Abstract

Five kinds of N-substituted 3-hydroxy-2-methyl-4(1H)-pyridinones, and three kinds of 1-hydroxy-2(1H)-pyrimidinones were synthesized. Treatment of 3-hydroxy-4(1H)-pyridinones with VO(acac)$_2$ in CH$_3$OH exclusively gave CH$_3$O-coordinated oxovanadium (V) complexes. On the other hand, treatment with VOSO$_4$ in H$_2$O at pH 10 for 3-hydroxy-4(1H)-pyridinones and at pH 7 for 1-hydroxy-2(1H)-pyrimidinones afforded the corresponding oxovanadium (IV) complexes. These complexes were fully characterized by means of IR, UV-vis, $^1$H-and $^{51}$V-NMR, FAB-MS, ESR spectroscopies, and combustion analysis. From the result of the inhibitory effect of oxovanadium (IV) complexes on free fatty acid (FFA) release from rat adipocytes treated with epinephrine in the presence of glucose in vitro, it was revealed that bis(1,2-dihydro-4,6-dimethyl-2-oxo-1-pyrimidinolato)oxovanadium (IV) showed the highest insulin-mimetic activity. Further, the in vivo insulin-mimetic activity was evaluated with streptozotocin (STZ)-induced diabetic rats. Blood glucose levels were substantially lowered from hyperglycemic to normal levels after the treatment with bis(1,2-dihydro-4,6-dimethyl-2-oxo-1-pyrimidinolato) oxovanadium (IV) by daily intraperitoneal injections.

Keywords: 3-hydroxy-4(1H)-pyridinone, insulin-mimetic activity

Introduction

The number of patients with diabetes mellitus (DM) was estimated to be approximately 173 million people in the world. DM results from an absolute or relative deficiency in insulin synthesis or secretion of pancreatic $\beta$-cells and a resistance of target tissues to the action of insulin. Patients with DM suffer from a number of secondary complications such as retinopathy, nephropathy, and neuropathy. In general, DM is classified into type 1 insulin-dependent DM (IDDM), characterized by hyperglycemia due to absolute deficiency of insulin, and type 2 noninsulin-dependent DM (NIDDM) characterized by a relative insulin deficiency due to low hyperglycemia due to low insulin sensitivity in target cells, according to the definition of WHO in 1985 [1]. Oral chemotherapeutic agents for type 2 DM have already been developed and are currently available [2]. Patients with type 1 DM can be only treated by daily injections of insulin. Owing to a relief of physically and mentally painful insulin injection for type 1 DM and reduction of severe side effects for type 2 DM, the development of new chemotherapeutic agents in place of insulin and current drugs is still desired [3-7].

In 1977 [8] and 1979 [9, 10], vanadate (+5 oxidation state of vanadium) ion was found to be a potent inhibitor of Na$^+$, K$^+$-ATPase. The interaction of
vanadium with ATPases and its expression on cellular, organ, and whole animal levels have been reviewed by Nechay [11]. Vanadate ion was demonstrated to show insulin-mimetic action in intracellular insulin receptor or GLUT4 [12, 13]. Further, it was found that vanadate ion was reduced to vanadyl one (+4 oxidation state or oxovanadium (IV)) in organs and organelles when it was administered to animals. When vanadyl sulfate (VOSO₄) and its complexes administered orally or intravenously to STZ-induced diabetic rats, they normalized the blood glucose [8, 14-17]. In addition, the vanadate form exhibited toxicity about 10-15 times higher than the vanadyl one in rats in terms of LD₅₀ value [18]. Therefore, many researchers focused on oxovanadium (IV) complexes. A number of orally active oxovanadium (IV) complexes have already been reported to show insulin-mimetic activities in vivo [16, 19-25]. Previously we pointed out that the amount of glucose in blood is mutually related to the amount of FFA in blood. Therefore, the in vitro insulin-mimetic activity of oxovanadium (IV) complexes has been evaluated measuring their inhibitory effects on FFA release from isolated rat adipocytes [20, 22, 26-29]. Unfortunately, the relationship between chemical structures of oxovanadium (IV) complexes and insulin-mimetic activity still remains obscure due to absolute lack of available data.

