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Synthesis, structures and antimicrobial activity of copper derivatives of N-substituted imidazolidine-2-thiones : unusual bio-activity against *Staphylococcus epidermidis* and *Enterococcus faecalis*†

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The main objective of this study was to explore the antimicrobial activity of several copper(I) complexes with N,S- donor thio-ligands against Gram positive bacteria, namely, *Staphylococcus aureus* (MTCC 740), *Staphylococcus epidermidis* (MTCC 435), *Enterococcus faecalis* (MTCC 439), Gram negative bacteria *Shigella flexneri* (MTCC 1457), *Escherichia coli* (MTCC 119) and yeast *Candida tropicalis* (MTCC 230). New copper complexes were prepared from copper(I) halides and imidazolidine-2-thiones (L-NR, R = Et; Pr^n; Bu^n; Ph) with triphenylphosphine as a co-ligand. Complexes are mononuclear, $[CuX(L\text{-}NR)(PPh_3)_2]$ (X, R: Cl, Pr^n, **1**; Br, Pr^n, **2**; Cl, Bu^n, **3**; I, Bu^n, **4**; I, Ph, **6**), $[CuBr(L\text{-}NPh)_2(PPh_3)]$ **5** and halogen-bridged dinuclear, $[Cu_2(\mu\text{-}X)_2(L\text{-}NR)_2(PPh_3)_2]$ (Br, Et, **7**; Cl, Pr^n, **8**; Br, Pr^n, **9**; I, Pr^n, **10**; Br, Ph, **11**;I, Ph, **12**). These complexes were characterized using analytical data, IR, ^{1}H-NMR spectroscopy, single crystal X-ray crystallography, electron spray ionization mass spectrometry (ESI-MS) and techniques for antimicrobial study (agar diffusion, agar dilution, MTT assay). All of the complexes are found to be bactericidal against *Staphylococcus aureus.* A most significant outcome of this investigation is that several complexes have shown significant activity against

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Staphylococcus epidermidis and *Enterococcus faecalis,* which is higher than that of the standard drug Gentamicin. Finally, these complexes were nearly inactive against *Shigella flexneri*, *Escherichia coli* and yeast *Candida tropicalis*.

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†Electronic supplementary information (ESI) available: ESI-MS data. CCDC 1814805–1814816 for complexes 1-12 respectively

1 Introduction

Coordination chemistry of copper with heterocyclic-2-thiones, an interesting class of N,S donor thio-ligands, has invited interest of several researchers in the past for several decades.[1-5] Among heterocyclic-2-thiones, 1,3-imidazolidine-2- thione and its derivatives have been used for the investigation of their interaction with metals.[1-8] The ligands, 1,3-imidazolidine-2-thione and its derivatives with mono substitution at one nitrogen (L-NR, R = H, Me, Et, ^{n}Pr, ^{i}Pr) with copper(I) halides / pseudo halides have yielded trigonal planar complexes, [CuX(L-NR)2] (*X* = Cl, Br, I, NCS),[9-17] tetrahedral complexes,[18] dinuclear, or polynuclear complexes.[17, 19-21] Further, 1,3-

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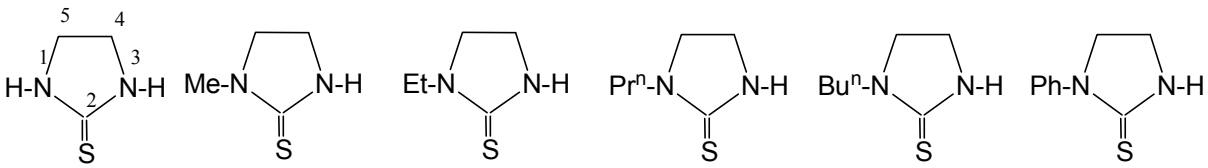
imidazolidine-2-thione and its derivatives (Chart 1) in their reactions with copper(I) halides at ambient conditions have shown unusual chemical transformations involving C-S rupture forming a variety of novel compounds.[22, 23]



L-NH L-NMe L-NEt L-NPr^n L-NBu^n L-NPh

Chart 1 Imidazolidine-2-thiones ligands (L-NR).

The coordination chemistry of heterocyclic-2-thiones is important from the bioinorganic perspective as well. To illustrate, a few examples of bio-activity of copper complexes are cited below. The antimicrobial activity of copper(I) halide complexes with N-substituted benzothiazole-2-thione[24, 25] and pyrimidine-2-thione[26] with triphenylphosphine as a co-ligand has been studied against Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus cereus*) and Gram-negative (*Escherichia coli* and *Xanthomonas campestris*) bacteria. The ability of complexes to interact with native calf thymus DNA (CT-DNA) in vitro as well as their anti-inflammatory activity have also been investigated.[24,26] Hetero-metallic complexes of Cu-Ni, Cu-Co, Cu-Co-Ni with 2-thiouracil have been screened in vitro against *Staphylococcus aureus* (Gram-positive bacteria), *Escherichia coli* (Gram-negative bacteria), *Aspergillus flavus* (filamentous fungi) and *Candida albicans* (yeast).[27] Similarly, another set of copper(I) halide complexes with 5-carbethoxy-2-thiouracil and PPh_3 as a co-ligand have been evaluated for *in vitro* antitumor properties.[28] Copper(II) halide complexes of *N*-(2-pyridyl)imidazolidin-2-ones, *N*,*N*'-bis(2-pyridyl)imidazolidin-2-ones, *N*-acyl-*N*'(2-pyridyl)imidazolodin-2-ones and *N*-

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Complexes (2-pyridyl)imidazolidine-2-thiones have shown high anti-tumor activity with promising results for developing anticancer agents.[29]

The antimicrobial activity of imidazolidine-2-thione (L-NH, Chart 1) is limited to some metal complexes of Hg, Ag, Cd, Fe, Pd and Zn which have shown activity against various microorganisms, namely, *Heterotrotropic Plate Counts* (HPC), *Pseudomonas aeruginosa*, *Fecal Streptococcus, Escherichia coli*, *Klebsiella pneumoniae, Salmonella typhi, Staphylococcus aureus, Bacillus cereus, Enterobacter aerogenes, Serratiam arescens, Salmonella enteric*, molds (*Aspergillus niger, Penicillium citrinum*), and yeasts (*Candida albicans, Saccharomyces cerevisiae*). However, there are limited systematic investigations in literature, generally preliminary accounts of bio-activity.[30-39]

Recently we have investigated several copper(I)-imidazolidine-2-thione complexes (trigonal planar, dinuclear, tetranuclear and hexanuclear) for their antimicrobial activity against *S. aureus,* (MRSA, *K. pneumoniae* 1, *S. typhimurium* 1 and a yeast *C. albicans*. These complexes have shown high antimicrobial activity and in a few cases the *in-vitro* cell viability was high (95%).[17] In this paper we are reporting the synthesis, spectroscopy, molecular structures and antimicrobial activity of copper(I) halide complexes with N-substituted-imidazolidine-2-thiones (L-NR, R= Et, Pr^n, Bu^n, Ph, Chart 1) using PPh_3 as a co-ligand.

2 Experimental section

2.1. Materials and techniques

Copper(I) halides were prepared by the reduction of $CuSO_4 \cdot 5H_2O$ using SO_2 in the presence of stoichiometric amounts of corresponding NaCl, NaBr or NaI salts in water.[40] The thio-ligands used, namely, 1-ethyl-imidazolidine-2-thione (L-NEt), 1-n-propyl-imidazolidine-2-thione (L-

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NPr^n), 1-n-butyl-imidazolidine-2-thione (L-NBu^n), and 1-phenyl-imidazolidine-2-thione (L-NPh) were prepared by the method as reported in the literature.[18,41] The melting points were determined by using an Gallenkamp electrically heated apparatus. Elemental analyses (C, H, N, S) were carried out using a THERMO FINNIGAN FLASH technique. The ^{1}H NMR spectra were recorded in $CDCl_3$ / DMSO using a Bruker Advance II 400 NMR spectrometer at 400 MHz and a Bruker Ascend 500 NMR spectrometer at 500 MHz using TMS as an internal reference. The IR spectra were recorded using KBr pellets on a Varian 660 FT IR Spectrometer in the 4000-400 cm^{-1} range. The ESI-mass spectra were recorded in DMSO or chloroform solvents using a Bruker Daltonik LS-MS high resolution micro TOF-Q II 10356 spectrometer.

2.2. Synthesis of complexes

[CuCl(L-NPr^n)(PPh$_3$)$_2$] 1. To a solution of copper(I) chloride (0.025 g, 0.25 mmol) in 10 mL of acetonitrile was added triphenylphosphine (0.13 g, 0.50 mmol), followed by stirring for 2 h at room temperature. To the white precipitates formed was added 1-propyl-1, 3-imidazolidine-2-thione (0.036 g, 0.25 mmol), it was stirred until a clear solution was obtained. Slow evaporation of the solution at room temperature gave colorless crystals of **1**. Yield (70 %). M.p 105-107 ˚C. Elemental analysis for $C_{42}H_{42}CuClN_2P_2S$: calcd. C 65.64; H 5.47; N 3.64; S 4.16 %; found: C 65.31; H 5.65; N 3.70; S 4.22 %. Complexes **2-4, 6** were prepared similarly.

[CuBr(L-NPr^n)(PPh$_3$)$_2$] 2. Colorless compound (yield 70 %, M.p 140-142 ˚C). Elemental analysis for $C_{42}H_{42}CuBrN_2P_2S$: calcd. C 62.05; H 5.17; N 3.45; S 3.94 %; found: C 62.02; H 5.22; N 3.49; S 3.65 %.

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[CuCl(L-NBu^n)(PPh$_3$)$_2$] 3. Colorless compound (yield 70 %, M.p 135-137 ˚C). Elemental analysis for $C_{43}H_{44}CuClN_2P_2S$: calcd. C 66.06; H 5.63; N 3.58; S 4.09 %; found: C 65.75; H 5.49; N 3.40; S 3.73 %.

[CuI(L-NBu^n)(PPh$_3$)$_2$] 4. Colorless compound (yield 75 %, M.p 120-122 ˚C). Elemental analysis for $C_{43}H_{44}CuIN_2P_2S$: calcd. C 59.14; H 5.04; N 3.20; S 3.66 %; found: C 59.12; H 5.24; N 3.31; S 3.80 %.

[CuBr(L-NPh)$_2$(PPh$_3$)] 5. To a solution of copper(I) bromide (0.025 g, 0.17 mmol) in 10 mL of acetonitrile was added 1-phenyl-1,3-imidazolidine-2-thione (0.062 g, 0.34mmol), followed by stirring for 2 h at room temperature. To the white precipitates formed was added triphenylphosphine (0.045 g, 0.17 mmol) and it was heated followed by addition of dichloromethane to it (*v/v*:: 1:1). Slow evaporation of the solution at room temperature gave colorless crystals of **5** (yield 65 %, M.p 147-149 ˚C). Elemental analysis for $C_{36}H_{35}CuBrN_4PS_2$: calcd. C 56.73; H 4.59; N 7.35; S 8.40 %; found: C 56.97; H 4.69; N 7.41; S 8.05 %.

[CuI(L-NPh)(PPh$_3$)$_2$] 6. Colorless compound (yield 70 %, M.p 148-150 ˚C). $C_{45}H_{40}CuIN_2P_2S$: calcd. C 60.45; H 4.47; N 3.13; S 3.58 %; found: C60.78; H 4.68; N 3.19; S 3.64 %.

[Cu$_2$(μ-Br)$_2$(L-NEt)$_2$(PPh$_3$)$_2$] 7. To a solution of copper(I) bromide (0.025 g, 0.17 mmol) in 10 mL of acetonitrile was added triphenylphosphine (0.045 g, 0.17 mmol), followed by stirring for 2 h at room temperature. To the white precipitate formed was added solid 1-ethyl-1,3-imidazolidine-2-thione (0.020 g, 0.17 mmol) and it was heated until a clear solution was obtained, then 1 mL of methanol was added to it. Slow evaporation of the solution at room temperature gave colorless crystals of **7** (yield 70 %, M.p 148-150 ˚C). Elemental analysis for

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$C_{46}H_{50}Cu_2Br_2N_4P_2S_2$: calcd. C 51.54; H 4.66; N 5.22; S 5.97 %; found: C 51.32; H 4.71; N 5.45; S 6.00 %. Complexes **8, 9, 11** and **12** were prepared similarly.

$[Cu_2(\mu\text{-}Cl)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ 8. Colorless compound (yield 75 %, M.p 123-125 ˚C). Elemental analysis for $C_{48}H_{54}Cu_2Cl_2N_4P_2S_2$: calcd. C 65.71; H 5.47; N 3.65; S 4.17 %; found: C 65.36; H 5.78; N 3.73; S 4.20%.

$[Cu_2(\mu\text{-}Br)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ 9. Colorless compound (yield 69 %, M.p 95-98 ˚C). Elemental analysis for $C_{48}H_{54}Cu_2Br_2N_4P_2S_2$: calcd. C 52.36; H 4.90; N 5.09; S 5.82 %; found: C 52.61; H 5.00; N 5.13; S 5.75%.

$[Cu_2(\mu\text{-}I)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ 10. To a solution of copper(I) iodide (0.025 g, 0.13 mmol) in 10 mL of acetonitrile was added 1-propyl-1,3-imidazolidine-2-thione (0.037 g, 0.26 mmol), followed by stirring for 2 h at room temperature. To the white precipitates formed was added triphenylphosphine (0.034 g, 0.13 mmol) and it was heated followed by addition of dichloromethane (*v/v* :: 1:1). Slow evaporation of the solution at room temperature gave colorless crystals of **10** (yield 65 %, M.p 100-102˚C). Elemental analysis for $C_{48}H_{54}Cu_2I_2N_4P_2S_2$: calcd. C 48.24; H 4.52; N 4.69; S 5.36%; found: C 48.57; H 4.64; N 4.75; S 5.21 %.

$[Cu_2(\mu\text{-}Br)_2(L\text{-}NPh)_2(PPh_3)_2]$ 11. Colorless compound (yield 67 %, M.p 155-157 ˚C). Elemental analysis for $C_{54}H_{50}Cu_2Br_2N_4P_2S_2$: calcd. C 55.48; H 4.28; N 4.79; S 5.47%; found: C 55.53; H 4.26; N 4.61; S5.25 %.

$[Cu_2(\mu\text{-}I)_2(L\text{-}NPh)_2(PPh_3)_2]$ 12. Colorless compound (yield 69 %, M.p 135-137 ˚C). Elemental analysis for $C_{54}H_{50}Cu_2I_2N_4P_2S_2$: calcd. C 51.39; H 3.96; N 4.44; S 5.07 %; found: C 51.63; H 4.02; N 4.52; S 4.87 %.

