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COPPER – QUINOLINE COMPLEXES AS BIOACTIVE AGENTS: A REVIEW

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ABSTRACT

Quinoline and its derivatives are important heterocyclic moieties widely used in the evolution of biologically active drugs because of their versatile applications. In past few years use of metal complexes of Quinoline has been continuously increasing. Metal complexation can improve drug stability, bioavailability and target specificity also introducing novel mechanisms of action. Through recent research it has been observed that copper complexes are potentially important as medicinal agents. The quinoline scaffold and its copper metal derivatives show high efficiency of biological activities, making them ideal for novel multifunctional therapeutic agents**.** This review focus on the extensive studies of quinoline based copper coordination compound emphasizing on their comparative biological evaluation. In this review work we highlighted the role of copper complexes as antibacterial, antifungal, anticancer, DNA cleavage and DNA binding agents.

INTRODUCTION

In present time, phenomenon of drug resistance presents a significant barrier in the treatment of infections, as the emergence of resistant microbial strains diminishes the efficacy of antimicrobial agents, consequently leading to an increase in morbidity and deaths caused by infectious diseases.[1,2] Therefore, there exists an urgent need to formulate new and more effective antimicrobial and anticancer therapeutics that utilize innovative mechanisms of action to effectively counteract drug resistance, that may be different from those of currently available medications, enhance therapeutic efficacy, minimize harmful effects, and ultimately improve overall clinical perspectives for patients.[3] The realization of these objectives may be facilitated through the advancement of various metallodrugs, given that metal-based coordination complexes exhibit notable reactivity, electronic properties, and redox chemistry.[4,5]

Metal ions are known for their capability to interact with various drugs and organic ligands, resulting in the form of complexes that exhibit improved bioactivity of the ligands.[6-10] Drug efficacy increases after formation of metal complexes because transfer of e^- occurs from ligand to metal ion and due to this lipophilicity enhances. This increased lipophilicity allows complexes to more easily cross the bacterial cell membrane, which contains high lipid content.[11] Nowadays, Transition metal complexes are frequently recommended as medications to treat a variety of human conditions, including infections, diabetes, cancer, and inflammation.[12-14] Copper is considered as an essential trace metal due to its involvement in necessary physiological functions. Copper metal possesses significant coordination and redox properties which is responsible for its versatile biological properties. Recent studies proved that complex of copper metal display wide range of biological activity and act as potent medicinal metal.[15]

Derivatives of heterocyclic compounds especially Nitrogen based, gained attraction in field of medicine and biological chemistry.[16] In this context, quinoline center has attracted major attention from both chemists and biologists, as it constitutes a central building block for numerous naturally occurring compounds.[17] Quinoline is classified as an organic heterocyclic compound characterized by a bicyclic configuration consisting of a benzene ring that is fused to a pyridine ring.[18] Quinoline represents a significant moiety identified within a diverse array of natural products, pharmaceutical pharmacophores, and functional molecules.[19-21] Natural compounds featuring quinoline

have exhibited diverse biological activities and have emerged as viable candidates for the advancement of drug development.[18]

Quinoline-based metal complexes have applications in various fields, including catalysis, material sciences, and medicinal chemistry. Quinoline derivatives, in conjunction with transition metal, serve as prominent scaffolding molecules in the continuous effort to discover novel and more efficacious bioactive compounds.[22] The compound has been employed as a chelating agent owing to its nitrogen-donor ligands in coordination chemistry field for the complexation with metals.[23] Quinoline derivatives and their Cu-metal complexes have appeared as compounds exhibiting highly effective biological and pharmacological properties, which encompass a broad spectrum of significance, including antibacterial, antifungal, anticancer, antimicrobial, antiprotozoal, anti-inflammatory, antidiabetic, antioxidants.[24-30] Further Computational study of newly synthesized scaffold offers a powerful complement to experimental approaches, empowering detailed insights into geometric structures, electronic configurations, various electronic transitions, reaction mechanisms, spectroscopic properties and their anti-microbial activity, including toxicity. There exist numerous computational study tools and techniques like structure activity relationship (SAR) study, mainly QSAR study[31], molecular docking, DFT and so on.[32-34]

ANTIBACTERIAL STUDIES

The increasing incidence of bacterial infections remains a major universal health concern, imposing continuous development of novel effective antibacterial agents. Common pathogenic bacteria responsible for human contaminations include Gram-positive bacterial species such as Staphylococcus aureus and Streptococcus pneumoniae, as well as Gram-negative strains like Escherichia coli and Pseudomonas aeruginosa. Conventional antibacterial drugs such as ciprofloxacin, amoxicillin, azithromycin, cephalexin and doxycycline which are related to fluoroquinolones, penicillins, cephalosporins, macrolides and aminoglycosides families have been extensively used for the treatment of a broad range of infections. Although after their clinical success, the common and regular use of these drugs has led to the rapid beginning of antibiotic resistance among infective bacteria.

Consequently, there is an instant requirement for the development of new antibacterial agents with novel mechanisms of action that can overcome resistance and effectively target pathogenic microorganisms. In this circumstance, researchers have focused on quinoline-based copper complexes, which may be serve as promising substitutes due to their unique modes of action.

Table 1: analysis of antibacterial studies.

Reference & Compound	Bacteria strain	Key findings	Analysis
Complex 1 and 2 Kulkarni et al. [35]	*E. coli* *P. aeruginosa*	Complex 2 is more active for bacterial strain than complex 1. Complex 2 is more active for *E.coli.* Higher activity in comparison to free ligand. Lower activity than standard drug Gentamycin.	Complex 2 shows higher biological activity because of several structural and chemical factors.
Complex 4 Patel et al. [36]	*S. aureus* *B. subtilis* *E. coli* *P. aerugionsa*	Less active than free ligand. Zone of inhibition for *B. subtilis* 25.5 mm, highest among all bacterial stain.	Free ligand was more effective, suggesting that chelation may have screened essential binding sites.
Complex 5 & 6 Narayanachar et al. [37]	*Streptococcus faecalis* *Staphylococcus aureus* *Bacillus subtilis* *Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Escherichia coli*	Both complexes were highly active as antibacterial agents having very low MIC value. Compound 6 displayed greater activity for all bacterial strains in comparison to compound 5. Both complexes showed comparatively low activity for *P. aeruginosa* (MIC 8 µg/mL for comp. 6 & 16 µg/mL for comp. 5.	Complex 6 showed higher activity due to containing nitro group which increases lipophilicity and electron transfer ability, improving biological efficacy.
Complex 8 a-c Zhang et al. [38]	*Staphylococcus aureus* *Escherichia coli* *P. aeruginosa* *Sarcina ureae*	All three complexes displayed enhanced or comparable activity in comparison to free ligand. 8a showed better inhibition against *S. aureus* and *E. coli* having 1.56 µg/mL MIC value.	Different antibacterial activity of all copper complexes against various bacterial strains appears due to difference in chemical structure, bacterial cell wall differences, and biological

