

New phenyl-triazolo-thiadiazine derivatives: Synthesis, computational insights, and anti-inflammatory potential

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ABSTRACT A series of some new 6-(substituted-phenyl)-3-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (**6a-m**) was synthesized through a multistep sequence starting from benzoic acid (**1**). The major step involved the condensation of 4-amino-5-phenyl-4*H*-[1,2,4]triazole-3-thiol (**5**) (**check the name**) with substituted ω -bromoacetophenones. We employed molecular docking, toxicity assessment, and density functional theory (DFT) analysis to evaluate all derivatives. Molecular docking revealed strong binding affinities for **6d** (-9.2 kcal/mol) and **6m** (-9.5 kcal/mol) compared to mefenamic acid (-8.0 kcal/mol). Toxicity predictions indicated comparable safety profiles for all derivatives. DFT analysis revealed that **6m** exhibited higher reactivity but lower stability due to a reduced highest occupied molecular orbital and lowest unoccupied molecular orbital (HOMO-LUMO) gap, while **6d** showed favorable electronic and stability characteristics. MD simulation of **6m** confirmed stable protein-ligand interactions but indicated conformational oscillations, supporting its reduced stability. *In vivo* rat paw edema assays confirmed **6d** as the most potent anti-inflammatory agent ($P < 0.01$).