



Syntheses, physicochemical characterization, antibacterial studies on potassium morpholine dithiocarbamate nickel (II), copper (II) metal complexes and their ligands



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ARTICLE INFO

Keyword:
Pharmaceutical chemistry

ABSTRACT

Organic molecule dithiocarbamate transition metal complexes are novel and very attractive pharmaceutical targets for the management and control of antibiotic resistant bacteria. The direct reaction has synthesized new transition metal nickel (II), copper (II) complexes of potassium morpholine dithiocarbamate ($K^+C_5H_8NOS_2^-$) ligands and characterized by UV-visible spectroscopy, Fourier-transform infrared spectroscopy (FTIR), as well as NMR physicochemical techniques. Antibacterial bioefficacy of the ligand and its metal complexes has been investigated *in vitro* on the growth of Gram-positive (*Staphylococcus aureus* MTCC 737, *Bacillus cereus* MTCC 1272) and the Gram-negative (*Listeria monocytogenes* MTCC 657, *Shigella flexneri* MTCC 1457) bacteria. The obtained electronic spectral bands are characteristic and consistent with the proposed composition of the ligand as well as its metal complexes. It also provides a further example of the bidentate coordination of dithiocarbamate ligands. Absorption peak values of FTIR are characteristic of the ligand as well as dithiocarbamate group molecules and exhibit their metal coordination. NMR 1H signal variations also correlate with the coordination mediated chemical shifts. Both the metal complexes showed significant antibacterial activity. However, enhanced antimicrobial activity of the ligands than metal complexes against Gram positive and Gram negative bacteria were observed. Thus, further study on this approach could pave a way for the development of dithiocarbamate-metal complex based antibacterial agent.

1. Introduction

Antimicrobial resistance is an increasingly serious global health security threat. Common bacteria's high rates of resistance make standard treatments no longer work; harder or impossible to control infections; increases the risk of infection spread to others; prolongs the illness and hospital stays with added economic and social costs; and the danger of death greater [1]. The upsurge of this most dangerous phenomenon indicates that our past scientific approaches are not adequate to address this challenge and warrants new research strategies as well as tactics for their minimization and so improving global health [2]. Microbiologists acknowledge that Gram-negative bacteria own mechanisms

like efflux pump, a mechanism by which it extrudes strange substances like antibiotics out of the cell and possess enzymes like β -lactamases having the capability of rendering drugs inactive. In the same way, the Gram-positive bacteria's thick peptidoglycan layers protect their cytoplasmic membrane. Hence, during the search for new antimicrobial compound controlling multiresistant bacterial infections due consideration should be given to new activation target drug synthesis and known antimicrobial compound activity potentialization [3]. Bioinorganic as well as medicinal chemists are continuously searching for new ways to attack these multidrug-resistant bacteria through some means. Design and synthesis of metal complexes having required antimicrobial activities. One among them are the development of metal complexes of

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biologically active ligands since they offer the dual possibility of both ligands and metal ions ability to interacting pathogen's life cycle at various levels [4].

Nowadays a wide range of chemistry developed around the versatile monoanionic 1,1-dithio ligand dithiocarbamates (R_2CNS_2) [5] draws a great deal of attraction owing to their unique chemistry and extensive application leading their production in vast quantities [6]. Currently, they are consumed to a tune of up to 25,000–35,000 metric tons throughout the world yearly due to their wide range of uses and applications. These small organic molecule dithiocarbamates (DTC) shows not only a strong inorganic species chelating ability but also the extensive usage in the agricultural industry for more than 80 years as pesticides, fungicides and now a day as vulcanization accelerators in the rubber industry. Antibacterial, antituberculosis, antifungal and antioxidant properties make them as biologically significant more valuable compounds [7]. DTCs complexes are known for their stupendous structural features, varied industrial and biological applications [8]. Recent literature survey evidences some reports on the antifungal, antibacterial, anti-alkylation anticancer and apoptosis-inducing activity of these metal dithiocarbamate complexes of the mixed ligands. Some developed metal dithiocarbamates are now available as radiopharmaceuticals and diagnostic kit components for medicinal and diagnostic use [9]. Their d^{10} configuration element complexes stand for recent year's extensively studied large and interesting group of inorganic compounds [8].

