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SYNTHESIS AND CHARACTERIZATION OF BIOLOGICALLY ACTIVE COMPOUND E-2-((2-AMINO PYRIDINE-3-YL) METHYLENE AMINO) ETHANE THIOL AND ITS METAL COMPLEXES

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Keywords:

Schiff base, Cystamine,
2-amino pyridine 3-carbaldehyde,
complexes, antibacterial activity

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ABSTRACT: A new physiologically active compound E-2-((2-amino pyridine-3-yl) methylene amino)ethane thiol derived from the condensation of Cysteamine and 2-amino Pyridine 3-Carbaldehyde was synthesized and characterized by spectral techniques like IR, UV-Vis, ^{1}H- NMR, TG-DTA, ESR, CHN analyses. The complexes were further screened for their biological activity at Nishka labs and Nickel and Cobalt complexes were found to be potent antibacterial agents. From the above analysis it was found that the ligand behaves as a neutral ligand with N: N: S:N:N donor sequence for octahedral complexes.

INTRODUCTION: Galinska et.al. reported new di and trinuclear Copper complexes containing two and three macro cyclic fragments bound by aliphatic linkers with –S-S- moieties by using Cysteamine dihydrochloride [1]. Nicolas Louvain reported the syntheses, crystal structures, and thermal properties of five cuprous bromides containing Cysteamine diprotonated dictation [2].

Mononuclear complexes of Pd(II) with Cysteamine dihydrochloride were studied by Gasanov. Kh. I.[3] The drastic decrease in the reactivity of thiols and disulfides complexes by cucurbit[6]uril (CB6)were studied by Strimbu Berbeci Lidia *et.al* [4].

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Electrochemical synthesis and characterization of zinc(II) and cadmium(II) complexes of dianionic tetra dentate Schiff base ligand were reported by Rodriguez, Laura [5]. The effect of chelating phosphines was tested on the structure and pH-dependent stability of Ni-cysteine binding by Desrochers, Patrick J [6]. McDonnell, Nazli B [7] have studied Zinc ejection as a new Rationale for the use of Cysteamine and Related Disulfide-Containing Antiviral Agents in the treatment of AIDS. Formation of a covalent complex between methylguanine methyltransferase and DNA via disulfide bond formation between the active site cysteine and a thiol-containing analog of guanine were studied by Paalman, Susan R [8] *et.al*.

A novel dinuclear iridium(III) complex with a bridging disulfide bond were studied by Konno Takumi [9] in which two octahedral Ir(III) units are linked by a coordinated disulfide bond. Cu(II) complexes of Schiff base ligands formed by the condensation of Cysteamine or 2,2'-

diaminodiphenyldisulfide with salicylaldehyde or pyridine-2-carboxaldehyde and their C:N reduced analogs were isolated and characterized by Uma R & Palaniandavar, M[10]. Kapanadze, T. Sh [11], studied the Stereochemistry of the isomerization of cobalt (III) complexes of cysteine and Cysteamine. Cu(II) and Ni(II) Cysteamine complexes were prepared and characterized by D. Carrillo et.al [12], which appeared to have a distorted octahedral and tetragonal symmetry. Cysteamine complex formation with DNA was studied by Ryadovoi, G. V. et.al.[13].

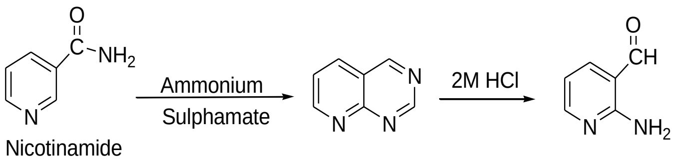
2-Amino-3-Carbaldehyde along with 2-methyl-7-amino-1,8-naphthyridine was used to design a colorimetric /fluorescent sensor with specific response to Cu(II) as this is a significant metal pollutant and an essential trace element in biological systems [14]. Schiff base condensation of the aldehydes function of pyridine 3- carbaldehyde with $-NH_2$ group of amino ester /peptide was studied by Alvarez et.al, and their metal complexes with Mn & Re were reported [15].

