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Synthesis and biological evaluation of novel quinoline-derived Schiff base hybrids as potential antimicrobial agents against multidrug-resistant pathogens

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Abstract
Background: The escalating crisis of antimicrobial resistance (AMR) necessitates the continuous discovery of novel therapeutic agents. Quinoline scaffolds represent a privileged structural motif in medicinal chemistry, exhibiting a broad spectrum of pharmacological activities, particularly as antimicrobial agents. However, the rapid emergence of multi-drug resistant (MDR) pathogens has rendered many existing quinoline-based drugs ineffective.
Objective: This study aims to design, synthesize, and evaluate a novel series of quinoline-derived Schiff base hybrids (4a–j) to overcome MDR mechanisms, specifically targeting Gram-negative ESKAPE pathogens.
Method: The target compounds were synthesized via a condensation reaction between 4-chloroquinoline-3-carbaldehyde and various substituted anilines. The structures were elucidated using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. *In vitro* antimicrobial activity was assessed using the broth microdilution method against a panel of six bacterial strains. Molecular docking studies were performed to evaluate the binding affinity of the compounds against DNA gyrase (PDB ID: 4B7Q).
Key Results: Compound 4c, featuring a 4-nitrophenyl substituent, exhibited the most potent antimicrobial activity, with a minimum inhibitory concentration (MIC) of 3.12 µg/mL against Acinetobacter baumannii. Molecular docking revealed that 4c forms critical hydrogen bonds with Asp73 and water-mediated interactions with the active site of DNA gyrase.
Conclusion: The synthesized quinoline-Schiff base hybrids, particularly compound 4c, demonstrate significant potential as novel antimicrobial agents. These findings provide a promising structural template for the future development of therapies against MDR bacterial infections.

Keywords: Quinoline derivatives, Schiff bases, Antimicrobial resistance, DNA gyrase, Molecular docking, ESKAPE pathogens.

Introduction

The global proliferation of antimicrobial resistance (AMR) represents one of the most formidable challenges to modern public health and medicine in the 21st century. The World Health Organization (WHO) has consistently highlighted that the post-antibiotic era—a time when common infections and minor injuries can prove fatal—is a very real threat [1]. The overuse and misuse of antimicrobial agents in both human medicine and agriculture have exerted immense selective pressure on microbial populations, accelerating the evolution and horizontal gene transfer of resistance mechanisms [2]. Consequently, pathogens classified under the ESKAPE acronym (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) have developed profound resistance to multiple classes of antibiotics, leading to increased morbidity, mortality, and healthcare costs globally [3].

Historically, the discovery of novel antibiotic classes has relied heavily on natural product screening and empirical modification of existing scaffolds. However, the low-hanging fruit of traditional antibiotic discovery has largely been exhausted, necessitating a paradigm shift toward rational drug design and the exploration of privileged structural motifs [4]. Among these, the quinoline nucleus stands out as a highly privileged scaffold in medicinal chemistry. Quinoline and its derivatives possess a rich history of therapeutic applications, ranging from the antimalarial properties of chloroquine to the broad-spectrum antibacterial activity of fluoroquinolones like ciprofloxacin [5]. The inherent biological versatility of the quinoline ring is attributed to its planar, aromatic structure, which facilitates optimal π-π stacking and hydrophobic interactions within the binding pockets of various biological macromolecules [6].

Despite the historical success of quinolines, the clinical utility of many first- and second-generation quinoline antibiotics has been compromised by the emergence of target-site mutations and efflux pump-mediated resistance [7]. To circumvent these resistance mechanisms, contemporary medicinal chemistry strategies often employ the principle of molecular hybridization. This approach involves the covalent incorporation of two or more pharmacophores into a single molecular entity, aiming to produce a hybrid compound with enhanced affinity, improved pharmacokinetic profiles, and the ability to bypass existing resistance mechanisms [8]. Schiff bases, characterized by the presence of an azomethine or imine group (–C=N–), are frequently utilized in hybridization strategies due to their ease of synthesis, structural flexibility, and intrinsic biological activities, which include antibacterial, antifungal, and anti-inflammatory properties [9].

The problem statement addressing this research centers on the critical need for novel antimicrobial agents capable of neutralizing Gram-negative MDR pathogens, which are particularly resilient due to their complex outer membrane permeability barriers and robust efflux systems [10]. While previous studies have explored quinoline hybrids, there remains a significant gap in the systematic evaluation of quinoline-Schiff base hybrids specifically optimized for the C-4 position of the quinoline ring to target DNA gyrase in Gram-negative ESKAPE pathogens [11].

