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Full Length Research Paper

α-Glucosidase inhibitory activities of some Oxovanadium(IV) complexes: Examples of low IC_{50} values

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α-Glucosidase inhibition measurements have been made on oxovanadium(IV) complexes of eight Schiff base ligands. Three of the complexes show exceptionally low IC_{50} values: $VO(sal\text{-}anl)_2$ = 2.105 μM, $VO(sal\text{-}mxyanl)_2$ = 1.26 μM and $VO(sal\text{-}ntranl)_2$ = 1.26 μM. *In-vivo* experiments for antihyperglycemic activity carried out on one of these complexes, viz., $VO(sal\text{-}mxyanl)_2$, reveal that the complex decreases blood glucose level by ~ 12% .

Key words: α-Glucosidase inhibition, oxovanadium (IV) complexes, Schiff bases, antihyperglycemic activity.

INTRODUCTION

Several metal ions and their complexes exhibit antidiabetic effects (Schwarz and Mertz, 1959; Rubenstein et al., 1962; Coulston and Dandona, 1980; Heyliger et al., 1985; Sakurai et al., 1990; Yoshikawa et al., 2000; 2010; Ueda et al., 2005). A large variety of oxovanadium(IV) complexes have earlier been studied for their antidiabetic activity (Thompson et al., 1999; Rehder et al., 2002; Sakurai, 2002; Sakurai et al., 2003a, b; Crans, 2005; Katoh et al., 2009). [Bis(maltolato)oxovanadium(IV)], BMOV and [bis(ethylmaltolato)oxovanadium(IV)], BEOV, have been studied most exhaustively (McNeill et al., 1992; Yuen et al., 1993; Dai et al., 1993; Caravan et al., 1995; Thompson et al., 2003; Saatchi et al., 2005); BEOV having completed phase I clinical trials in humans (Thompson et al., 2003). Search for newer and newer such drugs has become an important area of current biochemical research. Slowing down of digestion and absorption of dietary carbohydrate using α-glucosidase inhibitors has proved to be a promising therapeutic strategy for reducing risk of diabetes and other carbohydrate mediated diseases (Robinson et al., 1991; Braun et al., 1995; Dwek et al., 2002; Humphries et al., 1986; Mehta et al., 1998; Karpas et al., 1988; Zitzmann et al., 1999). Acarbose is the first α-glucosidase inhibitor approved for the treatment of diabetes (Yee et al., 1996). A variety of α-glucosidase inhibitors, extensively described in a recent review (de Melo et al., 2006), are all organic compounds, both synthetic and natural. There is paucity of data on α-glucosidase inhibition by oxovanadium (IV) complexes (Ashiq et al., 2008; 2009). We have, therefore, worked on rat intestinal α-glucosidase inhibition by oxovanadium(IV) complexes of a series of Schiff bases, derived from salicylaldehyde (and 5-bromosalicylaldehyde) and anilines. These Schiff bases act as ON-type bidentate ligands to form 5-coordinated square pyramidal oxovanadium (IV) complexes (structures and abbreviated names given in Figure 1).

MATERIALS AND METHODS

Preparation of the Schiff bases (Pandeya and Khare, 1992)

All the Schiff bases were prepared by refluxing, for 1-2 h, a mixture

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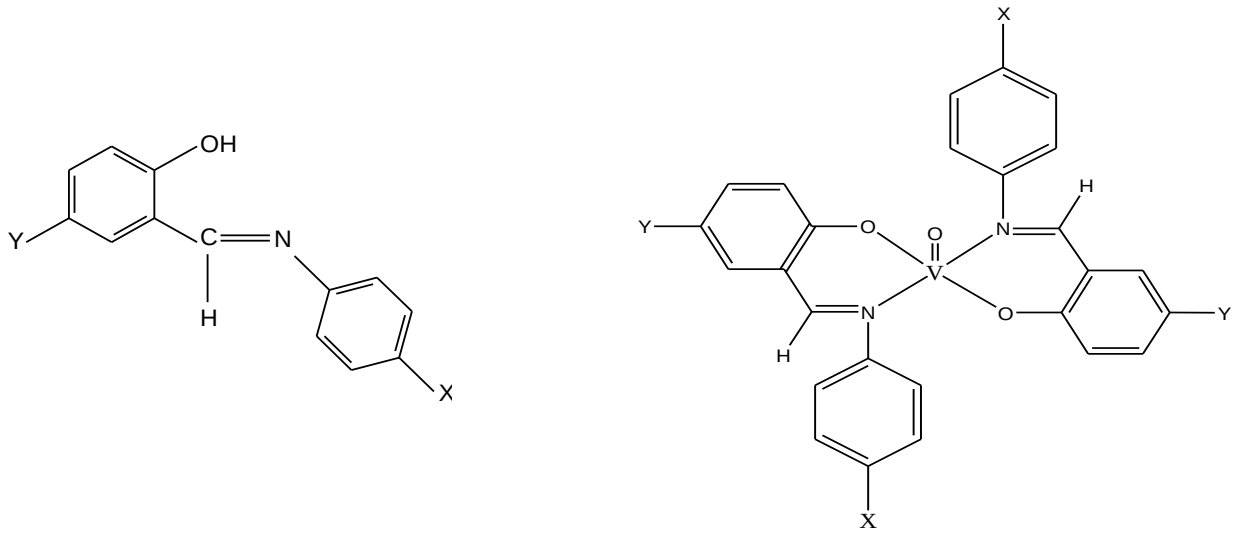

