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SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL AND CYTOTOXIC STUDIES ON SOME NOVEL TRANSITION METAL COMPLEXES OF SCHIFF BASE LIGAND DERIVED FROM SULFADIAZINE WITH MOLECULAR ORBITAL CALCULATIONS

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ABSTRACT

Some selected solid complexes of the Schiff base ligand HL derived from Sulfadiazine with Co(II), Ni(II) and Cu(II) ions were synthesized and characterized by Micro-analysis, FTIR, Electronic, Mass, and ESR Spectral Analyses, Magnetic susceptibility and Molar Conductance Measurements. The disappearance of ν(O-H) hydroxyl band of the phenolic and the lowering shift of the stretching frequency of the ν(CH=N) azomethine band in the ligand after complexation, indicated the coordination through the phenolic oxygen atom (after deprotonation) and azomethine nitrogen atom respectively of the Schiff base ligand HL. The lower values of molar conductance indicate the non-electrolytic nature of these complexes. The ESR spectrum of the HL copper complex has octahedral geometry. The molecular structures of the investigated compounds were studied by PM3 method, also the heat of formations, HOMO, LUMO and dipole moments were calculated to confirm the geometry of the ligand and the it's complexes. The antimicrobial screening of the synthesized compounds HL and its complexes 1-3 were investigated. The Schiff base ligand HL showed weaker to significant activity against one or more bacterial and fungal strains. In most of the cases higher activities were exhibited upon coordination with metal ions(II). In addition, calculations in silico, the Pharmacokinetic parameters have promising features for applying the ligand as drug.

Keywords: Sulfadiazine, Schiff base, ADMET, Molecular Orbital calculations.

1. INTRODUCTION

Chemistry of some Schiff bases and their transitions metal complexes have been studied by El- Sayed, et al. [1] in recent years Farag, et al. [2] .Sulfadiazine 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 [3], antithyroid [4], diuretic [5, 6], hypoglycaemic [7], and anti-carbonic anhydrase [8, 9]. The Lead (II) complexes of Schiff bases ligands derived from sulfa drugs were tested against gram positive (S.aureus and S.subtilis)

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and gram negative (E.coli) bacteria and showed high activity than the ligands [10]. Antimicrobial study of some novel metal complexes of Schiff base derived from [N1-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfanilamide]and 2-thiophene-carboxaldehyde suggested that metallation increases activity and the greater activity of these investigated complexes were explained on the bases of their particle size and the size of their metal ions [11, 12]. Also, complexes of Schiff bases ligand derived from sulfa drugs have been showed effective fungicidal activity [12]. Schiff base ligand under investigation in the present work used as analogs, as chelate extraction reagents for divalent metal cations such as Mn2+,Co2+, Ni2+, Cu2+, Zn2+, Cd2+ and Pb2+ [13, 14]. Some ruthenium(II) complexes have been synthesized by the interactions of K2RuCl5.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-voltametry by Maurya and Patel [15], Maurya and Rajput [16]. In view of this, it was encourage us to synthesize new ligand derived from sulfadiazine, and evaluate it's effect on the bioactivity when combined with *Salisaldehyde*, and study the effect of metals such as Cu, Co and Ni on the antimicrobial activity of these compounds. Thus, these ligand and it's complexes were tested for their antibacterial and antifungal activity, and tested it's cytotoxicity in silico against ligand.

2. EXPERIMENTAL

2.1. Materials

Sulfadiazine, Salicylaldehyde, absolute Ethanol (Fluka), Dimethylformamide (BDH), were used without further purification. Cobalt(II), Nickel(II), and Copper(II) nitrates (BDH), were reagent grade.

2.2. Synthesis of the HL Ligand Derived From Sulfadiazine

Add (1.2219g , 10 mmol) of Salicylaldehyde, in 50 ml absolute ethanol drop- wise with stirring to Sulfadiazine (2.50g, 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 (2.457g, 69.6 %), its melting point was 259 °C.

