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Synthesis, Characterization and Studying the Enzyme Activity of New 4-Aminoantipyrine Schiff Base Ligand [L^1] and Its complexes with some of Metal Ions

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Abstract

Schiff bases derived primarily from a variety of hetrocyclicring, were reported to possess abroad spectrum of pharma cological activities with various biological properties. A new heterocyclic Schiff bases ligand 4-(4-hydroxy -3,5 dimethoxy bezylidene amino)-1,5-dimethy -2-phenyl- 1H-pyrazol-3(2H)-one [L^1] derived from the condensation of 4- Amino antipyrine with 4-Hydoxy -3,5-dimethoxy benzaldehyde have been synthesized and characterized by FT-IR, Uv-Vis spectroscopy,$^1H_9$ and ^{13}C-NMR spectrum, mass spectrum, elemental microanalysis (C.H.N) and chloride content. Metal complexes with Co(II), Ni (II), Cu(II) and Pd(II) ions have been also synthesized and characterized by spectroscopic methods (FT-IR, Uv-Vis) spectroscopy, flam atomic absorption, molar conductivity measurements and magnetic susceptibility. This study indicates that the complex molar ratio (L:M) is (2:1). The complexes Co (II) and Ni(II) showed characteristics of octahedralgeometry with the (O, N) ligand coordinated in bidentate mode, while Cu(II) and Pd(II) showed square planer. The enzyme activity of the ligand and its metal complexes with Aspartate amino transferase (AST) have also been studied. The study of enzyme activity indicates that the ligand and its metal complexes revealed different inhibition behaviours.

Keywords: 4-Aminoantipyrine; Schiff bases complexes; enzyme effective.

1. Introduction

The Schiff bases are widely used ligands due to their facile synthesis, significant versatility and good solubility in a common solvent. thus, they have played a vital role in the development of coordination chemistry as they readily stable complexes with most metals in different oxidation states[(1)].In the Schiff bases, the azomethine linkage is important for biological activity, and several azomethines were reported to possess significant antibacterial[(2-4)], antifungal[(5,6)] anticancer[(7)] and diuretic activities[(8)]. Schiff base's complexes which have committed applications in medicine as antimicrobial, anti – oxidant, anti-inflammatory and industrial applications[(9)]. Several publications coverSchiff base's complexes rapeutic or biological applications either as potential drug candidates or diagnostic probes and analytical tools[(10)]. The activity of Schiff base's complexes as anticancer compounds including radio nuclide complexes, antibacterial, antifungal, and antiviral agents has been extensively studied[(11,12)], 4-amino -1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (4AAP) and its derivatives, naturally occurring antibiotics, are one of the most widely used as antibacterial, anticonvulsant and antimalarial drugs[(13-17)]. In recent decades, a great deal of interest in the metal complexes of nitrogen – oxygen chelating agents derived from 4-amino antipyrine Schiff bases have various applications in antifungal, antibacterial[(18)], analgesic, sedative, antipyretic, anti-inflammatory [19] and greater DNA binding ability [(20-24)]. In present work 4-(4-hydroxy-3,5- dimethoxy benzylideneamino)- 1,5- dimethyl 2- phenyl -1H-pyrazol-3 (2H)- one with Co(II), Ni(II), Copper(II) and Pd(II) are synthesized and their physical properties, enzyme activity were investigated.

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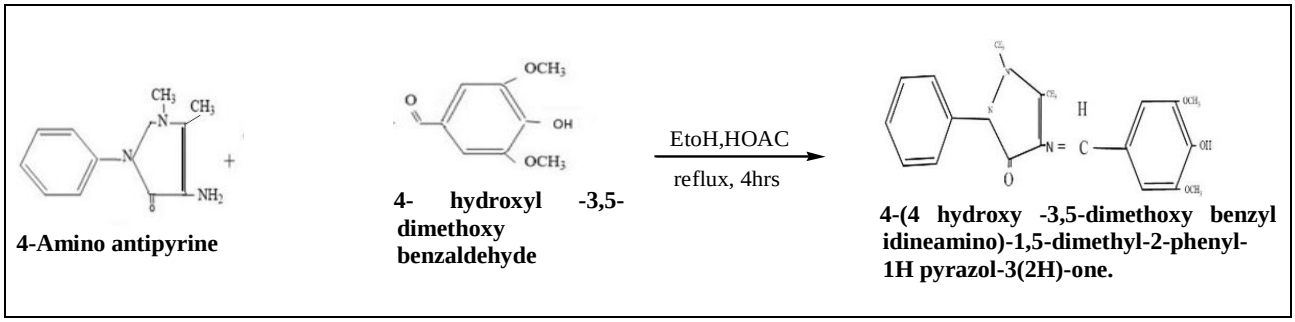
2. Experimental

