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Platinum (IV) thiohydrazide, thiodiamine and thiohydrazone complexes: A spectral, antibacterial and cytotoxic study

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Abstract

Some platinum (IV) complexes $[Pt(L)_2Cl_2]$ [where, L = 2-aminopyridine-*N*-thiohydrazide (L^1), (2-aminopyridine-*N*-thio)-1,3-propanediamine (L^2), benzaldehyde-2-aminopyridine-*N*-thiohydrazone (L^3) and salicylaldehyde-2-aminopyrtidine-*N*-thiohydrazone (L^4)] have been synthesized. The thiohydrazides, thiodiamine and thiohydrazones can exist as thione–thiol tautomer and coordinate as a bidentate N–S ligand. The ligands found to act in monobasic bidentate fashion. Analytical data reveals that metal to ligand stoichiometry is 1:2. The complexes have been characterized by elemental analysis, IR, mass, electronic and ^{1}H NMR spectroscopic studies. In vitro antibacterial and cytotoxic study have also been carried out for some complexes.

Keywords: Synthesis; Characterization; Spectral; Cytototoxic and Antibacterial

1. Introduction

Platinum (IV) complexes are widely applied in the treatment of various types of cancer such as testicular, ovarian and bladder carcinomas [1–5]. Cisplatin is used in the treating head and neck cancer, lung carcinoma, stomach carcinoma and so on [6,7]. However, the clinical usefulness of cisplatin has been frequently limited by its severe side effects such as nephrotoxicity, nausea, ototoxicity, neurotoxicity and myelotoxicity [8–10], development of acquired resistance low activity against breast and colon cancer. Therefore, it is desirable to develop new platinum based drugs with broader spectrum of activity, improved clinical efficacy and reduced toxicity, better than cisplatin [11].

The platinum (IV) complexes have revealed significantly greater activity in human than that of cisplatin is particularly disappointing in light of the report [12,13]. The high activity was ascribed to high cellular uptake, but in vivo reduction alters the pharmacological properties and thus the effectiveness of the drug. However, platinum (IV) complexes have enormous potential as anticancer agents in terms of both high activity and low toxicity, but this potential has not been realized by the drugs investigated to date, probably because they are reduced too readily in the bloodstream. The potential advantages of platinum (IV) complexes that remain in the higher oxidation state in the bloodstream are that their lower reactivity would diminish loss of active drugs and lower the incidence of unwanted side reactions that lead to side effects [14].

Platinum complexes suitable for oral administration have been known to be water-soluble, lipophilic, and robust enough to survive the gastric environment. For the platinum (IV) complexes, ligand substitution reactions are slow compared with their platinum (II) analogues and Pt(IV) complexes may be required to be reduced to the kinetically more labile and reactive Pt(II) derivatives in vivo [14,15]. Nowadays attention is focused on platinum (IV) complexes with bioactive ligands, because of the lower toxicity of platinum (IV) and the possibility of oral administration of some potent platinum (IV) compounds as well as the fact that they can coordinate to DNA. In view of number of applications of the thiohydrazides and thiohydrazones [16–18] and the well proven clinical utility the platinum–metal

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complexes, we have prepared platinum (IV) complexes of the thiohydrazides, thiodiamines and thiohydrazones in order to characterize and screen them for antibacterial and cytotoxic activity.

2. Experimental

2.1. Chemicals and materials

All the reagents used were AR grade. The analysis of CHNS/O contents of ligands and metal complexes were done on Elementar Analysensysteme Gmbh Vario El-III. IR and far IR were recorded on Perkin-Elmer spectrum 2000 FTIR spectrometer. Electronic spectra were recorded on Shimadzu UV–vis spectrophotometer Model 1601. Conductance measurements were carried out on Digital Conductometer Model PT-827, India. Model JEOL SX102/DA-600 (KV 10MA) was used for recording mass spectra of the ligands. ^{1}H NMR was recorded on Brucker spectrospin 300 spectrometer.

