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Synthesis and Characterization of Some Metal Complexes with their Sulfamethoxazoleand 4,4'-dimethyl-2,2'-bipyridyl and study Cytotoxic Effect on Hep-2 Cell Line

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Abstract:

The ligand 4-amino-*N*-(5-methylisoxazole-3-yl)-benzene-sulfonamide(L1) (as a chelating ligand) was treated with Pd(II),Pt (IV) and Au(III) ions in alcoholic medium in order to prepare a series of new metal complexes. Mixed ligand complexes of this primary ligand were prepared in alcoholic medium in presence of the co-ligand 4,4'-dimethyl-2,2'-bipyridyl(L2) with Cu(II) ,Pd(II) and Au(III) ions. The complexes were characterized in solid state using flame atomic absorption, elemental analysis C.H.N.S, FT-IR, UV-Vis Spectroscopy, conductivity and magnetic susceptibility measurements. The nature of some complexes formed in ethanolic solution has been studied following the molar ratio method, also stability constant was studied and the complexes found to be stable in molar ratio1:1.an octahedral geometry was suggested for PdL1L2, PtL1and AuL1L2 complexes, square planar was suggested for AuL1 and PdL1complexes,while CuL1L2 complex has a square pyramidal geometry. Cytotoxic effect of theprepared complexes as well as ligands was evaluated against Hep-2 cell line using four different concentrations (625, 1250, 2500&5000 µg/ml) respectively in an exposure time 48 hrs comparing this effect with control positive Cis-Pt as reference drug. The obtained results refers to the higher inhibition rates of all complexes and their ligands and ligand (L1) and its complexes give more activity against tested cell than ligand (L2) and its complexes comparable with control positive .

Key words: Sulfamethoxazole, Chelating agent, Cytotoxic, Hep-2 cell line, Exposure time.

Introduction:

The presence of donor atoms (N,S,O) at various positions in Sulfamethoxazole(SMX) molecules enable them to behave as multidentate ligands and thus form chelates of diverse structural types with a wide range of metal ions [1]. Despite the availability of numerous antibiotics

sulfonamides is still an important drug for therapeutic use, particularly in the treatment of acute urinary tract infection (UTI) [2]. It is well known that through exchanges of different functional groups without modification of the structural $-S(O)_2N(H)-$ features, sulfonamide derivatives can exhibit a wide variety of pharmacological activities, such as antidiabetic, antibacterial and antitumor [3]. It is also known that the pharmacological activity of these derivatives has often been increased by coordination with metal ions [4]. The chemistry of metal complexes with heterocyclic compounds containing nitrogen, sulfur, and /or oxygen as ligand atoms has attracted increasing attention which exhibit enhanced bactericidal, fungicidal, herbicidal, and insecticidal activities in addition to their application as potential drugs [5].The knowledge of metal complexes with drugs is essential to understand the complex physiological process and mode of action drugs and their effect on various body systems. The stability constant of metal complexes with drugs is important to measure the metal ligand selectivity in terms of relative strength of metal ligand bonds [6]. It plays a vital role in transportation, detoxification and catalytic process [7].

Instrumentation:

Elemental C.H.N.S analysis were carried out on a EM-017.mth instrument, the FT-IR spectra in range (4000-200 cm^{-1}) were recorded as CsI disc on IR-Prestige-21, Single beam path Laser, Shimadzu Fourier Transform infrared Spectrophotometer, UV-Visible spectra were measured using UV-1650PC Shimadzu, in the range (200-1100) nm. The magnatic susceptibility values of the prepared complexes were obtained at room temperature using Magnatic Suscceptibility Balance of Johanson mattey catalytic system division. Atomic absorption measurements of the prepared complexes were obtained using Shimadzu Atomic Absorption 680 Flame Spectrophotometer. The conductivity values of the prepared complexes were measured using 0.001M DMF as a solvent, (WTW) Conductometer. Melting point apparatus of Gallen Kamp M.F.B-60 was used to measure melting points of all prepared compounds.