(1) **(2)**

Figure 1. Chemical structures of the Schiff base ligands and their oxovanadium (IV) complexes.
X=H, Y=H (sal-anl 1a; VO (sal-anl)$_2$ 2a), X=Cl, Y=H (sal-clanl 1b; VO (sal-clanl)$_2$ 2b), X=OCH_3,Y=H (sal-mxyanl 1c; VO(sal-mxyanl)$_2$ 2c), X=NO_2, Y=H (sal-ntranl 1d; VO(sal-ntranl)$_2$ 2d), X=H, Y= Br (brsal-anl 1e; VO(brsal-anl)$_2$ 2e), X=Cl, Y= Br (brsal-clanl 1f; VO(brsal-clanl)$_2$ 2f), X=OCH_3,Y= Br (brsal-mxyanl 1g; VO(brsal-mxyanl)$_2$ 2g), X=NO_2, Y= Br (brsal-ntranl 1h; VO(brsal-ntranl)$_2$ 2h).

Table 1. Elemental analyses, IR and electronic spectra.

Complex	Elemental analyses Calculated (Found)			IR band (cm^{-1})	Electronic spectra (cm^{-1})
	%C	%H	%N	$\nu_{v=o}$	$^2B_2 \rightarrow {}^2E$
VO(sal-anl)$_2$ 2a	67.97 (67.64)	4.36 (4.06)	6.10 (6.02)	980	12000
VO(sal-clanl)$_2$ 2b	59.09 (59.47)	3.41 (3.63)	5.30 (5.14)	983	12950
VO(sal-mxyanl)$_2$ 2c	64.74 (64.46)	4.62 (4.20)	5.39 (5.19)	971	11840
VO(sal-ntranl)$_2$ 2d	56.83 (56.33)	3.28 (3.08)	10.20 (10.02)	987	10845
VO(brsal-anl)$_2$2e	50.57 (50.17)	2.92 (3.00)	4.57 (4.50)	986	12500
VO(brsal-clanl)$_2$ 2f	45.48 (45.31)	2.33 (2.39)	4.08 (4.12)	980	13040
VO(brsal-mxyanl)$_2$ 2g	49.63 (49.28)	3.25 (3.55)	4.14 (4.05)	980	NR*
VO(brsal-ntranl)$_2$ 2h	44.13 (44.00)	2.26 (2.60)	7.92 (7.61)	985	11765

*Not resolved (see text).

of the salicylaldehyde/5-bromo-salicylaldehyde and aniline/ substituted aniline in ethanol. In most cases the Schiff bases precipitated out on cooling. Wherever necessary, the excess solvent was evaporated to make the Schiff base precipitate out on cooling. The same was filtered, washed with small amount of ethanol and dried.

Preparation of the complexes (Pandeya and Khare, 1992)

A mixture of 2 mmol Schiff base and 1 mmol of NaOH was dissolved in methanol followed by addition of 1 mmol of vanadyl sulphate (trichurated in minimum amount of methanol). The solution was refluxed for nearly one hour to obtain clear solution. On cooling, the complex precipitated out in most cases. Wherever necessary, the excess solvent was removed by evaporation to get the complex precipitate out on cooling. The same was filtered out, washed with methanol and dried.

