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Synthesis, characterization and biological activity evaluation of Ni(II) and Cu(II) complexes of a Schiff base derived from S-benzyldithiocarbazate (SBDTC) and cinnamaldehyde

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Abstract
Bidentate NS donor ligand was prepared from the condensation reaction of cinnamaldehyde with *S*-benzyldithiocarbazate (SBDTC). Reaction of the Schiff base ligand with the metal ions Ni (II) and Cu (II) afforded complexes with the general formula $[M(II)(NS)_2]$. Molecular structures of the Schiff base ligand and its complexes were established through elemental analysis, conductivity and magnetic susceptibility measurements as well as spectroscopic data (FT-IR, UV-Vis and ESI-MS). The geometrical structures of the metal complexes are square planar. The biological activities of the ligand and its complexes were investigated against the gram-positive and gram-negative bacteria and the fungus strain. The metal complexes were shown to possess more bioactivity than the uncomplexed ligand.

Keywords: schiff base, metal complex, biological activity

1. Introduction

Schiff base ligands especially nitrogen-sulfur donor ligands have gained considerable attention to scientists. Dithiocarbazate (NH_2NHCS_2) and its derivatives have been prepared and examined over the past few decades [1-7]. Dithocarbazic acid and the Schiff bases derived from S-benzyl and –alkyl esters have been of great interests because of their different biological properties [8-10].

The development of the field of bioinorganic chemistry has expanded the interest in NS-donor ligands and its complexes, since it has been accepted that many of these compounds may serve as models for biologically significant types. Metal complexes containing N, S, and O donor atoms display a vital role in biological systems as they have uncommon electronic properties. It is reported that the presence of metal ions bonded to biologically active compounds may boost their activities [11-15].

On the other hand, Schiff bases including NS-donor ligands are also applied as catalysts [16, 17], dyes, pigments, Intermediates in organic synthesis, polymer stabilizers [18] and corrosion inhibitors [19]. Schiff bases ligands played a promising role in the growth of coordination chemistry and were involved as key point in the expansion of inorganic biochemistry and optical materials [20]. Furthermore, Schiff base complexes of the heterocycles type synthesized between amino compounds containing oxygen, nitrogen and sulfur donor atoms and carbonyl compounds were the subject of extensive studies because of their unusual electronic properties [21].

Taking into consideration the above discussed importance of Schiff base ligands and their complexes, herein, we report the synthesis, spectroscopic, and biological studies of Ni(II) and Cu(II) complexes with the ligand derived from cinnamaldehyde and S-benzyldithiocarbazate (SBDTC). Synthesized compounds have been investigated in *vitro* against two Gram positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, two Gram negative bacteria, *Salmonella typhimurium* and *Escherichia coli* and two fungus strains *Candida albicans* and *Aspergillus fumigates*.

2. Experimental

2.1 Materials and Methods

$NiNO_3.6H_2O$, $CuNO_3.3H_2O$, KOH, CS_2, hydrazine hydrate, cinnamaldehyde, benzyl chloride, DMF, DMSO, CH_3OH, and C_2H_5OH used in this research works were purchased from Sigma-Aldrich and Merck and used without further purification.

2.2 Physical Measurements

Elemental analysis (C, H, and N) for the ligand and complexes were carried out on a Perkin-Elmer automatic equipment model 240B. The melting points of synthesized compounds were obtained on a digital melting point apparatus (METTLER TOLEDO). Conductivity measurements were measured of freshly prepared 1.0×10^{-3} mol/dm^{-3} DMSO solutions of the synthesized compounds using a Jenway 4071 digital conductivity meter at room temperature. FT-IR spectra of the ligand and its complexes were recorded using KBr disc technique on a Nicolet 170 SX FT-IR spectrometer. UV-vis spectra were measured for 10^{-3} M solutions in DMSO at 25°C using a Shimadzu 160 spectrophotometer. ESI-MS spectra were recorded with an Agilent Technologies MSD SL Trap mass spectrometer with ESI source coupled with an 1100 Series HPLC system for the confirmation of molecular formulas of compounds. Magnetic moments were measured using a magnetic susceptibility balance (Johnson Matthey Catalytic System Division).

