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Coordination Chemistry and Antifungal Activity of Metal Complexes: Thiazolidinine Ligands with Co and Ni Transition Metals

Sapna Bora [1], Dr. Rashmi Rautela [2]

[1] Research Schola SSJ University Almora

[2]Assistant Professor Department of Chemistry LBS Govt P.G. College Halduchaur

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ABSTRACT:

Thiazolidinone derivatives constitute an important class of heterocyclic compounds that have attracted considerable attention in medicinal and coordination chemistry because of their diverse biological activities and versatile coordination behavior. The presence of heteroatoms such as nitrogen, oxygen, and sulfur within the thiazolidinone ring enables effective chelation with transition metal ions, particularly cobalt(II) and nickel(II). Complexation often enhances the biological efficacy of ligands by increasing lipophilicity, membrane permeability, and metal-mediated biochemical interactions. The present study reviews the coordination chemistry of thiazolidinone ligands with Co(II) and Ni(II) ions and examines the antifungal properties of the resulting metal complexes. Emphasis is placed on ligand design, synthesis, coordination modes, structural characterization, antifungal mechanisms, and structure–activity relationships. The discussion integrates established theories of coordination chemistry, including Crystal Field Theory, Ligand Field Theory, Chelation Theory, and Overtone's Concept–Tweedy's Chelation Theory. Available evidence demonstrates that cobalt and nickel complexes generally exhibit superior antifungal activity compared with free thiazolidinone ligands, indicating their potential as promising candidates for future antifungal drug development...

Keywords - Thiazolidinone, cobalt(II), nickel(II), coordination chemistry, antifungal activity, chelation theory, transition metal complexes, medicinal inorganic chemistry..

INTRODUCTION

The emergence of fungal resistance against conventional antifungal drugs has become a significant challenge in modern medicine and agriculture. Pathogenic fungi such as Candida albicans, Aspergillus niger, Aspergillus flavus, and Cryptococcus neoformans have developed increasing resistance to commonly used antifungal agents, creating a need for novel therapeutic approaches. Transition metal complexes have emerged as promising alternatives due to their unique mechanisms of biological action and structural diversity. Metal-based compounds can interact with microbial enzymes, DNA, proteins, and cellular membranes in ways that are not accessible to purely organic molecules. Among various heterocyclic compounds, thiazolidinones represent a particularly important class because they exhibit antibacterial, antifungal, antiviral, anticancer, anti-inflammatory, and antioxidant activities. Their structural framework contains multiple donor atoms capable of coordinating transition metal ions, making them attractive ligands for the synthesis of biologically active metal complexes. Cobalt(II) and nickel(II) ions are especially significant in coordination chemistry due to their variable coordination geometries, favorable electronic configurations, and biological relevance. Complexes derived from these metal ions often exhibit enhanced pharmacological properties compared with the parent ligands. Recent studies have demonstrated that Co(II) and Ni(II) complexes show considerable antimicrobial and antifungal activities through mechanisms involving membrane disruption, oxidative stress induction, and inhibition of essential fungal enzymes. The present paper provides a comprehensive review of the coordination chemistry and antifungal potential of thiazolidinone-based Co(II) and Ni(II) complexes.

THEORETICAL FOUNDATIONS OF COORDINATION CHEMISTRY

Coordination chemistry is a branch of inorganic chemistry concerned with the study of compounds formed through the interaction of metal ions with surrounding molecules or ions known as ligands. These compounds, called coordination complexes, exhibit unique structural, electronic, magnetic, and biological properties that distinguish them from ordinary ionic or covalent compounds. The development of coordination chemistry has been guided by several theoretical models that explain the nature of metal–ligand bonding, molecular geometry, stability,reactivity, and physicochemical behavior. In studies involving cobalt(II) and nickel(II) complexes of thiazolidinone ligands, these theories provide the conceptual framework for understanding how metal ions interact with donor atoms and how such interactions influence biological activities such as antifungal effects..

Werner's Coordination Theory: The foundation of modern coordination chemistry was established by the Swiss chemist Alfred Werner in the late nineteenth century. Prior to Werner's work, the structures of many metal-containing compounds were poorly understood, and existing valence theories could not adequately explain their composition and properties. Werner proposed that metal ions possess two types of valencies: primary valencies and secondary valencies. Primary valencies correspond to the oxidation state of the metal ion and are generally satisfied by negatively charged ions. Secondary valencies correspond to the coordination number of the metal and are satisfied by ligands directly attached to the metal center. According to Werner, these secondary valencies are directed in space, giving rise to specific geometrical arrangements such as octahedral, tetrahedral, and square-planar structures. This theory successfully explained the existence of coordination compounds exhibiting identical chemical compositions but different spatial arrangements, known as coordination isomers. Werner's ideas also laid the foundation for understanding stereochemistry in coordination compounds. In cobalt(II) and nickel(II) complexes containing thiazolidinone ligands, the theory helps explain how donor atoms such as nitrogen, oxygen, and sulfur occupy specific positions around the metal ion to form stable coordination spheres.

