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Synthesis, structures, and ESI-mass studies of silver(I) derivatives of imidazolidine-2-thiones: Antimicrobial potential and biosafety evaluation

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ABSTRACT

The basic objective of this investigation is to explore potential metallo-organic antimicrobial agents based on silver–heterocyclic-2-thiones. In this respect, a series of silver(I) halide complexes with imidazolidine-2-thiones (L-NR, R = H, Me, Et, Pr^n, Bu^n, Ph), namely, mononuclear $[AgX(L\text{-}NR)(PPh_3)_2]$ (X, R: Cl, Bu, **1**; Br, Ph, **7**); $[AgX(L\text{-}NR)_3]$ (Br, Bu, **5**; Br, Pr^n, **8**) and halogen bridged dinuclear $[Ag_2(\mu\text{-}X)_2(L\text{-}NR)_2(PPh_3)_2]$ (Cl, Bu^n, **2**; Cl, Ph, **3**; Cl, Pr^n, **4**; Br, Ph, **6**) have been synthesized and characterized using modern techniques. The thio-ligands are terminally S-bonded in all the complexes. The in vitro antimicrobial potential and biosafety evaluation of the above complexes as well as that of previously reported analogous silver complexes has been studied against Gram positive bacteria, namely, *Staphylococcus aureus* (MTCC 740) and Methicillin resistant *Staphylococcus aureus* (MRSA), Gram negative bacteria *Klebsiella pneumoniae* (MTCC 109), *Salmonella typhimurium* (MTCC 98) and a yeast *Candida albicans* (MTCC 227). Most of the complexes tested have shown significant antimicrobial activity with low values of minimum inhibitory concentration (MIC). Significantly, the activity against MRSA is an important outcome of this investigation. Among complexes tested for their cytotoxicity using MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay, some complexes showed low cellular toxicity with high percent cell viability. A dinuclear complex $[Ag_2(\mu\text{-}Cl)_2(L\text{-}NPh)_2(PPh_3)_2]$ **3** with 93.3% cell viability emerges the most important candidate for further investigations.

1. Introduction

In literature, the coordination chemistry of heterocyclic-2-thiones has been investigated by several research workers and a variety of compounds have been reported [1–14]. The molecular structures and spectroscopic aspects have been the major interests. As regards, the use of heterocyclic-2-thiones and their metal complexes for possible bio-active applications, the efforts are scarce and random with no intensive drive for developing these materials as non-toxic antimicrobial agents or anticancer agents. In the literature, the bio-active applications [15–38], of transition metals (Fe, Ru; Pd, Pt; Cu, Ag, Au) [16,19,20–22,24–38], and post-transition/main group metals (Zn, Cd, Hg, Sn, Sb) [15,17,18,23,30–38], with a series of thio-ligands, namely, imidazolidine-2-thione [15–23,35], benzothiazole-2-thione [26,32], benzoxazole-2-thione [32], pyrimidine-2-thiones [20–22,24,25,27–29,31,32], diazinane-2-thione [15,17,18,23,35], 1,3-diazipane-2-thione [15,17,18,23], pyridine-2-thiones [20–22,28,32,35,36], 6-mercaptopurine [20], 2-aminobenzothiazole [30], thiourea [21,22,28,34], and thiouracil [33] have been reported. These studies pertain to complexes acting as anti-inflammatory [26,27], anti-cancer [25,26,28–33,38], and anti-microbial agents [15–28,34–38].

The synthesis and structures of several silver(I) complexes with heterocyclic-2-thiones have been reported, but their biochemical activity has not been explored [12,39–47]. In view of our interest to explore potential metallo-organic antimicrobial agents based on N,S-donor thio-ligands [48–53], the present work was designed to investigate synthesis, structures and antimicrobial activity of new and previously reported silver(I)-N-substituted-imidazolidine-2-thioes [12]. The status of biochemical properties of silver(I) complexes reported in literature is briefly summarized here. The biochemical activity of silver (I) complexes with heterocyclic-2-thiones, namely, 3,4,5,6-tetrahydro-pyrimidine-2-thione [29,32], 6-amino-4-hydroxy-2-thiopyrimidine [31], pyrimidine-2-thione or 4,6-dimethyl-pyrimidine-2-thione [27], diazinane-2-thione [35], pyridine-2-thione [35], 2-mercapto-pyridine-