Materials and Methods:

1-Synthesis of Metal Complexes:

An ethanolic solution of the (SMX) sulphamethoxazole (L1)1mmole0.2533 gm was added slowly, into warm ethanolic solution of the metal salts ; 1 mmole of [$PdCl_2$(0.1774 gm); $H_2PtCl_6.6H_2O$(0.5180 gm) and $HAuCl_4.H_2O$(0.3579 gm)], and another series from 1 mmole 0.2533 gm (L1) as a primary ligand and 1 mmole 0.184 gm (4,4'dimethyl-2,2`- bipyridyl (L2) as a co-ligand, into warm ethanolic solution of metal salts 1 mmole [$PdCl_2$(0.1774 gm); $HAuCl_4.H_2O$ (0.3579 gm)and$Cu(NO_3)_2.3H_2O$ (0.2416 gm)].The mixture solutions were heated and refluxed with stirring for about (2-3) hrs. The colored precipitates were filtered, washed several times with ethanol and finally ether, and dried using desiccator.

2- Study of complexes formation in solution:

The ratio of metal to ligand in complexes using molar ratio method was evaluated in ethanolic solution [8].

3-Cytotoxic assay:

Cytotoxic assay was evaluated as described in literature [9]. Cancer cells were grown in DMEM medium containing 2 mM L-glutamine supplemented with 1000 U/L penicillin, streptomycin and 10% FBS. Briefly, cell lines suspended in DMED containing 10 % FBS were seeded with 1×10^4 cells (100 μL) per well in a 96-

well plate. The incubation was performed at 37 °C under humidified (95 % air, 5 % CO_2) for 24 hatmosphere. Additional medium (100 µL) containing the test compounds was added to a final concentrations of 5000, 2500, 1250 and 625 µg/ml, and further incubated for 2 days. All of the procedures concerning the cell culture maintenance, drug dissolution, and treatment were carried out in sterile conditions. After elapsing the incubation period, the culture medium was discarded from micro titer plates, 50 µl/well of neutral red dye solution was added to wells and the plates were incubated for 2 hrs. Plates were washed gently with phosphate buffered saline (PBS) and 100 µl/well of elution buffer was added, the absorbance was measured at 492nm by ELISA reader.

Results and Discussion:

A-Chemistry:

Stable complexes were isolated in all casesbasede on the metal analysis, spectroscopic data, molar conductance andmagnetic susceptibility studies. The general formula of the complexes can be depicted as:

$[ML1Cl_n]Cl.XH_2O$ where M=Au or Pt , n=2 or3 , X=3.5or1 respectivly and $[PdL1Cl]_2Cl_2.H_2O$,

$[ML1L2Cl_2]Cl_n.XH_2O$, M=Au or Pd , n=1 or 0 , X=2or0.5 respectivly and $[CuL1L2]_2(NO_3)_{2.}0.5H_20$.

The analytical data together with some physical properties of the complexes are summarized in (Table 1).

Table (1): Some analytical and physical data of primary ligand (L1) with co-ligand (L2) and their metal complexes.

Compond	Color	M.P ^oC	Yield %	M.Wt g.mol^{-1}	Elemental analysis Found (Calc.)				Metal% Found (Calc.)
					C	H	N	S	
$C_{10}H_{11}N_30_30_3S$ (L1)	White	167-169 (168-172)	—	253.3	—	—	—	—	—
$C_{12}H_{12}N_2$ (L2)	White	174-175 (174-176)	—	184.24	—	—	—	—	—
$[[Pd\ L1]_2Cl_2]Cl_2.H_2O$	Brown	200d	85	878.6	27.770 (27.31)	2.607 (2.95)	8.997 (9.56)	7.332 (7.28)	24.025 (24.129)
$[PtL1Cl_3H_2O]Cl.H_2O$	Light orange	148-150	84	626.4	19.294 (19.15)	2.607 (2.39)	6.663 (6.70)	5.352 (5.10)	30.98 (31.14)
$[AuL1Cl_2]Cl.3.5H_2O$	Yellowih-orange	186d	82	619.8	19.152 (19.36	2.880 (2.90)	6.680 (6.77)	5.347 (5.16)	31.57 (31.78)
$[Cu\ L1L2]_2(NO_3)_4.0.5H_2O$	Dark green	252d	88	1258.6	41.789 (41.95)	3.857 (3.73)	15.772 (15.57)	5.164 (5.08)	10.19 (10.09)
$[PdL1L2Cl_2].0.5H_2O$	Brown	130d	75	623.3	42.184 (42.35	3.976 (3.85)	11.124 (11.23)	5.442 (5.13)	17.08 (17.00)
$[AuL1L2Cl_2]Cl.2H_2O$	Dark orange	109-110	67.8	776.8	33.601 (33.98)	3.671 (3.47)	9.111 (9.01)	4.538 (4.11)	25.37 (25.36)

d = decomposition degree

FT-IR Spectra of Ligand L1 and its Metal Complexes.

