Synthesis, Spectral Characterization, *in vitro* cytotoxicity and antibacterial studies of a Novel Schiff Base Ligand derived from S-Carboxy Methyl-L-Cysteine and 5-Chloroisatin and its Cu(II), Ni(II) and Co(II) Metal complexes

Lisandra N.R.[1,2], Deena Antony C.[1,2*] and Saritha V.S.[1,2,3]
1. Centre for Research in Chemical Sciences, St. Joseph's College (Autonomous), Irinjalakuda, 680121, Kerala, INDIA
2. University of Calicut, Tirur - Calicut Rd, Thenhipalam, 673 635, Kerala, INDIA
3. Govt. Engineering College, Thrissur, 680 009, Kerala, INDIA
*deenarajan96@gmail.com

Abstract
A novel chiral Schiff base ligand, namely S-Carboxy Methyl-L-Cysteine 5-Chloroisatin (CMCCI) was synthesized through the condensation of the chiral amino acid S-Carboxy Methyl-L-Cysteine and 5-Chloroisatin in basic medium. The resulting amino acid Schiff base ligand and its metal complexes with Cu(II), Ni(II) and Co(II) were characterized using elemental analysis, FTIR, ^{1}H NMR and UV-visible spectroscopy, confirming the formation of CMCCI and (CMCCI)$_2$M type metal complexes. The formation of the ligand CMCCI was also confirmed by mass spectral analysis. The analytical results suggested that the Schiff base behaves as tridentate ONO donor ligand and coordinates with Cu(II), Ni(II) and Co(II) ions in octahedral geometry.

The ligands and their complexes were screened for their cytotoxicity and antibacterial activities. Cytotoxicity studies revealed that the Schiff base complexes of copper exhibited considerable cytotoxic effects than the Schiff base ligand. Copper complex showed high cytotoxicity even in lower concentrations and can be used as a potential anticancer drug after further studies. Antibacterial studies of the ligand and metal complexes were performed against Staphylococcus aureus and Escherichia coli, Gram positive and Gram negative bacterial strains respectively. Copper complex exhibited considerable activity against Staphylococcus aureus and cobalt complex showed moderate activity against Escherichia coli.

Keywords: S-Carboxy Methyl-L-Cysteine, 5-Chloroisatin, Schiff base, Cytotoxicity, *Staphylococcus aureus*, *Escherichia coli*.

Introduction

Deoxyribonucleic acid (DNA) is a critical target molecule in anticancer and antiviral research. Several studies have proved that certain drugs when administered as metal chelates exhibit enhanced activity and inhibit tumour growth[14]. Transition metal ions play a vital role in the proper functioning of different enzymes and certain drugs act as bio-ligands within biological systems.

Laila et al[21] investigated the interaction between DNA and amino acid derived Schiff base metal complexes using absorption spectra, viscosity measurements and gel electrophoresis. Amino acids which are functionally involved in a variety of biological processes contain coordinating sites such as -NH_2 and -COOH. These functional groups can undergo condensation reaction with aldehydes or ketones to produce Schiff base ligands. This condensation reaction is pH dependant and usually the reaction is carried out in basic medium[22].

Amino acid derived Schiff bases and their metal complexes act as potent pharmacologically active compounds within biological systems.[5,7,9,13,20,27,28,30] These metal complexes exhibit many bioactivities such as anticonvulsant, antibacterial, antifungal, antioxidant and anticancer properties.[11,16,23,26,29] Zhao et al[28] explored the DNA interaction and superoxide dismutase (SOD) activity of nickel (II) complexes containing L-phenylalanine Schiff base and 1, 10-phenantholine. [19] Moreover Schiff bases derived from amino acids and their metal complexes are found to be efficient catalysts for ester hydrolysis reactions.[6,10,19]

The presence of imine group in Schiff bases is mainly responsible for their biological activities[15,17]. Recently, the interaction between transition metal complexes and DNA has attracted much attention due to its importance in cancer therapy, the design of novel pharmaceutical molecules and molecular biology[1,25]. The transition metal complexes derived from Schiff bases have wide applications in diverse fields such as food industry, dye manufacturing, catalysis, fungicidal, agrochemical, anti-inflammable activity, antiradical activities and biological activities[2,3]. In addition, heterocyclic Schiff base ligands and their complexes possess great importance due to their pharmacological properties[24].

