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DEVELOPMENT OF NOVEL PHYTOCHEMICAL-SULFADRUG CONJUGATES AS PROSPECTIVE ANTI-MRSA DRUGS: A SYSTEMATIC MEDICINAL CHEMISTRY BASED COMPUTATIONAL APPROACH

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The Gram-positive bacterium, methicillin resistant *Staphylococcus aureus* (MRSA) causes common place infection at hospital and community sectors, with simultaneous aggrandizement of resistance to several antibiotics, resulting in additional morbidity and unexpected mortality. As a solution to this problem, this ingenious work describes synthesis of six phytochemical-sulfa drug conjugates adopting the dye-azo synthesis protocol and characterized by advanced spectral techniques such as, UV, FTIR, LC-MS, HPLC, ^{1}H NMR, ^{13}C NMR and SEM. As three-dimentional structures of dihydropteroate synthases (DHPSs), a target enzyme for sulfa drug is not available in protein database, homology model of MRSA-DHPS enzyme was generated and validated by Ramachandran plots and other bioinformatics tools. Synthesized conjugates were used as ligands in molecular docking against MRSA-DHPS and molecular dynamics simulations were performed to understand the conformational dynamics of protein-ligand complexes stability analysis using GROMACS v5.1 package. Additionally bioinformatics tools, PASS prediction, Lipinski rules of five, computational LD50 value, toxicity class, HOMO, LUMO and EPS plots were carried out to assess drug likeliness properties before synthesis. The zone of inhibition, MIC and MBC values of each conjugate were determined against isolated MRSA strains isolated from clinical samples. Conjugate, 4b (thymol- sulfadiazine) and 4d (thymol-sulfamethoxazole) had highest zone size inhibition on agar plates with 20 and 40 mg/mL as the lowest MIC and MBC values against MRSA, respectively; while the reference antibiotic ampicillin had the lowest MIC and MBC values at 80 to 180 mg/mL. In vitro host-toxicity testing was carried out with cultured human lymphocytes from umbilical cord blood, and 4b and 4d were broadly non-toxic to human cells at 15,000 mg/L. Thus, conjugate 4b and 4d could be promoted a newer anti-bacterial, against gruesome MRSA and other MDR bacteria.

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