(SMX) is a potentional ligand which may act as a bidentate or tridentate as illustred by its structureso it expected that IR mesurments are highly indicating with respect to the complexetion behivour with various metal ions. The most important diagnostic bands FTIR data for 4-amino-N-(5-methylisoxazol-3-yl)-benzenesulfonamide and its metal complexes have been listed in (Table 2).Infrared spectrum ofthe freeligand

shows two strong bands at 3468 and 3375 cm^{-1} corresponding to the asymmetric and symmetric stretching vibrations, respectively of the aromatic amino group[10]. The medium and strong band which appeared at 3298 $cm^{-1}$is due to the presence of asymmetric sulfonamide –NH and a weak band at 3242 cm^{-1} as symmetric frequency. Another band observed at 1645 $cm^{-1}$is related to methoxazole ring stretching vibration.Others two bands appeared at 1365 and 1188 cm^{-1} are due to asymmetric and symmetric stretching frequencies of sulfonyl group [10]. The stretching frequencies of the C–N band of sulfonamide is exhibited in the 1311 cm^{-1} region. The spectrum also shows another medium band at (1597 cm^{-1}) which assigned to the stretching frequency of (C=C) band ,while the bands appeared at (829,and 686 cm^{-1}) may be assigned to the bending of (S-O)group [11]. The two bands of the aromatic amino groups suffered a positive or negative shift in the positions observed in the spectra of all complexes .This is due to the resonance contribution from the amino group and also due to the possible hydrogen bonding interaction between the amine group and sulfonyl oxygen of the neighboring molecule [12]. The band of sulfonamide –NH in the spectrum of the ligandbecame multiband and change in position indicating that the amide group involved in chelation[13]. The bands of asymmetric and symmetric stretching frequencies, of the sulfonyl group undergoes a shift toward lower frequencies in all complexes.

The band of methoxazole ring stretching vibrations suffered a shift in the peak within a narrow range of ± 5 cm^{-1} in the spectra of the metal complexes indicating that the methoxazole moiety is not involved in coordination [14]. A negative shift toward lower frequencies in all complexes, of the C–N band of sulfonamide, this indicates the interaction of sulfamethoxazole with the metal ion through the sulfonamide nitrogen [13],while the absorption band related to stretching frequency of ν(C=C) which recorded not undergo shift in all metal complexes. Another new peakes which appeared refer to stretching vibrations of M–O, M–N and M–Cl bonds respectively(Table 2) as well as broad bands in all complexes appeared in the region (3650–3700) cm^{-1} related to the presence of lattice water or coordinated water molecules in coordination sphere[13].

FT-IR Spectra of the Mixed Ligands Complexes:

The tentative assignments of the peaks for the primary ligand (SMX) with the secondary ligand (4,4-dimethyl-2,2- bipyridyl)together with heavy metals as a metal complexes are listed in (Table 3).The bands related to aromatic amino group undergoes aslightly negative shift to lower frequencies from 4 to 8 cm^{-1} in the positions of Au(III) and Pd(II) complexes because of resonance contribution and also H-bonding [12],but in the case of Cu(II) the higher shift of ν NH_2 by (12) cm^{-1}indicating bonding of this ion to aniline N-atom [13]. The multiband and shifting of sulfonamide –NH in the spectra of the prepared complexes, indicating the involvement of this group in chelation with central metal ion by nitrogen of this group according to the data reported in literature [11]. The band related to methoxazole ring stretching vibrations suffered a very slight shift in range of ±5cm^{-1} in the spectra of the metal complexes indicating that the methoxazole moiety is not participation in coordination with metal ions [14]. The bands corresponding to asymmetric of sulfonyl group undergoes a shift toward higher frequencies which

observed at (1373-1384) cm^{-1} in Au(III), Pd(II) and Cu(II) complexes, while a small bands of the symmetric stretching suffered of a little shift toward lower frequencies about (23-31) cm^{-1} in Au(III) and Pd(II), complexes.

