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Mamta Dudeja^a, Rajesh Malhotra^a, Mohinder PaulGupta^a & Kuldeep SinghDhindsa^a

^a Department of Chemistry and Biochemistry ,
Haryana Agricultural University , Hisar, 125004,
India

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LIGATIONAL BEHAVIOUR OF SUBSTITUTED 4,5-DIHYDRO-PYRAZOLES TOWARDS OXOVANADIUM(IV) AND METAL-ATION EFFECT ON THE ANTIMICROBIAL ACTIVITY

Mamta Dudeja, Rajesh Malhotra, Mohinder Paul Gupta and
Kuldip Singh Dhindsa*

Department of Chemistry and Biochemistry, Haryana Agricultural
University, Hisar-125004, India

ABSTRACT

Complexes of 1-acetyl-5-aryl-3-(substituted thienyl)-4,5-dihydropyrazoles [AATP; Ar = 2-OCH₃, 4-OCH₃ and 3,4-(OCH₃)₂] with oxovanadium(IV) ion have been synthesized and characterized on the basis of elemental analyses, molar conductance, magnetic susceptibility, molecular weight determination and spectral (ESR, IR and UV) data. The pyrazoles behaved as bidentate ligands coordinating through oxygen and nitrogen N(2) of the carbonyl and azomethine groups, respectively. ESR data of the powdered samples of the complexes and in DMF solution suggested a distorted octahedral environment around oxovanadium(IV). The ligands and vanadyl complexes were evaluated for antifungal activity

against *Colletotrichum capsicum* and *Rhizoctonia solani* at 37°C and antibacterial activity against *Bacillus subtilis* and *Escherichia coli* at 28°C. Metalation had pronounced effects on the antimicrobial activity of the ligands.

INTRODUCTION

Pyrazoles and their derivatives have evoked considerable interest of coordination chemists because of their potential as versatile chelating agents towards various metal ions^{1,2} and their biological implications^{3,4}. Literature reports reveal that the activity of a ligand can be altered several-fold by coordination with suitable metal ions⁵⁻⁷, probably due to the increase in lipophilicity of the metal chelates⁸. In the present study we have investigated the interaction of VO²⁺ ion with some newly synthesized pyrazoles (Fig.1) and examined the biological effects of chelation against some microorganisms. The choice of oxovanadium is promoted by its proximity to Cu²⁺ ion in the Irving-Williams series⁹. Moreover, it is an essential trace element in both plants and animals^{10,11} displaying numerous physiological effects. There is ample evidence that in living organisms vanadium exists as VO²⁺ ion complexed with proteins and other cellular components¹².

LIGANDS	R	R'
L_I	H	2-OCH ₃
L_{II}	H	4-OCH ₃
L_{III}	H	3,4-(OCH ₃) ₂
L_{IV}	Cl	2-OCH ₃
L_V	Cl	4-OCH ₃
L_{VI}	Cl	3,4-(OCH ₃) ₂

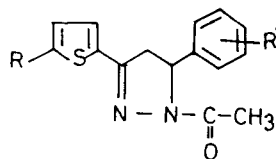


Fig. 1. Structures of the ligands

EXPERIMENTAL

Physico-chemical Measurements

IR spectra in Nujol mulls on KBr plates (λ_{\max} in cm^{-1}) were obtained using a Perkin-Elmer 621 Spectrophotometer. The electronic spectra of the complexes were recorded on a Hitachi 330 Spectrophotometer. ^1H NMR spectra in CDCl_3 were recorded on a Varian EM 390 (90 MHz) instrument using TMS as internal standard. ESR spectra of some of the complexes were recorded at room temperature (25°C) on a Varian E-line X-band Spectrometer operating at 9.57 GHz using 100 KHz field modulation. Spectra of powdered samples and DMF solutions of the complexes were recorded in quartz tubes. The magnetic field calibration was checked using TCNE ($g = 2.00277$) as a g marker. Conductance values were determined in dry DMSO or DMF at 10^{-3} M concentration on a Digital conductivity

