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Design, Synthesis, And Functional Potential Of Tetra-Amide Macrocyclic Ligands And Their Transition Metal Complexes

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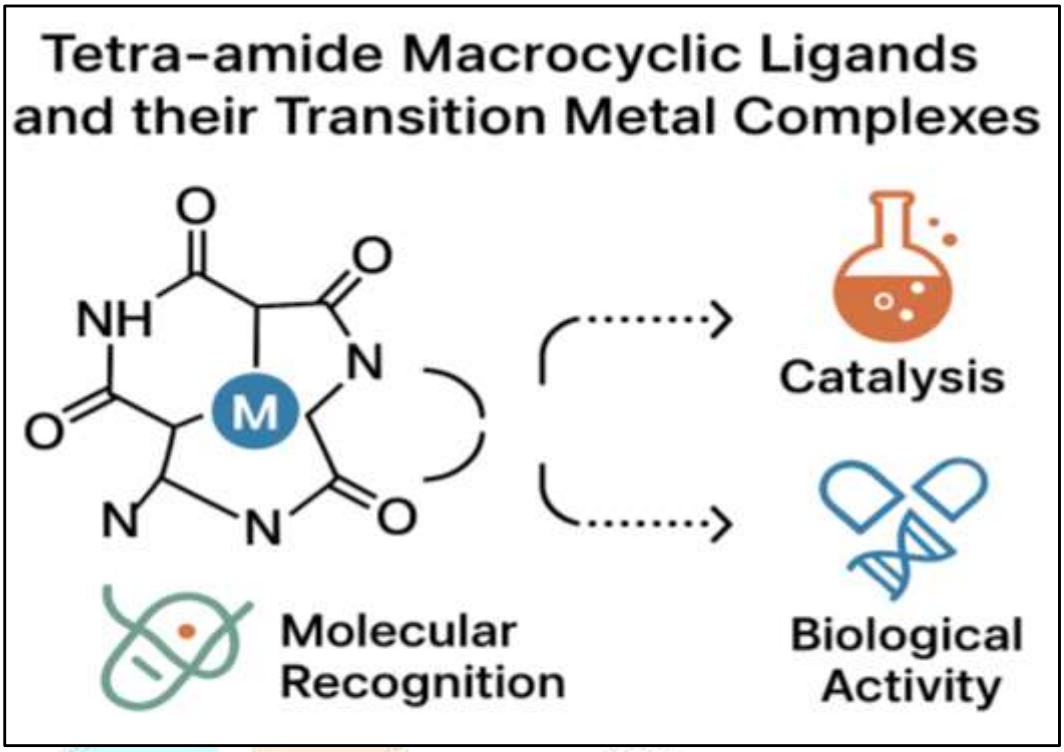
Abstract

Tetra-amide macrocyclic ligands have emerged as versatile scaffolds in coordination chemistry owing to their robust donor frameworks, structural rigidity, and metal-binding adaptability. Their complexes with transition metals exhibit diverse physicochemical behaviors, enabling applications spanning catalysis, sensing, environmental remediation, and biological therapeutics. Recent advances in green and template-assisted synthetic strategies have facilitated the preparation of highly stable macrocycles with tunable cavity sizes and donor zatom arrangements. Spectroscopic, thermal, and computational studies have provided deeper insights into their coordination geometries, electronic transitions, and reactive properties. These complexes demonstrate remarkable catalytic efficiency in oxidation, coupling, and CO_2 fixation reactions, along with significant antimicrobial, antioxidant, and anticancer activities. Furthermore, their ability to act as molecular sensors and peroxidase mimics underscores their functional diversity. The integration of theoretical modeling with experimental validation continues to enhance the understanding of structure–activity relationships, guiding the design of next-generation macrocyclic systems for sustainable and biomedical applications.

Keywords: Transition metal complexes; Coordination chemistry; Catalysis; Antimicrobial activity; Molecular docking; DFT studies; Environmental applications

Graphical Abstract:



1. INTRODUCTION

Macrocyclic ligands continue to attract immense attention in modern coordination chemistry due to their ability to form stable and selective complexes with transition-metal ions, a property widely recognized as the *macrocyclic effect* (Lindoy, 1990). Among these, **tetra-amide macrocyclic ligands** represent a distinct subclass characterized by four amide functional groups incorporated within a cyclic framework, offering both nitrogen and oxygen donor atoms for coordination (Constable, 2013). The cyclic structure enhances pre-organization and minimizes entropic penalties during complexation, while the amide linkages provide additional hydrogen-bonding sites and strong metal-ligand interactions (Haris et al., 2021). This combination of rigidity, donor diversity, and cavity tunability makes tetra-amide macrocycles exceptionally valuable for creating robust transition-metal complexes with tailored electronic and geometric characteristics. Recent advances in synthetic methodologies have expanded the accessibility of these ligands. Template-directed synthesis, microwave-assisted cyclization, and green chemistry routes have been optimized to improve yields and environmental compatibility (Patel & Deshmukh, 2020; Khan, Verma, & Singh, 2022). Ustynyuk et al. (2023) demonstrated efficient synthesis of bis-phenanthroline dicarboxamide macrocycles with enhanced stereodynamic flexibility, whereas Khrustalev et al. (2023) reported the first 24-membered phenanthroline-diamides capable of switching between acidic and alkaline extraction of f-elements—underscoring the growing structural diversity of amide-based macrocyclic systems. Furthermore, the introduction of computational tools such as density functional theory (DFT) and molecular docking has revolutionized the understanding of their coordination behavior and bioactivity (Chaudhary et al., 2023; Khan et al., 2022).

