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Research Article

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Antimicrobial Activity of Transition Metal Complexes Derived from Schiff Bases of Isatin and Aminophenols

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ABSTRACT

Co(II), Ni(II), Cu(II), and Zn(II) complexes has been prepared by the reaction of isatin with bromo and nitro derivative of aminophenol. The compounds were characterized by using various analytical techniques and spectroscopic studies like IR, UV-Vis, NMR and ESR which suggested octahedral type of geometry for the complexes. In this paper we have study the biological evaluation of these complexes. The compounds were screened for in vitro antimicrobial activity against gram positive bacteria viz Bacillus subtilis, Micrococcus luteus, gram negative bacteria- Pseudomonas aeruginosa, Pseudomonas mendocina and fungi Verticillum dahlia, Cladosporium herbarium, Trichophyton soudanense. The agar plate disc diffusion method was used for the evaluation of biological activity. The biological data revealed that transition metal complexes were more active than their Schiff base ligands.

Keywords: IR; NMR; Biological; Octahedral; Isatin

INTRODUCTION

Indole derivatives have acquired great significance due to their wide spectrum of biological and pharmacological profile. Isatin (1H-Indole-2,3-dione) is a indole derivative which bears a indole nucleus and keto group and lactum moieties [1,2]. Isatin pharmacophore is used to prepare large number of heterocyclic compound and is used as a starting material for synthesis of infinite drug molecules. Isatin is used as a color compound for proline (amino acid) which gives blue derivative and used for the estimation of amino acid in pollen grains and vegetables. Isatin moiety is used for the preparation of many biologically active compounds.

Schiff bases derived from isatin possess a large number of pharmacodynamics activities like antibacterial, antifungal, antiviral, anti-HIV, antileprosy, antileukemia, analgesic and antitumor activities due to its specific features. Research based on Schiff base metal complexes has vast interest in bioinorganic chemistry [3-14].

Encouraged by these findings, this manuscript has reported the antimicrobial activities of new Schiff base ligands derived from isatin and aminophenol and their cobalt, nickel, copper and zinc complexes.

EXPERIMENTAL

Material and Methods

All the chemicals used were of analytical grade obtained from Aldrich and used as such without any further purification. The CHN elemental analysis was performed using a Perkin–Elmer CHN 2400 elemental analyzer. 1H NMR and 13C NMR were recorded on Bruker Avance II 300 MHz NMR spectrometer and all chemical shifts were reported in parts per million relative to TMS as internal standard in CDCl3. IR spectra of compounds were recorded on Shimadzu IR affinity-I 8000 FT-IR spectrometer using KBr disc. UV spectra were recorded on UV-VIS-NIR

Varian Cary-5000 spectrometer in DMF. ESR spectra of Cu(II) complexes were carried on a Varian E 112 X-band spectrometer using tetracyanoethylene (TCNE) as the internal standard with g-value of 2.0023. Mass spectra were recorded on a API 2000 (Applied Biosystems) mass spectrometer equipped with an electro spray source and a Shimadzu Prominence LC. Molar conductance measurement of 1× 10-3 M solution in dry DMF at room temperature was carried out using a model-306-systronics conductivity bridge having cell constant equal to one.

Preparation of Schiff Bases and Transition Metal Complexes

Schiff base ligands were synthesized by the reaction of 2-aminophenol (10 mmol) with methanolic solution (10 mL) of isatin (10 mmol) with few drops of acetic acid in 1:1 molar ratio in methanolic solution. The resulting mixture was refluxed for 5 h and excess of solvent was evaporated and solid product was filtered, washed with methanol, recrystallized from methanol and dried. In the aqueous solution of hydrated metal salt, $M(NO_3)_2.xH2O$ (1mmol) added methanolic solution of Schiff base ligands (HLI-II) (1 mmol) and to this methanolic solution of 8-hydroxyquinoline (HQ) (1 mmol) was also added in 1:1:1 molar ratio with constant stirring. The mixture was refluxed for 4 h. Solid complex obtained after the evaporation of the solvent. Solid was filtered and washed with methanol to remove unreacted metal nitrates or ligands (Figure 1).

