Xplore Environment
An International Journal

OPEN ACCESS

ISSN 3117-6143
Short Communication

Transition Metal Complexes with Heterocyclic Ligands for Anticancer Drug Development

Amit Thakur*[1], Sarita Thakur[2] and Arvind Thakur[3]

[1]*Aadhrshila Academy, Jogindernagar, Distt Mandi, Himachal Pradesh 175015, India*
[2]*Government Senior Secondary School Barot, Himachal Pradesh 175013, India*
[3]*Abryl Laboratories Dera Bassi, Dera Bassi, Punjab 14050, India*

Corresponding author: **Amit Thakur** | E-mail: **thakur.amit422@gmail.com**

Citation: Amit Thakur, Sarita Thakur and Arvind Thakur (2021). Transition Metal Complexes with Heterocyclic Ligands for Anticancer Drug Development. *Xplore Environment: An International Journal.* **DOI: https://doi.org/10.51470/XE.2021.1.2.17**

Received 04 July 2021 | Revised 11 August 2021 | Accepted 13 September 2021 | Available Online October 19 2021

Abstract

Transition metal complexes containing heterocyclic ligands have emerged as an important class of candidates in contemporary anticancer drug development because they combine the structural diversity of organic heterocycles with the distinctive coordination, redox, and kinetic properties of metal centers. Unlike conventional organic drugs, metal complexes can undergo ligand exchange, participate in redox reactions, interact with nucleic acids and proteins, and generate reactive oxygen species, thereby providing multiple mechanisms for disrupting cancer-cell survival. Heterocyclic ligands containing nitrogen, oxygen, sulfur, and phosphorus donor atoms can further regulate the geometry, stability, lipophilicity, cellular uptake, and biological reactivity of metal complexes. This review discusses the principles underlying the design and synthesis of transition metal complexes containing heterocyclic ligands, with emphasis on ruthenium, platinum, copper, cobalt, nickel, palladium, zinc, and iron systems. Important heterocyclic scaffolds, including pyridine, imidazole, benzimidazole, quinoline, quinazoline, thiazole, triazole, indole, and thiosemicarbazone derivatives, are examined in relation to their coordination behavior and anticancer properties. The principal mechanisms of action include DNA interaction, oxidative stress, mitochondrial dysfunction, apoptosis, cell-cycle arrest, enzyme inhibition, and interference with cancer-associated signaling pathways. Approaches for improving selectivity, aqueous stability, cellular uptake, and pharmacological performance are also discussed. Particular attention is given to structure–activity relationships, biological evaluation, resistance mechanisms, toxicity, and emerging nanotechnology-assisted delivery strategies. Overall, rational integration of metal coordination chemistry and heterocyclic medicinal chemistry provides a versatile platform for developing next-generation metallotherapeutic agents.

Keywords: *Transition metal complexes; heterocyclic ligands; anticancer agents; coordination chemistry; apoptosis; reactive oxygen species; cancer therapy.*

1. Introduction

Cancer is a heterogeneous group of diseases characterized by uncontrolled cellular proliferation, genomic instability, altered metabolism, resistance to apoptosis, and the ability to invade surrounding tissues and establish metastases. Despite substantial advances in surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, the treatment of many malignancies remains challenging because of tumor heterogeneity, therapeutic resistance, systemic toxicity, and limited selectivity between malignant and normal cells. The development of structurally novel therapeutic agents capable of acting through mechanisms distinct from conventional organic drugs is therefore an important objective of modern medicinal chemistry. Metal-based compounds occupy a distinctive position in drug discovery because metal ions possess chemical properties that cannot readily be reproduced by carbon-based molecular frameworks.

Their variable oxidation states, coordination numbers, geometries, ligand-exchange kinetics, redox characteristics, and ability to interact with biological molecules provide numerous opportunities for therapeutic intervention. The clinical success of platinum compounds, particularly cisplatin and its subsequent generations, established metal coordination chemistry as a valuable foundation for anticancer drug development. However, conventional platinum chemotherapy is associated with important limitations, including nephrotoxicity, neurotoxicity, ototoxicity, gastrointestinal adverse effects, and the development of drug resistance [1]. These limitations have stimulated research into alternative transition metals and new ligand architectures. Ruthenium, copper, cobalt, iron, palladium, nickel, and other metals have consequently been investigated as potential components of anticancer complexes.

