



Preparation, Characterization, Theoretical and Biological Study of new Complexes with mannich base , 2chloro -N-5-(Piperidin -1-ylmethylthio)-1, 3, 4- Thiadiazol-2-yl)acetamide

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Abstract

A new Mannich base ligand was prepared by reacting the 2-chloro.-N-(5-mercapto-1, 3, 4-thiadiazol -2-yl) acetamide and Piperidine in the presence (formaldehyde) (L) ligand. A series of ligand complexes were prepared from (L) with the metal ion Co (II), Ni (II), Cu (II), Pd (II), Pt (IV), and Au (III). Various spectroscopic techniques such as C.H.N.S, FTIR, UV-VIS, ¹HNMR, ¹³CNMR, Magnetic moment, and molar conductivity successfully characterize the obtained compounds. The M: L ratio was determined using the molar ratio method in solution. All prepared compounds' antibacterial and antifungal activity was studied against two types of bacteria and one type of fungi at a rate of 0.02M. The standard ΔH°_f and ΔE_b of the ligands and all the prepared complexes were calculated using Hyperchem 8.0.7 program, and the study proved that the complexes are more stable than the ligands. In addition, the vibrational frequencies of the ligand were calculated, and the theoretical error rate of the process was calculated.

Keywords: Transition Metal Complexes, Mannich Base, 1,3,4-thiadazole Antibacterial and Antifungal.

1. Introduction

The thiosemicarbazide compound with the molecular formula ($\text{CH}_5\text{N}_3\text{S}$) and its complexes are of great biological importance due to their wide uses [1]. The compound thiodiazole compound with the molecular formula ($\text{C}_2\text{H}_2\text{SN}_2$) is a heterogeneous compound because it contains two atoms of Carbon, Two atoms of nitrogen, and one sulfur atom [2]. Two nitrogen atoms and the sulfur atom are electron-donating [3] and are essential ligands in complexes when they bond with metal elements [2]. It has several types, one of which is the compound 1,3,4-thiadiazole, which is applied as anti-tumor medicine. Several derivatives are used as carbonic anhydrase inhibitors and antiparkinsonian agents [3]. Industrial and biological in the medical field, compound 1,3,4 has many applications against bacteria [4], fungi [5], and cancer [6]. The Mannich reaction is of significant importance reactions in chemistry. It is a reaction that includes three or more components of a substance or solvent [7], and it is one of the early examples of a three-component reaction [8]. In the past years, the focus has been on the complexes of Mannich bases that have heterogeneous rings, taking into account the amino-methyl group and studying the relationship of structure, its effect on the biological activity as anticancer agents and toxic to cancer cells [9,10]. There was also a focus on studying their importance as antibacterial and antifungals [11], anticonvulsants, anti-inflammatory [9], analgesic, and antioxidant activities [10]. The complexes of Mannich's bases are essential and have wide applications in the medical and biological fields [11]. They are used as antioxidants [10], anticancer, antibacterial, and antifungal [12], and they have proven their effectiveness in all biological and medical fields [13].

2. Materials and Methods

In this paper, high-purity chemicals were used. CHNS elemental data were measured using an Eager300 elemental analyzer. The mineral content was determined using a Shimadzu 670 Flam Atomic Absorber Spectrophotometer. Conductivity data were acquired at 10^{-3} M in the DMF solution of the complexes using a WTW conductance meter at 25 °C. FT-IR spectra were measured with a Shimadzu and Perkin Elmer FT infrared spectrophotometer using CsI ($4000\text{-}200$) cm^{-1} . Tablet. Absorption in the UV-visible region was recorded in ethanol solution using UV-Vis. Shimadzu Spectrophotometer 1800pcs. The magnetic susceptibility measurement of the complexes was carried out using the Faraday method, and the magnetic correction factor (D) was calculated using the Pascal constants of the atoms that made up the prepared complexes and the Brukar Magent BM6 device. ^1H , ^{13}C NMR for compounds were at 25 °C using the Brukar400MHz. The grade of all prepared compounds was measured by Gallen Kamp MF.B-6.

Preparation of starting material 2-amino 5-mercapto 1,3,4 thiadiazole (S1)

