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A comprehensive analysis of transition metal (II) complexes with medicinally important heterocyclic compounds

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Abstract
In the present manuscript hydrated sulphate salt of Copper (II) Nickel (II) and Cobalt (II) were treated with furan and pyrrole derivatives separately and formed their adducts. Obtained adducts have been characterized by using magnetic moment. IR spectra, electronic spectra, TGA, molar conductance measurement, elemental analysis, relative molecular weight determinations, mass spectra data and biological studies. The studies suggested that above ligands are neutral in nature and their complexes are positively charged having general formaula $[ML_xnH_2O]y\ SO_4$ where $x \equiv (Ligand) = 1,\ n = 2\ \&\ 4,\ y = 1,$ with 1:1 electrolytic nature. Data suggested square planar structure for Cu (II) complexes and octahedral structure for Ni (II) and Co (II) complexes. The ligands and their metal complexes were subjected to antimicrobial studies. The studies showed the enhanced activity of metal complexes against one or more species as compared to the uncomplexed ligand.

Keywords: IR, UV, Mass spectra, TGA, ligands, complexes, biological activity etc.

Introduction
In recent years, growing attention has been paid to the synthesis of number of solid complexes by replacing some of the coordinated water molecule from divalent transition metal hydrated sulphate by using thiourea, oximes, heterocyclic schiff base and pharmaceuticals application [1-5]. Presence of heterocyclic derivatives in pharmaceuticals and natural products have continued to stimulate a great deal of interest in the development of new methodologies for their synthesis. There are several bioactive natural molecules with N-heterocyclic-one-moiety such as holomycin, thiolutin, pyrrocidine, have been successfully used as antibiotic, antitumor agent peptidomimetics, HIV integrase [6], DNA polymerase [7] inhibitors. However, some of these methods have drawbacks, such as high temperature and utilize a chlorinated solvent, therefore, the development of a milder and more efficient route for one-pot synthesis of the important heterocycles is still in demand. Substituted furan derivatives are fundamentally important heterocyclic molecules and are present in many natural and medicinal structures. In the present paper Cu (II), Ni(II) and Co(II) complexes with furan & pyrrole derivatives were prepared. As earlier in most of the cases two water molecules could be replaced while the third one could be replaced only if some stronger ligands like chelating di or tri amines were used [8, 9]. Present work deals with a similar study by using furan & pyrrole derivatives.

Material and Methods
All the chemicals and reagents used for this research work were supplied from CDH, Aldrich, Sigma. A known weight of hydrated metal such as Cu (II), Ni (II) and Co (II) Sulphate was suspended in methanol and equimolar amount of ligand dissolved in absolute ethanol, was added drop wise while the mixture was kept under reflex continuously, even if the ligands are added in excess only one equivalent of the same (corresponding to the replacement of two water molecules) is consumed in the reaction. The other equivalents remain unreacted even after continued refluxing. After the addition of the ligand was completed the reaction mixture was further refluxed for 6 hours on magnetic stirrer at 60 ^{0}C and the complexes was crystallized out from the solution by repeated treatment with petroleum benzine and dried at under the reduced pressure over $CaCl_2$ yield (73-90%).

Ligand and their complexes were subjected to elemental analysis for C, H, N, whereas metals were estimated gravimetrically in the Lab [10]. IR spectra of the ligand and their metal complexes were recorded in FT/IR-4100 type A in KBr/Nujol mull phase 4000-200 cm^{-1} ITL Labs Pvt. Ltd. Delhi. Electronic spectra of the complexes were recorded with the help of UV-Backmann Du-2-spectrophotometer at Bareilly College, Bareilly. Molar conductance of the complexes in different solvent *viz*., Nitrobenzene and DMSO in 10^{-3} M dilution were observed at 25 °C by philips conductivity bridge PR- 9500 with a dip type conductivity cell in Dept. of chemistry Bareilly College, Bareilly. Magnetic susceptibility measurement was carried out by gouy balance using $HgCo(SCN)_4$ as standard.

Antimicrobial and antifungal activity of the ligands and their complexes were tested utilizing agar diffusion methods against numerous strains of microorganism *viz*., Staphylococcus aureus and Escherichia coli, Candida albicans, they were identified and obtained on the basis of cell culture collection at the concentration level 10 µM. Standard manufacturer's procedure was used to prepare the nutrient agar. Ligand and their adducts were dissolved in DMSO and introduced into the inoculated agar following sterile procedure, which then incubated overnight at 35^0C. Standard antibacterial (ciprofloxacin) and antifungal (ketoconazole) were used as dredge references and the resulting inhibition zone (diameter, mm) were recorded as listed in the given table. The minimum inhibition concentration was defined as the lowest concentration of experimental compounds that lead to a decrease *in vitro* in triplicate by both dilution methods and average of them was considered.

