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Synthesis, Spectral Characterization *In Vitro* Biological and Pharmacokinetics Studies of Biologically Active Copper and Zinc Metal Chelates with 4-Mercaptoaniline and Nitrite Ion

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Abstract: Copper and zinc metal chelates were synthesized with 4-mercaptoaninilline and nitrite ion using microwave irradiation which is one of the eco-friendly techniques with less reaction time high yield, no hazardous waste, and economic. The prepared metal chelates were structurally characterized based on microanalysis, metal estimation, conductance, nuclear magnetic resonance, electronic spectra, IR and Far-IR, EPR, and powder X-ray diffraction studies. Mononuclear tetragonal geometry of copper complex and square planar geometry of Zn(II) complex was confirmed by the microanalysis, metal estimation, and spectral studies. The neutral nature of the complexes was confirmed by the low molar conductance values. The crystal nature of zinc metal chelate was also confirmed by the XRD data. Antibacterial and antifungal activities of the 4-mercaptoaniline and metal chelates were carried out by the Agar disc diffusion method with the bacterial strains *Bacillus, Streptococci, Shigella*, and fungal strain *Candida albicans*. The results indicated that the complexes are more potent against bacterial and fungal strains. The pharmacokinetics studies were computed by using Swiss ADME software to predict the lipophilicity, pharmacokinetics, and drug likeliness of the complexes.

Keywords: Microwave-assisted, 4-mercaptoaniline, Antibacterial, Antifungal, Pharmacokinetics

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Introduction

4-aminothiophenol or p-mercaptoaniline with nitrogen and sulphur donor atoms in their structure have a good chelating ability to metal ions (Telmel *et al*., 2008). The donor sites have a

keen interest in the donating capacity to the metal ions. The metal complexes of this type of ligands are important in a broad range of bacterial, fungal, and anticancer drugs (Kavitha and Reddy, 2014). The 4-ATP is one of the sulphur donor compounds due to this donor capacity it is used to remove heavy metals and to increase absorption capacity (Liu *et al*., 2009). From the recyclable materials, the metal ions were isolated using 4-ATP. It is one of the metal-binding terminals in nanowires. It is also existing in the form of a Zwitter ion (Raman *et al*., 2001; Kumaran *et al*., 2013). Schiff bases of aminothiophenol show many biological activities namely antimicrobial, antifungal, anticancer, antihypertensive, and anti-inflammatory (Mehta and Joseph, 2005; Sekhar *et al*., 2021).4-mercaptoaniline is used in the construction of functionally self-assembled film and they have semiconducting properties and are also used in surface-enhanced Raman spectroscopy. The present study emphasized the synthesis of copper(II), and zinc(II) chelates with 4-mercaptoaniline and nitrite ion under microwave irradiation and was structurally characterized using various physical, chemical, and spectral methods.

Materials and Methods

Copper nitrate, zinc nitrate, 4-mercaptoaniline, sodium nitrite, solvent viz. DMSO, methanol, and ethanol were of AR grade.

Preparation of metal complexes:

Cu(II) complex was synthesized by mixing 1.03 g of 4-mercaptoaniline in methanol, 1.21 g of sodium nitrite dissolved in water, and adding to 1 g of copper nitrate dissolved in CH_3OH. All the mixed compounds were irradiated in a CATA-R, model microwave oven. The dark green color metal chelate was filtered and dried in desiccators.

Zn(II) chelate was prepared by the addition of 0.840 g of 4-mercaptoaniline in methanol, and 0.98 g of sodium nitrite in water to the corresponding zinc nitrate for 1 g dissolved in CH_3OH. The mixture was subjected to microwave irradiation using the CATA-R model. The pale yellow colour complex was dried after filtration.

