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芳酰腙和麦芽酚混合配体钒(Ⅴ)配合物的合成、表征、晶体结构及其类胰岛素活性

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摘要:制备了 2 个钒配合物[VOLL^1] (**1**)和[VOLL^2] (**2**),其中 L 为 *N*′-(3,5-二溴-2-羟基苯甲基)-3-甲基苯甲酰肼,L^1 为甲基麦芽酚,L^2 为乙基麦芽酚。通过物理化学方法和单晶 X-射线衍射对配合物的结构进行了表征。在每个配合物中,钒原子都是由来自配体 L 中的 3 个配位原子,来自 L^1 或 L^2 中的 2 个配位原子,以及 1 个氧基配体进行配位的,形成八面体配位构型。将配合物通过灌胃对正常的大鼠和四氧嘧啶糖尿病大鼠给药 2 周时间,结果表明这 2 个配合物在剂量为 10.0 和 20.0 $mg_V \cdot kg^{-1}$ 时可以显著降低四氧嘧啶糖尿病大鼠的血糖值,而正常大鼠的血糖值却没有改变。

关键词:钒配合物;芳酰腙;晶体结构;类胰岛素活性
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Syntheses, Characterization, Crystal Structures and Insulin-Like Activity of Vanadium(Ⅴ) Complexes with Aroylhydrazone and Maltol Mixed-Ligands

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Abstract: Two vanadium(Ⅴ) complexes, [VOLL^1] (**1**) and [VOLL^2] (**2**) (L=*N*′-(3,5-dibromo-2-hydroxybenzylidene)-3-methylbenzohydrazide, L^1 =methylmaltol, L^2 =ethylmaltol), have been prepared. The complexes have been characte-rized by physico-chemical methods and single crystal X-ray determination. The V atom in each complex is coordinated by three donor atoms of L, two donor atoms of L^1 or L^2, and one oxo group, forming octahedral coordination. The complexes were administered intragastrically to both normal and alloxan-diabetic mices for two weeks. The biological activity results show that the complexes at doses of 10.0 and 20.0 $mg_V \cdot kg^{-1}$, can significantly decrease the blood glucose level in alloxan-diabetic mices, but the blood glucose level in the treated normal mices was not altered. CCDC: 1059791, **1**; 1059793, **2**.

Key words: vanadium complex; aroylhydrazone; crystal structure; insulin-like activity

Since 1980s, inorganic vanadium salts and vanadium complexes with various ligands have been reported to possess potent pharmacological effects of insulin-mimetic activity[1-4]. Studies indicated that vanadium compounds improve not only hyperglycemia in human subjects and animal models of type Ⅰ

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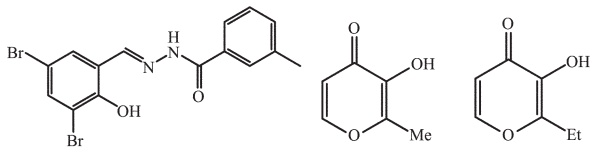
diabetes but also glucose homeostasis in type Ⅱ diabetes[5-6]. However, the inorganic vanadium salts are considered as less active and more toxic. In order to reduce the side effects of inorganic vanadium salts, vanadium complexes have received particular attention and demonstrated to be effective[7-9]. 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 concentration[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, in the present work, aroylhydrazone and maltol ligands were combined together by coordinating to V atom. Two vanadium complexes, [VOLL^1] (**1**) and [VOLL^2] (**2**), where L is the dianionic form of *N*′-(3,5-dibromo-2-hydroxybenzylidene)-3-methylbenzohydrazide, and L^1 and L^2 are the monoanionic form of methylmaltol (HL^1) and ethylmaltol (HL^2), respectively (Scheme 1), have been prepared and studied on their insulin-like activity to both normal and alloxan-diabetic mices.