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3-carboxylic acid [36,32], 5-chloro-2-mercaptobenzothiazole, 2-mercaptobenzothiazole, and 2-mercaptothiazolidine [26,54], pertains to anti-inflammatory [26,27], anti-cancer [26,29,31,32], and anti-microbial agents [27,35,36]. There are only preliminary reports on the antimicrobial activity of structurally uncharacterized silver(I) complexes with imidazolidine-2-thione [16,35] against bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*), molds (*Aspergillus niger*, *Penicillium citrinum*), and yeasts (*Candida albicans*, *Saccharomyces cerevisiae*) [16,35]. The antimicrobial activity of mixed ligand silver(I) complexes with 5-chloro-2-mercaptobenzothiazole, 2-mercaptobenzothiazole, 2-mercaptothia-zolidine, 2-mercapto-1-methyl-imidazole and triphenylphosphine as co-ligand was evaluated against *Pseudomonas aeruginosa* and *Escherichia coli* [26,54,55]. It is pointed out here that the investigations reported in the literature are scant and serious efforts to employ structurally characterized silver(I) complexes in a systematic manner such as use of time kill assay, MTT assay for biosafety, are missing [16,27,35,36].

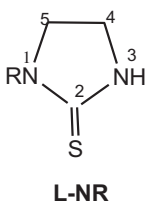
It may be added here that apart from the lack of investigations in this area as highlighted above, some interesting applications need to be introduced here which enhance interest in this area. For example, a silver(I) ion has the potential to act as a microbicidal to combat pathogens and is used in many health care products such as silver-wound dressing, burn creams, (silver sulfadiazine cream) to treat burns, traumatic wounds and ulcers [56–58].

In this paper, we are reporting the synthesis, characterization, NMR, ESI-mass and X-ray crystallography of several new silver(I) complexes (**1–8**) halides with imidazolidine-2-thiones (Chart 1: L-NPr^n, L-NBu and L-NPh ligands; Chart 2: Complexes synthesized). The antimicrobial activity against *Staphylococcus aureus* (MTCC 740), Methicillin resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae* (MTCC 109), *Salmonella typhimurium* (MTCC 98) and *Candida albicans* (yeast, MTCC 227) and cellular cytotoxicity of these as well as previously reported similar complexes, namely, [AgX(PPh$_3$)$_2$(L-NR)] and [Ag$_2$(μ-X)$_2$(L-NR)$_2$(PPh$_3$)$_2$] (X = Cl, Br; R = H, Me, Et, Pr^n, **9–18**) [12], is reported in this paper. This study acquires significance in the light of the antibacterial resistance exhibited by Gram-positive and Gram-negative bacteria and the increasing drug resistant bacteria are responsible for various nosocomial infections. Notably, Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most frequent nosocomial pathogen. Also *Candida albicans* are found to have developed resistance against a number of antifungal agents.

2. Experimental section

2.1. Chemicals and techniques

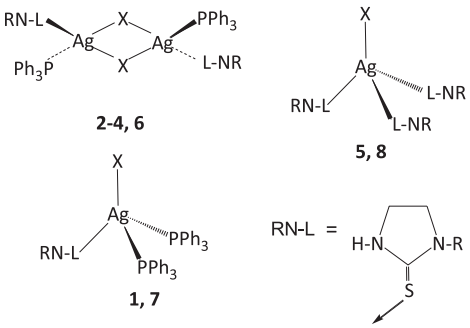
Silver(I) halides were prepared by a metathetical reaction of silver (I) nitrate with potassium halides (X = Cl, Br) in water, followed by washing with methanol and finally dried in vacuo. The thio-ligands, 1-methyl-imidazolidine-2-thione, 1-ethyl-imidazolidine-2-thione, 1-*n*-propyl-imidazolidine-2-thione, 1-*n*-butyl-imidazolidine-2-thione, and 1-phenyl-imidazolidine-2-thione were prepared as per the literature methods [5,59]. Elemental analysis (C, H, N, S) were carried out using the THERMO FINNIGAN FLASH technique. The melting points were determined with a Gallenkamp electrically heated apparatus. IR spectra



L-NR

R = H, imidazolidine-2-thione
R = Me, N-methyl-imidazolidine-2-thione
R = Et, N-ethyl-imidazolidine-2-thione
R = Pr^n, N-propyl-imidazolidine-2-thione
R = Bu^n, N-butyl-imidazolidine-2-thione
R = Ph, N-phenyl-imidazolidine-2-thione

Chart 1. Imidazolidine-2-thione ligands.



