

Review Article

Cu(II), Ag(I), and Au(I) complexes of imidazole derivatives as emerging anti-cancer agents: A comprehensive review

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ABSTRACT

Imidazole-based ligands and their transition metal complexes have gained increasing attention in medicinal chemistry owing to their versatile coordination behavior, stability, and wide spectrum of biological activities. Among them, Cu(II), Ag(I), and Au(I) complexes with imidazole derivatives have emerged as promising anti-cancer agents. This review provides a comprehensive overview of recent advances in the design, synthesis, structural features, and biological evaluation of imidazole-based Cu(II), Ag(I), and Au(I) complexes for anti-cancer applications. Special emphasis is placed on their mechanisms of action, including DNA binding and cleavage, apoptosis induction, oxidative stress mediation, enzyme inhibition, and cell cycle arrest. The influence of ligand substitution, geometry, and coordination environment on biological activity is discussed in detail, highlighting structure-activity relationships. Furthermore, the review summarizes *in vitro* and *in vivo* studies that demonstrate the therapeutic potential of these complexes against various cancer cell lines. Challenges related to stability, bioavailability, and selectivity are also critically examined, along with future prospects for clinical translation.

1. Introduction

Cancer remains one of the greatest health and societal challenges of the 21st century. In 2022, nearly 20 million new cases and about 9.7 million deaths were recorded worldwide, including nonmelanoma skin cancers. Current estimates indicate that one in five individuals will develop cancer during their lifetime, while roughly one in nine males and one in 12 females will die from it. Lung cancer was the most common diagnosis, accounting for 2.5 million cases (12.4%), followed by breast, colorectal, prostate, and stomach cancers, leading to global cancer mortality with 1.8 million deaths. Geographic variations are striking, with incidence rates ranging from over 500 per 100,000 in Australia/New Zealand to under 100 in Western Africa. With cases projected to rise to 35 million by 2050, effective prevention strategies addressing risk factors such as smoking, obesity, and infections are urgently needed [1]. Traditional cancer therapies such as surgery, chemotherapy, radiation, and hormonal treatment have advanced significantly, incorporating innovations such as robotic-assisted surgery, fluorescence-guided tumor removal, 3D imaging in radiotherapy, and improved synthetic chemotherapeutics. Hormonal therapy has also become vital for hormone-dependent cancers. However, major challenges persist: incomplete tumor removal in surgery, drug resistance and toxicity in chemotherapy, precision and accessibility issues in radiotherapy, and resistance development in hormonal therapy. While these approaches remain the foundation of cancer management, their limitations emphasize the need for continued innovation and the exploration of complementary or alternative strategies to improve patient outcomes [2,3]. Since the success of cisplatin and its derivatives in clinical oncology, transition metal complexes have attracted tremendous

interest in medicinal inorganic chemistry due to their ability to interact with biomolecules, induce apoptosis, and disrupt critical cellular processes [4-8]. Among transition metals, copper occupies a unique position, particularly when coordinated with biologically active ligands such as imidazole derivatives [9,10]. Copper is an essential trace element in humans, involved in diverse physiological processes [11,12]. Its redox-active nature enables participation in key enzymatic reactions, but this same property can also be exploited pharmacologically to generate cytotoxic reactive oxygen species (ROS) within tumor environments. Cancer cells, due to their high metabolic rate and altered redox homeostasis, are particularly susceptible to oxidative stress. Therefore, copper complexes have the potential to selectively target malignant cells while sparing healthy tissues, offering a therapeutic advantage over traditional chemotherapeutics [13-18]. Ag(I) complexes have also attracted attention as anti-cancer agents due to their ability to interact with DNA and proteins, leading to the disruption of cellular processes. They induce oxidative stress, generate ROS, and trigger apoptosis in tumor cells. Their relatively low toxicity toward normal cells and potential to overcome resistance make them interesting alternatives to platinum drugs [19-22]. On the other hand, Au(I) complexes exhibit strong anti-cancer potential. They act primarily by targeting mitochondria and inhibiting thiol-dependent enzymes. This leads to apoptosis and impaired proliferation, highlighting their role as potent candidates for novel anti-cancer therapies [23-27].

The imidazole ring is a five-membered aromatic heterocycle commonly found in both natural and synthetic compounds. Its electron-rich structure enables strong interactions with enzymes and receptors, supporting diverse biological functions. Imidazole derivatives have attracted growing attention in medicinal chemistry, with many already

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developed into clinically approved drugs. These compounds demonstrate significant therapeutic potential across a wide range of diseases, highlighting their value for future pharmaceutical innovation [28]. The strong affinity of imidazole for transition metals, combined with its biological compatibility, has inspired chemists to design imidazole-based metal complexes for pharmacological applications. When coordinated with Cu(II), Ag(I), or Au(I), imidazole ligands modulate its redox and biological activity, leading to enhanced cytotoxic potential against cancer cells. Over the past two decades, considerable research has focused on synthesizing and characterizing imidazole Cu(II), Ag(I), and Au(I) complexes and evaluating their anti-cancer activity [10,29-33]. This review aims to provide a comprehensive overview of the current state of research on imidazole-based Cu(II), Ag(I), or Au(I) complexes as anti-cancer agents. The review also discusses the underlying mechanisms of action, focusing on DNA interactions, ROS generation, enzyme inhibition, and apoptosis induction. Special attention is given to structure-activity relationships, which provide important guidelines for the rational design of more potent and selective complexes. In addition, this article critically assesses the challenges and

limitations of current research. It proposes future directions for the development of imidazole-based Cu(II), Ag(I), or Au(I) complexes as clinically viable anti-cancer agents.

2. Anti-cancer activity of imidazole-Cu(II) Complexes

Imidazole-based Cu(II) complexes exhibit significant anti-cancer activity through multiple mechanisms. Recently, considerable research has focused on designing imidazole Cu(II) complexes and evaluating their anti-cancer activity. For example, Song *et al.* prepared a novel Cu(II) complex (1) (Figure 1) of Schiff base ligand derived from benzimidazole. Comprehensive characterization of the complex was carried out through various analytical techniques, including elemental analysis, IR spectroscopy, UV-visible spectroscopy (UV-Vis), thermogravimetric analysis (TGA), and single-crystal X-ray diffraction (XRD). The structural investigation showed that the Cu center was four-coordinated by two nitrogen atoms from the azomethine and imine groups, a phenolic oxygen atom, and a chloride ion, resulting in a distorted quadrilateral geometry. The complex crystallized in a triclinic system, and structural

