

Copper(II)-Complexes of an Isatinic Quinolyl Hydrazone-Anion effect

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Abstract

New heteroleptic copper(II)- complexes (1:1 or 1:2; M:L) were obtained from the reaction of an isatinic quinolyl hydrazone (H_2L) with several copper(II)- salts viz. Cl^- , Br^- , NO_3^- , ClO_4^- , SO_4^{2-} and AcO^- . The obtained complexes have O_h , square planar (D_{4h} - symmetry) and square pyramid arrangements. The complexes fulfill the strong coordinating ability of Cl^- , Br^- , NO_3^- and SO_4^{2-} anions. Depending on the type of the anion, the ligand coordinates the copper(II)- ions either through its lactam (SO_4^{2-} and ClO_4^-) or lactim forms (the others). For the copper(II)- isatinic complexes the antimicrobial activity shows a gradual change with change of the coordinated anions. Also, depending on the type of the anion, the order of the antimicrobial activity is as follows $Cl^- > SO_4^{2-} > Br^-$.

Keywords: isatinic quinolyl hydrazones, copper(II)- complexes, anion effect.

Introduction

Of the several heterocyclic rings, the importance of the quinoline ring arises from its therapeutic and biological activities^{1,2}. Quinolyl hydrazones are known to function as chelating agents and have versatile modes of bonding. Recently, the biological activity of quinolyl hydrazones arises from their tendency to form metal chelates with transition metal ions^{2,4}. On the other hand, the indole ring occurring in Jasmine flowers and Orange blossoms¹ exhibit a wide range of biological activity^{3,4}. The incorporation of the quinoline ring with the indole ring may enhance the biological activity of such class of compounds. In continuation of our interest on the complexation of quinolyl hydrazones³⁻⁸, this study is planned to investigate the ligational behavior of the studied hydrazone (scheme 1); 3-[2-(4,6-dimethylquinolin-2-yl) hydrazono]indolin-2-one towards several copper(II)- salts (Cl^- , Br^- , NO_3^- , ClO_4^- , SO_4^{2-} and AcO^-). In general, this study exhibit the role of the anion on the isolated copper(II)- complexes; scheme 2.

Material and Methods

Material: The chemicals used in this investigation were of the highest purity available (Merck, BDH, Aldrich and Fluka). They included $CuBr_2$, $CuCl_2 \cdot 2H_2O$, $Cu(NO_3)_2 \cdot 2\frac{1}{2}H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, $Cu(AcO)_2 \cdot H_2O$ and $CuSO_4 \cdot 5H_2O$, *p*-toluidine, ethyl acetoacetate, phosphorus oxychloride, isatin and hydrazine hydrate (100%). The solvents used in this study were reagent grade and used without further purification.

Measurements: Microanalyses were carried out on a Perkin-Elmer 2400 CHN elemental analyzer. Thermal analyses were carried out on a Shimadzu-50 thermal analyzer. Electronic spectra were recorded on a Jasco V-550 UV/VIS spectrophotometer. IR spectra were recorded on a Bruker Vector 22 spectrometer using KBr pellets. ESR spectra were recorded on a Bruker Elexsys, E 500 operated at X- band

frequency. Mass spectra were recorded at 70 eV on a gas chromatographic GCMSQP 1000-EX Shimadzu mass spectrometer. 1H NMR spectra were recorded as DMSO- d_6 solutions on a Varian Mercury VX-300 NMR spectrometer using TMS as a reference. Molar conductivity was measured as DMF solutions on the Corning conductivity meter NY 14831 model 441. Magnetic susceptibility of the complexes was measured at room temperature using a Johnson Matthey, MKI magnetic susceptibility balance. Melting points were determined using a Stuart melting point apparatus.

Preparation of the Isatinic Hydrazone (H_2L): The ligand; 3-[2-(4,6-dimethylquinolin-2-yl)hydrazono] indolin-2-one was prepared according to our previous publication^{3,6}; an ethanolic mixture of 2-hydrazinyl-4,6-dimethyl quinoline (0.01mol) and isatin (0.012 mol) was refluxed for 15 min. The formed scarlet red compound was filtered off, washed with ethanol and crystallized from DMF; Yield: 67% and m.p 290°C. Analysis: Calcd. for $C_{19}H_{18}N_4O_2$ (334.3): C, 68.27; H, 5.38; N, 16.76. Found: C, 68.31; H, 5.15; N, 16.40.

