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A Nine-Coordinated Bismuth(III) Complex Derived from Pentadentate 2,6-Diacetylpyridine Bis(^{4}*N*-methylthiosemicarbazone): Crystal Structure and Both in Vitro and in Vivo Biological Evaluation

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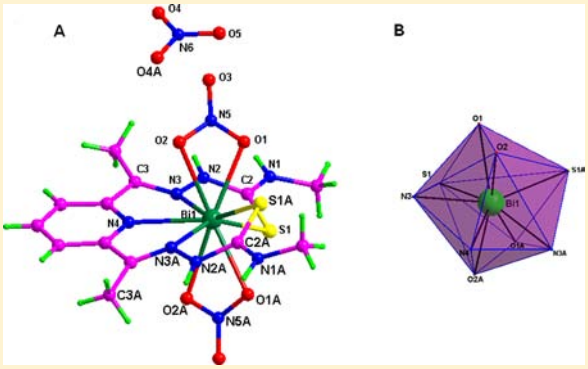
Supporting Information

ABSTRACT: Up to now, bismuth(III) complexes with thiosemicarbazones have been comparatively rare. Few in vivo biological studies have been carried out in comparison to the plentiful in vitro data. Here, an interesting nine-coordinated bismuth(III) complex, $[Bi(H_2L)(NO_3)_2]NO_3$ [**1**; H_2L = 2,6-diacetylpyridine bis(^{4}*N*-methylthiosemicarbazone)], has been synthesized and structurally characterized. The analytical data reveal the formation of 1:1 (metal/ligand) stoichiometry. In vitro biological studies have indicated that the bismuth complex **1** has shown much higher antibacterial and anticancer activities than its parent ligand, especially with MIC = 10.66 μM against *Bacillus cereus* and *Salmonella typhimurium* and IC_{50} = 26.8 μM against K562 leukemia cells, respectively. More importantly, it also evidently inhibits H22 xenograft tumor growth on tumor-bearing mice (10 mg/kg; inhibitory rate = 61.6%). These results indicate that coordination to bismuth(III) might be an interesting strategy in the discovery of new anticancer drug candidates.



INTRODUCTION

There have been a large number of studies on metal complexes of tridentate thiosemicarbazones derived from α-N-heterocyclic carboxaldehydes and ketones because of their significant biological activities.[1−5] However, metal complexes of pentadentate thiosemicarbazones that have demonstrated their versatility as chelating agents are less common.[6−9] Particularly, their main-group metal complexes, especially bismuth(III) complexes, have not received much attention. One reason may be that crystals suitable for the X-ray diffraction study of these compounds have been difficult to obtain. However, the widespread use of bismuth compounds in the medicinal realm for centuries is coming from their high effectiveness and low toxicity in the therapy of diverse microbial infections, involving syphilis, diarrhea, gastritis, and colitis.[10−13] In addition to antimicrobial activity, bismuth compounds reveal anticancer activities, radioisotopic ^{212}Bi and ^{213}Bi compounds have been applied as targeted radiotherapeutic agents for cancer therapy,[14,15] and furthermore they have the ability to reduce the side effects of cisplatin (*cis*-DDP) in carcinoma treatment. The bismuth(III) ion with a larger ionic radius (1.16 Å) may form complexes with higher coordination numbers. So, their structural characerization is interesting and meaningful.

In recent years, we have been working on the structural and biological properties of tridentate thiosemicarbazones and their metal complexes.[5] Our chemical strategy focuses on modifications to the ligand substitutions and the types of metal ions with the aim of enhancing biological activities and reducing the potential toxicity of these compounds. These results reveal that thiosemicarbazones derived from 2-acetylpyridine and their transition-metal complexes show significant cytotoxicity. After a careful literature search, main-group metal complexes of N_3S_2 pentadentate 2,6-diacetylpyridine bis(^{4}*N*-methylthiosemicarbazone) are not well documented.[6,16] It is envisaged that they are likely to exhibit interesting properties both structurally and biologically. Therefore, it seems important for us to obtain its bismuth complex as a strategy of the preparation of new drug candidates in which the metal and ligand could act synergistically.

