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Synthesis, Characterization, Antibacterial, Antifungal and Antimalarial Study of Mixed Ligand Metal Complexes Derived from Azo Quinoline with Thiosemicarbazone

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Mixed ligand metal complexes of azo quinoline and thiosemicarbazone with Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) metal ions were synthesized. The structure and possible geometry of all the metal(II) complexes were analyzed and supported by IR, mass spectrum, elemental analysis, TG-DTA, electronic spectra (UV), magnetic susceptibility and molar conductance. The synthesized compounds were studied for their antibacterial, antifungal and antimalarial activities. The antimicrobial activity was carried out against bacteria (two Gram-positive bacteria and two Gram-negative bacteria), three fungal strain and one malarial pathogen.

Keywords: Metal(II) complexes, 8-Hydroxyquinoline, Thiosemicarbazone, Biological activity.

INTRODUCTION

In past few years, researchers focused on metal-based drugs because of much more significance in medicinal and pharmaceutical field [1]. They are applied in pharmaceutical field for the treatment of cancer, diabetes, antifungal, antibacterial, antioxidant, antitumor, anticancer, antiviral activities, *etc.* [2,3]. Moreover, it also offer distinct advantages as DNA-binding agents [4] are exhibited by the heteroatom (nitrogen, sulphur and oxygen) containing organic compounds and their metal complexes. Mixed-ligand transition metal complexes involving heterocyclic compounds like pyridine [5], isatin [6], phenanthroline [7], quinoline [8], *etc*. have been reported due to their effectiveness as potential bioactive metal complexes. 8-Hydroxyquinoline and their derivatives are very important due to their stability, coordinating properties and pharmaceutical applications [9,10]. Azo derivatives of 8-hydroxyquinoline were synthesized by diazotization coupling reaction of 8-hydroxyquinoline and primary amines, azo linkage was formed at 5th position [11]. Azo compounds played important role in paper, textile, leather, printing and food industries [12]. The heteroatoms containing compounds with azo linkage also reported for potential biological agents [13,14].

Thiosemicarbazone is a sulphur and nitrogen containing compound which possess diverse pharmaceutical applications such as antibacterial [15,16], antitumor [17], antimalarial, antifungal [18], anti-inflammatory [19], *etc*. It acts as a versatile bidentate ligand in its metal complexes due to its better coordination tendency, selectivity and stability towards a range of metal ions [20,21]. As compared to simple ligands, metal complexes show increased bioactivity [22]. More advantage is given by mixed ligand metal complexes due to activation of enzymes and display better nucleolytic cleavage activity [23].

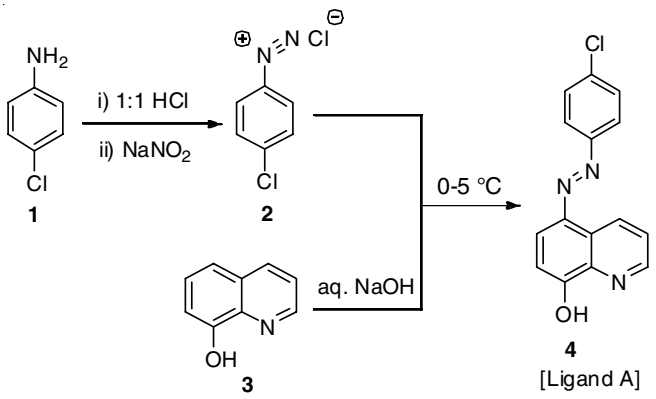
As 8-hydroxyquinoline consists of phenolic group, it displays typical phenolic properties which make it tending towards the numerous chemical reactions and structural alterations, may be due to electrophilic aromatic substitution, diazonium coupling, inter- or intra-molecular rearrangements, *etc*. Moreover, presence of hydroxyl grouo (-OH) and its proximately to N-atom, 8-hydroxyquinoline nucleus has a tendency to act as chelating agent. Thus, in keeping in mind to about the therapeutic values and potential building blocks for various pharmacologically active scaffolds of both azo derivative of 8-hydroxyquinoline and thiosemicarbazone, herein, we have synthesized and characterized Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) mixed ligand complexes of thiosemicarba-

zone. The bioactivity was also carried out on two Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). Antifungal activity against three pathogens such as *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. The antimalarial activity was evaluated against *Plasmodium falciparum* strain.