We have intensively investigated the synthesis of new hydroxyazine-type heterocycles and their application to functional molecules and chemotherapeutic agents over two decades [30, 31]. Four kinds of oxovanadium (IV) complexes of hydroxymonoazine- and hydroxydiazine-type heterocycles have been reported for the first time to show insulin-mimetic activities in vitro, as evaluated by IC₅₀ value, which defines 50% inhibitory concentration of FFA release from isolated rat adipocytes treated with epinephrine [32]. We focused on 3-hydroxy-4(1H)-pyridinones and 1-hydroxy-2(1H)-pyrimidinones.
Table 1  The partition coefficients of bidentate ligands

<table>
<thead>
<tr>
<th>Compound</th>
<th>log P</th>
<th>Compound</th>
<th>log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>-1.05</td>
<td>2a</td>
<td>*</td>
</tr>
<tr>
<td>1b</td>
<td>-0.57</td>
<td>2b</td>
<td>*</td>
</tr>
<tr>
<td>1c</td>
<td>-0.36</td>
<td>2c</td>
<td>*</td>
</tr>
<tr>
<td>1d</td>
<td>-0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1e</td>
<td>-0.16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* not measurable due to high water solubility.

VO(O₃) coordination mode [16, 23, 33], because there are the following advantages; 1) a facile synthetic procedure [34-37], 2) an easy introduction of various substituents at N-1, C-4, and C-6 positions, and 3) an easy adjustment of the hydrophilicity or lipophilicity of oxovanadium complex.

We describe here synthesis of oxovanadium (IV) and (V) complexes with 3-hydroxy-4(1H)-pyrimidinones and 1-hydroxy-2(1H)-pyrimidinones and their characterization on the basis of ¹H, ¹³C, ³¹V-NMR, IR, UV-vis, FAB MS and ESR spectroscopies, cyclic voltammetry (CV), and combustion analysis. The in vitro and in vivo insulin-mimetic activities of oxovanadium (IV) complexes are also discussed.

Results and Discussion

Synthesis of bidentate ligands

The synthetic procedure for N-substituted 3-hydroxy-2-methyl-4(1H)-pyrimidinones [25, 26] and 1-hydroxy-2(1H)-pyrimidinones [38] is depicted in Scheme 1. A commercially available maltol was treated with benzyl chloride (BnCl) in the presence of aqueous NaOH solution in MeOH to give 3-benzoxoxy-2-methyl-4-pyrene in a 80% yield. The 4-pyrene underwent the Michael addition with various alkylamines in EtOH-H₂O (3:1) mixture to give 3-benzooxy-2-methyl-4(1H)-pyridinones, which were then hydrogenated for 1 h in the presence of 10% Pd-C to give 3-hydroxy-2-methyl-4(1H)-pyridinones 1a-e as white powders. N-Benzoxoxyurea was treated with 1,1,3,3-tetraethoxypropane in the presence of HCl for 3 days at room temperature to give 3-benzoxoxy-2(1H)-pyrimidinone. On the other hand, N-benzoxoxyurea was refluxed with β-diketones in the presence of H₂SO₄ for 3 h to give 4,6-disubstituted 1-benzoxoxy-2(1H)-pyrimidinones. These compounds were subject-

![Fig. 2](https://example.com/) ¹H-NMR spectra in CD₃OD: a) free ligand 1e and b) oxovanadium (V) complex 3e.

Physical properties of bidentate ligands

The pKa value of 3-hydroxy-1-methoxyethyl-2-methyl-4(1H)-pyridinone 1e was measured in aqueous solution by means of the UV titration method. Compound 1e showed absorption maxima at 280 and 310 nm in the particular pH region. Therefore, the pKa value of compound 1e was estimated by the pH titration curve at 310 nm at various pH conditions. The pKa value of compound 1e was 9.8, while that of compound 2b was 6.1 [38]. This difference may be responsible for an additional electron-withdrawing nitrogen atom.

