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Synthesis, Investigation, Biological Evaluation and Application of Coordination Compounds—A Review

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Abstract: Coordination compounds, characterized by the coordination of metal ions with ligands, represent a pivotal area of research in chemistry due to their diverse structures and versatile applications. This review delves into the synthesis, characterization, biological evaluation, and practical applications of these compounds. A variety of synthetic methodologies (traditional solution-based techniques) are discussed to highlight advancements in the field. Investigations into the structural, electronic, and spectral properties of coordination compounds are emphasized to provide insights into their functional attributes. The biological evaluation section focuses on their roles in antimicrobial, anticancer, and enzyme-inhibitory activities, underscoring their potential in therapeutic development. Attention is paid to nanoparticles, which are increasingly used for the treatment of oncological diseases. The metal complexes have been shown to have antibacterial, antifungal, antiviral, antioxidant and antiproliferative properties. Additionally, the review explores their applications across domains such as catalysis illustrating their multifaceted utility. By synthesizing recent findings and trends, this article aims to bridge the gap between fundamental chemistry and applied sciences, paving the way for innovative uses of coordination compounds in both biological and industrial contexts.

Keywords: coordination compounds; biological properties; characterization

1. Introduction

Coordination compounds, formed by the interaction of metal ions with surrounding ligands, have long been a cornerstone of inorganic chemistry. Their structural diversity, arising from variations in metal centers, oxidation states, and ligand types, endows these compounds with unique physicochemical properties. These features not only provide a deeper understanding of chemical bonding and reactivity but also enable a wide range of applications spanning biological, industrial, and environmental fields. The synthesis of coordination compounds has evolved significantly, leveraging both conventional and modern techniques to optimize their yield, stability, and functionality (see Scheme 1–3). Characterization methods, such as spectroscopic, crystallographic, and electrochemical analyses, play a critical role in unraveling their structural intricacies and guiding their application.

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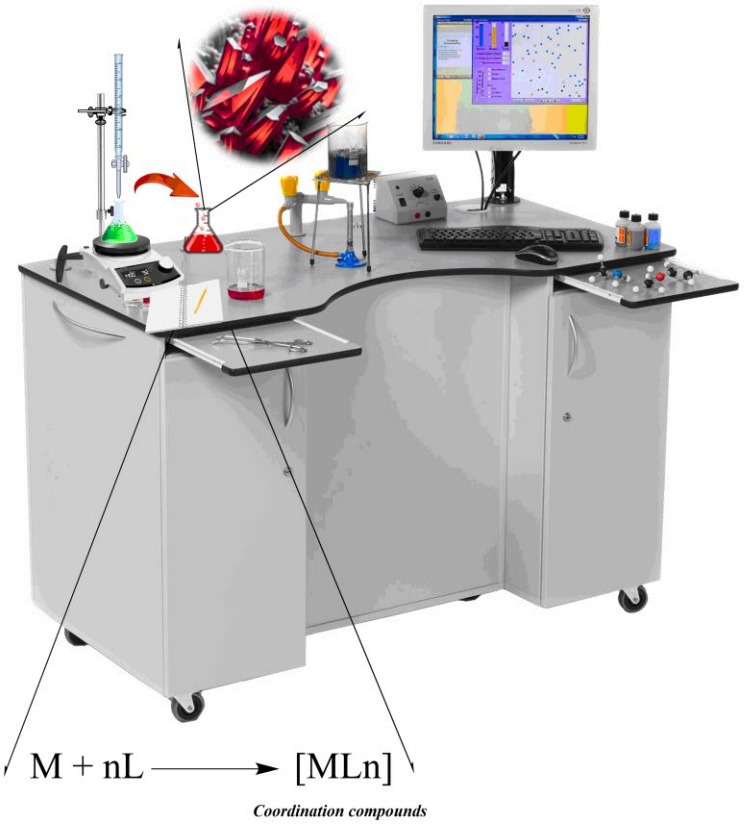
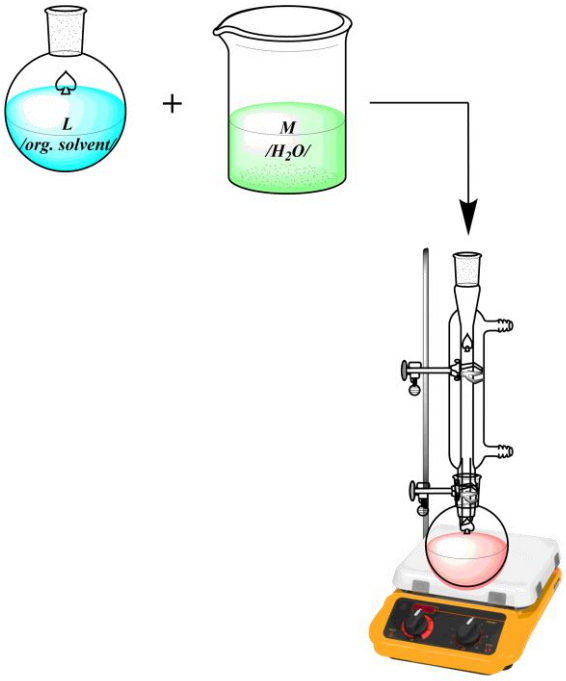


Scheme 1. Synthesis of metal complexes without heating.



Scheme 2. Possible synthesis of complexes upon heating.

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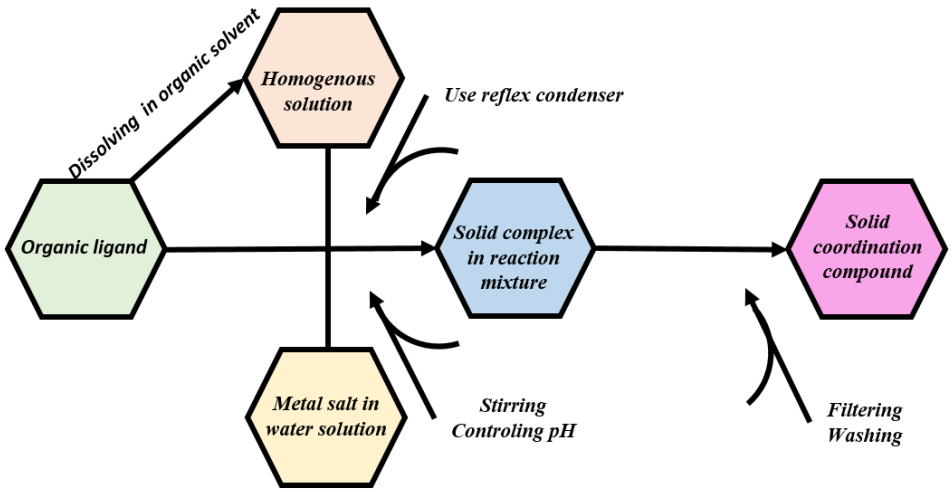

Scheme 3. Synthesis of solid metal(II), (III), (IV) or other oxidation state coordination compounds.

To date numerous metal complexes of different organic ligands were synthesized by using **Scheme 1** [1–12] or Scheme 2 [23–27]. The Figure 1 presents the classification of ligands and metal complexes.

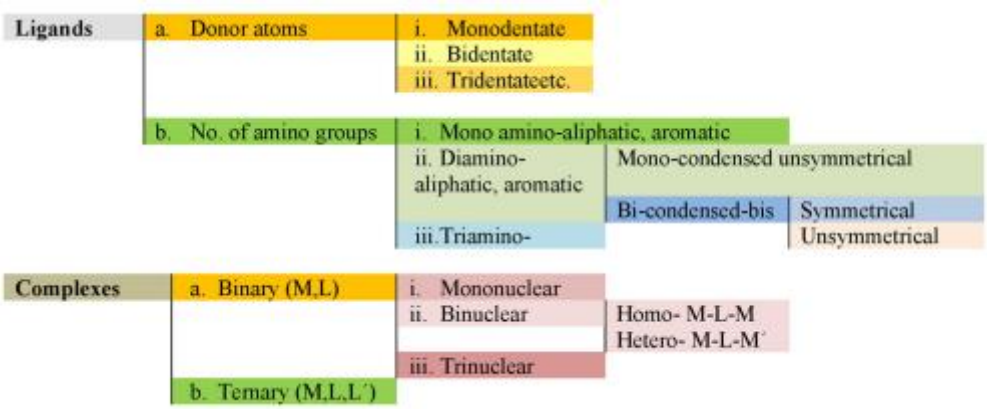

Figure 1. Flow diagram presenting the classification of ligands and metal complexes (L=Schiff base).

One of the most intriguing aspects of coordination compounds is their biological relevance. Many of these compounds exhibit promising activities, including antimicrobial, anticancer, and enzyme-inhibitory properties, positioning them as candidates for therapeutic development. Furthermore, their roles in catalysis, molecular sensing, and environmental remediation underscore their significance in addressing global challenges.

This review provides a comprehensive exploration of the synthesis, investigation, biological evaluation, and applications of coordination compounds. By integrating insights from recent studies and emerging trends, it aims to illuminate the potential of these compounds to advance science and technology.

Key Characteristics of Transition Metals and Their Complexes:

1. Charge Variation: Transition metals can exist as positively charged species in aqueous solutions, with charges adaptable based on their coordination environment. This enables binding to negatively charged biomolecules, which is critical in therapeutic applications [28].

2. Structural Diversity: Transition metal complexes can adopt a wide range of coordination geometries and bond configurations. This flexibility allows for unique shapes and molecular interactions, surpassing conventional carbon-based compounds [28–31].

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3. Metal-Ligand Interactions: These interactions form unique complexes with distinct thermodynamic and kinetic properties, enhancing ligand exchange reactions and biological compatibility [28].

4. Lewis Acid Properties: The high electron affinity of transition metals facilitates the polarization and hydrolysis of coordinated groups, contributing to their catalytic activities [28,29].

5.Partially Filled Shells: The electronic configurations of transition metals impact their magnetic and electronic properties, which are crucial for biochemical functions [29].

6. Redox Activity: Transition metals readily undergo redox reactions, a vital feature in biochemical redox catalysis and drug design [29].

2. Methods for characterization of coordination compounds

Characterization of coordination compounds involves determining their chemical composition, structural properties, and electronic behavior to understand their reactivity, functionality, and applications. Several analytical and spectroscopic methods are employed to explore these aspects. Techniques such as X-ray crystallography [32–43] are central to determining the three-dimensional arrangement of atoms, providing precise geometrical details about the coordination sphere. UV-Vis spectroscopy [44–74] is used to study the electronic transitions within the metal-ligand complexes, offering insights into the ligand field and electronic structure. Infrared (IR) spectroscopy identifies functional groups and bond vibrations, highlighting the types of ligands present and their binding modes [75–85]. Additionally, NMR spectroscopy (solid state or in solution) [86–101] can probe the chemical environment of nuclei within the ligands, especially in diamagnetic complexes. Other techniques like elemental analysis, mass spectrometry, and thermogravimetric analysis (TGA) provide quantitative data on the composition, stability, and thermal properties. Cyclic voltammetry and related electrochemical methods help in understanding redox behavior, while magnetic susceptibility measurements reveal information about unpaired electrons and the magnetic properties of the metal center. These techniques together provide a comprehensive understanding of coordination compounds, supporting their design and application in areas such as catalysis, medicine, and materials science. Several spectroscopic methods for investigation of coordination compounds are given in **Scheme 4**.

