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SYNTHESIS STRUCTURAL CHARACTERIZATION, ANTIMICROBIAL AND CYTOTOXIC STUDIES ON SOME NOVEL TRANSITION COMPLEXES WITH NO BIDENTATE SCHIFF'S BASE LIGAND DERIVED FROM SULFAGUANIDINE WITH MOLECULAR ORBITAL CALCULATIONS

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ABSTRACT:

*Some selected solid complexes of the Schiff base ligand **HL** derived from sulfa- guanidine with Cu(II), Ni(II), Co(II) and Zn(II) ions were synthesized and characterized by elemental analysis, FTIR, electronic, mass, and ESR spectral analyses, as well magnetic susceptibility, and molar conductance measurements. The disappearance of hydroxyl band ν(O-H) of the phenolic group, and the lowering shift of the stretching frequency of the ν(C=N) azomethine band in the ligand after complexation, indicate the coordination through the phenolic oxygen atom (after deprotonation) and azomethine nitrogen atom of the Schiff base ligand **HL**. The lower values of molor conductance indicate the non-electrolytic nature of these complexes. The ESR spectrum of the copper complex of **HL** has octahedral geometry. The molecular structures were studied by PM3 method, also the heat formation, HOMO, LUMO and dipole moment were calculated to confirm the geometry of the ligand and the its complexes. The antimicrobial screening for the compounds underinvestigation **HL** and **1-4** was reported. The Schiff base ligand **HL** showed weaker to significant activity against some tested microorganisms. In the most cases, the increasing activity was exhibited upon coordination with metal (II)ions. In addition, calculated in silico, the pharmacokinetic parameters have promising futures for application of the ligand as drug.*

KEY WORDS: Sulfa guanidine, Molecular orbital, ADMT, antimicrobial.

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INTRODUCTION:

In recent years, Chemistry of Schiff bases has been studied, owing to their coordination properties and potential applications. They are widely used as selective metal extracting agents and in spectroscopic determination of certain transition metals [1-5]. M. M. El-Ajaily et. al. [6] have been studied Cobalt(II) and Copper(II) Schiff base complexes derived

from Salicylaldehyde and anthranilic acid compounds.They are bidentate ligands and have a large applications in chemistry and medicine.K. K. Maurya et. al. [7] have been synthesized and characterized some substituted Schiff bases viz., cyano acetyl benzalidene hydrazone (CABH), cyano-acetyl salicylidene hydrazone (CASH) and cyanoacetyl3:5 diiodo salicylidene hydrazone (CAISH). These cyano derivatives have been extensively used in medicine as drugs [8,9]. C. Topacli et. al. [10-13] have been studied the molecular structures and infrared spectra of Co, Ni, Cu and Zn complexes of two Schiff base ligands, viz. N - (o-vanillinidene) sulfanilamide (oVSaH) and N – (o-vanillinidene)sulfamerazine (oVSmrzH) in detail by PM3 method. Some ruthenium(II) complexes have been synthesized by the interaction of K_2RuCl_5.H2O with Schiff bases derived from 4-benzoyl-3-methyl-1-phenyl-2-pyrazoline-5-one and sulfadrugs, viz. sulfamerazine, and sulfadiazine and were characterized using IR, electronic and 1H NMR spectral analysis as well their molar conductance, cyclic- voltammetry by R. C. Maurya et.al.[14]. Sulfa gundine is considered as a Sulfa-drug derived from the parent compound, Sulfanilamide, which consider important class of drugs with several types of pharmacological agents possessing antibacterial , antithyroid , diuretic , hypoglycaemic , and anti-carbonic anhydrase [15,16]..In view of this, it was encourage us to synthesize new ligand derived from sulfagunidine, and evaluate its effect on the bioactivity when combined with salicylaldehyde, and study the effect of its transition metal complexes with Co, Ni, Cu and Zn ions on the antimicrobial activity of these compounds. Thus, this ligand and its complexes were tested for their antibacterial and antifungal activity, as well their cytotoxicity were tested in silico against ligand.

MATERIALS AND METHODS:

Materials:

Sulfa guanidine, salicylaldehyde, absolute ethanol (Fluka), Dimethylformamide (BDH), were used without further purification. Cobalt(II), Nickel(II), Copper(II), and Zinc(II) nitrates (BDH), were reagent grade.

Synthesis of the (E)-N-(diaminomethylene)-4-(2-hydroxybenzyl-ideneamino)benzenesulfonamide (HL):

Add (1.2219g , 10 mmol) of Salicylaldehyde, in 50 ml absolute ethanol drop- wise with stirring to Sulfa guanidine (2.142g, 10 mmol) in 50 ml absolute ethanol in 250 ml round flask. The mixture was heated to reflux for 6 hours, during which the color of the solution changes to Yellow . The formed yellow solid product was left to coagulate, then filtered off and recrystallized from absolute ethanol. The yield was (2.18g, 68.6 %), its melting point was 240 ^oC.

Synthesis of the complexes 1-4:

General procedures for synthesis of Metal complexes:

The following general procedures were used for preparing all of the complexes underinvestigation like that of the Cu(II)complex:

A solution of the $M(NO_3)_2 .3H_2O$ (5 mmol) in 50 ml absolute ethanol was added dropwise to a hot solution of the **HL** (5 mmol) in 50 ml absolute ethanol with the molar ratio 1:1. The reaction mixture was heated to reflux for 24 hours. The color of solution was dark green in the beginning of the reaction, and then became pale green at the end of the reaction. On cooling, the reddish brown solid formed which separated out, was filtered, washed with ethanol and then air-dried. The yield between (66-82%) with melting points between 238-242 ^oC. The solid complexes were kept in a desiccator.

Physical methods

All melting points reported for the compounds were measured on a Melting point SMP. The FT-IR spectra (350-4000 cm-1) of the investigated compounds were reported as KBr discs using FT-IR 8400S FOURIER TRANSFORM INFR ARED SPECTROPHOTOMETER (Shimadzu). The Electronic spectra were recorded on Shimadzu UV-Vis (1601) PC Spectrophotometer equipped with a 10 mm quartz cells, Personal Spectroscopy Software Version 3.6 Shimadzu, Tcc-240 A controller-stability± 0.1 ^{o}C Shimadzu. The Conductance mesurments were carried out in DMF solutions for **HL** complexes using a conductivity meter Metrohm-712 at 25 ^{o}C ± 0.1^{o}C. Elemental analysis for C, H, and N was performed by elemental analyzer and the metal determination was carried out using (Perkin Elmer 3100(U.S.A)). The ^{1}H-NMR measurements was carried out on a Varian Gemini-200,using deuterated dimethyl sulfoxide (DMSO-d_6) solvent. The chemical shifts (δ) were given down field relative to tetramethylsilane (TMS), as internal stander. Mass spectrum was carried out using MSQP 1000 EX Shimadzu. TGA and DTA curves were obtained using NETZSCH-gerateban Bestell-Nr 348472 C Electronic Spin Resonance (ESR) Spectrum was recorded on the Brucker ELXSYS 500 E X-band, detection for peak without need any calibration. Magnetic measurements were measured by the Gouy method at room temperature using a magnetic susceptibility balance (Johnson Matthey alfa product, Model No.MKI). Diamagnetic corrections calculated from Pascal's constants.

Anti-microbial screening

The anti-microbial activity of the synthesized compounds was tested against: i-Gram-negative bacteria: Escherichia coli (NCTC 10416), .ii- Gram-positive bacteria: Bacillus subtilis (NCIB 3610). Against two fungi : Aspergillus *niger* (ATCC-22019), and Trechodenma *viride* (IMRU-3669) using nutrient agar medium.