It is recognized that the hydrophobic/hydrophilic balance of a compound affects the biological activity. The partition coefficient of bidentate ligands between an aqueous phase buffered at pH 7.4 and octanol was measured [27, 33]. To a solution of a ligand in Krebs-Ringer bicarbonate (KRB) buffer solution (1.0x10⁻⁴ M : 5 mL), which was used in the bioassay, was added octanol (5 mL). The mixture was stirred at 600 rpm for 4 h with a magnetic stirrer, and then centrifuged at 4000 rpm for 20 min with a centrifugal separator. The concentrations of two phases were measured using UV spectral data. The partition coefficient was calculated from the following equation: \( P = C_{octanol} / C_{buffer} \), and the results are summarized in Table 1. Among a series of 4(1H)-pyridinones 1a-e, an increase in the alkyl chain length at N-1 position results in an increase of the solubility in octanol. Unfortunately,
the partition coefficients of 1-hydroxy-2(1H)-pyrimidinones 2a-c could not be measured, because all compounds exists in the form of metal salts, judging from their pKa values.

**Synthesis of oxovanadium complexes**

3-Hydroxy-4(1H)-pyridinone 1e was treated with 0.5 equimolar amount of (acetylacetonato) oxovanadium (IV) [VO(acac)₂] in MeOH-H₂O (1:1) mixture [39]. When a solution of VO(acac)₂ (green) was added to a solution of compound 1e (colorless), a color of the solution turned into dark purple. After refluxing for 2 h, the solvent was evaporated, and the crude product was purified by gel chromatography with Sephadex LH 20 with MeOH as an eluent to give oxovanadium complex (compound A) as dark purple powders. A characteristic absorption band due to V = O stretching vibration was observed at 949 cm⁻¹ in IR spectrum. In general, an ε value of absorption band of oxovanadium (IV) complex at visible region was very small [40], but this complex showed λ max at 503 nm and ε was 3450. Because of the paramagnetic character of oxovanadium (IV) complex, NMR spectrum can not be measured. This complex, however, was found to be possible to measure ¹H-NMR spectrum. A signal based on protons at cis-OCH₃ appeared at 3.34 ppm as shown in Fig. 2, and this chemical shift was completely coincided with that of cis-bis (maltolato) methoxooxovanadium (V), cis-VO(OCH₃)₂(ma)₂ [41]. From these spectra data and combustion analysis, compound A was assigned to be oxovanadium (V) complex 3e (Scheme 2).

Complexation of 3-hydroxy-4(1H)-pyridinones 1a-e with VOSO₄ was carried out according to the literature methods [37, 40]. Compound 1e was treated with 0.5 equimolar amount of VOSO₄ in H₂O. When a solution of VOSO₄ (light blue) was added to a solution of compound 1e (colorless), a color of the solution turned into dark purple. The pH of the reaction mixture was adjusted to 10 with 10 M KOH, and then the resulting mixture was refluxed overnight. On raising the pH of the solution to 10, a color of the solution turned into dark green, and a blue precipitate came out. The precipitate was collected and washed well with H₂O to give oxovanadium (IV) complex 4e as blue powders. The structural assignment of the oxovanadium (IV) complex was carried out by means of IR, ESR, UV-vis and FAB-MS spectroscopies, and combustion analysis. The molecular ion peak of complex 4e was observed at m/z=432 ([M+H]+) in the FAB-MS. IR spectrum of complex 4e is very similar to that of free ligand 1e except the following points; a) the absorption band at 1625 cm⁻¹ attributable to C=O stretching vibration of free ligand 1e shifted to 1604 cm⁻¹, b) the absorption band at 1400 cm⁻¹ due to O-H in-plane deformation of the 3-OH of free ligand became small in the intensity, and c) a new absorption band owing to V=O stretching vibration appeared at 970 cm⁻¹. Similarly, Compounds 1a-d also gave oxovanadium (IV) complexes 4a-d (Scheme 2).

**Characterization of oxovanadium (V) complexes**

On measuring ¹H-NMR spectrum of complex 4e, the broading of each signal was observed as can be seen from Fig. 3. ¹H-NMR spectra, therefore, were measured at various temperatures. The shape of signals due to 2-CH₃ and 5-H apparently changed. At -30°C, two sets of signals were observed for 2-CH₃ and 5-H protons at the range from 2.4 to 2.6 ppm and from 6.2 to 6.4 ppm, respectively. On raising temperature of the solution up to 30°C, the signals coalesced into broad singlets. The similar behavior was observed on the
variable temperature $^1$H-NMR spectral studies of cis-VO(OMe)(ma)$_2$ [41]. This result indicated that the equilibrium between two isomers assigned tentatively may exist in CD$_3$OD solution as shown in Fig. 4. The activation free energy ($\Delta G^*$) of the conversion was calculated from the difference ($\Delta \nu$) in frequency between two signals and coalescence temperature ($T_c$) according to the following equation.

$$\Delta G^* = 19.14 \ T_c \ (9.97 + \log \ T_c / \Delta \nu)$$

$\Delta G^*$ was estimated to be 5.7 kcal/mol (22.8 kJ/mol).