2.3 Synthesis of S-benzyldithiocarbazate (SBDTC)

SBDTC was synthesized following the reported procedure [2]. Potassium hydroxide (0.05 mol) was dissolved in ethanol 90% (50 mL). To this solution, hydrazine hydrate (0.05 mol) was added and the mixture was cooled in an ice-salt bath to 0˚C. Carbon disulfide (0.05 mol) was added drop wise with constant stirring over a period of one hour. During this time, two layers were formed. The light-brown lower layer was separated and dissolved in 40% ethanol (50 mL), maintained at 5^0C. The mixture was kept in ice-bath and to this benzyl chloride (0.05 mol) was added drop wise with vigorous stirring. The white product (SBDTC) formed was filtered and washed with ethanol. It was recrystallized from absolute ethanol after drying. The recrystallized SBDTC was dried and kept in a desiccator.

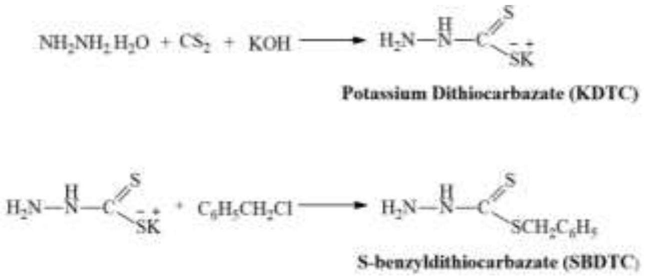

Fig 1: Synthesis of SBDTC

2.4 Preparation of the cinnamaldehyde Schiff base of SBDTC, benzyl 2-(3-phenylallylidene) hydra zine carbodithioate

Ethanolic solution (50 mL) of SBDTC (10 mmol) was mixed with equimolar ethanolic solution (20 mL) of cinnamaldehyde. The mixture was refluxed for 40 mins. The yellow precipitate which formed was separated and dried in *vacuo* over anhydrous $CaCl_2$.

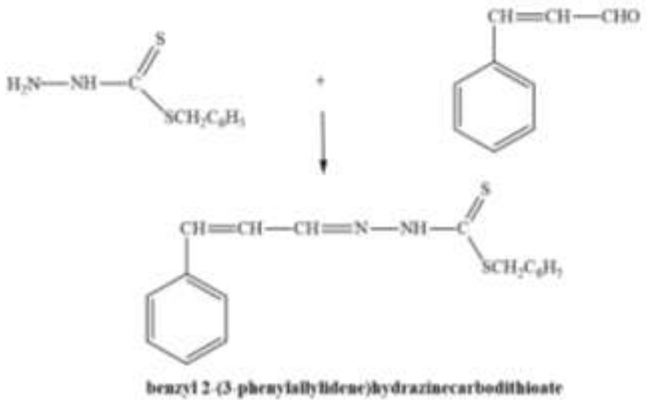

Fig 2: Synthesis cinnamaldehyde Schiff base of SBDTC

2.5 General method for the preparation of complexes with the Schiff base, benzyl 2-(3-phenylallylidene) hydra zine carbodithioate

Metal salt (0.5 mmol) was dissolved in absolute ethanol (20 mL) and to this, Schiff base ligand (1 mmol) dissolved in hot absolute ethanol (70 mL) was added. The mixture was then refluxed for 30 mins and then cooled**.** The precipitate formed was filtered off and washed with ethanol and dried in *vacuo* over anhydrous $CaCl_2$.

$M(NO_3)_2 . n H_2O + NS \rightarrow [M(II)(NS)_2]$

Where, M = Ni (II), Cu(II)

NS = Cinnamaldehyde Schiff base of SBDTC, benzyl 2-(3-phenylallylidene) hydrazinecarbodithioate.

2.6 Metal Content Estimation

A known quantity of metal complex was put into a conical flask whose weight was known. Then, concentrated H_2SO_4 (500 μL) was added. It was fumed until dry and the process was repeated three times. Concentrated HNO_3 (500 μL) and $HClO_4$ (500 μL) were then added and the mixture was further fumed until dry. The process of adding acids and fuming to dry was continued until there was no black materials. 100 mL distilled water was added to dissolve the residue. Finally, the weight of the metal was estimated complexometrically and gravimetrically using EDTA (Ethylenediamine tetraacetic acid) and DMG (Dimethyl glyoxime) [22].

