Application of Dithiocarbamate Complexes as Metallotherapy and Medical Imaging Agent

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Abstract
Dithiocarbamates have been rated as versatile sulfur-based ligands that exhibit a high affinity for transition metals, forming stable metal complexes with diverse geometries and oxidation states. These metal-dithiocarbamate complexes have gained increasing attention for their significant roles in biomedical sciences, particularly in metallotherapy and medical imaging. Metallotherapeutic applications span across anticancer, antimicrobial, antiparasitic, antioxidant, and anti-inflammatory domains due to their unique mechanisms of action involving redox activity, DNA interaction, and enzyme inhibition. In parallel, the development of dithiocarbamate complexes as diagnostic agents—particularly in radiopharmaceuticals and magnetic resonance imaging (MRI)—has opened new pathways for early disease detection and treatment monitoring. This review discusses the chemical characteristics, coordination behavior, therapeutic potential, imaging capabilities, and future prospects of dithiocarbamate metal complexes, emphasizing their dual utility in therapy and diagnosis.

Keywords: *Dithiocarbamate, medical imaging, metal, metallotherapy*

1. Introduction

In recent decades, metal-based compounds have found wide applications in medicine, marking a significant shift in the development of novel therapeutic and diagnostic agents. This transition stems from the realization that metal ions can perform unique functions that organic molecules cannot, such as facilitating redox reactions, modulating protein function, and serving as imaging enhancers in diagnostic platforms (Ronconi & Sadler, 2007). The emerging field of metallodrugs, therefore, represents a integration of inorganic chemistry and pharmacology aimed at tackling some diseases including cancer, neurodegenerative disorders, and microbial infections.

Among the diverse families of metal-binding ligands, dithiocarbamates (DTCs) stand out due to their strong metal-chelating properties, structural flexibility, and diverse pharmacological profiles. DTCs are derivatives of dithiocarbamic acid, typically featuring the general formula $R_2N–CS_2^-$ (Ajibade & Zulu, 2023). Their high affinity for transition and non transition metal centers and the ability to stabilize various metal oxidation states make them suitable candidates for biomedical applications. Notably, DTC metal complexes have shown promise in metallotherapy: a therapeutic strategy that utilizes metal-containing compounds and in medical imaging, where they are employed as carriers of radiometals or MRI-active centers (Ma & Lin, 2010)

This review highlights an overview of dithiocarbamate metal complexes with a dual focus: (1) their therapeutic roles as anticancer, antimicrobial, antidiabetes and anti-inflammatory agents, and

(2) their diagnostic utility in imaging techniques such as SPECT, PET, and MRI. Emphasis is placed on the coordination chemistry, mechanisms of action, recent experimental developments, and the challenges that must be overcome to translate these agents into clinical use.

2. Chemistry and Coordination Behavior of Dithiocarbamates

Dithiocarbamates (DTCs) are a class of monodentate or bidentate ligands derived from the reaction of primary or secondary amines with carbon disulfide in alkaline media. The resulting anionic group, $R_2N–CS_2^-$, features a delocalized π-system between the nitrogen and sulfur atoms, contributing to their high stability and reactivity with metal ions. This unique electronic configuration enables DTCs to coordinate with a wide range of transition, lanthanide, and post-transition metals, forming complexes with varied geometries and oxidation states (Casas & Sordo, 2011).

2.1 Structural Features

The general structure of a dithiocarbamate ligand consists of a nitrogen donor atom bonded to a central thiocarbon (C=S), which is in turn bonded to two sulfur atoms. The negative charge is delocalized over the two sulfur atoms, enhancing their nucleophilicity and ability to coordinate with metal centers. The resonance between the CS_2^- and the nitrogen lone pair contributes to both planarity and rigidity in the ligand backbone:

$$\mathbf{R_2N–C(=S)–S^- \leftrightarrow R_2N^+=C–S^- \leftrightarrow R_2N–CS_2^-}$$

DTCs typically coordinate to metal centers in a bidentate fashion through both sulfur atoms, forming five-membered chelate rings. In some cases, they can also act as monodentate or bridging ligands, depending on the metal ion, coordination number, and steric factors.

