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SYNTHESIS, STRUCTURAL ELUCIDATION AND BIOLOGICAL STUDIES ON 3d-METAL COMPLEXES OF THE HETEROCYCLIC LIGAND 3-{2-[4-(4-CHLOROPHENYL)-1, 3-THIAZOL-2-YL] HYDRAZINYLIDENE}-1, 3-DIHYDRO-2H-INDOL-2-ONE

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Abstract
The present work elaborates the synthetic, structural and biological properties of the 3d-metal complexes of the ligand 3-{2-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl] hydrazinylidene}-1,3-dihydro-2H-indol-2-one. The various spectrochemical techniques were employed to propose the structure of the ligand and its metal chelates. By electronic and magnetic susceptibility measurements the octahedral geometry was proposed for Cu(II) and Co(II) complexes, square planar geometry for Pd(II) and tetrahedral structure for Zn(II) complex. The molar conductivity results suggested the non-electrolytic nature of the metal chelates. The antimicrobial and ant tubercular investigations revealed the appreciable efficacy against the tested microbes. Furthermore, the cytotoxic studies reveal that the metal complexes showed enhanced protection against the cancer cell lines.

Keywords: Isatin derivatives, transition metal complexes, antimicrobial and anticancer activities.

1. Introduction

As we seen from the today's situation of serious impact of the pathogens on to the human life has become main task for the chemists. Even though there are plenty of drugs available for the treatment of deadly diseases, it is failed to analyse their dramatic changes in their structures with respect to the drug action on the pathogens. In order to overcome these impending challenges, chemists are enormously trying their best effort to solve these medical problems [I-VII].Among those, cisplatin is the best example to explore anticancer us properties of the metal based drugs. The metal ions (especially transition metal chelates) are able to explore excellent biochemical properties than the drugs bearing simple heterocyclic systems.Cisplatin, an effective anticancer drug and an effective medical model to cure different types of tumours and had a greater influence to many of the chemist to search for the metal based drugs. The selection

of the metal ion and the ligating system is so crucial in the development of metal based drugs **[**VIII, IX].Among those nitrogen based compounds like isatin derivatives[XXIV], played so effective in inhibiting the disease causing microbes. Therefore, the isatin based ligands and their transition metal complexes are excellent antibacterial[X-XII],ant tubercular [XIII], antioxidant [XIV]andantiviral properties [XV].

By observing the above important biochemical properties of the isatin derivatives as well as the transition metal ions, we planned to synthesize heterocyclic ligand containing isatin moiety and its metal complexes**[**XVI]. The synthesized complexes are structurally characterized by different spectroscopic methods and also the compounds are tested for their antimicrobial and anticancer studies.

2. Experimental

2.1 Materials and methods

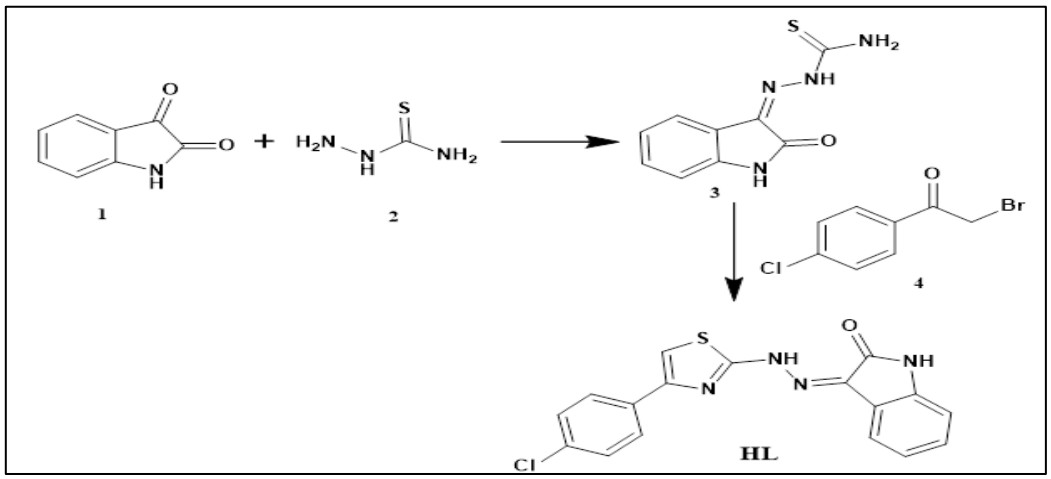
All the used chemicals and solvents for the synthesis are of analytical grade and are used as such without further purification. The percentage of metal present in the prepared complexes was estimated by using standard techniques reported in the literature and the purity of the new compounds prepared was analysed by thin layer chromatography (TLC). The elemental assay (C, H, N and M) was done by using Vario EL III CHN analyser. The FT-IR Spectra of the compound was taken in KBr Pellets on a Perkin Elmer- Spectrum RX-FTIR instrument within in the region 4000-400 cm^{-1}. The electronic absorption spectroscopy of the compounds was recorded in the region 200-800 nm on a Elico-SL 164 double beam spectrometer in DMF (10^{-6} M). The ^{1}H 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 analyser. The molar conductivity data of the compounds was taken on an ELICO CM-180 conductivity bridge in DMF (10^{-6}M)using a dip-type conductivity bridge fitted with a platinum electrode.The Vibrating Sample Magnetometer (VSM) plots for calculating magnetic susceptibility with Ni as celebrant at room temperature.