Results from various studies on metal complexes, especially dithiocarbamates and the necessary knowledge of their biocide action still justify newly synthesized metal-containing dithiocarbamate complex physical, chemical [10] and antibacterial properties. Given this, a new series of transition metal Ni (II), Cu(II) complexes of morpholine dithiocarbamate (MDTC) ligands were prepared and characterized by elemental analysis, conductivity, and magnetic measurements. *In vitro* antibacterial activity screening of the ligands and transition metal complexes against the pathogenic bacterial strains was also carried out towards the exploration of new prokaryotic targets novel molecules.

2. Materials and methods

2.1. Chemicals and culture media

All chemicals were analytical grade and were purchased from Sigma–Aldrich Co. They were all used as received from the sources without further purification. The bacterial media nutrient broth and Muller Hinton agar were purchased from Hi-Media, Mumbai, India.

2.2. Preparation of nickel (II) and copper (II) – potassium morpholine dithiocarbamate ($K^+C_5H_8NOS_2^-$) complexes

The nickel(II)- $K^+C_5H_8NOS_2^-$ complex was prepared by adding an aqueous 0.01M nickel (II) chloride ($NiCl_2 \cdot 6H_2O$; 2.3771 g) solution to potassium morpholine dithiocarbamate (1:2 M ratio) with stirring [11]. Similarly, copper (II)- $K^+C_5H_8NOS_2^- \cdot 2H_2O$ complex was synthesized using 0.01 M copper sulfate solution ($CuSO_4 \cdot 5H_2O$; 2.49 g). The resulting green colored nickel - potassium morpholine dithiocarbamate ($Ni^{2+} \cdot K^+C_5H_8NOS_2^-$) and the brown colored copper -potassium morpholine dithiocarbamate ($Cu^{2+} \cdot K^+C_5H_8NOS_2^-$) crystalline complexes were separated by precipitation, filtered, and washed several times with hot distilled water. The precipitates were then dried in a desiccator over anhydrous $CaCl_2$. The solid complexes so obtained recrystallized from acetone and again dried in a desiccator.

2.3. Synthesis of potassium salt of morpholine dithiocarbamate ($K^+C_5H_8NOS_2^-$) ligand

The ligand ($K^+C_5H_8NOS_2^-$) was prepared by the direct reaction as described by Ramos and Cavalheiro [12], by adding an ice-cooled 0.1 M carbon disulfide (CS_2 ; 7.6 g) to an ice-cooled 0.1M morpholine (C_4H_9NO ;

8.7 g) taken in a 250 ml beaker and well. The content of the beaker was cooled to 5 °C in an ice bath. To this mixture, a solution of 0.1 M potassium hydroxide (KOH; 5.61 g) which was prepared separately with a minimum quantity of distilled water and stirred vigorously for 1 h in cold condition. The resulting colorless potassium morpholine dithiocarbamate solid was filtered, washed with ether and dried. The dry solid was then recrystallized by dissolving in a minimum quantity of isopropyl alcohol. The water of recrystallization was removed by drying in vacuum over phosphorus pentoxide (P_2O_5) first at atmospheric temperature and then at 50 °C for 8 h.

2.4. Characterization of ligand-metal complexes

Potassium morpholine dithiocarbamate metal complexes were characterized by the physicochemical methods involving carbon (C), nitrogen (N), hydrogen (H) elemental analysis, UV-Visible, FTIR and 1H NMR spectroscopic techniques. Elemental Vario EL-III elemental analyzer (Elementar Analysensysteme GmbH, Germany) was used for C, H and N analysis. Electronic spectral changes in electron distribution between ligand-metal in complexes were recorded in the wavelength range of 200–700 using UV-Visible BioSpectrophotometer BL-198 (Elico Ltd, India). The FTIR spectral data corresponding to important functional groups of ligand-metal complexes were recorded using a Perkin-Elmer RXI IR (Perkin-Elmer, USA) spectrometer in the range of 4000–400 cm^{-1} using KBr pellet technique. The 1H NMR chemical shifts were recorded using Bruker AMX-400 NMR spectrometer (Bruker, Rheinstetten, Germany) employing TMS as reference and d_6 -DMSO as a solvent.

