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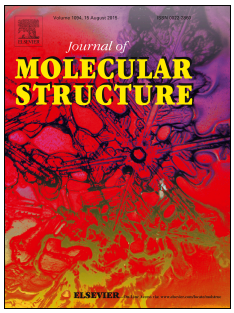

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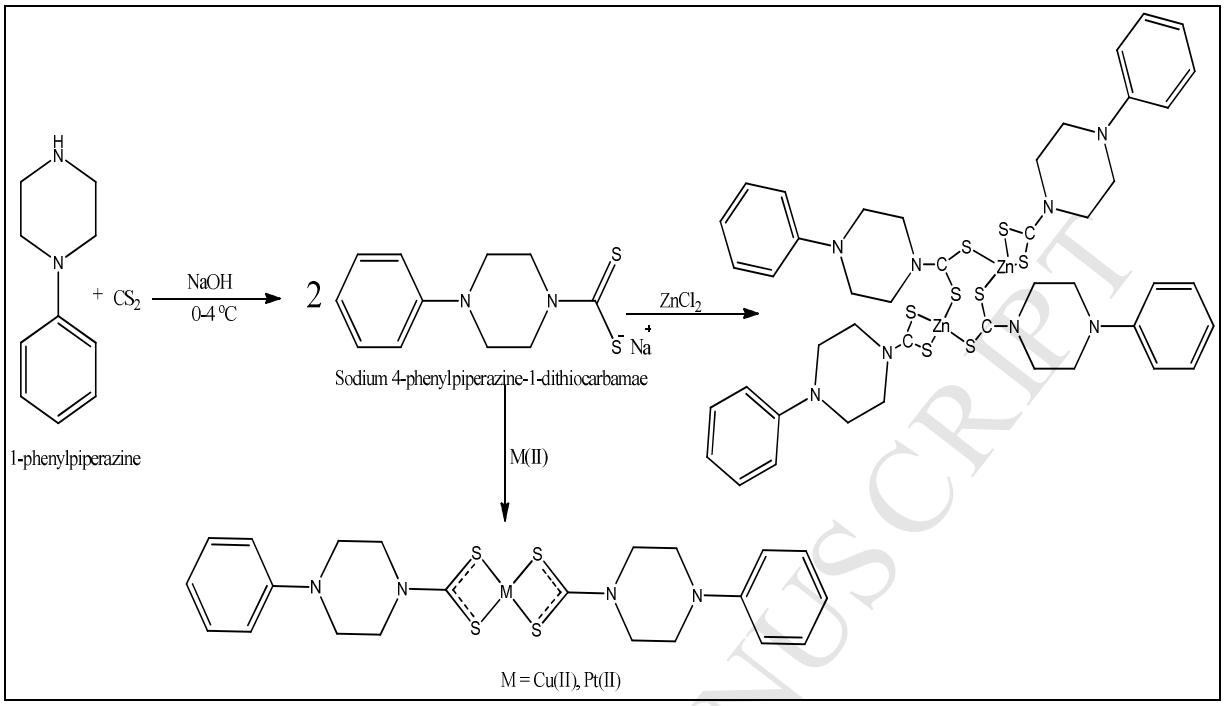
Graphical Abstract



Synthesis, characterization and anticancer studies of bis(1-phenylpiperazine dithiocarbamato) Cu(II), Zn(II) and Pt(II) complexes: Crystal structures of 1-phenylpiperazine dithiocarbamato-S,S' zinc(II) and Pt(II)

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ABSTRACT

Copper(II), zinc(II) and platinum(II) complexes of phenylpiperazine dithiocarbamate formulated as $[CuL_2]$, $[PtL_2]$ and $[Zn_2(\mu\text{-}L)_2(L)_2]$, where L = phenylpiperazine dithiocarbamate were prepared and characterized by elemental analysis IR, UV-Visible, ^{1}H and ^{13}C NMR spectroscopy. Single crystal X-ray structures of the Zn(II) and Pt(II) complexes are also reported. The FTIR spectra of the complexes confirm the bidentate coordination of the ligand to the metal ions by the single band due to $\nu_{(C\text{-}S)}$ observed in the range 1012-1014 cm^{-1} compared to that of the ligand at 994 cm^{-1}. Electronic spectra of both the Cu(II) and Pt(II) complex are consistent with square planar geometry, this is further confirm in the case of the Pt(II) complex by the single X-ray crystal structure. The molecular structure of the Zn(II) complex indicate a centrosymmetric dimeric compound in which each of the zinc ion is bonded to two molecules of the ligands acting as either bidentate chelating or as bridging coordinating ligand resulting in a distorted octagonal cycle comprising of two zinc ions, two thioureide carbons and four sulphur atoms. The geometry around each zinc ion is a distorted tetrahedral geometry. The Pt(II) complex consist of a monomeric entity where the Pt(II) ion is surrounded by four sulphur donor atoms from the two phenylpiperazine dithiocarbamate ligands forming a slightly distorted square planner geometry around the Pt(II) ion. Anticancer potency of the complexes against three cancer cell lines indicates UACC62 > MCF7 > TK10 at IC_{50} values of 3.34, 17.52 and 19.83 μM respectively for the Cu(II) complex. MCF7 > TK10 > UACC62 at IC_{50} of 8.42, 13.40 and 15.14 μM respectively for Zn(II), whereas for the Pt(II) the activity stands at concentration (IC_{50}) >100 μM for all the cell lines.

Keywords: Phenylpiperazine dithiocarbamate; metal (II) complexes; anticancer; crystal structure.

