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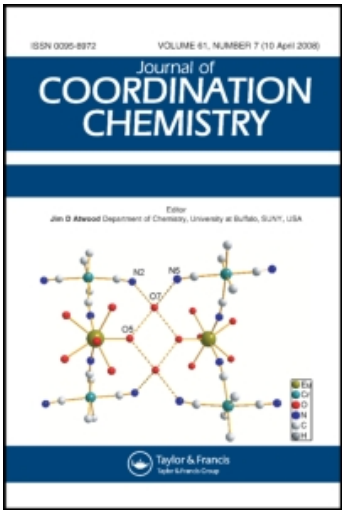

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Design and synthesis of triazole Schiff bases and their oxovanadium(IV) complexes as antimicrobial agents

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A new class of triazole Schiff bases have been prepared by the reaction of 3,5-diamino-1,2,4-triazole with methyl-, chloro-, and nitro-substituted furan-2-carboxaldehydes in an equimolar ratio (1 : 1). The bidentate ligands were characterized by IR, ^{1}H-, and ^{13}C-NMR, microanalysis, and mass spectrometry. The Schiff bases were complexed with vanadyl(IV) sulfate in a molar ratio (M : L) 1 : 2, $[M(L)_2]SO_4$ (where $L = L^1$–L^5 and $M = V^{IV}O$) in a square-pyramidal geometry. *In vitro* antibacterial activity was determined by screening the compounds against four Gram-negative (*Escherichia coli*, *Shigella flexenari*, *Pseudomonas aeruginosa*, and *Salmonella typhi*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacterial strains and *in-vitro* antifungal activity was carried out on *Trichophyton longifucus*, *Candida albican*, *Aspergillus flavus*, *Microscopum canis*, *Fusarium solani*, and *Candida glaberata* strains.

Keywords: 1,2,4-Triazole Schiff bases; Substituted furan-2-carboxaldehydes; Vanadyl(IV) complexes; Antimicrobial activity

1. Introduction

1,2,4-Triazoles [1, 2] and their metal-based [3–5] compounds have gained considerable interest due to their significant biological activity. Research has indicated that these compounds possess antibacterial [6–8], antifungal [9–11], antitumor [12, 13], antitubercular [14–18], anticonvulsant [19–22], anticancer [23, 24], analgesic [25], cytotoxicity [26], antiproliferative [27], and plant growth regulatory [28, 29] properties. The bioinorganic chemistry of oxovanadium(IV) also receives attention because of significant antimicrobial [30–32], antitumor [33], anti-leukemia [34], spermicidal [35], and most recently as insulin mimetic activities [36, 37]. Due to increased interest in bioactivities of triazole derivatives and oxovanadium(IV) compounds, we have made an effort to combine these compounds (scheme 1) and report their coordination behavior and bioactivities.

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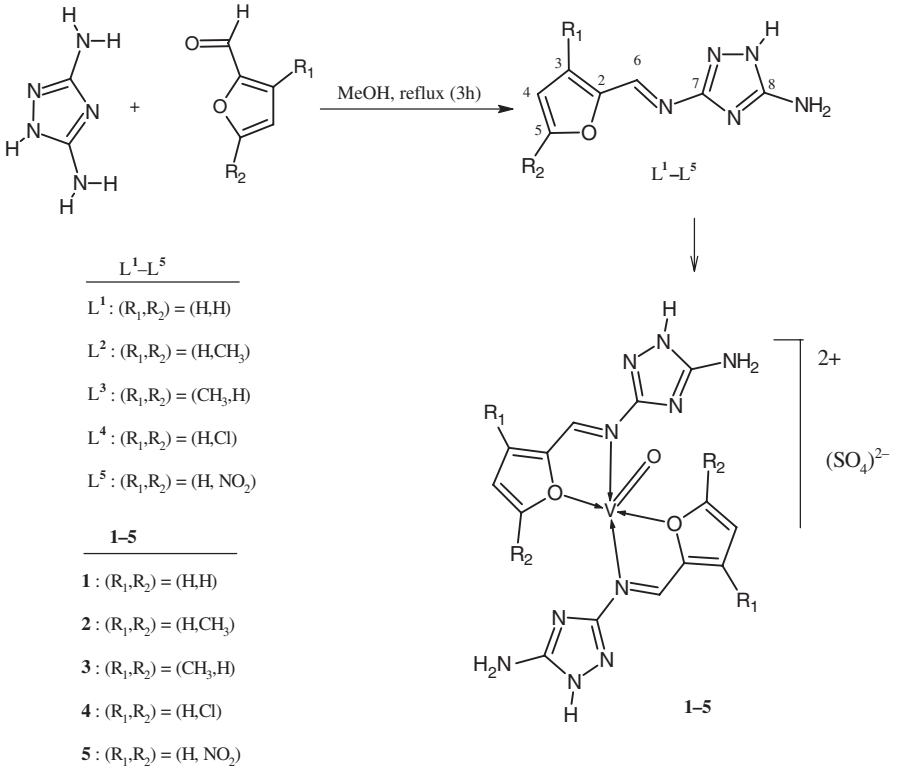

