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Synthesis, Characterization and Cytotoxicity of Ni (II), Pd (II), Pt (II) Complexes with 6-Methoxy-2, 3, 4, 5-tetrahydropyridine (MTP)

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ABSTRACT

Reaction of 2 moles of (MTP) with one mole of MCl_2 gave colored complexes with general formula; $[M(MTP)_2Cl_2]$. [M = Ni^{+2}, Pd^{+2}, and Pt^{+2}]. All synthesized complexes are well-characterized using, FT-IR, ^{1}HNMR, ^{13}C NMR, UV-Vis. Spectra furthermore of magnetic susceptibility, C,H,N analysis, and molar conductivity. The results illustrated that divalent metal ions were coordinated with the ligands through nitrogen atoms in square planar spatial arrangements. The complexes were screened for their cytotoxicity effects versus MCF-7 cell line and showed that $[Pt(MTP)_2Cl_2]$ complex has good cytotoxicity in comparison with the other complexes.

Keyword: MCF-7 cell line, Cytotoxicity, Cisplatin, Metal complexes.

INTRODUCTION

N-heterocyclic (NHC) compounds constitute a new type of ligands in coordination chemistry and organometallic chemistry[1], they belong to a new family of ligands with electronic characteristics similar to those of the phosphines[2]. The ligands of heterocyclic rings contain nitrogen atom as a donor set the have π-acidity properties and they form many color complexes with transition elements in various oxidation state[3]. Recently mixed ligand of dithizone metal ion complexes were reported to have anticancer activity *In vitro*[4]. The current work reports synthesis of new complexes contains nitrogenic ligand of general structure $[M(MTP)_2Cl_2]$ and their characterizations as tetra coordination number as square planar geometry. Also, the study of their anticancer ability versus MCF-7 cell line.

EXPERIMENTAL

Materials and Instrumentation

All chemicals used in this work are in of reagent grade and used without farther purification as supplied from Sigma, Solarbio, Fluka, Scharlue, BDH, Capricorn, Santacruze Biotechnology, and

Bio-world. Electromolar conductivities for the 10^{-3} M solution of the synthesized complexes in (DMSO) using [Senz μ Siemen tester 4200] college of education/Salahaddin University/Erbil. Elemental analysis (C.H.N) was measured using [EuroEA 3000/Italy] in the service laboratory at Ibn al-Haitham college of education/University of Baghdad. FT-IR spectra were recorded using [Ftir-600 FTIR Spectrometer Biotech Engineering Management.UK] in the service laboratory at Ibn al-Haitham college of education/University of Baghdad. The UV/Vis were recorded using, AE-UV1609 Spectrometer (UK) Co.] in the college of education/Salahuddin University/Erbil. ^{1}HNMR and ^{13}CNMR spectra were recorded on Brucker 300MHZ with tetramethylsilane as an internal standard in DMSO-d6 Measurements were made at water, environment and arid regions research center/Al- a Bayt University/ Jorden.

Synthesis of $[M(MTP)_2Cl_2]$

To a methanol (25 mL) solution of (MTP) (0.23g, 2mmol), an equivalent methanol (25 mL) solution of $NiCl_2.6H_2O$ (0.24g, 1mmol), $PdCl_2$ (0.18 g, 1mmol) and K_2PtCl_4 (0.42, 1mmol) was added in dropwise. Thereafter, the mixture was stirred for 9-14 h at room temperature. The resultant solution was filtered and set aside for a few days to give colored precipitates. The precipitates were filtered off and dried under vacuum.

Cytotoxicity assay

Cell lines

MCF-7 cells were provided from the Iraqi Cell Bank and kept and treated as in[5].

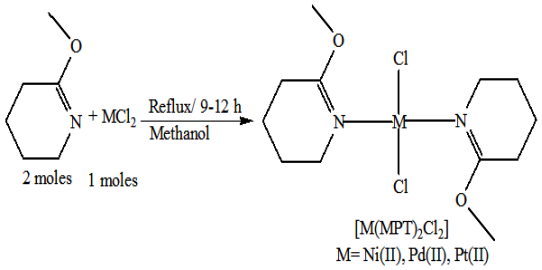
Cytotoxicity assay

To emphasize the effect of cytotoxicity, methyl thiazolyl tetrazolium (MTT)[5] viability test was measured using 96-well plates. MCF-7 were sowed at 1×10^{4} cells/well. Monolayer achievement has been occurred after 24 hours. The cell viability assay has been taken after 72 h by addition 28 μL of 2 mg/mL of MTT solution, the cells were incubated for 1.5 h at 37°C. The crystals which formed on the wells, during the incubating were dissolved by the addition of 130 μL of DMSO[6]. Absorbances were recorded at 492 nm. All tests were performed in triplicate and he inhibition rate of cell growth was obtained as follows:

Inhibition growth rate = A-B/A x 100 (where A and B are absorbances of control and tested compounds respectively).