MATERIALS:

Synthesis of the starting material: Cysteamine dihydrochloride was used as purchased from Sigma Aldrich. 2-Amino pyridine 3-carbaldehyde was prepared from Nicotinamide and the procedure is given below.

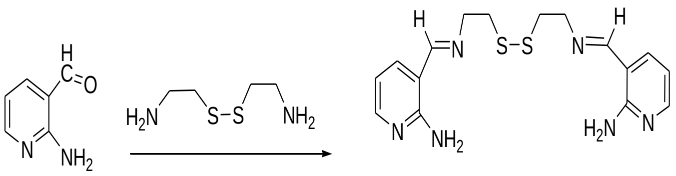
Preparation of 2-Aminopyridine -3-Carbaldehyde:

A mixture of ammonium sulfamate(52.0 g, 450 mmol) and Nicotinamide (36.5 g, 300 mmol)was heated at 150 °C (in a molten state) under nitrogen. Over 2 h, the temperature was raised to 200 °C and maintained for 8hour. After cooling, the solid was suspended in water (80 mL). After the mixture had been stirred for 1 h, the remaining solid was filtered off and washed with diethyl ether. It was dissolved in 2 M hydrochloric acid and heated under reflux for 6h.On neutralization of the cooled solution with solid sodium carbonate, a precipitate formed. The mixture was extracted eight times with diethyl ether (80 mL). The combined organic layers were dried with sodium sulfate and the solvent was evaporated to yield a yellow solid (8.0 g, 22%) sufficiently pure for further synthesis.



Preparation of Schiff base:

Cysteamine 44.73m mol(6.8g) and 2-Amino pyridine 3-Carbaldehyde 89.47m mol(10.92g) were reacted in a round bottom flask in Methanol under reflux conditions for 21 hours on a water bath. Yellow precipitated solid was filtered, washed with cold methanol and dried up. 14.1g(87.5%) of Pure yellow solid obtained.



Preparation of Metal complexes of the Schiff base: The ligand, 3-((1E)-(2-(2-((E)-2-((pyridine-2-amine-3-yl) methyleneamino) ethyl) disulfanyl) ethylimino) methyl) pyridine-2-amine, was sealed in a 50ml RBflask with small amount of methanol, then metal salts are dissolved in alcohol with small amount of water and were added to the ligand in 1:1 ratio, immediately the appearance of metal complexes was noticed. The complexes were further refluxed for 30 min. on a water bath and then filtered,purified and dried in vacuo for further spectral characterization.

RESULTS AND DISCUSSION:

Measurements: Infrared spectra (4000-400 cm^{-1}) were recorded as KBr pellets on Perkin-Elmer FT-IR system spectrophotometer, ^1H-NMR spectra was recorded on Avance-300 MHz NMR spectrometer with the samples dissolved in deuterated solvents using TMS as an internal standard at C.F., O. U. Elemental analyses (CHN) were performed using a C, H, N elemental analyzer at IICT, Hyd. UV-Vis spectra was recorded on a schimadzu make UV-Vis spectrophotometer.

The electronic spectra were measured in DMSO, DMF, Methanol respectively. The Mass spectra were recorded with Autospec Mass Spectrometer. Magnetic measurements were carried out at 25^0C using Gouy balance with $Hg [Co (SCN)_4]$ as a standard. Magnetic susceptibilities were calculated as B.M (Bohr magnetos') using the $\mu_{eff} = 2.83\sqrt{(\chi_m^{corr}(T-\theta)}$ equation. Thermo gravimetric analysis (TGA) was performed on Schimadzu DTA 50 model using 10mg samples in O.U. The molar conductivity of the ligand and their complexes were determined in DMSO, DMF, Methanol (10^{-3} M) at RT using Systronics model conductivity meter. Melting points were determined on an open capillary Sisco model melting point apparatus. Electron Paramagnetic Resonance spectra was measured at IIT Bombay. Antimicrobial activity of metal complexes was tested against *E.coli* and *Staph.aureus* by Well method at NISHKA labs, Uppal, Hyd.