Characterization of complexes

The complexes, so obtained, show satisfactory elemental analyses (Table 1). Their infrared spectra (in KBr) show sharp, symmetric $\nu_{v=o}$ bands (Table 2). Electronic spectra of oxovanadium(IV) complexes should exhibit three d-d bands corresponding to transitions $^2B_2 \rightarrow {}^2E$ (ν_1), $^2B_2 \rightarrow {}^2B_1$ (ν_2) and $^2B_2 \rightarrow {}^2A_1$ (ν_3). For the present complexes ν_2 and ν_3 have been obscured by strong charge-transfer absorptions, so that only ν_1 has been observed in the range 10845 to 13040 cm^{-1}. For VO (brsal-mxyanl)$_2$ even ν_1 has been obscured (Table 1). Solution epr spectra (in DMSO at room temperature) of all the complexes show eight hyperfine lines characteristic of oxovanadium(IV). One representative spectrum, VO (sal-anl)$_2$, has been shown in Figure 2.

Table 2. α-Glucosidase inhibition by the oxovanadium(IV) complexes and the Schiff base ligands.

Oxovanadium(IV) complexes	% inhibition at 200 µM	IC_{50} (µM)	Schiff Base Ligands	% inhibition at 200 µM	I C_{50} (µM)
$VO(sal\text{-}anl)_2$	82.06	2.105	sal-anl	36.6	n/d*
$VO(sal\text{-}clanl)_2$	68.89	13.12	sal-clanl	6.63	n/d*
$VO(sal\text{-}mxyanl)_2$	84.57	1.26	sal-mxyanl	11.45	n/d*
$VO(sal\text{-}ntranl)_2$	83.51	1.26	sal-ntranl	98.6	22.72
$VO(brsal\text{-}anl)_2$	79.44	16.92	brsal-anl	33.06	n/d*
$VO(brsal\text{-}clanl)_2$	43.46	n/d*	brsal-clanl	0.00	n/d*
$VO(brsal\text{-}mxyanl)_2$	66.11	92.43	brsal-mxyanl	67.21	74.11
$VO(brsal\text{-}ntranl)_2$	83.15	31.10	brsal-ntranl	43.38	245
$VOSO_4$	11.75	----			
Acarbose	----	18.59			

n/d*= Not determined.

