INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES
(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijcrcps Coden: IJCROO(USA) Volume 13, Issue 5- 2026

Review Article

DOI: http://dx.doi.org/10.22192/ijcrcps.2026.13.05.002

Versatile Applications of Schiff Bases of Benzo pyridine Moiety: A Comprehensive Review

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Abstract

Schiff bases incorporating the benzo-pyridine framework, particularly derivatives of Quinoline and Isoquinoline have attracted sustained interest owing to their structural diversity, facile synthesis, and remarkable coordination versatility. The presence of an azomethine (–C=N–) linkage conjugated with a benzo-pyridine moiety endows these ligands with enhanced electron delocalization, tunable donor properties, and the ability to stabilize a wide range of metal ions in different oxidation states. This comprehensive review critically surveys recent advances in their diverse applications in antimicrobial, antifungal, anticancer, antioxidant, and anti-inflammatory studies are systematically discussed. By integrating recent literature findings, this review aims to provide a consolidated platform for understanding the versatile potential of benzo-pyridine-based Schiff bases and to stimulate future research toward the rational development of functional materials and therapeutically relevant metal complexes suitable for interdisciplinary scientific advancement.

Keywords: Benzo-pyridine, Schiff bases, Biological Applications

Introduction

Heterocyclic Schiff bases represent a versatile and rapidly expanding class of azomethine-containing compounds that have attracted sustained attention due to their structural diversity, facile synthesis, and wide-ranging functional applications. The incorporation of heteroatoms such as nitrogen, oxygen, and sulfur within cyclic frameworks significantly enhances their electronic properties, coordination behavior, and biological potential.[1] Owing to the presence of the imine (–C=N–) moiety, these compounds readily form stable complexes with transition and inner transition metal ions, exhibiting diverse geometries and tuneable physicochemical characteristics.[2] In recent years, heterocyclic Schiff bases have demonstrated remarkable applications in medicinal chemistry, including antimicrobial,[3] antituberclosis,[4] antiviral,[5] antioxidant,[6] and anticancer activities.[7]

Among the numerous subclasses of Schiff bases, those incorporating the benzo-pyridine moiety particularly derivatives of Quinoline have emerged as highly promising systems. The benzo-pyridine framework, consisting of a fused benzene and pyridine ring, provides an extended π-conjugated system that enhances electron delocalization and structural rigidity. Such features significantly influence the ligand's coordination behavior, redox properties, and overall stability of the resulting complexes.[8]The presence of the pyridine nitrogen in conjunction with the azomethine group creates multidentate coordination sites capable of stabilizing transition, lanthanide, and main-group metals in diverse oxidation states and geometries.[9] Furthermore, substitution at various positions of the benzo-pyridine nucleus enables fine-tuning of electronic density, lipophilicity, and steric hindrance, thereby modulating reactivity and biological performance.[10]Due to their frequent use as "parent" compounds, quinoline compounds have the potential to be beneficial in a variety of medical applications, including antimicrobial,[11] anticancer,[12] Antioxidant,[13] antitumor properties.[14]Additionally, it has been noted that transition metal complexes may increase Schiff bases' biological efficacy while reducing their cytotoxic effects.[15]

This comprehensive review critically summarizes recent advances in biological activity of Benzopyridine Schiff bases, while highlighting emerging research trends and future prospects in this dynamic and interdisciplinary field.

Synthetic Strategies of Quinoline Derivatives:

The conventional approach for synthesis of Quinolineis well established but often involves quite severe reaction conditions for efficient progression. The Doebner–Miller reaction is a traditional method for synthesising quinoline, including the condensation of aniline with a carbonyl molecule to get quinoline derivatives.[16]The Knorr Quinoline synthesis is a significant synthetic method that employs 2-aminobenzyl alcohols and ketones to yield quinoline frameworks with various substitution patterns.[17] Traditional synthetic approaches commonly require elevated reaction temperatures, strong acidic or basic catalysts, and prolonged heating, which may promote undesirable side reactions and the possible decomposition of sensitive functional groups. In addition, these methods often involve the use of volatile and hazardous organic solvents, such as benzene, toluene, and chloroform, posing potential risks to both researchers and the environment. Furthermore, the overall process is generally time-consuming, requiring extended reaction periods and additional purification steps, which reduces the efficiency and sustainability of the synthetic procedure.

Green approaches typically employ milder reaction conditions, thereby minimizing the risk of side reactions and decomposition of sensitive functional groups. These methods often utilize environmentally benign solvents such as water or ethanol, or even solvent-free conditions, reducing the environmental and health hazards associated with volatile organic solvents.

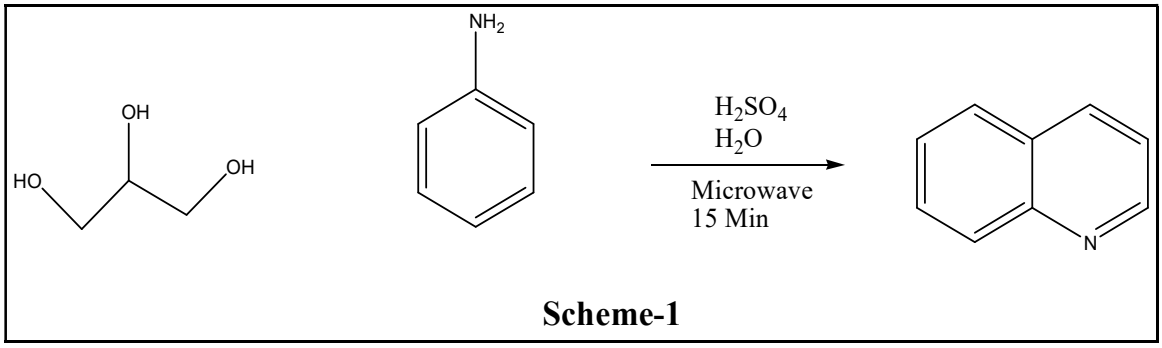
In addition, green synthesis frequently incorporates eco-friendly catalysts such as L-proline,[18] ionic liquids,[19] or heterogeneous catalysts,[20]which enhance reaction efficiency and selectivity. Techniques such as microwave-assisted synthesis, ultrasound irradiation, and multicomponent reactions further shorten reaction times and improve product yields.