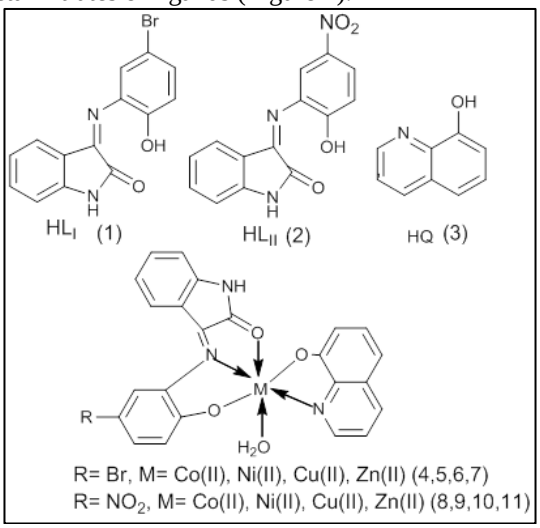

Figure 1: Structure of Schiff base ligands and transition metal complexes

BIOLOGICAL ACTIVITY

Tested Microorganisms

The Schiff bases and their transition metal complexes and standards were evaluated for antibacterial and antifungal activity against gram positive bacteria- Bacillus subtilis (MTCC No. 1790), Micrococcus luteus (MTCC No. 4821), gram negative bacteria- Pseudomonas aeruginosa (MTCC No. 9126), Pseudomonas mendocina (MTCC No. 7094) and fungi Verticillum dahlia (MTCC No. 2063), Cladosporium herbarium (MTCC No. 351), Trichophyton soudanense (MTCC No.7859). The bacteria and fungi were subcultured on Nutrient agar and Sabouraud dextrose agar and experimental values were compared with standard drugs Streptomycin for antibacterial activity and Fluconazole for antifungal activity.

Antibacterial Activity Assay

Antibacterial activity of samples (1-12) were determined by using agar well diffusion method and bacterial growth were subcultured on nutrient broth for their *in vitro* testing which were prepared by dissolving (24 g) of nutrient broth. The mixture was autoclaved for 15 minutes at 120°C. Stock solution for *in vitro* antibacterial activity was prepared by dissolving 5 mg of compound in 9 mL of DMSO to make the stock solution of 100 g/mL - 1.15 mL of liquid nutrient agar for activation were prepared separately for tested target microorganism cultures and 1 mL of nutrient broth for antibacterial activity. Inoculation was done with the help of micropipette with sterilized tips and 100 µL of activated strain was placed onto the surface of agar plate. It spread over the whole surface and then two wells having diameter of 10 mm were dug in media and incubated at 37°C for 48 h. Activity was determined by measuring the diameter of zone showing complete inhibition and has been expressed in mm.

Antifungal Activity Assay

For *in vitro* antifungal activity the moulds were grown on sabouraud dextrose agar (SDA) at 25°C for 7 days and determined by using agar well diffusion method and fungal growth were subcultured on nutrient broth for their *in vitro* testing. 15 mL of molten SDA (45°C) was added to 100 µL volume of each compound having concentration of 100 µg/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 centre with fungal plugs (10 mm) obtained from actively growing colony and incubated at 25°C for 7 days. Diameter of the fungal colonies was measured and expressed as percent mycelial inhibition:

Inhibition of mycelial growth %=(dc-dt)/dc × 100

dc=average diameter of fungal colony in negative control

dt=average diameter of fungal colony in experimental plates

RESULTS AND DISCUSSION

Schiff bases and their transition metal complexes (1-10) have been synthesized by using isatin and aminophenol derivatives and metal nitrates. These compounds were characterized by using spectroscopic techniques (IR, UV, NMR, ESR) and analytical techniques. The spectroscopic data revealed that compounds formed are hexa-coordinated with donation of azomethine nitrogen, isatin carbonyl group and hydroxyl oxygen of aminophenol. 8-hydroxyquinoline was also added to the reaction mixture with metal nitrate and it act as bidentate ligand to form mixed ligand complexes.

In this manuscript the synthesized compounds were evaluated for antimicrobial activity and conclusions obtained are summarized in Tables 1 and 2 and graphical representations are shown in Figures 2 and 3.

