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Novel Synthesis, And Biological Evaluation of Four Co-Ordinate Co (Ii)-Complexes Derived From 5-Amino 2(4'thiazolyl)[1]hbezimidazole (ATBZ) And Heterocyclic Bases

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ABSTRACT: Four coordinate Co (II) adducts were synthesized by the reaction of $CoCl_2.6H_2O$ with and 5-aminothiabendazole as chelate ligand in ethanol and heterocyclic bases in the ratio 1:1:1. The synthesized compound ATBZ was elucidated by elemental analysis, ^{13}C, ^{1}H NMR. The synthesized adducts were characterized by elemental analysis, magnetic measurements, conductivity measurements. Screenings of antimicrobial activity of prepared metal complexes were also carried out against different bacterial species such as *Pseudomonas putida*, *Escherichia coli*, and fungal species such as *Aspergillus Nigar*, *Candida Albicans*, Yields of the synthesized compounds were found moderate and some of them also indicated potent activity against bacterial and fungal species.

KEYWORDS: 5-aminothiabendazole, $CoCl_2.6H_2O$, antimicrobial assay.

I. INTRODUCTION

Sulfur and/or nitrogen heterocycles have acquired a great importance among the heterocycles, as these possess pharmaceutical activities and pest management potency. These widely occur in the nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. The utility of thiazoles in curative treatment has been firmly established. They exhibit anti-bacterial, anti-hypertensive, anti-anginal, anti-arrhythmetic, anti-histaminic, narcotic antagonist activities [1]. Thiazole nucleus is found in many antibiotics and vitamins in one or another form.The benzimidazole compounds have been proved to be the most important group of fungicides with systemic activity and are well known for their pronounced ability to control a large number of fungal diseases. Benomyl, thiabendazole and thiophanate methyl are main examples of this fungicide class. Because of their systematic activity, they can help to control some diseases after infection. Benzimidazole fungicides are also used to prevent post-harvest rots and in soil-drench treatments [2].

The 2-(4-thiazolyl)-*1H*-benzimidazoles are structurally analogous to benzimidazoles, well known as an anthelminitic agent and systemic fungicide. Its fungicidal properties and systemic properties in plants have already been reported as a fungicide with protective and curative action. It is used to control of *Aspergillus, Botrytis, Ceratocystis, Cercospora, Colletotrichum, Corticium, Diaporthe, Diplodia, Fusarium,* Gibberella, *Gloeosporium, Oospora, Penicillium, Phoma, Rhizoctonia, Sclerotinia, Septoria, Thielaviopsis, Verticillium spp., etc.[3]* in asparagus, avocados, bananas, barley, beans, cabbage, celery, chicory, cherries, citrus, cotton, some cucurbits, flax, mangoes, mushrooms, oats, onions, ornamentals, pawpaws, pome fruit, potatoes, rice, soyabeans, strawberries, sugar beet, sweet potatoes, tobacco, tomatoes, turf, vines and wheat. Also used for control of storage diseases of fruits and vegetables and for control of Dutch elm disease. It is commonly used as an anthelminitic in human and veterinary medicine too[4]. Again thiabendazole has significant anthelmentic activity for gastrointestinal parasites in sheep, goats, cattle, horses, swine, dogs, and poultry. This compound is well-tolerated and does not stain the skin, hair or wool of animals. It may be given orally for therapeutic use or in feed or mineral supplements for the prophylactic control of parasites in domestic animals.

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Benzimidazole and thiazole analogues have found applications in medicine and agriculture[5]. Therefore development of a simple, fast and flexible method to generate libraries of such compounds was desirable. The structural modification or derivatization and bioassay are highly essential to establish structure-activity relationships in order to exploit the molecules having better potency and efficacy. In continuation of our work on synthesis of biologically active compound using polymer-supported reactions, we report herein a simple, rapid and safer method for the preparation of N-alkyl and N-acyl derivatives of 2-(4-thiazolyl)-*1H*-benzimidazole. Easy separation of products with higher yield and purity by simple work-up, and speed are crucial features of the method. The metal complexes of thiabendazole structure, antimicrobial activity and photodynamic effects has been done [6].