Physical Data:

The synthesized ligand and metal complexes were analyzed for physical data like color, yield, melting point & Solubility. The magnetic moments were calculated from the equation:

$$\mu_{eff} = 2.83\sqrt{(\chi_m^{corr}(T-\theta)}$$

using the weight of the complex within the magnetic field and without the magnetic field by Gouy method. All the data is provided in **Table 1**.

TABLE 1: PHYSICAL DATA OF LIGAND & METAL COMPLEXES

Complex	Color	Yield	M.P (°C)	Geometry	Mol.wt	Mag.mom
Ligand $[C_{16}H_{20}N_6S_2]$	Lt.cream	75%	110	-	360	-
$[VOL]SO_4$	green	65%	>280	Sq. py.	427	1.8
$[MnL.H_2O]SO_4$	Pale brown	66%	220	Oh	433	-
$[CoL.H_2O]Cl_2$	black	65%	210	Oh	437	2.3
$[NiL.H_2O]Cl_2$	red	50%	Decomp. at 120	Td	437	2.27
$[CuL.H_2O]SO_4$	Dark green	55%	180	Oh	441	1.75
$[ZnL.H_2O](ACO)_2$	Lt.yellow	60%	120	Oh	443	0(dia)
$[CdL.H_2O]Cl_2$	white	65%	205	Oh	490	O(dia)

IR spectra:

The Infrared spectra of the free ligands and the metal complexes were obtained over a spectral range of 4000cm^{-1} – 400 cm^{-1}. However, the comparison of the spectral bands of the ligand with those of its complexes gives some important information regarding the nature of the ligand as well as the coordination sites through which metal ions coordinate with the ligand. The $\nu_{C=N}$ in the ligand appears at 1621cm^{-1} which decreases substantially in the metal complexes which indicates bond formation between the ligand and metal ion in the complex. The ν_{NH2} band in ligand appears at 3304 cm^{-1} which lowers in the metal complexes which indicates the participation of free –NH_2 rather than ring –C=N. The ν_{C-S} frequency in ligand and Vanadium complex appears at 717cm^{-1} whereas it decrease in other metal complexes which indicates the participation of one sulphur atom in bonding except vanadium which further supports the predicted structure. The other frequencies are given in the **Table 3** given below.

TABLE 3: INFRA RED FREQUENCIES OF LIGAND AND METAL COMPLEXES:

Complex	$\nu_{C=N}$	ν_{NH2}	ν_{NH2} defor.band#	ν_{C-N} (aliphatic)	ν_{C-S}	ν_{M-N}
Ligand	1621	3304	1563	1020	717	-
VOL	1586	3285	1550	1029	717	543
$MnL.H_2O$	1585	3289	1547	1028	715	543
$CoL.H_2O$	1586	3280	1548	1029	715	545
NiL.H2O	1585	3283	1550	1029	715	547
$CuL.H_2O$	1586	3289	1554	1029	714	545
$ZnL.H_2O$	1580	3285	1550	1028	715	541
CdL.H2O	1583	3280	1545	1028	713	542

defor.band=deformation band

UV-Visible:

The UV-Visible spectra was recorded from 190-1100nm in the respective solvents (DMF, DMSO and ethanol). Vanadium complex shows a single peak at 17000nm which corresponds to ^2D term derived from d^1 configuration and the transition corresponds to $^2T_{2g} \rightarrow {}^2E_g$. The three bands observed for Cobalt were assigned for $^4T_{1g}(F) \rightarrow {}^4T_{2g}$ (ν_1); $^4T_{1g}$ (F) → $^4T_{1g}$ (P) (ν_2); $^4T_{1g}(F) \rightarrow {}^4A_{2g}(\nu_3)$ at 8300, 16500, 19450 cm^{-1} respectively. Copper (II) complexes show a distorted Octahedral geometry which exhibits 3 bands, $^2B_1 \rightarrow {}^2E$ (ν_1); $^2B_1 \rightarrow {}^2B_2$ (ν_2); $^2B_1 \rightarrow {}^2A_1$ (ν_3) at 14450, 26500, 35000cm^{-1} respectively. Nickel tetrahedral complex shows 3 transitions from $^1A_{1g}(D) \rightarrow {}^1A_{2g}(G)(\nu_1)$, $^1A_{1g}(D) \rightarrow {}^1B_{1g}(G)(\nu_2)$, $^1A_{1g}$ $(D) \rightarrow {}^1E_g(G)(\nu_3)$ at 8200, 14500, 21500 cm^{-1} respectively.

