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Synthesis, Spectroscopic Characterization and Biological investigation of Cu^{2+}, Ni^{2+} and Zn^{2+} complexes with S-p-chlorobenzyl-β-N-(4-dimethylaminophenyl) methylenedithiocarbazate

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ABSTARCT

The complexes of $M(Db\text{-}scdtc)_2$ type [$Cu(Db\text{-}scdtc)_2$, $Ni(Db\text{-}scdtc)_2$, and $Zn(Db\text{-}scdtc)_2$] were synthesized by reaction of S-p-chlorobenzyl-β-N-(4-dimethylaminophenyl)methylenedithiocarbazate (H-Db-scdtc) and metal acetate salts in which Db-scdtc is anionic form of S-p-chlorobenzyl-β-N-(4-dimethylaminophenyl)methylenedithiocarbazate. The complexes and ligand were characterized by UV-Vis, Infrared spectroscopy, NMR (H^1 and C^{13}), elemental analysis and Molar conductance, and Magnetic moment. The Magnetic moment Data suggest that central zinc metal ion in zinc complex forms a four-coordinate tetrahedron with two bidentate Schiff base ligands shows tetrahedral geometry, while copper and nickel complexes exhibited square planar geometry. The biological activity experiment adopted by the well diffusion method. Preliminary studies showed that the dithiocarbazate ligand has a significant inhibitory effect on the proliferation of pathogenic strains compared to the metal complexes. Moreover, in metal complexes Cu^{2+} complexes showed prominent antibacterial activity against *Salmonella typhi and Staphylococcus aureus*In addition, Ni^{2+} complex exhibited good antifungal activity against *Candida albicans*.

Keywords: Schiff base, Antibacterial activity, Antifungal activity, Ligand, Metal complexes.

INTRODUCTION

In recent years, the Schiff base of hydrazine -carbodithioate with nitrogen and sulfur donor atoms and its coordination compounds gained people's interest. Curtius[1] was the first to discover dithiocarbazic acid. Since then, various S-alkyl/aryl-esters have been derived for their various biological uses such as antifungal activity[2–4], antibacterial[5–7], antiamoebic[8], anti-tripansoma cruzi[9] anti-inflammatory[10], anti-tumour[11–14], anti-inhibitory cell migration activities[15]. Aside from medicinal applications, dithiocarbazate ligands also can be utilized in the different areas of electronic engineering such as solar cell apparatuses[16], nano-materials[17], and non-linear optical materials[18]. The combination hard-soft character of N, S donor atoms of dithiocarbazates extremely desirable for coordination, two nitrogen out of four nitrogen atoms which are sterically unavailable for coordination with metal ions and two are easily for coordination with metal ions[19]. The dithiocarbazate ligand can coordinate with most of metal ions by carrying their sterically available nitrogen sulfur donor atoms[20]. With metal ions, free dithiocarbazate ligand are known to act as nitrogen sulphur donors, forming five-member chelate rings[21–23]. Introduction or replacement of a single substituent may lead to altered the properties of the ligands and complex to a great extent[24]. In addition, when metal ions coordinate with biologically active compounds (dithiocarbazate ligand) may increase their biological activities[25–29]. However, some Schiff bases with NS donor ligands and complexes are also suitable as a catalyst[30,31], pigments, dyes, urease inhibitors[32] as well as corrosion inhibitors[26]. Schiff bases ligands played a vital part in the expansion of inorganic biochemistry and optical materials, and they show a promising role in the growth of coordination chemistry[33]. In addition, because of their unique electrical characteristics, the heterocycle Schiff base complexes formed from amino and carbonyl compounds including oxygen, nitrogen, and sulphur donor atoms have been extensively studied[34].

Taking into the consideration overhead discussed the importance of dithiocarbazate ligand and metal complexes, the current work represents synthesis, spectroscopic characterization, and biological assay of M(Db-scdtc)$_2$ type complexes with s-p-chlorobenzyl-b-N-(4-dimethylaminobenzylidene) hydrazinecarbodithioate ligand. Synthesized compounds have been studied *In vitro* against four pathogens and one fungus strains.

