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ORIGINAL ARTICLE

Design, synthesis, DNA binding ability, chemical nuclease activity and antimicrobial evaluation of Cu(II), Co(II), Ni(II) and Zn(II) metal complexes containing tridentate Schiff base

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Abstract A novel Schiff base has been designed and synthesized using the bioactive ligand obtained from 4-aminoantipyrine, 3,4-dimethoxybenzaldehyde and 2-aminobenzoic acid. Its Cu(II), Co(II), Ni(II), Zn(II) complexes have also been synthesized in ethanol medium. The structural features have arrived from their elemental analyses, magnetic susceptibility, molar conductance, mass, IR, UV–Vis, ^{1}H NMR and ESR spectral studies. The data show that the complexes have composition of ML_2 type. The electronic absorption spectral data of the complexes suggest an octahedral geometry around the central metal ion. The interaction of the complexes with calf thymus (CT) DNA has been studied using absorption spectra, cyclic voltammetric, and viscosity measurement. The metal complexes have been found to promote cleavage of pUC19 DNA from the super coiled form I to the open circular form II. The complexes show enhanced antifungal and antibacterial activities compared with the free ligand.

1. Introduction

Interaction of transition metal complexes with DNA has gained considerable current interest due to their various applications in many areas like chemical, biological and medicinal significance as potential artificial gene regulators (or) cancer chemotherapeutic agents (Surendra Babu et al., 2010). The coordination chemistry of Schiff base complexes involving oxygen and nitrogen donor ligands has attracted considerable attention from the biochemists due to their applications in catalysis and their relevance to bioinorganic systems (Shanker et al., 2009).

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In recent years, a great deal of interest in the synthesis and characterization of transition metal complexes of 4-aminoantipyrine and its derivatives has been extensively examined due to their wide applications in various fields like biological, analytical and therapeutical. Further, they have been investigated due to their diverse biological properties as antifungal, antibacterial, analgesic, sedative, antipyretic, anti-inflammatory agents (Chandra et al., 2009) and greater DNA binding ability (Raman et al., 2010). In addition to this, DNA is an important cellular receptor, many chemicals exert their antitumor effects by binding to DNA thereby changing the replication of DNA and inhibiting the growth of the tumor cells, which is the basis of designing new and more efficient antitumor drugs and their effectiveness depends on the mode and affinity of the binding (Li et al., 2009).

Having all these in mind, in this paper, we are interested to explore synthesis and structural determination of 4-aminoantipyrine based Schiff base having oxygen and nitrogen donors, derived from 4-aminoantipyrine, 3,4-dimethoxybenzaldehyde and 2-amino benzoic acid and its complexes with Cu(II), Co(II), Ni(II), Zn(II) metal ions. Binding properties of the metal complexes with DNA has been investigated using electronic absorbance spectroscopy, viscosity measurement and voltammetry. In this work, the ability of these complexes having nitrogen and oxygen donors to induce DNA cleavage in presence of H_2O_2 has been analyzed. The antimicrobial evaluation of present complexes is also researched. These complexes may give an opportunity to provide routes toward rational drug design as well as means to develop sensitive chemical probes for DNA.

2. Experimental

All reagents, 4-aminoantipyrine, 3,4-dimethoxy benzaldehyde, 2-amino benzoic acid and various metal(II) chlorides, were Merck products and used as supplied. Commercial solvents were distilled and then used for the preparation of ligand and its complexes. DNA was purchased from Bangalore Genei (India). Microanalyses (C, H and N) were performed in Carlo Erba 1108 analyzer at Sophisticated Analytical Instrument Facility (SAIF), Central Drug Research Institute (CDRI), Lucknow, India. Molar conductivities in DMSO (10^{-2} M) at room temperature were measured using Systronic model-304 digital conductivity meter. Magnetic susceptibility measurements of the complexes were carried out by Gouy balance using copper sulfate pentahydrate as the calibrant. IR spectra were recorded with Perkin–Elmer 783 spectrophotometer in the 4000–400 cm^{-1} range using KBr pellets. NMR spectra were recorded on a Bruker Avance Dry 300 FT-NMR spectrometer in DMSO-d_6 with TMS as the internal reference. FAB-MS spectra were recorded with a VGZAB-HS spectrometer at room temperature in a 3-nitrobenzylalcohol matrix. Electron paramagnetic resonance spectra of the mixed ligand complexes of copper(II) were recorded on a Varian E 112 EPR spectrometer in DMSO solution both at room temperature and liquid nitrogen temperature (77 K) using TCNE (tetracyanoethylene) as the g-marker. The absorption spectra were recorded using Shimadzu model UV-1601 spectrophotometer at room temperature.

