ISSN 1070-3284, Russian Journal of Coordination Chemistry, 2017, Vol. 43, No. 10, pp. 679–684. © Pleiades Publishing, Ltd., 2017.

Synthesis, Characterization, and Crystal Structure of a Chiral Platinum(II) Complex with 2-(4-Methoxy-Phenyl)-Imidazo[4, 5-f][l,10]-Phenanthroline Binding Interaction with DNA[1]

X. J. Luo, S. L. Wang, J. M. Xu, Y. Yang*, Z. H. Luo, R. J. Liu, and W. J. Liang

Guangxi Key Laboratory of Farm Products Processing (Cultivation Base), Colleges and Universities Key Laboratory for Efficient Use of Agricultural Resources in the Southeast of Guangxi, College of Chemistry and Food Science, Yulin Normal University, Yulin, 537000 P.R. China

**e-mail: yy135175@163.com*

Received September 18, 2016

Abstract—A new platinum(II) complex of $[Pt(Chda)(4\text{-}MOPIP)]^{2+}2Cl^- \cdot H_2O$ (**I**) (Chda = cyclohexanediamine; 4-MOPIP = (4-methoxy-phenyl)-imidazo[4,5-f][l,10]-phenanthroline) has been synthesized by hydrothermal methods and characterized by elemental analysis, IR, single-crystal X-ray diffraction (CIF file CCDC no. 1472980), UV-Vis and fluorescent spectrum. In complex **I**, the platinum adopts a four-coordinated square planar geometry. The DNA-binding interaction has been investigated. The complex can bind to DNA by intercalative mode, presenting the high DNA-binding affinity.

Keywords: platinum complex, DNA-binding, fluorescent

DOI: 10.1134/S1070328417100050

INTRODUCTION

Many small molecules are essential for clinical uses like treatment of cancer, genetic disorders and viral diseases due to their strong ability to bind with nucleic acids and subsequent modification of genetic material [1–3]. As suggested by the biological studies, the anticancer property of small molecule depends on their ability to interact with DNA. Since this can frequently breaks DNA in cancer cells which causes blockage in cells division followed by cell death [4]. In general, small molecules interact with nucleic acids by covalent and noncovalent interaction. Furthermore, the noncovalent interaction can be classified in different modes, such as intercalation, groove binding and electrostatics binding. However, for cancer chemotherapy only DNA intercalative and groove binding compounds are extensively used [5]. On the other hand, From the ligand point of view imidazole is an important moiety which plays a vital role in the activity of many biological systems like iron-heme, vitamin B12, histamine, histidine, biotin, etc. In addition, its derivative can influence to stimulate the central nervous system, inhibit inflammation, combat against neurodegenerative diseases along with the anticancer and antifungal activities [6]. In addition, some experimental and theoretical studies of the DNA binding and related properties of the Ru(II) polypyridyl complexes have been reported [7–9]. These studies have provided significant contributions to understanding the trend in DNA-binding and related properties of the complexes inhibitors for cancer chemotherapy, we have recently designed and synthesized one new chiral platinum(II) complex in our laboratories and examined their interaction with G-quadruplex DNA. The synthetic routes for the preparation of complex **I** $[Pt(Chda)(4\text{-}MOPIP)]^{2+}2Cl^- \cdot H_2O$ (**I**), where Chda = cyclohexanediamine; 4-MOPIP = (4-methoxy-phenyl)-imidazo[4,5-f][l,10]-phenanthroline, are shown in Scheme 1.

