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Studies on phthalic acid based macrocyclic transition metal complexes biological activity, molecular docking, synthesis and characterization

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Abstract
A novel series of Macrocyclic complexes of [M(L)Cl2] (M = Co(II), Ni(II) and Cu(II), L = Macrocyclic ligand) were synthesized by template condensation method using 3,4-diaminotoluene and phthalic acid in the presence of divalent transition metal ions Example., Co(II), Ni(II) and Cu(II) in their chloride form. This synthesized Metal complexes were fully characterizetion by Spectroscopic Analyasis Techniques namely UV-Visible, IR, ESR and ESI-MS. Their thermal behaviour was determined by TGA and DTA. Further these macrocyclic complexes were screened for Antimicrobial activity against Bacterial species (*Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Escherichia coli*) and Fungi (*Aspergillus niger* and *Candida albicans*) and then compared against standard drug Streptomycin and itraconazole, respectively. In addition to these the antioxidant activity of the macrocyclic complexes were also investigated through scavenging effect on the DPPH radicals. Finally, the biological potency of synthesized compounds was evaluated using Auto Dock Vina. All the synthesized macrocyclic complexes were found to be potent against bacterial and fungal species, which suggest their potential application as antibacterial and antifungal agents.

Keywords: Molecular docking, antimicrobial agents, Macrocyclic complexes, Tetra-aza macrocyclic, UV-Visible

Introduction
Recent years have witnessed an immense deal of interest in the vicinity of synthesis of transition metal complexes with macrocyclic ligands. In past few years, the macrocyclic ligands have acquired great interest of chemists due to their mind- boggling chemical and biological properties. Various macro- cyclic Schiff bases are essential in the coordination chemistry owing to the fact they can selectively chelate certain metal ions relying at the wide variety, type and position of their donors [1]. The layout and synthesis of novel medicines that beautify their assessment and the simultaneous advances in relevant technology contributed to the recent trends on this vicinty [7]. Owing to these chemical properties among the chemistry of transition metals, several macrocyclic complexes have been found with high biological relevance. In spite of having these properties, these metal macrocyclic complexes serve as bio- chemical complex for related metalloenzymes. However, in addition they also provide insights into the biomimic models [8, 9].
These macrocyclic complexes of transition metal ions had been demonstrated to be a precious form of the auxiliary ligands for several metallomolecules such as porphyrins, corrins by the change within the size of ring and the donor atom in the macro- cyclic ligand [10]. Owing to their unique properties in the better understanding of the molecular processes of biochemical, clinical application, analytical, contrast agents in magnetic resonance imaging, antimicrobial agents [11] and catalysis [12] several polyaza macrocyclic complexes have been synthesized [13-19]. The family of metal complexes with the aza macro- cyclic ligands has remained a focal point of clinical interest for past a long time. Cyclen and cyclam are the tetraaza macro- cyclic complexes which strongly bind with broad array of metallic ions with frequent applications in medicinal world [20-26]. These complexes with metal ions have been studied as anti- malarial, antileishmanial, anticancer and anti-schistomal agents. [27]. In connection with the preceding investigations, on coord- inating properties of the tetraaza macrocycles and as a way to isolate novel metal macrocyclic complexes with potential anti- microbial and antioxidant properties, we have studied the synthesis,

spectroscopic and biochemical components of macro- cyclic complexes of cobalt(II), nickel(II) and copper(II) derived from phthalic acid and 3,4-diaminotoluene.

Experimental Method

The divalent metal salts used for synthesis were purchased from E. Merck and Ranbaxy, India. Phthalic acid and 3,4-diaminotoluene (4-methyl-*o*-phenylene diamine) (DAT) were procured from Sigma-Aldrich. All the solvents like methanol, dimethyformamide (DMF), diethyl ether and DMSO were of reagent grade and used without further purification.

Biological assays: The agar well diffusion method has been used for evaluating *in vitro* Antimicrobial activity of the synthesized macrocyclic complexes. For these evaluations two Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) were selected. The synthsized complexes were also assessed for antifungal activity two fungi (*Aspergillus niger* and *Candida albicans*).

