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Synthesis, spectral and cytotoxicity studies of palladium(II) and platinum(II) amino acid Schiff base complexes

Offiong E. Offiong*, Emmanuel Nfor and Ayi A. Ayi
Department of Chemistry, University of Calabar, Calabar, Nigeria

Sante Martelli
Dipartimento di Scienze Chimiche, Universita di Camerino, Camerino, Italy

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Abstract

Novel Pd^{II} and Pt^{II} complexes of substituted *o*-hydroxyacetophenone-glycine have been synthesized, and characterized by conductivity measurements, i.r., electronic and ^{1}H-n.m.r. spectra. The spectral data indicate that the ligands are monobasic bidentate, coordinating through imino nitrogen and the carboxylate group. A four coordinate square planar configuration has been proposed for all the complexes. The ligands, as well as their Pd^{II} and Pt^{II} complexes, exhibit potent cytotoxic activity against *Ehrlich ascites* tumour cells *in vitro*, but appear to be more active *in vivo*.

Introduction

Although there are numerous reports on transition metal complexes of Schiff bases derived from amino acids [1–8], information on the corresponding derivatives of palladium(II) and platinum(II) is still very scanty [9]. In continuation of our studies on the synthesis and characterization of biologically active metal complexes, we have prepared a variety of *o*-hydroxyacetophenone glycine imines coordinated to palladium(II) and to platinum(II). The complexes have been further characterized by conductivity measurements, electronic, i.r. and ^{1}H-n.m.r. spectral data. They have also been tested for their growth inhibitory activity on *Ehrlich ascites* tumour cells, *in vitro* and *in vivo*.

Experimental

All chemicals used were reagent grade. Substituted acetophenones were prepared by a procedure reported elsewhere [10].

Ligands

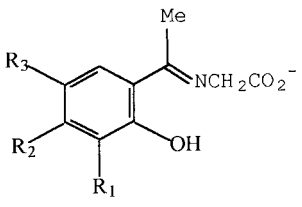
The ligands were prepared as follows: A hot aqueous solution of glycine (0.1 mol) was added with magnetic stirring to a hot EtOH solution of the substituted 2-hydroxyacetophenone (0.1 mol). The mixture was then boiled under reflux on a water bath for 2 h and the excess of solvent was removed by rotatory evaporation. Pale yellow needle-like crystals of the ligand were recrystallized from EtOH, filtered and dried *in vacuo* over P_2O_5. The ligands given in Figure 1a–1f were prepared.

Metal(II) complexes

The metal complexes were prepared by mixing a hot EtOH solution of each ligand (0.02 mol) with an aqueous EtOH solution of $PdCl_2$ or $PtCl_2$ (0.01 mol). The mixture was boiled under reflux on a water bath for 1–2 h, then allowed to cool to room temperature. The resulting precipitate was recovered by filtration, washed several times with EtOH and dried *in vacuo* over P_2O_5.

Physical measurements

I.r. spectra in the 4000–200 cm^{-1} region were recorded in nujol using a Perkin-Elmer 598 spectrometer (4000–600 cm^{-1}), and on a FT-IR Perkin-Elmer 2000



$R_1 = R_2 = R_3 = H$ *(1a)*: 2-hydroxyacetophenoneglycine
$R_1 = OMe$, $R_2 = R_3 = H$ *(1b)*: 2-hydroxy-3-methoxyacetophenoneglycine
$R_2 = OMe$, $R_1 = R_3 = H$ *(1c)*: 2-hydroxy-4-methoxyacetophenoneglycine
$R_3 = OMe$, $R_1 = R_2 = H$ *(1d)*: 2-hydroxy-5-methoxyacetophenoneglycine
$R_3 = Cl$, $R_1 = R_2 = H$ *(1e)*: 2-hydroxy-5-chloroacetophenoneglycine
$R_3 = Br$, $R_1 = R_2 = H$ *(1f)*: 2-hydroxy-5-bromoacetophenoneglycine

Fig. 1.