^{1}H-NMR: ^{1}H NMR Sprectum of 2-Aminopyridine -3-Carbaldehyde: (400 MHz, [D6]DMSO): δ 6.74 ppm (dd,J1 7.37Hz, J2 4.6Hz, 1 H, 5-H), 7.15 (br. s, 2 H, NH2), 7.84(dd, J1 7.37 Hz, J2 2Hz, 1 H, 4-H), 8.24 (dd, J1 4.6Hz, J2 1.8 Hz, 1 H, 6-H), 9.818(s, 1 H, CHO).

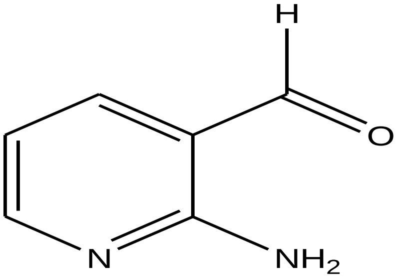


FIG.1: 2-AMINOPYRIDINE-3-CARBALDEHYDE

^{1}H NMR spectrum of Ligand (300 MHz, [D6]DMSO): δ7.49(s,1H), 7.12 ppm (dd, J1 1.51Hz, J2 4.721Hz, 1 H), 6.84 (br. s, 2 H, NH2), 6.74(dd, J1 1.511 Hz, J2 7.365Hz, 1 H), 5.72 (dd, J1 4.91Hz, J2 4.721 Hz, J3 7.55 Hz 1 H), 2.95(t, J 6.232Hz, 2 H), 2.17(t, 6.421Hz, 2 H).

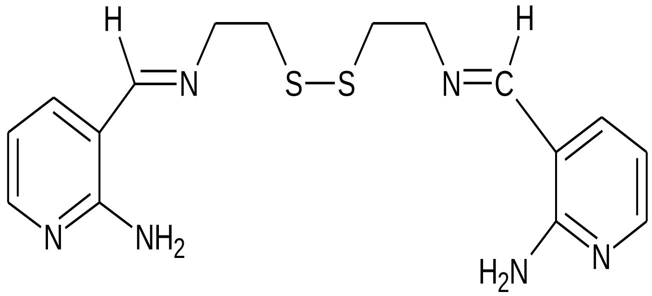
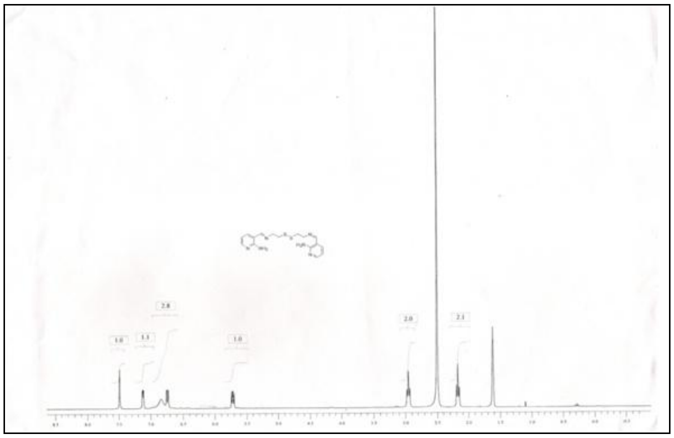
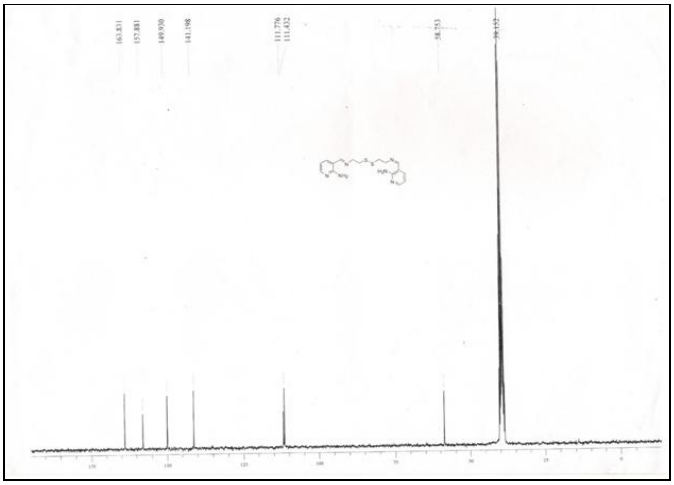