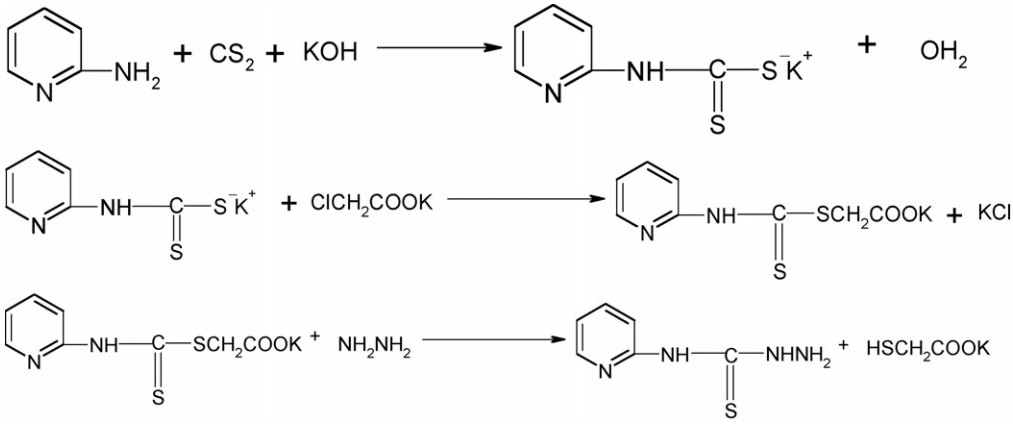
2.2. Preparation of thiohydrazides

Preparation of 2-aminopyridine-*N*-thiohydrazides, (2-aminopyridine-*N*-thio)-1,3-propanediamine, benzaldehyde-2-aminopyridine-*N*-thiohydrazone and salicylaldehyde-2-aminopyrtidine-*N*-thiohydrazone were prepared by modified [16–18] literature method [19].

2.2.1. Preparation of 2-aminopyridine-N-thiohydrazide (L^1)

In a three necked round bottle flask 4.71 g (0.05 mol) of 2-aminopyridine dissolved in 20 mL methanol taken and chilled it. To this, a chilled solution of 2.8 g (0.05 mol) potassium hydroxide in 1 mL water and 10 mL methanol was mixed with constant stirring. The mixed solution was treated with an ice-cold solution of 3.02 mL (0.05 mol) carbon disulphide (density 1.26) in 3 mL methanol. The temperature of the reaction mixture was maintained below 10 °C by keeping flask in a freezing mixture of common salt and ice. During the process, a yellowish-white crystalline precipitate of 2-aminopyridine dithiocarbamate separated. It was filtered, washed with ice-cold aqueous methanol. The product was then suspended in 10 mL methanol and treated with freshly prepared potassium chloroacetate [(0.05 mol) {potassium chloroacetate was obtained by dissolving 4.73 g chloroacetic acid in 3 mL ice-cold water and mixing it in 5 mL aqueous solution of 2.8 g potassium hydroxide}]. The temperature of the reaction mixture was kept at about 40 °C for an hour and the contents were left overnight at room temperature. After 24 h methanolic solution of 2.44 mL (0.05 mol) hydrazine hydrate (density 1.026) was added to the reaction mixture. The content was then heated on a water bath for about 45 min when the desired product began to separate out. It was cooled in ice for 24 h and filtered. 2-Aminopyridine-*N*-thiohydrazide thus obtained was recrystallized from methanol and dried under vacuum over $CaCl_2$ at room temperature.

The reactions taking place in the preparation are shown below.

