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An experimental insight into biological potent macrocyclic complexes: Template synthesis and biological studies

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Due to arising of problem of Antimicrobial resistance now a days, it is the requirement to develop novel antimicrobial agents. In the present research work we reported the preparation of macrocyclic divalent transition metal complexes by adopting the path of template methodology. The bivalent 3d-transition metal salts used are Co^{II}, Ni^{II} , Cu^{II} and Zn^{II} in their chloride form. The macrocyclic ligand is derived *in situ* by the help of 3,4-Diaminotoluene and Thiobarbituric acid. The synthesised complexes were fully characterised and analysed by the assistance of spectroscopic and physico-analytical techniques like IR, NMR, Electronic spectra, Electron Spray Ionisation-Mass Spectrometry, Electron Spin Resonance, CHN, Molar conductance and magnetic moment measurements. The selected analyses reveal that the macrocyclic complexes may be verbalized as $[MLX_2]$, where M is the divalent transition metal ion, L is the macrocyclic ligand and X is the counter ion of the metal salt. The Infra red spectral studies help in the primary identification for the successful development of macrocyclic complexes by the condensation reaction. The monomeric behaviour of the prepared compounds were explicated by the Mass Spectrometric and elemental analysis data. The geometry proposed was distorted octahedral in nature for all the metal complexes on the basis of results obtained from the Electronic spectra and ESR studies. Lower values of the molar conductance points in the direction of the non-electrolytic expression of the complexes. All the synthesised metal complexes were unveiled for their antifungal and antibacterial efficacies contrary to some fungal and bacterial strains. In addition to this, we have also performed the *in silico* ADME studies for the determination of various pharmacokinetic parameters that help in interpreting the dug like properties in the complexes.

Keywords: Antibacterial, Antifungal, Coordination chemistry, Spectroscopy, Transition metal

Macrocycle may be defined as "a cyclic backbone of minimum nine atom and three among them must be donor atom through which they can form a coordinate bond" and after coordination with the metal ion it is known as macrocyclic complexes[1].These complexes have enticed the attention of chemist due to their variable applications in the field of catalysis[2], environmental protection[3], molecular electronics and photonics[4] as well as in medicine[5]. These complexes have imparts their important role in various biological system. The macrocyclic complexes of diaminotoluene based moiety have been studied by various research groups and good antimicrobial, DNA binding activity have been exhibited by the complexes[6]. Since 2-thiobarbituric acid is the primary component of coenzymes, nucleic acids, and antibiotics, several research groups have previously reported on its importance in the fields of pharmacology, biology, and analysis[7,8].These barbiturates are widely known for their ability to treat a wide range of mental or neurological conditions, including epilepsy and anxiety. In the market there is lack of new antibiotics that keep a check on the drug resistant microbes. These pathogens are spreading in a noncontrolled manner in our society[9].

Many antibacterial and antifungal substances have been found and manufactured in recent decades, but medications including fluconazole, tetracycline, amphotericin-B, and penicillin are now commonly used on the market[10,11]. The availability of four nitrogen donor sites curbed to a single or slightly fourfold planar ring structure, which is an appropriate site for metal binding, makes synthetically designed tetrazamacrocyclic ligands and their metal complexes generally good models for carrying oxygen[12]. Additionally, these Schiff bases may find application in the well-known field of optoelectronics. These compounds have structural similarities to biological systems due to the availability of donor sites in Schiff

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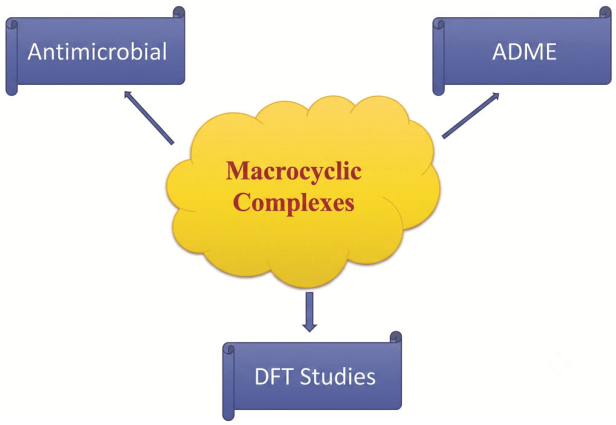
bases that include atoms such as oxygen, nitrogen, and sulfur[13]. Prompted from the above-mentioned applications and need of the present generation we have the following aims and objectives form the current research work:

1. To synthesize macrocyclic complexes by template methodology.
2. Use spectroscopic methods to characterise the prepared complexes.
3. Antimicrobial screening of the synthesized macrocyclic complexes.
4. To determine the drug likeness in the macrocyclic complexes.

Materials and Methods

Material and physical measurements

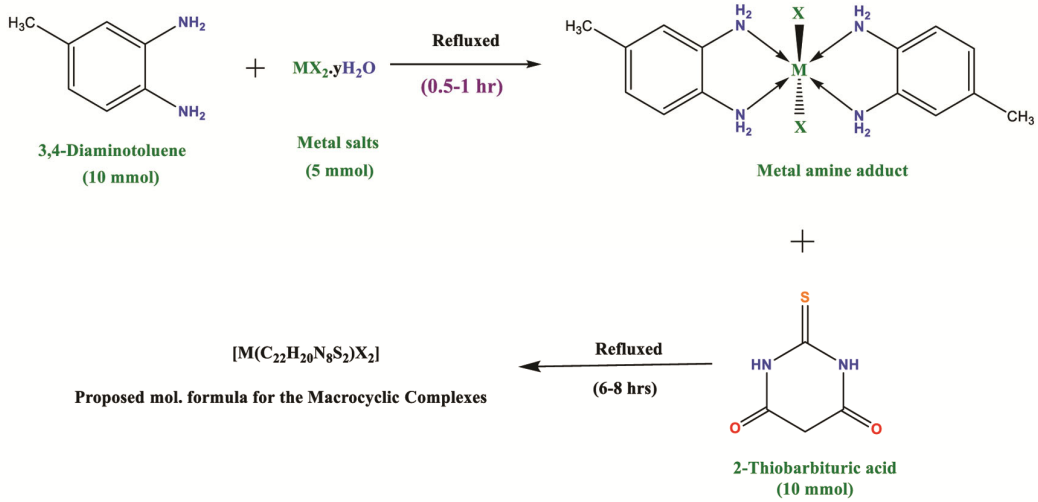
Procurement of 3,4-Diaminotoluene and Thiobarbituric acid was done from the Sigma Aldrich. Metal salts and solvents used for the synthesis and washing purposes were purchased from Merck and Avra, respectively. The NIT-Kurukshetra provided an FTIR spectrophotometer (Shimadzu) capability with a range of 4000-400 cm^{-1}. The Evolution 201 Spectrophotometer (Thermo Scientific) was used to capture electronic spectra in the 250–1100 nm range. The Hitachi TG/DTA 7200 equipment was used for the thermal investigations, which were conducted at a heating rate of 10 C/min and in the temperature range of 50 to 800°C. The complexe's metal contents were calculated using established literature techniques. The EuroEA elemental analyzer was used for microanalysis (CHN) at SAIF, Punjab University, and Chandigarh. The molar conductance values were determined using a digital conductivity meter (HPG System, G-3001). At SAIF, IIT-Bombay, the EPR studies of the Cu(II) complex at room temperature were conducted on ESR, Varian, USA. At IIT-Ropar's Central Research Facilities, the complexes' mass spectrum was recorded using the XEVO G2-XS QTOF device.



Graphical abstract

Synthetic route

To the hot methanolic solution of 3,4-diaminotoluene (10 mmol, 1.22 g) we have added the 2.5 mmol of respective metal salts and allowed to reflux for 0.5-1.0 h. After this, there was an addition of Thiobarbituric acid (10 mmol, 1.22 g) and keep the reaction mixture for refluxing for about 6-8 h. Now keep the obtained reaction mixture for overnight cooling and washed the obtained product with methanol and acetone. The proposed reaction mechanism is shown in (Scheme 1).



