

# Synthesis, Characterization and Biological Approach of N'-(3-(Hydroxy Imino) Butan-2-ylidene)-2-Oxo-2H-Chromene-3-Carbohydrazide Complexes

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## Abstract

A series of metal complexes of Cu(II), Co(II), Ni(II), Cd(II) and Hg(II) complexes with N'-(3-(hydroxyimino) butan-2-ylidene)-2-oxo-2H-chromene-3-carbohydrazide ( $H_2L$ ) were prepared. The structures illuminated by elemental and thermal analysis, besides spectroscopic methods (IR,  $^1H$  NMR, and UV-visible, MS) and physical measurements (molar conductance and magnetic susceptibility). In addition, DFT method used to approve the geometry of solid complexes. From conductometric measurements, all complexes were non-electrolytic and formed by molar ratio 1:2 expect Hg(II) complexes by 1:1. Moreover, the biological activity (Antibacterial, antifungal and DNA binding) performed for all prepared compounds.

**Keywords:** Coumarin compounds; Spectroscopy; DFT; Biological activity

## Introduction

Coumarin family considered an essential heterocyclic compounds which belong to benzopyrones family that contains of phenyl ring fused with a pyrone ring [1,2]. Coumarin classified into six groups count on chemical structure of compounds and these group are simple (coumarins, bi coumarins, phenyl coumarins, pyrano coumarins, furano coumarins and dihydrofurano coumarins) [3] Coumarin mainly existed in plant kingdom such as (leaves, roots, stems and fruits). Besides, they found in different oils as "lavender oil, cinnamon bark, oil and cassia oil" [4]. Moreover, coumarin derivatives have changed uses such as "optical brightening agents, laser dyes, cosmetic industry agrochemical industries and food additives" [5-7]. Furthermore, Coumarin derivatives have important biological activity as antibacterial, antifungal, anti-oxidant, anti-allergic, anti-inflammatory, anti-thrombotic, hepatoprotective, anti-viral, anti-carcinogenic activities [8-10]. So, this study involved the biological estimation of N'-(3-(hydroxyimino) butan-2-ylidene)-2-oxo-2H-chromene-3-carbohydrazide ( $H_2L$ ) and its metal complexes.

## Experimental

### Materials and reagents

All materials and reagents used obtained since viable sources such as (Aldrich, Fluka, or Merck). They involved (a) 2-oxo-2H-chromene-3-carbohydrazide and diacetyl monoxime as (organic substances), (b)  $[Cu(CH_3COO)_2] \cdot H_2O$ ,  $[Ni(CH_3COO)_2] \cdot 4H_2O$ ;  $[Co(CH_3COO)_2] \cdot 4H_2O$ ;  $HgCl_2$  and  $CdSO_4$  as (metal salts), and (c) absolute ethanol, dimethylformamide, dimethyl sulfoxide and diethyl ether as solvents.

### Instrumentations

IR spectrum noted on" Mattson 5000 FTIR Spectrophotometer" in the series (4000-400)  $cm^{-1}$  in "KBr" disk. The electronic spectra of the complexes verified in "DMSO" solution using a "Shimadzu UV 240 (P/N 204-58000) spectrophotometer"(USA) in the scale (200-900) nm. "Magnetic moment values" were calculated at room temperature ( $25 \pm 1^\circ C$ ) using a "Johnson Matthey magnetic susceptibility balance" using  $Hg[Co(SCN)_4]$  as calibrant  $^1H$  NMR spectra of the ligand, diamagnetic complexes were detailed in "DMSO" on an "EM-390 (200 MHz) spectrometer". The percentage of C and H determined by using "Perkine Elmer 2400 Series II" in the Micro Analytical Center, Cairo University. Molar conductance of complexes measured *via* organizing

( $10^{-3}M$ ) solutions of complexes in DMF at ( $25^\circ C$ ) and dignified on an "YSI Model32" conductivity bridge. The specific conductance values were detailed by conductivity bridge "HANNA, H1 8819N" with a cell constant equivalent to (1)  $cm^{-1}$ . The conductometer connected with ultra-thermostat of the type "Kottermann 4130" too a digital thermometer.

### Synthesis of $H_2L$

By mixing between 2-oxo-2H-chromene-3-carbohydrazide (0.01 mole, 2.04 g) and diacetyl monoxime (0.01 mole, 1.01 g) in 50 ml ethanol in presence of 3 drops of (GAA) (Figure 1). By refluxing 3 hours. After that, filter the precipitate and recrystallized from absolute ethanol. The analytical and physical properties collected in Table 1.

### Synthesis of metal complexes

The solid complexes performed *via* count identical amount of  $H_2L$  with hot ( $C_2H_5OH$  and/or  $H_2O$ ) of  $HgCl_2$ ;  $CdSO_4$  and  $Ni(II)$ ;  $Co(II)$ ;  $Cu(II)$  as acetate salt. The mix refluxed on a water bath for (3 hours). The formed precipitate filtered off, washed with hot absolute ethyl alcohol.

### Molecular modelling

Using Materials Studio package to calculated cluster calculations through DMOL3 [11]. The DFT method used to analyze of geometry of the sequestered complexes *via* "GAUSSIAN 09" program set [12]. The "DNP" source groups are of equivalent course to "6-31G" Gaussian basis groups [13]. The Gaussian basis groups are fewer accurate than DNP basis sets of the same size [14]. The brilliant exchange-correlation functional considered constructed on the (GGA) and (RPBE) functional [15].

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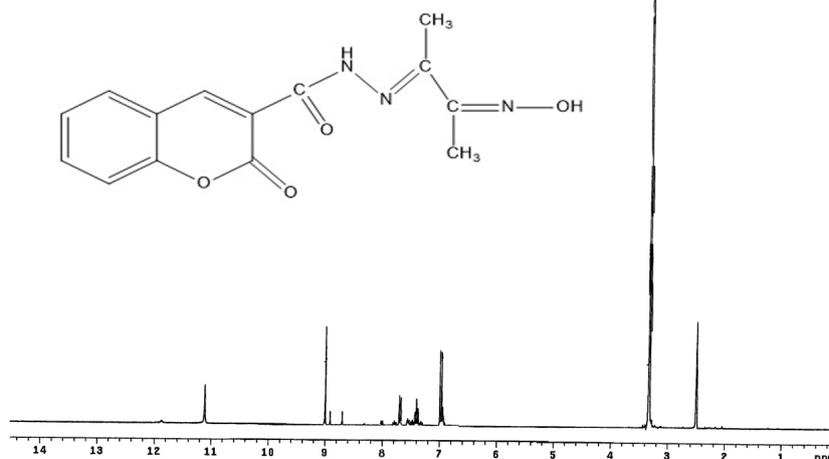


Figure 1: HNMR spectrum of N'-(3-(hydroxyimino) butan-2-ylidene)-2-oxo-2H-chromene-3-carbohydrazone in DMSO.

