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Review Article

Fluoroquinolones and Their Hybrid Derivatives: Evolution, Mechanism of Action, Structure–Activity Relationships, Resistance, Therapeutic Relevance, and Recent Advances in Hybrid Drug Design

Venkateswara Rao Gollapalli,[1,2] Hari Babu Bollikolla[2,3*]

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Author's Affiliations

[1]Chemical Research Department, APL Research Centre-II, Aurobindo Pharma Ltd., Sangareddy, Telangana, India–502329

[2]Department of Chemistry, Acharya Nagarjuna University, Guntur, Andhra Pradesh, India–522510

[3]Department of Chemistry, Andhra Kesari university, Ongole, Andhra Pradesh, India–523 001

Corresponding Author

Hari Babu Bollikolla
dr.b.haribabu@gmail.com

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Abstract

Fluoroquinolones (FQs) are synthetic broad-spectrum antibacterials, and due to their potent bactericidal activity and favorable pharmacokinetic properties they have been a major player in the modern chemotherapy of bacterial infections. The main antibacterial action of these compounds is the inhibition of bacterial type II topoisomerases, DNA gyrase and topoisomerase IV, by stabilization of drug-enzyme-DNA cleavage complexes that cause lethal DNA damage . Since their origin from nalidixic acid and early quinolones, systematic medicinal chemistry optimization, particularly fluorine substitution at the C-6 position and heterocyclic modification at C-7, has produced multiple generations of clinically important agents including ciprofloxacin, levofloxacin, moxifloxacin and gemifloxacin. Newer members such as finafloxacin, besifloxacin, zabofloxacin and delafloxacin have attracted interest in recent decades because of enhanced potency in certain infection settings and potential advantages against resistant pathogens. However, the clinical utility of fluoroquinolones has been limited by rising resistance rates stemming from target-site mutations, efflux pump overexpression, decreased permeability and plasmid-mediated resistance mechanisms. Safety concerns such as tendinopathy, dysglycemia, QT prolongation, effects on the central nervous system and phototoxicity have led to further restrictions on the use of some agents. Nonetheless, the quinolone scaffold is a privileged pharmacophore with well-defined structure-activity relationships (SAR) and excellent synthetic versatility. Hybridising fluoroquinolones with other pharmacophores has become an attractive strategy to enhance antibacterial potency, overcome resistance, and expand the biological spectrum to include antimycobacterial, antiviral, antifungal, and anticancer applications. The review highlights historical development, mechanism, SAR trends, resistance mechanism, clinical and emerging FQs, and modern hybrid and fused heterocyclic fluoroquinolone derivatives with focus on recent literature advances.

Keywords:

Fluoroquinolones; Topoisomerase-IV; DNA gyrase; Antimicrobial resistance; Hybrid antibiotics; Ciprofloxacin; Finafloxacin; Delafloxacin.

1. Introduction

Healthcare-associated infections are a major global clinical problem, affecting large populations of patients each year and contributing significantly to morbidity, mortality and economic loss[1]. Surgical site infections are associated with increased hospitalizations and accelerated selection of resistant organisms in hospitals[2].

In such cases, fluoroquinolones have remained among the most commonly prescribed broad-spectrum agents because of their potency against Gram-negative and Gram-positive organisms, availability of oral formulations and excellent tissue penetration[3,4]. Fluoroquinolones are also key medicinal chemistry scaffolds as their core pharmacophore is highly amenable to derivatization. Fluoroquinolone derivatives have been investigated in viral infections (hepatitis, HIV, herpes), tuberculosis, fungal diseases, cancer, malaria, immunosuppression-related disorders and neurological disorders besides antibacterial applications[5]. The structural reactivity and well-defined SAR of fluoroquinolones have sustained interest in development of next generation analogs for decades[5].

