Polyhedron 45 (2012) 49–54

Contents lists available at SciVerse ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Syntheses, structures and DNA cleavage activity of NNO-tridentate Schiff base copper complexes

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ARTICLE INFO

Article history:
Received 5 June 2012
Accepted 8 July 2012
Available online 22 July 2012

Keywords:
Copper complex
Schiff base
NNO-tridentate
DNA photocleavage

ABSTRACT

A series of heteroleptic copper(II) complexes, [Cu(**^{R}AIMP**)(bpy)](ClO_4) (**1**–**7**) and [Cu(**$^{4\text{-OMe}}$QYMP**)(**B**)](ClO_4) (B = bpy (**8**) or phen (**9**)), supported by NNO-tridentate Schiff base ligands (**AIMP** or **QYMP**) have been synthesized and characterized. X-ray crystal structural studies of complexes **1**, **6** and **8**, exhibit that these complexes are penta-coordinated mononuclear with a distorted square pyramidal geometry around the Cu center. Experimental results show that all of these complexes reveal good DNA cleavage activity in the presence of reducing agent 3-mercapto-propionic (MPA). However, in the photoinduced experiments at 365 nm, the activity was observed only at high concentration (200 μM) of the Cu complexes. The 1, 10-phenanthroline coordinated complex, **9**, shows the higher activity towards DNA photocleavage than its analogue complex **8** with the bipyridine base.

1. Introduction

Photodynamic therapy (PDT) has been widely used as an alternative treatment of localized tumors and intravascular diseases due to its fewer side effects as compared to chemotherapy and radiotherapy [1–5]. Psoralan has been used as a clinically drug in PDT for skin cancers and skin diseases upon excitation using UVA at 365 nm [6,7]. Recently, transition metal complexes photocleaving DNA under physiological conditions are interested for their various applications in nucleic acids chemistry [8–17]. Among transition metals, copper is one of the essential trace elements in human tissue and is involved in many important biological activities such as cytochrome c oxidase, superoxide dismutase and etc [18–20]. Many copper complexes have demonstrated great antitumor activity and are considered having relatively lower side effects than platinum-based drugs [21,22]. Most recently, heteroleptic copper(II) complexes associated with a variety pyridine based ligands have shown great reactivity toward photocleavage of DNA [23–29].

Schiff base ligands are among the most versatile and useful ligands and their metal complexes have been widely used as catalysts for many organic reactions such as ring-opening polymerization and oxidation [30–33]. In addition, copper complexes bearing Schiff base have shown good biological activities [23,34,35]. However, no copper complex of NNO-tridentate Schiff base ligands has been isolated to date, and the electronic effect of the substituents on the NNO-tridentate Schiff base derivatives might result in dramatic differences of biological activities. Herein, we report the syntheses, characterization and DNA cleavage activity of novel copper derivatives supported by NNO-tridentate Schiff base ligands.

2. Results and discussion

2.1. Synthesis and crystal structure of copper complexes

A series of NNO-tridentate Schiff base ligands (**^{R}AIMP**-H) (**^{H}AIMP**-H: R = 4-H; **$^{5\text{-NEt2}}$AIMP**-H: R = 5-NEt_2; **$^{4\text{-NO2}}$AIMP**-H: R = 4-NO_2; **$^{6\text{-OMe}}$AIMP**-H: R = 6-OMe; **$^{5\text{-OMe}}$AIMP**-H: R = 5-OMe; **$^{4\text{-OMe}}$AIMP**-H: R = 4-OMe; **^{Naph}AIMP**-H: R = 3,4-naphthalyl) were prepared in high yield from the reaction of N,N-dimethylethane-1,2-diamine with a variety of substituted 2-hydroxy-benzaldehyde, respectively (Scheme 1). Similarly, **$^{4\text{-OMe}}$QYMP**-H was synthesized by the reaction of 2-hydroxy-5-methoxybenzaldehyde with 8-aminoquinoline. All of these NNO-tridentate ligands were characterized by spectroscopic studies as well as microanalyses. For instances, the ^{1}H NMR spectra of **$^{4\text{-OMe}}$AIMP**-H exhibited resonances about δ 8.26 and 3.65 ppm for aldimine proton (N=CH) and the methylene protons of $-NCH_2CH_2$, and signals of methylene (δ = 2.58 ppm) or methyl (δ = 2.30 ppm) protons of $-CH_2CH_2N(CH_3)_2$, indicating the formation of the expected NNO-tridentate

