhibitory activity (IC_{50}) against *S. aureus* GyrB as well as minimum inhibitory concentration (MIC) against *S. aureus* (ATCC29213) (Supplementary Table S1) synthesized and tested under the same experimental conditions were employed in this work (Xue et al., 2020). The 3D structures of compounds were built and energetically minimized using Discovery Studio (*Discovery Studio Visualizer*, 2020). After, the ionization states were corrected according to physiological pH using QUACPAC software 2.0.0.3 (*QUACPAC*, 2020), followed by conformational analysis aiming to generate the most stable conformer of each compound employing OMEGA 3.1.0.3 (Hawkins et al., 2010; *OMEGA*, 2020). Both biological activities were converted to their negative logarithm values (pIC_{50} and pMIC) before chemometric analysis. All compounds were classified into active and inactive compounds for machine learning training. Three classes were calculated and used as input to ML algorithm: (i) compounds were classified as active/inactive using the average value of pIC_{50} (6.237); (ii) compounds were classified as active/inactive using the average value of pMIC (2.130); (iii) compounds were classified as active/inactive after Hierarchical Clustering Analysis (HCA) using both biological activities as a consensus classification (an attempt to classify the compounds that could inhibit the molecular target and, simultaneously, present antibacterial activity).

The dataset compounds were separated in training and test sets containing 80% and 20% of the total number, respectively, according to hierarchical cluster analysis (HCA) of three main spaces:

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