2.2 Synthesisof2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazine carbothioamide (3)

An equimolar mixture of 1H-indole-2, 3-dione (**1**) and thiosemicarbazide was heated in ethanol with small catalytic amount of acetic acid and stirred for 2h at reflux temperature. The reaction mixture was concentrated to one fourth of its initial volume and the precipitate thus formed was filtered. The precipitate was washed with hexane or diethyl ether and recrystallized from ethanol.

2.3 3-{2-[4-(4-chlorophenyl)-1, 3-thiazol-2-yl] hydrazinylidene}-1, 3-dihydro-2H-indol-2-one (CHI)

A mixture of obtained Isatin-3-thiosemicarbazone (**3**) and 2-bromo-1-(4-chlorophenyl) ethanone (**4**) was refluxed in 25 mL of ethanol for about 12-15 h. Then the reaction mixture is concentrated to one third by slow evaporation of the solvent. The obtained precipitate was filtered off and recrystallized from ethanol and the pure compound (**CHI**) was used as ligand for the preparation of transition metal complexes.



Scheme 1: Synthetic method adopted for the proportion of the ligand **CHI**

2.4 Preparation of metal complexes of the ligand (CHI)

The hot solution of the metal chlorides is added to the previously heated ethanol solution of (**CHI**) and obtained reaction mixture is heated with constant stirring at 60˚C for 6-7 h. After reflux is over, the coloured precipitates of the metal complexes are filtered off and washed with distilled water and hot ethanol to get the pure products. The melting point of the complexes was recorded in order to confirm the formation of the complexes and recrystallized from ethanol

2.5 Biological evaluation

2.5.1 Antimicrobial activity

The various synthesised compounds were tested for their antimicrobial efficacy by tube dilution method and three bacterial strains Staphylococcus aureus, Klebsiellapneumoniae and Pseudomonas aeruginosa and three fungal strains Candida albicans, Aspergillusflavus and Aspergillusfumigatus were used for the analysis. The method involves the treatment of the pathogens with the target compounds of series dilution in a freshly distilled DMSO solvent (dilution range: 100 to 0.2 mg/mL), together taken in a BHI (brain heart infusion) broth. This suspension of the compounds and the pathogens was incubated for 24 h at 37^{o}C and the turbidity appeared in the solutions was observed. The positive controls are ciprofloxacin and fluconazole used for the antibacterial and antifungal activities respectively and the DMSO as the negative control for both the studies. Further, the results were measured as minimum inhibitory concentration [XVIII](MIC).

