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Antibacterial and DFT Computational Studies of a Novel Schiff Base Ligand derived from the Chiral Amino acid S- Carboxy Methyl-L-Cysteine and its Transition Metal Complexes

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Abstract

Antibacterial and DFT studies of a novel chiral Schiff base ligand S-Carboxy Methyl-L- Cysteine and 5-bromoisatin (CMCBI) derived by the condensation of the chiral amino acid CMCBI in basic medium and its Co(II), Ni(II), Cu(II), Zn(II), complexes have been reported in this study. The elemental analysis, FTIR, H^1 NMR and UV-visible spectral data suggest the formation of the Schiff base ligand CMCBI and $M(CMCBI)_2$ type metal complexes. Cu (II) and Co (II) complexes show marked biocidal activities against different microbes.

The geometrical and electrical characteristics of the experimental data are compared with theoretical data obtained from the Density Functional Theory (DFT) calculations using Gaussian 09. Electronic properties such as highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), ionization potential (IP), electron affinity (EA), hardness (g), softness (S) and electronegativity (ϖ) are determined theoretically. Cu (II), Co (II) and Zn (II) complexes show promising activities against different bacterial strains such as Bacillus, Staphylococcus and Proteus.

Keywords: Schiff base ligand, S-Carboxy Methyl-L-Cysteine, 5-Bromoisatin, Agar well diffusion method, NMR, UV, FTIR, Schiff base, DFT, Bacillus, Staphylococcus, Proteus.

Introduction

Amino acids are biologically important organic molecules which are involved in many biological processes such as synthesis of proteins, metabolic pathways, neurotransmission and biosynthesis. Amino acids have coordinating sites of $-NH_2$ and –COOH and can be condensed with aldehydes or ketones to form Schiff bases which are easily coordinated to metal ions. Most amino acid derived Schiff bases and their metal complexes exhibit different pharmacological activities[17,18,26,27]. Cu (II) complexes derived from 5-bromosalicylaldehyde and α-amino acids (L-alanine, l-phenylalanine, L-aspartic acid, L-histidine and L-arginine) showed considerable antibacterial activity against different microbes[2,4].

The Schiff base ligand, 4-nitrobenzaldehyde-glycylglycine and its Co(II), Ni(II), Cu(II) and Zn(II) complexes strongly interact with *E. coli* DNA and are active against cancer cells[27]. Co(II), Mn(II), Cu(II) and Cd(II) transition metal complexes derived from the condensation of leucine with salicylaldehyde showed greater antibacterial and antifungal activities than the synthesized ligand[19]. Yichao et al[30] synthesized tin complexes with the Schiff bases derived from salicylaldehyde/bromosalicylaldehyde and L-tyrosine which showed remarkable cytotoxicity.

Schiff bases containing heterocyclic ring exhibit a wide range of biological and pharmacological activities[24]. Isatin derived Schiff bases show anticonvulsant, antibacterial, anti HIV and antifungal activities which make them an important class of compounds in pharmaceutical chemistry[23]. The complexing ability of the Schiff bases is due to the presence of azomethine group that can be coordinated to the metal ions through the lone pair of electrons present on nitrogen atom. The stability of the Schiff base complexes depends upon the strength of C=N bond, the basicity of amino group and steric factors[6,10,15].

Schiff base complexes of transition metal ions are efficient catalysts both in homogeneous and heterogeneous conditions and the activity of these complexes varied with the type of ligands, coordination sites and metal ions[3,11,12].

Material and Methods

The analytical grade reagents and chemicals including S-carboxy methyl-L-cysteine, 5-bromoisatin, ethanol, potassium hydroxide, metal acetates (Co, Ni, Cu and Zn) were purchased from Sigma Aldrich. All chemicals were used without further purification.