Scheme 1 — Plausible scheme for the synthesis of macrocyclic complexes

Biological Activity

Antimicrobial screening

The *in vitro* antibacterial and antifungal activities of all the synthesized macrocyclic complexes against pathogenic strains of bacteria and fungus were evaluated. The present study employs *Staphylococcus aureus*, *Escherchia coli*, *Candida albicans*, and *Candida tropicalis* as gram positive, gram negative, and fungal strains.

Antimicrobial Studies

Using the Agar Well Diffusion technique, six complexes were evaluated for their antibacterial activity. The microbial cultures were standardized to the 0.5 McFarland standard, approximately corresponding to a suspension of 1.5×10^8 cfu/mL in appearance. Each Petri plate was prepared with 20 mL of agar medium, swabbed with 100 µL of the test microorganism inoculum, and allowed to stand for 15 min for adsorption. Wells, 6 mm in diameter, were created in the seeded agar plates using a sterile cork borer and subsequently filled with 100 µL of each substance at a concentration of 6.25-100 mg/mL, reconstituted in dimethylsulphoxide (DMSO). The plates were then incubated at 37°C for 24 h. The inhibition zones against the test organisms were measured using a zone reader (also known as an antibiotic zone scale) to assess the biocidal potency of each complex. Amphotericin B was used as a positive control for yeast, while DMSO served as a negative control for bacteria. This procedure was repeated three times for each organism[14].

Determination of Minimum inhibitory concentration (MIC) of chemical compounds

Using a modified agar well diffusion method, the minimum inhibitory concentration (MIC) of the synthesized complexes against bacterial and yeast strains was determined. Each chemically synthesized compound was prepared through a twofold serial dilution, initially reconstituted in DMSO and then further diluted with sterile distilled water to achieve a concentration range of 100 to 6.25 µg/mL. Triplicate wells in agar plates, pre-seeded with 100 µL of standardized inoculum (10^6 cfu/mL) of the test microbial strain, were filled with each dilution. The plates were then incubated aerobically at 37°C for 24 h, and inhibitory zones were observed. The MIC, defined as the lowest concentration of the compound required to completely inhibit microbial growth, was recorded based on the presence of a clear inhibition zone. Ciprofloxacin and amphotericin B served as positive controls, while DMSO was used as a negative control[15].

In silico ADMET studies

SWISS ADME software was used for the calculations of various pharmacokinetic properties of the complexes. The software is available online and free of charge[16].

Computational studies

This research involved a DFT study of metal complexes to explore their theoretical properties. The structures were optimized using Density Functional Theory (DFT) to minimize strain energy. All computations were conducted in the gaseous phase. Geometry optimization of the synthesized complexes was performed using the Gaussian 09 program, employing the LANL2DZ basis set and the B3LYP functional level. These calculations provided various quantum chemical parameters[17].

Results and Discussion

The reaction yields a powdered product in various colors, which is soluble in DMSO. The macrocyclic complexes exhibit non-electrolytic behavior, as indicated by their low molar conductance values ranging from 13 to 30 (Ω^{-1} mol^{-1} cm^2). Based on spectral, analytical, and magnetic moment data, a probable structure for the complexes has been proposed.

(D1) $[Co(C_{22}H_{20}N_8O_2)Cl_2]$:Yield- ~59%,M.wt. = 557.04, Anal. Cal: M, 10.56; C, 47.33; H, 3.61, N, 20.07; Found: M, 10.47; C, 47.28; H, 3.54; N, 20.01; Molar conductivity (Ω^{-1} mol^{-1}cm^2) in DMSO 13.7. Magnetic moment μ_{eff} (BM): 3.86.

(D4) $[Ni(C_{22}H_{20}N_8O_2)Cl_2]$:Yield- ~67%, M.wt. = 556.04, Anal. Cal: M, 10.52; C, 47.35; H, 3.61, N, 20.08; Found: M, 10.48; C, 47.31; H, 3.52; N, 20.01; Molar conductivity (Ω^{-1} mol^{-1}cm^2) in DMSO 17.6. Magnetic moment μ_{eff} (BM): 3.07.

