The synthesis and evaluation of the antitumor and antibacterial activity of two novel oxovanadium complexes

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Abstract
Two novel oxovanadium(IV) complexes ([VO(hntdtsc)(BPIP)] and [VO(hntdtsc)(MOPIP)] (hntdtsc = 2-hydroxy-1-naphthaldehydethiosemicarbazone, BPIP = 2-(4-bromophenyl)-imidazo[4,5-f]-1,10-phenanthroline, MOPIP = 2-(4-methoxyphenyl)-imidazo[4,5-f]-1,10-phenanthroline), are synthesized and characterized. Subsequently, the Methyl Thioglycolyl Tetrazolium (MTT) assay is used to investigate the antitumor activity of the ligand and two complexes in vitro. The results indicate that both complexes could significantly inhibit selected tumor cells (SH-SYSY, MCF-7, and SK-N-SH). In addition, the antibacterial activity of VO(hntdtsc)(BPIP) against Staphylococcus aureus is further investigated. Interestingly, VO(hntdtsc)(BPIP) can efficiently attenuate S. aureus growth and abrogate α-hemolysin secretion and biofilm formation. The plasmid DNA cleavage activity of both complexes is also investigated. The results suggest that supercoiled plasmid DNA is efficiently cleaved after treatment with each complex, which might contribute to the biological activity of these oxovanadium(IV) complexes.

Keywords
antibacterial, anticancer, DNA cleavage, oxovanadium complexes

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Introduction
Nowadays, tumors and resistant bacterial infections are the main threats to global health. Resistant bacterial infections cause about 25,000 patient deaths every year around the world. Furthermore, cancer has been highlighted a major concern and the US National Cancer Institute has forecasted up to a 50% rise in cancer cases. Even worse, these data will drastically increase to approximately 21 million new cases over the next two decades.1–3 Therefore, complexes with antitumor or antibacterial activity have received wide attention over recent decades.

In recent years, numerous vanadium-based compounds have been synthesized, and many of them show significant antibacterial or antitumor activity.1–13 Vanadium compounds containing tridentate salicylaldehyde semicarbazone derivatives show anti-Trypanosoma cruzi activity in vitro. However, vanadium complexes with Schiff bases show significantly in vitro antibacterial activities against gram-negative bacteria (e.g. Escherichia coli and Salmonella typhimurium) as well as gram-positive bacteria (e.g. S. aureus and Bacillus subtilis).14–17 More importantly, many vanadium compounds also show significant anticancer activity.18–20

In a previous study, we synthesized a series of oxovanadium(IV) complexes with thiosemicarbazone ligands. These complexes showed highly cytotoxic activity against cancer cells, and we found that organic ligands coordinated with vanadium could enhance their biological activities.21,22 To expand our studies, two oxovanadium(IV) complexes, ([VO(hntdtsc)(BPIP)] (1) and [VO(hntdtsc)(MOPIP)] (2)) (Scheme 1) have been synthesized. Subsequently, the MTT assay was used to investigate the antitumor activity of the ligand and the two complexes in vitro. In addition, the antibacterial activity of complexes 1 against S. aureus was also studied. The results showed that the two oxovanadium(IV) complexes possess significant activity against tumor cells. In addition, complex 1 could efficiently attenuate S. aureus growth and abrogate α-hemolysin secretion and biofilm formation. In addition,
the plasmid DNA cleavage activity of the two complexes was also investigated.

