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Crystal structures, DNA-binding studies and antioxidant activities of the Ln(III) complexes with 7-methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone

Qian Wang · Zheng-Yin Yang · Gao-Fei Qi · Dong-Dong Qin

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Abstract The neutral mononuclear Ln(III) complexes (Ln = La, Sm) with 7-methoxychrom-one-3-carbaldehyde-isonicotinoyl hydrazone ligand (L) have been synthesized, characterized and investigated their interactions with calf-thymus DNA. The results show that the binding affinity of the La(III) complex is stronger than that of the Sm(III) complex and that of the ligand (L). Furthermore, the antioxidant activities of the ligand (L) and its Ln(III) complexes (Ln = La, Sm) were studied in detail.

Keywords 7-Methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone · DNA-binding · Antioxidant activity · Rare earth complex

Introduction

Since the intracellular target for a wide range of anticancer and antibiotic drugs is DNA, the binding studies of small molecules with DNA are extremely useful in understanding the drug–DNA interactions, designing new and promising drugs for clinical applications and developing sensitive chemical probes of nucleic acid structure (Dalton et al. 2008; Sun et al. 2008). During the last few decades, identifying small molecules that are capable of binding DNA through intercalation mode has attracted considerable interest (Dhara et al. 2006). Small molecule compounds would potentially be valuable tools in biotechnology, nanotechnology, therapeutic approaches and the study of nucleic acid conformations. A large number of metal complexes are being studied extensively in current researches (Kong et al. 2008; Firdaus et al. 2008).

The lanthanide/small molecule complexes to address DNA/RNA by non-covalent binding have long been an important area in the development of new reagents for biotechnology and medicine (Marinic et al. 2006; Kumar and Arunachalam 2007). Especially, DNA-binding affinities of metal complexes with chromone derivatives have attracted much attention (Selim et al. 2007; Melidou et al. 2005). Molecules containing the chromone moiety have a wide range of biological activities including tyrosine and protein kinase C inhibitors, antifungal, antiallergenic, antiviral, antitublin, antihypertensive and anticancer agents (Walenzyk et al. 2005). It has been reported that they could exert multiple biological effects, including DNA-bindings (Bi et al. 2006), antioxidants and free radical-scavenging abilities (Bors and Saran 1987; Negre-Salvayre and Salvayre 1992). In the aspect of application in free radical-scavenging, their antiradical property is excellently directed toward hydroxyl radical ($^{\bullet}$OH) (Husain et al. 1987) and superoxide

Q. Wang · Z.-Y. Yang (✉) · G.-F. Qi · D.-D. Qin
College of Chemistry and Chemical Engineering and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, 730000 Lanzhou, People's Republic of China
e-mail: yangzy@lzu.edu.cn; wang_q07@lzu.cn

radical ($O_2^{\bullet -}$) (Robak and Gryglewski 1988; Chen et al. 1990) which are highly reactive species implicated in the initiation of lipid peroxidation.

In our previous work, the lanthanide complexes derived from 6-hydroxy-3-carbaldehyde chromone Schiff base have been reported and all the complexes can strongly interact with DNA through intercalation mode (Wang et al. 2007; Wang and Yang 2008). It is well known that the different substitute and its different situation can affect the pharmacological activities and DNA-binding abilities of compound. Of particular interest, a recent epidemiological study provides strong support that the methoxylated chromones have potential cancer preventive properties (Walle 2007). In this regard, as a further research, the Schiff base ligand, 7-methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone (L) and its Ln(III) complexes (Ln = La, Sm) were synthesized and their DNA-binding modes were investigated systematically. In addition, the antioxidant activities of the metal complexes were studied by the hydroxyl radical ($^{\bullet}OH$) and superoxide anion ($O_2^{\bullet -}$). This continuing work on designing new ligands may help us study structure-activity relationship in the DNA-binding abilities and pharmacological activities. And we hope that the research results will have the application in biology and medicine.

Materials and methods

Instrumentation and materials

The metal contents of the complexes were determined by titration with EDTA. Elemental analyses were carried out on an Elemental Vario EL analyzer. IR spectra were obtained in KBr discs on a Therrno Mattson FTIR spectrometer in the 4,000–400 cm^{-1} region. ^1H NMR spectra were recorded on a Bruker Avance Drx 200-MHz spectrometer with TMS as an internal standard. The melting points of the compounds were determined on a Beijing XT4-100x microscopic melting point apparatus. Fluorescence spectra were obtained on a Shimadzu RF-5301 spectrophotometer at room temperature. The UV–visible spectra were recorded on a Perkin-Elmer Lambda-35 UV–vis spectrophotometer. The antioxidant activities were performed in DMF with a 721E spectrophotometer (Shanghai Analytical Instrument factory China).

CT-DNA (Calf thymus DNA), ethidium bromide (EB), NBT (Nitroblue tetrazolium), MET (methionine), and $VitB_2$ (vitamin B_2) were purchased from Sigma Chemical Co. EDTA, Safranin, $BF_3{\cdot}Et_2O$, $POCl_3$, and $Ln(NO_3)_3{\cdot}6H_2O$ (Ln = La, Sm) were produced in China. All the chemicals used were of analytical grade. Tris–HCl buffer, KH_2PO_4–Na_2HPO_4 buffers and EDTA-Fe(II) were prepared with doubly distilled water.

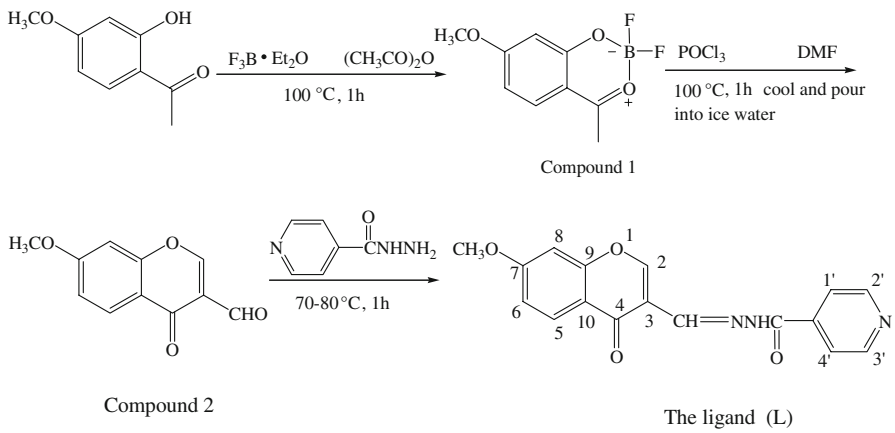
All the experiments involving the interactions of the ligand (L) and its Ln(III) complexes (Ln = La, Sm) with CT-DNA were carried out in doubly distilled water buffer containing 5 mM Tris and 50 mM NaCl, and adjusted to pH = 7.1 with hydrochloric acid. Solution of CT-DNA gave ratios of absorbance at 260 and 280 nm of about 1.8–1.9, indicating that the CT-DNA was sufficiently free of protein (Marmur 1961; Kumar and Asuncion 1993). The CT-DNA concentration per nucleotide was determined spectrophotometrically by employing an extinction coefficient of 6,600 M^{-1} cm^{-1} at 260 nm.

