SYNTHESIS AND CHARACTERIZATION OF NEW BINARY AND TERNARY PALLADIUM AND PLATINUM COMPLEXES AFFECTIVE TO ANTITUMOR

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Abstract

Binary and ternary complexes derived from ligands containing Oxygen, suppler and Nitrogen as donor atoms with Pd^{2+} and Pt^{2+} ions were synthesized. The isolated solid complexes were characterized by elemental analyses and spectral (IR, ^{1}H-NMR, mass spectrometry) measurements. The biological efficiency of the synthesized complexes on antitumor, antibacterial and antifungal was investigated. The results reveal that these complexes have strong affinity against the growth of bacteria and fungi. The mode of action may involve the formation of hydrogen bonding between the O and N donors and the active centers of the cell constituents, resulting in interference with the normal cell process. The biological results obtained were compared with that obtained using standard tetracycline as antibacterial and amphotericin B as antifungal. The complexes, PtL_3L_9 and PtL_3L_{10}, are considered as strong anticancer drugs, which have enhanced high biological activity.

Keywords: Binary and ternary complexes; Pd and Pt complexes, Spectroscopic studies, Biological activity

Introduction

Platinum-based drugs are widely used as anticancer agents with a broad range of antitumor activities. Cis-platin has a significant activity in ovarian, testicular, bladder, head and neck, and lung cancer, where it is most commonly used in combination with other drugs [1]. The resistance of tumor cells to cis-platin remains a major cause of treatment failure in cancer patients, while the high toxicity of cis-platin limits the dose that can be given to patients. Transition metal complexes of heterocyclic compounds

containing nitrogen as donor atoms such as pyridines;bi- and polypyridines, 2-(2'-pyridyl)-benzimidazole, 2-pyrazinecarboxylic acid, 2-pyrazinecarboxamide and 2-aminobenzimidazole; have a vital role in biology [5-8]. The aim of this work is to synthesize some binary and ternary Pd^{2+} and Pt^{2+} complexes with heterocyclic nitrogen donor ligands as well as selected ligands containing oxygen and/or sulfur donor atom. The biological activities for most of the complexes are studied. The cytotoxicity of three Pt^{2+}complexes were also screened against two breast cancer cell lines (MCF7 and T47D) and human liver carcinoma cell line (HepG2).

Materials and Methods

Synthesis of binary Pd^{2+}complexes

The reactions of 50 mL of $K_2[PdCl_4]$(0.5 mmol) with 0.5 mmol of the ligands (L_1-L_5) dissolved in a minimum amount of EtOH in different ratios and temperatures as shown in Table (1).

Table 1:

The ligand	Amount g	Temp.; ^oC	Time (min)	Color
2-aminobenzimidazole (L_1)	0.08	70	30	reddish-brown
2-(2'-pyridyl)benzimidazole (L_2)	0.10	RT	immediately	pale yellow
2-pyrazinecarboxamide (L_3)	0.06	RT	immediately	brown
2-pyrazinecarboxylic acid (L_4)	0.07	RT	immediately	yellow
2-aminothiazole (L_5)	0.05	70	30	brown

Synthesis of ternary Pd^{2+} complexes

The reactions of 50 mL of $K_2[PdCl_4]$ with two mixed ligands [L_1 is one of them] (0.5 mmol of each ligand dissolved in a minimum amount of EtOH) in different ratio and temperature as shown in Table (2).

Table 2:

mixed ligands (L_1) + L	Amount g	Temp.; ^oC	Time (min)	Color
2-aminobenzimidazole (L_1) + 2-aminothiazole (L_5) + Pd^{2+}salt	0.07 (L_1) + 0.05 (L_5)	70	30	reddish-brown needles
2-aminobenzimidazole (L_1) + urea (L_7) + Pd^{2+}salt	0.07 (L_1) + 0.03 (L_7)	70	30	reddish-brown
2-aminobenzimidazole (L_1) + thiourea (L_8) + Pd^{2+}salt	0.07 (L_1) + 0.04 (L_8)	70	30	reddish-brown
2-aminobenzimidazole (L_1) + pyridine (L_9) + Pd^{2+}salt	0.07 (L_1) + (L_5)	RT	immediately	yellow
2-aminobenzimidazole (L_1) + bipyridine (L_{10}) + Pd^{2+}salt	0.07 (L_1) + 0.08 (L_{10})	RT	immediately	yellow

Table (3) represented the reactions of 50 ml (0.5 mmol) $K_2[PdCl_4]$ with two mixed ligands, [L_2 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of EtOH) in different ratio and temperature.

Table 3.

The mixed ligands (L_2) + L	Amount g	Temp.; ^oC	Time (min)	Color
2-(2'-pyridyl)benzimidazole (L_2)+ 2-aminothiazole (L_5) + Pd^{2+}salt	0.19 (L_2) + 0.05 (L_5)	RT	immediately	buff
2-(2'-pyridyl)benzimidazole (L_2)+ urea (L_7) + Pd^{2+}salt	0.1 (L_2) + 0.03(L_7)	RT	immediately	buff
2-(2'-pyridyl)benzimidazole (L_2)+ thiourea (L_8) + Pd^{2+}salt	0.1 (L_2) + 0.04 (L_8)	RT	immediately	buff
2-(2'-pyridyl)benzimidazole (L_2)+ pyridine (L_9) + Pd^{2+}salt	0.1 (L_2) + 0.5 ml (L_5)	70	30	Greenish-yellow
2-(2'-pyridyl)benzimidazole (L_2)+ bipyridine (L_{10}) + Pd^{2+}salt	0.1 (L_2) + 0.08 (L_{10})	RT	immediately	buff

Table (4) represent the reactions of 50 ml (0.5 mmol) $[PdCl_4]^{2-}$ with two mixed ligands, [L_3 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of EtOH) in different ratio and temperature.