Synthesis of the novel chiral Schiff base Ligand (CMCBI): The Schiff base ligand was synthesized by reacting equimolar quantities of S-carboxy methyl-L-cysteine and 5-bromoisatin. S-carboxy methyl- L-cysteine (1mmol) and potassium hydroxide (2mmol) was dissolved in water ethanol mixture. 5-bromoisatin (1mmol) was dissolved in hot ethanol.

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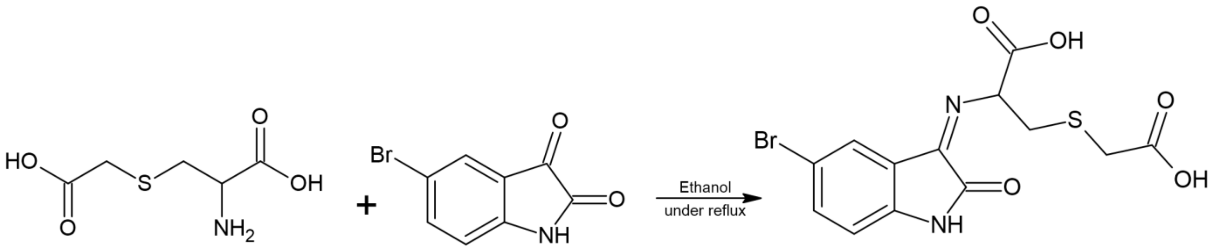
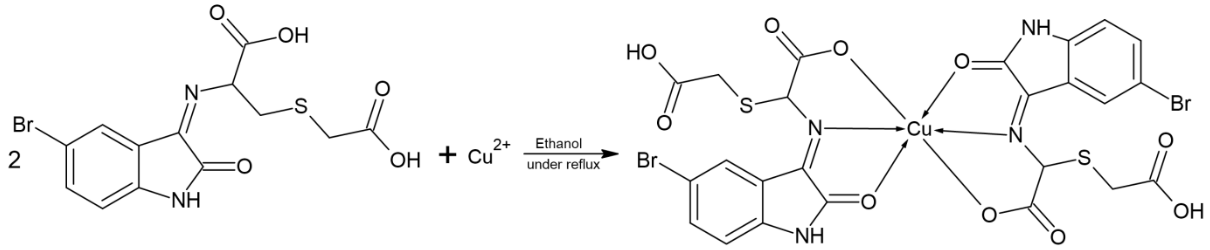


Scheme 1: Synthesis of Schiff base ligand CMCBI.



Scheme 2: Synthesis of the metal complex $(CMCBI)_2Cu$.

To the boiling solution of 5-bromoisatin, amino acid solution was added in small quantities. The dark violet coloured reaction mixture was refluxed for 6 hours at 70 °C. The solution was cooled overnight. The dark wine red coloured product obtained was filtered, washed with ethanol and dried[13].

Synthesis of Metal Complexes: S-carboxy methyl- L-cysteine (1mmol) and potassium hydroxide (2mmol) were dissolved in water ethanol mixture. 5- Bromoisatin (1mmol) was dissolved in hot ethanol. To the boiling solution of 5-Bromoisatin, amino acid solution was added in small quantities. The dark violet coloured reaction mixture was refluxed well for 3 hours at 70 °C. To the boiling solution of the ligand, ethanolic solution of metal acetate (Co, Ni, Cu, Zn) (0.5mmol) was added and refluxed at 70 °C for 3 hours more. The solution was cooled overnight. The precipitated product was filtered, washed with ethanol and dried.

Computational methodology: Density functional theory (DFT) with the Gaussian 09 software package was used to analyse the structure of the ligand (CMCBI) quantum mechanically[7,22,28,31]. Geometry optimization was done using the B3LYP/6-311++ G(d, p) level of theory[29]. Harmonic vibrational frequencies were calculated at the B3LYP/6-311++G (d, p) level using the optimised geometry ensuring local minima without imaginary vibrational frequencies. For the deeper understanding of the ligand (CMCBI) and its active sites, bond lengths, bond angles, frontier molecular orbitals (FMO), Mulliken atomic charges and surface electrostatic potential studies of the molecule (MEP) were carried out. The chemical reactivity and the hardness of the compound were calculated from the HOMO and LUMO energies.