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1. Introduction

Cancer is the second leading cause of death worldwide after cardiovascular diseases [1-4]. Although, platinum-based compounds are the main metal-based compounds used at present for the treatment of various type of cancers but various side effects such as; nephrotoxicity, neurotoxicity and drug resistance [5-7], these have, plague them significantly limit their clinical applications. Consequently, there has been a consistent search for anticancer agents with reduced toxicity, broader spectrum of activity and effectiveness against resistant cancer cells. The use of transition metal complexes as anticancer agents is increasing since the successful clinical integration of cisplatin in 1978 [8, 9]. Metal dithiocarbamates for instance has received much attention in developing anticancer agents [10-13]. In addition to their stable bonding configuration and various structural arrangement in solid state due to delocalized lone pair of electrons on carbon -nitrogen and carbon-sulphur ($NCSS^-$) backbone of the thioureide moiety [14]. Metal dithiocarbamates of various transition elements such as copper, platinum and zinc, are potential sources for effective anticancer agents [15, 16]. They have shown various degrees of DNA binding affinity and potential cytotoxic and antiproliferative activity [17-19]. They have been used to combat platinum drug resistance and toxicity [20, 21]. NF-κB that is known to promote tumor cell proliferation, suppresses apoptosis, attracts angiogenesis, and induces epithelial mesenchymal transition [22], is significantly inhibited by metal dithiocarbamates [23, 24]. In view of these potential properties of metal dithiocarbamates and the growing interest in alternative therapeutic compounds, we present the synthesis, characterization and anticancer screening of copper(II), zinc(II) and platinum(II) phenylpiperazine dithiocarbamate complexes. The single crystal X-ray structures of the Zn(II) and Pt(II) complexes are also presented and discussed.

2. Experimental

2.1 Material and method

All the starting materials used in this synthesis were of commercial source (from Aldrich and Merck) and were used as obtained. NMR spectra (^{1}H and ^{13}C) of the ligand and the complexes were obtained using Bruker Avance III 400 MHz spectrophotometer with TMS as internal standard. The proton and carbon shifts are presented in parts per million in relation to the relevant solvent signals. FT-IR spectra were obtained using Perkin Elmer spectrum 100 FTIR spectrophotometer (between 4000-500 cm^{-1}). The UV-Visible spectrum were recorded using Cary100-UV-Vis spectrophotometer Agilent Technology. Elemental analysis was carried out using Thermoscientific Flash 2000. Molar conductivity were measured in Jenway 4510 conductivity meter using 0.01M DMSO solution of the ligand and the complexes. The cell lines TK10, UACC62 and MCF7 were acquired from National Cancer Institute (NCI) in collaboration with Council for Scientific and Industrial Research (CSIR) South Africa. *In vitro* cytotoxic activity of the compounds was tested using sulforhodamine assay.

2.2 Synthesis of sodium salt of phenylpiperazine dithiocarbamate

2 mL cold aqueous solution of NaOH (2.0 g, 50 mmol) was added to 15 mL cold methanolic solution of 1-phenylpiperazine (8.0712 g, 50 mmol) followed by the addition of cold carbon disulfide (3.798 g, 50 mmol). It was stirred for 4 hrs under ice bath (0-4 °C), a precipitate (white) was obtained, filtered and washed with diethyl ether and dried in a desiccator over silica gel. % Yield = 78%, melting point; 159 °C, $\Lambda_m(\Omega^{-1}cm^2mol^{-1})$, 68, Anal. Cal for $Na(S_2CNC_4H_8NC_6H_5)\cdot 2H_2O$: C, 44.58; H, 5.78; N, 9.45; S, 21.64. Found: C, 44.28; H, 5.82; N, 9.35; S, 21.92, ^{1}H NMR (400 MHz, D_2O, δ, ppm); 7.41 (t, 2H), 7.17 (d, 2H), 7.08 (t, 1H), 4.50

(t, 4H), 3.23 (t, 4H), ^{13}C NMR (400 MHz, D_2O, δ, ppm), 209.01 (CS), 49.70, 50.45 (N-CH_4CH_4N-) 117.98, 122.16, 129.59, 150.34 (-C_6H_5), UV-Vis (H_2O, λ_{max}, nm) 261, 286 (shoulder), Selected IR (solid state, cm^{-1}) (ν_{C-N}), 1462, ($\nu_{(C-S2)}$, 994.

2.3 Synthesis of phenylpiperazyldithiocarbamato-S,S' copper(II) [Cu(L)$_2$]

10 mL aqueous solution of $CuCl_2 \cdot 2H_2O$ (0.3410 g, 2 mmol) was added slowly to aqueous solution of the sodium salt of phenylpiperazine dithiocarbamate (1.040 g, 4 mmol) and was stirred at room temperature for 3 hrs. The brown precipitate formed was filtered and washed many times with distilled water thereafter with methanol and was dried in a desiccator over silica gel to give a brown solid. % Yield = 66 %, melting point; 265 °C, $\Lambda_m(\Omega^{-1}cm^2mol^{-1})$, 0.17 Anal. Cal for [Cu($S_2CNC_4H_8NC_6H_5)_2$]: C, 48.74; H, 5.21; N, 10.33; S, 23.66. Found: C, 49.09; H, 4.87; N, 10.41; S, 23.83, Selected IR (solid state, cm^{-1}): (ν_{C-N}), 1480, ($\nu_{(C-S)}$) 1014, UV-Vis ($CHCl_3$, λ_{max}, nm); 272, 292 (shoulder), 440, 640.

