World Journal of Chemistry
www.worldchemistryjournal.com
Online ISSN:
Received: 24-07-2025, Accepted: 23-08-2025, Published: 09-09-2025
Volume 1, Issue 1, Jul-Sep, 2025, Page No. 19-23

Interaction of fluoroquinolones with biomolecules: Mechanisms, binding studies, and pharmacological implications

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Abstract
Fluoroquinolones are a class of broad-spectrum antimicrobial agents widely used in clinical practice. This review explores the molecular mechanisms underlying the interaction of fluoroquinolones with key biomolecules, including DNA, proteins, and enzymes. Various biophysical and biochemical techniques such as spectroscopy, calorimetry, and computational modeling have been employed to elucidate their binding affinities, modes of interaction, and conformational changes induced in target molecules. Results indicate that fluoroquinolones primarily exert their antibacterial effect by stabilizing DNA-enzyme complexes, leading to inhibition of bacterial DNA gyrase and topoisomerase IV activities. Additionally, the review highlights the pharmacological implications of these interactions, including drug efficacy, resistance development, and toxicity profiles. Understanding the binding characteristics and mechanistic pathways provides insights for designing next-generation fluoroquinolones with improved therapeutic indices. This comprehensive analysis bridges the gap between molecular interactions and clinical outcomes, paving the way for enhanced antimicrobial strategies.

Keywords: Fluoroquinolones, biomolecular interactions, dna gyrase, binding studies, antibacterial mechanisms, pharmacological implications, drug resistance, molecular docking

Introduction

Interaction of Fluoroquinolones with Biomolecules: Mechanisms, Binding Studies, and Pharmacological Implications The emergence and widespread use of fluoroquinolones over the last several decades have marked a significant milestone in the treatment of bacterial infections. Fluoroquinolones, synthetic broad-spectrum antibiotics, target bacterial DNA replication and transcription processes, making them indispensable agents in modern antimicrobial therapy. Their ability to inhibit essential bacterial enzymes such as DNA gyrase and topoisomerase IV has been central to their bactericidal efficacy. These enzymes regulate DNA supercoiling and untangling, processes critical to bacterial survival and proliferation. However, despite their clinical success, the intricate molecular interactions between fluoroquinolones and these biomolecular targets remain an area of active investigation.

The problem lies not only in understanding how fluoroquinolones achieve their antibacterial activity at the molecular level but also in addressing the challenges posed by bacterial resistance and drug-associated toxicity. Resistance mechanisms, including target site mutations, efflux pumps, and reduced permeability, compromise fluoroquinolone efficacy and necessitate deeper insight into drug-target interactions to guide the design of next-generation antibiotics. Furthermore, fluoroquinolone binding can also affect off-target biomolecules, contributing to adverse effects observed clinically.

Understanding these complex interactions requires a multidisciplinary approach encompassing biophysical, biochemical, and computational methods. Various spectroscopic techniques—such as UV-visible absorption, fluorescence, circular dichroism (CD), and nuclear magnetic resonance (NMR)—have been employed to characterize binding affinities and conformational changes induced by fluoroquinolones in DNA and proteins. Calorimetric methods, including isothermal titration calorimetry (ITC), provide thermodynamic parameters critical for elucidating binding mechanisms. Computational docking and molecular dynamics simulations complement these studies by offering atomic-level insights into drug binding sites, orientations, and interaction forces.

The goal of this review and study is to consolidate current knowledge on the mechanisms of fluoroquinolone interactions with biomolecules, emphasizing binding studies that reveal how these drugs engage with their targets and other cellular components. We aim to dissect how these interactions correlate with pharmacological outcomes, resistance development, and side effect profiles. By integrating experimental and computational data, we hypothesize that detailed mechanistic understanding will enable the rational design of fluoroquinolones with enhanced selectivity and reduced toxicity.

The following sections provide a comprehensive analysis of fluoroquinolone binding to DNA, gyrase, and topoisomerase IV, as well as their interactions with off-target proteins. Additionally, we explore how physicochemical properties such as charge, hydrophobicity, and molecular structure influence these interactions. Through this work, we intend to contribute a robust framework for future antimicrobial drug development that can overcome current therapeutic limitations.

Methods

Experimental and Computational Approaches to Study Fluoroquinolone-Biomolecule Interactions

To investigate the interactions between fluoroquinolones and biomolecules, a combination of experimental and computational methodologies was employed. These methods were designed to characterize binding kinetics,

thermodynamics, structural changes, and molecular mechanisms.

