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Advances in chromone-based copper(II) Schiff base complexes: synthesis, characterization, and versatile applications in pharmacology and biomimetic catalysis†

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Chromones are well known as fundamental structural elements found in numerous natural compounds and medicinal substances. The Schiff bases of chromones have a much wider range of pharmacological applications such as antitumor, antioxidant, anti-HIV, antifungal, anti-inflammatory, and antimicrobial properties. A lot of research has been carried out on chromone-based copper(II) Schiff-base complexes owing to their role in the organometallic domain and promise as potential bioactive cores. This review article is centered on copper(II) Schiff-base complexes derived from chromones, highlighting their diverse range of pharmacological applications documented in the past decade, as well as the future research opportunities they offer.

1. Introduction

Chromone, also known as 4*H*-chromen-4-one or 4*H*-1-benzopyran-4-one, is an *O*-heterocyclic compound characterized by its benzo-γ-pyrone structure. It is part of a category of naturally occurring molecules that are prevalent in the plant kingdom, ranging from algae to coniferous plants.[1] It forms the central backbone in flavonoids such as flavone, isoflavone, and flavonol (Fig. 1).[2,3] Chromones have become a compelling presence in the field of medicinal chemistry and drug development initiatives due to their potential to offer a wide range of chemical variations along with a diverse array of pharmacological effects.[4–6] Both naturally existing and artificially synthesized compounds containing a chromone component have exhibited a diverse range of biological characteristics including anti-inflammatory[7,8] anticancer[9,10] antitumor,[11] antimicrobial[12,13] anti-HIV,[14] antioxidant,[15] and many other activities.[16,17] Khellin, a furanochromone obtained from the seeds of the *Ammi visnaga* plant, serves as an illustrative instance of a natural chromone employed as a bronchodilator for asthma. Presently, it is also utilized in the management of vitiligo and psoriasis (Fig. 2).[18] Exploration rooted in khellin has given rise to novel chromone derivatives like cromolyn and nedocromil, which are employed as mast cell stabilizers for the treatment of allergic asthma and allergic conjunctivitis.[19] Diosmin, a flavone glycoside is known for its antioxidative, anti-inflammatory, antihyperglycemic, and anti-ulcer properties.[20] Another bioflavonoid, apigenin has been reported to modulate histamine release, is a bronchodilator, and also possesses anti-cancer properties.[21] Flavoxate is known as an anticholinergic agent because of its antimuscarinic effects (Fig. 2).[22]

Apart from the development of new chromone derivatives with promising properties, combining chromones with other pharmacophores to achieve hybrid structures with enhanced and multitarget therapeutic applications is an interesting proposition. One such pharmacophore is Schiff bases with varied applications across various domains, including pharmaceutical chemistry,[23] catalysis,[24] dye industry,[25] corrosion inhibitors[26,27] and chemo-sensors.[28,29] The conventional method for creating Schiff bases, which bears the name of Hugo Schiff, encompasses the combination of a carbonyl compound with an appropriate amine, employing suitable solvents and catalysts.[30] Schiff bases, a subclass of imines, feature a carbon–nitrogen double bond bound exclusively to alkyl or aryl groups, without

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† This article is a tribute to the cherished memory of our esteemed (late) Professor Ashok K. Prasad, who served as our enduring friend, collaborator, colleague, and mentor for many years. His enduring influence and guidance throughout the past several decades have profoundly impacted the careers of numerous aspiring scientists.

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any attached hydrogen atoms. Imines, organic compounds characterized by a C=N double bond, are pivotal entities in organic chemistry. They play essential roles in various fields such as synthesis, medicinal chemistry, coordination chemistry, and materials science. With their distinct reactivity and diverse structures, the imine functional group serves as a versatile and crucial component, facilitating the construction of intricate molecular architectures and functional materials.[31,32] Owing to the electron-rich nature of the azomethine nitrogen atom through which they coordinate with metal ions, Schiff bases are known as one of the strongest chelators. Schiff bases possess remarkable pharmacological activities such as antibacterial, antifungal, and anticancer activities due to the presence of C=N moiety.[33–35] A noteworthy number of Schiff base complexes are analogs of naturally occurring molecules and thus are of critical importance.[36] In this regard, Schiff bases can also be combined with chromones as they are ideal organic fluorescent probes possessing structural flexibility and pharmacological activity. 3-Formyl chromone serves as a commonly employed starting molecule in the construction of chromone Schiff bases, and it is typically generated through the Vilsmeier–Haack reaction.[37]

Chromone Schiff bases are organic compounds resulting from the condensation reaction between chromone derivatives and primary amines. Chromone-based Schiff bases have been the focal point of organic, medicinal, and organometallic chemistry. Known for their pharmacological potential, these compounds exhibit diverse activities such as anti-inflammatory,


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antioxidant, anticancer, antibacterial, and antifungal properties.[38] Owing to their established reputation as chelating ligands, these compounds are recognized for their enhanced bioavailability, decreased toxicity, ability to form stable metal complexes, and robust binding affinity for metal ions.[39–41] The synthesis of chromone Schiff bases typically involves mild conditions and allows for structural modifications to enhance their biological activities. Research has shown that these compounds possess promising therapeutic effects, making them valuable candidates for drug discovery and development.[42] A tremendous increase in the biological property of Schiff bases is observed when they are chelated with transition metal ions. Such metal complexes can be efficiently prepared through the addition of a suitable Schiff-base ligand to a metal precursor in an appropriate ratio and experimental conditions (Fig. 3). This is also true for chromone-based Schiff bases as exemplified by many examples. Chromone Schiff-base nano-complexes (**I**) such as those of Cu^{2+}, Ni^{2+}, Co^{2+}, Fe^{3+}, Zn^{2+}, Cd^{2+}, and UO_2^{6+}, and Zn^{2+} have been successfully prepared and evaluated as antimicrobial and antitumor agents, exhibiting

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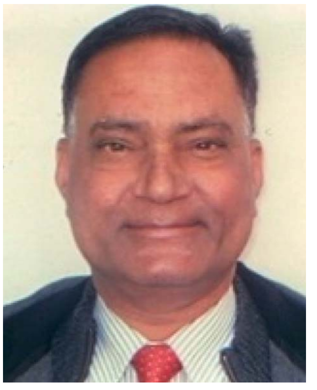

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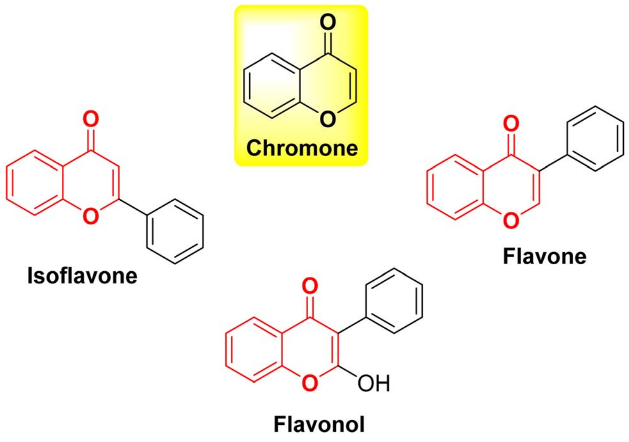


Fig. 1 Chromone skeleton in various flavonoids.

lower toxicity compared to cis-platin.[43] Chromone Schiff base (**II**) complexes with Pd^{2+} have also been successfully prepared, characterized, and investigated for circulating tumor DNA (ctDNA) binding, radical scavenging, and antimicrobial potency.[44] In a recent study, a fluorescent molecule appended with rhodamine and chromone (**III**) was synthesized as an efficient sensor for Fe^{3+}, Al^{3+}, and Cr^{3+} at trace levels. Further, they were assessed for anticancer activity and were found to be effective against MCF-7 cells, glucocorticoid, and progesterone receptors.[45] Barve *et al.*[46] synthesized copper ion conjugated chromone Schiff base complexes (**IV**) these compounds demonstrated their effectiveness as inhibitors against BT20, PC-3, as well as both COLO 357 and BxPC-3 cancer cell lines. Thus, it can be affirmatively suggested that the metal complexes exhibit better biological activity. The increase in activity can be ascribed to structural modifications resulting from coordination with the metal, and thus chelation makes metal complexes more potent compared to Schiff bases.[47] The report by El-Saghier *et al.*[48] established that Cu^{2+} complexes exhibit superior inhibition in comparison to the other complexes. This was ascribed to the presence of free mobilized electrons of Cu^{2+} complexes that permit strong oxidative inhibitory activity against microorganisms. This re-emphasizes that chromone-based Schiff bases are capable of forming d-block metal complexes amongst which copper complexes are predominantly effective as they have exhibited potent radical scavenging, anti-cancer, antimicrobial, and chemosensing properties.

The exploration of copper coordination chemistry is influenced by the crucial role copper assumes in numerous physiological processes, where it serves as an intrinsic component within metalloproteins like tyrosinase, cytochrome C oxidase, Cu/Zn superoxide dismutase, and blue copper proteins.[49,50] Equally significant is the fact that there are numerous copper(II) complexes with four, five or six-coordinate and different geometries such as square planar, flattened tetrahedral, trigonal bipyramidal, square-pyramidal, distorted octahedral, and penta-coordinated structures.[51–53] Owing to the pharmacological importance of chromones and Schiff bases, together with the multifaceted role of copper, there is a substantial interest in the development of chromone Schiff base copper complexes.

The primary goal of the current study is to perform an extensive review of published data from the past decade (2013–2023) pertaining to the synthesis and diverse applications of copper complexes derived from chromone-based Schiff bases. The impetus for undertaking this research stemmed from the observation that no comprehensive review had been available until now on Cu^{2+} complexes involving chromone Schiff bases. In this work, we initially delve into the use of chromone-based Schiff base ligands as a selective colorimetric tool for detecting Cu^{2+} ions. Subsequently, we provide a comprehensive examination of ongoing research on chromone Schiff base copper complexes, highlighting their wide-ranging medicinal and pharmaceutical applications, such as antimicrobial, antioxidant, and antitumor properties. Further, we have explained

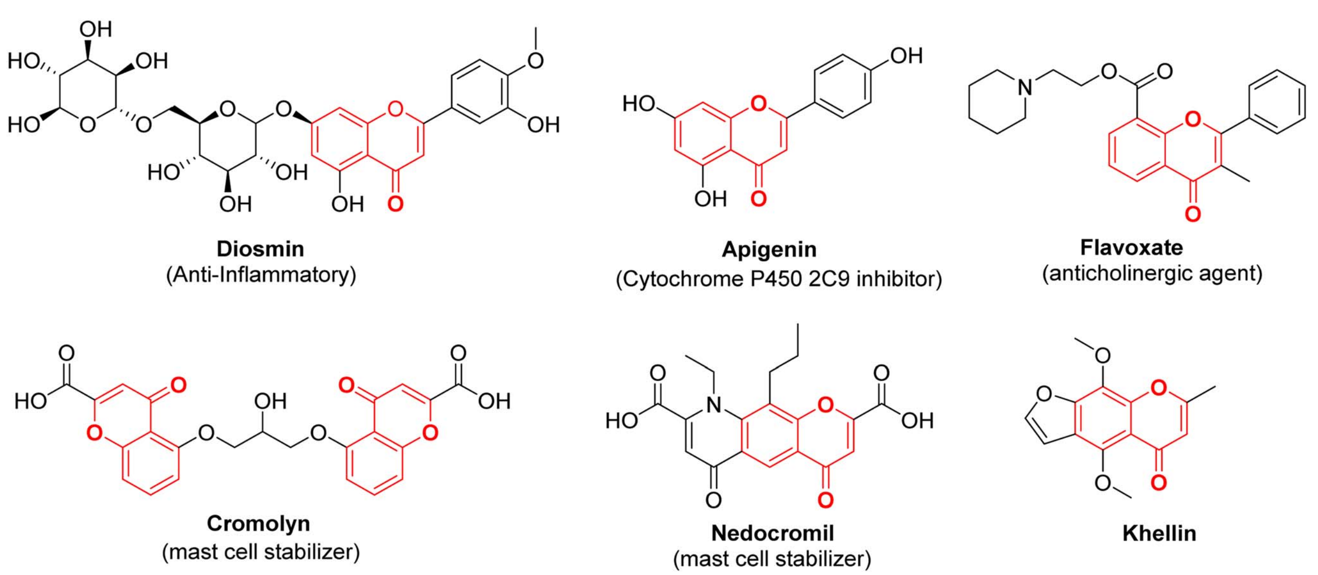


Fig. 2 Representative chromone derivatives as pharmaceutical agents.

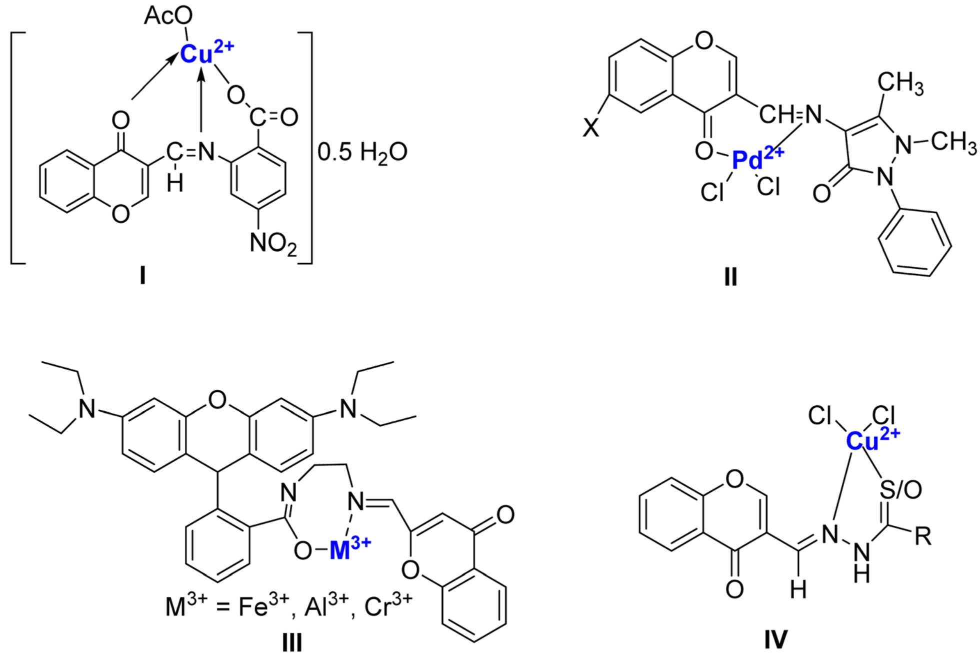


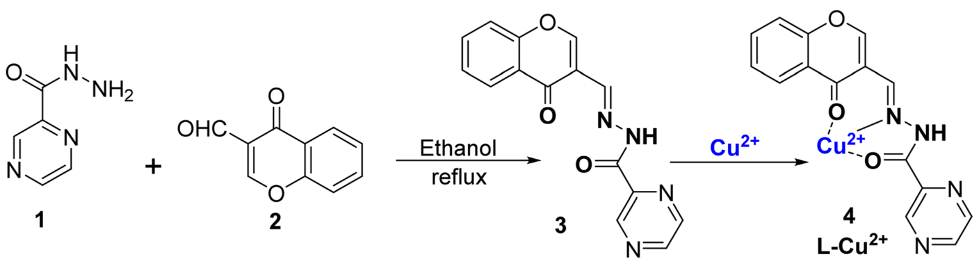
Fig. 3 Pharmacologically significant chromone-based Schiff base complexes reported in the literature.

the biomimetic catalytic activity of chromone-based Schiff bases together with some miscellaneous applications. Finally, the challenges and future developments have been deliberated upon to promote the research on copper chromone Schiff base agents.

2. Copper detection by chromone-based Schiff bases

Copper is regarded as an abundant and important metal which play a very useful role in various biological, medicinal, and environmental fields.[54] On one hand, excessive use of copper metal can cause serious problems in humans such as retardation of growth, Wilson's disease, and liver destruction while on the other, less intake of copper is also harmful, causing anemia, leukopenia, and myelopathy.[55] Excess Cu^{2+} ions in drinking water sources can cause damage to animals, humans, and plants. According to the U. S. EPA, the highest range of Cu^{2+} ions in water should not be more than 20 μM.[56,57] According to WHO, the maximum limit of Cu^{2+} ions is 31.4 μM.[58] Thus, preparing an efficient sensor for tracing Cu^{2+} ions in environmental bodies and organic species becomes all the more important.[59–61] Many traditional methods are available, which are otherwise costly or difficult to handle such as electrochemical sensing and atomic absorption spectroscopy (AAS).[62–64] Therefore, there is a need for a simple, cost-effective, accurate method for monitoring Cu^{2+} ions in samples. Colorimetric sensors are the solution for the detection of copper because they not only reduce the cost but also make the process of detection easy and fast. Due to this, the design and use of colorimetric probes is a flourishing area of research.[65,66] Nowadays, different variety of organic receptors and nanomaterials are used as colorimetric sensors.[67–69] In recent times, Schiff bases and chromone-derived colorimetric and optical sensors have also been used for metal ion detection.[70–72] This is due to their specific structure, and large binding affinity with metal ions.[73,74] Herein, we have discussed chromone Schiff base sensors which bind to Cu^{2+} ions making exclusive coloured copper complexes and thus can be used as colorimetric sensors.

In 2021, Tomer *et al.*[75] successfully synthesized a Schiff base ligand denoted as ligand **3**, which was derived from chromone. The synthesis of this ligand involved a condensation reaction between pyrazine-2-carbohydrazide **1** and 3-formylchromone **2**, as illustrated in Scheme 1. The synthesized ligand **3** underwent

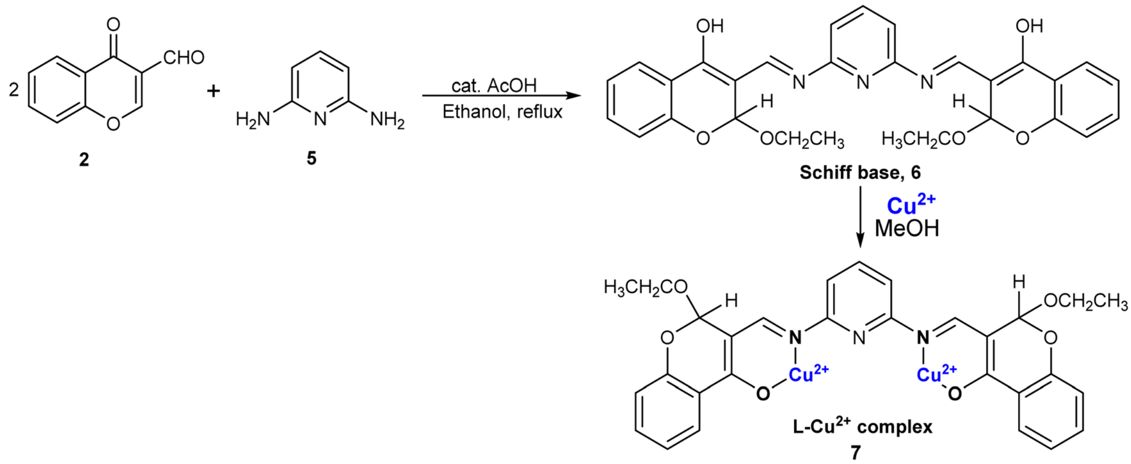


Scheme 1 Schiff base ligand **3** was synthesized, followed by the preparation of its Cu^{2+} complex **4**.

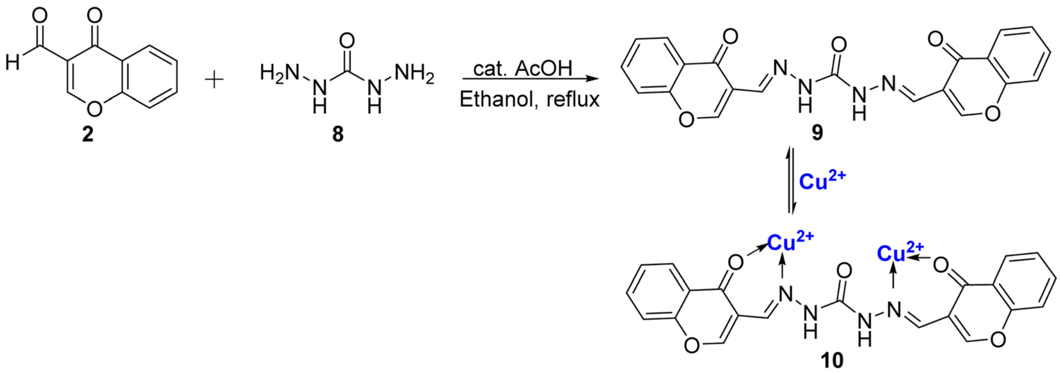
characterization such as ^{1}H-NMR, HRMS, FT-IR, and UV-Vis spectroscopy. Notably, ligand **3** was employed as a highly effective colorimetric probe for the detection of Cu^{2+} ions in different water sources, including canal water, groundwater, and tap water. The addition of Cu^{2+} ions to ligand **3** resulted in an immediate change in color from colorless to yellow, and the color change was because of the complex formation between the ligand and Cu^{2+} ions, referred to as complex **4**. Importantly, there was no color change with other tested metal ions. The absorption spectra of ligand **3** displayed two prominent absorption peaks at 258 nm and 311 nm. Nonetheless, with the introduction of Cu^{2+} ions, a fresh absorption peak became apparent at 428 nm, while the 311 nm band diminished. This shift in absorption, known as a bathochromic shift, was attributed to the complexation of Cu^{2+} ions and ligands through an intramolecular charge transfer process. When Cu^{2+} ions were incrementally introduced into the solution, another band at 428 nm continued to appear, while the 311 nm band gradually decreased. The researchers observed that ligand **3** displayed remarkable sensitivity across a wide pH range, particularly in neutral and basic conditions within the pH range of 6–11, although it was not effective at very low pH values, such as 2–3. The limit of detection for Cu^{2+} ions was determined to be 3.9×10^{-7} M, and the association constant was calculated to be 2.3×10^5 M^{-1} using the Benesi–Hildebrand equation. The stoichiometry between ligand **3** and Cu^{2+} ions as 1 : 1 was confirmed through Job's plot, which was also substantiated by HRMS and DFT. Moreover, the practical applicability of this developed ligand was assessed by testing its performance in actual water samples for the identification and quantification of Cu^{2+} ions.