2.4 Synthesis of phenylpiperazyldithiocarbamato-S,S' platinum(II) [Pt(L)$_2$]

Aqueous solution of K_2PtCl_4 (0.1245 g, 0.3 mmol) was slowly added to aqueous solution of sodium salt of phenylpiperazine dithiocarbamate (0.1562 g 0.6 mmol). The mixture was allow to stirred for 6 hrs under room temperature, a yellow precipitated was obtained, it was filtered, washed many times with water and methanol and dried over silica to give a yellow solid. % Yield = 72 %, melting point; 346 °C, $\Lambda_m(\Omega^{-1}cm^2mol^{-1})$, 2.4, Anal. Cal for [Pt($S_2CNC_4H_8NC_6H_5)_2$]: C, 39.45; H, 3.91; N, 8.36; S, 19.15. Found: C, 39.82; H, 3.56; N, 8.14;

S, 19.53, Selected IR (solid state, cm^{-1}): (ν_{C-N}), 1498, ($\nu_{(C-S)}$) 1013, UV-Vis ($CHCl_3$, λ_{max}, nm): 258, 293 (shoulder), 354, 408.

2.5 Synthesis of phenylpiperazyldithiocarbamato-S,S' zinc(II) [$Zn_2(L)_4$]

0.1363 g (1 mmol) of $ZnCl_2$ dissolved in 10 mL ethanol was slowly added to 0.520 g (2 mmol) of sodium salt of phenylpiperazine dithiocarbamate dissolved in water and stirred under room temperature for 3 hrs, a white precipitated was formed, filtered and wash many times with water and ethanol, and dried over silica gel. Slow evaporation of chloroform solution of the complex at room temperature result in a crystal for x-ray crystallography. %Yield = 89 % , melting point; 296 °C, $\Lambda_m(\Omega^{-1}cm^2mol^{-1})$, 1.8, Anal. Cal for $[Zn(S_2CNC_4H_8NC_6H_5)_2]$: C, 48.92; H, 4.85; N, 10.37; S, 23.75. Found: C, 48.77; H, 4.98; N, 10.13; S, 24.02, ^{1}H NMR (400 MHz, $(CD_3)_2SO$, δ, ppm); 7.23(t, 2H), 6.96(d, 2H), 6.79(t, 1H), 4.21(s, 4H), 3.21(t, 4H) ^{13}C NMR (400 MHz, $(CD_3)_2SO$, δ, ppm) 195.35 (CS), 49.71, 47.82 (N-CH_4CH_4N-) 115.55, 119.10, 128.92, 150.33 (-C_6H_5) Selected IR (solid state, cm^{-1}): (ν_{C-N}) 1501, ($\nu_{(C-S)}$) 1012, UV-Vis ($CHCl_3$, λ_{max}, nm); 265, 286 (shoulder).

2.6. In vitro anticancer studies

Sulforhodamine B assay [25] was used to probe the cell viability of the compounds *in vitro* against UACC62, TK10 and MCF7 human cancer cell lines. The cell lines were cultured in RPMI augmented with 5% fetal bovine serum, 2 mM L-glutamine and 50µg/ml gentamicin under the following condition; 37 ºC, 100 % humidity, 5 % CO_2 and 95 % air. The cells were lodged in 96 wells plates at 7-1 x 10^4 cells/well and incubated for 24 hours. It was then treated with the test compounds prepared in DMSO and made to 5 x 10-fold serial dilutions (50-0.005 µM) in medium. Blank was made of complete medium only without cells. Parthenolide and cells

without drug serve as standard and control respectively. The plates treated with the test compounds were cultured for 48 hours. Viable cell were sedimented by 50 % cold trichloroacetic acid. It was dyed with sulforhodamine when dried. The protein bound dye was then extracted with Tris base (10 mM) and optical density determined at 540 nm by multiwell spectrophotometer. GraphPad prism software was used in analyzing the data. IC_{50} was then determined by nonlinear regression.

[26-28].

2.7 X-ray crystallography

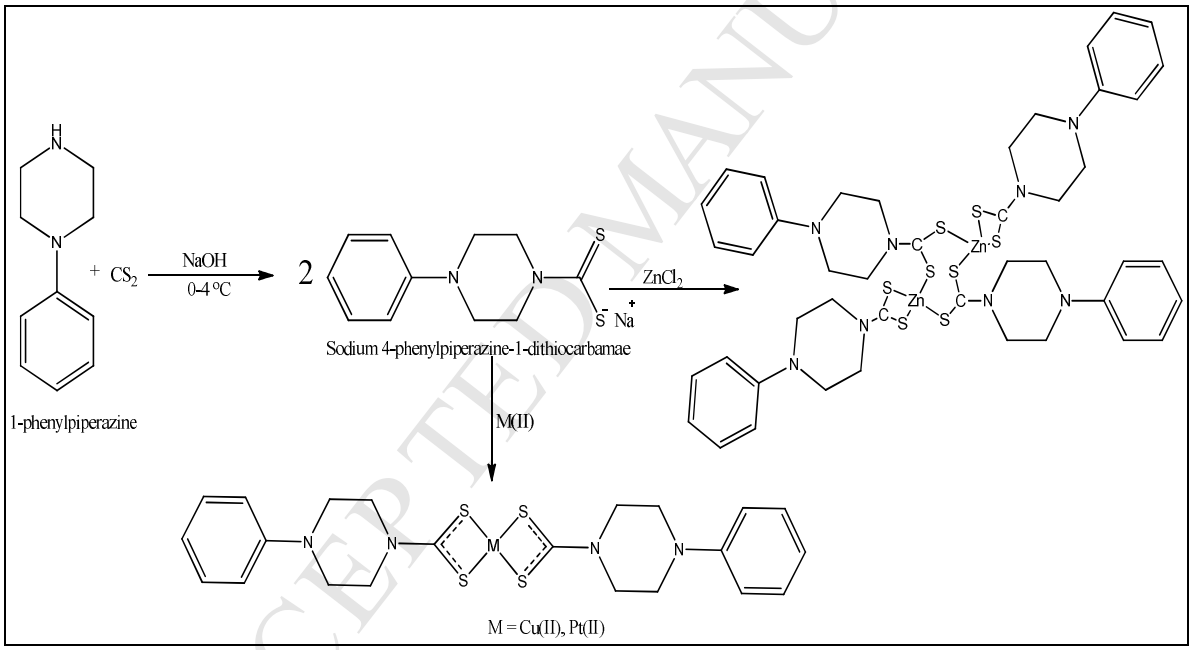
Single crystals of the Zn (II) and Pt(II) complexes were obtained by slow evaporation of chloroform and dichloromethane solution of their complexes respectively. Suitable crystals (0.460 x 0.280 x 0.200 and 0.27×0.16×0.09) mm^3 of the Zn(II) and Pt(II) respectively were selected and mounted on a MITIGEN holder in paratone oil on a Bruker APEX-II CCD diffractometer. The crystal was kept at T = 100(2) K during data collection. Using Olex2 [29], The structure was solved in the space group P-1 and $P2_1/c$ by Direct Methods using SHELXS-2013 [30] structure solution program and refined by Least Squares using version 2016/6 of SHELXL [31] All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