Material and Methods

The analytical grade reagents and chemicals including S-Carboxy Methyl-L-Cysteine, 5-chloroisatin, ethanol, potassium hydroxide, metal acetates (Cu, Ni, Co) were

purchased from Sigma Aldrich. All chemicals were used without further purification.

Synthesis of the Schiff base ligand CMCCI: Amino acid S-Carboxy Methyl-L-Cysteine (1mmol) was dissolved in 20 ml methanol water mixture. To this solution, 5-chloroisatin (1mmol) in 10 ml methanol was added drop wise with stirring. The resulting mixture was refluxed for 3 hours. The wine red coloured solution was cooled overnight, filtered and dried.

Synthesis of the metal complexes: The Schiff base ligand (1mmol) was dissolved in methanol. To the refluxing solution of the Schiff base ligand, metal acetate (Cu(II)/ Ni(II)/ Co(II)) (0.5mmol) was added. The resulting solution was refluxed for 5 hours. The mixture was cooled overnight. The separated solid was filtered, washed and dried.

***In vitro* Cytotoxicity Studies:** The test compound was studied for short term *in vitro* cytotoxicity using Dalton's Lymphoma Ascites cells (DLA). The test compounds CMCCI, $(CMCCI)_2Cu$, $(CMCCI)_2Ni$ and $(CMCCI)_2Co$ were dissolved in DMSO at concentrations ranging from 5µg/ml to 200µg/ml. The tumour ce1ls aspirated from the peritoneal cavity of tumour bearing mice were washed thrice with PBS. Cell viability was determined by trypan blue exclusion method. Viable cells suspension ($1x10^6$ cells in 0.lml) was added to tubes containing various concentrations of the test compounds 5**,** 7.5, 12.5, 25, 50, 100, 150, 200 µg/ml and the volume was made up to l ml using phosphate buffered cell line (PBS).

The control tube contained only cell suspension. These assay mixtures were incubated for 3 hours at 37^0C. Further cell suspension was mixed with 0.lml of l% trypan blue and kept for 2-3 minutes and loaded on a haemocytometer. Dead cells take up the blue colour of trypan blue while live cells do not take up the dye. The numbers of stained and unstained cells were counted separately.

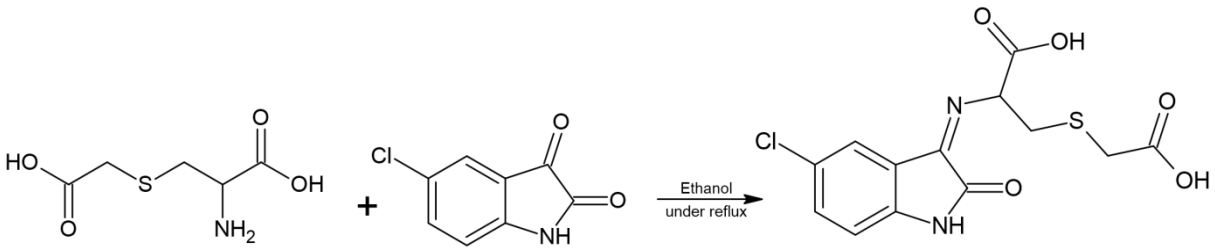
$$\% \text{ cytotoxicity} = \frac{No.of\ live\ cells}{No.of\ live\ cells + No.of\ dead\ cells} \times 100$$

Antibacterial Analysis: Nutrient agar medium plates were seeded with 18-24-hour-old cultures of microbial inocula. (*Staphylococcus aureus* and *Escherichia coli*). Three wells were cut into the agar media with sterilized micropipette tips and samples (CMCCI, $(CMCCI)_2Cu$, $(CMCCI)_2Ni$ and $(CMCCI)_2Co$) at concentration of 100mg/ml from 100µl micropipette were poured into the wells. An antibiotic (100 µl per well) and DMSO (100 µl per well) were also poured into one well each as a positive and negative control respectively. Inoculated plates were then incubated at 37ºC for 24 hrs and zones of inhibition were measured in mm[8].