TG analysis was carried out on perkin-Elemer TGS-2 thermo balance at 10 °C/min heating rate. Mass spectra data of the ligands and their complexes were recorded at TOF magnetic sector and Quadrupole- SIMS instrument at New Delhi. The molecular weights of the compounds were carried out by Rast's method using camphor as solvent.

Results and Discussion

Complexes were subjected to elemental analysis, molar conductance TGA and magnetic susceptibility values given in table (1 & 2) which revealed that ligands have reacted with metal in 1:1 ratio and molecular formula assigned to $[ML_xnH_2O]ySO_4$ where $x \equiv (Ligand) = 1,\ n = 2\ \&\ 4,\ y = 1,$ which show that only two coordinated water molecules have been replaced from the parent hydrated metal (II) sulphate by one ligand molecule.

In the ir spectra of all these complexes a sharp γOH band characteristic of co-ordinated water appears at ~3420 Cm^{-1} while the bands due to γ_3 and γ_4 modes of uncoordinated sulphate ion appear at 1110 and 650 Cms^{-1}, respectively.

In the spectrum of the free ligand furfuraloxime the bands corresponding to the intramolecularly bonded –OH group appear at 3160 and 3040Cms^{-1}, while these merge together in the complexes and only one sharp band appears at 3360Cm^{-1}. This shows the cleavage of hydrogen bonding of oxime oxygen[11, 12], which is also supported by the raising of γC=N of the free ligand from 1640 to 1660 Cms^{-1} in the complexes[13]. Furthermore the appearance of the two sharp bands at 670 Cm^{-1} ($\gamma M\text{-}O_{oxime}$) and 510 Cm^{-1} ($\gamma M\text{-}O_{oxime}$) suggested the coordination of the ligand through furan ring and oxime oxygens [14].

In free pyrrolidone the >NH and >C=O stretching frequencies are observed at 3300 and 1700 Cms^{-1} both of which undergo considerable negative shifts in the complexes and occur at 3250 Cm^{-1} and 1665 cm^{-1}, respectively showing co-ordination through N and O atoms.

The TGA measurement of the complexes in the temperature range 20° to 800 °C show no more weight loss around 100 °C indicating the absence of lattice water. The loss in weight between 240^0 and 400 ^{0}C corresponds to the loss of two molecules of water and one molecule of the ligand [15]. The metal II sulphate, thus formed, remains stable between 400° and 500 ˚C and decomposed to the metal oxide up to 600 °C which remains stable till 800 °C.

Table 1: Elemental analysis of the complexes

Complexes	Molecular weight	% C	% H	% N	% M	$\%SO_4$	m.p.^{0}C	Colour
$[Cu\ C_5H_5NO_2(H_2O)_2]\ SO_4$	308.20 (306.54)	20.85 (19.57)	3.11 (2.93)	4.24 (4.56)	19.48 (20.16)	31.92 (31.31)	124	Yellow Orange
$[Ni\ C_5H_5NO_2(H_2O)_4]\ SO_4$	331.61 (337.69)	16.28 (17.77)	3.23 (3.84)	3.85 (4.14)	16.62 (17.37)	29.03 (28.42)	144	Brown
$[Co\ C_5H_5NO_2(H_2O)_4]\ SO_4$	338.43 (337.93)	16.94 (17.75)	3.28 (3.85)	3.76 (4.14)	11.02 (12.29)	28.78 (28.41)	113	Dark brown
$[Cu\ C_4H_7NO(H_2O)_2]\ SO_4$	219.30 (280.54)	17.54 (17.11)	4.12 (3.92)	5.12 (4.80)	20.73 (22.63)	35.20 (34.22)	141	Radish brown
$[Ni\ C_4H_7NO(H_2O)_4]\ SO_4$	303.36 (311.69)	15.82 (15.40)	4.67 (4.80)	5.01 (4.49)	17.56 (18.82)	31.06 (30.80)	161	Pink
$[Co\ C_4H_7NO(H_2O)_4]\ SO_4$	309.24 (311.24)	14.87 (15.42)	5.01 (4.82)	4.87 (4.50)	18.03 (18.93	31.13 (30.84)	109	Gree-blue