		8b complex showed enhanced activity against *S. aureus & P. aeruginosa* (1.56 µg/mL MIC value). 8c highly active (1.56 µg/mL MIC value) for *Sarcina ureae.*	interactions of ligand and metal.
Complex 9 & 10 Nath et al. [39]	*Escherichia coli* *Staphylococcus aureus*	The copper complexes showed higher activity than ligand. 73.75 & 71.37% IZ against the bacterial stains at 100µg concentration.	Metal chelation enhanced the activity of complexes.
Complex 11 Karekal et al. [40]	*Escherichia coli* *Salmonella typhi* *Bacillus subtilis* *Staphylococcus aureus*	Most effective against *E. coli* having MIC value 12.50 µg/mL similar to standard Gentamycin.	Coordination with copper increase the lipophilicity and this is responsible for increased antibacterial activity.
Complex 12 Meghdadi et al. [41]	*Escherichia Coli* *Staphylococcus Aureus*	Zone of inhibition: *Escherichia coli* 20mm *Staphylococcus aureus* 30mm Higher activity than standard drug Penicillin. Potent active towards *S. aureus*.	The inertness of the metal-ligand linkage presumably increases its lipophilicity, cell permeability, and protection against enzymatic degradation.
Complex 13 Yernale et al. [42]	*Enterobacter aerogenes* *Pseudomonas aeruginosa*	Copper complex more active than ligand. MIC value- *E. aerogenes* (1.563 *µ*g/mL) *P. aeruginosa* (0.78 *µ*g/mL) These values support better activity for *P. aeruginosa.*	Metal coordination alters the electron distribution of the ligand, improving its ability to interact with biomolecules.
Complex 15 Abuthahir et al. [43]	*Staphylococcus aureus,* *Escherichia coli,* *Pseudomonas aeruginosa* *C. tropicalis.*	Cu complex showed greater activity than the standard drug Ciprofloxacin Higher for *P. aeruginosa* (24 mm IZ) among all bacterial strains.	Metal chelation of ligand significantly enhances the activity of complexes.
Complex 16 Lokesh et al. [44]	*Escherichia coli* *Salmonella typhi* *Staphylococcus aureus* *Bacillus subtilis*	Higher activity was found for all bacteria at 200 µg/ml. Low activity against *Salmonella typhi.* Moderate activity against *S. aureus* and highly active against *E.coli* and *B. subtilis*	For E.coli activity found to be better than standard drug Chloramphenicol.
Complex 17 Shakir et al. [45]	*E. coli* *S. typhimurium* *P. aeruginosa,* *Vibrio cholera* *S. aureus* *L. monocytogenes*	More active than ligand. Moderate active towards *E.coli* (MIC value 62.5 *µ*g/mL) Weak activity for all other bacterial strain.	Metal chelation enhances antibacterial activity.
Complex 18 Jai Devi et al. [46]	*P. aeruginosa* *P. mendocina* *B. subtilis* *M. Luteus*	Cu(LIV)(Q)H2O showed maximum zone of inhibition 24mm against growth of *P. medocina* with MIC of 3.12 *µ*g/mL	The NO_2 group enhances electron delocalization and strengthens metal–ligand bonding, which improves lipophilicity and cell membrane penetration.
Complex 19 Zou et al.[47]	*S. ureae* *P. aeruginosa* *E. coli* *S. aureus*	The ligand itself showed absolute specificity against *E. coli* (MIC 3.13 µg/mL). Cu complex showed strong inhibition against *S. ureae* (MIC value 3.13*µ*g/mL), comparable with standard drugs Ampicillin and Streptomycin	After coordination with metal centre there was decrease in antibacterial activity against *E.coli.* These finding may be area of future research.
Complex 20	*Klebsiella sp.*	*Bacillus subtilis* 20mm sensitive	These results show that copper

Hazmi et al. [48]	*Proteus sp.* *Bacillus subtilis*	*Klebsiella sp.*18 mm sensitive *Proteus sp.* 12 mm resistant	complex may propose new antibiotic drugs.
Complex 21 B. Vivekanand et al. [49]	*Staphylococcus aureus* *Pseudomonas aeruginosa*	IZ values *S. aureus* 40mm *P. aeruginosa* 38mm Potent activity against both bacterial strains approaching to activity of Gentamycin.	There are Clear correlation between geometry and bioactivity of complex.
Complex 22 Numan et al.[50]	*Staphylococcus aureus,* *Escherichia coli* *Bacillus subtilis* *Pseudomonas aeruginosa*	Less active in comparison to free ligand. Copper complex showed moderate activity for *S. aureus, E. coli, B. subtilis* (16-17 mm IZ) and much poorer activity for *P. aeruginosa* (11 mm IZ).	Chemical and structural changes are needed for enhance bacterial activity of complex
Complex 25 Pérez et al.[51]	*Escherichia coli* *Salmonella typhimurium* *Staphylococcus aureus* *Bacillus cereus*	Cu (II) showed maximum zone of inhibition against growth of *E.coli.*	Copper complex are better candidates for further drug development studies.
Complex 26 Numan et al. [52]	*Staphylococcus aureus* *Bacillus subtilis* *Enterobacter cloacae* *E. coli*	Zone of inhibition of copper complex: *Staphylococcus aureus* 34mm *Bacillus subtilis* 33mm *Enterobacter cloacae* 16mm *E coli* 30mm. Less active towards *Enterobacter cloacae*.	Findings shows that activity is not so high in comparison to trimethoprim's bioactivity.
Complex 28 Indira et al.[53]	*Escherichia coli* *Pseudomonas aeruginosa* *Staphylococcus aureus* *Enterococci species*	Higher activity for *P. aeruginosa* 22mm IZ. The copper complex demonstrates comparable or superior antibacterial activity to ampicillin	Its enhanced activity arises from chelation-driven lipophilicity, Cu(II) redox activity, and synergistic ligand effects.
Complex 29 Chagas et al. [54]	*Escherichia coli* *Pseudomonas aeruginosa* *Enterococcus faecalis* *Staphylococcus aureus*	The free ligands themselves were more effective, especially against *E. coli* ≤5.85 μg/mL MIC value. Both complex having MIC value: >3000 μg/mL much lower than standard drugs used: Vancomycin Piperacillin Ampicillin	These results suggests that coordination with Cu(II) may hinder rather than enhance antibacterial strength in quinoline derivatives.
Complex 33 Ali et al. [55]	*Bacillus subtilis* *Escherichia coli*	Cu (II) complex gave the enormous activity which exceeding the standard drug ampicillin. More active for *E.coli* with 18 ± 2 mm zone of inhibition.	Docking results of free ligand and complexes showed that there are increased interactions in copper complex which cause enormous activity of copper complex.
Complex 34 & 35 El-saied et al. [56]	*Escherichia coli* *Bacillus subtilis*	Complex 34 showed lower activity than standard tetracycline used. Complex 35 active against *E. coli* 40mm AI 114%.	H-bond formation between the azomethine group and the active centre of the cell components of bacteria may be the reason of increased activity of metal complexes.
Complex 36 Venugopal et al.[57]	*Bacillus subtilis* *Escherichia coli*	Copper complex shows stronger inhibition zones (*E.coli* 11±0.2mm, *B. subtilis* 11±0.3mm at 25mg/ml) compared to the ligand, indicating enhanced potency. Its activity is close to that of ciprofloxacin.	Its activity is explained by chelation-induced lipophilicity.
Complex 37	*E. faecalis, S. aureus*	For *S. aureus* 18 mm IZ.	Structural factors like distorted

Witwit et al. [58]	*P. mirabilis, S. typhi, E. coli, P. aeroginosa, A. baumanii and K. pneumoniae*	For other 7 bacterial strain IZ value was lying in range of 12-15mm (moderate in comparison with other complexes).	octahedral geometry and moderate lipophilicity explain its limited potency.
Complex 38 Damit et al.[59]	*Bacillus subtilis Staphylococcus aureus Pseudomonas aeruginosa Escherichia coli*	Greater zone of inhibition in the screening as compared to the free ligand. Cu complex showed more potency against *B. subtilis* (29mm IZ) as compared to other bacterial strains.	This may be due to the increased lipophilicity on complexation.
Complex 42 Damena et al.[60]	*Staphylococcus aureus Streptococcus pyogenes, Escherichia coli Pseudomonas aeruginosa*	Cu(II) complex showed highest inhibition zones (20.6 mm at 300 *µ*g/mL) against *P. aeruginosa* comparable to ciprofloxacin.	Cu(II) complex had the lowest band gap (3.27 eV), correlating with higher reactivity and biological activity.
Complex 44 & 45 Shumi et al.[61]	*Staphylococcus aureus Escherichia coli Pseudomonas aeruginosa*	Complex 44 demonstrated consistent inhibition against *S. aureus*, *E. coli*, and *P. aeruginosa*, with MIC values as low as 12.5 µg/mL. Complex 45 showed moderate activity against all bacterial strains in comparison to complex 44.	Lower band gap (higher reactivity) Stronger docking affinity (better target binding) the free ligand lacks the metal's catalytic contribution, and Complex 23 suffers from ligand excess masking the metal's activity.
Complex 49 Felczak et al. [76]	*S. aureus S. epidermidis S. pyogenes L.monocytogenes E. coli P. aeruginosa P. multocida C. jejuni*	Copper complex showed higher activity for *P. multocida* and *C. jejuni.* MIC value was 0.70 µg/mL for both strains. For other bacterial stains activity was similar to DNX.	For *L. monocytogenes* MBC was two times lower than DNX (stronger bactericidal effect).

DISCUSSION

The antibacterial studies summarized in the table 1 clearly reveal that copper complexes of quinoline derivatives exhibit noteworthy and broad-spectrum activity against a variety of pathogenic bacterial strains, including both Gram-positive and Gram-negative organisms (*S. aureus, B. subtilis, E. coli, P. aeruginosa)*. In most cases, the metal complexes show improved antibacterial efficacy compared to the free ligands, indicating a strong synergistic effect between the copper ion and the quinoline based ligand. This enhanced activity can be explained on the basis of chelation theory. The biological activity is also influenced by structural factors such as the nature and position of substituents on the quinoline ring, coordination geometry and oxidation state of the copper ion. Complexes with electron-withdrawing or lipophilic substituents often show improved activity due to better cellular uptake. In conclusion, copper complexes of quinoline derivatives represent a promising of antibacterial agents with enhanced usefulness compared to their parent ligands.

