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Metal based pharmacologically active agents: Synthesis, structural characterization, molecular modeling, CT-DNA binding studies and *in vitro* antimicrobial screening of iron(II) bromosalicylidene amino acid chelates

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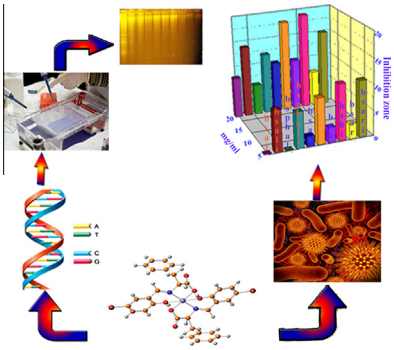
HIGHLIGHTS

- Novel Schiff base amino acid iron(II) chelates were designed and synthesized.
- They were characterized by different physicochemical and molecular modeling studies.
- DNA binding ability of the investigated complexes was studied using different tools.
- Biological activities have also been performed against different strain of organisms.

GRAPHICAL ABSTRACT



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ABSTRACT

In recent years, great interest has been focused on Fe(II) Schiff base amino acid complexes as cytotoxic and antitumor drugs. Thus a series of new iron(II) complexes based on Schiff bases amino acids ligands have been designed and synthesized from condensation of 5-bromosalicylaldehyde (bs) and α-amino acids (L-alanine (ala), L-phenylalanine (phala), L-aspartic acid (aspa), L-histidine (his) and L-arginine (arg)). The structure of the investigated iron(II) complexes was elucidated using elemental analyses, infrared, ultraviolet–visible, thermogravimetric analysis, as well as conductivity and magnetic susceptibility measurements. Moreover, the stoichiometry and the stability constants of the prepared complexes have been determined spectrophotometrically. The results suggest that 5-bromosalicylaldehyde amino acid Schiff bases (bs:aa) behave as dibasic tridentate ONO ligands and coordinate to Fe(II) in octahedral geometry according to the general formula $[Fe(bs:aa)_2]\cdot nH_2O$. The conductivity values between 37 and 64 $ohm^{-1}\ mol^{-1}\ cm^2$ in ethanol imply the presence of nonelectrolyte species. The structure of the complexes was validated using quantum mechanics calculations based on accurate DFT methods. Geometry optimization of the Fe-Schiff base amino acid complexes showed that all complexes had octahedral coordination. In addition, the interaction of these complexes with (CT-DNA) was investigated at pH = 7.2, by using UV–vis absorption, viscosity and agarose gel electrophoresis measurements. Results indicated that the investigated complexes strongly bind to calf thymus DNA via intercalative mode and showed a different DNA binding according to the sequence: bsari > bshi > bsali > bsasi > bsphali. Moreover, the prepared compounds are screened for their *in vitro* antibacterial and antifungal activity against three types of bacteria, *Escherichia coli*, *Pseudomonas aeruginosa* and *Bacillus cereus* and three types of anti

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fungal cultures, *Penicillium purpurogenium*, *Aspergillus flavus and Trichotheium rosium*. The results of these studies indicated that the metal complexes exhibit a stronger antibacterial and antifungal efficiency than their corresponding Schiff base amino acid ligands.