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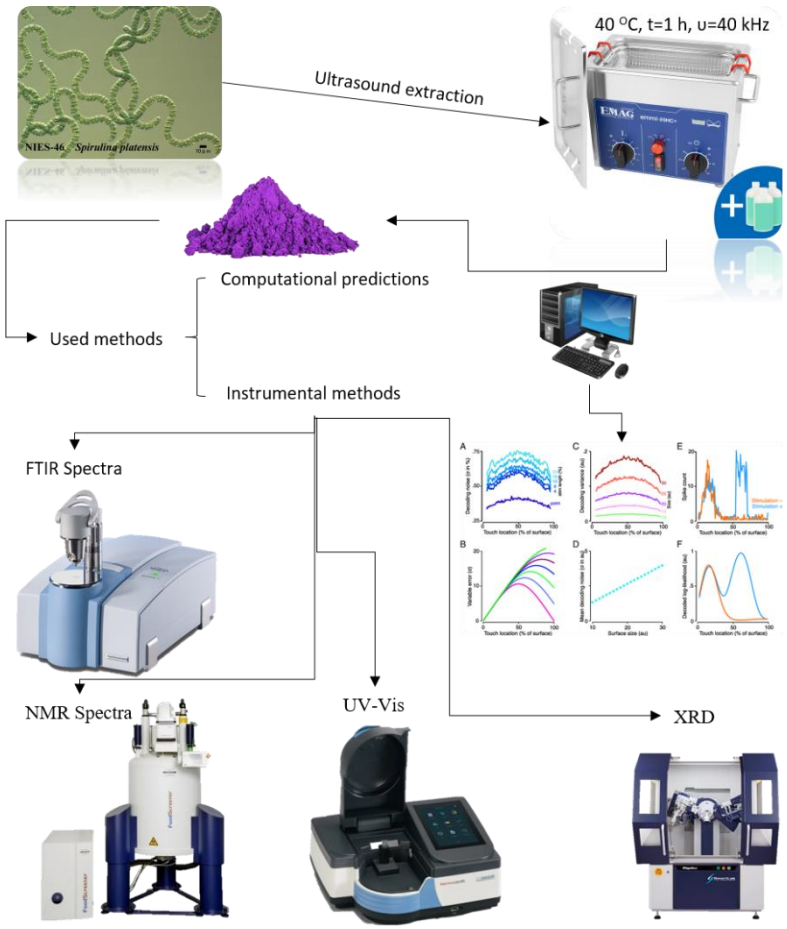

Scheme 4. Investigation of coordination compounds.

To date numerous metal complexes of spirohydantoins [1–5], thiouracils [6–8] and other derivatives [10–12,88,89,93] were synthesized and their composition and structure with various metals like copper, nickel, zinc, [1,2,12,102], as well as palladium, platinum and gold was studied [6–9]. Summary data on the structure of the complexes and the donor atoms involved in the coordination are given in **Table 1**.

Table 1. Summary data on the structure of the complexes and the donor atoms involved in the coordination.

technique	donor atom	metal	structure	references
^{13}C CPMAS NMR, IR and FAB-MS and theoretical DFT studies	N3^S4-bridging coordination	Cu(I) and Ni(II)	dimeric structures	[1]
^{13}C CPMAS NMR and theoretical DFT studies	N3^S2-bridging coordination for L1 with Cu(I); monodentate coordination (N3- and S2-) of two non-equivalent ligand molecules for L2 with Cu(I); N3^S4- bridging way for Ni(II)	Cu(I) and Ni(II)	dimeric structure for Cu(I) with L1; square planar for Ni(II) with L1 and L2	[2]
IR and ^{13}C CPMAS NMR and theoretical DFT studies	N and S	Pt(II)	square planar	[3]
^{13}C-NMR-CP-MAS, EPR, IR and	N for Cu(II) and N3 and S2 for Ni(II)	Cu(II) and Ni(II)	distorted tetrahedral for Cu(II)	[4]

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quantum-chemical (DFT/B3LYP-6-31G (d,p)) methods			and square planar for Ni(II)	
^{13}C CPMAS NMR and theoretical DFT studies, X-ray	O, Cl	Al(III)	six-membered chelate rings	[5]
melting point analysis, MP-AES for Cu and Pd, UV-Vis, IR, ATR, ^{1}H NMR, ^{13}C NMR and Raman, Solid-state NMR spectroscopy	O,S for L1 and S for L2 with Cu(II); N, S, O with Pd(II)	Cu(II) and Pd(II)	tetrahedral for Cu(II) with L1 and octahedral for L2; chelate for Pd(II) with L1 and L2	[6]
MP-AES for Cu and Au, ICP-OES for S, ATR, solution and solid-state NMR, and Raman spectroscopy	N,S for Au(III) and O,S for Cu(II)	Au(III) and Cu(II)	chelate structure	[7]
UV-Vis, IR, ATR, ^{1}H NMR, HSQC, and Raman, solid-state NMR spectroscopy	O, S	Au(III)	tetrahedral	[8]
IR, FAB-MS, XPS, solid-state NMR spectroscopy and theoretical DFT studies	N, S	Pt(II)	dimer, chelate structure	[9]
X-ray	O, N	Ag(I)	dinuclear complex, chelate structure	[10]
X-ray, ESR, MALDI mass-spectrometry, NMR spectroscopy	P, O, P	Ru(II) and Ru(III)	chelate structure	[11]
X-ray and ^{1}H-, ^{13}C-NMR, IR and UV-Vis spectroscopy and elemental analysis and theoretical DFT studies	O, N	Cu(II), Fe(II) and Zn(II)	chelate structure	[12]
elemental analysis, FAAS, FT-IR, MS, TG methods and X-ray for C3 and C4	N, Cl	Zn(II)	tetrahedral geometry, dinuclear coordination compounds	[102]
Elemental analysis, NMR and ESI-MS	C, Cl	Rh(I) and Ru(II)	Tetrahedral or square planar	[103]
X-ray and ^{1}H-, ^{13}C-NMR, IR and UV-Vis spectroscopy and elemental analysis	C, Cl	Au(III)	square planar	[104]
NMR and mass spectroscopy, X-ray	C, Cl	Au(I) and Ag(I)	Liner	[105]

The structure of ruthenium and rhodium complexes and Cu(II), Ni(II), Co(II), Zn(II), Cd(II) are given in **Figures 2–4**, respectively.

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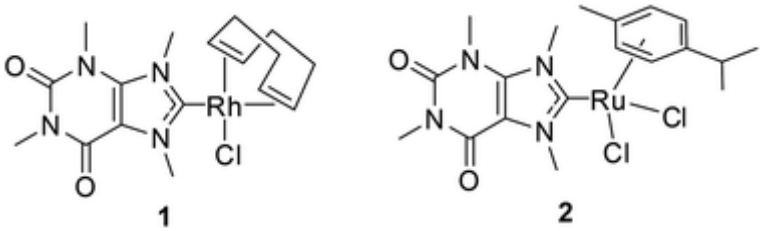
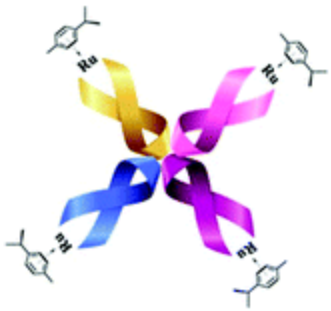


Figure 2. The structure of Rh and Ru complexes [103].



Ruthenium (II) carbosilane dendrimers as anticancer agents

Figure 3. Ru(II) complex as anticancer agents [106].

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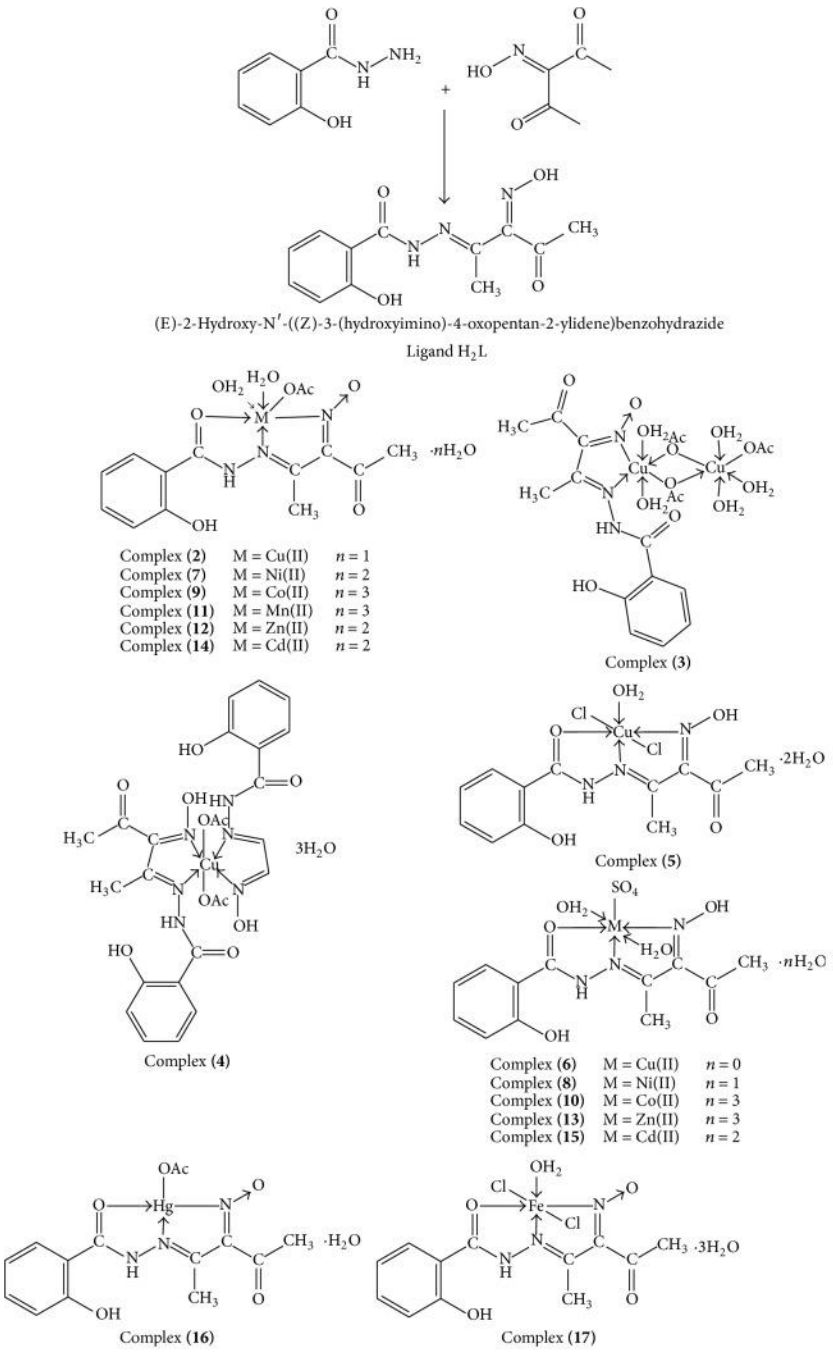

Figure 4. Proposed structures of the ligand [H2L] and its metal complexes [107].

X-ray analysis for C3 and C4 have been used to established the structure of metal complexes with Zn(II)) [102]. Molecular structures of two complexes are presented in Figure 5.

