

Synthesis, Characterization and Antimicrobial Studies of complexes of Some Metal Ions with 2-[2-Amino-5-(3,4,5-Trimethoxy-benzyl)-Pyrimidinyl-4-azo]-4-Bromo-Phenol

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Abstract-- The complexes of the 2-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4-bromo-phenol with metal ions Cr(III), Ni(II), Cd(II), Cu(II) and Zn(II) were prepared in ethanol solution. These complexes were characterized by spectroscopic methods, conductivity, metal analyses and magnetic moment measurements. The antibacterial activity in vitro tests shows that the most of prepared compounds display good activity to (*Staphylococcus aureus*) and (*Escherichia coli*).

Index Term-- Synthesis, 2-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4-bromo-phenol, biological activity.

I. INTRODUCTION

Trimethoprim and Trimethoprim derivative is a type of medicine called an antibiotic[1]. It is used to treat infections with bacteria[2,3], it is a significant antimicrobial activities [4,5], and its analogues[17]. The chemical designation of Trimethoprim is 2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine C₁₄H₁₈N₄O₃. was first describe by Roth and co-workers[4].

Coordination complexes of transition metal had been widely studies for their antimicrobial and anti cancer properties [6]. Most of the azo compound and their complexes have a variety of biological, clinical and analytical applications [7]. It is known that chelation of metal ions with organic ligand acts synergistically to increase their biological activities. Transition metal complexes with azo salt ligands have been extensively investigated as catalysts for a number of organic redox reaction and electro chemical reduction processes [8]. Cyclic voltammety has been a useful tool to investigate the mechanisms of catalysis by azo salt complexes as well as to study the structure reactivity relationship in these compounds[9-11].

II. MATERIALS AND METHODS

All the chemicals used were analytical and of highest purity. The metal analyses of the separated solid chelates

for metal content were performed by using AA-680 Shimadzu Atomic Absorption Spectrophotometer.

- ✚ The electronic spectra of the prepared compounds were recorded on a Shimadzu Uv-160 Spectrophotometer.
- ✚ FTIR spectra of the samples were recorded by using IR Prestige-21 Spectrophotometer as KBr discs.
- ✚ Magnetic susceptibility measurements of the complexes in the solid state were determined by using Burker BM6 instrumentation at room temperature.
- ✚ The molar conductance of the complexes was measured in DMSO as a solvent at room temperature using WTW conduct-meter type.
- ✚ Melting point apparatus of Gallen Kamp M.F.B-60 was used to measure melting points of all prepared compounds.

Synthesis of 2-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4-bromo-phenol and its metal complexes:

A ligand of 2-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4-bromo-phenol with formula structure, as shown in fig. (1), was prepared according to literature methods[12], the physical properties of the ligand are shown in table(I).

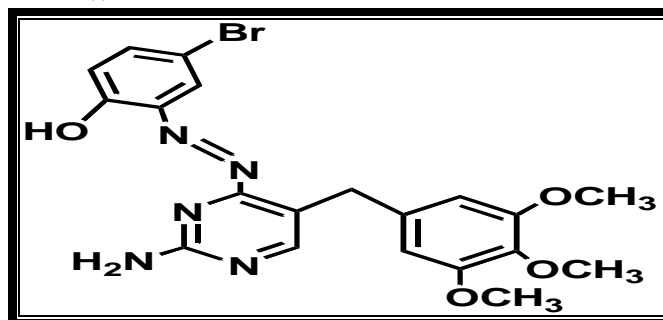


Fig. 1. the formula structure of 2-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4-bromo-phenol.

Preparation of Complexes:

Azo complexes under investigation were synthesized as following: the salts of Ni(NO₃)₂.3H₂O, Fe(NO₃)₂.9H₂O

,Cu(NO₃)₂.6H₂O, CrCl₃.6H₂O,CoCl₂.6H₂O , Cd(NO₃)₂.4H₂O were dissolved in ethanol and added to an ethanol solution of azo ligand in (1:2) for cadmium, cobalt, copper, iron, nickel and chromium complexes molar ratio with stirring the mixture an heated under reflex for two hours. The precipitation was collected by filtration, washed several times with ethanol and dried under vacuum.The physical properties of products are shown in table (I).

Study of complex formation in solution:

Azo complexes with metal ions were studied in solution using ethanol as a solvent[13], To determine the concentration of metal to the ligand ratio in the complex following molar ratio method. A series of solutions were prepared having a constant concentration 10⁻³ M for each metal ion and ligand. The ratio was determined from the relationship between the absorption of the absorbed light and mole ratio of (M/L). The results of the formation complexes in solution were listed in Table (I).

