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Synthesis and Characterization of Biopotent Transition Metal Complexes of Schiff Base 2-{(1)-1-[2-(1,3-Benzothiazol-2-yl)hydrazinylidene]ethyl}-6,10b-dihydro-3*H*-benzo[*f*]chromen-3-one and their Biological Evaluation

SHRIDHAR P. MELKERI[1], P. PARAMESHWARA NAIK[1,*], N.D. SATYANARAYAN[2], ITTE PUSHPAVATHI[3], G. KRISHNAMURTHY[1] and PRABHAKAR W. CHAVAN[1]

[1]Department of Chemistry, Sahyadri Science College, Kuvempu University, Shivamogga-577203, India
[2]Department of P.G. Studies and Research in Chemistry, P.G. Centre, Kadur-577458, India
[3]Department of Industrial Chemistry, Kuvempu University, Shankaraghatta-577451, India

*Corresponding author: E-mail: parashchem@gmail.com

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Three transition metal(II) complexes (M = Co/ Zn/Pd) were synthesized by using a newly synthesized Schiff base ligand 2-{(1*E*)-1-[2-(1,3-benzothiazol-2-yl)hydrazinylidene]ethyl}-6,10b-dihydro-3*H*-benzo[*f*]chromen-3-one (**L**) by conventional method. The structure of the compounds were determined by physical and analytical techniques like UV-visible, FT-IR, ^{1}H and ^{13}C NMR and mass spectroscopic techniques and the crystallinity and inter-planar distance of the complexes were confirmed by XRD. The electron density in HOMO and LUMO was determined by DFT studies. The studies of electronic spectra and measurements of magnetic susceptibility suggest that Co(II) complex shows an octahedral geometry, Pd(II) complexes show square planar geometry and (ZnL_2Cl_2) complex shows tetrahedral geometry. The molar conductivity results suggested the non-electrolytic nature of the metal(II) complexes. The synthesized compounds was tested against antibacterial activity for Gram-positive and Gram-negative bacteria. The molecular docking study demonstrated that the ligand and its metal(II) complexes possess antibacterial and anticancer properties, and the results showed that the compounds were effective against the microorganisms that were examined. Furthermore, the results found that metal(II) complexes provided enhanced immunity against cancer cell lines.

Keywords: Transition metal chelates, Schiff bases, Antimicrobial activities, Molecular docking studies.

INTRODUCTION

The present drug discovery for the curative purposes mainly focuses on the incorporation of transition metal ions into the heterocyclic system [1,2]. By altering their surrounding structure, metal ions enhance their capabilities through the use of heterocyclic moiety. The heterocyclic chelates having certain metals like zinc, cobalt, *etc*. have greater medicinal properties as like in metal-proteins which are present in oxygen carrier, involving electron transport reactions or in oxygen storage [3]. The electron density increases with the number of heteroatoms in the ligand, which in turn enhances the lyophilic nature of the metal chelates and diminishes the cell wall of pathogen [4,5]. Based on the aforementioned information, two significant heterostructures have been chosen for the current study, namely coumarin and benzothiazole. Moreover, Schiff bases originated from the heterocyclic system are effective towards numerous diseases causing from bacterial, fungal, viral and other toxic infections [6,7]. Many of the works proved the efficacy of these systems in the development of metal-based drugs. Particularly, the metal complexes having Schiff base ligand derived from benzothiazole nucleus are used as antibacterial [8], antifungal [9] antimalarial [10] anti-inflammatory, anticancer [11] and antioxidant agents [12].

By observing all these important landmarks in the development of metal chelates, herein an effort is made to synthesize transition metal complexes bearing Schiff base ligand and characterized by various physico-chemical techniques. The biological activities were carried out to investigate the effectiveness of the synthesized metal(II) complexes. Further, the theor-

etical modelling was also done by using quantum mechanical study to compare the practical observations with these values and arrived at a positive comparison between these two.

EXPERIMENTAL

To synthesize novel Schiff base and its metal(II) complexes, the starting materials used were obtained in the pure state from Merck and Sigma-Aldrich Chemical Company, USA. The metal contents in the complexes were estimated by following well known procedure available in the literature. The purity of the new molecules was analyzed by Thin Layer Chromatography. The elemental analysis (C, H, N and M) was done by using Vario EL-III CHN analyzer. The Fourier transform infrared spectra of the compounds were obtained from Perkin Elmer-Spectrum RX-IFTIR spectrophotometer using KBr pellets within the range of 4000-400 cm^{-1}. The UV-visible spectra of the molecules was taken on an Elico-SL 164 double beam spectrometer in DMF (10^{-3} M) in the wavelength range 200-800 nm. The ^1H NMR spectra of the ligand was recorded in DMSO-d_6 solvent on an Avance III instrument with tetra methyl silane (TMS) as an internal standard. The molecular weight of the compounds was calculated from mass spectrometry on a LCMS 2010, Shimadzu mass analyzer. The molar conductivity of the compounds were measured on an Elico CM-180 Conductivity Bridge in DMF (10^{-3} M) using a dip-type conductivity bridge fitted with a platinum electrode. The powder X-ray diffraction studies of the synthesized Schiff base metal(II) complexes was recorded at room temperature on Bruker AXS D8 Advance diffractometer along with monochromatic Cu$K\alpha$ radiation (λ = 1.5406 Å).

