



# Antimicrobial properties of metal piperidine dithiocarbamate complexes against *Staphylococcus aureus* and *Candida albicans*<sup>☆</sup>



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## ABSTRACT

In this study, a series of metal piperidine dithiocarbamate complexes ( $M = Zn, Cu, Co, Fe, Ni, Bi$  and  $Ag$ ) were synthesized and characterized using microelemental,  $^1H$ NMR, mass spectrometry and FT-IR analyses. Antimicrobial properties of the complexes were tested against *Staphylococcus aureus* and *Candida albicans* in a 96-well plate, using the broth dilution assay. The antimicrobial activity of the complexes was in the order  $Zn > Co > Cu > Ag = Bi = Ni > Fe$  against *Staphylococcus aureus* and  $Co > Zn > Fe > Ag = Bi = Cu = Ni$  against *Candida albicans*. The results indicate that the complexes were effective against the microorganisms at high concentrations.

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## Introduction

Dithiocarbamate complexes possess distinguished properties, making them useful in rubber vulcanization accelerators, pesticides, high-pressure lubricating agents, antioxidants and many other chemical applications [1–3]. They can form stable coordination compounds with metals, including the transition metals in different oxidation states while displaying varying properties and structures by strongly and selectively binding to metal ions through the two donor sulphur atoms [4]. Although the sulphur atoms in dithiocarbamates have O-donor and N-back donation properties, these ligands possess unique qualities because of extra  $n$ -electrons that migrate from nitrogen to sulphur through a planar delocalized p-orbital system [4–7].

Biologically active metal-based compounds used for drug purposes display advantageous pharmacological and toxicological potentials over other drugs [8,9]. Dithiocarbamate metal compounds have shown the potential to overcome existing drug limitations in recent times [10]. In biological systems, the two sulphur and nitrogen groups prompt the vast array of

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dithiocarbamate properties [4,7]. Notable among these are their antibacterial antifungal and anticancer properties [7,8,11]. Dithiocarbamates have exhibited traits of overcoming the drawbacks of existing antimicrobial drugs such as antibacterial resistance [12].

Over the past years, many authors have reported the usefulness of many derivatives of dithiocarbamates as antimicrobial agents [1,7,11,12]. Complexes containing the piperidine dithiocarbamate moieties have been used as a starting fragment to examine the optimal linker length mainly because previous studies have suggested that this moiety could potentially act as a selective inhibitor for acetylcholinesterase (AChE) [13]. This study synthesized metal (Zn, Cu, Co, Fe, Ni, Bi and Ag) piperidine dithiocarbamate complexes, characterized them using micro-elemental analysis, melting point, FTIR and <sup>1</sup>H NMR spectroscopies and examined their antimicrobial potency against *Staphylococcus aureus* and *Candida albicans*.

## Materials and methods

### Materials

Sodium hydroxide (ACS reagent, ≥97.0%, pellets), piperidine (ReagentPlus®, 99%), carbon disulphide (Anhydrous, ≥99%), zinc acetate dehydrate (99.999% trace metals basis), silver nitrate (ACS reagent, ≥99.0%), copper sulphate pentahydrate (ACS reagent, ≥98.0%), cobalt sulphate heptahydrate (ReagentPlus®, ≥99%), nickel chloride hexahydrate, (99.9% trace metals basis) bismuth nitrate pentahydrate (ACS reagent, ≥98.0%), iron(III) sulphate hydrate (ACS reagent, 97.0%), dimethyl sulfoxide (anhydrous, ≥99.9%), fluconazole and ciprofloxacin (Pharmaceutical Secondary Standard; Certified Reference Material) were used as received from Sigma Aldrich (St. Louis, USA). *Staphylococcus aureus* (ATCC 25923, Fisher Scientific) and *Candida albicans* (ATCC 10231, Fisher Scientific) were kind donations from the Department of Pharmaceutical Microbiology, KNUST.