3. Results and discussions

3.1 Synthesis and characterization

The synthesis of phenylpiperazine and its corresponding Cu(II), Pt(II) and Zn(II) complexes are presented in Scheme 1. The air stable complexes are soluble in chloroform, diethyl sulfoxide and

melt in the range 265-346 °C. The value of the molar conductivity 0.17 -2.4 $\Omega^{-1}cm^2mol^{-1}$ recorded at room temperature in 0.01M DMSO solution of the compounds indicate non-electrolytic nature of the complexes. The results obtained from spectroscopic studies are consistent with the proposed four coordinate geometry for Cu(II) and Pt(II) complexes in which two molecules of phenylpiperazine dithiocarbamate bond the central metal ions as bidentate chelating ligand. Single crystal X-ray crystallographic studies of the Zn(II) complex confirmed a dimeric molecular structure, whereas the molecular structure of the Pt(II) complex is a monomeric structural entity.



Scheme 1. Preparation of phenylpiperazine dithiocarbamate and its Cu(II), Zn(II) and Pt(II) complexes

3.2 Single crystal structures of $[Zn_2(\mu\text{-}L)_2(L)_2]$ and $[Pt(L)_2]$

The single crystal structures and unit cell packings of the Zn(II) and Pt(II) complexes are presented in Figure 1, 2, 3 and 4 respectively. Their crystal data and refinements are shown in

Table 1, some selected bond lengths and bond angles are shown in Table 2 and 3 respectively. The molecular structure of the Zn(II) complex exhibit a centrosymmetric dimeric entity with the zinc centers residing on crystallographic inversion center. Each of the zinc ion is bonded to two molecules of the dithiocarbamate ligand, with one acting as bidentate chelating ligand and the other as bridging coordinating ligand forming interconnected distorted octagonal cyclic ring consisting of two zinc ions, two thioureide carbons and four sulphur donor atoms all together forming a chair like configuration. The unequal bond length (Zn-S) and angle (S-Zn-S) (Table 2 and 3) around the zinc centers indicate an asymmetric bidentate coordination of the ligand to the zinc ions, this indicate the geometry around the zinc ions is distorted tetrahedral. The values of the Zn-S bond lengths and S-Zn-S bond angles (Table 2 and 3) are in the range of dinuclear bis-(dithiocarbamato-S,S′) Zn(II) complexes reported in literature [32-38].

The Pt(II) complex crystallized in monoclinic $P2_1/c$ space group. The crystal structure display monomeric structural entity where the Pt(II) ion is surrounded by four sulphur donor atoms from the two bidentate phenylpiperazine dithiocarbamate ligands forming a centrosymmetric slightly distorted square planner geometry. The bond lengths Pt1—S1 and Pt1—S2 are 2.3199(5) Å and 2.3275(5) Å respectively. The C1—S1 (1.722(2) Å) bond length is slightly shorter than typical C—S (1.815 Å) single bond and longer than C=S (1.671 Å) this suggest a partial double bond character as a consequence of delocalization of electron density in the S—C—S group [39]. The slight distortion of the geometry around the Pt(II) ion from a perfect square planner can be attributed to the small bite angle; S1—Pt1—S2 (75.057 19°) of the dithiocarbamate ligand. This is consistent with mononuclear bis-dithiocarbamate complexes [40-42]