(Parenthesis values are calculated values)

Table 2: Molar conductance, TGA data Magnetic susceptibility values of the complexes

Complexes	Molar Conductance (Ω) mhos		% of H_2O and ligand loss at 280^0-400^0c	µeff BM.
	DMSO	Nitrobenzene		
$Cu\ C_5H_5NO_2(H_2O)_2$	51	24.6	48.09 (47.96)	1.884 (1.73)
$Ni\ C_5H_5NO_2(H_2O)_4$	54	25.2	53.98 (54.20)	3.207 (2.83)
$Co\ C_5H_5NO_2(H_2O)_4$	52	25.0	54.10 (54.18)	4.940 (3.16)
$Cu\ C_4H_7NO(H_2O)_2$	53	22.8	42.99 (43.13)	1.881 (1.73)
$Ni\ C_4H_7NO(H_2O)_4$	50	21.8	50.80 (50.36)	3.078 (2.83)
$Co\ C_4H_7NO(H_2O)_4$	52	29.3	50.07 (50.34)	4.503 (3.16)

(Parenthesis values are calculated values)

The electronic observation spectra of ligands and their complexes along with the molar extinction coefficient were recorded at room temperature using nitrobenzene & DMSO as solvents. The important electronic spectral bands for furfuraloxime and pyrrolidone, their monometallic complexes along with molar extinction coefficient have been given in table-2. The electronic spectra is used to assign the stereochemistry of the metal ion in the complexes based on the position and number of d-d[1] transition bands. The absorption spectra of the ligands furan & pyrrole derivatives are characterized by two bands in the region, 35335- 35087 cms^{-1} and ~40101 cm, respectively. These bands are assigned to arise due to intraligands $\Pi \rightarrow {}^*\Pi$ and $n \rightarrow {}^*\Pi$ transition due to $> C = N$, $-OH$ groups in the ligands. The band at ~40055 Cm^{-1} is considered as the characteristic bond for the heterocyclic fraction of the ligands as has been observed in the monomeric zone [16].

The copper (II) complexes show a single broad band in the region of 15432-15384 cms^{-1} with a comparatively very low molar extinction coefficient in the range of 22.3-24.6 in nitrobenzene and 51-53 in DMSO mhos. Hence this band is assigned to arise due to d-d[1] transition. In octahedral and tetrahedral complexes of Cu (II) the bands due to d-d[1] transition occur at 12500 Cm^{-1} and 18333 Cm^{-1}, respectively. In this case it falls in the range 600-700 nm reported for square planar complexes [17]. Thus the band in the range of 16668-15384 Cms^{-1} with a low molar extinction coefficient is assigned to have its origin due to d-d[A]' transition. The essential features of this band suggested that it is the combination of their transitions.

$^2B_{1g} \rightarrow {}^2A_{1g}$ Cm^{-1}, $^2B_{1g} \rightarrow {}^2B_{2g}$ Cm^{-1}, and $^2B_{1g} \rightarrow {}^2E_{2g}$ Cm^{-1}

Thus it may be concluded that Cu (II) complexes are four coordinate with μeff values in the range 1.881-1.884 BM. The appearance of the band at ~1600 Cm^{-1} associated with a shoulder at ~1300Cm^{-1} is indicative of a square planar stereochemistry.

The μeff values of both the Ni (II) complexes are around 3.20 BM there is a quiet possibility of octahedral stereochemistry. The spectrum of Ni (II) complexes should d–d[1] transition bands in the region 25310, 13980 and 9660 Cms^{-1}, assigned to $3A_{2g} \rightarrow 3T_{1g}(P)(\gamma_3)$, $3A_{2g} \rightarrow 3T_{1g}(F)(\gamma_2)$ and $3A_{2g}(F) \rightarrow 3T_{2g}(F)(\gamma_1)$ transitions along with the Dq and B values of 966 Cm^{-1} and 850 Cm^{-1} confirm an octahedral structure [18].

The electronic spectra of Co(II) complexes DMSO exhibited bands around 17575 Cm^{-1} and a strong high energy band at 21725 Cm^{-1} which was assign to the transition $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g} \rightarrow {}^4T_{1g}(P)$, respectively and the derived Dq and B value of 844 and 875 Cms^{-1} for high spin octahedral geometry.[18] The magnetic susceptibility measurement value (4.95 & 4.60) for Co(II) complexes are indicative of the three unpaired e^{-s} in Co(II) ion consistent with their octahedral environment [18].