	R	X
1	Bu	Cl
2	Bu	Cl
3	Ph	Cl
4	Pr	Cl
5	Bu	Br
6	Ph	Br
7	Ph	Br
8	Pr	Br

Chart 2. Complexes synthesized.

were recorded using KBr pellets on a Varian 660 FT IR Spectrometer in the 4000–400 cm^{-1} range. ^{1}H NMR spectra were recorded in CDCl$_3$/DMSO using a Bruker Avance II 400 NMR spectrometer at 400 MHz using TMS as an internal reference. The ESI-mass spectra were recorded in dimethyl sulfoxide or chloroform solvents using Bruker Daltonik LS-MS high resolution micro TOF-Q II 10356 spectrometer.

2.2. Synthesis of silver(I) complexes

2.2.1. [AgCl(-L-NBu^n)(PPh$_3$)$_2$] **1**

To silver(I) chloride (0.025 g, 0.17 mmol) suspended in acetonitrile (5 mL) was added solid PPh$_3$ (0.045 g, 0.17 mmol) and the contents were stirred for a period of 24 h. The white precipitate formed were suspended in chloroform (5 mL) followed by the addition of solid 1-butyl-imidazolidine-2-thione (0.021 g, 0.17 mmol) which formed a clear solution after stirring for 15 min. Slow evaporation of this solution formed a white solid which after recrystallization from acetonitrile and dichloromethane mixture (4–6 mL, 1:1, v/v) yielded crystals of **1** (70%, M.p. 101–103 °C). C$_{43}$H$_{44}$ClAgN$_2$P$_2$S: calcd. C 62.47; H 5.32; N 3.39; S 3.87%; found: C 62.16; H 5.26; N 3.64, S 4.05%. IR (KBr, absorption bands): ν(N—H), 3182 m; ν(C—H), 3047 w, 2954 w, 2927 w; δ(N—H) 1585 m; ν(C—N) + δ(C—H) 1513 s, 1479 m, 1434 s; other bands, 1323 w, 1281 m, 1247 m, 1198 w; ν(C—S), 1120 w; ν(P—C$_{Ph}$), 1093 m; other bands, 1028 w, 996 w, 748 s, 696 s, 596 w, 512 s cm^{-1}.Complexes **3** and **6** were prepared similarly. Other complexes, namely, **2**, **4** and **7** were prepared by the same method except the difference in reaction ratios which was: Ag:PPh$_3$:thio-ligand: 1:2:1 for **2** and **7**, and 1:1:2 for **4**.

2.2.2. [Ag$_2$(μ-Cl)$_2$(L-NBu^n)$_2$(PPh$_3$)$_2$] **2**

Yield 65%, M.p. 126–128 °C. C$_{50}$H$_{58}$Cl$_2$Ag$_2$N$_4$P$_2$S$_2$: calcd. C 53.23; H 5.14; N 4.96, S 5.67%; found: C 53.17; H 5.00; N 5.01, S 5.61%. IR (KBr, absorption bands): ν(N—H), 3153 m; ν(C—H), 3046 w, 2953 w; δ(N—H) 1584 w; ν(C—N) + δ(C—H), 1513 s, 1479 s, 1433 s, 1369 w; other bands, 1323 m, 1278 m, 1251 w; ν(C—S), 1123 w; ν(P—C$_{Ph}$), 1093 m; other bands 1026 w, 997 w, 856 w, 747 s, 695 s, 622 m, 513 s, 431 w cm^{-1}.

2.2.3. [Ag$_2$(μ-Cl)$_2$(L-NPh)$_2$(PPh$_3$)$_2$] **3**

Yield, 69%, M.p. 125–127 °C. C$_{54}$H$_{50}$Cl$_2$Ag$_2$N$_4$P$_2$S$_2$: calcd. C 55.57; H 4.28; N 4.80; S 5.48%; found: C 55.18; H 4.58; N 4.56; S 5.32%. IR (KBr, absorption bands): ν(N—H) 3167 m; ν(C—H), 2950 w, 2887 w; δ(N—H) 1594 m; ν(C—N) + δ(C—H), 1499 s, 1477 s, 1439 s; 1335 m; other bands, 1292 m, 1248 s; ν(C—S) + ν(P—C), 1074 w; other bands, 1036 w, 1000 w, 950 w, 907 w, 761 m, 693 s, 665 w, 630 w, 548 m, 498 w cm^{-1}.

2.2.4. [Ag$_2$(μ-Cl)$_2$(L-NPr)$_2$(PPh$_3$)$_2$] **4**

Yield 75%, M.p. 175–178 °C. C$_{48}$H$_{54}$Cl$_2$Ag$_2$N$_4$P$_2$S$_2$: calcd. C 52.38; H 4.91; N 5.09; S 5.82%; found: C 52.00; H 5.10; N 5.37, S 6.03%. IR (KBr, absorption bands): ν(N—H), 3330 w; ν(C—H), 2974 w, 2931 w, 2870 w;