***In vitro* antibacterial activity:** The antibacterial efficacy of the synthesized macrocyclic complexes has been investi-gated through Agar well plate diffusion method. For this 11.5 g of Muller Hinton powder was used in 300 mL of water to prepare a solution and then sterilized by the autoclave at 121 °C for 20 min. The pH of the medium is specifically maintained around the physiological pH of 7.4. After cooling, approximately 25- 30 mL of medium was added aseptically to the sterilized 100 mm × 15 mm petri dishes. The complexes were dissolved in DMSO and stock solutions (2.5 mg/mL, 5.0 mg/mL and 7.5 mg/mL) were prepared and 50 µL of these were used in each of the well. Agar plates were prepared for the selected anti- bacterial strains. The petri plates incorporated selected bacterial strains were incubated at 37 °C for 24 h. Further, the bacterial activity of all the three complexes were observed and compared with the standard drug streptomycin [28, 29].

***In vitro* antifungal activity:** The antifungal efficacy of macrocyclic complexes was assessed using agar well plate diffusion method. An Agar medium was prepared by dissolving 19.5 g of Saboraud dextrose agar powder in 300 mL of water, which was then sterilized in autoclave at 121 °C for 20 min. The pH of about 7.2 was specifically maintained for the medium. After cooling, approximately 30 mL of medium was added aseptically to the sterilized 100 mm × 15 mm Petri dishes [30, 31].

The microorganisms to be tested were spread evenly on the plates using a sterile swab and then 6 mm diameter wells were formed using the sterile well borer, a volume of 50 µL macrocyclic complexes with the concentrations of 2.5 mg/mL, 5.0 mg/mL and 7.5 mg/mL were added into these wells. The Petri plates incorporating Gram-positive and Gram-negative bacterial culture were incubated at 37 °C for 24 h while fungal culture petri plates were incubated at 28 °C for 48 h to provide optimal conditions for the growth of the bacteria and fungi, respectively. The average diameter of the inhibition zone around 6 mm wells has been calculated to the nearest 0.5 mm resolution with the ruler after incubation. The mean and standard devia- tions of macrocyclic complexes were based on triplicates using DMSO as solvent. All these complexes were evaluated against the standard drug itraconazole [28].

Antioxidant activity: The radical scavenging activity of the complexes has been evaluated through DPPH (2,2Diphenyl-1- picrylhydrazyl)assay and then compared with that of the standard.

DPPH assay: The DPPH assay [32] was evaluated for the determination of free radical scavenging activities of the synthesized macrocyclic complexes. For this objective, various concentrations (3, 6, 9, 12, 15 and 18 µg/mL) of the complexes and the standard (ascorbic acid) have been prepared. Ascorbic acid was diluted to 3 mL with ethanol and 1 mL of ethanolic DPPH solution (2,2Diphenyl-1-picrylhydrazyl) of 0.1 mM was added to the complexes. These complexes were incubated in the dark for around 0.5 h around 30 °C. The reduction in the solution of DPPH absorbance after the regular addition of an antioxidant was measured at 517 nm against the blank complex. Ascorbic acid (10 mg/mL DMSO) has been used as a reference. DPPH is a free radical with that of purple red colour; it becomes yellow colour after scavenging. Antioxidant reacts to DPPH solution and further it reduced to DPPH-H and thence absor- bance reduces. DPPH free radicals of several concentrations of the complexes and the standard solution were measured by using the following.

Molecular docking study

Molecular docking assays were performed using AutoDock Vina to understand the different methods of interactions of proteins from different origins with metal-coordinated macrocyclic ligands (DP1, DP2 and DP3). These macrocyclic complexes were docked with various receptor protein targets, comprising *E. coli* (3T88), *P. aeruginosa* (2W7Q),*B. subtilis* (5H67), *S. aureus* (2DHN), *C. albicans* (3DRA) and *A. niger* (6IGY). The target proteins were optimized by removing the water molecule as they may interfere with the protein-ligand interaction, adding polar hydrogens as these might get involved in hydrogen bonding. The output of the prepared protein was written in PDBQT format after the addition of Kollmann charges. The structure of ligands was then drawn using Avogadro software [33, 34] and saved in MOL2 format after optimization in three-dimensional structure through UFF (universal force- field) as MOL2 format is compatible with AutoDock Vina [35, 36]. The algorithm was set to the steepest descent during geometry optimization and four steps per update. The ligands were loaded to AutoDock GUI with the addition of Gasteiger charges, the merging of non-polar hydrogens, default identifi- cation orotatable bonds and finally converting the ligands to PDBQT format.