EXPERIMENTAL

Materials and physical measurements. All reagents were bought from commercial sources and used without further purification. ^1H NMR spectra were carried out on a Bruker Avance 400 MHz NMR Spectrometer [10]. IR spectra were recorded in the range 4000–400 cm^{-1} on Perkin-Elmer Spectrum One FT/IR spectrometer using a KBr pellet. Elemental analysis (C, H, N) was performed on a Perkin-Elemer 2400II CHN elemental analyzer. UV-Vis absorption titration was performed on a Cary 100 Conc. UV-visible spectrophotometer (Agilent Technologies, Australia). Fluorescence study was performed on a Shimadzu RF-5301/PC spectrofluorometer (Tianmei Technologies, Japan). Calf thymus DNA (ct-DNA, ds26 DNA, Htel and Htel-1) was purchased from Sigma. Buffer (5 mM

[1] The article is published in the original.

tris(hydroxymethyl)aminomethane hydrochloride, 50 mM NaCl, pH 7.35) was used for UV-Vis absorption and FID assays. Assumed a molar absorption is 6600 M^{-1} cm^{-1} (260 nm) [11], the concentration of CT-DNA was spectrophotometrically determined. In the presence of a buffer containing 1% DMSO, the UV-Vis absorption titration of complexes I was performed by using a fixed complex concentration to which increments of the DNA stock solution were added ([DNA]/[complex] ranged from 0 to 10). In DNA interaction studies, the complex was dissolved in DMSO for preparation of stock solution at 2.0×10^{-6} M. Before the UV-Vis absorption spectrum was recorded, Complex-DNA solutions were allowed to incubate for 10 min. FID measurements were performed as described previously [12].

Synthesis (see Scheme) and characterization of compound II were performed in [13].

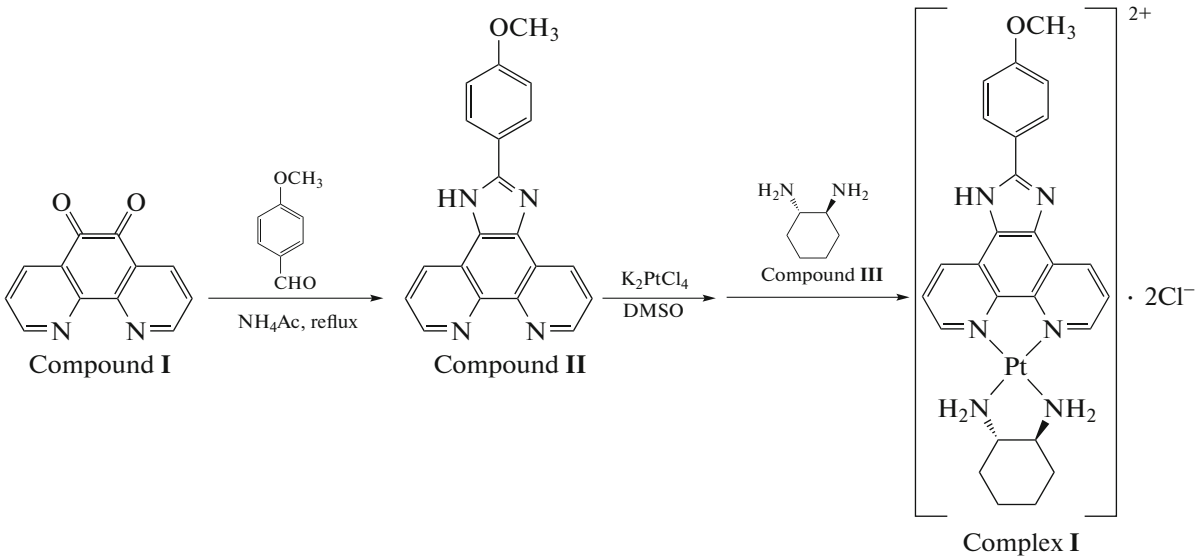
Synthesis of complex I. K_2PtCl_4 (5.0 mmol) was first dissolved in DMSO (5 mL) and heated to near boiling. This hot solution was added to a hot solution of compound 2 (5.0 mmol) in DMSO (5 mL). Finally (1*R*,2*R*)-diaminocyclohexane (5.0 mmol) in 30 mL MeOH–MeCN (20:1) was added to the hot solution, and the mixture was stirred at reflux for 12 h, cooled to room temperature. After filtration, the filtrate was allowed to stand at ambient temperatures for about 5 days, and red rhombic crystals were obtained (yield 24% based on compound **II**), filtered off, washed with distilled water and dried in air.

