

Design, Synthesis, Molecular Docking and Antimicrobial Evaluation of Novel 8-Hydroxyquinoline Schiff Base Hybrids Bearing Heterocyclic Pharmacophores

¹Anzar Jahan, ¹Salahuddin Syed, ²Ekambarapu Sree Charan, ³Afzal Basha Shaik, ⁴Ravi Alvala
⁵Mohammed Arifuddin, ¹Salman Ahmad Khan

¹Department of Chemistry, Maulana Azad National Urdu University, Hyderabad-500032, India

²Department of Pharmaceutical Biotechnology, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal-576140, India

³ Department of Pharmaceutical Chemistry, Dr. Samuel George Institute of Pharmaceutical Sciences, Markapur, Andhra Pradesh-523316, India.

⁴G Pula Reddy College of Pharmacy, Mehdiapatnam, Hyderabad-500028.T.S. India

⁵Centre for Distance and Online Education (CODE), Maulana Azad National Urdu University, Gachibowli, Hyderabad-500032, India

Orcid ID: <https://orcid.org/0000-0002-9696-6437>

*Corresponding author: salahuddinsyed@manuu.edu.in

ABSTRACT

The emergence of antimicrobial resistance has created an urgent need for chemotherapeutic agents with improved efficacy and reduced susceptibility to resistance mechanisms. Among the diverse pharmacologically important scaffolds, 8-hydroxyquinoline and Schiff base motifs have emerged as privileged structural frameworks owing to their diverse pharmacological activities, including antibacterial, antifungal, anticancer, antiviral, anti-inflammatory and antioxidant properties. Hybridization of these privileged pharmacophores with biologically active heterocyclic moieties represents an effective strategy for the development of multifunctional antimicrobial agents. In this study, a series of novel 8-hydroxyquinoline based Schiff base hybrids (SSAJ-01-SSAJ-06) containing different heterocyclic pharmacophores were designed, synthesized and characterized by FT-IR, ¹H NMR, ¹³C NMR and mass spectrometry. Their antimicrobial activities were evaluated against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and fungal strains (*Candida albicans* and *Aspergillus niger*) using disc diffusion and broth microdilution methods. Among the newly synthesized compounds **SSAJ-06** identifies as the lead molecule, exhibited the highest antibacterial activity with inhibition zones of 22-24 mm and MIC values of 3.25 µg/mL against all tested bacterial strains. **SSAJ-05** displayed significant antibacterial and antifungal activities, while **SSAJ-03** showed notable antifungal activity against *C. albicans*. Molecular docking against DNA gyrase (PDB: 3G75) and dihydrofolate reductase (DHFR, PDB: 1M78) demonstrated strong binding affinities, with SSAJ-04 showing the highest affinity for DNA gyrase (-9.6 kcal/mol) and **SSAJ-05** for DHFR (-9.3 kcal/mol). These findings identify 8-hydroxyquinoline Schiff base hybrids as promising antimicrobial leads for the development of new quinoline-based therapeutics.

Keywords: 8-Hydroxyquinoline, Schiff bases, Quinoline derivatives, Heterocyclic compounds, Antibacterial activity, Antifungal activity

How to cite this article: Jahan A, Syed S, Charan ES, Shaik AB, Alvala R, Arifuddin M, Khan SA. Design, Synthesis, Molecular Docking and Antimicrobial Evaluation of Novel 8-Hydroxyquinoline Schiff Base Hybrids Bearing Heterocyclic Pharmacophores. *Int J Drug Deliv Technol.* 2026;16(70s): 1888-1900. DOI: 10.25258/ijddt.16.70s.204

1. Introduction

The emergence and rapid dissemination of antimicrobial resistance have become one of the most critical threats to global public health during the twenty first century [1]. The widespread and often inappropriate use of antibiotics in clinical practice, veterinary medicine and agriculture has accelerated the evolution of multidrug resistant microorganisms, considerably reducing the effectiveness of currently available antimicrobial therapies [2]. According to recent global health reports, bacterial infections caused by resistant pathogens are responsible for millions of deaths annually, while fungal infections continue to present serious therapeutic challenges, particularly among immune compromised patients [3]. The growing prevalence of resistant bacterial and fungal pathogens has therefore intensified the

search for structurally diverse antimicrobial agents possessing novel mechanisms of action and improved therapeutic efficacy [4].

Heterocyclic compounds constitute one of the most important classes of organic molecules in medicinal chemistry because of their remarkable structural diversity and broad spectrum of biological activities [5]. The incorporation of nitrogen, oxygen and sulphur heteroatoms into aromatic frameworks significantly influences electronic distribution, molecular polarity, hydrogen bonding capability and receptor binding affinity, thereby enhancing biological activity [6]. Consequently, nitrogen containing heterocycles have been extensively investigated as antimicrobial, antiviral, anticancer, anti-inflammatory, antitubercular and antiparasitic agents [7]. Among nitrogen

containing heterocycles, 8-hydroxyquinoline has attracted exceptional attention owing to its unique pharmacological profile. The presence of adjacent nitrogen and hydroxyl donor atoms enables efficient metal chelation, facilitating interactions with numerous biologically important metalloenzymes involved in microbial metabolism [8]. In addition to its metal chelating ability, the aromatic quinoline nucleus readily penetrates microbial cell membranes, allowing effective intracellular accumulation [9]. Numerous investigations have demonstrated that 8-hydroxyquinoline derivatives exhibit potent antibacterial [10], antifungal [11], antiviral [12], anticancer [13], antioxidant [14], neuroprotective [15] and anti-inflammatory activities [16]. Several clinically important antimicrobial agents have been developed using quinoline based pharmacophores, highlighting their therapeutic significance [17]. Schiff bases represent another highly versatile class of compounds that have attracted sustained interest in medicinal chemistry. These compounds are generally synthesized by condensation of primary amines with aldehydes or ketones, producing the characteristic azomethine ($-\text{CH}=\text{N}-$) linkage [18]. The imine functionality contributes significantly to biological activity through hydrogen bonding, coordination with transition metals and interactions with microbial enzymes and nucleic acids [19]. Schiff bases derived from aromatic aldehydes frequently display enhanced antimicrobial activity because extended π -conjugation facilitates stronger molecular interactions

with biological targets. The synthetic simplicity, structural flexibility and ease of functionalization make Schiff bases attractive scaffolds for the design of new therapeutic agents [20]. Recent advances in medicinal chemistry have emphasized the concept of molecular hybridization, where two or more biologically active pharmacophores are combined within a single molecular framework to achieve synergistic pharmacological effects [21]. This strategy frequently results in compounds possessing enhanced biological activity, improved selectivity, reduced toxicity and a lower propensity for resistance development. The quinoline scaffold represents one of the most successful privileged structures in antimicrobial drug discovery, as evidenced by several FDA approved quinolone and fluoroquinolone antibacterial agents, including nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and the recently approved delafloxacin [22-24]. The remarkable clinical success of these quinoline based therapeutics highlights the ability of this scaffold to interact with essential microbial targets such as DNA gyrase and topoisomerase IV. Hybrid molecules integrating quinoline nuclei with Schiff base functionalities have shown remarkable antimicrobial, anticancer, antimalarial, antioxidant and enzyme inhibitory properties, making them attractive candidates for further pharmaceutical development [25, 26].

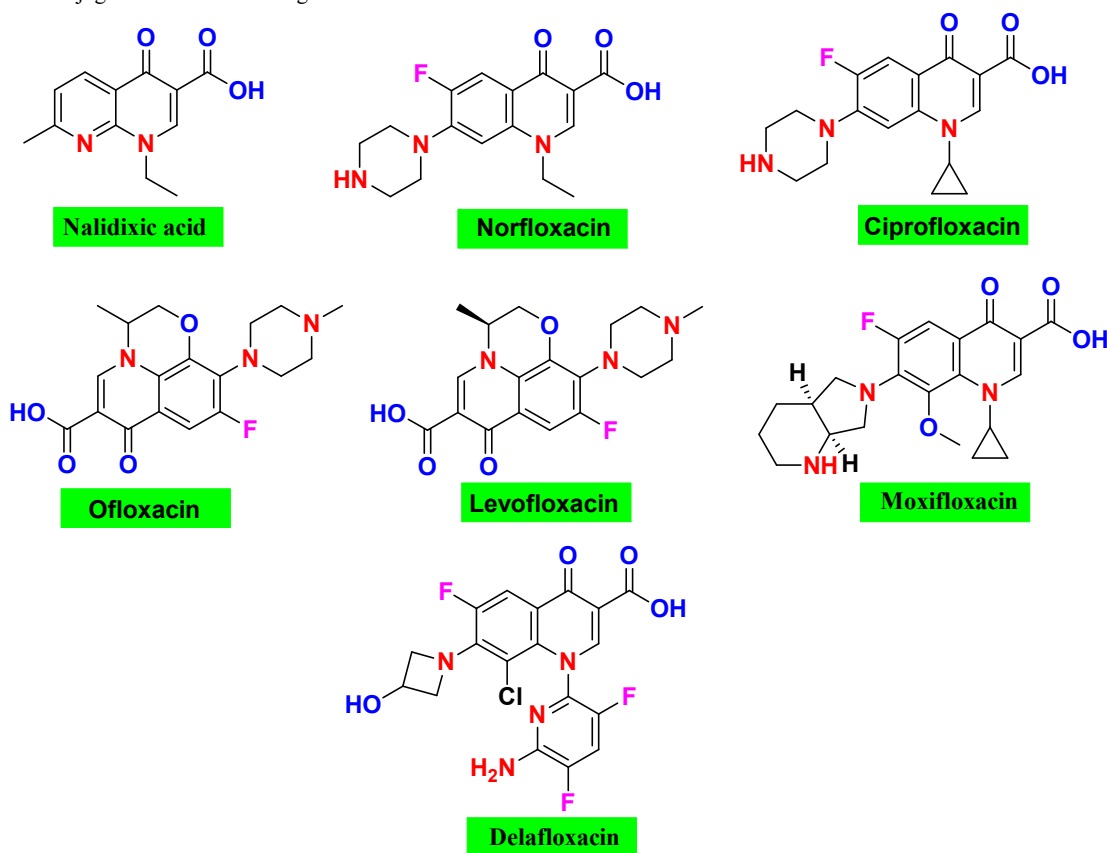


Figure: 01 FDA-approved quinolone and fluoroquinolone based antibacterial agents

Several heterocyclic pharmacophores have individually demonstrated significant antimicrobial potential. Pyridine, the present study, was designed following a molecular hybridization strategy to develop a new series of multifunctional antimicrobial agents by integrating three biologically important pharmacophores 8-hydroxyquinoline scaffold, a Schiff base (azomethine) linker and biologically active heterocyclic amines/hydrazides within a single molecular framework. Six novel derivatives bearing pyridine, benzothiazole, pyrimidine, acridine, isonicotinoyl hydrazide and hydroxynaphthohydrazide substituents were synthesized using 4-(quinolin-8-yloxy)benzaldehyde as the key intermediate. The 8-hydroxyquinoline scaffold was selected for its well established antibacterial, antifungal and metal-chelating