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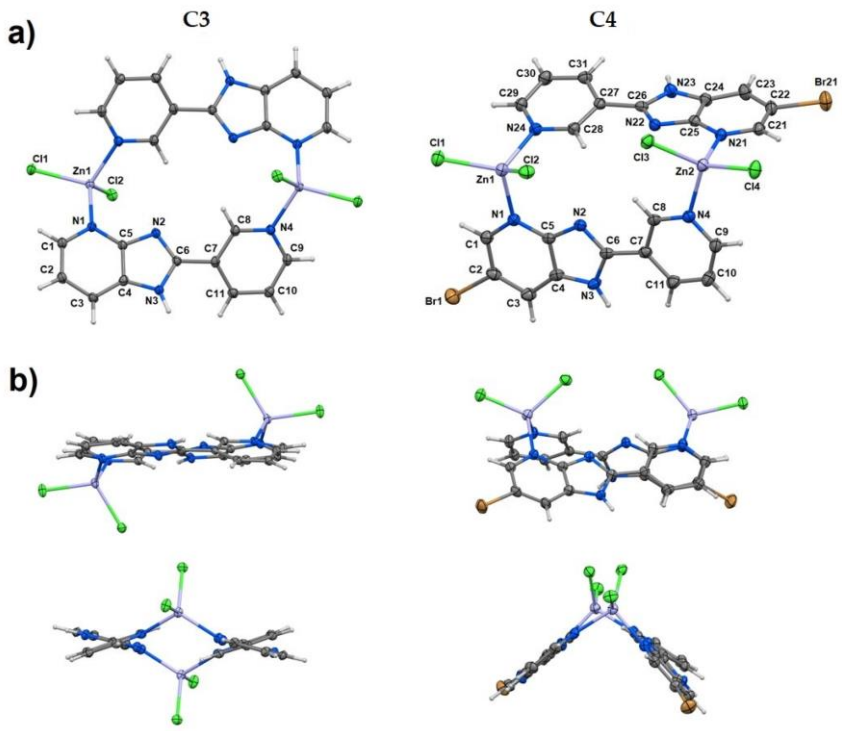

Figure 5. (a,b) Molecular structures of C3 and C4 with displacement ellipsoids of nonhydrogen atoms plotted with 50% probability (a). A comparison of the coordination entity structures (b) [102].

Strong stereospecific intramolecular H-bonding between an en NH proton oriented away from the arene and the C6O carbonyl of G is present in the crystal structures of Ru–arene adducts of 9-ethylguanine (9EtG) and guanosine (Figure 6; average N…O distance 2.8 A˚, N–H…O angle 163u). [108]

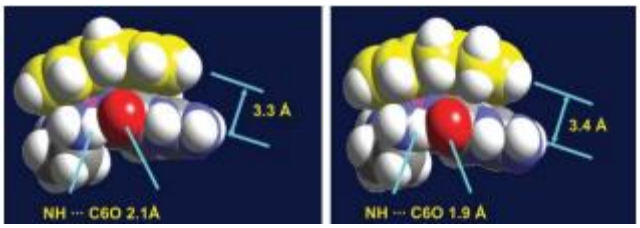

Figure 6. Crystal structures of [(η⁶ -DHA)Ru(en)(9EtG)]²⁺ (left) and [(η⁶ -THA)Ru(en)(9EtG)]²⁺ (right), showing the arene–purine p-stacking and hydrogen bonding between en NH and G C6O [108].

Molecular structures of Ru and Au complexes are presented in Figures 7–9, respectively.

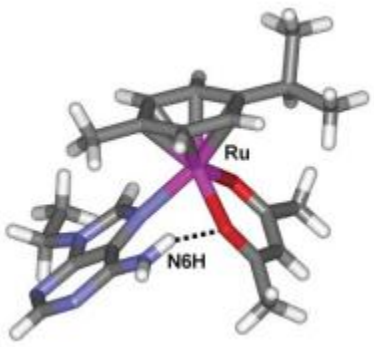

Figure 7. Molecular model of [(η⁶ -Cym)Ru(acac)(9EtA)]⁺ . The hydrogen bond between acac O and A N6H is represented by a dashed line. [109].

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Figure 8. ORTEP view of 2 (30% probability). The PF_6 counter anion and the H atoms have been omitted for the sake of clarity. Key bond lengths (angstroms) and angles (degrees): Au(1)−C(1) = 2.008(5), Au(1)−C(14) = 2.018(5), N(1)−C(1) = 1.373(8), N(2)−C(1) = 1.359(7), C(14)−N(4) = 1.354(7), C(14)−N(5) = 1.351(7), C(1)− Au(1)−C(14) = 176.7(2), N(1)−C(1)−N(2) = 104.1(5), and N(4)− C(14)−C(5) = 103.5(5). Note that two asymmetric units were present [104].

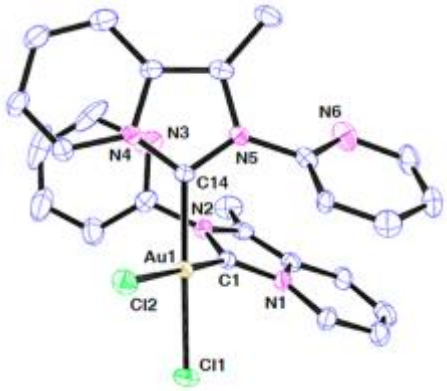

Figure 9. ORTEP view of 3 (30% probability). The H, PF_6, and H_2O species have been omitted for the sake of clarity. Pertinent bond lengths (angstroms) and angles (degrees): Au(1)−C(1) = 1.996(6), Au(1)−C(14) = 2.014(5), Au(1)−Cl(1) = 2.2984(16), Au(1)−Cl(2) = 2.3150(16), N(1)−C(1) = 1.360(7), N(2)−C(1) = 1.363(8), C(14)−N(4) = 1.338(7), C(14)−N(5) = 1.347(7), N(1)−C(1)− N(2) = 105.3(5), N(4)−C(14)−C(5) = 106.2(4), C(1)−Au(1)− C(14) = 89.9(2), C(1)−Au(1)−Cl(1) = 88.08(17), C(14)−Au(1)− Cl(1) = 177.89(15), C(1)−Au(1)−Cl(2) = 177.91(17), C(14)−Au(1)−Cl(2) = 90.22(16), and Cl(1)−Au(1)−Cl(2) = 91.86(7). [104].

3. Some Aspects of the Biological Significance of Coordination Compounds

Recently, Soroceanu et al. presented biomedical application of coordination compounds with Schiff-base ligands [110]. Raducka et al. provides insight into the structural and biological evaluation of zinc-based coordination compounds with benzimidazole derivatives [102]. Ndagi et al. evaluated the anticancer therapy with coordination compounds [111]. Possible biological application of coordination compounds are given in Figures 10 and 11.

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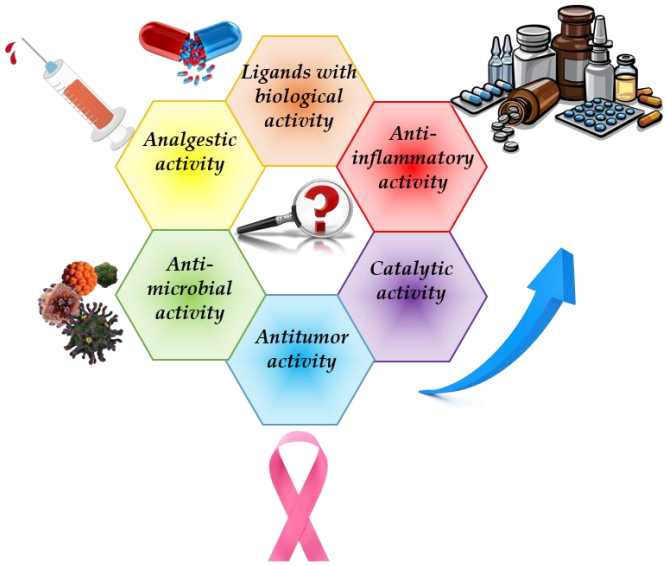

Figure 10. Biological application of coordination compounds.

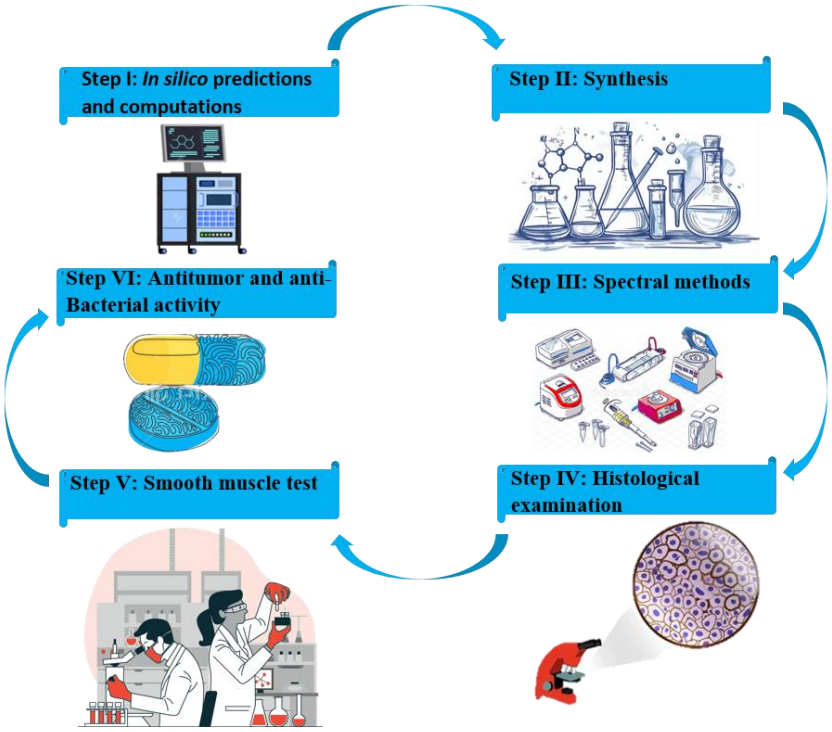

Figure 11. Relationship between chemistry and biology.

Schiff-base metal complexes have garnered significant attention in the fields of biological and inorganic chemistry due to their promising biological activities, particularly in the development of therapeutic agents for various bacterial infections. Schiff bases, which are derived from the condensation of primary amines with carbonyl compounds, often serve as effective ligands for transition metals. These metal complexes mimic biologically relevant species, making them valuable models for studying enzyme mechanisms and other biological processes. Many Schiff-base metal complexes demonstrate antimicrobial properties, showing efficacy against a wide range of bacterial strains, including both Gram-positive and Gram-negative bacteria [102,110,112]. The ability of these

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complexes to interact with biological molecules, such as enzymes and DNA, enhances their therapeutic potential, particularly for the treatment of bacterial diseases. For instance, Schiff-base complexes of metals like copper, iron, and zinc have been extensively studied for their antibacterial, antifungal, and anticancer activities [102,110,112]. The biological relevance of Schiff-base metal complexes also extends to their use as models for metalloenzymes, which are critical in various biochemical processes. These complexes can be designed to simulate the active sites of enzymes, allowing researchers to investigate the mechanisms behind their biological activity and to develop more targeted therapeutic agents. In summary, Schiff-base metal complexes represent a promising avenue for the design of new antibiotics and other therapeutic agents due to their biological activity and ability to mimic biologically significant species.

