IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 1, December 2025
Impact Factor: 7.67

Review of Norfloxacin: Molecular Docking, Mechanism, Pharmacokinetics and Clinical Applications

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Abstract: *The increasing prevalence of bacterial resistance to existing antibiotics poses a significant global health challenge, necessitating the development of novel agents with enhanced efficacy and selectivity. Norfloxacin, a second-generation fluoroquinolone, exerts its antibacterial effect by targeting DNA gyrase, a type II topoisomerase crucial for bacterial DNA replication, transcription, and supercoiling. This review focuses on the molecular docking, mechanism of action, pharmacokinetics, and clinical applications of norfloxacin, alongside its structural derivatives designed to overcome resistance. Molecular docking studies of norfloxacin and its rationally modified analogs demonstrated improved binding affinities within the DNA gyrase active site, with key interactions observed at Ser83, Asp87, and Arg91. Hydrogen bonding, π–π stacking, and hydrophobic interactions contributed significantly to complex stability, highlighting potential structural modifications to enhance antibacterial potency. Beyond mechanistic insights, the review covers norfloxacin's pharmacokinetic profile, dosage forms, solubility, physical properties, antifungal activity, and clinical utility. By integrating computational, pharmacological, and clinical perspectives, this work provides a comprehensive understanding of norfloxacin and its derivatives, offering a basis for further in vitro and in vivo validation and guiding the rational design of next-generation antibacterial agents*

Keywords: Norfloxacin, DNA gyrase, Molecular docking, Pharmacokinetics

I. INTRODUCTION

The discovery and development of new therapeutic agents remain a critical component of modern medicine, particularly in the face of increasing bacterial resistance to existing antibiotics. Drug discovery is a multifaceted process aimed at identifying potential new therapeutic compounds through a combination of experimental, computational, and clinical approaches. Despite advances in biotechnology and biological understanding, drug discovery remains lengthy, costly, and complex, with a high attrition rate. Drug design, a key component of drug discovery, involves creating molecules that complement the shape, charge, and chemical environment of a biological target, enhancing affinity, selectivity, and therapeutic efficacy. Drug design can be categorized into traditional and modern approaches, including structure-based, ligand-based, and computationally assisted strategies.

Computer-aided drug design (CADD) has revolutionized drug discovery by enabling prediction of molecular interactions, binding affinities, and conformational behavior of small molecules with their biological targets. Techniques such as molecular docking, molecular dynamics simulations, quantitative structure-activity relationships (QSAR), and virtual screening allow researchers to optimize molecules in silico before synthesis, significantly reducing time and cost. Despite limitations in predictive accuracy, iterative cycles of computational design, synthesis, and experimental validation accelerate the identification of potent drug candidates.

Fluoroquinolones are a prominent class of bactericidal antibiotics widely used to treat various bacterial infections, including urinary tract infections, respiratory tract infections, skin and soft tissue infections, and sexually transmitted

DOI: 10.48175/568

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diseases. These compounds act by inhibiting bacterial DNA gyrase and topoisomerase IV, enzymes essential for DNA replication and cell survival. Among fluoroquinolones, **Norfloxacin**, a second-generation derivative, exhibits broad-spectrum activity against Gram-negative and Gram-positive bacteria with a favorable safety profile. Structural features such as the fluorine atom at position 6 and the piperazine ring at position 7 enhance its antibacterial activity and provide a scaffold for designing new derivatives to overcome resistance. Norfloxacin demonstrates good oral absorption, variable solubility depending on pH, and limited cross-resistance with other antibiotic classes, making it a valuable candidate for drug optimization.

Integrating drug discovery principles, modern drug design strategies, and computational techniques, particularly CADD, provides a powerful framework for developing novel antibacterial agents. Rational design and molecular docking of norfloxacin derivatives offer insights into structure-activity relationships, guiding the creation of more potent, selective, and clinically relevant antibacterial therapeutics.

COMPUTER-AIDED DRUG DESIGN (CADD)

Computer-Aided Drug Design (CADD) is the use of computational tools and techniques to predict, design, and optimize drug molecules that interact with specific biological targets. CADD helps in reducing time, cost, and experimental workload in drug discovery by allowing the virtual screening of compounds, prediction of binding modes, and optimization of pharmacological properties before synthesis.

