Chromone-3-carboxaldehyde and Fouramine-PY-Based CIMC Ligand: Synthesis, structural characterization and anticancer evaluation

Gulafsha D. Khan[a], Mahadeo A. Sakhare[b], Shailendrasingh V. Thakur[b*]

[a]*Department of Chemistry, Balbhim Arts, Science and Commerce College, Beed 431122, Maharashtra, India*

[b]*Department of Chemistry, Milliya Arts Science and Management Science College, Beed 431122, Maharashtra, India*

khankg1994@gmail.com

Keywords: *Fouramine PY, chromone-3-carboxaldehyde, Schiff base ligand (CIMC), metal complexes, biological applications.*

The Schiff base ligand (CIMC), derived from fouramine PY and chromone-3-carboxaldehyde, and its Co(II), Ni(II), Cu(II), Zn(II), Mn(II), and VO(II) complexes were synthesized and characterized using mass, FT-IR, UV-visible spectroscopy, powder X-ray diffraction, thermal analysis, CHN elemental analysis, and molar conductivity measurements. The ligand and its metal complexes were screened for biological activities by using two gram-positive and two gram-negative bacterial strains and three fungal strains. The free ligand exhibits inhibition zones 15 mm for S. aureus, 34 mm for B. subtilis, 39 mm for S. typhi and 19.5 mm for K. pneumonia. Among all the complexes, Cu(II), Zn(II), Mn(II), and VO(II) showed highest activity with inhibition zone of 15.5-18 mm for S. aureus, Mn(II) showed the highest zone of inhibition for B. subtilis and Co(II), Cu(II) showed the highest activity with an inhibition zone of 20 and 32 mm against K. pneumoniae. For the T. viride antifungal strain, free ligand showed zone of inhibition 23.5 mm, whereas Mn(II) and VO(II) showed the highest value 34 and 27.5 mm, which indicates superior activity of the complexes. The anticancer evaluation was screened against the human MCF-7 breast cancer cell line by using the MTT assay. The results showed that the free ligand exhibits a significant IC_{50} value of 28.23 µg/ml compared with the reference drug 5-FU (IC_{50} = 42.08), indicating enhanced anticancer potential.

Introduction

Inorganic chemistry has been an alluring research area because of the extensive applications of inorganic pharmaceuticals in a variety of clinical therapies and diagnostics [1,2]. The nitrogen-containing organic compounds and their metal complexes show a vast scope in biological activity, like antimicrobial, antitumor, anticancer [3,4]. In the field of coordination chemistry, Schiff bases have been used very extensively as a ligands because in the formation of metal complexes, intramolecular hydrogen bonds between the hydroxyl (O) and the imine (N) atoms play an

important role [5,6]. The Schiff base ligand and their metal complex with imine moiety have many applications in different fields of chemistry, which are used as liquid crystals, dyes, polymer stabilizers, catalysts [7,8] and some of the transition metal complexes are used as luminescent marker.

Most of the Schiff bases have been derived from aromatic amines but some works deal with chromone derivatives. Chromone is the naturally occurring compound, especially in plants, which possesses a γ-pyrone nucleus, which is fused at the 5th and 6th positions with a benzene ring and has extensive biological applications, including anticancer, antioxidant, antimicrobial, antihypertensive, anti-inflammatory, and antimycobacterial applications [9-12]. In the synthesis of heterocyclic compounds, transition metal chelates and xanthones chromone and its derivatives are used as precursors [13]. Among these are the chromone-3-carboxaldehyde, which posseses three electrophilic sites, viz., the highly reactive electrophilic C-2, the carbonyl carbon of the aldehyde (-CHO), and the carbonyl center C-4 [14]. Moreover, for the treatment of obesity and diabetes as well as for tumor cells, chromone-3-carboxaldehyde provides a pharmacophore for drug design. The Schiff base and compounds of chromone have a broad range of medical applications. Studies on the complexes of Schiff bases have shown that these complexes have clinical, pharmacological and biological uses [15].

From the above facts, we report here the synthesis of the Schiff base ligand (CIMC) derived from chromone-3-carboxaldehyde and fouramine PY and the resulting Co(II), Cu(II) and Zn(II) complexes. The Schiff base ligand and its metal complexes have been characterized by using spectral, thermal, P-XRD analysis and molar conductivity measurements. In addition, the anticancer activity has been tested against the human MCF-7 breast cancer cell line by using the MTT assay.

