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PROPOSITION *IN SILICO* OF BENZOIC ANALOGS AGAINST *Staphylococcus aureus*

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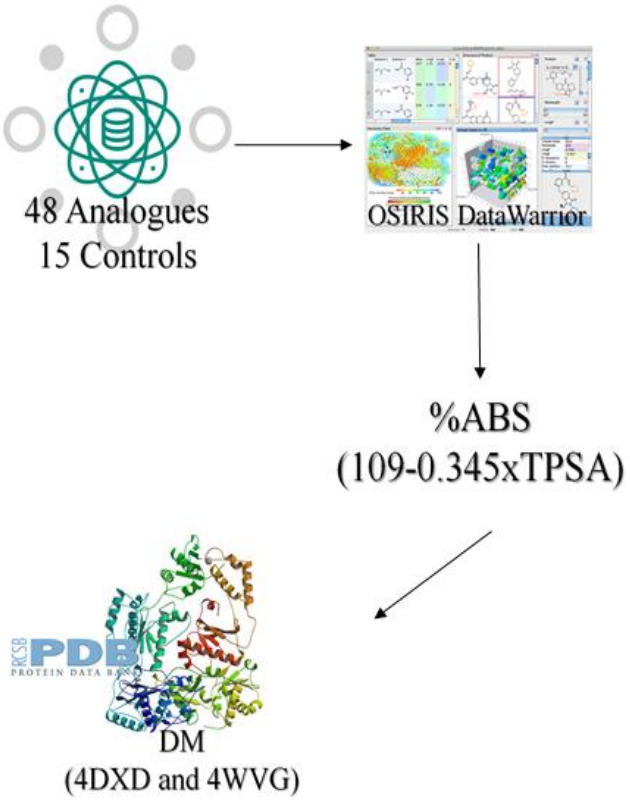
Graphical Abstract



Abstract

The microorganism Staphylococcus aureus is a gram-positive spherical bacteria present in the healthy human body, commonly found in the nostrils and skin. It is responsible for a number of infections such as inflammation in the follicles, contribution to the onset of acne, inflammation in the meninges, cardiovascular inflammation, lung inflammation and others. This work aims to propose new benzoic in silico bioactives to combat Staphylococcus aureus. To a prediction model of biological activity developed in the KNIME Analytics Platform 3.6, where the molecules that showed activity in the model were imported into OSIRIS DataWarrior 4.7.3 to predict the risks of cytotoxicity, the calculation of the absorption rate (% ABS). For the molecules approved by the virtual screening already commented, the calculation of the energies of interaction between receptor and binder by molecular docking and the analysis of the interactions with the residues of amino acids were carried out, comparing with the interactions of the drugs used as control in this research. As conclusion of this work it was possible to propose bioactive molecules against S. aureus based on the obtained computational data.

Materials and Methods

Initially the 48 molecules were designed with software Marvin Sketch 18.21 of ChemAxon© to obtain their structures 2D [1], so, each molecule was imported into the software HyperChemTM (RMS 0.1 kcal/mol in 600 cycles) [2,3] to obtain their structures in 3D with energy optimization in 2 modes: molecular mechanics (MM+) [4,5] and the semi-empirical method (AM1) [6,7]. The same was done with the 15 controls used, according to the Table 1. The methodology used in this research can be seen in Figure 1.