Programs used in theoretical calculations:

Computation chemistry may be defined as the application of mathematical and theoretical principles to the solution of chemical problems[14]. Molecular modeling, a subset of computation chemistry, concentrates on predicting the behavior of individual molecules within a chemical system. The most accurate molecular models use an initio or(first principles) electronic structure methods, based up on the principles of quantum mechanics, and generally vary

computer intensive. However, due to advances in computer storage capacity and processer performance, molecular modeling has been a rapidly evolving and expanding field, to the point that it is now possible to solve relevant problems in an acceptable amount of time [15]. Electronic structure calculations provide useful estimates of the energetic properties of chemical systems, including molecular structures spectroscopic features and probable reaction pathways.

Types of calculation

Single point calculation is the one that determines the molecular energy and properties for a given fixed geometry. Geometry optimization calculations employ energy minimization algorithms to locate stable structures. Vibration frequency calculations to find the normal vibration modes an optimized structure. The vibration of spectrum can be displayed and the vibration of motions associated with specific transition can be animated.

Biological Activity

The antibacterial activity of these compounds was determined by the agar diffusion method[16], using *staphylococcus aureus* (G+) and *Echerchia coil* ,10m M and 5m M of these compounds were placed on an agar seeded with the test organism .The plates were incubated for 24 hrs at 37⁰C ,The zone of inhibition formed was measured in mm and represented by (+), (++) and (+++) depending upon the diameter and clarity.

TABLE I
PHYSICAL DATA OF LIGAND (L) AND ITS METAL COMPLEXES

Comp.	Colour	m.p.	Yield%	Molecular weight	Molar ratio M:L	Metal percentage		Suggested Molecular formula
						found	Calc.	
L	Light Brown	250	75	474.31	-	-	-	octahedral
[CrL ₂]Cl	Dark Brown	210-212	77	1037.4	1:2	8.25	8.09	octahedral
[FeL ₂]	Brown-Redish	220-222	58	1003.8	1:2	7.40	7.55	octahedral
[CoL ₂]	Dark Brown	184-186	68	1007.5	1:2	6.00	5.20	octahedral
[NiL ₂]	Brown	202-204	62	1007.2	1:2	6.54	5.57	octahedral
[CuL ₂]	Dark Red	180-182	69	1011.5	1:2	6.21	5.59	Octahedral
[CdL ₂]	Brown	208-210	70	1060.4	1:2	9.21	9.48	octahedral

Infrared Spectra

Studies of infrared spectra for the the ligand and its complexes are done. The FT-IR spectrum of the ligand, as shown in fig. (2), displays characteristic bands at(3321, 33163)cm⁻¹, 1562cm⁻¹ .These bands were attributed to the ν (NH₂), ν (N=N) respectively [17]. The ν (NH₂) and ν (N=N)

at (3321 , 3163), 1562 cm⁻¹ in the free ligand shift to (3352 – 3344) cm⁻¹ and (1531 – 1504)cm⁻¹ respectively for the complexes. Also a weak band showed at 628 cm⁻¹ assigned to (νOH)out of plane bending vibration [18] .This assignment is supported by disappearance of the hydroxyl hydrogen which is replaced by a metal. The (C-O) phenolic

stretching vibrations, that appeared at 1261cm^{-1} in the ligand [19,20] underwent a shift confirms the participation of oxygen atoms in the C-O-M bond [17,18]. This observation indicates that this ligand behavior as a tridentate through nitrogen of NH_2 moiety, oxygen of phenolic moiety and azo moiety. All these absorptions were further supported by the appearance frequencies of $\nu \text{M-N}$, $\nu \text{M-O}$, respectively [18]. All prepared complexes are shown in (table II), fig.(3),(4),(5),(6).

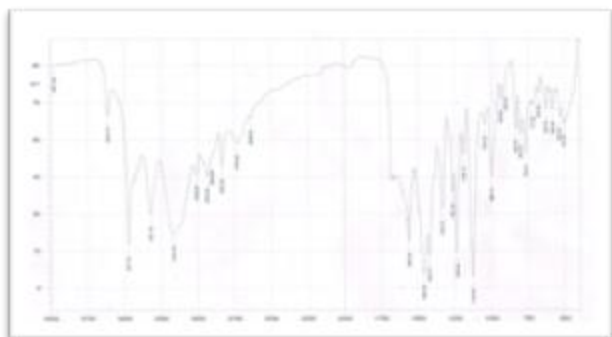


Fig. 2. FTIR spectra of 2-[2-Amino-5-(3,4,5-trimethoxy-benzyl)-pyrimidinyl-4-azo]-4-bromo-phenol.

