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ORIGINAL ARTICLE

Some biologically active oxovanadium(IV) complexes of triazole derived Schiff bases: their synthesis, characterization and biological properties

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Abstract

A series of biologically active oxovanadium(IV) complexes of triazole derived Schiff bases $\mathbf{L}_1$–$\mathbf{L}_5$ have been synthesized and characterized by their physical, analytical, and spectral data. The synthesized ligands potentially act as bidentate, in which the oxygen of furfural and nitrogen of azomethine coordinate with the oxovanadium atom to give a stoichiometry of vanadyl complexes 1:2 (M:L) in a square-pyramidal geometry. *In vitro* antibacterial and antifungal activities on different species of pathogenic bacteria (*E. coli*, *S. flexneri*, *P. aeruginosa*, *S. typhi*, *S. aureus*, and *B. subtilis*) and fungi (*T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani*, and *C. glabrata*) have been studied. All compounds showed moderate to significant antibacterial activity against one or more bacterial strains and good antifungal activity against most of the fungal strains. The brine shrimp bioassay was also carried out to check the cytotoxicity of coordinated and uncoordinated synthesized compounds.

Keywords: *Triazole Schiff base; oxovanadium(IV) complexes; antibacterial; antifungal*

Introduction

Diabetes mellitus (DM) is a lethal metabolic disease, which is caused by an increased blood sugar level. Chronic diabetes mellitus becomes a source of various secondary diseases such as retinopathy, microangiopathy, renal dysfunction, atherosclerosis, and ocular and cardiac disorders[1]. Many drug therapies are in practice to address this severe emerging issue. Amongst them, vanadium-based metallotherapy has proved[2,3] to be one of the most effective clinical remedies. Vanadium is an important trace transition metalloelement that exists in variable oxidation states, and many reports prove its insulin mimetic activity[4,5]. It interacts mostly with those biomolecules that have negatively charged oxygen donor groups such as carboxylate, phenolate, phosphate, phosphonate, and hydroxamate[6]. Apart from the potential insulin mimetic activity, the structural behavior of various vanadyl compounds is also a subject of great interest. The mechanism involved in the insulin-like effects of vanadium compounds is not yet clearly understood[7].

Triazoles are extensively used as potential ligands in various bioinorganic syntheses. They coordinate to the metal ion in many ways, depending upon the nature of the functional groups[8–11]. Studies have indicated that many triazole derived Schiff bases show antibacterial[12–14], antifungal[15,16], antimicrobial[17–20], anticancer[21,22], analgesic[23], anticonvulsant[24], antitumor[25–27], antitubercular[28–31], insecticidal, herbicidal, and plant growth regulatory[32–34] activities. Due to increased interest in the chemistry of vanadyl compounds and the potentially bioactive nature of triazoles, we have made an effort to combine the chemistry of vanadium(IV) with newly synthesized triazole Schiff bases $\mathbf{L}_1$–$\mathbf{L}_5$ (Scheme 1). The vanadyl(IV) Schiff base compounds were formed with a stoichiometric ratio of M:L (1:2) where M = V(IV) and L = $\mathbf{L}_1$–$\mathbf{L}_5$. The synthesized compounds have been characterized by their physical, analytical, and spectral data. In order to evaluate the effect of vanadium(IV) metal on the antibacterial and antifungal activity of the newly synthesized compounds, the synthesized Schiff bases and their vanadyl(IV) complexes have been subjected to *in vitro* antibacterial activity testing against *Escherichia coli*, *Shigella flexneri*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis* and

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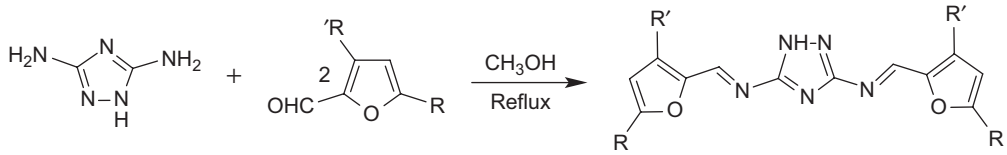


L_1 R = R′ = H
L_2 R = CH_3, R′ = H
L_3 R = H, R′ = CH_3
L_4 R = Cl, R′ = H
L_5 R = NO_2, R′ = H

Scheme 1. Preparation of proposed ligands.

antifungal activity testing against *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani*, and *C. glabrata*. The *in vitro* brine shrimp bioassay has also been carried out to study the cytotoxic properties of these compounds.

Materials and methods

All reagents and solvents used were of analytical grade. Infrared (IR) spectra were recorded on a Shimadzu FT-IR spectrophotometer. Elemental analysis was carried out on a PerkinElmer analyzer. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin Avance DPX-400 spectrometer using tetramethylsilane (TMS) as an internal standard and dimethylsulfoxide (DMSO)-d_6 as a solvent. Electron impact mass spectra (EIMS) were recorded on a Jeol MS Route instrument. *In vitro* antibacterial, antifungal, and cytotoxic properties were studied at the HEJ Research Institute of Chemistry, International Center for Chemical Sciences, University of Karachi, Pakistan.