As a part of our ongoing studies, we have synthesized and characterized a nine-coordinated bismuth(III) complex, $[Bi(H_2L)(NO_3)_2]NO_3$ (**1**), where H_2L = 2,6-diacetylpyridine bis(^{4}*N*-methylthiosemicarbazone) (Scheme 1). Growth inhibition assays have indicated that **1** exhibits significant enhancement of both antibacterial and anticancer activities with respect to H_2L. These results suggest that, at least in part, both the metal and ligand determine the biological activity. Indeed, the

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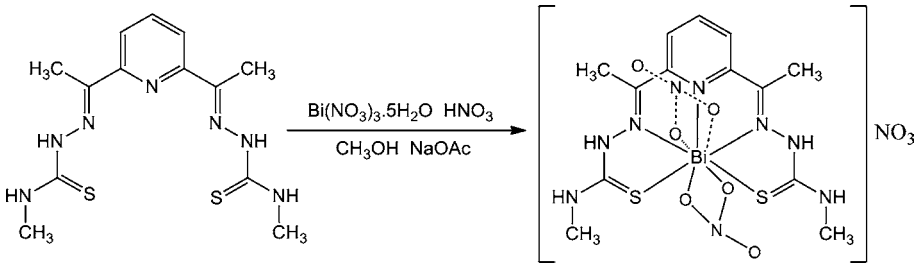
Scheme 1. Reaction Scheme for the Synthesis of 1



metal compounds could act through dual or even multiple mechanisms of action by combining the pharmacological properties of both the ligand and metal. In addition, its in vivo acute toxicity and the antitumor activity in the H22 hepatoma cells have been further investigated. Similar to other thiosemicarbazone derivatives,[17−20] **1** may have broad application in cosmetic, medicinal, food preservation, and insect control areas.

EXPERIMENTAL SECTION

General Procedures. All solvents and reagents used in this study were reagent grade and used without further purification. Gram positive bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Sarcina lutea*, and *Bacillus cereus*) and Gram negative bacteria (*Agrobacterium tumefaciens*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, and *Escherichia coli*) were purchased from the China General Microbiological Culture Collection Center (Beijing, China). K562 leukemia cells and H22 cells were purchased from the Shanghai Institute for Biological Science, Chinese Academy of Science (Shanghai, China). Kunming mice were purchased from the Laboratory Animal Center of Henan (Zhengzhou, China). The water used was redistilled and ion-free.

Elemental analysis of carbon, hydrogen, and nitrogen was performed with a Perkin-Elmer 240 analyzer. IR spectra were recorded from KBr disks on a Nicolet 170 FT-IR spectrophotometer. Mass spectrometry (MS) spectra were carried out on an Esquire 3000 LC-MS mass spectrometer. ^{1}H NMR spectra were recorded using a Bruker AV-400 spectrometer.

Synthesis of H_2L. H_2L was synthesized according to the literature method.[9a]

Synthesis of $[Bi(H_2L)(NO_3)_2]NO_3$ (1). A $Bi(NO_3)_3{\cdot}5H_2O$ (0.097 g, 0.2 mmol) solution dissolved in methanol with the help of a few drops of nitric acid was added dropwise to a methanol solution (20 mL) of 2,6-diacetylpyridine thiosemicarbazone (0.067 g, 0.2 mmol). After refluxing with stirring for 1 h, the resultant mixture was filtered. This crude product obtained was further recrystallized from methanol and dried over P_4O_{10} in vacuo. Yield: 68%. Calcd for $C_{13}H_{19}BiN_{10}S_2O_9$: C, 21.32; H, 2.61; N, 19.12. Found C, 21.35; H, 2.58; N, 19.15. IR (KBr, cm^{-1}): ν(NH) 3229, ν(C=N) 1585, ν(N−N) 1176, ν(C−S) 802. ESI-MS. Found: m/z 544.1 ($[Bi(L)]^+$). Calcd: m/z 544.1. ^{1}H NMR (DMSO-d_6): δ10.31 (s, 2H, NH), 8.64 (s, 2H, NH), 8.36 (d, J = 8 Hz, 2H, Py), 7.78 (t, J = 8 Hz, 1H, Py), 2.99 (s, 6H, CH_3) 2.37 (s, 6H, CH_3). Yellow crystals suitable for X-ray studies were obtained by the slow evaporation of a methanol solution of **1**.