Methods for characterization:

Microanalysis and estimation of metal ions of the prepared complexes were carried out using Vario make, EL-III model elemental analyzer, and standard volumetric and colorimetric analysis, respectively. 10^{-3} M metal complexes were mixed with CH_3CN and the conductance was measured at room temperature using Conductivity Bridge. The cyclic voltammetry of metal complexes was measured using the Versa Stat model electrochemical work station in DMSO. The electronic spectra of 4-ATP and its metal complexes in the solid-state using Varian make, CARY-5000 model instrument. IR spectra of ligand and its complexes were recorded Using Shimadzu, FT-IR, 8400 S Model IR spectrometer. The Far IR spectra of the complex were recorded in Bruker, Vertex 80 FTIR instruments. NMR spectra of the zinc complex were carried out using AVANCE III 500 NMR spectrometer. Powder XRD of the Zinc(II) complex was carried out using the Rigaku model instrument.

Bio-potential activity:

Biological activities of 4-ATP and metal chelates were carried out by Agar disc diffusion method at three different concentrations viz., 50 µl, 100 µl, and 150 µl using *Streptococci*, *Shigella*, *Bacillus Candida albicans*. The experiments were done in triplicate. The MIC values of the metal chelates were measured on a millimetre scale.

Results and Discussion

Elements such as copper, and zinc ions present in the complexes were estimated using elemental analysis which indicated the stoichiometry and molecular formulae of the complexes. It predicted that the general formula of Cu(II) and Zn(II) complexes is $[M(L_1)_2(L_2)_2]$ where L_1 is the 4-mercaptoaniline and L_2 is the nitrite ion (ambidentate). The conductance of 10^{-3} M concentrated metal complexes in CH_3CN showed low molar conductivity values at 50

$Ohm^{-1}cm^2mole^{-1}$ and 36 $Ohm^{-1}cm^2mole^{-1}$ corresponding to the neutral non-electrolytic nature of the complexes (Jhailani *et al*., 2018).

Cyclic voltammetry:

Cyclic voltammogram of Zn(II) complex show one anodic and cathodic peak E_{pa} = 0.6599 and E_{pc} = -0.5524 V respectively attributed to the oxidation and reduction process of Zn(II)/Zn(I) couple. This cyclic voltammogram confirmed the controlled one-electron transfer quasi-reversible reaction was further evidence that the peak potential separation ΔEp = -1.2123 V, Ipa/Ipc is at 0.7140 A, and the standard reduction potential (E_0) at 0.3837 V (Pawar *et al*., 2016).

UV-Visible:

The electronic spectra of 4-aminothiophenol give one broad peak at 271 nm corresponding to the π - π* transition it may be present in the longer wavelength at 284 nm in the copper complex for $^2B_{1g} \rightarrow {}^2E_g$ transition, the other two transitions 596 nm and 362 nm corresponding to $^2B_{1g} \rightarrow {}^2A_{1g}$ $^2B_{1g} \rightarrow {}^2B_{2g.}$ the magnetic moment is 1.86 BM tetragonally distorted octahedral geometry. The charge transfers spectra at 281 nm and 367 nm (27,247cm^{-1}) corresponding to the LMCT and MLCT in Zn(II) complex it is a filled configuration that is diamagnetic and there is no d-d transition ascribed to the Zn(II) complex possesses square planar geometry (Ejelonu, 2016; Rangarajan *et al*., 2021).

IR spectra:

Vibrational band assignment of 4-mercaptoaniline showed aromatic Ar-NH (asymmetric stretching) at 3418 cm^{-1}, N-H (symmetric stretching) at 3089 cm^{-1}, Ar-C-N (Stretching) at 3027 cm^{-1}, C-H (Aromatic stretching) at 3071 $cm^{-1}$and Ar- C-S (Stretching) 1307 cm^{-1}. These are found in the corresponding peaks which are slightly shifted to lower or higher frequency in Cu(II) and Zn(II) complexes. The ambidentate ligand nitrite ion exhibited asymmetric and symmetric NO_2 at 1470-1370 cm^{-1} and 1340-1320 cm^{-1} and the N=O, N-O corresponding to1485-1400 cm^{-1} and 1110-1050 cm^{-1}, these frequencies were shifted to higher wavenumber in Cu(II) and Zn(II) complexes. The deformation frequency was also found at 820-845 cm^{-1} which was also present in the same or slightly higher wave number in complexes (Prakash and Adhikari, 2011).