Table 4.

mixed ligands (L_3) + L	Amount g	Temp.; ^oC	Time (min)	Color
2-pyrazinecarboxamide (L_3) + 2-aminothiazole (L_5) + Pd^{2+}salt	0.06 (L_3) + 0.05 (L_5)	70	30	dark brown
2-pyrazinecarboxamide (L_3) + urea (L_7) + Pd^{2+}salt	0.06 (L_3) + 0.03 (L_7)	70	30	brown
2-pyrazinecarboxamide (L_3) + thiourea (L_8) + Pd^{2+}salt	0.06 (L_3) + 0.04 (L_8)	RT	immediately	brown
2-pyrazinecarboxamide (L_3) + pyridine (L_9) + Pd^{2+}salt	0.06 (L_3) + 0.5 ml (L_5)	RT	immediately	yellow
2-pyrazinecarboxamide (L_3) + bipyridine (L_{10}) + Pd^{2+}salt	0.06 (L_3) + 0.08 (L_{10})	70	30	yellow

Table (5) represent the reactions of 50 ml (0.5 mmol) $[PdCl_4]^{2-}$ with two mixed ligands, [L_4 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 5.

mixed ligands (L_4) + L	Amount g	Temp.; ^oC	Time (min)	Color
2-pyrazinecarboxylic acid (L_4) + 2-aminothiazole (L_5) + Pd^{2+}salt	0.07 (L_4) + 0.05 (L_5)	70	30	orange
2-pyrazinecarboxylic acid (L_4) + urea (L_7) + Pd^{2+}salt	0.07 (L_4) + 0.03(L_7)	70	30	yellow
2-pyrazinecarboxylic acid (L_4) + thiourea (L_8) + Pd^{2+}salt	0.07 (L_4) + 0.04 (L_8)	RT	Immediately	red
2-pyrazinecarboxylic acid (L_4) + pyridine (L_9) + Pd^{2+}salt	0.07 (L_4) + 0.5 ml (L_5)	70	30	yellow
2-pyrazinecarboxylic acid (L_4) + bipyridine (L_{10}) + Pd^{2+}salt	0.07 (L_4) + 0.09 (L_{10})	RT	Immediately	yellow

Synthesis of binary Pt^{2+} Complexes

Table (6) represent the reactions of 50 ml (0.5 mmol) $[PtCl_4]^{2-}$ with 0.5 mmol ligands L_1-L_5 (dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 6.

Ligand	Amount g	Temp.;^oC	Time(min)	Color
2-aminobenzimidazole(L_1) + Pt^{2+}salt	0.07	70	30	red
2-(2'-pyridyl)benzimidazole (L_2) + Pt^{2+}salt	0.10	70	30	pale yellow
2-pyrazinecarboxamide (L_3) + Pt^{2+}salt	0.06	70	30	brown
2-pyrazinecarboxylic acid (L_4) + Pt^{2+}salt	0.07	70	30	orange
2-aminothiazole (L_5) + Pt^{2+}salt	0.05	70	30	dark brown

Synthesis of ternary Pt^{2+} complexes

Table (7) represent the reactions of 50 ml (0.5 mmol) $[PtCl_4]^{2-}$ with two mixed ligands, [L_1 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 7.

mixed ligands (L_1) + L	Amount g	Temp.; ^oC	Time (min)	Color
2-aminobenzimidazole (L_1) + urea (L_7) + Pt^{2+}salt	0.07 (L_1) + 0.03 (L_7)	70	30	pale brown
2-aminobenzimidazole (L_1) + thiourea (L_8) + Pt^{2+}salt	0.07 (L_1) + 0.04 (L_8)	70	30	brown
2-aminobenzimidazole (L_1) + pyridine (L_9) + Pt^{2+}salt	0.07 (L_1) + 0.5 ml (L_5)	70	30	red
2-aminobenzimidazole (L_1) + bipyridine (L_{10}) + Pt^{2+}salt	0.07 (L_1) + 0.08 (L_{10})	70	30	orange

Table (8) represent the reactions of 50 ml (0.5 mmol) $[PtCl_4]^{2-}$ with two mixed ligands, [L_2 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 8.

mixed ligands (L_2) + L	Amount g	Temp.;^oC	Time (min)	Color
2-(2'-pyridyl)benzimidazole (L_2) + urea (L_7) + Pt^{2+}salt	0.1 (L_2) + 0.03 (L_7)	70	30	pale green
2-(2'-pyridyl)benzimidazole (L_2) + thiourea (L_8) + Pt^{2+}salt	0.1 (L_2) + 0.04 (L_8)	70	30	brown
2-(2'-pyridyl)benzimidazole (L_2) + pyridine (L_9) + Pt^{2+}salt	0.1 (L_2) + 0.5 ml (L_5)	70	30	pale green
2-(2'-pyridyl)benzimidazole (L_2) + bipyridine (L_{10}) + Pt^{2+}salt	0.1 (L_2) + 0.08 (L_{10})	70	30	pale green

Table (9) represent the reactions of 50 ml (0.5 mmol) $[PtCl_4]^{2-}$ with two mixed ligands, [L_3 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 9.

mixed ligands (L_3) + L	Amount g	Temp.;^oC	Time(min)	Color
2-pyrazinecarboxamide (L_3) + urea (L_7) + Pt^{2+}salt	0.0.06 (L_3) + 0.03 (L_7)	70	30	dark brown
2-pyrazinecarboxamide (L_3) + thiourea (L_8) + Pt^{2+}salt	0.06 (L_3) + 0.04 (L_8)	70	30	dark brown
2-pyrazinecarboxamide (L_3) + pyridine (L_9) + Pt^{2+}salt	0.06 (L_3) + 0.5 ml (L_5)	70	30	brown
2-pyrazinecarboxamide (L_3) + bipyridine (L_{10}) + Pt^{2+}salt	0.06 (L_3) + 0.08 (L_{10})	70	30	pale brown

Table (10) represent the reactions of 50 ml (0.5 mmol) $[PtCl_4]^{2-}$ with two mixed ligands, [L_4 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 10.

mixed ligands (L_4) + L	Amount g	Temp.;^oC	Time(min)	Color
2-pyrazinecarboxylic acid (L_4) + 2-aminothiazole (L_5) + Pt^{2+}salt	0.07 (L_4) + 0.05 (L_5)	70	30	orange
2-pyrazinecarboxylic acid (L_4) + urea (L_7) + Pt^{2+}salt	0.07 (L_4) + 0.03 (L_7)	70	30	reddish brown
2-pyrazinecarboxylic acid (L_4) + thiourea (L_8) + Pt^{2+}salt	0.07 (L_4) + 0.04 (L_8)	RT	immediately	Red
2-pyrazinecarboxylic acid (L_4) + pyridine (L_9) + Pt^{2+}salt	0.07 (L_4) + 0.5 ml (L_5)	70	30	orange
2-pyrazinecarboxylic acid (L_4) + bipyridine (L_{10}) + Pt^{2+}salt	0.07 (L_4)+ 0.08 (L_{10})	RT	immediately	orange

Table (11) represent the reactions of 50 ml (0.5 mmol) $[PtCl_4]^{2-}$ with two mixed ligands, [L_5 is one of them] (0.5 mmol of each ligand dissolved in minimum amount of ethanol) in different ratio and temperature.