The global crisis of antimicrobial resistance (AMR) is increasingly undermining the usefulness of established antibiotics. Hybridization approaches, which combine two pharmacophores into one molecule, have been proposed as a rational strategy to achieve "combination-like" benefits and more effective suppression of resistance evolution than monotherapy[6].

In this context, fluoroquinolones are attractive hybrid platforms because modifications at C-7 and other positions enable incorporation of diverse heterocycles and bioactive fragments.

2. Historical Development of Quinolones

2.1 Detection of quinolones and nalidixic acid

The finding of quinolones began in the early 1960s with the identification of a compound named 7-chloro-1-ethyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, a by-product formed during chloroquine production.

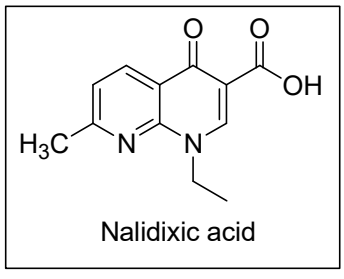


Fig. 1: Structure of nalidixic acid

Recognition of antibacterial activity led to chemical modification and synthesis of nalidixic acid, a 1,8-naphthyridine quinolone[7] (**Fig. 1**).

2.2 First-generation quinolones

Following nalidixic acid, medicinal chemists synthesized a number of related targets known as first-generation quinolones, including oxolinic acid, cinoxacin, flumequine, pipemidic acid, and piromidic acid, derived from the 4-quinolone core[8]. However, the early quinolones were reported to be limited by narrow spectrum and rapid resistance emergence.

2.3 Emergence of fluoroquinolones

The limited efficacy of early quinolones against diverse pathogens motivated development of 6-fluoro derivatives, which provided improved potency and spectrum[8]. In the 1980s, incorporation of fluorine yielded ciprofloxacin, widely recognized as the first clinically successful fluoroquinolone. Continued medicinal chemistry optimization produced thousands of analogues and multiple generations of broad-spectrum chemotherapeutics.

3. Introduction to Fluoroquinolones

Fluoroquinolones are broad-spectrum synthesized antibiotics that are effective against Gram-negative and Gram-positive bacteria. They play a crucial role in severe infections, especially hospital-acquired infections and infections where resistance to older antibiotic classes is anticipated [9,10]. After nalidixic acid discovery, more than ten thousand quinolone analogues were synthesized, resulting in four generations with expanded spectrum and improved clinical performance[11,12]. The antibacterial effect of quinolone drugs are results from inhibition of bacterial type-II topoisomerases, including DNA gyrase and topoisomerase-IV[13].

The FDA approved quinolone use for systemic UTI management early in their clinical history, and subsequent to norfloxacin identification, structure–activity relationship knowledge guided the creation of improved analogues with enhanced solubility and activity[14].

4. Classification and Chemical Framework

The name "quinolones" refers to derivatives of 1,8-naphthyridine-4-one, 4-quinolone, or pyrido-pyrimidine-5-one structures[15]. The carbons C-2, C-3,

and C-4 positions are strongly linked to mechanism, while N-1, C-5, C-7, and C-8 serve as key tunable substitution sites[15]. Four generations of fluoroquinolones have been developed to combat Gram-(+Ve), Gram-(-Ve), and anaerobic infections[16] [**Fig. 2**]. The term "fluoroquinolone" reflects the predominance of fluorinated structures within the class[17]. Third-generation agents such as levofloxacin show improved activity against *Streptococci*[18].

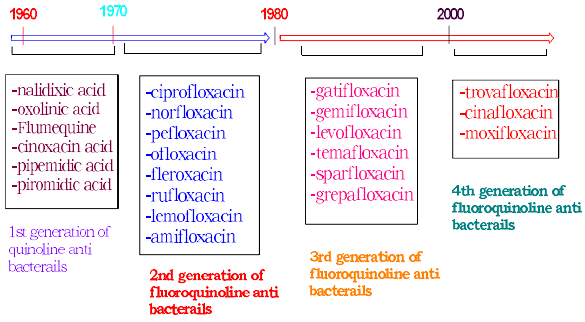


Fig. 2: Generational development of fluoroquinolones and spectrum expansion.