UV-vis spectra of oxovanadium (IV) complex 3e were measured in aqueous solution at various pH values (pH 2.1-11.3). The absorption bands due to the ligand-to-metal charge transfer (LMCT) were observed at 530-600 nm in the acidic region. An increase of pH caused the blue-shift of the absorption maximum, $\lambda_{\text{max}}$ being 536 nm with $\varepsilon$ value of 1380 at pH 4.6. However, in the basic region, the absorption band due to LMCT disappeared, indicating the decomposition of the complex.

$^{51}$V-NMR spectrum of complex 3e was measured in D$_2$O at pH 8, and VOCI$_3$ was used as an external standard. From $^{51}$V-NMR spectrum, it was found that three vanadium (V) species existed in D$_2$O solution, because three separated signals were observed at -480, -503 and -535 ppm (Fig. 5-a). When an excess of ligand 1e was added to the solution, two signals at -503 and -535 ppm completely disappeared (Fig. 5-b). From these and reported data [40, 41], the two minor signals were tentatively assigned to be the ligand dissociation products, [VO(L(D$_2$O)$_2$(OCH$_3$))]$^+$ and [VO(D$_2$O)$_2$(OCH$_3$)]$^{2+}$ as shown in Fig. 6.

![Fig. 3](image1.png)  
Fig. 3 $^1$H-NMR spectra of oxovanadium (V) complex 4e in CD$_3$OD at various temperatures; ○: free ligand.

![Fig. 4](image2.png)  
Fig. 4 A possible structure in equilibrium.

![Fig. 5](image3.png)  
Fig. 5 $^{51}$V-NMR spectra of oxovanadium (V) complex 3e in D$_2$O at pH 8; a) oxovanadium (V) complex, b) after addition of the ligand 1e.

![Fig. 6](image4.png)  
Fig. 6 The tentative assignment of the observed three signals in $^{51}$V-NMR spectrum of complex 3e.
Table 2  ESR parameters of oxovanadium (IV) complexes (4a-e and 5a-c)

<table>
<thead>
<tr>
<th>Complex</th>
<th>( g_0 )</th>
<th>( g_\parallel )</th>
<th>( g_\perp )</th>
<th>( A_0 )</th>
<th>( A_\parallel )</th>
<th>( A_\perp )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>1.979</td>
<td>1.947</td>
<td>1.995</td>
<td>79.4</td>
<td>153.9</td>
<td>42.1</td>
</tr>
<tr>
<td>4b</td>
<td>1.977</td>
<td>1.953</td>
<td>1.989</td>
<td>80.1</td>
<td>153.2</td>
<td>43.6</td>
</tr>
<tr>
<td>4c</td>
<td>1.971</td>
<td>1.950</td>
<td>1.982</td>
<td>80.6</td>
<td>159.9</td>
<td>40.9</td>
</tr>
<tr>
<td>4d</td>
<td>1.983</td>
<td>1.951</td>
<td>1.999</td>
<td>81.1</td>
<td>162.9</td>
<td>40.2</td>
</tr>
<tr>
<td>4e</td>
<td>1.979</td>
<td>1.950</td>
<td>1.994</td>
<td>79.6</td>
<td>162.9</td>
<td>37.9</td>
</tr>
<tr>
<td>5a</td>
<td>1.976</td>
<td>1.939</td>
<td>1.994</td>
<td>85.6</td>
<td>172.7</td>
<td>42.1</td>
</tr>
<tr>
<td>5b</td>
<td>1.974</td>
<td>1.940</td>
<td>1.991</td>
<td>88.1</td>
<td>171.9</td>
<td>46.2</td>
</tr>
<tr>
<td>5c</td>
<td>1.969</td>
<td>1.939</td>
<td>1.984</td>
<td>91.8</td>
<td>173.2</td>
<td>51.1</td>
</tr>
</tbody>
</table>

\( * g_0 = (g_\parallel + 2 g_\perp )/3 \); \( ^b A_0 = (A_\parallel + 2A_\perp )/3 \)