According to these results , the coordination mode of this ligand with heavy metal ions is clearlypredicted as a bidentate through the O atom of sulfonyl group and N atom of sulfonylamid group for all complexes except Cu(II) ion throw O,N,N as a tridentate chelats, more evidence new bands which appeared in the range (439-443)cm^{-1} and (513-516) cm^{-1} due to the stretching frequency of (M-O) and (M-N) bonds respectively, and another new bands in regions of (295-308) cm^{-1} in the spectra of Au(III), Pd(II) complexes which assigned to M–Cl stretching vibrations asshown in (Table 3). The coordination of the secondary ligand is indicated by the positive shift of (C=C), (C=N) ring stretching frequencies. The position of this band has been completely changed in the spectra of all the complexes and confirming the coordination nature of co-ligand, the band at (424) cm^{-1} observed of pby (C-C out of plane bending) shifts to higher frequency and splits into two components in the complexes which again confirms the coordination of secondary ligand through two nitrogen [15],the new bands were recorded at (272-271) cm^{-1} in the spectra of all complexes are attributedto($M–N_{bpy}$) bond indicating participation two nitrogen coordination with metal ion [16]. In all complexes a broad bandsappeared which refer to stretching of lattice water molecule or coordination in sphere as shown in (Table 3).

Table(2): The most diagnostic FTIR bands of the Sulfamethoxazole ligand (L1) and its metal complexes in (cm^{-1}).

Comp.	νNH_2 asy.,sym	ν NH asy.,sym	ν Methax-azol ring	ν C=C	ν S-O sulfonyl asy. , sym.	ν C-N sulfonyl	ν S-O	ν M-O	ν M-N	Others
$C_{10}H_{11}N_30_30_3S$ (L1)	3468 3375	3298 3242	1645	1597	1365 1188	1311	829 686	---	---	---
$[[Pd\ L1]_2Cl_2]Cl.2H_2O$	3457 3378	3290 3217	1641	1597	1323 1165	1269	833 (686, 675)	455	478	ν OH= 3700νPdCl=302
$[PtL1Cl_3H_2O]Cl.H_2O$	3498 3464 3373	3290 3201	1649	1597	1327 1168	1269	821 667	435	470	$^{p}H_2O$=891 νOH= 3650 νPtCl = 314
$[AuL1Cl_2]Cl.3.5H_2O$	3495 3465	3283 3201	1640	1597	1330 1168	1311 1273	825 667	447	478	νOH=3650 νAuCl=310

Table(3): The most diagnostic FTIR bands of the mixed ligand SMX as primary ligand(L1) and bpy asco-ligand L2 and Their metal complexes in (cm^{-1}).

Comp.	νNH_2 asy. sym.	ν NH asy. Sym.	ν Methax-azole Ring	νC=C	ν S-0 Sulf0nyl asy.sym	ν C-N Sulfonyl	ν C=N + C=C	ν CH alph. + arom.	δCH oop	δCH ip	ν M-N	ν M-O	ν M-N_{BPY}	Others
$C_{10}H_{11}N_30_30_3S$ (L1)	3468 3375	3298 3242	1645	1597	1365 1188	1311	…….	2931 3066 2870	925 887 829	1138	…..	....	….	……..
$C_{12}H_{12}N_2$ (L2)	.....	.....	.....	.....	.....	……	1604,1519 1481,1450	2981 3078	821 848	1273,1168 1114,1080	…..	....	….	.....
[Cu L1L2]$_2$ $(NO_3)_4$ .0.5H_2O	3480 3385	3290 3235	1649	1593	1384 1165	1325	1608,1477 1435	3000 3050 2893 2835	833,894 948,806	1273,1165 1111,1091	516	443	272	νOH=3803 νNO_3= 1384,1165,948
[PdL1L2Cl_2]. 0.5H_2O	3475 3379	3290 3221	1640	1597	1373 1157	1315	1600,1500 1462,1438	2981 2885 3070 2819	921 879 833	1273 1157 1091 1010	513	439	271	νOH=3700 Pd Cl= 308
[AuL1L2Cl_2] Cl.2H_2O	3464 3375	3280 3250	1648	1597	1373 1165	1315	1616,1496 1465,1423	2978 2947 3062 2819	925 833 875	1273,1165 1118,1091	516	443	271	νOH=3700 Au Cl= 295

oop=out of plane , ip=in plane, alph.=aliphatic , arom.=aromatic

Electronic spectral and Magnatic moment studies:

The electronic spectrum of the primary ligand (L1)exhibited two absorption bands in the ultraviolet region, the band at 212 nm assigned to the ($\pi \rightarrow \pi^*$) transition for the intera ligand aromatic system (C=C) and a strong absorption band at 270 nm which refer to ($n \rightarrow \pi^*$) transition for oxygen atom of S=O group or nitrogen atom of amine moiety and imine –N=C– group, respectively [17].The Electronic spectrum of L2 shows two main bands the first appeared at 243 nm due to inter a ligand (π-π^*) transition located on (C=C) group. The second absorption appeared at 297 nm arises from (n-π^*) transition may be located on nitrogen atom of imine –N=C-group[18], as listed in (Table 4).

