A SYNOPSIS

of the thesis

Syntheses, Molecular Structures, Spectroscopic Characterization and Bio-mimetic Activity of Vanadium Complexes

To be Submitted
As a partial fulfillment for the award of the degree of

DOCTOR OF PHILOSOPHY

in
Chemistry

By
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Under the supervision of
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Synopsis

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To be submitted to The Maharaja Sayajirao University of Baroda for the award of the degree of DOCTOR OF PHILOSOPHY in Chemistry.

Name of Student: Neetu Patel

Title of the Thesis: "Syntheses, Molecular Structures, Spectroscopic Characterization and Bio-mimetic Activity of Vanadium Complexes"

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Date of Registration: 28th August. 2018

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The Thesis will be presented in form of the following chapters:

Chapter 1

Introduction

Chapter 2

Metal-organic hybrids based on a [VO_2(L)]-tecton with cations of imidazole derivatives: Synthesis, characterization and in vitro antidiabetic activity

Chapter 3

New oxidovandium(IV/V) complexes with tridentate Schiff base ligands: Synthesis, molecular structure and in vitro antidiabetic activity

Chapter 4

Anionic dioxidovanadium(V) complexes [VO_2(L)]$^-$ with (Z)-N'-(2-hydroxy-3-methoxybenzylidene) isonicotinohydrazide as proligand and cation of imidazole units as ancillary ligands: Synthesis, characterization and in-vitro antidiabetic activity

Chapter 5

Syntheses, spectral characterization and antidiabetic activities of vanadium (IV/V) complexes with bi-and tridentate ligands (In situ rection)

Chapter 1

Introduction

Chemistry of Vanadium

The chemistry of vanadium is noteworthy for the accessibility of the four adjacent oxidation states [2–5]. In an aqueous solution, vanadium forms metal aqua complexes of which the colours are lilac $[V(H_2O)_6]^{2+}$, green $[V(H_2O)_6]^{3+}$, blue $[VO(H_2O)_5]^{2+}$, yellow-orange oxides, the formula for which depends on pH.Vanadium(II) compounds are reducing agents, and vanadium(V) compounds are oxidizing agents. Vanadium(IV) compounds often exist as vanadyl derivatives, which contain the VO^{2+} center [6,7].

Complexes of vanadium(II) and (III) are relatively exchange inert and reducing. Those of V(IV) and V(V) are oxidants. Vanadium ion is rather large and some complexes achieve coordination numbers greater than 6, as is the case in $[V(CN)_7]^{4-}$. Oxovanadium(V) also forms 7 coordinate coordination complexes with tetradentate ligands and peroxides and these complexes are used for oxidative brominations and thioether oxidations. The coordination chemistry of V^{4+} is dominated by the vanadyl center, VO^{2+}, which binds four other ligands strongly and one weakly (the one trans to the vanadyl center). An example is vanadyl acetylacetonate ($V(O)(O_2C_5H_7)_2$). In this complex, the vanadium is 5-coordinate, square pyramidal, meaning that a sixth ligand, such as pyridine, may be attached, though the association constant of this process is small. Many 5-coordinate vanadyl complexes have a trigonal bipyramidal geometry, such as $VOCl_2(NMe_3)_2$. The coordination chemistry of V^{5+} is dominated by the relatively stable dioxovanadium coordination complexes which are often formed by aerial oxidation of thevanadium(IV) precursors indicating the stability of the +5 oxidation state and ease of interconversion between the +4 and +5 states.Schiff base complexes have been used as a versatile ligand in coordination chemistry. Schiff base hydrazone are versatile tridentate ligands and several types of V^{IV}-O, V^{V}-O and V^{V}-O_2 complexes have been synthesized. Some of these complexes have been found as structural and functional mimics of antidiabetics [7-9]. However, very few studies have been explored the insulin mimicking effects of vanadium(IV/V) complexes.The interaction of vanadium species with Schiff base ligands bearing therapeutic applications is of the growing focus of attention and has driven a considerable amount of research. They represent an attractive field of research due to their structural features, special activities in pharmacology, biological systems and the wide range of applications [10,11].

The biological role of Vanadium

Vanadium is more important in marine environments than terrestrial.Several species of marine algae produce vanadium bromoperoxidase as well as the closely related chloroperoxidase (which may use a heme or vanadium cofactor) and iodoperoxidases. The bromoperoxidase produces an estimated 1–2 million tons of bromoform and 56,000 tons of bromomethane annually. Most naturally occurring organobromine compounds are produced by this enzyme, catalyzing the following reaction (R-H is hydrocarbon substrate):

$$R\text{-}H + Br^- + H_2O_2 \rightarrow R\text{-}Br + H_2O + OH^-$$

A vanadium nitrogenase is used by some nitrogen-fixing micro-organisms, such as *Azotobacter*. In this role, vanadium replaces more-common molybdenum or iron and gives the nitrogenase slightly different properties [12].

Vanadium is essential to ascidians and tunicates, where it is stored in the highly acidified vacuoles of certain blood cell types, designated "vanadocytes". Vanabins (vanadium binding proteins) have been identified in the cytoplasm of such cells. The concentration of vanadium in the blood of ascidians is as much as ten million times higher[*specify*] than the surrounding seawater, which normally contains 1 to 2 µg/l. The function of this vanadium concentration system and these vanadium-bearing proteins is still unknown, but the vanadocytes are later deposited just under the outer surface of the tunic where they may deter predation.

Vanadyl sulfate as a dietary supplement has been researched as a means of increasing insulin sensitivity or otherwise improving glycemic control in people who are diabetic. Some of the trials had significant treatment effects but were deemed as being of poor study quality. The amounts of vanadium used in these trials (30 to 150 mg) far exceeded the safe upper limit. The conclusion of the systemic review was "There is no rigorous evidence that oral vanadium supplementation improves glycaemic control in type 2 diabetes. The routine use of vanadium for this purpose cannot be recommended."

In the last 20 years, the anti-diabetic activity of vanadium complexes has been widely investigated. Due to its insulin-like effect, vanadium complexes have been extensively studied for their potential use in the treatment of type II diabetes mellitus.Diabetes mellitus affects about 5% of the global population and its management without any side effects is still a challenge to the medical system. Vanadium can improve sensitivity to insulin in both types of diabetes. It has been shown in studies to have some ability to lower cholesterol levels and blood pressure.Among these compounds, bis(maltolato)oxidovanadium(IV) (BMOV) has become the standard complex for the new vanadium-based molecules with antidiabetic action, while its derivative bis(ethylmaltolato)oxidovanadium-(IV) (BEOV) has entered phase IIa clinical trials, showing that complexes are more potent in decreasing the glucose concentration in blood serum than its corresponding $VOSO_4$ salt[13].

The chapter 1 also include the detailed and up to date literature survey in the subject of the thesis.

Aim and Objectives

- ✓ Synthesis of novel Schiff base ligands.

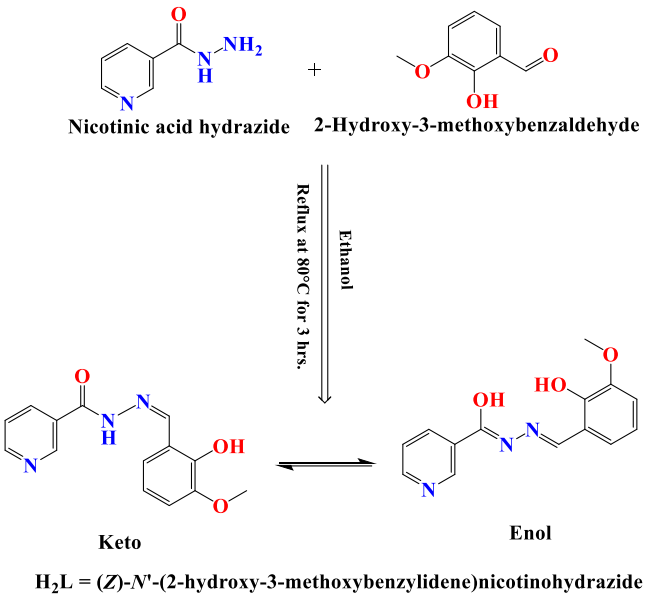
- ✓ Synthesis of vanadium complexes of Schiff base derivatives.
- ✓ To characterize synthesized compounds by various techniques such as IR, NMR, Mass, CV, etc.
- ✓ To study the *in vitro* antidiabetic activity of synthesized compounds.

Chapter 2

Metal-organic hybrids based on a [VO_2(L)]-tecton with cations of imidazole derivatives: Synthesis, characterization and in vitro antidiabetic activity

Synthesis of Schiff base (H_2L)

Nicotinic acid hydrazide (1.371 gm, 10 mmol) and o-Vanillin (1.521 gm, 10 mmol) were added to a ethanol (100 ml) and refluxed for 3 h (Scheme 1). After refluxing for 3 h the orange solution was cooled to room temperature and resulting precipitate was filtered and washed with cold ethanol and stored in a $CaCl_2$ desiccator.



H_2L = (*Z*)-*N*'-(2-hydroxy-3-methoxybenzylidene)nicotinohydrazide

Synthesis of Schiff base (H_2L).

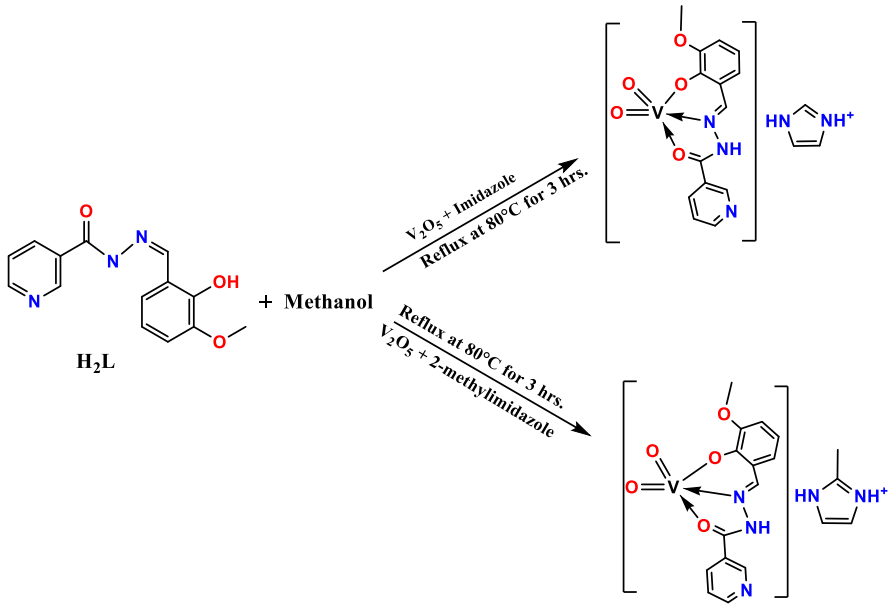
Synthesis of Complexes

Synthesis of [$V(O)_2$(L)]ImH 1

10 ml methanolic solution of vanadium pentaoxide (0.188 gm, 1 mmol) was added dropwise to a 10 ml methanolic solution of HL (0.271 gm, 1 mmol) at ambient temperature. To this reaction mixture (0.068 gm, 1 mmol) ImH was added(Scheme 2). The reaction mixture was refluxed for 30 min, cooled to room temperature. The reaction mixture was allowed to evaporate slowly in air. After one-week brown crystals of **1** separated out, which were collected on upon filtration and dried in $CaCl_2$ desiccator.