A chromone-functionalized pyridine-based chemosensor was also prepared by the same group for the sensing of Cu^{2+} ions.[76] In their study, the researchers reported the synthesis of a novel Schiff base labeled as Schiff base **6**. This compound was prepared by condensing **2** with 2,6-aminopyridine **5** in ethanol as the solvent, and glacial acetic acid as catalyst (Scheme 2). A significant finding was that the binding stoichiometry between Schiff base **6** and Cu^{2+} ions was established as 1 : 2, a conclusion supported by both Job's plot and HRMS spectra data. Schiff base **6** demonstrated exceptional sensitivity and selectivity for cupric ions in comparison to other metal ions, as revealed by absorbance and emission titration studies. The absorption spectrum of Schiff base **6** exhibited three distinct absorption bands at 306 nm, 357 nm, and 401 nm. Upon the introduction of cupric ions, a new absorption band emerged at 347 nm, attributable to ligand-to-metal charge transfer, while a reduction in intensity was observed at 306 nm and 401 nm. Regarding fluorescence emission spectra, Schiff base **6** displayed a peak at 465 nm. The addition of Cu^{2+} ions resulted in a decrease in fluorescence intensity because of the paramagnetic nature of Cu^{2+} ions, accompanied by the appearance of a new peak at 458 nm. This fluorescence quenching was specific to the binding of Schiff base **6** to Cu^{2+} ions, with no similar response observed with other ions. pH studies indicated that the optimal pH range for detecting cupric ions was between 6 and 11. At lower pH values, protonation of the azomethine linkage occurred, leading to reduced sensing capability. Schiff base **6** exhibited an association constant of 3.26×10^4 M^{-1} and a regression coefficient of 98.7% for Cu^{2+} ions. It displayed a detection value of 1.2 μM for the Schiff base–Cu^{2+} complex **7**, which was below the permissible limit for Cu^{2+} ions, thus confirming its effectiveness as a probe. Schiff base **6** was successfully employed in actual water samples, including canal water, distilled water, groundwater, and tap water for the detection of Cu^{2+} ions.

Tomer *et al.*[77] presented another Schiff base probe based on chromone **9**, in their study. This probe exhibited remarkable selectivity for Cu^{2+} ions and possessed the added capability of detecting *para*-nitrotoluene (*p*NT) with impressively low detection limits. The synthesis of this probe **9**, was accomplished through a straightforward, one-step condensation reaction involving **2** and **8**, (Scheme 3). Notably, Schiff base probe **9** displayed noticeable naked-eye colorimetric changes, shifting from colorless to yellow upon the introduction of Cu^{2+} ions, setting it apart from the response to other ions tested. In terms of its spectroscopic features, the Schiff base probe **9** exhibited two distinct absorption bands at 315 nm and 278 nm. With the



Scheme 2 Synthesis of Schiff base **6** and its complex with Cu^{2+} ions **7**.



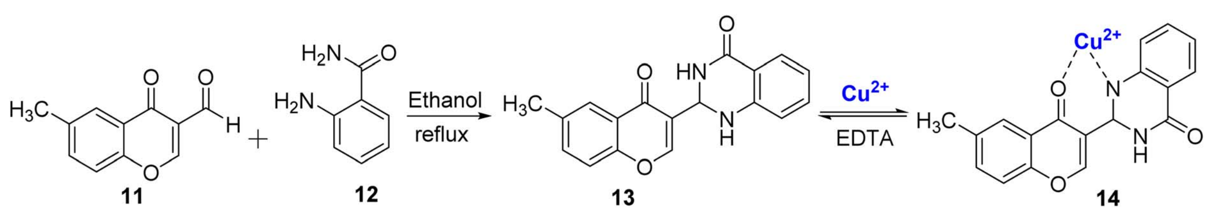
Scheme 3 Synthesis of probe **9** and its complex with Cu^{2+} ions **10**.

gradual addition of Cu^{2+} ions, a new absorption band emerged at 421 nm, accompanied by a reduction in the intensity of the bands at 315 nm and 278 nm. The binding stoichiometry of 1 : 2 between the complex and Cu^{2+} ions was confirmed through computational studies, Job's plot, and HRMS. The sensor exhibited reliable performance within a pH range of 5–9, and the sensing mechanism was found to be reversible, enhancing its practical utility. The binding constant was determined to be 4.5×10^5 M^{-1} for complex **10**, with a low detection limit of 11.4 $\times$ 10^{-7} M. For practical applications, it was demonstrated that the most noticeable color change can occur at a Cu^{2+} concentration of 10^{-4} M, using a paper strip test which underscores the efficacy of the probe **9** in real-world scenarios.

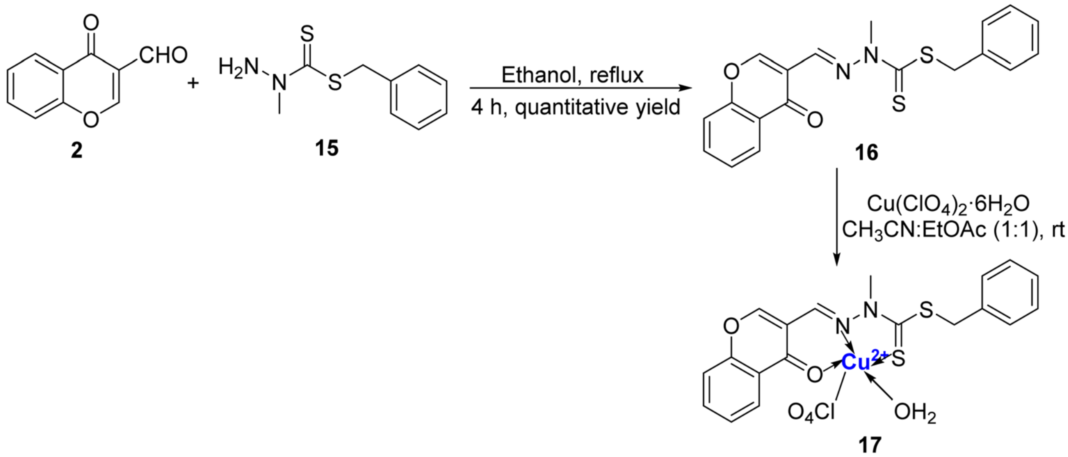
In another study, Mohammadi *et al.*[78] reported a novel optical sensor **13** for selective sensing of Cu^{2+} ions in acetonitrile–water solution. The sensor was synthesized by condensation reaction between **11** and 2-amino benzamide **12** followed by cyclization resulting in quinazolinone ring formation (Scheme 4). The chromone-based sensor **13** exhibited exceptional selectivity by undergoing a visible color change, transitioning from colorless to yellow when just 1 μM of Cu^{2+} ions were added. Notably, it retained its colorless appearance when tested individually with all twelve other metal ions at the same concentration. Upon the subsequent introduction of Cu^{2+} ions to the synthesized complex, a reduction in the intensity of the strong absorption band of the free ligand at 379 nm was observed, accompanied by the appearance of new absorption bands at approximately 306 nm and 456 nm. The stoichiometric ratio of 1 : 1 between the colorimetric sensor **13** and Cu^{2+} ions was corroborated through Job's plot and DFT studies. The binding constant for the **13**–Cu^{2+} complex was determined to be 3.27×10^4 M^{-1}, emphasizing the strength of the interaction of the sensor and Cu^{2+} ions. In anticipation of potential commercial applications, detection test strips were developed by coating filter paper with this chemosensor. These test strips allowed for the immediate naked-eye detection of copper ions in a wide concentration range, spanning from 10^{-3} M to 10^{-7} M, which enhances the practical utility and versatility of this sensor. The near nano detection limit (4.6×10^{-7} M), wide concentration range, short response time, and reversible properties of **14** were some of the salient features of the developed sensor.

Rahman *et al.*[79] prepared a sensitive and selective chromone and benzyldithiocarbazate based ligand **16** for colorimetric detection of Cu^{2+} ion in HEPES buffer media in a mixture of H_2O/CH_3CN (1 : 1). The ligand **16** was synthesized as a colourless cotton-like solid by taking *N*-methyl-*S*-benzyldithiocarbazate **15** with 3-formylchromone **2** in ethanol under reflux (Scheme 5). 100% selectivity was achieved in the case of Cu^{2+} with colourless to yellow colour change and there was no change in the presence of other metal ions and anions. Single crystal analysis of the green complex **17** formed with Cu^{2+} and **16** was found to be penta-coordinated with square pyramidal orientation. Complex **17** showed an absorption peak around 420 nm and also displayed a 1 : 1 stoichiometric ratio for Cu^{2+}: **16**. The detection limit was 0.12 nM and the association constant for **16** with Cu^{2+} was 5.24×10^6 M^{-1}. A colorimetric detection kit for Cu^{2+} ions was developed using the sensor and it was found that it could easily detect even 2 μM concentration of Cu^{2+} that is far beneath the WHO acceptable level.

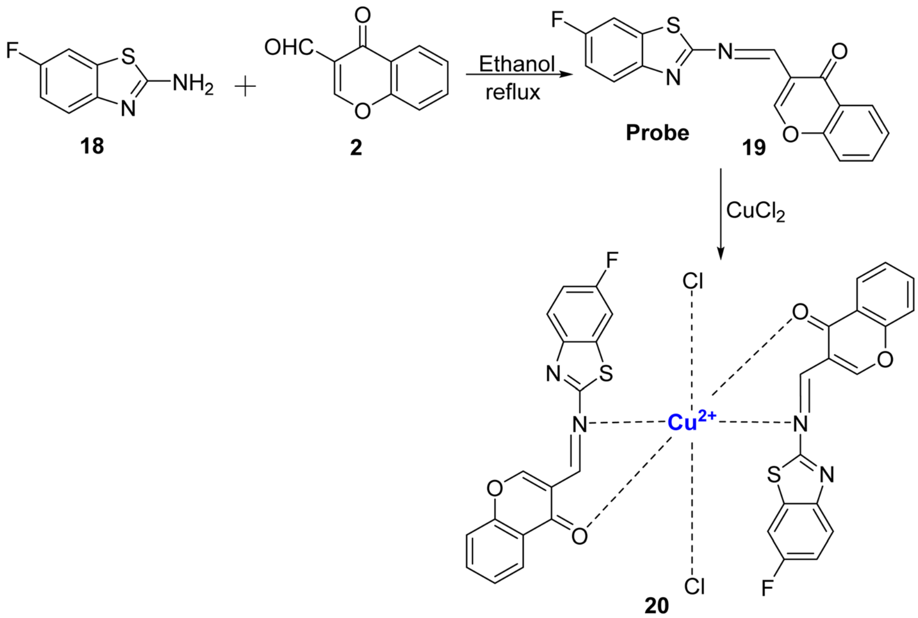
Kouser *et al.*[80] reported the development of a chemosensor probe denoted as **19**, based on the chromone molecule. This probe, **19**, was synthesized by reacting **2** with 2-amino-6-fluorobenzothiazole **18** under reflux conditions, (Scheme 6). Notably, probe **19** exhibited exceptional selectivity and sensitivity towards Cu^{2+} ions as opposed to a range of other metal ions. Two distinct absorption bands at 371 nm and 260 nm were assigned to n–π* and π–π* transitions. Upon the introduction of Cu^{2+} ions



Scheme 4 Synthesis of the colorimetric sensor **13** and it's its complex with Cu^{2+} ions **14**.



Scheme 5 Synthesis of ligand **16** and its complex **17** with Cu^{2+} ion.

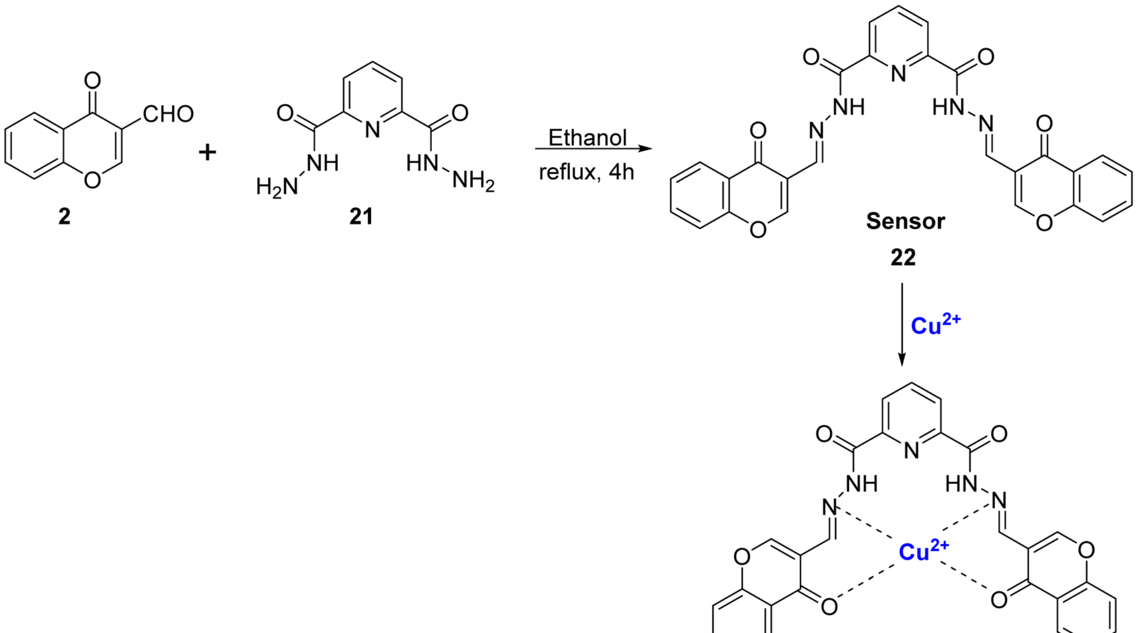


Scheme 6 Synthesis of chemosensor probe **19** and its complex with Cu^{2+} ion **20**.

into the solution of **19**, there was a noticeable change from daffodil yellow to green, and new bands emerged at 355 and 452 nm. These changes were attributed to the formation of charge transfer complexes, d–d transitions, and π–π* transitions. The sensor demonstrated rapid recognition of Cu^{2+} ions and a low detection limit of 0.273×10^{-6} mol L^{-1}. Furthermore, it displayed an increase in fluorescence intensity and a high association constant of 8.48×10^{8} M^{-2} with the addition of Cu^{2+} ions. By utilizing Job's plot analysis, it was determined that the stoichiometric ratio between probe **19** and Cu^{2+} in the complex was 2 : 1. The sensor's effectiveness in detecting copper-containing biomolecules was also assessed in various biological samples, including healthy liver tissues, *F. gigantica*-infected liver tissues, and adult *F. gigantica* worms.

Rezaeian *et al.* reported a chemo-sensor **22** obtained by the condensation reaction of **2** and 2,6-pyridinedicarbohydrazide **21** in high yields (Scheme 7).[81] The synthesized ligand **22** was used to sense and spot Cu^{2+} and Zn^{2+} ions both visually and spectrophotometrically among the different cations tested. With the increase in Cu^{2+} ions absorbance at 310 nm decreased with the concomitant formation of complex **23** and a new band at 425 nm. Cu^{2+} ion and ligand **22** had 1 : 1 stoichiometry and a binding constant of 3.41×10^{4} M^{-1}. From the experimental data, the detection limit for Cu^{2+} obtained was 5.5×10^{-7} mol L^{-1} which was lower as compared to the limit set for safe drinking water by WHO. Further, multiple and complex Boolean operations such as OR, NOR, AND, INH, and half adders such as AND and XOR were also conducted by varying anions and cations as chemical inputs and the absorption intensity as the logic output.

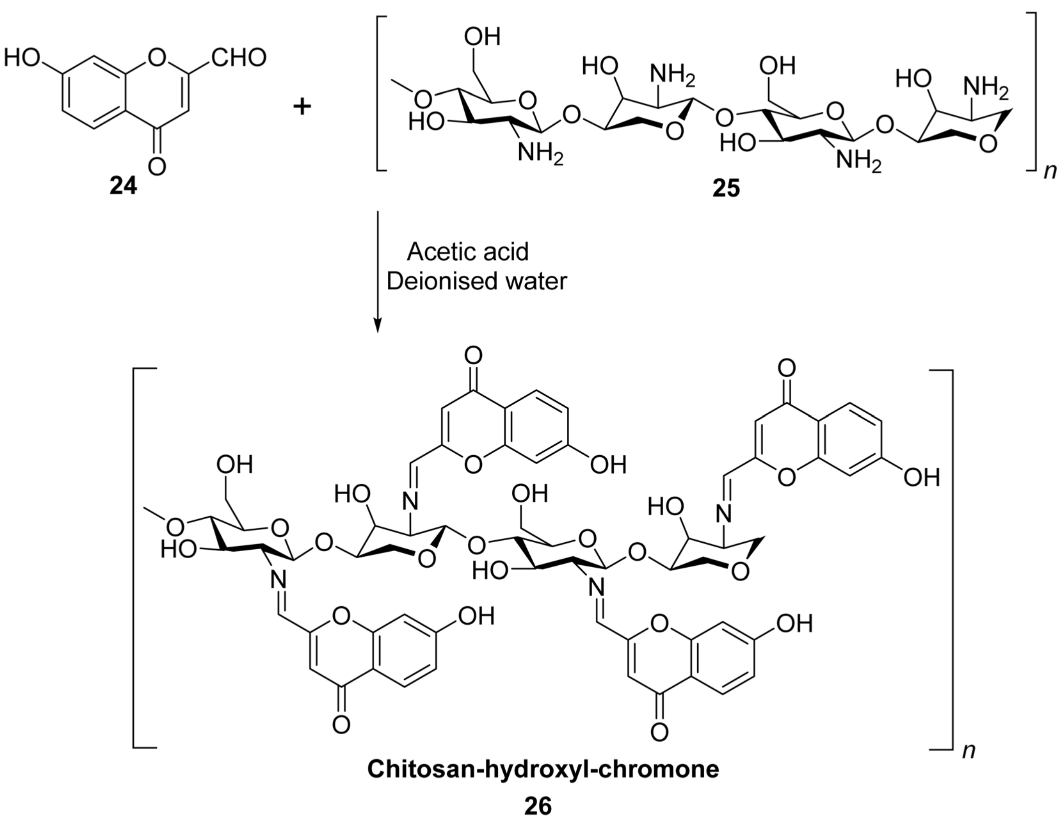
Gaidhane *et al.* used chitosan, which is a naturally occurring, environment-friendly bio-polysaccharide derived from chitin to synthesize a new chromone-based polymer **26**.[82] Polymer **26** was



2 21 22 23

Scheme 7 Synthesis of chemo-sensor **22** and its complex with Cu^{2+} ions **23**.

prepared by the treatment of **24** with chitosan **25** in deionized water (Scheme 8). It displayed specific, selective, and pH-influenced chelating efficiency with Cu^{2+} ions in comparison to Ni^{2+}, Co^{2+}, and Cd^{2+} heavy metal ions. At pH 4–6, polymer **26** showed selectivity in the order of $Cu^{2+} > Ni^{2+} > Cd^{2+} > Co^{2+}$. The adsorption capacity was also highest for Cu^{2+} with a concentration of 3 mmol g^{-1}. Chromone-based chitosan polymer **26** significantly inhibited lipid peroxidation emulsion system. It



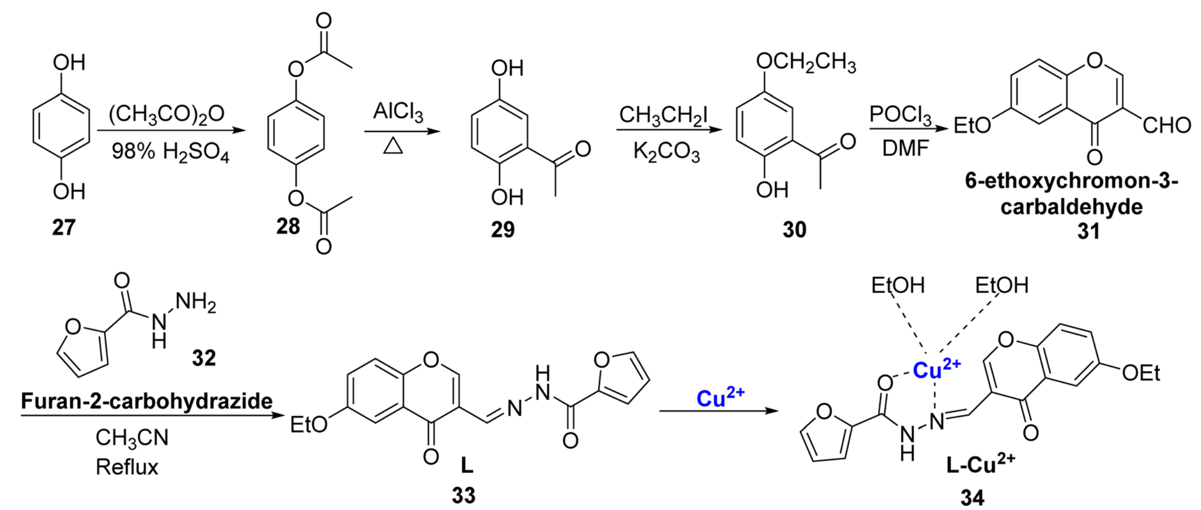
24 25 26

Scheme 8 Synthesis of chitosan-hydroxyl-chromone **26**.