PdL1 and PdL12: The spectra exhibit two absorption bands which are due to the allowed d-d transition the band in the range 10330.57 and10301.52cm^{-1} which corresponds to the transition $^3A_2g \rightarrow {}^3T_2g$, 24509.80 and 24038.46 cm^{-1}can be assigned to $^3A_2g \rightarrow {}^3T_1g$ transition [19], while aband appearing at 13020.83and 13929.90 cm^{-1}can be assigned to spin forbidden $^3A_2g \rightarrow {}^1E_1g$ transition for PdL1 and PdL1L2 respectivly. The bands exhibited at 37313.43and 43103.44 cm^{-1} for PdL1 and 37730.15 and 44565.26 for PdL1L2 which can be assigned to L→Pd CT transition due to charge transfer transition[20].From these obtained data which are in fairly good agreement and suggest that Pd(II) complex have Oh environments of ligands in both complexes[21].This is further supported by diamagnetic behavior of Pd(II) complex for PdL1, while PdL1L2 complex 2.28 B.M. Conductivity measurements showed the ionic behavior of PdL1 complex, while non-electrolyte behavior was shown for other complex.

PtL1: Two principle spin-allowed absorption bands at 22321.42 and 26041.66 cm^{-1} are to be expected corresponding to the transition from the ^1A_1g ground state to the ^1T_1g and ^1T_2g excited states in addition, band assigned to the spin-forbidden singlet-triplet transition may be observed at lower

energies than the spin allowed transition[22].The spectrum of the prepared orange platinum complex, shows bands at 30864.19, 34602.07 and 40322.58 cm^{-1} in the UV region may be due to charge transfer from the donor atoms of ligand to the platinum ionL→PtCTtransitions. The transition observed band at 10964.91 cm^{-1} is assigned to the spin- forbidden transition $^1A_1g\rightarrow\ ^3T_1g$ transition [23,24]. From analysis which done on this preapered complex an octahedral geometry around Pt(IV) structure can be suggested.

AuL1: In this work, diamagnatic of the gold complex exhibited two bands one at 26041.66 cm^{-1} which refer to$^1A_1g\rightarrow\ ^1B_1g$ transition and the other appeared at 30487.80 cm^{-1} which assigned to $^1A_1g\rightarrow\ ^1Eg$ in a square planar geometry [25].The bands at 3846.1 and 39062.5 cm^{-1} may be due to charge transfer from the donor atoms of ligand to the gold ion L→AuCT .The conductivity measurement for this complex showed to be ionic.

CuL1L2: The colour of DMF solution of this complex was noticed to change gradually from dark green to brown during dissolution of the solid compound, this refer change from weak field to strong field state,therefore it was postulated that DMF molecular coordinates through the empty position this means the geometry changes from square pyramidal to distorted octahedral.The electronic spectrum showed one broad band at 12122.68 cm^{-1} which corresponding to $^2B_1g\rightarrow\ ^2A_1g$ transition, and a shoulder band at 23767.08cm^{-1} which assigned to $^2B_1g\rightarrow\ ^2B_2g+^2Eg$ transition and others at 3267.97 and 36231.88 cm^{-1} could be due to charge transfer [26]. The magnetic moment of this complex is 1.28 B.M whichagreement with square pyramidal environment reported [27,28]. The conductance measurements indicate the ionic behavior of this complex, (Table 4). From these results and other studiesOh can be suggested for this complex.

AuL1L2 : Gold(III) complex is in high crystal filed effect due to the large size of gold(III) ion, being in the third transition series in addition to the high oxidation state of this ion [23,29]. The electronic spectrum of this complex exhibit two bands at 27277.68 and 32435.93 cm^{-1} which assignment to $^3A_2g\rightarrow{}^3T_2g$, $^3A_2g\rightarrow{}^3T_1g$ transition and other bands at 34328.87 and 42863.26 cm^{-1} could be charge transfer L→Au CT[26],the ligand field parameters were calculated by using Tanabe-Sugano diagram for octahedral d^8 system.The values in (Table 4) which shows approxamitlyagree with octahedral environment reported[30], The magnetic moment of this complex is 1.81 B.M , the conductivity measurement shows to be ionic.

