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Development and molecular modeling of Co(II), Ni(II) and Cu(II) complexes as high acting anti breast cancer agents

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Abstract A series of cobalt, nickel and copper complexes of bidentate Schiff base derived from the condensation reaction of 4-amino-5-mercapto-3-methyl-1,2,4-triazole with 2-nitrobenzaldehyde had been synthesized. The synthesized Schiff base and their metal complexes have been characterized with the support of more than a few physicochemical techniques, elemental evaluation, magnetic moment measurements, spectroscopic, thermo gravimetric techniques and X-ray powder diffraction. Spectral analysis exhibits square planer geometry for Cu(II) complex while octahedral geometry for Co(II) and Ni(II) complexes. The Schiff base and their complexes have been screened for their anticancer activity using MCF7 cell line. In molecular docking learn exhibits that Ni(II) complex is more active confirmed quantity of interaction in particular hydrogen bond interaction with ASN142 and charge interactions with ASP97 and GLU99.

1. Introduction

Cisplatin discovery in 1965 proved a milestone in the drug discovery of metal based anticancer agents. In recent years the metalo-pharmaceuticals attracted attention of the scientific fraternity.

Currently various metalo-pharmaceuticals such as bismuth subsalicylate (anti-diarrheal), auranofin (anti-inflammatory for treatment of arthritis), silver sulfadiazine (antibacterial) and zinc pyrithione (antibacterial and antifungal) are in the clinical use. Breast cancer is leading cause of death in women in recent years. Breast cancer is accounting for total 23% of all cancer cases in women, and the death percentage of the patient suffering from this cancer rises to 16% of all cancer deaths. The emergence of the some new types such as triple negative breast cancer, development of new and potent therapeutic agents targeting novel target against breast cancer is need of time. CDK or Cyclin-dependent kinases are the family of the heterodimer kinases which are having critical role in the regulation of cell cycle progression and transcription. Deregulation of these kinases leads to proliferation

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of cancer cells, and aberrant activity of the number of kinases has been found in variety of the cancers. So inhibition of these kinases will be acting as attractive target for development of new anticancer agents. The chemistry of Schiff bases and their structural analogues have occupied a position of considerable significance (Gornovskii et al., 2009) as they form steady complexes with most transition metal ions (Heshmatpour et al., 2007; Nuria et al., 2005) and exhibit well-established biological properties (Manikshete et al., 2011). 1,2,4-triazole nucleus and their derivatives emerge quickly with the advances of modern heterocyclic chemistry, promising a variety of scientific purposes comparable to antibacterial, antifungal, anticancer, antitumor, anticonvulsant, anti-inflammatory, and analgesic properties (Turan-Zitouni et al., 2005; Walczak et al., 2004; Mavrova et al., 2009; Al-Soud et al., 2003; Almasirad et al., 2004; Amir and Shikha, 2004).

Schiff bases of 1,2,4-triazoles find diverse applications and huge biological activity. The incorporation of the 1,2,4-triazole unit into Schiff base macro cycles is of colossal current curiosity as complexes of 1,2,4-triazoles are being developed for knowledge use in purposes akin to magnetic substances and image chemically pushed molecular instruments (Brandt et al., 2007). Schiff bases derived from 3-substituted 4-amino-5-mercapto-1,2,4-triazoles show analgesic, antimicrobial, anti-inflammatory and antidepressant activities (Bekircan and Bektas, 2006). These motives caused us to carry out gain knowledge of synthesis of Schiff base and its complexes with Co(II), Ni(II) and Cu(II) metal ions.

The intention of present communication is to gain knowledge of bioactivities of 1,2,4-triazole Schiff base and reap the relative derivatives with better curing effect and strengthen bioavailability with the aid of coordinating them with transition metal ions. The synthesized Schiff base and their metal complexes have been characterized with the aid of elemental analysis, magnetic moment measurements, spectroscopic, thermo gravimetric and X-ray powder diffraction approaches. The Current manuscript deals with development of transition metal complexes of 1,2,4-triazoles and their anticancer screening on the MCF 7 cell line. Thus, our study will give new useful insights for designing metallo-pharmaceuticals for anticancer therapy.

2. Experimental

All reagents used, hydrazine hydrate, carbon disulfide, 2-nitrobenzaldehyde, cobalt chloride, nickel chloride and copper chloride were of AR grade. The solvents used were ethanol, ethyl acetate, petroleum ether, dimethyl formamide (DMF) and dimethyl sulfoxide (DMSO). The synthesis of Schiff base ligand and metal complexes is proven in Scheme 1.