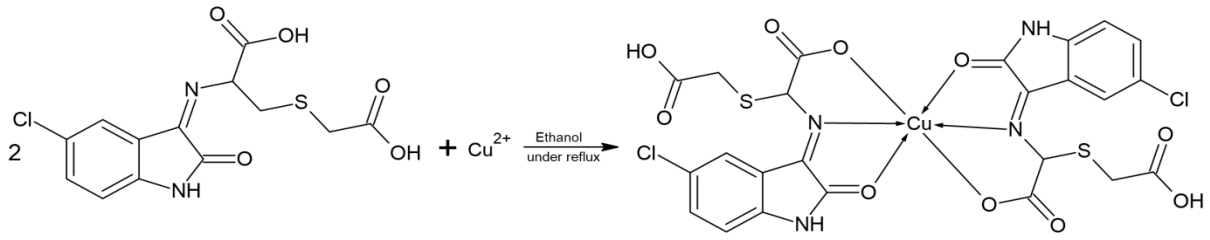
Results and Discussion

Physico-chemical Analysis: Elemental analysis was performed for the Schiff base ligands and the metal complexes. The experimental data was in close agreement with the theoretical values. This suggests complex formation.

FTIR Spectral analysis: In the FTIR spectra of the Schiff base ligand CMCCI, the bands due to -OH and -NH were observed at 3414cm^{-1} and 3212 cm^{-1} respectively. The azomethine band was observed at 1620 cm^{-1}. The band due to –C=O group appeared at 1706 cm^{-1} (Figure 1). In metal complexes, the band due to azomethine group was shifted to lower wavenumber (20-54 cm^{-1}) suggesting the coordination of azomethine nitrogen atom to the metal. The strong vibrational band of carbonyl group of the ligand showed a shift from 1706 cm^{-1} to lower frequency (2- 3 cm^{-1}) again supporting the coordination of the lone pair of electrons of oxygen atom of C=O group. Bands due to M-N bonds were observed 558-586 cm^{-1} in complexes confirming complex formation as these bands were absent in Schiff base ligands. Thus the IR data suggest the monobasic tridentate ONO donor behaviour of each Schiff base unit



Scheme 1: Synthesis of CMCCI.



Scheme 2: Synthesis of CMCCI Copper complex.

UV-Visible Spectral Analysis: The UV visible spectral analysis of the ligands and the complexes was carried out in DMSO solvent. In CMCCI, maximum absorbance was observed at 423nm and 523 nm due to intra ligand pi to pi* and n to pi* transitions (Figure 2). In metal complexes, maximum absorbance bands were shifted supporting complex formation. A broad absorption band at higher wavelength region was detected in some metal complexes which may be due to ligand to metal charge transfer LMCT transition[3,24].

Table 1
Physicochemical data of the ligand and metal complexes

S.N.	Compound	Molecular Formula	Colour	Melting Point	% of C Found (Calc.)	% of H Found (Calc.)	% of N Found (Calc.)
1	CMCCI	$C_{13}H_{11}N_2O_5SCl$	Red	263	45.45 (45.55)	3.18 (3.23)	8.13 (8.17)
2	$(CMCCI)_2Cu$	$C_{26}H_{20}N_4O_{10}S_2Cl_2Cu$	Grey	>275	41.75 (41.80)	2.58 (2.70)	7.45 (7.50)
3	$(CMCCI)_2Ni$	$C_{26}H_{20}N_4O_{10}S_2Cl_2Ni$	Red	>275	42.05 (42.07)	2.60 (2.72)	7.65 (7.55)
4	$(CMCCI)_2Co$	$C_{26}H_{20}N_4O_{10}S_2Cl_2Co$	Brown	>275	42.16 (42.06)	2.75 (2.71)	7.62 (7.55)