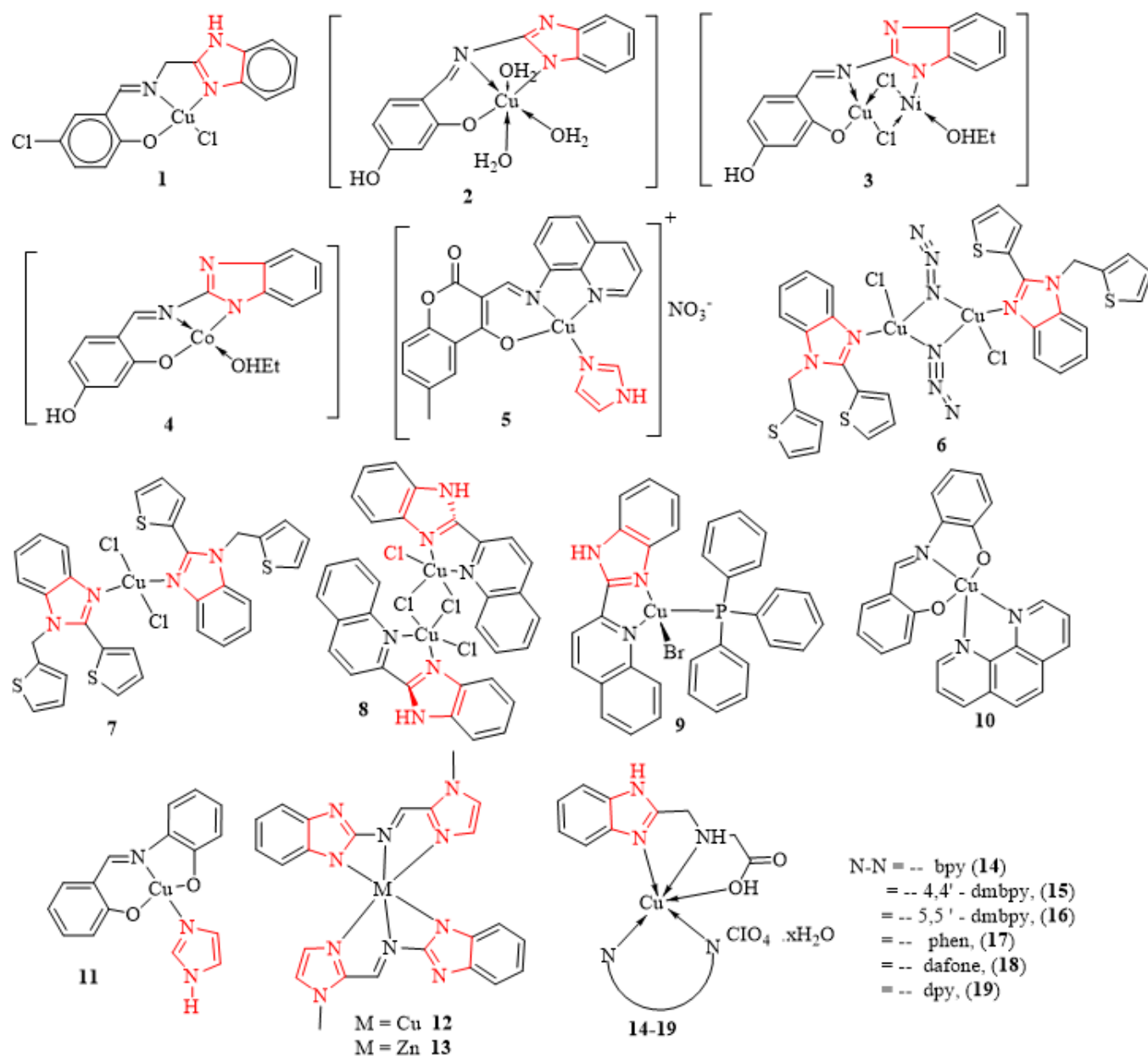


Figure 1. Chemical structure of imidazole-based Cu(II) complexes (1-19).

analysis suggested that π - π stacking interactions, along with hydrogen bonding involving methanol molecules, contributed to the stability of the crystal lattice. *In vitro* cytotoxicity assays demonstrated significant antiproliferative effects of complex (1) against michigan cancer foundation-7 (MCF-7) and colon-205 (COLO205) cell lines, with IC_{50} values of $16.9 \pm 1.5 \mu\text{mol}\cdot\text{L}^{-1}$ and $16.5 \pm 3.4 \mu\text{mol}\cdot\text{L}^{-1}$, respectively [34]. N. El-Wakiel *et al.* prepared Cu(II), Ni(II), and Co(II) complexes (2-4). The biological potential of these compounds was evaluated through various *in vitro* assays. Antimicrobial activity tests revealed that the metal complexes displayed noticeable activity against selected bacterial strains. Moreover, the cytotoxic effects of the free ligand and its metal complexes were assessed against the human hepatocellular carcinoma G2 (HepG2) cell line. The ligand exhibited the most promising anti-cancer effect, with an IC_{50} value of $9.08 \mu\text{g mL}^{-1}$, followed by the Cu(II) and Ni(II) complexes, which showed IC_{50} values of 18.2 and $19.7 \mu\text{g mL}^{-1}$, respectively [35].

Usman *et al.* prepared Cu(II) complex (5) of coumarin-derived Schiff base and imidazole ligand. The structural and electronic properties of the complex were thoroughly characterized through various techniques, including elemental analysis, UV-Vis, IR, Raman, electron paramagnetic resonance (EPR) spectroscopy, and single-crystal XRD. Computational analysis using density functional theory (DFT) with the B3LYP functional supported the spectroscopic findings, especially regarding vibrational modes. In particular, Raman and far-infrared spectra displayed characteristic doming mode vibrations of the copper center between $35\text{-}150 \text{ cm}^{-1}$, while additional out-of-plane and in-plane vibrational bands appeared in the ranges of $160\text{-}250 \text{ cm}^{-1}$ and $260\text{-}700 \text{ cm}^{-1}$, respectively. The binding interaction between the complex and calf thymus DNA (CT-DNA) was explored through multiple biophysical techniques. Results indicated that the complex exhibited stronger binding affinity compared to the free ligand and even the clinically used drug cisplatin, primarily through a partial intercalative binding mode. Further evaluation using plasmid DNA (pBR322) cleavage assays showed that the complex could promote double-stranded DNA cleavage, and this activity was confirmed by T4 ligase-mediated religation experiments. The cytotoxic effects of both the ligand and its copper complex were tested on A549 human lung carcinoma cells using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The copper complex displayed a notably low IC_{50} value of $4.6 \pm 0.3 \mu\text{M}$. In addition, treatment with the complex significantly elevated intracellular levels of ROS and thiobarbituric acid reactive substance (TBARS), while reducing glutathione (GSH) content, indicating ROS-mediated apoptosis [36].

Naveen *et al.* designed new Cu(II) complexes (6 and 7). The interaction of these copper complexes and their precursor ligand with calf thymus DNA was investigated using photophysical techniques. The results indicated that both complexes associate with DNA predominantly through electrostatic interactions. Additional studies assessed their binding affinity to bovine serum albumin (BSA), revealing that the complexes caused conformational changes in albumin by quenching the intrinsic fluorescence of tryptophan and tyrosine residues. The antioxidant capacity of the complexes was found to be substantial, further supporting their potential therapeutic relevance. The cytotoxic effects of the compounds were evaluated using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays against MCF-7 and henrietta lacks (HeLa) cell lines. Remarkably, both complexes and the free ligand were able to overcome cisplatin resistance. Importantly, the compounds exhibited low toxicity towards normal human embryonic kidney (HEK) cells, suggesting a favorable safety profile. Among the synthesized compounds, complex 6 displayed better anti-cancer activity, with IC_{50} values of 3.417 mM for MCF-7 cells and 0.6 mM for HeLa cells. These results showed that the designed Cu(II) complexes, especially 6, could serve as potential candidates for anti-cancer therapy [37]. Zhao *et al.* prepared two Cu(II) complexes (8 and 9). The structural characterization of these complexes was followed by a comprehensive investigation of their biological properties, particularly their interaction with CT-DNA and their anti-cancer potential. Spectroscopic analyses, including UV-Vis absorption and fluorescence measurements, demonstrated that both complexes bind to DNA through an intercalative mode. Additionally, both compounds exhibited significant DNA cleavage activity in the presence of ROS, indicating a

free radical-mediated mechanism of action. Among the two, complex 9 demonstrated stronger DNA binding and cleavage ability. The cytotoxic effects of the complexes were evaluated using MTT assays against four human cancer cell lines, including human hepatocellular carcinoma cell line (SMC-7721), gastric cancer cells (BGC-823), human colorectal cancer cells (HCT-116), and human colon tumor cell line (HT-29). Both complexes exhibited considerable cytotoxicity, with IC_{50} values ranging between 4.25 ± 0.39 and $9.24 \pm 0.16 \mu\text{M}$. Notably, complex 9 showed the most potent activity, particularly against HCT116 colorectal cancer cells, with an IC_{50} value of $4.25 \pm 0.39 \mu\text{M}$. Furthermore, complex 9 demonstrated lower toxicity toward normal liver LO-2 cells, with an IC_{50} of $12.76 \pm 0.52 \mu\text{M}$, suggesting selectivity for cancer cells. Additional biological evaluations of complex 9 revealed its ability to induce apoptosis in HCT116 cells, confirmed through morphological observations and flow cytometry analysis [38].

Koley *et al.* synthesized two Cu(II) complexes (10 and 11). Both complexes were structurally confirmed by XRD. The monomeric nature of these compounds in solution was supported by EPR spectroscopy. Electrochemical studies revealed that both complexes undergo irreversible redox behavior, suggesting the potential for redox-mediated biological interactions. Their interaction with calf thymus DNA was evaluated, and both complexes displayed strong intercalative binding capabilities. *In vitro* cytotoxicity assays demonstrated significant anti-cancer activity against A549 and MCF7 cell lines. Complex 10 exhibited IC_{50} values of $0.67 \mu\text{M}$ for A549 and $6.30 \mu\text{M}$ for MCF7, while complex 11 showed IC_{50} values of $0.59 \mu\text{M}$ and $8.88 \mu\text{M}$ for the same cell lines, respectively. These values indicate superior potency against A549 cells compared to some standard chemotherapeutic agents. An important aspect of this study is the minimal toxicity of the complexes toward normal human embryonic lung cells (L132), as reflected by high cell viability during testing. This selectivity highlights the therapeutic potential of these copper complexes, making them promising candidates for further development as targeted anti-cancer agents with reduced side effects on healthy cells [39].