2.5.2 Anti-tubercular activity

The micro plate Blue Almar assay was adopted to test the ant tubercular potency of the newly synthesised azo metal chelates and *Mycobacterium Tuberculosis* (H37 RV strain, ATCC 27294) is used as a target pathogen for the study. Briefly, the method involves the use of thoroughly sterilised 96-well plate wherein100 μL of the Middlebrooks 7H9 broth added and the solution of target compounds were added in serial dilution so that the final concentration range should in between 100-0.2 mg/mL. The solutions containing plate was incubated for about five days at 37^{o}C. After the incubation period, the plate was treated with 25 mL of freshly prepared 1:1 mixture of Almar blue reagent and 10% Tween-80 and further incubated for another 24 h at the same temperature. The appearance of blue colouration in the 96-well plate is an indication of the pathogenic growth otherwise treated as no bacterial growth. Finally, the results were recorded based on the above protocol in terms of MIC which is the lowest drug concentration which stops the change of colour from blue topink [XIX].

2.5.3 Anticancer activity

The cytotoxicity is a major cause in the world wide the maximum number of individuals suffering nowadays. The use of drugs designed on the basis of metal-organic frame work has resulted appreciable results in suppressing the growth of the cancerous cells. In the view, we attempted to preliminary investigation of the newly prepared complexes for anticancer activity. The 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method was utilised to test the cytotoxic activity of the synthesised compounds against HeLa (human cervix cancer) and A549 (human lung carcinoma)cell lines. The 96-well plate containing previously sub-cultured cancerous cells in a minimum essential media (MEM) with 10% inactivated fetal calf serum was treated with the title compounds of the dissolved in freshly distilled DMSO with varying concentration range from 10-50 mg/mL. The whole solution was incubated for 48 h at 37° C in humidified atmosphere of 5% CO_2. The 20 μL MTT solution (5 mg/mL) was added to each well and again incubated for 4 h at the same condition. Now, the 100 μL DMSO was added to solubilise the formed MTT formazan crystals. Further, the optical density of the solution mixture was recorded by using micro plate spectrophotometer at wavelength of 517 nm LISA plus instrument. The experiments were done on three replicate measurements and the percentage of relative cell viability was evaluated by using the following expression,

% the relative cell viability = [1-Abs (drug)/Abs (Control)] X100

The IC_{50} values of the titled compounds were obtained from the plot of 50% cell viability vs drug concentration [XX-XXI].

3 Results and discussion

The main focus of the article is to synthesise biocompatible transition metal chelates of the heterocyclic ligand having indole nucleus. The prepared ligand and its metal complexes were thoroughly characterised by various physical and spectroscopic techniques. These formed chelates are coloured solids, non-hygroscopic and stable at room temperature. The complexes are formed in 1:2 metal: ligand ratio with the general formula [M $(L)_2$] for all the complexes except for zinc which has [M(L)H_2O]. The complexes are non-electrolytic in nature due to low conductivity values which was carried out by molar conductivity measurements. The physical and analytical data of the compounds were tabulated in the below **Table 1**.

Table 1: The physical, analytical and elemental data of the ligand (CHI) and its complexes

Compounds	**Mol. Wt.**	**M.P. (°C)**	**Color**	**Elemental analysis (%) Calcd. (found)**				**λ_m (cm^2 Ω^{-1} mol^{-1})**
				C	**H**	**N**	**M**	
CHI $C_{17}H_{13}ClN_4OS$	356.82	142(144)	Yellow	57.22 (57.18)	3.67 (3.57)	15.70 (15.64)	-	-
$[Cu(CHI)_2]$ $C_{34}H_{24}Cl_2N_8O_2CuS_2$	775.18	219(120)	Reddish brown	52.68 (52.66)	3.12 (3.02)	14.45 (14.33)	8.20 (8.17)	38.21
$[Co(CHI)_2]$ $C_{34}H_{24}Cl_2N_8O_2CoS_2$	770.57	225(227)	Brown	52.99 (52.86)	3.14 (3.12)	14.54 (14.33)	7.65 (7.59)	21.06
$[Pd(CHI)_2]$ $C_{34}H_{24}Cl_2N_8O_2PdS_2$	818.06	213(215)	Reddish brown	49.92 (49.81)	2.96 (2.93)	13.70 (13.53)	7.76 (7.74)	31.48

