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Insights into Quinoline Schiff Bases as Anticancer Agents

Gandhi Mansi K. [a], ***Dr. Shashi V. Ranga*** [b]

[a] *Research Scholar, Department of Chemistry, Gujarat technological University, Ahmedabad 382424, Gujarat, India*
[b] *Assistant Professor, Department of Chemistry, Gujarat technological University, Ahmedabad 382424, Gujarat, India*
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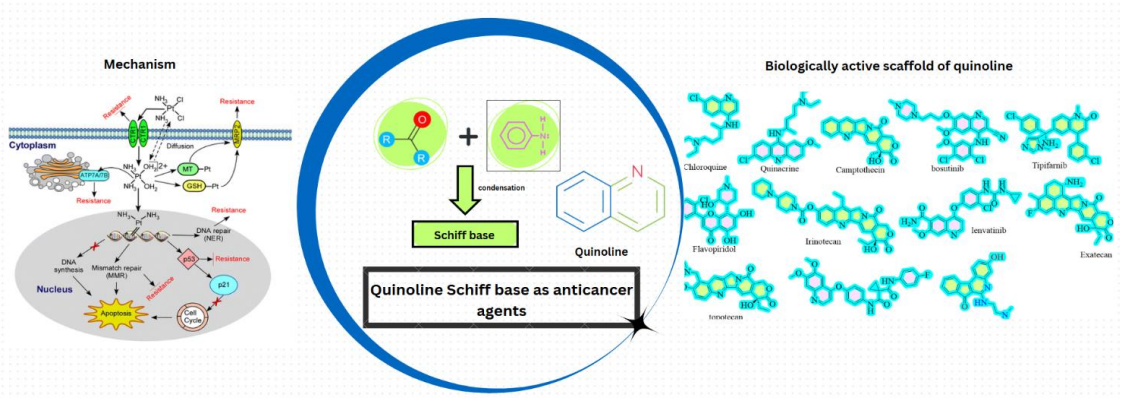
A B S T R A C T

Quinoline Schiff bases are a distinct category of chemical compounds that show potential anticancer characteristics due to their unique structural flexibility. The present study investigates how these compounds interact with several types of cancer, with a specific emphasis on understanding how structures affect their effectiveness. Important structures in this group have effects such as insertion into DNA, generating reactive oxygen species (ROS), triggering cell death, and blocking enzyme activity, all of which hinder the growth of cancer cells. Analysing structure-activity relationships (SAR) helps identify changes in the structure that enhance effectiveness and specificity while reducing harm. Future research will explore new delivery methods and enhancements to increase the availability and effectiveness of treatment. Overall, quinoline Schiff bases represent promising scaffolds for the development of next-generation anticancer drugs.

Keywords: Quinoline Schiff Bases (QSBs); Cancer Therapy; Anticancer Agents; Selective Cytotoxicity; Drug-Resistant Cancers; Metal Complexes

Graphical abstract:



Introduction

Cancer is a critical global health issue, with an estimated 19.3 million new cases and 10 million deaths reported in 2020 [1]. Low- and middle-income countries bear a disproportionate burden, accounting for approximately 70% of global cancer deaths [2]. Breast cancer has become the most diagnosed cancer worldwide, with 2.3 million new cases in 2020, and is the leading cause of cancer-related deaths among women [1,3] . Incidence rates vary significantly across regions, with higher rates in more developed countries [4]. However, survival rates are less favorable in less developed regions due to factors such as delayed diagnosis and limited access to effective treatment [3]. Projections indicate that by 2040, the global cancer burden may rise to 28.4 million cases annually, with a larger increase expected in transitioning countries [1].

In response to this growing crisis, Quinoline-based compounds have emerged as promising candidates for cancer therapy due to their diverse biological properties and mechanisms of action [5,6]. These compounds exhibit anticancer activities through various pathways, including apoptosis induction, cell cycle arrest, inhibition of angiogenesis, and disruption of cell migration [7,8] . Quinoline derivatives have shown strong effectiveness against several cancer types, including breast, colon, lung, and kidney cancers [6].Their synthetic versatility allows for the generation of structurally diverse derivatives, enhancing their potential as anticancer agents [8] . However, challenges such as poor bioavailability, potential off-target effects, and resistance mechanisms need to be addressed to fully realize the therapeutic potential of quinoline-based drugs [5] . Ongoing research is focused on developing more effective quinoline-derived anticancer drugs and overcoming these obstacles.

The structural diversity of quinoline-based compounds has positioned them as privileged scaffolds in anticancer drug discovery [8,9]. Modifying the quinoline scaffold by adding specific chemical groups can significantly enhance its anticancer activity, with electron-withdrawing groups typically yielding more potent effects than electron-donating groups [10]. Structure-activity relationship studies indicate that modifications at critical positions, particularly the third, sixth, and seventh carbons, can lead to improved potency and selectivity against cancer cells [10]. Quinoline derivatives have also shown promise in inhibiting essential cancer drug targets, including tyrosine kinases, proteasomes, and tubulin polymerization [8] . The inherent presence of hydrogen bond donor (-NH) and acceptor (-C=O) functionalities in the quinoline structure provides numerous opportunities for rational drug design and improvement [10]. Currently, quinoline-based compounds are undergoing clinical trials to assess their specific anticancer effects [9] .