In this review (table1), presentation of graphical study (fig. 1 and fig. 2) of antibacterial activity has been restricted to only MIC values which are in comparative range. This is because MIC (minimum inhibitory concentration) represents a standard and widely accepted quantitative parameter for assessing antimicrobial efficiency. It allows direct comparison across different studies while Zone of Inhibition values are dependent on experimental conditions and concentration. So, for ensuring a direct and meaningful analysis, only MIC values have been considered. Very high MIC values are excluded from the comparison graph.

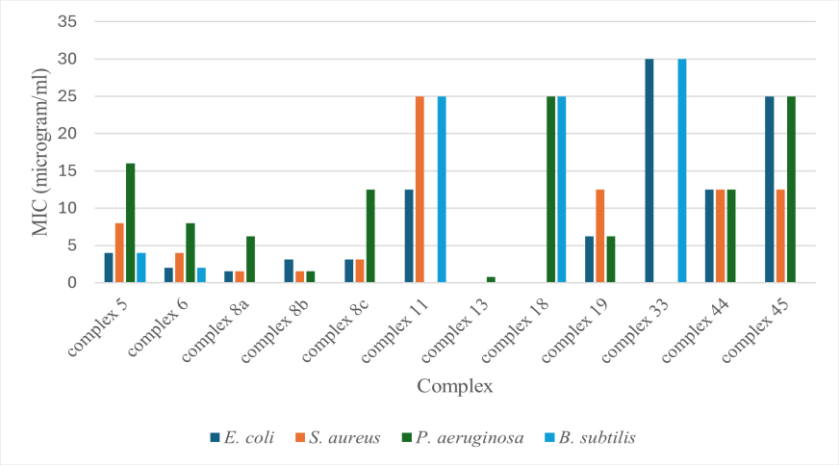


Fig. 1 Graphical comparison of MIC values of antibacterial study.

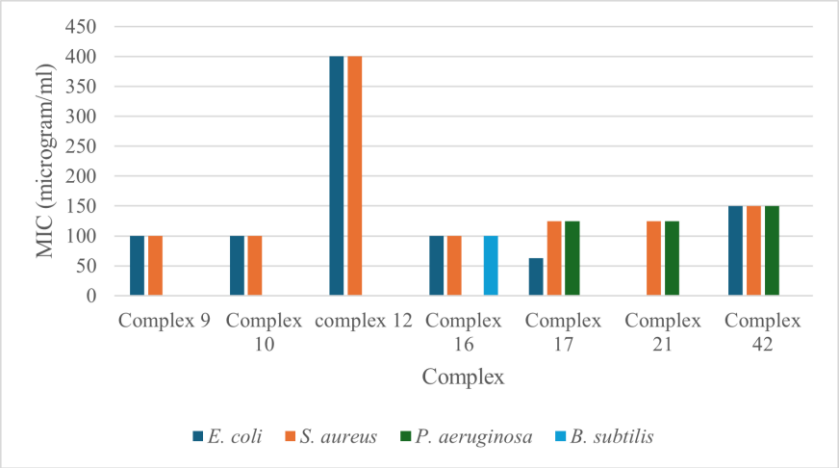


Fig. 2 Graphical comparison of MIC values of antibacterial study.

ANTIFUNGAL STUDIES

Recent scenario shows that there is urgent need for novel antifungal agents due to increasing resistance in pathogenic fungi towards existing drugs. Numerous studies have reported that copper complexes in coordination with quinoline derivatives exert potent antifungal effects. Progressive research in this field is going on and developing advanced antifungal agents based on unique mechanism of action.

Thus, a systematic and comparative study is essential to appropriate understanding of its possibility and limitations. In this review, the antifungal activity of copper-quinoline metal complexes is systematically summarized in table 2, highlighting significant parameters such as types of complexes, fungal strains tested, standard used, observed antifungal efficacy and analysis of findings.

Table 2: analysis of antifungal studies.

Reference & complex	Fungal species	Key findings	Analysis
Compound 1 & 2 Kulkarni et al.[35]	*Aspergillus niger Cladosporium*	Complex 1 is more active for both fungal species in comparison to complex 2, ligand and standard drug Fluconazole. Complex 1 and 2 are more active towards *A. niger.* Higher activity at 500 microgram conc.	Metal coordination alters the electron distribution of the ligand, improving its ability to interact with biomolecules.
Complex 3 Vashi et al.[62]	*Candida Albicans, Botrydepladia Thibromine, Nigrospora Sp,*	Highest zone of inhibition of copper complex was found for these fungal species: *Candida Albicans* 79%	Insertion of chlorine atom in phenyl ring of ligand has prominent effect on antifungal activity of metal complex.

	Aspergillus Fumigatus Rhizopur Nigricums.	*Aspergillus Fumigatus* 79%	
Complex 5 & 6 Narayanachar et al. [37]	*Candida albicans Aspergillus fumigatus Aspergillus niger Penicillium chrysogenum, Mucor fuscus Fusarium oxysporum*	Complex 5 was broadly active against *A. fumigatus, A. niger, F. oxysporum* with MICs as low as 8 µg/mL. Complex 6 (nitro-substituted) was particularly effective against *A. niger, P. chrysogenum*, and *Mucor fuscus having* (MIC value 8 *µ*g/mL).	In comparison to the standard drug Fluconazole, both copper complexes were comparable and slightly less potent. The ligands alone had much weaker activity, confirming that Cu(II) coordination is essential for increased antifungal action.
Complex 9 & 10 Nath et al. [39]	*Aspergillus niger Penecillium chrysogenum*	Extremely high activity, 100% zone of inhibition against *A. Niger*.	coordination stabilizes the Cu(II) centre in an octahedral geometry as a result biological activity increase.
Complex 11 Karekal et al. [40]	*C. albicans C. oxysporum A. niger*	Highly active against *C. oxysporum* (12.50 *µ*g/mL) and *A. niger* (12.50 *µ*g/mL).	C=N bond provides potent antifungal activity and higher activity of metal complex can be explained on the basis of chelation theory.
Complex 13 Yernale et al. [42]	*Aspergillus niger Aspergillus flavus*	Enhanced activity than free ligand. MIC value- *A. niger* (1.563 *µ*g/mL) *A. flavus* (3.125 *µ*g/mL) Strong inhibition for *A. niger*	Chelation improves biological activity of ligand.
Complex 16 Lokesh et al.[44]	*Aspergillus niger Candida albicans*	Potent antifungal agent. Higher activity for *A. niger* (32 mm IZ at 200 *µ*g/mL).	Enhanced anti-fungal activity in comparison to free ligand may be due to increased lipophilicity on complexation.
Complex 17 Shakir et al.[45]	*Candida albicans, Aspergillus niger*	MIC value: *C. albicans* 62.5 *µ*g/mL *A. niger* 125 *µ*g/mL Higher anti-fungal activity towards *Candida albicans.*	Structure of ligand and complex extremely affects biological activity of compound.
Complex 18 Devi et al.[46]	*V. dahlia C. herbarium T. soudanense*	Cu(LIV) (Q)H2O showed higher inhibition against *C. herbarium* with MIC of 3.12 *µ*g/mL.	Cu(LIV)(Q)H2O most potent antimicrobial agent. It may be due to nitro substitute.
Complex 21 Vivekanand et al. [49]	*Aspergillus niger Aspergillus flavus*	*A. Niger* IZ 35mm *A. Flavus* IZ 36mm at 125 ppm MIC. Activity higher than standard Fluconazole.	Cu complex may act as an effective antifungal agent.
Complex 28 Indira et al. [53]	*Aspergillus niger Penicillium species*	Moderate activity against both fungal species with 11 mm IZ. Less activity than Clotrimazole.	Its balanced activity across both fungi highlights copper's role in enhancing bioactivity of free ligand.
Complex 29 & 30 Chagas et al. [54]	*C. albicans*	Cu complexes having MIC >3000 *µ*g/mL. Fluconazole ≤16 *µ*g/mL.	Lower activity of Cu complex indicates that there are some structural and electronic changes are required.
Complex 33 Ali et al. [55]	*Aspergillus niger*	7 ± 0.5 mm zone of inhibition against *Aspergillus niger*, more than ligand while low in comparison to standard fluconazole.	Chelation effect and Square-planar geometry facilitate binding to fungal biomolecules.

