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Synthesis, spectroscopic characterization and in vitro anticancer activity of new platinum(II) complexes with some thione ligands in the presence of triethylphosphine

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Abstract Seven new platinum(II) complexes (1–7) of triethylphosphine (Et_3P) and thiones (L) with general formula, *cis*-$[Pt(Et_3P)_2(L)_2]Cl_2$ were prepared and characterized by elemental analysis, FTIR and NMR (^1H, ^{13}C & ^{31}P) measurements. The analytical and spectroscopic data suggested the formation of the desired complexes. The complexes were tested for in vitro cytotoxicity against four cell lines: Hela (human cervical adenocarcinoma), MCF-7 (human breast carcinoma), A549 (human lung carcinoma), and HTC15 (human colon carcinoma). The anticancer activity values of compounds 1–6 are much better than cisplatin and carboplatin as indicated by their IC_{50} values.

Keywords Anti-cancer activity · Pt(II) complexes · Thione ligands · Cancer cell lines

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Introduction

Platinum complexes are very important from the medicinal point of view because of the successful use of cisplatin, *cis*-$[Pt(NH_3)_2Cl_2]$ and its derivatives for the treatment of a number of cancers (Johnstone et al. 2016; Wheate et al. 2010; Wilson and lippard. 2014; Dilruba and Kalayda. 2016; Dasari and Tchounwou 2014; Komeda 2011; Kelland 2007; Zutphen and Reedijk 2005; Hambley 2001; Ahmad et al. 2006). The antitumor activity of cisplatin is believed to depend on its ability to modify the structure of the DNA of cancer cells in such a way that its enzymatic excision repair is avoided (Ahmad 2010; Jamieson and Lippard 1999; Jung and Lippard 2007; Wong and Lippard 2005). The main biochemical mechanism of cisplatin action involves cellular uptake and hydratization of the complex, monofunctional adduct formation, closure to a bifunctional adduct, distortion of the DNA helix, and recognition of this distortion by cellular proteins (Zutphen and Reedijk 2005; Hambley 2001 and Ahmad et al. 2006; Ahmad 2010; Jamieson

and Lippard 1999). The downstream effects activate the replication inhibition processes that ultimately lead to cell death (Ahmad 2010; Jamieson and Lippard 1999; Jung and Lippard 2007; Wong and Lippard 2005).

Although DNA is considered as the major target of platinum complexes, the soft platinum(II) ion also possesses strong affinity towards sulfur-containing ligands such as methionine and glutathione (Messori and Merlino 2016; Timerbaev et al. 2006; Wang and Guo 2007; Sooriyaarchchi et al. 2016; Reedjik 1999). It has been found that cisplatin-like drugs can induce renal toxicity in chemotherapy due to their reactions with the cysteine and methionine groups of proteins (Reedjik 1999; Hartmann and Lipp 2003; Screnci and Mckeage 1999). Several platinum(II) complexes with thiones have been found to possess anticancer properties (Marverti et al. 2008; Fuks et al. 2010; Mustafa et al. 2014; Mustafa et al. 2015; Augustus et al. 2003). Platinum(II) complexes with thiourea ligands demonstrated a different binding mechanism to DNA than that of cisplatin. Sulfur donors are known to replace chlorido ligands without prior solvolysis of the Pt–Cl bond (Martins et al. 2001). The platinum(II) complex, $[Pt(en)Cl(1\text{-}[2\text{-}(acridin\text{-}9\text{-}ylamino)ethyl]\text{-}1,3\text{-}dimethylthiourea)]^{2+}$ does not induce bifunctional covalent adducts (cross-links) in DNA but acts through a mechanism that involves monofunctional platination and intercalation of the planar chromophore into the DNA base stack. This type of adduct, which causes local unwinding of double-stranded DNA by 21°, is considered a potential cytotoxic lesion of the drug (Augustus et al. 2003).