Synthesis of [$V(O)_2$(L)]m-ImH 2

This complex was synthesized by a similar method to that described above except ImH was replaced by m-ImH (0.082 gm, 1 mmol)(Scheme 2). The yellow crystals was collected and dried in $CaCl_2$ desiccator.



Synthetic route of complex $[V(O)_2(L)]$ImH 1and $[V(O)_2(L)]$m-ImH 2.

***Synthesis of $[VO_2(L)]$M-ImH* 3**

To a suspension of H_2L (0.271 g, 1 mmol) in a methanol solution (20 ml) vanadium pentaoxide (0.188 g, 1 mmol) in methanol (10 ml) was added while stirring. To this reaction mixture 1-methylimidazole (0.082 g, 1 mmol) was added and cooled to room temperature and filtered. Filtrate was left to evaporation slowly in air. After one weak yellow polycrystalline powder of **1** separated out, which was collected upon filtration, washed with methanol and dried in $CaCl_2$ desiccator.

***Synthesis of $[VO_2(L)]$2-EthImH* 4**

To a suspension of H_2L (0.271 g, 1 mmol) in methanol, obtained after stirring, was added 10 ml methanolic solution of vanadium pentaoxide (0.188 g, 1 mmol). To this reaction mixture 2-ethylimidazole (0.082 g, 1 mmol) was added while stirring. The resulting solution was refluxed for 45 min, cooled to room temperature and filtered. The filtrate was allowed to evaporate in the open air. After 3-4 days, the light yellow microcrystalline powder was isolated, washed with cold methanol and kept in $CaCl_2$ desiccator.

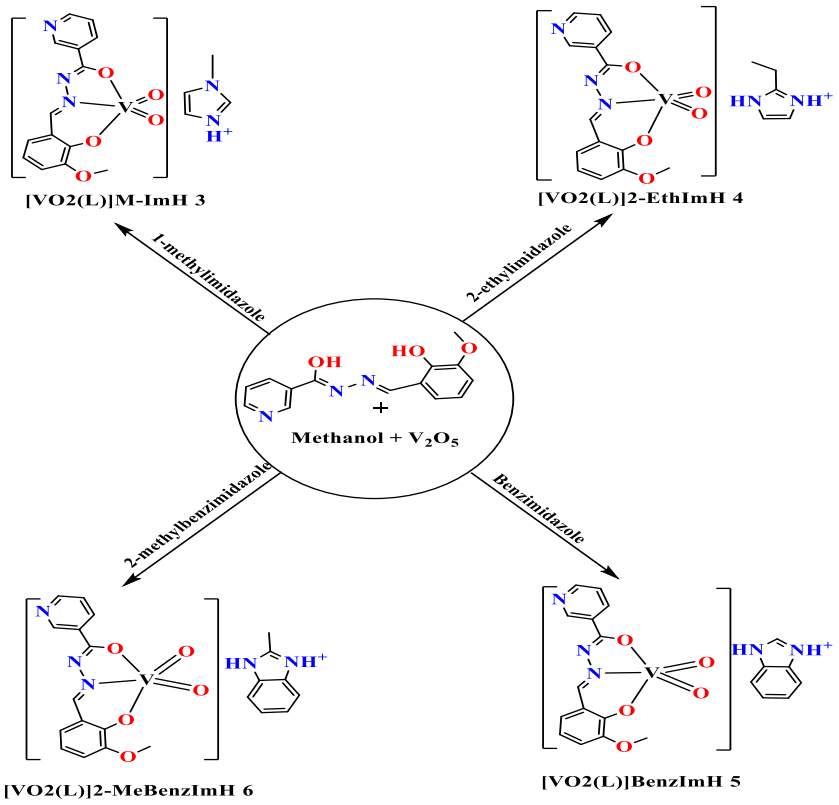
***Synthesis of $[VO_2(L)]$BenzImH* 5**

To H_2L (0.271 g, 1 mmol) dissolved in 20 ml methanol to get suspension after stirring. In suspension of H_2L 10 ml methanolic solution of vanadium pentaoxide (0.188 g, 1 mmol) was added and stirred for 30 min. To this stirred solution 10 ml of benzimidazole (0.118 g, 1 mmol) was added and the resulting solution was refluxed for 30 min. and cooled

to room temperature and filtered. Finally solution was filtered and filtrate was left overnight to slow evaporate. The yellow colored microcrystalline powder which obtained which was washed with cold methanol and stored in a $CaCl_2$ desiccator.

Synthesis of [VO_2(L)]2-MeBenzImH 6

To a 20 ml methanolic solution of H_2L (0.271 g, 1 mmol) was stirred for 10 min. to get suspension of H_2L. To this suspension 10 ml methanolic solution of vanadium pentaoxide (0.188 g, 1 mmol) was added dropwise while stirring. To the yellow solution 10 ml 2-methylbenzimidazole (0.132 g. 1 mmol) was added and stirring continued further for 1.5 hrs. The stirred solution was cooled to room temperature, filtered and the filtrate was left for slow evaporation at room temperature for a weak and polycrystalline yellow compound was obtained washed with methanol and stored under room temperature in $CaCl_2$ desiccator.



Synthetic route of complexes 3-6.

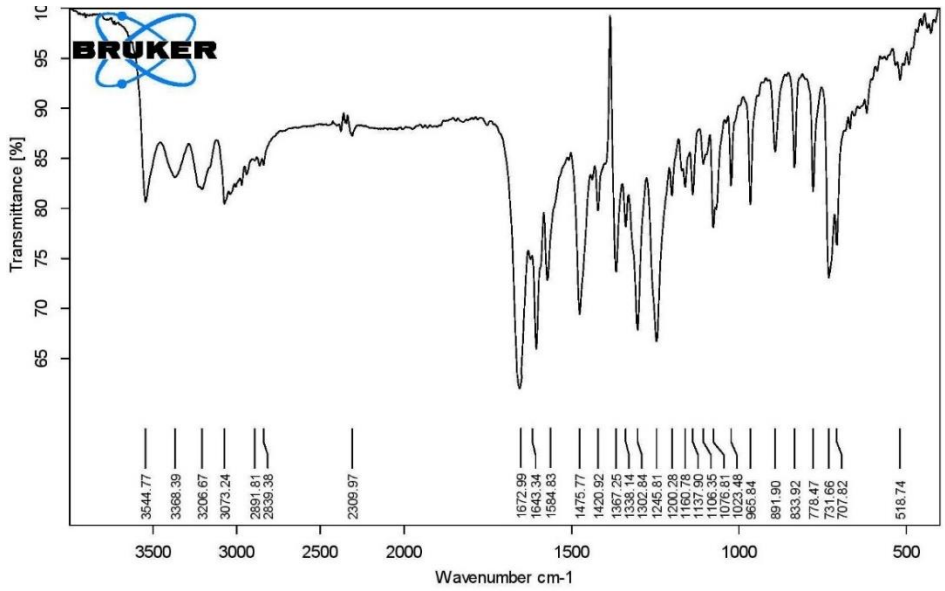
FTIR Spectra studies

The IR spectra of complexes were recorded in the 400-4000 cm^{-1} range in the KBr pellet. A comparison of the IR spectral data with these of the complexes reveals that the H_2L ligand is coordinated to the vanadium ions in the enol form in complexes.

IR spectral data for complexes 1-6 (v in cm^{-1})

Compound	v(N-H)	v(>C=N)	v(C-O)	v(V=O)	v(V-O)	v(V-N)

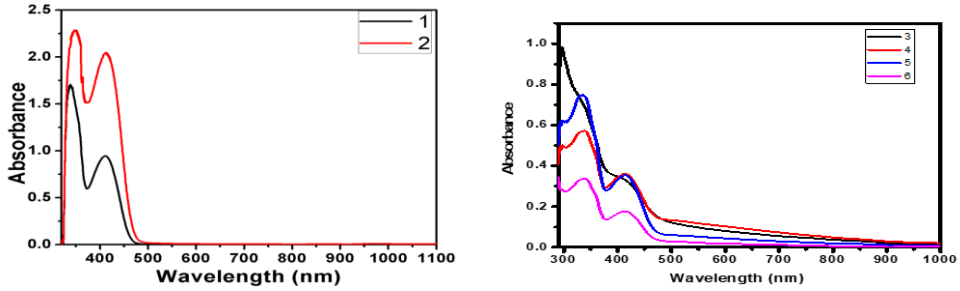
H_2L	3368	1672	-	-	-	-
1		1656	1223	951	465	424
2		1635	1248	967	465	424
3		1623	1254	965	474	436
4		1632	1250	942	459	410
5		1633	1281	950	459	425
6		1633	1280	947	470	442



FTIR spectra of ligand H_2L

UV-visible Spectra

Electronic spectra of all complexes were recorded using DMSO solutions [3.0×10^{-3}M] at RT.



Electronic spectra of all complexes were recorded using DMSO solutions [3.0×10^{-3}M] at RT.

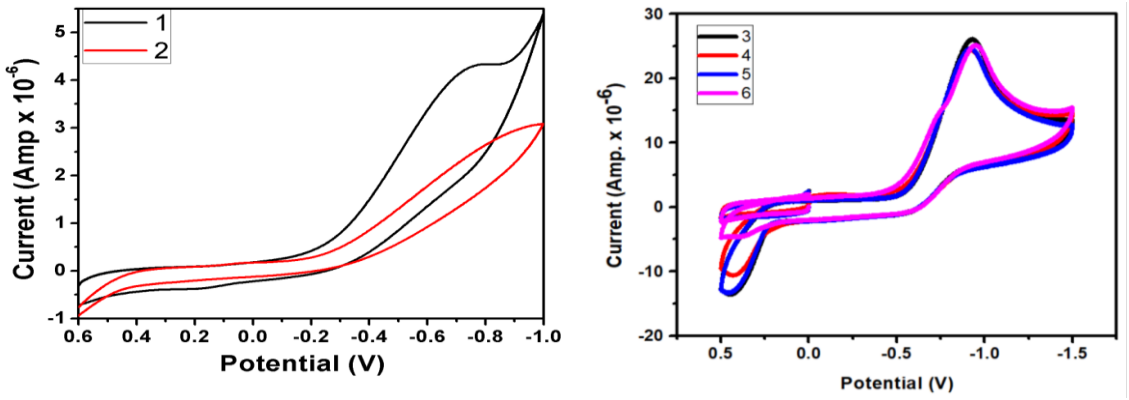
UV-visible spectral data of complexes 1-6

Complex	**λ_{max} (nm)**	
	ILCT	**LMCT**

1	**338**	**420**
2	**342**	**417**
3	**337**	**417**
4	**335**	**413**
5	**337**	**415**
6	**339**	**417**

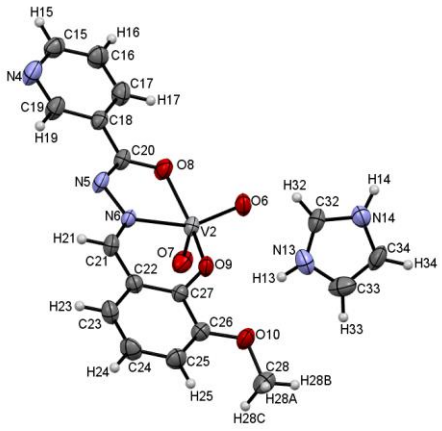
Electrochemical studies

The electrochemical studies of all complexes were performed using cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in 3.0 x 10^{-3} M DMSO solution. The electrochemical studies of both complexes **1** and **2** were performed using cyclic voltammetry (CV) and differential pulse voltammetry.CV experiments of complex **1** exhibited V^{V}/V^{IV} reductive responses with potential fairly on the negative side (-0.754 V) and Its anodic counterpart are not visible.Whereas complex **2** showed only one reduction at -0.625 V.We believe that the presence of electron-donating methyl group in substituted imidazole in this complex increased the electron density at the vanadium centre and therefore better stabilize the V^{V} state.DPV exhibited similar observations.



