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Synthesis, Characterization and Bioactivity of Transition Metal Complexes of New 3-Methyl-5-Mercapto-4-Triazole Schiff Bases.

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ABSTRACT

Three potential novel Schiff bases of 4-amino-3-methyl-5-mercapto triazole were prepared in excellent yields by condensing it with acetyl acetone/ ethylcyanoacetate / *p*-hydroxybenzaldehyde. Elemental analysis, HPLC, IR, NMR data confirmed the structure, purity of the newly synthesized compounds. These compounds were complexed with Ni/ Cu/ Ag salts to get the metal complexes. Structural investigation was done for these complexes by spectral analysis and further screened against Gram positive/ Gram negative bacteria and fungal strains. A comparative study of the MIC values of the synthesized compounds indicated that complexes exhibit better activity than the free ligands, giving a new thrust that metallization increases the activity.

Keywords: Substituted triazole Schiff bases, metal complexes, antimicrobial activity

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INTRODUCTION

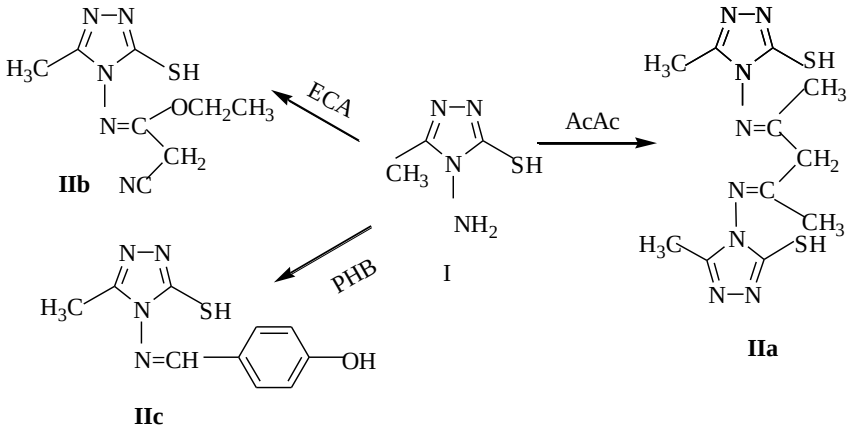
Azoles are a common structural motif found in numerous biologically interesting molecules [1-3] that display a number of pharmaceutical properties. 1,2,4-Triazoles [4,5] are an important class of heterocycles, and have been the subject of great interest due to their versatile biological activities. Specially 4-amino-3-substituted-5-mercapto-1,2,4-triazoles act as a bifunctional agent and their derivatives have been reported to possess broad spectrum of biological activities [6], which have stimulated much interest in the chemistry of triazoles. Schiff bases [7, 8] are an important class of organic compound having considerable biological importance and well used as ligands [9,10] in coordination chemistry. The triazole Schiff bases [11] constitute one of the most important classes of O, N and S donor atoms. The chemistry of transition metal complexes [12] containing heterocyclic donor continues to be of interest on account of their biological importance. Chelation can cause drastic changes in the biological behavior of both the ligands and the metal moiety. These observations and in continuation of our interest in the synthesis of biologically active compounds, prompted us to undertake the synthesis of compounds wherein the two biologically active moieties like triazole and Schiff bases are present together, their metal complexes and also to explore the activities associated with these nuclei. In this paper we report the synthesis, characterization and antimicrobial studies of the Ni(II),Cu(II) and Ag(I) chelates with Schiff base ligands of 4-Amino-5-methyl-3-mercapto- 1,2,4-triazole.

