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## Synthesis of Copper(II) and Manganese(II) complexes using 2-hydroxybenzyl-(pyridine-2-carbo) iminothiazone and 2-Furyl (pyridine-2-carbo) Iminothiazone: Evaluation of their antimicrobial properties

Dr. Sharad Kumar Jha

### Abstract

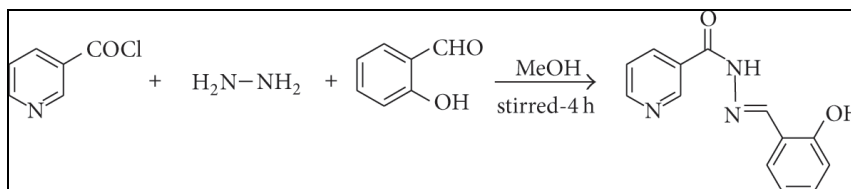
Three new coordination complexes [Cu(HPBH)<sub>2</sub>]Cl<sub>2</sub> (1), [Cu(FPFH)<sub>2</sub>]Cl<sub>2</sub> (2) and [Mn(HPBH)<sub>2</sub>] Cl<sub>2</sub> (3) (where HPBH=2- Hydroxybenzyl (pyridine-2-carbo) iminothiazone, and FPFH=2-furyl(pyridine-2-carbo) iminothiazone) have been synthesized using two different tridentate thiazones ligand. The ligands were prepared by condensation of Pyridine-2-acetylchloride, 2-Hydroxybenzaldehyde and Furan-2-carbaldehyde with hydrazine, respectively, in spite of varying the carbonyl functionality attached to the pyridine moiety present in the thiazones ligand. In both the Schiff bases, we obtained three mononuclear complexes 1, 2 and 3 which were clearly characterized from physicochemical studies. Antimicrobial studies have been performed for these compounds with different antimicrobial species.

**Keywords:** copper, manganese, pyridine-2-carbo, antimicrobial

### 1. Introduction

Thiazones are important class of ligands with interesting ligation properties due to the presence of several coordination sites <sup>[1]</sup> and are widely applied in the yield of insecticides, medicines, and analytical reagents due to their excellent bioactivity <sup>[2]</sup>. Various important properties of carbonic acid thiazides along with their applications in medicine and analytical chemistry have led to increased interest in their complexation characteristics with transition metal ions <sup>[3]</sup>. In this respect, the formation of metal complexes plays an important role to enhance their biological activity <sup>[4]</sup>. Studies have also shown that the azomethine nitrogen which has a lone pair of electrons in an sp<sup>2</sup> hybridised orbital has considerable biological importance. Thiazone derivatives are found to possess antimicrobial, antitubercular, anticonvulsant, and anti-inflammatory activities <sup>[5-11]</sup>. The problem of resistance to antimicrobial activity is being addressed by medicinal chemists, and various strategies have been devised and attempted in order to enhance the activity of drugs <sup>[12]</sup>. It has been demonstrated that transition elements play a very important role in various medicinal compounds. Coordination chemistry of manganese has been studied extensively <sup>[13, 14]</sup> due to its occurrence in the active site of several enzymes involved in the chemistry of reactive oxygen species <sup>[15]</sup>. EXAFS studies for the oxygen-evolving complex (OEC) <sup>[16]</sup> and crystal structure of the manganese peroxidase (isolated from *Phanerochaete chrysosporium*) <sup>[17]</sup> show that manganese center is surrounded by O- or N Donor ligands. Manganese complexes having tetradentate ONNO donor ligands are found to be artificial mimics of some of these enzymes. In addition, they also act as catalysts for important reactions <sup>[18]</sup>. In this paper we synthesized copper(II) and manganese(II) complexes with different pyridine thiazones ligand. The ligand and its metal complexes showed antibacterial activity against *S. aureus* ATCC 29253, *S. aureus* ATCC 3160, bacteria and antifungal activity towards the fungi *Candida albicans* (227) and *Staphylococcus cerevisiae*.