H_2L　　HL^1　　HL^2

Scheme 1

1 Experimental

1.1 Materials and measurements

Starting materials, reagents and solvents were purchased from commercial suppliers with AR grade, and used without purification. HL^1 and HL^2 were purchased from Haiqu Chemical Company (Shanghai). 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 4 000 ~400 cm^{-1} region. UV-Vis spectra were recorded on a Perkin-Elmer Lambda 900 spectrometer. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 300 MHz.

1.2 Synthesis of H_2L

3,5-Dibromosalicylaldehyde (2.80 g, 0.01 mol) and 3-methylbenzohydrazide (1.50 g, 0.01 mol) were reacted in 50 mL methanol. The mixture was stirred at room temperature for 1 h to give a clear colorless solution. The solvent was removed by rotary evaporation to give colorless solid, which was recrystallized from ethanol to give crystalline product of H_2L. Yield 83%. Anal. Calcd. for $C_{15}H_{12}Br_2N_2O_2$(%): C, 43.7; H, 2.9; N, 6.8. Found(%): C, 43.5; H, 3.1; N, 6.7. IR data (cm^{-1}): 3 376 (m), 3 212 (w), 1 653 (vs), 1 600 (s), 1 541 (s), 1 435 (s), 1 340 (m), 1 281 (s), 1 217 (m), 1 159 (m), 1 021 (m), 951 (m), 861 (w), 808 (m), 739 (w), 679 (m), 633 (w), 558 (w). UV (λ / nm, ε / ($L\cdot mol^{-1}\cdot cm^{-1}$)): 293, 2.08×10^4; 302, 1.90×10^4; 338, 8.73×10^3. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.76 (s, 1H, OH), 12.50 (s, 1H, NH), 8.53 (s, 1H, CH=N), 7.84~7.74 (m, 4H, ArH), 7.45 (d, 2H, ArH), 2.41 (s, 3H, CH_3).

1.3 Synthesis of the complexes

Complexes **1** and **2** were prepared by the same method as described here. A methanolic solution (30 mL) of $VO(acac)_2$ (0.27 g, 1.0 mmol) was added to a methanolic solution (20 mL) of H_2L (0.41 g, 1.0 mmol) and methylmaltol (0.13 g, 1.0 mmol) for 1 or ethylmaltol (0.14 g, 1.0 mmol) for 2, with stirring. The mixtures were stirred at room temperature for 30 min to give deep brown solution. The resulting solution was allowed to stand in air for a few days until three quarters of the solvent was evaporated. Brown block-shaped single crystals of the complexes, suitable for X-ray single crystal diffraction were formed at the bottom of the vessel. The crystals were isolated by filtration, washed three times with cold methanol and dried in air. Yields: 61% (**1**) and 73% (**2**).

1: Anal. Calcd. for $C_{21}H_{15}Br_2N_2O_6V$(%): C, 41.9; H, 2.5; N, 4.7. Found (%): C, 42.1; H, 2.6; N, 4.6. IR data (cm^{-1}): 1 609 (s), 1 595 (s), 1 529 (s), 1 430 (m), 1 354 (m), 1 264 (m), 1 196 (s), 1 039 (w), 976 (s),

928 (w), 860 (w), 825 (w), 728 (s), 650 (m), 595 (w), 479 (m), 437 (w). UV (λ / nm, ε / (L·mol^{-1}·cm^{-1})): 280, 2.05×10^4; 345, 8.06×10^3; 456, 4.77×10^3.

2: Anal. Calcd. for $C_{22}H_{17}Br_2N_2O_6V$(%): C, 42.9; H, 2.8; N, 4.5. Found (%): C, 42.8; H, 2.7; N, 4.7. IR data (cm^{-1}): 1 608 (s), 1 595 (s), 1 529 (s), 1 433 (m), 1 354 (m), 1 264 (m), 1 198 (s), 1 027 (w), 976 (s), 925 (w), 863 (w), 825 (w), 771 (w), 725 (s), 652 (m), 587 (w), 556 (w), 475 (m), 446 (w). UV (λ / nm, ε / (L·mol^{-1}·cm^{-1})): 280, 2.31×10^4; 337, 6.78×10^3; 456, 5.23×10^3.