(D7) $[Cu(C_{22}H_{20}N_8O_2)Cl_2]$:Yield- ~67%,M.wt. = 561.05, Anal. Cal: M, 11.29; C, 46.94; H, 3.58, N, 19.91; Found: M, 11.19; C, 46.86; H, 3.47; N, 19.87; Molar conductivity (Ω^{-1} mol^{-1}cm^2) in DMSO 11.4. Magnetic moment μ_{eff} (BM): 1.83

(D10) $[Zn(C_{22}H_{20}N_8O_2)Cl_2]$:Yield- ~59%,M.wt. = 562.04, Anal. Cal: M, 11.58; C, 46.79; H, 3.57, N, 19.84; Found: M, 11.55; C, 46.76; H, 3.54; N, 11.51; Molar conductivity (Ω^{-1} mol^{-1}cm^2) in DMSO 15.3. Magnetic moment μ_{eff} (BM): 0.0

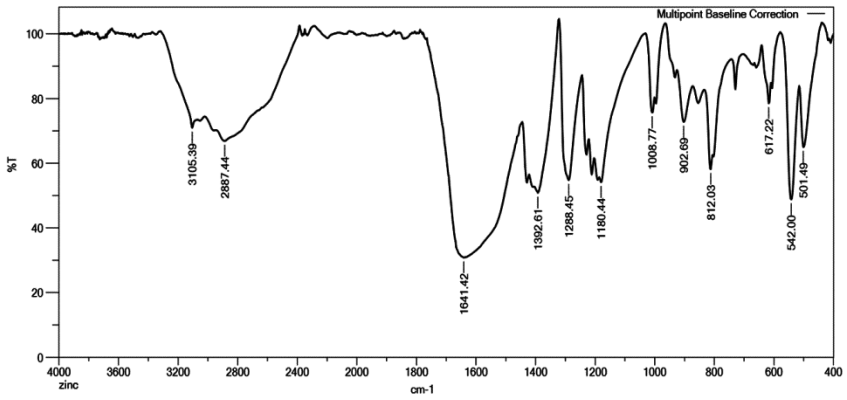


Fig. 1 — IR Spectrum of Complex D10

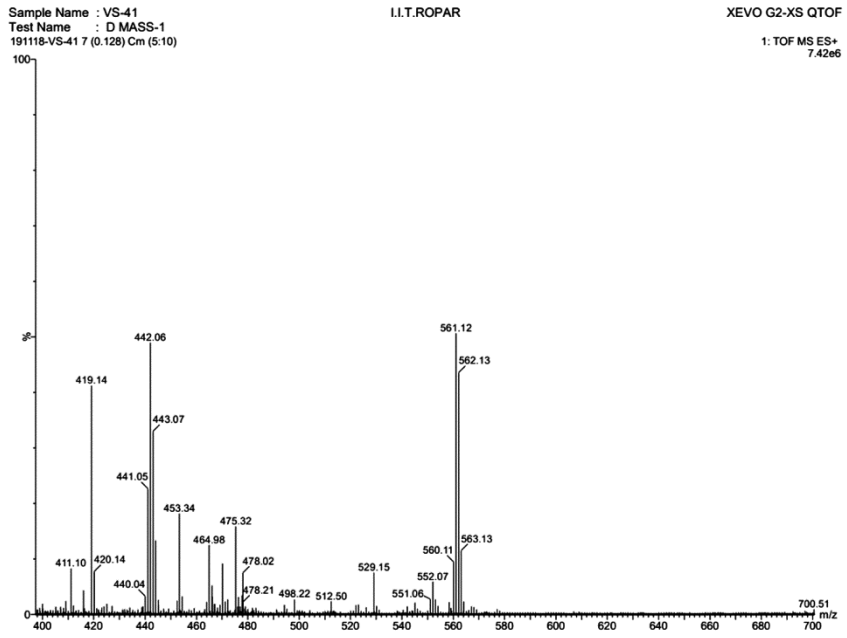


Fig. 2 — ESI-MS data of complex D1

Infra-red spectral studies

The IR spectra of the synthesized macrocyclic complexes play a key role in identifying the condensation reaction between primary amines and carbonyl/thiocarbonyl groups. The metal complexes exhibit a broad band in the 1580–1660 cm^{-1} region, which corresponds to the overlapping peak of the azomethine linkage (1580–1610 cm^{-1}). Additionally, peaks observed in the 1620–1660 cm^{-1} and 3100–3200 cm^{-1} regions can be attributed to the amide-I (ν C=O) and secondary amide (N-H) groups within the macrocyclic structure. The amide-II [ν(C-N)] + δ(N-H) and amide-III (N-H) bands appear at 1410 cm^{-1}, 1300–1350 cm^{-1}, and 800–810 cm^{-1}. (Fig. 1, and Suppl. Figs. S1–S3). The presence of a merged peak for the free C=O eliminates the possibility of condensation occurring at both carbonyl groups of the dicarbonyl moiety[18,19].

ESI-MS Data

The mass spectra of the complexes were recorded using ESI-MS in positive mode. The spectrum for complex D1 displayed a molecular ion peak at *m/z* 561.11, corresponding to [M+4H]+. Similarly, the molecular ion peak for the D4 complex appeared at *m/z* 556.81, aligning well with its molecular weight. For D7, a peak was observed at *m/z* 561.92, likely representing [M]+. Meanwhile, the molecular ion peak for the D10 complex was detected at *m/z* 562.07. (Fig. 2, and Suppl. Figs. S4–S6)