5. Mechanism of Action

Fluoroquinolones are inhibitors of DNA synthesis and cause cleavage of bacterial DNA in DNA-enzyme complexes containing DNA gyrase and topoisomerase-IV, resulting in rapid bacterial death[19]. DNA gyrase inhibition is usually linked to Gram-negative activity and topoisomerase IV inhibition to Gram-positive activity[19] [**Fig. 3**].

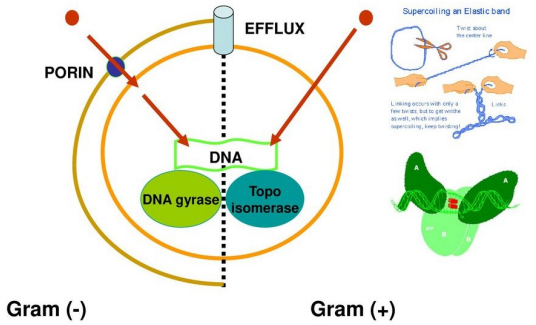


Fig. 3: Fluoroquinolones stabilization mechanism of DNA–topoisomerase cleavage complex.

Mechanistically, fluoroquinolones stabilize the cleavage complex, preventing religation and generating double-strand breaks that provoke lethal damage responses.

6. SAR (Structure–Activity Relationships) of Fluoroquinolones

SAR principles provide the framework for rational design of fluoroquinolones where predictable changes can be made in potency, spectrum, pharmacokinetics and safety.

6.1 Essential SAR features

The significant SAR features include the following substitution rules[20]:

Position 2: Hydrogen is optimal; larger substituents hinder C-3/C-4 alignment.

Position 3: Carboxyl group required for DNA gyrase/DNA base interaction.

Position 4: Keto group required for DNA gyrase/DNA base interaction.

Position 6: Small group required; fluorine is optimal and increases potency significantly.

Position 1: Influences pharmacokinetics and potency; cyclopropyl increases Gram-negative activity; 2,4-difluorophenyl enhances anaerobe activity but may increase toxicity risk (temafloxacin withdrawal).

Position 5: $-NH_2$ or $-CH_3$ may improve Gram-positive activity.

Position 7: N- heterocycles improve activity and PK; Amino-pyrrolidine increases Gram-positive activity; piperazine improves Gram-negative activity.

Position 8: Influences the PK and anaerobic activity.

6.2 SAR narrative expansion

Earlier compounds such as nalidixic acid, pipemidic acid, norfloxacin, enoxacin, cinoxacin and rosoxacin carried ethyl groups at N-1[21]. The C-3 carboxyl group is important for binding and stereochemical orientation, and should not be disturbed[22]. Modifications at C-5 can lead to increased Gram-positive activity[22]. Much of the evolution of quinolones was due to modifications at C-7, as heterocyclic rings of nitrogen lead to better

activity and pharmacokinetics[23]. C-8 modifications affect in vivo performance and anaerobic activity[24].

7. Clinical Relevance and Important Fluoroquinolone Drugs

Fluoroquinolones are extensively used for UTIs, respiratory infections, GI infections, skin infections, and systemic infections because of their broad coverage and tissue penetration[3,4].

7.1 Classical fluoroquinolones

Common clinical examples include:

- **Ciprofloxacin** (broad Gram-negative potency; UTI, GI infections, anthrax-related infections)
- **Norfloxacin** (primarily UTIs)
- **Ofloxacin / Levofloxacin** (respiratory and systemic use)
- **Moxifloxacin** (respiratory; some anaerobic coverage)
- **Gemifloxacin** (respiratory pathogens; activity against resistant S. pneumoniae)

7.2 Newer agents and emerging clinical positioning

In the past two decades, besifloxacin, delafloxacin, finafloxacin, and zabofloxacin have been authorized for clinical use, though classification as fourth vs fifth generation remains debated [20]. Besifloxacin is important in ophthalmic infections. Finafloxacin is positioned for otic and acidic environments.