2.5. Antibacterial activity of synthesized potassium morpholine dithiocarbamate and metal complexes

The antibacterial activity of nickel and copper complexes of $K^+C_5H_8NOS_2^-$ have been studied on the standard Gram positive *Staphylococcus aureus* MTCC 737, *Bacillus cereus* MTCC 1272 and the Gram negative *Listeria monocytogenes* MTCC 657, *Shigella flexneri* MTCC 1457 bacteria collected from Microbial Type Culture Collection Center, Chandigarh, India. The standard cup-plate method [13] was followed for determining their antibacterial activity. Briefly, inoculums of actively growing logarithmic phase test organisms were prepared by growing them aerobically in nutrient broth (g/L: peptone, 10; beef extract, 10; sodium chloride, 5) at 37 °C for 24 h and adjusting their density using McFarland turbidity standard. The standard drug, control dimethyl sulfoxide (DMSO), and the ligand and the different concentrations of the synthesized ligand – metal complexes were separately added into the wells (6 mm) made on the culture inoculated Muller Hinton agar plates and kept in the refrigerator (8–10 °C) allowing proper diffusion of the compounds. After 2 h of cold incubation, the Petri plates were incubated at 37 ± 2 °C for 18–24 h and the zone of inhibition formed in each test was measured in mm [14].

2.6. Statistical analysis

ANOVA, the analysis of variance (Minitab version 15) was used to analyze the study results, and the differences were considered to be statistically significant at $P < 0.05$. The figures were analyzed using Origin 6.0 (Microcal Software Inc., Northampton, MA).

3. Results

Potassium morpholine dithiocarbamate ligand and two of its transition metal complexes were synthesized by the direct reaction of the ligand potassium morpholine dithiocarbamate ($K^+C_5H_8NOS_2^-$) with nickel (II) chloride and copper sulfate in 2:1 M ratio. Nickel (II) - $K^+C_5H_8NOS_2^-$ complex is green while the copper (II) - $K^+C_5H_8NOS_2^-$ is brown in color. Both were insoluble in water, sparingly soluble in DMSO while the ligand ($K^+C_5H_8NOS_2^-$) is soluble in water. UV-visible electronic

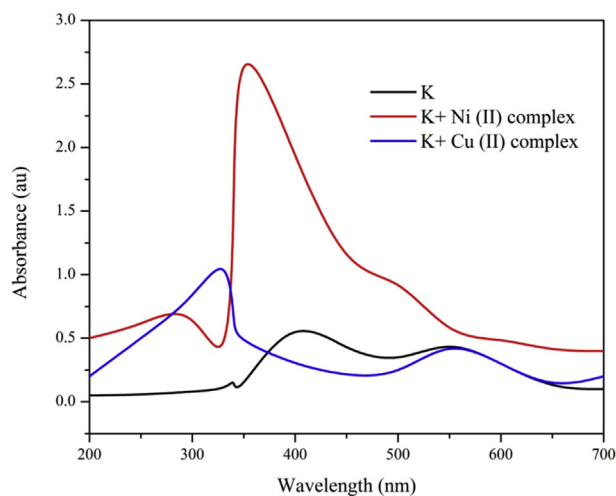


Fig. 1. Electronic absorption UV-vis spectra of the ligand potassium morpholine dithiocarbamate.

spectral, FTIR, and ^1H NMR studies were carried out to characterize the ligand and its metal complexes.

The UV-visible spectra of the ligand potassium morpholine dithiocarbamate and its metal Ni (II) and Cu (II) complexes recorded in dimethyl sulfoxide (DMSO). UV-vis spectra of the ligand ($\text{K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$), its metal nickel ($\text{Ni}^{2+}\text{-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$) and copper ($\text{Cu}^{2+}\text{-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$) recorded in DMSO are shown in Fig. 1. The electronic transitions in the ligands, as well as the ligand-metal charge transfer transitions, are evident from the λ_{max} values observed from their UV-visible spectra: $\text{K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$: 396 nm; $\text{Ni}^{2+}\text{-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$: 342.9 nm, 341.9 nm; $\text{Cu}^{2+}\text{-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$: 334.02 nm.

