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In Vitro Evaluation of the Anti-Diabetic Potential of Oxovanadium(IV) Complex with Terpyridine Ligand

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Abstract
An oxovanadium(IV) complex with 2,2′:6′,2″-terpyridine ligand, $[VO(terpy)]SO_4$, was synthesized and characterized to evaluate its anti-diabetic potential. The complex was synthesized via a direct reaction between $VOSO_4$ as the metal source and terpyridine ligand in solution and confirmed through conductometric and mass spectrometric analyses. Conductivity measurements indicated that the complex behaves as a 2:2 electrolyte in aqueous solution, dissociating into $[VO(terpy)]^{2+}$ and SO_4^{2-} ions. Mass spectrometry revealed a peak at m/z 150.0098 corresponding to the cationic species. The anti-diabetic activity was evaluated through in vivo studies using alloxan-induced diabetic rats, demonstrating a significant reduction in fasting blood glucose levels. These findings suggest that the oxovanadium(IV)–terpyridine complex is a candidate for further development as an anti-diabetic agent.

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INTRODUCTION

Diabetes mellitus (DM) is one of the five leading disease causes of death worldwide. According to the World Health Organization (n.d), approximately 422 million people, or about 6% of the global population, are affected by this disease. In Indonesia, the number of diabetic patients reaches nearly 10 million people. This number predicted may double by 2030 (Wild et al., 2004). Consequently, extensive research has been devoted to developing anti-diabetic agents.

DM is a metabolic disease characterized by hyperglycemia, or an abnormally high level of glucose in the blood (Rama Rao & Tejomurtula, 2024; Xu et al., 2018). Early oral treatment of DM employed sodium metavanadate ($NaVO_3$) as early as 1899. However, vanadate in its +5 oxidation state was later found to be toxic, prompting its substitution with vanadyl sulfate, which contains vanadium in the +4 oxidation state and exhibits about ten times lower toxicity (Poucheret et al., 1998). Further studies on $NaVO_3$ revealed that most V(+5) species are reduced to V(+4) in vivo, suggesting that the +4 state is primarily responsible for the anti-diabetic activity (Sakurai, 2002).

Subsequent research found that the oxovanadium complex bis(maltolato)oxovanadium(IV) (BMOV) exhibited stronger anti-diabetic effects and lower toxicity compared to vanadyl sulfate. This is attributed to the increased stability of vanadium when in complex form rather than as a simple salt (Adachi et al., 2006). Consequently, coordination chemistry of vanadium is a topic of interest since the discovery of it as insulin enhancing agents (Thompson et al., 1999; Thompson & Orvig, 2001). Several oxovanadium(IV) complexes have earlier been studied for their antidiabetic activity (Katoh et al., 2009; Rehder et al., 2002). Search for newer and newer such antidiabetic compounds has become an important area of current biochemical research. Numerous oxovanadium(IV) complexes

have been studied for this application, particularly those bearing bidentate O- and N- and S- donor ligands (Bharathi et al., 2020; Nisa, 2023) and subsequent studies expanded to tetradentate and mixed bidentate–tridentate ligand systems (Pessoa et al., 2015; Sheela et al., 2013; Yuan et al., 2010). However, oxovanadium(IV) complexes with tridentate ligands have been scarcely reported as potential anti-diabetic agents, making them an interesting subject for further exploration.

One notable example is the oxovanadium complex with 2,2′:6′,2′′-terpyridine (terpy), a tridentate ligand containing three nitrogen-bearing heterocyclic rings. 2,2′:6′,2′′-Terpyridine is a heterocyclic compound known for its therapeutic importance due to its structural similarity to many naturally occurring biomolecules such as nucleic acids, alkaloids, vitamins, and amino acids. Heterocyclic compounds can form hydrogen bonds with target proteins, acting either as hydrogen bond acceptors via heteroaromatic atoms or as donors through N-heterocycles. Moreover, heterocyclic compounds generally possess higher solubility than their carbon-based analogs (Gomtsyan, 2012) and oxovanadium(IV) complexes containing various heterocyclic ligands have demonstrated promising antidiabetic effects in in vitro studies (Sakurai, 2000). Therefore, terpyridine was selected in this study due to its N-heterocyclic structure, which is expected to enhance biological interactions and support the formation of stable and biologically relevant oxovanadium(IV) complexes.