Delafloxacin has gained clinical interest due to MRSA coverage and acidic-site potency. Zabofloxacin has been used for respiratory infections in selected regions.

8. Safety Profile and Adverse Effects

Despite clinical advantages, quinolones may cause adverse effects such as central nervous system reactions, tendinitis, phototoxicity, hypoglycemia and cardiac dysrhythmias[20]. Some agents have been withdrawn due to safety issues (e.g., clinafloxacin due to phototoxicity and hypoglycemia)[25] [**Fig. 4**]. Therefore, there remains a need for fluoroquinolones with better tolerability and optimized activity profiles[20].

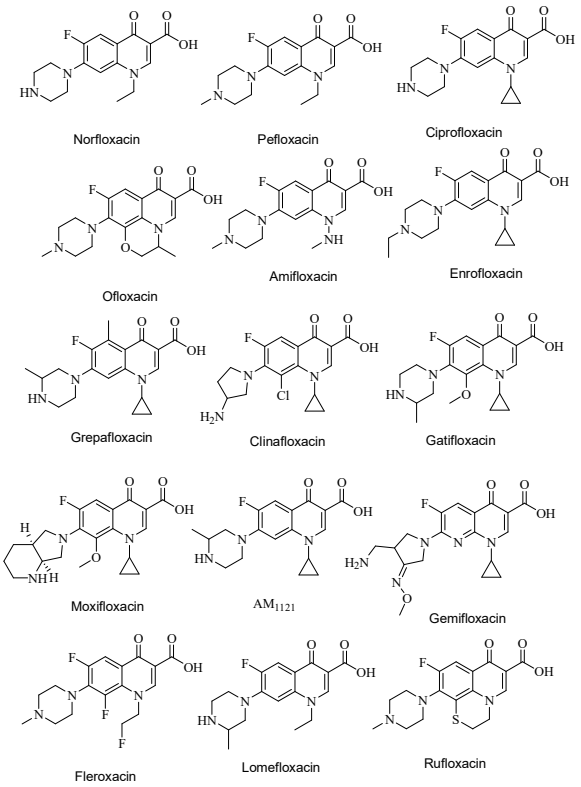


Fig. 4. Major adverse effects and safety concerns associated with fluoroquinolones.