3.1. Anticancer Properties

Therapeutic Potential in Cancer Treatment:

Transition metal-based compounds, such as platinum-based drugs (e.g., cisplatin), have demonstrated notable success in cancer therapy due to their ability to:

- Exhibit redox activity.
- Form complexes targeting specific biomolecules.
- Disrupt cellular mechanisms of proliferation.

Emerging research continues to focus on synthesizing new metal-based compounds with enhanced selectivity, reduced toxicity, and improved efficacy. These include compounds that modulate cellular mechanisms via novel pathways, offering hope for more effective cancer treatments (see Figures 12–14).

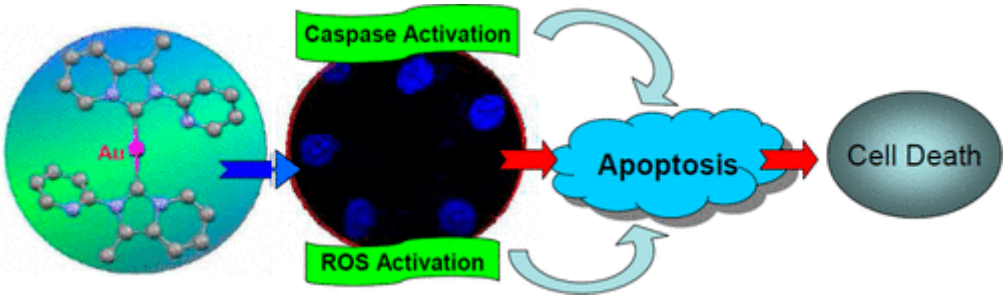

Figure 12. Biological application of Au(I) complex [104].

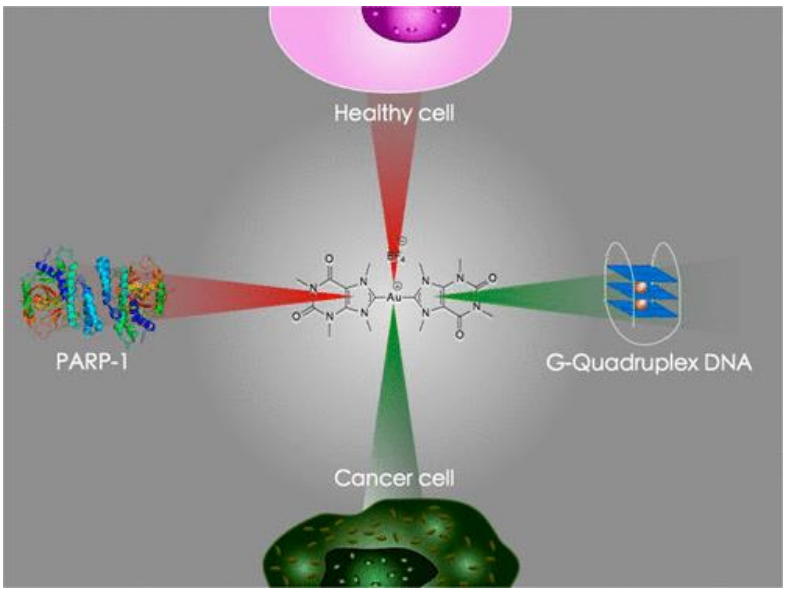

Figure 13. Possible mechanism of action of metal complex [113].

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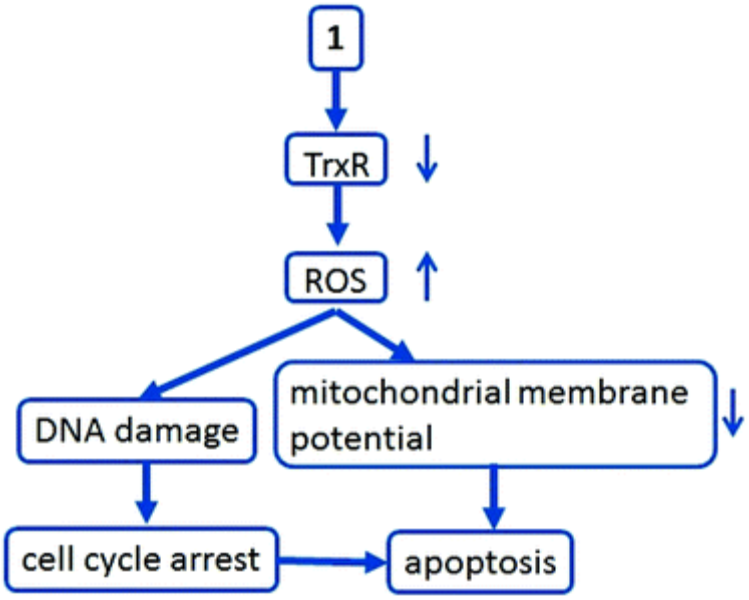

Figure 14. Proposed mechanism of the cytotoxic action of Rh(I) complex [103].

Table 1 summarizes the *in vitro* cytotoxic effects of various metal-based compounds over a 6-year period, with a focus on their proposed mechanisms of action and targets.

Table 2. An update on the anticancer activities of metal-based complexes (2010–2016) [111].

Metal complexes	Molecular formula	Proposed mechanism of action	Target enzymes/cell lines/ therapeutic indications	IC_{50} range (μM)	Reference
Carbene–metal complexes and related ligands					
Novel gold(I) and gold(III) NHC complexes	$C_{52}H_{44}Au_2N_{12}P_2F_{12}$	Induction of apoptosis	TrxR	$C_{52}H_{44}Au_2N_{12}P_2F_{12}$ 5.2±1.5 (A549) 3.6±4.1 HCT-116) 3.7±2.3 (HepG2) 4.7±0.8 (MCF7)	[104]
		Inhibition of TrxR	A549, HCT116, HepG2, MCF7	$C_{26}H_{24}AuC_{12}OF_6N_6P$	
	$C_{26}H_{24}AuC_{12}OF_6N_6P$	Induction of ROS	Chemotherapy of solid tumors	5.2±3.0 (A549) 5.9±3.6 (HCT-116) 5.1±3.8 (HepG2) 6.2±1.4 (MCF7)	[104]
Caffeine-based gold(I) NHCs	[Au(Caffeine-2-yielding)$_2$][BF_4]	Inhibition of protein PARP-I	DNA A2780, A2780R, SKO3, A549 HK-293T	0.54–28.4 (A2780) 17.1–49 (A2780/R) 0.75–62.7 (SKO3) 5.9–90.0 (A549) 0.20–84 (HK-293T)	[113]
Ester- and amidefunctionalized imidazole of NHC complexes	{[Im^A]AgCl} {[Im^A]AuCl}	Inhibition of tyrosine by gold(I) NHC ligands,	TrxR A375, A549, HCT-15 and MCF7	{[Im^A]AgCl} 24.65 (A375) 22.14 (A549)	[105]

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	{[Im^B]$_2$AgCl} {[Im^B]AuCl}	thereby targeting TrxR	Human colon adenocarcinoma	20.32 (HCT-15) 21.14 (MCF7) {[Im^A]AuCl}	
	Hm^ACl = [1,3-*bis* (2-ethoxy-2-oxoethyl)-1Himidazol-3-ium chloride]	CuNHC cell cycle arrest progression in G phase	Leukemia and breast cancer	44.64 (A375) 42.37 (A549) 41.33 (HCT-15) 38.53 (MCF7)	
	Hm^BCl={1,3-bis[2(diethylamino)-2-oxoethyl]-1H-imidazol-3-ium chloride}	Anticancer activity of Ag1 NHC is based on highly lipophilic aromaticsubstituted carbenes		{[Im^B]$_2$AgCl} 24.46 (A375) 16.23 (A549) 14.11 (HCT-15) 15.31 (MCF7)	
Novel Ru(II) NHCs83	η^6-p-cymene)$_2$$Ru_2$($Cl_2$)$_2$]NHC	Mimic iron Interact with plasmidic DNA	DNA as target Caki-1 and MCF7 Chemotherapy of solid tumor	13–500 (Caki-1) 2.4–500 (MCF7)	[114,115]
Caffeine-derived rhodium(I) NHC complexes	[Rh(I)Cl(COD)(NHC)] complexes	Inhibition of TrxR Increase in ROS formation DNA damage Cell cycle arrest Decrease in mitochondria membrane potentia	TrXR MCF7, HepG2 MDA-MB-231, HCT-116, LNCaP, Panc-I and JoPaca-I Chemotherapy of solid tumor85	84 (HepG2) 20 (HCF-7) 23 (MDA-MB-231) 35 (JoPaca-I) 49 (Panc-I) 80 (LNCaP) 9.0 (HCT-116	[103]
NHC–amine Pt(II) complexes	NHC (PtX2)–amine complexes	Nuclear DNA platination	Target DNA KB3-1, SK-O3, OCAR-8, M-4-11, A2780 and A2780/ DPP Chemotherapy of solid and non-solid tumors	2.5 (KB3-1) 4.33 (SK-O3) 1.84 (OCAR-8) 0.60 (M-4-11) 4.00 (A2780) 8.5 (A2780/DPP)	[116]
2-Hydroxy-3-[(hydroxyimino) -4- oxopentan-2-ylidene]	[(HL)Cu(OAc)(H_2O)$_2$]·$H_2OC_{14}H_{21}N_3O_9Cu$	Bind to DNA	Target DNA HepG2	2.24–6.49 (HepG2)	[117]

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benzohydrazide derivatives			Chemotherapy of solid tumors Target DNA		
Molybdenum(II) allyl dicarbonate complexes	[Mo(allyl)(CO)$_2$ (N-N)(py)]PF_6	DNA fragmentation Induction of apoptosis	NALM-6, MCF7 and HT-29 Chemotherapy of solid and non-solid tumors	1.8–13 (NALM-6) 2.1–32 (MCF7) 1.8–32 (HT-29)	[118]
Metal-arene complexes and other ligands					
Ru(II)–arene complex	[(η^6-arene)Ru(II)(en)Cl]$^+$	DNA damage Cell cycle arrest Induction of apoptosis	Target DNA AH54 and AH63 Chemotherapy of colorectal cancer	$C_{15}H_{18}ClF_6N_2PRu$ 16.6 (AH54) $C_{16}H_2OClF_6N_2PRu$ 10.9 (AH63)	[119]
Novel ruthenium–arene pyridinyl methylene complexes	[(η^6-p-cymene)RuCl(pyridinylmethylene)]	DNA binding	Target DNA MCF7 and HeLa Chemotherapy of solid tumor	07.76–25.42 (MCF7) 07.10–29.22 (HeLa)	[120]
Multi-targeted organometallic Ru(II)–arene	[(η^6-p-cymene)$RuCl_2$]$_2$-PARP and PARP-I inhibitors	DNA binding PARP-I inhibition Transcription inhibition	Target DNA A549, A2780, HCT-116, HCC1937 and MRC-5 Chemotherapy of solid tumors	85.1–500 (A549) 38.8–500 (A2780) 46.0–500 (HCT-116) 93.3–500 HCC1937) 143–500 (MRC-5)	[121]
Ru(II)–arene complexes with 2-aryldiazole ligands	[(η^6-arene)RuX(k^2-N,N-L)]Y	DNA binding Inhibition of CDK1	Target DNA A2780, A2780cis, MCF7 and MRC-5 Chemotherapy of solid tumors	11–300 (A2780) 11–34 (A2780cis) 26–300 (MCF7) 25–224 (MRC-5)	[122]
Osmiun(II)–arene carbohydrate base anticancer compound	Osmium(II)-bis [dichloride(η^6-p-cymene)]	DNA binding	Target DNA CH1, S480 and A549	50–746 (CHI) 215–640 (S480) 640 (A549)	[123]