EXPERIMENTAL

The melting point of the synthesized ligands and their metal(II) complexes were estimated by using open capillary method and are uncorrected. The FT-IR spectra were obtained by Shimadzu FTIR (KBr)-408 spectrophotometer. The conductance was measured on Equiptronics conductivity meter (EQ-) in DMF solvent. The ^{1}H NMR spectra were recorded at 500 MHz in DMSO-d_6 using TMS (as internal standard reference) with δ units. WATER, Q-TOF Micro mass instrument was used to record mass spectra. Elemental analysis was done on Perkin-Elmer EAL240 elemental analyzer. JASCO V-770ST UV/VIS/NIR spectrophotometer was used to record absorption spectra (200-800 nm). Thermogravimetric analysis study was done by using a Perkin-Elmer thermogravimerty analyzer at heating rate 10 ºC per min in nitrogen atmosphere.

Synthesis of [5-((4-chlorophenyl)diazenyl)quinolin-8-ol] (ligand A): A stirred solution of *p*-chloroaniline (**1**) (0.01 mol, 6.35 g) in 30 mL of 1:1 HCl was cooled at 0 ºC. To the above solution, cooled aqueous sodium nitrite solution (0.01 mol, 3.45 g in 15 mL H_2O) was added dropwise resulted in the formation of diazonium salt solution (**2**). The diazonium salt solution (**2**) was added slowly to a well-stirred clear solution of 8-hydroxyquinoline (**3**) (0.01 mol, 7.25 g) in 30 mL water containing NaOH (0.01 mol, 2.0 g) at 0-5 ºC with constant stirring. Stirring was continued for 1 h. The separated product (**4**) was filtered off and recrystallized from absolute ethanol.



Scheme-I: Synthesis of 5-((4-chlorophenyl)diazenyl)quinolin-8-ol (ligand A)

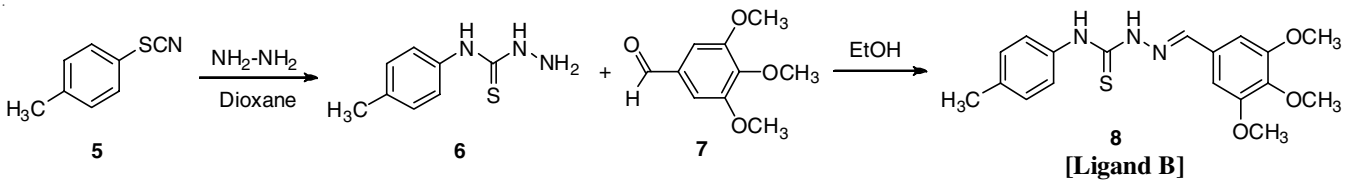
The structure was determined by FTIR, ^{1}H NMR and mass spectral analysis (**Scheme-I**).Colour: brown; yield: 89 %; m.p.: 216-218 ºC; IR (KBr, ν_{max}, cm^{-1}): 3287 (-OH), 1571, (C=N-Py), 1506, 1400 (N=N), 1289, 1232, 1134, 1088, 837, 788, 651 (-Cl). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.25 (d, 1H), 7.67 (d, 2H), 7.80 (dd, 1H), 8.01 (d, 3H) 9.01 (dt, 1H), 9.33 (d, 1H), 11.11 (brs, 1H); MS: M+1 = 284.08.

Synthesis of [*N*-(*p*-tolyl)-2-(3,4,5-trimethoxybenzylidene)hydrazine carbothioamide] (ligand B): A mixture of 1-methyl-4-thiocyanatobenzene (**5**) (0.01 mol, 5.0 g) and hydrazine hydrate (0.011 mol, 2.01 g) in 20 mL dioxane was stirred at room temperature for 2 h. The reaction was monitored by thin layer chromatography. The solvent dioxane was evaporated after completion reaction under reduced pressure, residue obtained was treated with cold water. The product thus obtained was filtered washed with water, dried and used for further reaction without purification.