Table 11.

mixed ligands (L_5) + L	Amount g	Temp.; ^oC	Time (min)	Color
2-aminothiazole (L_5) + urea (L_7) + Pt^{2+}salt	0.05 (L_5)+ 0.03 (L_7)	70	30	brown
2-aminothiazole (L_5) + thiourea (L_8) + Pt^{2+}salt	0.05 (L_5)+ 0.04 (L_8)	70	30	Reddish-brown
2-aminothiazole (L_5) + pyridine (L_9) + Pt^{2+}salt	0.05 (L_5)+ 0.5 ml(L_5)	70	30	brown
2-aminothiazole (L_5) + bipyridine (L_{10}) + Pt^{2+}salt	0.05 (L_5)+ 0.08 (L_{10})	70	30	brown

Measurements

IR measurements (KBr pellets) were carried out on a Unicam-Mattson 1000 FT-IR spectrometer. All ^{1}H-NMR measurements were carried

out on a Spectrospin-Bruker 300 MHz spectrometer using d_6-DMSOas solvent. Elemental analyses were performed on Perkin-Elmer 2400 CHN elemental analyzer. Mass spectrometry measurements of the solid complexes (70 eV, EI) were carried out on a Finnigan MAT SSQ 7000 spectrometer, National center for research of Egypt.

Results and discussion

Pd^{2+} and Pt^{2+}complexes derived from binary and ternary were synthesized using mono- and bidentate heterocyclic nitrogen donor ligands (Scheme 1).All the isolated solid complexes were characterized by elemental analyses and spectral (mass spectrometry, IR and NMR) measurements. Table 12 shows the color, yield, elemental analyses and mass spectral of the complexes. The elemental analyses suggest the molecular formulae of the complexes. The binary and ternary complexes show the variations in their molecular structures. They varied between mono- and binuclear, and covalent and ionic formulae. The values molar conductance in DMSO for the Pd^{2+} and Pt^{2+} complexes (the 23-36 μS) suggest that the complexes are non electrolytes. On the other hand the other complexes show higher molar conductance due to their electrolytic nature.

The IR spectra of the complexes exhibited the characteristic bands of the ligands, υ(OH), υ(NH), υ(C=N) and υ(C=O), with the corresponding shifts due to complex formation[28]as shown in Table 13. The υ(C=N) vibrations shifted are shifted to higher wave numbers, while the NH band shows shifts from higher to lower frequencies relative to those of free ligands [30-33]. In case of the complexes derived from PCA and PC ligands the (C=O) band is shifted to lower wave numbers confirming the participation of the carbonyl group in the coordination [28].Furthermore, the spectra show bands in the 651-419 cm^{-1}range attributed to the M-O and M-N bonds [29-32]. The ^{1}H-NMR spectra of the Pd^{2+} and Pt^{2+} complexes show due to the protons of NH, NH_2, OH, phenyl and pyrazine moieties with the corresponding shifts due to complex formation as shown in Table 13 [29-33]. The results show that the ligands,2-aminobenzimidazole and pyridine, act as monodentate through either the pyrazine or pyridyl nitrogen. The other ligands, [2-(2'-pyridyl)benzimidazole, 2-pyrazinecarboxamide, 2-pyrazinecarboxylic acid and bipyridine)], act as bidentate ligands coordinating through nitrogen and oxygen donor sites. It is worth to mention that the OH group of 2-pyrazinecarboxylic acid coordinates without proton displacement in consistent with ^{1}H-NMR data. Therefore, according to the elemental analyses and the spectroscopic data, the complexes structures (Schemes 2-5) are suggested.

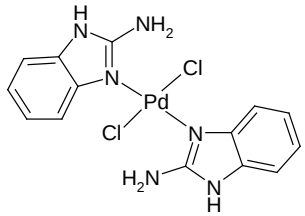
Table 12. Elemental analysis and mass spectrometry data of $Pd^{2+}$and Pt^{2+}complexes.

Complex	Color	Yield %	Elemental analysis Found (Calcd.)			Mass spectra	
			C	H	N	M.Wt.	m/z
PdL1	reddish-brown	63	37.85 (37.90)	3.25 (3.18)	19.11 (18.94)	443.61	438
PtL1	red	76	31.64 (31.60)	2.71 (2.65)	15.85 (15.89)	532.30	536, 533, 532
PdL2	yellow	82	38.55 (38.70)	2.60 (2.44)	11.35 (11.28)	372.53	368, 360, 356
PtL2	yellow	83	31.28 (31.30)	1.74 (1.97)	9.05 (9.11)	461.22	464, 462, 461
PdL3	brown	61	20.11 (20.00)	1.53 (1.68)	14.09 (14.00)	300.42	278, 279
PtL3	brown	85	23.48 (23.50)	1.86 (1.97)	16.49 (16.41)	512.22	477, 475, 468
PdL4	yellow	75	28.19 (28.20)	1.83 (1.89)	13.28 (13.17)	425.50	398, 383, 377
PtL4	orange	87	23.42 (23.40)	1.65 (1.57)	10.85 (10.90)	514.19	512, 508, 507, 501
PdL1L9	yellow	58	36.92 (37.00)	3.21 (3.10)	14.34 (14.38)	389.56	392, 391, 38, 388
PdL1L10	yellow	62	37.04 (37.10)	2.79 (2.85)	14.44 (14.42)	777.10	649, 648
PtL1L9	Red	55	24.73 (24.80)	2.09 (2.08)	8.59 (8.51)	823.35	788, 787, 785
PtL1L10	orange	57	30.17 (30.20)	2.28 (2.32)	11.82 (11.74)	954.48	919, 917, 882
PdL2L9	yellow	49	45.26 (45.20)	3,09 (3.12)	12.46 (12.40)	451.63	454, 453, 452, 450
PdL2L10	buff	53	37.38 (37.40)	2.55 (2.43)	9.98 (9.92)	706.02	707, 704, 697
PtL2L9	pale green	48	25.36 (25.30)	1.80 (1.75)	7.00(6.95)	806.32	772, 771, 770
PtL2L10	pale green	47	29.96 (29.90)	1.97 (1.94)	7.92 (7.93)	883.40	846, 845, 840
PdL3L9	yellow	56	31.69 (31.70)	2.68 (2.66)	14.79 (14.76)	379.52	346, 345, 343
PdL3L10	yellow	62	39.44 (39.50)	2.84 (2.87)	15.27 (15.34)	456.61	421, 420, 419
PtL3L9	brown	66	25.68 (25.70)	2.12 (2.15)	12.03 (12.00)	468.21	460, 422, 417, 415
PtL3L10	pale brown	69	22.18 (22.20)	1.68 (1.62)	8.68 (8.63)	811.29	552, 550, 466
PdL4L9	yellow	46	31.52 (31.60)	2.40 (2.38)	11.09 (11.04)	380.51	347, 345, 344
PdL4L10	yellow	48	39.35 (39.40)	2.60 (2.64)	12.22 (12.24)	457.59	422, 420, 418
PtL4L9	orange	76	25.53 (25.60)	2.01 (1.93)	8.99 (8.96)	469.20	424, 396, 394
PtL4L10	orange	81	22.21 (22.18)	1.55 (1.49)	6.95 (6.90)	812.28	615, 524, 515