Methods

Synthesis of the ligand

As shown in Scheme 1, Compound 1 and Compound 2 (7-methoxy-3-carbaldehyde chromone) were prepared according to the literature (Hogberg et al. 1984). Synthesis of the ligand (L) was in accordance with the following method: the ethanol solution (25 ml) which contained isoniazid (0.685 g, 5 mmol) was added dropwise to the Compound 2 (1.02 g, 5 mmol) of 10 ml chloroform solution with stirring. After stirring at 70–80°C for 6 h, the light yellow precipitate was collected then recrystallized from anhydrous methanol. Yield: 80%. Mp: 205–207°C. ^1H NMR (DMSO-*d*6, ppm): δ 12.13 (1H, s, –NH), 8.79 (1H, s, 2-H), 8.78 [2H, d, J = 5.8 Hz, pyridine-H(2,3,)], 8.62 (1H, s, CH=N), 8.02 (1H, d, J = 8.9 Hz, H-5), 7.83 [2H, d, J = 5.8 Hz, pyridine-H(1,4,)], 7.23 (1H, d, J = 2.3 Hz, 8-H), 7.12 (1H, dd, J = 2.3 and J = 8.9 Hz, H-6), 3.90 (3H, s, $-CH_3$). The label numbers of H-atoms were shown in Fig. 1. IR (KBr) cm^{-1}: $\nu_{(carbonyl)\ C=O}$: 1,667; $\nu_{(hydrazonic)\ C=O}$: 1,632; $\nu_{C=N}$: 1,612.

Scheme 1 The preparation of the ligand (L)



Synthesis of rare earth complexes

The ligand (L) (1 mmol, 0.32 g) was dissolved in anhydrous ethanol (20 ml) and another ethanol solution (10 ml) containing $La(NO_3)_3{\cdot}6H_2O$ (1 mmol, 0.46 g) was then added dropwise with stirring. After refluxing for 6 h, a large amount of yellow precipitate appeared, and was collected by filtration and dried for 48 h in vacuum. The Sm(III) complex was prepared by the same method.

$[LaL_2(NO_3)_3]$: Yield: 55%. IR (KBr) cm^{-1}: $\nu_{(carbonyl)\ C=O}$: 1,638; $\nu_{(hydrazonic)\ C=O}$: 1,622; $\nu_{C=N}$: 1,582; ν_{NO3}: 1,447, 1,284, 1,023, 780, 733; ν_{La-O}: 616, ν_{La-O}: 537. *Anal*. Calcd for $C_{34}H_{26}N_9O_{17}La$: C, 42.03; H, 2.70; N, 12.98; La, 14.30. Found: C, 42.05; H, 2.702; N, 12.92; La, 14.52.

$[SmL(NO_3)_3(C_2H_5OH)]$: Yield: 50%. IR (KBr) cm^{-1}: $\nu_{(carbonyl)\ C=O}$: 1,639; $\nu_{(hydrazonic)\ C=O}$: 1,626; $\nu_{C=N}$: 1,586; ν_{NO3}: 1,460, 1,287, 1,030, 816, 746; ν_{Sm-O}: 619, ν_{Sm-N}: 539. *Anal*. Calcd for $C_{21}H_{25}N_6O_{15}Sm$: C, 32.34; H, 2.71; N, 11.91; Sm, 21.31. Found: C, 32.58; H, 2.970; N, 11.63; Sm, 21.05.

X-ray crystallography The crystal of the La(III) complex, was obtained from a methanol and ethanol mixture solution at room temperature. Intensity data was collected on a Bruker Smart-1000 CCD diffractometer operating in $\omega/2\theta$ scan mode with graphitemonochromated Mo-K radiation (0.71073 Å). The structure was solved by direct methods. The positions of non-hydrogen atoms were determined from successive Fourier syntheses. The hydrogen atoms were placed in their geometrically calculated positions. The positions and anisotropic thermal parameters of all non-hydrogen atoms were refined on F^2 by full-matrix least-squares techniques with the SHELX-97 program package. Absorption correction was employed using Semi-empirical methods from equivalents. Take the similar way, the crystallography data of the Sm(III) complex were obtained.

Viscosity measurements Viscosity experiments were conducted using an Ubbelodhe viscometer that was immersed in a thermostated water-bath maintained at 25.0°C. Titrations were performed for the ligand (L) and its Ln(III) complexes (Ln = La, Sm) (0.5–3.0 μM), and each compound was introduced into CT-DNA solution (5.0 μM) present in the viscometer. Data were presented as $(\eta/\eta_0)^{1/3}$ versus the ratio of the concentration of the compound and CT-DNA, where η was the viscosity of CT-DNA in the presence of the compound and η_0 was the viscosity of CT-DNA alone (Cohen and Eisenberg 1969; Carter et al. 1989).

Fluorescence spectroscopy To understand the interaction pattern of the compounds with DNA more clearly, fluorescence titration method was used. The example solution of fixed amounts compounds (2 μM) were titrated with increasing amounts of DNA, over a range of DNA concentrations from 0.5 to 3.0 μM. An excitation wavelength 360 nm was used.

EB displacement experiment To further support for the ligand (L) and its Ln(III) complexes (Ln = La, Sm) binding to DNA via intercalation, fluorimetric competitive binding experiment was carried out using ethidium bromide as a probe. A 2 ml solution of

