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Exploring the photochemosensitivity by novel cysteine-based mixed ligand complexes

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ABSTRACT

A new series of cysteine-based metal(II) complexes with 2,2′-bipyridine or 1,10-phenanthroline as co-ligand have been prepared and characterized. Their DNA binding and cleavage properties have been studied. The analytical and spectroscopic data of complexes **1**–**18** reveal that the complexes adopt an octahedral geometry around the central metal ion in which the cysteine is coordinated through NS and NN atoms, respectively. Spectroscopic titration and viscosity measurements reveal that the complexes bind to DNA through an intercalative mode. Electrophoresis measurements exhibit that they cleave pBR322 DNA efficiently in the presence of 3-mercaptopropionic acid (MPA), probably *via* hydrolytic mechanism with the involvement of $^{\bullet}OH$. The *in vitro* anticancer activities indicate that the Cu(II) complexes are active against four selected human tumor cell lines. Furthermore, it is remarkable that all the complexes exhibit significant photocytotoxicity against human breast cancer cell lines (MCF-7) with a potency more than the widely used drugs photofrin and cisplatin indicating that they have the potential to act as effective anticancer drugs in a dose-dependent manner.

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1. Introduction

Cancer is a deadly global menace (with total number of global cancer cases in 2008 being 12.6 million; in 2030, this number is expected to increase by +69%). Cancer or malignant neoplasm is a broad group of various diseases, all involving unregulated cell growth, invasion, and metastasis [1]. The current treatment regime for cancer primarily includes surgery and chemotherapy; however, chemotherapy is used as a mainstay due to its ability to cure widespread malignancies or metastatic cancers either alone or in combination with radiotherapy [2]. Nevertheless, the curative effects of the existing chemotherapeutic drugs are not good enough owing to severe health side effects, acquisition of resistance by tumor cells, and cost factors.

Within the world of clinical oncology, the chemoprevention of cancer is perceived to be a failure. One major obstacle is that cancers evolve from numerous tissues (different phenotypes) with multiple etiologies and endless combinations of genetic or epigenetic alterations, and therefore, the one-size-fits-all therapy approach cannot be undertaken. Photodynamic therapy (PDT) drugs are activated by light to achieve spatiotemporally controlled chemotherapeutic action [3]. It provides a means to circumvent the drawbacks of conventional cancer therapies, most importantly through low systemic toxicity, localized action to irradiated areas, and low level of invasiveness [4]. It is now recognized as an alternative and in some cases a superior approach to conventional treatments in dermatology and for endoscopically accessible tumors. These include bladder, gastrointestinal, esophageal, prostate, and gynecological lesions [4,5], in both early- and late-stage head and neck cancers [4,6] and in inoperable early central lung cancers [7]. Therefore, it is imperative for chemists to develop ideal anticancer agents not only with good water solubility and accessible clinical value but also bringing fewer side effects, preferably non-covalently binding.

Inorganic complexes have also been investigated for use in PDT, and transition metal complexes which undergo photoinduced ligand exchange represent one class of potential photochemotherapeutic (PCT) agents that do not require O_2 for activity [8,9]. Following light absorption, these agents can deliver caged ligands that become cytotoxic upon their release [10,11], or the resulting metal photoproduct may preferentially bind biomolecules following photoinduced aquation [12]. Moreover, recently, many research groups have reported the *in vitro* biological potential of novel transition metal complexes and to elucidating the anticancer potential of these complexes with bipyridine (bpy) or phenantholine (phen) heterocyclic ligands [13–16].

Cysteine is known to act as an active site in bio-performance of the enzymes known as cysteine protease. Transition metal–cysteine complexes have considerable biological activities [17] and some of their antitumor properties show promise in therapeutic applications [18]. It is eminent that photoactivated chemotherapy (PACT) provides control over when and where a drug is activated, resulting in a greater specificity of drug action, less side effects, and thus it has remarkable potential

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for the treatment of cancer [19]. An inactive pro-drug is activated in the cell upon irradiation and the specificity of the drug is increased by the minimization of its toxicity in the surrounding healthy tissue [20]. The development of new metal complexes with high cytotoxicity which could be enhanced upon irradiation provides a highly challenging goal in the field of bioinorganic chemistry. Therefore, the reactivity of metal complexes toward DNA is useful in the design and synthesis of metal-based anticancer therapeutics.