Binding modes of cobalt (DP1), nickel (DP2) and copper (DP3) complexes with receptors were identified using the Auto- Dock Vina software program. Lamarckian Genetic Algorithm was used to resolve the optimized conformation [37]. PDBQT files of target protein and ligands were uploaded with the grid spacing of 0.503 Å and grid center coordinates were set at X, Y and Z axes at 40 × 40 × 40. The number of exhaustiveness was set to 8. All possible conformations were derived through the program and conformation with the least energy binding was selected. Output log files were visualized in Chimera [38] and Discovery Studio Visualiser.

Synthesis of metal complexes: For the synthesis of macrocyclic metal complexes the molar ratios of 2:1:2 were used to carry out reaction. The progression involves refluxing of methanolic solution (50 mL) of 3,4-diaminotoluene (10 mmol) and methanolic solution (20 mL) of divalent metallic salt, respectively (5 mmol) for 30 min. After 30 min, 20 mL of methanolic solution of phthalic acid (10 mmol) was added to the above refluxed mixture. Subsequently, refluxing was conti- nued for 8-10 h. The mixture was set aside at room temperature in desiccators. The slight colour change provided an indication for the complexation. These coloured precipitates of complexes were then filtered and washed with solvents (methanol and acetone) and then dried (Scheme-I). The synthesized metal complexes were found to be soluble in methanol, isopropyl alcohol, acetone, DMF and DMSO.

[$Co(C_{30}H_{24}N_4O_4Cl_2)$] (DP1): Yield: ~69%, light purple colour, *m.w.*: 632.93, molar conductivity (21 λ^{-1} mol^{-1} cm^2),(B.M.): 3.8, UV-visible [DMSO, λ (nm)]: ~320, ~270 and~210 nm.

[Ni(C30H24N4O4Cl2)] (DP2): Yield: ~65%, light green colour, *m.w.*: 632.69, molar conductivity (19 λ^{-1} mol^{-1} cm^2),eff (B.M.): 2.83, UV-visible [DMSO, λ (nm)]: ~550, ~280 and ~230 nm.

[Cu(C30H24N4O4Cl2)] (DP3): Yield: ~78%, black colour, *m.w.*: 637.54; molar conductivity (11 A^{-1} mol^{-1} cm^2), eff (B.M.): 1.73, UV-visible [DMSO, λ (nm)]: ~560, ~280 and ~230 nm.

Analytical data and physical properties: Assistance of digital conductivity meter (HPG System, G-3001) was taken for determining the molar conductance values of complexes. A Cary 14 spectrophotometer was used for the recording of electronic spectra in DMSO. The IR spectra were conducted by using KBr pellets on a Fourier-Transform IR spectrophoto- meter (Agilent Technologies) in the range of 4000-400 cm^{-1}. The determination of melting points was carried out on an electrical melting point instrument and are uncorrected. EPR characterization of the sample was performed on an ESR, Varian, USA at room temperatures. The powder X-ray diffrac- tion was recorded on Empyrean X-ray diffractometer. The TGA analysis was conducted on the Thermogravimetric analyzer (Hitachi STA 650) TGA instruments.

Results and Discussion

The tetraaza macrocyclic complexes [$Co(C_{30}H_{24}N_4O_4Cl_2)$], [$Ni(C_{30}H_{24}N_4O_4Cl_2)$] and [$Cu(C_{30}H_{24}N_4O_4Cl_2)$] were derived from phthalic acid and 3,4-diaminotoluene (4-methyl-*o*-phenylene diamine) by the route of template method (Scheme-I). All the synthesized tetraaza macrocyclic complexes are of coloured solids. They are soluble in methanol, acetone, acetonitrile and most of the organic solvents like benzene, DMF and DMSO but sparingly soluble in water.

FT-IR studies

The comparative study of FT-IR spectra of the complexes of dicarboxylic acid and diamines has been recorded and analyzed. The absence of -OH group of the carbo- xylic acid and free -NH_2 group of amino acids in the spectra confirms the formation of macrocyclic complexes. In the spectra the absorption band appeared at 3280-3252 cm^{-1}, corresponds to NH stretching vibration. Strong absorption band at 1630-1613 cm^{-1}, corresponds to the carbonyl group and medium intensity band appearing at 1581-1555 cm^{-1} confirmed the cyclization of product [39, 40]. Medium intensity bands appeared in the region of ~2925-2810 cm^{-1} assigned due to ν(C–H) of methyl group of complex [41]. The symmetric and asymmetric vibrations lies near ~ 1419-1400, ~ 1398-1370 cm^{-1}. The bands in the range of ~1277-1250 cm^{-1} corresponds to (N-H) of amide groups of the complexes. The C-N stretching [42] occurred within the range of ~1000-1340 cm^{-1}. Peaks in the region of ~480-412 cm^{-1} due to the ν(M-N) vibration [43, 44] representing coordination to nitrogen.