Paper disc diffusion technique

The sterilized (autoclaved at 120 °C for 30 min) medium at (40-50° C) was incubated (1 ml/100 ml of medium) with the suspension (10^5 cfu ml^{-1}) of the micro-organism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (mg\ml^{-1}) was placed on the solidified medium. The plates were pre-incubated for 1 h at room temperature and incubated at 37 °C for 24 and 48 hr for anti-bacterial and anti-fungal activities, respectively. Cefepime (mg/disc) was used as a standard for antibacterial and anti-fungal activity respectively.

Minimum inhibitory concentration (MIC)

MIC's. of the compounds were determined by agar streak dilution method. A stock solution for each synthesized compound (100 mg\ml^{-1}) in dimethyl formamide was prepared and graded quantities of test compounds were incorporated in specified quantities of molten sterile agar (nutrient agar for anti-bacterial activity and sabouraud dextrose agar medium for anti-fungal activity). A specified quantity of the medium at (40-50 °C) containing the compound was poured into a petridish to give a depth of 3-4 mm and allowed to solidify. Suspension of the micro-organism was prepared to contain approximately (10^5 cfu ml^{-1}) and applied to plates with serially diluted compounds in dimethylformamide to be tested and incubated at 37°C for 24 and 48 h for bacteria and fungi, respectively. The MIC was considered to be the lowest concentration of. the test substance exhibiting no visible growth of bacteria or fungi on the plate.

Molecular modeling

The structural model was built using the BUILDER module of MOE, optimization conformational analyses of the built molecules were performed in a two-steps procedure. First, these compounds were submitted to energy minimization tool using the included MOPAC 7.0, the geometry of the compounds was optimized using the semiemperical PM3 Hamiltonian with Restricted Hartree-Fock (RHF) and RMS gradient of 0.05 Kcal/mol. Then, the obtained model was implemented to the 'Systematic Conformational Search' of the MOE. All items were set as default with RMS gradient of 0.01 Kcal/mol and RMS distance of 0.1 Å.

RESULTS AND DISCUSSION:

The Schiff base ligand HL and its complexes

Infrared spectra

FTIR spectra of the complexes were recorded to confirm their structures . The vibrational modes frequencies and empirical assignments for the ligand and its transition metal complexes were listed in **(**Table 2**).** The vibrational modes assignments of the metal complexes were compared with those of the free ligand **HL**. There are some main features in the infrared spectra of the complexes. The first feature is the lowering shift of the stretching frequencies of the ν(— CH=N—) azomethine band occurs at 1627 cm^{-1} in the Schiff base free ligand ***HL*** by 6 cm^{-1} after complexation, indicating the coordination of azomethine nitrogen atom to metal ions [17,18]. The second feature is the disappearance of the ν(OH) phenolic band occured at 3430 cm^{-1} from the free ligand ***HL***, in all the complexes suggest the coordination of phenolic oxygen after deprotonation [19] . This result is further supported by the shift of ν(C– O) to 1289-1297 cm^{-1} (compared to that of the ***HL*** ligand) which was observed at 1280 cm^{-1}, after complexation. Also, the observed of two non ligand bands at low ranges 466-497 cm^{-1} and 358 – 383 cm^{-1} due to ν(M–O) [20], and ν(M–N) [21], respectively, in all the investigated complexes supported the coordination of phenolic oxygen and azomethine nitrogen atoms. The band observed at ~ 1321 cm^{-1} of the ν_{as} (O=S=O) of the ligand ***HL***, was remained almost at the same positions in its complexes which mean that the sulfonamide oxygen atom did not involve in coordination with the metal ions, the coordination of the water molecule was indicated by the appearance of a broad at 1439-1443 cm^{-1} due to $\delta(H_2O)$ in plane bending of coordinated water [22], and υ (OH) at 3429-3443 cm^{-1}

^{1}H-NMR spectra

^{1}H-NMR chemical shifts (ppm) of the Schiff base ligand **HL** were as follow, the signal observed at 12.719 ppm, was due to the phenolic OH proton of the **HL** ligand. The signal at 8.972 ppm (*j*=3 Hz) was assigned to azomethine group (CH═N—) which confirmed presence of Z form of ligand **HL**. The signals of H- protons of the phenyl group of salicylaldehyde (SALD) moiety were appeared at 7.042, 7.524, 7.875 ppm, while the signals of H- protons of the phenyl group of para substitution moiety were assigned at 6.752, 7.707 ppm for **HL** ligand. The chemical shifts of the (NH_2) protons of the sulfaguanidine (SG) moiety were observed at 6.961 ppm for the **HL** ligand.

Mass spectra

The mass spectrum of the ligand **HL**, revealed the molecular ion peaks at m/e 318 and base peak at m/e at 195 which support the identity of the proposed structure, and the fragmentation patterns was shown in (Sch. 3).

The mass spectrum of [Cu (HL)(NO_3)(C_2H_5OH)(H_2O)$_2$] complex **1**

revealed the molecular ion peak at m/e 524.30

Electronic spectra

Electronic spectral data of the ligand **HL** were recorded in DMF, and exhibited absorption bands at 284, 328, 362 and 367 nm. The first and second bands were correspond to $^1L \rightarrow {}^1A$ transitions of the phenyl rings [23]. The third and fourth bands correspond to $\pi \rightarrow \pi^*$'s of the azomethine group $(NH_2)_2C{=}N$ and –CH=N–, and $n \rightarrow \pi^*$ of the non-bonding electrons on the oxygen and nitrogen atoms [24]. On the other hand, the electronic spectrum of the Cu (II) complex **1** dissolved in DMF Table 4, which exhibited characteristic bands assigned to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ as well band due to $^2E_g \leftarrow {}^3T_{2g}$ (G) transition was observed at 712 nm. The electronic spectra of the Ni(II) complex dissolved in DMF, exhibited characteristic bands assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition, as well the Ni(II) complex **3** band at 715 nm was assigned to $^3T_{1g}(F) \leftarrow {}^3A_{2g}(F)$ Table 4. These bands associated with the octahedral structures [25]. Furthermore, the electronic spectra of the Co(II) complex **2** dissolved in DMF, exhibited the characteristic bands for $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ as shown in Table 4.

Magnetic measurements

The measured value of the magnetic moment μ_{eff} for complexes **1-4** (Table 1), were 1.76,1.77, 2.18 and 0 B.M. respectively, which indicate the octahedral structure [26]. The magnetic moment values measured were suggesting the possibility of the octahedral structures for the investigated complexes with low spin. The molar conductance measured for complexes **1-4** were 2.29, 2.52, 3.46 and 3.28 $Ohm^{-1}cm^{-2}$ mol^{-1} respectively, which indicate the non electrolytic nature of the reported complexes (Table 1).

The X-Band ESR spectrum of Cu (II) complex **1** was recorded in the solid state at 25^oC and was shown in figure 3. The spectrum show the $g\|$ = 2.058 and $g\perp$ = 2.035. These values indicate that the ground state of Cu(II) is predominately d_{x2_y2}, which supports octahedral geometry around the Cu (II) environment in the complex **1**[27]. The observed $g\|$ value for **1** is less than 2.3, which indicating that the bonds between the organic ligand and copper ion have a covalent character more than the ionic one. Furthermore, the exchange interaction between the copper centers in a polycrystalline solid was calculated (1.65) according to Hathway and Billing [28,29], it's value less than 4.0, which indicates a considerable exchange interaction in solid complex.

Finally, from the elemental analysis, molar conductivity, UV-visible spectral data, magnetic measurements, IR spectral data and EPR, we could confirmed the type of coordination of Schiff base **HL** ligand in its metal complexes, as monobasic ligand with NO bidentate sites. All the prepared complexes **1-4** were in the octahedral geometrical structures as shown in Scheme 2.

