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Mixed Ligand Complex of Ni(II) with Schiff Base Ligands derived from Isatin and its Bromo Derivative: Synthesis, Characterization and Biological Screening

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Abstract

Recently, isatin is considered interesting heterocyclic compound due to its wide range of biological activities. Our present work reports synthesis of two Schiff bases L_1, L_2 prepared by condensation of phenylhydrazine with isatin and 5-bromoisatin respectively, employing a method different from reported one. Synthesized ligands are 3-(2-phenylhydrazinyl)indol-2-one named as PHIO (L_1) and 5-bromo-3-(2-phenylhydrazinyl)indol-2-one named as BPHIO (L_2). Further, an attempt was made to synthesize a ternary complex using $NiCl_2.6H_2O$ as metal salt and L_1 and L_2 as ligands. All above synthesized ligands and complex are characterized by physicochemical analysis, elemental analysis, molecular weight determination, molar conductance measurement and various spectral techniques (UV, FTIR, Mass spectroscopy etc). In continuation of our research work, all newly synthesized compounds were screened against selective bacterial strains *S. aureus,P. aeruginosa* and one fungal pathogen *C.albicans* and results were compared with standard. We are further interested in recognition of pharmacophores to widen their applications in pharmacological and medical fields.

Keywords:* *Schiff bases; Isatin; Phenylhydrazine; Spectral techniques; Pharmacophores

Introduction

Over the last few decades, Schiff base ligands and their metal complexes have a great platform in basic and applied chemistry [1,2]. Schiff base containing azomethine group (-C=N-) have a vital role in coordination chemistry due to ease of modification in their structure and direct synthesis process, which enhance their activity with reducing side effects as compared to the parent molecules[3-5]. A wide range of Schiff base metal complexes exhibit various biological and pharmaceutical applications and many of them found to be effective and used in drugs[6,7]. Schiff bases have found various biological properties such as anti-inflammatory, anti-tumour, and antimicrobial, anticonvulsant, anti- HIV, antibacterial and antifungal activities[8-9]. Recently, metal ion(s) bearing pharmaceutical compounds have been used significantly in medicines [10,11]. Various transition metals such as Co, Cu, Zn, Ni, Mn, Fe, V and Cr present in trace amount play a vital role in living organisms[12]. Therefore,

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coordination of ligands with biologically potent metal is an important and versatile field of current research.

In present era, the biological and pharmaceutical properties, potential application of isatin(2,3-dihydro-2,3-dioxo-1H-indole) and its derivatives in medicinal chemistry have been dragged considerable attention[13-17]. In view of literature survey, these are found to exhibit various biological activities like anti-microbial[18,19], anticonvulsant[20], cytotoxicity[21], anti-viral[22], anti-oxidant[23], anti-inflammatory[24], anti-HSV[25], anti-fungal[26], anti-HIV[27], anti-tubercular[28] and anti-Alzheimer activities[29]. Therefore, based on the above facts, our interest in this field, the present work deals with the synthesis, characterization and biological evaluation of both Schiff base ligands derived from isatin and 5-bromoisatin with phenylhydrazine and mixed ligand complex of Ni (II) with these novel Schiff bases.

Materials and Methods

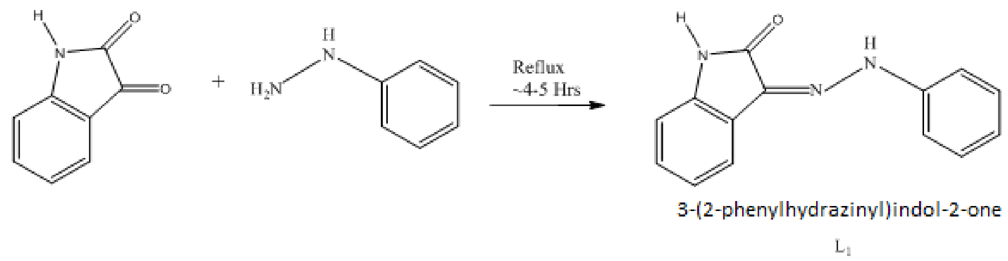
All chemicals, reagents and solvents used in our experimental work *viz.*, isatin, 5-bromoisatin, phenylhydrazine hydrochloride, $NiCl_2.6H_2O$ etc. were of analytical reagent (A.R.) grade purchased from Sigma aldrich and used as received without any further purification. The purity of compounds and completion of reaction was monitored by thin-layer chromatography (TLC) performed on pre-coated silica-gel plates (Merck, India). Melting points of compounds determined by open capillary electro-thermal apparatus and were uncorrected.Magnetic moment measurement was done by Gouy balance model no. HO-ED-EM-08. Molar conductivity measurement of complex was made employing Systronics Direct Reading Conductivity Meter-304 consisting of glass cell with cell constant 1.0 cm^{-1} in DMSO. Infrared spectra were recorded on Model PerkinElmer Spectrum Version 10.4.00 FTIR spectrophotometer in region 4000-400 cm^{-1} utilizing KBr pellets. Mass spectrum was recorded on TOF MS ES_+ mass spectrometer operating at an ionization potential of 70 eV. The electronic absorption spectra were recorded using Model PerkinElmer UV Lambda 750 UV/Vis spectrophotometer.

