



SYNTHESIS, CHARACTERIZATION, AND ENZYME ACTIVITY OF Co(II), Ni(II), Cu(II), Pd(II), Pt(IV) AND Cd(II) COMPLEXES WITH 2-THIOXOIMIDAZOLIDIN-4-ONE DERIVATIVE

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ABSTRACT

A series complexes of Co(II), Ni(II), Cu(II), Pd(II), Pt(IV) and Cd(II) were synthesized with new heterocyclic ligand 3-{{(Z)-(4-nitrophenyl) methylidene} amino}-2-thioxoimidazolidin-4-one. This ligand was characterized by C.H.N.S analysis, FTIR, UV-Vis, ¹H NMR, ¹³C NMR and Mass spectral analysis. The synthesized complexes were identified and their geometrical were suggested in solid state by using (FT-IR) and (UV-Vis) spectroscopy, elemental analysis (C.H.N.S), flame atomic absorption technique, in addition to magnetic susceptibility and conductivity measurements. The enzyme activity of the ligand and its complexes has been extensively studied on GOT and GPT.

Key words: Schiff base, 2-Thioxoimidazolidin-4-one, 2-Thioxoimidazolidin-4-one complexes, Spectral data, Enzyme activity.

INTRODUCTION

The first 2-thioxo-imidazolidin-4-one was prepared in 1890 by Klason^{1a,b}. 2-Thioxoimidazolidin-4-one belongs to heterocyclic compound, which has a wide range of biological and pharmacological properties², such as antimicrobial activity (antifungal, antibacterial)³, antitumor⁴, antiinflammatory⁵, anti HIV⁶, Anticonvulsant⁷. hypoglycemic⁸ effects. Thioxoimidazolidin is a five membered heterocyclic ring with two nitrogen atoms and contain two groups, thion (C=S) and carbonyl (C=O) at position, 2 and 4, respectively⁹. The coordination properties of 2-thioxoimidazolidin-4-one could produce promising biologically active substances^{10,11}. This motivated us to synthesize new metal complexes of a new Schiff base [3-{{(Z)-(4-nitrophenyl) methylidene} amino}-2-thioxoimidazolidin-4-one] [L] to investigate the coordination behavior of the new ligand toward some divalent metal ions, then compare the enzyme activities of ligand with the metal complexes.

EXPERIMENTAL

Instrumentation

Melting points were recorded on a GallenkampMF B600 melting point apparatus. Elemental analyses (C.H.N.S) were obtained using EA-034.mth. for ligand and their metal complexes. Metal contents

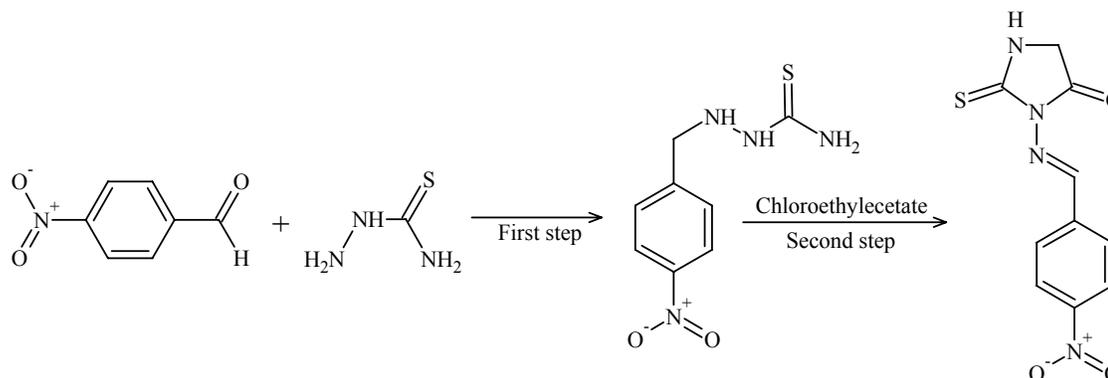
of complexes were estimated Spectrophotometrically using Flame atomic absorption Shimadzu-670 AA Spectrophotometer. Infrared spectra were recorded using FT-IR-8300 Shimadzu in the range of $(4000-350) \text{ cm}^{-1}$, samples were measured as (CsI) disc. Magnetic susceptibilities of samples in the solid state were measured by using Magnetic Susceptibility Balance of Sherwood Scietifi. The molar conductivity was measured by using Electrolytic Conductivity Measuring set Model MC-1-Mark V by using platinum electrode (EDC 304) with cell constant (1 cm^{-1}) , concentration (10^{-3} M) in dimethylformamide as a solvent at room temperature. Electronic spectra were obtained using UV-1650 PC-Shimadzu Spectrophotometer at room temperature. The measurement were recorded using a concentration of (10^{-3} M) of the ligand and its metal complexes.