The potential anticancer activity of platinum(II) complexes of thioureas encouraged us to synthesize new platinum(II) complexes with thiourea derivatives and to characterize them using different analytical techniques. Recently, we have reported the synthesis, crystal structure and cytotoxic activity of some platinum(II) complexes of thiones (Mustafa et al. 2014; Mustafa et al. 2015). In this study, we have extended our investigation towards the synthesis of mixed ligand platinum(II) complexes (1–7) of triethylphosphine and heterocyclic thiones. The complexes were characterized by various spectroscopic techniques and were also evaluated for in vitro anticancer activity. The structures of thione ligands used in this study are shown in scheme 1.

Experimental

Materials

Cis-bis(triethylphosphine)dichloridoplatinum(II), $[(Et_3P)_2PtCl_2]$ was purchased from Strem Chemicals, Inc. Carbon disulfide (CS_2) and diamines i.e., 1,2-diaminoethane, *N*-methyl-1,2-diaminoethane, *N,N'*-dimethyl-1,2-diaminoethane, *N,N'*-diethyl-1,2-diaminoethane, 1,3-diaminopropane, *N*-ethyl-1,3-diaminopropane, 1,4-diaminobutane, were obtained from Sigma-Aldrich Chemical Co. Germany. Dulbecco's Modified Eagle Medium (DMEM), (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) (MTT), Dimethylsulfoxide (DMSO) and deuterated solvents were also obtained from Sigma-Aldrich

The thione ligands were synthesized following a literature procedure by the reaction of carbon disulfide (CS_2) with diamines in diethyl ether solvent. The adduct was then heated at 100–110 °C for 2–3 h. The yellow product was recrystallized from methanol (Ahmad et al. 2002).

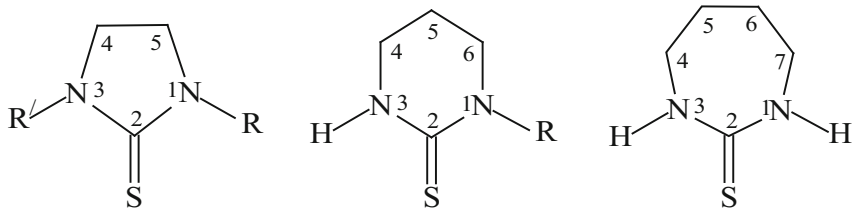
Instrumentation

Elemental analyses were performed on Perkin Elmer Series 11 (CHNS/O) Analyzer 2400. The solid state FTIR spectra of the ligands and their platinum(II) complexes were recorded on NICOLET 6700 FTIR spectrophotometer over the range 4000–400 cm^{-1}. NMR measurements were carried out on Jeol JNM-LA 500 NMR spectrophotometer at 297 K. The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded at frequencies of 500.01, 125.65 and 200.0 MHz respectively. The ^{13}C NMR spectra were obtained with ^{1}H broadband decoupling and referenced relative to TMS. The spectral conditions were: 32 k data points, 0.967 s acquisition time, 1.00 s pulse delay and 45° pulse angle.

Synthesis of complexes

All the complexes were synthesized according to the Scheme 2 as given below. Two equivalents of thiones dissolved in 10 ml methanol were added drop wise to 0.25 g (0.5 mmol) $[(Et_3P)_2PtCl_2]$ dissolved in 10 ml dichloromethane. Stirring the mixture for 3 h resulted

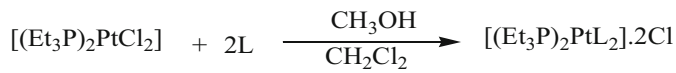
Scheme 1 The structures of thione ligands used and their resonance assignment



(1-4) (5-6) (7)

1. R = R′ = H; Imidazolidine-2-thione (Imt)
2. R = CH_3, R′ = H; *N*-methylimidazolidine-2-thione (MeImt)
3. R = R′ = CH_3; *N,N*′-dimethylimidazolidine-2-thione (Me2Imt)
4. R = R′ = C_2H_5; *N,N*′-diethylimidazolidine-2-thione (Et2Imt)
5. R = H; 1,3-Diazinane-2-thione (Diaz)
6. R = C_2H_5; *N*-ethyl-1, 3-Diazinane-2-thione (EtDiaz)
7. 1, 3-Diazipane-2-thione (Diap)

Scheme 2 Synthesis of Platinum Complexes 1–7



L = Imt, complex **1**; MeImt, complex **2**; Me_2Imt, complex **3**; Et_2Imt, complex **4**; Diaz, complex **5**; EtDiaz, complex **6**; Diap, complex **7**.

in a colored solution. The solution was filtered and kept at room temperature. Solid powder was obtained by slow evaporation of the solvent for all complexes. Purity of the products was assessed through elemental percentages of C, H, N, and S.