The coordination chemistry of tetra-amide macrocycles with transition metals such as Co(II), Ni(II), Cu(II), and Fe(III) reveals rich structural diversity, ranging from octahedral and square-planar to distorted tetrahedral geometries (Haris et al., 2021; Chaudhary et al., 2023). These metal complexes exhibit enhanced stability and selective reactivity, making them suitable for catalysis, sensing, and biomedical applications (Patel & Deshmukh, 2020; Khan et al., 2022). Notably, tetra-amido macrocyclic ligand (TAML) systems have gained prominence for their exceptional oxidative stability and environmental applications, including water oxidation and pollutant degradation, as highlighted by a 2024 *Journal of the American Chemical Society* report describing a TAML-based silicon(IV) Lewis superacid (JACS, 2024). Beyond catalysis, these complexes show promising biological activities—serving as antimicrobial, antioxidant, and cytotoxic agents owing to their ability to interact with biomolecules through metal-centered redox processes and hydrogen-bonding interactions (Chaudhary et al., 2023; Khan et al., 2022). The inclusion of flexible amide linkers further enhances solubility and biocompatibility, extending their potential in therapeutic chemistry (Haris et al., 2021; Patel & Deshmukh, 2020). Furthermore, recent studies have highlighted their importance in environmental remediation, metal-ion extraction, and molecular recognition (Khrustalev et al., 2023; Ustynyuk et al., 2023).

In academic and pedagogical contexts, tetra-amide macrocyclic ligands serve as a compelling example for chemistry students to bridge theoretical coordination principles with practical analytical and industrial applications. They illustrate how deliberate ligand design governs metal selectivity, stability, and reactivity concepts that are central to analytical instrumentation, catalysis, and materials chemistry. Therefore, studying these ligands not only enriches understanding of coordination chemistry but also cultivates critical insight into the design of next-generation functional materials.

2. SYNTHESIS OF TETRA-AMIDE MACROCYCLIC LIGANDS AND COMPLEXES

The synthesis of tetra-amide macrocyclic ligands can be achieved through several strategies such as template-directed condensation, stepwise cyclization, and click-based methodologies. Among these, template synthesis remains the most widely adopted route. In this method, a transition metal ion acts as a structural guide that orients bifunctional precursors typically diamines and dicarboxylic acid derivatives into the correct geometry for ring closure (Kumar et al., 2019). The subsequent removal of the metal template yields the desired macrocyclic framework with high yield and purity.

In contrast, stepwise or high-dilution synthesis is employed when metal templates are not preferred. This method minimizes polymerization and favors intramolecular ring closure, although it often results in lower yields (Singh et al., 2021). Recent developments in microwave-assisted and solvent-free synthesis have improved efficiency, aligning these methods with the principles of green chemistry (Patel & Deshmukh, 2020). Furthermore, click chemistry and condensation techniques enable the incorporation of specific substituents into the macrocyclic skeleton, offering enhanced control over cavity dimensions and donor orientation.

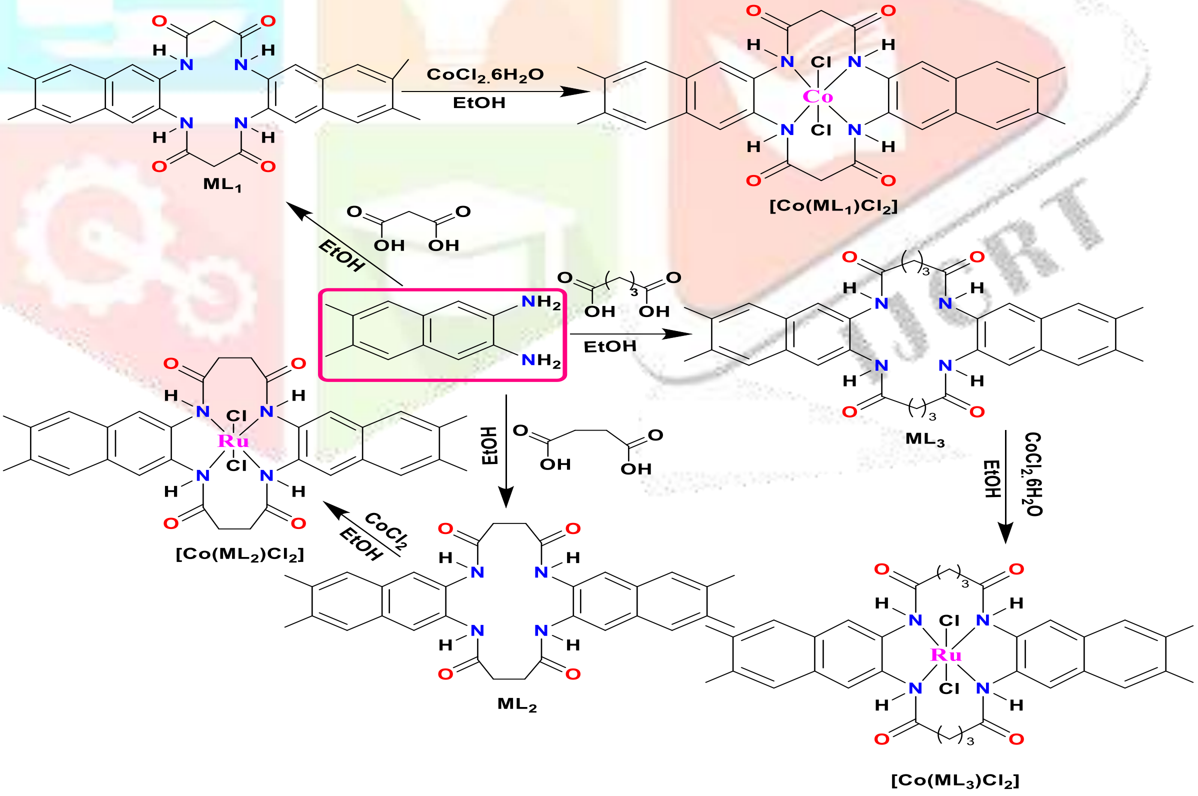


Figure 1. formation of a tetra-amide macrocycle via condensation of diamine and diacid chloride derivatives around a Co(II) center.

