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The State of Art in Coordination Compounds with Antifungal Activity

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ABSTRACT

Fifty five publications related to the seminal works on antifungal activity of coordination compounds were referred for the preparation of this article. Articles published in the twenty first century have been critically cited and reviewed. With a view to exploring the future prospects and root cause behind the antifungal activity, ligands, their transition metal complexes and activities against various fungi are summarized in this article. In general it is observed that the ligands, subsequent to the complexation exhibit an upsurge in antifungal activity. The review reveals that Nickel and Cobalt are the most inefficient transition metals of the first series for potential applications as antifungal agents. Copper, Zinc and Manganese complexes with ligands containing Sulphur atom(s) are the most promising moieties for studying biological activity of coordination compounds world-wide.

Keywords: antifungal activity; Schiff base; thiosemicarbazide; dithiocarbamate; sulphonamide.

INTRODUCTION

Research in coordination chemistry accounts for almost 75% of research in inorganic chemistry. The coordination compounds with metal atom at the center are recognized as metal complex. The theories behind the structure and bonding in these compounds were explained by Alfred Werner for which he was awarded Nobel Prize in 1913. Metal complexes have myriad applications which are accepted all over the world[1-6]. They are reported to have applications in chemical analysis, organic synthesis, biology of many living organisms, enzyme catalysis, dyes and pigments, synthesis of organometallic compounds and other countless applications. A wide variety of ligands have been used in combination with a handful

metal ions to produce numerous complexes with varied physicochemical properties for niche applications. The condensation reaction of primary amines with aldehyde and ketones yields compound with a azomethine functional group which consists of a carbon-nitrogen double bond with the nitrogen connected to an alkyl group which is generally termed as Schiff bases, since their synthesis reported by Hugo Schiff[7]. The presence of a lone pair of electron in sp^2 hybridized orbital of nitrogen atom of azomethine group is of considerable chemical importance[8,9]. This lone pair imparts an admirable coordinating property when taken in consideration with two or more than two donor atoms besides the azomethine group. Hence, Schiff bases are capable of forming chelates with the help of azomethine group and the electron donating groups besides the azomethine group present in the ligand[10,11]. This linkage also imparts a remarkable antibacterial, antifungal, anticancer and diuretic activities[12]. Coordination compounds have an important place for bridging ligands. Due to the characteristic of connecting two metal centers or two different atoms of a polynuclear complex. These polynuclear complexes tends to possess different yet, quite engrossing properties which have led the researchers to revisit the characteristic properties developing due to involvement of such bridging ligands in the metal complexes which tends to enhance the physiochemical properties as well as the biological properties of the metal complexes. The denticity of a ligand is commonly used to describe its bonding with the metals and other atoms to which it binds[13]. For example, a fused pyrazine has two donor atoms but each donor atom can bridge only one metal center[14]. Ligands such as 1,10-phenanthroline and 2,2′ bipyridine are bidentate bridging ligands[15]. Metal organic ligands can be described as the metal complexes in which ligand binds with one metal and in which ligand has another coordination site free which can useful in binding with another metal. Different complexes having one or more metal centers are able to react further with other complexes through one or more donor atoms and have gained much success[16]. These types of complex precursors considered as ligand named as metal organic ligands (MOLs)[17, 18]. The well recognized approach 'metal complexes as ligands' involving multi-nucleating ligands offers many potential advantages over the self-assembly route and it enables greater control over the route of the reaction and the products[19].

Several metal complexes and chelates have been prepared by coordination chemists with a view to improving the antifungal activity of organic ligands / metal salts. It is a usual practice to prepare a potential ligand which upon complexation with different metals exhibit improved biological activity. A well accepted Overtone's concept of cell permeability suggests that the lipophilicity plays a vital role as the lipid membrane that surrounds the cell prefers only lipid soluble compounds, on account of which, lipo-solubility is an important factor which administers the antifungal activity of the compound. Simultaneously, Tweedy's Chelation theory suggests that, on chelation the polarity of the metal atom gets reduced over a greater extent as the overlapping of ligand orbital and partial sharing of the positive charge of the metal atom occurs simultaneously which on other hand, enhances the π- electrons delocalization over the chelate ring which improvises the lipophilic character of the metal complex. Moreover, this enhanced lipophilicity increases the penetration of the metal complex

into the cell membrane which blocks the fungi to enter the cell membrane, also, it blocks the respiration process of the cell which inhibits the synthesis of protein, resulting the death of the micro-organism.