Alajmi *et al.* reported a novel benzimidazole-based ligand along with its Cu(II) and zinc(II) coordination complexes (12 and 13). These complexes were analyzed through elemental analysis and various spectroscopic techniques to confirm their structural properties. The interaction of both metal complexes with key biomolecules, including human serum albumin (HSA) and DNA, was investigated using fluorescence spectroscopy, UV-Vis absorption titration, and computational molecular docking approaches. The findings showed strong binding affinity for both complexes, with the copper complex demonstrating superior interaction capabilities toward HSA and DNA. Further studies on DNA cleavage activity were performed using pBR322 plasmid DNA. The results revealed that both complexes possess effective nuclease activity. Mechanistic investigations using radical scavengers indicated that ROS played a central role in DNA cleavage mediated by complex 12, whereas complex 13 might act through a hydrolytic pathway. Cytotoxicity assessments were conducted on five different human cancer cell lines, including HeLa, SK-MEL-1, HT018, HepG2, and MDA-MB-231. Among these, complex 12 showed particularly potent activity against MDA-MB-231, achieving IC_{50} values comparable to cisplatin. Flow cytometry (FACS) confirmed that complex 12 induces apoptosis in MDA-MB-231 cells. Additionally, both complexes were evaluated for their effects on cancer cell adhesion and migration, demonstrating inhibitory effects. Importantly, *in vivo* chronic toxicity studies were conducted in mice, examining the impact of the complexes on major organs. Results suggested that both complexes displayed low toxicity, indicating good biocompatibility [40]. Sabithakala and Chittireddy prepared Cu(II) ternary complexes (14-19) and characterized them by elemental and spectral analyses, with complex 14 further confirmed via single-crystal XRD, revealing a monomeric structure with distorted square pyramidal geometry. The anti-cancer potential of these Cu(II) complexes was evaluated using an MTT-based cytotoxicity assay against several human cancer cell lines, including HeLa, MCF-7, and A549 cancer cells. This assay relies on the conversion of the yellow tetrazolium dye (MTT) into purple formazan crystals by mitochondrial enzymes in metabolically active cells. The resulting color intensity, quantified spectrophotometrically after dissolving formazan in DMSO, provides a direct measure of cell viability. Complexes 15 and

17 displayed the most promising anti-cancer activities across the tested cell lines. Their enhanced cytotoxicity may be attributed to factors such as greater lipophilicity, efficient cellular uptake, and electronic effects imparted by the co-ligands. The presence of extended π -conjugation in complex 17, in particular, could facilitate better interaction with intracellular targets such as DNA, contributing to its superior activity. The variation in cytotoxic response highlights the role of co-ligands in modulating biological activity. These findings suggest that specific structural features in Cu(II) complexes, especially involving benzimidazole scaffolds and conjugated nitrogen-donor ligands, can be optimized for improved anti-cancer efficacy, making them promising candidates for future chemotherapeutic development [41].

Palamarcic *et al.* reported the design and synthesis of six novel methyl imidazole-based thiosemicarbazone ligands and their corresponding Cu(II) complexes (20-25) (Figure 2). The ligands were structurally characterized using a combination of ESI-MS, nuclear magnetic resonance (NMR), UV-vis, IR, elemental analysis, and XRD. NMR analysis showed that the ligands existed as both Z and E isomers in solution, with a 1:1 ratio in most cases, where the Z isomer was predominant. The compounds exhibited tautomeric behavior due to proton exchange, particularly involving the imidazole ring and the thiosemicarbazide moiety, especially at varying pH levels. In solution, the ligands acted as tridentate donors through NNS coordination, and when complexed with Cu(II) and dichloroacetate as a co-ligand, formed cationic complexes. These complexes were balanced by additional dichloroacetate anions, resulting in neutral ionic structures in the solid state. The copper centers in these complexes adopted either distorted square-planar (complexes 20, 23, 24) or square-pyramidal (complexes 21, 22, 25) geometries. Electrochemical analysis showed that the complexes underwent redox transformations within biologically relevant potential ranges. Biological evaluation of the complexes through MTT assays indicated that the Cu(II) complexes had significantly enhanced cytotoxicity compared to their uncoordinated ligands across several cancer cell lines, including A549, LS174, and MDA-MB-453. In particular, complexes 22 and 25, bearing phenyl groups on the terminal nitrogen of the thiosemicarbazide moiety, exhibited a 2.4-fold and 4.7-fold increase in antiproliferative activity, respectively, in the MDA-MB-453 cell line compared to their parent ligands. Complex 24 showed the highest activity in LS174 cells, with an IC_{50} of 13.7 μ M, surpassing that of cisplatin, used as a reference drug. However, all copper complexes, including the most active ones, displayed limited selectivity between cancerous and normal BEAS-2B cells, a drawback also observed with cisplatin. Notably, complexes 22 and 25 produced comparable effects to cisplatin in A549 cells but appeared to function through a different mechanism, possibly cytostatic rather than cytotoxic. Further analysis showed that complex 22 had a strong anti-adhesion effect on A549 cells [42].

Krasnovskaya *et al.* reported the synthesis and biological evaluation of a series of novel 2-amino-substituted (5Z)-3-phenyl-5-(pyridin-2-ylmethylene)-3,5-dihydro-4H-imidazole-4-one ligands and their corresponding Cu(II) and cobalt(II) complexes (26-41). Electrochemical studies using cyclic voltammetry indicated that both Co(II) and Cu(II) complexes undergo reversible reduction to their respective Co(I) and Cu(I) species, highlighting their redox-active nature. However, their biological action appeared to be independent of ROS generation, as there was no clear correlation between redox potential and cytotoxicity, suggesting a distinct, non-ROS-mediated mode of action. Cytotoxicity assays were carried out on several cell lines, including MCF-7, A549, and HEK293. The findings revealed that metal coordination significantly enhanced the cytotoxic potential of the ligands, with copper complexes demonstrating stronger activity than their cobalt counterparts. Among the copper derivatives, complex 30 displayed exceptional cytotoxicity toward HEK293 cells, comparable to that of cisplatin. Meanwhile, cobalt complexes 34 and 40 exhibited notable potency against MCF-7 cells, outperforming cisplatin by approximately 1.5 times. Substituent variations at the 2-position and N(3)-position of the imidazolone ring had a marked influence on bioactivity. Ligands containing a piperidine group were generally more potent than those with morpholine, and increasing the lipophilicity of N(3) substituents (Me < Allyl < Ph) correlated with increased cytotoxicity. HEK293 cells were found to be especially sensitive to these metal

complexes [43]. Kacar *et al.* prepared a novel Cu(II) complex (42) with 1-(4-(trifluoromethyl)benzyl)-1H-benzimidazole and 2,2'-bipyridyl as ligands. The structure of the synthesized complex was confirmed through single-crystal XRD analysis. The study focused on evaluating the biological effects of the complex, particularly its antiproliferative and cytotoxic activities on DU145 prostate cancer cells, alongside its effects on normal fibroblast NIH/3T3 cells and SPC212 mesothelioma cells. The antiproliferative activity of the complex was assessed using the MTT assay. The results demonstrated a time-dependent cytotoxic effect on DU145 cells, with IC_{50} values of 37.0 μ M at 24 h, 21.1 μ M at 48 h, and 10.0 μ M after 72 h of treatment, indicating enhanced efficacy with prolonged exposure. The compound also induced oxidative and endoplasmic reticulum (ER) stress in the treated cancer cells, as verified by enzyme-linked immunosorbent assay (ELISA) and Western blot analyses. Morphological evaluations using microscopy revealed characteristic features of apoptosis in the treated human prostate cancer cells (DU145), such as nuclear condensation, membrane blebbing, and cellular shrinkage. Further confirmation of apoptosis and proliferation status was provided by immunocytochemical analysis, which showed an upregulation of Bax, a pro-apoptotic marker, and a significant decrease in PCNA, a protein associated with cell proliferation. Importantly, the complex displayed better activity as compared to its individual ligand components, suggesting that complex formation enhanced its bioactivity [44]. Kaur *et al.* reported the synthesis of novel hydrazone derivatives derived from the anti-inflammatory drugs diclofenac and ibuprofen, using pyridine and imidazole-based aldehydes. The resulting compounds were thoroughly characterized using spectroscopic methods, including 1H NMR, ^{13}C NMR, and mass spectrometry. The corresponding Cu(II) complexes (43-46) were also synthesized, which demonstrated notable anti-cancer activity against several cancer cell lines, including A-549, HCT-116, and MDA-MB-231. Among them, the ibuprofen-imidazole hydrazone showed the highest potency, with an IC_{50} of 2.26 μ M. Its Cu(II) complex also exhibited impressive cytotoxicity toward MDA-MB-231 cells, with an IC_{50} of 3.58 μ M. These findings suggest that integrating nonsteroidal anti-inflammatory drugs (NSAIDs) with hydrazones and coordinating them with biologically active metal ions like Cu(II) could be a promising strategy for developing new non-platinum-based anti-cancer drugs [45].

