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Biological Evaluation of Cobalt, Nickel, Copper and Zinc Complexes of Thiosemicarbazones

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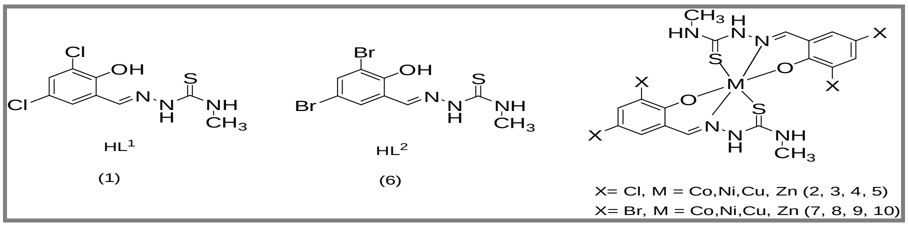
ABSTRACT

Transition metal complexes mainly of cobalt, nickel, copper and zinc of the type $[M(L^{1-2})_2]$ *were obtained from Schiff base ligands* $[H(L^{1-2})]$. *Ligands were synthesized from 2,5-dihalosalicylaldehyde and 4-methyl-3-thiosemicarbazide. The compounds were characterized by using various analytical techniques which suggested octahedral type of geometry for the complexes. The compounds were evaluated for in vitro antimicrobial activity against gram positive bacteria viz. Streptococcus gordonii, Staphylococcus aureus; gram negative bacteria viz. Escherichia coli, Pseudomona aeruginosa and two fungal strains viz. Candida albicans and Aspergillus niger. The serial dilution method was used for the evaluation of biological activity. The data revealed that transition metal complexes were more potent than their Schiff base ligands. The complexes were more potent against fungus as compared to bacterial strains.*

Graphical Abstract



Synthetic route of Schiff base ligands and their metal(II) complexes

Highlights:

- Synthesis and characterization of bidentate Schiff base transition metal complexes.
- *In vitro* antimicrobial activities at different concentrations of the compounds were carried out against gram positive bacteria *viz. Streptococcus gordonii*, *Staphylococcus aureus*; gram negative bacteria *viz. Escherichia coli*, *Pseudomona aeruginosa* and two fungal strains *viz. Candida albicans* and *Aspergillus niger*.
- Compounds (1-10) were found to be potent against all microbial strains.
- The complexes are more noxious than parent Schiff bases.

Keywords: Biological evaluation, Fungus, Transition metals, Schiff bases.