Molecular modeling

In trying to achieve better insight into the molecular structure of the most preferentially stereoisomer tautomeric ligand forms and it's complexes, the conformational analysis of the target compounds has been performed using the MMFF94 force-field [30,31], (calculations in vacuo, bond dipole option for electrostatics, PolakeRibiere algorithm, RMS gradient of 0.01 kcal/A mol) implemented in MOE [32]. The most stable conformer was fully geometrical optimized by PM3 [33] semi-empirical *Hamiltonian* molecular orbital calculation MOPAC package. The computed molecular parameters, total energy, binding energy, heat

of formation, the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) energies, and the dipole moment for studied compounds were calculated (Table 5 and 6). It is obvious that, there is a possibility of existence the prepared ligand in both E and Z stereoisomer forms (Structure 1, Scheme 4), and more than one tautomeric forms ***HL- HLc*** ligand (Structure 2, Scheme 4). The enhancement computed energies of calculated molecular parameters, showed that, the Z-isomer is most stable stereoisomer form of the prepared **HL** ligand(table 5, Fig.4), and ***Z-HL*** tautomeric form is most stable tatoumeric strcture (table 5, Fig.5).

The lowest minimization energy for the ligand **HL** and its Complexes structures **1-4** exhibited this features:

i- The lower HOMO energy values indicate that, weaker ability the molecules for donating electron. LUMO energy presents the ability of a molecule receiving electron (Table 5 and 6).

ii- The lowest minimization energy of the *Z*-form ligand **HL** structures exhibited a common arrangement of two phenyl ring coplanar with each other, and push H-salicaldehyde far from N-sulfa to prevent formation of hydrogen bond interaction, and the bond length for PhC N_{imin} and $C_{(5)}$—$O_{(7)}$ is 1.2863A° and 1.3556 (Fig. 4,5).

iii- The lowest minimization energy of the complexes **1-4** arranged the phenyl ring for sulfa guanidine perpendicular with each metal ring and phenyl ring of salicaldehyde (Fig. 6). The bond lengths of all the active groups taking part in coordination are longer than that already exist in the ligand.

iv- The bond angles of the $N_{(9)}$-$C_{(4)}$-$O_{(7)}$ moiety are changed due to coordination; which are altered from 116° on ligand to nearly range (63.1°- 71.8°) on complexes **1-4**.

v- All bond angles in complexes **1-4** are quite near to an octahedral geometry predicting sp^3d^2 hybridization.

Antimicrobial activity:

The main target of the production any antimicrobial compound is inhibiting the causal microbe without or with lowest any side effects on the patients. In addition, the basic idea of applying any chemotherapeutic agent, is depending on specificity of only one biological function control not multiple ones, which e.g. is the common in chemotherapeutic agent in anticancer treatment field. In the present time, the most anticancer agents used, was affected in both cancerous diseased cells and healthy ones. So, there is urgent need for having a chemotherapeutic agent, which controls only one function. The antibacterial activity of the tested compounds was higher than one test organism in vitro at 37 °C, which increase the chance of detecting antibiotic agent. The synthesized HL and it's complexes **1-4**, were tested using paper disc diffusion technique [34-38]. The tested bacterial strains were: (Gram-negative bacteria: Escherichia coli (NCTC- 10416), and Gram-positive bacteria: Bacillus subtilis (NCIB-3610). The tested fungus strains were: Trechodenma viride (IMRU-3669), and Aspergillus niger (ATCC-22019). Cefepime was used as standard drug. The results of antimicrobial activity taken as inhibition zone diameter and minimum inhibitory concentration (MIC.) were furnished in (Table 7 and 8) and depicted graphically in (Fig 5 a -d).

a. Against Escherichia coli(G^-):

The biological activity of Cu (II), Ni(II) and Zn (II) complexes is higher than free **HL** ligand, except Cu (II) complex **1** have same

activity at concentration (5mg/ml), and Zn(II) **4** complex with concentration (3mg/ml). While, all complexes (**1-4**) have low and\or same potency compared with standard drug.

b. Against *Bacillus subtilis* (G^+):

The biological activity of Cu (II), Ni(II) and Zn (II) complexes is higher than free **HL** ligand, except Cu (II) complex **1** has no activity with concentration (3mg/ml). While, all complexes (**1-4**) have low and\or same potency compared with standard drug.

c. Against *Fungi*:

The activity of Cu (II), Ni(II) and Zn (II) complexes have the same potency with free **HL** ligand. The (**HL** and **1-4**) have same potency compared with that of standard drug, excluded against Aspergillus niger and Trechodenma viride had low activity at (3mg/ml) .

Many scientists working in the new antitumours field search, depend basically on the line of antibiotics affecting Gram-negative bacteria [39-41], also, there are some organisms have proved to be difficult treat, and most of them are Gram-negative rods. It is therefore believed that, most of the complexes are biologically active against the Gram negative strains may affecting on barrier function of the envelope of these Gram-negative strains activity, which acting in similar way described earlier [39,41]. Since, Gram-negative bacteria are considered a quantitative microbiological method testing beneficial drugs in both experimental and clinical tumour chemotherapy [42]. Therefore we claimed that, the synthesis of these complexes might be established as a new line for searching about new antitumour agents.

ADMET factors profiling:

Oral bioavailability was considered playing an important role for the development of bioactive molecules as therapeutic agents. Many potential therapeutic agents fail to reach the clinic, because of their ADMET (absorption, distribution, metabolism, elimination and toxic) Factors. Therefore, a computational study for prediction of ADMET properties of the molecules was performed for compounds **HL** and **SG**, by the determination of topological polar surface area (TPSA), a calculated percent absorption (%ABS) which was estimated by Zhao et al. equation[43], and ‘‘rule of five’’, which have been formulated by Lipinski[44], which established that, chemical compound could be an orally active drug in humans, if no more than one violation of the following rule: i) ClogP (partition coefficient between water and octanol) < 5, ii) number of hydrogen bond donors sites ≤ 5, iii) number of hydrogen bond acceptors sites ≤ 10, iv), molecular weight <500 and molar refractivity should be between 40-130. In addition, the total polar surface area (TPSA) is another key property linked to drug bioavailability, the passively absorbed molecules with (TPSA>140) have low oral bioavailability[45]. All calculated descriptors were performed using MOE Package [32], and their results were disclosed in (Table 9). Our results revealed that, the CLogP (factor of the lipophilicity [46] was less than 5.0, the molecular weight (MW< 500), hydrogen bond acceptors (7) , hydrogen bond donors (5) and molar refractivity values approximately 85.87 more than (**SG**) drug which fulfill Lipinski’s rule. Also, the percent absorption of compounds **HL** was less than (**SG**) by about 2 degrees.From these data one can suggest that, (**HL**) ligand can be used as a good oral absorption antimicrobial compound with less toxicity than sulfagundine as reference drug.

CONCLUSIONS:

The synthesized Schiff base ligand HL derived from sulfaguanidine was coordinated with the Co, Ni, Cu and Zn(II) ions through azomethine-N atom and phenolic hydroxyl O atom . The structure of the ligand and its metal complexes were confirmed by Micoranalysis, different spectral analyses, moler conductance and magnetic measurements.As well as molecular orbital calculations supported the experimental results. Antimicrobial studies against most tested strains showed that, the structures of the metal complexes have moderate to significantly activity, and exhibited more potency than Schiff base ligand **HL**. Furthermore, the pharmakinetic screening showed that the **HL** is good oral absorption and less toxic than sulfagundine.

