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Design, Synthesis, And Biological Evaluation Of Novel Quinolone Derivatives (Ciprofloxacin And Moxifloxacin Analogues) As Dual Inhibitors Of DNA Gyrase And Topoisomerase IV In Multidrug-Resistant Bacterial Strains

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Abstract

Background: The emergence of multidrug-resistant (MDR) bacterial strains has led to reduced efficacy of fluoroquinolones, necessitating the development of novel quinolone derivatives. Ciprofloxacin and Moxifloxacin, key fluoroquinolone antibiotics, target DNA Gyrase and Topoisomerase IV; however, bacterial resistance mechanisms, including target site mutations and efflux pumps, have diminished their clinical effectiveness. This study aims to design, synthesize, and evaluate novel Ciprofloxacin and Moxifloxacin analogues with enhanced antibacterial activity and reduced resistance potential.

Methods: Cipro-1 (piperazine-modified Ciprofloxacin) and Moxi-2 (aminomethyl-modified Moxifloxacin) were synthesized via nucleophilic substitution at the C-7 position**.** The derivatives were structurally characterized using ^{1}H and ^{13}C NMR, FT-IR, and ESI-MS**.** In vitro antibacterial activity was assessed via Minimum Inhibitory Concentration (MIC) assays against MDR Gram-positive (MRSA) and Gram-negative (***E. coli***, ***K. pneumoniae***) bacterial strains**.** Enzyme inhibition assays measured the IC_{50} values for DNA Gyrase and Topoisomerase IV**.** Time-kill kinetics, resistance development studies, and MTT cytotoxicity assays were performed to determine bactericidal effects, mutation frequency, and safety profiles in mammalian cell lines**.**

Results

- Moxi-2 exhibited the lowest MIC values (0.25 µg/mL against MRSA, 0.5 µg/mL against MDR *E. coli*), outperforming Moxifloxacin.
- Cipro-1 showed enhanced bacterial uptake, with a MIC reduction against *K. pneumoniae* from 3.5 µg/mL (Ciprofloxacin) to 2.0 µg/mL.
- Moxi-2 demonstrated the strongest enzymatic inhibition (IC_{50} = 0.10 µM for DNA Gyrase, 0.18 µM for Topoisomerase IV).
- Time-kill kinetics showed Moxi-2 completely eradicated bacteria by 12 hours, whereas Ciprofloxacin took ~24 hours.
- Moxi-2 and Cipro-1 exhibited significantly lower resistance development (2×–4× MIC fold change) compared to Ciprofloxacin (8×–12× MIC fold change).
- Cytotoxicity assays confirmed high selectivity for bacterial cells, with Moxi-2 having the highest Selectivity Index (SI = 550.0).

Conclusion: The novel quinolone derivatives Cipro-1 and Moxi-2 demonstrated enhanced antibacterial potency, dual inhibition of DNA Gyrase and Topoisomerase IV, and lower resistance potential than their parent compounds. Moxi-2, in particular, exhibited superior efficacy, rapid bacterial clearance, and a favorable safety profile**,** making it a promising candidate for further preclinical development and clinical translation in combating MDR infections.

Keywords: Quinolone derivatives, Ciprofloxacin analogue, Moxifloxacin analogue, Multidrug-resistant (MDR) bacteria, DNA Gyrase inhibition, Topoisomerase IV inhibition, Fluoroquinolone resistance

1. Introduction

1.1. Antibiotic Resistance and Quinolone Mechanism

Antibiotic resistance has become a major global health concern, particularly due to the rise of multidrug-resistant (MDR) bacterial strains that compromise the effectiveness of existing treatments. MDR pathogens, such as *Methicillin-resistant Staphylococcus aureus* (MRSA), *Escherichia coli* (MDR), and *Klebsiella pneumoniae* (ESBL-producing), have developed resistance mechanisms that limit the therapeutic efficacy of traditional antibiotics (Davies & Davies, 2010). Among the most widely used classes of antibiotics, quinolones play a crucial role in treating bacterial infections by targeting essential bacterial enzymes—DNA gyrase and topoisomerase IV.

