Chapter – 11

Application of Copper-based Catalysts

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Abstract—*This chapter briefly elucidates the recent trends in Cu-based complexes and their application in DNA binding, DNA cleavage, and anticancer studies. A brief introduction of several Cu-based ligands has been discussed along with their findings.*

Introduction

The study of small molecules, which react at specific sites along a DNA strand as reactive models for protein-nucleic acid interactions, provide routes for the development of chemotherapeutic agents.[1] The reaction of metal complexes and their interaction with DNA has always been an active research area in relation to the advancement in reagents for medicine and biotechnology.[2] Transition metal complexes with their versatile structures, redox behaviour, and physicochemical properties are found to be useful as highly sensitive diagnostic agents. The metal or ligands in the complexes can be varied in an easily controlled way to facilitate individual application.[3] Copper is a trace element of great application and significance. It is found in several important enzymes (e.g., superoxide

ISBN: 978-93-85822-94-0

dismutase, cytochrome oxidase, and tyrosinase) and its redox-active property facilitates many biological functions.[4] Moreover, copper complexes have been reported to possess antibacterial, antifungal, antiviral, anti-inflammatory and anticancer properties.[5] Thus, copper complexes appear to provide a promising platform for designing novel anticancer drugs. Copper being a transition metal, the oxidation state, the number and types of coordinated ligands, and the coordination geometry of the complexes can afford a variety of properties. On the other hand, the ligands not only control the reactivity of the metal but also play crucial roles in defining the actual nature of interactions involved in recognition of biological target sites such as DNA, enzymes, and receptors. These properties provide for the design of a variety of copper-based metallodrugs.[6] However, from the very fact that copper is one of the most abundant and essential metals,[7] it is an excellent candidate for development of drugs for the treatment of cancers. Several synthetic copper(II) complexes have been reported to act as pharmacological agents with antitumor and chemoprevention properties.[8] Recently, certain mixed ligand copper(II) complexes, which strongly bind and cleave DNA, have been shown to exhibit prominent anticancer activity including induction of apoptosis.[9] Copper(II) complexes are considered as the best alternatives to cisplatin and its derivatives since copper is biocompatible and plays significant roles in the biological systems. To overcome the side effects caused by cisplatin like drugs, attempts are being made to replace the drugs with suitable alternatives, and numerous transition–metal

complexes are being synthesized and screened for their anticancer activities.[10]

Copper complexes with chelating ligands have shown a significant decrease in tumor volume, mitotic and proliferation indices in different types of human cancer cells[11] The oxidative stress has been attributed to the ability of some Cu(II) complexes to induce apoptosis that represents the most recurrent cell death mechanism.[12] Copper complexes with 1,10-phenanthroline (phen) have received considerable current interests in nucleic acids chemistry due to their various applications in the presence of hydrogen peroxide and a reducing agent.[13] The metal-chelating properties of phen ligand and its derivatives have been utilized in a range of analytical reagents as well as for the development of biological probes.[14] It has also been reported that copper(II) complexes of 1,10-phen inhibit DNA or RNA polymerase activities and strand scission of DNA in the presence of H_2O_2 or thiol.[15] In addition to the phen co-ligand many other ligands including amino acids, naphthyls, quinolyls, aminophenols, etc. can be incorporated in Cu based systems for designing anticancer drugs. Thus the Cu(II)-1,10-phen complex systems are considered as unique systems that can be further explored in the improvement of metal complexes.

Copper(II) complexes, [Cu(Hsal)(L)(ClO_4)] (where Hsal = salicylaldehyde, L = dpqC = dipyrido (6,7,8,9-tetrahydro)phenazine or L = dppz = dipyrido phenazine, have also been synthesized and characterized using elemental analysis and spectroscopic methods using modified phenanthroline ligands with increased aromatic surface using dipyridophenazine (dppz) and

reducing the aromatic surface area by attaching a dearomatized cyclohexyl ring (dpqC) to study the structure-activity relationship of these complexes.[16]