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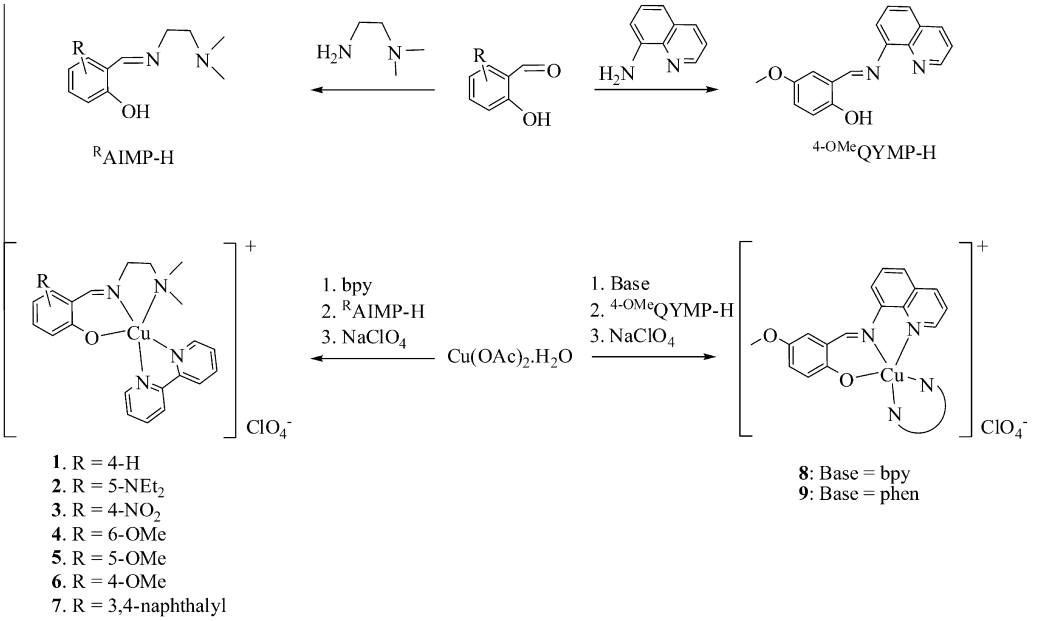
http://dx.doi.org/10.1016/j.poly.2012.07.009



Scheme 1. Synthetic routes of ligands **^{R}AIMP**-H, **$^{4\text{-OMe}}$QYMP**-H and complexes (**1**)–(**9**).

Schiff base ligand. The heteroleptic copper(II) complexes, [Cu(**^{R}AIMP**)(bpy)](ClO_4) (**1**–**7**) were obtained by stepwise reaction of $Cu(OAc)_2{\cdot}H_2O$ with 2,2′-bipyridine (bpy) and **^{R}AIMP**-H in the presence of $NaClO_4$ (1.0 molar equiv.) in high yield ($\geqslant$73%). Additionally, the copper complex, [Cu(**$^{4\text{-OMe}}$QYMP**)(**B**)](ClO_4) (**B** = bpy (**8**) or phen (**9**)) was prepared from the reaction of $Cu(OAc)_2{\cdot}H_2O$ with bpy or 1, 10-phenanthroline (phen) followed by the addition of **$^{4\text{-OMe}}$QYMP**-H and $NaClO_4$. All copper complexes were isolated as crystalline solids and were characterized on the basis of electron paramagnetic resonance (EPR) and cyclic voltammetry (CV) as well as elemental analysis. In EPR spectrum, one single peak in the solid state (Fig. S1) and a quartet splitting in CH_2Cl_2 solution (Fig. S2) at 298 K due to the coupling of copper nuclei (I = 3/2) and electron were observed for all the copper(II) complexes. Electrochemical studies of copper complexes were determined in DMF using 0.1 M tetrabutylammonium perchlorate (TBAP) as buffer solution. A quasi-reversible peak in CV is obtained at 0.1–0.2 V corresponding to the Cu(II)/Cu(I) redox couple as listed in Table S1, and the representative cyclic votammetry of complex **7** was exemplified as shown in Fig. S3. The structures of complexes **1**, **6** and **8** were further verified with X-ray single crystal measurements.

Single crystals of complexes **1**, **6** and **8** suitable for X-ray structural determinations were obtained by slowly cooling their MeOH solutions. Oak Ridge Thermal Ellipsoid Plots (ORTEP) displays selected bond lengths and angles of the molecular structure of **1**, **6** and **8** in Figs. 1–3, respectively. The solid-state structures of complexes **1** and **6** are isostructural, except either a hydrogen (–H) or a methoxy (–OMe) substituent at the 4-position of the phenoxy group. Both display a mononuclear species with a five-coordinated Cu(II) center, containing one six- and two five-membered chelating ring. Each Cu atom is penta-coordinated by two N atoms and one O atom from the tridentate-**AIMP** ligand and the two nitrogen atoms of the bipyridine group, displaying a distorted square pyramidal geometry (τ = 0.13 for **1** and τ = 0.24 for **6**) [36]. Their principal structural features include oxygen atom O(1), nitrogen atom N(1) and N(2) of the tridentate Schiff base and nitrogen atom N(3) of the bipy co-ligand occupying the square base; the O(1)N(1)N(2)N(3) are almost coplanar with mean deviation of 0.0755 Å for **1** and 0.1197 Å for **6**. The distances between the Cu atom and atoms O(1), N(1), N(2) and N(3) are 1.919(2), 1.937(3), 2.099(3) and 2.031(2) Å for **1**, which are all within a normal distance for a Cu–O and Cu–N bond length [23–29,34,35]. It was noted that the apical nitrogen atom N(4) of bipy is coordinated to copper with a Cu(1)–N(4) bond distance of 2.241(2) Å, which is longer than the other Cu–N distances of 1.937(3)–2.099(3) Å in **1**. In comparison, the Cu-containing bond distances of Cu(1)–O(1) = 1.9225(17) Å, Cu(1)–N(1) = 1.954(2) Å, Cu(1)–N(2) = 2.087(2) Å, Cu(1)–N(3) = 2.035(2) Å, Cu(1)–N(4) = 2.232(2) Å in **6** are all similar to those found in complex **1**. The solid structure of **8** also reveals a monomeric Cu(II) complex, penta-coordinated by the NNO-tridentate **$^{4\text{-OMe}}$QYMP** ligand and the NN-bidentate bipy co-ligand with Cu(1)–O(1) = 1.921(2) Å, Cu(1)–N(1) = 1.949(2) Å,