4-Amino-5-mercapto-3-methyl-1,2,4-triazole (AMMT) was prepared by reported literature Method (Bala et al., 1978). The AMMT (1.30 g, 0.01 M) and 2-nitrobenzaldehyde (1.511 g, 0.01 M) were dissolved in ethanol (25 ml) individually
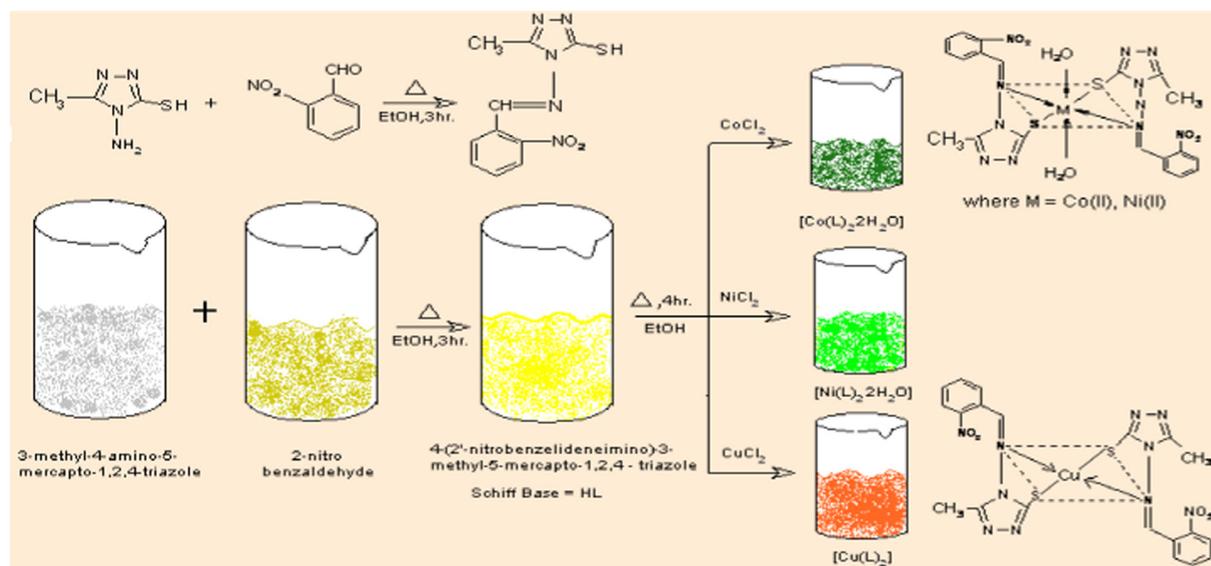
Scheme 1

Table 1 Analytical and physical data of the Schiff base (HL) and Co(II), Ni(II) and Cu(II) complexes.

Comp.	Molecular formula	Mol. Wt.	Color	Elemental analysis			
				C% found (calc.)	H% found (calc.)	N% found (calc.)	M% found (calc.)
HL	$C_{10}H_9N_5SO_2$	263	Pale yellow	45.20 (45.63)	3.52 (3.42)	26.48 (26.61)	–
HL-Co	$C_{20}H_{20}N_{10}S_2O_6Co$ [Co(L)$_2$2H$_2$O]	618.93	Olive green	38.84 (38.78)	3.16 (3.23)	22.71 (22.62)	9.42 (9.52)
HL-Ni	$C_{20}H_{20}N_{10}S_2O_6Ni$ [Ni(L)$_2$2H$_2$O]	618.91	Green	38.71 (38.78)	3.30 (3.23)	22.58 (22.62)	9.59 (9.52)
HL-Cu	$C_{20}H_{16}N_{10}S_2O_4Cu$ [Cu(L)$_2$]	587.54	Brick red	40.93 (40.85)	2.81 (2.72)	23.89 (23.83)	10.93 (10.81)

Table 2 Electronic spectral and magnetic measurement data.

Compd.	γ_1 cm^{-1}	γ_2 cm^{-1}	γ_3 cm^{-1}	Dq cm^{-1}	B cm^{-1}	γ_2/γ_1 cm^{-1}	β cm^{-1}	β %	$\mu_{eff. BM}$
HL-Co	10,810	22,703*	21,276	1189.3	770	2.10	0.792	20.70	4.89
HL-Ni	9891	16,129	24,992	989.1	788.16	1.63	0.757	24.29	3.45
HL-Cu	17,993	–	–	1799.3	–	–	–	–	1.92

* Calculated value.

Table 3 IR spectral data of Schiff base [HL] and Co(II), Ni(II) and Cu(II) complexes.

Sr. no.	Compound	$v_{C=N}$ cm^{-1}	v_{SH} cm^{-1}	$v_{C=S}$ cm^{-1}	$v_{(C--S)}$ cm^{-1}	v_{H2O} cm^{-1}	v_{M-S} cm^{-1}	v_{M-N} cm^{-1}
1	HL	1590	2760	1114	–	–	–	–
2	HL-Co	1525	–	–	718	3395	355	515
3	HL-Ni	1525	–	–	785	3206	379	483
4	HL-Cu	1567	–	–	750	–	350	493
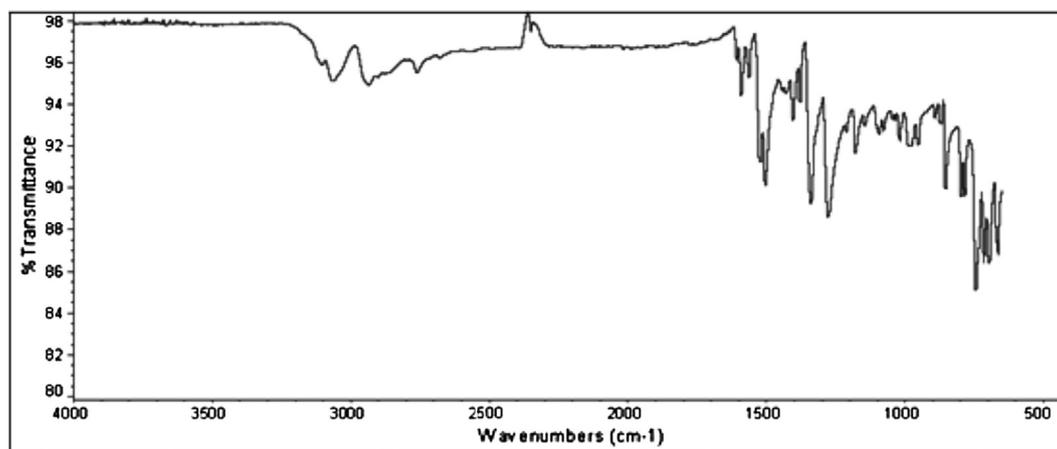
Figure 1 IR spectra of Schiff base (HL).

in 1:1 molar ratio. The ethanolic solutions were mixed together. The mixture was refluxed on water bath for 3 h. On cooling, a crystalline Schiff base, 4-(2′-nitrobenzylideneimino)-3-methyl-5-mercapto-1,2,4-triazole (HL), used to be separated via filtration and crystals were washed with cold ethanol and recrystallized from ethanol and dried in vacuum over anhydrous CaCl$_2$. The melting point of synthesized compound was found to be 224 °C.