Synthesis of 2-{(1)-1-[2-(1,3-benzothiazol-2-yl)hydrazinylidene]ethyl}-6,10b-dihydro-3*H*-benzo[*f*]chromen-3-one (L): An equimolar mixture of 2-acetyl-3*H*-benzo[*f*]-chromen-3-one) and 2-hydrazinyl-1,3-benzothiazole was refluxed for 6 h in the presence of few drops of acetic acid as catalyst in ethanol. The reaction mixture then cooled and precipitated in the crushed ice. The obtained precipitate was filtered, dried and recrystalized from ethanol [13-15] (**Scheme-I**).

Synthesis of metal complexes: To a stirred hot methanolic solution of ligand (**L**) (0.1 mg), the corresponding metal(II) chlorides (Co/ Zn/Pd) (0.03 mg/0.025 mg/0.026 mg) was added in a portion wise at 60 ºC and then the reaction mixture was refluxed for 5-6 h. The obtained precipitate was filtered, washed, dried and then purified by recrystallization in methanol. The metal(II) complexes were dried in an oven and preserved in a desiccator.

Biological evaluation

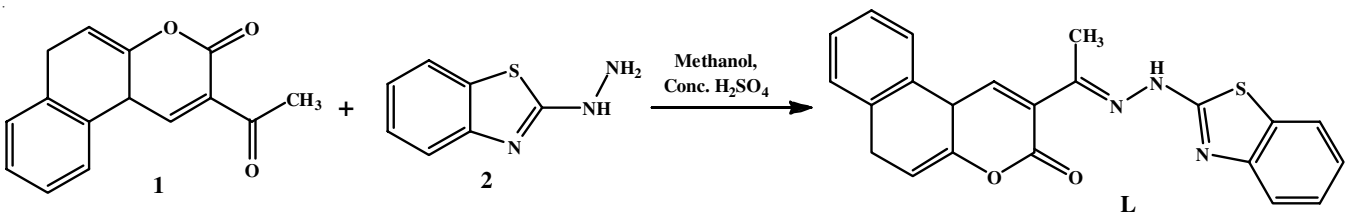
Antibacterial activity: The newly synthesized compounds were tested for antibacterial activity against Gram-positive bacteria (*S. aureus*, *B. subtilis*) and Gram-negative bacteria (*S. typhi* and *E. coli*) by well diffusion assay with some modifications [16]. The Petri plates were prepared by pouring 20 mL of sterilized nutrient agar media under aseptic condition and allowed to solidify. After solidification of media, 100 µL of standardized microorganisms were spreded uniformly using sterile cotton swabs 6 mm diameter agar was drawn from a plate to form a well using sterile cork borer. Antibiotic Gentamycin and freshly distilled DMSO were used as positive and negative controls, respectively. After maintaing at 4 ºC for 4 h for the diffusion of antibacterial metabolites, the plates were incubated for 24 h at 37 ºC. The diameter of the inhibition zone was measured in millimetre and the average triplicate readings were recorded [17].

Antitumor activity: The antitumor property of the ligand and its metal(II) complexes was evaluated against HepG2, human liver cancer cell lines by using the 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay with slight modifications. Cells was dispensed in a well cleaned sterilized 96-well microplate (5×10^4 cells/well) and incubated at 37 ºC with different concentrations of the test samples in DMSO solution for 48 h in a serum-free medium prior to the MTT assay. After incubation, media were carefully removed and 40 µL of MTT (2.5 mg/mL) were added to each well and then incubated for an additional 4 h. The yellow formazan dye crystals were solubilized by the addition of 200 µL of DMSO. The absorbance was measured at 570 nm using Multi-Mode micro plate reader analyzed using Megalen software. The relative cell viability were expressed as the mean percentage of viable cells compared to the control cells. The results were conducted in triplicate; all the values were represented as mean ± SD [18].

***In silico* molecular docking interaction:** The molecular interaction studies on the synthesized molecules were carried out to understand the interaction between the synthesized compounds and the protein structure. Bacterial DNA gyrase plays a pivotal role during the investigation of antibacterial activity, as it breaks double-stranded DNA by accelerate negative supercoiling, which is essential for DNA replication, transcription and recombination. Analysis of the co-crystallized DNA-gyrase cleavage complex with novobiocin, which is an effective antibacterial properties that cleaves DNA by restricting the ATPase binding site including the vital naked peptidoglycan of the cell wall (Ser55, Ala64, Asn65, Asp89, Tr164, Tr173 [19].