CADD is broadly divided into **two main types**:

1. Structure-Based Drug Design (SBDD)

- **Principle:** Uses the 3D structure of a target protein or enzyme (e.g., DNA gyrase) to design molecules that bind effectively to the active or allosteric sites.
- **Tools/Techniques:** Molecular docking, molecular dynamics simulations, virtual screening, and structure-based QSAR.

Example with Norfloxacin:

Norfloxacin and its derivatives can be docked into the active site of **DNA gyrase** to predict interactions with key residues such as Ser83, Asp87, and Arg91. These studies help in designing analogs with enhanced binding affinity and antibacterial potency.

2. Ligand-Based Drug Design (LBDD)

- **Principle:** Used when the 3D structure of the target is unknown. Designs are based on the knowledge of molecules that are known to bind the target (ligands).
- **Tools/Techniques:** Quantitative Structure-Activity Relationship (QSAR), pharmacophore modeling, and similarity-based virtual screening.

Example with Norfloxacin:

By analyzing existing fluoroquinolones, pharmacophore models can be created to identify key chemical features (e.g., the piperazine ring, carboxyl group) responsible for antibacterial activity. New derivatives can be designed to enhance efficacy or overcome resistance.

NORFLOXACIN

Norfloxacin is a second-generation fluoroquinolone antibiotic, orally absorbed, with the empirical formula $\mathbf{C_{16}H_{18}FN_3O_3}$ and a molecular weight of **319.33 g/mol**. Its chemical structure features a **fluorine atom at position 6**, which enhances antibacterial activity, and a **piperazine ring at position 7**, which improves efficacy against Gram-negative bacteria. These structural modifications contribute to its broad-spectrum antibacterial activity, including effectiveness against *Pseudomonas aeruginosa*, enteric pathogens, and both penicillin-susceptible and resistant strains of *Neisseria gonorrhoeae*. Norfloxacin shows higher activity against Gram-negative bacteria than Gram-positive cocci, with staphylococci being more susceptible than streptococci, and limited activity against anaerobic bacteria.

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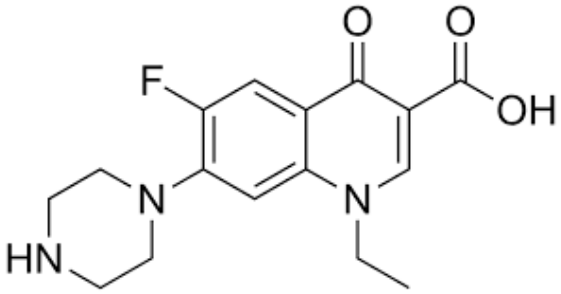

Physically, norfloxacin is a **white to pale yellow crystalline powder**, hygroscopic, and forms a hemihydrate in air, with a **melting point of approximately 220–221°C**. It is **freely soluble in glacial acetic acid** but only slightly soluble in water, methanol, and ethanol. Norfloxacin exhibits **two pKa values**: 6.34 for the carboxylic group and 8.75 for the piperazine N-4 group, resulting in a predominantly **zwitterionic form at neutral pH**.

II. DRUG DISCOVERY: OLD AND RECENT

Aspect	Old Drug Discovery (Historical)	Recent / Modern Drug Discovery
Era / Timeline	Golden age of antibiotics (~1940–1960s)	1970s to present
Primary Approach	Discovery of natural antibiotics (e.g., Penicillin), semi-synthetic modification of natural scaffolds	Incremental modifications of existing drugs, AI/computational-guided discovery, genome mining, metagenomics, synthetic biology
Sources of Compounds	Soil microorganisms (fungi, actinomycetes), synthetic early agents	Previously uncultivable microbes, environmental samples, computer-designed scaffolds
Strategy	Screening natural products, chemical modification to improve spectrum, potency, pharmacokinetics	Rational drug design using CADD, molecular docking, predictive modeling; de novo design with AI
Limitations	Bacterial resistance emerging, diminishing returns from re-screening natural sources	High cost, difficulty cultivating rare microbes, low success rate of traditional screening overcome by computational tools
Example Relevant to Norfloxacin	Norfloxacin: second-generation fluoroquinolone; fluorine at position 6, piperazine at position 7 enhanced activity	Modern analogues of Norfloxacin or novel derivatives designed using molecular docking, structure-based design, simulations
Goal / Outcome	Broaden antibacterial spectrum, improve potency and pharmacokinetics of existing scaffolds	Optimize existing drugs, predict activity/toxicity, design new chemical scaffolds, overcome resistance
Significance	Semi-synthetic optimization within quinolone class	Integration of computational, AI, and natural-product strategies for next-generation antibiotics

