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Novel Synthesis, Spectral and Biological Evaluation of Four Co-Ordinate Cu (Ii)-Complexes Derived From5-Amino 2(4'thiazolyl) ^{1}hbezimidazole (ATBZ) and Heterocyclic Bases

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ABSTRACT: Four coordinate Cu (II)-complexes were synthesized by the reaction of $CuCl_2.4H_2O$ with and 5-aminothiabendazole as chelate ligand in ethanol. The synthesized compound ATBZ was elucidated by elemental analysis, IR, NMR. Screenings of antimicrobial activity of prepared metal complexes were also carried out against different bacteria such as *Bacillus substilis, Staphylococcus aureus, pseudomonas aerogenish, proteus vulgaris, Escerchia coli.* Yields of the synthesized metal complexes were found to be moderate and some of them also indicate potent activity bacterial species.

KEYWORDS: 5-aminothiabendazole, $CuCl_2.4H_2O$, 5-thiabendazole.$6H_2O$, antimicrobial assay.

I .INTRODUCTION

Copper is one of the most abundant element in the earth's crust. lt occurs to the extent of 68 ppm by weight. The metal is used in the electrical industry because of its high conductivity. It is also used for waterpipes because of its inertness. The common oxidation states of copper are I (dm), II (d9), and lll (ds). The most common oxidation state of Cu is (ll), and Cu(Il) complexes have been extensively studied. These complexes havetetrahedral, octahedral, square planar and trigonal bipyramidal geometries [1]. Due to the presence of unpaired electron, all the copper(lI) complexes are paramagnetic.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 [2]. 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 [3].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.*[4] in asparagus, avocados, bananas, barley, beans, cabbage, celery, chicory, cherries, citrus, cotton, some cucurbits, flax, mangoes, mushrooms, oats, onions, ornamentals, papaws, pome fruit, potatoes, rice, soya beans, 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 [5]. Again thiabendazole has significant anthelmentic activity for gastrointestinal

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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. Benzimidazole and thiazole analogues have found applications in medicine and agriculture [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.

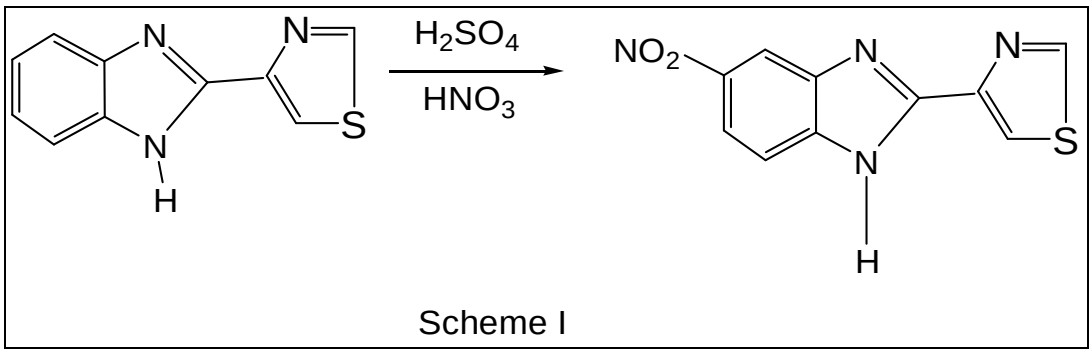
In present work 5-Aminothiabendazole,is selected as chelte ligand because of structural similarity to chelating agents such as 2,2' bipyridine and 1,10 phenanthroline.