Experimental part

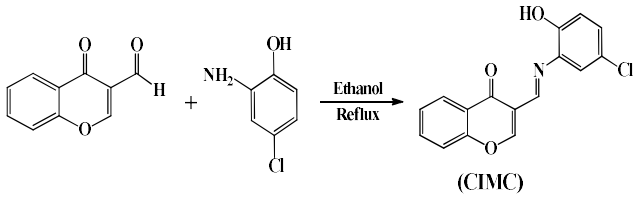
Material and methods

In the present work, all the chemicals and solvents used for the synthesis of the CIMC ligand and metal complexes were AR grade. The prepared Schiff base ligand and its metal complexes confirmed by FTIR spectra on a Jasco FT/IR-4700 spectrophotometer. The mass spectra were recorded on SYNAPT-XS #DBA06. The electronic spectra were recorded on a UV-1800 series PERKIN ELMER UV spectrophotometer by using DMSO as a solvent in the range of 200 to 1100 nm. The Powder XRD was carried out on a RIGAKU-JAPAN Miniflex 600 instrument. Thermal analysis of the complexes was performed under a nitrogen atmosphere on the TGA instrument NE NETZSCH NJA-STA 2500 Regulus TGA thermal system.

Synthesis

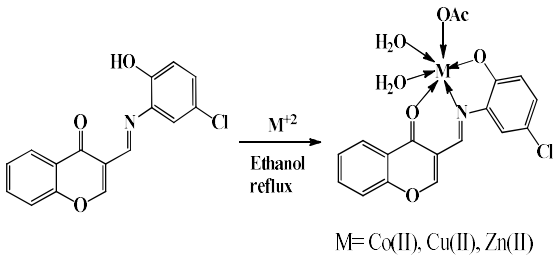
Synthesis of CIMC ligand. The Schiff base ligand (E)-3-(((5-chloro-2-hydroxyphenyl)imino)methyl)-4H-chromen-4-

one (CIMC) was synthesized by condensation of ethanolic solution of chromone-3-carboxaldehyde (0.001 mol) and fouramine PY (0.001 mol). The reaction mixture was refluxed 4-5 hours at 70-80℃. The yellow solid product was formed, separated by filtration, washed with cold ethanol and then dried under vacuum (**Scheme 1**).



Scheme 1. Synthesis of CIMC ligand

Synthesis of metal complexes. A solution of metal acetate(II) in ethanol (0.001mol) was added to an ethanolic solution of CIMC ligand (0.001mol) in 1:1 ratio and refluxed for 3-4 hours at 80-90℃. The pH of reaction mixture was maintained in between 7-8 by adding 10% alcoholic ammonia solution. The precipitated coloured solid metal complex was filtered off, washed with ethanol and dried underunder vacuum. (**Scheme 2**)



Scheme 2. Synthesis of metal complex

Results and discussion

The CIMC ligand and its Co(II), Ni(II), Cu(II), Zn(II), Mn(II) and VO(II) metal complexes are prepared and characterized by using different spectroscopic techniques like IR, Mass spectral analysis and also screened for biological activities. All the synthesized metal complexes are having different colours, soluble in chloroform, DMF and DMSO but insoluble in water. Analytical data confirm the metal to ligand molar ratio is 1:1 in all the metal complexes. From the existing spectral and analytical data, the coordination behaviour of the ligand toward the metal ion was interpreted. The IR spectra of the ligand upon complexation showed noticeable shifts in the specific bands, suggesting the contribution of donor atoms in coordination. Moreover, the PXRD analysis and the electronic (UV-Vis) spectra supported the formation of the metal complexes and indicated the possible geometry around the metal center.

The interpretation of Physical and analytical data of CIMC ligand and its metal complexes is shown below.

Physical and analytical data of CIMC ligand and its metal complexes

CIMC Ligand: Dark yellow solid. Yield. 88%. M.p.: 208 ℃. Elemental analysis found (%): C, 63.4; H, 4.27; N, 4.15. calcd.(%): C, 64.12; H, 3.36; N, 4.67%.

[Co(II)L(H_2O)$_2$(oAC)]: Dark Brown solid. Yield. 78%. M.p.: >300 ℃. Elemental analysis found (%): C, 47.60; H, 3.40; N, 3.09. calcd.(%): C, 47.76; H, 3.53; N, 3.097%.

[Ni(II)L(oAC)]: Orange solid. Yield. 76%. M.p.: >300 ℃. Elemental analysis found (%): C, 50.36; H, 3.98; N, 3.92. calcd.(%): C, 49.83; H, 3.22; N, 3.22%.

[Cu(II)L(H_2O)$_2$(oAC)].H_2O: Brown solid. Yield. 79%. M.p.: >300 ℃. Elemental analysis found (%): C, 45.48; H, 3.82; N, 2.95. calcd. (%): C, 45.52; H, 3.79; N, 2.95%.

[Zn(II)L(H_2O)$_2$(oAC)].2H_2O: Red solid. Yield. 81%. M.p.: >300 ℃. Elemental analysis found (%): C, 43.66; H, 4.07; N, 2.83. calcd.(%): C, 43.77; H, 4.05; N, 2.83%.

