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一种有机锡化合物的合成、晶体结构、抗肿瘤及荧光性能

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摘要:通过异烟肼和 4-*N*,*N*-二羟乙基苯甲醛来合成一种席夫碱及其锡配合物,并通过核磁、元素分析以及 X-射线单晶衍射来进行结构表征。该平面构型的席夫碱采取二齿配位模式,其中的-C=N-在配位后由反式变为顺式。晶体结构数据以及荧光光谱中的显著红移现象表明锡配合物中的 π-共轭体系通过配位反应得以延展。体外细胞毒性数据表明,席夫碱配体及其锡配合物对于 A-549,MCF-7 和 Hela 等肿瘤细胞的生长抑制活性要强于顺铂。还通过紫外可见光谱及荧光光谱初步研究了两种化合物与 DNA 的相互作用,结果表明锡配合物可能通过共价结合来导致 DNA 双螺旋链变形,而席夫碱分子中的氢键效应及其长平面结构可能会阻碍其嵌入 DNA 双螺旋链。

关键词:异烟肼;荧光有机锡;抗肿瘤;晶体结构
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Synthesis, Crystal Structure and Antitumor Ability of a Fluorescent Organotin Compound

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Abstract: A Schiff base derivate from isonicotinohydrazide and *p*-*N*,*N*-di(2-hydroxyethyl)amino benzaldehyde, together with its organotin complex, have been synthesized and characterized by ^{1}H NMR spectroscopy, elemental analyses and X-ray crystallography. The planar Schiff base compound coordinated to the tin center in a bidentate mode, with the *trans* -C=N- conformation changed to be *cis* in the complex. The crystal data of the complex and the large red shift in the fluorescence spectra demonstrated an extension of the π-conjunction due to the coordination. In vitro cytotoxicity data showed that both compounds were more cytotoxic than cisplatin against A-549, MCF-7 and Hela tumor cell lines. The interactions of both compounds with CT-DNA were preliminarily studied by UV-Vis and fluorescence spectroscopy, which suggested that the organotin complex likely induces the distortion of DNA double helix through covalent bonding, while the hydrogen bonds and the large planar structure of the molecule hindered the Schiff base compound from intercalating into the DNA double helix. CCDC: 838656, **2**; 838657, **1**.

Key words: isonicotinohydrazide; fluorescent organotin; antitumor; crystal structure

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Organotin compounds have been extensively studied for their diversified commercial applications, such as polyvinyl chloride stabilizers, industrial biocides, marine antiseptic agents, and so forth [1-2]. Some of the organotin complexes were even evaluated as anticancer drugs[3-4]. In general, the antitumor activity of organotin compound is influenced greatly by the structure of the molecule and the coordination environment of the tin atoms. In the choice of suitable ligands for the tin atom, Schiff base compounds have received much attention, as such compounds manifest remarkable coordination ability to most transition/rare-earth metal ions and thus form complexes with versatile structure, good stability and solubility in various solvents[5-7]. Furthermore, Schiff base compounds have been investigated in the research area of antiviral, antifungal, antiparasitic, antibacterial, anti-inflammatory, antitumor, antiHIV[8-12], etc. Moreover, it has been reported that the biological activities of their complexes are enhanced in comparison to the free ligands. It′s worthy to note that many metal complexes of Schiff base can cleave DNA[13-16], especially some organotin Schiff base complexes exhibit distinct bactericidal/antitumor activity and DNA binding ability[17-22].

In the construction of a novel Schiff base, isonicotinohydrazide was chosen for its fascinating coordination behavior and pharmacological applications[23-24], while *p*-*N*,*N*-di(2-hydroxyethyl) amino benzaldehyde was selected with the propose to introduce hydrogen bonds to the biological targets. Methyltin trichloride was preferred as the tin precursor for its smaller steric effect and higher reactive ability when compared with other starting organotin reagents. We reported here the synthesis and structural characterization of the novel Schiff Base compound and its tin complex. The antitumor activity and the DNA binding capability of the two compounds have been explored.