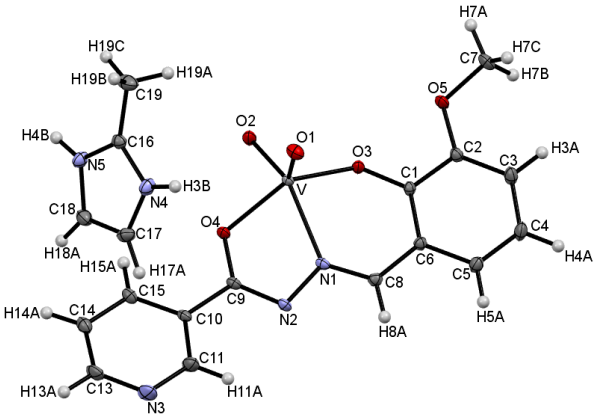
The electrochemical studies of all complexes were performed using cyclic voltammetry (CV) in 3.0 x 10^{-3} M DMSO solution.

Crystal structure of Complex 1



Complex **1** crystallizes in the *P-1* triclinic space group.In the structure of this complex, the vanadium metal is pentacoordinate by two oxido groups and monoanionic tridentate ONO Schiff base ligand. The coordination sphere of vanadium is distorted pyramidal, as ascertained by the structural parameter $\tau_5 = 0.024$ (0 for an ideal square pyramid and 1 for an ideal trigonal bipyramid). One imidazole molecule as lattice remains out the V^V coordination sphere. In the lattice of the complex, strong bifurcated intermolecular H-bonding interactions (N···O distances: 2.226-2.246 Å) between the Schiff base oxygen atoms (O5, O6, O9 and O10) and the -NH- groups of imidazole.

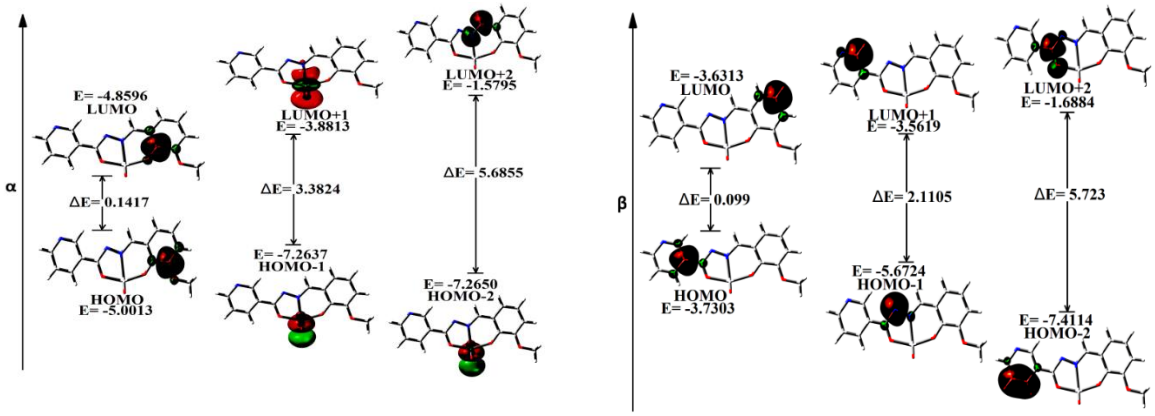
Crystal structure of Complex 2



The crystal structure of this complex consists of a vanadium atom pentacoordinate by monoanionic tridentate Schiff base (L^-) and two dioxide group. In the crystal structure of this complex 2-methylimidazole remains as a lattice molecule.Again, in this complex coordination geometry is a distorted square pyramidal, as ascertained by the structural parameter $\tau_5 = 0.04$.In this complex, each 2-methyimidazole moiety forms H-bonds of various types.N-H hydrogen atoms of 2-methyimidazole yield bifurcated robust intermolecular H-bonding with O of oxido L^-.

Computational studies

The electronic structure of complex **1** correlating the experimental bond distances and angles was investigated by the DFT calculations using B3LYP functional. The experimental single crystal X-ray analysis data bond distances and angles are in good agreement with calculated data. However, some bond distances and angles deviate significantly from those obtained from the single crystal X-ray data. The difference in data is an expected result because geometrical optimizations are performed in gaseous state in which intermolecular interactions are absent. The optimized molecular structure is more extended compared to experimental X-ray data calculated in solid state in which significant intermolecular interactions become prominent. Similarly DFT were performed for all complexes using Gaussian software.



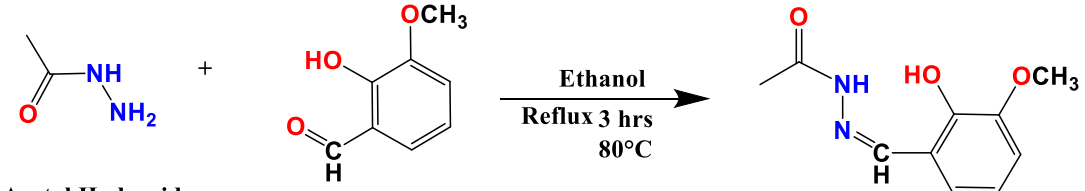
Conclusions

The diamagnetic dioxidovanadium(V) complexes $[VO_2(L)]$ImH**1,** $[VO_2(L)]$m-ImH**2,** $[VO_2(L)]$Him **3,** $[VO_2(L)]$H2Etim **4,** $[VO_2(L)]$HBenzim**5** and$[VO_2(L)]$H2Mebenzim **4** (ImH = Imidazole, m-ImH = 2-methylimidazole, Him = 1-methylimidazole, H2Etim = 2-ethylimidazole, Hbenzim = benzimidazole and H2Mebenzim = 2-methylbenzimidazole). and HL= ONO donor ligand) were synthesized in good yield and characterized by various spectroscopic techniques.In all complexes, the V(V) center is coordinated by ONO donar set of L^- ligand and two oxido groups in a distorted square pyramidal geometry. Isolated complexes are air-stable at ambient temperature. These complexes are mostly soluble in common organic solvents.They are electrically conducting in nature.These complexes are in +5 oxidation state so these are diamagnetic. These complexes were characterized by using various physicochemical techniques.The electrochemical behavior of complexes was studied by using **CV** and **DPV** techniques.

Chapter 3

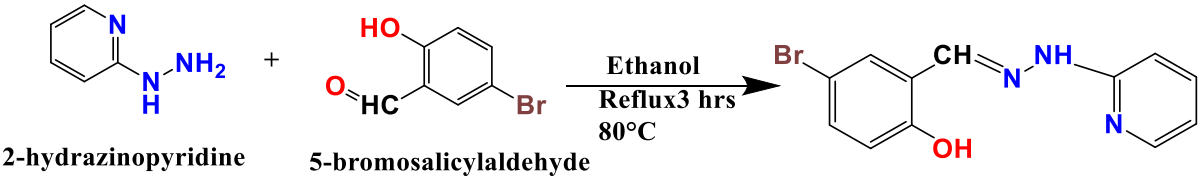
New oxidovandium(IV/V) complexes with tridentate Schiff base ligands: Synthesis, molecular structure and in vitro antidiabetic activity

Synthesis of ligand HL^1 = (Z)-N'-(2-hydroxy-3-methoxybenzylidene)acetohydrazide



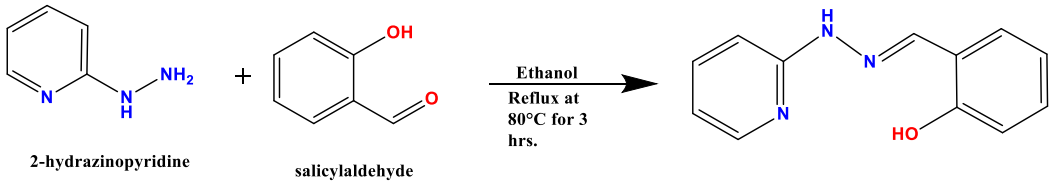
Acetyl Hydrazide **O-vanillin**

Synthesis of ligand HL^2 = (E)-4-bromo-2-((2-(pyridin-2-yl)hydrazono)methyl)phenol

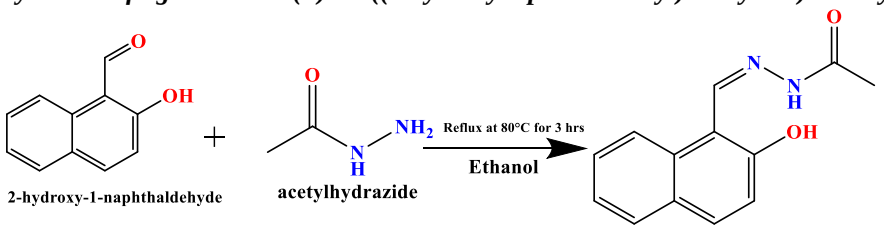


2-hydrazinopyridine **5-bromosalicylaldehyde**

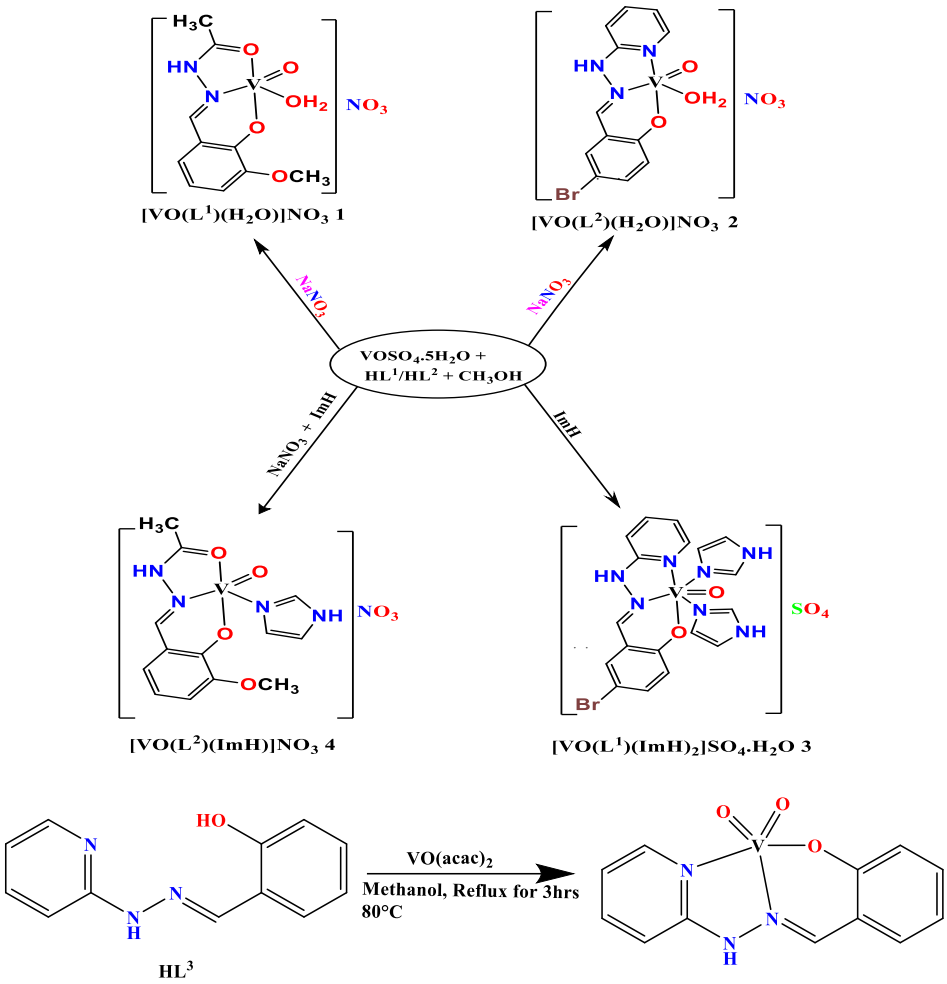
Synthesis of ligand HL^3 = (E)-2-((2-(pyridin-2-yl)hydrazono)methyl)phenol



