Innovative Antimicrobial Agents: A Comprehensive Review of Fluoroquinolone-Thiadiazole Hybrid Design, Synthesis, and Activity

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ABSTRACT

The rise in antimicrobial resistance (AMR) presents a critical challenge to public health, prompting an urgent need for innovative therapies to combat multidrug-resistant infections. Among various drug development strategies, the hybridization of fluoroquinolones with thiadiazole rings has emerged as a promising approach. Fluoroquinolones are known for their broad-spectrum antimicrobial activity, primarily targeting bacterial DNA gyrase and topoisomerase IV, which are crucial for bacterial DNA replication. However, the widespread and prolonged use of fluoroquinolones has led to a decline in their efficacy due to growing bacterial resistance. To counter this, recent research has explored the synthesis of fluoroquinolone-thiadiazole hybrids to achieve enhanced antimicrobial potency and potentially reduce the likelihood of resistance development. This review provides a comprehensive examination of fluoroquinolone-thiadiazole hybrids, focusing on their design, synthesis, and antimicrobial evaluation. By introducing thiadiazole moieties, known for their diverse pharmacological properties and intrinsic antimicrobial potential, these hybrid compounds can demonstrate improved efficacy against resistant bacterial strains. The design strategy discussed involves molecular docking and SAR (structure-activity relationship) analysis to optimize binding affinity to bacterial targets, especially DNA gyrase and topoisomerase IV. The SAR insights provided in this review offer guidance for future structural modifications to improve efficacy further. In conclusion, fluoroquinolone-thiadiazole hybrids represent a promising new class of antimicrobial agents, with enhanced activity against resistant bacteria. This innovative approach not only contributes to overcoming the limitations posed by traditional fluoroquinolones but also opens a pathway for the development of next-generation antibiotics capable of addressing the growing AMR crisis. Continued research into fluoroquinolone-thiadiazole hybrids may significantly impact the future landscape of antimicrobial therapy.

 https://doi.org/10.5281/zenodo.14546809

Keywords:: Fluoroquinolone-thiadiazole hybrid, antimicrobial resistance, multidrug-resistant bacteria, bacterial DNA gyrase inhibition, hybrid drug design, structure-activity relationship (SAR), innovative antimicrobial agents, broad-spectrum antibiotics.

INTRODUCTION

Antimicrobial resistance (AMR) represents one of the most pressing threats to global public health, rendering numerous infections more challenging and costly to treat. The phenomenon of AMR arises when bacteria, viruses, fungi, or parasites evolve to resist the drugs initially effective against them. Bacterial resistance, in particular, has created significant challenges in healthcare settings, where infections caused by drug-resistant strains lead to increased mortality, longer hospital stays, and higher treatment costs.[1] Each year, resistant infections are responsible for hundreds of thousands of deaths worldwide, and the World Health Organization (WHO) has warned that AMR could cause up to 10 million deaths annually by 2050 if current trends continue. Among the primary drivers of AMR are the overuse and misuse of antibiotics, which exert selective pressure on microbial populations and allow resistant strains to proliferate. This issue has escalated due to the shortage of new antibiotics reaching the market, leading researchers to explore alternative strategies to combat resistant pathogens. One promising area of focus has been the design of hybrid molecules that combine pharmacophores from different antimicrobial agents to create multifunctional drugs with enhanced potency and reduced risk of resistance.[2, 3]

In this context, fluoroquinolones have played a critical role as a broad-spectrum class of antibiotics effective against both Gram-positive and Gram-negative bacteria. Fluoroquinolones, such as ciprofloxacin, levofloxacin, and moxifloxacin, function by inhibiting bacterial DNA gyrase and topoisomerase IV, two essential enzymes required for DNA replication, transcription, and repair. This mechanism of action disrupts DNA replication and leads to bacterial cell death. The high efficacy, broad-spectrum activity, and favorable pharmacokinetics of fluoroquinolones initially made them popular choices for treating a wide range of infections, including urinary tract infections, respiratory tract infections, and skin infections.[4] However, extensive use over the years has led to the emergence of fluoroquinolone-resistant bacterial strains. Resistance mechanisms, such as mutations in the target enzymes (DNA gyrase and topoisomerase IV), overexpression of efflux pumps, and enzyme-modifying proteins, have significantly compromised the effectiveness of fluoroquinolones. Consequently, infections caused by fluoroquinolone-resistant *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* have become increasingly difficult to manage, highlighting the need for new therapeutic approaches that can overcome these resistance mechanisms.[5]

