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Transition Metal Complexes of Schiff Base Thiosemicarbazones: A Comprehensive Review of Anti-Cancer and Antiviral Activity

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Abstract
Scientific communities examine Schiff base thiosemicarbazones and their transition metal complexes because these compounds display exceptional biological properties. The compounds create distinct chemical properties because they allow structural changes through simple synthesis methods and they can bind with multiple metals which have biological importance including copper and cobalt and nickel and zinc and platinum. This review brings together evidence from in vitro, in vivo, and computational studies to examine how these complexes exert anti-cancer and antiviral effects. The anti-cancer activity occurs through four main processes which include DNA intercalation and ribonucleotide reductase inhibition and apoptosis induction and reactive oxygen species balance disruption. Antiviral activity shows potential against herpes simplex virus and HIV and influenza strains which have been researched less than other viruses. The structure-activity relationships demonstrate that three factors which include metal center characteristics and thiosemicarbazone backbone substituents and complex geometry determine the active compound strength. The article examines existing knowledge gaps between in vivo toxicity and clinical application to provide research paths for upcoming studies.
Keywords: *thiosemicarbazone, transition metal complexes, antiviral activity, Schiff base, anti-cancer activity, ribonucleotide reductase*

I. Introduction

Drug resistance presents itself as the primary challenge which modern medicine currently faces. The medical community requires new drugs with different chemical properties because cancer cells develop resistance to chemotherapy and viruses transform their structure to evade antiviral medications. Transition metal complexes have been discreetly developing their potential to function as therapeutic agents and Schiff base thiosemicarbazone complexes represent the most compelling candidates. The story begins with cisplatin. The 1960s discovery of this basic platinum compound which demonstrated powerful anti-cancer effects changed the way scientists viewed how inorganic substances functioned in medicine. The discovery opened a research pathway which scientists have followed to examine copper, cobalt, nickel, zinc, and vanadium together with various other metals as possible drug development frameworks.

Schiff bases are another piece of this puzzle. Primary amine molecules react with carbonyl compounds through a process that produces pure compounds which exhibit strong metal-building capabilities. The thiosemicarbazone group attached to the Schiff base structure creates a biologically active ligand that scientists should investigate. Thiosemicarbazones have known activity against cancer and viruses even on their own. The combination of a transition metal with this compound creates a new material which demonstrates increased performance through combined effects that scientists should investigate. The review presents the existing knowledge about how these complexes operate against cancer and viruses which structural aspects show the greatest importance and which scientific fields need further investigation.

II. Schiff Bases and Thiosemicarbazones: Understanding the Chemical Foundation

2.1 What Makes These Ligands Special

A Schiff base is defined by the azomethine linkage — the C=N bond that forms during condensation. The group has two important values because of its structural design and its ability to function as a medication. The nitrogen atom in the azomethine group possesses a lone electron pair which enables it to form metal ion bonds, thus enabling Schiff bases to function as effective chelating agents. The ligands establish metal binding through two to four coordination points depending on which donor groups are present such as hydroxyl group or thiol group or amino group.

Thiosemicarbazones create a picture which includes a sulfur-containing arm. The N-N-C=S fragment in thiosemicarbazones enables flexible coordination while introducing sulfur as a soft donor which biologically active metal ions naturally attract. The thione/thiol tautomerism in these compounds is also significant because

it determines their coordination chemistry and their ability to interact with biological targets which include enzymes and DNA.

The combination of the azomethine nitrogen from the Schiff base and the thiosemicarbazone fragment results in a ligand that possesses exceptional adaptability. The compound establishes metal coordination through multiple geometric forms while it carries different substituents which enable electronic property control and it maintains sufficient lipophilicity to cross cell membranes. The research community has been attracted to this class of compounds because of their distinctive features which explain their widespread appeal to research groups across the globe.