The Schiff base (2.63 g, 0.01 M) was dissolved in 25 ml ethanol and added to metal salt cobalt chloride (1.189 g, 0.005 M), Nickel chloride (1.188 g, 0.005 M) and copper chloride (0.852 g, 0.005 M)]. The mixture was refluxed for 4 h. The products formed were filtered and purified by washing thoroughly with absolute ethanol and finally with acetone and dried in vacuum over anhydrous CaCl$_2$.

The sulphorhodamine B (SRB) evaluates were used for cell density determination, based on the measurement of cellular protein content. The process described right here was once optimized for the toxicity screening of compounds to adherent cells in a 96 well format. After an incubation period, cell monolayers were fixed with 10% (w/v) trichloroacetic acid and stained for 30 min, after which the surplus dye was once removed with the aid of washing repeatedly with 1% (v/v) acetic acid. The protein-bound dye is dissolved in 10 mM tris base solution for OD resolution at 510 nm utilizing a micro plate reader. The results had been linear over a 20-fold variety of cell numbers and the sensitivity was comparable to those of fluorometric approaches.

2.1. Molecular docking

To ascertain the mode of action of the synthesized metal complexes molecular docking calculations are carried out using a biopredicta module of the V life MDS 4.3. Virtual analysis was carried out using the crystal structure of the Human CDK 7 (PDB ID: IUA2) downloaded from Protein Data Bank (www.rcsb.org/pdb) at a resolution of 3.02 Å. Protein structure was refined via deletion of all the heteroatoms including water molecules and addition of the polar hydrogen atoms to get a native conformation. All other bonds were allowed to be rotatable. Structures of the synthesized metal complexes are drawn in the builder module of the V life MDS 4.3 engine. The 2D structures of the molecules
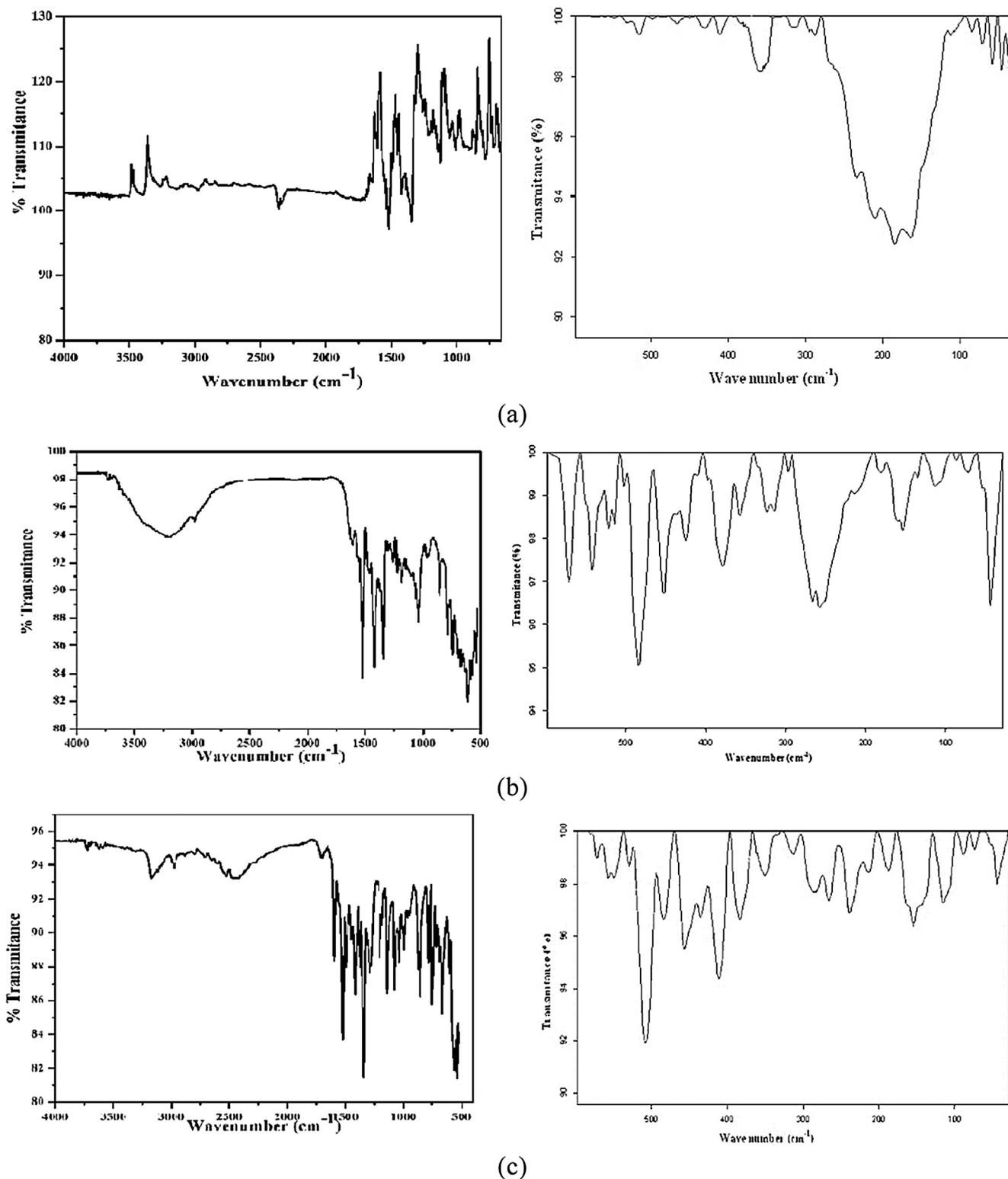
Figure 2   (a–c): IR spectra of Co(II), Ni(II) and Cu(II) complexes.