2.1. Reagents and physical measurements

All reagents and solvents were obtained from commercial sources and used as received without further purification. The melting point wasrecorded by a stuart melting point (digital) SMP30 apparatus. FT-IR spectra were recorded by a shimadzu (FT-IR) model 4800 s spectrophotometer in the range (4000-400) Cm^{-1} as KBr discs. UV-visible spectra were recorded by shimadzu UV-Vis 160ultraviolet photometer at 25℃using 1cm quartz cell and examined at the range of(200-1100) nm at $10^{-3}M$ in DMSO. The atomic absorption (A.A.) technique has been measured using ashimadzu AA680G atomic absorption spectrophotometer at the laboratories of Ibn- Sinaa company. Elemental analysis for the new ligand [L^1] and complexes were determined by (C,H,N) calibration c: Linear Regression Euro EA elemental analysis were made in Iran. Mass analysis was performed for a ligand on GC-MS (DIRECT PROBE). ^1H, ^{13}C-NMR spectrum of ligand was recoded at a Bruker DMX- 500 spectrophotometer (300MHZ), using DMSO-d_6 and $(CD_3)_2CO$. Auto magnetic susceptibility of prepared complexes wasdetermined at (R.T)℃ by Auto magnetic susceptibility Balance. Conductivity measurements were recorded at (R.T)℃ for solutions of samples in DMSO solvent using an Inolab muli 740, wtw 82362-Germany. These measurements have been done at Al-mustansiriyah University, College of science, chemistry Department.

2.2. Preparation of ligand [L^1]

The new Schiff base ligand [L^1] was synthesized by the condensation method of a solution of 4-amino antipyrine (0.203gm, 0.001mol) in absolute ethanol (15ml) was added gradually to acidified solution of 4- hydroxy -3,5- dimethoxy benzaldehyde (0.182gm, 0.001mol) in (15ml) from Same solvent. The final reaction mixture refluxed for (4hrs.), and yielded bright yellow precipitate filtered off, washed with ethanol, dried at room temperature and finally recrystallized from absolute hot ethanol. The synthesized ligand dissolved in the following solvent ethanol, methanol, chloroform acetone, DMF and DMSO. Purity of ligand [L^1] was detected by (TLC) using silica gel as stationary phase and (Hexane /Ethyl acetate) as eluent fig (1), in a ratio (82%). Melting point (172-174)℃. Scheme (1) represents the preparation reaction of ligand [L^1].



4-Amino antipyrine + **4- hydroxyl -3,5-dimethoxy benzaldehyde** → **4-(4 hydroxy -3,5-dimethoxy benzyl idineamino)-1,5-dimethyl-2-phenyl-1H pyrazol-3(2H)-one.**

Scheme 1. synthesis of 4-(4hydroxy -3,5-dimethoxy benzyl idineamino) -1,5- dimethyl- 2-phenyl-1H- pyrazol-3(2H)-one.

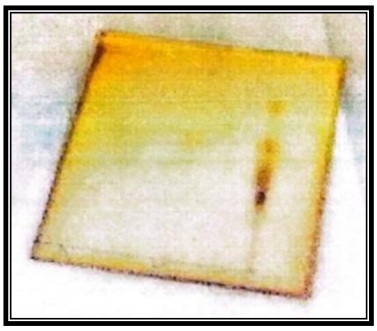


Fig 1. The TLC image for the ligand [L^1]

2.3. Preparation of metal complexes

One mole of ethanoic solution of metal salts was added to two moles of the ligand[L^1]. Where the salts of $[Cocl_2, 6H_2O(0.24gm, 1.00\ mmol)]$, $[Nicl_2.6H_2O(0.24gm.1.00\ mmol]$, $[Cucl_2.2H_2O(o.169gm, 1.00mmol)]$ and $[Pdcl_2(0.170gm.1.00mmol)]$ was added to (0.367gm, 2.00mmol) of the ligand [L^1] color change has

been noticed after mixing both solutions. The reaction mixture was then heated under reflux for 3hrs. The product was filtered and washed with ethanol, then dried at room temperature. The colour,melting point, yield, metal analysis and solubility of the ligand and its complexes are given in table (1).

Table 1. physical properties, yield percentage and Elemental analysis of ligand and it's metal complexes.