EXPERIMENTAL

Melting points were measured in open capillary tubes and are uncorrected. IR spectra (as KBr pellets), HPLC and elemental analysis were recorded on Thermo Nicolet FTIR spectrophotometer, Shimadzu LC 6A with Shimpack silica gel column and Micro Analytical centre along with the electronic spectra of the ligand and the complexes in DMF on a Shimadzu UV-1700 spectrophotometer at Andhra University, Visakhapatnam. The ^{1}H NMR and ^{13}C spectra were taken on JEOL Model AL 400 NMR at RRL, Bhubaneswar, in DMSO-d_6 and $CDCl_3$ using TMS as internal reference. Powder ESR spectra were taken on Varian E 112 at room temperature and as well as liquid nitrogen temperature using DPPH as standard at SAIF, IIT, Chennai. All the solvents were of analytical grade and were distilled before use. Reagents such as 2,4-pentanedione (AcAc), ethylcyanoacetate (ECA), *p*-hydroxybenzaldehyde (PHB) and metal chlorides were purchased from Across Ltd and used as it is. While 4-Amino-5-methyl-3-mercapto-1,2,4-triazole was prepared by literature procedure [13].

General Procedure for Synthesis of Schiff bases (IIa, IIb and IIc)

Schiff base ligands (IIa, IIb and IIc) were synthesized by condensing and refluxing 4-Amino-5-methyl-3-mercapto- 1,2,4-triazole (I) (1.3g,10mmol) in ethanol (20ml) with acetyl acetone (AcAc, 0.50 mL, 5 mmol for IIa), Ethylcyanoacetate (ECA, 1.06 mL, 10 mmol for IIb), *p*-Hydroxy benzaldehyde (PHB,1.22g, 10 mmol for IIc), in ethanol (10 mL) in separate reactions (Scheme 1), in a water bath for 6-7 hrs. The crude product was separated by filtration, washed several times with ethanol and finally with diethyl ether. The product were recrystallized from hot ethanol and dried. The physical and analytical data of the synthesized ligands are presented in Table 1.



Scheme 1: Synthesis of ligands IIa,IIb,IIc

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General Procedure for Synthesis of Metal Complexes

An ethanolic solution of $NiCl_2.6H_2O$(0.237g,1 mmol)[for IIIa and IIId], $CuCl_2.2H_2O$ (0.170g,1 mmol) [for IIIb and IIIe], $AgNO_3$ (0.169g,1 mmol)[for IIIc and IIIf] was added drop wise to the respective ligand IIa (0.324g,1 mmol); IIb (0.45g, 2 mmol); IIc (0.468g, 2 mmol; each in separate reactions) solution in ethanol (10 mL) while stirring followed by the addition of 2 to 3 drops of triethylamine. The reaction mixture was refluxed for 3-4 hrs and after completion of the reaction refrigerated overnight [14]. The crystalline compound thus obtained was filtered and washed successively with ethanol followed by ether and then dried in vacuo. The isolated complexes, described in this study are outlined in Fig.1.The percentage of Ni(II), Cu(II), Ag(I), in complexes, were determined gravimetrically. The physical and analytical data of the synthesized complexes are presented in Table 1.

