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Synthesis, crystal structures and insulin-like activity of three new oxidovanadium(V) complexes with aroylhydrazone ligand

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ABSTRACT

Three new oxidovanadium(V) complexes were designed, synthesized and characterized by C, H, N elemental analysis, single crystal X-ray diffraction , UV/Vis and IR spectra. Complex **1**: [VOL^1X] (H_2L^1 = (*E*)-N′-(2-hydroxybenzylidene)-3-methbenzohydrazide, HX = ethylmaltol = 2-ethyl-3-hydroxy-4-pyrone), Complex **2**: [$VOL^2(CH_3O)(CH_3OH)$], (H_2L^2 = $C_{16}H_{16}N_2O_4$ = (*E*)-N′-(2-hydroxybenzylidene)-3,5-dimethoxybenzohydrazide, CH_3OH = methanol), Complex **3**: [VOL^3X] (H_2L^3 = (E)-N′-(3-ethoxy-2-hydroxybenzylidene)-3,5-dimethoxybenzohydrazide). The insulin-like activity of the three complexes was tested. Both normal and streptozotocin (STZ)-diabetic mice were administered intragastrically for two weeks. It was found that the complexes at doses of 10.0 and 5.0 mg V·kg^{-1} can significantly decrease the blood glucose level in STZ-diabetic mice, and the blood glucose level in the treated normal mice was not altered. The lesions of kidney and liver caused by diabetes have varying degrees of improvement.

1. Introduction

Since 1980s, inorganic vanadium salts and vanadium complexes with various ligands have been reported to possess potent pharmacological effects of insulin-like activity [1–4]. Studies indicated that vanadium compounds improve not only hyperglycemia in human subjects and animal models of type I diabetes but also glucose homeostasis in type II diabetes [5,6]. However, the inorganic vanadium salts are considered as less active and more toxic. In order to reduce the side effects of inorganic vanadium salts, vanadium complexes have received particular attention and demonstrated to be effective [7–9]. Schiff bases play important role in the development of coordination chemistry related to their biological properties. Several vanadium complexes derived from Schiff bases have shown to normalize blood glucose level with high efficiency and low toxicity, even at low concentrations [10,11]. Schiff bases with hydrazone type are particular interesting due to their biological properties [12–16]. In addition, vanadium complexes with maltol ligands such as bis(maltolato)oxovanadium(IV) (BMOV) and bis(ethylmaltolato)oxovanadium(IV) (BEOV) have been proved to possess effective insulin enhancing activity [17–19]. In order to explore novel material with effective insulin-like activity, Three oxidovanadium complexes have been prepared and studied on their insulin-like activity to both normal and streptozotocin (STZ)-diabetic mice.

2. Experimental

2.1. Materials and measurements

Starting materials, reagents and solvents were purchased from commercial suppliers with AR grade, and used without purification. The aroylhydrazones were prepared according to the literature method [16]. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were recorded on a Jasco FT/IR-4000 spectrometer as KBr pellets in the 4000–400 cm^{-1} region.

2.2. Synthesis of the complexes

2.2.1. Complex *1*

Hydrazinium hydroxide (0.012 mol) were added to a ethanol solution (30 mL) of 3-methoxybenzoate (0.01 mol). After 10 h refluxing and stirring, the 3-methoxybenzohydrazide were obtained by reducing pressure distillation, filtering and recrystallizing. Mixing the 3-

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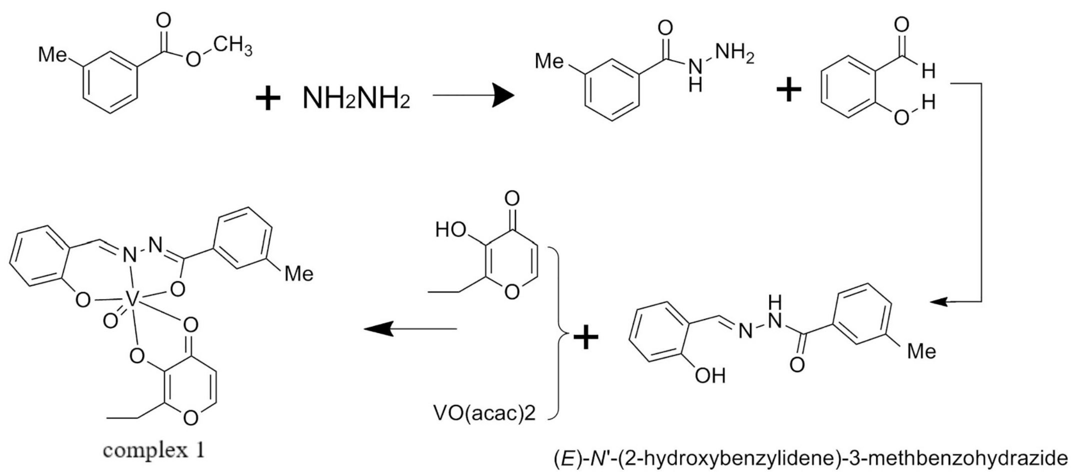


Scheme 1. Synthesis of complex 1.

methoxybenzohydrazide (1.0 mmol) and salicylaldehyde (1.0 mmol) into the methanolic solution (20 mL) with stirring. After 30 min, the ethyl maltol (1.0 mmol) and vanadyl acetylacetonate [$VO(acac)_2$] (1.0 mmol) were added to the solution with stirring and brown solution were obtained (Schemes 1). The solution were left for 7 days at room temperature, brown block shaped single crystals of the complex, which are suitable for the structure determination, were got at the bottom of the vessel because of the slow evaporation of the solvent. Yields: 63%.