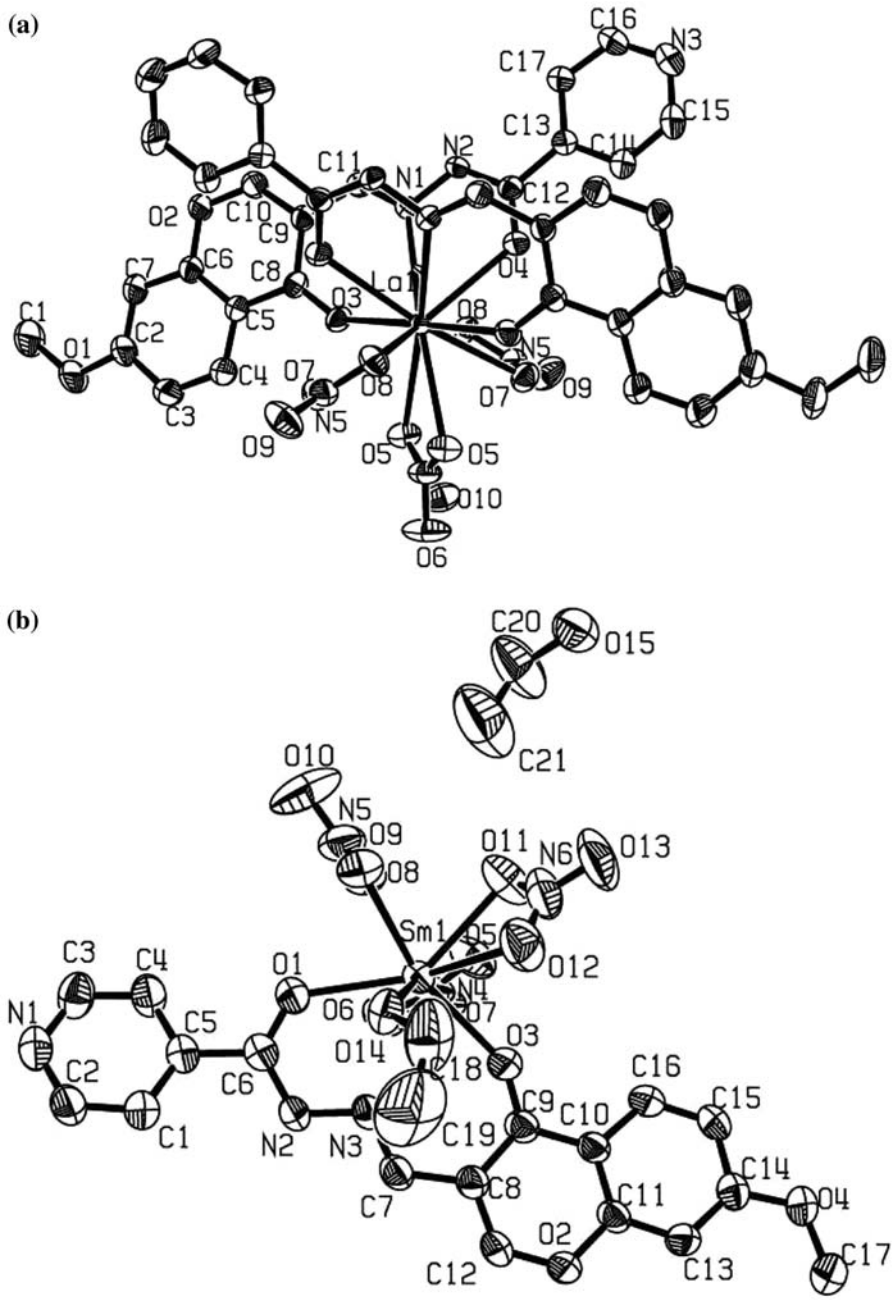


Fig. 1 **a** The structure of the La(III) complex; **b** the structure of the Sm(III) complex

50 μM DNA and 0.4 μM EB was titrated by 10–100 μM compounds (λex = 525 nm, λem = 540.0–650.0 nm, Slit = 10 nm). According to the classical Stern–Volmer equation (Efink and Ghiron 1981):

$$F_0/F = K_q[Q] + 1 \quad (1)$$

where F_0 was the emission intensity in the absence of quencher, F was the emission intensity in the presence of quencher, K_q was the quenching constant, and [Q] was the quencher concentration. Plots of F_0/F versus [Q] appear to be linear.

Electronic absorption spectroscopy In order to affirm quantitatively the affinity of the compounds binding to DNA, the intrinsic binding constants K_b of the ligand (L) and its Ln(III) complexes (Ln = La,

Sm) were obtained by the electronic absorption spectroscopy method. The ligand and the complexes were dissolved in a mixture solvent of 1% methanol and 99% Tris–HCl buffer (5 mM Tris–HCl; 50 mM NaCl, pH 7.1) at concentration 10 μM. Absorption titration experiments were performed with fixed concentration drugs (10 μM) while gradually increasing the concentration of CT-DNA with the range from 5 to 30 μM. The reference solution was the corresponding Tris–HCl buffer solution. While measuring the absorption spectra, equal amount of DNA was added to both the compounds solution and the reference solution to eliminate the absorbance of DNA itself. Each sample solution was scanned in the range 210–450 nm. The binding constant of the compound (K_b) was determined according to the following Eq. (2) (Xu et al. 2004) through a plot of [DNA]/($\varepsilon_A - \varepsilon_F$) versus [DNA]

$$[\mathrm{DNA}]/(\varepsilon_A - \varepsilon_F) = [\mathrm{DNA}]/(\varepsilon_A - \varepsilon_F) + 1/[K_b(\varepsilon_B - \varepsilon_F)] \quad (2)$$

where [DNA] was the concentration of DNA; ε_A, ε_F and ε_B is the apparent extinction coefficient (A_{obsd}/[compound]), the extinction coefficient for free compound and the extinction, respectively, coefficient for compound in the fully bound form. In plots of [DNA]/($\varepsilon_A - \varepsilon_F$) versus [DNA], K_b was given by the ratio of the slope to the intercept.

Scavenger measurements of hydroxyl radical ($^{\bullet}OH$) and superoxide radical ($O_2^{\bullet-}$) The hydroxyl radical ($^{\bullet}OH$) in aqueous media was generated by the Fenton system (Winterbourn 1981). The tested compound was prepared with DMF (*N*,*N*-dimethylformamide). The 5 ml assay mixture contained the following reagents: safranin (11.4 μM), EDTA-Fe(II) (40 μM), H_2O_2 (17.6 μM), the tested compound (1.0–8.0 μM) and a phosphate buffer (67 mM, pH = 7.4). The assay mixtures were incubated at 37°C for 30 min in a waterbath. After that, the absorbance was measured at 520 nm. All the tests were done triplicately and expressed as the mean and (±) standard deviation (SD). A_i was the absorbance in the presence of the tested compound; A_0 was the absorbance in the absence of the tested compound; A_c was the absorbance in the absence of the tested compound, EDTA-Fe(II), H_2O_2. The suppression ratio (η_a) was calculated on the basis of $(A_i - A_0)/(A_c - A_0) \times 100\%$.

The superoxide radical ($O_2^{\bullet-}$) was generated in vitro by the system of MET/VitB_2/NBT and determined spectrophotometrically by nitroblue tetrazolium (NBT) photoreduction method as described elsewhere (Winterbourn 1979; Sharma et al. 2005). The amount of $O_2^{\bullet-}$ and suppression ratio for $O_2^{\bullet-}$ can be calculated by measuring the absorbance at 560 nm. The solutions of VitB_2 and NBT were prepared under the condition of avoiding light. The tested compounds were dissolved in DMF. The assay mixture, in a total volume of 5 ml, was containing MET (10 mM), NBT (46 μM), VitB_2 (3.3 μM), the tested compound (1.0–8.0 μM) and a phosphate buffer (67 mM, pH = 7.8). After illuminating with a fluorescent lamp at 30°C for 10 min, the absorbance of the samples (A_i) was measured at 560 nm. The sample without the tested compound was used as control and its absorbance was taken as A_0. All experimental results were expressed as the mean and (±) standard deviation (SD) of triplicate determinations. The suppression ratio for $O_2^{\bullet-}$ was calculated from the following expression. The suppression ratio $\eta_a = (A_0 - A_i)/A_0 \times 100\%$.