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One promising approach to improving fluoroquinolone efficacy and mitigating resistance is the hybridization of fluoroquinolones with other bioactive pharmacophores. In recent years, thiadiazole rings have been identified as valuable scaffolds in the development of hybrid compounds with enhanced pharmacological properties. Thiadiazoles, five-membered heterocyclic rings containing nitrogen and sulfur atoms, exhibit diverse biological activities, including antimicrobial, anti-inflammatory, and anticancer properties.[6] The unique chemical structure of thiadiazoles allows for easy functionalization and modification, enabling the creation of derivatives with tailored bioactivity.[7]

Furthermore, thiadiazoles possess intrinsic antimicrobial activity, which, when combined with fluoroquinolones, could provide a dual mechanism of action that enhances bacterial inhibition and potentially reduces the likelihood of resistance development. Hybridization with thiadiazole has shown promise in increasing the binding affinity of fluoroquinolone hybrids to bacterial targets, improving cellular penetration, and extending the spectrum of activity.[8]

The rationale for hybridizing fluoroquinolones with thiadiazoles is based on their complementary mechanisms of action and potential for enhanced efficacy against resistant pathogens. This hybridization strategy is designed to combine the DNA-targeting capabilities of fluoroquinolones with the broad pharmacological activity of thiadiazoles, resulting in compounds that can better target resistant bacterial strains.[9] Furthermore, the incorporation of thiadiazole into fluoroquinolone molecules may also reduce the drug's susceptibility to bacterial efflux pumps, a common resistance mechanism, thereby retaining higher intracellular concentrations of the active compound within bacterial cells. In addition to improving antibacterial activity, fluoroquinolone-thiadiazole hybrids may also exhibit favorable pharmacokinetic and pharmacodynamic properties, including enhanced solubility, metabolic stability, and bioavailability.[10]

This review focuses on the potential of fluoroquinolone-thiadiazole hybrids as agents against resistant bacterial infections. It explores the design and synthesis of these hybrids, with an emphasis on how thiadiazole modifications contribute to antimicrobial efficacy and target binding. Additionally, the review discusses in vitro and in vivo antimicrobial evaluations, structure-activity relationship (SAR) studies, and the underlying mechanisms that make fluoroquinolone-thiadiazole hybrids promising candidates in the fight against AMR. By examining these aspects, this review underscores the potential of these hybrids to enhance the current arsenal of antimicrobials and address the growing challenge of resistant infections. In doing so, it provides insights into how hybridization strategies, particularly with fluoroquinolones and thiadiazoles, may pave the way for next-generation antibiotics that are both potent and resilient against the evolving threat of antimicrobial resistance

CHEMISTRY OF FLUOROQUINOLONES

 https://doi.org/10.5281/zenodo.14546809

Fluoroquinolones are a class of synthetic antibiotics with a core structure based on a quinolone ring, specifically a bicyclic ring system with nitrogen in the structure (figure 1). They are characterized by the presence of a fluorine atom at the C-6 position on the quinolone nucleus, which enhances their antimicrobial potency, broadens their spectrum of activity, and improves their pharmacokinetic properties.[11] Here is an overview of the chemistry of fluoroquinolones, including their structure, functional groups;

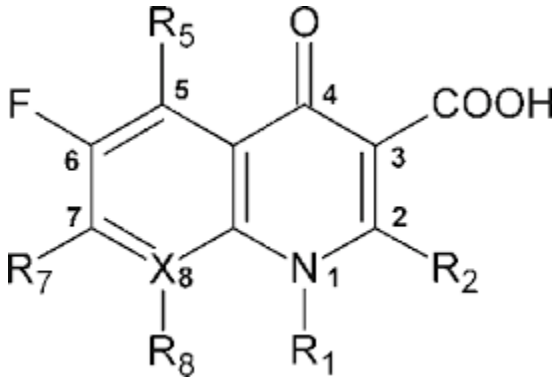

Figure 1: General Structure of Fluoroquinolone [12]

2.1 Core Structure [13]

- **Quinolone Ring**: Fluoroquinolones have a core structure of a 4-quinolone, a fused aromatic system comprising a benzene ring attached to a six-membered heterocyclic ring containing nitrogen and oxygen atoms. The quinolone ring system is key to the antibiotic's function, as it enables the binding to bacterial enzymes crucial for DNA processes.
- **Fluorine Substitution at C-6**: The introduction of a fluorine atom at the C-6 position is the defining feature of fluoroquinolones. This modification enhances the molecule's lipophilicity and increases cellular penetration, which is particularly beneficial for intracellular bacterial infections. The C-6 fluorine also increases the binding affinity of fluoroquinolones for bacterial DNA gyrase and topoisomerase IV, the primary target enzymes.