II .MATERIALS AND METHODS

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

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 till the effervescences 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

5-Nitrothiabendazole To 5-Aminothiabendazole

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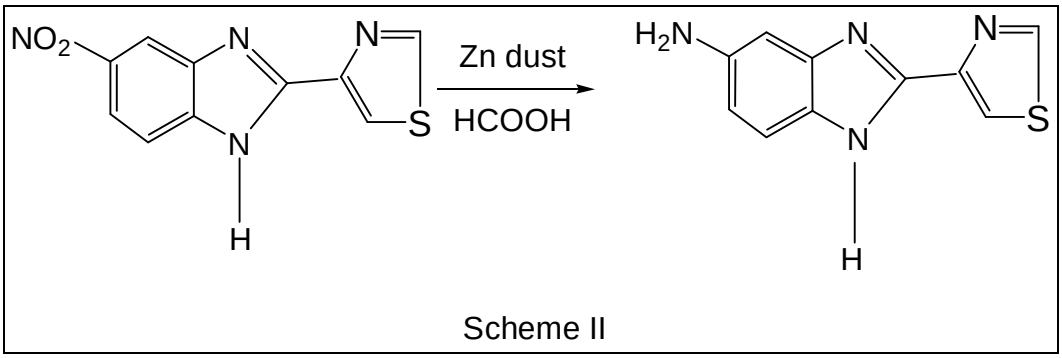
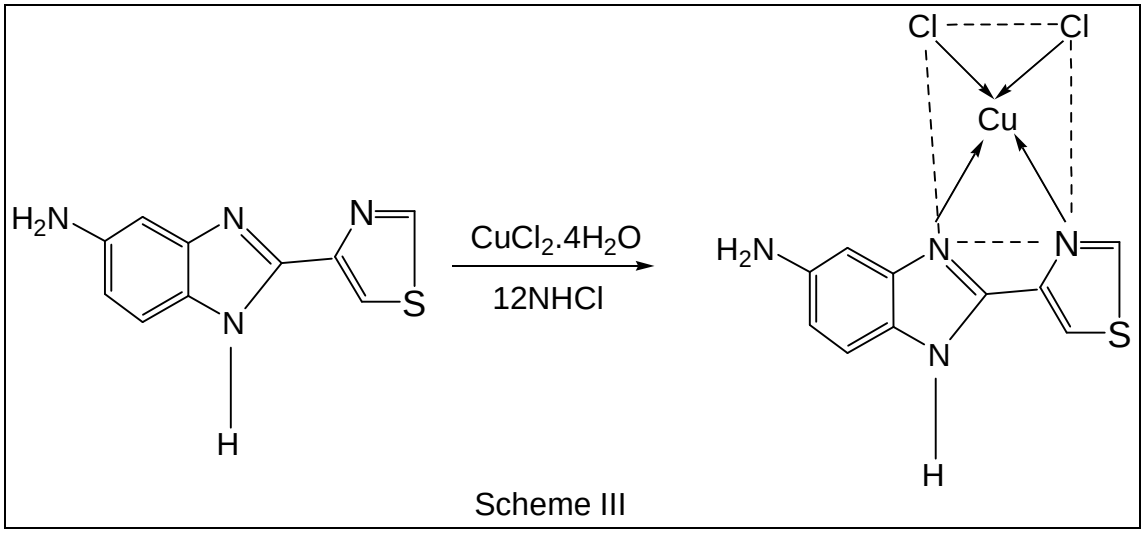
Methanol was added to homogeneous mixture of nitrothiabendazole and Zn dust. Formic acidwas then added slowly with constant stirring. The solution was then filtered. The filtrate was then warmed to evaporate the organic solvent completely. Few drops of chloroform and hot supersaturated solution of NaCl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



Scheme II

Synthesis of Cu (II) Complex:

This compound was prepared by dissolving 1gm of 5-Amino TBZ in 40 ml of boiling ethanol containing .0.27ml of 12N HCl. To this 0.50 gm of a copper chloride in ~25 ml of ethanol was added. 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

Synthesis of adduct:

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, copper 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.