### Synthesis of sodium piperidine dithiocarbamate ligand

The sodium piperidine dithiocarbamate ligand was obtained as an off-white powder from the reaction of equimolar amounts of sodium hydroxide (4 g, 100 mmol) and piperidine (8.5 g, 100 mmol), followed by the addition of carbon disulphide (7.6 g, 100 mmol) as reported elsewhere in the literature [14,15]. The ligand was recrystallized in acetone/petroleum ether mixture. Yield, 92.5%. Micro-elemental analysis; Calc (found): C, 35.8 (35.7); H, 6.0 (6.0); N, 7.0 (6.9). IR:  $\nu_{(O-H)}$  3362 cm<sup>-1</sup>,  $\nu_{(C-N)}$  1418 cm<sup>-1</sup> and  $\nu_{(C-S)}$  964 cm<sup>-1</sup>.

### Synthesis of metal piperidine dithiocarbamate complexes

Accurately measured quantities of the sodium piperidine dithiocarbamate ligand (3 g, 14.9 mmol) and metal (Zn, Cu, Co, Fe, Ni, Bi, Ag) salt were each dissolved in 50 mL distilled water in separate 250 mL beakers. The aqueous metal salt was then added dropwise to the sodium piperidine dithiocarbamate solution while stirring for 30 minutes. The precipitate obtained was filtered, washed with excess distilled water and dried in a vacuum oven at room temperature. The complexes were further recrystallized in chloroform.

### Instrumentation

The elemental compositions of the metal complexes were determined by micro-elemental analysis using the Analytik Jena® micro-elemental analyzer. The C, H, N, S as well as the metals in the complexes were determined. The experimentally determined percentage compositions were compared to the calculated values, and the closeness of the experimental values to the calculated ones indicated the purity of the complex. A Stuart melting point apparatus (SMP 10) was used to determine the melting point. A Bruker AVANCE III 400 MHz spectrometer was used for all NMR measurements. The mass spectroscopic analysis of the complexes was done on a Waters Mass Spectrometer using the Electrospray ionization (ESI) technique. The FT-IR spectra were obtained on a Bruker Alpha Platinum ATR instrument.

### Inoculum preparation

Isolates of *Staphylococcus aureus* and *Candida albicans* were streaked onto nutrient agar plates and then incubated at 37°C for 24 hours. Suspensions of each organism were then made in nutrient broth and incubated overnight at 37°C using the direct colony suspension method. For the broth microdilution test, colony suspensions in sterile saline were adjusted to 0.5 McFarland standard and further diluted in sterile double strength nutrient broth (~ 105 CFU/mL) [16].

### Antimicrobial assay

Minimum Inhibitory Concentration (MIC) of the metal complexes were determined by the broth microdilution method as described by Wiegand *et al.*, (2008) [17] for their antibacterial and antifungal activity against strains of *Staphylococcus aureus* and *Candida albicans* respectively. Serial concentrations of the metal (Zn, Cu, Co, Fe, Ni, Bi, Ag) piperidine dithiocarbamate complex were prepared to obtain final concentrations of 10, 5, 2.5, 1.25, 0.625, 0.312 and 0.156 mg/mL in a 96-well