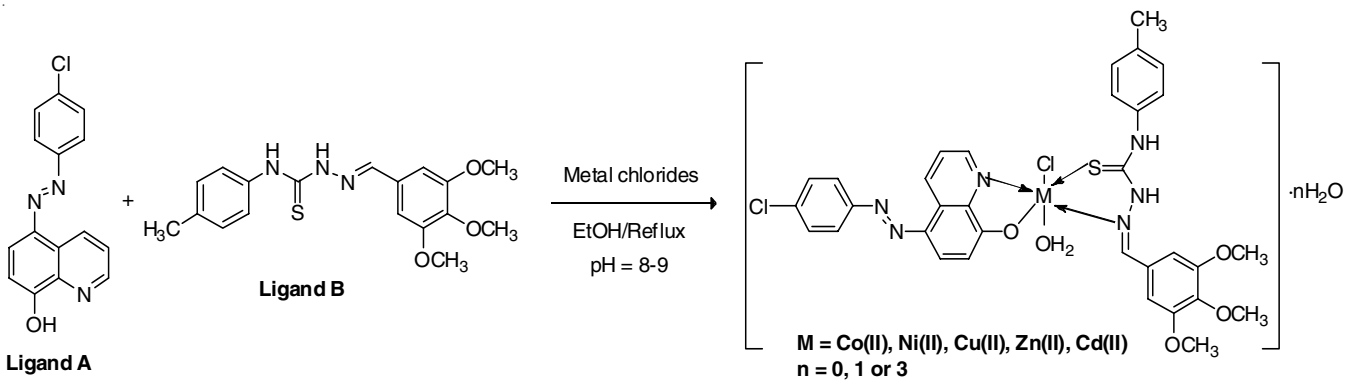
A mixture of *N*-(*p*-tolyl)hydrazinecarbothioamide (**6**) (0.01 mol, 5.5 g) and 3,4,5-trimethoxy benzaldehyde (**7**) (0.012 mol, 5.99 g) in 30 mL ethanol was stirred at reflux temperature for 2 h. The reaction was monitored by thin layer chromatography. The solvent ethanol was evaporated after completion reaction under reduced pressure, residue obtained was treated with cold water. The product thus obtained was filtered washed with water, dried. It was purified from ethanol to give a pure compound (**Scheme-II**). Yield: 86%; m.p.: 178-180 ºC, IR (KBr, ν_{max}, cm^{-1}): 3301-3148 (-NH), 2991-2946 (Ar C-H), 2836 (HC=N), 1611, (N=CH), 1273, 817 (C=S), 1131 (C-O). ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 2.3 (d, 3H), 3.70 (s, 3H), 3.84 (s, 6H), 7.17 (m, 4H), 7.41 (d, 2H), 8.07 (s, 1H), 9.99 (s, 1H) 11.80 (s, 1H). ES-MS (*m/z*): 360.01 [M+1].

Synthesis of metal complexes: A clear solution of 5-((4-chlorophenyl)diazenyl)quinolin-8-ol (**ligand A**) (0.01 mmol) and *N*-(*p*-tolyl)-2-(3,4,5 trimethoxybenzylidene)hydrazine carbothioamide (**ligand B**) (0.01 mmol) was synthesized in 30 mL ethanol at boiling temperature. To the above solution, ethanolic solution of metal salt, $MCl_2 \cdot xH_2O$ (0.01 mmol) was dropwise added. Basic pH of the medium was maintained 8 to 9 with ammonia solution. The mixture was heated to reflux for 2 and then separated precipitate was filtered through Whatman filter paper, washed with ethanol and dried in vacuum desiccators over anhydrous $CaCl_2$. The yield was about 80-90% (**Scheme-III**).

Antimicrobial activity: The *in vitro* antibacterial and antifungal activity of the synthesized ligands and their metal complexes was carried out by Broth dilution assay method [24]. Antibacterial activity was carried out with two Gram-positive bacteria strain such as *Staphylococcus aureus* and *Streptococcus pyogenus* and two Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*. Antifungal



Scheme-II: Synthesis of *N*-(*p*-tolyl)-2-(3,4,5 trimethoxybenzylidene)hydrazine carbothioamide (ligand B)



Scheme-III: Schematic representation of synthesis of mixed ligands metal complexes

activity study was carried out with three fungi species such as *Aspergillus clavatus*, *Candida albicans* and *Aspergillus niger*. For the growth of bacteria as well as fungi Muller-Hinton agar slants and Sabouraud dextrose agar slants were used respectively. Various concentrations of compounds were made by using DMSO as a solvent. Primary Screening was carried out with concentrations 2000, 1000, 500, 250 and 200 mg/mL of the compounds. The active compounds found in primary screening, further screened to found out minimum inhibitory concentration (MIC) with 100, 62.5, 50, 25, 12.5 and 6.25 mg/mL dilutions. Ampicillin as well as chloramphenicol were used as positive control for antibacterial while greseofulvin drug was used as standard in antifungal screening.

Antimalarial activity assay: The *in vitro* antimalarial activity was carried out for ligands and their metal(II) complexes with the micro assay protocol with some changes as Rickman *et al.* [25], *Plasmodium falciparum* malaria causing strain was maintained in medium RPMI 1640. The *P. falciparum* was synchronized by treatment of 5% D-sorbitol. Other general procedures were used as per given references [26,27]. The internal standard reference chloroquine was used as positive control. The results of antimalarial screening were confined as the half maximal inhibitory concentration (IC_{50}) values [28].