Scheme 1. Synthesis of triazole Schiff bases and their oxovanadium(IV) complexes.

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2. Experimental

2.1. *Materials and methods*

All chemicals used for preparation of the triazole Schiff bases and their oxovanadium(IV) complexes were of analytical grade. Melting points were recorded on Fisher Johns equipment. IR spectra were recorded on a SHIMADZU FT-IR spectrophotometer. Elemental analyses (C, N, H, and V) were carried out on a Perkin-Elmer (USA model). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Spectrospin Avance DPX spectrometer at 400 and 100 MHz, respectively. Electron impact mass spectra (EIMS) were recorded on a JEOL MSRoute instrument. Stanton SM12/S Gouy's balance was used to measure magnetic susceptibility of the oxovanadium complexes at room temperature. Molar conductances were measured on a Inolab Cond 720 Conductivity Bridge. *In vitro* antibacterial, antifungal, and cytotoxic properties were studied at HEJ Research Institute of Chemistry, International Centre for Chemical Sciences, University of Karachi, Pakistan.

2.2. *Antibacterial bioassay (*in vitro*)*

The triazole Schiff bases and their oxovanadium(IV) complexes were screened *in-vitro* for antibacterial activity against four Gram-negative (*Escherichia coli*, *Shigella*

flexenari, *Pseudomonas aeruginosa*, and *Salmonella typhi*) and two Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) bacterial strains by the agar-well diffusion method [38]. The wells (6 mm in diameter) were dug in the media with the help of a sterile metallic borer. Bacterial inocula (2–8 h old) containing approximately 10^4–10^6 colony-forming units (CFU mL^{-1}) were spread on the surface of the nutrient agar with the help of a sterile cotton swab. The recommended concentration of the test sample (1 mg mL^{-1} in DMSO) was introduced in the respective wells. Other wells supplemented with DMSO and reference antibacterial drug, imipenum, 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 zones showing complete inhibition (mm). In order to evaluate the interfering effect of DMSO on the biological screening, studies on DMSO solution showed no activity against any bacterial strains.

2.3. *Antifungal bioassay (*in-vitro*)*

Antifungal activities of all compounds were studied [38] against six fungal strains (*Trichophyton longifucus*, *Candida albican*, *Aspergillus flavus*, *Microscopum canis*, *Fusarium solani*, and *Candida glaberata*). Sabouraud dextrose agar (Oxoid, Hampshire, England) was seeded with 10^5 (cfu) mL^{-1} fungal spore suspensions and transferred to petri plates. Discs soaked in 20 mL (200 μg mL^{-1} 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 % inhibition and compared with standard drugs miconazole and amphotericin B.

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2.4. *Cytotoxic bioassay (*in-vitro*)*

All the synthesized compounds were screened for their cytotoxicity (brine shrimp bioassay) [39, 40]. From the data in table 6, it is evident that **2**, **4**, and **5** exhibited potent cytotoxic activity against *Artemia salina*, while the others were inactive for this assay. The activities of **2**, **4**, and **5** were obtained as $LD_{50} = 5.358 \times 10^{-3}$ mol L^{-1} mL^{-1}, $LD_{50} = 8.213 \times 10^{-4}$ mol L^{-1} mL^{-1}, and $LD_{50} = 6.819 \times 10^{-3}$ mol L^{-1} mL^{-1}, respectively. Only the oxovanadium(IV) complexes showed potent cytotoxicity, serving as a basis for future research in designing/development of cytotoxic agents used for clinical applications.

