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Drug design against nosocomial infections: Homology modelling and Virtual screening in shikimate dehydrogenase from *Enterobacter cloacae* to find potential inhibitors

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Introduction: *Enterobacter cloacae* is one of the major pathogens that cause nosocomial infections worldwide, and the main in México. These infections are due, in large part, to the widespread use of antimicrobials, which leads to the emergence of resistant strains, creating an increased necessity to the development of a new antimicrobial therapy. In this regard, shikimate dehydrogenase (SDH), which catalyzes the conversion of 3-dehidroshikimate to shikimate, belongs to the Shikimate Pathway, a pivotal route in the biosynthesis of aromatic amino acids, folates, and ubiquinone. Furthermore, this pathway is absent in humans, making the SDH from *E. cloacae* (EcSDH) an excellent target for the design of new microbicides agents.

Methods: Since there is no crystal structure of EcSDH, a model prediction strategy, named homology modeling, was applied to generate a 3D model of the enzyme. To this end, different programs such as Swiss model, EsyPred3D, Prime and MOE were used. The evaluation of the models was conducted with Qmean score and the Ramachandran plot. The model with the most favorable validation was used to develop a virtual screening. This was performed using MOE and Glide programs, having the active site of the enzyme as target. The small molecules "Drug like" subset of the ZINC database was employed, it contains around 15 million of compounds. The top 3 compounds which coincided in both programs were selected to perform an Induced Fit Docking procedure using InducedFit program.

Results: Structural analysis of Induced Fit data showed that the compounds ZINC34616948, ZINC83442116, and ZINC15206727 presented a binding energy of -6.706, -7.755 y -6.090 Kcal/mol, respectively. Compound ZINC34616948 made hydrogen bonds with Lys65, Asn86 and Tyr215; while ZINC83442116 formed it with Ser15, Ser17, Thr62 and Lys66. Finally, compound ZINC15206727 made hydrogen bonds with His14. Predicted drug likeness score from these molecules was in the range to be considered as potential drugs.

Conclusions: These molecules could be potential inhibitors of EcSDH and serve as a guide in the search of a new chemotherapy against nosocomial infections.

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