



Synthesis, Characterization and Antimicrobial activity of Novel 5-Amino-2-Mercapto-1,3,4-Thiadiazole Derivatives and their Metal Complexes

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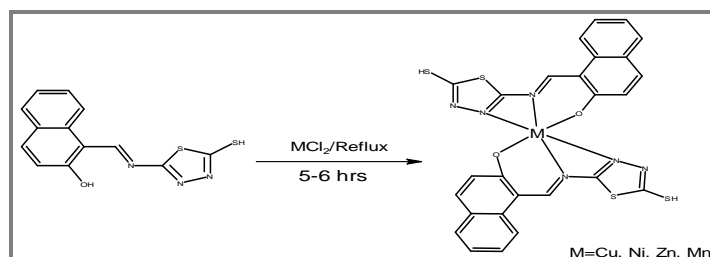
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ABSTRACT

Transition metal complexes of Schiff's bases were playing an essential role in the development of coordination chemistry. Thiadiazole moiety is present as a core structural component in many drug categories such as antimicrobial, anti-inflammatory, antiviral, analgesic and antitubercular agents etc. The potent activity and various types of biological activities of thiadiazole and their derivatives established them as pharmacologically and biologically important scaffolds in heterocyclic chemistry. The metal complexes of Schiff's bases were studied extensively because of their attractive chemical, physical properties and their wide range biological applications. Hence Schiff base with 5-amino-2-mercapto 1,3,4-thiadiazole derivatives and their Cu(II), Ni(II), Mn(II) and Zn(II) metal complexes were prepared and characterized by elemental analysis, ¹H-NMR, ¹³C-NMR, IR. using these Schiff base ligand.

Graphical Abstract



Keywords: Schiff's bases, Thiadiazole, Antimicrobial, Antitubercular agents, Metal complexes.

INTRODUCTION

Bacteria have been responsible for many of the most deadly diseases and widespread epidemics in human. Bacterial infections have increased significantly in recent years. The overuse and misuse of antibiotics led to a severe public health problem i.e, bacterial resistance to antibiotics. Consequently, the treatment of infectious diseases still remains an important and challenging problem due to several factors especially emerging new infectious diseases and the dramatically increasing number

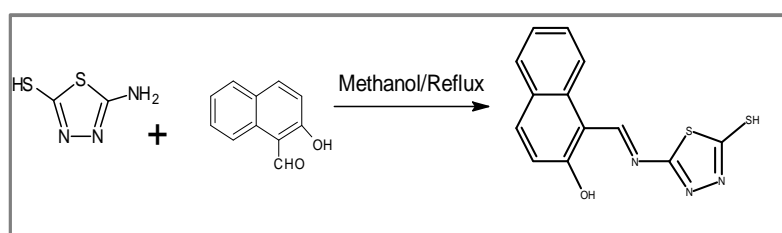
of multidrug resistant microbial pathogens. Transition metal complexes of Schiff's bases were playing an essential role in the development of coordination chemistry [1]. Thiadiazole moiety is present as a core structural component in many drug categories such as antimicrobial, anti-inflammatory, antiviral, analgesic and antitubercular agents etc [2-4].

Several five membered heteroaryl compounds with three hetero atoms at symmetrical positions, such as 1,3,4-thiadiazole, triazoles have attracted researchers interest over the years due to their interesting pharmacological activities [5-10]. Schiff bases and their complexes are significant scaffolds synthesized from the condensation of an amino compound with carbonyl compounds. Structurally, Schiff base is a nitrogen analog of an aldehyde or ketone. Transition metal complexes of Schiff's base ligand have been extensively studied due to their easy preparation, availability of low-cost raw materials and formation of stable and chelated co-ordination complexes with most of the transition metals. 1,3,4-Thiadiazoles have become an important class of heterocycles and attracted an interest of researches because of their various types of biological activity such as antimicrobial, anti-inflammatory, antiviral, analgesic and antitubercular agents etc.

