Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 126 (2014) 242–253

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Morphological and pharmacological investigation on some biopotent materials derived from substituted pyrimidine and imidazole enzyme constituents

Sutha Shobana [a], Perumal Subramaniam [b,*], Jeyapraksh Dharmaraja [c], Arvind Narayan [d]

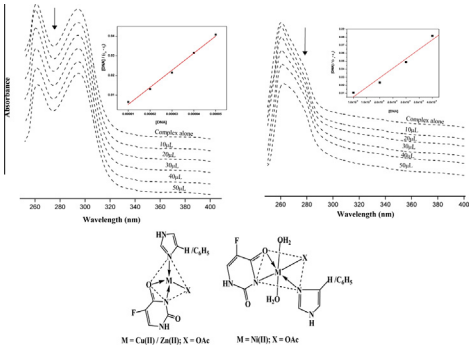
[a] Department of Chemistry, Division of Science and Humanities, Rajas International Institute of Technology for Women, Ozhuginaserri, Nagercoil 629 001, Tamil Nadu, India
[b] Department of Chemistry and Research Centre, Aditanar College of Arts and Science, Virapandianpatnam, Thiruchendur 628 216, Thoothukudi District, Tamil Nadu, India
[c] Department of Chemistry, Division of Science and Humanities, Sree Sowdambika College of Engineering, Chettikurichi, Aruppukottai 626 134, Tamil Nadu, India
[d] Division of Science and Humanities, K.N.S.K. College of Engineering, Therekalputhoor, Nagercoil 629 001, Kanyakumari District, India

HIGHLIGHTS

- Substituted halopyrimidine derivatives are used in colorectal cancer chemotherapy.
- 5-Fluorouracil plays a crucial role in Food and Drug Administration systems.
- The metal complexes show homogeneous morphology with microcrystalline environment.
- Gel electrophoresis shows CT DNA undergoes oxidative cleavage with the complexes.
- *In vitro* antimicrobial and antioxidant assessments show high inhibiting potential.

GRAPHICAL ABSTRACT

Novel N_2O type mixed ligand complexes **(1–6)** have been synthesized from substituted fluoropyrimidine [5-Fluorouracil (5-FU: A)] with imidazole(him) and benzimidazole(bim) enzyme constituents(B) in the presence of M(II) ions [where M(II) = Ni(II), Cu(II) and Zn(II)]. Synthesized complexes **(1–6)** were characterized by chemical analysis and various spectral studies. *In vitro* antimicrobial activities of 5-Fluorouracil(A) and their mixed ligand complexes were screened against some bacterial and fungal strains by well diffusion technique. Electronic absorption and oxidative cleavage studies of the chelates with DNA under aerobic conditions show remarkable activities. Also, the absorption binding studies of CT DNA with the M(II)-5-FU(A)-him(B) complexes show decrease of 5–15% intensity with minor red shift along with significant hypochromicity and the free energy change values ($\Delta^{\ddagger}G$) indicate the M(II) complexes can interact with DNA in a spontaneous manner.



ARTICLE INFO

Article history:
Received 29 December 2013
Accepted 22 January 2014
Available online 18 February 2014

Keywords:
Fluoropyrimidine

ABSTRACT

Coordinating behavior of novel N_2O type mixed ligand complexes **(1–6)** have been synthesized from substituted fluoropyrimidine [5-Fluorouracil (5-FU; A)] with biopotent imidazole enzyme constituents (B) *viz.*, imidazole(him) and benzimidazole(bim) in the presence of Ni(II), Cu(II) and Zn(II) ions. Synthesized complexes were characterized by chemical analysis, spectral studies, magnetic moment and conductivity measurements. The results of chemical analysis and the observed low molar conductance values propose their stoichiometry to be 1:1:1 (M:A:B) with non-electrolytic nature. From the spectral data, it is inferred that the ligands A & B coordinate with M(II) ions in bi and monodentate approach

* Corresponding author. Tel.: +91 94435 00381; fax: +91 4639 245247.
E-mail addresses: Subramaniam.perumal@gmail.com, psubramaniam.ac@gmail.com (P. Subramaniam).

http://dx.doi.org/10.1016/j.saa.2014.01.089

Imidazole enzyme constituents
Mixed ligand complexes
Spectral studies
Pharmacological evaluation
DNA studies

through $C_{(4)}$=O, $N_{(3)}$ and imidazole ring $N_{(3)}$ atoms respectively. The thermogravimetric analysis shows the dehydration, decomposition and thermal stability of mixed ligand complexes. XRD and SEM patterns show sharp crystalline peaks with homogeneous morphology. *In vitro* antimicrobial activities of free ligands (A & B) and their metal complexes were screened against some pathogenic strains by well diffusion technique. Absorption and gel electrophoresis experiments on the interaction of mixed ligand complexes with DNA suggest that all the complexes can bind as well as cleave the DNA by intercalation between chromophores and DNA base pairs. In addition, *in vitro* antioxidant activities were tested by DPPH free radical scavenging model.

