

# Advances in mixed ligand transition metal complexes: Chromone derivatives and N, O donor ligands – a comprehensive review

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## ABSTRACT

Mixed-ligand transition metal complexes have emerged as a significant area of research due to their tunable structural, electronic, and biological properties. This comprehensive review provides a detailed analysis of recent advances in the synthesis, characterization, and diverse applications of complexes formed by combining 3-formylchromone derivatives with auxiliary N, O-donor ligand 8-hydroxyquinoline. We systematically explore the coordination chemistry of chromone, a versatile pharmacophore, highlighting its role as a primary ligand. A critical examination of their biological properties, including antimicrobial, anticancer, and antioxidant activities, is presented. Furthermore, the review elucidates the key structure-activity relationships (SARs) that govern their efficacy. By compiling the current state of knowledge, this work aims to identify existing research gaps and propose future directions for the rational design of next-generation mixed-ligand complexes with tailored properties for advanced applications in medicine.

## 1. Introduction

### 1.1. General introduction to coordination chemistry of transition metals complexes

Coordination chemistry, a fundamental area of modern inorganic chemistry, examines complexes formed between transition metal ions and ligands, where partially filled d-orbitals enable diverse bonding, complex geometries, and unique electronic properties. Coordination

number, ligand type, and spatial arrangement govern both physico-chemical and biological behavior, with applications in catalysis, materials science, and medicinal chemistry. The field was pioneered by Sophus Mads Jørgensen and Alfred Werner, whose work on spatial arrangements and isomerism in metal complexes laid the foundation for rational design, with Werner receiving the Nobel Prize in 1913 [1,2]. Advances in X-ray crystallography, NMR, ESR, and mass spectrometry have enabled precise characterization of metal-ligand interactions, geometries, and stability [3]. Coordination compounds impact diverse

**Abbreviations:** AAS, Atomic absorption spectroscopy; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay; ADMET, Absorption distribution metabolism excretion toxicity; AFO, Algar-Flynn-Oyamada; AI, Artificial intelligence; BHT, Butylated HydroxyToluene; CCRF, CEM:Childhood Cancer Research Foundation-CEM; CDKs, Cyclin-dependent kinases; Cys, Cysteine; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DFT, Density functional theory; DMF, N,N-dimethylformamide; DNA, Deoxyribonucleic acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl assay; DTA, Differential thermal analysis; EDTA, Ethylene diamine tetra acetic acid; ESR, Electron spin resonance spectroscopy; FRAP, Ferric reducing antioxidant power assay; FTIR, Fourier transformer infrared spectroscopy; HepG2, Human hepatocellular carcinoma cell line; His, Histidine; HIV, Human Immuno virus; HTERT, Human telomerase reverse transcriptase; 8-HQ, 8-Hydroxyquinoline; LMCT, Ligand-to-metal charge transfer; **MB-231**, *Metastatic breast 231*; MCF-7, Michigan Cancer Foundation-7; MD, Molecular dynamics; **Met**, **Methionine**; MM-GBSA, Molecular mechanics generalized born surface area; MM-PBSA, Molecular mechanics Poisson-Boltzmann surface area; MRI, Magnetic Resonance imaging spectroscopy; mRNA, Messenger RNA; MRSA, Methicillin-resistant *S. aureus*; MSSA, Methicillin sensitive *Staphylococcus aureus*; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; N,O donors, Nitrogen and oxygen donors; NMR, Nuclear magnetic resonance spectroscopy; PDB, Protein data Bank; PEA, Poly(ester amide); POCl<sub>3</sub>, Phosphorus oxychloride; **pUC19**, *Plasmid universal cloning 19*; QM/MM, (quantum mechanics/molecular mechanics); QSAR, Quantitative structure activity relationship; ROS, Reactive oxygen species; SAR, Structure-activity relationship; SAR, Structural activity relationship; SEM, Scanning electron microscopy; SRB, Sulforhodamine B assay; TD-DFT, Time-dependent density functional theory; TG, Thermogravimetry; XRD, X-ray diffraction.

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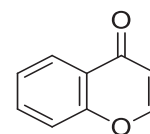
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areas, including nanotechnology [4], catalysis [5], materials science [6], pigments and dyes [7,8], color photography [9], mineral processing [10], nuclear fuel design [11], toxicology [12], ceramics [13], microelectronics [14], and photonics [15]. They are also essential in biological systems, such as hemoglobin, myoglobin [16–18], chlorophyll [19], cytochromes [20], and vitamin B<sub>12</sub>, playing key roles in oxygen transport, photosynthesis, electron transfer, and metabolism, and often act as enzyme cofactors [21].

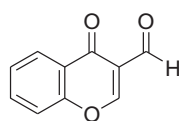
Research focuses on synthesis, structural optimization, and reactivity, with medical applications in chemotherapy [22], chelation therapy [23], and treatment of Wilson's disease [24], iron overload [25,26], and heavy metal detoxification [27]. Coordination complexes are also used in diagnostics, including Technetium-based nuclear imaging [28] and Rhenium [29], Maganase based MRI contrast agents [30]. Metal coordination complexes are increasingly employed to design biologically inspired metal complexes that mimic metalloenzymes [31,32]. Mixed-ligand complexes of chromones and 8-hydroxyquinoline (8-HQ) combine complementary donor properties, forming stable structures with enhanced geometry, lipophilicity, and electronic characteristics, resulting in synergistic improvements in biological activity, redox behavior, and selective binding [33]. Chromones coordinate via carbonyl and hydroxyl oxygen atoms, offering flexibility and stabilizing different metal oxidation states, while 8-HQ binds through its nitrogen and phenolic oxygen, providing rigid, planar chelation. Together, they



Chromone

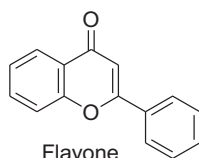
(1)

Chromones (1) represent a major class of naturally occurring heterocyclic compounds that are widely distributed across the plant kingdom. These oxygen-containing scaffolds are structurally and biologically significant, forming the core framework of numerous bioactive natural products. The basic chromone skeleton serves as a key structural motif in various subclasses of flavonoids, including 3-formylchromones (2), flavones (3), flavonols (4), and isoflavones (5), each of which exhibits diverse pharmacological properties. Due to their structural versatility and inherent biological activity, chromone derivatives have gained considerable attention in the development of novel therapeutic agents and in the design of metal-based coordination complexes for biomedical applications.



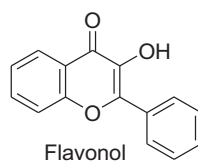
3-formylchromone

(2)



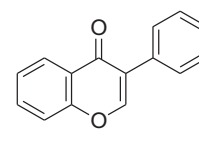
Flavone

(3)



Flavonol

(4)



Isoflavone

(5)

form stable mixed-ligand complexes with enhanced geometry, lipophilicity, and electronic properties, resulting in synergistic effects that improve biological activity, redox behavior, and selective binding.

## 1.2. Mixed ligand transition metal complexes

Recent advances in coordination chemistry have focused on mixed-ligand and polynuclear complexes [34], valued for their enhanced stability and structural diversity. These complexes often dominate in solution, making their formation and stability crucial for understanding analytical processes [35]. Mixed-ligand systems enable selective and sensitive determination, separation, and speciation of metal ions, particularly in complex matrices [36]. Understanding their coordination principles helps optimize extraction protocols for greater selectivity, efficiency, and accuracy [37].

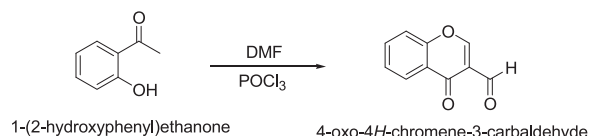
Mixed-ligand complex refers to a coordination compound in which a single metal center is simultaneously coordinated by two or more different types of ligands in this case, chromones and 8-hydroxyquinoline (8-HQ). For instance, certain Cu<sup>+2</sup>, Ni<sup>+2</sup>, and Pb<sup>+2</sup> complexes have been reported where the metal is chelated by both a chromone derivative (via carbonyl and hydroxyl O atoms) and 8-HQ (via N, O bidentate chelation), forming stable mixed-ligand chelates. These complexes often exhibit enhanced stability, planarity, and biological activity compared to complexes containing either ligand alone, illustrating the synergistic effect of combining both ligands on a single metal center.

### 1.2.1. General introduction to ligands

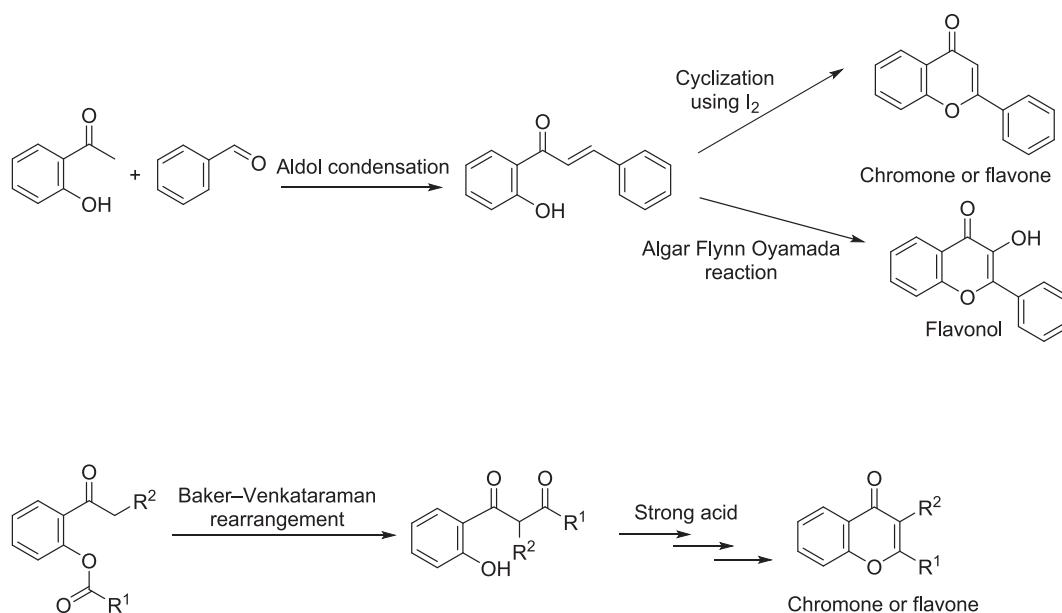
#### 1.2.1.1. Chromones as ligand

Chromone, also known as 1,4-benzopyrone, is a derivative of benzopyran featuring a substituted keto group on the  $\gamma$ -pyrone ring. Structurally, chromones are oxygen-containing heterocyclic compounds characterized by a benzo-annulated  $\gamma$ -pyrone core [38]. This scaffold serves as the fundamental backbone for a variety of biologically active molecules, including flavonoids and related natural products, and has attracted significant attention in both medicinal chemistry and bioinorganic research. Numerous chromone derivatives have demonstrated potent pharmacological effects, including neuroprotective [39], HIV-inhibitory [40], antimicrobial [41], antibacterial [42], antitumor [43], antifungal [44], antiallergic [45], antiviral [46], anti-inflammatory [47], and anticancer [48] properties. These diverse activities underscore the therapeutic potential of chromone-based compounds. Notably, chromone derivatives such as cromolyn sodium and nedocromil commonly known as cromoglycates are well-established in clinical practice as anti-asthmatic agents, further exemplifying the medical relevance of this chemical class. The ability of chromone ligands to coordinate metal ions, owing to the presence of electron-rich donor atoms, makes them particularly attractive for the development of metal-based drugs and diagnostic agents.

The synthesis of chromones is commonly achieved through cyclodehydration of 1-(O-hydroxyaryl)-1,3-diketones or via the Vilsmeier-



Scheme 1. Vilsmeier Haack reactions.



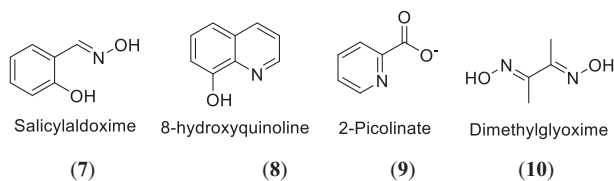
**Scheme 2.** Synthesis of chromone or flavonol using Aldol condensation or Baker-Venkataraman rearrangement.