Materials and methods

All chemical were of highest purity and were used as received.

Synthesis of ligand (L)

(0.02 mole, 3.0 g) 4-nitrobenzaldehyde was dissolved in 30 mL absolute ethanole, and then (0.02 mole, 1.8 g) thiosemicarbazide was added. The reaction mixture was refluxed for 4 hrs., then the resulting mixture was poured into crushed ice and stirred for 15 min. from the product (0.01 mole) and chloroethylacetate (0.01 mole, 1.225 g) were dissolved in 30 mL ethanol¹². The mixture was stirred for a few minutes, and then added (0.02 mole, 1.64 g) sodium acetate was added to the mixture. The mixture was refluxed for 6 hr. after cooling the precipitate was filtered off and recrystallization from ethanol (Scheme 1).



Scheme 1: Synthesis of Ligand (L)

Synthesis of metal complexes (R₁-R₆)

An ethanolic solution of each of the following metal ions salts (0.05 mmol) [CoCl₂.6H₂O, NiCl₂.6H₂O, CuCl₂.2H₂O, H₂PtCl₄.6H₂O, PdCl₂.6H₂O, and CdCl₂.4H₂O] was added to an ethanolic solution (0.264 g, 1 mmol) of (L). The reaction mixture was heated under reflux for (2-3) hours, during this time a precipitate was formed. The product was filtered off, washed with hot ethanol, followed by cold water and then dried under vacuum. All complexes were identified by elemental analysis (C.H.N.S), flame atomic absorption, FT-IR and Uv-Vis spectrophotometers, magnetic and conductivity measurements.

Study of enzyme activities for (L) ligand and their metal complexes (R₁-R₆)

Measurement of GOT and GPT activities

GOT and GPT activity was measured against reagent blank by using a RANDOX kit/UK, as shown in Table 1.

Table 1: Steps followed to measure GOT and GPT

	Blank (1)	Without	Blank (2)	With
Serum	-	100 μ L	-	100 μ L
Buffer	500 μ L	500 μ L	500 μ L	500 μ L
Distilled water	100 μ L	-	100 μ L	-
DMSO	100	100 μ L	-	-
Tested compound (in DMSO)	-	-	100 μ L	100 μ L

The tubes were incubated for 30 min. at 37°C and 20°C then 500 μ L of 2,4-DNPH were added to all tubes. The test tubes were allowed to stand for 20 min. at room temperature and then 500 μ L of NaOH were added to all tubes. After 5 min. the absorbance was read against blank at 546 nm¹³.

The effect of compounds on the activities of GOT and GPT enzymes in human serum

A set of stock solution (0.01 M) of selected compounds [L and R₁-R₆] was prepared by dissolving each compound in DMSO, then working solution (10⁻³ M) were prepared by diluting with DMSO. GOT and GPT activities were measured according to Table 1 in which 500 μ L of buffer were mixed with 100 μ L of serum (as the enzymes source) and 100 μ L of DMSO.

In the presence of synthesized compounds, the same steps were followed by using 100 μ L of the prepared compounds (dissolved in DMSO). The inhibition and activation percentage were calculated by comparing the activity with and without selected compounds under the same conditions, according to the equation¹³:

$$\% \text{ Inhibition} = 100 - \left(\frac{\text{The activity in the presence of inhibitor}}{\text{The activity in the absence of inhibitor}} \right) \times 100$$

$$\% \text{ Activation} = 100 \times \left(\frac{\text{The activity in the presence of activator}}{\text{The activity in the absence activator}} \right) - 100$$

RESULTS AND DISCUSSION

Elemental analyses

The physical and analytical data of the (L) ligand and (R₁-R₆) metal complexes are given in Table 1. The results obtained from elemental analysis are in satisfactory agreement with the calculated value. The suggested molecular formula was also supported by spectral measurement as well as magnetic moment. The new (R₁-R₆) complexes colored crystalline solid were soluble in (CH₂Cl₂, CHCl₃, DMF and DMSO). They are thermally stable and unaffected by atmospheric oxygen and moisture.