RESULTS AND DISCUSSION

Mixed ligand metal complexes of 5-((4-chlorophenyl) diazenyl)quinolin-8-ol (ligand-A) and *N*-(*p*-tolyl)-2-(3,4,5 trimethoxybenzylidene)hydrazine carbothioamide (ligand B) were synthesized with Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) metal ions. The structure of the ligands were characterized and supported by FTIR, ^{1}H NMR and mass spectra while the stoichiometry of mixed ligand metal complexes were supported by mass spectra and elemental analysis of complex (Table-1). The possible structural and geometry of the complexes was determined by UV spectroscopy, magnetic susceptibility and molar conductance while thermal stability was determined by TG-DTA thermal analysis.

FTIR analysis (ligand A): FTIR spectrum (Fig. 1) showed the peaks for different functional groups at 3287 (-OH), 1571 (C=N Py), 1506,1400 (N=N) and 1134 (-Cl). ^{1}H NMR spectra supports the structure of synthesized ligands. In ligand A, chemical shift was appeared at δ 7.26-9.33 ppm confirms the formation of azo linkage with nine aromatic protons. Synthesized compound also possess broad singlet at δ 11.11 ppm confirms the presence of –OH group. The mass spectra of ligand A show intense peak at 284.08 (M+1) confirms the formation of 5-((4-chlorophenyl)diazenyl)quinolin-8-ol (ligand-A).

TABLE-1
PHYSICAL PARAMETERS OF LIGANDS AND METAL COMPLEXES

Compounds	Colour	m.w.	Yield (%)	m.p. (°C)	Molar cond. (Ω^{-1} cm^2 mol^{-1})	Elemental analysis (%): Found (calcd.)			
						C	H	N	S
L1	Yellowish-Brown	284.08	89	216-218	–	63.20 (63.50)	3.42 (3.55)	14.78 (14.81)	–
L2	White	360.01	86	178-180	–	60.12 (60.15)	5.80 (5.89)	11.80 (11.69)	8.85 (8.92)
$Mn(L1)(L2)Cl_2·H_2O$	Brown	784.34	82	250<	3.96	50.40 (50.43)	4.12 (4.10)	10.75 (10.69)	4.10 (4.08)
$Co(L1)(L2)Cl_2·3H_2O$	Reddish brown	822.21	86	250<	2.00	47. 90 (47.98)	4.45 (4.39)	10.22 (10.17)	3.78 (3.88)
$Ni(L1)(L2)Cl·H_2O$	Reddish brown	758.32	81	250<	3.96	52.65 (52.55)	4.25 (4.28)	11.20 (11.14)	4.20 (4.25)
$Cu(L1)(L2)Cl_2·3H_2O$	Reddish brown	833.41	87	250<	2.30	47.62 (47.72)	4.31 (4.37)	10.15 (10.12)	3.78 (3.86)
$Zn(L1)(L2)Cl_2$	Reddish brown	781.14	84	250<	2.10	50.95 (50.88)	4.33 (4.40)	10.84 (10.79)	4.14 (4.12)
$Cd(L1)(L2)Cl_2$	Reddish brown	824.90	82	250<	2.40	43.20 (43.29)	4.44 (4.40)	9.20 (9.18)	3.46 (3.50)