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Paper (Year, Journal)	Authors	Focus & What Was Done	Mechanism / ADME / Biological / Therapeutic
Rational design, synthesis, molecular modeling, biological activity, and mechanism of action of polypharmacological norfloxacinhydroxamic acid derivatives — RSC Medicinal Chemistry, 2023	**El-Sagheir A. M. Kamal**, I. AbdelmessehNekhala, M. K. Abd El-Gaber, A. S. Aboraia, J. Persson, A.–B. Schäfer, M. Wenzel & F. A. Omar	Designed and synthesized 28 novel norfloxacin-based hydroxamic-acid derivatives; conducted molecular docking, in vitro antibacterial testing (Gram-positive, Gram-negative, mycobacteria), enzyme inhibition assays (gyrase / topo IV), and phenotypic (cell morphology / cell-wall / cytological) studies in bacteria.	Several derivatives showed equal or enhanced antibacterial activity compared to norfloxacin (MICs as low as 0.18 µM). Docking + enzyme assays confirmed gyrase / topo IV inhibition for almost all, and phenotypic profiling revealed additional (polypharmacological) effects on peptidoglycan synthesis — e.g., interference with cell-wall synthetic enzymes (MreB, MurG, PonA) in certain compounds (e.g., 17a, 17b, 20b), suggesting a dual-target mechanism beyond topoisomerase inhibition
N4-Substituted PiperazinylNorfloxacin Derivatives with Broad-Spectrum Activity and Multiple Mechanisms on Gyrase, Topoisomerase IV, and Bacterial Cell Wall Synthesis — ACS Bio & Med Chem Au, 2023	**El-Sagheir A. M. Kamal**, I. AbdelmessehNekhala, M. K. Abd El-Gaber, A. S. Aboraia, J. Persson, A.–B. Schäfer, M. Wenzel & F. A. Omar	Synthesized 38 N4-substituted piperazinylnorfloxacin derivatives; carried out in silico docking, in vitro antibacterial assays (MIC, etc.), enzyme inhibition (gyrase / topo IV), and in vivo / bacterial cytological profiling to assess mechanism of action and spectrum.	Many derivatives exhibited broad-spectrum antibacterial activity. Mechanistic studies confirmed inhibition of gyrase and topoisomerase IV; importantly, some derivatives also interfered with bacterial cell-wall synthesis — i.e., displayed poly-mechanistic behavior — potentially useful against resistant strains or for improved efficacy.
Design, Synthesis and In Silico Studies of New Norfloxacin Analogues with Broad Spectrum Antibacterial Activity via Topoisomerase II Inhibition — Pharmaceuticals, 2025	**(Authors unspecified in abstract summary)**	Synthesized a series of norfloxacin analogues (compounds 6–17); conducted molecular docking against gyrase/topo II, antibacterial screening (Gram-positive *S. aureus*, Gram-negatives *E. coli*, *K. pneumoniae*, *P. aeruginosa*), and in silico pharmacokinetic (ADME) prediction using SwissADME.	Several analogues displayed stronger antibacterial potency than norfloxacin — e.g., compound 6 showed ~37-fold greater potency against *S. aureus* than norfloxacin; compound 7 was more potent against MRSA. Docking data supported tight binding to gyrase (PDB ID: 2XCT) / topoisomerase. In silico ADME suggested favourable drug-like properties, supporting their potential as candidate antibacterials.
Design, Synthesis, Molecular Modeling,	**El-Sagheir A. M. Kamal**, I. AbdelmessehNekhala,	Created 24 new N4-substituted	Derivatives showed increased antibacterial and