Heterocyclic ligands are especially attractive for this purpose. Their aromatic and heteroatom-rich structures provide tunable electronic properties and multiple coordination sites. Nitrogen-, oxygen-, and sulfur-containing heterocycles can strongly influence the physicochemical and biological behavior of their metal complexes. The combination of a transition metal with a biologically active heterocycle may therefore produce compounds with enhanced target affinity, cellular uptake, and anticancer activity [2]. This review summarizes the development of transition metal complexes containing heterocyclic ligands, focusing on their synthesis, structural characterization, mechanisms of anticancer action, structure–activity relationships, biological evaluation, challenges, and future prospects.

2. Role of Heterocyclic Ligands in Metallodrug Design

Heterocyclic compounds are among the most frequently encountered structural motifs in pharmaceutical chemistry. Their biological importance arises from their ability to participate in hydrogen bonding, π–π interactions, hydrophobic interactions, electrostatic interactions, and metal coordination. When incorporated into coordination complexes, these characteristics can be substantially modified.

The presence of donor atoms such as nitrogen, oxygen, and sulfur enables heterocyclic ligands to bind transition-metal centers through monodentate, bidentate, tridentate, or multidentate coordination modes. The resulting complexes can exhibit different geometries, including octahedral, square-planar, tetrahedral, and distorted coordination environments. Ligand modification can also influence the lipophilicity and overall charge of a complex [3]. These parameters are important because cellular uptake is often dependent on membrane permeability, transporter interactions, and endocytic mechanisms. Highly hydrophobic complexes may exhibit improved membrane penetration but may also demonstrate poor aqueous solubility and nonspecific accumulation. Conversely, highly hydrophilic complexes may exhibit reduced membrane permeability. The ligand therefore acts not merely as a structural component but as a pharmacological determinant that can influence stability, biodistribution, cellular localization, target interaction, and toxicity.

3. Important Heterocyclic Ligands

3.1 Pyridine-Based Ligands

Pyridine is a simple aromatic nitrogen-containing heterocycle that serves as an effective coordination ligand for numerous transition metals. Substitution around the pyridine ring can modify steric and electronic properties and consequently influence the biological activity of the resulting complex.

Pyridine-containing complexes have been investigated for DNA interaction, enzyme inhibition, oxidative stress induction, and interference with cellular signaling. Substituted pyridines can additionally provide functional groups capable of hydrogen bonding or biological targeting.

3.2 Imidazole and Benzimidazole

Imidazole and benzimidazole derivatives possess nitrogen atoms capable of coordinating transition metals. Benzimidazole provides an extended aromatic surface that can facilitate interactions with nucleic acids and protein binding pockets.

Metal complexes containing benzimidazole ligands have demonstrated anticancer activity in various experimental models, with mechanisms involving DNA interaction, apoptosis, oxidative stress, and enzyme inhibition.

3.3 Quinoline and Quinazoline

Quinoline and quinazoline scaffolds are important pharmacophores in medicinal chemistry. Their fused aromatic structures facilitate π-stacking and hydrophobic interactions, while nitrogen atoms provide coordination sites.

Quinazoline derivatives are particularly important in kinase-targeted drug discovery. Coordination with transition metals can further modify their electronic properties and introduce additional biological mechanisms.

3.4 Thiazole and Thiazole-Derived Ligands

Thiazoles contain both nitrogen and sulfur atoms and can provide versatile coordination behavior. Their electronic characteristics and biological activity have made them useful components of anticancer ligand systems.

Thiazole-containing metal complexes have been investigated for cytotoxicity, oxidative stress induction, DNA interaction, and enzyme inhibition.

3.5 Triazoles

Triazoles contain multiple nitrogen atoms and can coordinate metal ions through different binding modes. Their chemical stability, hydrogen-bonding properties, and capacity for structural modification make them valuable scaffolds for metallodrug design.

3.6 Indole Derivatives

Indole is a biologically significant fused heterocycle found in numerous natural products and pharmaceutical compounds. Indole-based ligands can combine intrinsic biological activity with metal-mediated effects [4].

3.7 Thiosemicarbazones

Thiosemicarbazones are particularly important in metal-based anticancer research because their nitrogen and sulfur donor atoms readily coordinate transition metals. Both the free ligands and their metal complexes may possess biological activity, while metal coordination can modify redox properties, stability, and cellular behavior.