were converted into the 3D structures are optimized via application of the MMFF force field. These optimized structures were further utilized for the docking analysis. All calculations were performed on an Intel i3, based machine running windows 7 as operating system. The docked protein ligand complex was further analyzed via docking score of the each of the complex, which is nothing but the binding energy of the complex, for every derivative best 100 binding conformation was analyzed to select the best conformation having the minimum energy of the binding.

Figure 3 ^{1}H NMR spectra of Schiff base(HL).

Table 4   Thermal analysis Co(II), Ni(II) and Cu(II) complexes.

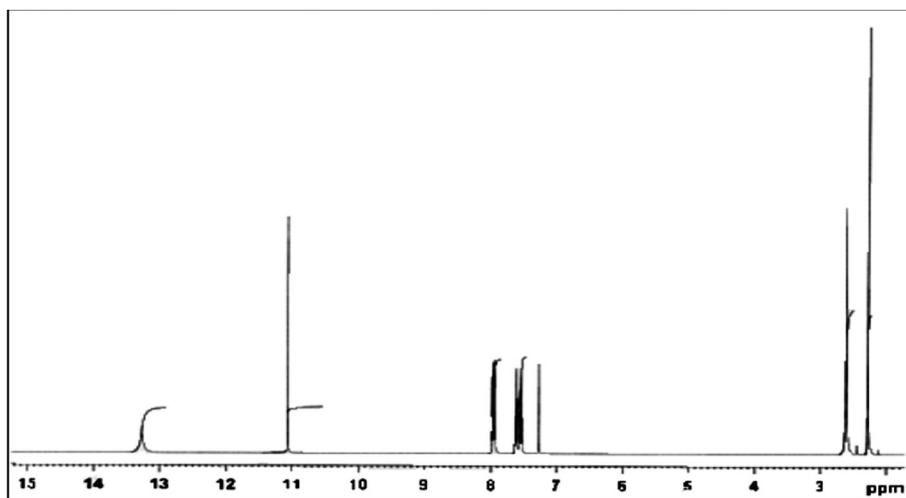| Compound.	Step	Temp. (°C)	TG mass%		No. of moles	Assignment
			Calc.	Found		
[Co(L)$_2$2H$_2$O]	1	50–175	5.81	6.74	2	—H$_4$O$_2$(water molecules)
	2	175–425	48.14	46.37	2	—C$_{14}$H$_{10}$N$_4$O$_4$(organic moiety)
	3	425–540	36.51	34.34	2	—C$_6$H$_6$N$_6$S$_2$(triazole ring)
			12.10	12.57		—CoO(residue)
[Ni(L)$_2$2H$_2$O]	1	50–180	5.81	6.92	2	—H$_4$O$_2$(water molecules)
	2	180–400	48.14	46.11	2	—C$_{14}$H$_{10}$N$_4$O$_4$(organic moiety)