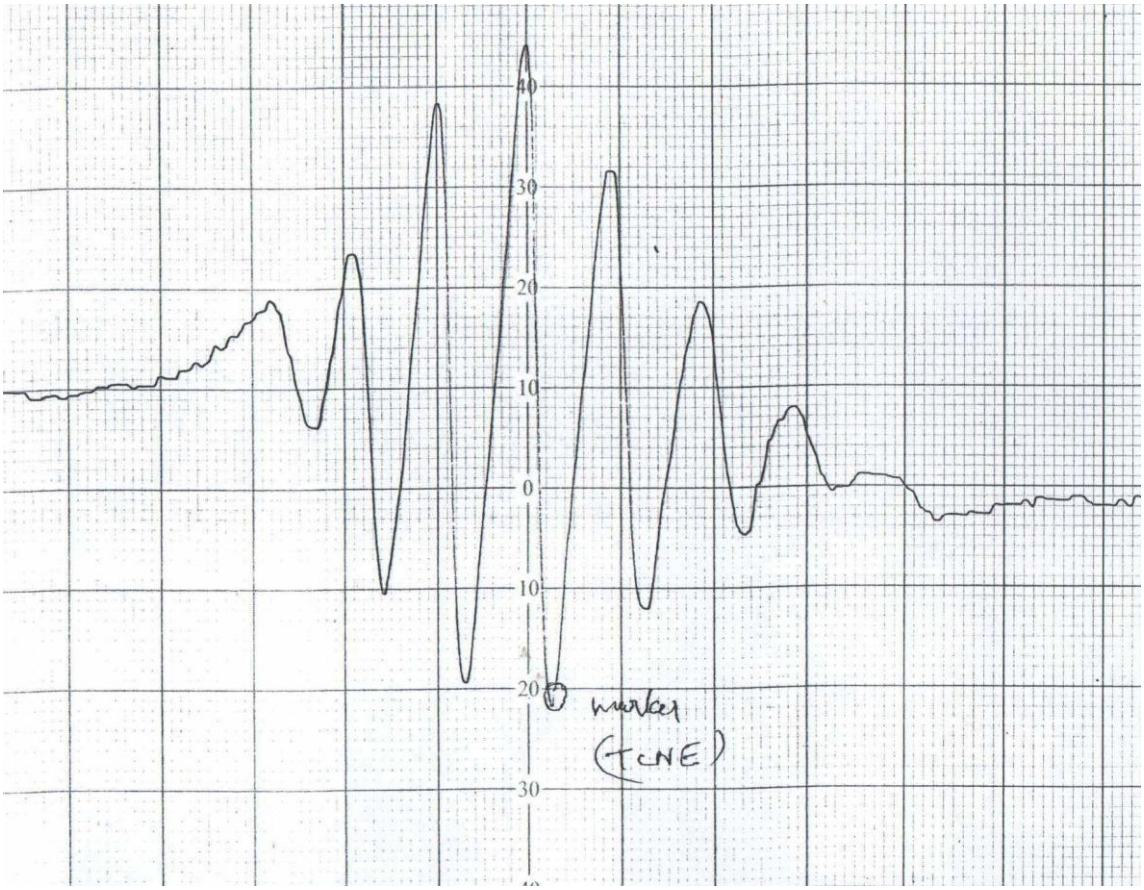

Figure 2. Solution epr spectrum (in DMSO at Room temperature) of VO(sal-anl).

***In-vitro* α-glucosidase inhibition**

Rat intestinal acetone powder (Sigma chemicals, USA) was sonicated properly in normal saline (100:1 w/v) and after centrifugation at 3000 rpm × 30 mins the supernatant was treated as crude intestinal α-glucosidase. Ten microliters of test samples dissolved in DMSO (5 mg/ml solution) were mixed and incubated with 50 µl of enzyme in a 96-well microplate for 5mins. Reaction mixture was further incubated for another 10 mins with 50 µl substrate (5 mM, p-nitrophenyl-α-D- glucopyranoside) prepared in 100 mM phosphate buffer (PH~6.8) and release of nitrophenol was read at, 405 nm spectrophotometrically ($SPECTRA_{max}$ PLUS ^{384}, Molecular devices, USA). Percent α-Glucosidase inhibition was calculated as (1-B/A) ×100, where A was the absorbance of