Preparation of the metal complexes: A methanolic solution of the copper(II)- salt was added gradually to a methanolic solution of the ligand; H_2L in the mole ratio 1 : 1 ; $Cu^{2+} : H_2L$. The reaction mixture was refluxed for 2-4 h to ensure the complete precipitation of the formed complexes. The precipitated solid complexes (1-6) were filtered off, washed several times with methanol to remove any excess of the unreacted starting materials. Finally, the complexes were washed with ether and dried in vacuum desiccators over anhydrous $CaCl_2$. All the isolated complexes are stable at room temperature, non hygroscopic and insoluble in water, partially soluble in alcohols and completely soluble in DMSO and DMF. The molar conductances of $10^{-3}M$ DMF solutions of the complexes indicate non-electrolytic nature for all complexes except

complex 2. The results of elemental and thermal analyses are in good harmony with the proposed structures (table 1).

Antimicrobial activity: The standardized disc- agar diffusion method⁶ was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* (ATCC 25923) and *Streptococcus pyogenes* (ATCC 19615) as Gram - positive bacteria, *Pseudomonas fluorescens* (S 97) and *Pseudomonas Phaseolicola* (GSPB 2828) as Gram - negative bacteria. The antibiotics chloramphenicol and cephalothin were used as standard reference in case of Gram- negative and Gram-positive bacteria, respectively. The tested compounds were dissolved in dimethyl formamide (DMF) which has no inhibition activity to get concentrations of 2 and 1 mg / mL. The test was performed on medium potato dextrose agar (PDA) which contain infusion of 200 g potatoes, 6 g dextrose and 15 g agar. Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10 μ L) from the specific concentration of dissolved tested compounds and carefully placed on inoculated agar surface. After incubation for 36 h at 27 °C, inhibition of the organisms which evidenced by clear zone surround each disk was measured and used to calculate the mean of inhibition zones.

Results and Discussion

Characterization of the hydrazone: The results of elemental analysis of the investigated hydrazone; 3-[2-(4,6-dimethylquinolin-2-yl) hydrazono] indolin-2-one are in good harmony with the proposed formula. The IR spectrum of the hydrazone (table 2) showed broad bands at 3422 / 3162 and very strong band at 1633 cm^{-1} which are assigned to $\nu(\text{OH/NH})$ and $\nu(\text{C=N})$, respectively. The lactam nature of the hydrazone was supported by a very strong band at 1683 cm^{-1} ; $\nu(\text{C=O})$. On the other hand, the electronic absorption spectra of the hydrazone in DMF exhibit two intense bands at 274 and 394 nm characteristic for $\pi-\pi^*$ transitions⁹. Also, a broad band at 480 nm assignable to charge transfer transition (CT) which impacts the ligand its red color. The higher energy bands are consistent with those reported for the aromatic quinoline ring^{4,6,8}. The mass spectrum of the ligand showed the M^+ peak at $m/z = 316$ confirming its non hydrated formula weight (316.36) and supporting its suggested structure. Finally, the ^1H NMR spectral data of the ligand in $\text{d}_6\text{-DMSO}$ relative to TMS; figure 1, lends a further support of the structure.