Anal. Calc. for $C_{22}H_{19}N_2O_6V$ (MW = 458.33): C, 57.60; H, 4.15; N, 6.11%.

Found: C, 57.57; H, 4.15; N, 6.13%.

IR data (cm-1): 3433(w), 1603(s), 1549(s), 1520(m), 1469(w), 1444(m), 1373(w), 1337(s), 1278(m), 1258(s), 1223(w), 1192(m), 972(s), 908(w), 837(m), 812(w), 763(m), 728(m), 650(m), 632(w), 588(w), 525(w), 478(w).

^{1}H NMR (300 MHz, DMSO) δ 9.18 (s, 1H,CH = N), 8.46 (d, 1H, ArH), 7.81 (d, 1H, ArH), 7.68–7.55 (m, 3H, ArH), 7.35 (t, 2H, ArH), 7.05 (t, 1H, ArH), 6.88 (d, 1H, ArH), 6.67 (d, 1H, ArH), 2.99 (q, 2H, CH2CH3), 2.34 (s, 3H, CH3), 1.30 (s, 3H, CH3).

2.2.2. Complex 2

Hydrazinium hydroxide (0.012 mol) were added to a ethanol solution (30 mL) of 3,5-dimethoxybenzoate (0.01 mol). After 10 h refluxing and stirring, the 3,5-dimethoxybenzohydrazide were obtained by reducing pressure distillation, filtering and recrystallizing. Mixing the 3,5-dimethoxybenzohydrazide (1.0 mmol) and salicylaldehyde (1.0 mmol) into the methanolic solution (20 mL) with stirring. After 30 min, the $VO(acac)_2$ (1.0 mmol) were added to the solution with stirring and brown solution were obtained (Schemes 2). The solution were left for 7 days at room temperature, brown block shaped single crystals of the complex, which are suitable for the structure determination, were got at the bottom of the vessel because of the slow evaporation of the solvent. Yields: 57%.

Anal. Calc. for $C_{18}H_{21}N_2O_7V$ (MW = 428.31): C, 50.43; H, 4.90; N, 6.53%.

Found: C, 50.44; H, 4.87; N, 6.50%.

IR data (cm^{-1}): 3420(w), 1602(s), 1552(s), 1522(m), 1471(w), 1455(w), 1425(w), 1396(w), 1379(m), 1344(m), 1277(m), 1205(m), 1153(s), 1061(m), 1001(w), 975(m), 912(w), 884(m), 822(m), 780(m), 668(w), 640(w), 623(w), 585(w), 456(w).

^{1}H NMR (300 MHz, DMSO) δ 9.06 (s, 1H,C*H* = N), 7.79 (d, 1H, Ar*H*), 7.58–7.50 (m, 2H, Ar*H*), 7.17 (s, 2H, Ar*H*), 7.09 (t, 1H, Ar*H*), 6.68 (s, 1H, Ar*H*), 5.28 (s, 1H, O*H*), 3.82 (s, 6H, OCH_3), 3.73 (s, 3H, CH_3), 3.17 (s, 3H, CH_3).

2.2.3. Complex 3

Hydrazinium hydroxide (0.012 mol) were added to a ethanol solution (30 mL) of 3,5-dimethoxybenzoate (0.01 mol). After 10 h refluxing and stirring, the 3,5-dimethoxybenzohydrazide were obtained by reducing pressure distillation, filtering and recrystallizing. Mixing the 3,5-dimethoxybenzohydrazide (1.0 mmol) and 3-ethoxysalicylaldehyde (1.0 mmol) into the methanolic solution (20 mL) with stirring. After 30 min, the ethyl maltol (1.0 mmol) and $VO(acac)_2$ (1.0 mmol) were added to the solution with stirring and brown solution were obtained (Schemes 3). The solution were left for 7 days at room temperature, brown block shaped single crystals of the complex, which are suitable for the structure determination, were got at the bottom of the vessel because of the slow evaporation of the solvent. Yields: 56%.

Anal. Calc. for $C_{25}H_{25}N_2O_9V$ (MW = 548.41): C, 54.70; H, 4.56; N, 5.11%.

Found: C, 54.72; H, 4.55; N, 5.10%.

IR data (cm^{-1}): 3393(w), 1603(s), 1560(m), 1499(s), 1465(w), 1445(s), 1341(m), 1269(s), 1226(m), 1192(m), 1112(w), 1083(w), 1018(w), 976(s), 942(w), 899(w), 858(w), 831(w), 764(m), 738(m), 649(m), 618(w), 602(w), 535(w), 475(w).

