Indian Journal of Chemistry
Vol. 63, June 2024, pp. 593-603
DOI: 10.56042/ijc.v63i6.9261

Synthesis and evaluation of pyridine-thiophene clubbed pyrazoline hybrids as potential antimicrobial and antimycobacterial agents: Experimental and computational insights

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Received 3 March 2024; accepted (revised) 22 May 2024

In light of the current scarcity of effective antimicrobial and antimycobacterial drugs, often limited by factors such as narrow spectrum, lack of oral formulations, and suboptimal pharmacokinetics, we embarked on synthesizing a series of hybrid pyridine-thiophene clubbed pyrazoline molecules (designated as **8a-j**) to enhance their potency. This has been achieved through a one-pot multicomponent reaction involving substituted benzylideneacetophenone **7a-j** and hydrazine hydrate catalyzed by CH_3COOH in ethanol at reflux temperature. Structure of all the compounds **8a-j** have been confirmed by employing elemental analysis, ESI-mass, ^{1}H NMR and FTIR which supported the suggested structures. Newly synthesized compounds have been screened for antibacterial, antifungal and antimycobacterial activities. Compounds **8a, 8d, 8f, 8g, 8h,** and **8j** have been identified as promising candidates for investigating *in vitro* antimicrobial and antimycobacterial activities in comparison to standard antibiotics. Additionally, studies on molecular docking targeting the functioning site of the KS-AT domains of Mycobacterial Pks13 enzyme has revealed binding affinities ranging from –10.5 to –9.8 kcal/mol. The docking score for the most active compound, **8i** is found to be –10.5 kcal/mol in PYRX Autodock VINA, demonstrating its favorable accommodation within the active site of the PKs enzyme.

Keywords: Pyridine-thiophene clubbed pyrazoline, Antimicrobial activities, Antitubercular activities, Molecular docking, KS-AT domains of Mycobacterial Pks13 enzyme