From amongst the metal ions of the first transition series, Copper (II), Zinc (II) and Manganese (II) ions have remained the most favorites for researchers preparing complexes with antifungal properties. While Nickel (II), Cobalt (II) and others have not shown promising activity against fungi. Subsequent to the establishment of superior biological activity of Copper (II), Zinc (II) and Manganese (II) complexes, the attention of the researchers has narrowed down to these complexes only. Similarly, after exploring a galaxy of ligands, the researchers are now concentrating their attention on ligands containing Sulphur. Thus, most potential antifungal complexes are now undoubtedly the ones containing the above-mentioned metals and Sulphur containing ligands. In continuation of our interest in coordination chemistry[20-27], in this article we report a review of state of art in the field of application of metal complexes as antifungal agents.

ANTIFUNGAL ACTIVITY OF SCHIFF BASES AND THEIR METAL COMPLEXES

Thiosemicarbazides and Thiosemicarbazones

Metal complexes consisting of Sulphur element have showed a remarkable antifungal activity[28-30]. Some Cu (II), Ni (II), Co (II), Mn (II), Fe (II) and Cr (III) complexes of N4-(&-Chloroquinoline) were synthesized and subjected to antifungal studies. The ligand has been obtained by the reaction of thiosemicarbazide with 2-hydroxy benzaldehyde[28]. Further, the ligand has been coordinated with the metal through thione sulfur, azomethine nitrogen and phenolic oxygen to form mononuclear complexes in which thiosemicarbazone behaved as a monobasic tridendate ligand. The ligand and its metal complexes have been further analyzed for their antifungal activity against fungal species such as *Candida Albicanns* and *fusarium solani*. The metal ligands which have consisted sulfur and nitrogen atoms have showed an enhanced antifungal activity against the species as when compared to the parent Schiff base molecule[28]. Some semicarbazidates and thiosemicarbazidates have been synthesized from the reaction of some salicylaldehydes with respective semicarbazide, thiosemicarbazide and S-methyl thiosemicarbazide tridentate ligands consisting of ONS donor group atoms[31]. These ligands have been further coordinated with metals such as Co (II), Co (III), Cu (II), Ni (II), Mn (II), Zn (II) and Fe (III) to form their metal complexes. Antifungal activity of selected metal complexes has been investigated for in vitro analysis on laboratory stems. These compounds were screened against fungal species such as *Aspergillus niger, Aspergillus fumigatusi, Candida albicans* and *Penicillium.* The result showed that the selected metal complexes screened were active towards the fungi stem in the concentration range of 18.7-300µg/m^2 [31]. Nistatine (an antifungal agent used in the medicine for mycose treatment) was taken as standard. Selected synthesized complexes exhibited antimycotic activity of 1.1- 6.4 times higher towards the fungi as compared to Nistatine. Also, the data showed that the copper salts exhibits higher antifungal activity[31]. Hence, these metal complexes of copper were proved

to have enhanced antifungal activity as compared to other metal complexes and Schiff base ligands. Thiosemicarbazide complexes consists of wide range of entities with a remarkable antifungal activity. Some thiosemicarbazide derivatives of pyrrolidone have been derived to study their antifungal activity[32]. Metal complexes of (z)-2-(pyrrolidine-2-ylidene) hydrazine carbothioamide (L) with Cu (II), Co (II) and Ni (II) chlorides have been screened against selected types of fungi, which were found to possess significant antifungal activities. The antifungal activity has been studied against the fungal species such as *Aspergillus Niger* and *Candida Albicans.* The result data have showed that the ligand does not possess any antifungal activity whereas, all the metal ligand complexes have exhibited good activities[32]. To conclude with, Cu (II) complexes have much enhanced antifungal activity as compared to Ni (II) and Co (II) complexes. Organometallic based 1,1'-diacetylferrocene derived antifungal thiocarbohydrazone, thiosemicarbazone and semicarbazone have been synthesized by the condensation reaction. The synthesized compounds were used as ligands and further coordinated with Co (II), Zn (II), Cu (II) and Ni (II) to form respective metal complexes. These compounds have been studied and screened for the antifungal activity against fungi species such as *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani* and *Candida glaberata*. The results showed that the antifungal activity of the synthesized compounds enhanced on further complexation with their respective metals[33].

