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Synthesis, Structure and Reactivity of Schiff base Transition Metal Mixed Ligand Complexes Derived from Isatin and Salal

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ABSTRACT

A series of Isatin derivative Schiff base ligands have been prepared by the nucleophilic addition of 5-Bromo isatin with various amine derivatives and characterized by CHNS analysis and spectral data. Similarly, two of salicylaldehyde ligand have been prepared by the nucleophilic addition of Salal with amine derivatives. In order to investigate the coordination behavior of these ligands and their metal complexes of the type $M(acac)_x$ L [M = Cu(II), Ni(II); L = Schiff base ligands; x = 0 or 2] mixed ligand (chelate) have been prepared from the reaction of these ligands with their corresponding metal (Ni, Cu) acetylacetonates. The present paper was an approach to understand the chelating mixed ligand formation in complexes. All the isolated Shiff base ligands and mixed acac metal complexes were characterized by using IR, ^{1}H NMR, UV-Vis, molar conductance and TGA/DTA analysis. The biological activities of all the isolated ligands and their corresponding mixed acac metal complexes have been used to screening against the microorganisms both *Gram-positive* and *Gram-negative* bacteria such as *E.coli* and *S.sureus* respectively, fungi *A. niger* and *C.albicans* and the results have been compared with standard and control. The main idea of these types of biological screening is to understand the role of these isolated compounds in pharmaceutical industries for drug development.

Keywords: Isatin, Salal, Schiff base, Acetylacetonates (Pentane-2,4-dione), Metal acac, Spectral studies, Metal complexes.

INTRODUCTION

The chemistry of Isatin (1H-indole-2, 3-dione) and other Schiff base compounds and some of their derivatives have been reported in the literature[1]. The N-functionalization of the Isatin core can be readily obtained by the deprotonation of the amino moiety, forming the corresponding sodium or potassium salt and subsequent addition of an electrophile (e.g. alkyl or acyl halides).[1] Variety of metal complexes of symmetrical monohydrozone derived from various aldehydes has been prepared and their stereo chemistries have been reported in the literature[2]. The coordination compounds derived from isatin Schiff base ligands is less reported[3]. The Isatin a monoamide upon the condensation with two molecules of various amine derivatives should give symmetrical structure.

The starting materials, metal acetylacetonates of nickel and copper are conveniently available from known synthetic methods.[4] By appropriately varying the stoichiometry of the reaction, it should be possible to prepare mixed-ligand acac complexes of the type $M(acac)_{n-x}L_x$ [M = Ni, Cu; $L=L_1$, L_2]. With the above idea in mind, attempts were made to prepare variety of mixed ligand complexes of nickel and copper.

Keeping in view efforts have been taken that synthesis of the various types of Schiff base mixed ligands derived from 5-Bromo isatin and Salal and also their metal acac complexes (Copper and Nickel). All the isolated ligands and metal complexes are characterized by using various analytical methods. Further, with metal acetylacetonates(acac), $M(acac)_x$ [M = Cu(II), Ni(II); x = 2] as precursor several complexes of the type ML_2, were prepared using these ligands and has been characterized by using IR, ^{1}H NMR, UV-Vis, Molar conductance and TGA/DTA measurements. The mixed acac-ligand complexes of Cu(II), Ni(II) containing isatin-salal and metal acetylacetonate (acac) have been prepared by the ligand exchange reactions. Isatin and Salal derivative ligands and complexes were found to demonstrate a range of chemotherapeutic activites.

All the isolated compounds were biologically screened by using the microorganisms both *Gram-positive* and *Gram-negative* and these results have been compared with standard and control.