Meter NDC 732. Molecular weight determinations were carried out cryoscopically in dry nitrobenzene. Magnetic susceptibilities were measured on a Sherwood magnetic susceptibility balance, (accuracy $\pm 2\%$) and carbon, hydrogen and nitrogen analyses were performed on an automatic elemental analyser Carlo Erba Strumentazione model 1106. Vanadium was determined as V_2O_5 after igniting the complex in an electrical furnace and sulphur was determined gravimetrically by the standard analytical procedure¹³.

Synthesis of Ligands

The ligands were synthesised in two steps:

I. Synthesis of 3-Aryl-1-(substituted thienyl)-2-propen-1-one (1).

0.02 mol of 2-acetylthiophene/ 2-acetyl-5-chlorothiophene was dissolved in 50 mL methanol and the pH of the solution adjusted to 10-11 with the help of $10^{-3}M$ sodium hydroxide. To this solution was added dropwise the corresponding aldehyde (0.02 mol) with constant stirring at $0-5^\circ C$ which was continued for another 2-4 h for the ligands $L_I - L_{III}$ and 14-18 h for the ligands $L_{IV} - L_{VI}$. The reaction mixture was then diluted with water and acidified with conc. sulphuric acid (25 mL). The solid separated was washed with water, recrystallized from methanol and dried under reduced pressure.

II. Synthesis of 1-Acetyl-5-aryl-2-(substituted thienyl)-4,5-dihydropyrazoles ($L_I - L_{VI}$).

A solution of (1) (0.01 mol) in acetic acid

(25 mL) was refluxed for 5-6h with excess of hydrazine hydrate (1.0 g, 0.02 mol). The reaction mixture was cooled and poured onto ice-water. The separated solid was washed with water and recrystallized from methanol.

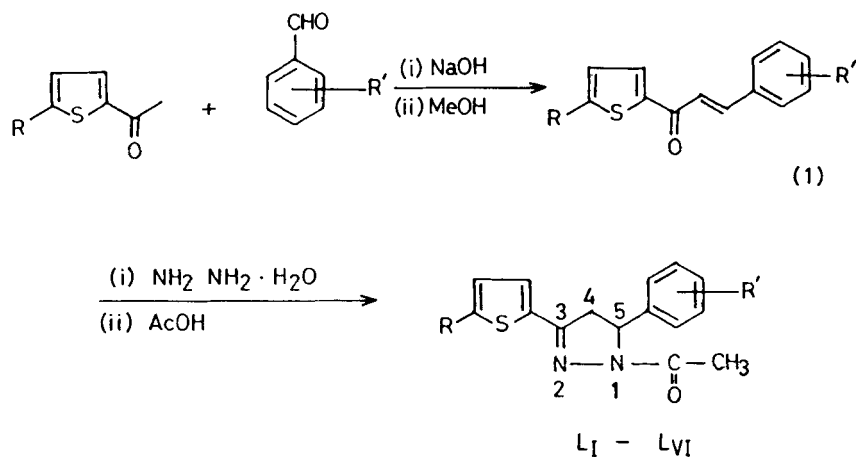
Synthesis of Metal Complexes

Vanadyl sulphate (2.17 g, 0.0100 mol), dissolved in the minimum amount of water (5 mL), was added to the solution of the corresponding ligand (0.02 mol) in ethanol (25 mL) and refluxed for 3 h. The solid thus separated was filtered, washed with ethanol and dried under vacuum.