Table-1
Physical and analytical data of the copper(II)- isatinic complexes

No.	Reactants $\text{H}_2\text{L} + \text{Cu(II)- salt}$	Complex (F. W.)	<i>M.F</i>	Yield %	Color	Elemental Analysis; % Found/(Calcd)		
						C	H	N
1	$\text{Cu}(\text{NO}_3)_2 \cdot 2\frac{1}{2}\text{H}_2\text{O}$	$[\text{Cu}(\text{H}_2\text{L})(\text{HL})(\text{NO}_3)] \frac{1}{2}\text{H}_2\text{O}$ (766.01)	$\text{C}_{38}\text{H}_{32}\text{N}_9\text{O}_{5\frac{1}{2}}\text{Cu}$	63	Dark brown	59.48 (59.58)	4.03 (4.18)	16.52 (16.45)
2	$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	$[\text{Cu}(\text{H}_2\text{L})_2(\text{OH}_2)_2](\text{ClO}_4)_2 \cdot \frac{1}{4}\text{H}_2\text{O}$ (935.40)	$\text{C}_{38}\text{H}_{36\frac{1}{2}}\text{N}_8\text{O}_{12\frac{1}{4}}\text{Cl}_2\text{Cu}$	51	Yellowish brown	48.77 (48.79)	3.98 (3.90)	11.9 (11.98)
3	$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$	$[\text{Cu}(\text{HL})(\text{Cl})(\text{OH}_2)] \frac{1}{2}\text{H}_2\text{O} \cdot \frac{1}{4}\text{MeOH}$ (449.23)	$\text{C}_{19\frac{1}{4}}\text{H}_{19}\text{N}_4\text{O}_{2\frac{3}{4}}\text{ClCu}$	55	Red	51.42 (51.46)	4.20 (4.23)	12.30 (12.47)
4	CuBr_2	$[\text{Cu}(\text{HL})(\text{Br})\text{MeOH}]$ (490.78)	$\text{C}_{20}\text{H}_{19}\text{N}_4\text{O}_2\text{BrCu}$	60	Deep red	48.94 (48.94)	3.85 (3.87)	11.72 (11.42)
5	$\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$	$[\text{Cu}(\text{H}_2\text{L})(\text{SO}_4)(\text{OH}_2)_2] 4\text{H}_2\text{O}$ (583.83)	$\text{C}_{19}\text{H}_{28}\text{N}_4\text{SO}_{11}\text{Cu}$	65	Reddish orange	38.99 (39.08)	4.80 (4.79)	9.62 (9.59)
6	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	$[\text{CuL}(\text{OH}_2)_3] 5\frac{1}{2}\text{H}_2\text{O} \cdot \frac{1}{4}\text{MeOH}$ (538.77)	$\text{C}_{19\frac{1}{4}}\text{H}_{32}\text{N}_4\text{O}_{9\frac{3}{4}}\text{Cu}$	60	Brick red	42.85 (42.91)	5.90 (5.93)	10.38 (10.39)

Table-2
Selected IR spectral bands (cm^{-1}) of the ligand and its complexes

Other bands	$\nu(\text{C=N})$	$\nu(\text{C=O})$	$\nu(\text{OH}) / \nu(\text{NH})$	Complex
	1633	1683	3422 / 3162	IsatinHQ
$\nu(\text{N-O})$; 1332 cm^{-1}	1608	1695	3167	1
$\nu(\text{Cl-O})$; 1115 cm^{-1}	1615	1705	3278 + 3191	2
	1610	—	3307	3
	1609	—	3295	4
$\nu_3(\text{S-O})$; 1113 cm^{-1}	1604	1695	3324	5
	1606 1559	—	3170	6

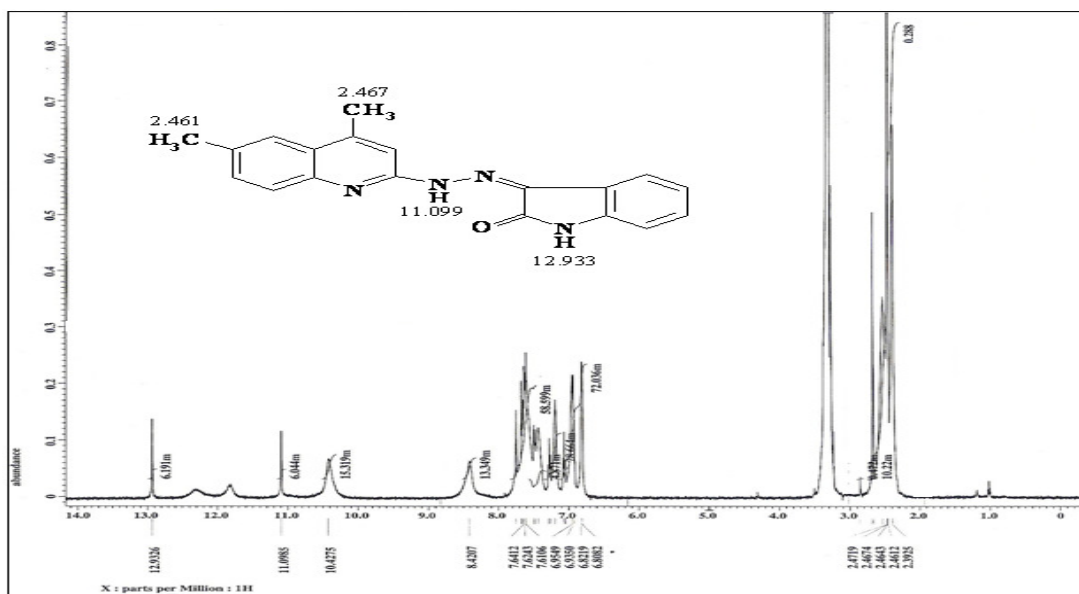


Figure-1

¹H NMR spectrum of the ligand (for aromatic protons $\delta = 6.81 - 7.75$)