Results and discussion

The complexes were prepared by direct reaction of the ligand (L) with the appropriate mole ratios of Ln(III) (Ln = La, Sm) nitrate in ethanol. The yields were good to moderate. The complexes were stable to air, and soluble in methanol, DMF (*N*,*N*-dimethylformamide) and DMSO (dimethylsulfoxide); slightly soluble in ethanol, acetone, acetonitrile, THF (tetrahydrofuran) and water; insoluble in benzene, ethyl acetate. The elemental analyses showed that formula of the complexes in powder conform to $[LaL_2(NO_3)_3]$ and $[SmL(NO_3)_3(C_2H_5OH)]$. However, according to the single-crystal X-ray analysis, the single-crystal structures of La(III) complex and Sm(III) complex were $[LaL_2(NO_3)_3]\cdot 2H_2O$ and $[SmL(NO_3)_3(C_2H_5OH)]\cdot C_2H_5OH$, respectively.

IR spectra

Since the characteristic absorption peaks of the La(III) complex and the Sm(III) complex were very similar, the structure of the La(III) complex and the Sm(III)

complex could be talked about in the same way. Take the Sm(III) complex for example, $\nu_{(carbonyl)\ C=O}$, $\nu_{(hydrazonic)\ C=O}$, $\nu_{C=N}$ vibrations of the Sm(III) complex were at 1,639, 1,626 and 1,586 cm^{-1}, respectively, while these peaks of the ligand (L) were at 1,667, 1,632 and 1,612 cm^{-1}, and ν(ligand–complex) was equal to 28, 6 and 26 cm^{-1}. These shifts demonstrated that the above three groups had taken part in coordination to rare earth ions. The absorption bands of the coordinated nitrates were observed at about 1,460 and 1,287 cm^{-1}. The difference between the two peaks was 173 cm^{-1} suggesting that the coordinated nitrate groups in the complexes were bidentate (Nakamoto 1986). In order to make sure the precise structures of the La(III) and Sm(III) complexes, respectively, the crystal structures of the La(III) and Sm(III) complexes were analyzed as follows.

Crystal structure of the complexes

The La(III) complex (formula $C_{34}H_{30}N_9O_{19}La$), crystallized in the monoclinic lattice with a space group C2/c. Each unit cell contained four molecules. The X-ray diffraction data for the La(III) complex were given in Table 1 and the selected bond lengths and angles were summarized in Table 2. The crystal structure in Fig. 1a showed that the composition of the La(III) complex was $[LaL_2(NO_3)_3]\cdot 2H_2O$ (L = 7-methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone). La atom was twelve coordination with two ligand and three nitrate. Each ligand (L) acted as a tridentate ligand, binding to La through the nitrogen atom from –CH=N– group of the Schiff base, oxygen atoms from 7-methoxy-3-carbaldehyde chromone unit and O=C–NH– of the isonicotinylhydrazine side chain. The nitrate anion had proved to be a very useful ligand for the construction of coordination complex. In the crystal structure of the La(III) complex, three nitrate took part in coordination with bidentate type. It was clearly that the carbonyl La(1)–O(4) distance (2.6738(19) Å) was significantly shorter than the hydrazonic La(1)–O(3) distance (2.5036(18) Å), which suggested that the carbonyl bond was stronger than the hydrazonic bond.

On the basis of the single-crystal X-ray analysis, the composition of the Sm(III) complex was $[SmL(NO_3)_3(C_2H_5OH)]\cdot C_2H_5OH$, where L was 7-methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone. The Sm(III) complex (formula $C_{21}H_{25}N_6O_{15}Sm$), crystallized in a triclinic lattice with a space group P-1. Each

Table 1 Crystal data and experimental data

Empirical formula	$C_{34}H_{30}N_9O_{19}La$	$C_{21}H_{25}N_6O_{15}Sm$
Formula weight	1,007.58	751.82
Temperature	296(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	C2/c	P-1
a (Å)	27.816(15)	8.692(4)
b (Å)	9.889(5)	10.873(5)
c (Å)	14.918(7)	16.809(7)
α (°)	90.00	90.743(6)
β (°)	102.677(12)	102.990(6)
γ (°)	90.00	110.883(5)
Volume ($Å^3$)	4,003(3)	1,438.7(11)
Z	4	2
Calculated density (Mg/m^3)	1.672	1.736
Absorption coefficient (mm^{-1})	1.159	2.122
F(000)	2,024	750
θ Range (°)	1.50–25.50	2.02–25.50
Reflections collected/unique	10,076/3,713 [R(int) = 0.0304]	7,569/5,290 [R(int) = 0.0145]
Goodness of-fit on F^2	1.002	1.013
R indices [$I > 2$sigma(I)]	R1 = 0.0250, wR2 = 0.0578	R1 = 0.0272, wR2 = 0.0539
R indices (all data)	R1 = 0.0291, wR2 = 0.0597	R1 = 0.0326, wR2 = 0.0557

Table 2 Selected bond lengths (Å) and angles (°) for $[LaL_2(NO_3)_3]\cdot 2H_2O$ complex

Selected bond	Bond lengths or angles	Selected bond	Bond lengths or angles	Selected bond	Bond lengths or angles
La(1)–O(3)	2.5036(18)	La(1)–O(4)	2.6738(19)	La(1)–O(8)	2.676(2)
La(1)–O(7)	2.713(2)	La(1)–O(5)	2.722(2)	La(1)–N(1)	2.879(2)
O(3)–La(1)–O(3)	178.19(7)	O(3)–La(1)–O(4)	113.99(6)	O(3)–La(1)–O(4)	67.19(6)
O(4)–La(1)–O(4)	106.81(8)	O(3)–La(1)–O(8)	113.03(7)	O(3)–La(1)–O(8)	66.65(7)
O(4)–La(1)–O(8)	124.99(5)	O(8)–La(1)–O(8)	160.86(8)	O(3)–La(1)–O(7)	69.80(6)
O(3)–La(1)–O(7)	109.27(6)	O(4)–La(1)–O(7)	170.28(5)	O(4)–La(1)–O(7)	65.76(6)
O(8)–La(1)–O(7)	47.32(5)	O(8)–La(1)–O(7)	121.17(6)	O(7)–La(1)–O(7)	122.33(8)
O(3)–La(1)–O(5)	67.48(5)	O(3)–La(1)–O5)	110.73(5)	O(5)–La(1)–O(5)	46.93(8)
O(3)–La(1)–N(1)	118.28(5)	O(3)–La(1)–N(1)	63.38(5)	O(4)–La(1)–N(1)	65.03(6)
O(4)–La(1)–N(1)	56.72(5)	O(4)–La(1)–N(1)	56.72(5)	O(8)–La(1)–N(1)	129.50(6)
O(8)–La(1)–N(1)	68.57(6)	O(7)–La(1)–N(1)	121.49(6)	O(7)–La(1)–N(1)	105.24(6)
O(5)–La(1)–N(1)	121.58(6)	O(5)–La(1)–N(1)	165.92(6)	N(12)–La(1)–N(1)	70.99(8)

