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Research paper

DNA binding and cleavage studies of copper(II) complex containing N_2O_2 Schiff base ligand

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ABSTRACT

A new series of copper (II) complexes $[Cu(L^{1\text{-}5})](ClO_4)]$ [**1–5**] were synthesized by condensation of salicylaldehyde with various diamines (1,2-diamino ethane, 1,3-diamino propane, 1,2-diamino benzene, 2-aminobenzyl amine and 1,8-diamino naphthalene) and characterized by several analytical techniques. The precursor ligand structure was confirmed by single crystal X-ray diffraction (XRD) techniques. The viscosity measurement and molecular docking studies were also carried out for newly synthesized Cu(II) complexes. Cyclic voltametry (CV) study showed a quasi-reversible reduction wave in cathodic region confirm the presence of Cu^{2+}. From the electronic spectral and DNA binding studies (K_b values are within the range from $0.47 \times 10^4\,M^{-1}$ to $1.18 \times 10^5\,M^{-1}$) it evidences that Cu(II) complexes were intercalated with DNA, this observation was further confirmed by fluorescence measurement studies ($K_{app} \sim 0.22 \times 10^5\,M^{-1}$–$0.26 \times 10^6\,M^{-1}$). Comparatively the maximum DNA cleavage was observed in the complex (**5**) and the possible mechanism of DNA cleavage activity has also been discussed. In addition, the interaction of complexes (**1–5**) with bovine serum albumin (BSA) was also examined. These encouraging results may pave the way towards the development of novel therapeutic agents in cancer biology.

1. Introduction

The transition metal complexes were known to have great importance in cancer biology, due to their tunable redox properties and physiological conditions, which make them for the development of novel therapeutic agents. The interactions between metal-ligand complexes and DNA have played a key role in DNA cleavage and protein binding studies [1,2]. Generally, the DNA and drug interaction mechanism can be expressed by the electrostatic attraction forces, intercalation, groove binding as well as the combination of all these modes. In addition, the DNA cleavage which occurs either by hydrolytic and/or oxidative pathways [3,4]. Platinum (Pt) based complexes [cisplatin, (*cis*-diamminedichloro-platinum)] were widely used as drugs for cancer therapy because it inhibits the proliferation of cancer cells through binding with DNA molecules [5,6]. However, most of the Pt (II) complexes possess inherent limitations such as side effects, oxidative stress ionic radius causes the cytotoxicity and it acquired resistance phenomena [7–11]. Therefore the utilization of therapeutic agents with permissible side effects has been extensively explored for the development of chemotherapeutics, which can work effectively against cancer cells.

Recently copper based complexes were alternative potential therapeutic agents when compared to an expensive drug like cisplatin, carboplatin etc., [12,13]. The Cu(II) complexes have awesome interest because of their flexible ligand conformations, thus make the oxidative DNA cleavage [14–21]. The interaction studies of Schiff base metal complexes with DNA/BSA are well known. Serum albumins are the major soluble proteins, which could regulate the pH and osmotic pressure of blood, by organic and inorganic agents [22–24]. BSA has been studied extensively in biology, structural homology with human serum albumin (HSA) [25–29]. Therefore, the interaction studies between the drugs and BSA has an important role in the storage and drug disposition, to understand the action mechanism, pharmacokinetics as well as the toxicity of drugs.

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Guanidine and N,N-heterocyclic ligands based Cu(II) complexes were also studied in the cleavage of plasmid pBR322 DNA, through oxidative pathway [17]. Recently Cu(II) complexes with thiosemicarbazones derivatives are reported and these complexes have shown good activity against human lung and breast cancer cell lines with non-toxic nature for normal keratinocyte cells [30]. The salicylaldehyde derived 2,4-diiodo-6-((2-phenylaminoethylimino)methyl)phenol Schiff base complexes were performed and the mechanical aspects were studied in HS-DNA and plasmid pUC19 DNA [31]. The dipyridylamine derived ligands with an anthracene moiety in presence of divalent metal ions Co(II), Cu(II), Ni(II), Zn(II) and Cd(II) were used for the DNA cleavage in the presence of hydrogen peroxide and dioxygen. Particularly the Cu(II) and Co(II) complexes were good in DNA cleavage in comparison with Cd(II), Ni(II) and Zn(II) complexes. Here active oxygen radicals such as $^{\cdot}OH$ and $O_2^{-\cdot}$ play a crucial role in the DNA cleavage studies and these radical ions were active in the presence of Cu (II) complexes, it can cleave the double-stranded CT DNA [19].