Table 1: Physical and Analytical Data of Synthesized Compounds

Compounds	Colour	Yield	Found(Calculated)%					
	M.P (^{0} C)	%	C	H	N	S	M	C l
II a= $C_{11}H_{16}N_8S_2$	Brown 245-250	80	40.20 (40.70)	4.10 (4.93)	34.28 (34.56)	19.02 (19.75)	-	-
II b= $C_8H_{11}N_5SO$	Light Yellow 250-256	75	42.48 (42.66)	4.28 (4.88)	31.02 (31.10)	14.10 (14.22)	-	-
II c = $C_{10}H_{10}N_4SO$	Yellow 230-235	70	51.34 (51.28)	4.32 (4.27)	23.70 (23.92)	13.50 (13.67)	-	-
IIIa[Ni(IIa)$(H_2O)_2(Cl)_2$]	Green >260	60	26.10 (26.93)	4.14 (4.08)	22.18 (22.84)	13.18 (13.05)	11.50 (11.97)	14.12 (14.48)
IIIb [Cu(IIa)$(H_2O)_2(Cl)_2$]	Blue >260	65	26.10 (26.69)	4.18 (4.04)	22.12 (22.64)	12.12 (12.94)	12.10 (12.83)	14.08 (14.35)
IIIc [Ag(IIa)$(H_2O)(NO_3)$]	Black >260	55	25.42 (25.77)	3.02 (3.51)	24.16 (24.60)	12.02 (12.49)	21.24 (21.07)	-
IIId [Ni(IIb)$_2(Cl)_2$]	Reddish Brown >260	60	33.18 (33.10)	3.84 (3.79)	24.28 (24.13)	11.22 (11.03)	10.30 (10.11)	12.18 (12.24)
IIIe [Cu(IIb)$_2(Cl)_2$]	Brown >260	65	32.14 (32.84)	3.24 (3.76)	23.50 (23.94)	10.72 10.94)	10.58 (10.85)	12.08 (12.14)
IIIf [Ag(IIb)$_2$]	Black >260	60	34.24 (34.40)	3.78 (3.94)	25.19 (25.08)	11.24 (11.46)	19.10 (19.33)	-
IIIg [Ni (IIc)$_2$ (Cl)$_2$]	Green >260	70	40.18 (40.12)	3.18 (3.34)	18.54 (18.72)	10.54 10.70)	9.62 (9.81)	11.64 (11.87)
III h [Cu(IIc)$_2(Cl_2)$]	Brown >260	65	39.64 (39.83)	3.08 (3.31)	18.40 (18.58)	10.28 10.61)	10.36 (10.53)	11.60 (11.77)
III i [Ag(IIc)$_2$]	Black >260	60	41.50 (41.66)	3.38 (3.47)	19.28 (19.44)	11.08 11.11)	18.58 (18.73	-

Antimicrobial assay

The synthesized compounds were evaluated for their antimicrobial activity against Gram positive bacterial strains, *Micrococcus luteus (ML), Micrococcus proteus (MP), Bacillus subtilis (BS),* Gram negative bacterial strains, *Klebseilla pneumoniae (KP), Escherichia coli (EC)* and *Pseudomonas syringe (PS)* and three fungal strains, *Rhizopus stolonifer (RS), Candida albicans (CA)* and *Aspergillus niger (AN)* by well diffusion method [15]. Standard antibacterial drug (Ampicillin) and antifungal drug (Nystatin) were used for comparison under similar conditions. DMSO was used as solvent to dissolve the compounds and also used as control. Activity was determined by measuring the diameter of the zone of inhibition in (mm).Two hundred mL of nutrient agar growth medium was dispensed into sterile conical flasks; these were then inoculated with 20 µL of cultures mixed gently and poured into sterile petridish. After setting a borer with 6 mm diameter was properly sterilized by flaming and used to make three uniform wells in each petridish. The wells were loaded with 50 µL of different investigated compounds. The solvent DMSO, used for reconstituting the solvent for diluting the compounds, was similarly analyzed for control. The plates were incubated at 37^{0}C for 24 h. The

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above procedure was also adopted for fungal assays. The used medium was potato dextrose agar and incubated at 27^0C for 48 h. The zone of inhibition was measured with a Hi Antibiotic Zone Scale in mm, and the experiment was carried out in duplicate. The results are shown in Tables 3 and 4.

Table 2: Electronic Spectral (in DMF Solution) and ESR(solid state) Data of Complexes

Complex	λ max mm	ν_1 λmax cm^{-1}	λ max mm	ν_2 λ max cm^{-1}	λ max mm	ν_3 λ max cm^{-1}	ν_2/ν_1	g_{II}	$g_{\perp}$	g_{av}	G
III a	950	10518	565	17680	398	25110	1.60	-	-	-	-
III b	817	12227	614	16262	390	25641	1.3	2.245	2.077	2.161	3.27
III c	-	-	-	-	410	24390	-	-	-	-	-
III d	941	10620	567	17610	404	24705	1.65	-	-	-	-
III e	807	12380	609	16420	405	24691	1.32	2.220	2.060	2.140	3.80
III f	-	-	-	-	371	26954	-	-	-	-	-
III g	930	10750	564	17720	399	25004	1.64	-	-	-	-
III h	803	12450	607	16470	311	25540	1.32	2.188	2.057	2.101	3.42
III i	-	-	-	-	380	26315	-	-	-	-	-