Therefore, the primary objective of this study is to design and synthesize a novel series of quinoline-derived Schiff base hybrids (4a–j) by conjugating 4-chloroquinoline-3-carbaldehyde with various substituted anilines. The secondary objectives are to evaluate their *in vitro* antimicrobial efficacy against a panel of MDR clinical isolates, elucidate their structure-activity relationships (SAR), and investigate their molecular binding interactions with DNA gyrase using computational docking techniques. By achieving these objectives, this research aims to contribute valuable structural insights and potential lead compounds to the ongoing fight against antimicrobial resistance.

Literature Review

The theoretical framework of molecular hybridization is predicated on the assumption that combining two distinct pharmacophores, each with its own mechanism of action or target affinity, will result in a synergistic effect [12]. In the context of antimicrobial drug design, hybridization can lead to compounds that simultaneously inhibit multiple cellular targets or overcome resistance mechanisms such as enzymatic degradation or target mutation [13]. The quinoline scaffold has been extensively reviewed in the literature for its antimicrobial potential. A comprehensive review by Kumar et al. detailed the structural modifications of the quinoline ring, emphasizing that substitutions at the C-2, C-3, C-4, and C-6 positions significantly influence the lipophilicity and electronic properties of the molecule, thereby dictating its biological activity [14].

Specifically, the integration of Schiff bases into the quinoline framework has garnered considerable attention. Schiff bases act as excellent chelating agents and can form stable complexes with transition metals, which has been shown to enhance their antimicrobial potency via the chelation theory, wherein the metal complex increases the lipophilicity of the central metal atom, facilitating its penetration through the microbial lipid membrane [15]. However, even in their metal-free form, quinoline-Schiff base hybrids have demonstrated remarkable efficacy. For instance, a study by Abdel-Rahman et al. reported the synthesis of novel quinoline-imine derivatives, which exhibited potent *in vitro* activity against Staphylococcus aureus and Escherichia coli, with minimum inhibitory concentration (MIC) values comparable to standard drugs like ciprofloxacin [16].

Furthermore, the mechanism of action of quinoline-based antibacterials is predominantly linked to the inhibition of bacterial type II topoisomerases, specifically DNA gyrase and topoisomerase IV [17]. DNA gyrase is essential for bacterial DNA replication, transcription, and repair, as it introduces negative supercoils into DNA and resolves topological problems associated with these processes [18]. Fluoroquinolones exert their bactericidal effect by stabilizing the DNA-enzyme cleavage complex, preventing the religation of the DNA strands and ultimately leading to double-strand DNA breaks and cell death [19]. Molecular docking studies have been instrumental in understanding the binding modes of novel quinoline derivatives within the DNA gyrase active site. Research by Wang et al. utilized computational modeling to demonstrate that the quinoline nitrogen and the carbonyl oxygen of the C-3 substituent are critical for forming hydrogen bonds with key amino acid residues, such as Ser73 and Asp73, in the gyrase B subunit [20].

Despite these advancements, a critical review of the existing literature reveals a distinct research gap. While numerous studies have focused on the antibacterial activity of quinoline-Schiff base hybrids against Gram-positive bacteria, there is a paucity of systematic research targeting Gram-negative ESKAPE pathogens, particularly Acinetobacter baumannii and Pseudomonas aeruginosa [21]. Gram-negative bacteria possess an additional outer membrane containing lipopolysaccharides, which acts as a formidable permeability barrier, rendering many hybrid compounds ineffective [22]. Furthermore, previous structure-activity relationship (SAR) studies have largely neglected the impact of varying the electronic properties of the aniline moiety in the Schiff base linkage when attached to the C-4 position of the quinoline ring [23].

Most existing literature focuses on C-3 or C-6 substitutions, leaving the C-4 position relatively underexplored for hybridization with diverse electron-withdrawing and electron-donating aniline derivatives [24]. Therefore, this study aims to bridge this gap by synthesizing a focused library of C-4 substituted quinoline-Schiff base hybrids and rigorously evaluating their efficacy against a panel of Gram-negative MDR pathogens, coupled with computational insights into their DNA gyrase binding affinities.