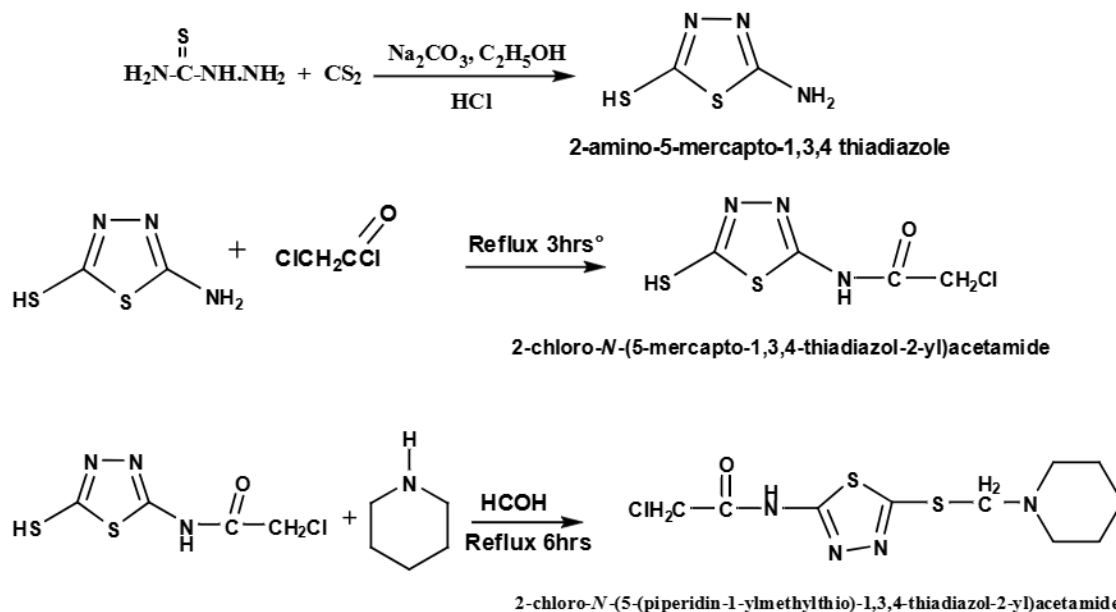
In a round bottom flask, (2gm,0.02mol) of thiosemicarbazide was dissolved in (25ml) ethanol (0.016gm,0.0002mol) of anhydrous sodium carbonate. (4.712 gm, 0.062 mol) of (CS_2) was added with stirring and heating at (40C^0) for an hour. Then, the mixture was raised for 7 hours after the solvent was evaporated (50ml) in distilled water, and drops of concentrated hydrochloric acid were added. A greenish-yellow was the precipitate. The color of the precipitate (was yellowish white, with a melting point of ($229\text{-}231$) C^0 and the molecular formula ($\text{C}_2\text{H}_3\text{N}_3\text{S}_2$) [14]. The sediment was washed, and the precipitate was filtered with a quantity of distilled water to get rid of the excess acid. It was recrystallized with the solvent ethanol.

Preparation of 2-chloro-N-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide (S2)

Dissolved (0.1 gm, 0.01M) of 2-amino 5-mercapto 1,3,4 thiadiazole (S1) in ethanol was added with stirring (0.1 g, 0.02M) of chloroacetyl chloride) in an ice bath. The mixture was refluxed with heating for 3 hours. The resulting precipitate was washed with distilled water and recrystallized with ethanol. A yellowish-white precipitate was obtained with a molecular formula $C_4H_4N_3S_2OCl$ and a melting point of (250-253) C^0 .

Synthesis of 2- Chloro -N-5-(Piperidine1-ylmethylthio)-1,3,4- Thiadiazol-2-yl)acetamide Ligand (Mannich ligand)(L)

Dissolved of (0.145 gm, 0.04M) of 2-chloro-N-(5-mercapto-1,3,4-thiadiazol-2-yl)acetamide in (10ml) of ethanol solvent was added with stirring and cooling (8ml) from formaldehyde and (0.08g, 0.03M) Piperidine. The mixture was refluxed and heated for six hours, leaving the solution to dry. The sediment was recrystallized in ethanol. The precipitate has a brown color, a molecular formula $C_{10}H_{15}ClN_4OS_2$, and a melting point of over 300 C^0 .



Scheme 1. Synthesis of Mannich Base, 2chloro -N-5-(Piperidin -1-ylmethylthio)-1, 3, 4- Thiadiazol-2-yl)acetamide (L)

2.2. Synthesis of Complexes

In the presence of ethyl alcohol solvent, some Mannich base complexes can be prepared. The ratio 1:1 of $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, $PdCl_2$, $H_2PtCl_6 \cdot 6H_2O$, and $HAuCl_4 \cdot H_2O$ and ligand. Then the mixture was refluxed for 3 hours. The resulting solids compounds were filtered off, washed with distilled water and ethanol, and dried in a desiccator. Some physical properties can be observed in **Table 1**.