Haack reaction [49] (Scheme 1). Among these, the Vilsmeier–Haack approach is particularly favoured due to its operational simplicity and ability to produce chromone derivatives with high purity and yield [50].

Two main synthetic routes are commonly used to prepare chromones. The first involves base-catalyzed aldol condensation of 2'-hydroxyacetophenones with aromatic or conjugated aldehydes to form chalcone intermediates [51,52], which can cyclize to flavones via iodine catalysis or to 3-hydroxyflavones through the Algar-Flynn-Oyamada (AFO) reaction using alkaline hydrogen peroxide [53]. The second route, the Baker-Venkataraman rearrangement, converts 2'-hydroxyacetophenones or their esters into β-diketones, which cyclize and dehydrate to yield the chromone core (Scheme 2). Both strategies offer versatile and efficient access to structurally diverse chromones for biological and coordination chemistry applications.

In recent years, synthetic strategies for chromones and flavones have evolved beyond classical methods. Well-established approaches like the Allan-Robinson reaction and Kostanecki acylation remain widely used, while oxidative cyclization of ortho-hydroxyacetophenones (using SeO<sub>2</sub>, DDQ, or FeCl<sub>3</sub>) and Friedel-Crafts acylation of phenols with β-keto acids or acid chlorides catalyzed by Lewis acids (AlCl<sub>3</sub>, BF<sub>3</sub>·Et<sub>2</sub>O) have expanded the toolkit. Modern catalytic methods, including gold- and palladium-catalyzed C–H activation, offer greener and highly selective routes. Additionally, cyclocarbonylation of ortho-iodophenols with terminal acetylenes provides a mild strategy to access chromones [54]. Chromones are important intermediates that readily form stable complexes with transition metals (Cu(II), Ni(II), Co(II), Zn(II), Mn(II)), yet mixed-ligand chromone complexes remain largely unexplored, highlighting an area for future research.

#### 1.2.1.2. N,O-donor ligands



N,O-donor ligands are bidentate or polydentate ligands containing both nitrogen and oxygen atoms, which coordinate to metal centers and strongly influence the stability, reactivity, and electronic properties of

metal complexes. Examples such as salicylaldoxime (7), 8-hydroxyquinoline (8), 2-picolinate (9), and dimethylglyoxime (10) readily form coordination compounds with transition metals and are widely used as chelating agents for metal ion analysis and separation. Notably, 8-hydroxyquinoline selectively precipitates metal ions e.g., copper at pH 2.6 and nickel at pH 7.3 facilitating their detection and separation [55,56]. Structurally, it exists with a protonated hydroxyl and unprotonated nitrogen, enabling bidentate coordination through tautomerization to a zwitterionic form [57]. This chelation is essential for its antimicrobial activity, as blocking the hydroxyl abolishes bioactivity [58].

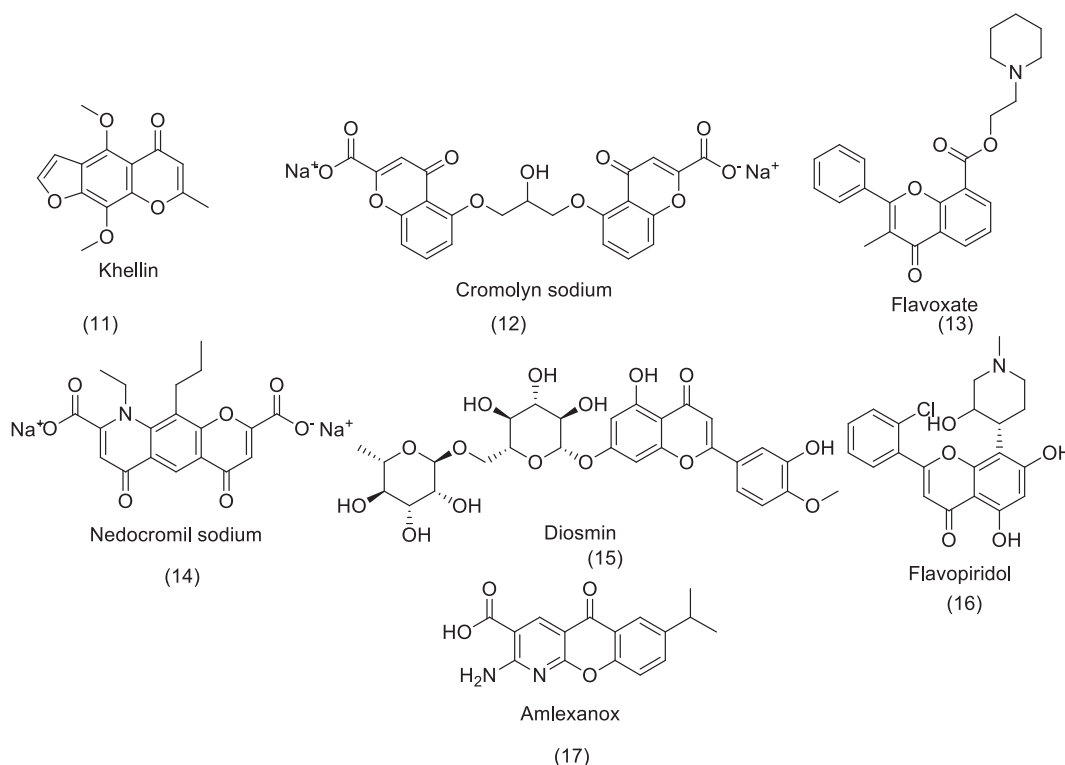
#### 1.2.2. Importance of chromones in medicinal chemistry

Chromones constitute a vital scaffold in medicinal chemistry due to their versatile biological activities including anti-inflammatory, antioxidant, antimicrobial, antiviral, anticancer, and neuroprotective effects and favorable pharmacokinetic profiles [59]. This multifaceted bioactivity arises from their ability to interact with various biological targets through hydrogen bonding, π–π stacking, and metal coordination. The chromone core is often incorporated into drug design because of its structural rigidity allowing fine-tuning of biological activity and selectivity. For example, clinically approved anti-asthmatic drugs such as cromolyn sodium and nedocromil are chromone derivatives that stabilize mast cells and prevent allergic responses. Furthermore, chromones have shown promising potential as lead compounds for cancer therapeutics, acting via mechanisms such as apoptosis induction, cell cycle arrest, and inhibition of key enzymes involved in tumor progression [60]. In addition to their intrinsic bioactivities, chromones serve as versatile ligands in coordination chemistry, forming metal complexes that can enhance their biological efficacy and specificity. This dual function as both therapeutic agents and metal-binding ligands positions chromones as key scaffolds in the development of novel metal-based drugs and diagnostic tools [61].

Although numerous chromone derivatives exhibit promising pharmacological activities, only a limited number have progressed to clinical use. One of the earliest clinically employed chromones is khellin (11), a naturally occurring compound isolated from the seeds of *Ammi visnaga*. Historically, khellin was utilized as a diuretic and subsequently for the treatment of angina and asthma in the 1950s, owing to its vasodilatory effects that relax smooth muscles in the airways and blood vessels. In contemporary medicine, khellin is primarily employed in the

management of vitiligo, highlighting its therapeutic versatility and continued clinical relevance [62].

diseases and flavoxate, prescribed as a smooth muscle relaxant for urge incontinence [65]. Current research continues to focus on the synthesis, isolation, and biological evaluation of chromone derivatives, with key



Cromolyn sodium (12), first marketed in 1968, is a synthetic chromone analogue widely used in the management of asthma, allergic rhinitis, and conjunctivitis. It exerts its therapeutic effect primarily by stabilizing mast cells and inhibiting the release of histamine and other inflammatory mediators, thereby preventing allergic responses. Introduced in 1970, flavoxate (13) is a synthetic drug used as a urinary antispasmodic to alleviate symptoms associated with bladder spasms and overactive bladder. Another synthetic chromone derivative, nedocromil sodium (14), launched in 1985, similarly prevents the release of inflammatory mediators from mast cells and is indicated for asthma and allergic conditions. Additionally, diosmin (15), a naturally occurring flavonoid abundant in citrus fruits, has been used therapeutically since the 1990's to treat chronic venous insufficiency, varicose veins, and hemorrhoids by strengthening vein walls and enhancing blood circulation.

Flavopiridol (16), a synthetic chromone derivative under investigation since the 1990's, has shown promising anticancer potential, particularly against leukemia and solid tumors. Its mechanism of action involves inhibition of cyclin-dependent kinases (CDKs), resulting in cell cycle arrest and induction of apoptosis in malignant cells. Although not yet widely marketed, flavopiridol represents a significant advancement in targeted cancer therapy. Another notable compound, amlexanox (17), introduced in 1996, is a synthetic drug used for the treatment of aphthous ulcers (canker sores). It exhibits anti-inflammatory and anti-allergic effects through the inhibition of inflammatory mediator release and modulation of immune responses.

These examples illustrate the therapeutic versatility of chromone derivatives in medicine. Other clinically relevant chromone-based treatments include sodium cromoglycate (Lomudal®), widely employed as a mast cell stabilizer in allergic rhinitis, asthma [63,64], and allergic conjunctivitis; diosmin (Daflon®), used for chronic venous

pharmacological activities encompassing anticancer, anti-diabetic, antimicrobial, anti-inflammatory, antioxidant, agents CDK inhibition, anti-HIV properties and anti-Alzheimer [66].

### 1.2.3. Importance of 8-hydroxyquinoline (8-HQ) in medicine

8-Hydroxyquinoline (8-HQ) is a compound of considerable medical significance due to its broad spectrum of applications. It possesses notable antimicrobial and antifungal activities [67,68], effectively inhibiting pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, as well as fungal species including *Candida albicans* and *Aspergillus niger*. Clinically, 8-HQ is employed in the treatment of wounds, skin infections, and various dermatological disorders such as acne, eczema, and psoriasis. It is also utilized in ophthalmology, particularly in eye drop formulations for managing conjunctivitis and other ocular infections. Beyond its antimicrobial properties, 8-HQ functions as a potent chelating agent, facilitating the removal of heavy metals from the body and serving as a diagnostic reagent for the detection of metal ions in biological samples. Despite its therapeutic advantages, careful dosing and medical supervision are imperative, as excessive concentrations of 8-HQ may induce toxicity.

The biological assays reported for chromone- and 8-hydroxyquinoline-based mixed-ligand complexes, including antimicrobial, antioxidant, and anticancer studies, were not always performed under fully consistent conditions across different investigations. Variations in experimental design, assay type, microbial strains, cell lines, incubation times, and reference standards often make direct comparison of results difficult. For instance, antimicrobial activity has been evaluated against different Gram-positive and Gram-negative organisms using varying concentrations and methods (disc diffusion vs. broth dilution), while antioxidant assays differ in the choice of radical scavenging systems (DPPH, ABTS, FRAP). Similarly, anticancer studies employ diverse cell lines, exposure times, and assay techniques (MTT, SRB, or flow

cytometry). These methodological differences introduce variability, limiting strict comparability across studies. Nevertheless, general trends such as enhanced activity of metal complexes compared to free ligands, or synergistic effects in mixed-ligand systems—remain evident and provide valuable insight, though systematic head-to-head evaluations under standardized protocols would be needed for more definitive conclusions [69].

