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# Crystal structure, antitumor activities and DNA-binding properties of the La(III) complex with Phthalazin-1(2H)-one prepared by a novel route

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**Abstract**

Phthalazin-1(2H)-one was prepared by a novel route. The La(III)-complex of phthalazin-1(2H)-one, $[La(NO_3)_3 \cdot 4H_2O \cdot C_8H_7N_2O] \cdot H_2O$, was synthesized and characterized on the basis of elemental analysis, thermal analyses (TG/DTA) and X-ray crystallography. In the complex, the coordination number of the La(III) ion is eleven. The interaction of the ligand and its complex with calf thymus DNA was investigated by spectrophotometric methods and viscosity measurements, respectively. Experimental results indicated that phthalazin-1(2H)-one and the complex can bind to DNA by intercalation modes, but the binding affinity of La(III)-complex is higher than that of the ligand. Comparative antitumor activities of La(III)-complex was investigated by HL-60 and A-549. $IC_{50} = 2.6 \times 10^{-8}$, $3.3 \times 10^{-5}$ mg/mL are given.


*Keywords:* Novel route; Phthalazin-1(2H)-one; Intercalation; DNA binding; Antitumor

## 1. Introduction

Over the years, due to lack of effective drugs, cancer is a fatal disease, rating the top three causes of death [1,2]. Since DNA is an important cellular receptor, many chemicals exert their antitumor effects through binding to DNA thereby changing the replication of DNA and inhibiting the growth of the tumor cell, which is the basis of designing new and more efficient antitumor drugs and their effectiveness depends on the mode and affinity of the binding [3–6]. A number of metal chelates have been used as probes of DNA structure in solution [7], as agents for mediation of strand scission of duplex DNA and as chemotherapeutic agents [8,9]. However, complexes of many rare earth metals have demonstrated cytotoxicity in cell culture and antitumor activity in tumor-bearing animals [10,11], with the discovery of rare earth elements in medicine field the study for the synthesis of rare earth complexes is appealing [12,13].

Phthalazin-1(2H)-one was synthesized many years ago [14], its bioactivity has been researched extensively [15–19]. However, its rare earth complexes seem not to be reported. Recently, we have prepared phthalazin-1(2H)-one by a novel route and got the crystal of La(III)-complex. We separated the intermediate product that was characterized on the basis of elemental analyses, $^1H$ NMR spectra, thermal analyses (TG/DTA) and X-ray crystallography. The DNA binding properties of this complex have been investigated by spectrophotometric methods and viscosity measurements. The result shows the complex binds to DNA by intercalation modes.

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## 2. Results and discussion

Ligand, phthalazin-1(2H)-one, always was synthesized by the classical reaction of 2-carboxybenzaldenhyde and hydrazine hydrate, however, the compound can be formed by a novel route in the paper, which La $(NO_3)_3 \cdot 2H_2O$ reacts with one of three different raw materials, such as 2-carboxybenzalde-hydeisonicotinichydrazone, 2-carboxybenzaldehyde-(4′-methoxy)-benzoylhydrazone and 2-carboxybenzaldehydebenzoylhydrazone in ethanol 95% solution, respectively. The results show that the performances of the three reactions are the same, which all product white solid firstly, then the white solid disappear and phthalazin-1(2H)-one was formed. But if we use some transition metal salts, such as $Zn(OAc)_2 \cdot 2H_2O$ and $Cu(OAc)_2 \cdot 2H_2O$, phthalazin-1(2H)-one cannot be produced. On the basis of above evidence and analyses, we think: 1. La(III) ion has an very important effect on the reactions. 2. The middling product (white solid) is not stable and it may be resolved under the La(III) ion catalyze. The mechanism of the reactions is still investigated (Scheme 1).

### 2.1. The structure of La(III) complex

#### 2.1.1. Elemental analysis

The crystal was analyzed for C, H, N with the following results (found (%)/calculated (%)); $[La(NO_3)_3 \cdot 4H_2O \cdot C_8H_7N_2O] \cdot H_2O$, $C = 17.15/17.12$, $H = 2.39/2.87$, $N = 12.71/12.48$.