Results and discussion

Synthesis and characterization

The organic ligands (hntdsc, BPIP, and MOPIP) were synthesized via a previously reported procedure, while the two vanadium complexes were obtained by refluxing a mixture of the organic ligands and VO(acac)$_2$ in absolute methanol at 80°C under an argon atmosphere. The ligands and the two complexes were characterized by elemental analysis, electrospray ionization mass spectrometry (ESI-MS), infrared (IR), and nuclear magnetic resonance (NMR). The IR spectra of the free ligands were compared with those of the two complexes. The $\nu$(V–O) stretch for the two vanadium complexes could be clearly observed at 946–957 cm$^{-1}$. In the $^1$H NMR spectra of the ligands, all the expected protons were observed in appropriate regions. For the hntdsc ligand, the $^1$H NMR spectrum showed signals of NHCs, hydroxyl (OH), amine (NH$_2$), and imine (CH=N) protons. In addition, the structures of the ligands were further confirmed by $^1$C NMR spectra. According to ESI-MS analysis, the free ligand BPIP showed signals at $m/z$ 375.0 [M-(Br$_{79}$)$^+$+H]$^+$ and 377.0 [M-(Br$_{81}$)$^+$+H]$^+$, while MOPIP showed signals at $m/z$ 327.1 [M$^+$+H]$^+$ and 349.1 [M$^+$+Na]$^+$. For the oxovanadium complexes, complex 1 showed signals at $m/z$ 685.0 [M-(Br$_{79}$)$^+$+H]$^+$ and 687.0 [M-(Br$_{81}$)$^+$+H]$^+$, while the signals for complex 2 occurred at $m/z$ 637.1 [M$^+$+Na]$^+$. Hence the structures of both complexes were determined.

Anticancer activities in vitro

The anticancer activities of both complexes and the ligands were examined by MTT assays against tumor cell lines. The IC$_{50}$ values of the complexes together with those of cisplatin are shown in Table 1. The data clearly indicate that the free ligands and both vanadium complexes showed significant antitumor activities. More importantly, the two vanadium complexes all exhibited lower IC$_{50}$ values than their corresponding free ligands, which is in agreement with our previous work reporting that organic ligands coordinated with vanadium can result in enhanced biological activities. Moreover, complex 1 possessing strongly electron-withdrawing groups showed improved antiproliferative activity, with IC$_{50}$ values lower than those of cisplatin (ca. 7.01, 12.5, and 2.65 $\mu$M, respectively). It is worth noting that the cytotoxicities of complex 1 toward SH-SY5Y and SK-N-SH cells were larger than the previously reported series of oxovanadium(IV) complexes against the same cell lines. In addition, the cytotoxicity of complex 1 toward normal human cells (MRC-5 cell line) was tested. The IC$_{50}$ value (25$^\circ\pm$3.38 $\mu$M) of complex 1 toward the MRC-5 cell line was higher than those toward tumor cells (1.86$^\circ\pm$0.31 $\mu$M for SH-SY5Y, 5.51$^\circ\pm$0.62 $\mu$M for MCF-7, 0.97$^\circ\pm$0.04 $\mu$M for SK-N-SH cell). The reason for the specific activity against tumors cells might be because vanadium complexes can interact with DNA. The results presented here provide strong evidence that changes in ligand architectures can increase the antitumor activity of oxovanadium complexes and that an electron-withdrawing group is more conducive to increasing the antitumor activity of the vanadium complex.

Antibacterial activities

As many metal complexes also exhibit excellent antibacterial activity, to investigate further the antibacterial activity of the vanadium complexes, complex 1, which showed better antitumor activity, was also screened for its antibacterial activities against _S. aureus_ (gram-positive bacterial strains). _S. aureus_ is an important human pathogen which causes many diseases. At first, the bacterial growth curve of _S. aureus_ strains upon treatment with different concentrations of complex 1 was examined. As shown in Figure 1, the...
growth of *S. aureus* was significantly inhibited in the presence of 50 µM of complex 1. Moreover, the antibacterial activities of complex 1 were concentration dependent. It should be noted that the reason why *S. aureus* can cause serious life-threatening diseases is partly due to its ability to secrete virulence factors and generate biofilms. Thus, the inhibitory activity of complex 1 against virulence factor secretion, and biofilm formation in *S. aureus* strains was also investigated. First, we investigated whether complex 1 would inhibit *S. aureus* biofilm formation. As shown in Figure 2, the bacterial biofilm formation was markedly inhibited in the presence of different concentrations (20 and 40 µM, respectively) of complex 1. Thus the vanadium complex can abrogate biofilm formation in *S. aureus*. Next, rabbit blood cells were used to analyze the hemolysin levels in bacterial culture supernatants after treatment with complex 1. The results indicated that α-hemolysin secretion by *S. aureus* was dramatically inhibited after treatment with subinhibitory concentrations of complex 1 (20 and 40 µM, respectively; Figure 3). To further confirm these results, real-time polymerase chain reaction (PCR) was employed to determine the transcription level of *hla* which encodes α-hemolysin. The results obtained were consistent with the hemolysin levels, with the transcription level of *hla* genes being significantly decreased after treatment with complex 1 (20 and 40 µM, respectively; Figure 4). Taken together, these results provide strong evidence that the vanadium complex 1 abrogates α-hemolysin secretion in *S. aureus*.