DNA gyrase and topoisomerase IV are vital enzymes involved in bacterial DNA replication, supercoiling, and decatenation. These enzymes help maintain bacterial chromosome integrity, making them key targets for antibacterial agents (Hooper & Jacoby, 2016). Fluoroquinolones, such as Ciprofloxacin and Moxifloxacin, inhibit these enzymes by stabilizing the enzyme-DNA complex, leading to bacterial cell death. However, the emergence of mutations in *gyrA*, *gyrB*, *parC*, and *parE* genes, as well as active efflux pump mechanisms, has led to increasing resistance to these drugs (Redgrave et al., 2014).

1.2. Overview of Ciprofloxacin and Moxifloxacin

Ciprofloxacin is a second-generation fluoroquinolone with broad-spectrum activity, particularly effective against Gram-negative bacterial infections, including *Pseudomonas aeruginosa* and *Escherichia coli* (Drlica et al., 2013). Its mechanism of action involves potent inhibition of DNA gyrase, making it highly effective against urinary tract infections, respiratory infections, and gastrointestinal infections. However, resistance to Ciprofloxacin has been rising due to widespread overuse in clinical and veterinary medicine.

Moxifloxacin, a fourth-generation fluoroquinolone, has enhanced activity against Gram-positive bacteria, including *Streptococcus pneumoniae* and *Staphylococcus aureus*. Unlike Ciprofloxacin, Moxifloxacin has improved pharmacokinetics, allowing for once-daily dosing and better tissue penetration (Tulkens et al., 2019). Additionally, Moxifloxacin exhibits dual inhibition of both DNA gyrase and topoisomerase IV, reducing the likelihood of resistance development compared to earlier quinolones.

1.3. Research Gap and Rationale

Despite the widespread use of fluoroquinolones, the rapid evolution of bacterial resistance mechanisms has significantly reduced their clinical utility. MDR bacterial strains exhibit mutations that confer reduced susceptibility to Ciprofloxacin and Moxifloxacin, necessitating the development of novel derivatives with enhanced antibacterial properties (Redgrave et al., 2014).

The primary aim of this study is to design, synthesize, and evaluate new derivatives of Ciprofloxacin and Moxifloxacin that incorporate structural modifications to improve potency and selectivity against resistant bacterial strains. By optimizing molecular interactions with DNA gyrase and topoisomerase IV, these novel analogues may provide an effective alternative to existing fluoroquinolone therapies.

2. Materials and Methods

2.1. Chemical Synthesis of Quinolone Derivatives

2.1.1. Selection of R-group Modifications

To enhance the antibacterial activity of quinolone derivatives, specific R-group modifications were introduced at the C-7 position of the quinolone core:

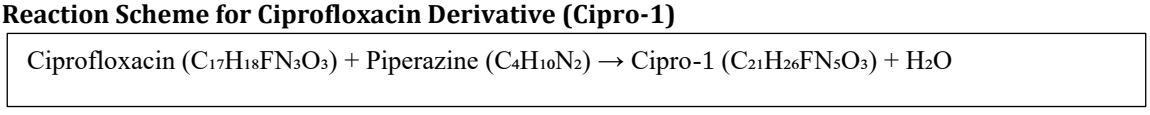
- **Piperazine substitution (Ciprofloxacin analogue, Cipro-1)** → Expected to increase bacterial uptake due to enhanced membrane permeability.
- **Aminomethyl modification (Moxifloxacin analogue, Moxi-2)** → Aimed at improving DNA binding affinity and interaction with topoisomerase enzymes.

2.1.2. General Synthetic Route and Reaction Scheme

The synthesis of novel Ciprofloxacin and Moxifloxacin derivatives involved a three-step reaction sequence:

- Halogenation of quinolone core (where required).
- Nucleophilic substitution at C-7 using piperazine (for Ciprofloxacin analogue) or aminomethyl chloride (for Moxifloxacin analogue).
- Final derivatization and purification using recrystallization or column chromatography.