No	Compound	formula	MWt	Yield	colour	m.p	Found (Calculated)			
							C	H	M	X
1	H <sub>2</sub> L	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub>	287.29	80	Pale yellow	290	(58.53) (59.00)	(4.56) (4.00)	- -	- -
2	[Cu(H <sub>2</sub> L) <sub>2</sub> (OAc) <sub>2</sub> ]	CuC <sub>32</sub> H <sub>32</sub> O <sub>12</sub> N <sub>6</sub>	756.22	80	Green	>300	(29.15) (28.65)	(4.26) (4.41)	(8.40) (8.91)	
3	[Cd(H <sub>2</sub> L) <sub>2</sub> (SO <sub>4</sub> )]	CdC <sub>28</sub> H <sub>28</sub> N <sub>6</sub> O <sub>12</sub> S	783.05	70	yellow	>300	(42.95) (42.50)	(3.35.) (3.00)	(14.35) (13.80)	(12.27) (11.80)
4	[Ni(H <sub>2</sub> L) <sub>2</sub> (OAc) <sub>2</sub> ]	NiC <sub>32</sub> H <sub>32</sub> O <sub>12</sub> N <sub>6</sub>	751.36	80	Reddish brown	>300	(51.14) (50.70)	(4.29) (4.80)	(7.84) (8.00)	- -
5	[Co(H <sub>2</sub> L) <sub>2</sub> (OAc) <sub>2</sub> ]	CoC <sub>32</sub> H <sub>32</sub> O <sub>12</sub> N <sub>6</sub>	751.603	75	Reddishbrown	>300	(51.14) (50.80)	(4.29) (3.80)	(7.84) (8.00)	- -
6	[Hg(H <sub>2</sub> L)(Cl) <sub>2</sub> (H <sub>2</sub> O)]	HgC <sub>14</sub> H <sub>15</sub> O <sub>5</sub> N <sub>3</sub> Cl <sub>2</sub>	576.91	80	brown	>300	(29.15) (28.65)	(2.62) (3.12)	(34.77) (34.20)	(12.31) (12.6)

X=Cl

Table 1: Elemental analysis and physical data of H<sub>2</sub>L and its metal complexes.

### Antibacterial and antifungal activities in terms of minimum inhibitory concentration

Using disc diffusion technique to govern MIC of the isolated compounds [16]. These involved (+ve) gram "Staphylococcus aureus, Bacillus subtilis". However, (-ve) gram "Escherichia coli, Pseudomonas aeruginosa" as bacteria, (Candida albinos, Aspergillus flavus) as fungi. By ampicillin (1000 µg/ml) as standard antibacterial, then Clotrimazole (1000 µg/ml) as standard antifungal. A (1000 µg/ml) standard solution of the studied compounds in DMSO was set and immunized media parallel running to the examination compounds at the same condition. The microorganism suspensions at (10 CFU/ml- colony forming unit/ml) concentration were immunized to the agreeing wells. Raising plate's temperature to (36°C) for one day. Finally, MIC values recorded as the lowest concentration of substances, which have no visible turbidity.

### Colorimetric assay for compounds that bind DNA

(20 mg) DNA methyl green suspended in (100 ml) of (0.05 M) Tris-HCl as buffer (pH 7.5) containing (7.5 mM) MgSO<sub>4</sub>; this mixture was stirred (24 h) at (37 °C). A series of (10,100, 1000 mg) were dissolved isolated compound in ethanol in Ependoff tubes, solvent was indifferent below vacuum, then (200 µl) of (DNA/methyl green) solution were added to all tube. Samples raised in darkness at ambient temperature. After one day, determine the absorbance at (642.5-645)

nm. The modification data for primary absorbance and normalized as the percentage of the untreated standard [17].

### Conductance measurement

The conductance was measured to (Cu, Ni and Co) as metal salts in mixture solvent (5% DMF/Methanol). The conduct metric titrations were measured (1 × 10<sup>-3</sup>) M of H<sub>2</sub>L ligand as original concentration from each metal salt solutions and using (1 × 10<sup>-4</sup>) M of these metal salt. (20) ml of salt in mixed solvent of (5% DMF-methanol) was full and titrated against small amount of ligand with (0.2) ml breaks were done as well as the (k<sub>s</sub>) specific conductance was considered. The temperature, in all quantities reached, adjusted at room temperature. The conduct metric titrations attained due to variance of metal salt concretion as titrated solutions with the ligand as a titrant.

### Results and Discussion

The types of metal complexes were obtained from the reaction of hydrazone with "Cu(II), Cd(II), Ni(II), Co(II), and Hg(II)" metal ions everywhere the ligand behaviour as (neutral mono, bi, and tridentate) manner. The molar conductivities of all solid complexes shown complexes were non-electrolysis.

### IR and <sup>1</sup>H NMR spectra

The IR spectra displayed that a significant H<sub>2</sub>L (Table 2) bands at

(3447, 3220, 1698, 1665, 1611 and 1566)  $\text{cm}^{-1}$  were assigned to  $\nu(\text{OH})_{\text{oxime}}$ ,  $\nu(\text{NH})$ ,  $\nu(\text{C}=\text{O})_1$ ,  $\nu(\text{C}=\text{O})_2$ ,  $\nu(\text{C}=\text{N})_{\text{azo}}$  and  $\nu(\text{C}=\text{N})$ , respectively [18-23]. In addition,  $^1\text{H NMR}$  spectrum of  $\text{H}_2\text{L}$  (Figure 2) was showed four signals at (11.11; 9.00; 3.30 and 2.49) ppm assignable to the protons of  $(\text{OH})_{\text{oxime}}$ ;  $(\text{NH})$ ;  $(-\text{C}(\text{CH}_3)=\text{N}(\text{OH})-)$  and  $(-\text{C}(\text{CH}_3)=\text{N}-\text{NH})$ . The signals of aromatic protons detected in (6.93-7.71) ppm. The IR spectrum of  $[\text{Cu}(\text{H}_2\text{L})_2(\text{OAc})_2]$  complex indicated that the  $\text{H}_2\text{L}$  acted as a neutral monodentate ligand coordinating through  $\nu(\text{C}=\text{O})_2$ . The coordination maintained by: (a) Band of  $\nu(\text{C}=\text{O})_2$  move to lower wave number at (1650)  $\text{cm}^{-1}$ ; (b) The appearance of new band at 530  $\text{cm}^{-1}$  that may be recognized to  $\nu(\text{Cu}-\text{O})$  and (c) the appearance of  $\nu(\text{C}=\text{O})_2$ ,  $\nu(\text{C}=\text{N})_{\text{azo}}$  and  $\nu(\text{C}=\text{N})$  nearly at the same position. Also, in  $[\text{Cd}(\text{H}_2\text{L})_2(\text{SO}_4)]$  complexes acted as neutral bidentate ligand coordinating via  $\nu(\text{C}=\text{O})_2$ ,  $\nu(\text{C}=\text{N})_{\text{azo}}$ . The complexation confirmed via: (a) the modification of  $\nu(\text{C}=\text{O})_2$  and  $\nu(\text{C}=\text{N})_{\text{azo}}$  to lower wave number at (1654 and 1545)  $\text{cm}^{-1}$ ; (b) the appearance of new bands at (568 and 457)  $\text{cm}^{-1}$  which sign to  $\nu(\text{Cd}-\text{O})$  and  $\nu(\text{Cd}-\text{N})$ ; (c) the  $^1\text{H NMR}$  spectrum proposed that  $(\text{NH}$  and  $\text{OH})$  not shared in complexation. But, in  $[\text{Ni}(\text{H}_2\text{L})_2(\text{OAc})_2]$  and  $[\text{Co}(\text{H}_2\text{L})_2(\text{OAc})_2]$  complexes acted as neutral bidentate ligand coordinating in  $\nu(\text{C}=\text{O})_1$  and  $\nu(\text{C}=\text{O})_{\text{azo}}$ . The chelation was supported by: (a) the shift of  $\nu(\text{C}=\text{O})_1$  and  $\nu(\text{C}=\text{O})_2$  to lower wave number (1670 and 1650)  $\text{cm}^{-1}$ . (b) The presence of new bands at (495)  $\text{cm}^{-1}$  which attributed to  $\nu(\text{M}-\text{O})$ . Finally, the IR spectra of  $[\text{Hg}(\text{H}_2\text{L})(\text{H}_2\text{O})(\text{Cl}_2)]$  complex acted as neutral tridentate coordinating via  $\nu(\text{C}=\text{O})_2$ ,  $\nu(\text{C}=\text{N})_{\text{azo}}$  and  $\nu(\text{NH})$ . The chelation maintained by: (a) the shift of  $\nu(\text{C}=\text{O})_2$ ,  $\nu(\text{C}=\text{N})$  and  $\nu(\text{NH})$  to lower wavenumbers (1652, 1546 and 3192)  $\text{cm}^{-1}$ . (b) Other evidence presence of new bands at (546 and 422)  $\text{cm}^{-1}$  which could be official to  $\nu(\text{Hg}-\text{O})$  and  $\nu(\text{Hg}-\text{N})$ .