No	Compounds	Chemical formula (M.wt) $g.mol^{-1}$	Color	M.PC° Or (dec)	Yield%	Metal analysis found (calculated)					Solubility
						C%	H%	N%	M%	Cl%	
1.	$C_{20}H_{21}NO_4$ $[L^1]$	367.0	Light Yellow	172-174	85	6.37 (65.39)	5.75 (5.77)	11.46 (11.44)	-	-	EtOH, MeoH $C_3H_6O, CHCl_3$ DMF, DMSO
2.	$[Co_{(}L^1)_2\ Cl_2]$	863.9	Green	140-142	78	55.57 (55.56)	4.84 (4.86)	9.70 (9.72)	6.83 (6.81)	8.19 (8.21)	DMF, DMSO
3.	$[Ni_{(}L^1)_2\ Cl_2]$	863.7	Light	204-206	63	55.56 (55.57)	4.88 (4.86)	4.70 (4.72)	6.79 (6.79)	8.20 (8.22)	DMF, DMSO
4.	$[Cu_{(}L1^1)_2]\ Cl_2$	868.5	Brown	198(dec)	52	55.23 (55.26)	4.85 (4.83)	9.66 (9.67)	7.29 (9.69)	8.16 (8.17)	DMF, DMSO
5.	$[Pd_{(}L^1)_2]\ Cl_2$	911.4	Brown	202	84	52.64 (52.66)	4.58 (4.60)	9.23 (9.21)	11.69 (11.67)	7.80 (7.79)	DMF, DMSO

dec= decomposition

3. Results and discussion

3.1. NMR and mass spectrum

3.1.1. ^1H – NMR spectrum of the ligand $[L^1]$

The ^{1}H – NMR spectrum of the ligand $[L^1]$are summarized in the chemical shift at $(\delta = 9.47\ ppm, 1H)$ assigned to phenolic (0-H) group[25]. While the singlet appeared at $(\delta = 8.88ppm\ ,1H)$refers to azomethine proton [26]. The spectrum reveals signals related to protons or aromatic rings $(\delta = 7.11 - 7.55\ PPm, s, d, 2H, benzo)$. Signals at (3.14, 3.83ppm, s, 3H) belong to the (OCH_3) group beside the signal of DMSO-d6 water molecules [27]. The signal of methyl group appeared at $(\delta = 1.06 - 1.29ppm, 6H)$ and the signal for DMSO-d_6 at $(\delta = 2.52\ ppm, 3H)$ fig.(2)

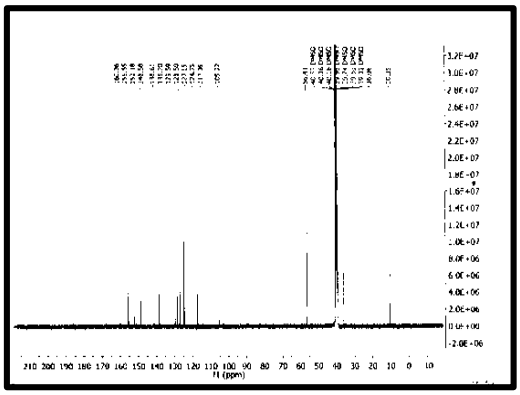


Fig 2. the $^1H - NMR$ Spectrum for the ligand $[L^1]$

3.1.2. ^{13}C – NMR spectrum of the ligand [L^1]

The $^{13}C - NMR$ Spectrum of the free ligand shows the chemical shift at $(\delta = 160.36ppm)$ assigned to the carbon for the carbonyl $(C = O)$ group [28]. The chemical shift of Schiff base azomethine carbonation appeared at $(\delta = 155.55ppm)$. The chemical shifts appeared at (105.22, 117. 36, 124.75, 127.15, 128.50, 129.59, 138.61 and 148.58) ppm were assigned to the carbon atoms of aromatic rings. The chemical shifts at (135.20ppm) due to $(C - OH), (152.18ppm)$ assigned to $(C - CH_3)$ and (56.41ppm) due to methoxy group. A signal at (36.06ppm) assigned to $(N - CH_3)$. The methyl carbon atom moiety appeared at δ(10.35ppm) [29] and a signal at (δ40.16 ppm) due to the solvent fig (3).

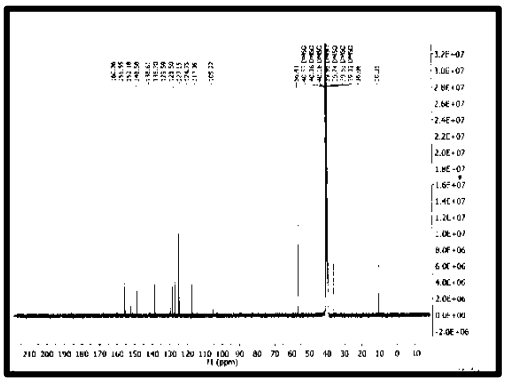


Fig 3.. the ^{13}C – NMR spectrum for the ligand [L^1]

3.1.3. Mass spectrum of the ligand $[L^1]$

Fig (4), showed the mother ion peak at (m/z = 367), as a base peak which corresponds to (M^+). Suggested fragmentation pathways and structural assignments of fragments are described in scheme (2).