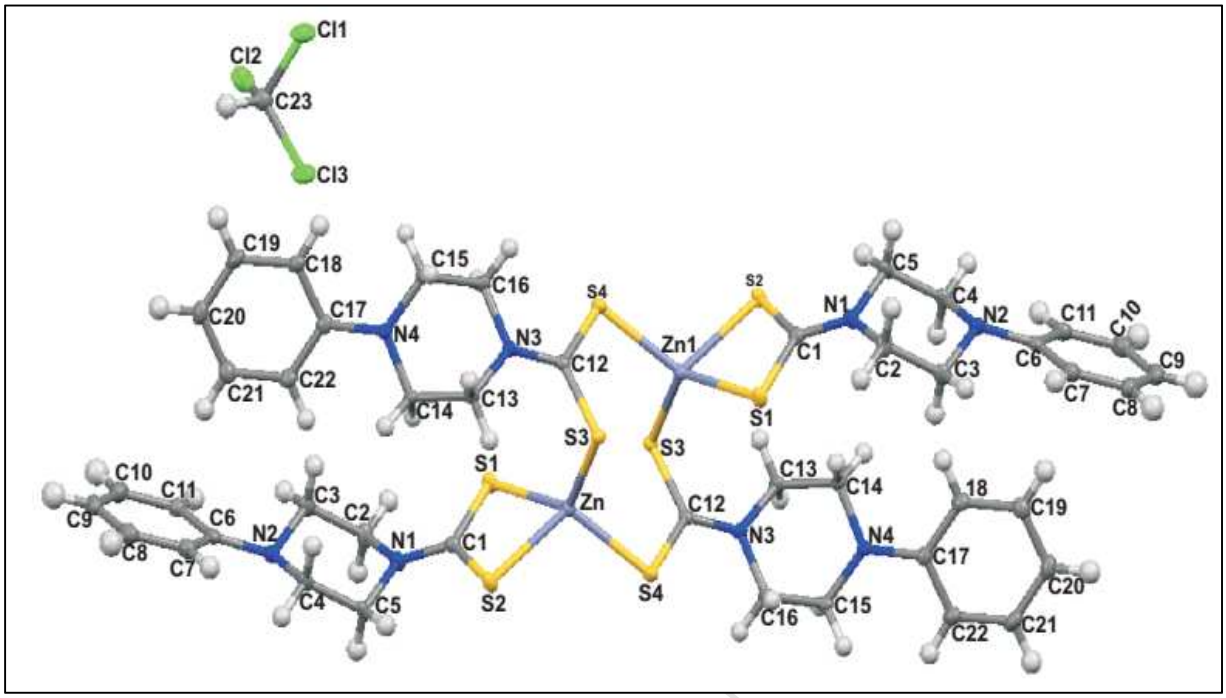


Figure 1. Molecular structure of $[Zn_2(\mu\text{-}L)_2(L)_2]$ showing atomic labelling displacement ellipsoid at 50% probability

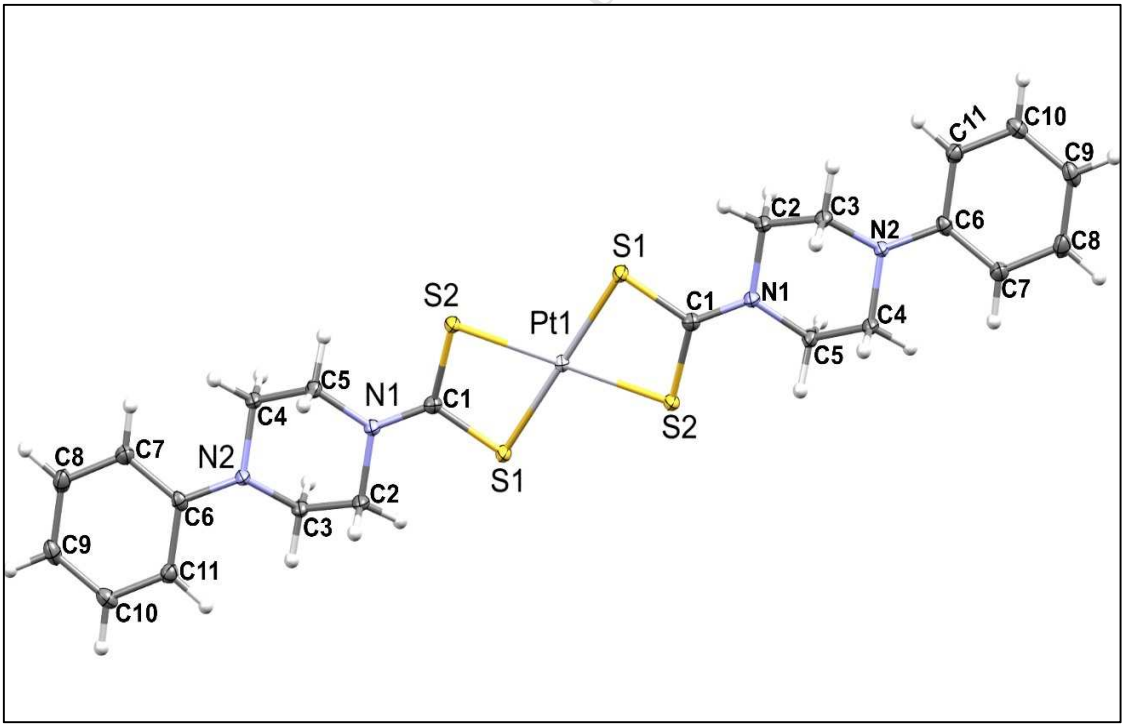


Figure 2. Molecular structure of $[Pt(L)_2]$ showing atomic labelling displacement ellipsoid at 50% probability