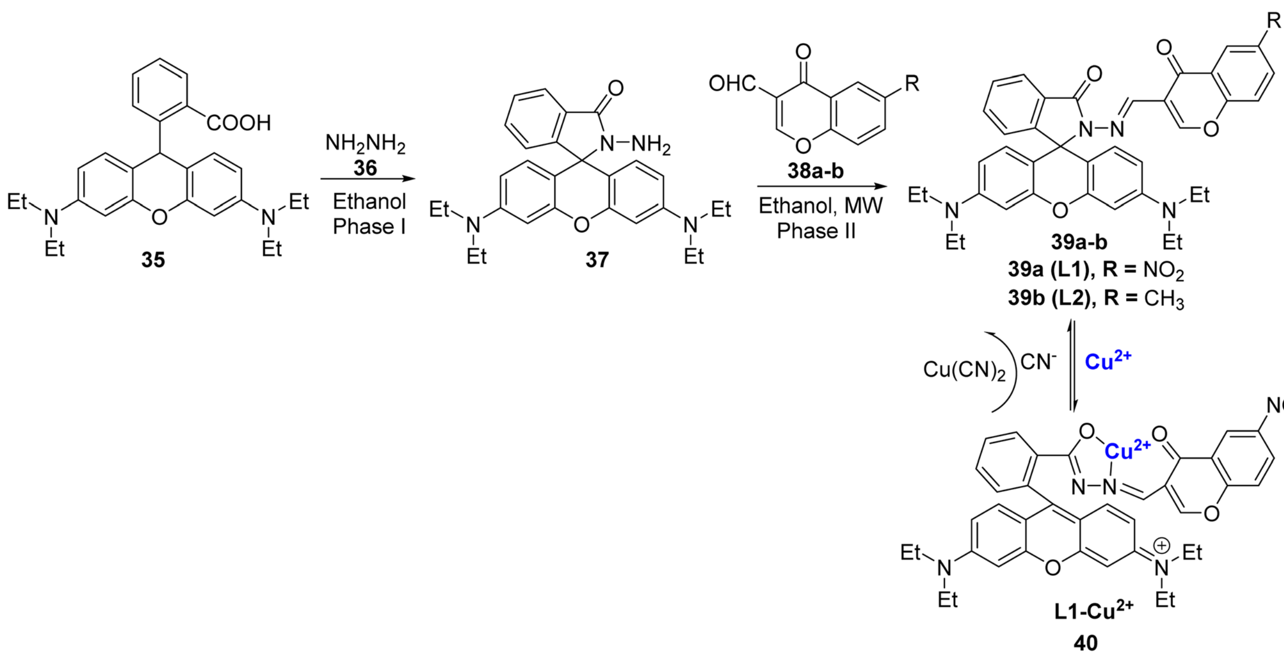
also demonstrated excellent results against Gram-negative bacteria *Pseudomonas aeruginosa* and decent activities with *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*.

Yang *et al.* reported a new probe *i.e.*, 6-ethoxychromone-3 carbaldehyde-(furanyl)hydrazone **33** with turn-on fluorescence and colorimetric properties.[83] The dual functional probe **33** was designed by refluxing a mixture of furan-2-carbohydrazide **32** and 6-ethoxychromon-3-carbaldehyde **31** in acetonitrile for 24 hours (Scheme 9). It showed colorimetric changes and high selectivity for Al^{3+} and Cu^{2+} as compared to other metal ions. When exposed to Cu^{2+} ions, it underwent a visible color change from colorless to yellow. When Cu^{2+} was introduced, the absorption peak at 319 nm steadily diminished, and a novel absorption band appeared at 422 nm. Analyzing the data through Job's plot and HRMS confirmed that the **33**–Cu^{2+} complex involved a 1 : 1 coordination ratio. The probe **33** demonstrated an impressive detection limit of 2.857×10^{-7} M for Cu^{2+} ions, which met the standards set by the WHO. Furthermore, the practical applicability of **33** as a solid-state probe was assessed by utilizing silica-coated slides and test papers immersed in the chromone-based probe **33**. Based on the findings, it is evident that **33** could serve as a prototype for a wide range of practical applications in environmental and biological systems.

Abebe *et al.* synthesized two rhodamine B-based chemosensors, **39a** and **39b** using microwave irradiation protocol (Scheme 10).[84] They were prepared in a two-step process, firstly by reacting rhodamine B **35** and hydrazine hydrate **36** in ethanol



Scheme 9 Synthesis of probe **33** and Cu^{2+}-probe complex **34**.



Scheme 10 Synthesis of ligands (**39a**) and (**39b**) and their complexation with Cu^{2+} ions **40**.

as green solvent to afford compound **37**, which further underwent condensation reaction with chromone aldehydes **38a–b** to furnish the final products **39a–b** (Scheme 10). The ligands **39a–b** were found to be selective for Cu^{2+} ions in the aqueous media. The ability of both the ligands **39a–b** was measured by using fluorescence titration, Job's plot, ^{1}H NMR, and DFT studies. Out of the two synthesized sensors, **39a** with electron-withdrawing substituent *i.e.*, the nitro group exhibited better response, good selectivity, and high sensitivity to Cu^{2+} ions in the aqueous solution. The fluorescence emission wavelengths for **39a** with Cu^{2+} ions appeared at 580 nm. The fluorescence intensity was observed mainly due to the formation of ring-open spirolactam **40** with Cu^{2+} ions whereas the other metal ions produced no substantial effect. Job's plot confirmed that both sensors bind to copper ions in 1 : 1 stoichiometry. The association constant of **39a** with Cu^{2+} was estimated to be 3.12×10^4 M^{-1} and the limit of detection was found to be 2.11 μM. The *in situ* synthesis of the L1–Cu^{2+} complex **40** displayed excellent selectivity for cyanide ions through the metal-displacement method. It is noteworthy that the addition of cyanide ions to complex **40** led to a change in colour from pink to colourless. However, anions, such as Cl^-, I^-, F^-, ClO_4^-, CH_3COO^-, HSO_4^-, $H_2SO_4^{2-}$, PO_4^{3-}, SCN^{2-}, HS^-, and OH^-, did not give any results.

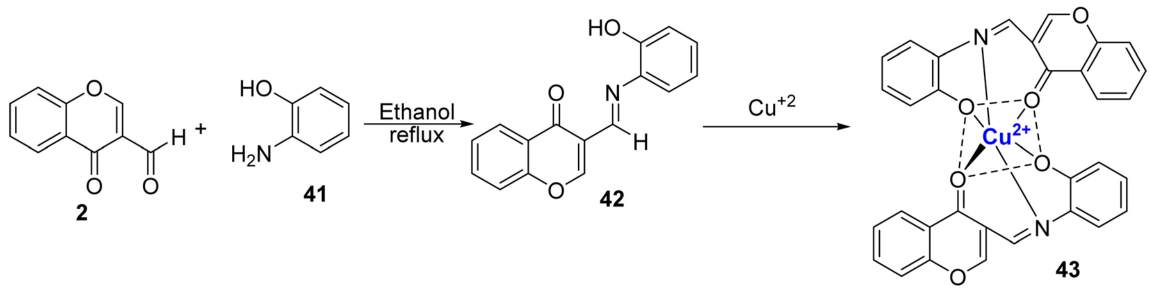
Recently, Alorabi *et al.* designed a multidentate Schiff base ligand, **42** through condensation of **2** and 2-aminophenol **41** (Scheme 11).[85] They examined its role as a colorimetric chemosensor. There was no significant colour change for metal ions other than Cu^{2+}, Fe^{3+}, and V^{5+}. It was proposed that the synthesized Schiff base ligand coordinates with metal ions through nitrogen atom from the azomethine group and with the oxygen atom from the phenolic group, and the ketonic group. Utilizing Job's plot, it was determined that the binding stoichiometry between the ligand and Cu^{2+} ions was 2 : 1. The detection limit for copper ions was 7.03 μM, and the binding constant was calculated to be 1.37×10^4 M^{-1}. To evaluate the real-world practicality of the chemosensor, various water samples were gathered, encompassing distilled water, household water sources, and a sample from the Al-Aqiq water reservoir dam.

3. Pharmacological activities of chromone-based Schiff bases

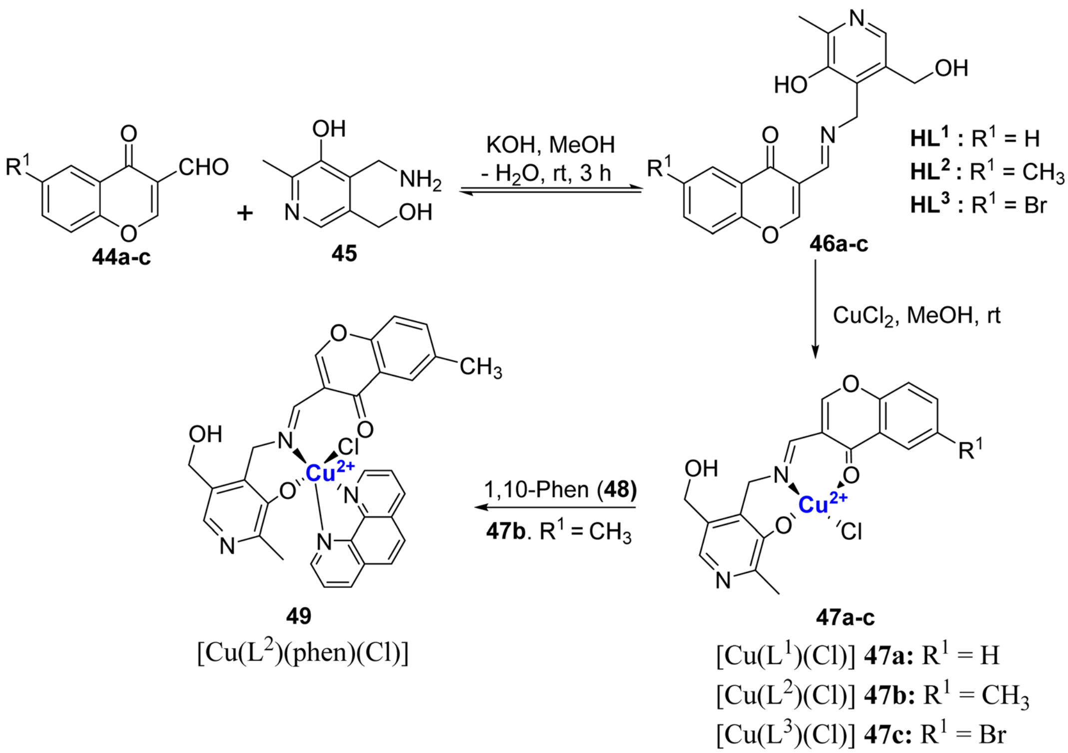
Transition metal ion such as copper that is biocompatible combined with a ligand framework of Schiff base induces a unique multi-modal mechanism of biological action. Incorporation of copper ions into the chromone moiety enhances their chemical and biological diversity. Thus, Schiff base-based metallo-drugs has great potential to combat disease like cancer, and microbial infections and circumvent multi-drug resistance problem. Copper complexes of chromone-based Schiff bases can cause oxidative DNA damage, base modification, and strand breaks.[86] The inhibition potential of metal complexes is far better than their ligands because of chelation which causes the delocalization of electrons over the chelate ring and the sharing of positive charge between metals and ligands enhances the lipophilic nature of the complex.[87] These factors boost the penetration of the metal complexes across the lipid membrane of the microbial cell wall thereby disrupting the membranes, blocking the enzyme's metal binding sites, and stopping the microbial growth.[88] Moreover, metal complexes can generate the bioactive compound *in situ* which could be another mode of action for metallodrugs. In this regard, chromone-based Cu^{2+} complexes Schiff bases with invigorating structural and electronic properties have received substantial attention.

In 2022, Nunes *et al.*[89] reported chromone Schiff bases **46a–c** synthesized *via* the condensation of 6-substituted-3-formylchromones **44a–c** with pyridoxamine **45** (Scheme 12). The Schiff bases **46a–c** were then treated with copper(II) chloride in MeOH at room temperature to furnish Cu(II)-Schiff base complexes [Cu(L^n)Cl] **47a–c**. Another ternary complex **49** [Cu(L^2)(phen)Cl] was also synthesized by the addition of bidentate 1,10-phenanthroline ligand **48** to complex **47b**. The synthesized complexes were subjected to elemental analysis such as FT-IR, ^{1}H- and ^{13}C-NMR spectroscopy, UV-Vis, EPR, and mass spectrometry. The investigations indicated that the chloride ion is bonded to the metal ions, which are coordinated to Schiff bases through donor atoms such as *O*-phenolate, *N*-imine, and *O*-carbonyl in compounds **47a–c** and **49**.

Amongst all the complexes, [Cu(L^2)(phen)Cl] **49** was the most stable and displayed higher stability in aqueous media. The presence of BSA protein further increased its stability. For other metal complexes it was predicted that ligand substitution, metal hydroxide formation, precipitation and partial oxidation in aqueous solution could be the reason for their instability. Compounds **46b**, **46c** as well as **47c** and **49** were tested for their cytotoxic characteristics on human cancer cells (MC7, HeLa, A2780, LN-229, and MCF7) and normal cells (RPE-1) with concentration 1.6–100 μM. The incubation periods ranged from 24–72 h with an interval of 24 h each. The metal complexes



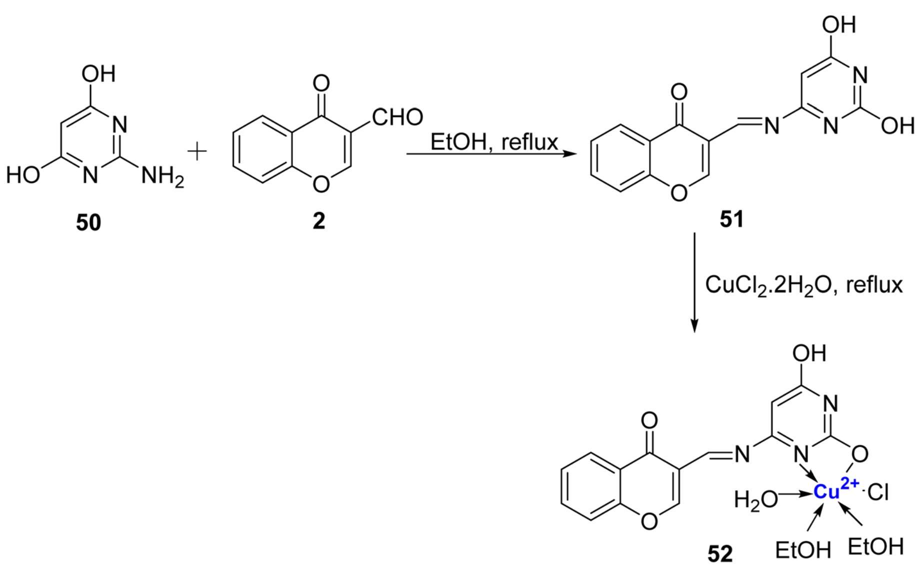
Scheme 11 Synthesis of ligand 42 and their complexation with Cu^{2+} ions 43.



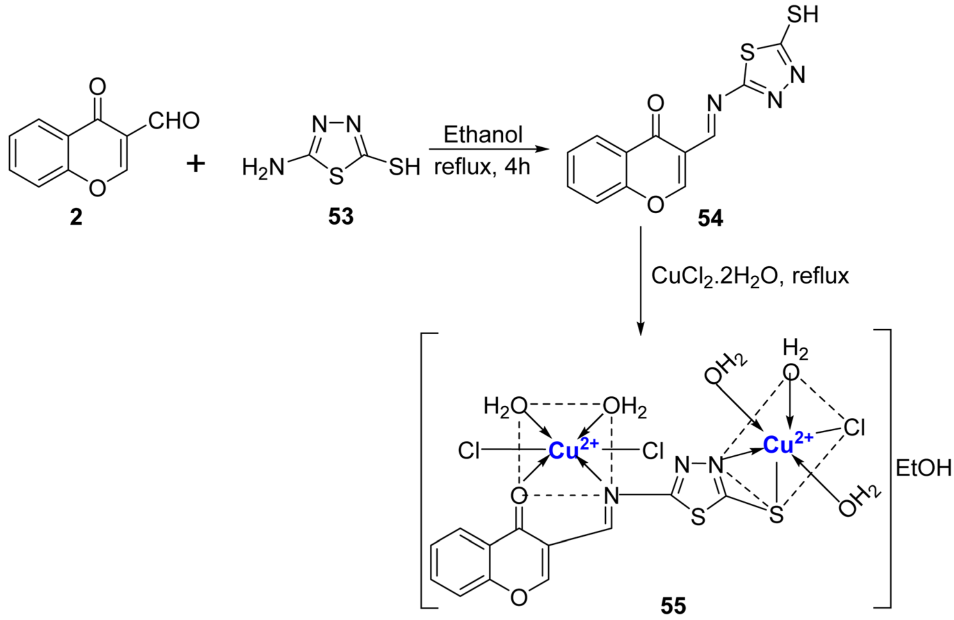
Scheme 12 Synthesis of ligands **46a–c** and their complexation with Cu^{2+} ions **47a–c** and **49**.

showed cytotoxicity in comparison to their ligand precursors but were not selective toward cancer cells. Complex **49** induced DNA cleavage, nicking supercoiled DNA to completion, activated higher levels of ROS and genotoxic damage. It also triggered cell death through apoptosis, as determined by apoptotic body formation, condensation, and fragmentation of DNA and TUNEL assay. The major challenge in this work was low aqueous solubility and less selectivity for cancer *vs.* normal cells.

In 2019, Gaber *et al.*[90] developed a Schiff base ligand, (*E*)-3-((2,6-dihydroxypyrimidin-4-ylimino) methyl)-4*H*-chromen-4-one **51** that was prepared by condensation of **2** with 4-amino-2,6-dihydroxypyrimidine **50** in absolute ethanol in good yields. Further, Cu^{2+} metal complexes were made using $CuCl_2 \cdot 2H_2O$. The spectral and magnetic studies revealed that the binding affinity of Cu(II) complex **52** was greater than the ligand **51** and the complexe have octahedral structure (Scheme 13). The ligand and Cu(II), complexes were assessed against *E. coli* and *S. aureus*



Scheme 13 Synthesis of ligand **51** and its Cu(II)-complex **52**.

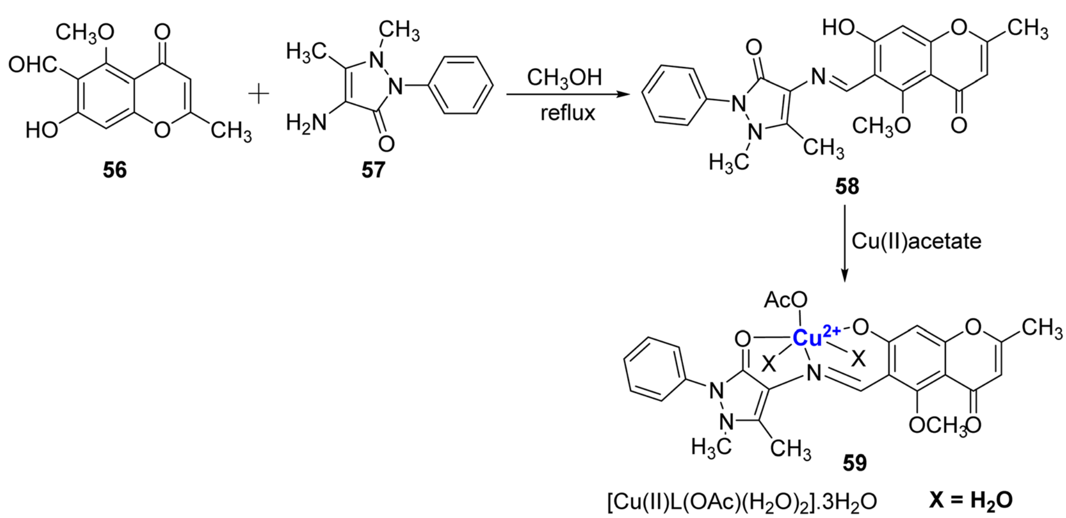


Scheme 14 Synthesis of ligand **54** and its copper(II)-complex **55**.

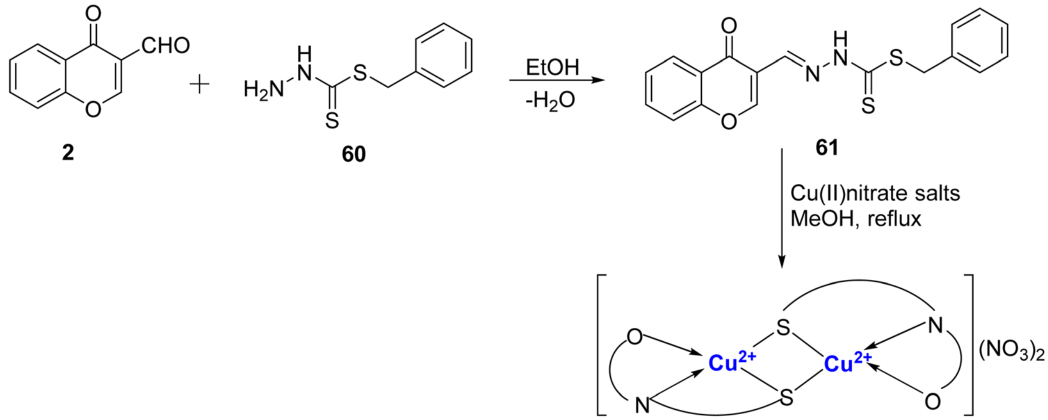
for their antibacterial activity and *C. albicans* and *Aspergillus niger* for antifungal activity. However, complex **52** as well as ligand **51** did not exhibit promising antibacterial and antifungal activity, and inhibition results against human cancer cell line HepG2 was also not very encouraging. The IC_{50} values for ligand **51** and its corresponding complex **52** against HepG2 were found to be 39.56 and 62.73 μg mL^{-1}. The intrinsic DNA-binding constant for Cu(II) complex **52** was found to be 4.3×10^5 M^{-1} indicating better intercalative-binding interaction with DNA.