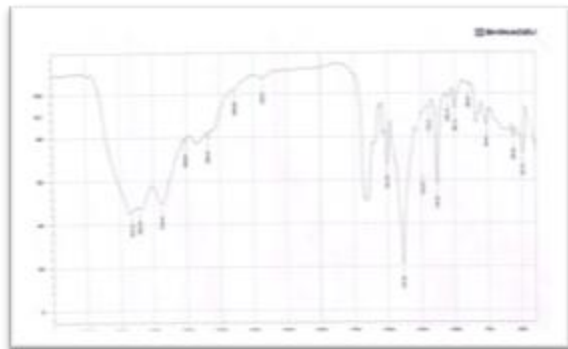


Fig. 3. FTIR spectra of FeL_2

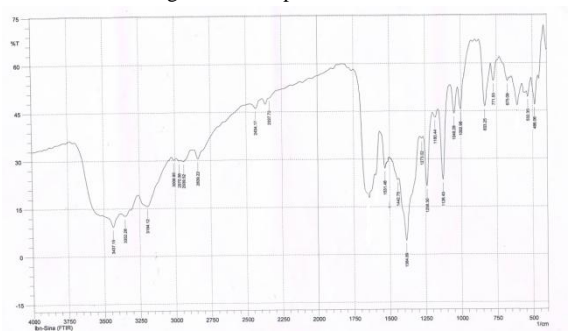


Fig. 4. FTIR spectra of CdL_2

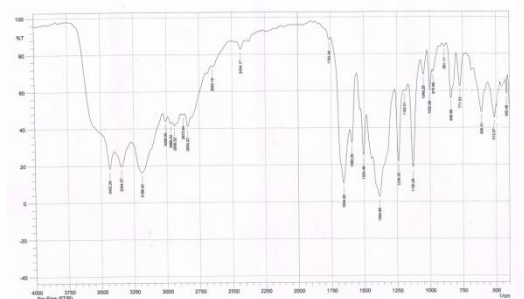


Fig. 5. FTIR spectra of CuL_2

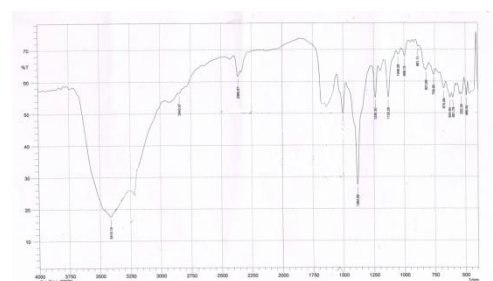


Fig. 6. FTIR spectra of NiL_2

Electronic spectra

The UV-Vis spectra data for the free ligand and all metal complexes are listed in (table III). The UV-Vis spectrum of the ligand shows three peaks at 256 nm, 340 and 362 nm assigned to $(\pi - \pi^*)$ and $(n - \pi^*)$ electronic transitions [21].

The electronic spectra of complexes

Chromium complex (Cr L_2)

The electronic spectrum of Cr (III) complex, showed three bands within the range measurement. They have maxima at 15343, 20630 and 32510 cm^{-1} . These are spin-allowed and Laporte forbidden transitions. Chromium is in the (+3) oxidation state, so this is a d^3 system. Reference to Orgel diagram in forms that three d-d bands are expected and they can be assigned as:

${}^4A_{2g} \longrightarrow {}^4T_{2g(v1)}$, ${}^4A_{2g} \longrightarrow {}^4T_{2g(v2)}$, ${}^4A_{2g} \longrightarrow {}^4T_{2g(p)(v3)}$ transitions respectively in octahedral geometry [22-26]. The electronic spectrum coupled with magnetic moment (3.35 BM). Conductivity measurement showed that the complex was ionic [21]. Considering these data and comparing with a large number of published works [20,22], the following structure is suggested as shown in fig. (7).