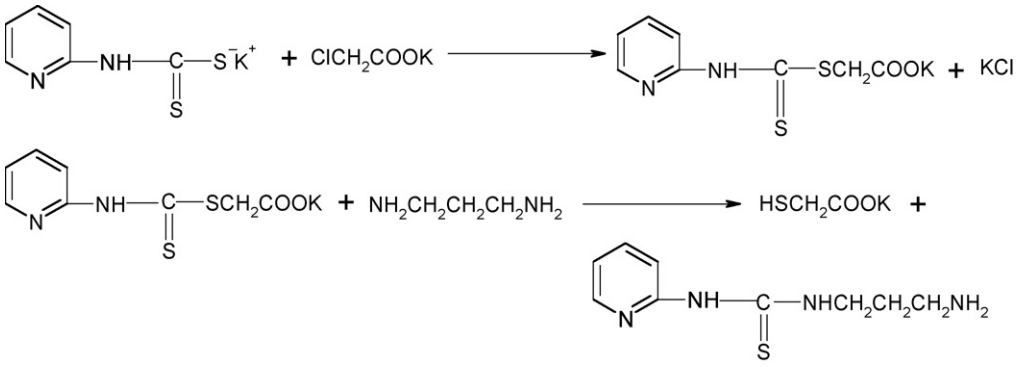


CHNS-analysis; found (calculated) %: C; 43.46 (42.86), H; 4.28 (4.77), N; 34.23 (33.33), S; (18.67) 19.0. Mass spectra (CH_3OH); *m*/*z*: 168.76.

2.2.2. Preparation of (2-aminopyridine-N-thio)-1,3-propanediamine (L^2)

10.4 g (0.05 mol) 2-aminopyridine dithiocarbamate prepared as earlier was suspended in 15 mL methanol and treated with freshly prepared potassium chloroacetate [(0.05 mol) {potassium chloroacetate was obtained by dissolving 4.73 g chloroacetic acid in 3 mL ice-cold water and mixing it in 5 mL aqueous solution of 2.8 g potassium hydroxide}]. The temperature of the reaction mixture was kept at about 40 °C for an hour and the contents were left overnight at room temperature. After 24 h methanolic solution of 4.36 mL (0.05 mol) 1,3-propanediamine (density 0.85) was added to the reaction mixture. The content was then heated on a water bath for about 45 min when the desired product began to separate out. It was cooled in ice for 24 h and filtered. (2-aminopyridine-*N*-thio)-1,3-propanediamine thus obtained was recrystallized from methanol and dried under vacuum over $CaCl_2$ at room temperature.

The reactions taking place in the preparation are shown below.



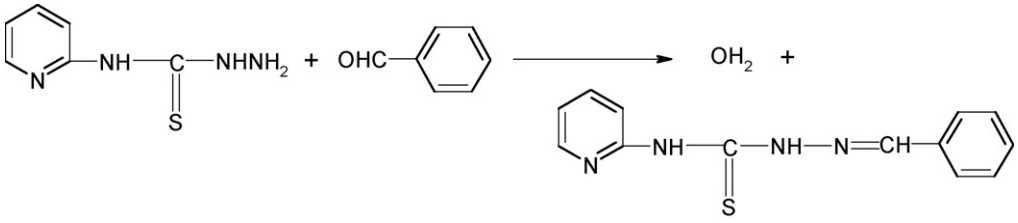
CHNS-analysis; found (calculated) %: C; 52.68 (51.40), H; 6.63 (6.67), N; 25.59 (26.67), S; (14.93) 15.20. Mass spectra (CH_3OH); *m/z*: 210.89.

2.3. Preparation of thiohydrazones

The thiohydrazones were prepared by refluxing the thiohydrazides with corresponding aldehydes or ketones in methanol.

2.3.1. Preparation of benzaldehyde-2-aminopyridine-N-thiohydrazone (L^3)

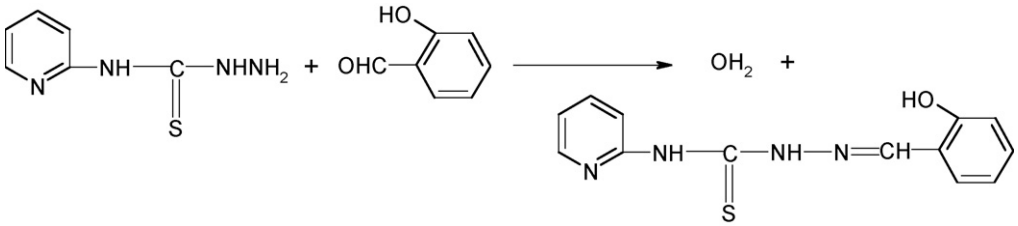
5.04 g (0.03 mol) of 2-aminopyridine-*N*-thiohydrazide and 3.05 mL (0.03 mol) of benzaldehyde (density 1.044) were refluxed in methanol for 3 h. On cooling yellowish mass obtained was filtered and washed with cold methanol. It was recrystallized from hot methanol.