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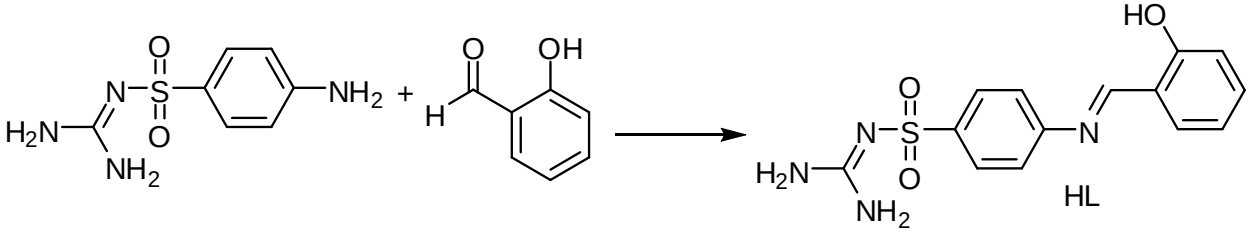
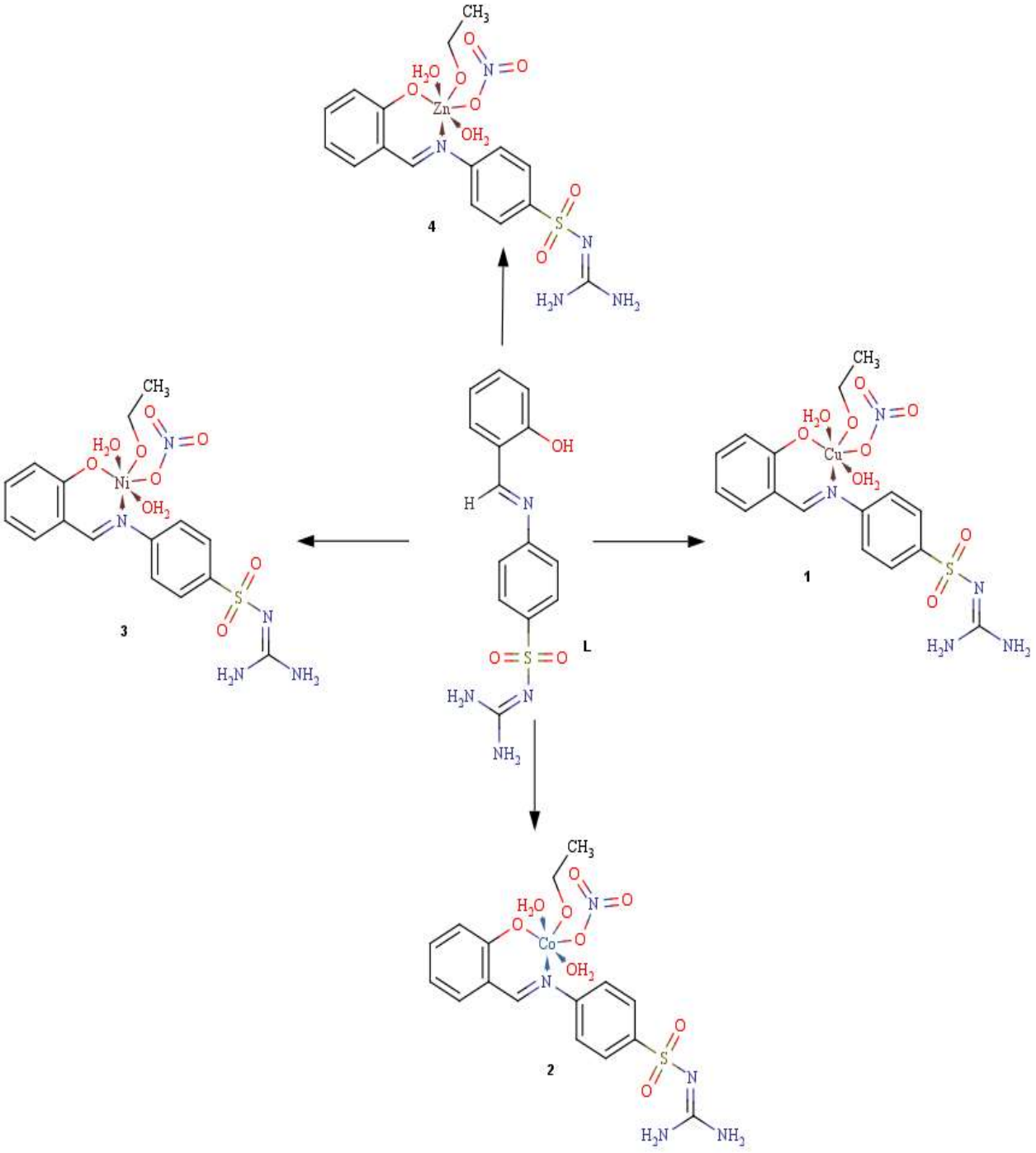
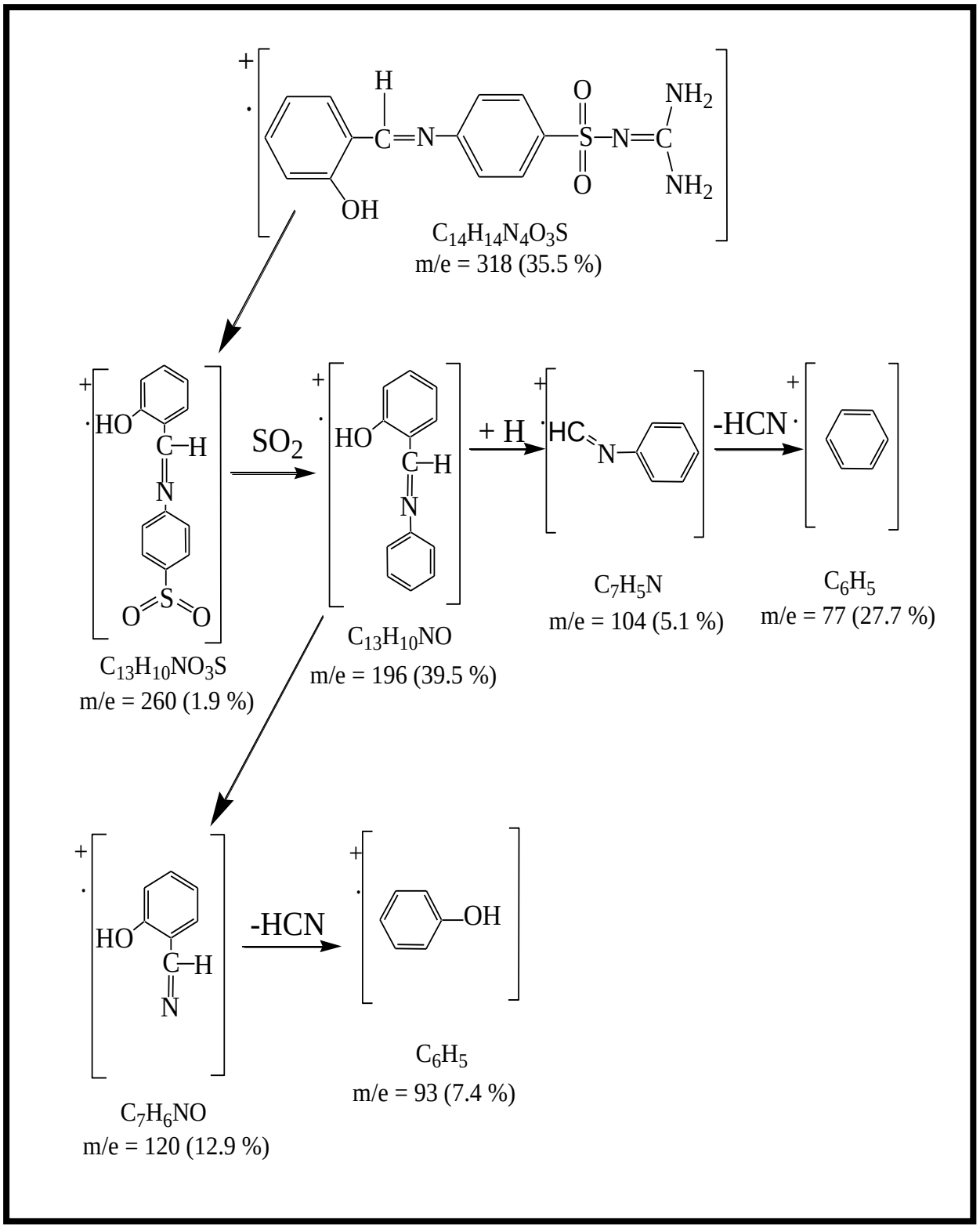
SCHEMES AND TABLES:



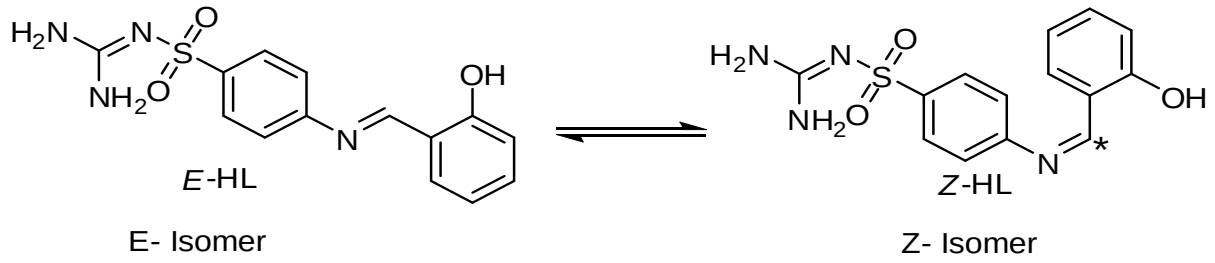
Scheme 1:Synthesis of Schiff bases derived from Sulfagundine.



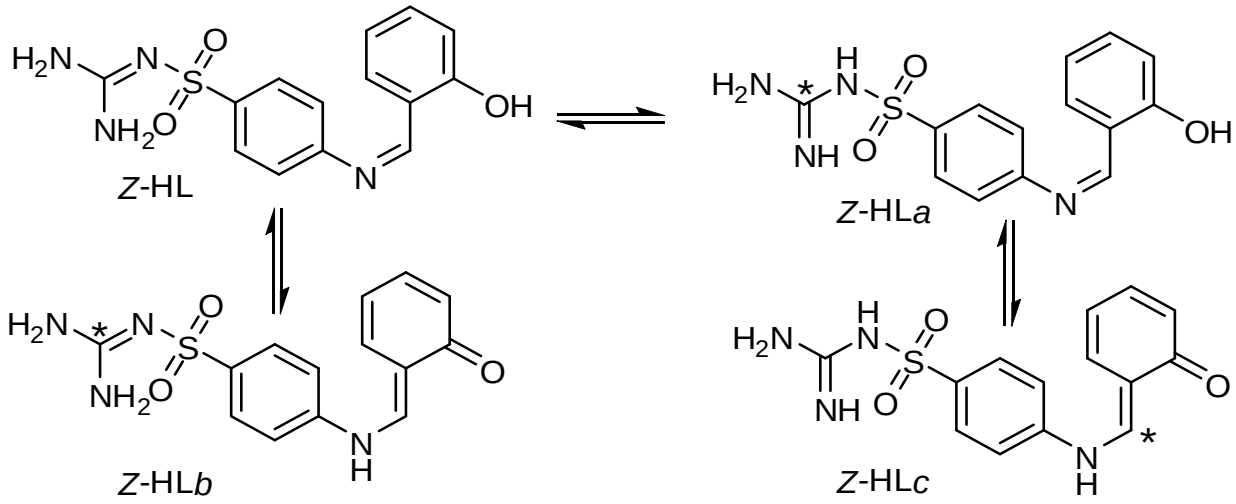
Scheme 2: synthesis of metal complexes Schiff bases derived from sulfagundine with Cu (II) 1 , Co (II) 2 , Ni(II) 3, and Zn(II) 3 ions.



Scheme 3: Fragmentation pattern of the mass spectrum of ligand **(HL)**.



Strcture 1: Stero isomer oF chief ligand HL



Strcture 2: tatoumaric forms of chief ligand HL

Scheme 4: The most stable stereoisomer (structure 1), the most stable tatoumaric structure (structure2).

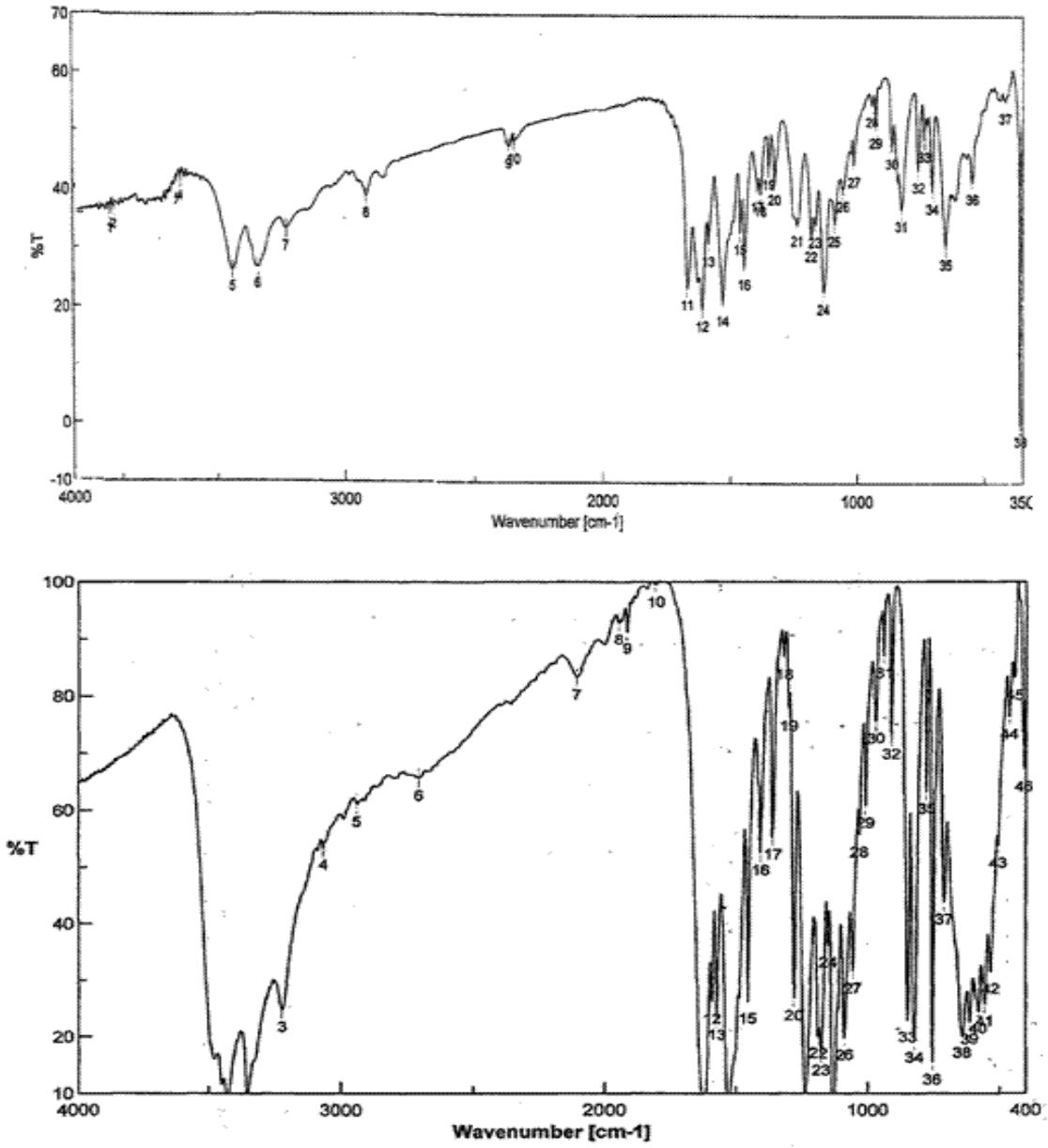


Fig. 1: Infrared spectra of the : (a)**HL** ligand , (b)[**HL**-Cu] complex.