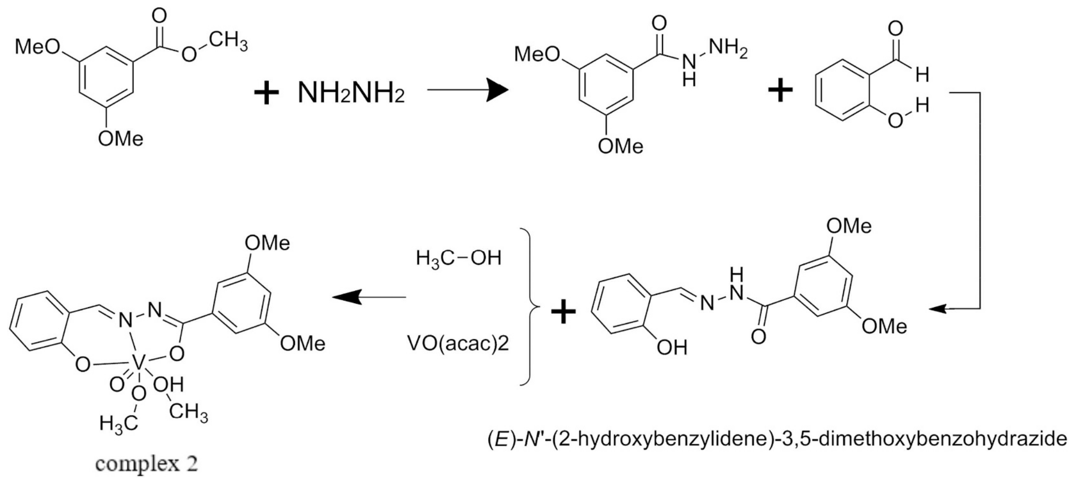
^{1}H NMR (300 MHz, DMSO) δ 9.21 (s, 1H,C*H* = N), 8.48 (d, 1H, Ar*H*), 7.41 (d, 1H, Ar*H*), 7.27 (t, 1H, Ar*H*), 7.00 (m, 3H, Ar*H*), 6.67 (m, 2H, Ar*H*), 4.07 (q, 2H, OCH_2CH$_3$), 3.80 (s, 6H, OCH_3), 3.02 (q, 2H, CH_2CH$_3$), 1.34–1.26 (m, 6H, CH_3).

2.3. X-ray crystallography

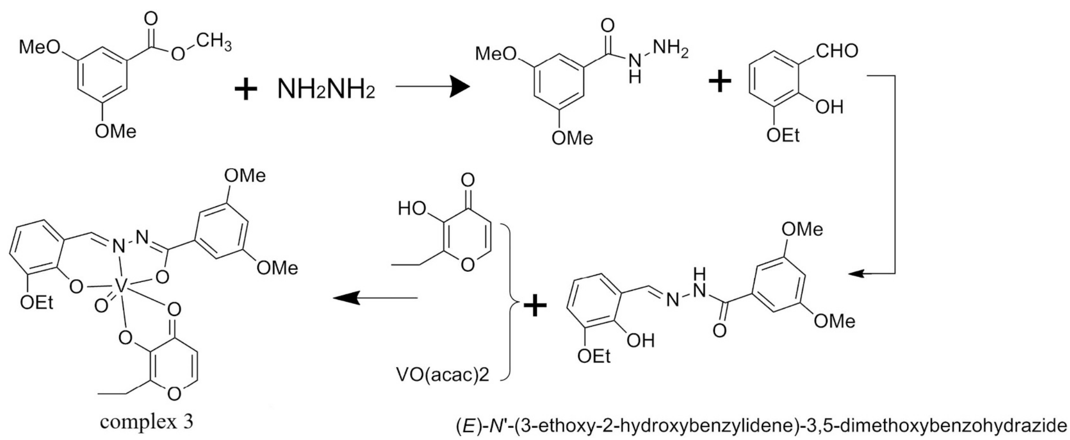
Diffraction intensities were collected at 298(2) K for complexes 1 and 3, 273(2) K for complex 2 using a Bruker SMART 1000 CCD area-detector diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The collected data were reduced with SAINT [20], and multi-scan absorption correction was performed using SADABS [21]. Structures of the complexes were solved by direct methods and refined against F^2 by full-matrix least-squares method using SHELXTL [22] and SHELXL-2017 [23]. All of the non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Crystallographic data for the complexes are summarized in Table 1. Selected bond lengths and angles are given in Table 2.

2.4. Glucose-lowering assay

The animal study was carried out according to the guidelines of Animals Ethics Committee. Male Kunming mice, weighing about 25–30 g, were obtained from Experimental Animal Center, Shandong Xinhua Pharmaceutical Co., Ltd. of China, and maintained on a light/



Scheme 2. Synthesis of complex 2.



Scheme 3. Synthesis of complex 3.

Table 1
Crystal data for the complexes.

