Original Article

Received: 2021-12-26
Accepted: 2022-02-01

BCCR
2021, No 2, Vol 13 :143-155
www.bccrjournal.com

Anticancer Effects of Copper (II) Hydrazone Schiff Base Complex: A review

Roghayeh Fekri[1], Arash Abdolmaleki[2], Asadollah Asadi[1*], Mehdi Salehi[3], Aida Karimian[1], Leila Taghizadehmomen[1], Rehab K. Raheem[4], Lia Karimian[5]

ABSTRACT

Cancer treatment has traditionally consisted of established treatments such as radiation, surgical excision, and chemotherapy, which can be used alone or in combination. Many therapeutic factors have been extracted from minerals, plants, and animals. The majority of them have been synthesized in the lab, making them a valuable source of innovation pharmacologically. A growing interest in metal complexes in cancer treatment is due to their cytotoxic effects in vitro. The electronic nature of metals, modifications in ligands, and conformational changes in functional groups give rise to the discovery of drugs with different cytotoxic and pharmacokinetic properties. In recent decades, the number of people receiving chemotherapy has increased considerably. Medicinal inorganic chemistry can take advantage of the unique properties of metal ions to generate new drugs. This has prompted chemists to use various approaches to create novel metal-based anticancer drugs with various mechanisms of action, which are significant in the pharmaceutical industry due to their potent anticancer properties. Schiff base ligands and transition metals are the most researched coordination chemicals. Their applications as anticancer medicines are becoming more significant. This review analyzes various publications on copper complexes based on Schiff base hydrazone ligand in cancer treatment.

Keywords: Anticancer, Copper (II) complexes, Hydrazone, Schiff base ligands

1

1. Department of Biology, Faculty of Science, University of Mohaghegh Ardabili, Ardabil, Iran
2. Department of Bioinformatics, Faculty of Advanced Technologies, University of Mohaghegh Ardabili, Namin, Iran
3. Department of Chemistry, College of Science, Semnan University, Semnan, Iran
4. Department of Chemistry, College of Education for Pure Sciences, Ibn -Al-Haitham, University of Baghdad, Baghdad, Iraq
5. Department of Chemistry, College of Science, University of Guilan, University Campus 2, Guilan, Iran

*Corresponding Author:
Dr. Asadollah Asadi,
Email: asad.asady@gmail.com

INTRODUCTION:

According to scientific studies, cancer and cardiovascular disease are considered the top two medical concerns facing the scientific community in the twenty-first century. They are the leading causes of death globally [1]. Cancer is a significant public health hazard, particularly in developed countries, despite significant biomedical research and technology breakthroughs [2]. The global burden of cancer is anticipated to increase to 21.7 million people in ten years. Sedentary behavior, cigarette smoking, urbanization and associated pollution, changing food choices, and other environmental variables may contribute to the worldwide cancer pandemic [3, 4]. On a biological level, cancer spreads when genetic alterations disrupt the orderly processes of apoptosis and mitosis, and living creatures' cells begin to grow uncontrollably, forming a tumor that can be malignant. The difference between a benign and malignant tumor is that a benign tumor can grow but not spread. However, a malignant tumor can develop and spread to other parts of the body [5-7].

Chemotherapy medications such as cabazitaxel, letrozole, paclitaxel, doxorubicin, granisetron, docetaxel, and platinum-based therapies like carboplatin, nedaplatin, oxaliplatin, and lobaplatin, are now used to treat cancer. Most of them have various adverse effects, including taste changes, exhaustion, appetite loss, sore mouth, anxiety, fever, infection, depression, nausea, and vomiting [8]. Current efforts increating contemporary metallodrugs have concentrated on using transition metal complexes to improve these conditions and lessen adverse effects [9, 10]. Organometallic compounds, intermediate between traditional inorganic and organic materials, offer new possibilities in medicinal chemistry. Both metal complexes and organic compounds are extensively utilized in cancer therapy. Extensive research has been conducted on the role of complexes and ligands in cancer treatment. The ligand amount, ligand type, and coordination architecture significantly affect the anticancer properties of metal-based complexes [11]. Hydrazonesas are a significant category of Schiff base ligands due to pharmaceutical activities, like DNA binding (Fig. 1) and antimicrobial (Fig. 2) activities [12-15].

They can form stable chelate combinations with transition metals, catalyzing physiological activities [16-20]. Due to their importance in biological studies, hydrazones can act as molecular binding in drug discovery, increase the therapeutic effects against cancer, and reduce its side effects [21]. Furthermore, hydrazones can form azomethine imine and are considered the main class of reagents in synthesizing organic compounds due to their significant advantages, such as easy availability, stability, and different reactivity depending on the structure and reaction conditions [20, 22]. In particular, hydrazone derivatives of isoniazid and other hydrazides have been created and studied for diagnostic antibacterial activity.