CHNS-analysis; found (calculated) %: C; 61.17 (60.93), H; 4.73 (4.70), N; 20.99 (21.87), S; (11.86) 12.50. Mass spectra (CH_3OH); *m/z*: 256.73.

2.3.2. Preparation of salicylaldehyde-2-aminopyridine-N-thiohydrazone (L^4)

5.04 g (0.03 mol) of 2-aminopyridine-*N*-thiohydrazide and 3.15 mL (0.03 mol) of salicylaldehyde (density 1.164) were refluxed in methanol for 3 h. On cooling yellowish mass obtained was filtered and washed with cold methanol. It was recrystallized from hot methanol.



CHNS-analysis; found (calculated) %: C; 56.96 (57.35), H; 4.26 (4.41), N; 19.47 (20.59), S; (11.98) 11.76. Mass spectra (CH_3OH); *m/z*: 272.43.

2.4. Preparation of complexes

Preparation of thiohydrazide $[Pt(L)_2Cl_2]$ complexes where $L = L^1$, L^2, L^3 and L^4. The corresponding ligand L [where $L = L^1$ (0.084 g, 0.5 mmol), L^2 (0.105 g, 0.5 mmol), L^3 (0.128 g, 0.5 mmol) and L^4 (0.141 g, 0.5 mmol)] in methanol was added to aqueous solution of H_2PtCl_6 (0.103 g, 0.25 mmol). The solution was stirred for 4–5 h. The colour of solution changed yellow to yellowish-orange. It was washed with double distilled water several times and dried in desiccator over $CaCl_2$ under vacuum.

2.5. In vitro antibacterial activity

Most of the compounds have been screened in vitro against *Streptomyces epidermidis*. Various methods [20–23] are available for the evaluation of the antibacterial activity of different types of drugs. However, the most widely used method [23] consists in determining the antibacterial activity of the drug is to add it in known concentrations to the cultures of the test organisms.

2.5.1. Disc diffusion assay

The disc diffusion assay was used to determine antibacterial activity of the drug using Gram positive and Gram negative strains of bacteria namely *S. epidermidis*. Base plates were prepared by pouring 10 mL of autoclaved Muller-Hinton agar (Biolab) into sterile Petri dishes (9 cm) and allowing them to settle. Molten autoclaved Muller-Hinton that had been kept at

Table 1
Elemental analysis

Complexes	% Found (calculated)					
	C	H	N	S	Cl	Metal
$Pt(L^1)_2Cl_2$	23.67 (23.92)	2.63 (2.66)	18.43 (18.60)	10.41 (10.63)	10.93 (11.79)	33.04 (32.39)
$Pt(L^2)_2Cl_2$	32.05 (31.48)	4.02 (4.08)	17.01 (16.33)	9.19 (9.33)	11.28 (10.35)	28.50 (28.43)
$Pt(L^3)_2Cl_2$	40.03 (40.10)	3.17 (3.08)	14.28 (14.39)	7.99 (8.22)	9.27 (9.13)	25.56 (25.06)
$Pt(L^4)_2Cl_2$	39.01 (38.52)	2.97 (2.96)	14.75 (14.83)	8.11 (7.90)	8.69 (8.77)	24.19 (24.07)

48 °C was inoculated with a broth culture (10^6 to 10^8 mL^{-1}) of the test organism and then poured over the base plate. The discs were air dried and placed on the top of the agar layer. Four replicants of each drug tested (four disc per plate) with a gentamycin disc (0.5 μg/disc) as a reference. The plates were then incubated for 18 h at room temperature. Antibacterial activity is expressed as a ratio of the inhibition zone produced by the drug to the inhibition zone produced by the gentamycin standard.