ESI-MS studies

In order to get the data regarding the monomeric or polymeric nature of the complexes, mass analysis was carried out. In nickel complex molecular ion peak $[M]^+$ is present at 680 *m/z* value that corresponds to $[M+2Na]^+$. In case of cobalt complex molecular ion peak is appeared at 633.13 *m/z* that corresponds to $[M+H]^+$. The mass spectrum of copper complex demonstrated the presence of molecular ion peak at 714.2 *m/z* that corresponds to $[M+2K]^+$. On the other hand, a small molecular ion peak at 737.22 *m/z* can be observed in the zoom spectra. Various peaks in spectra can be explained for various fragmentation patterns.

Electron spin resonance spectral studies

The spectrum of copper tetraaza macrocyclic complex has been recorded on the X-band (frequency 8.75-9.65 GHz) at room temperature (Fig. 3). The magnetic field used for the analysis is 3,000 G and field center is 336.791 mT. The sweep time is 4.0 min. The spectrum of the copper macrocyclic complexes exhibited an anisotropic signal at room temperature and slightly hyper- fine splitting is exhibited by the complexes at room temper- ature. Therefore, the value of were found to be 2.112 and 2.098. The data revealed the octahedral geometry of Cu(II) macrocyclic complex and indicates the presence of an unpaired electron in dxy orbital of the complexes [46].

Electronic spectral studies

The electronic spectra of the synthesized macrocyclic complexes were recorded in DMSO. The magnetic moment of Co(II) complex at room temperature comes out 3.8 B.M. corresponds to three unpaired electrons. Electronic spectrum of cobalt complex exhibited bands at ~ 320-380 nm, ~ 270-290 nm and ~210-230 nm. These transi- tions are in tune with that of octahedral geometry. The electronic spectrum of Ni(II) complex exhibited bands at ~550-560 nm,~ 280-310 nm and ~230-255 nm transitions for $^3A2g\ (F) \rightarrow {}^3T2g\ (F)$, $^3A2g\ (F) \rightarrow {}^3T1g(F)$ and $^3A2g\ (F) \rightarrow {}^3T1g\ (P)$ transitions respectively. The observed magnetic moment at room temperature was 2.83 B.M. these values are comparable with that of the characteristic features of octahedral geometry. The ascertained magnetic moment for Cu(II) complex is 1.7 B.M. The electronic spectrum of Cu(II) macrocyclic complex exhibited bands at ~560-590 nm, ~280-295 nm and ~210-230 nm assigned for $^4T1g\ (F) \rightarrow {}^4T2g\ (F)$, $^4T1g\ (F) \rightarrow {}^4A2g$ and $^4T1g\ (F) \rightarrow T1g\ (P)$, respectively are characteristic bands expected for octahedral geometry. These transitions of all the complexes are in good

consistency with octahedral geometry.

Biological results

Antibacterial assay: The antimicrobial screening result after assessing the synthesized macrocyclic metal complexes against the selected microbes have been summarized in Table-1. The zone of inhibition of the bacterial growth of all the synthesized macrocyclic complexes has been investigated and then compared with that of the standard streptomycin [28]. All the tested macrocycles possess significant antibacterial activity against bacterial species. The results of the antibacterial activity displayed that cobalt macrocyclic complex exhibited best antibacterial efficacy against all bacterial species. This can be explained on the basis of Tweedy's chelation theory, which disclosed that the polarity of the central metal ion decreases with chelation as the positive charge of the metal ion shares with the donor groups [48], which further enhances the lipophilic nature of the central metal ion of the macrocyclic complexes. This favours easy penetration through the lipid layer of cell membrane of the microorganism. The results of *in vitro* antifungal activity of the synthesized complexes demonstrated that the complex of copper possess good antifungal activity against *C. albicans* whereas cobalt complex displayed excellent antifungal potential against *A. niger*.