MATERIALS AND METHODS

All the chemicals used in this project were of AR grade were obtained from Sigma-Aldrich private limited, Nice chemicals and sd-fine chemicals. IR Spectra are recorded using KBr disc on a FTIR Perkin Elmer spectrometer within the range of 4000-400 cm^{-1} and Shimadzu Japan (FTIR, 8400). The solid reflectance spectra of the compounds were recorded in UV-Vis spectrophotometer Perkin Elmer USA-model Lambsa 35, ^{1}H NMR with DMSO-d^6 was recorded on Bruker 400 MHz high resolution multinuclear FT-NMR. Powder X-ray diffractometer studies on PAN analytical Empyrean, Netherlands, TGA studies using Perkin Elmer USA and Elemental analysis using Variomicro select, Elemental Germany and SEM-JEOL studies with JEOL-IT 300 with La 36 sources. Follow-up of the reactions and the check of the purity of the compounds were done by thin layer chromatography (TLC) on silica gel protected aluminum sheets and the spots were detected by exposure to UV-lamp at 254 nm for a few seconds.

Preparation of Metal$(acac)_2$

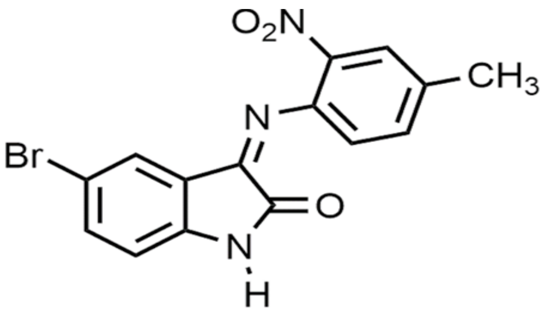
Metal acetylacetonates [$Ni(acac)_2$, $Cu(acac)_2$] were prepared by known methods[4]. Nickel chloride hexahydrate (1.2 g, 0.02 mol) was dissolved in 50 mL of distilled water. A solution of sodium acetylacetonate was prepared by adding drop-wise sodium hydroxide (1N) solution of acetylacetone (10 mL, 10 g, 0.10 mmol) until the oily emulsion formed dissolves. The nickel salt solutions were added to this solution with stirring when green coloured crystals of nickel acetylacetonates were separated, which was suction filtered and dried (M.P. 229.5^{0}C, yield 75%).

Similarly, $Copper(acac)_2$ was prepared by using Copper sulphate pentahydrate (1.7 g, 0.02 mol) as above procedure. Dark blue coloured crystals of copper acetylacetonates were separated, which was suction filtered and dried (m.p. 280^{0}C, yield 80%).

Preparation of ligands

1. (2Z)-5-bromo-2-[(4-methyl-2-nitrophenyl) imino]-1,2-dihydro-3-indole-3-one [L_1]

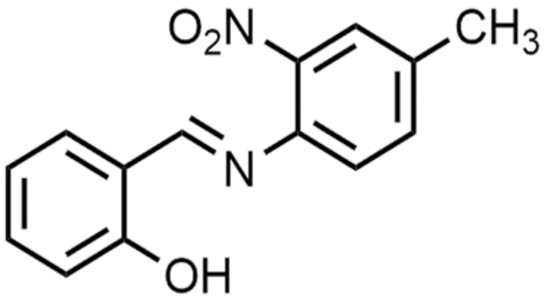
The pure crystals of 4-methyl-2-nitroaniline (1.57 g, 10 mmol) and 5-bromoisatin (2.26 g, 10 mmol) were mixed in ethanol medium and the mixture refluxed for about 120 minutes. The obtained ligand was crystalline orange colour and succession filtered and purification of it was repeated, recrystallized from ethanol to get pure compound (m.p. 215^{0}C, yield 85%).



(2Z)-5-bromo-3-[(4-methyl-2-nitrophenyl)imino]-1,2-dihydro-3H-indol-3-one

2. 2-{(E)-[4-methyl-2-nitrophenyl) methylidene] phenol [L_2]

The pure of salicylaldehyde (1mL, 10 mmol) and 4-methyl-2-nitroaniline (1.57g, 10 mmol) were mixed in ethanol medium and the mixture refluxed for about 120 minutes. The obtained compounds was crystalline yellowish orange and succession filtered and purification of these compounds were repeated, recrystallized from ethanol to get pure compound (m.p. 120^{0}C, yield 90%).