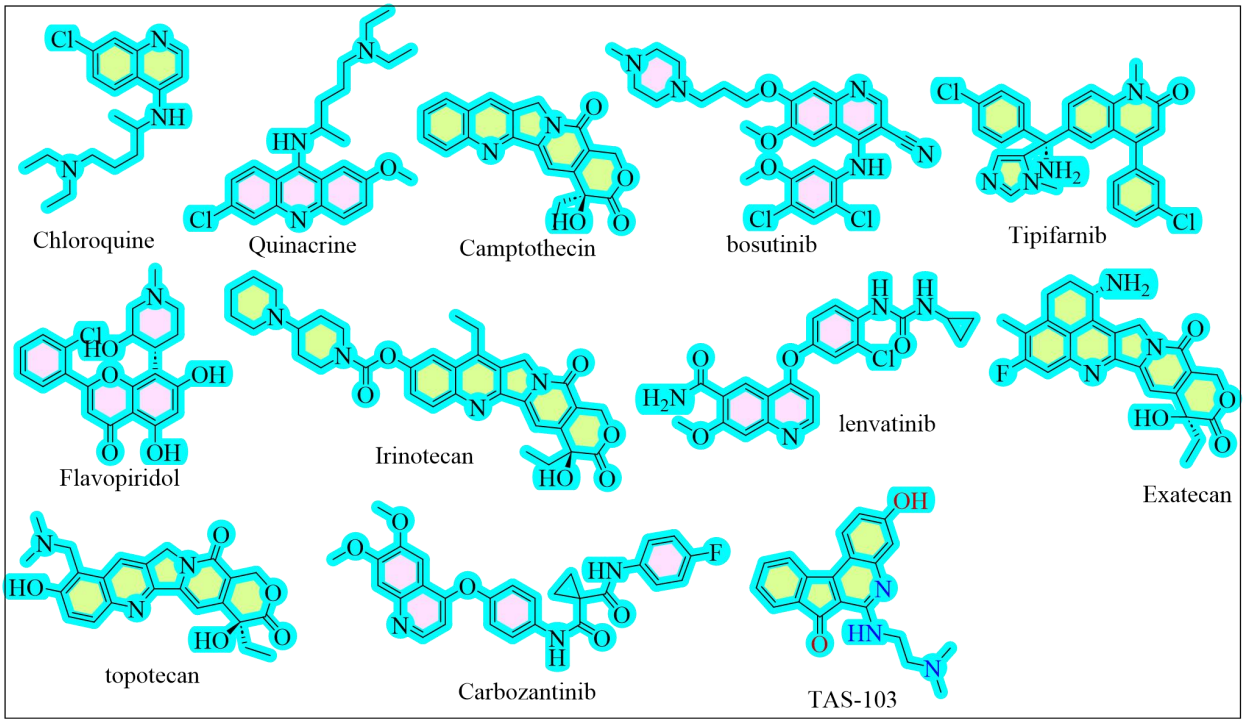


Figure 1: Available marketed drug containing quinoline motifs [11]

The discovery of quinoline derivatives has been pivotal in the development of anticancer drugs, highlighting diverse mechanisms of action and efficacy against various cancer types [6,7] .The landmark discovery of Camptothecin marked a significant milestone in quinoline-based anticancer drug research [7]Several quinoline-derived drugs have already been marketed or are currently in clinical trials, underscoring their clinical relevance [9,11,12].While the only approved quinoline-based anticancer drugs are topoisomerase and kinase inhibitors, over twenty drug candidates are in human trials [9]. The quinoline scaffold, with its well-known structure and established synthetic routes for enhancement, represents a valuable asset in modern medicinal chemistry [9]

This mini review aims to explore the role of quinoline Schiff bases in cancer therapy, focusing on their mechanisms of action, structure-activity relationships, and available market drugs. By analyzing existing literature and presenting successful case studies, this review seeks to stimulate future research on enhancing quinoline Schiff bases and uncovering novel derivatives. The findings will not only deepen our understanding of the anticancer capabilities of quinoline Schiff bases but also assist medicinal chemists in designing innovative compounds capable of effectively combating cancer, thus advancing the development of more effective cancer treatments in the future.

Quinoline: structural requirements for anticancer activity

Recent literature reports indicate the outstanding potential of quinoline derivatives in advancing anticancer drug development, where the structural flexibility of the quinoline ring enables a broad spectrum of therapeutic applications [13] . Through structure-activity relationship (SAR) studies, researchers have observed that the selective substitution of functional groups can increase anticancer properties. For instance, leaving the R_4 and R_5 positions unsubstituted significantly enhances anticancer activity, while introducing heterocyclic aromatic groups at the R_1 position and substituting secondary amino, alkyl, or hydrazone groups at the R_2 or R_3 positions further optimizes efficacy. Additionally, halogen substitutions, especially at R_6, have shown to be beneficial in potentiating the therapeutic effects of quinoline compounds [14–16] (Fig. 2).

Notably, the nitrogen atom in the quinoline core offers flexibility, as it can remain unsubstituted or modified with various alkyl or aryl groups to tailor drug activity, which have demonstrated robust antiproliferative effects across a range of cancer cell lines by inhibiting critical protein kinases such as PDK1, CDK2, and topoisomerase, thereby halting tumor progression [17]. These discoveries underscore a promising direction for medicinal chemistry,

where understanding specific functional groups and substitution sites within the quinoline framework can be leveraged to design highly potent anticancer agents with tailored activity against diverse cancer types [16]

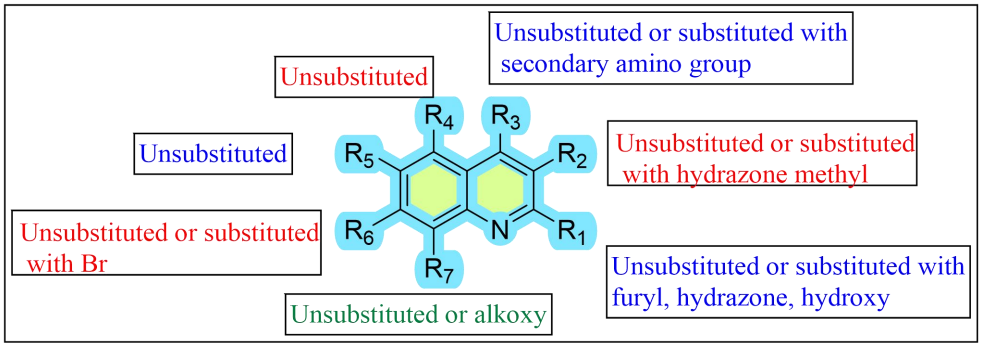


Figure 2 : structural modification of quinoline motifs [16]

Overview of Quinoline Schiff Bases as Anticancer Agents

Quinoline Schiff bases have garnered considerable attention in the field of medicinal chemistry due to their promising anticancer properties. These compounds are derived from quinoline, a heterocyclic structure, and exhibit a variety of mechanisms that can lead to effective cancer treatment.

Quinoline Schiff bases have demonstrated significant anticancer activity against various human tumor cell lines. Pyranoquinolinone-derived Schiff bases showed promising results against MCF-7 breast cancer, HepG2 liver cancer, and HCT-116 colon carcinoma cells, with compound exhibiting the highest potency [18]. Quinoline derivatives have proven effective against several cancer types through mechanisms such as apoptosis induction and cell cycle arrest [6]. Metal complexes of Schiff bases often enhance anticancer activity, with chitosan complexes of Pd(II) and Pt(II) showing high efficacy against MCF-7 cells [19]. A novel quinoline Schiff base and its metal complexes were synthesized and evaluated for cytotoxicity against A-549 and MCF-7 cell lines, with the Cu-complex demonstrating the most promising results[20]. These findings highlight the potential of quinoline Schiff bases and their metal complexes as anticancer agents.