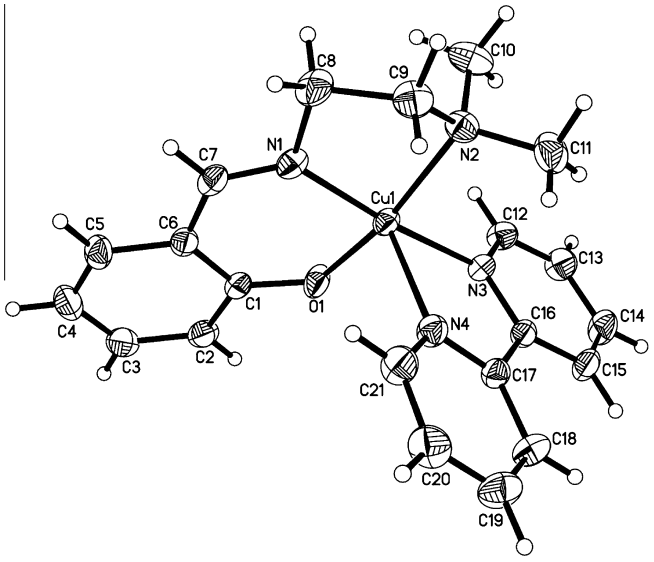


Fig. 1. ORTEP drawing of cationic structure of **1** with probability ellipsoids drawn at level 30%. Selected bond lengths/Å and angles/deg: Cu(1)–O(1) 1.919(2), Cu(1)–N(1) 1.937(3), Cu(1)–N(2) 2.099(3), Cu(1)–N(3) 2.031(2), Cu(1)–N(4) 2.241(2), O(1)–Cu(1)–N(1) 93.40(10), O(1)–Cu(1)–N(2) 165.30(11), O(1)–Cu(1)–N(3) 88.07(9), O(1)–Cu(1)–N(4) 99.16(10), N(1)–Cu(1)–N(2) 83.95(11), N(1)–Cu(1)–N(3) 173.61(9), N(1)–Cu(1)–N(4) 108.80(10), N(2)–Cu(1)–N(3) 93.06(10), N(2)–Cu(1)–N(4) 95.37(11), N(3)–Cu(1)–N(4) 77.05(9).

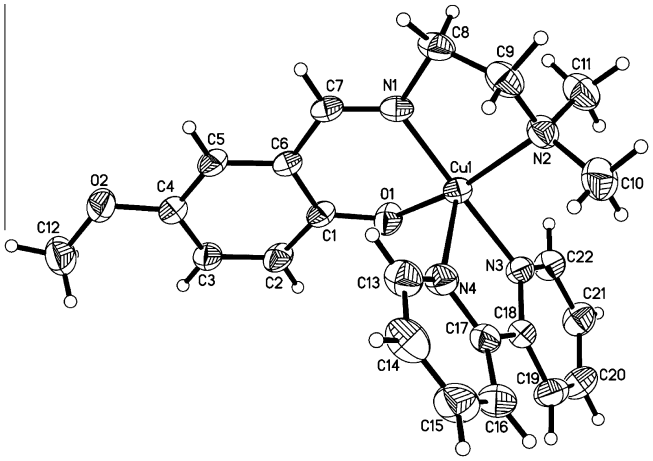


Fig. 2. ORTEP drawing of cationic structure of **6** with probability ellipsoids drawn at level 30%. Selected bond lengths/Å and angles/deg: Cu(1)–O(1) 1.9225(17), Cu(1)–N(1) 1.954(2), Cu(1)–N(2) 2.087(2), Cu(1)–N(3) 2.035(2), Cu(1)–N(4) 2.232(2), O(1)–Cu(1)–N(1) 91.41(8), O(1)–Cu(1)–N(2) 163.27(9), O(1)–Cu(1)–N(3) 88.30(8), O(1)–Cu(1)–N(4) 99.62(9), N(1)–Cu(1)–N(2) 83.57(9), N(1)–Cu(1)–N(3) 177.74(8), N(1)–Cu(1)–N(4) 104.78(8), N(2)–Cu(1)–N(3) 96.09(9), N(2)–Cu(1)–N(4) 97.09(9), N(3)–Cu(1)–N(4) 77.47(8).