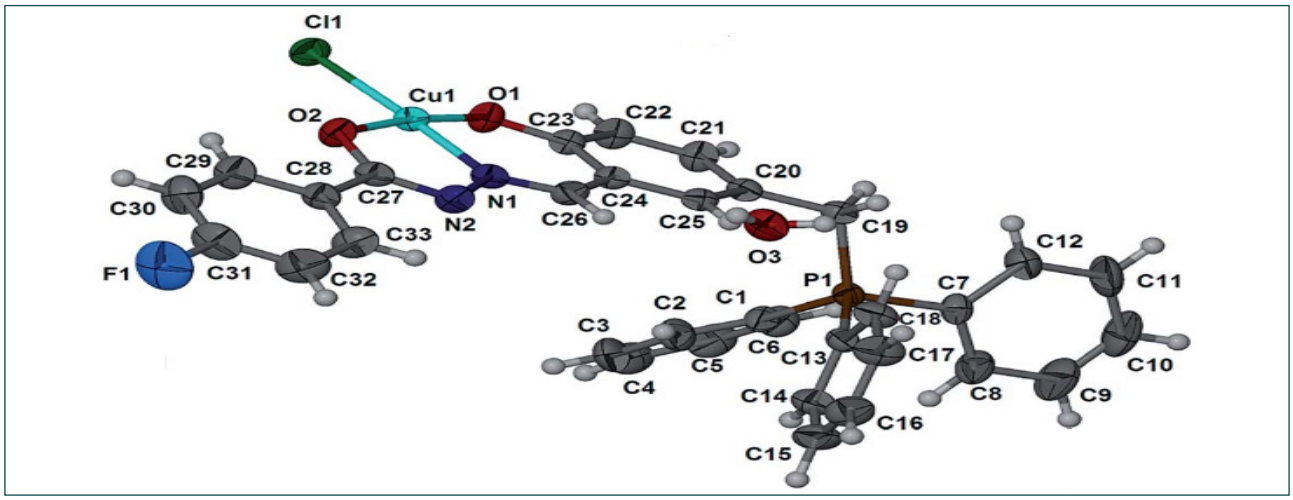

Figure.1. The crystal structure of the Cu complex with DNA binding properties

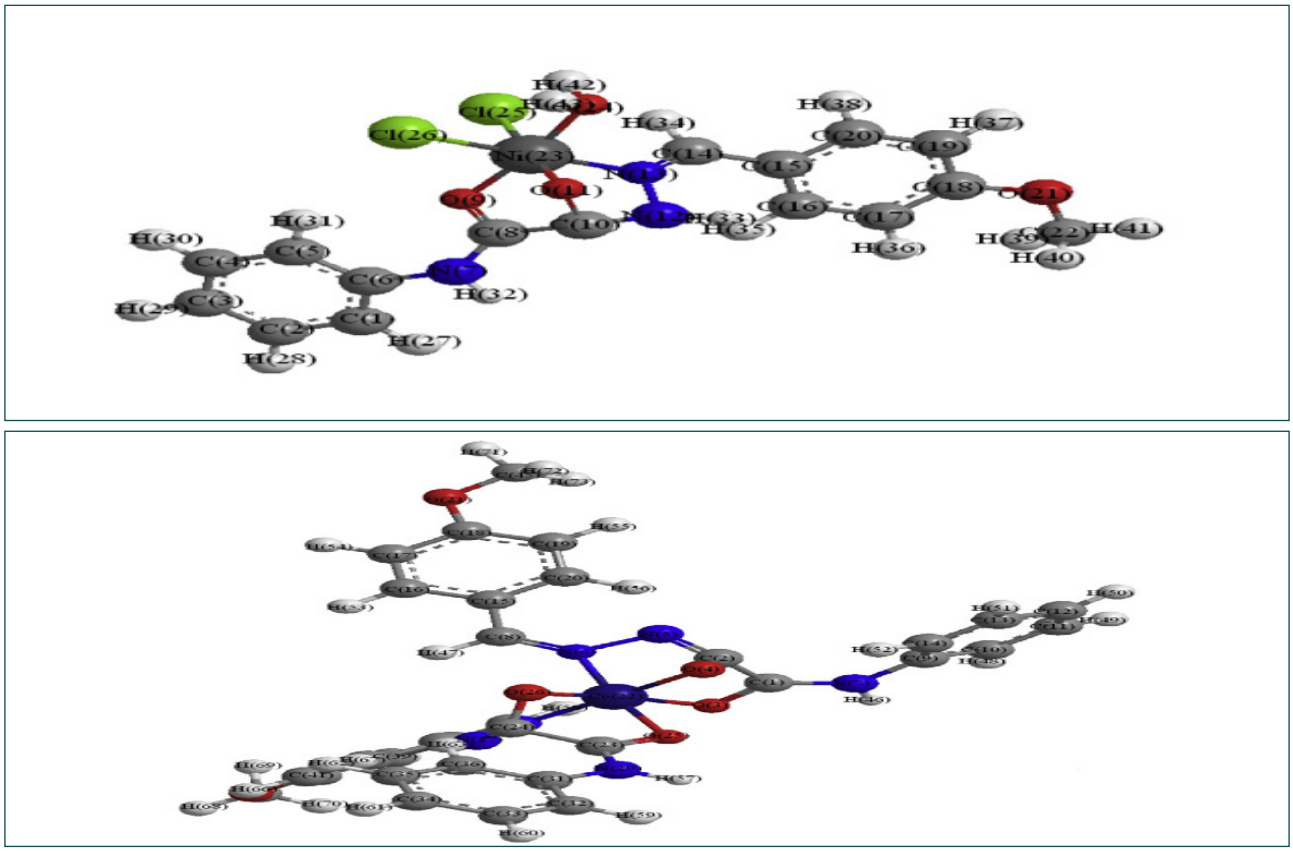

Figure.2. The crystal structure of the complexes with antibacterial properties (a:Ni, b: Co)

Until recently, transition metal hydrazone complexes have been acknowledged to provide good models for explaining their prospective therapeutic uses. In addition, the anticancer activity of a range of substituted hydrazones has been reported, with some encouraging findings. Hydrazone complexes have been discovered to enhance the selectivity of certain specific anticancer drugs by creating drug carrier systems [23]. It has been shown in some literature that the biological activity, particularly relevant for anticancer activity, of ligands alone, was lower than that of hydrazone copper complexes. Many copper complexes have recently been created, and many have shown promising anticancer action. These studies offered an overview of copper-based anticancer drugs with hydrazone ligands.

Copper is a bio-essential metal that may be used as a structural and catalytic cofactor in all living organisms. As a result, it plays a crucial role in organism function, redox chemistry, developmental pathways, and growth [24]. Brain, breast, and prostate cancer tissues absorb more copper than normal tissues [25-27]. Many copper-based anticancer treatments have been studied as potential anticancer drugs [28-30]. Copper's homeostasis and metabolism are essential in many human cancers, making it one of these valuable metals. Copper levels in cancer patients' tumor tissues are significantly greater than normal tissue [31]. Another benefit of copper metal is that it affects malignant cells' metabolism and has a different reaction to tumors than healthy cells [32]. Copper complexes have shown outstanding potential and are being studied as viable replacements to platinum medications in this field [33]. Schiff base copper complexes may enhance intracellular reactive oxygen species via binding to DNA or damaging DNA, activate the mitochondrial pathway, and induce caspase-dependent apoptosis [34-36]. The durability of Schiff's

base compounds relies on the intensity and conjugate base of the azomethine group and steric effects, which rely on the substituents. Hydrazones are made by reacting aldehydes with hydrazines in analytical chemistry. They may create alternative complexes with metal cations such as Fe(III), Cu(II), and Zn(II) and may coordinate in the form of monoanionic, dianionic, or neutral [37]. Hydrazonemolecules with ONO and NNO donor atoms have been presented in coordination chemistry such as (E)-N'-(2-hydroxybenzylidene)benzohydrazide and (E)-N'-(pyridine-2-ylmethylene)benzohydrazide. Hydrazones have antioxidant, antibacterial, antifungal, anticancer, antitubercular, and anti-inflammatory physiological and biological properties [38]. Copper, cobalt, and nickel Schiff base complexes formed from hydrazones have attracted much attention. Due to their structural variety and numerous applications, Schiff base complexes have remained one of the most popular stereo-chemical models in transition-metal coordination chemistry. Copper complexes may induce the production of reactive oxygen species (ROS) in human cells [39]. For instance, they may accumulate in malignant cells due to their preferential membrane permeability to copper compounds. For instance, they may accumulate in malignant cells due to their membranes' preferential permeability to copper compounds. Also, copper (II) complexes are extensively used in metal-mediated DNA cleavage for producing activated oxygen species [40-42]. The anticancer effect of metal complexes derived from hydrazones, such as nickel, cobalt, and copper complexes, has been reviewed in many recent publications. Various hydrazone derivatives were also synthesized and evaluated for antibacterial effectiveness against Gram-negative and Gram-positive bacteria [43]. The compounds' cytotoxic effects on AGS and SW742 cancer cell lines were examined [44-46].

Evaluation of the anticancer activity of Copper (II) complexes based on cytotoxicity assay

Targeting tumor cells to inhibit their proliferation with anticancer drugs is dependent on various factors [47]. Different methods can be used to assess the cytotoxicity of copper complexes based on the Schiff base hydrazone ligand as a transition metal. MTT assay is essential for determining the cell viability of cell lines in various drug concentrations and determining the IC50 of the desired drug [48]. The half-maximal inhibitory concentration IC50 is an essential value for determining a drug's efficacy. It demonstrates how much drug is required to inhibit a biological process by half. A low IC50 value indicates that the drug is less likely to cause side effects and more effective treatment [44, 45]. This section reviews articles investigating the cytotoxicity of various Copper (II) hydrazone Schiff base complexes on various cancer cell lines.