2.2 Key Functional Groups and Substituents [14]

- **C-3 Carboxylic Acid**: The quinolone ring generally contains a carboxylic acid (-COOH) group at the C-3 position, which is crucial for the antibiotic activity. This group forms ionic interactions with the bacterial enzyme targets, contributing to binding stability.

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- **C-7 Piperazine or Pyrrolidine Ring**: The addition of a nitrogen-containing ring, often a piperazine or pyrrolidine, at the C-7 position, enhances the antibacterial spectrum and improves binding properties. This substituent increases the molecule's activity against Gram-negative bacteria and contributes to the drug's potency and resistance profile.
- **C-8 and N-1 Substitutions**: Modifications at the C-8 position and N-1 position of the quinolone ring can further adjust the spectrum of activity and pharmacokinetic properties. For instance, some fluoroquinolones have a methoxy or halogen substitution at C-8, which enhances activity against certain anaerobes. Substituents at N-1 (such as a cyclopropyl or alkyl group) can improve bioavailability and distribution.

2.3 Structure-Activity Relationship (SAR) [15]

- **Fluorine at C-6**: Critical for potency and cellular penetration.
- **Carboxylic Acid at C-3**: Necessary for strong enzyme binding.
- **Nitrogen-containing Group at C-7**: Enhances the spectrum of activity, especially against Gram-negative bacteria.
- **Substituents at N-1 and C-8**: Influence pharmacokinetics and sometimes activity against specific pathogens.

2.4 Common Examples of Fluoroquinolones [16]

- **Ciprofloxacin**: Known for its potency against Gram-negative bacteria, especially *Pseudomonas aeruginosa*, and is widely used in urinary tract and respiratory infections.
- **Levofloxacin**: A broad-spectrum fluoroquinolone with activity against both Gram-positive and Gram-negative bacteria, including atypical pathogens.
- **Moxifloxacin**: Active against anaerobes and some mycobacteria, with applications in respiratory and skin infections.

CHEMISTRY OF THIADIAZOLE

Thiadiazole is a heterocyclic compound containing a five-membered ring with two nitrogen atoms and one sulfur atom (figure 2). Thiadiazole rings are versatile scaffolds in medicinal chemistry and exhibit diverse biological activities, including antimicrobial, anti-inflammatory, antiviral, anticancer, and anticonvulsant properties.[17]

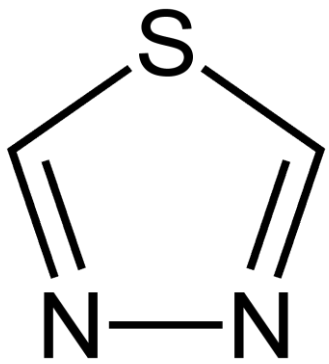

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Figure 2: Chemical Structure of Thiadiazole [18]

The chemistry of thiadiazoles includes unique structural features and chemical reactivity that make them valuable in drug design and the synthesis of bioactive molecules.[19]

3.1 Structure of Thiadiazole [20]

- Thiadiazole is a five-membered aromatic ring containing three heteroatoms: two nitrogen atoms (N) and one sulfur atom (S). The molecular formula for the parent structure is C2H2N2S
- There are four isomeric forms of thiadiazole based on the positions of nitrogen and sulfur atoms in the ring:
    - 1,2,3-Thiadiazole
    - 1,2,4-Thiadiazole
    - 1,2,5-Thiadiazole
    - 1,3,4-Thiadiazole (most commonly used in medicinal chemistry)
- Among these isomers, 1,3,4-thiadiazole and 1,2,4-thiadiazole are the most stable and commonly used in pharmaceutical applications.

3.2 Electronic Structure and Properties [21]

- **Aromaticity**: Thiadiazoles exhibit aromaticity, which stabilizes the ring structure and contributes to their unique reactivity and biological properties. The aromaticity arises from the delocalized π-electrons over the ring.
- **Electron-Withdrawing and Electron-Donating Effects**: The sulfur and nitrogen atoms in the ring impart electron-donating and electron-withdrawing properties, respectively. This dual nature affects the chemical reactivity of the ring and makes thiadiazoles suitable for functionalization at various positions.