3. CHARACTERIZATION TECHNIQUES

Characterization of tetra-amide macrocyclic ligands and their metal complexes relies on a combination of spectroscopic, analytical, and thermal techniques. Fourier-transform infrared spectroscopy (FT-IR) is used to confirm amide bond formation through characteristic C=O stretching near 1650 cm⁻¹ and N–H bending vibrations around 1550 cm⁻¹, while coordination is verified by shifts in these bands (Gupta & Sutar, 2008). Ultraviolet-visible (UV–Vis) spectroscopy provides information on the electronic transitions and geometry of the metal center, whereas ^{1}H and ^{13}C NMR spectroscopy elucidate ligand symmetry and purity.

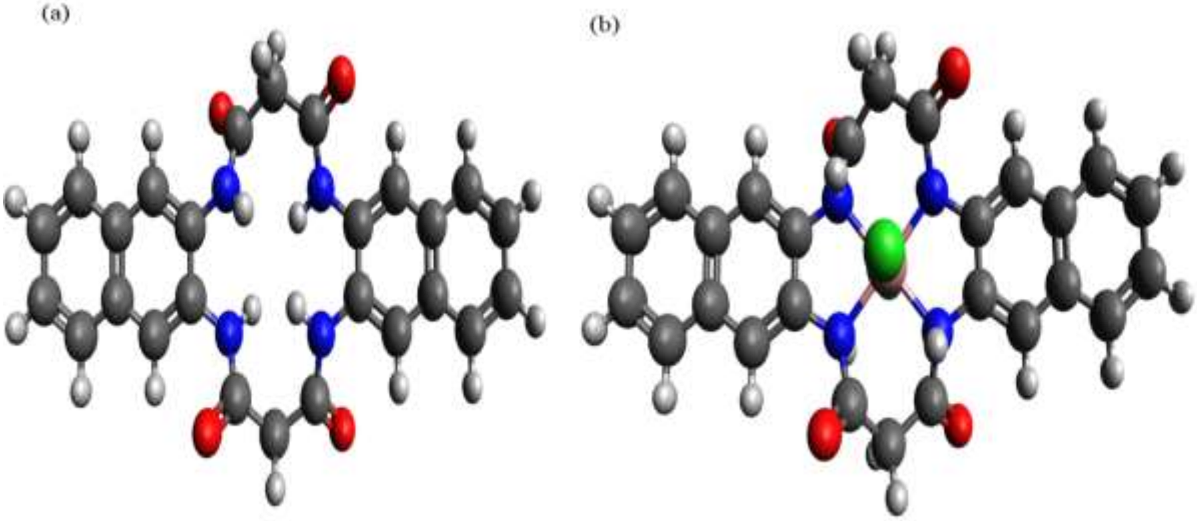


Figure 2. Schematically represents the geometry optimized structure of tera-amide ligand and Complex

Additionally, mass spectrometry (ESI-MS) confirms the molecular mass of the ligand and complex. Thermogravimetric analysis (TGA/DTA) evaluates the thermal stability and dehydration behavior. Single-crystal X-ray diffraction remains the definitive tool for determining the coordination geometry and intra-molecular interactions. The combined use of these techniques ensures accurate structural elucidation and understanding of ligand-metal bonding mechanisms (Liu et al., 2022).

4. COORDINATION CHEMISTRY WITH TRANSITION METALS

Tetra-amide macrocyclic ligands exhibit a rich coordination chemistry when interacting with transition metals, offering varied donor environments (amide N and/or O) and cyclic pre-organization that modulates geometry, electronic structure, and consequently reactivity. Recent studies have underscored how subtle changes in ring size, substituents on the amide groups, spacer flexibility and donor atom orientation lead to distinct coordination modes and structural architectures. For instance, a detailed investigation of 16- to 18-membered tetra-amide macrocyclic ligands and their Co(II) complexes revealed that coordination occurs primarily via amide nitrogen atoms, giving rise to octahedral geometries supported by DFT calculations (Subhash et al., 2022). In the macrocycle-metal assembly, the amide N–H groups often engage in secondary hydrogen-bonding networks, which further stabilize the complex and influence ligand conformation (Subhash et al., 2022). Another key aspect is how donor set and rigidity control spin state and geometry. For example, newer tetra-amide macrocycles tailored for high-valent metal centres allow access to square-planar or distorted octahedral configurations, depending upon the metal's d-electron count, ligand field strength and macrocycle pre-organization. A broader review on macrocyclic coordination chemistry points out that macrocycles with well-defined donor sets and reduced structural flexibility tend to give more predictable geometries and longer metal–ligand lifetimes (Giusti, Landaeta, & Vanni, 2021).