Hanen S. et al.[21]devised an efficient one-pot green Skraup reaction conducted in an aqueous solution utilising glycerol as a cost-effective, plentiful, and eco-friendly reagent. In this approach, substituted anilines were subjected to reaction at 200 °C with catalytic H_2SO_4 under microwave irradiation for 15–20 minutes. The protocol afforded the desired quinoline derivatives in yields ranging from 10–66% for p-aminophenol substrates and 15–52% for nitroaniline substrates. The technique produced the desired quinoline derivatives with yields between 10–66% for p-aminophenol substrates and 15–52% for nitroaniline substrates (Scheme-1).

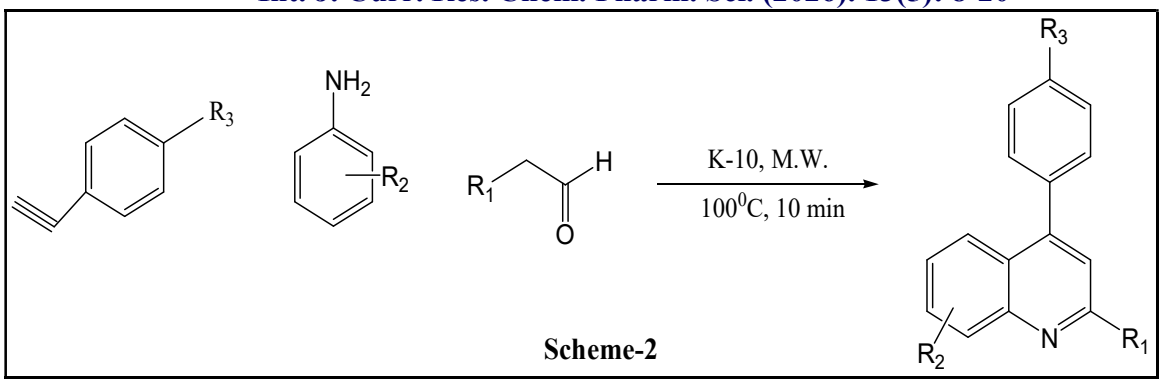
Aditya K. and Bela T.[22]reported an efficient three-component synthetic approach for the rapid preparation of substituted quinolines via the reaction of anilines, aldehydes, and 4-substituted phenylacetylenes. The transformation was carried out under microwave irradiation using montmorillonite K-10, a highly effective and environmentally benign solid acid catalyst. This method facilitated the rapid formation of the desired quinoline derivatives, affording high yields of 72–96% in just 10 minutes(Scheme-2).

Peng F. et al.[23]reported a novel and efficient one-pot sequential copper-catalyzed strategy for the synthesis of functionalized quinolines from substituted enamino esters and ortho-halogenated aromatic carbonyl compounds. The reaction was catalyzed by copper iodide (CuI) in the presence of L-proline at 120 °C for 18 hours, providing the desired quinoline derivatives in moderate to good yields ranging from 45–86%(Scheme-3).

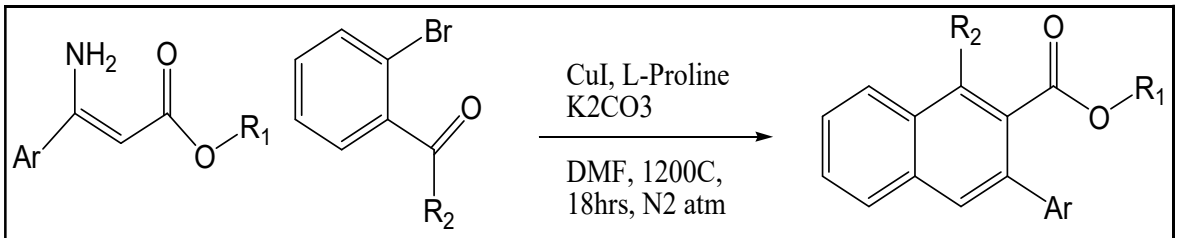
S. Tasqeerudin[24] described a one-pot, environmentally friendly, and efficient technique for synthesising quinoline derivatives from 2-aminoarylketones and active methylene compounds in the presence of L-proline and the ionic liquid 1,3-dimethylimidazolium methyl sulphate [MMIm] [MSO4]. The ionic liquid used as a catalyst can be reused numerous times. The approach has several advantages, including a quicker reaction time, softer conditions, easier workup, and higher yields. The catalyst [MMIm][MSO4] can be recovered for further reactions and reused with no significant loss of efficiency (Scheme-4).