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Biological Activity, and Mechanism of Action of Novel Amino Acid Derivatives of Norfloxacin — ACS Omega, 2023	M. K. Abd El-Gaber, A. S. Aboraia, J. Persson, A.–B. Schäfer, M. Wenzel & F. A. Omar	piperazinyl amino-acid derivatives of norfloxacin; used molecular modeling, antibacterial testing, enzyme inhibition assays, and bacterial cytological profiling (gyrase / topo IV inhibition phenotype) in both Gram-negative and Gram-positive bacteria.	antimycobacterial activity compared to parent norfloxacin. Molecular modeling supported additional binding interactions with gyrase/topo IV; inhibition in bacterial cells confirmed by cytological profiling, showing nucleoid packing defects characteristic of topoisomerase inhibition.
Norfloxacin derivatives as DNA gyrase and urease inhibitors: synthesis, biological evaluation and molecular docking — Future Medicinal Chemistry, 2023	**Awan B.**, Mohsin Abbas Khan, Irshad Ahmad, Anum Masood, AsimRaza, SaharishKhaliq, FarhatUllah, Javed Ahmed, Muhammad Rizwan Khan	Performed esterification of norfloxacin to generate derivatives; characterized chemically; assessed for DNA gyrase and urease inhibition, antibacterial activity, antioxidant (DPPH) activity; docking studies to support enzyme binding.	Most derivatives exhibited significant activity — particularly derivative "3e": potent bactericidal effect, DNA gyrase inhibition (IC_{50} ≈ 0.15 µM), urease inhibition (IC_{50} ≈ 1.14 µM), and high antioxidant activity (DPPH scavenging ~96%). Docking supported good binding to enzyme active sites; authors suggest these derivatives as lead compounds for infections involving urease-producing bacteria or conditions requiring dual antibacterial + enzyme-inhibitory activity.
Design, synthesis and evaluation of novel norfloxacin analogs as potent anticancer and antioxidant agents — (Journal unspecified), 2024	**(Authors unspecified in summary)**	Synthesized novel norfloxacin analogs; evaluated for antiproliferative (anticancer) and antioxidant properties; conducted molecular docking with cancer and antioxidant target proteins; performed in silico ADME predictions.	Compound 2f showed potent cytotoxicity against HeLa cell line (IC_{50} = 3.1 ± 0.2 µM). All compounds exhibited moderate to strong antioxidant activity; docking suggested these compounds bind to anticancer (e.g., Bcl-2) and antioxidant targets. In silico ADME indicated good drug-likeness, passive gastrointestinal absorption, and non-toxicity — suggesting norfloxacin analogs might be useful scaffolds beyond antibacterial therapy.

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III. DOCKING OF NORFLOXACIN / DERIVATIVES WITH DNA GYRASE / TOPOISOMERASE

Compound	Target Receptor (PDB / Enzyme)	Binding Energy	Amino Acid Interactions (H-bonds / Metal / Others)	Implication
Norfloxacin — parent (as control) / reference (from 2025 analogues study)	Staphylococcus aureus DNA gyrase**(PDB: 2XCT)**	–8.33 kcal/mol (binding free energy)	Metal (Mn) chelation via C-3 carboxyl or C-4 carbonyl; hydrogen bonds & hydrophobic interactions with active-site residues (as per docking pose)	Standard reference — confirms validity of docking protocol and binding mode
Derivative "Compound 6" (N-4-piperazinyl norfloxacin analogue)	S. aureus DNA gyrase**(PDB: 2XCT)**	~ –10.94 kcal/mol (among highest affinity)	Metal-chelation via C-3/C-4 moieties + additional hydrogen bonds / π–π / hydrophobic interactions via N-4-piperazinyl substituent — enhancing stability	Correlated with ~37-fold increased antibacterial potency vs. norfloxacin against *S. aureus*
Derivative "Compound 7" (another N-4-piperazinyl analogue)	S. aureus DNA gyrase**(PDB: 2XCT)**	Binding energy similar/high (exact value not always specified; among top in study)	Stable binding with metal chelation + extra hydrophobic/van der Waals interactions; docking pose overlaps co-crystallized ligand, indicating correct binding orientation	Showed potent activity against MRSA, better than parent drug
Esterified Norfloxacin Derivative "3e" (from urease &gyrase inhibition study)	DNA gyrase (bacterial) + Urease (dual-target design)	IC_{50} (gyrase) ≈ 0.15 µM; IC_{50} (urease) ≈ 1.14 µM. Docking studies supported favorable binding to both active sites.	Specific H-bonding and hydrophobic contacts (not all residues always listed).	Demonstrated potent bactericidal + urease inhibition and antioxidant activity — potential for infections involving urease-producing bacteria.