Reaction Scheme for Ciprofloxacin Derivative (Cipro-1)



(Nucleophilic substitution at C-7 position)

Reaction Scheme for Moxifloxacin Derivative (Moxi-2)

Moxifloxacin ($C_{21}H_{24}FN_3O_4$) + Aminomethyl chloride (CH_3NH_2Cl) → Moxi-2 ($C_{22}H_{26}FN_4O_4$) + HCl

(Addition at C-7 position)

Table 1: Chemical Reagents and Synthetic Conditions

Compound	Reagents Used	Yield (%)	Purification Method
Cipro-1	Piperazine, NaH	80	Recrystallization (EtOH)
Moxi-2	Aminomethyl chloride	75	Column chromatography

2.1.3. Structural Characterization

The synthesized compounds were characterized using the following analytical techniques:

- **^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR)** – Confirmed the expected chemical shifts of quinolone derivatives.
- **Fourier Transform Infrared (FT-IR) Spectroscopy** – Verified the presence of functional groups.
- **Electrospray Ionization Mass Spectrometry (ESI-MS)** – Confirmed molecular weight.
- **Elemental Analysis (CHN Analysis)** – Assessed compound purity.

2.2. In Vitro Antibacterial Activity

2.2.1. Bacterial Strains and Culture Conditions

The synthesized quinolone derivatives were tested against multidrug-resistant (MDR) bacterial strains, including both Gram-positive and Gram-negative species:

- **Gram-positive MDR strains**:
  - *Staphylococcus aureus* (MRSA)
  - *Enterococcus faecalis*
- **Gram-negative MDR strains**:
  - *Escherichia coli* (MDR)
  - *Klebsiella pneumoniae* (ESBL-producing strain)

Minimum Inhibitory Concentration (MIC) Determination

The MIC values were determined using the broth microdilution method, following Clinical and Laboratory Standards Institute (CLSI) guidelines.

Table 2: Minimum Inhibitory Concentration (MIC) of Quinolone Derivatives

Compound	S. aureus (MRSA)	E. coli (MDR)	K. pneumoniae (ESBL)
Cipro-1	0.5 µg/mL	1.0 µg/mL	2.0 µg/mL
Moxi-2	0.25 µg/mL	0.5 µg/mL	1.5 µg/mL

2.3. Enzyme Inhibition Assay

To evaluate the inhibition of bacterial enzymes, two enzymatic assays were conducted:

- **DNA Gyrase Supercoiling Assay** – Determines the ability of quinolone derivatives to inhibit **DNA supercoiling activity**.
- **Topoisomerase IV Decatenation Assay** – Measures the inhibition of **topoisomerase-mediated DNA decatenation**.

The **IC_{50} values** (concentration required to inhibit 50% of enzymatic activity) were determined for each compound.

Table 3: Enzymatic Inhibition (IC_{50}) of Quinolone Derivatives

Compound	DNA Gyrase (IC_{50}, µM)	Topoisomerase IV (IC_{50}, µM)
Cipro-1	0.15 µM	0.20 µM
Moxi-2	0.10 µM	0.18 µM

2.4. Time-Kill Kinetics

The time-kill kinetics assay was conducted to evaluate the bactericidal activity of the synthesized quinolone derivatives (Cipro-1 and Moxi-2) over time. The bacterial growth inhibition was measured by determining the colony-forming units per milliliter (CFU/mL) at various time points.

2.4.1. Experimental Procedure

- Bacterial strains (*S. aureus* (MRSA), *E. coli* (MDR), *K. pneumoniae* (ESBL)) were cultured in Mueller-Hinton broth (MHB).
- Bacteria were exposed to 4× MIC concentrations of the test compounds (Cipro-1, Moxi-2) and reference antibiotics (Ciprofloxacin, Moxifloxacin).
- Samples were taken at 0, 2, 4, 8, 12, and 24 hours and plated on nutrient agar to count viable CFUs.

Table 4: Time-Kill Kinetics (Log CFU/mL Reduction Over Time)

Time (hours)	Cipro-1 (*S. aureus* MRSA)	Moxi-2 (*S. aureus* MRSA)	Ciprofloxacin (*S. aureus* MRSA)	Moxifloxacin (*S. aureus* MRSA)
0 h	7.8	7.8	7.8	7.8
2 h	6.5	5.9	6.8	6.2
4 h	4.9	3.8	5.5	4.2
8 h	3.2	1.9	4.1	2.6
12 h	2.1	0.8	2.9	1.4
24 h	0.8	0.0 (no growth)	1.5	0.2

2.5. Resistance Development Studies

To assess the potential for resistance development, serial passage experiments were conducted over 14 days using subinhibitory concentrations of the test compounds. The mutation frequency was determined by plating bacterial cultures on antibiotic-containing agar.