Synthesis of Schiff base ligands

General procedure

*N,N′-Bis[(E)-furan-2-ylmethylidene]-1H-1,2,4-triazole-3,5-diamine (**L1**)* To a hot, magnetically stirred methanol (40 mL) solution of 3,5-diamino-1,2,4-triazole (0.99 g, 0.01 M), furan-2-carboxaldehyde (1.66 mL, 0.02 M) in methanol (20 mL) was added with constant stirring. The solution was refluxed for 4 h, during which a precipitated product was formed. The solution was refluxed for another 1 h. It was then cooled to room temperature, filtered, washed with methanol (3 × 5 mL) then with diethyl ether (2 × 5 mL), and dried. The same method was applied for the preparation of all other ligands $\mathbf{L_2}$–$\mathbf{L_5}$.

Physical, analytical, and spectral data of the ligands

N,N′-Bis[(E)-furan-2-ylmethylidene]-1H-1,2,4-triazole-3,5-diamine (L_1)

Yield (1.90 g, 74%); m.p. 172°C; IR (KBr, cm^{-1}): 3188 (NH), 1020 (N-N), 1627 (HC=N), 1610 (C=N, triazole), 1579, 1560 (C=C); ^{1}H NMR (DMSO-d_6): δ 7.1 (dd, 2H, furanyl), 7.39 (d, 2H, furanyl), 7.93 (d, 2H, furanyl), 8.75 (s, 2H, N=CH), 11.92 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 122.73, 126.15, 138.26, 146.39 (furanyl), 155.19, (2 × C, triazole), 166.2 (C=N, azomethine); EIMS (70 eV) *m/z* (%): 255 ([M]$^+$, 23), 228 (98), 177 (100), 161 (8), 134 (11), 121 (73), 120 (29), 108 (10), 97 (10), 78 (20), 52 (18); Anal. Calcd. for $C_{12}H_9N_5O_2$ (255.23): C, 56.47; H, 3.55; N, 27.44; Found: C, 56.43; H, 3.53; N, 27.38%.

N,N′-Bis[(E)-(5-methylfuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine (L_2)

Yield (1.16 g, 81%); m.p. 236°C; IR (KBr, cm^{-1}): 3195 (NH), 1019 (N-N), 1626 (HC=N), 1609 (C=N, triazole), 1581, 1563 (C=C); ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 6H, CH_3), 7.07 (d, 2H, furanyl), 7.23 (d, 2H, furanyl), 8.64 (s, 2H, N=CH), 11.84 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 14.5 (CH_3-furanyl), 121.33, 124.92, 141.67, 147.71 (furanyl), 155.12 (2 × C, triazole), 164.82 (C=N, azomethine); EIMS (70 eV) *m/z* (%): 283 ([M]$^+$, 36), 268 (8), 191 (100), 176 (16), 134 (23), 120 (22), 78 (19), 63 (13); Anal. Calcd. for $C_{14}H_{13}N_5O_2$ (283.28): C, 59.36; H, 4.63; N, 24.72; Found: C, 59.32; H, 4.60; N, 24.65%.

N,N′-Bis[(E)-(3-methylfuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine (L_3)

Yield (0.96 g, 67%); m.p. 242°C; IR (KBr, cm^{-1}): 3192 (NH), 1018 (N-N), 1628 (HC=N), 1608 (C=N, triazole), 1583, 1565 (C=C); ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 6H, CH_3), 7.11 (d, 2H, furanyl), 7.74 (d, 2H, furanyl), 8.68 (s, 2H, N=CH), 11.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 11.3 (CH_3-furanyl), 119.86, 125.11, 139.3, 146.63 (furanyl), 155.95 (2 × C, triazole), 164.44 (C=N, azomethine); EIMS (70 eV) *m/z* (%): 283 ([M]$^+$, 16), 268 (100), 253 (35), 191 (21), 176 (34) 134 (13), 108 (48), 81 (14), 53 (10); Anal. Calcd. for $C_{14}H_{13}N_5O_2$ (283.28): C, 59.36; H, 4.63; N, 24.72; Found: C, 59.34; H, 4.59; N, 24.78%.

N,N′-Bis[(E)-(5-chlorofuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine (L_4)

Yield (1.64 g, 72%); m.p. 227°C; IR (KBr, cm^{-1}): 3185 (NH), 1021 (N-N), 1630 (HC=N), 1612 (C=N, triazole), 1576, 1557 (C=C), 810 (C-Cl); ^{1}H NMR (DMSO-d_6): δ 7.32 (d, 2H, furanyl), 7.39 (d, 2H, furanyl), 8.78 (s, 2H, N=CH), 11.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 123.81, 128.35, 136.61, 148.23 (furanyl), 157.65 (2 × C, triazole), 165.18 (C=N, azomethine); EIMS (70 eV) *m/z* (%): 324 ([M]$^+$, 22), 289 (100), 253 (15), 176 (8), 155 (16), 140 (14), 134 (24), 129 (19), 112 (16), 76 (11); Anal. Calcd. for $C_{12}H_7Cl_2N_5O_2$ (324.12): C, 44.47; H, 2.18.; N, 21.61; Found: C, 44.43; H, 2.12; N, 21.57%.