Table 3: Mass spectra data of the ligands and their metal complexes

Compounds	Cal. Mas	Observed mass	Peaks
Furfuraloxime L_1	111	111.01	M
Pyrrolidone L_2	85	85.0	M
[Cu $C_5H_5NO_2(H_2O)_2$] SO_4	306.54	307.20	M
[Ni $C_5H_5NO_2(H_2O)_4$] SO_4	337.69	339.01	M+1
[Co $C_5H_5NO_2(H_2O)_4$] SO_4	387.93	339.20	M+1
[Cu C_4H_7NO $(H_2O)_2$] SO_4	280.54	282.59	M+2
[Ni C_4H_7NO $(H_2O)_4$] SO_4	311.69	313.02	M+1
[Co C_4H_7NO $(H_2O)_4$] SO_4	311.93	314.01	M+2

The mass spectra data of compounds and their metal complexes are given in table (3) which showed molecular ion peaks which were in good arrangement for expected values. All spectra showed characteristic common fragmentation pathways with intensive molecular ion peaks in most cases. The molecular ion peak in ligands L_1 & L_2 underwent fragmentation to produce peaks at M/Z 111.01 & 85.0, respectively corresponding to the molecular ion of furfuraloxime and pyrrolidone ligands which are assigned for HL peaks in figure 1. If further underwent pattern of furan derivatives [19]. A peak at m/z 93 and m/z 67 as a base peak found in both the ligands, respectively corresponds to the +ve ion $C_5H_3N^+$ and $C_4H_5N^+$ complexes with Cu (II), Ni (II) & Co (II) given same peaks *viz*., m/z 307.20, 282.59, m/z 339.01, 313.02 and m/z 339.20, 314.01 which assigned to peaks (M, M+2), (M+1, M+1) and (M+1, M+2), respectively in all cases as compared to ligands values [20].

Table (4 & 5) reveal biological results which showed diametric zone of inhibition in mm/MIC_{50}μM of the both ligands and their complexes. Both ligands showed lower activity against all tested bacteria and fungi as compared to standard drugs ciprofloxacin and ketoconazole while the metal complexes are more active compounds to the parent ligands and standard drugs comparing the antimicrobial results of the free ligands and their complexes showed that the complexation of the ligand with metals has enhance their antimicrobial potential and the P value was 0.05 indicate a significant statistical differences between the free ligands and their metal complexes. The data of the above tables are displayed by bar diagram in fig 2 & 3.

The enhancement was more pronounced in the case of Co(II) against *E. Coli*, Cu(II) complexes against staphylococcus aureus. These differences in the biological activities of the metal complexes for different metals could be related to the nature of the metal ion and the donor sequence of the ligands. In addition ligands exhibit different biological properties and the complexes of each metal could adopt the geometry around the metal ion. The polarity of the metal ion will be reduced on the complexation due to the partial sharing of the (+ve) charge with donor groups that increase the lipophilicity of the complexes. The enhanced lipophilicity increases the diffusion of the complexes through the lipid membrane and consequently blocking the allocated metal binding state in the targeted enzymes of the microorganism [21].