Copper (II) complexes based on quinoline-derived Schiff-base ligands show anticancer activity and non-covalent interactions with HSA in the C1–C3 complexes via sub-domain IIA and IIIA cavities. Kun Hu et al. studied synthesis, characterization, HSA/DNA binding ability, and anticancer effectiveness of copper complexes. Chemical complexes C2 and C3 demonstrated stronger antiproliferative activities against HeLa cells than C1, indicating that benzocaine's medicinal chemical was more effective than 4-aminobenzoic acid methyl ester in enhancing anticancer activity. The complexes bind to DNA and fit well into the curved contour of the target DNA in the minor groove region [46]. HSA fluorescence has a significant dampening ability and a high binding activity. The complexes showed less cytotoxicity in normal HL-7702 cell lines, implying that they are more effective on HeLa cells. According to mechanistic studies, C3 may affect the interpretation of CDKs and cyclins and capture the cell cycle during the G0/G1 phase [49]. C3 can activate the Bcl-2 protein family while causing apoptosis in HeLa cells through ROS-mediated mitochondrial pathways [50]. Adding active medications to ligands may enhance the biological effects of copper complexes containing quinoline-derived Schiff bases, according to DNA/HSA affinity and cell cytotoxicity [46]. Shanshan Shen et al. studied the synthesis, characterization, and anticancer properties of transition metal complexes containing a nicotinohydrazone ligand to create efficient anticancer medications [51]. According to Annexin V/PI staining and western blot analysis, the complexes have a

significant cytotoxic effect on three cancer cell lines and induce apoptosis in cancer cells. This research aimed to find a new therapy for non-small cell lung cancer [51]. Furthermore, whereas L-Cu and L-Zn complexes had a substantial cytotoxic effect on the A549 cell line, they were ineffective on the healthy lung cell line BEAS2B even at greater doses [52]. When their other benefits are considered, these chemicals, which work selectively against A549 cancer cells, have the potential to be excellent anticancer medications [52]. Qian Zhang and colleagues studied a wide range of physiologically active porphyrin and hydrazine Schiff base ligands. Three Cu(II) complexes were shown to have a strong affinity for calf thymus DNA. The cytotoxicity of the complexes and ligands against several cancer cells (A549, H-1975, HepG2, and T47D) was also studied. According to the findings of this study, the complexes had a stronger cytotoxic impact than the ligands. Furthermore, another study examined the cytotoxicity of ligands and complexes against the normal cell line Hs 578Bst, and complexes were found to be less dangerous than ligands [53]. Sulekh Chandra and colleagues studied Ni(II) complexes with hydrazine carboxamide, 2-[3-methyl-2-thienylmethylene]. These complexes were characterized and assessed their inhibitory potential using spectroscopic methods [54]. Khlood Abou-Melha synthesized a Schiff base N-allyl-2-(2,4dinitrophenyl) hydrazine-1-carbothioamide ligand and their metal complexes. Spectral analysis was used to characterize these complexes. The Cu(II) complex had square planar structures, whereas the Co(II), Ni(II), and Cd(III) complexes were octahedral. This author also looked into antioxidant and anticancer activity of complexes, which revealed that Schiff base and four metal complexes are very active in cancer cell death [55]. Fathy A. El-Saied et al. created Schiff bases hydrazone-oxime ligands from 3-(hydroxyimino) butan-2-one by condensation of acetohydrazide and pyridylhydrazide. The architectures of the Cu(II), Ni(II), and Co(II) complexes have been discovered through spectral studies. The novel complexes' in vitro effectiveness against three human cell lines was verified. The complexes' cytotoxic activity was compared to the anticancer medication doxorubicin [56]. Elif Eda Sengul et al. studied the consequences of DNA binding and cleavage of several copper complexes. All chemicals, according to UV-vis spectroscopy data, may be coupled to DNA via intercalation mode. Electrophoresis experiments revealed that these chemicals have concentration-dependent cleavage activity on plasmid DNA in the absence and presence of hydrogen peroxide [57]. Ummuhan O. Ozdemir et al. synthesised N-acetyl butane sulfonic acid hydrazide and its Cu(II) complex $[Cu(Absh)_2(CH_3COO)_2]$. The spectrometric methods (^1H–^{13}C NMR, FT-IR, LC-MS), thermal analysis, magnetic susceptibility, and conductivity tests were used to characterize the chemical. The complex showed one irreversible reduction and one irreversible oxidation potential and half-wave reduction [58]. The anticancer effects of Schiff base ligands derived from hydrazone (HL= (E)-N'-(pyridin-2-ylmethylene)benzohydrazide) were compared to those of a synthetic Copper (II) complex with HL. Human gastric cancer (AGS) and human colon cancer (SW742) cell lines were tested using the MTT assay. Increasing the Copper (II) complex with HL resulted in a stronger cytotoxicity effect on cancer cell lines, reducing cell viability [59]. Higher Copper (II) complex activity may be connected to a reduction in metal ion polarity due to positive charge partial sharing of the metal ion with donor groups. It can penetrate delocalization over the entire ring. As a result, the complex's lipophilicity increases, allowing it to penetrate cell plasma membranes [60, 61]. Patel et al. produced copper (II) hydrazone complexes using (Z)-2-(phenyl(2-(pyridin-2-yl)hydrazono)methyl pyridine (L) and tested their anticancer capabilities. Complex 1 is mononuclear, whereas the solid-state structure of complex 2 contains a mixture of co-crystals of the mono- and binuclear complexes 2a, $[Cu(L)(H_2O)(SO_4)]$, and 2b, $[Cu_2(L)_2(l\text{-}SO_4)_2]$. Using MTT assay for evaluating the anticancer activity of the ligand HL against four human cancer cell lines, including IMR 32 (neuroblastomas), MCF 7 (breast tumors), HepG2 (hepatocellular carcinoma), and A549 (lung cells) revealed that the IC50 values of complexes 1 and 2 effectively killed selected cell lines, particularly HepG2

[62]. Copper compounds have cytotoxic potential due to the transition between Cu(II) and Cu(I) ions, producing superoxide and hydroxyl radicals and inducing cell death. In addition, antiproliferative experiments revealed a similarity in the logGI50 of a copper complex with cisplatin and doxorubicin [63]. The anticancer effects of three copper (II) complexes ($Cu(L)_2$, [Cu(L)(bpy)(H_2O)] NO_3, and [Cu(L)(Phen)(H_2O)] NO_3) on MCF-7 (human breast cancer) cell lines demonstrated that complex cytotoxicity was greater than metal-free ligand, showing the importance of Cu(II) in cell death. The third complex had the highest activity in cell death due to the strong DNA binding ability of the planar "phen" co-ligand and deeper insertion between the DNA base pairs. Copper (II) complexes caused morphological alterations such as cell detachment and shrinking. Furthermore, lipid peroxidation and glutathione depletion were examined to better understand the complexes' mechanism of action, which demonstrated a substantial role for ROS generation in cytotoxicity [64]. Chang et al. studied the anticancer activity of Cu(II), Zn(II), and Cd(II) complexes with isonicotinohydrazide-derived hydrazone Schiff base on human lung cancer (A549) and human gastric cancer (SGC7901 and BGC823) cell lines. In the A549 cell line, it lowered the antiapoptotic factor Bcl-2 while enhancing the pro-apoptotic proteins Bax and caspase-3 [65]. Ebrahimipour et al. studied the antitumor activity of tridentate ONO ligand (E)-N'-((2-hydroxynaphthalen-1-yl) methylene) acetohydrazide [HL] and its cationic Cu(II) complex [Cu(L)(H_2O)]NO_3 on human breast cancer (MCF-7) and discovered that copper has a better anticancer function than ligand [66]. The production of Cu(L)(H2O)(NO3) and assessment of its cytotoxicity indicated that it has a significant impact in the cell death of the human skin carcinoma cell line A431. However, as compared to standard medications like cisplatin or doxorubicin, this compound is slightly less effective [67].