Mechanisms of Action of Quinoline Schiff Base Compounds

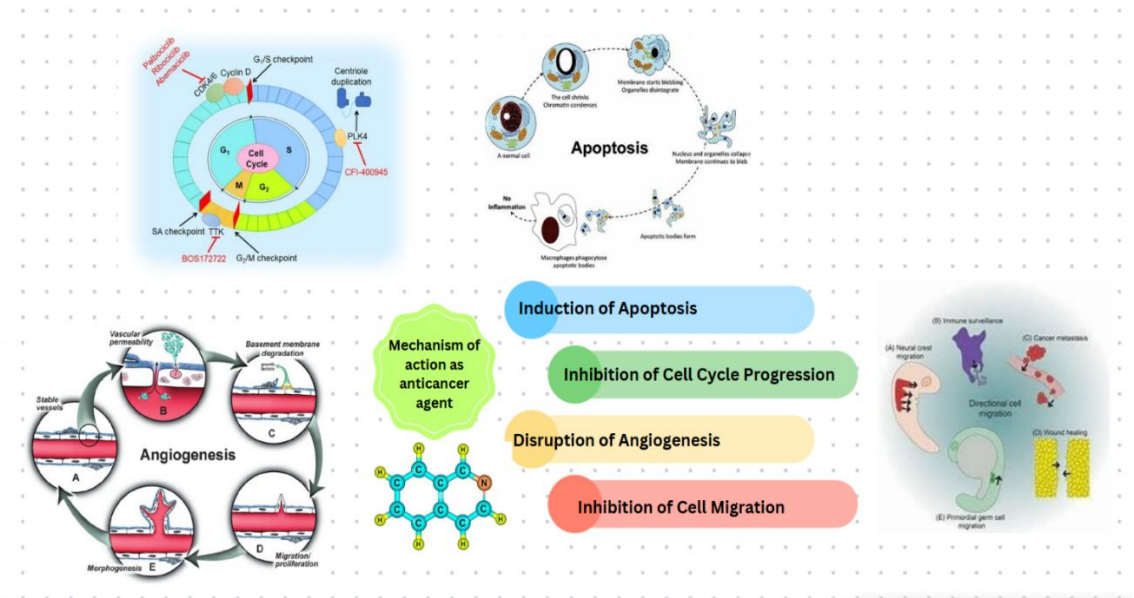


Figure 3 : Mechanism of action as anticancer agent

1. **Induction of Apoptosis**

Quinoline Schiff base compounds have shown promising anticancer properties by inducing apoptosis in various cancer cell lines [21] . These compounds activate both intrinsic and extrinsic apoptotic pathways, often involving the upregulation of pro-apoptotic proteins like Bax and downregulation of anti-apoptotic proteins such as Bcl-2 [19] The mechanism of action includes disruption of mitochondrial membrane potential and activation of caspases, particularly caspase-3[22].Studies have demonstrated the effectiveness of quinoline-based compounds in breast, lung, colon, and liver cancer cells [21,22] .Additionally, some derivatives have shown cell cycle arrest at the G2/M phase [22] .While these compounds show promise as

anticancer agents, challenges such as poor bioavailability and potential resistance mechanisms need to be addressed for successful clinical application[21]

2. **Inhibition of Cell Cycle Progression**

Quinoline-based compounds have emerged as promising anticancer agents, targeting cell cycle progression and inhibiting cancer cell proliferation [21] .These compounds interfere with cell cycle checkpoints, particularly in the G0/G1 or G2/M phases, by downregulating cyclins and cyclin-dependent kinases (CDKs)[23].Quinoline Schiff base structures have been shown to inhibit CDK2/4, blocking the G1 phase in colon cancer cells, and induce G2/M phase arrest in cervical cancer cells [21]Natural flavonoids, a class of phytochemicals, also demonstrate anticancer properties by targeting deregulated cell cycle progression [24] While cell cycle inhibitors show promise in preclinical and early clinical studies, they generally have limited efficacy as single agents [25] Combination strategies with chemotherapeutic agents may enhance their effectiveness against solid tumors and hematologic malignancies[25]

3. **Disruption of Angiogenesis**

Angiogenesis, the formation of new blood vessels, is crucial for tumor growth and metastasis. Inhibiting this process has become a key strategy in cancer treatment. Vascular endothelial growth factor (VEGF) is a primary driver of angiogenesis, and its overexpression is associated with tumor progression [26] .While VEGF-targeted therapies have shown promise, their effectiveness is often limited due to compensatory mechanisms [27] .Research has explored alternative approaches, such as targeting basic fibroblast growth factor (bFGF) with ruthenium(II) complexes [28] and stabilizing VEGF G-quadruplex structures with quindoline derivatives[29]These compounds have demonstrated anti-angiogenic and anti-tumor effects in various models. To overcome the limitations of single-pathway inhibition, recent efforts have focused on developing multi-targeted antiangiogenic agents that simultaneously inhibit multiple signaling pathways, including VEGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) [27]

4. **Inhibition of Cell Migration**

Recent studies have demonstrated the potential of quinoline Schiff bases and related compounds in inhibiting cancer cell migration and invasion [30] They showed that shikonin, a naphthoquinone compound, suppressed lung cancer cell adhesion, invasion, and migration by inhibiting integrin β1 expression and the ERK1/2 signaling pathway. Similarly, they found that 2-Methoxy-1,4-Naphthoquinone (MNQ) inhibited breast cancer cell invasion and migration, while also downregulating matrix metalloproteinase-9 (MMP-9) activity. Teshome reviewed various Schiff bases and their metal complexes, highlighting their anticancer potential against multiple cell lines [31]. Vibhute et al. synthesized a new quinoline Schiff base and its metal complexes, which exhibited excellent anticancer activity against lung cancer cells (A-549) and showed significant binding affinity with tubulin protein in molecular docking studies [20] . These findings suggest that quinoline Schiff bases and related compounds may be promising candidates for anti-metastatic cancer therapies.

5. **Other Relevant Pathways**

Quinoline derivatives have emerged as promising anticancer agents due to their versatile chemical structure and diverse biological activities [32,33] .These compounds exhibit multiple mechanisms of action, including inhibition of protein kinases, disruption of tubulin assembly, and interference with tumor growth signaling pathways [21,33]Quinoline-based molecules target specific receptors such as c-Met, VEGF, and EGF, which are crucial in carcinogenic pathways like Ras/Raf/MEK and PI3K/AkT/mTOR [32] . They also induce apoptosis, modify cell cycles, and generate reactive oxygen species in cancer cells [21] .Furthermore, quinoline compounds have shown inhibitory effects on tyrosine kinases, proteasomes, and topoisomerases [13]. Despite their potential, challenges such as poor bioavailability and resistance mechanisms need to be addressed to fully realize the therapeutic potential of quinoline-based drugs in cancer treatment[21]

These mechanisms collectively highlight the multi-targeted potential of quinoline Schiff base compounds as effective anticancer agents.

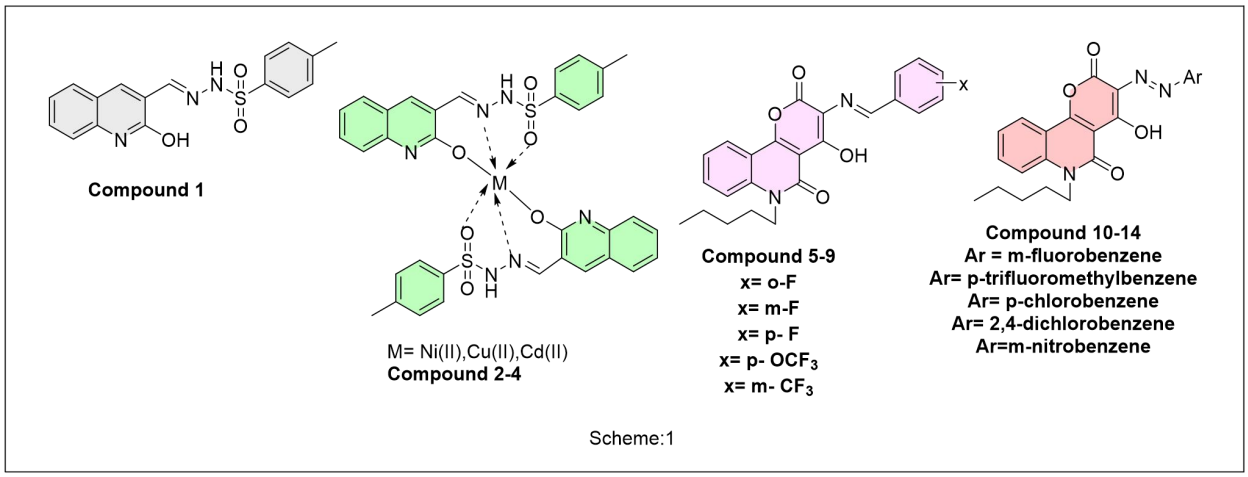
Biologically active scaffolds in relevance to quinoline schiff base as anticancer agents