The same research group[91] also designed novel Schiff base, **54** and its Cu(II)-complexes (Scheme 14). The Schiff base **54** was synthesized from chromon-3-carbaldehyde **2** and **53** in ethanol and its Cu(II) complex **55** was prepared by refluxing with hydrated metal chloride, $CuCl_2 \cdot 2H_2O$. Characterization of the Cu(II) complex **55** was done by elemental analysis, inductive coupled plasma, X-ray, IR, EI mass, UV-Vis, ESR, and ^{1}H- and ^{13}C-NMR which revealed octahedral shape for the complex. The complexes showed weak antimicrobial and anticancer activity. The IC_{50} values for the ligand **54** as well as its complex with Cu^{2+}, **55**, were quite high *i.e.* 23.00 μg mL^{-1} and 18.40 μg mL^{-1}, respectively against HepG2 in comparison to that of doxorubicin, the standard drug (IC_{50} = 4.73 μg mL^{-1}).

A Cu^{2+} complexes of a new chromone Schiff base was prepared by Shakdofa *et al.*[92] The ligand **58** was synthesized by refluxing **56** and **57** in a 1 : 1 M ratio (Scheme 15). Copper(II)-based chromone Schiff base complex **59** displayed a tetragonal distorted octahedral geometry. It was synthesized by refluxing a methanolic solution of copper(II)-acetate and the ligand **58** for



Scheme 15 Synthesis of ligand **58** and its copper(II)-complex **59**.



Scheme 16 Synthesis of tridentate monobasic ligand **61** and its complex **62** with Cu^{2+} ions.

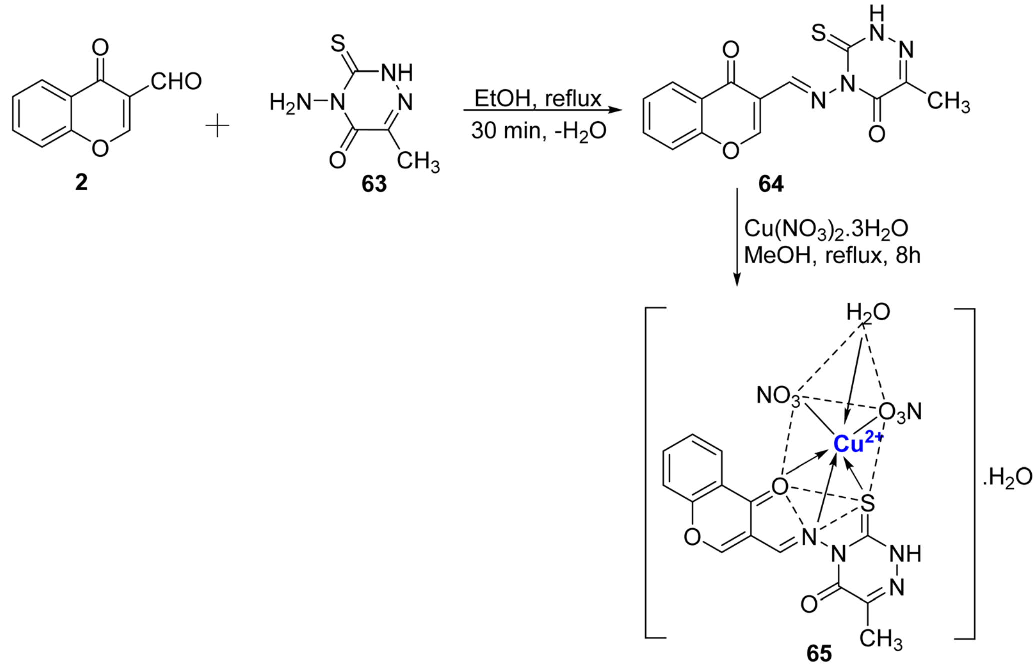
three hours. The designed molecules were analyzed for inhibition of tumor suppressor protein p53 ubiquitination. Ligand **58** exhibited an *in vivo* IC_{50} value of 12.13 μM. It is worth noting that inhibiting the interaction between p53 and the oncoprotein, MDM2, resulted in MDM2 blocking the ability of p53 to activate transcription. Copper complex **59** was found to disrupt the p53-MDM2 binding with IC_{50} values of 0.21 μM *in vitro*. Moreover, complex **59** with $IC_{50} = 1.79$ μM also activated the tumor suppressor p53 present in cancer cells and showed promising results for p53 ubiquitination *in vivo* when compared to the reference drug *i.e.*, diphenylimidazole ($IC_{50} = 0.26$ μM).

A new monobasic tridentate ligand **61** with sulfur, nitrogen and oxygen of γ-pyrone chelating centers was prepared by the condensation reaction of chromone-3-carboxaldehyde **2** and 5 benzyldithiocarbazate **60** by Adly *et al.* (Scheme 16).[93] Further, dimeric complex with Cu^{2+}, was made. The energy gap of the prepared complexes was lower than the free ligand and because of that these complexes were more reactive. The HOMO → LUMO electron transition and energy gap (ΔE) of the Cu(II) complex **62** was found to be 0.434 eV. The smaller energy gap of validates its high reactivity and low kinetic stability. The dimeric complex **62** was found to exist in square planar geometry. The ligand **61** (IC_{50} value = 14.90 mg mL^{-1}) and Cu(II)-complex **62** (IC_{50} value = 7.37 mg mL^{-1}) were active against HepG2 cancer cell lines when compared to the standard cisplatin (IC_{50} value = 3.67 mg mL^{-1}) and it was the electrophilicity and electronegativity that played a crucial role in their antitumor activities. Complex **62** also showed antimicrobial activity towards the Gram-positive/-negative bacteria as well as with fungus strains.

Recently, novel Cu^{2+} nano complex **65** based on hydrazone ligand **64** containing chromone and triazine moieties were synthesized.[94] The ligand **64** was synthesized by refluxing a mixture of **63** and **2** in ethanol (Scheme 17). The Cu^{2+} nano complex **65** was prepared by refluxing the methanolic solution of the neutral tridentate ligand **64** and $Cu(NO_3)_2 \cdot 3H_2O$ and was found to possess nano-rode morphology. The nanocomplex **65** exhibited excellent inhibition towards the cancer cell line HepG2 with IC_{50} value of 0.027 μM. The effectiveness of this sensor can be attributed to two key mechanisms. Firstly, it operates through reactive oxygen species generated by copper ions. These reactive species are known to inflict damage on the DNA within tumor cells, making it a promising tool in cancer treatment. Secondly, the chelation theory comes into play, where the positive charge on the metal ion boosts the ligand's acidity, enabling it to accept protons. This, in turn, strengthens the hydrogen bonds that pivotally enhance the sensor's biological activity. Docking results revealed Cu^{2+} nano complex **65** as a probable inhibitor of the CDK2 enzyme. Cu^{2+} nano-complex **65** showed better orientation with amino acids Phe82, Leu83, Asp86, and Lys89. It was also noticed that nano-formulations result in better cytotoxicity and proliferation.

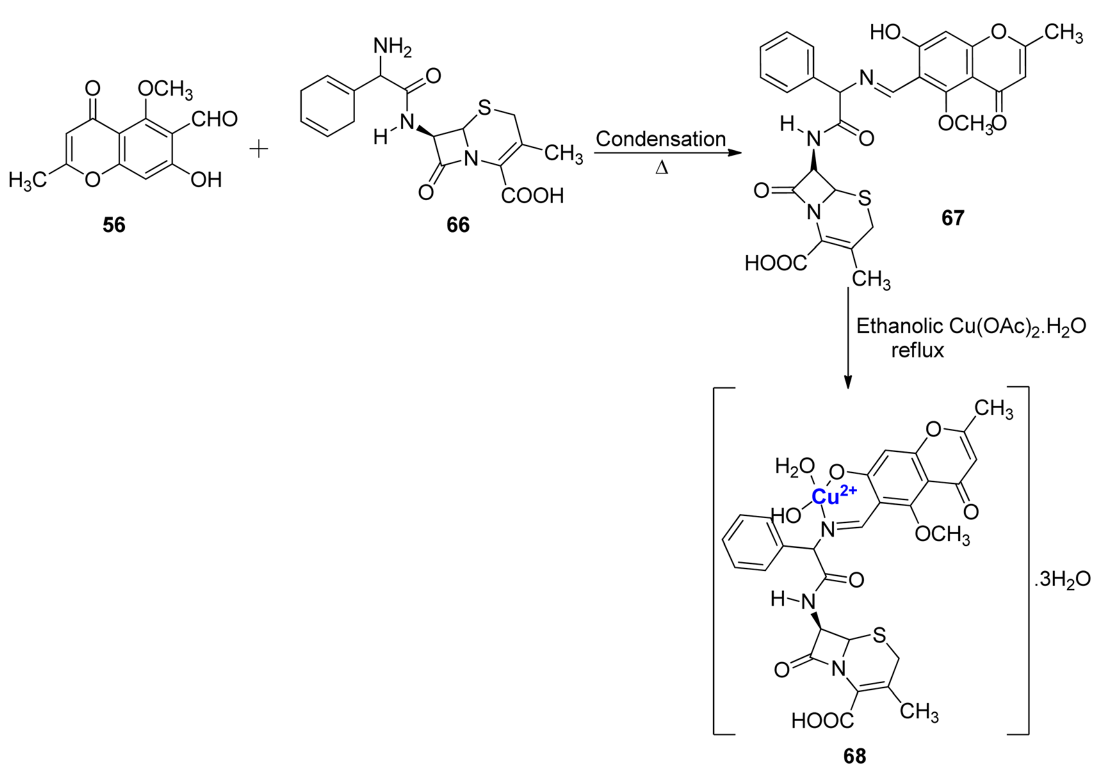
A new Schiff base ligand **67** *via* the condensation between **56** and cephradine drug **66** was developed (Scheme 18).[95] The ligand was monobasic bidentate, and its Cu(II), complex was also prepared. From experimental data, it was found that Cu(II)–ligand complex **68** was in the stoichiometric ratio of 1 : 1 (M : L). The spectrum of Cu(II)–L complex showed emission band at 443 and 726 nm. The intense fluorescence band emission was assigned to the intra-ligand fluorescence and intramolecular charge transfer between ligand and ion. As corroborated by the photostability studies, the complex **68** was less photostable than the Schiff base ligand **67** as absorption of photonic energy caused irreversible photochemical decomposition–bleaching. The photobiological larvicidal activity was conducted using mosquito larvae to examine the efficiency of complexes in controlling insects using direct sunlight. However, Cu(II) complexes did not show appreciable results. Cytotoxicity of the ligand **67** and complex **68** was also studied on the HepG2 cell line. The Schiff base ligand **67** displayed a better inhibitory effect of 55% towards the HepG2 cancer cell lines when compared to its Cu(II) complex **68** with 35% inhibition.

In 2018, Kalaiarasi *et al.*[96] prepared new Schiff base ligands **70a–b** by the reaction of **24** with **69a** and phenyl semicarbazone **69b** (Scheme 19). The Cu(II)-complexes **71a–b** were synthesized by the reaction of ligand **70a–b** with copper(II)-nitrate salts in methanol under reflux. Single crystal XRD studies established the structure of cationic complex **71a** as distorted square

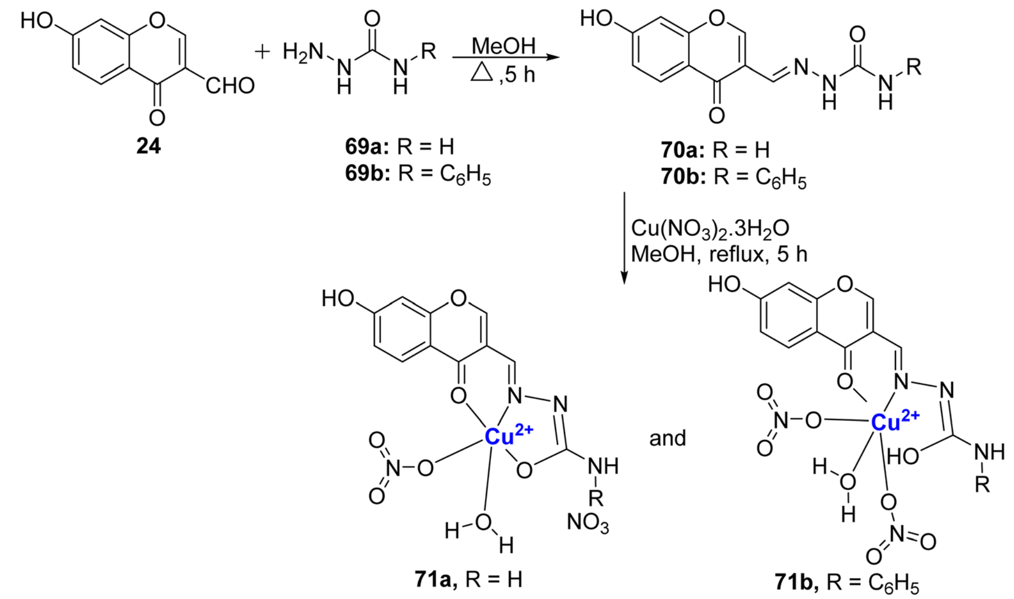


Scheme 17 Synthesis of hydrazone ligand **64** and its complex **65** with Cu^{2+}.

pyramidal geometry and the neutral complex **71b** as octahedral geometry. The intercalative mode of binding compounds with calf thymus DNA was confirmed by ethidium bromide displacement and viscosity measurement studies. Most pronounced EB-DNA fluorescence emission suppression was demonstrated by complex **71a**. The same complex was observed to induce an increase in the separation of base pairs at the intercalation site within DNA, subsequently leading to an extension in the molecular length of the DNA. Furthermore, in a protein binding study, it was demonstrated that the ligands and complexes exhibited a binding capacity with both BSA and HSA through a static quenching mechanism. To assess their



Scheme 18 Synthesis of ligand **67** and its complexation with Cu^{2+} ions to give **68**.



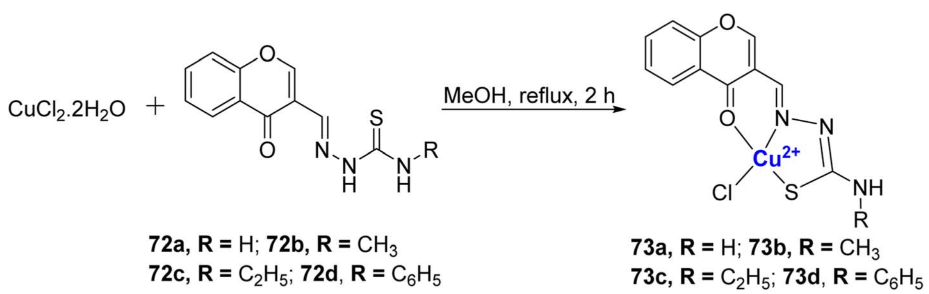
Scheme 19 Synthesis of the ligands **70a–b** and their complexation with Cu^{2+} metal ion **71a–b**.

Table 1 IC_{50} values for ligands **70a** and **70b** as well as for complexes **71a** and **71b** for cell lines MCF-7 and A549

	IC_{50} (μM)	
Compounds	MCF-7	A549
$Cu(NO_3)_2 \cdot 3H_2O$	>50	>50
70b	18.44 ± 0.16	19.15 ± 0.14
70a	15.96 ± 0.14	17.19 ± 0.29
71b	3.52 ± 0.09	3.69 ± 0.06
71a	2.49 ± 0.10	3.33 ± 0.09
Cisplatin	15.10 ± 0.05	16.79 ± 0.08

potential medical relevance, the compounds were tested against MCF-7 and A549 cancer cell lines (Table 1). Notably, complexes **71a** and **71b** displayed superior cytotoxicity results when compared to the drug cis-platin. The enhanced activity of **71a** may be attributed to its cationic nature, which sets it apart from the neutral octahedral complex **71b.** These results were further checked by lactate dehydrogenase release assay and nitric oxide assay. The complexes **71a–b** also displayed antimicrobial properties. The antibacterial activity of the compounds had the order: **71b** > **71a** > **70b** > **70a** for *S. aureus*, *A. baumannii* as well as *S. Pneumonie*, while for *P. aeruginosa*, the compounds **71a** and **71b** had similar MIC values. For *Aspergillus niger*, *Candida tropicalis*, and *Aspergillus fumigatus*, compound **71b** had more potency as an antifungal agent over **71a.**

The same research group also reported four water-soluble Cu(II)–chromone complexes **73a–d.**[97] The complexes **73a–d** were synthesized from $CuCl_2 \cdot 2H_2O$ and 3-formyl chromone-4(*N*)-substituted thiosemicarbazones **72a–d** ligands and it coordinated with the metal in a tridentate monobasic ONS donor fashion (Scheme 20). The binding ability of synthesized copper thiosemicarbazone to calf thymus DNA was analyzed and the results were in the order **73c** > **73b** > **73a** > **73d.** Notably, among the four complexes, the one with an ethyl group, **73c**, demonstrated a stronger affinity for DNA as evidenced by its performance in the ethidium bromide (EB) displacement assay and viscosity measurements. The interaction of complexes **73a–d** with plasmid pBR322 DNA showed that they cleave the supercoiled DNA. A static quenching mechanism was noted for BSA and HSA serum albumins by the complexes. These Cu(II) complexes **73a–d** displayed considerable antibacterial as well as antifungal activity, where **73c** was the most potent. Anti-



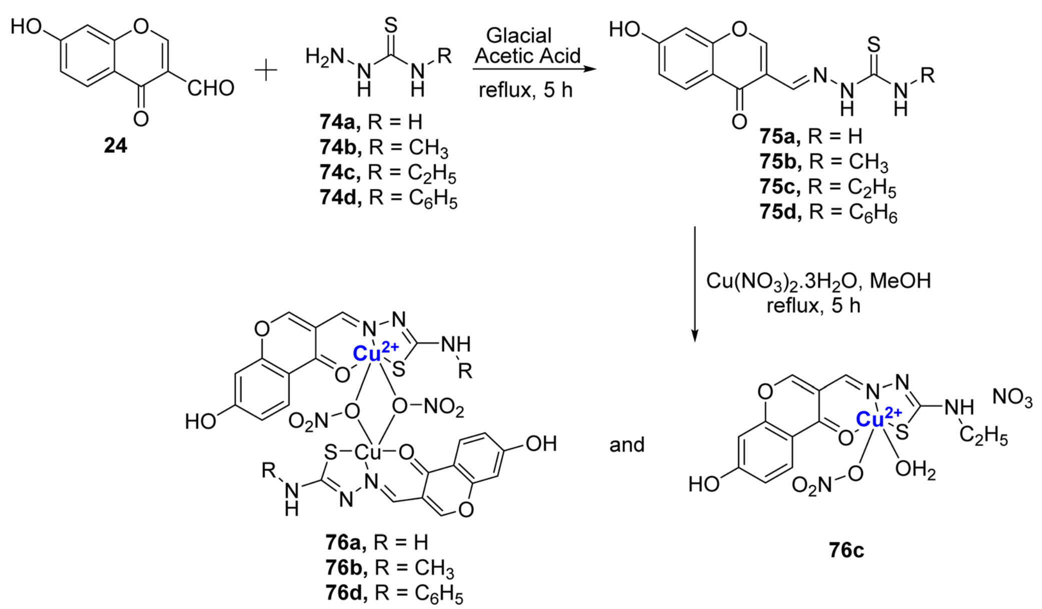
Scheme 20 Synthesis of complexes **73a–d**.

proliferation studies on MCF-7, HeLa, and HaCaT revealed that complexes **73a–d** could overcome cis-platin resistance in both cell lines. Significant cytotoxicity was observed with IC_{50} values of 5.05 ± 0.09 to 7.64 ± 0.13 μM for the MCF-7 cell line and for A549, it was 7.57 ± 0.10 to 8.67 ± 0.13 μM whereas for cisplatin the values are 16.79 ± 0.08 μM for MCF-7 and 15.10 ± 0.05 μM for A549. The synthesized compounds **72a–d** and **73a–d** were non-toxic toward the HaCaT. Complex **73c** was the most effective of all.