[Mn(II)L(H_2O)$_2$(oAC)].2H_2O: Black solid. Yield. 75%. M.p.: >300 ℃. Elemental analysis found (%): C, 44.60; H, 4.16; N, 2.89. calcd.(%): C, 44.58; H, 4.12; N, 2.88 %.

[VO(II)L(H_2O)SO_4]: Black solid. Yield. 70%. M.p.: >300 ℃. Elemental analysis found (%): C, 41.35; H, 2.60; N, 3.01. calcd.(%): C, 41.34; H, 2.58; N, 3.01%.

Mass spectrum of Schiff base

The molecular ion peaks verified the suggested structure for the synthesized ligand (CIMC) compound. The mass spectra of Schiff base ligand exhibit the molecular ion peak at m/z 300 (M+) corresponds to $[C_{16}H_{10}ClNO_3]^+$ ion and 302 (M+2) which is in good agreement with the molecular weight of the proposed structure.

FT-IR analysis

To determine coordination sites involved in chelation the IR spectrum of the synthesized ligand CIMC and its metal complexes are compared. The IR spectral data is presented in **Table 1**. In the IR spectrum of ligand, the band observed at 1642 cm^{-1} is assigned to υ(C=O) group of the chromone moiety in free ligand on complexation it was shifted to lower frequency number in their corresponding metal complexes indicates the coordination of carbonyl oxygen of the υ(C=O) group to the metal ion [16]. The C=N of (azomethine) shows band at 1603 cm^{-1} in free ligand shifted to lower frequency which indicates the participation of nitrogen of azomethine in coordination [17]. The broad band at 3280 cm^{-1} in free ligand is attributed to phenolic -OH group which is absent in all the metal complexes confirm the participation of phenolic oxygen in chelation. The IR spectral data of the metal complexes also shows new bands in the range of 577-572 and 468-431 cm^{-1} is due υ(M-O), υ(M-N) respectively [18]. Therefore, from the IR spectral data it is concluded that the Schiff base ligand act as tridentate ligand with NOO donor sites which coordinate to the central metal ions via the C=O of the chromone, phenolic hydroxyl group and nitrogen of azomethine. FT-IR spectra of Schiff base ligand and Cu(II) complex are shown in **Figure 1**.

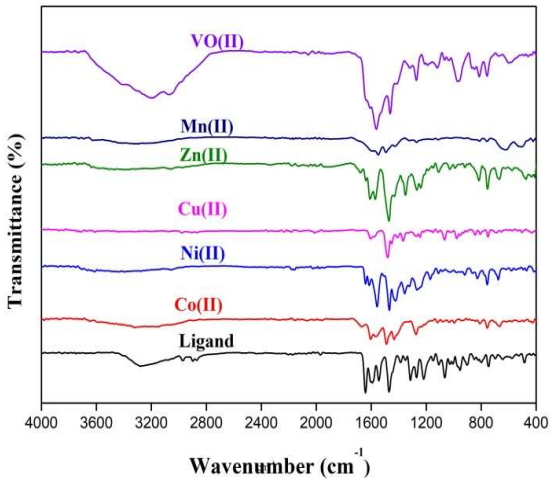


Figure 1. Comparative FTIR spectra of ligand CIMC and its complexes

Electronic spectral analysis and molar conductivity

The electronic spectra of Schiff base ligand and its metal complexes were recorded in DMSO in the range of 16666 to 50000 cm^{-1} and wavelength range of 200 to 1100 nm. The electronic spectrum of Co(II) complex exhibits an absorption band at 393 and 373 nm assigned to $^4T_1g \rightarrow {}^4T_2g$ and $^4T_{1g} \rightarrow {}^4T_{1g(P)}$ transition suggest the octahedral structure and electronic spectrum of Ni(II) complex shows absorption band at 400 nm assigned to $3T_1(F) \rightarrow 3T_1(P)$ transition suggest tetrahedral geometry [19]. The Cu(II) complex shows absorption band at 448 and 344 nm [20]. The Zn(II) complex shows band at 344 nm and Mn(II) complex shows bands at 393, 372 nm assigned to charge transfer transition suggest an octahedral geometry. The VO(II) complex shows band at 363 nm assigned to $^2B_2 \rightarrow {}^2E$ transition proposed a square pyramidal geometry [21-23]. The electronic spectral data of Schiff base ligand and its metal complexes with molar conductance are demonstrated in **Table 2**. The molar conductivity were recorded in DMSO solvent and the values lies in between 3.1-10.8 S mol^{-1} cm^2 shows nonelectrolytic nature of CIMC ligand and its transition metal complexes [24].