RESULTS AND DISCUSSION

Condensation of substituted 2-acetylthiophenes and substituted aldehydes in methanolic sodium hydroxide solution gave the substituted 3-aryl-1-(substituted thienyl)-2-propen-1-ones (**1**) in good yields which were assigned *trans* configuration on the basis of the coupling constant (16 Hz) between two olefinic protons appearing at 7.40 and 8.10 ppm in ^1H NMR spectra. The ligands $\text{L}_1\text{-L}_{\text{VI}}$ were obtained by the reaction of (**1**) with hydrazine hydrate in acetic acid. The first step in the formation of ligands involved a nucleophilic attack at the carbonyl group forming unstable α , β -unsaturated hydrazones which underwent intramolecular rearrangement at the double bond followed by *in situ* acylation due to the presence of

acetic acid as solvent^{14,15}. In these ligands, the *trans* C₄-H was observed at upfield (2.50 - 2.23 ppm) relative to its *cis* analogue (3.26-3.56 ppm) (Table I). Further, J_{4,5}-*trans* was found to be smaller in magnitude (4-6 Hz) as compared to J_{4,5}-*cis* (12 Hz) and was consistent with the literature values¹⁶. The integrated proton ratio of different groups, as evident from the spectrum of each ligand, was well in agreement with the proposed structure for these ligands.

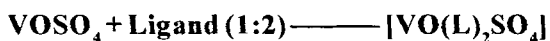


All the metal complexes obtained were coloured (greenish blue to greenish brown) and stable at atmospheric conditions. These were insoluble in most of the common organic solvents (ethanol, acetone, ether and benzene) except in polar solvents such as DMSO or DMF. The low molar conductance values (5.0-20.0 ohm⁻¹cm² mol⁻¹) in dry DMSO or DMF indicated their non-electrolytic nature

Table I. Analytical and ¹H NMR Spectral Data of 1-Acetyl-5-aryl-3-(substituted thienyl)-4,5-dihydropyrazoles

Compound	Empirical Formula	Yield (%)	M.P. °C	Analytical data % Found (calcd.)			¹ H NMR
				C	H	N	
L _I	C ₁₆ H ₁₆ N ₂ O ₂ S	72	95	63.6 (64.0)	5.1 (5.3)	9.0 (9.3)	2.09 (s, 3H, COCH ₃), 3.60 (s, 3H, ArOCH ₃), 2.53-2.83 (dd, 1H, C ₄ -H trans), 3.26 - 3.56 (dd, 1H, C ₂ -H cis) 5.43-5.63 (dd, 1H, C ₅ -H), 6.60-7.36 (m, 7H, Ar-H and thienyl H).
L _{II}	C ₁₆ H ₁₆ N ₂ O ₂ S	65	102	63.8 (64.0)	5.1 (5.3)	9.5 (9.3)	Same as in L _I above.
L _{III}	C ₁₇ H ₁₈ N ₂ O ₃ S	70	171	61.4 (61.8)	5.2 (5.4)	8.1 (8.5)	2.34 (s, 3H, OCH ₃), 3.81 (s, 6H, Ar(OCH ₃) ₂), 2.80-3.12 (dd, 1H, C ₄ -H-trans), 3.46-3.79 (dd, 1H, C ₂ -H cis), 5.63-5.89 (dd, 1H, C ₅ -H), 6.99-7.66 (m, 6H, Ar-H and thienyl-H)
L _{IV}	C ₁₆ H ₁₇ ClN ₂ O ₂ S	75	108	57.1 (57.4)	4.2 (4.5)	8.6 (8.4)	2.16 (s, 3H, COCH ₃), 3.50 (s, 3H, ArOCH ₃), 2.73-3.16, (dd, 1H, C ₂ -H trans), 3.35-3.82 (dd, 1H, C ₂ -H cis) 5.40-5.63 (dd, 1H, C ₅ -H cis 6.93-7.76 (m, 6H, Ar-H and thienyl H)
L _V	C ₁₆ H ₁₅ ClN ₂ O ₂ S	60	115	57.0 (57.4)	4.4 (4.5)	8.3 (8.4)	Same as in L _{IV} above
L _{VI}	C ₁₇ H ₁₇ ClN ₂ O ₃ S	70	125	55.6 (56.0)	4.2 (4.7)	7.3 (7.0)	2.23 (s, 3H, COCH ₃), 3.76 (s, 6H, Ar(OCH ₃) ₂), 2.83-3.23 (dd, 1H, C ₄ -H trans), 3.49-3.69 (dd, 1H, C ₂ -H cis), 5.63-5.86 (dd, 1H, C ₅ -H), 6.97-7.39 (m, 5H, Ar-H and thienyl H)

