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Computer-assisted antibacterial drug design. Searching potential inhibitors of acetohydroxyacid synthase from methicillin resistant *Staphylococcus aureus*

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Introduction: Nosocomial infections (NI) account for one of the most important health issues in hospitals and carry a high morbidity, mortality and economic cost. Around the world, the prevalence of NI occurs at rates as high as 40%. In recent years methicillin-resistant *Staphylococcus aureus* (MRSA) has become the the first pathogen worldwide and the second one reported in Mexico. The appearance of new resistant strains has created serious therapeutical problems. Therefore, there is an urgency to find new drugs against MRSA. In this context, the acetohydroxyacid synthase is a key enzyme because it catalyzes the first common step in the branched chain amino acids biosynthetic pathway, so acetohydroxyacid synthase from *Staphylococcus aureus* (SaAHAS) is a promising target for new drugs against MRSA.

Methods: The crystal structure of SaAHAS is still unavailable. Therefore, homology modeling was adopted to build the 3D structure of SaAHAS. The generated model was validated by PROCHECK and Qmean score. Then, we select the subset "Drug like" from ZINC data base to apply a virtual screening (VS) strategy, this subset contains over 15 million of compounds. The VS was performed using Glide (Grid-based Ligand Docking with Energetics) and MOE (Molecular Operating Environment) programs. The three common compounds between softwares were selected for induced fit docking studies.

Results: The three common molecules were ZINC39729580, ZINC15768417, and ZINC08536413 with a binding energy, of -8.161, -6.474, and -6.058 kcal/mol respectively. The first molecule made hydrogen bonds with Arg287 and Thr245, the second molecule formed hydrogen bonds with Asp289, Arg287, Leu247 and Thr245, the third one showed hydrogen bonds with Asp289, Arg287 and 266, being the interaction with the residue Arg287 common between the three compounds. According to their predicted drug likeness score, these molecules was in the range to be considered potential drugs.

Conclusions: The molecules reported here have the potential to inhibit SaAHAS, and would be used as starting point for the design of new drugs against MRSA.

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