Several authors have reviewed the diverse pharmacological activities exhibited by quinoline and its derivatives, underscoring their importance in medicinal chemistry. Quinoline derivatives, including Schiff bases, have been widely studied for their broad-spectrum efficacy, highlighting antimicrobial, antiviral, antimalarial, and anticancer properties. In this review, we highlight the anticancer activity of quinoline derivatives, particularly focusing on their potential as therapeutic agents.

This study, conducted by Patil *et al.*, reports the synthesis of a novel quinoline Schiff base (Compound 1) and its metal complexes with Cu(II), Ni(II), Co(II), and Cd(II) (Compounds 2, 3, and 4). Structural confirmation was achieved using FT-IR, NMR, ESI-MS, UV-Visible, and EPR spectroscopy. Cytotoxicity tests on A-549 lung and MCF-7 breast cancer cells showed that the Cu(II) complex (Compound 2) was the most active, with IC_{50} values of 37.03 and 39.43 μM, respectively. Photocleavage studies revealed significant DNA degradation by the Cu-complex, indicating its potential as a lead anticancer agent [20].

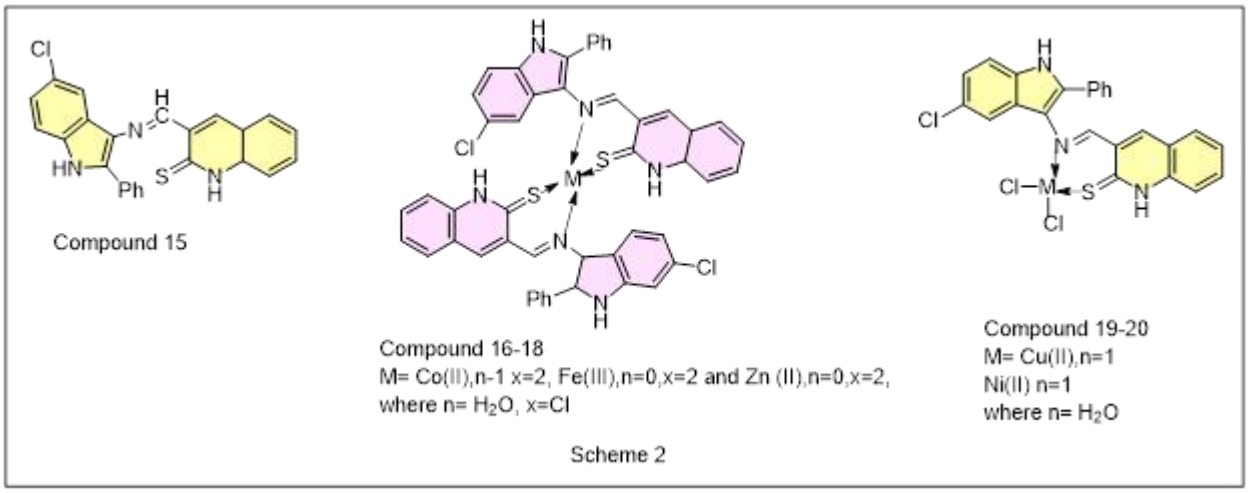
Saeed *et al.* synthesized novel Schiff bases and azo dyes (Compounds 5–14) from pyranoquinolinone, which were characterized and tested for anticancer activity against MCF-7, HepG2, and HCT-116 cell lines. Compounds 8, 9, and especially 10 showed strong activity, with 11

(trifluoromethoxy derivative) demonstrating the highest potency (IC_{50}: 1.82–8.06 µg/mL). These findings suggest pyranoquinolinone derivatives as promising anticancer candidates, warranting further research for potential clinical applications [34] .



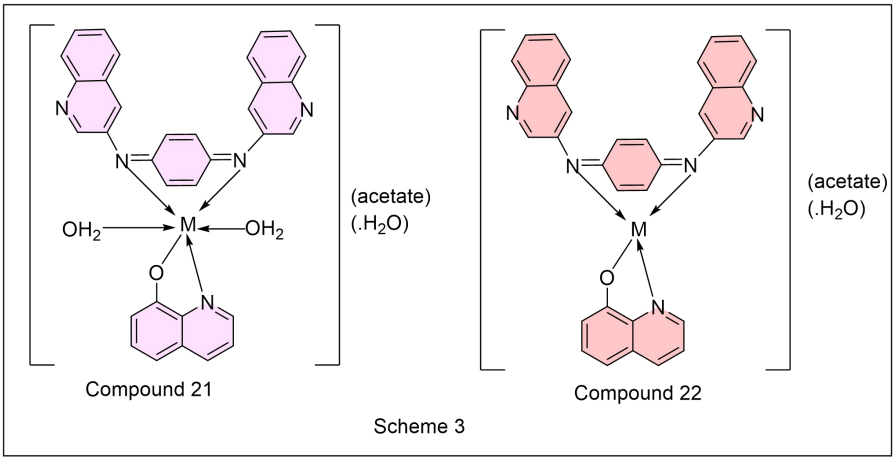
Scheme:1

Vivekanand *et al.* synthesized a quinolone-based Schiff base, 3-((5-chloro-2-phenyl-1H-indol-3-ylimino)methyl)quinoline-2(1H)-thione, along with its Cu(II), Co(II), Ni(II), Zn(II), and Fe(III) complexes. Characterization through various techniques confirmed their non-electrolytic nature and distinct geometries. Biological evaluations revealed that the Cu(II) and Co(II) complexes exhibited strong antibacterial and antifungal activities, while Cu(II), Ni(II), and Zn(II) complexes demonstrated significant antioxidant properties. Notably, their ability to cleave DNA suggests these complexes could serve as promising candidates for anticancer agents [35].