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**Scheme 1:** Route for the synthesis of the 2-Hydroxybenzyl-(pyridine-2-carbo)-iminothiohydrazone

**Table 1:** Synthesis of the 2-Hydroxybenzyl-(pyridine-2-carbo)-iminothiohydrazone and 2-furyl-(pyridine-2-carbo)-iminothiohydrazone Ligand

S. no.	Substrate (1)	Substrate (2 + 3)	Product	Time (hrs.)	Yield (%)
(1)		$\text{H}_2\text{N}-\text{NH}_2$ +		12	52
(2)		$\text{H}_2\text{N}-\text{NH}_2$ +		3	60

## 2. Experimental

All the chemicals used in the present investigation were of the analytical reagent grade (AR). Pyridine-2-acetylchloride, Furan-2-carbaldehyde, 2-Hydroxybenzaldehyde (Fisher Scientific), Hydrazine (Chemical Drug House, India), all metal salts and solvents (Qualigens Fine Chemicals, India) were purchased and used as received. The elemental analysis (C, H, N) was done at the Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of the samples were measured in  $\text{DMSO}-d_6$  at IIT Delhi, India. The IR spectra were recorded as KBr pellets using a Perkin-Elmer 783 spectrophotometer in the range 4000-400. UV/vis spectra of the complexes were recorded on a Shimadzu UV-1601 spectrophotometer. The EPR spectra of the complexes were recorded as polycrystalline sample on a Varian E-4 EPR Spectrometer.

### 2.1 Synthesis of ligand

#### 2.1.1 Ligand 1

In a round bottom flask (100 mL), a methanolic solution (10.0 mL) of Pyridine-2-acetyl chloride (0.001mmol, 0.141 mL) in an aqueous methanolic solution (10mL) of hydrazine (0.001mmol, 0.154g) and 2-Hydroxybenzaldehyde (0.001mmol, 0.102 mL) in methanol (5 mL) were taken and continued stir to at room temperature ~4 h. A yellowish crystalline solid was obtained as shown as Scheme 1. After the completion of this reaction, the product was monitored by thin layer chromatography and was taken in methanol and washed with hot water ( $3 \times 20$  mL) and then with brine

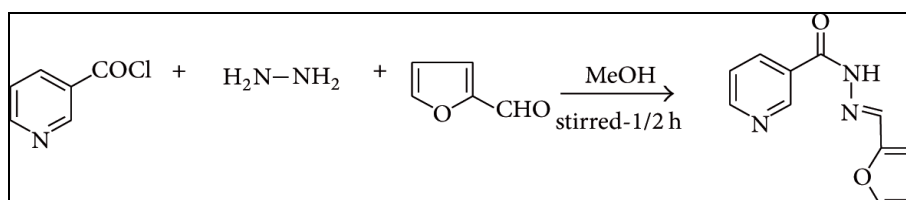
solution ( $3 \times 20$  mL), and then the solvent under reduced pressure to afford the product (Table 1).

#### 2.1.2 Ligand 2

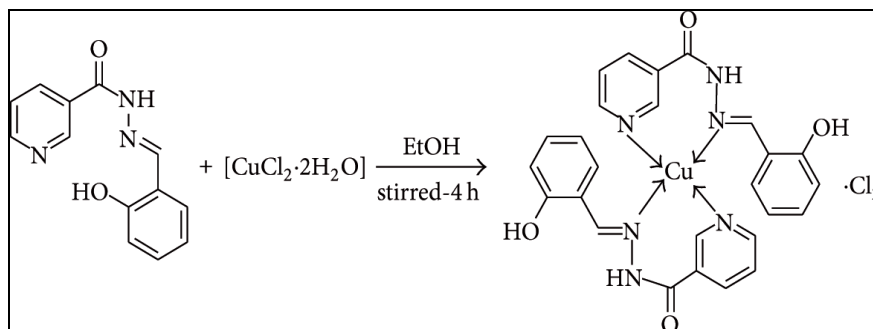
In a round bottom flask (100 mL), 0.001 mmol Pyridine-2-acetyl chloride (0.141 mL), in an aqueous methanolic solution (10 mL) of hydrazine (1.7 mmol, 0.154 g) and 0.001 mmol 2-Furanecarboxaldehyde (0.960 g) in water (5 mL) were taken and continued to stir at room temperature 1/2 h and then reflux the reaction mixture about 2 h. After the completion of this reaction, the reaction mixture was monitored by thin layer chromatography. Then, the reaction mixture was taken in methanol and washed with hot water ( $3 \times 20$  mL) (thrice) and then with brine solution ( $3 \times 20$  mL) (thrice), and then the solvent under reduced pressure was evaporated to afford the product; orange crystalline powder was obtained (Scheme 2) (Table 1).