Parameter	1	2	3
Empirical formula	$C_{22}H_{19}N_2O_6V$	$C_{18}H_{21}N_2O_7V$	$C_{25}H_{25}N_2O_9V$
Formula weight	458.33	428.31	548.41
T (K)	298	273	298
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	C2/c	P-1	P21/n
a (Å)	29.241(3)	8.3863(14)	9.0130(5)
b (Å)	8.2507(9)	11.5351(19)	13.1683(8)
c (Å)	18.899(2)	11.6142(17)	20.8106(12)
β (°)	112.178(3)	107.706(5)	92.588(1)
V (Å^3)	4222.2(8)	945.6(3)	2467.4(2)
Z	8	2	4
μ (mm^{-1})	0.511	0.568	0.460
D_{calc} (Mg m^{-3})	1.442	1.504	1.476
F(000)	1888	444	1136
θ (°)	2.2–25.4	2.2–25.4	1.8–25.5
Independent reflections	3841	4259	4574
Data/restraints/parameters	3841/0/281	4259/1/260	4570/0/338
Goodness-of-fit (GOF) on F^2	1.071	1.036	1.030
Final R indices	0.0524/0.1253	0.0416/0.1067	0.0325/0.0867
R indices (all data)	0.0764/0.1338	0.0567/0.1165	0.0400/0.0922
Largest difference peak and hole (e Å^{-3})	−0.27, 0.76	−0.23, 0.74	−0.320, 0.330

Table 2
Selected distances(Å) and angles(°) for the complexes.

1			
V1-O1	1.842(3)	V1-O2	1.941(2)
V1-O3	2.247(3)	V1-O4	1.856(2)
V1-O6	1.583(2)	V1-N1	2.086(3)
O1-V1-O2	152.71(11)	O1-V1-O3	81.34(10)
O1-V1-O4	103.76(11)	O1-V1-O6	100.54(13)
O1-V1-N1	83.46(12)	O2-V1-O3	80.81(10)
O2-V1-O4	92.45(10)	O2-V1-O6	98.67(12)
O2-V1-N1	75.10(11)	O3-V1-O4	77.87(9)
O3-V1-O6	175.96(12)	O3-V1-N1	86.80(10)
O4-V1-O6	98.17(11)	O4-V1-N1	161.70(10)
O6-V1-N1	96.95(12)		
2			
V1-O1	1.8418(16)	V1-O2	1.9457(17)
V1-O6	1.7681(18)	V1-O7	1.5840(19)
V1-N1	2.1205(17)	O1-V1-O2	151.78(7)
O1-V1-O6	103.96(7)	O1-V1-O7	100.71(9)
O1-V1-N1	83.95(7)	O2-V1-O6	91.06(7)
O2-V1-O7	98.80(9)	O2-V1-N1	74.14(6)
O6-V1-O7	103.35(9)	O6-V1-N1	157.95(8)
O7-V1-N1	95.15(8)		
3			
V1-O1	1.8414(13)	V1-O2	1.9302(14)
V1-O6	1.8650(13)	V1-O7	2.3034(14)
V1-O9	1.5895(13)	V1-N1	2.0875(15)
O1-V1-O2	153.03(6)	O1-V1-O6	103.23(6)
O1-V1-O7	83.97(6)	O1-V1-O9	99.11(7)
O1-V1-N1	83.85(6)	O2-V1-O6	92.79(6)
O2-V1-O7	78.66(5)	O2-V1-O9	99.65(6)
O2-V1-N1	74.67(6)	O6-V1-O7	76.85(5)
O6-V1-O9	98.96(6)	O6-V1-N1	160.87(6)
O7-V1-O9	175.33(6)	O7-V1-N1	86.39(6)
O9-V1-N1	97.39(6)		

dark cycle. All animals were allowed free access to food and water. Temperature and relative humidity were maintained at 24 °C and 50%. Mice were acclimatized for seven days prior to induction of diabetes. All care and handling of animals were performed with the approval of Institutional Authority for Laboratory Animal Care. Diabetes was induced by a single intra-peritoneal injection of freshly prepared streptozotocin (100 mg/kg body weight) in 0.1 M citrate buffer. The control mice were injected with an equal volume of citrate buffer. After seven days, blood was collected from the tail vein and serum samples were analyzed for blood glucose. Animals showing fasting (12 h) blood glucose higher than 11.1 mM were considered to be diabetic and used for the study.

The experimental animals were randomly divided into 11 groups with six mice each according to the blood glucose. Group 1, normal control group: normal mice treated with 0.5% carboxymethyl cellulose (CMC). Group 2–4, treated normal group: normal mice treated with 10 mg V·kg^{-1} vanadium complexes. Group 5, diabetic control group: Streptozotocin diabetic mice treated with 0.5% CMC. Group 6–11, treated diabetic group: STZ-diabetic mice treated with vanadium complexes at dose of 10 and 5 mg V kg^{-1}. The complexes were administered as suspensions in 0.5% CMC. The substances were administered intragastrically once a day at the volume of 10 mL·kg^{-1} for two week.

Throughout the experimental period of 3 weeks, the body weight and blood glucose level were monitored weekly, blood samples were obtained from the tail vein of the mice and blood glucose levels were determined with an Accu-Chek blood glucose monitor (Roche Diagnostics Gmb*H*, Mannheim, Germany.