Complex 34 & 35 El-saied et al. [56]	*Aspergillus niger and Candida albicans*	Complex 34: most bio-effective complex against *A. niger* with IZ = 42 mm and AI = 114%. Complex 34 and 35 are highly effective against *C. albicans* (41 & 43 mm IZ respectively).	Hydrogen bond formation between ligand entity and the active centre of the cell components interfere with normal cell functions increasing bioactivity.
Complex 36 Venugopal et al. [57]	*Candida albicans Aspergillus flavus*	29 % inhibition against *A. flavus* 24% inhibition against *C. albicans* at 50μg/mL.	Increased activity of complex may be due to the increased lipophilicity on complexation.
Complex 49 Felczak et al. [76]	*Candida albicans Candida parapsilosis Aspergillus flavus Aspergillus fumigatus*	MIC for *C. albicans* and *C. parapsilosis* was found 350 μg/mL. MEC value for *A. flavus, A.fumigatus* was >350 μg/mL.	Cu–DNX system showed broadens spectrum to fungi.

DISCUSSION

This compiled data (table 2) clearly indicate that quinoline based copper metal complexes exhibit significant antifungal activity against a diverse range of fungal strains. Species of *Candida* (particularly *Candida albicans*) and *Aspergillus* (such as *Aspergillus niger, Aspergillus flavus* and *Aspergillus fumigatus*) were frequently employed as testing fungal pathogens. These strains are clinically and agriculturally important, which highlights the practical importance of the investigated complexes. Mostly, Clotrimazole, Fluconazole and Nystatin used as standard drugs for these studies. Different type of experimental methods has been applied to estimate antifungal activity like agar well diffusion, disk diffusion and broth microdilution techniques. Broth microdilution methods provided results in terms of minimum inhibitory concentration (MIC) values, while diffusion-based assays were mainly used for calculation of zone of inhibition (IZ).

The analysis of results reveals a constant trend in which copper–quinoline complexes demonstrate enhanced antifungal activity compared to the free ligands. A few complexes showed comparable to or higher activity than standard used. These improvements can be attributed to chelation, which increases the lipophilicity of the complexes and facilitates their penetration through fungal cell membranes. Additionally, the ability of these complexes to disrupt vital cellular processes also contributes to their biological efficacy. A comparative analysis of antifungal study is presented in fig. 3.

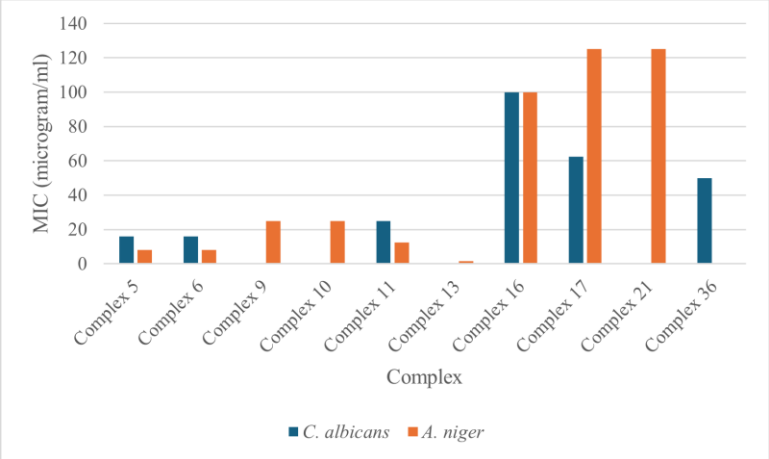


Fig. 3 Graphical representation of antifungal activity of complexes.

To ensure reliability, consistency, accuracy and scientific validity in graphical discussion zone of Inhibition values and higher MIC values are excluded from graphical representation.

CELL TOXICITY / ANTICANCER STUDY OF CU-QUINOLINE COMPLEXES

Cupper act as an essential metal ion in biochemical system of a living body and gained major attraction in medicinal chemistry. In coordination with heterocyclic ligand, especially with quinoline and its derivatives have emerged as anticancer or cytotoxic agents against various

cancer cell lines. Coordination with quinoline scaffold enhances cytotoxic efficiency of copper metal by improving electronic effect, stability, cellular uptake and interaction with intracellular targets.

In this review, the cytotoxic and anticancer activities of copper–quinoline metal complexes are systematically complied in table 3 which includes different parameters such as types of complexes, cancer cell lines and observed biological outcomes with analysis.

Table 3: anticancer study of cu- quinoline complexes.

Reference & complex	Cell line	Key findings	Analysis
Complex 14 Lu et al. [63]	7404, HeLa, MCF-7, HepG-2 cancer cells.	Low IC_{50} values (6.867 μM/ 5.957 μM) are less to cisplatin (3.92 μM/9.92 μM) against the MCF-7 and HepG-2 cell lines.	Cu complex may act as an effective metal-based anticancer drug with quinoline scaffold.
Complex 17 Shakir et al. [45]	MDA-MB-23, KCL22, HeLa, normal PBMC cells.	Significant inhibitory effect against MDA-MB231 and KCL22 cell line with IC_{50} < 2.50 μM.	This may be ascribed to increase in conjugation in ligand system on complexation.
Complex 23 Zou et al. [64]	TheBEL-7404, Hep-G2, SK-OV-3, MGC80-3, HeLa cancer cell	Complex 23 was more sensitive to MGC 80-3 and SK-OV-3 cells exhibiting low IC_{50} values of 10.17 μM and 10.35 μM, respectively. More potent than cisplatin. IC_{50} value for HeLa cell line was 22.89 μM.	It caused cancer cells to stop dividing in the S phase (DNA replication stage). It triggered apoptosis through mitochondrial dysfunction (the cell's energy factories stopped working properly).
Complex 24 a-c Kun Hu et al.[65]	HeLa cells, Hep-G2, NCI-H460, MGC80-3.	The complexes 24a-c showed high toxicity towards HeLa cell line with lower than cisplatin. IC_{50}values for a-c complex 18.72±1.03µM 15.76±1.19µM 9.98±0.87µM respectively.	24c's benzocaine-modified quinoline Schiff base makes it more electron-rich, planar, and hydrophobic, which enhances ROS-mediated apoptosis. That's why it shows superior anticancer activity compared to 24a and 24b.
Complex 27 (i-iii) Ramachandran et al. [66]	MCF-7, HCT-15, BxPC3, HEK293, Human ovarian cancer cell line2008, resistant subline C13*cells, A431.	Copper complexes were much stronger, especially against breast cancer (MCF-7). Complex 27 (ii) was ~175× more potent than cisplatin. Their IC50 values were very low: Complex 27 i - 0.13 µM Complex 27 ii - 0.05 µM Complex 27 iii - 0.07 µM	The different position of the OH moiety gave different profiles of cytotoxic activity. Copper complexes were more toxic to cancer cells than to normal HEK293 cells, suggesting therapeutic potential.
Complex 29 Chagas et al. [54]	MCF-7	Complex 29 showed 29% and 36% mortality in comparison with cisplatin (39.1%) and cyclophosphamide (38.9%).	Low toxicity. Cu-N/O coordination may stabilize the ligand but does not strongly enhance cytotoxicity of complex.
Complex 31 & 32 Choroba et al. [67]	A2780 (ovarian cancer derived cell line), HCT116 (colorectal cancer derived cell line).	Complex 31 best for A2780 (0.5±0.08µM). Cu Complexes showed effective activeness in both cancer cell lines. complex 32 best for HCT116 (0.2±0.08 µM).	They caused apoptosis (programmed cell death) in cancer cells.
Complex 39 Patil et al. [68]	lung cancer cell line (A-549), Human breast cancer cell line (MCF-7).	Among all prepared compounds, Cu-complex has shown prominent results with IC_{50} values 37.0347.3 µg/mL and 39.4347.3 µg/mL, for A-549 and MCF-7 cancer cells respectively.	This study concluded that Cu-complex can developed as a lead drug for cancer.

Complex 40 Vibhute et al. [69]	MCF-7, HCT-116, A549 (lung cancer cell line).	Copper complex proved non-toxic against MCF-7, A549 and HCT-116 cell lines with (GI50 /GI90) >100 µg/mL	Complex was effective against TB strains but not harmful to human cancer cells, succeeding them as promising candidates for safe antitubercular drugs.
Complex 41 Choroba et al.[70]	A2780 (ovarian carcinoma), HCT116 (colorectal carcinoma).	Cu complex showed highest cytotoxic effect in the HCT116 cell line.	Greater ligand planarity correlates with stronger DNA destabilization and cytotoxicity.
Complex 43 (1-12) Shen et al. [71]	MGC80−3, SKOV3, T24, HepG2.	Most of the copper complexes exhibited considerable cytotoxicity toward **T24 bladder cancer cells** as compared with other cells, which demonstrated selective cytotoxicity of the complexes. Results of this study showed that Halogen atoms at position R4 displayed higher antiproliferative activity than cisplatin.	Preliminary structure−activity relationship clearly indicated that the overall cell uptakes of complexes which had an F atom at position R of salicylaldehyde or a halogen substituent at position R4 of salicylaldehyde were relatively higher than those of other complexes.
Complex 44 & 45 Shumi et al. [61]	MCF-7 human breast cancer cell line	Complex 44 showed strong activity against MCF-7 breast cancer cells (IC_{50} 43.8µg/mL).	ROS generation enhanced cytotoxicity.
Complex 46 Seleem et al. [72]	Anticancer effect towards Ehrlich Ascites Carcinoma.	IC_{50} value for ligand 85.2 µg/mL IC_{50} value for copper complex 47.3 µg/mL	Higher than free ligand. Molecular docking with CDK-2 receptor showed enhanced binding affinities for complexes, correlating with their anticancer potency.
Complex 47 Primik et al. [73]	A549 (lung cancer), CH1 (ovarian cancer), SW480 (colon cancer).	MIC values: A549 – 29 ±4 µM CH1- 6.8 ±1.4 µM SW480 – 22 ±2 µM Active in micromolar range moderate potency.	Similar or slightly weaker than ligand in some cell lines.