* Author for correspondence

(600–150 cm^{-1}) instrument between CsI plates. A Perkin-Elmer model 575 spectrophotometer was used to obtain the electronic spectra. The ^{1}H-n.m.r. spectra of the ligands and their Pd^{II} and Pt^{II} complexes were recorded with a Brucker dpx 300 instrument using d_6-DMSO solutions and TMS as internal standard. The C, N and H content of the compounds were determined using a Carlo Erba E 1110 C, H, N, S-O analyzer. The amount of palladium in the complexes was determined gravimetrically using dimethylglyoxime as a precipitating agent. Platinum was determined by pyrolysis of the solid chelates at 600 °C and weighing the metal residue. Molecular weights were determined in $PhNO_2$ using cryoscopic techniques [11]. Conductivities were measured in DMF using an Elico-CM-82 conductivity bridge with a cell constant of 0.829 cm^{-1}. All measurements were performed at room temperature using 10^{-3} M solutions of the complex.

Antitumour activity

All the compounds were screened for their antitumour activity, by dissolving samples in a minimum amount of DMF and diluting with phosphate buffered saline (PBS) (pH = 7.2) to give the following concentrations, for the biological experiments: 50 $\mu g\ cm^{-3}$, 20 $\mu g\ cm^{-3}$, 0.5 $\mu g\ cm^{-3}$ and 0.1 $\mu g\ cm^{-3}$. Cytotoxicity studies using *Ehrlich ascites* tumour cells were carried out by incubating the cells with the various concentrations of the test compounds at 37 °C for 3 h and determining cytotoxicity by the trypan blue exclusion method [12]. The tissue culture experiments were done using Chinese Hamster Ovary (CHO) cells grown in Minimum Essential Medium with 10% calf serum and a little antibiotic. The cells were grown in the presence of various concentrations of the test compounds in four replicates for a week and the inhibition of cell growth was determined by counting the viable cells in the coulter counter (Electronics Ltd., Harpenden Herts, UK).

In vivo *anti-neoplastic screens*

Ehrlich ascites carcinoma cells (2×10^6) were implanted into male mice (*ca.* 30 g) on day zero. Test compounds were administered intraperitoneally at 8 mg kg^{-1} day^{-1} from day one to nine. On day ten the mice were sacrificed and the vol of tumour and packed cell vol was determined [13].

Results and discussion

Physical and analytical data

The reaction of aqueous solutions of metal salts with the ligands (L_1, L_2, L_3, L_4, L_5 and L_6) produced complexes of general formula [M(ligand)$_2$] as revealed by the microanalytical data (Table 1) and expressed by the following equation.

$$MX_2 + 2L^- \rightarrow [M(L)_2] + 2X^-$$

where M = Pd^{II}, Pt^{II}.

All the complexes are thermally and hydrolytically stable and could be stored for months. They are insoluble in water, ethanol, methanol but soluble in nitrobenzene, DMF and DMSO. The molecular weights indicate that the complexes are monomeric. The molar conductance values in DMSO (18.5–30.1 Ω^{-1} cm^2 mol^{-1}) shown that all the complexes behave as non-electrolytes, thus confirming their non-ionic character.

I.r. data

The i.r. spectra of the ligands and of their metal complexes are summarized in Table 2. The medium intensity band at *ca.* 3400 cm^{-1} in ligands is assigned to the ν(N—H) stretching vibration, and shifts to lower frequencies in the metal complexes, indicating coordination of the metal ions to the imino nitrogen. This therefore suggests that these Schiff bases derived from glycine and substituted *o*-hydroxyacetophenone exist predominantly in the keto-enamine form shown in Figure 2.