2-{(E)-[4-methyl-2-nitrophenyl)imino]methyl}phenol (L_2)

Preparation of Metal Complexes

1. Preparation of Nickel (II) and Copper (II) L1 mixed ligand-acac complexes

To an ethanolic solution (0.01 mol) of (2Z)-5-bromo-2-[(4-methyl-2-nitrophenyl) imino]-1,2-dihydro-3H-indole-3-one, (3.652 g, 0.01 mol), was added to nickel acetylacetonate (3.144 g, 0.01 mol) dissolved in 20 mL of ethanol, drop-wise, with constant stirring and continue for 20 min and the resulting mixture was refluxed for 120 minutes. The obtained nickel metal complex (light orange crystals) were filtered, washed with small amount of ethanol and dried over calcium chloride (m.p.187^{0}C, yield 75%).

Similarly Copper(II) Complexes was prepared using ethanolic solution (0.01 mol) of (2Z)-5-bromo-2-[(4-methyl-2-nitrophenyl)imino]-1,2-dihydro-3H-indole-3-one, (3.652 g, 0.01 mol), was added to copper acetylacetonate (2.638 g, 0.01 mol) dissolved in 20 mL of ethanol, drop-wise, with constant stirring. The ligand and metal acetylacetonate was mixed and stirring was continued for 20 min and the resulting mixture was refluxed for 120 minutes. The obtained copper metal complexes (orange crystals) were filtered, washed with small amount of ethanol and dried over calcium chloride (m.p. 202^{0}C, yield 80%).

2. Preparation of Nickel(II) and Copper(II) L2 mixed ligand-acac complexes

To a ethanolic solution (0.01 mol) of 2-{(E)-[4-methyl-2-nitrophenyl)methylidene]phenol (2.61 g, 0.01 mol), was added to nickel acetylacetonate (3.144 g, 0.01 mol) dissolved in 20 mL of ethanol, drop-wise, with constant stirring and continued for 20 min and the resulting mixture was refluxed for 120 minutes. The obtained nickel metal complexes (light orange crystals) were filtered, washed with small amount of ethanol and dried over calcium chloride (M.P.150^{0}C, yield 75%).

Similarly, Copper(II) Complexes was prepared using ethanolic solution (0.01 mol) of 2-{(E)-[4-methyl-2-nitrophenyl)methylidene]phenol (2.61 g, 0.01 mol), was added to copper acetylacetonate (2.638 g, 0.01 mol) dissolved in 20 mL of ethanol, drop-wise, with constant stirring. The ligand and metal acetylacetonate was mixed and stirring was continued for 20 min and the resulting mixture was refluxed for 120 minutes. The obtained copper metal complexes (orange crystals) were filtered, washed with small amount of ethanol and dried over calcium chloride (m.p. 200^{0}C, yield 75%).

Biological activities

The pharmacological activity of all the isolated schiff base ligands and mixed ligand acac compounds were studied by screening were done *In vitro* cup diffusion methods[5]. All the isolated ligands and their metal complexes against the microorganisms such as, *E.coli*, *S.Aureus* for antibacterial and against *A.niger* and *C.albicans* for antifungal behaviors. These biological activities of all the compounds were compared with standard (Gentamycin and Nystatin) and control (DMSO). In silico docking analysis was performed between ligands L_1 and L_2 and Gentamicin with APH(2″)-Ia of *Staphylococcus aureus*. The protein crystal structure was retrieved from the RCSB-PDB with the PDB id 5IQG in .pdb format. The protein was loaded to AutoDock vina(Trott & Olson, 2010) of the PyRx software for docking analysis. The structure of the ligands L_1 and L_2 were drawn in Marvin sketch and saved in the .sdf format. Energy minimization was performed using the Open Babel (O'Boyle *et al.,* 2011) in PyRx0.8. The grid box was set to the XYZ coordinates of 35.69, -1.15 and 64.11 respectively and box dimensions were 18.62, 22.70 and 14.30 along the XYZ axis, respectively to cover the entire protein. The protein-ligand interaction of the conformation complex with the lowest AutoDock vina score was visualized using PyMOL 2.4 and interaction analysed using LIGPLOT$^+$ software (Laskowski & Swindells, 2011). These results are summarized in this paper.