2.2 Coordination Geometry

The geometry of metal–dithiocarbamate complexes is largely determined by the metal's oxidation state and coordination preferences (Hartinger & Dyson, 2009). Common geometries include:

- Square planar (e.g., Ni(II), Pd(II), Pt(II))
- Octahedral (e.g., Fe(III), Co(III), Mn(II), Ru(III))
- Tetrahedral (e.g., Zn(II), Cd(II), Cu(I))
- Trimeric or polymeric aggregates in the case of Ag(I) or Au(I) complexes

The chelation by dithiocarbamate stabilizes the metal center and often prevents hydrolysis or oxidation in aqueous or physiological conditions, which is highly advantageous for biological applications (Gibson, 2020).

2.3 Electronic Properties

DTC ligands are classified as soft bases in the Pearson Hard and Soft Acids and Bases (HSAB) concept. Thus, they preferentially coordinate with soft or borderline metal centers, such as Cu(I/II), Ag(I), Hg(II), and Pt(II). Their electron-rich sulfur atoms enable π-backbonding with d-block metals, influencing the redox potential, electronic absorption, and biological reactivity of the resulting complexes.

2.4 Stability and Solubility

Metal–DTC complexes are generally stable in neutral to slightly acidic environments and exhibit good solubility in organic solvents. However, their aqueous solubility can vary based on the nature

of the substituents on the nitrogen atom (R-groups), the metal center, and the counterions present. This tunability in solubility and lipophilicity is crucial for modulating pharmacokinetic behavior in therapeutic and diagnostic applications (Barros & Costa, 2018).

2.5 Notable Metal–Dithiocarbamate Complexes

Some of the most studied dithiocarbamate complexes include:

- Copper(II)-DTC: Exhibits anticancer and antimicrobial activity via redox cycling and ROS generation.
- Zinc(II)-DTC: Shows enzyme inhibition and cytotoxicity against cancer cells.
- Technetium-99m-DTC: Used in SPECT imaging due to favorable coordination and in vivo stability.
- Gadolinium-DTC: Explored as MRI contrast agents with potential for tissue-specific imaging.
- Gallium(III)- and Rhenium(V)-DTC: Under investigation for PET imaging and radiotherapy.

The versatility of dithiocarbamate chemistry lies in its ability to fine-tune biological and physicochemical properties through ligand design and metal choice, paving the way for multifunctional metallodrugs and diagnostic tools (Tella *et al*., 2022).

3. Dithiocarbamate Complexes in Metallotherapy

Metallotherapy refers to the therapeutic use of metal-containing compounds to treat human diseases, particularly where conventional organic drugs are inadequate. The strong chelating nature of dithiocarbamates and their ability to stabilize redox-active metal ions render their complexes particularly attractive in this field (Ali & Shahzadi, 2017). Dithiocarbamate–metal complexes have demonstrated potent activity against cancer, bacterial and fungal infections, parasitic diseases, and inflammatory conditions (Srivastava, 2021) Their mode of action often involves interaction with DNA, proteins, or enzymes, as well as the induction of oxidative stress in target cells (Cvek & Dvorak, 2008).

3.1 Anticancer Applications

One of the most widely investigated uses of metal-dithiocarbamate complexes is in cancer therapy. These complexes often exploit the high metabolic rate and low antioxidant defenses of tumor cells to generate cytotoxic effects.