Characterization of oxovanadium (IV) complexes [42]

UV-vis spectra of oxovanadium (IV) complexes were measured both in \( H_2O \) and DMSO solutions. The absorption bands of complexes 4a-e at about 600 nm were assigned to be the d-d transition. On the other hand, the absorption bands of complexes 4a-e at \( \lambda_{max} \) 535-560 nm apparently increased with time. These bands were assigned to be LMCT ones of oxovanadium (V) complexes, indicating that oxovanadium (IV) complexes were prone to be oxidized to oxovanadium (V) ones even in aqueous solution.

Since oxovanadium (IV) ion is paramagnetic, ESR spectrum is a useful tool for investigation of electronic structure of oxovanadium (IV) complexes [14, 33]. Complexes 4a-e and 5a-c showed typical isotopic eight line ESR spectra at room and liquid nitrogen temperature, suggesting that they exist in a single isomer. The calculated ESR parameters, universal (g-values) and hyperfine coupling constants (A-values) are summarized in Table 2. These values were consistent with those of oxovanadium (IV) complexes with a VO\((\text{O}_4)\) coordination mode [14]. Further, VO(ma)_2 complex, which is structurally very similar to the present 4(1H)-pyridinone, has been proven to be the trans isomer by X-ray crystallographic analysis [41]. From these data, the obtained oxovanadium (IV) complexes probably exist in the trans form.

The electrochemical behavior of oxovanadium (IV) complexes was evaluated by means of cyclic voltammetry with a glassy carbon electrode. The measurement of cyclic voltammetry of oxovanadium (IV) complexes was carried out in aqueous solutions. A typical cyclic voltammogram of complex 4a is shown in Fig. 7. The electron transfer processes of complexes 4a,b,e and 5b are nearly reversible since \( ipa/ipc \) ratios are close to unity, although values of the peak-to-peak separation (\( \Delta E_p \)) are greater than 60 mV. It is noteworthy that \( E_{1/2} \) values of oxovanadium (IV) complexes are approximately 300 mV lower than those of oxovanadium (IV) ones with other VO\((\text{O}_4)\) and VO(N\(_2\text{O}_2\)) coordination modes [37, 41], indicating that these complexes are less stable toward oxidation. As the \( \Delta E_p \) values were larger than 60 mV, cyclic voltammograms were measured at various scan rates (V). A plot of \( ipc \) and \( V^{1/2} \) gave a straight line, indicating that the electron transfer proceeds at the diffusion control (Fig. 8).

\( \text{In vitro insulin-mimetic activity [43]} \)

Previously we have demonstrated that FFA release from isolated rat adipocytes is a good \textit{in vitro} evalua-

![Fig. 7 Cyclic voltammogram of complex 4a in 0.1 M NaCl aqueous solution. Scan rate: 100 mV·s\(^{-1}\).](image-url)
Oxovanadium (IV) and (V) complexes with heterocycles

Fig. 8 The plots of \( r^{1/2} \) vs. \( i_{pc} \) for complex 4a.

Fig. 9 The inhibitory effect of oxovanadium (IV) complexes 5a-c on epinephrine-stimulated FFA release from rat adipocytes.

Fig. 10 Serum glucose changes in (●) the STZ-rats and (○) STZ-rats given oxovanadium (IV) complex 5b by daily intraperitoneal injections. Data are expressed as the mean ± SD for 5-6 rats. *Significance at \( p < 0.05 \), **\( p < 0.005 \), ***\( p < 0.0005 \), ****\( p < 0.00005 \) vs. STZ-rats. Inset is an average dose of oxovanadium (IV) complex 5b in each day.

In order to find out a compound that exhibits the insulin-mimetic action [19]. The inhibitory effect of oxovanadium (IV) complexes 5a-c and \( \text{VOSO}_4 \) as a positive control on FFA release from rat adipocytes was shown in Fig. 9. All oxovanadium (IV) complexes inhibited FFA release in a dose-dependent manner. The IC\(_{50}\) value, which expresses the 50% inhibition concentration of the complex on FFA release stimulated by epinephrine (adrenaline) was calculated, and the results are summarized in Table 3. IC\(_{50}\) value (0.27 mM) of the complex 5b was different from that (0.39 mM [32] in Fig. 1) reported previously. This may be responsible for the use of different adipocytes in each experiment and different glucose concentrations (no addition of glucose causes to shorten the lifetime of adipocytes). Vanadyl complexes 5a-c showed higher activities than \( \text{VOSO}_4 \), and complex 5b showed the highest insulin-mimetic activity among these complexes.

