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ORIGINAL ARTICLE

Designing of some novel metallo antibiotics tuning biochemical behaviour towards therapeutics: Synthesis, characterisation and pharmacological studies of metal complexes of cefixime

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Abstract Cefixime is a broad spectrum semi synthetic cephalosporin antibiotic for oral administration. Metal complexes of cefixime with Cu(II), Zn(II), Cd(II), Fe(III) and Ni(II) have been synthesised and characterised by elemental analysis and IR, UV–Vis., NMR and ESR spectra. The electronic spectral behaviour and cyclic voltammetric studies have been carried out on the interaction of metal complexes with calf thymus DNA. The results suggest that the complexes can bind to DNA by intercalation mode. The Cu(II), Zn(II), Cd (II) and Ni(II) complexes exhibit square planar geometry. Fe(III) complex exhibits octahedral geometry. The complexes showed a slightly higher antimicrobial activity than the cefixime drug. Among the metal complexes, Fe(III) was found to be more active than other complexes when tested against bacterial species *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Pseudomonas aeruginosa* and fungal species *Aspergillus niger*, *Rhizopus stolonifer*, *Aspergillus flavus*, *Rhizoctonia bataicola* and *Candida albicans* by the disc diffusion method. SEM analysis provides the morphology of the metal complexes. The DNA binding interaction of metal complexes with CT DNA using the cyclic voltammetry technique and their salient features are discussed.

1. Introduction

Over the past few decades, intensive research efforts have been made to design novel compounds to deal with new strains of resistant micro-organisms. The on-going literature search for innovative drug delivery systems is predominantly a consequence of the well-established fact that the conventional dosages are not sufficiently effective in conveying the drug compounds to its site of action and this has necessitated the need to search for more potent drugs. The recognition of the

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chelates in therapeutic application provides useful outlets for outstanding research in transition metal chemistry.

Antibiotics can interact with a variety of biomolecules which may result in the inhibition of the biochemical or biophysical processes associated with biomolecules (David et al., 1992). There are a number of antibiotics that require metal ions to function properly such as bleomycin (BCM), Streptonigrin (sn) and Bacitracin. Metallo-antibiotics can interact with several biomolecules such as DNA, RNA, protein receptors and lipids, making them very unique and specifically bioactive. The coordinated metal ions in these antibiotics play an important role in determining proper structure and function of these antibiotics (Li-june, 2003). Cefixime is a semi synthetic third generation cephalosporin antibiotic for oral administration. Chemically it is 7-2(2-(amino-4-thiazolyl)-2(carboxymethoxyimino)acetamido)-3-vinyl-cephem-4-carboxylic acid (Ali, 2002), having molecular weight 507.50 as the trihydrate. The metal complexes play an essential role in pharmaceutical industry and in agriculture. The metallo-elements present in trace quantities play a vital role at the molecular level in the living system. The transition metal ions are responsible for proper functioning of different enzymes. The activity of bio metals is attained through the formation of complexes with different bioligands and the mode of biological action of complexes depends upon the thermodynamic and kinetic properties. The lipophilicity of the drug is increased through the formation of chelates and drug action is significantly increased due to effective permeability of the drug into the site of action. Interaction of various metal ions with the antibiotics may enhance their antimicrobial activity as compared to that of free ligands (Hariprasath et al., 2010).

Many drugs in the form of metal complexes possess modified toxicological and pharmaceutical properties .The most widely studied metal is copper (II) which has proved beneficial in diseases such as tuberculosis, gastric ulcers, rheumatoid arthritis and cancers (metals of life, 1971). These results encouraged us to investigate the coordination chemistry of antibiotics with transition and d^{10} metal ions in an attempt to examine the modes of binding in solid state and to study the biological activity.

Keeping in view of the importance of drug molecules, the present research work is focused on the synthesis and characterisation of metalloantibiotics (metal–cefixime). Further, to evaluate the changes in the antimicrobial activity of cefixime after complex formation with Cu(II), Zn(II), Cd(II), Ni(II) and Fe(III) against bacterial species *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris* and *Pseudomonas aeruginosa* and fungal species *Aspergillus niger, Rhizopus stolonifer, Aspergillus flavus, Rhizoctonia bataicola* and *Candida albicans* by the disc diffusion method.

2. Materials and methods

All chemicals were of reagent grade purchased from Sigma and used without further purification. Solvents were redistilled by a standard technique before use.

2.1. Physical methods

C, H, N and S were analysed in a ELECO CHNS 932 model micro analytical instrument. The metal content of each complex was determined by atomic absorption spectroscopy. The IR spectra of the ligand and metal complexes were recorded in KBr pellets in the 4000–400 cm^{-1} range with a Perkins Elmer series 2000 spectrophotometer. UV–Visible spectra were recorded using a Perkin–Elmer recording spectrometer. Electronic absorption spectra were recorded in DMSO using the UV–Vis., double beam spectrometer 2201. Molar conductance of the copper complexes was measured in DMSO solution using a coronation digital conductivity meter. The magnetic susceptibility values were calculated using the relation $\mu_{eff} = 2.83(\chi_m .T)$. The diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. Electrochemical experiments were performed on a CHI 604D electrochemical analysis system with a three-electrode system consisting of a glassy carbon working electrode, Pt wire auxiliary electrode and an Ag/AgCl reference electrode. Tetrabutylammoniumperchlorate (TBAP) was used as the supporting electrolyte. All solutions were purged with N_2 for 30 min prior to each set of experiments. EPR Spectrometer in DMSO solution was used both at room temperature (300 K) and at liquid nitrogen temperature (77 K) using TCNE (tetracyanoethylene) as the g marker.

2.2. DNA-binding assay

The interaction between metal complexes and DNA was studied using electrochemical methods. The disodium salt of calf thymus DNA was stored at 4 °C. A solution of DNA in the buffer containing 50 mM NaCl and 5 mM Tris HCl (pH 7.2) in water in a ratio of 1.9 gave UV absorbance at 260 and 280 nm, A_{260}/A_{280}, indicating that the DNA was sufficiently free from protein. The concentration of DNA was measured using its extinction coefficient at 260 nm (6600 M^{-1}) after 1:100 dilutions. Stock solutions were stored at 4 °C and used within 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 the experiments.

2.3. Antimicrobial activity

The *in vitro* evaluation of antimicrobial activity was carried out. The prepared compounds were tested against some fungi and bacteria to provide the minimum inhibitory concentration (MIC) for each compound. MIC is the lowest concentration of solution to inhibit the growth of a test organism. The in vitro biological screening effects of the investigated compounds were tested against the bacterial species *S. aureus, E. coli, K. pneumoniae, P. vulgaris* and *P.* aeruginosa and fungal species *A. niger, R. stolonifer, A. flavus, R. bataicola* and *C.* albicans by the disc diffusion method. One day prior to the experiment, the bacterial and fungal cultures were inoculated in nutrient broth (inoculation medium) and incubated overnight at 37 °C. Inoculation medium containing 24 h grown culture was added aseptically to the nutrient medium and mixed thoroughly to get a uniform distribution. This solution was poured (25 ml in each dish) into petri dishes and then allowed to attain room temperature. Wells (6 mm in diameter) were cut in the agar plates using proper sterile tubes. Then, the wells were filled up to the surface of agar with 0.1 ml of the test compounds dissolved in DMSO (200 μg/ml). The plates were al-