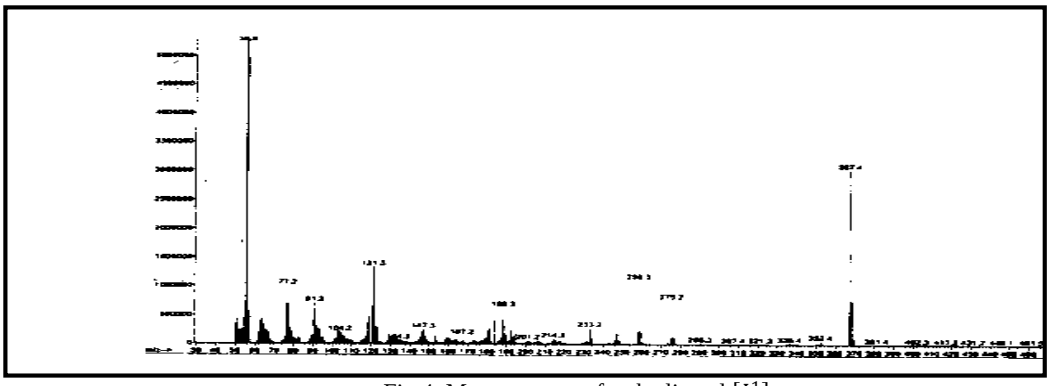
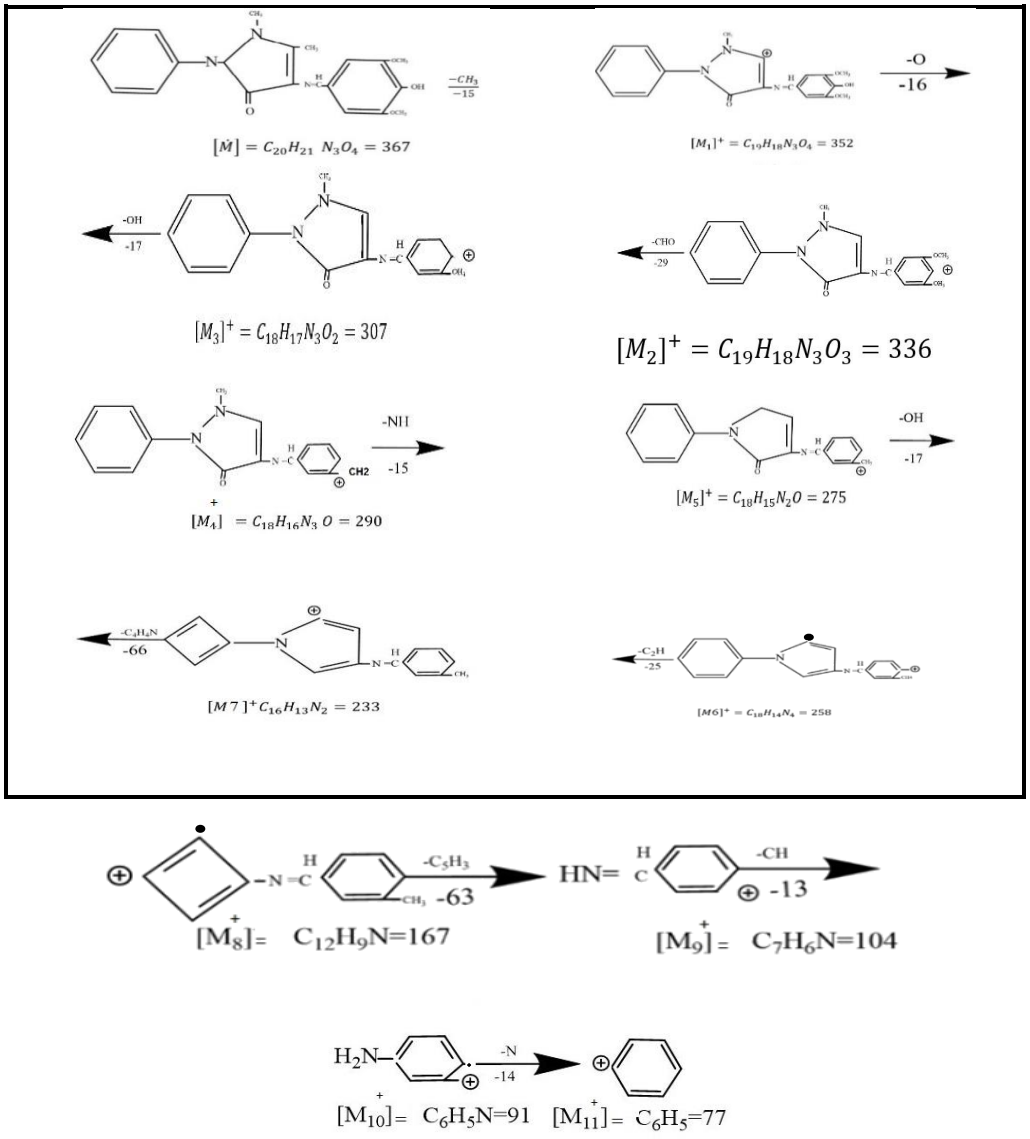