**Table 1**  
Characterization of complexes.

Complex	% Yield	Melting Point (°C)	MS (m/z)	Micro-elemental Analysis Calc. (Found)	<sup>1</sup> H NMR	FT-IR Absorb. (cm <sup>-1</sup> )	FT-IR Assign.
Zn(piperidine dithiocarbamate) <sub>2</sub>	90.2	234	161, 385	C, 37.3 (37.5) H, 5.3 (5.4) N, 7.3 (7.2) S, 33.2 (33.0) Zn, 16.9 (16.8)	1.60-1.73 (m, 4H) 2.16-2.22 (m, 8H) 4.02-4.07 (t, 8H)	2934 1484 1237 982 412	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Zn}-\text{S}}$
Cu(piperidine dithiocarbamate) <sub>2</sub>	84.6	267	161, 384	C, 37.5 (37.6) H, 5.3 (5.2) N, 7.3 (7.2) S, 33.4 (33.4) Cu, 16.5 (16.6)	1.54-1.58 (m, 12H) 2.18 (s, 8H)	2928 1504 1240 996 407	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Cu}-\text{S}}$
Co(piperidine dithiocarbamate) <sub>3</sub>	86.3	238	161, 539	C, 38.0 (38.2) H, 5.3 (5.3) N, 7.4 (7.3) S, 33.8 (33.6) Co, 15.5 (15.4)	1.35-1.86 (m, 4H) 2.17(br.s, 8H) 3.82 (br.s, 8H)	2936 1488 1236 950 407	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Co}-\text{S}}$
Fe(piperidine dithiocarbamate) <sub>3</sub>	89.2	205	161, 536	C, 40.3 (40.4) H, 5.6 (5.5) N, 7.8 (7.7) S, 35.9 (35.7) Fe, 10.4 (10.6)	1.23-1.83 (m, 4H) 2.19 (s, 8H) 3.49 (br.s 8H)	2938 1486 1235 1004 409	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Fe}-\text{S}}$
Ni(piperidine dithiocarbamate) <sub>2</sub>	88.1	295	161, 379	C, 38.0 (37.8) H, 5.3 (5.4) N, 7.4 (7.3) S, 33.8 (33.6) Ni, 15.5 (15.7)	1.53-1.68 (m, 4H) 2.17-2.25 (m, 8H) 3.72-3.75 (t, 8H)	2946 1508 1240 998 408	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Ni}-\text{S}}$
Bi(piperidine dithiocarbamate) <sub>3</sub>	87.8	195	161, 689	C, 31.3 (31.2) H, 4.4 (4.3) N, 6.1 (6.0) S, 27.9 (27.8) Bi, 30.3 (30.5)	1.56-1.60 (m, 4H) 1.68-1.80 (m, 8H) 4.00-4.03 (t, 8H)	2981 1428 1226 997 408	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Bi}-\text{S}}$
Ag(piperidine dithiocarbamate)	89.7	235	161, 268	C, 28.9 (28.8) H, 3.8 (3.7) N, 5.2 (5.4) S, 23.9 (23.8) Ag, 40.2 (40.3)	1.57-1.63 (m, 2H) 2.19-2.25 (m, 4H) 4.01-4.03 (t, 4H)	2934 1433 1225 1005 410	$\nu_{\text{C}-\text{H}}$ $\nu_{\text{C}-\text{N}}$ $\nu_{\text{C}=\text{S}}$ $\nu_{\text{C}-\text{S}}$ $\nu_{\text{Ag}-\text{S}}$

Note for 1NMR: br.s=broad singlet.

s=singlet.