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Ru(II)–arene complexes with carbosilane metallodendrimers	Gn-[$NH_2Ru(\eta^6$-p-cymene)Cl_2]m	Interaction with DNA Interaction with HSA94 Inhibition of cathepsin B	Target DNA HeLa, MCF7, HT-29 MDAMB-231 and HK-239T Chemotherapy of solid and non-solid tumors	6.3–89 (HeLa) 2.5–56.0 (MCF7) 3.3–41.7 (HT-29) 4–74 (MDA-MB-231) 5.0–51.9 (HK-239T)	[106]
Ru(II) complexes with aroylhydrazone ligand	[Ru(η^6-C_6H_6)Cl(L)]	Induction of apoptosis Fragmentation of DNA	Target DNA MCF7, HeLa, NH-3T3 Chemotherapy of solid tumor	10.9–15.8 (MCF7)95 34.3–48.7 (HeLa) 152.6–192 (NH-3T3)	[124]
Cyclopentadienyl complexes and other ligands					
Iridium(III) complexes with 2-phenylpyridine ligand	[(η^5-Cp*)r(2-(R'-phenyl)-Rpyridine)Cl]	Interaction with DNA nucleobases Catalysis of NADH oxidation	Target DNA A2780, HCT-116, MCF7 and A549 Chemotherapy of solid tumor	1.18–60 (A2780) 3.7–57.3 (HCT-116) 4.8–28.6 (MCF7) 2.1–56.67 (A549)	[125]
New iron(II) cyclopentadienyl derivative complexes	[Fe(η^5-C_5H_5)(dppe)L][X]	Interaction with DNA Induction of apoptosis	Target DNA HL-60 Chemotherapy of non-solid tumors	0.67–5.89 (HL-60)	[126]
Ru(II) cyclopentadienyl complexes with carbohydrate ligand	[Ru(η^5-C_5H_5)(PP)(L)][X]	Induction of apoptosis Activation of caspase-3 and -7 activity	HCT116CC, HeLa Chemotherapy of solid tumors	0.45 (HCT116CC) 3.58 (HeLa)	[127]
Ru(II) cyclopentadienyl complexes with phosphane co-ligand	[Ru(η^5-C_5H_5)(PP)(L)][X]	Induction of apoptosis	HeLa Chemotherapy of solid tumo	2.63 (HeLa)	[128]
Organoiridium cyclopentadienyl complexes	[(η^5-Cpx)r(L^L')Z]	Intercalation of DNA Coordination with DNA guanine	HeLa Chemotherapy of solid tumor	0.23 (HeLa)	[129]

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Abbreviations: IC_{50}, half maximal inhibitory concentration; NHC, N-heterocyclic carbene; TrxR, thioredoxin reductase; ROS, reactive oxygen species; PARP-1, Poly(ADP-ribose) polymerase-1; CDK1, cyclin-dependent kinase 1; HSA, human serum albumin; ADP, adenosine diphosphate.

Several metal-based compounds have been synthesized with promising anticancer properties. Some of these are already used in clinical practice for diagnosis and treatment, while others are still undergoing clinical trials. Recently, synthesized metal-based compounds are the result of targeted drug design aimed at achieving specific goals that the original compound could not. These new compounds display a different spectrum of cytotoxicity. The summary of metal-based compounds undergoing clinical trials in human [111] are given in Table 3 and evolution of organometallic complexes in cancer therapy was presented in Figure 15.

Table 3. Summary of metal-based compounds undergoing clinical trials in human [111].

Drug name	Developers	Phase of clinical trial	Indications	Reference
Picoplatin (JM473)	Pionard	Phase I	Treatment of colorectal cancer in combination with 5-FU and leucovorin	[129]
Lipoplatin™ (Nanoplatin™, Oncoplatin)	Regulon	Phase II and phase III clinical in different cancer cells	Treatment of locally advanced gastric cancer/ squamous cell carcinoma of head and nec	[129]
ProLindac™ (AP5046)	Access Pharm	Phase I, II ad III trials	Advanced ovarian cancer68 and head and neck cancers	[129]
Satraplatin (JM216)	Spectrum Pharm and Agennix AG	Phase I, II ad III trials	Treatment of colorectal cancer in combination with 5-FU and leucovorin, treatment of prostate cancer in combination with docetaxel and treatment of a patient with progressive or relapse NSCLC68	[129]
NAMIA-A	–	Phase I	Metastatic tumor (lung, colorecta, melanoma, ovaria and pancreatic)	[130]
KP1019	–	Phase II	Advanced colorecta cancer	[130]
^{64}Cu-ATSM	–	Phase II	PET/CT monitoring therapeutic progress in patient with cervica1	[131]

Abbreviations: FU, fluorouracil; NSCLC, non-small-cell lung cancer; ^{64}Cu-ATSM, ^{64}Cu-diacetyl-*bis*(N4 -methylthiosemicarbazone); PET, positron emission tomography; CT, computed tomography.

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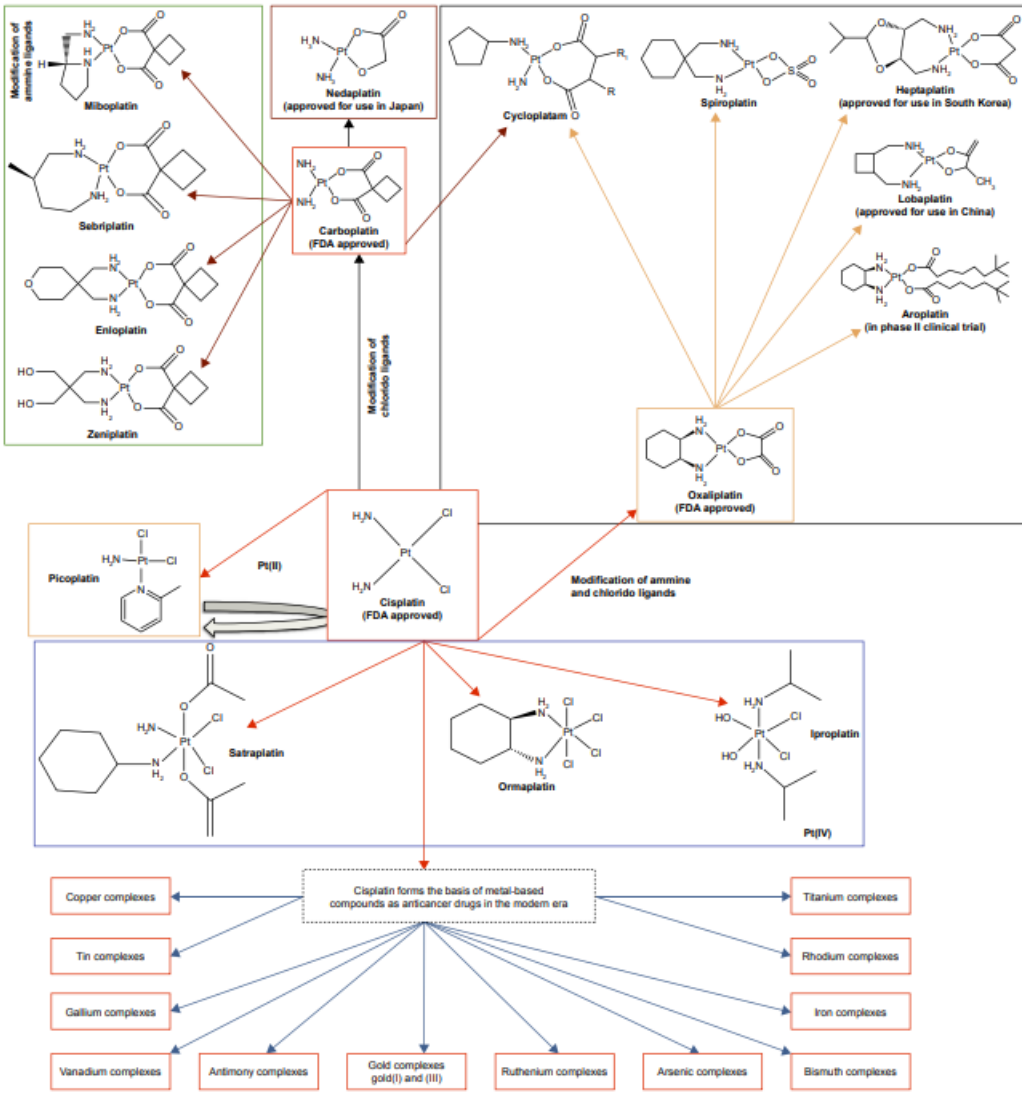

Figure 15. Evolution of organometallic complexes in cancer therapy Abbreviation: FDA, US Food and Drug Administration [111].

The cytotoxic efefct of the newly developed compounds, assessed as potential anticancer agents, was evaluated against adenocarcinoma (A549), neuroblastoma (SK-N-AS), glioblastoma (T98G) and lung cell cultures, along with normal human skin fibroblasts (CCD-1059Sk) [102]. The prediction results for the free ligand L3 and L4 are given in Table 4 and cytotoxic effect of metal complexes are presented in Table 5.

Table 4. Cancer cell line prediction results for the ligand—Pa (probability "to be active"), Pi (probability "to be inactive") [102].

Ligand	Pa	Pi	Cell-Line Name	Tissue	Tumor Type
L3	0.587	0.029	Oligodendroglioma	Brain	Glioma
L3	0.538	0.010	Colon adenocarcinoma	Colon	Adenocarcinoma
L3	0.490	0.022	Non-small-cell lung carcinoma	Lung	Carcinoma
L3	0.475	0.009	Pancreatic carcinoma	Pancreas	Carcinoma
L3	0.439	0.043	Pancreatic carcinoma	Pancreas	Carcinoma
L4	0.559	0.006	Pancreatic carcinoma	Pancreas	Carcinoma

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L4	0.554	0.009	Colon adenocarcinoma	Colon	Adenocarcinoma
L4	0.415	0.038	Cervical adenocarcinoma	Cervix	Adenocarcinoma
L4	0.426	0.099	Oligodendroglioma	Brain	Glioma

Table 5. Cytotoxic effect of the metal complexes against glioblastoma (T98G), neuroblastoma (SK-N-AS), lung adenocarcinoma (A549) cell lines and human normal fibroblasts (CCD-1059Sk) determined by MTT assay after 24 h incubation. IC50 ± SD (μg/mL) [102].