DISCUSSION

Commonly investigated cell lines in this review include breast cancer (MCF-7), cervical cancer (HeLa), colon cancer (HT-29), colorectal carcinoma (HCT116), lung cancer (A549). Few other cell lines also studied in this review. Above mentioned review study of scientific research showed that complexes synthesised from quinoline ligand and copper transition metal have significant toxicity against these cell lines. In most of cases, the increased toxicity showed by complexes in comparison to free ligand. These findings emphasized on the importance of metal coordination in enhancing biological efficacy.

For determining cell viability, MTT assay method is the most extensively used due to its simplicity and reliability. The reported IC_{50} values indicate that many copper–quinoline complexes possess moderate to strong anticancer activity, depending on their structural features such as greater ligand and its metal complex planarity correlates with stronger DNA destabilization and cytotoxicity. This review findings displayed that Complex 27 (ii) was ~175× more potent than cisplatin, which clearly demonstrated that copper-quinoline complex can act as potent anticancer agents. Cause of increased cytotoxicity, observed across the studies is that complexation with copper metal enhances the lipophilicity and redox properties of the compounds, enabling their cellular uptake and interaction with critical biomolecules such as DNA and cellular proteins. Mechanically, these complexes often induce apoptosis through ROS generation, oxidative stress, and mitochondrial damage. In conclusion, copper–quinoline metal complexes represent a promising class of anticancer agents with versatile mechanisms of action. Fig. 4 and 5 represent comparative analysis of potential of different complexes.

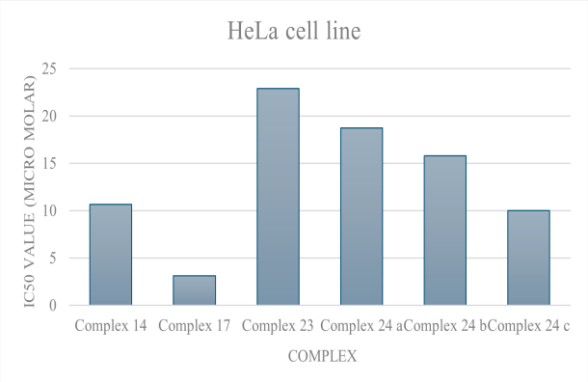


Fig. 4 Graphical analysis of IC_{50} values of complexes.

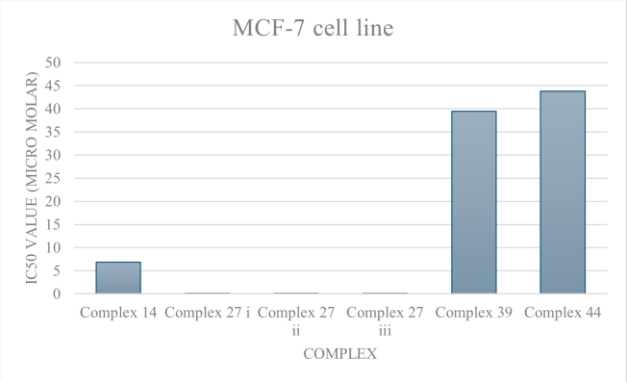


Fig. 5 Graphical analysis of IC_{50} values of complexes.

DNA BINDING AND DNA CLEAVAGE STUDY OF QUINOLINE BASED Cu COMPLEXES

Study about interaction of metal complex with DNA is a key feature in deep understanding of their biological and pharmacological potential, predominantly in the development of anticancer agents. DNA serves as a main intracellular target for many therapeutic compounds, and its binding or cleavage can significantly influence cellular processes such as replication and transcription. These processes decide mechanism of action of drugs. Therefore, the investigation of DNA binding and cleavage properties of metal complexes has attended large importance in field of medicinal chemistry. In recent year copper-based complexes in coordination with quinoline, have attracted attention due to their characteristic of coordination chemistry and redox properties.

In this review, the DNA binding and cleavage activities of quinoline-based copper complexes are systematically summarized in tabular form via table 4 and table 5 respectively, highlighting key parameters such as binding constants, modes of interaction, and cleavage efficiency.

Table 4: DNA binding studies.

Reference & complex	DNA	Key findings	Analysis
Complex 7a, 7b Dixit et al. [74]	Plasmid (pUC 19) DNA Calf Thymus DNA	Metal complexes bind DNA much better than free ligands. Copper complex 7a showed the strongest DNA binding. The DNA binding ability also In-creased as the conc. of metal complexes increased.	Copper's redox activity and planar ligand structure showed strongest intercalation
Complex 14 Lu et al. [63]	CT-DNA	Binding constants (K^b) for Cu Complex $1.89 \times 10^6\ M^{-1}$.	Moderate intercalative mode of binding.
Complex 24 a-c Kun Hu et al. [65]	human serum albumin (HSA) and calf thymus DNA (CT-DNA)	HAS binding as Comp. a< comp. b< comp. c All complexes showed effective binding ability towards CT- DNA via intercalative mode.	Greater binding of Complex 24c comparison to 24a and 24b is due to its higher solubility in aqueous medium.
Complex 27 (i-iii) Ramachandran et al. [66]	CT-DNA	Binding efficiency of complexes was found in order i < iii< ii .	Presence of free OH group at meta or para positions influence binding ability of complexes.
complex 48 a-d Bihai et al. [75]	CT-DNA base binding	Complexes 48 a-d inter-acted with CT-DNA in an intercalation manner. Complex 48c showed strong intercalation with calf thymus DNA (CT-DNA).	Structural and electronic factors influenced the binding of complex 48 c.

Table 5: DNA cleavage studies.

Reference & complex	DNA	Key findings	Analysis
Complex 5 & 6 Narayanachar et al. [37]	E. coli DNA S. aureus DNA A. niger DNA	Both complexes showed partial cleavage of E. coli DNA and S. aureus DNA whereas complete cleavage of A. niger DNA.	Confirms that the biological activity of these compounds is linked to their ability to damage DNA. Suggests these complexes could be developed as antimicrobial or anticancer agents.
Complex 11 Karekal et al. [40]	E. coli DNA	Cu complex showed complete cleavage of DNA of *E.coli.*	Finding of this research revealed importance of coordination of nitrogen and oxygen to the metal ion. Complex may emerge as potent agent against to growth of *E. coli*.
Complex 13 Yernale et al. [42]	plasmid DNA (pBR322)	Free ligand and its Cu(II) complex showed complete cleavage of super coiled DNA.	Good pathogenic microorganism inhibitor.
Complex 14 Lu et al. [63]	pBR322DNA	Complex efficiently cleaved supercoiled DNA, converting it to nicked and linear forms.	DNA cleavage results shows that complex can act as more potential anticancer drug candidate.
Complex 27 (i-iii) Ramachandran et al. [66]	Plasmid pUC19 DNA cleavage with reducing agent (ascorbic acid, 50 mM)a	Efficacy order for synthesized complex was iii > ii > i	The OH group's position on the phenyl ring influences how well the complex interacts with DNA and promotes cleavage.

DISCUSSION

This review of scientific studies specified that quinoline derivatives-based copper complexes display significant DNA binding affinity and effective cleavage activity, accompanying their capability as therapeutic agents. Various spectroscopic and analytical techniques have been employed to study DNA interactions, such as fluorescence spectroscopy, UV–visible absorption spectroscopy, circular dichroism and viscosity measurements. UV–visible and fluorescence studies are most frequently used techniques to determine binding constants and finally explain interaction modes of DNA binding.

Most of time, Copper–quinoline complexes bind to DNA through intercalation mode. In some cases, groove binding or mixed binding modes have also been reported. Binding modes depends on ligand structure and coordination geometry, and mode of binding are supported by hypochromic shifts, bathochromic shifts, and increased viscosity values. Binding constant (K^b) values decide the strength of binding.