RESULTS AND DISCUSSION

Magnetic Suceptibility

The analytical data shown in Table 2 indicate that all nickel(II) and copper(II) metal ions form 1:2 (metal:ligand) complexes. The complexes are light orange crystals and light yellow crystals respectively. All the acac complexes are dissolved in DMSO solvents and partially soluble in alcohol. The molar conductance data in solvent are too low to count for any dissociation of the complex. Therefore the obtained metal complexes are suggested as non-electrolyte.

The nickel-acac(II) complexes are found to be diamagnetic in nature. Hence these metal compounds suggested as ocahedral geometry[6]. The magnetic movements of copper-acac (II) complexes are in the range of 1.73 to 1.93 B.M. These values clear that there is no major spin interaction in these complexes.

Thermal studies

Thermal analysis[7] (TGA and DTA) techniques are used to find out the decomposition of the metal complex. The complexes were heated in the temperature ranges room temperature to 1000^{0}C. The temperature range and the experimental peak shows that the weight loss with the decomposition reactions are discussed below.

The TG curve of both $Cu(acac)_2$ and $Ni(acac)_2$ shows a three-step decomposition pattern. The first step occurring at 120^{0}C is endothermic and corresponds to weight loss of 11% and is attributed to the loss of water of hydration. The second step, occurring at 260^{0}C, is exothermic and corresponds to weight loss of 60% is attributed to the loss of a more volatile acac ligand. The third step occurring between 420-430^{0}C is also exothermic and corresponds to weight loss of 80% and is attributed to the loss of remaining acac ligand to form the final product CuO and NiO.

Thermal Study of Cu(II) complex

The mixed-ligand complex $Cu(acac)L_1$ (L = (2Z)-5-bromo-2-[(4-methyl-2-nitrophenyl)imino]-1,2-dihydro-3H-indole-3-one), on the other hand, exhibits a two-step decomposition pattern. The first step (exothermic) occurs at about 280^{0}C corresponds to weight loss of 52% and is attributed to the loss of a acac ligand. The second step (exothermic) occurring between 300-600^{0}C corresponds to weight loss 65% is attributed to loss of other ligands and the final loss of the chelating L_1 ligand. The significant absence of the peak at 100^{0}C corresponds to loss of H_2O, as observed in the TG of the $Cu(acac)_2$, suggests that the four-coordination site in Cu(acac)L is occupied by N atom of the chelating ligand L. These observations further support the structure proposed for Cu(acac)L.

Thermal Study of Ni(II) complex

The mixed-ligand complex $Ni(acac)L_1$ (L = (2Z)-5-bromo-2-[(4-methyl-2-nitrophenyl) imino]-1,2-dihydro-3-indole-3-one), on the other hand, exhibits a two-step decomposition pattern. The first step (exothermic) occurs at about 295^{0}C corresponds to weight loss of 50% and is attributed to the loss of an acac ligand. The second step (exothermic) occurring between 330-590^{0}C corresponds to weight loss 68% is attributed to loss of other ligands and the final loss of the chelating L_1 ligand. The significant absence of the peak at 100^{0}C corresponds to loss of H_2O, as observed in the TG of the $Cu(acac)_2$ and $Ni(acac)_2$, suggests that the four-coordination site in Cu(acac)L and Ni(acac)L is occupied by N atom of the chelating ligand L. These observations further support the structure proposed for Cu(acac)L and Ni(acac)L mixed ligand complexes.

Infrared spectra

Vibrational spectra of free Schiff base ligands L_1 and L_2 were compared to investigate the mode of binding present in the synthesized Nickel and Copper complexes. The FT-IR spectral data are summarized in Table 1.

