SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL AND ANTI-INFLAMMATORY STUDIES OF SOME NOVEL SCHIFF BASE METAL COMPLEXES DERIVED FROM THE DRUG, DICLOFENAC

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ABSTRACT

The synthesis of Schiff base transition metal complexes always appears to be fascinating because of the possibility of obtaining coordination compounds of unusual structure and stability. These compounds possess special attention in the field of pharmaceuticals because of their wide spectrum of biological applications. Schiff base complexes form versatile compounds which actively take part in metalloenzymes and also can act as biomimetic models because of their closeness to natural proteins and enzymes. Hence, the present paper mainly aims in the synthesis of Schiff base ligand by modifying the functional group of the drug, diclofenac and using that Schiff base ligand four novel metal complexes of Cu(II), Co(II), Ni(II), and Zn(II) were prepared. The nature of bonding and the stereochemistry of the metal complexes can be deduced from elemental analyses, molar conductance, magnetic susceptibility, IR, electronic, ¹H NMR and Mass. The analytical data reveals that the metal to ligand ratio is 1:2. Due to lower molar conductivity values, the metal complexes are considered nonelectrolytes. The spectral analysis data describes that all the metal complexes possess octahedral geometry. The drug diclofenac synthesized Schiff base ligand and novel metal complexes were subjected to antimicrobial as well as anti-inflammatory activities. The Schiff base ligand and metal complexes show promising biological activities.

Keywords: Coordination Compounds, Schiff Base, Metal Complexes, Diclofenac, Antimicrobial, Anti-inflammatory.

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INTRODUCTION

For decades, coordination chemistry seems to be a topic of inquisitiveness as it involves the synthesis of the diversity of ligands containing different functional groups and coordinates with metal ions of variable oxidation states, exhibiting different geometries with unique properties, novel reactivity, and infinite applications.¹ Schiff bases form an important class of organic compounds prepared by condensation of an aliphatic or aromatic primary amine with carbonyl compound.² Schiff bases are the most favored ligands that can stabilize metal ions in different oxidation states.³ The formation of stable complexes with metal ions is due to nitrogen lone pair of electrons of azomethine (–N=CH) bonding in their structure. Imine complexes have a diversity of biological properties, including antitumor, antiviral, antifungal, antibacterial and so on activities.⁴ Non-steroidal anti-inflammatory drugs (NSAIDs) are used for treating different types of arthritis. The pharmacological activity of NSAIDs is related to the suppression of the enzyme prostaglandin endoperoxidase, commonly known as cyclo-oxygenase (COX). It was discovered that COX exists in two isoforms, COX-1 and COX-2, which are regulated and are expressed differently. Since long-term usage of NSAIDs causes gastrointestinal problems, it has become important to synthesis novel drugs with lesser side effects.⁵⁻¹⁰ Literature survey reveals that Schiff base metal complexes had shown promising anti-inflammatory activities.^{11,12} Therefore, the current study was aimed at preparing, spectrally analyzing, and biologically evaluating a Schiff base ligand and its metal complexes.

EXPERIMENTAL

Material and Methods

All the chemicals and solvents used were of Sigma Aldrich (Analytical grade). The drug, diclofenac was purchased from Drugs India Mahaveeray, Hyderabad, India and was used without any further purification. The ethanol was distilled and then used as a solvent for synthesis. Melting points determined are uncorrected and TLC (Thin layer chromatography) was used to test the compound for the completion of the reaction. Elemental analysis was carried out using an elemental analyzer instrument. The molar conductance of the synthesized complexes in 1×10^{-3} mol dm³ DMF solution was measured using ELICO digital conductivity meter of CM-180 model. The infrared spectra of the ligand and complexes were recorded in FTIR Shimadzu spectrometer in the range 4000-400 cm⁻¹ by KBr pellets method. The electronic spectra were recorded by using 20 spectronic instruments. The ¹H NMR spectrum was obtained from IISC, Bangalore, India. Mass spectrum of the Schiff base ligand was recorded on Micromass UK PLATFORM II LC-MS Spectrometer.

General Procedure

The conversion of (2-(2-(phenylamino)phenyl)acetyl)sodium (Diclofenac sodium) to 2-(2-(phenylamino)phenyl)acetic acid (Diclofenac acid) was done by taking approximately 250mL of distilled water in a beaker and by heating it. To the hot water, 30 g of sodium diclofenac was added pinch by pinch until it was completely dissolved. This solution was kept in ice-cold water for some time and then 6 N HCl (250 mL) was added with constant stirring, the precipitate was obtained. The precipitate thus obtained from the above process was diclofenac acid. The precipitate was recrystallized in ethanol.