MATERIALS AND METHODS

General and Instrumental: Reagents required for the synthesis of Schiff's bases and their metal complexes were as well as solvents were purchased commercially from Merck and Sigma Aldrich and used without any further purification. Melting points of the compounds were recorded on a hot stage Gallen Kamp melting point apparatus. The Infrared (FTIR) spectra were recorded by using FTIR.8300 Shimadzu spectrophotometer by using CSU disc in the frequency range of 4000-200 cm^{-1} . The spectra of ^1H and ^{13}C -NMR spectra were recorded on a Joel 400MHz spectrometer using reiterate CDCl_3 as the solvent and tetramethylsilane (TMS) as the internal standard. Elemental analysis carried out by a standard method and UV spectra recorded on UV spectrophotometer [11, 12].

Preparation of Schiff's Base Ligand: To a hot stirred solution of 5-amino-1,3,4-thiadiazole-2-thiol (0.01mol) in methanol (30-40 mL), 2-hydroxy-1-naphthaldehyde (0.01 mol) was added. 1-2 drops of conc. H_2SO_4 and the resultant mixture was stirred under reflux for 5 h. Reaction progress was monitored by TLC. The reaction mixture was reduced to 10-15 mL and kept at room temperature for one hour. The reaction mixture was cooled and added to ice cold water and stirred for a few minutes resulted in the formation of a solid product which was collected by suction filtration. Compound was recrystallized by using ethanol [13-15].



Scheme 1. Synthesis of Ligand(L).

Yellow solid; **Yield:** 244 mg (90%); **M.P.:** 240-242°C; **Element. Anal. Calcd. (Found)** for $\text{C}_{13}\text{H}_9\text{N}_3\text{OS}_2$: C, 54.34; H, 3.16; N, 14.62; O, 5.57; S, 22.30; **FT-IR** (ν , cm^{-1}): 3077, 2876, 1748 (C=N), 1516 (C=C), 1264 (C-N); **UV-Vis.**, λ_{max} in nm: 457; ^1H NMR (DMSO- d_6 , δ ppm): 14.537 (s, OH), 12.993 (s, SH), 9.462 (s, C-H, H2), 8.873-8.851 (d, H8), 8.162-8.140 (d, H7), 7.944-7.924 (d, H6), 7.691-7.652 (t, H4), 7.499-7.462 (t, H5), 7.285-7.262 (d, H3);

^{13}C NMR (DMSO- d_6 , δ ppm): 186.457 (C₃; N=C), 165.165 (C₂), 163.168 (C₁), 163.350 (C₁₃), 138.006 (C₄), 131.944 (C₁₂), 129.101 (C₅), 869 (C₁₁), 127.769 (C₁₀), 124.364 (C₆), 122.559 (C₉), 118.686 (C₈), 109.869 (C₁₇).