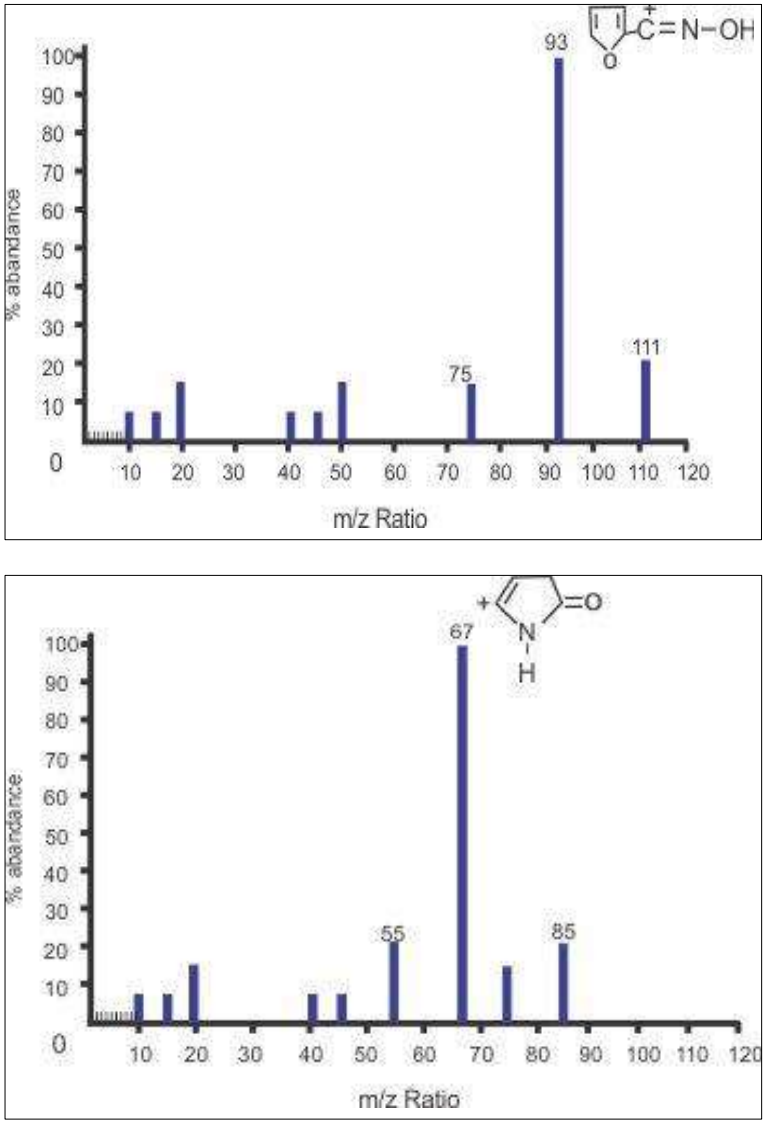


Fig 1: Show the ratio and percentage of abundance

Biological activity

Table 4: Biological activity results in terms of diametric zone of inhibition in mm. of the ligands and their metal complexes

Ligand/ Metal	L_1			L_2		
	E. Coli	***S. aureus***	***C. albicans***	***E. Coli***	***S. aureus***	***C. albicans***
L	25	21	20	29	26	23
Cu	27	30	26	30	35	30
Ni	24	23	20	29	28	23
Co	32	26	24	38	28	26
Ciprofloxacin Ketoconazole	33-	28-	-25	33-	28-	-25

Table 5: Biological activity results in term of MIC_{50} µM of the ligands and their metal complexes

Ligand/ Metal	L_1			L_2		
	E. Coli	***S. aureus***	***C. albicans***	***E. Coli***	***S. aureus***	***C. albicans***
L	0.07±0.002	2.20±0.003	0.042±0.002	0.071±0.001	1.52±0.002	-
Cu	0.072±0.002	1.52±0.004	±0.08±0.003	0.074±0.003	1.52±0.003	0.029±0.002
Ni	0.079±0.003	2.30±0.003	0.030±0.002	0.082±0.003	2.001±0.002	0.032±0.004
Co	0.001±0.004	1.32±0.004	0.029±0.004	0.064±0.004	1.32±0.007	0.007±0.001

*$p<0.05$, $p<0.005$

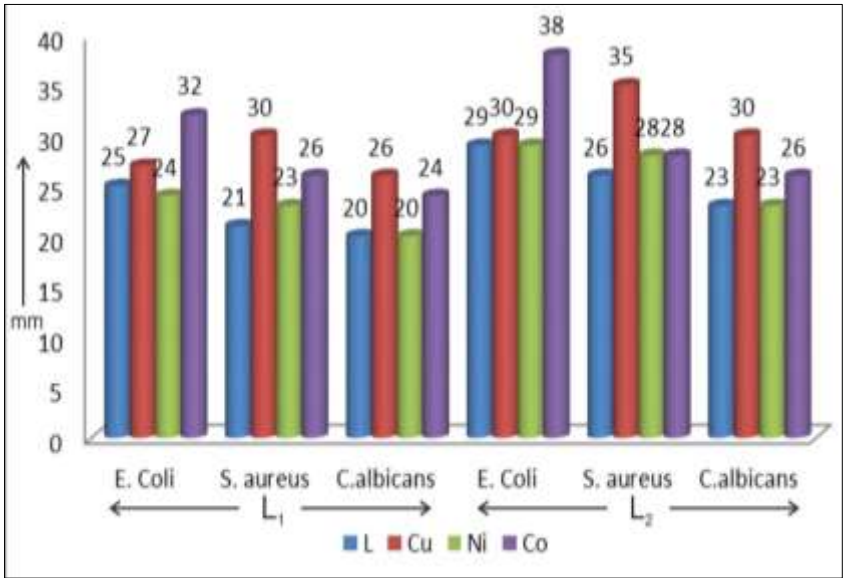


Fig 2: Bar Diagram showing diametric zone of inhibition of the ligands and complexes

