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Research Paper

Shiff Base Metal Complexes: Synthesis, Biological and Computational Studies

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Abstract
The current study focuses on the synthesis and characterization of Schiff base ligand and metal complexes with Co(II), Ni(II), Cu(II), and Zn(II) in their chloride forms. The ligand is composed of a thiol base amine (2-amino-4-chlorobenzenethiol) anddicarbonyl species i.e.1,3-diphenylpropane-1,3-dione. The compounds are identified by IR, UV-visible, Elemental Analysis, Magnetic moment, and EPR studies.All the complexes were tested for antibacterial characteristics using the Agar Well diffusion method. ADME experiments were also conducted through online computer-basedstudy to assess their pharmacokinetic properties. An octahedral geometry has been projected onto all metal complexes, and the ligand behaves as a tetradentate. The newly synthesized compound has demonstrated good antibacterial activity. The pharmacokinetic behaviour reveals information regarding their possible biological applicability. Theoretical studies were also employed to elucidate the optimised energy, stability order, Frontier Molecular Orbitals energy and energy difference between them.

Keywords: *Biological, Metal Complex, Divalent, Schiff base*

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I. Introduction

To address the worrying issue of microbial resistance to antibiotics, the identification of novel active molecules against new targets is critical. Many crude medications used in therapeutic formulations are still derived from wild-growing material. However, plant-based medications have reduced the longevity of the source material. There is an ongoing hunt for more powerful and cost-effective raw materials to feed the business.[1] Selecting appropriate amines and substituted aromatic carbonyls for the synthesis of Schiff bases is responsible for the development of numerous characteristics such as steric, electrical, and biological potential. [2][3], [4], [5]. Schiff bases are often used by chemists in procedures such as cycloaddition and nucleophilic addition with organometallic reagents because of their flexibility. Schiff bases can be used to overcome medication resistance in cancer and to immobilize enzymes. [6-9] As a result of conjugation, Schiff bases formed from primary aromatic amines and aromatic aldehydes exhibit greater stability and are less prone to polymerization compared to those created from primary aromatic amines and aliphatic aldehydes, which are more unstable and more susceptible to polymerization [10-11]. While both Schiff base ligands and their metal complexes have a range of applications, there remains a significant number that have yet to be investigated [12-13]