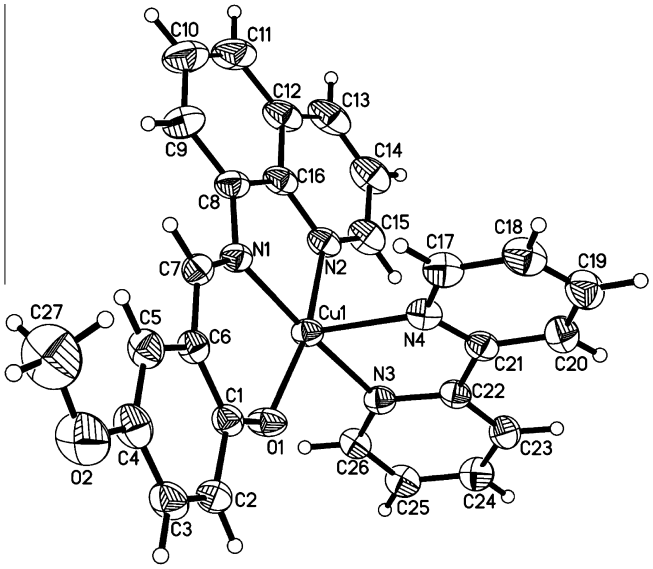


Fig. 3. ORTEP drawing of cationic structure of **8** with probability ellipsoids drawn at level 30%. Selected bond lengths/Å and angles/deg: Cu(1)–O(1) 1.921(2), Cu(1)–N(1) 1.949(2), Cu(1)–N(2) 2.055(2), Cu(1)–N(3) 2.027(2), Cu(1)–N(4) 2.246(3), O(1)–Cu(1)–N(1) 93.03(10), O(1)–Cu(1)–N(2) 167.02(10), O(1)–Cu(1)–N(3) 91.53(9), O(1)–Cu(1)–N(4) 99.45(10), N(1)–Cu(1)–N(2) 82.03(10), N(1)–Cu(1)–N(3) 175.31(9), N(1)–Cu(1)–N(4) 103.22(9), N(2)–Cu(1)–N(3) 93.28(10), N(2)–Cu(1)–N(4) 93.38(9), N(3)–Cu(1)–N(4) 77.06(9).

Cu(1)–N(3) = 2.027(2) Å and Cu(1)–N(4) = 2.246(3) Å, which are similar to the bond distances observed for complexes **1** and **6**. The geometry around Cu center is also distorted from square pyramid ($\tau = 0.14$) with an almost coplanar of O(1)N(1)N(2)N(3) and the Cu(1) atom is ca. 0.0872 Å above the O(1)N(1)N(2)N(3) mean plane. It is worth to note that Cu(1)–N(2) = 2.055(2) Å in **8** are ~0.04 Å shorter than those bond lengths found in **1** and **6**, indicating the better dative bonding between copper atom and aromatic nitrogen atom. Interestingly, the six-membered rings, Cu(1)O(1)C(1)C(6)C(7)N(1), consisting of a Cu center bonded by the oxygen atom O(1) and nitrogen atom N(1) of the Schiff base ligand are nearly coplanar with mean deviation of 0.0422 Å for **1** and 0.0850 Å for **8**.

2.2. Optical properties

UV–Vis experiment was conducted to explore the optical properties of copper complexes containing NNO-tridentate Schiff base ligands. The corresponding absorption wavelengths and molar absorption coefficients (ε) determined in methanol (MeOH) are summarized in Table 1. The major absorption bands of most complexes **1**–**7** are all around at 235–254, 275–285 and 354–405 nm, which can be assigned to intraligand π–π^* transitions of the Schiff base ligand and the bipy co-ligand. Experimental results show that the optical properties of these complexes are dramatically influenced by the electron donating and withdrawing group of the Schiff base ligand. For instance, the long-wavelength absorption for complex **6** with R = −OMe at the 4-position of phenoxy group shows a redshift ($\lambda = 405$ nm), whereas the analogue band of complex **3** with 4-NO_2 on the phenoxy group is blue-shifted to $\lambda = 354$ nm. In comparison, the long-wavelength absorption band of complex **6** is red-shifted by 51 nm relative to that of complex **3**. On the basis of Beer's law ($[M]_0 = 1.0 \times 10^{-5}$ M in MeOH), the ε of complexes **1**–**9** at maxima absorption wavelength (λ_{max}) is in a range of $(1.51–3.33) \times 10^4/M^{-1}\,cm^{-1}$, in which copper complex **7** gives the highest absorption among these complexes. For their visible absorptions (determined by $[M]_0 = 1.0 \times 10^{-3}$ M in MeOH), the absorption wavelengths of a very weak d–d transition were observed in the range from 623 to 646 nm with $\varepsilon < 180\ M^{-1}\,cm^{-1}$. It is worthy of noting that with increasing the conjugate chain of imine part of the Schiff base ligand cause the obvious red-shift to the long-wavelength absorption band (405 nm for **6** versus 483 nm for **8**). No photoluminescence (PL) was observed for all copper complexes.

2.3. DNA cleavage studies

The activity of copper(II) complexes **1**–**9** for cleavage of supercoiled (SC) pUC19 DNA (0.5 μg) in a medium of Tris–HCl/NaCl buffer (50 mM, pH 7.2) with 10% DMF solution has been investigated. Preliminary results indicate that all of complexes **1–9** (40 μM) are inactive at dark condition (Fig. S4). However, they show good DNA cleavage activity in the presence of reducing agent 3-mercaptopropionic acid (MPA) as shown in Fig. 4. In the photo-induced experiment, the cleavage activity was observed only at high concentration (200 μM) of the complexes under irradiation of 365 nm light (Fig. 5). It is worth noting that complex **9** is also active at 633 nm red light as illustrated in Fig. 6, a potential candidate for photodynamic therapy. It was therefore concluded that 1, 10-phenanthroline supported complex **9** is more efficient than 2,2′-bipyridine supported complex **8** towards DNA cleavage in all the experimental conditions. Further studies of their bioactivities are undergoing.

Table 1
UV–Vis spectra of complexes **1–9** in methanol at 25 °C.

Complex	λ, nm (10^{-3} ε, $M^{-1}\,cm^{-1}$)[a]	λ, nm (ε, $M^{-1}\,cm^{-1}$)[b]
1	243(15.1), 275(14.1), 402(2.32)	625(171)
2	236(26.5), 285(19.5), 360(29.1)	628(157)
3	244(21.7), 354(14.5)	646(160)
4	236(15.8), 279(14.8), 386(2.27)	638(133)
5	244(21.9), 285(28.2), 355(6.21)	637(149)
6	254(17.7), 275(17.1), 405(2.97)	630(125)
7	235(33.3), 285(17.1), 389(4.63)	623(166)
8	338(11.9), 483(8.1)	[c]
9	334(10.1), 482(6.3)	[c]

[a] $[M]_0 = 1 \times 10^{-5}$ M.
[b] $[M]_0 = 1 \times 10^{-3}$ M.
[c] Not available.