	3	400–550	36.51	34.09	2	—C$_6$H$_6$N$_6$S$_2$(triazole ring)
			12.10	12.94		—NiO(residue)
[Cu(L)$_2$]	1	50–425	45.95	44.46	2	—C$_{14}$H$_{10}$N$_4$O$_4$(organic moiety)
	2	425–750	43.22	42.84	2	—C$_6$H$_6$N$_6$S$_2$(triazole ring)
			12.10	12.69		—CuO(residue)
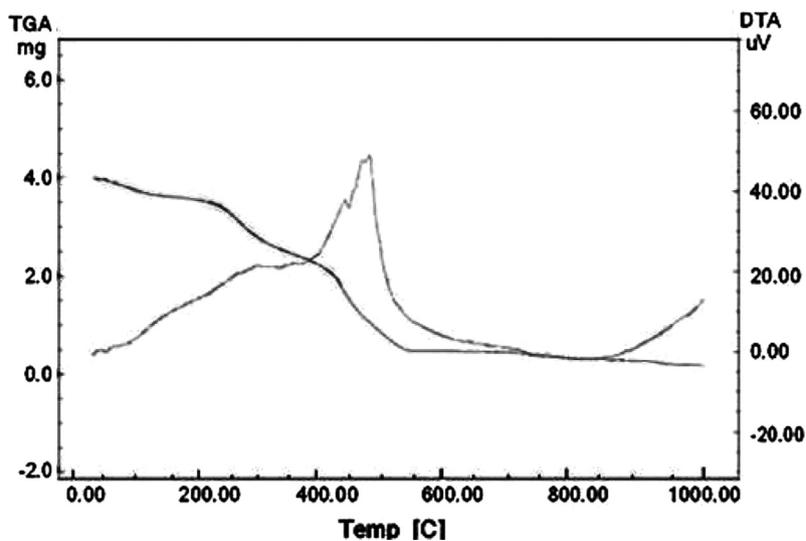
Figure 4   TGA-DTA curve of Co(II) complex.
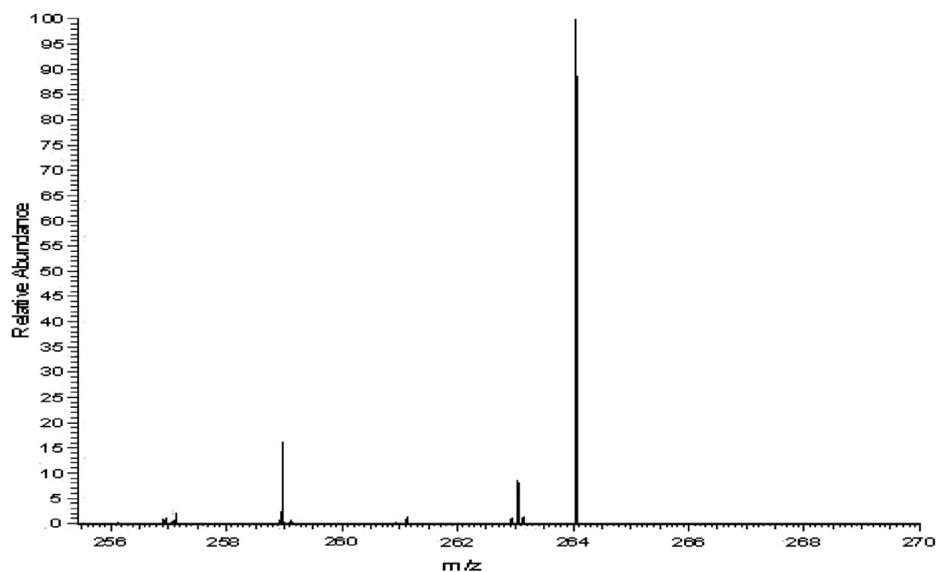
Figure 5 Mass spectrum of Schiff base (HL).
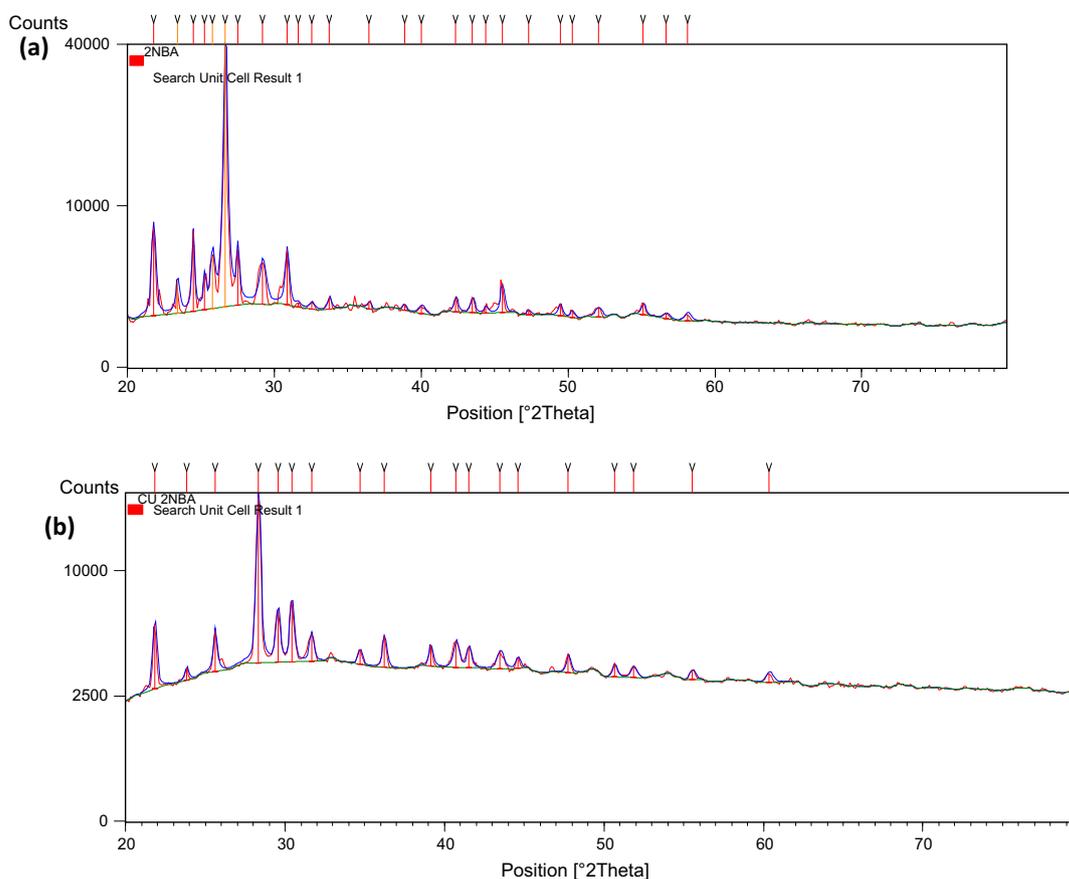
Figure 6 XRD pattern of (a) ligand and (b) Cu(II) complexes.

3. Results and discussion

3.1. Elemental and physical data

The Schiff base used to be soluble in ethanol, methanol, acetone, DMF and DMSO. The entire metal complexes are colored, non-hygroscopic solid which might be steady in air, insoluble in water and organic solvents but soluble in DMSO and decomposed at higher temperature. The purity of ligands and their metal complexes has been checked with the aid of TLC. Based on elemental and spectral studies the geometry of synthesized compounds has been elucidated. By the

Table 5   Crystallographic data of ligand (HL).