Experimental section

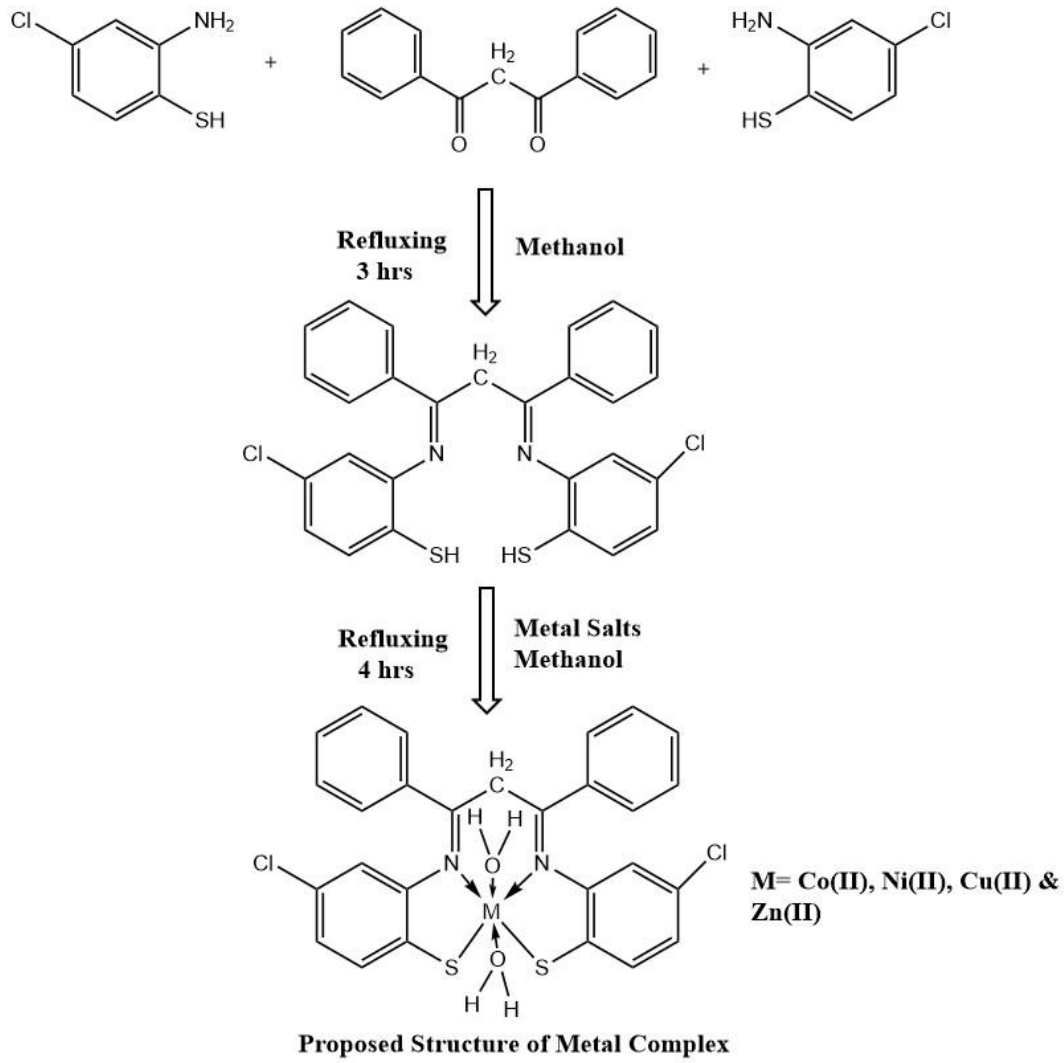
Materials and methods

All the chemicals used for the synthetic purposes were procured from Sigma Aldrich. Solvents were used as such without further distillation. IR, UV-visible spectra were MNIT-Jaipur. ESI-MS data were recorded form CIL-IIT Ropar. EPR studies of the complexes was analyzed from SAIF-IIT Bombay. CHN analyses was carried out from SAIF-PU Chandigarh.

Synthesis of Metal complexes

To prepare the ligand, we employed a condensation reaction method. We started by dissolving 20 mmol (1.34 g) of 1,3-diphenylpropane-1,3-dione in methanol. Following this, we performed a dropwise addition of the

amine compound, specifically 2-amino-4-chlorobenzenethiol, amounting to 40 mmol (3.19 g). Afterwards, the reaction mixture was refluxed for 3 hours, resulting in a light orange solution. The mixture was then allowed to cool overnight at room temperature, yielding orange-colored precipitates as the final product. The completion of the reaction was confirmed by observing a single spot on the TLC. Scheme 1



Scheme 1: Synthesis of Schiff base ligand and its metal complexes

Antimicrobial studies

The widely recognized disc diffusion method [14] was employed to assess the antibacterial and antifungal properties of the complexes. The bacterial strains utilized include E. coli and B. subtilis, while the fungal strains examined are C. albicans and A. niger. DMSO served as the negative control. For the antibacterial analysis, Ciprofloxacin and Amphotericin-B were used as positive controls. The MIC values were determined in µg/ml.

ADME Studies

In silico ADMET analyses of the ligand and its metal complexes were performed using the online Swiss ADME predictor tool. The similarities between the synthesized complex and existing drugs can be assessed by evaluating various properties such as absorption, distribution, metabolism, excretion, and toxicity. The Lipinski rule of five was emphasized due to its significant role in drug development. The rule, commonly referred to as Pfizer's rule of five or simply the rule of five (RO5), is essential in this context This is a guideline to assess or clarify the drug-likeness, if a chemical compound with a certain pharmacological or biological activity possesses chemical and physical attributes that would make it a likely oral drug for humans. Christopher

A. Lipinski formulated the rule in 1997, based on his observation that most orally administered drugs possess small and moderately lipidic properties.

II. Result and Discussion

Schiff base ligand was found to be good solubility in methanol, whereas its metal complexes were found to be good solubility in DMSO. Their non-electrolytic nature is reflected in the lower value of molar conductance.