#### 2.1.3 Analytical data of the ligand HPBH and FPFH

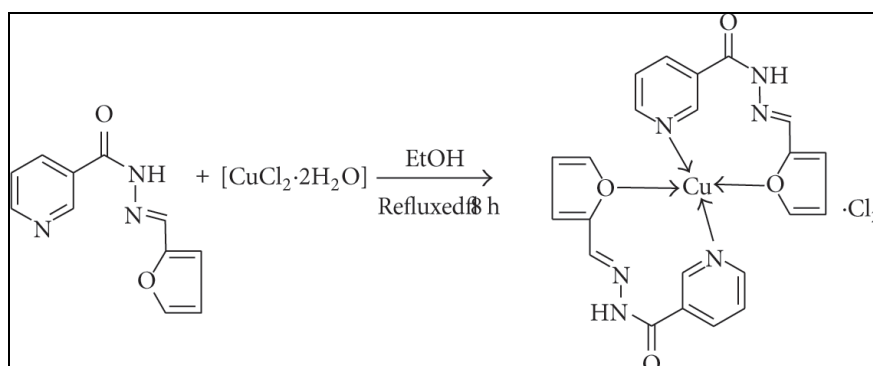
Ligand ( $\text{C}_{13}\text{H}_{10}\text{N}_3\text{O}_2$ ): Yield: 52%; M.P. 230 °C, Mol. wt. 241, color: yellowish; analytical data for HPBH found (calc.): C, 63.73 (63.11); H, 4.56 (4.21); N, 17.42 (16.97). IR (KBr,  $\text{cm}^{-1}$ ): 3216  $\nu_{\text{NH}}$ , 1690  $\nu_{\text{C=O}}$ , 1640  $\nu_{\text{C=N}}$ , 3415  $\nu_{\text{OH}}$ , 2228  $\nu_{\text{C-N}}$ . ESIMS, m/z Data found (calc.): 241 (240),  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  ppm: 1.601 (s, 1H, OH-Ar), 7.158–7.953 (m, 8H, Ar), 8.92 (s, 1H, CH=N).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  ppm: 117.53–121.07 (11C, CH-Ar.), 153.88 (1C, C=O), 164.95 (1C, CH=N).



**Scheme 2:** Route for the synthesis of the 2-furyl-(pyridine-2-carbo)-iminothiohydrazone Ligand



Scheme 3: Route for the synthesis of the copper complex



Scheme 4: Route for the synthesis of the copper complex

Ligand ( $C_{11}H_{10}N_3O_4$ ): Yield: 60%; M.P. 255 °C, Mol. wt. 216, color: Orange; analytical data for PPFH found (calc.): C, 61.11 (60.185); H, 4.62 (4.21); N, 19.44 (18.88). IR (KBr,  $cm^{-1}$ ): 3440  $\nu_{NH}$ , 1700  $\nu_{C=O}$ , 1640  $\nu_{C=N}$ , 1015  $\nu_{C-O}$ , 2228  $\nu_{C-N}$ . ESI-MS,  $m/z$  Data found (calc.): 216 (215),  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 7.158-7.953 (m, 8H, Ar), 8.92 (s, 1H, CH=N).  $^{13}C$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 117.53-121.07 (9C, CH-Ar.), 153.88 (1C, C=O), 164.95 (1C, CH=N).

## 2.2 Synthesis of metal complexes

### 2.2.1 Complex 1

A quantity of (0.002 mmol, 0.282 g) of 2-Hydroxybenzyl (pyridine-2-carbo) imino-hydrazone ligand was dissolved in 100 mL methanol and a solution of copper chloride (0.001 mmol, 0.170 g) in 25 mL methanol was added drop wise with continuous stirring; dark bluish product appeared after one night standing. The mixture was stirred for 4 h at 35 °C. The resulting precipitates were filtered and washed with acetone and dried over anhydrous calcium chloride in a vacuum desiccator (Scheme 3).