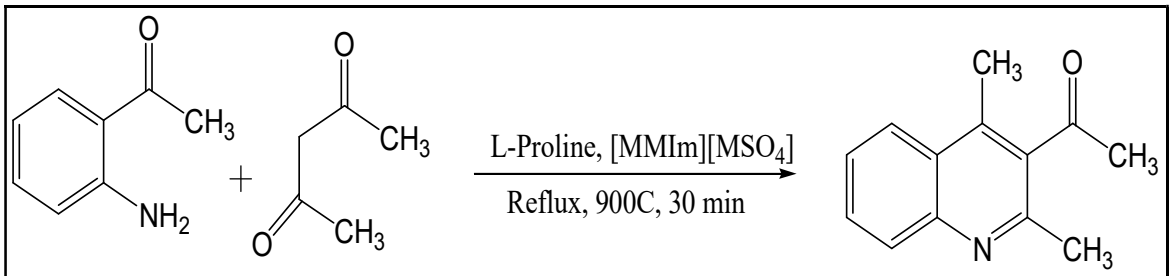
Scheme-1



Scheme-2



Scheme-3



Scheme-4

Diverse Applications of Quinoline Shiff Bases

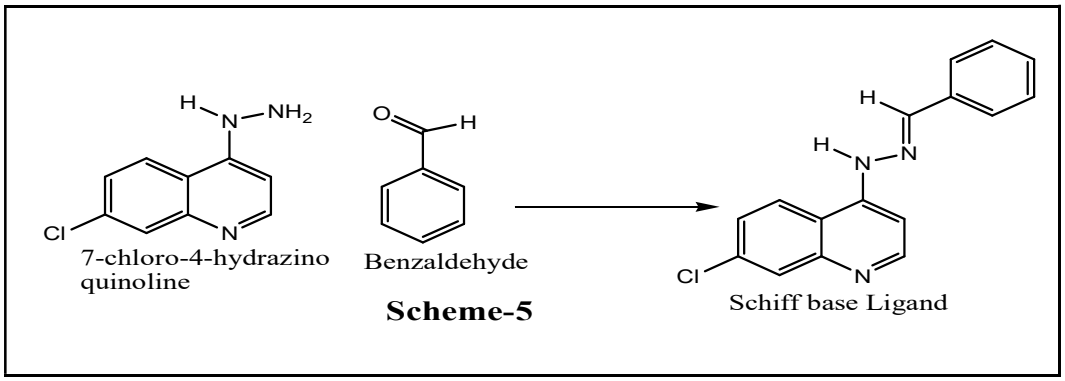
1. Biological Application

Quinolines constitute an important class of heterocyclic compounds that exhibit a wide range of biological activities. These molecules act as key structural frameworks for numerous pharmaceuticals employed in the treatment of various diseases. Owing to their favourable pharmacological characteristics, quinoline derivatives have gained considerable attention as potential therapeutic agents. In particular, they demonstrate enhanced metabolic stability and improved oral bioavailability. Moreover, their desirable physicochemical properties, such as optimal charge distribution, appropriate lipophilicity, and increased conformational rigidity, further contribute to their significance in medicinal chemistry and drug development.This present investigation provides a comprehensive account of the versatile biological applications of different Schiff bases

1.1 Antimicrobial Activity:

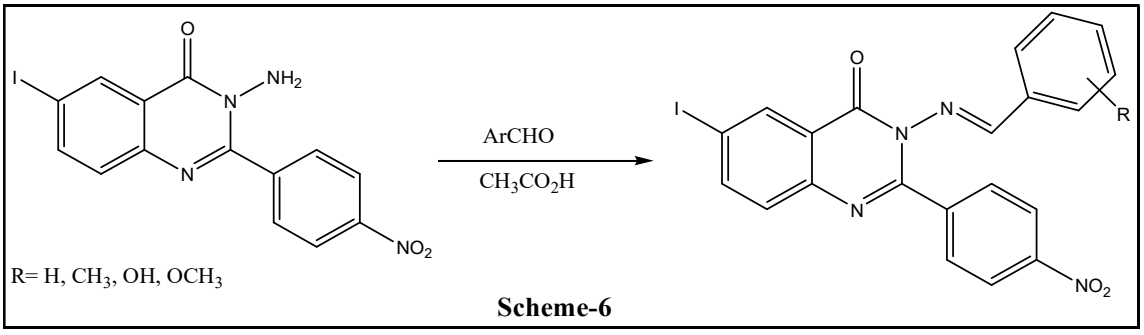
Nora H. Al-Sha'alan[25] reported the synthesis of Schiff bases through the condensation reaction of benzaldehyde with 7-chloro-4-hydrazinoquinoline in a 1:1 molar ratio, followed by the preparation of their corresponding metal complexes. The synthesized Schiff base ligand and its metal complexes were systematically characterized using appropriate analytical techniques. Biological evaluation revealed that the Schiff base ligand exhibited significant antimicrobial activity,

while its metal complexes demonstrated enhanced efficacy against one or more microbial strains. This increased antimicrobial potency upon complexation may be attributed to the chelation effect, which enhances the ligand's bactericidal properties by improving its stability and facilitating greater interaction with microbial cell membranes(Scheme-5).



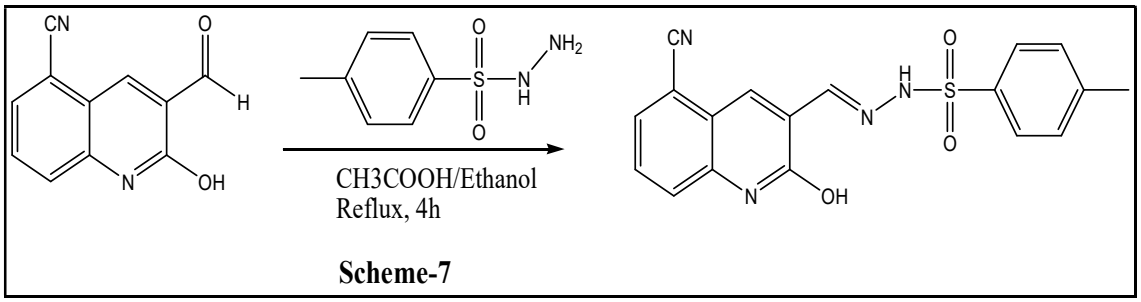
Scheme-5

Ahmed M. Alafeefy[26] and co-workers reported the synthesis of a series of novel quinazoline-based Schiff bases, whose structures were elucidated and confirmed through IR, NMR, MS, and elemental analytical techniques. The synthesized compounds were subsequently screened for antimicrobial efficacy against four fungal strains, two Gram-positive bacterial strains, and two Gram-negative bacterial strains. Among the tested derivatives, 3-((2-hydroxybenzylidene)amino)-6-iodo-2-(4-nitrophenyl)quinazolin-4(3H)-one demonstrated the most potent antibacterial activity, exhibiting minimum inhibitory concentration (MIC) values of 1.90 µg/mL against *Bacillus subtilis* and 3.9 µg/mL against *Staphylococcus aureus*. In antifungal evaluation, *Aspergillus fumigatus* and *Syncephalastrumracemosum* were found to be the most susceptible filamentous fungi, with the same compound showing MIC values of 15.63 µg/mL and 62.50 µg/mL, respectively(Scheme-6).