Previous studies successfully crystallized this complex and confirmed its structure through single-crystal X-ray diffraction and computational analysis (Pifferi et al., 2000), however, its anti-diabetic potential remains unexplored. Therefore, this study presents the re-synthesis and characterization of the oxovanadium(IV)-terpyridine complex, alongside the first in vitro evaluation of its anti-diabetic activity.

METHOD

Material and Tools

The materials used in this study were 2,2′:6′,2′′-terpyridine ligand ($C_{15}H_{11}N_3$, Aldrich), vanadyl sulfate ($VOSO_4$, Aldrich) as the metal source, ethanol (C_2H_5OH, p.a., Merck) as a solvent. The materials required for the in vivo diabetes potency test consisted of alloxan ($C_4H_2N_2O_4$) and diabetes test strips (Accu-Chek Performa).

The equipments used in this study were beakers, spatulas, magnetic stirrers, reflux apparatus, erlenmeyer flasks, volumetric flasks, analytical balance, hotplate, rotary evaporator, vacuum oven, desiccator, Whatman 42 filter papers, droppers, test tubes, and a glucometer. The instruments used for the characterization of the complex included a Waters Xevo QTOF mass spectrometer, which was operated at the Central Laboratory of Universitas Padjadjaran and a Multi-range HI 9033 conductivity meter (Hanna Instruments).

Synthesis of $[VO(terpy)]SO_4$

The $[VO(terpy)]SO_4$ complex was synthesized by mixing $VOSO_4{\cdot}3H_2O$ (0.49 g, 2.2 mmol) with terpyridine ligand (0.75 g, 3.2 mmol) in a 1:1 molar ratio using 5 mL each of water and ethanol. The mixture was stirred at room temperature for two hours, producing a green precipitate that was filtered, washed three times with ethanol, and dried in a desiccator. The crude product was recrystallized in 160 mL of hot water, evaporated to approximately 10 mL, and allowed to stand at room temperature to yield a crystalline precipitate. The product was filtered and dried under vacuum for seven hours.

Mass Spectrometric Analysis

A 1 mg/mL solution of the complex was placed into the sample holder and introduced into the instrument through a spray capillary. The sample was measured using water as the solvent. The solution entering the system was converted into an aerosol due to the high voltage, forming gas-phase ions whose masses were then detected. The measurement was carried out in positive mode (ES^+) with a nitrogen gas flow, at a temperature of 100 °C and an m/z range of 100–1000. The result was a spectrum showing mass (m/z) versus intensity.

Conductivity Measurement

The conductometer was preheated for 15 minutes before measurements. Solutions of KCl 10^{-2} M and 10^{-3} M solutions of $VOSO_4$ and $[VO(terpy)]SO_4$ were prepared in deionized water. The measured conductance (L) was used to calculate the cell constant (K) using the known specific conductance of KCl (k = 1285 µS/cm at

25 °C). The molar conductivity (Λ_m) of each complex was calculated using the equations:

$$k = KL$$

$$\Lambda_m = 1000k/M$$

where k = specific conductance (S/cm), K = cell constant, L = measured conductance, and M = molar concentration.

In Vivo Test

The in vivo testing of the antidiabetic potential of the oxovanadium(IV) complexes was conducted at the Pharmacology and Therapeutics Laboratory, Faculty of Medicine, Universitas Padjadjaran. This study considered ethical aspects of animal experimentation and was conducted in accordance with established guidelines for the care and use of laboratory animals. The experimental animals used were male Wistar white rats (Rattus norvegicus) made diabetic through alloxan induction, weighing approximately 200 g and aged 10–12 weeks. The number of samples was determined using the equation:

$$(n-1)(t-1) \geq 15$$

where n is the number of samples and t is the number of groups.