$[Zn(CHI)_2]$ $C_{17}H_{14}ClN_4O_2SZn$	439.24	158(160)	Orange yellow	46.48 (46.23)	3.21 (3.12)	12.76 (12.67)	14.89 (14.74)	32.56

3.4 IR spectral data of the ligand and its complexes

The functional groups present in the molecule can be identified by recording the FT-IR spectra and it is more convenient to propose the molecular geometry of the complexes. In the present case, the prepared compounds were subjected for FT-IR spectral study and the obtained absorption frequencies are reported. The IR spectrum of the ligand showed two broad peaks at 3414 and 3258 cm^{-1} due to the presence of -NH groups in imine and indole ring respectively. Among these one of the -NH group in the imine functional was disappeared in all the metal complexes indicating the formation of covalent bond between metal ion and the ligand via deprotonating. The peaks observed at 1692 and 1470 cm^{-1} in the ligand spectrum are corresponding to the carbonyl and nitrogen atom of the thiazole ring respectively. These peaks are slightly shifted towards higher frequency region due to coordination of the metal ions with the oxygen atom of the carbonyl group and nitrogen atom of the thiazole ring. But inthe case of Pd (II) complex [XXII, XXIII],there is no shift in the carbonyl frequency suggesting its non-involvement in coordination. The appearance of non-ligand bands in the region 493-482 cm^{-1} and 625-620 cm^{-1} corresponding to the (ν_{M-N} and ν_{M-O}) in all the complexes. These bands are further evidence for the coordination of the ligand with the metal ions.

3.5 Electronic and magnetic susceptibility data of the compounds

The electronic absorption spectra are an essential technique to interpret the geometrical environment around the central metal ion. The electronic spectra of the synthesized compounds were recorded in DMF (10^{-6} M) and the important absorption peaks obtained are depicted in the following **Table 2** and the corresponding transitions and the proposed geometry also shown in the respective table. The UV-Visible spectrum of (**CHI**) exhibited two peaks at 36363 and 24390cm^{-1} corresponding to the $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ respectively. The electronic spectrum of the copper complex showed broad bands in the region 20661-37037 cm^{-1} corresponding to the $^2B_{1g}\rightarrow{}^2A_{1g}$ (υ_1), 2B1g$\rightarrow{}^2B_{2g}$ (υ_2) and $^2B_{1g}\rightarrow{}^2E_g$ (υ_3) transitions. These transitions indicated octahedral geometry for the copper complex. The obtained magnetic moment 1.79 B. M. also in favour of the octahedral structure for the complex. The brown coloured Co(II) complex of the ligand showed prominent peaks at 37317, 20242 and 10570cm^{-1} due to $^4T_{1g}$ (F)$\rightarrow{}^4T_{2g}$ (F) (υ_1) $^4T_{1g}$(F)$\rightarrow{}^4A_{2g}$ (F) (υ_2) and $^4T_{1g}$ (F)$\rightarrow{}^4T_{2g}$ (P) (υ_3) respectively and also the magnetic moment was comes out to be 4.92 B. M. These data confirms the octahedral structure and is in consistent with the theoretical value in the range 4.70-5.20 B. M. The palladium complex exhibited three peaks at 23041, 36630 and 33898 cm^{-1} which are confined to $^1A_{1g}\rightarrow{}^1A_{2g}$ (υ_1) and $^1A_{1g}\rightarrow{}^1B_{1g}$ (υ_2) transitions respectively. The observed magnetic moment value shows diamagnetic nature therefore square planar geometry was proposed for Pd(II) complex[XXIII]. The diamagnetic zinc complex has not showed any d-d transitions since its outermost orbital is completely filled. Only anintra-ligand transition at broad bands observed at 24752 cm^{-1} in the visible region and from the theoretical analysis and the obtained values suggest the tetrahedral geometry.

Table 2: Electronic spectral data of ligand (**CHI**)and its metal complexes.