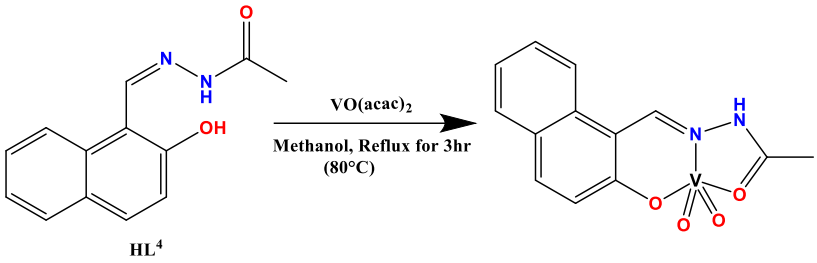
Synthesis of ligand HL^4 = (Z)-N'-((2-hydroxynaphthalen-1-yl)methylene)acetohydrazide



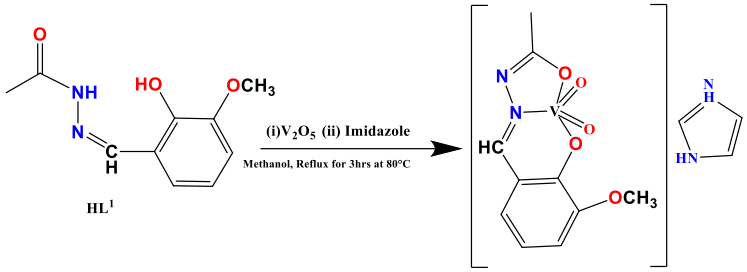
Synthesis of Complexes 1-4



Synthetic route of complex $[VO_2(L^3)]$ 5.

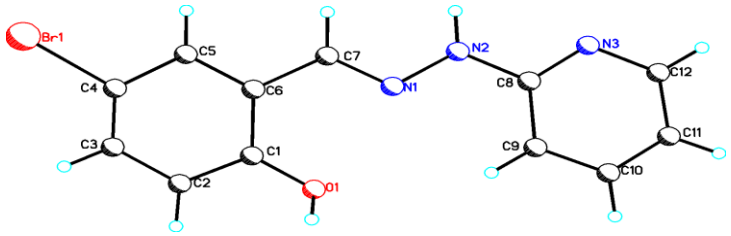


Synthetic route of the complex $[VO_2(L^4)]$ 6.



Synthetic route of the complex $[VO_2(L^1)]$ImH 7

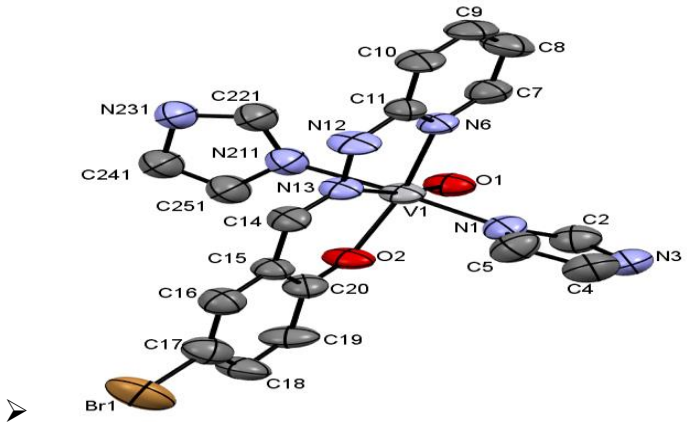
Crystal structure of Ligand HL^2



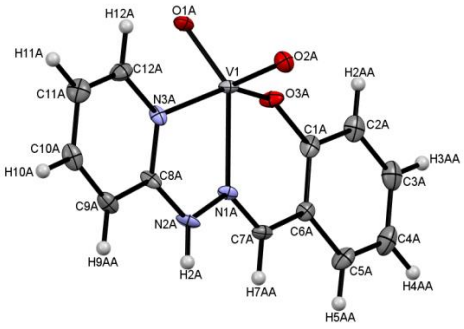
The HL^2 has three donors (NNO) sites, *viz* phenolic oxygen (O1), imine nitrogen (N2) and pyridine nitrogen (N3).The bromine and pyridine atoms in the Schiff base are involved in the intramolecular hydrogen bondings.

Molecular structure of complex 3

In the molecular structure, the vanadium ion has N_4O_2-donor environment, arranged in a distorted octahedral geometry.The equatorial plane consists of N1, N6, N211 and O2 atoms. While the oxido oxygen atom O1 and nitrogen atom of azomethine N13 of L^- occupies the axial positions. In the *trans* position to the terminal oxido group is N13 atom of the azomethine group with the bond length from vanadium atom of 2.231 A that is significantly longer than equatorial contacts V-O/N (1.921-2.132 A) as a consequence of *trans* effect.

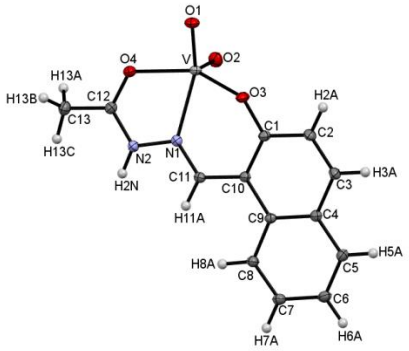


Crystal structure of Complex 5



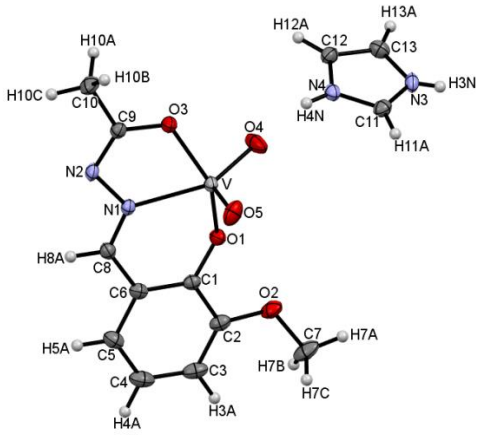
The monoanionic tridentate ligand (HL_3) spans the meridonal sites through pyridine and iminonitrogens and phenolate oxygen the basal plane and two dioxido groups at the apical position forming a five coordinated geometry.The distortion of a square pyramidal geometry ascertained by the structural parameter (τ_5) which is determined using (β-α)/60 where β is the larger and α is the smaller trans angles. The vanadium coordination sphere is a slightly distorted square pyramid, as τ_5 = 0.15 (0 for square pyramid and **1** for an ideal trigonal bipyramid).

Crystal structure of complex 6



In this complex, the vanadium coordination sphere is a distorted square pyramid as estimated by the structural parameter τ_5 = 0.03 which is very close to an ideal square pyramidal geometry. For this complex coordinating atoms of tridentate ligand are natphthalate O, imine N and ketonic O atoms at the basal plane and two dioxido oxygen atoms in the optical position forming a pentacoordinate geometry around the metal centre.

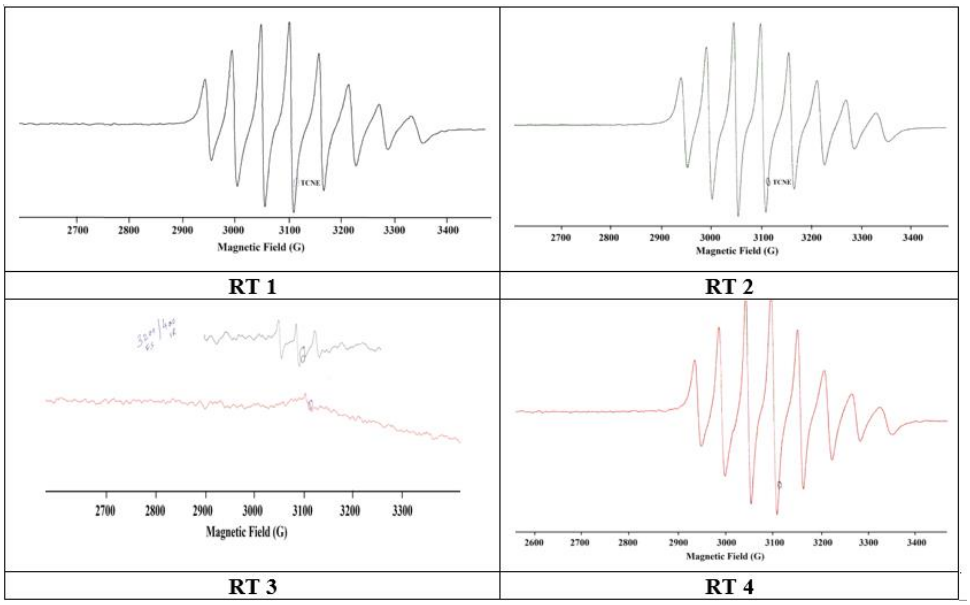
Crystal structure of complex 7



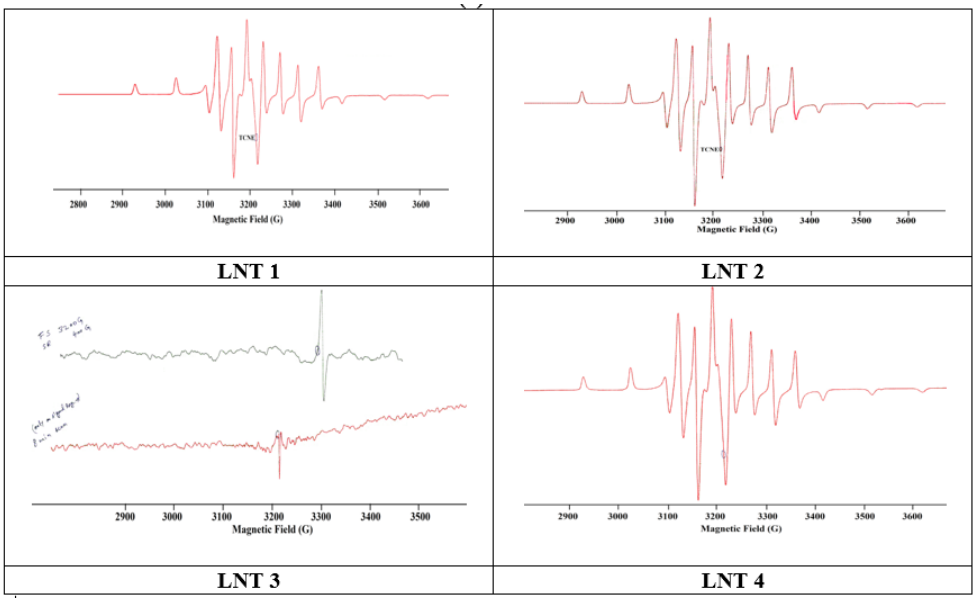
The vanadium (V) center in the complex has a distorted square-pyramidal coordination sphere. The two dioxide atoms are in a *cis* position and the Schiff base (L^1) coordinated to the VO_2^+ moiety through the imine nitrogen atom, one phenolate oxygen and one enolate oxygen atoms. The distorted geometry is characterized by structural parameter τ(0 for an ideal square pyramid and 1 for an ideal trigonal pyramid), which is for this complex is 0. 057.