unit cell contained two molecules. The crystal structure was shown in Fig. 1b. The X-ray diffraction data for the Sm(III) complex were given in Table 1 and the selected bond lengths and angles were summarized in Table 3. In the Sm(III) complex, each Sm atom was deca-coordinated by two O-atoms and one N-atom from one ligand, six O-atoms from three bidentate nitrates and the remaining one O-atom from ethanol molecule. Sm(1)–O(1) hydrazonic distance and Sm(1)–O(3) carbonyl distance was 2.424(2) and 2.358(2) Å, respectively. The Sm–imine distance was 2.740(3) Å, for Sm(1)–N(3). And the three bidentate nitrates were found to be 2.587(3) and 2.483(3) Å for Sm(1)–O(5) and Sm(1)–O(6); 2.477(3) and 2.530(3) Å for Sm(1)–O(8) and Sm(1)–O(9); 2.499(3) and 2.518(3) Å for Sm(1)–O(11) and Sm(1)–O(12). Finally, the ethanol molecule was found at 2.425(2) Å, for Sm(1)–O(14). Comparing the above data, the bond length of Sm(1)–O(3) was significantly shorter than any other bond lengths, which suggested that the coordinated ability of carbonyl bond was the strongest.

Observing the crystal structures of the La(III) and Sm(III) complexes, we found that, in both two complexes, the ligand (L) acted as a tridentate ligand, binding to Ln (Ln = La or Sm) atom through the nitrogen atom from –CH=N– group of the Schiff base, oxygen atoms from 7-methoxy-3-carbaldehyde chromone unit and O=C–NH– of the isonicotinylhydrazine side chain. In other words, the binding sites of the ligand in the two complexes were the same. Nevertheless, the main difference was the number of ligands which participated in coordination. In the La(III) complex, two ligands took part in coordination, while in the Sm(III) complexes there was only one. That was probably due to the different chelation between the ligand (L) and the rare earth metals. In the previous report, the crystal structures of the La(III) and Sm(III) complexes derived from 6-hydroxychromone-3-carbaldehyde benzoyl hydrazone (Wang and Yang 2007) both had the same number (two tridentate ligands) of ligands which participated in coordination and the same binding sites of the ligand.

Viscosity measurement

Because the viscosity of a DNA solution was sensitive to the addition of organic drugs and metal complexes bound by intercalation (Rao et al. 2008), viscosity measurement was considered as one of the most effective means studying the binding mode of complexes to DNA (Zhou et al. 2007). In Fig. 2, the specific viscosity of the DNA sample increased obviously with the addition of the compounds. The phenomenon of viscosity increase was ascribed to the reason that the ligand (L) and its Ln(III) complexes (Ln = La, Sm) could intercalate between adjacent DNA base pairs, causing an extension in the helix, and thus increased the effective length of the DNA (Liu et al. 1993; Shi et al. 2006). Consequently, it can be concluded that the ligand (L) and the La(III) and Sm(III) complexes bind DNA via an intercalation mode.

Table 3 Selected bond lengths (Å) and angles (°) for $[SmL(NO_3)_3(C_2H_5OH)]\cdot C_2H_5OH$ complex

Selected bond	Bond lengths or angles	Selected bond	Bond lengths or angles	Selected bond	Bond lengths or angles
Sm(1)–O(1)	2.424(2)	Sm(1)–O(3)	2.358(2)	Sm(1)–O(14)	2.425(2)
Sm(1)–O(5)	2.587(3)	Sm(1)–O(6)	2.483(3)	Sm(1)–O(8)	2.477(3)
Sm(1)–O(9)	2.530(3)	Sm(1)–O(11)	2.499(3)	Sm(1)–O(12)	2.518(3)
Sm(1)–N(3)	2.740(3)				
O(3)–Sm(1)–O(14)	96.02(9)	O(3)–Sm(1)–O(1)	126.03(8)	O(14)–Sm(1)–O(1)	73.86(8)
O(3)–Sm(1)–O(8)	143.82(10)	O(14)–Sm(1)–O(8)	120.07(10)	O(1)–Sm(1)–O(8)	71.68(9)
O(3)–Sm(1)–O(6)	82.13(10)	O(14)–Sm(1)–O(6)	134.05(9)	O(1)–Sm(1)–O(6)	70.84(9)
O(8)–Sm(1)–O(6)	74.76(10)	O(3)–Sm(1)–O(11)	92.48(11)	O(14)–Sm(1)–O(11)	114.43(10)
O(1)–Sm(1)–O(11)	140.53(11)	O(8)–Sm(1)–O(11)	71.33(11)	O(6)–Sm(1)–O(11)	111.52(10)
O(3)–Sm(1)–O(12)	73.05(11)	O(14)–Sm(1)–O(12)	71.58(10)	O(1)–Sm(1)–O(12)	142.15(10)
O(8)–Sm(1)–O(12)	113.80(11)	O(6)–Sm(1)–O(12)	146.76(10)	O(11)–Sm(1)–O(12)	49.59(11)
O(3)–Sm(1)–O(9)	156.23(9)	O(14)–Sm(1)–O(9)	72.94(10)	O(1)–Sm(1)–O(9)	72.05(9)
O(8)–Sm(1)–O(9)	50.48(9)	O(6)–Sm(1)–O(9)	120.83(9)	O(11)–Sm(1)–O(9)	74.09(11)
O(12)–Sm(1)–O(9)	83.40(10)	O(11)–Sm(1)–O(5)	63.86(10)	O(8)–Sm(1)–N(3)	126.50(9)
O(3)–Sm(1)–O(5)	72.68(10)	O(12)–Sm(1)–O(5)	101.15(11)	O(6)–Sm(1)–N(3)	67.86(8)
O(14)–Sm(1)–O(5)	168.19(9)	O(9)–Sm(1)–O(5)	116.18(10)	O(11)–Sm(1)–N(3)	158.39(10)
O(1)–Sm(1)–O(5)	115.33(9)	O(3)–Sm(1)–N(3)	65.92(8)	O(12)–Sm(1)–N(3)	118.57(10)
O(8)–Sm(1)–O(5)	71.14(10)	O(14)–Sm(1)–N(3)	69.64(9)	O(9)–Sm(1)–N(3)	125.77(8)
O(6)–Sm(1)–O(5)	49.35(9)	O(1)–Sm(1)–N(3)	60.83(8)	O(5)–Sm(1)–N(3)	107.51(9)