Table 3: Antibacterial Activity of Synthesized Compounds at concentration 1mg/ml

Bacterial strains	DMSO	II a	III a	III b	III c	II b	III d	III e	III f	II c	III g	III h	III i	STD
ML	NA	NA	22	NA	NA	10	25	12	NA	10	20	NA	NA	32
MP	NA	NA	21	NA	NA	NA	25	20	NA	13	21	12	NA	30
BS	NA	NA	NA	NA	NA	NA	17	10	NA	NA	20	10	10	25
KP	NA	NA	17	11	10	10	20	13	09	10	20	10	10	28
EC	NA	NA	27	15	11	14	28	11	10	18	20	NA	08	35
PS	NA	10	20	20	10	10	24	22	14	13	22	19	15	30

Micrococcus leuteus (ML), Micrococcus proteus (MP), Bacillus subtilis (BS), Klepsiella pneumonia (KP), Escherichia coli (EC);Pseudomonas syringe (PS), NA-Not active;STD- Ampicillin

Table 4: Antifungal activity of synthesized compounds at concentration 1mg/ml

Compound	RP	CA	AN
DMSO	NA	NA	NA
II a	11	NA	NA
III a	34	15	20
III b	10	NA	NA
III c	NA	NA	NA
II b	NA	NA	NA
III d	33	13	36
III e	14	NA	NA
III f	10	NA	10
II c	NA	10	10
III g	32	12	35
III h	NA	NA	NA
III i	NA	NA	NA
Nystatin	40	25	42

Rhizopus stolonifer (RS), Candida albicans (CA) and *Aspergillus niger (AN) ;NA-Not active*

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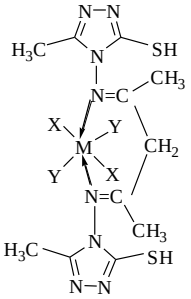
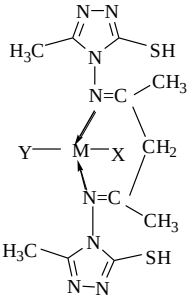
RESULTS AND DISCUSSION

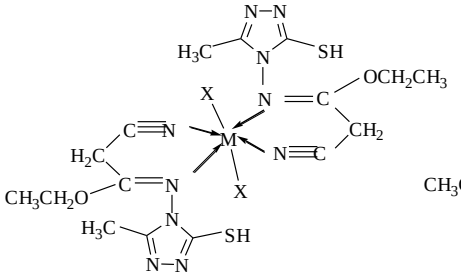
Three new Schiff bases of triazole were prepared by mixing and refluxing them with acetyl acetone (for IIa), ethylcyanoacetate (for IIb), *p*-hydroxy benzaldehyde (for IIc) (Scheme 1), in ethanol. HPLC (purity: 97.8% with retention time : 2.790min for IIa; purity: 98.5% with retention time : 2.781min for IIb and 98.2% with retention time : 2.850min for IIc;) and NMR spectra confirmed their purity. The complexes of these ligands were prepared by condensing 1mmol of an ethanolic solution of $NiCl_2.6H_2O$ (for IIIa and IIId), $CuCl_2.2H_2O$ (for IIIb and IIIe), $AgNO_3$(for IIIc and IIIf). Characterization of the complexes were achieved by IR, UV–Vis spectra, ESR(Cu complex), elemental analysis along with metal estimation, all of which gave results consistent with the proposed formulations (Fig.1).