RESULTS AND DISCUSSION

A synthesized divalent metal complexes (Scheme 1) were obtained from reaction of Ni (II), Pd (II) and Pt (II) chloride salts with (MTP) in (2:1) ratio produce neutral-colored complexes. All complexes have good solubility in dimethylsulphoxide. The conductivities in 10^{-3}M dimethylsulphoxide solutions are between (10-20) Ω^{-1} cm^2 mol^{-1} [7]. This is inconsistent with the stoichiometry suggested complexes. The analytical data of synthesized complexes are shown in the (Table 1), were agreement with the calculated values. The suggested molecular formulas were also supported by spectral and magnetic moment measurements.



Scheme 1. Formation of $[M(MTP)_2Cl_2]$ complexes

Table 1: Physical analytical data for synthesized complexes

No	Complexes	μ_{eff}	Color	Melting point	Yield %	Elemental analysis, calc. (found) %			
						M%	C	H	N
1	$[Ni(MTP)_2Cl_2]$	Dia.	Blue-green	-	72	15.68 (16.49)	40.25 (40.5)	6.19 (6.23)	7.63 (7.87)
2	$[Pd(MTP)_2Cl_2]$	Dia.	Yellow-orang	143-148	77	26.10 (26.37)	35.13 (35.71)	5.49 (5.47)	6.74 (6.94)
3	$[Pt(MTP)_2Cl_2]$	Dia.	Dark Brown-	-	68	38.11 (39.63)	28.36 (29.28)	4.26 (4.50)	5.66 (5.69)

Magnetic susceptibility

The magnetic moments were taking at 25^{0}C. The results proved square planar structures for all complexes[8].

Electronic transitions spectra

The electronic transition spectra of the ligand and its synthesized complexes in the 10^{-3} M (DMSO) solution were illustrated in (Table 2). The electronic transition band at 37450 cm^{-1} is for π- π^* transition within ligands. A given spins allowed transitions at (21978) cm^{-1} (υ1), (22883 - 24875) cm^{-1} (υ2), (26109-28571) cm^{-1} (υ3) were assigned to $^1A_{1g}\rightarrow{}^1A_{2g}$ (υ1), $^1A_{1g}\rightarrow{}^1B_{1g}$ (υ2) and $^1A_{1g}\rightarrow{}^1Eg$ (υ3) transitions respectively. The strong bands at (29850-31847) cm^{-1} are due to (MLCT) and d$\rightarrow$d transitions. The transition band at 32786- 36363 cm^{-1} is due to the n$\rightarrow$p* transitions (LMCT) of the pyridine ring. These transitions value is indicated to square planar geometry[9-11].

Table 2: UV-Vis transition for the synthesized complexes

No.	Complexes	Absorption band cm^{-1}	nm	Transitions	
1	$[Ni(MTP)_2Cl_2]$	22883	437	$^1A_{1g}\rightarrow{}^1B_{1g}$	
		28571	350	$^1A_{1g}\rightarrow{}^1E_g$	Sp.
		31847	314	C.T	
2	$[Pd(MTP)_2Cl_2]$	24875	402	$^1A_{1g}\rightarrow{}^1B_{1g}$	Sp.
		26109	383	$^1A_{1g}\rightarrow{}^1E_g$	
		32786	305	C.T	
3	$[Pt(MTP)_2Cl_2]$	21978	455	$^1A_{1g}\rightarrow{}^1A_{2g}$	
		24330	411	$^1A_{1g}\rightarrow{}^1B_{1g}$	Sp.
		29850	335	C.T	
		36363	275	C.T	

Infrared spectral

IR frequencies of the free ligand and complexes are tabulated in (Table 3). A peak at (3056) cm^{-1} is for υ(CH) stretching structure[12], a frequency band at (2960) cm^{-1} which may be due to the υ(CH) of methoxy group, generally it has been observed at lower frequencies than the normal υ(CH) for (CH_3-) group[13]. The frequency band at 1625 cm^{-1} is related to υ(C-C) in the pyridine ring. A υ(C-O-C) is at 1260 cm^{-1}. A frequency band at 1480 cm^{-1} which are corresponding to υ(CN) stretching vibrations, all complexes showed a negative shift in υ(CN) confirmed the participate of nitrogen in coordination[14].