Table 1. The physical properties of color and melting point in addition to the values of C.H.N.S and the percentage of all prepared compounds

Comp.	Color	m.p / C ⁰	Yield %	Atomic Abs.% Cal.(Found)	Elemental analysis Calc. (found)			
					C	H	N	S
Mannich (L)	Brown	Over 300	76	----	39.10 (38.66)	4.88 (3.98)	18.25 (19.01)	20.85 (21.34)
CoL	Dark green	118-120	80	12.22	24.90 (23.78)	4.15 (3.76)	11.62 (12.78)	13.28 (14.00)
NiL	Light green	182-185	76	11.96	24.46 (25.11)	3.87 (4.08)	11.00 (10.94)	13.04 (12.87)
CuL	Dark brown	167-170	84	12.81	24.22 (23.20)	4.23 (5.12)	10.90 (11.05)	12.92 (13.67)
PdL	Brown	218-221	67	32.06	19.72 (18.77)	2.46 (3.45)	8.87 (9.11)	10.51 (11.41)
PtL	Dark brown	202-205	74	21.88	23.89 (24.02)	3.38 (4.18)	10.75 (11.44)	12.74 (11.93)
AuL	Green	212-215	77	32.27	19.62 (18.56)	2.45 (3.04)	8.84 (9.94)	10.48 (11.05)

Theoretical study

In the theoretical study and using the hyperchem 8.0.7 program, the standard heat of formation and binding energy was calculated for all prepared compounds by PM3, ZINDO\I, and AMBER. The HOMO and LUMO were calculated to determine the active sites in the ligand molecule. The vibration frequencies were calculated theoretically for the ligand PM3 method, the practical results were compared with the theoretical results, and the error ratio between them was calculated, which was acceptable.

Antibacterial and Antifungal activity

- 1.40 g of culture medium for bacteria and fungi was dissolved in a liter of distilled water, as the culture medium used for bacteria (Agar Mueller Hinton) and for fungi (Sabroid Dextroes Agar).
2. After dissolving by heating, the culture medium was placed in the sterilizer for 15 minutes, then poured into sterilized plastic dishes and left to solidify.
3. A hole was made using a cork drill with a diameter of 8 mm to add the material that inhibited the growth of bacteria and fungi.
4. The prepared ligands and complexes dissolved in DMSO at a concentration of 0.02M were injected into the pits of the culture medium.
5. The dishes were placed in the incubator at 37 °C for 24 hour for antibacterial activity and 72 hours for antifungal activity, then the inhibition diameters were measured using a ruler in mm for each of the prepared compounds.

3. Results and Discussion

All complexes were soluble in organic solvents DMF & DMSO. The ratio of metal-ligand was (1:1) the ligand, and their metal complexes were characterized: (FT-IR), (UV-vis) (¹HNMR ¹HNMR and ¹³CNMR, magnetic susceptibility, and conductivity.

Fourier transforms spectroscopy (FT-IR) of Mannich ligand (L), and metal complexes

FT-IR spectra of all prepared compounds were carried out in 4000 to 200 cm^{-1} . The infrared spectra of Mannich ligand L and metal complexes appeared the active site number at 1701, 720, 1161, 2943, 2854, and 1620 cm^{-1} which was due to $[(\nu_{\text{C=O}})_{\nu_{\text{C-S}}})_{\nu_{\text{C-N}}}]_{\nu_{\text{CH}_2\text{N}}}$ and C=N 1,3,4thio. sequentially [15]. When a metal ion was bonded to the ligand through the nitrogen atom of C=N 1,3,4thio absorption bands shifted towards frequencies within the range (1602-1658) cm^{-1} in cobalt, nickel, copper, palladium, platinum, and gold complexes, respectively. In other absorption bands, the carbonyl group (C=O) has been shifted according to the frequencies (1728, 1728, 1691, 1690, 1686, 1722) cm^{-1} . In all the prepared complexes oxygen of carbonyl, $\nu_{\text{C=O}}$ took place in coordination. This supported compatibility with the C=O group [16]. We also noticed a shift in C-S and CSC groups for each of the Co(II), Ni(II), Cu(II), Pd(II), Pt(IV), and Au(III) complexes, which indicated the occurrence of coordination through them. According to these results, the coordination made of this ligand was predicted as a tridentate through $\nu_{\text{C=N}}$, $\nu_{\text{C=O}}$ group, and sulfur [17]. Other bands could be attributed to $\nu_{\text{M-N}}$, $\nu_{\text{M-O}}$, $\nu_{\text{M-S}}$, and $\nu_{\text{M-Cl}}$ for complexes [13]. Other bands can be shown in **Table 2**. Also, other bands belonging to the ν_{NH} group and the $\nu_{\text{CH}_2\text{-N}}$ group appeared that they did not have a displacement when the coordination occurred, indicating non-coordination through them [16].