#### 1.2.4. Effect of metal complexation on biological activity

The interplay between metal ions and biological activity represents a critical area of investigation. Coordination of organic compounds to metal ions can markedly enhance biological efficacy or activate otherwise inert molecules, with metal ions modulating pharmacological properties [70], although precise mechanisms remain incompletely understood [71]. Extensive efforts have focused on synthesizing novel metal complexes to explore how coordination influences antimicrobial, anticancer, and enzymatic activities [72]. Transition metals are essential cofactors for numerous enzymes, yet excessive levels can lead to toxicity, emphasizing the need for balanced strategies in drug design. Bio-ligands such as nitrogen-containing compounds (pyrrole, pyridine), amines (histamine), carbohydrates (glucose), and vitamins (ascorbic acid) contribute to metal ion homeostasis [73], where thermodynamic stability and kinetic behavior dictate biological activity [74]. Chelation enhances drug lipophilicity and membrane permeability, improving target penetration and therapeutic efficacy [75]. Many antimicrobial and anticancer agents require metal complexation for activity, with abnormalities in copper and chromium metabolism linked to diseases such as rheumatoid arthritis and diabetes [76,77]. Metal ions also regulate viral replication and antibiotic efficacy, with chelation playing a critical role in drug transport and bacterial targeting [78,79]. Schiff base-derived metal chelates exhibit strong coordination with transition metals, enhancing antitumor and antimicrobial activities, often with reduced toxicity compared to free ligands [80–83]. Chromones, recognized for antimicrobial, antibiotic, antituberculostatic, anticancer, and antioxidant activities [84–88], exert effects largely through metal chelation, though complexation with 8-hydroxyquinoline can sometimes suppress activity due to intra- and intermolecular interactions [89]. Mixed-ligand complexes with  $\text{Cu}^{+2}$ ,  $\text{Ni}^{+2}$ ,  $\text{Co}^{+2}$ , and  $\text{Mn}^{+2}$  show biological variability influenced by ligand and metal nature, with structural factors such as size, charge, stereochemistry, and redox potential playing key roles [90]. Coordination often enhances bioactivity, enabling inactive ligands to display significant pharmacological effects [91,92]. Transition metals like Cu, Ni, Mn, and Co also catalyze C–C bond formation in organic synthesis, facilitating construction of biologically active molecules [93]. Metal complexation generally improves antimicrobial, anticancer, and neuroprotective effects by increasing lipophilicity, membrane penetration, stability, and pharmacokinetics. Coordination geometry and spectroscopic properties are crucial: chromone ligands bind via carbonyl oxygen/hydroxyl groups, 8-hydroxyquinoline via N,O donors, with stronger chelation enhancing cytotoxicity and antimicrobial efficacy.

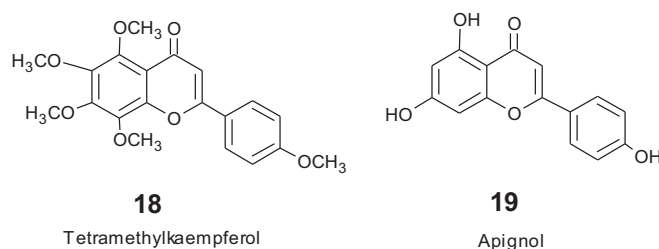
### 1.3. Transition metal complexes with ligands

#### 1.3.1. Chromones and their complexes

3-formylchromone emerging as a versatile synthon for incorporating the chromone moiety into diverse molecular frameworks [94]. Despite its synthetic utility, the application of 3-formylchromone is often constrained by the susceptibility of the chromone ring to ring-opening reactions, which can compromise its stability. Consequently, ongoing research efforts focus on developing strategies to enhance the stability and broaden the synthetic applicability of 3-formylchromone. A key advantage of 3-formylchromone lies in the relative ease of synthesizing various substituted derivatives from simple and cost-effective starting materials, such as o-hydroxyacetophenone and its analogues, primarily via the well-established Vilsmeier-Haack reaction. The formylating

species, commonly referred to as the Vilsmeier-Haack reagent, is generated in situ through the reaction between a substituted amidetypically *N,N*-dimethylformamide (DMF) and phosphorus oxychloride (POCl<sub>3</sub>). The active electrophilic species chloroiminium ion, formed when DMF reacts with POCl<sub>3</sub>. This reactive intermediate subsequently attacks the electron-rich arene, yielding the corresponding aromatic ketone or aldehyde [95].

According to Stankovicova et al. [96] (1996), a notable characteristic of **chromone-3-carboxaldehyde** is its propensity to undergo **ring-opening reactions**, which occur when nucleophiles attack the electron-deficient C-2 position of the  $\gamma$ -pyrone ring. This behavior has been substantiated through both spectroscopic analyses and theoretical investigations. Abdel-Rehman et al. [97] (1999) synthesized benzopyran derivatives such as Tetramethylkaempferol (**18**) and Apignol (**19**), which demonstrated multiple beneficial pharmacological activities, including coronary vasodilation, plasmolysis, and antiatherogenic effects. Notably, several benzopyran derivatives have exhibited anti-atherosclerotic activity, underscoring their potential therapeutic value in both the treatment and prevention of cardiovascular diseases.



When chromones and 8-hydroxyquinoline coordinate simultaneously to a metal center, the resulting mixed-ligand complexes exhibit enhanced biological activity compared to the free ligands. In the free state, chromones primarily interact via carbonyl or hydroxyl groups, and 8-hydroxyquinoline binds through N,O donor sites, but their cellular uptake and stability are limited. Upon coordination, both ligands chelate the metal, forming stable, planar or near-planar structures that increase lipophilicity and facilitate membrane permeability. Spectroscopic shifts in IR (C=O, C–O, C=N) and UV–Vis confirm stronger metal-ligand interactions, while EPR or NMR data indicate the preferred geometry. The combined effect of dual chelation and favorable geometry promotes DNA intercalation, protein binding, and redox activity, resulting in significantly higher cytotoxic, antimicrobial, and antioxidant properties than either ligand alone. Thus, the synergistic binding of chromone and 8-hydroxyquinoline in the same complex is a key factor in the observed enhancement of bioactivity.

Hosseini-mehr et al. [98] investigated the biological role of chromones, emphasizing their capacity to suppress free radical formation. Their study further demonstrated the radioprotective effects of various flavonoids and chromone derivatives against  $\gamma$ -irradiation, highlighting their significant potential in mitigating radiation-induced damage. Rybarczyk-Pirek et al. et al. [99] described theoretical and experimental work on chromone derivatives, likely focusing on their structural properties and intramolecular interactions. Nabil et al. [100] synthesized a series of metal complexes involving  $\text{Cu}^{+2}$ ,  $\text{Fe}^{+2}$ ,  $\text{Co}^{+2}$ ,  $\text{Ni}^{+2}$ ,  $\text{Cr}^{+2}$ ,  $\text{Pd}^{+2}$ ,  $\text{Pt}^{+2}$ , and  $\text{Zn}^{+2}$  coordinated with substituted chromones and their thiosemicarbazone derivatives. These complexes were extensively characterized using a variety of techniques, including spectroscopic, electrochemical, and thermal analyses. Structural elucidation revealed that  $\text{Pt}^{+4}$ ,  $\text{Fe}^{+3}$ ,  $\text{Co}^{+2}$ ,  $\text{Co}^{+3}$  and  $\text{Cr}^{+3}$  complexes adopt octahedral geometries, while  $\text{Pd}^{+2}$  and  $\text{Cu}^{+2}$  complexes are best described by square-planar configurations. Spectroscopic data further indicated that the  $\text{Ni}^{+2}$  complex assumes a square-planar geometry and the  $\text{Zn}^{+2}$  complex exhibits a tetrahedral structure.

Gasparova et al. [101] demonstrated the synthetic versatility of chromone-3-carboxaldehyde, highlighting its ability to act as a

heterodiene, dienophile, or Michael acceptor. They reported that fused heterocyclic compounds can be efficiently synthesized via direct reactions between chromone-3-carboxaldehydes and bifunctional nucleophiles. This reactivity underscores the potential of chromone-3-carboxaldehydes as versatile building blocks for the facile construction of a diverse array of novel heterocyclic architectures. Ganguly et al. [102] synthesized a novel class of 3-acyl flavones and chromones employing a modified Baker-Venkataraman reaction. Their study elucidated the mechanistic pathway underlying the formation of these compounds. The characterized properties of the synthesized 3-acyl flavonoids suggest their potential utility as key precursors for flavone synthesis, thereby expanding the synthetic toolbox for accessing diverse flavonoid derivatives.

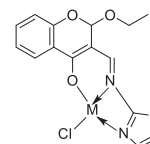
Grotewold [103] provided a detailed description of chromone (4H-1-benzopyran-4-one) as a benzopyran derivative featuring a substituted keto group at the 4-position of the pyran ring. Wang B.D. et al. [104] reported the synthesis of a novel ligand, 6-hydroxy chromone-3-carbaldehyde-(2'-hydroxy) benzoyl hydrazone, prepared via the condensation of 6-hydroxy-3-carbaldehyde chromone with 2-hydroxybenzoyl hydrazine. The study further detailed the synthesis and comprehensive characterization of four rare earth metal complexes with this ligand. Characterization techniques employed included elemental analysis, molar conductivity measurements, mass spectrometry, proton nuclear magnetic resonance ( $^1\text{H}$  NMR), thermogravimetric and differential thermal analysis (TG-DTA), UV-Vis spectroscopy, fluorescence spectroscopy, and infrared (IR) spectroscopy.

Cazarolli et al. [105] have provided an extensive review highlighting the therapeutic potential of the chromone nucleus across a spectrum of biological activities. Wang et al. [106] introduced a new ligand, 6-hydroxy chromone-3-carbaldehyde thiosemicarbazone, alongside its  $\text{Ni}^{+2}$  complex. The crystal structure of the  $\text{Ni}^{+2}$  complex was elucidated by single-crystal X-ray diffraction (XRD). Both the ligand and its  $\text{Ni}^{+2}$  complex were evaluated for in vitro cytotoxicity against THP-1, Raji and HeLa cancer cell lines, revealing significantly enhanced cytotoxic activity in the  $\text{Ni}(\text{II})$  complex compared to the free ligand. Additionally, their interactions with calf thymus DNA were investigated through spectrometric titration, ethidium bromide displacement assays, and viscosity measurements, providing insights into their DNA-binding modes and potential mechanisms of anticancer activity.

Grazul et al. [107] emphasized therapeutic properties of chromones, flavonoids, and coumarins. Importantly, they highlighted that the formation of metal ion complexes with these compounds often results in enhanced efficacy compared to the free ligands alone, marking a significant advancement in drug research. These metal complexes were effective against diabetes mellitus, certain bacterial infections, and cancers, Huntington's disease. Additionally, these metal complexes have been shown to modulate iron homeostasis, a critical factor in the treatment of disorders like Friedreich's ataxia and  $\beta$ -thalassemia. Chohana et al. [108] synthesized six chromone-derived ligands and their  $\text{Cu}(\text{II})$  complexes, confirming dimeric structures via elemental and spectral analyses. Antibacterial evaluation against Gram-negative (*E. coli*, *P. aeruginosa*, *S. typhi*, *S. flexneri*) and Gram-positive (*B. subtilis*, *S. aureus*) strains showed that metal coordination markedly enhanced activity, with  $\text{Cu}^{+2}$  complexation.

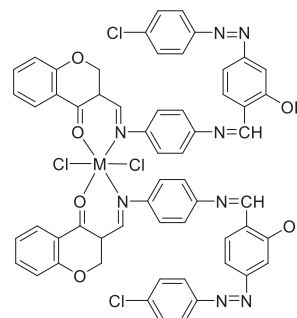
Yong Li et al. [109] prepared 3-carbaldehyde chromone thiosemicarbazone and its metal complexes. The  $\text{Zn}^{+2}$  complex displayed strong blue fluorescence, and DNA-binding studies revealed intercalative interactions, with the  $\text{Zn}^{+2}$  complex showing the highest

affinity. Antioxidant assays indicated that the  $\text{Cu}^{+2}$  complex had superior radical scavenging activity compared to  $\text{Zn}^{+2}$ ,  $\text{Ni}^{+2}$  and standard antioxidants. Yong Li et al. [110] synthesized the Schiff base ligand chromone-3-carbaldehyde-aminophenazone (L) and its  $\text{Ln}^{+3}$  (La, Yb) complexes. DNA-binding studies showed intercalative interactions, with  $\text{Ln}(\text{III})$  complexes binding more strongly than the free ligand. Antioxidant assays demonstrated enhanced activity for the complexes over the ligand, surpassing some standard antioxidants. Kalanithi et al. [111] reported  $\text{VO}^{+4}$ ,  $\text{Co}^{+2}$ ,  $\text{Ni}^{+2}$ ,  $\text{Cu}^{+2}$ , and  $\text{Zn}^{+2}$  complexes of a Schiff base derived from 2-aminothiazole and 3-formyl chromone. Structural analysis revealed distorted square planar geometry for  $\text{Cu}^{+2}$  and distorted tetrahedral geometries for  $\text{Co}^{+2}$ ,  $\text{Ni}^{+2}$ , and  $\text{Zn}^{+2}$  while  $\text{VO}^{+4}$  adopting square pyramidal geometry. Antimicrobial studies showed enhanced activity of the metal complexes over the ligand. Photophysical studies and SHG measurements indicated moderate nonlinear optical properties, while SEM of the  $\text{Cu}^{+2}$  complex (20) revealed  $\sim 2$  nm nanoparticles suitable for nanoscale applications.