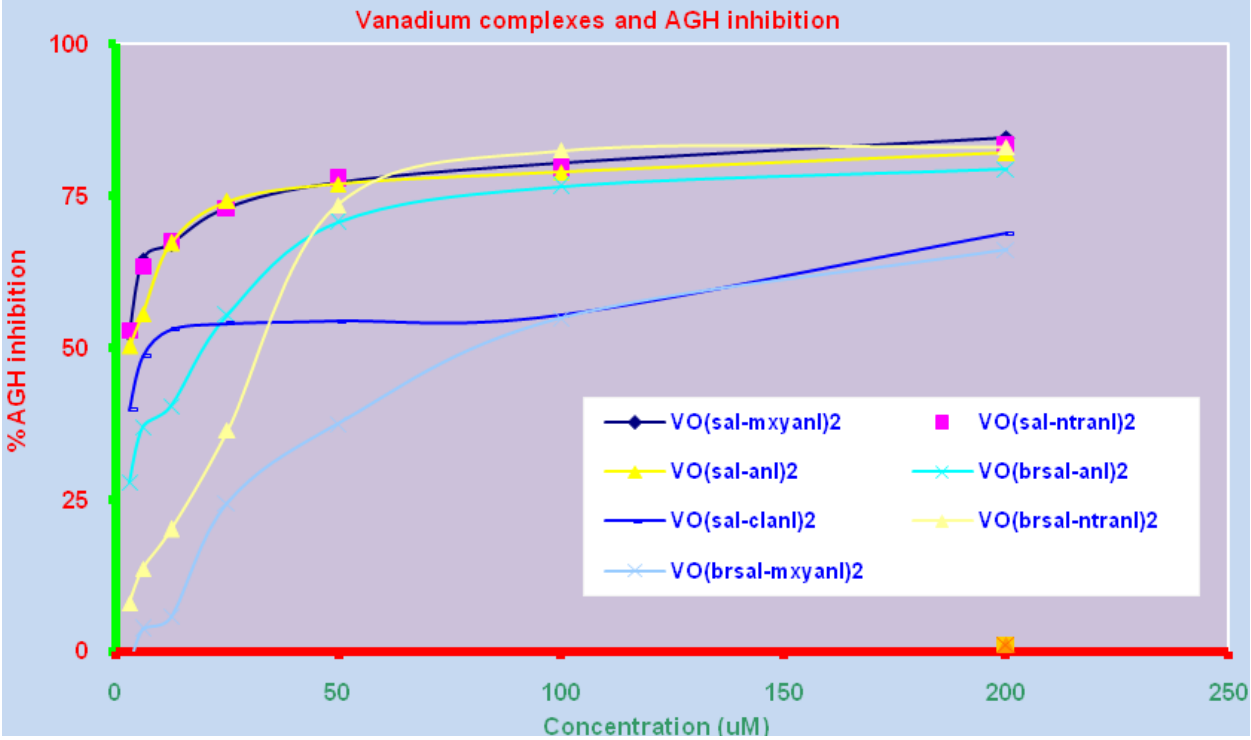

Figure 3. Concentration dependent rat intestinal α-glucosidase inhibitory activities of test compounds. Data represents mean ± SD. N=3.

reactants without test samples and B was absorbance of reactants with test samples. All the samples were run in triplicate and acarbose was taken as standard reference compound. Several dilutions of primary solution (5 mg/ml DMSO) were made and assayed accordingly to obtain concentration of the test sample required to inhibit 50% activity (IC_{50}) of the enzyme applying suitable regression analysis. The results of inhibition of α-glucosidase by oxovanadium (IV) complexes at various concentrations are presented graphically in Figure 3. Percentage inhibition at 200 µM for various compounds and IC_{50} values are collected in Table 2.

In-vivo experiment

In-vivo experiments for blood glucose lowering measurement were carried out on only one complex, viz., $VO(sal\text{-}mxyanl)_2$ 2c. Experiments were performed in Pharmacology Division of IICT Hyderabad, as per the animal ethical committee rules. Male Wistar rats (weight 195±10) were used for the *in-vivo* experiments. Animals were allowed for alternating 12 h light dark cycle at 22±1°C room temperature. Animals were kept for overnight fasting and next morning basal glucose value was measured by auto blood analyzer (Bayer Express Plus). The results of *in-vivo* experiments are shown in Figure 4 and the results of computation of AUC level have been presented in Figure 5.

RESULTS AND DISCUSSION

In-vitro α-glucosidase inhibition

α-Glucosidase inhibition data (percentage inhibition at 200 µM and IC_{50} values) for oxovanadium (IV) complexes are presented in Table 2. Table 2 also gives the data for uncoordinated (free) ligands and for vanadyl sulphate for the sake of comparison. The results of inhibition of α-glucosidase by oxovanadium (IV) complexes at various concentrations are also presented graphically in Figure 3. A perusal of the data reveals the following points:

i. Vanadyl sulphate itself is a poor α-glucosidase inhibitor; all the complexes show much higher inhibition.
ii. All oxovanadium (IV) complexes show much stronger α-glucosidase inhibition compared to the corresponding Schiff base ligands, except $VO(brsal\text{-}mxyanl)_2$ that shows almost same inhibitory potential as brsal-mxyanl.
iii. All complexes of the salicylaldehyde based Schiff bases are stronger α-glucosidase inhibitors compared to the corresponding complexes of bromosalicylaldehyde based Schiff bases.
iv. Among the complexes of salicylaldehyde based Schiff bases $VO(sal\text{-}mxyanl)_2$ and $VO(sal\text{-}ntranl)_2$ show nearly similar inhibition behaviour (IC_{50}=1.26 µM) and stand on top as α-glucosidase inhibitors.$VO(sal\text{-}anl)_2$ follows these two inhibitors and shows only slightly lower inhibition potential (IC_{50} =2.105 µM). Weakest inhibitor among these complexes is $VO(sal\text{-}clanl)_2$ with IC_{50} value of 13.12 µM. Among the complexes of bromosalicylaldehyde based Schiff base ligands $VO(brsal\text{-}clanl)_2$ is the weakest inhibitor and also weakest of all the complexes studied.