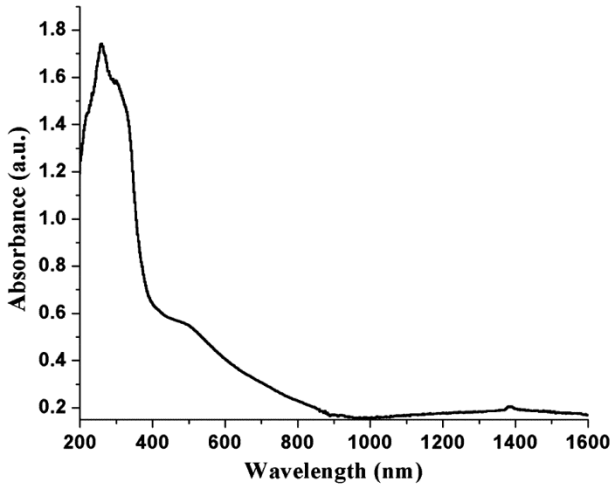


Fig. 3 — Electronic spectrum of Complex D7

Electronic spectra

The complex D1 showed the d-d transition band at 482.73 nm and the transition due to $\pi \rightarrow \pi^*$ is observed at 245-255 nm. (Suppl. Figs. S7 & S8). The absorption band at 300-310 nm can be ascribed to the $n \rightarrow \pi^*$, respectively. In the similar way the d-d transition band for the D4 complexes are present at 1350-1400nm, 490-510nm. The $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions are obtained at 250-250 nm 302-315 nm and, respectively. In the case of D7 complexes the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transition are existing at 260-270 nm and 310-330 nm, (Fig. 3) whereas d-d transition band is present at 490-500 nm[20,21].

^{1}H-NMR

The proton NMR spectrum was recorded for the Zn(II) complexes in d^6-dmso at 400 MHz instrument. Signal for two methyl groups are present at 1.9 ppm. Four N-H proton appeared at 11.8 ppm. Signal for four proton of methylene group are observed at 3.12 ppm, respectively[22].

ESR Studies

The EPR spectrum of the Cu(II) complex was analyzed to determine its geometry and the nature of the unpaired electron. A solid-state sample was used for this study. The spectrum was recorded in the X-band (frequency range: 8.75–9.65 GHz) at room temperature. The applied magnetic field was 3,000 G, with a field center of 336.791 mT. The sweep time for the analysis was 4.0 min. The spectrum of the complexes showed hyperfine splitting at low temperature (Fig. 4). The values of g(parallel) and g(perpendicular) for these complexes have possessed the value of 2.184 & 2.190, respectively. The data

Fig. 4 — EPR spectrum of Complex D7

points towards the distorted octahedral geometry of the Cu(II) complexes[23,24].