FIG. 2: STRUCTURE OF LIGAND

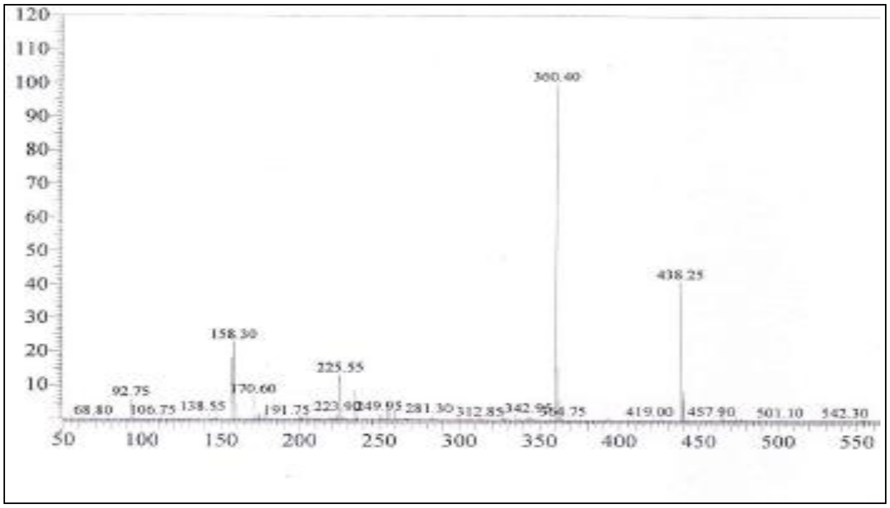


^{13}C NMR Spectra of the ligand: ^{13}C NMR (75 MHz, $CDCl_3$):

The ^{13}C nmr spectrum was recorded in $CDCl_3$: The chemical shift observed at δ 39.159 is due to the CH_2 carbon attached to Sulphur. The chemical shift observed at δ 58.75 is due to the CH_2 carbon attached to Nitrogen. The chemical shift value observed at δ 163.83 is due to C2 carbon of pyridine ring which is attached to both pyridine ring nitrogen and the amine nitrogen. The chemical shift value at δ157.881 is due to C6 of pyridine ring which is attached to pyridine ring nitrogen. The chemical shift value at δ149.93 is due to the olefinic carbon attached to nitrogen of azomethine group. The chemical shift value at δ141.198 is due to C3 carbon of pyridine ring. The chemical shif value of δ111.776 is due to C4 carbon of pyridine ring and the chemical shift value of δ111.432 is due to C5 carbon of pyridine ring.



Mass spectra: Mass spectral data has further confirmed the structure of the complex. The mass spectral fragment at 438 itself is the complex molecular weight which shows the two side condensation of the Cysteamine with the aldehydes. The base peak at m/z 360 is the ligand peak after the removal of H_2O and the metal atom. The other mass spectral peaks also confirm the predicted srutcture.



ESR Spectra:

Copper complex is showing a ‘g’ value of 2.118 which indicates the symmetric environment around the metal atom. Whereas the Vanadium complex is showing three different ‘g’ values at g_{xx}=2.12724, g_{yy}=2.08529, g_{zz}=2.03315 which itself is indicative of an uneven distribution of the electronic environment which further substantiates our prediction of square pyramidal geometry around the central metal ion.