Aminoantipyrine

Some complexes of derivatives of 4-aminoantipyrine have also been synthesized[34]. The ligand (4-aminoantipyrine and its derivatives) was then coordinated with metals such as Cu (II) and Ni (II) for their antifungal studies. The ligand and metal complexes have been screened against fungal species such as *Phoma Sorghina, Aspergillus Niger* and *Fusarium oxysporum.* Bavistin was used as a standard drug[35]. Amongst all the screened samples of Cu (II) and Ni (II) metal complexes, $Cu(L)SO_4$ showed an enhanced and significant antifungal activity at quite low concentration and can be considered as antifungal compound. Whereas, the ligands and [Ni(L)Cl]Cl metal complex showed the least antifungal activity, while the rest metal complexes exhibited moderate antifungal activity against all the fungal strains[35]. This enhanced antifungal activity of the Schiff base ligand has been due to the co-ordination with metal ions. This can be reasoned with the help of overtone's concept and Tweedy's chelation theory.

Cephalexin

Some novel cephalexin derived furanyl, thiophenyl, pyrrolyl, salicylyl and pyridyl Schiff bases and their Co (II), Cu (II), Ni (II) and Zn (II) complexes have been synthesized and studied for their antifungal activity[36]. The antifungal activity of metal complexes have been studied against fungi species such as *Trichophyton longifusus, Candida Albicans, Aspergillus Flavus, Microsporum canis, Fusarium Solani* and *Candida Glaberata*[36]. The new derivatives of drug (cephalexin) as ligands have exhibited an enhancement in its antifungal

activities as compared to the parent un-complexed Cephalexin sodium. Moreover, the complexation of the drug ligands with metals have also enhanced the antifungal activity.

Sulfonamides

A series of novel Schiff base have been derived from sulfonamide as well as their transition metal complexes of Co (II), Cu (II), Ni (II) and Zn (II) have been synthesized and studied for their antifungal activity. These novel Schiff bases derived sulfonamides and their metal complexes have been assayed for antifungal activity against *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani, Candida glaberata.* Miconazole and amphotericin B were taken as standard drug for the comparison of inhibition results. The result data showed that all the non-coordinated compounds i.e. ligands have moderate to enhanced antifungal activity. Moreover, the complexation of ligands with metals have enhanced their antifungal activity as compared to non-coordinated compounds[37]. Similarly, Antifungal activity of some new series of compounds derived from N-substituted sulfonamides with 4-hydroxy coumarin has been studied. These compounds which have been considered as ligands have been synthesized by the condensation reaction of 4-hydroxy coumarin with various sulfonamides such as sulfanilamide, sulfaguanidine, p-aminomethyl sulfanilamide, sulfathiazole, sulfamethoxazole, sulfamethazine and 4-[(2-amino-4-pyrimidinyl) amino] benzene sulfonamide) in presence of excess ethylorthoformate[38]. Antifungal activity of all the compounds have been screened against six fungal cultures which were *T. longifusus, C. albicans, A. flavus, M. canis, F. solani* and *C. glaberata.* The standard drug has been considered were amphotericin B and Miconazole. The results have arrayed that most of the synthesized metal complexes have been inactive against all the fungal cultures, although, few of them have exhibited significant activity against *M. canis* and against *F. solani.* Apart from these, the rest compounds have exhibited low to moderate activity against at least one of the fungal stain excluding *M. canis.* Likewise, a novel series of some furanyl derived sulfonamides have been obtained and further their Co (II), Cu (II), Ni (II) and Zn (II) metal complexes have been synthesized and studied for in-vitro antifungal activity screened against *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani* and *Candida glaberata*. Miconazole and amphotericin B were taken as standard drug. The results have indicated that all the metal complexes exhibited good to moderate antifungal activity against two or more fungal strains. The Zn (II) metal complexes have exhibited more remarkable activity as compared to other metal complexes[39]. Additionally, a series of sulfonamides (sulfanilamide, sulfaguanidine, sulfamethaxozole, 4-aminoethylbenzene sulfonamide, and 4-amino-6-trifluoro methyl-benzene-1,3-disulfonamide) derived chromones have been assayed for in-vitro antifungal activity against *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani* and *Candida glaberata*[40]. Out of which, only one compound has exhibited a significant antifungal activity against *T. longifusus, C. albican, M. canis, F. solani* and *A. flavus.* Rest of the compounds exhibited moderate to significant activity. Although, these Schiff base ligands can achieve an enhanced antifungal activity when coordinated with metals to form their respective