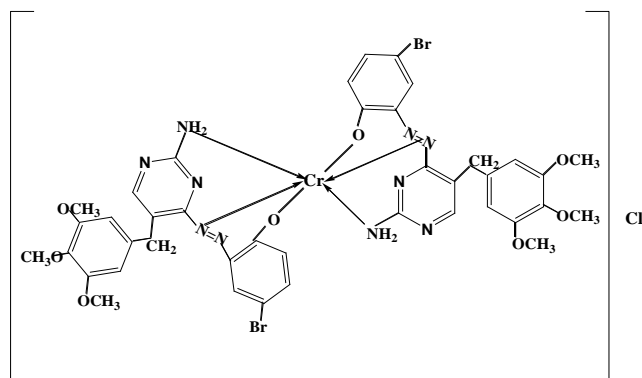


Fig. 7.

Iron complex (FeL₂)

The spectrum of Fe(II) complex which shows absorption peak at $(36127)\text{cm}^{-1}$, is ascribed to the transition LMCT [19]. These transitions are characterized to the octahedral geometry around Fe(II) ion. The value of magnetic moment is $(4.6)\text{BM}$ which confirms the structure [21,24]. Conductivity measurement value also confirms the nonionic structure [22]. Depending on this result, the following structure of this complex is proposed.

Cobalt complex (CoL₂)

The electronic spectra of Co(II) complex, exhibited bands in the region 15822.7cm^{-1} , 23752.9cm^{-1} due to the ${}^4\text{A}_{2g} \longrightarrow {}^4\text{T}_{2g(v2)}$, ${}^4\text{T}_{1g} \longrightarrow {}^4\text{T}_{1g(p)(v3)}$ transition respectively. These transition suggest octahedral geometry for the Co(II) complexes. These assignments are in agreement with reported values [22,23]. The observed magnetic moment value for the cobalt ion complex is 4.52BM which indicates clearly the octahedral geometry of Co(II) complex [24]. The conductivity measurement of this formation suggests the following structure.

Nickel complex (NiL₂)

The Electronic spectrum of Ni(II) complex in the present investigation exhibited three bands in the region 11134 , 18201 and 23200cm^{-1} . These bands are assigned due to ${}^3\text{A}_{2g} \longrightarrow {}^3\text{T}_{1g(v2)}$, ${}^3\text{A}_{2g} \longrightarrow {}^3\text{T}_{1g(p)(v3)}$ transition respectively. These transition suggested octahedral geometry for Ni(II) complex [21,23]. The magnetic moment measurement shows to be of high spin with $(3.30)\text{BM}$ and the conductivity measurement shows that it is a non-ionic compound [22]. The most probable structure of this complex is octahedral as shown in fig(5).

Copper complex (CuL₂)

The spectrum of Cu(II) complex, showed broad band at 16229cm^{-1} . The observed broad band in the present Cu(II) complex can be assigned to the envelope of

${}^2\text{B}_{1g} \longrightarrow {}^2\text{E}_g$ and ${}^2\text{B}_{1g} \longrightarrow {}^2\text{E}_{2g}$, transition in distorted octahedral geometry. The electronic spectra coupled with magnetic moment $(1.82)\text{BM}$, indicate octahedral geometry around Cu(II) complex [24,25]. The conductivity measurement shows that the complex is a non ionic [22]. Considering these data and comparing with a large number of published works [23], let proposed structure be as in fig(5).

Cadmium complex (CdL₂)

The prepared complex is a diamagnetic, due to the outer shell of Cadmium ion is d^{10} . The Uv- Vis spectrum of this compound shows relative change in the band position compare to that of free ligand. The conductivity measurement for this complex in DMF solvent at 25C^0 showed to be non conductance [22]. The most probable structural of this complex is octahedral [23], as shown below in fig. (8).

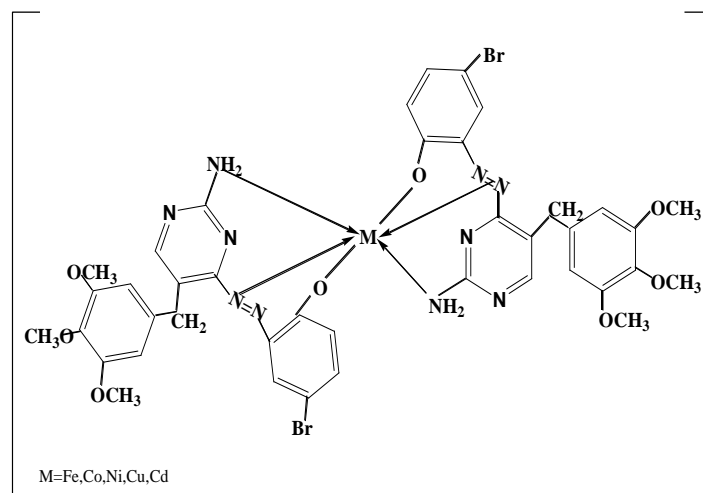


Fig. 8.

