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A Comprehensive Review On Quinoline And Its Derivatives As Antibacterial Agents

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ABSTRACT:-

The growing concern of Antimicrobial Resistance (AMR) requires ongoing advancements in the identification of new antibacterial compounds. The quinoline structure has long been one of the essential frameworks in medicinal chemistry, leading to the development of a highly effective group of antibiotics known as fluoroquinolones. This review examines the progression and contemporary advancements in quinoline-derived antibacterial agents. While classical fluoroquinolones target bacterial Type II topoisomerases (DNA gyrase and topo IV), the widespread emergence of resistance mechanisms (quinolone resistance determining region (QRDR) mutations and efflux pumps) has driven a strategic shift in synthetic efforts. We describe the Structure-Activity Relationship (SAR) for both traditional and novel derivatives, focusing on promising recent approaches. This encompasses the creation of hybrid compounds that feature dual mechanisms of action, C-2 oxo-quinolines that demonstrate strong anti-biofilm activity, and quinolinium salts crafted to overcome resistance through non-specific membrane disruption. We finish by addressing significant challenges, including systemic toxicity and the barrier posed by the Gram-negative outer membrane, and outline future pathways, highlighting the necessity for compounds that focus on non-topoisomerase mechanisms (such as ATP synthase) and the application of efflux pump inhibitors (EPIs) to maintain the quinoline scaffold as an essential resource in combating AMR.

KEYWORDS:-

Quinoline, Fluoroquinolone, Antibacterial Agents, Antimicrobial Resistance, SAR, Hybrid Molecules, DNA Gyrase.

INTRODUCTION:

- **The Antibiotic Resistance Crisis:**

The rise and swift worldwide spread of Antimicrobial Resistance (AMR) pose one of the most significant public health challenges of the 21st century [1]. The inappropriate use and excessive application of current antibiotics have hastened the development of Multi-Drug Resistant (MDR) bacteria, making once-reliable treatments ineffective [2, 3]. Especially worrisome pathogens include methicillin-resistant Staphylococcus aureus and highly resistant gram-negative bacteria like Acinetobacter baumannii and Pseudomonas aeruginosa [4]. Since the development of new antibiotics is still insufficient, there is a pressing and ongoing necessity to create new antimicrobial agents or modify existing compounds to enhance their effectiveness against these ‘superbugs’ [5].

- **The Importance of Heterocycles:**

In medicinal chemistry, nitrogen-containing heterocyclic compounds are consistently recognized as privileged scaffolds—molecules with inherent structural features that allow them to interact favorably with biological targets [6]. These structures often possess ideal lipophilicity, hydrogen-bonding capacity, and electronic characteristics required for drug-like properties. Among these, the quinoline nucleus, a bicyclic system composed of a benzene ring fused to a pyridine ring, is particularly prominent [7].

- **Quinoline: A Core Scaffold:**

The quinoline scaffold, chemically known as benzo [b]pyridine, has a rich history originating from natural sources like the Cinchona alkaloids (e.g., quinine) [8]. This core structure has been successfully adapted over decades to treat various diseases, most famously malaria, and is fundamental to the blockbuster class of antibacterial drugs, the quinolones [9]. The adaptability of the quinoline ring allows medicinal chemists to introduce various functional groups at multiple positions, enabling fine-tuning of activity, spectrum, and pharmacokinetic profiles to combat resistance.