### Electronic spectra and magnetic moment measurements

The electronic spectrum of  $[\text{Cu}(\text{H}_2\text{L})_2(\text{OAc})_2]$  complex (Table 3) was showed abroad band at (16501)  $\text{cm}^{-1}$  with shoulder at (14925)  $\text{cm}^{-1}$  which may be allocated to ( $^2\text{B}_{1g} \rightarrow ^2\text{E}_g$ ) and ( $^2\text{B}_{1g} \rightarrow ^2\text{A}_g$ ) transition,

$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$	$\nu(\text{C}=\text{N})_2$	$\nu(\text{C}=\text{N})_1$	$\nu(\text{C}=\text{O})_2$	$\nu(\text{C}=\text{O})_1$	$\nu(\text{NH})$	$\nu(\text{OH})$	Compound
-	-	1566	1611	1665	1698	3220	3447	1
-	530	1568	1613	1650	1701	3220	3425	2
457	568	1545	1611	1654	1710	3188	3448	3
-	495	1613	1650	1650	1676	3220	3422	4
-	495	1568	1614	1650	1670	3240	3422	5
422	546	1546	1605	1652	1712	3192	3423	6

Table 2: Most important IR spectral bands of  $\text{H}_2\text{L}$  and its metal complexes.

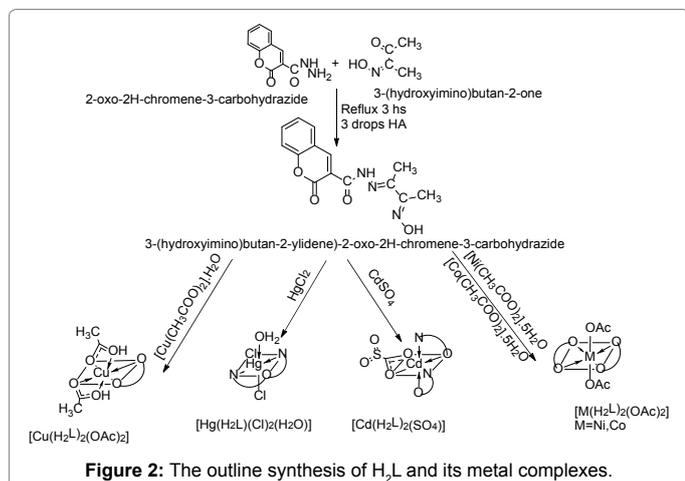


Figure 2: The outline synthesis of  $\text{H}_2\text{L}$  and its metal complexes.

individually, in tetragonally distorted an octahedral configuration. The value of magnetic moment of  $\text{Cu}(\text{II})$  complex equal to (2.1 BM) [24]. The electronic spectrum of  $[\text{Ni}(\text{H}_2\text{L})_2(\text{OAc})_2]$  complex was displayed two bands at (17094 and 28571)  $\text{cm}^{-1}$  described to ( $^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}(\text{F})$ ) besides ( $^3\text{A}_{2g} \rightarrow ^3\text{T}_{1g}(\text{p})$ ) transitions, in octahedral structure. Calculated value of ( $\text{Dq}$ ,  $\text{B}$ ,  $\beta$  and  $(\nu_2/\nu_1)$ ) values lie in the series told for an octahedral structure. In addition, the magnetic moments value (3.2 BM). The value of  $\nu_1$  (9777.89)  $\text{cm}^{-1}$  was calculated theoretically [24]. The electronic spectrum of  $[\text{Co}(\text{H}_2\text{L})_2(\text{OAc})_2]$  complex showed two bands at (17857 and 23364)  $\text{cm}^{-1}$  attributed to ( $^4\text{T}_{1g} \rightarrow ^4\text{A}_{2g}(\text{F})$ ) also ( $^4\text{T}_{1g} \rightarrow ^4\text{T}_{1g}(\text{P})$ ) transitions, individually, in an octahedral geometry. The calculated values of ( $\text{Dq}$ ,  $\text{B}$ ,  $\beta$  and  $(\nu_2/\nu_1)$ ) are good agreement with those informed for octahedral  $\text{Co}(\text{II})$  complexes. The point of  $\nu_1$  (8104)  $\text{cm}^{-1}$  was intended theoretically. In addition, the magnetic moment value (5.1) BM was proof octahedral around  $\text{Co}(\text{II})$ .

### Geometry optimization with DFT method

The structure of new compounds can be accepted in applying computational chemistry tools that is a potent protocol for construing their stabilities and calculated many structural parameters for hydrazone ligand (Table 4). DFT calculations reached to guess the host-guest interface among the hydrazone and numerous metal ions. The modeling structure of  $\text{H}_2\text{L}$  and these metal complexes appeared in Figure 3. In addition, the bond lengths and bond angles were calculated as showed in Figures 1S-13S.

### Molecular parameters

The Quantum chemical parameters (the energies of the HOMO and LUMO) of calculated compounds achieved. Furthermore, (the total energy, electrostatic energy, exchange-correlation energy, binding energy, kinetic energy, sum of atomic energy, spin polarization energy, and dipole moment) intended. From the outcome data we can supposed that The isolated complexes were stable due to the difference energies between "LUMO and HOMO" are negative values (Figure 4). While, the minor values of "HOMO" energy designate to electron donating ability of molecule is weaker. On contrasting, the highest value of "HOMO" energy stated that the molecule is a decent electron donor. However, the complexes were more stable than free ligand due to the binding energy of complexes was higher than free ligand and difference between (HOMO and LUMO) in complexes was lower than difference between (HOMO and LUMO) in free ligand. Then, the free ligand is moderate values of dipole moment in than the isolated solid complexes that enhanced the powerful activities of free ligand and showed biological activity of ligand moderate between complexes.

### Global reactivity descriptors

The LUMO ( $\pi$  acceptor) and HOMO ( $\pi$  donor) were essential parameters in quantum chemical measurements [25]. The values of HOMO was great surrounded on  $\text{O}_{13} > \text{O}_{12} > \text{O}_{11} > \text{N}_{14} > \text{C}_{16}$  atoms characteristic they capacity be the greatest well liked exposed with respect to nucleophilic attack. The value of  $E_{\text{HOMO}}$ ,  $E_{\text{LUMO}}$  and their neighboring orbitals were a sign of the highest stability of complexes [26]. The definite overlap about "HOMO and LUMO" was typically a

$\nu_2/\nu_1$	$\beta$	$\text{B} (\text{cm}^{-1})$	$\text{Dq} (\text{cm}^{-1})$	Band position ( $\text{cm}^{-1}$ )	$\mu_{\text{eff}}$ (BM)	Compound
-	-	-	-	16501, 14925	2.1	2
2.155	1.13	1101	935	23364, 17857	5.1	4
1.657	.988	1029	977	28571, 17094	3	5

Table 3: Magnetic moments, electronic spectra, and ligand field parameters of metal complexes of  $\text{H}_2\text{L}$ .

major took into version many reactions. As outcome data, the ligand orbitals along with great molecular orbital coefficients value could be the best suitable web position correct complexation. Gap energy was main index for stability supported to report the kinetic stability and chemical reactivity of the compounds [27].