RESULTS AND DISCUSSION

Novel transition metal(II) complexes derived from Schiff base ligand [2-{(1)-1-[2-(1,3-benzothiazol-2-yl)hydrazinylidene]ethyl}-6,10b-dihydro-3*H*-benzo[*f*]chromen-3-one)] is



Scheme-I: Synthesis of Schiff's base ligand (**L**)

explored in this work. The obtained coloured metal(II) complexes are stable and non-hygroscopic in nature. The cobalt(II) complex is formed in 1:2 ratio metal and ligand with the general formula $[ML_2Cl_2]$ (M = Co/ Zn/Pd). The molar conductivity data indicates that the metal(II) complexes exhibit a non-electrolytic character, however their conductivity values are rather low, which can be attributed to the physico-chemical properties of the ligand and its chelates (Table-1) [20].

IR spectral studies: The IR spectrum of the Schiff base ligand exhibited a strong absorption band at 3348 cm^{-1} which corresponds to the N-H group attached to the imine structure. This absorption band was disappeared in all the metal(II) complexes indicate the M-L bonding. There is a sharp absorption bands appeared each at 1723 and 1605 cm^{-1} corresponds to the azomethine ν(C=N) and ν(C=O) groups, respectively in the ligand. In the metal(II) complexes, these two bands shifted towards downfield suggesting the coordination of metal ions with the carbonyl and imine groups of the ligand (Table-2). The metal-ligand bonding was further confirmed in the region 480-469 and 617-615 cm^{-1} due to ν(M=N) and ν(M=O), respectively. Further, the broad band was observed in the region 3472-3466 cm^{-1} in the metal(II) complexes assigned for the water molecules.

Electronic and magnetic susceptibility studies: The UV-visible spectra of the synthesized compounds were studied in DMSO solvent in the wavelength range of 200-800 nm using UV-visible spectrophotometer. The key absorption bands appeared in the spectra and corresponding transitions are presented in Table-3. The data are correlated with the magnetic susceptibility studies to identify the molecular geometry of the complexes. The ligand exhibited medium intensity broad band's at 37878 and 24752 cm^{-1} which corresponds to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ transitions, respectively due to the presence of imine group and conjugated system. The Co(II) complex exhibited three important bands at 18726, 27624 and 36764 cm^{-1} corresponds to $^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$ (ν_1), $^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$ (ν_2) and $^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$ (ν_3), respectively (Fig. 1). The magnetic moment obtained by analysis was found to be 4.89 BM and it is in consistent with octahedral structure. The complex of palladium(II) showed two absorption maxima at 33670 and 24937 cm^{-1} respectively to the $^1A_{1g}\rightarrow{}^1A_{2g}$ (ν_1), $^1A_{1g}\rightarrow{}^1B_{1g}$ (ν_2), LMCT (M←N) (Fig. 1). Based on the diamagnetic be moment values and the spectra data of the synthesized metal(II) complex the square planar geometry was proposed and are in good agreement with the literature values.

^{1}H NMR studies: The ^{1}H NMR ligand spectrum exhibited a singlet at δ 2.38 ppm correspond to the methyl group. The signal resonated as a multiplet in the region of δ 7.05-8.89 ppm due to the presence of 12 aromatic protons of the ligand. The broad signal appeared as a singlet at δ12.01 ppm is due to the presence of HC=N- proton. The ligand also exhibited $[M^+ + 2]$ and $[M^+ + 3]$ peaks each at *m/z* 387 and 388, respectively.The spectral data confirms the proposed structure of the ligand. The mass spectrum of the metal(II) complexes exhibited a molecular ion peak at *m/z* 386 ($M^+ + 1$), which corresponds to the molecular weight of the compound (385.43).

Powder XRD studies: The crystalline nature of the metal(II) complexes was determined by powder X-ray diffraction technique. The Co(II) and Pd(II) complexes showed crystallinity (Fig. 2)

TABLE-1
THE PHYSICO-CHEMICAL AND ELEMENTAL DATA OF THE (**L**) AND ITS COMPLEXES

m.f.	m.w.	Colour	Elemental analysis (%): Calcd. (found)				λ_m ($cm^2\ \Omega^{-1}\ mol^{-1}$)
			C	H	N	M	
L $[C_{22}H_{15}N_3O_2S]$	385.43	Yellow	68.55 (57.18)	3.92 (3.57)	10.90 (15.64)	–	–
$[Co(L)_2Cl_2]$ $[C_{44}H_{28}N_6O_4CoS_2]$	827.79	Navy black	63.84 (63.78)	3.41 (3.32)	10.15 (10.03)	7.12 (7.49)	20.18
$[Pd(L)_2Cl_2]$ $[C_{44}H_{28}N_3O_3PdS_2]$	877.25	Green	51.93 (51.22)	3.17 (3.12)	08.26 (08.01)	20.91 (20.68)	30.15
$[Zn(L)_2Cl_2]$ $[C_{22}H_{16}N_3O_3ZnS]$	467.85	Pale green	56.48 (55.97)	3.45 (3.12)	8.98 (8.17)	13.98 (13.76)	29.45