Table 1. A review of studies on the anticancer effect of copper complexes

Compound	cell line	IC_{50} value	reference
$Cu(L1)(NO_3)_2$ $Cu(L2)Cl_2$ $(Cu(L2)SO_4)_2 \cdot H_2O$	HeLa HeLa HeLa	18.72 ± 1.03 15.76 ± 1.19 9.98 ± 0.87	[46]
$Cu(penh)_2$	A549 BGC823 Eca109	7.3 9.7 6.5	[51]
$Na[CuL(H_2O)]H_2O$	A549	12	[68]
CuP1	A549 H-1975 HepG2 T47D	18.82 17.34 13.62 34.51	[68]
CuP2	A549 H-1975 HepG2 T47D	14.64 13.52 26.98 43.81	[53]
CuP3	A549 H-1975 HepG2 T47D	19.16 17.07 27.85 31.68	[53]
Cu(II) complex	HePG2	26.71±0.28	[55]
$Cu(HL)_2$	MCF-7 Hep-G2 HL-60	28.9 ± 2.10 5.8 ± 0.71 62.1 ± 18.91	[55]

$Cu(HL)(NO_3)$	MCF-7 Hep-G2 HL-60	2.5 ± 0.31 53.7 ± 8.26 3.8 ± 0.71	[55]
$[Cu(L)_2].0.5H_2O$	MCF-7 Hep-G2 HL-60	18.7 ± 2.10 66.2 ± 15.81 41.2 ± 13.71	[56]
$Cu(L)(NO_3)$	MCF-7 Hep-G2 HL-60	8.9 ± 1.00 43.8 ± 12.80 55.2 ± 17.36	[56]
Doxorubicin	MCF-7 Hep-G2 HL-60	2.1 ± 0.30 0.7 ± 0.02 12.1 ± 3.81	[56]
$Cu[L_2(CH3COO)_2]$	MCF-7	8.01	[58]
Cu(L)(Cl)2	MCF 7 IMR 32 HepG2 A549	105.6236 112.6543 101.209 119.194	[62]
[Cu2(L)2(l-SO4)2]	MCF-7	184.2575	[62]
[Cu(L)(H2O)(SO4)]2	IMR 32 HepG2 A549	207.68 168.6424 174.107	[62]
$[Cu_4(L)_4Cl_4]\cdot H_2O$	A549 BGC-823 SGC-7901	3.6 4.5 2.3	[69]
$Cu(Van\text{-}val)(pz)_2Sn(CH_3)_2(H2O)_2$	HepG2	6.2 ± 0.10	[70]
[CuL]Cl	A549 PC-3 MRC-5	>30 16.6 ±3.1 >30	[70]
[Cu(phen)L]Cl	A549 PC-3 MRC-5	4.2 ± 0.8 3.2 ± 0.2 5.1 ± 0.3	[71]
[Cu(dbpy)L]Cl	A549 PC-3 MRC-5	6.7 ± 1.7 4.6 ± 0.5 4.9 ± 0.1	[71]
$Cu(L)(H_2O)(NO_3)$	A431	78.7 ± 0.53	[72]
Doxorubicin	A431	27.6 ± 0.58	[72]

3. Mechanisms underlying the anticancer effects of the copper complexes

Copper (II) Schiff base complexes have anticancer properties through various processes, including cell cycle arrest, apoptosis, and autophagy, leading to cell death. Copper complexes release anticancer action by causing DNA damage, generating ROS, inhibiting topoisomerase, and changing the expression level of molecules involved in the cell cycle, apoptosis, and autophagy activation or inhibition [73, 74] (Fig.3).

3.1. Cell cycle arrest

The cell cycle is a series of interconnected activities that enable a cell to grow and reproduce. Kinases and phosphatases are primary proteins involved in cell cycle progression. Cyclin-dependent kinases (Cdks) are essential kinases activated by cyclins and play an important role in cell cycle checkpoints. G1/S transition, G2/M, and mitotic spindles are three checkpoints that ensure proper

cell cycle progression [75]. Cancer cells disrupt the cell cycle and uncontrollably reproduce cells with defective DNA. Cell cycle arrest is a stage in the cell cycle in which the cell is no longer active in replication and division to repair the damage. As a result, blocking cell cycle checkpoints before DNA repair may initiate an apoptotic cascade, ending in cell death [76]. The anticancer impact of [Cu(L2)SO4]2H2O based on quinoline-derived Schiff base ligand on HeLa cells was obtained in a concentration-dependent manner by lowering CDK2, cyclins D1 and E1, and cell cycle arrest in G0/G1-phase [77]. Cu(BrHAP)2 Schiff base compound also prevented HT-29 cells from entering the S phase, as demonstrated by an increase in G1 cell population after 24 and 48h [78]. Flow cytometry analysis of MDA-MB-231 cells treated with complexes [Cu(R-L 2)2]·EtOAc and [Cu(S-L 2)2]·EtOAc at a dose of 15 μM increased the number of cells in the G2/M phase compared to the G0/G1 and S phases, indicating G2/M arrest [79]. [N,N' -bis(2' -hydroxyphenylacetone) - o -ethanediamine] copper complex inhibited cell proliferation by inhibiting DNA synthesis and increasing p21 protein expression level in a time and dose-dependent manner [73].

3.2. Apoptosis promotion

Schiff base Copper (II) compounds can trigger apoptosis by targeting proteins involved in apoptosis pathways while also producing ROS to boost ROS-mediated mitochondrial apoptosis pathways [80]. External signals that enter the cell via transmembrane death receptors, such as tumor necrosis factor, activate the extrinsic route (TNF) [81]. The intrinsic or mitochondrial-dependent signaling pathway affects the inner mitochondrial membrane, leading the mitochondria to lose transmembrane potential and permeability and release proapoptotic chemicals into the cytosol, including cytochrome c, Smac/DIABLO, and HtrA2/Omi [82]. P53 is another proapoptotic protein that pauses the cell cycle at the G1/S phase to detect DNA damage. If the DNA damage is irreparable, p53 directs the cell to apoptosis via the intrinsic pathway [83]. Caspase is a protein family essential for a cell to die. They are classified into three groups: initiators (caspases-8, -9, and -10), effectors (caspases-3, -6, -7), and inflammatory caspases (caspases-1, -4, and -5) [84]. Apoptosis is connected with morphological alterations such as DNA segregation, chromatin condensation, shrinkage, membrane blebbing, and organelle packing [85]. The protein family B-cell lymphoma-2 (BCL-2) regulates cell apoptosis. Some of them (for example, BAX and BAK) promote cell death, whereas others (for example, Bcl-2 and BCL-XL) have an antiapoptotic impact [86]. According to a study conducted by Kun Hu et al., copper (II) complexes based on Schiff-base ligands can lower mitochondrial membrane potential (MMP), increase oxidative damage, upregulate BAX, and downregulate Bcl-2 in HeLa cells to promote apoptosis in a dose-dependent way [77]. In a study on two separate gastric cancer cell lines, these complexes inhibited NF-B signaling, reduced Bcl-2, produced ROS, increased Bax, activated caspase-3, and cleaved PARP-1 in a time-dependent manner. Blebbing and chromatin condensation after 24 and 48 hours of treatment and late apoptosis after 72 hours also revealed the morphology of treated cancer cells [87]. Furthermore, the copper complex induces apoptosis in a colon cancer cell line by boosting ROS and, as a result, lowering MMP and cytochrome c levels in mitochondria and activating caspases 3/7 [78]. The production of [Cu4(L)4Cl4]5H2O and in vitro apoptosis testing of the complex against the SGC7901 cell line revealed that it increases BAX and p53 while decreasing Bcl-2 [88]. Treating Eca-109 cells with [Cu(sal-trp)(phen)]•0.5H2O•0.5CH2Cl2•CH3OH caused apoptosis by mitochondrial dysfunction, generation of ROS, upregulation of Bad and Bax, and downregulation of Bcl-2 and Bcl-xL [74].

3.3. DNA damage

Copper complexes based on Schiff base ligands can bind to the DNA and cleave it to block replication, cause DNA damage, cell cycle arrest, and apoptosis. For example, in an investigation, Schiff base copper (II) complexes increased DNA damage and repair marker γH2AX in both time and dose-dependent manners and p-Chk1/2 (checkpoint kinase 1/2) after 8 hours in HeLa cells. These findings indicate the DNA damage and DNA damage response induction of copper complexes [89].

In the presence of H2O2, DNA breakage was observed in four chiral mononuclear copper (II) complexes with mono-anionic bidentate Schiff-base ligands. They can all produce ROS and employ them to promote apoptosis and DNA cleavage [90].