Table 1 : Physical and analytical data for the **HL** and it's transition metal complexes**(1-3):**

Compounds	Molecular formula (M . Wt)	Color	M.P °C	%Yield (g)	Elemental analyses;calc .(found).%				μ_{eff} (BM)[a]	Λ^{b}
					C	H	N	M		
HL	$C_{17}H_{14}N_4O_3S$ (354)	Yellow	259	69.0	57.6 (57.2)	3.9 (4.0)	15.8 (15.9)	—	—	—
1	$C_{19}H_{23}N_5O_9SCu$ $[Cu(L)(NO_3)(C_2H_6O)(H_2O)_2]$ (561.0)	Pale green	309	78.0	48.97 (49.55)	3.12 (3.24)	13.44 (14.12)	—	1.36	3.88
2	$C_{19}H_{23}N_4O_3SCo$ $[Co(L)(NO_3)(C_2H_6O)(H_2O)_2]$ (556.4)	Orange	319	72.0	49.52 (57.55)	3.15 (4.32)	13.59 (16.26)	10.58 (8.33)	1.46	5.83
3	$C_{19}H_{23}N_4O_3SNi$ $[Ni(L)(NO_3)(C_2H_6O)(H_2O)_2]$ (556.2)	Pale yellow	316	70.0	49.55 (52.67)	3.15 (4.11)	13.60 (15.84)	10.55 (13.62)	1.28	5.18

(a) Magnetic moment values , μ_{eff} is the magnetic moment of the metal ions B.M : (Bohr magnetone) .
(b) Molar conductance (Ohm^{-1} cm^{-1} mol^{-1}) was measwed in ($10^{-4}mol^{-1}m^{-1}$) DMF solvent .

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2.3. Synthesis of the Complexes 1-3

2.3.1. General Procedures for Synthesis of the Metal Complexes

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

A solution of the $Cu(NO_3)_2 .3H_2O$ (1.208 g, 5 mmol) in 50 mL absolute ethanol was added dropwise to a hot solution of the HL (1.77 g, 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 yields were between (70-78%), with melting points between 309-319 ^oC. The solid complexes were kept in a desiccator.

2.4. 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 ^oC Shimadzu. The Conductance mesurments were carried out in DMF solutions for HL complexes using a conductivity meter Metrohm-712 at 25 ^oC ± 0.1^oC. 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 spectra were 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 and 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.

2.5. 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 fungis: Aspergillus *niger* (ATCC-22019), and Trechodenma *viride* (IMRU-3669) using nutrient agar medium.

2.5.1. 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

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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 hrs for anti-bacterial and anti-fungal activities, respectively. Cefepime (mg/disc) was used as a standard for antibacterial and antifungal activity respectively.

2.5.2. Minimum Inhibitory Concentration (MIC)

MIC's. of the compounds were determined by agar streak dilution method. A stock solution for each the synthesized compound (100 mg\ml^{-1}) in dimethyl formamide was prepared and graded quantities of the test compounds were incorporated in specified quantity 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 (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 hrs 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.

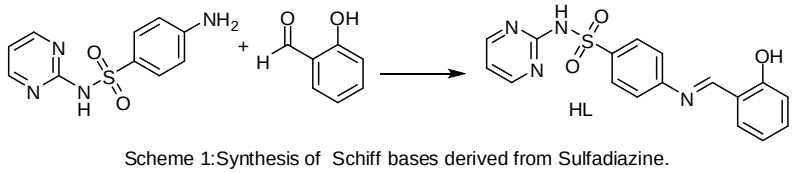
2.6. Molecular Modeling

The structural model was built using the BUILDER module of MOE, Optimization Conformational analyses of the built molecules were performed in a two-step 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.

3. RESULTS AND DISCUSSION

3.1. The Schiff base Ligand HL and its Complexes

The Schiff base of sulfadiazine ligand HL was prepared by the condensation of salicylaldehyde (SALD) with sulfadiazine (SD) in the molar ratio 1:1 (Scheme1). The ligand HL was reacted with Cu(II), Co(II) and Ni(II) ions to yield the corresponding metal complexes (Scheme 2), the physical and analytical data of HL and corrspponding transition metal complexes 1-3 were listed in (Table 1).



Scheme 1:Synthesis of Schiff bases derived from Sulfadiazine.

