



SYNTHESIS AND CHARACTERISATION OF MIXEDLIGAND METAL COMPLEXES OF TRIMETHOPRIM AND ISONIAZID

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ABSTRACT:

Trimethoprim (tmp) is a bacteriostatic antibiotic mainly used for prophylaxis and also in the treatment of urinary tract infections. It belongs to the group of chemotherapeutic agents known as dihydrofolatereductaseinhibitor. Trimethoprim can bind to dihydrofolatereductase and inhibits the reduction of dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). THF is an essential precursor in the synthesis of thymidine pathway and interference with this pathway inhibits bacterial DNA synthesis.

KEYWORDS: Population, Species.

INTRODUCTION

Trimethoprim's affinity for bacterial dihydrofolate reductase is found to be greater than its affinity for human dihydrofolate reductases. Isoniazid (Laniazid, Nydrazid), also known as isonicotinyhydrazine (INH), is an organic compound can block the natural enoyl-AcpM substrate and the action of fatty acid synthase. This process inhibits the synthesis of mycolic acid, required for the mycobacterial cell wall.

SYNTHESIS OF METAL COMPLEXES

0.01 M of the solution of the metal salts were dissolved in a beaker containing 20ml of

the suitable solvents and solution of 0.01M of the ligands were also dissolved in a beaker containing 20ml of their suitable solvents. The solutions were mixed together and refluxed for 5 hours but no precipitate was formed. The refluxed solution was left for two weeks. The precipitate obtained was washed and dried. On the basis of elemental analysis the complexes were formulated as $[Cu(inh)(tmp)]Cl_2 \cdot 2H_2O$, $[Zn(inh)(tmp)]Cl_2 \cdot 2H_2O$, $[Ni(inh)(tmp)]Cl_2 \cdot 6H_2O$ and $[Fe(inh)(tmp)(H_2O)Cl]Cl_2 \cdot 5H_2O$

RESULTS AND DISCUSSION

Elemental analysis

Elemental analysis (Table 1) shows that the ligands (Trimethoprim and isoniazid) and the metal salts are in the ratio of 1:1:1

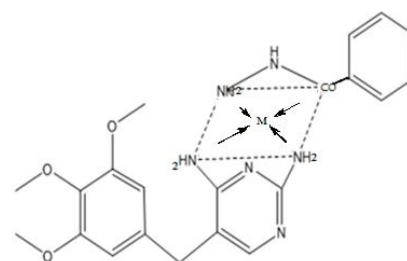
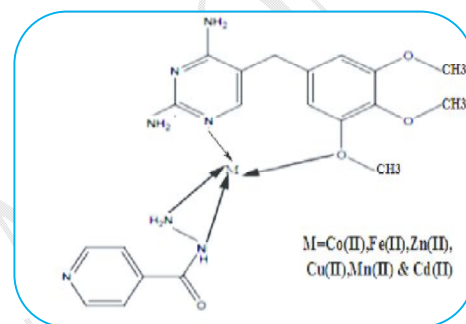


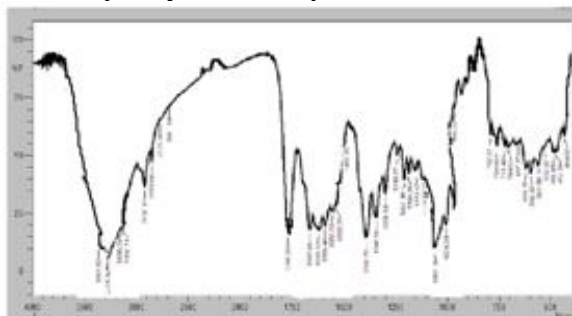
Fig.1 Geometry of mixed ligand metal complex of isoniazid and trimethoprim
M= Cu(II)

Table .1 Elemental analysis of mixed ligand complexes of isoniazid and trimethoprim

Compound	C%(found)	H%(found)	N%(found)	Metal%(found)
[Cu(inh)(tmp)]Cl ₂ .2H ₂ O	41.26(41.19)	5.02(5.38)	16.85(16.64)	10.92(10.89)
[Zn(inh)(tmp)]Cl ₂ .2H ₂ O	41.13(41.26)	5.07(5.12)	16.80(16.79)	11.92(11.87)
[Fe(inh)(tmp)(H ₂ O)Cl]Cl ₂ .5H ₂ O	39.71(40.12)	6.04(6.18)	15.87(15.93)	9.04(9.14)
[Ni(inh)(tmp)]Cl ₂ .6H ₂ O	41.03(41.56)	6.38(6.27)	16.76(16.84)	10.04(10.87)

IR spectra

The IR spectrum of isoniazid shows bands at 1725cm⁻¹ and 3243cm⁻¹ due to carbonyl group and NH group. During complexation (Fig 2) these bands get shifted to higher frequency indicating the coordination of the drug through the nitrogen of the amine group. In the infrared spectra of trimethoprim, the band due to NH group gets shifted indicating the involvement of these groups in complex formation. The reaction of isoniazid and trimethoprim with the metal salts was evidenced by the shifting of the band to lower frequency in the complexes.