According to Koopmans' theorem, electron affinity (EA) and ionization potential (IP) have taken as $EA = -E_{LUMO}$ and $IP = -E_{HOMO}$[24]. The global chemical reactivity descriptors were calculated as: electronegativity $(\chi) = (IP+EA)/2$ chemical potential $(\mu) = -(IP+EA)/2$ chemical hardness $(\eta) = (-IP-EA)/2$ chemical softness $(\sigma) = 1/2\eta$, electrophilicity index $(\omega) = \mu^2/2\ \eta$. Gauss view was used to visualize the optimized structures, molecular orbitals, electron densities, electrostatic potentials and other surfaces[25].

Antibacterial Analysis: The antibacterial activity analysis was carried out by using agar well diffusion method. In this well-known procedure, agar plates were inoculated with a standardized inoculum of the test microorganism. Then wells (about 8 mm in diameter) were punched and the test compound at a desired concentration was added in to the wells. The Petri dishes were incubated under suitable conditions. Antimicrobial agent diffused into the agar and inhibited the growth of the test microorganism and then the diameters of inhibition growth zones were measured. Streptomycin was used as the positive control and DMSO was used as the negative control in this analysis.

Procedure

1. Inoculum containing bacterial culture (*Staphylococcus*, *Bacillus*, *Proteus* and *Escherichia coli*) to be tested was spread on nutrient agar plates with a sterile swab moistened with the bacterial suspension.

2. Subsequently, wells of 8 mm diameter were punched into the agar medium and filled with different concentrations of samples and allowed to diffuse at room temperature for 2 h. Wells containing the same volume of DMSO (10%) served as negative controls.

3. The plates were then incubated in the upright position at 37°C for 24 hours.

4. After incubation, the diameters of the growth inhibition zones were measured in mm. Three replicates were carried out for each sample against each of the test organism.

Results and Discussion

Physicochemical 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.

FT-IR Analysis: In the FTIR spectra of the Schiff base ligand, the band due to azomethine group (HC=N) appeared at 1632 cm^{-1} and the band due to O-H of carboxylic group was observed at 3345cm^{-1}. The band due to –C=O group appeared at 1716cm^{-1}. The strong band at 1632cm^{-1} due to CH=N stretch in the Schiff base ligand shifts to a lower frequency (14-53 cm^{-1}) in metal complexes indicating the participation of azomethine nitrogen atom in coordination. The strong vibrational band of carbonyl group of the ligand showed a shift from 1716cm^{-1} to lower frequency (2-9 cm^{-1}) which again supported the coordination of the lone pair of electrons of oxygen atom of C=O group. Weak bands for the M-N bond were detected at 537-599 cm^{-1} range which confirmed the formation of complexes[14,21]. Thus the IR data strongly suggest the monobasic tridentate ONO donor behaviour of each Schiff base unit.

^{1}H NMR analysis: The proton NMR spectral studies of the Schiff base ligand were carried out using TMS as reference standard and D_2O as solvent. Aromatic protons appeared as multiplet at 7.5-7.8 ppm range. NH proton peak was found at 8 ppm. Peak due to CH_2 proton was observed at 4.3 ppm. The chiral –CH- proton of the amino acid was found at 2.9ppm. In D_2O solvent, peak due to OH group of the carboxylic acid disappeared due to deuterium exchange and a peak due to DOH was observed at 4.6ppm.

UV visible spectral analysis: The UV visible spectral analysis of the ligand and the complexes was carried out in DMSO solvent. In CMCBI, maximum absorbance was observed at 265nm and 383nm due to intra ligand pi to pi* and n to pi* transitions (Figure 1). In metal complexes, maximum absorbance band was shifted to higher wavelength region supporting complex formation. A broad absorption band at 532nm range was detected in metal complexes which may be due to ligand to metal charge transfer transition[5,9] (Figure 2).