Powder X-ray diffraction

The X-ray diffractograms of the Co(II), Ni(II), Cu(II), Zn(II), Mn(II) and VO(II) complexes were scanned in the range of 2θ = 20-80˚ where X-ray has wavelength of 1.540 Å. The P-XRD data is useful for prediction of cell parameter, lattice parameters, crystal system [19,20]. The P-XRD analysis of all complexes confirms the presence of monoclinic, triclinic and cubic crystal systems. Zn(II) crystallizes in a monoclinic system with lattice constants a = b = c = 27.254 Å, α = β = γ = 90° unit cell volume V = 20243.740 $Å^3$ and Z = 1. The strongest reflection occurs at 2θ = 71.18° corresponding to the (220) plane with d = 9.636 Å.

Co(II), Ni(II) and Mn(II) exhibits monoclinic symmetry.

Co(II) complex: a = 9.235 Å, b = 25.569 Å, c = 12.611 Å, β = 98.750, strongest reflection (020) at d = 12.785 Å.

Ni(II) complex: a = 3.811 Å, b = 10.538 Å, c = 9.572Å, β = 99.709, strongest reflection (011) at d = 7.029 Å.

Mn(II): a = 19.150 Å, b = 8.997 Å, c = 24.182 Å, β = 108.305, strongest reflection (01-1) at d = 17.106 Å.

Cu(II) and VO(II) showing triclinic symmetry, with the strongest reflections corresponding to the (001) plane, d-values as

listed in **Table 3**. All the samples posses well-established crystalline structures revealed from PXRD findings are in agreement with their corresponding crystal systems with unit cell volumes, lattice parameters and Miller indices.

Thermal analysis

The metal complexes Ni(II), Zn(II), Mn(II) and VO(II) are investigated by using thermal gravimetric analysis in the range of ambient temperature to 800˚C in nitrogen atmosphere with 30°C/10.0(K/min)/800°C heating rate and it can be observed that the metal complexes of Schiff base ligand decomposes at higher temperature range in three steps presented in **Table 4**. In all metal complexes up to 280°C temperature, decomposition of coordinated and lattice water molecule is takes place in the first step. Above 300°C loss of ligand along with acetate molecule in the temperature range 300-700°C and finally metal oxides are formed above 700°C [21,22]. The graph of the data is shown in **Figure 2**.

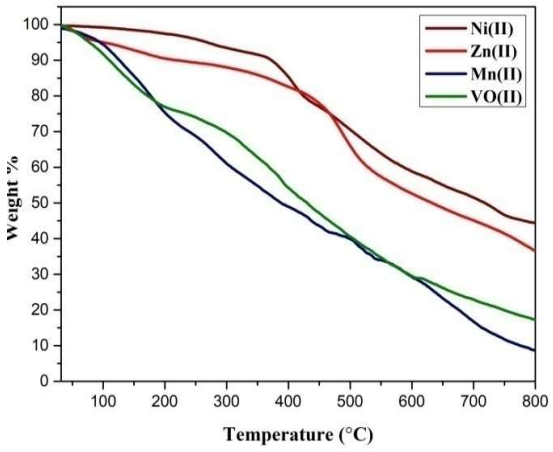


Figure 2. TGA of metal complexes

Anticancer activity

5-FU is considered as one of the best antimetabolite chemotherapy drug. It act as anticancer agent for several human cancers particularly breast, colorectal, pancreatic, brain digestive, respiratory system and skin cancer [25,26]. A pyrimidine analogue 5-FU extensively used in cancer chemotherapeutic treatment, which is a key enzyme essential for synthesis of DNA, mainly functions by suppressing thymidylate synthase. The inhibition of this enzyme give rise to a deficiency of thymidine nucleotides, thereby inhibiting replication of DNA and promoting cytotoxic effects in actively growing malignant cells. Furthermore, 5-FU metabolic products can be integrated in RNA and DNA, impairing normal genetic process and promoting cellular apoptosis. In this study, the evaluated compound showed significant % inhibition of cell growth in MCF-7 cells in the MTT assay, indicating its potential to disrupt cellular metabolic pathways involved in malignant cell growth. The analogous antiproliferative effect seen in relation to 5-FU demonstrates that the compound may manifest its chemotherapeutic effect through cellular pathways responsible for suppression of cell growth and triggering apoptosis in malignant breast cells.