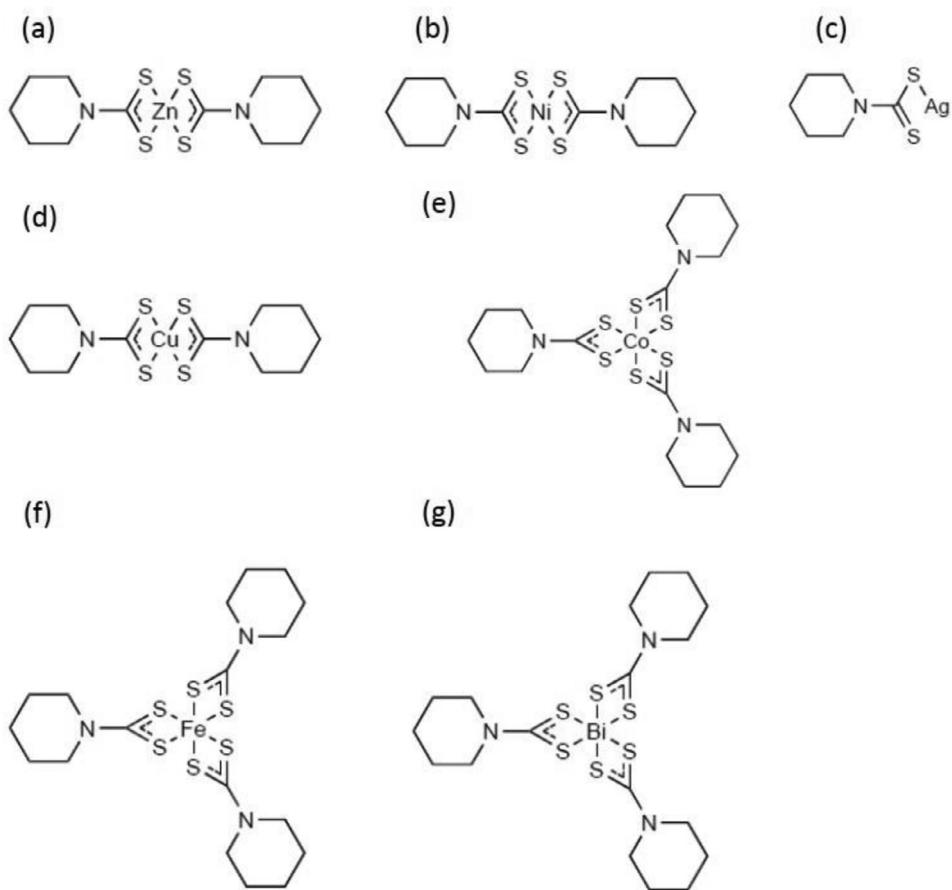
m=multiplet.

t=triplet.

microplate. To each well was added 50 µL of double strength nutrient broth containing an inoculum size of ~2.0 × 10<sup>5</sup> CFU/mL, giving a total well volume of 100 µL. The plates were covered and incubated for 24 hours at 37°C. The plates were removed from the incubator and then 3- (4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) dye (20 µL, 1.25 mg/mL) was added to each well and incubated for 30 minutes at 37°C. MICs were taken as the lowest concentration that inhibited the growth of microorganisms. This was indicated by the absence of purple colouration upon the addition of the MTT dye. Wells in which growth of microbes occurred were colored purple after MTT addition whereas a clear pale yellow colour was observed in wells where microbial growth was inhibited. Ciprofloxacin and fluconazole were used as the reference antibiotic and antifungal drugs, respectively. The reference materials were prepared at the same concentrations as the piperidine complexes.

## Results and discussion

**Table 1** shows the chemical characteristics of the complexes. The complexes were all air-stable and their yields ranged from 84.6 and 90.2%. Metal dithiocarbamate complexes have been reported to have high yields [11,18–20]. The piperidine dithiocarbamate complexes of Zn, Cu, and Ni formed bis (dithiocarbamate) complexes, Ag formed a mono (dithiocarbamate) complex, and Co, Fe and Bi formed tris (dithiocarbamate) complexes (Fig. 1). The Zn(PDTC) complex has a distorted tetrahedral geometry with four sulphur atoms coordinating to Zn atom [21]. Cu(PDTC) and Ni(PDTC) complexes have a square planar geometry with four sulphur atoms coordinating the central metal atom [22]. For Ag(PDTC) complex, one sulphur atom coordinates one Ag(I), and the other sulphur atom is used to bridge two Ag(I) ions within the cluster through argentophilic interactions. The three Ag–S bonds form a triangle, which links the Ag(I) to three other Ag(I) through another triangle, forming a trigonal prism [23]. Co(PDTC) complex forms a distorted octahedron with Co coordinating to six sulphur