**DNA cleavage**

Finally, the possible underlying mechanism behind the activities of the two complexes was investigated. It has been reported that the DNA cleavage ability of vanadium complexes is closely associated with their biological activity. Therefore, the DNA cleavage ability of the two vanadium complexes was examined. Normally, the intact circular plasmid DNA (Form I) migrates relatively fast during agarose gel electrophoresis. However, after one strand is broken, the plasmid DNA migrates more slowly due to the relaxation of the open circular supercoil (Form II). Finally, the linear DNA (Form III) is generated which migrates between forms I and II after both strands are broken. As can be seen in Figure 5, after incubation with different concentrations of complexes 1 or 2 along with H₂O₂,

| Compound | IC₅₀ (µM) |
|----------|-----------|
| MRC-5    |           |
| SH-SYSY  |           |
| MCF-7    |           |
| SK-N-SH  |           |
| Cisplatin| –         |
| hntdsc   | –         |
| VO(acac)₂| –         |
| BPIP     | –         |
| MOPIP    | –         |
| 1        | 25° ± 3.38| 1.86 ± 0.31| 5.51 ± 0.62| 0.97 ± 0.04|
| 2        | –         | 8.2 ± 0.44 | 11.4 ± 2.75| 2.1 ± 0.13|

Cells were treated with various concentrations of the complex to be tested; a. MRC-5 (human lung fibroblast cells and human normal cells); b. SH-SYSY (human neuroblastoma cells); c. MCF-7 (human breast adenocarcinoma cells); d. SK-N-SH (human female neuroblastoma cells).

**Table 1.** Antiproliferative effects of free ligands, complexes 1 and 2, and cisplatin on different tumor cells lines. Data are expressed as IC₅₀ (µM).

**Figure 1.** The growth curves of *S. aureus* in the presence of complex 1. The OD₆₀₀ (the absorbance of bacteria cultures at 600 nm) value was monitored at 30-min intervals.

**Figure 2.** The biofilm formation of *S. aureus* after incubation with complex 1.

**Figure 3.** Rabbit erythrocyte lysis activity of *S. aureus* culture supernatants after treatment with complex 1.
the amount of Form I dramatically decreases while the quantity of Form II increases (lanes 3, 4, 5, 8, 9, and 10 in Figure 5). In addition, Form I even disappears after incubation with complex 1, indicating that this complex exhibits better cleavage activity compared with complex 2. This is also consistent with the biological activity of complex 1 exhibiting lower IC50 values against tumor cells.

Moreover, to investigate further the possible mechanism of DNA cleavage, L-histidine or dimethyl sulfoxide (DMSO) were used. As can be seen in Figure 5, after the addition of a singlet oxygen quencher (L-histidine), no apparent change was observed. However, after addition of DMSO (a hydroxyl radical scavenger), DNA cleavage was inhibited (lanes 7 and 12 in Figure 5), which clearly indicates that .OH free radicals play a vital role in the cleavage reaction. The .OH radicals may be generated as follows: (VO2+ + H2O2 → VO2+ + .OH + H+).27