EXPERIMENTAL

Reagents and instrumentation

Reagent and Chemicals: Potassium hydroxide (KOH), 80% hydrazine hydrate ($N_2H_4.H_2O$), carbon disulfide (CS_2), p-chlorobenzyl chloride, p-dimethylaminobenzaldehyde, and acetate salts such as copper acetate, Nickel acetate, and Zinc acetate were chemically Pure and obtained from SRL (India). The reagents needed to determine biological activity are made and provided by the department of biotechnology, Shivaji University, Kolhapur.

Instrumentation: UV-Visible spectra were performed using a Shimadzu spectrophotometer. FTIR spectra of dithiocarbazate ligand and complexes were recorded using Lambda FTIR-7600 infrared spectrometer (4000-400 cm^{-1}). The ^{1}H, ^{13}C-NMR spectra, were taken using Bruker AV III HD NMR in (500 MHz) in $CDCl_3$ with TMS as internal standard at CIF center, Savitribai Phule Pune University, Pune. The Magnetic susceptibility balance was utilized to determine magnetic moments of compounds by Gouy's Method. Further, A CHNS microanalyzer was used to record microanalyses for the elements C, H, N, and S.

Preparation of (S-p-chlorobenzyl-β-N-(4-dimethyl -aminophenyl) methylenedithiocarbazates)

The ligand (1) was synthesized by adopting the following procedure[9,13]. The mixture of potassium hydroxide (2.8 g, 50 mmol) and 80% hydrazine hydrate (2.5 mL, 50 mmol) in 40 mL ethanol cooled down to 5°C, the solutions of carbon disulfide (3.8 g, 50 mmol) and p-chlorobenzyl chloride (8.05 g, 50 mmol) were added one by one with stirring and cooling in the ice bath. After sufficient time to the resultant white precipitate, a solution of p-dimethylaminobenzaldehyde (7.45 g, 50 mmol) in ethanol (20 mL) was added and the final solution was refluxed for 45 minute. A yellow precipitate was obtained, which then filtered off, washed, dried over silica gel to obtain the yellow powder.

S-p-chlorobenzyl-β-N-(4-dimethylaminophenyl) methylenedithiocarbazates, (1)

(H-Db-scdtc) yield is 76%, m.p. 188°C Element analysis according to $C_{17}H_{18}ClN_3S_2$, calculated value (%): C 56.11, H 4.99, N 11.55, S 17.62; Measured value (%): C56.09, H 4.98, N 11.58, S 17.62.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H, -NH), 7.81 (s, 1H, CH=N), 7.58 (d, J = 8.9 Hz, 2H, Ar), 7.39 (d, J=8.4 Hz, 2H, Ar), 7.30 (d, J=8.4 Hz, 2H, Ar), 6.68 (d, J=8.9 Hz, 2H, Ar), 4.56 (s, 2H, S-CH_2), 3.04 (s, 6H, -$N(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.04 (s), 152.36 (s), 147.04 (s), 135.19 (s), 133.19 (s), 130.76 (s), 129.63 (s), 128.70 (s), 120.08 (s), 111.72 (s), 40.10 (s), 38.35 (s).

Synthesis of complex

The complexes (2-4) prepared by reaction between acetate salts of Copper, Nickel, and zinc [$C_6H_4CuO_4 \cdot H_2O$ (0.100 g, 0.5 mmol), $C_6H_4NiO_4 \cdot 2H_2O$ (0.124 g, 0.5 mmol), $C_6H_4ZnO_4 \cdot 4H_2O$(0.129 g, 0.5 mmol)] with Schiff base (0.363 g, 1 mmol) in an appropriate amount of ethyl alcohol solvent. The final solutions of ligand and metal salts were refluxed for 45 minute. The precipitates obtained were filtered off from the mother liquor washed, dried over silica gel.

$Cu(Db\text{-}scdtc)_2$(2): The yield is 64 %, Bluish black, melting point: 212°C. Elemental analysis is calculated according to $C_{34}H_{34}Cl_2N_6S_4Cu$, calculated value (%): C 51.80, H 4.31, N, 10.66 S 16.25; found value (%): C 51.78, H 4.30, N 10.67, S 16.25.