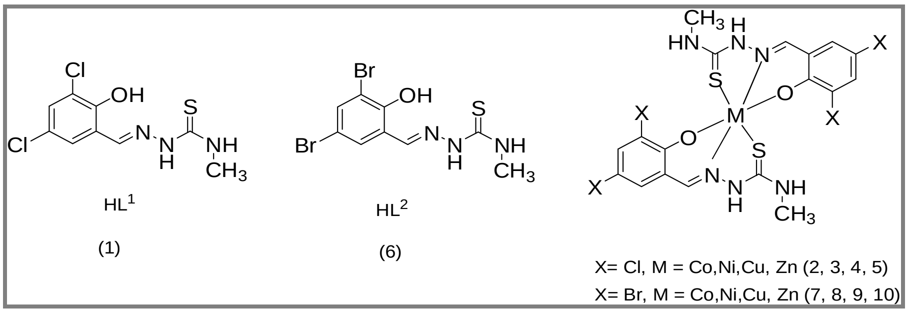
INTRODUCTION

Schiff bases are aldehyde or ketone like compounds in which carbonyl group is replaced by an imine or azomethine moiety. Schiff bases are versatile ligands prepared by condensation of an amino compound with carbonyl compounds under specific conditions [**1-3**]. Schiff base ligands are most widely used organic compounds for industrial purposes. They are used as catalyst in several reactions like polymerization reactions, oxidations of organic compounds, reduction of ketones etc [**4**]. Schiff base ligands have numerous applications in biology including antibacterial, antifungal, antiviral, antimalarial, antioxidant, anti-inflammatory, anticancer etc [**5-11**]. The field of Schiff base complexes of transition metals is developing rapidly due to their wide variety of intriguing structure of ligands and their complexes, which generally depends upon structure of starting reacting materials like aldehyde and amines [**12, 13**]. Transition metal complexes of Schiff bases exhibit interesting physical, chemical and biological properties. The use of transition metal complexes as analytical reagents is increasing because they allow simple and inexpensive determination of different organic and inorganic substances, helps in removing heavy metal ions from aqueous media by holding metal ions selectively [**14, 15**]. The present work uses thiosemicarbazide and salicylaldehyde derivatives for preparation of Co(II), Ni(II), Cu (II), Zn(II) complexes. Thiosemicarbazide and its derivatives are versatile sulphur donor compounds bonding through sulphur (C=S) and azomethine (C=N–) groups which are known to have a promising biologically activity such as antimicrobial, antitubercular, anticancer, anti convulsants activity [**16-18**]. Furthermore, Thiosemicarbazones are subject of interest in recent decades due to their versatile applications in industry and analytical chemistry. Thiosemicarbazide based compounds have structural diversity due to condensation of different carbonyl and alkylation of different part of thiosemicarbazide moiety. Inspired by biological profile of these compounds, in this manuscript we describes the antibacterial and antifungal activity of Schiff bases derived from dihalosalicylaldehyde and 4-methyl-3-thiosemicarbazide and their transition metal (II) complexes.

MATERIALS AND METHODS

All the chemicals used were of analytical grade obtained from Aldrich and used as such without any further purification. Solvent used for synthesis, recrystallization and extraction of compounds were methanol, chloroform, DMSO, hexane, DMF and diethyl ether. The C, H, N elemental analysis was performed using a Perkin–Elmer CHN 2400 elemental analyzer. Molar conductance measurements of ligands and their complexes with concentration 10^{-3} molL^{-1} in DMSO were carried out using a Jenway 4010 conductivity meter. ^{1}H-NMR spectra was recorded using a Bruker 400MHz spectrometer with DMSO as solvent; chemical shifts are taken in parts per million (ppm) relative to tetramethylsilane. Electron impact mass spectra were recorded on a Jeol, JMS, DX-303 mass spectrometer. IR spectra (4000-400 cm^{-1}) were recorded as KBr pellets on a Bruker FT-IR spectrophotometer. ESR spectra in DMF were recorded at room temperature on Varian E112 X-band spectrometer using tetra-cyanoethylene (TCNE) as the internal standard with g value of 2.0023.

Synthesis of ligands and their transition metal complexes: We have synthesized the Schiff bases HL^1(1) and HL^2 (6) by condensation of 4-methyl-3-thiosemicarbazide with 2, 5-dicholorosalicyl aldehyde and 2, 5-dibromorosalicylaldehyde in methanol solution. The reaction mixture was refluxed for 2-3 h. The product formed was filtered and dried to give ligands. For the preparation of complexes the methanolic solution of ligands was added to the solution of metal(II) acetates in same solvent with constant stirring. The resulting solution was refluxed for 2-3 h. On cooling to room temperature, the solid product separated out was filtered off and washed with hot methanol or petroleum ether to remove excess of metal nitrates and ligand and finally dried in vacuum. Structure of synthesized ligands and complexes are presented in scheme 1.



Scheme1. Synthetic route of Schiff base ligands and their metal(II) complexes.

Antimicrobial activity: In continuation of our previous work [19] the synthesized Schiff bases (HL^1 and HL^2), their transition metal complexes $M(L^{1-2})_2$ and standards Ciprofloxacin and Fluconazole were evaluated for antibacterial and antifungal activity against two strain of gram positive bacteria *Streptococcus gordonii*, *Staphylococcus aureus*,two gram negative bacteria *viz. Escherichiacoli*, *Pseudomon aaeruginosa* and two fungal strains *viz. Candida albicans* and *Aspergillus niger* [20]. Ciprofloxacin and Fluconazole were used as positive control for antibacterial and antifungal activity. DMSO was used as negative control. The obtained result are described in table 1 and graphical representations for antibacterial and antifungal activity is represented in figure 2 and 3.Serial dilution method was used for evaluating biological activity of synthesized compounds. In this procedure the bacterial growth were subcultured on nutrient broth(NB)and the fungal on potato dextrose broth(PDB) for their *in vitro* testing which were prepared by dissolving (24 g) of nutrient broth and potato dextrose broth in 1 L of distilled water .The mixture was autoclaved for 15 min at 120°C. Stock solutions were made by dissolving 5 mg of synthesized compounds in 5ml of DMSO. Now add 1 mL of the prepared solution to 9 mL of DMSO to make the stock solution of 100 $\mu g\ mL^{-1}$. This stock solution of was diluted to make concentrations of 50, 25, 12.5, 6.25, 3.12,1.56, and 0.25 $\mu M\ mL^{-1}$ through serial dilution method and added to test tube containing 1 mL of the nutrient broth for antibacterial activity and PDB for antifungal activity. The subcultured bacteria and fungus were inoculated to each solution and the solution was then kept in incubator at 37°C for one day in case of bacteria and for seven days of case of fungi. Then the minimum inhibitory concentration (MIC) was determined through the experiment. The experiment values were compared with the standard drug i.e and Ciprofloxacin for antibacterial and Fluconazole for antifungal activity.