Table 2: Physical properties and elemental analysis of ligand and its metal complexes (R₁-R₆)

Comp. Symbol	General formula	M.wt. (g.mol ⁻¹)	Color	M.P (°C)	Elemental analysis (%)				
					Found (Calc.)				
					C	H	N	S	M
L	C ₁₀ H ₈ N ₄ O ₃ S	264	Yellow	252-254	44.74 (45.45)	3.26 (3.05)	21.72 (21.20)	11.95 (12.13)	-
R ₁	[Co(L ₂) ₂ Cl ₂]	657.93	Yellowish-brown	291	37.02 (36.48)	2.96 (2.43)	17.89 (17.02)	9.69 (9.73)	9.01 (8.96)

Cont...

Comp. Symbol	General formula	M.wt. (g.mol ⁻¹)	Color	M.P (°C)	Elemental analysis (%)				
					Found (Calc.)				
					C	H	N	S	M
R ₂	[Ni(L ₁) ₂ Cl ₂]	545.69	Orange	336	35.25 (35.67)	2.93 (3.11)	20.52 (21.03)	11.93 (12.08)	10.76 (10.94)
R ₃	[Cu(L ₁)Cl ₂ .H ₂ O]	568.546	Dark brownish	274	33.77 (33.89)	3.17 (3.36)	19.69 (20.11)	11.26 (11.76)	11.18 (12.03)
R ₄	[Pt(L ₂) ₂ Cl ₂]Cl ₂	865.078	Dark-brown	342	27.69 (27.74)	2.02 (1.85)	13.14 (12.95)	7.30 (7.39)	22.37 (22.55)
R ₅	[Pd(L ₂) ₂]Cl ₂	705.42	Brown	288	34.65 (34.02)	2.84 (2.27)	16.49 (15.88)	9.19 (9.07)	15.73 (15.09)
R ₆	[Cd(L ₂) ₂]Cl ₂	711.41	Off white	318	33.68 (33.74)	2.40 (2.25)	16.29 (15.74)	9.12 (8.99)	15.72 (15.80)

Mass spectrum of Ligand (L)

The mass spectrum of ligand (L) Fig. 1, showed the parent ion peak at ($m/z = 264$), as a base peak, which corresponds to (M^+). The others fragments and their relative abundances and fragmentation pathways are shown in **Scheme 2**:

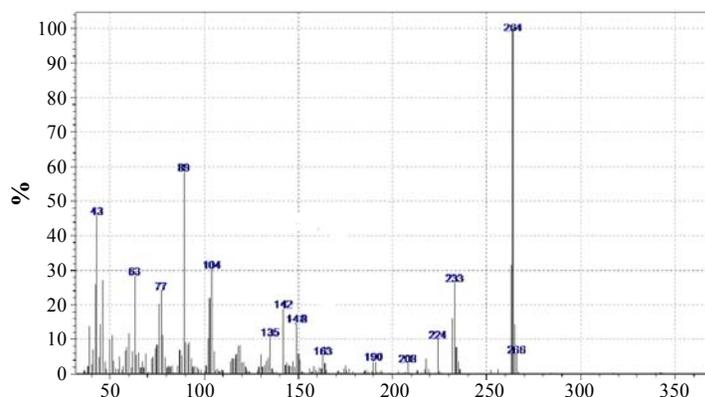


Fig. 1: Mass spectrum of Ligand (L)

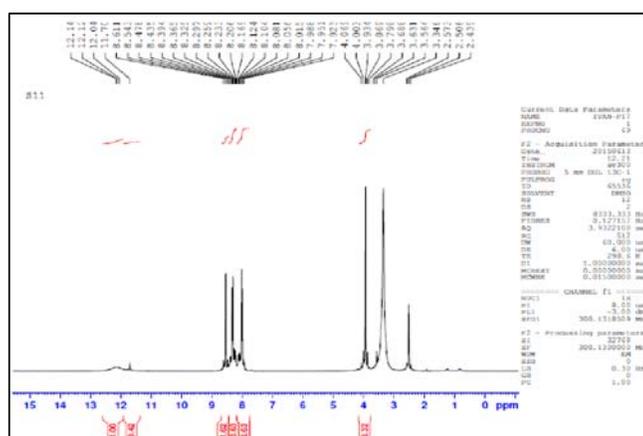


Fig. 2: ¹H-NMR spectrum of (L) in DMSO-d₆

^{13}C -NMR spectrum of ligand

^{13}C -NMR spectrum of ligand, Fig. 3, in DMSO-d_6 exhibited chemical shifts, at (174.22, 167.87, 154.19 and 33.34 ppm) assigned to carbonyl carbon atom, carbon of (C=S) group of imidazolidine ring, carbon atom of (C=N) group of azomethane ring and carbon atom of (CH_2) group, respectively, chemical shifts at (148.18, 140.70, 129.70, 124.03) attributed to carbon atoms of aromatic ring^{14,15}.