The compound 4-amino-5-(2-(phenylamino)benzyl)-1,2,4-triazolidine-3-thione was synthesized as follows: Firstly, the compound 1,3-diaminothiurea (thiocarbohydrazide) was prepared by referring to the reported literatures^{13,14} and then the compound 4-amino-5-(2-(phenylamino)benzyl)-1,2,4-triazolidine-3-thione was synthesized by the fusion of thiocarbohydrazide and diclofenac acid in 1:1 molar ratio at 180 °C for about 3 hours. The fused mass formed was triturated with hot water. The precipitate obtained was filtered, washed with sodium bicarbonate solution, dried and finally recrystallized using ethanol.¹⁵

The compound 2-(((3-mercapto-5-(2-(phenylamino)benzyl)-1,2,4-triazolidin-4-yl)imino)methyl)phenol (Schiff base ligand) was synthesized by mixing an equimolar ratio of 4-amino-5-(2-(phenylamino)benzyl)-1,2,4-triazolidine-3-thione and salicylaldehyde. This solution was refluxed for about 5 hours. The yellow-colored precipitate formed was the Schiff base ligand. It was filtered, washed several times with water, dried and recrystallized in ethanol.

The synthesis of metal complexes was carried out by concentrating an ethanolic solution of the respective metal salts Cu(II), Co(II), Ni(II), and Zn(II) with an ethanolic solution of Schiff base ligand in 1:2 (metal: ligand) molar ratio and the solution was heated under reflux for about 3 hours. The colored precipitates obtained were filtered, washed several times with water and dried.

RESULTS AND DISCUSSION

The synthesized Schiff base ligand and its metal complexes were found to be intensely colored, stable at room temperature, soluble in solvents like DMF and DMSO. The elemental analysis data represented in Table-1 shows that they are in good agreement with those calculated for the suggested molecular formulae revealing that the complexes have 1:2 metal-ligand stoichiometry ratio.^{16,17} The molar conductance values for the complexes were found to be very low and so they are considered as non-electrolytes.

Table-1: Elemental Analytical Data of Schiff Base Ligand and its Metal Complexes.

Ligand/Complexes	Physical Color	Elemental Analysis (Observed, Calculated) %			
		C	H	N	Metal
C ₂₂ H ₂₃ N ₅ OS	Yellow	65.20(65.16)	5.60(5.72)	17.25(17.27)	-----
C ₄₄ H ₄₂ CuN ₁₀ O ₂ S ₂	Brown	60.75(60.71)	4.80(4.86)	16.20(16.09)	7.75(7.30)
C ₄₄ H ₄₂ CoN ₁₀ O ₂ S ₂	Red	61.11(61.03)	4.04(4.08)	16.51(16.18)	6.86(6.81)
C ₄₄ H ₄₂ NiN ₁₀ O ₂ S ₂	Yellow	61.09(61.05)	4.72(4.89)	16.60(16.18)	6.60(6.78)
C ₄₄ H ₄₂ ZnN ₁₀ O ₂ S ₂	Cream	60.72(60.58)	4.22(4.85)	16.55(16.06)	7.77(7.49)

The comparative study of the Infrared (IR) spectra of the Schiff base ligand and its metal complexes gives valuable information regarding the nature of functional groups coordinated to the metal atom.¹⁸ The selected IR Spectral data is represented in Table-2. The IR spectra of complexes indicate that Schiff base

ligand coordinates with metals via –SH group of triazole, azomethine nitrogen group and phenolic –OH group. The Schiff base ligand shows a peak at 1640 cm^{-1} which can be assigned to C=N (azomethine) group. The same peak in all the metal complexes has been shifted towards the lower wavenumber by 20-30 cm^{-1} . This indicates that complexation has taken place through azomethine group. The peak at 3272 cm^{-1} has appeared in the Schiff base ligand and is due to the phenolic –OH group. This peak is absent in all the metal complexes which indicate the involvement of the phenolic group in complex formation. Further the –SH group in Schiff base ligand has been assigned at 2926 cm^{-1} . This peak doesn't appear in all the metal complexes indicating that complexation also occurred from –SH group. Moreover, the new peaks in the range of 764-743, 671-641, and $476\text{--}436\text{ cm}^{-1}$ in all the metal complexes are due to M-O, M-S and M-N bonding, respectively.¹⁹⁻²²