Infra-Red Studies

Figures 1 and 2 show the assignments of the distinctive infrared spectral bands of the ACD ligand and its metal chelate, ACD-2. Patterns revealed that the ligand spectrum had a peak at 1630 cm^{-1}, which may be ascribed to the ν(CH=N) vibration that arises from the condensation of carbonyl and amine species. [15]

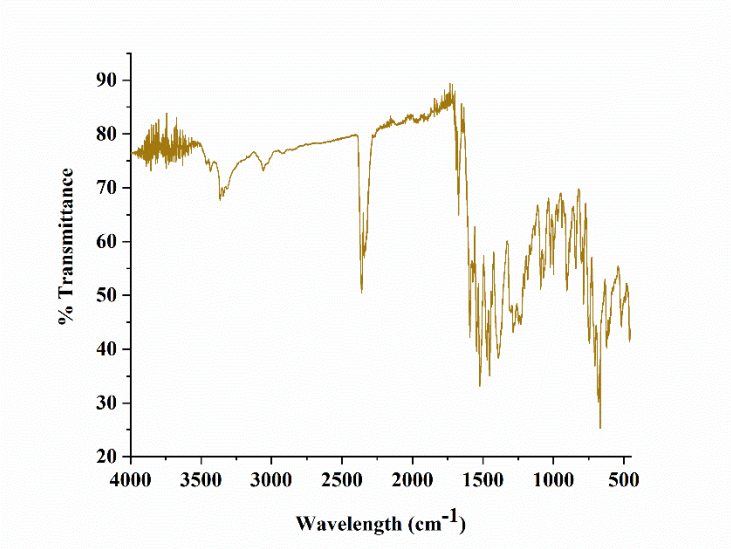


Figure 1: IR Spectrum of ligand ACD

The complexes' peak was moved to the 16120–1624 cm^{-1}range, indicating that it was coordinated with a metal ion. In addition to the azomethine peak, the -SH group causes vibration, which is absent in the case of a metal complex, almost at 2450 cm^{-1}. This suggests that thiol group hasbeen deprotonated and bonded to a metal ion. Because of the water of coordination, the complexes' spectra showed the appearance of ν(OH) vibrations. [16]

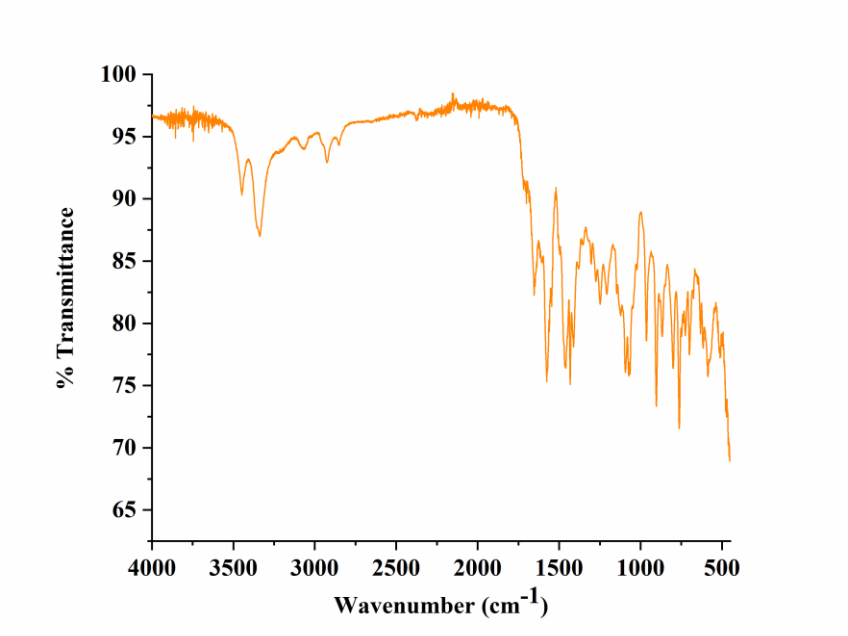


Figure 2: IR Spectrum of ligand ACD-3

UV-visible studies

In the absorption spectra of the synthesized ligand ACD we got an absorption band at nearly 340 nm that may corresponds to n→π* transition. In addition to this transition an lower wavelength transition also appear at 290 nm that may be attributed to the π→π* transition of the azomethine linkage of the Schiff base ligand. In the metal complexes additional band were also obtained for the d-d transition. In case of Complex ACD-1 band appear at 670 nm, ACD-2 at 840 nm, ACD-3 at 930 nm. In case of ACD-4 no d-d transition is possible hence no absorption band corresponds to these transitions are obtained. [17]

