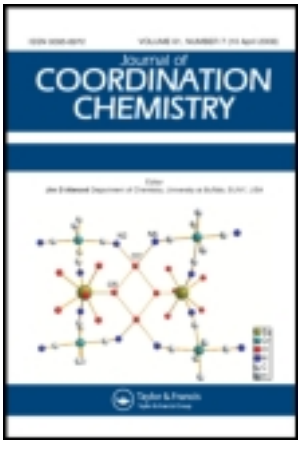

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Synthesis, spectral characterization, and antidiabetic study of new furan-based vanadium(IV) complexes

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Synthesis, spectral characterization, and antidiabetic study of new furan-based vanadium(IV) complexes

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We have synthesized furan-based vanadium complexes, *bis*(5-nitrofuran-2-carboxylato) oxovanadium(IV) – $[VO(5NF)_2]$, *bis*(1-furan-2-yl-ethanonato)oxovanadium(IV) sulfate – $[VO(2AF)_2]SO_4$, and *bis*(5-methyl-2-furalato)oxovanadium(IV) sulfate – $[VO(MFFA)_2]SO_4$ possessing $[VO(O_4)]$ coordination mode. These complexes are characterized by physico-chemical and spectroscopic methods. Based on electron paramagnetic resonance parameters, the proposed geometry is close to a distorted square pyramid. Animal study was carried out using standard protocol and the complete profile of glucose, protein, and total cholesterol levels were analyzed followed by an oral glucose tolerance test.

Keywords: Furan-like ligands; EPR; Oral glucose tolerance test

1. Introduction

Diabetes mellitus is a metabolic disorder which manifests itself as Type I – insulin-dependent diabetes mellitus, characterized by low or insufficient secretion of insulin and Type II – non-insulin-dependent diabetes mellitus, characterized by ineffective utilization of insulin [1]. Type I is treated by subcutaneous injection of insulin and Type II by various synthetic therapeutics. Current bioinorganic research toward antidiabetics is focused on the development of oral alternatives in the place of daily painful insulin injection and synthetic therapeutics without secondary complications such as nephropathy, neuropathy, retinopathy, etc., and without any undesirable side effects [2–5]. Use of vanadium compounds for the treatment of diabetes have been known for the past 25–30 years.

The earliest evidence of the insulin-like effects of the vanadium salt, sodium orthovanadate (Na_3VO_4), was published by Lyonnet *et al.* [6] in 1899, 22 years before the discovery of insulin. Subsequent work was carried out by Tolman *et al.* [7] demonstrating *in vitro* insulin-mimetic effect of vanadium salts kindling further research in this field. Work reported by Heyliger *et al.* [8] in 1985 was the first to show that vanadate normalized hyperglycemia *in vivo* in animals; this was subsequently confirmed by Meyerovitch *et al.* [9]. Since then, extensive studies exploring vanadium chemistry

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and biochemistry in various coordination modes like [$VO(O_4)$], [$VO(S_4)$], [$VO(N_2S_2)$], and [$VO(N_2O_2)$] have been pursued both *in vivo* and *in vitro* [10–17]. In addition to glucose lowering effects, certain vanadium complexes in +4 and +5 oxidation states exhibit antimicrobial activity [18–20]. Organo-vanadium complexes are considered to be advantageous in bringing about greater therapeutic efficacy at lower dosage when compared to vanadium salts and hence have emerged as potential antidiabetic agents. The vanadyl state (+4) seems to be less toxic than vanadate (+5) [21].

This area of research has importance including several human trials. The 6th International Symposium on vanadium held at Portugal in July 2008 reported the completion of Phase IIa clinical trial of BEOV, *bis*(ethylmaltolato)oxovanadium(IV), in comparison with vanadyl sulfate [22–25]. A few reviews reported by Orvig, Sakurai, Kiss, and Crans reveal the extensive research in this field and the enormous potential that needs to be tapped in the future [26–30].

Although extensive studies on the biological action of vanadium in both +4 and +5 oxidation states are known, the complete mechanism by which it exerts insulin-mimetic activity is yet to be proved. Several mechanisms have been proposed with respect to activation of certain enzymatic reactions involving insulin receptor tyrosine kinase and insulin signaling enzymes. Vanadyl ions have multiple sites of action in adipocytes unlike insulin for which insulin receptor is the only site of action. Thus, the mechanism of action has been called an "ensemble mechanism" [31]. Modeling studies have been used to determine the actual form of oxovanadium(IV) in various biological environments responsible for antidiabetic action [32].

Several physiologically compatible ligands have been complexed with vanadium, which act as effective antidiabetic agents due to the synergic effects of ligands and metals. A few important ligands possessing synergistic effect upon vanadium's antidiabetic efficacy include maltol [33], picolinic acid [34], acetylacetone [35], and furan [36]. We have chosen furan-based ligands for our study based on the report on insulin-mimetic activity of *bis*(furan-2-carboxylato)oxovanadium(IV) – BFOV studied by Xie [37] and subsequently by other groups [38, 39].