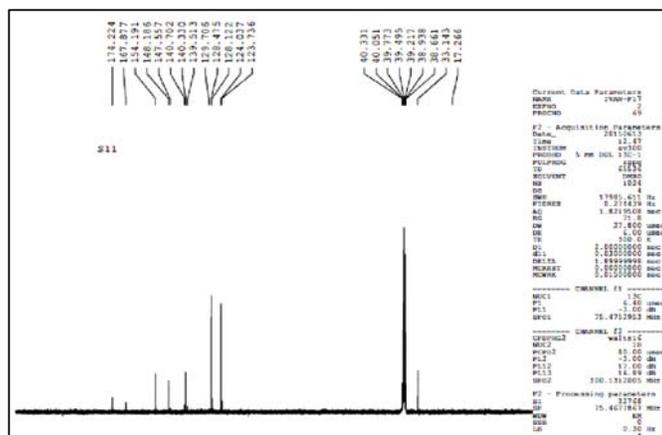


Fig. 3: ^{13}C -NMR spectrum of (L) in DMSO-d_6

FTIR Spectra of ligand (L) and their metal complexes (R_1 - R_6)

FTIR spectra of the ligand and its complexes and important vibration modes are listed in Table 2.

FTIR spectrum of the ligand showed bands at (3128 cm^{-1}) due to $\nu(\text{N-H})$ vibration of thioxoimidazolidine ring, also observed at complexes spectra, this mean that this group does not participates in coordination, spectrum of the ligand showed band at (1708 cm^{-1}) attributed to $\nu(\text{C=O})$ vibration¹⁴, This band not change in all complexes of ligand. Various changes have occurred at frequencies of $\nu(\text{C=N})$ vibrations of Schiff base and thione group, were the first observed at (1635 cm^{-1}) in the spectrum of free ligand shifted by ($13\text{-}46\text{ cm}^{-1}$) to a lower frequencies in the spectra of complexes as shown in Table 2, The $\nu(\text{C=S})$ vibration which observed at (1099 cm^{-1}) in free ligand shifted by ($15\text{-}54\text{ cm}^{-1}$) to a lower frequencies, These two different behaviors indicated the involvement of (C=N) group of Schiff and thion group in the coordination with metal ions. The frequencies of $\nu(\text{M-N})$ and $\nu(\text{M-S})$ in the spectra of complexes were observed at ($535\text{-}528\text{ cm}^{-1}$) and ($462\text{-}455\text{ cm}^{-1}$), respectively¹⁶.

Table 3: FTIR spectral data (cm^{-1}) of ligand and its metal complexes

Comp.	L	R_1	R_2	R_3	R_4	R_5	R_6
$\nu(\text{N-H})$	3329 (w)	3259 (w)	3287 (w)	3259 (w)	3240 (w)	3263 (w)	3254 (w)
$\nu(\text{C=O})$	1708 (s)	1707 (m)	1708 (m)	1705 (m)	1710 (m)	1708 (m)	1705 (m)
$\nu(\text{C=N})$	1633 (s)	1620 (s)	1589 (s)	1620 (s)	1593 (s)	1620 (s)	1587 (s)
$\nu(\text{C=S})$	1099 (m)	1072 (s)	1076 (w)	1078 (m)	1072 (m)	1082 (m)	1062
$\nu(\text{M-N})$	-----	535 (w)	530 (w)	528 (w)	533 (w)	530 (w)	533 (w)
$\nu(\text{M-S})$	-----	462 (w)	458 (w)	460 (w)	455 (w)	462 (w)	458 (w)

Where : S = Strong, W = Weak, M = Medium

Electronic absorption spectra, magnetic susceptibility, and conductivity measurements

The (U.V-Vis) spectrum of ligand, in absolute ethanol exhibited three absorption bands at (218 nm, 45871 cm^{-1}), (255 nm, 39215 cm^{-1}) were assigned to ($\pi \rightarrow \pi^*$) transitions, and band at (308 nm, 32467 cm^{-1}) assigned to ($n \rightarrow \pi^*$) transitions¹⁴. Complexation of (L) with metal ions appearance a new bands in the visible and UV. These bands were attributed to M-L charge transfer and to ligand field transitions. Table 3 describes bands of maximum absorption of (R₁-R₆) complexes in chloroform with their assignments.