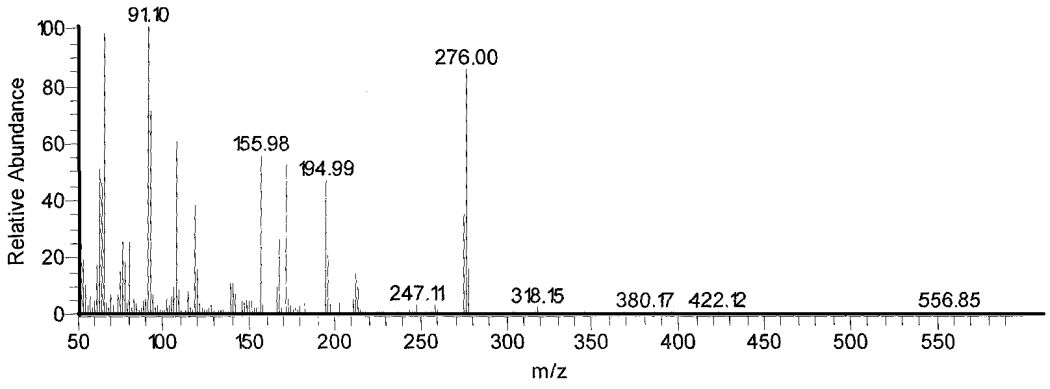


Fig. 2: Mass spectrum of the (a) $[Cu(L_a)(NO_3)(C_2H_5OH)(H_2O)_2]$.

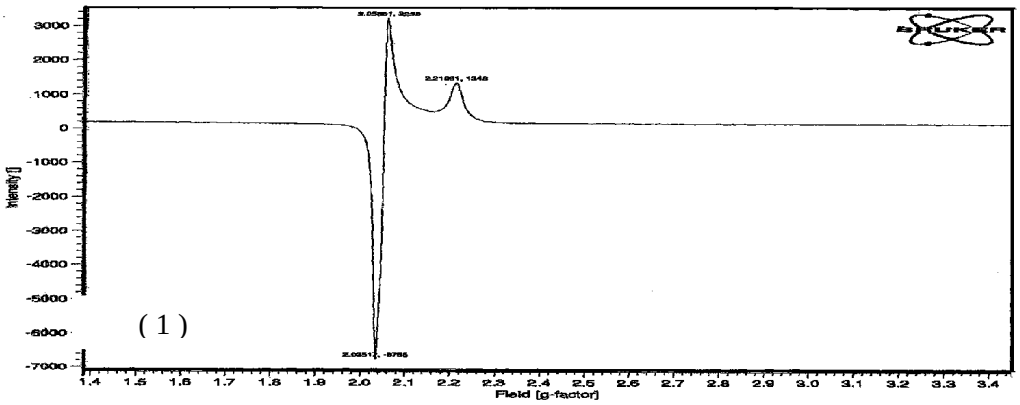


Fig.3 : ESR spectrum of the $[Cu(HL)(NO_3)(C_2H_5OH)(H_2O)_2]$ complex.

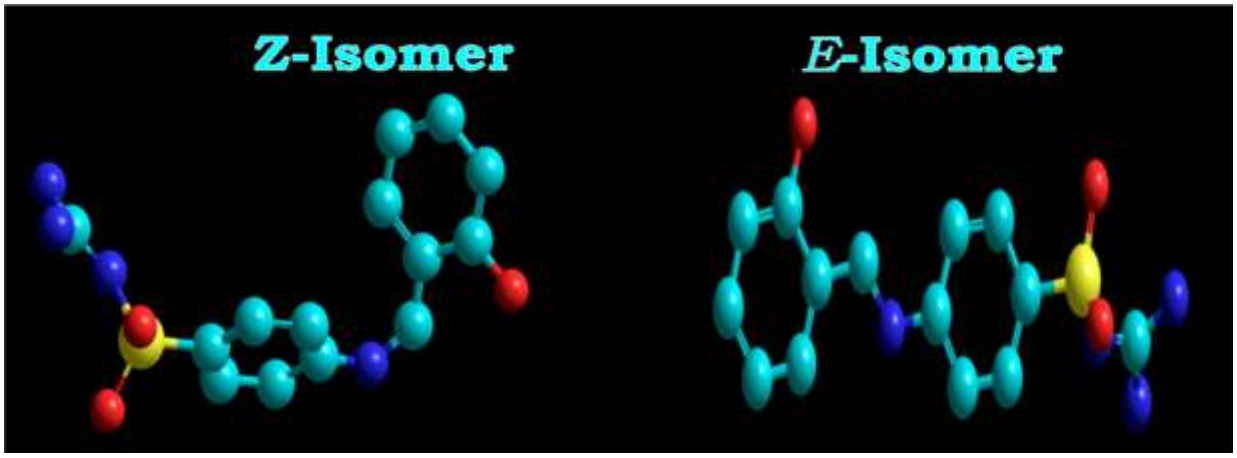


Fig. 4. Ball and stick rendering for the major tatoumeric structure of the ligand as calculated by PM3 semi-empirical molecular orbital calculations.

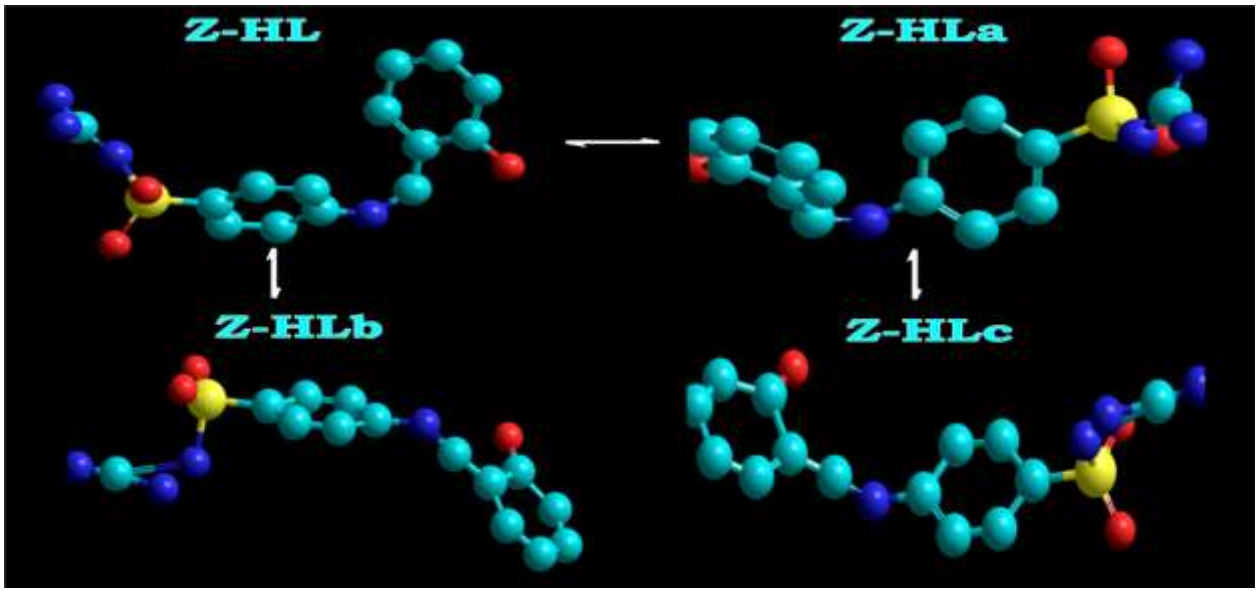


Fig. 5. Ball and stick rendering for the major tatoumeric structure of the ligand as calculated by PM3 semi empirical molecular orbital calculations.