TABLE-2
THE IR SPECTRAL DATA OF **L** AND ITS METAL COMPLEXES

Compounds	ν(NH)	ν(H_2O)	ν(C=O)	ν(C=N) azomethine	ν(M-N)	ν(M-O)
L	3348	–	1723	1605	–	–
$[Co(L)_2]Cl_2$	Present	3466	1638	1553	480	617
$[Pd(L)_2Cl_2]$	Present	3472	1636	1568	469	615
$[Zn(L)_2Cl_2]$	Present	3472	1615	1569	469	615

TABLE-3
ELECTRONIC SPECTRAL DATA OF LIGAND AND ITS METAL COMPLEXES

Ligand/complexes	Wavenumber (cm^{-1})	Assignments	μ_{eff} (B.M.)	Geometry
L	37878	$\pi\rightarrow\pi^*$	–	–
	24752	$n\rightarrow\pi^*$		
$[Co[L]_2Cl_2]$	18726	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(F)$ (ν_1)	4.89	Octahedral
	27624	$^4T_{1g}(F)\rightarrow{}^4A_{2g}(F)$ (ν_2)		
	36764	$^4T_{1g}(F)\rightarrow{}^4T_{2g}(P)$ (ν_3)		
$[Pd[L]_2Cl_2]$	33670	$^1A_{1g}\rightarrow{}^1A_{2g}$ (ν_1)	Diamagnetic	Square planar
	24937	$^1A_{1g}\rightarrow{}^1B_{1g}$ (ν_2)		
		LMCT (M←N)		

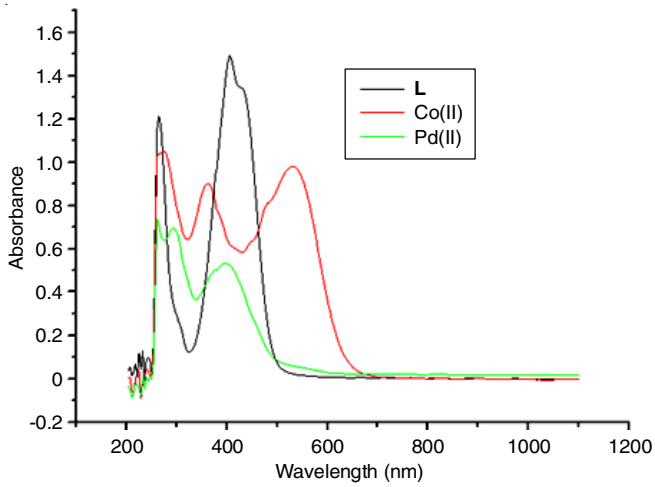


Fig. 1. UV-visible spectrum of ligand, $[Co[L]_2Cl_2]$and $[Pd[L]_2Cl_2]$

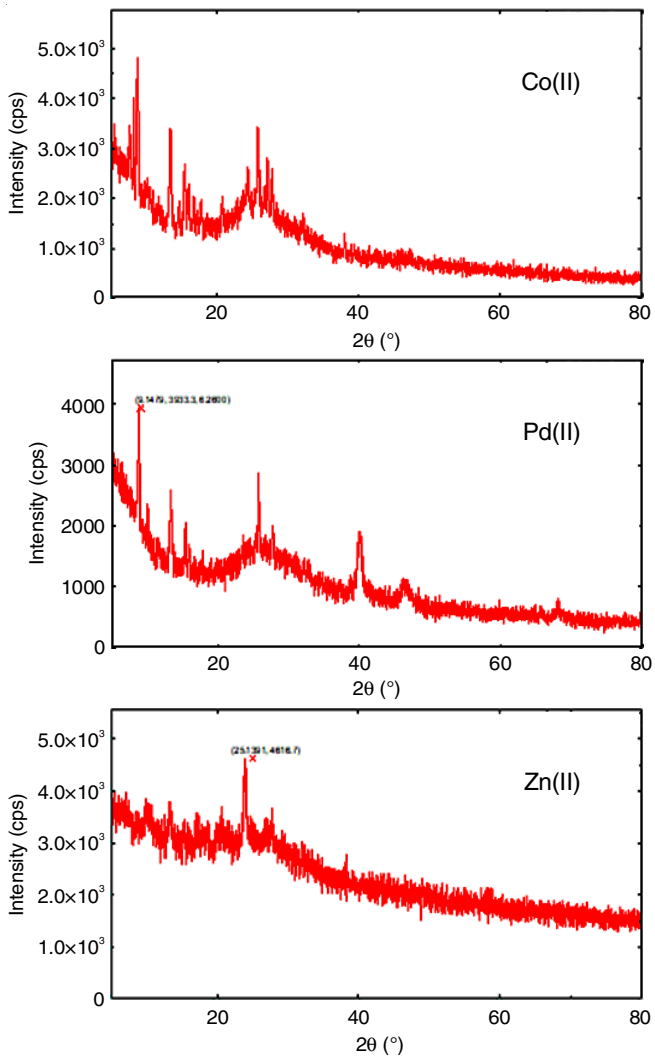


Fig. 2. Powder X-ray diffraction pattern metal complexes

whereas the Zn(II) complex is in amorphous in nature. The cobalt complex showed six reflections in which 2θ values in between 8-25º (2θ). The inter-planar spacing between the planes was calculated using Bragg's equation: 2d sin θ = nλ, where λ = 1.5406 Å and correlated with the obtained values [21,22].