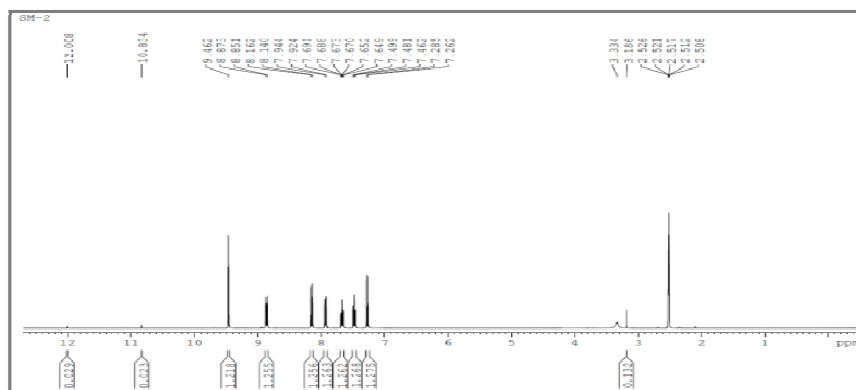


Table 1. Analytical Data of Metal Complexes

Compound	Empirical Formula	Mol.Wt	C	H	M (Cu,Ni, Mn,Zn)	N	S	O
L	C ₁₃ H ₉ N ₃ OS ₂	287.02	54.34	3.16	-	14.62	22.30	5.57
1d	C ₂₆ H ₁₆ NiN ₆ O ₂ S ₄	629.96	49.46	2.55	9.30	13.31	20.31	5.07
3d	C ₂₆ H ₁₆ CuN ₆ O ₂ S ₄	634.95	49.08	2.53	9.99	13.21	20.16	5.03
2d	C ₂₆ H ₁₆ MnN ₆ O ₂ S ₄	626.93	49.76	2.57	8.75	13.39	20.43	5.10
4d	C ₂₆ H ₁₆ ZnN ₆ O ₂ S ₄	635.29	48.94	2.53	10.25	13.17	20.10	5.01

RESULTS AND DISCUSSION

Schiff base ligands LH were obtained in high yields (90–95%) by the condensation reaction of 2-Amino-5-mercapto-1,3,4-thiadiazole with 2-hydroxy-1-naphthaldehyde in the equimolar ratio in dry Methanol as solvent. The mononuclear Ni(II), Cu(II), Mn(II) and Zn(II) complexes were obtained by direct reaction of ligands (LH) with metal ion precursors (NiCl₂·6H₂O, CuCl₂·2H₂O, Mn(OAc)₂·4H₂O, and Zn(OAc)₂·2H₂O in 1:2 M ratio. The equations for the reactions of the synthesis of ligands and complexes were given in scheme 1.

The ligands are yellow solids and are soluble in some of the common polar organic solvents such as CHCl₃, CH₂Cl₂, CH₃OH, DMSO and DMF whereas partially soluble in diethyl ether, while they are insoluble in non-polar solvents like hexane, heptane, benzene and toluene at room temperature. The yields of the complexes (70–80%) are also as high as that of ligands. The ligands and complexes were recrystallized in mixture solvents.

Bands in the region of 2900 to 3200 cm⁻¹ are due to ν(O-H) stretching vibration for LH. The strong bands at 1578 to 1748 cm⁻¹ were assigned to ν(C=N) stretching mode of the imine group for ligands. These bands showed a blue shift of about 20–40 cm⁻¹ in all the complexes, thus indicating there is strong coordination of imine nitrogen to the metal ions. The strong absorption bands between 1550 and 1500 cm⁻¹ in all ligands and complexes could be reasonably attributed to the presence of the ν(C=C) stretching vibration of the aromatic ring backbone.

Antibacterial Activity: In this assay, antibacterial activities of the different solvent fractions were investigated against pathogenic organisms by agar well diffusion method [15, 16] on Luria Bertani (LB) agar plates. Bacterial pathogenic strains like Gram-positive *Staphylococcus aureus* and Gram-negative organisms like *E. coli* were swabbed on top of agar media plates. By using sterilized cork borer (6 mm) was punctured alongside in the dish. 300 μL of each solvent extracted sample was carefully loaded into the well and left for 30 minutes in aseptic laminar air flow chamber for slow diffusion of compounds at room temperature. These plates were incubated at 37°C incubator for 24h and the growth inhibition of bacterial pathogens was assessed by the corresponding zone of inhibition (ZOI) [17].

