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Synthesis, Characterization and *In vitro* Antimicrobial Studies of Ternary Mn(II) Complexes with Isatinphenylhydrazone, Glycine and 8-hydroxyquinoline

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ABSTRACT

In our present research work, we have synthesized two ternary metal complexes of Mn(II), complex-I as [Mn(L)(Gly)(Cl)(H_2O)] and complex-II as [Mn(L)(Q)(Cl)(H_2O)]; where L is Isatinphenylhydrazone (IPH) as primary ligand, whereas glycine (Gly) and 8-hydroxyquinoline (HQ) as secondary ligand in complex-I and II respectively, in 1:1:1 (M : L : Gly or M : L : Q) molar ratios. Above synthesized complexes are employed for characterization using various analytical techniques including elemental analysis, melting point determination, magnetic moment measurements, molar conductance measurements, and spectral techniques (FTIR, UV, ^{1}H NMR) etc. Further, their antimicrobial activities were evaluated against selected bacterial strains i.e., *B. subtilis, S. aureus* (*Gram-positive*) and *P. aeruginosa, E. coli* (*Gram-negative*) and fungal strains (*T. reesei, A. niger, C. albicans*) and found significantly active.

Keywords: Ternary metal complexes, Isatinphenylhydrazone, Glycine, 8-hydroxyquinoline, Antimicrobial activity.

INTRODUCTION

According to present scenario, ternary complexes[1] have great interest of researchers owing to their importance in biological, medicinal, pharmaceutical and agricultural fields. IPH is a Schiff base[2], derivative of isatin and phenylhydrazine and possesses a variety of biological[3] potency such as; antibacterial efficiency against some *Gram-positive* bacteria like *B. subtilis* and *Gram-negative* bacteria like *P. aeruginosa, E. coli* etc. and promising activity against fungal strain like *C. albicans* and anti-HIV[4] activities. Hence, IPH is very useful in prospect to synthesize biologically active mixed ligand complexes with selective amino acids[5] like-glycine[6], histidine, phenylalanine etc. and 8-hydroxyquinoline[7]. Such type of mixed ligand complexes[8-9] possess broad spectrum of pharmaceutical, medicinal, and biological activities such as-antimicrobial[10-12], anti-tumour[13-14], antioxidant[15], antimalarial[16], and anti-inflammatory[17] etc. These Schiff base derivatives and ternary complexes act as potent agents in drug[18-19] design process. Compounds from transition metal ions and amino acids can be applied as models to

study the pharmacy dynamic effects[20] from drugs or with increasing the biocompatibility as well to reduce poisonous effects. 8-hydroxy quinoline is an important compound which has the ability to coordinate with the central metal ion and form five membered chelate ring that increases the stability of the complexes[21], as well as the biological activity.

EXPERIMENTAL

Materials and methodology: In our experimental work, all solvents and chemicals used in their original form, purchased from Sigma Aldrich and TCI chemicals. Infrared spectra (FTIR) for the complexes were recorded employing a model PerkinElmer FT-IR (4000-400 cm^{-1}) spectrophotometer. Electronic spectra of complexes were recorded with PerkinElmer Lambda UV 750 ultraviolet-visible Spectrometer in ethanol within a wavelength range 200-950 nm. ^1H Nuclear Magnetic Resonance spectra of both prepared complexes were noted in DMSO-d_6 and $CDCl_3$ solutions using an internal standard (TMS) with a Jeol Resonance ECS-400 Spectrometer at 400 MHz. Magnetic moment measurements of complexes were made on the Gouy balance having model no: HO-ED-EM-08. For conductance measurements, compounds were dissolved in DMSO and measured using Systronics Direct Reading Conductivity Meter-304 (with cell constant 1.0 cm^{-1}). Purification test of prepared compounds were monitored by TLC on Silica Gel-G plates. The plates were developed selecting suitable solvent and visualisation in UV-chamber.

Methodology

Synthesis of Ligand L(IPH)

Isatin-3-phenylhydrazone (IPH) was synthesized according to the earlier proposed research process[22]. This ligand was used for further complexation with metal ion.