DFT studies: In DFT studies, the geometries of Schiff base and its metal complexes (Pd^{2+} and Zn^{2+}) were fully optimized with respect to the energy using the 6-31+g(d,p) basis set (Fig. 3). The optimization energy, dipole moment, energy gap and hardness (η) values are shown in Table-4. The frontier molecular orbitals (FMOs) of the molecules helped to determine their physico-chemical nature. The electron density on a molecule helps to determine the energy of highest occupied molecular orbital (HOMO) and the lower unoccupied molecular orbital molecular orbital (LUMO). The FMOs for ligand were determined using the B3LYP/6-31G (d,p) method and are shown in Fig. 3. It was observed that the HOMO to be localized on coumarin ring hydrazone (hydrazone) link (-C=N-H-), thiazole (benzothiazole) and L (lumorphone) to be mainly found on benzothiazole (hydrazine). Coumarin linked with -C=N-NH- acts as an electron donor, whereas benzothiazole core act as acceptors. The ionization potential of the HOMO is proportional to the LUMO, while the electron affinity is proportional to the HOMO. The difference between the two is referred to as the energy gap between HOMO and LUMO. The soft molecules with a small gap and those with a wide gap are called hard molecules. The values of HOMO energy, LUMO energy and the energy gap between the two are shown in Fig. 3 and its values are 3.072 eV and 1.611 eV, respectively (Table-4).

TABLE-4
THE ENERGY OF HOMO AND LUMO OF LIGAND AND ITS COMPLEXES

Parameter	L	$[Zn(L_2)]Cl_2$	$[Pd(L_2)Cl_2]$
EHOMO (eV)	3.072	-2.7467	-3.6700
ELUMO (eV)	1.611	2.107	2.3116
Energy gap (Δ) (eV)	1.461	0.639	1.359
Ionization energy (IE) (eV)	3.072	2.746	3.670
Electron affinity (EA) (eV)	1.611	2.107	2.311
Electronegativity (χ) (eV)	2.341	2.426	2.990
Chemical potential (μ) (eV)	-2.341	-2.426	-2.990
Global hardness (η) (eV)	0.730	0.319	0.679

The quantum chemical parameters like electronegativity (χ), chemical potential (μ), global hardness (η) were evaluated to understand the chemical behaviour of the ligand. The following equations were used to calculate these global reactivity parameters and the results are listed in Table-4.

$$\chi = -1/2\ (E_{HOMO} + E_{LUMO}) \quad (1)$$

$$\mu = -\chi - 1/2\ ((E_{HOMO}) + (E_{LUMO}) \quad (2)$$

$$\eta = 1/2\ (E_{HOMO} - E_{LUMO}) \quad (3)$$

The compound with a small gap of HOMO-LUMO is reactive and softer molecule. As the energy gap of the complex decreases, the reactivity of complexes of Pd(II) and Zn(II) increases the reactivity and softness of the ligand increase after its coordination to metal ion, due to the magnitude of their dipole moments. The E_{HOMO} and E_{LUMO} are all negatives and represents that the products are stable. The electron density distributions of the FMO, HOMO and LUMO of the metal(II) complexes chelate are shown in Fig. 3. In HOMO, the electron density is distributed mainly over the aliphatic part of the ligand, metal