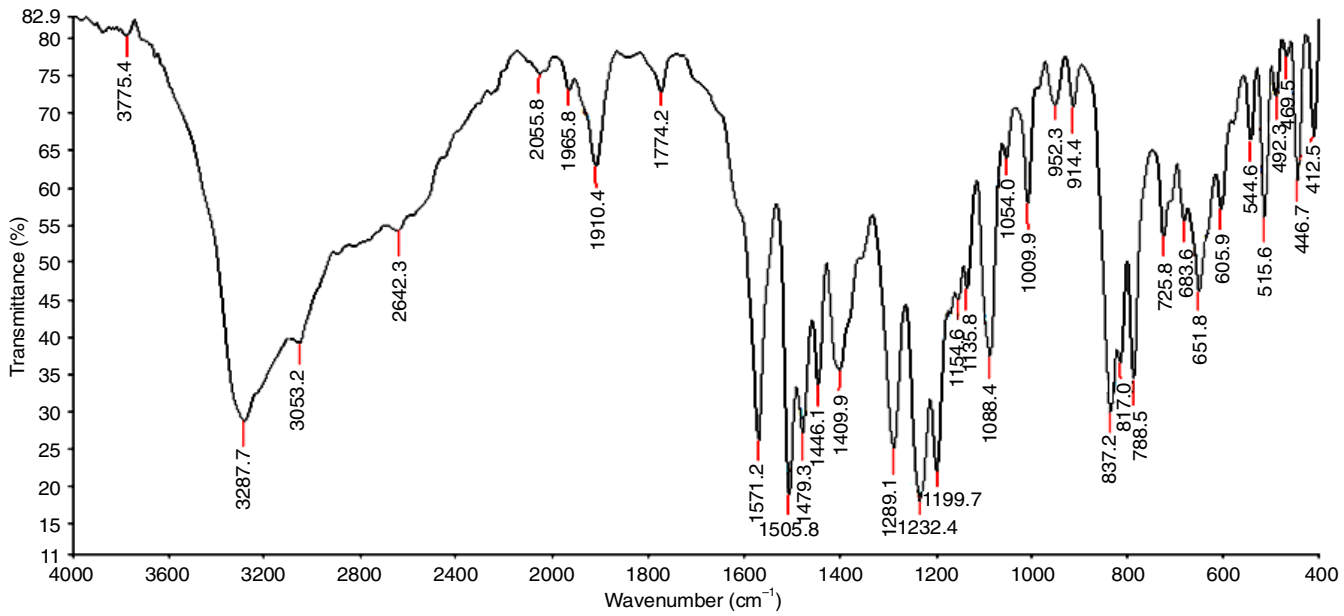


Fig. 1. IR spectrum of [5-((4-chlorophenyl)diazenyl)quinolin-8-ol] (ligand A)

Ligand B: FT-IR spectrum (Fig. 2) of ligand B showed peaks for different functional groups at 3301-3148 (-NH), 2991-2946 (Ar C-H), 2836 (HC=N), 1611 (N=CH), 1273, 817 (C=S). The ^{1}H NMR spectrum of ligand B showed the characteristic chemical shifts such as the singlet at δ 2.3 ppm for the CH_3 group, singlet at δ 3.70 and 3.84 ppm for the OCH_3 groups, singlet at δ 8.07 ppm for azomethine proton, singlet at δ 9.99 and 11.80 ppm for NH groups and the signals at δ 7.17-7.41 ppm suggested the presence of the protons of two aromatic benzene rings. The mass spectra of ligand A show intense peak at 360.01 (M+1) confirms formation of *N*-(*p*-tolyl)-2-(3,4,5 trimethoxybenzylidene)hydrazine carbothioamide (ligand B).

Metal(II) complexes: The key IR bands of the synthesized metal(II) complexes are tabulated in Table-2. A band at 3287 cm^{-1} due to presence of phenolic –OH group in ligand A was not observed in metal complexes, which confirms the formation of C-O-M bonding in complexes [25-29]. Similarly, a strong band at 1289 cm^{-1} due to phenolic (C-O) (ligand A) has been shifted to lower frequencies in between 1250-1248 cm^{-1} in all the metal complexes. The frequencies of C=N of quinoline ring (ligand A) and C=N of thiosemicarbazone (ligand B) which appeared at 1506 cm^{-1} [30] and 1611 cm^{-1} [31], respectively, were observed to be shifted towards the lower frequencies in all the metal(II) complexes. Also in ligand B, a band at 3148 cm^{-1} due to -NH vibration disappeared in the spectra of the