In this text we have reported the anticancer activity of synthesized ligand CIMC and its Co(II), Cu(II) and Zn(II) complexes, measured at different concentration (10, 40, 100 µg/ml) against MCF-7 human breast cancer cell line

using 5-FU as a reference drug by MTT assay method shown in **Figure 3**. The anticancer activity of metal complexes and standard drug in triplicate at concentration of 10, 40 and 100 µg/ml was evaluated and the findings are presented as mean ± SD. Among all the metal complexes, Zn(II) showed the highest % inhibition (71.50-82.76%), which was in agreement with ligand but slightly lower than the reference drug. IC_{50} analysis indicated that all the metal complexes had IC_{50} values comparable to the standard drug (42.08 µM), whereas the ligand (28.23 µM) was the most potent. At all concentrations, statistical analysis showed significant inhibition ($p < 0.05$, 0.01, <0.001). Some concentrations manifest relatively high standard deviations (11.23, 12.7 and 13.9), suggesting variability among experimental replicates; however, to ensure transparency and reliability of the results all data points were retained in the analysis without excluding any outliers [28]. The % of inhibition and IC50 values of the compound are presented in **Table 5**.

Table 1. FT-IR data of CIMC ligand and its metal complexes

Ligand/ Complexes	CIMC	Co(II)	Ni(II)	Cu(II)	Zn(II)	Mn(II)	VO(II)
Chromone, C=O	1642	1604	1640	1603	1640	1596	1612
-OH	3280	--	--	--	--	--	--
Azomethine C=N	1603	1568	1563	1580	1570	1548	1563
M-O	--	574	577	572	572	532	577
M-N	--	448	468	431	434	423	434

Table 2. Electronic spectra of Schiff base ligand and its metal complexes

Ligand/ Complexes	Maximum absorption (nm)	Maximum absorption (cm^{-1})	Band assignment	Molar conductance S mol^{-1} cm^2
CIMC	285	35087	n→π*	7.2
	223	44843	π →π*	
Co(II)	393	25445	$^4T_1g \rightarrow {}^4T_2g$	9.8
	373	26809	$^4T_{1g} \rightarrow {}^4T_{1g(P)}$	
Ni(II)	400	25000	$3T_1(F) \rightarrow 3T_1(P)$	9.1
Cu(II)	448	22321	Charge transfer	8.3
	344	29069	Charge transfer	
Zn(II)	344	29069	Charge transfer	10.8
Mn(II)	393	25445	Charge transfer	8.2
	372	26881	Charge transfer	
VO(II)	363	27548	$^2B_2 \rightarrow {}^2E$	8.9

Table 3. P- XRD data of metal complexes

Complexes	Co(II)	Ni(II)	Cu(II)	Zn(II)	Mn(II)	VO(II)
No. of reflection	30	05	20	39	26	40
Maxima (2θ)	36	75.93	98.98	71.18	32.72	46.83
Intensity	100	100	100	100	100	100
d value	12.785	7.029	7.140	9.636	17.106	15.919
Lattice constant (Å)	a = 9.235 b = 25.569 c = 12.611	a = 3.811 b = 10.538 c = 9.572	a = 2.951 b = 2.954 c = 7.334	a = 27.254 b = 27.254 c = 27.254	a = 19.150 b = 8.997 c = 24.182	a = 6.162 b = 7.212 c = 16.053
Unit cell volume	2943.334	378.949	52.611	20243.740	3956.027	705.307
Axis and axis angle	$a \neq b \neq c$ and $\alpha = \gamma = 90^o \neq \beta$	$a \neq b \neq c$ and $\alpha = \gamma = 90^o \neq \beta$	$a \neq b \neq c$ and $\alpha \neq \beta \neq \gamma \neq 90^o$	$a = b = c$ and $\alpha = \beta = \gamma = 90^o$	$a \neq b \neq c$ and $\alpha = \gamma = 90^o \neq \beta$	$a \neq b \neq c$ and $\alpha \neq \beta \neq \gamma \neq 90^o$
Z Value	8	2	1	1	4	1
Crystal system	Monoclinic	Monoclinic	Triclinic	Cubic	Monoclinic	Triclinic

Table 4. Thermogravimetric data

Complexes	Temperature	Mass loss % (Calc.)	Compound decomposed	Metallic residue
Ni(II)	380-540	79.62 (79.20)	Acetate + L	NiO
Zn(II)	55-180	11.43 (11.31)	H_2O + 2H_2O(Coord)	ZnO
	250-585	75.26(75.05)	Acetate + L	
Mn(II)	55-170	14.91 (14.87)	2H_2O + 2H_2O(Coord)	MnO
	250-620	73.03 (73.96)	Acetate + L	
VO(II)	55-210	24.24 (24.78)	H_2O+ SO_4	VO
	250-590	64.43 (64.57)	Ligand	