Magnetic and EPR spectral study

The complexes **1**, **2** and **4** show magnetic moment of 1.79, 1.77 and 1.83 BM respectively in accord with a spin only value of a $d^1$the system, whereas vanadium(V) complex **3**, which is a $d^0$the system is diamagnetic.EPR spectral measurements at room temperature (RT) and liquid nitrogen temperature (LNT) by dissolving complexes in DMSO. RT of the oxidovanadium(IV) complexes viz., **1**, **2** and **4** reveal eight resonance lines attributable to a single S = 1/2 complex in which the unpaired electron in a d_{xy} orbital is coupled to the nuclear spin I = 7/2 of the vanadium nucleus.

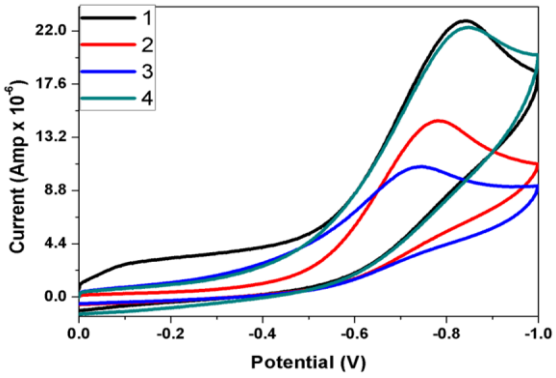


EPR spectra of complexes **1-4** at Room temperature.



EPR spectra of complexes **1-4** at Liquid nitrogen temperature.

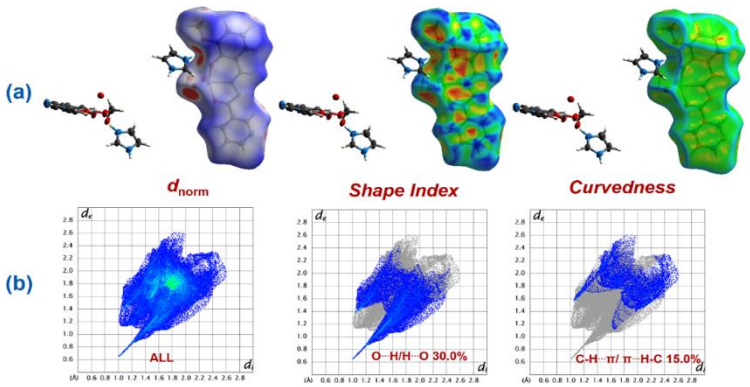
Cyclic Voltammetry



Complex	E_{pc}(V)	E_{pa}(V)	Reduction Process	Equatorial donor set
1	-0.83	Not defined	IV → III	NO_3
2	-0.77	Not defined	IV → III	N_2O_2
3	-0.73	Not defined	V → IV	N_3O
4	-0.84	Not defined	IV → III	N_2O_2

Cyclic voltammograms of vanadium(IV/V) complexes **1-4** in DMSO at an Ag/AgCl electrode with scan rate of 300 mVs^{-1} and temperature 20°C.The cyclic voltammetry studies in DMSO reveal one-electron reduction process in the range of -0.73 to -0.84 V.

Hirshfeld Surface Analysis

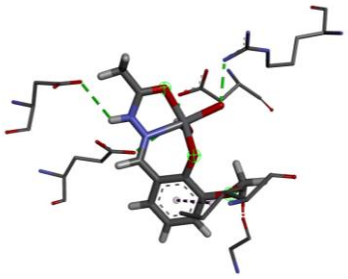


(a) Hirshfeld surfaces mapped with d_{norm}, shape index and curvedness for the complex; (b) Fingerprint plots for the complex showing percentages of contact contributed to the total Hirshfeld surface area in the complex.

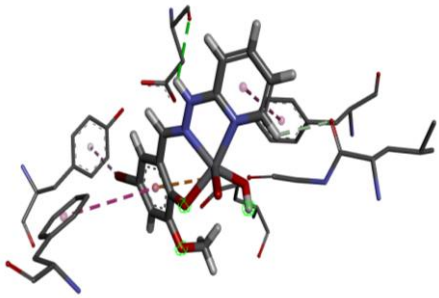
For gain idea about the molecular framework especially the aromatic and chelate rings the surfaces are plotted as transparent. The d_{norm} surface is mapped between -0.25 to 1.25 Å range, shape index plots are constructed between -0.8 to 0.8 Å while curvedness plots are mapped in the range -3.0 to 0.3 Å. In this complex, the O···H interactions as described in crystal structure description (*vide supra*) can be seen as the large circular deep red depressions and the weaker π···π interactions is shown as the faint red shaded area. The most important interaction in the complex is the O···H/H···O interaction which appear as discrete

spikes 1.0 Å < (d_e + d_i) < 2.4 Å in the total fingerprint plot of the complex. Similarly HAS was perfomed for all crystal structure of complexes.

Molecular Docking



1



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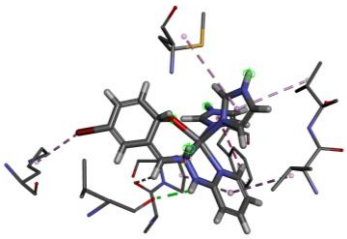

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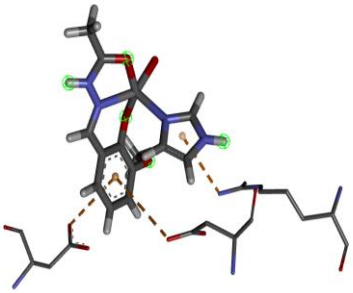
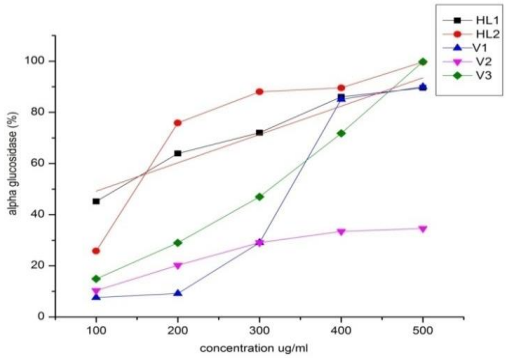
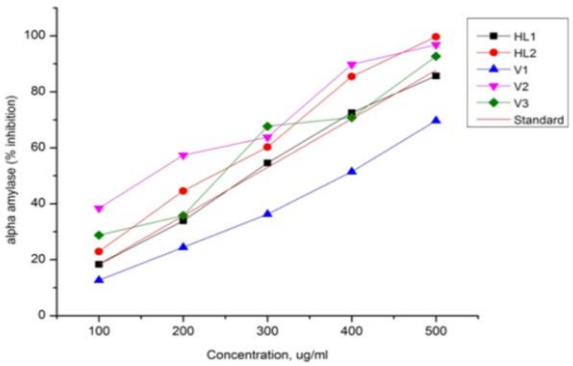


4

Antidiabetic activity



Alpha Glucosidase Inhibition graph of Compounds



Alpha amylase inhibition graph of compounds

The activity of HL^1, HL^2, complexes 1-4 were carried out, against alpha-glucosidase. We found the lowest IC50 value for V1(complex 1) while the highest IC_{50} was found in HL^2 and moderately in V2,V3,V4. The IC_{50} values for α-glucosidase inhibition activity were ranged from 4-500µg/ml.The V2 (complex 2) observed the most potent among all the complexes with an IC_{50} value of 4 µg/ml while HL^2 was the cheapest inhibitor with an IC_{50} value of 432

µg/ml. Therefore, it can be concluded that the complexes gave remarkable alpha-glucosidase inhibition and showed concentration-dependent activities.In the present study activity of HL^1, HL^2, complexes V1, V2, V3 (**1-3**) were carried out against alpha-amylase. Lowest IC_{50} value observed in V1(complex **1**) while highest IC50 were found in HL^2; V2 and V3 showing moderate inhibition against α Amylase at different concentration.It can be concluded that these complexes are potent alpha-amylase inhibitors. Therefore, all compounds gave remarkable alpha-amylase inhibition and showed concentration-dependent activities.

Conclusions

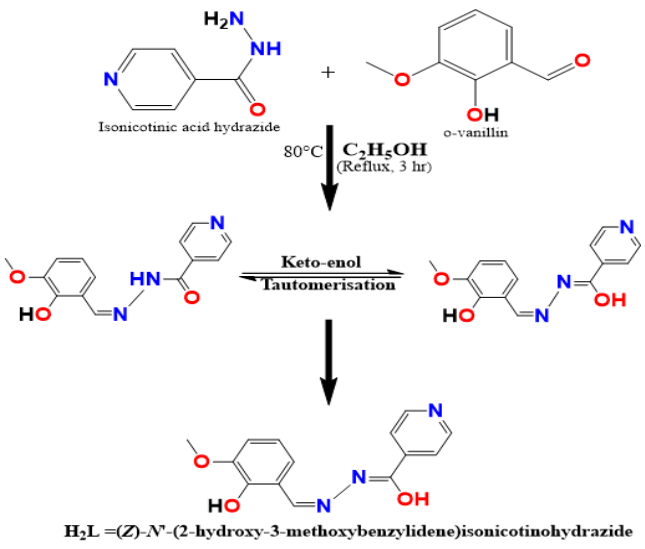
In this work, a series of vanadium (IV/V) complexes of tridentate Schiff base was synthesized and characterized by various physicochemical methods such as microanalysis, IR, UV-Vis, CV, and EPR techniques. The geometry of five coordinated complexes (**1**, **2**, **4**, **5**, **6** and **7**) can be described in terms of trigonal bipyramidal or square pyramidal. While complex **3** is distorted octahedral due to the presence of a sixth donor ligand. The room temperature magnetic measurements of complex **1**, **2** and **4** are in the range 1.79 to 1.83 B.M and all other complexes show zero B.M. value due to diamagnetic nature.In complex **3**, due to aerial oxidation converted in Vanadium(V) and becomes diamagnetic.The molecular structure of complex **3** shows that the central metal ion has an N_4O_2-donor environment and has octahedral geometry. In vitro, α-glucosidase inhibition activity and α–Amylase Inhibition activity results proved that these complexes are promising anti-diabetic agents.