The vibration spectra of the ligand were calculated by using a semi-empirical PM₃. The results obtained for wave numbers are presented in (table IV), and the comparison with the experimental values indicate some deviations. These deviations may be due to the harmonic oscillator approximation and lack of electron correlation [26].

Optimization Energy :

A theoretically probable structure of metal complexes with a ligand has been calculated to search the most probable model of the stable building structure. These shapes fig(9) shows the calculated optima geometries for (L) and its metal complexes.

Antibacterial Activates:

The data of antibacterial activities of the prepared ligand and its complexes are given in Table(VI), the result showed that the complexes have more toxicity against the bacterial species than the free ligands. This can be attributed to the Tweed's chelation theory[27], according to which the chelation reduces the polarity of the metal atom mainly

because of the partial sharing of its positive charge with donor group and possible electron delocalization over the whole chelating ligand. Such coordination could also enhance the lipophilic character of the central atom, which subsequently favour its permeation through the lipid layer of the cell membranes. [28].

TABLE II
FT-IR FREQUENCIES (CM-1) OF THE LIGAND AND ITS COMPLEXES

Comp.	ν NH ₂	ν N=N	ν C-O pheno.	ν M - N	ν M - O
L	3321 3163	1562	1261		
[CrL ₂]Cl	3348 3161	1512	1257	551	455
[FeL ₂]	3352 3186	1504	1273	559	493
[CoL ₂]	3356 3176	1531	1279	524	462
Ni[NiL ₂]	3348 3186	1512	1238	532	489
[CuL ₂]	3344 3186	1504	1192	513	420
[CdL ₂]	3352 3194	1531	1273	532	486

TABLE III
ULTRA VIOLET -VISIBLE SPECTRA OF FREE LIGAND AND THEIR COMPLEXES IN 10⁻³ M IN DMF, MAGNETIC MOMENTS AND MOLAR CONDUCTANCE IN DMSD

Comp.	λ_{\max} (nm)	Wave number (cm ⁻¹)	(d-d) transitions	Molar conductance $\Delta m(\Omega^{-1} \text{ cm}^2 \text{ mol}^{-1})$	M_{eff} (BM)
L	256 340	39062 29411	-----	----	---
[CrL ₂]Cl	651.2 484.7 307.5	15343 20630 32510	${}^4A_{2g} \longrightarrow {}^4T_{2g}(v_1)$ ${}^4A_{2g} \longrightarrow {}^4T_{2g}(v_2)$ ${}^4A_{2g} \longrightarrow {}^4T_{2g}(p)(v_3)$	25.31	3.35
[FeL ₂]	276.8	3612.7	LMCT	15.22	4.60
[CoL ₂]	632.0 421.0	15822 23752	${}^4T_{1g} \longrightarrow {}^4A_{2g}(v_2)$ ${}^4T_{1g} \longrightarrow {}^4T_{1g}(p)(v_3)$	12.34	4.52
[NiL ₂]	898.1 549.4 431.0	11134 18201 23200	${}^3A_{2g} \longrightarrow {}^3T_{1g}(v_1)$ ${}^3A_{2g} \longrightarrow {}^3T_{1g}(v_2)$ ${}^3A_{2g} \longrightarrow {}^3T_{1g}(p)(v_3)$	20.20	3.30
[CuL ₂]	616.1	16229	${}^2B_{1g} \longrightarrow {}^2E_g$ ${}^2B_{1g} \longrightarrow {}^2E_{2g}$	19.39	1.82
[CdL ₂]	290 370	34482 27027	--	16.12	Zero

TABLE IV
CONFORMATION ENERGETIC (IN KJ.MOL-1) FOR (L) AND THEIR METAL COMPLEXES.

Conformation	PM3	
	ΔH_f°	ΔE_b
L	-21.3697026	-5311.1857026
[CrL ₂]Cl	-204.3377260	-5758.7947260
[FeL ₂]	-22.6018287	-4871.6458287
[CoL ₂]	-394.2312573	-6090.8612573
[NiL ₂]	-64.9548639	-10583.2808639
[CuL ₂]	-432.9087654	-6762.6984320
[CdL ₂]	-38.9700126	-46908.9669863

TABLE V
COMPARISON OF EXPERIMENTAL AND THEORETICAL VIBRATIONAL FREQUENCIES(CM-1) FOR LIGAND(L).