2.7 Antimicrobial Activity

Disc-agar diffusion method was used to check the antimicrobial activity of the Schiff base ligand and its metal complexes in DMF against two Gram positive bacteria, *Staphylococcus aureus* and *Bacillus subtili*s, two Gram negative bacteria, *Salmonella typhimurium* and *Escherichia coli* and two fungus strains *Candida albicans* and *Aspergillus fumigates*. The antibiotic *chloramphenicol* was used as reference in the case of Gram-positive bacteria, *cephalothin* in the case of Gram-negative bacteria and *cycloheximide* in the case of fungi.

3. Results and Discussion

3.1 Syntheses and Characterization

The Schiff base ligand was synthesized by 1:1 condensation of *S*-benzyldithiocarbazate (SBDTC) and cinnamaldehyde in ethanol under reflux, which on following reaction with metal salts in 2:1 molar ratio, generated the metal complexes. All the synthesized compounds are air stable and non-hygroscopic.

Table 1 Analytical data and physical properties of the compounds

Compounds	**Color**	**Melting point or decomposition temperature (± 5°C)**	**Molar conductance ($ohm^{-1}cm^2 mol^{-1}$)**	**μ_{eff} (BM)**
NS	White	181	2.50	-
$[Ni(II)(NS)_2]$	Brown	220	5.30	Dia
$[Cu(II)(NS)_2]$	Brown	235	3.50	1.98

3.2 Elemental Analysis

The microanalysis data (**Table 2**) indicates that the complexes are mononuclear. These data also exposed that the metal-to-ligand ratio for the synthesized complexes were 1:2. The proposed structure of the ligand and complexes were consistent with elemental analysis data.

Table 2 Microanalysis data of the ligand and its complexes.

Compound	**Found (Calculated) (%)**			
	Metal	**C**	**H**	**N**
NS	-	65.21 (65.35)	5.09 (5.16)	8.88 (8.97)
$[Ni(II)(NS)_2]$	8.52 (8.61)	59.78 (59.91)	4.37 (4.44)	8.49 (8.61)
$[Cu(II)(NS)_2]$	9.12 (9.26)	59.36 (59.49)	4.34 (4.41)	8.04 (8.16)

3.3 Molar Conductivity Measurements

The molar conductivity of the synthesized compounds were determined at room temperature at a concentration of 10^{-3} M in DMSO. The conductance value exposed that the complexes are non-electrolyte in nature [23] (**Table 1**).

3.4 FI-IR Studies

In a neutral medium, condensation of SBDTC with cinnamaldehyde provided the isomeric Schiff base (Scheme 2) with high yield. The Schiff base exist in tautomeric forms through the loss of thiol protons as shown in Fig. 1. Schiff base behaved as uninegatively charged bidented ligand by coordinating through the thiol sulfur and the azomethine nitrogen. The IR spectra of the Schiff base showed strong band at 3106 cm^{-1} due to the vibration of secondary amine group [*v*(N-H)] of the free ligand. The thione form is relatively unstable in the monomeric form and tend to turn to the more stable thiol form by enethiolization in solution (Fig. 1). The absence of *v*(S-H) absorbance at approximately 2575 cm^{-1} indicated that in the solid state, the Schiff base exists primarily in the thione form. The disappearance of *v*(N-H) band in the FT-IR spectra of the metal complexes suggested deprotonation and consequent coordination through the thiolate anions. The Schiff base also showed strong band at 1623 cm^{-1} assigned to the ν(C=N) stretching. In the metal complexes, this band shifted to lower frequencies due to the lowering of the C=N bond order as a result of the metal–nitrogen bond formation. The Schiff base also displayed *v*(C=S) stretching at 1031 cm^{-1}. The *v*(C=S) mode observed in the free ligand disappeared in the complexes, thus supporting the above argument of thiolate bonding with metal ions. Consequently, the *v*(C-S) mode was observed in the spectra of the complexes supporting thiolate coordination.