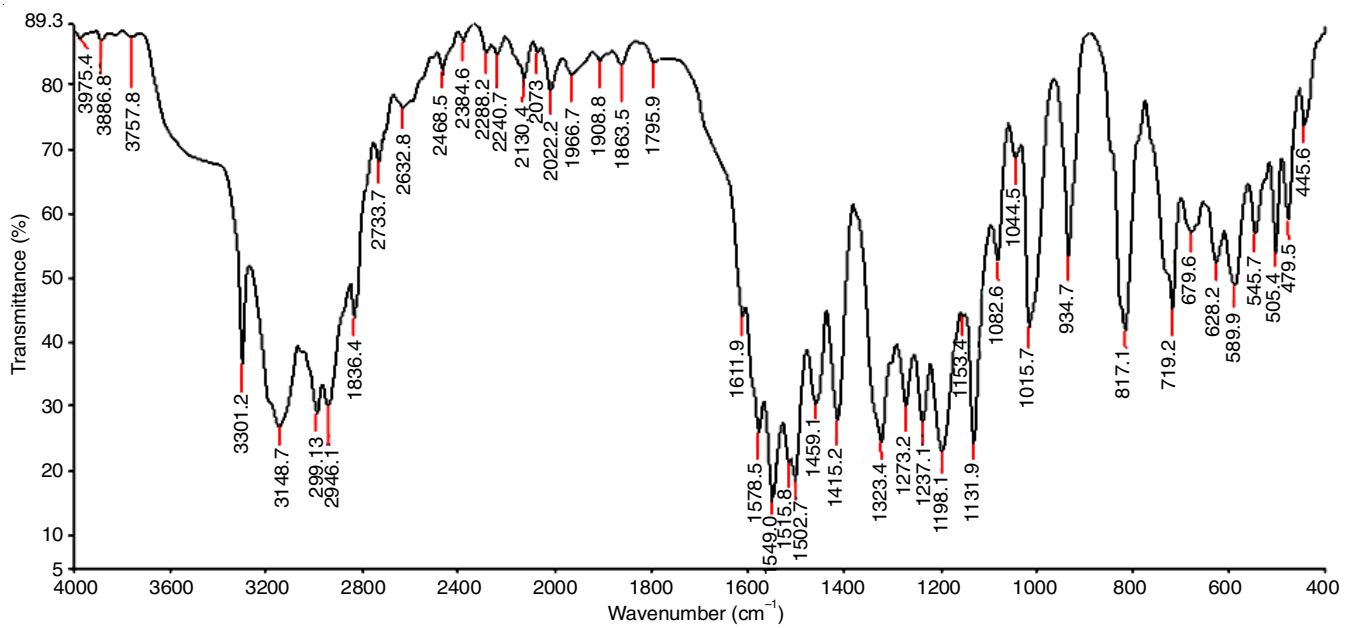


Fig. 2. IR spectrum of [*N*-(*p*-tolyl)-2-(3,4,5-trimethoxybenzylidene)hydrazine carbothioamide] (ligand B)

TABLE-2
CHARACTERISTIC INFRARED ABSORPTION BANDS (cm^{-1}) OF THE LIGANDS AND METAL COMPLEXES

Entry	Co-ordinated water	ν(OH)	ν(Phenolic C-O)	ν(Py–N)	ν(C=S) (L2)	ν(HC=N) (L2)	ν(M-O)	ν(M-N)
1	–	3287	1289	1506	–	–	–	–
2	–	–	–	–	817	1611	–	–
3	3436	–	1249	1498	746	1595	495	425
4	3410	–	1248	1500	785	1596	468	421
5	3403	–	1250	1501	784	1598	475	425
6	3430	–	1249	1499	787	1596	489	417
7	–	–	1247	1496	780	1593	468	418
8	–	–	1246	1494	782	1595	480	416

metal(II) complexes, which may be attributed due to the deprotonation of ligand. A strong band at 817 cm^{-1} suggested the presence of C=S (thione) in ligand B, this band in complexes shifted to lower wavelength 785-745 cm^{-1} indicating the presence of metal-thione coordi-nation through sulphur atom. A broad band in complexes of Mn^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} around 3436-3403 cm^{-1} confirmed the presence of coordinated water molecules. While such peaks were absent in Zn^{2+} and Cd^{2+} complexes, thus confirming the absence of coordinated water molecules. The two new bands at 495-457 cm^{-1} and 425-412 cm^{-1} confirmed the M-O and M-N bonding in all the metal(II) complexes [32].

Molar conductance: The molar conductance of the metal(II) complexes were recorded at room temperature in DMF (concentration 10^{-3} mol L^{-1}) [33]. All the metal-complexes showed values in the range 2.00 to 3.96 Ω^{-1} cm^2 mol^{-1} indicating non-electrolytic nature of complexes (Table-1).

Mass spectra: The synthesized ligand A, [5-((4-chlorophenyl)diazenyl)quinolin-8-ol] showed a molecular ion peak at *m/z* 284.08 (calcd. 283) and ligand B, [*N*-(*p*-tolyl)-2-(3,4,5-trimethoxybenzylidene)hydrazine carbothioamide] showed molecular ion peak at *m/z* 360.01 (calcd. 259), which contest molecular formula of ligands. Also mass spectra of prepared metal complexes with Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) showed molecular ion peaks corresponding to newly synthesized molecules and molecular weight of unstable fragments may be due to degradation of target metal complex and collision of ions. Molecular ion peak and mass of various fragments of metal complexes confirm the stoichiometry of metal chelates as [ML1, L2] type.