1　Experimental

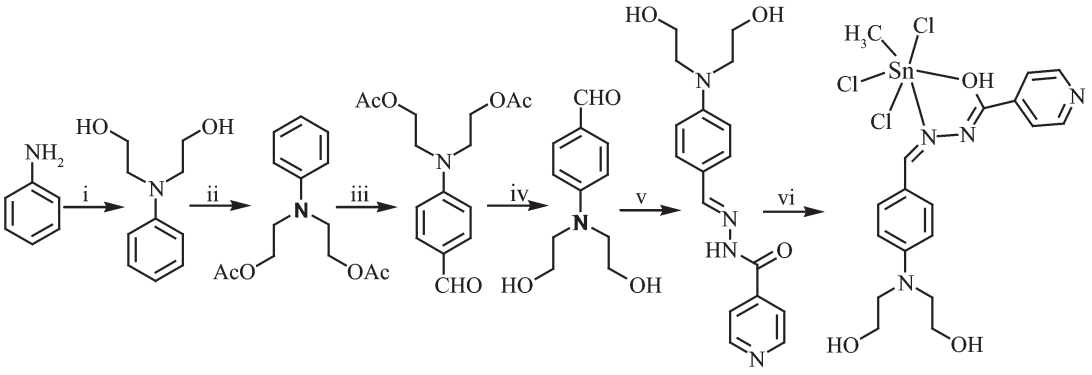
1.1　Instruments

The ^{1}H NMR analyses were performed on a 400 MHz Bruker DMX spectrometer. Elemental analysis data were acquired using a Vario EL(Ⅲ) analytical instrument. The UV-Vis spectra were obtained with a Shimadzu UV3600 spectrometer. Fluorescence spectra were recorded by a PerkinElmer LS50 Luminescence Spectrometer. The crystal structures were determined using a Bruker Smart APEX Ⅱ diffractometer. Reflection data were measured at 296 K using graphite monochromatic Mo *Kα* (λ=0.071 073 nm) radiation.

1.2　Preparations of the compounds

1.2.1　*N*,*N*-di(2-hydroxyethyl) aniline

A mixture of 0.25 mol aniline, 0.75 mol 2-chloroethanol, 0.35 mol $CaCO_3$ and 200 mL H_2O were refluxed for 12 h with vigorous stirring, and then filtered to remove the $CaCO_3$. The filtrate was extracted with ethyl acetate and the organic phase was washed with water twice. The yellow solution was dried on anhydrous Na_2SO_4 overnight. The solvent was removed and the crude product was collected as pale yellow oil (200~210 ℃ / 266 Pa) and recrystallized from ethanol:H_2O (1:3, *V*/*V*) solution as white crystals. Yield: 84%. mp: 55~56 ℃. Calcd. for $C_{10}H_{15}NO_2$(%): C,



i: $ClCH_2CH_2OH$; ii: $(AcO)_2O$; iii: DMF, $POCl_3$,; iv: NaOH; v: Isonicotinohydrazide; vi: $MeSnCl_3$

66.27, H, 8.34, N, 7.73. Found(%): C, 65.43, H, 8.34, N, 7.52. ^{1}H NMR: (d-chloroform): δ (ppm) 7.2 (2H), 6.7 (3H), 4.5 (2H), 3.7 (4H), 3.5 (4H).

1.2.2 *N*-benzenyl-*N*,*N*-bis(ethyl acetate)

A mixture of 52 g *N*,*N*-di(2-hydroxyethyl)aniline, 90 g acetic anhydride and 70 g pyridine was stirred at 90 ℃ for 24 h. The resulted dark solution was cooled down to 20 ℃ and then washed with 400 mL H_2O. The mixture was extracted with ethyl acetate and the organic phase was washed with water twice. The yellow solution was dried on anhydrous $MgSO_4$ overnight, and then the solvent was removed. The crude product was collected as pale yellow oil (190~200 ℃/ 266 Pa). Yield: 95%. Calcd. for $C_{14}H_{19}NO_4$(%): C, 63.38, H, 7.22, N, 5.28. Found(%): C, 63.05, H, 7.19, N, 5.31. ^{1}H NMR: (d-chloroform): δ (ppm) 7.2 (2H), 6.8 (3H), 4.3 (4H), 3.6 (4H), 2.1 (6H).