$[(Et_3P)_2Pt(Imt)_2]Cl_2$ (1). M. p. 223–225 °C, Yield: 89%. C, H, N, and S% [Calculated C: 30.60, H: 5.99, N: 7.93, S: 9.08, Found: C: 30.49, H: 6.22, N: 8.03, S: 8.91]. IR bands, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

$[(Et_3P)_2Pt(MeImt)_2]Cl_2$ (2). M. p. 246–250 °C, Yield: 82%. C, H, N, and S% [Calculated C: 32.70, H: 6.31, N: 7.63, S: 8.73, Found: C: 32.49, H: 6.28, N: 7.82, S: 8.69]. IR bands, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

$[(Et_3P)_2Pt(Me_2Imt)_2]Cl_2$ (3). M. p. 214–216 °C, Yield: 69%. C, H, N, and S% [Calculated C: 34.64, H: 6.61, N: 7.35, S: 8.41, Found: C: 34.59, H: 6.68, N: 7.42, S: 8.46]. IR analysis, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

Table 1 IR absorption bands for free ligands (cm^{-1}) and their platinum(II) complexes

Species	*v* (C=S)	*v* (N–H)	*v* (Pt–P)	*v* (Pt–S)
Imt	510, 1199	3200	–	–
1	496, 1034	3531	272	305
MeImt	520, 1200	3200	–	–
2	514, 1052	3418	280	299
Me_2Imt	516, 1201	–	–	–
3	511, 1048	–	281	307
Et_2Imt	514, 1199	–	–	–
4	408, 1088	–	279	311
Diaz	510, 1206	3210	–	–
5	509, 1038	3448	274	311
EtDiaz	505, 1217	3210	–	–
6	499, 1043	3422	282	309
Diap	527, 1190	3214	–	–
7	522, 1034	3522	267	306

Table 2 ^{1}H and ^{13}C NMR chemical shifts of the free ligands and their complexes in $CDCl_3$

Species	N–H	C-2	C-4	C-5	C-6	N–C1	N–C2	P–C1	P–C2
$[(Et_3P)_2PtCl_2]$	–	–	–	–	–	–	–	16.63	8.42
Imt	7.98	182.11	45.38	45.38	–	–	–	–	–
1	9.19	174.50	46.60	46.60	–	–	–	14.93	9.30
MeImt	7.93	181.38	42.00	51.82	–	34.35	–	–	–
2	8.65	174.32	42.56	52.13	–	34.47	–	13.82	8.11
Me_2Imt	–	180.46	48.73	48.73	–	34.80	–	–	–
3	–	174.33	49.71	49.71	–	35.16	–	14.21	7.99
Et_2Imt	–	178.74	46.13	46.13	–	42.69	11.92	–	–
4	–	171.94	47.38	47.38	–	43.77	12.08	14.32	8.01
Diaz	7.77	173.34	38.36	19.29	38.36	–	–	–	–
5	9.13	166.68	41.53	19.92	41.53	–	–	14.37	8.82
EtDiaz	7.70	173.36	41.14	20.93	46.14	49.54	12.33	–	–
6	8.32	168.24	41.35	20.91	47.03	49.66	12.43	13.75	8.35
Diap	7.70	183.99	45.86	26.70	45.86	–	–	–	–
7	8.50	175.22	46.44	26.46	46.44	–	–	13.49	7.87

Table 3 ^{31}P NMR chemical shift of the precursor and synthesized complexes in $CDCl_3$