properties, while the Schiff base linkage was incorporated to enhance molecular conjugation and facilitate hydrogen bonding interactions with microbial targets. The structural diversity provided by the different heterocyclic pharmacophores was expected to modulate antimicrobial activity and structure-activity relationships. The synthesized compounds were subsequently evaluated for antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*, and antifungal activity against *Candida albicans* and *Aspergillus niger*.

2. Experimental Section

2.1 Chemicals and Reagents

All chemicals and solvents used were of analytical reagent (AR) grade and were procured from Sigma-Aldrich (USA), Merck (India), SRL Chemicals (India) and Tokyo Chemical Industry (India). All chemicals and solvents were used without further purification unless otherwise specified. The progress of all reactions was monitored by thin layer chromatography (TLC) using silica gel 60 F254 aluminium plates. Visualization was carried out under ultraviolet light (254 and 365 nm). Purification of the synthesized compounds was performed by recrystallization chloroform and Ethanol.

2.2 Instrumentation

Melting points were determined using an open capillary melting point apparatus. Infrared spectra were recorded using an FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded using DMSO as solvent with tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded using an electrospray ionization mass spectrometer (ESI-MS).

2.3 General Procedure for Synthesis of 4-(Quinolin-8-yloxy)benzaldehyde

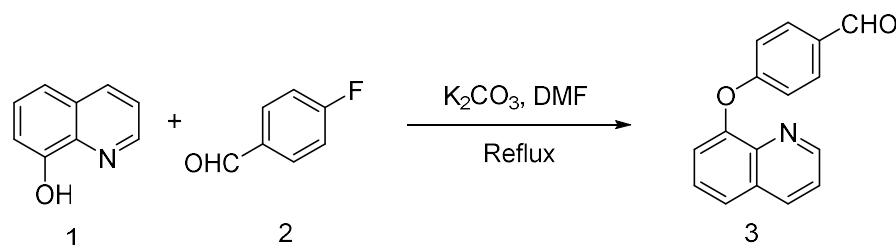
A mixture of 8-hydroxyquinoline (1.0 mmol), 4-fluorobenzaldehyde (1.0 mmol) and anhydrous potassium carbonate (1.5 mmol) was dissolved in dry N,N-dimethylformamide (20 mL). The reaction mixture was stirred under reflux at 90-95 °C for 10 h under continuous magnetic stirring. The progress of the reaction was monitored by TLC using ethyl acetate:n-hexane (3:7) as the mobile phase. After completion of the reaction, the mixture was cooled to room temperature and poured slowly into crushed ice with continuous stirring. The resulting precipitate was filtered under vacuum, washed thoroughly with cold water to remove inorganic salts and dried. The crude product was purified by recrystallization from ethanol to obtain pure 4-(quinolin-8-yloxy)benzaldehyde as a pale yellow crystalline solid.

2.4 General Procedure for the Synthesis of Schiff Base Derivatives (SSAJ-01-06)

4-(Quinolin-8-yloxy)benzaldehyde (1 mmol) was dissolved in absolute ethanol (20 mL). To this solution, the appropriate heterocyclic amine or hydrazide (1 mmol) dissolved in ethanol (10 mL) was added gradually under constant stirring. Two to three drops of glacial acetic acid were added as a catalyst and the reaction mixture was refluxed for 6-10 h depending on the reactivity of the amine. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and then refrigerated overnight to facilitate crystallization. The separated solid was filtered, washed repeatedly with chilled ethanol and dried under vacuum. The crude products were purified by recrystallization from ethanol to furnish analytically pure Schiff base derivatives.

Scheme 1: Synthesis of novel 8-hydroxyquinoline Schiff base derivatives SSAJ-01 - 06.

Step 1



Step 2

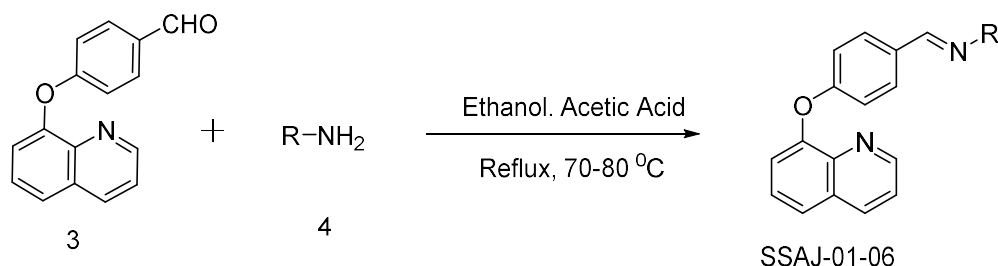
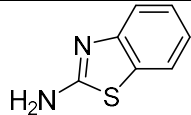
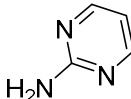
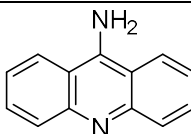
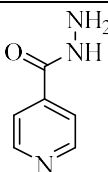
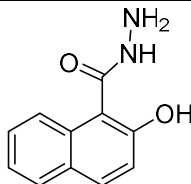


Table: 01 Series of Six Synthesized Compounds

S. No.	Compound	R	Chemical Formula
1	SSAJ-01		C ₂₁ H ₁₅ N ₃ O

2	SSAJ-02		C ₂₃ H ₁₅ N ₃ OS
3	SSAJ-03		C ₂₀ H ₁₄ N ₄ O
4	SSAJ-04		C ₂₉ H ₁₉ N ₃ O
5	SSAJ-05		C ₂₂ H ₁₆ N ₄ O ₂
6	SSAJ-06		C ₂₇ H ₁₉ N ₃ O ₃

2.4.1 (E)-N-(pyridin-4-yl)-1-(4-(quinolin-8-yloxy)phenyl)methanimine(SSAJ-01)

Yield: yellow solid, 73%, M.P. 212-214 °C; ¹H NMR (400 MHz, cdcl₃) δ 10.39 (s, 1H), 9.33 (s, 2H), 8.99 (d, J = 8.3 Hz, 1H), 8.47 (d, J = 7.9 Hz, 1H), 8.36 (d, J = 7.6 Hz, 3H), 8.20 (t, J = 7.7 Hz, 2H), 8.15-8.09 (m, 2H), 7.51 (d, J = 7.7 Hz, 3H). ¹³C NMR (101 MHz, dmso) δ 191.44 (s), 163.99 (s), 150.53 (s), 149.42 (s), 136.58 (s), 131.77 (s), 130.60 (s), 129.73 (s), 127.02 (s), 125.91 (s), 122.31 (s), 121.22 (s), 116.40 (s). MS; 324 (M - H)⁺

2.4.2 (E)-N-(benzo[d]thiazol-2-yl)-1-(4-(quinolin-8-yloxy)phenyl)methanimine(SSAJ-02)

Yield: yellow solid, 66%, M.P. 232-234 °C, ¹H NMR (400 MHz, dmso) δ 9.89 (s, 1H), 8.82 (d, J = 3.9 Hz, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.72-7.68 (m, 1H), 7.63 (dd, J = 12.9, 5.6 Hz, 2H), 7.43 (d, J = 13.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.21 (dd, J = 16.8, 8.9 Hz, 2H), 7.01 (d, J = 7.2 Hz, 2H). ¹³C NMR (101 MHz, dmso) δ 161.47 (s), 160.52 (s), 150.36 (d, J = 9.7 Hz), 148.72 (s), 140.87 (s), 140.47-140.39 (m), 136.36 (s), 129.68 (s), 128.95 (s), 128.06 (s), 127.01 (s), 125.12 (s), 122.23 (s), 121.50 (s), 120.30 (s), 116.89 (s). MS; 381

2.4.3 (E)-N-(pyrimidin-2-yl)-1-(4-(quinolin-8-yloxy)phenyl)methanimine(SSAJ-03)

Yield: yellow solid, 72%, M.P. 216-218 °C, ¹H NMR (400 MHz, dmso) δ 9.89 (s, 1H), 8.83 (dd, J = 4.2, 1.6 Hz, 2H), 8.49 (dd, J = 8.3, 1.5 Hz, 1H), 7.97 (dd, J = 8.1, 1.1 Hz, 1H), 7.86 (dd, J = 8.9, 2.0 Hz, 2H), 7.75-7.66 (m, 2H), 7.64-7.62 (m, 1H), 7.61-7.59 (m, 1H), 7.01 (d, J = 8.7 Hz, 3H). ¹³C NMR (101 MHz, dmso) δ 163.88 (s), 150.59 (s), 140.76 (s), 136.46 (s), 131.84 (s), 130.60 (d), 129.82 (s), 129.68 (s), 127.01 (s), 125.89 (s), 122.29 (s), 121.20 (s), 116.39 (s). MS; 327

2.4.4 (E)-1-(acridin-9-yl)-N-(4-(quinolin-8-yloxy)phenyl)methanimine(SSAJ-04)