Fig 4. Mass spectrum for the ligand $[L^1]$



Scheme 2. Mass spectra fragmentation pattern FT-IR spectrum of ligand $[L^1]$ and its metallic complexes

The main stretching frequencies of characteristic bands related to the free ligand and its metal complexes, and their assignments are presented in table (2).

The $v(O-H)$ vibration of phenolic group appeared at (3201 cm^{-1}) in the free ligand spectrum. [30] The band at ($1631cm^{-1}$) which refers to $v(C=O)$ for 4-aminoantipyrine ring in the spectrum of free ligand $[L^1]$. The band was overlap or shifted to higher frequencies at the range (1631-1674)cm^{-1} in the spectrum of all complexes [31]. Showing that the coordination was happened via Oxygen atom of this group (C=0) with metal ions. The $v(C=N)$ vibrational frequency of the Schiff base which appeared at (1608 cm^{-1}), shifted to higher frequencies in all complexes[32]. The IR spectrum of all complexes showed new bands which are not present in the spectrum of free ligand, these bands were noted at range (532-551) cm^{-1} and (420-466) cm^{-1}were attributed to $v(M-N)$ and $v(M-0)$ respectively [33].

Table 2.
FT-IR spectral Data (cm^{-1}) for ligand $[L^1]$and its metal complexes.

No	Compounds	$v(O-H)$	$v(c=0)$	$(c=N)$ imine	$v(N-N)$	$v(c=c)$ *Aro.*	$v(c-H)$ *Aro.*	$v(C-H)$ aliph	$v(M-N)$	$v(M-0)$
1	$C_{20}H_{21}NO_4$ $[L^1]$	3201(s)	1631(s)	1608(w)	1076(sh)	1589(s)	3055(s)	2962(m) 2843(m)	-	-
2	[Co $(L^1)_2$ Cl_2]	3402(s)	1631(s)	1620(sh)	1099(s)	1581(s)	3066(s)	2997(s) 2843(s)	551(s)	424(s)
3	[Ni $(L^1)_2$ Cl_2]	3414(s)	1670(s)	1635(S)	1041(m)	1589(s)	3059(m)	2993(m) 2843(m)	532(s)	420(s)
4	[Cu $(L1^1)_2$] Cl_2	3448(m)	1674(m)	1640(m)	1037(s)	1589(m)	3040(m)	2939(m) 2839(m)	547(m)	455(s)
5	[Pd $(L^1)_2$] Cl_2	3417(s)	1674(s)	1639(s)	1039(s)	1589(s)	3059(m)	2943(m) 2843(m)	551(s)	466(m)