1.2.3 *p*-*N*,*N*-di(2-ethylacetate)amino benzaldehyde

4 g $POCl_3$ was added dropwise into 5 mL DMF under 0 ℃ with vigorous stirring, the resulted pink oil was continued to stir for another 15min under 0 ℃. 5 g *N*-benzenyl-*N*,*N*-bis(ethyl acetate) in 3 mL 1,2-dichloroethane solution was added dropwise into the pink oil. The temperature of the mixture was raised to 60 ℃ slowly and kept for 15 min, then the mixture was stirred for 3 h under 90 ℃ to get a deepgreen solution. The mixture was cooled down to 20 ℃ and then poured into ice-water. The pH value was adjusted to 6~8 using 30% Na_2CO_3 solution. The yellow precipitate was collected by filtration, washed with water and dried in vacuum. Yield: 90%. Calcd. for $C_{15}H_{19}NO_5$ (%): C, 61.42, H, 6.53, N, 4.78. Found (%): C, 61.28, H, 6.48, N, 4.95. ^{1}H NMR(d-chloroform): δ (ppm) 9.6 (1H), 7.68 (2H), 6.75 (2H), 4.2 (4H), 3.6 (4H), 2.0 (6 H).

1.2.4 *p*-*N*,*N*-di(2-hydroxyethyl)amino benzaldehyde

A yellow mixture of 15 g *p*-*N*,*N*-di(2-ethylacetate) amino benzaldehyde in 175 mL ethanol and 12.5 g NaOH in 75 mL water was stirred for 7 h at 25 ℃, and then the pH was adjusted to 8~9 using diluted HCl solution. The solvent ethanol and water were removed and the residue solid was dissolved in 50 mL ethyl acetate. Filtered and the solvent of the filtrate was evaporated. Yellow crystals could be obtained and collected by filtration, and then dried in vacuum. Yield: 92%. Calcd. for $C_{11}H_{15}NO_3$ (%): C, 63.14, H, 7.23, N, 6.69. Found (%): C, 63.28, H, 7.48, N, 6.75. ^{1}H NMR (d-chloroform): δ (ppm) 9.65 (1H), 7.71 (2H), 6.71 (2H), 3.91 (10H).

1.2.5 (*E*)-*N*′-4-di(hydroxyethyl)amino benzylideneisonicotinohydrazide (compound **1**)

A mixture of 8.36 g *p*-*N*,*N*-di(2-hydroxyethyl) amino benzaldehyde and 5.44 g isonicotino-hydrazide in 100 mL ethanol were refluxed for 5 h. Yellow tiny crystals could be observed after being cooled down and was collected by filtration. Yield: 82%. Crystals suitable for X-ray diffraction were obtained by diffusion of isopropanol into the DMF solution. Calcd. for $C_{17}H_{20}N_4O_3$(%): C, 62.18, H, 6.14, N, 17.06. Found (%): C, 62.28, H, 6.48, N, 17.65. ^{1}H NMR (d-chloroform): δ (ppm) 8.77 (2H), 8.32 (1H), 7.93 (2H), 7.68 (2H), 6.75 (2H), 3.52 (10H).

1.2.6 (*Z*)-*N*′-4-di(hydroxyethyl)aminobenzylideneisonicotinohydrazide methyltin trichloride (compound **2**)

A mixture of 0.1 mmol (*E*)-*N*′-4-di(hydroxyethyl) amino benzylideneisonicotinohydrazide and 0.1 mmol CH_3SnCl_3 in 50 mL CH_3OH were refluxed with vigorous stirring for 4 h, dark red precipitate could be obtained. The solid was collected by filtration and washed with ethanol twice, then dried in vacuum. Yield: 90%. Crystals suitable for X-ray diffraction were obtained by slow evaporation of the methanol solution for one week. Calcd. for $C_{18}H_{23}Cl_3N_4O_3Sn$(%): C, 38.03, H, 4.08, N, 9.86. Found (%): C, 38.21, H, 4.16, N, 9.72. ^{1}H NMR (d_6-DMSO): δ (ppm) 8.83 (2H), 8.52 (1H), 7.97 (2H), 7.72 (2H), 6.81 (2H), 3.49 (10H), 1.02 (3H).

1.3 Crystal structure determination

The crystal data were collected by SMART program, reduced using SAINT program and refined by SHELXTL software package. SADBAS was used for data absorption corrections[25-26]. The structure of the two compounds were solved to locate all the non-hydrogen atoms from the trial structure and then refined anisotropically with SHELXTL using full-

matrix least-squares procedure. All the hydrogen atoms were geometrically fixed at calculated positions and refined using a riding model. The carbon atoms of the pyridine loop were disordered in the structure of compound **1**, so their positions were split, and two sets of coordinates for C1 C3 C4 C5 and C1′ C3′ C4′ C5′ were obtained using part order with FVAR values of 0.16633 and 0.38725, then their displace parameters were refined using SADI and ISOR orders.