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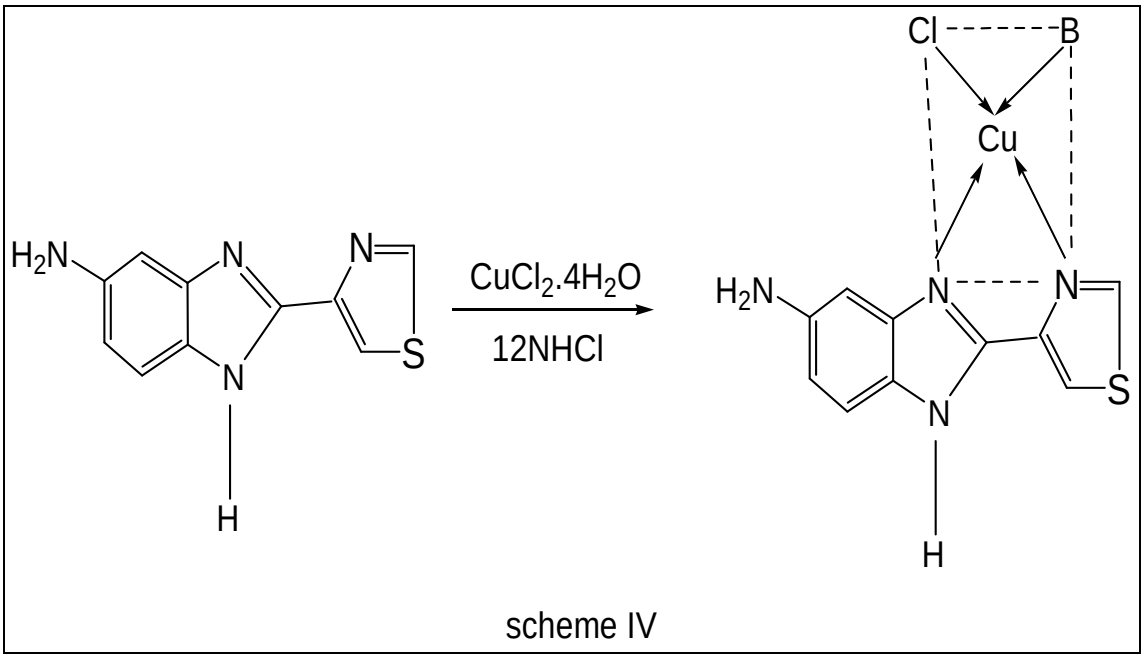
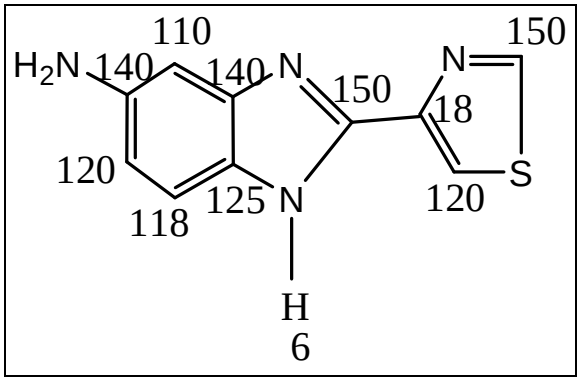


scheme IV

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

. The 1H-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-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 $Cu.L.Cl_2$ 350.10 (350.69),ESI-MS m/z for Cu.L.Cl.py 394.74 (394.34),ESI-MS m/z for Cu.L.Cl.α-pico 408.94 (408.36),ESI-MS m/z for Cu.L.Cl.β-pico 408.64 (408.36),ESI-MS m/z for Cu.L.Cl.γ-pico 408.86 (408.36).Mass spectral data confirmed the structures of ligand, complex and adducts as indicated by molecular ion peak (M+1) corresponding to their molecular weights.