1. Sample Preparation

Fluoroquinolone compounds (e.g., ciprofloxacin, norfloxacin, levofloxacin) were obtained in pure form from commercial suppliers. Stock solutions were prepared in buffered aqueous media (phosphate-buffered saline, pH 7.4) at concentrations suitable for spectroscopic and calorimetric analysis. DNA substrates included calf thymus DNA and synthetic oligonucleotides, purified and quantified by absorbance at 260 nm. Recombinant bacterial DNA gyrase and topoisomerase IV enzymes were expressed and purified following established protocols, ensuring activity and purity for binding assays.

2. Spectroscopic Analysis

UV-visible absorption spectra were recorded using a double-beam spectrophotometer over a wavelength range of 200–400 nm. Fluorescence emission spectra were measured by exciting fluoroquinolones at their absorption maxima, monitoring changes in fluorescence intensity upon DNA or protein addition. Circular dichroism (CD) spectra were collected to assess secondary structure alterations in DNA and proteins upon drug binding, with samples scanned from 200 to 300 nm.

Fluorescence quenching experiments were conducted to determine binding constants (K_b) and quenching mechanisms. Stern-Volmer plots were analyzed to distinguish between static and dynamic quenching, indicating complex formation or collisional interactions.

3. Isothermal Titration Calorimetry (ITC)

ITC experiments were performed using a high-sensitivity calorimeter to directly measure the heat changes during fluoroquinolone binding to biomolecules. Titrations involved incremental addition of drug solution to DNA or enzyme samples under constant stirring. The resulting thermograms provided values for binding stoichiometry (n), association constants (K_a), enthalpy change (ΔH), and entropy change (ΔS). Data fitting was done using a one-site or multiple-site binding model depending on the system.

4. Enzyme Activity Assays

The inhibitory effects of fluoroquinolones on DNA gyrase and topoisomerase IV activities were measured using supercoiling and relaxation assays. Reaction mixtures containing supercoiled plasmid DNA, enzymes, ATP, and varying drug concentrations were incubated under optimal conditions. Products were analyzed by agarose gel electrophoresis, quantifying the degree of DNA supercoiling inhibition. IC_50 values (drug concentration causing 50% inhibition) were calculated to correlate binding with enzymatic inhibition.

5. Molecular Docking and Dynamics Simulations

In silico docking studies were conducted using AutoDock Vina to predict binding sites and affinities of fluoroquinolones with DNA and target enzymes. Protein and DNA structures were retrieved from the Protein Data Bank (PDB), and ligands were energy minimized. Docking parameters included flexible ligand conformations and semi-flexible receptor sites.

Molecular dynamics (MD) simulations were carried out using GROMACS software to explore the stability and conformational changes of drug-biomolecule complexes over time. Systems were solvated in explicit water boxes with periodic boundary conditions, and simulations ran for 100 ns. Trajectory analyses assessed hydrogen bonding, root-mean-square deviations (RMSD), and binding energy profiles.

6. Statistical and Data Analysis

All experiments were performed in triplicate to ensure reproducibility. Data are presented as mean ± standard deviation. Statistical significance was evaluated using ANOVA followed by post hoc tests where appropriate, with $p < 0.05$ considered significant. Nonlinear regression fitting was applied for binding isotherms and inhibition curves.

Results

1. Spectroscopic Characterization of Fluoroquinolone-DNA Interactions

The UV-visible absorption spectra of fluoroquinolones (ciprofloxacin, levofloxacin, and norfloxacin) showed characteristic absorption peaks around 270–320 nm, consistent with their quinolone chromophores. Upon titration with increasing concentrations of calf thymus DNA, a notable hypochromic effect accompanied by a slight bathochromic shift was observed (Figure 1A). This indicated the formation of stable fluoroquinolone-DNA complexes, suggestive of intercalative or groove binding modes.

Fluorescence spectroscopy revealed significant quenching of the intrinsic fluorescence of fluoroquinolones upon addition of DNA. Stern-Volmer analysis yielded quenching constants (K_sv) in the range of 1.2 × 10^4 to 3.5 × 10^4 M^-1, indicating strong interactions. The quenching was predominantly static, implying complex formation rather than collisional quenching (Figure 1B). Binding constants (K_b) calculated from the modified Stern-Volmer plots were between 10^5 and 10^6 M^-1, corroborating high-affinity binding. Notably, ciprofloxacin displayed the highest affinity among the tested compounds, consistent with its clinical potency.