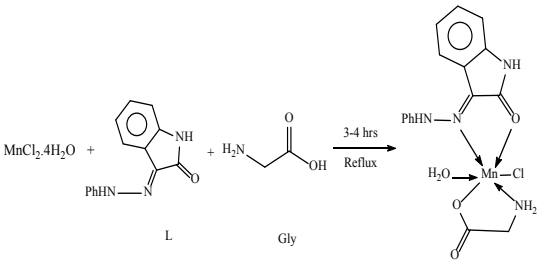
Synthesis of complex-I [Mn(L)(Gly)(Cl)(H_2O)]

The ternary metal complex-I of Mn (II) was prepared by the mixing 5 mL of ethanolic solution of IPH (10mmol; 0.0237 g), 5 mL of aqueous solution of glycine (10mmol, 0.0075 g) and 5 mL of aqueous solution of metal salt $MnCl_2.4H_2O$ (10mmol; 0.0197 g) with constant stirring. Yellowish precipitate formed was further refluxed for ~3-4 h at 55°C for reaction completion. Purification test of synthesized compound was checked using TLC on Silica Gel-G plates in appropriate developing solvent (benzene: chloroform in 1:4 ratio). Coloured precipitate was obtained that was further filtered, washed, recrystallized using ethanol, dried properly in vacuum and weighed. Dark brown coloured compound formed with 48.5% yield and m.p. 245.5°C. (Scheme I)

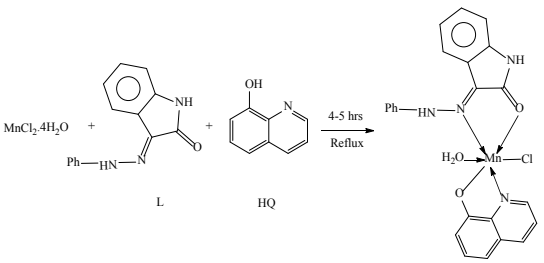
Synthesis of ternary complex-II [Mn(L)(Q)(Cl)(H_2O)]

Similar method was employed as above. Equimolar solutions of IPH, 8-HQ and $MnCl_2.4H_2O$ (5 mL of each) were allowed to mix with continuous stirring. No precipitation was obtained, this reaction content was allowed to reflux for ~4-5 h at constant temperature (55°C). Reaction accomplishment was monitored by TLC using developing solvent benzene: $CHCl_3$ in 1:4 ratio, then the resultant solution was cooled and set overnight at room temperature. Coloured solid product was obtained that was further filtered and thoroughly washed and recrystallized using alcohol and completely dried in vacuum and weighed. Brownish green coloured compound formed with 45.4% yield and m.p. 254.4°C. (Scheme II)

Plausible reaction scheme for ternary Complex-I and II



Scheme 1. Proposed synthesis of Complex-I



Scheme 2. Plausible synthesis of Complex-II

Antimicrobial study

Antibacterial evaluation

The *In vitro* determination of antibacterial activity of both the complexes was done against

two *Gram-positive* bacteria (*B. subtilis* and *S. aureus*) and two *Gram-negative* (*E. coli* and *P. aeruginosa*) by agar well diffusion method[23]. The test compounds (20-80 µg/mL) were injected in the well. For calculation of zone of inhibition, subtraction of control zones from the test zones is made and finally the measurement of resultant zone diameter done with antibiotic zone reader (in mm). For antimicrobial spectrum, zone of inhibition diameters of compounds was compared with the standard i.e. Streptomycin.

Antifungal evaluation

Antifungal activity determination of the complexes was done with agar well diffusion method[24] (Cup plate method) against three fungal strains, *T. reesei*, *A. niger* and *C. albicans*. Subculture of yeasts and saprophytic fungi were done onto dextrose agar, after then incubation for 24 h at 37°C and 2 to 5 days at 25°C respectively. Fungal spores suspensions were formed in sterile PBS and adjustment of concentration upto 106 cells/mL. Plates were incubated for 48 h at 37°C then after determination of bioactivities was performed by measurement of diameter of inhibition zone (in mm) and compared with standard i.e. Ketoconazole.

RESULTS AND DISCUSSIONS

Physicochemical and analytical data reveal that both the complexes are coloured, stable and soluble in ethanol, DMSO, DMF, and $CHCl_3$. The metal complexes are characterized by physicochemical, elemental analysis, molar conductivities, magnetic moment measurements and spectral techniques (FTIR, UV, ^{1}HNMR etc.). For both complexes, analytical data are in good agreement with calculated values (Table 1 and 2). In synthesized complexes, stoichiometry revealed 1:1:1 metal ligand ratio.