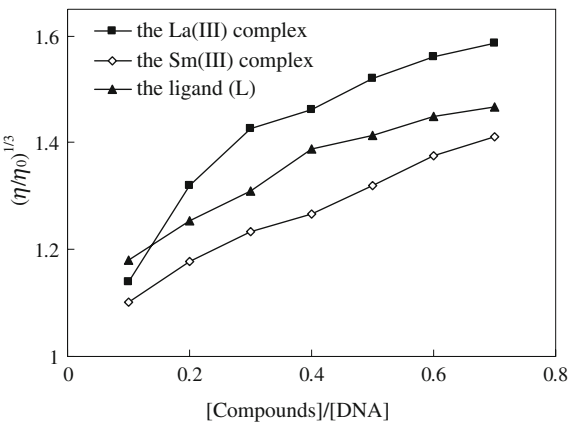


Fig. 2 Effect of increasing amounts of the ligand (L), the La(III) and Sm(III) complexes on the relative viscosity of CT-DNA at 25.0°C

Fluorescence spectra

The fluorescence titration spectra of the ligand (L) and its Ln(III) complexes (Ln = La, Sm) in the absence and presence of CT-DNA were given in Fig. 3. The ligand (L) and its Ln(III) complexes (Ln = La, Sm) could emit luminescence in Tris–HCl buffer with a maximum appearing at 438 nm (ex = 360 nm). As shown in Fig. 3, the enhancement of emission intensities of the ligand (L) and its Ln(III) complexes (Ln = La, Sm) was observed with the increasing concentration of the CT-DNA at a [DNA]/[compound] ratio of 1.5, which might be largely due to the reason that the compounds were protected from solvent water molecules by the hydrophobic environment inside the DNA helix, accordingly the accessibility of solvent water molecules to these compounds was reduced. The marked increase in emission intensity of these three compounds was also in accordance with those observed for other intercalators (Wang et al. 2006, 2007; Wang and Yang 2008), so fluorescence titration spectra measurement provided further support that the ligand (L) and its Ln(III) complexes (Ln = La, Sm) can interact with DNA through intercalation mode.

EB displacement experiment

The results obtained from fluorescence titration spectra indicated that the ligand (L), the La(III) and Sm(III) complex could effectively bind to DNA. In order to

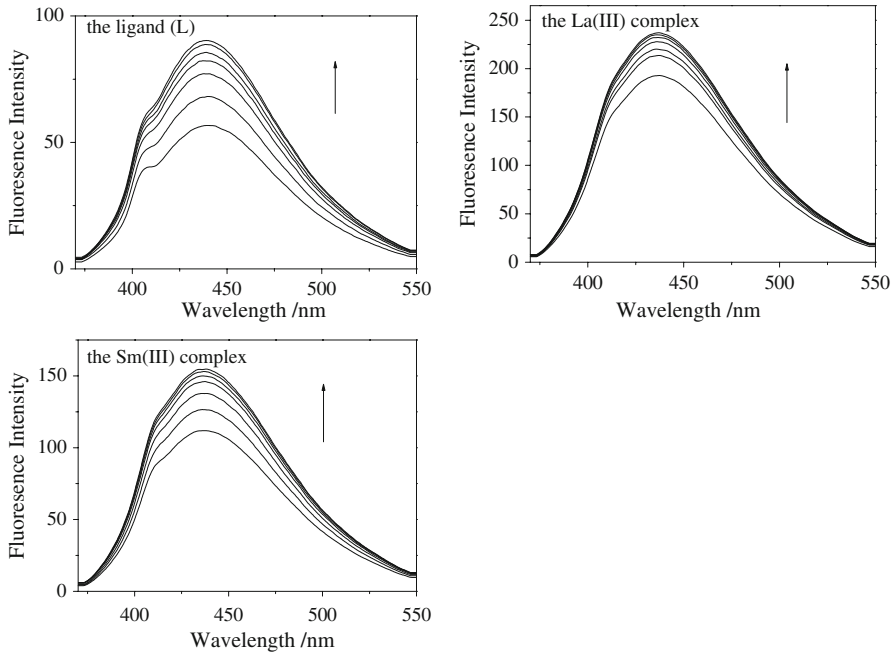


Fig. 3 Emission enhancement spectra of the ligand (L), the La(III) and Sm(III) complexes in the absence and presence of increasing amounts of CT-DNA

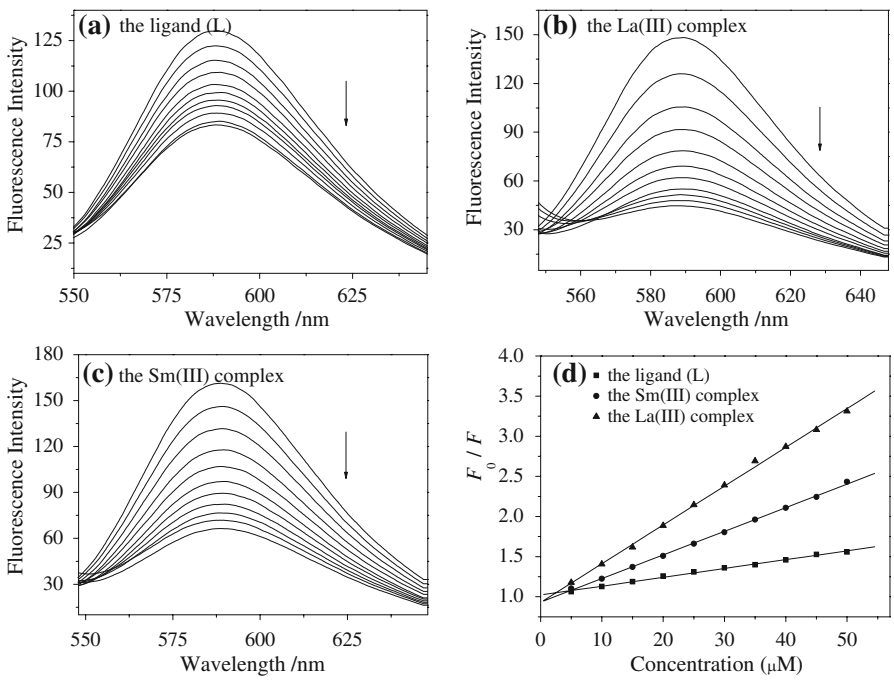


Fig. 4 The emission spectra of DNA–EB system in the presence of **a** the ligand; **b** the La(III) complex; **c** the Sm(III) complex; **d** Plot of F_0/F versus [Q] for the titration of the La(III) complex with DNA–EB