#### 2.1.2. Thermal stability of the complex

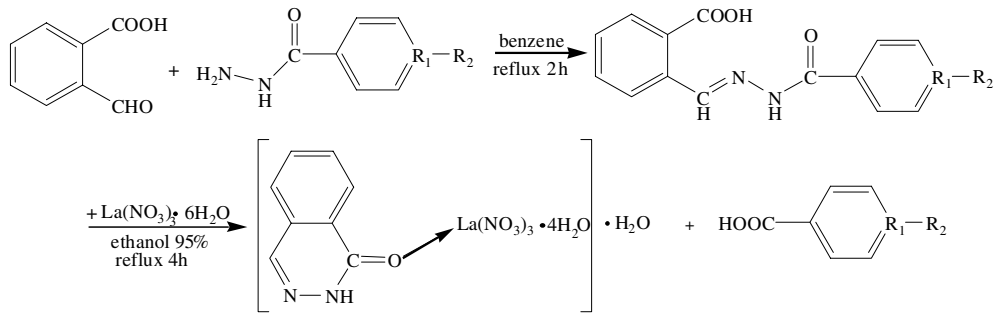
The La(III) complex has an endothermic peak at 146 °C and the corresponding TG curves show that the weight loss is equal to four water molecules. This fact suggests that the complexes contain four coordinated water molecules, this being also confirmed by X-ray diffraction. Three exothermic peaks appear around 283–520 °C (Table 1).

Table 1
Crystal data and structure refinement for the $LaC_8H_{16}N_5O_{15}$ complex

| | |
|---|---|
| Compound | $[La(NO_3)_3 \cdot 4H_2O \cdot C_8H_7N_2O] \cdot H_2O$ |
| Empirical formula | $C_8H_{16}LaN_5O_{15}$ |
| Formula weight | 569.17 |
| Temperature (K) | 296(2) |
| Wavelength (Å) | 0.71073 |
| Crystal system | Triclinic |
| Space group | $P\bar{1}$ |
| *Unit cell dimensions* | |
| $a$ (Å) | 7.182(1) |
| $b$ (Å) | 11.224(1) |
| $c$ (Å) | 12.819(2) |
| $\alpha$ (°) | 101.24(1) |
| $\beta$ (°) | 103.22(1) |
| $\gamma$ (°) | 108.56(1) |
| Volume (Å$^3$) | 912.6(2) |
| $Z$ | 2 |
| Density, calculated (Mg/m$^3$) | 2.042 |
| Absorption coefficient (mm$^{-1}$) | 2.430 |
| $F(000)$ | 552 |
| Crystal size (mm) | $0.52 \times 0.34 \times 0.18$ |
| $\theta$ range for data collection (°) | 1.71–26.00 |
| Index ranges | $0 \leqslant h \leqslant 8$, $-13 \leqslant k \leqslant 12$, $-15 \leqslant l \leqslant 15$ |
| Reflections collected | 3972 |
| Independent reflections | 3540 ($R_{int} = 0.0131$) |
| Reflections with $I > 2\sigma(I)$ | 3317 |
| Absorption correction | Empirical |
| Maximum and minimum transmission | 0.9828 and 0.5231 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data/restraints/parameters | 3540/11/307 |
| Goodness-of-fit on $F^2$ | 1.089 |
| Final $R$ indices [$I > 2\sigma(I)$] | $R_1 = 0.0212$, $wR_2 = 0.0455$ |
| $R$ indices (all data) | $R_1 = 0.0193$, $wR_2 = 0.0450$ |
| Extinction coefficient | 0.0126(5) |
| Largest difference peak and hole | 0.684 and −0.697 (e Å$^{-3}$) |

#### 2.1.3. Structure of the complex

The molecular geometry of La(III)-complex was shown by an X-ray diffraction study to have the structure depicted in Fig. 1 (with the geometrical data shown




$R_1 = N$; $R_1 = C$, $R_2 = H$; $R_1 = C$, $R_2 = OCH_3$

Scheme 1.