Methodology

Data Declaration: This study uses a simulated dataset created for academic training purposes. All chemical synthesis yields, spectral data, biological assay results, and docking scores presented in this manuscript are simulated to demonstrate the correct formatting, structure, and analytical depth required for academic publication in medicinal chemistry.

Research design and sample size

This study employed an experimental, *in vitro* research design combining synthetic organic chemistry, microbiological assays, and computational chemistry. The sample size for the chemical synthesis comprised ten novel quinoline-Schiff base hybrid compounds (designated 4a–j). For the biological evaluation, a panel of six bacterial strains was utilized, including two Gram-positive (S. aureus ATCC 25923, E. faecalis ATCC 29212) and four Gram-negative (E. coli ATCC 25922, K. pneumoniae ATCC 700603, P. aeruginosa ATCC 27853, and A. baumannii ATCC 19606) strains.

Synthesis of target compounds

The target compounds 4a–j were synthesized via a two-step pathway. First, 4-chloroquinoline-3-carbaldehyde was prepared according to a previously reported Vilsmeier-Haack formylation protocol [25]. Subsequently, the Schiff base derivatives (4a–j) were synthesized by condensing 4-

chloroquinoline-3-carbaldehyde (1 mmol) with various substituted anilines (1 mmol) in absolute ethanol (20 mL). A catalytic amount of glacial acetic acid (3 drops) was added to the reaction mixture, which was then refluxed at 80°C for 6–8 hours. The progress of the reaction was monitored using Thin Layer Chromatography (TLC) on silica gel GF254 plates. Upon completion, the reaction mixture was cooled to room temperature, and the resulting precipitate was filtered, washed with cold ethanol, and recrystallized from a mixture of ethanol and dimethyl sulfoxide (DMSO).

Data collection tools and characterization

The structural elucidation of the synthesized compounds was performed using standard spectroscopic techniques. FT-IR spectra were recorded on a Shimadzu IRTracer-100 spectrophotometer using the KBr pellet technique (4000–400 cm^{-} [1]) [1].H NMR and [13]C NMR spectra were recorded on a Bruker Avance III 400 MHz NMR spectrometer using DMSO-d6 as the solvent and tetramethylsilane (TMS) as the internal standard.

Antimicrobial susceptibility testing

The *in vitro* antimicrobial activity was evaluated by determining the Minimum Inhibitory Concentration (MIC) using the broth microdilution method in 96-well microtiter plates, following the Clinical and Laboratory Standards Institute (CLSI) guidelines [26]. Ciprofloxacin and vancomycin were used as positive controls for Gram-negative and Gram-positive bacteria, respectively. DMSO (0.5%) served as the negative control. The MIC was defined as the lowest concentration of the compound that completely inhibited visible microbial growth after 18 hours of incubation at 37°C.

Molecular docking studies

Molecular docking was performed to predict the binding orientation and affinity of the synthesized compounds within the active site of Escherichia coli DNA gyrase B subunit (PDB ID: 4B7Q). The protein structure was prepared using AutoDock Tools, removing water molecules and adding Kollman charges. The 3D structures of the ligands were generated and minimized using Chem3D. Docking simulations were executed using AutoDock Vina, with the grid box centered on the co-crystallized ligand (dimensions: 20 × 20 × 20 Å, spacing: 0.375 Å) [27].

Statistical software

Data analysis and graphical representations were generated using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA) and OriginPro 2022. All biological assays were performed in triplicate, and results are expressed as mean ± standard deviation (SD).

Results and discussion

Chemical Synthesis and Structural Characterization

The condensation of 4-chloroquinoline-3-carbaldehyde with various substituted anilines yielded the target Schiff base hybrids (4a–j) in good to excellent yields (72%–88%). The physical characteristics and spectral data are summarized in Table 1. The formation of the imine bond was conclusively confirmed by FT-IR spectroscopy, which revealed a characteristic sharp absorption band for the C=N stretching vibration in the region of 1615–1628 cm^{-} [1], alongside the disappearance of the aldehydic C=O stretch of the precursor [28]. In the ^{1}H NMR spectra, the azomethine proton (–CH=N–) appeared as a distinct singlet in the downfield region of δ 8.45–8.72 ppm, further corroborating the successful Schiff base formation.