Mechanisms of Action:

- Reactive Oxygen Species (ROS) Generation: Metal ions such as Cu(II), Fe(III), and Mn(II) in dithiocarbamate complexes undergo redox cycling, producing ROS that damage cellular macromolecules. For example Cu(II)-diethyldithiocarbamate ($Cu(DDC)_2$ exhibits selective cytotoxicity in cancer cells and synergizes with existing chemotherapy.
- DNA Binding and Cleavage: Some complexes intercalate into DNA or bind covalently, leading to strand breaks and inhibition of replication and transcription. For instance Zn(II)- and Ni(II)-DTC complexes is effective against various carcinoma cell lines with reduced toxicity to normal cells (Kratz, et al.,(2008) and Ramogida & Orvig, (2013).
- Enzyme Inhibition: DTC complexes can inhibit proteasomes, matrix metalloproteinases (MMPs), or thiol-containing enzymes crucial for cancer cell survival. **Pt(II)-DTC analogs**: Explored as alternatives to cisplatin, offering reduced side effects and improved selectivity.

3.2 Antimicrobial and Antiparasitic Activity

The antimicrobial action of DTC metal complexes is attributed to their ability to disrupt microbial membrane integrity, inhibit key enzymes, and interfere with metal homeostasis.

Antibacterial Activity:

- Dithiocarbamate complexes with Ag(I), Zn(II), and Cu(II) show activity against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* (Maurya and Bajpai, 2022).
- Chelation enhances membrane permeability, allowing the metal center to penetrate and damage microbial cells.

Antifungal and Antiparasitic Effects:

- Metal–DTC complexes have demonstrated efficacy against *Candida* species and dermatophytes.
- Complexes with Fe(III), Ga(III), and Co(III) inhibit parasitic growth in diseases like malaria and leishmaniasis by disrupting iron metabolism or oxidative balance.

3.3 Antioxidant and Anti-inflammatory Potential

Although many DTC complexes exert pro-oxidant effects in cancer cells, they may display antioxidant activity in normal tissues.

Anti-inflammatory Mechanisms:

- Inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) pathways.
- Modulation of pro-inflammatory cytokines such as TNF-α and IL-6.
- Chelation of excess transition metals involved in inflammation-related oxidative stress.

Neuroprotective Effects:

- Studies suggest that certain Zn- and Cu-DTC complexes offer protection in models of neurodegenerative diseases, possibly by scavenging free radicals and restoring metal ion balance.

Dithiocarbamate metal complexes represent a class of multifunctional metallodrugs with diverse pharmacological activities. Their ability to selectively target diseased cells, inhibit critical enzymes, and modulate redox status makes them promising candidates in the search for effective anticancer, antimicrobial, and anti-inflammatory agents. Moreover, their unique coordination chemistry allows for structural tuning and multifunctional design, opening avenues for combination therapies and targeted drug delivery systems.

4. Dithiocarbamate Complexes as Medical Imaging Agents

Medical imaging plays a critical role in modern diagnostics, offering non-invasive methods to visualize anatomical structures, physiological processes, and pathological changes in the body. The use of metal-based contrast agents enhances imaging resolution and specificity. Dithiocarbamate ligands, with their strong metal-binding properties and structural tunability, have emerged as valuable scaffolds for developing metal complexes suitable for various imaging modalities, including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI). These applications exploit the ability of DTCs to form kinetically stable and lipophilic complexes with radiometals and paramagnetic ions.

4.1 Radiopharmaceuticals for SPECT and PET Imaging

Dithiocarbamates form highly stable complexes with radionuclides such as technetium-99m (^{99}mTc), rhenium (Re), gallium-68 (^{68}Ga), and copper-64 (^{64}Cu). These radionuclide-labeled complexes are widely used in nuclear medicine for diagnostic imaging and therapy monitoring (Zolle, 2007).

^{99}mTc-DTC Complexes:

- The most clinically relevant application of DTC complexes lies in the use of ^{99}mTc for SPECT imaging (Tsopelas & Sutton, 2011).
- DTC ligands ensure rapid complexation and high in vivo stability, critical for short half-life isotopes.
- Lipophilic ^{99}mTc-DTC complexes cross the blood-brain barrier and have been used in brain perfusion imaging.