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2.3. X-ray crystallography

Single crystals of complexes were mounted on polymer loops and data for these complexes were measured on a Rigaku-Oxford Diffraction Eos, Gemini –CCD auto diffractometer at 173(2) (**1, 3, 4-12**) and 293(2) (**2**) K. The diffractometer was equipped with a graphite monochromator with Mo–Kα radiation (λ = 0.71073 Å; **3, 11, 6**), or Cu-Kα radiation (λ = 1.54178 Å; **1, 2, 4, 5, 7, 8, 10, 12**). The structures were solved by direct methods and refined using full-matrix least-squares techniques based on F^2 using ShelXL-2014. In all the structures, the non-hydrogen atoms were refined anisotropically and hydrogens were fixed geometrically except for the ones attached to the imidazole nitrogens. Further it was checked that none of these structures in question (**1-7**, **10**) have any disorder in their refinement. Table 1 contains crystal data.

Table 1 Crystallographic data for complexes **1–12**

	1	**2**	**3**	**4**
Empirical formula	$C_{42}H_{42}ClCuN_2P_2S$	$C_{42}H_{42}BrCuN_2P_2S$	$C_{43}H_{44}ClCuN_2P_2S$	$C_{43}H_{44}CuIN_2P_2S$
M	767.76	812.22	780.78	873.24
T /K	173(2)	293(2)	173(2)	173(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P 2_1/n	P 2_1/n	P 2_1/n	P 2_1/n
a(Å)	13.0220(4)	13.0009(2)	13.0881(4)	12.8975(3)
b(Å)	20.5063(5)	20.8461(4)	20.2471(5)	21.2368(4)
c(Å)	14.8412(5)	14.7070(3)	15.2533(4)	15.1545(3)
α (°)	90	90	90	90
β (°)	105.560(4)	105.105(2)	105.139(3)	105.562(2)

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γ (°)	90	90	90	90
V(Å^3)	3817.8(2)	3848.13(13)	3901.77(19)	3998.66(15)
Z	4	4	4	4
D_{calcd} (g.cm^{-3})	1.336	1.40	1.329	1.451
μ (mm^{-1})	0.813	3.550	0.797	8.317
F(000)	1600	1672	1628	1776
Reflns collected	31662	15911	32675	17017
Unique reflns.	12752	7353	13050	7650
	($R_{int,}$ 0.0352)	($R_{int,}$ 0.0420)	($R_{int,}$ 0.0368)	($R_{int,}$ 0.0559)
Data/ restraints / parameters	12752/0/443	7353/0/444	13050/43/472	7650/0/453
Reflecs. with [I>2σ(I)]	9523	6325	9625	6852
Final R indices	R_1 = 0.0468	R_1 = 0.0416	R_1 = 0.0416	R_1 = 0.0522
[I>2σ(I)]	wR_2 = 0.1005	wR_2 = 0.1102	wR_2 = 0.0885	wR_2 = 0.1373
Final R indices	R_1 = 0.0722	R_1 = 0.0488	R_1 = 0.0693	R_1 = 0.0570
(all data)	wR_2 = 0.1152	wR_2 = 0.1168	wR_2 = 0.1026	wR_2 = 0.1427
Largest diff.	0.987 and	0.570 and	0.539 and	2.065 and
Peak/ hole e.Å^{-3}	-0.487	-0.512	-0.436	-1.790

	5	**6**	**7**	**8**
Empirical formula	$C_{36}H_{35}BrCuN_4PS_2$	$C_{45}H_{40}CuIN_2P_2S$	$C_{46}H_{50}Br_2Cu_2N_4P_2S_2$	$C_{48}H_{54}Cl_2Cu_2N_4P_2S_2$
M	762.22	893.23	1071.86	1010.99
T /K	173(2)	173(2)	173(2)	173(2)
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic
Space group	Pī	Pī	Pī	Pī

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a(Å)	9.9322(4)	10.5257(4)	9.1793(5)	9.4283(5)
b(Å)	10.6993(4)	12.8802(5)	10.2484(7)	10.2759(7)
c(Å)	17.6677(8)	15.7569(5)	13.4319(9)	13.1681(10)
α (°)	76.569(3)	76.632(3)	79.123(6)	78.871(6)
β (°)	80.316(4)	79.082(3)	73.321(5)	73.632(5)
γ (°)	69.508(4)	79.691(3)	69.953(6)	70.704(5)
V($Å^3$)	1702.79(13)	2020.19(13)	1131.33(14)	1148.27(14)
Z	2	2	1	1
D_{calcd} ($g.cm^{-3}$)	1.487	1.468	1.573	1.462
μ (mm^{-1})	4.116	1.470	2.907	1.242
F(000)	780	904	544	524
Reflns collected	11854	27355	13541	13314
Unique reflns.	6451	13280	7448	7559
	($R_{int,}$ 0.0376)	($R_{int,}$ 0.0302)	($R_{int,}$ 0.0285)	($R_{int,}$ 0.0490)
Data/ restraints / parameters	6451/0/407	13280/0/469	7448/0/263	7559/0/273
Reflecs. with [I>2σ(I)]	6036	9097	6134	6276
Final R indices	R_1 = 0.0387	R_1 = 0.0476	R_1 = 0.0330	R_1 = 0.0457
[I>2σ(I)]	wR_2 = 0.1052	wR_2 = 0.1145	wR_2 = 0.0726	wR_2 = 0.1150
Final R indices	R_1 = 0.0411	R_1 = 0.0804	R_1 = 0.0467	R_1 = 0.0570
(all data)	wR_2 = 0.1079	wR_2 = 0.1357	wR_2 = 0.0787	wR_2 = 0.1275
Largest diff.	0.651 and	0.854 and	0.487 and	0.520 and
Peak/ hole e.$Å^{-3}$	-0.517	-1.111	-0.649	-0.544

	9	**10**	**11**	**12**

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Empirical formula	$C_{48}H_{54}Br_2Cu_2N_4P_2S_2$	$C_{48}H_{54}Cu_2I_2N_4P_2S_2$	$C_{54}H_{50}Br_2Cu_2N_4P_2S_2$	$C_{54}H_{50}Cu_2I_2N_4P_2$
M	1099.91	1193.89	1167.94	1261.92
T /K	173(2)	173(2)	173(2)	173(2)
Crystal system	Triclinic	Triclinic	Monoclinic	Monoclinic
Space group	Pī	Pī	P 2_1/c	P 2_1/c
a(Å)	9.4815(6)	9.6418(12)	10.5137(3)	10.7515(2)
b(Å)	10.3547(6)	10.5247(8)	20.7529(6)	20.6834(4)
c(Å)	13.2247(8)	13.4048(12)	11.7654(3)	11.9733(3)
α (º)	79.062(5)	79.580(7)	90	90
β (º)	73.412(6)	72.802(9)	103.798(3)	106.826(2)
γ (º)	70.630(5)	70.907(9)	90	90
V(Å^3)	1167.40(13)	1222.6(2)	2493.00(12)	2548.61(10)
Z	1	1	2	2
D_{calcd} (g.cm^{-3})	1.565	1.622	1.556	1.644
μ (mm^{-1})	2.819	2.320	2.645	12.212
F(000)	560	596	1184	1256
Reflns collected	13822	14548	19058	9026
Unique reflns.	7700 ($R_{int,}$ 0.0400)	8056 ($R_{int,}$ 0.0306)	8252 ($R_{int,}$ 0.0407)	4872 ($R_{int,}$ 0.0376)
Data/ restraints / parameters	7700/0/273	8056/0/273	8252/2/99	4872/0/299
Reflecs. with [I>2σ(I)]	5909	6449	6208	4527
Final R indices [I>2σ(I)]	R_1 = 0.0410 wR_2 = 0.0865	R_1 = 0.0343 wR_2 = 0.0748	R_1 = 0.0416 wR_2 = 0.0859	R_1 = 0.0425 wR_2 = 0.1063

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Final R indices	$R_1 = 0.0609$	$R_1 = 0.0487$	$R_1 = 0.0664$	$R_1 = 0.0454$
(all data)	$wR_2 = 0.0966$	$wR_2 = 0.0832$	$wR_2 = 0.0979$	$wR_2 = 0.1103$
Largest diff.	0.519 and	0.738 and	0.656 and	1.670 and
Peak/ hole e.Å^{-3}	-0.778	-0.710	-0.620	-1.139

2.4. Antimicrobial studies

Test organisms and inoculum preparation. The reference strains of bacteria and yeast were obtained from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh, India. Reference strains included Gram positive bacteria: *Staphylococcus aureus* (MTCC 740), *Staphylococcus epidermidis* (MTCC 435), *Enterococcus faecalis* (MTCC 439), Gram negative bacteria *Shigella flexneri* (MTCC 1457), *Escherichia coli* (MTCC 119) and yeast *Candida tropicalis* (MTCC 230). A loopful of broths bacterial and yeast colonies were inoculated into 5 mL of their respective medium and incubated at 37 °C and 25 °C, respectively for 4 h. This was used as inoculum after adjusting the turbidity as per the McFarland turbidity standard. This turbidity is equivalent to approximately (1 to 2) $\times 10^8$ colony forming units per mL (CFU/mL). The inoculums thus prepared were used for further testing. In relation to live subject statement it is submitted here that the study has been carried out as per Institutional Bioethics Committee and National Guidelines .It is further stated it did not involve any experimentation on live animals or Humans.

Antimicrobial screening. A 100 µL of activated test organism (prepared as above) sample was inoculated onto suitable medium plates by the spread plate method. Wells measuring 8 mm in diameter were cut out in the medium using a sterilized stainless steel borer. A stock solution

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of each test complex of concentration 50 mg/mL was prepared in DMSO and each well was filled with 0.1 mL of this test complex and kept for incubation in an upright position for 18–24 h. Sensitivity was measured in terms of a diameter of the zone of inhibition. Any organism with a clear zone of inhibition ≤12 mm was considered to be resistant to the compound.[42]

Minimum inhibitory concentration (MIC). Minimum inhibitory concentration of the selected coordination compound dissolved in DMSO was worked out by the agar dilution method for their antimicrobial activity against the sensitive microorganisms. From the stock solution, the concentration of a complex in the range (0.001–2 mg/mL) was mixed with a Muller Hinton agar medium and then poured on plates. These plates were then inoculated with 0.1 mL of the activated bacterial and yeast strains by streaking with a sterile swab. The plates were incubated at 37°C for bacteria and 25 °C for yeast for 24 h each. The minimum concentration of the extract causing inhibition of the visible growth was taken as MIC. The results were compared with that of DMSO as a control.

MTT toxicity assay. In order to check the level of cellular toxicity of the test compounds, MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay was performed[43] as follows. Ten milliliter of sheep blood was taken into an injection syringe containing 3 mL of Alsever's solution (anticoagulant) and transferred to sterile centrifuge tube. The blood was centrifuged at 16,000 rpm at room temperature (25 °C) for 20 min so as to separate the plasma from the cells. The supernatant was discarded and 6 mL phosphate buffer saline (PBS) was added and it was again centrifuged. The blood cells were washed thrice with PBS by centrifugation and the pellet was re-suspended in 6 mL of PBS. Various dilutions of these cells were prepared using PBS and counted with the help of a hemocytometer under a light microscope so as to obtain cells equivalent to 1×10^5 cells/mL. One hundred microliters (100 µL)

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of this diluted suspension was added in each well and incubated at 37 °C for overnight. The supernatant was removed carefully and 200 µL of the sample solution (contains 10 mg/mL) was added and incubated further for 24 h. The supernatant was removed again and 20 µL MTT solution (5 mg/mL) was added to each well and incubated further for 3.5 h at 37 °C on an orbital shaker at 60 rpm. After incubation, the supernatant was removed without disturbing the cells and 50 µL of DMSO was added to each well to dissolve the formazan crystals. The absorbance was measured at 590 nm using an automated microplate reader (Biorad 680-XR, Japan). The wells with untreated cells served as a control. Reduction of MTT can only occur in metabolically active cells, as MTT is converted into formazan crystals and hence the absorbance directly represents the viability of the cells (% viability = (optical density (OD) of Treated/ OD of Control) × 100). If the percent viability of the blood cells is quite high, then the compounds are non-cytotoxic in nature.

3 Results and discussion

3.1. Synthetic comments. Scheme 1 depicts formation of complexes **1-12.** Reactions of copper(I) halides with imidazolidine-2-thiones (L-NR) having bulky substituents (R = Pr^n, Bu^n, Ph) at one nitrogen atom of an imidazolidine ring in the presence of PPh_3 as a co-ligand have yielded mononuclear $[CuX(PPh_3)_2(L\text{-}NR)]$ (R, X: Pr^n, Cl, **1**; Pr^n, Br, **2**; Bu^n, Cl, **3**; Bu^n, I, **4**; Ph, I, **6**) and dinuclear $[Cu_2(\mu\text{-}X)_2(PPh_3)_2(L\text{-}NR)_2]$ (R, X: Et, Br, **7**; Pr^n, Cl, **8**; Pr^n, Br, **9**; Pr^n, I, **10**;Ph, Br, **11**;Ph, I, **12**) complexes. Mononuclear complexes **1-4, 6**, were formed by reacting a mole of copper(I) halide with two moles of PPh_3 in organic solvents followed by reaction with one mole of the respective L-NR thio-ligand (Cu : PPh_3 : L-NR : : 1 : 2 : 1 molar ratio).