Topoisomerases are enzymes necessary for proper DNA replication, recombination, and repair. They break DNA strands to prevent overwound or underwound DNA structure during replication or transcription. There are two types of topoisomerase enzymes: type I, which cleaves single-strand DNA, and type II, which cleaves two DNA strands and decatenates DNA [91]. Topoisomerase inhibitors cause DNA damage, inhibit DNA synthesis, arrest tumor cell proliferation and promote apoptosis [92]. Chew et al. demonstrated that copper (II) complexes based on hydrazone ligand could block topoisomerase I by binding to the enzyme and DNA in human lung cancer cell lines (A549) and human prostate adenocarcinoma cell line (PC-3) [71]. Studies revealed that the tridentate chiral Schiff base copper complexes (C21H31N5O6CuSn and Cu(Van- Val)(Pz)2Sn(CH3)2(H2O)2]) can inhibit Topoisomerase I by binding to the major groove of DNA and as a result, DNA damage and cancer cell apoptosis on Hepatoma HuH7 and Hepatoma HepG2 cell lines [70, 93]. However, Schiff-based ligands have shown topoisomerase inhibitory action against cancer cell lines in two studies, but when combined with copper, no anticancer activity by topoisomerase inhibition was observed [94, 95].

3.4. Autophagy

Autophagy reduces cell survival and promotes cell death in cancer cells, inhibiting carcinogenesis. The autophagy pathway begins with the suppression of mTORC1 (one of the Mammalian targets of rapamycin (mTOR) complexes) and the activation of the Unc-51-like autophagy-activating kinase (ULK) complex [96]. Beclin-1 recruits many proteins involved in autophagosome formation and elongation, followed by LC3I to LC3II conversion, resulting in autophagosome-lysosome fusion and autophagolysosome formation [97, 98]. Jianfang Dong et al. synthesized [Cu(sal-trp)(phen)]•0.5H2O•0.5CH2Cl2•CH3OH complex and treated the Eca-109 cells with it. They observed the autophagosome of cancer cells induced by p62 and LC3BI downregulation and Beclin-1 and LC3BII upregulation [74]. Furthermore, autophagy was promoted in gastric cancer cells treated with Schiff base copper coordinated compound (SBCCC) in a time-dependent manner [87]. Nazanin Kordestan et al. synthesized cop-

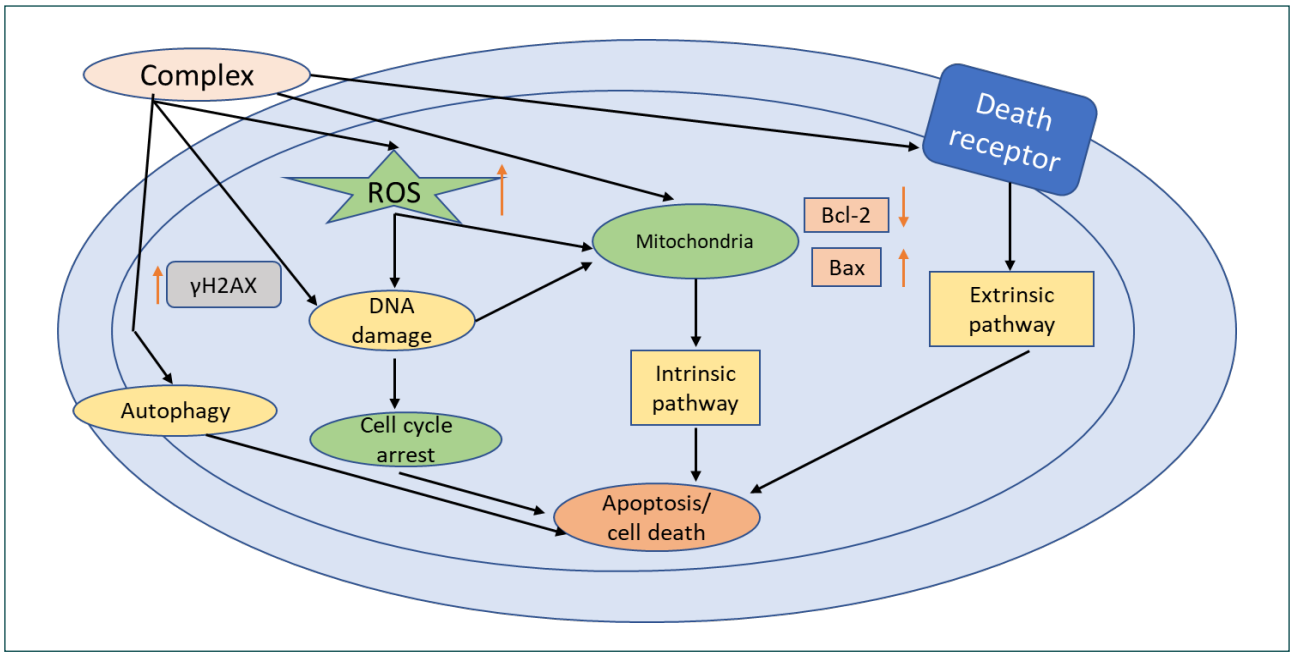

Figure.3. The general anticancer mechanism of Cu complexes

per complexes with tridentate halogen-substituted Schiff base ligand L1 (containing a 2-pycolylamine-type motif), including Cu(BrCl-L1)Cl, Cu(Cl2-L1)NO3, Cu(Br2- L1) Cl, and Cu(Cl2-L1)Cl. They exposed the A2780 cell line to IC50 concentrations of manufactured complexes and found that treated cancer cells with Cu(BrCl-L1)Cl and Cu(Cl2-L1)NO3 had a significantly higher autophagic cell number [99].

Conclusion

Schiff bases and their metal complexes are among the most significant chemical compounds, sharing many substances' structural variety and active medicinal agent characteristics. This review intended to highlight the anticancer potential of Schiff base Copper (II) hydrazone complexes. These complexes, in general, have a promising future as anticancer medicines. However, more research into these compounds' side effects and lipophilicity is needed to ensure their efficacy in cancer therapy.

