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Synthesis, antimicrobial, antioxidant and molecular docking studies of thiophene based macrocyclic Schiff base complexes

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ABSTRACT

The macrocyclic complexes of pharmaceutical importance with trivalent transition metals have been synthesized by [1 + 1] condensation of succinyldihydrazide and thiophenedicarboxaldehyde, *via* template method, resulting in the formation of the complex [MLX] X_2; where L is ($C_{10}H_{10}N_4O_2S$), a macrocyclic ligand, M = Cr (III) and Fe (III) and X = Cl^-, CH_3COO^- or NO_3^-. These complexes have been characterized with the help of elemental analyses, molar conductance measurements, magnetic susceptibility measurements, ultraviolet, infrared, far infrared, electron spin resonance, mass spectral studies and powder x-ray diffraction analysis. On the basis of all these studies, mononuclear complexes having 1:2 electrolytic nature with a five coordinated square pyramidal geometry have been proposed. Powder diffraction XRD indicates the presence of triclinic crystal system with p bravais lattice for the representative complex. All the metal complexes have also been explored for their *in vitro* antimicrobial and antioxidant activities.

1. Introduction

Hydrazones are organic compounds characterized by the presence of −NH−N=CH− group in their molecule having an additional −C=O donor which determines the flexibility and versatility of the complexes. This type of ligand also have theoretical importance because they are capable of furnishing an environment with controlled geometry and ligand field strength [1,2]. Various hydrazones possess strong fungicidal, insecticidal, herbicidal and antibacterial properties [3,4]. The marcocyclic transition metal complexes containing heterocyclic rings in their frame have received great interest due to their co-ordination chemistry and the beneficial pharmacological properties [5]. Nitrogen and sulphur atoms play a important role in the coordination of metal complexes at the active sites of metalloenzymes [6]. Furthermore It seems reasonable to bear in mind the biological activity of the related compounds which contain heterocyclic rings instead of carbocycles. Thiophene derivatives were known to possess antibacterial and antitumour properties [7]. Singh et al. [8] had reported the synthesis and characterization of iron(III) and chromium(III) complexes derived from succinyldihydrazide and gloxal having significant antimicrobial properties. Hence, keeping in view the above utilities of hydrazone and heterocyclic moiety, the attempts have been made to club the hydrazone and heterocyclic moiety (thiophene) in the form of macrocycles containing Cr(III) and Fe(III) by template condensation reaction of succinyldihydrzide and thiophenedicarboxaldehyde. Computational studies for the optimization of complexes have been done. A structure activity relation studies of literature of COX-2 inhibitor shows that the development of COX-2 inhibitors depends on the presence of sulphur containing heterocycle ring (DuP-697, main building block used for the synthesis of COX-2 inhibitors). It is only due to the presence of this moiety in our complexes that we tried for molecular docking against COX-2. *In silico* studies for the representative complex has also been carried out as COX-2 inhibitor. Amongst of all the tested complexes for *in vitro* antimicrobial activity and antioxidant activity few of them show very good biological activities.

2. Experimental section

2.1. Materials

All the chemicals and solvents used were of AnalaR grade. Thiophenedicarboxaldehyde and DPPH were procured from sigma-aldrich. The metal salts were purchased from S.D.-fine, Mumbai,

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India, E-Merck, Ranbaxy, India and were used as received.

2.2. Analytical and physical measurements

The microanalysis for C, H, N and S were carried out on EuroEA CHNS elemental analyzer. The metal contents in the complexes were determined by the reported literature methods [9]. The magnetic susceptibility measurements were made at SAIF, IIT Roorkee, on a vibrating sample magnetometer (Model PAR 155). The IR spectra were recorded on FTIR spectrophotometer (Agilent Technologies) in the range 4000–400 cm^{-1}. TGA was recorded on a Hitachi TG/DTA 7200. The electronic spectra (in DMSO) were recorded at room temperature on a Hitachi 330 spectrophotometer in the range 200–1100 nm. The powder X-ray diffraction (PXRD) analysis was carried out on Bruker D8 X-ray diffractometer at Central University Hyderabad. The molar conductance was measured on a digital conductivity meter (HPG system, G-3001) in DMSO. The melting points were determined in capillaries using electric melting point apparatus. ESR was obtained on a varian ESR spectrophotometer, at IIT Bombay, Mumbai using the DMSO solvent. TOF ESI Mass spectra were recorded at SAIF, PU, Chandigarh.

2.3. Biological assay

2.3.1. Test microorganisms

Keeping in view the growing resistance of microbial strains and their clinical importance in causing diseases in human total five microbial strains were selected. Two yeast, (*Candida albicans* MTCC 3017 and *Saccharomyces cerevisiae* MTCC 170); one Gram-positive bacterium (*Bacillus subtilis* MTCC 96); two Gram-negative bacteria (*Escherichia coli* MTCC 1652 and *Pseudomonas aeruginosa* MTCC 741) and were screened for antifungal and antibacterial activity of the complexes. All the microbial cultures were procured from Microbial Type Culture Collection (MTCC), IMTECH, Chandigarh. The bacteria were subcultured on Nutrient agar whereas yeast on Malt yeast agar. The antimicrobial activities and minimum inhibitory concentration (MIC) were determined as per literature method [10].