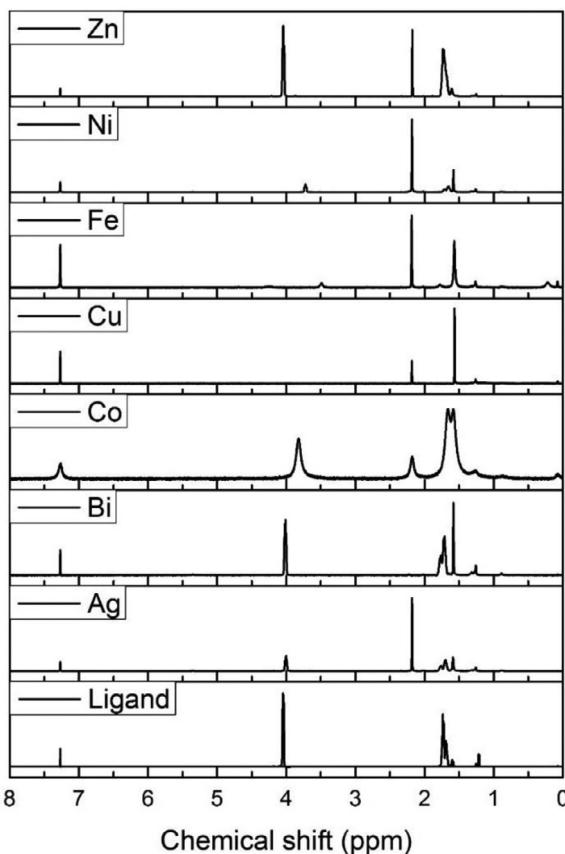


**Fig. 1.** Chemical structures of (a) Zinc, (b) Nickel, (c) Silver, (d) Copper, (e) Cobalt, (f) Iron, and (g) Bismuth piperidine dithiocarbamate complexes.

atoms [24]. Fe(PDTC) has an octahedral geometry with the Fe atom coordinating six sulphur atoms from three bidentate piperidine dithiocarbamate ligands [25]. The Bi(PDTC) complex assumes a pentagonal pyramidal geometry with the Bi atom coordinating five sulphur atoms at the base and one sulphur atom at the apical position [26].

The micro-elemental analysis of the complexes indicated that they were of high purity. The melting points of the complexes were sharp, indicating pure compounds and corroborating the results from the microelemental analysis. A broad melting range is a consequence of the superposition of sharp melting transitions of individual crystals at different temperatures giving rise to several metastable states [27]. The mass spectra of the complexes gave the base peak ( $m/z$  161) that corresponded to the piperidine dithiocarbamate moiety ( $\text{C}_6\text{H}_{11}\text{NS}_2$ ) and molecular ion peaks corresponding to the molecular masses of the complexes. The  $^1\text{HNMR}$  showed a triplet at 3.42–4.06 ppm, indicating the presence of  $\text{CH}-\text{N}$ , a multiplet at 2.09–2.25 ppm indicating the  $\text{CH}_2$  groups at the meta positions to the amide group and a multiplet at 1.60–1.80 ppm, indicating the  $\text{CH}_2$  at the para position to the amide group. This confirmed the piperidine substituents in the metal complexes. A stacked plot of the  $^1\text{HNMR}$  spectra for the ligand and complexes (Fig. 2, Table 1) indicates a slight chemical shift of the complexes' spectra from the ligand spectra. The shift is due to the coordination of the individual metals to the ligand and the geometry of the complexes. The paramagnetic nature of some transition metal complexes such as copper, cobalt, iron and nickel distorts the  $^1\text{NMR}$  spectra, making interpretation difficult [28]. The problem of acquisition arises because the paramagnetic shifts and shift anisotropies are often large, resulting in the excitation of the nuclei with inefficient and insufficiently broadband radio-frequency powers, and the large paramagnetic relaxation enhancements cause the coherences to decay rapidly in the excited state [29].

The FT-IR analyses (Table 1) showed strong to medium absorption bands at  $2947\text{--}2850\text{ cm}^{-1}$ ,  $1505\text{--}1434\text{ cm}^{-1}$ ,  $1238\text{--}1107\text{ cm}^{-1}$ ,  $1006\text{--}846\text{ cm}^{-1}$  and  $409\text{--}402\text{ cm}^{-1}$ , which were attributed to C–H vibrations on the piperidine ring, C–N asymmetric stretching, C=S, C–S and M–S bond, respectively. The C–N asymmetric stretching is characteristic of a thioureide bond between the single and double bond energies, giving specific information about the partial double bond character [30]. The C=S vibration and C–S stretching bands show the bidentate coordination of dithiocarbamate through the two sulphur atoms [31].