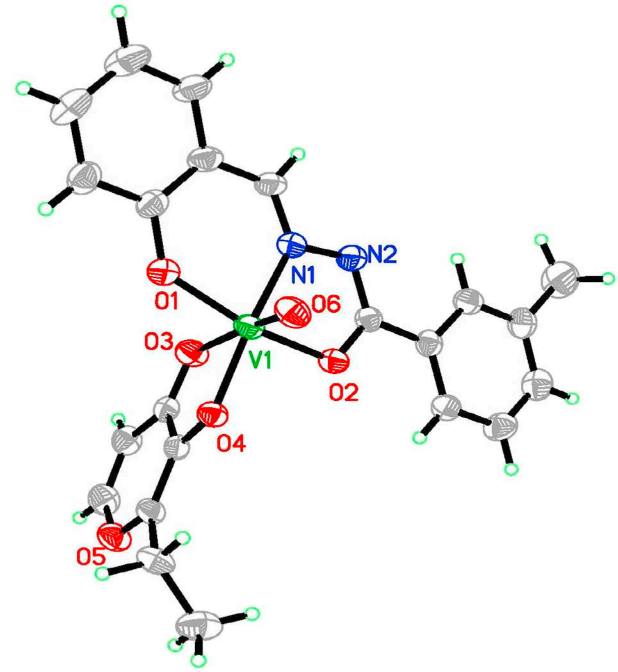


Fig. 1. Molecular structure of 1, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

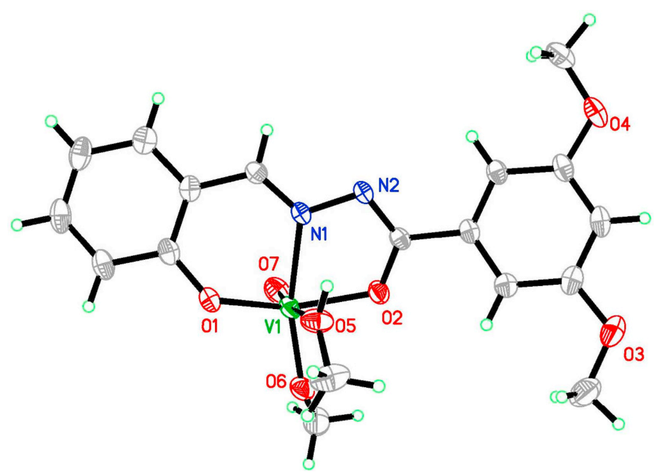


Fig. 2. Molecular structure of 2, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

3. Results and discussion

Three new oxidovanadium(V) complexes with complex **1**: [VOL^{1}X] (H_2L^1 = $C_{15}H_{14}N_2O_2$ = (*E*)-N′-(2-hydroxybenzylidene)-3-methbenzohydrazide, HX = $C_7H_{10}O_3$ = ethylmaltol = 2-ethyl-3-hydroxy-4-pyrone), Complex **2:** [VOL^2(CH_3O)(CH_3OH)], (H_2L^2 = $C_{16}H_{16}N_2O_4$ = (E)-N′-(2-hydroxybenzylidene)-3,5-dimethoxybenzohydrazide, CH_3OH = methanol), Complex **3**: [VOL^{3}X] (H_2L^3 = $C_{18}H_{20}N_2O_5$ = (E)-N′-(3-ethoxy-2-hydroxybenzylidene)-3,5-dimethoxybenzohydrazide) It should be pointed out that the vanadium in the starting materials is in V(IV) oxidation state, but it appears to be V(V) in the complexes, indicating that it was oxidized by air during the reaction procedures. From the X-ray analysis, it can be seen that the five negative charges come from the hydrazone ligand (−2), the oxo group (−2), and the secondary ligands (−1), viz. ethylmaltolate for 1 and 3, and methoxide for 2. Crystals of the complexes are stable in open air at room temperature. Elemental

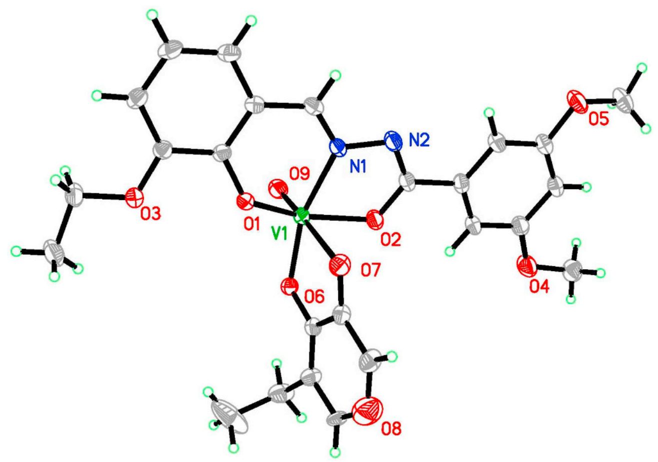


Fig. 3. Molecular structure of 3, showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

analyses are in good agreement with the chemical formulae proposed for the compounds.

3.1. Structure description of the complexes

Figs. 1–3 give perspective view of complex 1–3, respectively, together with the atomic labeling system. All of the V atoms in the complexes are in octahedral coordination.