metal complexes. Some Schiff base ligands derived from benzenesulfonamides such as 4-[(4-hydroxy-3-methoxybenzylidene)amino]benzenesulfonamide (L_1), 4-{2-[(4-hydroxy-3-methoxybenzylidene)amino]ethyl}benzenesulfonamide (L_2), 4-[2-hydroxybenylidene amino] benzenesulfonamide (L_3), 4-{[(2-hydroxybenzylidene)amino]methyl}benzenesulfonamide (L_4), 4-{2-[(2-hydroxybenzylidene)amino]ethyl}benzene sulfonamide (L_5) were reported. Over and above, their metal complexes with Co (II), Cu (II), Ni (II) and Zn (II) have been synthesized for their antifungal study against six fungal cultures such as *T. longifusus, C. albicans, M. canis, F. solani* and *C. glaberata.* The inhibition results of these synthesized metal complexes have been compared to the standard drug miconazole and amphotericin B. The Schiff base ligands derived from the benzenesulfonamides derivatives have exhibited an enhanced antifungal activity when chelated with the metals to derive as metal complexes. Hence, all the metal complexes have portrayed a remarkable antifungal activity[41]. Seven new indolenyl sulfonamides have been synthesized by the condensation reaction of indole-3-carboxaldehyde with different sulfonamides such as sulphanilamide, sulfaguanidine, sulfathiazole, sulfamethazine, sulfamethoxazole, sulfisoxazole and sulfadiazine. Further, their metal complexes of Co (II), Cu (II), Ni (II) and Zn (II) were synthesized. All these compounds were studied and evaluated for their antifungal activity against six fungal strains such as *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani* and *Candida glaberata.* The inhibition results of these compounds have been compared with the standard drug Miconazole and amphotericin B. Reported compounds exhibited a good range of antifungal activity against all the fungal strains[42].

Sulpirides

Sulpiride- a substituted benzamide antipsychotic drug, have been used as a ligand. Metal complexes of this substituted benzamide have been synthesized and studied for its potentiality towards in-vitro systems. Antifungal activity of these synthesized compounds has been assayed against two fungal strains- *Aspergillus flavus* and *Candida albicans.* The inhibition results were compared to the standard drug amphotericin B. It was found that the metal complexes exhibited a significant antifungal activity as compared to the parent drug molecule but less activity compared to the standard drug[43].

Thiocarbazates and Thiocarbamates

Schiff base ligand have been synthesized by the reaction of 4-acetylbiphenyl and S-benzyldithiocarbazate. Next it was coordinated with metals to give complexes having general formula $[M(AB)_2]$. Metals used for the complexation were Cu (II), Zn (II), Ni (II) and Co (II). The antifungal activity has been studied against *Phytophthira capsica*. The results indicated that the Cu (II) complex possess antifungal activity in the range of concentration (2000-200 ppm) and above 1000 ppm it showed remarkable activity. It inhibits the growth of fungus at 2000 ppm for at least 5 days. Also, the other compounds synthesized showed that the free ligand and the Zn (II) complexes have much lesser antifungal activity as compared to Cu (II) complex, whereas, Co (II) and Ni (II) complex have found to be inactive against fungi[44]. Some

novel complexes with general formula [M(NNS)X] have been obtained. The NNS tridentate Schiff base ligand were obtained by the reaction of S-methyl di-thiocarbazate with 2-aminoaldehyde[45]. Transition metals such as Ni (II), Cu (II), Pd (II) or Pt (II) have been taken where, X= Cl, Br, I, NCS, NO_3 and AcO. The metal complexes have been further assayed for its antifungal study. The Schiff base and metal complexes have been screened against fungal species such as *Alternaria alternate, Curvularia geniculata* and *fusarium moniliform.* The antifungal results have indicated that the Ni (II) complexes have less activity due to chelation[45]. Moreover, the chelation with Cu (II) metal have enhanced the antifungal activity.

Dithiocarbamates have been versatile ligands capable of forming complexes with most of the elements and adjusting to the variety of oxidation states of the transition metal elements[46-48]. Some Mn (II), Au (II) and Ru (II) complexes of dithiocarbamates have been synthesized. The Mn (II) complex were synthesized with 2-hydroxy-3-methyl pyridine and a Sulphur donor ligand; dithiocarbamate sodium salt, whereas, the Au (II) complex have been synthesized with 2-amino-3-hydroxy pyridine and dithiocarbamate. Ru (II) complexes were also prepared in a similar fashion. The antifungal activity of these compounds were examined against pathogenic fungal strains such as *Candida albican, Aspergillus flavus* and *Aspergillus niger.* Ketocanazole was kept as reference drug for the respective analysis.