**Fig. 2.** A stacked plot of the  $^1\text{H}$ NMR spectra for the ligand and complexes.

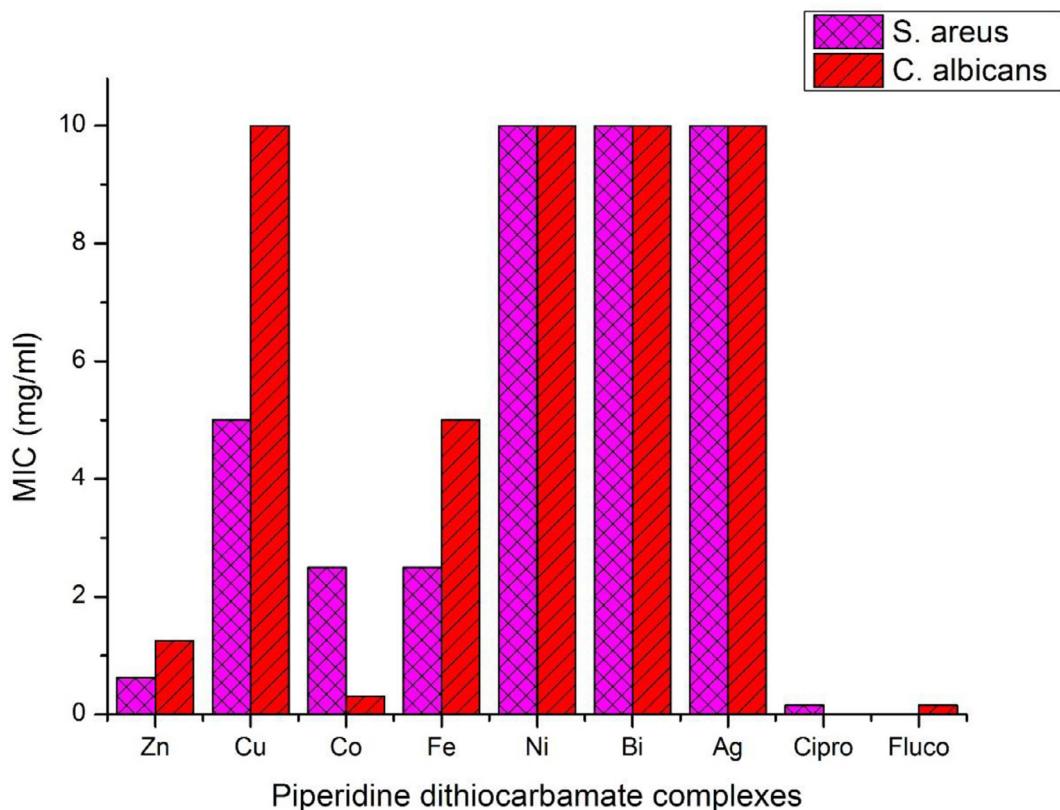
There were no peaks observed in the region of  $3600 \text{ cm}^{-1}$  because there were no primary or secondary amines present as nitrogen in piperidine dithiocarbamate is bonded to three carbon atoms, leaving all hydrogen atoms substituted.

The complexes were screened against *Staphylococcus aureus*, and *Candida albicans* and their minimum inhibitory concentrations (MIC) were ascertained (Fig. 3). Fluconazole and ciprofloxacin were used as reference antifungal and antibacterial drugs, respectively. All the complexes showed antimicrobial activity against the selected organisms. Zinc piperidine dithiocarbamate complex inhibited the growth of *Staphylococcus aureus* at  $0.625 \text{ mg/mL}$  and *Candida albicans* at  $1.250 \text{ mg/mL}$ . Cobalt piperidine dithiocarbamate showed inhibition for *Staphylococcus aureus* at  $2.500 \text{ mg/mL}$  and *Candida albicans* at  $0.312 \text{ mg/mL}$ .