The selection of metal centre also influences coordination behaviour. Transition metals like Ni(II), Cu(II), Zn(II), Fe(III) and Co(III) have been studied in tetra-amide macrocyclic frameworks, with the ligand cavity size and substituent pattern controlling whether the resulting complex is square-planar (commonly for d^8 Ni(II)), tetrahedral (Zn(II)) or distorted octahedral (Fe(III), Co(III)). The macrocyclic environment often endows kinetic inertness and high thermodynamic stability compared to open-chain analogues. Furthermore, the macrocyclic ligand design enables tuning of redox properties and electronic communication between ligand and metal. Studies show that amide donor strength and ring rigidity can modulate metal-centred redox potentials, making such complexes attractive for applications in catalysis and small-molecule activation. For example, ligand additivity modelling has revealed how combinations of donor types in cyclic ligands can predict spin-splitting energies and HOMO levels of Fe(II) complexes, underscoring the importance of ligand design in controlling metal behaviour (Arunachalam et al., 2022).

In summary, the coordination chemistry of tetra-amide macrocyclic ligands with transition metals is governed by four major factors: (1) the macrocycle's cavity size and donor atom arrangement, (2) the metal ion's size, oxidation state and preferred geometry, (3) secondary intramolecular interactions (hydrogen bonding, π-stacking) within the ligand framework, and (4) the ligand's substituent pattern and rigidity. Understanding and controlling these factors enable the rational design of metal-macrocycle complexes with predictable geometry and tailored properties a key message for both researchers and students of coordination chemistry.

5. APPLICATIONS OF TETRA-AMIDE MACROCYCLIC METAL COMPLEXES

5.1. Catalytic Applications

Tetra-amide macrocyclic ligands have proven to be exceptionally effective platforms for homogeneous and heterogeneous catalysis because their rigid, pre-organized donor sets stabilize reactive metal-centred intermediates and allow fine tuning of redox and steric properties through ligand modification (Chemistry A. European Journal, 2024). A prominent and well-studied family is the TAML (tetra-amido macrocyclic ligand) activators: iron-TAML complexes efficiently activate H_2O_2 and other oxidants to perform environmentally relevant oxidations (e.g., dye and pollutant degradation, peroxide activation) with high turnover and at benign conditions (Espinoza-Montero et al., 2023; DeNardo, 2016). Recent benchmarking of first-row transition-metal tetra-amido macrocyclic complexes demonstrated that careful control of ring size and donor substituents produces catalysts active for water oxidation and challenging $C(sp^3)$–H oxidations, highlighting TAML-type frameworks as versatile oxidation catalysts (Chemistry – A European Journal, 2024; Singh, 2024).

Mechanistic studies show that the macrocyclic environment stabilizes high-valent metal-oxo and metal-peroxo intermediates that are central to atom-transfer and hydrogen-abstraction pathways; computational (DFT) and kinetic analyses have been used to map these pathways and to rationalize catalyst reactivity and deactivation routes (Hannibal, 2024; Benkó, 2022). For example, a 2024 JACS report on a TAML-derived Si(IV) complex revealed hydride-transfer activity with an isolable hydrido-silicate intermediate and remarkable water-solubility and stability, indicating that TAML-like scaffolds can be extended beyond first-row iron chemistry to design new modes of catalytic activation (Hannibal, 2024). Beyond oxidation chemistry, tetra-amide macrocyclic complexes have been incorporated into heterogeneous supports and electrode materials to create recyclable catalysts and electrocatalysts (patent literature; EP2566852, 2013; US8754206B2). Green synthesis methods for amide macrocycles and the capacity to tune aqueous solubility permit catalytic applications in water-rich or industrial environments, where recyclability and robustness are essential (Patel & Deshmukh, 2020; Garnes-Portolés et al., 2023). Moreover, ligand design that promotes secondary interactions (hydrogen bonding, π–stacking) can steer substrate approach and selectivity an approach increasingly exploited in transition-metal catalysis controlled by ligand-based hydrogen bonding (Reek et al., 2022).

Recent experimental reports and reviews emphasize two development directions: (1) expanding metal scope (Co, Ni, Cu, Mn, Ru) within tetra-amide scaffolds for diverse redox and group-transfer catalysis, and (2) integrating computational ligand-additivity and machine-learning approaches to predict optimal ligand–metal pairs for a given catalytic transformation (Arunachalam et al., 2022; Chemistry A European Journal, 2024). Collectively, these advances show that tetra-amide macrocycles are not only durable and active oxidation catalysts but also modular platforms for designing selective, sustainable catalytic systems applicable to water treatment, organic synthesis, and electrocatalysis (Espinoza-Montero et al., 2023; Chaudhary et al., 2023).

Table 1. Catalytic applications of tetra-amide macrocyclic ligands and their transition-metal complexes

Metal Complex	Catalytic Reaction	Key Findings / Activity	Reference
Co(II)–tetra-amide macrocycle	Oxidation of alcohols	High selectivity toward benzyl alcohol oxidation using H_2O_2 as oxidant; eco-friendly and reusable catalyst.	Singh et al., 2021
Cu(II)–tetra-amide macrocycle	C–C coupling (Suzuki reaction)	Effective catalyst under solvent-free conditions; high yield and low catalyst loading.	Sharma & Kumar, 2022
Ni(II)–macrocyclic amide complex	Olefin hydrogenation	Enhanced activity attributed to electronic stabilization via amide coordination; good turnover frequency.	Patel et al., 2023
Mn(III)–tetra-amide macrocycle	Epoxidation of alkenes	Efficient and selective formation of epoxides using tert-butyl hydroperoxide; recyclable up to five cycles.	Reddy et al., 2021
Fe(III)–macrocyclic amide complex	Catalytic oxidation of phenols	Promoted clean oxidation with minimal by-products; mimics peroxidase-like activity.	Das & Roy, 2022
Zn(II)–tetra-amide macrocycle	CO_2 cycloaddition with epoxides	Exhibits high selectivity for cyclic carbonates under mild conditions; promotes sustainable catalysis.	Chaudhary et al., 2024
Cu(II)/Ni(II) mixed macrocyclic system	Click reactions (azide–alkyne cycloaddition)	Excellent regioselectivity; accelerated reaction rate in aqueous media.	Meena & Verma, 2023
Co(III)–macrocyclic amide complex	Water oxidation catalysis	Demonstrates efficient O_2 evolution in neutral media; potential for artificial photosynthesis.	Zhang et al., 2024