Table 2. The main absorption bands of the infrared spectrum of ligand (L), and its metal complexes (cm^{-1})

COMP.	$\nu_{\text{C=O}}$	$\nu_{\text{CH}_2\text{-N}}$	$\nu_{\text{C=N}}$ 1,3,4thio.	ν_{CSC}	ν_{CS}	$\nu_{\text{M-O}}$	$\nu_{\text{M-N}}$	$\nu_{\text{M-S}}$	$\nu_{\text{M-Cl}}$
L	1701	2943 2854	1620	1161	702	----	----	----	----
CoL	1728	2943 Broad	1602	1145	678	586	520	478	345
NiL	1728	2943	1658	1153	686	547	513	416	337
CuL	1691	2942	1639	1175	729	590	513	470	320
PdL	1690	2947 2854	1608	1171	77	540	520	482	345
PtL	1686	2943 2858	1608	1190	744	559	516	451	310
AuL	1722	2947	1639	1188	786	540	516	470	337

Uv-vis Spectra, Magnetic susceptibility and molar conductivity

The electronic spectra of all prepared compounds are shown in **Table (3)**. The UV-vis spectrum of the free ligand displayed a sharp band at (25773) cm^{-1} is attributed to $n \rightarrow \pi^*$ transition. Transitions appeared in the region (33112) cm^{-1} and 37314 cm^{-1} is attributed to $\pi \rightarrow \pi^*$ transitions [18].

In the UV- visible spectrum of dark green Co (II) complex, two peaks were observed at (10240, 19230 cm^{-1}) dedicated to ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$, ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g(p)}$ transitions sequentially and (28659, 41838) cm^{-1} . It was due to the transition $\text{IL} \rightarrow \text{Co CT}$, which indicated the octahedral geometry of Co (II). Magnetic moment. (4.00) B.M showed a higher orbital contribution. Conductivity measurement in DMF (67 $\mu\text{S.cm}^{-1}$) showed that the complex was ionic. The electronic spectrum of this complex can be seen in **Table (3)** [19].

In the UV- visible of Ni (II) complex, three peaks were observed at (10582, 15772, 24875 cm^{-1}). They were dedicated to ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g}$, ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g(i)}$, ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g(p)}$ sequentially and (26109, 40983) cm^{-1} was due to $\text{IL} \rightarrow \text{NiCT}$ which indicated the octahedral geometry of Ni. The magnetic moment, (3.09) B.M showed a higher orbital contribution [20] Conductivity measurement in DMF (21 $\mu\text{S.cm}^{-1}$) appearing that the complex was nonionic [19]. Light Green complex showed paramagnetic and high spin octahedral. The electronic spectrum of this complex can be seen in **Table (3)**.

In the UV- visible region of the Cu(II) complex, one peak was observed at (15197 cm⁻¹), dedicated to ²E_g → ²T_{2g}, and (27629, 29069, 42918) cm⁻¹ was due to IL → CuCT which indicated the octahedral geometry of Cu (II) [20]. Magnetic moment, (1.78) B.M [21]. Conductivity measurement in DMF (61 μS.cm⁻¹) showed that the complex was ionic. Dark brown complex showed paramagnetic and high spin octahedral. The electronic spectrum of this, complex can be seen in **Table (3)**.

In the UV-visible region of the Pd (II) complex, one peak was observed at (24038cm⁻¹), dedicated to ¹A_{1g} → ¹B_{1g} transition, and (31446, 45248) cm⁻¹ was due to IL → PdCT, which indicated square planer geometry of Pd (II) [19]. Magnetic moment (0) B.M. Conductivity measurement in DMF (70 μS.cm⁻¹) showed that the complex was ionic, low spin and square planer geometry [22]. The electronic spectrum of this complex can be seen in **Table (3)**.

In the UV- visible region of the Pt(II) complex two peaks were observed at (10812, 12050 cm⁻¹) was assigned to ¹A_{1g} → ³T_{2g}, (23980 cm⁻¹) was assigned to ¹A_{1g} → ¹T_{1g}, transitions which indicated the octahedral geometry of Pt (IV). Magnetic moment, (0) B.M [23]. Conductivity measurement in DMF (69 μS.cm⁻¹) showed that the complex was ionic [24].

In the UV- visible region of the Au (III) complex, two peaks were observed at (251889, 30030cm⁻¹) dedicated to ¹A_{1g} → ¹B_{1g} and ¹A_{1g} → ¹E_g transitions sequentially and (40983) cm⁻¹ was due to IL → AuCT which indicated the square planner geometry Au (III). The magnetic moment was (0) B.M [25]. The conductivity measurement in DMF was (88 μS.cm⁻¹) [22]. This complex was ionic, low spin and square planer geometry. The electronic spectrum of this complex can be seen in **Table 3** [26].