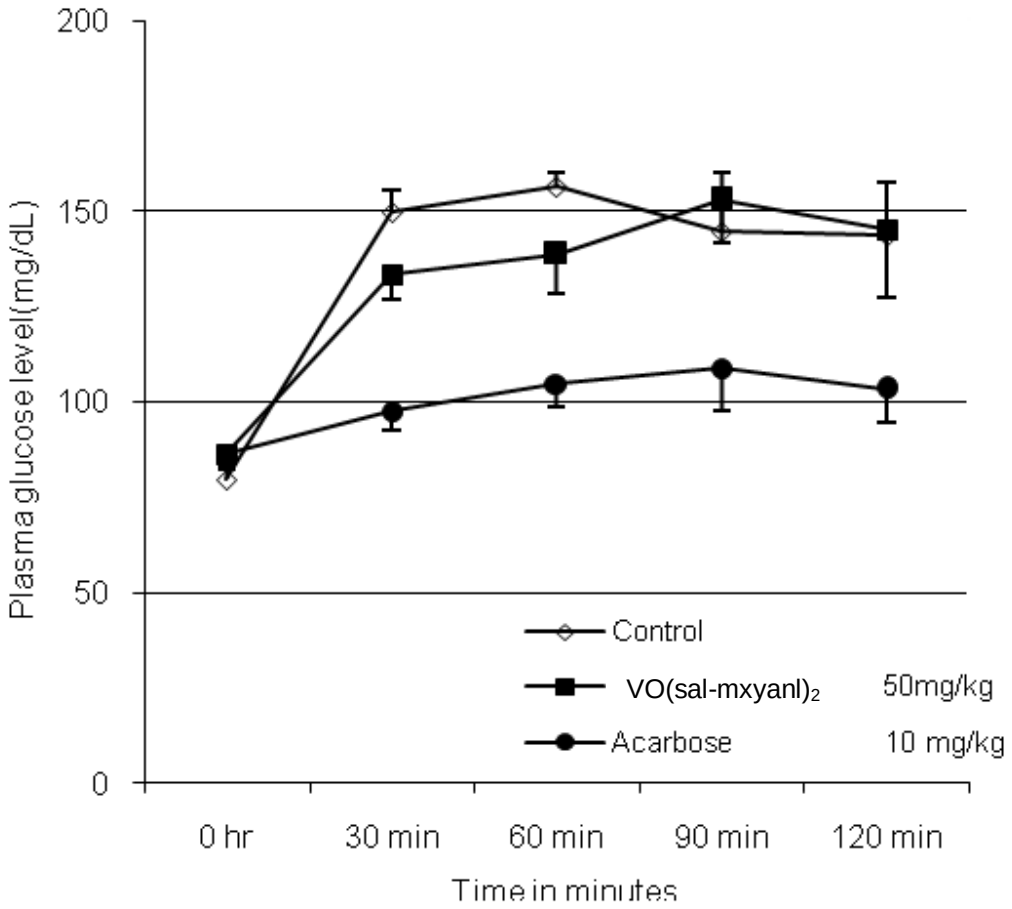

Figure 4. Plasma glucose level under the influence of VO(sal-mxyanl)$_2$ after starch feeding. VO(sal-mxyanl)$_2$ (50 mg/kg body weight) and standard α-glucosidase inhibitory antihyperglycemic drug acarbose (10 mg/kg body weight) were administered 15 min before starch (2 g/kg body weight) feeding to respective group of animals. Plasma glucose levels were measured at different time points post starch feeding. One-way ANOVA followed by Bonferroni's multiple comparison tests was applied to find differences between the groups. Values represent mean ± SD, n=5.

At 200 µM inhibitor concentration this complex shows percentage inhibition value of 43.5 only. Other three complexes of this series viz., VO(brsal-anl)$_2$ (IC_{50}=16.92 µM), VO(brsal-mxyanl)$_2$ (IC_{50} =92.43 µM) and VO(brsal-ntranl)$_2$ (IC_{50} =31.10 µM), show only moderate α-glucosidase inhibitory potential.

In Table 2, % inhibition at 200 µM of sal-ntranl has higher value compared with VO(sal-ntranl)$_2$, but the IC_{50} values of VO(sal-ntranl)$_2$ is much lower compared with sal-ntranl. One would normally expect that if the value of % inhibition at 200 µM was high, the IC_{50} value should be low. Our data in case of sal-ntranl and VO (sal-ntranl)$_2$ is reverse. Higher value of % inhibition, however, does not necessarily lead to lower value of IC_{50}. If the inhibitor concentration vs. % inhibition curves have different nature and cross each other, it may be reverse. Same is the case of sal-ntranl vs. VO(sal-ntranl)$_2$, presumably because of different modes of inhibitory action.