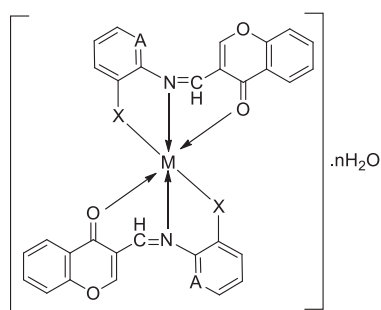
M = Cu(II), Co(II), Ni(II), and Zn(II)

Arjmand et al. [112] synthesized chiral Schiff base ligands (*R*)/(*S*)-2-amino-3-(1-hydroxypropan-2-ylimino)methyl-4H-chromen-4-one (L1 and L2) and their  $\text{Cu}^{+2}$  and  $\text{Zn}^{+2}$  complexes. DNA-binding studies and molecular docking showed preferential binding to GC-rich regions, with the (*R*)-enantiomer exhibiting the highest affinity. Anitha et al. [113] prepared azo-Schiff base complexes of  $\text{VO}^{+2}$ ,  $\text{Co}^{+2}$ ,  $\text{Ni}^{+2}$ ,  $\text{Cu}^{+2}$ , and  $\text{Zn}^{+2}$ , characterized via multiple analytical and spectroscopic techniques. These complexes (21) displayed strong  $\pi$ - $\pi^*$  fluorescence enhanced by metal coordination, notable SHG activity, potential for photoactive and NLO applications. Kavitha et al. [114] synthesized  $\text{Cu}(\text{II})$  complexes from various Schiff bases, including chromone-based ligands (22). Characterization revealed a 1:2 metal-to-ligand stoichiometry with distorted octahedral geometry, lattice water, and triclinic crystallization. The complexes exhibited significantly enhanced antimicrobial, antioxidant, and DNA cleavage activities compared to the free ligands, highlighting their potential as biologically active agents.



M = Co, Ni, Cu, and Zn

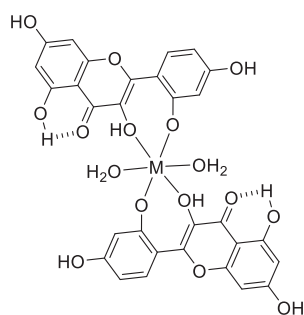
(21)



A=C and X=O/S/COO  
 A=N and X=O  
 M = Cu(II)/Ni(II)/Zn(II)

(22)

Carlos Vila et al. [115] developed a copper-catalyzed method to achieve high regio- and enantio-selectivity across a broad range of functionalized chromones and secondary alkyl magnesium reagents. Kavitha et al. [116] synthesized Ni<sup>+2</sup> and Zn<sup>+2</sup> complexes of tridentate 3-formyl chromone Schiff bases, which displayed enhanced antimicrobial, antioxidant, and moderate nematocidal activities compared to the free ligands. The complexes also showed cytotoxic effects via MTT assay and significant DNA cleavage in the presence of hydrogen peroxide. Hikisz et al. [117] prepared three gold(I) alkynyl chromone complexes. X-ray analysis confirmed linear d10 gold(I)-alkynyl coordination. These complexes exhibited and anticancer activity via multiple mechanisms including thioredoxin reductase inhibition, caspase activation, DNA damage, and cell cycle disruption. They exhibit potent antibacterial against MSSA and MRSA, but inactive against *E. coli*. Grazu et al. [118] reviewed metal complexes of naturally occurring chromones, flavonoids, and coumarins. Zn<sup>+2</sup> and Pd<sup>+2</sup> complexes (23) show markedly improved biological activities over free ligands. These complexes demonstrated potential in treating diabetes, infections, cancers, and neurodegenerative disorders, while also modulating iron homeostasis relevant to Friedreich's ataxia and  $\beta$ -thalassemia.



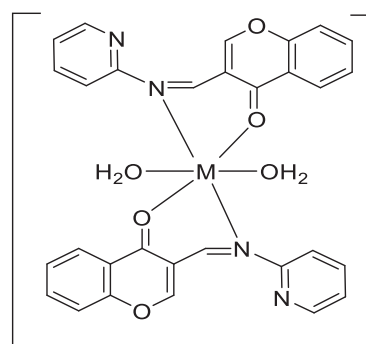
M = Pd(II), and Zn(II)

(23)

Kavitha et al. [119] synthesized and characterized palladium(II) complexes (23) of Schiff bases derived from 3-formylchromone. Spectroscopic and analytical data confirmed that the Pd(II) complexes adopt a square-planar geometry and powder X-ray diffraction (XRD) studies revealed their crystalline nature. The antimicrobial efficacy of these complexes was assessed against two Gram-negative bacteria, two Gram-positive bacteria, and a fungal strain. The Pd<sup>+2</sup> complexes demonstrated superior antimicrobial activity compared to the free ligands.

Additionally, antioxidant studies showed that the complexes exhibited free radical scavenging activity comparable to that of the standard antioxidant butylated hydroxytoluene (BHT). DNA cleavage assays, performed using agarose gel electrophoresis, further demonstrated the ability of the Pd<sup>+2</sup> complexes to cleave pUC19 plasmid DNA, suggesting their potential utility in molecular biology and therapeutic applications.

Kavitha et al. [120] synthesized Cu<sup>+2</sup>, Co<sup>+2</sup>, Ni<sup>+2</sup>, and Zn<sup>+2</sup> complexes (24) using 3-((pyridin-2-ylimino)methyl)-4H-chromen-4-one as a Schiff base ligand, derived from the condensation of 3-formylchromone and 2-aminopyridine. The synthesized complexes were thoroughly characterized using various spectroscopic and analytical techniques. Scanning electron microscopy (SEM) images revealed distinct surface morphologies for each metal complex. All complexes exhibited notable fluorescence properties. Biological evaluations demonstrated that the metal complexes possessed enhanced antimicrobial and nematocidal activities in comparison to the parent ligand. Furthermore, both the free ligand and its metal complexes exhibited significant DNA cleavage activity in the presence of hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), indicating their potential as DNA-targeting agents.



M = Cu(II), Co(II), Ni(II)

(24)

### 1.3.2. N, O donor's ligands and their complexes

8-Hydroxyquinoline (8-HQ), also known as oxine, is a bicyclic compound derived from quinoline (1-azanaphthalene) and comprises a fused ring system containing a benzene and a pyridine moiety, with a hydroxyl group substituted at the 8-position. Among the seven isomeric hydroxyquinolines, 8-HQ uniquely exhibits significant antimicrobial activity and is the only isomer capable of forming stable chelate complexes with metal ions. Structurally, 8-HQ behaves similarly to phenols; it gives a characteristic violet coloration with ferric chloride, undergoes coupling with diazonium salts, and participates in classical reactions such as Reimer-Tiemann and Bucherer syntheses. Its acetate ester can undergo Fries rearrangement in the presence of aluminum chloride to produce acetyl derivatives.

The close proximity of the hydroxyl group to the heterocyclic nitrogen allows 8-HQ to form stable, insoluble chelates with a wide range of metal ions, including Cu<sup>2+</sup>, Bi<sup>2+</sup>, Mn<sup>2+</sup>, Mg<sup>2+</sup>, Fe<sup>3+</sup>, Al<sup>3+</sup>, Zn<sup>2+</sup>, and Ni<sup>2+</sup> [121]. During complex formation, the hydrogen of the hydroxyl group is displaced, enabling the metal ion to coordinate through both the phenolic oxygen and the nitrogen atom of the quinoline ring. Consequently, two molecules of 8-HQ are typically required to form four-coordinate metal complexes (25), while three molecules are necessary for the formation of six-coordinate complexes (26). These coordination modes contribute to the compound's broad utility in analytical chemistry, medicinal chemistry, and metal ion sensing.

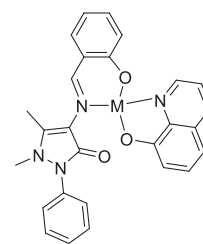


industrial applications. The increasing interest in metal chelates is reflected in the expanding literature on their synthesis, characterization, and practical uses [130]. The synthesis of mixed-ligand complexes, such as those containing both chromones and 8-hydroxyquinoline (8-HQ), presents several challenges due to ligand competition, differences in donor strength, and steric effects. Controlling the pH is critical, as protonation of phenolic or carbonyl groups can prevent coordination, while overly basic conditions may cause hydrolysis or precipitation of the metal. Solvent choice also plays an important role: polar aprotic solvents can facilitate ligand exchange, whereas coordinating solvents may compete with the ligands for the metal center. The stoichiometry of metal to ligands must be carefully balanced to favor simultaneous binding of both ligands and avoid formation of homoleptic complexes. Additionally, the reaction sequence and temperature can influence product formation, with stepwise ligand addition or controlled heating helping to minimize side reactions and decomposition. Overall, fine-tuning these conditions is essential to obtain stable, well-defined mixed-ligand complexes with the desired geometry and properties [131–134].

Arun Singh et al. [135] synthesized poly(ester amide) (PEA) via the polycondensation of 1,4-phenylenebisphthalamic acid and diglycidyl ether of bisphenol-A. The resulting polymer was further functionalized with 5-chloromethyl-8-hydroxyquinoline hydrochloride, facilitating its coordination with Cu(II), Zn(II), Mn(II), Ni(II), and Co(II) ions to form stable metal chelates. These complexes exhibited favorable coordination characteristics and suggested potential applications in analytical separations and sensing technologies. Liu et al. [136] developed a solid-phase extraction (SPE) method employing an ion-imprinted, cross-linked HQ-type chitosan resin, which demonstrated high efficiency for the preconcentration of uranium (VI) from aqueous samples. This selective and reusable sorbent material underscores the potential of functionalized 8-hydroxyquinoline-based materials in environmental and radiochemical applications.

Patel et al. [137] synthesized a novel bis-bidentate ligand, 5,5'-(3,3'-(phenylmethylene)bi(1H-indole-3,1-diy))bis(methylene)diquinolin-8-ol). This ligand was prepared via the condensation of 5-chloromethyl-8-hydroxyquinoline hydrochloride with 3,3'-(phenylmethanediyl)bis(1H-indole) in the presence of a base catalyst. The resulting PBIQ ligand was used to form coordination polymers with transition metal ions, including Cu(II), Ni(II), Co(II), Mn(II), and Zn(II), reflecting its strong metal-chelating ability and structural versatility. Subsequently, Oza et al. [138] synthesized a novel quinoline-based ligand, 5-([5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl]thio)methylquinolin-8-ol (K), through a base-catalyzed reaction of 5-chloromethyl-8-hydroxyquinoline with 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol. The ligand was further complexed with various transition metal salts to afford metal-containing heterochelates, expanding the chemical diversity and potential bioactivity of 8-HQ derivatives in coordination chemistry. Zidan et al. [139] synthesized a series of transition metal complexes incorporating both glycinyldithiocarbamate and 8-hydroxyquinoline (8-HQ) moieties.

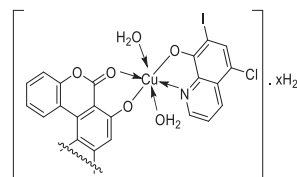
Shah et al. [140] reported the synthesis of a new chelating copolymer via copolymerization of 8-HQ with dimethylolacetone monomers in the presence of a base catalyst. This copolymerization strategy offers an efficient route to produce functional polymeric materials capable of metal ion sequestration and chemical sensing. Shaker et al. [141] synthesized several transition metal complexes combining 8-HQ with O-hydroxybenzylidene-1-phenyl-2,3-dimethyl-4-amino-3-pyrazolin-5-one (28). These complexes are of particular interest due to their potential biological activities and coordination versatility.