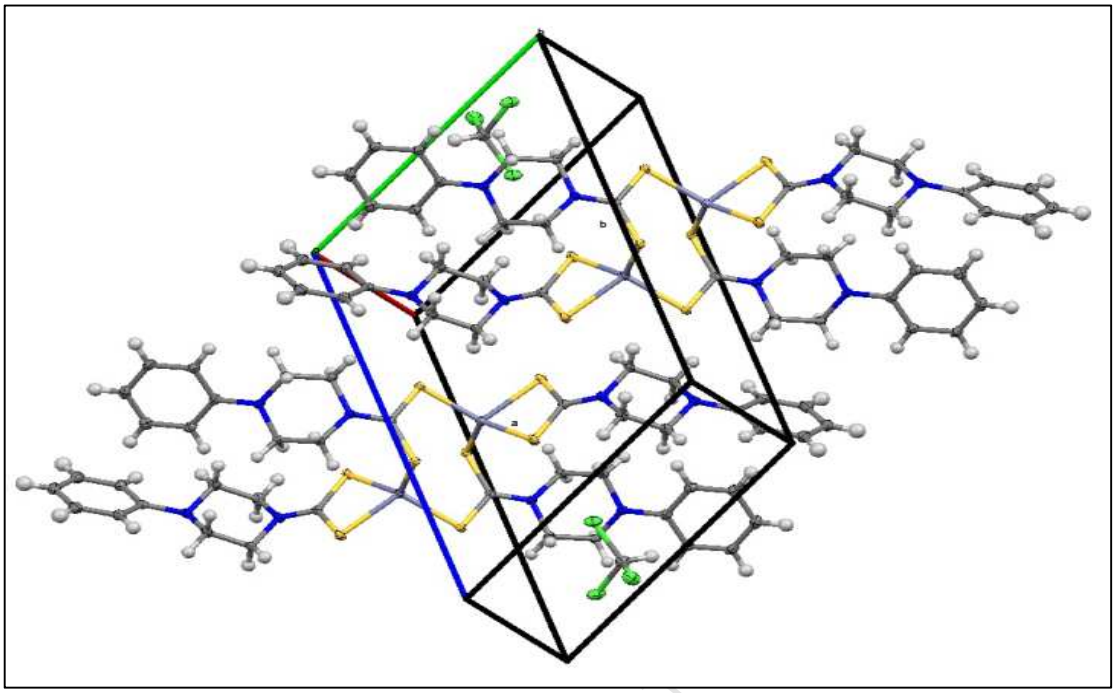


Figure 3. Unit cell packing diagram of $[Zn_2(\mu\text{-}L)_2(L)_2]$

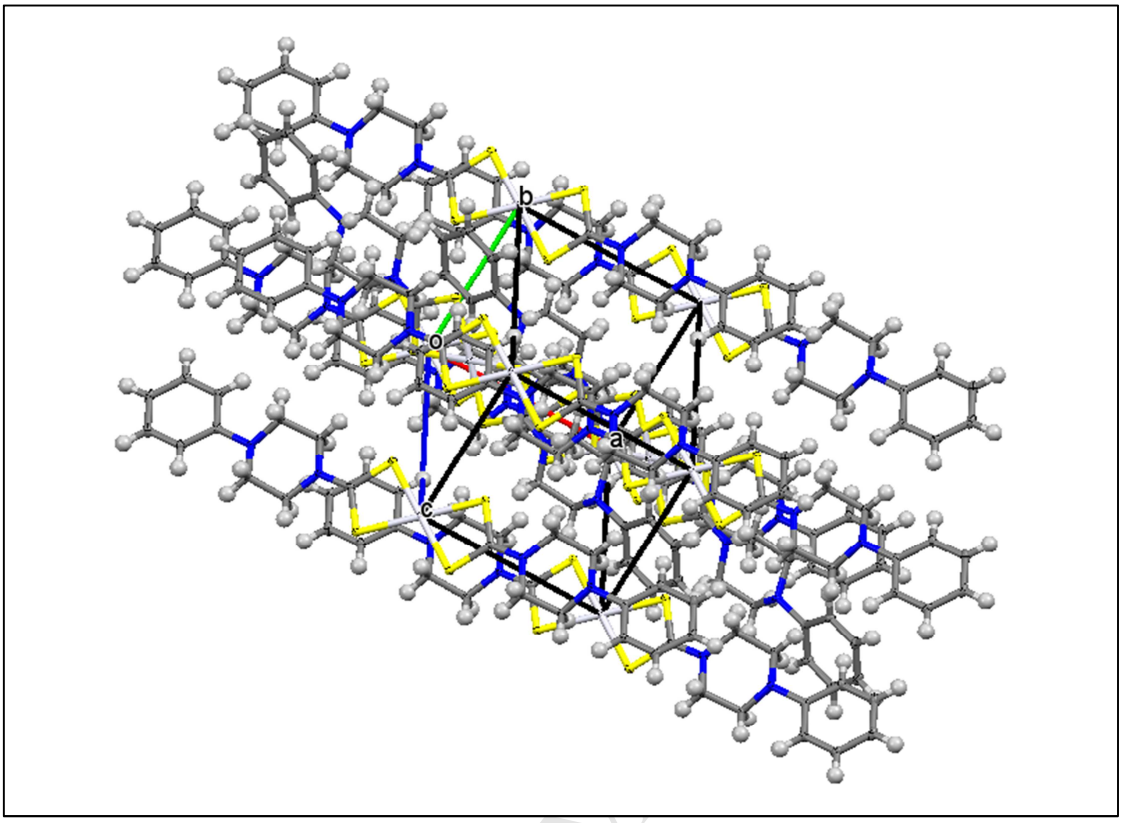


Figure 4. Unit cell packing diagram of [Pt(L)$_2$]

Table 1. Crystal data and structure refinement for [Zn_2(μ-L)$_2$(L)$_2$] and [Pt(L)$_2$]

Compound	$[Zn_2(C_{11}H_{13}N_2S_2)_4]\cdot(HCCl_3)_2$	$[Pt(C_{11}H_{13}N_2S_2)_2]$
Formula	$C_{45}H_{54}Cl_6N_8S_8Zn_2$	$C_{22}H_{26}N_4PtS_4$
$D_{calc.}$/ g cm^{-3}	1.577	1.977
μ/mm^{-1}	1.495	6.627
Formula Weight	676	669.80
Size/mm^3	0.460 x 0.280 x 0.200	0.27×0.16×0.09
T/K	100(2) K	100(2)
Crystal System	Triclinic	monoclinic
Space Group	P -1	$P2_1/c$
a/Å	7.969(3)	7.2456(2)
b/Å	11.538(4)	6.12860(10)
c/Å	16.318(6)	25.3873(6)
α/°	100.623(14)	90
β/°	97.165(16)	93.7290(10)
γ/°	106.519(14)	90
V/Å^3	1388.5(9)	1124.95(4)
Z	1	2
Wavelength/Å	0.71073	0.71073
Θ_{min}/°	1.293	2.817
Θ_{max}/°	27.531	27.999
Measured Refl.	18975	16695
Independent Refl.	6200	2708
Reflections Used	5755	2447
R_{int}	0.0194	0.0223
Parameters	316	142
Restraints	3	2
Largest Peak	0.375	0.627
Deepest Hole	-0.208	-0.514
GooF	1.039	1.070
wR_2 (all data)	0.0524	0.0333
wR_2	0.0512	0.0322