2.5.2. Micro dilution antibacterial assay

The serial dilution technique described by using 96-well micro plates to determine the minimum inhibitory concentration (MIC) of the drugs for antibacterial activity was used. Two milliliter cultures of four bacterial strains of *S. epidermidis* was prepared and placed in a water bath overnight at 37 °C. The overnight cultures were diluted with sterile Muller-Hinton broth. The drugs were resuspended to a concentration of 60 μg/disc (in DMSO) with sterile distilled water in a 96-well micro plate. A similar two-fold serial dilution of gentamycin (Sigma) was used as positive control against each bacterium. One hundred microliters of each bacterial culture was added to each well. The plates were covered and incubated overnight at 37 °C. To indicate bacterial growth *p*-iodonitrotetrazolium violet was added to each well and the plates incubated at 37 °C for 30 min. Bacterial growth in the wells were indicated by a red colour, whereas clear wells indicated inhibition.

2.6. In vitro cell growth inhibition assay (cytotoxicity test)

Cells were seeded in 96-well plates at a concentration of 0.1–1.0 × 10^4 cells/well in 200 μL of complete media and incubated for 24 h at 37 °C in 5% CO_2 atmosphere to allow for cell adhesion. Stock solutions (4 mM) of the compounds made in DMSO were filter sterilized, then diluted to 1 mM in incomplete media. The 1 mM solutions were further diluted to 500 μM and 50 μM incomplete media for treatment against HeLa cell lines, where 40–4 μL of compound solutions were added to 160–196 μL, respectively, of fresh medium in wells to give final concentrations of 100–1 μM. All assays were performed in two independent sets of quadruplicate tests. Control group containing no drug as well as equivalent amounts of DMSO was run in each assay.

Following 48 h of exposure of cells to drug, each well was carefully rinsed with 200 μL PBS buffer. Cytotoxicity was assessed using MTT (3-[4,5-dimethylthiazol-2yl]-2,5-diphenyltetrazolium bromide). MTT solutions 20 μL (5 mg/mL dd H_2O) along with 200 μL of fresh, complete media were added to each well and plates were incubated for 4 h. Following incubation, the medium was removed and the purple formazan precipitate in each well was sterilized in 200 μL DMSO. Absorbance was measured using Techman Magellan microplate reader (molecular device) at 570 nm and the percentage (%) cytotoxicity was calculated as:

$$\text{Cytotoxicity}\,(\%) = 1 - \frac{\text{O.D. in sample well}}{\text{O.D. in control well}} \times 100$$

FCS is the fetal calf serum, PBS is phosphate buffered saline (FCS was obtained from Genetix, DMSO from cell culture tested, MTT from SRL, and DMEM were purchased from Sigma, USA).

3. Results and discussion

3.1. Elemental analysis

Elemental analysis (Table 1) reveals the purity of the complexes. All complexes are soluble in DMSO. The molar conductance values of the isolated complexes measured in DMSO are found to be less than 15 Ω^{-1} cm^2 mol^{-1} suggesting their non-electrolytic nature.

3.2. Electronic spectra

The electronic spectra (Table 2) of the thiohydrazides (L^1), thiodiamines (L^2), thiohydrazones (L^3 and L^4) show spectral

Table 2
Electronic spectra

Complexes	λ_{max} (nm)	Log ε
$Pt(L^1)_2Cl_2$	270	3.98
	312	2.87
	398	2.21
$Pt(L^2)_2Cl_2$	282	3.88
	324	2.65
	386	2.02
$Pt(L^3)_2Cl_2$	277	3.59
	330	2.87
	393	2.45
$Pt(L^4)_2Cl_2$	280	3.89
	322	3.57
	386	2.78