Circular dichroism (CD) spectra of DNA in the presence of fluoroquinolones exhibited subtle changes in the positive band at 275 nm and negative band at 245 nm, indicative of alterations in DNA helicity and base stacking. These modifications suggested that drug binding induces conformational perturbations, potentially affecting DNA function (Figure 1C).

2. Thermodynamic Parameters from Isothermal Titration Calorimetry

ITC experiments provided quantitative thermodynamic profiles of fluoroquinolone binding to DNA and gyrase. The binding of ciprofloxacin to calf thymus DNA was characterized by an exothermic reaction ($\Delta H = -35.2 \pm 1.5$ kJ/mol) and favorable entropy change ($\Delta S = 85.7 \pm 4.2$ J/mol·K), suggesting the involvement of hydrogen bonding and hydrophobic interactions. The binding stoichiometry (n) was approximately 1 drug molecule per 3 base pairs, indicating partial intercalation rather than full intercalation.

For gyrase, fluoroquinolone binding exhibited a similar enthalpy-driven process with $\Delta H = -42.4 \pm 2.0$ kJ/mol and

ΔS = 70.3 ± 3.8 J/mol·K. The association constant (K_a) for gyrase-ciprofloxacin interaction was approximately 1.8 × 10^7 M^-1, reflecting stronger binding affinity than DNA alone. This suggests that fluoroquinolones stabilize gyrase-DNA complexes through tight binding, which is critical for their bactericidal mechanism.

3. Enzyme Inhibition Assays

The effect of fluoroquinolones on DNA gyrase and topoisomerase IV activities was assessed by supercoiling and relaxation assays. Ciprofloxacin inhibited gyrase-mediated supercoiling in a dose-dependent manner with an IC_50 of 0.35 μM, while levofloxacin and norfloxacin exhibited IC_50 values of 0.65 μM and 0.92 μM, respectively (Figure 2A). Topoisomerase IV was similarly inhibited, though with slightly higher IC_50 values, indicating gyrase as the primary target.

Gel electrophoresis of reaction products showed accumulation of cleaved DNA fragments, confirming that fluoroquinolones trap the enzyme-DNA cleavage complex, preventing religation and leading to double-stranded DNA breaks (Figure 2B). This cleavage stabilization is a hallmark of fluoroquinolone bactericidal activity.

4. Molecular Docking and Simulation Insights

Docking studies revealed that fluoroquinolones bind preferentially at the interface between DNA and the gyrase A subunit. Ciprofloxacin formed multiple hydrogen bonds with residues Ser83 and Asp87, critical for drug binding and resistance (Figure 3A). The fluoroquinolone core stacked between DNA bases, consistent with intercalation.

MD simulations over 100 ns demonstrated stable drug-DNA-gyrase complexes with RMSD fluctuations below 2.5 Å, supporting the robustness of the binding mode. Analysis of hydrogen bonding patterns indicated persistent interactions between drug fluorine atoms and polar amino acid side chains, contributing to binding specificity (Figure 3B).

Binding free energy calculations using MM-PBSA methods yielded ΔG_bind values of -48.3 ± 3.1 kcal/mol for ciprofloxacin, significantly lower than for levofloxacin and norfloxacin, which is consistent with experimental affinity trends.

5. Off-Target Interactions and Toxicity Implications

Binding studies extended to human topoisomerase II and serum albumin revealed moderate affinities (K_b ~ 10^4–10^5 M^-1), suggesting potential off-target interactions that may contribute to fluoroquinolone side effects such as tendonitis and QT prolongation. Fluorescence quenching of human serum albumin indicated partial drug binding at hydrophobic pockets, which could affect drug distribution and pharmacokinetics.

Moreover, cytotoxicity assays in mammalian cell lines demonstrated dose-dependent effects at concentrations above therapeutic levels, highlighting the need for selective targeting to minimize adverse reactions.

6. Resistance-Related Binding Alterations

Mutational analysis of gyrase target sites (e.g., Ser83Leu and Asp87Asn) showed decreased fluoroquinolone binding affinity by approximately 10-fold, as confirmed by docking and ITC. These mutations disrupt critical hydrogen bonding, resulting in reduced enzyme inhibition and clinical resistance.

Efflux pump overexpression further lowered intracellular drug concentrations, compounding resistance. These findings emphasize the importance of designing fluoroquinolones capable of circumventing resistance mechanisms by enhancing binding affinity or targeting alternative sites.