Sh=shoulder , s=strong , m=Medium

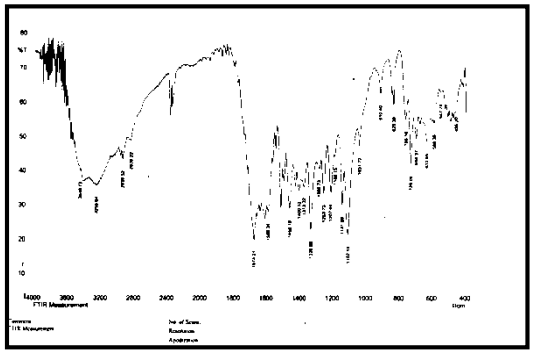


Fig 5. FT-IR for the ligand $[L^1]$

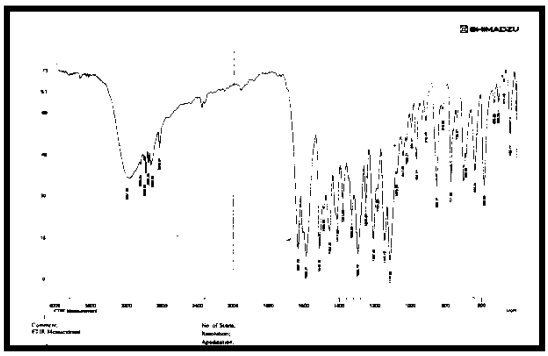


Fig6. FT.IR for the $[Cu(L^1)_2]Cl_2$

3.2. Electronic spectra and magnetic properties of the ligand $[L^1]$ and its complexes.

The magnetic susceptibility measurements were used in combination with electronic spectral data to establish the structure of complexes. the effective magnetic moment (μ_{eff}) values were observed at room temperature ($307°k$)for the complexes have been listed in table (3) with electronic spectrum of ligand and its complexes were recorded in DMSO solution at wavelength range (200-1100)nm. The UV-Vis spectrum of yellow solution of the prepared ligand reveals two peaks at (264nm, $37878cm^{-1}$) and (346nm, $28901cm^{-1}$). This may attributed to the ($\pi \rightarrow \pi^*$) and($n \rightarrow \pi^*$) transition [34]. Those electronic transition have been shifted toward higher or lower frequencies in the electronic spectra of every prepared complexes, verity the ligands coordination with ions of the metal. The absorption peaks observed in spectrum of Co (II) at (269nm, $3717cm^{-1}$) and (346nm, $28901cm^{-1}$) were assigned to ligand field transition. The absorption peak at (608nm, $16447cm^{-1}$) due to ${}^4T_1g_{(f)} \rightarrow {}^4T_1g_{(p)}$and(673nm,$14858cm^{-1}$) due to ${}^4T_1g_{(f)} \rightarrow {}^4A_2g_{(f)}$[35]. The calculated value of effective magnetic moment was seen at (4.19)B.M within the expected range of octahedral geometry[36]. The spectrum of Ni(II) complex exhibited two peaks in UV. region at (263nm, $38022cm^{-1}$) and (346nm, $28901cm^{-1}$) were assigned to ligand field spectra [37]. While the spectrum showed three new peaks in visible region at (413nm, $24213cm^{-1}$), (681nm, $14684cm^{-1}$), (715nm, $13986cm^{-1}$) were assigned to

$^3A_2g_{(F)} \rightarrow {}^3T_1g_{(P)}$, $^3A_2g_{(F)} \rightarrow {}^3T_1g_{(F)}$ and $^3A_2g_{(F)} \rightarrow {}^3T_2g_{(F)}$. The magnetic moment value was (2.83) B.M and the ligand field parameters confirmed an Octahedral configuration around Ni (II) [38]. The spectrum of Cu(II) complex revealed two peaks in UV. region exactly at (262nm, $38167cm^{-1}$)and (306nm, $3278cm^{-1}$) were assigned to ligand field spectra. The spectral also showed the third peak at (414nm, $24154cm^{-1}$) assigned to $^2B_1g \rightarrow {}^2B_2g + {}^2Eg$ transition. The position of this peak is in a good agreement with that reported for square planer geometry. The magnetic moment value (1.67) B.M and configuration around Cu(II) ion.The UV- Vis spectrum of pd(II) complex exhibited a new absorption peak at (434nm, $18975cm^{-1}$)due to $^3A_{Ig} \rightarrow {}^3B_{2g}$. The pd(II) complex were square planer geometry in nature because of $4d^8$ - system. The magnetic moment of the pd(II) complex were found to be diamagnetic [39].

Table 3. Electronic spectral Data, magneticmoment, Molar conductance and proposed geometry for ligand and its complexes.

No	Compounds	λnm	$\bar{\nu}cm^{-1}$	$\varepsilon_{max}\, mo^{-1}.l.cm^{-1}$	Transition	Molar conductance S.cm^2.mol^{-1}	μ_{eff}(B.M) suggested Geometry
1	$C_{20}H_{21}N_3O_4$ $[L^1]$	264 346	37878 28901	1143 2316	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-	-
2	$[Co_{(}L^1_{)_2}Cl_2]$	269 346 608 673	37174 28901 16447 14858	857 2349 629 962	Intra -ligand Intra-ligand $^4T_1g_{(F)} \rightarrow {}^4T_{2g}(P)$ $^4T_1g_{(F)} \rightarrow {}^4A_{2g(F)}$	11.30	4.19 o.h
3	$[Ni_{(}L^1_{)_2}Cl_2]$	263 346 413 681 715	38022 28901 24213 14684 13986	1033 1835 123 214 208	Intra -ligand Intra-ligand $^3A_{2g(F)} \rightarrow {}^3T_{Ig}(P)$ $^3A_{2g(F)} \rightarrow {}^3T_{Ig(F)}$ $^3A_{2g(F)} \rightarrow {}^3T_{2g(F)}$	7.71	2.83 o.h
4	$\left[Cu_{(}L^1_{)_2}\right]Cl_2$	262 305 414	38167 3278 24154	2200 1650 994	Intra -ligand Intra-ligand $^2B_{Ig} \rightarrow {}^2B_{2g} + {}^2E_g$	74.51	1.67 Square planer
5	$\left[pd_{(}L^1_{)_2}\right]Cl_2$	263 294 360 434	38022 34013 27777 23041	1810 1184 1071 812	Ligand-Field Ligand-Field Charge-Transfer $^3A_{Ig} \rightarrow {}^3T_{2g}$	70.63	Diamagnetic Square planer