Table 1. Antibacterial and Antifungal activity data of the Schiff-base ligands and their transition metal complexes(MIC in $\mu M\ mL^{-1}$)

S. No.	**Compounds**	**Gram + bacteria**		**Gram - bacteria**		**Compounds**	**Antifungal activity**	
		S. gordonii	***S. aurues***	***E. coli.***	***P. aerugenosa***		***C. albicans***	***A. niger***
1	HL^1	0.044	0.044	0.044	0.044	HL^1	0.044	0.044
2	$Co(L^1)_2$	0.020	0.020	0.020	0.020	$Co(L^1)_2$	0.020	0.020
3	$Ni(L^1)_2$	0.010	0.010	0.010	0.010	$Ni(L^1)_2$	0.010	0.020
4	$Cu(L^1)_2$	0.009	0.009	0.009	0.009	$Cu(L^1)_2$	0.009	0.009
5	$Zn(L^1)_2$	0.020	0.020	0.020	0.020	$Zn(L^1)_2$	0.014	0.023
6	HL^2	0.034	0.034	0.034	0.034	HL^2	0.017	0.034
7	$Co(L^2)_2$	0.015	0.017	0.017	0.017	$Co(L^2)_2$	0.017	0.017
8	$Ni(L^2)_2$	0.007	0.007	0.007	0.007	$Ni(L^2)_2$	0.007	0.007
9	$Cu(L^2)_2$	0.007	0.007	0.015	0.015	$Cu(L^2)_2$	0.007	0.007
10	$Zn(L^2)_2$	0.015	0.015	0.015	0.015	$Zn(L^2)_2$	0.007	0.007
11	Ciprofloxacin	0.043	0.041	0.047	0.047	Fluconazole	0.051	0.010

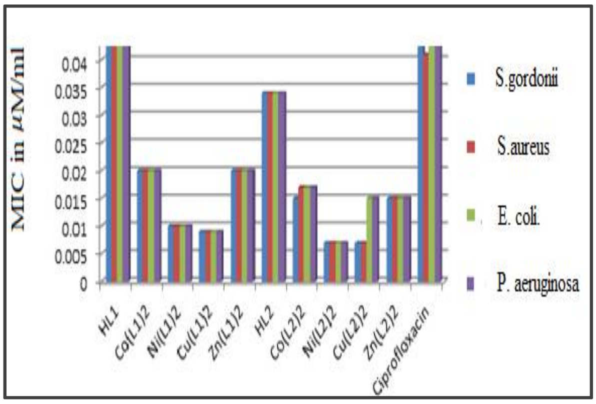


Figure 1. Graphical representation of antibacterial data for compounds 1-10.

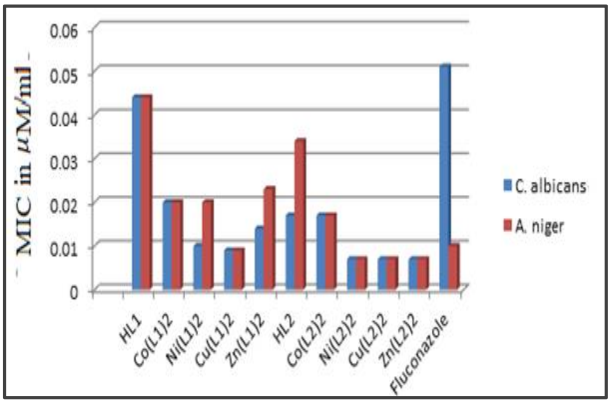


Figure 2. Graphical representation of antifungal data for compounds 1-10.