2.5. *Minimum inhibitory concentration*

Compounds containing promising antibacterial (above 80%) activity were selected for minimum inhibitory concentration (MIC) studies. The MIC was determined using the disc diffusion technique [41] by preparing discs containing 10, 25, 50, and 100 μg mL^{-1} concentrations of the compounds along with standards at the same concentrations.

2.6. *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 commercial

salt mixture and doubly 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 matter compartment was opened to ordinary light. After 2 days, a pipette collected nauplii from the lighter side. A sample of the test compound was prepared by dissolving 20 mg of each compound in 2 mL of DMF. From this stock solutions of 500, 50, and 5 $\mu g\,mL^{-1}$ were transferred to 9 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 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 shrimp 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 were counted and analyzed by Finney computer program to determine the LD_{50} values [39, 40].

2.7. *Calculation of molecular physicochemical properties*

2.7.1. Log *P* (octanol/water partition coefficient). Log *P* is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. The method is very robust and able to process practically all organic and most organometallic molecules [42].

2.7.2. Molecular polar surface area TPSA. It is calculated based on the methodology published by Ertl *et al.* [42a] as a sum of fragment contributions. O- and N-centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood–brain barrier penetration (table 8).

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3. Synthesis

3.1. *Synthesis of N^3-[(E)-furan-2-ylmethylidene]-1H-1,2,4-triazole-3,5-diamine (L^1)*

An equimolar methanol solution of 3,5-diamino-1,2,4-triazole (0.99 g, 10 mmol, 20 mL) and furan-2-carboxaldehyde (0.83 mL, 10 mmol, 20 mL) was stirred for 2 h and monitored by TLC. Precipitation took place during stirring. The solution was further stirred for another 1 h. It was then filtered, washed with methanol, dried with diethyl ether, and recrystallized in methanol to get required pure product (L^1). The same method was applied for the preparation of other ligands (L^2)–(L^5). Yield (1.15 g, 65%); m.p. 155°C; IR (KBr, cm^{-1}): 3345 (NH_2), 3189 (NH), 1629 (HC=N), 1608 (C=N, triazole), 1579, 1560 (C=C), 1132 (C–O), 1016 (N–N); ^{1}H-NMR (DMSO-d_6): δ 6.05 (s, 2H, NH_2), 7.1 (dd, 1H, $J = 3.6$, 1.8 Hz, furanyl C_4-H), 7.39 (d, 1H, $J = 3.6$ Hz, furanyl C_3-H), 7.93 (d, 1H, $J = 1.8$ Hz, furanyl C_5-H), 8.75 (s, 1H, C_6-H), and 11.92 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 122.89 (C_3), 126.53 (C_4), 138.16 (C_5), 146.39 (C_2), 155.92 (C_6), and 161.43 (C_8), 164.21 (C_7); EIMS (70 eV) m/z (%): 177 ($[M]^+$, 100), 161 (8), 146 (7), 136 (8), 134 (11), 121 (73), 106 (65), 95 (10), 80 (15), 78 (19), 52 (18), and 51 (21);

Anal. Calcd for $C_7H_7N_5O$ (177.16) (%): C, 47.46; H, 3.98; and N, 39.53; Found (%): C, 47.43; H, 3.96; and N, 39.50.

3.2. *Synthesis of N^3-[(E)-(5-methylfuran-2-yl)methylidene]-1H-1,2,4-triazole-3, 5-diamine (L^2)*