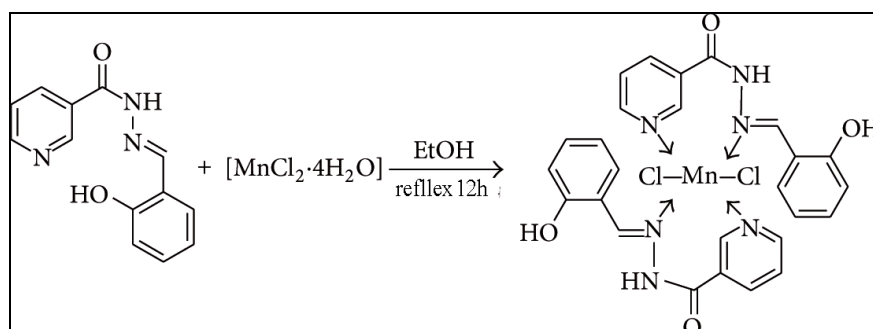
### 2.2.2 Complex 2

A hot ~70 aqueous ethanolic solution (20 mL, 1: 1 v/v) of

the copper chloride metal salt (0.001 mmol, 0.170 g) and a hot ethanolic solution (20 mL) of the 2-furyl (pyridine-2-carbo) imino-hydrazone (0.001 mmol, 0.216 g) were mixed in the molar ratio (1: 2). The mixture was refluxed for about 8 h at a temperature of ~78 °C. On cooling the contents to a temperature ~5 °C the compounds were separated. After this the compound was taken in hot methanol and washed with hot water, and then the solvent under reduced pressure was evaporated to afford the product; bluish solid was obtained (Scheme 4).

### 2.2.3 Complex 3

An ethanolic solution of 2-Hydroxybenzyl (pyridine-2-carbo) imino-hydrazone ligand (0.282 g, 0.002 m mol) was added drop wise to a 0.001 m mol solution of manganese chloride (0.197 g) in methanol solution with continuous refluxed at 55 °C for 12 h. One night standing, the reaction mixture was monitored by thin layer chromatography. The organic layers were collected; then crude products were taken in hot methanol and washed with water was evaporated and then the solvent under reduced pressure to afford the product; a dirty brownish solid was obtained (Scheme 5).



Scheme 5: Route for the synthesis of the manganese complex

## 2.3 Analytical data of the metal complexes 1, 2 and 3

### 2.3.1 Complex 1

Yield: 26%; MP: 256 °C; Mol. wt. 722; color: bluish; analytical data for  $[\text{CuC}_{26}\text{H}_{20}\text{N}_6\text{O}_4]\text{Cl}_2$  found (calc.): C, 43.21 (42.15); H, 2.77 (2.11); N, 11.63 (11.17); IR (KBr,  $\text{cm}^{-1}$ ): 3216  $\nu_{\text{NH}}$ , 1700  $\nu_{\text{C=O}}$ , 1602  $\nu_{\text{C=N}}$ , 3415  $\nu_{\text{OH}}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 1.601 (s, 1H, OH-Ar), 7.158-7.953 (m, 8H, Ar), 8.92 (s, 1H, CH=N).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 117.53-121.07 (11C, CH-Ar.), 153.65 (1C, C=O), 164.85 (1C, CH=N).

### 2.3.2 Complex 2

Yield: 25%; MP: 268 °C; Mol. wt. 672; color: bluish; analytical data for  $[\text{CoC}_{22}\text{H}_{20}\text{N}_6\text{O}_4]\text{Cl}_2$  found (calc.): C, 36.40 (35.15); H, 2.52 (2.11); N, 14.15 (13.17); IR (KBr,  $\text{cm}^{-1}$ ): 3440  $\nu_{\text{NH}}$ , 1700  $\nu_{\text{C=O}}$ , 1608  $\nu_{\text{C=N}}$ , 1015  $\nu_{\text{C-O}}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 7.158-7.953 (m, 8H, Ar), 8.92 (s, 1H, CH=N).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 117.53-121.07 (9C, CH-Ar.), 153.88 (1C, C=O), 164.95 (1C, CH=N).