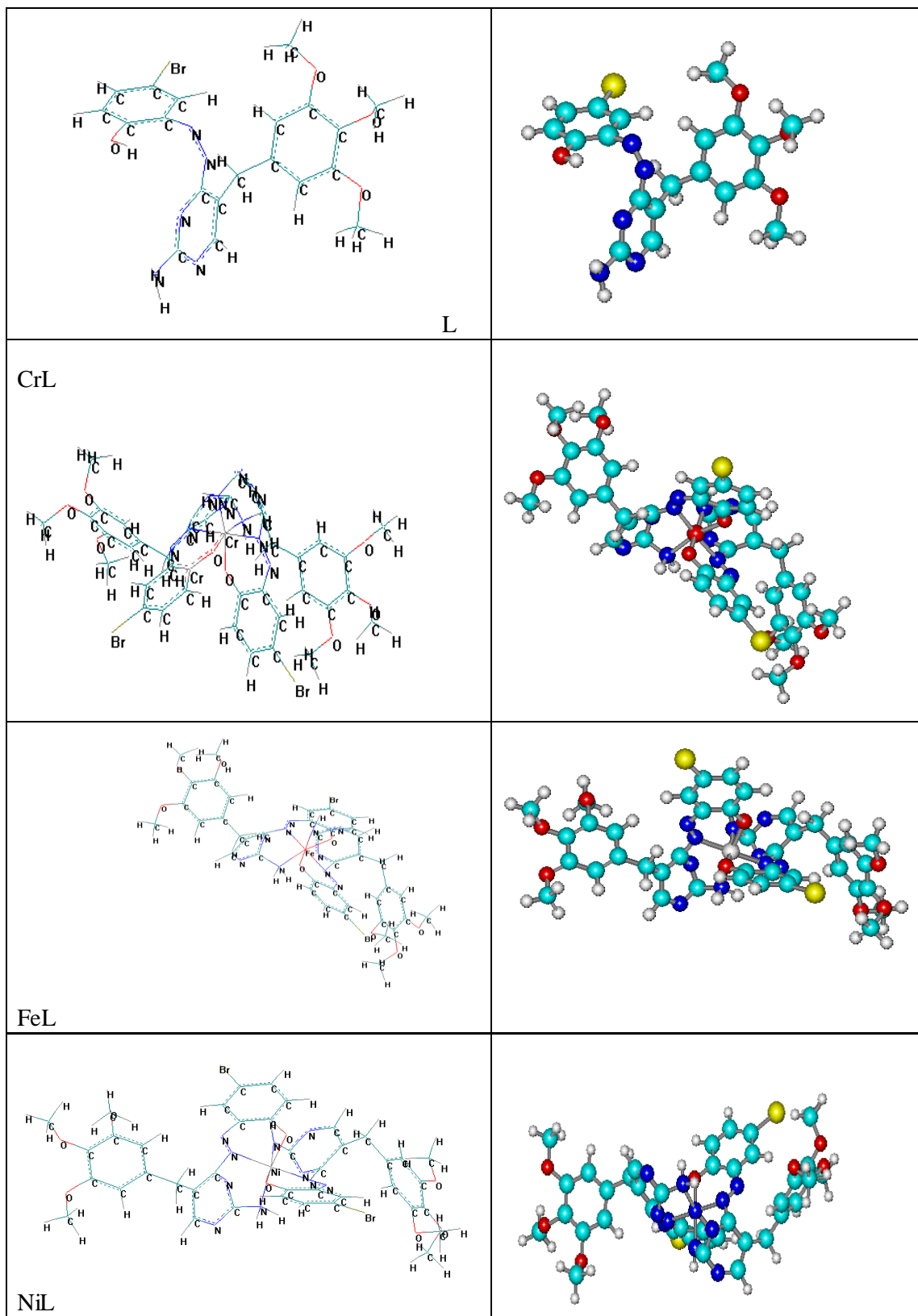
COMP.	ν C-O	N=N ν	ν NH ₂
L			(3321)*
			(3294)**
			(0.81)***
	(1261)*	1562)*	(3163)*
	(1275)**	(1483)**	(3099)**
	(-1.11)***	(5.05)***	(2.02)***

*: Experimental frequency, **: Theoretical frequency, ***: Error % due to main difference in the experimental measurements and theoretical treatments of vibrational spectrum.

TABLE VI
ANTIBACTERIAL ACTIVITY OF THE LIGAND AND IT'S METAL COMPLEXES .