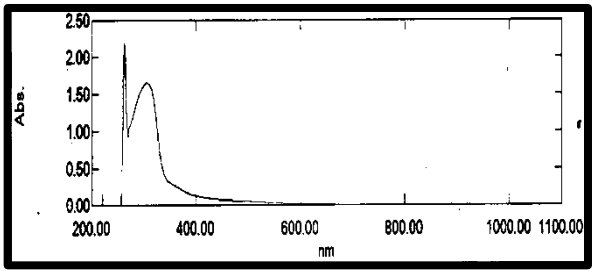


Fig 7. UV-vis for the ligand

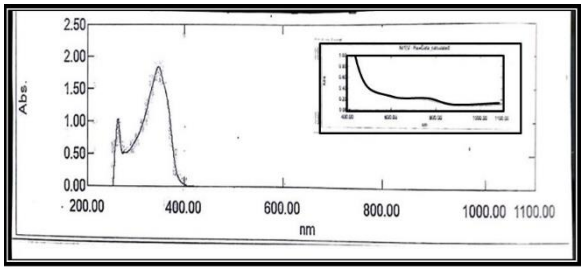


Fig 8. UV-vis for the $[Ni_{(}L^1_{)_2}\,Cl_2]$

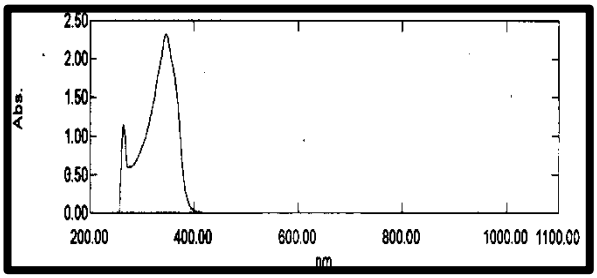
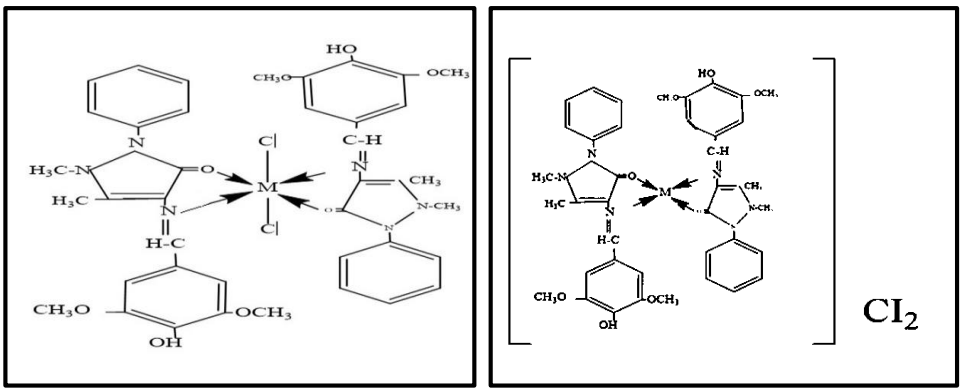


Fig (9): UV-vis for the $[Cu(L^1)_2]CI_2$

3.3. Molar conductance for prepared complexes

The values of molar conductance of Co(II) and Ni(II) complexes in DMSO were (11.3 and 7.7) $s.cm^2Mol^{-1}$, indicated non-electrolyte nature. The values of the other complexes Cu(II), and Pd(II) on DMSO is (74.5 and 70.6 $s.cm^2.\ mol^{-1}$) indicated electrolyte nature of these complexes[40]. According to all previously mentioned analysis, we proposed the following structures of prepared complexes as shown in fig (10).