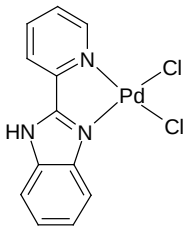
Table 13. IR and NMR data of the $Pd^{2+}$and Pt^{2+} complexes.

^{1}H-NMR data (ppm)	IR data (cm^{-1})				Compound
	υ(C=O)	υ(C=N)	υ(NH)	υ(OH)	
12.47 (bs), 8.52 (bs), 7.38 (m), 7.30(m)	--	1669 (s)	3309 (m) 3229 (m) 3198 (m) 3155 (m)	--	PdL1
12.54 (bs), 8.50 (bs), 7.36 (m), 7.21(m)	--	1666 (s)	3304 (m) 3228 (m) 3198 (m) 3157 (m)	--	PtL1
12.65 (bs), 9.48 (d), 8.83 (d), 8.39 (m), 7.81 (m), 7.49 (m)	--	1609 (m)	3156 (m) 3084 (m)	--	PdL2
12.68 (bs), 9.46 (d), 8.79 (d), 8.39 (m), 7.80 (m), 7.47 (m)	--	1617 (m)	3165 (s) 3108 (m)	--	PtL2
9.20 (d), 8.86 (d), 8.74 (dd), 8.31 (bs), 7.84 (bs)	1701 (m)	1652 (s)	3304 (m) 3171 (m) 3090 (m)	--	PdL3
9.17 (d), 8.88 (d), 8.76 (dd), 8.28 (bs), 7.87 (bs)	1705 (s)	1692 (sh)	3278 (m) 3189 (m) 3103 (m) 3074 (m)	--	PtL3
9.15 (d), 9.13 (s), 8.89 (d), 8.85 (s), 8.83 (d), 8.76 (s)	1674 (s)	1609 (m)	--	3451 (b)	PdL4
9.19 (d), 9.15 (s), 8.86 (d), 8.83 (s), 8.80 (d), 8.79 (s)	1715 (s)	1627 (w) 1595 (w)	--	3468 (b)	PtL4
12.60 (bs), 8.97 (m), 8.68 (m), 8.52 (s), 8.13 (m), 7.32 (m), 7.24 (m)	--	1602 (m) 1570 (w)	3106 (w) 3067 (w) 3041 (w) 3004 (w)	--	PdL1L9
12.64 (bs), 9.43 (m), 8.56 (m), 8.40 (m), 8.82 (m)	--	1682 (w) 1646 (w) 1602 (m)	3108 (w) 3078 (m) 3048 (m)	--	PdL1L10
12.62 (bs), 8.93 (m), 8.64 (m), 8.55 (s), 8.10 (m), 7.30 (m), 7.19 (m)	--	1681 (s) 1634 (m)	3193 (m) 3149 (m) 3071 (m)	--	PtL1L9
12.60 (bs), 9.47 (m), 8.57 (m), 8.40 (m), 8.83 (m)	--	1681 (w) 1606 (m) 1561 (w)	3110 (w) 3085 (w) 3050 (m)	--	PtL1L10
12.67 (bs), 9.43 (d), 8.82 (d), 8.40 (m), 8.32 (m), 7.83 (m), 7.45 (m)	--	1608 (s) 1568 (m)	3083 (m) 3054 (m)	--	PdL2L9
12.63 (bs), 9.49 (d), 8.83 (d), 8.61 (m), 8.39 (m), 7.81 (m), 7.86 (m), 7.65 (m)	--	1603 (m) 1564 (m)	3062 (sh) 3079 (s) 3046 (s)	--	PdL2L10
12.64 (bs), 9.45 (d), 8.79 (d), 8.44 (m), 8.32 (m), 7.80 (m), 7.47 (m)	--	1613 (m) 1564 (sh)	3164 (m) 3101 (m) 3001 (m)	--	PtL2L9
12.63 (bs), 9.47 (d), 8.78 (d), 8.59 (m), 8.39 (m), 7.85 (m), 7.82 (m), 7.60	--	1608 (m) 1562 (sh)	3199 (m) 3112 (m) 3052 (m)	--	PtL2L10