Synthesis of ligand L_1 (PHIO): 3-(2-phenylhydrazinyl)indol-2-one

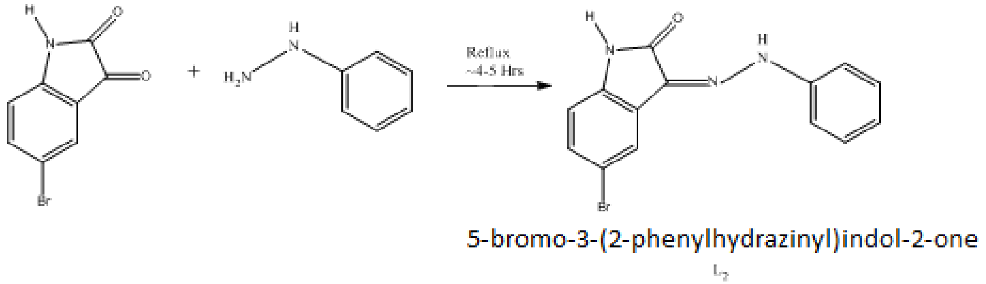
10 ml of ethanolic solution of Isatin (1.47 g, 10 mmol) was added to 10 ml of ethanolic solution of phenylhydrazine hydrochloride (1.44 g, 10 mmol) with constant stirring.Above reaction mixture shifted to a 250 mL round bottom flask and allowed to reflux in presence of condensing agent with few drops of glacial acetic acid for ~ 4-5 hours until color of the solution changed from red-orange to yellow. Afterward, the reaction mixture was allowed to cool at room temperature and kept overnight for crystallization *via* slow evaporation of the solvent. Yellow coloured microcrystals were crystallized out that were filtered off, washed with ethanol and dried properly. Yield 85.63% (Scheme 1).

Synthesis of ligands L_2 (BPHIO): [5-bromo-3-(2-phenylhydrazinyl)indol-2-one]

10 ml of ethanolic solution of 5-bromoisatin (2.26 g, 10 mmol) was added to 10 ml of ethanolic solution of phenylhydrazine hydrochloride (1.44 g, 10 mmol) with constant stirring.Above reaction mixture poured in a 250 mL round bottom flask and allowed to reflux in presence of condensing agent with few drops of glacial acetic acid for ~4-5 hours until colour of the solution changed from red-orange to orangish yellow. Afterward, the reaction mixture was cooled at room temperature and kept overnight for complete crystallization through slow evaporation of the solvent. Orangish yellow coloured microcrystals were crystallized out that were filtered off, washed with ethanol and dried properly. Yield 94.53% (Scheme 2).