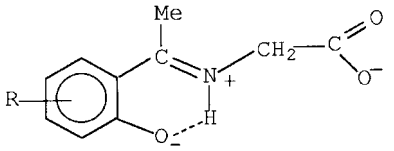
The 1665–1670 cm^{-1} band in the ligand spectra is assigned to an asymmetric carboxyl stretch. It is shifted to a lower frequency in the complexes ($\Delta\nu$ = 35 cm^{-1}) and is characteristically broad. The ligand bands in the

Table 1. Analytical and physical data for the Pd^{II} and Pt^{II} complexes

Complex	Empirical formula	Yield (%)	Found (Calcd.) (%) C	H	N	M	Molar conductance (Ω^{-1} cm^2 mol^{-1})
$Pd(L_1)_2$	$(C_{10}H_{10}O_3N)_2Pd$	60.3	41.1 (40.3)	3.1 (3.0)	4.8 (4.7)	21.8 (21.7)	18.5
$Pt(L_1)_2$	$(C_{10}H_{10}O_3N)_2Pt$	58.7	31.1 (31.0)	2.4 (2.3)	3.7 (3.6)	33.8 (33.7)	19.3
$Pd(L_2)_2$	$(C_{11}H_{11}O_4N)_2Pd$	68.3	40.3 (40.2)	3.8 (3.7)	4.4 (4.3)	19.3 (19.2)	20.0
$Pt(L_2)_2$	$(C_{11}H_{11}O_4N)_2Pt$	62.5	31.7 (31.6)	3.2 (2.9)	3.5 (3.4)	30.5 (30.4)	20.0
$Pd(L_3)_2$	$(C_{11}H_{13}O_4N)_2Pd$	63.9	40.3 (40.2)	3.8 (3.7)	4.4 (4.3)	19.4 (19.3)	25.5
$Pt(L_3)_2$	$(C_{11}H_{13}O_4N)_2Pt$	65.0	31.7 (31.6)	3.1 (2.9)	3.4 (3.4)	30.6 (30.4)	25.0
$Pd(L_4)_2$	$(C_{11}H_{13}O_4N)_2Pd$	63.8	40.3 (40.2)	3.8 (3.7)	4.3 (4.3)	19.3 (19.3)	21.8
$Pt(L_4)_2$	$(C_{11}H_{13}O_4N)_2Pt$	62.0	31.7 (31.6)	3.0 (2.9)	3.4 (3.4)	30.5 (30.4)	18.9
$Pd(L_5)_2$	$(C_{10}H_{10}O_3NCl)_2Pd$	68.5	36.2 (36.1)	2.7 (2.7)	4.2 (4.2)	18.9 (19.0)	28.5
$Pt(L_5)_2$	$(C_{10}H_{10}O_3NCl)_2Pt$	70.1	28.4 (28.5)	2.1 (2.2)	3.3 (3.3)	29.9 (30.0)	28.9
$Pd(L_6)_2$	$(C_{10}H_{10}O_3NBr)_2Pd$	77.5	31.9 (31.8)	2.4 (2.3)	3.8 (3.7)	18.6 (18.7)	30.1
$Pt(L_6)_2$	$(C_{10}H_{10}O_3NBr)_2Pt$	73.3	25.9 (25.8)	2.2 (2.0)	3.1 (3.0)	29.5 (29.6)	29.3

Table 2. Selected i.r. and electronic spectral data (cm^{-1})

Compound	ν(N—H)	$\nu_{asy}(COO^-)$	ν_{sym}(C=N) + ν(C=C)	$\nu_{sym}(COO^-)$	ν(M—N)	ν(M—O)	$^1A_{1g} \rightarrow {}^1A_{2g}$	$^1A_{1g} \rightarrow {}^1B_{2g}$	$^1A_{2g} \rightarrow {}^1E_g$
L_1	3395	1670	1610	1370	–	–	–	–	–
$Pd(L_1)_2$	3350	1640br	1620	1400	515	420	17500	21000	25000
$Pt(L_1)_2$	3351	1647br	1621	1395	500	415	15700	20000	23100
L_2	3400	1680	1615	1380	–	–	–	–	–
$Pd(L_2)_2$	3350	1641	1625	1410	500	430	17000	20250	24500
$Pt(L_2)_2$	3340	1633	1630	1410	495	429	15000	19500	23000
L_3	3400	1680	1618	1385	–	–	–	–	–
$Pd(L_3)_2$	3350	1645	1628	1415	502	425	17000	20300	24500
$Pt(L_3)_2$	3350	1638	1625	1410	500	418	14900	19500	23100
L_4	3400	1684	1620	1385	–	–	–	–	–
$Pd(L_4)_2$	3340	1650	1630	1420	500	420	16700	20000	24250
$Pt(L_4)_2$	3350	1651	1627	1420	505	415	14800	19000	22800
L_5	3390	1680	1625	1390	–	–	–	–	–
$Pd(L_5)_2$	3360	1630	1630	1410	510	430	17700	21500	25100
$Pt(L_5)_2$	3350	1627	1630	1420	512	415	16000	20500	23000
L_6	3380	1665	1615	1375	–	–	–	–	–
$Pd(L_6)_2$	3350	1640	1625	1400	505	425	17500	21200	25000
$Pt(L_6)_2$	3345	1635	1625	1403	500	420	15500	20350	23000