4. Transition Metals in Anticancer Complexes

4.1 Platinum

Platinum is the most clinically established transition metal in cancer chemotherapy. Platinum complexes can undergo aquation and subsequently interact with nucleophilic sites in DNA, particularly guanine residues. This can produce DNA adducts, distort DNA architecture, and interfere with replication and transcription [5].

Despite their efficacy, platinum drugs are associated with toxicity and resistance. Consequently, current research focuses on developing platinum complexes with alternative geometries, different ligand-exchange properties, and improved tumor selectivity.

4.2 Ruthenium

Ruthenium has become one of the most extensively investigated alternatives to platinum. Ruthenium complexes can display variable oxidation states and ligand-exchange behavior and may exploit biological pathways associated with tumor microenvironments. Ruthenium complexes have been investigated for DNA binding, protein interaction, oxidative stress, mitochondrial disruption, and inhibition of metastatic processes. Their coordination chemistry also permits extensive ligand modification.

4.3 Copper

Copper is an endogenous trace element involved in numerous physiological processes. Copper complexes are attractive because they can participate in redox cycling and influence intracellular reactive oxygen species. Copper complexes containing heterocyclic ligands may promote oxidative stress selectively under certain cellular conditions. However, careful optimization is necessary because excessive copper-mediated oxidative activity can also damage normal tissues.

4.4 Cobalt

Cobalt possesses diverse coordination chemistry and can exist in several oxidation states. Cobalt complexes containing nitrogen- and sulfur-donor ligands have demonstrated experimental anticancer activity through oxidative stress, DNA interaction, and enzyme modulation.

4.5 Iron

Iron is an essential biological metal involved in oxygen transport, electron transfer, and cellular metabolism. Iron-containing complexes may influence redox homeostasis and can potentially exploit the altered iron metabolism characteristic of some tumors.

4.6 Palladium

Palladium complexes share certain structural characteristics with platinum compounds but exhibit different ligand-exchange kinetics. Heterocyclic palladium complexes have been investigated for DNA interaction, enzyme inhibition, and cytotoxicity.

4.7 Nickel and Zinc

Nickel complexes have demonstrated diverse biological activities, although toxicity and biological compatibility require careful evaluation. Zinc complexes are particularly interesting because zinc is an essential biological metal and can influence enzyme function and protein structure.

5. Synthesis of Transition Metal–Heterocyclic Complexes

The synthesis of transition metal complexes generally involves the reaction of a preformed heterocyclic ligand with an appropriate metal precursor under controlled conditions. The choice of solvent, temperature, pH, reaction time, metal-to-ligand ratio, and counterion can substantially affect the final complex. A typical approach involves dissolving the ligand in an appropriate solvent and subsequently adding a metal salt under continuous stirring. The reaction may be conducted at room temperature or under reflux. The product is isolated through precipitation, filtration, solvent evaporation, or crystallization [6]. Chelating ligands often produce complexes with enhanced thermodynamic stability. The chelate effect is particularly important in biological applications because excessive instability may result in premature metal release, whereas excessively stable complexes may fail to undergo the ligand-exchange reactions required for biological activity. Modern synthetic strategies increasingly include microwave-assisted synthesis, mechanochemical reactions, solvent-minimized processes, and greener solvents. These approaches may reduce reaction time and environmental impact while improving synthetic efficiency.

6. Structural Characterization of Metal Complexes

Reliable structural characterization is essential because biological activity is strongly influenced by coordination geometry and molecular composition.

FTIR spectroscopy

FTIR spectroscopy can identify functional groups involved in coordination. Changes in the positions or intensities of bands associated with C=N, C=O, N–H, O–H, and C–S groups can provide evidence of metal–ligand interactions.

NMR spectroscopy

^{1}H and ^{13}C NMR can provide valuable information for diamagnetic complexes. Coordination-induced changes in chemical shifts can help establish the binding mode of the ligand.

UV-visible spectroscopy

Electronic spectra can provide information regarding ligand-centered transitions, charge-transfer transitions, and d–d transitions. These data can assist in assigning electronic configurations and probable coordination geometries.

Mass spectrometry

Mass spectrometry helps verify molecular composition and can provide evidence regarding the stoichiometry of metal–ligand assemblies.