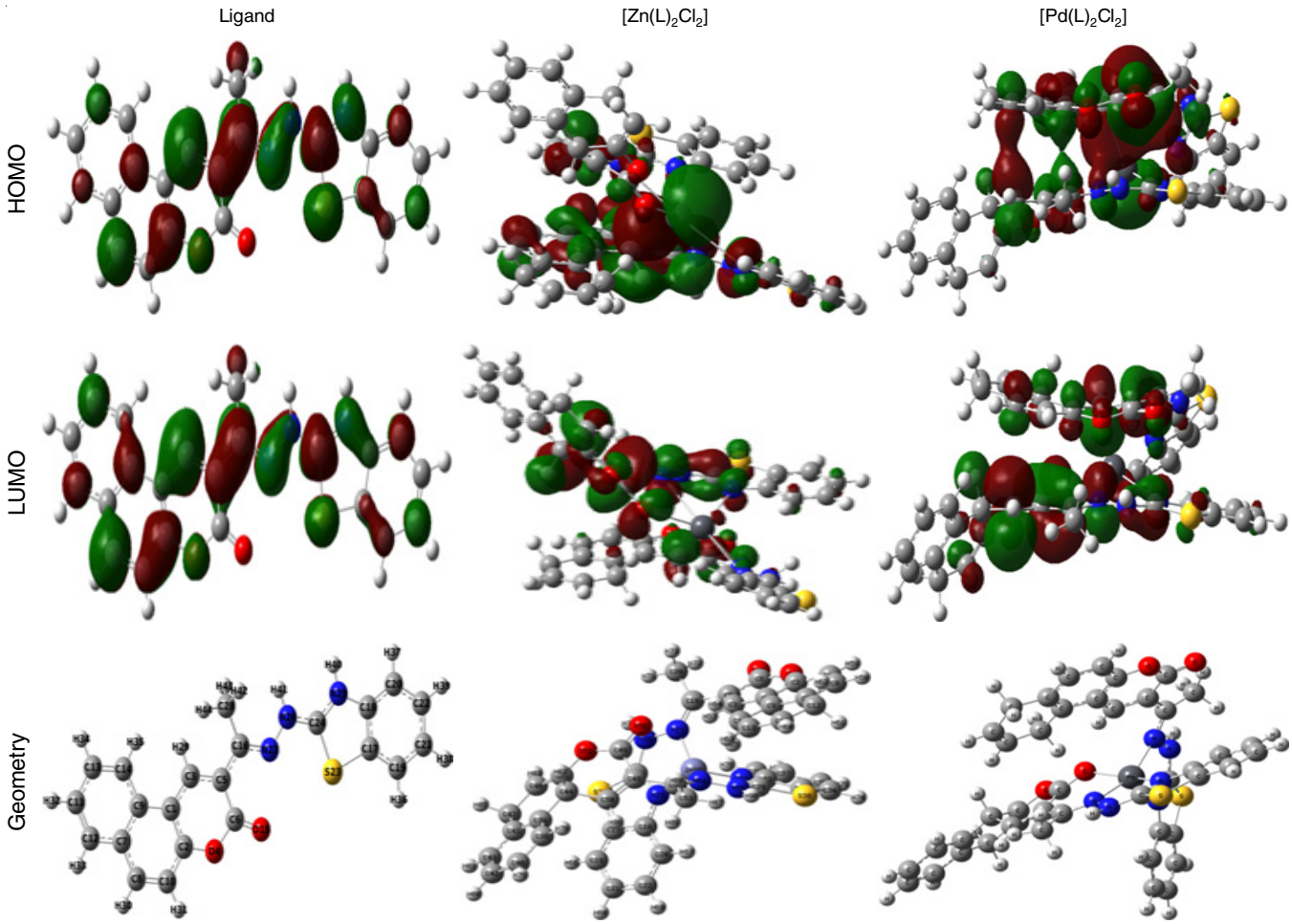


Fig. 3. Structure of HOMO and LUMO of ligand and its complexes

ion and coordinated water molecules but in LUMO, the electron density is extended to the whole ligand molecule, (aliphatic and the aromatic rings), metal ion and the coordinated water molecules [23-25].

Biological activities

Antimicrobial studies: The antimicrobial efficacy of the newly synthesized compounds was studied against four bacterial strains *S. aureus*, *B. subtilis*, *S. typhi* and *E. coli* by agar well diffusion assay. The results obtained as zone of inhibition (mm) was depicted in Table-5 and it is evident that the cobalt(II) complex showed the maximum zone of inhibition against all the studied organisms and also having comparatively similar to the standard drug gentamycin. All the metal(II) complexes have higher value than that of ligand for all the studied microbes. Therefore, the chelation has an vital important role in enhancing the antibacterial activity as it is in accordance with the literature [26,27].

Anticancer study: A preliminary screening of the novel compounds against human liver cancer cell line, HepG2 by MTT assay were determined and the results are presented in Table-6. From the results, it is stated that the metal chelates are effective in inhibiting the tested cancerous cell line than the free ligand. Therefore, it is concluded that synthesized metal(II) complexes are proved to be effective anticancer agents [28].