Chapter 4

Anionic dioxidovanadium(V) complexes $[VO_2(L)]^-$ with (Z)-N'-(2-hydroxy-3-methoxybenzylidene)isonicotinohydrazide as proligand and cation of imidazole units as ancillary ligands: Synthesis, characterization and *in-vitro* antidiabetic activity

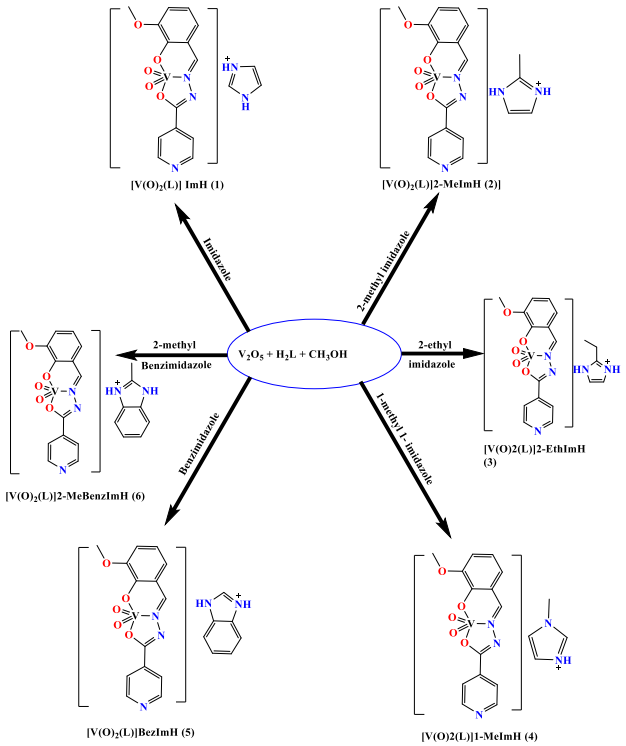
Synthesis of Schiff base

(H_2L = (Z)-N'-(2-hydroxy-3-methoxybenzylidene)isonicotinohydrazide)

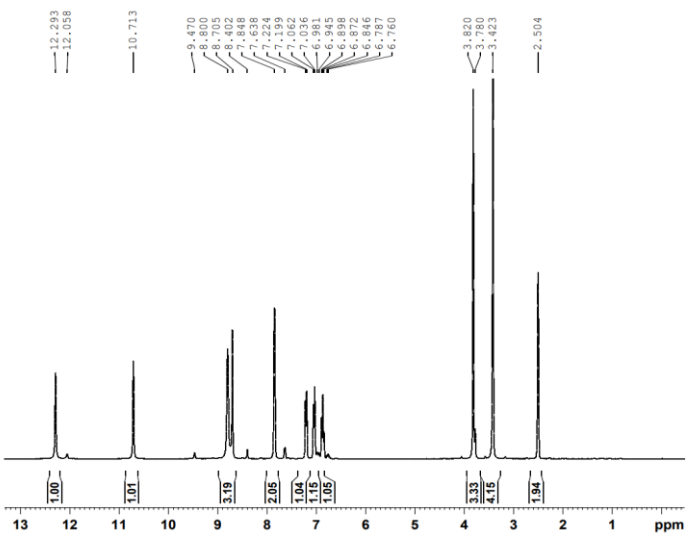


H_2L =(Z)-*N'*-(2-hydroxy-3-methoxybenzylidene)isonicotinohydrazide

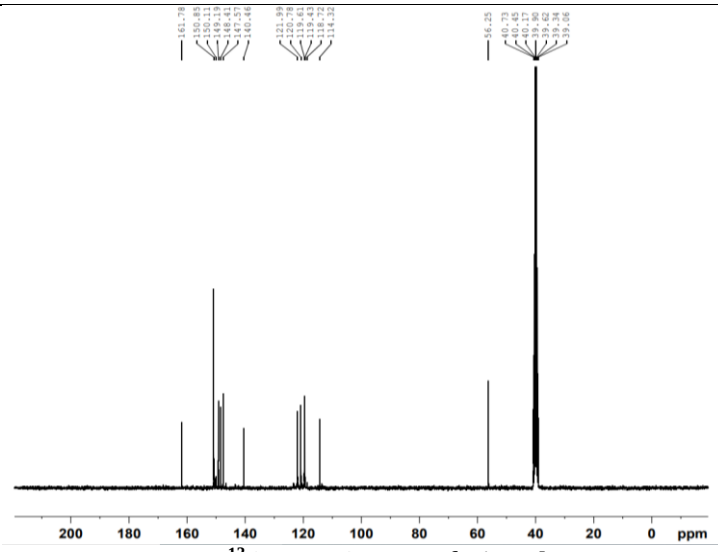
Synthesis of Complexes 1-6



Synthetic route of dioxidovanadium(V) 1-6 complexes.

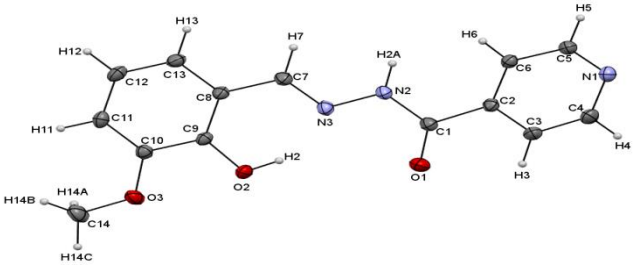


^{1}H NMR Spectra of Ligand H_2L



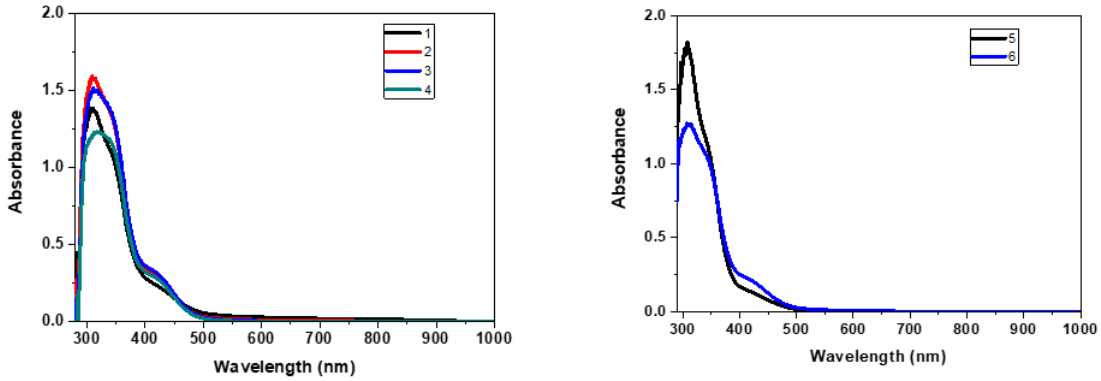
^{13}C NMR Spectra of Ligand H_2L

Crystal Structure of Ligand H_2L



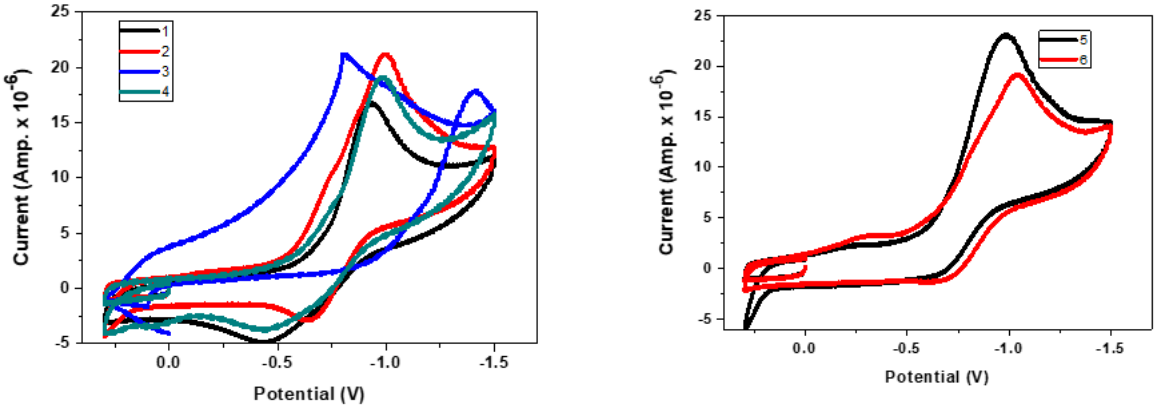
The single-crystal structure of displays that the enolic proton is transferred to the imine nitrogen and hence ligand is in keto-amine form.The phenolic proton forms intramolecular hydrogen bonding with imine nitrogen and thus a six-atom pocket, $R_1^1(6)$ is generated.

Electronic spectral studies



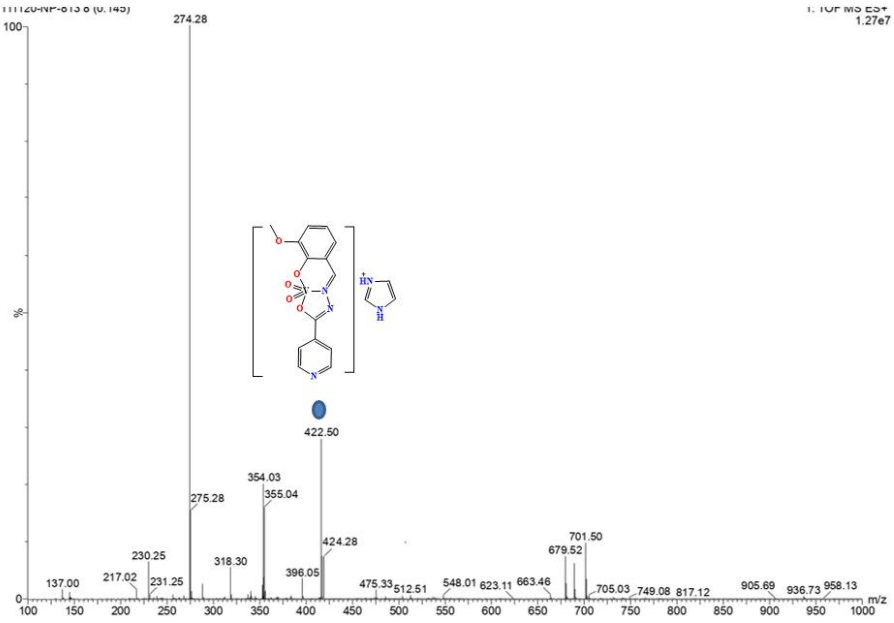
Electronic spectra were recorded using DMSO solutions (1.0×10^{-3} M). The absorption bands in the region 286-293 nm are ascribed to a intra ligand charge transfer band, while the new bands of medium intensity appear at 415-437 nm are assigned to ligand to metal charge transfer (LMCT) band which arises from the *p*-orbital lone pair of the phenolate oxygen atom to an empty *d*-orbital of vanadium (V) centre.These complexes having V(V) (d^0 system) did not show the *d-d* transition.