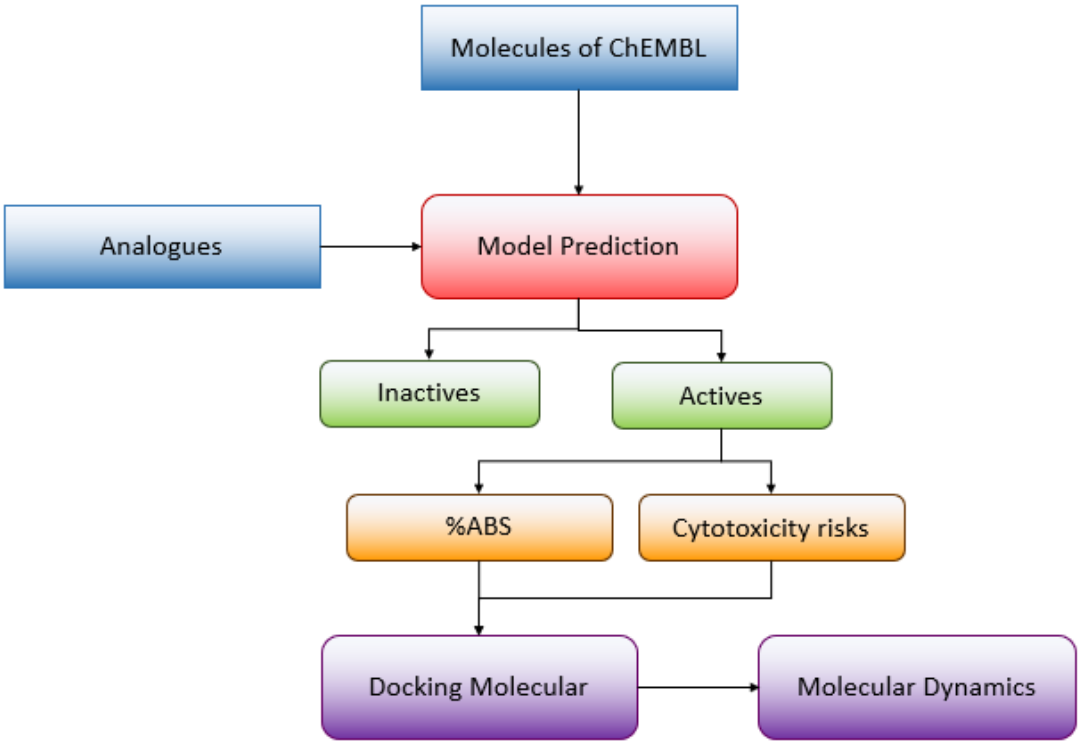


Figure 1. General scheme of virtual screening used in this research.

A virtual screening was performed taking into account the biological activity prediction model developed in the software KNIME Analytics Platform 3.6 [8] using the classifier "Random Forest" [9] and the predictor "Weka predictor 3.7" [10]. The active molecules were imported into the OSIRIS DataWarrior 4.7.3 [11] software to estimate the risks of cytotoxicity based on four parameters: mutagenicity, carcinogenicity, skin irritability and effect on the reproductive system. Of the active molecules that did not present any risk of cytotoxicity and only those that had good absorption rates (lower absorption rate among the controls used) were considered, so with the remaining molecules, molecular docking with proteins PDB ID 4DXD and 4WVG to obtain the ligand-receptor interaction energies and the amino acid residues involved in this interaction using software Molegro Virtual Docker 6.0 [12,13,14]. At end. A molecular dynamics simulation was performed with the three compounds that presented the lowest energies for each protein studied.

Table 1. List of controls used in this research.

ID	Name	ID	Name	ID	Name
C01	Amoxiciline	**C06**	Daptamicine	**C11**	Platensimicine
C02	Cefaclor	**C07**	Doxicicline	**C12**	Quinupristine
C03	Cefalotine	**C08**	Linezolide	**C13**	Teicoplamine

C04	Ciprofloxacine	**C09**	Meticiline	**C14**	Tigecicline
C05	Clindamicine	**C10**	Oxaciline	**C15**	Vancomicine

Results and Discussion

Of the derivatives submitted to the prediction model, ten compounds were classified as active by the model whose ROC curve was 0.8662, the accuracy of the model was 0.801, proving the prediction efficiency of the model created. However, three of these compounds presented toxicity risks in one of the four analyzed parameters, and were not considered in the next analyzes.

All the seven derivatives had a good absorption rate, above the absorption of the lowest control, also presented solubility in aqueous medium and good probability of oral absorption, being these the most promising of the series with great biological potential against the bacterium *S. aureus*.