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
21.7677	6477.85	0.2922	4.08292	16.87
23.4049	1732.92	0.2922	3.80089	4.51
24.4578	5927.24	0.1948	3.63961	15.44
25.2393	1805.91	0.1948	3.52865	4.70
25.7877	3311.21	0.2922	3.45484	8.62
26.6576	38391.45	0.2922	3.34404	100.00
27.5059	3839.91	0.1948	3.24280	10.00
29.1995	2666.54	0.4871	3.05847	6.95
30.8622	3803.80	0.2922	2.89737	9.91
31.6022	186.68	0.2922	2.83120	0.49
32.5568	302.31	0.3897	2.75034	0.79
33.7386	576.15	0.2922	2.65665	1.50
36.4505	341.38	0.2922	2.46498	0.89
38.8494	258.24	0.2922	2.31812	0.67
40.0260	335.37	0.4871	2.25265	0.87
42.3468	700.98	0.2922	2.13441	1.83
43.4795	733.64	0.2922	2.08140	1.91
44.3787	282.75	0.2922	2.04129	0.74
45.5015	1526.86	0.2922	1.99350	3.98
47.2986	207.64	0.2922	1.92186	0.54
49.4470	535.30	0.2922	1.84328	1.39
50.2646	286.13	0.2922	1.81520	0.75
52.0517	385.04	0.4871	1.75700	1.00
55.1115	524.00	0.2922	1.66648	1.36
56.6904	200.42	0.4871	1.62376	0.52
58.1296	234.93	0.4752	1.58564	0.61

Table 6   Crystallographic data of Cu(II) complex.

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
21.8271	3375.11	0.2922	4.07195	26.67
23.8238	577.05	0.2922	3.73499	4.56
25.6116	2163.59	0.2922	3.47820	17.09
28.3234	12657.35	0.2922	3.15104	100.00
29.5388	3022.92	0.2922	3.02410	23.88
30.4227	3626.43	0.2922	2.93823	28.65
31.6520	1500.20	0.2922	2.82686	11.85
34.6912	762.07	0.2922	2.58585	6.02
36.2253	1666.66	0.2922	2.47979	13.17
39.1207	1117.85	0.2922	2.30266	8.83
40.7282	1366.82	0.3897	2.21542	10.80
41.5311	1083.03	0.2922	2.17443	8.56
43.4820	876.44	0.4871	2.08128	6.92
44.5875	551.90	0.2922	2.03222	4.36
47.7587	940.21	0.2922	1.90442	7.43
50.6635	654.54	0.2922	1.80184	5.17
51.8466	532.77	0.3897	1.76347	4.21
55.5373	465.59	0.3897	1.65471	3.68
60.3664	362.06	0.4752	1.53212	2.86

elemental analysis, the stoichiometry of ligand and their metal complexes is confirmed. The elemental analyses of ligand and metal complexes are found in agreement with the proposed structure of ligand and the metal complexes. Analytical and physical data of the Schiff base(HL) and Co(II), Ni(II) and Cu(II) complexes are listed in Table 1.

3.2. Electronic spectral analysis and magnetic studies

The electronic spectra and magnetic moments of the compounds are very useful in the evaluation of results acquired by using different ways of structural investigation. The information regarding the geometry of the complexes around the

Table 7 Unit cell parameters, volume and space group of ligand and Cu(II) complexes.

Compound	Lattice constants (Å)	Volume, (Å)^3	Space group	Crystallite size, (Å)
HL	$a = 16.61$, $b = 8.16$, $c = 3.91$	529.96	I m a m	337
HL-Cu	$a = 4.90$, $b = 4.90$, $c = 21.1$,	506.90	I 41/a c d	182

Co(II), Ni(II) and Cu(II) ion was obtained from electronic spectral studies and magnetic moments. The electronic spectra of ligand and their metal complexes were recorded at room temperature utilizing DMSO as a solvent.

The electronic spectra of ligand exhibit band at 29,585 cm^{-1} which will also be assigned to $n \rightarrow \pi^*$ transition of azomethine group. Within the spectra of complexes, the bands of azomethine chromophore because of $n \rightarrow \pi^*$ transition are shifted to lower frequencies indicate that imine nitrogen is concerned in the coordination of metal ion.

Co(II) complex exhibits two absorption bands at 10,810 cm^{-1} (γ_1) and 21,276 cm^{-1} (γ_3) which might be assigned to $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ (γ_1); $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ (γ_3) transitions (Avji et al., 2008; Kulkarni et al., 2011). These are attribute bands of high spin octahedral Co(II) complexes; γ_2 is not observed, but it may be calculated by using relation $\gamma_2 = \gamma_1 + 10Dq$, which may be very nearly (γ_3) transition. These transitions propose a octahedral environment around Co(II) ion which was once extra supported by using its magnetic moment value of (μeff) 4.89BM.

Ni(II) complex generally shows three absorption bands in octahedral environment corresponding to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$ (γ_1), $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ (γ_2), and $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ (γ_3) transitions (Cotton et al., 2003). Ni (II) complex exhibits above three transitions at 9891 cm^{-1} (γ_1), 16,129 cm^{-1} (γ_2), and 24,992 cm^{-1} (γ_3) suggesting octahedral geometry which

Table 8 GI$_{50}$ values of ligand and metal complexes.