The FTIR spectra of the potassium morpholine dithiocarbamate transition metal complexes exhibit bands characteristic of the ligand and coordinated dithiocarbamate group molecules. Bands observed in the range 1447–1415 cm^{-1} characterizes $\bar{\nu}(\text{C-N})$ vibration. The asymmetric stretching bands occur in the 1226–1238 cm^{-1} was attributed to $\bar{\nu}(\text{C=S})$ vibration. Another band observed between 1104 and 1148 cm^{-1} was due to the $\bar{\nu}(\text{C-O-C})$ stretching mode whereas the FTIR spectral band observed

around 2854–2877 cm^{-1} was assigned to the $\bar{\nu}(\text{C-H})$ stretching. The bands in the 1104–1148 cm^{-1} ranges are due to the absorption of the KCS_2 group that shows shifts to a higher frequency in both metal complexes (Fig. 2). The FTIR spectrum indicates that both the metal complexes are doublets and DTC act as a bidentate ligand. The positive shifts observed in the $\text{Ni(II)-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$ and $\text{Cu(II)-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$ spectrum shows the coordination between dithiocarbamate ligand and metals through sulfur atoms.

The ligand potassium morpholine dithiocarbamate and its Ni (II) and Cu (II) metal complex ^1H NMR spectrum (Fig. 3) recorded in CDCl_3 solvent shows coordination mediated variations in the ^1H signals. The values for the ^1H signal are in close confirmatory with the values of ligand and its Ni (II) as well as Cu (II) metal complexes. The ^1H NMR spectrum of $\text{K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$ shows presence of aromatic proton in the ring between 6.928 to 7.473 δ . In rings (a) and (b), the proton in the 4-methoxyphenyl group attached to tetrahydro-1, 4-oxazine is observed in the down field 6.928 δ to 7.473 δ ($H_a = 6.928$, $H_b = 6.947$, $H_c = 7.261$, $H_d = 7.455$, $H_e = 7.473\delta$). In ring (c), tetrahydropyran protons are observed at the 1.378 to 4.344 δ . In ring (a) and (b) the proton in the methoxy group attached to 4-methoxyphenyl are shown in the down field 3.823. ^1H NMR of the potassium morpholine dithiocarbamate Ni (II) ($\text{Ni}^{2+}\text{-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$) shows coordination mediated increased conjugation since the signals of the aromatic proton appeared downfield. The signals of the aromatic proton in the ring (a) are observed in the range of 6.978 δ to 7.097 δ . In ring (a) and (b) the proton in the 2-chlorophenyl group attached to tetrahydro-1, 4-oxazine are shown in the down field 6.596 δ to 7.128 δ ($H_a = 6.078$, $H_b = 6.987$, $H_c = 7.018$, $H_d = 7.167\delta$). In ring (c) tetrahydropyran proton is observed at the 1.237 to 4.845 δ . The potassium morpholine dithiocarbamate Cu (II) complex ($\text{Cu}^{2+}\text{-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$) ^1H NMR spectrum also evidences the chemical shift viz. the aromatic proton in the ring (a) are observed in the range of 6.978 δ to 7.137 δ . In ring (a) and (b) the proton in the 2-chlorophenyl group attached to tetrahydro-1, 4-oxazine are displayed in the down field 6.978 δ to 7.137 δ ($H_a = 6.978$, $H_b = 6.998$, $H_c = 7.018$, $H_d = 7.137\delta$). In ring (c), tetrahydropyran protons are observed at the 1.397 to 4.860 δ .

The obtained bacterial susceptibilities to ligand and its metal complexes presented (Fig. 4) shows that both the newly synthesized ligand ($\text{K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$) as well as its $\text{Ni(II)-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$ and $\text{Cu(II)-K}^+\text{C}_5\text{H}_8\text{NOS}_2^-$ complexes possess good antibacterial activity against