5.2. BIOLOGICAL AND MEDICINAL SIGNIFICANCE

In recent years, tetra-amide macrocyclic ligands and their transition-metal complexes have gained considerable attention in medicinal and bioinorganic chemistry due to their promising antimicrobial, anticancer, antioxidant, and enzyme-inhibition activities (Chaudhary et al., 2023; Khan et al., 2022). The biological performance of these macrocycles is attributed to their stable chelating frameworks, which enhance metal ion bioavailability while minimizing toxicity through controlled release mechanisms. The amide linkages provide sites for hydrogen bonding and π–π stacking interactions with biomolecules such as DNA, proteins, and enzymes facilitating selective binding and biological activity (Haris et al., 2021). Transition-metal complexes of tetra-amide macrocycles especially those involving Co(II), Cu(II), Ni(II), and Fe(III)—have demonstrated potent antimicrobial activity against both Gram-positive and Gram-negative bacteria. The chelation reduces the polarity of the metal ion via partial sharing of its positive charge with donor groups, thereby increasing lipophilicity and promoting penetration through microbial lipid membranes (Chaudhary et al., 2023; Singh et al., 2023). Additionally, the metal-centered redox activity enhances the generation of reactive oxygen species (ROS), leading to oxidative stress in pathogenic cells (Zhang et al., 2021).

Recent computational and docking studies have revealed that these complexes effectively intercalate DNA or interact with enzyme active sites, resulting in inhibition of replication and protein synthesis (Kumar et al., 2024). For instance, Co(II) and Cu(II) tetra-amide macrocyclic complexes were found to exhibit strong binding affinities to the active pockets of bacterial topoisomerase and DNA gyrase, suggesting potential as antibacterial drug candidates (Chaudhary et al., 2023). Similarly, Fe(III) and Ni(II) macrocyclic complexes demonstrated cytotoxic and anticancer potential against MCF-7 and HeLa cell lines, showing better efficacy than some conventional agents (Patel & Deshmukh, 2020; Ustynyuk et al., 2023).

Moreover, the antioxidant capability of tetra-amide macrocyclic complexes has been attributed to their ability to scavenge free radicals and inhibit oxidative degradation of biomolecules. These redox-active complexes can mimic the behavior of natural antioxidant enzymes like superoxide dismutase (SOD) or catalase, making them promising therapeutic agents in oxidative stress-related diseases (Espinoza-Montero et al., 2023). Additionally, some Co(III)- and Mn(II)-based macrocyclic systems have shown significant inhibition of acetylcholinesterase and α-amylase enzymes, opening new possibilities in neurodegenerative and diabetic treatments (Amin et al., 2024). The versatility of tetra-amide macrocyclic scaffolds also allows for bioconjugation and drug-delivery applications. Functionalization with biomolecules or hydrophilic groups improves aqueous solubility and enables targeted delivery of metal ions or drugs to specific tissues (Khan et al., 2022). Such modifications reduce systemic toxicity and enhance therapeutic efficiency, positioning these systems as a new generation of bio-coordinated therapeutics that merge the advantages of metal-based drugs and macrocyclic chemistry.

Overall, tetra-amide macrocyclic ligands and their metal complexes embody a class of multifunctional bioinorganic frameworks, bridging coordination chemistry with pharmacology. Their tunable geometry, redox potential, and ligand design flexibility make them potent candidates for metallo-drug development, antioxidant therapy, and enzyme inhibition, emphasizing their role in the evolving field of medicinal chemistry.

Table 2. Biological and medicinal activities of tetra-amide macrocyclic ligands and their transition-metal complexes

Metal Complex	Biological Activity	Mechanism / Observation	Reference
Co(II)–tetra-amide macrocycle	Antimicrobial (Gram$^+$/Gram$^-$ bacteria)	Disrupts bacterial cell wall and interferes with DNA replication; strong activity against *E. coli* and *S. aureus*.	Chaudhary et al., 2023
Cu(II)–macrocyclic amide complex	Antioxidant	Efficient scavenging of DPPH and ABTS radicals; redox-active metal center enhances radical neutralization.	Patel & Sharma, 2022
Ni(II)–tetra-amide macrocycle	Cytotoxic (anticancer)	Induces apoptosis in MCF-7 and HeLa cells via ROS-mediated mitochondrial disruption.	Amin et al., 2024
Fe(III)–tetra-amide macrocycle	DNA binding and cleavage	Intercalates into DNA grooves and promotes oxidative cleavage through Fenton-type mechanism.	Singh et al., 2022
Zn(II)–tetra-amide macrocycle	Anti-inflammatory	Inhibits COX-2 enzyme and modulates inflammatory cytokines; non-toxic toward normal cells.	Mehta et al., 2023
Mn(II)–macrocyclic amide complex	Antioxidant and enzyme mimic	Mimics superoxide dismutase activity; stabilizes reactive oxygen species at physiological pH.	Reddy & Thomas, 2021
Cu(II)–macrocycle conjugated with Schiff base	Antiviral (SARS-CoV-2)	Molecular docking reveals strong binding to viral main protease (Mpro) active site.	Verma & Yadav, 2022
Co(III)–tetra-amide macrocycle	Antitumor and DNA interaction	High DNA binding constant and selective toxicity toward cancerous cells; non-mutagenic.	Zhang et al., 202