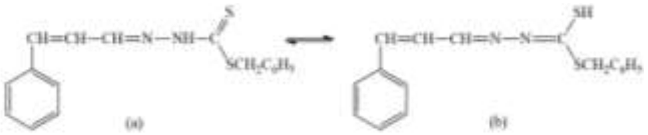

Fig 3: Tautomeric forms (a) Thione form (b) Thiol form

The Schiff base coordinated to the metal through the thiolate sulphur and the azomethine nitrogen atoms as evident from the FT-IR spectrum showing bands at 409 and 389cm^{-1} due to M-S bond stretching and bands at 485 and 481 cm^{-1} due to M-N bond stretching.

Table 3: Important infrared spectral bands of the ligand and the metal complexes (cm^{-1})

Compound	ν(N-H)	ν(C=S)	ν(C=N)	ν(C-S)	ν(M-S)	ν(M-N)
NS	3106	1031	1623	-	-	-
[Ni(II)$(NS)_2$]	-	-	1607	751	409	485
[Cu(II)$(NS)_2$]	-	-	1610	752	389	481

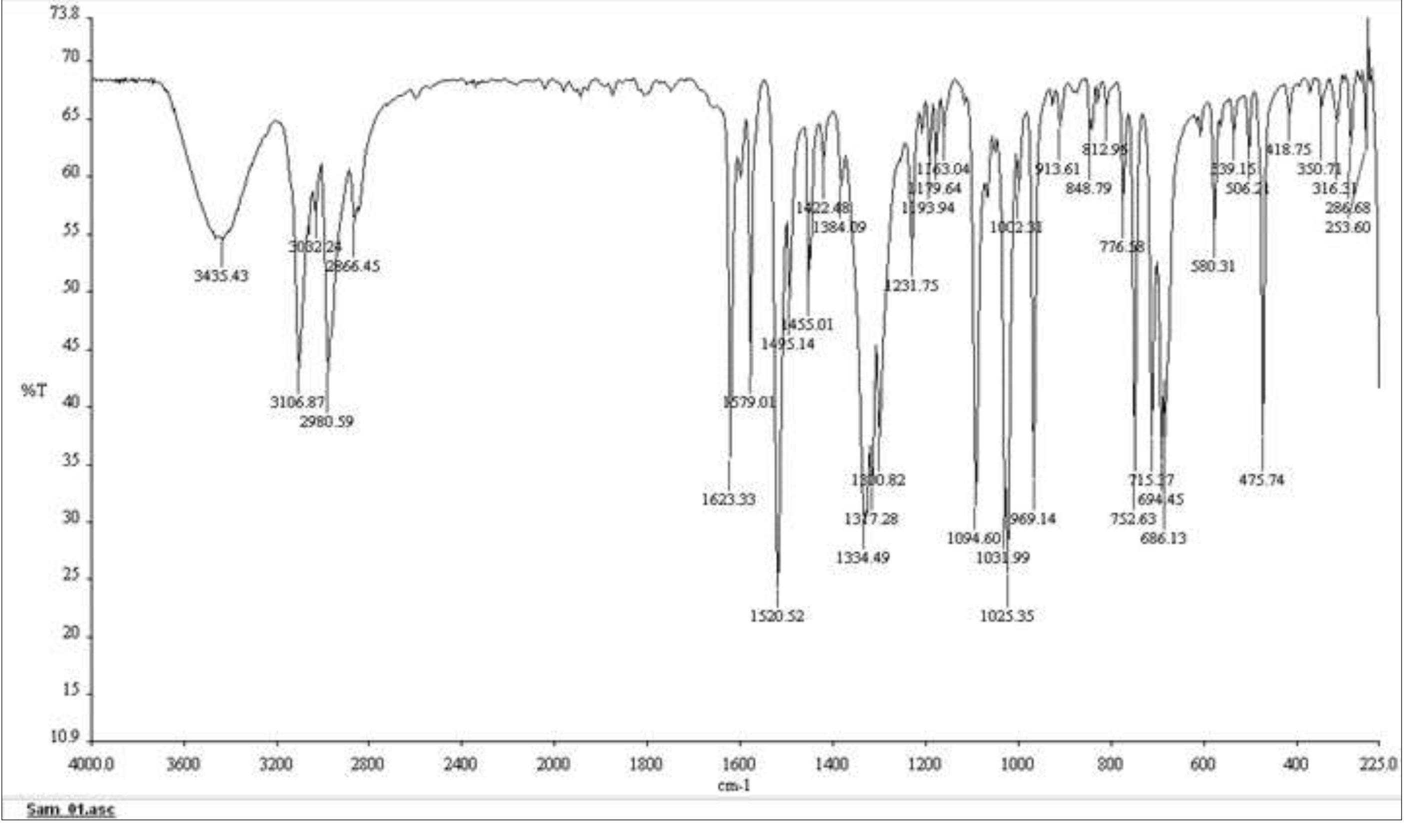

Fig 4: FTIR spectrum of cinnamaldehyde Schiff base of SBDTC (NS).