Electrochemical studies



Complexes **1-6** show one reductive wave and one oxidative wave. Although oxidative wave for complexes **5** and **6** are not defined.The ΔE value of **1, 3 & 4** is 465-589 mV, indicating the irreversible nature of redox waves. The redox couple for complex **2** is found to be quasi reversible with ΔE = 316 mV. Thus, experiments show that the reduction waves are due to one-electron transfer processes in complexes and these reduction processes are metal-centered reductions to the V(V) for all complexes **1-6.**

ESI-Mass

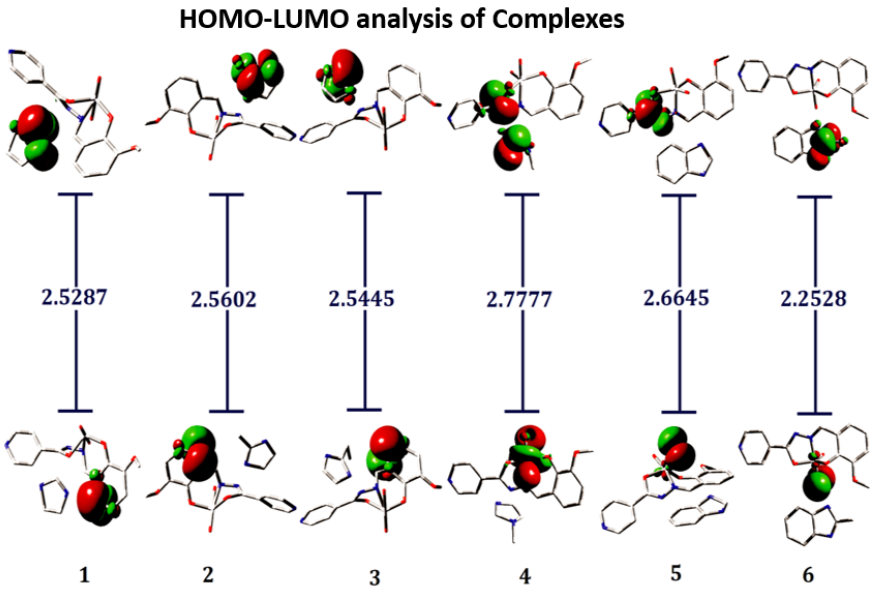


ESI-MS of Complex 1

Similarly ESI-Mass of all complexes were obtained**.**

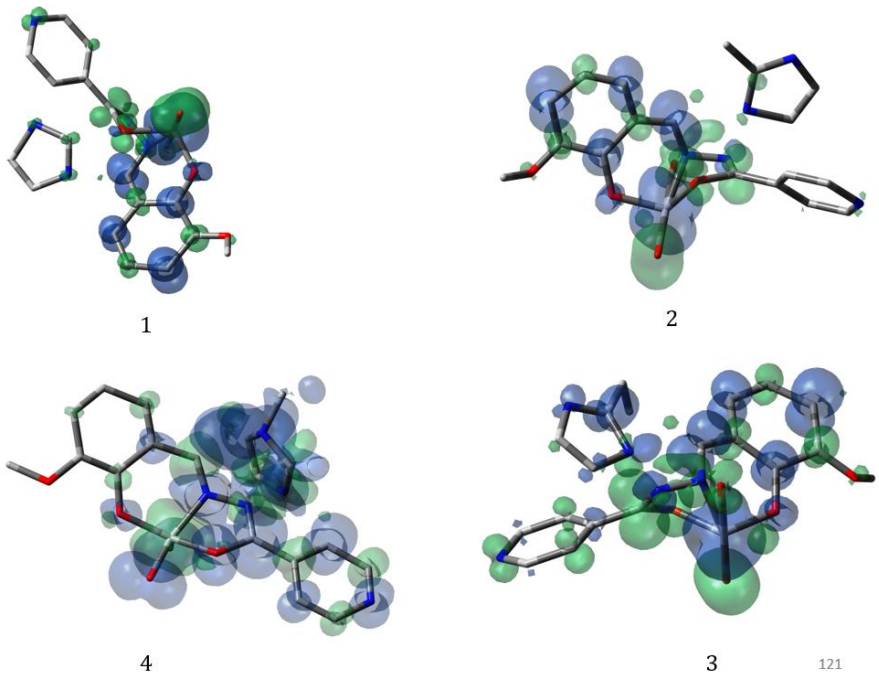
Computational Study of Complexes

Optimization of geometry of molecules is the primary step to determine the structural parameters such as bond distances and bond angles. The optimized structures are obtained using DFT studies at B3LYP/ LANL2DZ basic set level. The geometry of vanadium(V) centre is distorted square pyramidal. The Schiff base ligand is diaionic (L^2) with ONO donor sites. The VO_2^+ entity accommodated in the ONO binding site of tridentate ligand yields $[V(O_2)L]^-$ anion. One imidazolium ion satisfy the charge of unit. The double bonds between V(V) dioxide oxygen atoms of 1.630-1.636 Å in distorted square pyramidal geometry are comparable to those reported in the similar complexes.The fourth equatorial position is occupied by second dioxo oxygen atom.The τ_5 = 0.759-0.770 value for 1, 2 and 3 are very close to 1 authenticating the distorted trigonal bipyramidal geometry around the V(V) centre. For complexes 4, 5 and 6 the value of τ = 0.385, 0.198 and 0.010 and suggesting the distorted square planar geometry of V(V) centers.



Energy profile diagram of complexes **1-6**.

The ΔE_g of the present complexes have the trend: **6**(-2.252 eV) < **1**(-2.506 eV) < **3**(-2.544 eV) < **2**(-2.560 eV) < **5**(-2.664) < **4**(-2.777 eV).

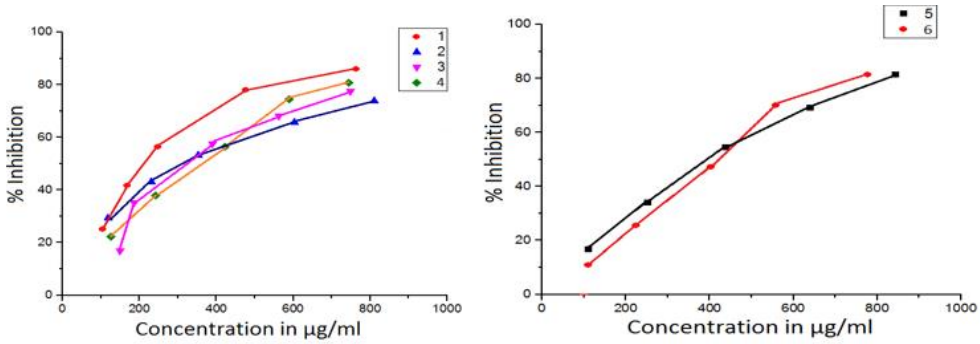


Spin density plot of complexes

Antidiabetic activity

The enzymatic inhibitory activity (antidiabetic activity) of vanadium complexes was measured.The pharmacologically active state of vanadium was estimated with respect to the interaction of vanadium ions and isolated rat intestinal acetone powder. It is observed that the inhibition activity increased as the concentration of complex increased. The α-glucosidase inhibition activity compared to acarbose (standard medicine). The observed trend in the

present complexes is **1** > 2 ≈ 3 > 4. Thus, inhibition could be modulated by the electronic effect that depends upon different substituents.The present complexes exhibit many fold more catalytic activity than the standard inhibitor acarbose. Thus such complexes may prove to be of importance in antidiabetic chemotherapy.



α-Glucosidase inhibition graph of complexes **1**-**6**.

Conclusion

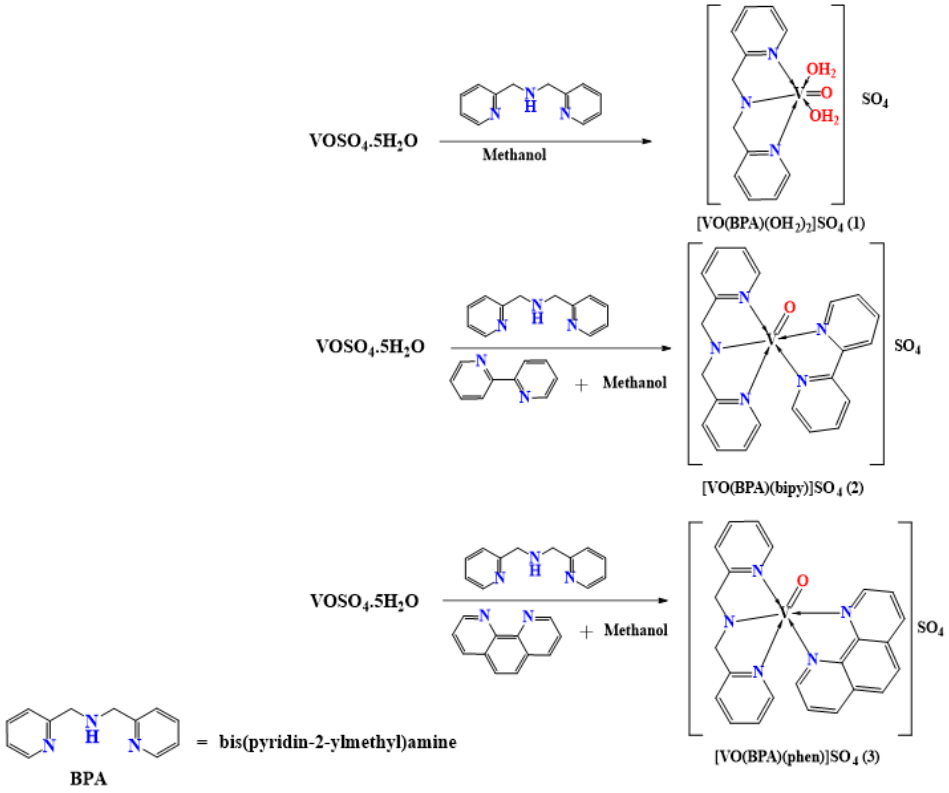
Six new dioxidoanadium(V) complexes of ONO-Schiff base hydrazone has been synthesized using (**H_2L)**, **H_2L** = Isonicotinic acid (2-hydroxy-3-methoxy-benzylidene)-hydrazide ligand. Due to small formed crystals, and the problem with complex recrystallization, complex decomposition, the single X-ray crystal structure could not be determined. These complexes have been characterized for their spectroscopic and redox properties. These complexes having V(V) (d^0 system) did not show *d-d* transition is not shown in electronic spectra. The geometry of these complexes can be described in terms of trigonal bipyramidal or square pyramidal. Complexes **1-6** show one reductive wave and one oxidative wave. Although oxidative wave for complexes **5** and **6** are not defined. The ΔE value of **1, 3 & 4** is 465-589 mV, indicating the irreversible nature of redox waves.Besides, *in-vitro* antidiabetic activity behaviors have also been explored using α-glucosidase and α-amylase methods. The observed trend in the present complexes is **1** > 2 ≈ 3 > 4.

Chapter 5

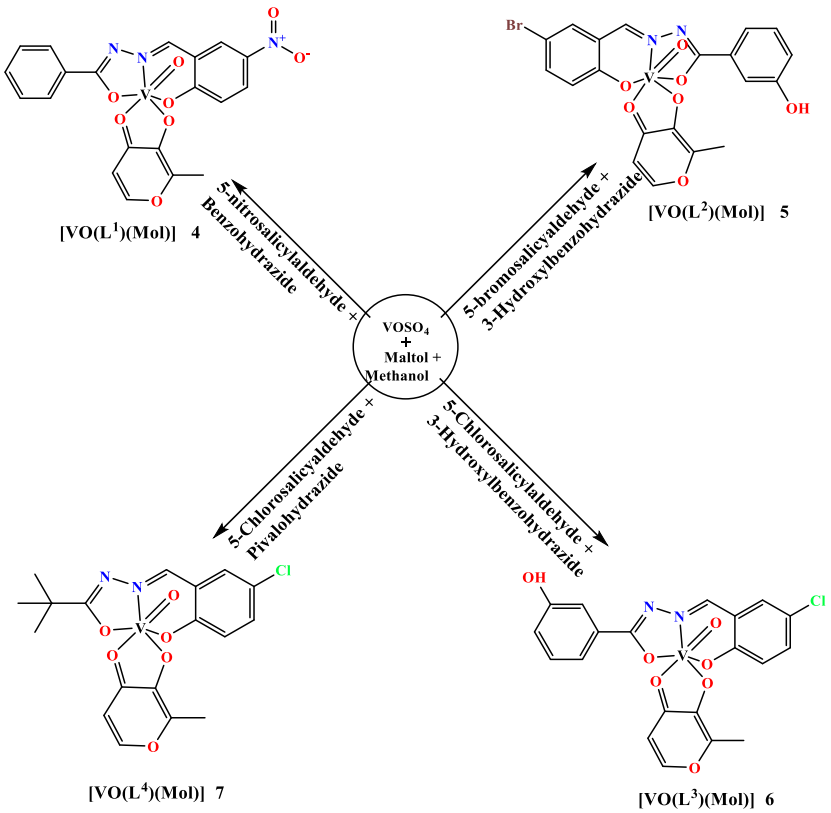
Syntheses, spectral characterization and antidiabetic activities of vanadium (IV/V) complexes with bi-and tridentate ligand (In situ rection)