2.2 Synthesis: Straightforward and Adaptable

The compounds drew extensive research attention because researchers found them to be easy to produce. Scientists use the typical synthetic route which requires them to combine thiosemicarbazide with an appropriate aldehyde or ketone through a process that occurs under mildly acidic conditions. The metal complex typically forms through the reaction of Schiff base thiosemicarbazone ligand with its metal salt in an organic solvent system which uses ethanol or methanol as its primary solvent. Researchers use the simple method of producing new compounds to develop libraries of structurally related compounds which enable them to assess different substituent combinations on the aromatic ring and the thiosemicarbazone nitrogen atoms and the metal center. The combinatorial approach provides valuable insights which demonstrate this method's effectiveness for building structure-activity relationship mapping.

III. Anti-Cancer Activity of Metal-Thiosemicarbazone Complexes

3.1 The Ribonucleotide Reductase Connection

The most thorough scientific knowledge about how thiosemicarbazones combat cancer operates through ribonucleotide reductase as the key mechanism. The process of cancer cell division requires continuous deoxyribonucleotide supply because cancer cells replicate DNA at an unending pace. RNR serves as the enzyme that creates these essential components by transforming ribonucleotides into their deoxy counterparts. Cancer cells lose their ability to reproduce when RNR function is blocked because this process prevents them from obtaining necessary resources.

Thiosemicarbazones act as highly effective RNR enzyme inhibitors. The compound 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, known as Triapine, reached clinical trials precisely because of this mechanism and remains one of the most studied thiosemicarbazone-type drugs in oncology. Thiosemicarbazone ligands achieve superior RNR inhibition when transition metals, especially copper and iron, form coordination complexes with them. The metal catalyzes redox cycling that prevents RNR function by damaging the tyrosyl radical which RNR needs to operate.

3.2 DNA Binding and Intercalation

The complexes establish direct contact with DNA through their interactions which lead to cellular death. The studies used UV-visible spectroscopy and fluorescence displacement assays and circular dichroism to demonstrate that metal-thiosemicarbazone complexes bind to DNA through intercalation because their flat aromatic structures penetrate the double helix base pairs. The process creates physical alterations to DNA which block transcription and replication while leading to programmed cell death.

The research has focused on Copper(II) complexes which use Schiff base thiosemicarbazone ligands as their main component. Ramesh and his research team discovered that copper complexes with condensed aromatic thiosemicarbazones showed binding constants between 10^4 and 10^6 M^{-1} which matched the binding strength of established intercalating drugs. The complexes demonstrated nuclease activity which allowed them to break DNA strands and disrupt cancer cell replication.

The anti-cancer action mechanism of these complexes involves multiple pathways which together reduce cancer cell survival according to Figure 1.