^1H NMR (500 MHz, $CDCl_3$) δ 9.65 (s, 2H), 7.32 (d, J=8.6 Hz, 4H), 7.22 (d, J=8.2 Hz, 4H), 7.07 (d, J=8.2 Hz, 4H), 6.91 (d, J=8.6 Hz, 4H), 4.29 (s, 4H), 2.93 (s, 12H).

$Ni(Db\text{-}scdtc)_2$(3): The yield is 68%, greenish black, melting point: 208°C. Elemental analysis is calculated according to $C_{34}H_{34}Cl_2N_6S_4Ni$, calculated value(%): C 52.12, H 4.34, N 10.71, S 16.35 ; found value(%): C 52.15, H 4.33, N 10.73, S 16.35.

^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 2H), 7.46 (d, J = 8.7 Hz, 4H), 7.39 (d, J = 8.1 Hz, 4H), 7.31 (m, J = 8.1 Hz, 4H), 6.63 (d, J = 8.7 Hz, 4H), 4.34 (s, 4H), 3.07 (s, 12H).

Zn(Db-scdtc)2 (4): The yield is 65%, pale yellow, melting point: 213°C, Elemental analysis is calculated according to $C_{34}H_{34}Cl_2N_6S_4Zn$, calculated value(%): C 51.68, H 4.30, N 10.64, S 16.21; found value(%): C 51.69, H 4.28, N 10.66, S 16.33.

^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 2H), 7.66 (d, J = 8.9 Hz, 4H), 7.30 (d, J = 8.4 Hz, 4H), 7.24 (d, J = 8.4 Hz, 4H), 6.69 (d, J = 8.9 Hz, 4H), 4.26 (s, 4H), 3.04 (s, 12H)

Biological activity experiment

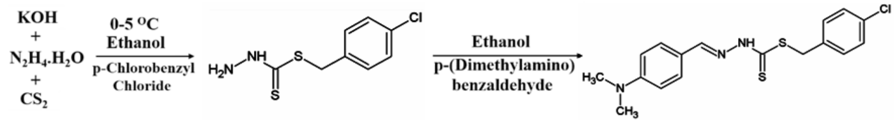
The antimicrobial analysis of the dithiocarbazate ligand and complexes of metal against four pathogenic bacteria (*Gram-negative Salmonella typhi, Proteus vulgaris* and *Gram-positive Staphylococcus aureus, Bacillus cereus*) and one fungus (*Candida albicans*) were investigated by the agar well diffusion technique[35,36]. Pipetting and evenly distributing inoculums over nutritional agar put in Petri plates for the bacteria resulted in a lawn of microorganisms. Similarly, for anti-fungal activity, the fungal suspension was dispersed on a potato dextrose agar plate with the help of a sterile glass spreader to achieve lawn growth. Well of a diameter size of 6 mm were filled with the compound in DMSO stock solution. To prepare stock solutions 2 mg of each chemical was dissolved in 1 mL of DMSO to make the stock solution. 25 µL of the stock solution with 0.1 µL sensitive micropipette introduced into a well of Petri plates. The prepared plates for biological analysis were incubated for one day (24 h) at 30°C for bacteria and four days at 37°C for fungi. The plates were inverted and stacked on top of each other. Kanamycin and nystatin (Sigma-Aldrich, Germany) (1.0 mg ml^{-1}), and DMSO were used as control. The investigation of antimicrobial potential depended on the extent of the inhibition zone on the nutrient agar medium surface around the well. The zones of inhibition created by metal complexes and ligands were (diameter in mm) compared to conventional antibiotics (Kanamycin 30 µg /well and Amoxycillin).

RESULTS AND DISCUSSION

Syntheses and characterization

Ethanoic solution of S-chlorobenzyl dithiocarbazate (SCDTC) and p-Dimethylamin-obenzaldehyde were refluxed (1:1 molar ratio) under stirring to produce the Schiff base (Scheme 1).

In this type of Schiff base, the molecule exists in the thiol form or thione form, Or coexist in both forms shown in Figure 1.