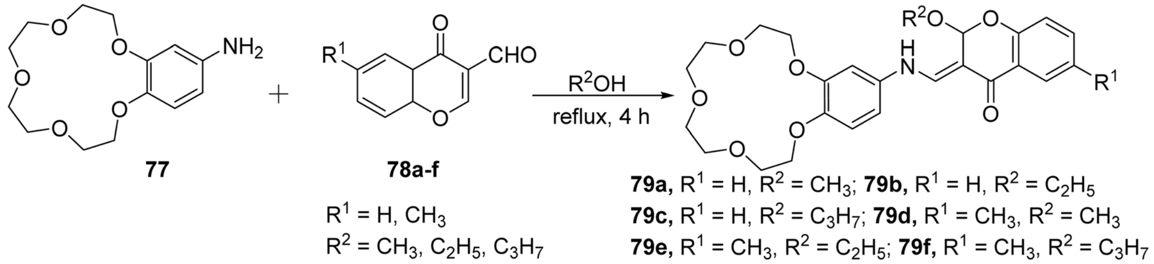
The same group further reported four Schiff bases **75a–d** and their resultant water-soluble Cu(II)-complexes **76a–d**.[98] The Cu(II)-complexes **76a–d** were prepared from different thiosemicarbazones **75a–d**, which were initially synthesized by refluxing the **24** with thiosemicarbazide **74a–d** in glacial acetic acid for 5 hours (Scheme 21). The compounds showed good antibacterial and antifungal properties towards the different tested microbial species. For fungi *T. rubrum* and *C. albicans*, the compounds displayed the activity in the following order: **76c** > **76b** > **76a** > **76d**; for *C. tropicalis*: **76c** > **76d** > **76b** > **76a**; for *A. fumigatus*: **76c** > **76a** > **76b** > **76d**; for *A. niger*: **76c** > **76b** > **76d** > **76a**. Complex **76c** was the most effective against *S. aureus* and *P. aeruginosa* and activity order was as follows, **76c** > **76d** > **76b** > **76a**. In the case of *S. pneumoniae*, the activities of the complexes followed the order **76c** > **76b** > **76a** > **76d**, and against *A. baumannii*, complex **76d** stood out with **76d** > **76a** > **76c** > **76b**. The cytotoxic assessment was also conducted against MCF-7 and A549 cells. Cu(II)-complexes followed the order with IC_{50} values for MCF-7 as **76c** (2.94 ± 0.09 μM) > **76b** (3.71 ± 0.06 μM) > **76d** (3.87 ± 0.08 μM) > **76a** (4.21 ± 0.09 μM); for A549 the inhibitory activity was as follows: **76c** (2.31 ± 0.07 μM) > **76b** (3.20 ± 0.05 μM) > **76d** (4.00 ± 0.09 μM) > **76a** (4.30 ± 0.09 μM). The results were better than the standard drug cis-platin for which IC_{50} for MCF-7 is 15.10 ± 0.05 μM and for A549 it is 16.79 ± 0.08 μM. It is noteworthy that complex **76c** which contains an electron-rich ethyl group displayed the highest activity that further authenticated by LDH and NO release assays. The binding affinity of the complexes with calf thymus DNA confirmed intercalative binding mode, which was also supported by EB displacement and viscosity measurements. Also, the copper complexes quenched the fluorescence of serum albumins through a static mechanism. It is motivating to note that *N*-terminal ethyl substituted thiosemicarbazone exhibited higher cytotoxicity and thus it will be interesting to assess compounds with longer alkyl chain lengths.

Sahin Gul *et al.* synthesized a series of chromone-crown ether-based Schiff base ligands **79a–f**.[99] The chromone-crown ethers **79a–f** were prepared by the reaction of **77** with 6-substituted-3-formylchromones **78a–f** (Scheme 22). The synthesized Schiff base ligands **79a–f** were tested as chemosensors using UV-visible and fluorescence spectroscopy and were found to be selective for Cu^{2+} and Fe^{3+} ions in the presence of various other competing ions. A sharp blue shift in the absorption spectrum and fluorescence quenching was detected for chromone compounds **79a–f**, on increasing the metal concentration. The synthesized ligands were also found active against both Gram-positive, Gram-negative bacteria and displayed good antifungal activity.

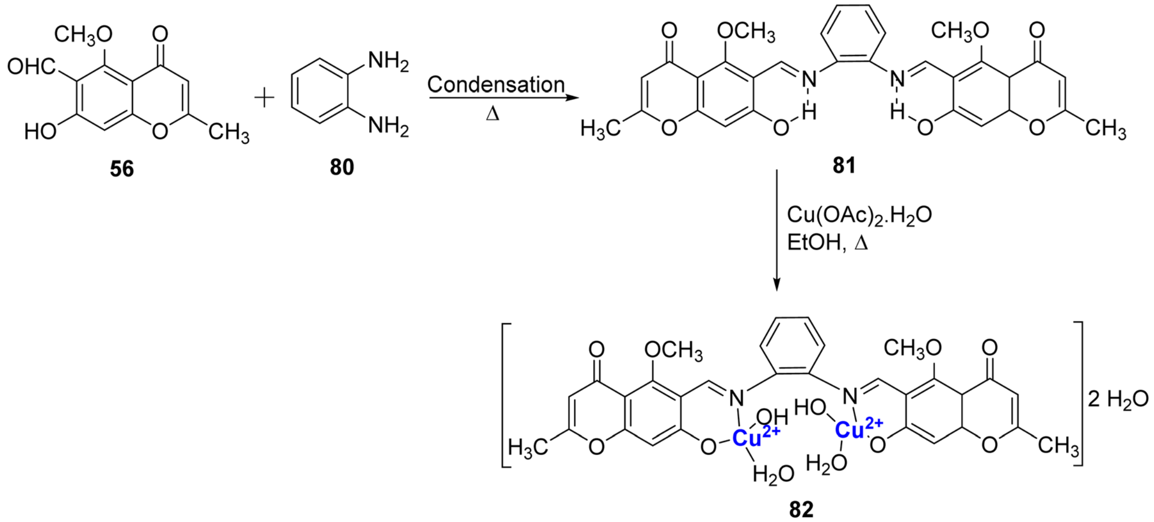
Synthesis of a Cu(II)-complex **82** from Schiff base ligand **81** has been attempted.[100] The ligand **81** was prepared by the reaction amid **80** and **56** (Scheme 23). Characterization of both the ligand **81** and the complex **82** was done by elemental analysis, Mass, FT-IR, thermal analysis, electronic spectra, magnetic susceptibility measurements, and conductivity. The analytical data confirmed 2 : 1 stoichiometry for the Cu_2–**81** complex with square planar geometry. However, the copper complex showed minimal biological activity towards *S. aureus*, *B. Subtilis*, *P. aeruginosa* and *E. coli* bacteria. This may be due to their lower permeability across the bacterial cell membrane. The studies



Scheme 21 Schiff base ligands **75a–d**, were synthesized, and subsequently, Cu(II)-complexes **76a–d** were formed.



Scheme 22 Synthesis of chromone crown-ether based ligands 79a–f.

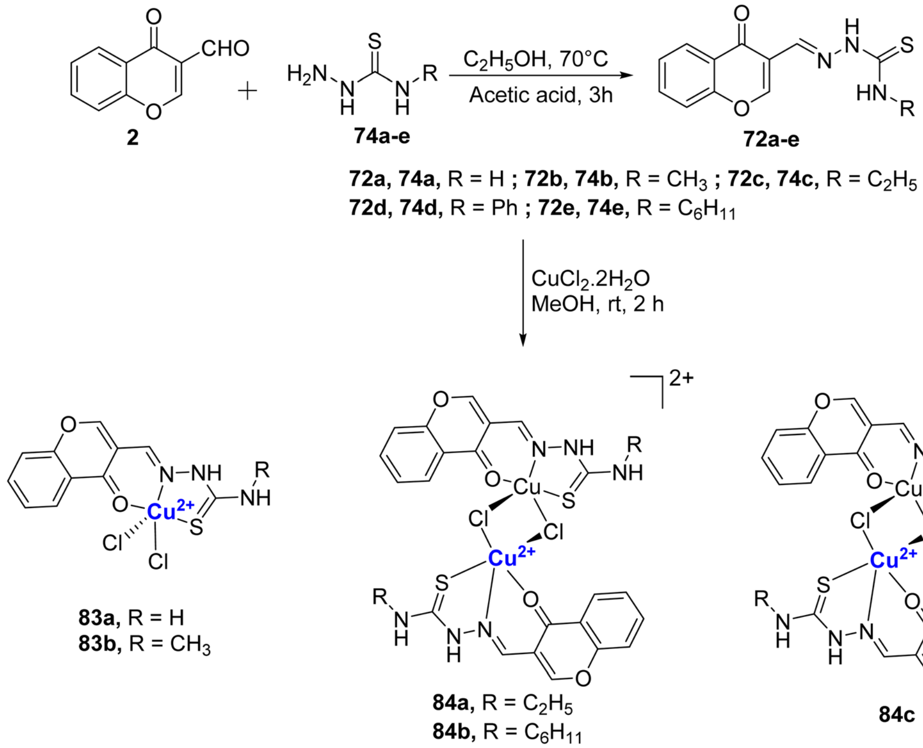


Scheme 23 Synthesis of ligand 81 and its Cu(II)-complex 82.

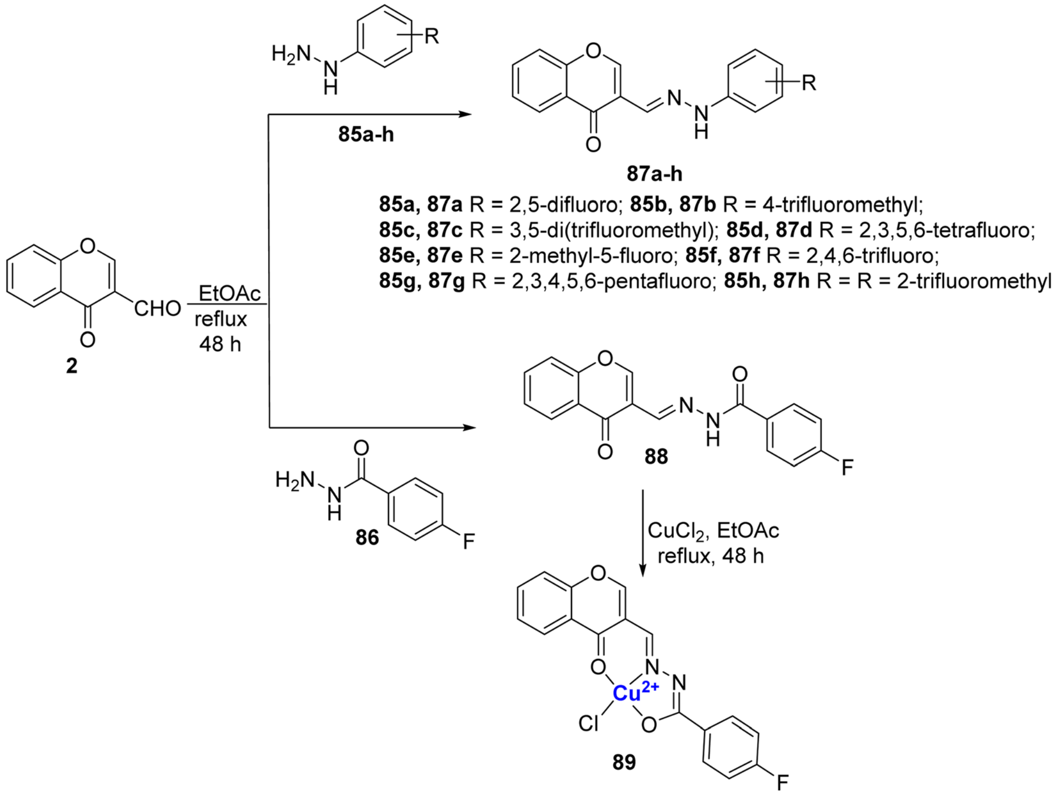
show that penetration of the complexes through the lipid membrane is crucial for the inhibition of microbial growth.

Balakrishnan *et al.* synthesized different chromone appended thiosemicarbazone ligands **72a–e** by refluxing **2** with thiosemicarbazides **74a–e** and treated them with copper salt to procure copper complexes **83a–b** and **84a–c** (Scheme 24).[101] It was inferred that the variation in the terminal *N*-substitution in the ligands influenced the complexes' stoichiometry and due to the bulkiness of $-C_2H_5$, $-C_6H_{11}$ and $-C_6H_5$ in the ligands, dicationic bimetallic complexes **84a–b** and neutral bimetallic **84c** were formed. Monometallic complexes of Cu(II), **83a** and **84b** were obtained from **72a** and **72b**, respectively. The complexes were found to be stable under physiological conditions. The designed complexes **83a–b** and **84a–c** displayed catecholase-mimicking activity, and the result showed that except **84c** with the bulky phenyl group, all other complexes **83a–b, 84a–b** could oxidize 3,5-di-*tert*-butylcatechol into 3,5-di-*tert*-butylquinone molecule in the presence of air or aerobic conditions. It was seen that the bimetallic complexes **84a** and **84b** underwent dissociation into monomers as a necessary step to participate in the catalytic cycle. The catalytic activity followed the order **84a** > **84b** > **83b** > **83a**. Phosphatase like activity of the complexes were also studied with the help of 4-nitrophenylphosphate (4-NPP). The catalytic ability of the Cu(II) complexes to hydrolyse the phosphomonoester followed the order **84a** > **84b** > **83a** > **83b** > **83d**. Complexes **84a–b** showed superior radical scavenging activity due to their cationic nature and electron-releasing group. On the other hand, mononuclear **83b** with electron-donating methyl group showed better activity in comparison to the binuclear complex **84c** with an electron-withdrawing group. Each complex exhibited the capacity to prevent hemolysis and, importantly, did not display any toxicity towards red blood cells. Three complexes **84a–c** also showed better cytotoxicity towards the HeLa-cancer cells exhibiting IC_{50} values of 2.24 μM (**84a**), 2.25 μM (**84b**), and 3.77 μM (**84c**) that is two times higher activity when compared to the standard drug cis-platin. The complex **84a–b** displayed full inhibition of the colony formation at 10 μM. The results are promising and further development could lead to a potential anticancer metallodrug.

Slomiak *et al.*[102] prepared a library of hydrazine **87a–h** and hydrazide derivatives **88** of 3-formylchromone **2**. The ligands **87a–h** and **88** were synthesized by reacting **2** with different hydrazines **85a–h** or hydrazide **86** (Scheme 25). The neutral mononuclear copper(II)-complex **89** was synthesized by the treatment of the ligand **88** with copper(II) chloride. On studying their antimicrobial and antiproliferative properties, it was observed that the compounds **87a–h, 88**, and **89** were capable of inhibiting the growth of microorganisms. Complex **89** was found to have improved antiproliferative properties than ligand



Scheme 24 Synthesis of ligands **72a–e** and their mono- **83a–b**/bi-metallic **84a–c** Cu(II) complexes.



Scheme 25 Hydrazine derivatives **87a–h** and hydrazide derivatives **88**, originating from 3-formylchromone, were synthesized, and Cu(II)-complex denoted as **89** was also prepared.

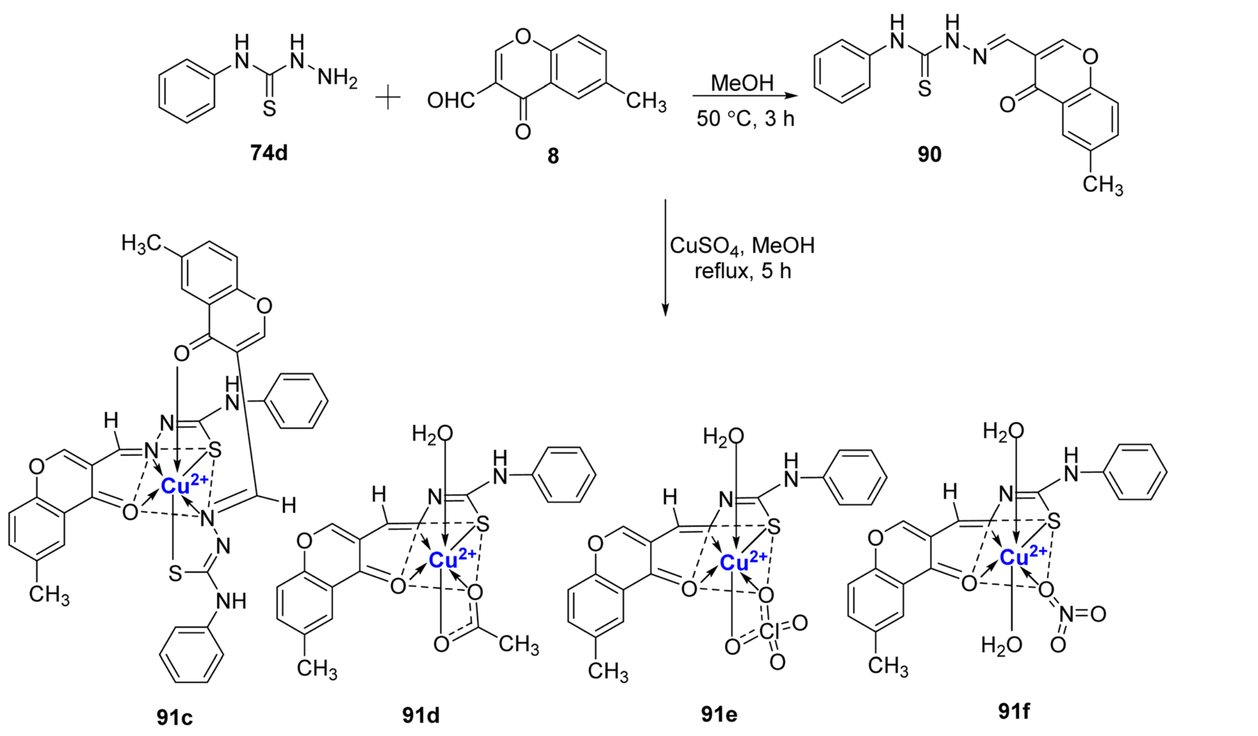
88, with its IC_{50} value 35.01 μmol L^{-1} for the L929 and 0.04 μmol L^{-1} for EA.hy926.

Copper complexes **91a–f** were synthesized from the ligand, 3-formyl-6-methylchromone-4-phenylthiosemicarbazone **8** using copper(II) salt solutions in molar ratio of 1 : 2 (M : L) by Ilies *et al.*[103] The ligand was synthesized by treating 4-phenylthiosemicarbazide **74d** with 3-formyl-6-methylchromone **8** in a methanolic solution (Scheme 26).[104] Complex **91a** was found to have a distorted square-planar shape and complex **91b** was found to be square-pyramidal. All of the Cu(II)-complexes **91a–f** exhibited antimicrobial activity against *S. aureus*, *E. faecalis*, *E. coli*, *S. enteritidis* and *C. albicans*. Complex **91e** displayed the most promising activity towards all the strains with MIC values between 16 μg mL^{-1} to 64 μg mL^{-1} and it was attributed to the bulky ClO_4^- anion. The antifungal and antibacterial data showed that the metal complexes **91a–f** have higher activity in comparison to the free ligand **90**.

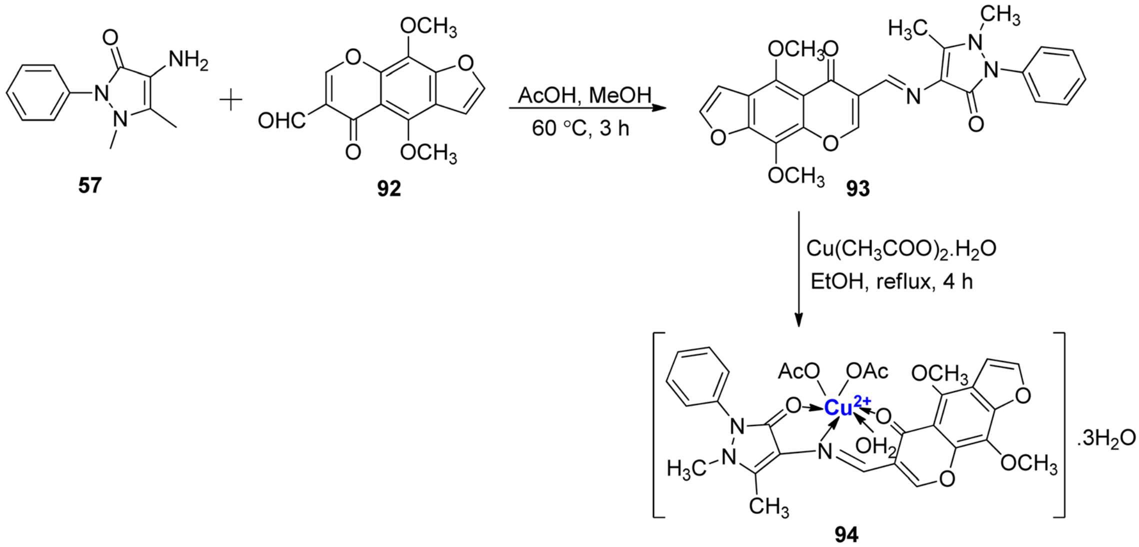
Furochromone-based Cu(II)-complexe of Schiff base, resulting from the reaction of **57** and **92**, has been reported.[105] Initially, the furochromone based ligand **93** was synthesized from **57** and **92** (Scheme 27). Copper complex **94** was prepared by the treatment of ligand **93** with the metal salt $Cu(CH_3COO)_2 \cdot H_2O$. The structure of the complex **94** was reported to be of distorted octahedral geometry that was confirmed *via* spectral techniques and elemental analysis. All substances were tested for their *in vitro* antimicrobial activity. The findings demonstrated that copper complex **94** to be effective against *C. albicans* and *A. niger*. It showed moderate activity against *E. coli* and *S. aureus* whereas with *A. faecalis* and *B. subtilis*, very little activity was reported.

In the same year, Cu(II)-chromanone complexes **98a–b** was reported by Jose *et al.*[106] Firstly, the methoxy-substituted ligands **97a–b** were synthesized by the reaction of 95 with 2-aminopyridine **96a**/2-amino-5-nitropyridine **98b** in the presence of methanol (Scheme 28). The complexes **98a–b** were then prepared by treating the ligands **97a–b** with the metal salt at 45 °C. The Cu(II)-complexes **98a–b** thus synthesized were found to show exceptional stability due to tetragonal distortion and Jahn–Teller effect. Among the prepared compounds, The complex CuL **98b** exhibited the most potent α-amylase inhibitory activity, yielding an IC_{50} value of 0.251 ± 0.2 mM. Conversely, the complex CuL **98a** demonstrated the highest α-glucosidase activity, with an IC_{50} value of 0.060 ± 0.3 mM. Furthermore, these compounds were screened for their antimicrobial effectiveness. Moreover, the complexes **98a–b** also displayed excellent antibacterial activity with MIC of 15.3 μg mL^{-1} against *S. aureus* which was found equivalent to that of the standard drug.