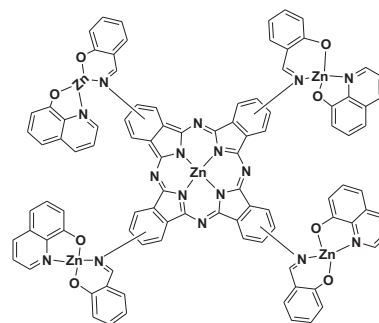
M = Mn(II), Fe(II), Co(II), Ni(II) and Cu(II)

(28)

Kharadi et al. [142] synthesized a series of Cu(II) transition metal complexes utilizing clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) (29) in combination with four distinct coumarin-derived ligands. These complexes were designed to explore the coordination behavior and potential biological activities stemming from the combination of two pharmacologically active scaffolds hydroxyquinoline and coumarin which are known for their metal-chelating ability and bioactivity.



(29)



(30)

Kharadi et al. [143] synthesized a series of transition metal complexes employing clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) and 1,10-phenanthroline as ligands. Comparative biological evaluation revealed that these metal complexes exhibited significantly higher antimycobacterial activity than either the free ligands or the corresponding metal salts, suggesting a synergistic effect arising from metal coordination. Gümürükçü et al. [144] synthesized a novel phthalocyanine derivative functionalized with four salicylideneimino donor groups directly attached to the macrocyclic core. This was achieved via condensation of tetramino-phthalocyanine with salicylaldehyde. The formation of peripheral pentanuclear complexes was carried out by two routes: either through direct reaction with 8-hydroxyquinoline (8-HQ) and a zinc(II) salt, or by preparing the Zn(II)-8-HQ complex (30) followed by subsequent reaction with the phthalocyanine framework. Furthermore, a new mixed-ligand Schiff base Zn<sup>2+</sup> complex, incorporating both a salicylaldimine ligand and 8-HQ, was synthesized and used as a model system to compare the structural and functional characteristics with the corresponding phthalocyanine-based assemblies.

Gao et al. [145] synthesized five mononuclear Cd<sup>2+</sup> and Zn<sup>2+</sup> complexes using a slow-release method with 5-nitro-8-hydroxyquinoline, derived from 5-nitro-quinoline-8-yl acetate. These complexes were

comprehensively characterized using elemental analysis, infrared (IR) spectroscopy, thermogravimetric analysis (TGA), fluorescence spectroscopy and single-crystal X-ray diffraction (XRD). Notably, all the complexes exhibited strong luminescence in the solid state at room temperature, making them promising candidates for optoelectronic applications. Kumar Rahul et al. [146] reported the synthesis and characterization of a novel electroluminescent material, [8-hydroxyquinoline] bis[2,2'-bipyridine aluminum. This compound demonstrated excellent thermal stability up to 300 °C and showed a characteristic emission peak at 515 nm, indicating its potential application in organic light-emitting devices.

Magdy Shebl et al. [147] reported the synthesis of mononuclear copper(II) complexes with 3-formylchromone, resulting in complexes with varying molar ratios and geometries (octahedral and square planar). The complexes were characterized using spectroscopic analysis. The ligand and some complexes exhibited antimicrobial activity against various microorganisms. A series of novel mononuclear copper(II), nickel(II), and cobalt(II) complexes with a hydrazone ligand. The complexes exhibit diverse structures and properties, including phenoxazinone synthase activity and antimicrobial potential. The study highlights the ligand's monoanionic tridentate behavior and the complexes varying stoichiometries and geometries, providing insights into their electronic structures and biological activities. These findings suggest potential applications in catalysis and medicine, meriting further research and development.

Reddy et al. [148] synthesized Co(II) and Cu(II) mixed-ligand complexes of chromone Schiff bases with 8-HQ via conventional reflux. The spectral and thermal data confirmed the formation of stable complexes. These compounds exhibited notable antimicrobial and antitubercular activity, particularly against *Mycobacterium tuberculosis*. Docking studies indicated effective binding with enoyl-acyl carrier protein reductase, supporting their anti-TB mechanism of action. Kolhe et al. [149] successfully synthesized and characterized novel heteroleptic complexes of Mn(II), Co(II), Ni(II), and Cu(II) using 6-chloro-5,7-dimethyl-4-oxo-4H-chromene-3-carbaldehyde and quinolin-8-ol as ligands. These complexes demonstrated promising antimicrobial activity.

The study by Shebl et al. [150] explores the synthesis and characterization of new binary and ternary Cu(II), Ni(II), and Co(II) complexes with a tridentate ONO hydrazone ligand. Comprehensive analyses, including spectroscopic, magnetic, and DFT calculations, confirmed the stability and structure of these complexes. Biological evaluations revealed significant antimicrobial activity, particularly against *B. subtilis* and *C. albicans*. Additionally, the complexes demonstrated phenoxazinone synthase biomimetic catalytic activity, suggesting their potential as bioinspired catalysts. Singh et al. [151] synthesized mixed-ligand complexes of Cu(II), Ni(II), and Co(II) using chromone hydrazone and 8-HQ in refluxing ethanol. The resulting complexes were thoroughly characterized using UV-Vis, FTIR, NMR, thermal analysis (TGA), and XRD. The data confirmed octahedral geometries, and the complexes showed strong antibacterial activity against *E. coli* and *S. aureus* as well as high antioxidant potential in DPPH assays.

Patel et al. [152] extended this line of research by using a microwave-assisted synthesis to prepare Zn<sup>+2</sup> and Cu(II) complexes with 3-formylchromone and 8-HQ. This green synthetic method significantly reduced reaction time and improved yield. Structural characterization was performed using mass spectrometry, IR, SEM, and EDX. DNA-binding studies indicated an intercalative mode of binding, supported by viscosity and spectrophotometric analyses. Additionally, molecular docking studies showed strong interactions with DNA base pairs and topoisomerase enzymes. These complexes also exhibited cytotoxicity against MCF-7 breast cancer cells, suggesting potential anticancer applications. Seema et al. [153] highlighted the potential of combining 8-hydroxyquinoline (8 HQ) with chromone or quinone-type ligands in mixed-ligand systems, resulting in enhanced biological profiles. The chromone-quinoline Schiff-base ternary complexes involving 1,2-naphthoquinone derivatives and 8 HQ exhibited promising antimicrobial,

anti-inflammatory, and antidiabetic activities.

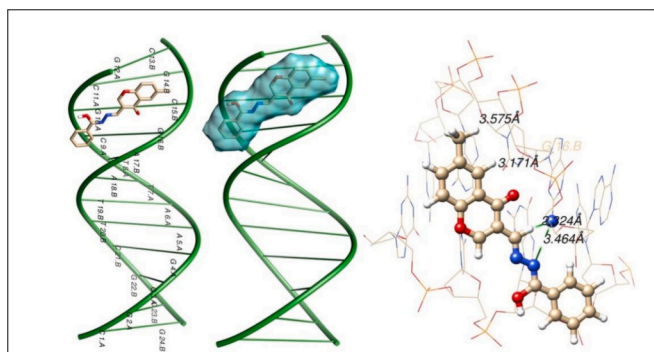
Du et al. [154] synthesized and characterized twenty zinc(II)-8-hydroxyquinoline complexes with 1,10-phenanthroline ligands, evaluating their anticancer potential. Complex DQ6 showed the highest cytotoxicity against cisplatin-resistant ovarian cancer cells (IC<sub>50</sub> = 2.25 μM) while sparing normal cells. Mechanistic studies indicated apoptosis via mitophagy, and in vivo tests demonstrated ~49.7 % tumor growth inhibition. These findings suggest complexes as a promising anticancer candidate. Run-Chun et al. [155] investigated the design and synthesis of two novel 8-hydroxyquinoline platinum(II) derivatives, which exhibit potent anticancer activity against MDA-MB-231 breast cancer cells with notable selectivity over non-cancerous HL-7702 cells. Mechanistic studies reveal that ligands induce senescence and apoptosis by triggering DNA damage and downregulating hTERT mRNA expression, with ligand showing greater efficacy.

Beyond simple DNA binding, several alternative mechanisms have been proposed to explain the biological activity of metal complexes. A key pathway involves reactive oxygen species (ROS) generation, where redox-active complexes undergo electron transfer processes leading to the production of hydroxyl radicals, superoxide, or singlet oxygen that trigger oxidative stress and apoptosis [156–158]. In addition, enzyme inhibition plays a significant role, as metal centers can coordinate to active-site residues or cofactors, thereby blocking essential enzymes such as topoisomerases, kinases, or proteases. Some complexes also induce mitochondrial dysfunction, disrupting membrane potential and promoting cytochrome-c release, which activates intrinsic apoptotic pathways [159]. Furthermore, membrane disruption is increasingly recognized, with amphiphilic complexes inserting into lipid bilayers and compromising membrane integrity, leading to leakage of cellular contents. Interaction with proteins is another important mode of action, as coordination with amino acid residues (His, Cys, Met) can modify protein conformation and function, while certain complexes also induce cell cycle arrest by interfering with regulatory pathways. Collectively, these multifaceted mechanisms act either independently or synergistically with DNA binding, thereby enhancing the therapeutic and antimicrobial potential of such complexes [160].

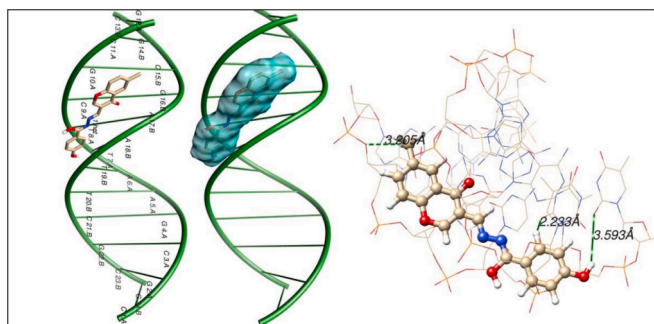
#### 1.4. Toxicity and selectivity

Metal-chromone and metal-8-HQ complexes generally display strong cancer-cell cytotoxicity but only modest selectivity over normal cells. For example, Patrique Nunes et al. found that Cu(II)-phenanthroline complexes of 6-substituted chromone Schiff bases were highly cytotoxic but not selective toward cancer cells. More recent work on Cu(II) complexes of chromone-2-carboxylic acid showed only slightly better selectivity: HepG2 liver cancer cells were ~ 1.4–1.6× more sensitive than normal human fibroblasts. This selectivity is modest because the chromone ligand itself (e.g. 2-carboxylate) is largely non-toxic, so the metal ion (Cu) drives the effect. In fact, introducing a 2-carboxylate on the chromone markedly increased ant proliferative potency but even these Cu-chromone carboxylate complexes showed only SI ≈ 1–1.6. Thus, most reported chromone-metal complexes exhibit low safety windows [161].

Likewise, 8-hydroxyquinoline derived complexes tend to be broadly cytotoxic with only moderate cancer selectivity. For instance, novel Cu (II) and Zn<sup>+2</sup> complexes of 8-quinoline Schiff bases were reported to have IC<sub>50</sub> < 10 μM in melanoma cells yet only “moderate selectivity” versus normal fibroblasts. In a recent study by Lopes et al., V(IV) = O, Ni (II) and Fe(III) complexes bearing an 8-HQ-benzothiazole ligand all showed sub-μM to low-μM IC<sub>50</sub>, but SI values were mostly near 1. Only the V(IV) complex achieved an I ≈ 4.0 (A375 melanoma cells) most other SIs were < 3 (e.g. SI < 1 in murine B16F10). In general, adding lipophilic or halogen substituents to 8-HQ improves cancer potency but often equally raises normal-cell toxicity with small SI. Copper(II) 8-HQ Schiff-base complexes similarly reach IC<sub>50</sub>'s in the single-digit μM range but only give SI ≈ 1–2. Overall, both chromone- and 8-



**Fig. 1.** Molecular docked model of 6-methyl-4-oxo-4H-chromen-3-yl)methylene) benzohydrazide with DNA and showing H-bonding interaction of ligand with B-DNA.