### 2.3.3 Complex 3

Yield: 47%; MP: 276 °C; Mol. wt. 749; color: dirty brownish; analytical data for  $[\text{MnC}_{26}\text{H}_{20}\text{N}_6\text{O}_4]\text{Cl}_2$  found (calc.): C, 41.65 (40.68); H, 2.67 (2.11); N, 11.21 (11.17); IR (KBr,  $\text{cm}^{-1}$ ): 3216  $\nu_{\text{NH}}$ , 1700  $\nu_{\text{C=O}}$ , 1602  $\nu_{\text{C=N}}$ , 3415  $\nu_{\text{OH}}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 1.601 (s, 1H, OHAr), 7.158-7.953 (m, 8H, Ar), 8.92 (s, 1H, CH=N).  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  ppm: 117.53-121.07 (11C, CH-Ar.), 153.65 (1C, C=O), 164.85 (1C, CH=N).

## 3. Microbiology properties

*In vitro* antibacterial activity studies were carried out by using the standardized disc-agar diffusion method [19, 20, 21] to investigate the inhibitory effect of the synthesized ligands and complexes against *S. aureus* ATCC 29253, *S. aureus* ATCC 3160 antibacterial, and *S. cerevisiae* MTCC 316, *Candida albicans* (227) as a kind of fungi. For the antibacterial and antifungal assays, the compounds were dissolved in dimethylformamide. Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 500 and 1000 ppm concentrations with dextrose broth. The minimum inhibitory concentrations (MICs) were determined using the twofold serial dilution technique. A control test was also performed containing inoculated broth supplemented at the same dilutions used in our experiments and found inactive in the culture medium. Gentamycin and Amphotericin B were used as control drugs.

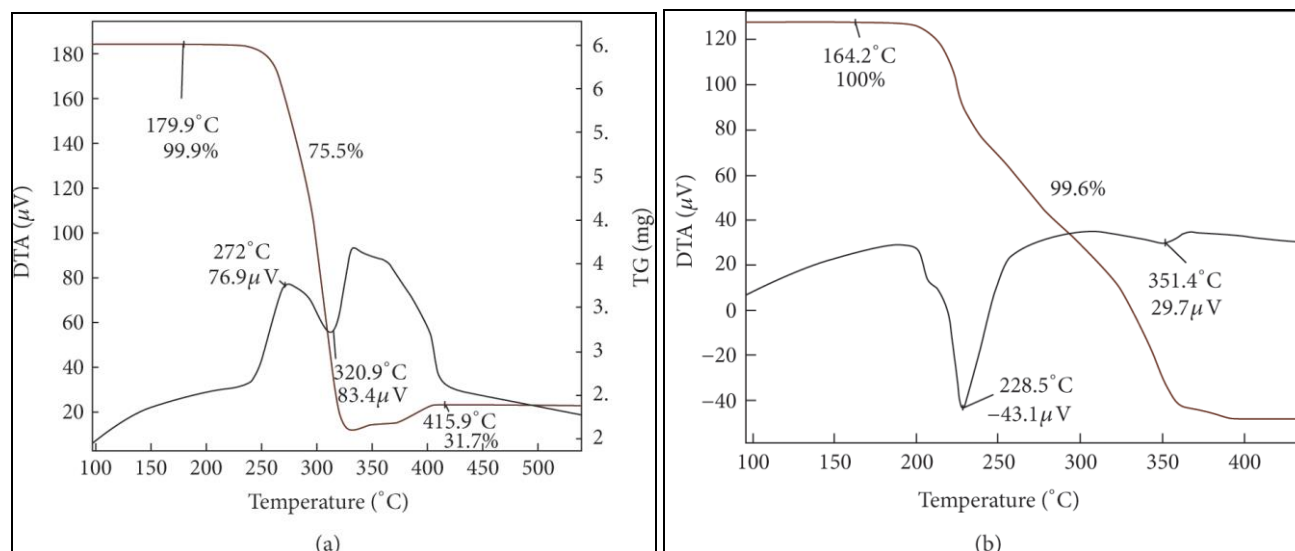
The data on the antimicrobial activity of the compounds and the control drugs as MIC values are given in Table 2. The cultures were obtained from SRL broth for all the bacterial strains after 24 h of incubation at 37 °C. *C. albicans* were maintained in dextrose broth after incubation for 24 h at 25 °C. Testing was carried out in dextrose broth at pH 7.4 and the two fold serial dilution technique was applied. A set of tubes containing only inoculated broth was used as controls.