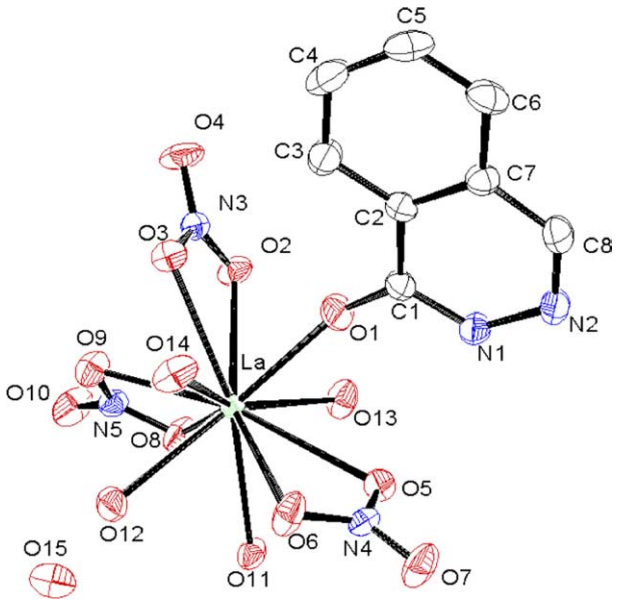



Fig. 1. An ORTEP drawing of the complex showing the atomic numbering scheme.

Table 2
Selected bond lengths [Å] and angles [°]

| | | | |
|---|---|---|---|
| *Bond lengths [Å]* | | | |
| La–O(1) | 2.475(2) | La–O(11) | 2.617(2) |
| La–O(12) | 2.554(2) | La–O(3) | 2.664(2) |
| La–O(14) | 2.562(2) | La–O(2) | 2.717(2) |
| La–O(13) | 2.574(2) | O(1)–C(1) | 1.244(3) |
| O(2)–N(3) | 1.270(3) | O(3)–N(3) | 1.250(3) |
| O(4)–N(3) | 1.226(3) | N(1)–C(1) | 1.349(4) |
| N(1)–N(2) | 1.373(3) | N(1)–H(1N) | 0.89(4) |
| N(2)–C(8) | 1.290(4) | C(1)–C(2) | 1.445(4) |
| C(2)–C(3) | 1.395(4) | C(2)–C(7) | 1.402(4) |
| *Bond angles [°]* | | | |
| O(1)–La–O(12) | 141.58(8) | O(1)–La–O(14) | 73.77(8) |
| O(1)–La–O(11) | 128.56(7) | O(1)–La–O(13) | 76.66(8) |
| O(1)–La–O(8) | 137.55(7) | O(12)–La–O(8) | 80.24(7) |
| O(14)–La–O(8) | 139.56(7) | O(13)–La–O(8) | 68.81(7) |
| O(1)–La–O(5) | 66.87(7) | O(1)–La–O(3) | 69.05(7) |
| O(12)–La–O(3) | 103.29(7) | O(14)–La–O(3) | 63.10(7) |
| O(13)–La–O(3) | 110.10(7) | O(11)–La–O(3) | 161.91(6) |
| O(8)–La–O(3) | 100.17(6) | O(1)–La–O(2) | 73.05(7) |
| O(12)–La–O(2) | 130.42(7) | O(14)–La–O(2) | 109.39(7) |
| O(13)–La–O(2) | 65.47(7) | O(11)–La–O(2) | 127.86(6) |
| O(8)–La–O(2) | 70.64(7) | O(3)–La–O(2) | 47.19(6) |
| O(3)–La–O(5) | 135.80(6) | O(2)–La–O(5) | 119.30(6) |
| O(1)–La–O(9) | 129.52(7) | O(1)–La–O(6) | 80.32(7) |
| O(3)–La–O(9) | 62.53(6) | O(2)–La–O(9) | 64.28(7) |
| O(2)–La–O(6) | 153.35(7) | O(3)–La–O(6) | 122.92(6) |
| C(1)–O(1)–La | 160.7(2) | N(2)–C(8)–C(7) | 124.4(3) |
| N(3)–O(2)–La | 96.04(15) | N(3)–O(3)–La | 99.18(15) |
| La–O(11)–H(11A) | 119(2) | N(1)–C(1)–C(2) | 116.1(2) |
| C(1)–N(1)–N(2) | 127.2(2) | C(1)–N(1)–H(1N) | 120(2) |
| N(2)–N(1)–H(1N) | 113(2) | C(8)–N(2)–N(1) | 116.0(2) |
| O(4)–N(3)–O(3) | 121.8(2) | O(4)–N(3)–O(2) | 120.7(2) |
| O(3)–N(3)–O(2) | 117.6(2) | C(3)–C(2)–C(7) | 120.7(3) |
| O(1)–C(1)–N(1) | 119.8(3) | O(1)–C(1)–C(2) | 124.1(3) |