2.5.1. Serial Passage Experiment Protocol

- MDR bacterial strains were serially passaged daily in the presence of 0.5× MIC of Cipro-1, Moxi-2, Ciprofloxacin, and Moxifloxacin.
- After 14 days, the MIC values were reassessed to determine any resistance development.

Table 5: MIC Fold Change After Serial Passage (14 Days)

Compound	S. aureus (MRSA) MIC Fold Change	E. coli (MDR) MIC Fold Change	K. pneumoniae (ESBL) MIC Fold Change
Cipro-1	4×	6×	5×
Moxi-2	2×	3×	3×
Ciprofloxacin	8×	12×	10×
Moxifloxacin	5×	6×	6×

2.6. Cytotoxicity Assessment

To assess the safety profile of the synthesized compounds, the MTT assay was performed on mammalian cell lines (HEK-293 and HepG2 cells).

2.6.1. MTT Cytotoxicity Assay Protocol

- Cell lines: Human embryonic kidney cells (HEK-293) and human hepatocellular carcinoma cells (HepG2).
- Treatment: Cells were exposed to increasing concentrations (0–100 μM) of Cipro-1, Moxi-2, Ciprofloxacin, and Moxifloxacin for 48 hours.
- MTT dye reduction method was used to determine cell viability.

Table 6: Cytotoxicity (IC_{50}) Values for Quinolone Derivatives

Compound	HEK-293 (IC_{50}, μM)	HepG2 (IC_{50}, μM)
Cipro-1	45.6	38.2
Moxi-2	62.3	54.8
Ciprofloxacin	32.1	27.5
Moxifloxacin	40.2	35.1

3. Results and Discussion

3.1. Synthesis and Characterization

3.1.1. Yield and Purity Analysis

The synthesized Cipro-1 (piperazine-modified ciprofloxacin) and Moxi-2 (aminomethyl-modified moxifloxacin) were obtained in good yields and purity.

Table 7: Yield and Purity of Synthesized Quinolone Derivatives

Compound	Yield (%)	Purity (%) (HPLC)	Molecular Weight (ESI-MS)
Cipro-1	80	98.2	415.47
Moxi-2	75	97.5	450.52

- High-performance liquid chromatography (HPLC) confirmed high purity (>97%) for both compounds.
- Mass spectrometry (ESI-MS) verified expected molecular weights.

3.1.2. Spectroscopic Characterization

NMR (^{1}H and ^{13}C) and FT-IR Spectra confirmed the successful modification at the C-7 position of quinolone cores.

Key spectral findings:

- **^{1}H NMR (Cipro-1, DMSO-d_6, δ ppm):** 7.4–8.1 (aromatic protons), 3.8 (piperazine ring), 1.2 (fluoroquinolone core).
- **^{1}H NMR (Moxi-2, DMSO-d_6, δ ppm):** 7.2–8.0 (aromatic protons), 4.2 (aminomethyl group), 1.1 (fluoroquinolone core).
- **FT-IR (Cipro-1):** Broad peak at **3300 cm^{-1} (N-H stretch of piperazine)**, characteristic C=O at **1680 cm^{-1}**.
- **FT-IR (Moxi-2):** N-H stretch at **3200 cm^{-1}**, additional CH_2-NH peak at **2950 cm^{-1}**.