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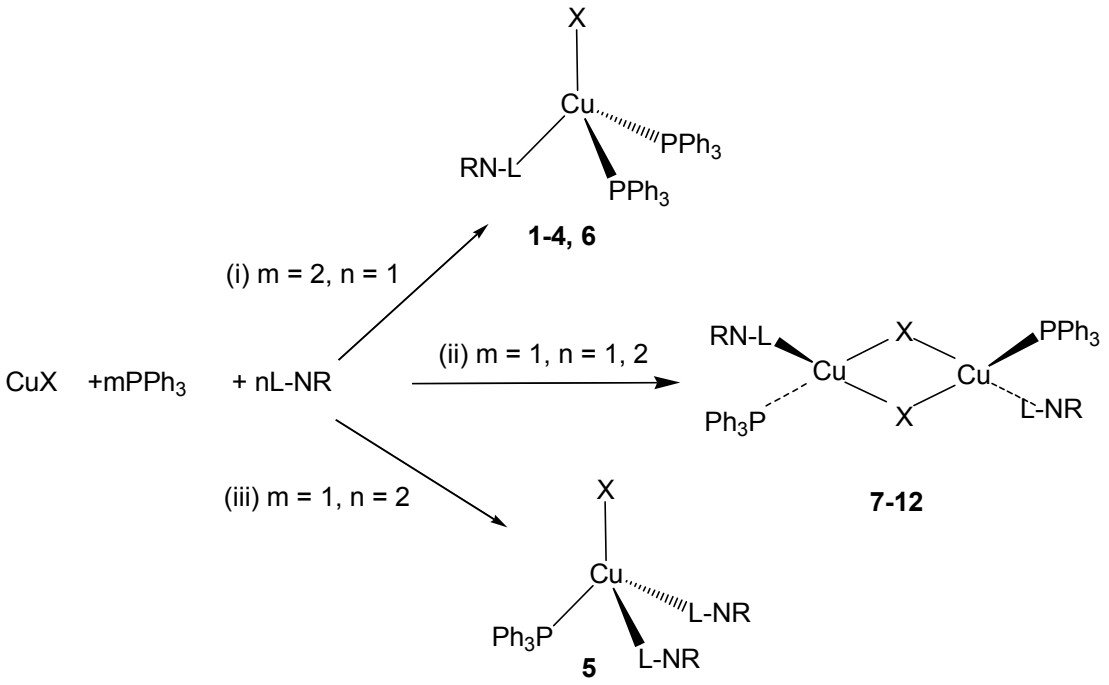
Similarly, dinuclear complexes **7, 9, 11** and **12** were obtained by reacting a mole of copper(I) halide with a



Scheme 1. Synthesis of complexes; (i) CH_3CN, **6**; CH_3CN-MeOH, **1- 4**;
(ii) CH_3CN-MeOH, **7**; CH_3CN, **8**; CH_3CN-CH_2Cl_2 **9-12**;
(iii) CH_3CN-CH_2Cl_2 **5**

mole of PPh_3 and a mole of thio-ligand (Cu : PPh_3 : L-NR : : 1 : 1 : 1 molar ratio). Dinuclear complex **10** could not be obtained by a similar equimolar reaction owing to a turning of the reaction mixture green and no product could be characterized. Thus complex **10** was obtained by reacting first copper(I) iodide with L-NPr^n followed by addition of PPh_3 in 1 : 2 : 1 molar ratio (Cu : L-NPr^n : PPh_3). Here, an excess of L-NPr^n thio-ligand appears to have stabilized the Cu(I) oxidation state. A similar reaction of copper(I) bromide with L-NPh and PPh_3 in 1 : 2 : 1 molar ratio (Cu : L-NPh : PPh_3) did not yield a complex similar to **10**, rather it formed a mononuclear complex, [$CuBr(PPh_3)(L\text{-}NPh)_2$] **5,** with less common stoichiometry.[44] This thio-ligand, L-NPh,

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was previously reported to form [$CuBr(PPh_3)_2$(L-NPh)] with PPh_3 coordinated.[18] It is added here that reaction of copper(I) chloride/bromide with the thio-ligands under discussion in the absence of PPh_3 involved C–S rupture forming copper(II) sulfate, but other products could not be identified. Thus generally the order of reaction followed binding of copper(I) halides to PPh_3 followed by binding to thio ligands.[18]

In literature several thio-ligands,[45-51] similar to 1, 3-imidazolidine-2-thione, such as 2-thiohydantoin, [45] 5,5-diphenyl-2-thiohydantoin,[45] imidazolidine-2-thione,[46,50] N-methyl-imidazoline-2-thione,[47,48,51] N-methyl-imidazolidine-2-thione,[18] N-ethyl-imidazolidine-2-thione,[18] N-phenyl-imidazolidine-2-thione,[18] and imidazolidine-2-thione[49] on reaction with copper(I) halides have also yielded analogous mononuclear,[18,45,46,50,47,48,49] halogen-bridged dinuclear[18] and sulfur-bridged dinuclear[18,51] complexes.

3.2. IR and NMR spectroscopy. All of the complexes have shown IR stretching and bending bands within a range of 4000 – 400 cm^{-1}, varying in intensity from weak to strong (See Supporting Information, Fig.S35 - Fig.S51 for IR Spectra of complexes / ligands). The ν(N-H) bands occur in the region 3142-3241cm^{-1} (strong to medium in intensity) in complexes (Table 2) and this presence confirms the coordination of a thio-ligand to a metal center as a neutral ligand. In comparison to the uncoordinated thio-ligands [$\nu_{(N-H)}$: 3191s, $\nu_{(L-NEt);}$ 3207 s, $\nu_{(L-NPr^n)}$; 3196 s, $\nu_{(L-NBu^n)}$; 3203 s, $\nu_{(L-NPh)}$], these ν(N-H) bands have been found to be shifted either to a low energy region (**1, 3, 6, 8**) or to a high energy region (**2, 4, 5, 7, 9, 10-12**). Compounds containing thioamide group H-N-C=S give rise to four characteristic thioamide bands in their IR spectra.[52] Thioamide band I has contribution from δNH + δC-H + υC=N, band II from υC–N + δNH + δCH + υC=N, band III from υC–N + from υC–S and band IV from υC–S. Thioamide bands III and IV which contain main contribution from υ(C–S), undergo red shift of 8-12 cm^{-1} and 7-63

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cm^{-1} in complexes as compared to the free ligand. This red shift indicates the metal-sulphur bonding. Band I and band II have main contribution from δNH + υC-N + υC=S, remain nearly unshifted which imply that there is no coordination through nitrogen atom of thioamide group. The appearance of ν(P-C_{Ph}) bands in the region 1084-1099 cm^{-1} (weak to medium in intensity) confirm the presence of coordinated PPh_3 in the complexes .

Table 2 IR spectral bands of complexes and free thio-ligands

Complexes/ Free thio-ligand	ν(N-H)	ν(P-C_{Ph})	Band I	Band II	Band III	Band IV
[CuCl(L-NPr^n)$(PPh_3)_2$] (**1**)	3176 s	1093 s	1512 s	1281 s	1027 m	747 s
[CuBr(L-NPr^n)$(PPh_3)_2$] (**2**)	3217 s	1093 s	1514 s	1283 m	1029 w	751 m
[CuCl(L-NBu^n)$(PPh_3)_2$] (**3**)	3142 w	1099 m	1483 m	1314 s	1024 m	740 s
[CuI(L-NBu^n)$(PPh_3)_2$] (**4**)	3222 s	1084 s	1496 s	1300 w	1037 m	771 w
[CuBr(L-NPh)$_2(PPh_3)$] (**5**)	3210 s	1095 m	1510 s	1288 m	1028 m	750 s
[CuI(L-NPh)$(PPh_3)_2$] (**6**)	3200 s	1094 s	1515 s	1291 s	1027 m	744 s
[Cu_2(μ-Br)$_2$(L-NEt)$_2(PPh_3)_2$] (**7**)	3226 s	1093 m	1515 s	1283 m	1028 w	752 m
[Cu_2(μ-Cl)$_2$(L-NPr^n)$_2(PPh_3)_2$] (**8**)	3194 s	1094 s	1514 s	1282 m	1029 w	751 s
[Cu_2(μ-Br)$_2$(L-NPr^n)$_2(PPh_3)_2$] (**9**)	3218 s	1093 m	1513 s	1283 m	1028 w	751 m
[Cu_2(μ-I)$_2$(L-NPr^n)$_2(PPh_3)_2$] (**10**)	3239 s	1092 m	1510 s	1281 m	1027 w	747 s
[Cu_2(μ-Br)$_2$(L-NPh)$_2(PPh_3)$] (**11**)	3210 m	1095 m	1502 s	1239 s	1029 w	750 s
[Cu_2(μ-I)$_2$(L-NPh)$_2(PPh_3)_2$] (**12**)	3241 s	1095 s	1506 s	1305 w	950 w	750 s
L-NEt	3191 s	-	1513 s	1279 m	1037 m	792 m
L-NPr^n	3207 s	-	1514 s	1280 s	1037 w	806 w
L-NBu^n	3196 s	-	1514 s	1284 s	1041 w	803 w
L-NPh	3203 s	-	1518 s	1288 m	1040 m	757 s

s = strong, m = medium, w = weak

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The ^{1}H NMR spectral data of coordination compounds **1-12** are given in Table 3. The N-H protons of the uncoordinated thio-ligands showed a single peak in each case in the range 5.91-6.38 ppm, which after coordination to the metal centre shifted to the low field in the range, 7.83-9.43 ppm in compounds **1-12**. These changes suggest coordination through S donor atoms of the thio-ligands. The C^4H_2 ring protons showed NMR signals at low magnetic field as compared to the C^5H_2 ring protons. Both types of these ring protons showed multiplets. The N-CH_2 protons of the N-R moiety have shown low field shifts and in some cases merge with the C^4H_2 /C^5H_2 ring protons in the coordination compounds. The o-H, m-H and p-H protons of the coordinated PPh_3 phenyl rings appear as multiplets and showed a low field shift as compared to the protons of the uncoordinated PPh_3.

In ^{13}C NMR spectroscopy, the C^2 signal of a coordinated thio-ligand showed a significant upfield shift and thus these ^{13}C NMR signals in complexes occurred in the range, 179.64-181.74 ppm relative to the free ligands (cf. L-NR, range 182.92-183.70 ppm) (Table 4). The C^4, C^5 and N-R carbon NMR signals of the thio-ligands showed minor variations. The upfield shift of the C^2 NMR signal showed coordination of a thio-ligand to Cu(I) metal centre through S donor atom. As regards the coordinated PPh_3, the ^{13}C NMR signals undergo variations of ipso, ortho, meta and para carbons as follows: (i) ipso-carbons of P-Ph moiety have shown upfield shifts, (ii) ortho- and meta-carbons of P-Ph have displayed irregular trend (up-field or low-field shifts) and (iii) the para-carbons showed low field shifts. It is found that $^{1}J(^{13}C–^{31}P)$ coupling of p-carbon is observed in all complexes which was absent in free PPh_3 ligand (Table 4). The $^{13}C–^{31}P$ coupling constants (J_{C-P}) pertaining to o-, m-, and p-carbons of P-Ph moiety are found to increase in the complexes. These variations in J_{C-P} coupling constants are attributed to a dative bond formation

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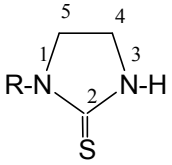
between PPh_3 and Cu metal centre (See Supporting Information, Fig.S52 - Fig.S83 for NMR ($^1H/^{13}C$) spectra of complexes/ligands)

Table 3 ^1H NMR spectral data (δ in ppm) of complexes **1-12**

Free thio-ligand (L-NR)[e]/ Complex	-NH / (C^4H_2) / (C^5H_2) 	-NR , R =Et, Pr, Bu, Ph	$P(C_6H_5)_3$
L-NEt[b]	6.09 (s; 1H) / 3.68(m; 4H)[a]/ 3.58 (m; 2H)	3.68(m; N-CH_2; 4H)[a], 1.20 (t; CH_3; 3H)	-
L-NPr[n,b]	5.91 (s; 1H) / 3.71(t; 2H) / 3.46 (t; 2H)	3.58 (m; N-CH_2; 2H)[a], 1.65 (m; CH_2;2H), 0.97 (t; CH_3;3H)	-
L-NBu[n,b]	6.02 (s; 1H) / 3.69 (m; 2H) / 3.59 (m; 2H)[a]	3.59 (m; N-CH_2; 2H)[a], 1.59 (m; CH_2; 2H), 1.32 (m; CH_2; 2H), 0.97 (t; CH_3; 3H)	-
L-NPh[b]	6.38 (s; 1H)/ 4.20 (t; 2H)/ 3.76 (t; 2H)	7.60 (m; o-H, 2H), 7.42 (m; m-H, 2H), 7.27 (m; p-H, 2H)	-
PPh_3[b]	-	-	7.32 (m; o-H, m-H, p-H)
1[b] (Cl, L-NPr[n])	9.22 (s; 1H)/ 3.72 (m; 2H)[a]/ 3.49 (t; 2H)	3.72 (m; N-CH_2; 2H)[a], 1.65 (m; CH_2; 2H), 0.96 (t; CH_3; 3H)	7.69 (m; o-H, 12H), 7.42 (m; m-H, p-H, 18H)
2[b] (Br, L-NPr[n])	8.34 (s; 1H)/ 3.61 (dt; 2H)[a]/ 3.46 (t; 2H)	3.61 (dt; N-CH_2; 2H)[a], 1.61 (sx; CH_2;2H), 0.93 (t; CH_3;3H)	7.43 (m; o-H, 12H), 7.36 (m; m-H, 12H), 7.30 (m; p-H, 6H)
3[b] (Cl, L-NBu[n])	8.96 (s; 1H)/ 3.71 (m; 2H)[a]/ 3.50 (t; 2H)	3.71 (m; N-CH_2; 2H)[a], 1.59 (m; CH_2; 2H), 1.33 (m; CH_2; 2H), 0.93 (t; CH_3; 3H)	7.40 (m; o-H, 12H), 7.25 (m; m-H, 12H), 7.16 (m; p-H, 6H)
4[b] (I, L-NBu[n])	7.83 (s; 1H)/ 3.62(dt;	3.62 (dt; N-CH_2; 2H)[a], 1.54	7.70 (m; o-H, 12H), 7.43

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	2H)[a]/ 3.50 (t; 2H)	(quint; CH_2; 2H), 1.35 (m; CH_2; 2H), 0.95 (t; CH_3;3H)	(m; m-H, p-H, 18H)
5[b] (Br, L-NPh)	8.20 (s; 2H)/ 4.16 (t; 4H)/ 3.80 (t; 4H)	[d]	7.40 (m; o-H, m-H, p-H, 25H)
6[b] (I, L-NPh)	8.43 (s; 1H)/ 4.07 (m; 2H)/ 3.70 (t; 2H)	[d]	7.37 (m; o-H, m-H, p-H, 35H)
7[b] (Br, L-NEt)	8.92 (s; 1H)/ 3.74 (m; 4H)[a]/ 3.59 (m; 4H)	3.74 (m; N-CH_2;4H)[a], 1.21 (t; CH_3;6H)	7.52 (m; o-H, 12H), 7.39 (m; m-H, p-H, 18H)
8[b] (Cl, L-NPr[n])	9.26 (s; 1H)/ 3.71 (m; 4H)[a]/ 3.48 (t; 4H)	3.71 (m; N-CH_2; 4H)[a], 1.65 (m; CH_2 4H), 0.96 (t; CH_3; 6H)	7.69 (m; o-H, 12H), 7.46 (m; m-H, p-H, 18H)
9[b] (Br, L-NPr[n])	8.70 (s; 1H)/ 3.71 (m; 4H)[a]/ 3.49 (t; 4H)	3.71 (m; N-CH_2; 4H)[a], 1.66 (m; CH_2; 4H), 0.96 (t; CH_3;6H)	7.69 (m; o-H, 12H), 7.48 7.46 (m; m-H, p-H, 18H)
10[c] (I, L-NPr[n])	8.12 (s; 1H)/ 3.67 (t; 2H)[c]/ 3.49 (t; 4H) [a]	3.49(t; N-CH_2 ; 4H)[a], 1.50 (m; CH_2;2H), 0.81 (t; CH_3;3H)	7.56 (m; o-H, m-H, p-H, 30H)
11[b] (Br, L-NPh)	9.43 (s; 1H)/ 4.18 (t; 4H)/ 3.86 (t; 4H)	[d]	7.69 (m; o-H, 16H), 7.43 (m; m-H, p-H, 24H)
12[b] (I, L-NPh)	8.80 (s; 1H)/ 4.17 (t; 4H)/ 3.86 (t; 4H)	[d]	7.45 (m; o-H, m-H, p-H, 40H)