Table 3: IR band in cm^{-1} for the ligand and the complexes

Compound	ν(CH) ring	ν(CH) methoxy	ν(CN)	ν(CC)	ν(C-O-C)
MTP	3056	2960	1260	1625	1480
$[Ni(MTP)_2Cl_2]$	3100	2962	1256	1655	1442
$[Pd(MTP)_2Cl_2]$	3036	2954	1247	1666	1438
$[Pt(MTP)_2Cl_2]$	3085	2955	1256	1630	1448

NMR spectra

^{1}H and ^{13}C NMR bands were obtained using (DMSO-d6) as a solvent (Table 4) and (Fig. 1-3). The spectra showed two sets of bands which attributed to the pyridine part and substituted aliphatic of the MTP ligand. The ^{1}H NMR bands of coordinated ligand were shifted more than free ligand and they agree with complexion with metal ions through N of pyridine ring[15]. The ^{13}C NMR data in all complexes show. No observed change in this signal in complexes formation and this due to uncoordinated aromatic carbon in the metal ion complexes[16].

Table 4: NMR spectral for band in δ(ppm) for the ligand and their complexes

Compound	Atom	^{1}HNMR	Atom	^{13}CNMR
MTP	1H	3.53	1C	45.4
	2H	1.3	2C	22.2
	3H	1.77	3C	16.4
	4H	2.11	4C	29.7
	5H	3.47	5C	161.7
			6C	53.2
$[Ni(MTP)_2Cl_2]$	1H	2.6	1C	38.66
	2H	1.3	2C	22.24
	3H	1.96	3C	16.58
	4H	2.1	4C	37.65
	5H	3.53	5C	162.14
			6C	54.15
$[Pd(MTP)_2Cl_2]$	1H	2.82	1C	38.67
	2H	1.3	2C	21.65
	3H	1.77	3C	18.2
	4H	2.23	4C	29.74
	5H	3.59	5C	159.41
			6C	51.2
$[Pt(MTP)_2Cl_2]$	1H	2.94	1C	39.39
	2H	1.3	2C	21.36
	3H	1.6	3C	18.23
	4H	2.53	4C	31.34
	5H	3.88	5C	162.47
			6C	51.620

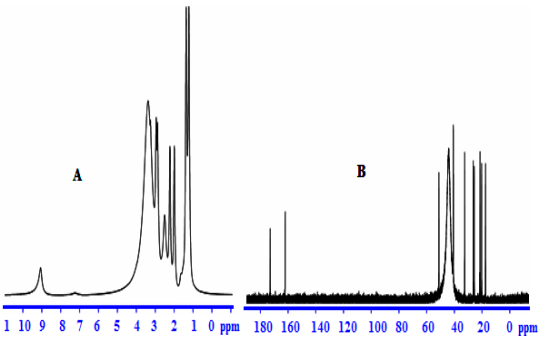


Fig. 1. ^{1}HNMR for $[Ni(MTP)_2Cl_2]$ (A) and ^{13}CNMR for $[Ni(MTP)_2Cl_2]$ (B)

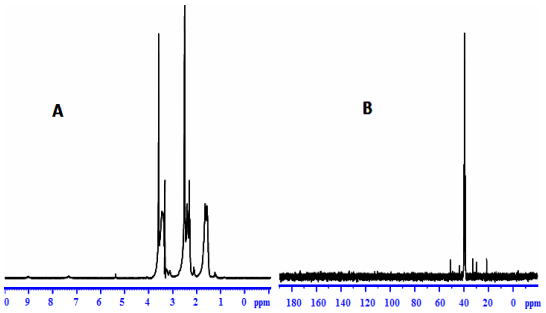


Fig. 2. ^{1}HNMR for $[Pd(MTP)_2Cl_2]$ (A) and ^{13}CNMR for $[Pd(MTP)_2Cl_2]$ (B)

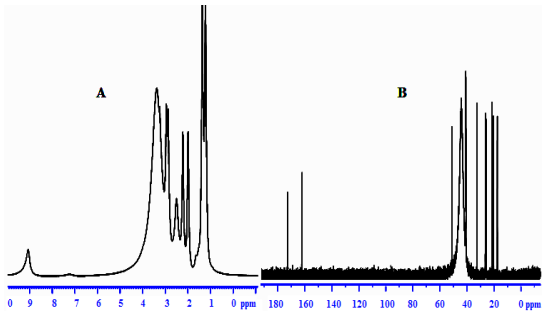


Fig. 3. ^{1}HNMR for $[Pt(MTP)_2Cl_2$ (A) and ^{13}CNMR for $[Pt(MTP)_2Cl_2]$ (B)

Cytotoxicity Results

Our study on synthesized Ni (II), Pd (II) and Pt (II) metal ion complexes were evaluated against human MCF-7 cells. Cisplatin was employed as in a reference[6]. It is found that the $[Pt(MTP)_2Cl_2]$ complex has the highest IC_{50} cell viability and p-value[17]. The results included (cell growth %) or (% of cell treatment). The low concentration kills about 19% of MCF-cell line (Table 5) and (Fig. 4-6). Whilst Ni (II), Pd (II) complexes were less active than cisplatin is in the micromolar range. On the basis of existence of methoxy moiety on both pyridine rings play important role in inhibition linking of N of DNA with central metal, thus leading to increase cytotoxicity meta lion from the complex[18].