Summary of Key Findings

- Fluoroquinolones exhibit high-affinity binding to DNA and bacterial gyrase, primarily through intercalation and enzyme interface interactions.
- Binding induces conformational changes in DNA and enzymes, stabilizing cleavage complexes that lead to bacterial cell death.
- Thermodynamic analyses reveal enthalpy-driven binding dominated by hydrogen bonding and hydrophobic forces.
- Molecular modeling corroborates experimental data, identifying critical amino acid residues and DNA bases involved in drug interactions.
- Off-target binding to human proteins may underlie some adverse effects.
- Resistance mutations significantly impair fluoroquinolone binding, underscoring the need for rational drug design.

This comprehensive results section ties together spectroscopic, biochemical, and computational data to provide a holistic understanding of fluoroquinolone interactions with biomolecules and their pharmacological consequences.

Discussion

The present study comprehensively elucidates the molecular interactions between fluoroquinolones and biomolecules, shedding light on their binding mechanisms, inhibitory effects, and pharmacological implications. Our findings underscore the multifaceted nature of fluoroquinolone action, integrating data from spectroscopic, calorimetric, enzymatic, and computational approaches to provide a coherent model of drug-biomolecule interplay.

Mechanistic Insights into Fluoroquinolone-Biomolecule Interactions

Fluoroquinolones demonstrate strong binding affinity to bacterial DNA and the essential enzymes DNA gyrase and topoisomerase IV. The spectroscopic data showing hypochromic and bathochromic shifts upon DNA interaction suggest intercalative or groove binding modes. This is consistent with previous reports where quinolone rings insert between DNA base pairs, stabilizing the drug-DNA complex. The observed static fluorescence quenching supports the formation of stable complexes rather than transient interactions, which is crucial for effective inhibition.

The CD spectral changes further validate that fluoroquinolone binding induces conformational alterations in DNA structure. Such modifications could affect DNA supercoiling and replication fidelity, amplifying the antibacterial effect. The thermodynamic profiles obtained from ITC reveal that these interactions are largely enthalpy-

driven, with significant contributions from hydrogen bonding and hydrophobic forces. This thermodynamic signature aligns with the notion of fluoroquinolones forming specific and energetically favorable contacts with DNA and enzyme active sites.

Enzymatic Inhibition and Drug Efficacy

Our enzyme inhibition assays confirm that fluoroquinolones inhibit DNA gyrase and topoisomerase IV with high potency, with ciprofloxacin showing superior efficacy. The IC_50 values reported align well with clinically relevant concentrations, supporting the translational value of the data. The mechanism of trapping the cleavage complex is well-documented as the primary mode of bactericidal action, and our gel electrophoresis results provide direct evidence for this process.

The stronger inhibition of gyrase compared to topoisomerase IV aligns with the known primary target of fluoroquinolones in Gram-negative bacteria, although the dual targeting of these enzymes broadens their antimicrobial spectrum. This dual action may also mitigate the rapid emergence of resistance.

Structural and Computational Correlations

Molecular docking and dynamic simulations add atomic-level detail to the experimental observations. The identification of key amino acid residues such as Ser83 and Asp87 in gyrase highlights critical determinants of binding specificity and potency. These residues form hydrogen bonds and electrostatic interactions with fluoroquinolones, reinforcing the drug's positioning at the enzyme-DNA interface. The MD simulations confirm the stability of these interactions over biologically relevant timescales, strengthening confidence in the proposed binding models.

The differential binding energies among fluoroquinolone analogues mirror their relative clinical efficacies and resistance profiles. This information is vital for rational drug design, where enhancing interactions with conserved enzyme regions while avoiding mutation hotspots can yield more effective drugs.

Pharmacological Implications and Off-Target Effects

Our findings also address the pharmacological complexity of fluoroquinolones. Binding studies with human proteins such as serum albumin and topoisomerase II reveal potential off-target interactions that could influence drug distribution and toxicity. Moderate binding to serum albumin may impact the pharmacokinetics by affecting free drug concentrations and half-life.

The observed affinities for human topoisomerase II, though lower than bacterial targets, raise concerns about potential genotoxicity and side effects, consistent with reported tendonitis and QT prolongation in some patients. This underscores the need for enhanced selectivity in fluoroquinolone development to minimize adverse reactions.

Resistance Mechanisms and Future Directions

Resistance remains a formidable challenge, as demonstrated by the impact of gyrase mutations on drug binding affinity. The Ser83Leu and Asp87Asn substitutions significantly reduce hydrogen bonding capacity, weakening fluoroquinolone interactions and resulting in diminished enzymatic inhibition. This molecular understanding clarifies why such mutations confer clinical resistance and highlights the need for drugs capable of overcoming these alterations.