As a result of the molecular docking, it is possible to notice that the interaction data are also shown to be quite promising, since for both tested proteins there were derivatives with better interactions than many controls. As for example, two compounds presented lower energies in the 4DXD protein, whereas for the 4WVG protein the DER18 presented the best energies among the 7 controls: C01, C06, C07. C12, C13, C14 and C15.

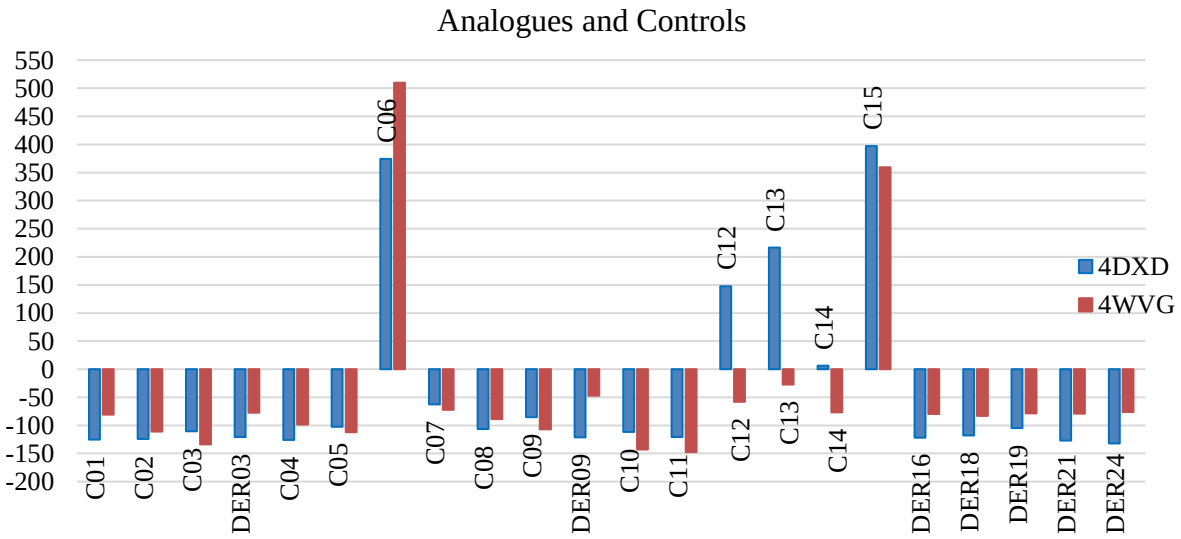


Figure 1. Graph showing the rank between controls and compounds. "DER" is the suffix of the derivatives and the "C" is the suffix of the controls.

According to the data obtained in molecular docking, the platensimicine, oxacillin, cefalotine, clindamycin, cefaclor, meticiline, ciprofloxacin and linezolide controls (in this order, according to Figure 2) showed better ligand-receptor energies than the analogue with better interaction for this protein.