R = H, OMe, Cl, Br

Fig. 2.

1610–1625 cm^{-1} region are assigned to a combination of ν(C=C) and ν(C=N) vibrations [14]. In the complexes, the band shifts to higher frequency by *ca.* 15 cm^{-1}, indicating involvement of nitrogen of the azomethine group [15]. A band corresponding to $\nu_{sym}(COO^-)$ appears at 1370–1390 cm^{-1}. In the complexes, the band due to $\nu_{sym}(COO^-)$ changes from this well-defined sharp band to a broad split peak at *ca.* 1415 cm^{-1}, indicating possible M—O bond formation. The separation between the asymmetric and symmetric frequencies is *ca.* 250 cm^{-1} suggesting that the M—O bond is covalent [16].

The 1275 cm^{-1} band in the ligands has been assigned to the ν(C—O) phenolic stretching vibration. It neither changes position nor disappears on complexation, which indicates that the *o*-hydroxy group of the acetophenone moiety is not involved in bonding. The carboxyl wagging vibration appearing at *ca.* 700 cm^{-1} in the ligands is shifted to *ca.* 750 cm^{-1} in the complexes. A band in the 415–430 cm^{-1} range in the complexes, is absent in the ligands and is assigned to the ν(M—O) stretch. The ν(M—N) stretching vibration is attributed to the band in the 495–515 cm^{-1} range [17]. We therefore deduce from the i.r. spectral data that the ligands all have a similar bonding pattern, coordinating to the metal ion through the azomethine nitrogen and the carboxylate of the glycine moiety.

^{1}*H-n.m.r. spectra*

The ^{1}H-n.m.r. spectral data (Table 3) are characterized by four types of signal, assigned to methyl, methylene, phenyl and imino nitrogen protons. The 2.19–2.30 p.p.m. signal, assigned to the methyl protons in the ligands, is split on complexation in some of the complexes, while in others, there is a downfield or upfield shift. This observation has prompted us to assign a *trans*-geometry to the complexes. The methylene protons are observed in the 3.11–3.30 p.p.m. range. The multiple signal appearing within the 6.90–8.10 p.p.m. range in the ligands is assigned to the phenyl protons, and is shifted upfield to 6.70–7.95 p.p.m.

Table 3. ^{1}H-n.m.r. shifts[a] in p.p.m. of the ligands and their metal complexes

Compounds	Assignments (imino proton)	Phenyl protons	Methylene protons	Methyl protons
L_1	8.90	7.00–8.10	3.21	2.21
$Pd(L_1)_2$	8.21	6.83–7.85	3.20	2.19, 2.29
$Pt(L_1)_2$	8.24	6.85–7.90	3.21	2.20, 2.30
L_2	8.90	6.90–8.00	3.17	2.24
$Pd(L_2)_2$	8.20	6.75–7.80	3.20	2.34, 2.50
$Pt(L_2)_2$	8.35	6.80–7.85	3.20	2.35, 2.50
L_3	8.73	7.00–8.00	3.29	2.21
$Pd(L_3)_2$	8.03	6.70–7.80	3.24	2.32, 2.45
$Pt(L_3)_2$	8.05	6.75–7.80	3.24	2.33, 2.49
L_4	8.90	7.20–8.10	3.15	2.28
$Pd(L_4)_2$	8.14	6.90–7.85	3.11	2.32
$Pt(L_4)_2$	8.10	6.93–7.80	3.12	2.33
L_5	9.10	7.00–7.90	3.20	2.23
$Pd(L_5)_2$	8.30	6.95–7.80	3.20	2.19
$Pt(L_5)_2$	8.35	6.92–7.81	3.21	2.20
L_6	9.18	7.00–7.95	3.30	2.30
$Pd(L_6)_2$	8.29	6.90–7.75	3.30	2.28
$Pt(L_6)_2$	8.33	6.90–7.80	3.29	2.30