1.4 X-ray crystallography

Diffraction intensities for complexes **1** and **2** were collected at 298(2) K using a Bruker SMART 1000 CCD area-detector diffractometer with Mo $K\alpha$ radiation (λ=0.071 073 nm) and Cu $K\alpha$ radiation (λ=0.154 178 nm), respectively. The collected data were reduced with SAINT[20], and multi-scan absorption correction was performed using SADABS[21]. Structures of the compounds were solved by direct methods and refined against F^2 by full-matrix least-squares method using SHELXTL[22]. 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.

CCDC: 1059791, **1**; 1059793, **2**.

Table 1 Crystal data and structure refinement of complexes 1 and 2

	1	**2**
Empirical formula	$C_{21}H_{15}Br_2N_2O_6V$	$C_{22}H_{17}Br_2N_2O_6V$
Formula weight	602.1	616.1
Crystal shape	Block	Block
Colour	Brown	Brown
Crystal size / mm	0.23×0.21×0.18	0.15×0.13×0.12
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$
a / nm	1.272 5(1)	1.639 83(3)
b / nm	1.305 1(1)	1.507 18(3)
c / nm	1.456 5(1)	0.924 07(2)
α / (°)	94.457(2)	90
β / (°)	112.372(2)	91.726(1)
γ / (°)	91.415(2)	90
V / nm^3	2.226 0(3)	2.282 82(8)
Z	4	4
μ (Mo $K\alpha$) / cm^{-1}	4.076	8.106
T_{min}	0.454 1	0.376 1
T_{max}	0.527 4	0.443 0
Reflections / parameters	19 855 / 577	19 631 / 300
Restraints	0	0
Goodness of fit on F^2	1.003	1.027
R_1, wR_2 [$I \geqslant 2\sigma(I)$]	0.060 6, 0.108 6	0.053 6, 0.147 1
R_1, wR_2 (all data)	0.150 7, 0.139 2	0.062 9, 0.156 5
$(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ / (e·nm^{-3})	732, −434	905, −800

Table 2 Selected bond lengths (nm) and angles (°) for the complexes

1					
V1-O1	0.186 1(4)	V1-O2	0.192 9(5)	V1-O4	0.185 6(4)
V1-O6	0.157 7(5)	V1-O3	0.228 4(5)	V1-N1	0.208 9(6)

Continued Table 1

V2-O7	0.185 2(5)	V2-O8	0.193 0(5)	V2-O12	0.157 8(5)
V2-O10	0.186 8(5)	V2-O9	0.224 6(5)	V2-N3	0.209 5(5)
O6-V1-O4	99.2(2)	O6-V1-O1	99.6(2)	O4-V1-O1	105.8(2)
O6-V1-O2	99.1(2)	O4-V1-O2	89.8(2)	O1-V1-O2	153.2(2)
O6-V1-N1	97.9(2)	O4-V1-N1	158.3(2)	O1-V1-N1	84.3(2)
O2-V1-N1	74.3(2)	O6-V1-O3	176.4(2)	O4-V1-O3	77.55(19)
O1-V1-O3	82.85(18)	O2-V1-O3	79.41(18)	N1-V1-O3	84.9(2)
O12-V2-O7	99.7(2)	O12-V2-O10	98.4(2)	O7-V2-O10	104.0(2)
O12-V2-O8	97.8(2)	O7-V2-O8	153.9(2)	O10-V2-O8	92.3(2)
O12-V2-N3	100.3(2)	O7-V2-N3	83.4(2)	O10-V2-N3	158.3(2)
O8-V2-N3	74.5(2)	O12-V2-O9	175.1(2)	O7-V2-O9	83.66(19)
O10-V2-O9	77.24(18)	O8-V2-O9	80.24(18)	N3-V2-O9	83.50(19)
			2		
V1-O1	0.185 5(3)	V1-O2	0.193 5(3)	V1-O3	0.185 5(3)
V1-O6	0.158 1(4)	V1-O4	0.230 2(3)	V1-N1	0.210 5(4)
O6-V1-O3	98.21(16)	O6-V1-O1	98.58(19)	O3-V1-O1	102.50(14)
O6-V1-O2	100.80(18)	O3-V1-O2	94.10(14)	O1-V1-O2	152.31(15)
O6-V1-N1	97.55(17)	O3-V1-N1	162.08(14)	O1-V1-N1	83.47(14)
O2-V1-N1	74.57(13)	O6-V1-O4	175.22(16)	O3-V1-O4	77.01(12)
O1-V1-O4	82.86(14)	O2-V1-O4	79.45(13)	N1-V1-O4	87.13(13)