R_1 (all data)	0.0234	0.0183
R_1	0.0210	0.0151

Table 2. Selected bond lengths (Å) for *[$Zn_2(\mu\text{-}L)_2(L)_2$] and [$Pt(L)_2$]*

[$Zn_2(\mu\text{-}L)_2(L)_2$]	Bond	Length	[$Pt(L)_2$]	Bond	Length
	S1—Zn1	2.3400(8)		Pt1—S1	2.3199(5)
	S2—Zn1	2.4558(9)		Pt1—S2	2.3275(5)
	S3—Zn1	2.3554(7)		S1—C1	1.722(2)
	S4—Zn1^1	2.3282(9)		S2—C1	1.724(2)
	C1—S1	1.7397(14)		C1—N1	1.321(3)
	C1—S2	1.7261(15)		N1—C5	1.467(3)
	C1—N1	1.3275(19)		C3—N2	1.458(3)
	C12—N3	1.3221(18)		N1—C2	1.467(3)
	C12—S4	1.7213(14)		N2—C4	1.462(3)
	C12—S3	1.7514(15)		N2—C6	1.414(2)

Table 3. Selected bond Angles (°) for *[$Zn_2(\mu\text{-}L)_2(L)_2$] and [$Pt(L)_2$]*

[$Zn_2(\mu\text{-}L)_2(L)_2$]	Bond	Angle (°)	[$Pt(L)_2$]	Bond	Angle (°)
	S1—Zn1—S2	75.84(3)		S1^1—Pt1—S1	180
	S1—Zn1—S3	122.17(2)		S1^1—Pt1—S2	104.943(19)
	S2—C1—S1	116.60(8)		S1—Pt1—S2	75.057(19)
	S3—Zn1—S2	111.05(3)		S1^1—Pt1—S2^1	75.057(19)
	S4—Zn1—S1	129.27(2)		S1—Pt1—S2^1	104.943(19)
	C1—S1—Zn1	85.40(6)		C1—S1—Pt1	87.29(7)
	C12—S3—Zn1	101.10(5)		C1—S2—Pt1	86.99(8)
	N1—C1—S2	121.82(10)		S1—C1—S2	110.46(11)

N3—C12—S4	119.10(10)	N1—C1—S1	124.26(17)
$S4^1$—Zn1—S2	106.95(2)	N1—C1—S2	125.25(17)

3.3 Infrared spectra studies of the complexes

The FTIR spectrum of phenylpiperazine dithiocarbamate and the Cu(II), Zn(II) and Pt(II) complexes were compared and carefully assigned. There are two significant region of FTIR vibrational frequencies in metal dithiocarbamates, one lies in the region 1580 - 1450 cm^{-1} due to thioureide C-N stretching vibration and the second one lies in the region 1060 – 940 cm^{-1} due to C-S stretching vibration [43, 44]. The absorption at 1462 cm^{-1} is due to $\nu_{(C-N)}$ of the thioureide. A shift to higher frequencies in all the complexes upon coordination was observed at 1480, 1498 and 1501 cm^{-1} for $[CuL_2]$, $[PtL_2]$ and $[Zn_2(L)_4]$ respectively. The shift could be due to the electron flow towards the metal center consequence of $\nu_{(C-N)}$ double bond character [43]. Single band observed at 994 cm^{-1} in the free ligand was assigned to $\nu_{(C-S)}$ stretching vibration. This band also shift to appreciably higher frequency ~ 20 cm^{-1} difference upon complexation. Usually absorption observed in this region defines the coordinated denticity of dithiocarbamates. Single band at 950-1050 cm^{-1} according to Ugo and Bonati indicates bidentate chelation of the dithiocarbamate, whereas double band suggest a monodentate coordination of dithiocarbamate ligands to metal ions [45]. A single band at 1014, 1013 and 1012 cm^{-1} for $[CuL_2]$, $[PtL_2]$ and $[Zn_2(L)_4]$ respectively were assigned to $\nu_{(C-S)}$ stretching vibration, indicating a bidentate coordination of the ligand to the metal ions via the two sulphur atoms [46-48]. The vibrational frequencies reported here are in agreement with a typical dithiocarbamate complexes previously reported in literature [49-52].

3.3 *Electronic spectra*

Electronic spectrum of the phenylpiperazine dithiocarbamate ligand in water exhibit absorption at 261 nm (38314.18 cm^{-1}) and a shoulder at 286 nm (34965.03 cm^{-1}) (Table 4) assigned to intraligand π-π^* transition corresponding to S–C=S and N–C=S of the dithiocarbamate moiety [53]. The electronic spectrum of the Cu(II) complex (Fig. S9) exhibit four bands, the first and second bands at 272 nm (36740.73 cm^{-1}) and shoulder at 292 nm (34246.58 cm^{-1}) are ascribed to intraligand π-π^* transitions [53]. The third and fourth absorption bands at 440 nm (22727.27 cm^{-1}) and 640 nm (15625 cm^{-1}) are assigned to metal to ligand charge transfer (MLCT) and $^2B_{1g} \rightarrow {}^2A_{1g}$ transitions respectively of the Cu(II) ion in a square planner environment [54-56].

Similarly, the spectrum of the Pt(II) complex (Fig. S10) exhibit four absorption bands, the first and second bands at 257 (38910.51 cm^{-1}) and a shoulder at 293 (34129.69 cm^{-1}) are due to intraligand π-π transitions. The third and fourth transitions at 354 (28248.59 cm^{-1}) and 408 (24509.80 cm^{-1}) are assigned to metal to ligand charge transfer (MLCT) and $^1A_{1g} \rightarrow {}^1E_g$ transitions respectively of Pt(II) ion in a square planner geometry [57-58] this is in agreement with the crystal structure (Fig. 2). The Zn(II) complex being a d^{10} system there is no LFSE associated with its compounds the d-orbital is fully filled as a result d-d bands are not observed. Bands observed in their spectra are normally due ligand and/or MLCT transition. Therefore, absorption at 265 nm (37735.85 cm^{-1}) is assigned to π-π^* and MLCT transition [59].