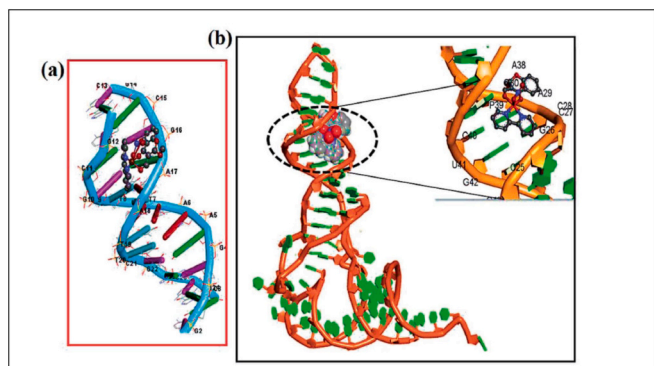


**Fig. 2.** Molecular docked models of 4-hydroxy-N'-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)benzohydrazide with DNA and showing H-bonding interaction of HL2 with B-DNA.

hydroxyquinoline-based metal complexes exhibit strong cytotoxicity ( $IC_{50} \approx 0.5\text{--}10 \mu\text{M}$ ) but limited selectivity toward cancer cells. Although modifying substituents or metal centers (e.g., adding carboxyl or halogen groups; using Cu, Ni, V, Zn, or Fe) can slightly tune potency, substantial selectivity improvements are uncommon. Selectivity indices ( $SI > 2\text{--}4$ ) are rare, highlighting that these complexes typically affect both cancerous and normal cells with comparable toxicity [162,163].

### 1.5. Advance studies on molecular docking, DFT studies and clinical translation

Over the last decade, significant progress has been made in the design and study of transition metal complexes involving chromone derivatives and 8-hydroxyquinoline (8-HQ), especially with the



**Fig. 3.** Molecular docked model of complex 2 with (a) ct-DNA (PDB ID: 1BNA) and (b) tRNA (PDB ID: 6TNA).

integration of computational methods such as molecular docking and DFT. These ligands are structurally rich in oxygen and nitrogen donor atoms, allowing them to form stable chelates with various transition metals like Cu(II), Ni(II), Co(II), Fe(III), and Zn(II). Their biological potential, including antibacterial, antifungal, antioxidant, and anti-cancer activities, has been extensively explored through both experimental and theoretical approaches. Molecular docking has emerged as a pivotal technique in understanding the interaction between these metal complexes and biological macromolecules. It allows prediction of binding affinity, interaction modes, and potential molecular targets, thereby offering mechanistic insight into observed bioactivity.

Shebl et al. [147] were carried out docking simulations using the Molecular Operating Environment (MOE) software, which enabled evaluation of binding affinities of Schiff base metal complexes toward DNA and selected proteins, while their DFT calculations were performed with Gaussian 09, applying the B3LYP functional for geometry optimization and electronic property analysis. Structural variety in copper(II) complexes of 3-formylchromone presents a comprehensive investigated the coordination behavior and structural diversity. The study successfully synthesized a series of new Cu(II) complexes and characterizes them using various techniques such as elemental analysis, IR, UV-Vis, ESR spectroscopy, and thermal gravimetric analysis. Molecular modeling and density functional theory (DFT) calculations further supported the proposed geometries and electronic properties. Importantly, the biological activities of the synthesized complexes are evaluated, revealing promising antibacterial and antifungal properties.

Philip et al. [164] synthesized hydrazone derivatives of 6-methyl-3-formylchromone complexed with Ni(II), Cu(II), and Zn<sup>2+</sup> ions. Molecular docking was employed to explore their interaction with calf-thymus DNA (Figs. 1 and 2) and relevant biological targets associated with antidiabetic and antimicrobial action. AutoDock 4.2 employed for molecular docking to probe DNA and protein binding of copper(II) complexes, while Gaussian 09 used for DFT optimization and frontier molecular orbital (FMO) studies. The metal complexes exhibited strong affinity through minor groove and intercalative binding modes. These computational observations were supported by experimental studies, including viscosity and spectral titrations, indicating that metal coordination enhanced the biological potency of the chromone-based hydrazones.

Farukh Arjmand et al. [165] synthesized and characterized three new Cu(II) complexes using bioactive chromone pharmacophore and N, N-donor ancillary ligands as potential antitumor agents. These complexes were thoroughly characterized using various spectroscopic techniques and single X-ray crystallography. The DNA/RNA binding profile and cleavage activity of the complexes were investigated, revealing higher binding propensity for tRNA compared to ct-DNA and efficient single-strand cleaving ability. The cytotoxic activity of the complexes was evaluated against four human cancer cell lines, with complex 1 showing greater potency than the standard drug ADR in certain cell lines. Critically, the study highlighted the importance of varying N,N-donor ligands in modulating the biological activity of the complexes (Fig. 3). This work also integrated molecular docking studies using AutoDock Vina to rationalize anticancer activity, and DFT calculations were conducted in Gaussian 09 to estimate HOMO-LUMO gaps and charge distribution.

Nabil et al. [166] comprehensively explores the synthesis and characterization of novel Ni(II) and Co(II) binary and ternary complexes derived from 3-formylchromone (L), demonstrating their octahedral geometries through elemental analysis, thermal studies, IR, electronic spectroscopy, magnetic susceptibility, and molar conductivity measurements. The 3-formylchromone ligand acts as a neutral bidentate chelator, coordinating to metal ions via its formyl and  $\gamma$ -pyrone oxygen atoms, forming complexes with stoichiometries of 1:2 and 1:3 (M: L) for binary systems and 1:2:1 and 1:1:1 (M: L:L') for ternary systems incorporating auxiliary ligands (8-hydroxyquinoline or 1,10-phenanthroline). The synthesized complexes exhibit significant antimicrobial

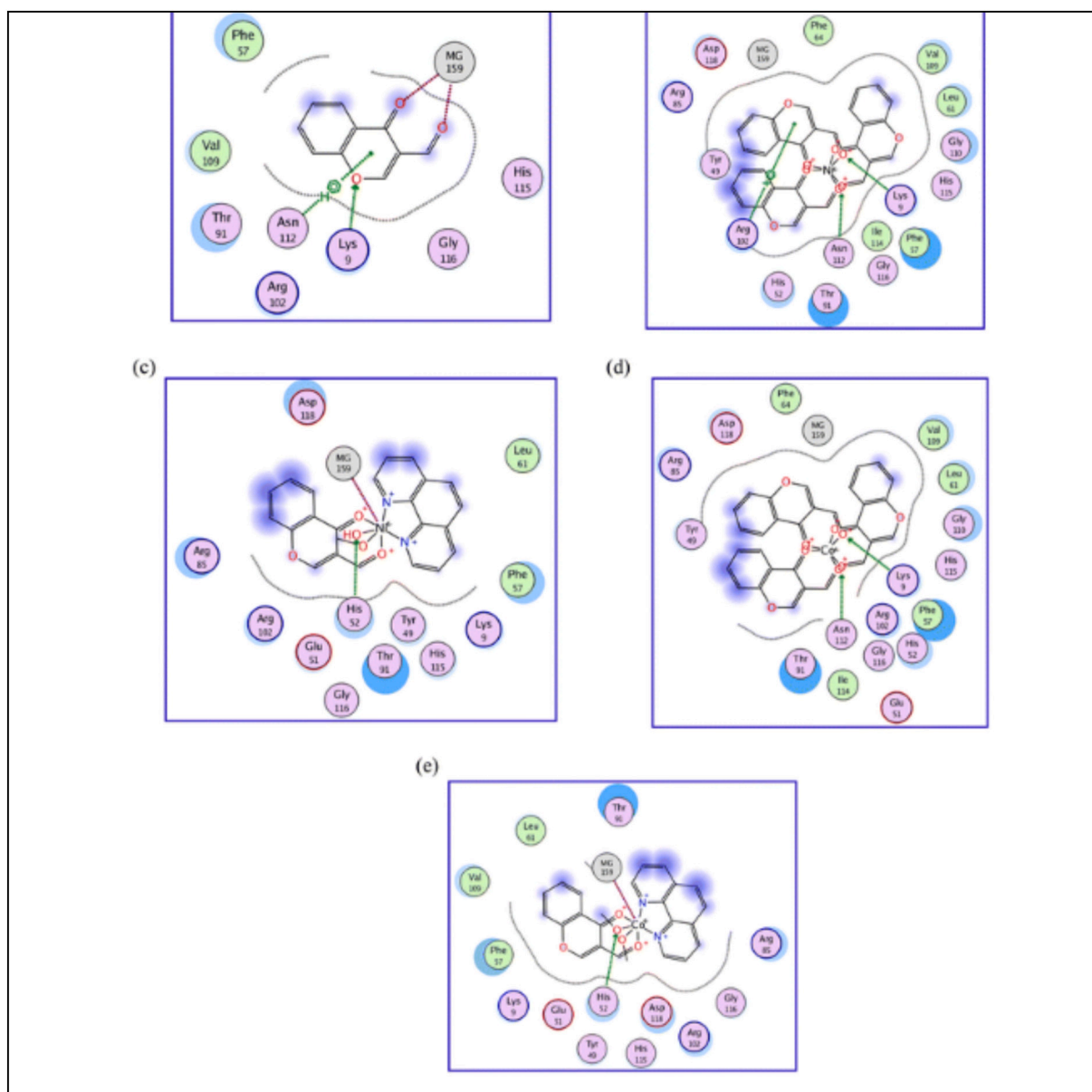


Fig. 4. 2D diagram of Ligand, Ni(II) and Co(II) interaction with PDB ID 3Q89.

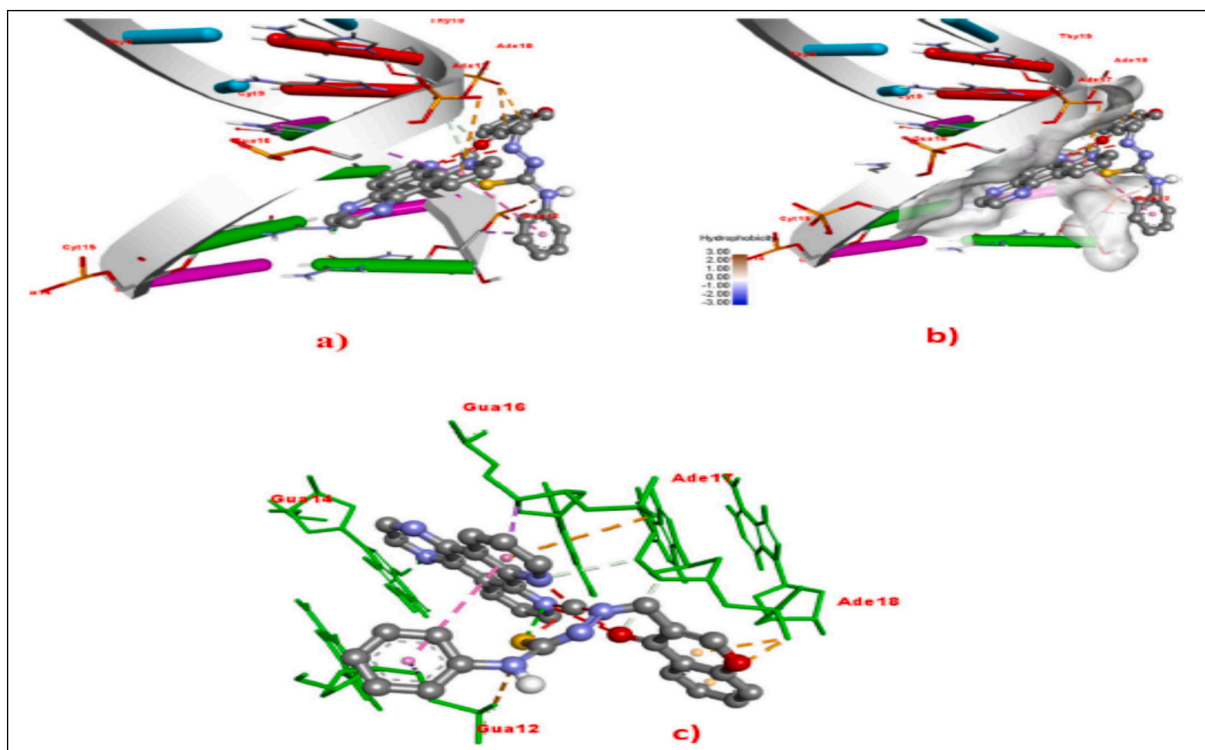
activity, particularly against *C. albicans* and *B. subtilis*, which is corroborated by docking studies that reveal strong binding affinities (Fig. 4). Molecular modeling performed using Hyperchem.