Table 3
IR spectra

Compounds	ν(C=N)	ν(N–N)	ν(C=S)	ν(M–N)	ν(M–S)	ν(M–Cl)
L^1	–	1025	876	–	–	–
$Pt(L^1)_2Cl_2$	–	1028	767	469	385	265
L^2	–	1032	880	–	–	–
$Pt(L^2)_2Cl_2$	–	1016	785	462	376	270
L^3	1633	1026	890	–	–	–
$Pt(L^3)_2Cl_2$	1628	1018	745	481	378	305
L^4	1614	1036	888	–	–	–
$Pt(L^4)_2Cl_2$	1635	1028	767	471	382	310

bands because of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition. In UV spectra of ligand L^1 two bands at 230 nm ($\log \varepsilon = 3.35$) and 281 nm ($\log \varepsilon = 2.47$). Two absorption bands are observed for ligand L^2 at 239 nm ($\log \varepsilon = 3.75$) and 285 nm ($\log \varepsilon = 2.36$). Thiohydrazones (L^3 and L^4) show three bands, ligand L^3 absorbs at 227 nm ($\log \varepsilon = 3.99$), 265 nm ($\log \varepsilon = 3.37$) and 302 nm ($\log \varepsilon = 2.25$). Ligand L^4 absorbs at 238 nm ($\log \varepsilon = 4.02$), 290 nm ($\log \varepsilon = 3.45$) and 303 nm ($\log \varepsilon = 2.55$). On complexation these bands are shifted. Strong charge transfer transitions may interfere and prevent the observation of all the expected bands [24,25]. Strong bands ~340 nm is assignable to a combination of metal ligand charge transfer (M → LCT) and d–d band. The very intense band ~390 is assignable to combination of sulphur → metal charge transfer (Lπ → MCT) and d–d bands.

3.3. Infrared spectra

The IR spectra (Table 3) of the thiohydrazides, thiodiamines and thiohydrazones contain groups –NH–C=S as a potential bond forming site. The IR bands are shifted on complex formation due to increased double bond character of C=N group on complexation. The band due to ν(C=S) 750–900 cm^{-1} is a major contributor and ν(C=N) as minor. This is shifted to lower frequency on complexation indication the coordination to metal ion is through thioamide sulphur C=S. This shift is ~80–140 cm^{-1}, if coordination is through thiol sulphur [26] and 30–40 cm^{-1}, if coordination is through the thione sulphur [27]. In all the complexes the thiohydrazide, thiodiamine and thiohydrazone ligand, no band for ν(S–H) in the region 2600–2800 cm^{-1} is observed which shows the absence of any thiol (–SH) tautomer in the solid state. However, in solution and in the presence of certain metal ion, the ligands may exist in equilibrium with the tautomeric thiol form.

In all the Pt(IV) complexes the metal nitrogen vibration, ν(M–N) are assigned to the new bands [28] in the far IR between 460 and 490 cm^{-1}, while in the region between 350 and 390 cm^{-1} gives metal–sulphur, ν(M–S) band stretching [29]. The band at ~330–270 cm^{-1} is assigned due to ν(Pt–Cl) stretching vibrations.

3.4. NMR spectra

^{1}H NMR spectra of ligands and complexes were recorded in d_6-DMSO taking TMS as internal standards.

- L^1—δ (ppm): 7.73–6.4 (m, 4H, Py-H), 9.16 (br s, $1H^a$, –NH), 3.43 (br s, $2H^b$, $–NH_2$).
- $[Pt(L^1)_2Cl_2]$—δ (ppm): 8.93–7.86 (m, 8H, Py-H), 9.21 (br s, $2H^a$, –NH), 3.68 (br s, $4H^b$, $–NH_2$).
- L^2—δ (ppm): 7.7–6.6 (m, 4H, Py-H), 9.12 (br s, $1H^a$, –NH), 3.3 (t, $4H^b$, $–CH_2$), 1.8 (m, $2H^c$, $–CH_2$), 3.67 (br s, $2H^d$, $–NH_2$).
- $[Pt(L^2)_2Cl_2]$—δ (ppm): 8.43–7.74 (m, 8H, Py-H), 9.17 (br s, $2H^a$, –NH), 2.43 (t, $8H^b$, $–CH_2$), 1.9 (m, $4H^c$, $–CH_2$), 4.5 (br s, $4H^d$, $–NH_2$).
- L^3—δ (ppm): 7.7–6.51 (m, 4H, Py-H), 9.6 (br s, $1H^a$, –NH), 9.16 (br s, $1H^b$, –NH), 8.23 (s, $1H^c$, –CH), 7.3–6.4 (m, 5H, –Ar–H).
- $[Pt(L^3)_2Cl_2]$—δ (ppm): 8.43–7.41 (m, 8H, Py-H), 9.43 (br s, $2H^a$, –NH), 9.19 (br s, $2H^b$, –NH), 8.23 (s, $1H^c$, –CH), 7.7–6.7 (m, 10H, –Ar–H).
- L^4—δ (ppm): 7.21–6.42 (m, 4H, Py-H), 10.42 (br s, $1H^a$, –NH), 9.1 (br s, $1H^b$, –NH), 8.3 (s, $1H^c$, –CH), 7.4–6.26 (m, 5H, –Ar–H), 11.3 (br s, $1H^d$, –OH).
- $[Pt(L^4)_2Cl_2]$—δ (ppm): 8.41–7.6 (m, 8H, Py-H), 10.21 (br s, $2H^a$, –NH), 9.17 (br s, $2H^b$, –NH), 8.15 (s, $1H^c$, –CH), 7.9–6.5 (m, 10H, –Ar–H), 11.26 (br s, $2H^d$, –OH).