Lack of structural information about the nature of the interaction between α-glucosidase and the inhibitors has been a big hurdle in the interpretation of the available inhibition data in terms of the structures of the inhibitors. Zhou et al. (2006) and more recently Park et al. (2008) have carried out computational calculations yielding some important conclusions about the structural insight into the inhibitory mechanisms. Zhou et al. (2006) have established the importance of the capability of the inhibitor to form hydrogen bond with the catalytic residue of α-glucosidase in the inhibition action. Such hydrogen bonds may be formed between a hydrogen bond donor on the inhibitor and a hydrogen bond acceptor on the enzyme residue or between an acceptor on the inhibitor and a donor on the enzyme residue.

All the Schiff base ligands of the present study fall into the ‘non-glycosidic derivative’ category of de Melo et al. (de Melo et al., 2006) and contain phenyl hydroxyl group. Studies on structure activity relationship on such compounds (Niwa et al., 2003) have shown that this

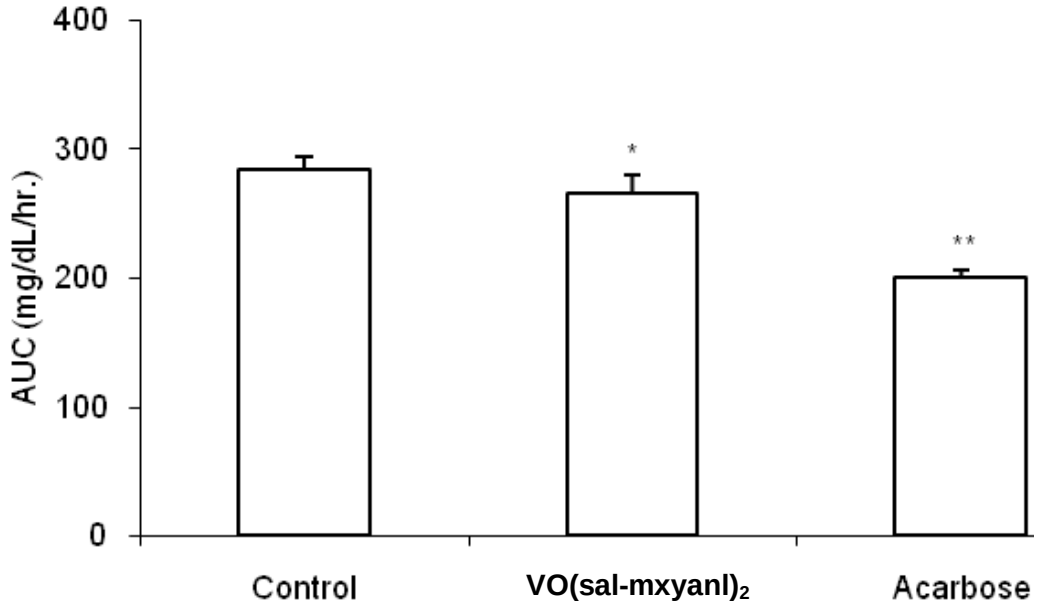

Figure 5. Area under the curve (AUC) represents over all plasma glucose load per hour in respective group of animals after starch feeding under the influence of VO(sal-mxyanl)$_2$ (50 mg/kg body weight) and standard α-glucosidase inhibitory antihyperglycemic drug acarbose (10 mg/kg body weight) administered 15 minutes before starch (2 g/kg body weight) feeding to respective group of animals. Plasma glucose levels were measured at different time points post starch feeding. AUC was calculated applying formula published earlier [39]. One-way ANOVA followed by Bonferroni's multiple comparison tests was applied to find differences between the groups. Values represent mean ± SD, n=5. *p<0.05; **p<0.001 when compared with control group.

phenyl hydroxyl group is fundamental for their inhibition activities. In the present study, variation in the inhibitory potential of the Schiff bases arises due to the substituent groups like bromide on the salicylaldehyde moiety and chloro, methoxy and nitro groups in the para position of the aniline moiety. These groups may influence the hydrogen bond donor capability of the phenyl hydroxyl group and may also act as hydrogen bond acceptors to appropriate hydrogen bond donors of the protein side chains.

Oxovanadium (IV) complexes show much stronger α-glucosidase inhibition compared to the corresponding ligands. For oxovanadium(IV) complexes as inhibitors, α-glucosidase may coordinate to the central vanadium ion at sixth (vacant) coordination position of the five coordinated VO-Schiff base complex (Figure 6). Cornman et al. (1995) have earlier suggested formation of such a bond between the metal ion and protein side chain for inhibition or activation of the enzymes. The inhibitors can be further stabilized in the active site through hydrogen bonds with catalytic residues and the establishment of hydrophobic contacts in a cooperative fashion. For acarbose and acarbose-type molecules as α-glucosidase inhibitors, for example, (Park et al., 2008) have shown that in α-glucosidase, side chain of Thr 215 acts as the hydrogen bond acceptor and the side chain hydroxyl group of Ser244 serves as a hydrogen bond donor.