Scheme 1. Synthetic route of dithiocarbazate ligand

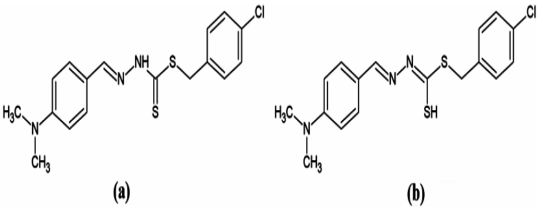


Fig. 1. Tautomeric forms of ligand (1) (H-Db-scdtc) a) Thione form b) Thiol form

Further reaction of the dithiocarbazate ligand with metal salts [Nickel(II), Zinc(II), and Copper(II), salts] in a 2:1 molar ratio of ligand to metal respectively produced the respective metal chelates (M(Db-scdtc)$_2$) Figure 2.

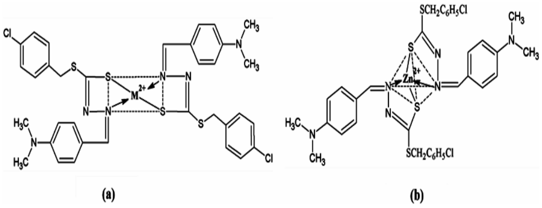


Fig. 2-a) Square planar structure of complex (M=Cu(II), Ni(II) and b) Tetrahedral structure of Zn(II) complex

The experimental section presents physical (such as yield, color, melting point, magnetic susceptibility, solution molar conductivity) and spectroscopic characterizations. Their suggested structures are in good agreement with their physicochemical and spectroscopic data.

The infrared spectra

The IR spectrum of the dithiocarbazate ligand shows the presence of a medium intensity peak at 3124 cm^{-1} predicted to ν(N-H) fragment that was vanished in metal complexes, indicating that dithiocarbazate ligand underwent complexation through thiolate ion Fig. 3[37]. In addition, complexes do not show a peak near 3124 cm^{-1} which indicates that, when the ligand forms a complex, it removes protons on α nitrogen. while, missing of ν(S-H) peak near 2570 cm^{-1}, indicating that the S atom has lost its proton and becomes coordinated with the metal ion Cu, Ni, and Zn[38]. The strong absorption peak at 1603 cm^{-1} can be predicted as azomethine (C=N) moiety of ligand while, in metal complexes, the same absorption band was shifted to lower frequency due to coordination of azomethine fragment with metal ions[16,39]. In addition, the absorption peak ν(N-N) band assigned at 1018 cm^{-1}, also shifted to a higher frequency (1025-1026 cm^{-1}) indicate the coordination of azomethine fragment with metal ions. The characteristic absorption peak at 1078 cm^{-1} predicted for C=S Stretching vibration peak while the absence of the same peak in metal complexes spectra suggests that, thiolate sulfur complexation with particular metal ions. The absorption peak of ν(N-H) and ν(C=S) stretching frequency in metal complexes become disappeared in metal complexes spectra indicate that the ligand (N-H) proton first undergoes tautomerism of thione to thiol functionality followed by deprotonation and combination with metal ions. In metal complexes, a new absorption peak was observed in the range of 473-501 cm^{-1} assigned for the M-N bond while another low absorption peak in the range of 417-421 cm^{-1} was predicted for the M-S bond which shows M-N and M-S bond formation in complexes.

Table 1: Significant IR bands of dithiocarbazate ligand and complexes

Sr.No.	Compounds	(N-H)	(C=S)	(C=N)	(C-S)	(M-N)	(M-S)
1	H-Db-scdtc	3124	1089	1603	822	--	--
2	Cu(Db-scdtc)$_2$	--	--	1567	800	501	418
3	Ni(Db-scdtc)$_2$	--	--	1567	803	487	417
4	Zn(Db-scdtc)$_2$	--	--	1586	808	473	421