For $[Pt(Chda)(4\text{-}MOPIP)]^{2+}2Cl^- \cdot H_2O$

Anal. calcd., %:	C, 43.12;	H, 3.90;	N, 11.61.
Found, %:	C, 43.23;	H, 3.93;	N, 11.66.

IR data (KBr; ν, cm^{-1}): 3376, 3226, 2940, 1591, 1461, 1360, 1242, 1175, 1027, 810, 753, 715.

^{1}H NMR (DMSO; 400 MHz; δ, ppm): 9.24 (d., J = 7.9 Hz, 2H), 8.87 (s., 2H), 8.34 (d., J = 8.2 Hz, 2H), 8.05–7.97 (m., 2H), 7.21 (s., 2H), 7.04 (d., J = 8.3 Hz, 2H), 6.52 (s., 2H), 3.84 (s., 3H), 2.13 (d., J = 11.9 Hz, 1H), 1.96 (s., 1H), 1.81 (s., 2H), 1.62 (s., 1H), 1.45 (d., J = 22.8 Hz, 1H), 1.22 (s., 1H).



Scheme 1.

X-ray structure determination. The diffraction data for I were collected on a Bruker Smart Apex CZN diffractometer with graphite-monochromated MoK_α radiation (λ = 0.71073 Å) at 296 K. Absorption correction was applied by Sadabs [14]. The structure was solved by Direct Methods and refined with full-matrix least-squares technique using Shelxtl [15]. All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were positioned with idealized geometry and refined with fixed isotropic displacement parameters. Experimental details for X-ray data collection of complex are presented in Table 1, selected bond lengths and angles for complex **I** are listed in Table 2, while the hydrogen bond lengths and bond angle are listed in Table 3.

Supplementary material for structure **I** has been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 1472980; deposit@ccdc.cam.ac uk or http://www.ccdc.cam.ac.uk).

RESULTS AND DISCUSSION

The structure unit of complex **I** with labeled atoms is shown in Fig. 1. In complex **I**, the platinum(II) center adopts four coordinated square planar geometry and is surrounded by one deprotonated 2-(4-

Table 1. Crystallographic data and refinement details for complex **I**

Parameter	Value
Empirical formula	$C_{26}H_{33}N_6O_4ClPt$
Formula weight	724.12
Crystal system	Triclinic
Space group	$P\overline{1}$
a, Å	7.9337(7)
b, Å	9.8688(10)
c, Å	17.7833(17)
α, deg	85.460(8)
ß, deg	80.005(8)
γ, deg	70.310(9)
V, Å^3	1290.7(2)
Z	2
ρ_{calcd}, g cm^{-3}	1.863
μ, mm^{-1}	5.585
F(000)	716
θ Range for data collection, deg	2.91–25.01
Index ranges (h, k, l)	$-9 \le h \le 9$, $-11 \le k \le 11$, $-19 \le l \le 21$
Reflections measured	8909
Unique reflections (R_{int})	4560 (0.0878)
Observed reflections ($I > 2\sigma(I)$)	4475
Refinement parameters	342
R, wR_2, S	0.0696, 0.1906, 1.326
Largest diff. peak and hole, e/Å^3	2.160 and –2.207