in Table 2). The La(III) ion is linked to the three dibenate chelating nitrates, to four water molecules and to one O-donor atom of the phthalazin-1-(2H)-one. The coordination number is eleven. The bond lengths C1–O1 of 1.244 (3) Å and N2–C8 of 1.290 (4) Å clearly indicate they are double bond, however, the bond length C1–N1 of 1.349 (4) Å indicate it is single bond. The bond length N1–H(N1) of 0.89 (4) Å show that it is not –HOC=N–, but –CO–NH–. The bond length La–O1 of 2.475(2) Å is the shortest in the average bond length La–O(2–14) of 2.664(2) Å (Fig. 2). There is π,π-stacking between phthalazin-1(2H)-one group in the crystal state, the distance is ca. 3.54 Å and the angle is ca. 0° (Fig. 3).

### 2.2. Biological activity

#### 2.2.1. UV Spectra

The interaction of the compounds with the DNA was investigated using absorption spectra. The absorption spectra of two compounds in the absence and presence of the DNA (at a constant concentration of the

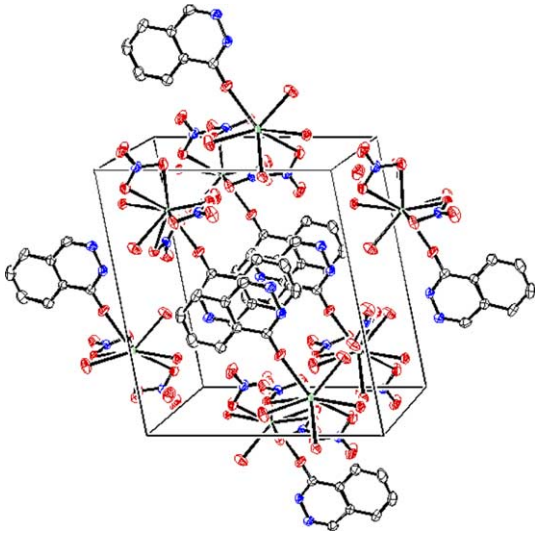


Fig. 2. Crystal packing of La(III) complex.

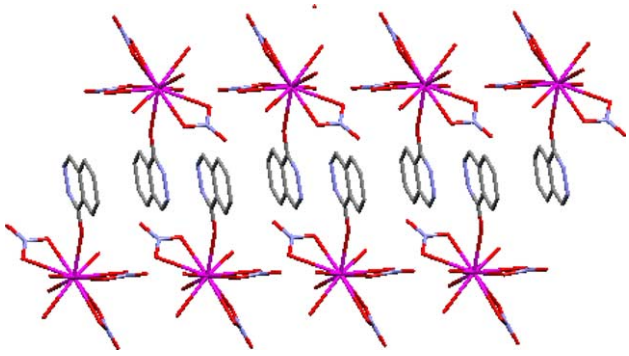


Fig. 3. Crystal π,π-stacking of La(III) complex.

compounds) are given in Fig. 4. As the concentration of DNA is increased, the Soret (at 212 and 210 nm) band of the compounds exhibit hypochromism of ca. 44% and 58%, and the bandochromism of 4 and 13 nm, respectively. These spectral characteristics may suggest that there are some interactions between the compounds and DNA [20], but for the La(III)-complex, it inserts into DNA more deeply.

### 2.2.2. Fluorescence spectra

The enhancements in the emission intensity of the La(III)-complex with increasing DNA concentration are shown in Fig. 5. In the absence of DNA it emits weak luminescence in Tris-buffer at ambient temperature, with a maximum appearing at 447 nm. Upon addition of DNA the emission intensity of the complex grows steadily. Although the emission enhancement could not be regarded as a criterion for binding mode, they are related to the extent to which the complex gets into a hydrophobic environment inside DNA and avoids the complex effect of solvent water molecules. However, there is no luminescence intensity changes in the fluorescence spectra of phthalazin-1(2H)-one, either in the absence or presence of DNA.