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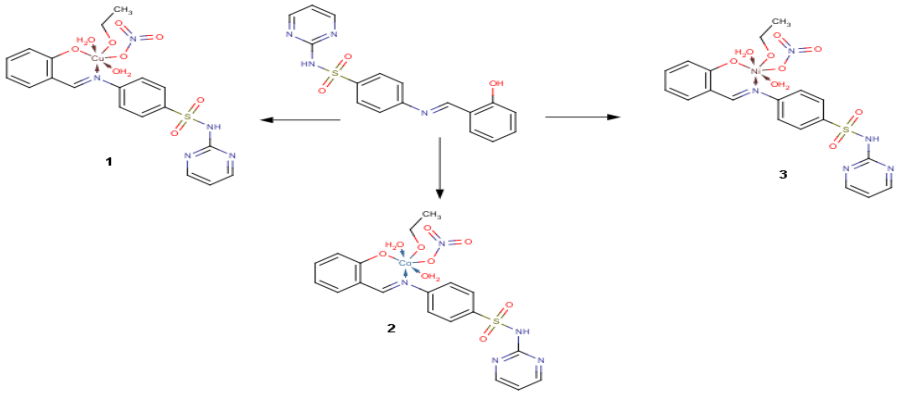
3.1.1. Infrared Spectra

The vibrational modes of Infrared spectrum of the ligand HL, the empirical assignments was listed in (Table 2). The disappearance of both stretching frequencies, ν (NH_2) of para position of the amino group, NH_2 in the infrared spectrum of the HL ligand which occurs as broad bands at 3422*s* cm^{-1}, 3260*s* cm^{-1} and 3356*m* cm^{-1} in the free Sulfadiazine (SD), and the stretching frequency of the C=O group of aldehyde, which occurs at 1664 *v.s.* cm^{-1} in the free salicylaldehyde (SALD),confirmed the formation of the ligand. On the other hand, the appearance of the most intense band at 1620 *s.* cm^{-1} which was assigned to the stretching frequency of the azomethine (-CH=N) group the ligand HL, which confirmed the proposed structure of ligand HL (Scheme 1) [16].



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

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

Assignments	δ(^{1}H) ppm in acetone-d_6	IR bands
δ (OH) phenolic group	12.524	3478 w, br
δ (CH) Azomethine	8.963	1620 vs
(NH) SO_2NH	11.840	3210 vs, br 3190 s, br
Pyrmidine ring	7.000- 8.500	
Phenyl ring (1)	6.590- 7.709	
phenyl ring (2)	7.413- 7.491- 7.567- 7.709	3090 br, w
SO_2		1135 s 1365 s

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

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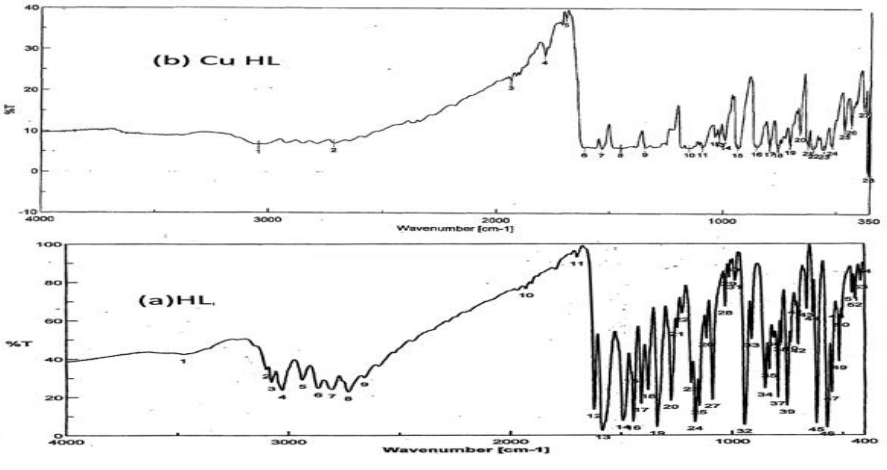
FTIR spectra of the complexes were recorded to confirm their structures. The vibrational modes frequencies and empirical assignments for the ligand and its transition metal complexes were listed in Table 3 and shown in Figure 1. The vibrational modes assignments of the metal complexes were compared with 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 1620 cm^{-1} in the Schiff base free ligand *HL* by 38 cm^{-1} after complexation, indicating the coordination of azomethine nitrogen atom to metal ions [17], The second feature is the disappearance of the ν(OH) phenolic band occured at 3478 cm^{-1} in the free ligand *HL*, in all the complexes suggest the coordination of phenolic oxygen after deprotonation [18] . This result is further supported by the shift of ν(C– O) to 1362 cm^{-1} (compared to that of the *HL* ligand) which was observed at 1281 cm^{-1}, after complexation. Also, the observed of two non ligand bands at range 457- 497 cm^{-1} and 375 – 395 cm^{-1} due to ν(M–O) [19], and ν(M–N) [11], respectively, in all the investigated complexes supported the coordination of phenolic oxygen atom and azomethine nitrogen atom. The ν(NH) bands due to amino group in the uncoordinated Schiff base free ligand HL remains unchanged in the spectra of it's complexes. This confirmed that the amino nitrogen atom were not contribute in coordination. The band observed at ~ 1339 cm^{-1} of the ν_{as} (O=S=O) of the ligand *HL*, were remained almost at the same positions in its complexes which mean that the sulfonamide oxygen atom did not contribute in coordination with the metal ions, the coordination of the water molecule was indicated by the appearance of a broad at 1529-1574 cm^{-1} due to $\delta(H_2O)$ of coordinated water [20].