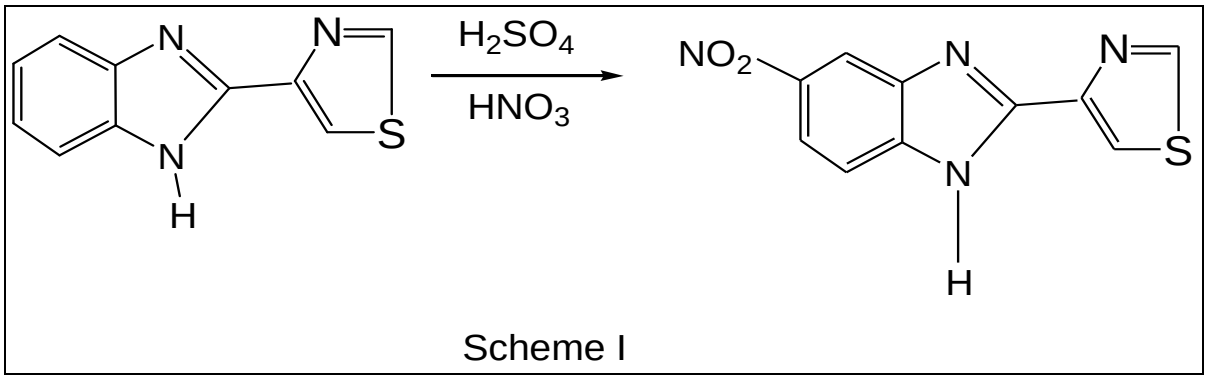
5-Aminothiabendazole (ANTBZ) acts as both acid and base, thus it is possible to make compounds which are neutral, cationic or anionic in nature, as well as report biological activity of metal complexes. The potential N, N'-donor chelating agent are quite rare. In present paper we report synthesis and characterization of derivatives of 5-Aminothiabendazole, and differentiate fungi toxic activity with those of nitrothiabendazole. Nitrogen heterocycles have acquired an immense importance among the heterocycles, possessing pharmaceutical activities and widely occur in the nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. The utility of thiazoles in curative treatment has been firmly established. They exhibit anti-bacterial, anti-hypertensive, anti-anginal, anti-arrhythmetic, anti-histaminic, narcotic antagonist, etc. activities. Thiazole nucleus is found in many antibiotics and vitamins in one or another form. Benzimidazole and many of its derivatives exhibit a variety of biological actions, including antibacterial, antiviral, anticancer and antifungal activity [**7**]. Benomyl, thiabendazole and thiophnate methyl are main examples of this fungicide class. Because of their systematic activity, they can help to control some diseases after infection. In present work 5-Aminothiabendazole,is selected as chelte ligand because of structural similarity to chelating agents such as 2,2' bipyridine and 1,10 phenanthroline.

II. MATERIALS AND METHODS

Thiabendazole (A.R.Grade), Cobalt Chloride (A.R.Grade), zinc dust, methanol, formic acid, chloroform, sodium bicarbonate, super saturated solution of NaCl (A.R.Grade).

Synthesis of Thiabendazole to 5-Nitrothiabendazole

Ice cold conc.H_2SO_4 was added to thiabendazole with constant stirring .The reaction mixture was warmed at 50º C for 10 min. till thiabendazole dissolved completely. In ice bath below - 4º C. Nitrating mixture (ice cold 1.5 ml conc.H_2SO_4 and 10.2 ml of conc. HNO_3) was added with constant stirring. After complete addition the reaction mixture was kept aside for 45 min (i.e. at R.T.25º C). The reaction mixture was then warmed at 85-90º C for 90 min. The reaction mixture was then cooled at room temperature. Crushed ice was then added with constant stirring, very faint yellowish white precipitate was then separated out. Sodium bicarbonate was then added to it till the effervesces of CO_2 completely stopped and precipitate became neutral. The precipitate was then filtered off, washed with water and finally with diethyl ether and dried under IR lamp.