Species	δ ppm	^{1}J (^{195}Pt–^{31}P), Hz
$[(Et_3P)_2PtCl_2]$	7.2	2932
1	9.2	2244
2	8.6	2559
3	9.1	2358
4	9.0	2658
5	9.2	2273
6	8.3	2547
7	7.8	2300

The shifts were measured relative to external reference, phosphoric acid (0 ppm); each peak appeared as a triplet with two satellites

$[(Et_3P)_2Pt(Et_2Imt)_2]Cl_2$ (4). M. p. 189–191 °C, Yield: 73%. C, H, N, and S% [Calculated C: 36.45, H: 6.88, N: 7.09, S: 8.11, Found: C: 34.51, H: 7.28 N: 7.46, S: 8.56]. IR bands, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

$[(Et_3P)_2Pt(Daiz)_2]Cl_2$ (5). M. p. 208–210 °C, Yield: 84%. C, H, N, and S% [Calculated C: 32.70, H: 6.31, N: 7.63, S: 8.73, Found: C: 32.41, H: 6.22, N: 7.53, S: 8.66]. IR bands, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

$[(Et_3P)_2Pt(EtDiaz)_2]Cl_2$ (6). M. p.188–190 °C, Yield: 67%. C, H, N, and S% [Calculated C: 36.45, H: 6.88, N: 7.09, S: 8.11, Found: C: 36.21, H: 6.83, N: 7.23, S: 8.26]. IR bands, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

$[(Et_3P)_2Pt(Diap)_2]Cl_2$ (7). M. p.159–161 °C, Yield: 77%. C, H, N, and S [calculated C: 34.64, H: 6.61, N: 7.35, S: 8.41, Found: C: 34.33, H: 6.64, N: 7.43, S: 8.37]. IR bands, ^{1}H & ^{13}C NMR chemical shifts, and ^{31}P solution NMR (see Tables 1, 2, 3).

In vitro cytotoxic activity

In vitro cytotoxic activities of the synthesized complexes, $[(Et_3P)_2PtCl_2]$, cisplatin and carboplatin were evaluated against four human cancer cells; Hela (cervical cancer), A549 (lung cancer), MCF-7 (breast cancer) and HTC15 (colon cancer) cell lines. The cells were seeded at 4×10^3 cells/well in 100 µL DMEM (Dulbecco's Modified Eagle's Medium) containing 10% FBS (Fetal Bovine Serum) in 96-wells tissue culture plate and incubated for 72 h at 37 °C, 5% CO_2 in the air and 90% relative humidity in the CO_2 incubator. After incubation, 100 µL of the test sample; complexes 1–7, $[(Et_3P)_2PtCl_2]$, cisplatin and carboplatin (50, 25, 12.5 and 6.25 µM prepared in DMEM), was added to cells and the cultures were incubated for 24 h. The medium of wells was discarded and 100 µL

DMEM containing MTT (3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide) (5 mg/mL) was added to the wells and incubated in a CO_2 incubator at 37 °C in dark for 4 h. After incubation, a purple colored formazan (artificial chromogenic dye, a product of the reduction of water insoluble tetrazolium salts e.g., MMT by dehydrogenases and reductases) in the cells was produced and appeared as dark crystals at the bottom of the wells. The medium of culture was discarded from each well carefully to avoid disruption of monolayer and 100 µL of dimethylsulfoxide (DMSO) was added to each well. The solution was thoroughly mixed in the wells to dissolve the formazan crystals, which ultimately resulted in a purple solution. The absorbance of the 96-wells plate was taken at 570 nm with Labsystems Multiskan EX-Enzyme-linked immunosorbent assay (EX-ELISA) reader against a reagent blank. The IC50 values were calculated from three independent experiments by generating an equation of logarithmic trend line of percentage cell viability against the concentration of compounds in Microsoft excel.