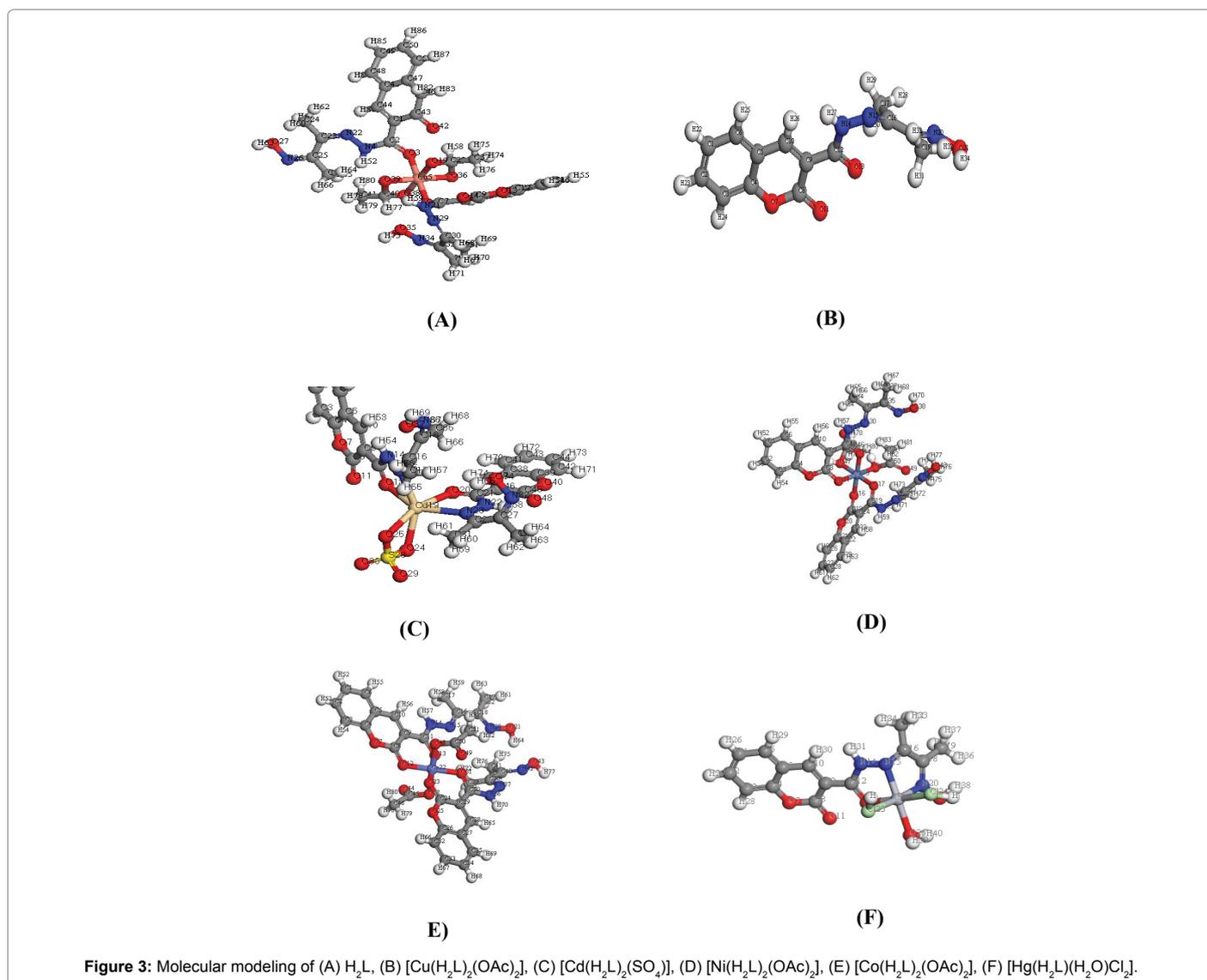
The DFT labeled the site selectivity of the molecular systems chemical reactivity and chemical reactivity. Global electrophilicity index ( $\omega$ ), Global hardness ( $\eta$ ) and global softness (S). Frontier energy of molecular orbitals ( $E_{\text{HOMO}}$  and  $E_{\text{LUMO}}$ ), energy band gap ( $E_{\text{HOMO}}$  -

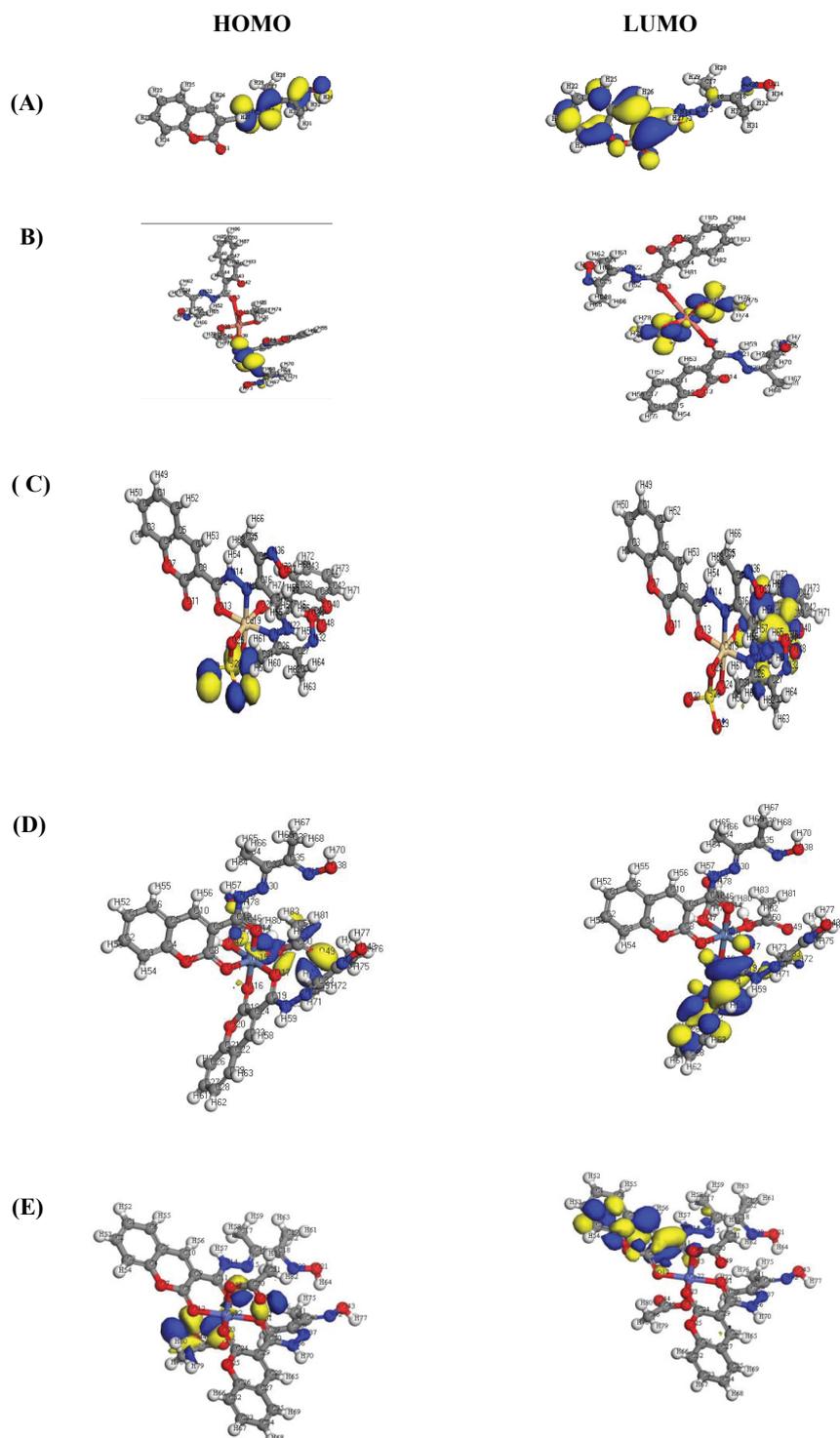
$E_{\text{LUMO}}$ ), chemical potential ( $\mu$ ), electronegativity ( $\chi$ ) [28,29], were listed in Table 5, " $X=(-1/2(EL+EH))$ " " $\mu=-X=(1/2(EL+EH))$ " " $\eta=1/2 (E_{\text{LUMO}} - E_{\text{HOMO}})$ " " $S=1/2 \eta$ " " $\omega=\mu^2/2$ "