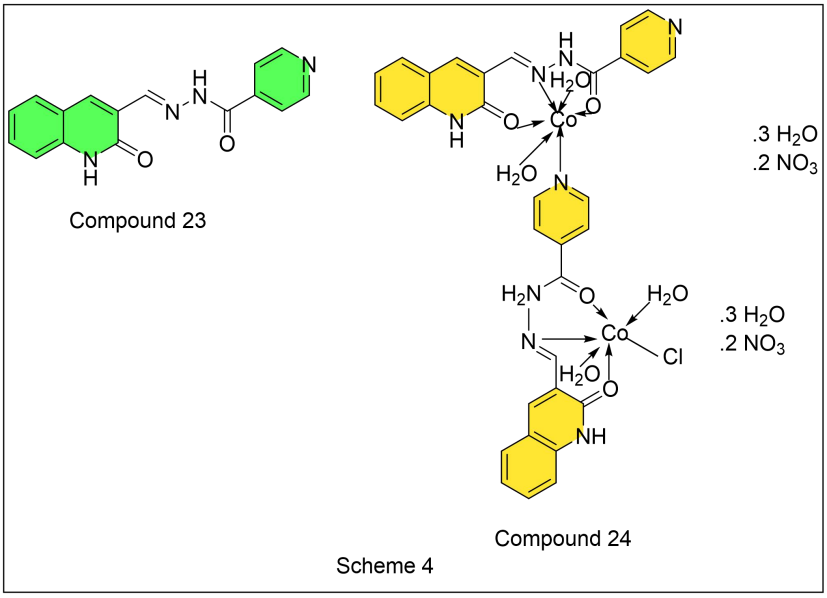


Scheme 2

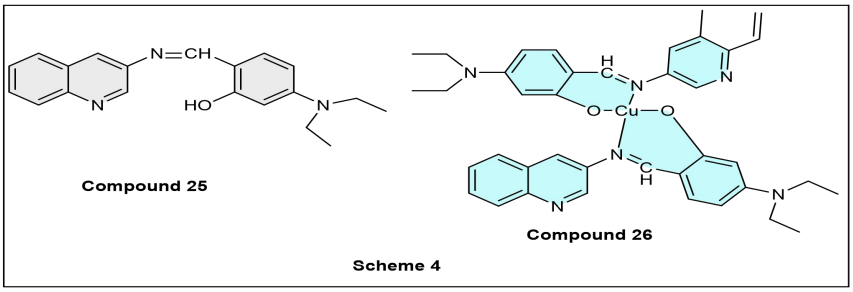
Vedanayaki *et al.* synthesized a quinoline Schiff base from 1,4-benzoquinone and 3-aminoquinoline, along with its Ni(II), Cu(II), Zn(II), and Co(II) complexes, which were characterized by various techniques, confirming octahedral structures. These compounds showed notable bioactivity in anti-inflammatory assays, with the copper complex displaying particularly strong effects. Compounds 21 and 22 demonstrated significant potential due to their stability and bioactive profiles, positioning these Schiff base complexes as promising candidates for further anticancer evaluation [36].



Raja, D. S et al. described a synthesis of compounds 23 and 24 are water-soluble cobalt(II) coordination polymers derived from 2-oxo-1,2-dihydroquinoline-3-carbaldehyde (isonicotinic) hydrazone, forming a one-dimensional polymeric unit with a slightly distorted octahedral geometry. Spectroscopic studies showed the complex binds to CT-DNA via intercalation and interacts strongly with BSA through static quenching. The complex exhibited notable radical scavenging abilities and substantial cytotoxicity against HeLa, HEp-2, Hep G2, and A431 cancer cell lines, showing higher specificity and potency against Hep G2 cells, with activity three times that of cisplatin. These findings suggest the complex's promise for anticancer applications [37].

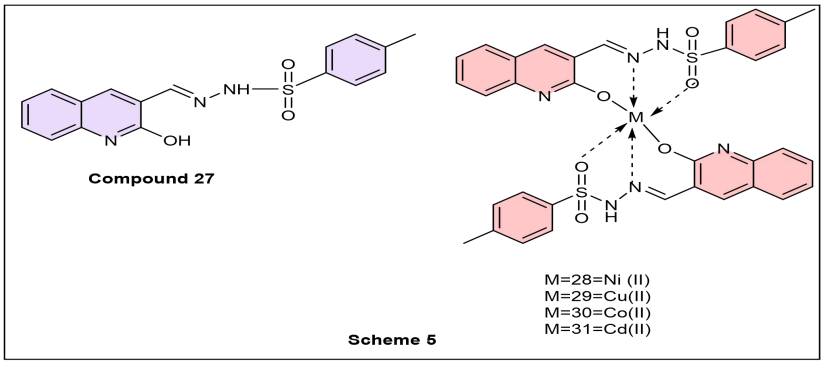


Thirunavukkarasu et al. synthesized the Schiff base 4-(diethylamino)-3-quinolin-3-ylimino-methyl-2-phenol from 3-aminoquinoline and 4-(diethylamino) salicylaldehyde , then reacted it with $CuCl_2(PPh_3)_2$ to form the copper (II) complex. The ligand demonstrated moderate cytotoxicity against A549 and MCF7 cell lines, while the copper (II) complex exhibited enhanced activity against MCF7 (IC_{50} 24–34 μM) compared to doxorubicin, attributed to the ligand's extended π system. Further investigation of Schiff base 25 and metal complexes 26 is recommended for their biological activities [38] .



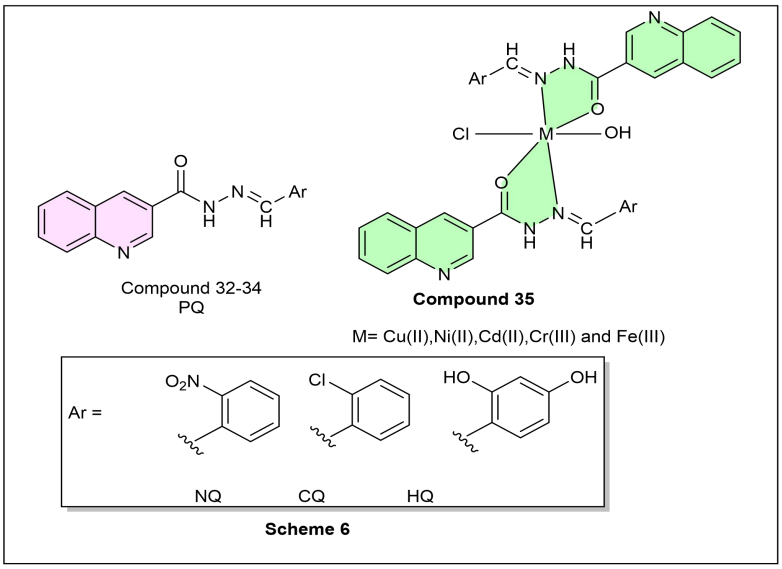
Patil and Vibhute synthesized Schiff base 27 and metal complexes 28-31, including a copper complex with notable anticancer activity against A-549 and MCF-7 cancer cells. Derived from 2-hydroxyquinoline-3-carbaldehyde and 4-methylbenzene sulfonohydrazide, the Schiff base led to complexes

with Ni(II), Co(II), Cu(II), and Cd(II). The copper complex demonstrated IC_{50} values of 37.03 µM for A-549 and 39.43 µM for MCF-7, alongside significant DNA photo-cleavage activity with pBR322 DNA, suggesting potential as an anticancer agent [20].