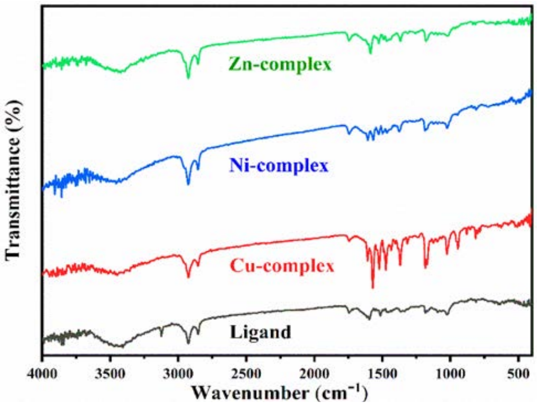


Fig. 3. FT-IR spectra of Ligand and complexes

NMR

H^1-NMR

The (N–H) proton was given a wide singlet at 10.65 ppm by ^{1}H NMR of the dithiocarbazate ligand (1) as shown in Fig. 4[40]. In most cases, these compounds can be found in solution as a combination of thione and thiol tautomeric forms. It's worth noticing that the SH proton shows no signal for dithiocarbazate ligand (1) (around 4.0 ppm), implying that the thiol form is not present.[37,40]. The lack of an NH signal in the ^{1}H NMR spectra of complexes (2-4) suggested that, the group (-NH) underwent tautomerism with C=S moiety followed by deprotonation of thiol fragment during the complexation process[37,40,41]. The azomethine proton of ligand had another singlet at 7.81 ppm, in complexes same signal transferred to the upfield, demonstrating coordination of ligand through nitrogen atom of the azomethine moiety. The multiple signals for the phenyl rings (7.58, 7.39, 7.30, and 6.68 ppm) were observed as a doublet in ligand and complexes spectra, singlet bands for the S-CH_2 (4.56 ppm) in the ligand spectrum revealed no notable change in the spectra of complexes as shown in Fig. 4,5 and 6. The protons of dimethylamino moiety show singlet signal at 3.04 ppm in ligand spectrum which remains nearly the same position in complexes spectra.

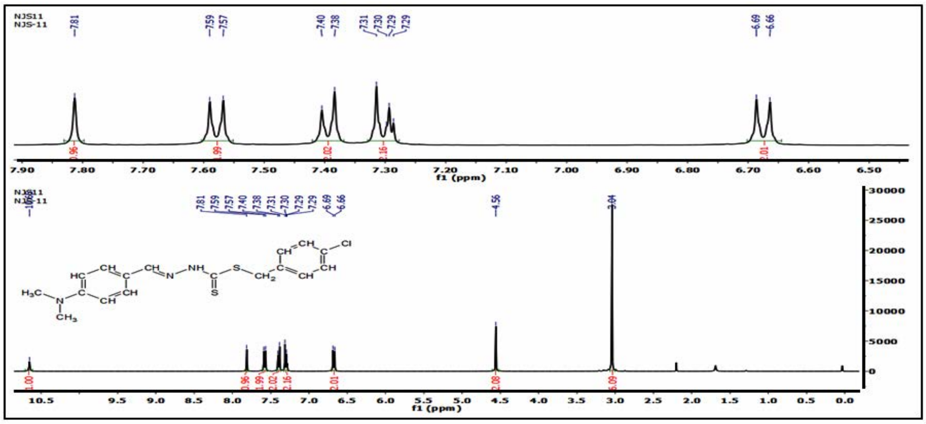


Fig. 4. ^1H NMR spectra of Ligand

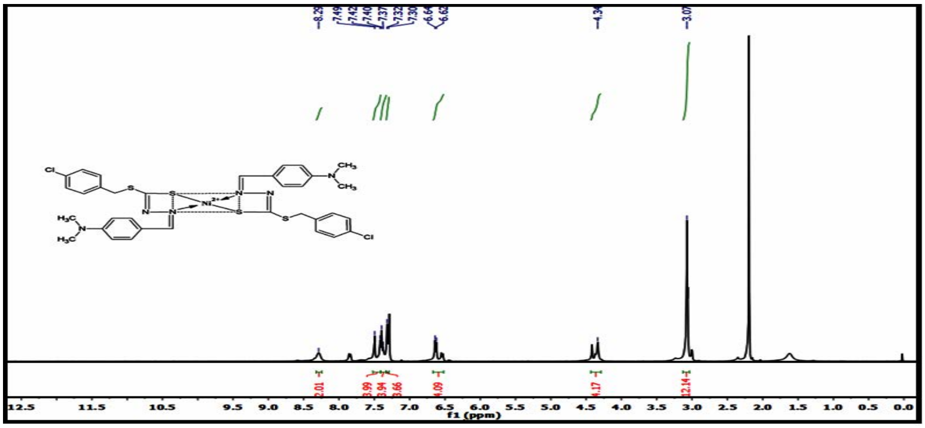


Fig. 5. ^1H spectra of Ni-Complex (3)