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Table I Physical properties:

Compounds	% yield	Empirical Formula	Molar conductance $Ohm^{-1}cm^2mole^{-1}$	Magnetic Moment B.M.
L	80.2	$C_{10}H_8N_4S$	-	-
Cu-L.Cl_2	78.1	$C_{10}H_8N_4SCuCl_2$	80.2	1.83
Cu-L.Cl.Py	82.3	$C_{15}H_{13}N_5SCuClpy$	90.2	1.89
Cu L.Cl.α-Pico	88.4	$C_{16}H_{15}N_5SCuCl$α-pico	96.2	1.85
CuL.Cl.β-Pico	85.2	$C_{16}H_{15}N_5SCuCl$β-pico	50.0	1.84
CuL.γ-Pico	87.6	$C_{16}H_{15}N_5SCuCl$γ-pico	30.2	1.84

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. The magnetic moment measurement was carried out at room temperature in polycrystalline state by Faraday method fall in the range 1.80-1.90 B.M. These are close to the spin only value of 1.73 B.M. for d^9 case

Table II Analytical data:

Compounds	Elemental Analysis Found (Calculated) %				
	Metal%	%C	%H	%N	%S
L	-	55.71 (55.54)	3.21 (3.73)	25.27 25.91)	14.30 (14.30)
Cu-L.Cl_2	17.94 (18.12)	34.61 (34.25)	2.67 (2.30)	15.52 (15.98)	9.36 (9.14)
Cu-L.Cl.Py	15.70 (16.11)	45.87 (45.68)	3.47 (3.32)	17.14 (17.76)	8.41 (8.13)
CuL.Cl.α-Pico	15.94 (15.56)	47.50 (47.06)	3.14 (3.70)	17.85 (17.15)	7.11 (7.85)
CuL.Cl.β-Pico	15.11 (15.56)	47.85 (47.06)	3.25 (3.70)	17.94 (17.15)	7.07 (7.85)
CuL.Cl.γ-Pico	15.31 (15.56)	47.31 (47.06)	3.94 (3.70)	17.71 (17.15)	7.64 (7.85)

.Elemental analysis data showed 1:1 ratio of metal ion and ligand for complex and 1:1:1 ratio of metal ion, ligand and heterocyclic base for all adducts. The metal in the complex and adducts was determined by E.D.T.A. using muroxide indicator.

III. IR SPECTRAL DATA IN cm^{-1}:

1. L: : ν (C=N)1722 ν (N=C-S)1668
2. Cu-L.Cl_2: ν(C=N), 1625,ν (N=C-S)1575

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3. Cu-L.Cl.Py : ν(C=N)1645 ν(N=C-S) 1560,ν(M-N)base,270, Bands due to heterocyclic base 1450.
4. CuL.Cl.α-Pico::ν(C=N)1640)ν (N=C-S)1566,ν(M-N) base,275, Bands due to heterocyclic base 1455.
5. CuL.Cl.β-Pico:ν(C=N) 1659 ν(N=C-S) 1529,ν(M-N) base,278, Bands due to heterocyclic base 1435.
6. CuLCl..γ-Pico: :ν(C=N) 1652(N=C-S)1558,,ν(M-N) base, 280, Bands due to heterocyclic base 1458.

The position of IR bands is used to detect the bonding sites of all ligand molecules interacted with the metal. The coordination of nitrogen shifted ν (C = N), ν (N=C-S) to lower wave numbers. The band shifted from 1722.-1668 cm^{-1} in un complexed compound spectra to about 1500-1800 cm^{-1} in the spectra of complexes. The coordination of N atom of heterocyclic base is confirmed by ν (CoN) band in the range 270-280 cm^{-1}.The bands of coordinated heterocyclic bases have also been observed in IR spectra of all complex and adducts.

