Original Article

SYNTHESIS, CHARACTERIZATIONS AND *IN-VITRO* (ANTIMICROBIAL AND ANTIFUNGAL) STUDY OF OXOVANADIUM (IV) TETRAAZAMACROCYCLIC COMPLEX

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Abstract

The in situ reaction of 1,2-diaminobenzene and isatin/5-chloroisatin /5-bromoisatin in the existence of oxovanadium (IV) sulphate in methanol yielded a three different series of oxovanadium (IV) tetraazamacrocyclic complexes of type $[VO(mac)]SO_4$. On the basis of physio-chemical or elemental (CHN) analyses, conductance measurements, magnetic characteristics, spectral, and electron paramagnetic resonance (EPR) data (at ambient conditions and liquid nitrogen temperature), the newly synthesized complexes were satisfactorily characterised. For all of the complexes, the spectral investigations support a square pyramidal geometry. At room temperature, the synthesized oxovanadium(IV) complexes were found to be constant in air. The oxovanadium complexes were also verified *in-vitro* against gram-positive bacteria (*Bacillus subtilis, Staphlococcus aureus)*, and gram-negative (*Escherichia coli*), as well as fungal strains such as *Aspergillus niger* and *Candida albicans*. The findings were compared to those obtained with common antibiotics such as tetracycline and the antifungal medication fluconazole.

Keywords: Macrocyclic, oxovanadium (IV), 1,2-diaminobenzene, isatin, 5-choloroisatin,5-bromoisatin, antimicrobial, antifungal.

INTRODUCTION

In chemistry, the design and training of well-arranged metal-containing macrocycles is a fascinating issue [1,2]. In recent years, macrocyclic complex chemistry has aroused the interest of both in-organic and bio-inorganic chemists due to its popularity in the field of coordination chemistry [3]. Artificial macrocycles and associated metal complexes have piqued researchers' interest due to structural and functional similarities to naturally occurring macrocyclic compounds, as well as their diverse chemical activity [4-7]. Furthermore, the study of macrocyclic ligand metal complexes looks to be intriguing due to the possibility of creating coordination molecules with unique structures and stability [8]. The macrocycle's dimensions are determined by the nature of its contributor atoms, and the complexing behaviors of the anions involved in coordination have an impact on the creation of macrocyclic complexes [9-11].

Macrocyclic ligands are also theoretically interesting since they can provide a regulated shape and ligand field strength environment [12]. Macrocylic compounds and derivatives are stimulating ligand-systems and are

particularly useful in fundamental research, such as phase transfer catalysis and biological studies, because they are suitable hosts for metal anions, neutral molecules, and organic cation guests [13-17].

Several macrocyclic substances, both synthetic and natural, have been developed [18,19]. For decades, scientists have been interested in the household of complexes with aza-macrocyclic ligands [20-22]. In general, macrocyclic compounds have been synthesised using in-situ one-pot pattern condensation techniques [23,24]. The templating agent is transition metal ions [25]. In the process, metal ions preferentially favour cyclic rather than oligomeric or polymeric products [26-29]. The chemistry of oxovanadium (IV) has garnered a lot of attention since the VO^{2+} unit can coordinate a variety of donor atoms to generate a range of complexes [30**]**. This oxocation's interactions with a variety of biomolecules and other ligands of biological and pharmacological significance have been investigated [31]. Most of the study is presently focused on coordination complexes of VO2+ since it is probably the most relevant species present in biological systems since a number of systematic model studies on the interaction of this oxo cation with different proteins and other molecules. [32]. Due to its intriguing structural features, catalytic applications [33,34], and biological roles in a variety of biochemical processes such as halo-peroxidation [35], nitrogen fixation, phosphorylation [36,37], glycogen metabolism [38], and insulin mimicking [39], much research has recently focused on the coordination chemistry of vanadium complexes [39,40]. Vanadium has a wide range of coordination numbers, a strong affinity for oxygen, and the ability to serve as a Lewis acid, allowing it to be employed in redox and Lewis acid catalysed or promoted reactions [41,42]. Due to its intriguing medical and biological implications, vanadium complexes produced from a range of ligands have gained a lot of research in recent years [43]. Antibacterial, antifungal, and anticancer characteristics are among the biological features of Schiff bases and complexes [44-46]. Isatin-derived macrocyclic complexes with divalent metal ions have been observed [47-49]. However, there has been no comprehensive study of the chemistry of oxovanadium (IV) complexes with macrocyclic ligands such as isatin/5-chloroisatin/5-bromoisatin and 1,2-diaminobenzene. The current study discusses the synthesis and characterization of oxovanadium (IV) complexes with a new class of tetraazamacrocyclic ligands produced by the reaction of 1,2-diaminobenzene with isatin/5-chloroisatin/5-bromoisatin.