Table-2: Selected Infrared Data of the Schiff Base Ligand and its Metal Complexes

Compounds	Wavenumber(cm^{-1})					
	ν (O-H)	ν (S-H)	ν (C=N)	ν (M-O)	ν (M-N)	ν (M-S)
Schiff base ligand	3272	2926	1640	-	-	-
Copper complex	-	-	1617	743	671	476
Cobalt complex	-	-	1621	755	641	436
Nickel complex	-	-	1596	764	645	448
Zinc complex	-	-	1617	743	671	476

Electronic Spectra and Magnetic Susceptibility

The electronic spectra of complexes provide valuable information regarding the stereochemistry of metal ions in complexes.²³ The electronic spectra of all the compounds were obtained in DMSO solution and the results are tabulated in Table-3. The electronic spectrum of Schiff base ligand shows two bands at 298 and 371 nm which can be attributed due to $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, intraligand charge transfer transitions of benzene and non-bonding electrons present on the nitrogen atom of azomethine group. The Cu (II) is a d^9 ion and provides a good example for the Jahn-Teller effect. The electronic spectrum of Cu (II) complex shows absorption bands at 343 and 670 nm due to ${}^2B_{1g} \rightarrow {}^2E_g$, ${}^2B_{1g} \rightarrow {}^2A_{1g}$ transitions. The magnetic moment value for Cu (II) complex is 1.82 BM. These studies indicate that Cu (II) complex possesses octahedral geometry. The magnetic moment of Co (II) at room temperature shows a value of 4.75 BM and exhibits three bands at 332, 642, and 681 nm due to ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(P)$, ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$ transitions. This can be explained based on octahedral symmetry which involves a high degree of orbital contribution. The Ni (II) complex exhibits bands at 250, 303, 636 and 684 nm which may be due to $\pi \rightarrow \pi^*$, ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(P)$, ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(F)$, ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(F)$ transitions. Ni (II) complex shows a magnetic moment value at 3.16 BM depending upon the magnitude of orbital contribution. These observations suggest that Ni (II) possess an octahedral configuration in the complexes. Zn (II) is diamagnetic with d^{10} configuration and therefore it does not show any d-d transitions.²⁴⁻²⁶

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

The ${}^1\text{H}$ NMR spectrum of the drug diclofenac and Schiff base ligand were recorded in DMSO solvent and are represented in Fig.-1 and 2.²⁷ When compared the spectrum of diclofenac drug to that of Schiff base ligand, the following changes have been noted. In the spectrum of the drug, the peak at δ 3.697 ppm is due to the presence of –CH protons whereas the same peak appears at δ 4.115 ppm in the spectrum of ligand. The appearance of multiplets in the region δ 6.275-7.532 ppm in drug spectrum can be assigned to the aromatic protons, these peaks in the Schiff base ligand spectrum appear between δ 6.234-7.76 ppm. A signal at δ 7.972 ppm can be seen in the ligand spectrum and this can be mainly assigned because of azomethine group (HC=N) group of Schiff base ligand whereas there is no such peak in the drug spectrum. The –NH proton peak in the drug spectrum appears at δ 12.673 ppm and in the ligand spectrum,

it has appeared at δ 10.594 ppm. Further, in the ligand spectrum, a singlet peak at δ 10.684 ppm can be seen and this can be assigned due to the –OH proton of salicylaldehyde and also a singlet at δ 13.592 ppm mainly corresponded due to –SH proton of triazole ring. These peaks are absent in the drug spectrum. Therefore, these results confirmed the formation of Schiff base ligand.²⁸⁻³³

Table-3: Electronic Spectral Data of Schiff Base Ligand and its Metal Complexes

Compounds	Absorption Bands (nm)	Assigned Transitions
Schiff base ligand	298, 371	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
Copper complex	343, 670	${}^2B_{1g} \rightarrow {}^2E_g$, ${}^2B_{1g} \rightarrow {}^2A_{1g}$
Cobalt complex	332, 642, 681	${}^3T_{1g}(F) \rightarrow {}^3T_{1g}(P)$, ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, ${}^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$
Nickel complex	250, 303, 636, 684	$\pi \rightarrow \pi^*$, ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(P)$, ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(F)$, ${}^3T_{2g}(F) \rightarrow {}^3T_{1g}(F)$
Zinc complex	293	$\pi \rightarrow \pi^*$