DNA cleavage studies, in general performed using agarose gel electrophoresis, show that these complexes can efficiently split supercoiled DNA into nicked or linear forms. The cleavage activity is often enhanced in the presence of oxidizing agents, light which indicate an oxidative mechanism mediated by ROS by radicals. The redox-active nature of copper metal plays an important role in accelerating such nuclease-like behaviour.

This review highlighted that structural modifications in quinoline ligands significantly influence both DNA binding affinity and cleavage efficiency. Complexes with planar aromatic systems tend to show stronger intercalative interactions, while substituents affecting electronic properties can modulate redox activity and, consequently, DNA cleavage potential. In conclusion, quinoline-based copper complexes exhibit strong DNA binding and efficient cleavage activity through multiple mechanisms, including intercalation and ROS-mediated oxidative cleavage.

LIGANDS IUPAC NAME AND COORDINATION COMPOUND FORMULA

The IUPAC names of the ligands and the chemical formulas of their corresponding Cu complexes investigated in this review are listed in Table 6.

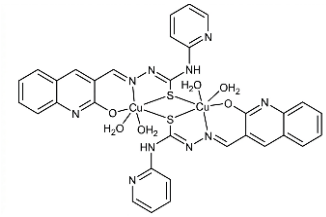
Table 6: Ligands IUPAC name and coordination compound formula.

C.N.	Ligand	Complex formula
1	2-[(2-hydroxyquinolin-3-yl)methylidene]-methyl hydrazine-1-carbothioamide	$[CuL\,H(H_2O)Cl]$
2	2-[(2-hydroxyquinolin-3-yl)methylidene]- -(pyridinyl)hydrazine-1-carbothioamide	$[Cu_2L^2(H_2O)_4]$
3	6-bromo-2-chloromethyl-3-(8-hydroxyquinolin-5-yl)-3(H)quinazolin-4-one	$[Cu(HL)_2(H_2O)]Cl_2$

4	5-{(4-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-ylsulfonyl)phenyl amino)-methyl} quinolin-8-ol	$[Cu(L)_2(H_2O)_2]$
5	N,N′-bis((8-hydroxyquinoline-2-yl)methylidene)benzene	$[Cu(L)(H_2O)_2]$
6	N,N′-bis((8-hydroxyquinoline-2-yl)methylidene)-4-nitrobenzene	$[Cu(L)(H_2O)_2]$
7a	LAH AHQMBSH (4-amino-N'-[(8-hydroxyquinolin-5-yl)methyl]benzenesulfonohydrazide)	$[Cu(LAH)_2(H_2O)_2]$
7b	LH HQMABS (4-{[(8-hydroxyquinolin-5-yl)methyl]amino}benzenesulfonamide)	$[Cu(LH)_2(H_2O)_2]$
8a	8-((pyridin-2 yl)methylthio) quinoline ($TQMP_2$)	$[Cu(TQMP_2)_2](BF_4)_2(H_2O)_2$
8b	8-((pyridin-3-yl)methylthio) quinoline ($TQMP_3$)	$\{Cu(TQMP_3)(CF_3CO_2)_2\}$
8c	2,6-bis (8-quinolinylthiom ethyl) pyridine (DTQMP)	$[Cu(DTQMP)(CF_3CO_2)](CF_3CO_2)(H_2O)_2$
9	3-{(2E)-2-[(2hydroxyquinolin-3yl)methylidene]hydrazinyl}quinoxalin-2-ol (QZOH)	$[Cu(QZOH)_2]$
10	3-{(2E)-2-[(2-sulfanylquinolin-3yl)methylidene]hydrazinyl}quinoxalin-2-ol (QZSH)	$[Cu(QZSH)_2]$
11	5-chloro-N-(2′-dihydro-2′-oxoquinolin-3′-yl methylene) 3-phenyl-1H-indole-2-carbohydrazide (HL)	$[Cu(L)_2]H_2O$
12	N-(quinolin-8-yl)pyrazine-2-carboxamide	$[Cu(L)(OAc)]\cdot H_2O$
13	N-(4-phenylthiazol-2yl)-2-((2-thiaxo-1,2-dihydroquinolin-3-yl)methylene)hydrazinecarboxamide	$[CuL(Cl)_2]$
14	N,N-bis(quinolin-2-ylmethyl) quinolin-8-amine	$[CuLCl]ClO_4$
15	1-(8-Hydroxy quinolin-2yl-methyl) thiourea	[CuL]
16	3-[(E)-(4H-1,2,4-triazol-4-ylimino)methyl]quinoline-2-thiol	$[Cu(L)_2(OAc)_2]$
17	(E)-N-(furan-2-ylmethylene)quinolin-8-amine	$[CuL_2]Cl_2$
18	Mix ligand: 8-hydroxyquinoline (HQ) and (3Z)-3-{[2 hydroxybenzylidene]hydrazinylidene}-1,3dihydro-2-indol-2-one (HL)	$[Cu(L)(Q)H_2O]$
19	2,6-bis (8-quinolinylthiomethyl) pyridine	$[Cu(L)(CF_3SO_3)](CF_3SO)$
20	(1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid)	$[Cu(NO_3)_2(LH)_2]H_2O$
21	3-((5-chloro-2-phenyl-1H-indol-3-ylimino)methyl)quinoline-2(1H)-thione	$[CuLCl_2]$
22	Mix ligand: dipotassium sodium7-((E)-2-(2-((Z)-1-carboxylatoethylidene amino)thiazol-4-yl)-2(carboxylatemethoxyimino)acetamido)-8-oxo-3-vinyl-5- thia-1-azabicyclo[4.2.0]oct-2- ene-2-carb oxylate [NaK2L] 8-hydroxyquinoline [HQ]	$[(Cu_2(Q)_2(KL)(H_2O)_4]$
23	6-methyl-2-oxo-quinoline-3-carbaldehyde thiosemicarbazone	$[Cu(H\text{-}L)NO_3H_2O].NO_3$
24	a: (E)-methyl4-((quinolin-8-ylmethylene)amino) benzoate	$[Cu(L)(NO_3)_2]$
	b: (E)-ethyl4-((quinolin-8-ylmethylene)amino) benzoate	$[Cu(L)(Cl)_2]$
	c: (E)-ethyl4-((quinolin-8-ylmethylene)amino) benzoate	$[(Cu)_2(L)_2(SO_4)_2]\cdot H2O$
25	6-methoxyquinoline (6-MeOQ)	$[CuCl_2(6\text{-}MeOQ)_2]$
26	Mix ligand 2-((4-amino-5-(3,4,5-trimethoxybenzyl)pyrimidine2 -ylimino) (phenyl)methyl)benzoic acid [HL] 8-hydroxyquinoline [HQ]	$[Cu(L)(Q)(H_2O)]$
27	2-Oxo-1,2-dihydrobenzo[h]quinoline-3-carbaldehyde(R′-hydroxybenzoyl)hydrazine *Here R′- represents different positions of OH group*	$[Cu(HL_1)(CH_3OH)(NO_3)]$ $[Cu(HL_2)(CH_3OH)(NO_3)]$ $[Cu(HL_3)(H_2O)(NO_3)]$
28	Mix ligand 2,2′(((2(dimethylamino)ethyl)azanediyl)bis(methylene))bis(4-	$[Cu(L)(Q)]$