and also pointed to the presence of



coordinated sulphate. The effective magnetic moment values of the vanadyl complexes (Table II), calculated at room temperature (25°C), were in the normal range (1.72 - 1.77 B.M.) as expected for the spin-only value of a d¹-system and were consistent with mononuclear distorted octahedral complexes of oxovanadium(IV)¹⁷.

IR Spectra

In the IR spectra of the ligands the band due to $\nu(\text{C=O})$ at 1655-1640 cm⁻¹ was shifted to lower frequency, to 1635-1620 cm⁻¹, on complexation suggesting that coordination had taken place through the oxygen atom of the carbonyl group. The strong band at 1610-1600 cm⁻¹ assigned to the combination of $\nu(\text{C=N})$ and $\nu(\text{C=C})$ modes showed a spectral shift to lower frequency of the order of 20-35 cm⁻¹ which indicated coordination through the azomethine nitrogen. This was further confirmed by the shifting of the $\nu(\text{N-N})$ frequency from 980-930 cm⁻¹ to 960-945 cm⁻¹ in the spectra of the complexes¹⁸. The presence of mono-coordinated sulphate in these complexes was confirmed by the splitting of the antisymmetric stretching and bending vibrations (ν_3 and ν_4) of free sulphate ion into two bands at 1135, 1040 cm⁻¹ and 640, 610

Table II. Analytical and Magnetic Data of Oxovanadium(IV) Complexes of 1-Acetyl-5-aryl-3-substituted thienyl)-4,5-dihydropyrazoles

Compound	Empirical Formula	Yield %	Analytical data % Found (Reqd.)	H	N	Metal	μ_{eff} (B.M)
$[\text{VO}(\text{L}_I)_2\text{SO}_4]$	$\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_9\text{S}_3\text{V}$	65	50.7 (50.3)	4.4 (4.2)	7.0 (7.3)	6.2 (6.7)	1.72
$[\text{VO}(\text{L}_{II})_2\text{SO}_4]$	$\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_9\text{S}_3\text{V}$	60	50.0 (50.3)	4.3 (4.2)	7.8 (7.3)	6.2 (6.7)	1.73
$[\text{VO}(\text{L}_{III})_2\text{SO}_4]$	$\text{C}_{34}\text{H}_{36}\text{N}_4\text{O}_{11}\text{S}_3\text{V}$	68	50.1 (49.6)	4.8 (4.4)	6.4 (6.8)	6.4 (6.2)	1.77
$[\text{VO}(\text{L}_{IV})_2\text{SO}_4]$	$\text{C}_{34}\text{H}_{30}\text{Cl}_2\text{N}_4\text{O}_9\text{S}_3\text{V}$	75	46.4 (46.1)	3.2 (3.6)	6.5 (6.7)	6.0 (6.1)	1.72
$[\text{VO}(\text{L}_V)_2\text{SO}_4]$	$\text{C}_{34}\text{H}_{30}\text{Cl}_2\text{N}_4\text{O}_9\text{S}_3\text{V}$	70	46.0 (46.1)	3.4 (3.6)	6.2 (6.7)	6.5 (6.1)	1.74
$[\text{VO}(\text{L}_{VI})_2\text{SO}_4]$	$\text{C}_{34}\text{H}_{34}\text{Cl}_2\text{N}_4\text{O}_{11}\text{S}_3\text{V}$	69	45.4 (45.7)	3.4 (3.8)	6.8 (6.3)	5.2 (5.7)	1.72