Compounds	**Wave number (cm^{-1})**	**Assignments**	**μ_{eff} (B.M)**	**Geometry**
CHI	36363 24390	$\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	-	-
$[Cu(CHI)_2]$	20661 27624 37037	$^2B_{1g} \rightarrow {}^2A_{1g}(\upsilon_1)$ $^2B_{1g} \rightarrow {}^2B_{2g}(\upsilon_2)$ $^2B_{1g} \rightarrow {}^2E_g(\upsilon_3)$	1.79	Octahedral
$[Co(CHI)_2]$	37317 20242 10570	$^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)(\upsilon_1)\ {}^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)(\upsilon_2)$ $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)(\upsilon_3)$	4.92	Octahedral
$[Pd(CHI)_2]$	23041 36630 33898	$^1A_{1g} \rightarrow {}^1A_{2g}(\upsilon_1)$ $^1A_{1g} \rightarrow {}^1B_{1g}(\upsilon_2)$ LMCT (M←N)	Diamagnetic	Square planar
$[Zn(CHI)_2]$	24752	$^6A_{1g} \rightarrow {}^4T_{1g}(F)$ $^6A_{1g} \rightarrow {}^4T_{2g}$ LMCT (M←N)	Diamagnetic	Tetrahedral

3.6 ^{1}H NMR data of the CHI

The nuclear magnetic resonance spectrum of the (**CHI**) was recorded at room temperature in DMSO-d_6 solvent. The spectrum showed two signals each at 13.34 and 11.23 ppm corresponding to the -NH protons of the imine and indole moiety respectively. A multiplet was appeared in the region 7.92-6.90 ppm due to the presence of nine aromatic protons of the prepared molecule. From the above interpretation it is evident that the proposed structure of the ligand is in consistent with the ^{1}H NMR spectral data [13.34 (1H, s, NH), 11.23 (1H, s, NH), 7.92-6.90 (9H, m, Ar-H)].

3.7 Mass spectral data

The mass spectral analysis of the ligand and its metal complexes has been carried out and the mass spectrum of the (**CHI**) exhibited a molecular ion peak at m/z 357 (M^++1) which is equivalent to its molecular weight 356.82 and therefore the obtained spectrum is in consistent with the proposed molecular structure. The LCMS spectra of the copper, cobalt, palladium and zinc complexes of the (CHI) exhibited molecular ion peak at 774 (Mol. Wt. 775.18), 769 (Mol. Wt. 770.57), 818 (Mol. Wt. 818.06) and 440 (Mol. Wt. 439.24) which are in consistent with the proposed molecular structure.

3.5 Powder XRD data of the metal complexes

The powder XRD data for the newly synthesized metal chelates was collected in order to check the degree of crystallinity. The XRD patterns for all the complexes are provided in the **Fig. 1**. From those patterns it is noticed that the only copper and cobalt complexes have some amount of crystallinity where as the other complexes behave as amorphous solids. The XRD pattern of a copper complex showed 11 reflections between the ranges of 7.063-32.768 (2θ). The inter-planar spacing between the planes of a crystal is calculated by using the Bragg's equation $2d\sin\theta = n\lambda$ (λ=1.5406Å). Further, the obtained value of d is compared with calculated one and the unit cell parameters are evaluated and are presented in the **Table 3**. The unit cell parameters were evaluated for the cubic symmetry for all the peaks and $h^2 + k^2 + l^2$ values are also determined and they are 1, 5, 8, 9, 10, 11, 13, 14, 21 and 22. The lattice parameter a = b = c =8.22. The forbidden number 7 and 22 was present and it indicates that the copper complex may belong to hexagonal or tetragonal system. Similarly calculations have been done for the Co(II) and Pd(II) complexes**[**XXVIII]and the values are represented in the **Tables 4** and **5.**

These are also found to have hexagonal or tetragonal system. But, the zinc complex was appears to be amorphous and there are no sharp peaks appeared in the XRD pattern [XXVI, XXIX, XXX].