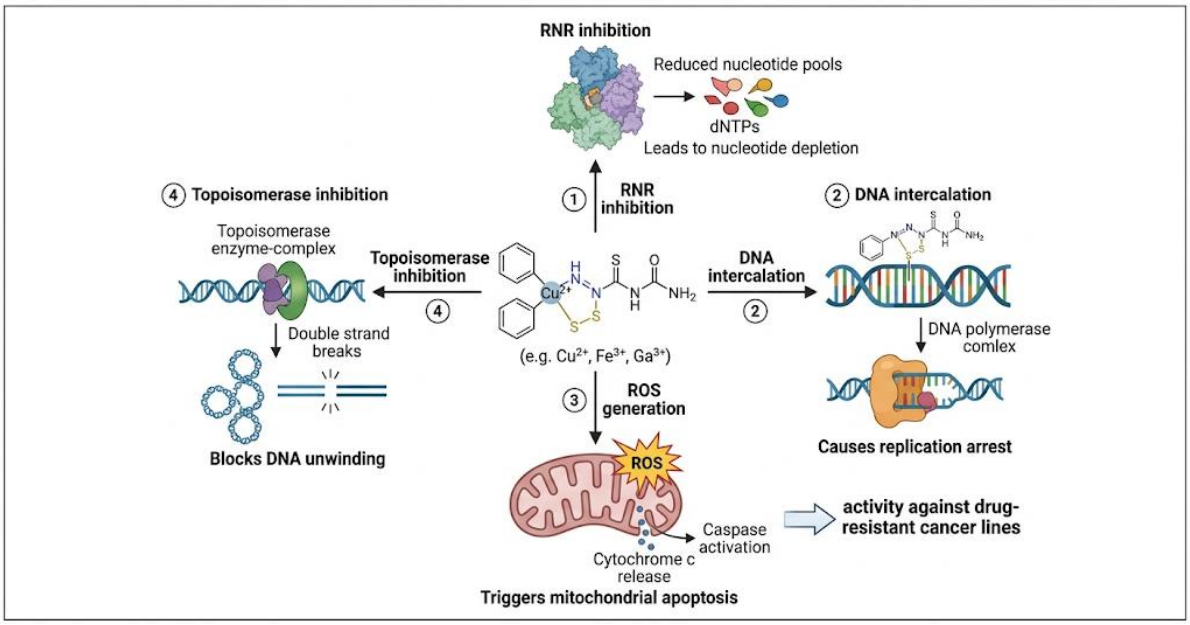

Figure 1: Proposed Mechanisms of Anti-Cancer Action of Transition Metal-Thiosemicarbazone Schiff Base Complexes

The diagram shows the main pathways through which transition metal Schiff base thiosemicarbazone complexes display their anti-cancer effects. The central molecule represents a generic metal-thiosemicarbazone complex, with arrows branching outward to four targets: RNR inhibition leading to nucleotide depletion, DNA intercalation causing replication arrest, ROS generation triggering mitochondrial apoptosis, and topoisomerase inhibition blocking DNA unwinding. The branch displays an abbreviated description of how the cellular function will be affected. The diagram shows that these compounds create multiple active sites which scientists think help them combat cancer types that do not respond to treatment.

3.3 Reactive Oxygen Species and Apoptosis

Copper complexes show the ability to produce reactive oxygen species (ROS) through their redox process between Cu(I) and Cu(II) states. The process creates excessive oxidative stress which surpasses the cell's antioxidant defenses and destroys the mitochondria until the cell undergoes programmed death. The drug design method attracts interest because cancer cells show increased ROS production which creates a dangerous situation for them. Increasing their ROS levels with an external source results in their destruction.

Multiple research groups have discovered that copper(II)-thiosemicarbazone complexes effectively eliminate cancer cells while sparing normal cells during cell culture tests. The scientific community continues to investigate whether this selectivity maintains its effectiveness in real-world situations.

3.4 Activity Against Specific Cancer Lines

Research teams across multiple countries have screened these complexes against common cancer cell lines. The reported results demonstrate treatment effectiveness against breast cancer which uses MCF-7 cells and cervical cancer which uses HeLa cells and lung cancer which uses A549 cells and colon cancer which uses HCT-116 cells and multiple additional cancer types. The needed concentration to achieve 50 percent cell death which represents IC_{50} values has shown results which fall below the established level of standard chemotherapeutic drugs including cisplatin which serves as a positive outcome. The nickel(II) and cobalt(II) complexes which researchers created from heterocyclic aldehyde thiosemicarbazones show exceptional ability to kill HeLa cells according to multiple studies which report IC_{50} values that fall within the low micromolar range. Zinc complexes demonstrate lower toxicity to normal cell lines compared to copper yet they produce moderate biological activity which creates an additional advantage.

IV. Antiviral Activity: A Promising but Less-Charted Territory

4.1 Historical Context and Early Discoveries

The antiviral effects of thiosemicarbazones existed before most cancer studies started. Research during the 1950s revealed that certain thiosemicarbazone derivatives could stop vaccinia virus from spreading. Although this discovery never became an approved clinical antiviral at the time, it created a foundation which future researchers returned to investigate further.

The metal complexes of these ligands have added a new dimension to this older story. Multiple studies conducted since the early 2000s demonstrate that thiosemicarbazones show increased antiviral activity when they bind with metals such as copper or zinc or cobalt compared to their unbound state.