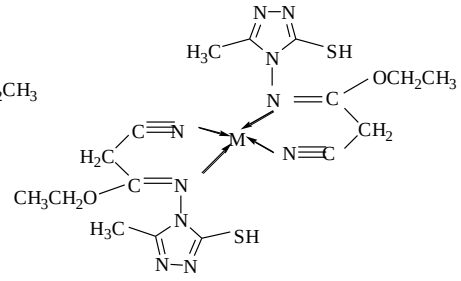
IIIa M=Ni; IIIb M=Cu;X=Cl, Y=H_2O



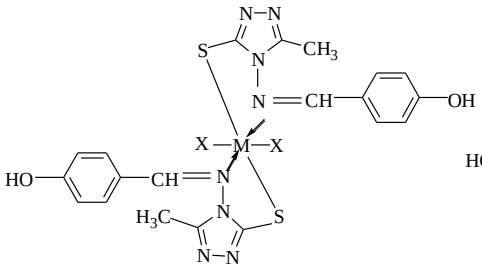
IIIc M=Ag,X=NO_3,Y=H_2O



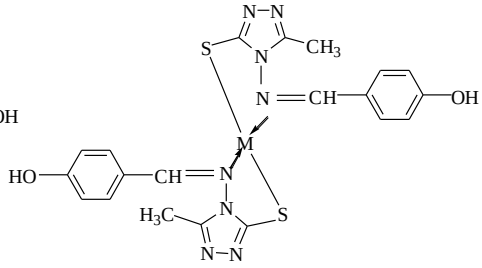
IIId M=Ni; IIIe M=Cu;X=Cl



IIIf M=Ag



IIIg M=Ni; IIIh M=Cu;X=Cl



IIIi M=Ag

Fig.1: Proposed structure of the complexes

Spectral analysis

The IR spectral bands (cm^{-1}) of ligands appeared at 3162, 3165, 3170; ~2956, ~ 2982 ; 2788, 2862, 2776 ; 1683, 1674, 1660 and 1583, 1596 , 1570 and were attributed to aromatic protons; asymmetric CH_3 stretching attached to heterocyclic ring; for asymmetric CH_3 stretching attached to AcAc/ECA; -SH; azomethine group and C=N of the ring respectively [16]. The additional peak observed in the IR spectra of ligand IIb at 2368 was assignted to C≡N stretching [17]. The IR spectra of complexes IIIa, IIIb and IIIc showing major peaks at the range 3348-3420 (broad) are found to arise from the coordinated water molecules. The lowering in the IR values for C≡N was observed in the range 2363-2344 in the complexes IIId, IIIe and IIIf. This lowering upon

complexation could be understood in view of the participation of their π electrons in coordination with the metal ions [18]. However in the IR spectra of the complexes the peaks due to azomethine group were shifted to lower frequency in the range 1671 -1619 further suggested the coordination of the azomethine group [19,20] to the metal through nitrogen. A characteristic medium intensity band in the range 2862-2491 due to S-H indicates the thiol form of the ligands IIa, IIb, IIc and complexes IIIa to IIIf. The ligands IIa, IIb, IIc and complexes IIIa to IIIf showed a band at the range 700-850 due to thione C=S. The coordination via thio- keto sulphur atom of the complexes IIIg, IIIh and IIIi causes the decrease in frequency of the C=S. These complexes show a new band at the range 650- 680 due to conversion of C=S to C-S band and also indicates the thione ↔ thiole tautomerism [21] followed by deprotonation of thiol group and consequent coordination of sulphur atom [22] with metal as indicated by absence of band at 2776 cm^{-1} due to thiol SH in the spectra of complexes IIIg, IIIh and IIIi. The complexes showed bands in the range 490-416 assigned to M-N, M-O and M-S bonds.