N,N′-Bis[(E)-(5-nitrofuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine (L_5)

Yield (1.96 g, 80%); m.p. 198°C; IR (KBr, cm^{-1}): 3180 (NH), 1023 (N-N), 1632 (HC=N), 1613 (C=N, triazole), 1570, 1555 (C=C), 1355 (NO_2); ^{1}H NMR (DMSO-d_6): δ 7.84 (d, 2H, furanyl), 7.99 (d, 2H, furanyl), 8.86 (s, 2H, N=CH), 12.1 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ 121.12, 127.34, 142.71, 149.65 (furanyl), 158.1 (2×C, triazole), 166.12 (C=N, azomethine); EIMS (70 eV) *m/z* (%): 345 ([M]$^+$, 6), 299 (12), 222 (100), 176 (22), 166 (11), 152 (24), 134 (62), 110 (13), 79 (53), 68 (9), 57 (25), 51 (26); Anal. Calcd. for $C_{12}H_7N_7O_6$ (345.22): C, 41.75; H, 2.04; N, 28.40; Found: C, 41.79; H, 2.08; N, 28.38%.

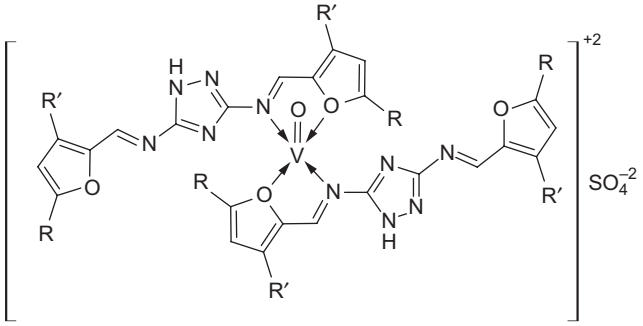
Synthesis of vanadyl(IV) complexes

General procedure

*Oxovanadium(IV) complex of N,N′-bis[(E)-furan-2-ylmethylidene]-1H-1,2,4-triazole-3,5-diamine (**1**)* To a hot, magnetically stirred 1,4-dioxane (50 mL) solution of L_1 (1.02 g, 0.002 mol), a methanolic solution (20 mL) of vanadyl sulfate (0.163 g, 0.001 mol) was added. The mixture was refluxed for 3 h during which precipitated product was formed. It was then cooled to room temperature. The precipitates thus formed were filtered, washed with methanol (3×5 mL) then with diethyl ether, and dried. All other complexes (**2**)–(**5**) were prepared following the same method using the same vanadyl salt with different ligands, respectively (Figure 1).

Antibacterial studies

All the synthesized compounds L_1–L_5 and their oxovanadium(IV) complexes (**1**)–(**5**) were screened *in vitro* for their antibacterial activity against four Gram-negative (*E. coli*, *S. flexneri*, *P. aeruginosa*, *S. typhi*) and two Gram-positive (*S. aureus*, *B. subtilis*) bacterial strains by the agar-well diffusion method[35,36]. The wells (6 mm in diameter) were dug in the media with the help of a sterile metallic borer with centers at least 24 mm apart. Two to eight hours old bacterial inocula containing approximately 10^4–10^6 colony-forming units (CFU/mL) were spread on the surface of the nutrient agar with the help of a sterile cotton swab. The recommended concentration of test sample (1 mg/mL in DMSO) was introduced in the respective wells. Other wells supplemented with DMSO and reference antibacterial drug, imipenem, served as negative and positive controls, respectively. The plates were incubated at 37°C for 24 h. Activity was determined by measuring the diameter of the zone showing complete inhibition (mm). In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with solutions of DMSO alone and showed no activity against any bacterial strain.



(1)–(5)

VO(IV) N,N′-bis[(E)-furan-2-ylmethylidene]-1H-1,2,4-triazole-3,5-diamine **(1)**
VO(IV) N,N′-bis[(E)-(5-methylfuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine **(2)**
VO(IV) N,N′-bis[(E)-(3-methylfuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine **(3)**
VO(IV) N,N′-bis[(E)-(5-chlorofuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine **(4)**
VO(IV) N,N′-bis[(E)-(5-nitrofuran-2-yl)methylidene]-1H-1,2,4-triazole-3,5-diamine **(5)**

Figure 1. Proposed structure of the oxovanadium(IV) complexes.

Antifungal activity (in vitro)

Antifungal activities of all compounds were studied[37] against six fungal strains (*T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani*, and *C. glabrata*). Sabouraud dextrose agar (Oxoid, Hampshire, England) was seeded with 10^5 CFU/mL fungal spore suspensions and transferred to Petri plates. Disks soaked in 20 mL (200 µg/mL in DMSO) of the compounds were placed at different positions on the agar surface. The plates were incubated at 32°C for 7 days. The results were recorded as percentage inhibition and compared with standard drugs miconazole and amphotericin B.

Minimum inhibitory concentration

Compounds containing high antibacterial activity were selected for minimum inhibitory concentration (MIC) studies. The minimum inhibitory concentration was determined using the disk diffusion technique[38] by preparing disks containing 10, 25, 50, and 100 µg/mL of the compounds and applying the protocol[39].