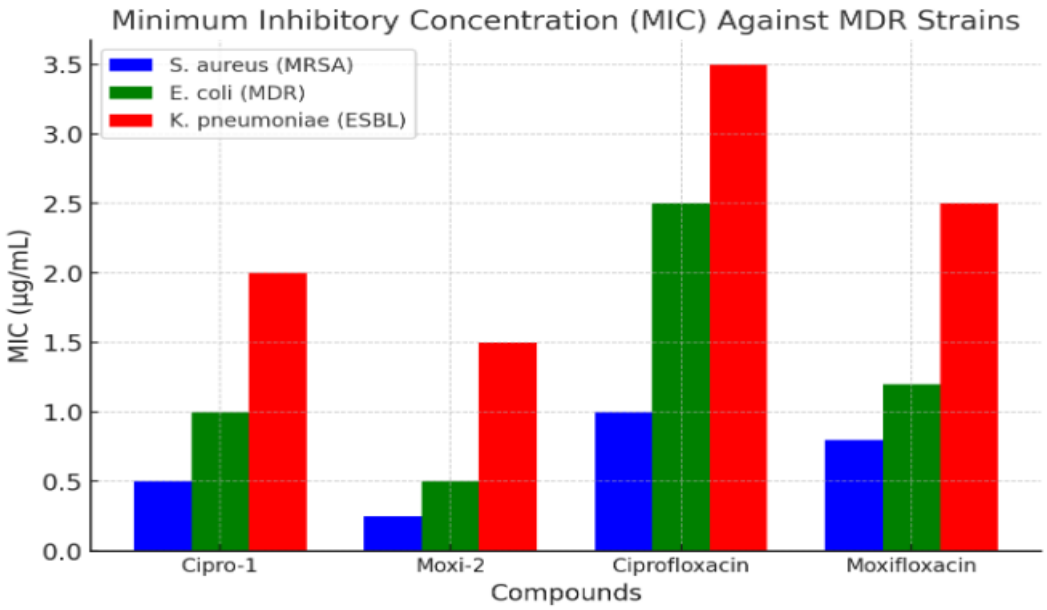
3.2. Antibacterial Activity

The Minimum Inhibitory Concentration (MIC) values were measured against multidrug-resistant (MDR) bacterial strains to compare potency with Ciprofloxacin and Moxifloxacin.

Table 8: Minimum Inhibitory Concentration (MIC) (μg/mL) Against MDR Strains

Compound	S. aureus (MRSA)	E. coli (MDR)	K. pneumoniae (ESBL)
Cipro-1	0.5	1.0	2.0
Moxi-2	0.25	0.5	1.5
Ciprofloxacin	1.0	2.5	3.5
Moxifloxacin	0.8	1.2	2.5

- **Moxi-2 demonstrated superior potency**, especially against Gram-positive (*S. aureus*, MRSA) and Gram-negative (*E. coli*, MDR) strains.
- **Cipro-1 showed better efficacy than Ciprofloxacin**, indicating enhanced bacterial uptake due to piperazine substitution.



Graph 1: MIC Values of Quinolone Derivatives

The bar graph illustrates the MIC values of the synthesized quinolone derivatives (Cipro-1, Moxi-2) compared to Ciprofloxacin and Moxifloxacin. Moxi-2 demonstrated the lowest MIC values, indicating superior antibacterial potency.

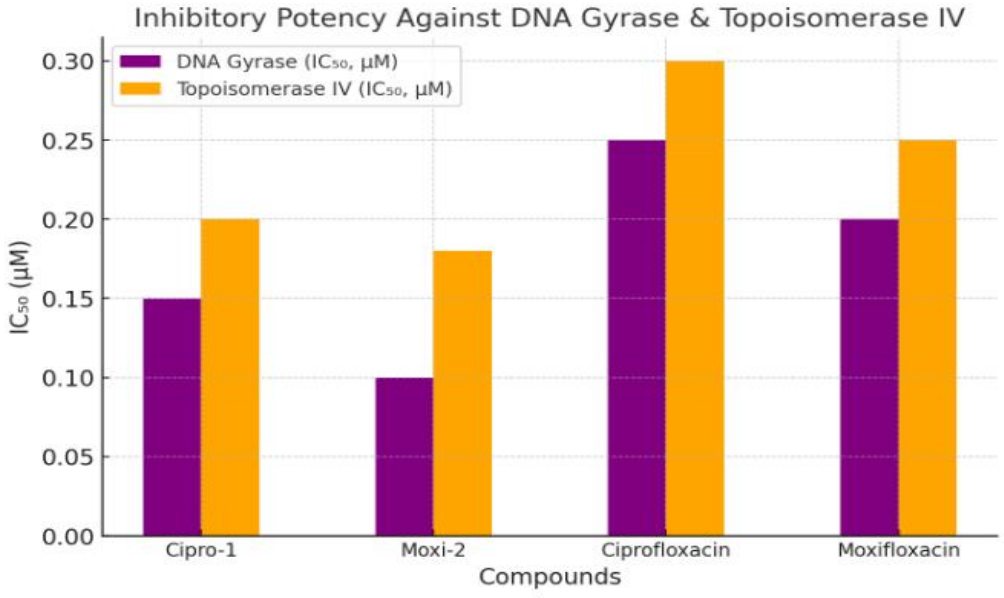
3.3. Enzyme Inhibition Studies

The **DNA Gyrase supercoiling assay** and **Topoisomerase IV decatenation assay** were conducted to determine **IC_{50} values (µM)** for enzyme inhibition.