Table 3: The powder-XRD data calculated for[$Cu(L)_2$]

Peak no.	2θ	θ	Sin θ	Sin^2 θ	1000 Sin^2 θ	$h^2 + k^2 + l^2$ (Sin^2 θ/CF)	(h k l)	d		a in Å
								Obs.	Calcd.	
1	7.063	3.5315	0.0615	0.0037	3.7	1 (1)	100	12.505	12.525	8.2199
2	7.7075	3.8537	0.0672	0.0045	4.5	1.216 (1)	100	11.461	11.462	8.2192
3	15.5068	7.7534	0.1349	0.0181	18.1	4.891 (5)	210	5.7097	5.710	8.2191
4	20.3142	10.1706	0.1765	0.0311	31.1	8.405 (8)	220	4.3680	4.364	8.2197
5	21.2062	10.6031	0.1840	0.0338	33.8	9.135 (9)	300	4.1862	4.186	8.2198
6	21.8405	10.9202	0.1894	0.0358	35.8	9.675 (10)	310	4.0661	4.067	8.2196
7	23.002	11.501	0.1993	0.0397	39.7	10.729 (11)	311	3.8633	3.865	8.2196
8	25.0299	12.5149	0.2166	0.0469	46.91	12.678 (13)	320	3.5547	3.556	8.2207
9	28.0532	14.0266	0.2437	0.0593	59.38	16.048 (14)	321	3.1781	3.160	8.2253
10	31.9724	15.9862	0.2754	0.0758	75.84	20.497 (21)	421	2.7969	2.797	8.2220
11	32.7688	16.3844	0.2820	0.0795	79.52	21.491 (22)	---	2.7307	2.731	8.2208

Table 4: The powder-XRD calculated data for [$Co(L)_2$]

Peak no.	2θ	θ	Sin θ	Sin^2 θ	1000 Sin^2 θ	$h^2 + k^2 + l^2$ (Sin^2 θ/CF)	(h k l)	d		a in Å
								Obs.	Calcd.	
1	6.9603	3.48010	0.0607	0.0036	3.68	1 (1)	100	12.6896	12.6902	8.3333
2	20.311	10.1555	0.1763	0.0310	31.08	8.445 (8)	220	4.3686	4.3692	8.2525
3	21.822	10.911	0.1892	0.0357	35.79	9.725 (10)	310	4.0694	4.0713	8.2524
4	22.968	11.484	0.1990	0.0396	39.60	10.760 (11)	311	3.8689	3.8708	8.2419
5	28.043	14.0215	0.2422	0.0586	58.66	15.940 (16)	400	3.1791	3.1804	8.2464

Table 5: The powder-XRD calculated data for [Pd(L)$_2$]

Peak no.	2θ	θ	Sin θ	Sin^2 θ	1000 Sin^2 θ	h^2 + k^2 + l^2 (Sin^2 θ/CF)	(h k l)	d		a in Å
								Obs.	Calcd.	
1	19.6125	9.8062	0.1703	0.0290	29.00	1 (1)	100	4.5227	4.5231	2.9361
2	21.2081	10.604	0.1840	0.0338	33.85	1.167 (1)	100	4.1859	4.1864	2.9379
3	23.1165	11.5582	0.2003	0.0401	40.12	1.383 (1)	100	3.8444	3.8457	2.9363
4	39.1881	19.594	0.3353	0.1124	112.4	3.875 (4)	200	2.2969	2.2973	2.9357

3.6 TGA Analysis of synthesised compounds

In order to study the thermal stability of the metal complexes, thermo gravimetric (TG) were carried out for Co(II), Pd(II) and Zn(II) complexes in N_2 atmosphere from room temperature to 900 °C at the heating rate of 10 °C /min . The suggested stepwise thermal degradation pattern of all the complexes with respect to temperature and formation of respective metal oxides are depicted in table. The TGA analysis curves of Co(II) complex showed that the weight loss occurred degradation in two successive stages. The first stage of degradation occurred from 25-405°C due to the loss of two molecules of (2*Z*)-but-2-ene and two molecules of 1-chloro-4-methylbenzenewith a practical weight loss of 38.4%. The resultant complex on further degradation of ($C_{20}H_{28}N_{10}Cl_2O$) gave a break at 405-958 °C by the loss of two molecules 5-ethenyl-4-methyl-2-[(2*E*)-2-(pyrrolidin-3-ylidene)hydrazinyl]-1*H*-imidazoletwo chlorine molecules and CH_3moiety with a practical weight loss of 52. 4%. The final weight of the residue corresponds to cobalt oxide. In the thermo gram of the [Pd(L)$_2$] complex the first stage of decomposition represents the weight loss of two molecules of 1-chloro-4-(prop-1-en-2-yl)benzene and its related molecules at 25-296 °C with a practical weight loss of 32.1% . The resultant complex underwent further degradation and gave a break at 296-721°C with a weight loss of 54.6% which corresponds to the simultaneous decomposition of (3*E*)-3-[2-(5-methyl-1*H*-imidazol-2-yl)hydrazinylidene]-2,3-dihydro-1*H*-indole, one molecule of (3*E*)-3-[2-(1*H*-imidazol-2-yl)hydrazinylidene]-1,3-dihydro-2*H*-indol-2-one and two chlorine atom moiety. Further, the weight of the residue corresponds to nickel oxide.