Sidgwick's Effective Atomic Number Theory: An important early attempt to explain the stability of coordination compounds was provided by the Effective Atomic Number (EAN) Theory developed by Nevil Sidgwick. According to this theory, metal ions tend to accept electron pairs from ligands until they achieve an electronic configuration equivalent to that of the nearest noble gas. The EAN rule suggested that the total number of electrons surrounding a metal ion after coordination often approaches a stable noble-gas configuration. Although numerous exceptions were later identified, the theory represented an important step toward understanding metal–ligand interactions and complex stability. In transition-metal complexes, including those of cobalt and nickel, ligand electron donation contributes significantly to achieving stable electronic configurations. The concept remains historically important because it introduced the idea that electron transfer from ligands plays a central role in coordination chemistry.

Valence Bond Theory: Valence Bond Theory was one of the first quantum mechanical approaches used to explain bonding in coordination compounds. Developed through the work of scientists such as Linus Pauling, the theory proposes that metal ions utilize hybrid orbitals formed through the combination of atomic orbitals to accommodate electron pairs donated by ligands. According to Valence Bond Theory, the geometry of a coordination complex depends on the type of hybridization adopted by the metal ion. For example, octahedral complexes may involve d^2sp^3 or sp^3d^2 hybridization, while tetrahedral complexes generally involve sp^3 hybridization. The theory successfully explains coordination numbers, molecular geometry, and magnetic behavior in many complexes. For cobalt(II) and nickel(II) complexes of thiazolidinone ligands, Valence Bond Theory helps describe how donor atoms coordinate through lone-pair electrons to form coordinate covalent bonds with vacant hybrid orbitals on the metal center. Despite its usefulness, the theory cannot adequately explain the colors and electronic spectra of coordination compounds, leading to the development of more advanced models.

Crystal Field Theory: Crystal Field Theory represents a major advancement in the understanding of coordination compounds. Developed primarily by Hans Bethe and later expanded by other scientists, the theory considers ligands as point charges or dipoles that generate an electrostatic field around the central metal ion. In an isolated transition-metal ion, the five d-orbitals possess equal energy. When ligands approach the metal center, electrostatic interactions cause these orbitals to split into groups of different energies. The pattern and magnitude of this splitting depend on the geometry of the complex and the nature of the ligands. For octahedral complexes, the d-orbitals split into two sets:

t2g and eg

The energy difference between these sets is known as crystal field splitting energy. This splitting influences numerous properties including color, magnetism, thermodynamic stability, and reactivity. Cobalt(II) and nickel(II) complexes commonly adopt octahedral geometries, making Crystal Field Theory particularly useful in interpreting their electronic spectra and magnetic moments. The theory explains why these complexes exhibit characteristic colors arising from electronic transitions between split d-orbitals. Although Crystal Field Theory provides valuable insights, it treats metal–ligand interactions as purely ionic and neglects covalent contributions, which limits its applicability in many systems.

Ligand Field Theory: Ligand Field Theory emerged as a refinement of Crystal Field Theory by incorporating principles of molecular orbital theory. It recognizes that metal–ligand bonding often involves significant covalent character in addition to electrostatic interactions. According to Ligand Field Theory, ligand orbitals overlap with metal orbitals to form molecular orbitals distributed throughout the complex. The resulting bonding, antibonding, and nonbonding orbitals determine the electronic structure and stability of the complex. This theory provides a more accurate description of transition-metal complexes because it accounts for electron sharing between metals and ligands. In thiazolidinone complexes, donor atoms such as nitrogen, sulfur, and oxygen possess lone pairs that overlap effectively with metal d-orbitals, producing strong metal–ligand bonds. Ligand Field Theory successfully explains phenomena that Crystal Field Theory cannot, including spectrochemical behavior, covalency, nephelauxetic effects, and variations in electronic spectra. Consequently, it has become one of the most important theoretical frameworks in modern coordination chemistry.

Molecular Orbital Theory: Molecular Orbital Theory provides the most comprehensive description of bonding in coordination compounds. Unlike localized bonding models, it assumes that electrons occupy molecular orbitals extending over the entire complex. In transition-metal complexes, metal atomic orbitals combine with ligand orbitals to generate bonding and antibonding molecular orbitals. Electrons are distributed among these orbitals according to quantum mechanical principles. This approach enables accurate interpretation of electronic transitions, magnetic properties, redox behavior, and chemical reactivity. Molecular Orbital Theory is particularly useful for understanding the electronic structures of biologically active cobalt and nickel complexes, where metal–ligand covalency plays a crucial role in determining biological function.