Computational analysis: Deeper information on the molecular and electronic structures of the ligand was obtained by optimizing the geometry of the compound using density functional theory. The optimised geometry of the compound is depicted in figure 3.

Frontier molecular orbitals (FMO) analysis of CMCBI: The electronic transitions, reactivity and optical properties of the compound CMCBI were obtained from the studies of the frontier molecular orbitals. The electron transport capability of a molecule depends on the energy gap between MOs. A soft molecule will have high reactivity with low kinetic stability and low frontier orbital gap whereas a chemically hard molecule will be stable and unreactive with a larger orbital energy gap.

Table 1
Physicochemical data of the ligands and metal complexes.

S.N.	Compound	Molecular Formula	Colour	Molecular Formula	% of C Found (Calc.)	% of H Found (Calc.)	% of N Found (Calc.)
1	CMCBI	$C_{13}H_{11}N_2O_5SBr$	Black	268^{0}C	40.50 (40.32)	2.81 (2.86)	7.34 (7.24)
2	$(CMCBI)_2Cu$	$(C_{13}H_{10}N_2O_5SBr)_2Cu$	Black	>280^{0}C	37.25 (37.35)	2.45 (2.41)	6.55 (6.70)
3	$(CMCBI)_2Ni$	$(C_{13}H_{10}N_2O_5SBr)_2Ni$	Brown	>280^{0}C	37.67 (37.57)	2.40 (2.42)	6.64 (6.74)
4	$(CMCBI)_2Co$	$(C_{13}H_{10}N_2O_5SBr)_2Co$	Black	>280^{0}C	37.44 (37.56)	2.43 (2.42)	6.64 (6.74)
5	$(CMCBI)_2Zn$	$(C_{13}H_{10}N_2O_5SBr)_2Zn$	Brown	>280^{0}C	37.15 (37.27)	2.39 (2.40)	6.53 (6.69)

Table 2
Characteristic FT-IR stretching frequencies of the ligand CMCBI and its metal complexes.

Compound	ν(C=O)	ν(C=N)	ν(O–H)	ν(M–N)
CMCBI	1716	1632	3331	-
$Zn(CMCBI)_2$	1709	1579	3208	540
$Co(CMCBI)_2$	1714	1588	3221	537
$Cu(CMCBI)_2$	1704	1618	3073	599
$Ni(CMCBI)_2$	1703	1586	3199	540