Table 6: The TGA data of Co and Pd complex.

Complex	Steps	Decomposition Temp (°C)	Assignment	Loss of mass in (%)	Residue species
[Co(L)$_2$]	1	24-405	$C_{22}OCl_2$	38.4	CoO
	2	405-958	$C_{20}H_{28}N_{10}Cl_2O$	52.4	
[Pd(L)$_2$]	1	22-296	$C_{19}H_8Cl_2$	32.1	PdO
	2	296.-721.	$C_{23}H_{18}N_{10}Cl_2O$	54.2	

3.7.1 Antimicrobial studies

The microbial infections are very common nowadays as many drugs available in the market. This has many issues like increased resistance of the microbes against, multidrug resistance strain, lack of selectivity, etc. in view of these impending challenges, many of the researchers trying to minimise the shortcomings and involved in designing new metal based drugs. In this view, the synthesised compounds were subjected for the antimicrobial activity. The MIC values for the three bacterial strains Staphylococcus aureus, Klebsiellapneumoniae and Pseudomonas aeruginosa and three fungal strains Candida albicans, Aspergillusflavus and Aspergillusfumigatus are provided in the **Table 7**. Among the studied compounds, the metal chelates are found to have greater antimicrobial activity compared to the ligand. The copper complex showed almost higher inhibitory effect compared to all the studied compounds against the tested pathogens. From this observation it is evident that the metal complexes are more efficient in inhibiting the activity of the pathogen and this may led to the development of metal based drugs which can be used for the treatment for the diseases caused by the microbes.[XXVII**].**

Table 7:Antimicrobial activity results in MIC of the (CHI) and its metal chelates

E.coli

Compound	100mg/mL	50 mg/	25mg/mL	12.5mg/mL	6.25mg/mL	3.12mg/mL	1.5mg/mL	0.8mg/mL	0.4mg/mL	0.2mg/mL
CHI	S	S	S	S	S	S	S	S	S	R
[Cu(CHI)$_2$]	S	S	S	R	R	R	R	R	R	R
[Co(CHI)$_2$]	S	S	S	S	S	S	S	R	R	R
[Pd(CHI)$_2$]	S	S	S	S	S	S	R	R	R	R
[Zn(CHI)$_2$]	S	S	R	R	R	R	R	R	R	R

P.aureginosa

CHI	S	S	S	S	S	S	S	S	R	R
[Cu(CHI)$_2$]	S	R	R	R	R	R	R	R	R	R
[Co(CHI)$_2$]	S	S	S	R	R	R	R	R	R	R
[Pd(CHI)$_2$]	S	S	S	S	R	R	R	R	R	R
[Zn(CHI)$_2$]	S	S	R	R	R	R	R	R	R	R

E.Faecalis

CHI	S	S	S	S	S	R	R	R	R	R
[Cu(CHI)$_2$]	S	S	S	R	R	R	R	R	R	R
[Co(CHI)$_2$]	S	S	S	S	R	R	R	R	R	R
[Pd(CHI)$_2$]	S	S	S	R	R	R	R	R	R	R

[Zn($CHI)_2$]	S	S	S	S	R	R	R	R	R	R

C.albicans

CHI	S	S	S	S	S	R	R	R	R	R
[Cu($CHI)_2$]	S	S	S	R	R	R	R	R	R	R
[Co$(CHI)_2$]	S	S	S	S	R	R	R	R	R	R
[Pd($CHI)_2$]	S	S	S	R	R	R	R	R	R	R
[Zn($CHI)_2$]	S	S	S	S	R	R	R	R	R	R