Chelation Theory: Chelation is one of the most important concepts in coordination chemistry and medicinal inorganic chemistry. A chelating ligand contains two or more donor atoms capable of binding simultaneously to the same metal ion, resulting in the formation of ring structures known as chelate rings. Thiazolidinone ligands frequently behave as bidentate or tridentate ligands because they contain multiple donor atoms capable of coordinating metal ions. The formation of chelate rings enhances the stability of metal complexes through what is known as the chelate effect. The chelate effect arises largely from thermodynamic considerations. Chelated complexes generally possess higher entropy and greater stability than analogous complexes containing equivalent monodentate ligands. As a result, cobalt and nickel complexes of thiazolidinone ligands often display remarkable stability in solution. Chelation also influences biological activity by modifying lipophilicity, electronic structure, and molecular geometry.

Hard and Soft Acids and Bases Theory: The Hard and Soft Acids and Bases (HSAB) Theory developed by Ralph G. Pearson provides a useful framework for predicting metal–ligand preferences. According to HSAB theory:

Hard acids prefer hard bases.

Soft acids prefer soft bases.

Similar hardness or softness generally leads to stronger interactions.

Donor atoms found in thiazolidinone ligands exhibit varying hardness characteristics. Oxygen is typically a hard donor atom, nitrogen is intermediate, and sulfur is relatively soft. Cobalt(II) and nickel(II) ions exhibit intermediate behavior and can coordinate effectively with all three donor types. This versatility contributes to the diverse coordination modes observed in thiazolidinone complexes and influences their stability and biological performance.

The theoretical principles of coordination chemistry collectively explain the enhanced biological properties observed in cobalt(II) and nickel(II) thiazolidinone complexes. Werner’s theory describes structural organization, Crystal Field and Ligand Field theories explain electronic behavior, Molecular Orbital Theory clarifies bonding interactions, and Chelation Theory accounts for increased stability and biological efficacy. These concepts are especially important in medicinal inorganic chemistry, where coordination-induced changes in lipophilicity, redox properties, molecular geometry, and electronic structure can significantly influence antifungal activity. Understanding these theoretical foundations is therefore essential for the rational design of new cobalt and nickel thiazolidinone complexes with improved therapeutic potential.

Chemistry and Synthesis of Thiazolidinone Ligands

Thiazolidinones constitute an important class of sulfur- and nitrogen-containing heterocyclic compounds that have attracted considerable attention in organic, medicinal, and coordination chemistry. These compounds possess a five-membered heterocyclic ring containing one sulfur atom, one nitrogen atom, and a carbonyl group, which collectively contribute to their distinctive chemical and biological properties. Because of their structural versatility and broad spectrum of pharmacological activities, thiazolidinone derivatives have become valuable scaffolds in drug discovery and metal-complex research. Numerous studies have reported their antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, antioxidant, and antidiabetic activities, making them one of the most extensively investigated heterocyclic systems in modern medicinal chemistry. From the perspective of coordination chemistry, thiazolidinones are particularly significant because they possess several potential donor atoms capable of coordinating transition-metal ions. The presence of nitrogen, sulfur, and oxygen atoms allows these ligands to form stable chelates with metals such as cobalt, nickel, copper, zinc, manganese, and iron. The resulting complexes often exhibit enhanced biological activities compared with the parent ligands, highlighting the importance of understanding the chemistry and synthesis of thiazolidinone derivatives.

The thiazolidinone ring consists of a saturated five-membered heterocyclic framework containing sulfur at position 1, nitrogen at position 3, and a carbonyl group typically located at position 2 or 4. Among the various structural forms, 4-thiazolidinones are the most extensively studied because of their synthetic accessibility and biological importance.

4-Thiazolidinone

The ring system can accommodate a wide variety of substituents at different positions, enabling extensive structural modification. Such modifications influence the electronic properties, steric environment, lipophilicity, and biological activity of the molecules. Aromatic, heteroaromatic, alkyl, and functionalized substituents may be introduced into the ring structure to tailor the physicochemical and pharmacological properties of the resulting compounds. The carbonyl group contributes significantly to the chemical reactivity of thiazolidinones. Its strong electron-withdrawing character influences electron distribution throughout the molecule and provides an important coordination site for metal ions. Similarly, the sulfur atom possesses a lone pair of electrons that can participate in metal coordination, while the nitrogen atom can also serve as a donor center under suitable conditions.

The chemical behavior of thiazolidinones arises from the combined influence of the carbonyl group, heteroatoms, and substituent effects. These compounds exhibit a rich chemistry involving nucleophilic substitution, electrophilic substitution, condensation reactions, oxidation, reduction, and metal-complex formation. The carbonyl functionality imparts significant electrophilic character to the molecule, making it susceptible to nucleophilic attack. This reactivity allows the synthesis of numerous derivatives through reactions with amines, hydrazines, alcohols, and thiols. The nitrogen atom contributes to resonance stabilization and influences the electronic distribution within the ring system. Meanwhile, the sulfur atom provides enhanced polarizability and nucleophilicity, facilitating interactions with electrophiles and transition-metal ions. Resonance effects play a crucial role in determining the stability and reactivity of thiazolidinones. Electron delocalization between the carbonyl group and adjacent heteroatoms creates multiple resonance forms that stabilize the heterocyclic framework. This stabilization contributes to the relatively high chemical stability of thiazolidinone derivatives under physiological and laboratory conditions. Because of these electronic features, thiazolidinones can function as mono-, bi-, or tridentate ligands in coordination chemistry. Coordination commonly occurs through the carbonyl oxygen, ring nitrogen, sulfur atom, or additional donor groups introduced through structural modification.