The electronic spectrum of the (R₁) complex showed two transitions at (644 nm, 15527 cm^{-1}) and (545 nm, 18018 cm^{-1}), which might be assigned to the transition ${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g(\text{F})}$ (\mathbf{v}_2) and ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g(\text{P})}$ (\mathbf{v}_3) respectively^{17,18}, these indicate an octahedral geometry. On the basis of these assignment it was possible to calculate (\mathbf{v}_1) for d^7 of (Tanaba-Sugano) diagram, the calculated value of (\mathbf{v}_1) to be (7612) cm^{-1} due to the transition ${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g(\text{F})}$. The magnetic susceptibility and molar conductivity measurement indicated that the complex to be a paramagnetic (4.4 B.M) and non conducting.

The electronic spectrum of (R₂) complex, shows two bands, (698 nm, 14326 cm^{-1}) and (420 nm, 23809 cm^{-1}) assigned to ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g(\text{F})}$ (\mathbf{v}_2) and ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g(\text{P})}$ (\mathbf{v}_3) transitions respectively¹⁹. These bands indicate an octahedral geometry around Ni (II)ion, the calculated value of (\mathbf{v}_1) to be (881 nm, 11341 cm^{-1}), may be attributed to the transition ${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g(\text{F})}$ ^{17,19}. The magnetic value (3.22 B.M) for Ni(II) is observed and it is within the range of (2.8-3.5 B.M)^{20,21}. This agree with octahedral geometry around Ni(II) ion. The conductance measurements indicate the non-ionic behavior of this complex.

The electronic spectrum of (R₃) complex shows one broad band at (602 nm, 16393 cm^{-1}), which corresponds to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$ transition, and a shoulder band at (380 nm, 26315 cm^{-1}), which assigned to MLCT transition²². The position of these bands is in a good agreement with octahedral configuration. The value of magnetic moment at room temperature was found to be (1.82 B.M), which agree well with distorted octahedral geometry around Cu(II) complex^{18,22,23}. Conductivity measurement in DMF showed that the complex non-ionic behavior.

The electronic spectrum of (R₄) complex, shows bands, (525 nm, 19047 cm^{-1}), (438 nm, 22831 cm^{-1}) and (355 nm, 28169 cm^{-1}) assigned to ${}^1\text{A}_{1g} \rightarrow {}^3\text{T}_{1g}$, ${}^1\text{A}_{1g} \rightarrow {}^3\text{T}_{2g}$ and (L \rightarrow M_{CT}), respectively^{19,21,23}. The complexes may have an octahedral coordination of the central metal ion by the surrounding ligands. The magnetic value (1.2 B.M) for Pt(IV) is observed, this agree with octahedral geometry around Pt(IV)ion²²⁻²⁴. The conductance measurements indicate the ionic behavior of this complex.

The electronic spectrum of (R₅) complex, shows two bands, (485 nm, 20491 cm^{-1}) and (420 nm, 23809 cm^{-1}) assigned to ${}^1\text{A}_{1g} \rightarrow {}^1\text{B}_{1g}$ and ${}^1\text{A}_{1g} \rightarrow {}^1\text{E}_g$ transitions, respectively^{18,22,24}. The complex may have a square-planar coordination of the central metal ion by the surrounding ligands. The magnetic moment data of Pd(II) complexes indicate that this complex is diamagnetic. This agree with square-planar geometry around Pd(II) ion^{18,23}. The conductance measurements indicate the ionic behavior of this complex.