Cytotoxicity (in vitro)

Brine shrimp (*Artemia salina* Leach) eggs were hatched in a shallow rectangular plastic dish (22×32 cm) filled with artificial seawater, which was prepared with a commercial salt mixture and double distilled water. An unequal partition was made in the plastic dish with the help of a perforated device. Approximately 50 mg of eggs were sprinkled into the large compartment, which was darkened, while the other compartment was opened to ordinary light. After 2 days a pipette collected nauplii from the light side. A sample of the test compound was prepared by dissolving 20 mg of each compound in 2 mL of dimethyl formamide (DMF). From this stock solution, 500, 50, and 5 µg/mL were transferred to nine vials (three for each dilution were used for each test sample, and LD_{50} is the mean of three values) and one vial was kept as a control, having 2 mL of DMF only. The solvent was allowed to evaporate overnight. After 2 days, when shrimp larvae were ready, 1 mL of seawater and 10 shrimps were added to each vial (30 shrimps/dilution) and the volume was adjusted with seawater to 5 mL per vial. After 24 h the number of survivors was counted. Data were analyzed by a Finney computer program to determine the LD_{50} values[40,41].

Results and discussion

Chemistry

The triazole-derived Schiff bases $\mathbf{L_1}$–$\mathbf{L_5}$ were prepared as shown in Scheme 1. All ligands were only soluble in dioxane, DMF, and DMSO, but not in common organic solvents. The composition of the ligands is consistent with their micro-analytical data. The oxovanadium(IV) complexes (**1**)–(**5**) were prepared according to the following equations:

$$VOSO_4 + 2\,\text{Ligand (L)} \rightarrow [VO(L)_2]SO_4^{-2}$$
$$L = \mathbf{L_1} - \mathbf{L_5}$$

Physical measurements and micronalytical data for complexes (**1**)–(**5**) are given in Table 1.

Physical measurements (*conductance and magnetic susceptibility*)

The molar conductance values (in DMF) of complexes (**1**)–(**5**) fall within the range 80–89 Ω^{-1} cm^2 mol^{-1} (Table 2), showing their electrolytic[42] nature. The room temperature magnetic moment values of the complexes are given in Table 2. The observed magnetic moment (1.70–1.78 BM) is consistent with half-spin (S = 1/2) square-pyramidal geometry of the oxovanadium(IV) complexes[43].

IR spectra

IR spectra of the Schiff bases showed the absence of bands at 1735 and 3325 cm^{-1}, originally assigned to carbonyl ν(C=O) and ν(NH_2) stretching vibrations. The appearance of a strong new band at 1626–1632 cm^{-1} gave a clue of condensation of the carbonyl ν(C=O) group of furfuraldehyde with the amino groups of triazole to develop an azomethine ν(HC=N) linkage[44]. IR peaks at 1610–1613 cm^{-1} and 1555–1583 cm^{-1} were assigned to ν(C=N) and ν(C=C), respectively. Comparison of the IR spectra of the Schiff bases with their vanadyl complexes indicated that the Schiff bases were principally coordinated to the metal ion bidentately through oxygen of furfural and nitrogen of triazole. The band appearing at 1616–1623 cm^{-1} in the spectra of the vanadyl complexes due to the azomethine vibration was shifted to a lower frequency by 10–15 cm^{-1}, indicating[45] coordination of the azomethine nitrogen to the vanadyl metal atom. Furthermore, the coordination of these Schiff bases with the vanadyl metal ion was confirmed by the appearance of weak low-frequency new bands at 455–466 and 485–496 cm^{-1}, assigned to ν(V-N) and ν(V-O), respectively (Table 2). These new bands were only assignable to the spectra of the vanadyl complexes and not to the spectra of the Schiff bases. This, in turn, supported the evidence of the participation of heteroatoms, O and N, in the coordination. The presence of a band at 3180–3195, 1605–1611, and 1018–1023 cm^{-1}, due to NH, C=N, and N-N vibrations of triazole, remained unchanged in all the ligands, indicating that NH, C=N, and N-N of triazole were not taking part in the complexation, respectively. In all the vanadyl complexes, bands appearing at 978–982 and 1085–1088 cm^{-1} were assigned to ν(V=O)[43] and attributed due to SO_4[46]. All this evidence corresponds with formation of the vanadyl(IV) complexes with the prepared Schiff bases.

^{1}H NMR spectra

^{1}H NMR spectra of the free ligands were recorded in DMSO-d_6. The ^{1}H NMR spectral data along with the possible assignments are recorded above in "Physical, analytical, and spectral data." All the protons due to heteroaromatic/aromatic groups were found to be in their expected region[47]. ^{1}H NMR spectra of the compounds $\mathbf{L_1}$–$\mathbf{L_5}$ displayed a characteristic azomethine (CH=N) peak at δ 8.64–8.86 as a singlet, and protons of the furanyl ring fell in the region of δ 7.07–7.99

Table 1. Micronalytical data of the oxovanadium(IV) complexes.

				Calc. (Found) (%)		
No.	Complex	M.P. (dec.) (°C)	Yield (%)	C	H	N
(**1**)	$[VO(\mathbf{L_1})_2]SO_4$ [673.15] $C_{24}H_{18}N_{10}O_9SV$	239–241	90	42.80 (42.76)	2.69 (2.67)	20.80 (20.77)
(**2**)	$[VO(\mathbf{L_2})_2]SO_4$ [729.19] $C_{28}H_{26}N_{10}O_9SV$	260–262	85	46.10 (46.07)	3.59 (3.56)	19.20 (19.16)
(**3**)	$[VO(\mathbf{L_3})_2]SO_4$ [729.19] $C_{28}H_{26}N_{10}O_9SV$	254–256	89	46.10 (46.05)	3.59 (3.57)	19.20 (19.17)
(**4**)	$[VO(\mathbf{L_4})_2]SO_4$ [810.18] $C_{24}H_{14}Cl_4N_{10}O_9SV$	246–248	83	35.53 (35.49)	1.74 (1.71)	17.27 (17.25)
(**5**)	$[VO(\mathbf{L_5})_2]SO_4$ [853.39] $C_{24}H_{14}N_{14}O_{17}SV$	220–222	87	33.78 (33.74)	1.65 (1.63)	22.98 (22.95)

Table 2. Physical, spectral, and IR data of oxovanadium(IV) complexes.