CCDC: 838656, **2**; 838657, **1**.

1.4 Cytotoxicity assay

Tumor cells were grown in RPMI-1640 medium supplemented with 10% (*V*/*V*) fetal bovine serum, 2 mmol·L^{-1} glutamine, 100 U·mL^{-1} penicillin, and 100 ug/mL streptomycin in a highly humidified atmosphere of 95% air with 5% CO_2 at 310 K. The cytotoxicity of the ligand and tin complex against the human non-small-cell lung cancer cell line (A-549), the human breast cancer cell line (MCF-7) and the human cervix carcinoma cell line (Hela) cells were examined by the microculture tetrozolium (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide, MTT) assay. Briefly, cells in 100 uL of culture medium were plated in each well of 96-well plates (Falcon, CA). The cells were treated in triplicate with grade concentrations of the compound and the reference drug cisplatin at 37 ℃ for 48 h. A 20 uL aliquot of MTT solution (5 mg·mL^{-1}) was added directly to all the appropriate wells. The culture was then incubated for 4 h. Then 100 uL of "triplex solution" (10% SDS/5% isobutanol/12 mmol·L^{-1} HCl) was added. After the plates were incubated at 37 ℃ overnight, they were measured by the absorbance at 570 nm using a multiwell spectrophotometer. The percent growth inhibitory rate of treated cells was calculated by $(OD_{control}-OD_{test})/OD_{control}\times100\%$. Results of complexes were expressed as IC_{50} (the drug concentration that reduces by 50% the absorbance in treated cells with respect to untreated cells) that was calculated by the Logit method. Finally, the mean IC_{50} was calculated using the data from three replicate tests[27].

1.5 Spectroscopic studies on DNA interaction

Compound **1** and **2** were dissolved in the mixed solvent of CH_3CN and Tris-HCl buffer (50 mmol·L^{-1} NaCl, 5 mmol·L^{-1} Tris, pH 7.42) in 1:1 ratio and incubated with DNA for 1 h before measurement.

The concentration of CT-DNA per base was determined by recording the UV absorption at 260 nm using the molar absorption coefficient of 6 600 L·mol^{-1}·cm^{-1}. The UV absorbance at 260 and 280 nm of the CT-DNA solution in Tris-HCl buffer gives a ratio of 1.87, indicating that the DNA was sufficiently free of protein. The concentrations of the compounds were both 2.0×10^{-5} mol·L^{-1}.

The fluorescence spectra were recorded at room temperature with excitation wavelength at 525 nm and emission wavelength at 600 nm. The experiment was carried out by titrating compound (2.0 mmol·L^{-1}) into the mixture containing 5.0×10^{-5} mol·L^{-1} DNA and 5.0×10^{-5} mol·L^{-1} EB.

2 Results and discussion

2.1 Synthesis and characterization

The *N*-benzenyl-*N*,*N*-bis(ethyl acetate) could also be obtained in one step using the aniline and ethyl 2-bromoacetate. However, the above reported procedure is selected in preference due to its high overall yield. In the neutralization process to achieve *p*-*N*,*N*-di(2-ethylacetate) amino benzaldehyde, 30% Na_2CO_3 should be chosen instead of the commonly used sodium acetate and added dropwise into the raw solution to achieve pure compound in pale yellow solid, which could be conveniently separated by filtration, otherwise, red stick oil could be observed and need further purification by column chromatography. The titled tin complex was quite stable in air, unlike the methyltin trichloride sensitive to the moisture.