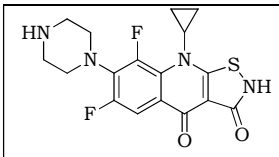
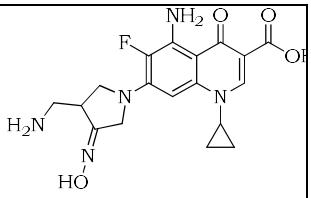
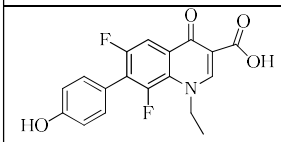
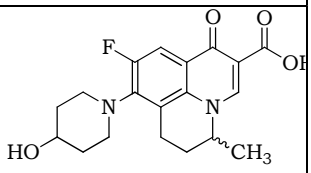
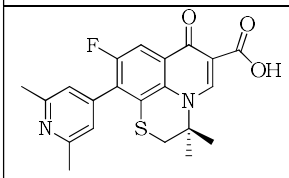
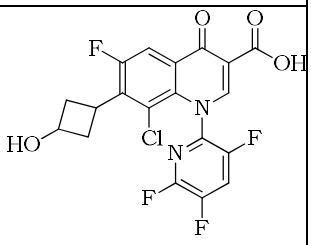
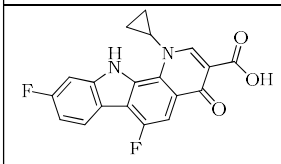
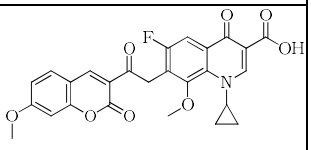
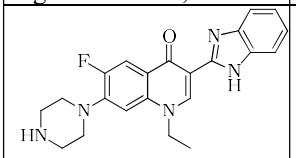
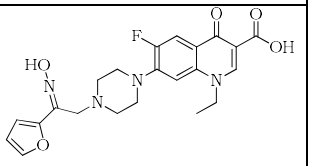
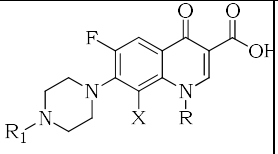
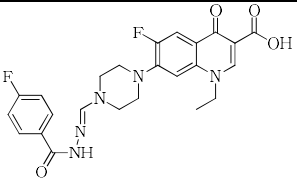
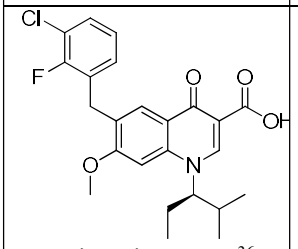
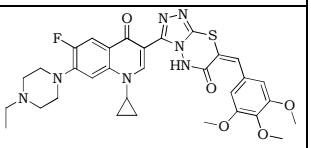
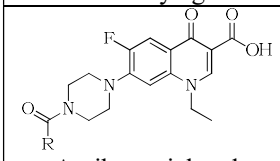
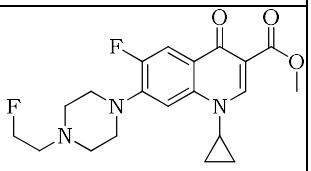
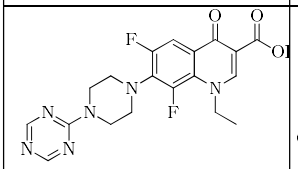
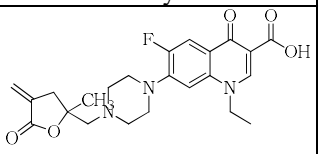
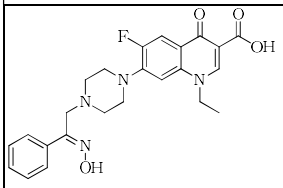
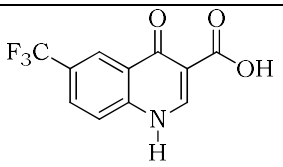
9. Biological Potentials Beyond Antibacterial Activity

The fluoroquinolone scaffold has been explored for diverse biological activities. Your file lists multiple reported activities (**Table 1**), including:

- Topoisomerase-II inhibition[26]
- Activity against resistant Gram-positive and Gram-negative strains[27]
- Anticancer activity against MCF-7, A549, A172[28,29]
- Antimycobacterial activity including MDR strains[30]
- HIV-1 inhibition[31]
- Anticancer activity against HL60/L1210[32]
- Antibacterial and antifungal activity[33]
- DNA gyrase inhibition[34]
- Potential anti-MRSA/anti-VRSA activity[35]
- Antiviral activity in quinolone derivatives[36]

This supports the concept that quinolones are privileged scaffolds that can be redirected toward multiple disease areas.

Table 1: Reported biological activities of quinolones/fluoroquinolones beyond antibacterial action.