confirm the bind mode and compare their binding affinities, EB displacement experiment was carried out. Ethidium bromide (EB) emits intense fluorescence in the presence of DNA due to its strong intercalation between the adjacent DNA base pairs. This enhanced fluorescence can be quenched by the addition of a second molecule (Suh and Chaires 1995) which can be used to monitor the mode of binding thereby indicating the ability of a compound to prevent intercalation of EB to DNA. The emission spectra of EB bound to DNA in the absence and in the presence of the complex are given in Fig. 4. The addition of the complex to DNA

pretreated with EB causes obvious reduction in emission intensity, indicating that the complex competes with EB in binding to DNA (Bai et al. 2004; Tysoe et al. 1999). In the further investigation, the binding of the compounds in title were evaluated by K_q (the quenching constant) value. Figure 4d showed the mathematic method of evaluating K_q (the quenching constant) value, which was calculated from the plot of F_0/F versus [Q]. The K_q values of the ligand (L), the La(III) and Sm(III) complex were $(1.15 \pm 0.035) \times 10^4$, $(3.27 \pm 0.072) \times 10^4$ and $(1.52 \pm 0.025) \times 10^4$ M^{-1}, respectively. These data suggested that the interaction of the La(III) complexes with CT-DNA is stronger than that of the Sm(III) complex and that of the ligand (L). Compare their K_q values with those of other known DNA-intercalative complexes which possess analogical structure, $[LaL'_2(CH_3OH)(H_2O)(NO_3)]\cdot[NO_3]\cdot H_2O$ 5.28×10^4 M^{-1}; $[SmL'_2(NO_3)_2]\cdot[NO_3]\cdot 0.5H_2O\cdot 2CH_3OH$ 1.37×10^4 M^{-1} (L'_2 = 6-hydroxychromone-3-carbaldehyde benzoyl hydrazone; Wang et al. 2007), the La(III) and Sm(III) complex in our paper have weaker affinities with CT-DNA. This is probably due to the affection of the different substitute. The CH_3O- which has larger steric hindrance than the OH– is not favorable to the tested ligand and its complexes when they intercalated into DNA.

Electronic absorption titration

The electronic absorption spectroscopy is the most common way to investigate the interactions of complexes with DNA (Barton et al. 1984; Belicchi-Ferrari et al. 2008). The complex binding to DNA through intercalation usually results in hypochromism and bathchromism, due to the intercalation mode involving a strong π–π stacking interaction between an aromatic chromophore and the base pairs of DNA. It seems to be generally accepted that the extent of the hypochromism in the UV–visible band is consistent with the strength of intercalative interaction (Psomas 2008). In the presence of CT-DNA, the absorption bands of the La(III) complex and the Sm(III) complex at about 300 nm exhibited obvious hypochromism of about 31.39 and 30.67%, respectively, and the bathochromism were both 7 nm. The ligand (L) at 302 nm exhibited hypochromism of about 19.59%. The electronic absorption spectra of the ligand (L) and its Ln(III) complexes (Ln = La, Sm) in the absence and presence of CT-DNA were shown in Fig. 5a, b and c. The spectral characteristics obviously suggested that the ligand (L) and its Ln(III) complexes (Ln = La, Sm) interact with DNA most likely through an intercalation mode that involved a

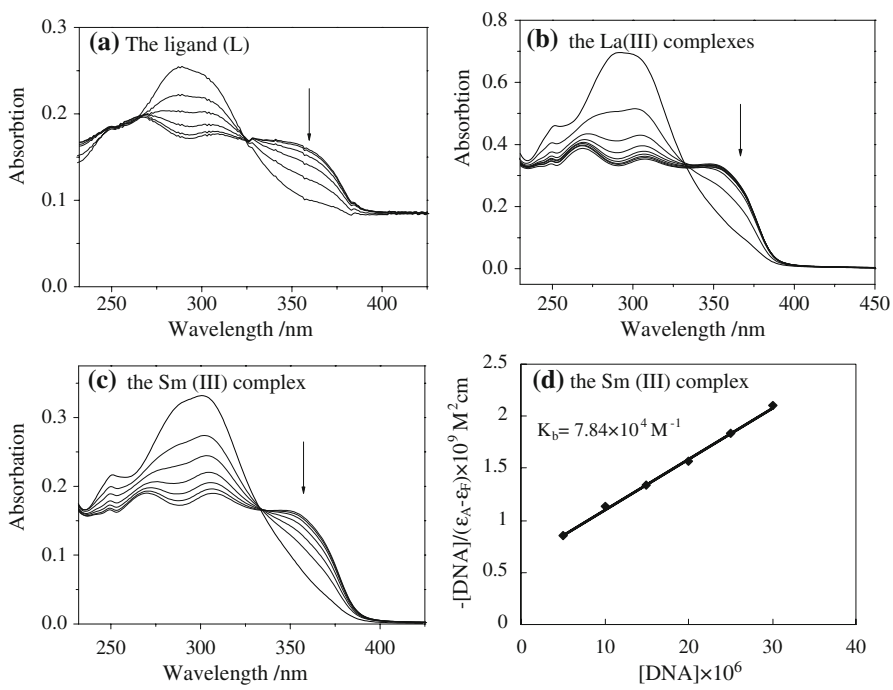


Fig. 5 Electronic absorption spectra of **a** the ligand; **b** the La(III); **c** Sm(III) complexes in the absence and presence of increasing amounts of CT-DNA **d** Plot of [DNA]/($\varepsilon_A - \varepsilon_F$) versus [DNA] for the titration of the Sm(III) complex with CT-DNA