Results and discussion

IR spectroscopy

The selected IR vibrational bands for the free ligands and their platinum(II) complexes are listed in Table 1. In the IR spectra of thiones, the characteristic bands were observed in three frequency regions; around 600 and 1100 cm^{-1} for thiocarbonyl stretch, ν(C=S), and near 3200 cm^{-1} for ν(N–H). Upon coordination, to metals, the ν(C=S) band shifts towards lower frequency upon complexation, while the ν(N–H) band shifts to higher wavenumbers due to increasing in the double bond character of the C–N bond (Ahmad et al. 2002; Isab et al. 2002; and Kennedy and Lever 1972). A similar trend was observed in the present series of the complexes and this implies that these ligands exist in the thione form in the solid state.

The far-infrared spectra in the frequency region below 400 cm^{-1} have been recorded to investigate ν(M–S) and ν(M–P) stretching frequencies, which lie in the range of about 300 cm^{-1} for the transition-metal complexes according to the literature (Adam and Cornell 1967). In all complexes, sharp peaks around 280 and 300 cm^{-1} were observed, which were assigned to Pt–P and Pt–S stretching bands respectively.

NMR Studies

All the signals detected in the ^{1}H and ^{13}C NMR spectra of the appropriate thione ligand molecules were also observed in the spectra of the synthesized Pt(II) complexes. The N–H signal of thiones shifted slightly toward high frequency from 0.8 to 1.4 with respect to their positions in uncomplexed forms. These signals were shifted as a consequence of the coordination of ligands to the Pt(II) atom and the formation of the targeting products. The deshielding of the N–H proton is related to an increase of the π electron density in the C–N bond upon complexation (Ahmad et al. 2002; Isab et al. 2002). The ^{13}C NMR chemical shifts of the

Table 4 IC_{50} values (in µM) of the prepared compounds (1–7), the precursor, cisplatin and carboplatin against four human tumor cell lines

Compounds	$IC_{50} \pm SEM$[a]			
	HeLa	A549	MCF7	HCT15
Cisplatin	19.20 ± 1.81	41.67 ± 1.17	22.40 ± 1.37	29.67 ± 2.35
Carboplatin	56.47 ± 2.23	71.20 ± 2.84	55.63 ± 2.53	63.90 ± 2.25
$[Pt(Et_3P)_2Cl_2]$	45.80 ± 2.33	55.60 ± 2.53	59.77 ± 2.15	39.13 ± 1.98
1	1.40 ± 0.29	3.50 ± 0.74	4.67 ± 1.05	7.03 ± 1.04
2	1.83 ± 0.26	3.93 ± 0.47	2.63 ± 0.88	8.60 ± 0.93
3	1.50 ± 0.21	2.37 ± 0.29	3.77 ± 0.61	4.23 ± 0.73
4	9.90 ± 1.65	12.63 ± 1.09	13.50 ± 1.36	16.07 ± 1.13
5	2.23 ± 0.52	4.50 ± 0.78	4.73 ± 0.95	6.87 ± 1.07
6	1.83 ± 0.35	3.60 ± 0.72	1.23 ± 0.34	5.70 ± 0.91
7	17.27 ± 1.34	27.73 ± 1.48	22.33 ± 1.35	37.10 ± 1.86

[a]Standard error of the mean (SEM) as standard deviations determined from at least three independent experiments