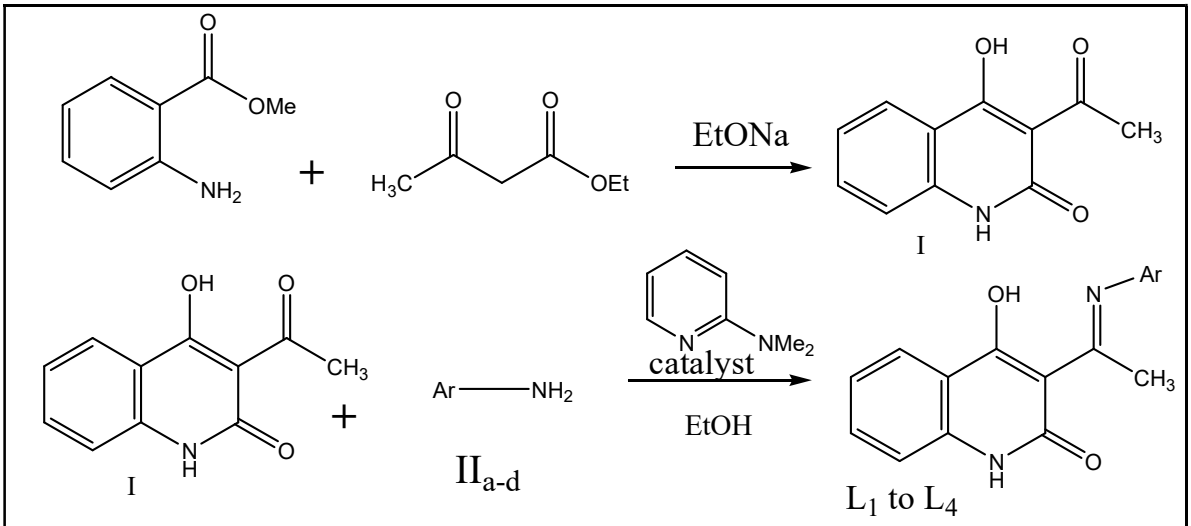
Scheme-6

R. Mamatha Rani and P. Kavitha[27] described the synthesis of a novel quinoline-derived Schiff base through the condensation reaction of 3-formyl-2-hydroxyquinoline-5-carbonitrile with 1-tosylhydrazine. Subsequent complexation of the Schiff base ligand with Cu(II), Ni(II), and Co(II) ions afforded the corresponding metal complexes. The synthesized ligand and its metal complexes were evaluated for their antimicrobial potential against *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans*. Biological studies revealed that the prepared compounds exhibited significant antibacterial and antifungal activities when compared with standard drugs ciprofloxacin and ketoconazole. Notably, the free ligand as well as its Cu(II) and Co(II) complexes demonstrated the highest inhibitory activity against *E. coli*, *B. subtilis*, *T. reesei*, and *C. albicans*, with minimum inhibitory concentration (MIC) values ranging from 20 to 80 µg mL^{-1}(Scheme-7).



Scheme-7

S. Anjanikar and S. Chandole[28] reported the synthesis of a series of novel Schiff base derivatives obtained through the condensation of 3-acetyl-4-hydroxyquinolin-2-one with substituted aminopyridine moieties. The structures of the synthesized compounds were confirmed by spectroscopic techniques, including IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analyses. The in vitro antimicrobial potential of these Schiff bases was evaluated against selected bacterial and fungal strains using the agar well diffusion method. The results indicated that all synthesized derivatives exhibited notable antibacterial and antifungal activities, with the highest zones of inhibition observed against *Salmonella Typhi*. Among the tested compounds,3-(1-((5-chloropyridin-2-yl)imino)ethyl)-4-hydroxyquinolin-2(1H)-one displayed the most pronounced activity against all bacterial strains, which may be attributed to the presence of the chlorine substituent in its molecular framework(Scheme-8).

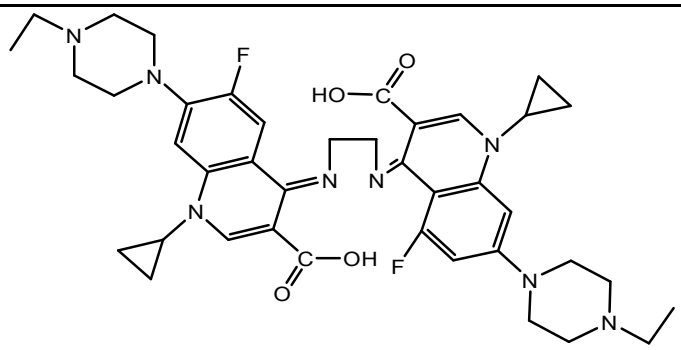


Ar= 4-methylpyridin-2-amine, 5-methylpyridin-2-amine, 6-methylpyridin-2-amine, and 4-methyl-3-nitropyridin-2-amine

Scheme-8

A. Mohamed[29] and co-workers reported the synthesis of a quinoline-derived Schiff base and its corresponding metal complexes. The Schiff base ligand, N,N-ethylene bis(1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-1,4-dihydroquinoline-3-carboxylic acid) (H_2Erx-en), was synthesized via the condensation of enrofloxacin with ethylenediamine in the presence of glacial acetic acid. Acting as a tetradentate ligand, H_2Erx-en was subsequently coordinated with Fe(III), Y(III), Zr(IV), and La(III) ions to yield a series of novel metal chelates. The antimicrobial activities of the free ligand and its metal complexes were investigated against various foodborne and phytopathogenic microorganisms using the disc diffusion method.