Scheme 5

Mahmoud Sunjuk et al. synthesized Schiff bases (NQ, CQ, HQ) from quinoline-3-carbohydrazide and aldehydes, creating metal complexes with Cu(II), Ni(II), Co(II), Cd(II), Cr(III), and Fe(III). Proposed structures included octahedral forms. HQ and its Cu and Ni complexes exhibited significant inhibition against MCF-7 and K562 cells, with Cu and Ni complexes showing higher potency than Fe and Co. Compounds Co-CQ, CQ, Cu-CQ, and Fe-CQ displayed limited cell proliferation, each with IC50 values over 50 µM (compounds 32-35) [39].



Scheme 6

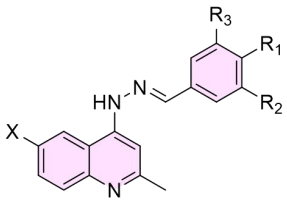
Katariya, Shah, and Reddy synthesized a series of quinoline hydrazone analogues based on the bioactive quinoline core, starting from 6-bromo/6-chloro-2-methyl-quinolin-4-yl-hydrazines. Cytotoxic screening at the National Cancer Institute (NCI) identified nine compounds with significant anti-proliferative effects, showing GI_{50} values from 0.33 to 4.87 µM and LC50 values from 4.67 µM to >100 µM. The most potent was comparable to bendamustine and chlorambucil. All quinoline hydrazones exhibited good to excellent antimicrobial activity (MIC 6.25–100 µg/mL). Molecular docking suggested promising interactions with human DNA topoisomerase I, supporting their potential as lead compounds for anticancer development, Compounds 36-44 mention [40] .

The novel scaffold *(E)-N1-((2-chloro-7-methoxyquinolin-3-yl)methylene)-3-(phenylthio) propanehydrazide* (compound 45-46) led to a series of active hydrazide compounds. Parent compound and derivatives were synthesized via EDC-mediated coupling, with some modifications by replacing the quinoline moiety. Compounds were tested for anti-cancer activity against SH-SY5Y and Kelly neuroblastoma, and MDA-MB-231 and MCF-7 breast cancer cell lines. Compounds 45 and 46 showed potent neuroblastoma activity, and compound 22 also induced G1 cell cycle arrest with upregulation of p27kip1 [41].

Venkatareddy Gayam *et al.* designed a series of quinoline hydrazide derivatives was synthesized from vanillic acid using multistep reactions, leading to quinoline-hydrazides (compounds 47-58). These compounds, characterized by IR, NMR, and MS, were tested for cytotoxicity against cancer cells with assays comparable to bosutinib. Compound 51 showed significant activity with IC_{50} values of 26.93 ± 2.8 µg/mL and 28.92 ± 1.6 µg/mL. Molecular docking revealed strong binding of compound 51 to BCR-ABL T315I, similar to other tyrosine kinase inhibitors[42] .

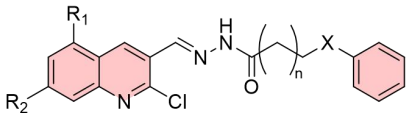
Chen *et al.* synthesized indole-, benzofuran-, and quinoline-based derivatives (Compounds 59-60), including indoloquinolin-2(1H)-ones, pyrroloquinolin-2(1H)-ones, and 6-anilinoindoloquinolines, which were evaluated for in-vitro cytotoxicity against MCF7 (breast), SF-268 (CNS), and NCI-H460 (lung) cell lines. The most potent compounds, 1-(3-(11H-indole(3,2-c)quinoline-6ylamino)phenyl) ethanone oxime hydrochloride and its 2-

chloro derivative exhibited mean GI_{50} values of 1.70 and 1.35 μM, respectively, and were particularly effective against SNB-75 cancer cells, with GI_{50} values under 0.01 μM [43].



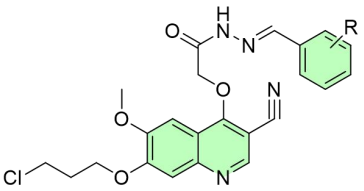
Compound 36-44

X= Cl, R_1 =OC_2H_5,R_2 & R_3=H
X= Cl, R_1 =OC_3H_7,R_2 & R_3=H
X= Br, R_1 =OC_3H_7,R_2 & R_3=H
X= Cl, R_1 =OC_4H_9,R_2 & R_3=H
X= Br, R_1 =OC_5H_{11},R_2 & R_3=H
X= Cl, R_1 =OC_5H_{11},R_2 & R_3=H
X= Br, R_1 =OC_6H_{13},R_2 & R_3=H
X= Cl, R_1 =OC_6H_{13},R_2 & R_3=H
X= Cl, R_1 =OC_8H_{17},R_2 & R_3=H



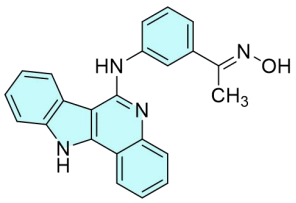
X= O, n=1, R_1 =H,R_2 =OCH_3
X= O, n=1, R_1,R_2 =OCH_3