HISTORICAL DEVELOPMENT OF ANTIBACTERIAL QUINOLINES:

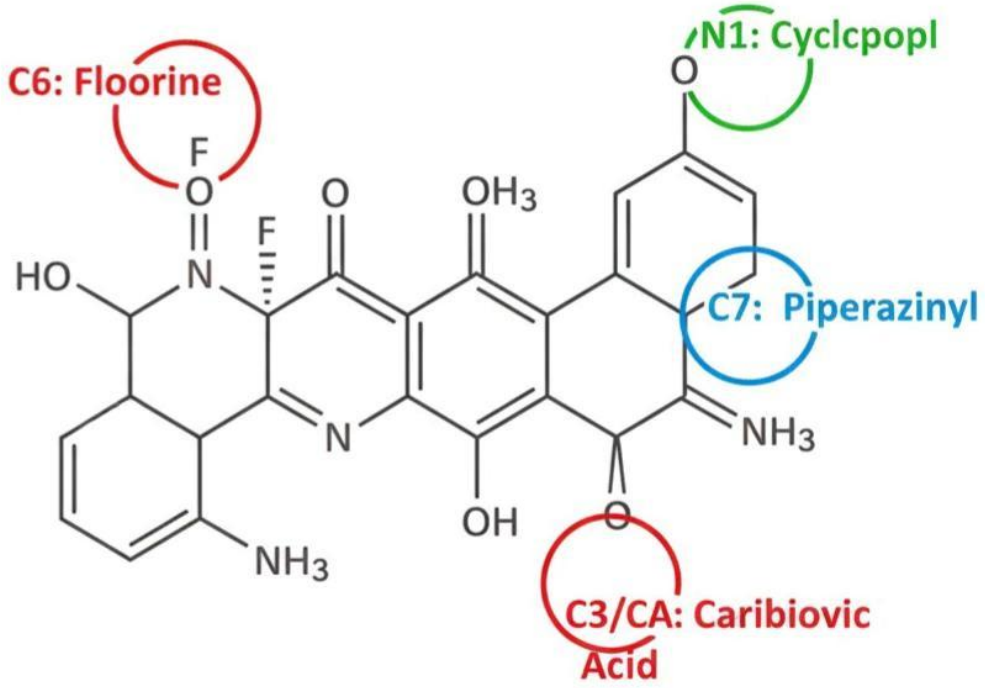


Figure 1: Structure of Ciporioacion (A 2nd-generation Fluoroquinlone)

The creation of antibacterial agents derived from quinoline represents one of the most notable achievements in synthetic medicinal chemistry [10], progressing from basic treatments for urinary tract infections to widely applicable systemic antibiotics.

- **Early Discoveries: The First Generation:**

The exploration commenced in the early 1960s with the identification of nalidixic acid [11]. Initially serving as an intermediate, it was later discovered to have selective antibacterial properties. Nalidixic acid emerged as the model compound of the first-generation quinolones [12]. Its effectiveness was somewhat limited, primarily aimed at Gram-negative bacteria, and its application was mainly confined to uncomplicated urinary tract infections due to its low serum levels and the quick development of resistance [13]. Other first-generation drugs include oxolinic acid and pipemidic acid.

- **The Fluoroquinolone Revolution**

The revolution began with the launch of the second generation, known as fluoroquinolones. A crucial structural change was the incorporation of a fluorine atom at position C6. This modification was essential, significantly boosting lipophilicity, membrane penetration, and the affinity for the target enzyme.

During the second generation (1980s), drugs like ciprofloxacin and norfloxacin broadened the spectrum to include numerous Gram-positive bacteria and important Gram-negative pathogens such as Pseudomonas aeruginosa. Ciprofloxacin, noted for a cyclopropyl group and a piperazinyl group, became one of the most commonly prescribed antibiotics worldwide.

The third and fourth generations, including levofloxacin and moxifloxacin, provided even more extensive spectrums, enhancing their efficacy against atypical respiratory pathogens and anaerobes through modifications mainly at specific positions.

- **Non-Fluoroquinolone Derivatives**

Non-fluoroquinolone derivatives, commonly known as Non-Fluorinated Quinolones (NFQs) or first-generation quinolones, represent a category of synthetic antibacterial drugs that contain a fundamental quinolone framework but do not possess the fluorine atom usually located at the C6 position of the more widely utilized fluoroquinolones.