M=Co(II) and Ni (II) M=Cu(II) and Pd(II)

Fig 10. Proposed structures for the prepared complexes; $M = Co(II\ and\ Ni(II)$

3.4. Studying of Enzyme Activity

3.4.1. Determination of Aspartate amino transferase (AST) activity

Aspartate amino transferase in all body tissues, but the greatest activity occurs in the liver, heart, skeletal muscle and in erythrocytes. Minimal activity occurs in the skin, kidney, and pancreas[41]. Although serum levels of Aspartate amino transferase (AST) become elevated whenever disease processes affect liver cells integrity. Measurement of Aspartate amino transferase has some value in distinguishing hepatitis from other parenchymal lesions. Human serum Aspartate amino transferase (AST) activity was determined using colorimetric method [42].

3.5. Determination of biological activity of ligand and its metal complexes and type of inhibition[43].

The inhibition percentage was calculated by comparing the activity between with and without inhibitor under the same conditions according to the following equation:

$$\%inhibition=100-\frac{the\ activity\ in\ the\ presence\ of\ inhibitor}{the\ activity\ in\ the\ absence\ of\ inhibitor}*100$$

The Present work determined the activity of human Aspartate amino transferaseAST in the absence and presence of ligand and its metal complexes under different substrate concentrations and designed to investigate the biological activity and effects and series of compounds listed in table (4). The first experiment tried to study the effect of solvent DMSO which didn't show any inhibitory effect. Then examine the ligand and complexes in the mixture at different concentration $(10^{-2}, 10^{-4}, 10^{-6}, 10^{-8})$ M. Before each set of inhibition experiments were conducted, the Aspartate amino transferase (AST) activity was measured by using four different concentrations of substrate (0.03, 0.08, 0.08, 0.09) gm as shown in Fig (11). The biochemical tests indicated that all compounds have caused noticed inhibitory effects on enzyme activity compared with the measured normal enzyme activity values. Table (4) showed that the greater inhibition precent was found at concentration (10^{-2}) M for Cu(II) and pd(II) complexes. It has been observed that the nature of these metals to chelate with ligand make aless steric hinders compared to other complexes which gave it more freedom to compute with substrate.

Table 4. The effect of different concentration of ligand and its metal complexes the Human Serum Aspartate amino transferase AST Activity.

Compounds	Inhibition conc. (M)	AST activity (IU/L)	%inhibition
Control	Zero	360	-
$[L^1]$	10^{-2}	270	25*
	10^{-4}	300	16.7
	10^{-6}	340	5.6
	10^{-8}	340	5.6
$[Co_(L^1)_2Cl_2]$	10^{-2}	140	61.2*
	10^{-4}	225	37.5
	10^{-6}	340	5.6
	10^{-8}	341	5.3
$[Ni_(L^1)_2Cl_2]$	10^{-2}	265	26.4*
	10^{-4}	340	5.6
	10^{-6}	360	0
	10^{-8}	360	0
$[Cu_(L^1)_2]Cl_2$	10^{-2}	70	80.6*
	10^{-4}	310	13.9
	10^{-6}	359	0.3
	10^{-8}	360	0
$[Pd_(L^1)_2]Cl_2$	10^{-2}	73	79.8*
	10^{-4}	335	7
	10^{-6}	354	1.7
	10^{-8}	355	1.3

*maximum Inhibition concentration of Aspartate amino transferase AST compound

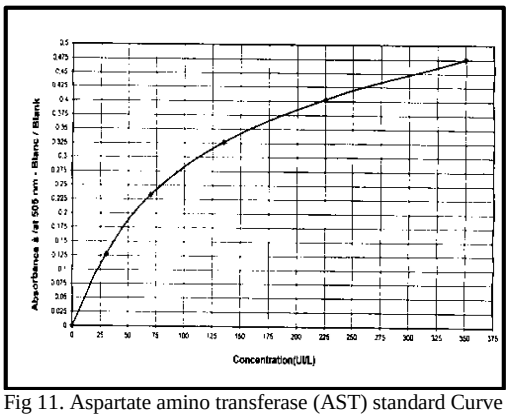


Fig 11. Aspartate amino transferase (AST) standard Curve

4. Conclusion

Condensation of 4- aminoantipyrine with 4-hydroxy-3,5- dimemethoxy benzaldehyde products a new Schiff bases ligand having potential binding sites to words metal ions five member chelate ring. Heterocyclic Schiff base ligand acats as a bidentate ligand by coordination through, azomethine nitrogen and oxygen atom. different geometries have been obtained from coordination of the prepared ligand with selected bivalent metal ions. DMSO has been used in preparation of solution in studying of enzyme activity. The inhibition concentration was (10^{-2}) for Cu(II) and Pd(II) complexes.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

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8. References

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