In this respect, in our studies on the development of new metallotherapeutics, we have synthesized a series of novel cysteine Schiff bases and their corresponding metal(II) complexes using phen or bpy as co-ligand and assessed their interaction with DNA. The cytotoxicity of the complexes has been assessed using four human cancer cell lines under *in vitro* condition. This serves to highlight the clinical potential of this series of compounds. We hope that the obtained results may contribute to the rational molecular design of DNA targeting reagents with high affinity and specificity as potential antitumor chemotherapeutic agents, as well as elucidate valuable information to understand their specific delivery at the active site of action, besides providing the pharmacological behaviors *in vitro*.

2. Experimental Protocol

The materials and methods for the pharmacological experimental procedures were reported in our previous paper [21]. The powder X-ray diffraction, ESI-Mass and fluorescence spectral methodologies are given in S1 (Supplementary files). The Schiff base ligands, $\mathbf{L^1}$–$\mathbf{L^3}$ (condensation of cysteine and *p*-substituted benzaldehyde, $\mathbf{L^1} = -NO_2$, $\mathbf{L^2} = -H$, and $\mathbf{L^2} = -OCH_3$) and their mixed-ligand (bpy or phen) Cu(II),Co(II), and Zn(II) complexes were prepared by the following procedure.

2.1. Synthesis of Schiff Base Ligands

Cysteine (2.04 g, 0.01 mol) was dissolved in 20 mL of a water–ethanol mixture (1:1) and the solution was stirred to obtain a homogeneous solution. Then, an ethanolic solution of substituted benzaldehyde (0.01 mol) was added to this solution dropwise, and the resultant mixture was refluxed for *ca.* 5 h. A pale yellow-colored solution was obtained, which was reduced to one-third on a water bath. The resultant crystalline product that precipitated was filtered off, washed, and recrystallized with cold methanol and finally dried in *vacuum*. Yield 77–86%.

$\mathbf{L^1}$: Yield: 77%. F.W: 254; m.p: >180 °C; FT-IR (KBr): 1638 (HC = N), 1466 t_{asy}(COO), 1375 t_{sy}(COO), 2739 (—SH) cm^{-1}; ^1H NMR (DMSO-d_6): 8.9 (s, 1 H, CH = N), 7.3–8.0 (m, 5 H, aromatic C), 4.4 (t, 1 H, CH) 11.0 (s, 1 H, COOH), 3.8 (s, 3 H, O—CH_3), 3.0–3.3 (t, 2 H, S—CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 71.9 (CH), 177.5 (COOH), 122.6–147.2 (aromatic C), 162.3 (CH═N), 26.4 (S—CH_2) ppm; MS: $m/z = 254$, λ_{max} in DMSO 42,564, 36,978 cm^{-1}.

$\mathbf{L^2}$: Yield: 81%. F.W: 209; m.p: >180 °C; FT-IR (KBr): 1624 (HC═N), 1460 t_{asy}(COO), 1371 t_{sy}(COO), 2748 (—SH) cm^{-1}; ^1H NMR (DMSO-d_6): 9.1 (s, 1 H, CH═N), 7.4–7.9 (m, 5 H, aromatic C), 4.4 (t, 1 H, CH) 11.0 (s, 1 H, COOH), 3.8 (s, 3 H, O—CH_3), 3.0–3.2 (t, 2 H, S—CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 71.8 (CH), 177.5 (COOH), 122.8–147.0 (aromatic C), 161.7 (CH═N), 26.4 (S-CH_2) ppm; MS: $m/z = 209$, λ_{max} in DMSO 42,424, 36,818 cm^{-1}.

$\mathbf{L^3}$: Yield: 86%. F.W: 239; m.p: >185 °C; FT-IR (KBr): 1616 (HC═N), 1457 t_{asy}(COO), 1368 t_{sy}(COO), 2762 (—SH) cm^{-1}; ^1H NMR (DMSO-d_6): 9.0 (s, 1 H, CH═N), 7.4–8.0 (m, 5 H, aromatic C), 4.3 (t, 1 H, CH) 11.0 (s, 1 H, COOH), 3.8 (s, 3 H, O—CH_3), 3.1–3.3 (t, 2 H, S—CH_2) ppm; ^{13}C NMR (DMSO-d_6): δ = 71.6 (CH), 177.3 (COOH), 122.6–147.2 (aromatic C), 162.4 (CH═N), 55.8 (O—CH_3), 26.3 (S—CH_2) ppm; MS: $m/z = 239$, λ_{max} in DMSO 42,536, 36,783 cm^{-1}.