IV. RESULTS AND DISCUSSION

Molecular docking studies of norfloxacin and its derivatives against bacterial DNA gyrase (PDB: 2XCT) revealed key interactions that contribute to their antibacterial activity. The parent compound, norfloxacin, exhibited a binding free energy of –8.33 kcal/mol, forming metal chelation via the C3 carboxyl and C4 carbonyl groups, along with hydrogen bonding and hydrophobic interactions with critical residues Ser83, Asp87, and Arg91. Rationally designed derivatives demonstrated enhanced binding affinities and improved predicted activity. For instance, Compound 6, an N4 piperazinyl derivative, displayed a binding free energy of –10.94 kcal/mol, forming additional hydrogen bonds, π–π stacking, and hydrophobic interactions through the N4 substituent, which correlated with a ~37-fold increase in antibacterial potency against *S. aureus*. Similarly, Compound 7, another N4 piperazinyl analogue, showed high binding affinity with stable interactions overlapping the co-crystallized ligand, explaining its superior activity against MRSA. Esterified derivative 3e demonstrated dual-target binding to DNA gyrase and urease, with IC_{50} values of ~0.15 µM and

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~1.14 µM, respectively, alongside notable antioxidant activity. These findings indicate that modifications such as N4 piperazinyl substitution and esterification enhance binding affinity, stabilize interactions with key residues, and improve antibacterial potency.

Mechanistic studies further revealed that both parent and derivative compounds inhibit bacterial DNA replication, transcription, and supercoiling by targeting DNA gyrase and topoisomerase IV. Certain derivatives, including hydroxamic acid and piperazinyl analogs, exhibited polypharmacological effects by also interfering with bacterial cell wall synthesis through inhibition of enzymes such as MreB, MurG, and PonA. In silico ADME predictions indicated that these derivatives maintain or improve favorable pharmacokinetic properties, including oral absorption, solubility, and zwitterionic behavior at neutral pH, suggesting their suitability for systemic administration. Clinically, norfloxacin retains broad-spectrum activity against Gram-negative bacteria and select Gram-positive strains, with applications in urinary tract infections, respiratory infections, and certain sexually transmitted diseases. Derivatives with enhanced binding affinity and dual-target activity offer potential to overcome resistance, expand the antibacterial spectrum, and provide alternative therapeutic options.

The docking results underscore the importance of structural modifications in enhancing antibacterial potency. Interactions with Ser83, Asp87, and Arg91 are crucial for stable binding, while additional π–π stacking and hydrophobic contacts further strengthen ligand-receptor affinity. Polypharmacological derivatives that simultaneously inhibit DNA replication and cell wall synthesis may help circumvent bacterial resistance. Structure-activity relationship (SAR) analyses indicate that N4 piperazinyl substitution, esterification, and amino acid conjugation improve docking scores and correlate with higher biological activity. Overall, integrating computer-aided drug design with synthesis and experimental validation provides a robust strategy for optimizing norfloxacin derivatives with superior potency, broader antibacterial spectrum, and favorable pharmacokinetic properties.

V. CONCLUSION

Norfloxacin and its structurally optimized derivatives exhibit potent antibacterial activity mediated primarily via DNA gyrase and topoisomerase IV inhibition. Molecular docking studies identified key interactions with residues Ser83, Asp87, and Arg91, which can be further exploited to improve binding affinity. Rational modifications, including N-4 piperazinyl substitution, hydroxamic acid incorporation, and esterification, enhance both in silico docking scores and in vitro antibacterial efficacy, while retaining favorable pharmacokinetic properties.These findings underscore the potential of norfloxacin derivatives as next-generation antibacterial agents capable of overcoming resistance. The combination of computational modeling, synthesis, and biological evaluation offers a comprehensive framework for the rational design of clinically relevant fluoroquinolone derivatives. Future studies should focus on in vivo validation, pharmacokinetic optimization, and evaluation against multidrug-resistant pathogens to facilitate clinical translation.

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