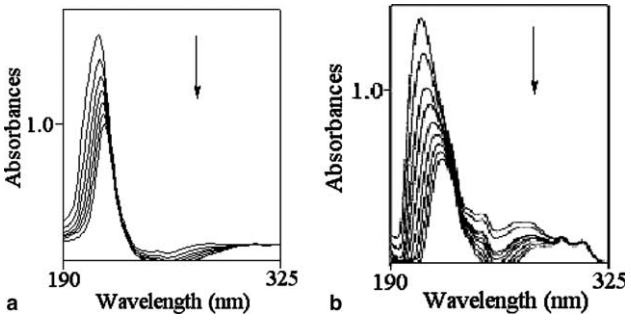



Fig. 4. Absorption spectra of the compounds in the absence and presence of increasing amounts of DNA concentration. The arrows show the absorbance changes on increasing DNA concentration. [Compound] = 10 μmol $L^{-1}$, [DNA] = 0–60 μmol $L^{-1}$. (a) The spectra of the ligand. (b) The spectra of the La(III)-complex.

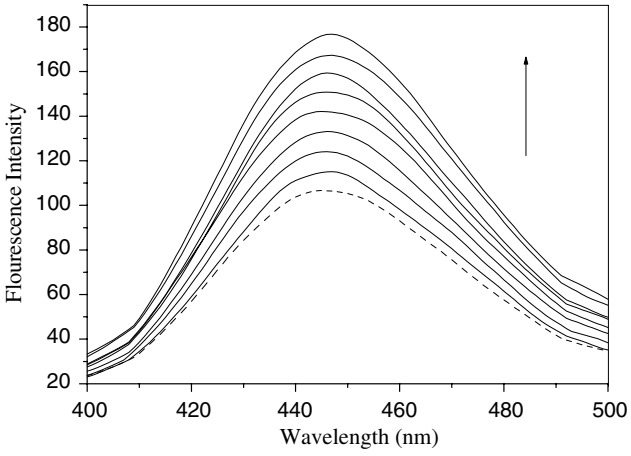



Fig. 5. Electronic spectra of the complex addition of DNA.

To compare quantitatively the affinity of the complex bound to DNA, the intrinsic binding constants $K$ of it was obtained by the luminescence titration method. The concentration of the bound complex was calculated by the equation [21]: $C_b = C_t[(F - F^0)/(F^{max} - F^0)]$.

$C_t$ is the total complex concentration; $F$ is the observed fluorescence emission intensity at given DNA concentration; $F^0$ is the intensity in the absence of DNA; and $F^{max}$ is the fluorescence of the totally bound complex; $C = C_b - C_t$. According to the classical Scatchard equation, a plot of $\gamma/C$ vs. $\gamma$, we obtained the binding constants of $1.4 \times 10^7$ L $mol^{-1}$ from the fluorescence data (Fig. 6). $\gamma$ is binding ratio $C_b$/[DNA].

Further support for La(III)-complex to DNA by intercalation mode is given through the emission quenching experiment. Ethidium bromide (EB) was employed as a fluorescent probe [22,23]. Fig. 7 shows the emission spectra of DNA-EB system upon the increasing amounts of the complexes. The emission intensity of the DNA-EB system ($\lambda = 578$ nm) decreased apparently as the concentration of the complexes increased and an isobathic point appeared at 555 nm, which indicated the formation of the new system of DNA. These changes show that the complex replaced EB from the DNA-EB system leading to the decreased emission of the DNA-EB system. The results were caused by EB changing from a hydrophobic environment to water solution [1].

According to the classical Stern–Volmer equation [24]: $F_0/F = K_q[Q] + 1$, where $F_0$ is the emission intensity in the absence of quencher, $F$ is the emission intensity in the presence of quencher, $K_q$ is the quenching constant and $[Q]$ is the quencher concentration. The shape of Stern–Volmer plots can be used to characterize the quenching was being predominantly dynamic or static. Plots of $F_0/F$ versus $[Q]$ appear to be linear and $K_q$ depends on temperature [24]. The emission quenching of addition of the complexes to the DNA-EB system at