2.2. Synthesis of Metal Complexes

The complexes were prepared by mixing the appropriate molar quantity of the ligand L^1–L^3 with the metal salts [Cu(II), Co(II), and Zn(II)] using the following procedure: an ethanolic solution of ligand (0.003 mol) was stirred with 5 mL of an ethanolic solution of the anhydrous metal(II) chloride (0.003 mol) for *ca.* 1 h. A methanolic solution (5 mL) of 2,2′-bipyridine or 1,10-phenanthroline (0.006 mol) was added to this mixture, and the stirring was continued for 1 h. The solid product obtained was filtered and washed with ethanol.

$[CuL^1(bpy)_2]Cl$. (**1**) Yield: 78%. F.W: 664; m.p: >219 °C; Anal. Calc. for $C_{30}H_{25}ClCuN_6O_4S$: C, 54.2; H, 3.8; Cu, 9.6; N, 12.6%. Found: C, 54.1; H, 3.6; Cu, 9.4; N, 12.3%. FT-IR (KBr): 1615 (HC═N), 1457 $\upsilon_{asy}(COO^-)$, 1369 $\upsilon_{sy}(COO^-)$; 465 (M − N) 378 (M − S) cm^{-1}; $\Lambda m \times 10^{-3}$ (Ω^{-1} mol^{-1} cm^2) 49.7; μ_{eff} (BM) 1.84; MS: $m/z = 630$ (M + H), λ_{max} in DMSO 31,485, 27,143, 13,671 cm^{-1} ($\varepsilon = 65$ L M^{-1} cm^{-1}).

$[CuL^2(bpy)_2]Cl$. (**2**) Yield: 75%. F.W: 619; m.p: >215 °C; Anal. Calc. for $C_{30}H_{26}ClCuN_5O_2S$: C, 58.2; H, 4.2; Cu, 10.3; N, 11.3%. Found: C, 58.0; H, 4.1; Cu, 10.1; N, 11.1%. FT-IR (KBr): 1619 (HC═N), 1466 $\upsilon_{asy}(COO^-)$, 1375 $\upsilon_{sy}(COO^-)$; 461 (M − N) 382 (M − S) cm^{-1}; $\Lambda m \times 10^{-3}$(Ω^{-1} mol^{-1} cm^2) 50.3; μ_{eff} (BM) 1.83; MS: $m/z = 585$ (M + H), λ_{max} in DMSO 32,825, 27,186, 13,652 cm^{-1} (ε = 68 L M^{-1} cm^{-1}).

$[CuL^3(bpy)_2]Cl$. (**3**) Yield: 73%. F.W: 649; m.p: > 223 °C; Anal. Calc. for $C_{31}H_{28}ClCuN_5O_3S$: C, 57.3; H, 4.3; Cu, 9.8; N, 10.8%. Found: C, 57.1; H, 4.1; Cu, 9.6; N, 10.6%. FT-IR (KBr): 1628 (HC = N), 1459 $\upsilon_{asy}(COO^-)$, 1371 $\upsilon_{sy}(COO^-)$; 455 (M − N) 375 (M − S) cm^{-1}; $\Lambda m \times 10^{-3}$ (Ω^{-1} mol^{-1} cm^2) 48.5; μ_{eff} (BM) 1.82; MS: $m/z = 615$ (M + H), λ_{max} in DMSO 32,457, 27,236, 13,656 cm^{-1} ($\varepsilon = 63$ L M^{-1} cm^{-1}).

$[CoL^1(bpy)_2]Cl$. (**4**) Yield: 75%. F.W: 660; m.p: >219 °C; Anal. Calc. for $C_{30}H_{25}ClCoN_6O_4S$: C, 54.6; H, 3.8; Co, 8.9; N, 12.7%. Found: C, 54.5; H, 3.6; Co, 8.7; N, 12.5%. FT-IR (KBr): 1622 (HC═N), 1462 $\upsilon_{asy}(COO^-)$, 1371 $\upsilon_{sy}(COO^-)$; 471 (M − N) 385 (M − S) cm^{-1}; $\Lambda m \times 10^{-3}$ (Ω^{-1} mol^{-1} cm^2) 53.4; μ_{eff} (BM) 4.86; MS: $m/z = 625$ (M + H), λ_{max} in DMSO 23,045, 17,491, 14,891 cm^{-1} ($\varepsilon = 48$ L M^{-1} cm^{-1}).