Biological application

Study's on the interaction of Cu(II)-based complexes with DNA has been done extensively owing to their several fundamental functions such as cytotoxicity towards cancer cells, DNA cleavage activity, etc. Reaction based on metal complexes and their interactions with DNA has always been a broad area of exploration owing to the importance of new materials like reagents to be used for medicine and biotechnology.[17] Important organic synthetic area like asymmetric synthesis is also a newer field where such DNA–metal complex systems are very useful.[18]Several derivatives of Cu(II)1,10-phenanthroline (phen) complexes are another group of complexes that have fascinated great attention due to their utility as chemical nucleases. The role of $[Cu(phen)_2]^+$ complex in inhibiting DNA or RNA polymerase activities along with the induction of DNA strand scission in the presence of thiol groups or H_2O_2has been shown by Sigman and his coworkers.[15,19,20] After this success, several other groups have studied many Cu(II) ternary complexes of phen derivatives and several other ligands and it has been observed that most of such complexes display influencing properties like antiviral, antitumor, and DNA cleavage activities.[21,22,23]

The prominent cytotoxicity of certain mixed ligand Cu(II) complexes[24] is consistent with the ability of the complexes to effect double-strand DNA

ISBN: 978-93-85822-94-0

cleavage. Many other copper(II) complexes are capable of mediating non-random double-strand cleavage of plasmid DNA.[25]In order to expand the effectiveness of such metal complexes in the field of organic synthesis, medicine, biotechnology, etc., the redox potential, p*K*a of ligands, and their accessibility in drug delivery must be tuned. The process of intercalation follows the general sequence: (1) ligand binding in the minor groove, (2) ligand positioning, (3) partial opening of base pairs and partial insertion of the ligand, (4) flipping out of both the bases and full ligand insertion in the cavity, followed by (5) reorientation of the ligand inside the cavity as shown in the following diagrams.[26]

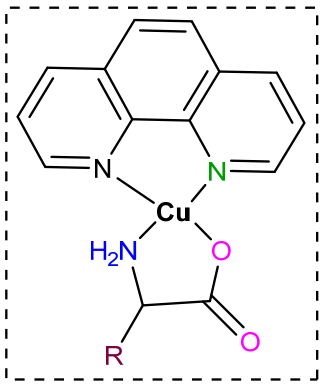

Figure 1. [Cu(phen)(amino acid)]$^{+}$.

Some interesting reported Cu (II) complexes include the mono (1,10-phenanthroline)-copper(II) and the ternary complexes with amino acids (Figure 1) that bind to DNA with several different binding modes.[2] Also, the mononuclear copper (II) complex[Cu(L)(diimine)] (Figure 2), has been characterized and is reported to be cytotoxic to human breast cancer cell MCF-7 and cervical cancer cell ME-180.[27] The water-soluble mixed ligand

copper(II) complexes of the type [Cu(bimda)-(diimine)] (Figure 3),been isolated and studied. DNA binding experiments reveal that the intrinsic DNA binding affinity of the complexes depends upon the diimine co-ligand functioning as the DNA recognition element.[28]

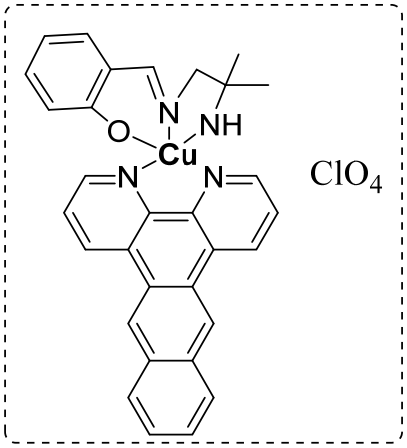

Figure 2. [Cu(L)(diimine)].

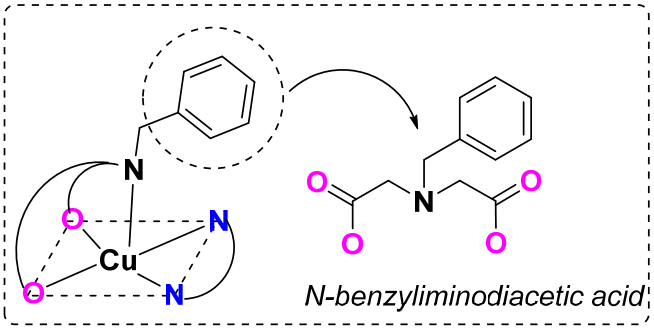

Figure 3. [Cu(bimda)-(diimine)].

Conclusion

In conclusion, a brief review of different Cu-based, mixed ligand complexes and its role in DNA binding, DNA cleavage, and anticancer study has been

discussed in this chapter. Different literature reviews on recent progress are also been highlighted.

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ISBN: 978-93-85822-94-0