The ^{1}H NMR and ^{13}C NMR spectra (δ ppm) of ligands IIa and IIb were recorded in DMSO-d_6 while IIc was done in $CDCl_3$. The ^{1}H NMR spectra of IIa peaks at 11.0-11.2(-SH), 3.20 (-CH_2), 2.3 -2.4 (-CH_3 on the triazole ring), 1.1-1.3 (-$CH_3$of AcAc) were assigned .^{13}C spectrum of IIa peaks at 172 (-N-C-S of the ring), 167(-C=N azomethine), 154(C-C-N of the ring), 26 (CH_2 of AcAc), 17 (-CH_3 of AcAc),10 (-CH_3 of triazole ring) were assigned. Based on the above spectral data the structure of the compound is established as IIa. However peaks observed in the ^{1}H NMR spectra of ligand IIb at 10.9- 11.3 (-SH), 3.2 (-CH_2 of azomethine), 2.29-2.47 (-OCH_2 of ECA), 2.21 (-CH_3 on the triazole ring) 1.0-1.18 (-CH_3 of ECA) were assigned. ^{13}C NMR spectrum of IIb peaks at 172 (-C-C-N of the ring), 167 (-C=N azomethine), 156 (N-C-S of the ring), 153 (-C≡N of ECA), 26 (-CH_2 of ECA), 17 (-OCH_2 of ECA), 11 (CH_3 on the triazole ring), 9.37(-CH_3 of ECA) were assigned. Based on the above spectral data the structure of the compound is established as IIb. The ^{1}H NMR spectrum of ligand IIc peaks at 9.8 (-SH), 8.6 (N=CH azomethine), 7.8-6.9 (aromatic ring), 2.5 (-OH), 1.2 (-CH_3 of triazole ring) were assigned. ^{13}C NMR spectrum of IIc peaks at ppm 192 (C-OH attached to benzene ring), 174 (NCS of triazole ring), 162 (-C=N azomethine), 155 (-C-C-N of triazole ring), 132 (-C-C=N benzene ring), 129 (-C-C-C benzene ring), 116 (-C-C-C benzene ring), 27 (-CH_3 of the triazole ring) assigned. Based on the above spectral data the structure of the compound is established as IIc.

The UV- Visible electronic spectral data of Ni (II), Cu (II) and Ag (I) complexes of the ligands were recorded in DMF as shown in Table 2. Ni(II) complexes exhibit three absorption bands in the regions 7,000-13,000, 13,000-19,000 and 20,000-27,000 cm^{-1} for ν_1 ,ν_2 andν_3 transitions $^{3}A_{2g}(F) \rightarrow {}^{3}T_{2g}(F)$ (ν_1), $^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}(F)$($\nu_2$), and $^{3}A_{2g}(F) \rightarrow {}^{3}T_{1g}$ (p)(ν_3) respectively, which were in confirmation with the octahedral geometry for the Ni(II) ion. The electronic spectra of Ni(II) complexes IIIa,IIId and IIIg at the range 10,518-10,750 cm^{-1} (ν_1), 17,610-17,720 cm^{-1} (ν_2), 24,705-25,110cm^{-1}(ν_3) respectively indicating octahedral geometry around the Ni(II) ion. The ratio$\nu_2/\ \nu_1$ was found and it was well in the range (1.40-1.65) indicating octahedral geometry for these Ni(II) complexes[23] . The electronic spectra of the Cu(II) complexes of IIIb, IIIe,IIIh asymmetric band was in the range of 12,227-12,450cm^{-1}(ν_1), 16,262-16,470 cm^{-1}(ν_2), 24,691-25,641cm^{-1}(ν_3) in distorted octahedral geometry[24]. The broadness of distortion was assigned to $^{2}T_{2g} \rightarrow {}^{2}E_g$ transitions. The electronic spectra of the Ag (I) complexes IIIc, IIIf, IIIi at the range 24,390-26, 954cm^{-1} was assigned presumably; and square planar structure suggested for the diamagnetic Ag (I) complexes [25].

The powder state ESR spectra of Cu (II) complexes were recorded at RT and LNT. The ESR spectral data of IIIb, IIIe, and IIIh are shown in Table 2. From the data the considerable covalent character of metal-ligand in the complexes was predicted. The spin hamiltonian parameters for the copper complexes were calculated from the spectra $g_{\parallel} > g_{\perp}=2.0023$ and indicates the complex was axially elongated octahedral geometry [14]. Further; it was supported by the fact that the unpaired electron lies predominantly in the dx^2-y^2 orbital. The G values calculated for the complexes were in the range 3.27-3.8. In all the complexes G values less than 4.0 was consistent with a dx^2-y^2 ground state [26].