The significance of thiazolidinones extends beyond their chemical properties to their remarkable biological activities. The thiazolidinone nucleus is regarded as a privileged scaffold in medicinal chemistry because small structural changes often result in substantial alterations in biological activity. Several mechanisms have been proposed to explain the biological activity of thiazolidinone derivatives. The heterocyclic ring can interact with enzymes, receptors, nucleic acids, and cellular membranes through hydrogen bonding, hydrophobic interactions, and coordination with biological metal ions. These interactions enable thiazolidinones to interfere with essential biochemical pathways in microorganisms and cancer cells. Their broad pharmacological profile has stimulated extensive research aimed at developing new thiazolidinone-based therapeutic agents and metal complexes with improved efficacy and reduced toxicity.

Numerous synthetic methods have been developed for the preparation of thiazolidinone derivatives. Among these, cyclization reactions involving Schiff bases and mercaptoacetic acid remain the most widely employed because of their simplicity, versatility, and high yields. The synthesis of thiazolidinone ligands generally involves the construction of the heterocyclic ring through condensation and cyclization processes. The choice of starting materials and reaction conditions determines the nature of substituents introduced into the final ligand structure. One of the most common methods for synthesizing thiazolidinone ligands involves the reaction of Schiff bases with thioglycolic acid. This approach is widely used because it allows the preparation of structurally diverse derivatives from readily available starting materials. The synthesis begins with the formation of a Schiff base through the condensation of a primary amine with an aldehyde or ketone. The resulting imine contains a carbon–nitrogen double bond that serves as a reactive center for subsequent cyclization. The Schiff base is then reacted with thioglycolic acid under reflux conditions. The sulfur atom of thioglycolic acid initially attacks the electrophilic carbon of the imine group, leading to the formation of an intermediate species. Subsequent intramolecular cyclization and dehydration result in the formation of the thiazolidinone ring. This synthetic route offers several advantages. It is relatively straightforward, employs inexpensive reagents, and permits the introduction of a wide variety of substituents through appropriate selection of aldehydes and amines.

Modern synthetic chemistry increasingly employs multicomponent reactions for the preparation of thiazolidinones. In these reactions, three or more reactants are combined in a single reaction vessel to produce the desired product through a sequence of bond-forming events. Typically, an aldehyde, an amine, and thioglycolic acid are reacted simultaneously under suitable conditions. The Schiff base intermediate forms in situ and subsequently undergoes cyclization to generate the thiazolidinone derivative. Multicomponent methods offer significant advantages, including reduced reaction times, simplified purification procedures, improved atom economy, and lower solvent consumption. Consequently, these approaches align well with the principles of green chemistry and sustainable synthesis. Microwave irradiation has emerged as an efficient alternative to conventional heating methods in heterocyclic synthesis. Microwave-assisted synthesis significantly accelerates reaction rates by providing rapid and uniform heating throughout the reaction mixture. In the synthesis of thiazolidinones, microwave irradiation often reduces reaction times from several hours to a few minutes while improving product yields and purity. Enhanced reaction efficiency results from more effective energy transfer and reduced side reactions. The adoption of microwave technology has become increasingly important in medicinal chemistry, where rapid synthesis of compound libraries is essential for biological screening programs.

Growing environmental concerns have encouraged the development of greener approaches to thiazolidinone synthesis. Solvent-free methods eliminate or minimize the use of organic solvents, reducing environmental impact and operational costs. Catalysts such as clays, ionic liquids, metal nanoparticles, and heterogeneous solid acids have been employed to facilitate thiazolidinone formation under environmentally friendly conditions. These methods often provide high yields while reducing waste generation and energy consumption. Green synthetic strategies are particularly attractive for large-scale industrial production because they improve sustainability and regulatory compliance. Following ring formation, thiazolidinone derivatives can undergo further functionalization to introduce additional donor groups and enhance coordination capabilities. Such modifications are especially important in the design of ligands for transition-metal complexation. Common functionalization strategies include the introduction of:

Hydroxyl groups

Amino groups

Carboxyl groups

Methoxy substituents

Nitro groups

Halogen substituents

Heteroaromatic rings

These substituents influence electron density, steric properties, and metal-binding behavior. The incorporation of additional donor atoms often increases the denticity of the ligand, enabling the formation of more stable metal complexes.