Complex	T98G	SK-N-AS	A549	CCD-1059-Sk
L1	41.25 ± 2.30	>100	>100	>100
C1	32.22 ± 0.92	35.59 ± 1.03	33.51 ± 1.29	18.42 ± 0.37
L2	34.98 ± 1.44	81.35 ± 3.31	43.08 ± 2.17	>100
C2	24.29 ± 0.11	33.72 ± 0.39	34.44 ± 0.75	27.27 ± 1.05
L3	>100	>100	>100	>100
C3	46.54 ± 1.86	41.60 ± 1.93	41.34 ± 2.17	30.84 ± 1.11
L4	>100	>100	>100	>100
C4	30.05 ± 1.81	36.17 ± 0.44	35.01 ± 0.86	33.62 ±0.85
Etoposide	>100	67.83 ± 2.03	>100	>100

Recently, Nandaniya et al. presented a mini review with biological application of Schiff base metal complexes [132]. The text explores both the challenges and advancements related to the safety and efficacy of metal complexes in cancer therapy and the innovative role of nanotechnology in addressing these issues. Here's a summary of the main points:

Safety Issues with Metal Complexes

1. Toxicity Challenges: Despite their effectiveness, metal-based cancer drugs like cisplatin are associated with severe side effects, including nephrotoxicity, neurotoxicity, and ototoxicity [133]. These challenges have spurred the development of derivatives such as carboplatin, which, while promising, still face regulatory hurdles due to adverse effects.

2. Examples of Failed Derivatives: Several platinum-based drugs (e.g., JM-11, ormaplatin, zeniplatin, and spiroplatin) failed to gain market approval due to severe or unpredictable toxicities [129].

3. Gold and Copper Complexes: Gold(III) complexes, while studied for anticancer applications, can cause toxicity, particularly affecting skin and mucous membranes [134]. Elevated copper levels have been linked to cancer progression, further underscoring safety concerns [135].

4. Strategies to Mitigate Toxicity: Structural modifications of metal complexes aim to improve their selectivity for cancer cells and reduce adverse effects on healthy tissues.

Nanoparticles in Cancer Therapy

1. Advantages of Nanotechnology: Nanoparticles (NPs) offer targeted drug delivery, improving therapeutic index and reducing off-target effects [136]. They enhance bioavailability, solubility, and stability while facilitating sustained release and selective targeting of cancer cells.

2.Metal-Based Nanoparticles: Metal-based NPs (e.g., nickel, gold, silver, iron oxide, gadolinium) provide significant advantages in drug delivery and diagnosis due to their large surface area, which can carry higher drug loads.

3. Tumor-Specific Targeting: NPs can be functionalized with peptides, proteins, nucleic acids, or small molecules to target tumor-specific receptors or biomarkers, ensuring precise delivery [137]. This reduces toxicity in non-cancerous tissues.

4. Imaging and Therapeutic Applications: NP-based platforms are used for advanced optical imaging and therapeutic delivery. Their multifunctional nature enables combined diagnostic and

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therapeutic applications, paving the way for synergistic effects when combined with multidrug regimens.

While metal complexes remain a cornerstone of cancer treatment, their clinical use is often limited by toxicity and side effects. Innovations in nanotechnology provide a promising pathway to enhance the safety, efficacy, and specificity of metal-based cancer therapies, offering a brighter future for targeted and less toxic treatments.

3.2. Antimicrobial Activity (Antibacterial and Antifungal)

In recent years, particularly from 2015 onwards, Schiff-base metal complexes have garnered significant interest due to their noteworthy biological properties. Numerous studies have been published highlighting their applications in biological sciences [138,139]. Schiff-bases have demonstrated potential as antibacterial agents, with their metal complexes exhibiting superior antibacterial activity compared to the free ligands themselves [140–145]. Recent literature underscores the promising antimicrobial potential of Schiff-base metal complexes and highlights progress in the study of other intriguing topoisomerase inhibitors [146]. For instance, the Cu(II)-picolinic acid complex has been shown to act as a significant inhibitor in gel electrophoresis experiments [147]. Additionally, thiosemicarbazone derivatives of copper(II) have exhibited strong antibacterial activity, effectively targeting pathogens such as *S. aureus*, *S. typhimurium*, and *K. pneumoniae* after just six hours of incubation [148]. Literature reviews show that Schiff bases with antibacterial properties can be synthesized from coordination compounds with different ligands such as indole [149,150], pyridine [151–153], isatin [154,155], hydrazide [156,157], benzimidazole [158,159], thiazolidiones [160,161], thiazole [162], thiosemi-carbazone [163,164], lysine/curcumin [165,166], and siloxane [167]. Further examination of the literature reveals a significant rise in systemic fungal infections, which can be life-threatening [168]. Numerous studies highlight that Candida species (both albicans and non-albicans) and *Aspergillus species* (Asp.) are responsible for causing the most severe fungal infections [169–173]. Consequently, the development of new antifungal agents with reduced resistance and increased effectiveness has become a priority [174,175]. Extensive and meticulous research has been conducted, with several Schiff ligands identified as highly effective antifungal agents [176,177]. Researchers have also pointed out that specific groups, such as methoxy, halogen, and naphthyl, enhance the fungicidal activity of these ligands [178,179]. While still widespread, recent literature strongly emphasizes the promising potential of metal complex-based antifungal drug development [180,181]. In another study, Schiff base ligands and their mononuclear chelate complexes, incorporating metals like Cr(III), Fe(III), Mn(II), Cu(II), Zn(II), Ni(II), and Cd(II), were synthesized from the 4-((1-5-acetyl-2,4-dihydroxyphenyl)ethylidene) amino)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one ligand, a tridentate ligand. These complexes were used for in vitro tests to assess their antimicrobial activity against both Gram-negative and Gram-positive bacteria, as well as fungal organisms. In this research, the MOE 2008 software was used for drug screening by molecular docking at protein sites of the novel coronavirus, and the study included molecular docking validation through MD simulations [182]. The antimicrobial potential of zinc complexes, their unbound ligands, and standard drugs was examined against six strains of Gram-positive bacteria, five Gram-negative bacterial strains, and three yeast strains [102]. The minimum inhibitory concentrations (MICs) of the tested derivatives were determined against a panel of reference microorganisms from the American Type Culture Collection (ATCC). The panel included Gram-negative bacteria such as *Escherichia coli* (ATCC 25922), *Salmonella Typhimurium* (ATCC 14028), *Klebsiella pneumoniae* (ATCC 13883), *Pseudomonas aeruginosa* (ATCC 9027), and *Proteus mirabilis* (ATCC 12453). Gram-positive bacteria tested included *Staphylococcus aureus* (ATCC 25923), *Staphylococcus epidermidis* (ATCC 12228), *Micrococcus luteus* (ATCC 10240), *Enterococcus faecalis* (ATCC 29212), *Bacillus subtilis* (ATCC 6633), and *Bacillus cereus* (ATCC 10876). The antifungal activity was assessed against *Candida albicans* (ATCC 10231), *Candida parapsilosis* (ATCC 22019), and *Candida glabrata* (ATCC 90030). The antibacterial and antifungal efficacy was quantified using the minimum inhibitory concentration (MIC), expressed in milligrams per liter. The activity of zinc complexes was compared to the antimicrobial profiles of their corresponding ligands. Vancomycin (Van), ciprofloxacin (Cip), and nystatin (Nys) were employed as reference standards. The evaluated compounds demonstrated no activity against Gram-negative bacteria and yeasts. However, against Gram-positive

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bacteria, moderate activity was observed, with a slight enhancement in bioactivity for the zinc complexes [102].

3.2. Antioxidant Activity

There has been considerable interest in discovering compounds with antioxidant properties (see Figure 16). While natural antioxidants are typically the most costly, researchers have turned to synthetic antioxidants as a more cost-effective and efficient alternative. As a result, various metal complexes have been studied for their ability to act as effective scavengers of reactive oxygen species (ROS), functioning as antioxidants [183].

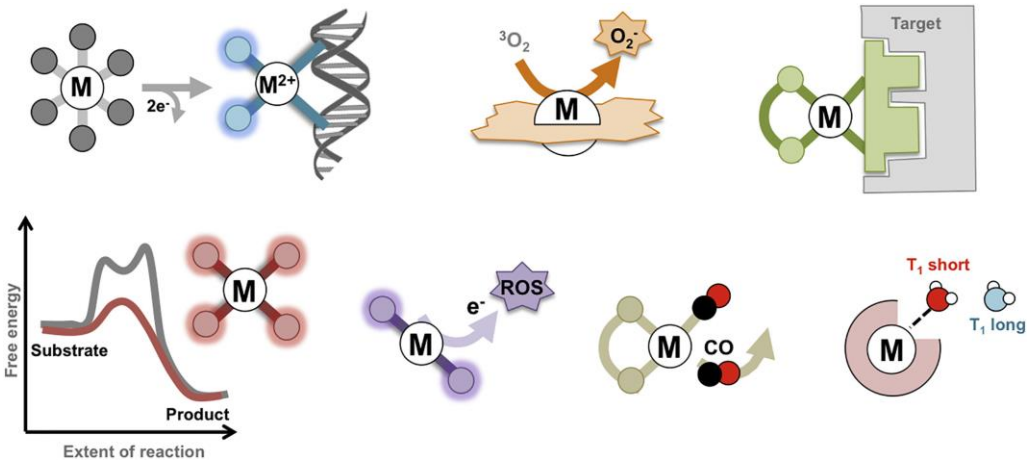

Figure 16. Summary of the Mechanism of Action of Metal-Based Drugs [178].

In a study by Devi and colleagues [184], 16 novel Ni(II), Cu(II), Co(II), and Zn(II) metal complexes were synthesized starting from four Schiff-base ligands. These ligands were created through a condensation reaction involving 4-(benzyloxy)-2-hydroxybenzaldehyde and various aminophenol derivatives. The antioxidant properties of these metal(II) complexes were evaluated *in vitro*, and the results revealed that the complexes exhibited notable potential (see Figure 17). Particularly, the Cu(II) complexes displayed excellent antioxidant activity, significantly decolorizing the purple DPPH solution, with an IC_{50} value ranging from 2.98 to 3.89 μM, which was more effective compared to the free ligands.

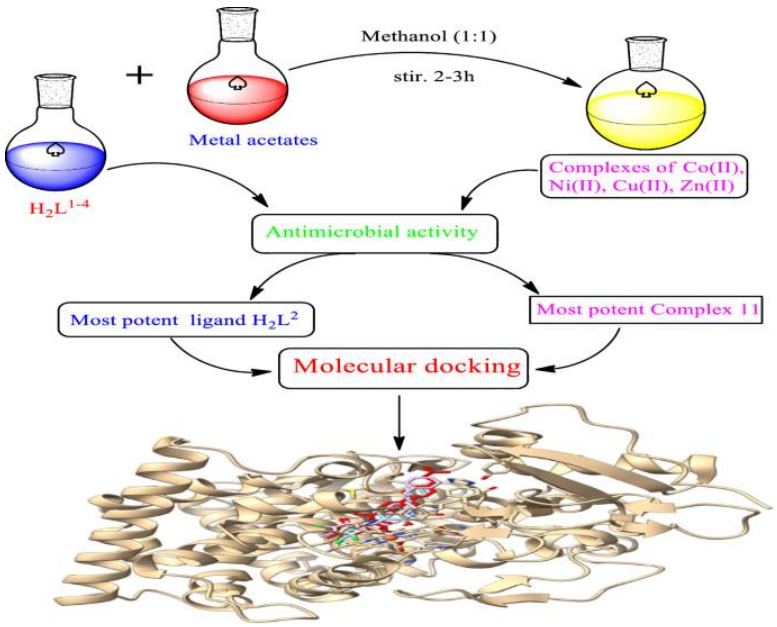

Figure 17. Possible mechanism of action of metal complex [184].