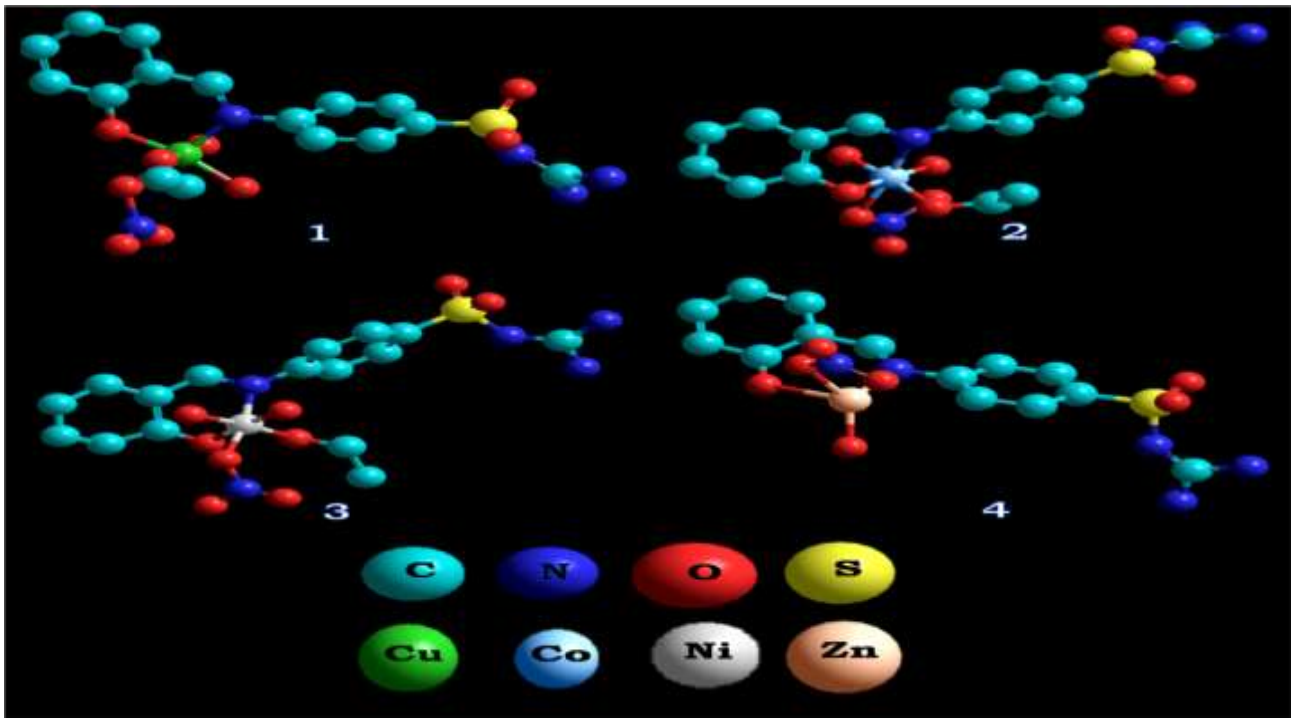


Fig. 6. Ball and stick rendering of the complexes as calculated by PM3 semi-empirical molecular orbital calculations.

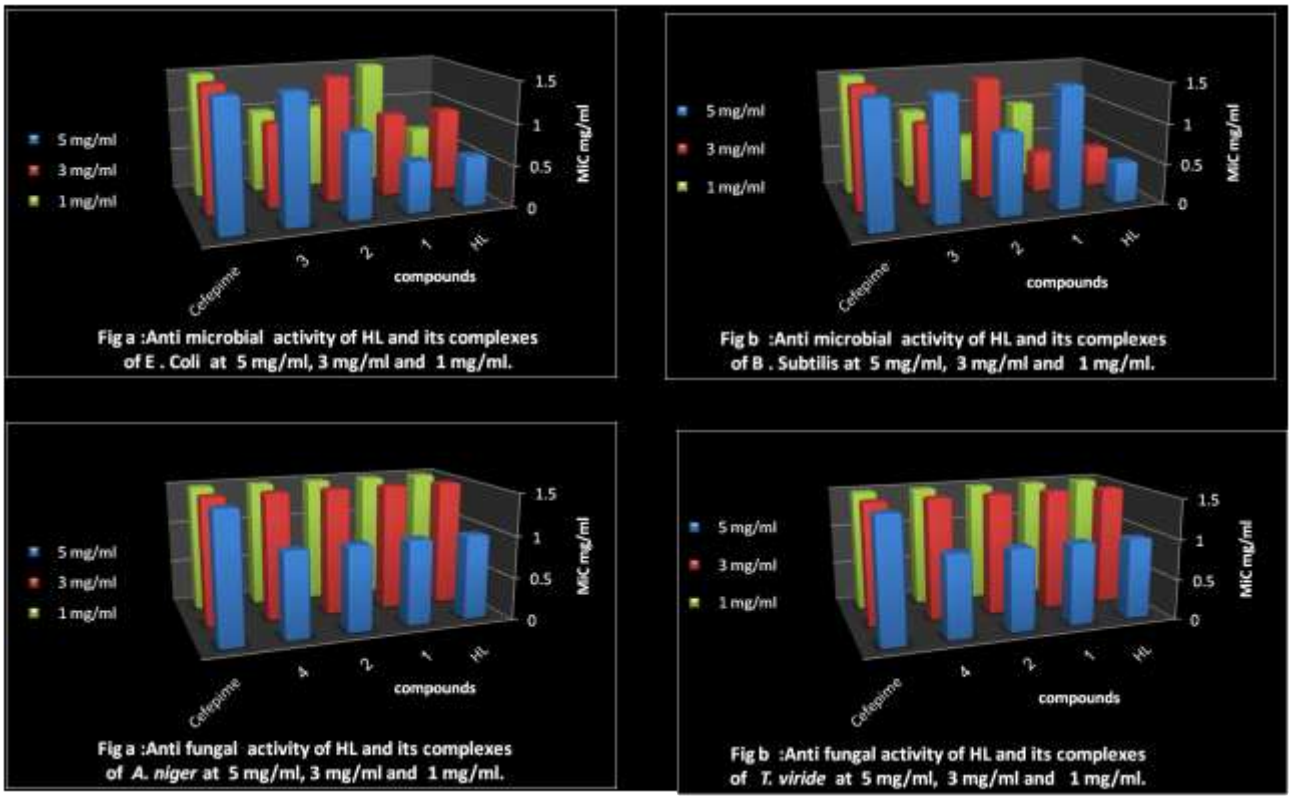


Fig.7: Biological activity of HL and its complexes at (5, 3 and 1) mg/ml.