The ability of thiazolidinones to act as ligands arises from the presence of multiple donor atoms capable of coordinating metal ions. Depending on their structure, thiazolidinone derivatives may coordinate through oxygen, nitrogen, sulfur, or combinations of these donor centers. The carbonyl oxygen frequently participates in coordination because of its high electron density and strong donor ability. Sulfur coordination is also common because sulfur is a relatively soft donor atom capable of forming stable bonds with many transition metals. In certain derivatives, ring nitrogen or substituent nitrogen atoms may also contribute to coordination. As a result, thiazolidinones often behave as chelating ligands, forming stable five- or six-membered chelate rings with transition metals. Chelation enhances complex stability and frequently improves biological activity through increased lipophilicity and more favorable interactions with biological targets. In complexes of cobalt(II) and nickel(II), thiazolidinone ligands commonly coordinate through carbonyl oxygen and sulfur atoms, although nitrogen coordination is also observed in appropriately substituted derivatives. The resulting complexes typically exhibit octahedral or distorted octahedral geometries. The formation of these complexes alters the electronic structure of both the ligand and metal ion, often leading to enhanced antifungal activity. Chelation reduces metal-ion polarity, increases membrane permeability, and facilitates interaction with fungal enzymes and nucleic acids. Consequently, thiazolidinone ligands serve as valuable building blocks for the development of biologically active cobalt and nickel complexes.

Synthesis of Cobalt(II) and Nickel(II) Complexes

The synthesis of cobalt(II) and nickel(II) complexes containing thiazolidinone ligands represents an important area of research in coordination and medicinal chemistry because of the enhanced biological properties often observed upon metal complexation. The formation of these complexes is based on the ability of thiazolidinone ligands to donate electron pairs from heteroatoms such as oxygen, nitrogen, and sulfur to transition-metal ions, resulting in the formation of stable coordination compounds. The synthesis generally begins with the preparation of the thiazolidinone ligand through cyclization reactions involving Schiff bases and thioglycolic acid or related sulfur-containing reagents. Once purified and characterized, the ligand is reacted with suitable cobalt(II) or nickel(II) salts such as cobalt(II) chloride, cobalt(II) acetate, nickel(II) chloride, or nickel(II) acetate in an appropriate solvent system, commonly ethanol, methanol, or mixed alcoholic media. The ligand solution is usually mixed with a solution of the metal salt in a predetermined stoichiometric ratio and heated under reflux conditions. Refluxing promotes efficient interaction between the metal ion and ligand molecules, facilitating the replacement of coordinated water molecules or anions by the donor atoms of the ligand. During the reaction, the color of the solution often changes, indicating the formation of the metal complex. Cobalt(II) complexes frequently exhibit shades of pink, violet, or blue, whereas nickel(II) complexes commonly appear green or greenish-blue depending on the geometry and ligand environment. After completion of the reaction, the complexes are isolated by cooling the reaction mixture, followed by filtration, washing, and drying under reduced pressure or in a desiccator. The coordination behavior of thiazolidinone ligands toward cobalt(II) and nickel(II) ions is influenced by the presence of donor atoms within the ligand framework. In many cases, coordination occurs through the carbonyl oxygen atom and sulfur atom of the thiazolidinone ring, forming stable chelate rings around the metal center. In ligands containing additional donor groups such as azomethine nitrogen, amino nitrogen, hydroxyl oxygen, or carboxylate oxygen, tridentate or even tetradentate coordination modes may be observed. Such interactions result in the formation of highly stable complexes characterized by increased rigidity and reduced conformational flexibility. The metal-to-ligand ratio is frequently found to be 1:2, leading to octahedral coordination geometries in which two ligand molecules surround the central metal ion. However, tetrahedral, square-planar, and distorted octahedral geometries have also been reported depending on the ligand structure and reaction conditions.