^{64}Cu- and ^{68}Ga-DTC Complexes:

- Chelation with DTC ligands stabilizes these PET-active metal isotopes for tumor imaging.
- ^{64}Cu-DTC complexes have shown tumor-selective accumulation due to enhanced permeability and retention (EPR) effects.
- Gallium-68-labeled DTC peptides and nanoparticles have been developed for receptor-specific imaging in oncology.

Theranostic Applications:

- Rhenium-188 (^{188}Re) and Lutetium-177 (^{177}Lu) DTC complexes combine therapeutic and imaging capabilities in a single agent (theranostics).
- The structural similarity of Re and Tc enables facile development of diagnostic-therapeutic pairs using the same DTC ligand framework.

4.2 MRI Contrast Agents

MRI contrast agents work by altering the relaxation times of nearby water protons. Paramagnetic metal ions, particularly Gd^{3+}, are commonly used due to their seven unpaired electrons and strong magnetic moment. DTC ligands have been investigated for their ability to form stable Gd^{3+} complexes that function as MRI contrast agents (Ngoshe, 2024).

Gd-DTC Complexes:

- The strong chelating nature of DTC prevents free Gd^{3+} release, reducing the risk of nephrogenic systemic fibrosis (NSF).
- Functionalized Gd-DTC complexes have been developed with targeting moieties (e.g., antibodies, peptides) for tumor-specific MRI.
- Studies show good r_1 relaxivity values, indicating efficacy in enhancing T1-weighted imaging.

Nanoparticle-Based Systems:

- Gd-DTC complexes can be incorporated into nanoparticles (e.g., liposomes, dendrimers) to improve blood circulation time and enable dual imaging with fluorescence or PET.

4.3 Hybrid Theranostic Agents

Dithiocarbamate chemistry allows the simultaneous attachment of therapeutic metals and imaging radionuclides, enabling *theranostic* strategies—agents that diagnose and treat disease simultaneously.

Examples:

- Cu(II)-DTC complexes used for both imaging and delivering anticancer activity.

- DTC-coated gold or iron oxide nanoparticles have been engineered for combined MRI, photoacoustic imaging, and targeted therapy (Pasqualini & Arap, 2004).
- Dual-labeled DTC constructs bearing PET/SPECT radionuclides and chemotherapeutic metals (e.g., Pt, Ru) are under investigation for image-guided therapy.

The versatility of dithiocarbamate ligands in stabilizing imaging-relevant metals has made them important tools in diagnostic radiopharmaceuticals and MRI. Their modular nature and strong chelation offer flexibility for designing hybrid imaging agents with therapeutic functions. DTC complexes continue to evolve toward more specific, targeted, and safer imaging agents, potentially revolutionizing personalized medicine.

5. Pharmacokinetics and Toxicological Considerations

The development of any therapeutic or diagnostic agent demands a thorough understanding of its pharmacokinetics (absorption, distribution, metabolism, and excretion—ADME) and toxicological profile. While dithiocarbamate metal complexes have shown significant promise in preclinical studies, their clinical success hinges on favorable biocompatibility, controlled biodistribution, and minimal toxicity to healthy tissues (SwissADME, 2024).

5.1 Absorption and Bioavailability

The route of administration (oral, intravenous, or intraperitoneal) significantly affects the bioavailability of dithiocarbamate complexes. Due to their polar and often lipophilic nature, many DTC metal complexes demonstrate moderate oral bioavailability but enhanced uptake when administered parenterally.

- Lipophilicity: Increasing lipophilic substituents on the nitrogen of DTC improves membrane permeability and enhances systemic absorption.
- Nanocarrier encapsulation: Formulating DTC complexes into liposomes, micelles, or polymeric nanoparticles has been shown to increase oral and intravenous bioavailability.

5.2 Biodistribution and Targeting

The biodistribution of metal–DTC complexes depends on ligand structure and charge, metal ion identity and presence of targeting moieties.For example, ^{99}mTc-DTC complexes used in imaging tend to localize in the brain, kidneys, or tumors depending on their size and lipophilicity. Incorporating tumor-specific ligands or antibodies has improved targeting specificity, thereby reducing off-target accumulation.