Scheme I

Synthesis of 5-Nitrothiabendazole To 5-Aminothiabendazole

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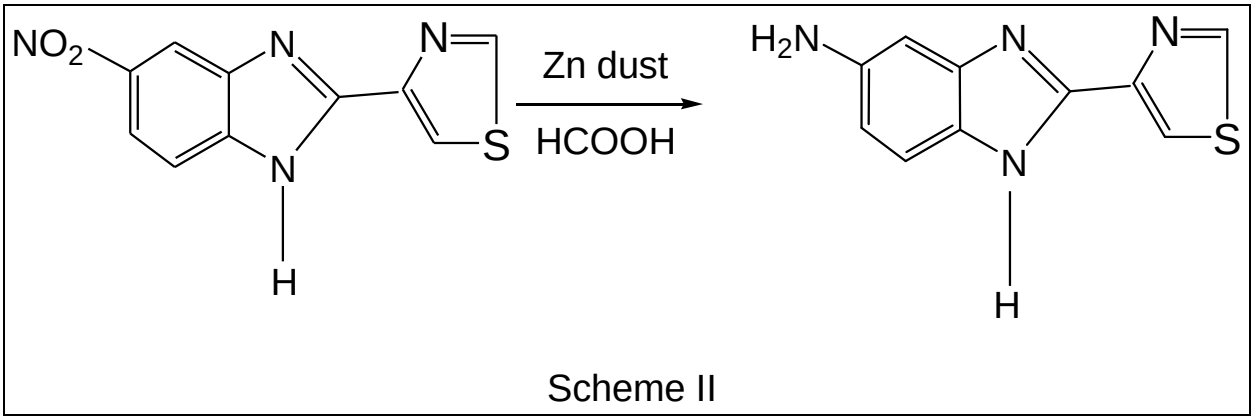
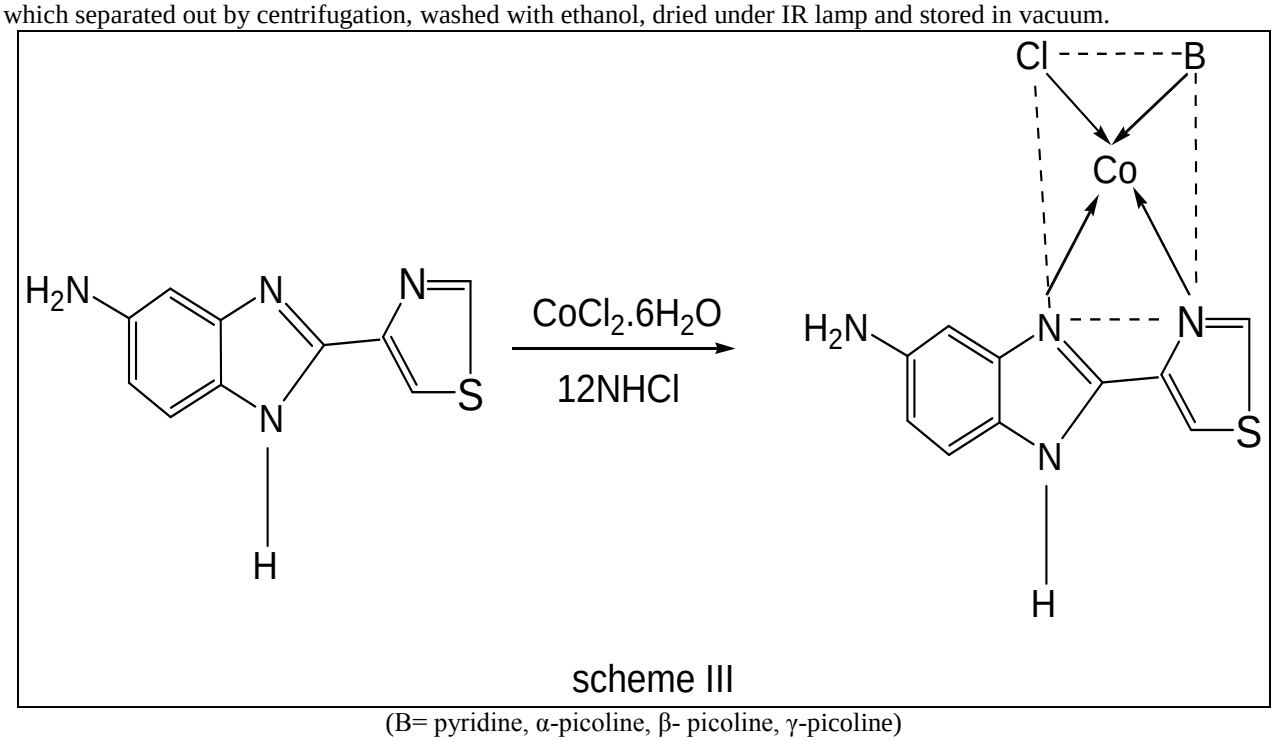
Methanol was added to homogeneous mixture of nitro thiabendazole and Zn dust. Formic acid was then added slowly with constant stirring. The solution was filtered. The filtrate was then warmed to evaporate the organic solvent completely. Few drops of chloroform and hot supersaturated solution of NaCl were added to remove the formic acid completely. Sticky residue formed washed to convert to the powdered residue, filtered, dried under IR lamp and stored in vacuum.