Gerçek *et al.* designed new Cu(II) complexes (47 and 48) (Figure 3). The primary aim of the study was to explore the DNA-binding affinity and cytotoxic potential of these complexes. Comprehensive investigations using UV-Vis spectroscopy, viscosity measurements, and gel electrophoresis were conducted to assess the DNA interaction profiles. The findings revealed that complex 47 exhibits stronger DNA binding ability compared to complex 48, with binding constants of $1.9 \times 10^5 M^{-1}$ and $3.9 \times 10^4 M^{-1}$, respectively. Furthermore, complex 47 more effectively displaced ethidium bromide from DNA strands at lower concentrations, indicating superior intercalative binding. Under oxidative conditions, both complexes were capable of causing complete cleavage of plasmid DNA, highlighting their potential as DNA-damaging agents. The biological efficacy of these Cu(II) complexes was also evaluated across five human cell lines, including A549, PC-3, BEAS-2B, HCT-116, and MDZ. The IC_{50} of the synthesized complexes was found to be below 10 μ M for all tested cell lines, indicating high cytotoxic potency. The promising DNA-binding and cleavage results, along with cytotoxicity screening, suggest that these complexes may serve as potential candidates for further anti-cancer drug development [46].

Alshehri *et al.* successfully synthesized three Cu(II) complexes (49-51) using imidazole-based ligands. These complexes were comprehensively characterized through various analytical techniques, including elemental analysis, IR spectroscopy, and thermal analysis. In the IR spectra, the emergence of new absorption bands in the 500-300 cm^{-1} range confirmed the coordination of metal ions with the ligands. EPR data suggested that all complexes adopted a compressed octahedral geometry involving six donor atoms. To further validate the proposed structures, DFT calculations at the Becke-3-parameter-lee-yang-parr (B3LYP) level were employed. Theoretical models supported the experimental findings, showing distorted octahedral geometries, particularly in the case of 51, which also demonstrated the most favorable quantum reactivity parameters. Biological evaluation was carried out to assess DNA binding affinity and anti-cancer potential.

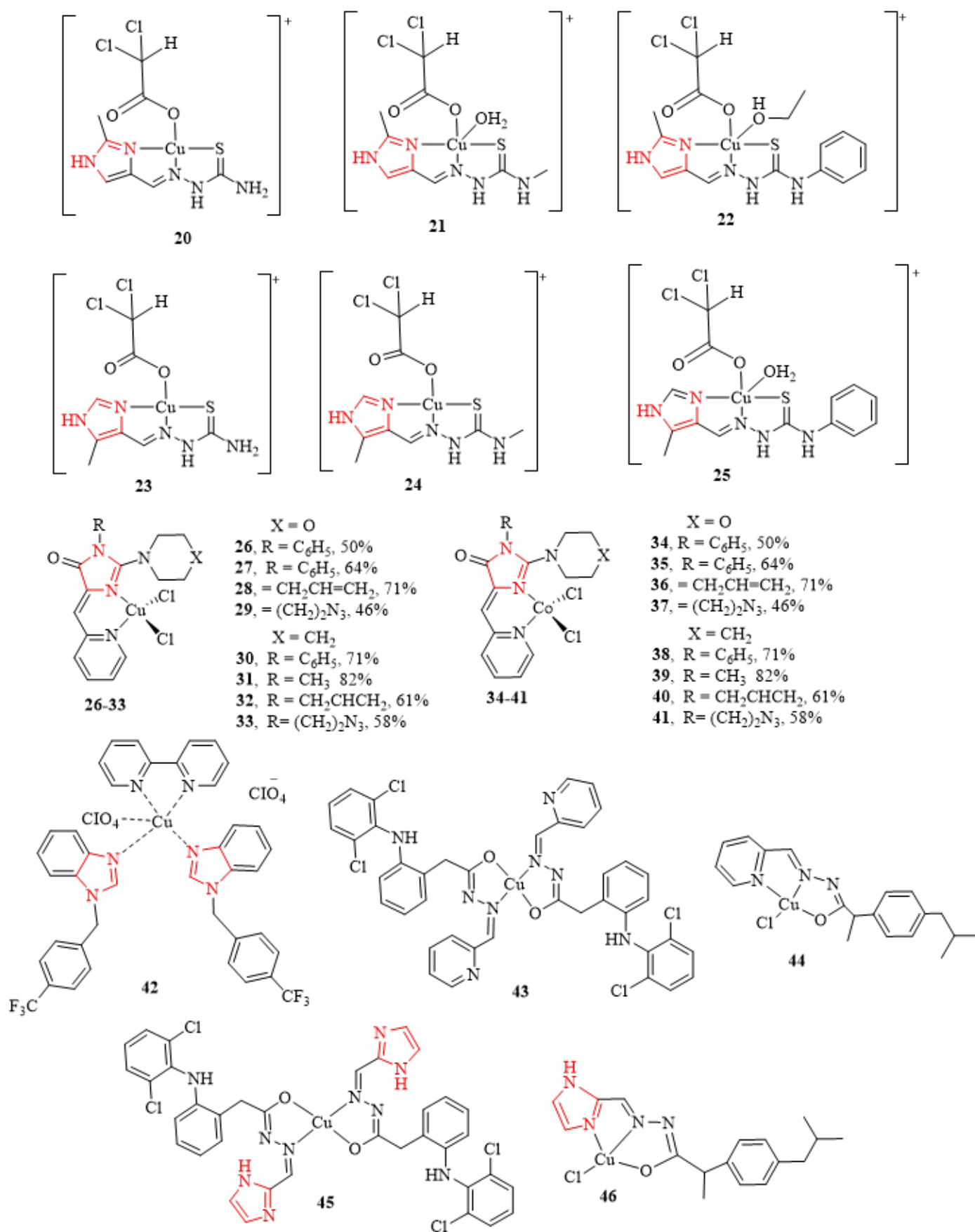


Figure 2. Chemical structure of imidazole-based Cu(II) complexes (20-46).

