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Evaluation of DNA cleavage, antimicrobial and anti-tubercular activities of potentially active transition metal complexes derived from 2,6-di(benzofuran-2-carbohydrazono)-4-methylphenol

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ABSTRACT

A 2,6-diformyl-4-methyl phenol based multidentate novel symmetric ligand and it is late first-row transition metal complexes have been prepared. The ligand and metal complexes were characterized by different spectroscopic techniques. The ligand shows a symmetric polydentate coordination mode through the phenoxide bimetallic bridge, two azomethine nitrogen atoms and two carbonyl oxygen atoms. All the complexes appear to be binuclear with octahedral geometry and nonelectrolytic nature. Complexes have shown significant growth inhibitory activity against tested bacterial and fungal strains as compared to that of ligand. The cobalt complex exhibited better antifungal potency than the standard used. Copper complex exhibits good antifungal activity whereas cobalt and zinc complexes are found to be good antibacterial agents. Ligand and complexes have shown excellent anti-tubercular activity and Calf Thymus-DNA cleavage property.

1. Introduction

Phenoxo compounds are of great interest in the design of compartmental ligands to study the intermetal interactions in multinuclear metal complexes. These ligands contain two adjacent, similar to dissimilar compartments [1–4] which can coordinate one, two identical or different metal ions in close proximity [3–7]. The donor sites of these ligands afford a significant diversification of the coordination sites making them good candidates for metal ion complexation and for mimicking biological systems [8]. 2,6-diformyl-4-methylphenol (dfp) is a well-known molecule in coordination chemistry, as a starting material for the synthesis of different compartmental ligands [9,10]. First row transition metal hydrazone complexes of dfp with NOO, NON and N2O2 coordination sites are well characterized. The study of their catalytic, electronic, magnetic, stereochemical, spectroscopic and also biological properties have provided the scope of probes for some important applications [11,12].

Planar ligands with an amine or imine donor groups and bridging phenolic oxygen are referred to as Robson-type ligands [13]. The Robson-type ligands are usually obtained by the condensation of appropriate formyl and amine precursors. In the present investigation, we have used dfp and a benzofuran derivative, as a result giving a compartmental "end-off" type ligand. Benzofuran derivatives possess a broad range of important biological activities including antimicrobial [14,15], antitumor [16,17] and anti-inflammatory [18] activity. For a better understanding of the various parameters that dictate the structural properties and biological activity, we have prepared and studied the transition metal complexes of novel hydrazone ligand derived from 2,6-diformyl-4-methyl phenol and benzofuran-2-carbohydrazide.

2. Experimental

2.1. Chemistry

2.1.1. Materials and methods

Metal and chloride determinations were carried out by the standard procedures [19]. The molar conductivity measurements

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were made on ELICO-CM-82 Conductivity Bridge. The ^{1}H and ^{13}C NMR spectra were recorded in the DMSO-d_6 solvent on a Bruker AV III-500 MHz FT-NMR spectrophotometer at room temperature, using TMS as an internal reference. IR spectra were acquired in a KBr matrix using an Impact-410 Nicolet (USA) FT-IR spectrometer in 4000–400 cm^{-1} range. The electronic spectra of the complexes were obtained on a Hitachi 150-20 spectrophotometer in the range of 1000–200 nm. The ESR spectrum of the copper complex was scanned on a JES - FA200 ESR spectrometer, using TCNE as the g-marker. Magnetic susceptibility measurements were carried out by using a Faraday balance at room temperature using $Hg[Co(SCN)_4]$ as a reference. The mass spectrum was measured with SHIMADZU GCMS-QP2010S spectrometer. The ESI-MS data were drawn from Waters UPLC-TQD Mass spectrometer.

2.1.2. Synthesis

All chemicals used were of reagent grade. Solvents were dried and distilled before use, according to the standard procedures [20]. Benzofuran-2-carbohydrazide [21] and dfp [22] were prepared according to the earlier reports. The zinc chloride used was anhydrous whereas all other metal salts were in their hydrated form, i.e., $CoCl_2.6H_2O$, $NiCl_2.6H_2O$ and $CuCl_2.2H_2O$.

2.1.3. Synthesis of ligand L

The hot methanolic solution (25 mL) of dfp (0.164 g, 1 mmol) and hot methanolic solution (25 mL) of benzofuran-2-carbohydrazide (0.352 g, 2 mmol) were mixed slowly with constant stirring. The resulting mixture was stirred at room temperature for 4 h. The yellow precipitate formed was filtered off, washed with hot methanol and air dried. (M. P.: 165 °C, Yield: 90%). The reaction pathway is given in Scheme 1.