No.	Ω_M (Ω^{-1} cm^2 mol^{-1})	BM (μ_{eff})	λ_{max} (cm^{-1})	IR (cm^{-1})
(**1**)	80	1.78	13,339, 18,805, 29,860	1616 (HC=N), 490 (V-O), 455 (V-N), 978 (V=O), 1088 (SO_4)
(**2**)	82	1.75	13,298, 18,826, 29,875	1619 (HC=N), 485 (V-O), 461(V-N), 980 (V=O), 1086 (SO_4)
(**3**)	87	1.73	13,258, 18,845, 29,903	1618 (HC=N), 491 (V-O), 458(V-N), 982 (V=O), 1087 (SO_4)
(**4**)	85	1.70	13,376, 18,870, 29,944	1621 (HC=N), 495 (V-O), 466(V-N), 981 (V=O), 1085 (SO_4)
(**5**)	89	1.76	13,402, 18,889, 29,965	1623 (HC=N), 496 (V-O), 463(V-N), 979 (V=O), 1087 (SO_4)

as doublets, except for the H-3 proton of $\mathbf{L}_1$ that was found at δ 7.1 as a double doublet. A singlet at δ 11.84–12.1 was observed for the NH proton in all ligands. Ligands $\mathbf{L}_2$ and $\mathbf{L}_3$ displayed a singlet at around δ 2.26–2.36, attributable to the methyl group. Furthermore, the number of protons calculated from the integration curves[48] and those obtained from the values of the expected, CHN analysis agreed well with each other.

^{13}C NMR spectra

^{13}C NMR spectra of the free ligands were also recorded in DMSO-d_6. The ^{13}C NMR spectral data along with the possible assignments are recorded above in "Physical, analytical, and spectral data." The conclusions drawn from these studies present further support to the modes of bonding discussed above for their IR and ^{1}H NMR spectra. The ^{13}C NMR spectra of the ligands $\mathbf{L}_1$–$\mathbf{L}_5$ showed an azomethine carbon (CH=N) at δ 164.44–166.2. The furanyl carbons were present in the region of δ 119.86–149.65. Triazole carbons appeared in the region of δ 155.12–158.1 in all ligands. In $\mathbf{L}_2$–$\mathbf{L}_3$, ($CH_3 \times 4$) appeared in the region of δ 11.84–11.89. Moreover, the numbers of carbons present were well in agreement with the expected values.

Mass spectra

The electron impact mass spectral (EIMS) compositions were: $C_{12}H_9N_5O_2$, 255 (calcd. 255.23); $C_{14}H_{13}N_5O_2$, 283 (283.28); $C_{14}H_{13}N_5O_2$, 283 (283.28); $C_{12}H_7Cl_2N_5O_2$, 324 (324.12); $C_{12}H_7N_7O_6$, 345 (345.22). $\mathbf{L}_1$ showed a base peak at 177 of fragment $[C_7H_7N_5O]^+$; for $\mathbf{L}_2$ this was observed at 267 of fragment $[C_{13}H_9N_5O_2]^+$; for $\mathbf{L}_3$ at 267 of fragment $[C_{13}H_9N_5O_2]^+$; for $\mathbf{L}_4$ at 288 of fragment $[C_{12}H_7ClN_5O_2]^+$; and for $\mathbf{L}_5$ at 299 of fragment $[C_{12}H_7N_6O_4]^+$; these are the most expected stable fragments. The most likely fragmentation pattern followed the cleavage of C=N (exocyclic as well as endocyclic), C=C, C-C, C-Cl, and C-NO_2 bonds.

Electronic spectra

The electronic spectra of the oxovanadium(IV) complexes in DMF exhibited three distinct low-intensity bands (labeled as ν_1, ν_2 and ν_3) which were assigned to b_2 (d_{xy}) → e_π(d_{xz}, d_{yz}), b_2 (d_{xy}) → b_1 ($d_{x^2-y^2}$), and b_2 (d_{xy}) → a_1 (d_{z^2}) transitions, respectively[49]. The first band at 13,250–13,410 cm^{-1} can be assigned to $b_2 \rightarrow e_\pi$ d-d transitions. The second band at 18,790–18,910 cm^{-1} can be attributed to $b_2 \rightarrow b_1$, and the band at 29,850–29,970 cm^{-1}can be assigned to transitions $b_2 \rightarrow a_1$. These observations correspond with the square-pyramidal geometry of the oxovanadium(IV) complexes[50–52].