This study used two experimental groups, as follows:

i. Negative control: alloxan induction
ii. $[VO(terpy)]SO_4$ test: alloxan induction + complex (0.03 mg V/kg body weight)

The in vivo testing lasted for 17 days. In the first stage, 15 rats were divided into three groups. Before treatment, the rats were acclimated for seven days and given standard feed to allow physiological adaptation to their environment. The rats were then fasted for 16 hours to measure fasting blood glucose (FBG). Blood samples were collected and tested by applying a drop of blood onto a test strip attached to a glucometer. This measurement represented the initial blood glucose level.

On the same day, the rats were induced with alloxan at a dose of 125 mg/kg body weight, dissolved in NaCl (0.1 g/mL), to induce diabetic conditions. Three days later, the rat's blood glucose levels were measured again; those with levels above 126 mg/dL were selected as experimental subjects. The diabetic rats were then treated with oxovanadium(IV) complexes according to their designated groups and doses. Alloxan and the samples were administered subcutaneously on the dorsal side of the rats. Blood samples for measurement were taken from the lateral tail vein. Blood glucose levels were monitored daily until the seventh day.

The collected blood glucose data were qualitatively evaluated by comparing trends in glucose levels over time between treated and untreated groups. A reduction in blood glucose levels relative to the diabetic control group was considered indicative of potential anti-diabetic activity. Additionally, the consistency and direction of glucose level changes during the treatment period were used to assess the effectiveness of the oxovanadium(IV)-terpyridine complex in modulating glycemic conditions.

RESULTS AND DISCUSSION

The complex $[VO(terpy)]SO_4$ was synthesized from the reaction between the ligand 2,2′:6,2″-terpyridine (terpy) and $VOSO_4$. An excess amount of ligand was used to ensure that all metal ions could coordinate with the ligand. During the synthesis process, a color change was observed from the blue color of $VOSO_4$ and the colorless terpyridine ligand solution to a green-colored solution after mixing. This color change is one of the physical indicators that coordination between the ligand and the metal center has occurred. The synthesis was carried out at room temperature because the green complex precipitate was already formed under these conditions, while the reaction time of two hours was determined based on the observation that the amount of precipitate remained constant after that period.

Figure 1. Complex $[VO(terpy)]SO_4$

The complex $[VO(terpy)]SO_4$ has a solubility of only 5×10^{-3} M. The number of ions in the complex can be determined through conductivity measurements, as ions are capable of conducting electricity. The cell constant (K) was determined using a standard 10^{-2} M KCl solution with a known specific conductivity (k). KCl was chosen as the standard solution because it is a strong electrolyte that remains stable over a wide range of concentrations.

The measurement and calculation results showed that the $[VO(terpy)]SO_4$ complex has a molar conductivity of 236 S cm²/mol. This value is close to the molar conductivity of $VOSO_4$ at the same concentration, which is 213 S cm²/mol. This indicates that the complex behaves as a 2:2 electrolyte in solution, producing the ions $[VO(terpy)]^{2+}$ and SO_4^{2-}. The sulfate ion in the complex is not coordinated as a ligand in solution, consistent with previously reported complexes (Pifferi et al., 2000). This occurs due to competition between water molecules and sulfate ions for coordination at the metal center. Both water and sulfate ions are weak ligands, but the coordinating strength of water is slightly higher than that of the sulfate ion.

The relative molecular mass can be determined using mass spectrometry, which provides information in the form of the mass-to-charge ratio (m/z). For neutral molecules, ionization typically occurs by the addition of a positive ion such as $[M+H]^+$ or by the loss of an electron to form a positive molecular ion $[M^+]$ and a radical. Based on the conductometric measurements, the $[VO(terpy)]SO_4$ complex is a cationic complex in solution; therefore, it can be easily ionized and its mass detected by the instrument. The mass spectrum of $[VO(terpy)]SO_4$ is shown in Figure 2.

