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Antifungal Properties of Hydrazine Derivatives and Metal Complexes

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Abstract: Hydrazine derivatives and their metal complexes have attracted considerable attention from the medicinal chemists because of their wide-range biological activities including antifungal properties. These complexes contain the hydrazine (–NH–NH2) moiety with sites for functionalization and chelation with different metal ions. Owing to their structural flexibility, Many hydrazine derivatives can be easily synthesized and several proved to have potential antifungal activity such as hydrazones, thiosemicarbazones and Schiff bases. When formed with copper, cobalt, zinc, nickel and iron, these molecules have a pronounced antifungal activity. The metal complexation increases not only the stability of the ligand scaffold, but also lipophilicity and bioavailability of the compounds and, consequently, increased their potential therapeutic properties. It was recently reported that hydrazine-metal complexes exert their antifungal activity through various kind of actions such as disruption of membrane potential, inhibition on the biosynthesis of ergosterol, intercalation into DNA, and production of reactive oxygen species (ROS). These mechanisms of action are critical in defeating resistance to fungi. For instance, hydrazone ligands have been demonstrated to form complexes with Cu(II), Zn(II) or Co(II) ions that are potent against clinical strains of Candida albicans, Aspergillus niger and Fusarium oxysporum[12. In addition, comparisons of several kinds of metal complex have demonstrated the attachments of central metal ions on the antifungal efficacy. The pharmacokinetic improvements mediated by the metal-hydrazine complexes are also remarkable. Such advantages extend from better permeation through the membrane, to lower toxicity and in vivo systemic availability, to a more prolonged therapeutic effectiveness of the controlled release of the metal ion. In addition, metal-binding could shield hydrazine derivatives from rapid metabolic clearance, improving their potential clinical utility. Nevertheless, it has many attractive properties; however, the problems with such potential cytotoxicity to human cells, low water solubility, and poor in vivo and clinical efficacy. This review summarizes the synthetic method, structural parameters, antifungal mechanisms, comparative effectiveness and the pharmacokinetic properties of hydrazine-metal complexes. It also considers the problems that need to be overcome to support the clinical development of these agents. The future prospects of research are discussed, which involve study on biocompatible metal ions as new gene carriers, targeted systems for delivery, and synthesis through green chemistry approaches. Given the escalating pattern of fungal resistance to current antifungal drugs, the metal complexes of hydrazine derivatives appear to be one of the most promising sources for the development of new antifungal drugs, which may be particularly useful to fill the existing gap with the current antifungal agents.

Keywords: antifungal, drugs, promising, resistance

Introduction

Fungal diseases are emerging as a public health threat worldwide especially in immunocompromised people. Opportunistic fungal pathogens C. albicans, A. fumigatus, and C. neoformans cause high levels of morbidity and mortality in immunocompromised individuals like AIDS, cancer, or organ transplants patients. Resistance to classical antifungal drugs such as azoles and polyenes has further increased the demand for new therapeutic options displaying novel activity and increased efficacy. In such vein, hydrazine derivatives and their metal complexes have been of interest because of their wide range of biological activity, structural diversity, and encouraging antifungal profile.

Hydrazine derivatives containing the diimide (-NH-NH_2) functionality are generally known for their nucleophilic behaviour due to its unique reactivity toward a diverse content of electrophilic substrates. Such

properties make hydrazines suitable as precursors for hydrazones, Schiff bases and other heterocycles. Crucially, nitrogen atoms in hydrazine also possess unshared pairs of electrons, which render hydrazine effective as a ligand for metal complexation, with particular affinity to transition metals such as copper (Cu), cobalt (Co), nickel (Ni), and zinc (Zn). These metal ions can bind to the hydrazine core to produce stable, biologically active complexes with increased physicochemical and pharmacological characteristics.