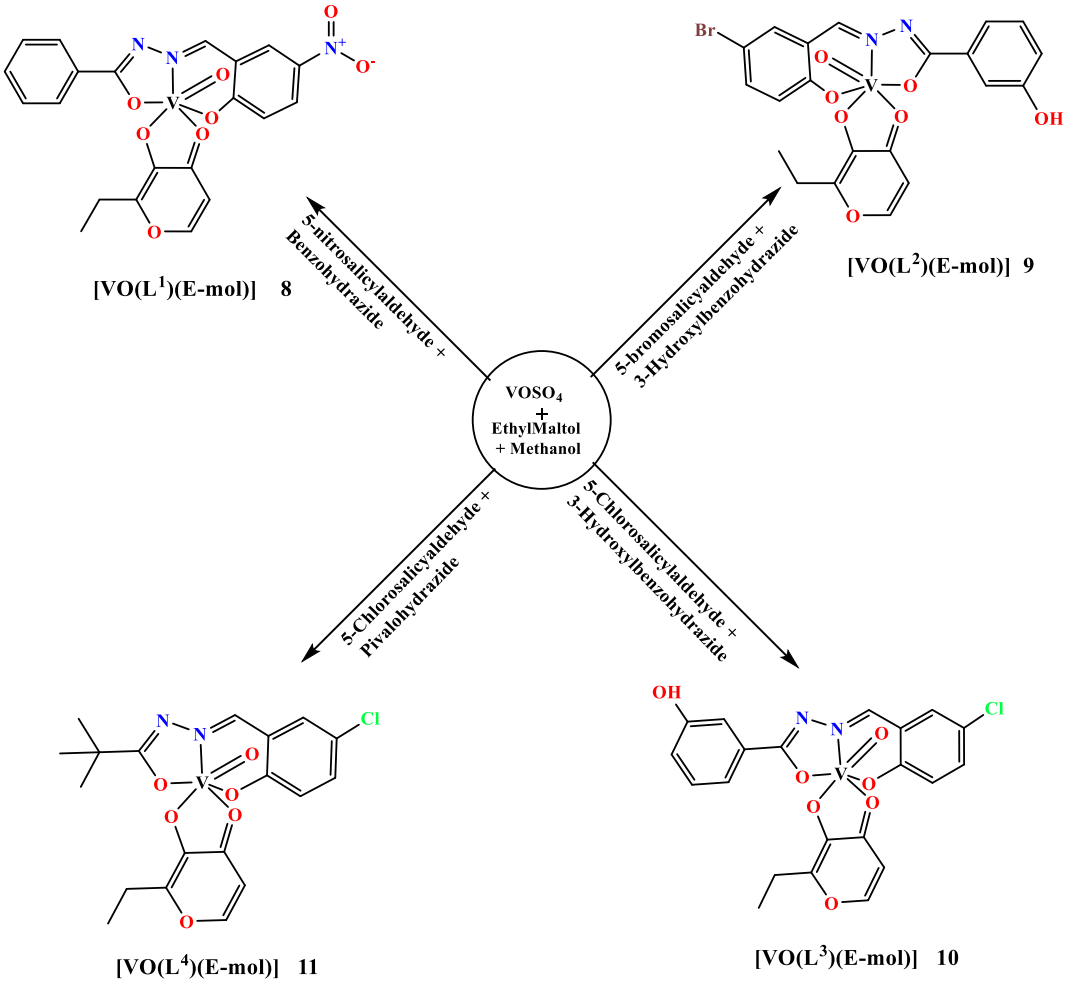
Synthesis of complexes

The binary and mixed ligand complexes were synthesized by taking aqueous vanadyl sulphate solution and methanolic solution of 2,2'-bis(pyridylmethyl)amine in a 1:1 ratio (Scheme 1). Similarly mixed ligand complexes **2** and **3** were synthesized by taking a methanolic solution of vanadyl sulphate, 2,2'-bis(pyridylmethyl)amine and 1,10-phenanthroline or 2,2-bipyridyl in 1:1:1 molar solution.This chapter describes syntheses, spectral characterization and electrochemical behaviour of eight new vanadium (V) complexes with tridentate aroylhydrazones and moltol or ethylmoltols as ancillary ligands. Their antidiabetic activities were also explored.



Scheme I Synthetic route of complexes 1-3.



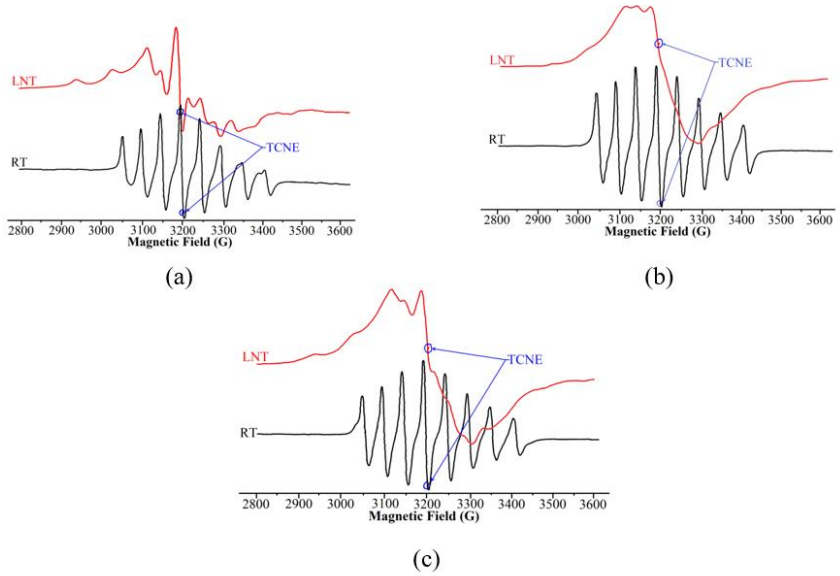


FTIR Analysis

In all complexes, a strong band was observed in the region of 978-956 cm^{-1}, which is consistent with six-coordinated vanadium complexes.In all spectra, the band corresponding to ν(N-H) at ~ 3079 cm^{-1} is observed due to the tertiary amine moiety of BPA.The IR spectrum of complex **1** shows a band at 3434 cm^{-1}, which can be attributed to the coordinated water molecules.The band corresponding to ν(C=N) of pyridyl moieties of the ligand is observed at ~ 1608 cm^{-1}, similarly, ionic sulphate shows the stretch mode in the range is 1153-1074 and 657-621 cm^{-1}.In IR spectra of the complexes ν(C=O) band are absent in the complexes.

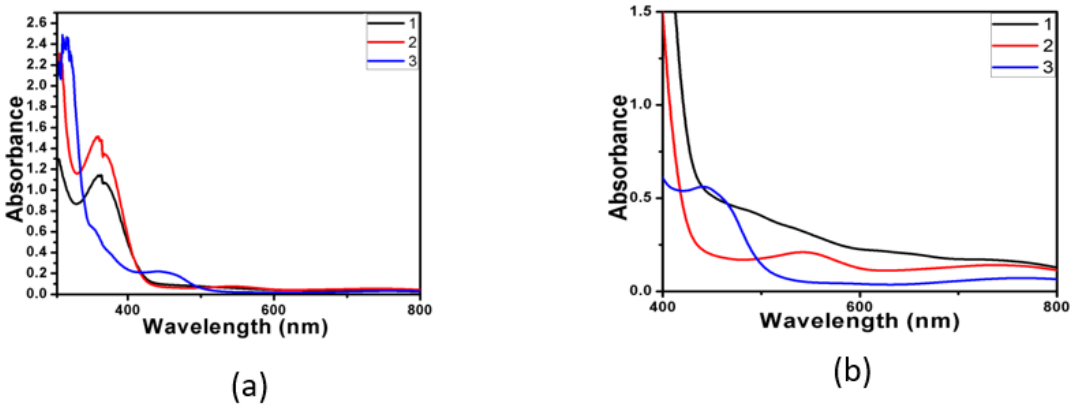
Magnetic and EPR spectral properties

The complexes 1-3 exhibit magnetic moment 1.81, 1.79 and 1.83 BM respectively, in accord with a spin only value of vanadium complexes having VO^{2+} ion. The full range (3200–2000 G) X-band ESR spectra for the oxidovanadium(IV) complexes (frozen liquid state and room temperature solid-state) were recorded. The ESR spectra of all the complexes show a typical eight-line pattern which suggests that single vanadium is present in the molecule, i.e. it is mononuclear.EPR spectra of all complexes in DMSO solution at RT yield light isotropic lines in which unpaired electron is coupled to the nuclear spin I = 7/2 of oxidovanadium(IV) nucleus. The values of room temperature EPR parameters (A_{iso} and g_{iso}) confirm the presence of oxidovanadium(IV), $3d^1$ in a distorted octahedral geometry.



EPR spectra of complexes 1-3 in polycrystalline state (RT) and DMSO solution at LNT.

Electronic spectra



(a) Display strong absorption bands in the high energy region of complexes 1–3 in 3.0 × 10^{-3} DMSO solution. (b) Absorption spectra of the complexes 1-3 show low intensity broadband in 6.0 × 10^{-5} M DMSO solution.

All oxidovanadium(IV) complexes exhibit bands in the range 250-500 nm, among which the two high energy bands in the UV region are attributed to the ligand centered transitions π-π* and n-π* transitions.Also, a new band of medium intensity appears in the range 450-550 nm, which is assigned to the ligand to metal charge transfer bandupon dissolution these complexes tend to hydrolyze and oxidize.These bands at 750 nm are due to *d-d* transitions. Such bands observed in oxidovanadium(IV) octahedral complexes, such electronic spectra reveal that in present complexes vanadium is present in V^{4+} state.In the electronic spectra of all complexes, the bands in the range 300-375 nm are due to the intra-ligand π→π* absorption of the azomethine group.The absorption bands of 400-425 nm are assignable to n→π* of the carbonyl group.In all complexes, an intense absorption band at 425-500 nm is assigned to the phenolic $N_{(p)}/O_{(p)}\rightarrow V_{(dx)}$ ligand to metal charge transfer (LMCT) band.The d-d absorption bands were not observed in all complexes being d^0 vanadium systems.

Conclusion

The molecular structures complexes **1-3** show the presence of six donor atoms around the oxidovanadium(IV) and hence octahedral geometry is proposed.Paramagnetic d^1 configuration of vanadium complexes (**1-3**) was supported by EPR spectroscopy. These complexes were also evaluated using thermogravimetric, The optimized molecular **1-3** structures show the presence of N_3O_3/N_5O donor atoms in six coordinated geometry. Eight oxidovanadium(V) complexes derived from ethyl maltol/ethyl maltol and various tridentate aroylhydrazones were prepared and well-characterized by various spectroscopic techniques. In complexes, **4-11** d-d absorption bands were not observed in all complexes being d^0 vanadium systems.The V ions in the complexes **4-11** are in octahedral coordination.In complexes,the **4-11** reduction process exhibits one-electron transfer i.e. the reduction of vanadium(V) to vanadium (IV).

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Synopsis

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