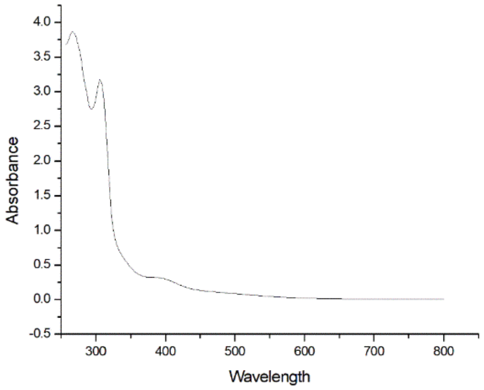


Figure 1: UV-visible spectrum of the ligand CMCBI

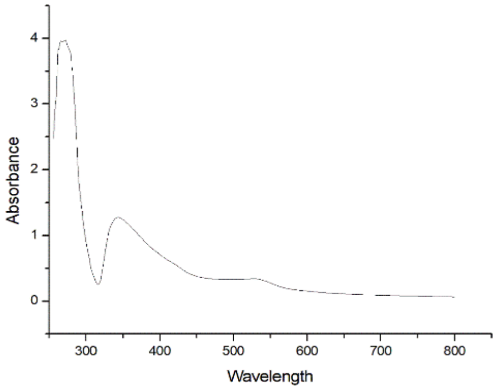


Figure 2: UV-visible spectrum of the metal complex Zn(CMCBI)$_2$

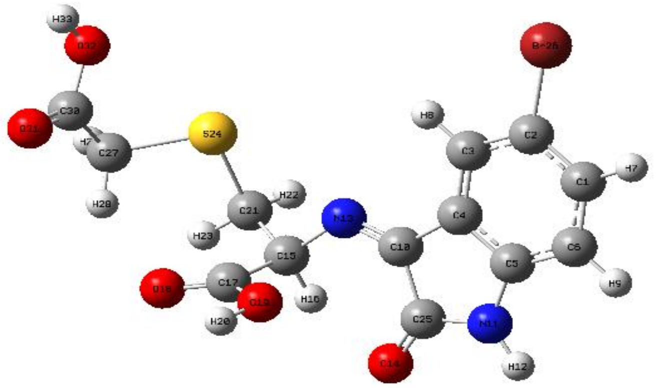


Figure 3: Optimised geometry of the ligand CMCBI with 33 atoms 194 electrons, neutral, singlet.

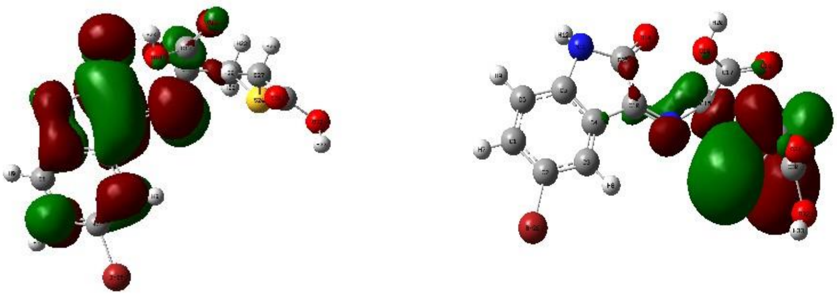


Figure 4: a) LUMO of CMCBI. b) HOMO of CMCBI.

Table 3
Calculated electronic parameters of the compound CMCBI using DFT/B3LYP/6311Gdp level of theory.

Electronic Parameter	Calculated value
E HOMO (eV)	-5.79
E LUMO (eV)	-2.77
Band Gap Energy (eV)	3.02
Ionization potential (IP)	5.79
Electron affinity (EA)	2.77
Hardness (η)	1.51
Softness (S)	0.33
Electronegativity (χ)	4.28
Chemical potential (μ)	-4.28
Electrophilicity index (ω)	6.06

Chemical hardness of a compound indicates the resistance of a chemical entity to alter the number of electrons[20]. The 2D and 3D plots of the frontier orbitals, HOMO and LUMO of the compound are shown in fig. 4. The calculated HOMO and LUMO energies, electro negativity (χ), chemical hardness (η), electron affinity (EA), chemical potential (μ), ionization potential (IP) and total energy of CMCBI have been summarized in table 3. Mulliken charge distribution of the compound CMCBI is given in figure 5.

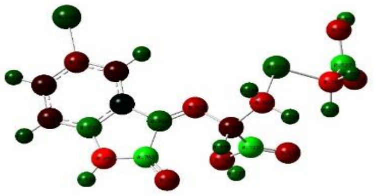


Figure 5: Mulliken charge distribution of the ligand CMCBI

Molecular Electrostatic potential (MEP) studies of CMCBI: The chemical and physical characteristics of any chemical system can be examined using an MEP plot. This plot helps in understanding where electrophilic or nucleophilic attacks are likely to occur on chemical structures. The MEP surface features various standard colors: orange, red, yellow, blue and green that indicate the strength of the electrostatic potential. The electrostatic potential decreases in the order: blue > green > yellow > orange > red. The red-colored areas indicate regions with negative potential, making them favourable for electrophilic attacks, while the blue regions, representing the highest positive potential are sites for nucleophilic attack[16].