1.5 Glucose-lowering assay

The animal study was carried out according to the guidelines of Animals Ethics Committee. Male Kunming mices, weighing about 25 ~32 g, were obtained from Experimental Animal Center, Shandong Lukang Pharmaceutical Co., Ltd of China, and maintained on a light/dark cycle. All animals were allowed free access to food and water. Temperature and relative humidity were maintained at 24 ℃ and 50%. Mices 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 alloxan (200 $mg \cdot kg^{-1}$ body weight) in 0.9% saline. The control mices were injected with an equal volume of vehicle. 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 $mmol \cdot L^{-1}$ were considered to be diabetic and used for the study.

The experimental animals were randomly divided into six groups with six mices each according to the blood glucose. Group 1, normal control group: normal mices treated with 0.5% carboxymethyl cellulose (CMC). Group 2 ~4, treated normal group: normal mices treated with 20 $mg_V \cdot kg^{-1}$ vanadium complexes. Group 5, diabetic control group: alloxan diabetic mices treated with 0.5% CMC. Group 6 ~11, treated diabetic group: alloxan diabetic mices treated with vanadium complexes at dose of 10 and 20 $mg_V \cdot kg^{-1}$ by intragastrical administration. The complexes were administered as suspensions in 0.5% CMC. The substances were administered intragastrically once a day at the volume of 10 $mL \cdot kg^{-1}$ for two weeks.

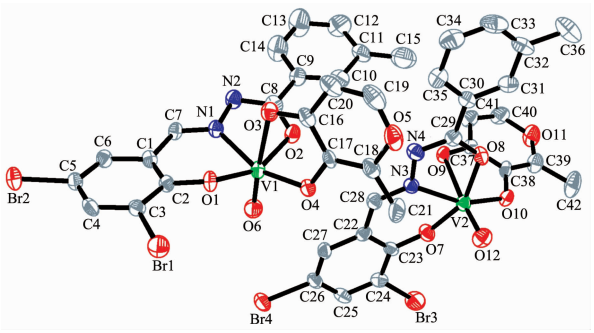
Throughout the experimental period, the body weight of mices was monitored daily. Blood samples were obtained from the tail vein of the mices and blood glucose levels were determined with an Accu-Chek blood glucose monitor (Roche Diagnostics GmbH, Mannheim, Germany).

2 Results and discussion

The aroylhydrazone compound *N*′-(3,5-dibromo-2-hydroxybenzylidene)-3-methylbenzohydrazide was readily prepared by condensation reaction of 3,5-dibromosalicylaldehyde with 3-methylbenzohydrazide in methanol. The complexes were prepared by reaction of equimolar quantities of the aroylhydrazone, VO(acac)$_2$ and maltol ligands in methanol. Crystals of the complexes are stable in open air at room temperature. Elemental analyses are in good agreement with the chemical formula proposed for the compounds.