Table (4): Electronic spectra, Conductance in DMF solventand magnetic moment (B.M) for the prepared ligand L1, co-ligand L2 and their metal complexes.

Comp.	Absorption	Assignment	$\mu_{eff\ B.M}$	μ_{scm}^{-1}	Suggested Structure
L1L1	37037.00 47169.00	n →π* π →π*			
L2	42918.00 33670.00	n →π* π →π*			
***P1*PdL1**	13020.83 10330.57 24509.80 37313.43 43103.44	$^3A_2g\rightarrow{}^1Eg$ $^3A_2g\rightarrow{}^3T_2g$ $^3A_2g\rightarrow{}^3T_1g_{(F)}$ L →Pd CT	0.00	150.2	O.h
PtL1	10964.91 22321.42 26041.66 30864.19 34602.o7	$^1A_1g\rightarrow{}^3T_1g$ $^1A_1g\rightarrow{}^1T_1g$ $^1A_1g\rightarrow{}^1T_2g$ L →PtCT	0.00	66.9	O.h
AuL1	26041.66 30487.80 38461.53 39062.50	$^1A_1g\rightarrow{}^1B_1g$ $^1A_1g\rightarrow{}^1Eg$ L→AuCT	0.00	72.4	D_4h
CuL1L2	12122.68 23767.08 3267.97 36231.88	$^2B_1g\rightarrow{}^2A_1g$ $^2B_1g\rightarrow{}^2B_2g + {}^2Eg$ L →CuCT	1.28	126.2	O.h
PdL1L2	13929.90 10301.52 24038.46 37730.15 44565.26	$^3A_2g\rightarrow{}^1Eg$ $^3A_2g\rightarrow{}^3T_2g$ $^3A_2g\rightarrow{}^3T_1g_{(F)}$ L →Pd CT	2.28	43.4	O.h
AuL1L2	27277.68 32435.93 34328.87 42863.26	$^3A_2g\rightarrow{}^3T_2g$ $^3A_2g\rightarrow{}^3T_1g_{(F)}$ L→AuCT	1.80	85.1	O.h

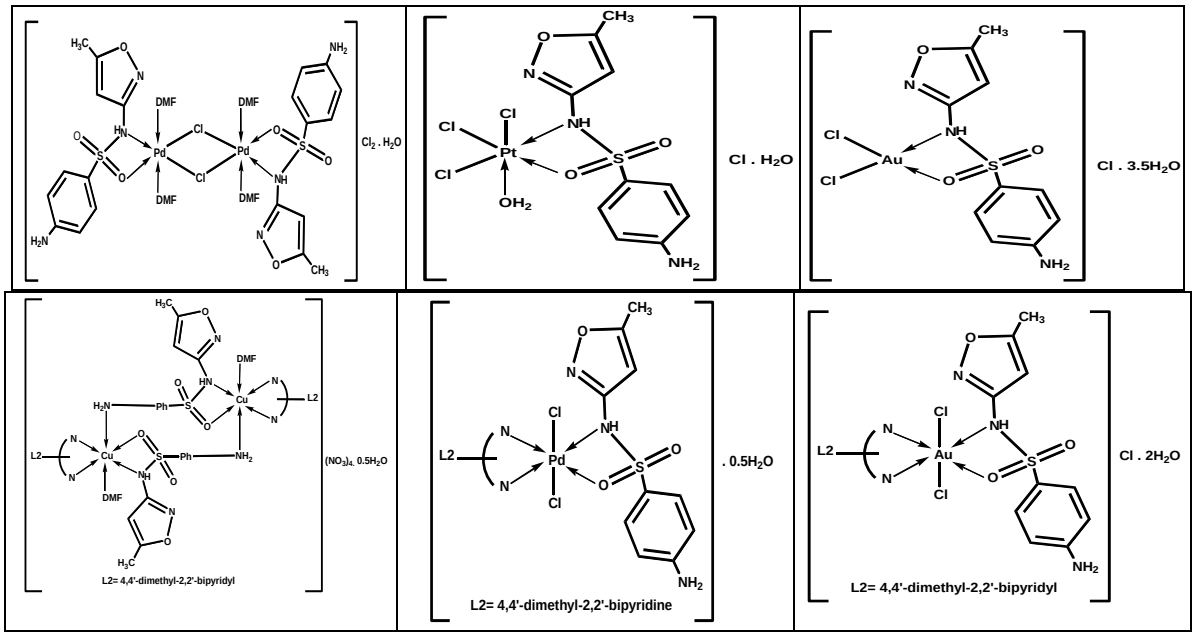

Fig.(1):Suggested structure of the prepared complexes.