Biological activity

Antibacterial bioassay (in vitro)

The *in vitro* antibacterial results are summarized in Table 3 and Figures 2 and 3. The antibacterial studies revealed that all the triazole derived Schiff bases and their oxovanadium(IV) complexes contributed significantly toward enhancing the biological activity. It is evident that coordination made the ligands more strongly antibacterial and inhibited the growth of bacteria more, compared with the parent ligand[53,54]. All compounds were tested against four Gram-negative (*E. coli*, *S. flexneri*, *P. aeruginosa*, *S. typhi*) and two Gram-positive (*S. aureus*, *B. subtilis*) bacterial strains (Table 3) according to literature protocols[35,36]. The results were compared with those of the standard drug imipenem (Figure 2). The percentage of activity was compared with the activity of the standard drug, considering its activity as 100%. All ligands and their vanadyl complexes possessed good biological activity against all Gram-negative and Gram-positive bacterial strains. $\mathbf{L}_1$ showed significant (57%) activity against *S. flexneri*, (b), and a weaker (30%) activity against *S. typhi*, (d). A greater (42.5%) activity for *P. aeruginosa*, (c), was found than for (d) and less than for (b). The ligand $\mathbf{L}_2$ possessed good (43.33%) activity against *B. subtilis*, (f), and weaker (25.71%) against *E. coli*, (a). $\mathbf{L}_3$ exhibited maximum (66.66%) activity against (f), weakest (26%) against (d), and moderate (65%) activity against *S. aureus*, (e). Similarly, $\mathbf{L}_4$ possessed maximum (70%) activity against (e), weakest (28.57%) against (b), and (45%) against (c). $\mathbf{L}_5$ showed significant (70%) activity against (e), weaker (23%) against (b), and moderate (30%) against (c). Compounds (**1**)–(**5**) exhibited overall a significant activity against (a)–(f), except (b). The results of these studies indicate that antibacterial activity was overall enhanced upon complexation (Figure 2). On comparison, the metal complex (**1**) showed significant (80%) activity against (b) and (d). Compound (**2**) had maximum (85%) activity against

Table 3. Antibacterial activity (concentration used 1 mg/mL of DMSO) of triazole derived Schiff bases and oxovanadium(IV) complexes.

	Zone of inhibition (mm)										
Bacteria	$\mathbf{L}_1$	$\mathbf{L}_2$	$\mathbf{L}_3$	$\mathbf{L}_4$	$\mathbf{L}_5$	**1**	**2**	**3**	**4**	**5**	SD
Gram-negative											
(a)	12	09	13	19	15	21	24	18	22	25	35
(b)	20	10	16	10	08	28	18	23	15	19	35
(c)	17	11	15	18	12	19	15	23	30	26	40
(d)	15	08	13	17	18	20	30	15	21	19	50
Gram-positive											
(e)	10	07	13	14	09	11	17	15	19	12	20
(f)	12	13	20	13	21	18	23	25	16	25	30
SA	3.7237	2.1602	2.7568	3.4302	5.1153	5.4681	5.5647	4.4007	5.3944	5.4037	10

Note. (a), *E. coli*; (b), *S. flexneri*; (c), *P. aeruginosa*; (d), *S. typhi*; (e), *S. aureus*; (f), *B. subtilis*; <10, weak; >10, moderate; >16, significant; SD, standard drug (imipenem); SA, statistical analysis.

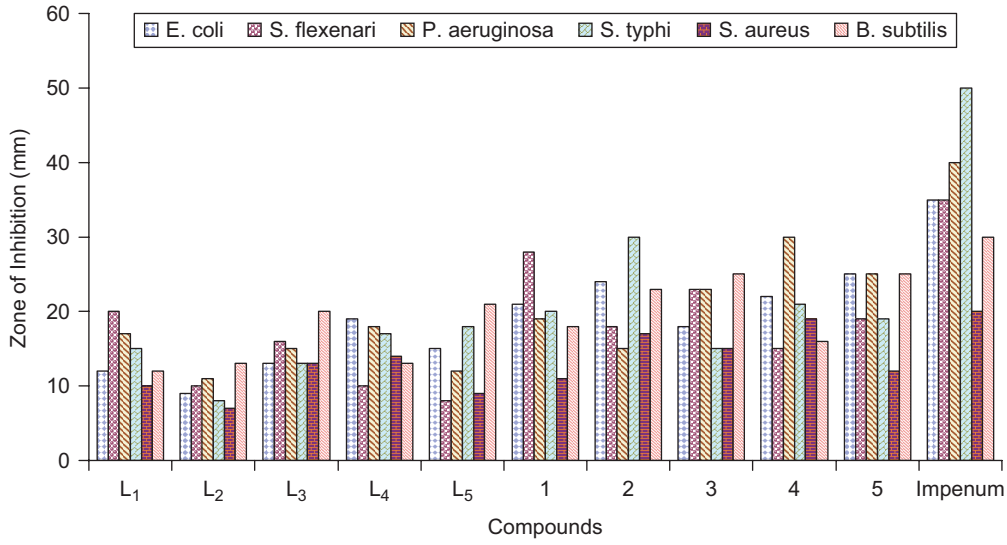


Figure 2. Comparison of antibacterial activity.