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



3.1.2. ^{1}H-NMR Spectra

^{1}H-NMR chemical shifts (ppm) of the Schiff base ligand **HL** listed in (table 2). From (table 2), the signal observed at 12.524 ppm was due to phenolic OH proton of the ligand **HL**. The signal (δ) at 8.963 ppm was assigned to the azomethine group (CH=N–) . The signals of H-

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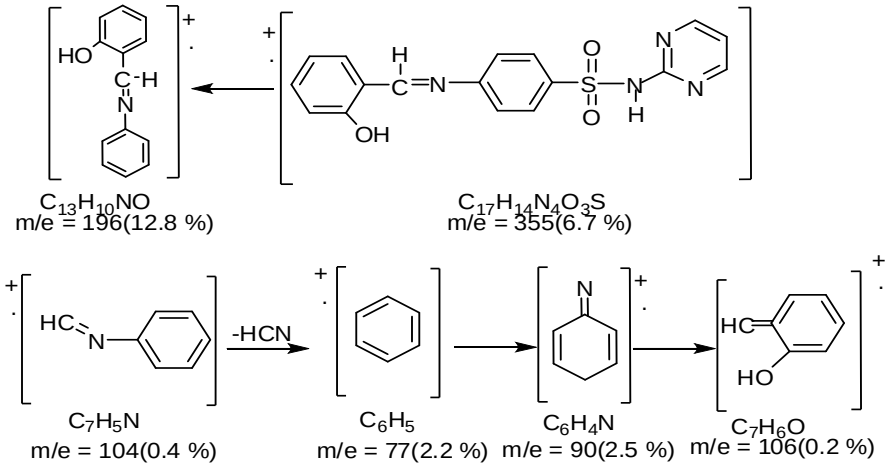
protons of the phenyl group of salicylaldehyde (SALD) moiety were appeared at 7.413, 7.567 ppm while the H- protons for the phenyl signals of the *para* substitution moiety were assigned at 6.590, 7.709 ppm. The chemical shift of the amino NH proton of the sulfadiazine (SD) moiety was observed at 6.961 for the ligand.

3.1.3. Mass Spectra

The mass spectrum of the ligand HL, revealed the molecular ion peaks at m/e 354 and base peak at m/e at 290 which support the identity of the proposed structure, and the fragmentation patterns was shown in (Scheme 3).



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

3.1.4. Electronic Spectra

Electronic spectral data of the ligand **HL** were recorded in DMF, and exhibited absorption bands at 291, 330, 362 and 370 nm. The first and second bands were correspond to $^1L \rightarrow {}^1A$ transitions of the phenyl rings [21]. The third and fourth bands correspond to the $\pi \rightarrow \pi^*$'s of the azomethine groups –CH=N– . The last band corresponds to the $n \rightarrow \pi^*$ due to the non-bonding electrons on the oxygen and nitrogen atoms [22]

Table 3 : Vibrational frequencies of the HL- 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	1614v,s	1347v.s	___	762m	464s	375w
2	1582v,s	1278m	836m	706s	457w.sh	395sh
3	1583v,s	1279m	836m	706s	457v.w	382v.w