REFERENCES

1. Martínez Andrade KA, Lauritano C, Romano G, Ianora A. Marine microalgae with anti-cancer properties. Marine drugs. 2018;16(5):165.
2. Abdolmaleki A, Asadi A, Gurushankar K, Shayan TK, Sarvestani FA. Importance of nano medicine and new drug therapies for cancer. Advanced Pharmaceutical Bulletin. 2021;11(3):450.
3. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5):e1S-e29S.
4. French SA, Story M, Neumark-Sztainer D, Fulkerson JA, Hannan P. Fast food restaurant use among adolescents: associations with nutrient intake, food choices and behavioral and psychosocial variables. International journal of obesity. 2001;25(12):1823-33.
5. Suzen S, Tekiner-Gulbas B, Shirinzadeh H, Uslu D, Gurer-Orhan H, Gumustas M, et al. Antioxidant activity of indole-based melatonin analogues in erythrocytes and their voltammetric characterization. Journal of Enzyme Inhibition and Medicinal Chemistry. 2013;28(6):1143-55.
6. Hossain MS, Sarker S, Shaheed AE, Hossain MM, Alim-Al-Bari A, Karim MR, et al. Thermal and Spectral Characterization of Cr (III), Co (II) and Cd (II) Metal Complexes Containing Bis-Imine Novel Schiff Base Ligand Towards Potential Biological Application. Chemical and Biomolecular Engineering. 2017;2(1):41-50.
7. Shaabani B, Khandar AA, Mobaiyen H, Ramazani N, Balula SS, Cunha-Silva L. Novel pseudohalide-bridged Cu (II) complexes with a hydrazone ligand: Evaluation of antimicrobial activity. Polyhedron. 2014;80:166-72.
8. Muthu V, Mylliemngap B, Prasad KT, Behera D, Singh N. Adverse effects observed in lung cancer patients undergoing first-line chemotherapy and effectiveness of supportive care drugs in a resource-limited setting. Lung India: Official Organ of Indian Chest Society. 2019;36(1):32.
9. Mo Q, Deng J, Liu Y, Huang G, Li Z, Yu P, et al. Mixed-ligand Cu (II) hydrazone complexes designed to enhance anticancer activity. 2018;156:368-80.
10. Abd-Elzaher MM, Labib AA, Mousa HA, Moustafa SA, Ali MM, El-Rashedy AAJb-sujob, et al. Synthesis, anticancer activity and molecular docking study of Schiff base complexes containing thiazole moiety. 2016;5(1):85-96.
11. Mo Q, Deng J, Liu Y, Huang G, Li Z, Yu P, et al. Mixed-ligand Cu (II) hydrazone complexes designed to enhance anticancer activity. European Journal of Medicinal Chemistry. 2018;156:368-80.
12. Hosseini-Yazdi SA, Mirzaahmadi A, Khandar AA, Eigner V, Dušek M, Lotfipour F, et al. Synthesis, characterization and in vitro biological activities of new water-soluble copper (II), zinc (II), and nickel (II) complexes with sulfonato-substituted Schiff base ligand. Inorganica Chimica Acta. 2017;458:171-80.
13. Gönül İ. Synthesis and structural characterization of ONO type tridentate ligands and their Co (II) and Ni (II) complexes: Investigation of electrical conductivity and antioxidant properties. Inorganica Chimica Acta. 2019;495:119027.
14. Bitu MNA, Hossain MS, Zahid A, Zakaria C, Kudrat-E-Zahan M. Anti-pathogenic activity of cu (II) complexes incorporating Schiff bases: a short review. American Journal of Heterocyclic Chemistry. 2019;5(1):11-23.
15. Abu-Dief AM, Nassr LA. Tailoring, physicochemical characterization, antibacterial and DNA binding mode studies of Cu (II) Schiff bases amino acid bioactive agents incorporating 5-bromo-2-hydroxybenzaldehyde. Journal of the Iranian Chemical Society. 2015;12(6):943-55.
16. Anacona JR, Noriega N, Camus J. Synthesis, characterization and antibacterial activity of a tridentate Schiff base derived from cephalothin and sulfadiazine, and its transition metal complexes. Spectrochim Acta A Mol Biomol Spectrosc. 2015;137:16-22.
17. Lazny R, Nodzewska A. N, N-dialkylhydrazones in organic synthesis. From simple N, N-dimethylhydrazones to supported chiral auxiliaries. Chemical Reviews. 2010;110(3):1386-434.
18. Crisalli P, Kool ET. Importance of ortho proton donors in catalysis of hydrazone formation. Organic letters. 2013;15(7):1646-9.
19. Parvarinezhad S, Salehi M. Synthesis, characterization, crystal structures, Hirshfeld surface analysis and DFT computational studies of new Schiff Bases derived from Phenylhydrazine. Journal of Molecular Structure. 2020;1222:128780.
20. Parvarinezhad S, Salehi M. Synthesis, characterization, anti-proliferative activity and chemistry computation of DFT theoretical methods of hydrazine-based Schiff bases derived from methyl acetoacetate and α-hydroxyacetophenone. Journal of Molecular Structure. 2021;1225:129086.
21. Ye W-l, Zhao Y-p, Li H-q, Na R, Li F, Mei Q-b, et al. Doxorubicin-poly (ethylene glycol)-alendronate self-assembled micelles for targeted therapy of bone metastatic cancer. Scientific reports. 2015;5(1):1-19.
22. Ji H, Ni H-q, Zhi P, Xi Z-w, Wang W, Shi J-j, et al. Visible-light mediated directed perfluoroalkylation of hydrazones. Organic & Biomolecular Chemistry. 2017;15(28):6014-23.
23. Bae Y, Nishiyama N, Fukushima S, Koyama H, Yasuhiro M, Kataoka K. Preparation and biological characterization of polymeric

micelle drug carriers with intracellular pH-triggered drug release property: tumor permeability, controlled subcellular drug distribution, and enhanced in vivo antitumor efficacy. Bioconjugate chemistry. 2005;16(1):122-30.
24. Tisato F, Marzano C, Porchia M, Pellei M, Santini C. Copper in diseases and treatments, and copper-based anticancer strategies. Medicinal research reviews. 2010;30(4):708-49.
25. Zhang Z, Yu P, Gou Y, Zhang J, Li S, Cai M, et al. Novel brain-tumor-inhibiting copper (II) compound based on a human serum albumin (HSA)-cell penetrating peptide conjugate. Journal of Medicinal Chemistry. 2019;62(23):10630-44.
26. Chen D, Peng F, Cui QC, Daniel KG, Orlu S, Liu J, et al. Inhibition of prostate cancer cellular proteasome activity by a pyrrolidine dithiocarbamate-copper complex is associated with suppression of proliferation and induction of apoptosis. Front Biosci. 2005;10(1-3):2932-9.
27. Balsa LM, Ruiz MC, de la Parra LSM, Baran EJ, León IE. Anticancer and antimetastatic activity of copper (II)-tropolone complex against human breast cancer cells, breast multicellular spheroids and mammospheres. Journal of Inorganic Biochemistry. 2020;204:110975.
28. Aslan HG, Akkoç S, Kökbudak Z, Aydın L. Synthesis, characterization, and antimicrobial and catalytic activity of a new Schiff base and its metal (II) complexes. Journal of the Iranian Chemical Society. 2017;14(11):2263-73.
29. Bal S, Orhan B, Connolly JD, Dığrak M, Köytepe S. Synthesis and characterization of some Schiff bases, their metal complexes and thermal, antimicrobial and catalytic features. Journal of Thermal Analysis and Calorimetry. 2015;121(2):909-17.
30. Dhayabaran V, Prakash TD, Renganathan R, Friehs E, Bahnemann DW. Novel Bioactive Co (II), Cu (II), Ni (II) and Zn (II) Complexes with Schiff base ligand derived from histidine and 1, 3-Indandione: synthesis, structural elucidation, biological investigation and Docking analysis. Journal of fluorescence. 2017;27(1):135-50.
31. Diez M, Arroyo M, Cerdan F, Munoz M, Martin M, Balibrea J. Serum and tissue trace metal levels in lung cancer. Oncology. 1989;46(4):230-4.
32. Shanbhag VC, Gudekar N, Jasmer K, Papageorgiou C, Singh K, Petris MJ. Copper metabolism as a unique vulnerability in cancer. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2021;1868(2):118893.
33. Marzano C, Pellei M, Tisato F, Santini C. Copper complexes as anticancer agents. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents). 2009;9(2):185-211.
34. Kesavan M, Kumar GV, Raja JD, Anitha K, Karthikeyan S, Rajesh J. DNA interaction, antimicrobial, antioxidant and anticancer studies on Cu (II) complexes of Luotonin A. Journal of Photochemistry and Photobiology B: Biology. 2017;167:20-8.
35. Bao X, Xue Y, Xia C, Lu Y, Yang N, Zhao Y. Synthesis and assessment of novel anti-chlamydial benzylidene acylhydrazides derivatives. Letters in Drug Design & Discovery. 2018;15(1):31-6.
36. Hrušková K, Potůčková E, Hergeselová T, Liptáková L, Hašková P, Mingas P, et al. Aroylhydrazone iron chelators: Tuning antioxidant and antiproliferative properties by hydrazide modifications. European journal of medicinal chemistry. 2016;120:97-110.
37. Codd R. Traversing the coordination chemistry and chemical biology of hydroxamic acids. Coordination Chemistry Reviews. 2008;252(12-14):1387-408.
38. Kaplánek R, Havlík M, Dolenský B, Rak J, Džubák P, Konečný P, et al. Synthesis and biological activity evaluation of hydrazone derivatives based on a Tröger's base skeleton. Bioorganic & medicinal chemistry. 2015;23(7):1651-9.
39. Guo W-j, Ye S-s, Cao N, Huang J, Gao J, Chen Q-y. ROS-mediated autophagy was involved in cancer cell death induced by novel copper (II) complex. Experimental and Toxicologic Pathology. 2010;62(5):577-82.
40. Gou Y, Zhang Y, Zhang Z, Wang J, Zhou Z, Liang H, et al. Design of an anticancer copper (II) prodrug based on the Lys199 residue of the active targeting human serum albumin nanoparticle carrier. Molecular Pharmaceutics. 2017;14(6):1861-73.
41. Lian W-J, Wang X-T, Xie C-Z, Tian H, Song X-Q, Pan H-T, et al. Mixed-ligand copper (II) Schiff base complexes: the role of the co-ligand in DNA binding, DNA cleavage, protein binding and cytotoxicity. Dalton Transactions. 2016;45(22):9073-87.
42. Jia L, Xu J, Zhao X, Shen S, Zhou T, Xu Z, et al. Synthesis, characterization, and antitumor activity of three ternary dinuclear copper (II) complexes with a reduced Schiff base ligand and diimine coligands in vitro and in vivo. Journal of inorganic biochemistry. 2016;159:107-19.
43. Singh P, Meena AK, Singh R, Singh J. Synthesis of 2-(3, 4-Dichloro-Benzoyl)-Benzoic acid Hydrazide derivatives and assessment of antimicrobial efficacy against E. coli and B. Subtilis WJPR. 2019;8(13):857-69.
44. He Y, Zhu Q, Chen M, Huang Q, Wang W, Li Q, et al. The changing 50% inhibitory concentration (IC50) of cisplatin: A pilot study on the artifacts of the MTT assay and the precise measurement of density-dependent chemoresistance in ovarian cancer. Oncotarget. 2016;7(43):70803.
45. Ndagi U, Mhlongo N, Soliman M. Metal complexes in cancer therapy-an update from drug design perspective. Drug Des Devel Ther 11: 599–616. 2017.
46. Hu K, Liu C, Li J, Liang F. Copper (ii) complexes based on quinoline-derived Schiff-base ligands: Synthesis, characterization, HSA/DNA binding ability, and anticancer activity. Medchemcomm. 2018;9(10):1663-72.
47. Sui X, Chen R, Wang Z, Huang Z, Kong N, Zhang M, et al. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. Cell death & disease. 2013;4(10):e838-e.
48. Meerloo JV, Kaspers GJ, Cloos J. Cell sensitivity assays: the MTT assay. Cancer cell culture: Springer; 2011. p. 237-45.
49. Yang K, Wu Y, Cheng P, Zhang J, Yang C, Pi B, et al. YAP and ERK mediated mechanical strain-induced cell cycle progression through RhoA and cytoskeletal dynamics in rat growth plate chondrocytes. Journal of Orthopaedic Research. 2016;34(7):1121-9.
50. Deng J, Gou Y, Chen W, Fu X, Deng H. The Cu/ligand stoichiometry effect on the coordination behavior of aroyl hydrazone with copper (II): Structure, anticancer activity and anticancer mechanism. Bioorganic & Medicinal Chemistry. 2016;24(10):2190-8.
51. Shen S, Chen H, Zhu T, Ma X, Xu J, Zhu W, et al. Synthesis, characterization and anticancer activities of transition metal complexes with a nicotinohydrazone ligand. Oncology Letters. 2017;13(5):3169-76.
52. DEMİR BS, GÖNÜL İ, ÇELİK GG, İPEKBAYRAK S, SAYGIDEĞER Y. Synthesis and Anticancer Activities of Water Soluble Schiff Base Metal Complexes. Adıyaman University Journal of Science. 2020;10(2):441-54.