A general procedure has been followed for the preparation of complexes. 0.1 mmol (0.480 g) of the ligand was dissolved in 10 mL of THF and a solution of 0.2 mmol of $MCl_2.nH2O$ in 15 mL THF was added with continuous stirring. The reaction mixture was refluxed on a water bath for 4 h. The precipitated compounds were separated by filtration, washed with THF, methanol and dried in vacuum desiccators.

3. Pharmacology

3.1. Antibacterial assay

Media Used (Nutrient broth): Peptone-10 g, NaCl-10 g, Yeast extract 5 g and Agar 20 g in 1000 mL of distilled water.

Primarily, the stock cultures of bacterial strains were revived by inoculating in broth media and grown at 37 °C for 18 h. The agar plates of the media were equipped and wells were made in the plate. Each plate was inoculated with 18 h old cultures (100 μL, 10^4 CFU) and spread uniformly on the plate. After 20 min, the wells were filled with a different concentration of sample solutions in DMSO. The control wells were filled with Gentamycin. All the plates were incubated at 37 °C for 24 h and the diameters of inhibition zones were noted.

3.2. Antifungal assay

Media Used (Czapek-Dox Agar): Composition (g/L) Sucrose-30.0, Sodium nitrate-2.0, K_2HPO_4-1.0, $MgSO_4.7H2O$-0.5, KCl-0.5, $FeSO_4$-0.01, Agar-20.

Primarily, the stock cultures were revived by inoculating in broth media and grown at 27 °C for 48 h. The agar plates of the above media were equipped and wells were made in the plate. Each plate was inoculated with 48 h old cultures (100 μL 10^4 CFU) and spread uniformly on the plate. After 20 min, the wells were filled with a different concentration of sample solutions in DMSO. The control wells were filled with Amphotericin. All the plates were incubated at 27 °C for 48 h and the diameter of inhibition zone was noted.

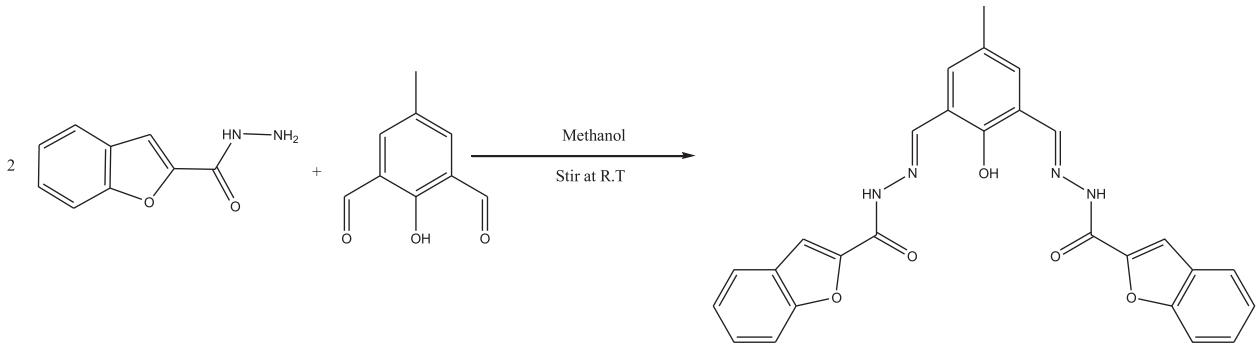
3.3. Antituberculosis assay using alamar blue dye [23].

The antimycobacterial activities of compounds were performed against M. *tuberculosis* ATTC 27294 using microplate Alamar Blue assay (MABA). The method is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200 μL of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to reduce the evaporation of medium in the trial wells during incubation. The 96 wells plate received 100 μL of the Middlebrook 7H9 broth and serial dilution of compounds was made directly on the plate. The ultimate drug concentrations tested were 100 to 0.2 μg/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for five days. After this time, 25 μL of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth and pink color was interpreted as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

3.4. DNA cleavage studies

3.4.1. Preparation of culture media

DNA cleavage experiment was done according to the literature [24]. The nutrient broth was used as the media. The composition of the media (g L^{-1}): peptone 10, yeast extract 5, NaCl 10. Calf thymus DNA was used for the experiment.



Scheme 1. Preparation of complexes.