Compounds	<i>Echerchia coil</i>		<i>Staphylococcus aureus</i>	
	5mM	10mM	5mM	10mM
L	-	-	-	-
[CrL ₂]Cl	+	++	+	++
FeL ₂	-	-	-	-
CoL ₂	++	++	++	++
NiL ₂	++	++	++	++
CuL ₂	+	++	++	++
CdL ₂	++	++	++	++

(-) inactive ; (+) moderate active ; (++) active



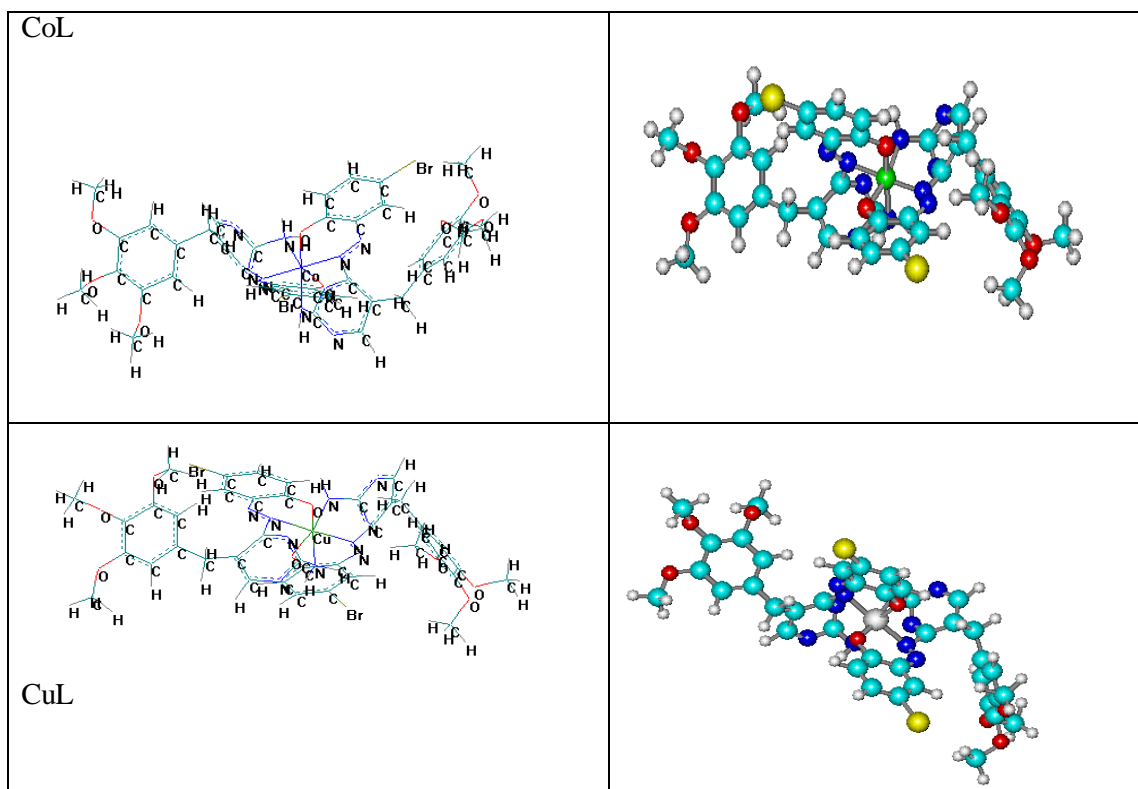


Fig. 9. conformation structure of Ligand and its complexes