C, H, N Analysis of metal complexes:

Carbon, Hydrogen, Nitrogen and Sulphur were analysed and the data is compiled in the following table.

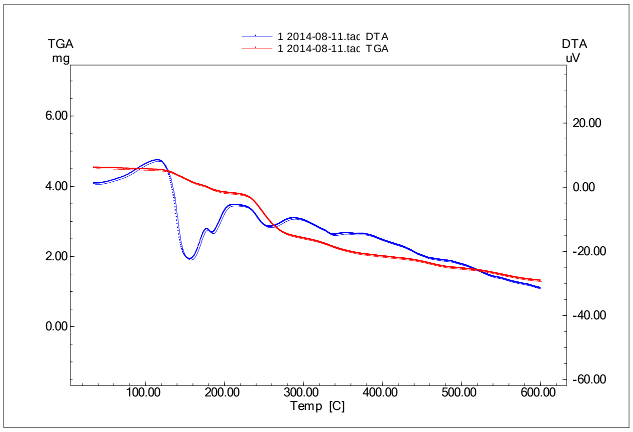
TABLE: C, H, N, S ANALYSIS

Complex	% of C (calc)	% of H (calc)	% of N (calc)	% of S(calc)	% M (calc)
Ligand	53.34(53.33)	5.57(5.55)	23.35(23.33)	17.79(17.77)	-
VOL	44.98(44.96)	4.69(4.68)	19.68(19.67)	15.01(14.98)	11.97(11.94)
MnL.H2O	44.35(44.34)	5.09(5.08)	19.40(19.39)	14.79(14.78)	12.73(12.70)
CoL.H2O	44.94(44.93)	5.04(5.03)	19.23(19.22)	14.65(14.64)	13.52(13.50)
NiL.H2O	43.94(43.93)	5.05(5.03)	19.23(19.22)	14.68(14.64)	13.52(13.50)
CuL.H2O	43.54(43.53)	4.97(4.98)	19.06(19.04)	14.53(14.51)	14.30(14.28)
ZnL.H2O	43.35(43.34)	4.97(4.96)	18.97(18.96)	14.47(14.44)	14.69(14.67)
CdL.H2O	39.20(39.18)	4.49(4.48)	17.16(17.14)	13.08(13.06)	22.87(22.85)

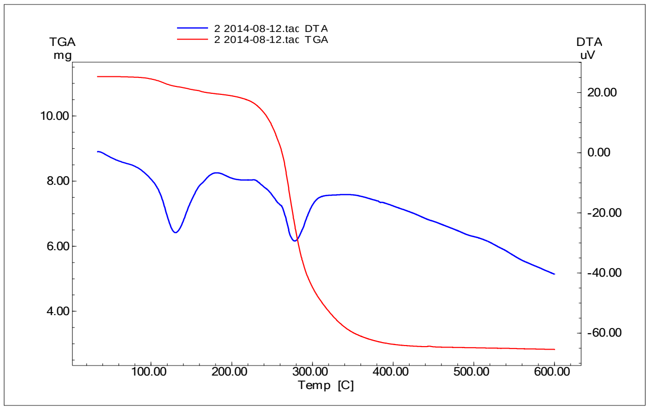
TG-DTA:

TG-DTA of the complexes were carried out in air atmosphere, in platinum pan and from 36^0 C to 600^0C temperature. The air flow was maintained at 50 ml/min. The data shows the loss of water molecule in the Ni(II)complex at around 160-180°C which further supports our predicted structure of one coordinated water molecule. In the Zn(II) complex the loss of water occurs at 120^0C which substantiates the presence of coordinated water in the metal complex. This is in concurrence with the proposed structure of the metal complexes.