MEP analysis of the compound CMCBI is given in figure 6. From figure 6a, it could be seen that the pure red colour zone on MEP was present on the oxygen atoms of the carbonyl group, bromine atom and oxygen atoms on the two carboxylic acid groups. These are the electron rich zones and are prone to electrophilic attack. Blue colour zones are displayed on the two nitrogen atoms which define an electron deficient area and could be favourable sites for the attack of nucleophilic species.

DFT based vibrational analysis of the ligand CMCBI: The calculations for theoretical vibrational spectra were conducted using Gaussian 09 program package. The findings of theoretical IR data based on DFT and experimental FTIR vibrations of CMCBI are given in table 4.

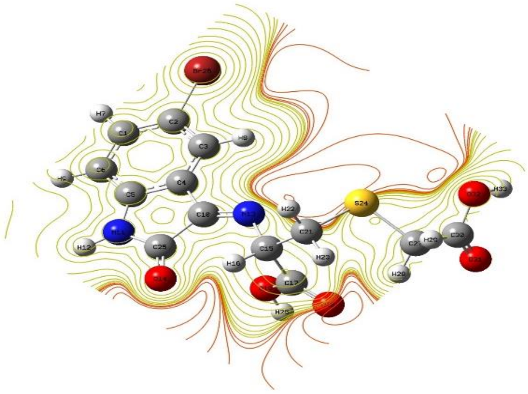


Figure 6a: MEP Analysis-2D Contour map of the ligand CMCBI

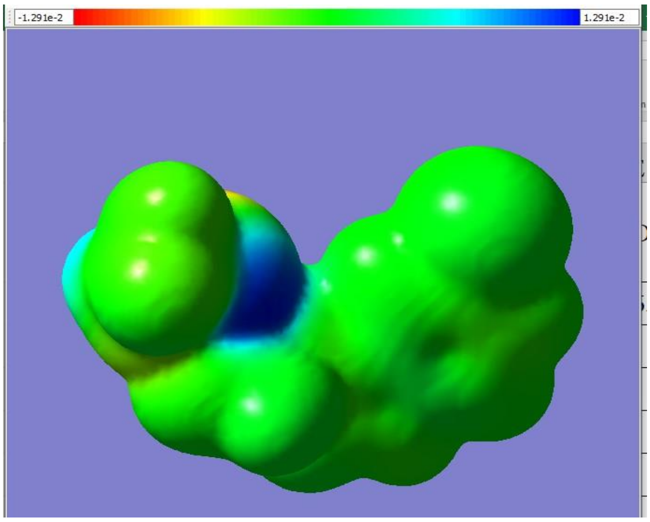


Figure 6b: 3D contour map of CMCBI.

The experimental FTIR vibrations are in good agreement with theoretical data based on DFT studies. A strong band at 1716 cm^{-1} due to carbonyl group in the experimental FTIR spectrum was observed at 1723 cm^{-1} in the theoretical spectrum. The peak due to azomethine group was found at 1632 cm^{-1} in the experimental FTIR spectrum and in the DFT based theoretical spectrum, the azomethine vibration was observed at 1617 cm^{-1}. The band due to hydroxyl group was found at 3331 cm^{-1} in experimental spectrum and at 3514 cm^{-1} in theoretical spectrum. The N-H vibration band is found at 769 cm^{-1} in experimental spectrum and at 868 cm^{-1} in theoretical spectrum. The C-N vibration band was observed at 1278 cm^{-1} and1300 cm^{-1} in experimental and theoretical spectrum respectively.

Antibacterial studies: The synthesised compounds were tested to check their antimicrobial potentials against a variety of bacterial strains. Four bacterial strains were used i.e. *E.coli, Bacillus, Staphylococcus* and *Proteus*[1]. The results revealed that the metal complexes showed greater antibacterial activities than the synthesized ligands. The detailed results are given in table 5.