**In vivo insulin-mimetic activity [43]**

The effect of oxovanadium (IV) complex 5b on lowering the blood glucose level was examined using streptozotocin-induced diabetic rats (STZ rats), which is a model animal for type 1 DM. When oxovanadium (IV) complex 5b was injected at a dose of 5.0 and 4.0 mg of vanadium (V)/kg of body weight for the first and second days, respectively, the serum glucose level lowered to the subnormal range as shown in Fig. 10. It was maintained in almost normal range (100-200 mg/dL) for two weeks by daily injections of 0.9-2.6 mg V/kg for the following 12 days.

In order to investigate whether oxovanadium (IV) complex 5b improved glucose tolerance in type 1 STZ-rats, an oral glucose tolerance test (OGTT) was performed after treatment with oxovanadium (IV) complex 5b. The blood glucose levels of the STZ-diabetic rats were elevated to a maximal concentration of about 500 mg/dL at 30 min after the administration of glucose, after which the levels gradually decreased. On the contrary, the elevation in the blood glucose levels of STZ-rats treated with oxovanadium (IV) complex 5b for two weeks were significantly lower than those of the diabetic animals, indicating that oxovanadium (IV) complex 5b improved the diabetic state of animals.
Table 3  IC₅₀ values and the partition coefficients of oxovanadium complexes 4a-e and 5a-c in the presence of 5 mM glucose

<table>
<thead>
<tr>
<th>Complex</th>
<th>IC₅₀/mM</th>
<th>log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>a)</td>
<td>b)</td>
</tr>
<tr>
<td>4b</td>
<td>a)</td>
<td>-1.22</td>
</tr>
<tr>
<td>4c</td>
<td>2.54</td>
<td>-0.02</td>
</tr>
<tr>
<td>4d</td>
<td>31.2</td>
<td>0.27</td>
</tr>
<tr>
<td>4e</td>
<td>a)</td>
<td>-1.15</td>
</tr>
<tr>
<td>5a</td>
<td>0.53</td>
<td>c)</td>
</tr>
<tr>
<td>5b</td>
<td>0.27</td>
<td>0.48</td>
</tr>
<tr>
<td>5c</td>
<td>0.29</td>
<td>1.04</td>
</tr>
<tr>
<td>VOSO₄</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

a) not measurable due to the low activity.

b) not measurable due to high water solubility.

c) not measurable due to its water insolubility.

HbA1c analysis was used as an index to assess the glycemic control levels in DM. In STZ-rats, the HbA1c levels was 8.8±0.7% (after). In contrast, the HbA1c levels of the STZ-rats treated with oxovanadium (IV) complex 5b significantly decreased to 6.3±0.8%, suggesting that oxovanadium (IV) complex 5b sustained the longitudinal blood glucose-controlling effect.

Conclusion

Through this work, the following points became clear: 1) two types of bidentate ligands, 3-hydroxy-4(1H)pyridinones 1a-e and 1-hydroxy-2(1H)-pyrimidinones 2a-c, were synthesized; 2) the treatment of compounds 1 with VO(acac)₂ in MeOH under various conditions gave not oxovanadium (IV) but oxovanadium (V) complexes, which were characterized by means of IR, UV-vis, ¹H- and ⁵¹V-NMR spectroscopies, and combustion analyses; 3) the treatment of compounds 1 and 2 with VOSO₄ in H₂O under appropriate pH conditions afforded oxovanadium (IV) complexes, which were fully characterized by means of IR, UV-vis, FAB-MS and ESR spectroscopies, and combustion analyses; 4) oxovanadium (IV) complex 5b showed the highest insulin-mimetic activity in terms of IC₅₀ value; 5) using STZ-induced diabetic rats, blood glucose levels substantially lowered from hyperglycemic to normal levels after the treatment with oxovanadium (IV) complex 5b; and 6) oxovanadium (IV) complex 5b showed great potential as a possible agent to treat type 1 DM.

Acknowledgements

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References

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