Complex **1** coordinate with two O atoms and one N atom from the (*E*)-N′-(2-hydroxybenzylidene)-3-methbenzohydrazide ligand, two O atoms from ethylmaltol ligand, and one O atom from the oxo group. Complex **2** coordinate with two O atoms and one N atom from the (E)-N′-(2-hydroxybenzylidene)-3,5-dimethoxybenzohydrazide ligand, two O atoms from two methanol moleculars, and one O atom from the oxo group. Complex **3** coordinate with two O atoms and one N atom from the (E)-N′-(3-ethoxy-2-hydroxybenzylidene)-3,5-dimethoxybenzohydrazide ligand, two O atoms from ethylmaltol ligand, and one O atom from the oxo group.

3.2. Effects of complex on blood glucose and body weight

The complexes were administered intragastrically to both treated normal and treated STZ-diabetic group for two weeks. The results (Table 3) showed that all the complexes had blood glucose-lowering effect at doses of 10.0 and 5.0 mg V·kg^{-1}, can significantly decrease the blood glucose level of STZ-diabetic mice, but the blood glucose level in the treated normal mice (10.0 mg V·kg^{-1} ig for two weeks) was not altered as compared with the untreated normal mice ($P > 0.05$). After one-week administration with the complex 1 or two-week administration with the complex 3 (10.0 mg V·kg^{-1}), the blood glucose level of treated diabetic group was decreased compared with the diabetic control group ($P < 0.05$). Compared with complex 2, complex **1** and complex 3 had a quicker effect of glucose-lowering, but when the treatment was stopped, the blood glucose level had a slight increase. Complex 2 have a slower effect but its durability is better. One week after the administration (10.0 mg V·kg^{-1}) was stopped, complex **1** and 2 still exhibit excellent insulin-like activity, $P < 0.05$ vs STZ-diabetic group, $P > 0.05$ vs normal group, that means the blood glucose of the treated groups have return to normal blood-glucose levels. During the experiment, no mice died, the complex did not exhibited toxicity to the mice at dose of 10.0 mg V·kg^{-1}.

Effects of the vanadium complexes on body weight was shown in Table 4, the untreated normal mice gained weight over the three weeks, the body weight reach 39.7 g after 3 weeks, the body weight of STZ-diabetic group dropped from 27.8 g to 23.5 g during the 3 weeks. The treated group complex 1 (10 and 5 10.0 mg V·kg^{-1}), complex 2 (10.0 mg V·kg^{-}1) and complex 3 (10 mg V·kg^{-1}) gained weight, the increase was smaller than the untreated normal group, the body weight was 30.3–33.2 g after 3 weeks. It can be seen that the complex have positive effect on gaining body weight.

3.3. Biochemical indexes and organs

Liver is an important organ for sugar metabolism in human body, and diabetes can cause liver damage. The ratio of glutamic-oxaloacetic transa minase (GOT) to glutamic pyruvic transaminase (GPT) increases when liver was damaged. The blood biochemical index value were measured (Table 5). We can find that the ratio of the model group GOT/GPT is 60.4/116.9. After the treatment, the ratio of GOT/GPT in each group has decreased in varying degrees, proving that the degree of liver damage is decreased. The three complexes have a certain degree of protection to the liver, and can reduce the liver damage caused by diabetes.

Total cholesterol and triglycerides are important indicators to blood health. With the increase of total cholesterol and triglyceride levels, the probability of form thrombosis will rise. According to the data in Table 5, the three complexes can effectively reduce triglyceride content but have no obvious effect on total cholesterol content.

Impaired renal function is another complication of diabetes. When

Table 3
Effects of the vanadium complexes on blood glucose levels in both normal and diabetic mices.

Group	Dose (mgV·kg^{-1})	Blood glucose (mM)			
		0 week	1st week	2nd week	3rd week
Normal mices	CMC	6.6 ± 0.7	6.9 ± 1.1	6.4 ± 0.5	7.0 ± 0.6
Normal mices A10	10	6.8 ± 0.3	6.5 ± 1.3	7.1 ± 0.5	6.9 ± 0.9
Normal mices B10	10	6.4 ± 1.0	6.4 ± 0.3	6.8 ± 1.7	6.4 ± 1.7
Normal mices C10	10	6.0 ± 1.1	5.9 ± 0.6	6.3 ± 1.4	6.1 ± 0.7
STZ mices	CMC	12.3 ± 0.7[a]	12.6 ± 0.9[a]	14.1 ± 1.7[a]	14.7 ± 3.4[a]
STZ mices A10	10	12.60 ± 1.37[a]	7.90 ± 0.45[b]	6.83 ± 0.62[b]	7.40 ± 0.42[b]
STZ mices A5	5	12.27 ± 1.00[a]	7.40 ± 0.30[b]	6.67 ± 0.93[b]	8.37 ± 1.20
STZ mices B10	10	11.60 ± 0.51[a]	10.68 ± 1.21[a]	8.58 ± 2.04	7.23 ± 2.19[b]
STZ mices B5	5	16.95 ± 3.75[a,b]	16.60 ± 2.29[a,b]	14.15 ± 1.95[a]	11.88 ± 3.85[a]
STZ mices C10	10	13.03 ± 0.94[a]	9.15 ± 0.58[a]	7.25 ± 0.53[b]	8.50 ± 0.45
STZ mices C5	5	13.83 ± 1.68[a]	10.86 ± 1.3[a]	9.20 ± 1.67[a]	10.63 ± 1.85[a]

Data were expressed as mean ± standard deviations for six mices in each group.
A = complex 1, B = complex 2, C = complex 3.
[a] $P < 0.05$ vs. normal mices.
[b] $P < 0.05$ vs. STZ-diabetic mices (Dunnett's test).