Table 1: Physicochemical analysis of synthesized complexes

Compound Empirical formula	Colour	m.p.	Mol. Weight found (cal.)	% Elemental analysis found (cal.) C	H	N	O	Cl	Mn
1. Complex-I	Dark	245.5°C	417.8	45.86	4.05	13.4	15.27	8.5	13.1
$C_{16}H_{17}N_4O_4ClMn$	Brown		(418.4)	(45.88)	(4.06)	(13.38)	(15.29)	(8.48)	(13.12)
2. Complex-II	Brownish	254.4°C	488.6	56.40	3.90	11.42	9.80	7.27	11.20
$C_{23}H_{19}N_4O_3ClMn$	green		(489.1)	(56.43)	(3.88)	(11.44)	(9.78)	(7.25)	(11.22)

Table 2: Molar conductivities and magnetic moment of compounds

Compound	Molar cond. ohm^{-1} cm^2 mol^{-1} appr.	μeff BM appr.
[Mn(L)(Gly)(Cl)(H_2O)]	11.9	5.92
[Mn(L)(Q)(Cl)(H_2O)]	12.4	5.91

Spectral characterization of both the complexes was done employing different techniques. FTIR spectra (Table 3) give important information regarding all the functional groups. The –OH group of carboxyl group in free glycine appears at ~ 3100 cm^{-1} that disappears in complex-I specify that COOH group getting deprotonated during complexation with metal ion and the broad peak at 3124 cm^{-1} recommend the water molecule presence in complex-I. A broad peak for -NH_2 appears at 2900 cm^{-1} in glycine shift to 3028 cm^{-1} in complex-I. When spectrum of free ligand HQ is observed, the peak seen at 3182 cm^{-1} assigned for υ(OH) stretching frequency disappears due to deprotonation of HQ to form anion in complex-II and a broad peak at 3434 cm^{-1} indicating presence of water molecule. Azomethine group (C=N) shows a sharp peak at 1597 cm^{-1} and 1616 cm^{-1} in complex-I and II respectively, lower than that of in free ligand appearing at 1622 cm^{-1} support complexation of N of azomethine group with metal ion. Formation of ternary complexes was further evidenced by existence of four additional bands 900 cm^{-1}, 744 cm^{-1}, 676 cm^{-1}, 503 cm^{-1} for complex-I and 788 cm^{-1}, 745 cm^{-1}, 688 cm^{-1}, 520 cm^{-1} for complex-II assigned to M-Cl, M-OH_2, M-O and M-N bonds, respectively. (Figure 1, 2).

Table 3: IR spectral vibrations υ (cm^{-1}) for ligands and complexes

Compound	-OH	NH_2	C=N	M-Cl	M-OH_2	M-O	M-N
Glycine	3093	2900	-	-	-	-	-
8-HQ	3182	-	-	-	-	-	-
IPH (NH)	3438	-	1622	-	-	-	-
[Mn(L)(Gly)(Cl)(H_2O)]	3124	3028	1597	900	744	676	503
[Mn(L)(Q)(Cl)(H_2O)]	3434	-	1616	788	745	688	520

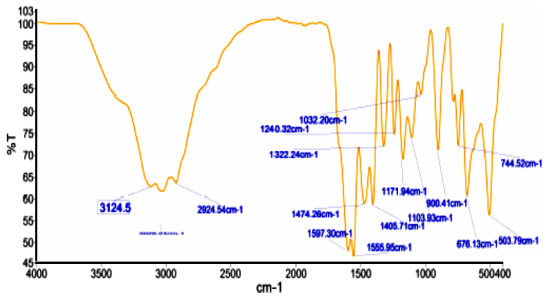


Fig. 1. FTIR spectrum of Complex-I [Mn(L)(Gly)(Cl)(H_2O)]

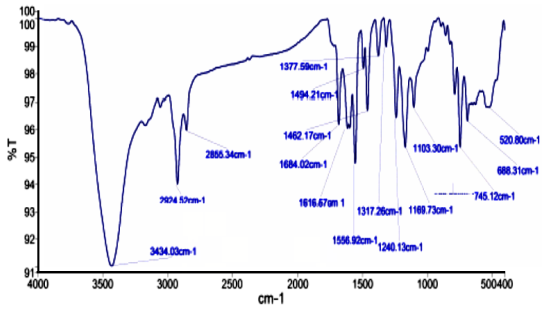


Fig. 2. FTIR spectrum of Complex-II [Mn(L)(Q)(Cl)(H_2O)]

In UV-Visible spectra, λ_{max} (nm) and ε_{max} values recorded in ethanol for both ternary complexes (Table 4). Electronic spectra comprise of two absorption maxima at 295nm assigning π-π^* transition and 375nm assigned for n-π^* transition for isatinphenylhydrazone[3]. However, spectra of both synthesized complexes exhibit π-π^* transition at 300nm, 301nm and n-π^* transition at 404nm, 406nm respectively, showing bathochromic shift and support metal complex formation. (Figure 3, 4).