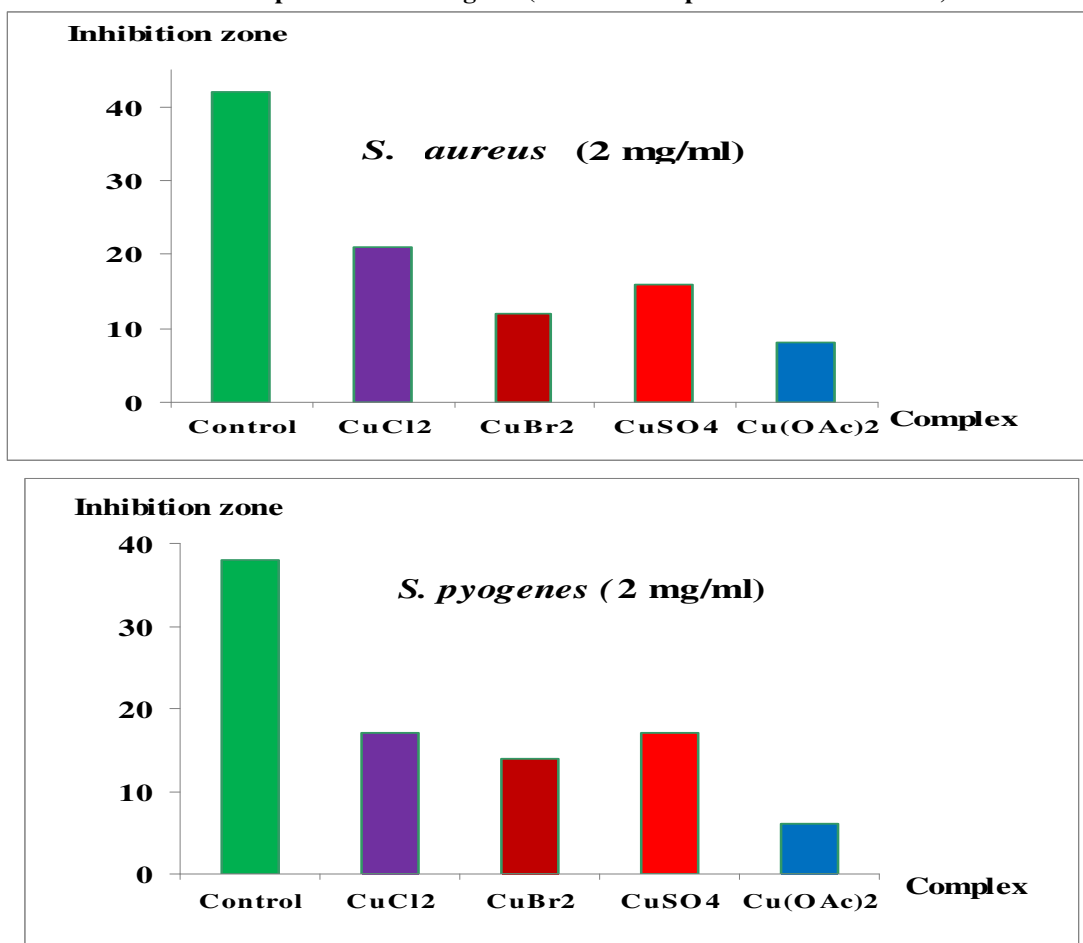


Figure-2

Biological activity of the isatinic complexes

Characterization of the complexes: For examining the role of the anions on the formed products, the ligand was allowed to react with several copper(II)- salts *viz.* Cl^- , Br^- , NO_3^- , SO_4^{2-} , ClO_4^- and AcO^- (scheme 2). The obtained copper(II)-complexes reflect the strong coordinating power of SO_4^{2-} , Cl^- , Br^- and NO_3^- as compared to the non coordinating power of ClO_4^- . This is consistent with the donor ability of the anions¹⁰; ($\text{DN}_x = 36.2, 33.7, 21.1$ and 8.44 for Cl^- , Br^- , NO_3^- and ClO_4^- , respectively). The isatinic hydrazone has mainly two tautomeric forms (scheme 1); the lactam- lactim forms are useful in explaining the different coordinating properties. The obtained complexes are mononuclear and heteroleptic. In complex 6, the acetate anion acts as a base enough to deprotonate the ligand. The obtained complexes have the octahedral (O_h), square pyramid and square planar (D_{4h}) geometries; (scheme 2). The isatinic hydrazone (H_2L) behaves as dianionic, monoanionic or neutral NNO- or NO- donor. Depending on the type of the anion, the ligand uses its lactam (SO_4^{2-} and ClO_4^-) or lactim forms (the others). In case of the NO_3^- anion, the ligand uses a mixed mode; lactam / lactim (complex 1). Characterization of the obtained complexes was achieved *via* elemental and thermal analyses, magnetic and conductivity measurements as well as spectral studies.

IR spectra of the complexes: The mode of bonding was studied by comparing the IR spectral bands of the metal complexes with those of the free ligand (table 2). Inspection of the data revealed the following: i. All complexes showed a broad band in the range $3342\text{--}3167\text{ cm}^{-1}$ due to $\nu(\text{OH})$ of the associated water or methanol molecules. ii. The band located at 1633 cm^{-1} assignable to the $\nu(\text{C}=\text{N})$ in the free hydrazone was shifted to lower values confirming its participation in the chelation. iii. For complexes (3, 4 and 6), the band located at 1683 cm^{-1} due to $\nu(\text{C}=\text{O})$ of the free ligand disappeared indicating the participation of the lactim- form in the chelation. In contrast, the lactam- form