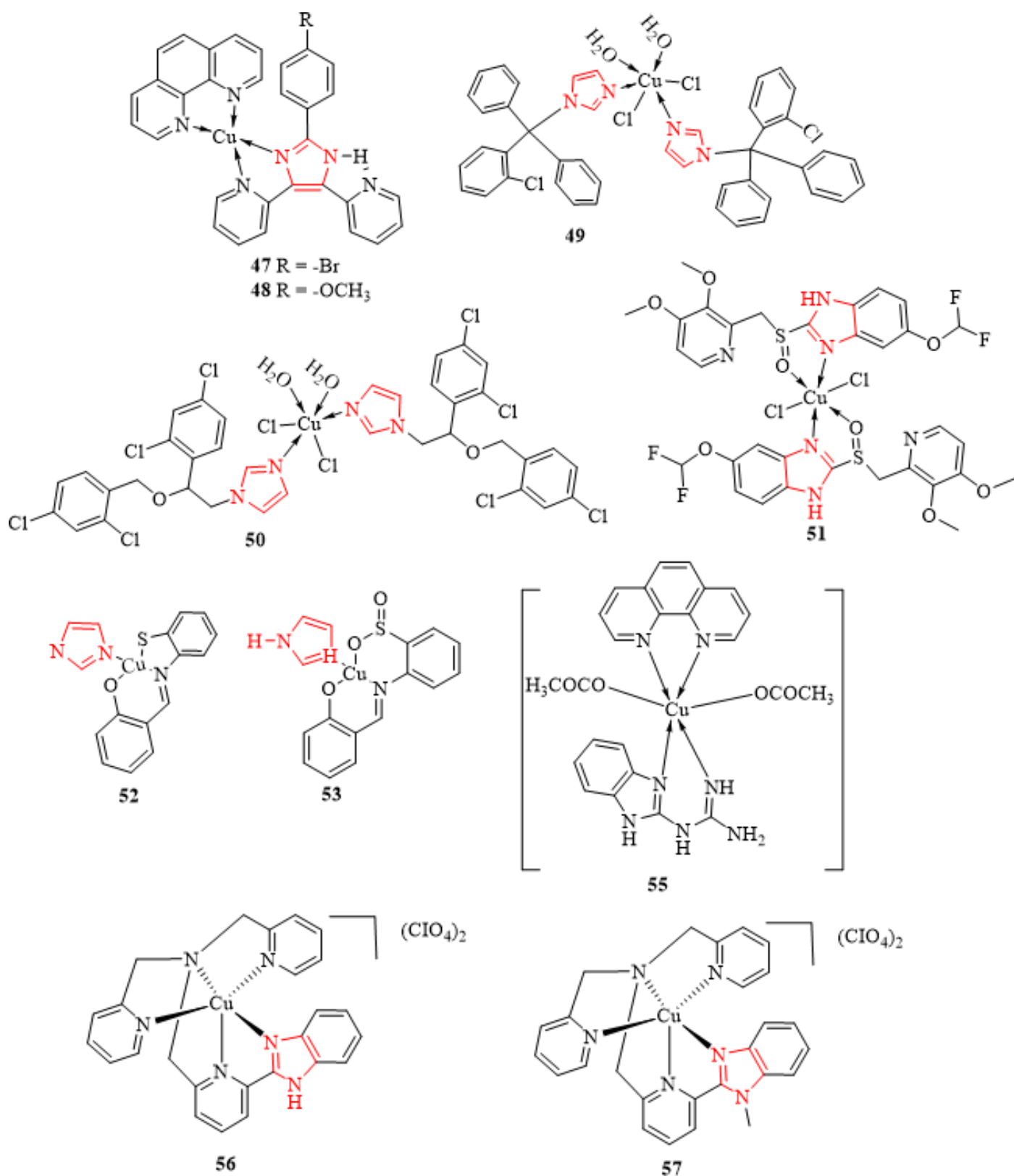


Figure 3. Chemical structure of imidazole-based Cu(II) complexes (47-57).

All complexes were found to interact with CT-DNA via intercalation. Molecular docking studies revealed strong binding affinities with α,β -tubulin protein targets, showing a descending order of interaction: $49 > 50 > 51$. These predictions were supported by *in vitro* cytotoxicity assays conducted on the M14 human melanoma cell line. Among the complexes, **51** demonstrated the highest cytotoxic activity, with an

IC₅₀ of 6.05 ± 0.01 mg mL⁻¹, followed by **49** at 6.65 ± 0.068 mg mL⁻¹, and **50** at 8.83 ± 0.01 mg mL⁻¹. Notably, these complexes demonstrated significantly better anti-cancer activity than both their parent ligands and cisplatin (IC₅₀ = 39.8 mg mL⁻¹), underscoring their potential as promising metal-based chemotherapeutic agents [9].

Paliwal *et al.* prepared two new Cu(II) complexes (52 and 53). The DNA-binding and cleavage capabilities of the complexes were thoroughly evaluated. UV-Vis spectroscopy, viscosity studies, and molecular docking analyses confirmed that both 52 and 53 interact with calf thymus DNA primarily through intercalation, with moderate binding affinity. Both complexes facilitated oxidative DNA cleavage, while complex 53 additionally demonstrated hydrolytic cleavage activity. Interactions with human serum albumin (HSA) revealed efficient fluorescence quenching via a static quenching mechanism, supported by Förster resonance energy transfer data indicating short donor-acceptor distances (~2.75-2.85 nm). Further, the binding of complex 53 with HSA involved strong hydrogen bonding interactions near site-I, confirmed through docking simulations. Biological assays demonstrated significant cytotoxic effects of both complexes against HeLa, A549, and MDA-MB-231 cancer cell lines, with HeLa cells being the most susceptible ($IC_{50} = 2.04 \mu\text{M}$ for 52 and $1.86 \mu\text{M}$ for 53). Flow cytometry analysis indicated that both compounds induced S and G2/M phase cell cycle arrest, followed by apoptosis. Morphological features such as chromatin condensation, cytoskeletal disruption, and caspase-3 activation further confirmed apoptosis induction, which was substantiated by western blot results. Collectively, these findings position the complexes as promising anti-cancer agents with dual DNA interaction and apoptosis-triggering mechanisms [47].

Abu-Dief *et al.* designed and synthesized bioactive Cu(II) mixed-ligand complex 54 and characterized it using multiple techniques, including mass spectrometry, FT-IR, UV-visible, NMR, magnetic susceptibility measurements, TGA, and Job's method for stoichiometry determination. The complex exhibited noteworthy antimicrobial and anti-cancer activities. Cytotoxicity evaluations via MTT assays against human cancer cell lines (HCT-116, HePG-2, and MCF-7) revealed that the complex had greater anti-cancer effects compared to the free ligand, though slightly less effective than the reference drug doxorubicin. This enhanced cytotoxicity may result from increased lipophilicity and membrane permeability conferred by metal chelation, along with potential inhibition of proteasomes and induction of apoptosis in tumor cells. Moreover, the 1,10-phenanthroline ligand, known for its planar, aromatic structure, contributes significantly to DNA binding and biological activity. The improved cytotoxic potential upon metal coordination is attributed to enhanced ligand acidity and stronger hydrogen bonding capabilities, facilitating cellular uptake and biological interaction [48]. Muley *et al.* reported the design and synthesis of two novel Cu(II) complexes, 55 and 56. The coordination geometry of both

complexes was determined to be trigonal bipyramidal, as confirmed by crystallographic analysis and various spectroscopic techniques. Electrochemical studies were conducted to investigate their redox properties. Their interactions with salmon sperm DNA were analyzed through UV-visible spectroscopy, revealing moderate binding affinities with binding constants around 10^4 M^{-1} .

To evaluate the binding mechanism, fluorescence quenching assays using ethidium bromide (EB)-bound DNA were performed. The Stern-Volmer constants were found to be $6.93 \times 10^3 \text{ M}^{-1}$ for complex 55 and $2.34 \times 10^4 \text{ M}^{-1}$ for complex (Figure 3) 56, suggesting effective displacement of ethidium bromide (EB) and strong DNA interaction. Circular dichroism analysis showed conformational changes in DNA upon complexation. Moreover, both complexes demonstrated the ability to cleave plasmid DNA, converting it from circular to linear form. Biological assessment using MDA-MB-231 breast cancer cells showed promising cytotoxicity, with IC_{50} values of $5.34 \mu\text{M}$ for 55 and $0.83 \mu\text{M}$ for 56. These findings highlight the DNA-binding and anti-cancer potential of these Cu(II) complexes, offering an economical alternative to platinum-based drugs [49].

Teodoru *et al.* prepare five new Cu(II) complexes featuring imidazole-based ligands (58-62) (Figure 4). These complexes were confirmed through elemental analysis, cyclic voltammetry, Fourier transform-infrared (FTIR), UV-Vis, thermal analysis, and XRD. Most of the complexes exhibited distorted octahedral geometries, except the 61 derivative, which displayed square pyramidal coordination. Given the biological relevance of copper in therapeutic applications, particularly as an alternative to platinum-based drugs, these compounds were investigated for their cytotoxic potential against B16 melanoma cells and compared with BJ human fibroblast cells. The free ligands displayed negligible toxicity to normal BJ cells. The Cu(II) complexes themselves also demonstrated selective cytotoxicity. When tested at concentrations up to $100 \mu\text{M}$, minimal toxicity was observed in BJ cells, while a time- and dose-dependent increase in toxicity was evident in melanoma cells. Among the five complexes, compound 62 exhibited the most potent antiproliferative effect, decreasing B16 cell viability to 50%. The findings emphasize the potential of these copper-imidazole compounds in anti-cancer therapy, especially due to their selective action on cancer cells over normal ones. Prior research on similar copper-based systems supports their dual antimicrobial and anti-cancer activities, often outperforming cisplatin in specific cell models due to enhanced DNA interactions and lower toxicity profiles [10].