The converse importance of the global hardness as the softness  $\sigma$  as follow: " $\sigma=(1/\eta)$ " Hardness linked to molecules stability according to Pauling the theory of electronegativity as the influence of "an atom in a molecule to attract electron to it-self". While, according to Parr et al. the electrophilicity index acted as energy value is low because of full electron transfer between donor and acceptor. The electrophilicity

Comp.	Total Energy(Ha)	Binding Energy(Ha)	Dipolemoment (debye)	HOMO (ev)	LUMO (ev)	Spin polarization energy	Exchange-correlation Energy(Ha)	Electrostatic Energy (Ha)	Kinetic Energy(Ha)	Sum of atomic Energies (Ha)
1	-1006	-6.187	7.399	-5.829	-3.112	2.189	2.433	2.433	-13.525	-100
2	-2657	-14.572	5.522	-4.960	-4.761	4.814	5.338	-0.964	-23.760	-2463
3	-2665	-13.871	11.349	-4.482	-4.357	4.133	5.345	-0.850	-22.499	-2789
4	-2665	-15.459	10.230	-3.837	-3.649	4.766	6.865	-0.348	-26.743	-2650
5	-2664	-8.685	7.3196	-4.671	-3.562	2.324	3.275	-1.491	-12.794	-2256
6	-4465	-15.459	6.750	-3.631	-2.583	1.958	3.202	2.891	-14.970	-2225

Table 4: The molecular parameters of the ligand and its complexes.





**Figure 4:** The HOMO and LUMO of (A)  $H_2L$ , (B)  $[Cu(H_2L)_2(OAc)_2]$ , (C)  $[Cd(H_2L)_2(SO_4)]$ , (D)  $[Ni(H_2L)_2(OAc)_2]$ , (E)  $[Co(H_2L)_2(OAc)_2]$ , (F)  $[Hg(H_2L)(Cl)_2(H_2O)]$ .

is used to descriptor of reactivity that agrees quantitative organization of the global electrophilic environment of a molecule within a relative scale. Besides, to recognize the toxicity of numerous pollutants in terms of reactivity and site selectivity.

#### Molecular electrostatic potential (MEP) of $H_2L$

The "MEP" was measured a good descriptor for extensive position

for (nucleophilic and electrophilic attack) [23]. In the current study, 3D designs of "MEP" were wan for the ligand and its metal complexes (Figure 5). Constructed on the "MEP", one can mostly order the electron-rich area with has red color of a map which prefer site for electrophilic attack. However, the electron-poor region has blue color favors site for nucleophilic attack [30]. Nevertheless, the green region point to neutral electrostatic potential region.

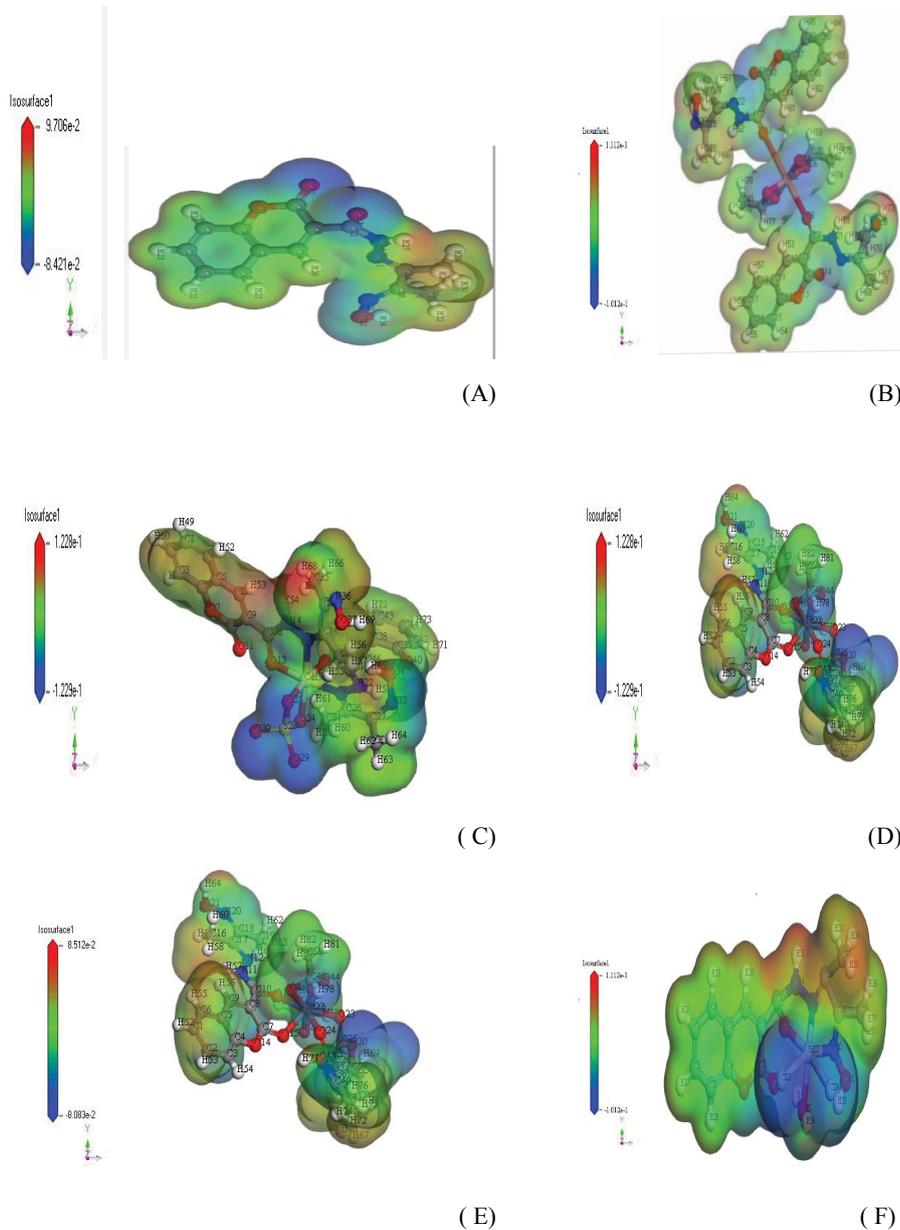


Figure 5: Molecular electrostatic potential map for (A)  $H_2L$ , (B)  $[Cu(H_2L)_2(OAc)_2]$ , (C)  $[Cd(H_2L)_2(SO_4)]$ , (D)  $[Ni(H_2L)_2(OAc)_2]$ , (E)  $[Co(H_2L)_2(OAc)_2]$ , (F)  $[Hg(H_2L)(Cl)_2(H_2O)]$ .