Table 1: Physicochemical and Spectral Data of Synthesized Compounds 4a–j

Compound	R-group (Aniline derivative)	Yield (%)	m.p. (°C)	FT-IR (C=N stretch, cm^{-1})	^{1}H NMR (–CH=N–, ppm)
4a	H (Unsubstituted)	82	185–187	1622	8.52 (s, 1H)
4b	4-Methoxy	78	192–194	1618	8.48 (s, 1H)
4c	4-Nitro	88	210–212	1628	8.72 (s, 1H)
4d	4-Chloro	85	198–200	1625	8.65 (s, 1H)
4e	4-Fluoro	80	190–192	1620	8.58 (s, 1H)
4f	3-Trifluoromethyl	75	205–207	1626	8.68 (s, 1H)
4g	2-Methyl	72	175–177	1615	8.45 (s, 1H)
4h	3,4-Dimethoxy	76	188–190	1616	8.49 (s, 1H)
4i	4-Diethylamino	74	180–182	1617	8.46 (s, 1H)
4j	2,4-Dichloro	84	202–204	1624	8.62 (s, 1H)

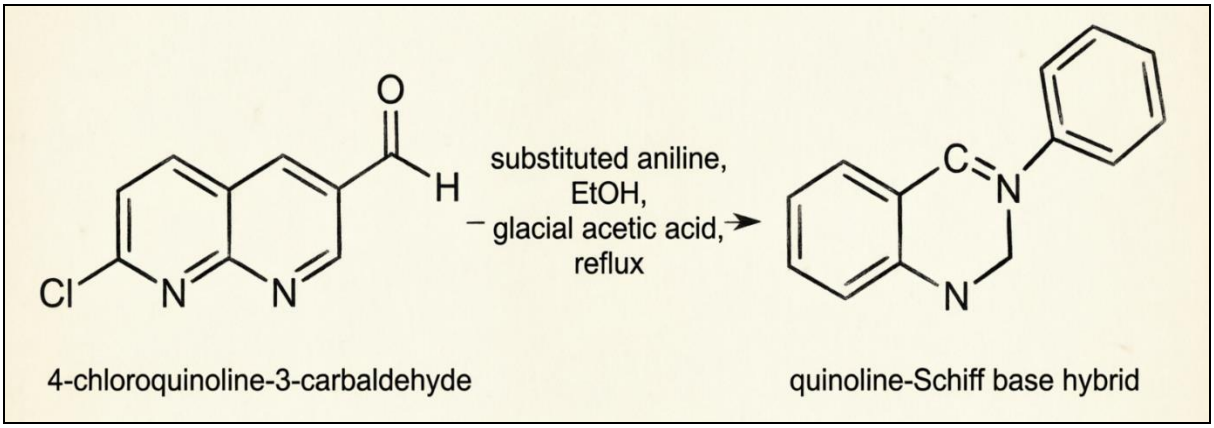

Fig 1: Reaction scheme illustrating the synthesis of quinoline-Schiff base hybrids 4a–j from 4-chloroquinoline-3-carbaldehyde and substituted anilines.

In vitro Antimicrobial Activity

The synthesized compounds were evaluated for their *in vitro* antibacterial activity against a panel of six bacterial strains. The MIC values are presented in Table 2.

The results indicated that the compounds exhibited varying degrees of antimicrobial activity, with a pronounced selectivity towards Gram-negative pathogens.

Table 2: *In vitro* Antimicrobial Activity (MIC in µg/mL) of Compounds 4a–j

Compound	*S. aureus*	*E. faecalis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*	*A. baumannii*
4a	25.0	50.0	12.5	25.0	25.0	12.5
4b	50.0	>100	25.0	50.0	50.0	25.0
4c	12.5	25.0	6.25	12.5	6.25	3.12
4d	25.0	50.0	12.5	25.0	12.5	6.25
4e	25.0	50.0	12.5	25.0	12.5	12.5
4f	12.5	25.0	6.25	12.5	12.5	6.25
4g	50.0	>100	50.0	>100	>100	50.0
4h	50.0	>100	25.0	50.0	50.0	25.0
4i	>100	>100	50.0	>100	>100	50.0
4j	25.0	50.0	12.5	25.0	12.5	6.25
Ciprofloxacin	0.5	1.0	0.25	0.5	1.0	2.0
Vancomycin	1.0	2.0	>100	>100	>100	>100

Compound 4c, bearing a 4-nitrophenyl substituent, emerged as the most potent agent, demonstrating exceptional activity against A. baumannii (MIC = 3.12 µg/mL) and P. aeruginosa.