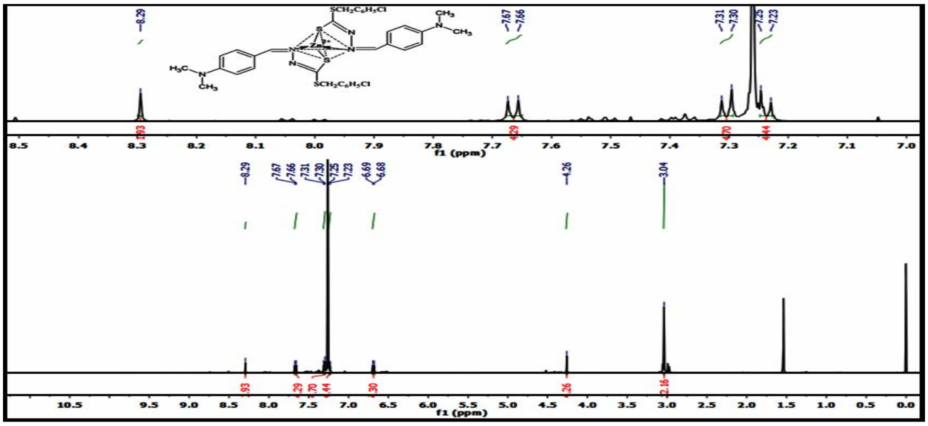


Fig. 6. ^1H spectra of Zn-Complex (4)

^{13}C NMR

In ^{13}C NMR spectra of dithiocarbazate ligand of SCDTC showed peaks at 196.04 for C=S and 147.04 ppm for C=N moiety of carbon respectively as shown in Fig. 7. The peaks observed in the ^{13}C spectrum of ligand due to methylene group (S-CH$_2$), the methyl group of dimethylamino moiety of dithiocarbazate ligand appear at 40.10, 38.35 ppm respectively, while aromatic carbons show peaks at 111.72,120.08,128.63,128.70,130.76,133.19,135.19 and 152.36 ppm.

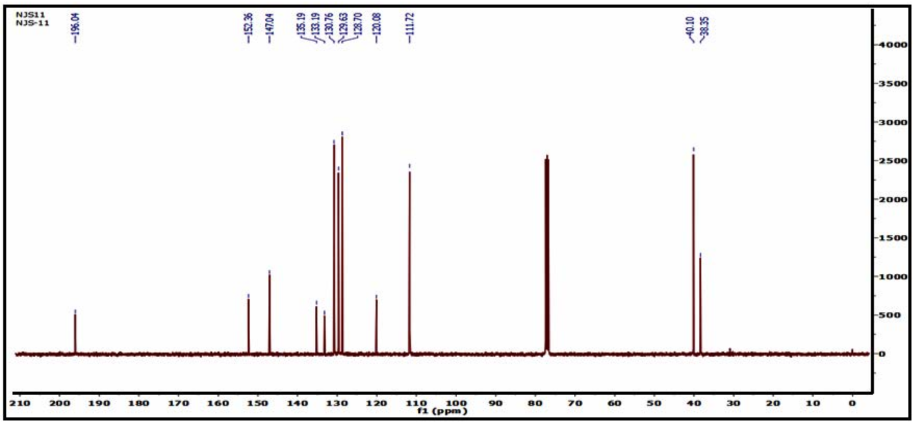


Fig. 7. ^{13}C NMR spectra of Ligand

Table 2: UV-Visible data of ligand and complexes

Sr.No.	Compounds	λ_{Max}(nm)			
		Band-I	Band-II	Band-III	Band-IV
1	H-Db-scdtc	279	330	392	467
2	Cu(Db-scdtc)$_2$	283	319	401	--
3	Ni(Db-scdtc)$_2$	277	352	392	--
4	Zn(Db-scdtc)$_2$	276	332	380	--