3.3 Key Functional Groups and Substituents [22]

- **Position 2 and 5 in 1,3,4-Thiadiazole**: These positions are particularly reactive and allow for substitution, enabling the incorporation of various functional groups. Functionalization at these positions is crucial in drug design for adjusting pharmacokinetic and pharmacodynamic properties.
- **Amino, Alkyl, Aryl, and Acyl Groups**: Thiadiazoles can be functionalized with amino, alkyl, aryl, acyl, and other substituents, leading to a wide range of derivatives with distinct biological activities.

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- **Electron-Rich Heteroatoms**: The nitrogen and sulfur atoms enhance hydrogen bonding potential and increase lipophilicity, both of which are beneficial for bioavailability and target affinity.

3.4 Chemical Reactivity of Thiadiazoles [23]

- **Nucleophilic and Electrophilic Substitution**: Thiadiazoles can participate in nucleophilic and electrophilic substitution reactions due to the electron-dense nature of the ring. These reactions enable modifications at the nitrogen, sulfur, and carbon atoms, allowing for the introduction of bioactive side chains.
- **Oxidation and Reduction**: Thiadiazoles can undergo redox reactions. For instance, oxidation of thiadiazole derivatives can yield sulfoxides or sulfones, which may exhibit different biological properties.
- **Cyclization Reactions**: Thiadiazoles are synthesized through cyclization reactions that typically involve the formation of the sulfur-nitrogen bond, often using thiourea or thiosemicarbazide precursors. These reactions provide a convenient route for generating the thiadiazole ring and tailoring substituents.

3.5 Hybrid Compounds with Thiadiazole

- Thiadiazole rings are often incorporated into hybrid drug molecules with other pharmacophores, such as fluoroquinolones, to create multi-target drugs. The hybridization approach aims to enhance the biological activity of both components and provide synergistic effects against pathogens. These hybrids, combining the DNA-targeting action of fluoroquinolones with the bioactivity of thiadiazoles, may be effective against drug-resistant bacteria.

3.6 Examples of Bioactive Thiadiazole Compounds [24]

- **1,3,4-Thiadiazole Derivatives**: These derivatives have shown significant activity against microbial, viral, and parasitic infections, as well as potential anti-tumor and anti-inflammatory effects.
- **Sulfones and Sulfoxides**: Oxidized forms of thiadiazole derivatives, such as sulfones and sulfoxides, demonstrate different biological activities and are explored as anticancer and anti-inflammatory agents.

REVIEW OF LITERATURE

1. Hadeer K. Swedan *et al.*, (2023); Reported a series of novel ciprofloxacin (CP) derivatives The synthesized compounds showed significant Topo II inhibitory activity. CP derivatives promising leads for further studying, designing and synthesis of potent anti-proliferative candidates.[25]

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2. Hend A. A. Ezelarab*et al.*, (2023); Synthesized Ciprofoxacin-Piperazine C-7 linked 1,3,4 oxadiazole linkage and carbonyl linkage quinoline derivatives and investigated for their antibacterial, antifungal, and anti-proliferative activities. The hybrid compounds could be considered a promising lead compound for finding new dual antibacterial/anticancer agents. [26]

3. Keyvan Pedrood*et al.*, (2022); Designed and synthesized some N-thioacylatedciprofoxacin derivatives and evaluated antibacterial activity. A considerable number of compounds displayed antibacterial activity against gram positive and gram negative bacteria in comparison with the parent drug ciprofoxacin. [27]

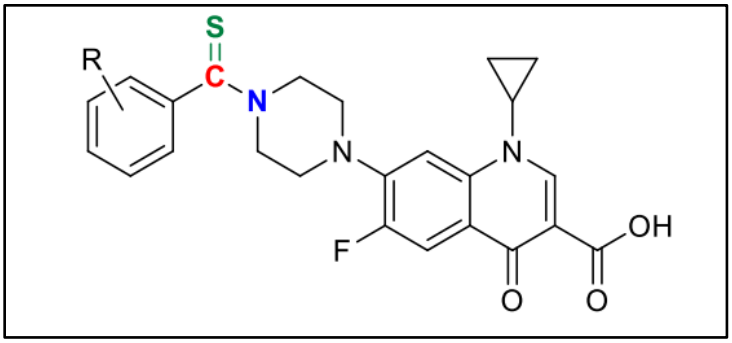

Figure 3: N-thioacylatedciprofoxacin derivatives [28]