Thermal analysis: Thermal properties of Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes were investigated by thermogravimetric analysis. For TGA and DTA analyses, the samples were heated in the range of 25-800 °C at a heating rate of 10 ºC min^{-1} in nitrogen atmosphere and the loss in weight is recorded as a function of temperature. As per thermogram, Mn(II), Co(II), Ni(II), Cu(II) complexes decomposed in two steps (Table-3). The first decomposition occurs between 200-390 ºC with an exothermic peak at 341-378 ºC, exhibiting a weight loss of 28-30%. It may lose water molecule, chloride ion and aromatic ring with azo linkage of ligand-A from the complex. In second step, decomposition started from 350-560 ºC with a complete decomposition of complex with exothermic peak at 400-550 ºC. It exhibiting weight loss around 70%, leaving behind metal residue and carbon around 10% of the total mass. Zn(II) and Cd(II) complexes showed single stage decomposition showed exothermic peak around 376 and 453 ºC, respectively as these two complexes don't have water molecules in its coordination sphere. Hence, Mn(II), Co(II), Ni(II), Cu(II) complexes are stable up to 200 ºC while Zn(II), Cd(II) complexes are stable up to 250 ºC on further heating undergoes a complete decomposition in the certain range of temperature and leaving behind metal residue [34].

Magnetic susceptibility and electronic spectra: The UV visible spectra of ligands A and B and their metal complexes were recorded in DMF at 298 K and magnetic susceptibility data is tabulated in Table-4. The electronic spectrum of free ligand-A shows absorption at 236, 255 nm and 333, 396 nm due to π-π* and n-π* transitions, respectively [35]. Also ligand-

TABLE-3
THERMAL DATA FOR MIXED LIGAND METAL COMPLEXES (**3-8**)

Complex	Temperature range (°C)	Weight loss (%)		Assigned decomposition product
		Found	Expected	
$Mn(L1)(L2)Cl_2,H_2O$	150-265	11.24	11.35	2Cl, H_2O
	265-341	17.75	17.80	C_6H_4, Cl and N_2
	341-550	49.84	50.23	All remaining organic part
$Co(L1)(L2)Cl_2,3H_2O$	150-300	13.74	13.96	2Cl, $3H_2O$
	300-447	17.38	17.54	C_6H_4, Cl and N_2
	448-600	59.25	59.60	All remaining organic part
$Ni(L1)(L2)Cl,H_2O$	150-270	7.20	7.32	Cl, H_2O
	280-435	18.12	18.24	C_6H_4, Cl and N_2
	436-560	57.38	57.45	All remaining organic part
$Cu(L1)(L2)Cl_2,3H_2O$	150-305	14.54	15.12	2Cl, $3H_2O$
	305-390	16.34	16.80	C_6H_4, Cl and N_2
	400-600	50.81	51.12	All remaining organic part
$Zn(L1)(L2)Cl_2$	100-550	79.75	81.23	2Cl & Organic part of complex
$Cd(L1)(L2)Cl_3$	150-611	80	81.54	2Cl & Organic part of complex

TABLE-4
MAGNETIC MOMENT AND ELECTRONIC SPECTRAL DATA OF THE LIGANDS AND THEIR METAL-COMPLEXES

Entry	μ_{eff} (BM)	π–π* (nm)	n–π* (nm)	*d-d* transition (nm)
1	–	236, 255	333, 396	–
2	–	256	289	–
3	5.62	218, 256	322	430
4	3.83	213, 256	337, 340	470
5	2.96	218, 258	329, 340	522
6	1.84	218, 254	333, 348	464
7	Diamagnetic	213, 257	353	460
8	Diamagnetic	217, 260	387	–

B shows absorption at 256 and 289 nm due to π-π* and n-π* transitions, respectively [31]. An intense absorption band for all the metal(II) complexes observed in the range 218-260 nm is due to π-π* transitions in the aromatic units and bands at 322-387 nm region are due to n-π* transitions of all the metal(II) complexes. A band in the region of 430-470 nm is due to the LMCT transition [36]. Mn(II) complex showed a absorption band at 430 nm is assigned to the $^6A_{1g} \rightarrow {}^4T_{2g}$ transition for a distorted octahedral Mn(II) complex, which was further arrested by its μ_{eff} value 5.62 B.M. The cobalt(II) complex showed an absorption band at 337 and 340 nm are assigned to the $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transitions for a distorted octahedral geometry of the complex, which was further confirmed by its μ_{eff} value 3.83 B.M. [37]. The Ni(II) complex shows a *d-d* band at 522 nm due to $^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)$ transition which corresponds to the octahedral geometry, which was further arrested by its μ_{eff} value 2.96 B.M. [37]. The diffuse electronic spectrum of Cu(II) complex contains two broad bands at 464 and 348 nm, attributed to the ^2E_g-$^2T_{2g}$ transition and to charge transfer, respectively. This proposes distorted octahedral structure of the complex, which was further arrested by its μ_{eff} value 1.84 B.M. [38]. Moreover, the Zn(II) and Cd(II) complexes are diamagnetic, exhibited charge transfer transitions (LMCT) 353, 387 and 29585 cm^{-1}, respectively [39,40].