NMR spectra of ligand and Zn(II) complex:

4-mercaptoaniline have four different types of proton at 2.503 ppm, 7.873 to 7.885 pm, 7.263 to 7.275 ppm, and 7.100 to 7.120 ppm corresponding to the SH, aromatic C-H (1), aromatic CH(2) and NH_2, in Zn(II) complex the SH proton shifted to deshielded and downfield whereas NH2 proton shifted to up-field and shielded, finally the two aromatic protons were shifted to up-field region indicating the diamagnetic square planar geometry of the complex (Jabbi *et al*., 2020).

EPR spectrum:

EPR spectrum of the copper complex gives the isotropic signal corresponding to the g_{iso}=2.0158 which indicated that the value is higher than the free electron and the three axes $g_x = g_y = g_z$ confirm the covalent tetragonal geometry of Cu(II) complex (Fig. 1) (Yahaya and Mukhtar, 2021).

Powder X-ray diffraction:

The powder X-ray diffraction pattern of the Zn(II) complex showed the monoclinic crystal system based on the data such as miller indices, lattice constant a, b, c, and crystal angle were found at a = 7.290 Å, b = 19.140 Å and c = 7.620 Å with the crystal angles of α = 90°, β = 94°, ν = 90° and a. The fact a ≠ b ≠ c and α = ν ≠ β indicated g the monoclinic crystal system (Fig. 2) (Liang *et al*., 2019).

Biological activity:

Metal chelates showed higher antibacterial and antifungal activities due to their chelate nature of them, more chelation makes the π electron delocalization on the whole chelate ring which favours the lipophilic nature of the complexes. According to Tweedy's chelation theory polar and non-polar nature of the metal, chelates make the cell permeation to the cell which favours the

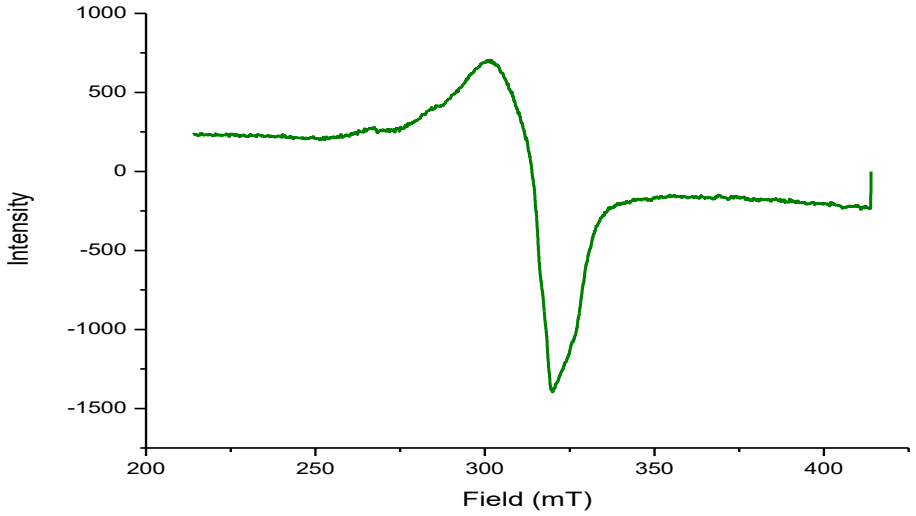

Fig. 1: EPR spectrum of Cu(II) complex.

