Journal of Saudi Chemical Society (2014) **18**, 953–962

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Antimicrobial mechanism of copper (II) 1,10-phenanthroline and 2,2′-bipyridyl complex on bacterial and fungal pathogens

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Received 19 September 2011; accepted 29 November 2011
Available online 8 December 2011

KEYWORDS

Copper (II) complex;
Bacteria;
Fungi;
DNA;
Molecular docking

Abstract Copper based metallo drugs were prepared and their antibacterial, antifungal, molecular mechanism of [Cu(SAla)Phen]·H_2O and [Cu(SAla)bpy]·H_2O complexes were investigated. The [Cu(SAla)Phen]·H_2O and [Cu(SAla)bpy]·H_2O were derived from the Schiff base alanine salicylaldehyde. [Cu(SAla)Phen]·H_2O showed noteworthy antibacterial and antifungal activity than the [Cu(SAla)bpy]·H_2O and ligand alanine, salicylaldehyde. The [Cu(SAla)Phen]·H_2O complex showed significant antibacterial activity against *Salmonella typhi*, *Staphylococcus aureus*, *Salmonella paratyphi* and the antifungal activity against *Candida albicans* and *Cryptococcus neoformans* in well diffusion assay. The mode of action of copper (II) complex was analyzed by DNA cleavage activity and *in silico* molecular docking. The present findings provide important insight into the molecular mechanism of copper (II) complexes in susceptible bacterial and fungal pathogens. These results collectively support the use of [Cu(SAla)Phen]·H_2O complex as a suitable drug to treat bacterial and fungal infections.

1. Introduction

Antimicrobial resistance is fast becoming a global concern with rapid increase in multidrug resistant bacteria. To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency. Many of the crude drugs, which are sources of medicinal preparations, still originate from wild growing material. This revival interest was generated by the

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Peer review under responsibility of King Saud University.

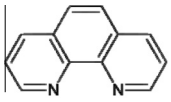
Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2011.11.020

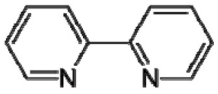
discovery of the antibacterial, antifungal and anticancer activity of several metal complexes (Saha et al., 2009).

The medicinal application of metal complexes has been a subject of great interest recently (Guo and Sadler, 2000). Apart from the huge success of platinum based drugs, some other metal compounds such as titanium and ruthenium complexes have shown some potential for chemotherapy. The toxicity of metallo drugs is problematic; therefore, it is proposed that drugs based on essential metals may be less toxic, which has led to the investigation of copper based drugs. Copper complexes have indeed demonstrated a wide range of pharmacological activity such as Antibacterial (Gao et al., 2004; Geraghty et al., 2000; Creaven et al., 2006), Antifungal (White et al., 1998; Abu Salah, 1996; Kavanagh et al., 2004) antiviral (Kaska et al., 1978; Ranford et al., 1993; West and Owens, 1998), anticancer (Berners-Price et al., 1987; Moubaraki et al., 1999; Kong et al., 2000) and anti-inflammatory activity (Andrade et al., 2000). It was found that copper complexes often demonstrate enhanced biological activity than the parent ligand alone (Mohindru et al., 1983; Ainscough et al., 1998).

Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. Probably the most widely studied cation in this respect is Cu^{2+}, since a host of low molecular weight copper complexes have been proven beneficial against several diseases such as tuberculosis, rheumatoid, gastric ulcers, and cancers (Sorenson, 1976; Brown et al., 1980; Ruiz et al., 1995). Twenty natural amino acids comprise the building blocks of proteins, which are chemical species indispensable to perform a huge number of biological functions, as exemplified by the role of enzymes. From these 20 amino acids, eight are essential and cannot be produced by the human body. Complexes of transition metals with amino acids in proteins and peptides are utilized in numerous biological processes, such as oxygen conveyer, electron transfer and oxidation. In these processes, the enzymatic active site, which is very specific, forms complexes with divalent metal ions (Vemrlinov et al., 2006). 1,10-Phenanthroline (1,10-phen), 2,2′-bipyridine (2,2′-bipy) and their substituted derivatives, both in the metal-free state and as ligands coordinated to transition metals, disturb the functioning of a wide variety of biological systems. When the metal-free N, N-chelating bases are found to be bioactive it is usually assumed that the sequestering of trace metals is involved, and that the resulting metal complexes are the actual active species.