Table 1 : Physical and analytical data for the **HL** and transition metal complexes**(1-4):**

Compounds	Molecular formula (M . Wt)	Color	M.P ^{o}C	%Yield (g)	Elemental analyses;calc .(found).%				μ_{eff} (BM)[a]	Λ^{b}
					C	H	N	M		
HL	$C_{14}H_{14}N_4O_3S$ (318)	Yellow	240	68.6	52.8 (52.5)	4.4 (5.0)	17.6 (16.7)	___	___	9.54
1	$C_{16}H_{23}N_5O_9SCu$ $[Cu(HL)(NO_3)(C_2H_6O)(H_2O)_2]$ (524.9)	Brown	244	66	44.15 (47.67)	3.4 (4.15)	14.7 (15.29)	___	1.66	2.29
2	$C_{16}H_{23}N_5O_9SCo$ $[Co(HL)(NO_3)(C_2H_6O)(H_2O)_2]$ (520.3)	Pale yellow	233	82	44.6 (52.67)	3.45 (4.85)	14.8 (17.14)	11.32 (11.27)	1.37	2.52
3	$C_{16}H_{23}N_5O_9SNi$ $[Ni(HL)(NO_3)(C_2H_6O)(H_2O)_2]$ (520.1)	Pale yellow	242	92	44.7 (52.72)	3.46 (4.91)	14.90 (17.03)	___	1.55	3.46
4	$C_{16}H_{23}N_5O_9SZn$ $[Zn(HL)(NO_3)(C_2H_6O)(H_2O)_2]$ (526.8)	Pale yellow	238	68	43.93 (52.21)	3.39 (4.88)	14.64 (16.93)	12.41 (10.88)	1.44	3.28

Table 2: ^{1}H- NMR chemical shifts (ppm) and infrared bands for the Schiff bases **HL** ligand at room temperature.

Assignments	δ(^{1}H) ppm in acetone-d_6	IR bands
δ (OH) phenolic group	12.719 -12.728	3430 vs, br
δ (CH) Azomethine	8.972- 8.982	1618 vs
δ (NH_2)$_2$ and NH	6.961	3210 vs, br 3190 s, br
Phenyl ring (1)	6.752- 7.707	
phenyl ring (2)	7.042 -7.481 -7.524 - 7.875	3090 br, w
SO_2		1130 s 1350 s

s = strong, m = medium, w = weak, vs = very strong, br = broad

Table 3 : Vibrational frequencies of the transition metal complexes and theirs assignments.

Cpds	ν (-CH=N-)	NO_3			ν(M-O)	ν(M-N)
		ν_{as}	δ_{aop}	δ_{Ip}		
1	1612v.s	1352m	841m,sh	742m	497sh	497sh
2	1619v,s	1303w.s	—	—	466v.w	381sh
3	1618v.s	1281m	—	—	466v.w	382v.w
4	1618v,s	1281m	—	—	466w	358v.s

s = strong , m = medium , w = weak , vs = very strong , br = broad , sh= shoulder , δ_{aop} : out –of plane Bend, δ_{Ip} : In– plane Bend.

Table 4: Electronic absorption bands (nm) of the **HL** ligand and its transition metal complexes **1-4** and their assignments.

CPD	$^1La \rightarrow {}^1A$ phenyl ring	$^1L_b \rightarrow {}^1A$	$\pi \rightarrow \pi^*$ phenyl ring	$n \rightarrow \pi^*$	d-d transition	d-d transition Assignment
HL	291(0.82)	330(0.83)	362(0.48)	367(0.55)	—	
1	292(0.85)	326(0.88)	360(0.46)	362(0.55)	712(0.35)	$^3T_{2g}(G) \leftarrow E_g$
2	292(0.85)	328(0.82)	359(0.51)	369(0.42)	525(0.57)	$^1A_{2g} \leftarrow {}^1A_{1g}$
3	293(0.92)	329(0.88)	365(0.39)	368(0.64)	747(0.26)	$^4A_{2g}(F) \leftarrow {}^4T_{1g}(F)$

(a) Values of the absorbances at λ_{max} are in parentheses

Table 5: Calculated energies of possible steroisomer and tatoumaric forms of HL ligand:

Cpd.	***E*[a]**	***HF*[b]**	***HOMO*[d]**	***LUMO*[e]**	***Dipol*[e]**
E-HL	-82744.422	-29.610	-9.2455196	-9.014	4.15
Z-HL	-82766.961	-29.918	-9.2455196	-9.041	4.755
Z -HL*a*	-82757.961	-19.179	-9.2455196	-9.040	6.694
Z -HL*b*	-82747.031	-10.459	-8.9082203	-8.586	6.337
Z -HL*c*	-82741.375	-4.931	-9.1496296	-8.892	6.423

[a]E: The total energy (kcal/mol).,[b]HF: heat of formation (kcal/mol), [c]*HOMO*: Highest Occupied Molecular Orbital(eV)*]*., [d]LUMO: Lowest Occupied Molecular Orbital(eV), [e]Dipole*: dipole moment calculated* (*Deby)* .

Table 6: Calculated energies of complexes(**1-4**) of HL ligand*:*

Cpd.	***E***[a]	***BE***[b]	***HF***[c]	***HOMO***[d]	***LUMO***[e]	***E.Gap***[f]	***Dipol***[g]
1	-16205.35	-5322.69	-298.28	-9.09	-9.08	-0.01	3.252
2	-152932.23	-5472.407	-426.2	-8.736	-8.66	-0.076	7.908
3	-158324.53	-5300.734	-306.325	-7.00925	-9.22	2.21075	8.883
4	-113673.65	-4099.91	49.351	-9.73	-9.72	0.01	9.243

[a]E: The total energy (kcal/mol).,[b] ***BE***: binding energy (kcal/mol), [c]HF: heat of formation (kcal/mol),[d]*HOMO*: Highest Occupied Molecular Orbital(eV)*]*., [e]LUMO: Lowest Occupied Molecular Orbital(eV) **,** [f]***E.Gap:*** *Energy Gap,,*[g]Dipole*: dipole moment calculated(Deby).*

Table 7: Antibacterial activity of L ligand and its metal complexes.

Compound	*Escherichia coli*			*B acillus. Subtilis*		
	5 mg/ml	3 mg/ml	1 mg/ml	5 mg/ml	3 mg/ml	1 mg/ml
HL	+	++	+	_	_	_
1	+	++	+++	+ + +	_	+ +
3	++	+++	++	+ +	+ + +	+
4	+ + +	+ +	+ +	+ + +	+ +	+ +
Cefepime	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +

The test was done using the diffusion agar technique.
Weak active: Inhibition values = 0.1–0.6 cm beyond control = +.
Moderate active: Inhibition values =0.65–1.0 cm beyond control =++.
Highly active: Inhibition values = 1.1–1.5 cm beyond control =+++.

Table 8 : Antifungal activity of **HL** ligand and its metal complexes.

Compound	*Aspergillus niger*			*Trechodenma viride*		
	5 mg/ml	3 mg/ml	1 mg/ml	5 mg/ml	3 mg/ml	1 mg/ml
HL	++	+++	+++	++	+++	+++
1	++	+++	+++	++	+++	+++
3	++	+++	+++	++	+++	+++
4	++	+++	+++	++	+++	+++
Cefepime	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +

The test was done using the diffusion agar technique.
Weak active: Inhibition values = 0.1–0.6 cm beyond control = +.
Moderate active : Inhibition values =0.65–1.0 cm beyond control =++.
Highly active : Inhibition values = 1.1–1.5 cm beyond control =+++.

Table9: Pharmacokinetic parameters important for good oral bioavailability of compounds (**SG and HL**):

Cpd.	**TPSA**	**%ABS**	***C*LogP**	***LogS***	***MW***	***nON***	***nOHNH***	***Lip-V.***	**V**	***mr***
SG	*124.56*	66.026	- 0.97	*-1.67*	204.00	*6*	*6*	*1*	*210.30*	53.26
HL	*131.13*	63.026	*1.12*	*-3.52*	304.00	*7*	*5*	*0*	*341.63*	*85.87*

TPSA: Total Polar surface area, **%**ABS: 109-0.345 * TPSA, *C Log P: Calculated lipophilicity., , Log S: Solubility parameter, nON: Number of hydrogen bond acceptor, nOHNH: Number of hydrogen bond donor, Lip-V: Number of violation from Lipinski's rule of five.,* **V***: Volume (A^3), mr: Molar Refractivity*

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