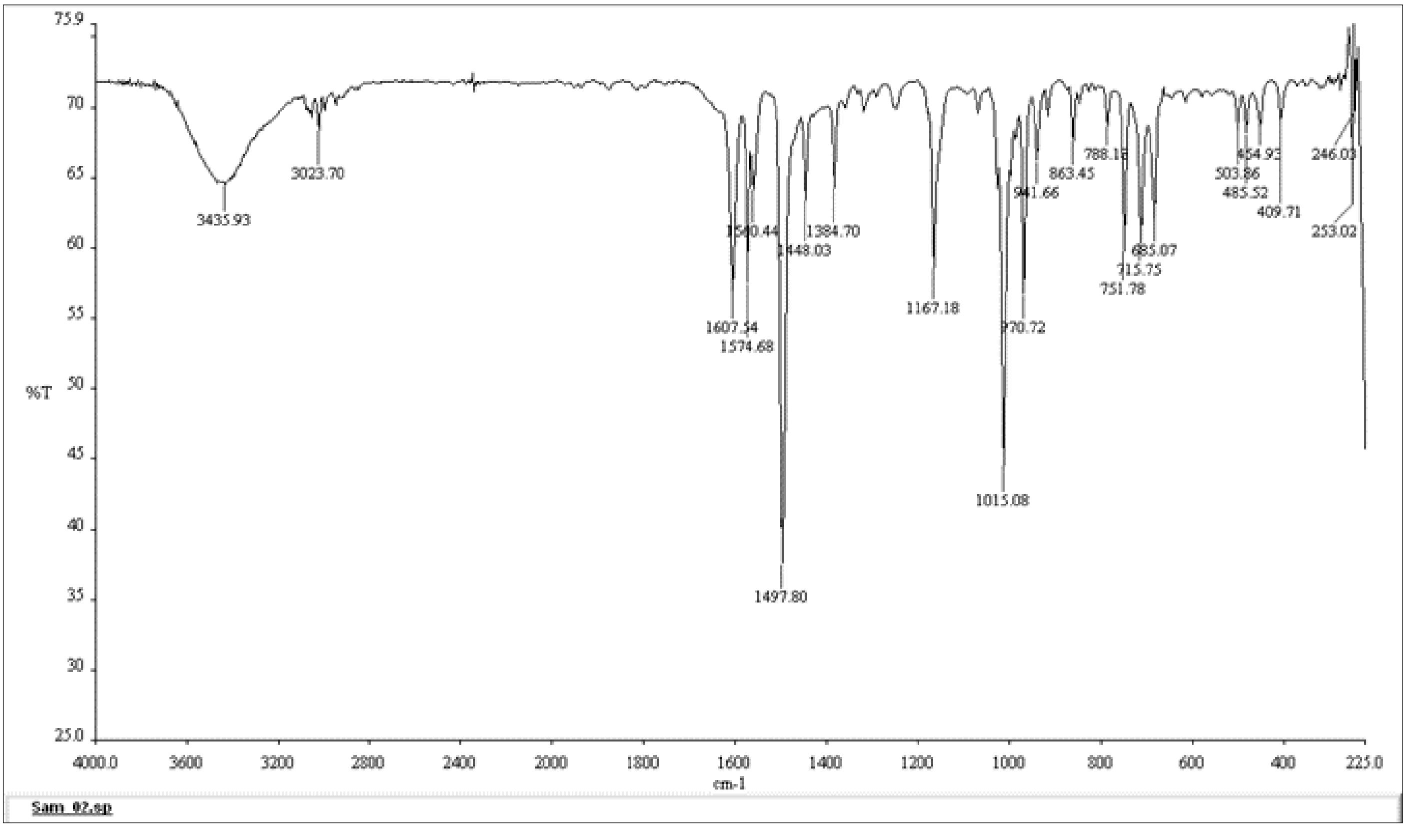

Fig 5: FTIR spectrum of [Ni (II)(NS)$_2$]