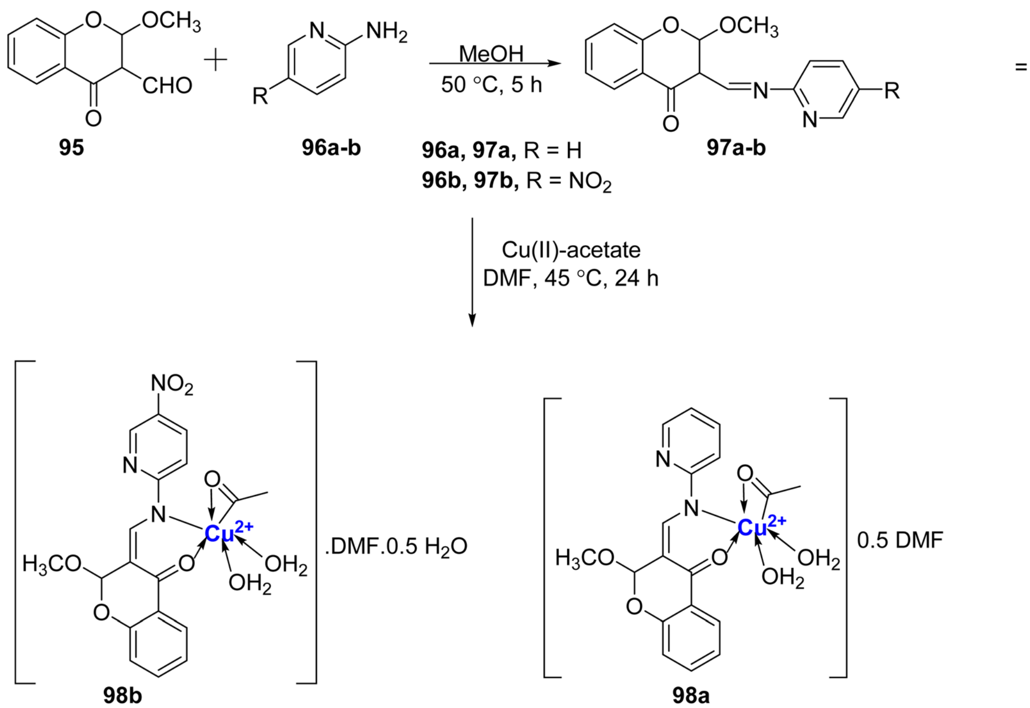
A Cu(II), complex was designed and prepared using Schiff base **100** was synthesized by Pahontu *et al.*[107] The ligand **100**, was prepared from **57** and **99** in ethanol (Scheme 29), and it was further treated with methanolic $CuBr_2$ solution to yield the desired complex **101** in 73% yield. The structure of complex **101** was confirmed as tetrahedral with the aid of analytical techniques. Copper complex **101** showed both bacteriostatic and bactericidal properties against Gram-positive (concentration: 0.007–0.25 mg mL^{-1}) as well as Gram-negative bacteria (concentration: 0.0312–0.5 mg mL^{-1}). Additionally, ten cancer cell lines, namely MSC, A375, B16 4A5, HT-29, MCF-7, HEp-2, BxPC-3, RD, MDCK, and L20B, were employed to evaluate the



Scheme 26 Synthesis of ligand 90 and their Cu(II)-complexes 91c–f.



Scheme 27 Synthesis of ligand **93** and its copper(II)-complex **94**.

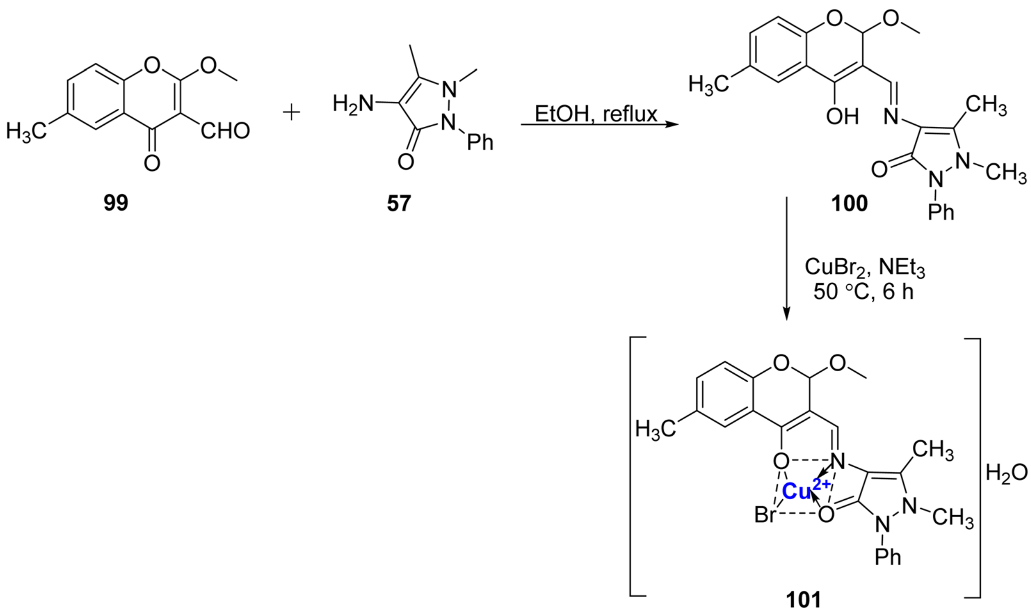


Scheme 28 Synthesis of 2-methoxy-4-chromanone based ligands **97a–b** and its copper(II)-complex **98a–b**.

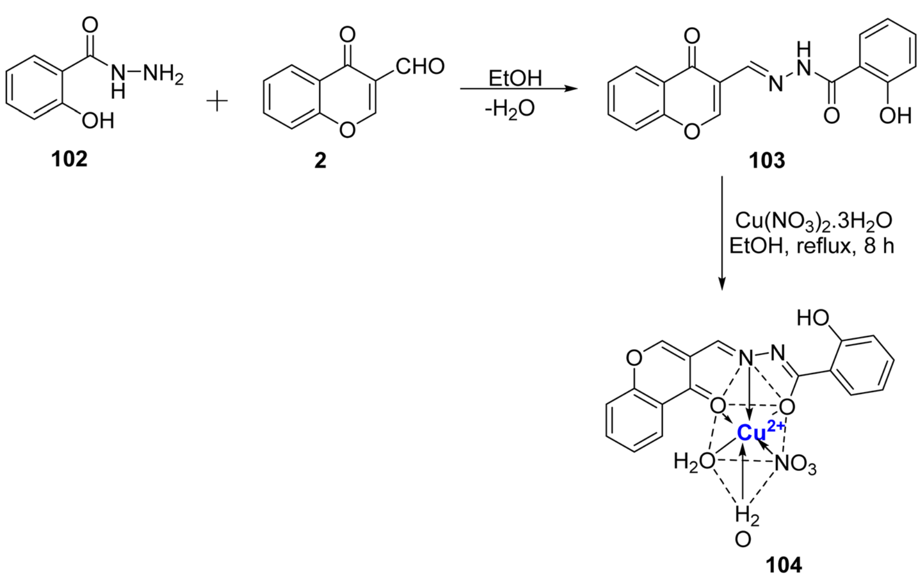
in vitro antiproliferative properties of the ligand and complex. It was found that ligand **100** also has promising antimicrobial properties. The ligand **100** showed promising antifungal results, but the copper complex **101** was found to be inactive in comparison to the standard drugs nystatin and miconazole.

A new class of octahedral nano-complex of Cu^{2+} **104** with chromone Schiff base **103** was prepared by Saif *et al.*[108] (Scheme 30). The complex **104** was synthesized by refluxing **103** with copper–nitrate salt in ethanol as a reaction medium. The synthesized complex **104** exhibited excellent antioxidant activity (IC_{50} = 0.93 μM) as compared to the standard used (ascorbic acid). The Cu(II) nano-complex **104** demonstrated significant effectiveness in inhibiting the growth of EAC cells, with an IC_{50} value of 47 μM. This efficacy surpassed that of its parent compound and the other complexes that were synthesized. Moreover, Cu(II) **104** nano-complex was also found to show cytotoxic effects and was less toxic than cis-platin. The chemical structure of complex **104** was confirmed *via* elemental analysis.

Kavitha *et al.*[109] used 3-formylchromone **2** and 2-aminopyridine **96a** as the reactants to synthesize the ligand **106**, and



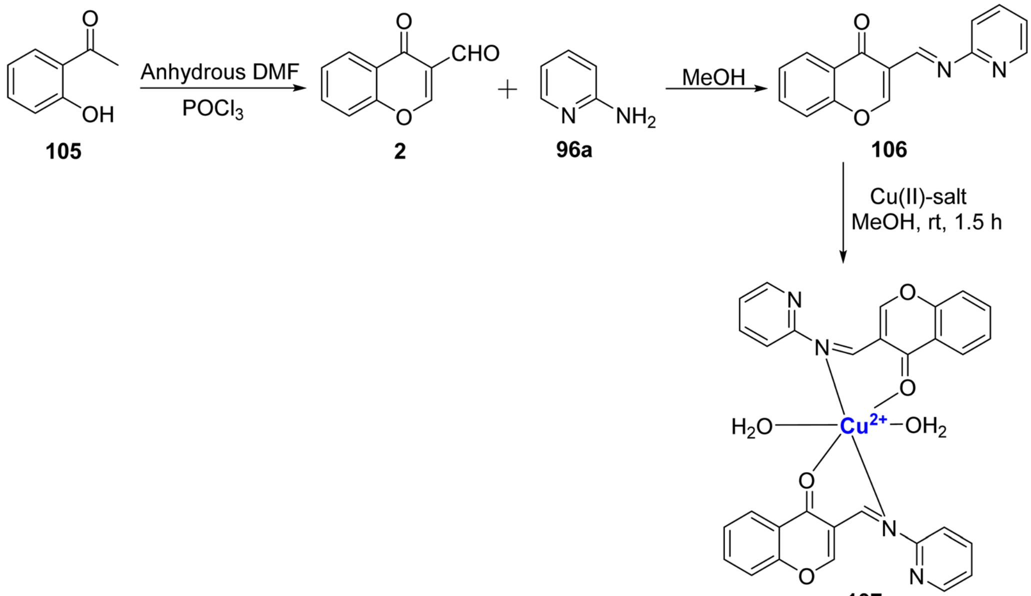
Scheme 29 Synthesis of ligand **100** and its Cu(II)-complex **101**.



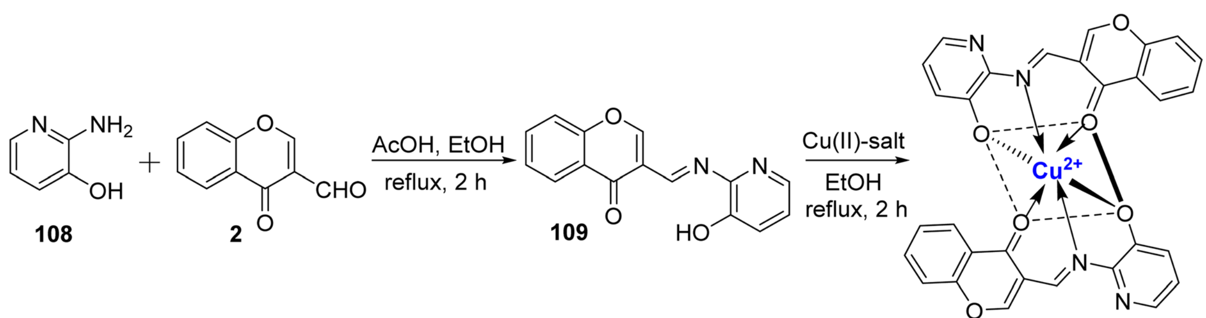
Scheme 30 Synthesis of ligand **103** and its octahedral nano-copper(II)-complex **104**.

its complex **107** with Cu^{2+} ion (Scheme 31). Characterization of the ligand **106** and complex **107** was done by analytical methods including IR, ESR, XRD, and SEM. Based on magnetic and electronic spectrum data, the complexes had octahedral geometry. The nematicidal and antibacterial effects of the metal complex were stronger than those of the parent ligand. In the presence of H_2O_2, the ligand and its metal complex DNA cleaving activity was detected.

Ammar *et al.*[110] conducted a study in which they synthesized a metal Cu(II) complex **110**. These complexe were derived from a tridentate ligand **109**, which was prepared using readily available starting materials, **108** and **2**, with the assistance of a catalytic amount of acetic acid (Scheme 32). Both the ligand **109** and its corresponding complex **110** were thoroughly characterized using spectral data and elemental analysis. The octahedral geometry of complex **110** was verified through various methods, including DFT calculations, UV-Vis spectroscopy, and ligand field parameters. Furthermore, the researchers assessed the antibacterial properties of both the ligand and the metal complex *in vitro* against a range of bacterial and fungal strains. The collected findings support the investigated compounds potential as bactericides and fungicides. The most effective cytotoxic compound against malignant cells is the Cu(II) complex. Against *B. subtilis*, every substance exhibited



Scheme 31 Synthesis of ligand **106** and its copper(II)-complex **107**.



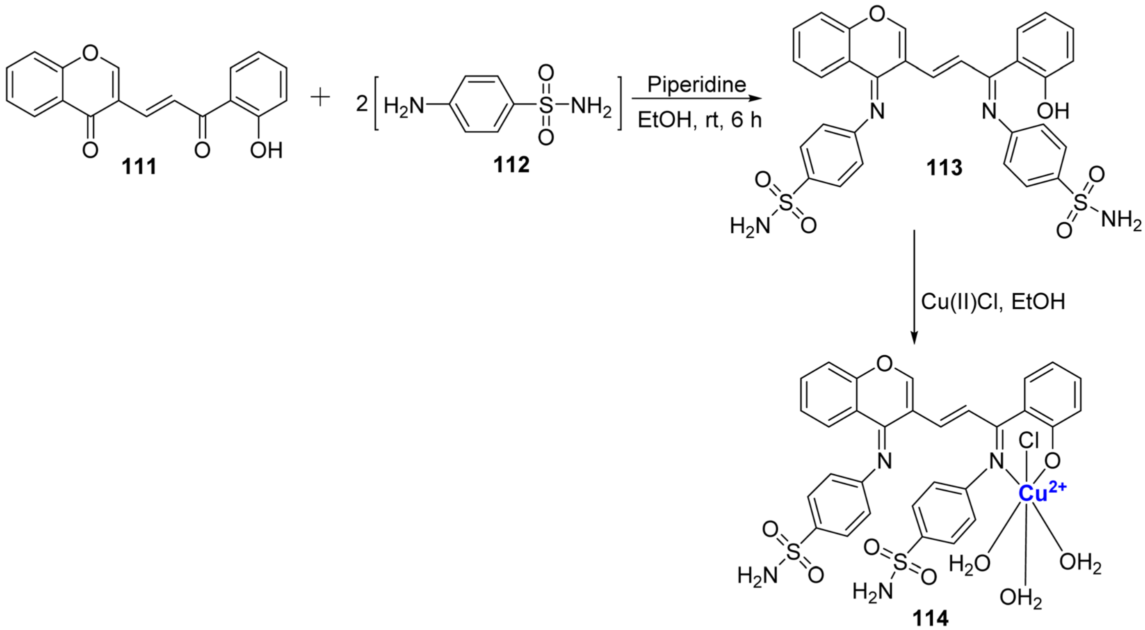
Scheme 32 Synthesis of ligand **109** and its copper(II)-complex **110**.

antibacterial action. The data demonstrates that the Cu(II) complex had substantial activity against *S. aureus* and *E. coli*, respectively. Cu(II) complex also displayed the antioxidant activity.

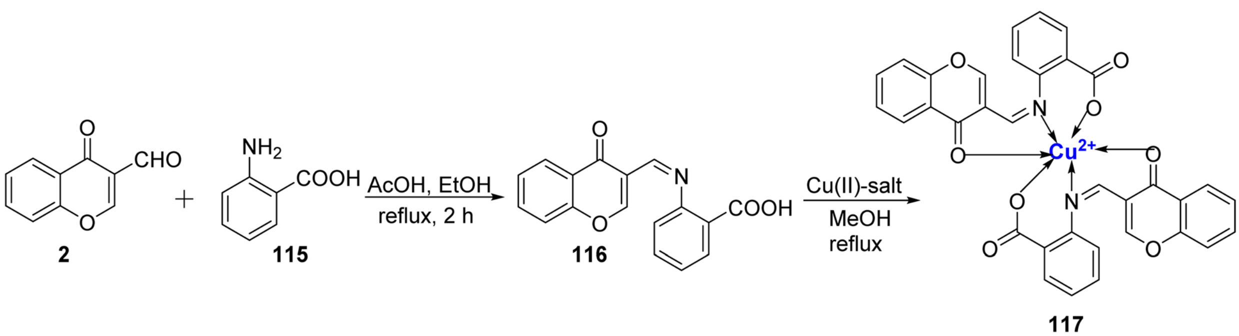
A fluorescent, octahedral, and non-electrolytic Cu(II)-complex **114** was reported by Sumathi *et al.*[111] (Scheme 33). The ligand **113** was synthesized using **111** and sulphanilamide **112** in the presence of piperidine. The structure of ligand **113** and complex **114** was further evaluated *via* various analytical techniques such as IR, NMR, *etc.* Generally, mostly metal chelates show higher biological activity because of the chelation theory.[112] In this context as well, it's worth noting that most metal chelates exhibit superior antimicrobial activity when compared to ligand **113**. The developed complex **114** may also assist as a photoactive compound as shown by its fluorescence studies.

Padmaja *et al.*[113] synthesized a Cu(II) complexes with ligand **116** and further characterized both the ligand **116** as well as the metal complex **117** *via* elemental/thermal analysis, ESR studies, magnetic susceptibility, and spectroscopic techniques. All six complexes share a common octahedral coordination geometry surrounding the metal ion. Ligand **116** was synthesized through a condensation reaction between **2** and **115** (Scheme 34). In these complexes, the ligand **116** interacts with the metal ion in a 1 : 2 stoichiometric ratio. It's worth noting that the metal complexes **117** displayed superior antimicrobial properties compared to the unbound ligand **116**.

In yet another research by Kavitha *et al.*,[114] fluorescent Cu(II)-complexes **120a–d** were synthesized with four Schiff bases, **119a**, **119b**, **119c**, and **119d** (Scheme 35). The ligands, **119a–d**, along with the corresponding complexes **120a–d**, were subjected to comprehensive characterization using techniques such as mass spectrometry, as well as ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. The complexes **120a–d** adopted a tetragonally distorted octahedral geometry, while the ligands **119a–d** coordinated with the Cu(II) metal ion in a tridentate manner. Significantly, the complexes **120a–d** displayed superior antimicrobial properties when compared to the



Scheme 33 Synthesis of ligand **113** and its copper(II)-complex **114**.

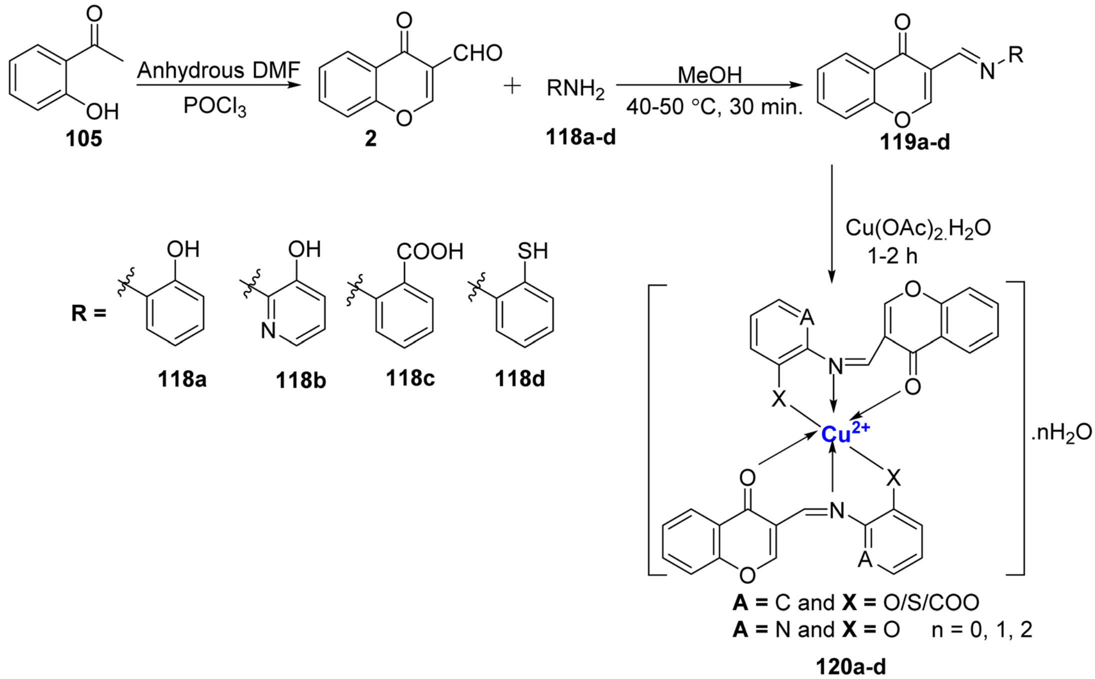


Scheme 34 Synthesis of ligand **116** and its complex **117** with Cu(II).