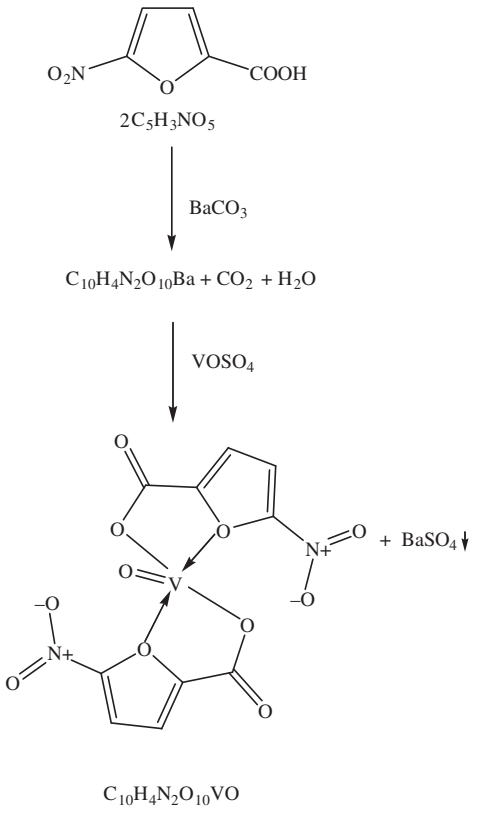
We report here the synthesis and characterization of a few new furan-based vanadium complexes, [$VO(5NF)_2$], [$VO(2AF)_2]SO_4$, and [$VO(5MFFA)_2]SO_4$. The glucose lowering ability of the compounds is assessed based on *in vivo* study.

2. Experimental

2.1. *Materials and methods*

Vanadium pentoxide, vanadyl sulfate pentahydrate (S.D. Fine), 5-nitrofuran-2-carboxylic acid, 1-(furan-2-yl)ethanone, 5-methyl-2-furaldehyde (Sigma–Aldrich), barium carbonate (Sisco Research Laboratory), concentrated H_2SO_4, ethanol, DMSO (S.D. Fine), potassium carbonate (Qualigens), standard rodent pellet diet (Hindustan Lever & Co., Bangalore) and streptozotocin (SZT; Sigma–Aldrich) were of analytical grade (99.9% purity).

2.1.1. Preparation of BFOV. The preparation of *bis*(furan-2-carboxylato) oxovanadium(IV) – BFOV is carried out as per the method reported in [39].



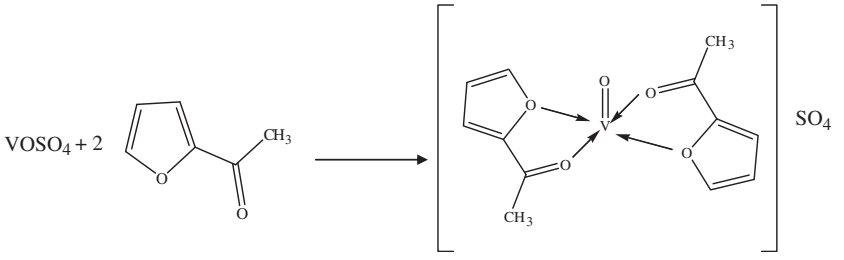
Scheme 1. Structure of *bis*(5-Nitrofuran-2-carboxylato)oxovanadium(IV).

2.1.2. Preparation of $[VO(5NF)_2]$. The ligand, 5-nitrofuran-2-carboxylic acid (200 mmol) was dissolved in 100 mL of hot water and barium carbonate (100 mmol) was added. The mixture was stirred for 4 h at 45°C, and then the colorless solution was collected by filtration. Vanadyl sulfate (100 mmol) was added to this solution and stirred for 3 h. The precipitated barium sulfate was removed by filtration. The mother liquor was collected and concentrated by distillation, causing the separation of green solid (yield: 77% – scheme 1).