[a] (N-CH_2) and (ring proton of CH_2) got merged; [b] $CDCl_3$; [c] DMSO, [d] N-Ph protons obscured by phenyl ring of PPh_3

Table 4 C^{13} NMR spectral data (δ in ppm) of complexes **1-12**

Free thio-ligand (L-NR)[e]/ Complex	C^2/(C^4H_2)/(C^5H_2)	-N-R	$P(C_6H_5)_3$
L-NEt[b]	182.92/ 41.39/ 47.97	41.67 (N-CH_2), 12.21 (CH_3)	-
L-NPr[n,b]	183.70/ 41.39/ 48.62[a]	48.62 (N-CH_2)[a], 20.44	-

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		(CH_2), 11.16 (CH_3)	
L-NBu^{n,b}	183.42/ 41.44/ 48.61	46.77 (N-CH_2), 29.26 (CH_2), 19.99 (CH_2), 13.89 (CH_3)	-
L-NPh^{b}	182.99/ 41.65/ 52.13	139.95 (N-C), 124.47 (o-C), 128.82 (m-C), 126.44 (p-C)	-
PPh_3^{b}	-	-	137.14 (*i*-C), (40 Hz); 133.83 (o-C), (76 Hz); 128.60 (m-C), (28 Hz) 128.85 (p-C)
1^{b} (Cl, L-NPr^{n})	180.77/ 41.94/ 48.64	47.82 (N-CH_2), 20.54(CH_2), 11.23 (CH_3)	134.45 (*i*-C), (100 Hz); 134.13 (o-C), (56 Hz); 128.30 (m-C), (36 Hz) 129.29 (p-C), (8 Hz)
2^{b} (Br, L-NPr^{n})	180.49/ 41.71/ 48.59	47.76 (N-CH_2), 20.49 (CH_2), 11.21 (CH_3)	134.26 (*i*-C), (96 Hz); 134.17 (o-C), (60 Hz); 128.29 (m-C), (32 Hz) 129.29 (p-C), (4 Hz)
3^{b} (Cl, L-NBu^{n})	180.89/ 41.82/ 48.49	45.93 (N-CH_2), 29.27 (CH_2), 19.86 (CH_2), 13.94 (CH_3)	134.56 (*i*-C), (88 Hz); 134.13 (o-C), (56 Hz); 128.27 (m-C), (36 Hz) 129.19 (p-C), (8 Hz)
4^{b} (I, L-NBu^{n})	179.99/ 41.57/ 48.68	45.82 (N-CH_2), 29.20 (CH_2), 19.87 (CH_2), 13.94 (CH_3)	134.11 (*i*-C), (160 Hz); 134.16 (o-C), 128.30 (m-C), (36 Hz); 129.38 (p-C), (4 Hz)
5^{b} (Br, L-NPh)	181.18/ 42.02/ 52.43	139.23 (N-C), 124.43 (o-C), 128.93 (m-C), 126.79 (p-C)	133.97 (*i*-C), (60 Hz); 133.19 (o-C), (125 Hz); 128.50 (m-C), (40 Hz); 129.64 (p-C), (5 Hz)
6^{b} (I, L-NPh)	181.02/ 42.22/ 52.49	139.13 (N-C), 124.96 (o-C), 128.96 (m-C), 126.88 (p-C)	133.91 (*i*-C), (60 Hz); 133.28 (o-C), (110 Hz); 128.55 (m-C), (40 Hz); 129.65 (p-C), (5 Hz)

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7[b] (Br, L-NEt)	179.64/ 41.01/ 48.32	41.94 (N-CH_2), 12.21 (CH_3)	133.94 (*i*-C), (60 Hz); 132.49 (o-C), (130 Hz); 128.66 (m-C), (40 Hz); 129.94 (p-C), (5 Hz)
8[b] (Cl, L-NPr^n)	180.49/ 42.09/48.90	47.93 (N-CH_2), 20.49 (CH_2), 11.10 (CH_3)	133.91 (*i*-C), (60 Hz); 132.54 (o-C), (135 Hz); 128.68 (m-C), (40 Hz); 129.95 (p-C)
9[b] (Br, L-NPr^n)	180.25/ 41.97/ 49.00	47.94 (N-CH_2), 20.46 (CH_2), 11.13 (CH_3)	133.94 (*i*-C), (60 Hz); 132.51 (o-C), (130 Hz); 128.67 (m-C), (40 Hz); 129.96 (p-C), (5 Hz)
10[c] (I, L-NPr^n)	180.52/ 41.82/ 49.01	48.07 (N-CH_2), 20.49 (CH_2), 11.26 (CH_3)	134.13 (*i*-C), (60 Hz); 132.13 (o-C), (40 Hz); 128.44 (m-C), (36 Hz) 129.62 (p-C), (8 Hz)
11[b] (Br, L-NPh)	180.74/ 42.12/ 52.28	139.28 (N-C), 124.87 (o-C), 128.88 (m-C), 126.65 (p-C)	134.15 (*i*-C), (80 Hz); 133.94 (o-C), (65 Hz); 128.39 (m-C), (35 Hz) 129.33 (p-C)
12[b] (I, L-NPh)	181.02/ 42.22/ 52.49	138.58 (N-C), 125.15 (o-C), 129.03 (m-C), 127.17 (p-C)	134.06 (*i*-C), (60 Hz); 132.10 (o-C), (40 Hz); 128.54 (m-C), (35 Hz) 129.84 (p-C)

[a] (N-CH_2) and (ring carbon CH_2) got merged; [b] $CDCl_3$

3.3 . Molecular structures

The analytical data of these coordination compounds are supported by their stoichiometry as follows: [CuX(PPh_3)$_2$(L-NR)] (**1-4, 6**), [CuX(PPh_3)(L-NR)$_2$] (**5**) and {CuX(L-NR)(PPh_3)}(**7-12**). The single crystal x-ray crystallography has supported **1-6** as mononuclear complexes and **7-12** as dinuclear complexes. Complexes **5-10** each crystallized in the triclinic crystal system in space group Pī, whereas complexes **1-4, 11, 12** crystallized in monoclinic crystal system in space groups $P2_1/n$ (**1-4**) or $P2_1/c$ (**11, 12**) (Table 1).

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Mononuclear coordination compounds. The crystal structure of coordination compound **1** shows that the Cu metal centre is coordinated to one S atom of the L-NPr^n thio-ligand, the P donor atom of two PPh_3 ligands and one Cl anion at bond distances of 2.3735 (6); 2.2779 (5), 2.2634 (5), and 2.3531 (5) Å, respectively (Table 5). These distances are comparable to the sum of covalent radii of metal and the donor group (Cu-S, 2.35; Cu-P, 2.43; Cu-Cl, 2.32 Å)[53] (Fig. 1). The Cu-S and Cu-P bond distances in coordination compounds **2-4** lie in the range, 2.3673-2.4391 (S) Å, and 2.2634-2.291(P) Å, and are similar to those found in compound **1** (Fig. 2-4). The copper-halogen bond distances vary in the order: Cu-Cl < Cu-Br < Cu-I, as expected. In compound **5**, with two thio-ligands (L-NPh) and one PPh_3 bonded to the copper metal centre, Cu-S, Cu-P distances are shorter than those found in analogous compounds (Table 5) (Fig. 5). The bond angles around Cu metal centre fall in the range, 102.62–123.50^o, with P1-Cu-P2 being the largest, and P1-Cu-S1, the shortest. The bonding patterns of the other coordination compounds (**2-4, 6**) are similar to that observed in complex **1** (Fig. 6), except for the differences in the halogen anion (Br, **2**; Cl, **3**; I, **4**, **6**) and thio-ligand, which alter the bond parameters around Cu(I). The largest P-Cu-P bond angle lies within a range of 123.46–123.973^o. Another type of mononuclear complex reported here is [CuBr(PPh_3)(L-NPh)$_2$] (**5**), where Cu(I) is bonded to two sulfur atoms of two thio-ligands, a P donor atom of PPh_3 and a bromide anion with the bond lengths of 2.3484, 2.3247 (S), 2.2408 (P), and 2.5183 (Br) Å, respectively (Table 5). Bond angles around the central Cu atom lie within the range 99.74–112.84^o, and where the P-Cu-X is the largest angle (112.84^o).

Dinuclear complexes. The single crystal x-ray crystallography showed that coordination compound **7** existed as a dinuclear complex (Fig. 7). In this dinuclear complex, [Cu_2(μ-Br)$_2$(κ^1:S-L-NEt)$_2$(PPh_3)$_2$], bromine atoms form bridges and each copper metal is further bonded

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to one P donor atom of a PPh_3 ligand and one S donor atom of a thio-ligand. The Cu-S and Cu-P bond distances of 2.3021(6) Å and 2.2421(5) Å respectively are less than the sum of covalent radii of Cu/S (2.35 Å) and Cu/P (2.43Å).[53] The unequal Cu-Br bond distances of 2.5063(3) Å and 2.6124(4) Å of Cu_2Br_2 core are longer than the sum of covalent radii of Cu/Br (2.44 Å) due to bridging and it reveals that the Cu_2Br_2 core forms a parallelogram. The angles around each metal centre in the range, 97.73–115.31° are typical of a distorted tetrahedral geometry.[18] The Cu_2Br_2 core angles for Cu/Br are 97.73 and 82.26° respectively. The bonding parameters of the other dinuclear compounds **8-12** are similar to those of compound **7** (Table 5) (Fig. 8-12). The Cu_2Br_2 core angles of bromo-bridged dinuclear compound **9** are similar to those of compound **7**. Interestingly, in compound **11**, the Cu_2Br_2 core angles for Cu/Br are 102.87and 77.12°, respectively, and are different from the corresponding angles found in the **7**/**9** compounds. The difference may be attributed to the presence of a bulky group at an N atom of the imidazolidine ring of the L-NPh thio-ligand in compound **11**. The choro-bridged dinuclear compound **8** has shown Cu_2Cl_2 core angles comparable to those of compound **9** having the same thio-ligand, L-NPr^n. The bulky bridging iodine atoms in dinuclear compounds **10** and **12** make angles of 102-106/73-78° at Cu/I, respectively, which are similar to those in compound **11**.

The C–S bond lengths in compounds **1-12** fall in the range, 1.68–1.70 Å, which are less than the C–S single bond length (1.81 Å) but longer than the C=S double bond length (1.62 Å), suggesting a partial double bond character in the C–S bond.[53,54] Finally, the Cu-Cu separations of 3.157–3.410 Å in all the dimeric compounds are more than twice the sum of van der Waals radius of Cu atom, 2.80 Å.[53] It shows that there are no metal-metal interactions in dinuclear compounds.

Table 5 Bond lengths (Á) and bond angles (°) of complexes **1 – 12**

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Mononuclear complexes

	1(Cl)	**2**(Br)	**3**(Cl)	**4**(I)	**6**(I)		**5**(Br)
Cu1–S1	2.3735(6)	2.3721(7)	2.3791(5)	2.3673(9)	2.4390(8)	Cu1–S1	2.3484(7)
Cu1–X1	2.3531(5)	2.4817(5)	2.3554(5)	2.6548(5)	2.6065(4)	Cu1–S2	2.3247(6)
Cu1–P1	2.2779(5)	2.2766(7)	2.2655(5)	2.2853(9)	2.2773(8)	Cu1–X1	2.5183(4)
Cu1–P2	2.2634(5)	2.2706(7)	2.2810(5)	2.2800(10)	2.2908(8)	Cu1–P1	2.2408(6)
S–C	1.695(2)	1.703(3)	1.698(2)	1.704(4)	1.691(3)	S1–C1	1.684(2)
P1–Cu1–S1	102.62(2)	102.64(3)	108.828(18)	103.67(4)	104.08(3)	S2–C10	1.691(2)
P2–Cu1–S1	109.12(2)	109.06(3)	104.972(18)	108.64(4)	106.63(3)	P1–Cu1–S1	112.69(3)
P1–Cu1–X1	109.90(2)	108.67(2)	100.735(18)	106.85(3)	103.18(2)	P1–Cu1–S2	112.16(2)
P2–Cu1–X1	102.66(2)	102.46(2)	108.627(19)	102.22(3)	108.96(2)	P1–Cu1–X1	112.849(19)
X1–Cu1–S1	108.55(2)	109.98(2)	109.18(2)	112.12(3)	107.41(2)	X1–Cu1–S1	108.79(2)
P2–Cu1–P1	123.50(2)	123.78(3)	123.973(18)	123.44(4)	125.46(3)	X1–Cu1–S2	109.83(2)
						S1–Cu1–S2	99.74(2)

Halogen-bridged dinuclear complexes

	7(Br)	**8** (Cl)		**7**(Br)	**8** (Cl)
Cu1–S1	2.3021(6)	2.3055(6)	P1–Cu1–S1	115.31(2)	113.82(2)
Cu1–X1	2.5063(3)	2.3806(5)	P1–Cu1–X1	112.933(17)	111.041(19)
Cu1–X1*	2.6124(4)	2.5020(6)	P1–Cu1–X1*	108.956(17)	114.281(18)
Cu1–P1	2.2421(5)	2.2238(5)	S1–Cu1–X1	104.618(16)	103.640(19)
S1–C1	1.707(2)	1.6960(19)	S1–Cu1–X1*	115.173(16)	114.687(19)
Cu···Cu	3.368	3.221	X1–Cu1–X1	97.738(11)	97.500(17)
			Cu1–X1–Cu1	82.263(11)	82.499(17)
	9 (Br)	**10** (I)		**9** (Br)	**10** (I)
Cu1–S1	2.3027(7)	2.3070(8)	P1–Cu1–S1	114.48(3)	113.92(3)
Cu1–X1	2.5061(4)	2.6642(4)	P1–Cu1–X1	112.49(2)	109.87(2)
Cu1–X1*	2.6206(4)	2.6642(4)	P1–Cu1–X1*	110.014(19)	111.43(2)
Cu1–P1	2.2370(6)	2.2567(7)	S1–Cu1–X1	102.78(2)	101.97(2)

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S1–C1	1.709(2)	1.701(2)	S1–Cu1–X1*	115.487(19)	116.16(2)
Cu···Cu	3.300	3.410	X1–Cu1–X1	99.910(14)	102.179(14)
			Cu1–X1–Cu1	80.090(14)	77.821(14)
	11(Br)	**12** (I)		**11**(Br)	**12** (I)
Cu1–S1	2.3210(6)	2.3302(9)	P1–Cu1–S1	116.21(3)	115.83(4)
Cu1–X1	2.5233(3)	2.6866(6)	P1–Cu1–X1	109.164(19)	107.16(3)
Cu1–X1*	2.5233(3)	2.6867(6)	P1–Cu1–X1*	113.290(18)	111.16(3)
Cu1–P1	2.2387(6)	2.2584(9)	S1–Cu1–X1	102.617(18)	102.28(3)
S1–C1	1.689(2)	1.693(4)	S1–Cu1–X1*	111.215(18)	112.94(3)
Cu···Cu	3.157	3.222	X1–Cu1–X1	102.874(12)	106.462(19)
			Cu1–X1–Cu1	77.12(12)	73.540(19)