1,10-phenanthroline



2,2'-Bipyridine

Copper complexes of 1,10-phenanthroline and its derivatives are able to target DNA and have been used as DNA nuclease as foot printing agents (Sigman, 1990; Mazumder et al., 1993; Sigman et al., 1993; Mahadevan and Palaniandavar, 1998). Modification of 1,10-phenanthroline copper complex has resulted in the discovery of a series of anticancer agents casiopeinas (Ruiz-Ramírez et al., 1993, 1995), and one of the complexes has been shown to induce apoptosis of murine leukemia cell lines (Vizcaya-Ruiz et al., 2000). The casiopeinas are a group of Cu^{2+} mixed-ligand antineoplastic agents which contain 1,10-phenanthroline or 2,2′-bipyridine and other bidentate ligands. These compounds exhibit cytotoxicity, genotoxicity, and antitumor effects, but their mode of action is presently unknown (Shi et al., 2010).

A number of reports have appeared in the literature highlighting the use of transition metal complexes as both antibacterial and antifungal agents (Geraghty et al., 1999). The *in vitro* antibacterial action of 1,10-phenanthroline has been demonstrated on several species of bacteria. Phenanthroline metal complexes can be bacteriostatic and bacteriocidal toward many Gram-positive bacteria they are relatively ineffective against Gram-negative organisms.

Metal based drugs represent a novel group of antifungal agents with potential applications for the control of fungal infections. 1,10-Phenanthroline and substituted derivatives, both in the metal-free state and as ligands coordinated to transition metals, disturb the functioning of a wide variety of biological systems (Butler et al., 1969).

DNA binding and cleavage are two critical events for gene mutation and carcinogenesis in biological systems. Metal complexes have demonstrated a natural DNA-targeting aptitude and have been studied extensively (Boerner and Zaleski, 2005). In addition to this, the interaction of these Schiff base metal complexes with DNA has been extensively studied in the past decades. Due to the site specific binding properties and many fold applications in cancer therapy, these coordination compounds were suitable candidates as DNA secondary structure probes, photo cleavers, and antitumor drugs (Chan and Wong, 1995; Pratviel et al., 1998; Liang et al., 2004). One of the most effective metal-based nucleases is the copper complex of 1,10-phenanthroline which has been extensively used for mapping protein and drug binding sites on DNA as well as for studying DNA structure (Sigman et al., 1993). DNA degradation by a 1,10-phenanthroline-Cu (II) complex requires both a reducing agent and molecular oxygen.

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. The cytochrome P450 superfamily (officially abbreviated as CYP) is a large and diverse group of enzymes. The function of most CYP enzymes is to catalyze the oxidation of organic substances. The substrates of CYP enzymes include metabolic intermediates such as lipids and steroidal hormones, as well as xenobiotic substances such as drugs and other toxic chemicals. CYP 51 shows structural relationships with P450 enzymes involved in the synthesis of polyketide antibiotics. CYP 51 inhibitors block ergosterol synthesis at one or more sites with the accumulation of 14α-methyl sterol. Depletion of ergosteroland accumulation of sterol precursors, results in the formation of a plasma membrane with altered structure and function of several membrane bound enzymes. For this purpose, the docking of Cu (II) metal complex into the active site of the model was explored. The structurally and functionally important residues identified allowed for a better understanding of the structure–function relationships of the enzyme. The modes of the enzymes substrate and enzyme-inhibitor interactions would be useful in developing more potent antifungal and antibacterial drugs.