The complexes of Ag, Ni, Bi and Cu showed higher MICs against both *S. aureus* and *C. albicans* than Zn, Co, and Fe complexes, which had MICs of  $10 \text{ mg/mL}$  for both microbes. The results demonstrate the severe dose-dependence effect of both microbes; increasing complex concentrations increase the microbial inhibition properties.

$[\text{Zn}(\text{piperidine dithiocarbamate})_2]$  and  $[\text{Co}(\text{piperidine dithiocarbamate})_2]$  were the best antimicrobial agents against both *S. aureus* and *C. albicans*, respectively. The high antimicrobial activity of these complexes may be attributed to increased lipophilicity of the metal upon complexation with the ligand as explained by Overton's and Tweedy's chelation theory [3,32,33].

This theory explains that upon chelation of metal with ligands, the polarity of the central metal reduces due to the partial sharing of its positive charge with donor sulphur atoms and the delocalization of the p-electron, increasing the lipophilicity of the complex and making it possible to permeate the hydrophobic cell membrane of the microbe [34]. As low as  $0.625 \text{ mg/mL}$  of  $[\text{Zn}(\text{pDTC})_2]$  showed antibacterial activity and  $0.312 \text{ mg/mL}$  of  $[\text{Co}(\text{PDTc})_3]$  showed antifungal activity.  $[\text{Fe}(\text{PDTc})_3]$ ,  $[\text{Cu}(\text{PDTc})_2]$ ,  $[\text{Ni}(\text{PDTc})_2]$ ,  $[\text{Bi}(\text{PDTc})_3]$  and  $[\text{Ag}(\text{PDTc})]$  exhibited antimicrobial activities at higher concentrations. A similar study conducted by Al-Janabi et al [35] showed high zones of inhibition of the bipyridal derivatives of  $\text{Zn}(\text{PDTc})$  against *S. aureus* ( $16 \text{ mm}$ ) and *C. albicans* ( $11 \text{ mm}$ ). Also, they showed good antimicrobial activities against *E. coli*, *P. aeruginosa* and *A. niger*. Earlier research on the antimicrobial studies of several metal dithiocarbamate derivatives has been reported. These include Ni(II), Cu(II) and Zn(II) complexes of diphenylthiocarbamate against *Rhodococcus*, *Actinomyces viscosus*, *Bacillus subtilis*, *Escherichia coli* and the fungi, *Aspergillus niger*, *Aspergillus flavus*, *Candida* and *Acetomyceta* [36], Zn(II), Cd(II), Hg(II), Cu(II), Co(II) and Ni(II) complexes of p-chlorophenyl-, p-bromophenyl-dithiocarbamates against gram-positive and gram-negative bacteria (*Escherichia coli*, *Serratia marcescens*, *Salmonella typhi*, *Shigella flexneri* and *Staphylococcus aureus*) and fungi (*Tricho-*



**Fig. 3.** Minimum inhibitory concentrations of piperidine dithiocarbamate complexes against *S. aureus* and *C. albicans*.

*derma viride*, *Monilia albicans*, *Saccharomyces ludwigii*, *Rhizopus stolon* and *Mucor mucedo*) [37], organotin(IV) complexes of *N*-methyl-*N*-phenyldithiocarbamate against *Escherichia coli*, *Klebsiella Pneumonia* and *Pseudomonas Aeruginosa*, *Bacillus cereus* and *Staphylococcus aureus*, *Candida albicans* and *Aspergillus flavus* [34], *Ni(II)-* and *Cu(II)-N,N'*-diaryl formamidine dithiocarbamate against *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* (methicillin resistant) and *Staphylococcus aureus* [19]. The complexes in all these studies showed good antimicrobial activities against both the bacterial and fungal strains. This study further confirms the antimicrobial properties of the piperidine dithiocarbamates with  $M^+$ ,  $M^{2+}$  and  $M^{3+}$  ions.