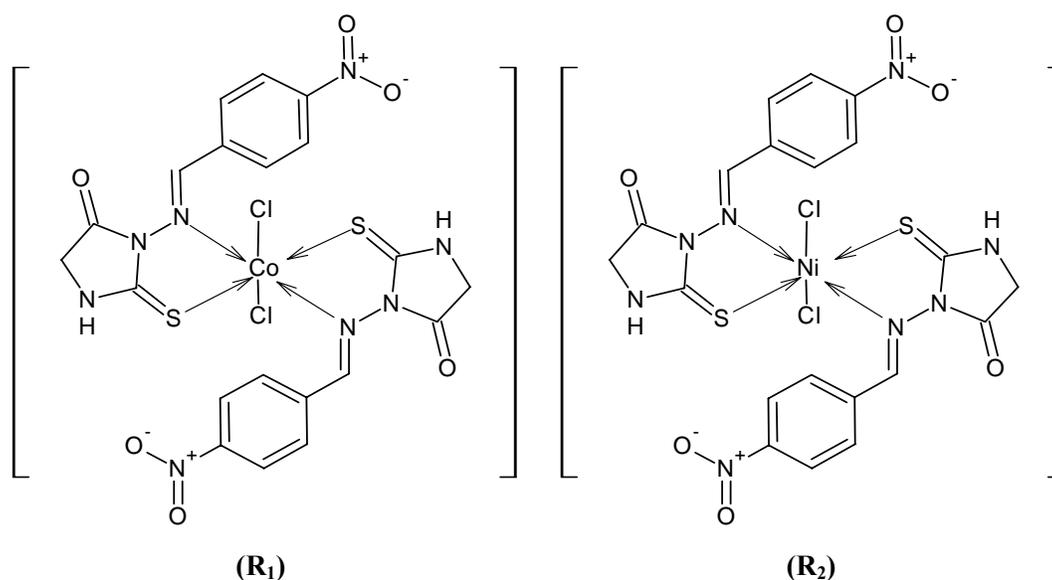
According to the electronic spectrum of (R₆) complex, no d-d transition is located as it belongs to d^{10} . The prepared complexes are off white in color with the diamagnetic being expected, The U.V-Vis spectrum of (R₆), in CHCl_3 , displayed three bands at (258 nm, 38959 cm^{-1}), (273 nm, 36630 cm^{-1}) and (350 nm, 28571 cm^{-1}), respectively, assigned to ($\pi \rightarrow \pi^*$), ($n \rightarrow \pi^*$) and (M \rightarrow L_{CT}) transitions^{18,22,23}. The conductivity measurements indicate ionic conducting behavior of the complex.

Table 4: Electronic spectra, magnetic moment (B.M) and conductance in (DMF) for (R₁-R₆) complexes

No.	Maximum absorption $\nu_{\max}(\text{cm}^{-1})$	Band assignment	B ^s	β	10Dq	Molar Cond. $\text{S.cm}^2.\text{mol}^{-1}$	$\mu_{\text{eff.}}$ B.M.	Suggested geometry
(R ₁)	15527	${}^4\text{T}_{1g} \rightarrow {}^4\text{A}_{2g}$ (F)	380	0.39	7421.7	16.69	4.4	O.h
	18348	${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{1g}$ (P)						
	7612	${}^4\text{T}_{1g} \rightarrow {}^4\text{T}_{2g}$ (F)) (calc.)						
(R ₂)	14326	${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$ (F)	503	0.45	11066	16.49	3.22	O.h
	23809	${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{1g}$ (P)						
	11341	${}^3\text{A}_{2g} \rightarrow {}^3\text{T}_{2g}$ (F)						
(R ₃)	16393	${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$	----	----	----	15.49	1.82	O.h
	26315	LMCT						
(R ₄)	19047	${}^1\text{A}_{1g} \rightarrow {}^3\text{T}_{1g}$	----	-----	-----	171	1.2	O.h
	22831	${}^1\text{A}_{1g} \rightarrow {}^3\text{T}_{2g}$						
	28169	LMCT						
(R ₅)	20491	${}^1\text{A}_{1g} \rightarrow {}^1\text{B}_{1g}$	-	-	-	177	0.0	S.p
	23809	${}^1\text{A}_{1g} \rightarrow {}^1\text{E}_g$						
(R ₆)	38759	$\pi \rightarrow \pi^*$	----	----	---	170	0.0	T.h
	36630	$n \rightarrow \pi^*$						
	28571	MLCT						

Suggested chemistry structure of metal complexes (R₁-R₆)

According to the results obtained from elemental and spectral analysis as well as magnetic moment and conductivity measurements, the structure of the above mentioned compounds can be illustrated as follows, Fig. 4.