Various physicochemical approaches, including as elemental analysis, magnetic moment and conductance measurements, and spectrum (electronic, IR, and EPR) data, were used to describe the complexes. These macrocyclic complexes were further tested i*n vitro* for antibacterial activity against Gram negative *E. coli* (MTCC 40) and Gram positive *Bacillus subtilis* (MTCC 441), as well as *Staphlococcus aurcus* (MTCC 6571). The results were compared to those of the conventional antibiotic tetracycline. *Candida albicans* (MTCC 10180) and *Aspergillus niger* (MTCC 10180) were used in the antifungal experiments (MTCC 183). The results were compared to fluconazole, a commonly used antifungal medicine.

EXPERIMENTAL DETAILS

Materials Required

All of the solvents and compounds used were reagent grade and were not purified further. Aldrich Chemical Co. in England provided the oxyvanadium(IV) sulphate. Two bacteria, '*Escherichia coli* (MTCC 40)' and Gram positive '*Bacillus subtilis* (MTCC 441)', as well as one fungus, '*Aspergillus niger* (MTCC 10180)', were purchased from the Microbial Type Culture Collection and Gene Bank (MTCC) of the CSIR-Institute of Microbial Technology, Sector-39A Chandigarh, India, whereas one bacteria, '*Staphlococcus aureus* (MTCC 6571)', and one fungi '*Candida albicans* (MTCC 183') were collected from Department of Microbiology, BRD Medical college, Gorakhpur.

Analytical and Physical Measurements

A Perkin–Elmer 1400C analyzer was used to measure the elemental analyses (C,H,N). The vanadium metal was identified as 'vanadate' by gravimetric analysis. On a Jasco V650 Spectrophotometer, complex infrared spectra (4000–200 cm-1) were recorded as KBr pellets. Gouy's approach was used to determine magnetic susceptibility

at room temperature. The compounds' electronic spectra were acquired using a Shimadzu UV-2600 UV–Visible spectrophotometer and DMSO as a solvent. In DMSO(10-3M), conductance measurements were taken with an Elico conductivity bridge type CM-82 equipped with a dip type conductivity cell with Pt electrodes. The JEOL Model JES FA200 Electron Spin Resonance spectrometer was used to record electron paramagnetic resonance (EPR) spectra of complexes at room temperature and liquid nitrogen temperature.

Synthesis of macrocyclic complexes

Oxovanadium (IV) sulphate (0.01mol) dissolved in methanol ($20cm^3$) and subjected to heat, swirling methanolic solution ($50cm^3$) of 1,2-diaminobenzene (0.02mol). The solution was then refluxed for 30 minutes. Following that, isatin (0.02mol) dissolved in methanol (30 cm^3) was added to the refluxing mixture, which was then refluxed for another 12-20 hours. The required macrocyclic complex of [VO(mac)]SO4 was obtained by filtering, washing with methanol, and drying in vacuum oven a reddish brown to yellowish brown colored precipitate. The final yield obtained is 72-76%.