$Co(CMCBI)_2$ and $Zn(CMCBI)_2$ complexes showed antibacterial activity against all the four tested organisms, *Escherichia Coli, Bacillus, Staphylococcus* and *Proteus*. The maximum activity was shown by the copper complex against *Staphylococcus* and *Bacillus* with a zone diameter of 17mm at the concentration 1000 µg/ ml. $Co(CMCBI)_2$ complex showed highest activity against *Bacillus* with a zone diameter of 12mm. $Zn(CMCBI)_2$ complex also showed greater activity against *Bacillus* with a zone diameter of 11 mm. $Ni(CMCBI)_2$ complex showed comparatively less activity. The Schiff base ligand CMCBI was found to be active against *Staphylococcus* and *Proteus*. It was found that antimicrobial activity increases with increase in concentration of the ligand and metal complexes.

Conclusion

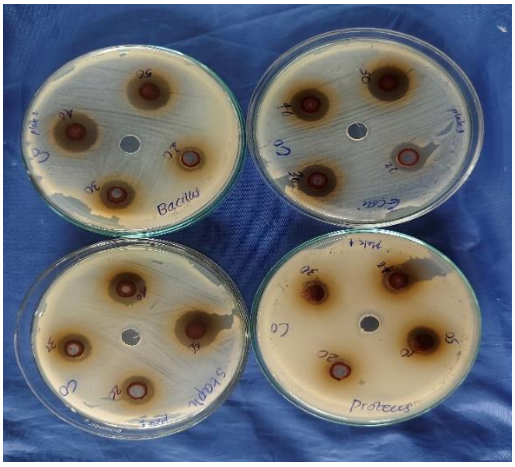
The novel chiral Schiff base ligand (CMCBI) was synthesized by combining S- Carboxy Methyl-L-Cysteine and 5-Bromoisatin in basic medium. The formation of the Schiff base ligand was confirmed by elemental analysis, FT-IR, ^{1}H NMR and UV-visible spectroscopic techniques.

Table 4
Experimental and Theoretical FTIR data of CMCBI.

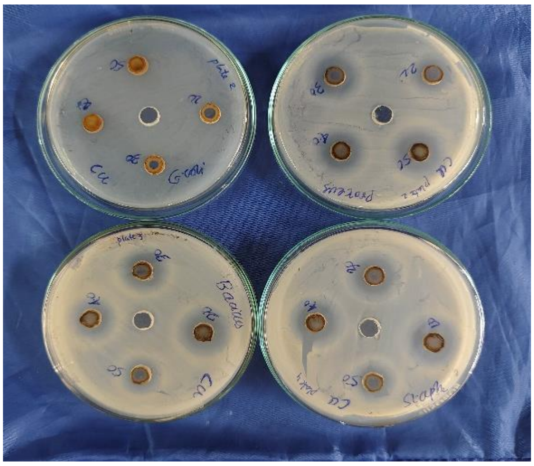
CMCBI	ν(C=O)	ν(C=N)	ν(O–H)	ν(N–H)	ν(C–N)
Experimental FTIR	1716	1632	3331	769	1278
DFT based IR	1723	1617	3514	868	1300

Table 5
Antimicrobial activity data of CMCBI ligand and its metal complexes at various concentrations.