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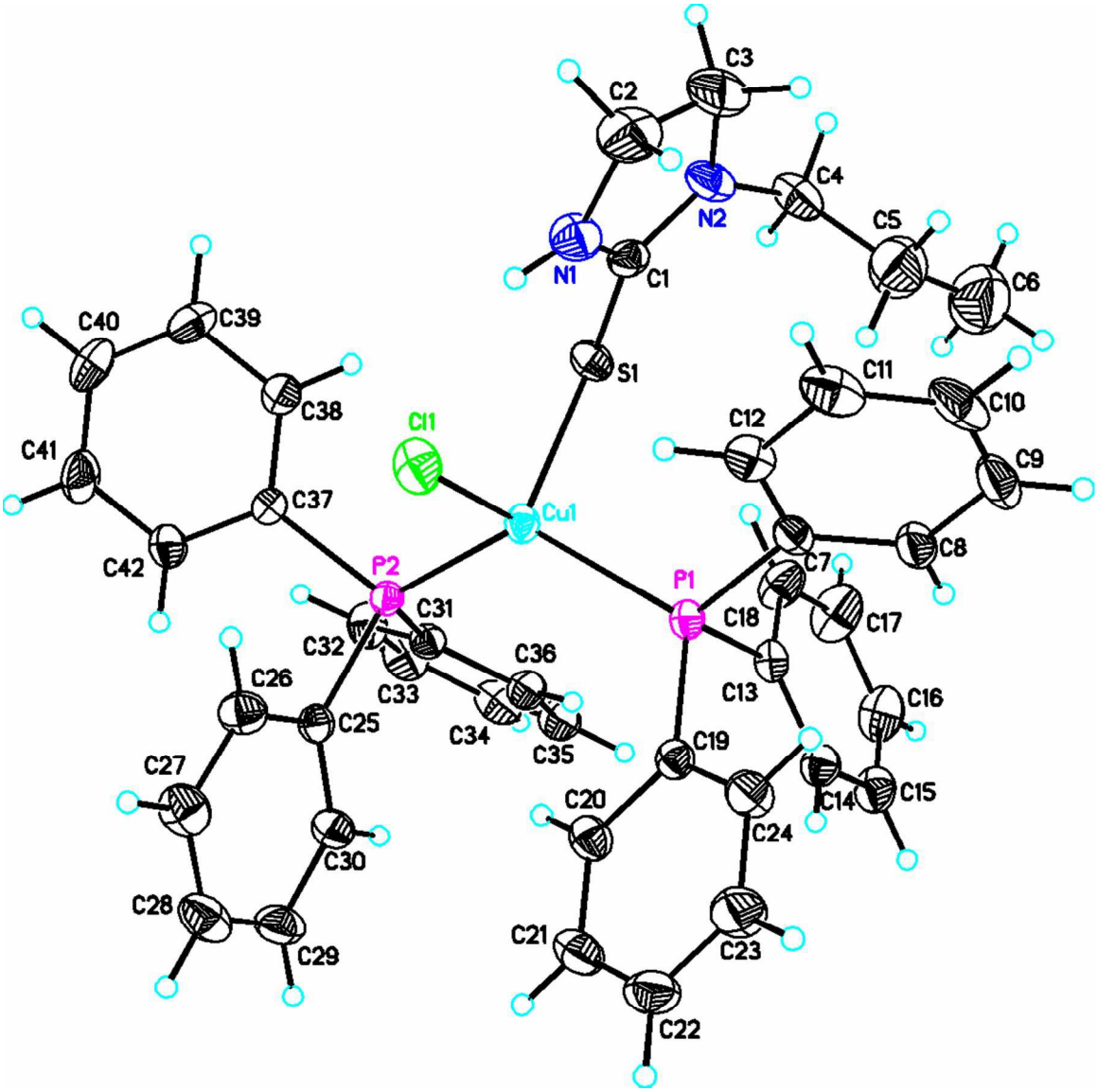

Fig. 1 Molecular structure of complex [CuCl(L-NPr^n)(PPh_3)$_2$] **(1).** Displacement ellipsoids are drawn at the 40% probability level.

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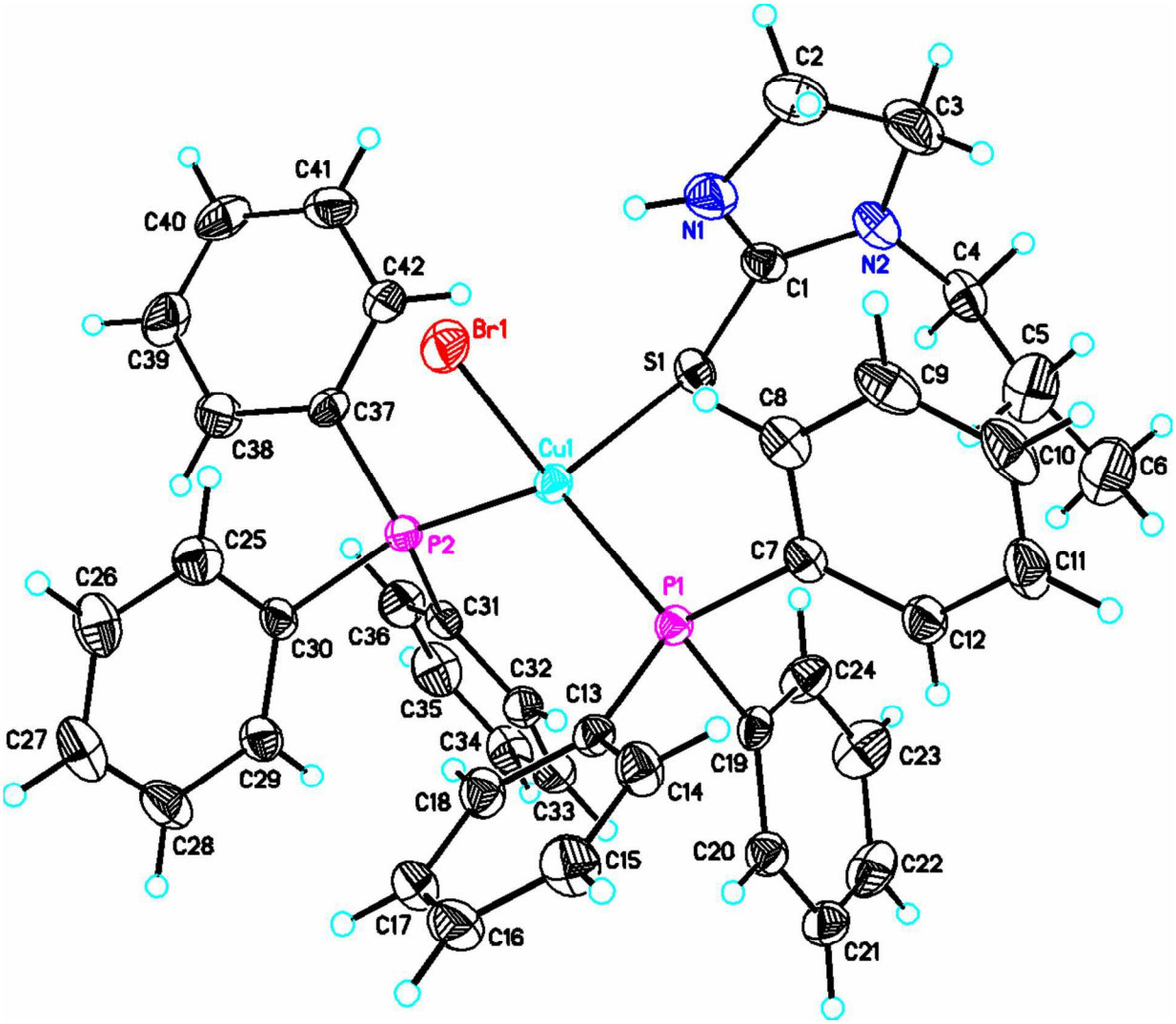

Fig. 2 Molecular structure of complex [CuBr(L-NPr^{n})(PPh_3)$_2$] **(2).** Displacement ellipsoids are drawn at the 40% probability level.

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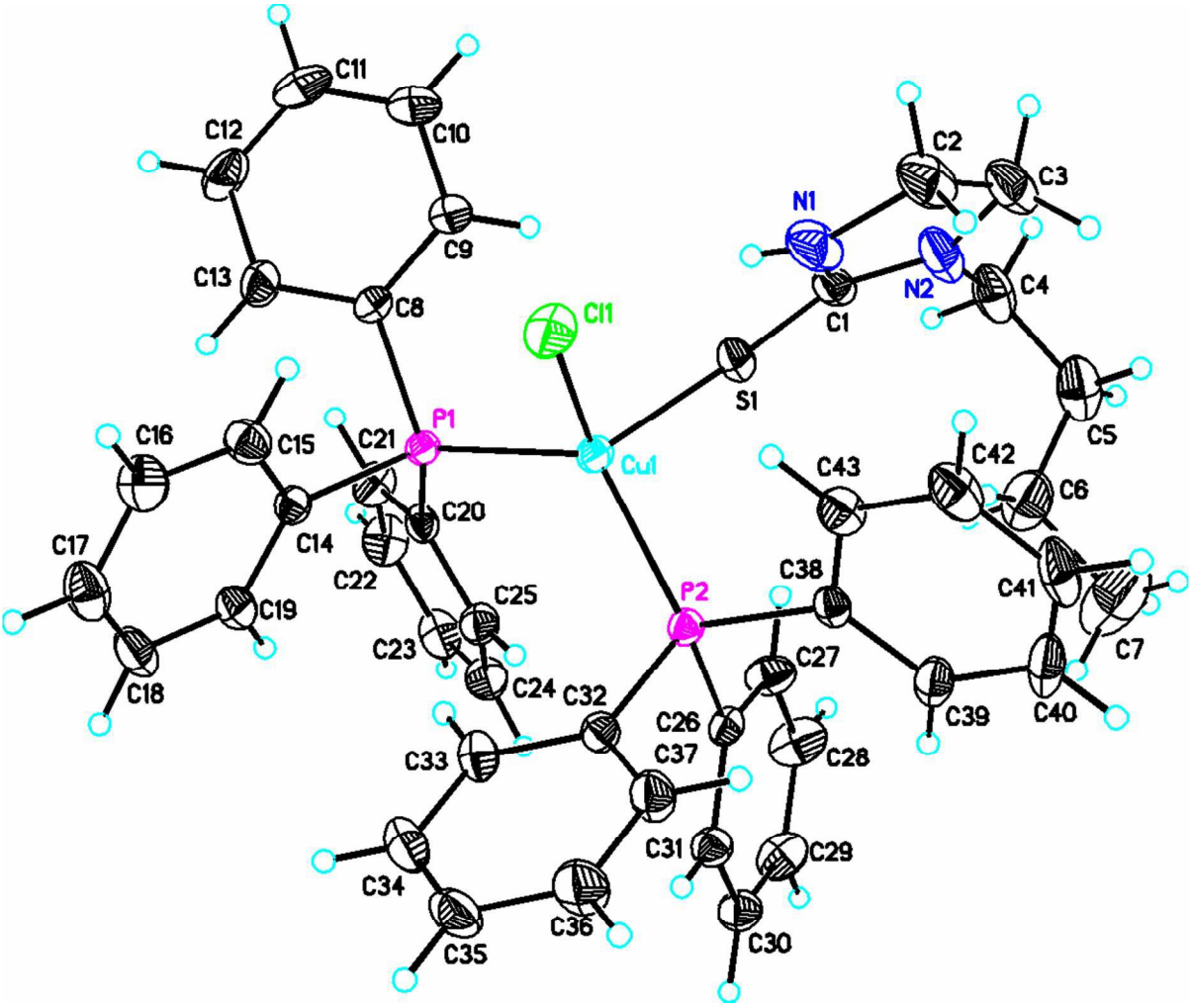

Fig. 3 Molecular structure of complex [CuCl(L-NBu^{n})(PPh$_3$)$_2$] **(3).** Displacement ellipsoids are drawn at the 40% probability level.

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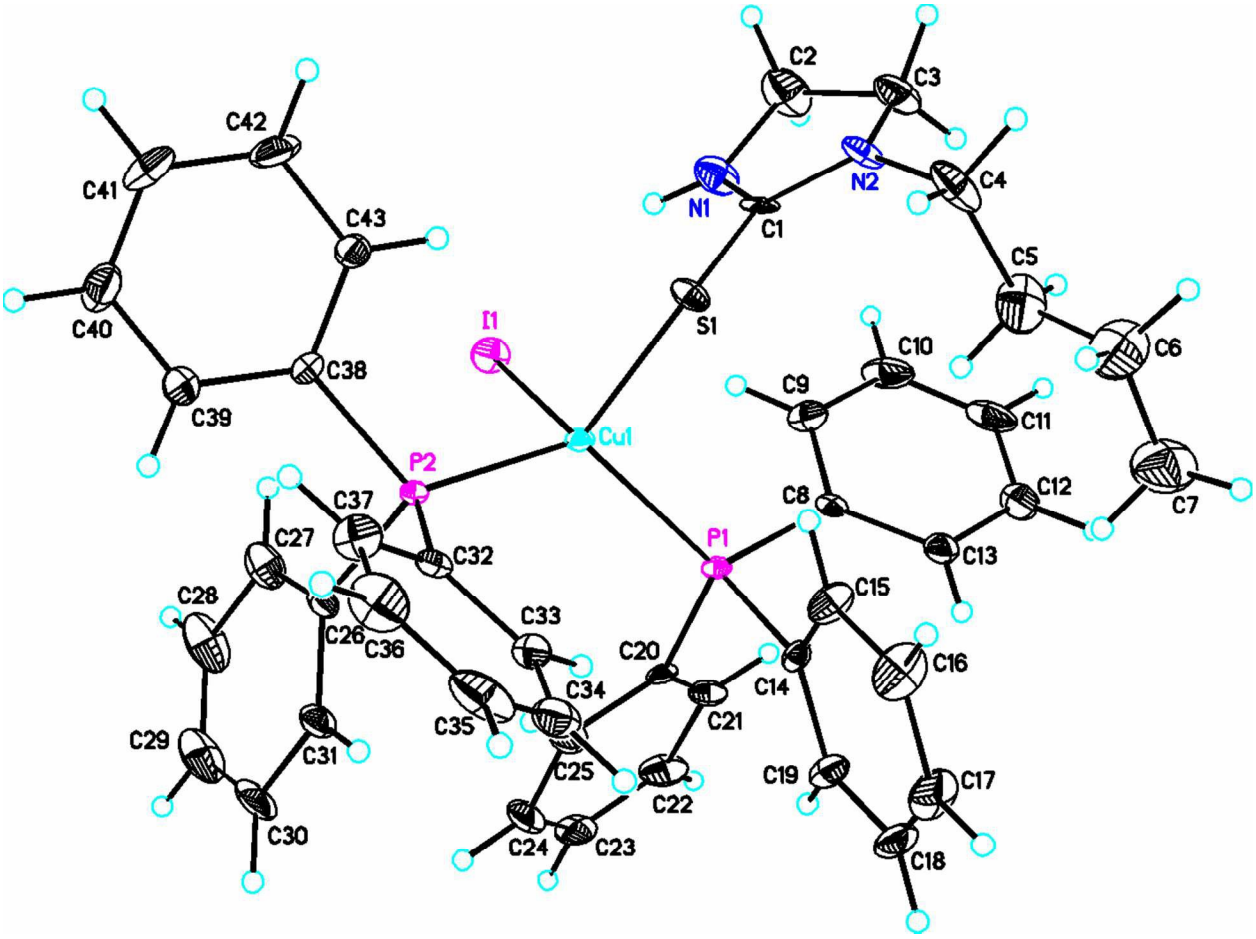

Fig. 4 Molecular structure of complex [CuI(L-NBu^{n})(PPh_3)$_2$] **(4).** Displacement ellipsoids are drawn at the 40% probability level.