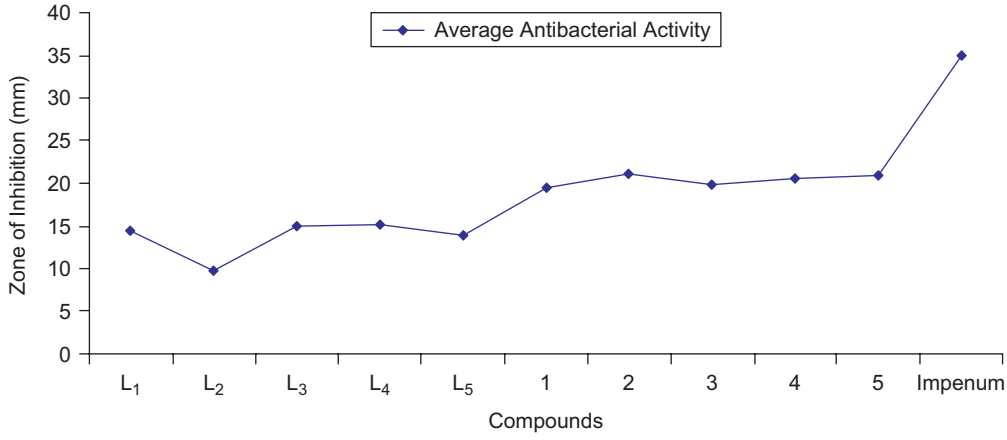


Figure 3. Average antibacterial activity of triazole derived Schiff bases versus oxovanadium(IV) complexes.

(e) and strong (83.5%) against (c). Similarly, compound (**3**) had significant (83.33%) activity against (f). Compound (**4**) exhibited maximum (95%) activity against (e) and weak (42.85%) against (b). Compound (**5**) showed strong (83.33%) activity against (f).

Antifungal bioassay (in vitro)

The antifungal screening of all compounds was carried out against *T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani*, and *C. glabrata* fungal strains (Table 4) according to the literature protocol[37]. All synthesized ligands and their vanadyl(IV) complexes showed good antifungal activity against different fungal strains. The results of inhibition were compared with the results for standard drugs, miconazole and amphotericin B (Figures 4 and 5). The ligand $\mathbf{L}_1$ possessed maximum (43%) activity against *M. canis*, (d), and showed weaker (15%) activity against *F. solani*, (e). $\mathbf{L}_2$ similarly showed good (32%) activity against (d) as compared to all other fungal strains, but minimum (15%) activity against *T. longifusus*, (a). Compound $\mathbf{L}_3$ possessed significant (24%) activity against (a) and (d), but weaker (10%) against *C. glabrata*, (f). $\mathbf{L}_4$ showed maximum (33%) activity against (e) and weaker (15%) against *C. albicans*, (b). $\mathbf{L}_5$ possessed significant (40%) activity against *A. flavus*, (c), and weaker (10%) against (a). The vanadyl complexes (**1**) and (**5**) showed good (45–55%) activity against strain (f); similarly, compounds (**2**) and (**3**) also possessed good (40–60%) activity against (f). Compound (**4**) showed significant (50%) activity against (d), and (**1**) and (**2**) weaker (19 and 24%) against (e) and (a), respectively. Compounds (**3**) and (**5**) similarly showed weaker (14–20%) activity against (f), and the same weaker (21%) activity was observed for compound (**4**) against (b)[55–57].

Minimum inhibitory concentration for antibacterial activity

The results of preliminary antibacterial screening concluded that compounds (**2**), (**3**), and (**4**) were the most (above 80%) active. These compounds were therefore selected for antibacterial minimum inhibitory concentration (MIC) studies (Table 5). The MIC values of compounds (**2**), (**3**), and (**4**)

Table 4. Antifungal activity (concentration used 200 µg/mL) of triazole derived Schiff bases and oxovanadium(IV) complexes.

	%age Inhibition										
Organism	L_1	L_2	L_3	L_4	L_5	**1**	**2**	**3**	**4**	**5**	SD
(a)	20	15	24	21	19	28	24	30	27	25	A
(b)	21	18	12	15	30	35	60	40	21	35	B
(c)	30	16	20	2	40	55	28	35	40	45	C
(d)	43	32	24	29	20	45	3	29	50	27	D
(e)	15	23	17	33	25	19	40	26	42	36	E
(f)	23	22	10	28	10	32	28	14	39	20	F
SA	9.9331	6.2609	5.9469	6.4627	10.2956	12.7383	13.1706	8.8543	10.5971	9.080	

Note. (a), *T. longifusus*; (b), *C. albicans*; (c), *A. flavus*; (d), *M. canis*; (e), *F. solani*; (f), *C. glabrata*; SD, standard drugs, MIC: A, miconazole (70 µg/mL, 1.6822×10^{-7} M/mL); B, miconazole (110.8 µg/mL, 2.6626×10^{-7} M/mL); C, amphotericin B (20 µg/mL, 2.1642×10^{-8} M/mL); D, miconazole (98.4 µg/mL, 2.3647×10^{-7} M/mL); E, miconazole (73.25 µg/mL, 1.7603×10^{-7} M/mL); F, miconazole (110.8 µg/mL, 2.66266×10^{-7} M/mL); SA, statistical analysis.