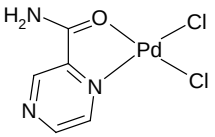
(m)					
9.20 (d), 8.90 (m), 8.84 (d), 8.75 (dd), 8.25 (bs), 8.08 (m), 7.92 (bs), 7.61 (m), 7.59 (m)	1709 (w)	1604 (m) 1572 (w)	3106 (w) 3068 (w) 3040 (w) 3004 (w)	--	PdL3L9
9.53 (d), 9.22 (d), 8.81 (m), 8.74 (dd), 8.61 (bs), 8.45 (m), 8.30 (bs), 7.82 (m)	1704 (m)	1602 (m) 1564 (w)	3107 (w) 3078 (m) 3049 (m)	--	PdL3L10
9.18 (d), 8.91 (m), 8.86 (d), 8.72 (dd), 8.25 (bs), 8.04 (m), 7.90 (bs), 7.65 (m), 7.56 (m)	1703 (vs)	1655 (m) 1594 (m)	3108 (m) 3101 (m) 3072 (m)	--	PtL3L9
9.50 (d), 9.18 (d), 8.85 (m), 8.71 (dd), 8.57 (bs), 8.42 (m), 8.30 (bs), 7.84 (m)	1692 (s)	1650 (sh) 1585 (m)	3209 (m) 3165 (m) 3111 (m) 3072 (m)	--	PtL3L10
9.23 (d), 9.14 (s), 8.86 (d), 8.80 (d), 8.64 (d), 8.04 (m), 7.63 (m), 7.52 (m)	1714 (s)	1673 (s) 1598 (m)	--	3454 (b)	PdL4L9
9.45 (d), 9.20 (s), 8.83 (d), 8.78 (d), 8.55 (d), 8.48 (s), 8.40 (m), 7.80 (m)	1743 (w)	1679 (w) 1602 (m)	--	3734 (b)	PdL4L10
9.19 (d), 9.11 (s), 8.86 (d), 8.82 (d), 8.66 (d), 8.04 (m), 7.65 (m), 7.55 (m)	1767 (sh) 1725 (s)	1683 (s) 1596 (m)	--	3464 (b)	PtL4L9
9.48 (d), 9.19 (s), 8.86 (d), 8.80 (d), 8.58 (d), 8.50 (s), 8.41 (m), 7.84 (m)	1713 (s)	1605 (sh) 1598 (m)	--	3464	PtL4L10