Sr. no.	Molecular code	GI$_{50}$
1	HL	64.1
2	HL-Co	35.7
3	HL-Ni	59.9
4	HL-Cu	54.9

Figure 7 Growth curve: human breast cancer cell line MCF-7.

is further proven through its magnetic moment value of (μ$_{eff}$) 3.45 BM.

The electronic spectra of Cu(II) complex show large band at 17,993 cm^{-1} which could also be cheap be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ (γ_1) transition, consistent with a square planar geometry around Cu(II) (Osman et al., 2004) which is further verified with the aid of its magnetic of moment value (μeff) 1.92 BM. The ligand field parameters like crystal field stabilizing energy (Dq), Racah parameter (B), Nephelauxetic ratio (β) and β% have been calculated for Co(II), Ni(II), Cu(II) complex and observed data are shown in Table 2.

3.3. IR and ^1H NMR spectroscopic studies

The prominent bands observed in IR spectra of Schiff base (HL) and its complexes are represented in Table 3. The IR spectrum of free ligands shows a strong band at 1590 cm^{-1} assigned to $v(N=CH)$ indicating the formation desired shift base ligand. This used to be further proven by the presence of a new band observed in 483–515 cm^{-1} region assigned to $v(M-N)$, which is coordination of metal to azomethine nitrogen. The Schiff base (HL) (Fig. 1) a band at 2760 cm^{-1} is assigned to $v(SH)$ vibration (Singh et al., 2006a,b). This band disappeared in the spectra of the metal complexes indicating deprotonation and complexation via sulfur. In the spectra of Schiff base a band due to tautomeric form of C=S is appeared at 1114 cm^{-1}, in metal complexes this peak was disappeared.

Co(II), Ni(II) and Cu(II) complexes (Fig. 2a–c) show band at 350–379 cm^{-1} have been assigned to $v(M-S)$ (Liver, 1968). Within the spectra of all complexes, bands appeared at 718–785 cm^{-1} and 350–379 cm^{-1} were assigned to $v(C-S)$ and $v(M-S)$, respectively (Osman et al., 2004; Singh et al., 2006a,b). In the spectra of Co(II) and Ni(II) complexes, a broad band in the region 3206–3395 cm^{-1} indicated the presence of coordinated water molecules. The presence of water molecule was also confirmed by thermal analysis.

The ^1H NMR spectrum of Schiff base was recorded in DMSO, using Tetramethylsilane (TMS) as an internal standard. The ^1H NMR spectrum of ligand shows characteristic azomethine proton singlet at δ 11.07 ppm. The signal at δ 13.27 ppm is ascribed to SH proton. The aromatic proton of Schiff base appeared as multiplate at δ 7.27–7.99 ppm and singlet at δ 2.28 ppm is due to methyl group. Since Co(II), Ni(II) and Cu(II) complexes are paramagnetic, their ^1H spectra could not be obtained (Canpolat and Kaya, 2005). ^1H NMR spectrum of Schiff base(HL) is indicated in Fig. 3.

3.4. Thermal analysis

Thermal decomposition of Co(II), Ni(II) and Cu(II) complexes has been studied as a function of temperature by means of TGA-DTA method. The decomposition temperatures, paralyzed products, percentage mass losses of the complexes and

ash percentage are listed in Table 4. The Co(II) and Ni(II) complexes exhibit three steps of decomposition. In first step, decomposition takes place from 50 to 180 °C due to total cleavage of the base metal complex along with hydroxide to oxide transformation followed by concomitant release of water molecules corresponding to loss of coordinated water molecules. The second decomposition takes place from 175 to 425 °C attributed to the release of organic moiety. Third decomposition around 400–550 °C can be attributed to the release of triazole moiety. The decomposition of both the complexes ended with oxide formation above 550 °C. For Cu(II) complex, first step of decomposition at 50–425 °C corresponds to loss of organic moiety while second step corresponds to removal of triazole molecules at 425–750 °C. After 750 °C metal oxide is formed as a residue. Thermal curve analysis of Co(II) complex is shown in Fig. 4.

3.5. Mass spectroscopic studies

The mass spectrum of ligand reveals parent peak due to molecular ion (M^+). The proposed molecular formulation of this compound used to be proven through comparing their molecular formula weight with m/z value. The molecular ion peak used to be acquired at m/z 264. This worth is in excellent agreement with the proposed molecular components of compound. A mass spectrum of Schiff base (HL) is exhibited in Fig. 5.

3.6. X-ray diffraction analysis

The X-ray diffraction measurements were obtained using a X-ray diffractometer (Rigaku Ultima IV, Japan made). The Cu Kα radiation tube with line focus was operated at 40 kV and 40 mA. The X-ray powder diffraction patterns were obtained in the range of 20–80° in steps of 0.0990. X-ray powder diffraction analysis of the ligand and its metal complexes was carried out to determine the type of crystal system, lattice parameters and the cell volume. As shown in Fig. 6(a) and (b) the XRD patterns indicate a crystalline nature for the ligand and Cu (II) complex, while Ni(II) and Co(II) complexes have amorphous nature. Indexing of the diffraction patterns was performed using High Score Plus software. For the ligand and Cu(II) complex d values, FWHM and relative intensities are

Figure 8   (a): Hydrogen bond interactions and charge interactions of HL; (b): hydrogen bond interactions and charge interactions of HL-Co.

Table 9 Binding energy and critical interaction of ligand and metal complexes.