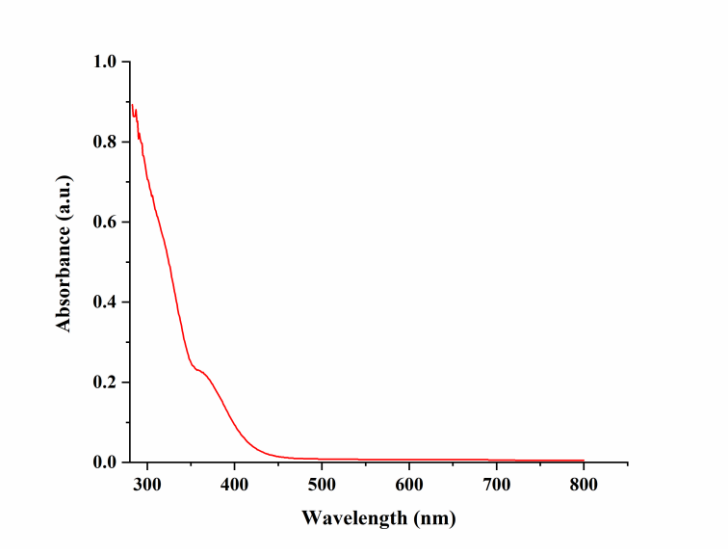
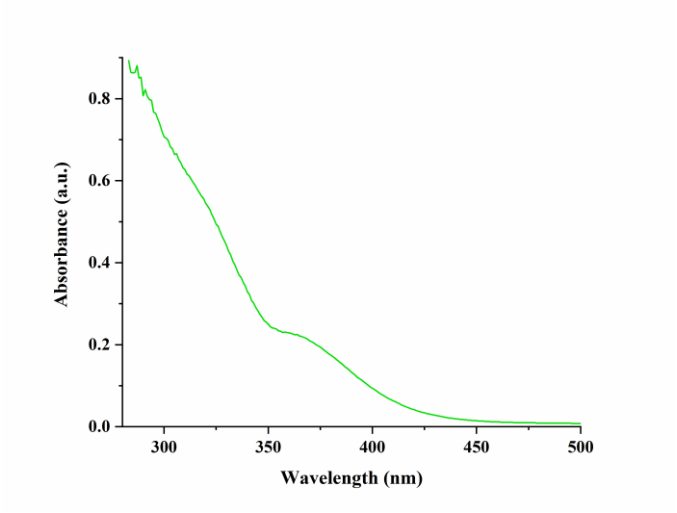


Figure 3 : Electronic Spectrum of ligand ACD



Electron Spray Ionisation-Mass Spectrometric Studies

Mass spectrometric data are collected Electron Spray Ionization technique in a positive mode. In case of free ligand ACD we got molecular we got molecular ion peak at m/z 530.51 that may be because of $[M+Na]^+$. In rest of the complexes, we got molecular ion peak at m/z 600.44, 600.20, 605.5, 606.89 for ACD-1, ACD-2, ACD-3 & ACD-4. Data is in good consistency with the monomeric nature of the complexes.

Electron Paramagnetic Resonance Studies

The electron paramagnetic resonance evaluation of the complex of Copper (II) was taken at X-Band Frequency of 9.4 GHz at ambient room temperature. There was a field strength of 3000 Gauss used. The calculated values of g(parallel) and g(perpendicular) for the complex support the condition $g_{parallel} > g_{prependicular} > 2.0023$, which indicates [18-19] that the odd or unpaired electron occupies the$dx^2 - y^2$. The G value reveals significant exchange interaction of the complex, as the value is less than 4.

Elemental Analysis and physico-analytical data

Ligand(ACD)

Yield: 71 %, Mol. Wt. 507.49; Anal. Found: C,63.51; H, 3.86; N, 5.50; % Calc.: C, 63.90; H, 3.97; N, 5.52;Color, Yellowish .

ACD1 complex

Yield: 74 %, Mol. Wt.600.44; Anal. Found: C, 53.97; H, 3.60; N, 4.65; M, 9.74 % Calc.: C, 54.01; H, 3.69; N, 4.67; M, 9.82. Color, Reddish Brown ; Molar conductivity (Ω^{-1} $mol^{-1}cm^2$) in DMSO 17. Magnetic moment μ_{eff} (BM): 3.74.

ACD2 complex

Yield: 68 %, Mol. Wt. 600.20; Anal. Found: C, 54.02; H, 3.60; N, 4.63; M, 9.67 % Calc.: C, 54.03; H, 3.69; N, 4.67; M, 9.78. Color, Light green; Molar conductivity (Ω^{-1} $mol^{-1}cm^2$) in DMSO 19. Magnetic moment μ_{eff} (BM): 3.06.