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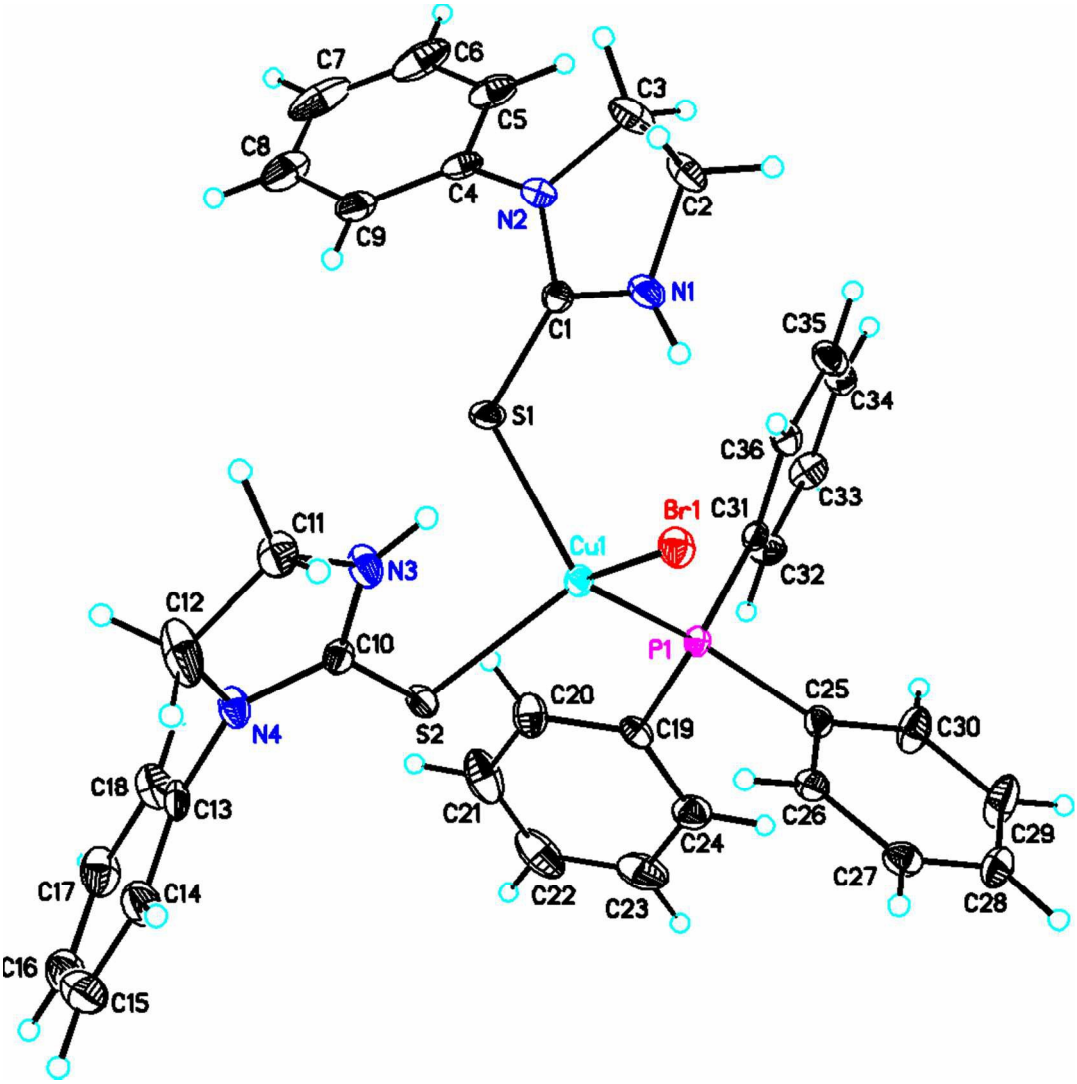

Fig. 5 Molecular structure of complex [CuBr(L-NPh)$_2$(PPh$_3$)] **(5).** Displacement ellipsoids are drawn at the 40% probability level.

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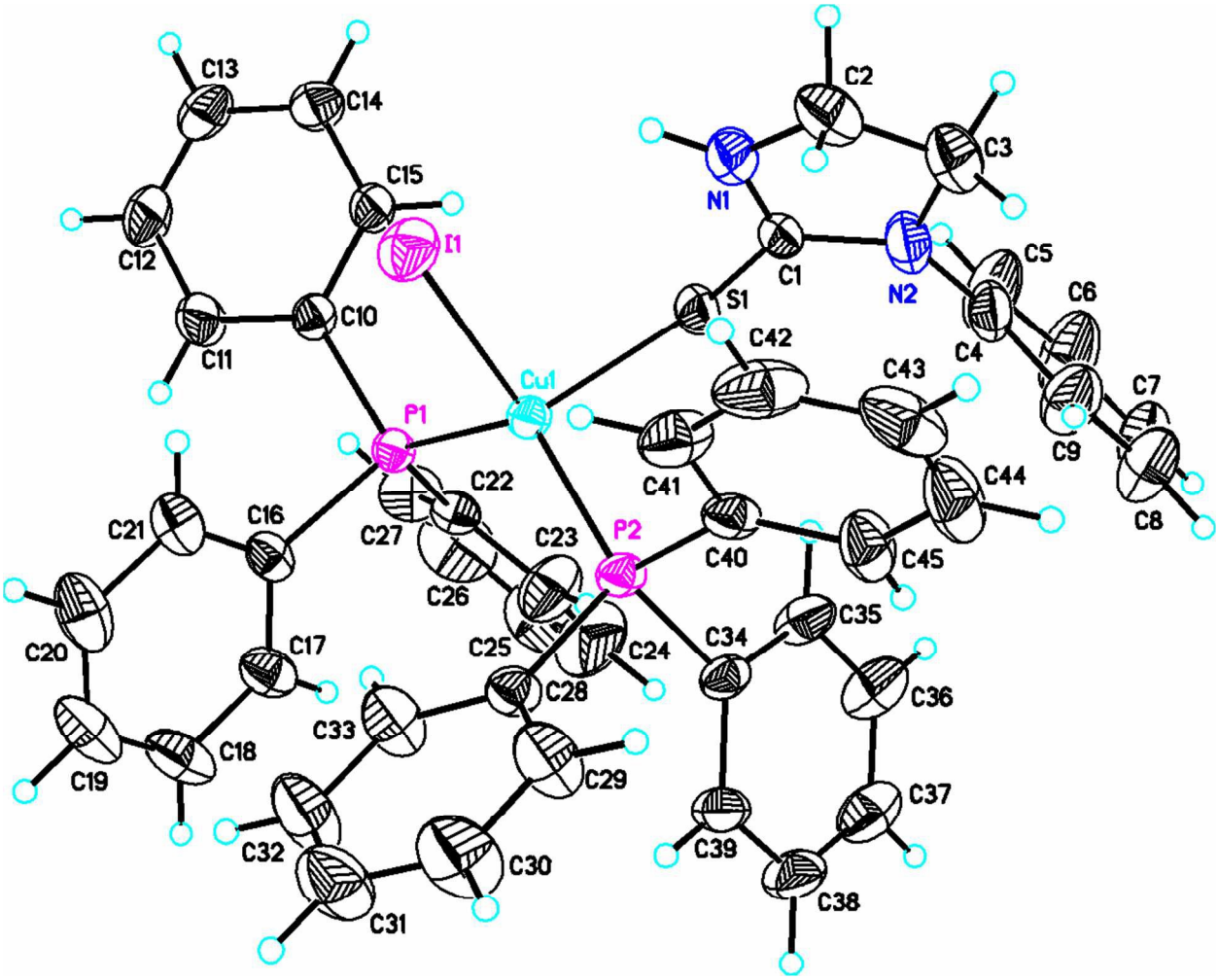

Fig. 6. Molecular structure of complex [CuI(L-NPh)(PPh_3)$_2$] **(6).** Displacement ellipsoids are drawn at the 40% probability level.

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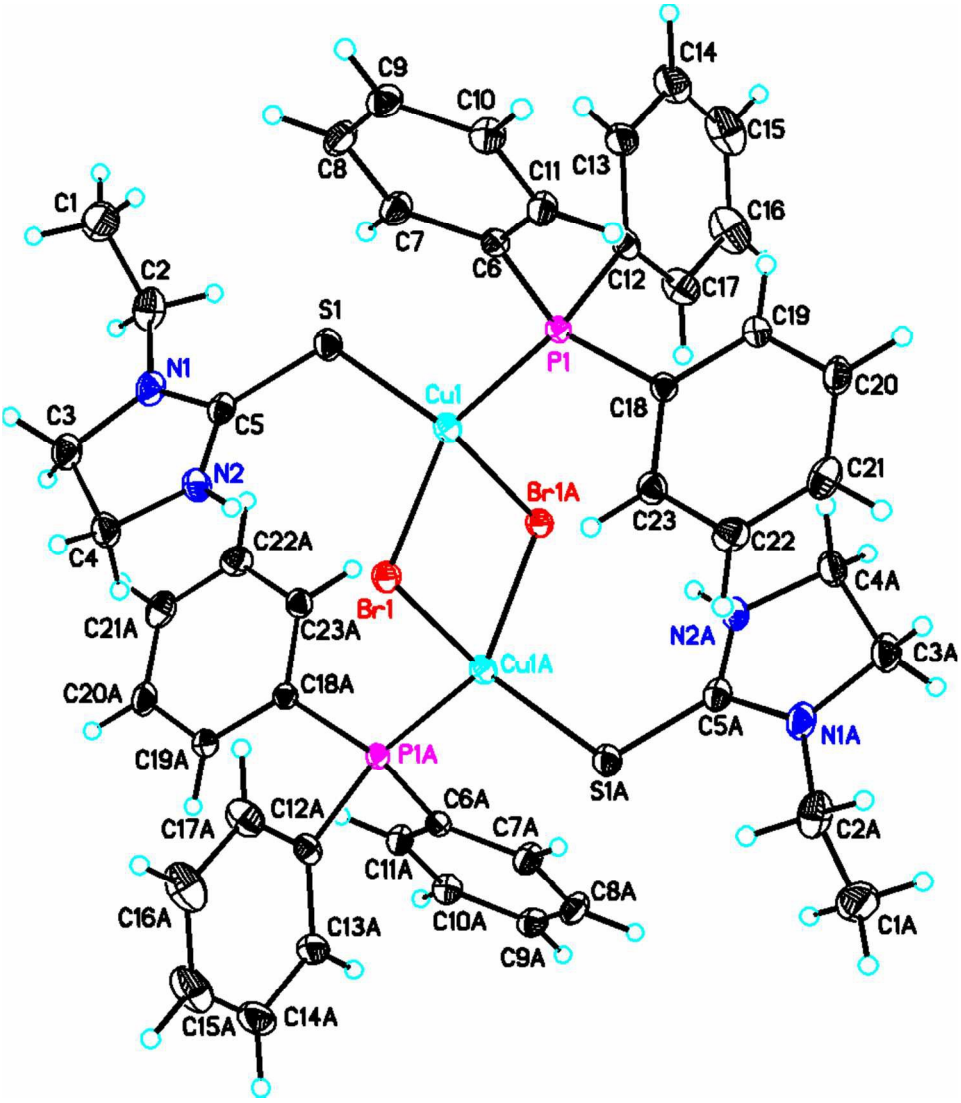

Fig. 7 Molecular structure of complex $[Cu_2(\mu\text{-}Br)_2(L\text{-}NEt)_2(PPh_3)_2]$ **(7).** Displacement ellipsoids are drawn at the 40% probability level

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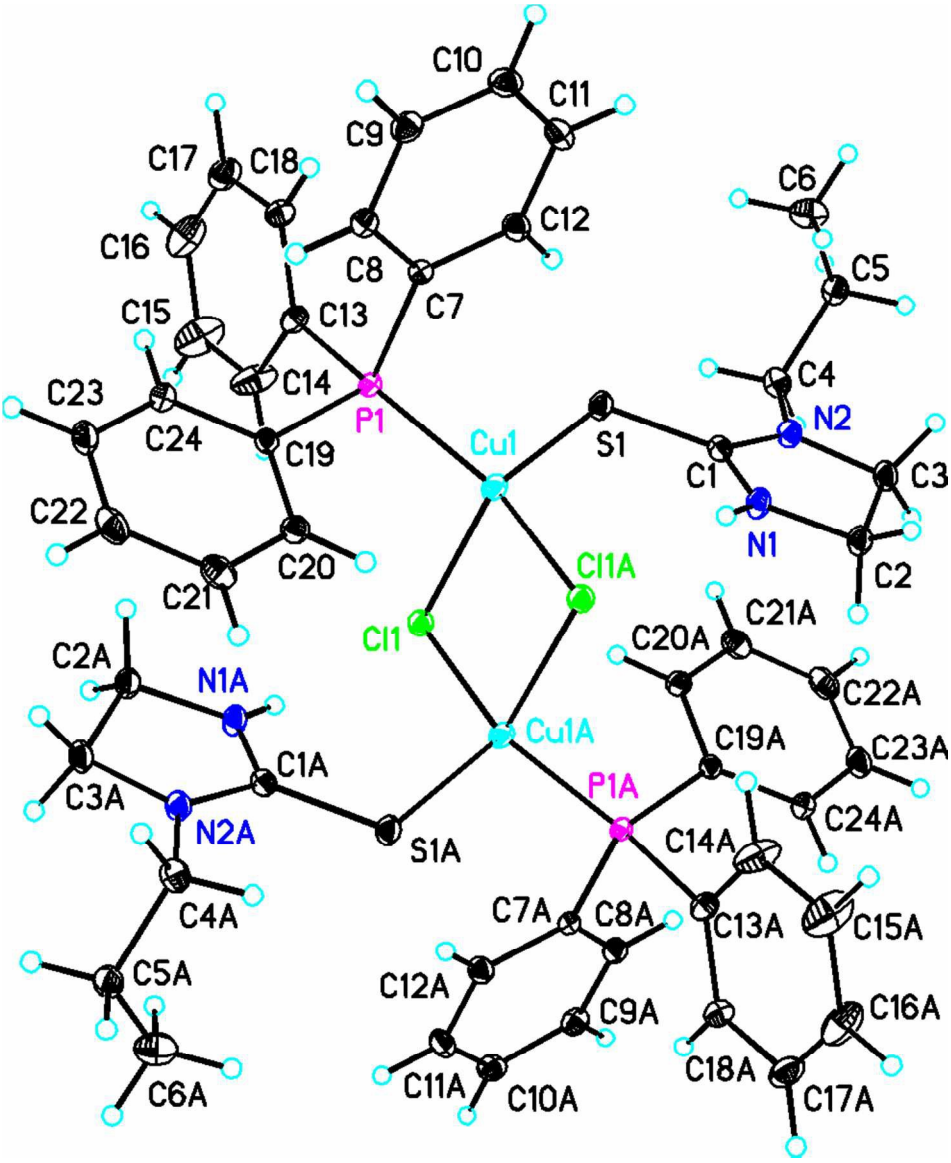

Fig. 8 Molecular structure of complex $[Cu_2(\mu\text{-}Cl)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ **(8).** Displacement ellipsoids are drawn at the 30% probability level.