Sr. no.	Molecule code	Binding energy kcal/mol	Interaction with amino acid		
			H-Bond	Charge	Hydrophobic
1	HL	−40.53	GLN22	–	LYS41 VAL26
2	HL-Co	−48.98		–	
3	HL-Ni	−84.54	ASN142	GLU99, ASP97	GLY21, GLU99
4	HL-Cu	−69.36	ASN142	–	LYS41 ALA39

given in Tables 5 and 6. From the indexed data the unit cell parameters, volume, space group and average crystallite size were also calculated and are listed in Table 7. The powder XRD patterns of the Cu(II) complex are completely different from those of ligand. XRD studies reveal that ligand has an orthorhombic structure, while Cu(II) complex has tetragonal structure. The full width at the half-maximum (FWHM) of the diffraction peaks obtained from the refinement was used to calculate the particle size. The X-ray diffraction data were determined by using Cu Kα radiation (λ = 1.54060 Å). The average size of the samples was calculated with the help of the Debye-Scherrer equation,

$$D = (0.90\lambda)/(\beta Cos\theta)$$

where λ is the wavelength (Cu Kα), β is the full width at the half maximum (FWHM) and θ is the diffraction angle. The diffraction peaks indicate that the synthesized materials are in the nanometer range.

3.7. Biological activity studies

All the newly synthesized compounds were screened for their anticancer activity using SRB assay on the MCF 7 breast cancer cell line. In the current protocol each cell line is inoculated on a pre-incubated microtiter plate. The test agents are added at a single concentration and the culture is incubated for 48 h. End point determinations are made with Sulforhodamine B, a protein binding dye. The results for each test agents are reported as the percentage growth of the tested cells. The compounds that reduce the growth of any one of the cell lines to 32% or less (negative numbers indicates cell kill) are passed on for evolution over a 5-log dose range. In the present screening program all the compounds possessed growth to less than 32% are regarded as active compounds (Holla et al., 2003, 2006). Adriamycin was served as positive control compound in the cytotoxic assay. The observed results are listed in Table 8.

3.8. Structure activity relationship (SAR studies)

In Fig. 7 of Co(II), Ni(II) and Cu(II) complexes are found to be active against MCF 7 cell line up to molar dose of 10^{-4} M which indicates their anticancer potential. SAR analysis of the synthesized complexes indicated following points,

- 1,2,4-Triazole shows moderate activity against MCF −7 cell line. HL shows GI_{50} value, 64.1 which indicates the substitution of the good electron withdrawing group —NO₂ sufficiently affecting the polarity of the molecules.
- Cobalt metal complex showing profound activity than the corresponding nickel and copper complexes. Chemical properties of copper make it to take part in number of
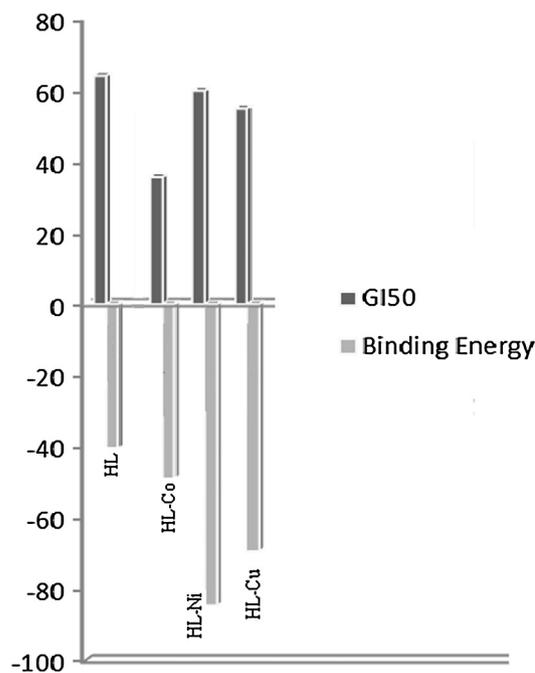

Figure 9 Correlation of binding energy and GI_{50} of HL and its complexes.

biological process such as electron transfer and catalysis. Cobalt complex has ability to kill cancer cells are correlated with the induction of the oxidative stress. Cobalt is an important trace elements for humans in the form of vitamin B12 (Cobalamin), and this metal plays a vital role in Protein synthesis.

3.9. Molecular docking studies

In order to understand the possible mode of action of the synthesized metal complex the molecular docking analysis was carried out using crystal structure of the Human CDK 7. Optimized structure of the metal complexes was utilized for the grip based docking simulation was protein structure is kept rigid and ligand structure is kept flexible. All the molecules were docked into the similar binding site of CDK 7 with binding energy ranging from −33.57 kcal/mol to 96.36 kcal/mol. Nickel complex is most active molecule having binding score of −84.54 kcal/mol having critical interaction with amino acids such as ASN142 (Hydrogen Bond interaction), GLU99 and ASP97 (Charge Interaction) and hydrophobic interaction with GLY21 and GLU99. Hydrogen Bond Interactions and Charge Interactions of Schiff base (HL) and Co(II) Complex

are shown in Fig. 8(a) and (b) respectively. Binding energy and critical interaction of all the compounds are given in Table 9. Correlation of binding energy and GI_{50} of derivatives of Schiff base and metal complexes are shown in Fig. 9.

4. Conclusion

The synthesized Schiff base acts as bidentate ligands and is coordinated with the metal ion via nitrogen and sulfur. The bonding of ligand to metal ion is validated through elemental evaluation, spectral reviews (electronic, IR, ^{1}H NMR, mass), TGA and magnetic measurement. The Co(II) and Ni(II) complexes exhibit octahedral and Cu(II) tricky displays square planar geometry. The entire compounds show off anticancer endeavor against MCF-7 cell line. Metal complexes are more potent in comparison with free ligand. The Co(II) complex indicates quality anticancer exercise.

Acknowledgment

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