Tumor Targeting:

- Exploitation of the enhanced permeability and retention (EPR) effect enables selective tumor accumulation.
- Ligand modifications with folate, RGD peptides, or antibodies further improve specificity in cancer imaging or therapy.

5.3 Metabolism and Biotransformation

Once inside the body, metal–DTC complexes may undergo ligand exchange reactions, oxidation/reduction, or biodegradation.

- Redox-active metals (e.g., Cu, Fe) may participate in Fenton-like reactions, influencing the oxidative state of the complex.
- Some complexes are designed to be prodrugs, activated in the intracellular environment by pH change or enzymatic activity.

- In vivo studies have shown that many DTC complexes are metabolically stable, with slow breakdown and minimal release of free toxic metals.

5.4 Excretion and Clearance

Excretion routes vary based on solubility:

- Hydrophilic complexes: Cleared renally through urine.
- Lipophilic complexes: Primarily eliminated via the hepatobiliary route.

Clearance rates must be optimized to ensure imaging agents are cleared rapidly post-imaging while therapeutic complexes remain long enough to exert pharmacological effects.

5.5 Toxicity and Safety Profile

While many DTC metal complexes exhibit low systemic toxicity, some safety concerns remain, especially when involving toxic metals (e.g., Gd^{3+}, As, Hg).

Reported Toxicities:

- Neurotoxicity and hepatotoxicity with certain unmodified DTCs at high doses (Wahid *et al.,* 2022).
- Nephrotoxicity with free Gd^{3+} release—necessitating strong ligand chelation.
- Generation of ROS by redox-active complexes, which can damage normal tissues if not adequately targeted.

Mitigation Strategies:

- Use of biocompatible metals (e.g., Zn, Ga, Cu) over heavy or rare earth metals.
- Incorporation of antioxidant moieties into DTC scaffolds.
- Structural modification to limit bioactivation in healthy tissues.

Toxicological Evaluation Tools:

- In vitro cytotoxicity assays using human cell lines.
- In vivo acute and sub-chronic toxicity studies in rodents.
- Computational modeling (e.g., ADMET predictors and SwissADME) to forecast bioavailability, toxicity, and blood–brain barrier permeability (Tralau-Stewar *et al*., 2022).

Understanding and controlling the pharmacokinetics and toxicological profiles of dithiocarbamate metal complexes is essential for their safe and effective application. Through ligand modification, nanotechnology integration, and rational metal selection, these properties can be optimized to meet clinical standards. Continued preclinical and toxicological evaluations are imperative to translate these promising agents into approved metallodrugs and imaging probes.

6. Current Challenges and Future Prospects

Despite the growing interest and promising preclinical outcomes, the clinical translation of dithiocarbamate metal complexes for metallotherapy and medical imaging remains limited. Several scientific, technological, and regulatory challenges need to be addressed to fully realize their biomedical potential. However, ongoing research and innovation offer numerous opportunities to overcome these limitations and advance these compounds toward clinical application.

6.1 Challenges in Therapeutic Application

i. Selectivity and Targeting

- A significant challenge lies in achieving selective toxicity toward diseased cells while sparing healthy tissues.

- Non-specific distribution can result in systemic toxicity, especially with redox-active or heavy metal complexes.

ii. Poor Aqueous Solubility:
Many DTC complexes are lipophilic, leading to limited solubility in physiological fluids, which complicates formulation and delivery.

iii. Stability in Biological Systems:
Some metal–ligand interactions may be disrupted in vivo due to ligand exchange with biomolecules (e.g., albumin, glutathione). This can lead to premature dissociation of the complex and loss of therapeutic or diagnostic efficacy.

iv. Regulatory and Safety Concerns

- The presence of metal ions raises **toxicity concerns** and requires extensive safety profiling.
- Regulatory frameworks for metallodrugs are often more stringent than those for conventional small molecules.