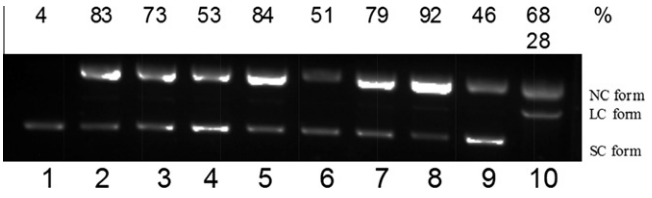


Fig. 4. Cleavage of SC pUC19 DNA (0.5 μg) by complexes **1–9** (40 μM) in the presence of MPA (5 mM) using using 10% DMF 50 mM Tris–HCl/NaCl buffer solution (pH 7.2). Lane 1, DNA control; lane 2, DNA + **1**; lane 3, DNA + **2**; lane 4, DNA + **3**; lane 5, DNA + **4**; lane 6, DNA + **5**; lane 7, DNA + **6**; lane 8, DNA + **7**; lane 9, DNA + **8**; lane 10, DNA + **9**.

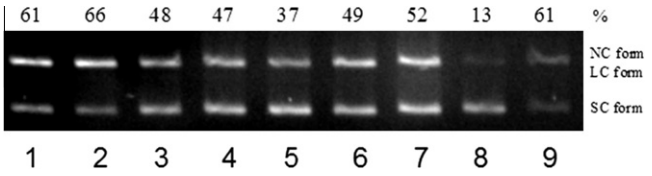


Fig. 5. Cleavage of SC pUC19 DNA (0.5 μg) by **1–9** (200 μM) in 50 mM 10% DMF Tris–HCl/NaCl solution (pH 7.2) under UV light (365 nm, 8 W, 30 min) exposure followed by incubation under dark conditions and electrophoresis. Lane 1, DNA + **1**; lane 2, DNA + **2**; lane 3, DNA + **3**; lane 4, DNA + **4**; lane 5, DNA + **5**; lane 6, DNA + **6**; lane 7, DNA + **7**; lane 8, DNA + **8**; lane 9, DNA + **9**.

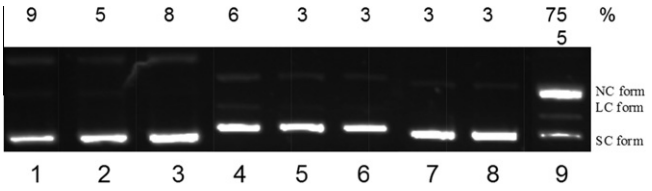


Fig. 6. Cleavage of SC pUC19 DNA (0.5 μg) by **1–9** (40 μM) in 50 mM 10% DMF Tris–HCl/NaCl solution (pH 7.2) under 633 nm (3 W, 3 h) exposure followed by incubation under dark conditions and electrophoresis. Lane 1, DNA + **1**; lane 2, DNA + **2**; lane 3, DNA + **3**; lane 4, DNA + **4**; lane 5, DNA + **5**; lane 6, DNA + **6**; lane 7, DNA + **7**; lane 8, DNA + **8**; lane 9, DNA + **9**.

3. Conclusions

Nine new copper complexes bearing NNO-Schiff base ligands and the bipy or phen co-ligand are synthesized and characterized by EPR, CV and UV–Vis spectroscopic studies as well as X-ray single crystal determinations. Structural characterizations of complexes **1**, **6** and **8** were also discussed, in which the main feature was that the central Cu(II) ion possesses a distorted square pyramidal geometry. Experimental results indicate that the complex **9** with heterocyclic base 1, 10-phenanthroline is more active than **8** with bipyridine base, towards DNA cleavage in the presence of MPA or under irradiation light (365 or 633 nm). In an investigation of NNO-tridentate Schiff base-related Cu complexes for DNA photocleavage, different Cu systems using various bipyridine based ligands as the co-ligands are in progress in our group.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer with chemical shifts given in ppm from the internal TMS or the center line of $CHCl_3$. Microanalyses were performed using a Heraeus CHN-O-RAPID instrument. EPR spectra were determined by Bruker EMX-10: CW EPR at 25 °C using CH_2Cl_2 as solvent. UV–Vis spectra were determined by JASCO U-530 UV–Vis spectrometer at 25 °C using CH_2Cl_2 as solvent. (*E*)-2-((2-(dimethylamino)ethylimino)methyl)phenol (**^{H}AIMP**-H) and (*E*)-1-((2-(dimethyl-aminoethylimino)methyl)-naphthalen-2-ol (**^{Naph}AIMP**-H) were preparated according to the literature method.