[a] In p.p.m. (σ) relative to TMS.

in the metal complexes. The azomethine proton (imino nitrogen) is assigned to the singlet observed in the 8.73–9.18 p.p.m. range. This band is shifted upfield to *ca*. 8.00 p.p.m. in the complexes, suggesting involvement of the azomethine group in bonding to the metal ion.

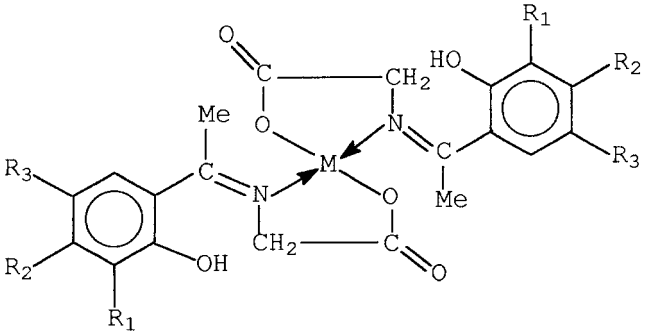
Electronic spectra

The electronic spectral data of the complexes are presented in Table 2. In the ligands, the band appearing in the 410–425 nm range is assigned to the azomethine chromophore π–π^* transition. Bands at higher energies (250–290 nm) are attributed to the benzene π–π^* transition. In the complexes, the azomethine chromophore π–π^* transition is shifted to *ca*. 380 nm indicating that the imino nitrogen is involved in coordination to the metal ion. An intense charge transfer band is observed for the complexes in the 36000–33500 cm^{-1} region, as has previously been reported as a characteristic of four coordinate complexes [18]. The absorption spectral bands for the palladium(II) complexes with λ_{max} at 16700–17700 cm^{-1}, 20000–21500 cm^{-1} and 24250–25100 cm^{-1} ranges may be assigned to spin-allowed d–d type transitions, corresponding to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$ and $^1A_{1g} \rightarrow {}^1E_g$ transitions, respectively. Absorption spectra with λ_{max} at 14900–16000 cm^{-1}, 19000–20500 cm^{-1} and 22800–23100 cm^{-1} ranges are attributed to $^1A_{1g} \rightarrow {}^1A_{2g}$, $^1A_{1g} \rightarrow {}^1B_{1g}$ and $^1A_{1g} \rightarrow {}^1E_g$ transition in a square planar field [19, 20].

Based on the physical, chemical and spectral data, a four coordinate and *trans* square planar geometry (Figure 3) has been suggested for the palladium(II) and platinum(II) Schiff base complexes.

Cytotoxicity studies

Table 4 gives the growth inhibition effected by each of the complexes at dosages: 50, 25, 0.5 and 0.1 $\mu g\ cm^{-3}$.



$R_1 = R_2 = R_3 = H$ *(3a)*; 2-hydroxyacetophenoneglycinato
R_1 = OMe, $R_2 = R_3 = H$ *(3b)*; 2-hydroxy-3-methoxyacetophenoneglycinato
R_2 = OMe, $R_1 = R_3 = H$ *(3c)*; 2-hydroxy-4-methoxyacetophenoneglycinato
R_1 = OMe, $R_1 = R_2 = H$ *(3d)*; 2-hydroxy-5-methoxyacetophenoneglycinato
R_3 = Cl, $R_1 = R_2 = H$ *(3e)*; 2-hydroxy-5-chloroacetophenoneglycinato
R_3 = Br, $R_1 = R_3 = H$ *(3f)*; 2-hydroxy-5-bromoacetophenoneglycinato
M = Pd^{II}, Pt^{II}

Fig. 3.