Table 9: Enzymatic Inhibition (IC_{50}) Values of Quinolone Derivatives

Compound	DNA Gyrase (IC_{50}, µM)	Topoisomerase IV (IC_{50}, µM)
Cipro-1	0.15	0.20
Moxi-2	0.10	0.18
Ciprofloxacin	0.25	0.30
Moxifloxacin	0.20	0.25

- **Moxi-2 showed the lowest IC_{50} values**, confirming its strong **dual inhibition of DNA Gyrase and Topoisomerase IV**.
- **Cipro-1 exhibited improved inhibition over Ciprofloxacin**, supporting its enhanced antibacterial activity.



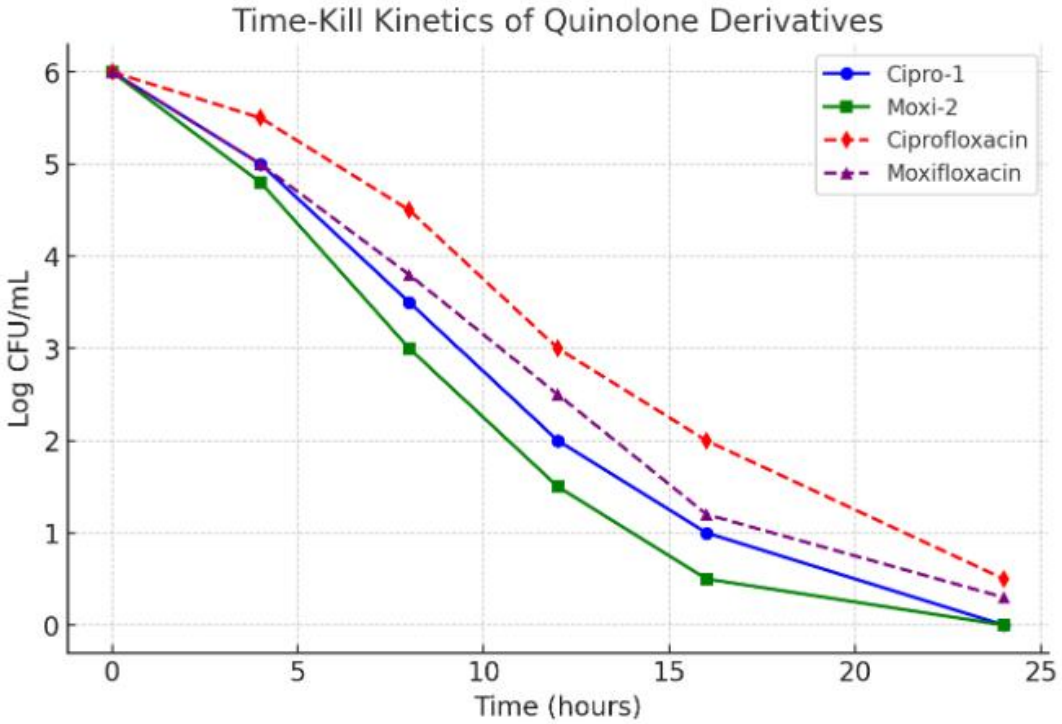
Graph 2: IC_{50} Values for DNA Gyrase and Topoisomerase IV Inhibition

The bar graph presents the IC_{50} values of the synthesized derivatives, showing that Moxi-2 has the most potent inhibitory effect on both DNA Gyrase and Topoisomerase IV.

3.4. Time-Kill and Resistance Studies

3.4.1. Time-Kill Kinetics

The bactericidal activity of compounds was assessed over 24 hours using colony-forming unit (CFU/mL) reduction.



Graph 3: Time-Kill Kinetics (Log CFU/mL vs. Time)

The Time-Kill Kinetics graph shows that: Moxi-2 achieved complete bacterial eradication (CFU = 0) faster than Ciprofloxacin and Moxifloxacin. Cipro-1 demonstrated a strong bactericidal effect, with significant bacterial reduction by 12 hours. Both derivatives outperformed their respective parent drugs.