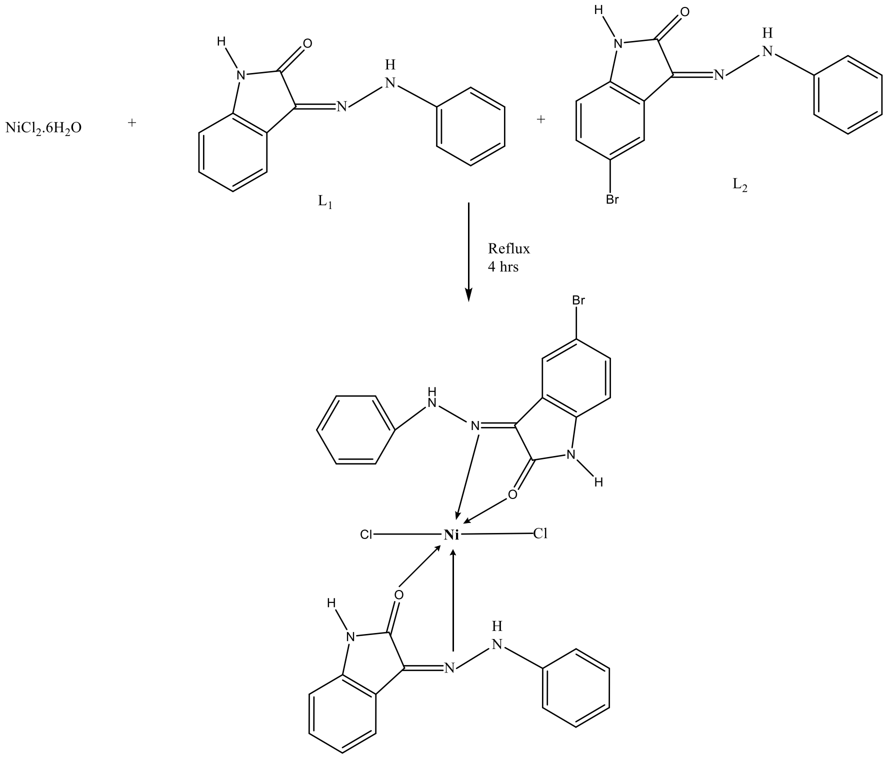
Scheme 1. **Synthetic route of ligand (L_1)**



Scheme 2. **Synthetic route of ligand (L_2)**

Synthesis of mixed ligand complex [Ni L_1 L_2 Cl_2]

Common procedure was adopted, where equimolar amount of L_1 and L_2 (10 mmol) dissolved in 10 mL ethanol. Further, 5 mL of equimolar aqueous solution of nickel chloride $NiCl_2.6H_2O$ (2.37 g, 10 mmol) was added drop wise to above solution with constant stirring. The reaction mixture was taken in a 250 mL round bottom flask and allowed to reflux for ~4 hours until yellow-orange colour turns into dark brown. After then, the solution was cooled at room temperature,crystals started to appear, later kept overnight for complete crystallization. After 24 hours, dark brown microcrystals of Ni(II) complex obtained that were filtered off, washed properly with ethanol. Yield 58.97% (Scheme 3).



Scheme 3. **Synthetic route of mixed ligand complex**

Biological studies

For biological study *in vitro*, both ligands(L_1, L_2) and Ni(II) complex were evaluated against selective bacterial and fungal strains for determination of growth inhibiting potential through measurement of zone of inhibition in mm employing conventionalCup-Plate method. For antimicrobial study, Gram positive bacteria *S. aureus*(MTCC-96), Gram negative bacteria *P.aeruginosa* (MTCC-424) and fungal strain *A. niger*(MTCC-1344) were selected. For antibacterial study, Nutrient agar was employed whereas Czapek Yeast agar used as culture medium for antifungal study. Norfloxacin and Clortrimazolewere employed as standard drugs for antibacterial and antifungal studies, respectively. Further, sterilization of culture medias, petridishes and other glasswares was done by autoclaving. Incubation period for antibacterial study was 48 hrs at 37 ± 2^0 C whereas for antifungal study, incubation period was 72 hrs at 25 ± 2^o C.Test Solution of compounds were prepared by dissolving them in DMF with two different concentration i.e. 100 µg/ml, 50 µg/ml. Zone of inhibition was measured and the diameter was calculated in mm after incubation.

Results and Discussion

Physicochemical analysis of synthesized ligands and their mixed ligand complex are compared and it is observed that both ligands and complex are coloured with sharp melting point and soluble in methanol, ethanol, DMSO, DMF and chloroform. Physicochemical data are tabulated in Table 1.

Elemental analysisrevealed that observed values are in good agreement with calculated values. Elemental analysis of C, H, N and Cl were done by CHNX method. Molecular weights of synthesized compounds were determined by Rastmethod. Nickel was estimated by gravimetric method. Elemental analysis is tabulated in Table 2.

The reaction of Nickel chloride and ligands (L_1,L_2) was performed in equimolar ratio which is further confirmed by stoichiometric ratio 1:1:1(M:L_1:L_2) in metal complex. Molar conductivityin dry DMF measured and found ~12.93 ohm^{-1} cm^2 mol^{-1} to indicate that complex is non-electrolyte.Magnetic moment measurement for complex was found ~2.94 BM which coincide with spin only formula with little orbital contribution, also supports distorted octahedral geometry of Ni(II) with two unpaired electrons and paramagnetic nature.