Computational studies

Geometry optimisation

The geometry of the four representative metal complexes were optimised for their energy minimisation[25]. The minimised energy for the complexes *i.e.* D1 was found to have value of 3.141eV whereas the complex D4 was consisting the energy value of -0.320 eV. In the similar way for the complex D7 and D10 energies were found at the value of 1.161 eV and -1.476 eV.

FMO's and Quantum Chemical parameters

The HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) play a crucial role in determining the electrical and optical properties of a material. Additionally, they hold significant importance in quantum chemistry. The energy level of the HOMO influences a molecule's ability to donate electrons to an appropriate acceptor, such as the LUMO. As widely discussed in the literature (Figs. 5 & 6), a system with a large HOMO-LUMO energy gap tends to be less reactive than one with a smaller gap. Various quantum chemical parameters, including absolute hardness (η), global softness (S), electronic charge (ΔN_{max}), global electrophilicity (ω), absolute electronegativity (χ), and separation energy (ΔE), were calculated using the equations provided below (1–8).

$$\Delta E = E_{LUMO} - E_{HOMO} \quad \ldots (1)$$

$$\chi = -(E_{HOMO} + E_{LUMO})/2 \quad \ldots (2)$$

$$\eta = (E_{LUMO} - E_{HOMO})/2 \quad \ldots (3)$$

$$\sigma = 1/\eta \quad \ldots (4)$$

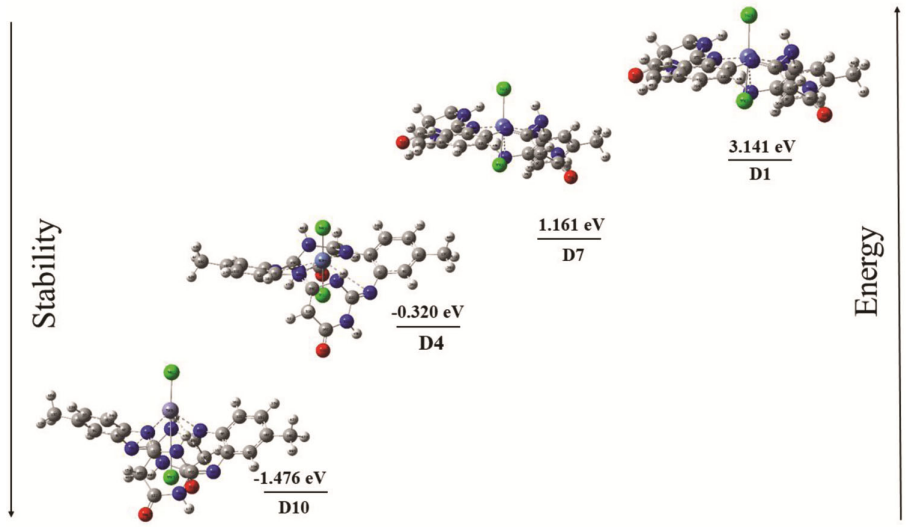


Fig. 5 — Stability order of metal complexes

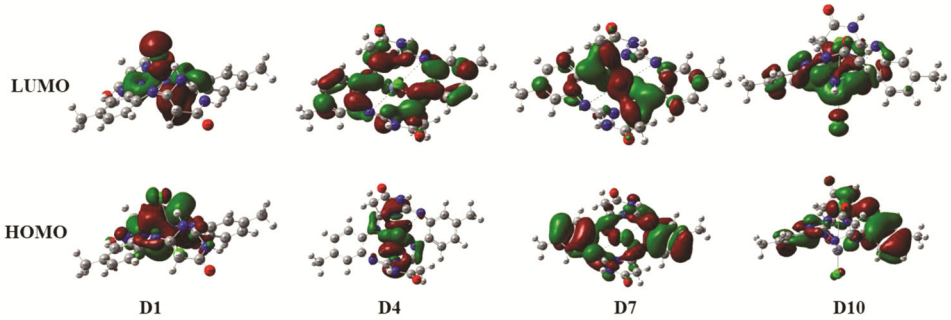


Fig. 6 — Frontier molecular orbitals of metal complexes

Table 1 — Quantum Chemical parameters of synthesised complexes

	HOMO	LUMO	ΔE	χ	η	σ	*Pi*	S	ω	ΔN_{max}
D1	-8.70	-4.28	4.42	-6.49	2.21	0.45	6.49	0.22	9.52	-2.93
D4	-7.25	-1.16	6.09	-4.20	3.04	0.32	4.20	0.16	2.90	-1.38
D7	-9.07	-1.40	7.66	-5.24	3.83	0.26	5.24	0.13	3.58	-1.36
D10	-9.43	-1.21	8.22	-5.32	4.11	0.24	5.32	0.12	3.45	-1.29

$Pi = -\chi$ … (5)

$S=1/2\ \eta$ … (6)

$(\omega)= Pi^2/2\ \eta$ … (7)

$\Delta N_{max} = -Pi/\eta$ … (8)

Each parameter Table 1 is having difference significance and imparts a particular property to the compound. For example, the hardness of a molecule is represented by 'η' and this parameter tells about the reactivity of a compound. If the value of 'η' is higher it seems that there is large energy gap between HOMO-LUMO and the system is less reactive and hence more stable. The result obtained from the above calculation points towards that the order of the stability of metal complexes are in D10>D7>D4>D1.