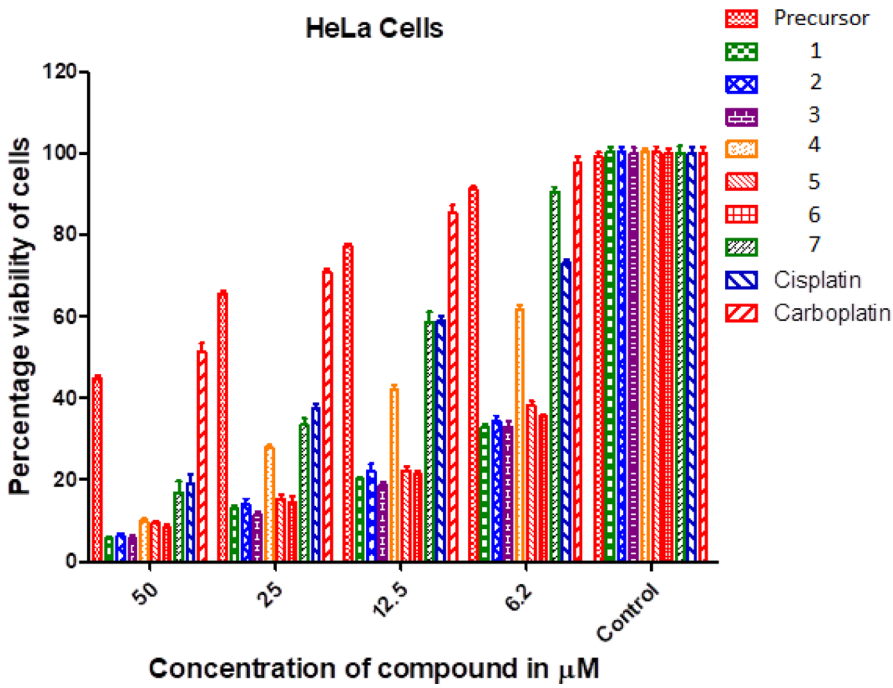


Fig. 1 *Graph* showing the concentration dependent in vitro cytotoxic effect of complexes (1–7), precursor, cisplatin and carboplatin on the viability of HeLa cancer cells

free ligands and their platinum(II) complexes are given in Table 2. In ^{13}C NMR of all complexes, the C = S resonance appeared upfield by 6–9 ppm compared to free ligands. This shift is attributed to decrease in the bond order of C=S bond upon coordination. The increase in the double bond character of the C–N bond leads to a small downfield shift in the C-N resonances (Ahmad et al. 2002; Isab et al. 2002).

In the ^{31}P NMR of the complexes, three resonances were observed with relative integral values of 1:4:1 around 8 or 9 ppm, as shown in Table 3. The NMR active ^{195}Pt nucleus (I = ½) has a natural abundance of 33.8%. Therefore, in ^{31}P NMR two satellite peaks with the ratio of 1:1 were observed due to the presence of heteronuclear coupling between ^{31}P and ^{195}Pt with a high spin coupling constant (^{1}J ^{195}Pt–^{31}P). This high spin coupling constant is in agreement with the values reported in the literature for the bisphosphine in the classic example of square-planar platinum(II) complexes between 1462 and 5698 Hz (Pidcock et al. 1966; Mendia et al. 2006). The presence of a pair of satellites points to the mononuclear structures of the complexes similar to the reported ones (Mendia et al. 2006).

The slight down field shifts were observed in all the synthesized complexes as compared to the precursor. This shift is likely due to back donation from platinum d-orbital to the empty π* orbital of the thiocarbonyl, which is known as strong π-accepting ligand, leading the lone pair of phosphorus to shift electron density towards platinum (Power and Wasylishen 1992; Pidcock et al. 1966). As tabulated in Table 3, the coupling constant values ^{1}J (^{31}P, ^{195}Pt) of the synthesized complexes were decreased compared to the precursor. This can be attributed to the strong trans influence of the thiocarbonyl group of the thione ligands compared to the chloride atoms in the case of the precursor.

In vitro cytotoxic effects of complexes 1–7

The anticancer activity of complexes 1–7 as well as $[Pt(Et_3P)_2Cl_2]$, cisplatin and carboplatin was examined against a panel of representative human tumor cell lines, which include, human cervical adenocarcinoma (Hela), lung cancer cells (A549), breast cancer cells (MCF7) and colon cancer cells (HCT15). The results of in vitro cytotoxic activity are expressed as IC_{50} and are presented in Table 4. The percentage of cell viability at various concentrations of the studied compounds is shown in Figs. 1, 2, 3 and 4.