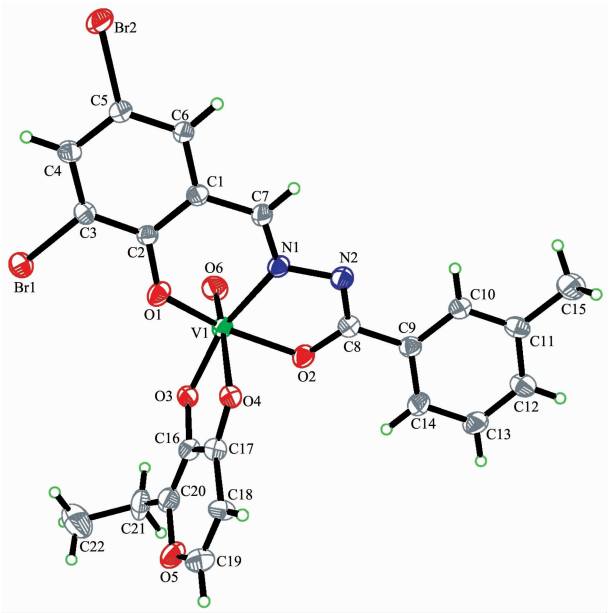
2.1 Structure description of the complexes

Fig.1 and 2 give perspective view of complexes **1** and **2** together with the atomic labeling system. The asymdium complex molecules. Structures of the complexes are very similar except for the slight difference of the maltol ligands, *viz*. methylmaltol for **1** and ethylmaltol for **2**. The V atoms in the complexes are in octahedral coordination, with the phenolate O, imino N, and enolate O atoms of L, and the hydroxy O atom of the maltol ligand defining the equatorial plane, and with one oxo O and the carbonyl O atom of the maltol ligand locating at the axial positions. The V atoms deviate from the least-squares planes defined by the equatorial atoms by 0.030 1(1) nm for **1** and 0.029 2(1) nm for **2**. The coordinate bond lengths in both complexes are similar to each other, and also comparable to those observed in vanadium complexes with aroylhydrazone ligands[23-25]. Distortion of the octahedral coordination can be observed from the



Displacement ellipsoids are drawn at the 30% probability level and H atoms are omitted for clarity

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

coordinate bond angles, ranging from 74.3(2)° to 105.8(2)° for **1**, and from 74.6(1)° to 102.5(1)° for **2**, for the perpendicular angles, and from 153.2(2)° to 176.4(2)° for **1**, and from 152.3(2)° to 175.2(2)° for **2**, for the diagonal angles. The dihedral angles between the benzene rings of the aroylhydrazone ligands are 16.1(3)° for the V1 molecule and 4.7(3)° for the V2 molecule for **1**, and 8.1(4)° for **2**.

2.2 IR and UV-Vis spectra

The medium and broad absorption centered at 3 376 cm^{-1} in the spectrum of H_2L substantiates the presence of phenol group, which is absent in the complex. The sharp band indicative of the N-H vibration is located at 3 212 cm^{-1}, and the intense band indicative of the C=O vibration is located at 1 653 cm^{-1} in the spectrum of H_2L, which are absence in the complexes, indicating the enolisation of the amide functionality and subsequent proton replacement by the V atoms. The strong absorption bands at 1 600 cm^{-1} for H_2L and 1 609 cm^{-1} for the complexes are assigned to the azomethine ν(C=N)[26]. The typical absorption at 976 cm^{-1} can be assigned to the V=O vibration[23].

Electronic spectra of H_2L and the complexes

were recorded in 10^{-5} mol·L^{-1} in methanol and acetonitrile, respectively, in the range of 200~600 nm. In the UV-Vis region the complexes show bands at approximately 340 nm and weak bands at about 456 nm. The weak bands are attributed to intramolecular charge transfer transitions from the $p\pi$ orbital on the nitrogen and oxygen to the empty d orbitals of the metal[27]. The intense bands observed at about 280 nm for the complexes and 293 nm for H_2L are assigned to intraligand π-π* transitions[27].