Compound 45-46

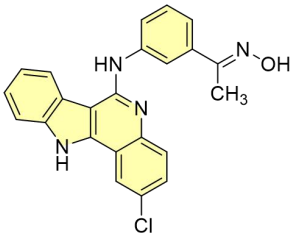


R= both electron donating and withdrawing functional groups

Compound 47-58



Compound 59



Compound 60

Scheme 7

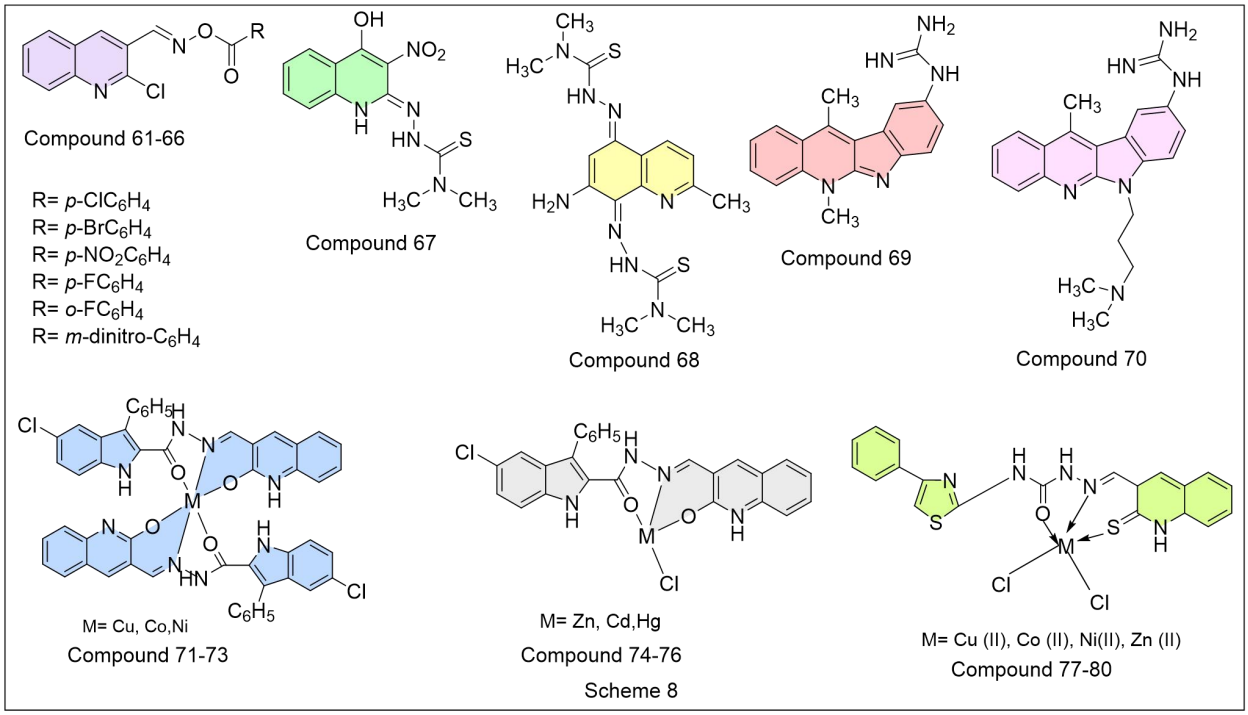
Bindu et al. synthesized derivatives of 2-chloro-3-formyl quinoline oxime esters and studied their nucleolytic activity through electrophoretic measurements. DNA cleavage experiments on neutral agarose gel electrophoresis, conducted at concentrations of 30 μM and 70 μM, showed that some quinoline oxime esters (Compound 61-66) converted supercoiled pUC19 plasmid DNA into its linear form or nicked it. Structure-activity relationship (SAR) analysis indicated that electron-rich groups enhance anticancer activity, while halogen and nitro groups exhibit lower reactivity. These electron-rich sites in B-DNA facilitate the removal of hydrogen atoms from C-40 of 2-deoxyribose [44].

Serda et al. synthesized quinoline-based thiosemicarbazones (Compounds 67-68) using microwave-assisted techniques, which are efficient, environmentally friendly, and cost-effective. The structures of the compounds were confirmed through spectroscopic methods. Anticancer activity was assessed against the HCT116 human colon cancer cell line using the MTT assay, showing improved anticancer effects [45].

Sidoryk et al. synthesized indolo[2,3-b]quinoline compounds with guanidine and guanylamino acid. These compounds significantly increased cytotoxicity against cancer cell lines while reducing toxicity to normal cells. Compounds (69-70) showed the highest cytotoxicity, with compound (69) being 600-fold less toxic to normal fibroblasts than to MCF-7 and A549 cells. Both compounds induced apoptosis and inhibited DNA synthesis, arresting cells in the S phase. Compound (69) exhibited stronger DNA binding and greater apoptosis induction than compound (70), indicating that guanidine-linked derivatives possess potent and selective anticancer activity [46] .

Karekal et al. designed and a novel Schiff base from 5-chloro-3-phenyl-1H-indole-2-carboxyhydrazide and 3-formyl-2-hydroxy-1H-quinoline (HL) was synthesized with Cu(II), Co(II), Ni(II), Zn(II), Cd(II), and Hg(II) complexes (Compound 71-73 and 74-76). Both the ligand and metal complexes demonstrated antibacterial and antifungal activity, and DNA cleavage was observed via agarose gel electrophoresis. Additionally, free radical scavenging activity was evaluated through DPPH interaction across varying concentrations [47] .

Nagesh et al. synthesized *N-(4-phenylthiazol-2-yl)-2-((2-thioxo-1,2-dihydroquinolin-3-yl)methylene)hydrazine carboxamide* and its Cu(II), Zn(II), Co(II), and Ni(II) complexes (Compound 77-80). Biological assays (MIC and brine shrimp bioassay) showed enhanced antibacterial, antifungal, and cytotoxicity with complexation. DNA cleavage activity was confirmed using electrophoresis with pBR322 plasmid DNA[48] .



Scheme 8

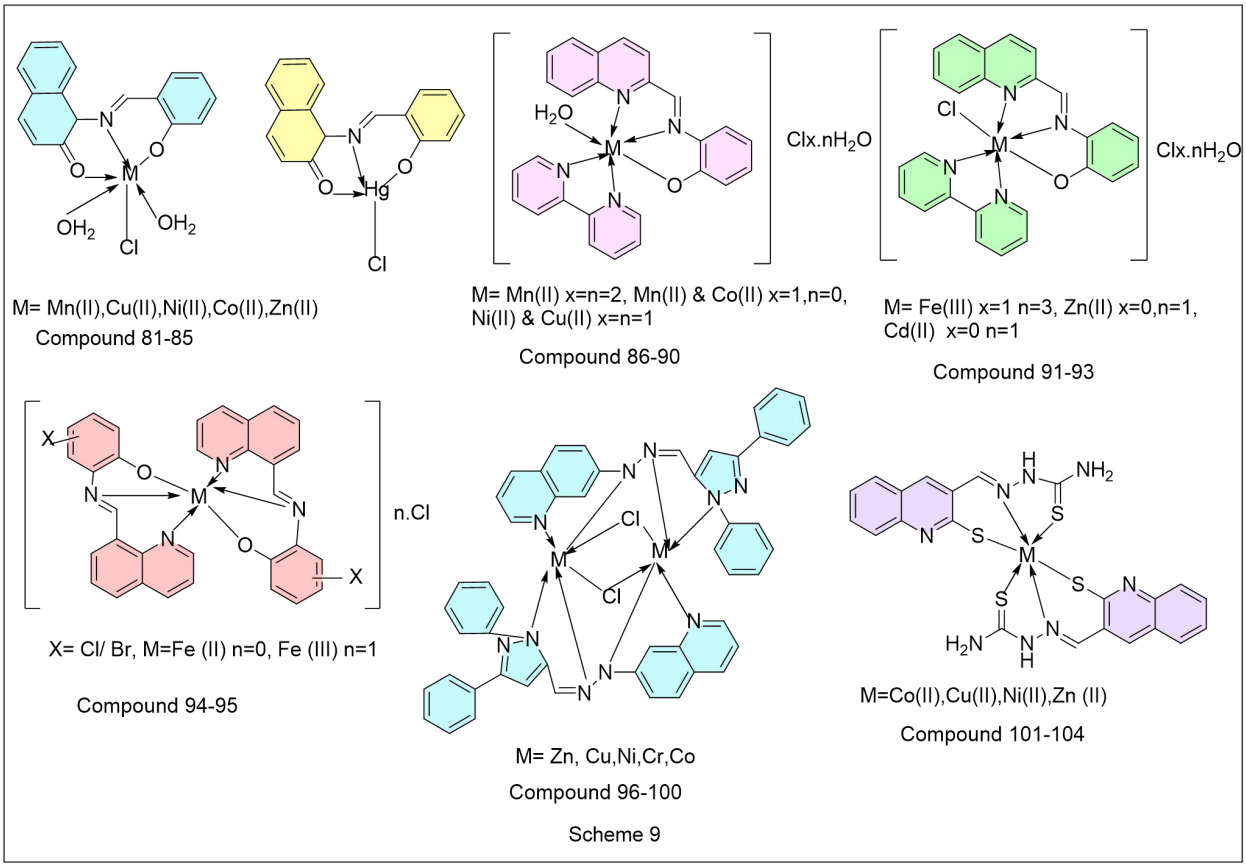
Asma A.A. et al. synthesized a novel Schiff base by condensing 1-aminoquinolin-2(1H)-one with 2-hydroxybenzaldehyde and formed complexes with Co(II), Cu(II), Ni(II), Mn(II), Hg(II), and Zn(II). Characterization via mass, FT-IR, CHN, 1H, 13C, and 15N NMR, ESR, and TGA indicated tridentate ligand behavior, with octahedral geometry for all complexes except Hg(II), which was tetrahedral (Compound 81-85). Anticancer and DNA binding studies were also conducted on the compounds [49].