**DNA binding affinities, anti-oxidant, antimicrobial and molecular docking activities of Pd(II) complexes of chromone Schiff bases** reported by Husain, Ach, and Anupama et.al[167]. The synthesized Pd(II) complexes were characterized using various spectroscopic techniques, and their interactions with DNA were studied via UV-Vis absorption, viscosity measurements, and fluorescence quenching methods, revealing strong DNA binding affinities suggestive of intercalative binding modes. Additionally, the complexes exhibited notable antioxidant and antimicrobial activity, supported by molecular docking simulations that revealed favorable interactions with biological targets. Schrödinger's Glide module for docking simulations and Gaussian 09 for DFT were utilized. This study provides valuable insights into the potential of Pd(II) Schiff base complexes as multifunctional bioactive agents and lays a foundation for their future development in therapeutic applications.

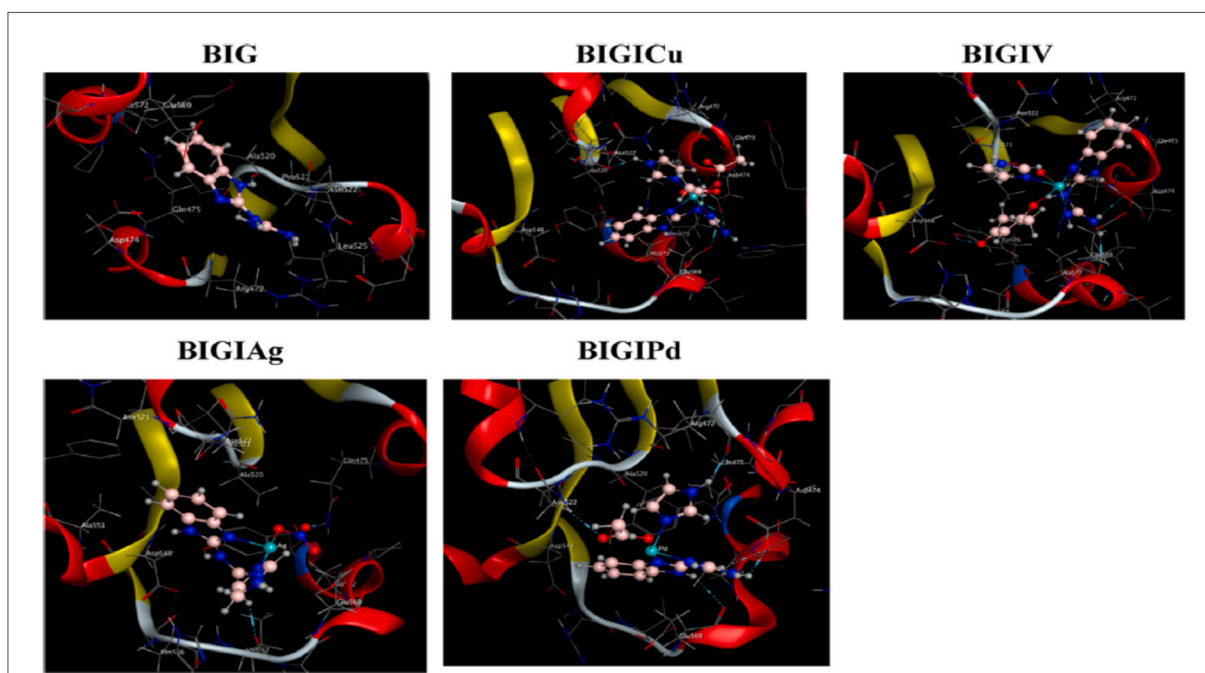
Mamindla et al. [168] synthesized mixed-ligand Cu(II) complexes incorporating a chromone-derived Schiff base with various diimine

ligands, and evaluated their biological potential through combined experimental and computational approaches (Fig. 5). Docking studies using AutoDock Vina and AutoDock 4.2 revealed strong DNA binding affinities ( $-10.97$  to  $-12.04$  kcal/mol) toward duplex DNA (PDB 1BNA), with interactions occurring predominantly via the minor groove and intercalation. The planarity and extended conjugation of the ligands were identified as key contributors to enhanced binding scores, which were consistent with in vitro DNA-binding experiments. Complementary DFT and TD-DFT calculations (Gaussian 16) provided insights into the electronic transitions underlying spectroscopic features.

Aljohani et al. [169] synthesized and characterized mixed-ligand metal complexes of 2-guanidinobenzimidazole and imidazole with Cu (II), VO(II), Ag(I), and Pd(II). Spectroscopic and theoretical analyses confirmed their coordination modes and geometries. Biological assays and molecular docking revealed strong DNA binding (Fig. 6), antimicrobial, antioxidant, and cytotoxic activities, with the Pd(II) complex showing the highest potential. Docking studies supported the experimental findings, highlighting key biomolecular interactions and suggesting these complexes as promising therapeutic candidates.



**Fig. 5.** Molecular docking of the dpq complex 4 with DNA (PDB: 1BNA). (a) Full 3D-view of DNA with complex 4 in the minor groove. (b) Detailed interactions of 4 with surrounding nucleobase residues. (c) 3D-view of hydrophobic interactions with dodecamer DNA nucleobase residues.



**Fig. 6.** 3D interactions of mixed ligand of 2-guanidinobenzimidazole and imidazole with Cu(II), VO(II), Ag(I), and Pd(II) complexes with the 2Vf5 receptor.

Wassila Derafa *et al.* [170] reported the successful synthesis and detailed characterization of novel Co(II), Ni(II), and Cu(II) complexes derived from the Schiff-base ligand 2-[(4-[(4-methylphenyl)sulfonyl]methylene]aminobenzoic acid]. Complemented by density functional theory (DFT) calculations, revealed distinct coordination modes and geometries tetrahedral for the Co(II) complex and octahedral for the Ni(II) and Cu(II) analogues. The ligand coordinates in a bidentate

manner via azomethine nitrogen and carboxylic oxygen donor atoms, forming stable metal-ligand frameworks. Quantum chemical parameters, particularly the HOMO–LUMO energy gap, indicated that the Cu(II) complex exhibits the highest reactivity and lowest stability among the synthesized compounds. Biological evaluation demonstrated significant antibacterial and antifungal activities against both Gram-positive and Gram-negative strains, with molecular docking studies further

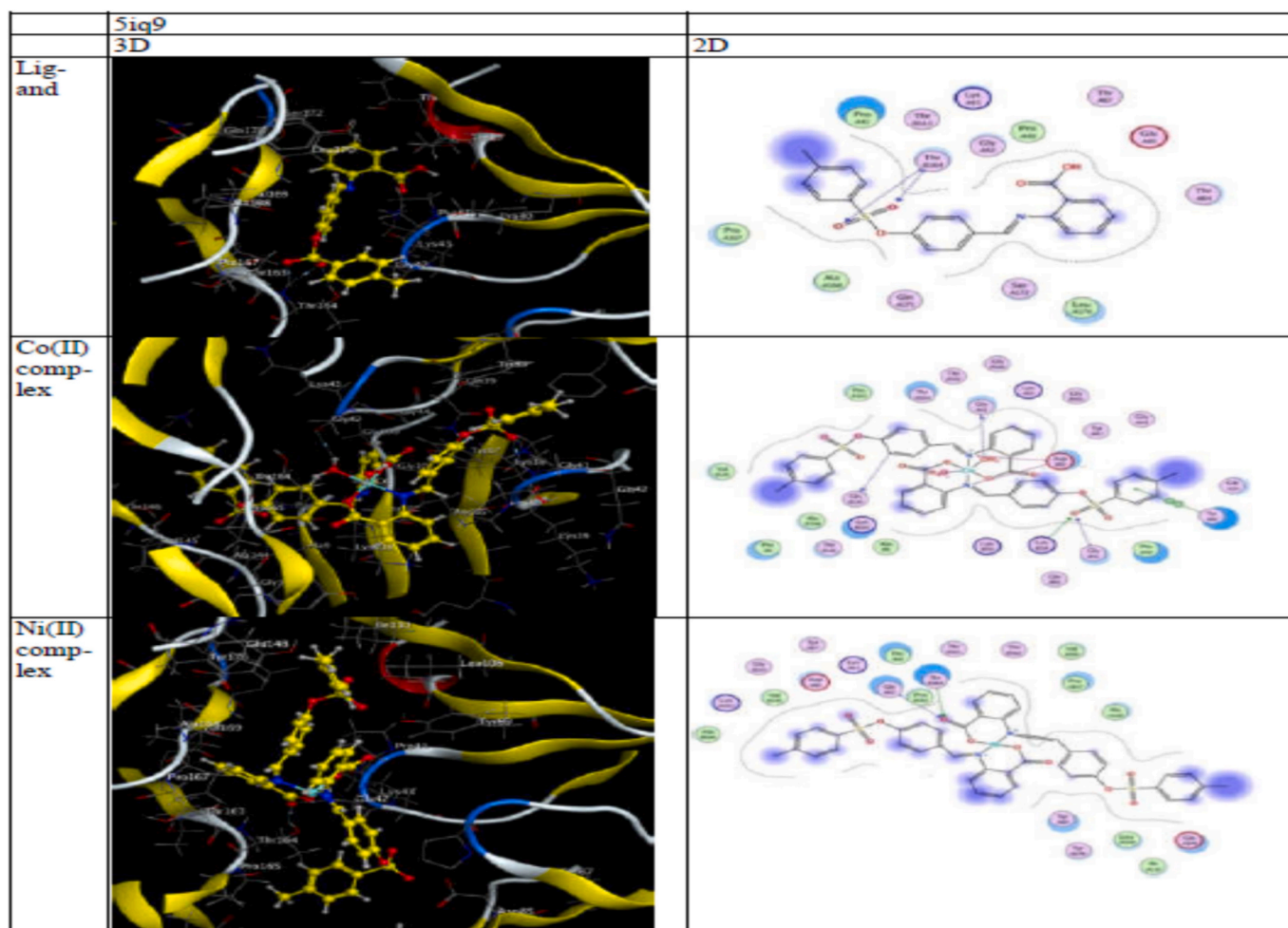


Fig. 7. Molecular docking studies further validating these results. Docking simulations against bacterial protein targets (PDB IDs: 5JQ9 and 6CLV).