The studies on acyclic piperazine based Cu(II) complexes have been extensively implemented for various biological applications. In particular, piperazine containing Mannich base metal complexes have shown anti-anginals, anti-cancer, anti-tuberculosis, anthelmintic action, hypolipidemic and flavouring activity [31,32]. However, many intensive studies on DNA/BSA binding and cleavage using acyclic piperazine Cu(II) complexes has not been well explored in all respect. Therefore our aims in the present work are to synthesis acyclic mono piperazine Cu(II) complexes for DNA/BSA studies.

In continuation of our previous work [33,34], herein we have extended our study and synthesized multidentate copper complexes (**1–5**) for DNA/BSA studies. These complexes have been employed for DNA binding as well as cleavage studies using plasmid DNA. Furthermore, the reactivity towards protein BSA of acyclic Cu(II) complexes has been carried out. Furthermore, the molecular docking studies with DNA and BSA have also been carried out.

2. Experimental

2.1. Synthesis of 2-hydroxy-5-methyl-3-[(4-phenylpiperazine-1-yl)methyl] benzaldehyde

A flask charged with N-phenylpiperazine, paraformaldehyde and 5-methylsalicylaldehyde in methanol medium and was refluxed for 20 h. The obtained methanolic solution was allowed to evaporate which gives colourless solid contains 2-hydroxy-5-methyl-3-[(4-phenylpiperazine-1-yl)methyl]benzaldehyde. The residue obtained was purified by column chromatography over silica gel using ethyl acetate: hexane (1:1) followed by CH_2C1_2:MeOH (9:1) as eluent gets as a yellow solid. The recrystallization from hexane/ether gave as colourless crystals. The FTIR, NMR and ESI mass spectra were provided in the supporting information.

2.2. Synthesis of Cu(II) complexes (1–5)

The precursor complexes denoted as PC, PC-1, PC-2, PC-3, PC-4 and PC-5 for their corresponding [Cu(sal-diamines)(py)](ClO_4), 1,2-diamino ethane, 1,3-diaminopropane, 1,2-diamino benzene, 2-aminobenzylamine, 1,8-diamino naphthalene respectively [33–37]. The precursor complexes with the precursor ligand reacted in the alcoholic solution to achieve the Mannich based ligand complexes. A new series of Mannich based Cu(II) complexes were synthesized by varying the aliphatic and aromatic diamines and synthetic aspects are provided in the Scheme 1. All the complexes were soluble in DMF, DMSO, methanol, ethanol and 1% DMF/50 mM Tris-HCl buffer solution (Scheme 2).

2.2.1. $[CuL^1](ClO_4)$ (1)

Precursor ligand (PL) 2-hydroxy-5-methyl-3-[(4-phenylpiperazine-1-yl)methyl] benzaldehyde (0.31 g, 1 mmol) dissolved in 30 mL methanol and then, PC (precursor complex)-1 (0.405 g, 1 mmol) added to it, the reaction mixture was refluxed for 3 h. The resulting solution was filtered in the hot condition and allowed to room temperature until the dark blue colour solid was obtained. Yield: 0.38 g (62%); dark blue colour solid; Anal. Cal for $C_{28}H_{31}ClCuN_4O_6$: C, 54.37; H, 5.05; N, 9.06; Found: C, 54.29; H, 5.01; N, 9.01%; ESI-MS: displays a peak at *m/z* 518 (calculated *m/z* 518). Selected FT-IR (KBr, ν/cm^{-1}): 1605 (C═N), 1090, 623 (ClO_4). UV–visible in DMF [λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$)]: 584(7 5 0), 372(40000), 273(94000).