RESULTS AND DISCUSSION

Schiff base HL^1 and HL^2 have been synthesized by the condensation of the 2,5 dihalosalicylaldehyde with 4-methyl-3-thiosemicarbazide readily which were identified by UV, IR, NMR, and mass spectra. Six -co ordinate complexes were obtained from 2:1 molar ratio of Schiff base ligand with $Cu(CH_3COO)_2.3H_2O$, $Ni(CH_3COO)_2.7H_2O$, $Co(CH_3COO)_2.4H_2O$ and $Zn(CH_3COO)_2.2H_2O$. The Schiff-base ligands and their complexes are highly stable at room temperature in solid state and these compounds are generally soluble in DMF and DMSO [21]. The analytical data are in agreement with the proposed stoichiometry of the complexes and the metal: ligand ratio in the complexes was found to be 1:2. The molar conductivity values for all the compounds in DMSO was in the range 11–19 $Ohm^{-1}cm^2$ mol^{-1}, suggesting non electrolytic in nature [22]. IR, NMR, UV-Vis and ESR data indicate the formation of complexes of tridentate ligands. In this manuscript the compounds synthesized were evaluated for antimicrobial activity was summarized as:

1) Among Schiff base ligands HL^1 and HL^2, HL^2 having bromo group on salicyaldehyde are more potent as compared to one having chloro group $HL^1 < HL^2$.

2) Transitions metal complexes are more active than their respective ligands. This can be explained by Tweeedy's chelation theory. According to Overtone's concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials so that liposolubility is an important factor which controls the microbial activity [23]. On chelation, the polarity of the metal ion will be reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further, it increases the delocalization of p-electrons over the whole chelate ring and enhances the lipophilicity of the complexes. This increased lipophilicity enhances the penetration of the complexes into lipid membranes and blocks the metal binding sites in bacterial enzymes. These complexes also disturb the respiratory processes of the cell and thus block the synthesis of proteins which restricts further growth of the organism. Furthermore, the mode of action of the compounds may involve the formation of a hydrogen bond through the azomethine group with the active centre of cell constituents, resulting in interference with normal cell processing [24]. Although there is a sufficient increase in the bactericidal activity of the complexes as compared to the free ligands, metal salts and the control (DMSO), the complexes show moderate activities as compared to the standard drug.

3) For ligand HL^1 and its complexes the antibacterial activity trend was found to be $[Cu(HL^1)_2] > [Ni(HL^1)_2] > [Co(HL^1)_2] = [Zn(HL^1)_2]$and for ligand HL^2 the order of activities was $[Ni(HL^2)_2] > [Cu(HL^2)_2] > [Co(HL^2)_2] = [Zn(HL^2)_2]$.

4) For anti-fungal activity the trend of Schiff bases was found to be $HL^1 < HL^2$ and the complexes follow the order $[Cu(HL^{1-2})_2] > [Ni(HL^{1-2})_2] > [Zn(HL^{1-2})_2] > [Co(HL^{1-2})_2]$.

5) Almost all the compounds synthesized were more active towards taken fungal strain as compared to bacterial strains and compounds 7,8,9,10 were found to be most active among entire series.

6) The compound $Ni(L_2)_2$ is most active in entire series against tested fungus and bacterial strains.

APPLICATION

The present work exhibits a lot of applications in biological field. The results evaluated for the synthesized Schiff bases and their complexes shows that the compounds are good antifungal and antibacterial agents and acts as a hopeful drugs in the treatment of attacks caused by microbes with least harmful effects in patients' body. The results of antimicrobial action reveal that the complexes were more biological active than Schiff bases and could be capable antimicrobial drug aspirants.

CONCLUSION

All synthesized ligands and their transition metal complexes showed promising antimicrobial activities against tested microorganism and complexes have better potency as compared to free ligands. The results also show that metal complexes exhibit more antifungal activities than the free ligands. The Schiff bases having bromo groups on salicylaldehyde possess more potency against microbial strains as compared to one having chloro group i.e. $HL^1 < HL^2$.So these compounds can be used as a good substitute for future bactericide and fungicides.

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