2.2 Crystal structure of the compounds

The molecular structure and atoms labeling of the two compounds were shown in Fig.1. The crystal data, details concerning data collection and structure refinement were given in Table 1. Selected hydrogen bond lengths and angles could be found in Table 2. The structure of the compound **1** revealed the quasi coplanarity of the whole molecular skeleton (without considering the two hydroxyethyl groups) and the main

Table 1 Crystal data and structure refinement parameters for the two compounds

Compound	Tin complex	Ligand
empirical formula	$C_{18}H_{23}Cl_3N_4O_3Sn$	$C_{17}H_{20}N_4O_3$
Formula weight	568.44	328.37
T / K	296(2)	296(2)
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a / nm	1.036 65(8)	0.763 18(9)
b / nm	1.853 82(15)	1.995 1(2)
c / nm	1.210 14(10)	1.056 39(13)
β / (°)	97.462 0(10)	96.247(2)
V / nm^3	2.305 9(3)	1.598 9(3)
Z	4	4
D_c / (g·cm^{-3})	1.637	1.364
F(000)	1 136	696
Absorption coefficient / mm^{-1}	1.482	0.096
θ range for data collection / (°)	2.02~27.51	2.19~26.00
Reflections collected	21 091	13 044
Independent reflections	5 287	3 140
R_{int}	0.066 5	0.025 2
Goodness-of-fit on F^2	0.998	1.05
R_1 ($I>2\sigma(I)$)[a]	0.041 4	0.045 5
wR_2 ($I>2\sigma(I)$)[a]	0.077 5	0.123 3

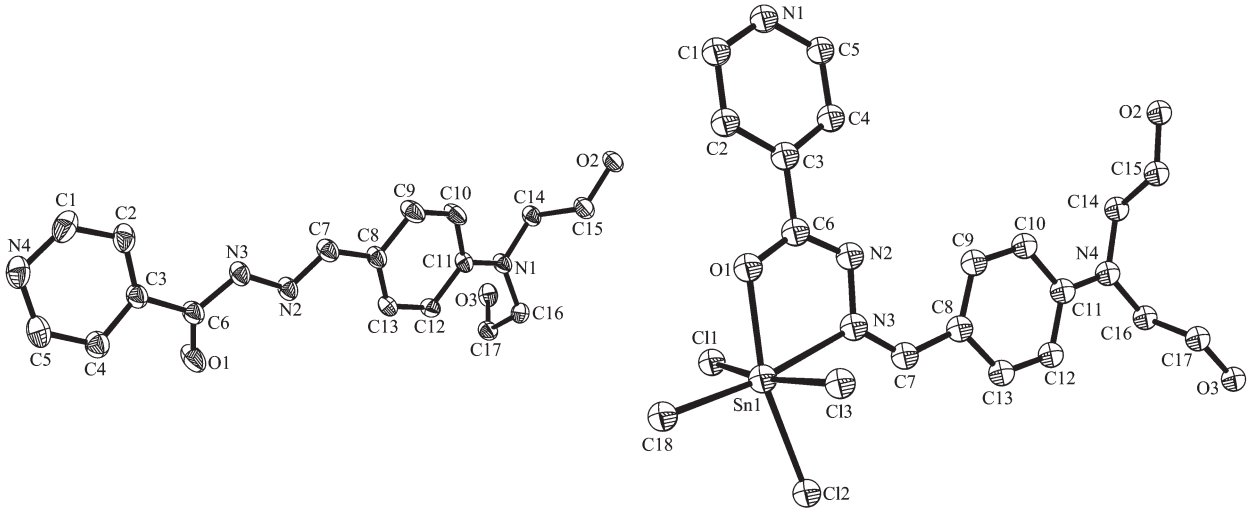
[a] $R_1=\sum||F_o|-|F_c||/\sum|F_o|$, $wR=[\sum w(F_o^2-F_c^2)^2/\sum w(F_o^2)^2]^{1/2}$.

Table 2 Selected hydrogen bonds lengths and angels for compound 1 and 2

D–H···A	d(D-H) / nm	d(H···A) / nm	d(D···A) / nm	∠(DHA) / (°)
1				
O(3)–H(3)···O(2)^{i}	0.082	0.204	0.284 0(2)	166.4
O(2)–H(2)···N(2)^{ii}	0.082	0.256	0.321 0(2)	137.6
O(2)–H(2)···O(1)^{ii}	0.082	0.2	0.2747 5(19)	151.2
N(3)–H(3A)···O(3)^{iii}	0.09	0.247	0.2976 1(19)	116.3
2				
C(4)–H(4)···N(2)	0.093	0.244	0.275 6(5)	99.7
C(7)–H(7)···Cl(2)	0.093	0.266	0.335 3(4)	131.4
C(9)–H(9)···N(2)	0.093	0.232	0.291 1(5)	121
O(2)–H(2A)···O(3)^{i}	0.082	0.183	0.264 1(5)	172.5
O(3)–H(3A)···Cl(2)^{ii}	0.082	0.239	0.315 9(4)	155.5
C(18)–H(18B)···O(2)^{iii}	0.096	0.245	0.333 5(6)	153.8