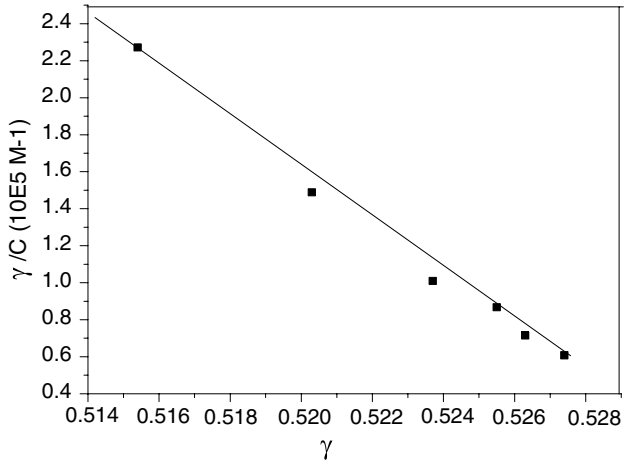



Fig. 6. Schtchard plot of the fluorescence titration data of the complex, $K = 1.4 \times 10^7$ L $mol^{-1}$.

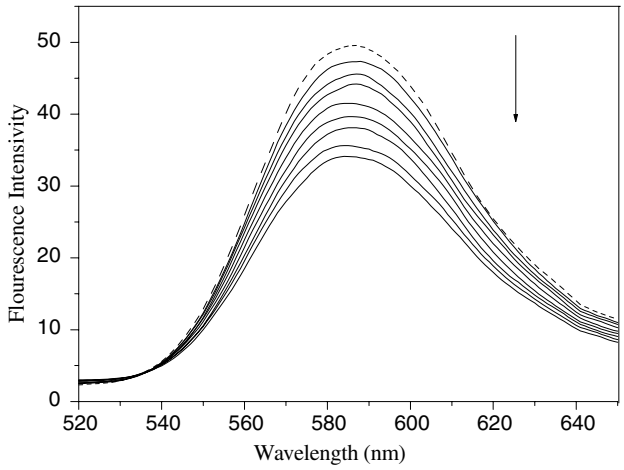



Fig. 7. The emission spectra of DNA-EB system (10 μmol $L^{-1}$ DNA and 0.33 μmol $L^{-1}$ EB), $\lambda_{ex} = 500$ nm, $\lambda_{em} = 520$–650 nm, in the absence (---) and presence (—) of increasing amount of La(III) complex.

25 °C is shown in Fig. 8. The quenching plots illustrate that the quenching of EB bound to DNA by complex is in good agreement with the linear Stern–Volmer equation, which also proves that the two complexes bind to DNA. In the plots of $F_0/F$ versus [complex]/[DNA], $K_q$ is given by the ratio of the slope to intercept. The $K_q$ value is $6.2 \times 10^3$ L $mol^{-1}$.

### 2.2.3. Viscosity measurements

To further clarify the interactions between the compounds and DNA, viscosity measurements were carried out. Hydrodynamic measurements that are sensitive to length change (i.e. viscosity and sedimentation) are regarded as the least ambiguous and the most critical tests of binding in solution in absence of crystallographic structural data. A classical intercalation model results in lengthening the DNA helix as base pairs are separated

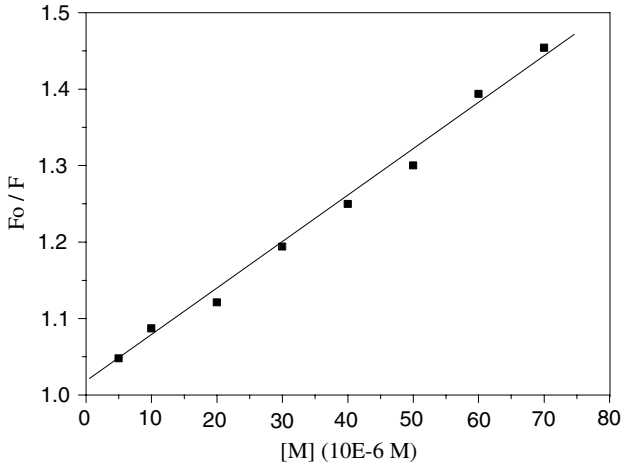



Fig. 8. Stern–Volmer equation.