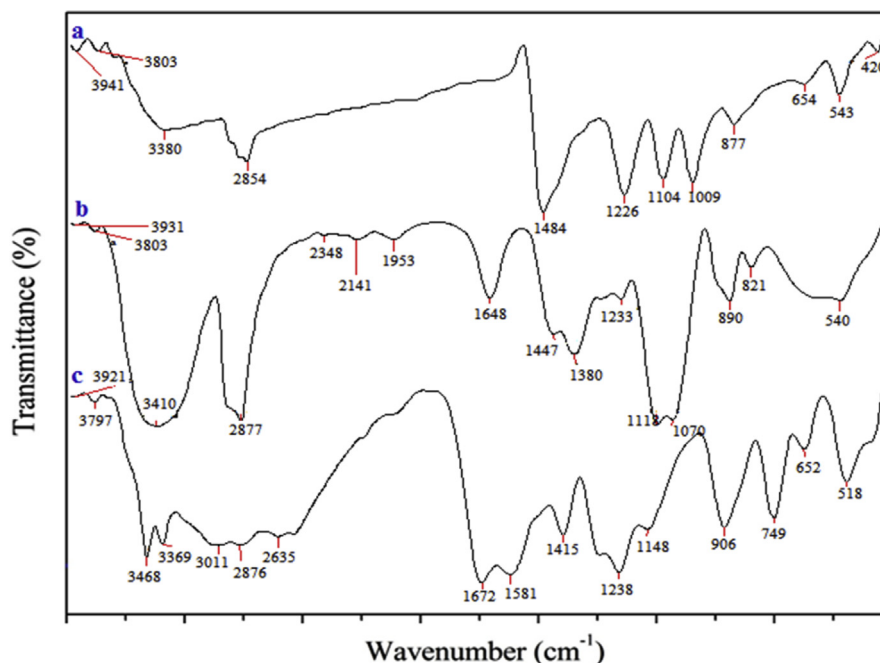


Fig. 2. FT-IR vibrational spectra of the ligand potassium morpholine dithiocarbamate (a), its Ni(II) (b) and Cu (II) (c) metal complexes.