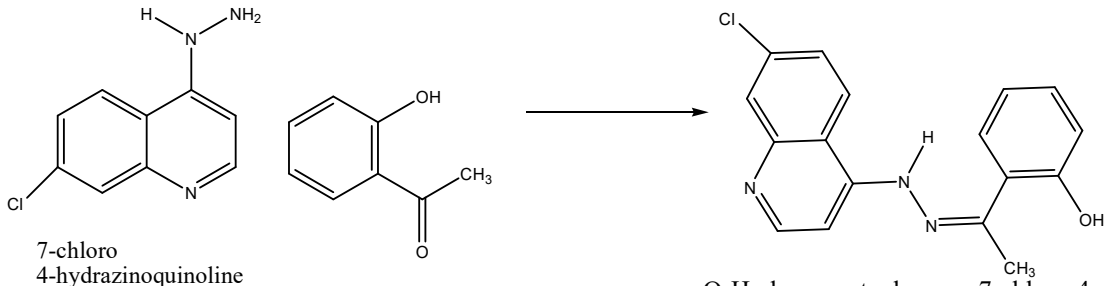
Their antibacterial efficacy was specifically assessed against four bacterial species, among which the zirconium(IV) complex exhibited the strongest antibacterial activity, showing remarkable potency particularly against *Salmonella typhi*(Fig.-1).



.N,N-ethylene(bis1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-1,4-dihydroquinoline 3-carboxylicacid ((H?Erx-en))

fig-1

Nora H. Al-Shaalan[30]synthesised novel Schiff base hydrazone ligand via a condensation reaction between 7-chloro-4-quinoline and *o*-hydroxyacetophenone. The ligand exhibits dual coordination behaviour functioning either as a monobasic bidentate or a dibasic tridentate ligand, possessing ONN donor sites. The synthesized ligand and its corresponding metal complexes were systematically characterized using elemental analysis, infrared (IR) spectroscopy, nuclear magnetic resonance (NMR), mass spectrometry, and UV–Visible spectroscopy. The antimicrobial activity of these compounds was evaluated against Gram-positive (*Staphylococcus aureus*), Gram-negative (*Escherichia coli*) bacteria, and the fungal strain (*Candida albicans*). The findings indicated that the ligand and its metal complexes display significant antibacterial activity.(Scheme-9).



7-chloro
4-hydrazinoquinoline

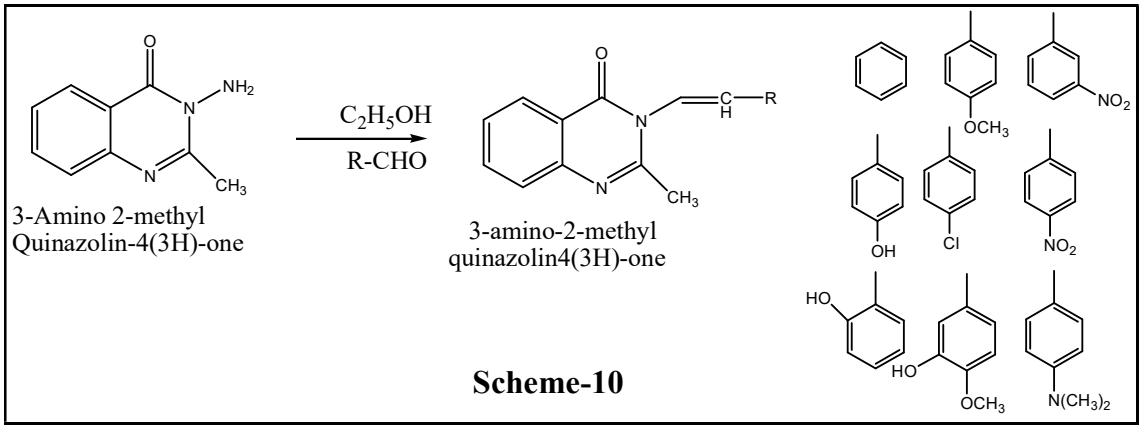
o-hydroxyacetophenone

O-Hydroxyacetophenone-7-chloro-4 quinoline Hydrazone

Scheme-9

A series of novel Schiff bases were reported by G. Saravanan et al.[31]through the condensation of 3-amino-2-methylquinazolin-4(3H)-one with various aromatic aldehydes. The precursor, 3-amino-2-methylquinazolin-4(3H)-one, was prepared from anthranilic acid via the intermediate 2-methylbenzoxazin-4-one. The structures of the synthesized compounds were confirmed using infrared (IR) spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry, and elemental analysis.The synthesized compounds were evaluated for their antibacterial and antifungal activities employing the paper disc diffusion method, while their minimum inhibitory concentrations (MICs) were determined using the