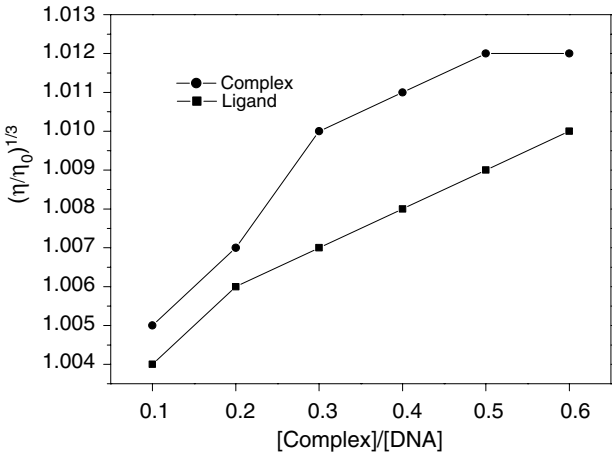



Fig. 9. Effect of increasing amounts of the complexes on the relative viscosity of DNA at 35 °C.

to accommodate the binding ligand, leading to the increase of DNA viscosity. In contrast, a partial, non-classical intercalation of ligand could bend (or kink) the DNA helix, reduce its effective length and, concomitantly, its viscosity [25,26]. The effects of the compounds on the viscosity of rod-like DNA at 35 °C are shown in Fig. 9. With an increasing amount of the compounds, the relative viscosity of DNA increased steadily, which suggests that two complexes can bind to DNA by classical intercalation. But the binding affinity of La(III) complex is higher than that of the ligand.

### 2.3. Antitumor activity

Because La(III)-complex can bind to DNA by intercalation modes, which indicates the La(III)-complex maybe have better antitumor activity, we investigate that the inhibiting effects of La(III)-complex against two kinds of tumor cells (A-549 and HL-60) were studied and the result are listed in Tables 3 and 4. From these two tables, it can be seen that the antitumor activities are in accord with the experiment results at the concentration for the complex, which increases with the increase of the concentration. It submits a reference for the further research.

## 3. Experimental

### 3.1. Measurements

Elemental analyses were carried out on an Elemental Vario EL analyzer. The thermal behavior was monitored on a PCT-2 differential thermal analyzer (Beijing Guangxue Instrument Factory, China). UV spectra were obtained using a Shimadzu Unicam UV-240 spectrophotometer in the 190–325 nm (Hitachi, Japan). The melting points of the compounds were determined on

Table 3
Inhibition effect against human leukemia HL-60

| Compound | Average inhibition effect (%) | | | | Equation | $IC_{50}$, mg/mL |
|---|---|---|---|---|---|---|
| | [a]$C_1$ | [a]$C_2$ | [a]$C_3$ | [a]$C_4$ | | |
| Complex (24 h) | 77 | 65 | 54 | 33 | $y = 7.7x + 108.4$ | $2.6 \times 10^{-8}$ |

$IC_{50}$ values were calculated from regression lines where: $x$ was log of the tested compound concentration and $y$ was percent inhibition of the tested compounds. When the percent inhibition of the tested compounds was 50%, the tested compound concentration was $IC_{50}$.
[a] $C_{i\,(i=1-4)} = 5 \times 10^{-6}$, $5 \times 10^{-7}$, $5 \times 10^{-8}$, $5 \times 10^{-10}$ mg/mL.

Table 4
Inhibition effect against lung adenocarinoma A-549

| Compound | Average inhibition effect (%) | | | | Equation | $IC_{50}$, mg/mL |
|---|---|---|---|---|---|---|
| | [a]$C_1$ | [a]$C_2$ | [a]$C_3$ | [a]$C_4$ | | |
| Complex (48 h) | 88 | 78 | 54 | 40 | $y = 12.2x + 104.7$ | $3.3 \times 10^{-5}$ |

[a] $C_{i(i=1-4)} = 1 \times 10^{-1}$, $1 \times 10^{-3}$, $1 \times 10^{-4}$, $1 \times 10^{-5}$ mg/mL.

an XT4-100X microscopic melting point apparatus (Beijing Electrooptical Instrument Factory, China). Fluorescence measurements were made on a Shimadzu RF-540 spectrofluorophotometer (Hitachi, Japan). $^1$H NMR spectra were recorded on a Varian VR 300-MHz spectrometer with TMS (tetramethylsilane) as an internal standard. Mass spectra was performed on a VG ZAB-HS (FAB, fast atom bombardment ion source) instrument.