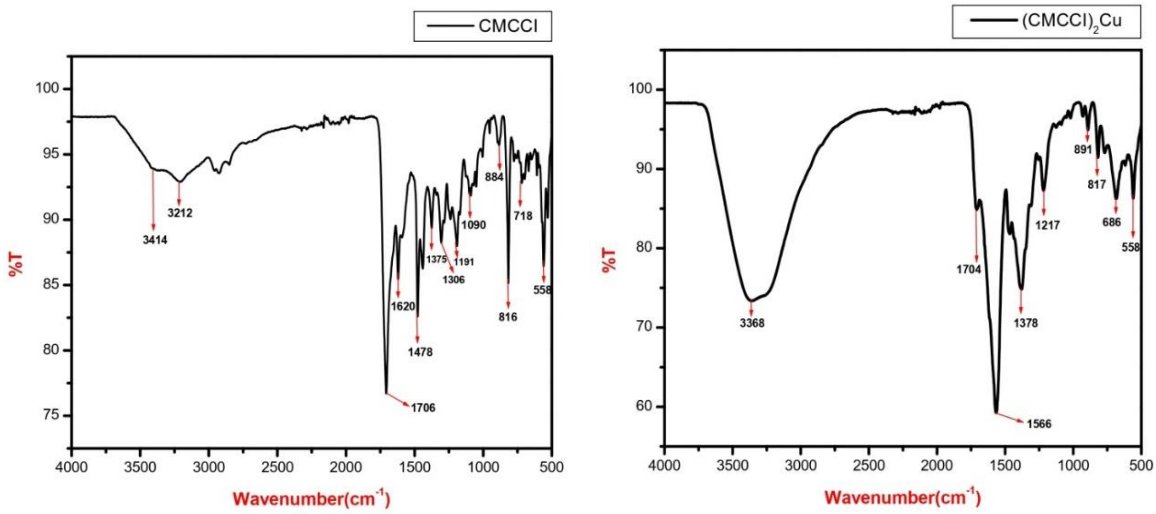


Figure 1: IR Spectra of CMCCI and $(CMCCI)_2Cu$ Complex.

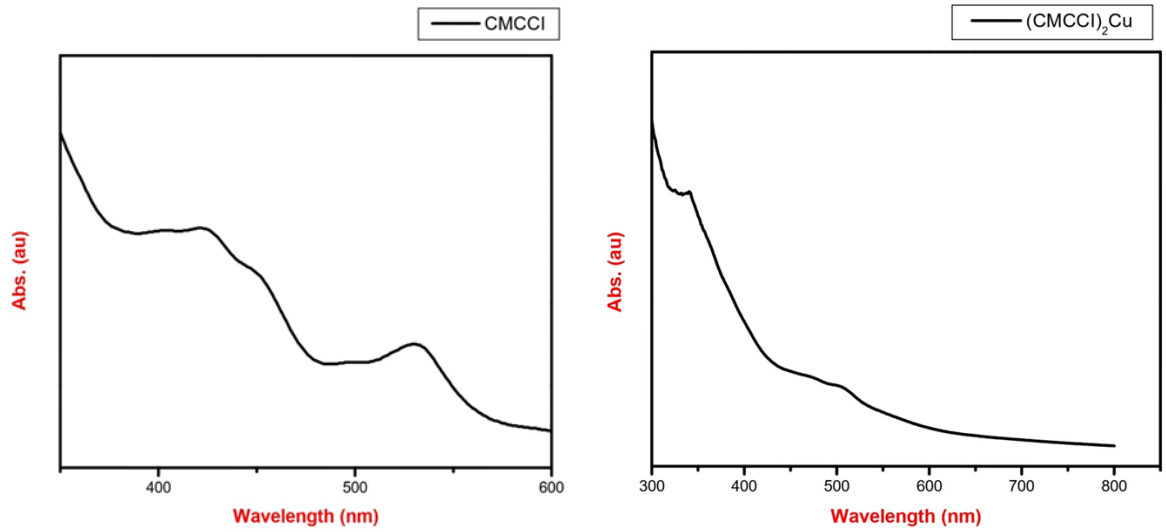


Figure 2: UV-visible Spectra of CMCCI and $(CMCCI)_2Cu$ Complex.