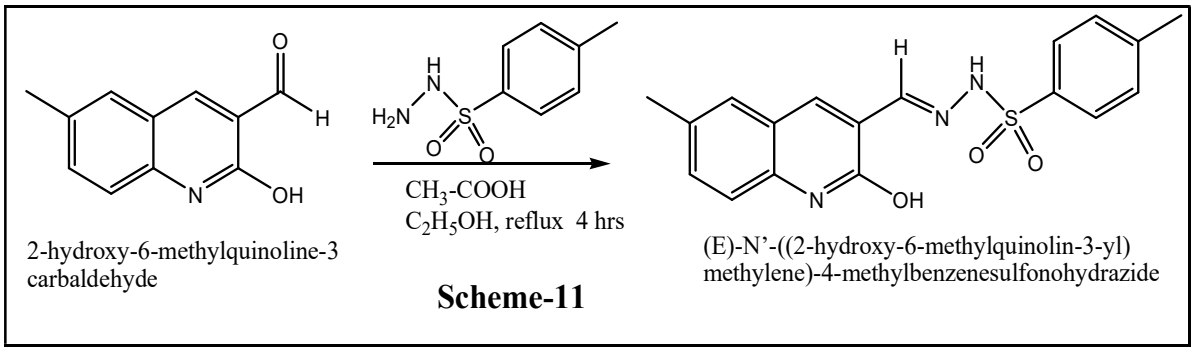
agar streak dilution technique. The results indicated that the majority of the compounds exhibited considerable antibacterial and antifungal activities. (Scheme-10)



Scheme-10

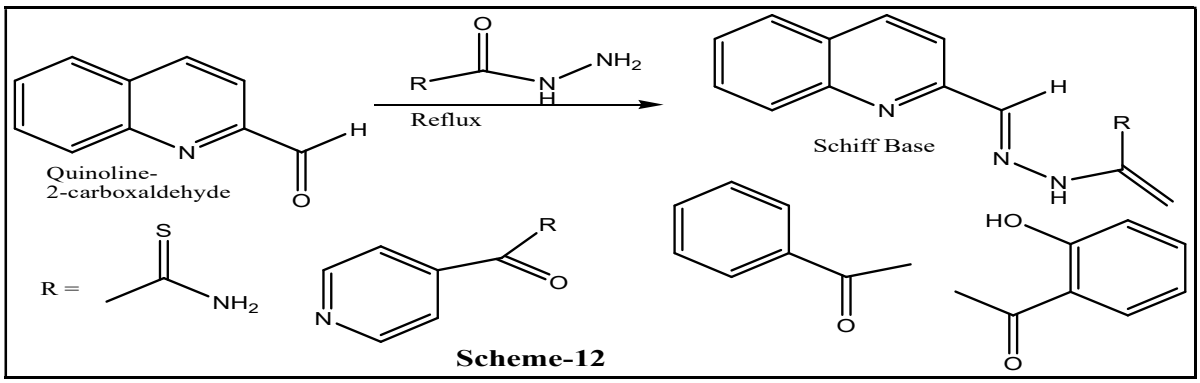
1.2 Anticancer Activity

S. K. Patil et al[32] have reported novel quinoline-based Schiff base These Schiff bases were synthesized via the condensation of 2-hydroxyquinoline-3-carbaldehyde with 4-methyl benzene-sulfonohydrazide. The resulting ligand was subsequently employed for the preparation of metal complexes with Cu(II), Ni(II), Co(II), and Cd(II) ions. The synthesized compounds were further assessed for their *in vitro* cytotoxic activity against A-549 and MCF-7 cancer cell lines using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Among the investigated compounds, the Cu(II) complex exhibited the most significant cytotoxic activity, with IC_{50} values of 37.03 µM and 39.43 µM against A-549 and MCF-7 cell lines, respectively (Scheme-11).



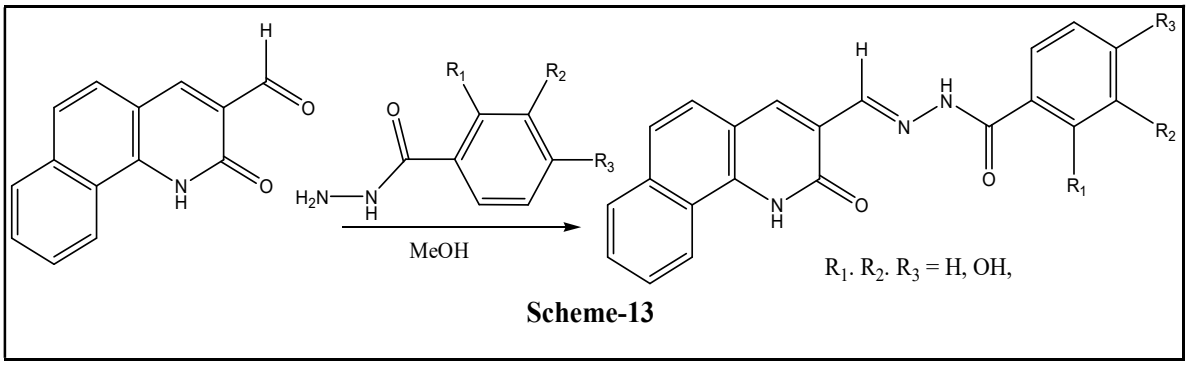
Scheme-11

Shreelekha Adsule[33]and co-workers reported the synthesis and characterization of four Schiff bases derived from quinoline-2-carboxaldehyde, along with their corresponding copper complexes. The synthesized ligands and their metal complexes were comprehensively characterized using various analytical and spectroscopic techniques. Biological evaluation revealed that these quinoline-based Schiff bases and their copper complexes exhibited significant dose-dependent antiproliferative and pro-apoptotic effects against PC-3 and LNCaP prostate cancer cell lines. Among the investigated compounds, the quinoline thiosemicarbazone derivative demonstrated the highest potency, effectively inhibiting proteasome activity in intact human prostate cancer cells (PC-3 and LNCaP).(Scheme-12)