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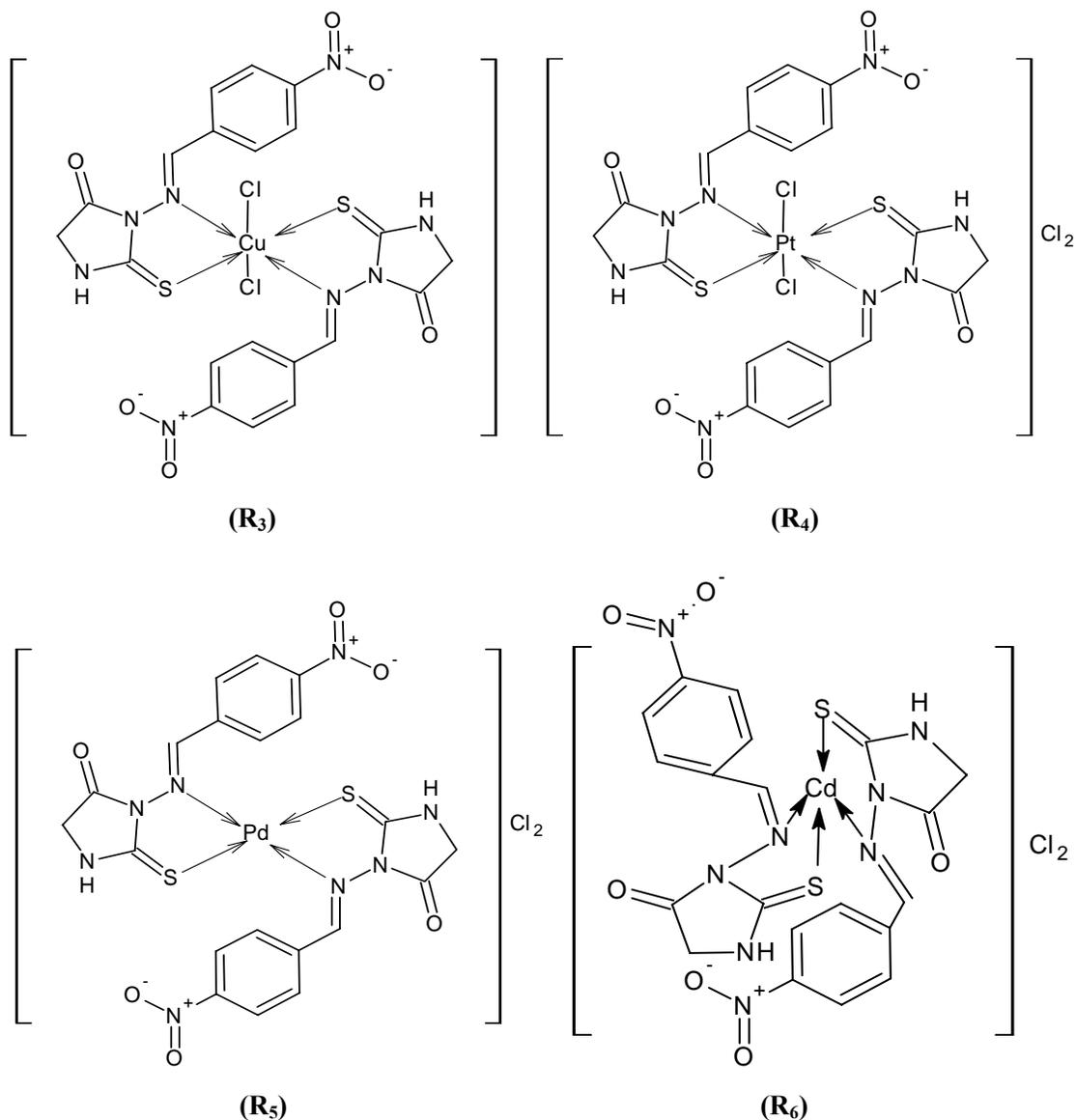


Fig. 4: Suggested chemistry structure of metal complexes (R₁-R₆)

Enzyme activity studies

The results of L showed that L, R₁, R₂, R₃, and R₄ cause decrease in GOT activity in the following order R₁ > R₃ > R₂ > L = R₄ as shown in Table 5 and Fig. 5 while R₆ and R₅ showed high activation effects on GOT Enzyme as in Table 5.