Solution study:

Molar ratio method was followed to determine the M:L ratio. The results of complexes in ethanol solution, suggested that the metal to ligand ratio was (1:1) for Palladium, platinum and gold complexes which were approximately agreement with that obtained from solid state study(Table 5),indicated the value of stability constant variable between high and low values for the others , this is according to the size of metal ion , type of the coordination , geometry and the oxidation state , all these parameter refers to change in stability constant.

Table(5):Stability constant of prepared complexes at room temperature.

Comp.	A_S	A_m	α	ε_{max} *L.mol* $^{-1}$ *cm* $^{-1}$	K L.mol^{-1}	$\lambda_{max/nm}$
PdL1	0.132	0.185	0.286	1850	$8.7x10^3$	375
PtL1	0.016	0.019	0.157	190	$3.42x10^4$	410
AuL1	0.014	0.016	0.125	160	$5.6x10^4$	412

B-Cytotoxicity assay:

Cytotoxicity was evaluated against Hep-2 Larynx carcinoma cells(Table 6) using cis-platin as a reference drug. Results showed that the cytotoxic activity for all of the prepared compounds toward Hep-2 cell line with high and medium inhibition rates compare with control positive cis-Pt, the results suggested that the substituent groups governed their cytotoxicities. It is evident that an electron withdrawing groups (SO_2) exhibited the highest cytotoxicity, as well as to presence of electron releasing groups i.e. NH_2 provided the compound with higher cytotoxicity[31]. The novel sulfonamide derivatives have been reported to show potent inhibition of growth against several leukemia, non-small cell lung, ovarian, melanoma, colon, renal, prostate and breast cancer cell line [32]. A lot on antitumor drugs posses a limited bioavailability due to low chemical stability limited oral absorption or rapid metabolism [33], because of these is advantage, several prodrug models that can be activated into antitumor drugs have been designed. An important aspect of prodrug design in the need for converting rapidly to the active therapeutic agent *in vivo* [34], the two nitrogen atoms of co-ligand 4,4'-dimethyl-2,2'-bipyridyl may be due to cytotoxic activity of this ligand, the results reflect the complexes with (SMX) as a ligand alone is perfect than mixed ligand and the PtL1 is the highest inhibition rates this is may be attributed that the sulfonamide to through exchanges of different functional groups without modification of the structural $-S(O)_2N(H)-$ features and this is make a novel drug as antitumor[3], and from inorganic side many factors may be responsible in the activity of these prepared complexes in pharmacological composition field like size of metal, charge distribution, geometry shape, and polarity [35],from these results this highest data for this complexes may be attrbuited to the gold (III) complex have square planner geometry and high charge of gold (III) may be reduced inside the cell into low charge gold(I) and make more stable complex which may be due to increasing the inhibition rates on Hep-2 cell line. While the platinum (IV) complex has octahedral geometry and the high charge (IV) may be reduced inside the cell into low charge (II) and this makes more stable complex and increase from inhibition rates on cell line, and the dimer structure of Pd(II) and Cu(II)complex give it the highest inhibition rates (Fig.2).

Table (6): Inhibition rates of ligands and thier metal complex comparable withcontrol positive cis-Pton Hep-2 cell line.

Con.µg/ml	Cis-Pt	L1	L2	PdL1	PtL1	AuL1	CuL1L2	PdL1L2	AuL1L2
5000	30.765	27.799	20.657	35.689	40.789	32.765	39.678	32.654	30.789
2500	52.543	45.559	37.654	55.543	58.678	39.789	53.567	55.567	36.789
1250	58.789	52.509	43.543	63.578	67.897	47.456	62.658	60.578	43.234
625	75.753	68.33	58.777	73.659	77.789	55.789	69.879	74.879	51.345