TABLE 1.**Physicochemical data.**

Ligand / Metal complex	**Molecular weight found (Calc.)**	**Empirical formula**	**Colour**	**Melting point(°C)**	**Yield (%)**
Ligand [L_1]	238.2 (237.1)	$C_{14}H_{11}N_3O$	Yellow	203.3	85.63
Ligand [L_2]	315.9 (316.0)	$C_{14}H_{10}BrN_3O$	Orangish-yellow	221.2	94.53
Metal complex [$NiL_1L_2Cl_2$]	683.9 (682.8)	$C_{28}H_{21}BrN_6O_2Cl_2Ni$	Dark-Brown	224.4	58.97

TABLE 2.**Elemental analysis.**

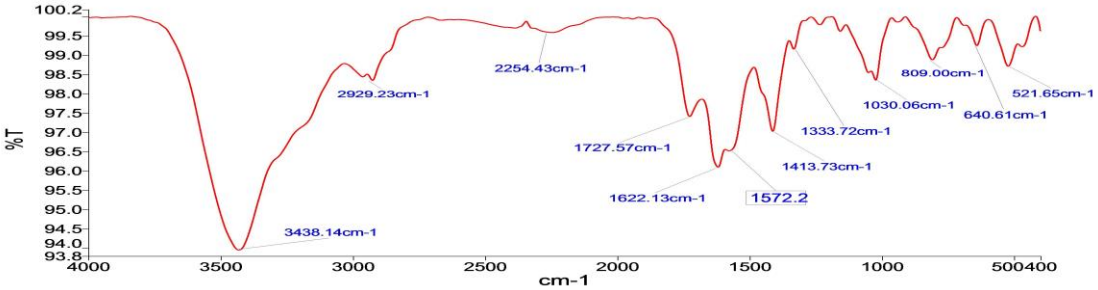
Ligand/ Metal complex	**Elemental analysis (%) Found (Calculated)**					**Molar Cond. (ohm^{-1} cm^{2} mol^{-1}) approx.**	**μ_{eff} approx.**
	C	**H**	**N**	**Cl**	**Ni**		
Ligand [L_1]	70.87 (70.90)	4.67 (4.42)	17.71 (17.89)	-	-	-	-
Ligand [L_2]	53.19 (53.58)	3.19 (3.76)	13.29 (13.82)	-	-	-	-
Metal complex [$NiL_1L_2Cl_2$]	49.24 (49.74)	3.10 (3.25)	12.30 (12.67)	10.38 (10.57)	8.59 (8.23)	12.93	2.94

Spectral characterization

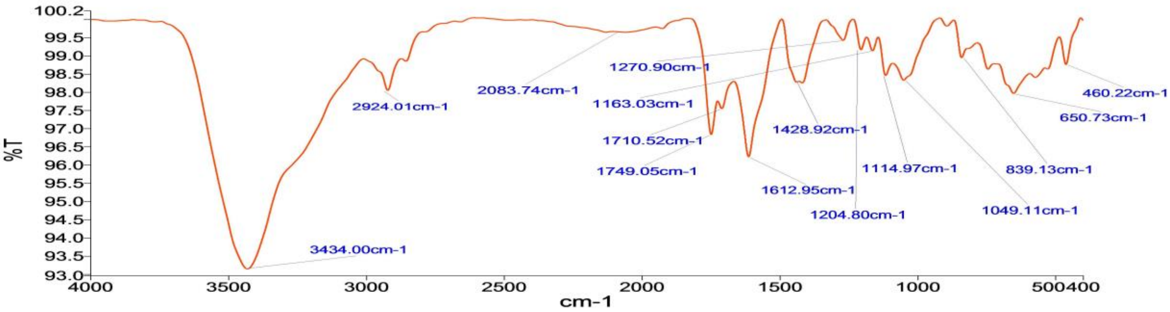
FTIR spectraof the metal complex show some new bands at specific frequencies confirming the formation of metal ligand coordinate bond. FTIR spectraprovides valuable information regarding the nature of azomethine linkage (-C=N-) present in L_1 and L_2 when coordinated to metal ion in complex. The mixed ligand metal complex [$NiL_1L_2Cl_2$] exhibits a strong absorption band in the region 1618 cm^{-1} as compared to the band at 1622 and 1612 cm^{-1} in free ligands. This shift of absorption band to lower frequency region confirms coordination of C=N to metal ion. Similarly, the characteristic absorption band of *v*C=O observed at 1727 cm^{-1}, 1749 cm^{-1} for L_1, L_2 respectively shift towards lower frequency region in complex that appears at 1736 cm^{-1} supporting coordination. In addition, absorption bands observed at 526 cm^{-1} and 753 cm^{-1} correspond to *v*Ni-N and *v*Ni-O bonds, respectively in metal ligand complex. However, other vibrational bands can also be seen in FTIR spectra due to stretching and bending vibrations of other bonds present in ligands and complexes (Figure 1) (Table 3) .