Occasionally, the antifungal activity of hydrazine-metal complexes is much higher than that of their free ligands and this is attributed mainly to changes in lipophilicity, nature of electron distribution and the binding affinity of the complexes to biological targets. Such complexescan have various effects, including disrupting the integrity of the fungal cell wall and membrane, producing reactive oxygen species (ROS), and inhibiting essential enzymes, DNA replication, and the synthesis of proteins. In addition, the structural diversity of hydrazines enables regulating antifungal activity through different substituents or types of metal ion used in synthesis.

Antifungal activity of some hydrazine complexes with metal has been proved in recent years. Copper and cobalt complexes of isonicotinoyl hydrazones are found to exhibit good inhibitory activity towards Aspergillus niger and Candida albicans, for example. Likewise, hydrazone complexes of zinc and manganese have exhibited widespread antifungal activity whereas; fluconazole on the other hand is a known synthetic antifungal drug, implying that promising trypanocidal candidates are readily applicable to both clinical and antifungal struggles.

The objective of this review is to give an overview on the antifungal activity of hydrazine derivatives and their metal complexes. It discusses their methods of synthesis, structural characteristics, modes of action, relative effectiveness of different metal complexes, and pharmacokinetic advantages. It also describes limitations in its current status and future prospects to develop these compounds as potential antifungal agents as well in the field of modern medicinal chemistry.

Synthesis and Structure-Diversity of the Hydrazine Derivatives

Owing to their structural diversity and synthetic adaptability, hydrazine analogues are attractive intermediates in medicinal chemistry. The hydrazine radical (-NH-NH_2) is a versatile nucleophilic species and can be reacted with different aldehydes/ketones/carboxylic acids/isocyanates for efficient couplings to obtain functionalized molecules such as hydrazones, thiosemicarbazones, semicarbazides, and the corresponding Schiff bases. In return, these compounds are considered to be multidentate ligands which have high affinity for many metal ions leading to stable coordination complexes.

An example of a frequently used synthetic step is the reaction between hydrazine hydrate or substituted hydrazines with aldehydes or ketones in ethanol or methanol at reflux. This leads to the generation of C=N double bonds that are the hallmark of Schiff bases that are frequently bioactive. Substituents in the aromatic or aliphatic backbone can be modified to improve solubility, electronic distribution, and metal-binding capacity. Electron-donating or electron-withdrawing groups can have a major impact on the antifungal activity and the metal centers binding affinity.

Further versatility of hydrazine ligands is achieved due to the potential of cyclization to heterocyclic systems, including pyrazoles, triazoles, and isoxazoles—molecules well-known for their antimicrobial activity. When utilized as chelating ligands, these hydrazine derivatives frequently will coordinate via nitrogen or oxygen or sulfur atoms as mono, bis or polydentate ligands and will stabilize the metal-ligand complex by the chelate effect.

Complexes of transition metals, e.g. Cu(II), Co(II), Zn(II), Mn(II) and Ni(II) have been used most often for complexation, for the reasons that transition metals have variable oxidation states and flexible coordination geometries (such as octahedral, tetrahedral, and square planar). For example, salicylaldehydehydrazones can behave as tridenate ligands via the phenolato oxygen, azomethine nitrogen, and hydrazinicc nitrogen atoms,

yielding very stable metal chelates. These structural characteristics endow the compounds with improved physicochemical stability as well as membrane permeability and bioavailability.

In addition, bimetallic and mixed-ligand complexes have been prepared in order to take advantage of synergistic biological effects. Use of secondary ligands, such as amino acids, thiols, or phosphines with hydrazine platforms also further adjusts antifungal activity and selective targeting. These newer structures exhibit more coordinated behavior, a greater redox potential and more lipophilicity, all factors of considerable importance considering for their role in antifungal drug development.

Finally, introduction of a hydrazine derivative to molecular structures and extensive opportunity for metal complexation allow us to design different types of libraries of compounds with potential for therapeutic purposes. The synthetic accessibility, utility in different modes and favourable coordination chemistry of these ligands are the underlying reasons responsible for the rising importance of pincer complexes as antifungal agents in pharmaceutical as well as agricultural purposes.