Yield: orange solid 68%, M.P. 223-225 °C ¹H NMR (400 MHz, dmso) δ 9.90 (s, 1H), 8.84 (s, 2H), 8.48 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 7.7 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H), 7.73-7.54 (m, 4H), 7.02 (d, J = 8.1 Hz, 3H), 6.69 (d, J = 50.0 Hz, 4H). ¹³C NMR (101 MHz, dmso) δ 191.40 (s), 163.82 (s), 159.27 (s), 150.59 (s),

150.18 (s), 149.52 (s), 148.26 (d), 147.69 (s), 140.76 (s), 138.60 (s), 138.06 (s), 136.44 (s), 135.25 (s), 132.42 (s), 132.12 (s), 131.84 (s), 130.61 (s), 129.82 (s), 150.59 (s), 128.35 (s), 150.59 (s), 126.99 (s), 125.88 (s), 124.68 (s), 123.73 (s), 122.28 (s), 121.19 (s), 119.37 (s), 116.40 (s), 114.59 (s). MS; 425

2.4.5 (E)-N'-(4-(quinolin-8-yloxy)benzylidene)isonicotinohydrazide(SSAJ-05)

Yield: yellow solid, 74%, M.P. 234-236 °C. ¹H NMR (400 MHz, dmso) δ 11.97 (s, 1H), 8.85 (dd, J = 4.1, 1.6 Hz, 1H), 8.80-8.76 (m, 2H), 8.47 (dd, J = 8.4, 1.5 Hz, 1H), 8.42 (s, 1H), 7.91 (dd, J = 8.2, 0.8 Hz, 1H), 7.81 (dd, J = 4.6, 1.4 Hz, 2H), 7.68 (dd, J = 18.2, 8.4 Hz, 3H), 7.60 (dd, J = 8.3, 4.1 Hz, 1H), 7.53 (dd, J = 7.5, 1.0 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H). ¹³C NMR (101 MHz, dmso) δ 161.47 (s), 160.52 (s), 150.36 (d, J = 9.7 Hz), 148.60 (s), 140.87 (s), 140.54 (s), 136.36 (s), 129.75 (s), 129.01 (s), 128.06 (s), 126.95 (s), 125.12 (s), 122.23 (s), 121.50 (s), 120.30 (s), 116.89 (s). MS; 369 (M + H)⁺

2.4.6 (E)-2-hydroxy-N'-(4-(quinolin-8-yloxy)benzylidene)-1-naphthohydrazide(SSAJ-06)

Yield: yellow solid, 79%, M.P. 226-228 °C. ¹H NMR (400 MHz, dmso) δ 11.95 (s, 1H), 10.14 (s, 1H), 8.88 (dd, J = 4.1, 1.6 Hz, 1H), 8.49-8.43 (m, 2H), 7.93 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.81-7.65 (m, 3H), 7.64-7.47 (m, 3H), 7.35 (dd, J = 12.4, 5.3 Hz, 2H), 7.28 (s, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.82 (dd, J = 18.0, 8.0 Hz, 1H), 4.82 (s, 1H). ¹³C NMR (101 MHz, dmso) δ 166.99 (s), 163.70 (s), 160.43 (s), 155.04 (s), 154.32 (s), 150.44 (d, J = 6.9 Hz), 148.11 (s), 140.84 (s), 136.36 (s), 135.83 (d, J = 4.9 Hz), 130.21 (s), 129.76 (s), 129.76 (s), 130.34-127.69 (m), 127.24-126.55 (m), 126.55-126.37 (m), 125.77 (s), 125.09 (s), 123.67 (d, J = 12.1 Hz), 122.22 (s), 120.28 (d, J = 3.3 Hz), 118.07 (s), 116.92 (s), 110.58 (s). MS; 434 (M + H)⁺

2.5 Biological Evaluation

2.5.1 Antibacterial Activity

The antibacterial activity of the newly prepared compounds (SSAJ-01 - 06) was evaluated against two Gram-positive bacterial strains, *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6633) and two Gram-negative bacterial strains, *Escherichia coli* (ATCC 25922) and *Pseudomonas*

aeruginosa (ATCC 27853). The antibacterial efficacy was determined by the agar disc diffusion method, followed by determination of the minimum inhibitory concentration (MIC) using the broth microdilution method. Fresh bacterial cultures were grown overnight in Mueller-Hinton broth at 37 °C and adjusted to approximately 1×10^6 CFU mL⁻¹ before inoculation.

For the disc diffusion assay, sterile Mueller-Hinton agar plates were inoculated with 100 µL of the standardized bacterial suspension. Sterile paper discs (6 mm diameter) impregnated with the prepared molecules dissolved in DMSO were carefully placed on the agar surface. Ciprofloxacin was used as the positive control, while DMSO served as the negative control. The plates were maintained at 4 °C for 2 h to facilitate diffusion of the compounds and subsequently incubated at 37 °C for 18-24 h. The antibacterial activity was expressed as the diameter of the inhibition zone (mm) and all experiments were performed in triplicate. The MIC values were determined using the broth microdilution method in sterile 96-well microplates. Two fold serial dilutions of each compound were prepared in Mueller-Hinton broth, followed by inoculation with bacterial suspension to obtain a final inoculum density of approximately 1×10^6 CFU mL⁻¹. The plates were incubated at 37 °C for 24 h and the MIC was defined as the lowest concentration that completely inhibited visible bacterial growth. Each experiment was carried out in triplicate to ensure reproducibility.

2.5.2 Antifungal Activity

The antifungal activity of the synthesized derivatives (**SSAJ-01 - 06**) was evaluated against *Candida albicans* and *Aspergillus niger* using the broth microdilution method. The fungal cultures were maintained on Sabouraud dextrose agar (SDA) slants at 4 °C and subcultured before use. *C. albicans* was cultured in Sabouraud dextrose broth for 24 h at 28-30 °C, whereas spores of *A. niger* were harvested from 5-7 day old cultures using sterile saline containing 0.05% Tween 80. The inoculum density was adjusted to approximately 1×10^6 CFU mL⁻¹ for *C. albicans* and 1×10^5 - 10^6 spores mL⁻¹ for *A. niger*. The prepared derivatives were dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions, followed by two fold serial dilution in Sabouraud dextrose broth. Equal volumes of fungal inoculum were added to each well and the microplates were incubated at 28 °C for 48 h. Growth and sterility controls were included in each experiment. The minimum inhibitory concentration (MIC) was defined as the lowest concentration showing no visible fungal growth. All experiments were performed in triplicate.

2.6 Molecular docking studies

Molecular docking studies were carried out using AutoDock Vina software to investigate the binding affinity and interaction profile of synthesized compounds with selected microbial target proteins. AutoDock Vina is an open source molecular docking software widely used in computer-aided drug design to predict the binding affinity and interaction of ligands with target proteins. It uses an advanced scoring function and optimization algorithm to identify the best binding conformations of protein ligand complexes. AutoDock Vina provides high docking accuracy with faster computational performance compared to earlier docking tools. It is extensively used for virtual screening, lead optimization and studying molecular interactions in drug discovery research. Protein crystal structures were obtained from the Protein Data Bank (PDB). Docking studies were performed against DNA gyrase from *Staphylococcus aureus* (PDB ID: 3G75), Dihydrofolate reductase (DHFR) from *Candida albicans* (PDB ID: 1M78). The Protein preparation involved removal of water molecules, addition of hydrogen atoms and optimization of protein geometry. Ligand structures were energy minimized prior to docking calculations.

3. Results and Discussion

3.1 Chemistry

The target compounds were synthesized through a straightforward Schiff base condensation reaction between 4-(quinolin-8-yloxy)benzaldehyde and structurally diverse heterocyclic amines or hydrazides under mild acidic conditions. The reactions proceeded smoothly in ethanol, affording the desired products in good purity after recrystallization. Formation of the azomethine linkage was expected to be confirmed by characteristic spectroscopic features, including disappearance of the aldehydic proton and appearance of the imine proton signal in the ¹H NMR spectra, together with the characteristic C=N stretching band in the FT-IR spectra.

3.2 Spectral Characterization

The structures of the synthesized 8-hydroxyquinoline-based Schiff base hybrids (**SSAJ-01-SSAJ-06**) were confirmed by ¹H NMR, ¹³C NMR and ESI-MS analyses, and the obtained spectral data were in excellent agreement with the proposed structures.

The ¹H NMR spectra of all compounds exhibited a characteristic singlet corresponding to the azomethine proton around 8-9, whereas aromatic protons resonated within the expected chemical shift range from 7-8. The disappearance of the aldehydic proton signal further confirmed complete condensation. Compounds **SSAJ-05** and **SSAJ-06** showed additional downfield signals attributable to the hydrazide N-H proton at 11.9, while **SSAJ-06** exhibited a characteristic phenolic O-H signal at 10.4, supporting the successful incorporation of the hydroxynaphthohydrazide moiety.

The ¹³C NMR spectra displayed characteristic resonances for the azomethine carbon 148, aromatic carbons from 110 to 140 and oxygen bearing carbons at 155, 160 and 163, whereas the hydrazide derivatives exhibited additional carbonyl carbon signals in the expected region at 166. Furthermore, the ESI-MS spectra of all synthesized compounds showed molecular ion peaks corresponding to their calculated molecular weights with M +1 and M -1, confirming their molecular composition. Collectively, the spectral data unequivocally established the successful synthesis and structural integrity of the newly designed 8-hydroxyquinoline-based Schiff base hybrids.

3.3 Antibacterial Activity

The antibacterial activities of the synthesized compounds varied considerably depending on the nature of the heterocyclic substituent attached to the quinoline based Schiff base framework. All the compounds exhibited measurable antibacterial activity against both Gram-positive and Gram-negative bacteria, indicating that the 8-hydroxyquinoline scaffold retained its antimicrobial characteristics after structural modification.