Elemental analysis

Elemental analysis is routinely used to confirm the proposed empirical composition of synthesized complexes.

Single-crystal X-ray diffraction

When suitable crystals are available, X-ray crystallography provides direct information concerning metal–ligand bond lengths, bond angles, coordination number, and three-dimensional geometry.

Thermal analysis
TGA and DSC can provide information regarding thermal stability, solvent or water loss, decomposition, and phase transitions.

7. Anticancer Mechanisms of Transition Metal Complexes

The biological activity of transition metal complexes is often multifactorial. Their anticancer mechanisms may involve direct interaction with biomolecules as well as indirect disruption of cellular homeostasis.

7.1 DNA Interaction

DNA remains an important target for several metal-based anticancer agents. Metal complexes can bind DNA through covalent coordination, electrostatic attraction, groove binding, or intercalation.
Planar heterocyclic ligands may facilitate intercalation between DNA base pairs, while the metal center may establish additional interactions with nucleophilic sites. These interactions can interfere with DNA replication and transcription [7].

7.2 Reactive Oxygen Species

Some metal complexes can promote the formation of reactive oxygen species through redox cycling. Increased ROS levels may result in oxidative damage to DNA, proteins, and lipids.
Because many cancer cells already exhibit elevated oxidative stress, further disruption of redox balance may push them beyond their tolerable threshold.

7.3 Apoptosis

Apoptosis is a major mechanism through which metal complexes induce cancer-cell death. Complexes may activate caspases, alter Bcl-2 family proteins, disrupt mitochondrial membrane potential, and promote cytochrome c release.

7.4 Cell-Cycle Arrest

Transition metal complexes can interfere with cyclins, cyclin-dependent kinases, DNA synthesis, and other regulatory mechanisms. Depending on the compound and cancer model, cell-cycle arrest may occur at G_0/G_1, S, or G_2/M phases.

7.5 Mitochondrial Dysfunction

Mitochondria are increasingly recognized as important targets for metal-based anticancer agents. Alteration of mitochondrial membrane potential and oxidative phosphorylation can initiate intrinsic apoptotic pathways.

7.6 Enzyme Inhibition

Heterocyclic ligands can provide molecular recognition sites for enzymes, while metal coordination can further modify their binding affinity. Potential targets include kinases, topoisomerases, proteases, carbonic anhydrases, and other enzymes involved in tumor growth.

8. Structure–Activity Relationships

The biological activity of transition metal complexes is closely related to structural parameters.
Important factors include the identity and oxidation state of the metal, ligand donor atoms, coordination geometry, molecular charge, lipophilicity, ligand-exchange kinetics, and overall stability.
Substituents on heterocyclic rings can significantly influence activity by modifying electron density and hydrophobicity. Electron-withdrawing groups may alter metal-binding strength, whereas hydrophobic substituents may improve membrane permeability but potentially increase nonspecific binding. The metal-to-ligand ratio is also important [8]. Changes in stoichiometry may produce entirely different coordination geometries and biological properties. A useful structure–activity investigation should therefore evaluate a systematic series of related complexes rather than relying on a single compound.

9. Evaluation of Anticancer Activity

Initial anticancer screening is commonly performed using established human cancer cell lines. Breast, lung, colon, liver, prostate, cervical, ovarian, and hematological cancer models are frequently employed.
The MTT assay remains widely used to determine changes in cellular metabolic activity following treatment. However, complementary assays such as resazurin reduction, ATP-based viability measurements, clonogenic assays, and live/dead staining can provide additional information.
The IC_{50} value is useful for comparing potency, but it should not be interpreted independently. Evaluation against normal cells is necessary to determine selectivity [9].

Mechanistic assays may include:

- Annexin V/propidium iodide staining for apoptosis;
- caspase-3, -8, and -9 analysis;
- cell-cycle analysis by flow cytometry;
- mitochondrial membrane-potential measurements;
- ROS detection;
- DNA-binding studies;
- Western blotting;
- gene-expression analysis; and
- molecular docking and computational target prediction.

10. Selectivity Toward Cancer Cells

A major objective in metallodrug development is achieving preferential toxicity toward malignant cells. Many experimental complexes demonstrate strong cytotoxicity, but nonspecific toxicity can prevent therapeutic application. Selectivity may arise from differences in cancer-cell metabolism, membrane transport, redox status, mitochondrial activity, pH, or expression of particular molecular targets.
Cancer cells often exhibit altered metal metabolism and increased requirements for certain trace elements. These characteristics may provide opportunities for metal-based therapeutic strategies, although such hypotheses require rigorous experimental validation.