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A range of Schiff-base compounds, derived from diamine, sulfanilamide, hydroxyquinoline, thiocarbohydrazide, and benzohydrazide, with substituted ketone or aldehyde groups, as well as their Co(II), Zn(II), Cu(II), Fe(II), Ni(II), Pd(II), Cd(II), and Ru(II) metal complexes, have been examined for their antioxidant potential. Compounds with methyl and nitro groups exhibited stronger antioxidant activity compared to those with 4-hydroxy groups, leading to an enhancement in antioxidant performance [185,186].

A study conducted by Inan et al. demonstrated the antioxidant activity of these complexes using the L-ascorbic acid-standard method (DPPH) [187]. The complexes showed greater activity than the ligands themselves, likely due to the coordination of the metal ion with the organic ligand. Specifically, [Cu(II)-(furfural-MAP)$_2$Cl$_2$] and [Ni(II)-(furfural-MAP)$_2$Cl$_2$] showed significant antimicrobial activity, while [Zn(II)-(furfural-MAP)$_2$Cl$_2$] displayed moderate activity. The variance in antioxidant activity among the complexes was attributed to differences in their coordination sphere and redox properties [187]. Kizilkaya et al. explored the antioxidant capabilities of Schiff-bases synthesized using ABTS radical scavenging and DPPH free radical scavenging methods [188]. The synthesized compounds demonstrated good antioxidant activity, suggesting their potential as synthetic antioxidant agents.

3.4. Enzyme-Inhibitory Activities

Che et al. presented the metal complexes in medicine with a focus on enzyme inhibition [189]. Metal complexes containing labile ligands have long been recognized for their ability to undergo ligand-substitution reactions with biomolecular targets (see Figure 18).

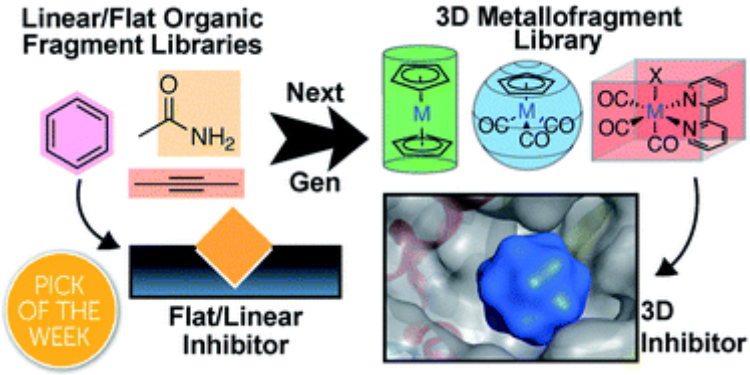

Figure 18. Fragment-based drug discovery (FBDD) is a powerful strategy for the identification of new bioactive molecules [179].

These metal ions interact with nitrogen, sulfur, or selenium atoms in histidine, cysteine, or selenocysteine residues found in proteins, often resulting in therapeutic effects. Some notable examples include:

Gold: Auranofin, a gold(I) phosphine complex (illustrated in Figure 19), is an established drug for managing rheumatoid arthritis. Recent findings indicate that gold from auranofin can transfer to the selenoprotein thioredoxin glutathione reductase, producing therapeutic effects against parasitic diseases. Additionally, auranofin demonstrated tumor cell growth inhibition *in vitro* [190]; however, its high reactivity with protein thiols limits its antitumor efficacy *in vivo* [191]. New research highlights a gold(I) phosphine complex with a naphthalimide ligand as a potent thioredoxin reductase inhibitor with significant antiproliferative and anti-angiogenic activities [192]. Furthermore, studies on a gold(III) dithiocarbamate complex (depicted in Figure 19) identified the proteasome as its main target [193], showing promise in therapeutic applications.

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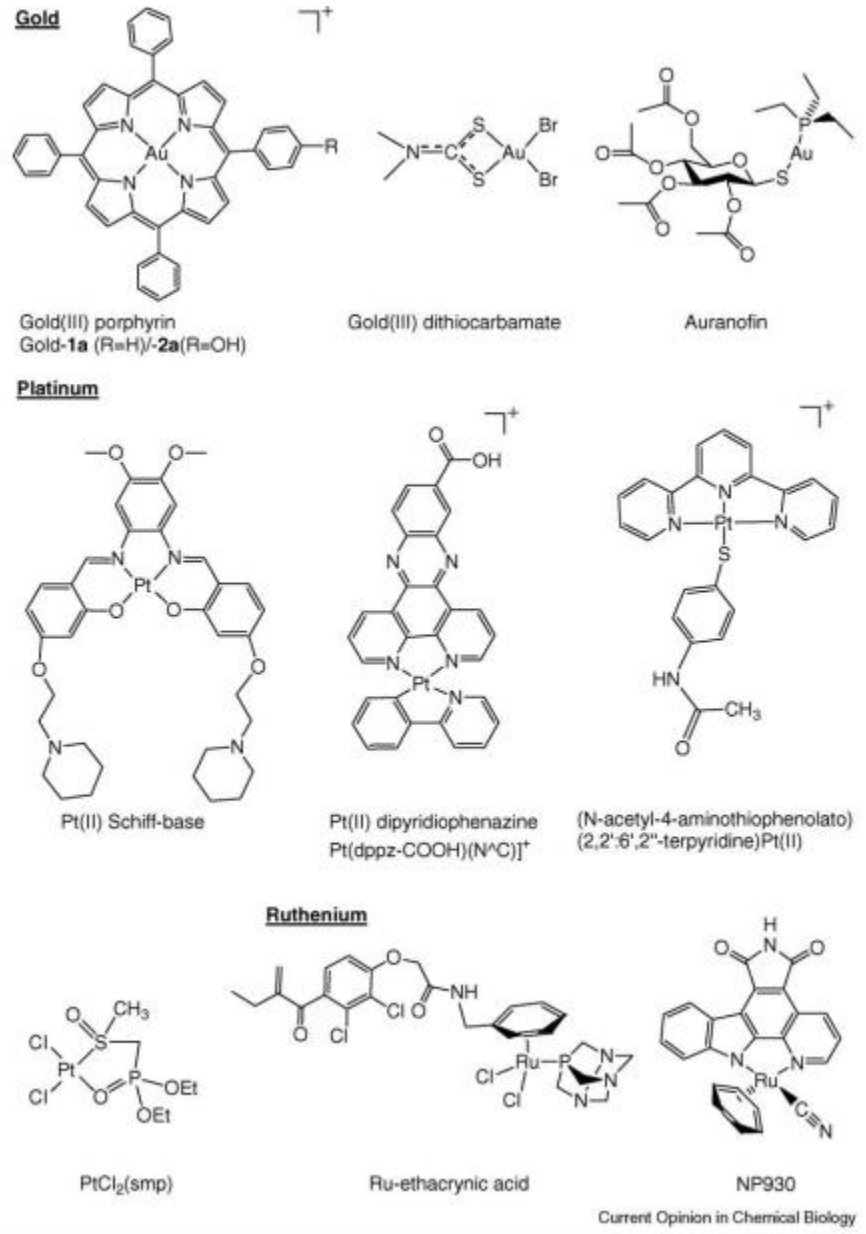

Figure 19. Examples of metal-based drugs with enzyme inhibitory effects [189].

Platinum: Selenoenzyme thioredoxin reductase has been identified as a target effectively inhibited by (2,2′:6′,2″-terpyridine)platinum(II) complexes (shown in Figure 19) with IC_{50} values at the nanomolar level [194]. Recently, research by Lo et al. employed X-ray crystallography and mass spectrometry to demonstrate that aromatic thiolato platinum(II)-terpyridine complexes inhibit human thioredoxin reductase 1 by blocking its C-terminal active-site selenocysteine [195]. Furthermore, a series of platinum(II)-terpyridine complexes exhibited inhibitory activity against topoisomerase II (top2). The mechanisms of top2 inhibition are diverse, involving DNA intercalation, enzyme binding, and modification of enzyme thiol groups. As such, these platinum(II)-terpyridine complexes are thought to inhibit topoisomerase II by ligand exchange reactions with the thiol groups of enzymes [195]. Additionally, a series of platinum(II) complexes with two or three labile ligands ($PtCl_2$(smp), Figure 19) demonstrated inhibitory effects on matrix metalloproteinase-3 (MMP-3) [196].

Ruthenium: A novel class of glutathione transferase inhibitors (denoted as Ru–EA, shown in Figure 1) was synthesized by coupling ethacrynic acid (EA), a potent glutathione transferase inhibitor, with a ruthenium complex [197]. Analysis using mass spectrometry and X-ray crystallography revealed that the Ru–EA complex initially loses two chloride ligands, followed by cleavage to release a ruthenium-containing fragment (Figure 19). Overall, metal complexes with labile

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ligands predominantly target proteins featuring selenocysteine or cysteine in their active sites, such as thioredoxin glutathione reductase, thioredoxin reductase, and glutathione transferase.

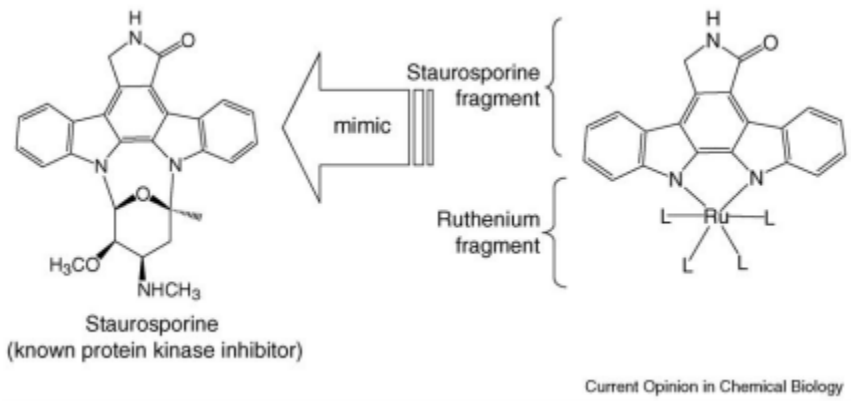

Figure 20. Ruthenium-based enzyme inhibitors [189].

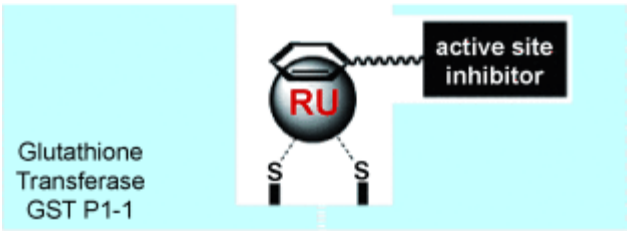

Figure 21. Ruthenium complex as glutathione transferase inhibitor [197].

A notable limitation of the metal complexes mentioned earlier is their lack of selectivity. These complexes often interact with human serum albumin or other proteins that have potential metal-binding sites, such as histidine, cysteine, or selenocysteine. Such interactions make it challenging to deliver metal complexes to specific biomolecular targets. For instance, while auranofin is known to inhibit thioredoxin glutathione reductase and suppress tumor cell growth *in vitro* [190], its strong reactivity with protein thiols significantly reduces its antitumor efficacy *in vivo* [191]. To address this, Berners-Price and Filipovska developed a series of gold(I) complexes engineered to preferentially target proteins containing selenocysteine while avoiding cysteine, achieved by optimizing ligand exchange reactions at the gold(I) center [198].