The decomposition temperatures of all the complexes were > 230°C.

cm^{-1} , respectively, while the symmetric stretching vibration (ν_1) was located¹⁹ at 985 cm^{-1} . The characteristic ν ($\text{V}=\text{O}$) mode was observed in the $980\text{-}960 \text{ cm}^{-1}$ region. The ν ($\text{V}-\text{O}$) stretching mode which originated in the interaction of the cation with carbonyl oxygen was observed in the lower frequency region ($410\text{-}390 \text{ cm}^{-1}$) in the spectra of the complexes. No further splitting was observed in the ν ($\text{V}=\text{O}$) mode suggesting thereby that the ligands occupied equatorial positions with the vanadyl oxygen and unidentate sulphate at axial positions²⁰ (Fig. 2). The bands due to the thienyl moiety remained unaltered indicating the non-involvement of the sulphur atom of the thienyl group in coordination.

Electronic Spectra

The electronic spectra of the oxovanadium(IV) complexes exhibited a strong band at $760\text{-}750 \text{ nm}$ ($13,757\text{-}13,333 \text{ cm}^{-1}$) and a well defined shoulder at $635\text{-}615 \text{ nm}$ ($15,748\text{-}16,260 \text{ cm}^{-1}$). The main peak was assigned to the ${}^2\text{E} \longrightarrow {}^2\text{B}_2$ and the shoulder to the ${}^2\text{B}_1 \longrightarrow {}^2\text{B}_2$ transition according to the Ballhausen and Gray energy level diagram¹⁷.

ESR Spectra

In the X-band ESR spectra of powdered samples of four oxovanadium(IV) complexes, one signal around 3420G was observed. The ESR spectrum of $\text{VO}(\text{L}_{\text{II}})_2\text{SO}_4$ in DMF solution, shown

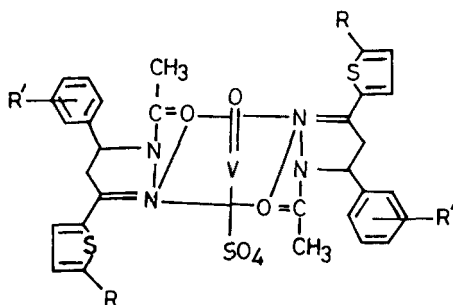


Fig.2. Suggested Structure of the Complexes

in Fig.3 (spectra of three other complexes were similar) exhibited a set of eight hyperfine lines arising due to the interaction of the unpaired electron of oxovanadium(IV) ion with the single vanadium nucleus²¹ (^{51}V , $I = 7/2$). The nature of the spectrum (Fig. 3) corresponded to a d^1 oxovanadium(IV) acceptor centre, placed in a distorted octahedral environment with the unpaired electron occupying predominantly the b_2 level in the ground state²². The g_{\parallel} , g_{\perp} and g_{iso} values for the complexes (Table III) were consistent with the reported values^{21,22}.

Investigation of Antimicrobial Activity

The antimicrobial activity of the ligands and their vanadyl complexes was evaluated for *in vitro* growth inhibition against phytopathogenic fungi viz., *Colletotrichum capsicum* and *Rhizoctonia solani* and bacteria viz., gram positive *Bacillus subtilis*