Table 3. The electronic spectra, μ_{eff} of complexes, conductivity and suggested geometry for ligand and its metal complexes

Comp.	Absorption Cm ⁻¹	Assignments	μ _e eff B.M.	Conductivity μS.cm ⁻¹	Suggested geometry
L	25773 33112 37314	n → π* π → π* π → π*	----	----	----
CoL	10240 19230 28659 41838	⁴ T _{1g} → ⁴ T _{2g} ⁴ T _{1g} → ⁴ T _{1g(p)} IL → CoCT IL → CoCT	4.00 (3.87)	67	Octahedral
NiL	10582 15772 24875 26109 40983	³ A _{2g} → ³ T _{2g} ³ A _{2g} → ¹ T _{1g(F)} ³ A _{2g} → ³ T _{1g(p)} IL → Ni CT IL → Ni CT	3.09 (2.82)	21	Octahedral
CuL	15197 27629 29069 42918	² E _g → ² T _{2g} IL → Cu CT IL → Cu CT IL → Cu CT	1.78 (1.73)	61	Octahedral
PdL	24038 31446 45248	¹ A _{1g} → ¹ B _{1g} IL → Pd CT IL → Pd CT	0.00	73	Square planer
PtL	108551 12050 23980 26881 34602 45662	¹ A _{1g} → ³ T _{2g} ¹ A _{1g} → ³ T _{1g} ¹ A _{1g} → ¹ T _{1g} IL → Pt CT IL → Pt CT IL → Pt CT	0.00	69	Octahedral
AuL	25575 27624	¹ A _{1g} → ¹ B _{1g} ¹ A _{1g} → ¹ E _g IL → Au CT	0.00	88	Square planer

The $^1\text{H-NMR}$ spectra of 2-Chloro -N-5-(Piperidin-1-ylmethylthio)-1,3,4- thiadiazol-2-yl)acetimide

The $^1\text{H-NMR}$ spectrum of the L can be observed in table 4 in DMSO-d₆. The proton nuclear resonance ($^1\text{H-NMR}$) spectrum of ligand showed some signals in ppm. Two signals appeared at (1.54, 1.64) ppm and another signals appeared at (2.42,2.43,2.45) ppm, attributed to the proton of Piperidin [11]. The Proton of CH₂-N and CH₂-Cl groups appeared at (4.49) ppm and (3.97) ppm. The signal at (12.39) ppm was attributed to proton of NH group **Table 4**.

The $^{13}\text{C-NMR}$ Spectra of 2-Chloro -N-5-(Piperidine1-ylmethylthio)-1,3,4- thiadiazol-2-yl)acetimide

The $^{13}\text{C-NMR}$ spectrum of ligand showed some signal. The signal at 43.7 can be assigned to carbon of (CH₂-Cl) group. The signals at 23.1,24.4 and 54.1 ppm returned to carbon of CH₂ of Piperidin and CH₂-N of Piperidin [3]. Other signals appeared at 163.2 and 168.4 can be assigned to carbon of (C-S,1,3,4 thio.) group and carbon of carbonyl group, respectively [4]. Another peak can be observed in table 4.

Table 4. ^1H and ^{13}C nuclear magnetic resonance spectra of Mannich base ligand (L)

$^1\text{H-NMR}$	$^{13}\text{C-NMR}$
$^1\text{H-NMR}$ (DMSO- d ₆) δ ppm:2.42,2.43,2.45 (d,2H, CH ₂ of Piperidine) 1.64 and 1.54 (d,2H, CH ₂ of Piperidine) ,12.39 (S,H,NH) of amide, 3.97,4.49 (S,H,CH ₂ alphatic of CH ₂ -N and CH ₂ -Cl respectively	Mannich (L) : $^{13}\text{C-NMR}$ (DMSO-d ₆) δ ppm:43.7 (CH ₂ -Cl), 23.1,24.4 (CH ₂ of Piperidine), 53.1 (CH ₂ -N of Piperidine) ,54.1 (CH ₂ -N) of methylene group, 163.2 (S-C of 1,3,4 thiadiazole group ,168.4 (C=O group).