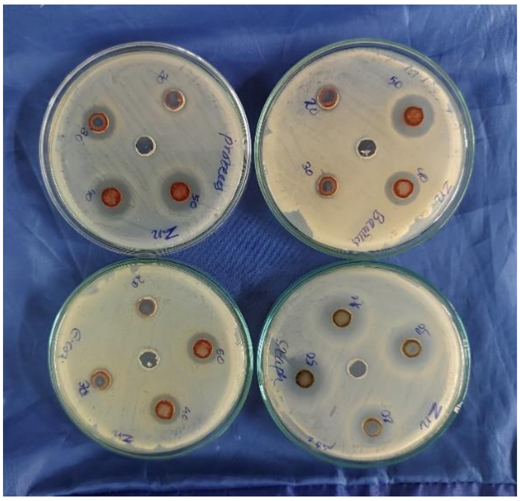
Compound	Concentration (µg/ ml)	*Escherichia coli* Zone Diameter (mm)	*Bacillus* Zone Diameter (mm)	*Staphylococcus* Zone Diameter (mm)	*Proteus* Zone Diameter (mm)
$Co(CMCBI)_2$	1000	5	14	11	10
	500	4	11	8	8
	250	4	7	5	8
	100	2	4	3	6
$Cu(CMCBI)_2$	1000	-	17	17	10
	500	-	15	16	7
	200	-	13	14	7
	100	-	8	10	4
$Zn(CMCBI)_2$	1000	6	11	8	9
	500	5	7	7	8
	250	3	4	5	7
	100	-	3	3	3
$Ni(CMCBI)_2$	1000	-	5	2	2
	500	-	3	-	1
	250	-	3	-	-
	100	-	1	-	-
CMCBI	1000	-	-	4	4
	500	-	-	3	3
	250	-	-	2	2
	100	-	-	2	1



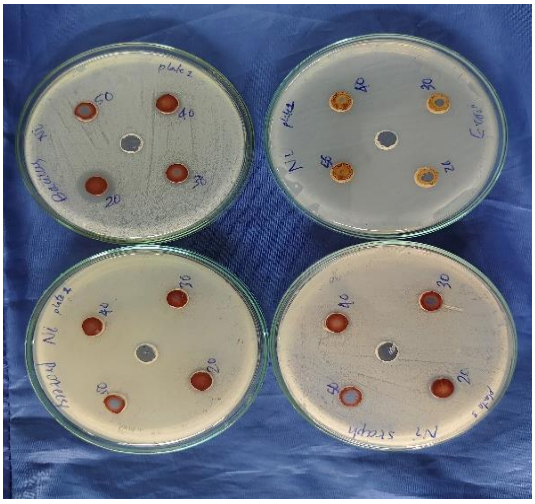
Co(CMCBI)$_2$



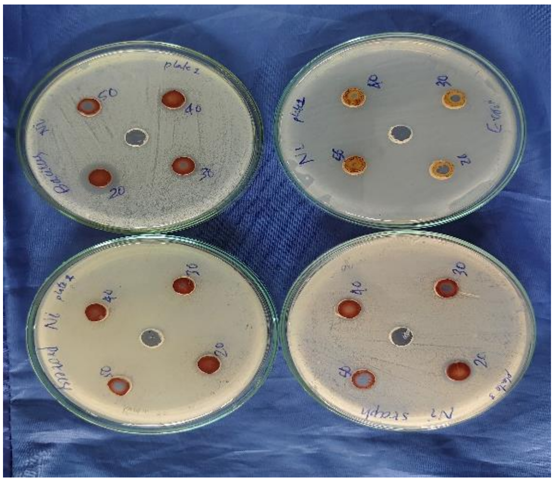
Cu(CMCBI)$_2$



Zn(CMCBI)$_2$



Ni(CMCBI)$_2$



CMCBI

The ligand formed stable complexes with transition metals which were also confirmed by elemental analysis, FTIR and UV visible spectroscopic techniques. The calculations for theoretical vibrational spectra were conducted using Gaussian 09 program package and it was found that the experimental FTIR vibrations show good agreement with theoretical data. Electronic properties such as highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), ionization potential (IP), electron affinity (EA), hardness (g), softness (S) and electronegativity (ϖ) are determined theoretically. The ligand and complexes were screened for antibacterial activities against four different bacterial strains. The antimicrobial activity studies revealed that the Schiff base metal complexes showed considerable anti-bacterial activity against the bacterial strains more than the free Schiff base ligand and the activity increases with increase in concentration. The maximum biocidal property was exhibited by copper complex.

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