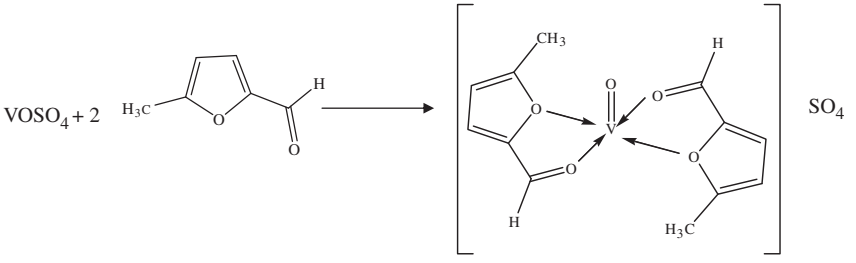
2.1.3. Preparation of $[VO(2AF)_2]SO_4$ and $[VO(5MFFA)_2]SO_4$. These complexes were synthesized in two steps. In the first step, vanadium pentoxide was reduced to vanadyl sulfate (50 mmol) with conc. H_2SO_4 and ethanol. In the second step, it was mixed with 1-(furan-2-yl)ethanone or 5-methyl-2-furaldehyde – 100 mmol) and was neutralized by adding K_2CO_3 with stirring. The product was filtered, washed with water, ethanol, and dried in air (yield: $[VO(2AF)_2]SO_4$: 78%; $[VO(5MFFA)_2]SO_4$: 65% – schemes 2 and 3).

2.2. *Physical measurements*

Electronic spectra were recorded on a Shimadzu-1601 double beam UV-Vis spectrometer. FT-IR used KBr window on a Thermo Nicolet, Avatar 330 FT-IR spectrometer,



Scheme 2. Structure of *bis*(1-Furan-2-yl-ethanonato)oxovanadium(IV) sulfate.



Scheme 3. Structure of *bis*(5-Methyl-2-furalato)oxovanadium(IV) sulfate.

USA, and ESI mass on a Q-TOF micromass spectrometer. Magnetic moments were measured at room temperature (RT) using vibrating sample magnetometer make (Lake Shore: model 7404) from 1 μemu to 56 emu. CHN analyses were done on an elemental analyzer Elementar Vario EL III Carlo Erba 1108. The X-band electron paramagnetic resonance (EPR) spectra were recorded on an E-112, Varian EPR spectrometer, X-band (8.5–9.5 GHz), and Q-band (35.5 GHz) up to 2 Tesla magnetic field, with crystal rotation in X- and Q-band as 0–180°. The analyzer grade kit for animal study was obtained from Erba Diagnostics, Germany.

2.3. *Test protocol*

The synthesized complexes $[VO(5NF)_2]$, $[VO(2AF)_2]SO_4$, $[VO(5MFFA)_2]SO_4$, and [BFOV] were subjected to *in vivo* animal study as per the following protocol to assess their glucose lowering ability.

Albino wistar rats weighing 200–250 g of either sex were chosen and the study was carried out according to the guidelines of the Animal Ethics Committee. The rats were maintained at RT in polypropylene cages. They were placed in six groups: normal control, diabetic control – treated (glibenclamide), drug treated (synthesized compounds, $[VO(5NF)_2]$, $[VO(MFFA)_2]SO_4$, $[VO(2AF)_2]SO_4$, and [BFOV], and diabetic control – untreated (SZT), of six rats each.

The animals were kept fasting for 24 h with water and a dose of SZT (50 mg kg^{-1} in 0.1 mol L^{-1} of citrate buffer – pH 4.5 was injected intraperitoneally [40]. After 1 h, the animals were provided feed *ad libitum*. Five days after administering the SZT injection,

Table 1. Test groups and their dosage levels.

Test groups	Compound	Dosage level ($mg\,kg^{-1}$)
Normal control	Only vehicle	2 mL
Diabetic control treated	Glibenclamide	10
Drug treated-1	$[VO(5NF)_2]$	15
Drug treated-2	$[VO(5MFFA)_2]SO_4$	15
Drug treated-3	$[VO(2AF)_2]SO_4$	15
Drug treated-4	[BFOV]	15
Diabetic control untreated (negative control)	SZT	125

the blood glucose levels were checked using an autoanalyzer by withdrawing blood from retro-orbital puncture under mild ether anesthesia. The rats with blood glucose level greater than $250\,mg\,dL^{-1}$ were considered to be diabetic [41] and used for the current study. Normal control rats were injected only with the vehicle.

Body weights were measured daily during the experiments. Intake of solid food and water in each rat was checked everyday throughout the experiments. The test groups and dosage levels are tabulated (table 1). At concentrations $15\,mg\,kg^{-1}$ ($0.04\,mmol\,kg^{-1}$) for each compound $[VO(5NF)_2]$: $2\,mg\,V\,kg^{-1}$; $[VO(2AF)_2]SO_4$, $[VO(5MFFA)_2]SO_4$: $2\,mg\,V\,kg^{-1}$, and [BFOV]: $2\,mg\,V\,kg^{-1}$] were made into a suspension and administered orally for 4 weeks to the rats.

At the end of each week, the blood samples were collected from each rat in the individual groups under mild ether anesthesia. The collected blood samples were centrifuged at 2000 rpm for 10 min and the supernatant serum was separated from each blood sample into respective tubes using suitable micropipettes. The separated serum was taken for the analysis of glucose, total cholesterol, and protein and compared with the standard drug (glibenclamide)-treated group. Data are expressed as means + standard error for the animal groups. Statistical significance was accepted at p-values < 0.05.