The results displayed in Table 4 demonstrate that six (1–6) of the seven prepared complexes exhibited

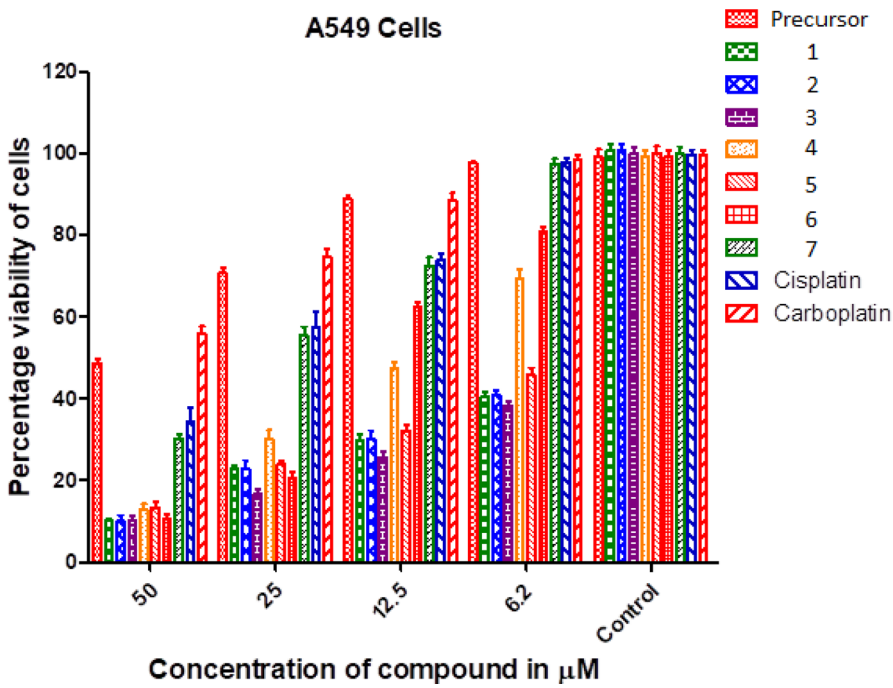


Fig. 2 Effect of concentration of complexes (1–7), precursor, cisplatin and carboplatin on the viability of A549 cancer cells

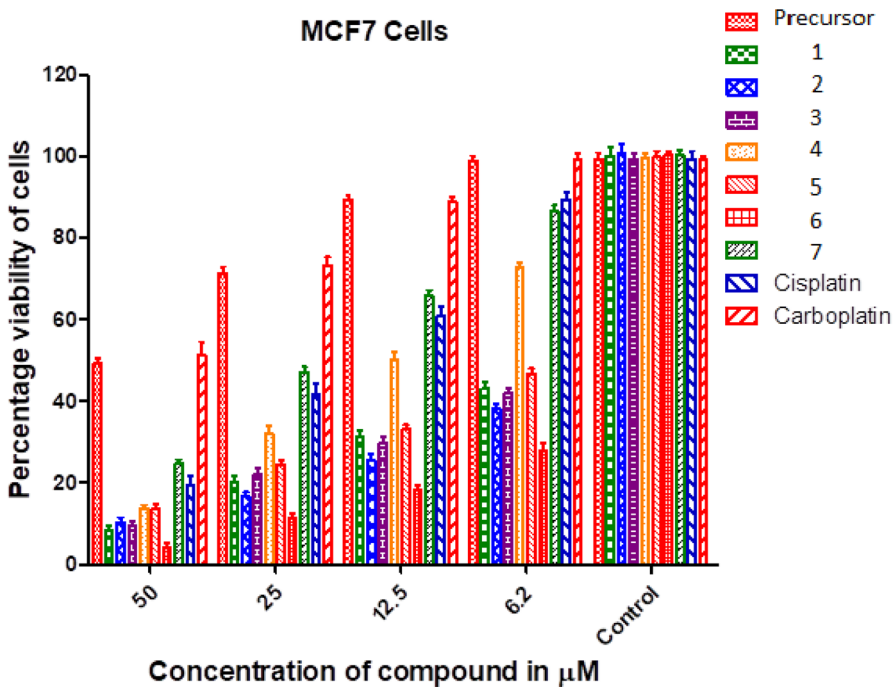


Fig. 3 Effect of concentration of complexes 1–7, precursor, cisplatin and carboplatin on the viability of MCF7 cancer cells

significantly higher activity than the standard anti-cancer drugs (cisplatin and carboplatin) available in the market, against all four cells. The precursor complex, $[Pt(Et_3P)_2Cl_2]$ showed poor activity. The in vitro cytotoxicity of complexes 1–3, 5 and 6 against Hela (human cervical cancer) cell line is exceptionally better than cisplatin (8–14 times) and carboplatin (25–40) times. The antiproliferative activity of