TABLE-5
ZONE OF INHIBITION CALCULATED FOR THE TARGET COMPOUNDS FOR VARIOUS MICROBES

Name	*E. coli*	*B. subtilis*	*S. aureus*	*S. typhi*
L	6	6	7	6
$[Co(L)_2Cl_2]$	12	12	11	11
$[Pd(L)_2Cl_2]$	9	9	10	11
$[Zn(L)_2Cl_2]$	8	10	10	10
Gentamycin	12	12	13	13

TABLE-6
PERCENTAGE OF INHIBITION AGAINST HepG2 AT DIFFERENT CONCENTRATIONS OF THE SCHIFF'S BASE **L** AND ITS COMPLEXES

Name	25 mg/mL	50 mg/mL	75 mg/mL	100 mg/mL
L	20.879	30.769	37.362	48.351
$[Co(L)_2Cl_2]$	24.175	32.967	56.043	79.120
$[Pd(L)_2Cl_2]$	23.076	35.164	41.758	52.747
$[Zn(L)_2Cl_2]$	22.046	31.193	40.176	43.231

***In silico* molecular docking studies:** The *in silico* molecular docking studies has been carried out against DNA gyrase B (PDB ID: 4URO) with respect to antibacterial activity and VEGFR2 (PDB ID: 3VHF) with respect to anticancer activity. Bacterial DNA gyrase play a vital role during the investigation of antibacterial agents as it breaks double-stranded DNA by