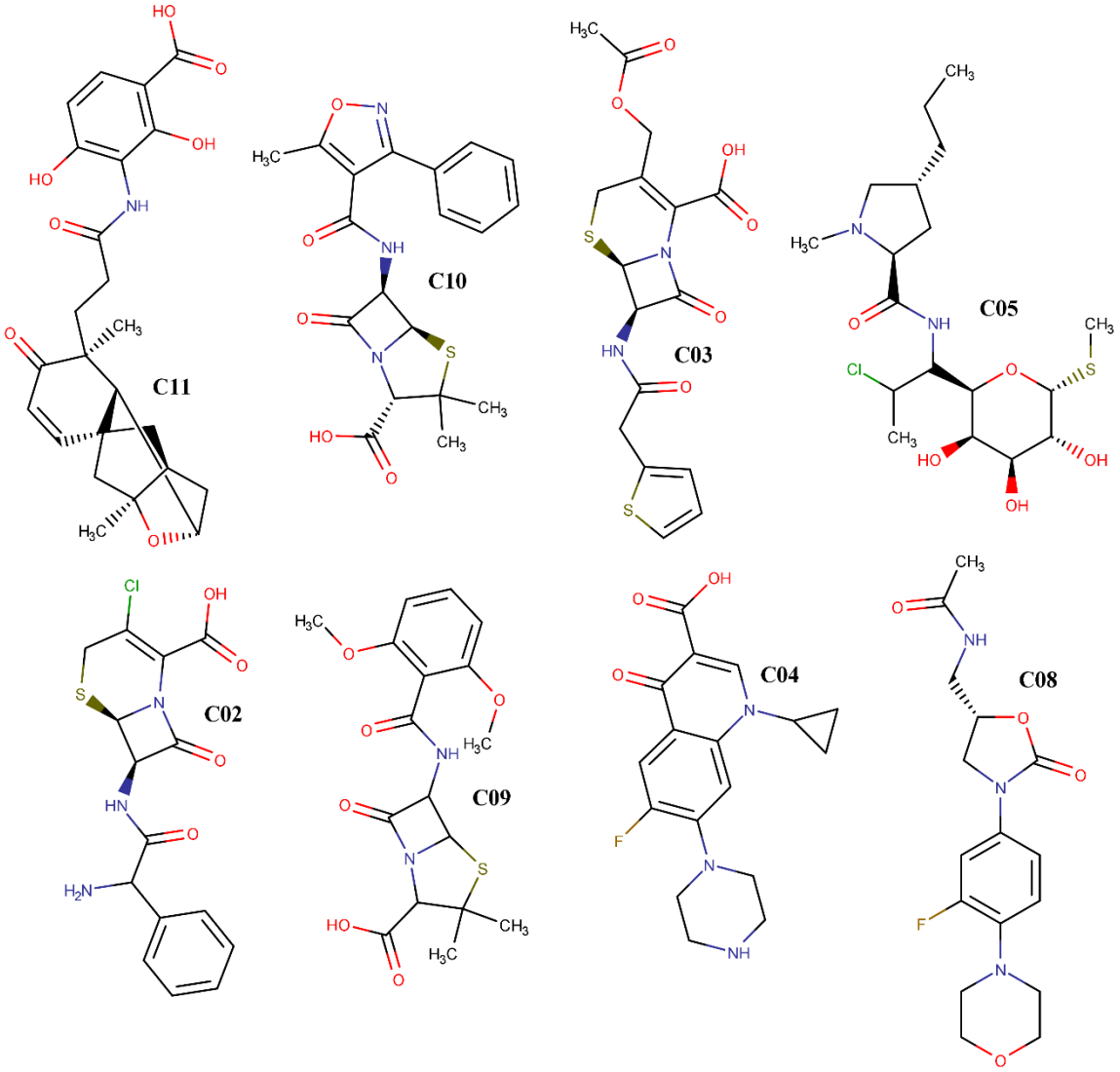


Figure 2. Control structures that presented better energy than the analogues tested for PDB ID 4WVG protein.

Conclusions

With the data presented in this research it is possible to see promising results in the use of benzoic compounds as bactericidal agents in the fight against *S. aureus*. Seven compounds of 48 were approved by the screening as bactericidal agent, presenting possibilities of no cytotoxicity risks for the parameters analyzed in this work, besides the possibility of good bioavailability due to good absorption rate, probability of absorption, solubility in aqueous medium. Of course, other studies need to be carried out on these molecules to prove the efficacy of these bioactives. However, studies like this have great relevance for the scientific community because they indicate classes of synthetic products, such as benzoic compounds, as potential antibacterial bioactives.

For the PDB ID 4DXD protein the energy band of ligand-receptor interaction was -104.4760kcal.mol^{-1} to -148.9910kcal.mol^{-1}, whose complexed ligand with the protein presented equal energy -164.5720kcal.mol^{-1}. For protein PDB ID 4WVG the track goes from -47.2085kcal.mol^{-1} to -110.0990kcal.mol^{-1} whose binder showed -164.6310kcal.mol^{-1}.

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