2.2.2. $[CuL^2](ClO_4)$ (2)

Cu(II) complex (**2**) was synthesized by the method used as (**1**), PC-2 (0.42 g, 1 mmol) was used instead of PC-1, offered green solid. Yield: 0.43 g (68%); Green solid; Anal. Cal for $C_{29}H_{33}ClCuN_4O_6$: C, 55.06; H, 5.26; N, 8.86; Found: C, 54.97; H, 5.19; N, 8.81%; ESI-MS: displays a peak at *m/z* 532 (calculated *m/z* 532). Selected FT-IR (KBr, ν/cm^{-1}): 1626 (C═N), 1101, 626 (ClO_4). UV–visible in DMF [λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$)]: 603(3 0 0), 379(85000), 276(130000).

2.2.3. $[CuL^3](ClO_4)$ (3)

Brown coloured complex (**3**) was synthesized the same procedure used as (**1**), PC-3 was used instead of PC-1, offered yellow colour solid. Yield: 0.46 g (69%); Yellow solid; Anal. Cal for $C_{32}H_{31}ClCuN_4O_6$: C, 57.66; H, 4.69; N, 8.40; Found: C, 57.63; H, 4.58; N, 8.36%; ESI-MS: displays at *m/z* 566 (calculated *m/z* 566). Selected FT-IR (KBr, ν/cm^{-1}): 1606 (C═N), 1086, 627 (ClO_4). UV–visible in DMF [λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$)]: 605(2 8 9), 380(70000), 279(190000).

2.2.4. $[CuL^4](ClO_4)$ (4)

Cu(II) complex (**4**) was synthesized by the method used as (**1**), PC-4 was used instead of PC-1, offered green colour solid. Yield: 0.48 g (70%); Green colour solid; Anal. Cal for $C_{33}H_{33}ClCuN_4O_6$: C, 58.23; H, 4.89; N, 8.23; Found: C, 58.16; H, 4.81; N, 8.18%; ESI-MS: displays at *m/z* 580 (calculated *m/z* 580).Selected FT-IR (KBr, ν/cm^{-1}): 1622 s (C═N), 1089, 624 (ClO_4) UV–visible in DMF [λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$)]: 611(2 1 0), 379(7800), 278(12800).

2.2.5. $[CuL^5](ClO_4)$ (5)

Cu(II) complex (**5**) was synthesized by the method used as (**1**), PC-5 was used instead of PC-1, offered brown colour solid. Yield: 00.52 g (72%); Brown colour solid; Anal. Cal for $C_{36}H_{33}ClCuN_4O_6$: C, 60.33; H, 4.64; N, 7.82; Found: C, 60.21; H, 4.60; N, 7.76%; ESI-MS: displays a peak at *m/z* 617 (calculated *m/z* 616). Selected FT-IR (KBr, ν/cm^{-1}): 1606 (C═N), 1088, 627 (ClO_4). UV–visible in DMF [λ_{max}/nm ($\varepsilon/M^{-1}\,cm^{-1}$)]: 657(3 0 0), 410(100000), 367(155000), 296(198000).

3. Results and discussion

3.1. FT-IR, electronic spectral and ESI-mass spectral analysis

FT-IR spectra of the complexes (**1–5**) displayed characteristic peaks in the region of 1610–1636 cm^{-1} ascribed to the ν(C═N) stretching vibrations, which confirms the C═N bond formation, and disappearance of the peak around 1690 cm^{-1} characteristic for C═O bond. Furthermore, the perchlorate band at 1090 cm^{-1} and 620 cm^{-1} has not shown any splitting, it might be the presence of uncoordinated perchlorate ion in their crystal lattices. The peaks at around 540 cm^{-1} and 480 cm^{-1} are due to the formation of Cu−O and Cu−N coordinated bonds respectively. From the FTIR spectral analysis, it confirms the formation of Schiff base copper complexes [20]. The electronic spectra of the complexes (**1–5**) were provided in the Fig. S1, from the spectral analysis the complexes (**1–5**) a weak broad absorption band was observed in the region of 560–630 nm, indicates the central metal ion gets distorted to square planar geometry. It has been noticed that the absorption peak position gets red shifted with the increase in chain length