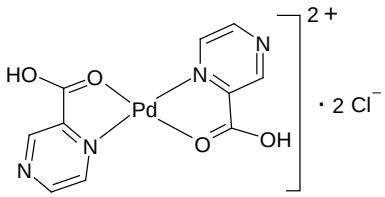
PdL_1



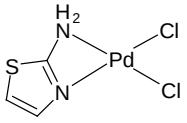
PdL_2



PdL_3

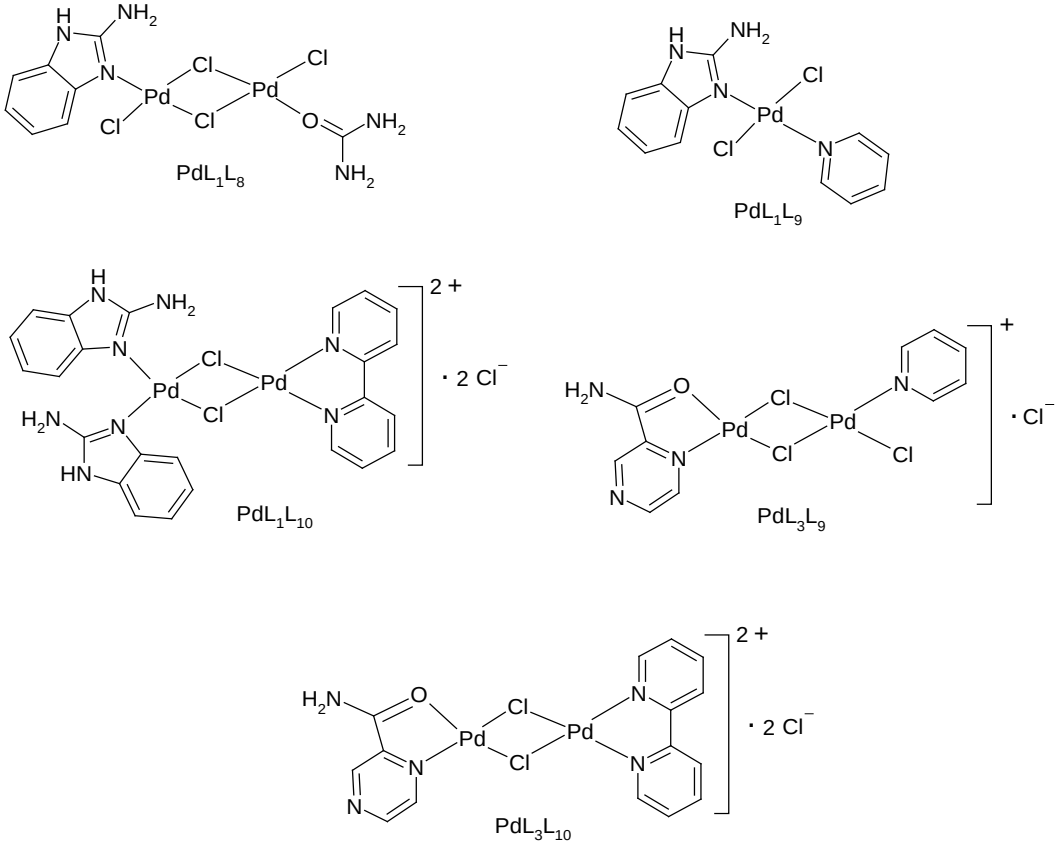


PdL_4

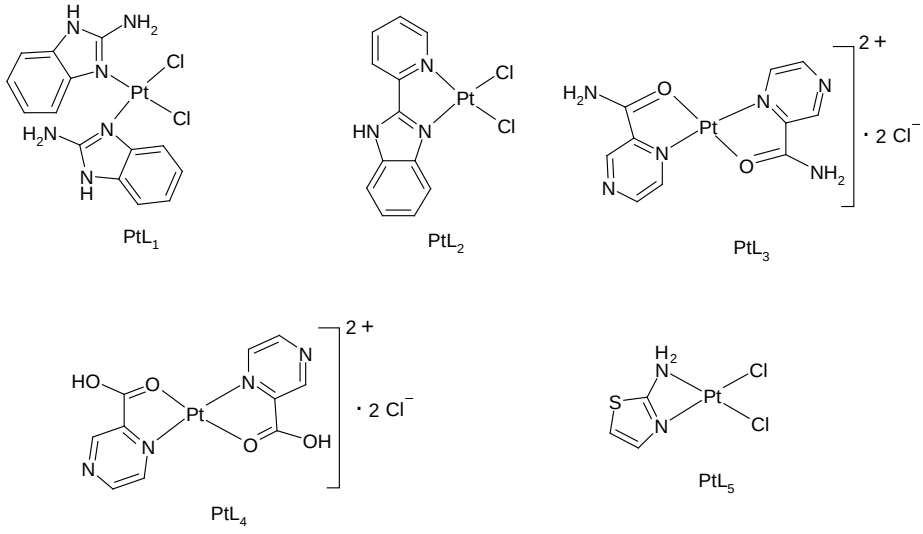


PdL_5

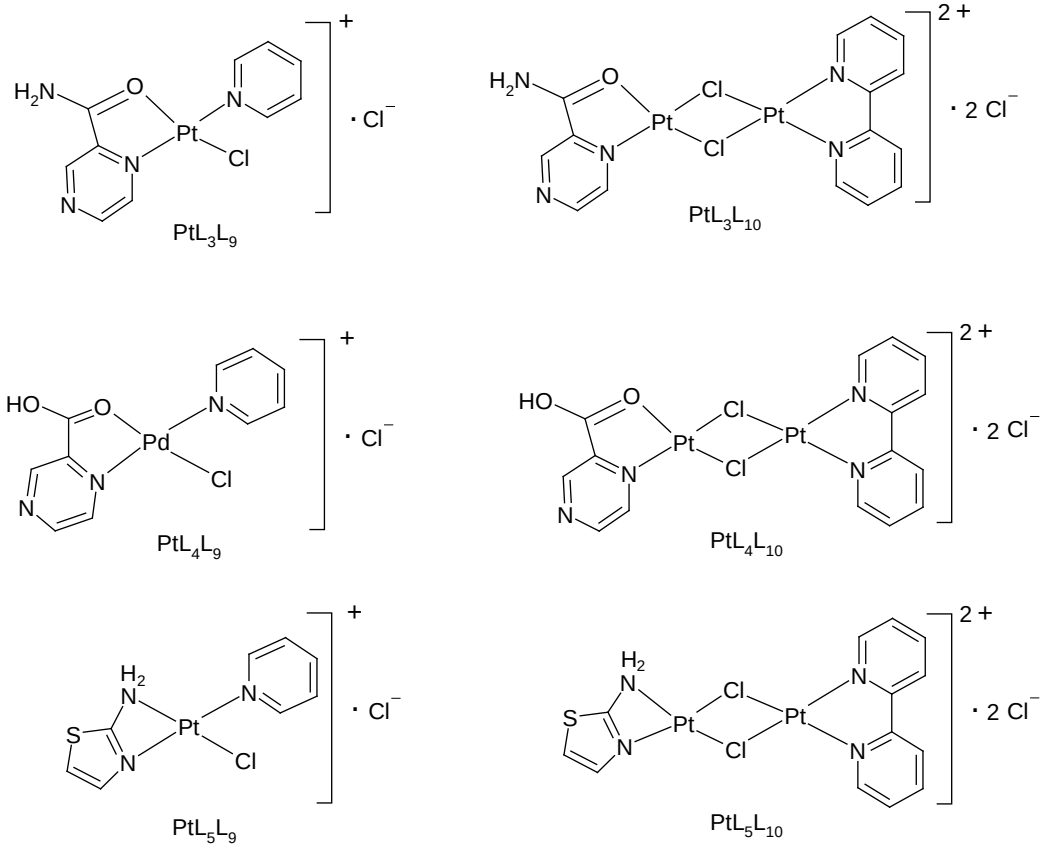
Scheme 2. Proposed structures of some binary Pd^{2+}complexes



Scheme 3. Proposed structures of some ternary Pd^{2+}complexes.



Scheme 4. Suggested structures of some binary Pt^{2+} complexes.



Scheme 5. Suggested structures of some ternary Pt^{2+}complexes.

Applications

Antibacterial and antifungal activity

The free ligands and some of their binary and ternary Pd^{2+} and Pt^{2+} complexes were screened against the *Escherchia coli* as Gram-negative bacteria and *Staphylococcus aureus* as Gram-positive bacteria, and the two fungus *Aspergillus flavus* and *Candida albicans* to assess their potential activity relative to the two standards: Tetracycline antibacterial agent and Amphotericin B antifungal agent (Figs. 1-3). The data showed that the free ligands have the capacity of inhibiting the metabolic growth of the investigated bacteria and the fungus to different extents, which may indicate broad-spectrum properties. The activity of these compounds may be arising from the functional groups moieties. The mode of action may involve the formation of hydrogen bonding between the O and N donors and the active centers of the cell constituents, resulting in interference with the normal cell process [33]. All the tested metal complexes showed activity against both *Escherchia coli* and *Staphylococcus aureus*. However, although the complexes showed promising activities against the two bacteria, their

activities were less than the standard Tetracycline. On the other hand, the ligands and complexes showed antifungal activities against the tested fungus. It is important to point out that some ligands are more toxic against the *Candida albicans* fungus and the *Aspergillus flavus* fungus compared to the standard Amphotericin B antifungal agent. The antibacterial l data revealed that some of the Pd^{2+} and Pt^{2+} complexes are more bioactive than the free ligands. The enhanced activity of the metal complexes may be retained to the increase dlipophilic nature of the complexes which arose from the chelation. It was also noted that the toxicity of the metal complexes increases on increasing the metal ion concentration. This elevation is probably due to faster diffusion of the chelates as a whole through the cell membrane. The chelated metal may block the enzymatic activity of the cell or it may catalyze the toxic reactions among cellular constituents.

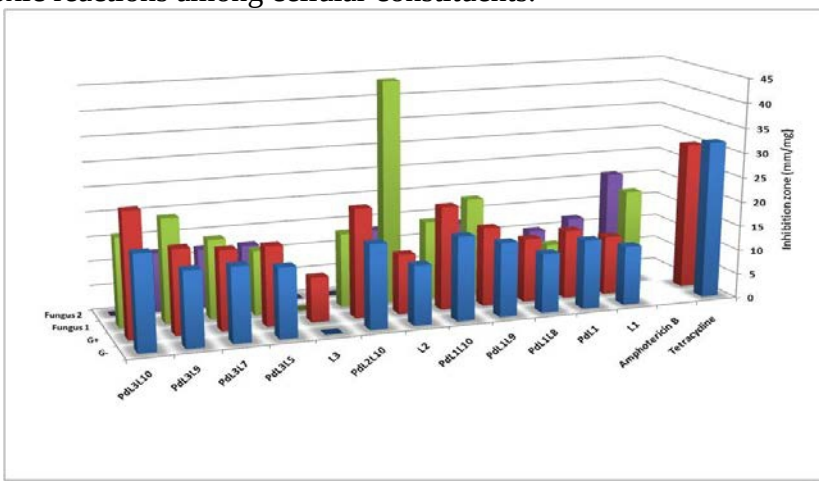


Fig 1. In vitro antibacterial and antifungal activities of some of the ligand and some Pd^{2+} complexes. (G^-):Gram-negative *Escherchia coli* bacteria; (G^+): Gram-positive *Staphylococcus aureus* bacteria; fungus1: *Aspergillus flavus*; fungus2: *Candida albicans*.