 Topoisomerase-II Inhibitor[28]	 Gram (+) and Gram (-) bacteria[29]
 CP-67, 804 Topoisomerase-II Inhibitor[30]	 Gram (+) and Gram (-) bacteria[30]
 WIN 58161 Topoisomerase-II Inhibitor[28]	 Gram (+) and Gram (-) bacterial resistance strain[29]
 Anticancer activity against MCF-7, A549[30]	 Antimycobacterial activity[31]
 Solo205 (carcinoma cancer)[32]	 Anticancer activity against MCF-7, A549, A172[33]
 Inhibition of HIV-1[34]	 $H_{37}Rv$ ATCC27294 and MDRTB A8241 inhibitors[35]
 Anti-anxiety agent[36]	 Anticancer activity against L1210 HL60[37]
 Antibacterial and antifungal activity[38]	 Inhibitory Activity against DNA Gyrase[39]
 As potential methicillin and vancomycin-resistant *Staphylococcus aureus*[40]	 Anticancer activity against CAKI-1, RXF 393, UO-31[41]
 Inhibition of *E. coli* ATCC-25922[42]	 Quinolones exhibiting antiviral activity[43]

10. Antibiotics Overview and Global Resistance Context

The antibiotic term originated from Greek "anti" (against) and "bios" (life), describing substances used to inhibit bacterial growth (bacteriostatic) or kill bacteria (bactericidal)[37]. Antimicrobials include naturally derived antibiotics, chemically modified antibiotics, and synthetic compounds such as fluoroquinolones[38].

The WHO global surveillance report (2014) identified AMR as a profound global health and economic threat[39]. Predictions suggest AMR could cause hundreds of millions of premature deaths by 2050 if unchecked[40]. The Waksman platform rapidly identified major antibiotic classes in the 1940s such

as aminoglycosides, beta-lactams, chloramphenicol, macrolides and tetracyclines[41] [**Fig. 5**]. Synthetic chemistry then enabled conversion of narrow-spectrum agents into broader-spectrum analogs and introduced synthetic antimicrobials like fluoroquinolones[42–46].

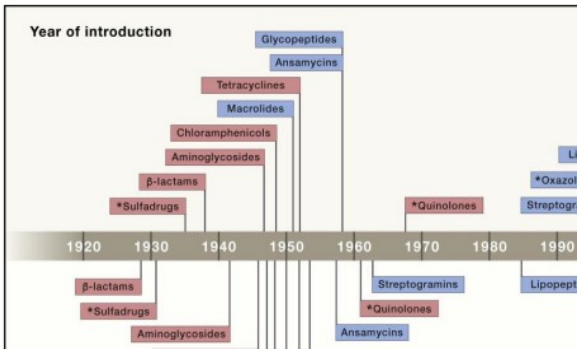


Fig. 5: Timeline of antimicrobial discovery and introduction for clinical use

11. Resistance Mechanisms Against Fluoroquinolones

Resistance mechanisms are multifactorial and include target modification, drug intake limitation, drug inactivation and efflux[47].

For fluoroquinolones specifically, the key mechanisms are as follows[47]:

Gram-negative: DNA gyrase modification

Gram-positive: topoisomerase IV modification

Drug inactivation: acetylation

Efflux pumps: MATE, MFS, RND

These resistance mechanisms reduce the concentration of the drug inside the cell and/or reduce the affinity for the target, resulting in higher MICs and clinical treatment failure.

12. Hybridization Strategy and Fluoroquinolone Hybrids

Hybrid drug design is the combination of two active pharmacophores into one chemical entity. Your file highlights that hybridization can lead to benefits that are not observed in the single molecules, since combination-like strategies can prevent the emergence of resistance more effectively than monotherapy[6].

12.1 Why fluoroquinolones are attractive hybrid scaffolds

The fluoroquinolone scaffold offers several sites for derivatization (especially at C-7 and N-1) to allow conjugation with heterocycles, antibacterial fragments, efflux pump inhibitors, permeability-enhancing moieties, and metal-binding units.

Hybrids may have a better activity against the resistant strains, a greater binding affinity for the topoisomerases or dual mechanisms that the bacteria have a hard time evading.

12.2 Fused heterocycles as antibacterial agents

In some analyses, the total cost of medical care, hospitalization, AMR and lost productivity has been estimated to be around 30 billion USD[48]. Previously, a number of infectious diseases were among the leading causes of death[48]. Your file[49] offers a detailed summary of the resistance mechanisms developed by bacteria against antibiotic classes.