Ni-cys complex:



Zn-cys complex:



Biological activity:

Determination of zone of inhibition of test substances against *Escherichia coli*, *&Staphylococcus aureus* were studied at NISHKA labs, Uppal, Hyderabad. Sterile Nutrient Agar plates were prepared and 0.1 ml of the inoculum from standardized culture of test organism was spread uniformly. Wells were prepared by using a sterile borer of diameter 10mm and 100µl (To get the final concentration of 1000, 500, 250, µg/well) of the test substance. The plates were placed at 40^0 C for 1 h to allow the diffusion of test solution into the medium and plates were incubated at a temperature optimal for the test organism and for a period of time sufficient for the growth of at least 10 to15 generations. The zone of inhibition of microbial growth around the well was measured in mm.

Three metal complexes of Vanadium, Nickel and Cobalt were analyzed for their antimicrobial activity against *E.coli* & *Staph.aureus* at three different concentrations i.e. at 1000µg, 500 µg & 250 µg. Out of the three complexes Vanadium did not show any promising results whereas Ni^{+2} show a ZOI of 10.50 mm against Staph.aureus at 1000 µg, whereas Co^{+2} showed activity against both the organisms, with 13.00mm ZOI at 1000 µg for *E.coli* and 15.0 mm ZOI at 1000 µg for *Staph.aureus*.

Ni-Cys –Staph

Co-Cys-E.Coli

Co-cys-Staph:

Structures:

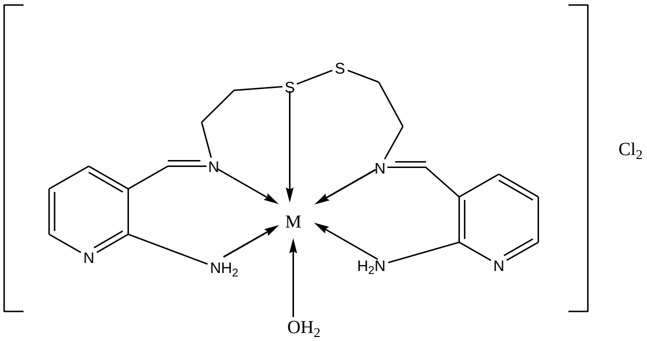


FIG.3: WHERE M= Mn(II), Co(II), Cu(II), Zn(II) and Cd(II) IN OCTAHEDRAL GEOMETRY

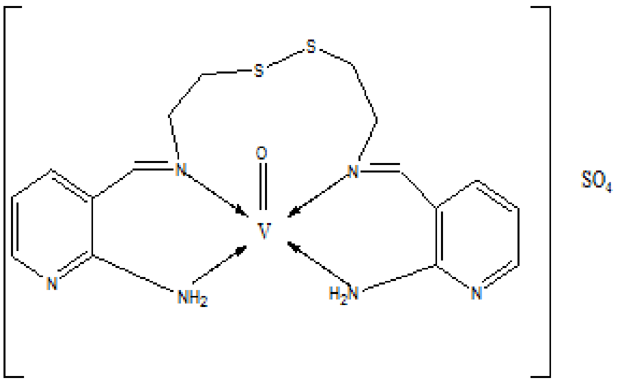


FIG. 4: VO (IV) COMPLEX; SQUARE PYRAMIDAL GEOMETRY

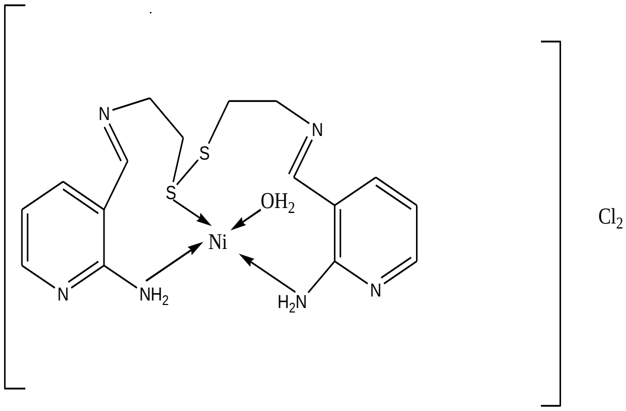


FIG. 5: Ni (II) COMPLEX

CONCLUSIONS: The prepared complexes were analyzed and characterized and it was found that few of the complexes were found to be good antibacterial agents. Further the complexes were found to be having N:N:S:N:N donor sequence for octahedral complexes.

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