4.2 Mechanisms of Antiviral Action

Scientists continue to study how these complexes block viral activity because current research still does not fully explain their mode of action. First, many viruses depend heavily on metalloenzymes — proteases, polymerases, and integrases — that can be disrupted by metal-chelating compounds. The thiosemicarbazone complex competes with viral metal cofactors to destroy vital enzymes which are required for standard virus operation.

Some complexes block viral DNA and RNA production by forming direct links with viral nucleic acids which work similarly to their earlier described connections with mammalian DNA. The same mechanism that causes ROS generation to harm cancer cells also operates as a selective agent which destroys both viral particles and infected host cells.

4.3 Activity Against Specific Viruses

Scientists have researched multiple viruses which include herpes simplex virus (HSV-1 and HSV-2) and human immunodeficiency virus (HIV) and influenza A and hepatitis B and human cytomegalovirus. The copper(II) complexes which contain thiosemicarbazone Schiff base ligands demonstrate substantial inhibitory power against HSV in plaque reduction tests. The selectivity index of these compounds which measures the ratio between cytotoxic concentration and antiviral effective concentration has been found to exceed 10 for several compounds which creates a safe therapeutic window.

HIV has been another target of interest. Some vanadium and copper thiosemicarbazone complexes have shown activity against HIV reverse transcriptase in enzyme assays. The transition from enzyme assays to cell culture and animal models has proven more challenging for antiviral research than it has for anti-cancer research. Sriram and his team conducted research which tested thiosemicarbazone derivatives against influenza strains. Their study showed that copper complexes performed better than both free ligand and silver and zinc analogs. The study shows that copper provides unique advantages which enhance both anti-cancer and anti-viral treatments.

Figure 2 summarizes comparative antiviral activity data across different metal complexes and virus types, highlighting where the strongest effects have been observed.

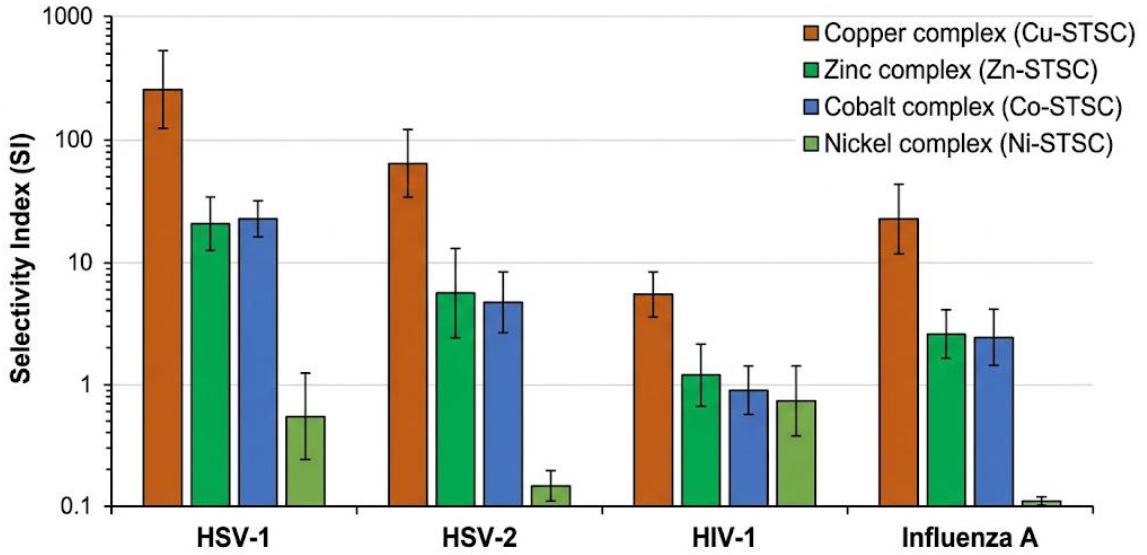

Figure 2: Comparative Antiviral Activity of Selected Transition Metal-Thiosemicarbazone Complexes Against Common Viral Pathogens