Table 4. Growth inhibition (%) of *Ehrlich ascites* tumour cells

Compounds	Growth inhibition[a] (%) (50 $\mu g\ cm^{-3}$)	(25 $\mu g\ cm^{-3}$)	(0.5 $\mu g\ cm^{-3}$)	(0.1 $\mu g\ cm^{-3}$)
L_1	100	82	65	39
$Pd(L_1)_2$	100	82	70	41
$Pt(L_1)_2$	100	90	69	40
L_2	100	83	61	40
$Pd(L_2)_2$	100	80	63	38
$Pt(L_2)_2$	100	85	63	39
L_3	100	80	62	38
$Pd(L_3)_2$	100	81	62	37
$Pt(L_3)_2$	100	80	63	37
L_4	100	83	66	36
$Pd(L_4)_2$	100	87	70	38
$Pt(L_4)_2$	100	85	71	38
L_5	100	93	69	46
$Pd(L_5)_2$	100	100	74	49
$Pt(L_5)_2$	100	98	72	49
L_6	100	100	70	48
$Pd(L_6)_2$	100	95	76	50
$Pt(L_6)_2$	100	95	73	51

[a] Expressed as $100(C - T)/C$, where C = number of live cells in control and T = number of live cells in drug treated.

The amino acid Schiff base ligands derived from glycine and substituted *o*-hydroxyacetophenone, as well as their palladium(II) and platinum(II) complexes, possess some level of potent cytotoxicity activity *Ehrlich ascites* tumour cells. However, the growth inhibition (%) of *Ehrlich ascite* tumour cells effected by the present set of compounds at lower concentrations fall slightly less than those previously reported for platinum metal complexes of 2-acetylpyridine thiosemicarbazone [21]. A further comparison with available data on copper(II) and iron(II) chelates of 2-formyl pyridine, 1-formylisoquinoline, 2-acetylpyrazine and other 2-acetylpyridine *N*-alkyl/N^4-arylthiosemicarbazones [22, 23], reveals that the present compounds exhibit a slightly lower tumour

Table 5. Antineoplastic activity of compounds at 2, 4 and 8 mg kg^{-1} day^{-1} (i.p) in mice pre-inoculated with *Ehrlich ascites*

Compounds	% inhibition of growth at dose (mg kg^{-1} day^{-1}, i.p) 8	4	2
L_1	Toxic	–	80.5
$Pd(L_1)_2$	80.5	–	–
$Pt(L_1)_2$	Toxic	Toxic	85.1
L_2	90.7	–	83.5
$Pd(L_2)_2$	Toxic	–	50.1
$Pt(L_2)_2$	Toxic	–	55.3
L_3	88.0	–	80.1
$Pd(L_3)_2$	90.1	–	86.5
$Pt(L_3)_2$	90.3	–	87.0
L_4	86.8	–	80.0
$Pd(L_4)_2$	Toxic	–	90.1
$Pt(L_4)_2$	Toxic	–	92.0
L_5	94.5	–	90.0
$Pd(L_5)_2$	96.0	–	92.0
$Pt(L_5)_2$	Toxic	–	95.0
L_6	Toxic	Toxic	84.3
$Pd(L_6)_2$	88.3	–	87.0
$Pt(L_6)_2$	Toxic	Toxic	90.0

inhibitory effect towards *Ehrlich ascites* tumour cells. The marginal difference in activity of the present compounds compared to those reported elsewhere [21–23], may be attributed to their relatively poor solubility. Thus, it might be argued that the seemingly low sensitivity of *Ehrlich* cells towards the tested compounds, results from their inability to reach critical sites within the cells in adequate concentrations [24–26]. The *in vivo* antineoplastic activity demonstrated against *Ehrlich ascites* carcinoma growth in the 2–8 mg kg^{-1} day^{-1} dosage range is compiled in Table 5. The complexes are cytotoxic to tumour cells *in vivo*. It is possible that the ligands may be activated by the metal ions. The complexes have a marked inhibitory effect at lower concentrations upon the capacity of *Ehrlich* cells to grow in the mice. Details of the *in vivo* anti-neoplastic screens will be published elsewhere.