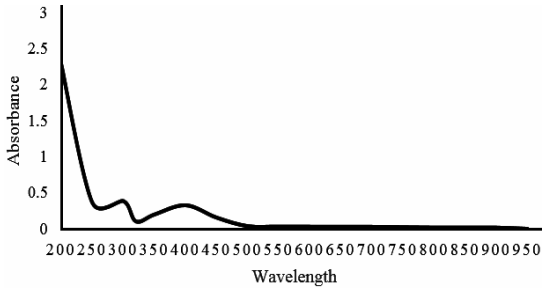


Fig. 3. UV spectrum of Complex-I [Mn(L)(Gly)(Cl)(H_2O)]

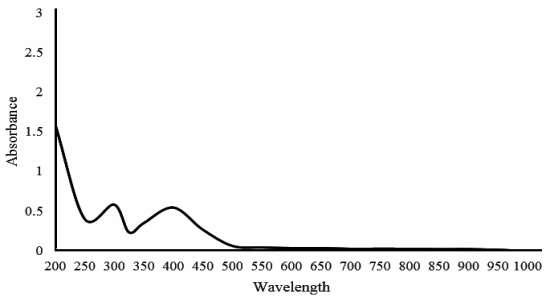


Fig. 4. UV spectrum of Complex-II [Mn(L)(Q)(Cl)(H_2O)]

Table 4: UV Spectral Bands of IPH and Complexes

Compound	λ_{max} in nm (ε_{max}) π-π^*	n-π^*
IPH	295 (0.346)	375(0.260)
[Mn(L)(Gly)(Cl)(H_2O)]	300 (0.415)	404 (0.327)
[Mn(L)(Q)(Cl)(H_2O)]	301 (0.585)	406 (0.548)

^{1}H-NMR spectrum of complex-I recorded in DMSO-d_6 and that of complex-II recorded in $CDCl_3$. Results of ^{1}H-NMR spectra are tabulated (Table 5) and the chemical Shift values expressed in δ (ppm), it can be concluded that each complex shows a broad singlet for amide hydrogen (CO-NH) at δ = 11.1 ppm and 12.4 ppm for complex-I and II, respectively. Disappearance of a singlet at δ =12 ppm in complex-I shows that COOH group of glycine present as COO- with loss of hydrogen. This group can show amido-iminol tautomerism. Aromatic hydrogens appeared as multiplet within the range of δ = 6.9-7.5 and 6.6-7.7 ppm. The NH_2 group of glycine obtained at δ = 3.8 ppm (broad, singlet). H_2O and NH_2 peak collapse in complex-I, hence, it is getting broad. While in complex-II, H_2O peak observed at δ = 4.0ppm, this supports that both complexes fulfil their secondary valency with a water molecule. The DMSO signal[25] also appeared at δ = 2.5 ppm in spectra. (Figure 5,6).

Table 5: ^{1}H NMR spectral values in δ (ppm) of synthesized complexes

Compound	CO-NH	Ar-H	NH_2	HO-H
[Mn(L)(Gly)(Cl)(H_2Oa)]	11.1	6.9-7.5 (multiplet)	3.8 (broad, singlet)	3.9
[Mn(L)(Q)(Cl)(H_2O)]	12.4	6.6-7.7 (multiplet)	-	4.0

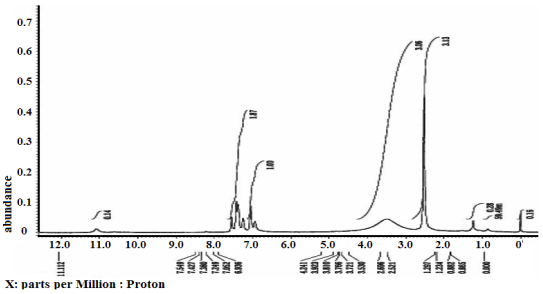


Fig. 5. ^{1}H NMR spectrum of Complex-I [Mn(L)(Gly)(Cl)(H_2O)]