stacking interaction between the aromatic planar structure and the base pairs of DNA. In order to compare their DNA-binding affinities quantitatively, their intrinsic binding constant K_b to DNA was obtained according to Eq. (1) and found to be the La(III) complex, $(1.97 \pm 0.16) \times 10^5\ M^{-1}$; the Sm(III) complex, $(7.84 \pm 0.32) \times 10^4\ M^{-1}$; the ligand (L), $(4.30 \pm 0.46) \times 10^4\ M^{-1}$. As an example of the Sm(III) complex, Fig. 5d showed the mathematic method of evaluating K_b value, which was calculated from the plot of $[DNA]/(\varepsilon_A - \varepsilon_F)$ versus [DNA]. These values were effective arguments that the La(III) complex had the strongest binding affinity. This phenomenon was probably due to different coordination types of the La(III) and the Sm(III) complex. Furthermore, comparing the K_b values of two rare earth complexes with those of other known DNA-intercalative complexes (for instance, $[Ru(bpy)_2MPPIP]^{2+}$, $4.11 \times 10^4\ M^{-1}$; $[Ru(phen)_2MPPIP]^{2+}$, $6.08 \times 10^4\ M^{-1}$ (Tan et al. 2007), $[Ru(bpy)_2(PPIP)]^{2+}$, $4.30 \times 10^4\ M^{-1}$ (Tan et al. 2005), $[Ru(dmb)_2(NMIP)]^{2+}$, $5.46 \times 10^3\ M^{-1}$; $[Ru(bpy)_2(NMIP)]^{2+}$, $1.15 \times 10^4\ M^{-1}$ (Tan and Chao 2007), $[Co(en)_2PIP]^{3+}$, $5.34 \times 10^3\ M^{-1}$; $[Co(en)_2IP]^{3+}$, $4.57 \times 10^3\ M^{-1}$ (Nagababu and Satyanarayana 2007), $[Pd_2(\mu\text{-bzta})_4] \cdot 1.5DMSO$, $1.2 \times 10^3\ M^{-1}$ (Gao et al. 2007), it was obviously that the values of the La(III) and Sm(III) complexes were higher. The test results met our expectation, since the complexes in title possessed a greater planar area (supported by the crystal structure), which would lead to the compounds penetrating deeper and stacking more strongly. The variation in electronic absorption spectra was strongly indicative of the intercalation of the ligand, the La(III) and Sm(III) complexes with DNA, which was also in accordance with the investigating in the viscosity study, fluorescence titration spectra and EB displacement experiment.

Antioxidant activity

Since the ligand (L) and its two rare earth complexes exhibited good DNA-binding affinity, it was considered worthwhile to study other potential aspects of these compounds such as antibacterial and antioxidant activity. The hydroxyl radical ($^{\bullet}OH$) and superoxide radical ($O_2^{\bullet-}$) were the most reactive products of reactive oxygen species (ROS), which could result in cell membrane disintegration, membrane protein damage, DNA mutation and further initiate or propagate the

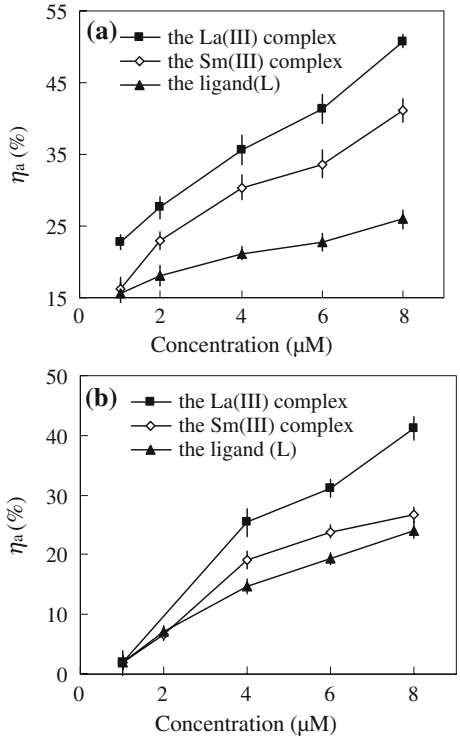


Fig. 6 **a** Effect of the tested compounds on $^{\bullet}OH$; **b** effect of the tested compounds on $O_2^{\bullet-}$

development of many diseases, such as cancer, liver injury and cardiovascular disease (Valentao et al. 2002; Bektasoglu et al. 2006). Consequently, in this paper, the ligand (L) and its Ln(III) complexes (Ln = La, Sm) were studied for its antioxidant activity by comparing their scavenging effect on hydroxyl radical ($^{\bullet}OH$) and superoxide radical ($O_2^{\bullet-}$).

As shown in Fig. 6a and b, the inhibitory effects of the tested compounds on $^{\bullet}OH$ and $O_2^{\bullet-}$ were concentration related and the suppression ratio increased with the increasing of sample concentration in the range of 1.0–8.0 μM. The suppression ratio against $^{\bullet}OH$ varied from valued from about $15.66 \pm 2.23\%$ to $25.95 \pm 1.33\%$ for the ligand (L), $22.74 \pm 0.93\%$ to $50.81 \pm 1.65\%$ for the La(III) complex and $16.29 \pm 2.23\%$ to $41.13 \pm 1.33\%$ for the Sm(III) complex. Mannitol which was employed as a standard since it is known to selectively inhibit the $^{\bullet}OH$ radical (Laskowski et al. 1995; Kostopanagiotou et al. 2006) was almost no scavenging effects at the same tested concentration range. According to previous literature (Qi et al. 2006), the experiment was carried out again at higher concentration. The suppression ratio of mannitol

varied from 24.10 ± 0.95% to 71.79 ± 1.78% at a concentration from 5 to 40 μM. However, the results suggest that the ligand (L) and its La(III) and Sm(III) complexes possess a stronger scavenging activity against hydroxyl radical than Mannitol. The suppression ratio against $O_2^{\bullet-}$ varied from about 1.98 ± 0.00% to 24.11 ± 1.32% for ligand, 1.91 ± 1.22% to 1.92 ± 2.12% to 41.15 ± 2.00% for the La(III) complex and 26.67 ± 1.25% for Sm(III) complex. The results show that the abilities against superoxide radical of these three compounds were significantly higher than that of the previous reported natural products (Fiorentino et al. 2006). It can be seen clearly that the La(III) complex was the most efficient scavenger against $^{\bullet}OH$ and $O_2^{\bullet-}$, and the suppression ration took the order of the La(III) complex > the Sm(III) complex > the ligand (L) at the same concentration both in the experiment of investigating the hydroxyl radical ($^{\bullet}OH$) and the superoxide radical ($O_2^{\bullet-}$) scavenging activities. The results suggested that the scavenging effect on $O_2^{\bullet-}$ and $^{\bullet}OH$ could be enhanced by the formation of metal–ligand coordination complexes and the rare earth metal ions had different and selective nature for scavenging $O_2^{\bullet-}$ and $^{\bullet}OH$. It was believed that the information obtained from the present work would ultimately be helpful to develop new potent antioxidants and new therapeutic reagents for some diseases.

Conclusion

A novel chromone Schiff base, 7-methoxychromone-3-carbaldehyde-isonicotinoyl hydrazone (L) and its Ln(III) complexes (Ln = La, Sm) were successfully prepared, and the structures of the complexes were fully determined by X-ray crystallography. This work is well documented that the combination of a chromone Schiff base ligand and lanthanide metals formed good complexes which had strong DNA-binding affinities and excellent antioxidative abilities. These results also suggested different coordination types could be envisioned for the reason that the La(III) and the Sm(III) complex have different biochemical activities.

Supplementary data

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC (689987 and 695647). Copy of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/deposit).

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