Crystallography. Crystal data, experimental details, and refinement results are listed in Table 1. Crystallographic data were collected with a Siemens SMART-CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined by full-matrix least squares on F^2 with anisotropic displacement parameters for all non-hydrogen atoms using *SHELXTL*.[21] The hydrogen atoms were added in idealized geometrical positions.

Determination of Minimum Inhibitory Concentrations (MICs). The in vitro antibacterial activities of the title compounds were investigated against selected Gram positive bacteria (*B. subtilis*, *S. aureus*, *S. lutea*, and *B. cereus*) and Gram negative bacteria (*A. tumefaciens*, *S. typhimurium*, *P. aeruginosa*, and *E. coli*). The MICs (μM) were estimated by the disk diffusion method.[22,23] All determinations were performed in triplicate and confirmed by three separate experiments.

Table 1. Summary of Crystal Data and Refinement Results for 1

empirical formula	C_{13} H_{19} Bi N_{10} O_9 S_2
fw	732.50
cryst size (mm)	0.32 × 0.23 × 0.08
cryst syst	monoclinic
space group	*P*2/*c*
a (Å)	9.111(7)
b (Å)	13.899(11)
c (Å)	9.708(8)
V (Å^3)	1217.7(17)
β (deg)	97.904(14)
D_c (g/cm^3)	1.998
Z	2
μ (mm^{-1})	7.475
θ (deg)	2.26−25.00
F(000)	708
hkl range	$-10 \le h \le 10$, $-16 \le k \le 16$, $-11 \le l \le 8$
T (K)	293(2)
no. of measd reflns	2154
no. of unique reflns	1560
R_{int}	0.1612
no. of param	163
R1, wR2 [$I \ge 2\sigma(I)$]	0.0608, 0.1458
R1, wR2 (all data)	0.0799, 0.1532
GOF on F^2	1.118
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e/Å^3)	2.817, −3.621

Cytotoxicity Assay. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was carried out to evaluate the cytotoxicity. K562 leukemia cells were placed in 96-well plates at a density of 1 × 10^4 cells and then incubated with tested compounds. After 24 h of incubation, cultures were incubated in 100 μL of the medium with 10 μL of a 5 mg/mL MTT solution for 4 h at 37 °C. The medium with MTT was removed, and 100 μL of dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan. The absorbance at 570 nm was measured with a microplate reader (Bio-Tek ELX800, USA). The inhibitory percentage of each compound at various concentrations was calculated, and the IC_{50} value was determined.

Single-Dose Acute Toxicity Testing. All animal care and experimentation conformed to the *Guide for the Care and Use of Laboratory Animals* published by Henan University. A total of 70 male Kunming mice (laboratorial animal center of Henan, Zhengzhou, China), aged 5 weeks (weighing 18−22 g), were randomly divided into seven groups. The next day **1** was injected via caudal vein. The doses were 70, 59.5, 50.6, 43, 36.5, 31.1, or 26.4 mg/kg, respectively. All mortalities, clinical signs, time of onset, duration, and reversibility