Wave number (cm⁻¹)
Fig 2 IR spectrum of [Cu(inh)(tmp)]Cl₂.2H₂O

Table 2 IR spectral data of mixed ligand complexes of isoniazid and trimethoprim (cm⁻¹)

Compound	$\nu(\text{N-H})$	$\nu(\text{M-O})$	$\nu(\text{M-N})$
Trimethoprim	3242	-	-
Isoniazid	3243	-	-
Cu(inh)(tmp)]Cl ₂ .2H ₂ O	3142	465	565
Zn(inh)(tmp)]Cl ₂ .2H ₂ O	3125	460	654
Ni(inh)(tmp)]Cl ₂ .6H ₂ O	3221	462	573
[Fe(inh)(tmp)(H ₂ O)Cl]Cl ₂ .5H ₂ O	3317	465	525

ELECTRONIC SPECTRA

The electronic spectrum of copper complex (Fig 3) in chloroform consists of two bands 396 and 554nm. These were assigned to ${}^2B_{1g} \rightarrow {}^2E_{2g}$ and ${}^2B_{1g} \rightarrow {}^2A_{1g}$ respectively. The spectrum pattern suggested a square planar geometry around the copper(II) ion [1,2]. The Ni(II) complex has a magnetic moment of 3.72 BM, as predicted for high spin d⁸ systems with two unpaired electrons suggesting a tetrahedral geometry around the nickel(II) ion [3]. The Zn(II) complex shows only charge transfer transition from M→L and $\pi-\pi^*$ transitions, and no d-d transition. This complex is diamagnetic, confirming its tetrahedral geometry [4]. The band around 477-498 nm is assigned to ${}^6A_{1g} \rightarrow {}^4T_{2g}(G)$ transition suggesting an octahedral geometry which is confirmed by the magnetic moment value of 5.9 – 5.63 B.M [5].

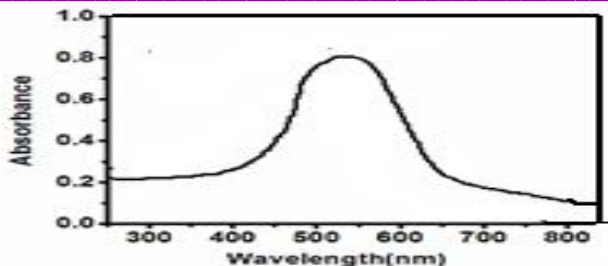


Fig.3 Electronic spectrum of $[\text{Cu}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$

Table .3 Electronic spectral data of mixed ligand complexes of isoniazid and trimethoprim (cm^{-1})

Compound	Transition	Wavelength(nm)	Geometry	μ_{eff}
Ligand	$n - \pi / \pi - \pi^*$	Below 250	-	-
$[\text{Cu}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$	${}^2\text{B}_{1g} \rightarrow {}^2\text{E}_{2g}$ ${}^2\text{B}_{1g} \rightarrow {}^2\text{A}_{1g}$	396 and 554	Squareplanar	1.72-1.82
$[\text{Zn}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$	-	-	tetrahedral	diamagnetic
$[\text{Fe}(\text{inh})(\text{tmp})(\text{H}_2\text{O})\text{Cl}]\text{Cl}_2 \cdot 5\text{H}_2\text{O}$	${}^6\text{A}_{1g} \rightarrow {}^4\text{T}_{2g}(\text{G})$	477-498	octahedral	5.9-5.63
$[\text{Ni}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 6\text{H}_2\text{O}$	${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{1g}(\text{P})$	620	Tetrahedral	3.72

ESR spectrum

The ESR spectrum of the copper complex (Fig 4) shows that the unpaired electron lies in the $d_{x^2-y^2}$ orbital giving ${}^2\text{B}_{1g}$ as the ground state with $g_{\parallel} > g_{\perp} > 2$, while the unpaired electron lies in the d_{z^2} orbital giving ${}^2\text{A}_{1g}$ as the ground state with $g_{\parallel} > g_{\perp} > 2$. From the observed values, it is clear that $A_{\parallel} > A_{\perp}$ and $g_{\parallel} > g_{\perp} > 2$ which suggest that the complex is of square planar geometry and the system is axially symmetric [6]. The α^2 values indicate that complexes have some covalent character while the β^2 and γ^2 values indicate that there is out-of-plane π -bonding, whereas the in-plane π -bonding is completely ionic.