Electronic Spectra, Magnetic moment and Molar conductance

Electronic Spectra

The electronic spectra of dithiocarbazate ligand and metal complexes was shown in Fig. 8. The electronic spectra of dithiocarbazate ligand (1) show various bands of different intensity at 279, 330, 392, 467 nm, out of four, the first two are tentatively predicted for ($\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition) of azomethine fragment while remaining last two bands assigned for ($\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition) of dithiocarbazate fragment[42] The dithiocarbazate transitions ($\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$) in the free ligand were combined into a single wideband at 380-401 nm in its complexes after complexation, implying coordination through the thiolate sulfur[43] As seen in Fig. 5, the Copper complex (2) exhibited three d-d bands at 283, 319 nm generally predicted for $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$ transitions, characteristic of square-planar geometry transition. Additionally, with an effective magnetic moment of 1.94 BM, equivalent to one unpaired electron. Further, Nickel complex (3) exhibits three bands at 277, 352, 392 nm which generally corresponds to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$, $^1A_{1g} \rightarrow {}^1E_g$ transitions characteristic of square-planar geometry[1,2,44,45] At 332 nm, the charge-transfer band of the Zinc complex (4) was identified, indicating that the complex is diamagnetic, while magnetic moment suggest tetrahedral geometry of complexes.

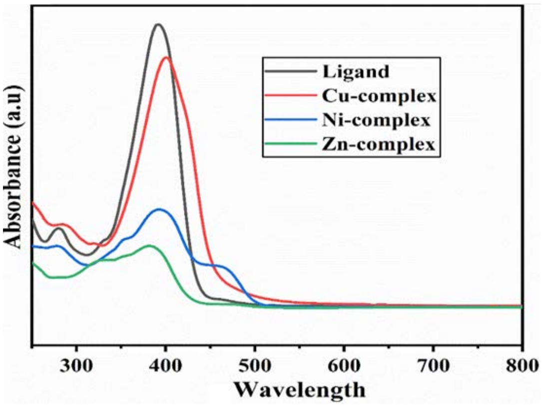


Fig. 8. UV spectra of Ligand and complexes

Molar conductance and Magnetic moments

The Magnetic moment and molar conductance data of dithiocarbazate ligands (H-Db-scdtc) and M(Db-scdtc)$_2$ complexes were mentioned in Table 2. The data showed that of both ligand and M(Db-scdtc)$_2$ complexes of nickel, copper, and zinc had the low molar conductivity, suggesting non-electrolytic nature[46]. The magnetic moment data showed that Cu(Db-scdtc)$_2$ (2) complex was paramagnetic behaviour (magnetic moment, 1.94 B.M), while Ni(Db-scdtc)$_2$ complex (3) and Zn(Db-scdtc)$_2$ complex (4) both were diamagnetic in nature. Overall data of magnetic moment indicate that the Cu(Db-scdtc)$_2$ and Ni(Db-scdtc)$_2$ complexes have square planar geometry with two dithiocarbazate ligands present at four stereochemical sites in the structure while Zn(Db-scdtc)$_2$ complex has square planar geometry.

Bioactivity analysis

The complexes were tested for antibacterial sensitivity against three microbial pathogens and one fungus. Table 4 shows the test findings as a clear zone of inhibition in diameter (mm).

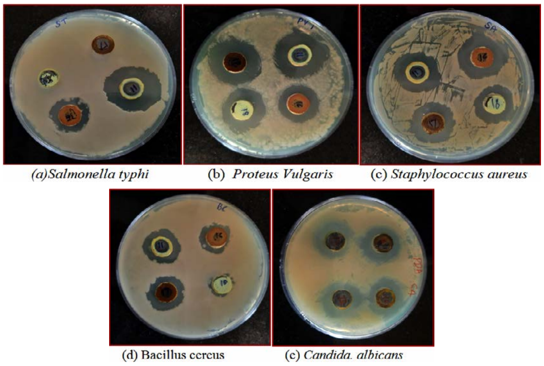
Table 3: Molar conductance and magnetic moments data of ligands and complexes

Sr.No	Compounds	Molar Conductance, (Ω^{-1} cm^2 mol^{-1})	μeff, (B.M)
1	H-Db-scdtc	8.12	--
2	Cu(Db-scdtc)$_2$	4.77	1.94
3	Ni(Db-scdtc)$_2$	4.54	Dia
4	Zn(Db-scdtc)$_2$	5.75	Dia

Table 4: Biological activity of the dithiocarbazate ligand and metal complexes.