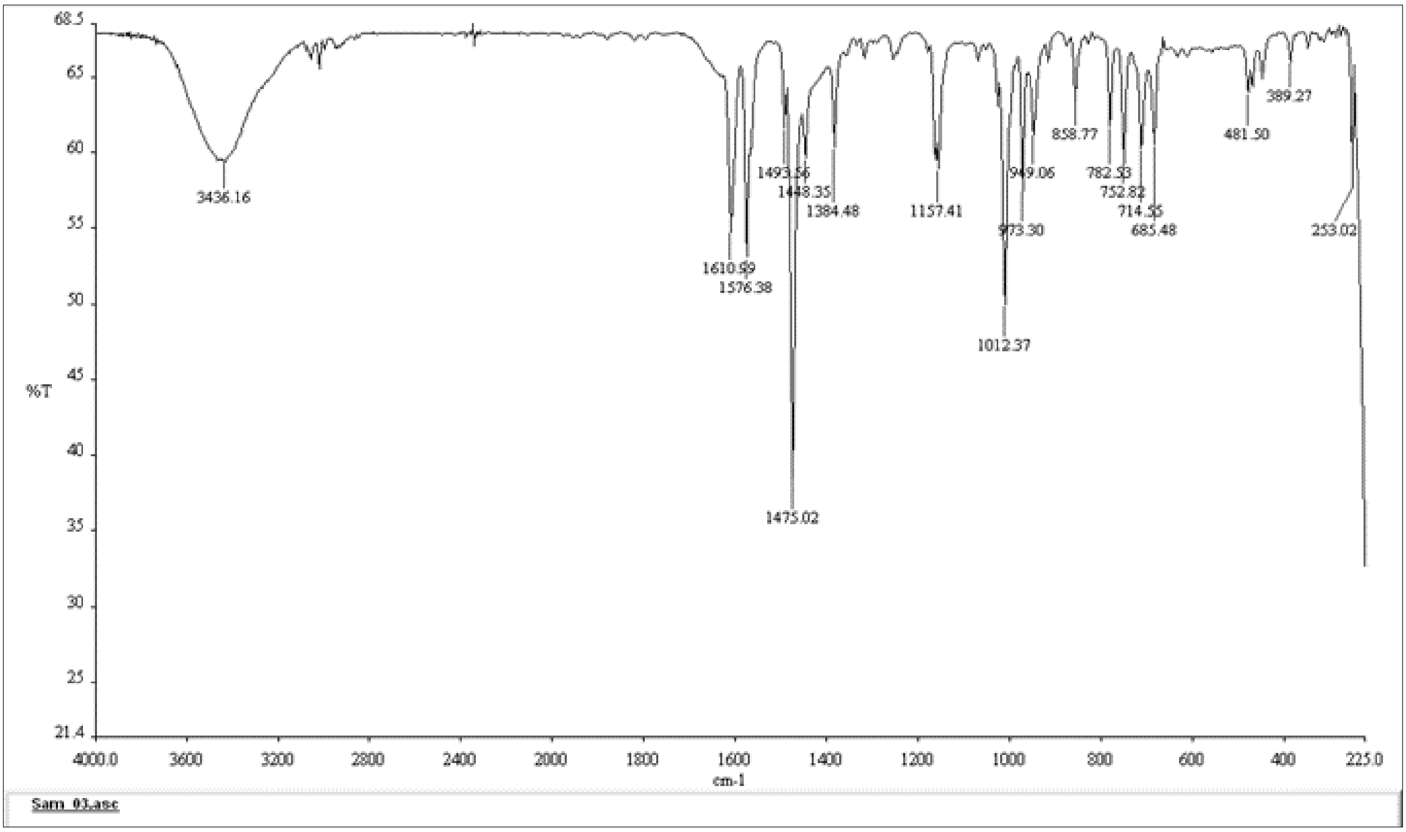

Fig 6: FTIR spectrum of [Cu (II) (NS) $_2$]