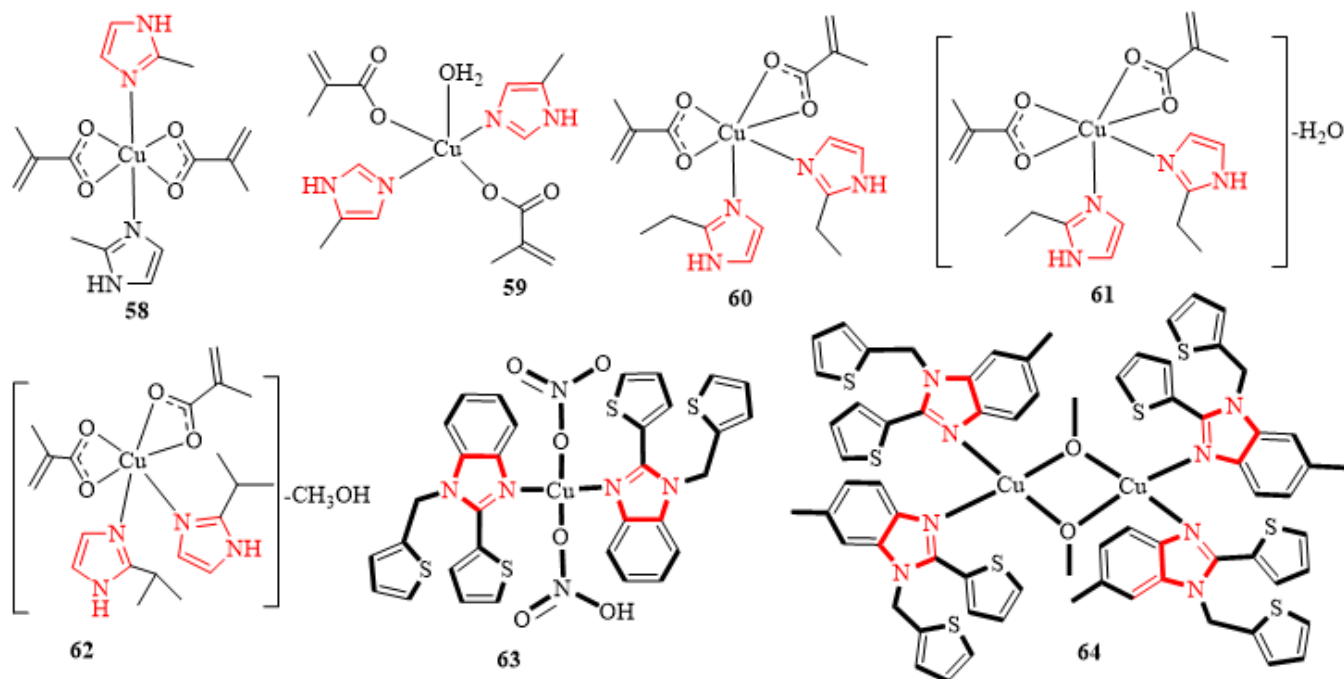


Figure 4. Chemical structure of imidazole-based Cu(II) complexes (58-64).

Saha *et al.* explored the anti-cancer potency of two Cu(II) complexes (63 and 64). Toxicological evaluation was carried out using MTT and hemolysis assays to determine their safety on normal human peripheral blood mononuclear cells (PBMCs) and red blood cells (RBCs). Results indicated that both complexes, up to concentrations of 80 $\mu\text{M mL}^{-1}$, exhibited negligible toxicity toward healthy human cells. The cytotoxic properties of the complexes were assessed against various cancer cell lines, including Sarcoma-180, 4T1 mouse breast cancer cells, and MCF-7 human breast cancer cells. Both complexes showed notable anti-cancer activity, especially in MCF-7 cells, where they induced dose-dependent apoptotic cell death. Flow cytometry using Annexin V staining revealed that complex 63 resulted in 10.45%, 24.17%, and 24.52% apoptotic cells at 40, 60, and 80 μM concentrations, respectively. In comparison, complex 64 induced even higher levels of apoptosis: 18.97%, 29.64%, and 33.32% under similar conditions. Further investigation into the mechanism of action revealed that both complexes activated caspases in a concentration-dependent manner, confirmed through the use of the pan-caspase inhibitor benzoyloxycarbonyl-Val-Ala-Asp (OMe) fluoromethylketone (*z*-VAD. FMK). DNA interaction studies suggested an intercalative binding mode for both complexes, leading to conformational shifts from B-like to C-like DNA structures. Notably, complex 64 demonstrated a stronger DNA binding affinity and induced more pronounced structural changes than complex 63 [50].

3. Anti-cancer activity of imidazole-Ag complexes

Imidazole-based Ag complexes have gained attention due to their ability to interact with DNA, generate ROS, and disrupt mitochondrial function in cancer cells. These complexes often show enhanced cytotoxicity compared to free ligands or silver salts, with selective activity toward tumor cells while sparing normal cells. For example, Medvetz, Doug A., *et al.* explored the anti-cancer potential of a series of Ag(I) N-heterocyclic carbene (NHC) complexes (65-67) (Figure 5) derived from 4,5-dichloro-1H-imidazole. These silver complexes were evaluated *in vitro* against three human cancer cell lines, including metastatic breast-157 (MB157), ovarian carcinoma-3 (OVCAR-3), and HeLa, using the MTT assay. The assay was conducted over 72 h after treatment with the silver complexes, their imidazolium salt precursors, silver salts (nitrate and acetate), and cisplatin for comparison. The MTT reagent, once reduced in viable cells, forms formazan crystals that were solubilized using sodium dodecyl sulfate (SDS) in dilute HCl, and the absorbance was read at 570 nm to assess cell viability. The results demonstrated that the imidazolium precursors lacked cytotoxic activity, while the silver complexes exhibited significant inhibitory effects on ovarian and breast cancer cell lines, with minimal impact on cervical cancer cells. The IC_{50} values confirmed that these compounds were especially potent against OVCAR-3 and MB157. Additionally, phase contrast microscopy revealed morphological changes in OVCAR-3 and MB157 cells treated with 50 μM of the test compounds for 36 h, indicating cellular damage. Preliminary *in vivo* testing of compound 65 showed promising activity against ovarian cancer in mice, suggesting that further *in vivo* evaluation of these silver-based agents is warranted [32].

Iqbal *et al.* prepared para-xylyl linked bis-benzimidazolium salts and their corresponding dinuclear silver-N-heterocyclic carbene (Ag-NHC) complexes (68-70). Structural elucidation of these compounds was achieved through techniques such as FT-IR, NMR, XRD, and elemental analysis. Their biological evaluation focused on cytotoxic potential against HCT 116 and HL-60 cell lines. The cytotoxic activity was assessed using the MTT assay, revealing that both the ligands and complexes exhibited dose-dependent antiproliferative effects. IC_{50} values for the HCT 116 cells ranged from 0.01 to 18.7 μM , while for HL-60 cells, the range was 0.7 to 55.7 μM . These results were compared to 5-fluorouracil, which displayed IC_{50} values of 19.2 μM (HCT 116) and 5.4 μM (HL-60), indicating superior or comparable efficacy of the tested compounds. Interestingly, the study noted that increasing the N-alkyl chain length on benzimidazolium salts reduced their cytotoxic effect, whereas in the silver complexes, longer N-alkyl chains enhanced cytotoxicity. This contrast highlights the influence of structural modifications and metal coordination on biological activity, suggesting that these Ag complexes could be promising anti-cancer candidates [51].

Haque *et al.* explored the synthesis and biological evaluation of Ag(I) complexes (71-73) derived from nitrile-functionalized imidazolium salts. Both symmetrical and asymmetrical imidazolium salts were reacted with Ag(I) oxide in methanol at room temperature, yielding silver complexes (71-73). The characterization of these compounds was carried out using NMR, FTIR, and elemental composition analysis. The anti-cancer potential of all synthesized compounds was tested *in vitro* against HCT 116 cells using the MTT assay. Results indicated that the silver complexes exhibited significantly greater cytotoxicity than their precursor imidazolium salts. The IC_{50} values for complexes (71-73) were 6.0 ± 0.2 , 14.0 ± 0.6 , and 4.0 ± 0.2 μM , respectively, while the imidazolium salts had IC_{50} values ranging from >200 μM to 20.3 ± 0.2 μM . Additionally, complex 73 demonstrated remarkable cytotoxicity against MCF-7 breast cancer cells, showing an IC_{50} of 0.9 ± 0.4 μM , highlighting its strong potential as a metal-based anti-cancer agent [52]. Achar *et al.* reported the synthesis of a series of silver(I) complexes (74-79). Biologically, the silver complexes exhibited noteworthy antibacterial and anti-cancer activity. Specifically, complex 79 showed potent antimicrobial efficacy, with MIC of 2 $\mu\text{g mL}^{-1}$ against *S. aureus* and 4 $\mu\text{g mL}^{-1}$ against both *E. coli* and *P. aeruginosa*. Furthermore, complexes 75-77 and 79 demonstrated cytotoxicity toward lung cancer cell lines A549 and H1975, with IC_{50} values below 10 μM . Importantly, all tested complexes were comparatively less toxic toward normal human skin fibroblast (Hs68) cells. These results support the therapeutic promise of Ag(I) complexes as antimicrobial and anti-cancer agents [53].