TABLE 3. **FTIR data $\underline{v}$(cm^{-1}) for newly synthesized ligands and mixed ligand complex.**

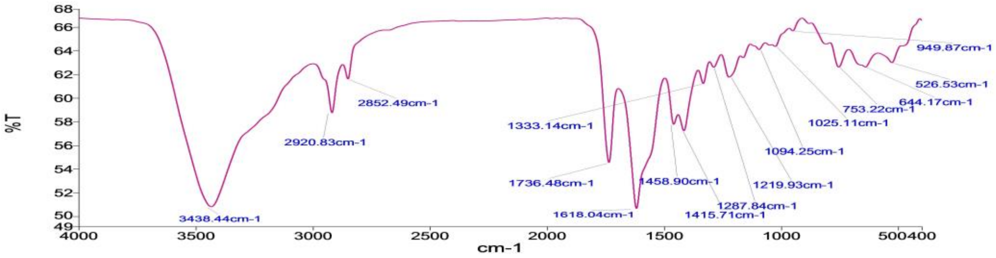
Ligand/complex	**N-N (str.)**	**C=N (str.)**	**C=O (str.)**	**C-Br (str.)**	**Ar-H (str.)**	**N-H (str.)**	**Ni-O (str.)**	**Ni-N (str.)**	**Ni-Cl (str.)**
Ligand [L_1]	1030	1622	1727	-	2929	3438	-	-	-
Ligand [L_2]	1049	1612	1749	650	2924	3434	-	-	-
Metal complex [$NiL_1L_2Cl_2$]	1025	1618	1736	644	2920	3438	753	526	949



(a) Ligand (L_1)



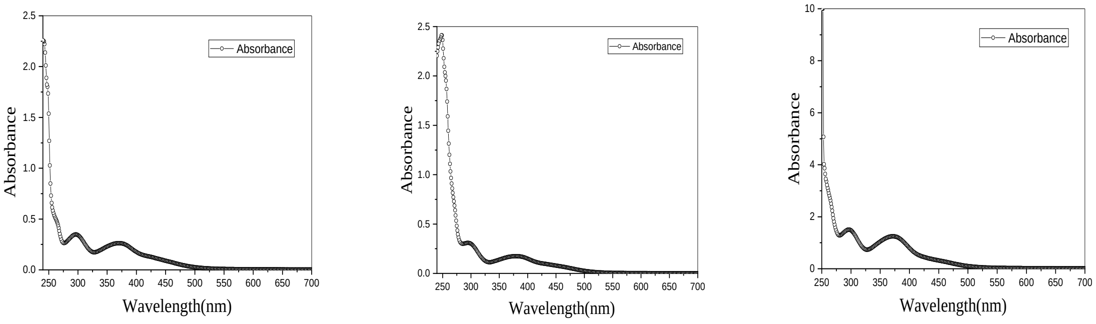
(b) Ligand (L_2)



(c) $[NiL_1L_2Cl_2]$

FIG. 1. **FTIR spectra of synthesized ligands and mixed ligand complex.**

UV-Vis spectra of the ligands and metal complex were performed in ethanol in the range of 200-800 nm and several bands have been observed below 500 nm due to the n→π* / π→π* transitions (Figure 2). Infree ligands (L_1, L_2), two bands are observed at 294 nm, 370 nm and 292 nm, 374nm which are attributed to π→π* transition of the heterocyclic moieties and n→π* transition of the azomethine group of the ligand, respectively. In the metal complex π→π* and n→π* transitions were found to shift to longer wavelengths as a consequence of coordination to metal centre. In Ni(II) complex, the bands were shifted to 297 nm for π→π* transition and 380 nm for n→π* transition. These results indicate the formation of M-L coordination bond (Figure 2).