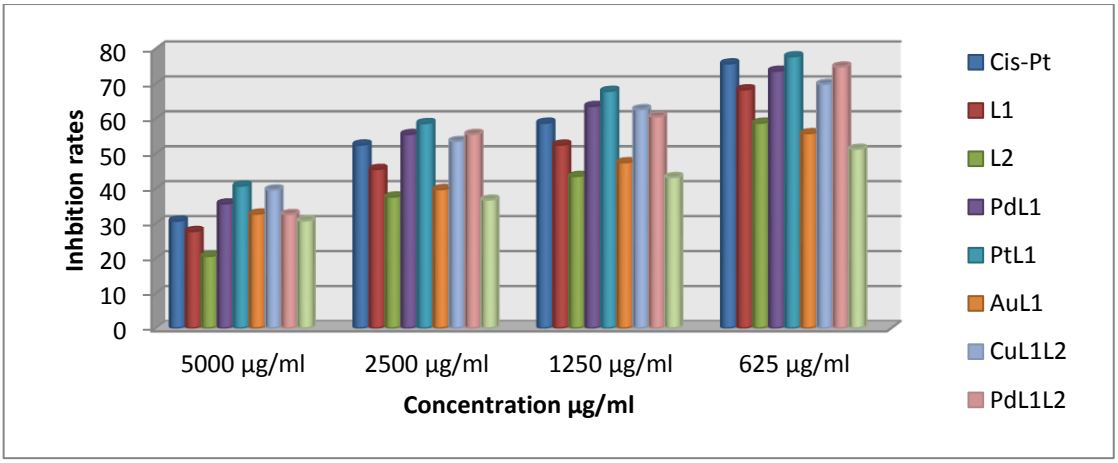

Fig. (2): Shows the percentage inhibition rate on Hpe-2 cell lines after exposure to ligands and their metal complexes.

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تحضير وتشخيص بعض المعقدات الفلزية الثقيلة من السلفاميثاكزول و 4,4'- ثنائي مثيل-2,2'-بايبريدالوتأثيرها السمي على الخط الخلوي لسرطان الحنجرة

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الخلاصة:

تم تحضير معقدات جديدة لليكاند4-amino-*N*-(5-methylisoxazole-3-yl)-benzene-sulfonamide مع ايونات عناصر Pd(II)، Pt(IV) و Au(III) في وسط كحولي .كذلك تم تحضير معقدات لليكاندات الممزوجة 4-amino-*N*-(5-methylisoxazole-3-yl)-benzene-sulfonamideكليكاند اولي بوجود الليكاند المشارك 4,4'-dimethyl-2,2'-bipyridalمع ايونات عناصر Pd(II) , Cu(II) وAu(III)في وسط كحولي .حضرت جميع المعقداتبالطريقة التقليدية و شخصت بواسطة تقنيات الاشعة تحت الحمراء والاشعة فوق البنفسجية-المرئية والحساسية المغناطيسية والامتصاص الذري اللهبي وكذلك التحليل الدقيق للعناصر والتوصيلية الكهربائية. تم دراسة طبيعة بعض معقدات الليكاند في الحالة السائله باتباع طريقة النسبة المولية ، وقد أعطت هذه الدراسة نتائج متطابقة تقريباً مع تلك الدراسة التي تم الحصول عليها بالحالة الصلبة المعزولة و درست ثوابت الاستقرار للمعقدات المحضرة ووجد بأنها مستقرة عند النسب المولية 1:1.

من خلال الدراسة الطيفية اقترح الشكل الهندسي ثماني السطوح لمعقدات PtL1, PdL1L2 وAuL1L2 ومربع مستوي لمعقدات AuL1 و PdL1 بينمايمتلك معقدCuL1L2 شكلاً هرم مربع القاعدة.كما درس التاثير السمي لليكاندات وللمعقدات المحضرةضد الخط الخلوي السرطاني نوع Hep-2باستخدام اربعة تراكيز مختلفة (625,1250, 2500و5000مايكرو غرام / مل) على التوالي وبوقت تعريض48 ساعة وتم مقارنة هذا التاثير مع العقارالمضاد للسرطان سيز- بلاتين وكانت النتائج المستحصلة تشير الى ان نسب تثبيط عالية لجميع المعقدات والليكاندات وان الليكاند L1 ومعقداته اعطت فعالية اكثر ضد الخلايا المختبرة من الليكاند L2 ومعقداته مقارنه بالسيطرة الموجبة .

الكلمات المفتاحية: السلفاميثاكزول، عامل مخلبي، السمية، خط الخلية Hep-2، زمن التعرض.