~~Non-classical quinoline derivatives that intentionally bypass the -carboxylic acid and -fluorine~~ substitutions to circumvent established resistance mechanisms [19].

One significant achievement in clinical settings is bedaquiline (a diarylquinoline), mainly used as an anti-tuberculosis medication that focuses on mycobacterial ATP synthase instead of [20]. This demonstrates the adaptability of the quinoline structure for unconventional antibacterial actions.

MECHANISMS OF ACTION (MOA):

Quinolones and fluoroquinolones are antibiotics that kill bacteria by interfering with vital bacterial processes necessary for the maintenance and replication of DNA [21].

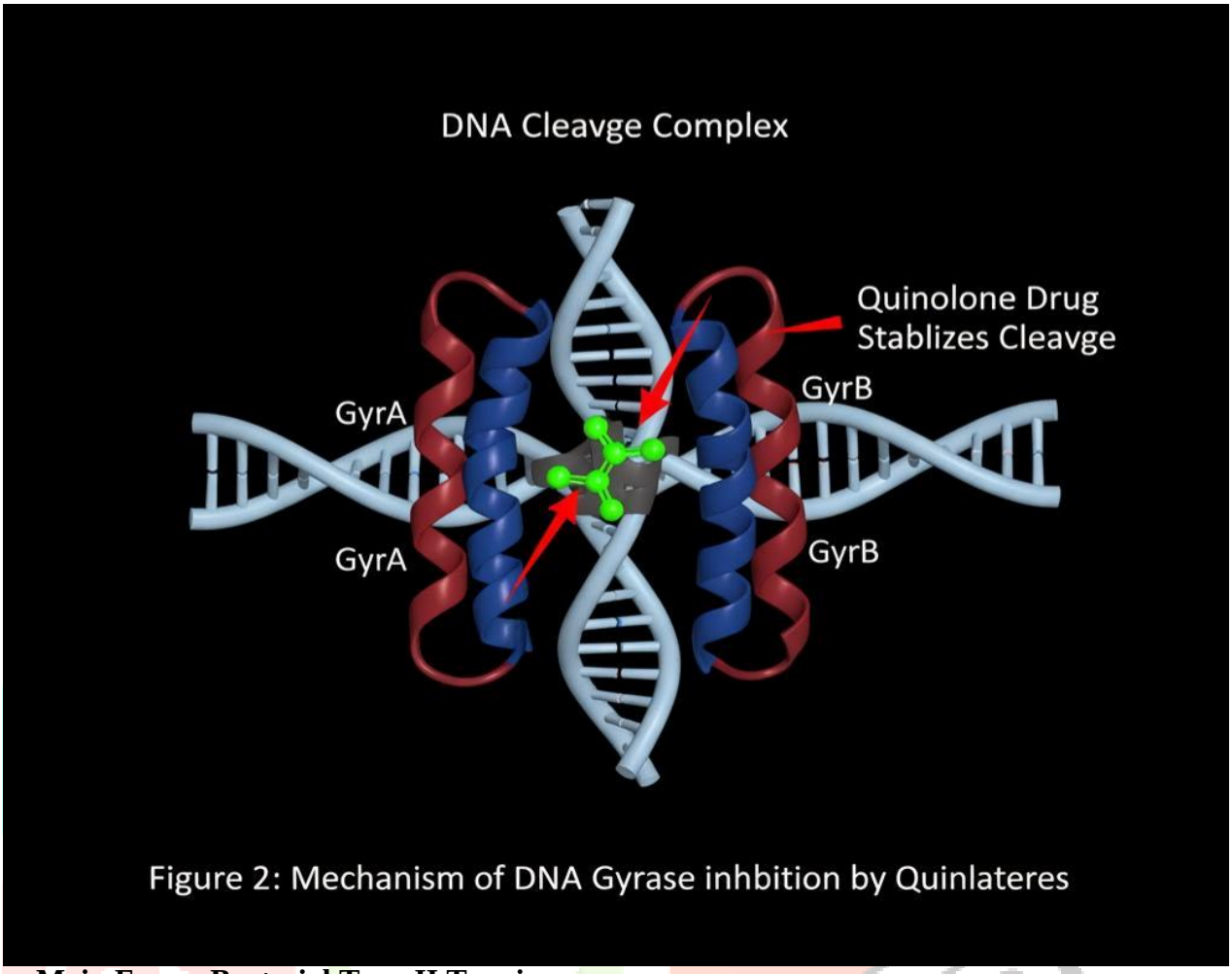


Figure 2: Mechanism of DNA Gyrase inhbition by Quinlateres

- **Main Focus: Bacterial Type II Topoisomerases**

The primary action centers around the blockage of two essential bacterial enzymes: DNA gyrase and topoisomerase IV [22]. These enzymes regulate the topological strain (supercoiling and entangling) of the bacterial chromosome, which is crucial for both replication and transcription [23].

- **The DNA Cleavage Complex**