Sr. No.		Compounds zone of inhibition (diameter in mm)				
		Gram-ve		*Gram+ve*		Fungi
		S. typhi	*P. vulgaris*	*S. aureus*	*B. cereus*	*C. albicans*
1	H-Db-scdtc	16	13	15	14	15
2	Cu(Db-scdtc)$_2$	14	10	16	11	16
3	Ni(Db-scdtc)$_2$	-	12	13	12	18
4	Zn(Db-scdtc)$_2$	-	11	13	8	14
5	Reference	20	22	23	24	23

The tested compounds were investigated against four bacteria (two *Gram-negative Salmonella typhi, Proteus vulgaris* and two *Gram-positive Staphylococcus aureus, Bacillus cereus*) and one fungi *C. albicans* as shown in Fig. 9. The results showed that ligand and complexes had a narrower inhibition zone than the conventional medicines (kanamycin), implying that they are less susceptible to organisms. The data of antibacterial potential of ligand (1) shows inhibition zone in the range of 13-16 mm and antifungal (15 mm) while Cu-complex (2) exhibited inhibition zone in the range of 10-16 mm and antifungal (16 mm). Additionally, Ni-complex (3) exhibited inhibition zone in the range of 12-13 mm but it becomes inactive against *S. typhi* and shown strong antifungal activity against *C. albicans* (18 mm). The Zinc complex (4) exhibited inhibition zone in the range of 08-13 mm but becomes inactive against *S. typhi* and shown strong antifungal activity against *C. albicans* (14 mm). The results show that the complexes had lesser or sometimes same activity than the free ligand implying that the ligand's biological potential has been reduced by its combination with these metal ions. In addition both ligand and metal complexes showed moderate to good antimicrobial activities and prominent antifungal activity. In metal complexes, the Nickel(II) (3) and zinc(II) (4) complexes demonstrated moderate to good activity, whereas the Copper(II) (2) complexes demonstrated strong activity to the tested pathogens. The ligand (1) and Nickel complexes (3) show moderate activity against fungal strain. However, the reason of alteration of (increased or decreased) antibacterial and antifungal activity of complexes of metal when compared to the free ligand has been thoroughly investigated. In addition, due to the incorporation of metal in complexation with ligands, complexes (2-4) exhibited lower or sometimes nearly same activity for all evaluated analyses, which contributes to antimicrobial and antifungal activity.


(a)*Salmonella typhi* (b) *Proteus Vulgaris* (c) *Staphylococcus aureus*

(d) Bacillus cereus (e) *Candida. albicans*

Fig. 9. Antimicrobial activity of ligand (1) i.e (11), Cu-Complex (2) i.e (16), Ni-Complex (2) i.e (17) and Zn-Complex (4) i.e (18) shows against selected bacteria and fungi

CONCLUSION

In this article, we have reported synthesis, characterization, and an bioactivity analysis of dithiocarbazate ligand, H-Db-scdtc)$_2$ (1) and Cu(Db-scdtc)$_2$ (2), Ni(Db-scdtc)$_2$, and Zn(Db-scdtc)$_2$ (4) complexes. The spectroscopic characterisation and magnetic susceptibility data of Cu(Db-scdtc)$_2$ (2), Ni(Db-scdtc)$_2$ (3) complexes showed square planar geometry, while Zn(Db-scdtc)$_2$ complexes exhibited tetrahedral geometry. The ligand (1) occurs in thione-thiol tautomeric form. It went through thiol tautomerism, deprotonation then combination with corresponding metal ions, producing bis-chelated M(Db-scdtc)$_2$ complexes. The dithiocarbazate ligand formed four coordinate inner complexes by bonding with metal ions in a uni-negative bi-dentate state. Further, dithiocarbazate ligand (1) show superior bio-activity responses when compared to the metal complexes and amongst the complexes, copper(II) complex show good antibacterial activity against *S. typhi, S. aureus* than other complexes. The synthesized ligand and metal complexes show prominent antifungal activity, out of which Nickel complexes (3) exhibited higher antifungal activity.

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Conflict of Interest

No conflict of interest was declared by the authors.

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