Table 1

Summary of Metal Complexes, Bioactivity,  $IC_{50}$  / MIC / Kb, Computational studies Insights, and Key Finding.

| Sr-N | Metal complexes / structures   | Bioactivity ( $IC_{50}$ / MIC / Kb)  | Computational studies insights  | Key findings   |
|------|--|--|---|--|
| 1.   | Co(II), Ni(II), Cu(II) complexes of tridentate ONO/ONS Schiff bases. | Showed antimicrobial activity with MIC values 8–16 $\mu\text{g}/\text{mL}$ .             | DFT showed octahedral geometry; HOMO–LUMO gap correlates with reactivity. | Coordination via azomethine N and phenolic O enhanced stability and bioefficacy. |
| 2.   | Cu(II), Zn(II), Ni(II) Schiff base–hydrazone complexes.              | Potent cytotoxicity vs. MCF-7 and HeLa; $IC_{50}$ = 8–15 $\mu\text{M}$ .                 | Docking revealed strong DNA groove/intercalative binding.                 | Photoinduced ROS generation linked to cytotoxic mechanism.                       |
| 3.   | Cu(II)/Ni(II) complexes with quinoline-based Schiff bases.           | $IC_{50}$ (Cu) = 6.2 $\mu\text{M}$ ; (Ni) = 10.8 $\mu\text{M}$ against HeLa.             | DFT: Square-planar geometry; docking supports DNA intercalation.          | DNA cleavage and antioxidant activity enhanced by metal coordination.            |
| 4.   | Mn(II), Fe(III), Cu(II), Zn + 2 chromone Schiff base complexes.      | MIC = 4–12 $\mu\text{g}/\text{mL}$ ; Cu(II) most active.                                 | TD-DFT confirmed LMCT transitions; HOMO localized on ligand.              | Antimicrobial and antioxidant efficacy linked to ligand planarity.               |
| 5.   | Co(II), Ni(II), Cu(II) mixed-ligand Schiff base complexes.           | $IC_{50}$ (Cu) $\approx$ 9 $\mu\text{M}$ vs. HepG2 cells.                                | DFT and docking support stable chelation and DNA groove binding.          | Strong correlation between theoretical and biological results.                   |
| 6.   | Cu(II)–chromone–Schiff base mixed-ligand complexes.                  | $IC_{50}$ = 4.5 $\mu\text{M}$ (Cu $_2$ ); high ROS generation.                           | DFT/docking reveal strong $\pi$ – $\pi$ stacking with DNA bases.          | Effective anticancer agents via oxidative stress pathway.                        |
| 7.   | Co(II), Ni(II), Cu(II) complexes with bidentate N,O ligands.         | MIC = 6–10 $\mu\text{g}/\text{mL}$ vs. <i>S. aureus</i> , <i>E. coli</i> .               | Frontier molecular orbital study supports high chemical reactivity.       | Metal–ligand synergy enhances antibacterial properties.                          |
| 8.   | Cr(III), Mn(II), Cu(II) complexes of Schiff bases with heterocycles. | Antifungal activity > standard fluconazole (MIC = 3.2 $\mu\text{g}/\text{mL}$ ).         | DFT: Low HOMO–LUMO gap $\rightarrow$ high biological reactivity.          | Strong ligand–metal conjugation enhances redox activity.                         |
| 9.   | Zn(II), Cu(II), Fe(III) complexes of phenolic–Schiff ligands.        | Kb (DNA) = $1.3 \times 10^5 \text{ M}^{-1}$ ; $IC_{50}$ = 7–12 $\mu\text{M}$ vs. MCF-7.  | Docking: Minor groove and hydrogen-bond interactions.                     | Potential food-safe antioxidants and anticancer agents.                          |
| 10.  | Cu(II), Zn + 2 mixed-ligand chromone–8HQ complexes.                  | $IC_{50}$ = 5.8 $\mu\text{M}$ ; strong antibacterial (MIC = 4 $\mu\text{g}/\text{mL}$ ). | DFT + docking: Stable chelate, low energy gap, DNA intercalation.         | Exhibited dual anticancer–antimicrobial activity with ROS mediation.             |

validating these results. Docking simulations against bacterial protein targets (PDB IDs: 5JQ9 and 6CLV) revealed strong binding affinities, especially for the Cu(II) complex, which showed the lowest binding energies (–8.46 and –8.38 kcal/mol), suggesting efficient bio-target

interactions (Fig. 7).

Overall, the combined experimental and in silico analyses establish a strong structure activity relationship, highlighting the Cu(II) complex as the most promising candidate for antimicrobial development. Continued

exploration of such Schiff-base metal complexes could contribute significantly to the design of next-generation metal-based antimicrobial agents. Computational studies, including docking and DFT analyses, generally align well with experimental observations for chromone- and 8-hydroxyquinoline-based complexes. Cu(II)-chromone Schiff base systems show strong DNA binding via intercalation or groove interactions (binding energies  $-10$  to  $-12$  kcal/mol), consistent with low micromolar  $IC_{50}$  values. Similarly, 8-hydroxyquinoline derivatives exhibit HOMO–LUMO gaps and docking affinities that correlate with cytotoxicity and DNA/protein binding, as seen in Cu(II) and  $Zn^{+2}$  complexes with sub-10  $\mu M$   $IC_{50}$  values while maintaining selectivity for normal cells. Mixed-ligand 8-HQ–benzothiazole complexes also show good agreement between predicted docking interactions and experimental antiproliferative activity, highlighting the usefulness of computational methods while indicating that further refinement is needed for quantitative predictions [171].

In conclusion, the integration of molecular docking and DFT in the study of chromone and 8-hydroxyquinoline-based transition metal complexes represents a powerful approach to drug discovery and bioinorganic chemistry. These tools have provided significant mechanistic insights, improved ligand design, and strengthened the understanding of structure–activity relationships. However, for these computational strategies to reach their full potential, methodological standardization, dynamic modeling, and multi-disciplinary integration are essential. The future of metal-based therapeutics will undoubtedly be driven by a deeper and more unified application of these *in silico* techniques. Summary of the metal complexes, highlighting their bioactivity,  $IC_{50}$  and MIC values, computational insights, and key findings, which collectively demonstrate in [Table 1](#).

The future of transition metal complexes with chromone derivatives and 8-hydroxyquinoline in bioinorganic and medicinal chemistry will heavily rely on computational tools like molecular docking and DFT. These tools will enable researchers to design more effective metal-based therapeutics through multi-target simulations, dynamic modeling, and accurate binding affinity predictions. Integrated platforms combining docking, DFT, pharmacokinetics, and QSAR modeling will accelerate the screening of novel complexes for therapeutic applications. Machine learning and AI will also play a key role in predicting biological activities and guiding *de novo* design. Furthermore, green chemistry principles will be integrated into computational planning to promote sustainable synthesis. By synergizing advanced computational methods with experimental validation, researchers can discover more potent metal-based therapeutics efficiently. This integrated approach will deepen mechanistic understanding and bridge the gap between theoretical modeling and clinical application.

Mixed-ligand transition metal complexes of 8-hydroxyquinoline and chromone derivatives face major barriers to clinical translation due to challenges in stability, bioavailability, and toxicity. In biological media they often undergo ligand exchange, redox changes, poor solubility, and metabolic degradation, making their active form unpredictable. Their bioavailability is limited by low solubility, strong serum protein binding, rapid clearance, and unpredictable metal redistribution, which complicates pharmacokinetics and dosing. Toxicity risks arise from intrinsic metal accumulation, off-target chelation disrupting metal homeostasis, and ROS generation, leading to organ damage or genotoxicity. Additional hurdles include analytical difficulties in tracking speciation, manufacturing consistency, and regulatory uncertainty. Strategies like designing more kinetically inert complexes, advanced formulations (e. g., nanoparticles, prodrugs), targeted delivery, and early speciation/PK studies can mitigate these barriers but add cost and complexity compared to traditional small molecules.

Molecular docking supports the clinical translation of metal complexes by predicting their binding modes, affinities, and potential targets, thus guiding rational design and structure–activity relationship studies before extensive synthesis and testing. It helps identify likely biomolecular interactions and possible off-target effects, reducing

attrition in preclinical stages. While docking cannot fully account for metal speciation, redox behavior, or dynamic ligand exchange *in vivo*, when combined with molecular dynamics, QM/MM, and experimental validation it provides valuable mechanistic insights that accelerate optimization and selection of lead complexes for further development.

### 1.6. Green synthesis

A green synthetic pathway for mixed metal complexes can be designed by integrating sustainable methods at each step. Chromone ligands may be prepared via metal-free, water-based annulation, while 8-HQ or its derivatives can be obtained through mechanochemical routes that avoid solvents. The mixed-ligand complexes are then formed by mechanochemical grinding with minimal liquid assistance or by aqueous/ethanol complexation, optionally ultrasound-assisted, followed by simple recrystallization or antisolvent precipitation. This approach minimizes hazardous solvents, reduces waste and energy use, and supports ligand and metal recovery. Combined with early stability, speciation, and toxicity screening, such routes enhance both environmental sustainability and translational potential of these complexes. Some complexes synthesized by green methods are

Green synthesis and characterization of 8-hydroxyquinoline magnesium complex was reported by Junchen Liu et al. [172] using environmentally friendly methods. By adopting a green synthesis approach, the research demonstrates a sustainable and eco-friendly route for the development of these compounds, reducing the environmental impact associated with traditional synthesis methods. The findings suggest that this approach could be extended to the synthesis of other metal complexes with potential applications in various fields. Synthesis *in vitro* antimicrobial activity of metal complexes with 8-Hydroxyquinoline by Amira Cipurković et al. [173] explores antimicrobial properties. It highlights the potential for adopting green synthesis approaches in the development of metal-based antimicrobial agents. Future studies could build upon this work by investigating environmentally friendly synthesis methods to further enhance the sustainability and potential applications of these complexes. The findings demonstrate the potential of these complexes as antimicrobial agents, warranting further research in this area.

El-Saghier et al. [174] reported a focused design, synthesis, and biological assessment of novel 1,3,4-thiadiazine/thiadiazole-benzene-sulfonamide derivatives as potential insecticidal agents against *S. littoralis*. The study demonstrated their insect growth-regulating (IGR) activity highlighting their potential as novel pest control agents. Seema, N.et.al. [175] highlights the eco-friendly methods for green synthesis and biological significance of chromone derivatives with amino acids and their metal complexes. The research demonstrates the potential of these compounds as antimicrobial, anti-diabetic, and antioxidant agents. This approach not only reduces environmental impact but also opens up new avenues for the development of therapeutic agents.

The major issue in the green synthesis of transition metal complexes of 8-hydroxyquinoline and chromone derivatives is achieving controlled coordination and product purity under solvent-free or aqueous conditions. These ligands are prone to multiple binding modes and tautomerism, and in “green” media (water, ethanol, mechanochemical grinding) the reaction often leads to mixed or polymeric species, poor selectivity, or incomplete complexation. In addition, many metal salts are poorly soluble in green solvents, making stoichiometric control, reproducibility, and scale-up difficult. Ensuring that the desired, well-defined complex forms rather than ill-characterized mixtures, while still avoiding toxic solvents and energy-intensive conditions remains the key challenge for sustainable synthesis.

## 2. Conclusion

In conclusion, this comprehensive review has summarized the significant advances in the field of mixed-ligand transition metal complexes

featuring 3-formylchromone derivatives and N, O-donor auxiliary ligands. It demonstrates that the synergistic interplay between the biologically active chromone scaffold and versatile N, O-donor ligands is a powerful strategy for engineering complexes with superior and tunable properties. The overall enhanced biological profile (antimicrobial, anticancer, and antioxidant) when compared to their parent components, emphasize the immense potential of mixed-ligand approach. The computational studies like molecular docking and DFT offers valuable insight into their bioactive behavior and interaction mechanisms. However, despite these promising advances, several challenges remain. The stability and speciation of these complexes in biological environments are not fully understood, limiting translational potential. Bioavailability, pharmacokinetics, and systemic toxicity pose additional barriers, as metal coordination and ligand exchange can unpredictably alter distribution and efficacy. A significant gap exists in the translation of in vitro to in vivo models, with detailed pharmacokinetic and toxicological studies. Utilization of green chemistry principals can enhance sustainability and facilitate scalable production. Additionally, integrating computational modeling with experimental pharmacology including can accelerate rational design of complexes with improved selectivity and reduced off-target effects. Addressing these gaps will not only deepen our understanding of mixed-ligand transition metal complexes but also pave the way for the development of next-generation metal-based therapeutics with enhanced efficacy, safety, and clinical applicability. The journey from bench to bedside is long, but the versatile and nature potent of these mixed-ligand chromone complexes provides a compelling and robust foundation.

#### CRediT authorship contribution statement

**Nitin H. Kolhe:** Writing – review & editing, Writing – original draft, Visualization, Software, Conceptualization. **Yasinalli Tamboli:** Writing – review & editing, Visualization, Resources. **Huda A. Bawazir:** Writing – review & editing, Resources. **Vijay Singh Parihar:** Writing – review & editing, Writing – original draft, Visualization, Software, Conceptualization.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Data availability

The authors declare that the data supporting the findings of this study are available within the paper. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request.

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