4.2. General procedures for tridentate-Schiff base ligands *$^{5\text{-}NEt2}$AIMP-H*∼*$^{4\text{-}OMe}$AIMP-H are followed the procedures for the preparation of ^{H}AIMP-H*

4.2.1. (E)-5-Diethylamino-2-((2-(dimethylamino)ethylimino)methyl)-phenol (*$^{5\text{-}NEt2}$AIMP-H*)

4-Diethyaminosalicylaldehyde (0.97 g, 5.0 mmol) was used. Yield: 1.09 g (83%). ^{1}H NMR ($CDCl_3$, ppm): 8.00 (1H, s, N=C*H*), 6.97 (1H, d, *J* = 8.7 Hz, Ar*H*), 6.13 (1H, dd, *J* = 8.7, 2.7 Hz, Ar*H*), 6.08 (1H, d, *J* = 2.4 Hz, Ar*H*), 3.59 (2H, t, *J* = 6.9 Hz, NCH_2), 3.36 (4H, q, *J* = 7.2, CH_2), 2.57 (2H, t, *J* = 6.6 Hz, NCH_2CH_2), 2.29 (6H, s, N(CH_3)$_2$), 1.18 (6H, t, *J* = 7.2, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 167.43 (*C*=N), 162.96 (*C*OH), 151.69, (*C*N(CH_2)$_2$(CH_3)$_2$), 132.82, 108.14, 102.87, 98.31 (Ar), 59.89 (CC=NCH_2), 54.58 (CC=NCH_2CH_2), 45.58, 45.34, 44.29 ppm (N(CH_3)$_2$, and (CN(CH_2)$_2$(CH_3)$_2$)). *Anal.* Calc. for $C_{15}H_{25}N_3O$: C, 68.40; H, 9.57; N, 15.95%. Found: C, 67.84; H, 8.97; N, 16.03%.

4.2.2. (E)-4-Nitro-2-((2-(dimethylamino)ethylimino)methyl)phenol (*$^{4\text{-}NO2}$AIMP-H*)

2-Hydroxy-5-nitrobenzaldehyde (0.84 g, 5.0 mmol) was used. Yield: 1.03 g (87%). ^{1}H NMR ($CDCl_3$, ppm): 8.36 (1H, s, N=C*H*), 8.24 (1H, d, *J* = 2.7 Hz, Ar*H*), 8.17 (1H, dd, *J* = 9.0, 3.0 Hz, Ar*H*), 6.93 (1H, d, *J* = 9.3 Hz, Ar*H*), 3.75 (2H, t, *J* = 6.3 Hz, NCH_2), 2.66 (2H, t, *J* = 6.3 Hz, NCH_2CH_2), 2.31 (6H, s, N(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, MHz): δ171.90 (*C*=N), 164.91 (*C*OH), 137.57, 129.13, 128.46, 120.12, 115.67 (Ar), 58.75 (CC=NCH_2), 53.84 (CC=NCH_2CH_2), 45.41 ppm (N(CH_3)$_2$). *Anal.* Calc. for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.31; H, 6.08; N, 17.81%. Mp: 110–112 °C.

4.2.3. (E)-6-Methoxy-2-((2-(dimethylamino)ethylimino)methyl)phenol (*$^{6\text{-}OMe}$AIMP-H*)

2-Hydroxy-3-methoxybenzaldehyde (0.76 g, 5.0 mmol) was used. Yield: 0.89 g (80%). ^{1}H NMR ($CDCl_3$, ppm): 8.31(1H, t, *J* = 1.2 Hz, N=C*H*), 6.72–6.89 (3H, m, Ar*H*), 3.86 (3H, s, OCH_3), 3.68 (2H, t, *J* = 6.6 Hz, NCH_2), 2.60 (2H, t, *J* = 6.6 Hz, NCH_2CH_2), 2.27 (6H, s, N(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, MHz): δ165.17 (*C*=N), 152.09, 148.15 (*C*OH and *C*OCH_3), 122.54, 118.01, 117.21, 113.48 (Ar), 59.33 (CC=NCH_2), 56.61 (OCH_3), 55.60 (CC=NCH_2CH_2), 45.31 ppm (N(CH_3)$_2$). *Anal.* Calc. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.39; H, 8.06; N, 12.66%.

4.2.4. (E)-5-Methoxy-2-((2-(dimethylamino)ethylimino)methyl)phenol (*$^{5\text{-}OMe}$AIMP-H*)

2-Hydroxy-4-methoxybenzaldehyde (0.76 g, 5.0 mmol) was used. Yield: 0.90 g (81%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ8.13 (1H, s, N=C*H*), 7.05 (1H, d, *J* = 8.4 Hz, Ar*H*), 6.36 (1H, d, *J* = 2.4 Hz, Ar*H*), 6.33 (1H, dd, *J* = 8.4, 2.7 Hz, Ar*H*) 3.77 (3H, s, OCH_3), 3.61 (2H, t, *J* = 6.9 Hz, NCH_2), 2.58 (2H, t, *J* = 6.9 Hz, NCH_2CH_2), 2.27 (6H, s, N(CH_3)$_2$). ^{13}C NMR ($CDCl_3$, MHz): δ166.47 (*C*=N), 163.97, 163.56.15 (*C*OH and *C*OCH_3), 132.43, 111.87, 105.96, 101.07 (Ar), 59.51 (CC=NCH_2), 55.22 (OCH_3), 54.95 (CC=NCH_2CH_2), 45.39 ppm (N(CH_3)$_2$). *Anal.* Calc. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.41; H, 7.96; N, 12.68%.