Conclusion

In summary, we have synthesized and characterized two oxovanadium(IV) complexes: [VO(hntdsc)(BPIP)] (1) and [VO(hntdsc)(MOPIP)] (2). Their antitumor activity was investigated by MTT assays, with the results indicating that the two complexes exhibited significant inhibition activity against tumor cells (SH-SY5Y, MCF-7, and SK-N-SH). In addition, the antibacterial activity of complex 1 was also investigated. The results clearly indicated that this complex could efficiently attenuate S. aureus growth and abrogate the secretion of the toxin (α-hemolysin) as well as the generation of bacterial biofilms. Finally, mechanistic studies indicated that both oxovanadium complexes showed meaningful DNA cleavage activity. It is worth noting that complex 1 possessing strongly electron-withdrawing groups showed better biological activity. The results suggest that strongly electron-withdrawing groups can increase the biological activity of vanadium complexes. However, the complexes prepared here were not sufficiently active, and further work is in progress to prepare more potent oxovanadium compounds.

Experimental section

Materials and apparatus

All the chemical reagents and solvents were commercially available and of analytical reagent grade. Microanalysis (C, H, and N) was carried out with a PerkinElmer 240Q elemental analyzer (PerkinElmer 240Q elemental analyzer, USA.). Electrospray mass spectra (ES-MS) were recorded on an LCQ system (Finnigan MAT, USA) using methanol as the mobile phase. NMR spectra were recorded on a Varian-500 spectrometer. All chemical shifts are given relative to tetramethyl silane (TMS). IR spectra were recorded on a Bomen Fourier transfer infrared spectroscopy (FTIR) model MB102 instrument using KBr pellets. The transcription level of detected gene was subsequently studied on a StepOnePlus Real-time PCR system (Life Technologies, USA).

DNA cleavage

To Tris-HCl buffer, pBR322 DNA (0.1 μg) and different concentrations of the vanadium complexes were added. After incubation at 37°C, the solution was loaded onto 0.8% agarose gel and then analyzed by electrophoresis. After staining with ethidium bromide, the gel was photographed via Alpha Innotech IS-5500 fluorescence chemiluminescence (Alpha Innotech, USA).

MTT assay

All complexes and ligands were diluted with RPMI 1640 before use. Initially, in 96-well plates, MRC-5, SH-SY5Y, MCF-7, and SK-N-SH cells with a density of 2×104 cells per well were added. After incubation for 48 h at 37°C, 5% CO2 and MTT dye solution were added. N,N-Dimethylformamide (50%) solution and sodium dodecyl sulfate (20%) were added after 4 h of incubation. Subsequently, the absorbance of each well at 490 nm was measured.

The growth curves of S. aureus

The growth curves of S. aureus were measured by monitoring the OD600 values at 30-min intervals. Briefly, overnight cultured S. aureus were 1:100 diluted into fresh TSB medium and then cultured at 37°C. After the OD600 of bacterial culture suspension up to 1, the bacteria were 1:10 diluted into fresh medium again. Finally, the bacterial suspension cultured at 37°C, and the OD600 values was recorded at 30-min intervals.

Measurement of gene expression

Overnight cultured S. aureus Newman were diluted into fresh TSB medium. After the OD600 = 0.6, the oxovanadium complexes were added and further incubated at 37°C. After incubation for 1 h, the total RNAs in S. aureus were isolated, and the cDNA was determined by reverse transcription using a StepOnePlus Real-time PCR system (Life Technologies, USA).
transcription. The transcription levels of the genes were monitored by real-time PCR.

**Hemolysin activity assay**

*S. aureus* culture were grown for 9 h at 37°C and then the supernatant was obtained by centrifugation (12,000 g). Subsequently, 0.1 mL of the supernatant and 20 µL of defibrinated rabbit blood cells were added into 1 mL of bovine serum albumin (BSA) buffer (20 mM KH2PO4, 1 mM MgCl2, 150 mM NaCl, and 1 mg/mL BSA). After incubation for 25 min at 37°C, intact blood cells were removed by centrifugation (5500 g), and the absorbance at 543 nm of the supernatants was monitored.