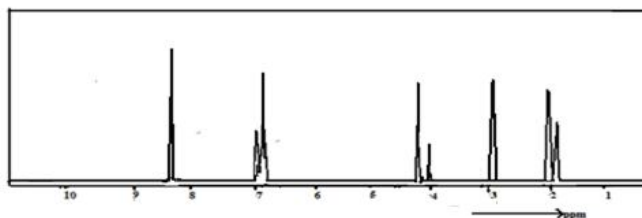


Fig 4 ${}^1\text{H}$ NMR spectrum of $[\text{Zn}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$

Table 4 ESR spectral data of $[\text{Cu}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$

Complex	g_{\parallel}	g_{\perp}	g_{iso}	K_{\parallel}	K_{\perp}	α^2	β^2	γ^2	G
$[\text{Cu}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ 77K	2.245	2.532	-	0.769	0.654	0.745	0.735	0.756	6.1
$[\text{Cu}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ 300K			2.10						

${}^1\text{H}$ NMR spectrum

In the NMR spectrum of trimethoprim, the NH_2 protons appear at $\delta 6.69$, δCH protons of 2-pyrimidine appear at $\delta 7.76$, CH protons of benzene moiety appear at $\delta 6.46$, CH_2 protons appear at $\delta 3.96$ and CH_3 protons appear at $\delta 3.83$ and in the second ligand NH protons appears at $\delta 8.0$, NH_2 protons

appears at δ 2.0, CH protons of 4-pyridine appear at δ 8.89. There is a shift in the position of peaks of NH_2 and NH groups, indicating the involvement of these groups during complexation (Fig 5).

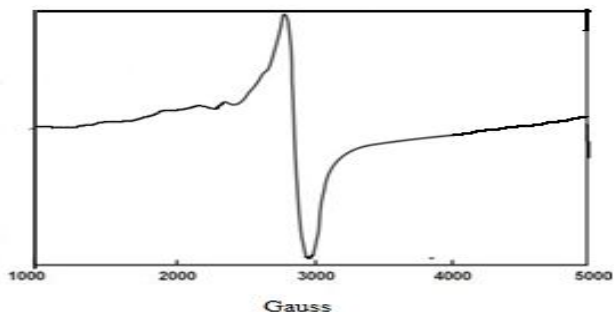


Fig .5. ESR spectrum of $[\text{Cu}(\text{inh})(\text{tmp})]\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ at 300K

XRD studies

The XRD pattern of the metallo drugs are studied in the 2θ range of 10° - 70° . The crystalline size of the complex was calculated from Scherer's formula. From the observed spectrum the average crystalline size for the metallo drug was found to be 39 nm indicating that it is nano crystalline in nature (Fig 6).

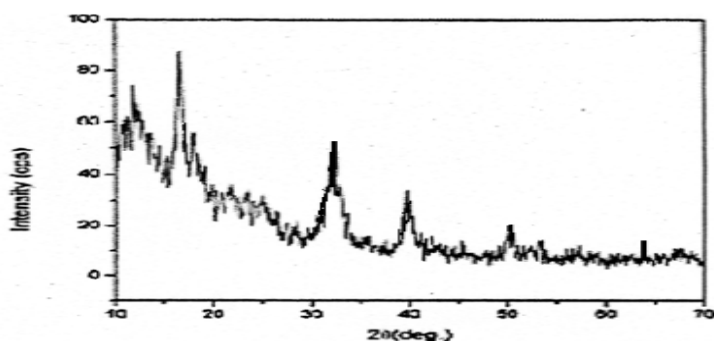


Fig .6 Powder XRD pattern of $[\text{Fe}(\text{inh})(\text{tmp})(\text{H}_2\text{O})\text{Cl}]\text{Cl}_2 \cdot 5\text{H}_2\text{O}$

TGA studies

The TGA experiments were carried out to explore the thermal stability of the complexes. The thermal behaviour of Fe(III) was studied in temperature range of 35°C - 800°C . The TGA studies of the complex (Fig 7) reveal that the decomposition proceeds in three steps. In the first stage weight loss at 70°C corresponds to the presence of the lattice water in the complexes. The weight losses in the temperature range 120°C - 210°C is due to the presence of the coordinated water in the complexes. A plateau was obtained after heating above 650°C , which corresponds to the formation of stable metal oxide [7,8].