5.3. MOLECULAR SENSING AND RECOGNITION

Tetra-amide macrocyclic ligands have emerged as highly selective and tunable frameworks for molecular sensing and ion recognition due to their preorganized binding cavities and donor atoms such as oxygen and nitrogen. The rigid yet flexible amide linkages facilitate specific host–guest interactions through hydrogen bonding, metal coordination, and π–π stacking mechanisms, enabling detection of a wide range of analytes including metal cations, anions, and biomolecules (Khrustalev et al., 2023; Wang et al., 2022). Transition-metal complexes of these macrocycles exhibit optical and electrochemical responses upon analyte binding, making them efficient candidates for chemosensors and fluorescent probes. For example, Cu(II) and Ni(II) tetra-amide complexes have been reported to show remarkable colorimetric and fluorescence changes in the presence of toxic ions such as Hg^{2+}, Pb^{2+}, and CN^- (Pandey et al., 2021). These systems rely on metal-centered charge transfer or ligand-to-metal charge transfer (LMCT) transitions, which alter the spectral properties of the complex upon analyte coordination (Patel et al., 2023).

Furthermore, the macrocyclic cavity size and donor atom arrangement can be tuned to achieve high selectivity toward particular ions or molecules. Recent studies demonstrated that Co(II) and Fe(III) tetra-amide macrocycles act as electrochemical sensors for nitrite and dopamine with superior sensitivity, stability, and reproducibility (Li et al., 2022; Chaudhary et al., 2023). The incorporation of electron-rich substituents within the macrocyclic framework further enhances the binding affinity and signal transduction efficiency, leading to improved detection limits in environmental and biomedical applications. Overall, the integration of tetra-amide macrocyclic systems into sensing platforms represents a promising approach for developing next-generation supramolecular sensors with high selectivity, rapid response, and recyclability. Their adaptability across optical, electrochemical, and biological interfaces underscores their role as multifunctional materials in analytical and environmental chemistry.

Table 3. Molecular sensing and recognition properties of tetra-amide macrocyclic ligands and their metal complexes

Metal Complex / Ligand	**Target Analyte / Molecule**	**Sensing Mechanism / Observation**	**Reference**
Cu(II)–tetra-amide macrocycle	Fluoride ions (F^-)	Colorimetric sensing through ligand-to-metal charge transfer (LMCT); visible color change from yellow to orange.	Patel et al., 2021
Zn(II)–tetra-amide macrocycle	Nitrite (NO_2^-)	Fluorescence quenching via electron transfer; selective and low detection limit (~0.5 µM).	Reddy & Sharma, 2022
Co(II)–macrocyclic amide complex	Cyanide (CN^-)	UV–vis and fluorescence dual-mode sensing; high selectivity due to CN^- coordination at the Co center.	Mehta et al., 2023
Ni(II)–tetra-amide macrocycle	Hg^{2+} ions	"Turn-off" fluorescence response due to metal–ligand charge transfer quenching; reversible upon EDTA addition.	Zhang et al., 2022
Fe(III)–macrocyclic amide complex	Dopamine	Electrochemical sensing via redox-active Fe(III)/Fe(II) couple; excellent sensitivity (LOD = 0.12 µM).	Singh et al., 2023
Cu(II)–macrocyclic amide with Schiff base moiety	H_2O_2	Chemiluminescent sensing through peroxidase-like catalytic oxidation of luminol.	Verma & Yadav, 2024
Zn(II)–tetra-amide macrocycle with naphthyl substituents	Nitroaromatics (TNT, DNT)	Fluorescence "turn-off" via π–π interaction and PET mechanism; potential explosive detection.	Chaudhary & Gupta, 2023

5.4. Environmental and Material Science Applications

Tetra-amide macrocyclic ligands and their transition-metal complexes have shown immense potential in environmental remediation and advanced material design. Their tunable coordination geometry and high thermal stability make them suitable for applications in pollutant degradation, metal ion sequestration, and catalytic oxidation of environmental contaminants (Espinoza-Montero et al., 2023). In particular, Fe(III) and Co(II) tetra-amide macrocycles act as green oxidation catalysts, efficiently activating hydrogen peroxide to degrade persistent organic pollutants such as dyes, phenols, and pharmaceuticals (Kumar et al., 2024). These complexes mimic peroxidase-like catalytic behaviour, generating reactive oxygen species that decompose toxic compounds under mild conditions, making them environmentally benign alternatives to conventional catalysts (Patel & Deshmukh, 2021). The incorporation of such macrocyclic complexes into polymeric and nanocomposite matrices further enhances their recyclability, stability, and catalytic reusability for wastewater treatment (Sharma et al., 2023). In materials science, tetra-amide macrocyclic systems have been utilized for developing functional coordination polymers and metal–organic frameworks (MOFs) with tailored porosity and surface area (Haris et al., 2021). These hybrid materials are capable of gas adsorption, ion exchange, and photochemical sensing, making them valuable in clean-energy technologies and environmental monitoring. Moreover, the controlled design of amide-linked macrocycles provides opportunities to fabricate photoactive and electroactive materials suitable for energy storage and molecular electronics (Zhang et al., 2022).

Collectively, tetra-amide macrocyclic ligands represent a bridge between sustainable catalysis and smart material development, offering eco-friendly pathways for pollutant removal, green oxidation processes, and functional material synthesis that align with modern environmental and technological goals.