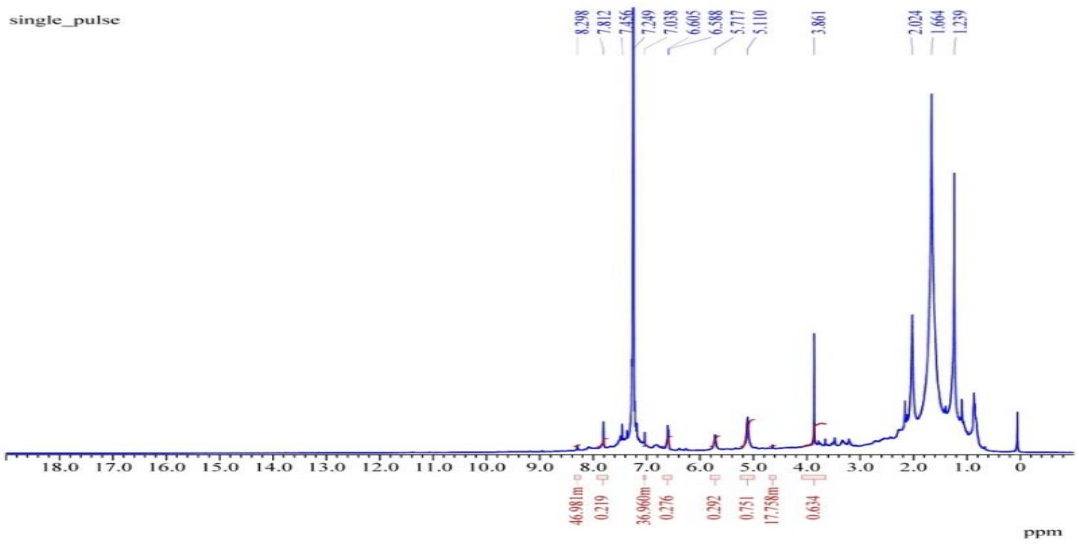


Figure 3: ^{1}H NMR spectrum of CMCCI Schiff base ligand.

Table 2
FTIR Spectral data of the ligand and metal complexes.

Compound	ν(C=O)	ν(C=N)	ν(O–H)	ν(N–H)	ν(M–N)
CMCCI	1706	1620	3414	3212	-
$(CMCCI)_2Cu$	1708	1566	3368	-	558
$(CMCCI)_2Ni$	1709	1574	3342	3342	555
$(CMCCI)_2Co$	1712	1584	3374	3358	562

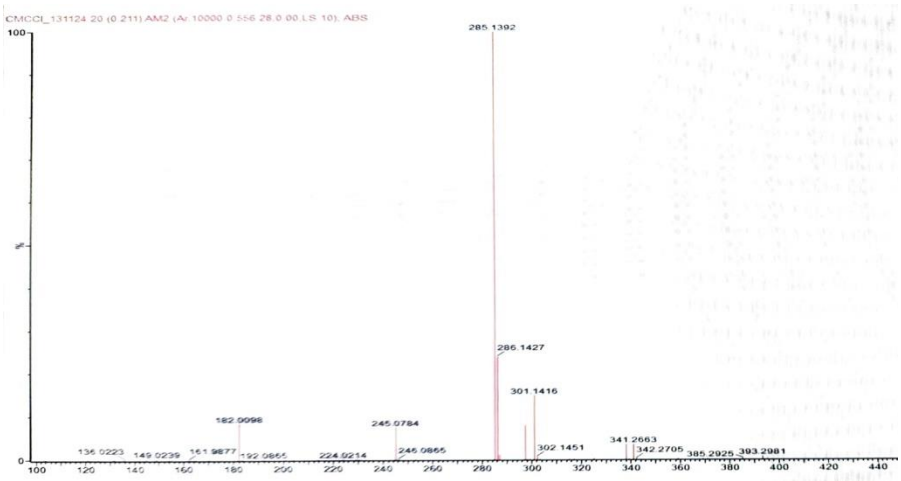


Figure 4: Mass spectrum of CMCCI Schiff base ligand.

Table 3
***In vitro* cytotoxicity data of the ligand and metal complexes at various concentrations.**