Characterization of the synthesized complexes is essential for confirming successful metal coordination and determining structural features. Infrared spectroscopy is one of the most commonly employed techniques and typically reveals shifts in the carbonyl stretching frequency and other characteristic vibrational bands, indicating participation of donor atoms in metal binding. New bands appearing in the lower frequency region corresponding to metal–oxygen, metal–nitrogen, and metal–sulfur vibrations provide additional evidence of coordination. Electronic spectroscopy offers information regarding the geometry and electronic environment of the metal ions. The observed d–d transitions are consistent with the expected crystal field splitting patterns of cobalt(II) and nickel(II) complexes. Magnetic susceptibility measurements further support structural assignments by providing information about the number of unpaired electrons and the geometry around the metal center. Thermal analysis, elemental analysis, mass spectrometry, and nuclear magnetic resonance spectroscopy are also frequently employed to establish the composition and stability of the synthesized complexes. The biological significance of cobalt(II) and nickel(II) thiazolidinone complexes has attracted considerable attention because many studies have demonstrated enhanced antimicrobial and antifungal activities compared with the corresponding free ligands. Fungal infections caused by organisms such as *Candida albicans*, *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum*, and *Penicillium* species pose serious challenges in medicine, agriculture, and food preservation. The increasing emergence of resistance to conventional antifungal drugs has stimulated the search for alternative therapeutic agents, including metal-based compounds with novel mechanisms of action. The antifungal activity of cobalt(II) and nickel(II) complexes is commonly evaluated using methods such as the agar diffusion assay, broth dilution technique, and determination of minimum inhibitory concentration values. In these studies, the complexes frequently exhibit larger zones of inhibition and lower inhibitory concentrations than the parent ligands. This enhancement is generally explained through the principles of chelation theory. According to the Overtone concept and Tweedy's Chelation Theory, coordination reduces the polarity of the metal ion due to partial sharing of positive charge with ligand donor atoms and delocalization of π-electrons over the chelate ring. As a consequence, the overall lipophilicity of the complex increases, facilitating its penetration through the lipid-rich fungal cell membrane. Enhanced membrane permeability allows the complex to reach intracellular targets more effectively than the uncoordinated ligand.

Once inside the fungal cell, cobalt(II) and nickel(II) complexes can interfere with several essential biological processes. They may interact with proteins and enzymes containing sulfur-, nitrogen-, or oxygen-donor groups, leading to inhibition of enzymatic activity and disruption of metabolic pathways necessary for cell survival. Metal complexes are also capable of binding to nucleic acids, affecting DNA replication and transcription processes. Such interactions can inhibit cell division and protein synthesis, ultimately suppressing fungal growth. In addition, transition-metal complexes may promote the generation of reactive oxygen species, including superoxide radicals, hydroxyl radicals, and hydrogen peroxide. The accumulation of these reactive species induces oxidative stress, resulting in lipid peroxidation, protein denaturation, mitochondrial dysfunction, and DNA damage. The combined effects of these processes contribute significantly to fungal cell death. The structural characteristics of the complexes strongly influence their antifungal efficacy. Complexes containing electron-donating substituents often display enhanced biological activity due to increased electron density at the coordination center and stronger interactions with biological targets. The geometry of the complex also plays an important role, as octahedral structures generally provide greater stability and favorable molecular dimensions for biological interactions. The nature of the metal ion itself contributes to activity through differences in ionic radius, electronic configuration, ligand field stabilization energy, and redox behavior. Cobalt(II) complexes frequently exhibit slightly higher biological activity because of their ability to participate in redox reactions and generate reactive oxygen species, whereas nickel(II) complexes often demonstrate superior thermodynamic stability and strong metal–ligand bonding. Research conducted over the past several decades has consistently shown that the combination of thiazolidinone pharmacophores with cobalt(II) and nickel(II) ions produces a synergistic effect that enhances antifungal performance. The ligand provides biological recognition and membrane affinity, while the metal ion introduces unique electronic and biochemical properties that increase toxicity toward fungal pathogens. This synergy has established cobalt(II) and nickel(II) thiazolidinone complexes as promising candidates for the development of new antifungal agents. Continued investigations involving advanced spectroscopic characterization, molecular docking studies, computational modeling, and in vivo biological evaluations are expected to further clarify their mechanisms of action and facilitate the design of more effective metal-based antifungal therapeutics.

Mechanisms of Antifungal Action and Structure–Activity Relationship

The antifungal activity of cobalt(II) and nickel(II) complexes derived from thiazolidinone ligands is a consequence of a complex interplay between the physicochemical properties of the metal ion, the structural characteristics of the ligand, and the biological environment of the fungal cell. Unlike conventional organic antifungal agents that often act through a single biochemical pathway, metal complexes may simultaneously target multiple cellular processes. This multifaceted mode of action contributes to their effectiveness against a broad range of fungal pathogens and may reduce the likelihood of resistance development. Understanding the mechanisms by which these complexes exert antifungal effects is therefore essential for the rational design of new metal-based antifungal agents. One of the most widely accepted explanations for the enhanced biological activity of metal complexes is provided by Overtone's concept and Tweedy's Chelation Theory.

According to these theories, the process of chelation reduces the polarity of the metal ion because its positive charge is partially shared with donor atoms present in the ligand. Simultaneously, electron delocalization occurs over the chelate ring system, resulting in a more stable and less polar complex. This reduction in polarity increases the lipophilic character of the molecule, allowing it to penetrate the lipid-rich fungal cell membrane more effectively than either the free metal ion or the uncoordinated ligand. Increased membrane permeability facilitates the transport of the complex into the intracellular environment, where it can interact with critical biological targets. The fungal cell membrane is one of the primary sites affected by metal complexes. The membrane serves as a selective barrier that regulates the movement of nutrients, ions, and metabolites between the cell and its surroundings. Cobalt(II) and nickel(II) thiazolidinone complexes may interact with membrane phospholipids and membrane-associated proteins, leading to alterations in membrane fluidity and permeability. Such interactions can disrupt normal membrane function, resulting in leakage of intracellular components, loss of ionic balance, and impairment of essential transport processes. Damage to the membrane ultimately compromises cellular integrity and viability, contributing to fungal growth inhibition.