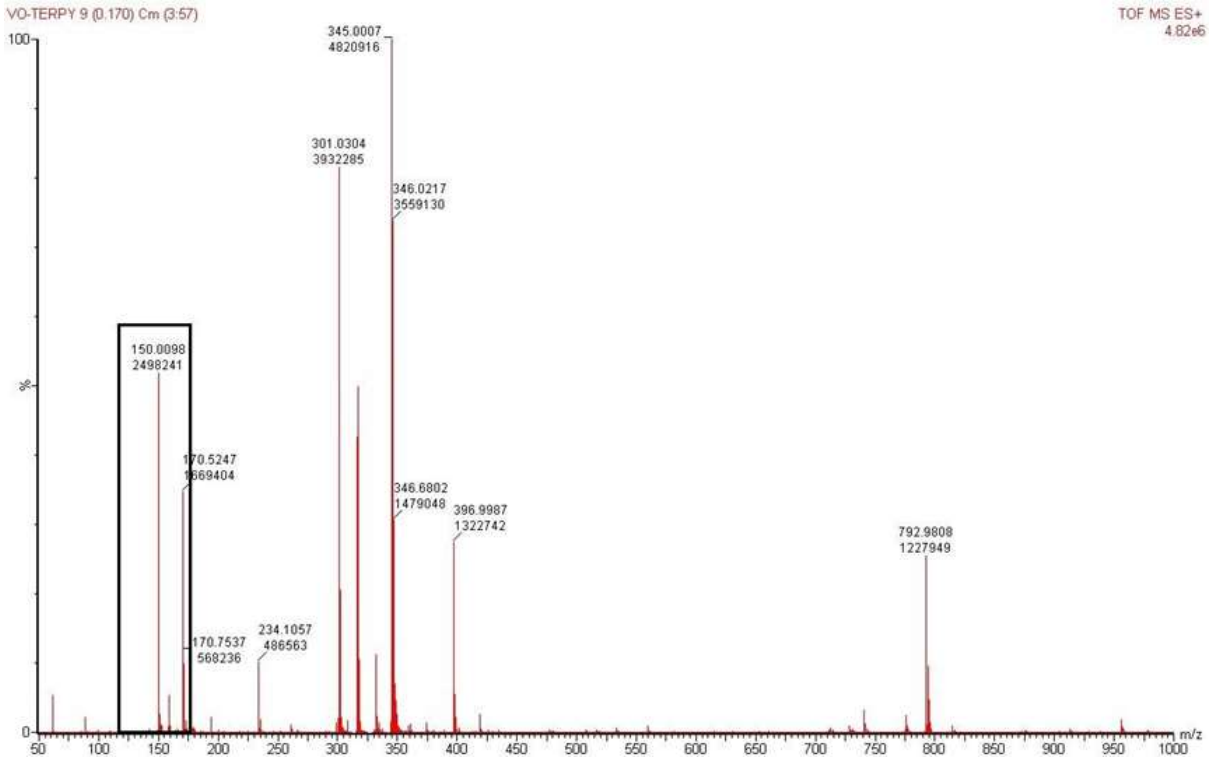

Figure 2. $[VO(terpy)]SO_4$ mass spectrum

According to the mass spectrum results in Figure 2, a peak at 150.0098 corresponds to the m/z value of $[VO(terpy)]^{2+}$. The other peaks observed in the mass spectrum are presumed to result from solvent contamination or other impurities. From the results of both characterization analyses, it can be inferred that the $[VO(terpy)]SO_4$ complex was successfully synthesized. Subsequently, the antidiabetic potential of this complex was evaluated in vivo using male wistar rats.

This experiment used male wistar rats as test animals because male rats provide more stable research results, as they are not affected by menstrual cycles or pregnancy, unlike female rats. Male white rats also exhibit faster drug metabolism and more stable biological conditions compared to female rats (Gochfeld, 2017).Alloxan was used as the diabetogenic agent because it is more economical than STZ and can induce permanent hyperglycemia in rats within two to three days (Macdonald Ighodaro et al., 2018).Alloxan is a strong oxidizing agent that is reduced in the body to dialuric acid, producing by-products such as alloxan radicals (HA•) or superoxide radicals. These superoxide radicals can reduce Fe^{3+} to Fe^{2+} and subsequently undergo dismutation to form hydrogen peroxide. The presence of Fe^{2+} ions and hydrogen peroxide can then lead to the formation of reactive hydroxyl

radicals. As a result, these radicals damage the DNA of pancreatic β-cells, leading to the development of diabetes (Szkudelski, 2001)

Before treatment, the rats were fasted for 16 hours to ensure that the measured blood glucose levels were not influenced by food intake. The blood glucose levels of the rats after administration of the oxovanadium(IV) complexes, compared to the negative control (diabetic rats without treatment), are shown in Table 1.