Symmetry codes: ^{i} 0.5+x, 0.5−y; 0.5+z, ^{ii} x, y, −1+z; ^{iii} 1.5−x, −0.5−y, −z+0.5, for **1**; ^{i} −x, −y, 2−z; ^{ii} x−0.5, 0.5−y, 0.5+z; ^{iii} 1−x, −y, 1−z for **2**.

deviation of the plane (C1 to C13, N1 to N4 and O1 atoms) was 0.012 5 nm. The O1 atom and the hydrazinic N2 atom were cis with respect to C6-N3 bond. The localization of the double bonds in the central -C=N-N-C=O adopted an E-configuration with respect to the double bond of the hydrazone bridge. The bond lengths C7-N2 (0.126 9 nm) and C6-O1 (0.122 2 nm) were typical of double bonds. There are three types of intermolecular hydrogen bonds in the crystal structure shown in Fig.2(a). The interactions



All hydrogen atoms are omitted for clarity

Fig.1　ORTEP drawing of the two compounds, Ellipsoids are drawn at 30% probability

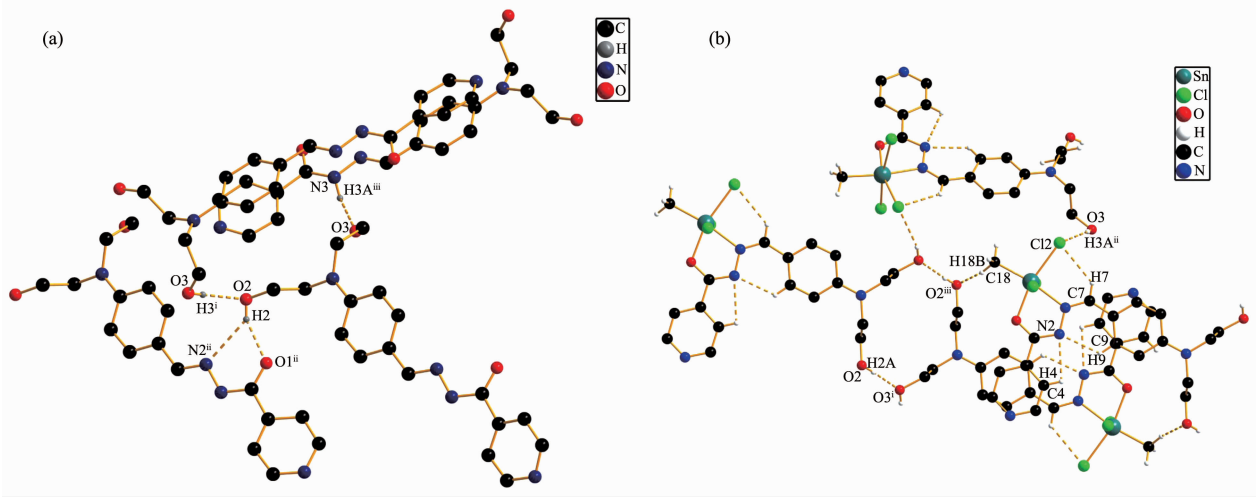


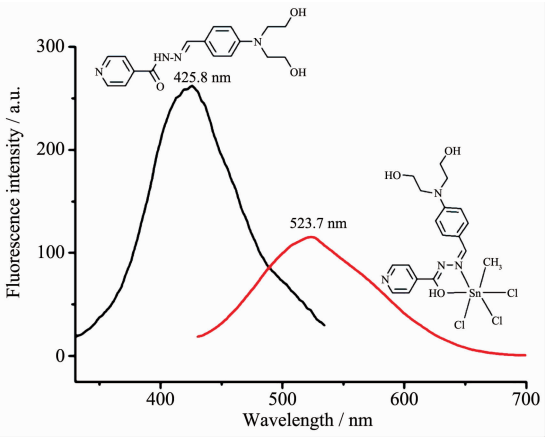
Fig.2　(a) Three types of hydrogen bonds existed in the crystal structure of compound **1**; (b) Intermolecular and intramolecular hydrogen bonds found in compound **2**