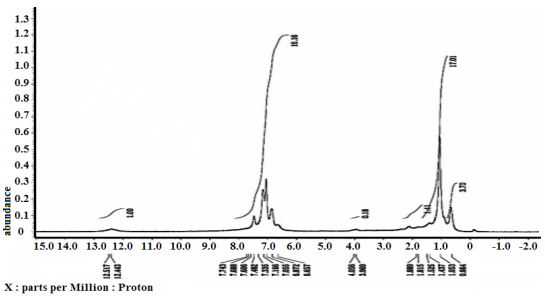


Fig. 6. ^{1}H NMR spectrum of Complex-II [Mn(L)(Q)(Cl)(H_2O)]

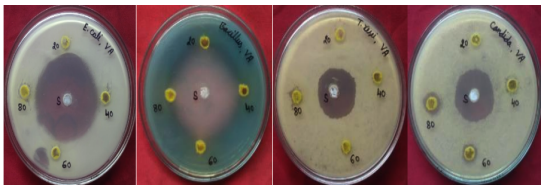
Biological Assay

The *In vitro* biological evaluation of above synthesized compounds carried out against selective strains of bacteria and fungi using agar well diffusion method. Complex-I screened against bacteria- *E. coli* (G^-) and *B. subtilis* (G^+) whether Complex-II screened against *S. aureus* (G^+) and *P. aeruginosa* (G^-) and results compared with Streptomycin. For antifungal studies, three fungal pathogens- *T. reesei, A. niger* and *C. albicans* were taken for evaluation. Results showed that both the complexes have significant antimicrobial activity and more activity obtained for complexes than the free schiff base ligand. Results revealed that complex-II have more zone of inhibition than the complex-I and also found more effective for fungal strain rather than bacterial strain. Complex-I is almost inactive against *B. subtilis*. The results of antimicrobial study are tabulated in Table 6.(Figure 7).

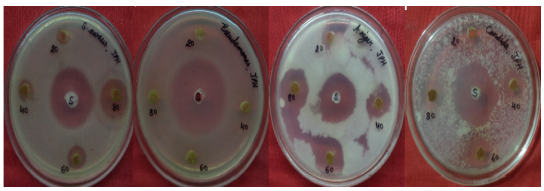
Table 6: Antimicrobial evaluation of synthesised compounds

Compound	Conc. (µg/mL)	Zone of inhibition (mm)						
		Antibacterial activity				Antifungal activity		
		B. subtilis	*E. coli*	*S. aureus*	*P. aeruginosa*	*T. reesei*	*A. niger*	*C. albicans*
IPH	500 mg/cm^3	45	100	140	240	NT	NT	160
Complex-I	20	NS	0	NT	NT	0	NT	0
	40		0			0		9
	60		0			0		11
	80		9			10		13
Complex-II	20	NT	NT	10	11	NT	10	12
	40			12	13		17	15
	60			15	15		21	18
	80			22	16		24	19
Standard	80	51	46	35	42	28	30	35

NS- Not Seen, NT- Not Tested



(a)



(b)

Fig. 7. Antimicrobial activity at different conc. of complex-I (a) and complex-II (b) show inhibition zone against selected bacteria and fungi

CONCLUSION

On the basis of all spectral and analytical evidences, distorted Octahedral geometry proposed for both synthesized complexes of Mn(II). Conductivity measurement reveals the non-electrolytic behaviour of both complexes and magnetic moment measurements support the paramagnetic nature of the synthesized complexes of Mn(II) with five unpaired electrons. In complex-I, ligand L (IPH) coordinates with metal with two donor sites i.e. N of azomethine (C=N) group and O of carbonyl group of isatin ring, whereas glycine acts as monoanionic bidentate ligand after deprotonation, coordinate through N of NH_2 group and O- of carboxylate group. Similarly, in complex-II the secondary ligand is deprotonated hydroxyquinoline which coordinates through N of quinoline ring and O- of hydroxyl group. Remaining valances of Mn(II) are satisfied with chloride ion and one water molecule confirmed by presence of corresponding absorption band in FTIR spectra. Antimicrobial results indicate both the complexes to be more effective against fungal pathogens but less active for bacterial strains. It can be concluded that complex-I exhibits more zone of inhibition against *C. albicans* as compared to others, However, complex-II shows significant antifungal activity against *A. niger*. These results confirm both the complexes to possess more penetration effect through the cell wall of microbes. Further, other complexes of Mn(II) are to be synthesized and studied against other microbial strains to recognize the pharmacophore to develop and explore for drug designing with minimal side effects on physiological and biological systems.

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Conflict of interest

No conflict of interest is declared by authors.

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