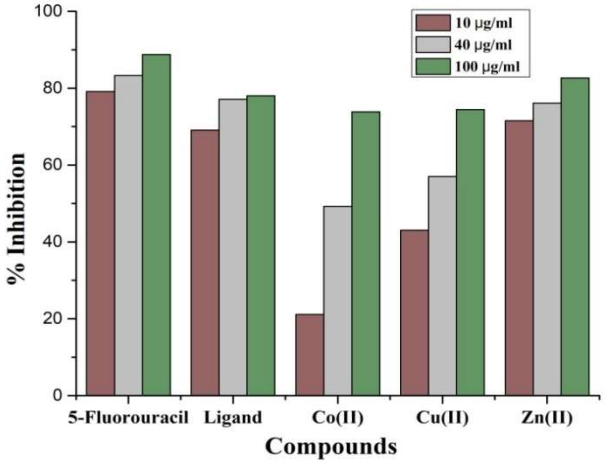


Figure 3. Graphical interpretation anticancer activity

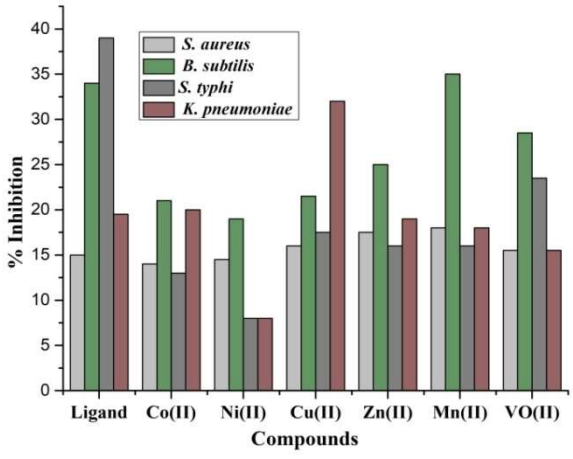


Figure 4. Graphical interpretation of antibacterial activity of CIMC ligand and its metal complexes

Antimicrobial screening

The Schiff base ligand (CMIC) and its Co(II), Cu(II) and Zn(II) complex were screened for antifungal and antibacterial strain. All the synthesized compounds were found bioactive. The observation showed that the bioactive than the Schiff base ligand (CMIC) for different bacteria [29]. Variation of activity for ligand and complexes depends on the chelation, cell membrane permeability and type of ligand donor atoms [30].

Recommended values consider:

(-) Resistant	Intermediate sensitive	Sensitive	Highly sensitive
Upto 8mm	> 8 to 12mm	> 12-18 mm	≥ 18 mm

Antibacterial activity

The antibacterial activity of prepared ligand CMIC and its Co(II), Ni(II),Cu(II), Zn(II), Mn(II) and VO(II) complexes were tested against *Staphylococcus aureus, Bacillus subtilis, Salmonella typhi* and *Klebsiella pneumonia* by using disc diffusion method. **Figure 4** shows the graphical interpretation of antibacterial activity data. It was found that except Co(II) complex all the metal complexes show higher activity than ligand for *Staphylococcus aureus* bacterial strain and for *Klebsiella pneumonia* bacterial strain Co(II) and Cu(II) complex show higher activity due to their chelation capability [31]. The zone of inhibition for prepared compounds is summarized in **Table 6**.

Antifungal activity

The antifungal activity of prepared ligand CMIC and its Co(II), Ni(II), Cu(II), Zn(II), Mn(II) and VO(II) metal complexes were tested against *Penicillium chrysogenum, Trichoderma viride, Aspergillus niger* fungal strain using disc diffusion method [31]. The finding shows that Mn(II) and VO(II) complex show higher antifungal activity than CMIC ligand against *Trichoderma viride* fungal strain. However, the CMIC ligand and all the metal complexes show resistant antifungal activity against different fungi. The zone of inhibition for the prepared compounds is presented in **Table 6**.

Table 5. Anticancer activity of ligand CIMC and its metal complexes

Compounds	Concentrations (µg/ml)	% inhibition ± SD	P-value	Ic50
Ligand	10	69.12 ± 4.60	P < 0.001	28.23
	40	77.03 ± 3.45	P < 0.001	
	100	78.02 ± 0.83	P < 0.001	
Co(II)	10	21.11 ± 11.23	P < 0.05	40.79
	40	49.55 ± 12.7	P < 0.05	
	100	71.37 ± 3.58	P < 0.001	
Cu(II)	10	43.16 ± 2.77	P < 0.001	41.92
	40	57.3 ± 13.9	P < 0.05	
	100	74.41 ± 0.94	P < 0.01	
Zn(II)	10	71.50 ± 3.13	P < 0.001	42.86
	40	76.09 ± 055	P < 0.001	
	100	82.76 ± 3.58	P < 0.001	
5-FU (Standard)	10	79.12 ± 0.91	P < 0.001	42.08
	40	83.27 ± 0.56	P < 0.001	
	100	88.79 ± 1.24	P < 0.001	

Table 6. Antibacterial and antifungal activity of Schiff base ligand and its metal complexes