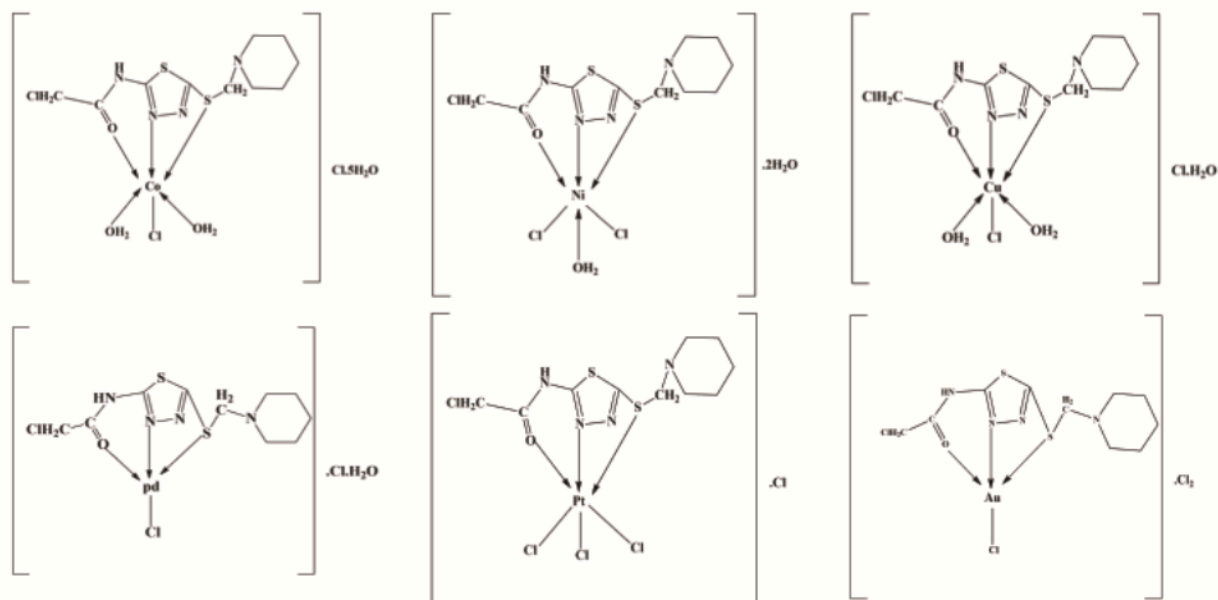


Figure 1. The proposed geometry of the prepared complexes

Molar ratio Method

In the solution state, the ratio metal to ligand can be calculated using molar ratio method at the maximum wavelength, and at concentration 1×10^{-3} of all the prepared complexes. The results proved that the ratio of metal to ligands was (1:1).

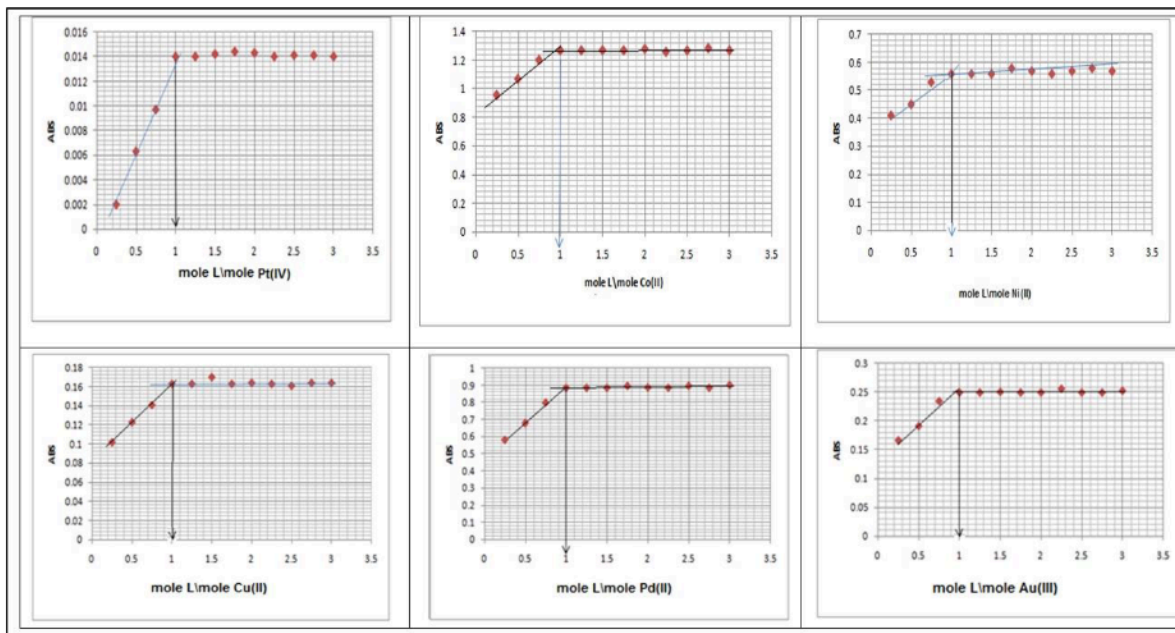


Figure 2. Molar ratio plot of, L metal complexes

4. Antibacterial and antifungal Activity

The biological activity of all prepared compounds was tested by two types of bacteria and one type of fungi at a concentration of 0.02M. The results obtained for the antibacterial and antifungal of the Mannich ligand and its new complexes are presented in **Table 5**. The diameter of the inhibition zone was measured in (mm) using amoxicillin and metronidazole as standard drugs for bacteria and fungi, respectively. The ligand and complexes generally showed moderate activity, and some were high towards bacteria and fungi tested. The nickel complex showed higher activity against all bacteria and fungi than standard drugs. This would suggest that the chelation could facilitate the ability of a complex to cross-brand into the cell wall of bacteria and fungi and kill them [27].