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References

1. J.A.R. Henderson and I.M. Heilbron, *J. Chem. Soc*., **86**, 1740 (1915).
2. V. Hovorka and L. Divis, *Chem. Commun*. **14**, 116 (1949).
3. L.J. Theriot, G.O. Carlisle and H.J. Hu, *J. Inorg. Nucl Chem*., **31**, 2841 (1969), *Ibid*, **31**, 2891.
4. G.N. Weinstein, M.J. O'Connor and R.H. Holm, *Inorg. Chem*., **9**, 2104 (1970).
5. J.B. Hodgson and G.C. Percy, *Spectrochim. Acta*, Part A; **32**, 1291 (1976).
6. T.M. Aminabhavi, N.S. Biradar, S.B. Patil and V.L. Roddabasanagoudar, *Inorg. Chim. Acta*, **107**, 231 (1985).
7. A.M.A. Hassan, E.M. Soliman and M. Elshabasy, *Synth. React. Inorg. Met.-Org. Chem*., **12**, 773 (1989).
8. W. Zhong, W. Zishen, Y. Zhenhuan, L. Zifong, Z. Xinde and H. Quinghua, *Synth. React. Inorg. Met.-org. Chem*., **24**, 1453 (1994).
9. B.T. Khan, S. Shamsuddin and K. Venkatasubramanian, *Polyhedron*, **11**, 671 (1992).
10. N. RabJohn, '*Organic Synthesis*' *Coll*. vol 4, p106 (1963). 165 (1975).
11. G. Barrow, Physical Chemistry 3rd Edit. McGrawHill, New York, 1974.
12. G. Kutan, D.M. Vasudevan and R. Kuttan, *Cancer Lett*., **41**, 307 (1988).
13. C. Piantadosi, C.S. Kim and J.L. Irving, *J. Pharm Sci*., **58**, 821 (1969).
14. L.C. Marcotrigiano, L. Menabue and G.C. Pellacani, *J. Inorg. Nucl. Chem*., **40**, 165 (1975).
15. P. Teysee and J.J. Charette, *Spectrochim. Acta*, **19**, 1407 (1963).
16. K. Nakamoto, Y. Morimoto and A.E. Martell, *J. Am. Chem. Soc*., **83**, 4528 (1961).
17. R.A. Condrate and K. Nakamoto, *J. Chem. Phys*., **42**, 2590 (1965).
18. E.J. Lukosius and K.J. Coskran, *Inorg. Chem*., **14**, 1922 (1975).
19. S.K. Sahni, P.C. Jain and V.B. Rana, *Indian J. Chem*. **18A**, 161 (1979).
20. A.B.P. Lever, *Inorganic Electronic Spectroscopy*, Elsevier Publishing Corp. Amsterdam, 1968.
21. O.E. Offiong and S. Martelli, *Transition Met. Chem*., **22**, 263 (1997).
22. W.E. Antholine, J.M. Knight and D.H. Petering, *J. Med. Chem*., **19**, 339 (1976).
23. I.H. Hall, K.G. Rajendran, D.X. West and A.E. Liberta, *Anticancer Drugs*, **4**, 231 (1993).
24. E.J. Blanz, Jr., F.A. French, J.R. Do Amaral and D.A. French, *J. Med. Chem*., **13**, 1124 (1970).
25. F.A. French, E.J. Blanz, Jr., J.R. Do Amaral and D.A. French, *J. Med. Chem*., **13**, 1117 (1970).
26. F.A. French, E.J. Blanz, Jr., S.C. Shaddix and R.W. Brockman, *J. Med. Chem*., **17**, 172 (1974).