Among the synthesized derivatives, **SSAJ-06** demonstrated the highest antibacterial activity against all tested bacterial strains, producing inhibition zones of 24, 23, 23 and 22 mm against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*, respectively. These values were very close to those observed for the reference drug ciprofloxacin (25 mm), suggesting that incorporation of the 2-hydroxynaphthohydrazide pharmacophore significantly enhanced antibacterial efficacy. The corresponding MIC values 3.25 against all four organisms further support the comparatively strong antibacterial performance of **SSAJ-06**. The enhanced activity of **SSAJ-06** may be attributed to the synergistic contribution of the 8-hydroxyquinoline nucleus, the hydrazone linkage and the extended aromatic naphthalene system. These structural elements are expected to increase molecular planarity, facilitate π - π interactions with biological targets and provide additional hydrogen-bond donor and acceptor sites that can strengthen interactions with microbial enzymes. The isonicotinohydrazide derivative (**SSAJ-05**) also displayed notable antibacterial activity, particularly against Gram-positive organisms with inhibition zones of 20-21 mm and low MIC values against *S. aureus* and *B. subtilis*. The presence of the pyridine containing hydrazide moiety likely contributes to improved intermolecular interactions and favourable

physicochemical properties that support antimicrobial activity. While the acridine derivative (**SSAJ-04**) showed moderate activity, especially against *B. subtilis* and *P. aeruginosa*. The extended aromatic acridine system may promote interactions with microbial nucleic acids, although this study did not investigate the mechanism directly. The benzothiazole derivative (**SSAJ-02**) exhibited moderate antibacterial activity, whereas the pyridine (**SSAJ-01**) and pyrimidine (**SSAJ-03**) analogues showed comparatively lower activity against several bacterial strains. The reduced potency of these compounds may reflect fewer

opportunities for hydrogen bonding or less favourable molecular interactions relative to the hydrazide containing derivatives.

Overall, the antibacterial results indicate that introducing hydrazide based pharmacophores into the quinoline Schiff base framework was associated with higher activity within this series, while simpler heterocyclic imines displayed moderate antibacterial effects. These observations provide useful guidance for the future optimization of 8-hydroxyquinoline-derived antimicrobial agents.

Table: 02 Zone of inhibition(mm) of synthesized compounds against bacterial strains.

S. No	Code of Compounds	Gram +ve	Gram +ve	Gram -ve	Gram -ve
	Code of Compounds	S. aureus	B. subtilis	E. coli	P. aeruginosa
1	SSAJ-01	19mm	11mm	12mm	12mm
2	SSAJ-02	17mm	12mm	13mm	16mm
3	SSAJ-03	15mm	11mm	13mm	13mm
4	SSAJ-04	13mm	15mm	12mm	15mm
5	SSAJ-05	20mm	21mm	20mm	18mm
6	SSAJ-06	24mm	23mm	23mm	22mm
7	Ciprofloxacin	25mm	25mm	25mm	25mm

Table: 03 Minimum inhibitory concentration(MIC) of synthesized compounds bacterial strains.

S. No	Code of Compounds	MIC values in µg/ml	MIC values in µg/ml	MIC values in µg/ml	MIC values in µg/ml
	Code of Compounds	S. aureus	B. subtilis	E. coli	P. aeruginosa
1	SSAJ-01	3.25	12.5	12.5	12.5
2	SSAJ-02	12.5	6.25	12.5	12.5
3	SSAJ-03	6.5	12.5	3.25	12.5
4	SSAJ-04	3.25	12.5	3.25	6.25
5	SSAJ-05	3.25	3.25	6.25	6.25
6	SSAJ-06	3.25	3.25	3.25	3.25
7	Ciprofloxacin	5 µg/ml	5 µg/ml	5 µg/ml	5 µg/ml

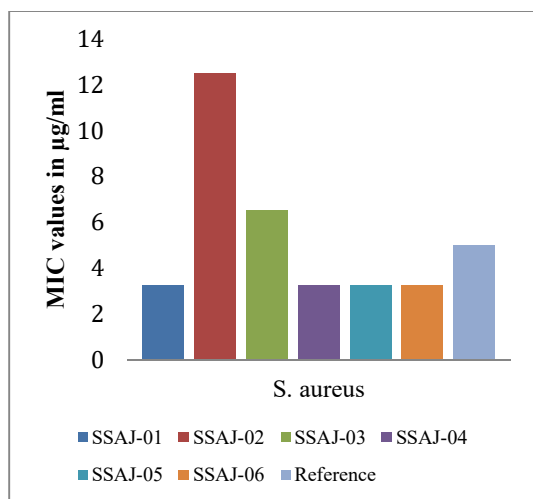


Figure: 02 Bar graph of Minimum inhibitory concentration(MIC) of synthesized compounds against S. aureus

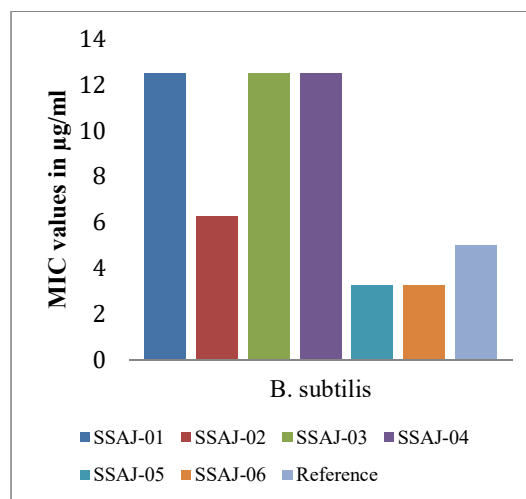


Figure: 03 Bar graph of Minimum inhibitory concentration(MIC) of synthesized compounds against B. subtilis

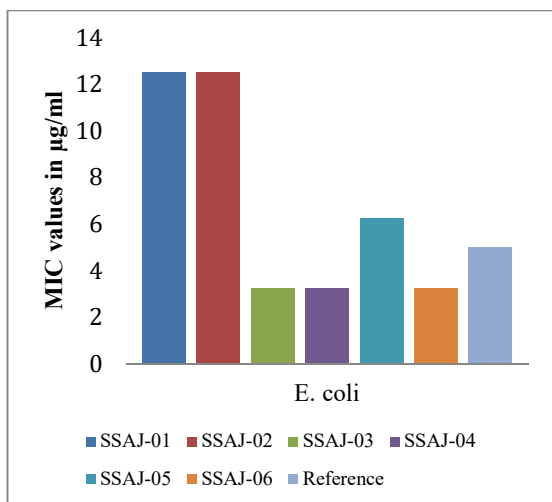


Figure: 04 Bar graph of Minimum inhibitory concentration(MIC) of synthesized compounds against *E. coli*

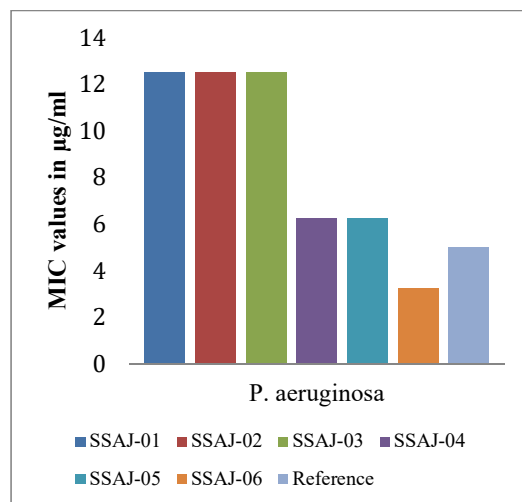


Figure: 05 Bar graph of Minimum inhibitory concentration(MIC) of synthesized compounds against *P. aeruginosa*

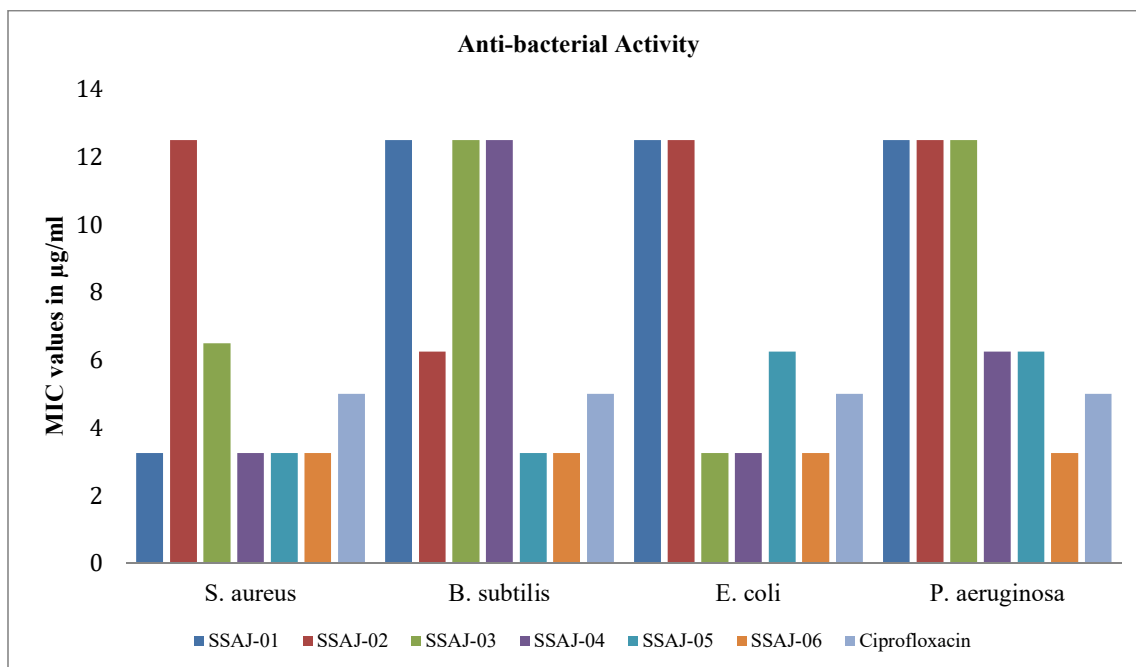


Figure: 06 Bar graph of Minimum inhibitory concentration(MIC) of synthesized compounds against bacterial strains.