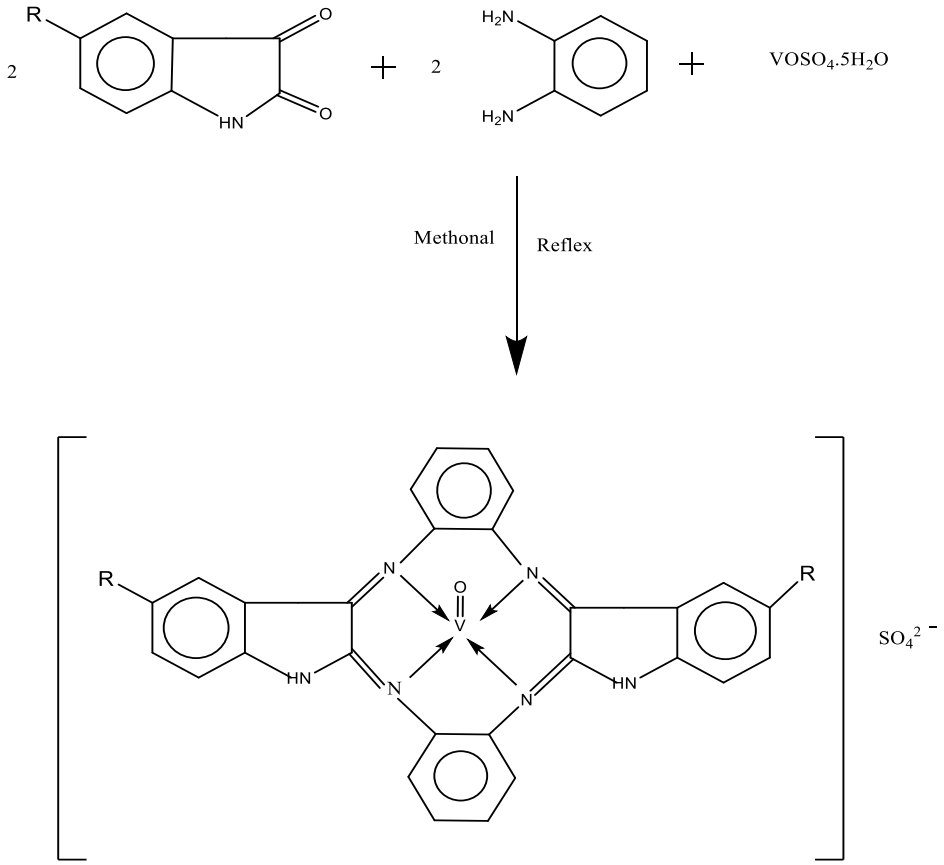
EXPERMIANTAL DETAILS OF ANTIMICROBIAL ACTIVITY

Staphlococcus aurcus and Bacillus subtilis both Gram positive and *Escherichia coli* Gram negative bacteria, and two fungus, *Aspergillus niger* and *Candida albicans*, were used to test all of the produced macrocyclic compounds for antibacterial activity. The minimum inhibitory concentrations (MICs) were determined using the agar well-diffusion method [50] to determine the nutritional agar medium (28 gm) for antibacterial activity and the sabouraud dextrose agar (SDA) medium (28 gm) for antifungal activity were combined with 1000 mL of double distilled water and autoclaved into an 80 mm sterile Petri plate. The medium was allowed to harden before 8 mm wells were bored with a sterile metallic borer. The test sample DMSO solution (2.0 mg / mL, 1.0 mg / mL, 0.5 mg / mL, 0.25 mg / mL, and 0.125 mg / mL) was then added to the respective wells. Tetracycline was utilised as a typical medicine for antibacterial action, whereas fluconazole was employed for antifungal activity. Each bacterial strain/fungal strain was generated in triplicate plates and incubated at 37°C for 24 hours/48 hours, respectively. The lowest concentration at which the chemical demonstrated inhibition zone was recorded as a minimum inhibitory concentration.

RESULTS AND DISCUSSION

The interactions of 1,2-diaminobenzene with isatin/5-chloroisatin/5-bromoisatin in the presence of vanadyl salt in a 2:2:1 molar ratio yielded a new series of tetraazamacrocyclic oxovanadium (IV) complexes with the postulated stoichiometry, as shown in Scheme-1.