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

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The electronic spectrum of the Cu (II) complex **1** dissolved in DMF (Table 4), which exhibited characteristic bands assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ as well band due to $^2E_g \leftarrow {}^3T_{2g}$ (G) transition was observed at 712 nm. The electronic spectra of the Co(II) complex **2** dissolved in DMF, exhibited characteristic bands assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition. As well band at 525 nm was assigned to $^3T_{1g}(F) \leftarrow {}^3A_{2g}(F)$, These bands associated with the octahedral structures [23] (Table 4). Furthermore, the electronic spectra of the Ni(II) complex **3** dissolved in DMF, exhibited the characteristic bands for $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ as shown in Table 4.

However, from the obtained date of the elemental analysis, infrared, mass spectra, ^{1}H-NMR and Electronic spectra, one can suggest, that, Schiff base **HL** act as monobasic ligand with NO bidentate sites.

3.1.5. Magnetic and Molar Conductivity Measurements

The measured values of the magnetic moment μ_{eff} for complexes **1-3** (Table 1), were 1.36, 1.46 and 1.28 B.M. respectively, which indicate the octahedral structure [24]. The magnetic moment values measured were suggesting the possibility of the octahedral structures for the investigated complex with low spin. The molar conductance measured for complexes **1-3** were 3.88, 5.83 and 5.18 $Ohm^{-1}\ cm^{-2}\ mol^{-1}$ respectively, which indicate the non electronic nature of the complex (Table 1) .

Table 4 : *Electronic absorption bands (nm) of the* ***HL*** *ligand and its transition metal complexes* ***1-3*** *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	284(0.74)	328(0.83)	362(0.48)	367	—	
1	282(0.88)	322(0.85)	361(0.43)	364(0.54)	712(0.35)	$^3T_{2g}(G) \leftarrow E_g$
2	282(0.87)	325(0.74)	363(0.49)	366(0.53)	531(0.57)	$^1A_{2g} \leftarrow {}^1A_{1g}$
3	282(0.89)	321(0.92)	358(0.38)	360(0.49)	712(0.26)	$^4A_{2g}(F) \leftarrow {}^4T_{1g}(F)$

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

3.1.6. ESR Spectrum Measurement

The X-Band ESR spectrum of Cu (II) complexes **1** was recorded in the solid state at 25°C and was shown in figures 2. The spectrum show the $g||$ = 2.106 and $g\perp$ = 2.044. 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** [25]. The observed $g||$ value for **1** is less than 2.3, which indicating that the bond 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 (2.40) according to Hathway and Billing [26, 27], it's value less than 4.0, which indicates a considerable exchange interaction in solid complex.

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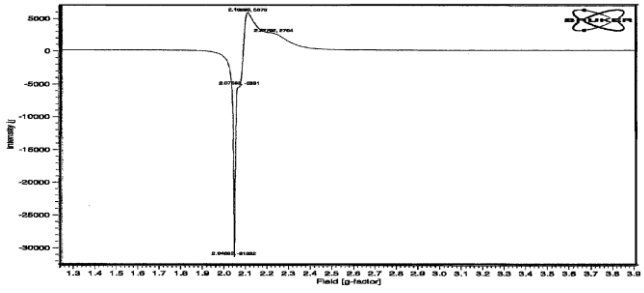
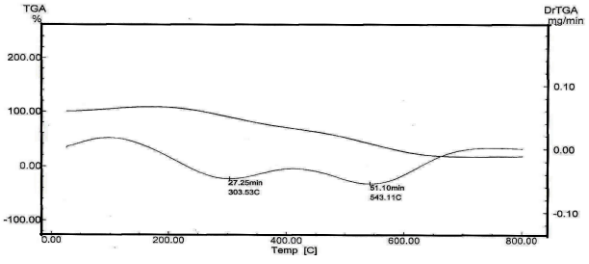
Figure-2. ESR spectrum of the [$Cu(HL)(NO_3)(C_2H_5OH)(H_2O)_2$] complex **1**.