2.3.1. Oral glucose tolerance test. After the drugs were administered intragastrically in both normal and SZT-induced diabetic rats for 4 weeks, an oral glucose tolerance test (OGTT) was undertaken. The experimental rats were fasted for 14 h and given an oral glucose challenge at a dose of $2.0\,g\,kg^{-1}$ body weight [42]. Blood glucose levels were measured at 0, 60 min, 120 min, and 180 min after glucose loading.

3. Results and discussion

Elemental analyses and physical properties of the complexes are summarized in table 2. The effective magnetic moment at RT for these complexes are within the expected range of 1.73 BM, indicating the paramagnetic and mononuclear nature of these complexes.

Table 2. Analytical data and some physical properties of the complexes.

Complex	Found (F)/calculated (C) (%) C	H	M	Color	μ_{eff} (BM)
$[VO(5NF)_2]$ $C_{10}H_4O_6VO(NO_2)_2$ (379)	F: 31.5 C: 31.7	F: 1.2 C: 1.1	F: 13.7 C: 13.5	Green	1.72
$[VO(5MFFA)_2]SO_4$ $[C_{12}H_{12}O_4VO]SO_4$ (383)	F: 37.2 C: 37.6	F: 3.2 C: 3.1	F: 13.2 C: 13.3	Green	1.74
$[VO(2AF)_2]SO_4$ $[C_{12}H_{12}O_4VO]SO_4$ (383)	F: 37.5 C: 37.6	F: 3.3 C: 3.1	F: 13.2 C: 13.3	Green	1.69

Table 3. IR stretching frequencies of the ligands and complexes.

Ligand	Stretching frequency (cm^{-1})	Complex	Stretching frequency (cm^{-1})
5-Nitro-2-furoic acid	C=O: 1690; V=O: nil	$[VO(5NF)_2]$	υ_a (COO^-): 1627; υ_s (COO^-): 1384; V=O: 992
5-Methyl-2-furaldehyde	C=O: 1678; V=O: nil	$[VO(5MFFA)_2]SO_4$	C=O: 1625; V=O: 1015
1-(Furan-2-yl)ethanone	C=O: 1674; V=O: nil	$[VO(2AF)_2]SO_4$	C=O: 1625; V=O: 999

3.1. *FT-IR spectra*

The characteristic IR stretching frequencies are given in table 3. In $[VO(5NF)_2]$, the difference in asymmetric and symmetric carboxylate stretching frequency $[\upsilon_a(COO^-) - \upsilon_s(COO^-)]$ is 243 cm^{-1}, indicating unidentate coordination of carboxylate. The characteristic oxovanadium frequency occurs at 992 cm^{-1} and V–O frequency occurs at 552 cm^{-1} [43–45]. For $[VO(2AF)_2]SO_4$ and $[VO(5MFFA)_2]SO_4$, shift by about 50 cm^{-1} in the carbonyl frequencies from coordination is observed and characteristic oxovanadium stretching frequencies are at 1000 cm^{-1}. Absorptions of sulfate, in the range of 1110–1120 cm^{-1} for υ_3 band and 610–620 cm^{-1} for υ_4 band, for both the complexes indicate that it is ionic, which is further confirmed by the absence of υ_2. The non-splitting of υ_3 indicates that tetrahedral symmetry is retained [46]. The assignment of υ_1 (SO_4^{2-}) is quite difficult as it lies in the region of the stretching vibration of the oxovanadium bond. Thus, the above two complexes are five-coordinate with four donors in the coordination sphere of the oxovanadium ion (VO^{2+}) with sulfate as the counter ion. Conductivity measurements in DMSO of about 70 $'\Omega^{-1}\,cm^2\,mol^{-1}$ show 1 : 1 electrolytes [47].

3.2. *Diffuse reflectance spectra*

The electronic spectra in solution showed very weak bands in the visible region that could not be resolved, so we resorted to the solid-state diffuse reflectance spectra (table 4). Diffuse reflectance spectra show four bands in the visible regions, 420–440, 580–590, 630–640, and 800–810. The spectra can be explained in terms of energy level scheme

Table 4. Diffuse reflectance spectra.