### Local reactivity descriptors

The Fukui function is very vital then universal reactivity descriptors in DFT [31,32]. This function is derived from electron density,  $(\rho(r))$ , with impudence to  $(N)$  is total number of electrons of the system, below  $(v(r))$  is constant external potential,

$$\rho(r) = \left( \frac{\partial \rho(r)}{\partial N} \right)_{v(r)}$$

The Fukui function shows the tendency of the electronic density to collapse at assumed site upon accepting or donating electrons [33]. There are three kinds of Fukui function, which are specifically  $f_k^+$  for nucleophilic attack,  $f_k^-$  for electrophilic attack and  $f_k^0$  for radical

$$f_k^+ = qk(n+1) - qk(N) \text{ For nucleophilic attack}$$

$$f_k^- = qk(N) - qk(N-1) \text{ For electrophilic attack}$$

$$f_k^0 = 1/2[qk(N+1) + qk(N-1)] \text{ For radical attack}$$

And, local softness ( $S_k^+, S_k^0, S_k^-$ ) and electrophilicity can be showed as the creation of the Fukui function by the following equations:

$$(S_k^- = Sf_k^-, S_k^- = Sf_k^-, S_k^0 = Sf_k^0)$$

$$(\omega_k^- = \omega f_k^-, \omega_k^- = \omega f_k^-, \omega_k^0 = \omega f_k^0)$$

From the Fukui value of  $H_2L$  was described in Table 6 the reactivity order for the nucleophilic was predicted as  $O_{13} > O_{12} > O_{11} > N_{14} > C_{16}$ . The calculated  $f_k^-$  value predicted that the probable positions for electrophilic attack was  $C_{10} > O_{11} > O_{13} > C_9 > C_6$  site and the radical attack was expected as  $O_{13} > O_{11} > C_{10} > O_{11} > C_{16}$  site. Whereas, the

order for the nucleophilic in (Compound 2)  $O_3 > C_{23} > Cu_5 > O_6 > O_{19}$  though calculated  $f_k^-$  value expected that the allowed sites for electrophilic attack was  $O_{19} > Cu_5 > O_6 > O_3 > C_{20}$  site and radical attack was likely as  $O_{19} > Cu_5 > O_6 > C_{23} > O_3$  site. However, order for the nucleophilic in Compound 3  $C_{45} > N_{23} > C_{38} > O_{34} > C_{27}$  though calculated  $f_k^-$  value predicted that the possible sites for electrophilic attack was  $C_{10} > O_{11} > C_8 > O_{13}$  site and the radical attack was predicted as  $O_{11} > N_{36} > N_{29}$  site. Yet order for the nucleophilic in Compound 4  $O_{27} > C_{35} > O_{23} > Ni_{22} > N_{12} > O_{21}$  though calculated  $f_k^-$  value predicted that the promising sites for electrophilic attack was  $Ni_{22} > O_{27} > O_{39} > O_{40}$  site and the radical attack was predicted as  $O_{27} > Ni_{22} > O_{39} > O_{40}$  site. Yet, the order for the nucleophilic in Compound 5  $O_{40} > O_{27} > O_6 > C_{42} > C_{44}$  though calculated  $f_k^-$  value predicted that the possible sites for electrophilic attack was  $O_{27} > O_6 > Co > C_{44}$  site and the radical attack was predicted as  $O_{27} > Co > C_{44} = O_{50}$  site. However, the order for the nucleophilic in Compound 6  $O_{21} > N_{20} > N_{14} > O_{13} > N_1$  though calculated  $f_k^-$  value predicted that the possible sites for electrophilic attack was  $C_{10} > O_{11} > C_9 > O_{13}$  site and the radical attack was predicted as  $C_{10} > O_{13} > C_{16} > N_{20} > C_9$  site.

### Biological activity

**Antifungal activity:** The results data showed that  $H_2L$  and their metal complexes have a significant activity against *Candida albicans* and *Aspergillus flavus* (Table 7). The (5) and (6) complexes were more effective against *Aspergillus flavus* than *Candida albicans* in association with the Colitrimazole as standard drug [34].

**Antibacterial activity:** The investigated compounds along with Ciprofloxacin (standard drug) and DMSO as (solvent control) carried separately for their antibacterial activity. The activity of the tested compounds was corresponding to the activity of Ciprofloxacin as a standard antibiotic. The MIC values showed that complexes (1 and 4) have the highest antibacterial activity (Table 7) [35].

**Colorimetric assay for compounds that bind DNA:** Methyl green reversibly binds to DNA, and the colored complex is stable

at (pH=7), where methyl green only disappears at this pH value. Whereas, the DNA binding active compounds replace DNA from its methyl green complex. The displacement was measured by a spectrophotometric examine as a reduction in the absorbance at 630 nm. The outcomes data shown that compounds (6 and 1) exhibited the maximum attraction to DNA, which established through retentive the complex at the source or by transferring for very small spaces, then by evaluating  $IC_{50}$  values. While, compounds (3, 4 and 5) exhibited moderate activity (Table 8) [36].

**Conductance measurement:** The formation constants, association constants and Gibbs free energies of  $H_2L$  complexes were intended in (DMF-methanol) at room temperature (298.15K).

$$\Lambda_m = (K_s - K_{solv})K_{cell} \times 1000/C$$

( $K_s$ ) is specific conductance value of the solution of (Cu(II), Ni(II) and Co(II)) in 5%DMF/Methanol at (298.15K); ( $\Lambda_m$ ) is molar conductance [37]; ( $K_{solv}$ ) is the specific conductance of the solvent; ( $K_{cell}$ ) is the cell constant (1); (C) is the molar concentration of the metal ion in solutions. The ( $\Lambda_0$ ) is limiting molar conductance at infinite dilutions was valued for (Cu(II), Co(II) and Ni (II))ions in nonappearance of the ligand through extrapolating the relative between (( $\Lambda_m$ ) and (c)) to zero concentration for each line, ( $\gamma \pm$ ) is the activity co-efficient (Figure 6).

Likewise, the molar conductance ( $\Lambda_m$ ) drawn against the molar ratio [M/L] in the occurrence of ligand; where the metal concentration (M) and the ligand concentration (L). Dissimilar straight lines gained with sharp disruptions in existence of ligand express to molar ratios (Figure 7).