All the experiments involving the interaction of La(III)-complex with DNA was carried out in doubly distilled water buffer containing 5 mmol $L^{-1}$ Tris (tris (hydroxymethyl) aminomethane) and 50 mmol $L^{-1}$ NaCl and adjusted to pH 7.0 with hydrochloric acid. A solution of DNA in Tris–HCl (Tris buffer) gave a ratio of UV absorbance at 260 and 280 nm, $A_{260}/A_{280}$, of about 1.8–1.9:1, indicating that the DNA was sufficiently free of protein [27]. EB was prepared as 1.0 mg $L^{-1}$ by dissolving in doubly distilled water. The DNA concentration was determined spectrophotometrically by employing an extinction coefficient of 6600 $M^{-1}$ $cm^{-1}$ at 260 nm.

Viscosity experiments were carried on an Ubbelodhe viscometer, immersed in a thermostated water-bath maintained at 35 °C. Titrations were performed for the complex and it was introduced into DNA solution (50 μmol $L^{-1}$) present in the viscometer. Data were presented as $(\eta/\eta_0)^{1/3}$ versus binding ratio where $\eta$ is the viscosity of DNA in the presence of complex, and $\eta_0$ is the viscosity of DNA alone. Viscosity values were calculated from the observed flow time of DNA-containing solution corrected from the flow time of buffer alone ($t_0$), $\eta = t - t_0$.

### 3.2. Crystal structure determination

A prismatic white transparent crystal of dimensions $0.52 \times 0.34 \times 0.18$ mm was centered on a four-circle Siemens P4 diffractometer operating in $\omega/2\theta$ scan mode with graphite-monochromated Mo Kα radiation (0.71073 Å), $\theta$ range: $1.71 \leqslant \theta \leqslant 26.00$, $0 \leqslant h \leqslant 8$, $-13 \leqslant k \leqslant 12$, $-15 \leqslant l \leqslant 15$, 3972 unique reflections were collected at 296 (2) K, 3570 observed $[I > 2(I)]$ of which were used to solve the structure and least-squares refinement. The refinement converged at $R_1 = 0.0212$ and $wR_2 = 0.0451$ values for reflections. The absolute configuration of the space group was assigned on the basis of Flack parameter. The final geometrical calculations were carried out with SHELXTL-97 and Patterson programs used for structure solution and refinement on $F^2$ using all reflections.

### 3.3. Preparation of La(III) complex

2-Carboxybenzaldenhyde was prepared according to the literature [28]. A benzene solution (200 mL) of 2-carboxybenzaldehyde (3.0 g, 20 mmol) and isonictinyl hydrazine (2.8 g, 20 mmol) was refluxed for 4 h. After cooling to room temperature, the white precipitated solid was filtered, washed with benzene, and recrystallized from benzene to give the 2-carboxybenzalde-hydeisonicotinichydrazone in a yield of 95%; m.p. 196–197 °C. FAB-MS: $m/z = 270$ $[M+H]^+$. A ethanol 95% solution (50 mL) of 2-carboxybenzalde-hydeisonicotinichydrazone (0.269 g, 1 mmol) and $La(NO_3)_3 \cdot 6H_2O$ (0.433 g, 1 mmol) was refluxed for 10 min and there was a white precipitate in the solution. After 0.5 h, the white precipitate was disappeared and the color of solution became yellow. The reflux last 4 h and then the solution was concentrated to 5 mL. The reaction solution was placed and the single crystals were formed at the bottom of the solution after 20 days. The crystals was filtered and a white solid (Phthalazin-1(2H)-one) was obtained by column chromatographic (petroleum:ether-ethyl acetate = 8:1) from the mother water. m.p. 182–183 °C. $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 7.82–8.22 (4H, m,

ArH); 8.35 (1H, s, –CH=N); 12.63 (1H, s, H–N). Then 2-carboxybenzaldehyde-(4′-methoxy)benzoylhydrazone [29] and 2-carboxybenzalde-hydebenzoylhydrazone [30] were used to replace 2-carboxybenzalde-hydeisonicotin-ichydrazone in the same reaction, phthalazin-1(2H)-one was obtained, too.

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