11. Resistance to Metal-Based Anticancer Drugs

Resistance is a major challenge in cancer chemotherapy. Mechanisms of resistance to metal complexes can include reduced drug uptake, increased efflux, enhanced DNA repair, detoxification by intracellular thiols, altered apoptosis signaling, and changes in cellular redox systems. For platinum compounds, for example, resistance may involve reduced intracellular accumulation, increased DNA repair, and sequestration by sulfur-containing biomolecules. Heterocyclic ligand modification may provide a strategy for circumventing some resistance mechanisms by altering cellular uptake, intracellular localization, or molecular targets. Complexes that act through mechanisms distinct from DNA crosslinking may also provide opportunities for overcoming classical platinum resistance.

12. Nanotechnology-Assisted Delivery

Nanotechnology offers opportunities to improve the pharmaceutical properties of transition metal complexes. Poorly soluble or unstable complexes can potentially be incorporated into liposomes, polymeric nanoparticles, dendrimers, micelles, metal–organic frameworks, or other nanocarriers.

Nanocarriers may improve aqueous dispersibility, protect the active compound from premature degradation, and modify pharmacokinetic behavior. Surface functionalization can potentially enhance tumor targeting through receptor-mediated mechanisms. Stimuli-responsive systems are particularly attractive because they can respond to tumor-associated pH, redox conditions, enzymes, or ROS. However, nanocarrier-associated toxicity, reproducibility, scale-up, biodistribution, and regulatory considerations must be carefully evaluated.

13. Combination Therapy

Combining metal complexes with established anticancer drugs is another emerging strategy. Combination therapy can potentially produce additive or synergistic effects while allowing lower doses of individual agents. Heterocyclic metal complexes may be combined with DNA-damaging drugs, kinase inhibitors, ROS-modulating agents, or immunotherapeutic approaches. However, synergy should be demonstrated experimentally using appropriate dose–response and combination-index methodologies rather than inferred simply from enhanced cytotoxicity.

14. Future Perspectives

Future development should increasingly combine coordination chemistry, medicinal chemistry, molecular biology, computational chemistry, and nanotechnology. Rational ligand design can be used to optimize metal-binding strength, target recognition, solubility, and cellular localization.

Computational approaches, including molecular docking, molecular dynamics, quantum chemical calculations, and quantitative structure–activity relationship modeling, can assist in identifying promising ligand–metal combinations before experimental synthesis. Mechanism-based screening should complement conventional cytotoxicity assays. Instead of identifying compounds solely on the basis of low IC_{50} values, future studies should establish the molecular pathway responsible for activity and determine whether the mechanism is selective for malignant cells. The development of multifunctional complexes capable of simultaneously targeting DNA, mitochondria, enzymes, or redox pathways represents another promising direction. Similarly, tumor-targeted nanoparticles and stimuli-responsive delivery systems may improve the therapeutic window of otherwise promising complexes. Greater emphasis should also be placed on reproducibility, appropriate controls, pharmacokinetics, *in vivo* efficacy, toxicological evaluation, and standardized reporting.

Table 1. Representative transition metals and potential anticancer roles

Metal	Important chemical characteristics	Potential anticancer mechanisms
Platinum	Strong coordination chemistry and DNA binding	DNA adduct formation, apoptosis
Ruthenium	Multiple oxidation states and adaptable ligand exchange	DNA/protein interaction, ROS, apoptosis
Copper	Biologically essential redox-active metal	ROS generation, mitochondrial dysfunction
Cobalt	Variable oxidation states and coordination geometry	Oxidative stress, DNA interaction
Iron	Redox activity and biological relevance	ROS modulation, metabolic disruption
Palladium	Flexible coordination chemistry	DNA/protein interaction, apoptosis
Nickel	Diverse coordination geometries	Oxidative stress, enzyme interaction
Zinc	Essential non-redox metal	Enzyme modulation, apoptosis

Table 2. Important heterocyclic ligands used in transition-metal anticancer research