Introduction

The rapid development and understanding of the chemistry of molecular biology and amino acids have created a significant class of compounds that are now helpful in understanding biological functions of macromolecules like proteins. It is well known that the human body contains essential elements which play important roles and interact with many biological molecules. Schiff base complexes own a lot of activities against bacteria [1], fungi [2], and certain types of tumors [3]. They have been used as radiotracers in nuclear medicine and drugs [4]. Some drugs show increased activity when administered as metal chelates and inhibit the growth of tumors [5]. Moreover, the development in the field of bioinorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species [6–8]. It is clear that Schiff base transition metal complexes are very important chelates because they are cheap, easy to synthesize and chemically and thermally stability. Moreover, these complexes have extensive applications in the fields of medicine, photo and magnetic chemistry [9], and electrochemistry [10]. Schiff base amino acid complexes act as good chelating agents [11], behave as efficient biologically active [12] and cytotoxic agents [13]. In addition, Schiff base amino acid complexes are considered to combine new kinds of potential antibacterial and anticancer reagents [14]. From a bioinorganic point of view, iron Schiff base complexes provide useful structural and electronic models for the similarly coordinated sites found in the heme iron enzymes. Moreover, these complexes are also important for the asymmetric oxidation of organic substrates, since their structure and catalytic activity are analogous with those of iron porphyrins [15]. Studying the interaction between transition metal complexes and DNA has attracted many interests due to their importance in cancer therapy, design of new types of pharmaceutical molecules and molecular biology [16–20]. On the other hand, few studies were carried out about the interaction of DNA with Schiff base amino acid complexes [21–23]. In addition to, the capability of transition metal complexes of cleaving DNA on irradiation with visible light, they have important potential applications in photodynamic therapy (PDT) of cancer [24]. PDT has emerged as a non-invasive mode of treatment for cancer in which selective photo activation of the drug at the cancer cells leads to damage of the photo-exposed cells only, leaving healthy cells unaffected [25,26]. Therefore, the main target of this paper is to prepare and characterize novel Fe(II) Schiff base amino acid complexes and to study the interaction of these complexes with DNA. These Schiff base amino acid complexes under study would be expected to help to understand the binding mode interaction and the effect of the side chain of these different amino acids towards the binding to DNA. Moreover, the efficiency of the interaction of the investigated complexes with CT-DNA was monitored by agarose gel electrophoresis experiments. This will be helpful to understand the mechanism of the interaction of small molecules with nucleic acids, and should be useful in the development of potential probes of DNA structure and conformation. Also, the main aim of the production and design of any antimicrobial compound is to inhibit the causal microbe without any side effects on the patients. The chemotherapeutic agent affecting only one function has a highly sounding application in the field of treatment by anticancer, since most anticancer agents used in the present time affect both cancerous diseased cells and healthy ones which in turns affect the general health of the patients. Therefore, there is a real need for having a chemotherapeutic agent which controls only one function. For this reason, *in vitro* antibacterial and antifungal activities of the prepared compounds are screened. The structures of the Schiff base amino acid ligands studied in this investigation are shown in Scheme 1.

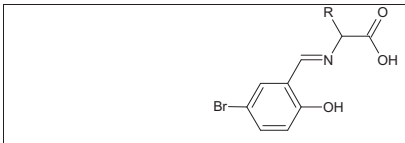
Experimental

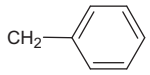
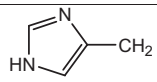
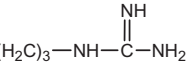
Material and reagents

All chemicals used in this investigation such as 5-bromosalicylaldehyde (bs), amino acids, the metal salt ($FeSO_4{\cdot}(NH_4)_2SO_4{\cdot}6H_2O$), calf thymus DNA (CT-DNA), ethidium bromide (EB), EDTA and Tris[hydroxymethyl]-aminomethane (Tris) were purchased from Sigma–Aldrich Chemie (Germany). Analytical grade ethanol, acetic acid, boric acid and hydrochloric acid products were used.

Synthesis of Schiff base amino acid ligands

The studied Schiff base ligands were synthesized using a method similar to the literature [22,23,27]. By dissolving 5 mmol of 5-bromosalicylaldehyde (1.01 g) in 40 ml ethanol and mixing it with 5 mmol of each amino acid (L-alanine, L-phenylalanine, L-aspartic acid, L-histidine, L-arginine) in aqueous–ethanol mixture (50% ethanol). The mixture was refluxed for 5 h and the solution was evaporated to 1/4 of its original volume and then cooled to ambient temperature. After one day, the yellow precipitates were obtained in case of L-alanine, L-phenylalanine and L-aspartic acid while brown and green powder in case L-histidine and L-arginine was obtained. After that, they filtered off washed with ethanol then with diethyl ether and finally dried in vacuum over silica gel. The results of the elemental analysis are in Table 1.



Acronym		R
Ligand	Complex	
bsal	bsali	CH_3
bsphal	bsphali	
bsas	bsasi	CH_2COOH
bsh	bshi	
bsar	bsari	

Scheme 1. Structures and abbreviations of the Schiff base ligands and their corresponding complexes.