Compound	λ1 (nm)	λ2 (nm)	λ3 (nm)	λ4 (nm)
$[VO(5NF)_2]$	427	587	639	806
$[VO(2AF)_2]SO_4$	434	594	635	802
$[VO(5MFFA)_2]SO_4$	424	587	635	809

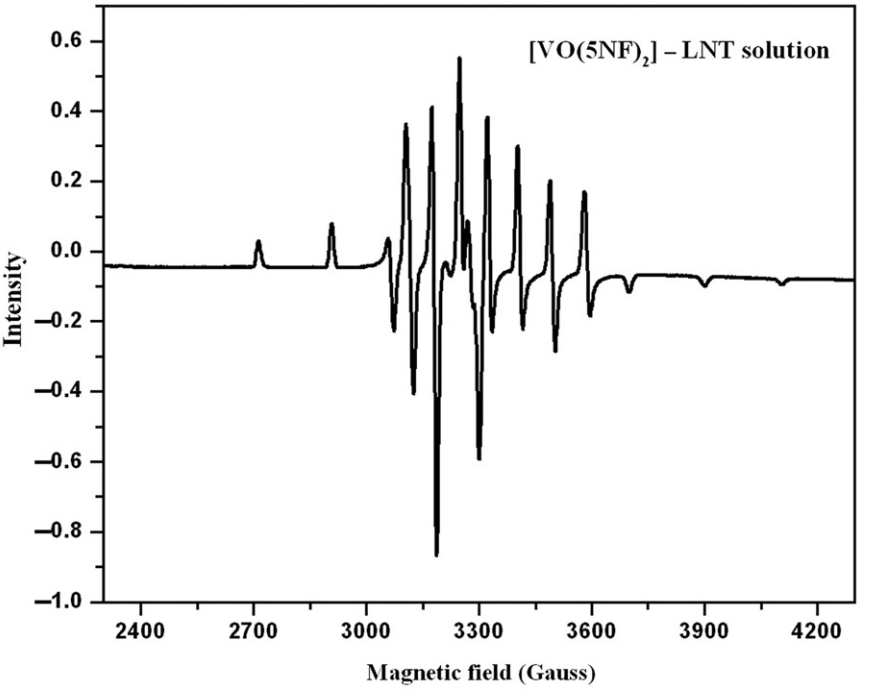


Figure 1. EPR spectra $[VO(5NF)_2]$ in methanol at LNT.

defined by Ballhausen and Gray [48] for a oxovanadium(IV) square pyramidal C_{4V} structure. The transitions are assigned as $d_{xy} - d_{xz}$, $d_{xy} - d_{yz}$, $d_{xy} - d_{(x^2-y^2)}$ and $d_{xy} - d_{z^2}$ in the order of decreasing wavelength [48–51].

3.3. *EPR spectra*

The X-band EPR spectra for all the complexes are recorded as solids at RT and solutions (methanol for $[VO(5NF)_2]$ and DMSO for $[VO(2AF)_2]SO_4$ and $[VO(5MFFA)_2]SO_4$) at 298 K and 77 K (LNT) using microwave frequency of about 9.5 GHz. A representative LNT (methanol) spectrum for $[VO(5NF)_2]$ (figure 1) and RT (solid and DMSO) and LNT (DMSO) spectra for $[VO(2AF)_2]SO_4$ (figures S1, S2, and S3 in Supplementary material) are given. The observed spectral parameters $g_{\|}$, $g_{\perp}$, $A_{\|}$, $A_{\perp}$, g_{iso}, and A_{iso} for the complexes are shown in table 5. EPR spectra for all three complexes in polycrystalline form at RT displayed a single resonance attributed to

Table 5. EPR spectral assignments of oxovanadium(IV) in polycrystalline state at 298 K and DMSO solution at 77 K.

Complex	Polycrystalline state (298 K)	DMSO					
	g	$g_{\parallel}$	$g_{\perp}$	g_{iso}	$A_{\parallel}$[a]	$A_{\perp}$[a]	A_{iso}
$[VO(5NF)_2]$	1.900	1.900	1.999	1.966	183	69	108
$[VO(5MFFA)_2]SO_4$	1.972	1.901	1.995	1.964	177	68	104
$[VO(2AF)_2]SO_4$	2.015	1.936	2.021	1.992	172	68	103

[a]Expressed in units of cm^{-1} multiplied by a factor of 10^{-4}.

ferromagnetic exchange coupled d^1–d^1 system observed for dimeric vanadium(IV) compounds [52, 53].

The RT isotropic EPR spectra, in dissolved state, for all three complexes show eight resonances characteristic of the vanadyl state, the $S = 1/2$ spin system interacting with $I = 7/2$ nuclear spin. The spectral parameters are consistent with single paramagnetic vanadyl species. This indicates that the exchange interactions in the solid state at RT are disrupted upon dilution with solvents. In the frozen solution anisotropic spectra of all the complexes in DMSO, two sets of eight lines are obtained as expected [54]. The g values are comparable with the values reported for oxovanadium(IV) complexes [55, 56]. Sakurai *et al*. [57] has reported that the coordination structure of the complexes can be assigned based on the EPR $g_{\parallel}$ and $A_{\parallel}$ values. The magnitude of EPR parameters $g_{\parallel}$ and $A_{\parallel}$ are consistent with four oxygens as equatorial ligands and the order $g_{\parallel} < g_{\perp}$ and $A_{\parallel} > A_{\perp}$ is characteristic of oxovanadium site of C_{4V} symmetry [58, 59]. Thus, the spectral details obtained are typical of $[VO(O_4)]$ complexes and the moderate changes in the magnitude of $g_{\parallel}$ and $A_{\parallel}$ indicate a very slight distortion from C_{4V} symmetry of the vanadyl center. Thus, the proposed geometry of the synthesized complexes is distorted square pyramidal geometry.