The results in Table 6 and Fig. 6 have also showed that GPT is activated by the effect of some compounds in the following order R₅ >> R₁ > R₂ > R₄ > R₆ = L and was inhibited by compound [R₃].

Our results have revealed that the examined 3-[(Z)-(4-nitrophenyl) methylidene] amino}-2-thioxoimidazolidin-4-one ligand inhibit or activated both GOT and GPT Enzyme to different extents possibly due to the different nature and amino acid content hence the structure of the two enzymes. On the other hand, the presence of different functional groups in the ligand might exhibit different inhibition effects on the enzyme^{25,26}

The results obtained from this study have shown that the prepared complexes have variable effects on the enzymatic activities of GOT and GPT and it can be noticed from Tables 5 and 6 that some complexes exhibit an activation effect on both enzymes while other complexes inhibit their activities, these results can be attributed to several factors including the metal type, the ligand type and its donor atoms^{25,26}.

Table 5: Activity of GOT Enzyme in presence and absence of Ligand (L) and metal complexes (R₁-R₆)

Symbol	Activity of Enzyme		Inhibition (%)	Activation (%)
	With	Without		
L	42	-	32	-
R ₁	2	-	96	-
R ₂	38	-	38	-
R ₃	4	62	93	-
R ₄	42	-	32	-
R ₅	66	-	-	6.5
R ₆	70	-	-	12.6

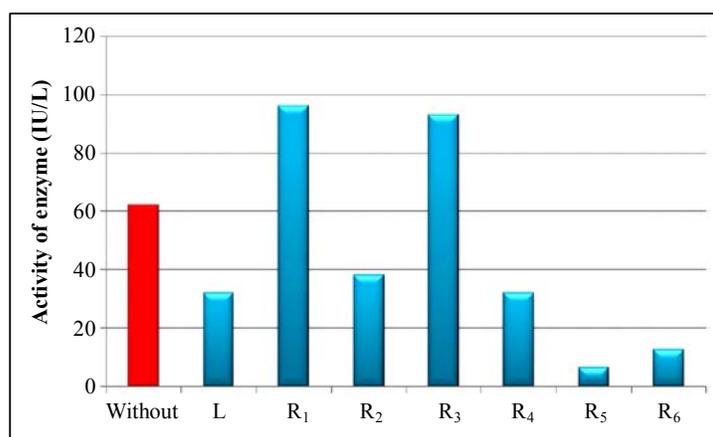


Fig. 5: Activity of GOT enzyme in presence and absence of (L) and its metal complexes (R₁-R₆)

Table 6: Activity of GPT enzyme in presence and absence of Ligand (L) and metal complexes (R₁-R₆)

Symbol	Activity of Enzyme		Inhibition (%)	Activation (%)
	With	With out		
L	21	-	-	5
R ₁	29	-	-	45
R ₂	27	-	-	35
R ₃	12	20	40	-
R ₄	25	-	-	25
R ₅	48	-	-	140
R ₆	21	-	-	5

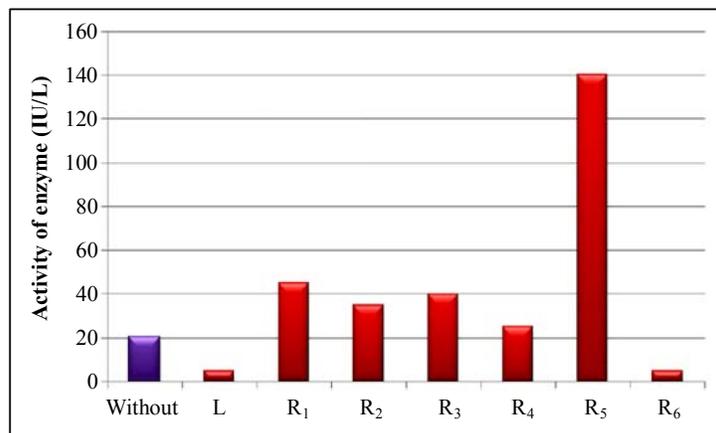


Fig. 6: Activity of GPT enzyme in presence and absence of (L) and its metal complexes (R₁-R₆)

CONCLUSION

The new 3-[(Z)-(4-nitrophenyl) methylidene] amino}-2-thioxoimidazolidin-4-one (**L**) ligand and its metal complexes (R₁-R₆) were successfully synthesized and characterized. The free ligand and its metal complexes show significant enzyme activity in activation or inhibition.

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