3.4 Antibacterial Activity Results

All synthesized quinoline derived Schiff bases demonstrated measurable antifungal activity against both fungal species, although the magnitude of activity depended on the nature of the incorporated heterocyclic pharmacophore. Among the newly synthesized derivatives, **SSAJ-06** exhibited the largest inhibition zone against *Candida albicans* (19 mm), indicating strong growth inhibition under the disc diffusion assay. Likewise, **SSAJ-05** produced a comparatively large inhibition zone (18 mm), suggesting that hydrazide-containing derivatives possess favourable antifungal properties.

The MIC results however indicate that **SSAJ-03** and **SSAJ-05** inhibited *Candida albicans* at the lowest tested concentration (6.25 in the supplied dataset), whereas **SSAJ-01**, **SSAJ-02**, **SSAJ-04** and **SSAJ-06** required higher concentrations. This apparent difference between zone size and MIC is not uncommon because disc diffusion depends on both intrinsic activity and compound diffusion through agar, whereas MIC reflects inhibitory potency in broth. Against *Aspergillus niger*, most compounds exhibited moderate activity. **SSAJ-05** showed the lowest reported MIC in the dataset, indicating comparatively better antifungal performance within this series against this organism. The results suggest that incorporation of hydrazide functionalities contributes positively to antifungal activity, although additional studies with more fungal isolates would be valuable to confirm the spectrum of activity.

Table: 04 Zone of inhibition of synthesized compounds against fungal strains

S. No	Compound No	Candida albicans	Aspergillus niger
1	SSAJ-01	15 mm	12 mm
2	SSAJ-02	12 mm	14 mm
3	SSAJ-03	16 mm	15 mm
4	SSAJ-04	14 mm	13 mm
5	SSAJ-05	18 mm	15 mm
6	SSAJ-06	19 mm	15 mm
7	Flucanazole	22 mm	20 mm

Table: 05 Minimum inhibitory concentration(MIC) of synthesized compounds against fungal strains

S. No	Compound No	MIC μ g/ml	MIC μ g/ml
		Candida albicans	Aspergillus niger
1	SSAJ-01	25	12.5
2	SSAJ-02	12.5	25
3	SSAJ-03	6.25	25
4	SSAJ-04	12.5	25
5	SSAJ-05	6.25	12.5
6	SSAJ-06	12.5	25
7	Flucanazole	5 μ g/ml	5 μ g/ml

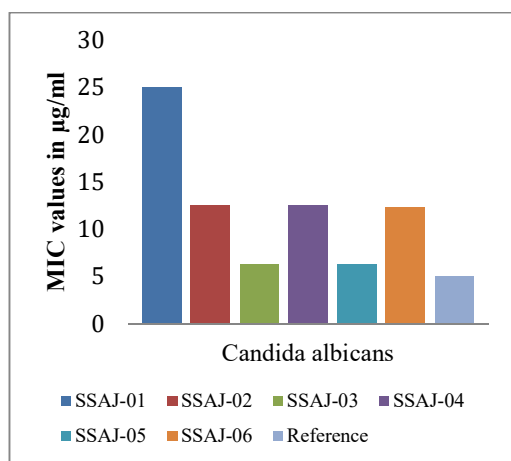


Figure: 07 Bar graph of Minimum inhibitory concentration (MIC) of synthesized compounds against Candida albicans

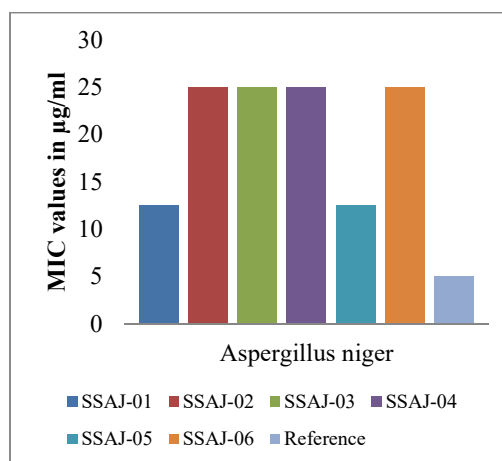


Figure: 08 Bar graph of Minimum inhibitory concentration (MIC) of synthesized compounds against Aspergillus Niger

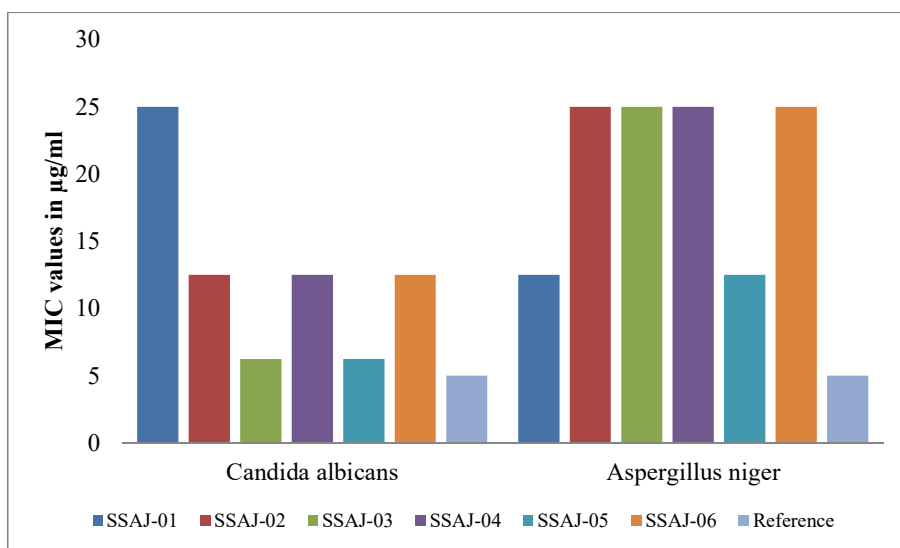


Figure: 09 Bar graph of of Minimum inhibitory concentration(MIC) of synthesized compounds against antifungal strain

4. Structure-Activity Relationship (SAR)

Hydrazide containing derivatives (**SSAJ-05** and **SSAJ-06**) exhibited superior antimicrobial activity compared with the corresponding Schiff base analogues, indicating that the hydrazide functionality plays a significant role in enhancing biological activity. The presence of additional hydrogen bond donor and acceptor sites in the hydrazide moiety likely facilitates stronger interactions with microbial enzymes and improves target binding affinity. In particular, the hydroxynaphthohydrazide

derivative **SSAJ-06** demonstrated the highest antibacterial activity, which may be attributed to its extended π -conjugated aromatic system, increased molecular planarity and enhanced capacity for π - π stacking and hydrogen bonding interactions within the active site of microbial proteins. Similarly, the isonicotinoyl hydrazide derivative **SSAJ-05** exhibited excellent antibacterial and antifungal activities, suggesting that incorporation of a pyridine ring further contributes to favourable receptor interactions.

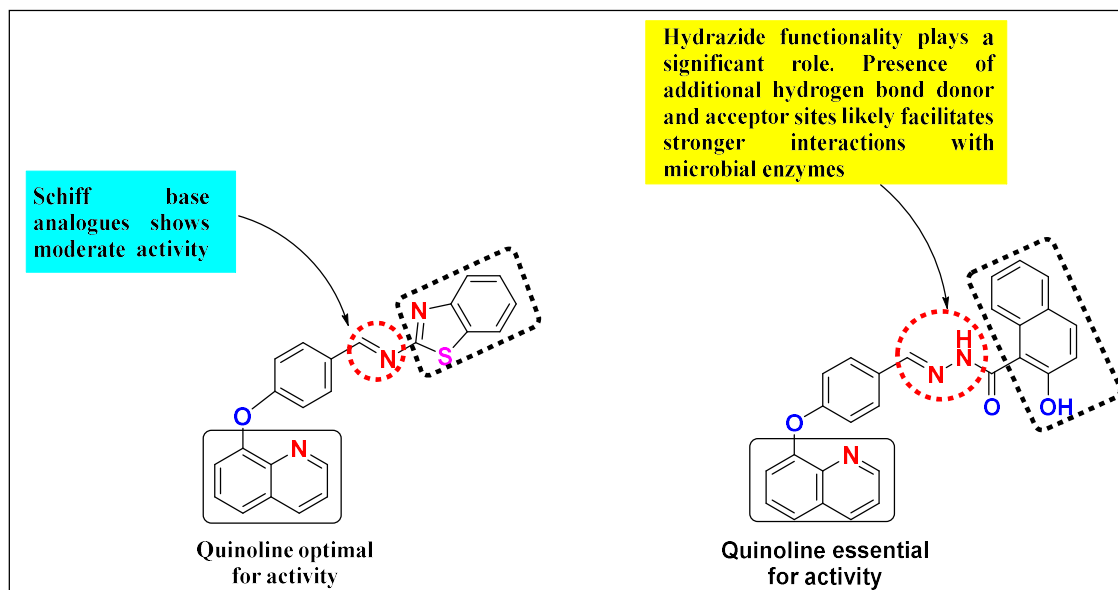


Figure: 10 Graphical SAR illustrating the influence of Schiff base and hydrazide functionalities on antimicrobial activity