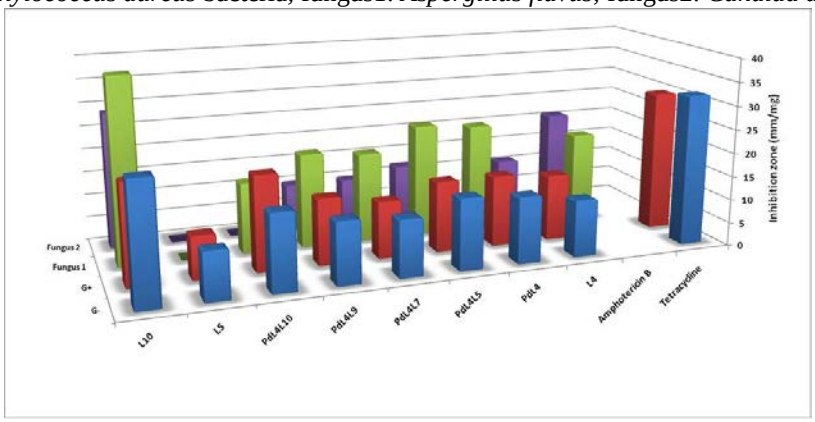


Fig 2. In vitro antibacterial and antifungal activities of some of the ligand and some Pd^{2+} complexes. (G^-):Gram-negative Escherchia *coli* bacteria; (G^+): Gram-positive *Staphylococcus aureus* bacteria; fungus1: *Aspergillus flavus*; fungus2: *Candida albicans*.

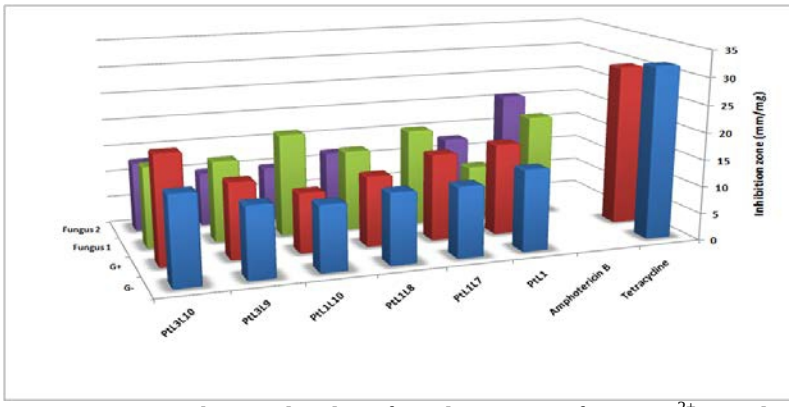


Fig 3. In vitro antibacterial and antifungal activities of some Pt^{2+} complexes. (G^-) :Gram-negative *Escherchia coli* bacteria; (G^+): Gram-positive *Staphylococcus aureus* bacteria; fungus1: *Aspergillus flavus*; fungus2: *Candida albicans*.

Cytotoxicity of some platinum complexes

To evaluate the potential usefulness of some of the reported platinum complexes (*cis*-platin analogous) as antitumor agent, three human cell lines (two breast cancer cell lines, MCF7 and T47D, and liver carcinoma cell line, HepG2) were treated by the PtL1, PtL3L9 and PtL3L10; and compared with *cis*-platin. The complexes showed promising activity against the studied cell lines. The IC_{50} value (the concentration that produce 50% inhibition of cell growth) of Pt complexes and *cis*-platin were determined. The IC_{50} values of the reported platinum complexes were found to be: PtL1 complex: MCF7 (11.3 µg/ml, 21.6 µM), T47D (19.2 µg/ml, 34.4 µM) and HepG2 (15.9 µg/ml, 25.7 µM); PtL3L9 complex: MCF7 (3.3 µg/ml, 5.3 µM), T47D (3.9 µg/ml, 5.7 µM) and HepG2 (3.15 µg/ml, 5.0 µM); PtL3L10 complex: MCF7 (4.05 µg/ml, 5.1 µM), T47D (4.5 µg/ml, 5.3 µM) and HepG2 (3.75 µg/ml, 4.9 µM). According to the IC_{50} values, the PtL1 complex is, thus, considered as weak anticancer drug compared to *cis*-platin (11.9-9.9 µM) [34]. On the other hand, the two complexes (PtL3L9 and PtL3L10) are considered as strong anticancer drugs compared to *cis*-platin (11.9-9.9 µM) [34]. However, the validity of the complexes as anticancer drugs require further investigation such as in vivo study on the effect of the compounds on Ehrlich solid carcinoma induced in mice including the study of tumor growth, apoptosis/necrosis ratio, hematological profile, liver and kidney functions and histological examination of the tumor cells and some organs.

Conclusion

Interaction of some mono- and bidentate heterocyclic nitrogen and oxygen donor ligands with $Pd^{2+}$and Pt^{2+}resulted in the formation of a variety of binary and ternary complexes. The spectroscopic studies of the complexes revealed different structural arrangements. The antibacterial and cytotoxicity of some complexes showed promising biological activity.

References:

Loehrer,P. J., Einhorn, L. H.,1984.Drugs five years later. CisplatinAnnals of Internal Medicine100(5), 704–713.

Brabec,V., Kasparkova, J.,2005.Modifications of DNA by platinum complexes: relation to resistance of tumors to platinum antitumor drugs. Drug Resistance Updates.8(3),131–146.

Wang, D., Lippard,SJ.,2005.Cellular processing of platinum anticancer drugs. Nature Reviews Drug Discovery.4 (4),307–320.