	(tert-butyl)phenol) (L) 8-hydroxyquinoline (Q)	
29	5-nitro-8-hydroxyquinoline	$[CuL_2]$
30	5-chloro-8-hydroxyquinoline	$[CuL_2]$
31	4′-(2-quinoline)- 2,2′:6′,2″-terpyridine	$[Cu(L)(Cl)_2]$
32	4′-(2-quinoline)- 2,6-di(pyrazin-2-yl)pyridine	$[Cu(L)(Cl)_2]$
33	2-oxo-1,2-dihydroquinoline-4-carbohydrazide	$[Cu(L)_2](NO_3)_2.(H_2O)_2$
34	N-(4-fluorobenzylidene)-2-(quinolin-8-yloxy) acetohydrazide (HL)	$[Cu(L)_2].5H_2O$
35	N-(4-fluorobenzylidene)-2-(quinolin-8-yloxy) acetohydrazide (HL)	$[Cu(L)(H_2O)Cl]$
36	N^1 ,N^2-bis(4-methyl quinolin-2-yl)benzene-1,2-diamine	$[Cu(L)Cl_2]2H_2O$
37	Mix ligand: L_1 : 2-(8-quinolyl azo)-4,6-dimethyl phenol and L_2: Imidazole molecule	$[Cu(L_1)(L_2)_2Cl]$
38	HNNS: Quinoline-2-carboxaldehyde 4-methyl-3-thiosemicarbazone	$[Cu(HNNS)(NO_3)_2]$
39	LH: (E)-N′-((2-hydroxyquinolin-3 yl) methylene)-4-methylbenzenesulfonohydrazide	$[Cu(L)_2]$
40	(E)-N′-((2-hydroxy 6-methylquinolin-3-yl) methylene)-4-methyl benzenesulfonohydrazide	$[Cu(L)_2]$
41	4-(2-quinolinyl)-2,2′:6′,2″-terpyridine	$[Cu(4\text{-}(2\text{-quin})\text{-terpy})Cl](PF_6)$
42	((E)-2-(((2-((2 hydroxyethyl)amino)quinolin-3-yl)methylene)amino)ethanol.	$[Cu(H_2L)(H_2O)(NO_3)]$
43	H-L1−H-L12 (E)-2-(((2-(2-fluorophenyl)quinoline-3-yl)imino)methyl)-3-R1-4-R2-5-R3-6-R4-phenol	$[Cu(L_1)_2]-[Cu(L_{12})_2]$
44	(Z)-3-(((2-((2-Aminophenyl) Thio)phenyl)imino)methyl)-7-chloronaphthalen-2-ol	$[Cu(L)(H_2O)_2(Cl)_2]$
45	(Z)-3-(((2-((2-Aminophenyl) Thio)phenyl)imino)methyl)-7-chloronaphthalen-2-ol	$[CuL_2(Cl)_2]$
46	3-[2-(4,7-dimethylquinolin-2-yl)hydrazinylidene]butan-2-one	$[Cu_2(L)(Cl)_3].½MeOH$
47	Diethyl-2,2′-((3-(((5H-indolo[3,2-c]quinolin-6(11H)-ylidene) hydrazono)methyl)-2-hydroxy-5-methylbenzyl)azanediyl) diacetate	$[Cu_2(L)(CH_3COO)_2]$
48	(16E)-2,6-dimethyl-N-(2-phenylquinoline-4(1H)-ylidene)-5-(phenylselanyl) pyrimidine-4-amine	$[Cu(L)(OAc)_2]$
49	1-cyclopropyl-6-fluoro-1,4-dihydro-7-[(1S,4S)-5 methyl-2,5-diazabicyclo [2.2.1]hept-2-yl]-4-oxoquinoline-3-carboxylic acid	$[Cu(DNX)_2](NO_3)_2$

STRUCTURES OF STUDIED COPPER COMPLEXES



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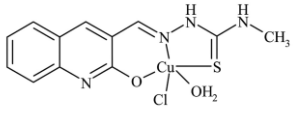

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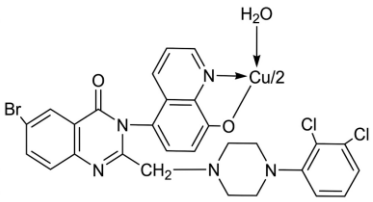

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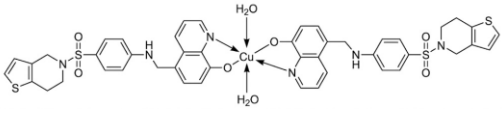

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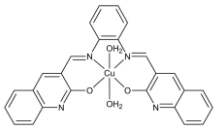

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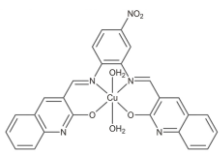

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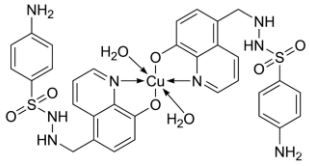

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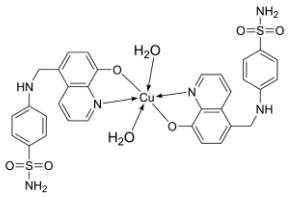

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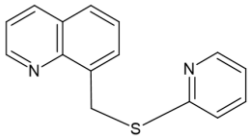
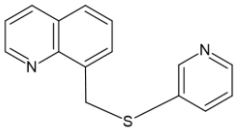


8 a ligand



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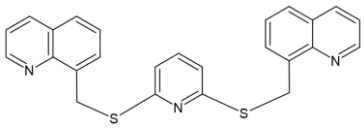
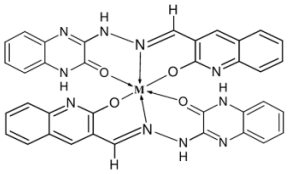


8 c ligand



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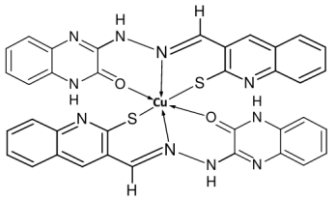

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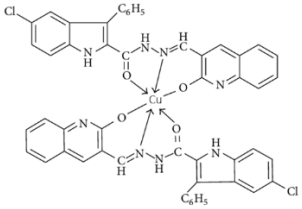

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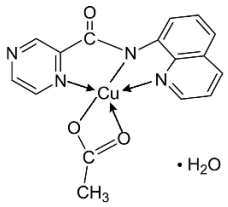

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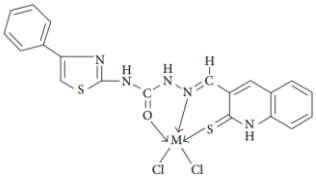

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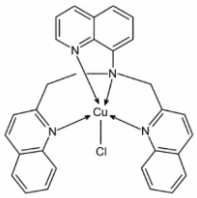

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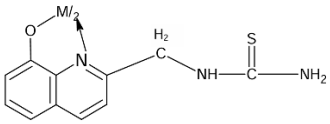

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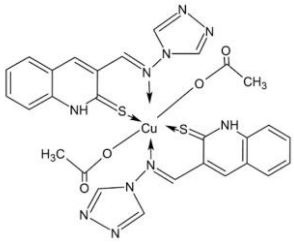

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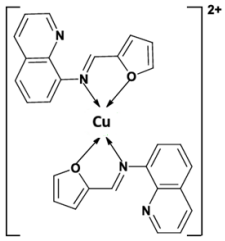

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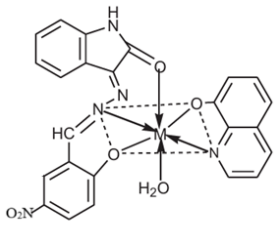
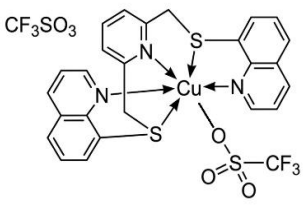


Complex 18



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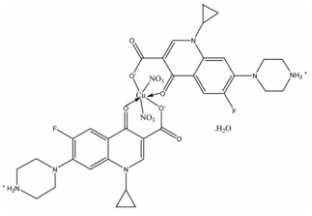
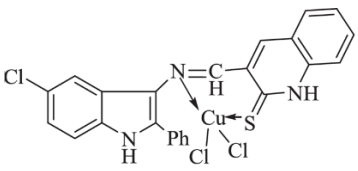


Complex 20



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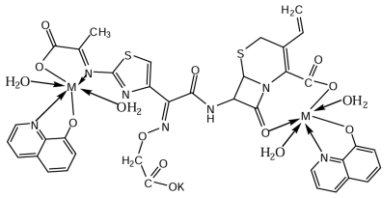

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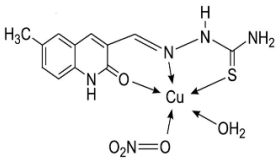

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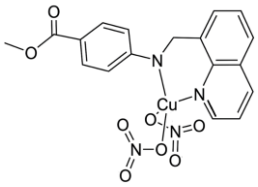
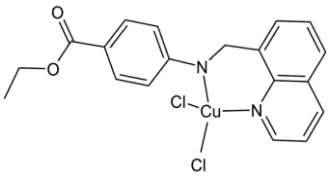
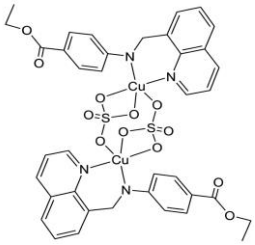


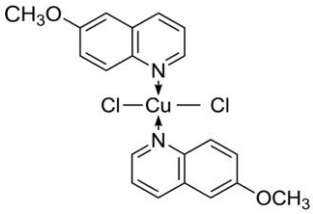
Complex 24 a



Complex 24 b



Complex 24 c



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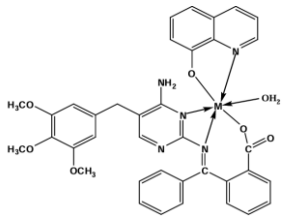
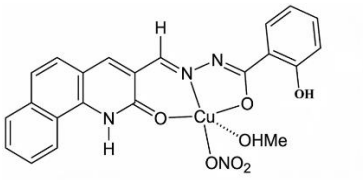
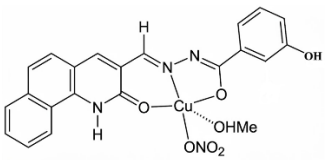