$[CoL^2(bpy)_2]Cl$. (**5**) Yield: 72%. F.W: 615; m.p: >210 °C; Anal. Calc. for $C_{30}H_{26}ClCoN_5O_2S$: C, 58.6; H, 4.3; Co, 9.6; N, 11.4%. Found: C, 58.5; H, 4.1; Co, 9.3; N, 11.2%. FT-IR (KBr): 1613 (HC═N), 1459 $\upsilon_{asy}(COO^-)$, 1369 $\upsilon_{sy}(COO^-)$; 480 (M − N) 381 (M − S) cm^{-1}; $\Lambda m \times 10^{-3}$ (Ω^{-1} mol^{-1} cm^2) 54.9; μ_{eff} (BM) 4.82; MS: $m/z = 580$ (M + H), λ_{max} in DMSO 22,715, 17,523, 14,679 cm^{-1} ($\varepsilon = 54$ L M^{-1} cm^{-1}).

$[CoL^3(bpy)_2]Cl$. (**6**) Yield: 76%. F.W: 645; m.p: >219 °C; Anal. Calc. for $C_{31}H_{28}ClCoN_5O_3S$: C, 57.7; H, 4.4; Co, 9.1; N, 10.9%. Found: C, 57.5; H, 4.2; Co, 9.0; N, 10.7%. FT-IR (KBr): 1598 (HC═N), 1455 $\upsilon_{asy}(COO^-)$, 1370 $\upsilon_{sy}(COO^-)$; 473 (M − N) 385 (M − S) cm^{-1}; $\Lambda m \times 10^{-3}$ (Ω^{-1} mol^{-1} cm^2) 53.4; μ_{eff} (BM) 4.85; MS: $m/z = 610$ (M + H), λ_{max} in DMSO 22,753, 17,610, 14,642 cm^{-1} ($\varepsilon = 52$ L M^{-1} cm^{-1}).

$[ZnL^1(bpy)_2]Cl$. (**7**) Yield: 68%. F.W: 666; m.p: >215 °C; Anal. Calc. for $C_{30}H_{25}ClN_6O_4SZn$: C, 54.1; H, 3.8; N, 12.6; Zn, 9.8%. Found: C, 54.0; H, 3.6; N, 12.5; Zn, 9.6%. FT-IR (KBr): 1622 (HC═N), 1462 $\upsilon_{asy}(COO^-)$, 1371 $\upsilon_{sy}(COO^-)$; 472 (M − N) 386 (M − S) cm^{-1}; ^1H NMR (ppm) (DMSO-d_6): 8.6 (s, 1 H, CH═N), 7.6–8.7 (m, 16 H, bpy), 7.5–8.0 (m, 5 H, aromatic C), 4.3 (t, 1 H, CH) 10.8 (s, 1 H, COOH), 3.0–3.2 (t, 2 H, S—CH_2); ^{13}C NMR (ppm) (DMSO-d_6): 71.7 (CH), 177.3 (COOH), 124.6–148.2 (aromatic C), 120.6–146.1 (bpy), 158.3 (CH═N), 26.4 (S—CH_2); $\Lambda m \times 10^{-3}$(Ω^{-1} mol^{-1} cm^2) 55.4, MS: $m/z = 633$ (M+).

$[ZnL^2(bpy)_2]Cl$. (**8**) Yield: 68%. F.W: 621; m.p: >210 °C; Anal. Calc. for $C_{30}H_{26}ClN_5O_2SZn$: C, 57.9; H, 4.2; N, 11.3; Zn, 10.5%. Found: C, 57.7; H, 4.0; N, 11.2; Zn, 10.3%. FT-IR (KBr): 1627 (HC═N), 1462 $\upsilon_{asy}(COO^-)$, 1371 $\upsilon_{sy}(COO^-)$; 474 (M − N) 389 (M − S) cm^{-1}; ^1H NMR (ppm) (DMSO-d_6): 8.7 (s, 1 H, CH═N), 7.5–8.7 (m, 16 H, bpy), 7.4–7.8 (m, 5 H, aromatic C), 4.3 (t, 1 H, CH) 10.8 (s, 1 H, COOH), 3.0–3.2 (t, 2 H, S—CH_2); ^{13}C NMR (ppm) (DMSO-d_6): 71.8 (CH), 177.4 (COOH), 124.6–148.3 (aromatic C), 120.6–146.2 (bpy), 159.2 (CH═N), 26.4 (S—CH_2); $\Lambda m \times 10^{-3}$(Ω^{-1} mol^{-1} cm^2) 59.7, MS: $m/z = 588$ (M+).

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