ACD3 Complex

Yield: 66 %, Mol. Wt. 605.05; Anal. Found: C, 53.46; H, 3.55; N, 4.52; M, 10.39 % Calc.: C, 53.60; H, 3.66; N, 4.63; M, 10.50. Color, Black; Molar conductivity (Ω^{-1} $mol^{-1}cm^2$) in DMSO 25. Magnetic moment μ_{eff} (BM): 1.74.

ACD4 Complex

Yield: 77 %, Mol. Wt. 606.89; Anal. Found: C, 53.38; H, 3.60; N, 4.57; M, 10.62 % Calc.: C, 53.44; H, 3.65; N, 4.62; M, 10.77. Color, Cream; Molar conductivity (Ω^{-1} $mol^{-1}cm^2$) in DMSO 21. Magnetic moment μ_{eff} (BM): 0.0

Antimicrobial Efficacies

Each synthesized compound's MIC value was determined after it was screened for antimicrobial efficacy. As can be seen from the data gathered, complex ACD4 exhibits good activity against E.Coli, B. Subtilis and A. Niger, and this activity is even better than that of the free ligand ACD. Complex ACD3 is also imparting good activity against C. albicans by possessing a MIC of 16 (ug/ml).In the similar fashion MIC value of 16 (ug/ml) was also found in free ligand ACD against the fungal strain A. niger, Complex ACD-2 for bacterial strain B. subtilis. We can conclude, in summary, that every complex ACD-4 has good activity against three stains.Based on Tweedy's chelation theory, the good activity could be explained. [20]

Compounds	E. coli	B. Subtilis	C. albicans	A. niger
Ligand-ACD	128	64	32	16
ACD-1	32	128	32	64
ACD-2	64	16	64	128
ACD-3	64	64	16	128
ACD-4	32	32	128	32
Ciprofloxacin	6.25	6.25	-----	------
Amphotericin	------	-----	12.5	12.5

Table 1: MIC (ug/ml) of the newly synthesised compounds

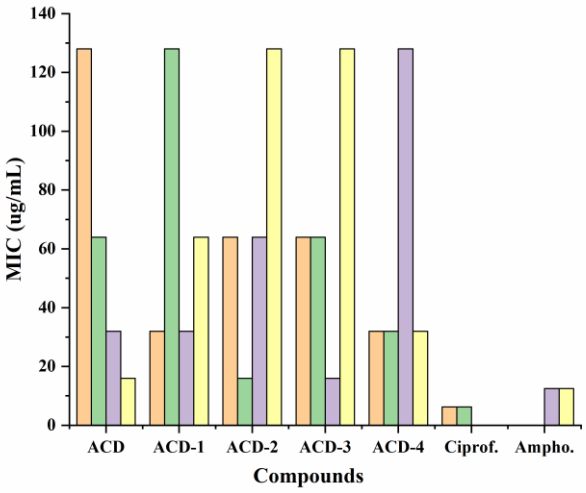


Figure 5 : Graphical representation of MIC (ug/ml) of the ligand and its metal complexes

ADME Studies

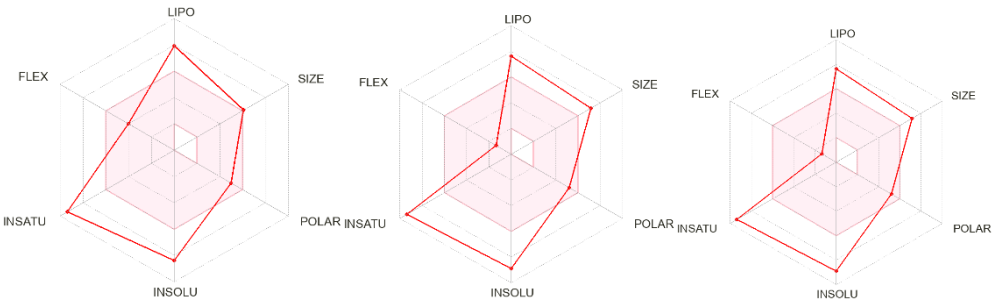
In Tables 2 and 3, the different parameters computed for the ligand and complexes are listed. Every one of the parameters has a distinct meaning that defines a specific characteristic of the compound. The acronym TPSA represents Topological Polar Surface Area. This parameter is related to the compound's polar atom surface, as the name suggests. Finding the drugs' or compound's transport characteristics is aided by it. For the present study range between 102.32 and 108.1 Å exists for TPSA. These compounds are made flexible by a number of rotating hydrogen atoms. Nevertheless, in the current study, no (Tables 2 and 3). of the rotational hydrogen bonds has value of six, while the for other compounds have value of two.. This indicates that the ligand is more flexible than the other complexes. A bioavailability score of 0.17 was found for all complexes and ligands, indicating a higher likelihood of bioactivity.In all cases, the number of hydrogen donors is two, but the ligand donor is zero. All compounds are drug-like, and pharmacokinetics studies show that none of the complexes have synthetic accessibility scores or BBB penetration comparable to the free ligand. Compound ACD-3 acts as CYP3A4 inhibitor. The skin permeation value is highest in case of ligand and lowest for ACD-4. The Synthetic Accessibility scoreis highest in case of compound ACD-4. The radar for bioavailability is displayed in Figure 7. The image's pink region displays each parameter's ideal range, while the red line displays the measured values for each parameter.

