Chapter 17
Classification of Staphylococcus Aureus FabI Inhibitors by Machine Learning Techniques

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ABSTRACT

Enoyl-acyl carrier protein reductase (FabI) is a key enzyme in the fatty acid metabolism of gram-positive bacteria and is considered a potential target for new antibacterial drugs development. Indeed, triclosan is a widely employed antibacterial and AFN-1252 is currently under phase-II clinical trials, both are known as FabI inhibitors. Nowadays, there is an urgent need for new drug discovery due to increasing antibacterial resistance. In the present study, classification models using machine learning techniques were generated to distinguish SaFabI inhibitors from non-inhibitors successfully (e.g., Mathews correlation coefficient values equal to 0.837 and 0.789 calculated with internal and external validations). The interpretation of a selected model indicates that larger compounds, number of N atoms and the distance between central amide and naphthyridinone ring are important to biological activity, corroborating previous studies. Therefore, these obtained information and generated models can be useful for design/discovery of novel bioactive ligands as potential antibacterial agents.

1. INTRODUCTION

In the last decades, methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been considered a threat to humanity due to their high mortality rate. The lower respiratory tract, skin (followed by necrosis) and bloodstream are the main tissues affected by MRSA infections (Lowy, 2003), and it is considered endemic in several hospitals worldwide (CDC, 2016; Klevens et al., 2006). Moreover, antibiotics resistance is a major public health issue and there is an urgent need for new antibacterial drugs. In this sense, the World Health Organization (WHO) recently released a priority list of microbial infections which needs discovery/design of new drugs treatment (Shrivastava, 2018; Wenzel, 2004).

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In general, essential pathogen enzymes, which are not present in host cells, are considered good molecular targets for drug design. Furthermore, type II fatty acid biosynthesis (FAS-II) pathway is considered a good source of drug targets and its main difference from mammals (type I) fatty acid biosynthesis is that the last one occurs in a multidomain enzymatic complex (Chirala et al., 1997). The enoyl acyl-carrier-protein (ACP) reductase (FabI) is the key enzyme FAS-II pathway (Heath & Rock, 1995) and have known inhibitors, such as triclosan (McMurry et al., 1998) and AFN-1252 (an antibacterial designed specifically against *S. aureus* including MRSA which is tested in clinical phase-II) (Hafkin et al., 2015). In last decades, several new classes of *S. aureus* FabI (*Sa*FabI) inhibitors have been reported on literature: triclosan analogs (Gerusz et al., 2012), diazaborines (Baldock et al., 1996), 1,4-disubstituted imidazoles (Heerding et al., 2001), indole derivatives (Miller et al., 2002; Seefeld et al., 2001; Seefeld et al., 2003), thiopyridine (Ling et al., 2004), 4-pyridone derivatives (Kitagawa et al., 2007), spironaphthyridinones piperidines derivatives (Sampson et al., 2009), tetrahydropyridodiazepines (Ramnauth et al., 2009), azetidine ene-amides derivatives (Takhi et al., 2014), benzimidazole derivatives (Mistry et al., 2016), and N-carboxy pyrrolidine derivatives (Kwon et al., 2018). Most of these inhibitors were successfully tested mainly against wild-type *S. aureus* and MRSA, while a fraction was also tested against other strains and/or bacteria such as triclosan-resistant *S. aureus*, *Escherichia coli*, methicillin-resistant *Staphylococcus epidermidis*, and *Haemophilus influenzae.* Furthermore, selected molecules were tested against *in vivo* infection models indicating then their potential as therapeutic agents. Natural products also have been identified as FabI inhibitors such as luteolin, curcumin (Yao et al., 2010) and jaceosidin, a flavonoid isolated from *Artemisia californica* (Allison et al., 2017).

The diversity of FabI inhibitors in terms of chemical classes provides a large amount of structural information allowing the application of computer-aided drug design (CADD) techniques to study and design inhibitors as new antibacterial agents. Recently, a study combining molecular docking, molecular dynamics and binding free energy to describe the ligand-enzyme interactions was reported (Yang et al., 2017). Quantitative structure-activity relationship (QSAR) studies also were published highlighting the importance of molecular structures and its substituent to FabI inhibition (Lu et al., 2012; Kronenberger et al., 2017). In general, those computational works suggested three main findings: (i) interactions with Tyr-156 and NADPH are essential for inhibition; (ii) hydrophobic interactions at Tyr-146 pocket are important to biological activity and; (iii) H-bond with Ala-95 and π-stacking with NADPH ring A could be responsible for potency (Yang et al., 2017; Lu et al., 2012; Kronenberger et al., 2017).

QSAR models are generated with mathematical methods, which correlate molecular properties and structural features with biological activity, and thus providing direct or indirect insights of binding mode and/or other related molecular mechanisms. This approach has been widely used to predict the biological activities of unknown compounds in virtual screening and scaffold hopping campaigns (Braga et al., 2014; Passeri et al., 2018; Soufan et al., 2018). In the last decades, machine learning techniques (MLT) such as artificial neural networks (ANN), support vector machines (SVM) and random forest (RF) have been applied to generate regression and classification models to predict pharmacodynamics, pharmacokinetics and toxicological endpoints (Soufan et al., 2018; Lima et al., 2016; Gertrudes et al., 2012; Maltarollo et al., 2015). In this work, several MLT models were generated by using different techniques aiming to classify known compounds as *Sa*FabI inhibitors or non-inhibitors.