participates in the chelation in case of the nitrato (1), perchlorato (2) and sulfato (5) complexes as indicated by the shift of the above band to higher wave numbers; lactam- complexes indicate π - electron delocalization i.e. resonance stabilization in the formed chelate ring¹⁰ (table 2). iv. In complex 2, The ionic nature of the ClO_4^- anion is supported by the appearance of strong antisymmetric stretch band¹¹ at 1115 cm^{-1} ; $\nu(\text{Cl-O})$. This is consistent with the electrolytic nature of complex. v. For the sulfato complex (5), the chelating bidentate nature of the SO_4^{2-} group is indicated by the appearance of $\nu_3(\text{S-O})$ strong band at 1113 cm^{-1} characteristic for the high symmetry T_d (tetrahedral) point group. vi. The nitrato complex (1) showed a band at 1332 cm^{-1} confirming the monodentate nature of the coordinated NO_3^- group; C_{2v} symmetry¹¹.

Conductivity, magnetic properties and electronic spectra: The recorded conductance for 10^{-3} molar DMF solutions of the complexes indicates that all complexes are non- conducting due to their neutrality. The only exception is the perchlorato complex (2) which showed molar conductance of $173\text{ }\Omega^{-1}\text{ cm}^2$

mol^{-1} , indicating its 2:1 electrolytic nature which is consistent with the IR spectra; $\nu_3(\text{Cl-O})$ at 1115 cm^{-1} . On the other side, the effective magnetic moments (μ_{eff}) of the copper(II)-complexes (1-6) lie in the range $2.10\text{--}1.79\text{ B.M.}$ which is consistent with one unpaired electron and falls within the range reported for mononuclear copper(II)- complexes^{12,13}. On the other side, the electronic spectra of the complexes as DMF solutions showed a new intense broad band in the range $505\text{--}519\text{ nm}$ confirming its charge transfer (CT) nature. Therefore, the type of the d-d transitions cannot be identified due to the strong CT bands tailing from UV region to the visible region¹². In general, the color of all complexes is dominated by the CT transition which obscured the weak d-d transition occurring in the same region; a phenomenon encountered with isatinic complexes^{4,6}. Also, the electronic spectra of all complexes are nearly similar in terms of the position, intensity and shape of the bands.