Compounds	Mol. wt.	TPSA	H-Acceptor	H-Donor	No. of Rotatable Bonds	Bioactivity score
ACD	507.5	102.32	2	0	6	0.17
ACD-1	600.4	108.1	2	2	2	0.17
ACD-2	600.2	108.1	2	2	2	0.17
ACD-3	605.5	108.1	2	2	2	0.17
ACD-4	606.8	108.1	2	2	2	0.17

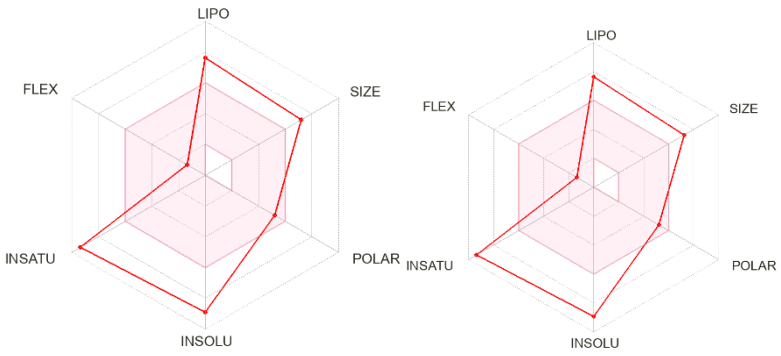
Table 2 : Phyico-chemical parameters of the compounds

Compounds	Gastrointestinal Absorption	BBB Permeation	P-glycoprotein Substrate	CYP3A4 inhibitor	Skin Permeation (log K_p)	Synthetic Accesibility score
ACD	Low	No	Yes	No	-3.47	3.43
ACD-1	Low	No	Yes	No	-4.38	4.72
ACD-2	Low	No	Yes	Yes	-4.37	4.61
ACD-3	Low	No	Yes	No	-4.40	4.73
ACD-4	Low	No	Yes	No	-4.41	4.82

Table 3 : Pharmacokinetic parameters of the newly synthesised compounds



Ligand ACD **ACD-1** **ACD-2**



ACD-3ACD-4

Figure 6 : Radar Digram of the ligand (ACD) and its metal complexes

Theoretical studies

For the better understanding about the stability of ligand and its metal complex Semi-empirical studies were performed[21] out with PM6 parameter.**(Figure 7 &8)** The geometry of the Schiff base ligand ACD and one of its metal complexes ACD-4 were optimised for getting the value of minimum energy at which these proposed structure are stable. The values of dipole moment were also calculated and tabulated in Table. Theligand ACDpossessminimised energy value as 0.179 a.u., whereas its complex ACD-4 is having a value of -0.050 a.u. The observed data revealed that complex is having higher stability than free ligand. The energy difference between HOMO and LUMO were interpreted and revealed that the stability order isACD-4> ACD. The conclusion is drawn on the basis of their energy difference calculations.