(a) Ligand (L_1) (b) Ligand (L_2) (c) [$NiL_1L_2Cl_2$]

FIG. 2. **UV-Visible spectra of ligands and mixed ligand complex.**

In ^{1}H NMR spectrum ofNi(II) complex, a downfield broad signal at 10.24 ppm observed which is attributed to –NH proton of isatin moiety. Further, the aromatic protons of isatin moiety show multiplet in the range 6.85 to 7.49 ppm (Figure 3).

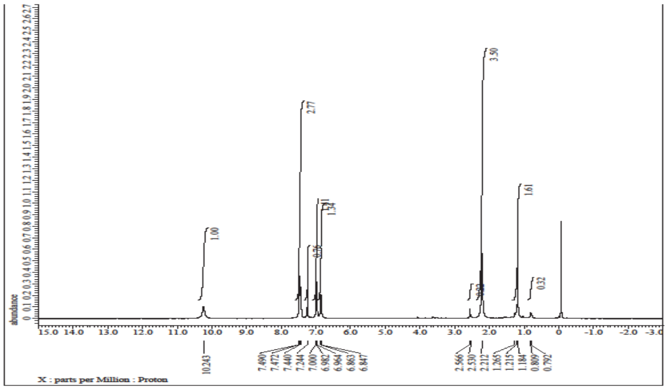


FIG. 3. ^{1}**H NMR spectra of mixed ligand complex.**

The ESI-MS spectrum of metal complex show molecular ion peak and daughter ion peaks. The molecular ion peak M^+ for complex observed at *m/z* 684.19 that coincide with molecular weight of complex and its mononuclear nature. The peaks present at *m/z* 143. 85 and 237.92 are also prominent (Figure 4).

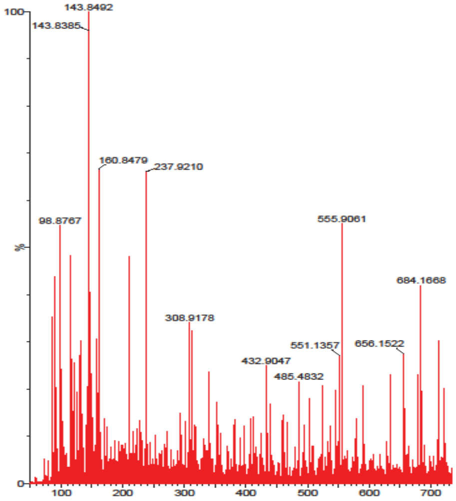


FIG. 4. **Mass spectra of mixed ligand complex [$NiL_1L_2Cl_2$].**

Biological evaluation reveals the ligands to be strongly active against *S. aureus*, but moderate for*P.aeruginosa* as compared to standard. However, L_2 possesses more potency due to presence of bromo moiety. In addition, both ligands show remarkable activity against fungal strain*A.niger*. Moreover, ligands after coordination to metal exhibit enhanced antimicrobial potency consistent with penetrating effect of synthesized compounds (Table 4).

Table 4. **Antimicrobial Activity of Synthesized Compounds**

Ligand/complex	**Conc. (μg/ml)**	**Zone of inhibition (mm)**		
		Antibacterial Activity		**Antifungal Activity**
		S.aureus	***P.aeruginosa***	***A.niger***
Ligand [L_1]	100 50	30 19	28 19	21 15
Ligand [L_2]	100 50	31 21	31 22	29 16
Metal complex [$NiL_1L_2Cl_2$]	100 50	32 23	31 22	29 18
Norfloxacin (for antibacterial)	50	19	21	NT
Clortrimazole (for antifungal)	50	NT	NT	17

NT - Not Tested

Conclusion

On the basis of above analytical data, it is obvious that both ligands act as neutral bidentate donor which form mono nuclear mixed ligand complex with Ni (II) metal. An octahedral geometry with slight distortion has been proposed for synthesized complex which is supposed to be a non-electrolyte with paramagnetic nature. There is no water molecule coordinated to metal ion as no characteristic FTIR absorption band could be observed regarding this. Further, biological screening reveals moderate bacteriocidal and fungicidal activity of ligands by either killing microbes or blocking their active sight when screened against selective pathogens. Metal ligand coordination further increases potency but mostly at lower concentration of test compounds as compared to standards. It can be further concluded that various isatin derivatives and their complexes can be synthesized and evaluated biologically to develop and recognize novel pharmacophores in field of drug design and pharmaceutical science.

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