Table III IV.ELECTRON PARAMAGNETIC RESONANCE SPECTRAL DATA:

Complex	g_{11}	$g_{\perp}$	g_{av}	G	A_{11}	$A_{\perp}$	R	f	α^2	β^2	$K_{\parallel}$	K_o
Cu L Cl_2	2.20	2.12	2.13	1.50	183	52	0.72	115	0.515	0.725	0.372	0.365
Cu L Cl Py	2.21	2.11	2.14	1.65	172	33	0.80	123	0.486	0.764	0.373	0.272
Cu L.Clα–pico	2.21	2.12	2.13	1.67	171	31	0.72	125	0.475	0.819	0.383	0.265
Cu L.Cl β–pico	2.21	2.12	2.12	1.79	172	51	0.80	129	0.475	0.815	0.382	0.310
Cu LCl. γ-pico	2.19	2.11	2.11	1.80	173	52	0.88	128	0.475	0.816	0.385	0.310

The EPR parameters of Cu (II) complexes obtained in DMF at liquid nitrogen temperature (LNT) and presented in Table III. In frozen DMF the four coordinate complexes show well resolved four copper hyperfine lines, characteristic of monomeric Cu (II) complexes and nine super hyperfine lines due to nitrogen and nitrogen atom of the coordinated heterocyclic base in frozen DMF. Since super hyperfine coupling by nitrogen of the heterocyclic base is observed, the coordinated heterocyclic base is found to be coplanar with the NNCl bichelate rings [8]. Hence a square planar structure can be assigned for CuL . B (B = py, α,β,γ –picoline) complexes. The variations in g values indicate that the geometry of the compound which is affected by the nature of the coordinating gegenions. The geometric parameter G is calculated by the relation G = ($g_{11-2}/g_{\perp-2}$) is a measure of the exchange interaction between copper centres in the polycrystalline compound. If G > 4, the exchange interactions is negligible and if it is less than 4 exchange interaction is indicated in the complex. All complexes have values $g_{11} > g_{\perp} > 2$ and G values falling within this range 1 to 3 are consistent with a $dx^2 – y^2$ ground state corresponding to square planer geometry The rhombic spectral values R is calculated by the relation $R = g_2 – g_1/g_3 – g_2$. If R > 1, a predominant $dx^2 – y^2$ ground state is present and when R= 1 then the ground state is an approximately equal mixture of dz^2 and $dx^2 – y^2$, the structure is intermediate between square planar and trigonal bipyramidal geometries. For all complexes R < 1 suggests a distorted square planar geometry with a $dx^2 – y^2$ ground state. The empirical factor $f = g_{11}/A_{11}$ (cm) is an index of tetragonal distortion. The value may vary from 110 to 135 for square planer complexes. In presence of tetragonally distorted structures the values can be higher. The orbital reduction factor K_{11} was calculated by the relation $K_{11} = \alpha^2 \beta^2$. According to Hathway [9] for pure σ bonding $K_{11} = K_{\perp} = 0.77$. For all compounds $K_{11} \approx 0.32 \sim 0.40$. The contribution of s electrons to the hyperfine interaction can be estimated by the value of Fermi contact hyperfine interaction term (K_0). K_0 is a dimensionless quantity and is generally found to have a value of 0.3. The values calculated for all complexes are in the range of 0.25 to 0.36. . The bonding parameters α^2, β^2 are regarded as measures of the covalence of the in plane σ bonds, in plane π bonds α^2, β^2 values are much less than 1.0 which is expected for 100 % ionic character of the bonds, and become smaller with increasing covalent bonding. The evaluated values of α^2, β^2 of the complexes are consistent with both strong in plane σ and in–plane π bonding.

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V. ANTIMICROBIAL ASSAY

The antimicrobial activity was carried out by agar well diffusion method. 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 IV.