Quinolones act as "topoisomerase poisons" by disrupting the ligation phase of the enzyme's catalytic process [24]. The medication attaches to the temporary complex created by the enzyme and the severed strands, stabilizing this formation, which is referred to as the Quinolone-DNA-Enzyme Cleavage Complex [25]. The buildup of these double-strand breaks activates the bacterial SOS response, resulting in swift bacterial cell death [21].

- **Target Specificity and Resistance**

The main target usually varies by species: in Gram-negative bacteria, DNA gyrase is predominantly targeted, whereas topoisomerase IV tends to be the more susceptible target in Gram-positive species [22].

Resistance mainly arises through two mechanisms:

1. Target Modification (QRDR): The most prevalent pathway is through mutations in the genes that code for topoisomerases IV located within the Quinolone Resistance Determining Region (QRDR) [26]. These mutations change the structure of the enzyme, hindering effective binding of the drug [27].

2. Efflux Pumps: Bacteria create efflux pumps—membrane proteins that actively expel the drug from the cell before it can achieve its target, lowering the intracellular concentration to non-lethal levels [28].

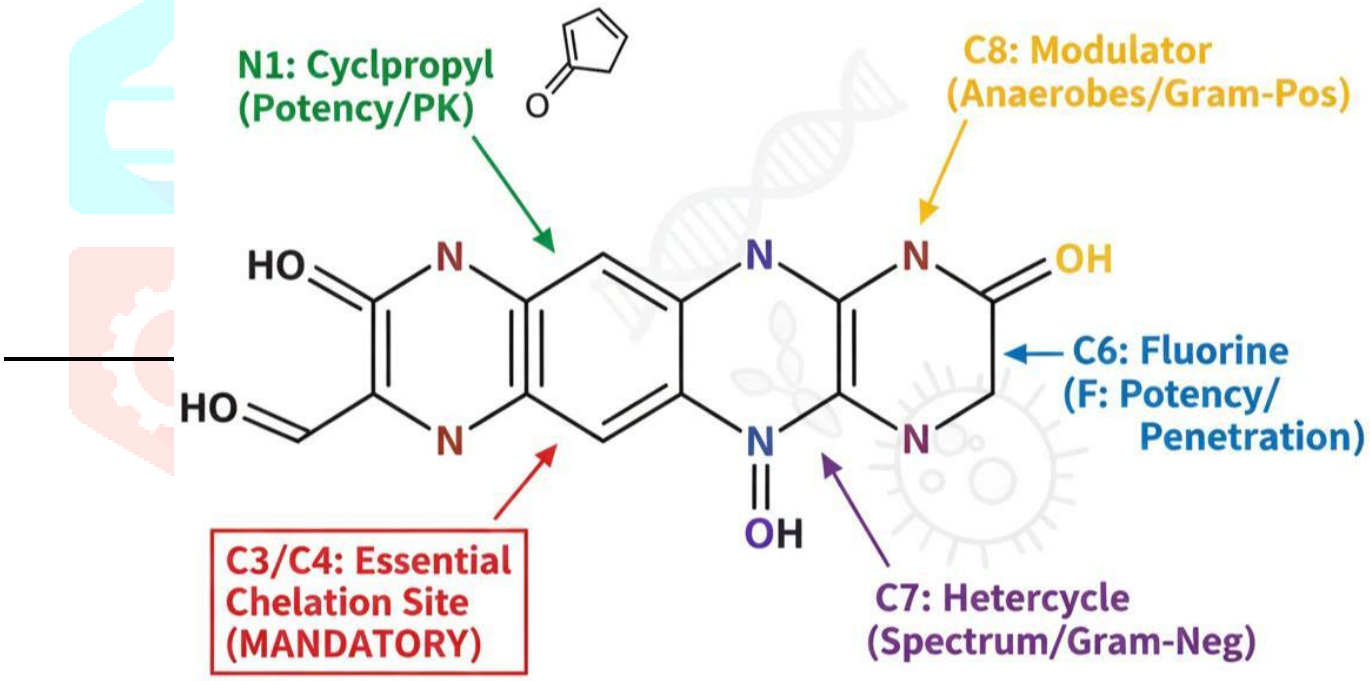
- **Alternative/Non-Classical Mechanisms**