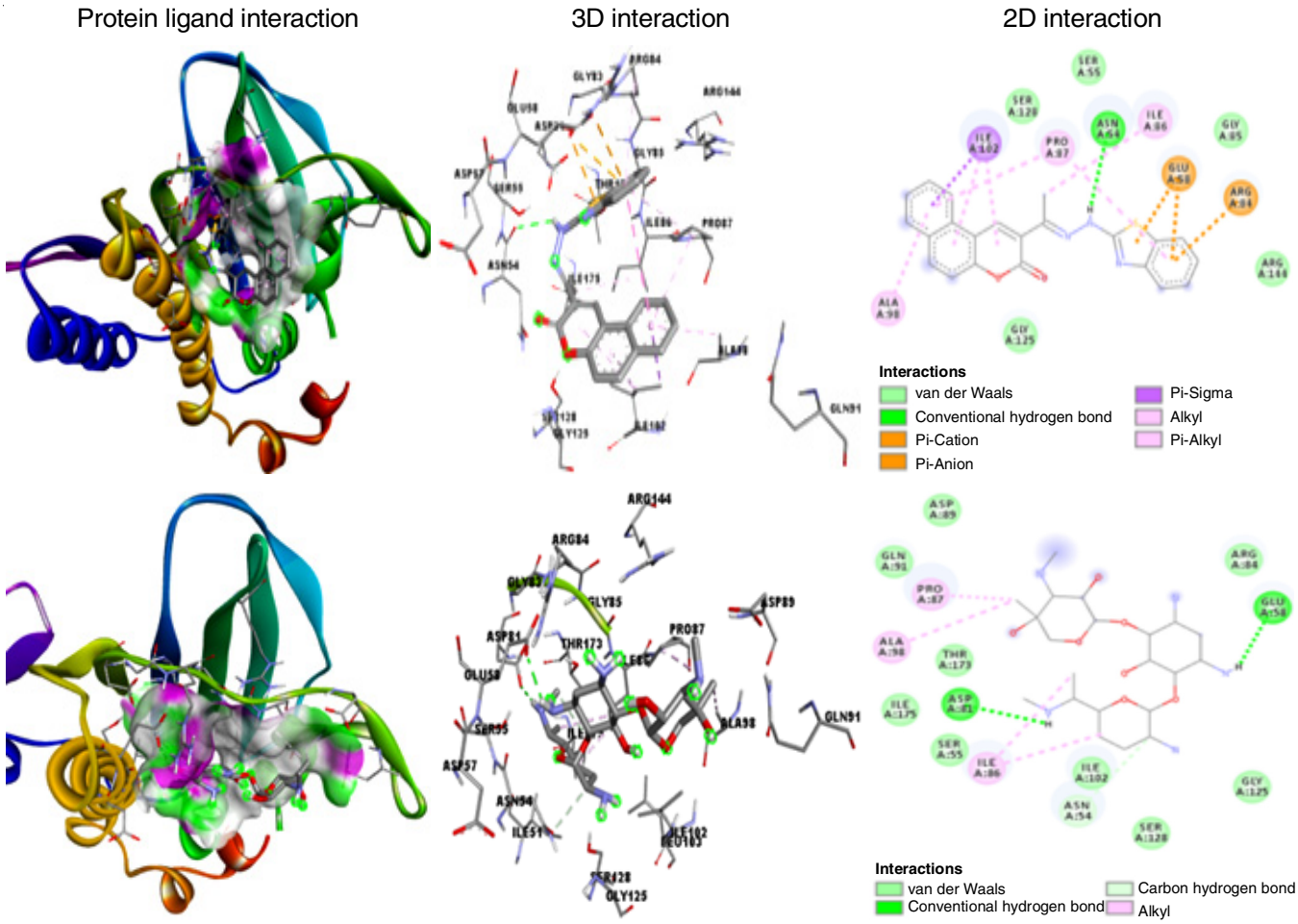


Fig. 4. Docking results of **L** against antibacterial activity

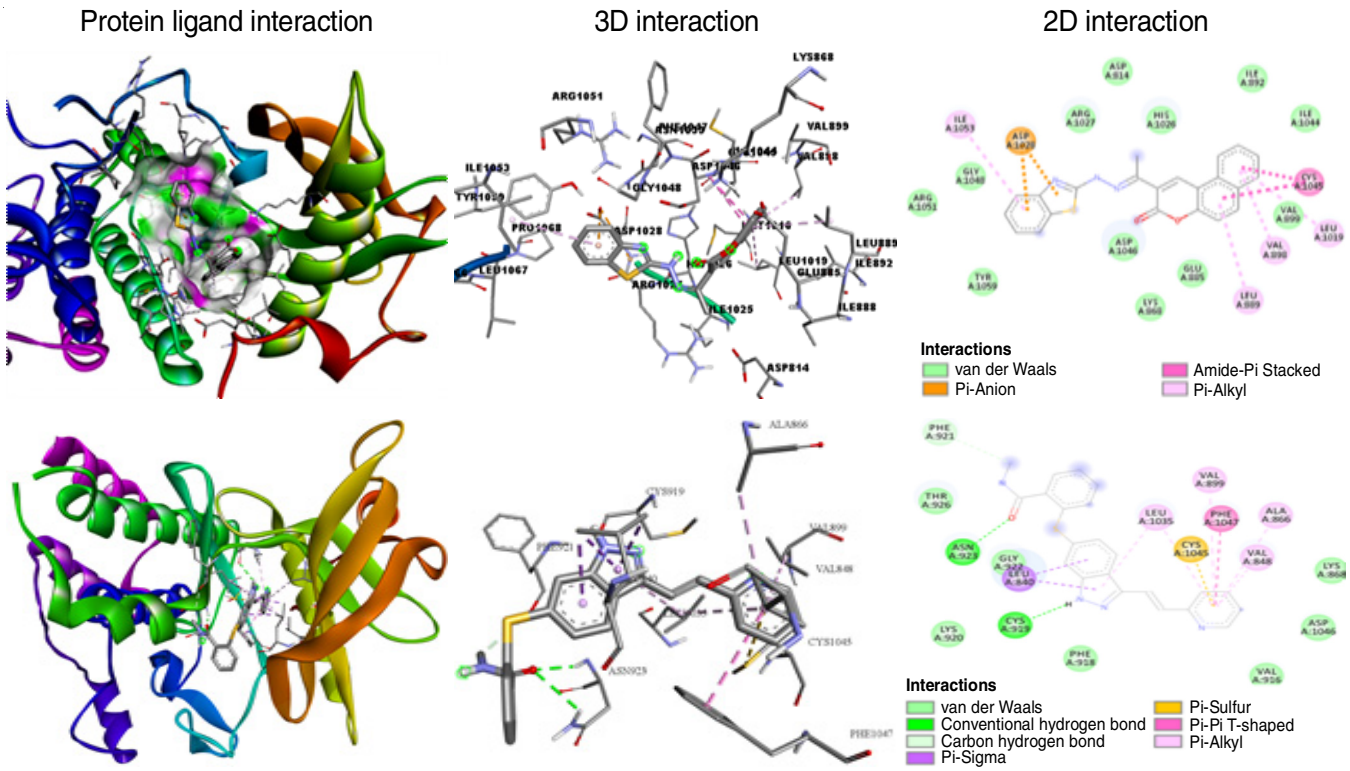


Fig. 5. Docking results of **L** against anticancer activity

catalysing negative super coiling effect, which is essential for DNA replication, transcription and recombination [29]. The assessment of the co-crystallized DNA-gyrase cleavage complex with novobiocin, a potent antibacterial drug that cleave DNA by restricting the ATPase binding site, which includes a crucial cell wall naked peptidoglycan (Ser55, Ala64, Asn65, Asp89, Tr164, Tr173) (Fig. 4). Similarly, the docking interaction was carried out for the anticancer activity against VEGFR2 protein and showed interaction with the active sites ILE1053, CYS1045, LEU1019, VAL898, LEU898, ASP1046, ARG1027, HIS1026 (Fig. 5) [30-32].

Conclusion

Three metal(II) complexes of 2-{(1*E*)-1-[2-(1,3-benzothiazol-2-yl)hydrazinylidene]ethyl}-6,10b-dihydro-3*H*-benzo[*f*]chromen-3 have been synthesized and characterized by UV-visible, FTIR, ^{1}H NMR, mass spectroscopy, magnetic susceptibility, powder XRD and DFT study. The XRD data showed that the zinc complex is in an amorphous form while the other metal complexes appear to have crystalline form and all other complexes posse-ssing hexagonal or tetragonal structure. These characterization indicate an octahedral geometry for cobalt complex, while square planar and tetrahedral structure Pd(II) and Zn(II) complexes, respectively. Further, the antimicrobial, anti-tubercular and anticancer activities for the synthesized compounds have been evaluated. All the complexes showed enhanced biological activities as compared to the uncoordinated ligand. Therefore, the present complexes proven to be effective in the design of metal based drugs.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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