% activity index was calculated by the formula

$$\% \text{ Activity Index} = \frac{\text{Zone of inhibition of test compound}}{\text{Zone of inhibition of standard (diameter)}} x100$$

Table IV

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

Compound % Activity Index	Pseudomonas putida		Escherichia coli		Asper gillus 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	29.41	25.00	42.30	32.26	55.56	47.36	64.71	50.00
Cu L.Cl_2	45.13	37.90	49.02	37.70	70.20	64.20	80.30	64.00
Cu L.Cl.Py	49.04	43.45	50.00	38.71	71.20	65.18	81.34	66.10
Cu.L.Cl α-pico	37.25	32.34	44.16	34.40	65.60	55.90	69.90	54.01
Cu.L.Cl β-pico	42.20	35.12	45.16	34.42	64.15	56.63	75.44	66.00
Cu.L.Cl γ-pico	40.55	35.30	46.12	35.20	64.23	55.13	74.12	63.22
Standered	100	100	100	100	100	100	100	100
$CuCl_2.4H_2O$	80.42	65.66	91.30	82.80	135.90	125.30	120.54	112.10

(Std-amphiciline, bicip)

The chelate Cu.L.Cl py showed maximum activity against bacterial and fungal species than free ligand. The Cu L.Cl py exhibited high activity against all the bacteria and fungi. This might be due to heterocyclic base pyridine in coordination. Thus the coordination of metal ion to ligand is responsible for high biological activity. The metal ion in salt solution showed higher activity than complex. The metal ion chloride salts were more effective than complexes. This shows free metal ions are more effective than binded in complexes.. It has been observed that the % activity index decreases on dilution ie it is more in concentrated solution.

The results of spectral, magnetic and EPR study confirmed $CuLCl_2$, CuLClpy, CuLClα/ β- pico complexes have square planer geometry with ligand acting as N-N donor bidentate and N-atom of heterocyclic base occupying the fourth coordination site of the Cu (II) atom in CuLClpy, CuLClα/ β- pico complexes. The ligand provided covalent environment around Cu (II) with important in plane σ and Π bonding contributions.

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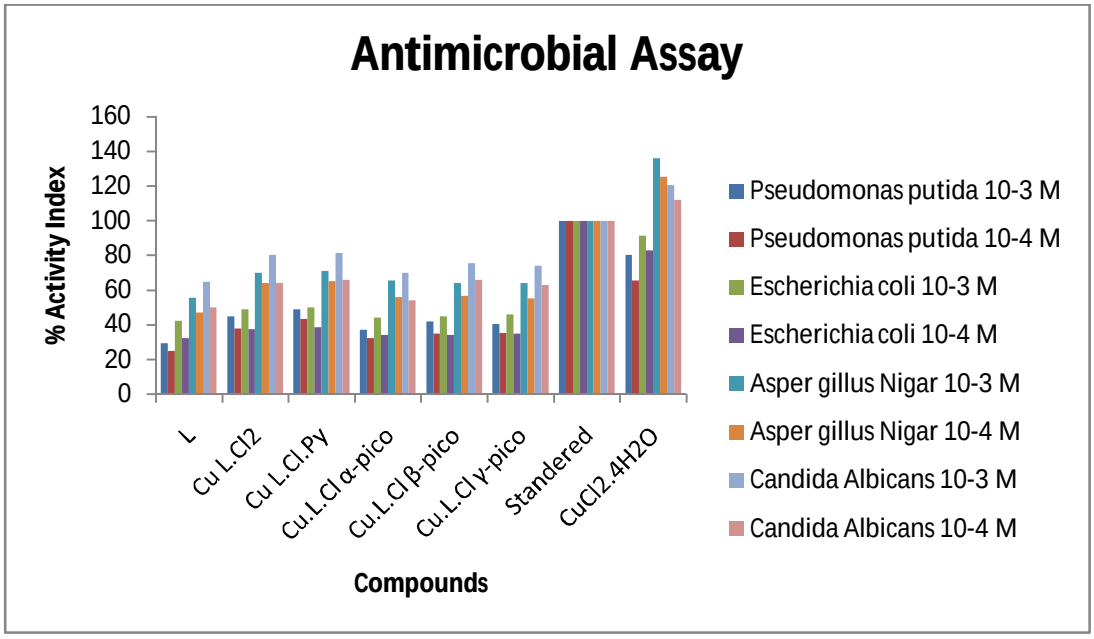
Figure. I % Activity index bar grph



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