3.4. *Biological study*

3.4.1. Blood glucose level. The three vanadium complexes show considerable glucose lowering effect in 4 weeks (figure 2) when compared to that of the group treated with the standard drug glibenclamide and the group treated by the reported complex BFOV. This is also proved by observations that the normal control group, treated only with the vehicle, and the diabetic group – untreated (negative control) showed no decrease in the glucose level. The complexes under study exhibit greater efficacy with respect to blood glucose level even at a lower dosage level as compared to the reported data [39]; there were no noticeable side effects in the animal groups.

3.4.2. Total cholesterol level. The total cholesterol level in all the four animal groups treated with four drugs is given in figure 3. The standard drug was also studied for comparison. The animal group treated with the standard drug shows a steady decrease in total cholesterol levels. The drug-treated animal groups with $[VO(5NF)_2]$ and $[VO(5MFFA)_2]SO_4$ show a gradual increase and a subsequent decrease in the

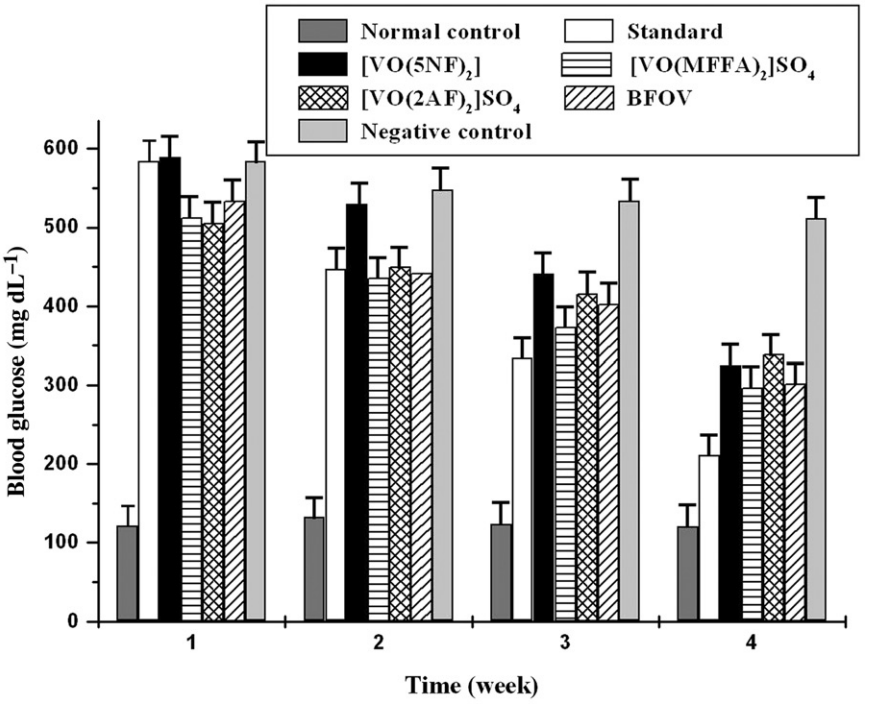


Figure 2. Blood glucose levels for $[VO(5NF)_2]$, $[VO(2AF)_2]SO_4$, $[VO(5MFFA)_2]SO_4$, and [BFOV] with respect to normal control, standard glibenclamide (diabetic control – treated) and negative control (diabetic control – untreated). Normal value: 80–120 mg dL^{-1}.

cholesterol level, whereas in $[VO(2AF)_2]SO_4$- and [BFOV]-treated groups, a steady increase in the total cholesterol level was observed. Though there are variations in the total cholesterol levels in the drug-treated groups, the level has not raised to the level observed in negative control group. The study can be extended further to probe the actual effects of the drug. There is a possibility that these compounds may metabolize by a different mechanism than that of the standard drug.

3.4.3. Protein level. The protein level shows a marked increase in 4 weeks (figure 4), whereas in the negative control protein level decreases. All four vanadium complexes show increasing protein level as that of the standard. Though the studies on the protein level before and after treatment are debatable, a detailed report by Charlton and Nair [60] indicates that there has been net protein loss during insulin deprivation. In this study, the drug-treated animal groups show an increasing trend in 4 weeks as for the standard, thus regulating the conditions of diabetes and showing the trend toward alleviating the disease condition.