Fig.-1: ${}^1\text{H}$ NMR Spectrum of Diclofenac Drug Fig.-2: ${}^1\text{H}$ NMR Spectrum of Schiff Base Ligand

Mass Spectrum

In addition to the ^1H NMR Spectrum, the Schiff base ligand ($\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{N}_5\text{OS}$) has also been confirmed from its mass spectrum which is represented in Fig.-3. The mass spectrum of the Schiff base ligand showed a molecular ion peak at m/z 469.88 which coincides with the proposed molecular weight for the Schiff base ligand. (469.05). The various other peaks observed are due to fragmentations at different stages.^{34,35}

Fig.-3: Mass Spectrum of the Schiff Base Ligand.

Antimicrobial Analysis

The drug diclofenac, newly synthesized Schiff base ligand and its metal complexes were screened for antibacterial and antifungal activities. The compounds were dissolved in DMSO solvent. For antibacterial analysis, Gram +ve *Staphylococcus aureus* and Gram -ve *Escherichia coli* were used and for antifungal activity, *Penicillium brocae* and *Aspergillus terreus* fungal strains were chosen. Antibacterial activity was performed on nutrient agar medium, Czapek dox agar medium was used for antifungal activity. The zones of inhibition in mm have been recorded and the results are shown in Tables-4 and 5.³⁶⁻⁴³

Table-4: Antibacterial Activity of Drug, Ligand, and Metal Complexes

Compounds	<i>E.coli</i> (mm)			<i>S. aureus</i> (mm)		
	20 $\mu\text{g/mL}$	50 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$	20 $\mu\text{g/mL}$	50 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$
Diclofenac	2	0	0	0	0	0
Schiff base Ligand	0	0	0	5	0	0
Cu complex	2	0	0	0	0	0
Co complex	0	0	0	0	0	0
Ciprofloxacin (standard)	25	32	36	28	36	48

Table-5: Antifungal Activity of the Drug, Ligand and Metal Complexes

Compounds	<i>P. brocae</i> (mm)			<i>A. terreus</i> (mm)		
	20 $\mu\text{g/mL}$	50 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$	20 $\mu\text{g/mL}$	50 $\mu\text{g/mL}$	100 $\mu\text{g/mL}$
Diclofenac	3	0	0	0	0	0
Schiff base Ligand	2	0	0	5	0	0
Cu complex	1	0	0	0	0	0
Zn complex	2	0	0	0	0	0
Ciprofloxacin (standard)	20	31	38	30	33	38

Anti-inflammatory Activity

The transcription factor nuclear kappa B (NF- κ B) plays a major role in innate immunity and inflammatory responses and it is considered the major link between inflammation and tumorigenesis. In

this study, Test Compounds namely D3 (Diclofenac drug), DCU-1 (Cu complex), DSB-2 (Schiff base ligand) and DZN-1 (Zn complex) were used to evaluate the Pro inflammatory marker (PE conjugated Mouse anti-NF-kB p65 antibody) expression Study on the LPS stimulated cell line namely, Raw 264.7. The test compounds, D3, DCU1, DSB2 and DZN1 with the nontoxic concentration viz., 25 ug/mL showed 23.21, 34.29, 22.45, and 33.74 in terms of mean fluorescence intensity of NF-kB expression respectively, after the pre-stimulation of Raw 264.7 cell line with Lipopolysachride (2 ug/mL). The LPS alone showed 109.72 mean fluorescence intensity of NF-kB compared to the cell control without LPS treatment showing 10.61 mean fluorescence intensity of NF-kB expression respectively.⁴⁴⁻⁴⁹ Figure-4 represents mean fluorescence intensity values of NF-kB against the Untreated, LPS alone and drug with a combination of LPS stimulated Raw 264.7 cells.

Fig.-4: Overlay Bar Graph

CONCLUSION

The study of analytical and spectral data suggested that the metal complexes exhibit octahedral geometry with 1:2 metal to ligand ratio. The antimicrobial analysis shows that the ligand and metal complexes show better activities than the original drug, diclofenac and this can be explained based on the overtone concept and Tweedy chelation theory. The anti-inflammatory observations suggest that the metal complexes possess satisfactory anti-inflammatory potential properties in the Raw 264.7 cell line by suppressing the expression of pro-inflammatory cytokine (NF-kB) compared to the LPS treated Raw 264.7 cells expression.

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