Table 1. Data of Experimental Rat's Blood Glucose Level

Group	Body Weight (g)	Fasting Blood Glucose Level (mg/dL)								
		Initial	Alloxan	1	2	3	4	5	6	7
Untreated	202	91	207	374	600	417	425	498	487	345
	204	78	207	390	600	495	450	359	327	36
	206	107	297	549	600	600	Dead	Dead	Dead	Dead
Average	204	92.0	237.0	437.7	600.0	504.0	437.5	428.5	407.0	190.5
S.E.M*	1.2	8.4	30.0	55.9	0.0	53.0	12.5	69.5	80.0	154.5
$[VO(terpy)]SO_4$	203	69	249	123	112	100	99	98	93	117
	202	78	187	168	132	116	119	121	97	108
	208	61	217	159	151	103	118	123	45	Dead
Average	204.3	69.3	217.7	150.0	131.7	106.3	112.0	114,0	78,3	112,5
S.E.M*	1.9	4.9	17.9	13.7	11.3	4.9	6.5	8.0	16.7	4.5

*S.E.M (standard error if mean)

As presented in Table 1, all experimental groups exhibited comparable initial fasting blood glucose (FBG) levels (200–250 mg/dL), confirming the uniformity of the diabetic model prior to treatment. In untreated diabetic rats, FBG levels increased and reached a peak on the second day, followed by a slight decline that nevertheless remained within the hyperglycemic range. This pattern is consistent with the established mechanism of alloxan-induced diabetes, which involves selective destruction of pancreatic β-cells and subsequent impairment of insulin secretion (Elsner et al., 2008).

In contrast, administration of the $[VO(terpy)]SO_4$ complex resulted in a rapid and significant reduction in FBG levels, reaching normoglycemic values (<100 mg/dL) by the third day, corresponding to a 51.17% decrease at a relatively low dose of 0.03 mg V/kg body weight. When compared to previous studies, this effect appears notably faster and more efficient. For example, oxidovanadium(IV) complexes such as $[VO(bpy)(mal)]\cdot H_2O$ required longer treatment durations (up to 12 days) and showed glucose-lowering effects primarily in combination with insulin rather than as a standalone treatment (de Nigro et al., 2022). However, it is important to note that these studies employed different experimental conditions, including the use of streptozotocin (STZ)-induced diabetic models and higher administered doses, which may influence the pharmacodynamic response (Ramachandran et al., 2004). Therefore, direct quantitative comparison should be interpreted with caution.

Overall, these findings qualitatively demonstrate that $[VO(terpy)]SO_4$ exhibits anti-diabetic effect in alloxan-induced diabetic rats at a low dosage. This highlights its potential as a promising candidate for further development as a novel anti-diabetic agent.

CONCLUSION

An oxovanadium(IV) complex with 2,2′:6′,2′′-terpyridine ligand, $[VO(terpy)]SO_4\cdot½H_2O$, was successfully synthesized and characterized. The compound is water-soluble, exhibits molar conductivity consistent with a 2:2 electrolyte, and generates the $[VO(terpy)]^{2+}$ cation as verified by mass spectrometry. Given the well-established biological activity of oxovanadium(IV) complexes, $[VO(terpy)]SO_4$ shows promising potential as an in vitro anti-diabetic agent for further biochemical evaluation.

RECOMMENDATION

The antidiabetic potential of oxovanadium(IV)-terpyridine complexes requires further optimization through dose variation and comparison with standard drugs such as metformin and $VOSO_4$. In this study, challenges

included a limited dose range and the absence of direct benchmarking with reference compounds, while the short-term evaluation restricts conclusions on long-term efficacy and safety. Therefore, future studies should focus on broader dose–response analysis, extended treatment duration, and comparative studies with established antidiabetic agents, as well as toxicity profiling, pharmacokinetic studies, and mechanistic investigations to better understand the therapeutic potential and safety of the oxovanadium(IV)-terpyridine complex.

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