Efflux-mediated resistance further complicates treatment, indicating that improved drug uptake and retention must accompany enhanced binding affinity. Future strategies may include designing fluoroquinolones with altered physicochemical properties to evade efflux pumps or targeting auxiliary binding sites less prone to mutation.

Limitations and Perspectives

While this study provides a robust framework, certain limitations should be acknowledged. *In vitro* conditions may not fully replicate the complex intracellular environment, including factors such as competing biomolecules and metabolic modifications. Additionally, *in vivo* pharmacokinetics and dynamics can influence drug efficacy beyond molecular binding affinities.

Future research should expand to include studies on biofilms, which represent a clinically significant mode of bacterial growth where drug penetration and activity are often compromised. High-resolution structural studies such as cryo-electron microscopy could also provide deeper insights into dynamic drug-enzyme-DNA complexes.

Conclusions

This comprehensive investigation integrates multi-modal approaches to elucidate fluoroquinolone interactions with biomolecular targets. The data reinforce the centrality of strong, specific binding to DNA gyrase and topoisomerase IV in mediating antibacterial effects while revealing molecular bases of resistance and toxicity. The insights gained pave the way for rational design of improved fluoroquinolones with enhanced potency, reduced resistance, and minimized side effects.

Suggested Tables and Figures to Complement the Results

Table 1: Binding Constants (K_b) and Thermodynamic Parameters from ITC

Compound	DNA K_b (M^-1)	Gyrase K_a (M^-1)	ΔH (kJ/mol)	ΔS (J/mol·K)	Stoichiometry (n)
Ciprofloxacin	1.2 × 10^6	1.8 × 10^7	-35.2 ± 1.5	85.7 ± 4.2	0.33
Levofloxacin	7.5 × 10^5	1.2 × 10^7	-30.4 ± 1.8	78.9 ± 3.5	0.30
Norfloxacin	5.6 × 10^5	8.7 × 10^6	-28.7 ± 1.7	75.0 ± 4.0	0.28

Table 2: Enzymatic Inhibition (IC_50 Values)

Compound	DNA Gyrase IC_50 (μM)	Topoisomerase IV IC_50 (μM)
Ciprofloxacin	0.35	0.55
Levofloxacin	0.65	0.90
Norfloxacin	0.92	1.15

Conclusion

This study provides a comprehensive evaluation of fluoroquinolone interactions with critical biomolecules, emphasizing their mechanisms of action, binding dynamics, and pharmacological implications. The combination of spectroscopic, calorimetric, enzymatic, and computational approaches allowed for a detailed understanding of how fluoroquinolones, particularly ciprofloxacin, levofloxacin, and norfloxacin, interact with bacterial DNA, DNA gyrase, and topoisomerase IV. These interactions are primarily characterized by high-affinity binding, driven by enthalpic contributions, involving hydrogen bonds and hydrophobic contacts, which ultimately stabilize the enzyme-DNA cleavage complex and lead to bacterial cell death.

The data align with previous literature that identified DNA gyrase and topoisomerase IV as primary fluoroquinolone targets (Hooper & Jacoby, 2016; Aldred *et al*., 2014) [1, 4], but this study further clarifies how specific structural and thermodynamic features determine binding efficacy. For example, our results confirm that mutations at Ser83 and Asp87 in gyrase significantly reduce binding affinity, consistent with clinical resistance mechanisms (Redgrave *et al*., 2014) [10]. Furthermore, the computational models provide detailed maps of drug-enzyme-DNA interactions, reinforcing earlier structural studies (Laponogov *et al*., 2009) [6].

Importantly, we identified moderate binding of fluoroquinolones to off-target human proteins such as topoisomerase II and serum albumin. These findings correlate with known adverse effects, including tendinopathies and cardiac events (García *et al*., 2019) [3]. This raises critical concerns about drug selectivity and underlines the importance of future fluoroquinolone derivatives with improved specificity for bacterial over human targets.

The study's limitations include the *in vitro* nature of the experiments, which, while informative, cannot fully replicate the complexity of *in vivo* systems. Moreover, the impact of metabolic degradation, cellular uptake variability, and biofilm-associated resistance was beyond the scope of this work but merits future investigation.

Overall, this research not only validates known mechanisms but extends them by integrating molecular binding data with functional assays and modeling. These insights are essential for the rational design of next-generation fluoroquinolones that can overcome resistance while minimizing toxicity.

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