**Association constants of the metal salt solutions:** In absence of ligand, series of conduct metric series measurement carried out in 5%DMF/Methanol. The Gibbs of free energy change of association ( $\Delta G_A$ ) of Cu(II), Ni (II) and Co(II)metal salt solutions were estimated from the association constant ( $K_A$ ) in using equation (2) [38,39]  $\Delta G_A = -2.303RT \log K_A$  Where (R) is gas constant; in addition, (T) is absolute

Compound	$E_{H(ev)}$	$E_{L(ev)}$	$E_H - E_L$	$E_L - E_H$	$\chi_{(ev)}$	$\mu_{(ev)}$	$\eta_{(ev)}$	$S_{(ev^{-1})}$	$\omega_{(ev)}$	$\sigma_{(ev)}$
1	5.829	3.112	2.717	2.717	4.4705	4.4705	1.3585	0.67925	7.355675	0.736106
2	5.153	5.075	0.078	0.078	5.114	5.114	0.039	0.0195	335.2498	25.64103
3	4.482	4.357	0.125	0.125	4.4195	4.4195	0.0625	0.03125	156.2558	16
4	3.837	3.649	0.188	0.188	-3.743	3.743	0.094	0.047	74.52154	10.6383
5	3.859	3.696	0.163	0.163	-3.7775	3.7775	0.0815	0.04075	87.54298	12.26994
6	3.631	2.583	1.048	1.048	-3.107	3.107	0.524	0.262	9.211306	1.908397

**Table 5:** Calculated EHOMO, ELUMO, energy band gap (EH – EL), chemical potential ( $\mu$ ), electronegativity ( $\chi$ ), global hardness ( $\eta$ ), softness (S), global electrophilicity index ( $\omega$ ) and softness ( $\sigma$ ) for  $H_2L$  and its metal complexes.

Radical attack	Electrophilic attack	Nucleophilic attack	Compound
$O_{13} > O_{11} > C_{10} > O_{11} > C_{16}$	$C_{10} > O_{11} > O_{13} > C_9 > C_6$	$O_{13} > O_{12} > O_{11} > N_{14} > C_{16}$	1
$O_{19} > Cu_5 > O_6 > C_{23} > O_3$	$O_{19} > Cu_5 > O_6 > O_3 > C_{20}$	$O_3 > C_{23} > Cu_5 > O_6 > O_{19}$	2
$O_{11} > N_{36} > N_{29}$	$C_{10} > O_{11} > C_8 > O_{13}$	$C_{45} > N_{23} > C_{38} > O_{34} > C_{27}$	3
$O_{27} > Ni_{22} > O_{39} > O_{40}$	$Ni_{22} > O_{27} > O_{39} > O_{40}$	$O_{27} > C_{35} > O_{23} > Ni_{22} > N_{12} > O_{21}$	4
$O_{27} > Co > C_{44} = O_{50}$	$O_{27} > O_6 > Co > C_{44}$	$O_{40} > O_{27} > O_6 > C_{42} > C_{44}$	5
$C_{10} > O_{13} > C_{16} > N_{20} > C_9$	$C_{10} > O_{11} > C_9 > O_{13}$	$O_{21} > N_{20} > N_{14} > O_{13} > N_1$	6

**Table 6:** Ordering the nucleophilic, electrophilic, and radical attack sites for  $H_2L$  and its metal complexes.

Compound	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>C. albicans</i>	<i>A. flavus</i>
Ampicillin	125	187.5	187.5	93.7	-	-
Colitrimazole	-	-	-	-	5.8	3.9
1	500	250	250	187.5	23.4	15.6
2	NA	500	250	187.5	31.2	23.4
3	250	187.5	375	250	46.9	62.5
4	187.5	125	187.5	93.7	15.6	7.8
5	NA	750	500	375	93.7	93.7
6	NA	NA	NA	NA	375	500

**Table 7:** Antibacterial and antifungal activities in terms of MIC ( $\mu$ g/mL).

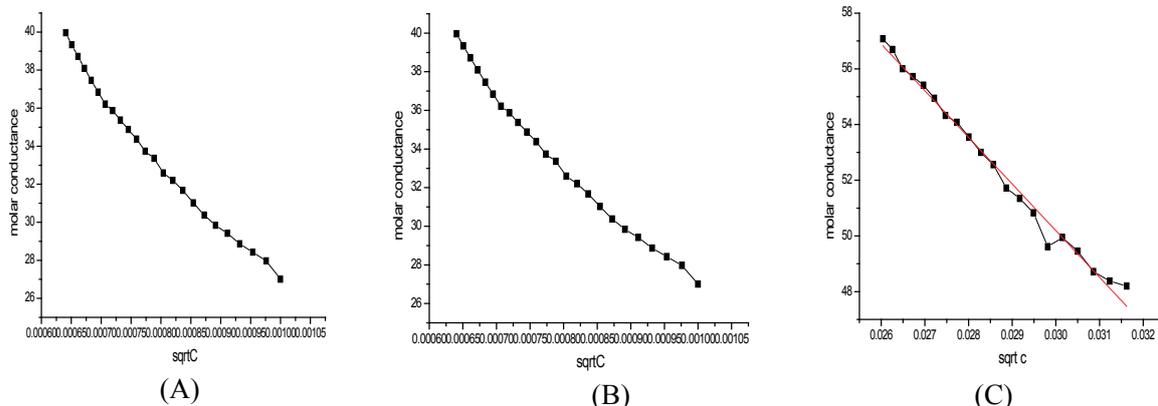


Figure 6: The relation between molar conductance ( $\Lambda_m$ ) and C of Cu(II), Ni(II) and Co(II) metal ions in DMF-methanol at 298.15 K

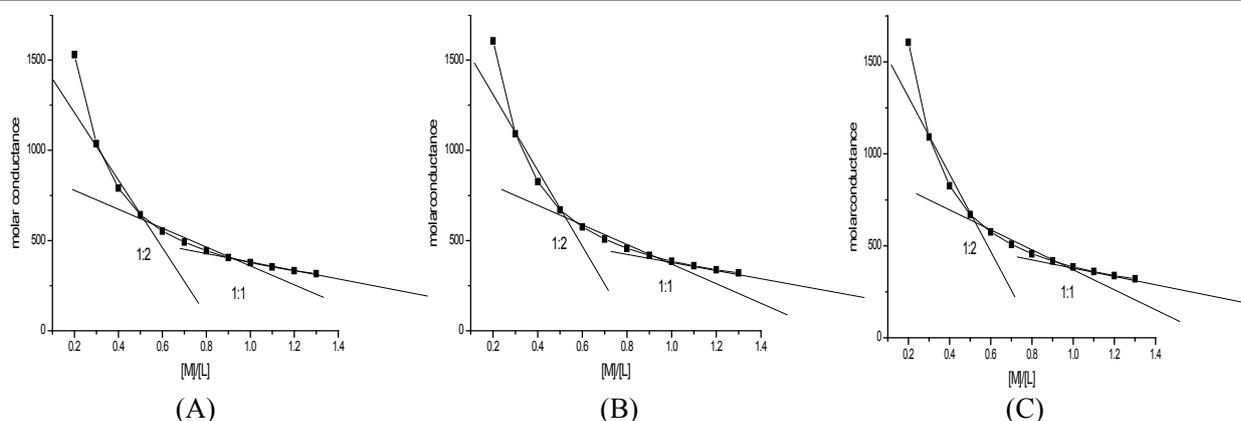


Figure 7: The relation between molar conductance ( $\Lambda_m$ ) and  $[M]/[L]$  in DMF-methanol at 298.15 K.

Compound	DNA/methyl green ( $IC_{50}$ , $\mu\text{g/ml}$ )
1	42.8 $\pm$ 2.2
2	46.7 $\pm$ 2.6
3	49.6 $\pm$ 2.5
4	39.3 $\pm$ 2.0
5	58.4 $\pm$ 2.9
6	82.5 $\pm$ 4.1

Table 8: DNA/methyl green colorimetric assay of the DNA-binding compounds.