The effectiveness of bedaquiline [20] and the introduction of novel quinolinium salts [29] have validated that quinoline derivatives can function through non-topoisomerase pathways, such as interfering with the bacterial cell membrane [30] or obstructing bacterial energy production. This transition is significant for circumventing known mechanisms and efflux routes [19].

- **Progress in Non-Topoisomerase Quinoline Mechanisms**

Overcoming Known Resistance: The main mechanism of resistance to conventional fluoroquinolones includes mutations in the genes for DNA gyrase and topoisomerase IV (the specific targets of the drugs) or the increased activity of efflux pumps. By targeting non-topoisomerase sites, such as the bacterial cell membrane or processes related to energy production, these innovative quinolines make these established resistance strategies ineffective.

STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF ANTIBACTERIAL QUINOLINES:



The foundational remains the benchmark for inhibitors [31].

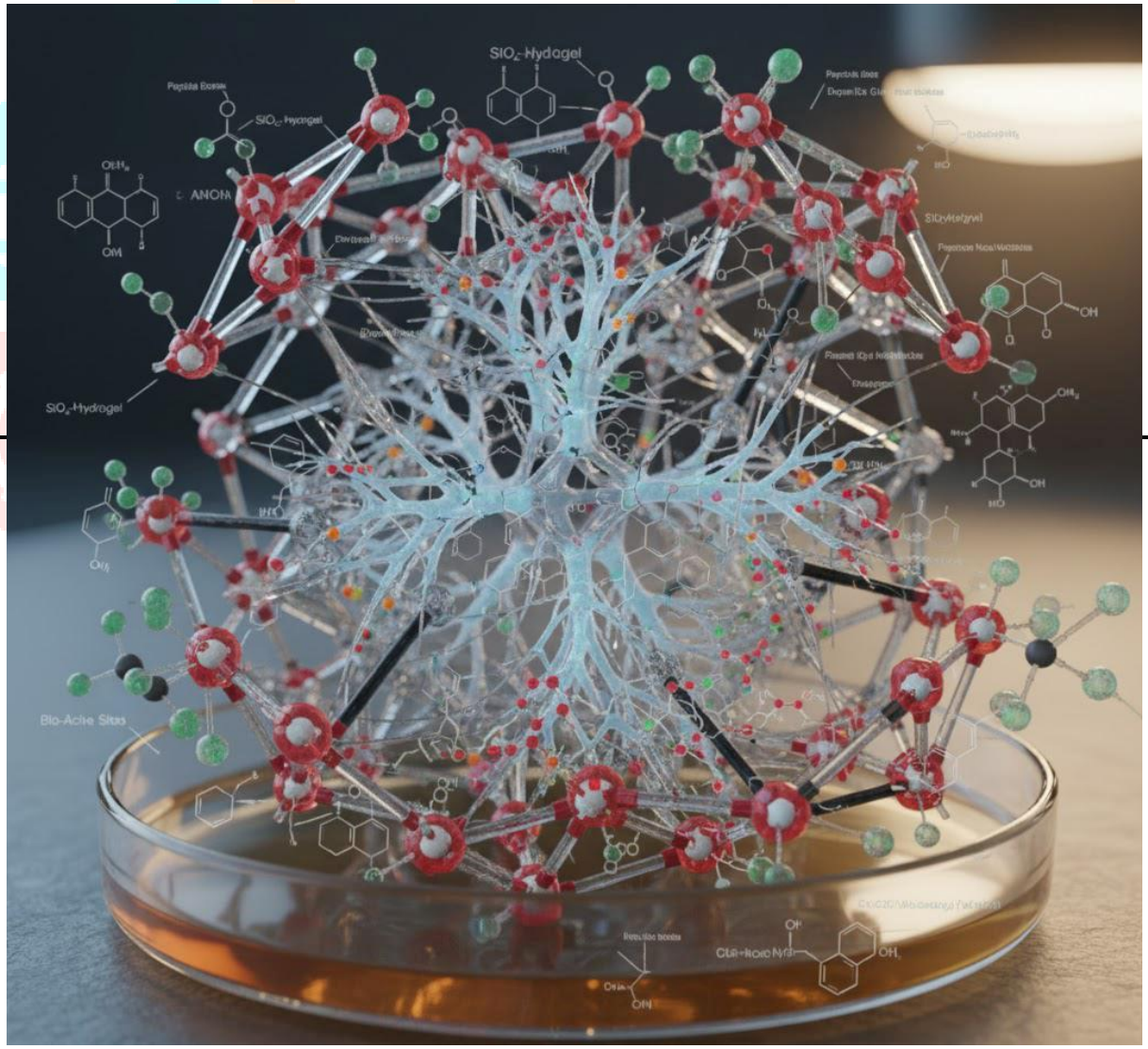
- **C3 and C4 Positions:** The 1,4-dihydro-4-oxo-pyridin-3-carboxylic acid moiety is mandatory for classical activity and essential for chelation with a hydrated magnesium ion ( ) at the binding site [32].
- **N1 Position:** A small, lipophilic group, such as the cyclopropyl group (e.g., in ciprofloxacin), significantly enhances enzyme inhibition and overall potency [16].