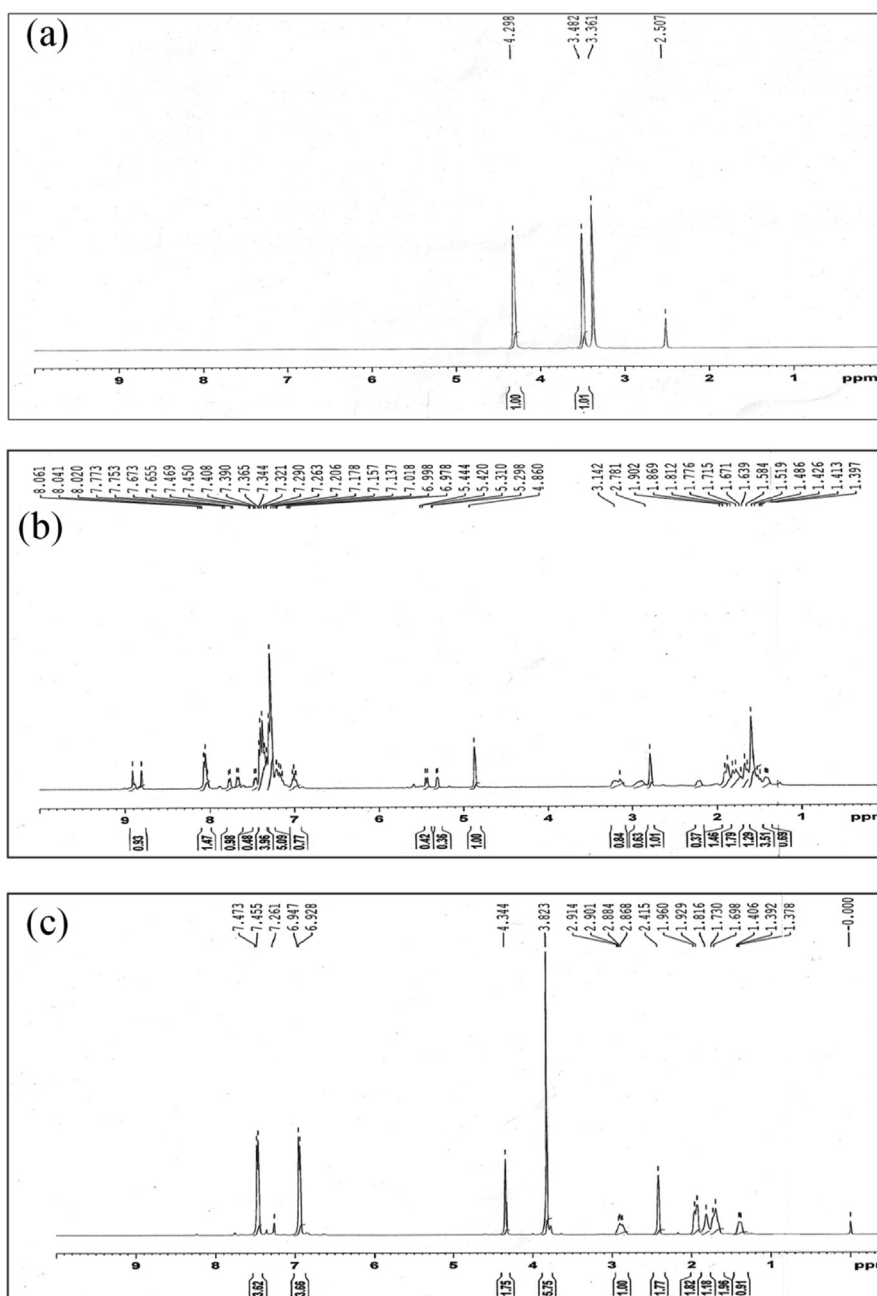


Fig. 3. ^1H NMR spectra of the ligand potassium morpholine dithiocarbamate (a), its Ni-II (b) and Cu (II) (c) metal complexes.

Staphylococcus aureus MTCC 737, *Bacillus cereus* MTCC 1272, *Listeria monocytogenes* MTCC 657, *Shigella flexneri* MTCC 1457. However, an enhanced antimicrobial activity was observed against all the test organisms by the ligands than metal complexes.

4. Discussion

Organic compounds and their metal complexes having nitrogen and sulfur are proven to possess wide-ranging biological activities [15]. One example of them, the dithiocarbamates (DTCs) finds extensive applications in a various pharmaceutical area that exhibits quite much oxidation state metal cation stabilizing ability [10]. Apart, the DTC ligand's complexation with metal ions especially with transition metal ions is attributed mostly to their growing application viz. as fungicides, pesticides, vulcanization accelerations in analytical chemistry, flotation agents and high pressure lubricants in industry, and antibacterial,

cytostatic, antifungal, immunoregulatory agents in biology [16] and medicine. The Cu (II) and Ni (II) complexes of DTCs have more literature records [10]. However, most of these studies focused only on the antifungal, antioxidant, immunomodulatory anticancerous like biological activities and hence their possible applications as antifungal or human therapeutic agent. The recently available genome studies have provided a better understanding of the closeness between the eukaryotic fungal kingdom and the human species. The difficult to treat mammal's fungal diseases due to the chemical and genetic similarities also explain the same [17]. Despite significant progress of DTC metal complexes exploration, only a little attention has been given to their antibacterial activity. Hence, to augment the arsenal of prokaryotic antibacterial war, the current work is interested in the synthesis, characterization and antibacterial activity determination of functionalized DTC ligands attached to transition metal Cu and Ni cations as a consequence of the new bonding, and chemical or structural properties [10].