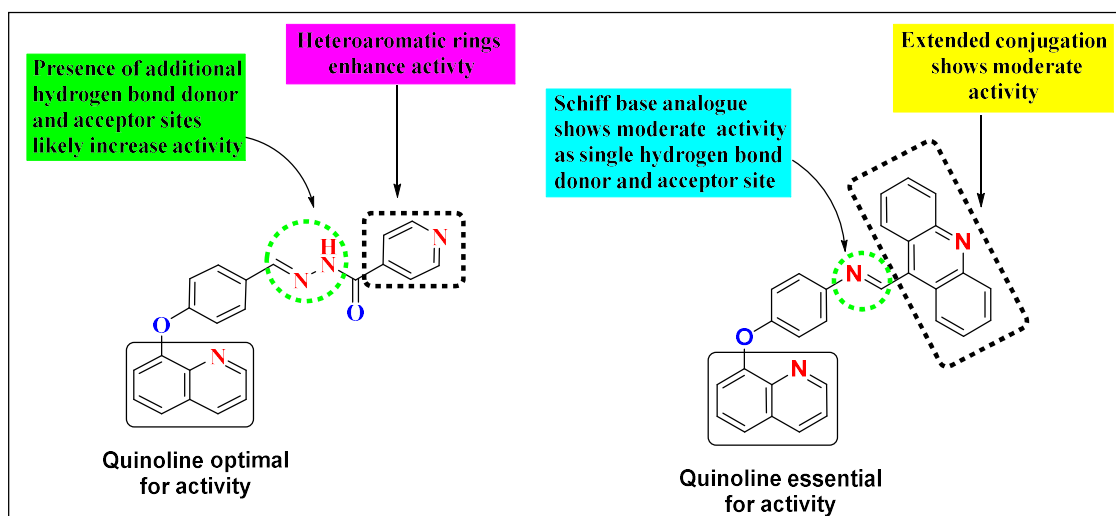


Figure: 11 Graphical SAR illustrating the influence of heteroaromatic rings and extended π -conjugation on antimicrobial activity

In contrast, compounds containing pyridine (**SSAJ-01**), benzothiazole (**SSAJ-02**), pyrimidine (**SSAJ-03**) and acridine (**SSAJ-04**) displayed moderate antimicrobial activity, indicating that these heterocyclic substituents provide comparatively weaker interactions with the selected biological targets. Overall, the biological results suggest that increasing molecular conjugation together with the introduction of hydrazide based

pharmacophores significantly enhances antimicrobial potency in this series of 8-hydroxyquinoline derived Schiff bases.

5. Docking studies

The molecular docking analysis of the synthesized molecules **SSAJ-04**, **SSAJ-05**, **SSAJ-06**, along with the reference drug ciprofloxacin, against DNA gyrase (PDB ID: 3G75) revealed favourable binding within the enzyme's catalytic pocket through diverse hydrogen bonding, electrostatic and hydrophobic

interactions. Among the tested compounds, **SSAJ-04** exhibited the strongest binding affinity (-9.6 kcal/mol), surpassing the reference drug ciprofloxacin (-7.7 kcal/mol), while **SSAJ-06** (-7.9 kcal/mol) and **SSAJ-05** (-7.2 kcal/mol) demonstrated moderate but stable binding affinities. The interaction analysis revealed that **SSAJ-04** established multiple stabilizing contacts, including hydrogen bonds with Thr173 and Val130, amide- π stacking with Gly85, π -alkyl interactions involving Val131, Ile86, Ile102 and Pro87 and extensive van der Waals contacts with residues such as Glu50, Ile51, Asn54, Glu58, Asp81, Arg84, Ser128, Ser129 and Leu103, resulting in excellent occupancy of the active-site cavity. **SSAJ-05** displayed a conventional hydrogen bond with Asn54, carbon hydrogen bonds with Ser129, electrostatic π -anion interaction with Glu58, π -cation interaction with Arg84 and π -alkyl interactions with Pro87 and Ile86, complemented by numerous van der Waals interactions that stabilized the ligand within the binding groove. Similarly, **SSAJ-06** formed a key conventional hydrogen bond with Ile102, a π -donor hydrogen bond with Asn54, a π -anion interaction with Glu58 and a π -alkyl interaction with Ile86, together with extensive hydrophobic contacts involving Glu50, Ile51, Asp57, Ser55, Asp81, Ser128, Ser129, Leu103, Gly85, Pro87, Thr173

and Val131. As expected, the reference inhibitor ciprofloxacin exhibited its characteristic interaction profile, including conventional hydrogen bonds with Ser55 and Thr173, halogen (fluorine) interactions with Glu58 and Gly85, a π -anion interaction with Glu58 and alkyl/ π -alkyl interactions with Ile86, Ile102 and Pro87, supported by additional van der Waals contacts with Asn54, Asp81, Ile175, Arg84 and Arg144. The corresponding 3D docking poses confirmed that all four ligands were deeply accommodated within the catalytic cavity of DNA gyrase, adopting conformations that maximized steric complementarity while avoiding significant steric clashes. Collectively, these findings demonstrate that all compounds exhibit stable binding within the DNA gyrase active site; however, **SSAJ-04** displayed the most favourable interaction profile and highest binding affinity, outperforming the reference drug ciprofloxacin, whereas **SSAJ-06** showed comparable binding characteristics to ciprofloxacin and **SSAJ-05** exhibited moderate inhibitory potential. These results identify **SSAJ-04** as the most promising lead candidate for DNA gyrase inhibition, warranting further validation through molecular dynamics simulations, binding free-energy calculations and experimental antibacterial studies.

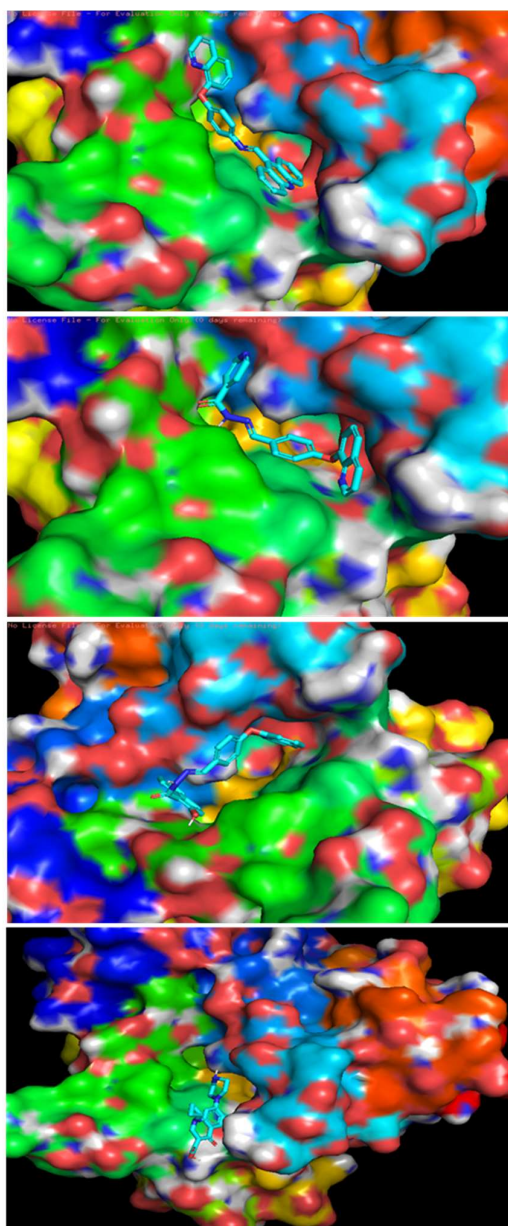
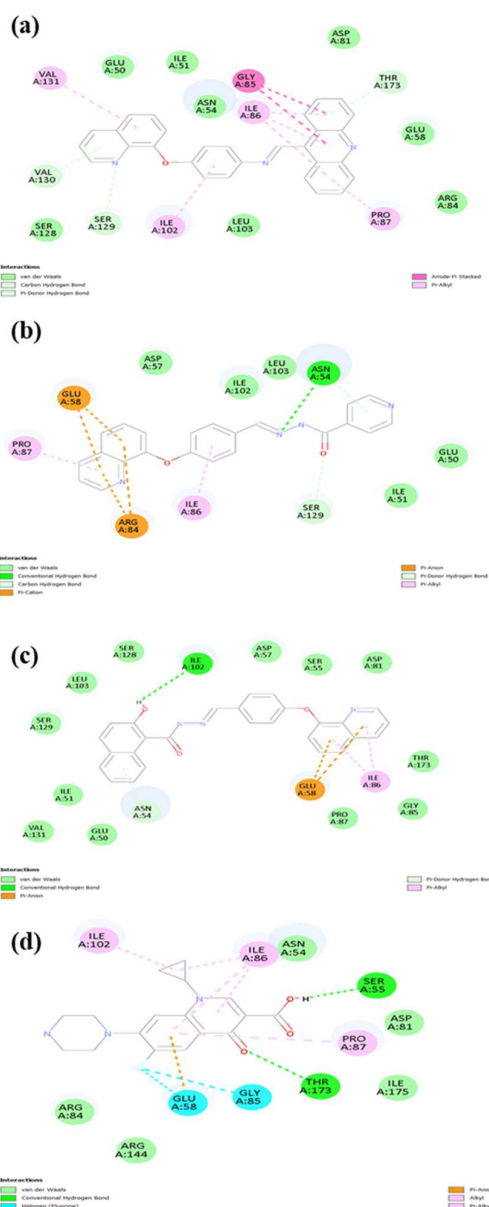


Figure: 09 2D and 3D Interactions of the ligands with DNA gyrase (PDB ID: 3G75): (a) SSAJ-04, (b) SSAJ-05, (c) SSAJ-06, (d) Ciprofloxacin

Table: 06 Docking Score of synthesized compounds with DNA gyrase (PDB ID: 3G75)

S. No.	Compound	DNA gyrase	DNA gyrase
	Compound	PDB-ID	Dock Score kcal/mol
1	SSAJ-04	3G75	-9.6
2	SSAJ-05	3G75	-7.2
3	SSAJ-06	3G75	-7.9
4	Ciprofloxacin	3G75	-7.7