3.5 Magnetic Moment and Electronic Spectra

The magnetic susceptibility measurement (Table 1) showed that the complex, [Ni (II)(NS)$_2$] was diamagnetic. Three bands corresponding to the transitions $^1A_{1g} \rightarrow {}^1A_{2g}$ (255 nm), $^1A_{1g} \rightarrow {}^1B_{1g}$ (343 nm) and $^1A_{1g} \rightarrow {}^1A_{2g}$ (415 nm) were observed in the electronic spectrum of such square–planer Nickel (II) complex [24]. The UV-vis spectrum of the paramagnetic Cu (II) complex showed bands at 250 nm and 298 nm arising from the $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$ transitions, respectively, characteristic of a square- planar stereochemistry [25, 26]. The intense band at 378 nm was presumably caused by charge transfer.

Table 4: Electronic spectral data of the complexes

Complex	Band I (nm)	Band II (nm)	Band III (nm)
$[Ni(II)(NS)_2]$	255	343	415
$[Cu(II)(NS)_2]$	250	298	378

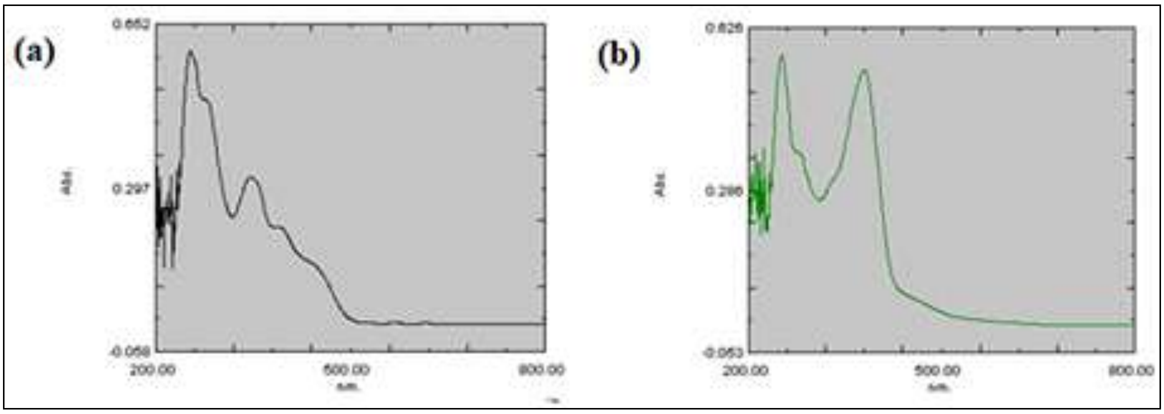

Fig 5: UV visible spectrum of the complexes, (a) $[Ni (II) (NS)_2]$ and (b) $[Cu (II) (NS)_2]$

3.6 ESI-MS Spectral Studies

ES-MS has been increasingly used as a dominant structural characterization method in coordination chemistry. The spectra of the ligand and Ni(II) and Cu(II) complexes show molecular ion peaks at m/z = 312.45, 681.58 and 686.43 amu respectively, which are equivalent to their molecular mass respectively. The molecular ion peaks are in good agreement with the proposed molecular formulae indicated from microanalysis.