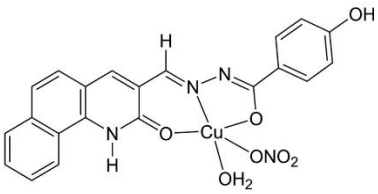
Complex 26



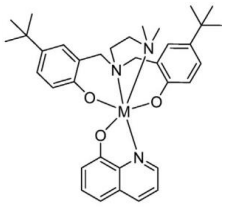
Complex 27 (i)



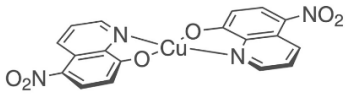
Complex 27 (ii)



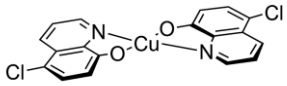
Complex 27 (iii)



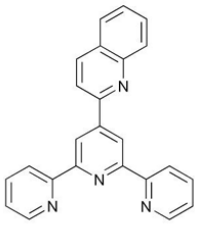
Complex 28



Complex 29

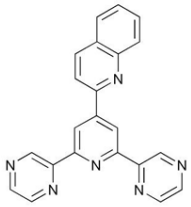


Complex 30



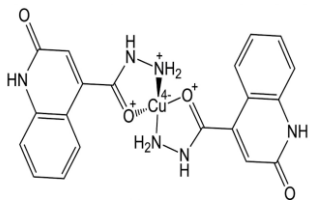
4'-(quinol-2-yl)-terpy

31 ligand

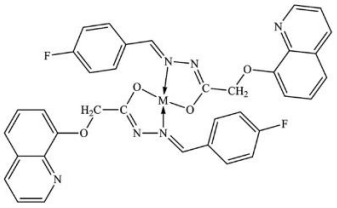


4-(quinol-2-yl)-dppy

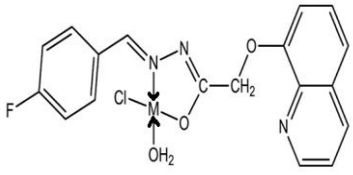
32 ligand



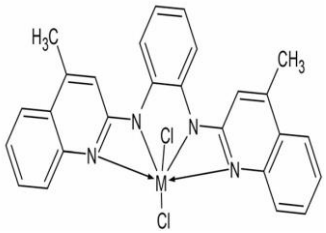
Complex 33



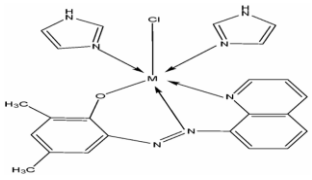
Complex 34



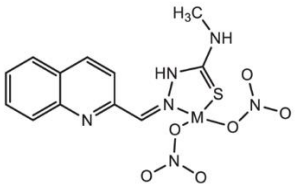
Complex 35



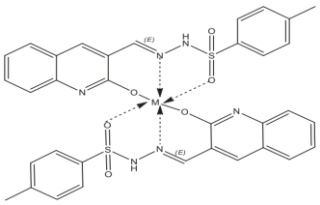
Complex 36



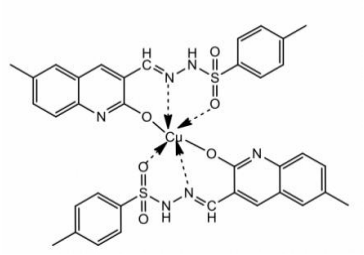
Complex 37



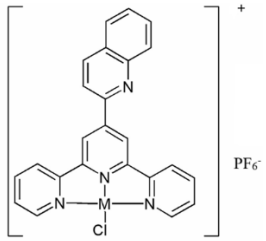
Complex 38



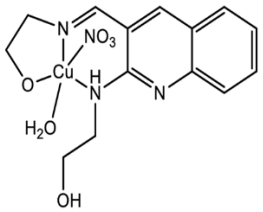
Complex 39



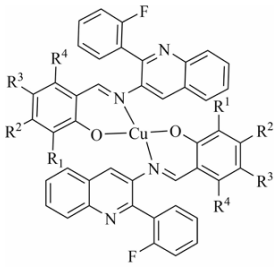
Complex 40



Complex 41



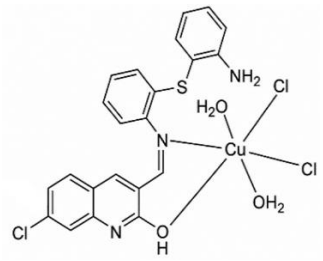
Complex 42



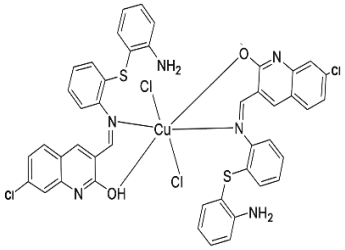
Complex 43 (1-12)

Here

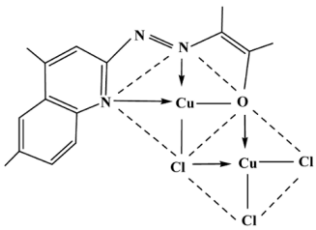
L_1	R^1=F, R^2, R^3, R^4=H	L_7	R^3=F, R^1, R^2, R^4=H
L_2	R^1=Cl, R^2, R^3, R^4=H	L_8	R^3=Cl, R^1, R^2, R^4=H
L_3	R^1=Br, R^2, R^3, R^4=H	L_9	R^3=Br, R^1, R^2, R^4=H
L_4	R^2=F, R^1, R^3, R^4=H	L_{10}	R^4=F, R^1, R^2, R^3=H
L_5	R^2=Cl, R^1, R^3, R^4=H	L_{11}	R^4=Cl, R^1, R^2, R^3=H
L_6	R^2=Br, R^1, R^3, R^4=H	L_{12}	R^4=Br, R^1, R^2, R^3=H



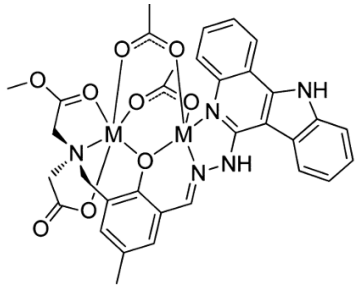
Complex 44



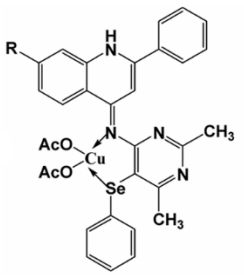
Complex 45



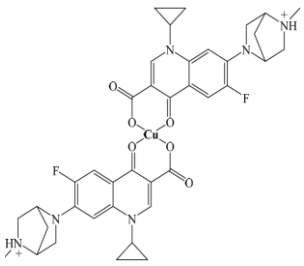
Complex 46



Complex 46



Complex 48 (a-d)



Complex 49

For complex 48 a-d
a, R=H
b, R=OH
c, R=NO_2
d, R=Cl

[M=Cu]

Fig. 6 Complexes structures.

CONCLUSION AND FUTURE ASPECT

On the basis of above review study, it may be concluded that Copper–quinoline metal complexes have appeared as a promising class of coordination compounds which exhibits significant biological activities such as antibacterial, antifungal, anticancer, DNA binding and DNA cleavage properties. Incorporation of cupper metal with free quinoline based ligand enhances the pharmacological capability of these ligands. This improvement in antimicrobial properties may be due to increase in their stability, lipophilicity, and ability to interact with biological targets on chelation (Tweedy's chelation theory). Numerous studies have demonstrated that increased antibacterial, antifungal, anticancer, DNA binding and DNA cleavage properties can accomplish them as potential candidates for antimicrobial drug, chemotherapeutic agents. Structure activity relationships explain the role of ligand substitution, geometry, structure of complexes, oxidation state of copper ion in biological efficiency. Even after showing incredible biological possibility by copper–quinoline complexes there are several challenges and limitations which may be turn in future opportunities for medicinal chemistry. Insufficient knowledge about effect of structure, geometry and position of different substituents on complexes' antimicrobial potential, makes the drug development process lengthy, costly, difficult and time consuming. To overcome from these challenges extended SAR studies, molecular docking studied and DFT calculation are required. These computational tools develop understanding about ligand-complex modifications which further enhance antibiological properties, selectivity and toxicity.

ACKNOWLEDGEMENT

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