For the antibacterial assay after incubation for 24 h at 37 °C and after incubation for 48 h at 25 °C for the antifungal assay, the last tube with no growth of microorganism and/or yeast was recorded to represent the MIC expressed in ppm. Every experiment in the antibacterial and antifungal assays was replicated twice, and the data is given in Table 2.

The observation on the biological assay indicates that the antibacterial action due to all compounds has N, O groups which is of considerable chemotherapeutic interest. From Figure 1 and Table 2, it is evident that among all the newly synthesized compounds 1, 2 and 3 tested for their antibacterial and antifungal activities against *Staphylococcus aureus* (ATCC 25923), *Staphylococcus aureus* (ATCC 3160), *Candida albicans* (227) and *Staphylococcus cerevisiae* (361) were determined as MIC values. All the investigated compounds showed good activity against *S. aureus*. The zone of inhibition in mL of the test compounds against the microorganism *Staphylococcus aureus* (ATCC 25923), *Staphylococcus aureus* (ATCC 3160), *Candida albicans* (227), and *Staphylococcus cerevisiae* (361). These data indicate that among the bacteria employed, *S. aureus* is found to be more sensitive to these compounds whereas the gram-negative bacteria show resistance to most of the compounds. The zone of inhibition tabulated reveals that the antibacterial activity of the compounds is specific to the microorganism examined. Analysis of the data showed that generally the fungi *C. albicans* (227) was more susceptible to the irreversible toxic effects of screened compounds than *S. cerevisiae* (361). Variation in the response of fungi studies to chemical screened may be attributed to the tolerance of them by test fungi. The effects of assayed chemicals on test fungi differed in accordance with the concentrations used. Generally fungi toxicity enhanced with the increase in the dose of compounds. The higher the concentration, the longer was the persistence of chemicals.

**Table 2:** Antimicrobial activity of hydrazones ligand and their metal complexes

Compounds	Time hrs	Diameter of zone of inhabitation (mm)							
		S. aureus MTCC 3160		S. aureus MTCC 25923		C. albicans MTCC 227		S. cerevisiae MTCC 361	
		100µg	50µg	100µg	50µg	100µg	50µg	100µg	50µg
HPBH	24	40	41	41	42	23	12	13	15
	48	42	45	43	43	25	15	15	18
FPFH	24	-	-	32	33	23	11	-	-
	48	-	-	34	35	20	21	-	-
1	24	10	12	13	16	19	17	19	18
	48	11	14	14	19	11	10	12	19
2	24	19	18	20	28	25	27	21	18
	48	-	-	-	-	11	29	12	19
3	24	-	-	-	-	13	10	12	10
	48	14	10	13	12	14	13	14	11
Gentamycin	24	32	34	32	34	-	-	-	-
	48	32	34	32	34	-	-	-	-
Amphotericin-B	24	-	-	-	-	17	21	17	21
	48	-	-	-	-	17	21	17	21



**Fig 2:** Showing the bar graph (a) and (b) of antibacterial and antifungal activities at 1000 ppm concentration after 48

#### 4. Conclusion

This research work has achieved the synthesis of hydrazone tetradentate nitrogen and oxygen donor ligands. Antimicrobial results showed that metal complexes have high killing activity compared to the ligand. A whole line of current antifungals target ergosterol biosynthesis pathway or its end product which is unique to fungi. At respective MIC values Cu(II) complexes lead to enormous reduction in ergosterol content followed by Cu(II) complex, Mn(II) complex, and the ligand, respectively.

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