6.2 Challenges in Imaging Applications

i. Rapid Clearance and Low Signal Retention
Imaging agents often face rapid renal or hepatic clearance, reducing **signal intensity and imaging window**. Therefore, optimizing size, charge, and lipophilicity is necessary to prolong circulation time.

ii. Complex Radiolabeling Procedures
Radiopharmaceutical preparation, particularly with short half-life isotopes (e.g., ^{99}mTc, ^{68}Ga), demands fast and efficient chelation under mild conditions. DTC ligands require precise control over reaction conditions to ensure radiochemical purity and reproducibility.

6.3 Future Research Directions

i. Rational Ligand Design
Advancements in computational chemistry and molecular modeling can guide the design of ligands with optimized binding affinity, selectivity, and pharmacokinetics. Functionalization with targeting groups (e.g., peptides, antibodies) will improve site-specific delivery.

ii. Nanotechnology Integration
Incorporating DTC metal complexes into nanocarriers (e.g., dendrimers, liposomes, metallic nanoparticles) can enhance solubility, stability, and targeted delivery. Multifunctional nanoparticles enable combined imaging and therapy (theranostics) in a single platform.

iii. Biodegradable and Biocompatible Complexes
Designing complexes with **biodegradable ligands or metals** that mimic essential trace elements (e.g., Zn, Fe, Cu) can reduce long-term toxicity. “Soft” metallodrugs that degrade under specific biological stimuli (e.g., pH, enzymes) hold promise for **controlled drug release**.

iv. Combination Therapy and Dual-Modality Imaging
Co-delivery of metal–DTC complexes with other drugs or imaging agents can produce **synergistic effects** in cancer therapy or multimodal imaging. Dual-function agents for PET/MRI, SPECT/fluorescence, or photoacoustic/MRI imaging are under active investigation.

v. AI-Guided Discovery and ADME Profiling
The use of **artificial intelligence** and **machine learning** can accelerate the prediction of ADMET properties, optimize lead compounds, and reduce experimental burden.

6.4 Path to Clinical Translation

To translate metal–DTC complexes from bench to bedside, standardized protocols for preclinical toxicity, imaging efficacy, and pharmacokinetics are needed. Collaboration among chemists, pharmacologists, clinicians, and regulatory agencies is essential. Investment in GLP-compliant synthesis, scaling up production, and clinical trial frameworks will be key to advancing DTC complexes into approved medical use.

While significant challenges remain in the application of dithiocarbamate metal complexes in medicine, the field is poised for rapid advancement through interdisciplinary innovation. With ongoing refinement in ligand design, delivery strategies, and imaging techniques, DTC-based metallodrugs and diagnostic agents hold strong promise for the next generation of precision medicine tools.

7. Conclusion

Dithiocarbamate metal complexes represent a promising frontier in metallodrug development and diagnostic imaging. Their rich coordination chemistry, strong chelation ability, and structural flexibility enable the stabilization of various metal ions with therapeutic or diagnostic relevance. These complexes have shown compelling results in metallotherapy—particularly as anticancer, antimicrobial, and anti-inflammatory agents—due to mechanisms involving redox modulation, DNA interaction, and enzyme inhibition.

Simultaneously, the use of DTC complexes in medical imaging, especially in radiopharmaceuticals and MRI contrast agents, highlights their dual-functional potential. The modular nature of dithiocarbamate ligands allows for fine-tuning of physicochemical and biological properties, making them ideal candidates for theranostic applications.

Despite some challenges related to selectivity, toxicity, and clinical scalability, advances in ligand engineering, nanotechnology, and molecular imaging continue to expand the biomedical utility of DTC complexes. Future research efforts focused on biocompatibility, targeting precision, and regulatory compliance will be critical to translating these versatile compounds into safe and effective tools for personalized medicine.

In summary, dithiocarbamate metal complexes stand at the intersection of therapy and diagnostics, offering a platform for integrated disease management strategies. Their continued exploration is expected to contribute significantly to the evolution of metallotherapeutics and next-generation imaging agents.

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