Compounds	Antibacterial activity				Antifungal activity		
	S. aureus	***B. subtilis***	***S. typhi***	***K. pneumoniae***	***P. chrysogenum***	***T. viride***	***A. niger***
Ligand	15	34	39	19.5	-	23.5	-
Co(II)	14	21	13	20	-	-	-
Ni(II)	14.5	19	-	-	-	-	-
Cu(II)	16	21.5	17.5	32	-	-	-
Zn(II)	17.5	25	16	19	-	-	-
Mn(II)	18	35	16	18	-	34	-
VO(II)	15.5	28.5	23.5	15.5	-	27.5	-
Control	-ve	-ve	-ve	-ve	-ve	-ve	-ve

Conclusions

In this research paper the Schiff base ligand (*E*)-3-(((5-chloro-2-hydroxyphenyl)imino)methyl)-4*H*-chromen-4-one (CIMC) along with its Co(II), Ni(II), Cu(II), Zn(II), Mn(II) and VO(II) complexes were described. Based on all spectroscopic techniques, ligand shows tridentate character. Based on P-XRD data, the Co(II), Ni(II) and Mn(II) complexes shows monoclinic, Cu(II) and VO(II) complexes shows triclinic and Zn(II) complex shows cubic crystal system. From the biological studies findings shows that metal complexes shows good antibacterial activity than ligand and also some metal complexes shows good anticancer activity than ligand in comparison with reference drug.

Acknowledgements

The authors are thankful to the Director SAIF Chandigarh for providing the facility of mass spectroscopy, Principal Shri Shivaji Science College Amravati for providing XRD analysis. The authors are gratefully acknowledging to the Principal, Department of Chemistry, Balbhim Arts, Science and Commerce College, Beed (MS) for providing research facilities..

References

[1] Ronconi L, Sadler P. Using coordination chemistry to design new medicines. Coordination Chemistry Reviews 2007;251(13-14):1633-1648.

[2] Storr T, Thompson K, Orvig C. Design of targeting ligands in medicinal inorganic chemistry. Chemical Society Reviews 2006;35(6):534.

[3] Arjmand F, Mohani B, Ahmad S. Synthesis, antibacterial, antifungal activity and interaction of CT-DNA with a new benzimidazole derived Cu(II) complex. European Journal of Medicinal Chemistry 2005;40(11):1103-1110.

[4] Maji M, Chatterjee M, Ghosh S, Chattopadhyay S, Wu B, Mak T. Chemistry of ruthenium(II) complexes of the tridentate NNS donor methyl 2-pyridyl ketone 4-(4-tolyl)thiosemicarbazone. Isolation and structural characterisation of a novel ruthenium(II) complex containing a co-ordinated imine of an α-N heterocyclic ketone. Journal of the Chemical Society, Dalton Transactions 1999;(2):135-140.

[5] Zhang J, Zhou H, Lachgar A. Directed Assembly of Cluster-Based Supramolecules into One-Dimensional Coordination Polymers. Angewandte Chemie International Edition 2007;46(26):4995-4998.

[6] Hosseini M, Mertens S, Ghorbani M, Arshadi M. Asymmetrical Schiff bases as inhibitors of mild steel corrosion in sulphuric acid media. Materials Chemistry and Physics 2003;78(3):800-808.

[7] Anand P, Patil V, Sharma V, Khosa R, Masand N. Schiff bases: A Review on Biological Insights.

International Journal of Drug Design and Discovery 2025;3(3):851-868.

[8] Cleiton M, Daniel LS, Luzia VM, Rosemeire BA, Maria AR, Cleide VBM, Angelo F. Schiff bases: A short review of their antimicrobial activities. J Adv Res. 2011;2(1):1-8.

[9] Li Y, Yang Z, Wu J. Synthesis, crystal structures, biological activities and fluorescence studies of transition metal complexes with 3-carbaldehyde chromone thiosemicarbazone. European Journal of Medicinal Chemistry 2010;45(12):5692-5701.

[10] Shim Y, Kim K, Chi D, Lee K, Cho H. Formylchromone derivatives as a novel class of protein tyrosine phosphatase 1B inhibitors. Bioorganic & Medicinal Chemistry Letters 2003;13(15):2561-2563.

[11] Khan K, Ambreen N, Mughal U, Jalil S, Perveen S, Choudhary M. 3-Formylchromones: Potential antiinflammatory agents. European Journal of Medicinal Chemistry 2010;45(9):4058-4064.

[12] Mhaske G, Nilkanth P, Auti A, Davange S, Shelke S. Aqua medicated, microwave assisted, synthesis of Schiff bases and their biological evaluation. Int. J. Innov. Res. Sci. Eng. Technol. 2014;3(1): 8156–8162.

[13] Arjunan V, Subramanian S, Mohan S. FTIR and FTR spectral studies of 2-amino-6-bromo-3-formylchromone. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 2004;60(5):995-1000.