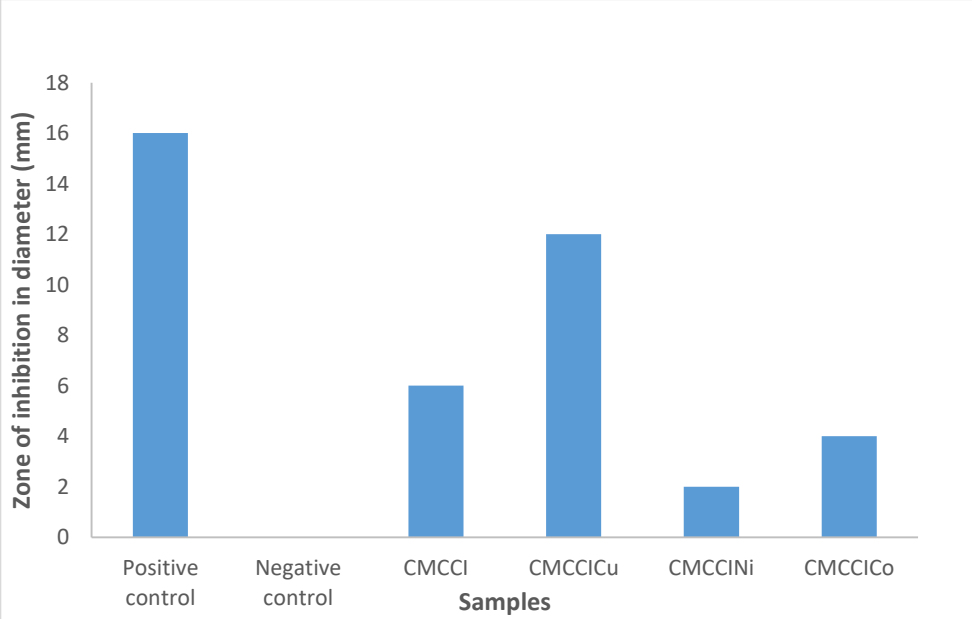
Drug concentration (µg/ml)	CMCCI	$(CMCCI)_2Cu$	$(CMCCI)_2Ni$	$(CMCCI)_2Co$
5	-	4.42±0	-	-
7.5	-	14.1±1.4	-	-
12.5	5.01±0.4	41.4±1.8	3.57±0	3.51±0
25	7.28±0.8	49.1±2.8	4.33±0.4	4.46±0
50	15.1±1.1	63.1±1.7	7.25±1.5	4.68±0.4
100	19.9±1.6	67.5±1.3	12.6±1.1	6.68±0.9
150	27±1.5	74.7±1.5	17.2±1	7.5±1.8
200	34.1±2.5	78.4±1.7	22.1±1.4	12.5±1.5

^{1}H NMR Spectral Studies: The proton NMR spectral analysis of the Schiff base ligand CMCCI was carried out using D_2O as solvent. The aromatic protons appeared as multiplet at 7.0-7.8 ppm range. NH proton peak appeared at 8.2ppm. -CH_2 peak was observed at 3.8 ppm. -COOH proton was observed at 1.23ppm. The chiral –CH- proton of the amino acid was found at 2.0 ppm. In D_2O solvent, peak due to OH group of carboxylic acid disappeared due to deuterium exchange and the peak due to DOH was observed at 5.1ppm.

Mass Spectral Studies: Mass spectrum of the CMCCI Schiff base ligand showed the molecular ion peak at 342. This clearly confirmed the formation of the Schiff base ligand.

***In vitro* Cytotoxicity Studies:** *In vitro* cytotoxicity studies using Dalton's lymphoma ascites cells (DLA) showed that percentage cell death is maximum in the case of copper complex.

Samples	Zone of inhibition in diameter (mm)
Positive control	16
Negative control	No zone
CMCCI	6
$(CMCCI)_2Cu$	12
$(CMCCI)_2Ni$	2
$(CMCCI)_2Co$	4