In-vivo results

A close perusal of the diagram showing time evolution of the serum glucose levels after single oral administration of various compounds (Figure 4) and the AUC level diagram (Figure 5) reveal that, compared to the control, the blood glucose level in VO (sal-mxyanl)$_2$-fed rats is lower by nearly 12% between 30-60 min time interval. For acarbose-fed rats this lowering is nearly 35%. The antihyperglycemic property of VO(sal-mxyanl)$_2$ is, thus, not proportionate to its α-glucosidase inhibition property. At this point it may be mentioned that the α-glucosidase inhibition measurement is an *in-vitro* experiment, while the antihyperglycemic activity measurement is an *in-vivo* experiment. Inside the intestine of the animal the oxovanadium (IV) complex has to face the acidic environment which may cause dissociation of the complex (Kiss et al., 2008).

Conclusion

α-Glucosidase inhibitory potentials of three of the complexes viz., VO(sal-anl)$_2$ 2a, VO(sal-mxyanl)$_2$ 2c, VO(sal-ntranl)$_2$ 2d, are impressively high. Their IC_{50} values are smaller than the IC_{50} value of even acarbose (Table 3). *In-vivo* experiments carried out on one of the

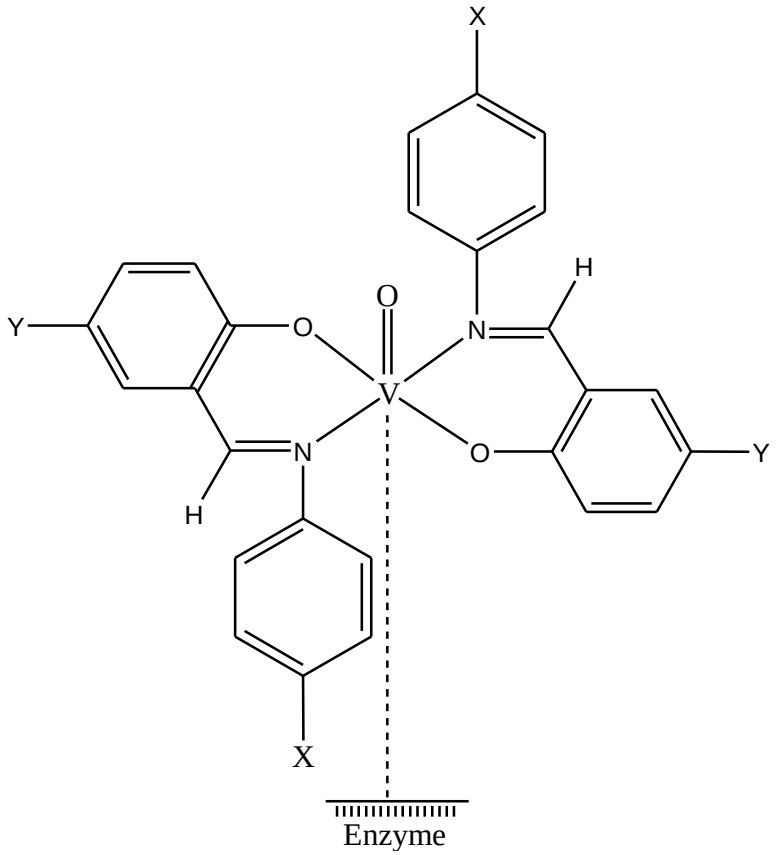

Figure 6. Binding of the α-glucosidase active site residue to the oxovanadium(IV) complex.

Table 3. Inhibitory potentials some complexes.

Inhibitor	IC_{50} (in µM)
Acarbose	18.59
2a, $VO(sal\text{-}anl)_2$	2.11
2c, $VO(sal\text{-}mxyanl)_2$	1.26
2d, $VO(sal\text{-}ntranl)_2$	1.26

complexes viz., $VO(sal\text{-}mxyanl)_2$ 2c, shows lowering in blood glucose level by nearly 12% compared to control, while this lowering for acarbose is nearly 35%.

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