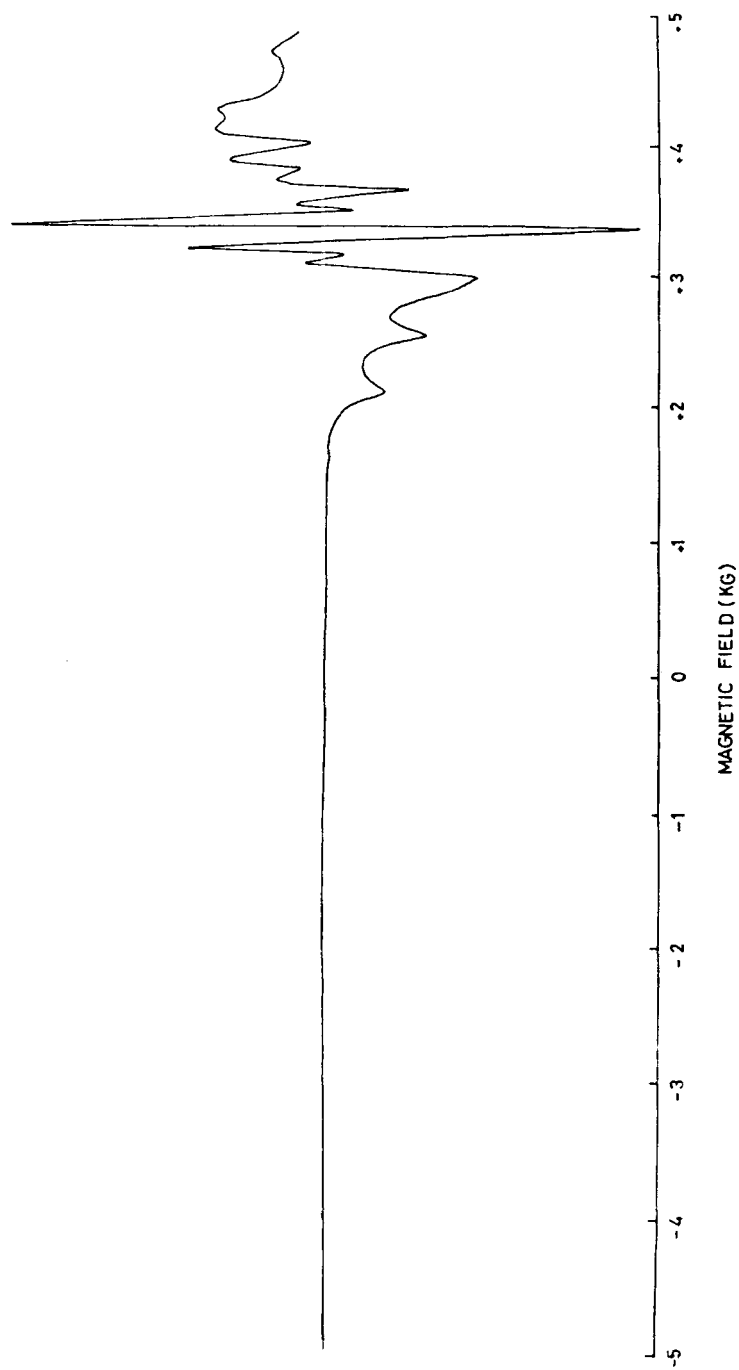


Fig.3. The Electronic Spin Resonance Spectrum of $\text{VO}(\text{Li})_2\text{SO}_4$ in DMF Solution at Room Temperature

Table III. The ESR Parameters of Vanadyl Complexes in DMF Solution at Room Temperature

Compound	g_{\parallel}	g_{\perp}	g_{iso}
$\text{VO}(\text{L}_\text{I})_2\text{SO}_4$	1.961	1.991	1.981
$\text{VO}(\text{L}_\text{II})_2\text{SO}_4$	1.968	1.993	1.984
$\text{VO}(\text{L}_\text{V})_2\text{SO}_4$	1.963	1.992	1.982
$\text{VO}(\text{L}_\text{VI})_2\text{SO}_4$	1.970	1.991	1.984

and *Escherichia coli* using the serial dilution technique²³. The stock solutions were prepared by dissolving the compounds in DMSO. Proper conditions (temperature, pH, necessary nutrients and growth media) were employed for the preparation of cultures of fungi and bacteria. The incubating period for fungi and bacteria was 72 h at 37°C and 24 h 28°C, respectively. The conventional fungicide 2-(methoxycarbamoyl)benzimidazole (bavistin) and bactericide streptopencillin were used for assessing the activity of the compounds. All the tests were carried out in triplicate and the concordant value reported. The plots (concentration vs. compounds) drawn to compare the fungicidal and bactericidal activities are given in Fig. 4. A comparative study of the MIC (minimum inhibitory concentration) values showed that the ligand L_I was active at more