4. Feng Gao *et al.*, (2019); Reported synthesis and biological evaluation of moxifloxacin-acetyl-1,2,3-1H triazole-methylene-isatin hybrids as potential anti-tubercular agents against both drug-susceptible and drug-resistant Mycobacterium tuberculosis strains. The structure-activity relationship and structure-cytotoxicity relationship demonstrated that substituents on the C-7 positions of isatin framework were closely related with the antimycobacterial activity and cytotoxicity. [29]

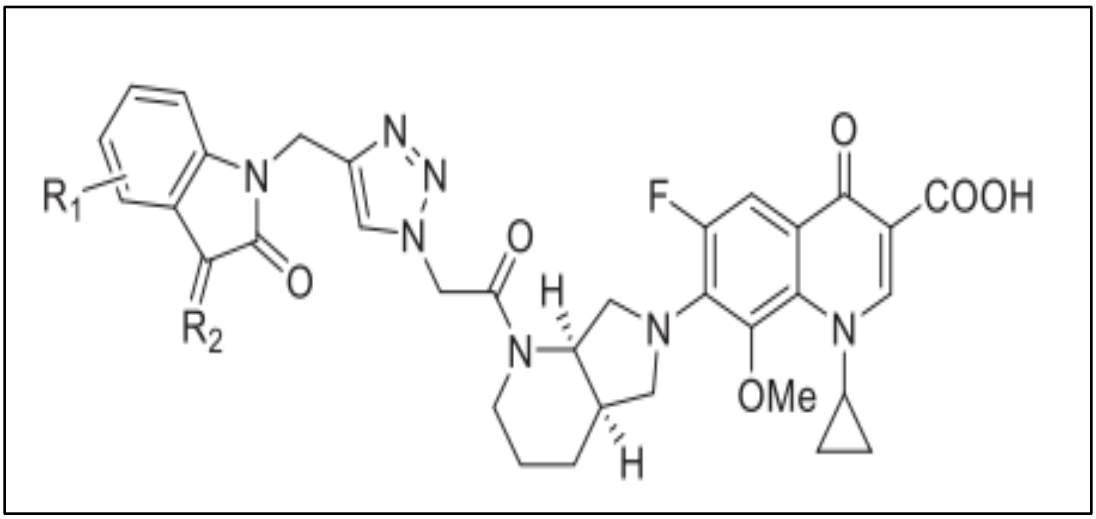

Figure 4: moxifloxacin-acetyl-1,2,3-1H triazole-methylene-isatin hybrids [31]

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5. Serpil Demirci*et al.*, (2018); Norfloxacin-azole hybridswere synthesized starting from norfloxacin. The treatment of these compounds with amines as a one-pot three-component reaction produced the corresponding amino derivatives in good yields. All compounds were screened for their antimicrobial activities. Most of them exhibit excellent antibacterial activity.[32]

6. Pradeep Yadav *et al.*, (2013); Reported the syntehsis of 1,3-dione derivatives of 1-cyclopropyl-7-[4-(2,6-dimethyl/ dimethoxy-pyrimidin-2-yl-diazenyl) piperzin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.The compounds were evaluated for their in-vitro antibacterial activity against some Gram-positive and Gram-negative bacteria using conventional agar-dilution method. [33]

7. Seyyedehsamira Jazayeri, *et al.*, (2009); a number of gatifloxacin analogues containing a nitroaryl-1,3,4-thiadiazole moiety attached to the piperazine ring at C-7 position were prepared and evaluated as antibacterial agents against a panel of Gram-positive and Gram-negative bacteria. [34]

SIGNIFICANCE OF FLUOROQUINOLONE-THIADIAZOLE HYBRIDS [35, 36]

The development of fluoroquinolone-thiadiazole hybrids represents a significant advancement in medicinal chemistry, aimed at addressing pressing healthcare challenges, particularly antimicrobial resistance (AMR). These hybrid compounds combine the well-established antimicrobial potency of fluoroquinolones with the versatile biological activity of thiadiazoles, offering a promising approach to overcome drug resistance, enhance pharmacological profiles, and achieve broader therapeutic applications.

1. Combating Antimicrobial Resistance (AMR)

- Antimicrobial resistance is a major global health issue, reducing the efficacy of many conventional antibiotics and demanding new strategies in drug design. Fluoroquinolones, while highly effective against a broad range of bacterial infections, have seen diminishing success against resistant strains due to overuse and the development of bacterial defense mechanisms.
- By integrating thiadiazole moieties with fluoroquinolone structures, researchers aim to create drugs that can evade or inhibit resistance mechanisms. Thiadiazole rings have shown the potential to disrupt bacterial cellular functions and target multiple pathways within the cell, offering a multi-pronged attack on resistant bacteria. Hybridization with thiadiazole may prevent the emergence of resistance as rapidly as it might with fluoroquinolones alone, as the hybrid approach adds a layer of complexity to the bacterial targets.