The thermal properties of synthesized complex IIId was examined by Thermogravimetric Analysis (TGA), and Differential thermogravimetric analysis (DTG). The complex IIId was heated upto 1400^{o}C in a nitrogen atmosphere. The TG-DTG results were in good agreement with the proposed chemical formula. The decomposition of the complex proceeded with an exothermic peak at 107.4^{0}C. The first stage at 247.6^{0}C with mass loss of 7.2% (calcd: 6.12%) corresponds to the loss of one chlorine atom. The second stage at 1275.1^{0}C with mass loss of 46% (calcd: 47.3%) corresponds to the loss of second chlorine atom and ligand molecule $C_{10}H_{14}N_4O_2$. Finally at 1350^{0}C the TGA curve represents the complete decomposition of organic molecule with

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the formation of stable metal oxide (NiO) as the final product. Thus on the basis of above analytical, physical and spectral data, the proposed structures of complexes are given in Fig.1.

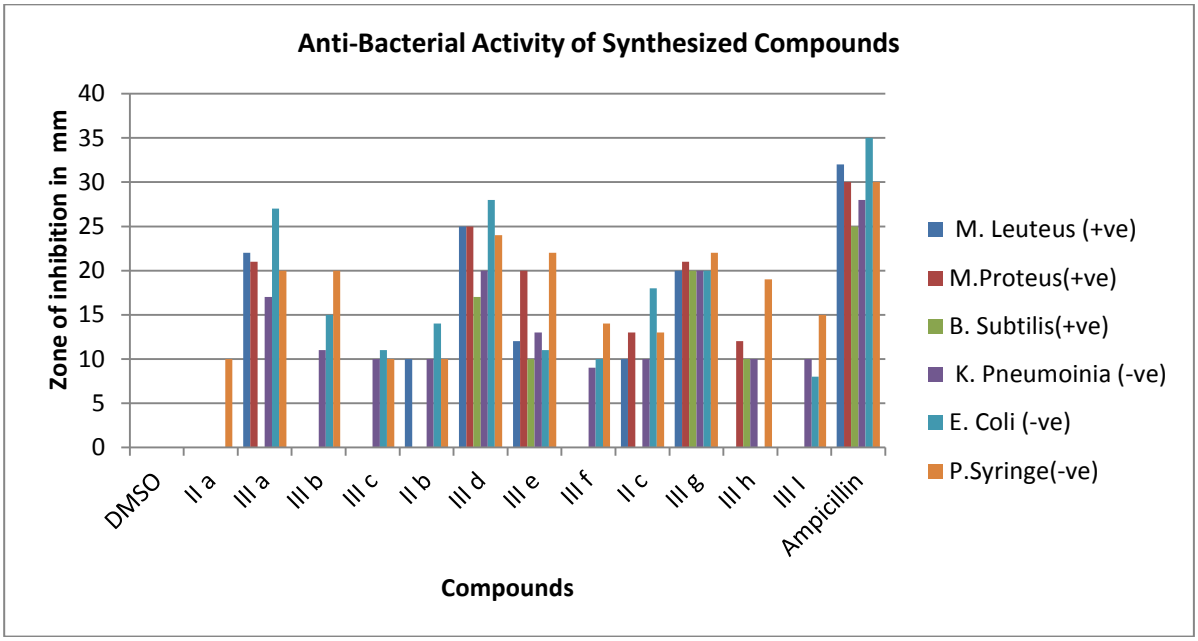

Figure 2: Antibacterial Activity of Synthesized Ligands (IIa-IIc) and Complexes (IIIa-IIIi)