Compounds	**Minimised Energy (a.u.)**	**Energy (a.u.) HOMO**	**Energy (a.u.) LUMO**	**ΔE (a.u.)**
ACD	0.1794	-0.31509	-0.02522	0.289
ACD-4	-0.05049948	-0.29258	-0.03632	0.256

Table 4 : Optimised energy and energy gap of the ligand ACD and complex ACD-4

Compounds	**Dipole moment**
ACD	4.4093 Debye
ACD-4	6.7767 Debye

Table 5 : Dipole moment of the ligand ACD and complex ACD-4

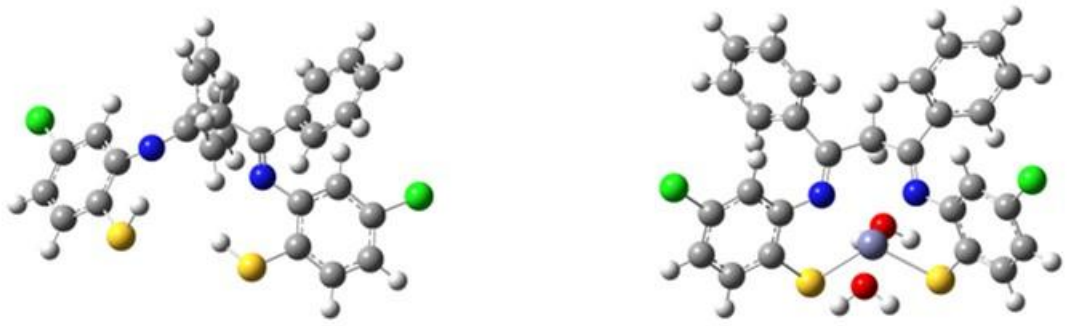


Figure 7 : Optimised geormtry of ligand (ACD) (left) and metal complex ACD-4(right)

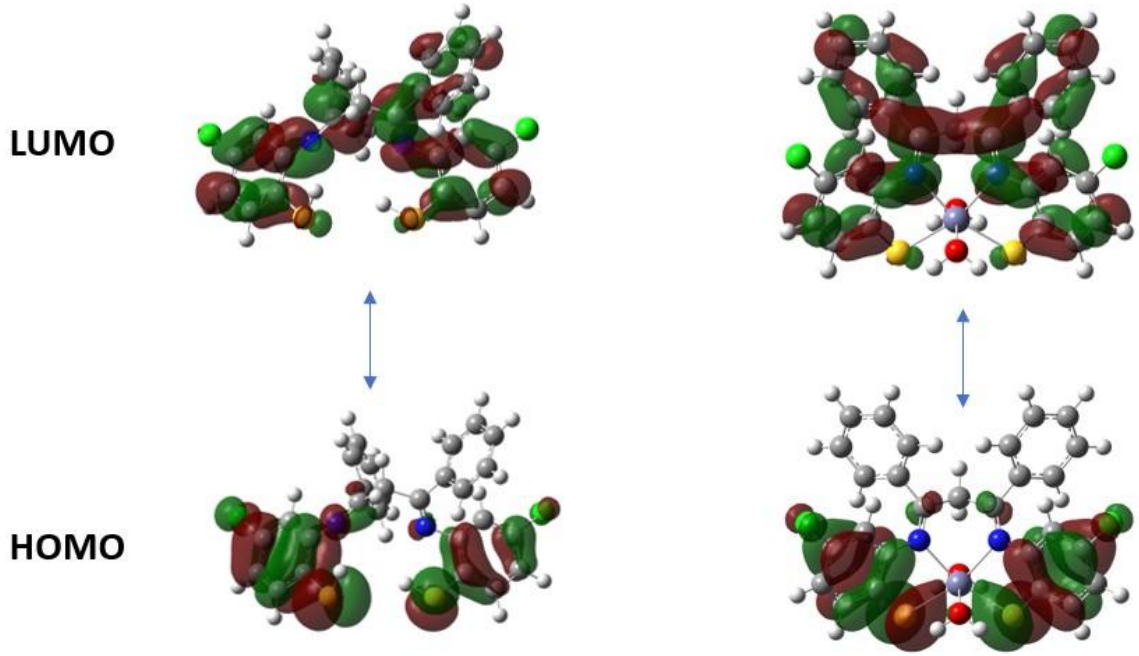


Figure 8 : Frontier Molecular Orbitals of ligand (ACD) (left) and metal complex ACD-4(right)

III. Conclusion:

A thiol and diketone-based Schiff base ligand (ACD) and its metal complex with four divalent transition metal ion have been prepared and characterized in the present study. An octahedral geometry have been proposed to all the complex and ligand behaves astetradentate ligand. All the compounds were screened for antimicrobial efficacies and found that ACD-4 possess betteractivity and good pharmacokinetic behavior have also been observed in the complexes. Structure of ligand and one of the metal complexes were computationally studied for getting better insight into the energy values.

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