Table 1 Micro Dilution Activity of Some Complexes against Selected Fungal Strains

Complex	***Candida Albicans***	***Aspergillus flavus***	***Aspergillus niger***
AHPDTC	223	218	180
$Au(AHPDTC)_2$	250	206	271
$Mn(AHPDTC)_2$	226	274	200
$Ru(AHPDTC)_2$	228	296	297

From the results shown in **Error! Reference source not found.**, it has been interpreted that, all the metal complexes showed an enhanced invitro antifungal activity as compared to the free ligand. The reason been explained is related to the presence of dithiocarbamate group in the complex which enhances the antifungal activity as the positive charge over the metal atom is being shared by the ligand itself.

Miscellaneous

Some furanyl-methyl and thienyl-methyl derivatives of dithiolene were coordinated with Co (II), Cu (II), Ni (II) and Zn (II) complexes and screened for their invitro antifungal analysis against *Trichophyton longifusus, Candida albicans, Aspergillus flavus, Microsporum canis, Fusarium solani* and *Candida glaberata.* The results were evaluated as % of inhibition of growth as compared with standard drugs miconazole and amphotericin B. The results have indicated that all the ligands exhibit an antifungal activity which further enhances upon complexation. The compounds which have showed weak or moderate antifungal activity have also showed an enhancement when complexed with metals. Thus, complexation plays an important role. Although, the antifungal activity of these synthesized compounds and complexes have been less as compared to the standard drugs[49]. A series of Mn (II) and Cu (II) complexes with reduced Schiff base as a ligand derived from o-phenylendiamine have been

synthesized[50-53]. The complexes of $[MnL(H_2O)_n]$ and $[CuL(H_2O)_n]$ were screened for their antifungal properties against different human fungi including yeasts of *Candida Genus (C. albicans, C.glabrata, C.tropicalis* and *C. parapsilopsis),* some molds belonging to *Aspergillus (A. Fungigatus, A. terreus, A. Flavus), Scedosporium genus (S. apiospermum* and *S. prolificans)* and some dermatophyes (*M.gypseum, M.periscolon, T. mentagrophytes, M.canis and T. tonsurans)*[54]. The Mn (II) complexes have exhibited significant growth inhibition of the dermatophytes which were tested and fungi of the genus *Scedosporium.* All the fungal strains used have been poorly susceptible to the antifungal drug Amphotericin B and Itraconazole which have been used as a standard drug. The copper complexes exhibited inefficient antifungal activity. The corresponding ligand also did not show remarkable activity[54]. The complexation with Mn (II) enhanced the antifungal activity. Moreover, the Mn (II) metal complex have showed a substantial activity against yeasts and *Aspergillus spp.* A Schiff base ligand has been synthesized by the condensation reaction of 2-mercaptobenzimidiazole and diethyloxalate. This ligand when reacted with bis(ethylene-diamine) Cu (II)/Ni (II) complexes yielded $[C_{20}H_{22}N_8S_2Cu]Cl_2$ and $[C_{20}H_{22}N_8S_2Ni]Cl_2$ complexes[55]. Antifungal activity of the $[C_7H_6N_2S]$, $[C_4H_{16}N_4Cu]Cl_2$, $[C_{16}H_{10}N_4S_2O_2]$ and $[C_{20}H_{22}N_8S_2Cu]Cl_2$ were screened against fungal strain of *Aspergillus Niger*. It has been reported that the copper complexes possessed higher antifungal activity as compared to the Nickel complexes.

SUMMARY

After the above mentioned rigorous survey, it becomes evident that Cu (II), Mn (II) and Zn (II) are the most preferred metals for studying the antifungal activity of metal complexes. In addition to these, we have also observed that if the metal has been selected with proper diligence, it is very likely that the complexation enhances the activity of the ligands. Presence of Sulphur in the ligand system is undoubtedly an important reason behind the excellent antifungal activity of certain moieties. However, it will be interesting in coming times to explore the structure activity relationship in this small group of complexes to be potentially used as antifungal agents.

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