The chart shows a comparison of antiviral effectiveness which is measured by selectivity index values for copper zinc cobalt and nickel Schiff base thiosemicarbazone complexes that were tested against four different viruses which include HSV-1, HSV-2, HIV-1, and Influenza A. The x-axis lists the virus types while the y-axis shows the selectivity index on a logarithmic scale. The results demonstrate that copper complexes maintain their highest SI values throughout testing because they exceed 10 for both HSV strains and show

moderate results for HIV. The zinc and cobalt complexes display moderate effects against HSV. The figure shows how the metal center functions as the main component that decides antiviral efficacy and selectivity.

5.1 Structure-Activity Relationships: What the Data Actually Tells Us

Understanding which structural features drive biological activity is arguably the most practically useful goal in this field. Over dozens of studies, some clear patterns have emerged — even if the picture is still far from complete.

5.2 The Role of the Metal Center

The selection of metal remains the primary factor that determines all other elements. Copper(II) complexes exceed their zinc(II) nickel(II) and cobalt(II) counterparts in both anticancer and antiviral testing. The phenomenon occurs because copper exhibits redox behavior through its ability to alternate between its +1 and +2 oxidation states which enables it to create reactive oxygen species that disrupt enzyme activity.

Platinum and palladium complexes, which take their design cues from the cisplatin framework, have demonstrated potent therapeutic effects. Multiple research teams have developed platinum-thiosemicarbazone complexes which they intend to use as either standalone treatments or together with current platinum-based medications. The complexes demonstrate ability to combat cisplatin-resistant cell lines, which constitutes an important discovery because cisplatin resistance has become a widespread problem in clinical practice.

5.3 Substituent Effects on the Ligand

The substituents on the aromatic ring of the Schiff base portion — whether electron-donating or electron-withdrawing — significantly affect both the electronic properties of the ligand and the geometry of the resulting complex. Electron-withdrawing groups like nitro ($-NO_2$) or halogens tend to increase the Lewis acidity at the metal center and often enhance DNA binding. Electron-donating groups like methoxy ($-OCH_3$) or amino ($-NH_2$) tend to improve lipophilicity and membrane permeability.

Methyl or phenyl substitution on the terminal nitrogen of the thiosemicarbazone arm also affects activity. N(4)-phenyl substituted thiosemicarbazones generally form more stable complexes and show enhanced biological activity compared to the unsubstituted parent compounds. This observation has been reproduced across multiple studies using different metals.

5.4 Geometry and Denticity

Tetrahedral, square planar, and octahedral geometries all appear in this class of compounds depending on the metal and the ligand design. Square planar copper and nickel complexes with bidentate or tridentate Schiff base thiosemicarbazones tend to be the most biologically active, possibly because their flat geometry facilitates DNA intercalation. Octahedral cobalt and iron complexes with tridentate or tetradentate ligands show more moderate activity but sometimes excellent selectivity for cancer cells over normal cells.

VI. Conclusion

Transition metal complexes of Schiff base thiosemicarbazones represent a genuinely exciting area of medicinal inorganic chemistry. The evidence accumulated over the past two decades leaves little doubt that these compounds have real biological activity — against a range of cancer types and, more tentatively, against several clinically important viruses. The field has matured enough to have a reasonable understanding of which structural features matter and why, even if the mechanistic picture is still incomplete in places.

What the field needs now is not more in vitro screening studies — there are hundreds of those already. What it needs is deeper mechanistic work, better in vivo pharmacokinetic data, and serious efforts to understand and minimize toxicity to normal tissues. The chemistry is clearly rich enough to support a new generation of drugs. The biological science just needs time to catch up.

For researchers entering this space, the opportunities are significant. Questions about antiviral selectivity, the role of metal speciation in biological media, and the combination of these complexes with established drug classes are all largely open. The molecules themselves are inviting collaboration between synthetic chemists, cell biologists, virologists, and pharmacologists. That kind of interdisciplinary energy is exactly what translating promising compounds into real medicines requires.

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