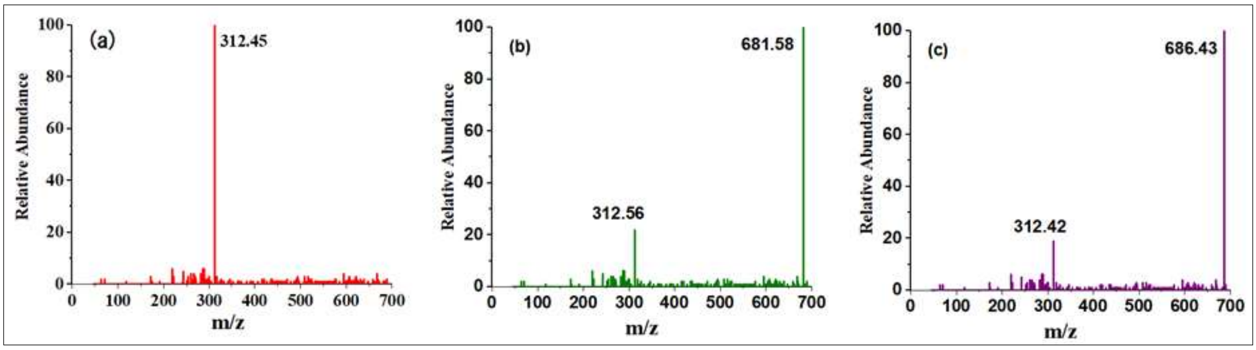

Fig. 6. ESI-MS spectra of (a) ligand (NS); (b) $[Ni (II) (NS)_2]$ and(c) $[Cu (II) (NS)_2]$

3.7 Structure

On the basis of the different physicochemical and spectral data presented and conferred above, the structures of the Ni (II) and Cu(II) complexes are shown in Fig. 7.

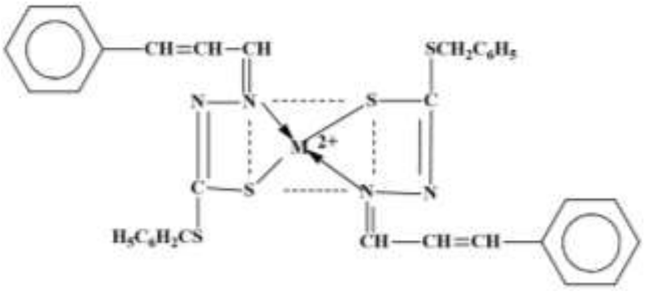

Fig 7: Square planar structure of the complexes [M = Ni (II) and Cu (II)].

3.8 Biological Studies

The biological activity of the Schiff base ligand and its metal complexes were investigated against the sensitive organisms *Staphylococcus aureus* and *Bacillus subtilis* as Gram-positive bacteria, *Salmonella typhimurium* and *Escherichia coli* as Gram-negative bacteria, *Candida albicans* and *Aspergillus fumigatus* as fungus strains. It was observed that the biological activity of all the synthesized compounds improved on coordination. Improved activity on coordination can be explained on the basis of chelation theory along with considering the nature of the ligand and metal ions, stereochemistry of the complexes etc.[27-29]. The metal complexes showed higher activities than the Schiff base ligand.

Table 5: Biological activity of the ligand and complexes expressed in mean of inhibition zone diameter (mm)

Compound	Gram-positive Bacteria		Gram-negative Bacteria		Fungi	
	Staphylococcus aureus	*Bacillus subtilis*	*Salmonella typhimurium*	*Salmonella typhimurium*	*Candida albicans*	*Candida albicans*
NS	6	5	2	4	4	5
[Ni(II)(NS)$_2$]	21	22	18	21	16	20
[Cu(II)(NS)$_2$]	22	24	21	23	18	23
Reference	34	36	27	24	31	29

3. Conclusion

Condensation reaction of *S*-benzyldithiocarbazate with cinnamaldehyde afforded the bidentate NS donor ligand. The reaction of the ligand with Ni (II) and Cu(II) generated colored complexes. The Schiff base ligand and its metal complexes have been characterized on the basis of elemental analysis, spectroscopic data (FT-IR, UV-vis, and ESI-MS) as well as the molar conductivity and magnetic susceptibility measurements. Square planar structures of the metal complexes have been proposed. The synthesized metal complexes, in comparison to the uncomplexed Schiff base ligand, were screened for their biological activity against pathogenic bacterial species. The activity of the Schiff base complexes became more pronounced when coordinated with metal ions.

4. Acknowledgements

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5. Conflicts of interest

The authors declared no potential conflicts of the interest with respect to the research and authorship of this article.

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