Scheme II

Synthesis of adducts:

This adduct of the type Cu.L.B (where B is heterocyclic bases pyridine,α-picoline,β- picoline,γ-picoline)was prepared by mixing 5-Amino TBZ in 40 ml of boiling ethanol containing 0.27ml of 12N HCl, cobalt chloride and heterocyclic bases in the ratio 1:1:1 in ~25 ml of ethanol. The mix was refluxed for 2 hrs on a steam bath. The greenish complex which separated out by centrifugation, washed with ethanol, dried under IR lamp and stored in vacuum.



scheme III

(B= pyridine, α-picoline, β- picoline, γ-picoline)

The ^{1}H-NMR signals at 4.2 δ-ppm corresponds to-NH_2, at 8.00 δ-ppm corresponds to N=C-H ,at 7.20 δ ppm corresponds to C=C-H-S,at 5.2 δ-ppm corresponds to N-H.The aromatic protons show multipletes at 6.4,6.8,7.40 δ-

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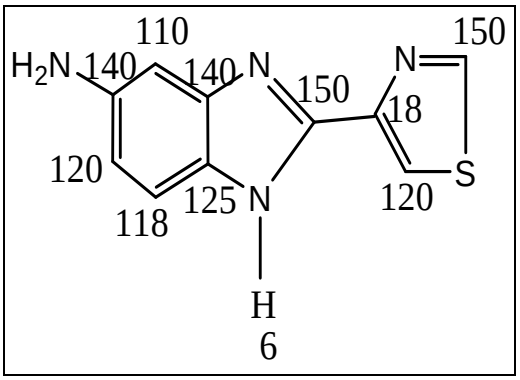
ppm.13C-NMR (DMSO-D6):δ-ppm 110 (C=C),140 (C=C),120 (C=C),118 (C=C),125 (C=C),140 (C=C),150 (N=C),150 (N=C),18 (C=C),120 (C=C).6 (N-H).



ESI-MS m/z for ligand (L) 216.58 (216.25) , ESI-MS m/z for Co.L.Cl.py 389.25 (388.86),ESI-MS m/z for Co.L.Cl.α-pico 404.10 (403.75),ESI-MS m/z for Co.L.Cl.β-pico 404.60 (403.75),ESI-MS m/z for Co.L.Cl.γ-pico 403.35 (403.75).Mass spectral data confirmed the structures of ligand and adducts as indicated by molecular ion peak (M+1) corresponding to their molecular weights.

Table I Physical properties:

Compounds	% yield	Empirical Formula	Molar conductance Ohm^{-1}cm^{2}mole^{-1}	Magnetic Moment B.M.	Elemental Analysis Found (Calculated) %				
					Metal%	%C	%H	%N	%S
L	80.2	$C_{10}H_8N_4S$	-	-	-	55.71 (55.54)	3.21 (3.73)	25.27 25.91)	14.30 (14.30)
Co.L..Cl.Py	82.3	$C_{15}H_{13}N_5SCoClpy$	90.2	2.63	15.70 (15.15)	45.87 (46.32)	3.47 (3.37)	17.14 (18.00)	8.41 (8.24)
CoL.Cl.α-Pico	88.4	$C_{16}H_{15}N_5SCoClα$-pico	96.2	2.65	15.22 (14.60)	47.90 (47.56)	3.14 (3.74)	17.85 (17.35)	7.11 (7.94)
Co.L.Cl.β-Pico	85.2	$C_{16}H_{15}N_5SCoClβ$-pico	50.0	2.67	15.10 (14.60)	47.85 (47.56)	3.25 (3.74)	17.94 (17.35)	7.07 (7.94)
Co.L..Cl.γ-Pico	87.6	$C_{16}H_{15}N_5SCoClγ$-pico	30.2	2.69	15.18 (14.60)	47.31 (47.56)	3.94 (3.74)	17.71 (17.35)	7.64 (7.94)