***In silico* ADME studies**

The different parameters determined for the metal complexes are organized in (Table 2). All the determined parameters are having a variable degree of importance that primarily centres around one kind of property of the complex. Lipinski's Rule of Five was considered due to its significant role in drug development. Also known as Pfizer's Rule of Five or simply the Rule of Five (RO5), this principle serves as a guideline for evaluating drug-like properties in molecular complexes. Established by Christopher

Table. 2 — Various pharmacokinetic parameters of the macrocyclic complexes

Complexes	Mol. Formula	Molecular weight(g/mol)	Log P	TPSA	No. of H-acceptor	No. of H-donor	No. of rotatable bonds	Bioactivity score
D1	$C_{22}H_{20}Cl_2CoN_8O_2$	558.29	4.59	137.63	2	4	0	0.55
D4	$C_{22}H_{20}Cl_2N_8NiO_2$	558.05	4.59	137.63	2	4	0	0.55
D7	$C_{22}H_{20}Cl_2CuN_8O2$	562.9	4.59	137.63	2	4	0	0.55
D10	$C_{22}H_{20}Cl_2N_8O2Zn$	564.73	4.59	137.63	2	4	0	0.55

A. Lipinski in 1997, the rule is based on the observation that most orally administered drugs are relatively small and moderately lipophilic molecules. Differently determined parameters have distinctive significance and variable point of applications that bestows them towards great medications (Table 2).

Log P is a crucial parameter in drug design, used to evaluate a compound's hydrophobic behavior. It plays a vital role in determining drug adsorption and bioavailability within biological systems. From the above calculations, it was found that the value obtained for all the complexes are in acceptable limit that is below than 5.

TPSA can be expanded as Topological Polar Surface Area. As the title specifies this parameter is mainly associated with the surface of the compound having polar atoms. It assistances in the elucidation of the transport properties of the drugs or compound. The value for TPSA lies in the array of 137.63 – 149.83 Å^2. The complexes D1, D4, D7, D10 are possessing the least value of TPSA i.e. 137.63. For rest of the complexes the values are found in between these ranges. This is studied by the ability of H-bonding of the compound.

Rotational hydrogen atoms (RHA) offer flexibility to the compounds. But for the present synthesized complexes no. of rotational hydrogen atoms ranges in between 0-5. Complex D1, D4, D7, D10 are possessing the zero no. of RHA, whereas this number was 4 in rest of the compounds.

Bioavailability score for all the complexes were found to have a value of 0.17- 0.55. The score value for complexes D1, D4, D7 and D10 was 0.55. The obtained results specifies the there would be higher probability of bioactivity of these four complexes in whole of the series.

Number of hydrogen donor are less than 5 in every complex that divulges that these complexes are active in oral mode of administration.