Table 4
Effects of the vanadium complexes on body weight.

Group	Dose ($mgV{\cdot}kg^{-1}$)	Body weight (g)			
		0 week	1st week	2nd week	3rd week
Normal mices	CMC	26.4 + 1.5	31.4 + 1.2	35.4 + 1.2	39.7 + 1.3
STZ mices	CMC	27.8 + 2.0	26.5 + 1.7	25.5 + 2.2	23.5 + 1.3
STZ mices A10	10	25.4 + 1.9	25.1 + 2.2	28.5 + 2.1	33.2 + 1.8
STZ mices A5	5	26.2 + 1.8	25.9 + 2.2	27.4 + 1.6	31.3 + 1.4
STZ mices B10	10	27.3 + 2.0	27 + 1.2	28.6 + 1.9	31.2 + 1.3
STZ mices B5	5	26.2 + 1.4	25.5 + 1.2	25.0 + 1.5	25.4 + 1.0
STZ mices C10	10	25.6 + 1.9	25.1 + 2.1	28.2 + 2.5	30.3 + 1.2
STZ mices C5	5	26.8 + 1.8	25.6 + 1.8	27.1 + 1.1	26.2 + 1.2

Table 5
Blood biochemical index value.

Index	Abbreviation	Unit	Value			
			A10	B10	C10	Model
Glutamic-pyruvic transaminase	GPT/ALT	U/L	83.30	143.50	150.10	116.90
Glutamic-oxaloacetic transaminase	GOT/AST	U/L	21.20	34.00	46.00	60.40
Triglyceride	TG	mM	1.56	1.57	2.03	2.35
Total cholesterol	TCHO	mM	2.32	3.07	2.97	2.48
Blood urea nitrogen	BUN	mM	7.04	7.75	12.04	15.51

A = complex 1, B = complex 2, C = complex 3.

Table 6
Liver, kidney and body weight of each group.

Group	Liver (mg)	Kidney (mg)	Body weight (g)
A10	2100.3	683.7	33.2
A5	2403.2	600.2	31.3
B10	1913.4	614.6	31.2
B5	2660.6	697.8	25.4
C10	2486.1	615.6	30.3
C5	2526.6	665.6	26.2
Normal	1749.1	578.8	39.7
Model	2847.3	699.8	23.5

A = complex 1, B = complex 2, C = complex 3.

the renal function is impaired, the glomerular filtration rate will decrease, thus increasing the blood urea nitrogen content. It is known from the Table 5 that all the three complexes can reduce the blood urea nitrogen content in the blood of diabetic mice to varying degrees, and prove that the complexes have certain protective effect on kidney damage caused by diabetes in mice.

From the data in Table 6, it is found that the kidney weight/body weight and liver weight/body weight is the lowest in the normal group and the highest in the model group, and the ratio of complex groups have varying degrees of decrease after the treatment compared to the model group. It is concluded that the three vanadium complexes play an important role in maintaining normal kidney weight/body weight and liver weight/body weight ratio in mice, and the complexes have protective effects on the lesions of kidney and liver caused by diabetes.

The photographs of mice kidneys and livers were taken. For kidneys (Fig. 4), there is no obvious difference between the normal group, the complex group and the model group in appearance. The liver (Fig. 5) of the normal group is healthy. In the model group, there are many big transparent vesicles on the surface of liver. With the deterioration of the situation, it may cause the unknown liver disease. After treatment, the liver of complex groups shows a relatively healthy state with only a few small white granular matter on the surface. The photographs provided the evidence of protective effects of complexes on the lesions liver caused by diabetes.

The liver biopsy was carried out (Fig. 6). The gap between the liver cells of the normal mice was obvious, and the color was brighter than model group. The liver cell gap of model group was not obvious, and the color was slightly dark red. These two kinds of situation were not obvious for complex groups. However, the subtle changes in the gap and color of liver cells do not confirm whether the liver cells are diseased or not.

4. Conclusion

The present study reports synthesis, crystal structures and insulin-like activity of three new oxidovanadium(V) complexes. The complexes have fine insulin-like activity on streptozotocin diabetic mice. Complex 1 and complex 3 had a quicker effect of glucose-lowering, complex 2 have a slower effect but its durability is better. One week after the administration ($10.0\,mg\,V{\cdot}kg^{-1}$) was stopped, complex **1** and 2 still exhibit excellent insulin-like activity, the blood glucose of the treated groups have return to normal blood-glucose levels. The complexes have