Table 4. Electronic spectra of ligand and complexes

Compound	Wavelength, λ_{max} nm/(cm^{-1})	Assignment
Free Ligand	261 (38314.18 cm^{-1})	n-π^*/π-π* intraligand
	286 (34965.03 cm^{-1}) (shoulder)	
$[CuL_2]$ (1)	272 (36740.73 cm^{-1}),	n-π^*/π-π* intraligand
	292 (34246.58 cm^{-1}) (shoulder)	
	440 (22727.27 cm^{-1})	MLCT
	640 (15625 cm^{-1})	$^2B_{1g} \rightarrow {}^2A_{1g}$
$[PtL_2]$ (2)	257 (38910.51 cm^{-1}),	n-π^*/π-π* intraligand
	293 (34129.69 cm^{-1}) (shoulder)	
	354 (28248.59 cm^{-1})	MLCT
	408 (24509.80 cm^{-1})	$^1A_{1g} \rightarrow {}^1E_g$
$[Zn_2(\mu\text{-}L)_2(L)_2]$ (3)	265 (37735.85 cm^{-1})	Ligand band and MLCT

3.4. NMR spectra studies

The aromatic protons of the phenyl moiety in the free ligand appeared in the range 7.41 – 7.08 as two triplets and a doublet. The four methylene -CH_2 protons of the piperazine moiety appeared at 4.50 ppm and 3.23 ppm as triplets. There is an upfield shift upon coordination to the Zn(II) ion with respect to those of the ligand. Consequently, the aromatic protons appeared in the range 7.23 – 6.76 ppm as two triplets and one doublet and the methylene -CH_2 proton appeared at 4.21 and 3.21 ppm as triplets.

Similarly, in the ^{13}C NMR spectrum of the free ligand, the quaternary thioureide (CS_2) carbon resonate at 209.01 ppm. This signal appeared at 195.35 upon complexation, the upfield shift with respect to that of the ligand could be due to the movement of electron density from the thioureide moiety to the Zn(II) ion upon complexation that could have because the thioureide carbon nuclei to be deshielded hence the upfield shift [60]. The aromatic carbons of the free ligand, which resonate in the range 117.98-150.34 ppm, appeared also at upfield upon complexation in the range 115.55-150.33 ppm. This is similar with the methylene carbons they appeared at 49.70 and 50.45 ppm; however, upon complexation there was an upfield shift to 47.83ppm and 49.70 ppm respectively.

3.5. Anticancer studies

All the three complexes were evaluated *in vitro* by testing for inhibition extent of cell proliferation against three human carcinomas; TK10 (renal), UACC62 (melanoma) and MCF7 (breast) using Sulforhodamine B (SRB) assay. The growth inhibition effect of the Cu(II) complex against the cell lines followed the order UACC62 > MCF7 > TK10 at concentrations (IC_{50}) of 3.34, 17.52 and 19.83 μM respectively, whereas for the Zn(II) complex followed the order MCF7 > TK10 > UACC62 at concentration (IC_{50}) of 8.42, 13.40 and 15.14 respectively. However, the platinum(II) complex is active at a higher concentration (IC_{50}) > 100 μM. The growth inhibition activity exhibited by Cu(II) and Zn(II) complexes may be because copper and zinc are essential elements and have excellent biological activity [61].

Table 5. IC_{50} (μM) values of the against TK10, UACC62 and MCF7 cell lines

Complex	TK10	UACC62	MCF7
$[CuL_2]$	19.83	3.34	17.52
$[PtL_2]$	>100	>100	>100
$[Zn_2(\mu\text{-}L)_2(L)_2]$	13.40	15.14	8.42

4. Conclusion

Divalent copper, platinum and zinc phenylpiperazine dithiocarbamate complexes were Synthesized and characterized by FTIR, UV-Visible, and NMR spectroscopy. Spectroscopic studies indicate that the metal ions are bonded to two molecules of the phenylpiperazine dithiocarbamate in bidentate coordination mode. The crystal structures of the Zn(II) complex revealed dinuclear zinc centers with two phenylpiperazine ligands acting as bidentate chelating ligands and the other two as bridging coordinating ligands between the two Zn(II) ions forming a chair like eight membered ring consisting of two zinc ions, two thioureide carbon and four sulphur donor atoms. The crystal structure of the Pt(II) complex consist of a monomeric structural entity in which the Pt(II) ion is surrounded by four sulphur donor atoms from the two bidentate phenylpiperazine dithiocarbamate ligands forming a centrosymmetric slightly distorted square planner geometry. All the three complexes were screened against three cancer cell lines: TK10 (renal), UACC62 (melanoma) and MCF7 (breast). The copper(II) was active against UACC62 at a concentration as low as (IC_{50}) 3.34 μM and zinc(II) was active against MCF7 at a concentration as low as (IC_{50}) 8.42 μM.

Supplementary crystallographic data

CCDC 1585991 and 1841548 contain supplementary crystallographic data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: + 44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Highlights

- Cu(II), Zn(II) and Pt(II) phenylpiperazine dithiocarbamate were synthesized.
- Spectroscopic studies indicates bidentate coordination of ligands to metal ions.
- X-ray crystal structure of the Zn(II) complex revealed dinuclear zinc centers.
- The compounds were screen against three cancer cell lines.
- Cu and Zn complexes are more active against the cell lines compared to platinum.