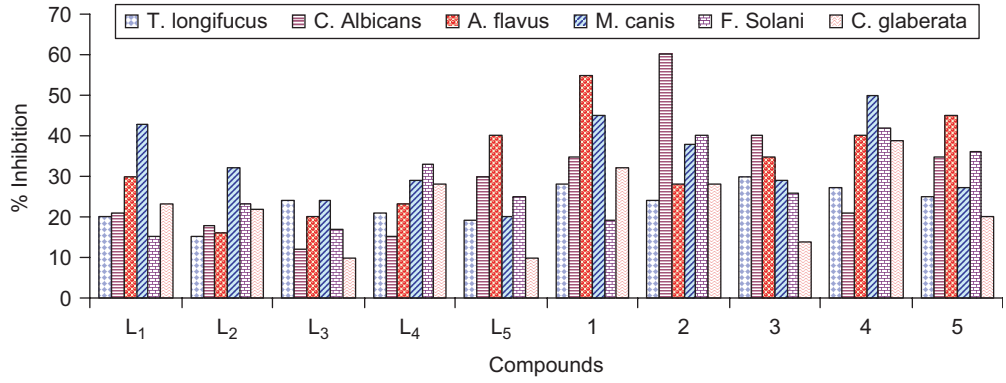


Figure 4. Comparison of antifungal activity.

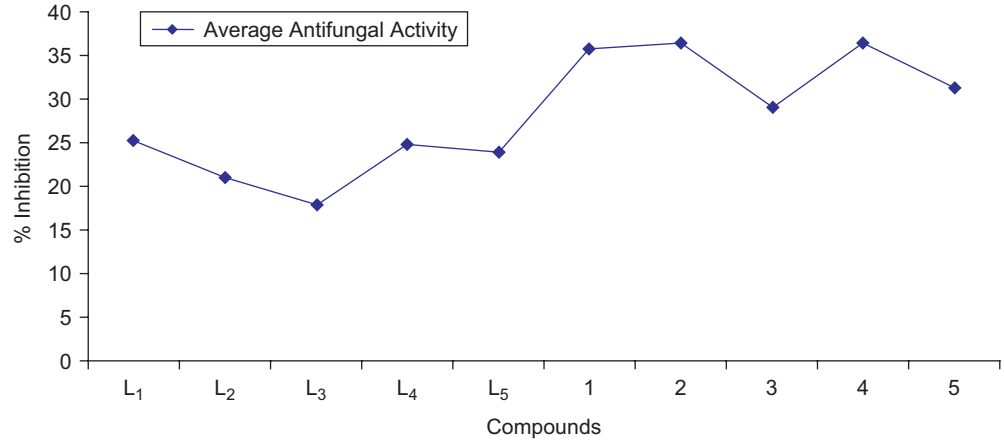


Figure 5. Average antifungal activity of triazole derived Schiff bases versus oxovanadium(IV) complexes.

were found to be in the range 5.476×10^{-7} to 2.303×10^{-5} M. However, compound (**2**) was found to be the most active, showing inhibition of 5.476×10^{-7} M against bacterial species *B. subtilis*.

Cytotoxic bioassay (in vitro)

All the synthesized compounds were screened for their cytotoxicity (brine shrimp bioassay) activity[41]. From the data recorded in Table 6, it is evident that the three compounds (**2**), (**4**), and (**5**) exhibited potent cytotoxic activity against *Artemia salina*, while all others were inactive for this assay. Compound (**2**) possessed activity (LD_{50}) of 5.358×10^{-3} M/mL, (**4**) of 8.213×10^{-4} M/mL, and (**5**) of 6.819×10^{-3} M/mL in the present series of compounds. It was interesting to note that only the oxovanadium complexes showed potent cytotoxicity. This activity relationship may help to serve as a basis for future research pursuits in the design/development of cytotoxic agents used for clinical applications[58,59].

Conclusion

The synthesized ligands L_1–L_5 acted bidentately via coordination of the azomethine nitrogen and furanyl oxygen to the oxovanadium metal ion. The binding of ligands to the

Table 5. Minimum inhibitory concentration (M/mL) of selected compounds (**2**), (**3**), and (**4**) against selected bacteria.

No.	**2**	**3**	**4**
Gram-negative			
E. coli	—	—	1.628×10^{-6}
S. flexneri	—	—	—
P. aeruginosa	3.432×10^{-7}	—	—
S. typhi	—	—	—
Gram-positive			
S. aureus	1.213×10^{-6}	—	5.476×10^{-7}
B. subtilis	—	2.303×10^{-5}	—

Table 6. Brine shrimp bioassay data of triazole derived Schiff bases $\mathbf{L}_1$–$\mathbf{L}_5$ and oxovanadium(IV) complexes (**1**)–(**5**).

Ligand/complex	LD_{50} (M/mL)
$\mathbf{L}_1$	2.506×10^{-3}
$\mathbf{L}_2$	3.752×10^{-3}
$\mathbf{L}_3$	4.936×10^{-3}
$\mathbf{L}_4$	3.342×10^{-3}
$\mathbf{L}_5$	5.893×10^{-3}
(**1**)	1.781×10^{-3}
(**2**)	5.358×10^{-3}
(**3**)	2.325×10^{-3}
(**4**)	8.213×10^{-4}
(**5**)	6.819×10^{-3}

vanadium metal atom was confirmed by their physical, analytical, and spectral data. The results of antibacterial and antifungal studies confirm that all ligands are biologically active and their vanadyl complexes show pronounced activity against one or more bacterial and/or fungal strains. All these observations lead us to the conclusion that those compounds that are not biologically active become biologically active, and those that are biologically active become more active, upon coordination/chelation with the metal ions.

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Declaration of interest

The authors report no conflict of interest and are responsible for the contents and writing of the paper.

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