The ^{1}H NMR spectrum of thiohydrazides, thiodiamines and thiohydrazones [30,31] shows two signals at δ ~9.0–10.3 and δ ~4.0 ppm, due to the presence of NH protons, which are lost on D_2O exchange. This is observable in the complexes also suggesting that hydrogen bonding to the solvent occurs in the complexes as well as free ligands. The resonance assigned to aldehyde –CH is generally shifted upfield, indicating coordination of azomethine nitrogen [32].

3.5. Antibacterial study

In the current study (Table 4), some synthesized complexes were tested against pathogenic bacterial strains such as *Staphylococcus epidermidis* (*S. epidermidis*) using the disc diffusion method. Gentamycin was used as reference drug for bacteria.

3.6. Cytotoxic study

In the present studies (Table 5), the cytotoxic property of one metal complex has been determined. The study was used to test the growth inhibition assay by MTT assay. Data expressed in terms of percentage (%) cytotoxicity. The metal complexes caused ~50% inhibition. The results of the antitumour activity of the metal complexes suggested that the complexes are an effective inhibitor at moderate concentrations. The importance

Table 4
Antibacterial study

Serial no.	Complexes	Zone of inhibition (mm), *S. epidermidis*
1	$Pt(L^1)_2Cl_2$	8
2	$Pt(L^2)_2Cl_2$	8

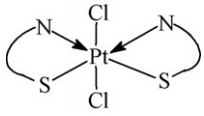
Table 5
Cytototoxic study

Serial no.	Complexes	Concentrations (μg/mL)		
		100	10	1
1	$Pt(L^1)_2Cl_2$	45.5	13.6	9.1

of such work lies the possibility that the new complexes might more efficacious drug against tumours for which a thorough investigation regarding the structure activity of the complexes and their stability is required in order to understand the variation in their biological effects, which could be helpful in designing more potent antitumour agents for therapeutic use.

4. Conclusion

All the complexes are found to be diamagnetic, so the Pt(IV) complexes must be octahedral. Pt(IV) is d^6 system and four bands are expected corresponding to $^1A_{1g} \rightarrow {}^3T_{1g}$, $^1A_{1g} \rightarrow {}^3T_{2g}$, $^1A_{1g} \rightarrow {}^1T_{1g}$ and $^1A_{1g} \rightarrow {}^1T_{2g}$ transitions. The shift towards lower frequency on complexation, indicates the coordination to metal ion is through thioamide sulphur. The antibacterial study of the complexes shows significant activity. The bacterial strains with the zone of inhibition were observed, 8 mm. One complex was tested for the cytotoxic activity. The complex was tested on primary adenocarcinoma (colour). The complex showed good activity at 100 and 1 μM solutions. On dilution activity decreases, which show that, the complex is an effective inhibitor at moderate concentrations. On the basis of these spectroscopic studies the probable structure of the complexes is:



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