- **C6 Position**: The fluorine atom (F) here defines the fluoroquinolone class, increasing lipophilicity and potency against [14].
- **C7 Position:** A heterocyclic ring, typically a piperazinyl or pyrrolidinyl group, is essential. This group tunes the spectrum, influencing activity against Gram-negative bacteria and affecting efflux pump susceptibility [17, 33].

Recent efforts are focused on evading resistance by exploring non-classical structures [19]:

- **Hybrid Molecules:** Covalent linking of the quinoline core to another pharmacophore (e.g., triazole, oxadiazole) creates dual-target agents that exhibit synergy [34]. Studies show potent quinoline-triazole hybrids successfully inhibit both and efflux pumps, restoring activity against [35].
- **C-2 Oxo-Quinolines (Quinolin-2-ones):** These molecules lack the classical C4-carboxy/C3-keto motif. Activity is instead derived from a C2-keto group and substitutions at C3 or N [36]. Crucially, N-substituted quinolin-2-one Schiff bases have demonstrated potent activity against Gram-positive bacteria (MSRA, VRE) and significant anti-biofilm activity, superior to vancomycin in some models [37].
- **Quinolinium Salts:** The existence of a constant positive charge on these salts allows for robust electrostatic interactions with the negatively charged bacterial membrane, resulting in a mechanism of action that disrupts the membrane. This physical process is particularly effective against Gram-positive bacteria and shows reduced vulnerability to existing molecular resistance.