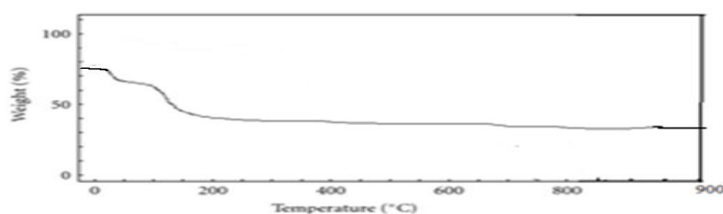


Fig .7 TGA pattern of $[\text{Fe}(\text{inh})(\text{tmp})(\text{H}_2\text{O})\text{Cl}]\text{Cl}_2 \cdot 5\text{H}_2\text{O}$

DSC studies

DSC behaviour of the Fe(III) complex (Fig 8) has been studied in the temperature range of 0-400°C. The metal complex shows the single T_g during the melting of the complex. The endothermic peak noted at 246°C can be attributed to the decomposition of the complex. Broad exothermic peak obtained at 280°C and 361.6°C can also be due to the decomposition of the complex [9,10].

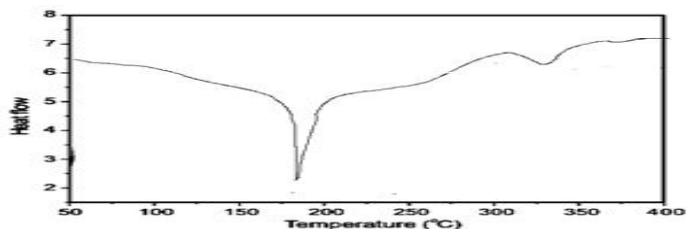


Fig.8 DSC pattern of $[\text{Fe}(\text{inh})(\text{tmp})(\text{H}_2\text{O})\text{Cl}]\text{Cl}_2 \cdot 5\text{H}_2\text{O}$

SEM studies

The surface morphology of the zinc complex (Fig 9) was recorded with energy of 20KV with magnification X150. The SEM images of the complexes are different from the ligand. This is an indication that the ligand changed the surface property of the metal complexes. Although the complexes gave the same colour and stereochemistry with the zinc salt, the surface of the compound showed a different morphology compared to the starting drug molecule.

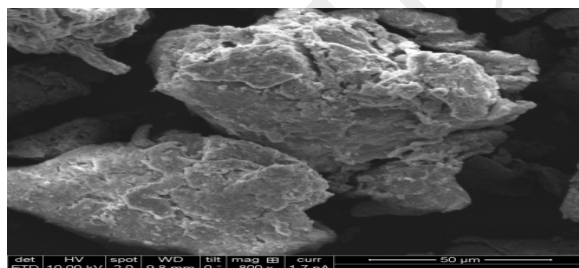


Fig 9 SEM image of $[\text{Zn}(\text{inh})(\text{tmp})\text{Cl}_2 \cdot 2\text{H}_2\text{O}$

FAB mass spectra

The FAB spectrum (Fig 10) gives a molecular ion peak M^+ at m/z 427, which corresponds to the molecular mass of the ligand. The observed molecular ion peaks M^+ at m/z 663 in Ni(II) complex accounts for the molecular mass of $[\text{Ni}(\text{inh})(\text{tmp})\text{Cl}_2$

$\cdot 6\text{H}_2\text{O}$ and the loss of four coordinated water molecules with the molecular mass of $[\text{Ni}(\text{C}_{20}\text{H}_{37}\text{N}_7\text{O}_{10}\text{Cl}_2)]^+$ respectively. Further the complex undergoes demetallation to form the species at m/z 181, 90 and 109 corresponding to the fragments $(\text{C}_{10}\text{H}_{13}\text{O}_3)^+$, $(\text{C}_6\text{H}_4\text{N})^+$ and $(\text{C}_4\text{H}_5\text{N}_4)^+$ respectively.

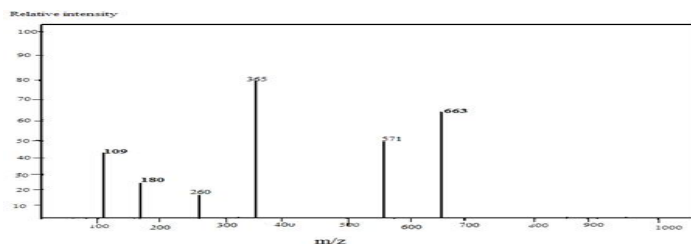


Fig 10. FAB mass spectrum of $[\text{Ni}(\text{inh})(\text{tmp})\text{Cl}_2 \cdot 6\text{H}_2\text{O}$

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