Table 5. Antibacterial activity of L and its Metal Complexes at 0.02 M

Compounds		Inhibition Zone (mm.)				
		Gram Positive		Gram negative		Fungi
		<i>staph</i>	<i>Bacillus</i>	<i>E.coli</i>	<i>Klebsiella</i>	<i>Candida</i>
1	CoL	27	29	16	20	24
2	NiL	35	27	32	22	27
3	CuL	21	18	22	14	18
4	PdL	18	17	14	14	21
5	PtL	20	15	15	13	15
6	AuL	20	12	20	15	15
7	DMSO	-ve	-ve	-ve	-ve	-ve
8	L	28	25	25	21	25
10	Amoxicillin	12	12	13	11	----
11	Metronidazole	----	----	----	----	13

Table 6. The vibrational frequencies of L using HyperChem-8.0.7 program

<i>Symb.</i>	$\nu(\text{C}=\text{N})$ ring	$\nu\text{C}=\text{O}$	νCSC	$\nu\text{CH}_2\text{-N}$	νCS
Experimental	1620	1701	1161	2854 2943	702
Theoretical	*1623	1768*	1190*	2928 2998*	*739
Percentage of error	(0.18)	(3.78)	(2.43)	(-1.49) (1.83)	(5.00)

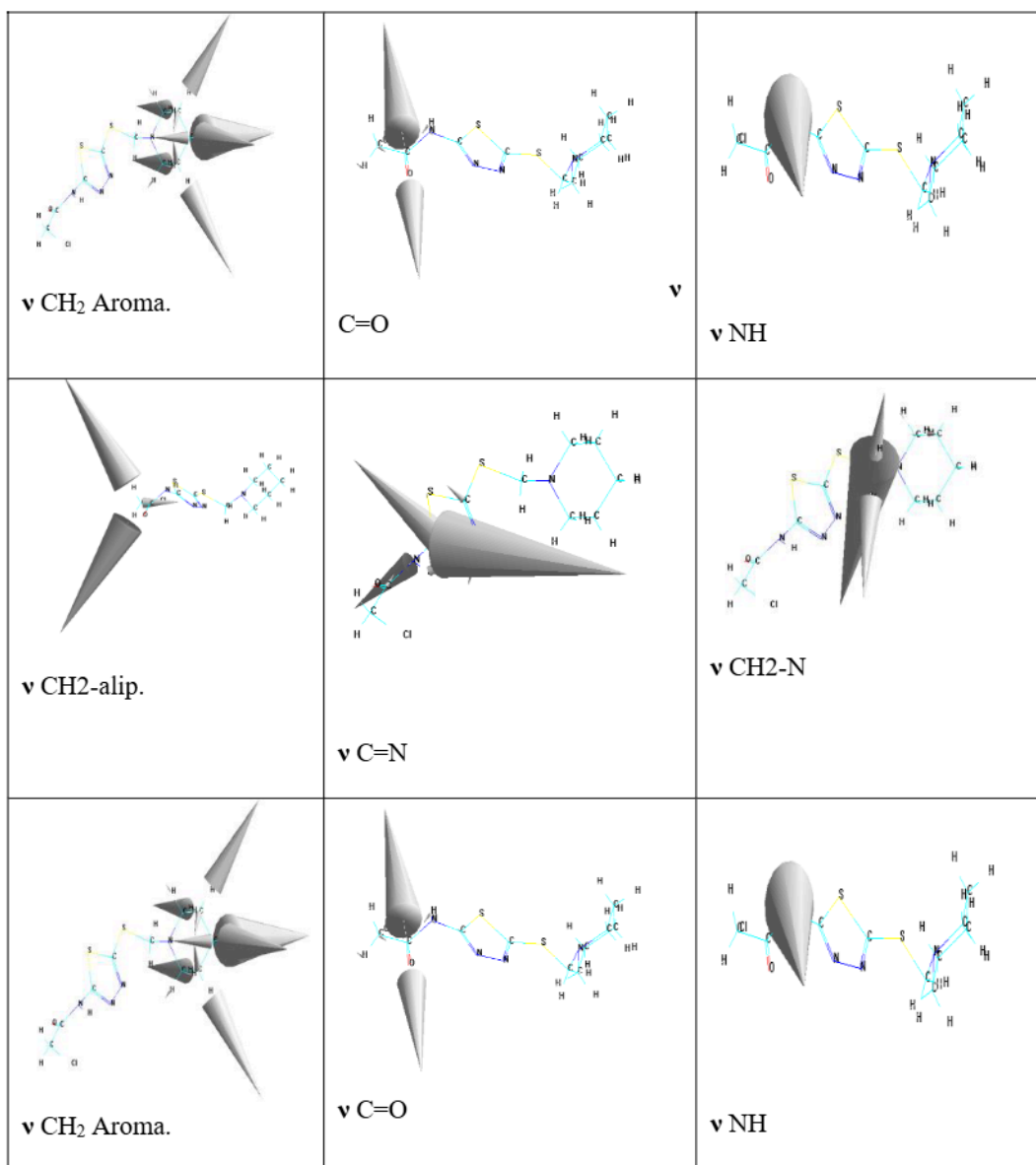


Figure 3. Vibration spectra of ligand Mannich base (L)