## Conclusion

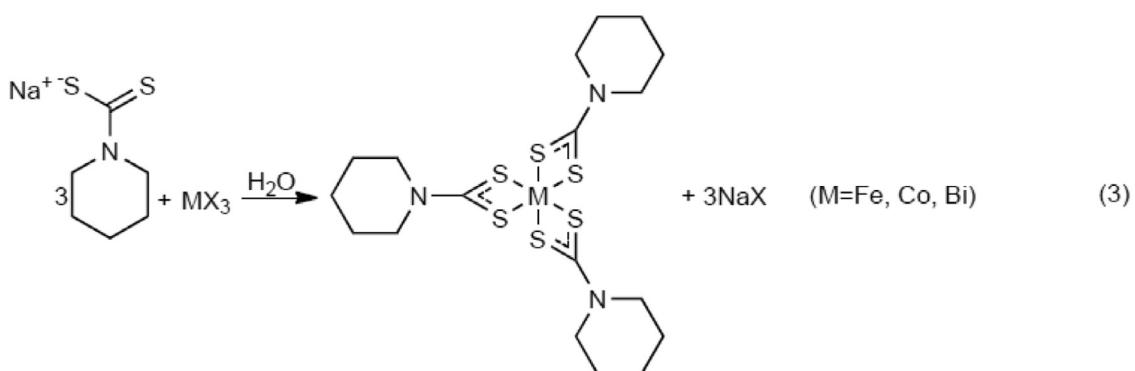
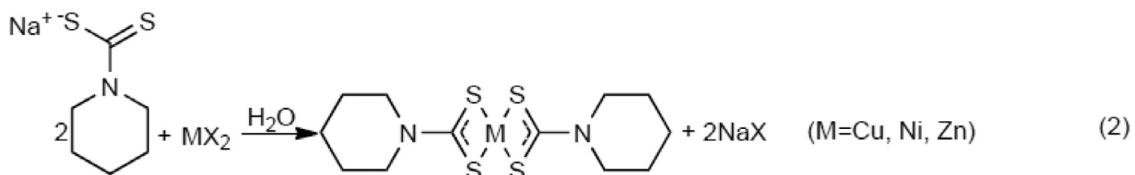
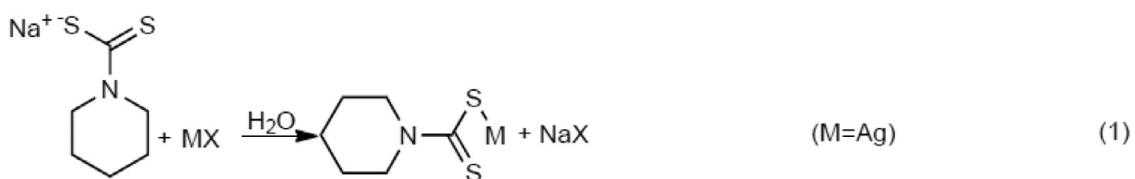
In this study, metal ( $M = \text{Zn, Cu, Co, Fe, Ni, Bi and Ag}$ ) piperidine dithiocarbamate complexes were synthesized and characterized (using  $^1\text{H}$ NMR, UV-visible, and FT-IR spectroscopy) and their antimicrobial properties were tested against *Staphylococcus aureus* and *Candida albicans*. The complexes after characterization were found to be in their pure form. The minimum inhibitory concentrations obtained indicated that the complexes were effective against *S. aureus* in the order  $\text{Zn} > \text{Co} > \text{Cu} > \text{Ag} = \text{Bi} = \text{Ni} > \text{Fe}$  and *C. albicans* in the order  $\text{Co} > \text{Zn} > \text{Fe} > \text{Ag} = \text{Bi} = \text{Cu} = \text{Ni}$ . The complexes were effective against the microbes screened at varying concentrations. The metal piperidine dithiocarbamate complexes studied in this work could be further derivatized to optimize their antimicrobial action. Work in this regard is currently ongoing in our laboratories **Scheme 1**.

## Data availability

Supplementary data will be available from the corresponding author upon request.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



**Scheme 1.** Synthesis of piperidine dithiocarbamate complexes.

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