13. Chronological Development of Antibiotics and Resistance

Over the last century, the antibiotics have drastically changed medicine and increased human lifespan substantially.

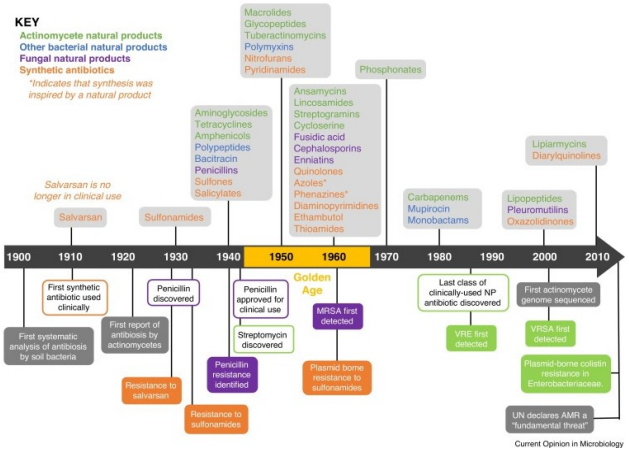


Figure 6. Parallel timeline of the history of antibacterial agents and emergence of antibacterial resistance. Timeline of the decade in which new classes of antibiotics were introduced into the clinic. The antibiotics are colored according to the origin: (green = actinomycetes, blue = other bacteria, purple = fungi and orange = synthetic).

The finding of penicillin initiated the golden age of antibiotic discovery, and resistance evolution

has followed antibiotic introduction patterns[50,51] [**Fig. 6**]. The 5-membered heterocycles (fused or non-fused) constitute a broad class of bioactive molecules[52,53].

14. Recently Approved Antibiotics and Pipeline Perspective

The FDA approves antibiotics for U.S. marketing, and approvals since 2005 highlight that drugs using the same mechanisms as older agents may carry increased resistance risk[54].

Your file lists multiple modern agents and their mechanisms (**Table 2**), including gemifloxacin and other clinically relevant antibiotics[54].

Table 2. Selected FDA-approved antibiotics (since 2005) and their mechanisms of action.

Drug	**Mechanism of action**
Linezolid	Methicillin-resistant *Staphylococcus aureus* (MRSA)
Cefditoren	Treats un-complicated skin and soft-tissue infections caused by MSSA, as well as pharyngitis and tonsillitis caused by *Streptococcus pyogenes*
Ertapenem	Gram-positive and Gram-negative microorganisms
Gemifloxacin	Gram-positive and Gram-negative organisms; including multidrug-resistant *Streptococcus pneumoniae*
Daptomycin	Gram-positive bacteria; including MRSA
Telithromycin	Gram-positive and Gram-negative bacteria; including multidrug-resistant strains of *Streptococcus pneumoniae*
Tigecycline	Gram-positive and Gram-negative bacteria; including MRSA
Retapamulin	Gram-positive infections
Doripenem	Gram-positive and Gram-negative bacteria
Telavancin	Gram-positive bacteria, including MRSA
Oritavancin	Glycopeptides family of antibiotics
Iclaprim	Dihydrofolate reductase inhibitor
Ceftobiprole	MRSA
Cethromycin	Community-acquired pneumonia and against biodefense pathogens such as anthrax, plague, tularemia, and melioidosis
Ceftaroline	MRSA
Fidaxomicin	RNA polymerase inhibitor
Ramoplanin	Glycolipdepsi peptide class of antibiotics and works by inhibiting cell wall biosynthesis
Pagibaximab	The treatment of bacterial infections
Levofloxacin	*P. aeruginosa*
Rifampin	*S. epidermidis*
Ciprofloxacin	Gram-positive and Gram-negative organisms; including multidrug-resistant *Streptococcus pneumoniae*
Amikacin	*P. aeruginosa, S. aureus*
Vancomycin	*P. aeruginosa, S. aureus, S. Epidermidis*