4.2.5. (E)-4-Methoxy-2-((2-(dimethylamino)ethylimino)methyl)phenol (*$^{4\text{-}OMe}$AIMP-H*)

2-Hydroxy-5-methoxybenzaldehyde (0.76 g, 5.0 mmol) was used. Yield: 0.87 g (78%). ^{1}H NMR ($CDCl_3$, ppm): δ8.26 (1H, s,

N=C*H*), 6.84–6.85 (2H, m, Ar*H*), 3.71 (3H, s, OCH_3), 3.65 (2H, t, *J* = 6.3 Hz, NCH_2), 2.58 (2H, t, *J* = 6.3 Hz, NCH_2CH_2), 2.30 (6H, s, N(CH_3)$_2$). ^{13}C NMR (CDCl_3, MHz): δ165.06 (*C*=N), 154.95, 151.63 (*C*OH and *C*OCH_3), 118.90, 118.16, 117.33, 114.51 (Ar), 59.54 (CC=NCH_2), 57.41 (OCH_3), 55.51 (CC=NCH_2CH_2), 45.37 ppm (N(CH_3)$_2$). *Anal.* Calc. for $C_{12}H_{18}N_2O$: C, 64.84; H, 8.16; N, 12.60. Found: C, 63.90; H, 8.91; N, 12.32%.

4.3. General procedures for the preparation of [Cu(**^{R}AIMP**)(bpy)](ClO$_4$) (**1**-**7**) and [Cu(**$^{4\text{-OMe}}$QYMP**)(**B**)](ClO$_4$) (**B** = bpy (**8**) or phen (**9**))

4.3.1. [Cu(**^{H}AIMP**)(bpy)](ClO$_4$) (**1**)

A mixture of Cu(OAc)$_2$·H$_2$O (0.40 g, 2.0 mmol), 2,2′-bipyridine (0.35 g, 2.2 mmol) in MeOH (5.0 mL) was stirred at 25 °C for 30 min and (*E*)-2-((2-(dimethylamino)-ethylimino)methyl)phenol (**^{H}AIMP**-H) (0.47 g, 2.4 mmol) in MeOH (2.0 mL) was added and the resulting mixture was stirred for another 1 h. NaClO$_4$ (0.25 g, 2.0 mol) was then added resulting green precipitation after 30 min. The precipitate was filtered and washed with MeOH (5 mL) three times and dried under vacuum. Yield: 0.77 g (75%). *Anal.* Calc. for $C_{21}H_{23}ClCuN_4O_5$: C, 49.41, H, 4.54; N, 10.98. Found: C, 48.96; H, 4.95; N, 10.44%. IR (KBr, cm^{-1}): 1634.2 (C=N). Mp: 218–220 °C.

4.3.2. [Cu(**$^{5\text{-NEt2}}$AIMP**)(bpy)](ClO$_4$) (**2**)

Similar to the methods used for **1** with (E)-5-(diethylamino)-2-(((2-(dimethylamino)-ethyl)imino)methyl)phenol (**$^{5\text{-NEt2}}$AIMP**-H) (0.64 g, 2.4 mmol) was used. Yield: 0.84 g (73%). *Anal.* Calc. for $C_{25}H_{32}ClCuN_5O_5$: C, 51.63; H, 5.55; N, 12.04. Found: C, 51.71; H, 5.39; N, 12.31%. IR (KBr, cm^{-1}): 1598.3 (C=N). Mp: 244–246 °C.

4.3.3. [Cu(**$^{4\text{-NO2}}$AIMP**)(bpy)](ClO$_4$) (**3**)

$^{4\text{-NO2}}$AIMP-H (0.57 g, 2.4 mmol) was used. Yield: 0.89 (80%). *Anal.* Calc. for $C_{21}H_{22}ClCuN_5O_7$: C, 45.41; H, 3.99; N 12.61. Found: C, 45.10; H, 4.20; N, 12.55%. IR (KBr, cm^{-1}): 1641.3 (C=N). Mp: 254–256 °C.

4.3.4. [Cu(**$^{6\text{-OMe}}$AIMP**)(bpy)](ClO$_4$) (**4**)

$^{6\text{-OMe}}$AIMP-H (0.54 g, 2.4 mmol) was used. Yield: 0.84 g (78%). *Anal.* Calc. for $C_{22}H_{25}ClCuN_4O_6$: C, 48.89; H, 4.66; N, 10.37. Found: C, 48.80; H, 4.90; N, 10.63%. IR (KBr, cm^{-1}): 1631.9 (C=N). Mp: 242–244 °C.

4.3.5. [Cu(**$^{5\text{-OMe}}$AIMP**)(bpy)](ClO$_4$) (**5**)

$^{5\text{-OMe}}$AIMP-H (0.54 g, 2.4 mmol) was used. Yield: 0.81 g (75%). *Anal.* Calc. for $C_{22}H_{25}ClCuN_4O_6$: C, 48.89; H, 4.66; N, 10.37. Found: C, 48.66; H, 4.79; N, 9.97%. IR (KBr, cm^{-1}): 1606.0 (C=N).

4.3.6. [Cu(**$^{4\text{-OMe}}$AIMP**)(bpy)](ClO$_4$) (**6**)

$^{4\text{-OMe}}$AIMP-H (0.54 g, 2.4 mmol) was used. Yield: 0.89 g (82%). *Anal.* Calc. for $C_{22}H_{25}ClCuN_4O_6$: C, 48.89; H, 4.66; N, 10.37. Found: C, 48.59; H, 4.90; N, 10.39%. IR (KBr, cm^{-1}): 1632.4 (C=N). Mp: 216–218 °C.