A.flavus

CHI	S	S	S	S	S	S	S	S	R	R
[Cu($CHI)_2$]	S	S	S	S	S	S	R	R	R	R
[Co($CHI)_2$]	S	S	S	S	S	S	S	S	R	R
[Pd($CHI)_2$]	S	S	S	S	S	S	S	S	R	R
[Zn($CHI)_2$]	S	S	R	R	R	R	R	R	R	R

A.niger

CHI	S	S	S	S	S	S	R	R	R	R
[Cu($CHI)_2$]	S	S	R	R	R	R	R	R	R	R
[Co($CHI)_2$]	S	S	S	S	S	R	R	R	R	R
[Pd($CHI)_2$]	S	S	R	R	R	R	R	R	R	R
[Zn($CHI)_2$]	S	S	S	S	S	S	R	R	R	R

3.7.2 Antmycobacterial study

The ant tubercular activity of the synthesized compounds was carried out against M. tuberculosis and the obtained results were tabulated in the **Table 7**. From thistable**,** it is clear that the copper and palladium complexes exhibited higher MIC values of 50 and 25 µg/mL respectively. The remaining complexes exhibited moderate activity while ligand exhibited least activity with MIC value equal to 1.6 µg/mL. Therefore, it is said that the metal based drugs are efficiently inhibit the bacterial growth and proved to be effective in controlling the abnormal activity of the pathogen on the humankind.(XXV)

Table 8: **Antmycobacterial results of the(L) and its metal complexes at different concentrations**

Compound	**100 µg/mL**	**50 µg/mL**	**25 µg/mL**	**12.5 µg/mL**	**6.25 µg/mL**	**3.12 µg/mL**	**1.6 µg/mL**	**0.8 µg/mL**
CHI	S	S	S	S	S	S	R	R
[Cu$(CHI)_2$]	S	R	R	R	R	R	R	R
[Co $(CHI)_2$]	S	S	S	S	S	S	R	R

[Pd(CHI)$_2$]	S	S	R	R	R	R	R	R
[Zn(CHI)$_2$]	S	S	S	S	R	R	R	R

S-Sensitive, R-Resistance

3.7.3 Anticancer study

The cytotoxic effect of the target compounds was analysed by MTT assay against two cancer cell lines HeLa and A549. The inhibitory effect of the compounds on the pathogen was recorded in terms of IC_{50} (µg/mL) and the same values are presented in the **Table 9**. The obtained IC_{50}values for the all the titled compounds clearly indicated that, the copper and zinc complexes have approached the appreciable anticancerous behaviour of the standard drug cisplatin by showing least IC50 values in the range 5.12-13.16µg/mL. From this explanation it is established that, the present chelates are better anticancer agents and they may be screened for the further analysis to be incorporated in the design of the new drugs for the cancer treatment. (XXXI, XXXII)

Table 9: Cytotoxic activity results of the target compounds against HeLa and A549 cell line in comparison with the standard drug cisplatin.

Compound	**IC_{50} values (µg/mL)**	
	HeLa Cell line	**A549 cell line**
CHI	59.32	41.23
[Cu(CHI)$_2$]	9.12	13.16
[Co(CHI)$_2$]	61.35	39.22
[Pd(CHI)$_2$]	17.22	22.15
[Zn(CHI)$_2$]	5.12	8.69
Cisplatin	2.63	7.36

4 Conclusion

Four new coordination compounds of the ligand 3-{2-[4-(4-chlorophenyl)-1,3-thiazol-2-yl]hydrazinylidene}-1,3-dihydro-2H-indol-2-onehave been synthesised and analysed by UV-visible, FT-IR, NMR, mass, magnetic susceptibility and powder XRD. The XRD data showed that the zinc complex is in amorphous from while the other metal complexes appears to have crystalline formed all the complexes possessing hexagonal or tetragonal structure from these characterisations, octahedral geometry was assigned for copper and cobalt complexes, whereas square planar and tetrahedral structure was proposed for the 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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