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2. Enhanced Mechanisms of Action

- Fluoroquinolones function primarily by inhibiting DNA gyrase and topoisomerase IV, enzymes essential for bacterial DNA replication and transcription. This action prevents bacteria from replicating effectively, leading to cell death. Thiadiazole rings, on the other hand, contribute unique bioactivity, potentially adding secondary modes of bacterial inhibition.
- The thiadiazole moiety can enhance the hybrid's binding interactions with bacterial enzymes or structural components, thereby augmenting the primary action of fluoroquinolones. For instance, the nitrogen and sulfur atoms in the thiadiazole ring enhance hydrogen bonding and electron-donating effects, which may increase affinity for target sites within bacterial cells, allowing these hybrids to inhibit enzyme systems more effectively. This dual mechanism makes it harder for bacteria to develop resistance, as it would require simultaneous mutations across multiple pathways.

3. Improved Pharmacokinetics and Bioavailability

- Combining fluoroquinolones with thiadiazoles often results in hybrids with improved pharmacokinetic profiles, such as enhanced solubility, stability, and cellular uptake. Fluoroquinolones are generally well-absorbed, but the addition of a thiadiazole ring can enhance lipophilicity, helping the compound better penetrate cell membranes and reach intracellular pathogens.
- Furthermore, certain modifications to the thiadiazole ring can increase metabolic stability, reducing the rate of degradation by liver enzymes and resulting in longer systemic retention. This is particularly valuable for infections requiring prolonged or higher dosing to eradicate resistant organisms.

4. Broader Spectrum of Activity

- Fluoroquinolone-thiadiazole hybrids exhibit a broader spectrum of antimicrobial activity, effective against Gram-positive, Gram-negative, and often even atypical bacteria. The thiadiazole component is also known for its activity against fungi and some parasites, thus expanding the hybrid’s potential applications beyond bacterial infections.
- Such broad-spectrum activity is advantageous in treating mixed infections or infections caused by less common pathogens. In regions where accurate diagnostic tools may be limited, a drug with broad-spectrum efficacy can be critical in managing infections and reducing morbidity and mortality.

5. Potential in Non-Antimicrobial Applications

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- Beyond their antimicrobial action, fluoroquinolone-thiadiazole hybrids show promise in areas like anticancer, anti-inflammatory, and antiviral therapy. Thiadiazoles are associated with various pharmacological activities, including anti-inflammatory and anticancer effects, due to their ability to interact with cellular targets involved in inflammation and cell proliferation.
- Hybrids designed with specific substitutions on the thiadiazole ring can target enzymes or pathways relevant to diseases beyond infectious ones. This multifunctionality opens avenues for repurposing these hybrids to manage a range of conditions, making them versatile agents in drug discovery.

6. Reduction in Side Effects and Improved Safety Profile

- While fluoroquinolones are effective, they can carry risks of side effects, particularly in high doses or long-term treatments. Hybridizing with thiadiazole may allow for effective dosing at lower concentrations, potentially reducing adverse effects associated with fluoroquinolone therapy, such as gastrointestinal disturbances and musculoskeletal issues.
- Additionally, thiadiazole modifications may mitigate toxicity by altering the distribution of the drug within the body, reducing off-target effects and improving patient tolerance.

7. Chemical Flexibility for Customization

- Thiadiazole is a flexible scaffold that allows for extensive functionalization, meaning chemists can easily modify the fluoroquinolone-thiadiazole hybrid to achieve desired biological and pharmacokinetic properties. Adjusting substituents on the thiadiazole ring can tailor the hybrid for specific infections or pharmacological needs, allowing the creation of analogs that target specific pathogens or cellular processes.

CONCLUSION

Fluoroquinolone-thiadiazole hybrids represent a promising frontier in medicinal chemistry, offering innovative solutions to challenges like AMR, limited pharmacokinetics, and narrow therapeutic spectrum. By combining the established potency of fluoroquinolones with the diverse biological properties of thiadiazoles, these hybrids may provide more potent, safe, and versatile antimicrobial agents. As researchers continue to explore and refine these compounds, fluoroquinolone-thiadiazole hybrids could lead to the next generation of multifunctional drugs, addressing urgent global health challenges and laying the groundwork for more resilient therapeutic solutions.

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 https://doi.org/10.5281/zenodo.14546809