2.3 Effects of complex on blood glucose in both normal and alloxan-diabetic mices

The complexes were administered intragastrically to both normal and alloxan-diabetic mices for two weeks. The results (Table 3) showed that both complexes had blood glucose-lowering effect at doses of 10.0 and 20.0 $mg_V \cdot kg^{-1}$, could significantly decrease the blood glucose level in alloxan-diabetic mices, but the blood glucose level in the treated normal mices (20.0 $mg_V \cdot kg^{-1}$ by intragastrical admini-stration for two weeks) was not altered as compared with the untreated normal mices (P>0.05). After two-week administration with the complexes, the blood glucose level was decreased compared with the diabetic control group (P<0.05). During the experiment, the mean body weight in alloxan-diabetic mices was lower than normal mices. Two-week administration of the complexes had no effect on the body weight in the diabetic group, compared with the diabetic control group (Table 4).

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

Group	Dose / ($mg_V \cdot kg^{-1}$)	Blood glucose / (mmol·L^{-1})			
		0 week	1st week	2nd week	3rd week
Normal mices	CMC	5.50±0.98	6.21±1.01	5.92±1.23	5.23±1.07
Normal mices+1	20.00	6.27±0.64	5.45±0.36	5.73±0.72	5.64±0.90
Normal mices+2	20.00	6.10±0.57	5.63±0.85	5.87±1.03	5.51±0.35
alloxan mices	CMC	16.36±2.83[a]	15.96±1.54[a]	16.31±2.72[a]	14.66±1.76[a]
alloxan mices+1	20.00	17.70±2.32[a]	6.12±1.78[a,b]	6.90±1.65[a,b]	8.32±2.10[a,b]
alloxan mices+1	10.00	16.22±1.80[a]	7.77±1.93[a,b]	8.25±2.06[a,b]	9.58±2.31[a,b]
alloxan mices+2	20.00	17.45±1.87[a]	6.34±1.45[a,b]	7.09±1.78[a,b]	8.51±2.44[a,b]
alloxan mices+2	10.00	15.91±2.13[a]	7.72±1.06[a,b]	9.00±2.35[a,b]	9.46±1.93[a,b]

*Data were expressed as mean±standard deviations for six mices in each group; [a]P<0.05 or less vs normal mices; [b]P<0.05 or less vs alloxan-diabetic mices (Dunnett′s test)

Table 4　Effects of the complexes on body weight of both normal and diabetic mices*

Group	Dose / ($mg_V \cdot kg^{-1}$)	Average body weight / g			
		0 week	1st week	2nd week	3rd week
Normal mices	CMC	32.37±1.67	35.93±2.85	36.23±1.10	37.87±1.48
Normal mices+1	20.00	32.66±2.03	35.35±2.26	35.90±1.81	37.67±2.39
Normal mices+2	20.00	32.53±1.85	35.63±1.92	36.14±2.22	37.55±2.10
alloxan mices	CMC	28.15±1.58[a]	28.18±1.26[a]	29.28±1.14[a]	30.18±2.77[a]
alloxan mices+1	20.00	27.27±2.30[a]	25.55±1.79[a]	26.02±0.96[a]	29.77±2.65[a]
alloxan mices+1	10.00	26.81±1.67[a]	28.80±2.10[a]	29.67±1.82[a]	33.32±2.54[a]
alloxan mices+2	20.00	28.45±2.13[a]	24.33±1.64[a]	25.57±2.05[a]	29.46±2.32[a]
alloxan mices+2	10.00	27.92±1.16[a]	29.06±2.68[a]	30.20±2.37[a]	34.19±2.71[a]

*Data were expressed as mean±standard deviations for six mices in each group; [a]P<0.05 or less vs normal mices; [b]P<0.05 or less vs alloxan-diabetic mices (Dunnett′s test)

3 Conclusions

The present study reports synthesis, characterization and crystal structures of two vanadium (Ⅴ) complexes with N'-(3,5-dibromo-2-hydroxybenzylidene)-3-methylbenzohydrazide and maltol mixed ligands.

Methylmaltol and ethylmaltol as co-ligands are readily coordinate to the V atoms through the carbonyl and deprotonated phenol groups. The complexes have effective insulin-like activity on alloxan-diabetic mices. Methylmaltol and ethylmaltol as coligands in the complexes have not obvious difference for the antidiabetic effect on alloxan-diabetic mices.

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