Scheme-1: Synthetic route for macrocyclic complexes of Oxovanadium (IV)



(LXXXV)

(R= -H, 5-Br,5-Cl)

PHYSIO-CHEMICAL AND CONDUCTANCE MEASUREMENT

The findings of the energy dispersive X-ray analysis (EDX) qualitative elemental analysis for the synthesised oxovanadium (IV) complex are shown in Table 1. In Table 1, shows the calculated % elemental presence of Carbon, Hydrogen, Nitrogen, and Vanadium for all three complexes. Oxovanadium (IV) complexes produced in this study are stable in air at ambient temperature and soluble in dimethylsulphoxide and dimethylformamide. The compositions of the desired products are in agreement with the elemental analysis results for all produced ligands and complexes. Analytical data predicted that the chemical formula of the synthesized compound would be L1 = $C_{37}H45N_6O_5S$, which is reddish brown in colour, L2 = $C_{37}H_{43}$ $Br_2N_6O_5S$, which is brown in colour, and L3= $C_{37}H_{45}Cl_2N_6O_5S$, which is yellowish brown in colour. These empirical formulae are further supported by other spectral analyses also. The molar conductance values of the complexes in DMF lie in the range of ($VC_{37}H_{45}N_6O_5S$)~76 $\Omega^{-1}cm^2mol^{-1}$; ($VC_{37}H_{43}Br_2N_6O_5S$) ~85 $\Omega^{-1}cm^2mol^{-1}$ and ($VC_{37}H_{45}Cl_2N_6O_5S$)~90 $\Omega^{-1}cm^2mol^{-1}$ [51]. The molar conductance of the complexes indicates that they are 1:1 electrolytes, as evidenced by their molar conductance.

Table.1: Properties and analytical data of oxyvanadium (IV) complexes

Physical properties and analytical data of oxovanadium(IV) complexes.

Complex	Emperical formula	colour	yield(%)	conductance ($\Omega^{-1}cm^2\ mol^{-1}$)	Analysis %found (calcd.)			
					C	H	N	V
$[VO(mac_1)]SO_4$	$(VC_{37}H_{45}N_6O_5S)$	Reddish brown	76	74	69.34 (69.26)	7.04 (7.18)	13.10 (13.12)	7.92 (7.92)
$[VO(mac_2)]SO_4$	$(VC_{37}H_{43}Br_2N_6O_5S)$	Brown	74	85	55.62 (55.75)	5.41 (5.48)	10.50 (10.62)	6.36 (6.48)
$[VO(mac_3)]SO_4$	$(VC_{37}H_{43}Cl_2N_6O_5S)$	Yellowish Brown	72	90	62.61 (62.82)	6.10 (6.11)	11.82 (11.94)	7.15 (7.28)

Where,
mac_1 = macrocyclic ligands derived form 1,2-diaminobenzene and isatin
mac_2= macrocyclic ligands derived form 1,2-diaminobenzene and 5-bromoisatin
mac_3 = macrocyclic ligands derived form 1,2-diaminobenzene and 5-chloroisatin

Magnetic Moments and Electronic Spectra

The magnetic moments of the oxovanadium(IV) complexes at room temperature range from 1.70 to 175 B.M., corresponding to one unpaired electron ($d_1$species). For monomeric oxovanadium(IV) complexes, these values are ideal [52-54].

The electronic spectra of oxovanadium(IV) complexes with a square pyramidal or deformed octahedral geometry are most commonly analysed using Ballhausen and Gray's energy level methodology [55]. Usually, three optical bands are observed in the visible region, assigned to '$^2B_2(d_{xy}) \rightarrow {}^2E(d_{xz},d_{yz})$' ($\nu_1$), '$^2B_2(d_{xy}) \rightarrow {}^2B_1(d_{x2-y2})$'($\nu_2$), and '$^2B_2(d_{xy}) \rightarrow {}^2A_1(d_{z2})$' ($\nu_3$). The ν_3 band is often masked by intense charge–transfer absorptions. The nujol mull spectra of the complexes **(Table-2),** stated in this section, displays two bands at *ca.* 12,500–13,500 cm^{-1} (ν_1) and 18,700–19,500 cm^{-1} (ν_2) and one band at *ca.* 29,800 cm^{-1} is probably due to a oxo → vanadium(IV) charge–transfer mixed with '$d_{xy} \rightarrow d_{z2}$' ($\nu_3$) transition.