Table 2. Selected bond lengths (Å) and angles (deg) for **I**

Bond	d, Å	Bond	d, Å
Pt(1)–N(1)	2.013(7)	Pt(1)–N(5)	2.042(8)
Pt(1)–N(2)	2.006(8)	Pt(1)–N(6)	2.015(8)
Angle	ω, deg	Angle	ω, deg
N(1)Pt(1)N(5)	178.1(3)	N(2)Pt(1)N(5)	98.6(3)
N(1)Pt(1)N(6)	99.4(3)	N(2)Pt(1)N(6)	178.3(3)
N(2)Pt(1)N(1)	80.7(3)	N(6)Pt(1)N(5)	81.3(3)

methoxy-phenyl)-imidazo[4,5-f]- [1, 10]phenanthrolin ligand and one hexamethylene diamine, in which the N(1) and N(2) atoms are from the bidentate 4-MOPIP and the other N(5) and N(6) atoms are from one (1*R*,2R)-hexamethylene diamine. The Pt(1)–N bond lengths are in the range of 2.006–2.042 Å, which are within the normal range. The whole molecule retains the planar structure, which may favor the intercalation between the neighboring bases of the G4-DNA.

In complex **I**, there exist interesting intermolecular hydrogen bonding interactions. The O–H···N and N–H···O hydrogen bonds are between nitrogen atoms (N(3), N(4) and N(5)) from 2-(4-methoxy-phenyl)-imidazo[4,5-f]- [1, 10]phenanthrolin and the water molecule (O(2) and O(3)) with O···N separations of 2.816(10) and 3.200(13) Å (Fig. 1, Table 3). The hydrogen bonds are involved in chloridions of $[Pt(Chda)(4\text{-}MOPIP)]^{2+}2Cl^- \cdot H_2O$ and water molecules (O(3)) and nitrogen atoms (N(6)) of 2-(4-

Table 3. Geometric parameters of hydrogen bonds for complex **I**

D–H···A	Distance, Å			Angle D–H···A, deg	Symmetry code
	D–H	H···A	D···A		
O(2)–H(2*A*)···N(3)	0.85	1.99	2.816(10)	162	
O(2)–H(2*B*)···N(5)	0.85	2.36	3.200(13)	170	$1-x, 1-y, 1-z$
O(3)-H(3*B*)···Cl(1)	0.82	2.56	3.324(8)	156)	$1-x, 1-y, 1-z$
O(4)-H(4*A*)···(N4)	0.85	2.00	2.853(10)	176	$1+x, y, z$
O(4)-H(4*B*)···O(3)	0.85	1.88	2.730(11)	177	$1+x, y, z$
N(5)-H(5*A*)···O(3)	0.90	2.59	2.985(12)	107	$-x, 2-y, 1-z$
N(5)-H(5B)···O(2)	0.90	2.50	3.200(13)	135	$1-x, 1-y, 1-z$
N(5)-H(5*B*)···O(3)	0.90	2.55	2.985(12)	111	$-x, 2-y, 1-z$
N(6)-H(6*B*)···Cl(1)	0.90	2.40	3.283(8)	166	

methoxy-phenyl)-imidazo[4,5-f]-[1, 10]phenanthrolin. O–H···O hydrogen bonds are between oxygen atoms (O(3) and O(4)). The O(2)–H(2*A*)···N(3) distance of 2.816(10) Å and the O(4)–H(4*A*)···N(4) distance of 2.853(10) correspond to strong interactions (Fig. 1, Table 3). As a consequence, the interchain hydrogen-bonding interactions all help stabilizing the two-dimensional framework.

Absorption titration is the most common method for investigating the interaction of transition metal complexes with DNA. In general, transition metal complexes exhibit hypochromism and red shift in their electronic spectra when bound to DNA. The degree of hypochromism depends on the binding mode and affinity. The DNA sample was sequentially added in aliquots to the complex solutions, and the absorbance spectra were recorded after each addition. Based on previous studies [16], the absorption bands at λ = 385–412 nm are assigned to metal-to-ligand charge transfer (MLCT) and ligand-to-ligand charge transfer (LLCT) transitions. As shown in Fig. 2, the hypochromisms of MLCT bands of complex I for CT-DNA, Htel and Htel-1 were calculated to be approximately 63.64, 43.59 and 47.37%, respectively. The addition of the G rich sequence to the solutions of complex I led to the red shifts of 1, 1 and 1 nm of the band at 290, 290, and 275 nm, respectively. These experimental data indicated that complex I preferred to bind with the G-quadruplex.