3.4.4. Oral glucose tolerance test. Glucose tolerance test was conducted to investigate the effect of the vanadyl complexes on glucose tolerance. It is evident from figure 5 that at 1 h after glucose loading, the blood glucose level raised to the maximum level and subsequently decreased to fasting glucose level which was observed in all four test groups.

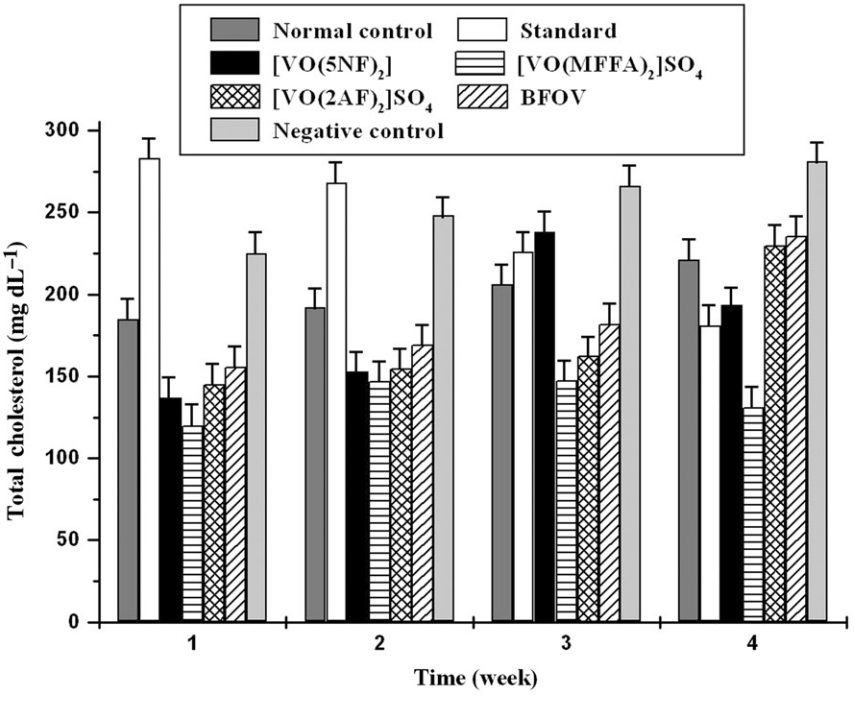


Figure 3. Total cholesterol levels for $[VO(5NF)_2]$, $[VO(2AF)_2]SO_4$, $[VO(5MFFA)_2]SO_4$, and [BFOV] with respect to normal control, standard glibenclamide (diabetic control – treated) (diabetic control – untreated). Normal value: 180–220 mg dL^{-1}.

This change in the blood glucose level is the same as shown by the standard drug glibenclamide, which indicates that the synthesized drugs behave almost like the standard antidiabetic drug. Thus, these vanadium complexes show an improved glucose tolerance in STZ-diabetic rats, showing that the impaired glucose tolerance was increased due to the treatment of drugs, in the same way as shown by BFOV reported by Xie *et al*. [38].

As part of the study, the food and water intake for 4 weeks in STZ-induced diabetic rats treated with the synthesized complexes are monitored (table 6). The food and water consumption are normal and comparable to that of the reported compound BFOV within experimental error. Although there are variations in the food consumption, there is a steady increase in body weight of the animals (table 7), proving that these drugs do not possess negative effects and indicating no toxicity of the complexes on the animals.

Thus, the above results of animal study with the complete profile of glucose, total cholesterol, and protein reveal that these furan-based complexes are potential antidiabetic drugs comparable to that of the standard drug. The trend shown by the negative control group proves the ability of the complexes as antidiabetic agents.

4. Conclusion

Three new complexes, $[VO(5NF)_2]$, $[VO(2AF)_2]SO_4$, and $[VO(5MFFA)_2]SO_4$, have been synthesized and characterized. The local structure and site symmetry of the