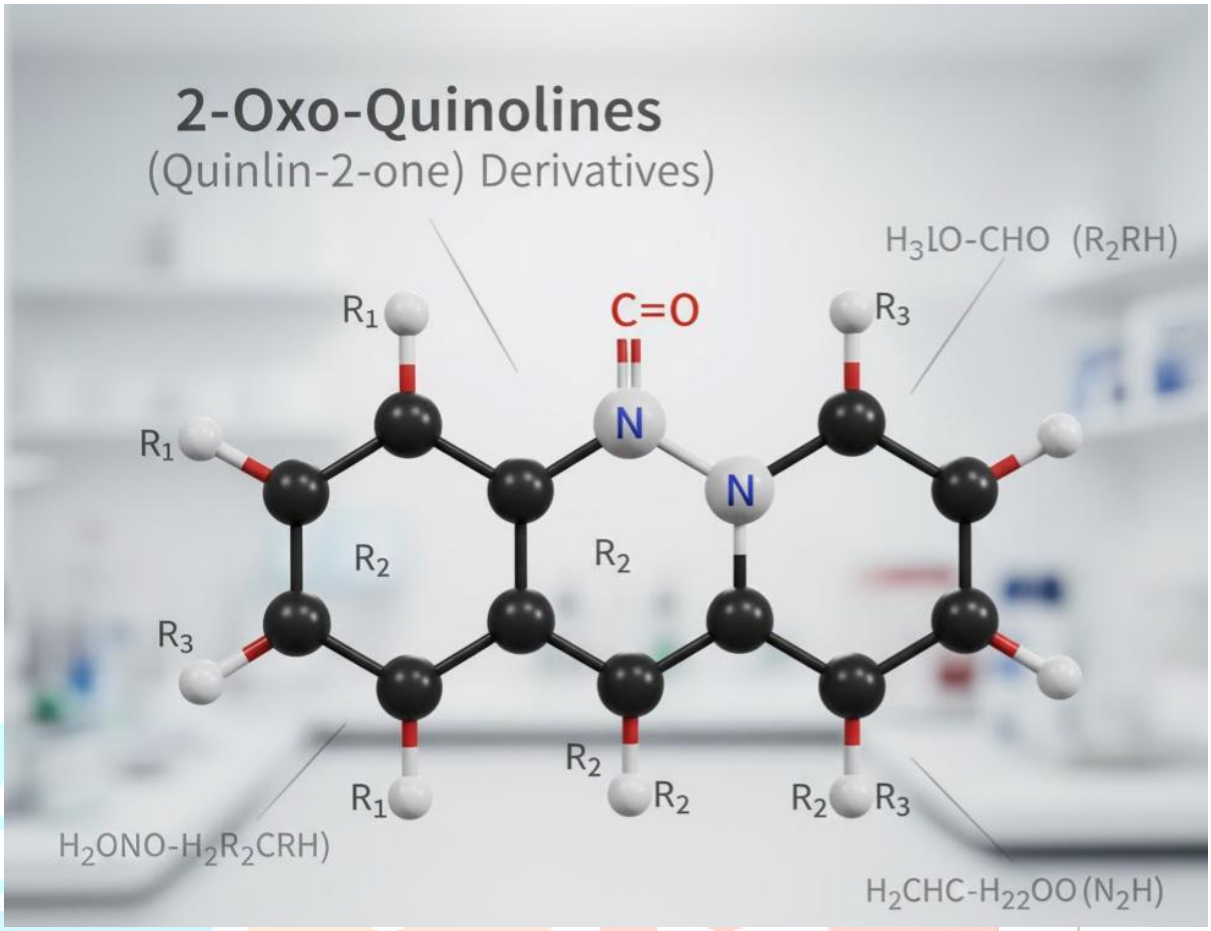
NOVEL QUINOLINE DERIVATIVES:

1. **Novel Hybrid Scaffolds:** The hybridization strategy aims to achieve synergistic activity or capability [34]. These hybrids successfully overcome resistance by increasing intracellular



concentration and, in some cases, targeting multiple independent bacterial pathways simultaneously [39].