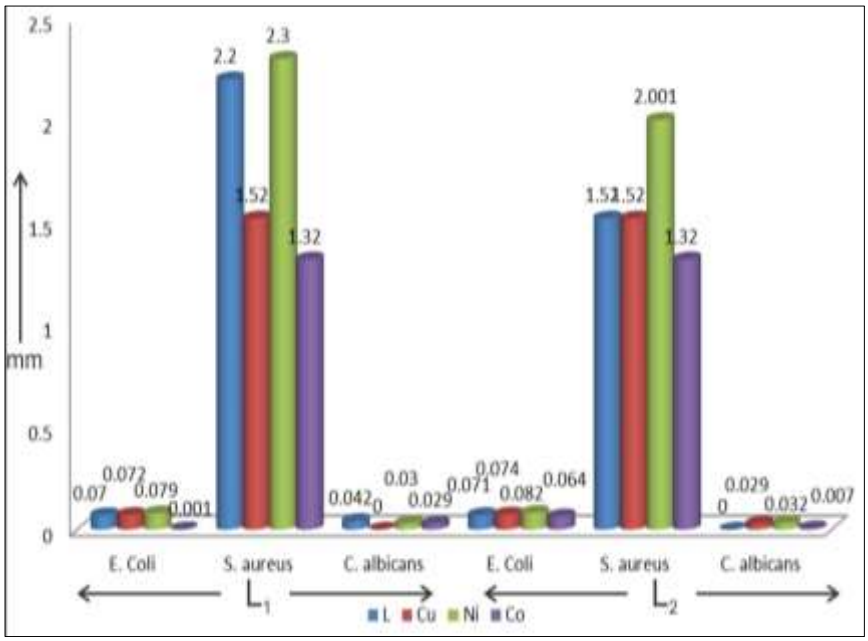
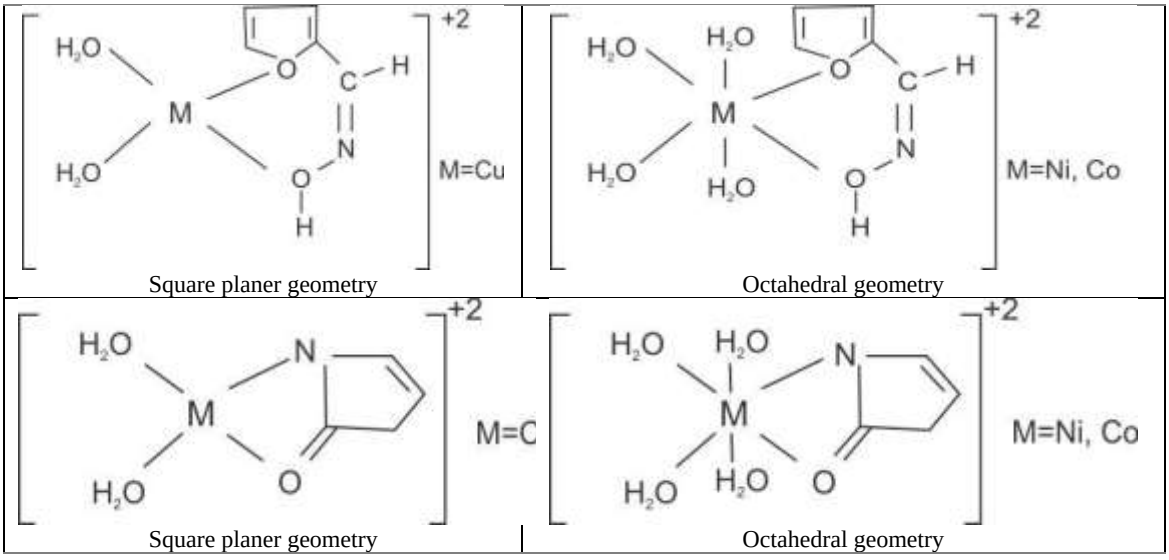


Fig 3: Showing biological activity in terms of mm/$MIC_{50\mu}M$

On the basis of above facts possible geometry of the complexes can be shown below:



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