Fabbrini *et al.* introduced and characterized a novel monocationic Ag(I) N-heterocyclic carbene complex (80), which incorporates an anthracene-based fluorescent moiety. This compound was thoroughly analyzed using NMR spectroscopy, elemental analysis, high-resolution ESI mass spectrometry, and single-crystal XRD. Interestingly, substituting the methyl group on the imidazole ring in complex with an ethyl group led to the formation of a stable bis-carbene silver complex. The complex exhibits exceptional chemical stability in both organic and physiologically relevant aqueous solutions and shows minimal reactivity with small proteins, making it a suitable candidate for biological applications. When tested on a neuroblastoma cell line, the complex demonstrated a cytotoxicity approximately ten times stronger than cisplatin. This enhanced activity is attributed to its higher lipophilicity, which facilitates cellular uptake. Moreover, the complex effectively inhibits thioredoxin reductase (TrxR), displaying an IC_{50} of 0.493 μM , and binds specifically to the enzyme C-terminal peptide, likely targeting the S-Se redox site through a unique transmetalation-like mechanism involving silver displacement. Its anthracene fluorophore also enables cellular localization studies, where fluorescence imaging revealed accumulation in vesicle-like structures, suggesting endocytosis-based uptake. These features make the complex a promising anti-cancer agent with both therapeutic and imaging capabilities [33].

Rahali *et al.* explored the synthesis and anti-cancer potential of a series of Ag(I) complexes (81-85). The newly formed ligands and their corresponding silver complexes were characterized through multiple analytical techniques, including FT-IR, NMR, liquid chromatography-mass spectrometry (LC-MS), and elemental analysis. Further structural insights were provided through DFT calculations at the BLYP/TZ2P level, with charge distribution analysis performed using Voronoi Deformation Density (VDD) methods. The biological activity of these compounds was assessed through *in vitro* cytotoxicity screening against three human cancer cell lines: HePG2, A549, and MCF7, using the MTT assay. Compared to cisplatin, several Ag(I) complexes showed remarkable cytotoxic activity. Notably, complexes 83 and 84 demonstrated much lower IC_{50} values across all three cell lines, indicating potent anti-cancer activity. In particular, complex 84 exhibited IC_{50} values as low as 1.77 μM against A549 and 4.44 μM against HePG2, significantly outperforming cisplatin [54].

4. Anti-cancer activity of imidazole-based Au(I) complexes

Imidazole-based Au complexes are widely studied as potential anti-cancer agents. For example, Kunz *et al.* investigated the coordination behavior and anti-cancer potential of Au(I) complexes derived from imidazolyl-4(5)-phosphane ligands (86-90) (Figure 6). Upon reaction with Au(I), these ligands gave rise to structurally distinct complexes.

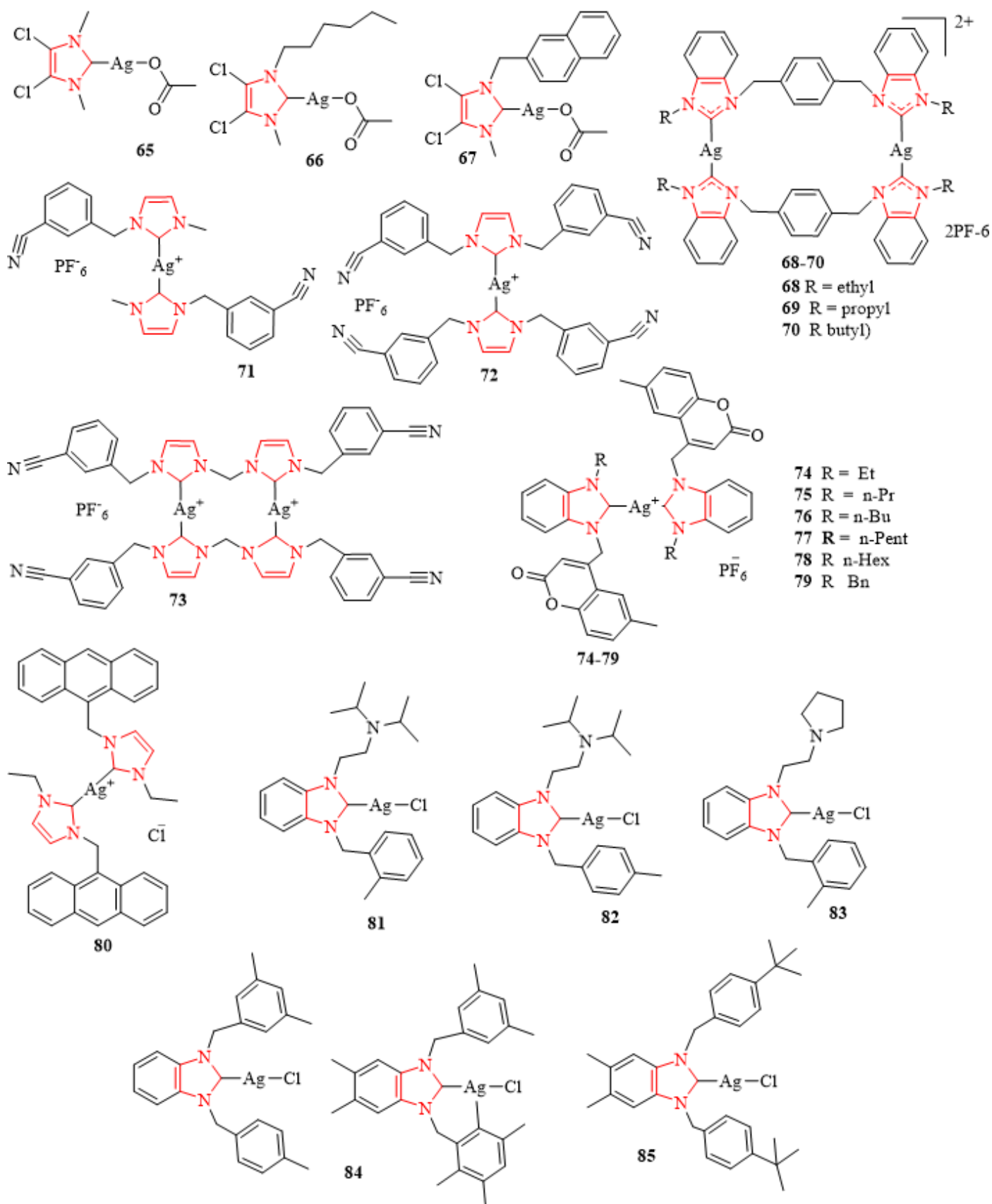


Figure 5. Chemical structure of imidazole-based Ag(I) complexes (65-85).

The biological evaluation of Au(I) complexes (86-90) was conducted across nine human cancer cell lines, which included seven ovarian cancer lines (with varying cisplatin sensitivities) and two leukemia

lines (HL60 and K562). Among these, compound 89 exhibited a cytotoxicity pattern closely resembling that of cisplatin, with drug-resistant ovarian cancer cell lines also showing reduced responsiveness

