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THEORETICAL INVESTIGATION AND DESIGN OF BIOACTIVE QUINOLINE DERIVATIVES AS INHIBITORS OF DNA GYRASE OF *SALMONELLA TYPHI*

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ABSTRACT

The ever-increasing rate of resistance to existing antibiotics by Salmonella typhi has made the search for novel drug candidates a necessity. In this study, Molecular docking technique was used to screen 18 bioactive quinoline derivatives against DNA gyrase of Salmonella typhi using PyRx graphical user interface of AutoDock Vina software. Ligand with the best binding affinity against the target macromolecule was used as prototype to design novel analogues with enhanced potencies. With the aid of Swiss ADME online server and Osiris DataWarrior v5.5.0 programme, the absorption, distribution, metabolism, excretion and toxicity (ADMET) profiles of the ligands were evaluated and their electronic properties were computed using density functional theory (DFT) method of Spartan 14.0 software. Ligand 3 (L3) with the best binding affinity (ΔG) value of −10.5 kcal/mol was chosen as a prototype to design La and Lb with ΔG value of −10.7 kcal/mol and −10.8 kcal/mol; binding constant (k_a) of 7.04 × 10^7 and 8.35 × 10^7; and dissociation constant (k_d) of 1.42 x 10^{-8} and 1.2 × 10^{-8}, respectively. When compared with ciprofloxacin (ΔG = −7.7 kcal/mol), the ligands could be more potent. Likewise, the ligands were found to possess excellent oral bioavailability and pharmacokinetic profiles. Furthermore, DFT calculations on La and Lb revealed that they possess highest occupied molecular orbital-lowest unoccupied molecular orbital (HOMO-LUMO) energy gap of 3.46 eV and 3.45 eV; and global electrophilicity index of 3.83 eV and 3.96 eV, respectively. The designed ligands tend to be consistent with all the validation protocols deployed in this study and as such could be recommended as novel drug candidates for treatment of Salmonella typhi induced salmonellosis.

Keywords: Quinoline, *Salmonella typhi*, DNA gyrase, HOMO, LUMO

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