Abd El-Halim et al. synthesized a novel Schiff base from quinoline-2-carboxaldehyde and 2-aminophenol, forming mixed ligand complexes with Cr(III), Mn(II), Cu(II), Fe(III), Ni(II), Zn(II), Cd(II), and Co(II) (Compound 86-90, 91-93) . Spectral analysis confirmed octahedral geometry in all complexes. Anticancer testing against HCT-116 (colon) and MCF-7 (breast) cancer cells revealed that Cd(II) showed the highest IC50, indicating significant activity across all tested cell lines [50].

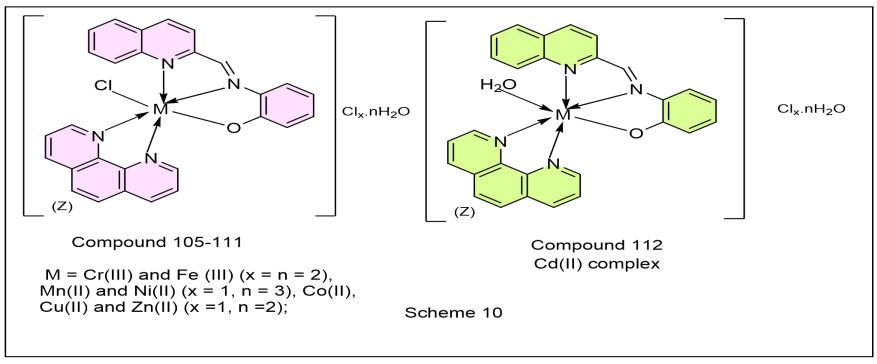
Wongsuwan S. et al. synthesized and characterized Fe(II) and Fe(III) quinoline Schiff base complexes from Fe chloride and N-(8-quinolyl)-X-salicylaldimine. The structures were confirmed using FTIR, TGA, 1H NMR, ESIMS, and X-ray crystallography (Compound 94-95). DNA-binding studies via fluorescence and UV-Vis spectroscopy showed stronger interaction for metal complexes than the Schiff base alone. In vitro tests against A549 lung cancer cells revealed anticancer activity for all complexes, with $[Fe(used\text{-}Cl_2)_2]Cl_6$ showing the highest potency (IC_{50}=10 μM) [51].

Ammar R. A. et al. synthesized and characterized a new quinoline Schiff base ligand from 2-hydrazineylquinoline and 1,3-diphenyl-1H-pyrazole-5-carbaldehyde, along with its dimeric Cu(II), Zn(II), Co(II), and Ni(II) complexes. Characterization via magnetic susceptibility, elemental analysis, and electrochemical methods confirmed the complexes' dimeric octahedral structure, coordinated through four nitrogen atoms. The compounds showed anticancer activity against MCF-7 breast and A549 lung cancer cell lines (Compound 96-100) [52].

El-Halim et al. synthesized a Schiff base ligand from 2-mercaptoquinoline thiosemicarbazone and its Co(II), Ni(II), Cu(II), and Zn(II) metal complexes (Compound 101-104). Characterization by ESR, FT-IR, ESI-MS, CHNS, and NMR indicated that the ligand coordinates with metal ions via SNS donor atoms, forming octahedral complexes. Cytotoxicity testing on MCF-7 cells showed enhanced activity for the metal complexes compared to the ligand alone [53].



Halim et al. synthesized a Schiff base ligand by condensing quinoline-2-carboxaldehyde with 2-aminophenol, producing metal complexes with 1,10-phenanthroline as a co-ligand, as seen in compounds 105-111 and 112. The copper (II) complex showed the highest anticancer potency, particularly against MCF-7 breast cancer cells (IC_{50} = 3.79 µg/mL) and HCT-116 colon cancer cells (IC_{50} = 16.4 µg/mL). Antimicrobial testing against bacteria and fungi indicated moderate efficacy, with minimal antifungal activity in Mn(II), Fe(III), and Ni(II) complexes [54].



Limitations

Quinoline Schiff base compounds have potential in cancer treatment. However, they face challenges like limited absorption, unintended toxicity, resistance in cancer cells, and regulatory obstacles. Researchers are exploring methods to enhance absorption due to limited solubility, such as using nanoparticles and prodrugs. Unintended effects harm healthy cells, leading to the need for research on targeted delivery to minimize toxicity. Challenges like drug resistance can reduce effectiveness. Therefore, combining treatments or creating drugs that bypass resistance could be beneficial. Regulatory obstacles delay medical use; however, thorough early-stage studies can speed up approval. Addressing these constraints is critical for realizing the full promise of quinoline Schiff bases in cancer treatment.

Clinical applications and future directions

Research on quinoline Schiff base compounds in cancer therapy shows promise as it aims to enhance bioavailability and target tumors using nanoparticle and liposomal delivery systems. Exploring chemical modifications to increase specificity and reduce toxicity, and combining these

compounds with other treatments, may help overcome resistance in cancer cells. Advances in computational modeling will aid in designing more selective derivatives with improved pharmacokinetics. With the expansion of preclinical data, partnerships with regulatory bodies can speed up clinical trials, bringing these compounds closer to being viable cancer treatment options. Quinoline Schiff bases show promise for clinical applications in oncology. The capability of quinoline Schiff bases to target specific tumor types and address drug resistance indicates their potential integration into combination therapies or use as standalone agents. Further studies are needed to explore systematic clinical trials and the development of these compounds into viable therapeutic options for cancer patients. In summary, quinoline Schiff bases are a key focus in anticancer drug development, highlighting their diverse mechanisms of action and essential role in tackling cancer treatment obstacles. More comprehensive clinical studies will be crucial for fully establishing their therapeutic potential.

Conclusion

In general, Quinoline Schiff bases (QSBs) show enormous potential in cancer treatment. This is due to their unique chemical structure and ability to activate pathways involved in cancer growth. These actions, including triggering cell death (apoptosis), inhibiting cell growth, and interfering with key tumor pathways, highlight their potential for targeted therapy. However, additional research is required to enhance the pharmacokinetic properties, assess safety profiles, and determine the clinical effectiveness of Quinoline Schiff bases (QSBs). Further research in this field may lead to Quinoline Schiff bases (QSBs) complementing existing cancer treatments, offering targeted and potentially less harmful options in the fight against cancer.

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