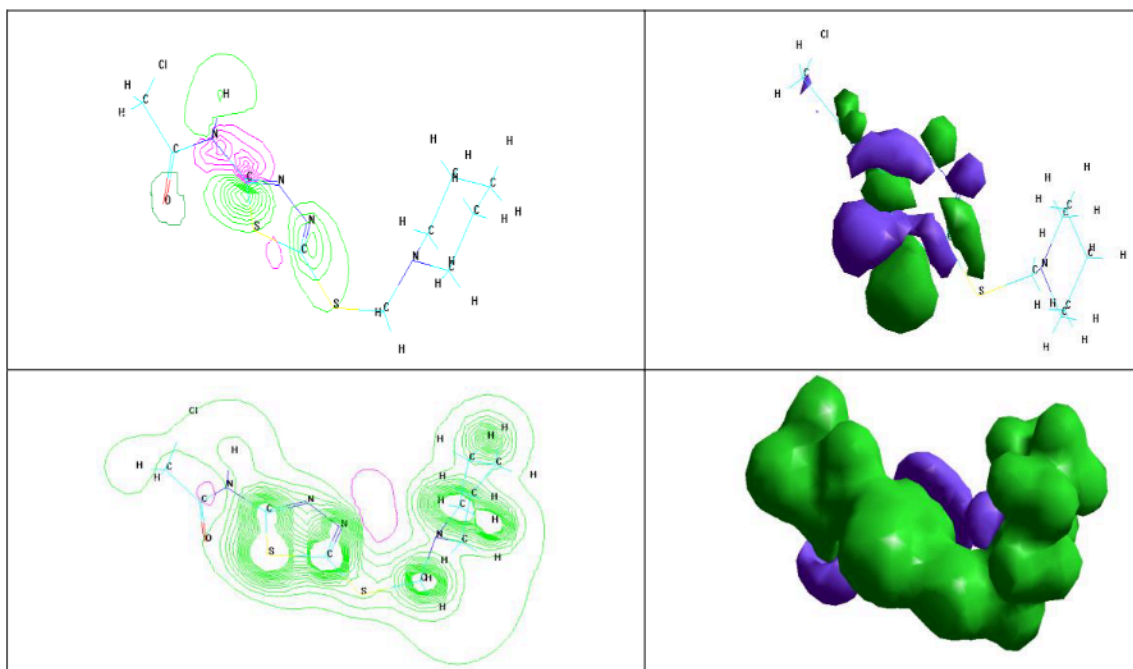


Figure 4. HOMO, LUMO and Electrostatic Potential of ligand L

Table 7. Heat of formation, binding energy (in KJ.mol^{-1}) and dipole moment (in Debye) for ligand, (L) and its metal complexes using HyperChem-8.0.7 program

Comp.	PM3			ZINDO/1			AMBER	
	ΔH_f°	ΔE_b	μ	ΔH_f°	ΔE_b	μ	$\Delta E_b = \Delta H_f^\circ$	μ
L	17.09737	3146.68162-	1.73	-8705.7206	-12205.5026	3.23	----	----
CoL	330.3585-	3953.05357-	4.78	-6958.85848	-10581.55348	9.57	----	----
NiL	185.61811-	-3673.94011	4.32	-6893.90242	-10382.22442	6.30	----	----
CuL	175.42755-	3776.42255-	2.22	-6999.43292	-10600.42792	5.17	----	----
PdL	----	----	----	----	----	----	88.4691	3.35
PtL	----	----	----	----	----	----	255.7924	4.06
AuL	----	----	----	----	----	----	89.5963	3.22

5. Conclusion

Mannich base ligand complexes have been successfully synthesized using the conventional method. The assembly of the six proposed complexes was successfully achieved by the procedures previously described. The results obtained from this investigation were obtained according to the data presented by the physical and chemical analysis. The results showed that the complexes have an octahedral geometry for the cobalt, nickel, copper, and platinum complexes and a square-planer geometry for the palladium and gold complexes. Ni complex showed good activity against positive and negative bacteria and fungi compared to amoxicillin and metronidazol. The standard heat of formation and binding energy was calculated using the hyperchem 8.0.7 program, proving that the complexes are more stable than the ligand.

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