Table 1: Infrared spectral Data

Sl. No.	Formula of the ligand	CH Aromatic	C=O	C=N	OH	C-N	C-Br	N-H
1	$C_{15}H_{10}N_3O_3Br$	3203	1756	1594	3476	1613	1096	3203
2	$C_{14}H_{12}N_2O_3$	3350	1638	1580	3472	1515	-	3350
Sl. No.	**Formula of the complex**	**CH Aromatic**	**C=O**	**C=N**	**OH**	**C-N**	**C-Br**	**C-O**
1	$(C_{20}H_{18}N_3O_5Br)Ni$	3094	1728	1594	3350	1613	1096	1315
2	$(C_{19}H_{19}N_2O_5)Ni$	3095	1606	1580	3481	1345	-	1346
3	$(C_{20}H_{18}N_3O_5Br)Cu$	3102	1692	1610	3444	1585	1106	1314
4	$(C_{19}H_{19}N_2O_5)Cu$	3110	1610	1602	3489	1355	-	1340

All the ligands shows broad peak with medium intensity in the range of 3250-3200 cm^{-1}, that attributed to the $\nu_{NH/OH}$ vibrations.[8] A medium intensity to high observed in the range of 1630-1610 cm^{-1} is attributed to the $\nu_{C=N}$ vibrations due to presence of azomethine group. A group of three peaks of medium intensity observed in the frequency range of 1580-1480 cm^{-1} is due to presence of $\nu_{C=C}$ aromatic vibrations. Addition to this it is observed that a high intensity at 1270 cm-1 is attributed to phenolic ν_{C-O}[9]. A high intensity band appearing frequency range of 1680-1670 cm^{-1} has been allocated to the $\nu_{C=O}$ vibration is due to ketonic group.

All the metal complexes exhibit medium intensity bands at 3250-3100 cm^{-1} that can be assigned to ν_{NH} frequencies. There is a high intensity appear around 1270 cm^{-1} due to presence of phenolic ν_{C-O} and appears as a high intensity in the region of 1310-1280 cm^{-1} for these complexes. The FTIR spectrum of free ligand shows characteristic band assignable to ν_{OH} which disappears in the metal complexes indicating de-protonation of the OH group upon binding with metal ions[10-13].

It has been reported in the literature that in Schiff base, phenolic $\nu_{C=O}$ vibrations have been used as diagnostic probe to know the formation of monodentate and oxygen bridging complexes. In the mononuclear complexes, where in oxygen acts as a monodentate, the ν_{C-O} around 1510 cm^{-1} [13] shifts to higher frequency by about 10-15 cm^{-1}. In the bridging case, the shift is of the order of 35 cm^{-1} [14-15]. In these complexes observed that intensity band around 1510 cm^{-1} can be assigned to the phenolic $\nu_{C=O}$. In these complexes this band is located around 1540 cm^{-1} as medium intensity band. In all these cases it is observed that is shifted in the order of 15-20 cm^{-1}. This emphasizes that in these complexes the phenolic oxygen exhibits monodentate behavior.[23]

In all the metal complexes shows strong peak appears in the range of 1610 cm^{-1} is due to $\nu_{C=N}$ and it clearly indicates that the coordination of $V_{C=N}$ shifts lower range to the metal through nitrogen. The vibrational frequency of C-N group blue shifts by[9-14] cm^{-1}, the meal complexes indicating coordination through the imine nitrogen. The $\nu_{C=O}$ is disappearing in all the complexes. This is due to a lowering of $V_{C=O}$ along with usual lowering of $\nu_{C=N}$ group. In addition to these frequencies the metal complexes shows two bands in the region of 1640-1650 cm^{-1} and 1695-1700 cm^{-1} can be assigned to $\nu_{C=O}$ vibrations of the carbon-bonded acetylacetonate ligand which confirms the formation of mixed ligand metal compelxes[16]. The assignment of the band to various ν_{M-N} and ν_{M-O} vibrations in the lower region. The ν_{M-N} vibrations assigned in the region of 600-500 cm^{-1} [17]. For Ni(II) and Cu(II) complexes with N and O donor ligands, these bands are assigned at 483-442 cm^{-1} respectively. The bands appear in the frequency regions of 475-435 cm^{-1} and 548-470 cm^{-1} is assigned to ν_{Cu-o} and ν_{Ni-O} vibrations respectively.