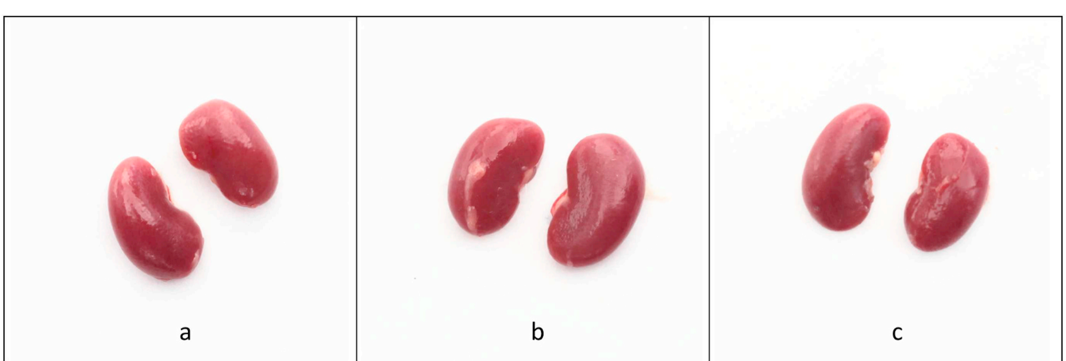


Fig. 4. Mice kidney.
a: The kidney of normal group, b: The kidney of complex group, c: The kidney of model group.

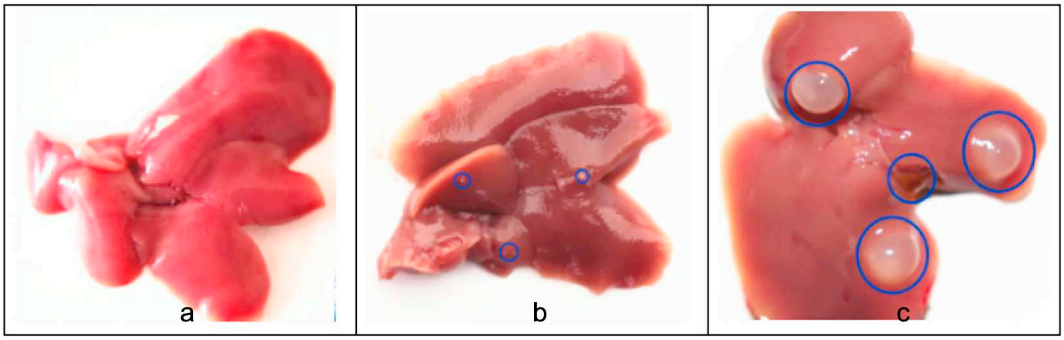


Fig. 5. Mice liver.
a: The liver of normal group, b: The liver of complex group, c: The liver of model group.

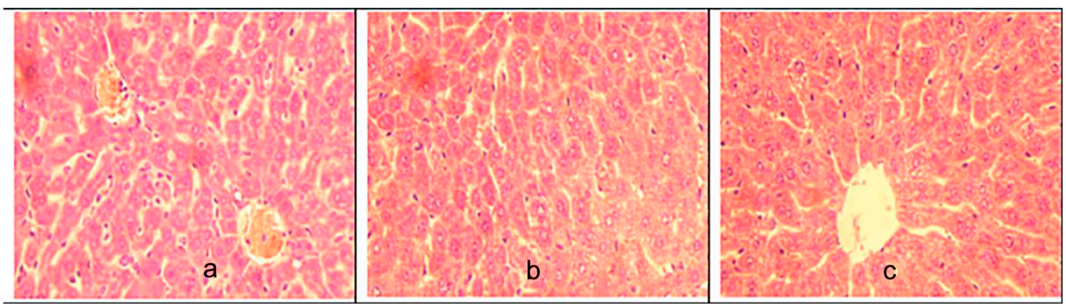


Fig. 6. Mice liver biopsy (400 ×).
a: The liver biopsy of normal group, b: The liver biopsy of complex group, c: The liver biopsy of model group.

protective effects on the lesions of kidney and liver caused by diabetes.

Various mechanisms of action have been implicated in the anti-diabetic effects of V.

The most widely accepted mode of action for V compounds thus far is attributed to the inhibition of protein tyrosine phosphatases, some V compounds are reversible inhibitors, whereas others are irreversible by modifying the protein through redox processes [24]. Vanadium compounds exert antidiabetic effects both on glucose and lipidmetabolism, they can attenuate basal lipolysis in adipocytes, AKT pathway activation contributes to the antilipolytic effect of vanadium compounds [25]. Some vanadium compound show antitumor activity through triggering a decrease of in situ AKT1 expression in cell [26].

Abbreviations

BEOV	bis(ethylmaltolato)oxovanadium(IV) [ethylmaltol = 2-ethyl-3-hydroxy-4-pyrone]
BMOV	bis(maltolato)oxovanadium(IV)
STZ	streptozotocin
VO(acac)2	vanadyl acetylacetonate
CMC	carboxymethyl cellulose
GPT	glutamic pyruvic transaminase
GOT	glutamic-oxaloacetic transa minase
TG	triglyceride
TCHO	total cholesterol
BUN	blood urea nitrogen

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Conflicts of interest

There is no interest conflict in this paper.

Appendix A. Supplementary data

CCDC 1854600, 1,500,374 and 1,854,603 contains the supplementary crystallographic data for complexes 1–3. These data can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223–336,033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk). Supplementary data to this article can be found online at doi: https://doi.org/10.1016/j.jinorgbio.2019.03.020.

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