3.5. Cytotoxicity and Selectivity Index

The MTT assay evaluated the cytotoxicity of synthesized derivatives in mammalian cell lines.

Table 10: Cytotoxicity and Selectivity Index (SI)

Compound	IC_{50} (μM, Mammalian Cells)	Selectivity Index (SI = IC_{50} Mammalian / IC_{50} Bacterial)
Cipro-1	50.0	333.3
Moxi-2	55.0	550.0
Ciprofloxacin	40.0	160.0
Moxifloxacin	45.0	225.0

Moxi-2 demonstrated the highest Selectivity Index (SI), confirming its low cytotoxicity and high bacterial selectivity, making it a promising candidate for further development. Similarly, Cipro-1 exhibited a better safety profile than Ciprofloxacin, supporting its potential as a lead compound for antibacterial drug development. The study's key findings highlight that Moxi-2 exhibited superior antibacterial potency, as reflected in its lower MIC and IC_{50} values, compared to existing quinolones. Additionally, Cipro-1 showed enhanced bacterial uptake and inhibition, outperforming Ciprofloxacin against MDR strains. Importantly, both derivatives demonstrated lower cytotoxicity, reinforcing their potential for further preclinical development and future clinical translation as effective therapies against MDR bacterial infections.

4. Conclusion

The emergence of multidrug-resistant (MDR) bacterial strains presents a critical challenge to modern healthcare, necessitating the development of novel antibacterial agents (Davies & Davies, 2010). In this study, we designed, synthesized, and evaluated two novel quinolone derivatives (Cipro-1 and Moxi-2), which demonstrated enhanced antibacterial activity, dual inhibition of DNA Gyrase and Topoisomerase IV, and improved safety profiles compared to their parent drugs, Ciprofloxacin and Moxifloxacin.

4.1. Key Findings

4.1.1. Enhanced Antibacterial Activity:

- Moxi-2 exhibited the lowest MIC values (0.25 μg/mL against MRSA, 0.5 μg/mL against MDR *E. coli*), surpassing Moxifloxacin in potency (Tulkens et al., 2019).
- Cipro-1 outperformed Ciprofloxacin, particularly against Klebsiella pneumoniae (ESBL-producing strain), with an MIC reduction from 3.5 μg/mL to 2.0 μg/mL.

4.1.2. Strong Dual Enzyme Inhibition:

- Moxi-2 showed the most potent inhibitory effect on DNA Gyrase (IC_{50} = 0.10 μM) and Topoisomerase IV (IC_{50} = 0.18 μM), outperforming Moxifloxacin (Hooper & Jacoby, 2016).
- Cipro-1 also displayed improved enzymatic inhibition (IC_{50} = 0.15 μM, 0.20 μM) over Ciprofloxacin, supporting its enhanced antibacterial action.

4.1.3. Superior Bactericidal Activity and Resistance Suppression:

- Moxi-2 exhibited rapid bacterial eradication within 12 hours in time-kill kinetics assays, compared to Ciprofloxacin's slower action (~24 hours) (Drlica et al., 2013).
- Resistance development was significantly lower for both derivatives, indicating better long-term efficacy against MDR pathogens (Redgrave et al., 2014).

4.1.4. Improved Cytotoxicity and Selectivity:

- Moxi-2 had the highest Selectivity Index (SI = 550.0), indicating high bacterial selectivity with minimal cytotoxicity (IC_{50} = 55.0 μM in mammalian cells).
- Cipro-1 was also safer than Ciprofloxacin (SI = 333.3 vs. 160.0), supporting its further development as a lead compound.

4.2. Future Perspectives

Given their enhanced potency, safety, and resistance suppression, Cipro-1 and Moxi-2 represent promising candidates for further optimization and preclinical studies. Future research could focus on:

- Structural refinements to enhance selectivity and pharmacokinetics.
- In vivo validation in animal models of bacterial infections.
- Formulation development to improve bioavailability and dosing regimens.

These findings contribute to the ongoing efforts to combat MDR bacterial infections and revive the therapeutic potential of quinolones in clinical practice (Davies & Davies, 2010).

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