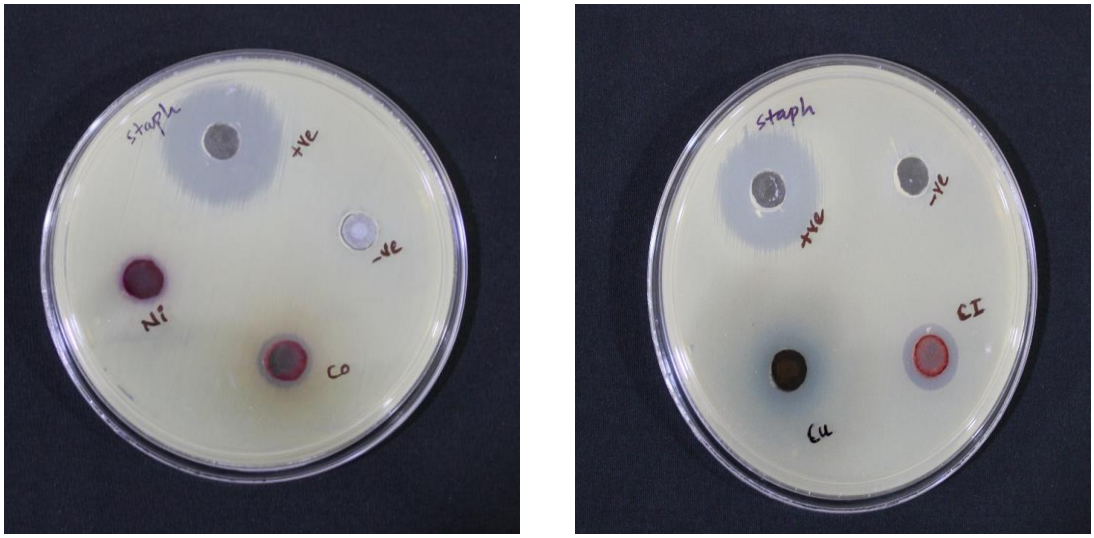
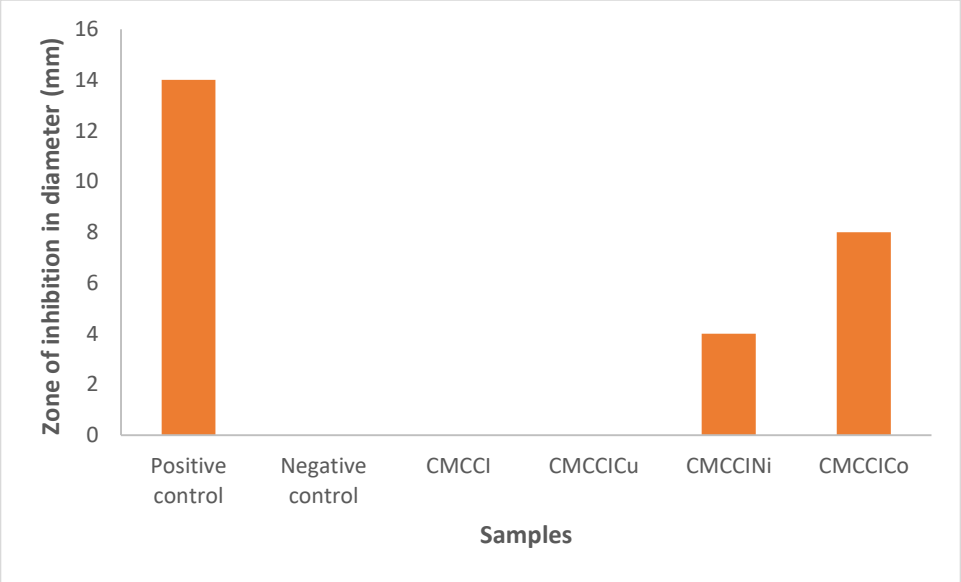


Figure 5: Zone inhibition of samples against *Staphylococcus aureus*

Samples	Zone of inhibition in diameter (mm)
Positive control	14
Negative control	No zone
CMCCI	No zone
$(CMCCI)_2Cu$	No zone
$(CMCCI)_2Ni$	4
$(CMCCI)_2Co$	8