3.1.7. Thermal Analysis

Thermal gravimetric and differential Thermal analysis for Ni(II) complex ***3*** were obtained to give information concerning the thermal stability of the complex and to suggest whether the water and ethanol molecules in the inner or outer coordination sphere of the central metal ion. From the TGA and DTA data water molecules and ethanol molecule were lost within the temperature rang 25-190°C (weight loss, Found/Colc ; 14.72 / 14.75 %) whit indicate that two water and ethanol molecules were coordinated. The thermal gravimetric analysis of the complex ***3*** was shown in Scheme 3 and Figure 3. Finally, from the elemental analyses, molar conductivity, UV-visible spectral data, magnetic measurements, IR spectral data and TGA, it is possible to determine the type of coordination of the Schiff base HL higands in their metal complexes, the ligand behave as monobasic ligand with NO bidentate sites. All complexes of **1-3** were on the octahedral structures as shown in Scheme 2.

Figure-3. Thermal gravimetric of the [$Ni(HL)(NO_3)(C_2H_5OH)(H_2O)_2$] complex **(*3*)**.



3.2. Molecular Modeling

In trying to achieve better insight into the molecular structure of the most preferentially stereoisomer tautomeric ligand forms and complexes, the conformational analysis of the target compounds has been performed using the MMFF94 force-field [28, 29], (calculations in vacuo, bond dipole option for electrostatics, Polake Ribiere algorithm, RMS gradient of 0.01 kcal/A mol) implemented in [30] (Chemical Computing Group). The most stable conformer was fully geometrical optimized by PM3 [31] semi-empirical *Hamiltonian* molecular orbital calculation MOPAC package.

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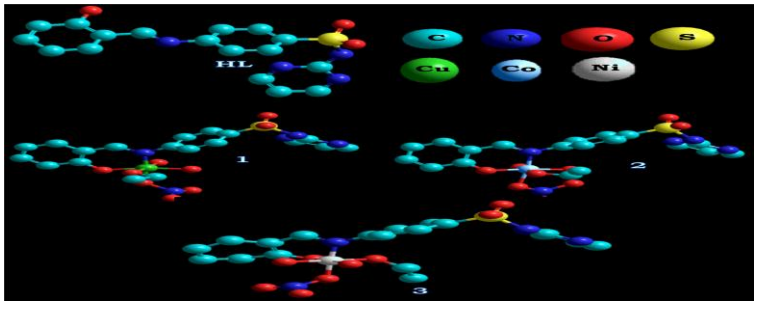
Table-5. Calculated energies of possible steroisomer and tatoumaric forms of HL ligand:

Cpd.	E[a]	HF[b]	HOMO[d]	LUMO[e]	Dipol[e]
E-HL	-90947.914	-3.69	-9.234	-9.20	3.91
Z-HL	-85344.10	649.98	-8.022	-3.67	10.30
E-HLa	-90947.914	4.48	-8.478	-1.568	5.077

[a]E: The total energy (kcal/mol).,[a]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)* .

Figure-4. Ball and stick rendering for the most stable isomer and \ or tatoumer form of the ligand and complexes as calculated by PM3 semi-empirical molecular orbital calculations.



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 investigated 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- HLa*** ligand (Structure 2, Scheme 4) . The enhancement the computed energies of calculated molecular parameters, illustrated the Z-form is the most stable isomer form of the prepared **HL** ligand, and ***Z-HL*** tautomeric form (table 5, Fig.4). The lowest minimization energy of the E-form ligand structures exhibited a common arrangement of two phenyl ring in plane with each other **HL** (Fig. 4), while phenyl ring of sulfa guanidine perpendicular with each metal ring and phenyl ring of salicaldehyde **1-3** (Fig. 4).

Table-6. Calculated energies of complexes(**1-3**) of HL ligand

Cpd.	E[a]	BE[b]	HF[c]	HOMO[d]	LUMO[e]	E.Gap[f]	Dipol[g]
1	-170235.71	-5804.83	-267.75	-9.06	-9.18	0.12	4.4
2	-161117.92	-5962.86	-404.08	-8.71	-8.89	0.18	5.27
3	-166567.23	-5848.20	-341.12	-9.11	-9.33	0.22	7.66

[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).*

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3.3. Antimicrobial Activity

The main target of the production any antimicrobial compound is inhibiting the causal microbe without or 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 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 these compounds we used more than one test organism in vitro at 37 °C, which increase the chance of detecting antibiotic. The synthesized HL and corresponding complexes **1-3**, were tested using paper disc diffusion technique [32-36]. 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 depicted graphically in (Fig 5 a -d).