Table -2: Magnetic moments and electronic spectral bands of oxyvanadium (IV) complexes

Magnetic moments and electronic spectral bands of oxovanadium(IV) complexes

Complex	Electronic spectral bands (cm^{-1})			
	μ_{eff}(300 K)BM	$^2B_2 \rightarrow {}^2E$	$^2B_2 \rightarrow {}^2B_1$	$^2B_2 \rightarrow {}^2A_1$ + charge transfer
$[VO(mac_1)]SO_4$	1.75	13500	18700	29800
$[VO(mac_2)]SO_4$	1.70	13000	19000	29700
$[VO(mac_3)]SO_4$	1.72	12500	19500	29600

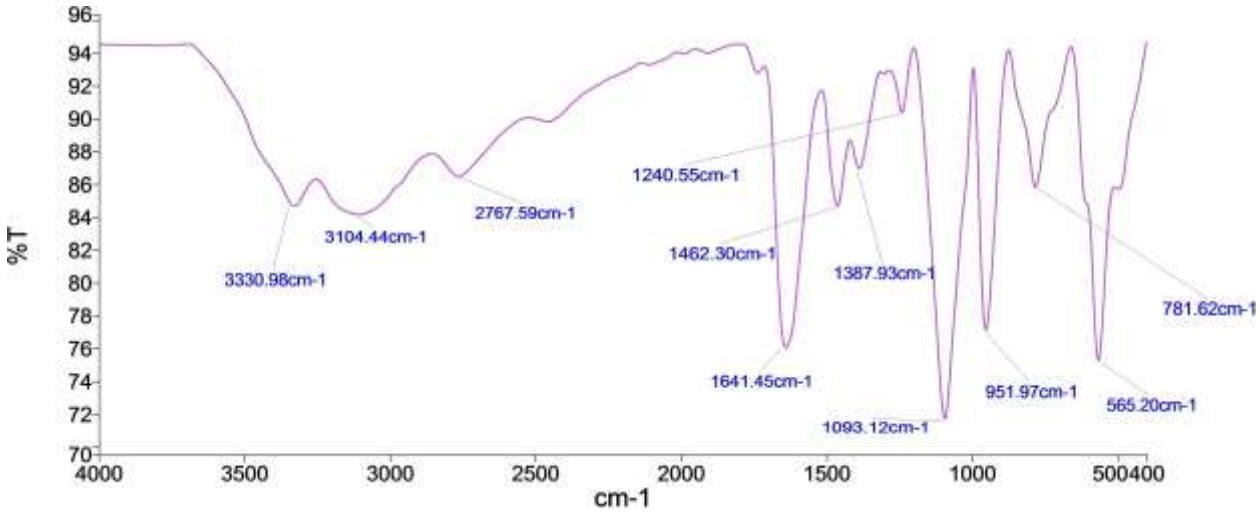
3.3 FT-IR spectra

Fig.1. Represents the FT-IR spectrum and interaction of molecules between them. Due to condensation of the amino group of 1,2-diaminobenzene with the keto group of isatins (isatin/5-chloroisatin/5-bromoisatin), a pair of medium intensity bands corresponding to $\nu(NH_2)$ were present in the infrared spectra of all synthesised oxovanadium(IV) complexes at 3240 and 3275 cm^{-1}, but were absent in the infrared spectra of all. In the spectra of isatins (isatin/5-chloroisatin/5-bromoisatin), a prominent transition band was found at roughly 1730 cm^{-1},

which might be attributable to the >C=O group. All of the oxovanadium (IV) complexes lacked this band in their spectra. This indicates that all of the produced complexes lack the >C=O group of isatins (isatin/5-chloroisatin/5-bromoisatin) and drives the condensation of the carbonyl group of isatins (isatin/5-chloroisatin/5-bromoisatin) and the amino group of 1,2-diaminobenzene [56,57].A prominent absorption band at 1595–1610 cm^{-1} could be attributed to the newly formed azomethine group *ν*(C=N). [58,59] These findings support the creation of the hypothesized macrocyclic ligand frameworks [60,61] The lower values of *ν*(C=N) can be explained by the drift of azomethine nitrogen's lone pair density towards the oxovanadium cation, as well as the coordination of azomethine nitrogen with oxovanadium [62]. Furthermore, the emergence of a prominent intensity band at roughly 400–420 cm^{-1} in all oxovanadium (IV) complexes corresponding to *ν*(V–N) indicates azomethine nitrogen coordination to oxovanadium (IV) [63].