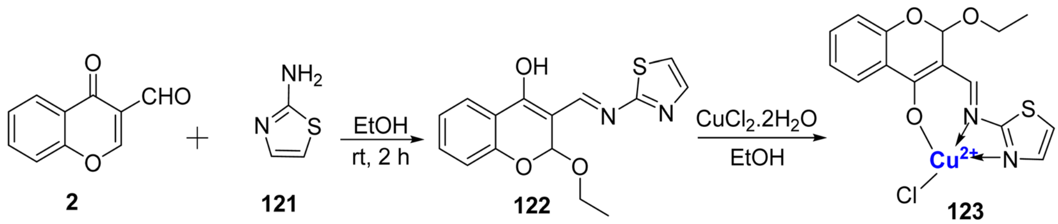
ligands **119a–d.** Furthermore, the radical scavenging activities of the synthesized compounds were assessed based on their IC_{50} values. Notably, complex **120a** exhibited a particularly low IC_{50} value of 0.16 μg mL^{-1}, indicating strong radical scavenging activity. Further, the scavenging properties based on the IC_{50} values was in the following order: **120a** > **120b** > **120c** > **120d**.

In 2011, Kalanithi *et al.*[115] synthesized coordination compound involving Cu(II), with Schiff base **122**. This Schiff base was obtained through the condensation of 3-formyl chromone **2** and 2-aminothiazole **121**, as outlined in Scheme 36. The structural confirmation of these complex was established through various spectroscopic techniques, including EPR, NMR, mass spectrometry, and magnetic susceptibility measurements. The ligand **122** coordinated to the metal ion from three sites namely, enolic oxygen, the nitrogen of the thiazole ring as well as from nitrogen of the azomethine group, thereby behaving as a tridentate entity. Due to chelation effects, the copper complex **123** was potent against pathogens. Therefore, chelation affected the biological outcome of the synthesized copper complex. The inhibition ability of the complex **123** against bacteria *C. albicans* also showed promising outcomes.

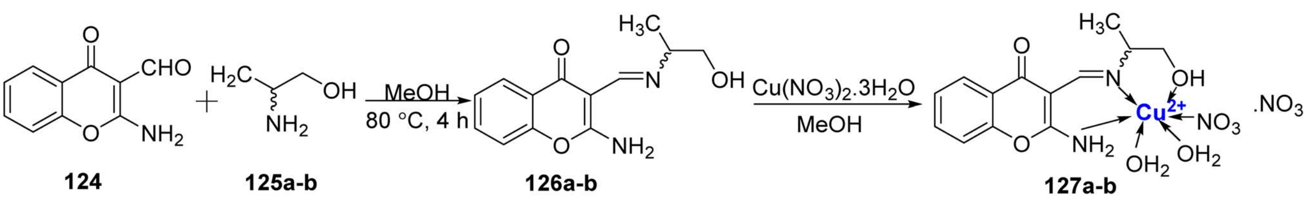
DNA cleavage ability of Cu(II)-metal complex **127a–b** was studied by Arjmand *et al.*[116] in 2012. (*R*)- and (*S*)-2-amino-3-(((1-hydroxypropan-2-yl)imino)methyl)-4*H*-chromen-4-one **126a–b** were prepared from **124** and **125a–b,** which on complexation with Cu(II) ion afford complexes **127a–b** (Scheme 37). They were then characterized by NMR, mass, IR, elemental analysis, and molar conductance calculations. It was observed that the complexes **127a–b** preferred to attach themselves to the guanine–cytosine region of the DNA molecule and the (*R*) enantiomer **127a** was found to be more active as compared to the (*S*) enantiomer **127b**. Topoisomerase II inhibition property as well as the cytotoxic effects of the complexes **127a–b** against human carcinoma lines were also examined. Complex **127a** was found to be selective for two cancer cell lines: A2780 (GI_{50} value = 17.6 μg mL^{-1}) as well as MCF-7 (GI_{50} value = 18.4 μg mL^{-1}), however complex **127b** displayed moderate activity with GI_{50}



Scheme 35 Synthesis of ligands **119a–d** and their Cu(II)-complexes **120a–d**.



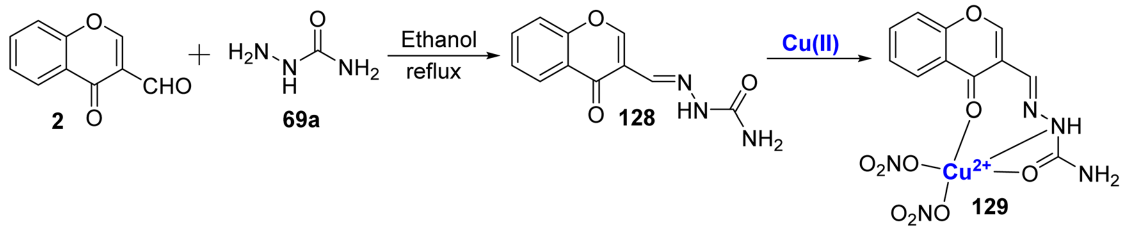
Scheme 36 Synthesis of ligand **122** and its Cu(II)-complex **123**.



Scheme 37 Synthesis of ligand **126** and their Cu(II)-complexes **127a–b**.

value of 20 μg mL^{-1} for A2780 and 26.6 μg mL^{-1} for MCF-7 cell lines. For cell lines Zr-75-1, SiHa as well as A549, the activity was observed to be very marginal.

In 2010, Li *et al.*[117] also utilized Cu(II)-complex **129** in studying DNA binding properties. The characterization of 3-carbaldehyde-chromone semicarbazone **128** and its complex with Cu(II) was carried out using a variety of methods, including crystallography. Complexes showed better binding interactions as compared to the free ligand **128** as studied by spectroscopic measurements (Scheme 38). The developed complex **129** interacted with DNA through intercalation binding mode. The antioxidant activity of these compounds is quantified by their IC_{50} in μM against hydroxyl radicals (HO$^•$). The IC_{50} values for ligand **128** and its Cu(II) against HO$^•$ are 10.170, and 1.195 μM, respectively. Notably, the metal complex exhibit significantly higher scavenging activity against hydroxyl radicals when compared to standard antioxidants like mannitol (IC_{50}: 10.19 μM). For scavenging superoxide anions, the IC_{50} values for the ligand, and Cu(II) complex are 32.810, and 0.943 μM, respectively. The metal complex **129** exhibit superior antioxidant properties compared to the ligand. Thus, the study showed that the metal ions can act as selective scavenging agents in



Scheme 38 Synthesis of ligand **128** and its complex **129** with Cu(II)ions.

biological systems and paved a pathway for further advancements in this field.

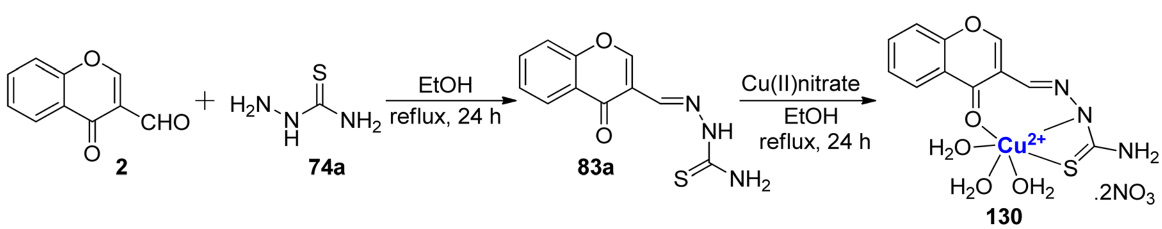
Yang *et al.*[118] developed the transition metal complexes of **83a** to study its fluorescence as well as DNA binding by spectral and viscosity studies (Scheme 39). The ligand **83a** was synthesized from ethanolic solutions of 3-carbaldehyde chromone **2** and thiosemicarbazide **74a**. Ligand **83a** was reacted with copper(II)nitrate in ethanol at reflux to afford the complex **130**. Moreover, the antioxidant properties (superoxide dismutase activity) for ligand **83a** (IC_{50} = 263.028 μM) and its corresponding Cu^{2+} complex **130** (0.799 μM) were also tested and found to be significant and higher than that of the standards used (IC_{50} for vitamin $C = 852$ μM). The ligand **83a** and complex **130** were characterized by various structural methodologies. The Cu(II) complex demonstrates superior antioxidant activity against superoxide and hydroxyl radicals and exhibits stronger scavenging effects.

Rosu *et al.*[119] conducted a study in which they synthesized coordination compounds **132a–f** with Cu(II) ions, using the Schiff base ligand **131**. The Schiff base, **131**, was obtained through the reaction between **57** and **8** as outlined in Scheme 40. To characterize these compounds, various techniques such as NMR, FT-IR, UV-Vis, ESR spectroscopy, X-ray diffraction, molar electric conductibility, and elemental analysis were employed. Furthermore, the antibacterial activity of the synthesized compounds was investigated *in vitro*. The results of the antibacterial study clearly indicated that the antibacterial properties of the Schiff base compounds were significantly enhanced when coordinated with metal ions.

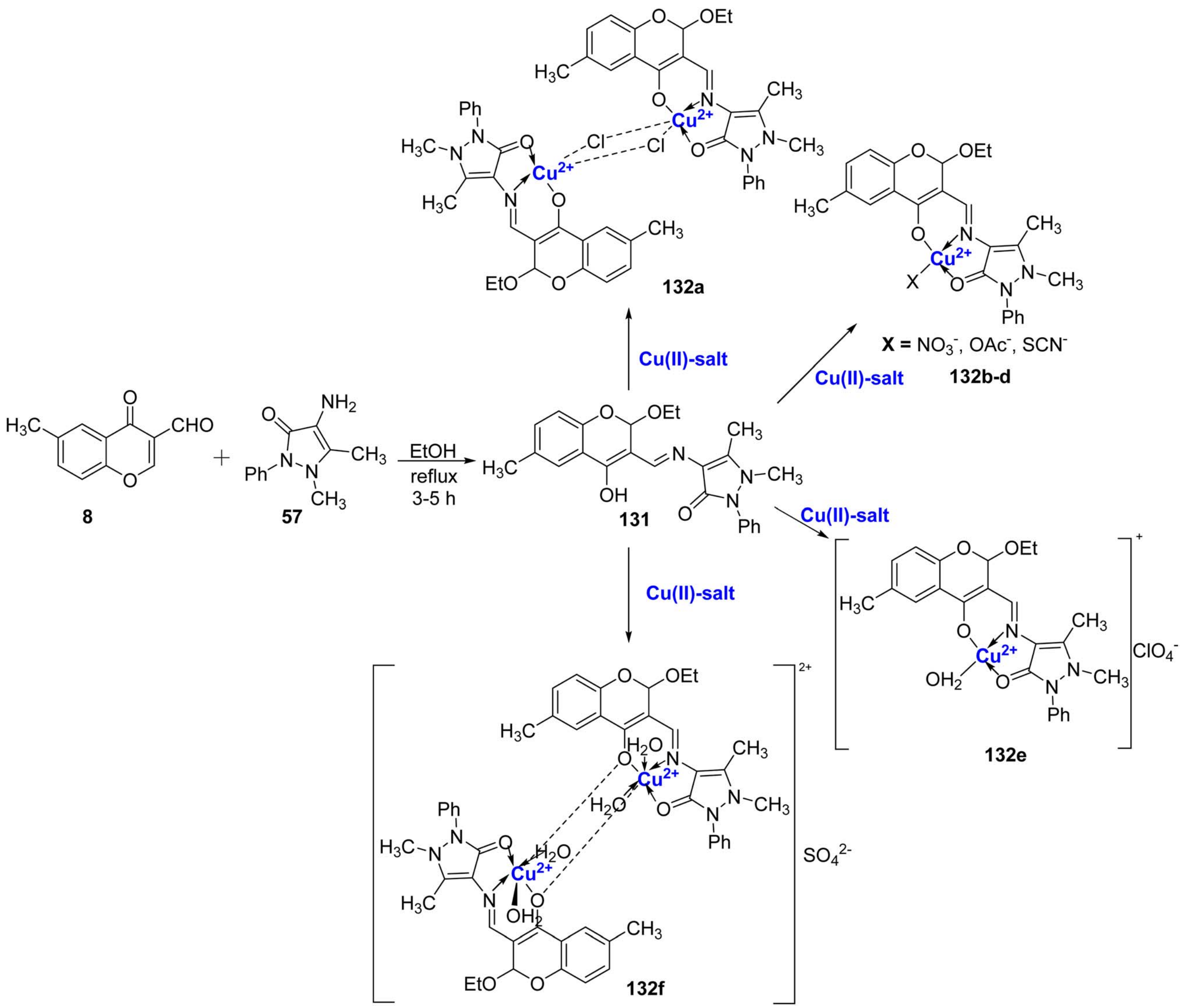
Anitha *et al.*[120] designed 1 : 2 complex of Cu(II) ions in conjunction with azo Schiff base **136**. Conductance data indicate that the complex are generally non-electrolytic in nature. The synthesis of Schiff base **136** involved the condensation of *p*-phenylenediamine **133**, **135**, and **2**. Subsequently, this Schiff base was treated with copper(II) chloride, resulting in the desired metal complex 137 (Scheme 41). The Schiff bases and their corresponding metal complex were also subjected to antibacterial and antifungal studies. The Cu(II) complexes showed promising antibacterial activity towards bacteria, *S. aureus*, *E. coli*, *S. enterica typhi*, and *B. subtilis*.

Mendu *et al.*[121] explored the synthesis of the Schiff base known as 4-chloro-2-((4-oxo-4*H*-chromen-3-yl)methyleneamino) benzoic acid **139**, along with a Cu(II) complex (Scheme 42). The Schiff base ligand **139** obtained by the reaction of **2** and 4-chloroanthranilic acid **138.** The synthesized ligand **139** and its respective complex were also subjected to antimicrobial assessments against different bacteria using well disc and fusion methods. The metal complex exhibited higher potency against microorganisms when compared to the free Schiff base ligand. The Cu(II)-complex function through redox chemistry in cleaving DNA. The structure (octahedral geometry) and characterization were done *via* analytical and spectroscopic measurements. The complexation of the ligand **139** was found to occur from three sites: the nitrogen atom of azomethine, the oxygen atom of ketonic functionality as well as the hydroxyl of the carbonyl functional group.

Bheemarasetti *et al.*[122] developed a novel Schiff base ligand known as 3-(((1*H*-1,2,4-triazol-3-yl)imino)methyl)-4*H*-chromen-4-one (L) **141** through the reaction of **2** and **140** in methanol (Scheme 43). Additionally, they synthesized Cu(II), complex. Comprehensive characterization of both the ligand **141** and the complex **142** was carried out using techniques such as FT-IR, ESR, UV-Vis, SEM, NMR, mass spectrometry, TGA, and X-ray analysis. The shape of complex **142** was found to be square planar. The complex **142** also demonstrated good antiproliferative and anticancer results compared to the remaining compounds. They could be used as a promising antitumor agent. Additionally, DNA binding studies revealed that these compounds interact with CT-DNA *via* an intercalative mode.



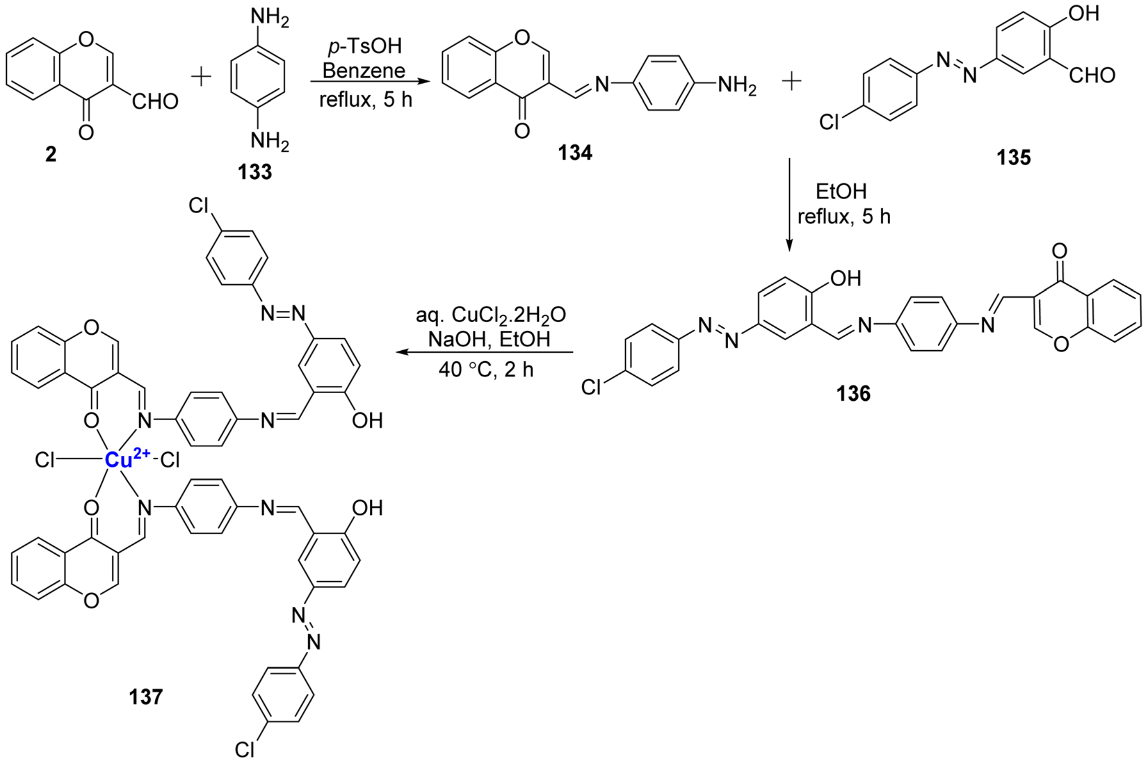
Scheme 39 Synthesis of ligand **83a** and its Cu(II)-complex **130**.



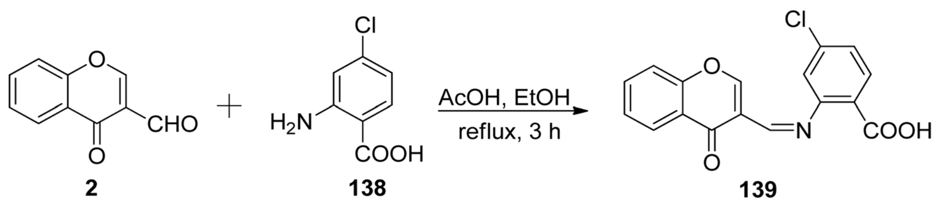
Scheme 40 Synthesis of ligand **131** and their Cu(II)-complexes **132a–f**.

In 2011, Arjmand *et al.*[123] conducted a study in which they synthesized a Cu(II) complex based on chromone and investigated its interactions with DNA molecules, as well as its DNA cleavage properties. The ligand **144** was prepared by combining **124** and **143**, (Scheme 44). The Cu(II)-complex **145** was then synthesized with a metal-to-ligand ratio of 1 : 2. Significant absorption enhancements were observed, confirming the binding of complex **145** with the DNA backbone, particularly in the 5′-GMP region. Consistent findings supporting this interaction were obtained through other experimental measurements. Gel electrophoretic mobility assay was employed to assess the complex's artificial nuclease activity, revealing that complex **145** effectively cleaves plasmid pBR322 DNA, transforming it from form I to form II and ultimately generating linearized form III as the complex concentration increases.

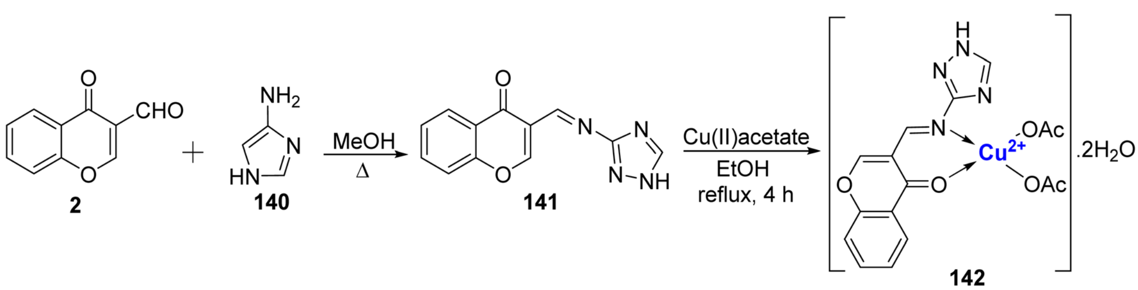
In a study conducted by Alturiqi *et al.*,[124] they synthesized new complex of Cu(II), **148** by combining **146** with **2**, as outlined in Scheme 45. The complex was then evaluated for their potential as agents against microbial infections and tumors. The researchers assessed the antimicrobial properties of complex against a range of bacteria, as well as fungi. The hexacoordinated octahedral copper complex **148** demonstrated the most robust antibacterial activity, with a zone of inhibition ranging from 13 to 20 mm. This enhanced activity was attributed to the larger atomic radius and electronegativity of the Cu(II) ion, which reduced the effective positive charge on the complex and facilitated its interaction with cellular membranes. Additionally, the complex exhibited outstanding scavenging activity against the DPPH radical, with the copper complex showing an IC_{50} value of 83.28. However, when it came to their impact on human tumor cell lines, including A427, LCLC-103H, and SISO, none of the tested compounds displayed toxicity. Remarkably, the Cu(II) complex displayed moderate activity, with IC_{50} values of 18.365 μM.



Scheme 41 Synthesis of ligand **136** and its complex with Cu(II) ion **137**.