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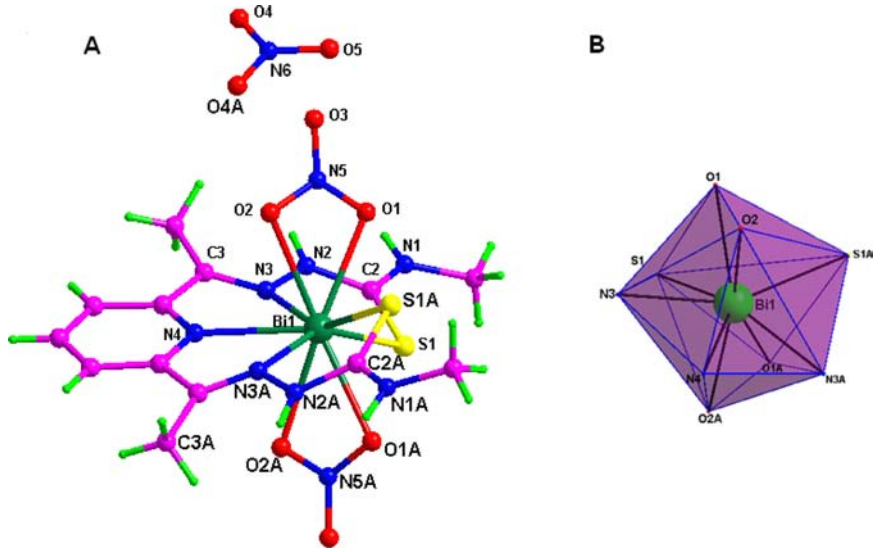

Figure 1. (A) Structure of **1** with an atomic numbering scheme. (B) Polyhedra showing distorted geometry around the bismuth atom.

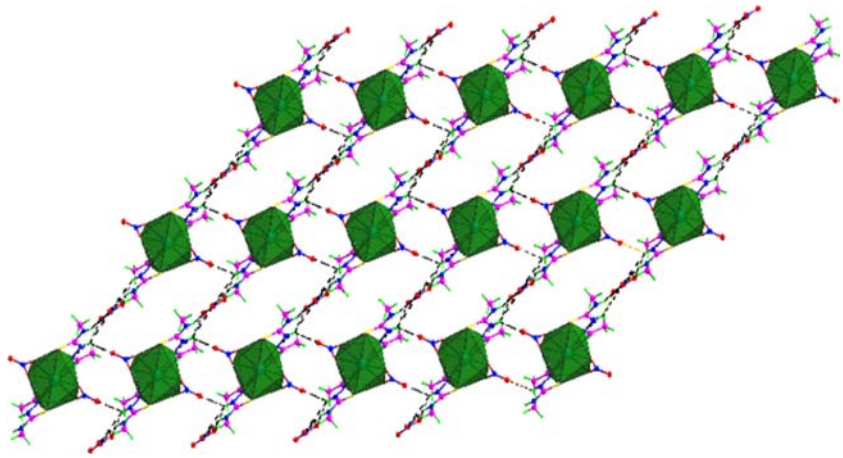

Figure 2. Molecular packing projected along the *b* axis of the crystals.

of the toxicity would be recorded for 14 days, and then the LD_{50}, which is the dose of 50% animal death, was calculated.

Subcutaneous Xenograft of H22 Hepatoma Cells in Kunming Mice. A total of 30 male Kunming mice (laboratorial animal center of Henan, Zhengzhou, China), aged 5 weeks (weighing 18−22 g), were randomly divided into three groups (control, **1**, and mitoxantrone). For solid tumor development, the Kunming mice were injected subcutaneously with 2×10^6 H22 cells. On the eighth day after inoculation, mice were administered by caudal vein injection **1** (10 mg/kg), mitoxantrone (0.4 mg/kg, as a positive control), or physiological saline for 7 consecutive days. On day 16, the mice were killed by ether anesthesia, and solid tumors were removed and weighed. The inhibitory rate was calculated as follows: inhibitory rate (%) = $[(A - B)/A] \times 100$, where A is the mean tumor weight of the control group and B is that of the drug-treated or positive group. After being weighed, the tumors were fixed in formalin and stained with hematoxylin and eosin.