Introduction

The heterocyclic ring systems containing bioactive donor of N/O atoms present in pyrimidine moieties are the basic building blocks in modern drug designing architecture. These derivatives have occupied a unique and significant position in the field of medicinal, biological and therapeutical applications since they possess antibacterial, fungicidal, antitumor, antimitotic, antithyroid and surface anaesthesia activities [1,2]. Further, these derivatives are essential antimicrobial, antineoplastic, antiviral, antitumor, anti-HIV, antiinflammatory, antimalarial and cardiovascular agents in chemotherapeutical and agricultural areas [3–6]. They also bring into play an imperative role in hypnotic drugs for the nervous system, antagonists of the human A2A adenosine and calcium sensing receptors [7]. It is well known that pyrimidine derivatives of uracil, thymine and cytosine are the fundamental components in nucleic acids of DNA and RNA. In adjuvant chemotherapy, substituted pyrimidine derivatives alone or with leucovorin are functional to standard healing for high-risk Duke's C colon cancer (Stage II or Stage III). At very low concentration (<20 ppm), 5-Fluorouracil exhibits a cheerful inspiring effect on plant tumor growth which is produced by F1 hybrid of Nicotiana glauca Grah and Nicotiana langsdorffii Weinm [8]. Further, 5-Fluorouracil is a novel oral tumor-activated and tumor-elective fluoropyrimidine carbamate and an oral chemotherapeutic agent which is also used in the treatment of breast, esophageal and larynx, gastrointestinal and genitourinary tract cancers. The diazole ring moieties of imidazole derivatives are suggested as effective antifungal drugs (bifonazole, butoconazole, clotrimazole, miconazole, etc.,) and they possess some medicinal applications which include anticancer, β-lactamase inhibitors, antiaging agents, anticoagulants, antimalarial, antiinflammatory, antidiabetic and antitubercular activities [9,10]. Benzimidazole moiety acts as a fraction of the nucleotide fragment in vitamin B_{12} and in a range of biological and pharmacological actions [11].

Copper is an elementary micronutrient, necessary for all the living organisms and it is ubiquitous in catalytic co-factor for a range of metalloenzymes, electron transfer and oxygen transport proteins [12]. The copper containing proteins play a dynamic role in three major cellular processes namely amino acid metabolism, coagulation cascade and tyrosine metabolism with melanin biosynthesis. In addition to this, it concerned with many biological and physiological processes such as hemoglobin regulation, iron metabolism, mitochondrial respiration, biosynthesis of neurotransmitter, free radical detoxification, development of embryo and connective tissue, nerve coverings and bone [12]. Nickel is necessary to human and higher animal species like chickens, rats, pigs, cows, sheep and goats [13]. It also stabilizes DNA and RNA against thermal denaturation [13] and activates many enzymes. Zinc is the second richest trace element in human body which is intracellular in bone, muscle, skin, hair and liver [14]. It plays a chief role in all the biochemical pathways, perpetuation of genetic materials and in the function of retina, retinal pigment epithelium (RPE) and choroid.

The interactions of transition metal ions with DNA are significant, often changing the structure and function of genetic materials. Mixed ligand complexes have been introduced into DNA in order to gain the knowledge about the binding and/or cleaving mechanism, in particular to understand pre-requisites of specificity [15]. In addition, they have been used in the development of new target molecules for bio-reactivity of these metal complexes with DNA [16]. In absorption studies, the change in the intensities can be used to explain the nature and strength of the stacking interaction between chromospheres and DNA base pairs. In a sequel to our attempt [17–23], the novel N_2O type mixed ligand complex systems of Ni(II)/Cu(II)/Zn(II)-5-FU(A)-him/bim(B) were synthesised and characterized by means of analytical and spectral techniques. The *in vitro* antimicrobial and antioxidant activities of 5-Fluorouracil and their complexes have been studied. Electronic absorption and oxidative cleavage interaction of 5-Fluorouracil(A) and their metal complexes with DNA was also studied.

Experimental

Materials and reagents

All the ligands are extra pure Sigma Aldrich, Fluka (Puriss) products and they are used without further purification. Solvents for the physical measurements were of analytical grade and purified according to literature methods [24]. DNA was purchased from Genie (Bangalore, India), agarose (molecular biology grade) and ethidium bromides (EB) were obtained from Sigma Aldrich (USA). 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ascorbic acid (AA) were purchased from Sigma Aldrich.

Instruments

Melting points (m.p.) of all the mixed ligand complexes were determined on Gallenkamp apparatus in open glass capillaries and are uncorrected. C, H and N analytical data were performed on Elementar Vario EL III CHNS analyzer. Metal content of the mixed ligand complexes were estimated gravimetrically by the standard procedure. Molar conductances of the mixed ligand complexes (1×10^{-3} mol) were measured using an Elico CM 180 conductivity bridge by using 0.01 M KCl solution as calibrant. Fast atomic bombardment mass spectra (FAB-MS) were recorded using a VGZAB-HS spectrometer in a 3-nitrobenzylalcohol matrix. Magnetic susceptibility measurements were carried out on a Gouy balance at room temperature using mercuric tetra(thiocyanato)cobaltate(II) as the calibrant. Diamagnetic corrections were applied in compliance with Pascal's constant [25]. Electronic absorption spectra were recorded with a Hitachi U-2000 double beam spectrophotometer in the 200–1100 nm range. Vibrational spectra were recorded using KBr pellets on a JASCO FT/IR-410 spectrometer, in the 4000–400 cm^{-1} range. ^1H NMR and ^{13}C NMR spectra of the diamagnetic Zn(II) complexes were carried out in DMSO-d_6 at room temperature using TMS as internal standard on