Mechanism of Antifungal Action

Hydrazine derivatives and their metal complexes have been proven to possess antifungal activity against fungal pathogens at various molecular levels, leading to interference of the survival and proliferation of pathogenic fungi. It is observed that these modes act synergistically and they are sometimes more effective in their metal-coordinated states than in the free ligands. They are fungicidal/fungistatic depending on the ability of the compound to adhere to the type of fungal building material, such as fatty membranes, containing ergosterols or nucleic acids. The presence of the metal ion however is a key factor determining their activity, as it affects redox potential, lipophilicity, and their affinity for the fungal targets.

One major mechanism is damaging to fungal cell membrane. Hydrazine-metal chelates by virtue of their higher lipophilic features can readily cross the membranes of the fungi. Upon entry they disrupt the membrane, causing a loss of the membrane integrity and a leakage of intracellular ions and biopolymers. The breakdown of selective permeability and osmotic regulation leads to lysis and loss of viability of the cells. Investigations under electron microscope showed extensive structural damage in the cell envelope of the fungi treated with specific Cu(II) and Zn(II) hydrazone complexes.

Another prominent action is the induction of ROS. Metal ions (Cu(II) and Fe(III) in particular) can take part in the redox cycling in the fungal cell, leading to the formation of superoxide anions, hydroxyl radicals, and hydrogen peroxide. This oxidative stress induces cellular protein, lipid and DNA damage. Fungal cells frequently do not have efficient antioxidant defence systems and are therefore particularly sensitive for ROS-induced activation of apoptosis. The role of ROS in anti-fungal action was further confirmed by Ramalingam and Selvi (2021) who showed that thiosemicarbazone complexes of Ni(II) mediated oxidative damage in Candida albicans.

Metal-hydrazine complexes are also known to block fungal enzymes that play a role in wall synthesis and metabolic functions. For example, inhibition of 14-α-demethylase, an enzyme essential for the biosynthesis of ergosterol, produces a decrease in ergosterol, an essential constituent of the fungal cell membrane. Without ergosterol, the membrane is weakened and more permeable, resulting in loss of viability of the fungus. Some complexes are also capable of inhibiting the ATPase activity, which leads to energy metabolism block.

Furthermore, interaction with the carcinogenic fungal DNA is a prime mechanism as well. Some hydrazine-containing metal complexes can intercalate or groove-bind into DNA, and inhibit transcription and replication. The cytostatic effect of such turns to be accompanied by retardation of the fungal growth and may lead to cell cycle arrest or apoptosis at a higher concentration. The binding of Cu(II)-hydrazone complexes to DNA has been further supported by fluorescence quenching and gel electrophoresis studies.

Efficacies of Various Metal Complexes Compared

The antifungal ability of hydrazine related compounds is highly dependant on the metal ion coordinated with acceptors in the complex. Transition metals including Cu, Co, Zn, Ni, Mn, and Fe contribute distinctive electronic and structural features and consequently biological activities to their related complexes. Comparative investigations of these metal ions coordinated with the same or similar hydrazine ligands have indicated remarkable differences in antifungal activity, spectrum of activity and toxicity patterns.

Among metal ions, Cu 2+ is one of the most extensively researched in this respect. It is also a non-heme, iron-binding siderophore and it can increase the Fenton-type reaction to form reactive oxygen species (ROS) that are cytotoxic to mycotic cells. Patel et al. (2023) found that, the complexation with copper enhanced the antifungal efficacy of isonicotinoyl hyadrazdide against Candida albicans and Aspergillus niger in comparison to its corresponding ligands and it proved more effective than the standard antifungal drug fluconazole in some experimental conditions. Fungal membrane permeabilization and disruption, as well as the inhibition of ergosterol biosynthesis were among the most pronounced activities of the Cu(II) complexes.