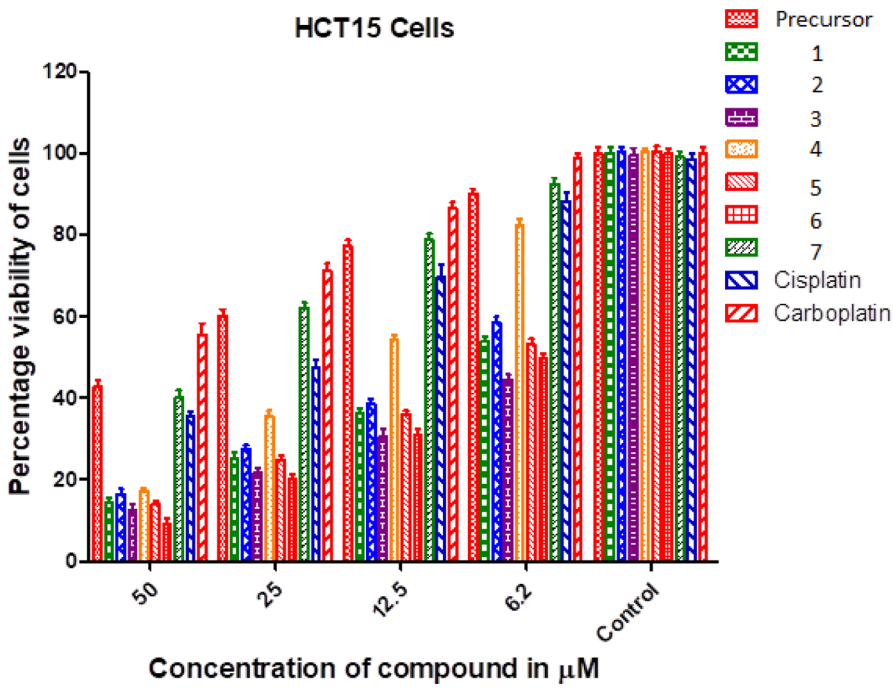


Fig. 4 Effect of concentration of complexes 1–7, precursor, cisplatin and carboplatin on the viability of HTC15 cancer cells

complex 6 against the MCF-7 cells ($IC_{50} = 1.23 \pm 0.34$ μM) is particularly remarkable. It is about 20 times more effective than cisplatin and 45 times as compared to carboplatin. With respect to A549 and HCT15 cells, the complex 3 showed the highest activity. Overall among the seven complexes investigated, 3 was found to be the most effective, while 7 was the least active against all cancer cell lines. Ongoing from a non-ionic precursor, $[Pt(Et_3P)_2Cl_2]$ to the ionic compounds (1–7) brought about a 1.05–50 times increase in the antiproliferative activity. The strong in vitro anticancer effect of the Et_3P-platinum(II)-thione complexes observed in the present study could be related to the presence of a lipophilic Et_3P ligand and ionic nature of the complexes. The excellent antiproliferative potency of these new complexes against the particular cancer cell lines would make them strong candidates for clinical testing as potential anticancer agents.

Conclusion

A new series of platinum(II) complexes (1–7) with general formula, *cis*-$[(Et_3P)_2Pt(L)_2]Cl_2$, (L = Thione) was investigated for their potential as new anticancer drug agents. Six of the seven prepared compounds (1–6) were found to be more efficient than cisplatin and carboplatin against Hela, A549, MCF-7 and HTC15 cell lines. The significant in vitro cytotoxicity of the synthesized complexes makes them strong candidates for clinical testing as potential anticancer agents for future drug discovery.

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