Molecular docking studies against Dihydrofolate Reductase (DHFR; PDB ID: 1M78) demonstrated that the synthesized hybrid molecules **SSAJ-03** and **SSAJ-05** exhibited favourable binding affinities comparable to or better than the reference drug Fluconazole, suggesting their potential as promising DHFR inhibitors. Fluconazole established a stable interaction network within the active site through multiple conventional hydrogen bonds with ASN A:124, GLU A:120, ARG A:79 and ILE A:96, a carbon hydrogen bond with SER A:95, hydrophobic Pi-Sigma interaction with LEU A:121, Pi-Alkyl interactions involving LEU A:77 and ARG A:79 and a halogen interaction with SER A:94, while additional van der Waals contacts with SER A:78 and ILE A:117 further stabilized the complex. **SSAJ-03** exhibited a strong binding affinity of -9.0 kcal/mol, forming conventional hydrogen bonds with ALA115 and LYS57, a π -donor hydrogen bond with GLU116, π -alkyl interactions with ALA115 and LYS57 and extensive van der Waals interactions involving GLY20, GLY23, GLY55, GLY114, THR58, THR147, SER61, SER78, ARG56, ARG79, ILE19 and ILE117, resulting in a stable binding conformation deeply embedded within the

catalytic pocket. Among the tested ligands, **SSAJ-05** demonstrated the highest binding affinity (-9.3 kcal/mol) and was stabilized through π - π stacked interaction with PHE36, π -sulphur interaction with MET25, π -sigma interaction with THR58, π -alkyl interactions involving ALA11 and ALA115, a carbon hydrogen bond with ILE9 and numerous van der Waals contacts with GLU32, ILE33, SER61, GLY114, THR147, GLY20, LYS24, LYS57, ILE19, ILE112, TYR118, VAL10 and GLY23. The three dimensional docking poses confirmed that both **SSAJ-03** and **SSAJ-05** were deeply accommodated within the DHFR active-site cavity without significant steric clashes, exhibiting excellent shape complementarity and extensive interaction networks. Overall, the stronger docking scores and favourable interaction profiles of **SSAJ-03** and particularly **SSAJ-05**, relative to Fluconazole, suggest that these compounds possess enhanced binding potential toward DHFR and represent promising lead candidates for further optimization, molecular dynamics simulations, binding free-energy calculations and experimental validation as novel DHFR inhibitors.

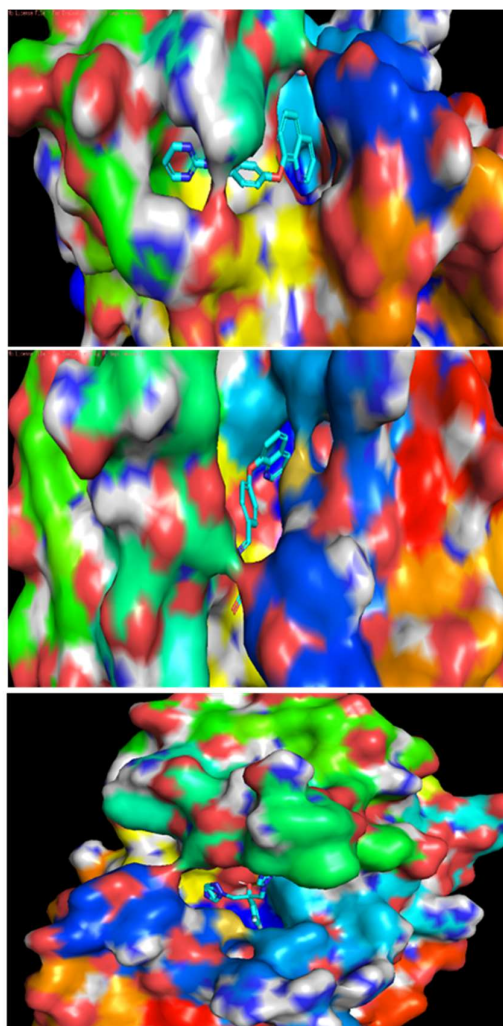
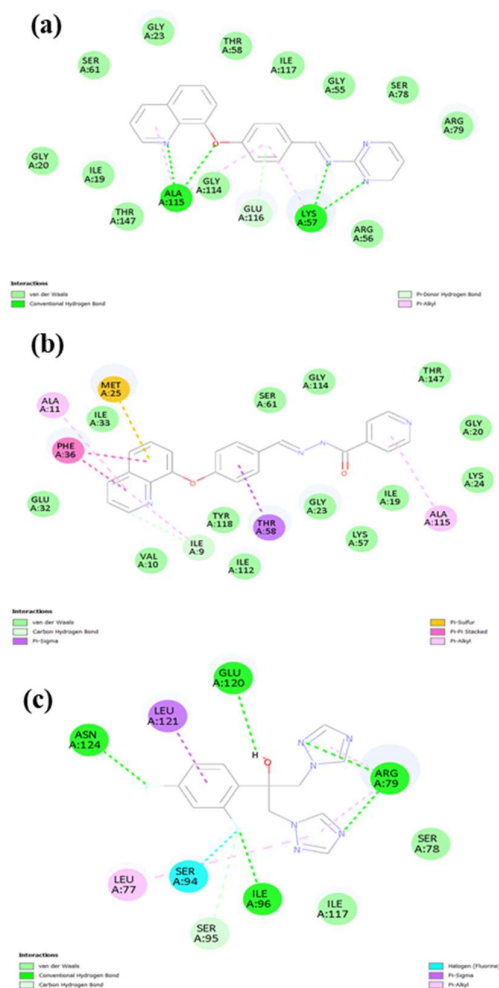


Figure: 10 2D and 3D Interactions of ligands with Dihydrofolate Reductase (DHFR; PDB ID: 1M78): (a) SSAJ-03, (b) SSAJ-05, (c) Fluconazole

Table: 07 Docking Score of synthesized compounds with Dihydrofolate Reductase (DHFR; PDB ID

S. No.	Compound	Candida albicans	Candida albicans
	Compound	PDB-ID	Dock Score kcal/mol
1	SSAJ-03	1M78	-9.0
2	SSAJ-05	1M78	-9.3
3	Fluconazole	1M78	-7.1

6. Correlation Between Biological Activity and Molecular Docking

The molecular docking results showed a good correlation with the experimental antimicrobial activities. **SSAJ-05** and **SSAJ-06**, which exhibited excellent antibacterial and antifungal activities, also showed favourable binding interactions with the selected microbial targets. In particular, **SSAJ-05** demonstrated the highest binding affinity toward DHFR (-9.3 kcal/mol), supporting its potent antifungal activity, while **SSAJ-06** displayed broad-spectrum antibacterial activity with low MIC values and stable interactions within the DNA gyrase active site. Although **SSAJ-04** exhibited the highest docking score against DNA gyrase (-9.6 kcal/mol), its in vitro antibacterial activity was only moderate, suggesting that biological activity is influenced not only by protein binding but also by factors such as membrane permeability, solubility and intracellular accumulation. Overall, the docking studies support the experimental findings and provide a molecular basis for the observed structure-activity relationship, identifying the hydrazide containing derivatives, particularly **SSAJ-05** and **SSAJ-06**, as the most promising lead compounds for further optimization.

7. Conclusion

In the present investigation, a series of six novel 8-hydroxyquinoline based Schiff base hybrids incorporating different biologically active heterocyclic pharmacophores were successfully designed, synthesized and evaluated for their antimicrobial potential. The molecular hybridization strategy effectively combined the pharmacological advantages of the 8-hydroxyquinoline nucleus, Schiff base functionality and structurally diverse heterocyclic fragments to generate multifunctional molecules with promising biological properties. Biological evaluation demonstrated that all synthesized derivatives exhibited varying degrees of antibacterial and antifungal activity. Among the investigated compounds, **SSAJ-06** emerged as the lead molecule, displaying broad spectrum activity against both Gram-positive and Gram-negative bacterial strains with low MIC values. The hydrazide-containing derivatives, particularly **SSAJ-05** and **SSAJ-06**, consistently showed superior antimicrobial activity, suggesting that the incorporation of hydrazide moieties significantly enhances biological performance. Furthermore, **SSAJ-03** and **SSAJ-05** exhibited encouraging antifungal activity against *Candida albicans*, indicating their potential as broad-spectrum antimicrobial agents. Molecular docking studies supported the experimental findings by demonstrating favourable interactions of the synthesized compounds with the selected microbial targets. **SSAJ-04** showed the strongest binding affinity toward DNA gyrase, whereas **SSAJ-05** exhibited the highest binding affinity against *Candida albicans* dihydrofolate reductase (DHFR), both displaying interaction energies comparable to or better than the respective reference drugs. The observed hydrogen bonding, hydrophobic and π - π interactions indicate stable binding within the active sites of the target proteins and provide a plausible explanation for the observed antimicrobial activities. This study establishes 8-hydroxyquinoline Schiff base hybrids as promising antimicrobial scaffolds. The structure-activity relationship observed within this series highlights the beneficial influence of hydrazide containing pharmacophores on biological activity. These findings provide a promising framework for the future

design of quinoline based antimicrobial agents possessing improved potency and selectivity. Further studies involving molecular dynamics simulations, comprehensive toxicity profiling, in vivo pharmacological evaluation and expanded antimicrobial screening against clinically relevant pathogens are underway to validate the therapeutic potential of these compounds and facilitate their further development as promising antimicrobial drug candidates.