53. Zhang Q, Li Z, Liu J. Applying Cu (II) complexes assisted by water-soluble porphyrin to DNA binding and selective anticancer activities. Applied Organometallic Chemistry. 2020;34(10):e5857.
54. Chandra S, Kumar S. Synthesis, spectroscopic, anticancer, antibacterial and antifungal studies of Ni (II) and Cu (II) complexes with hydrazine carboxamide, 2-[3-methyl-2-thienyl methylene]. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 2015;135:356-63.
55. Abou-Melha K. Spectral, modeling and anticancer activity studies on the newly synthesized N-allyl-2-(2, 4-dinitrophenyl) hydrazine-1-carbothioamide and some bivalent metal complexes. Journal of Molecular Structure. 2021;1223:128949.
56. El-Saied FA, Salem TA, Shakdofa MM, Al-Hakimi AN, Radwan AS. Antitumor activity of synthesized and characterized Cu (II), Ni (II) and Co (II) complexes of hydrazone-oxime ligands derived from 3-(hydroxyimino) butan-2-one. Beni-Suef University journal of basic and applied sciences. 2018;7(4):420-9.
57. Şengül EE, Göktürk T, Topkaya CG, Gup R. Synthesis, characterization and dna interaction of Cu (II) complexes with hydrazone-Schiff base ligands bearing alkyl quaternary ammonium salts. Journal of the Chilean Chemical Society. 2020;65(2):4754-8.
58. Özdemir ÜÖ, Aktan E, Ilbiz F, Gündüzalp AB, Özbek N, Sarı M, et al. Characterization, antibacterial, anticarbonic anhydrase II isoenzyme, anticancer, electrochemical and computational studies of sulfonic acid hydrazide derivative and its Cu (II) complex. Inorganica Chimica Acta. 2014;423:194-203.
59. Fekri R, Salehi M, Asadi A, Kubicki M. Synthesis, characterization, anticancer and antibacterial evaluation of Schiff base ligands derived from hydrazone and their transition metal complexes. Inorganica Chimica Acta. 2019;484:245-54.
60. Prasad KS, Kumar LS, Shekar SC, Prasad M, Revanasiddappa HD. Oxovanadium complexes with bidentate N, O ligands: synthesis, characterization, DNA binding, nuclease activity and antimicrobial studies. Chemical Sciences Journal. 2011;12:1-10.
61. Thangadurai TD, Natarajan K. Mixed ligand complexes of ruthenium (II) containing α, β-unsaturated-β-ketoaminesand their antibacterial activity. Transition Metal Chemistry. 2001;26(4):500-4.
62. Patel AK, Jadeja RN, Roy H, Patel R, Patel SK, Butcher RJ, et al. Copper (II) hydrazone complexes with different nuclearities and geometries: Synthesis, structural characterization, antioxidant SOD activity and antiproliferative properties. Polyhedron. 2020;186:114624.
63. Bergamini FR, Nunes JH, de Carvalho MA, Ribeiro MA, de Paiva PP, Banzato TP, et al. Polynuclear copper (II) complexes with nalidixic acid hydrazones: Antiproliferative activity and selectivity assessment over a panel of tumor cells. Inorganica Chimica Acta. 2019;484:491-502.
64. Hussain A, Alajmi M, Rehman MT, Amir S, Husain F, Alsalme A, et al. Copper (II) complexes as potential anticancer and Nonsteroidal anti-inflammatory agents. vitro; 2019.
65. Chang H-Q, Jia L, Xu J, Xu Z-Q, Chen R-H, Wu W-N, et al. Syntheses, characterizations, antitumor activities and cell apoptosis induction of Cu (II), Zn (II) and Cd (II) complexes with hydrazone Schiff base derived from isonicotinohydrazide. Inorganic Chemistry Communications. 2015;57:8-10.
66. Ebrahimipour SY, Sheikhshoaie I, Castro J, Haase W, Mohamadi M, Foro S, et al. A novel cationic copper (II) Schiff base complex: Synthesis, characterization, crystal structure, electrochemical evaluation, anti-cancer activity, and preparation of its metal oxide nanoparticles. Inorganica Chimica Acta. 2015;430:245-52.
67. Biswas N, Saha S, Biswas BK, Chowdhury M, Rahaman A, Junghare V, et al. The DNA-and protein-binding properties and cytotoxicity of a new copper (II) hydrazone Schiff base complex. Journal of Coordination Chemistry. 2021;74(9-10):1482-504.
68. DEMİR BS, GÖNÜL İ, ÇELİK GG, İPEKBAYRAK S, SAYGIDEĞER Y. Synthesis and Anticancer Activities of Water Soluble Schiff Base Metal Complexes. Adıyaman University Journal of Science.10(2):441-54.
69. Chang H-Q, Jia L, Xu J, Xu Z-Q, Chen R-H, Wu W-N, et al. Syntheses, characterizations, antitumor activities and cell apoptosis induction of Cu(II), Zn(II) and Cd(II) complexes with hydrazone Schiff base derived from isonicotinohydrazide. Inorganic Chemistry Communications. 2015;57:8-10.
70. Tabassum S, Asim A, Khan RA, Arjmand F, Rajakumar D, Balaji P, et al. A multifunctional molecular entity CuII–SnIV heterobimetallic complex as a potential cancer chemotherapeutic agent: DNA binding/cleavage, SOD mimetic, topoisomerase Iα inhibitory and in vitro cytotoxic activities. RSC Advances. 2015;5(59):47439-50.
71. Chew ST, Lo KM, Lee SK, Heng MP, Teoh WY, Sim KS, et al. Copper complexes with phosphonium containing hydrazone ligand: topoisomerase inhibition and cytotoxicity study. Eur J Med Chem. 2014;76:397-407.
72. Biswas N, Saha S, Biswas BK, Chowdhury M, Rahaman A, Junghare V, et al. The DNA-and protein-binding properties and cytotoxicity of a new copper (II) hydrazone Schiff base complex. Journal of Coordination Chemistry. 2021:1-23.
73. Bao R-D, Song X-Q, Kong Y-j, Li F-F, Liao W-H, Zhou J, et al. A new Schiff base copper(II) complex induces cancer cell growth inhibition and apoptosis by multiple mechanisms. Journal of Inorganic Biochemistry. 2020;208:111103.
74. Dong J, Li Y, Zhao P, Xu T, Zhang B, Gao L, et al. Synthesis and Biological Evaluation of Six L-tryptophan Schiff base Copper(II) Complexes as Promising Anticancer Agents In Vitro. Journal of Molecular Structure. 2022:132578.
75. Matthews HK, Bertoli C, de Bruin RAM. Cell cycle control in cancer. Nature Reviews Molecular Cell Biology. 2022;23(1):74-88.
76. Roskoski R, Jr. Cyclin-dependent protein serine/threonine kinase inhibitors as anticancer drugs. Pharmacol Res. 2019;139:471-88.
77. Hu K, Liu C, Li J, Liang F. Copper(ii) complexes based on quinoline-derived Schiff-base ligands: synthesis, characterization, HSA/DNA binding ability, and anticancer activity. Medchemcomm. 2018;9(10):1663-72.
78. Hajrezaie M, Paydar M, Zorofchian Moghadamtousi S, Hassandarvish P, Gwaram NS, Zahedifard M, et al. A Schiff Base-Derived Copper (II) Complex Is a Potent Inducer of Apoptosis in Colon Cancer Cells by Activating the Intrinsic Pathway. The Scientific World Journal. 2014;2014:540463.
79. Zhou XQ, Li Y, Zhang DY, Nie Y, Li ZJ, Gu W, et al. Copper complexes based on chiral Schiff-base ligands: DNA/BSA binding ability, DNA cleavage activity, cytotoxicity and mechanism of apoptosis. Eur J Med Chem. 2016;114:244-56.
80. Lian WJ, Wang XT, Xie CZ, Tian H, Song XQ, Pan HT, et al. Mixed-ligand copper(ii) Schiff base complexes: the role of the co-ligand in DNA binding, DNA cleavage, protein binding and cytotoxicity. Dalton Trans. 2016;45(22):9073-87.
81. Kucka K, Wajant H. Receptor Oligomerization and Its Relevance for Signaling by Receptors of the Tumor Necrosis Factor Recep-