Table 1: The *in vitro* antibacterial activity of Isatinimine Schiff base ligands, 8-hydroxyquinoline and their transition metal (Ii) complexes

S. No	Compounds	Zone of Inhibition (mm)															
		Gram +ve								Gram -ve							
		B. subtilis				*M. Luteus*				*P. aeruginosa*				*P. mendocina*			
		25	50	100	200	25	50	100	200	25	50	100	200	25	50	100	200
1	HLI	11	13	14	15	12	14	14	16	11	12	12	15	10	12	14	16
2	HLII	10	11	14	14	11	12	14	15	10	12	12	13	10	12	12	14
3	HQ	8	8	10	11	9	10	10	11	8	9	10	10	8	10	10	11
4	Co(LI)(Q)H_2O	12	14	15	18	11	14	16	17	15	16	17	19	13	14	15	18
5	Ni(LI) (Q)H_2O	13	16	16	19	13	17	17	20	15	15	18	21	15	16	16	19
6	Cu(LI)(Q)H_2O	15	19	19	21	16	19	20	23	17	19	22	25	16	18	20	21
7	Zn(LI)(Q)H_2O	11	14	14	17	12	14	16	17	12	15	15	17	11	14	14	17
8	Co(LII)(Q)H_2O	13	15	15	18	14	14	16	18	13	16	16	18	15	15	16	18
9	Ni(LII) (Q)H_2O	14	16	17	19	13	14	14	18	14	17	17	20	15	18	19	20
10	Cu(LII)(Q)H_2O	14	18	18	21	16	18	18	20	16	19	21	22	16	19	19	23
11	Zn(LII)(Q)H_2O	12	14	15	18	13	13	15	16	11	14	14	16	12	14	14	16
12	Streptomycin	19	21	25	26	19	20	23	25	20	23	25	28	22	25	27	30

Table 2: The *in vitro* antifungal activity of Isatinimine Schiff base ligands, 8-hydroxyquinoline and their transition metal (II) complexes

S. No	Compounds	Mycelial Growth Inhibition (%)											
		V. dahlia				*C. herbarium*				*T. soudanense*			
		25	50	100	200	25	50	100	200	25	50	100	200
1	HLI	48.2	49.4	50.3	52.4	49.4	49.9	50.2	51.4	47.3	47.8	48.5	49.3
2	HLII	46.4	48.2	50.4	52.8	48.3	48.8	49.2	49.9	46.3	47.4	48.2	48.8
3	HQ	42.3	44.8	46.4	48.9	42.3	44.1	45.2	46.8	41.2	41.9	42.3	43.7
4	Co(LI)(Q)H_2O	55.4	56.8	57.5	58.2	59.9	60.8	61.5	63.4	54.5	55.4	57.1	58.9
5	Ni(LI) (Q)H_2O	56.4	56.9	57.4	58.7	57.8	57.9	58.4	59.2	55.9	56.2	57.4	58.3
6	Cu(LI)(Q)H_2O	58.4	59.9	60.2	62.4	59.2	59.9	60.4	62.2	57.4	57.9	58.4	59.9
7	Zn(LI)(Q)H_2O	54.2	55.4	56.3	57.6	56.3	56.8	57.2	59.4	56.2	56.9	58.1	58.9
8	Co(LII)(Q)H_2O	54.2	56.3	57.4	58.9	56.4	57.2	58.3	59.8	55.4	56.3	57.6	58.4
9	Ni(LII) (Q)H_2O	54.3	56.4	57.8	59.4	55.9	57.1	57.9	59.4	55.2	55.8	57.4	59.2
10	Cu(LII)(Q)H_2O	56.3	58.3	59.4	62.2	58.2	58.8	59.4	60.4	56.2	57.6	58.9	59.4
11	Zn(LII)(Q)H_2O	52.5	54.3	55.3	56.7	53.2	55.4	55.9	57.3	52.2	53.8	54.2	55.8
12	Fluconazole	76.2	79.4	79.8	81.2	75.8	77.2	78.3	81.9	74.1	76.4	79.6	83.3