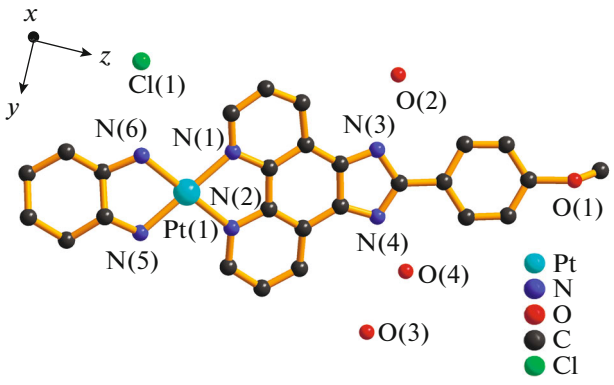


Fig. 1. The structure unit of complex **I**.

When the complex is being added into DNA solution, it is probably penetrated into adenine base stacks in DNA helix, causing the changes of base hydrophobic interaction and van der Waals forces and affecting the stability of DNA conformation and unwinding the double-helical structure of DNA. It can be considered that interaction of the complexes with the DNA base pairs may destroy DNA helix, stimulate DNA cleavage and increase UV-Vis absorption of purine and pyrimidine bases and then hypochromic effect occurs [17]. According to [18], the intercalation of complexes into DNA base pairs is accompanied by bathochromism and hypochromism, while groove binding or electrostatic interaction shows no (or minor) change in the UV-Vis absorption spectra. In conclusion, complexes I may bind to CT-DNA, Htel and Htel-1 via an intercalative mode.

The intrinsic binding constant (K_b) of complex **I** with DNA by UV-Vis absorption spectral analysis was calculated by the equation [19]:

$$[DNA]/(\varepsilon_a - \varepsilon_f) = [DNA]/(\varepsilon_b - \varepsilon_f) + 1/[K_b(\varepsilon_b - \varepsilon_f)],$$

where [DNA] is the concentration of DNA per nucleotide in base pairs, ε_a indicates the extinction coefficient of complexes at a given DNA concentration, and ε_f and ε_b represent the extinction coefficients of complexes free in solution, and the complexes fully bound to DNA, respectively, K_b is the equilibrium binding constant. In the plot of $[DNA]/(\varepsilon_a - \varepsilon_f)$ vs. [DNA],