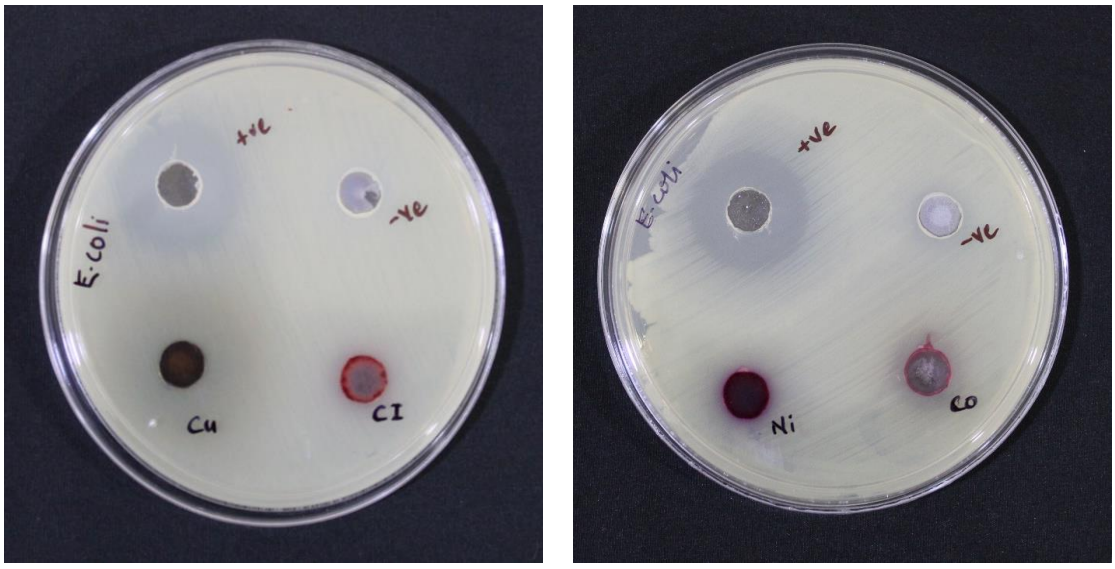


Figure 6: Zone inhibition of samples against *Escherichia coli*

Furthermore, cytotoxicity effect of all the compounds increases with increase in concentration. Cobalt and nickel complexes exhibit lower cytotoxicity compared to the Schiff base ligand. From the data, it is evident that the copper complex shows remarkable cytotoxicity even at lower concentrations and can be used as a potent anticancer drug after further investigations.

Antibacterial studies: The antibacterial activity of the tested samples (CMCCI, $(CMCCI)_2Cu$, $(CMCCI)_2Ni$ and $(CMCCI)_2Co$) against *Staphylococcus aureus* was evaluated by measuring the zone of inhibition (ZOI) in millimeters (mm). The positive control exhibited a 16 mm inhibition zone, confirming its strong antibacterial effect, while the negative control showed no inhibition zone, indicating the absence of antimicrobial activity. Among the tested samples, $(CMCCI)_2Cu$ exhibited the highest antibacterial activity with a 12mm inhibition zone. CMCCI showed a moderate inhibition zone of 6 mm, indicating some antibacterial activity but at a lower level than $(CMCCI)_2Cu$. $(CMCCI)_2Co$

exhibited a smaller inhibition zone (4 mm) while $(CMCCI)_2Ni$ had the weakest antibacterial effect, with only a 2mm zone of inhibition.

The antibacterial effectiveness of the tested samples (CMCCI, $(CMCCI)_2Cu$, $(CMCCI)_2Ni$ and $(CMCCI)_2Co$) against *Escherichia coli* was assessed by measuring their zones of inhibition (ZOI) in millimeters. The positive control displayed a 14 mm inhibition zone, confirming its strong antibacterial effect, while the negative control exhibited no zone, indicating a lack of antimicrobial activity.

Interestingly, CMCCI and $(CMCCI)_2Cu$ failed to show any inhibition, suggesting that these materials lack antibacterial properties against *E. coli* under the tested conditions. In contrast, $(CMCCI)_2Co$ demonstrated the highest antibacterial activity, with an inhibition zone of 8 mm, indicating its potential effectiveness against *E. coli*. The $(CMCCI)_2Ni$ sample exhibited a smaller inhibition zone (4 mm), showing some level of antibacterial activity, though considerably weaker than $(CMCCI)_2Co$.

Conclusion

A novel Schiff base ligand CMCCI was synthesized by combining S-Carboxy Methyl-L-Cysteine and 5-Chloroisatin in basic medium. The formation of the Schiff base ligand was confirmed by CHN analysis, FT-IR, ^1H NMR, UV-visible and mass spectroscopic techniques. Stable metal complexes of Cu(II), Ni(II) and Co(II) were formed from CMCCI and their formation was confirmed by CHN analysis, FTIR and UV visible spectroscopic techniques. The ligand and complexes were screened for their *in vitro* cytotoxicity. Cytotoxicity studies revealed that the Schiff base complexes of copper showed considerable activity even at lower concentrations suggesting the complex to be used as a potential anticancer drug after further studies.

At a concentration of 25µg/ml, about 50% cell death was observed for copper complex. Antibacterial studies of the ligand and metal complexes were performed against *Staphylococcus aureus* and *Escherichia coli*, Gram positive and Gram negative bacterial strains respectively. Copper complex exhibited considerable activity against *Staphylococcus aureus* and cobalt complex showed moderate activity against *Escherichia coli.*

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