RESULTS AND DISCUSSION

Crystal Structure of 1. The molecular structure of **1** along with the atomic numbering scheme is shown in Figure 1. The molecular packing projected along the *b* axis of the crystals is provided in Figure 2. Selected bond lengths and angles are listed in Table 2.

Table 2. Selected Bond Lengths (Å) and Angles (deg) for 1

Bi1−N4	2.494(10)	N4−Bi1−O1	113.4(2)
Bi1−O1	2.528(9)	N4−Bi1−O2	70.0(2)
Bi1−O2	2.546(9)	O1−Bi1−O2	157.0(3)
Bi1−N3	2.550(7)	O1−Bi1−O2	49.6(3)
Bi1−S1	2.807(3)	N4−Bi1−N3	63.23(17)
S1−C2	1.664(10)	O1−Bi1−N3	75.4(3)
C2−N2	1.391(14)	O1−Bi1−N3	127.7(3)
N2−N3	1.349(10)	O2−Bi1−N3	87.3(3)
N3−C3	1.287(11)	O2−Bi1−N3	74.9(3)
C3−C5	1.475(12)	N4−Bi1−S1	124.22(7)
N4−C5	1.336(9)	O2−Bi1−S1	120.0(2)
		O2−Bi1−S1	83.3(2)
		N3−Bi1−S1	152.7(2)
		N3−Bi1−S1	67.53(18)
		O1−Bi1−S1	76.1(2)
		O1−Bi1−S1	78.0(2)

Single-crystal X-ray analysis reveals that **1** crystallizes in the monoclinic system, with space group $P2/c$. The molecular structure of **1** contains one $[Bi(H_2L)(NO_3)_2]^+$ cation and one nitrate ion acting as the counterion (see Figure 1). The bismuth(III) ion is nine-coordinated by three nitrogen and two

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Table 3. MIC (μM) of the Tested Compounds

	MIC (μM)				
microorganism	H_2L	**1**	$Bi(NO_3)_3{\cdot}5H_2O$	Cm	Kan
B. subtilis	92.60	21.32	2062	48.34	26.81
S. aureus	1482	21.32	2062	193.4	13.41
S. lutea	*a*	42.66	1031	48.34	214.6
B. cereus	23.14	10.66	1031	96.71	107.3
A. tumefaciens		21.32	1031	48.34	6.690
S. typhimurium	370.4	10.66	1031	96.71	53.64
P. aeruginosa	2963	42.66	515.4	96.71	6.690
E. coli		170.7	1031	96.71	53.64

[a]No inhibition.