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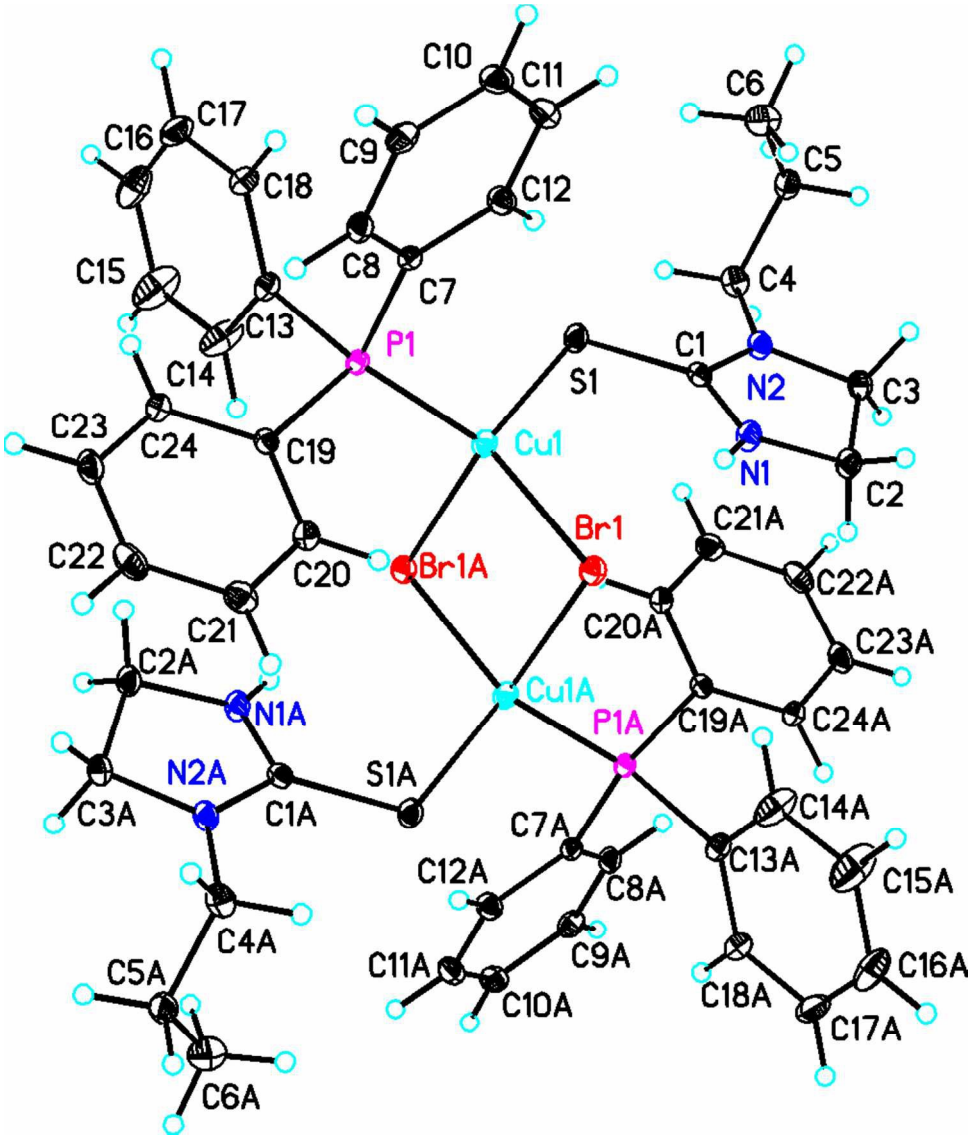

Fig. 9 Molecular structure of complex $[Cu_2(\mu\text{-}Br)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ **(9).** Displacement ellipsoids are drawn at the 30% probability level.

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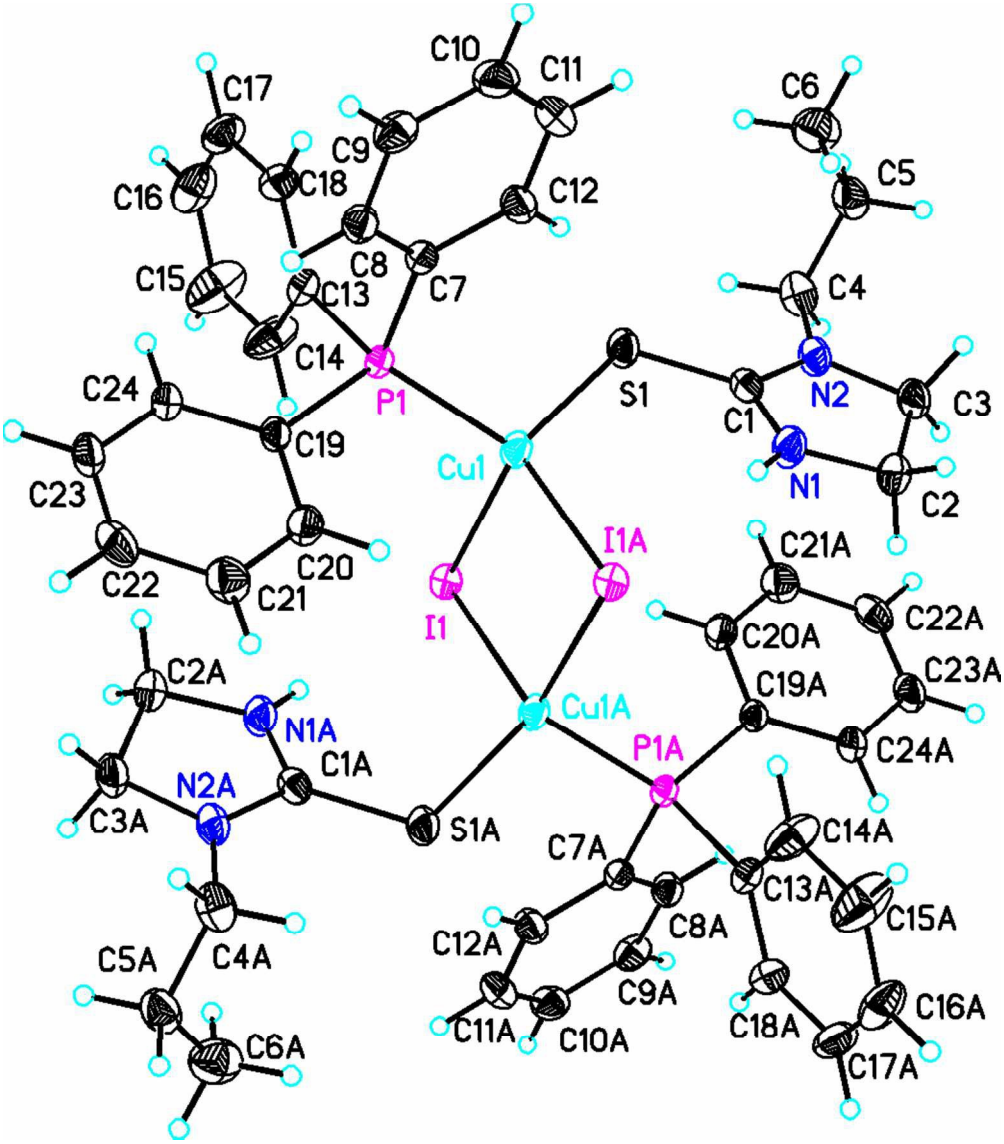

Fig. 10 Molecular structure of complex $[Cu_2(\mu\text{-}I)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ **(10).** Displacement ellipsoids are drawn at the 30% probability level.

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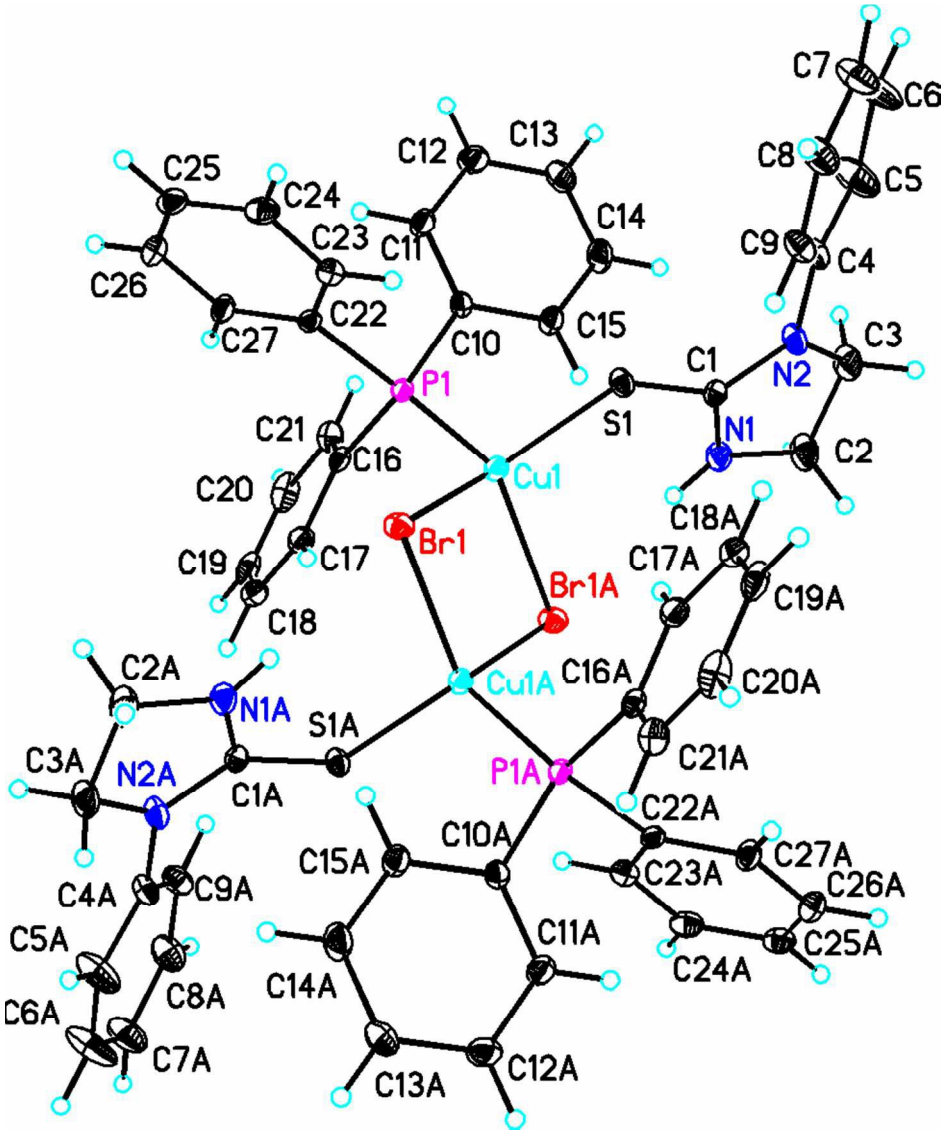

Fig. 11 Molecular structure of complex $[Cu_2(\mu\text{-}Br)_2(L\text{-}NPh)_2(PPh_3)_2]$ **(11).** Displacement ellipsoids are drawn at the 30% probability level.

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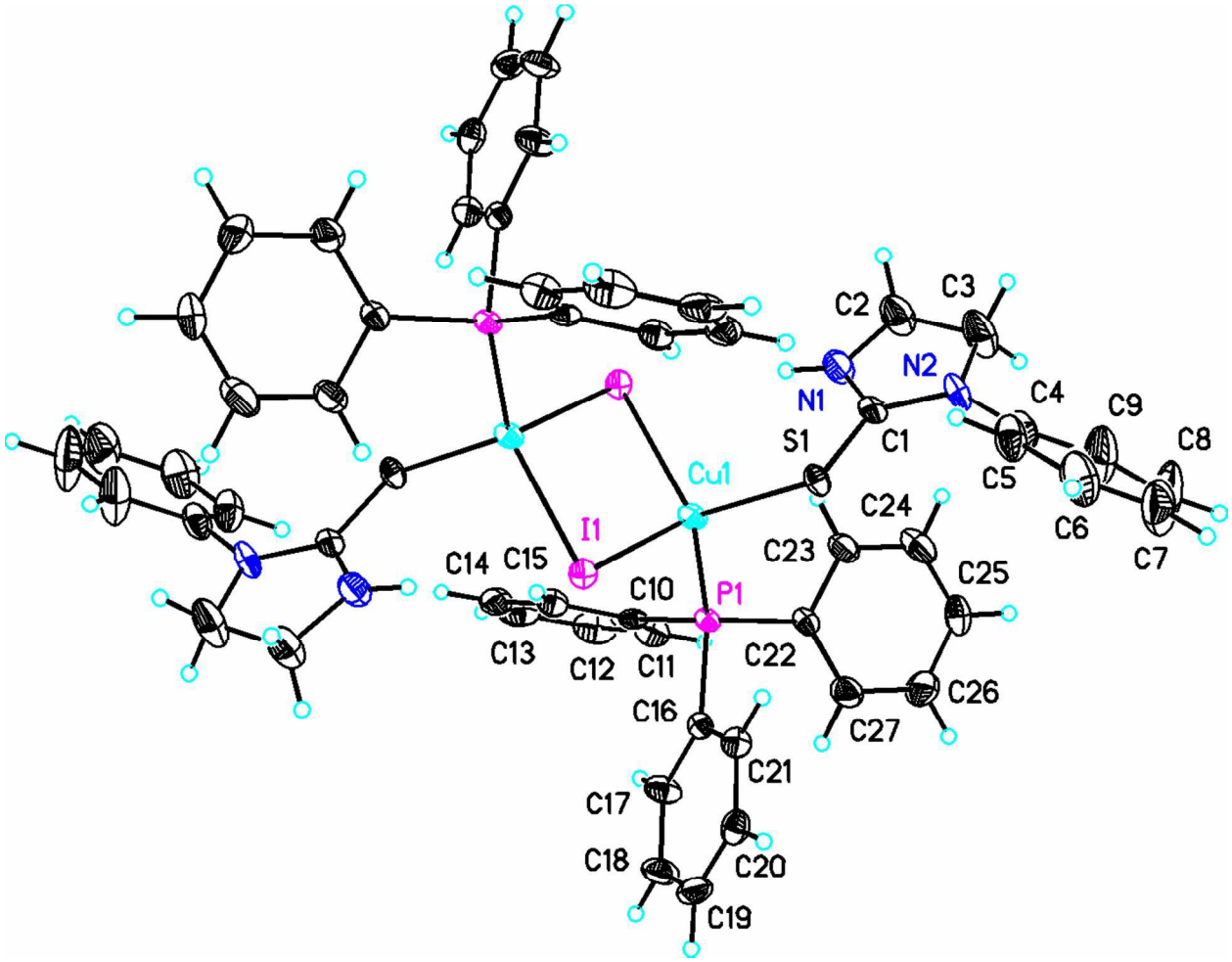

Fig. 12 Molecular structure of complex $[Cu_2(\mu\text{-}I)_2(L\text{-}NPh)_2(PPh_3)_2]$ **(12).** Displacement ellipsoids are drawn at the 30% probability level.