between O–H⋯O–H and O–H⋯N–C=O connected two adjacent ligand molecules through a head-to-tail fashion, and the distance between the two parallel molecules was 0.345 nm. The short interactions between the O–H⋯O=C joined the molecules into zigzag configuration with the zigzag angle was 145.1°. Compound **2** had a distorted octahedral coordination geometry and central metal was connected by the {N, C} atoms from the ligand together with three chloride atoms and a methyl group. The bond lengths of three Sn-Cl were in accordance with the literature reports[28-29]. The bond lengths of the O=C-N-N=C group changed evidently due to the coordination, e.g., the C=O bond extended from 0.122 2 to be 0.129 nm, while the C-N bond length was shorted to be only 0.130 5 from 0.134 1 nm in the free ligand. The changes in the bond length indicted that an O-C=N-N=C configuration may be adopted in the crystal structure of the complex, which will largely extend the π-conjunction system in the molecule. It was reported that this configuration transformation will result in significant color change[23], which could also be evidenced by the color changes from bright yellow to deep red for the ligand and tin complex, respectively. It is worth to mention that the C=N configuration changed to be Z, possibly in order to minimize the electron repulsion between the coordination core and benzyl group. It was clearly shown in Fig.2(b) that the intermolecular

interactions between the two hydroxyl groups and the methyl groups, together with the hydrogen bonds of O–H···Cl linked the molecules in a two-dimensional network.

2.3 Emission properties of the compounds

Fluorescent chemosensors for organotin compounds should be of great use for studying the absorption, accumulation, degradation and delayedtoxicity of the related organotin compounds in aquatic organisms[30-31]. The emission spectra were acquired in the ethanol solution. As shown in Fig.3, compound **1** exhibited an intensive emission peak at 425.8 nm when being excited at 288 nm, which can be attributed to π-π* transition of the Schiff base. Noticeably a red shift of nearly 100 nm of the emission bands was observed when excited the tin complex at 365 nm. As can be seen from the crystal data, equilibrium between keto and enol forms[32] was in the tin complex and enol form was dominant. The red shift may arise from the extended π-conjunction system in the enol form, with pyridine served as an electron acceptor and the bis (hydroxyethyl)amino group as the donor. Molecules with D-π-A structure were always high fluorescent, which were extremely attractive for photoluminescent sensing of metal ions and imaging of chemical species in biological tissue using confocal microscopy[33-35]. The fluorescence intensity of the tin complex was lower than the free ligand due to the heavy atom effect of the three chloride atoms.

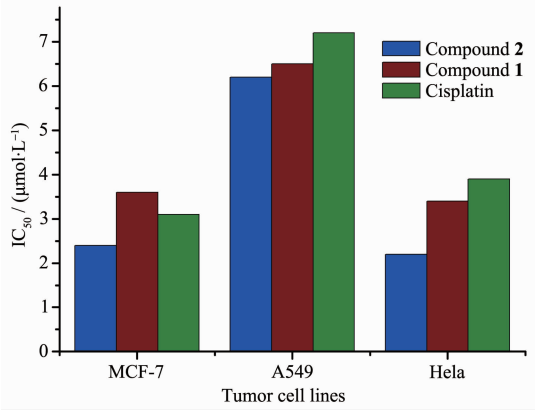


Concentrations for both compounds are 2×10^{-5} mol·L^{-1}

Fig.3 Fluorescence spectra of the two compounds in the ethanol solution

2.4 Cytotoxic activities and DNA binding properties

The *in vitro* cytotoxicity data of two compounds against A-549, MCF-7, and Hela tumor cells are shown in Fig.4. Compared to cisplatin, both compound **1** and **2** have demonstrated higher *in vitro* cytotoxicity for all tested cell lines and the tin complex was a bit more cytotoxic than the free ligand.