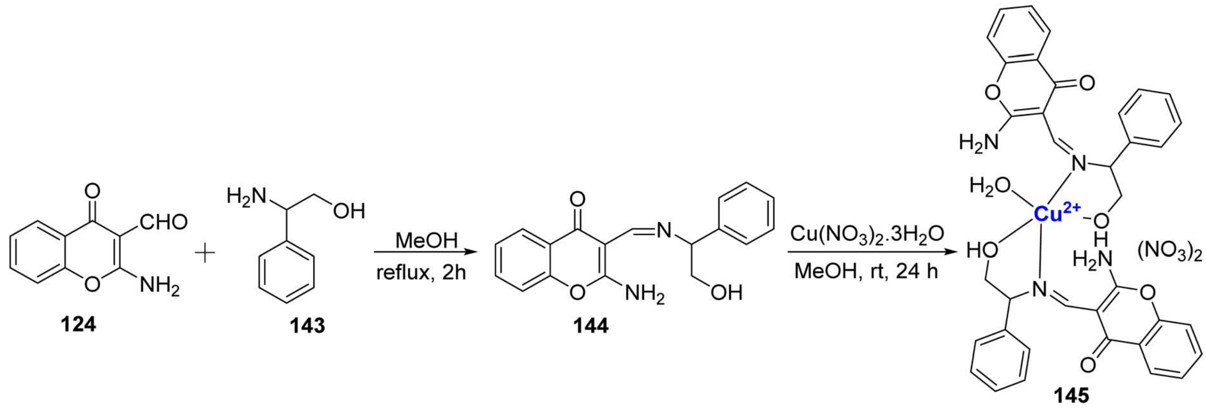


Scheme 42 Synthesis of Schiff base ligand **139**.

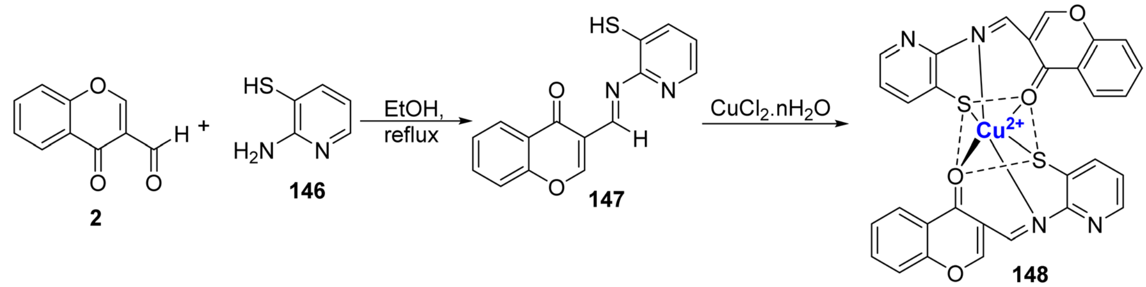


Scheme 43 Synthesis of ligand **141** and Cu(II)-ion complex **142**.

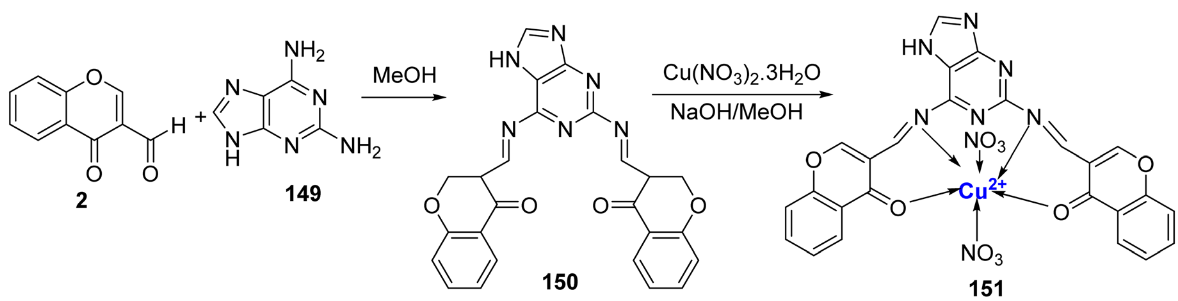
Singh *et al.*[125] conducted a study where they synthesized a metal complex involving Cu(II), using Schiff base ligand 150 (Scheme 46). Through UV absorption studies, they identified characteristic peaks for the Cu(II) complexes, designated as **151**, in combination with the chromone ligand. These peaks appeared at 274 nm, 278 nm, and 279 nm, respectively, representing π–π* transitions, and also showed charge transfer transitions in the range of 465–481 nm. The geometric structure of the copper complexes was determined through DFT studies, revealing a distorted octahedral geometry. To investigate how these metal complexes interacted with DNA, the researchers employed various techniques, including UV-vis absorption



Scheme 44 Synthesis of ligand **144** and its Cu(II)-complex **145**.



Scheme 45 Synthesis of ligand **147** and its Cu(II)-complex **148**.



Scheme 46 Synthesis of ligand **150** and its Cu(II)-complex **151**.

spectroscopy, fluorescence titration, and viscosity measurements. Changes in spectral position and intensity were observed to assess the interaction between the metal complexes and DNA. Notably, when the metal complexes bound to DNA, a hypochromic effect was observed, accompanied by a bathochromic shift. The copper complexes associated with chromone displayed absorption peaks at 299, 310, and 356 nm due to π–π* transitions. These complexes were found to bind to DNA through non-covalent interactions or by causing the uncoiling of the DNA double helix. As a result, the complexes adopted an intercalation mode of binding, effectively stacking among the aromatic chromophores and DNA base pairs. Fluorescence quenching studies revealed a decrease in emission intensity, signifying the interaction of the complexes with DNA. Further confirmation of the intercalation mode of interaction was provided by replacing EB with the complex molecules in EB-bound DNA. Hydrodynamic viscosity measurements furnished additional evidence by showing that the complexes inserted themselves between the DNA base pairs. This action caused the separation of the DNA double helix, resulting in an increase in DNA length and viscosity.

4. Biomimetic catalytic activity of chromone-based Schiff bases

Copper has a vital role in different enzymatic activities.[126] The reason for the significant interest in Schiff base metal complexes is not only because of their high stability and biological activity[127,128] but also because of their unique features of functioning as catalysts.[129] Within the array of bio-inspired structures capable of emulating catecholase activity, copper complexes of Schiff bases emerge as a particularly promising candidate. While the active site of the catecholase enzyme typically features a hydroxo-bridged dicopper(II) center, it is widely acknowledged that numerous monometallic copper(II) complexes exhibit catecholase activity. In this context, we have presented a study on the synthesis, characterization, and catalytic attributes of certain chromone-based metal complexes of Schiff bases.

In 2016, Beyazit *et al.*[130] reported a novel tetradentate, unsymmetrical Schiff base ligand **153** and its Cu^{2+} ion complex **154**. The ligand **153** was obtained by reacting a mixture of **56** (prepared by oxidation of visnagin [131]) and 2-aminobenzylamine **152** in $CHCl_3$ for 2 hours under reflux condition (Scheme 47). The complex **154** was obtained as a dark green precipitate by refluxing the ligand **153** and $Cu(CH_3COO)_2\cdot H_2O$ in methanol for 5 hours. The ligand **153** and the complex **154** were confirmed by using characterization techniques such as NMR, mass, elemental analysis, and electronic spectra. The complex **154** complex exhibited catecholase-like biocatalytic activity against the oxidation of 3,5-di-*tert*-butylcatechol to quinone form. This revealed that complex **154** complex had moderate catalytic activity.

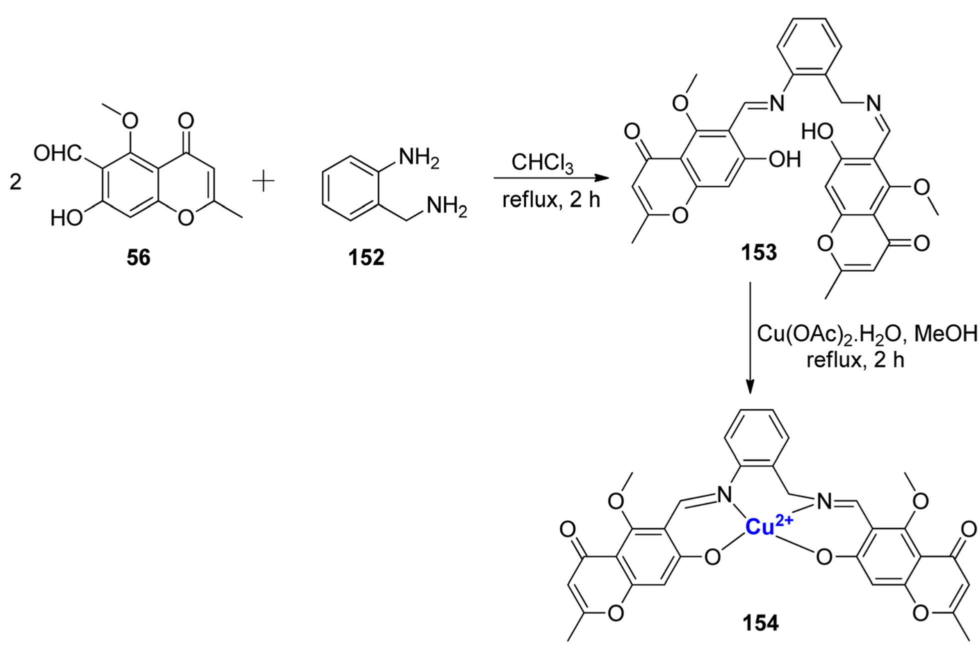
In continuation of their previous work (Scheme 47), they synthesized two chromone-based ligands **156a–b** and their corresponding transition metal complexes (Scheme 48).[132] The complexes **157a–b** thus obtained were screened for their catechol oxidase activity. The study revealed that the presence of substituents on ligands **156a–b** significantly influenced the catalytic activity of the resulting metal complexes **157a–b**. Notably, electron-donating substituents led to an enhancement in catalytic performance. The oxidation of catechol was found to adhere to first-order kinetics, according to the results of the kinetic measurements. All the synthesized compounds **156a–b** and **157a–b** were well characterized *via* thermal/elemental analysis, FT-IR, UV-vis spectroscopy, and NMR.

Beyazit *et al.*[133] also utilized visnagin derivative **56** to synthesize Schiff base ligands **160** and **161** by reacting it with the 2,3-diaminonaphthalene **158** and 1,8-diaminonaphthalene **159** (Scheme 49). The synthesized ligands **160** and **161** were treated with copper salts in a mixture of EtOH/$CHCl_3$ to afford Cu^{2+}–L complexes **162** and **163**. The structure of the ligands **160** and **161** as well as the complex **162** and **163** were confirmed *via* various spectroscopic techniques and elemental analysis. The complexes Cu(II) thus prepared were investigated for its catecholase potential and found to display moderate activity against 3,5-DTBC oxidation.

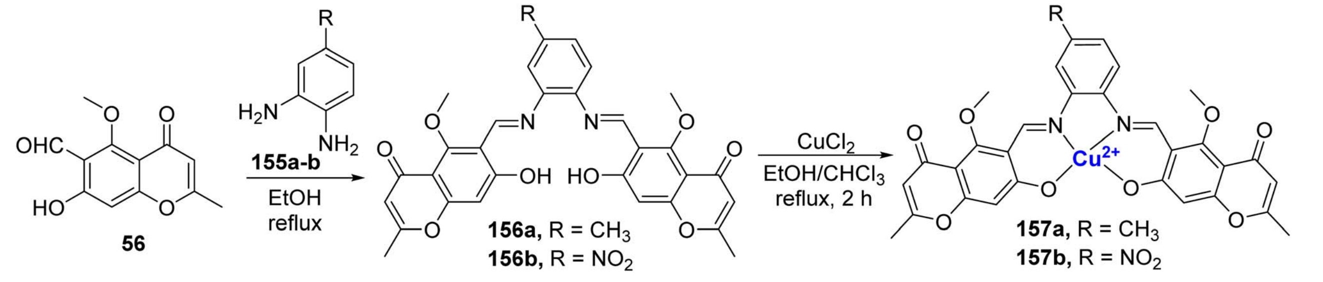
In 2021, Shebl *et al.*[134] synthesized novel mononuclear Cu(II)–hydrazone complexes **166a–c** with the aid of ligand **165** (Scheme 50). Characterization was done by elemental analysis, IR, TEM, powder XRD, thermal analysis, conductivity, mass, and ESR. Three different complexes of Cu(II) were reported: $[Cu(L)(NO_3)]$ EtOH **166a**, $[Cu(L_2)]\cdot 5H_2O$ **166b**, and $[Cu(L)(8\text{-}HQ)NO_3]\cdot H_2O$ **166c**. These complexes **166a–c** also showed phenoxazinone synthase property by oxidizing 2-aminophenol into the 2-aminophenoxazine-3-one. The complexes **166a–c** were found to be active against *Candida albicans*. The ligand **165** also displayed activity against *Candida albicans* but was found to be less than that of the complexes **166a–c**.

5. Miscellaneous

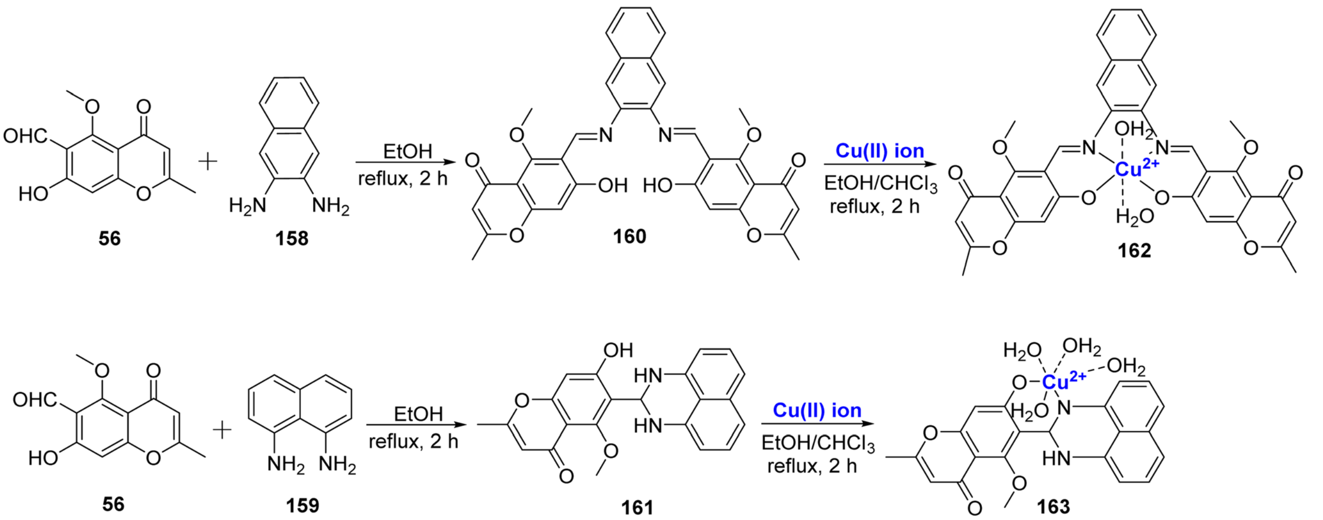
A tridentate chromone-based ligand **169** was developed by Alaghaz *et al.*[135] When an equimolar mixture of Girard T (2-ethyl-5-methoxy-6-formyl-7-hydroxy chromone) **167** and



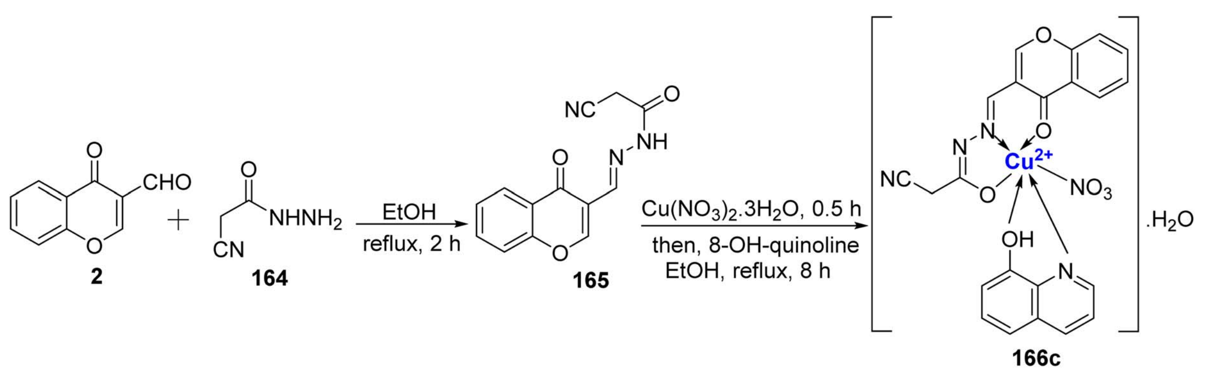
Scheme 47 Synthesis of ligand **153** and its Cu^{2+}–L complex **154**.



Scheme 48 Synthesis of ligands **156a–b** and Cu(II)-metal complexes **157a–b**.

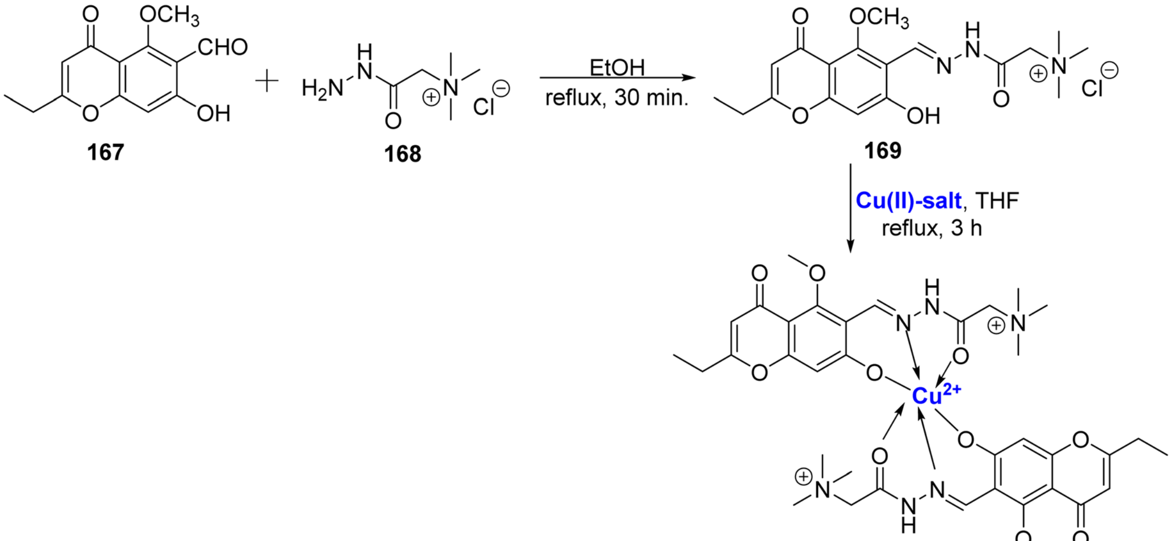


Scheme 49 Synthesis of ligands **160–161** and Cu(II) ion complexes **162–163**.



Scheme 50 Synthesis of ligand **165** and Cu(II)-ion complex **166c**.

trimethylammoniumacetyl hydrazine chloride **168** was refluxed, it gave chromone-based Schiff base ligand **169** (Scheme 51). This tridentate ligand which was confirmed *via* an elemental analysis as well as spectral data, was further utilized by the authors to synthesize its Cu(II)-complex **170** which was found to be non-electrolytic in nature. DFT calculations affirmed the octahedral geometry of complex **170**.



Scheme 51 Synthesis of chromone Girard T ligand 169 and its Cu(II)-complex 170.

6. Conclusion and future perspectives

Schiff bases hold a significant position within the realm of organic compounds, owing to their pharmacological attributes and their capacity to establish stable bonds with transition metal ions, notably copper. Copper complexes featuring Schiff bases have garnered notable attention in recent times because of their diverse applications in biological processes and their role in the advancement of novel therapeutic drugs. Consequently, chromone-based Schiff base complexes with copper constitute a noteworthy category of compounds. It has been revealed that Cu(II) complexes formed with chromone Schiff bases exhibit potent *in vivo* antitumor properties by impeding DNA replication in tumor cells, thereby inhibiting tumor growth. These compounds have also gained prominence for their utility as not only anticancer agents but also as antimicrobial agents, antioxidants, and more.

Nevertheless, there remain certain challenges, particularly concerning water solubility and selectivity issues between cancer and normal cells. These challenges can potentially be addressed by incorporating them into nano-level formulations. Furthermore, Schiff base ligands have demonstrated their potential as excellent probes for detecting cupric ions. Chromone-based Schiff base ligands, in particular, exhibit high specificity and selectivity in detecting Cu^{2+} ions, with potential applications in environmental and biological monitoring, as well as various pharmaceutical applications.

Abbreviations

AAS	Atomic absorption spectroscopy
HIV	Human immunodeficiency virus
NMR	Nuclear magnetic resonance
CS	Colorimetric sensor
U. S.	United States
FTIR	Fourier transform infra-red
UV-Vis	Ultraviolet-visible
EPA	Environmental Protection Agency
TGA	Thermal Gravimetric Analysis
EPR	Electron paramagnetic resonance
IR	Infra-red
EI Mass	Electron ionization mass
HRMS	High resolution mass spectrometry
TGA	Thermal gravimetric analysis
ICP	Inductively coupled plasma
5-BDTC	5-Benzyldithiocarbazate
DFT	Density functional theory
PNT	*Para*-Nitrotoluene
ESR	Electron spin resonance
FESEM	Field emission scanning electron microscopy
DTCB	*N*-methyl-5-benzyldithiocarbazate
TEM	Transmission electron microscopy
WHO	World Health Organization
SEM	Scanning electron microscopy
DTBC	Di-*tert*-butylcatechol
CTAB	Cetrimonium bromide
TG–DSC	Thermogravimetry and differential scanning colorimetry
TD-DFT	Time dependent density-functional theory
EPDM	Ethylene propylenediene monomer
XRD	X-ray diffraction
DAN	Diaminonaphthalene
IC_{50}	Half-maximal inhibitory concentration
DNA	Deoxyribonucleic acid
GMP	Guanosine monophosphate

GI_{50}	Growth inhibition by 50%
CT-DNA	Circulating-tumor DNA

Conflicts of interest

There are no conflicts to declare.

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