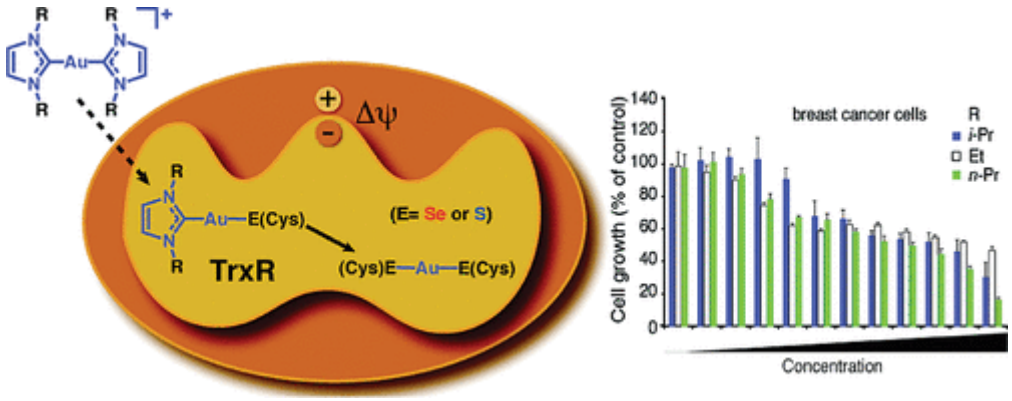

Figure 22. Gold(I) complex inhibit the activity of thioredoxin reductase (TrxR) but not the closely related and Se-free enzyme glutathione reductase [198].

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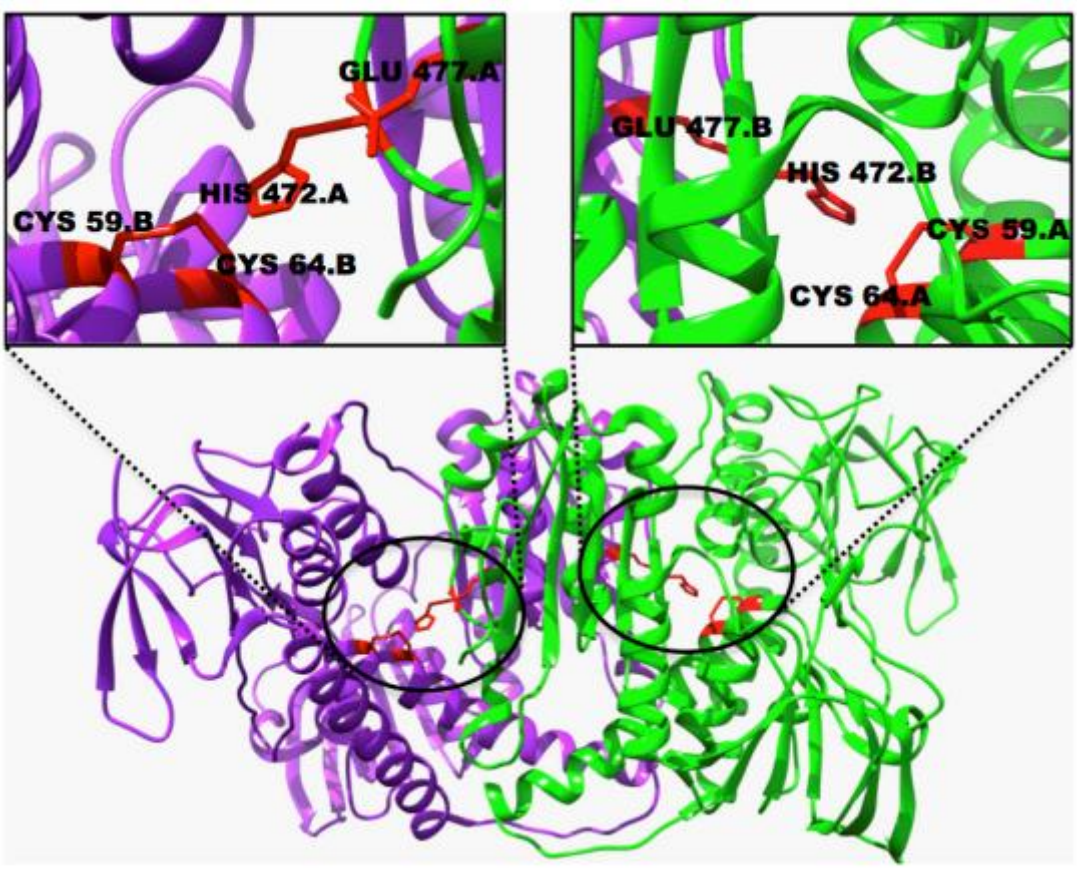

Figure 23. A 3D structure of the TrxR reductase homodimer (PDB entry 2J3N), with two chains in green and purple. Note: The active site residues CYS 59.B, CYS 64.B, HIS 472.A and GLU 477.A represent the possible binding site for the gold(III) compou Abbreviations: TrxR, thioredoxin reductase; PDB, Protein Data Bank; CYS, cysteine; HIS, histidine; GLU, glutamate [104].

Additionally, the role of labile ligands or leaving groups in metal complexes has been rigorously investigated [199]. Efforts are ongoing to enhance the stability of metal complexes under physiological conditions to discover unique anticancer properties in substitution-inert complexes.

4. Schiff-Base Complexes as Catalysts

Schiff-base complexes with transition metals have become highly sought-after co-catalysts due to their accessibility and the versatility of metal centers that can be integrated into the N_2O_2 coordination sphere [200,201]. Their structure allows for a wide range of substituents, enabling chemical flexibility and covalent stability, which is crucial when such catalysts are used on supports [202,203]. Numerous studies have demonstrated that Schiff-base metal complexes possess excellent catalytic activity, which can enhance product selectivity and yield in various processes [204–206]. The synthesis methods and thermogravimetric stability of these complexes play a key role in their performance as metal catalysts.

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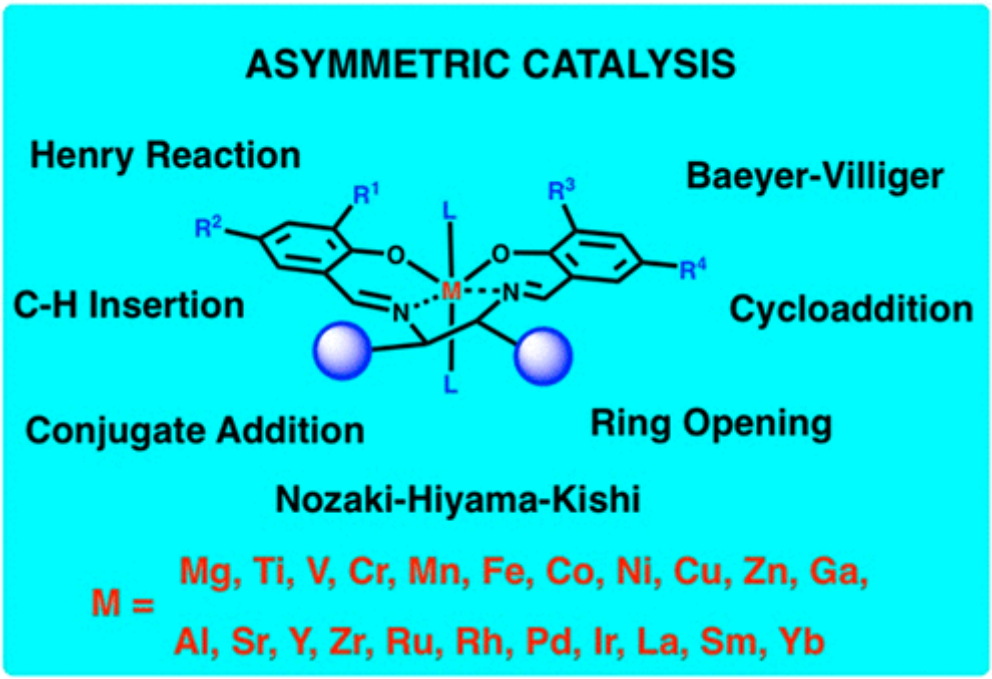

Figure 23. Application of metal complexes as catalysts [206].

These complexes, formed from transition metal ions, are effective in both homogeneous and heterogeneous catalytic processes. Their catalytic activity depends on factors like the type of metal ion, ligands, and coordination sites. Schiff-bases are particularly useful because they can coordinate a variety of metals at different oxidation states, enhancing the metal ions' catalytic performance across various reactions [207]. For example, the catalytic activity of Congo red (CR) in photodecomposition under natural light was assessed using a Co-complex of CX and EBPy, showing a discoloration efficiency of nearly 82% after 80 minutes of exposure to sunlight [208].

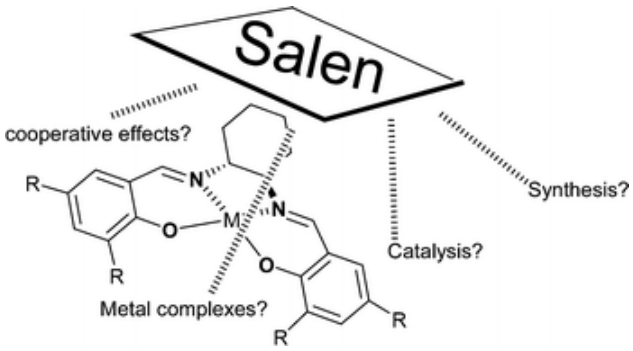

Figure 24. Different coordination compounds used in catalysis [207].

Schiff-base complexes with metals like V, Mn, Fe, Co, Ni, Cu, and Zn have also been studied as catalysts for alkene peroxidation reactions, such as those involving limonene, cyclohexene, and styrene [209]. These polymer-supported complexes have shown promising catalytic properties when compared to unsupported catalysts, offering unique advantages in material science and catalysis.

The average particle size of the prepared nanofilms, derived from the organic ligand and its chromium(III) complex, were 94 nm and 98 nm, respectively [210]. Optical properties revealed that the direct energy gaps of the nanoparticles (L and M) were 2.6 eV and 3.2 eV, respectively. These results can be attributed to the quantum size effect. X-ray diffraction (XRD) data confirmed the polycrystalline nanostructures of (L and M), with no other phases detected. The efficiency of the fabricated inorganic silicon solar cell (M/Si) was found to be higher than that of the organic solar cell (L/Si).

5. Conclusions

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Coordination compounds have demonstrated unparalleled versatility due to their structural diversity and range of applications. The synthesis of these compounds has progressed significantly, incorporating both conventional techniques and innovative approaches to achieve desired properties. Their structural and spectroscopic investigations reveal insights into their reactivity and stability, underpinning their functional potential.

Biologically, coordination compounds stand out for their significant roles as antimicrobial agents, anticancer drugs, and enzyme inhibitors. These properties underscore their potential in therapeutic development and biomedical applications. Beyond biology, their applications in catalysis and advanced material science illustrate their broad utility across various fields.

By bridging fundamental inorganic chemistry with applied sciences, coordination compounds hold promise for addressing some of the most pressing global challenges. The continued exploration of novel synthetic methods, coupled with detailed biological and structural evaluations, will pave the way for innovative solutions in healthcare and technology.

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