ESI-mass Studies. From the ESI-mass spectra of these complexes the species (Chart 2) which could be identified are: $[Cu(L\text{-}NR)(PPh_3)_2]^+$ (type A, **1, 2, 7, 9, 12**) , $[Cu(L\text{-}NR)(PPh_3)]^+$ (type B, **1-12**), $[Cu(L\text{-}NR)_2]^+$ (type C, **1-5, 9-12**), $[Cu(PPh_3)_2]^+$ (type D, **1, 2, 5-12**) and $[Cu(L\text{-}NR)_2(PPh_3)]^+$ (type E, **5**). These complexes did not show molecular ion species and all of the complexes have shown loss of a halogen atom (See supporting information, Fig. S1 –Fig. S35)

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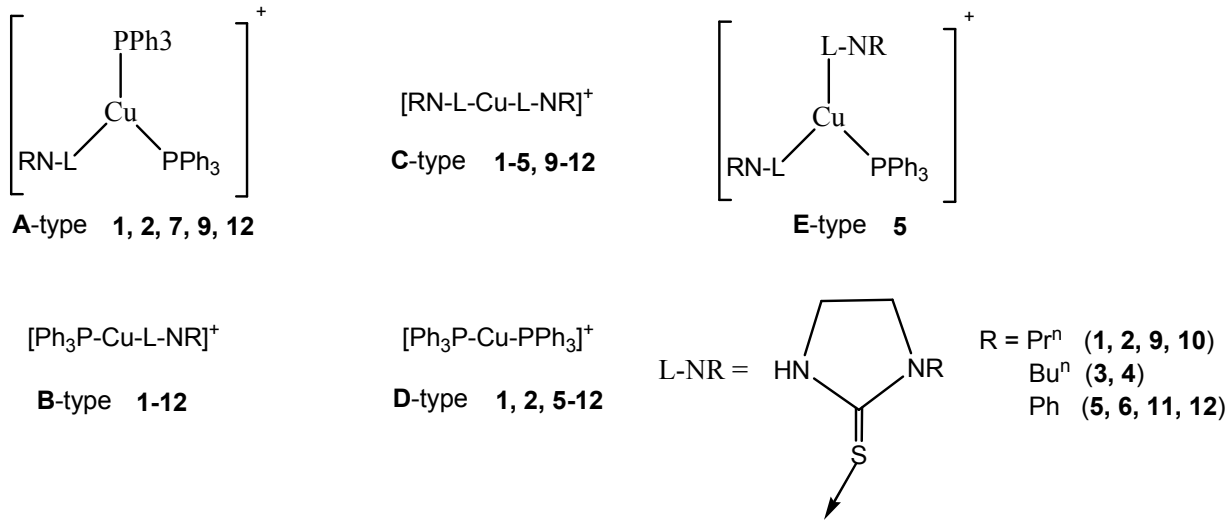

Chart 2 Common species found in mass-spectra of complexes.

Antimicrobial studies. The antimicrobial activity of the coordination compounds have been investigated against Gram positive bacteria, namely, *Staphylococcus aureus* (MTCC 740), *Staphylococcus epidermidis* (MTCC 435), *Enterococcus faecalis* (MTCC 439), Gram negative bacteria *Shigella flexneri* (MTCC 1457), *Escherichia coli* (MTCC 119) and a yeast *Candida tropicalis* (MTCC 230) by the Agar well diffusion assay technique. The antimicrobial activity of these coordination compounds measured on the basis of zone of inhibition (zoi) parameter is placed in Table 6, while minimum inhibitory concentration (MIC) is given in Table 7. It was observed that these coordination compounds exhibited higher activity as compared to the uncoordinated thio-ligands, many of which showed no activity. A brief commentary of activity is discussed as follows.

Coordination compounds **1-5, 7-11** have shown activity against *Staphylococcus aureus* with zone of inhibition values (zoi) in the range 13-20 mm. Complex **11** showed activity of 20 mm (zoi) which is less than that of the standard drug Gentamicin (26 mm zoi) and likewise the

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corresponding MIC values are 10 μg mL^{-1} and 0.5 μg mL^{-1} respectively; other compounds showed much higher MIC values (Tables 6 and 7). It is interesting to note that several compounds (**1, 2, 5, 8, 9, 11)** have shown activity in the range 24-28 mm, against *Staphylococcus epidermidis*, which is comparable to or higher than that of the standard drug Gentamicin (zoi= 25 mm). The MIC values of compounds (5-7 μg mL^{-1}) are much lower than that of the reference compound (30 μg mL^{-1}). The microorganism *Enterococcus faecalis* is found to be sensitive to all the compounds studied, with activity varying in the range 15-31 mm (zoi). Significantly, compounds **3, 4, 8, 10** have shown activity of 28-31 mm with MIC in the range 7-10 μg mL^{-1} which are comparable with or better than that of the reference compound with respect to bio-activity and MIC values (7-10 μg mL^{-1}) (Gentamicin; 27 mm, MIC, 30μg mL^{-1}). These compounds have shown low (14-17 mm) or no activity against *Shigella flexneri*, *Escherichia coli* and a yeast *Candida tropicalis*. Only compound **9** has shown activity against two bacteria and one yeast. The cellular toxicity of all the complexes **1-12** investigated using MTT assay was found to be high.

Table 6 Antimicrobial activity of complexes **1-12**[abc]

	Average zone of inhibition (mm)					
Complex/ Standard drug	*S. aureus*[f]	*S. epidermidis*[g]	*E. faecalis*[h]	*S. flexneri*	*E. coli*[j]	*C. Tropicalis*[k]
$[CuCl(L\text{-}NPr^n)(PPh_3)_2]$ (**1**)	18	24	21	15	14	NA
$[CuBr(L\text{-}NPr^n)(PPh_3)_2]$ (**2**)	14	25	23	NA	NA	NA

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$[CuCl(L\text{-}NBu^n)(PPh_3)_2]$ (**3**)	18	23	30	14	15	NA
$[CuI(L\text{-}NBu^n)(PPh_3)_2]$ (**4**)	13	20	28	NA	NA	NA
$[CuBr(L\text{-}NPh)_2(PPh_3)]$ (**5**)	14	27	25	14	NA	NA
$[CuI(L\text{-}NPh)(PPh_3)_2]$ (**6**)	NA	NA	20	NA	NA	NA
$[Cu_2(\mu\text{-}Br)_2(L\text{-}NEt)_2(PPh_3)_2]$ (**7**)	17	14	27	14	11	NA
$[Cu_2(\mu\text{-}Cl)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ (**8**)	17	28	30	15	11	NA
$[Cu_2(\mu\text{-}Br)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ (**9**)	18	26	26	15	15	17
$[Cu_2(\mu\text{-}I)_2(L\text{-}NPr^n)_2(PPh_3)_2]$ (**10**)	18	20	31	14	NA	14
$[Cu_2(\mu\text{-}Br)_2(L\text{-}NPh)_2(PPh_3)]$ (**11**)	20	28	22	15	NA	NA
$[Cu_2(\mu\text{-}I)_2(L\text{-}NPh)_2(PPh_3)_2]$ (**12**)	15	NA	15	NA	NA	NA
L-NEt	NA	13	12	NA	NA	NA
$L\text{-}NPr^n$	NA	13	12	NA	NA	NA
$L\text{-}NBu^n$	NA	NA	12	NA	NA	NA

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L-NPh	NA	13	12	NA	NA	NA
Gentamicin[d/l]	26[d]	25[d]	27[d]	34.5[d]	30.5[d]	NA
Amphotericin B[e/l]	-	-	-	-	-	25[e]

[a] All measurements are in mm diameter of the inhibition zone (N.A. indicates no activity). [b] The standard deviation varied in the range 0-1 based on three readings.[c] Studies were made in dmso. [d] Commercially available antimicrobial agents. [e]Commercially available antimicrobial agents.[f]*Staphylococcus aureus*. [g]*Staphylococcus epidermidis*. [h]*Enterococcus faecalis*. [i]*Shigellaflexneri*. [j]*Escherichia coli*. [k]*C. Tropicalis*. [l]Gentamicin acts as positive control against bacteria (*S. aureus, S. epidermidis, E. faecalis, S. flexneri*, *E. coli*) and Amphotericin B acts as positive control against yeast (*C. Tropicalis*).

Table 7 Minimum inhibitory concentration (μg mL^{-1}) of copper(I) complexes **1-12**[a]

	MIC (μg mL^{-1})					
Complex/ Standard drug	*S. aureus*	*S. epidermidis*	*E. faecalis*	*S. flexner*	*E. coli*	*C. Tropicalis*
$[CuCl(L\text{-}NPr^n)(PPh_3)_2]$ (**1**)	500	7	500	500	ND	ND
$[CuBr(L\text{-}NPr^n)(PPh_3)_2]$ (**2**)	ND	7	500	ND	ND	ND
$[CuCl(L\text{-}NBu^n)(PPh_3)_2]$	1000	50	7	ND	500	ND

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(**3**)						
[CuI(L-NBu^n)(PPh$_3$)$_2$]	ND	500	10	ND	ND	ND
(**4**)						
[CuBr(L-NPh)$_2$(PPh$_3$)]	ND	5	10	ND	ND	ND
(**5**)						
[Cu$_2$(μ-Br)$_2$(L-NEt)$_2$(PPh$_3$)$_2$] (**7**)	500	ND	50	ND	ND	ND
[Cu$_2$(μ-Cl)$_2$(L-NPr^n)$_2$(PPh$_3$)$_2$] (**8**)	500	5	10	1000	ND	ND
[Cu$_2$(μ-Br)$_2$(L-NPr^n)$_2$(PPh$_3$)$_2$] (**9**)	50	7	50	1000	500	1250
[Cu$_2$(μ-I)$_2$(L-NPr^n)$_2$(PPh$_3$)$_2$] (**10**)	500	50	7	ND	ND	ND
[Cu$_2$(μ-Br)$_2$(L-NPh)$_2$(PPh$_3$)] (**11**)	10	5	500	1250	ND	ND
Gentamicin	0.5	30	30	5	5	-
Amphotericin B	-	-	-	-	-	50

[a]MIC in μg mL^{-1}.

3.6 Structure-activity relationship (SAR). This section mainly considers the change in antimicrobial activity of these coordination compounds as a result of the change in the R substituent of the thio-ligand L-NR, halogen atom or change in molecular structure of the compound (mononuclear versus dinuclear). The dimeric compounds [Cu$_2$(μ-X)$_2$(L-NR)$_2$(PPh$_3$)] generally showed more activity than the mononuclear compounds [CuX(L-NR)(PPh$_3$)$_2$] (Table

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6). It was noted that changing the halogen atom (Cl / Br / I) or the R substituents (R = Et, Pr^n, Bu^n, Ph) of the thio-ligand, made irregular effect on antimicrobial activity of compounds. Most of complexes showed bio-activity against *S. aureus* in the range 13-20 mm (zoi) for all three CuX halides with substituent R varying as Et, Pr^n, Bu^n or Ph. Out of these, the dimeric compound **9** $[Cu_2(\mu\text{-}Br)_2(L\text{-}NPr)_2(PPh_3)]$ was found to be the most active compound with the lowest MIC value of 10 μg mL^{-1}. All these complexes have shown either low or no activity against *Shigella flexneri*, *Escherichia coli* and the yeast *Candida tropicalis*. Interestingly only compound **9** showed bio-activity against all these three bacteria/yeast. Further mononuclear and dinuclear compounds **1, 2, 5**, **8**, **9** and **11** (CuCl/CuBr with L-NPr^n and L-NPh as thio-ligands) have shown good antimicrobial activity of 24-28 mm (zoi) against *S. epidermidis* with MIC in the range 5-7 μg mL^{-1} . This activity is comparable to, or more than that of the standard drug used (25 mm zoi) which, however, required higher MIC of 30 μg mL^{-1}. Both mononuclear and dinuclear complexes (**3**, **4**, **5**, **8** and **10**) (CuX, X = Cl, Br, I; L-NPr^n, L-NPr^n and L-NPh as thio-ligands) have shown antimicrobial activity of 28-31 mm against *E. faecalis* with MIC in the range 7-10 μg mL^{-1} and this activity is higher than that of the standard compound (zoi, 27 mm; MIC, 30 μg mL^{-1}).

4 Conclusion

Mixed ligand copper(I) halide complexes of N-substituted imidazolidine-2-thiones and triphenylphosphine were structurally characterized as mononuclear / dinuclear and were further tested for their antimicrobial activity against Gram positive bacteria, namely, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, Gram negative bacteria *Shigella flexneri*, *Escherichia coli* and yeast *Candida tropicalis*. All of the complexes are found to be bactericidal against *Staphylococcus aureus* but activity was lower than that of the standard drug

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Gentamicin. This activity against *Staphylococcus aureus* is found to be similar to the activity of copper(I) halide complexes of N-substituted imidazolidine-2-thiones.[17] Interestingly, several compounds (**1, 2, 5, 8, 9, 11)** have shown comparable or higher activity against *Staphylococcus epidermidis* and *Enterococcus faecalis* than the standard drug Gentamicin with lower MIC values. Whereas, these complexes were nearly inactive against Gram negative bacteria *Shigella flexneri*, *Escherichia coli* and yeast *Candida tropicalis*. The bioactivity of complexes against *Staphylococcus epidermidis* and *Enterococcus faecalis* is an interesting outcome as these bacteria pose resistance to various antibiotics used for curing various infections in the human body.[55-58]

Conflicts of interest

There are no conflicts to declare

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