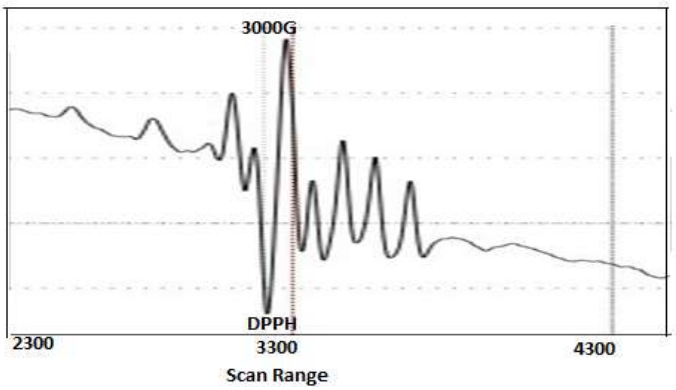
The existence of single medium intensity bands in the complexes in the range 3240–3350 cm^{-1} could be attributed to *ν*(N–H) stretching vibrations [64]. Another set of medium intensity bands in the 1500–1570 cm^{-1} range is due to *ν*(C=C) phenyl group vibrations [65], while bands in the 880–900 cm^{-1} region are assigned to (C–H) out of plane bending of phenyl groups [66]. The stretching vibrations ν(C–N) are found in the range of 1360–1010cm^{-1}. All oxovanadium (IV) complexes have new bands at roughly 980 cm–1 that are ascribed to the ν (V=O) vibration [67]. The emergence of three bands at ca. 1130((ν_3), 900((ν_1), and 610 cm–1((ν_4) showed the presence of an ionic sulphate group [68].Td symmetry is still retained despite the absence of a ν_2 band and non-splitting of the ν_3 band. In the presence of oxovanadium (IV) ion, the produced macrocyclic ligands act as an N_4 tetradentate ligand that coordinates to the oxovanadium (IV) cation via azomethine nitrogen.

Fig.1. FT-IR spectrum



Electron Paramagnetic Resonance *Analysis*

Fig.2. ESR Spectra of [VO(MDABCI)]SO4 in DMSO at Liquid Nitrogen Temperature



EPR spectroscopy can be used to determine the stereochemistry, ligand type, and degree of covalency of oxovanadium(IV) complexes. In the solid state, the electron paramagnetic resonance (EPR) or electron spin resonance (ESR) spectra of complexes display a single line with the characteristic g ≈1.97. The X-band EPR spectra of one representative complex oxovanadium(IV) in DMSO at Liquid nitrogen temperature is given in Fig.1.

At ambient conditions, the fluid solution (DMSO) spectra exhibit an eight-line arrangement, which is characteristic of mononuclear oxovanadium(IV) complexes (^{51}V; I = 7/2) with g_{iso} ≈1.97 and A_{iso} ≈ 0.009 cm^{-1}. The spectra display resolved axial anisotropy with two sets of eight line pattern at liquid nitrogen temperature. The $g_{\|}$, $g\perp$, $A_{\|}$ and $A\perp$ values were estimated and the values, thus obtained, are tabulated in Table 3. The results are representative of the spectra of "square–pyramidal" oxovanadium(IV) complexes with an un-paired [52,53] electron in a mainly "d_{xy}" orbital (ligand along x and y axes). The spectral characteristics acquired at ambient temperature and those obtained at liquid nitrogen temperature are nearly identical, demonstrating that the complexes preserve their structural identity over this temperature range [69].