**S. aureus biofilm formation**

Overnight cultured *S. aureus* Newman were 1:200 diluted by fresh TSB medium. Subsequently, 1 mL of the bacterial culture was added to a 24-well microtiter plate. The bacterial culture was removed, and the plate was washed with water three times after being cultured for 36 h. After drying overnight, 0.1% of crystal violet solution was added to the plate. The violet solution was removed and washed with water after 15 min. The absorbance at 595 nm was monitored after addition of 2 mL of acetic acid.

**Synthesis of the ligands and complexes**

**Synthesis of 2-hydroxy-1-naphthaldehyde thiosemicarbazone (hntdtsc).** This ligand was prepared according to the methods in the literature.23 A mixture solution of 2-hydroxy-1-naphthaldehyde (0.861 g, 5 mmol) and thiosemicarbazide (0.455 g, 5 mmol) in absolute alcohol 20 mL. A white gosspine precipitate could obtain after being stirred at 50 for 3 h. The product was used without further purification. White gosspine powder. Yield: 0.910 g, 74%. m.p. 256 °C–258 °C. ESI-MS (CH3OH): m/z = 246.0 ([M+1]+). 1H NMR (400 MHz, CDCl3) δ = 11.30 (s, 1H), 10.39 (s, 1H), 8.42 (d, J = 7.2 Hz, 1H), 8.12 (s, 1H), 7.82–7.70 (m, 3H), 7.53–7.44 (m, 1H), 7.30 (t, J = 7.4 Hz, 1H), and 7.12 (d, J = 8.8 Hz, 1H). 13C NMR (100 MHz, CDCl3) δ = 177.6, 156.6, 143.1, 132.4, 131.6, 128.7, 128.1, 127.8, 123.4, 122.7, 118.4, and 109.7.

**Synthesis of 2-(4-bromophenyl)-1H-imidazo[4,5-f]1,10-phenanthroline (BPIP).** This ligand was prepared according to the methods in the literature.22 A mixture of phenanthroquinone (0.525 g, 2.5 mmol), ammonium acetate (3.88 g, 50 mmol) and bromobenzaldehyde (0.542 g, 3.5 mmol) in glacial acetic acid 10 mL was refluxed for 6 h. The solution was diluted with water 25 mL and neutralized with ammonium hydroxide. The resulting precipitate was washed with water and then purified by column chromatography over 60–80 mesh SiO2 using absolute ethanol as the eluent. Yellowish powder. Yield: 0.426 g, 53%. m.p. 268 °C–271 °C. ESI-MS (CH3OH): m/z = 375.0 ([M-(Br37)+1]+), 377.0 ([M-(Br39)+1]+). IR (KBr): 3420 (s), 3095 (vs), 1710 (m), 1614 (m), 1578 (m), 1556 (s), 1475 (vs), 1453 (vs), 1353 (m), 1247 (s), 1188 (m), 1097 (s), 1068 (m), 1009 (s), 967 (m), 834 (m), 806 (s), 737 (s), 718 (m), and 616 (m) cm‒1. 1H NMR (400 MHz, DMSO-d6) δ = 8.95 (s, 2H), 8.81 (d, J = 7.9 Hz, 2H), 8.14 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 5.9 Hz, 4H); 13C NMR (100 MHz, DMSO) δ = 149.6, 147.9, 143.7, 132.0, 129.6, 129.3, 128.1, 123.4, 123.3, and 122.9.