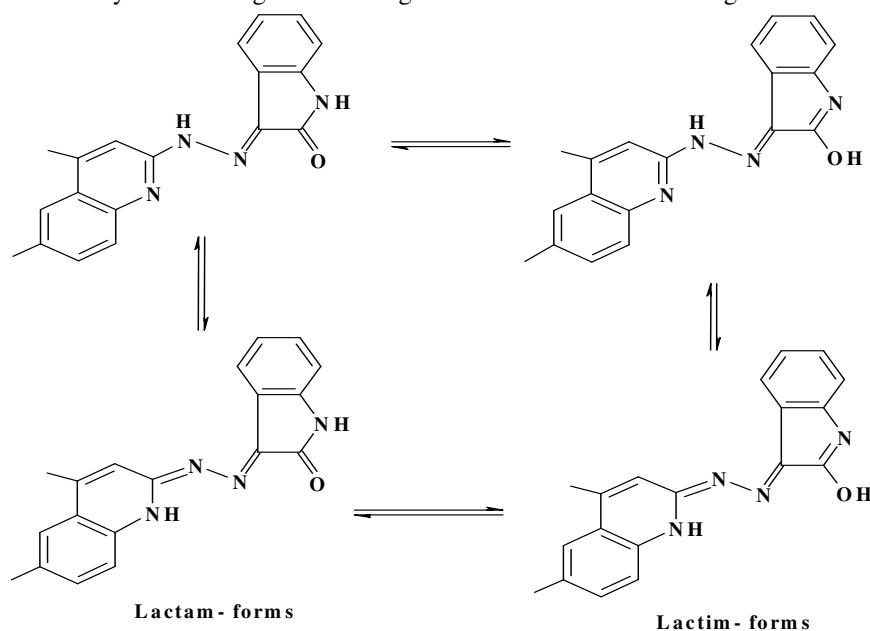
ESR Spectra: For obtaining further information about the stereochemistry and bonding of the complexes¹⁴, the room temperature ESR spectra of the powder solid complexes were recorded for complexes 4 and 5 as representative examples. The ESR spectra of the sulfato complex; $[\text{Cu}(\text{H}_2\text{L})(\text{SO}_4)(\text{OH}_2)_2] \cdot 4\text{H}_2\text{O}$ (5) showed two types of resonance components, one set is due to the parallel(\parallel) features and the other set due to perpendicular(\perp) features in consistency with axial symmetry supporting its octahedral geometry. Inspection of the data reveals that; $g_{\parallel} > g_{\perp} > 2.0023$, corresponding to the presence of the unpaired electron in the $d_{x^2-y^2}$ orbital. However, the unpaired electron is not located in the orbitals of identical composition due to the delocalization of the d- electron towards the ligand donor atoms. On the other hand, the complex; $[\text{Cu}(\text{HL})(\text{Br})] \cdot \text{MeOH}$ (4) showed a broad signal with $g_{\text{iso}} = 2.153$ suggesting its square planar geometry. The ESR spectral profiles reflect the non equivalence of the environment around copper(II)- ions.

Thermal analysis: The thermal degradation behavior of the investigated complexes (1, 2, 5, 6) was followed by the thermogravimetric (TG) technique. The decomposition occurs in several steps according to the nature of each complex. Attempts to generalize the thermal degradation patterns were unsuccessful indicating that there is no simple relation or general trend for explaining these thermal degradations. However, the decomposition ends with the formation of Cu_2O in case of complexes (1, 2). Inspection of the thermograms reveals the following: i. The thermogram of complex (2) showed a high degree of the thermal stability as indicated by its first step of decomposition. ii. For the complexes (5, 6), the decomposition is not completed up to 800°C , indicating strong metal - ligand bonds.