Table -3: ESR paramters of oxyvanadium (IV) complexes

ESR parameters of oxovanadium(IV) complexes

Complex	g_{av}	$g_{\|}$	$g_{\perp}$	A_{av}	$A_{\|}$ $\times 10^4$ cm^{-1}	$A_{\perp}$
$[VO(mac_1)]SO_4$	1.972	1.952	1.982	89.0	165.0	50.0
$[VO(mac_2)]SO_4$	1.975	1.954	1.986	90.0	166.0	52.0
$[VO(mac_3)]SO_4$	1.974	1.956	1.983	92.0	168.0	54.0

Antimicrobial Activity

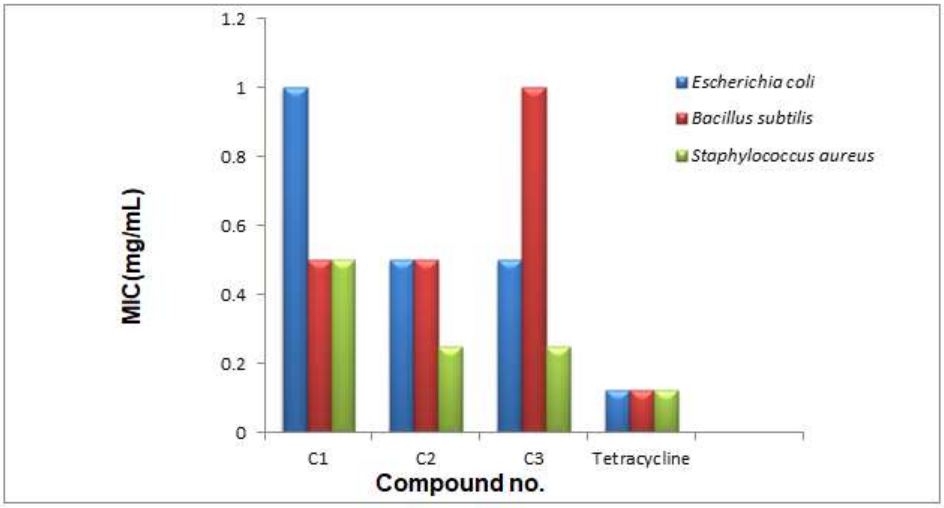
As stated in Table 4, all chemically produced complexes were evaluated in-vitro for antibacterial and antifungal activities. All of the complexes in the examined series demonstrated good to moderate antibacterial activity

against all bacterial strains. The complexes' MIC (minimum inhibitory concentration) was compared to the MIC of the conventional antibiotic tetracyclin. (Fig 2.,Table.4). The minimum inhibitory concentration (MIC) is the lowest antimicrobial agent concentration that precludes observable microorganism growth following an overnight incubation period. The compound [VO(mac2)]SO4 showed the highest activity (MIC=0.25mg/mL) against *S.aureus* and (MIC=0.50mg/mL) against *E.coli* and *B. subtilis.* The complex [VO(mac2)]SO4 demonstrated good activity by showing (MIC=0.25mg/mL) for *S.aureus* and (MIC=0.50mg/mL) for *E.coli* and *B.subtilis*. These findings show that the macrocyclic group's electron withdrawing groups play a crucial role in increasing activity. All oxovanadium(IV) complexes inhibited all Gram positive bacteria strains much more than Gram negative bacteria strains. Gram negative bacteria have an additional outer layer on their cell walls that functions as a barrier, requiring significant penetration of chemicals to reach the cells [69].

Table.4. Bactericidal screening data of Oxovanadium(IV) complexes

Compound	Minimum inhibitory concentration (MICs) in mg/mL		
	Gram - negative	Gram - positive	
	E. coli	*B.subtilis*	*S. aureus*
C1	1.00	0.50	0.50
C2	0.50	0.50	0.25
C3	0.50	1.00	0.25
Tetracycline	0.125	0.125	0.125