[14] Ali T, Ibrahim M, El-Gohary N, El-Kazak A. 3-Formylchromones as diverse building blocks in heterocycles synthesis. European Journal of Chemistry 2013;4(3):311-328.

[15] Gaber M, El-Baradie K, El-Wakiel N, Hafez S. Synthesis and characterization studies of 3-formyl chromone Schiff base complexes and their application as antitumor, antioxidant and antimicrobial. Applied Organometallic Chemistry 2019;34(2).

[16] Elsayed S, Butler I, Claude B, Mostafa S. Synthesis, characterization and anticancer activity of 3-formylchromone benzoylhydrazone metal complexes. Transition Metal Chemistry 2014;40(2):179-187.

[17] Pawar RK, Sakhare MA, Arbad BR. Synthesis, spectroscopic characterization and thermal studies of some transition metal complexes of novel Schiff base ligand. Int. J. Chem. Sci. 2016;14(4):2575-2584.

[18] Kavitha P, Laxma Reddy K. Synthesis, Structural Characterization, and Biological Activity Studies of Ni(II) and Zn(II) Complexes. Bioinorganic Chemistry and Applications 2014;2014:1-13.

[19] Survase SA, SakhareMA, Sakhare KB, Patil CS. Synthesis, Spectral Investigation And Biological Assessment of Tetradentate Schiff Base Ligand And Its Metal Complexes. Afr. J. Biomed. Res. 2024;27(2):225-233.

[20] Bharate YN, Sakhare MA, Jadhav SB, Naikwade SD. Synthesis, characterization and antibacterial screening of ni[ii], cu[ii] andzn[ii]acetate complexes of schiff base ligand. J. Glob. Resour. 2019;5(02):345-352.

[21] Bharate Y, Sakhare M, Jadhav S, Naikwade S. Synthesis, characterization and antibacterial screening of Mn[II], Co[II] acetate and VO[II] sulphate complexes of schiff base ligand.Rasayan Journal of Chemistry 2021;14(01):479-485.

[22] Sarwade KN, Sakhare KB, Sakhare MA, Thakur SV. Anti - alzheimer, anticancer and antimicrobial assessment of novel tridentate azo-Schiff base ligand and it's metal complexes. Heterocycl. lett. 2024;14(4):797-811.

[23] Sakhare K, Sarwade K, Bharate Y, Sakhare M. Anticancer acitivity of Schiff base ligand(E)-4-((5-chloro-2 hydroxybenzylidene) amino)-1, 5-dimethyl-2-phenyl-1H-pyrazol-3(2H)- one and its Co(II), Cu(II) and Zn(II) metal complexes. Journal of the Serbian Chemical Society 2024;89(2):165-175.

[24] Al-Amery M. Synthesis and Characterization of New Complexes of 2-(6- Methoxybenzo[d]thiazol-2-ylamino)-2-phenyl acetonitrile Ligand with Manganese (II), Cobalt (II), Nickel (II), Copper (II), Zinc (II) Cadmium (II) and Mercury (II) Divalent Transition Metal Ions. IOSR Journal of Applied Chemistry 2013;4(5):29-34.

[25] Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. The Lancet 1995;345(8955):939-944.

[26] Longley D, Harkin D, Johnston P. 5-Fluorouracil: mechanisms of action and clinical strategies. Nature Reviews Cancer 2003;3(5):330-338.

[27] Ma Z, Qiao X, Xie C, Shao J, Xu J, Qiang Z, Lou J. Activities of a novel Schiff Base copper(II) complex on growth inhibition and apoptosis induction toward MCF-7 human breast cancer cells via mitochondrial pathway. Journal of Inorganic Biochemistry 2012;117:1-9.

[28] Kavitha P, Rama Chary M, Singavarapu B, Laxma Reddy K. Synthesis, characterization, biological activity and DNA cleavage studies of tridentate Schiff bases and their Co(II) complexes. Journal of Saudi Chemical Society 2016;20(1):69-80.

[29] Al Zoubi W, Al-Hamdani A, Ahmed S, Ko Y. Synthesis, characterization, and biological activity of Schiff bases metal complexes. Journal of Physical Organic Chemistry 2017;31(2):1-7.

[30] Saeed S, Alomari B, Alhakimi A, Abd El-Hady M, Alnawmasi J, Elganzory H, El-Sayed W. Pyrimidine hydrazide ligand and its metal complexes: synthesis, characterization, and antimicrobial activities. Egyptian Journal of Chemistry 2023;66(5):315-329.

[31] Khan G, Sakhare M, Survase S, Bharate Y, Thakur S. Synthesis, characterization, anticancer and biological activities of transition metal complexes derived of chromone-3-carboxaldehyde schiff base ligand. Journal of Dynamics and Control 2025;9(7):183-204.