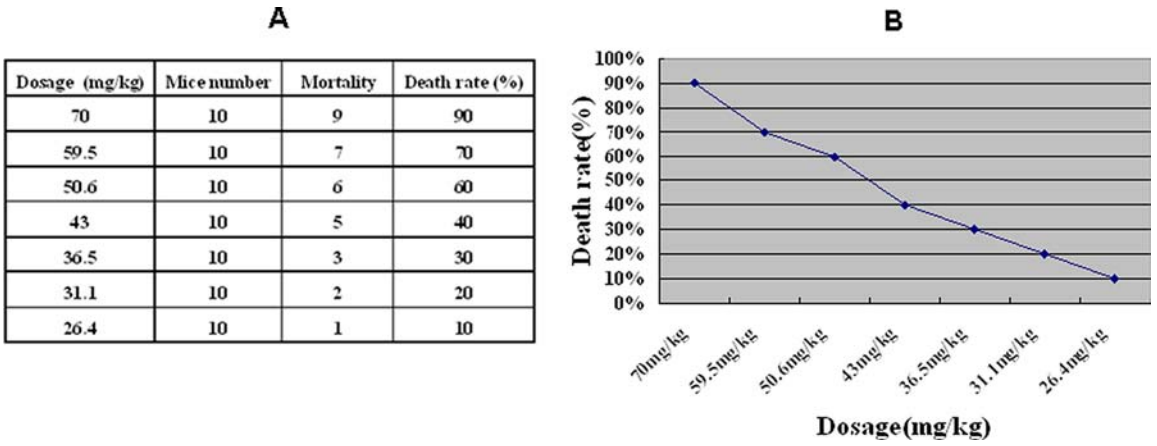

Figure 3. (A) Dose-dependent manner of the effects of **1** on the growth of mice. (B) LD_{50} of **1** = 44.7 mg/kg (95% confidence interval 39−51.2 mg/kg).

sulfur atoms from the pentadentate N_3S_2 ligand and four oxygen atoms from two nitrate ions. There are fewer reports in the literature on nine-coordinated bismuth(III) complexes containing a pentadentate thiosemicarbazone ligand.[24−28] The pentadentate neutral thiosemicarbazone ligand coordinates to the bismuth(III) ion through the pyridine nitrogen atom, two azomethine nitrogen atoms, and two sulfur atoms, respectively. Two bidentate nitrate ions coordinate to the bismuth atom via [O, O], forming two four-membered chelate rings symmetrically coordinated to the bismuth(III) center from two sides of the plane formed by N3, N4, and N3A. The bond distances around the bismuth(III) ion [Bi1−N4 2.494(10), Bi1−O1/O1A 2.528(9), Bi1−O2/O2A 2.546(9), Bi1−N3/N3A 2.550(7), Bi1−S1/S1A 2.807(3) Å; Table 2] are compared with other data in related bismuth(III) complexes.[27] The bond lengths agree well with an imine−thione form of the ligand (supported by the presence of hydrazinic N−H and a C═S distance of ca.1.664(10) Å, which is much shorter than a single C−S bond).[4] The longer Bi−N and Bi−S bonds result from the larger ionic radius of Bi^{3+} compared to that of Mn^{2+}, Zn^{2+} and Ni^{2+}, respectively.[5] Although the azomethine nitrogen atoms are typically stronger donors than pyridine, the two $Bi-N_{imine}$ bond distances [2.550(7) Å] in the present complex are longer than the $Bi-N_{py}$ distance [2.494(10) Å]. While $M-N_{imine}$ bond distances in complexes of tridentate NNS thiosemicarbazone derived from heterocyclic aldehydes and ketones are invariably shorter than the $M-N_{pyridine}$ distances, the reverse appears to be true for metal complexes of pentadentate thiosemicarbazone ligands.[29] This is probably due to the geometrical requirements of the pentadentate N_3S_2 ligand and the fact that the pyridine nitrogen donor occupies the central position of the pentadentate ligand and is forced into a shorter than normal interaction with the metal because of the restraints of the two chelating arms.

The molecules of **1** are held together in the crystal packing through intermolecular hydrogen bonds involving the terminal nitrogen atom N1, the hydrazine nitrogen atom N2, the nitrogen atom N6 of the nitrate group, the oxygen atom O3 of the bidentate nitrate group, and the oxygen atoms O4 and O5 of the nitrate ion, respectively (Figure 2). The separations for N1···O5 and N1···N6 (symmetry code: x, y, z −1) are 2.876(10) and 3.491(14) Å, with the N1−H1A···O5 angle being 157.6° and N1−H1A···N6 angle 158.2°, the separations for N1···O4 and N2···O4 (symmetry code: $-x+1$, y, $-z+{}^1/_2$) are 3.262(12) and 2.854(10) Å, with the N1−H1A···O4 angle being 135.6° and the N2−H2A···O4 angle 140.0°, and the separation for N2···O3 is 2.981(16) Å, with the N2−H2A···O3 angle being 127.7° (symmetry code: $x+1$, y, z), respectively (Table S1 in the Supporting Information).