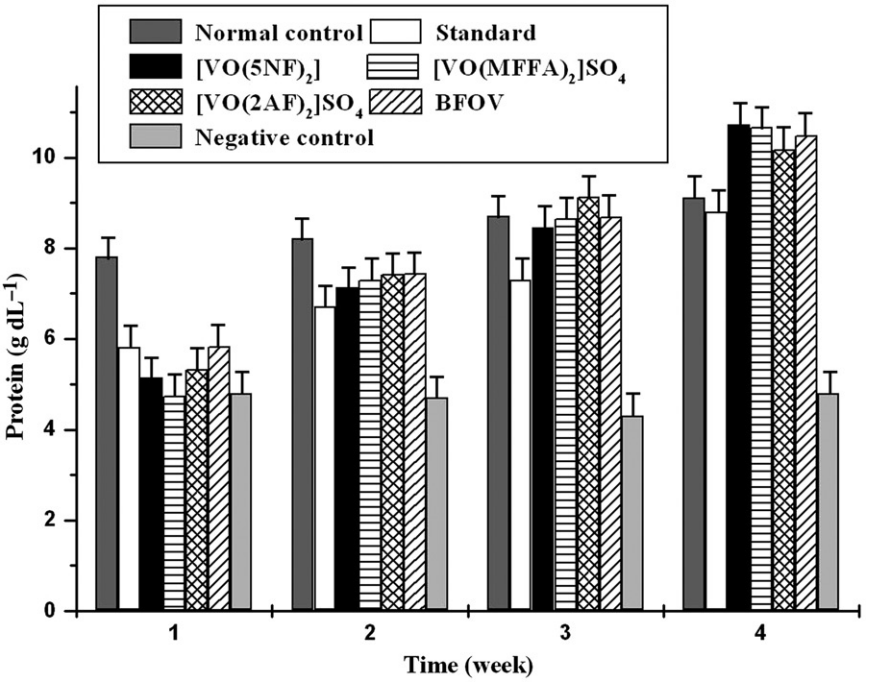


Figure 4. Protein levels for $[VO(5NF)_2]$, $[VO(2AF)_2]SO_4$, $[VO(5MFFA)_2]SO_4$, and [BFOV] with respect to normal control, standard glibenclamide (diabetic control – treated) and negative control (diabetic control – untreated). Normal value: 6–8 g dL^{-1}.

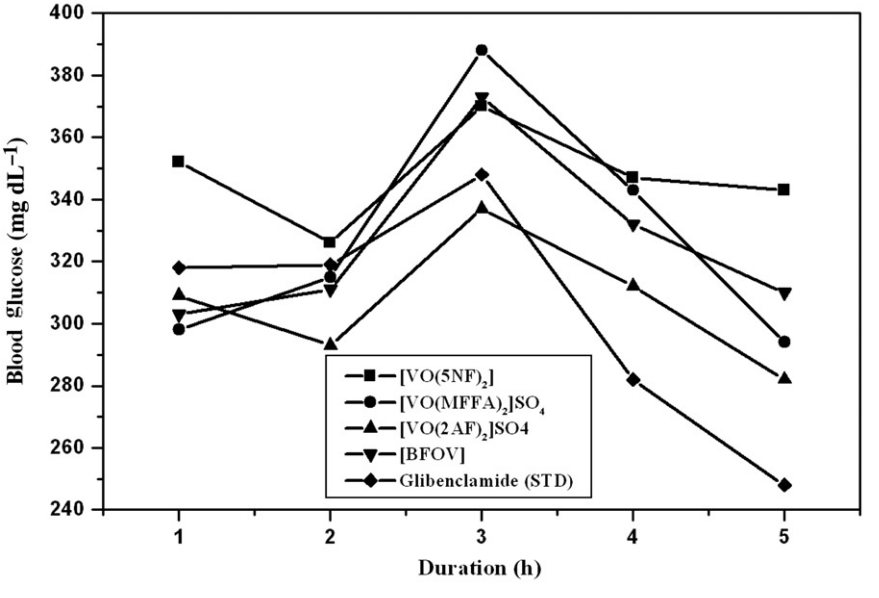


Figure 5. Effect of vanadium complexes on glucose tolerance in STZ-induced diabetic rats (1 = Fasting; 2 = 0 h; 3 = 1 h; 4 = 2 h; 5 = 3 h) – OGTT.

Table 6. Food (F) (g) and water (W) (mL) intake (uncertainties ± 4).

	Week 1		Week 2		Week 3		Week 4	
Test groups	F	W	F	W	F	W	F	W
$[VO(5NF)_2]$	30	140	20	180	49	133	35	120
$[VO(5MFFA)_2]SO_4$	30	120	25	160	30	232	20	310
$[VO(2AF)_2]SO_4$	40	158	36	175	48	220	58	295
[BFOV]	25	185	38	195	46	235	57	308

Table 7. Body weight (uncertainties = ±5).

Test groups	Week 1	Week 2	Week 3	Week 4
$[VO(5NF)_2]$	124	132	140	167
$[VO(5MFFA)_2]SO_4$	155	160	159	170
$[VO(2AF)_2]SO_4$	158	182	194	206
[BFOV]	148	178	195	227

complexes are assigned based on EPR parameters $g_{\|}$ and $A_{\|}$ and further supported by characteristic FT-IR stretching frequencies (stretching frequency of oxovanadium bond obtained above 970 cm^{-1} indicating the presence of five-coordinate geometry). Thus, the structure may be assigned to be distorted square pyramidal. A biological study proves that all the complexes possess blood glucose lowering ability when compared to BFOV and the standard drug glibenclamide and also improve the glucose tolerance after glucose loading. Thus, the study shows that the synthesized furan complexes have possibility to be developed as potential antidiabetic drugs.

Acknowledgments

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