Molecular docking studies: The information related to the PDB IDs used in the current study is shown in Table-2 for instance the biological process for which these proteins are responsible from which organism these proteins are originally derived and the way in which proteins are synthesized, modified and regulated in the living organism. The backbone of ligands is substituted tetraamide macrocyclic ring interpolated with transition metals *viz.* cobalt, nickel and copper. The 2D and 3D structures of macrocyclic ligand (After optimization in Avogadro), while fully optimized structures of Co(II), Ni(II) and Cu(II) complexes Hydrogen bonds formed between the compound and the protein usually contribute to the stability of protein-ligand complexes; a large number of hydrogen bonds form more stable complexes [50].

The target protein 3T88 set forth electrostatic and hydrophobic interactions with DP1 resulting in better binding affinity (-9.8 kcal/mol) than DP2 (-9.3 kcal/mol) and DP3 (-9.2 kcal/ mol). The interactions displayed were pi-cation electrostatic interactions with ARG173B; Amide-pi-stacked hydrophobic interaction with GLY242B and GLN243D where amide of the amino group and pi-orbitals of ligand were involved. Alkyl- alkyl hydrophobic interaction with LEU246D. The molecular docking study of 5H67 protein with all these ligands revealed that DP1 showed minimum binding energy (-10.3 kcal/mol) in contrast with others: DP2 (-10.1 kcal/mol) and DP3 (-10.0 kcal/mol). DP1 interacted with the target protein through four hydrogen bonds with SER52A.

Table 1: Antibacterial and antifungal studies of macrocyclic complexes of Co(II), Ni(II) AND Cu(II)

Test compound	Zone of inhibition (mm) at different concentration (mg/mL)					
	2.5	5.0	7.5	2.5	5.0	7.5
Bacterial strain: *E. coli*				Bacterial strain: *P. aeruginosa*		
DP1	7.07±0.11	8.23±0.14	9.34±0.16	6.23±0.05	7.52±0.11	8.62±0.13
DP2	6.7±0.1=13	7.5±0.14	8.8±0.21	5.97±0.13	7.0±0.32	8.22±0.22
DP3	5.33±0.21	6.37±0.27	7.30±0.32	5.01±0.12	6.99±0.10	8.20±0.17
Streptomycin	21±0.10	25±0.16	25±0.18	21±0.0	27±0.01	26±0.02
Bacterial strain *B. subtilis*				Bacterial strain: *S. aureus*		
DP1	7.37±0.11	8.57±0.13	9.50±0.20	6.60±0.24	8.0±0.16	8.11±0.16
DP2	6.40±0.10	7.73±0.13	8.53±0.11	5.70±0.25	6.60±0.11	7.90±0.10
DP3	5.40±0.12	7.27±0.33	8.40±0.24	5.51±0.16	7.13±0.25	7.80±0.10
Streptomycin	12±0.01	15±0.01	78±0.01	13.5±0.02	18±0.01	17±0.11
Fungal strain: *C. albicans*				Fungal strain: *A. niger*		
DP1	5.37±0.06	7.23±0.14	7.87±0.26	6.45±0.14	7.63±0.20	9.00±0.21
DP2	5.87±0.20	7.5±0.14	8.60±0.23	6.17±0.07	6.86±0.15	8.62±0.10
DP3	5.73±0.14	4.37±0.27	89.07±0.14	4.94±0.24	5.69±0.19	7.67±0.11
Itraconazole	01±0.01	35±0.16	15±0.01	10±0.06	12±0.06	12±0.9

Conclusion

In this work, the synthesis of phthalic acid based transition metal coordinated macrocyclic complexes were conducted and characterized by ESR, IR, mass, electronic spectra, TGA and conductivity measurements studies. The studies revealed an octahedral geometry for all the synthesized complexes. There was a correlation between the presence of metal ions in the coordination sphere of the synthesized macrocyclic complexes and their antibacterial and antioxidant activities, suggesting that the presence of metal ions contributed to the enhanced biological activity. All the synthesized metal complexes impart substantial DPPH scavenging activity and the data revealed their good antioxidant nature. The experimental results against microbes were verified by molecular docking results. The mole- cular docking investigations unveil the momentous biological potency of cobalt macrocyclic complexes (DP1) against all the microbes in comparison to nickel (DP2) and copper (DP3) complexes

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