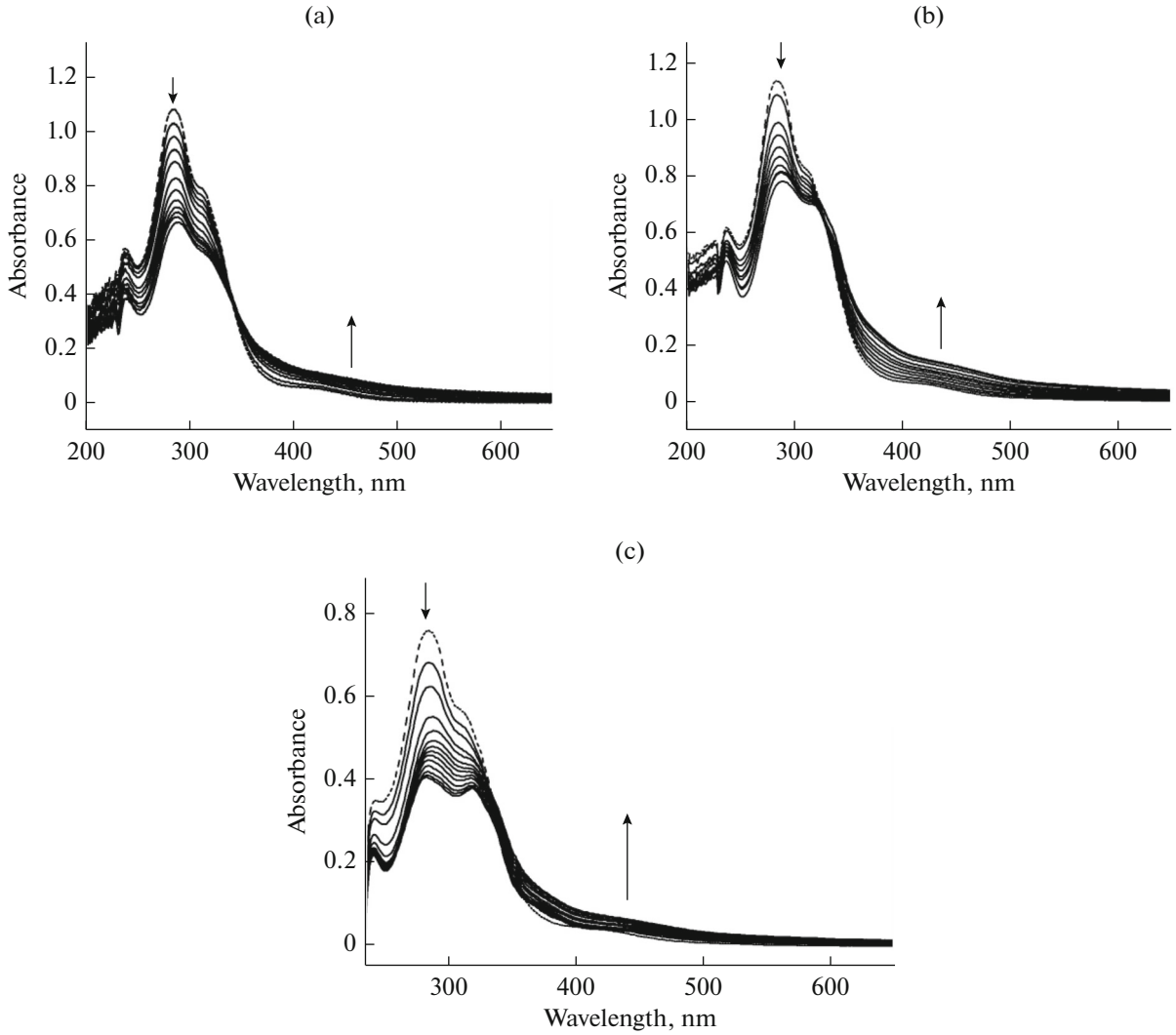


Fig. 2. UV-Vis absorption spectrum of complex **I** with increasing concentrations of ct-DNA (a), Htel (b) and Htel-1 (c) ([complex] = 1.0×10^{-6} mol/L, [DNA]/[complex] ranged from 0 to 10).

K_b, the intrinsic binding constants, can be given by the ratio of the slope to intercept. K_b values, the binding constants of complexes **I** for Htel and Htel-1, are 2.24×10^5 and 1.12×10^6 M^{-1}, respectively.

As the primary pharmacological target of many antitumour drugs, DNA and DNA binding activities of metal complexes provide important insight for the development of effective metal-based chemotherapeutic drugs. To determine whether the induced apoptosis is mediated through the intrinsic apoptotic pathway, the binding affinities of complexes **I** with G-quadruplex DNA (Htel and Htel-1) compared to double helix DNA (ds26 DNA) were studied using a FID assay (Fig. 3) 12]. As shown in Fig. 3, complexes **I** are approved to be effective G-quadruplex DNA binders (i.e. 0.35 μM < $^{G4}DC_{50}$ < 0.55 μM) [20]. Complex **I** exhibit better binding affinities to ds26 ($^{ds26}DC_{50}$ > 0.37 μM).