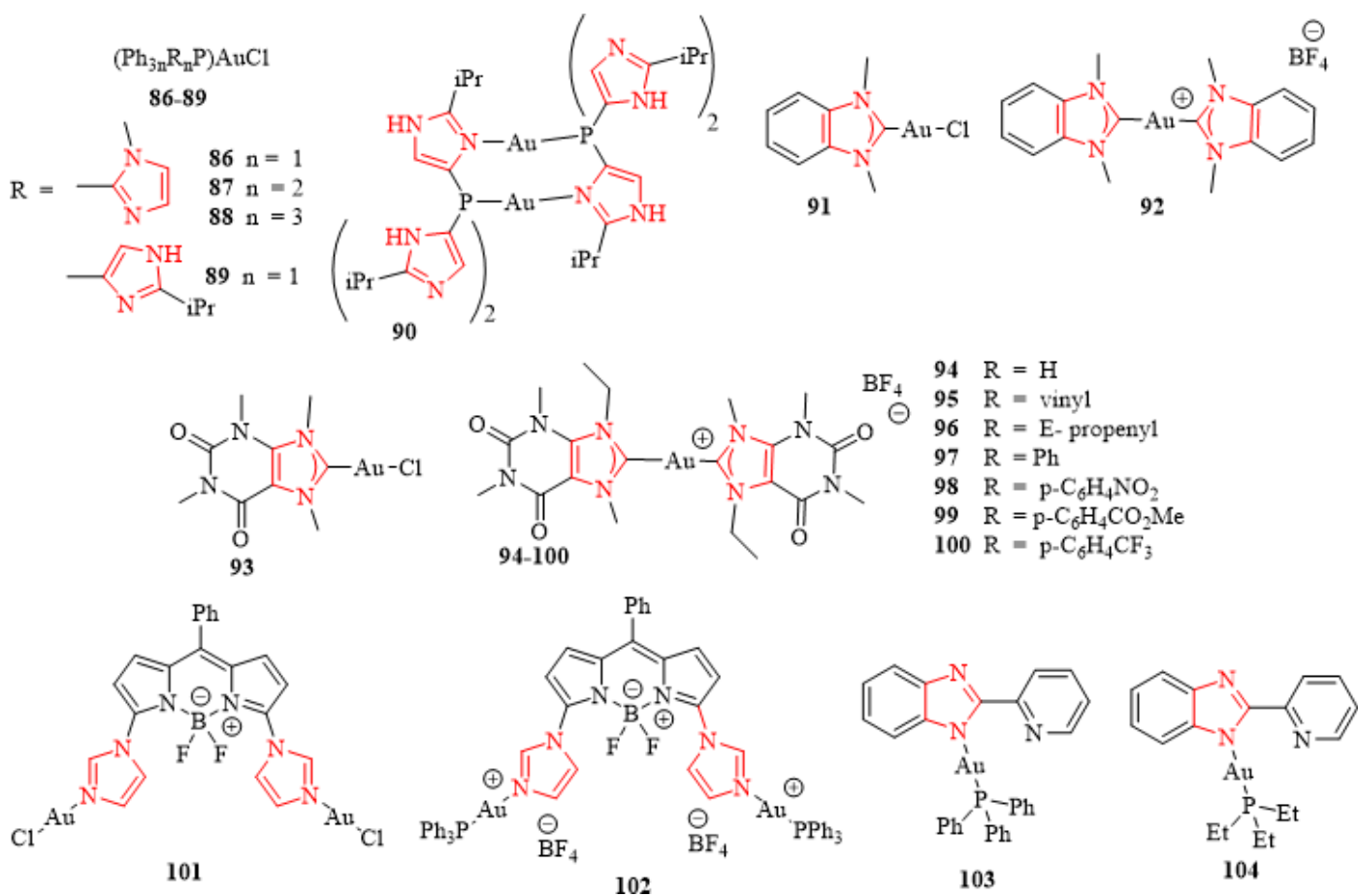


Figure 6. Chemical structure of imidazole-based Au(I) complexes (86-104).

to this gold complex, suggesting similar mechanisms of action. In contrast, compound **86** demonstrated broader cytotoxic activity and outperformed cisplatin across most tested lines except HL60. Notably, compound **86** maintained better activity against resistant ovarian cancer cells compared to compound **89**, showing only a 3.7-fold reduction in potency. Moreover, a decrease in overall cytotoxicity was observed as the hydrophilicity of the gold complexes increased from compounds **86** to **88**, which correlated with a diminished ability to differentiate between sensitive and resistant lines. The dimeric compound **90** followed a similar trend, showing reduced overall potency and limited variability across different cancer cell lines [55].

Bertrand *et al.* explored a new class of Au(I) N-heterocyclic carbene complexes (**91-100**) and evaluated their anti-cancer potential. These compounds were tested *in vitro* across various cancerous and noncancerous cell lines. Complex **94** demonstrated promising antiproliferative activity against both cisplatin-sensitive (A2780) and cisplatin-resistant (A2780/R) ovarian cancer cell lines. Notably, it exhibited low toxicity towards non-tumorigenic HEK-293T cells and *ex vivo* healthy tissues, suggesting potential for reduced side effects compared to traditional chemotherapeutics. An intriguing aspect of this study was the ability of complex **94** to selectively interact with G-quadruplex DNA structures. While many existing G-quadruplex ligands lack specificity, especially in the presence of duplex DNA, complex **94** displayed strong selectivity, marking a significant advancement. The proposed mechanism of action likely involves non-covalent interactions with nucleic acid structures, as opposed to irreversible covalent modifications of targets like PARP-1 [56].

A. Trommenschlager *et al.* developed two novel bimetallic Au(I) complexes (**101** and **102**) based on a BODIPY-derived bisimidazole ligand designed to serve as both therapeutic and trackable agents. These complexes demonstrated potent antiproliferative activity across several cancer cell lines, including MDA-MB-231, prostate cancer-3 (PC-3) and human colon cancer cell line SW480 with cytotoxicity levels comparable to that of auranofin. The bis-chlorido complex BODI-

Au-5 also showed notable anti-inflammatory activity and low toxicity toward peripheral blood mononuclear cells (PBMCs), suggesting a favorable therapeutic index. These compounds accumulate in the cytoplasm and remain fluorescent even at low concentrations, allowing for straightforward tracking via optical imaging. Among the two, **101** emerged as particularly promising due to its balanced antiproliferative and anti-inflammatory properties. Importantly, both **101** and **102** exhibited stronger cytotoxicity, potentially due to the presence of two gold centers. The role of metal coordination was found to be critical for biological activity, as the uncomplexed ligand displayed considerably weaker effects. Notably, **102** generally showed greater cytotoxicity than **101**, except in SW480 cells, where **101** was more effective. Gold uptake studies using inductively coupled plasma (ICP)-MS revealed that **102** accumulated more efficiently in SW480 cells, approximately 4.5 times more than **101**, and even exceeded auranofin uptake levels despite containing two gold atoms. This enhanced uptake may stem from the cationic nature of **102**, which likely promotes better membrane penetration. However, gold accumulation did not directly correlate with cytotoxicity, highlighting the complexity of intracellular behavior and potential multiple mechanisms of action [57].

Rouco *et al.* prepared two Au(I) benzimidazole-based complexes incorporating either triphenylphosphine or triethylphosphine (**103** and **104**). These compounds were evaluated for their cytotoxic effects against human neuroblastoma cells (SH-SY5Y). Structural characterization was confirmed by conventional analytical techniques, and XRD was used to resolve their solid-state structures. The biological evaluation involved treating SH-SY5Y cells with varying concentrations of each compound (ranging from 1 nM to 10 μM) over a 24-h period. Both Au(I) complexes exhibited potent cytotoxicity, with IC_{50} values of 2.7 μM for compound **103** and 1.6 μM for compound **104**. To investigate the mode of cell death, annexin V-fluorescein isothiocyanate (Annexin V-FITC) and propidium iodide staining were used. The fluorescence data indicated that apoptosis was being induced; however, pretreatment with the pan-

caspase inhibitor Z-VAD did not mitigate cell death. Further studies revealed that both compounds significantly increased caspase-3 activity and ROS generation, suggesting a dual mechanism involving both caspase-dependent and independent pathways [58].

5. Conclusions

Imidazole-based transition metal complexes, particularly those of Cu(II), Ag(I), and Au(I), represent a rapidly advancing frontier in medicinal inorganic chemistry. Their unique structural versatility, stability, and ability to engage in diverse biochemical interactions make them attractive candidates for anti-cancer drug development. Studies reviewed here clearly demonstrate that these complexes exhibit significant cytotoxicity against a variety of cancer cell lines through multiple mechanisms, including DNA binding and cleavage, modulation of oxidative stress, inhibition of thiol-containing enzymes, apoptosis induction, and interference with cell cycle progression. The incorporation of imidazole ligands not only enhances the stability of metal complexes but also contributes to fine-tuning their lipophilicity, redox properties, and biological selectivity. Importantly, variations in ligand substitution and coordination geometry have been shown to strongly influence activity, establishing crucial structure-activity relationships that guide rational drug design. Despite these promising outcomes, several challenges hinder the clinical translation of imidazole-metal complexes. Issues such as poor aqueous solubility, potential off-target toxicity, metabolic instability, and limited bioavailability remain major obstacles. Moreover, while *in vitro* studies have yielded encouraging results, systematic *in vivo* evaluations and pharmacokinetic studies are still scarce. The limited understanding of long-term safety profiles and possible immunological responses further restricts their progression to clinical trials. Addressing these limitations will require the integration of modern drug delivery technologies, including nanoparticle carriers, liposomal encapsulation, and polymer-based delivery systems, to enhance stability and tumor-targeting efficiency. Looking forward, the future of imidazole Cu(II), Ag(I), and Au(I) complexes in anti-cancer therapy appears highly promising. Advances in computational chemistry, molecular docking, and high-throughput screening are expected to accelerate the discovery of lead complexes with optimized biological activity and reduced toxicity. Furthermore, designing multifunctional imidazole-based complexes that combine anti-cancer activity with imaging or photodynamic properties could open avenues for theranostic applications.

CRedit authorship contribution statement

Ahmed Abdullah Al Awadh: Conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft, writing – review & editing, visualization, supervision.

Declaration of competing interest

The author declares that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the author used QuillBot (Chicago, USA) and Grammarly (San Francisco, USA) for language editing and grammar improvement. After its use, the author thoroughly reviewed, verified, and revised all AI-assisted content to ensure accuracy and originality. The author takes full responsibility for the integrity and final content of the published article.

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