The assigned the region between 500-400 cm^{-1} for $\nu_{M=O}$ vibrations is due to metal acetylacetonates[18]. In nickel acetylacetonates, two bands appearing in the range of 323 and 295 cm^{-1} and in copper acetylacetonate, two bands appearing in the range of 340-246 cm^{-1}.

Table 2: Electronic Spectral Data

Sl. No.	Formula of the complex	π-π*	n-π*	d-d	LCMT	BM
1	$(C_{20}H_{18}N_3O_5Br)Ni$	40984	27908	16990	28950	Dia
2	$(C_{19}H_{19}N_2O_5)Ni$	41000	28028	16140	29830	Dia
3	$(C_{20}H_{18}N_3O_5Br)Cu$	41900	29810	16750	28680	1.73
4	$(C_{19}H_{19}N_2O_5)Cu$	41100	29602	16345	31230	1.93

Copper(II) complexes

The observed band maxima for copper(II) mixed ligand-acac complexes are listed in table. The spectrum of the ligand showed an absorption band at 22000 cm^{-1} which has been assigned to n-π^*. The electronic spectra of these complexes in DMF solution show two bands in the region centered at 22000-23000 cm^{-1} and 28500-29585 cm^{-1}. These bands are assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions respectively.[19-20] The spectral data indicate copper is exhibiting higher coordination number.

Nickel(II) complexes

The observed band maxima for these Nickel (II) mixed ligand-acac complexes are listed in the table. The electronic spectra shows that all Schiff base complexes exhibit sharp two or three electronic spectral bands. The bands in the region 32000-34000 cm^{-1} are assigned to ligand-to-metal charge transfer band between the lowest empty d-orbital of nickel and highest occupied ligand molecular orbital.[21]

The spectral data indicate nickel is exhibiting octahedral geometry.

The interpretation of ultraviolet spectra of metal complexes of Isatin derived Schiff bases revealed that charge transfer bands occur in the same region with π-π^* transition.

Table 3: ^{1}HNMR data of ligands and complexes

Sl.	Formula of the ligand	NH	=CH	-OH	C_6H_5
1	$C_{15}H_{10}N_3O_3Br(L_1)$	7.75	8.4	10.8	6.9
2	$C_{14}N_{12}N_2O_3(L_2)$	7.24	7.75	12.0	6.9
Sl.	**Formula of the Complexes**	**NH**	**=CH**	**-OH**	**C_6H_5**
1	$(C_{20}H_{18}N_3O_5Br)Cu$	-	9.6	11	7.4
2	$(C_{19}H_{19}N_2O_5)Cu$	-	8.0	12.3	7.5

^{1}H NMR Spectra

The ^{1}H NMR spectra of a representative Schiff base ligands and its mixed ligand acac-complexes are reported in the table. The ligand shows a resonance signal are about 7.75 δ corresponding to the resonance absorption of protons of the amide -NH group. The observed signals at about 8.4 δ corresponds to the azomethine protons of =CH group and signals at 10.8 δ corresponds to the hydrogens of the -OH groups of the ligand. The multiplets centers at about 6.9 δ and 7.5 δ are attributed to aromatic protons.

In the proton NMR spectra[22] of the metal acac-complex, the azomethine =CH signal is shifted to downfield, as expected, and appears at about 9.6 δ. However, the resonance signals of the protons of the -NH group does not appear, has been shifted significantly. Whereas, the signals due to the protons of -OH group of the ligand have diminished in the spectrum of the metal complex indicating the deprotonated form of the ligand and enolization. The observed broad signals of the metal complex indicate the paramagnetic nature of the copper complexes.