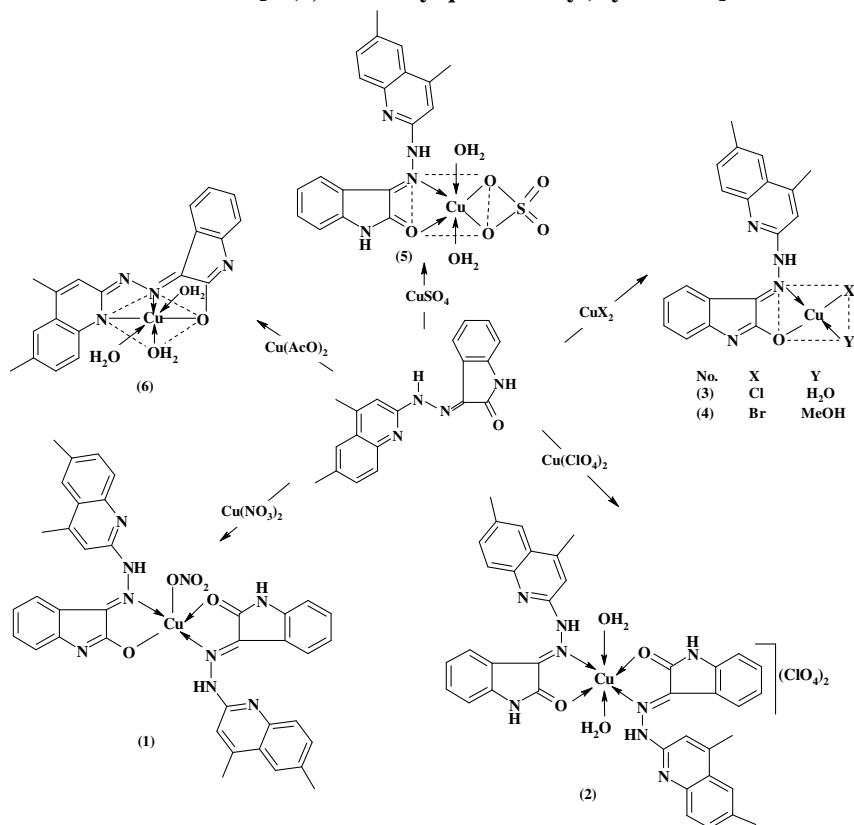
Antimicrobial activity: The antibacterial activity of the ligand and its metal complexes was summarized in table 3 and represented graphically in figure 2. Inspection of the data reveals the following: The ligand and its complexes 1 and 2

have no activity towards the studied organisms; Gram- positive bacteria (*S.aureus* and *S. pyogenes*) and Gram- negative bacteria (*P.phaseolicola* and *P.fluorescens*). For the copper(II)- isatinic complexes the antimicrobial activity shows a gradual change

with change of the coordinated anions^{4,6}. The order is as follows $\text{Cl}^- > \text{SO}_4^{2-} > \text{Br}^- > \text{nil}$. This order confirms that the nature of the coordinated anions plays a significant role on the inhibition of the bacteria growth.



Scheme-1
Tautomeric forms of 3-[2-(4,6-dimethylquinolin-2-yl)hydrazono] indolin-2-one



Scheme-2
Copper(II)- complexes of 3-[2-(4,6-dimethylquinolin-2-yl)hydrazono] indolin-2-one

Table-3
Antimicrobial activity of IsatinHQ and its complexes

Organisms	Mean* of zone diameter , nearest whole mm.							
	Gram - positive bacteria				Gram - negative bacteria			
	<i>S. aureus</i>		<i>S. pyogenes</i>		<i>P. Phaseolicola</i>		<i>P. fluorescens</i>	
Concn.	2 mg /ml	1mg /ml	2 mg /ml	1mg /ml	2 mg /ml	1mg /ml	2 mg /ml	1mg /ml
Complexes	2 mg /ml	1mg /ml	2 mg /ml	1mg /ml	2 mg /ml	1mg /ml	2 mg /ml	1mg /ml
IsatinHQ	—	—	—	—	—	—	—	—
[Cu (HL)(Cl)(H ₂ O)] ½H ₂ O ¼MeOH (3)	21	12	17	14	7	6	10	12
[Cu (HL)(Br)] MeOH (4)	12	7	14	11	6	6	8	5
[Cu (H ₂ L)(SO ₄)(OH ₂) ₂] 4 H ₂ O (5)	16	13	17	12	—	—	—	—
[Cu L (OH ₂) ₃] 5½H ₂ O .¼MeOH (6)	8	5	6	4	4	4	5	4
Control #	42	28	38	30	36	25	38	30

Conclusion

The ligational behavior of the isatinic hydrazone ligand as well as the geometry of the isolated complexes (O_h, D_{4h} and square pyramid) is highly affected by the type of the anion. Also, depending upon the type of the anion, the antimicrobial activity shows a gradual change with change of the coordinated anions^{4,6}.

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