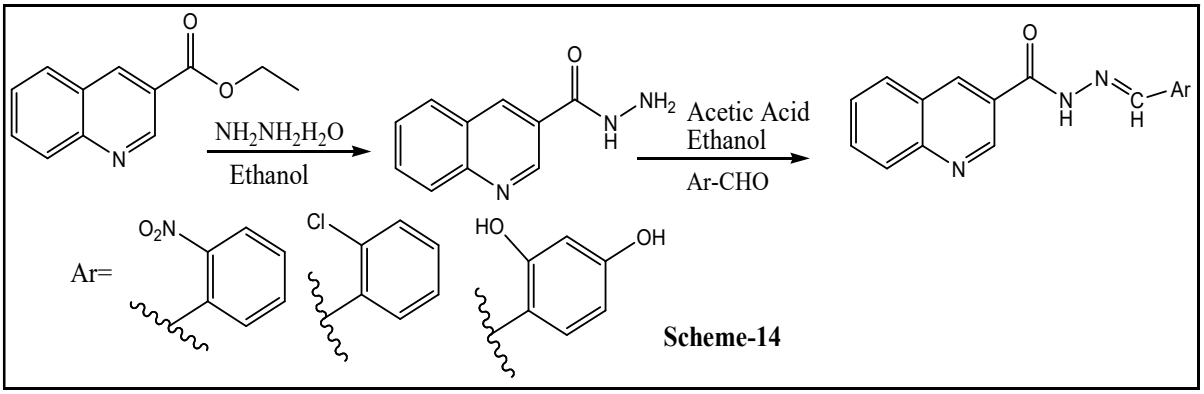
Scheme-12

Eswaran Ramachandran[34] and co-workers reported the synthesis of a novel series of dihydrobenzoquinolinearoylhydrazone derivatives. These ligands were obtained via condensation of 2-oxo-1,2-dihydrobenzo[h]quinoline-3-carbaldehyde with the corresponding hydrazides. The synthesized compounds were thoroughly characterized by elemental analysis and various spectroscopic techniques, including IR, ESI-MS, UV–Vis, ^{1}HNMR, and ^{13}CNMR spectroscopy. The in vitro antitumor activity of both the synthesized copper (II) complexes and the corresponding free ligands was evaluated against a range of human cancer cell lines derived from solid tumors using the MTT assay. The cytotoxicity results demonstrated that the copper complexes exhibited significantly enhanced antitumor activity compared to the uncoordinated ligands, and notably surpassed the efficacy of cisplatin. (Scheme-13)



Scheme-13

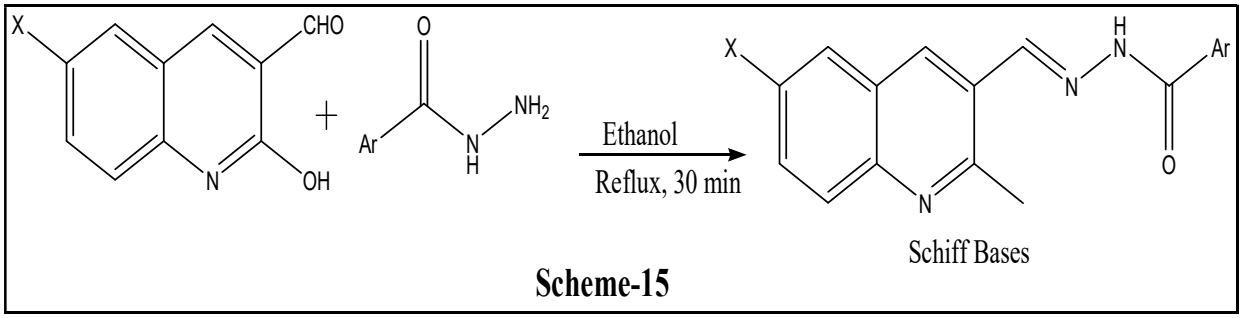
Mahmoud Sunjuk et al.[35] reported the synthesis of three Schiff base ligands derived from the condensation of quinoline-3-carbohydrazide with 2-nitrobenzaldehyde, 2-chloro benzaldehyde, and 2,4-dihydroxybenzaldehyde, respectively. These ligands were subsequently examined for their coordination behavior with Cu(II), Ni(II), Co(II), Cd(II), Cr(III), and Fe(III) chloride salts. The preparation of the NQ ligand, along with the X-ray crystal structures of the ligands and the corresponding transition metal complexes were also elucidated. Furthermore, the ligand derived from 2,4-dihydroxybenzaldehyde and its Cu(II) and Ni(II) complexes demonstrated significant inhibitory activity against human breast adenocarcinoma (MCF-7) and chronic myelogenous leukemia (K562) cell lines.