Biological activities

The pharmocological activity,[23] of the all isolated ligands and their metal complexes are molds were grown on sabouraud dextrose agar (SDA) at 25^{0}C for 48 h and determined by using agar well diffusion method and fungal growth were sub cultured on nutrient broth for their *In vitro* testing. 15 mL of molten SDA (45^{0}C) was added to 100 µL volume of each compound having concentration of 100 µL/mL in the DMSO and poured into a sterile Petri plate. The solid appeared at the petri plate which poisoned agar plates were inoculated at the center with bacterial and fungal plugs (8 mm) obtained from activity growing colony and incubated at 25^{0}C for 48 hours. Diameter of the bacterial and fungal colonies was measured and expressed as present zone of inhibition. The antibacterial and antifungal activities of all the isolated ligands and metal complexes are summarized below.

Table 4: *In vitro* antibacterial and antifungal activities of the mixed ligand metal complexes

Sl. No.	Compounds ligands and complexes	Concentration (in µL)	Bacteria (Inhibition zone in mm)		Fungus (Inhibition zone in mm)	
			E.coli (*Gram-negative*)	*S.aureus* (*Gram-positive*)	*A.niger*	*C.albicans*
1	L_1	100	12	13	13	14
2	Ni(acac) L_1	100	18	19	19	20
3	Cu(acac) L_1	100	19	18	18	18
4	L_2	100	11	14	13	13
5	Ni(acac) L_2	100	16	17	17	18
6	Cu(acac) L_2	100	18	18	19	19
7	Control (DMSO)	100	8	8	8	8
8	Standard (Gentamycene)	100	20	20	--	--
9	Standard (Nystatine)	100	--	--	20	20

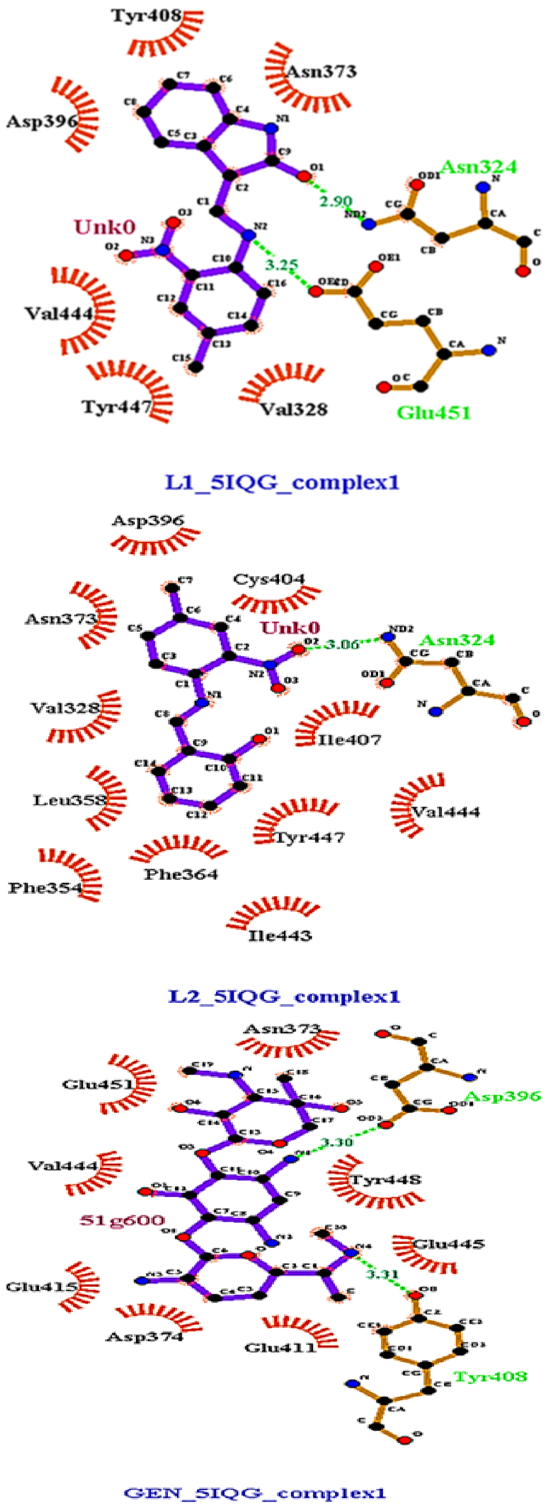


Fig. 1. 2D schematic representation of interaction of 5IQG with Ligands. The hydrophobic interactions are represented as red semi-circles with spokes. Hydrogen bonds are represented by dotted lines