4.3.7. [Cu(**^{Naph}AIMP**)(bpy)](ClO$_4$) (**7**)

^{Naph}AIMP-H (0.59 g, 2.4 mmol) was used. Yield: 0.94 g (84%). *Anal.* Calc. for $C_{25}H_{25}ClCuN_4O_5$: C, 53.57; H, 4.50; N, 10.00. Found: C, 53.48; H, 4.72, N, 10.04%. IR (KBr, cm^{-1}): 1619.8 (C=N). Mp: 240–242 °C.

4.3.8. [Cu(**$^{4\text{-OMe}}$QYMP**)(bipy)](ClO$_4$) (**8**)

$^{4\text{-OMe}}$QYMP-H (0.67 g, 2.4 mmol) was used. Yield: 0.98 g (82%). *Anal.* Calc. for $C_{27}H_{21}ClCuN_4O_6$: C, 54.37, H, 3.55; N, 9.39. Found: C, 53.90; H, 4.60; N, 9.35%. IR (KBr, cm^{-1}): 1602.3 (C=N). Mp: 228–230 °C.

4.3.9. [Cu(**$^{4\text{-OMe}}$QYMP**)(phen)](ClO$_4$) (**9**)

$^{4\text{-OMe}}$QYMP-H (0.67 g, 2.4 mmol) and 1, 10-phenanthroline (0.40 g, 2.2 mmol) were used. Yield: 1.02 g (82%). *Anal.* Calc. for $C_{29}H_{22}ClCuN_4O_6$: C, 56.04, H, 3.57; N, 9.01. Found: C, 56.35; H, 3.99; N, 9.04%. IR (KBr, cm^{-1}): 1603.5 (C=N). Mp: >300 °C.

4.4. DNA cleavage experiments

The photocleavage of (SC) pUC19 DNA by the copper(II) complexes was investigated by the agarose gel electrophoresis method. The reactions were carried out under illuminated conditions using a UV lamp of 365 nm (8 W, Vilber Lourmat). Eppendorf was used for respective UV experiments in a dark room at 25 °C using (SC) pUC19 DNA (1 μL, 0.5 μg) in a 50 mM Tris–HCl buffer (pH 7.2) containing NaCl (50 mM) and the copper complex (1.8 μL in DMF) with constant concentrations. The concentration of the complexes

Table 2
Crystallographic data of complexes **1**, **6** and **8**.

Complex	**1**	**6**	**8**
Empirical formula	$C_{21}H_{23}ClCuN_4O_5$	$C_{22}H_{25}ClCuN_4O_6$	$C_{27}H_{21}ClCuN_4O_6$
Formula weight	510.42	540.45	596.47
T (K)	293(2)	293(2)	293(2)
Crystal system	triclinic	monoclinic	monoclinic
Space group	*P*$\bar{1}$	*P*2(1)/c	*C*2/c
a (Å)	7.4484(5)	15.4296(10)	23.503(2)
b (Å)	12.2457(8)	11.9065(8)	17.1647(16)
c (Å)	12.7337(9)	14.1178(9)	13.9247(14)
α (°)	88.7370(10)	90	90
β (°)	73.1390(10)	113.3030(10)	109.503(2)
γ (°)	84.5000(10)	90	90
V (Å^3)	1106.39(13)	2382.0(3)	5295.2(9)
Z	2	4	8
D_{calc} (Mg/m^3)	1.532	1.507	1.496
μ (MoKα) (mm^{-1})	1.149	1.075	0.975
F(000)	526	1116	2440
Reflections collected	6020	12609	5209
No. of parameters	289	308	352
Independent reflections (R_{int})	4249(0.0133)	4657(0.0215)	5209(0.0000)
R_1 [$I > 2\sigma(I)$]	0.0465	0.0390	0.0455
wR_2 [$I > 2\sigma(I)$]	0.1769	0.1299	0.1370
Goodness-of-fit on F^2	1.006	1.015	1.071

in DMF corresponded to the quantity after dilution of the 1.8 μL stock solution to the 18 μL final volume using the Tris–HCl buffer. Following light exposure, each sample was incubated at 37 °C for 1.0 h and analyzed for the photocleavage products using gel electrophoresis.

4.5. X-ray crystallographic studies

Suitable crystal of **1**, **6** and **8** were mounted on a Bruker AXS SMART 1000 diffractometer. Intensity data were collected in 1350 frames with increasing *w* (width of 0.5° per frame). The absorption correction was based on the symmetry-equivalent reflections using SADABS program [37]. The space group determination was based on a check of the Laue symmetry and systematic absence, and was confirmed by the structure solution. The structures were solved with direct methods using a SHELXTL package [37]. All non-H atoms were located from successive Fourier maps, and hydrogen atoms were treated as a riding model on their parent C atoms. Anisotropic thermal parameters were used for all non-H atoms, and fixed isotropic parameters were used for H-atoms. Drawing of the molecules was done using Oak Ridge Thermal Ellipdoid Plots (ORTEP) [38]. Crystallographic data of complexes **1**, **6** and **8** are summarized in Table 2.

Acknowledgments

We gratefully acknowledge the financial support from the National Science Council, Taiwan (NSC98-2113-M-005-MY3 to C.-C. Lin, NSC97-2314-B384-004 and 99-2314-B-384-002-MY3 to F.-J. Lai, and NSC99-2113-M-033-007-MY2 to B.-T. Ko).

Appendix A. Supplementary data

CCDC 884542–884544 contain the supplementary crystallographic data for complexes **1**, **6** and **8**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.poly.2012.07.009.

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