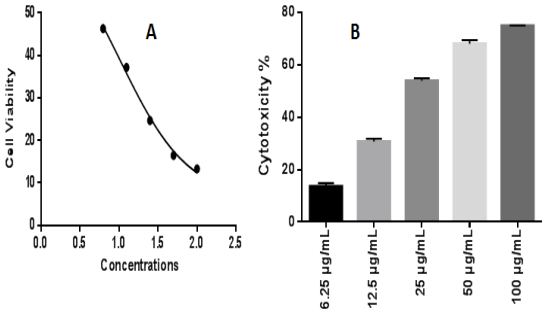


Fig. 4. A: IC_{50} on MCF-7 cell line for $[Ni(MTP)_2Cl_2]$ B: Histograph of five different concentration of MCF-7 versus % cytoxicity

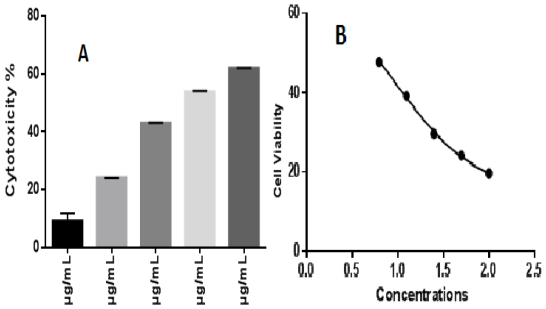


Fig. 5. A: IC_{50} on MCF-7 cell line for [Pt(MTP)2Cl2] B: Histograph of five different concentration of MCF-7 versus % cytoxicity

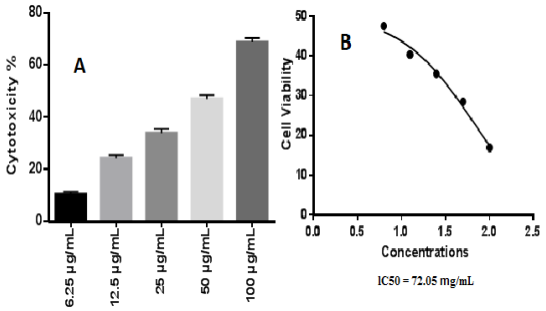


Fig. 6: A: IC_{50} on MCF-7 cell line for $[Pd(MTP)_2Cl_2]$ B: Histograph of five different concentration of MCF-7 versus % cytoxicity

Table 5: Cytotoxic abilities of the synthesized complexes on the MCF-7 cells

Sample	Con.	6.25 µg/mL	12.5 µg/mL	25 µg/mL	50 µg/mL	100 µg/mL
Cisplatin	Mean	24.67	51.80	71.87	88.10	94.00
	P value	0.0343	0.0148	0.0100	0.0065	0.0068
	Significant (alpha=0.05)	Yes	Yes	Yes	Yes	Yes
$[Pt(MTP)_2Cl_2]$	Mean	13.66	30.71	53.87	68.00	74.98
	P value	0.0024	0.0004	0.0001	0.0094	0.0001
	Significant (alpha=0.05)	Yes	Yes	Yes	Yes	Yes
$[Ni(MTP)_2Cl_2]$	Mean	9.091	23.97	42.84	53.69	61.89
	P value	0.1318	0.0008	0.0024	0.0036	0.0011
	Significant (alpha=0.05)	No	Yes	Yes	Yes	Yes
$[Pd(MTP)_2Cl_2]$	Mean	10.40	24.18	33.79	46.91	68.91
	P value	0.0367	0.0215	0.0228	0.0147	0.0101
	Significant (alpha=0.05)	Yes	Yes	Yes	Yes	Yes

CONCLUSION

All complexes have been synthesized and characterized; the results indicate that all of them have square planer geometry in which the metal ions coordinate with the ligand through a nitrogen atom. The cytotoxicity effects study of the prepared complexes versus MCF-7 cell line in different concentrations showed that [Pt $(MTP)_2Cl_2$] has good cytotoxicity in comparison with the other complexes.

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Conflict of interests
No conflict of interest.

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