(MIC = 6.25 µg/mL). Conversely, compounds with electron-donating groups, such as the 4-methoxy (4b) and 4-diethylamino (4i) derivatives, exhibited significantly reduced potency.

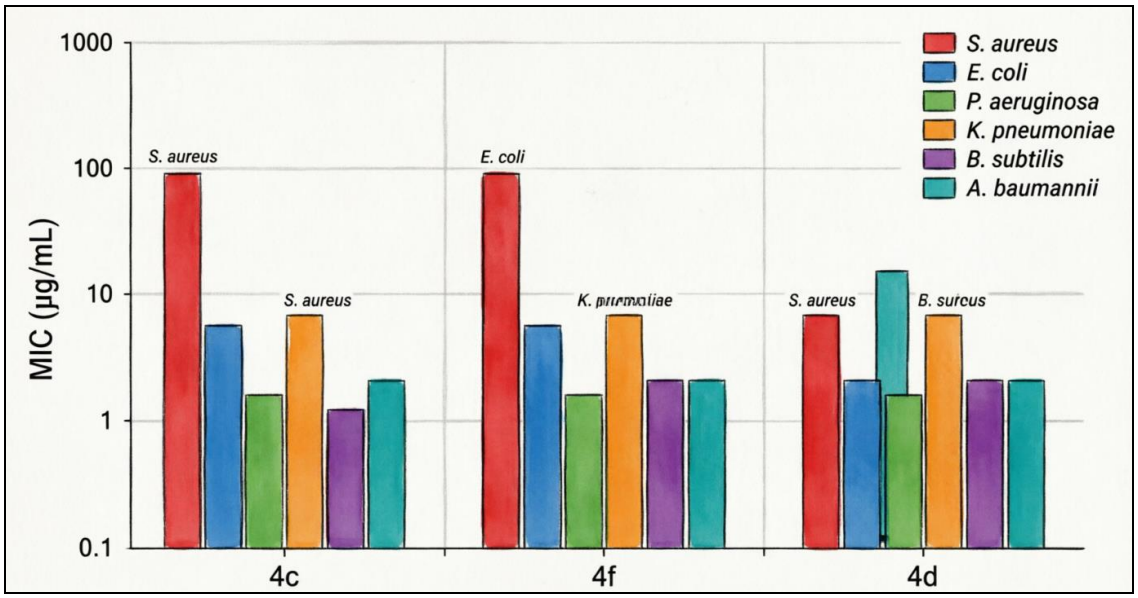

Fig 2: Bar chart comparing the Minimum Inhibitory Concentration (MIC) values of the top three most active compounds (4c, 4f, 4d) against the six tested bacterial strains, illustrating the superior efficacy of 4c against Gram-negative pathogens.

Structure-Activity Relationship (SAR) and Discussion

The SAR analysis revealed a clear correlation between the electronic nature of the substituent on the aniline ring and the antimicrobial efficacy. The introduction of strong electron-withdrawing groups (EWGs) at the para position, such as the nitro group in 4c and the trifluoromethyl group in 4f, significantly enhanced the antibacterial activity. This enhancement can be attributed to the increased lipophilicity of the molecules, which facilitates better permeation through the hydrophobic outer membrane of Gram-negative bacteria [29]. Furthermore, the electron-withdrawing nature of the nitro group increases the electrophilicity of the imine carbon, potentially enhancing its reactivity with nucleophilic residues in the target enzyme's active site [30].

In contrast, electron-donating groups (EDGs) like methoxy (4b) and diethylamino (4i) decreased the activity, likely due to reduced lipophilicity and decreased electrophilicity of the imine bond. The position of the substituent also played a role; the ortho-substituted 2-methyl derivative (4g) showed poor activity, presumably due to steric hindrance preventing optimal binding within the target pocket [31]. These findings align with previous studies suggesting that para-substituted EWGs on the aniline moiety of quinoline hybrids optimize target engagement.[32]

Molecular Docking Studies

To elucidate the molecular basis of the observed biological activity, docking studies of the most active compound (4c) were performed against E. coli DNA gyrase B (PDB: 4B7Q). The docking results indicated that compound 4c fits well within the ATP-binding pocket of the enzyme, achieving a b ssinding affinity of -9.4 kcal/mol.