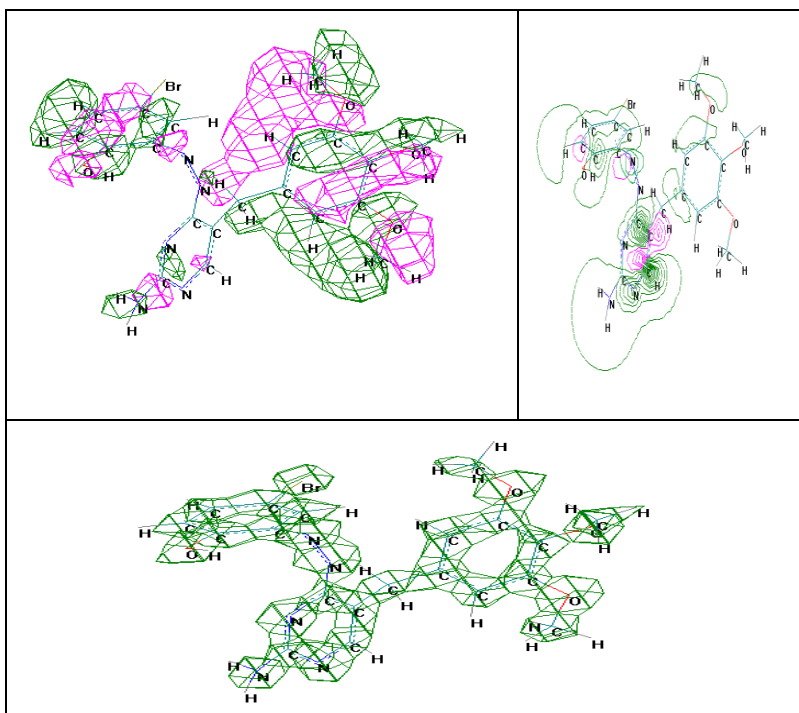


Fig. 10. HOMO & Electrostatic potential as 2D Contours for Ligand

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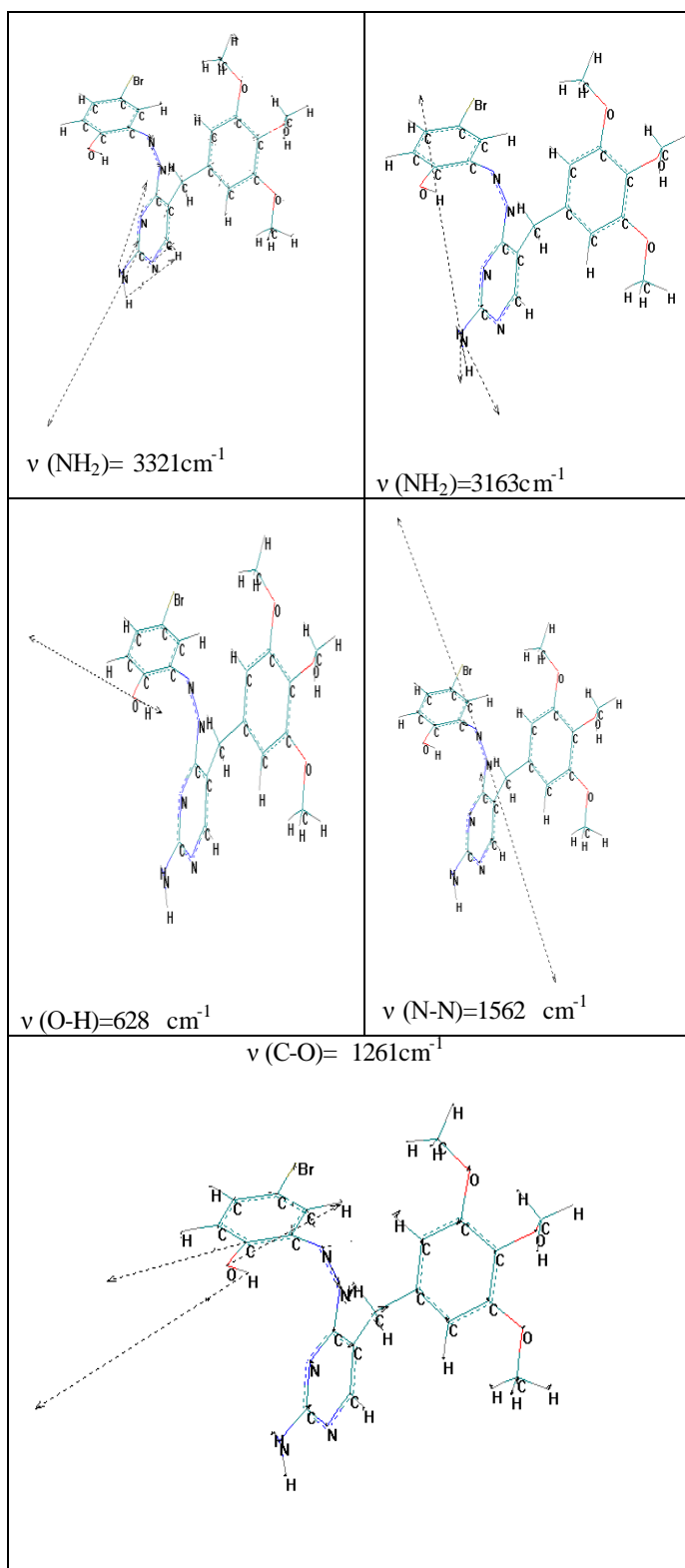


Fig. 11. Calculated vibrational frequencies of ligand

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