15. Recent Literature Updates (2020–2025): Modern Fluoroquinolones and Hybrid Design

Recent literature continues to investigate the newer fluoroquinolones and optimization strategies, including the newer clinical FQs and hybrid frameworks. The antibiotic pipeline has been summarized in reviews, which have identified modern fluoroquinolones as continuing clinical opportunities[55]. In addition, recent literature discusses newer platforms and resistance-aware strategies for antibacterial discovery, through modern AI-driven and screening-based discovery efforts[56–58].

15.1 Delafloxacin (broad spectrum, MRSA, acidic-site activity)

Delafloxacin is a novel fluoroquinolone that has received significant attention for ABSSSI and CABP indications and is commonly discussed in recent clinical and pharmacological reviews[59–61].

15.2 Finafloxacin (acidic environments and otic use)

Finafloxacin has been discussed as an interesting fluoroquinolone with specific application and activity at low pH[62,63].

15.3 Besifloxacin (ophthalmic fluoroquinolone)

Besifloxacin is extensively reviewed in the ophthalmic infection literature due to formulation design and topical activity[64–66].

15.4 Zabofloxacin (respiratory pathogens and COPD exacerbations)

Zabofloxacin has been studied in respiratory infections and COPD exacerbations and remains a key example of regionally approved newer FQ therapy[67,68].

15.5 Hybrid fluoroquinolones as future solutions

Hybrid FQ design is increasingly being explored to overcome efflux, permeability challenges and resistance selection. Current reviews[69–73] summarize strategies with FQ conjugates, fused heterocycles and dual-mechanism inhibitors.

15.6 Fluoroquinolone–Triazole Hybrid Derivatives

The hybridization of fluoroquinolones with nitrogen-rich heterocycles is a promising strategy in medicinal chemistry to improve antimicrobial profiles and potentially reduce resistance development by enhancing target binding and improving physicochemical properties. Among these, conjugates containing triazole are particularly interesting because the triazole units provide metabolic stability, hydrogen bonding ability and conformational rigidity that could result in enhanced interactions with the active sites of bacterial topoisomerase.

Recently, Gollapalli and co-workers reported the synthesis of new fluoroquinolone-1,2,4-triazole derivatives as potential antibacterial agents. The study included rational design, multi-step synthesis, molecular docking analysis and in silico ADME profiling and emphasized the power of computational guidance to optimization in the creation of contemporary fluoroquinolone hybrids[74]. The present findings further support that the introduction of triazole pharmacophores can yield promising antibacterial hybrids with acceptable predicted drug-likeness parameters.

Furthermore, the same group also reported the synthesis and antimicrobial evaluation of fluoroquinolones bearing oxadiazolyl-triazole derivatives supported by in silico studies, which further demonstrated the versatility of quinolone scaffolds for construction of multifunctional heterocyclic hybrids[75]. Together, the present studies lend themselves to the continued exploration of fluoroquinolone-triazole based hybridization, particularly as a means to achieve improved potency and broadened activity in the face of rising antimicrobial resistance.

Conclusions

Fluoroquinolones are still useful broad-spectrum synthetic antibacterials because of their potent bactericidal action through inhibition of DNA gyrase and topoisomerase-IV. However, clinical limitations include resistance by target modification, uptake limitation, efflux and drug inactivation, as well as safety concerns. The fluoroquinolone scaffold continues to be a privileged platform as SAR principles support rational optimization at positions N-1, C-5, C-6, C-7 and C-8. Hybridization approaches are an attractive direction, which may provide increased potency, lower resistance development and broader biological profiles. Thus, future research should focus on optimizing the antibacterial activity with increased safety, reducing the potential for resistance development, and developing clinically feasible fluoroquinolone hybrids.

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Conflict of interests

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