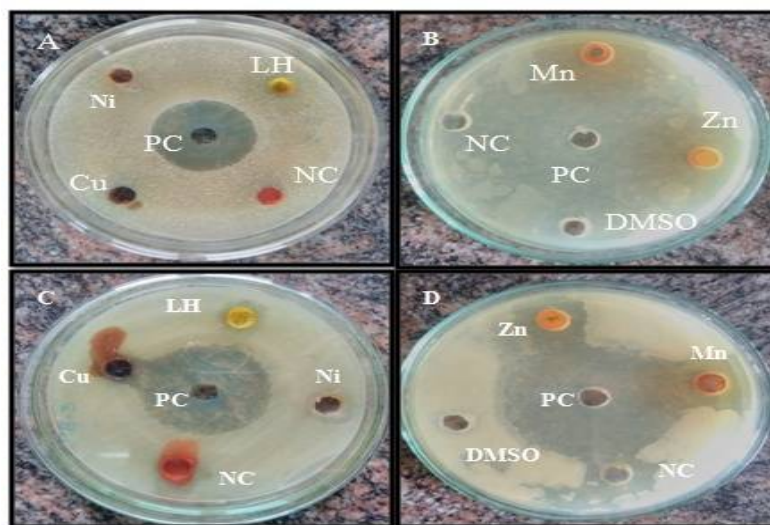
ZOI was calculated by using a standard antibiotic Zone scale TM Himedia (Mumbai, India). (Figure 4 and Table 2). The antibacterial activity of new Schiff base ligands (LH) complexes such as Ni(II), Cu(II), Mn(II) and Zn(II) was screened by agar well diffusion method against two bacteria namely *E. coli* and *Staphylococcus aureus*. Nutrient and LB broth was used to culture the bacteria. Plates of Nutrient agar were prepared and swabbed using sterile L-shaped glass rod with 100 μL of 24 hrs mature broth culture of individual bacterial strains.

The wells of 6 mm were created into each Petri plate using sterile cork borer. Two test solutions of each 1, 2, 3, 4 and 5 were prepared by dissolving 5 mg in 0.5 ml of sterile DMSO respectively to get 10 mg mL⁻¹ concentration of each compound and assessed their antibacterial activity. Similarly a standard antibiotic solution was prepared by dissolving 5 mg kanamycin sulphate (as a positive

control) in 50 μL of sterile water to get $0.1 \mu\text{g } \mu\text{L}^{-1}$ concentration. These solutions were added into the wells by sterile micropipettes. The plates were incubated at 37°C for 36 h. After the completion of the period of incubation, the zone of inhibition of each well was measured and the values were noted. The measurements were made in duplicate for each compound and their average values are reported.

Table 2. Zone of inhibition (in mm) against pathogenic organisms

S.No	Microorganisms	Zone of Inhibition (mm)							
		LH	Ni	Cu	Mn	Zn	DMSO	PC	NC
1.	<i>E.coli</i>	4	-	-	3	1	-	15	-
2.	<i>Staphylococcus Aureus</i>	5	1	8	6	5	-	16	4



A-*E.coli*, B-*E.coli* C-*Staphylococcus aureus*, D-*Staphylococcus aureus*, LH-Ligand, NC-Negative control, PC-Kanamycin($1\text{mg } 1\text{mL}^{-1}$), Ni-Nickel complex, Cu-Copper complex, Mn-Manganese complex, Zn-Zinc complex, DMSO-Dimethyl sulphoxide (Solvent)

Figure 4. An image of the antibacterial activity of ligand and its complexes.

APPLICATION

The synthesized ligand and metal complexes are pharmacologically important molecules because they possess mild antibacterial and antifungal activities.

CONCLUSION

New Schiff's base ligands have been synthesized via condensation of 2-Amino-5-mercapto-1,3,4-thiadiazole with 2-hydroxy-1-naphthaldehyde(LH). Ni(II), Cu(II), Mn(II) and Zn(II) complexes have been synthesized. The ligand and complexes were characterized by FT-IR, UV-Vis, ^1H NMR and ^{13}C NMR spectroscopy. The antibacterial activity of new ligand (LH) and their Ni(II), Cu(II), Mn(II) and Zn(II) complexes was evaluated by agar well diffusion method against pathogenic bacterial strains. Nutrient and agar media were used to culture the bacteria. Antibacterial activity against *E.coli*, *Staphylococcus aureus* strains was investigated. In case of *E.coli* strain, ligand shows 4mm of Zone of inhibition whereas Ni, Cu, NC, DMSO does not show any activity towards bacteria but PC (Kanamycin) shows Zone of inhibition for about (15 mm), Zn and Mn Shows moderate activity. In case of *Staphylococcus aureus*, ligand, Cu, PC, Zn, NC, Mn, Ni shows Zone of inhibition for about 4mm, 8mm, 16mm, 5mm, 4mm, 6mm, 1mm respectively. Thus ligand and its metal complexes showed antibacterial activity.

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