$\Delta G_A$	$K_d$	$K_a$	$\gamma \pm$	$\Lambda_m^\wedge$	C
-22.5381	0.000113	8871.745	0.771178	32.4625	8.2E-04
-22.399	0.000119	8387.894	0.771563	33.66	0.000784
-22.2631	0.000126	7940.367	0.77195	34.8475	0.000755
-22.1536	0.000132	7597.43	0.772721	35.8875	0.000727
-22.0234	0.000139	7208.527	0.773108	37.05	0.000702

Table 9: Association constants and Gibbs free energies of association for Cu(II) in DMF-methanol at 298.15 K.

temperature. The intended Gibbs free energies appeared on Tables 9-11. Formation constant for the complexation of the metal salt with ligand. The formation constant ( $K_f$ ) of Cu(II), Co(II) and Ni(II) complexes were estimated from the direct relation of  $[M]/[L]$  against ( $\Lambda_m$ ), by using equation(3) [40,41].

$K_f = \frac{\Lambda_m - \Lambda_{obs}}{(\Lambda_{obs} - \Lambda_{ML}) [L]}$  Anywhere, ( $\Lambda_m$ ) is the molar conductance of the Cu (II), Co (II) and Ni (II) ions previously adding of the ligand,

$\Delta G_A$	$K_d$	$K_a$	$\gamma \pm$	$\Lambda$	C
-20.2006	0.000289	3455.886	0.731973	52.5525	8.2E-04
-20.1361	0.000297	3367.069	0.734436	53.55	0.000784
-20.1002	0.000301	3318.619	0.737215	54.325	0.000755
-20.0834	0.000303	3296.246	0.740144	54.945	0.000727

Table 10: Association constants and Gibbs free energies of association for Ni(II) in DMF-methanol at 298.15 K.

$\Delta G_A$	$K_d$	$K_a$	$\gamma \pm$	$\Lambda_m^\wedge$	C
-22.5815	0.000111	9028.376	0.771924	30.9925	8.2E-04
-22.4203	0.000118	8460.215	0.771922	32.2575	0.000784
-22.2858	0.000125	8013.261	0.772326	33.39	0.000755
-22.1787	0.00013	7674.725	0.77313	34.375	0.000727
-22.05	0.000137	7286.287	0.773534	35.4825	0.000702

Table 11: Association constants and Gibbs free energies of association for Co(II) in DMF-methanol at 298.15 K.

( $\Lambda_{obs}$ ) is the molar conductance of solution in titration and ( $\Lambda_{ML}$ ) is the molar conductance of the complex. Similarly, the Gibbs free energy of the formation for each Cu (II), Co (II) and Ni (II) complex was calculated from the formation constants by equation (4) (Tables 12-14) [42].

$$\Delta G_f = -RT \ln K_f$$

**Association and formation constants for metal complexes with ( $H_2L$ ) in 5% (DMF-methanol) solutions at 298.15K:** The Gibbs free energies of association and association constants for (Cu (II), Ni (II)

and Co (II) ions complexes in 5% (DMF-methanol) solutions at (298.15 K) were calculated by applying relations (3), (4). The results were presented and collected on Tables 15-17 that, there two straight lines with one breakdown characteristic the foundation of (1:1) and (1:2) (M/L) stoichiometric complexes for (Cu (II), Ni (II) and Co (II)), respectively in mixed solvent at (298.15K).

## Conclusions

In this paper, Cu(II), Ni(II), Hg (II) Co(II) and Cd(II) with N<sup>2</sup>-(3 (hydroxyimino)butan-2-ylidene)-2-oxo-2H-chromene-3-carbohydrazone (H<sub>2</sub>L) were synthesised and characterized by various methods). The consequences showed that the H<sub>2</sub>L the IR spectra shown that ligand behavior as monodentate, bidentate and/or tridentate ligand. The electronic spectrum as well as magnetic moments proposing geometry of complexes is octahedral structure. DFT calculations done to calculate the host-guest interaction between the hydrazone and several metal ions. Moreover, the ligand and its complexes carried for biological activity. The result data shown that the H<sub>2</sub>L, Cd(II) and Ni(II) complex have highest biological activity.

ΔGA	K <sub>d</sub>	K <sub>a</sub>	γ ±	m <sup>Λ</sup>	C
-27.3409	1.62E-05	61562.72	0.929782	551.8333	5.6E-05
-27.9395	1.28E-05	78374.19	0.927636	461.0038	0.000071111
-28.6279	9.67E-06	103459.4	0.927754	383.8894	0.000085106
-29.3116	7.34E-06	136309.4	0.929037	322.5783	0.00009759
-29.2742	7.45E-06	134270.6	0.927509	316.3642	0.000104

**Table 12:** Association constants and Gibbs free energies of association for Cu(II) with (H<sub>2</sub>L) in DMF-methanol at 298.15 K.

ΔGA	K <sub>d</sub>	K <sub>a</sub>	γ ±	m <sup>Λ</sup>	C
-27.4512	1.55E-05	64363.34	0.927746	575.125	8.2E-04
-28.1171	1.19E-05	84194.44	0.925152	474.61223	0.000784
-28.7969	9.03E-06	110758.4	0.923982	395.15657	0.000755
-29.4583	6.91E-06	144618.3	0.924217	333.84548	0.000727
-29.5312	6.71E-06	148933.5	0.923189	320.139	0.000702

**Table 13:** Association constants and Gibbs free energies of association for Ni(II) with (H<sub>2</sub>L) in DMF-methanol at 298.15 K.

ΔGA	K <sub>d</sub>	K <sub>a</sub>	γ ±	m <sup>Λ</sup>	C
-26.9375	1.91E-05	52318.89	0.927746	609.1667	5.6E-05
-27.4995	1.52E-05	65631.19	0.925152	514.41323	7.111E-05
-28	1.25E-05	80310.86	0.923982	443.88352	8.511E-05
-28.5329	1E-05	99567.54	0.924217	384.62101	9.759E-05
-26.1951	9.8E-06	101997.2	0.923189	371.15	0.000104

**Table 14:** Association constants and Gibbs free energies of association for Co(II) with (H<sub>2</sub>L) in DMF-methanol at 298.15 K.

ΔG <sub>f</sub>	log k <sub>f</sub>	K	[L]	Λ <sub>obs</sub>	Λ <sub>ml</sub>	Λ <sub>m</sub>	[M]	[L]	[M]/[L]
-20.604	3.549689	3545.594	8.42E-5	642.6	147.8	790.4	0.00004762	0.0000952	1:2
-28.7639	4.955479	90256.57	2.57E-5	378.4	264.25	642.6	8.5106E-05	0.0000851	1:1

**Table 15:** Formation constant and Gibbs free energies for Cu(II) in DMF-methanol at 298.15 K.

ΔG <sub>f</sub>	log k <sub>f</sub>	K	[L]	Λ <sub>obs</sub>	Λ <sub>ml</sub>	Λ <sub>m</sub>	[M]	[L]	[M]/[L]
-20.6696	3.560985	3639.023	8.4E-5	669.9	156.9	826.8	0.00004762	0.0000952	1:2
-29.6165	5.102368	126581	2.23E-5	385.4	284.5	669.9	8.5106E-05	0.0000851	1:1

**Table 16:** Formation constant and Gibbs free energies for Ni(II) in DMF-methanol at 298.15 K.

ΔG <sub>f</sub>	log k <sub>f</sub>	K	[L]	Λ <sub>obs</sub>	Λ <sub>ml</sub>	Λ <sub>m</sub>	[M]	[L]	[M]/[L]
20.2644	3.54972	3545.843	8.42E05	693	159.4	852.4	0.00004762	0.0000952	1:2
26.3435	4.614608	41172.59	3.49E05	435.9	257.075	693	8.5106E-05	0.0000851	1:1

**Table 17:** Formation constant and Gibbs free energies for Co(II) in DMF-methanol at 298.15 K.

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