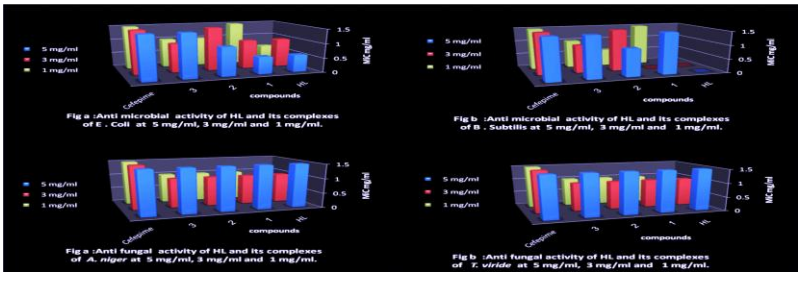
a. Against Escherichia coli(G^-)

The biological activity of Cu (II), Co(II) and Ni(II) complexes are the same of free ligand HL, except of Cu (II) 1 and Co(II) 2 have higher potency than HL with concentration (3mg/ml), and Ni(II) 3 at concentration (5mg/ml) while, all complexes (1-3) have low and\or same potency compared with standard drug.

b. Against Bacillus subtilis (G^+)

The biological activity of Cu(II), Co(II) and Ni(II) complexes is higher than free HL ligand, except Ni(II)3 has lower activity than HL at (5mg/ml) , the Cu(II)1 and Ni(II) 3 have no activity with concentration (1mg/ml). While, all complexes 1-3 have low and\or same potency compared with standard drug.

Figure-5. Biological activity of HL and its complexes at (5, 3 and 1) ppm.



c. Against Fungi

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The activity of Cu(II), Co(II) and Ni(II) complexes have the same potency like free **HL** ligand. The HL and 1-3 have same potency compared with 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 [37-39] 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 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 [37-39].Since, Gram-negative bacteria are considered a quantitative microbiological method testing beneficial drugs in both experimental and clinical tumour chemotherapy [40]. Therefore we claimed that, the synthesis of these complexes might be established a new line for search to new antitumour agents.

3.4. 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 ADMET (absorption, distribution, metabolism, elimination and toxic) Factors. Therefore, a computational study for prediction of ADMET properties of the molecules was performed for the compounds HL and (SD), by determination of topological polar surface area (TPSA), a calculated percent absorption (%ABS) which was estimated byZhao, et al. [41]. Equation [41] ,and "rule of five", which have been formulated by Lipinski, et al. [42], 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 [43] .

Table-9. Pharmacokinetic parameters important for good oral bioavailability of compounds (SG and HL)

Cpd.	TPSA	%ABS	CLogP	LogS	MW	nON	nOHNH	Lip-V.	V	mr
SD	104.54	72.9337	1.96	-4.11	248	7	2	0	163.62	64.2
HL	97.9	75.2245	2.75	-1.69	354	6	2	2	216.87	96.81

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

All calculation descriptors were performed using MOE Package, the results were disclosed in (Table 9). Our results of HL revealed that, the CLogP (factor of the lipophilicity [44]less than 5.0, the molecular weight (MW< 500), hydrogen bond acceptors (6), hydrogen bond donors (2)

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and molar refractivity values approximately 96.81 more than (SD) drug which fulfill Lipinski's rule. Also, the percent absorption of compounds HL more than (SD). These data may suggest that, the ligand HL good oral absorption as antimicrobial compounds than SD as reference drug.

4. CONCLUSIONS

The synthesized Schiff base ligand derived from sulfadiazine has been coordinated with the Cu(II), Co(II) and Ni(II) metal ions through azomethine-N and phenolic oxygen atoms and their structures have been confirmed by analytical and spectral data. The molecular structures of the investigated compounds were studied by PM3 method, also the heat of formations, HOMO, LUMO and dipole moments were calculated to confirm the geometry of the ligand and the it's complexes. Antimicrobial studies against most tested strains showed, the metal complexes have moderate to significantly activity, and exhibited more potency than Schiff base of sulfadiazine. Furthermore, the pharmakinetic screening showed the HL is good oral absorption than sulfadizine.

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