Zinc(II) complexes have also shown good antifungal activity, mainly because of their excellent solubility and less cytotoxicity. Bhatia et al. (4) Zinc is redox-inactive, and does not produce ROS in the manner of copper or iron, so its mechanism of activity seems to be more due to inhibition of enzymes and to interaction with membranes. It has been considered for a therapeutic application in which the toxicity of this compound may be an issue.

Cobalt(II) and Nickel(II) complexes were also proved to be active against various fungal strains, even though their cytotoxicity must be determined accurately. These complexes may bind to the DNA and inhibit the mitochondrial function and these might be the possible mechanism through which the Co(II) complexes of salicylaldehyde hydrazones exert strong activity against C.tropicalis. Where as, Ni(II) complexes seem to promote ROS generation and inhibit the protein synthesis in fungi as narrated by Ramalingam and Selvi (2021).

Another promising class is that of iron(III) complexes, particularly those coordinated to thiosemicarbazone-based hydrazine ligands. Their high charge density and redox-catalytic properties enhance their fungicidal activity. But, their higher valency is frequently associated with lower stability in aqueous solutions due to reduced bioavailability.

In general, comparative investigations unequivocally show that the metal ion is key in determining the antifungal activity of the hydrazine complexes. The metal used not only determines the useful life and dissolution ability but also the biological mode of action. Thus, reasonable choice of the metal center is necessary for the design of novel hydrazine-metal antifungal agents.

Conclusion and Future Perspectives

The presence of drug-resistant fungal infections combined with the drawbacks of current antifungal drugs call for the urgent development of new chemical profiles displaying improved efficacies and reduced toxicities. In this vein, hydrazine derivatives and their metal complexes have demonstrated great potential in terms of structural diversity, multi-target MOAs (mechanism of actions), and improved pharmacokinetic profiles. These molecules harness the generic reactivity of the hydrazine core and the biological properties of transition metal ions to engender an enhancement in the antifungal efficacy of the complexes when used in combination.

Throughout this review, it is obvious that metal complexes terminated with hydrazine work through several antifungal mechanisms such as membrane permeabilization, ergosterol biosynthesis, induction of oxidative stress, and disruption of the DNA and enzymatic systems in fungi. These conjugates endow them with effective broad-spectrum antifungal properties also against drug-resistant fungal strains. It is also clearly evident from further comparative studies that the selection of metal ion is critical to antifungal activity. Metals such as Cu(II),

Zn(II) and Co(II) have proven to be especially successful when bound to hydrazine ligands, displaying a mixture of stability, bioactivity and low cytotoxicity.

Metal complexation raises the therapeutic applicability of hydrazine derivatives from a pharmacokinetic point of view. Higher lipophilicity, enhanced cell membrane permeability, higher metabolic stability and gradual release of metal ions are some of the advantages, which make them suitable candidates for clinical applications. Furthermore, their multi-route administration and possibility for structure modification also reflect their versatility.

But, despite all of its benefits there are still issues. One of the biggest challenges is the cytotoxicity of selected metal complexes, especially the ones containing redox-active metals such as copper or iron, which can influence non-target human cells. There are also solubility, in vivo stability, and environmental toxicity issues that should be carefully studied. In addition, most published studies are involving in vitro investigations, in-depth in vivo and clinical studies are needed to establish their therapeutic index, safety, and clinical beneficial effect.

In the next study, we plan to address these limitations by developing more selective and less toxic hydrazine-metal complexes. Tactics like the greener synthetic pathways, biocompatible/endogenous metal limiters (magnesium salt, calcium salt) or the inclusion of targeting moiety and nanocarrier system can greatly expand their utility dept-wise. The development of dual-action agents with both antifungal and antioxidant or anti-inflammatory activities could also extend their therapeutic range.

In summary, hydrazine derivatives and their metal complexes are a promising group of antifungal agents, which can also be useful as adjuvant or replacement of the current therapies. These compounds may become valuable tools to combat the worldwide problem of fungal infections and antifungal resistance, provided further interdisciplinary research and clinical validation.

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