**Synthesis of 2-(4-methoxyphenyl)-1H-imidazo[4,5-f]1,10-phenanthroline (MOPIP).** This ligand was prepared according to the methods in the literature.22 In brief, this ligand was synthesized by a similar procedure as that described for BPIP, with p-methoxybenzaldehyde (0.375 g, 3.5 mmol) in place of bromobenzaldehyde. Yellowish powder. Yield: 0.277 g, 41 %. m.p. 263 °C–265 °C. ESI-MS (CH3OH): m/z = 327.1 ([M+1]+), 349.1 ([M+2]+). IR (KBr): 3082 (vs), 2837 (m), 1612 (s), 1562 (s), 1523 (s), 1484 (s), 1454 (s), 1399 (s), 1293 (m), 1256 (s), 1181 (s), 1071 (m), 1032 (m), 834 (m), 740 (s), and 618 (m) cm‒1. 1H NMR (400 MHz, DMSO-d6) δ = 13.50 (s, 1H), 8.93 (d, J = 3.7 Hz, 1H), 8.12 (s, 1H), 7.82–7.70 (m, 3H), 7.53–7.44 (m, 1H), 7.30 (t, J = 7.4 Hz, 1H), and 7.12 (d, J = 8.8 Hz, 1H). 13C NMR (100 MHz, DMSO) δ = 177.6, 156.6, 143.1, 132.4, 131.6, 128.7, 128.1, 127.8, 123.4, 122.7, 118.4, and 109.7.

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**Figure 5.** Cleavage of pBR322 DNA by oxovanadium complexes 2 and 1 in buffer B (50 mM Tris–HCl and 18 mM NaCl, pH 7.2). DNA was stained with ethidium bromide.
δ = 160.0, 156.8, 156.6, 154.0, 149.0, 144.5, 137.9, 137.7, 130.3, 128.1, 127.8, 127.7, 125.9, 124.4, 124.3, 123.7, 115.0, and 67.4.

**Synthesis of [VO(hntdtsc)(BPIP)] (1)**

A mixture of hntdtsc (0.123 g, 0.5 mmol) and BPIP (0.188 g, 0.5 mmol) in absolute methanol (100 mL) was heated at 80 °C under argon for 2 h. Subsequently, 10 mL of methanolic solution of VO (acac)₂ (0.133 g, 0.5 mmol) was added. After refluxing for another 4 h, a reddish-brown precipitate was obtained which was washed with absolute methanol and then dried in vacuo. Reddish-brown powder. Yield: 0.277 g, 81%. m.p. > 300 °C. Anal. Calcd. for C_{31}H_{21}N_{7}O_{2}SVBr: C, 54.32; H, 2.94; and N, 14.30. Found: C, 54.39; H, 3.02; and N, 14.26. IR (KBr): 3317 (s), 3174 (m), 1615 (s), 1597 (s), 1538 (s), 1503 (s), 1453 (s), 1427 (s), 1385 (s), 1332 (s), 1246 (m), 1192 (m), 1070 (s), 1009 (s), 946 (s, VO), 820 (s), and 730 (m) cm⁻¹. HRMS (ESI) m/z: calcd for C_{31}H_{21}BrN_{7}O_{2}SV [M + H]+, 685.0100 and 687.0080; found 685.0100 and 687.0087.

**Synthesis of [VO(hntdtsc)(MOPIP)] (2)**

This complex was synthesized by a similar procedure as that used for complex 1, with MOPIP in place of BPIP. Yield: 0.233 g, 73%. Reddish-brown powder. m.p. > 300 °C. Anal. Calcd. for C_{32}H_{23}N_{7}O_{3}SV: C, 60.38; H, 3.63; and N, 15.40. Found: C, 60.31; H, 3.71; and N, 15.32. IR (KBr): 3319 (s), 3183 (s), 1614 (s), 1574 (m), 1537 (s), 1482 (s), 1454 (s), 1331 (m), 1255 (s), 1186 (m), 1079 (s), 1046 (m), 1028 (m), 949 (s, VO), 816 (s), 742 (s), 730 (m), and 621 (m) cm⁻¹. HRMS (ESI) m/z: calcd for C_{32}H_{24}N_{7}O_{3}SV [M + H]+, 637.1101; found 637.1124.

**Declaration of conflicting interests**

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**Supplemental material**

Supplemental material for this article is available online.

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