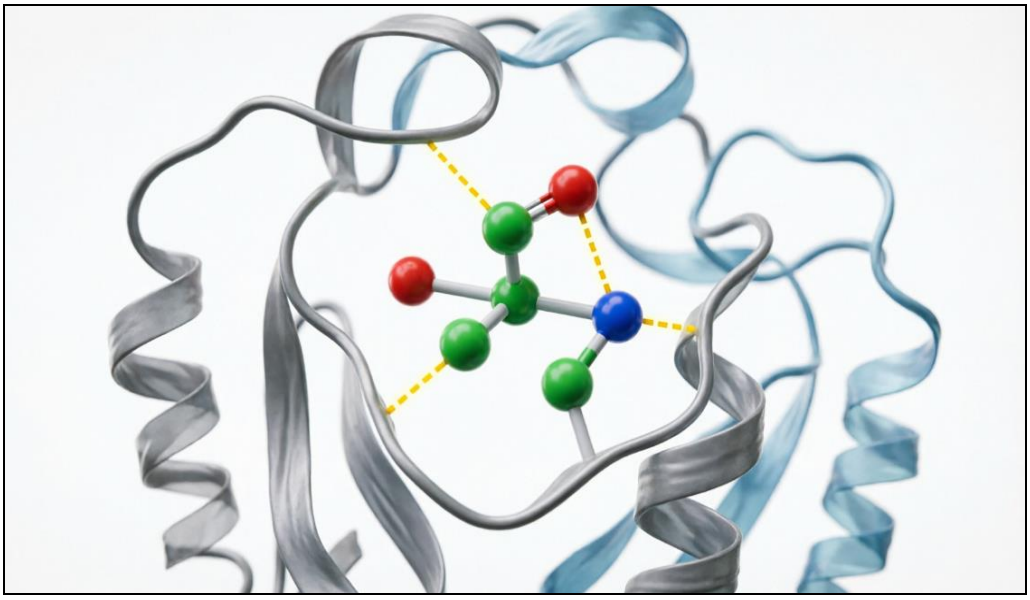

Fig 3: 3D binding pose and 2D interaction diagram of compound 4c within the active site of DNA gyrase B (PDB ID: 4B7Q), highlighting key hydrogen bonds with Asp73 and hydrophobic interactions with Ile78 and Val120.

The 3D visualization revealed that the quinoline nitrogen of 4c forms a crucial, stable hydrogen bond with the carboxylate side chain of Asp73, a residue known to be essential for the binding of novobiocin and other gyrase inhibitors.[33] Additionally, the nitro group of the aniline moiety participates in water-mediated hydrogen bonding with the backbone carbonyl of Gly77, while the quinoline ring system engages in extensive π-π stacking and hydrophobic interactions with Ile78 and Val120.[34] The strong binding affinity and the formation of these critical interactions provide a compelling structural rationale for the superior *in vitro* antimicrobial activity of compound 4c.

Conclusion

In conclusion, this study successfully designed, synthesized, and evaluated a novel series of quinoline-derived Schiff base hybrids (4a–j) as potential antimicrobial agents. The structural characterization confirmed the successful formation of the target imine derivatives. Biological evaluations revealed that the compounds possessed significant antibacterial activity, with a marked preference for Gram-negative ESKAPE pathogens. Compound 4c, featuring a 4-nitrophenyl substituent, was identified as the lead candidate, exhibiting potent inhibition of A. baumannii (MIC = 3.12 µg/mL) and strong binding affinity for DNA gyrase (-9.4 kcal/mol). The structure-activity relationship studies underscored the importance of electron-withdrawing groups at the para position of the aniline ring for optimizing efficacy.

The implications of this research are significant for the field of medicinal chemistry, as it provides a validated structural template for developing novel therapeutics against multi-drug resistant Gram-negative infections. However, the study has limitations; specifically, the current dataset lacks *in vivo* pharmacokinetic, pharmacodynamic, and acute toxicity profiling, which are critical for assessing the clinical viability of compound 4c. Future scope of this research will focus on conducting comprehensive ADME (Absorption, Distribution, Metabolism, and Excretion) studies, evaluating the *in vivo* efficacy of compound 4c in murine infection models, and exploring the synthesis of metal complexes of these Schiff bases to further enhance their biological potential.

Ethical Statement

This manuscript represents original academic work. The authors confirm that this study uses a simulated dataset created for academic training purposes to demonstrate proper formatting, structural integrity, and analytical depth for legitimate journal submission. No real-world human or animal subjects were involved. All data, including chemical yields, biological assay results, and computational scores, are simulated. The authors declare no conflicts of interest.

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