Fig.2. Comparison of MIC of complexes with standard antibiotic



Where,C1=$[VO(mac_1)]SO_4$, C2= $[VO(mac_2)]SO_4$ C3=$[VO(mac_3)]SO_4$

Antifungal Activity

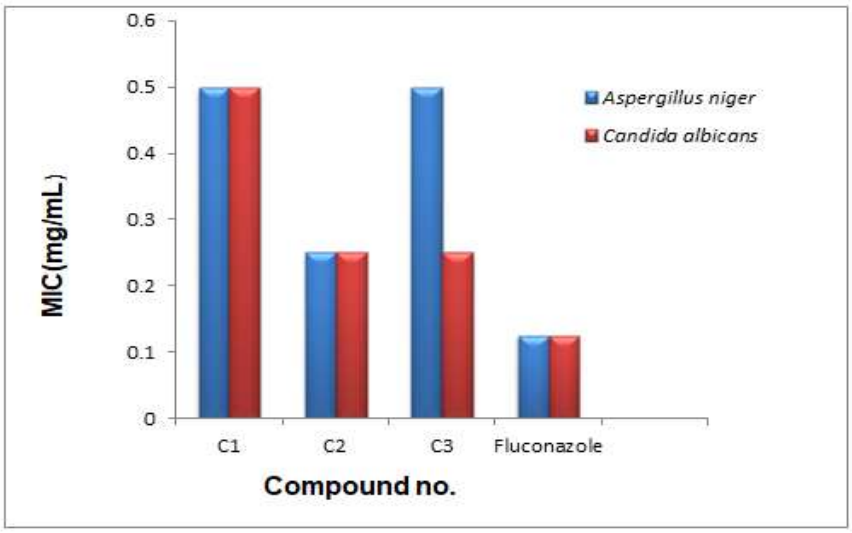
Antifungal activity experiments were performed on the fungal strains '*Aspergillus niger'* and '*Candida albicans'* (Table-5). The results were compared to fluconazole, a common antifungal medicine. The activity of oxyvanadium (IV) macrocyclic complexes containing the –Cl and $–NO_2$ groups was higher than that of other complexes. When compared to C.ablicans, several complexes had marginally higher activity against A.niger. Despite the fact that the complexes have activity, they are nowhere near as effective as the usual medicine fluconazole. Some substances are less efficient than others, and the difference in efficiency is due to either the

impermeability of microbe cells or modifications in the ribosomes of microbial cells [45]. Fig.3. depicts antifungal action.

Table.5. Fungicidal screening data of Oxovanadium (IV) complexes

Compound	Minimum inhibitory concentration (MICs) in mg/mL	
	Aspergillus niger	*Candia albicans*
C1	0.50	0.50
C2	0.25	0.25
C3	0.50	0.25
Fluconazole	0.125	0.125

Fig.3. Comparison of MIC of complexes with standard antifungal



CONCLUSION

By using a template reaction of substituted 1,2-diaminobenzene and substituted isatins, a novel series of oxovanadium (IV) complexes was created. VC37H45N6O5S (reddish brown), VC37H43 Br2N6O5S (brown), and VC37H45Cl2N6O5S (yellowish brown) are three distinct complexes with visible colour differences. Molar conductance in the range 74-90 $\Omega^{-1}cm^2mol^{-1}$ were obtained. The molar conductance of the complexes indicates that they are 1:1 electrolytes, as evidenced by their molar conductance. The infrared data demonstrate that ligands operate as set N4 chelating agents, bonding to the oxovanadium (IV) ion with all four azomethine nitrogen atoms. The magnetic moments of the oxovanadium (IV) complexes at room temperature range ~1.70 to 175 B.M. is determined. The square pyramidal geometry of synthesized complexes is observed. All the complexes of were tested for their antibacterial and antifungal activity against several microorganisms and showed moderate to good activity. The presence of electron withdrawing group increased the activity of complexes. Gram positive bacteria strains were inhibited substantially more by all oxovanadium (IV) complexes than Gram negative bacteria strains. Gram negative bacteria have an extra layer on their cell walls that acts as a barrier, requiring extensive chemical penetration to reach the cells. Several complexes demonstrated marginally stronger activity against A.niger than C.ablicans. Despite the fact that the complexes are active, they are not equivalent to fluconazole, which is commonly recommended.

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Conflict of Interest

No conflict of interest between authors

Abbreviations

DMF-N,N dimethylformamide, DMSO-dimethylsulfoxide, B.M._Bohr Mangeton, IR-Infra red, EPR- Electron paramagnetic resonance, MIC-Minimum Inhibitory Concentration,MTCC- Microbial Type Culture Collection SDA-Sabouraud Dextrose Agar , DOTA-tetraazacyclododecanetetraacetic acid.

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