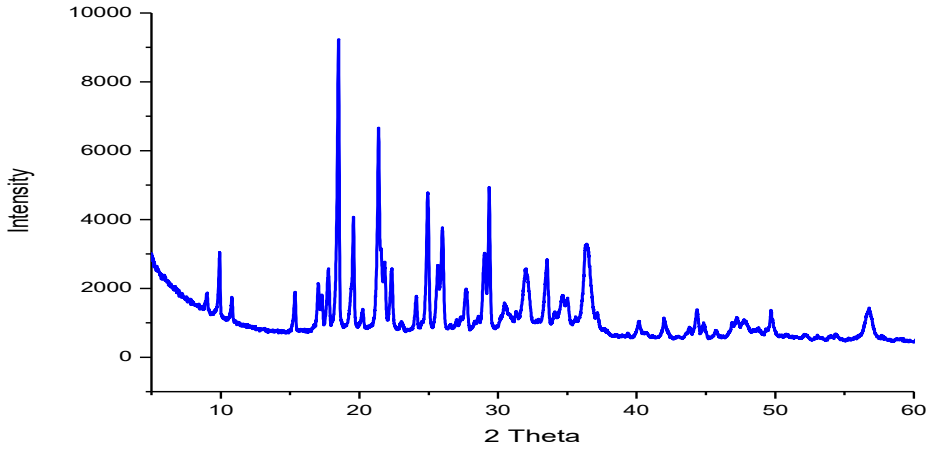

Fig. 2: Powder XRD pattern of Zn(II) complex.

lipophilic nature of the complexes (Mukthar *et al*., 2020). Complex nature, neutral nature, and conductivity also increased the biological activities of the complexes. The MIC values of the complexes are given in Table 1.

Pharmacokinetics Study: computational methodology:

The SMILES of the complexes were derived with the help of a structure file generator. The SMILES is a freely available web page in Swiss ADME, using this tool, Physico-chemical, PPSA, membrane diffusion, ADME, and pharmacokinetics behavior were found. The lipophilic nature was also predicted using five types of models of computational parameters such as XlogP, WlogP, MlogP, SILICON-IT, and logo (Table 2). The results indicated that the complexes showed a pharmacokinetics effect and lipophilic nature. The pharmacokinetic values such as GI absorption was low and BBB permeant, CYP1A2, CYP2C19, CYP2D6, and CYP3A4 inhibitor was absent but P-gp substrate is present in the metal complexes.

Table 1: Antimicrobial activities : Minimum Inhibitory Concentratipn of the compounds: inhibition zone – (mm)

S. No.	Compounds	*Bacillus*	*Streptococci*	*Shigella*	*C. albicans*
1	4-mercaptoaniline	8	8	6	8
2	Cu(II) complex	10	6	7	7
3	Zn(II) complex	13	12	9	10

Table 2: Lipophilicity and drug likeliness of Cu(II) complex

S. No.	Lipophilicity			Drug likeliness		
	Parameters	**Cu(II) complex**	**Zn(II) complex**	**Parameter**	**Cu(II) complex**	**Zn(II) complex**
1	Log $P_{o/w}$ (iLOGP)	-10.30	-13.29	Lipinski	No; 2 violations: MW>500, NorO>10	Yes; 0 violation
2	Log $P_{o/w}$ (XLOGP3)	2.64	0.01	Ghose	No; 2 violations: MW>480, MR>130	Yes
3	Log $P_{o/w}$ (WLOGP)	0.74	2.24	Veber	No; 1 violation: TPSA>140	No; 1 violation: TPSA>140
4	Log $P_{o/w}$ (MLOGP)	1.78	1.10	Egan	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>131.6
5	Log $P_{o/w}$ (SILICOS-IT)	1.46	1.46	Muegge	No; 1 violation: TPSA>131.6	No; 1 violation: TPSA>150
6	Consensus Log $P_{o/w}$	-0.73	-1.69	Bioavailability Score	0.17	0.55

The medicinal chemistry data like PAINS is 0 alert whereas brenk is 3 alert with aniline, nitro, and thiol group, the Leadlikeness is absent and the synthetic accessibility for Cu(II) is 3.54 and Zn(II) is 1.72 (Krishnamurthy *et al*., 2007; Sivakumar *et al*., 2022).

Conclusion

Cu(II), and Zn(II) complexes were synthesized under the microwave irradiation method. All the complexes are neutral mononuclear. The redox property of the Zn(II) complex confirmed its oxidation and reduction property. Tetragonal geometry of copper complex and square planar geometry of Zn(II) complex confirmed by its UV-Visible, IR, NMR spectral study. The monoclinic nature of the complex from XRD and metal-ligand covalence from EPR spectra were also confirmed. The antibacterial and antifungal activities and pharmacokinetics studies of the complexes were also confirmed.

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