Heterocyclic ligand	Key donor atoms/features	Potential contribution to anticancer activity
Pyridine	Nitrogen donor	Coordination and target recognition
Imidazole	Nitrogen donors	DNA/protein interaction
Benzimidazole	Fused N-containing ring	DNA interaction and enzyme inhibition
Quinoline	Aromatic N donor	Intercalation and hydrophobic interactions
Quinazoline	Nitrogen-rich aromatic system	Kinase-related interactions
Thiazole	N and S donors	Metal coordination and biological activity
Triazole	Multiple nitrogen donors	Strong coordination and hydrogen bonding
Indole	Fused aromatic heterocycle	Target recognition and apoptosis
Thiosemicarbazone	N/S donor system	Chelation and redox-mediated activity

15. Conclusion

Transition metal complexes containing heterocyclic ligands represent a highly versatile platform for the development of next-generation anticancer agents. The combination of a biologically active heterocyclic framework with a transition-metal center can generate chemical entities with properties that differ substantially from those of either component alone. Metal centers provide unique coordination and redox characteristics, while heterocyclic ligands regulate molecular geometry, stability, lipophilicity, cellular uptake, and biomolecular recognition. Ruthenium, platinum, copper, cobalt, iron, palladium, nickel, and zinc complexes have demonstrated diverse experimental anticancer mechanisms, including DNA interaction, ROS generation, mitochondrial dysfunction, apoptosis, cell-cycle arrest, and enzyme inhibition. Nevertheless, successful translation requires considerably more than demonstration of in vitro cytotoxicity. Selectivity toward malignant cells, physiological stability, pharmacokinetics, metal speciation, long-term toxicity, and *in vivo* efficacy must be established systematically. Future progress will depend on rational ligand design, mechanism-oriented biological screening, computational modeling, targeted delivery, and rigorous pharmacological evaluation. The convergence of heterocyclic medicinal chemistry and transition-metal coordination chemistry therefore offers considerable potential for producing innovative metallotherapeutic candidates capable of addressing limitations associated with conventional cancer treatments.

References

1. Zou, T., Lok, C. N., Wan, P. K., Zhang, Z. F., Fung, S. K., & Che, C. M. (2018). Anticancer metal-N-heterocyclic carbene complexes of gold, platinum and palladium. *Current opinion in chemical biology*, *43*, 30-36.
2. Du, Y., Chen, W., Fu, X., Deng, H., & Deng, J. (2016). Synthesis and biological evaluation of heterocyclic hydrazone transition metal complexes as potential anticancer agents. *RSC advances*, *6*(111), 109718-109725.
3. Benjamin Garbutcheon-Singh, K., P Grant, M., W Harper, B., M Krause-Heuer, A., Manohar, M., Orkey, N., & R Aldrich-Wright, J. (2011). Transition metal based anticancer drugs. *Current Topics in Medicinal Chemistry*, *11*(5), 521-542.
4. Aher, S. B., Muskawar, P. N., Thenmozhi, K., & Bhagat, P. R. (2014). Recent developments of metal N-heterocyclic carbenes as anticancer agents. *European Journal of Medicinal Chemistry*, *81*, 408-419.
5. Fereidoonnezhad, M., Ramezani, Z., Nikravesh, M., Zangeneh, J., Golbon Haghighi, M., Faghih, Z., & Shahsavari, H. R. (2018). Cycloplatinated (II) complexes bearing an O, S-heterocyclic ligand: search for anticancer drugs. *New Journal of Chemistry*, *42*(9), 7177-7187.
6. Ndagi, U., Mhlongo, N., & Soliman, M. E. (2017). Metal complexes in cancer therapy–an update from drug design perspective. *Drug design, development and therapy*, 599-616.
7. Zhi, S., Li, Y., Qiang, J., Hu, J., Song, W., & Zhao, J. A. (2019). Synthesis and anticancer evaluation of benzo-N-heterocycles transition metal complexes against esophageal cancer cell lines. *Journal of Inorganic Biochemistry*, *201*, 110816.
8. Liang, J. X., Zhong, H. J., Yang, G., Vellaisamy, K., Ma, D. L., & Leung, C. H. (2017). Recent development of transition metal complexes with in vivo antitumor activity. *Journal of Inorganic Biochemistry*, *177*, 276-286.
9. Liberta, A. E., & West, D. X. (1992). Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status. *Biometals*, *5*(2), 121-126.