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Ligand optimization of triazolothiadiazole and triazolothiadiazine derivatives through *in silico* technique for anti-inflammatory therapy: A density functional theory, docking, and molecular dynamics simulation approach

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ABSTRACT The presence of a carboxylic acid causes gastric burning; the removal of this group facilitates the development of more potent, safer, and selective cyclooxygenase (COX)-II inhibitors as anti-inflammatory agents. The paper represents an *in silico* study that aims at screening through the various stages for the optimization of triazolothiadiazole and triazolothiadiazine derivatives with COX-II inhibition. There was a total of 518 ligands were designed with different electron-withdrawing and donating group with different positions by using ChemDraw Ultra 8.0, and then systematically treated with drug-likeness filtering based on Lipinski Rule of Five. This was succeeded by pharmacophore screening, Drug likeness, Lead optimization, profiling, adverse drug reactions (Absorption, Distribution, Metabolism, Excretion, and Toxicity), molecular docking, toxicity prediction, density functional theory and molecular dynamics (MD) simulations. The compound pool was narrowed down upon successive screening stages, which came down to 6 lead ligands. Between them, ligand_163 was the most strongly binding (−10.0 kcal/mol), fairly toxic (median lethal dose: 1000 mg/kg, Class IV) and Energy Gap (ΔE Gap) 0.08785, which shows very soft and reactive, could be highly biologically active, and exhibited the most favorable by stability in MD over 100 ns trajectory. These data indicate that ligand_163 could be a successful candidate to be followed in experiments as an anti-inflammatory agent.