Hartmann, JT., Lipp, H-P.,2003.Toxicity of platinum compounds.Expert Opinion on Pharmacotherapy.4(6),889–901.

Murray,R.K., Granner,D.K., Mayes,P.A. and Rodwell,V.W.,1988 .Harper's Biochemistry (Appleton and Lange, California, 21st Edn.

N. Dodoff, S. Varbanov, G.,Borisov, and N. Spassovska, 1990 .J. Inorg. Biochem. 39, 201

C. Mock, I. Puscasu, M.J. Rauterkus, G. Tallen, J.E.A. Wolff and B. Krebs, Inorg. Chim.Acta 319, 109 (2001).

N. Trendafilova, G. Bauer, I. Georgieva, T. Tosheva and S. Varbanov, Spectrochim. Acta 59A, 169 (2003).

A. Kozubík, A. Vaculová, K. Souček, J. Vondráček, J. Turánek and J. Hofmanová. Novel Anticancer Platinum(IV) Complexes with Adamantylamine: Their Efficiency and Innovative Chemotherapy Strategies Modifying Lipid Metabolism. Met Based Drugs. 2008; 2008: 417897.

Varbanov H, Valiahdi SM, Legin AA, Jakupec MA, Roller A, Galanski M, Keppler BK. Synthesis and characterization of novel bis(carboxylato)dichloridobis(ethylamine)platinum(IV) complexes with higher cytotoxicity than cisplatin, Eur J Med Chem. 2011, 46:5456-64.

Ivchuk VV, Polishko TM, Golichenko OA, Shtemenko OV, Shtemenko NI. Influence of antitumor system rhenium-platinum on biochemical state of the liver, UkrBiokhimZh. 2011, 83:76-84.

D'Errico S, Oliviero G, Piccialli V, Amato J, Borbone N, D'Atri V, D'Alessio F, Di Noto R, Ruffo F, Salvatore F, Piccialli G. Solid-phase synthesis and pharmacological evaluation of novel nucleoside-tethered dinuclearplatinum(II) complexes, Bioorg Med ChemLett. 2011, 21:5835-8.

Ulukaya E, Ari F, Dimas K, Sarimahmut M, Guney E, Sakellaridis N, Yilmaz VT. Cell death-inducing effect of novel palladium(II) and platinum(II) complexes on non-small cell lung cancer cells in vitro.J Cancer Res ClinOncol.2011, 137:1425-34.

De Pascali SA, Lugoli F, De Donno A, Fanizzi FP. Mutagenic Tests Confirm That New AcetylacetonatePt(II) Complexes Induce Apoptosis in Cancer Cells Interacting with Nongenomic Biological Targets, Met Based Drugs. 2011, 2011:763436.

Abdel Ghani NT, Mansour AM. Structural and in vitro cytotoxicity studies on 1H-benzimidazol-2-ylmethyl-N-phenyl amine and its Pd(II) and Pt(II) complexes.SpectrochimActa A MolBiomolSpectrosc.2011, 81:529-43.
Pichler V, Valiahdi SM, Jakupec MA, Arion VB, Galanski M, Keppler BK. Mono-carboxylateddiaminedichloridoplatinum(IV) complexes--selective synthesis, characterization, and cytotoxicity. Dalton Trans. 2011; 40:8187-92
J.L. Butour, S.Wimmer, F. Wimmer, P. Castan, Chem. Biol. Inter.104 (1997)
E. Bermejo, R. Carballa,A. Castineiras, R. Dominguez,A.E. Liberta, C.Maichelle-M◌ssmer, M.M. Salberg, D.X.West, Eur. J. Inorg.Chem. (1999)
A.G. Quiroga, J.M. Perez, I. Lopez-Solera, J.R. Masaguer, A. Luque, P. Roman, A. Edwaeds, C. Alonso, C. Navarro-Ranninger, J. Med. Chem. 41 (1998) 1399.
Cleare, M. J.; Hoeschele, J. D. Bioinorg.Chem., 1973, 2, 187.
Connors, T. A.; Cleare, M. J.; Harrap, K. R. Cancer Treat.Rep., 1979, 63, 1499.
A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis, in: M. Gielen, E.R.T. Tiekink (Eds.), Metals in Medicine, Palladium (Pd), in Metallotherapeutic Drugs and Metal-based Diagnostic Agents: The Use of Metals in Medicine, John Wiley & Sons, Ltd., 2005, p. 399 (Chapter 21).
A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis, Coord. Chem. Rev.,253 (2009) 1384–1397.
A.S. Abu-Surrah, M. Kettunen, Current Medicinal Chemistry, 2006, 13, 1337-1357.
A. Rodrguez-Castro, A. Fernandez, M. Lopez-Torres, D.Vazquez-Garcia, L. Naya, J.M. Vila, J.J. Fernandez, Polyhedron 33 (2012) 13–18.
C.M. Lozano, O. Cox, M.M. Muir, J.D. Morales, J.L. Rodriguez-Cabain, P.E. Vivas-Mejfa, F.A. Gonzalez, Inorg. Chim.Acta, 271 (1998) 137.
A. Monks, D. Scudiero, P. Skehan, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Viagro-Wolff, M. Gra-Goodrih, J. Natl. Cancer Inst., 83 (1991) 757.
R.M. Silverstein, G.C. Bassler, T.C. Morrill, Spectrometric Identification of Organic Compounds, 4th Ed, Wiley, NewYork, 1991.
D.Y. Sabry, T.A. Youssef, S.M. EL-Medani, R.M. Ramadan, J.Coord. Chem. 56 (2003) 1375.
S.M. EL-Medani, O.A.M. Ali, R..Ramadan, J. Mol. Struct., 738 (2005) 171.
O.A.M. Ali, L.H. Abdel-Rahman, R.M. Ramadan, J. Coord. Chem., 60 (2007) 2335.
M.A. Taher, S. E. Jarelnabbi, A.G.M. Al-Sehemi,S. M. El-Medani, R.M. Ramadan, J. Coord. Chem., 62 (2009) 1293.
N.T. Abdel Ghani and A.M. Mansour, Spectrochim. Acta,, A81 (2011) 529.
W.T. Shier, Mammalian Cell Culture on $5 a day: A Lap Manual of Low Cost Methods, University of Philippines, Los Banos, 1991.