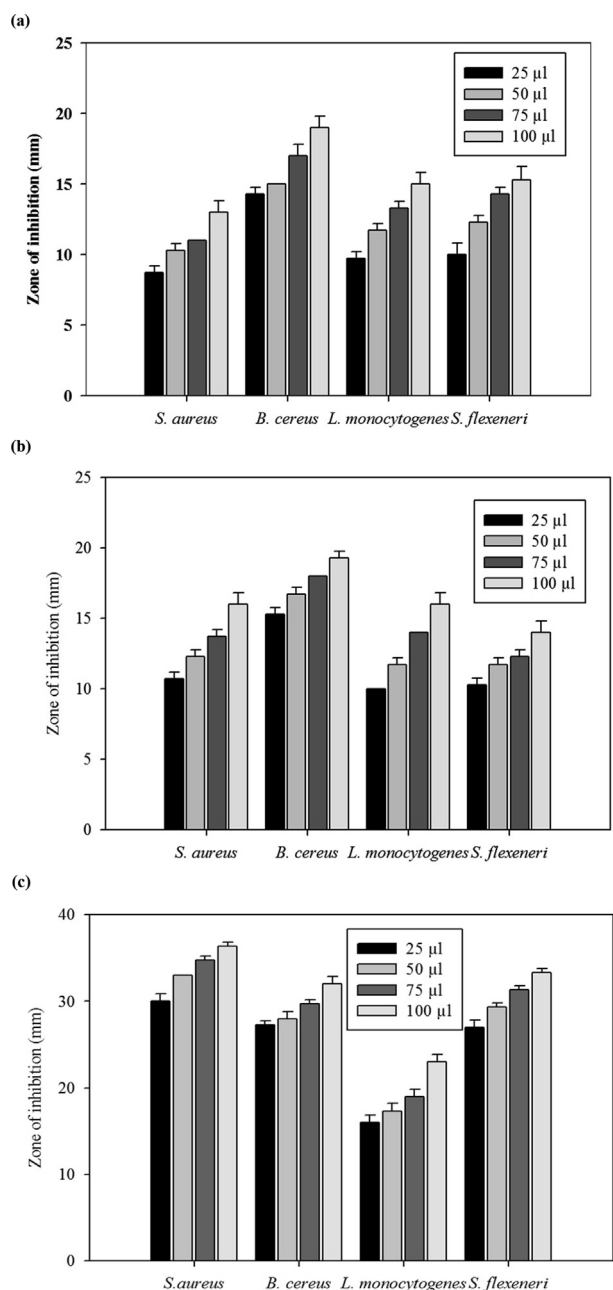


Fig. 4. Antimicrobial activity (a) K (MDTC) Ni-II complex (b) K (MDTC) Cu-II complex (c) K (MDTC) ligand compound.

The ligand potassium morpholine dithiocarbamate ($K^+C_5H_8NOS_2^-$) and its metal $Ni^{2+}-K^+C_5H_8NOS_2^-$ and $Cu^{2+}-K^+C_5H_8NOS_2^-$ complexes were synthesized satisfactorily by direct reaction method. Characterization of these complexes and study on the coordination behavior of $K^+C_5H_8NOS_2^-$ moiety were made employing current physicochemical methods viz. UV, FTIR, and 1H NMR analysis. The spectrophotometric method electronic spectral analysis could be used to determine the stability constants of DTC metal complexes since DTCs shows strong absorbance in the UV region [16]. The monodentate dithiocarbamate moiety would exhibit either no change in position or undergo a red shift, move toward long wavelength on the corresponding free ligand frequency. The blue shift, move toward short wavelength in ligand-metal complex electronic spectrum shows that the bidentate behavior of dithiocarbamate moiety [18]. The $K^+C_5H_8NOS_2^-$ ligand and its Cu (II) as well as Ni (II) metal complexes 1H signals are very close. The general larger δ value shift between the ligand and its metal complex probably

might be due to the existence of larger electron density around these protons [19]. The expected lower electron density in the ligand-metal complexes (neutral) than in the anionic ligands might be ascribed to the signal positions shifting to larger δ value in the spectra of the complexes [20].

The test compounds showed moderate to high inhibitory activity on of both Gram positive and Gram negative bacteria could be attributed to their broad spectrum active nature. The test bacterial strains are more susceptible to ligand than metal. According to Tweedy's theory metal complexes shows increased activity than their ligands due to the increased π electron delocalization throughout the chelate ring of ligands. Chelation leads to reduction in metal ion's polarity and increases chelates lipophilic nature which ultimately favors microbial cell membrane lipid layer permeation and enzyme metal binding site block [21]. However, Fe(III) and Zn(II) showed decreased antimicrobial activity when compared with the parent drugs [22]. Hence, the observed enhanced antimicrobial activity of metal-ligand complex could also be due to the influence of several factors.

5. Conclusion

We have reported the synthesis, characterization and antibacterial study of nickel ($Ni^{2+}-K^+C_5H_8NOS_2^-$) metal complexes, copper ($Cu^{2+}-K^+C_5H_8NOS_2^-$) metal complexes and potassium morpholine dithiocarbamate ligand ($K^+C_5H_8NOS_2^-$). UV, FTIR, and NMR spectral data are consistent with the proposed composition and provides a further example of the bidentate coordination of dithiocarbamate ligands. Their antibacterial activity against *S. aureus* MTCC 737, *B. cereus* MTCC 1272, *L. monocytogenes* MTCC 657 and *S. flexneri* MTCC 1457 bacteria were found to be enhanced ligand than metal complexes. Thus, further study on this approach could pave a way for the development of dithiocarbamate-metal complex based antibacterial agent against wide range of bacterial pathogens.

Declarations

Author contribution statement

Senthilkumar Balakrishnan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Senbagam Duraisamy, Murugan Kasi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Selvam Kandasamy: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Rajesh Sarkar, Anbarasu Kumarasamy: Analyzed and interpreted the data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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