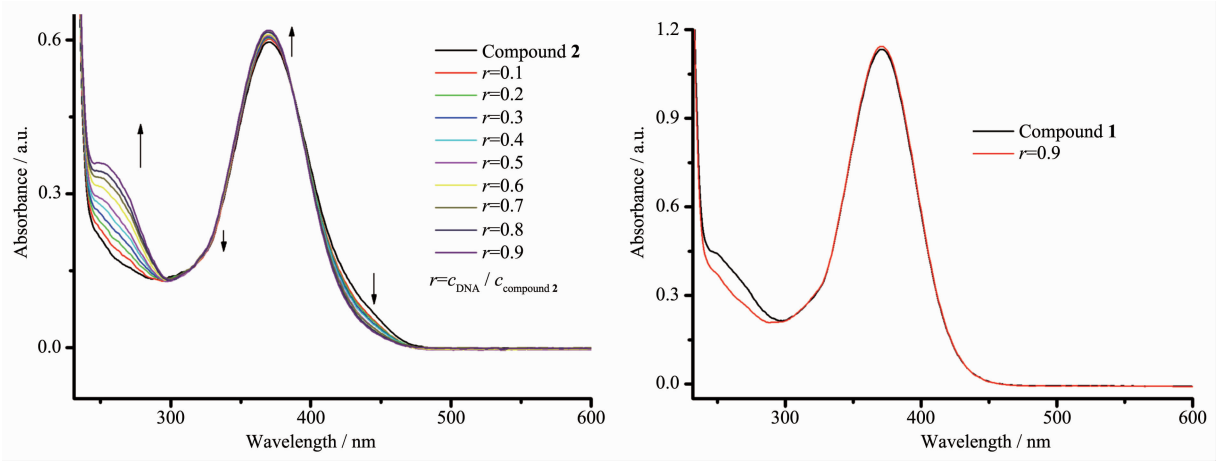


Cisplatin was tested for comparison

Fig.4 *In vitro* cytotoxicity data of the two compounds against three tumor cell lines

In order to investigate whether DNA is the biological target of the two compounds, their interactions with Calf-thymus DNA (CT-DNA) were followed by UV-Vis, Fluorescence spectroscopy. The UV-vis spectrum of the tin complex showed intense high-energy band at 369 nm due to ligand-based π-π* transition, which showed a hyperhromism with the increasing ratio of $c_{DNA}/c_{compound}$. Interestingly upon addition of DNA there was an isobestic point observed. The band around 450nm assigned as the ligand-metal charge transfer (LMCT) decreased about 48.8% in intensity when the ratio increased from 0.0 to 0.9, revealing a strong interaction of the coordination core with the DNA. However, the absorption spectrum of the compound **1** changed very slightly in the presence of DNA, indicting no evident interactions between **1** and DNA.

It was commonly believed that molecules with a planar configuration could intercalate into DNA[36-37], the DNA-EB system was used to further probe the DNA binding mode. Ethidium bromide (EB) is an intercalator that gives a significant increase in



Buffer: 5 mmol·L^{-1} tris, 50 mmol·L^{-1} NaCl, pH 7.42; Concentration of the compound is 2.0×10^{-5} mol·L^{-1}, r=0~0.9

Fig.5　UV-Vis absorption spectra of compounds in 1:1 mixed solution of CH_3CN and Buffer with increasing concentration of CT-DNA

fluorescence emission when bound to DNA and its displacement from DNA results in decrease in fluorescence intensity[38]. It could be found from the fluorescence titration spectra that the emission intensity of the DNA/EB system changed very slightly with the increase of the concentration of the compound, which suggests that the two compounds cannot replace EB from CT-DNA efficiently through the intercalation effect. It is likely that molecule of **1** was too long (>1.29 nm) to be embedded in the DNA double helices, at the same time, the hydroxyethyl group may form intermolecular hydrogen bonds outside the DNA band, which may hinder its intercalation into the DNA base pairs. The steric hindrance from coordination core in the tin complex may block its intercalating into DNA double helices. Molecular simulation based on DFT calculations to examine the exact DNA binding mode is under investigation.

3　Conclusion

A novel Schiff base compound and its tin (Ⅳ) complex were synthesized and characterized. The crystal structure data revealed a notable π-conjunction extension and distinct configuration conversion between the two compounds. Hydrogen bonds were vital in the construction of three-dimensional structures. The tin complex is highly fluorescent with a large red shift compared to the emission of the free ligand, indicting the Schiff base may be suitable as an optical probe for organotin compounds. The DNA binding properties of the tin complex could be relevant to its remarkable cytotoxicity against A-549, MCF-7 and Hela tumor cells. Steric effect and hydrogen bonds played a great role in the DNA binding mode.

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