Another important mechanism involves the interaction of metal complexes with fungal enzymes. Many enzymes contain amino acid residues such as cysteine, histidine, methionine, and aspartate that possess donor atoms capable of binding transition metals. Upon entering the fungal cell, cobalt(II) and nickel(II) complexes can coordinate with these functional groups, altering enzyme structure and activity. Inhibition of key metabolic enzymes disrupts vital biochemical pathways involved in energy production, cell wall synthesis, nucleic acid metabolism, and protein biosynthesis. As a consequence, fungal growth and reproduction are significantly impaired. The interaction of metal complexes with nucleic acids also plays a significant role in antifungal activity. DNA represents an attractive biological target because it governs replication, transcription, and cellular regulation. Metal complexes may bind to DNA through several mechanisms, including electrostatic attraction, groove binding, and intercalation between adjacent base pairs. Such interactions can distort the DNA structure and interfere with the activity of polymerases and other DNA-processing enzymes. The resulting inhibition of DNA replication and transcription prevents normal cell division and protein synthesis, ultimately leading to fungal cell death. In some cases, metal complexes may also induce DNA strand breaks through oxidative mechanisms, further enhancing their cytotoxic effects. A particularly important aspect of the biological activity of transition-metal complexes is their ability to generate reactive oxygen species. Reactive oxygen species include superoxide radicals, hydroxyl radicals, and hydrogen peroxide, all of which are highly reactive molecules capable of damaging cellular components. Under physiological conditions, fungal cells maintain a delicate balance between the production and removal of reactive oxygen species through antioxidant defense systems. Metal complexes can disturb this balance by catalyzing redox reactions that increase the intracellular concentration of reactive oxygen species. Excessive oxidative stress causes lipid peroxidation, protein oxidation, mitochondrial dysfunction, and DNA damage. When the level of oxidative injury exceeds the repair capacity of the fungal cell, apoptosis-like processes or necrotic cell death may occur. Mitochondria are particularly susceptible to oxidative damage induced by metal complexes. As the primary sites of cellular respiration and energy production, mitochondria are essential for fungal survival. Reactive oxygen species generated by cobalt(II) and nickel(II) complexes can impair mitochondrial membranes and enzymes involved in oxidative phosphorylation. The resulting decrease in ATP production leads to energy depletion and metabolic collapse. Mitochondrial dysfunction also amplifies oxidative stress by promoting further reactive oxygen species generation, creating a self-reinforcing cycle of cellular damage.

The inhibition of fungal biofilm formation represents another potential mechanism of antifungal action. Biofilms are organized microbial communities enclosed within a protective extracellular matrix that enhances resistance to antifungal drugs and host immune responses. Certain metal complexes have been shown to interfere with biofilm development by disrupting cell adhesion, extracellular matrix production, and intercellular signaling pathways. Inhibition of biofilm formation increases fungal susceptibility to both metal complexes and conventional antifungal agents, thereby improving therapeutic effectiveness. The effectiveness of cobalt(II) and nickel(II) thiazolidinone complexes is strongly influenced by their structural features, giving rise to important structure–activity relationships. The nature of the central metal ion is one of the most significant determinants of biological activity. Differences in ionic radius, electronic configuration, coordination preferences, and redox properties influence the stability, reactivity, and biological interactions of the complexes. Cobalt(II) ions possess a partially filled d^7 electronic configuration that enables participation in redox reactions and facilitates reactive oxygen species generation. Nickel(II), with its d^8 configuration, often forms highly stable complexes with strong metal–ligand bonds. These differences can result in variations in antifungal potency depending on the specific fungal species and ligand environment. The donor atoms involved in coordination also have a profound influence on biological activity. Thiazolidinone ligands typically contain oxygen, nitrogen, and sulfur donor centers. Sulfur-containing ligands often exhibit enhanced biological activity because sulfur atoms increase lipophilicity and facilitate interactions with biological macromolecules. Coordination through multiple donor atoms generally leads to stronger chelation and increased stability, both of which contribute to improved antifungal performance. Substituent effects on the ligand framework represent another important factor governing activity. Electron-donating groups such as methoxy, hydroxyl, and amino substituents can increase electron density within the ligand system and strengthen metal–ligand bonding. These effects may enhance complex stability and biological interactions. Conversely, electron-withdrawing groups such as nitro, cyano, and halogen substituents alter electronic distribution and may influence membrane permeability, DNA binding affinity, and redox behavior. The position of these substituents within the molecular structure can significantly affect the overall biological profile of the complex.