2. **C-2 Oxo-Quinolines (Quinolin-2-one) Derivatives:** Quinolin-2-ones represent a significant structural alteration that effectively bypasses resistance mechanisms [36]. The most striking result



is their strong effectiveness against bacterial biofilms [41]. Research on N-substituted quinolin-2-ones has shown Minimum Biofilm Eradication Concentrations (MBECs) that are superior to comparator antibiotics like vancomycin, confirming their potential for treating chronic and device-related infections [37, 42].

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1. **Quinolinium Salts and Membrane-Targeting Agents:** Quaternary quinolinium salts, which are permanently charged, function as cationic amphiphiles and strongly interact with the negatively charged bacterial membrane, resulting in physical disruption and depolarization. This non-specific mechanism makes it challenging for bacteria to develop targeted resistance, contributing to their high effectiveness against hard-to-treat Gram-positive strains.

CHALLENGES AND FUTURE DIRECTIONS:

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1. **Clinical and Safety Challenges**

The primary hurdles for new quinoline derivatives involve safety concerns inherited from earlier generations [43].

- Toxicity and Side Effects: There are regulatory boxed warnings related to severe adverse effects, such as tendinopathy and tendon rupture [44], as well as Central Nervous System (CNS) effects [45]. A higher lipophilicity, which is often sought for better cellular penetration, typically links to a greater risk of CNS & cardiotoxicity [46].
- Cardiotoxicity (QT Prolongation): The possibility of extending the interval, which increases the risk of life-threatening cardiac arrhythmias, requires thorough screening for cardiotoxicity in all new quinoline derivatives [47].
- The outer membrane of Gram-negative bacteria serves as a significant physicochemical barrier that is difficult to penetrate [48]. Numerous highly effective in vitro compounds do not succeed in vivo

due to their inability to reach adequate intracellular levels, necessitating approaches to enhance passive diffusion or take advantage of bacterial nutrient uptake mechanisms [49].

1. **• The Future of Quinoline Research:**

Future quinoline drug discovery is expected to concentrate on three main strategies:

Non-Topoisomerase Targets and MoA Shift Moving away from it is critical to bypass existing QRDR resistance [19]. Key focus areas include:

- Inhibition of ATP Synthase: Discovering quinoline derivatives that selectively hinder the energy production in bacteria, akin to the effects of bedaquiline [20].
- Disruption of Membranes: Utilizing the natural membrane-binding properties of cationic structures (quinolinium salts) to provoke bacterial lysis, proving to be particularly effective against chronic infections and biofilm formations [30, 41].

Efflux Pump Inhibitors (EPIs): Creating quinoline derivatives that act as efflux pump inhibitors is an important focus area. This approach enhances the effectiveness of older, safer antibiotics (such as ciprofloxacin) against resistant strains by stopping their removal from the cell.

Computational and AI-Driven Design: Computational approaches accelerate development and mitigate risk [52]:

- In Silico Prediction of ADMET: Utilizing Artificial Intelligence (AI) and Machine Learning (ML) models to predict toxicity (especially cardiotoxicity) and penetration before costly synthesis [46].
- Targeting Non-Canonical Binding Sites: Using computational docking to identify new, unexplored binding pockets on bacterial proteins that are outside the established QRDR, leading to compounds less susceptible to mutational resistance [53].

CONCLUSION:

The quinoline framework is still largely untapped. Its chemical adaptability guarantees that it will remain ~~a promising source for creating the next wave of antibiotics needed to address the growing global issue of~~ drug-resistant bacteria.

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