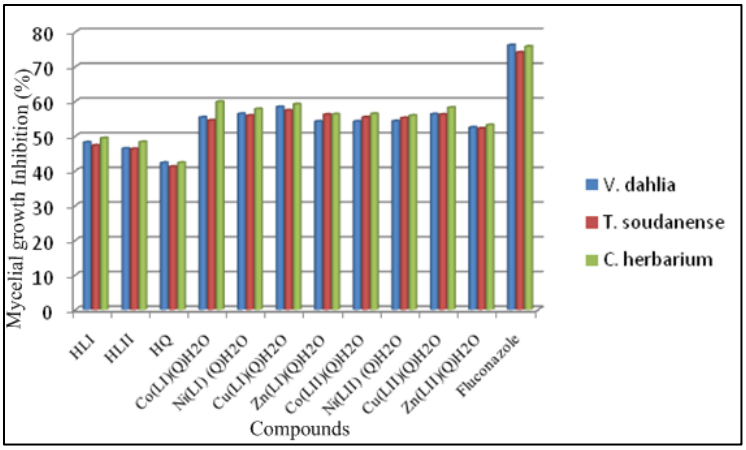

Figure 2: Graphical representation of antifungal data for compounds 1-12

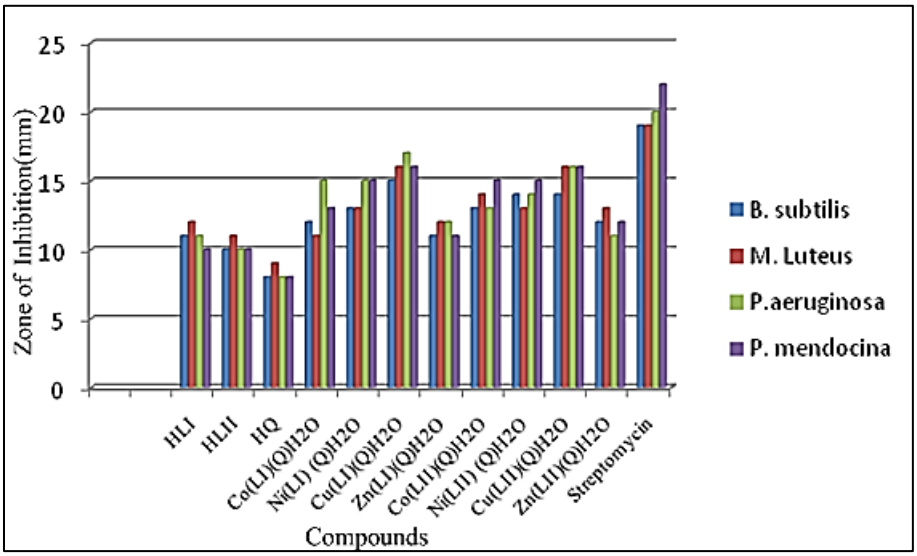

Figure 3: Graphical representation of antibacterial data for compounds 1-12

Antimicrobial data showed that the synthesized compounds were found to be highly potent against fungal strains as compared to bacterial strains. Ligands HL (I-II) and HQ were found to be less active than their respective transition metal (II) complexes and showed zone of inhibition for antibacterial activity in range of 8-16 mm, with complexation it increased in range of 11-25 mm. All the ligands showed mycelial growth inhibition in the range of 42.3-52.8% and it increased in the range of 50.2-63.4% in case of complexes. Among Schiff bases, the order of reactivity of ligands were HLII>HLI>HQ. Ligand with nitro group is more active than the bromo group.

Among all the complexes Cu(II) and Ni(II) complexes were greatly active against bacterial and fungal strains. Zone of inhibition against all strains follows the order: Cu(II)>Ni(II)>Co(II)>Zn(II)>HLI-II>HQ.

The increase in biological activity on complexation is explained on basis of Tweedy chelation theory. According to this theory, metal chelates display both polar and non-polar properties which make them suitable for permeation into cells and tissues and the normal cell process may be affected by the formation of hydrogen bond through the donor atoms with the active centres of cell constituents. The polarity of metal ion gets reduced due to overlap of ligand orbitals when chelated, chelation increases the delocalization of pi-electrons over the entire chelate ring and enchance the penetration of the complexes into lipid membranes. It increases the hydrophilic and lipophilic nature of the cental metal ions, leading to liposolubility and permeability through the lipid layer of cell membranes.

Complex Cu(LI)(Q)H_2O and Cu(LII)(Q)H_2O with 62.4% and 62.2% mycelia growth is found to be most effective antimicrobial agent in the whole series and can be used in pharmaceutical industry for mankind after testing its toxicity to human beings.

CONCLUSION

Compound 1-11 have been synthesized and characterized by analytical and spectroscopic techniques. All synthesized compounds showed potential antimicrobial activities against tested bacteria and fungi. The antimicrobial data revealed that metal complexes exhibit more antimicrobial activities than the free ligand. Ligands having nitro group shows better activity than ligand having bromo group. So these compounds can be used as a good pharmacophore for the synthesis of antimicrobial drugs.

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