Journal of Applied Biosciences 197: 20864 - 20885
ISSN 1997-5902

In vitro screening, molecular docking, and ADME-Tox investigations for the design of novel beta-lactam antibiotics (Ampicillin and Ceftriaxone) derivatives as PBP2a inhibitors

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Submission 6th May 2024. Published online at https://www.m.elewa.org/Journals/ on 25th June 2024.
https://doi.org/10.35759/JABs.197.6

ABSTRACT
Objective: In previous studies on chickens (*Gallus domesticus*) roaming in Kinshasa, the antibiotic resistance profile of their gut microbiota was established using the conventional bacteriological test of their excreta and susceptibility testing using the diffusion disc method. Several *Enterobacteriaceae* were resistant to antibiotics commonly sold in the city, including *Staphylococcus aureus*. To identify novel therapeutics effective against this pathogen, an *in-silico* study was undertaken to develop analogs of ampicillin and ceftriaxone.
Methodology and Results: Six (6) ampicillin derivatives and four (4) ceftriaxone derivatives were generated through an *in silico* pharmacochemical study and subsequent molecular docking. The corresponding molecular structures were visualized by employing specialized computer tools. Subsequently, employing advanced bioinformatics methodologies, the physicochemical properties, pharmacokinetic profile, potential toxicity, and molecular docking studies of these derivatives with PBP2a proteins were executed.
Conclusion and application of results: The investigated compounds show promising results as potential drug candidates for PBP2a inhibitors. The development of novel Ampicillin and ceftriaxone derivatives, as well as the *in* silico ADMET properties provide valuable insights for further research in the field of antibacterial drug discovery. Their potential affinity with PBP2a and convenient oral administration make them candidates for clinical use. Their favorable pharmacokinetic properties and limited toxicity reinforce their appeal as therapeutic options. In addition, some ceftriaxone derivatives have demonstrated significant inhibition of the PBP2a enzyme, which is implicated in antibiotic resistance. Although ampicillin derivatives did not show greater inhibition capacity than ampicillin itself, one specific derivative revealed

comparable inhibition. These results provide valuable insights into the discovery of new antibacterial drugs and pave the way for future in vivo animal studies and development in this field.

Keywords: Commensal birds, MRSA, Cross-resistance, Antibiotic-resistance, Antibiotic discovery.