Scheme-14

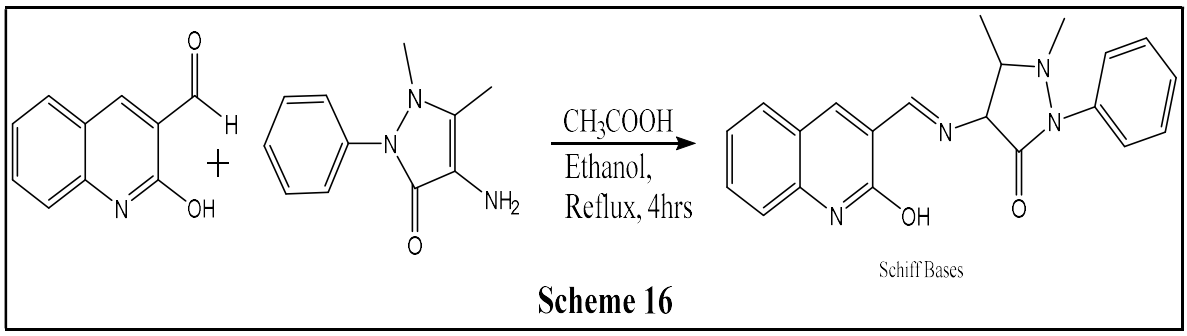
1.3 Antituberculosis Activity

Mustapha C. Mandewale et al[36] described synthesis of Quinoline hydrazone ligands and their Zn(II) complexes via a multistep synthetic route. The ligands were obtained through the condensation of 2-hydroxy-3-formylquinoline derivatives with various hydrazide derivatives (2a–2c). Structural elucidation of both the ligands and their corresponding Zn(II) complexes was accomplished using elemental analysis along with spectroscopic techniques, including FT-IR, ^{1}H and ^{13}C NMR, mass spectrometry, UV–Visible, and fluorescence studies. Preliminary antitubercular evaluation against *Mycobacterium tuberculosis* (H37Rv strain, ATCC 27294) revealed that the Zn(II) complexes exhibit significant activity, whereas the free ligands display moderate efficacy. Notably, the activity of several complexes was found to be comparable to that of established first- and second-line antitubercular drugs.(Scheme-15)



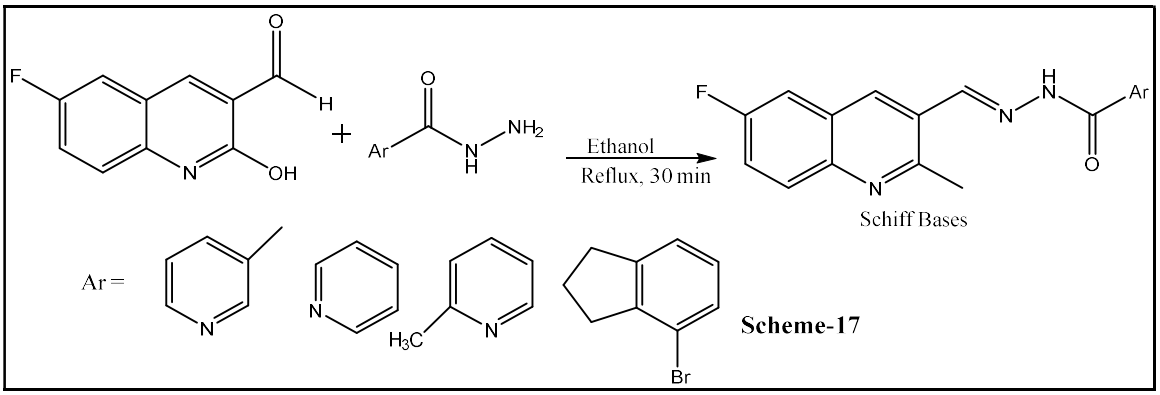
Scheme-15

Dhananjay V. Bondar *et al.*[37] reported the synthesis of novel quinoline-based Schiff bases and their corresponding metal complexes with Cu (II), Ni (II), Co (II), Zn (II), and Cd (II), followed by evaluation of their antitubercular activity against *Mycobacterium tuberculosis* H37Ra and *Mycobacterium bovis* BCG strains. Most of the synthesized compounds exhibited significant activity, with minimum inhibitory concentration (MIC) values in the range of 0.061–1.5 µg mL^{-1} against *M. bovis* BCG and 0.54–2.2 µg mL^{-1} against *M. tuberculosis* H37Ra. The most potent derivatives demonstrated low cytotoxicity and a high selectivity index (>10) against MCF-7, HCT-116, and A549 cell lines, as determined by the MTT assay, indicating their potential as promising antitubercular agents. (Scheme-16)



Scheme 16

Bapu Thorat *et al.*[38] reported the synthesis of a novel series of quinoline hydrazone derivatives along with their corresponding metal complexes, followed by evaluation of their biological activity against *Mycobacterium tuberculosis* (H37Rv strain). The majority of the synthesized compounds exhibited complete (100%) inhibitory activity at concentrations ranging from 6.25 to 25 μg mL^{-1}. In addition, the fluorescence properties of all prepared compounds were systematically investigated.(Scheme-17)



Scheme-17

Conclusion

In recent years, bioinorganic chemistry has emerged as a dynamic and influential discipline within pharmaceutical research, significantly expanding the scope of metal-based therapeutics. The growing advancement of quinoline-derived Schiff bases, particularly those progressing toward clinical evaluation, is anticipated to strengthen their position in drug discovery and stimulate further exploration of this versatile scaffold. Schiff bases with established medicinal relevance represent a promising platform for the rational design of novel therapeutic agents, especially for the treatment of diseases that remain refractory to conventional approaches.

Notably, the incorporation of metal ions into these ligands has frequently been shown to enhance biological efficacy, underscoring the importance of metal coordination in modulating pharmacological activity. This review highlights diverse synthetic strategies employed in the preparation of quinoline Schiff base metal complexes, with particular emphasis on sustainable and environmentally benign methodologies aligned with green chemistry principles. Such approaches not only improve synthetic efficiency but also contribute to the development of safer and more sustainable pharmaceutical processes.

Overall, this work consolidates current progress in the design and application of quinoline Schiff base metal complexes as potential therapeutic agents exhibiting broad-spectrum biological activities with reduced adverse effects. Future advancements in this field will depend on the integration of innovative synthetic techniques, computational modelling, and rigorous clinical evaluation within a multidisciplinary framework.

Through such coordinated efforts, quinoline-based systems are poised to offer substantial opportunities for the discovery and development of next-generation therapeutics targeting a wide array of diseases.

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DOI: 10.22192/ijcrcps.2026.13.05.002	

How to cite this article:
Shivraj S. Anjanikar. (2026). Versatile Applications of Schiff Bases of Benzo pyridine Moiety: A Comprehensive Review. Int. J. Curr. Res. Chem. Pharm. Sci. 13(5): 8-20.
DOI: http://dx.doi.org/10.22192/ijcrcps.2026.13.05.002

