Synthesis and evaluation of novel 4-thiazolidinone-5-nitrofuran hybrids as promising antimicrobial agents

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Highlights

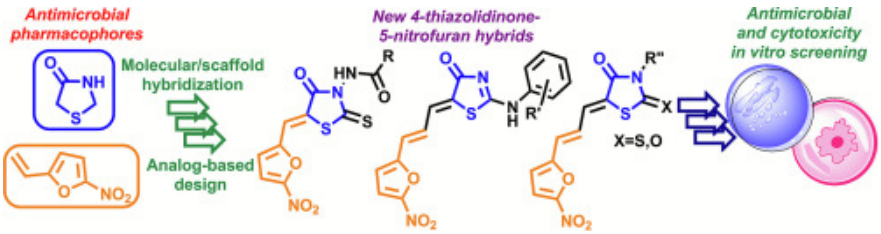
- Series of novel of novel 4-thiazolidinone-5-nitrofuran hybrids were synthesized.
- The structure of synthesized compounds was characterized by spectral data.
- For all molecules antimicrobial activity and cytotoxicity screening was performed.
- Compounds possess broad-spectrum activity towards Gram(+)/(−) bacteria and fungi.
- Compounds are characterized by a low level of toxicity towards normal cells.

Abstract

Searching for new effective small molecules targeting resistant strains of microorganisms is an emerging task for modern medicinal chemistry. Taking into account potential antimicrobial features of 4-thiazolidinone and 5-nitrofurane pharmacophores, two series of hybrid molecules were synthesized based on 5-nitrofuran-2-carbaldehyde, bioisosteric *(E)*-3-(5-nitrofuran-2-yl)acrylaldehyde, and structure-modified 4-thiazolidinone scaffolds. For all synthesized compounds, antimicrobial activity screening and cytotoxicity evaluation were performed. Novel highly active hybrid molecules with a low level of toxicity were identified, showing high broad-spectrum activity towards Gram-positive and Gram-negative bacteria, fungi, in particular *Staphylococcus*

highlighted. The obtained results will contribute to the rational design of novel agents of this pharmacological profile among 4-thiazolidinone-5-nitrofuran hybrids and related heterocyclic molecules.

Graphical abstract



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Keywords

4-Thiazolidinones; 5-Nitrofuranes; Hybrid molecules; Antimicrobial/antifungal activity; Cytotoxicity; SAR

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Introduction

Antibiotic resistance has become a major global health challenge, threatening the effectiveness of current treatments for bacterial infections.[1] The rapid emergence of resistant strains limits the efficacy of many conventional antibiotics, leading to increased morbidity and mortality.[2] Consequently, there is an urgent need to discover and develop new therapeutic agents that can overcome this resistance.[3,4] Small molecules have garnered significant attention as promising candidates due to their ability to target bacterial pathways selectively and their potential for chemical modification.[5] Advances in medicinal chemistry and high-throughput screening have accelerated the identification of novel small molecules with potent antibacterial activity.[6,7] Exploring these new compounds offers hope for combating antibiotic-resistant pathogens and addressing the growing public health crisis.

Among the diverse heterocyclic frameworks explored, 4-thiazolidinone derivatives have garnered considerable attention due to their broad spectrum and potent antimicrobial activity and favorable structural modifiability. As a flexible and functionally rich scaffold, 4-thiazolidinones are often used for the design of agents with enhanced activity against drug-resistant strains of microorganisms. 4-Thiazolidinones have demonstrated high affinity towards a range of biologically relevant antimicrobial targets, acting as potent ligands impacting essential pathways for microorganisms (Fig. 1). Several 4-thiazolidinone derivatives have been identified as potential inhibitors of DNA gyrase, an essential bacterial enzyme involved in DNA replication and supercoiling. Their inhibitory properties have been demonstrated both in *in vitro* assays8, 9, 10 and through *in silico* studies,[11,12] indicating a consistent affinity towards this clinically relevant target. 4-Thiazolidinones have been reported as inhibitors of FabZ, a key enzyme in bacterial fatty acid synthesis.[13] Additionally, numerous 4-thiazolidinone-bearing molecules have demonstrated significant activity in inhibiting biofilm formation.[14]

aeruginosa, *Candida albicans*, and synergistic effects with amoxicillin against multidrug-resistant clinical isolates of *Klebsiella pneumoniae*.[15] Thiazol-4-thiazolidinone hybrids have demonstrated activity against ESKAPE pathogens and fungi, likely exerting their antimicrobial effects through MurB inhibition and antifungal effects *via* CYP51 reductase inhibition.[16] The hybridization of 4-thiazolidinone scaffolds with nitro-containing pharmacophores represents a rational strategy in the design of potential antimicrobial agents, combining effects and mechanisms of antimicrobial action. Several series of 4-thiazolidinone hybrids incorporating 5-nitrothiophene,[17] 5-nitrofuran,[18] and 5-nitrothiazole[19] pharmacophores have been developed as promising antimicrobial agents. Many of the synthesized compounds demonstrated enhanced antibacterial activity against resistant strains such as MRSA, *Staphylococcus epidermidis*, *Bacillus cereus*, and metronidazole-resistant *Helicobacter pylori*. Molecular docking studies confirmed favorable interactions of the most active compounds with key bacterial targets, including MurB and *H. pylori* urease. Additionally, nitrothiazole–thiazolidinone hybrids have shown superior potency over standard antibiotics, while maintaining low cytotoxicity.17, 18, 19 Moreover, the hybridization of diverse bioactive scaffolds with 4-thiazolidinone cores represents a rational approach for the development of novel antimicrobial agents. A series of structurally modified hybrids incorporating moieties such as cycloalkyl,20, 21, 22 thiophene,[23] pyrazole,[24,25] pyrrole,[26] benzothiazole,[27] benzothiazole,[28] quinolone,[29] coumarin[30] quinoxaline[31] have been synthesized and identified as compounds with promising antimicrobial potential.

All of the above suggests that 4-thiazolidinone-bearing hybrids, especially with nitro-containing pharmacophores, serve as promising objects for the design of novel antibacterial/antifungal compounds and highlight their potential in developing agents active against drug-resistant strains.

In light of the above considerations and the ongoing search for effective antimicrobial therapies, this study focuses on the design and synthesis of a new series of 4-thiazolidinone-based hybrid molecules incorporating a 5-nitrofuran pharmacophore (Fig. 2). The design of the hybrids was motivated by the complementary properties of the two pharmacophores: 4-thiazolidinones consistently demonstrate affinity towards essential bacterial enzymes, while nitrofuran fragments provide a validated antimicrobial effect. Combining these features addresses a key limitation of many current agents - narrow target specificity and reduced efficacy against resistant strains. Thus, the hybridization strategy was selected as a rational approach to enhance antibacterial potency and improve the likelihood of overcoming antimicrobial resistance. The synthesized compounds are subjected to comprehensive antimicrobial evaluation against a panel of bacterial and fungal strains, including drug-resistant clinical isolates. Their cytotoxic properties are also examined to assess safety and potential therapeutic relevance. In addition, structure-activity relationship (SAR) analysis is performed to identify the key molecular features associated with biological activity. Overall, this work aims to contribute to the development of structurally novel and biologically relevant 4-thiazolidinone-based antimicrobial agents.