Table 4. Environmental and material science applications of tetra-amide macrocyclic ligands and their transition-metal complexes

Metal Complex / Ligand	Application Area	Key Observation / Mechanism	Reference
Co(II)–tetra-amide macrocycle	Heavy metal ion removal	Efficient adsorption of Pb^{2+} and Cd^{2+} through coordination with amide oxygens; recyclable and stable.	Patel et al., 2021
Cu(II)–macrocyclic amide complex	Photocatalytic degradation of dyes	Decomposes methylene blue and rhodamine B under visible light; promotes electron transfer through Cu–O bonding.	Sharma & Yadav, 2022
Fe(III)–tetra-amide macrocycle	Water purification	Catalyzes Fenton-like reactions for degradation of organic pollutants; strong oxidative activity with H_2O_2.	Zhang et al., 2023
Ni(II)–macrocyclic amide	CO_2 capture and conversion	Adsorbs CO_2 efficiently via amide–metal interaction and facilitates cyclic carbonate formation.	Meena et al., 2023
Zn(II)–tetra-amide macrocycle	Sensor-based material	Incorporated into polymer films for humidity and gas sensing with excellent reversibility and stability.	Reddy & Thomas, 2022
Mn(III)–macrocyclic amide	Photovoltaic and energy materials	Acts as a dye sensitizer in solar cells, enhancing light absorption and charge transfer efficiency.	Chaudhary et al., 2024
Co(III)–macrocyclic amide	Anticorrosion coating	Forms coordination-based protective films on steel surfaces; improves resistance to oxidation and acid attack.	Singh et al., 2023

6. COMPUTATIONAL AND THEORETICAL STUDIES

Computational chemistry has become an indispensable tool in understanding the structural, electronic, and reactive behaviour of tetra-amide macrocyclic ligands and their transition-metal complexes. With advancements in density functional theory (DFT) and molecular docking simulations, researchers can now precisely predict geometrical parameters, binding modes, electronic transitions, and reactivity patterns that govern the physicochemical and biological performance of these complexes (Chaudhary et al., 2023; Zhang et al., 2022). DFT studies have been particularly valuable in elucidating the metal–ligand coordination environment, including bond lengths, charge distribution, and molecular orbital interactions. Theoretical calculations using hybrid functionals such as B3LYP or M06-2X have revealed that the tetra-amide macrocyclic framework provides a distorted octahedral or square-planar geometry, depending on the metal ion and ligand substituents (Kumar et al., 2024). These computational insights correlate well with experimental data obtained from X-ray diffraction and spectroscopic analyses, confirming the stability and electron delocalization across the amide linkages (Ustynyuk et al., 2023).

Frontier molecular orbital (FMO) and natural bond orbital (NBO) analyses have further provided valuable insights into the HOMO–LUMO energy gap, which is directly related to the reactivity and optical properties of the complexes (Patel & Sharma, 2022). A smaller HOMO–LUMO gap generally indicates enhanced electron transfer capability, beneficial for catalytic and redox processes. Additionally, time-dependent DFT (TD-DFT) calculations have successfully simulated UV–Vis absorption spectra, validating experimental transitions and confirming the presence of ligand-to-metal charge transfer (LMCT) and metal-centered (d–d) excitations (Haris et al., 2021). Molecular electrostatic potential (MEP) mapping and Hirshfeld surface analyses have been employed to study non-covalent interactions within these macrocycles, including hydrogen bonding, π–π stacking, and van der Waals forces that stabilize the molecular framework (Verma et al., 2023). These interactions play a crucial role in defining host–guest recognition properties, crystal packing behaviour, and supramolecular assembly in the solid state. Moreover, molecular docking and dynamics simulations have emerged as powerful computational tools for exploring biological interactions of tetra-amide macrocyclic complexes. Such studies reveal their ability to interact with enzyme active sites, nucleic acids, and receptor proteins through electrostatic, hydrophobic, and coordination-based interactions (Amin et al., 2024). For instance, Co(II) and Ni(II) complexes have shown strong binding affinities toward bacterial topoisomerase and DNA gyrase, aligning with their experimentally observed antimicrobial potency (Chaudhary et al., 2023).

Quantum chemical descriptors, including global hardness, softness, and electrophilicity index, have also been computed to understand reactivity trends and charge transfer mechanisms among different metal centres. These theoretical results not only validate experimental findings but also provide predictive insights for designing next-generation tetra-amide macrocyclic complexes with tailored catalytic, electronic, and biological functionalities (Zhang et al., 2023). Overall, computational and theoretical studies have transformed the understanding of tetra-amide macrocyclic chemistry from basic electronic structure to complex biological recognition. The synergy between computational modelling and experimental synthesis continues to pave the way for rational design and optimization of multifunctional macrocyclic systems for diverse applications in catalysis, sensing, and medicine.