In Vitro Antibacterial Activity. In view of the antimicrobial activity of thiosemicarbazones,[17,30] we have tested the inhibition ability of the obtained compounds as well as the starting compound $Bi(NO_3)_3{\cdot}5H_2O$ against the selected four Gram positive bacteria and four Gram negative bacteria by the disk diffusion method. Our results demonstrate that **1** exhibits broad and excellent activities against the tested microorganisms (Table 3). However, $Bi(NO_3)_3{\cdot}5H_2O$ alone is inactive, and H_2L only shows effective activity against *B. cereus* (MIC = 23.14 μM) under the same experimental conditions. Therefore, the coordination of bismuth(III) has a pronounced effect on the

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antibacterial activity of the ligand. It should be emphasized that **1** also shows much higher activities with MIC = 10.66 μM against Gram positive bacteria *B. cereus* and Gram negative bacteria *S. typhimurium* than control antibiotics chloramphenicol (Cm) and kanamycin sulfate (Kan), respectively. These gratifying results are encouraging its further in vivo screening. A detailed evaluation of the mechanism will be investigated in the future.

In Vitro Cytotoxicity. In terms of the cytotoxic activity of thiosemicarbazones,[31−34] we have tested the ability of the obtained compounds to inhibit cancer cell growth against K562 leukemia cells (Figure S1 in the Supporting Information). The investigation has clearly shown that **1** shows a lower IC_{50} value (26.8 μM) than both H_2L (82.3 μM) and $Bi(NO_3)_3{\cdot}5H_2O$ (41.2 μM) against K562 leukemia cells. Thus, coordination to bismuth(III) is essential for the anticancer activity. These results are consistent with the cases of many other analogues of thiosemicarbazones.[9,18,20,35]

Acute Toxicity. Acute toxicity studies in animals are usually necessary for any pharmaceutical intended for human use.[35] Acute toxicity studies may also aid in the selection of starting doses for phase 1 human studies and provide information relevant to acute overdosing in humans. In this study, **1** produces dose-dependent effects in mice H22 hepatoma models (Figure 3A), and the LD_{50} of **1** is 44.7 mg/kg in Kunming mice by caudal vein injection (95% confidence interval 39−51.2 mg/kg; Figure 3B).

Antitumor Activity in Vivo. 2,6-Diacetylpyridine bis(thiosemicarbazone)s and their metal complexes have attracted more attention because of their analytical applications and biological activities.[34,36−39] However, few in vivo studies have been carried out in comparison to the plentiful in vitro data. Indeed, in vivo and in vitro experiments may give contradictory information in many cases. The excellent in vitro impacts are often not translated into the expected potency in vivo. Therefore, in vivo trials may be more important than in vitro ones.[40] To further evaluate the antitumor activity of **1** in vivo, we chose the H22 (mice hepotoma cell lines) tumor transplant models: solid tumor (tumor growth inhibition evaluation). Mitoxantone (mito) is a kind of antibiotic antitumor drug, used as the reference compound for comparison. The tumor growth inhibition rates of each group were calculated, and the ratios are 61.6% (0.54 ± 0.16 g) and 43.5% (0.79 ± 0.22 g) for **1** and mitoxantone compared to the control mice (1.41 ± 0.18 g), respectively (Figure S2 in the Supporting Information). Thus, tumor growth inhibitory rates in mice treated with **1** and mitoxantone were dramatically enhanced.

In summary, the bismuth(III) complex **1** derived from the pentadentate thiosemicarbazone has been synthesized and structurally characterized. The formation of a nine-coordinated structure of the bismuth(III) ion is unusual and interesting. Coordination of the bismuth(III) ion enhances both the antibacterial activity and cytotoxicity of the free ligand in vitro. More importantly, **1** also indicates an effective H22 xenograft tumor growth inhibition in vivo. The findings of this study provide important information for the exploitation and utilization of bismuth(III)-based drugs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Data of hydrogen bond lengths and angles, the results of cytotoxicity in vitro and antitumor activity in vivo, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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