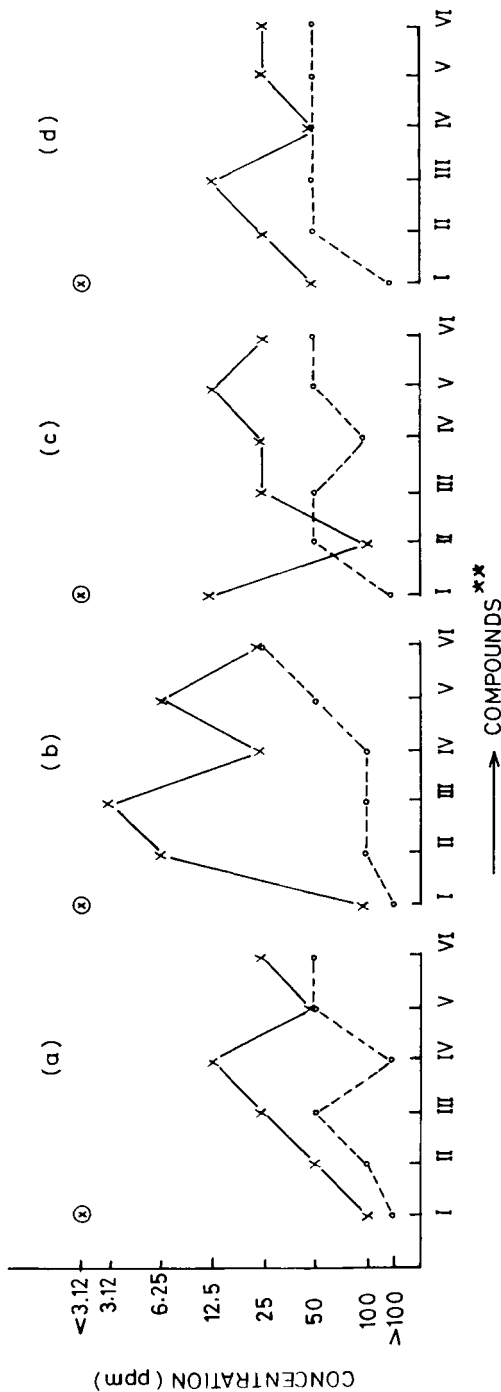


Fig.4. Antimicrobial Activity Data of Ligands L_I - L_{VI} (o.....o) and their Vanadyl Complexes (x---x) against *Colletotrichum capsicum* (a), *Rhizoctonia solani* (b), *Bacillus subtilis* (c) and *Escherichia coli* (d)

⊙ indicates standard fungicide and bactericide

** I-VI correspond to compounds L_I - L_{VI} (o.....o) and $VO(L_I)$ - $VO(L_{VI})_2$ (x---x)

than 100 ppm against *Colletotrichum capsicum*, *Rhizoctonia solani*, *Bacillus subtilis* and *Escherichia coli* but its vanadyl complex exhibited growth inhibition at 100, 100, 12.5 and 100 ppm respectively. The ligands L_{II} and L_{III} showed complete growth inhibition at 100 ppm against *Rhizoctonia solani* but their complexes were active at 6.25 and 3.12 ppm, respectively against this organism. The ligands L_{II}-L_{VI} were found to be active at 50 ppm against *E. coli* while activity of their vanadyl complexes varied between 50-12.5 ppm. A perusal of the antimicrobial activity data reveals that the activity of the ligands was enhanced on their chelation to the oxovanadium (IV) acceptor centre. However, none of the compounds possessed better inhibitory action than the conventional fungicide and bactericide.

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Referee II: K. Moedritzer