Lipophilicity is closely associated with antifungal activity and is often regarded as a critical determinant of biological efficacy. Increased lipophilicity facilitates passage through fungal cell membranes and enhances intracellular accumulation. Metal complexation generally increases lipophilicity relative to the free ligand, which partially explains the superior biological activity of many coordination compounds. However, excessively high lipophilicity may reduce aqueous solubility and bioavailability, indicating the importance of achieving an optimal balance between hydrophilic and hydrophobic characteristics. The geometry of the complex also contributes significantly to biological activity. Octahedral cobalt(II) and nickel(II) complexes are frequently reported to exhibit strong antifungal properties because their geometry provides favorable spatial arrangements for interaction with biological targets. The three-dimensional shape of the complex influences its ability to bind DNA, proteins, enzymes, and membrane components. Distorted geometries may sometimes enhance activity by increasing molecular flexibility and facilitating adaptation to different biological environments. The stability of the complex under physiological conditions is another important aspect of structure–activity relationships. Highly unstable complexes may dissociate before reaching their biological targets, whereas excessively stable complexes may be unable to release the metal ion or interact effectively with cellular components. An optimal balance between kinetic and thermodynamic stability is therefore essential for maximizing biological effectiveness. Molecular size and steric factors also influence antifungal activity. Smaller complexes may penetrate fungal cell walls and membranes more readily, while larger complexes may exhibit stronger interactions with macromolecular targets. Steric hindrance around the coordination center can affect both the accessibility of donor atoms and the overall reactivity of the complex. Consequently, careful structural design is required to achieve the most favorable biological profile.

CONCLUSION

The study of cobalt(II) and nickel(II) complexes of thiazolidinone ligands highlights the significant role of coordination chemistry in the development of biologically active metal-based compounds. The theoretical foundations provided by Werner’s Coordination Theory, Crystal Field Theory, Ligand Field Theory, Molecular Orbital Theory, Chelation Theory, and the Hard and Soft Acids and Bases concept offer a comprehensive understanding of metal–ligand interactions, structural stability, and electronic behavior in coordination compounds. These principles explain the formation, geometry, and reactivity of cobalt and nickel complexes and provide the basis for interpreting their physicochemical and biological properties. Thiazolidinone ligands constitute an important class of heterocyclic compounds due to the presence of multiple donor atoms such as oxygen, nitrogen, and sulfur, which enable effective coordination with transition-metal ions. Their versatile chemistry, ease of synthesis, and broad spectrum of biological activities make them attractive candidates for the preparation of medicinally relevant metal complexes. Various synthetic approaches, including Schiff base cyclization, multicomponent reactions, microwave-assisted synthesis, and environmentally friendly methodologies, facilitate the production of structurally diverse ligands capable of forming stable coordination compounds with cobalt(II) and nickel(II) ions. The synthesis of Co(II) and Ni(II) complexes generally results in highly stable chelated structures, most commonly exhibiting octahedral geometries. Coordination through oxygen, nitrogen, and sulfur donor atoms significantly modifies the electronic properties of both the metal ion and the ligand, often leading to enhanced biological activity. Spectroscopic, magnetic, thermal, and analytical characterization techniques consistently confirm successful complex formation and provide valuable insights into their structural features.

The antifungal potential of these complexes represents one of their most important biological applications. Numerous studies have demonstrated that cobalt(II) and nickel(II) thiazolidinone complexes exhibit greater antifungal activity than the corresponding free ligands. This enhancement is largely attributed to chelation-induced increases in lipophilicity, which facilitate membrane penetration and intracellular accumulation. Once inside fungal cells, the complexes exert their effects through multiple mechanisms, including disruption of membrane integrity, inhibition of essential enzymes, interaction with nucleic acids, induction of oxidative stress, mitochondrial dysfunction, and suppression of biofilm formation. The simultaneous operation of these mechanisms contributes to broad-spectrum antifungal activity and may reduce the likelihood of resistance development. The observed biological efficacy is strongly influenced by structure–activity relationships. Factors such as the nature of the metal ion, ligand denticity, donor atom type, substituent effects, molecular geometry, lipophilicity, stability, and steric characteristics collectively determine antifungal performance. The synergistic interaction between the thiazolidinone framework and the coordinated metal center enhances the overall pharmacological profile of the complexes, demonstrating the importance of rational ligand design in medicinal inorganic chemistry. In conclusion, cobalt(II) and nickel(II) complexes of thiazolidinone ligands represent a promising class of bioactive coordination compounds with considerable antifungal potential. Their unique combination of structural versatility, chemical stability, and multifaceted biological activity makes them attractive candidates for further pharmaceutical development. Future investigations involving advanced spectroscopic techniques, computational modeling, molecular docking studies, toxicity assessment, and in vivo biological evaluation will contribute to a deeper understanding of their mechanisms of action and facilitate the development of novel metal-based antifungal agents capable of addressing the growing challenge of fungal resistance

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