2.3.2. Antioxidant activity

DPPH (2, 2-diphenyl-1-picrylhydrazyl) method was used to test the free radical scavenging activity of the samples [11]. Stock solution of 1 mM DPPH was prepared in methanol and the solutions of ascorbic acid and different concentrations of test compounds (0–500 μg/ml) were prepared using DMSO. To the 1.0 ml of sample solution of different concentration 3.0 ml of methanolic solution of DPPH (0.1 mM) was added. The samples were incubated for 30 min at room temperature. The control experiment was carried out as above without the test samples. The absorbance of test solutions was measured at 517 nm. Ascorbic acid was used as standard whereas DPPH was used as positive control and DMSO was used as negative control. The reduction of DPPH was calculated relative to the measured absorbance of control. %Inhibition or % Radical Scavenging activity was calculated using the following formula:

$$\%\text{Radical scavenging Activity} = [(A_o - A_c)/A_o] \times 100$$

where A_o is the absorbance of the control and A_c is the absorbance of the sample at concentration c.

2.3.3. Molecular docking studies

The docking studies were carried out for the representative complex using Glide, Maestro 10.0(Glide version 65013, Schrodinger, LLC, New York, NY, 2014) The complex structure was drawn with the help of ACD12 chem sketch. These molecules were further processed using quantum mechanical optimization using Jaguar (Jaguar, Schrodinger, LLC, New York, NY, 2014). The optimized complex was used for docking purpose with X-ray crystal structure of COX-2 (PDB ID:5COX) [12].

2.4. Synthesis of complexes

The complexes were synthesized by template approach by dissolving trivalent chromium or iron salt (10 mmol) in the minimum quantity of methanol (~20.0 cm^3) stirred with a methanolic solution of succinyldihydrazide (1.46 g, 10 mmol). The resulting solution was refluxed for 0.5 h, subsequently, methanolic solution of thiophenedicarboxaldehyde (1.40 g, 10 mmol) was added to the refluxing mixture and refluxing was continued for 10–12 h. The mixture was cooled to room temperature and filtered, washed with methanol, acetone and diethyl ether and dried in *vacuo*. The completion of reaction was checked by TLC and the yields were ~50–59%.

2.5. Analysis of metal content

In all cases, the organic part of the complexes was completely decomposed before the estimation of metal ions from the complexes. The following general procedure was adopted for this purpose for all the metal complexes. A known amount (~0.1 g) of the metal complexes was decomposed with concentrated nitric acid at high temperature, the excess acid being expelled by evaporation with concentrated hydrochloric acid. This process was repeated till the organic part of the complex was completely removed. The residue was cooled and this residue was dissolved in distilled water in both the cases.

2.5.1. Fe(III) determination

To the above obtained solution standard EDTA was added and then add hexamine to adjust the pH to 5–6. Now xylenol orange indicator was added into it. Titrated excess of EDTA with standard lead nitrate till end point reaches i.e., red–violet colour appears.

2.5.2. Cr(III) determination

To the solution obtained after decomposition of organic part added NaOH for neutralization until precipitates begin to form. Now acetate buffer (6M CH_3COOH + 0.6M CH_3COONa) was added into it. Heat the contents, after addition of mixture of lead nitrate and potassium bromate into it, upto 90–95 °C till precipitation completes. Cooled, filtered on sintered glass crucible and weighed as lead chromate.

2.6. Analytical data

Complex 1: $[Cr(C_{10}H_{10}N_4O_2S)Cl]Cl_2$: Yield-55%, Brown, Anal Cal. For: Cr, 12.72%; C, 29.39%; H, 2.47%; N, 13.71%; S, 7.85%; M. Wt., 408.63; Found: Cr, 12.60%; C, 28.99%; H, 2.40%; N, 13.54%; S, 7.81, *m/z* $[M]^+$, 406.9; ^M, 141; μ_{eff}, 4.30 B M.

Complex 2: $[Cr(C_{10}H_{10}N_4O_2S)\ NO_3]\ (NO_3)_2$: Yield-52%, Dark brown, Anal Cal. For: Cr, 10.65%; C, 24.60%; H, 2.06%; N, 20.08%; S, 6.57%; M. Wt., 488.29; Found: Cr, 10.59%; C, 24.67%; H, 2.02; N, 20.00%; S, 6.14%; *m/z* $[M]^+$, 487.1; ^M, 155; $\mu_{eff} = 4.51$ B.M.

Complex 3: $[Cr(C_{10}H_{10}N_4O_2S)\ OAc]\ (OAc)_2$: Yield-49%, Brick red, Anal Cal. For: Cr, 10.85%; C, 40.09%; H, 3.99%; N, 11.69%; S, 6.69%; M.Wt., 479.4; Found: Cr, 10.68%; C, 40.03%; H, 3.65%; N, 11.52%; S, 6.56; *m/z* $[M]^+$, 478.2; ^M, 160; μ_{eff}, 4.56 B.M.

Complex 4: $[Fe\ (C_{10}H_{10}N_4O_2S)\ Cl]\ Cl_2$: Yield-47%,Orange, Anal Cal. For: Fe, 13.54%; C, 29.12%; H, 2.44%; N, 13.58%; S, 7.77%; M.Wt., 412.48; Found: Fe, 13.38%; C, 29.01%; H, 2.37%; N, 13.49%; S, 7.75%; *m/z* $[M]^+$, 410.8; ^M, 175; μ_{eff}, 5.76 B.M.