tor Superfamily. Frontiers in Cell and Developmental Biology. 2021;8.
82. Urbani A, Prosdocimi E, Carrer A, Checchetto V, Szabò I. Mitochondrial Ion Channels of the Inner Membrane and Their Regulation in Cell Death Signaling. Frontiers in Cell and Developmental Biology. 2021;8.
83. Farmer KM, Ghag G, Puangmalai N, Montalbano M, Bhatt N, Kayed R. P53 aggregation, interactions with tau, and impaired DNA damage response in Alzheimer's disease. Acta Neuropathologica Communications. 2020;8(1):132.
84. Julien O, Wells JA. Caspases and their substrates. Cell Death Differ. 2017;24(8):1380-9.
85. Xu X, Lai Y, Hua Z-C. Apoptosis and apoptotic body: disease message and therapeutic target potentials. Biosci Rep. 2019;39(1):BSR20180992.
86. Kale J, Osterlund EJ, Andrews DW. BCL-2 family proteins: changing partners in the dance towards death. Cell Death & Differentiation. 2018;25(1):65-80.
87. Xia Y, Liu X, Zhang L, Zhang J, Li C, Zhang N, et al. A new Schiff base coordinated copper(II) compound induces apoptosis and inhibits tumor growth in gastric cancer. Cancer Cell International. 2019;19(1):81.
88. Xu J, Zhou T, Xu Z-Q, Gu X-N, Wu W-N, Chen H, et al. Synthesis, crystal structures and antitumor activities of copper (II) complexes with a 2-acetylpyrazine isonicotinoyl hydrazone ligand. Journal of Molecular Structure. 2017;1128:448-54.
89. Bao RD, Song XQ, Kong YJ, Li FF, Liao WH, Zhou J, et al. A new Schiff base copper(II) complex induces cancer cell growth inhibition and apoptosis by multiple mechanisms. J Inorg Biochem. 2020;208:111103.
90. Zhou X-Q, Li Y, Zhang D-Y, Nie Y, Li Z-J, Gu W, et al. Copper complexes based on chiral Schiff-base ligands: DNA/BSA binding ability, DNA cleavage activity, cytotoxicity and mechanism of apoptosis. European Journal of Medicinal Chemistry. 2016;114:244-56.
91. Garnier F, Couturier M, Débat H, Nadal M. Archaea: A Gold Mine for Topoisomerase Diversity. Frontiers in Microbiology. 2021;12.
92. Liu J, Qu L, Meng L, Shou C. Topoisomerase inhibitors promote cancer cell motility via ROS-mediated activation of JAK2-STAT1-CXCL1 pathway. Journal of Experimental & Clinical Cancer Research. 2019;38(1):370.
93. Tabassum S, Asim A, Khan RA, Hussain Z, Srivastav S, Srikrishna S, et al. Chiral heterobimetallic complexes targeting human DNA-topoisomerase Iα. Dalton Transactions. 2013;42(48):16749-61.
94. Dankhoff K, Gold M, Kober L, Schmitt F, Pfeifer L, Dürrmann A, et al. Copper (II) complexes with tridentate Schiff base-like ligands: solid state and solution structures and anticancer activity. Dalton Transactions. 2019;48(40):15220-30.
95. Duff B, Thangella VR, Creaven BS, Walsh M, Egan DA. Anti-cancer activity and mutagenic potential of novel copper (II) quinolinone Schiff base complexes in hepatocarcinoma cells. European journal of pharmacology. 2012;689(1-3):45-55.
96. Towers CG, Wodetzki D, Thorburn A. Autophagy and cancer: Modulation of cell death pathways and cancer cell adaptations. Journal of Cell Biology. 2020;219(1).
97. Yun CW, Lee SH. The Roles of Autophagy in Cancer. Int J Mol Sci. 2018;19(11):3466.
98. Raudenska M, Balvan J, Masarik M. Crosstalk between autophagy inhibitors and endosome-related secretory pathways: a challenge for autophagy-based treatment of solid cancers. Molecular Cancer. 2021;20(1):140.
99. Kordestani N, Amiri Rudbari H, Fernandes AR, Raposo LR, Luz A, Baptista PV, et al. Copper(ii) complexes with tridentate halogen-substituted Schiff base ligands: synthesis, crystal structures and investigating the effect of halogenation, leaving groups and ligand flexibility on antiproliferative activities. Dalton Transactions. 2021;50(11):3990-4007.