2.1. Preparation of ligand

The Schiff base ligand and its Cu(II), Co(II), Ni(II), and Zn(II) complexes were prepared as follows: an ethanolic solution of (40 mL) aminoantipyrine (4.06 g, 0.02 mol) was added to an ethanolic solution of 3,4-dimethoxy benzaldehyde (3.14 g, 0.02 mol). The resultant mixture was refluxed for *ca.* 3 h. The solid product formed was filtered and recrystallized from ethanol (Scheme 1). An ethanolic solution of 3,4-dimethoxy benzylidene-4-aminoantipyrine (3.51 g, 0.01 mol) was added to an ethanolic solution of 2-aminobenzoic acid (1.37 g, 0.01 mol), and the resultant mixture was refluxed for *ca.* 10 h after the addition of anhydrous potassium carbonate. The potassium carbonate was filtered off from the reaction mixture and the solvent was evaporated. The pale orange solid separated was filtered and recrystallized from ethanol (Scheme 2).

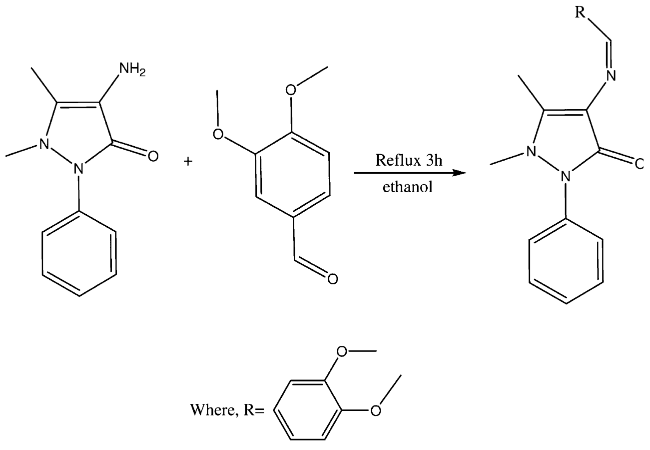
2.2. Preparation of metal(II) complexes

An solution of metal(II) chlorides in ethanol (2 mmol) was stirred with an ethanol solution of the Schiff base (4 mmol), for *ca.* 2 h on a magnetic stirrer at room temperature. Then the solution was reduced to one-third on a water bath. The solid complex precipitated was filtered off and washed thoroughly with ethanol and dried in *vacuo*.

2.3. DNA binding experiments

2.3.1. Absorption spectroscopic studies

The interaction between metal complexes and DNA were studied using electrochemical and electronic absorption methods. Disodium salt of calf thymus DNA was stored at 4 °C. Solution of DNA in the buffer 50 mM NaCl/ 5 mM Tris–HCl (pH 7.2) in water gave a ratio 1.9 of UV absorbance at 260 and 280 nm, A_{260}/A_{280}, indicating that the DNA was sufficiently free from protein (Marmur, 1961). The concentration of DNA was measured using its extinction coefficient at 260 nm (6600 M^{-1} cm^{-1}) after 1:100 dilution. Stock solutions were stored at 4 °C and used for not more than 4 days. Doubly distilled water was used to prepare solutions. Concentrated stock solutions of the complexes were prepared by dissolving the complexes in DMSO and diluting suitably with the corresponding buffer to the required concentration for all of the experiments. The data were then fitted to Eq. (1) to obtain the intrinsic binding constant (K_b) values for interaction of the complexes with DNA.



Scheme 1 Preparation of 4-(3,4-dimethoxybenzaldehydene) 2-3-dimethyl-1-phenyl-3-pyrazolin-5-one.