Elemental analysis, % yield, magnetic moment molar conductance and other physical properties are presented in Table I. Elemental analysis data showed 1:1:1 ratio for metal ion, ligand and heterocyclic base for all adducts. The compounds are insoluble in polar and non polar solvents and soluble in DMF in which conductivity measurement was carried out. The conductivity data indicate all compounds are non electrolyte [8]. The magnetic moment measurement was carried out at room temperature in polycrystalline state by Faraday method. The magnetic susceptibility falls in the range 2.6 - 2.7 B.M. for square planer complexes CoL.Clpy, CoLα-pico, CoLβ-pico, CoL.γ -pico [9].

III. ANTIMICROBIAL ASSAY

The antimicrobial activity was carried out by agar well diffusion method. The well was dug in the media with a sterile borer and eight-hour bacterial inoculums containing ca. 104 - 106 colony-forming units (CFU)/ml was spread on the surface of the nutrient agar using a sterile cotton swab. The concentration of the best sample (2 mg/ml in

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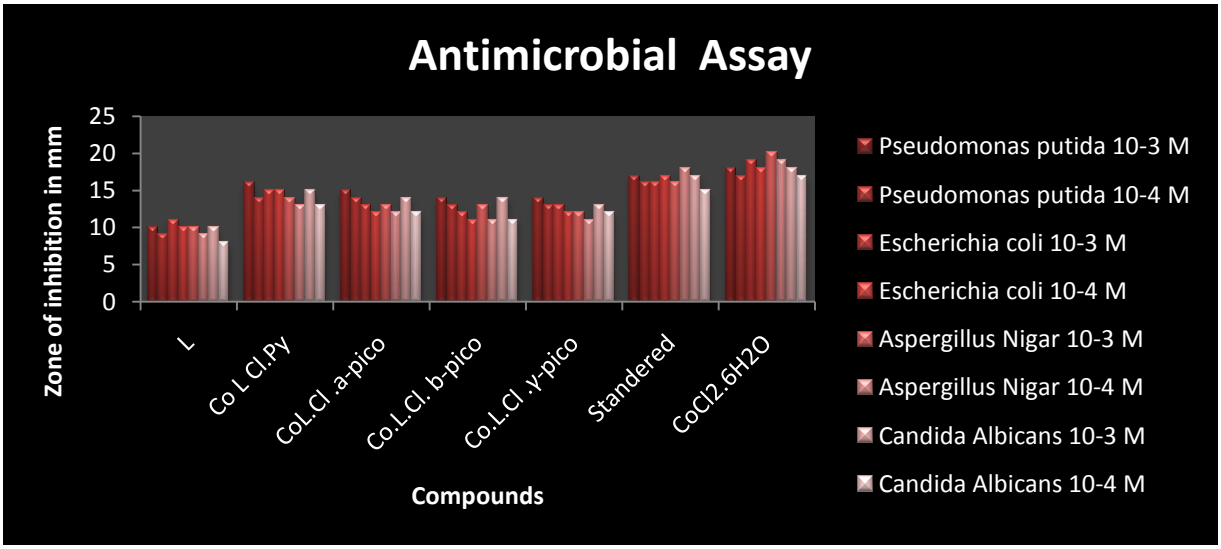
DMSO) was introduced into respective wells. Other wells containing DMSO and the reference antibacterial drug served as negative and positive controls, respectively. The plates were incubated immediately at 38°C for 21 h. The activity was confirmed by measuring the diameter of the inhibition zone (in mm) showing by the hanging drop method. Activity was measured in two different molar concentrations (10^{-3}M, 10^{-4} M). The results of antibacterial and antifungal studies are given in Table II and III.