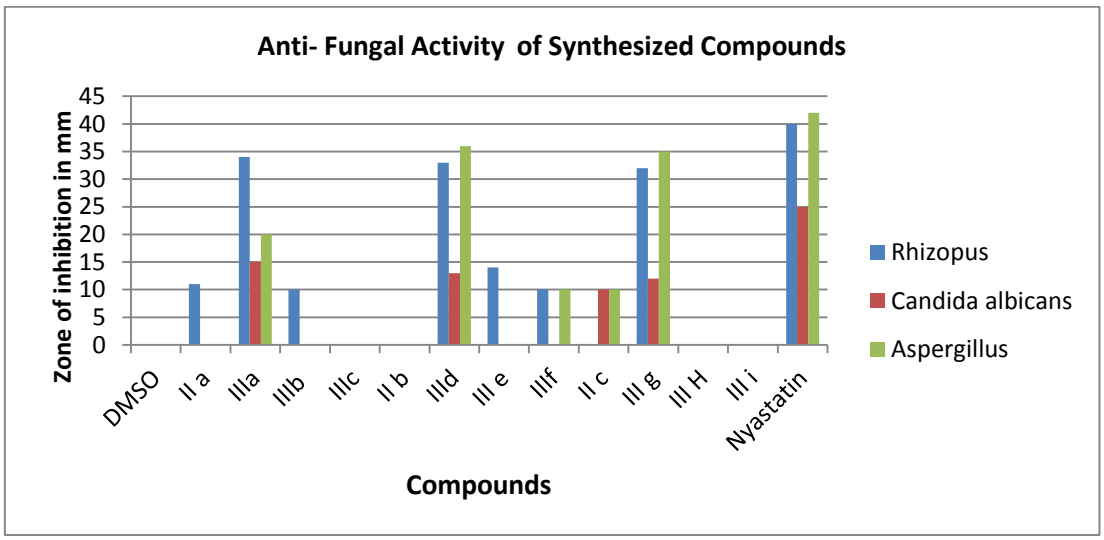

Figure 3: Antifungal Activity of Synthesized Ligands (IIa-IIc) and Complexes (IIIa-IIIi)

Antimicrobial Activity

The ligands (IIa–IIc) and their metal complexes(IIIa-IIIi) were examined for antimicrobial assay against six bacterial and three fungal strain using the well diffusion method.The values of the tested compounds are shown in Table 3 (graphically shown in Fig.2) and Table 4 (graphically shown in Fig.3) respectively. It was observed from these studies that metal chelates had a higher activity than the free ligands against both bacterial and fungal strains. The complexes IIIa, IIId and IIIg exhibited siginificant antibacterial activity against all bacterial strains except IIIa against *Bacillus subtilis (BS).* These complexes also exhibited profound activity against fungal strains *Rhizopus stolonifer* and *Aspergillus niger.* The complex IIIe exhibited remarkable antibacterial activity against *Micrococcus proteus* and *Pseudomonas syringe*. The complexes IIIb, IIIh exhibited marked antibacterial activity against *Pseudomonas syringe*. The weak antifungal activity of complexes IIIb, IIIe,

IIIh may be indicates fungi were resistant to the compounds. The increased activity of the metal chelates than ligands can be explained on the basis of overtone's concept and chelation theory [27,28]. According to overtone's concept of cell permeability the lipid membrane that surrounds the cell favours the passage of only lipid soluble materials due to which liposolubility was an important factor that controls antimicrobial activity. On chelation, the polarity of the metal ion was reduced to a greater extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal with donor groups. Further, it increases the delocalization of π electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances penetration of the complexes into lipid membranes and blocking of metal binding sites on the enzymes of the microorganism. It was however, known that the chelating, tends to make the Schiff bases act as more powerful and potent bacteriostatic agents, thus inhibiting the growth of bacteria and fungi more than the parent Schiff bases. It was assumed that factors, such as solubility, conductivity, dipole moment, and cell permeability mechanism (influenced by the presence of metal ions) may contribute to the increase in the activity of the metal complexes relative to Schiff bases.

CONCLUSION

A new series of substituted triazole Schiff bases (ligands) along with their nickel, copper and silver complexes were synthesized. The octahedral geometry was inferred around Ni and Cu from their spectral data, however square planar geometry was assigned for Ag complex. A comparative study of the MIC values of the ligands and their complexes indicates that complexes exhibit higher antimicrobial activity than the free ligands, giving a new thrust of these compounds in the field of metallo-drugs (bio-inorganic chemistry). Metallization increased the activity compared with the free ligand. However, Cu complexes showed more activity against almost all bacteria and fungi. In view of the structural formula of the complexes that exhibit antimicrobial activity, metal moiety may play a significant role. From the results, it is also clear that these compounds would be better used in drug development to combat bacterial and fungal infections.

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