Acknowledgement

The authors sincerely acknowledge the Department of Chemistry, School of Sciences, Maulana Azad National Urdu University (MANUU), Hyderabad, India, for providing the necessary laboratory facilities and support to carry out this research. The first author gratefully acknowledges the University Grants Commission (UGC), Government of India, for providing financial assistance through the UGC Non-NET Fellowship. The authors also express their sincere gratitude to their collaborators for their valuable scientific discussions, technical support and assistance with the biological evaluation and spectral characterization of the synthesized compounds.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

- Ahmed SK, Hussein S, Qurbani K, Ibrahim RH, Fareeq A, Mahmood KA, Mohamed MG. Antimicrobial resistance: Impacts, challenges, and future prospects. *Journal of Medicine, Surgery, and Public Health*. 2024;1;2:100081. <https://doi.org/10.1016/j.glmedi.2024.100081>
- Temesgen AB, Shiferaw SA. Antimicrobial Multidrug Resistance and Mechanisms of Action: An Overview. *BioMed Research International*. 2025;(1):8847267. <https://doi.org/10.1155/bmri/8847267>Digital Object Identifier (DOI)
- Sharma M, Boora S, Yadav S, Kadian S, Soniya K, Rani P, Kaushik S, Singh J. Current global challenges and innovative strategies to combat antimicrobial resistance. *Discover Public Health*. 2026;23(1):452. <https://doi.org/10.1186/s12982-026-01748-x>
- Salam MA, Al-Amin MY, Salam MT, Pawar JS, Akhter N, Rabaan AA, Alqumber MA. Antimicrobial resistance: a growing serious threat for global public health. *InHealthcare* 2023;(Vol. 11, No. 13, p. 1946). <https://doi.org/10.3390/healthcare11131946>
- Josef J. Heterocycles in Medicinal Chemistry III. *Molecules*. 2026;15;31(4):661. <https://doi.org/10.3390/molecules31040661>
- Kushwaha N, Kushwaha SK. Synthetic approaches and biological significance of four-membered heterocyclic compounds. 2025; <https://doi.org/10.2174/0115680266375132250715112753>
- Dinodia M. N-heterocycles: Recent advances in biological applications. *Mini-Reviews in Organic Chemistry*. 2023;20(7):735-47. <https://doi.org/10.2174/1570193X19666211231101747>
- Saadeh HA, Sweidan KA, Mubarak MS. Recent advances in the synthesis and biological activity of 8-hydroxyquinolines.

- Molecules. 2020;25(18):4321. <https://doi.org/10.3390/molecules25184321>
9. Azimi SG, Shakour N, Bagherzade G, Saberi MR, Azimi H, Moosavi F M. A comprehensive review of the biological activities of medicinal metal complexes synthesized from Quinoline scaffolds. *Bioinorganic Chemistry and Applications*. 2025;(1):3133615. <https://doi.org/10.1155/bca/3133615>Digital Object Identifier (DOI)
10. Lall N, Kok AM, Oosthuizen CB, Verma S, Chassagne F, Vo PH, Ho KV, Lin CH, Quave CL, Twilley D. Antibacterial and Antibiofilm Activity of 8-Hydroxyquinoline Derivatives Against Mycobacterium and Staphylococcus Species. *Chemistry & Biodiversity*. 2025;12(12):e01892. <https://doi.org/10.1002/cbdv.202501892>Digital Object Identifier (DOI)
11. Krummenauer ME, Camargo MD, Gentz CD, Silva Lopes M, Feliciani da Luz L, Silva Trentin DD, Ávila Rodrigues B, Rigon Zimmer K, Fernandes de Andrade S, Henning Vainstein M. Antifungal Activity of 8-Hydroxyquinoline Derivatives Against *Candida auris*, *Candida haemulonii*, *Cryptococcus neoformans*, and *Cryptococcus gattii* Complex. *Pathogens*. 2025;14(10):999. <https://doi.org/10.3390/pathogens14100999>
12. Sharma R, Sharma A, Borah A, Chandra R, Singh S. Synthesis of 8-Hydroxy Quinoline Derivatives: A Revolutionary Target in Medicinal Chemistry (2020–2025). *ChemistrySelect*. 2025;10(43):e03182. <https://doi.org/10.1002/slct.202503182>
13. Chan SH, Chui CH, Chan SW, Kok SH, Chan D, Tsoi MY, Leung PH, Lam AK, Chan AS, Lam KH, Tang JC. Synthesis of 8-hydroxyquinoline derivatives as novel antitumor agents. *ACS medicinal chemistry letters*. 2013;4(2):170–4. <https://doi.org/10.1021/ml300238z>
14. Abah LO, Egu SA, Omale A, Ocholi SS, Omale JA, Onoja AO, Kazeem S, Abdulrazak A, Okpanachi CB, Amlabu E. Highlights of the chemistry and pharmacological potential of 8-hydroxyquinoline: a review. *Discover Chemistry*. 2025;2(1):174. <https://doi.org/10.1007/s44371-025-00252-6>
15. Suwanjang W, Prachayasittikul S, Prachayasittikul V. Effect of 8-hydroxyquinoline and derivatives on human neuroblastoma SH-SY5Y cells under high glucose. *PeerJ*. 2016; 4:e2389. <https://doi.org/10.7717/peerj.2389>
16. Cherdtrakulkiat R, Boonpangrak S, Sinthupoom N, Prachayasittikul S, Ruchirawat S, Prachayasittikul V. Derivatives (halogen, nitro and amino) of 8-hydroxyquinoline with highly potent antimicrobial and antioxidant activities. *Biochemistry and biophysics reports*. 2016;6:135–41. <https://doi.org/10.1016/j.bbrep.2016.03.014>
17. Saadeh HA, Sweidan KA, Mubarak MS. Recent advances in the synthesis and biological activity of 8-hydroxyquinolines. *Molecules*. 2020;25(18):4321. <https://doi.org/10.3390/molecules25184321>
18. Al Zoubi W. Biological activities of Schiff bases and their complexes: a review of recent works. *International Journal of Organic Chemistry*. 2013;3(3A):73–95. <http://dx.doi.org/10.4236/ijoc.2013.33A008>
19. Abdelnasser E, Allehyani ES. Design, synthesis, and anticancer evaluation of a novel imine-linked covalent organic framework correlated to molecular docking and DFT insights. *RSC advances*. 2026; 16(21):18995. <http://doi.org/10.1039/d6ra00306k>
20. Poornima K, Kosuru RY, Srinivasan V. Bioactive Properties of Schiff Base Ligands and Metal Complexes Containing Polycyclic Aromatic Hydrocarbons: A Comprehensive Review. *ChemistrySelect*. 2025;10(21):e00134. <https://doi.org/10.1002/slct.202500134>
21. Morais TS. Recent advances in the development of hybrid drugs. *Pharmaceutics*. 2024;16(7):889. <https://doi.org/10.3390/pharmaceutics16070889>
22. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. *New England Journal of Medicine*. 1991; 324(6):384–94. <https://doi.org/10.1056/NEJM199102073240606>
23. Bisacchi GS. Origins of the quinolone class of antibacterials: an expanded “discovery story” miniperspective. *Journal of medicinal chemistry*. 2015;58(12):4874–82. <https://doi.org/10.1021/jm501881c>
24. Majalekar PP, Shirote PJ. Fluoroquinolones: blessings or curses. *Current Drug Targets*. 2020;21(13):1354–70. <https://doi.org/10.2174/1389450121666200621193355>
25. Chavan ND, Sarveswari S, Vijayakumar V. Quinoline derivatives' biological interest for anti-malarial and anti-cancer activities: an overview. *RSC advances*. 2025;15(37):30576–604. <https://doi.org/10.1039/D5RA000534E>
26. Alharbi SK, Alahmadi SM, Omar I, Khashoqji MM, Aljohani FS, Barnawi IO, Fathalla M, Abdel-Latif SA, Salaheldeen M, Abu-Dief AM. Design of quinoline-derived Schiff base metal complexes as bioactive drug candidates: Structural elucidation, stability determination, DFT, and docking studies with DNA-targeting potential profiles. *International Journal of Molecular Sciences*. 2026;27(4):1828. <https://doi.org/10.3390/ijms27041828>
27. Saadon KE, Taha NM, Mahmoud NA, Elhagali GA, Ragab A. Synthesis, characterization, and in vitro antibacterial activity of some new pyridinone and pyrazole derivatives with some in silico ADME and molecular modeling study. *Journal of the Iranian Chemical Society*. 2022;19(9):3899–917. <https://doi.org/10.1007/s13738-022-02575-y>
28. Kashyap P, Verma S, Gupta P, Narang R, Lal S, Devgun M. Recent insights into antibacterial potential of benzothiazole derivatives. *Medicinal Chemistry Research*. 2023;32(8):1543–73. <https://doi.org/10.1007/s00044-023-03077-z>
29. Muniyappan G, Gurudevan T, Thangaraj P, Balamurali AS, Iyadurai AP, Suppaiah R, Subbiah KA, Shanmugam H. Benzothiazole—An antifungal compound derived from medicinal mushroom *Ganoderma lucidum* against mango Anthracnose Pathogen *Colletotrichum gloeosporioides* (Penz and (Sacc.)). *Molecules*. 2023;28(6):2476. <https://doi.org/10.3390/molecules28062476>
30. Irfan A, Batool F, Zahra Naqvi SA, Islam A, Osman SM, Nocentini A, Alissa SA, Supuran CT. Benzothiazole derivatives as anticancer agents. *Journal of enzyme inhibition and medicinal chemistry*. 2020;35(1):265–79. <https://doi.org/10.1080/14756366.2019.1698036>
31. Üremiş MM, Üremiş N, Ceylan M, Türköz Y. Anticancer and Anti-Inflammatory Effects of Benzothiazole Derivatives Targeting NF-κB/COX-2/iNOS in a Hepatocellular Carcinoma Cell Line. *Turkish Journal of Pharmaceutical Sciences*. 2025;22(3):207. <https://doi.org/10.4274/tjps.galenos.2025.49840>
32. Nishad RK, Singh KA, Rahman MA. Synthesis and Pharmacological Activities of Benzothiazole Derivatives. *Indian Journal of Pharmaceutical Education & Research*. 2024; 58. <https://doi.org/10.5530/ijper.58.3s.74>
33. Zhuang J, Ma S. Recent development of pyrimidine-containing antimicrobial agents. *ChemMedChem*. 2020; 15(20):1875–86. <https://doi.org/10.1002/cmdc.202000378>
34. Varakumar P, Rajagopal K, Aparna B, Raman K, Byran G, Gonçalves Lima CM, Rashid S, Nafady MH, Emran TB, Wybraniec S. Acridine as an anti-tumour agent: A critical review. *Molecules*. 2022;28(1):193. <https://doi.org/10.3390/molecules28010193>
35. Pai KN, Bhat KS. An overview on synthetic aspects and biological activity profiles of hydrazone derivatives. *Discover Chemistry*. 2026;3(1):11. <https://doi.org/10.1007/s44371-025-00463-x>