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Synthesis and multitarget activity of thiadiazole–thiocoumarin hybrids: A new class of broad-spectrum anti-infective agents

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Emerging resistance across infectious pathogens has escalated the demand for chemotherapeutics with multitarget efficacy and minimal cytotoxicity. Herein, we report synthesizing a novel series of thiadiazole–thiocoumarin hybrid derivatives (A1–A10), designed to integrate redox activity with pharmacophoric rigidity. These compounds have been evaluated for a spectrum of biological activities, including trypanocidal, antitubercular, antimalarial, antimicrobial, and antioxidant potential. The synthesized hybrids display varying degrees of efficacy against *Trypanosoma cruzi* (NINOA and INC-5 strains), *Mycobacterium tuberculosis* H37Rv, *Plasmodium falciparum*, and multiple bacterial and fungal strains. Among the series, compound A9 shows exceptional trypanocidal and antitubercular activity (LC_{50} = 35.69 μM; MIC = 62.5 μg/mL), while A6 exhibits potent antimalarial effects (IC_{50} = 0.58 μg/mL), and A10 demonstrates the highest antibacterial activity. The antioxidant profile reveals A8 and A2 as strong radical scavengers *via* DPPH and ABTS assays. Structure-activity relationship (SAR) analysis indicates that electron-withdrawing groups favour trypanocidal activity but often increased cytotoxicity, whereas electron-donating or moderately lipophilic substituents improve selectivity. Notably, most compounds exhibit low toxicity in J774A macrophages, yielding favorable selectivity indices. Collectively, these findings highlight thiadiazole-thiocoumarin hybrids as versatile scaffolds for developing next-generation antiparasitic and antimicrobial agents.

Keywords: Thiadiazole, Thiocoumarin, Trypanocidal, Antitubercular, Antimalarial, Antioxidant, Structure-Activity Relationship, Multitarget Agents