Table II Antimicrobial Assay of L, Co (II) adducts

Compound	Pseudomonas putida		Escherichia coli		Aspergillus Nigar		Candida Albicans	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
L	10	9	11	10	10	9	10	8
Co L Cl.Py	16	14	15	15	14	13	15	13
CoL.Cl .α-pico	15	14	13	12	13	12	14	12
Co.L.Cl. β-pico	14	13	12	11	13	11	14	11
Co.L.Cl .γ-pico	14	13	13	12	12	11	13	12
Standered	17	16	16	17	16	18	17	15
$CoCl_2.6H_2O$	18	17	19	18	20	19	18	17

(Zone in mm)

Fig II Antimicrobial Assay Bar Graph



% activity index was calculated by the formula

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$$\% \text{ Activity Index} = \frac{\text{Zone of inhibition of test compound}}{\text{Zone of inhibition of standard (diameter)}} x\,100$$

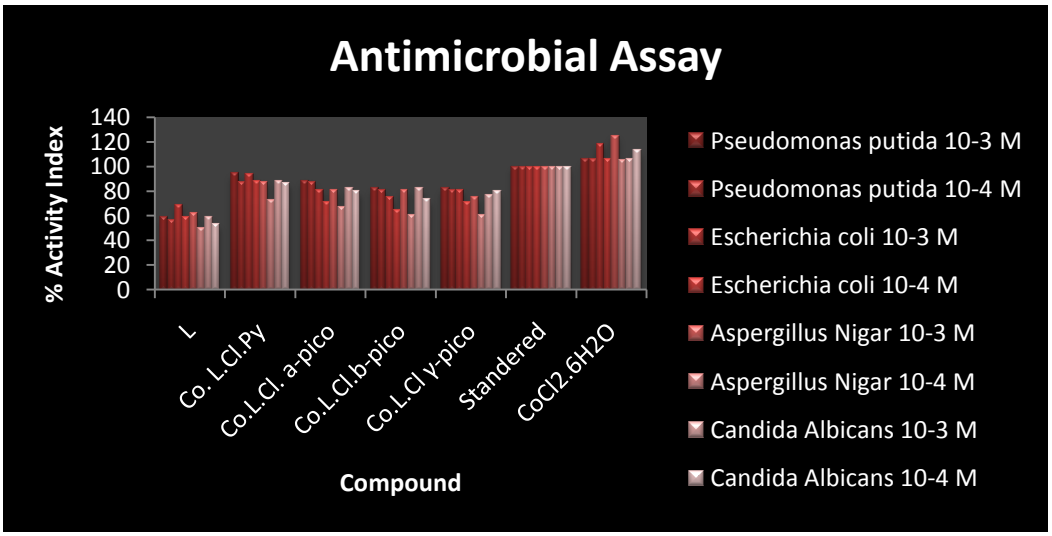
Table III

% Activity index of L, Co (II) complexes and standard

Compound % Activity Index	Pseudomonas putida		Escherichia coli		Aspergillus Nigar		Candida Albicans	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
L	58.82	56.25	68.75	58.82	62.5	50	58.82	53.33
Co. L.Cl.Py	94.11	87.50	93.75	88.24	87.50	72.22	88.24	86.67
Co.L.Cl. α-pico	88.24	87.50	81.25	70.59	81.25	66.67	82.35	80
Co.L.Cl.β-pico	82.35	81.25	75.00	64.71	81.25	61.11	82.35	73.33
Co.L.Cl γ-pico	82.35	81.25	81.25	70.59	75.00	61.11	76.47	80.00
Standered	100	100	100	100	100	100	100	100
$CoCl_2.6H_2O$	105.88	106.25	118.75	105.88	125.00	105.56	105.88	113.33

(Std-amphiciline,bicip)

Figure III: % Activity Index Bar Graph



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The chelate Co.L.Cl py showed maximum activity against bacterial and fungal species than free ligand Thus the coordination of metal ion to ligand is responsible for high biological activity. It has been observed that the % activity index decreases on dilution i.e. it is more in concentrated solution.The most probable reason for this difference might be due to chelation which reduces the polarity of the central metal atom because of the partial sharing of its positive charge with donor groups and possible π-electron delocalization within the whole chelating ring. As a result of this, the lipophilic nature of the central metal atom increases, which favors the permeation of the complexes through the lipid layer of the cell membrane [10].

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