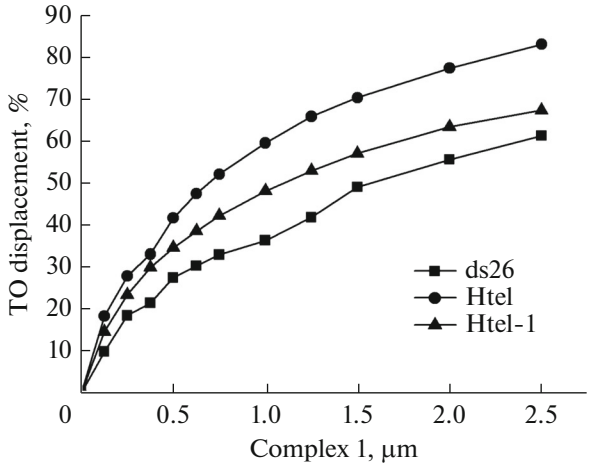


Fig. 3. FID assay for complex **I** bound with different types of DNA, including ds 26, Htel and Htel-1.

ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (nos. 51463023 and 21461028), Guangxi Key Laboratory of Farm Products Processing (Cultivation Base) and Guangxi Colleges and Universities Program of Innovative Research Team and Outstanding Talent.

REFERENCES

1. Denny, W.A., *Anticancer Drug Des.*, 1989, vol. 4, p. 241.
2. Hurley, L.H., *Biochem. Soc. Trans.*, 2001, vol. 29, p. 692.
3. Hurley, L., *Nat. Rev. Cancer*, 2002, vol. 2, p. 188.
4. Hecht, S.M., *J. Nat. Prod.*, 2000, vol. 63, p. 158.
5. Paul, A. and Bhattacharya, S., *Curr. Sci.*, 2012, vol. 102, p. 212.
6. Sundberg, R.J. and Martin, R.B., *Chem. Rev.*, 1974, vol. 74, p. 471.
7. Shi, S., Liu, J., Li, J., et al., *Dalton Trans.*, 2005, p. 2038.
8. Nazeeruddin, M.K., Zakeeruddin, S.M., Humphry-Baker, R., et al., *Coord. Chem. Rev.*, 2000, vol. 208, p. 213.
9. Ciofini, I., Laine, P.P., Bedioui, F., et al., *J. Am. Chem. Soc.*, 2004, vol. 126, p. 10763.
10. Li, X., Peng, Y., Ren, J., et al., *Proc. Natl. Acad. Sci. USA*, 2006, vol. 103, p. 19658.
11. Arounaguiry, A. and Bhaskar, M.G., *Inorg. Chem.*, 2000, vol. 39, p. 4256.
12. Monchaud, D., Allain, C., and Teulade-Fichou, M.P., *Bioorg. Med. Chem.* Lett., 2006, vol. 18, p. 4842.
13. Shi, S., Liu, J., Li, J., et al., *Inorg. Biochem.*, 2006, vol. 100, p. 385.
14. Sheldrick, G.M., *SHELXS-97, Program for Crystal Structure Determination*, Göttingen: Univ. of Göttingen, 1997.
15. Sheldrick, G.M., *SHELXS-97, Program for Crystal Structure Refinement*, Göttingen: Univ. of Göttingen, 1997.
16. Tam, A.Y.Y., Lam, W.H., Wong, K.M.C., et al., *Chem. Eur. J.*, 2008, vol. 14, p. 4562.
17. Reichmann, E.M., Rice, S.A., Thomas, C.A., et al., *J. Am. Chem. Soc.*, 1954, vol. 76, p. 3047.
18. Zheng, S.L., Tong, M.L., Fu, R.W., et al., *Inorg. Chem.*, 2001, vol. 40, p. 3562.
19. Wu, S.S., Zhang, Y.F., Du, J.F., et al., *Spectrosc. Spect. Anal.*, 2008, vol. 28, p. 374.
20. Suntharalingam, K., White, A.J.P., and Vilar, R., *Inorg. Chem.*, 2010, vol. 18, p. 8371.