Antibacterial activity: The *in vitro* antibacterial study of synthesized ligands and their metal(II) complexes was done towards the four pathogenic bacterial strains. Two Gram-positive (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacterial strains were used. Amoxicillin and chloramphenicol which are used as standard drugs served as positive controls. Evaluation was done by broth dilution assay method. The *in vitro* screening and evaluation results (minimum inhibitory concentration) against microorganisms tested are tabulated in Table-5. All the synthesized ligands and their complexes show good to excellent antibacterial activity. The copper(II) complex showed better activity among all the compounds. With regard to the activity against *E. coli*, ligand A, Mn(II), Cu(II) and Zn(II) exhibited the excellent activity which is equally or more potent than ampicillin (100 µg/mL) but 50% less active than chloramphenicol. Furthermore, all compounds showed activity against *P. aeruginosa*, compounds Mn(II), Co(II), Ni(II) and Cd(II) are equally potent as ampicillin. Cu(II) complex showed excellent activity 25 µg/mL as compared to both standard drugs. Moreover, both ligands and complexes showed extraordinary activity toward *S. aureus* bacterial strain. Finally, another Gram-positive pathogen *S. pyogenus* was potentially inhibited by all the compounds with respect to ampicillin and 50% less inhibited by chloramphenicol.

Antifungal activity: Three fungal stains such as *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* were used to study the antifungal activity of the synthesized ligands and their metal(II) complexes. The results are tabulated in Table-5. The results of synthesized compounds were compared with the standard drug greseofulvin. Antifungal data showed that among all the reported analogs are potentially active against *C. albicans*, ligand B, Cu(II) and Cd(II) showed excellent activity (250 µg/mL) with respect to greseofulvin. Moreover, both ligands and all the metal(II) complexes showed a moderate inhibition effici-ency against other two pathogens.

Antimalarial activity: The synthesized ligands and metal complexes were investigated for their *in vitro* antimalarial activity against *P. falciparum*. The antimalarial activity of the reference compound quinine showed a 50% inhibitory concentration (IC_{50}) of 0.268 µg/mL. All the synthesized compounds showed moderate antimalarial activity (Table-5).

TABLE-5
ANTIMICROBIAL AND ANTIMALARIAL ACTIVITIES OF SYNTHESIZED COMPOUNDS

Compound	Bacterial pathogens				Fungal pathogens			Antimalarial
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*	
Ligand 1 (L1)	100	125	62.5	100	500	1000	1000	1.80
Ligand 2 (L2)	125	250	25	125	250	500	1000	1.34
$Mn(L1)(L2)Cl_2 \cdot H_2O$	100	100	50	125	500	1000	1000	1.08
$Co(L1)(L2)Cl_2 \cdot 3H_2O$	250	100	50	100	500	500	500	0.92
$Ni(L1)(L2)Cl \cdot H_2O$	125	100	250	100	500	1000	500	1.49
$Cu(L1)(L2)Cl_2 \cdot 3H_2O$	50	25	125	100	250	250	500	1.36
$Zn(L1)(L2)Cl_2$	100	250	50	62.5	1000	1000	1000	0.98
$Cd(L1)(L2)Cl_3$	250	100	100	100	250	500	1000	0.96
Ampicillin	100	100	250	100	–	–	–	–
Chloramphenicol	50	50	50	50	–	–	–	–
Greseofulvin	–	–	–	–	500	100	100	–
Quinine: IC_{50}	–	–	–	–	–	–	–	0.268

Mean IC_{50} value (µg/mL)

Conclusion

In summary, few transition metal(II) complexes were synthesized with azo quinolone (ligand A), thiosemicarbazone (ligand B) and characterized by various spectroscopic and physico-chemical techniques. Further, antibacterial, antifungal and antimalarial activities were examined in order to determine the biological activities of the ligand and its transition metal(II) complexes. The synthesized metal(II) complexes were found to be more effective towards *Staphylococcus aureus* bacterial strain. Moreover, all the compounds showed antifungal activity but more effective towards *Candida albicans* fungal stain. Similarly, all the studied compounds showed moderate anti-malarial activity.

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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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