Table 5: Docking interaction analysis of 5IQG with the ligands

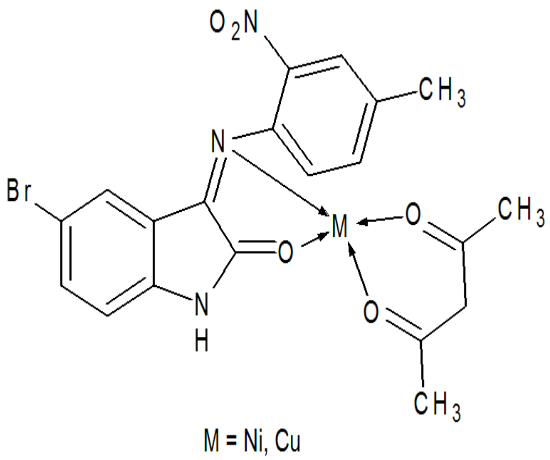
Ligand	Vina score (kcal/mol)
L_1	-7.6
L_2	-7.1
Gentamicin	-5.9

Vina score shows highest value for L_1 ligand when compared to other ligands synthesized. Both the copper and nickel complexes shows moderate to high in both antibacterial and antifungal activity and results are compared with the standards and control.

Structures

Magnetic measurements, infrared, electronic and [1]NMR spectral data have been provided evidences for the structures of the isolated metal complexes. On the basis of these studies, probable structures for Nickel(II) and Copper(II) mixed ligand acac-complexes are proposed (1 and 2).

Our spectral data provide reasonably good evidences for their solution structures. It is clear from the [1]NMR spectral patterns observed for those compounds, that the symmetrical Schiff base ligands introduces metal attached at the center of the ligands. However, complete solid-state structural characterization by X-ray methods are studied but yet to determine the stereo chemical influence of the symmetrical Schiff base ligands in the geometries of the transition metals. Fortunately, attempts to obtain crystals for X-ray diffraction analysis, so far have been successful. From all the above parameter analysis, tentative structures have been proposed.



M(acac)L_1

CONCLUSION

Schiff base isatin derivative and salan derivative ligands and their mixed ligand acac-transition metal complexes have been synthesized and studied by analytical and spectroscopic techniques. All the synthesized ligands and mixed-acac complexes shows potential antimicrobial activities against bacteria and fungi. The antimicrobial data revealed that metal complexes exhibit more antimicrobial activities than free ligand, Ligands having both bromo and nitro groups shows better activity than the ligands having only nitro groups. Structure activity relationship studies revealed that substitution at position 5 was favoured over position 4, 6 or 7, leading to greater anticancer activities. There was no negative effect observed between nitro group of amine derivative and carbonyl group of Isatin, exist as a lactum group which observed to involve in delocalization of electrons between oxygen and nitrogen atoms. The FTIR spectra of the complexes indicate the presence of deprotonated form of chelating complexes. To understand the mode of action of the ligands which possess a significant anti-bacterial inhibitory activity in the *In vitro* experiment against *Staphylococcus aureus* was considered for the in silico study. Gentamicin interacting residues for APH(2″)-IIa and the substrate binding in APH(2″)-IVa, are all completely conserved in both APH(2″)-Ia and APH(2″)-IIIa enzymes. The PDBSum interaction of Gentamicin with 5IQG was considered as reference and based on the energy and the hydrogen bonding interaction the best conformation of the ligands were selected and further analysed. Ligand L_1 forms two hydrogen bonds (2.90Å & 3.25Å) with Asn324 and Glu451. Hence these compounds can be used as a good pharmacophore for the synthesis of antimicrobial drugs.

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Conflicts of Interest

The authors declare no conflict of interest.

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