Number of hydrogen acceptor in the current situation lies at 2. The value is two in the case of complex D1, D4, D7 and D10.

Table. 3 — MIC (ug/mL) of macrocyclic complexes

Complexes	S.aureus	*E. coli*	C. albicans	C. tropicalis
D1	50	12.5	12.5	50
D4	50	12.5	50	12.5
D7	12.5	50	50	6.25
D10	6.25	6.25	12.5	12.5
Ciprofloxacin	*6.25*	*6.25*	-	-
Amphotericin	-	-	*12.5*	*12.5*

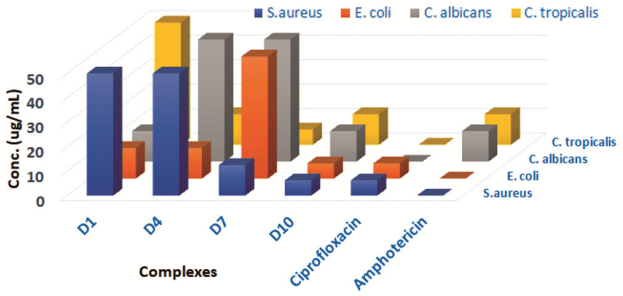


Fig. 7 — Pictorial representation MIC (ug/mL) of macrocyclic complexes

Antimicrobial studies

Among all the macrocyclic complexes Complex D10 showed the notable MIC of 6.25 µg/mL against gram positive bacteria *S. aureus* and gram negative *E. Coli*. This Complex also have the lowest MIC against the fungal strains. Rest of the complexes showed the moderate activity against the fungi and bacteria. On comparing with the commercially available standard antibiotic, it was found that complexes D10 shows MIC values (Table 3) comparable to ciprofloxacin hence it can be said the complexes D10 is effective antibiotic (Fig. 7) and could the future antibiotic. It is suggested that coordination or chelation reduces the polarity of the metal ion, primarily due to the partial sharing of charge with donor atoms or groups within the complete chelate ring system. This process enhances the lipophilic nature of the central metal atom, facilitating its penetration through the lipid layer of the microbial membrane. As a result, metal complexes can effectively cross the membrane, thereby increasing their biological activity. Furthermore,

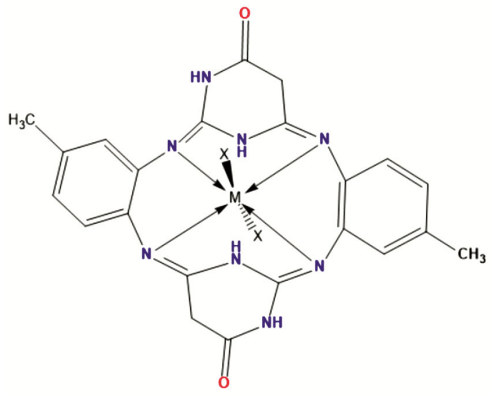


Fig. 8 — Proposed structure of the complex

several other factors, such as dipole moment, solubility, and conductivity, influenced by the metal ion, may also contribute to the biological activity of these complexes. Additionally, the introduction of certain functional groups, such as an azomethine linkage, has been observed to enhance biological activity. This could be attributed to an increase in hydrophobic character and lipo-solubility, which aids in the compounds' ability to traverse microbial cell membranes, ultimately improving their bioavailability and effectiveness[26-29].

Conclusion

This study involves the synthesis of four novel divalent transition metal ion-based macrocyclic complexes. The compounds were thoroughly characterized using various techniques, including IR, UV-Vis, mass spectrometry, CHN analysis, and magnetic moment measurements. Based on the obtained data, all metal complexes are proposed to exhibit a distorted octahedral geometry.Complexes were analysed by computational studies and found that D10 is having higher stability among all complexes. Antimicrobial results also points towards good activity of complexes D10 that may be formulated as antimicrobial agent after cytotoxicity analysis. ADME studies were also carried out to know the pharmacokinetic behaviour of the complexes. The proposed structure of the complex is shown in (Fig. 8).

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Conflict of interest

All authors declare no conflict of interest.

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