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ORIGINAL ARTICLE

Synthesis, structural elucidation, microbial, antioxidant and nuclease activities of some novel divalent M(II) complexes derived from 5-fluorouracil and L-tyrosine

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Antioxidant property

Abstract Novel N_2O_2 sequence of mononuclear amino acid metal(II) complexes (**1a**–**1e**) was synthesized from 5-fluorouracil (5-FU: A) and L-tyrosine (tyr: B) with Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) ions. The synthesized complexes were structurally characterized by analytical, spectral (FT-IR, UV–vis, ^{1}H NMR, FAB-Mass, TGA/DTA and EPR) as well as molar conductance and magnetic studies. From spectral studies, both the ligands act as bidentate and they bind metal(II) ions through deprotonated-N_3 and C_4=O atoms and amino-N and deprotonated carboxylato-O atoms, respectively, to form a stable metal chelate. The observed low molar conductance values suggest a non-electrolytic nature. Calculated *g* tensor values of Cu(II) complex (**1d**) at 77 and 300 K confirm their geometry. Thermal behavior of metal(II) complexes (**1a**–**1c**) shows loss of coordinated water molecules in the first step followed by decomposition of ligand moieties in a respective manner and leads to form air stable metal oxide as final residues. Powder X-ray diffraction and SEM

Abbreviations: AA, ascorbic acid; CT DNA, calf thymus deoxyribonucleic acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EB, ethidium bromide; 5-FU, 5-fluorouracil; Tyr, L-tyrosine; SEM, Scanning Electron Micrography.

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studies illustrate that all the complexes have uniform microcrystalline with homogenous morphology. Mn(II), Ni(II) and Cu(II) complexes show significant *in vitro* antimicrobial and antioxidant activities than 5-fluorouracil(A). Moreover, the nuclease studies of Ni(II) and Cu(II) complexes (**1c** and **1d**) show considerable DNA binding and oxidative DNA cleavage activities than other complexes.

1. Introduction

Generally, most of the bioactive organic compounds or molecules containing hard and soft donor sites of N, O and/S atoms occur in nature. Such bioactive organic molecules which contain heterocyclic nitrogen are predominantly present in biomolecules, vitamins and agrochemicals. Mainly heterocyclic nitrogen containing bases i.e. pyrimidine bases are powerful antiviral and anticancer agents in physiological and pharmacological fields [23]. The discovery of novel potent anticancer agents by laboratory preparation has been in progress for the improvement to design drugs based on the drug–receptor or drug–enzyme interaction for example, a fluorinated pyrimidine base like 5-fluorouracil (5-FU) has proved its best anticancer activity and other pyrimidine derivative bases have been found to show significant fungicidal, antibacterial, antimitotic, antithyroid and surface anesthesia activities [9]. The pyrimidine nitrogen base analogues of uracil, cytosine and thymine are useful to kill or retard the cancer cells in living organisms. Mostly, 5-fluorouracil (Trade name: Adrucil, Carac) is used to kill or destroy the tumor cells [9,36] in colon, rectum, breast, stomach and pancreas cells. In addition, it inhibits and stimulates incorporation of amino acids into nucleoprotein, bacterial cell wall synthesis and thymidine into DNA, respectively [9]. Further, 5-fluorouracil is applied as a cream (Carac, Efudex, Fluoroplex) for curing the skin lesions (keratoses) on the face and front part of the scalp.

Manganese is a necessary trace nutrient in the photosynthesis process for plants like spinach and also manganese containing enzymes like oxidoreductases, transferases, hydrolases, lysaes, etc., have shown a broad spectrum of functionality. It plays an important role in many biological redox processes, catalase activities and superoxide dismutases (SOD) [42]. Transition metal of cobalt is a necessary element for healthy humans and animals. It largely presents in the form of vitamin B_{12} (cobalamin) series of coenzymes. This cobalamin is necessary for DNA synthesis, formation of RBC, maintenances of CNS, myelin formation, etc. [8]. Nickel is a trace element which is necessary for healthy life to human and higher animals like chickens, rats, pigs and cows [28]. It enters the human cell directly and undergoes redox metabolism to form reactive oxygen species (ROS). Also, it stabilizes RNA and DNA against thermal denaturation and activates many enzymes [28]. An essential micronutrient of copper is present in a variety of biological processes, proteins and enzymes [19,39]. It is found in erythrocytes, blood plasma protein, sweat and urine. The second most abundant nontoxic zinc is present in numerous biological systems like microorganisms, animals, plants and humans. In addition, it plays a vital role in an extensive range of processes like DNA and RNA synthesis, genetic message transmission, growth and development, lipid metabolism and immune and brain functions [38]. Furthermore, ~98% of total zinc element is physiologically found in cell organelles and the remaining is present in the cell membrane [38,41].

Amino acids are the basic components for healthy living organisms and building blocks for protein synthesis. Generally, L-amino acids are present in several natural products in food, medicine, animal feed areas and drugs. L-Tyrosine (tyr) is found in various food products like milk, fish, cheese, peanuts, almonds, chicken, etc. It acts as a potent anti-depressant agent and enhances the cellular strength and immune systems in human body. The phenolic-OH group in L-tyrosine is significant for stimulating antibacterial activity and precursor of diverse hormones and neurotransmitters [7]. Also, the metal(II) complexes of L-amino acids play a vital role in biology, industry, pharmacy and laboratory reagents [30]. Currently, there is great attention paid to the study of natural and safer antioxidant compounds because they play a crucial part in food, cosmetics and pharmaceutical products [35]. Also, these compounds have increased the shelf life or prevention of age related diseases by retarding the process of lipid peroxidation and chain reaction [17].

As part of our ongoing research [11,27,32,33], in this work, we now synthesized a series of novel bioactive amino acid metal(II) complexes that were derived from 5-fluorouracil (5-FU: A) and L-tyrosine (tyr: B) with M(II) ions [M(II) = Mn, Co, Ni, Cu and Zn]. The synthesized amino acid metal(II) complexes were characterized by means of analytical and various spectral techniques. Also, we have to evaluate the *in vitro* antimicrobial and antioxidant activities of 5-fluorouracil and their metal(II) complexes with standard control drugs. Moreover, the DNA binding and oxidative DNA cleavage experiments were also carried out.

2. Experimental

2.1. Materials and spectral measurements

All the chemicals, ligands and metal(II) salts used for this present work were extra pure Sigma Aldrich and Fluka (Puriss) products and used without further purification. The solvents used for the preparation and physical measurements were purified according to the standard procedures [29]. 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ascorbic acid (AA) were purchased from Sigma Aldrich. Calf thymus (CT) DNA was purchased from Gene (India). Agarose (Molecular Biology Grade) and Ethidium bromide (EB) were obtained from Sigma (USA). Tris–(hydroxymethyl)aminomethane–HCl (Tris–HCl) buffer solution was prepared by using deionized triple distilled CO_2 free water. Melting point (m.p.) of all the metal(II) complexes was determined on Gallenkamp apparatus in open glass capil-