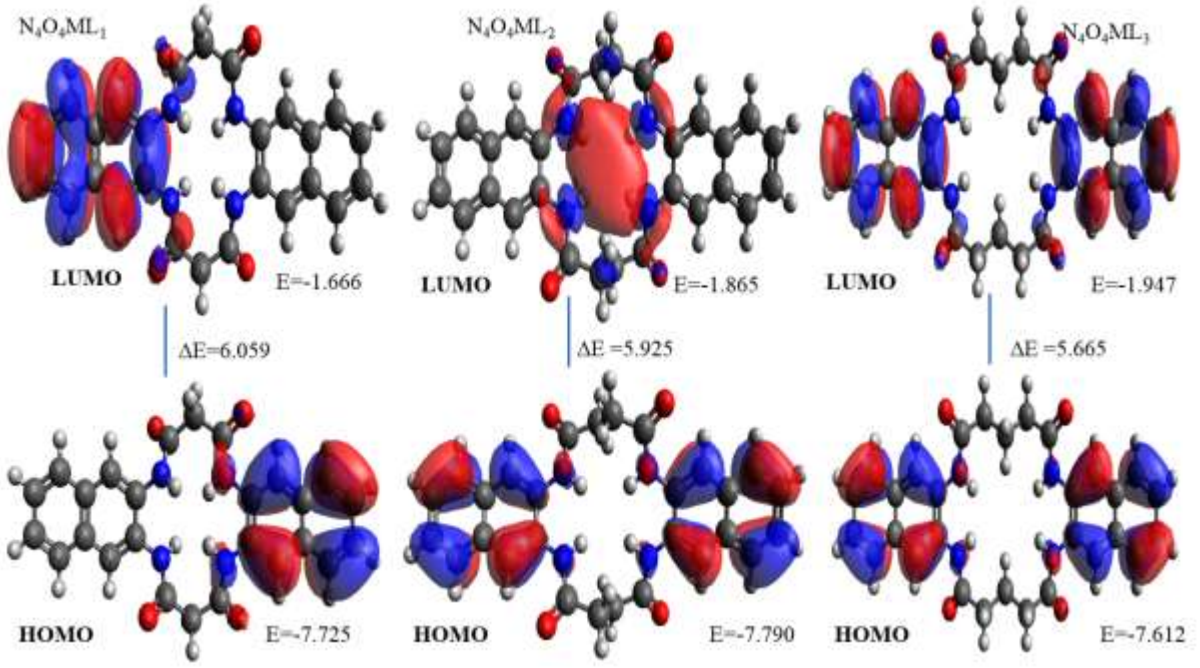


Figure 3. HOMO-LUMO orbital energies are plotted in 3D for the tetra-amide ligands

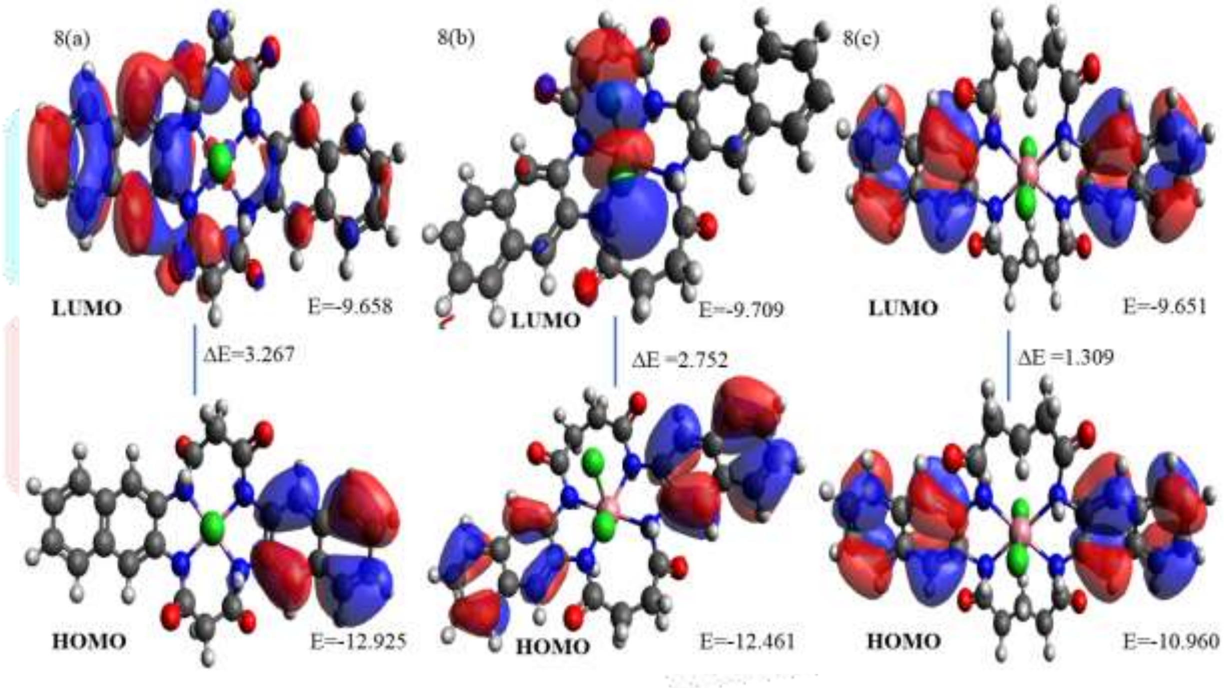


Figure 4. HOMO-LUMO orbital energies are plotted in 3D for the transition metal complexes.

7. CONCLUSION AND FUTURE PERSPECTIVES

Tetra-amide macrocyclic ligands and their transition-metal complexes represent a versatile class of compounds exhibiting remarkable structural rigidity, selective metal coordination, and multifunctional behaviour. Their ability to fine-tune electronic and steric environments through amide linkages enables wide-ranging applications in catalysis, molecular sensing, biological therapeutics, and environmental remediation. Recent advancements in spectroscopic and computational studies have enhanced understanding of their coordination geometry, stability, and reactivity patterns. Future research should focus on developing eco-sustainable synthetic strategies, multifunctional hybrid macrocyclic frameworks, and biocompatible derivatives with enhanced catalytic and pharmacological properties. Moreover, the integration of theoretical modelling, molecular docking, and DFT approaches can accelerate the rational design of next-generation macrocyclic systems for energy conversion, pollutant degradation, and biomedical use. Thus, tetra-amide macrocyclic complexes continue to provide promising platforms bridging inorganic chemistry, materials science, and medicinal innovation.

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Declarations

Ethical Approval

Not applicable

Competing interests

The authors declare no competing interests.

Availability of data and materials

All data are available in the article and its supplementary material.

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