Yield (1.38 g, 72%); m.p. 216°C; IR (KBr, cm^{-1}): 3343 (NH_2), 3193 (NH), 1628 (HC=N), 1606 (C=N, triazole), 1581, 1563 (C=C); ^{1}H-NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 6.02 (s, 2H, NH_2), 7.07 (d, 1H, $J = 3.4$ Hz, furanyl C_4-H), 7.23 (d, 1H, $J = 3.5$ Hz, furanyl C_3-H), 8.64 (s, 1H, C_6-H), and 11.84 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 14.5 (CH_3-furanyl), 121.33 (C_3), 124.92 (C_4), 141.67 (C_2), 147.71 (C_5), 155.72 (C_6), 161.78 (C_8), and 165.56 (C_7); EIMS (70 eV) m/z (%): 191 ($[M]^+$, 17), 176 (100), 161 (15), 134 (33), 120 (48), 110 (25), 108 (6), 94 (20), 79 (22), 67 (13), and 53 (8); Anal. Calcd for $C_8H_9N_5O$ (191.19) (%): C, 50.26; H, 4.74; N, and 36.63; Found (%): C, 50.23; H, 4.72; and N, 36.59.

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3.3. *Synthesis of N^3-[(E)-(3-methylfuran-2-yl)methylidene]-1H-1,2,4-triazole-3, 5-diamine (L^3)*

Yield (1.22 g, 64%); m.p. 227°C; IR (KBr, cm^{-1}): 3344 (NH_2), 3193 (NH), 1629 (HC=N), 1609 (C=N, triazole), 1583, 1565 (C=C), 1133 (C–O), and 1019 (N–N); ^{1}H-NMR (DMSO-d_6): δ 2.26 (s, 3H, CH_3), 5.98 (s, 2H, NH_2), 7.11 (d, 1H, $J = 1.7$ Hz, furanyl C_4-H), 7.74 (d, 1H, $J = 1.9$ Hz, furanyl C_5-H), 8.68 (s, 1H, C_6-H), and 11.89 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 11.3 (CH_3-furanyl), 119.86 (C_4), 125.11 (C_3), 139.31 (C_5), 146.63 (C_2), 156.12 (C_6), 161.53 (C_8), and 164.44 (C_7); EIMS (70 eV) m/z (%): 191 ($[M]^+$, 14), 176 (100), 161 (11), 134 (33), 122 (10), 110 (36), 108 (8), 94 (9), 79 (17), 67 (11), and 53 (10); Anal. Calcd for $C_8H_9N_5O$ (191.19) (%): C, 50.26; H, 4.74; and N, 36.63; Found (%): C, 50.22; H, 4.73; and N, 36.61.

3.4. *Synthesis of N^3-[(E)-(5-chlorofuran-2-yl)methylidene]-1H-1,2,4-triazole-3, 5-diamine (L4)*

Yield (1.52 g, 72%); m.p. 227°C; IR (KBr, cm^{-1}): 3347 (NH_2), 3184 (NH), 1632 (HC=N), 1611 (C=N, triazole), 1576, 1557 (C=C), 1135 (C–O), 1021 (N–N), 810 (C–Cl); ^{1}H-NMR (DMSO-d_6): δ 6.06 (s, 2H, NH_2), 7.32 (d, 1H, $J = 3.6$ Hz, furanyl C_4-H), 7.39 (d, 1H, $J = 3.7$ Hz, furanyl C_3-H), 8.78 (s, 1H, C_6-H), and 11.95 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ 123.81 (C_4), 128.35 (C_3), 136.61 (C_5), 148.23 (C_2), 157.18 (C_6), 162.28 (C_8), and 165.42 (C_7); EIMS (70 eV) m/z (%): 211 ($[M]^+$, 100), 176 (27), 154 (21), 130 (11), 128 (19), 114 (7), 97 (10), 83 (13), 67 (8), and 57 (7); Anal. Calcd for $C_7H_6ClN_5O$ (211.61) (%): C, 39.73; H, 2.86; and N, 33.10; Found (%): C, 39.69; H, 2.83; and N, 33.07.

3.5. *Synthesis of N^3-[(E)-(5-nitrofuran-2-yl)methylidene]-1H-1,2,4-triazole-3, 5-diamine (L^5)*

Yield (1.60 g, 72%); m.p. 231°C; IR (KBr, cm^{-1}): 3349 (NH_2), 3182 (NH), 1633 (HC=N), 1613 (C=N, triazole), 1570, 1552 (C=C), 1355 (NO_2), 1138 (C–O), and 1024 (N–N); ^{1}H-NMR (DMSO-d_6): δ 6.08 (s, 2H, NH_2), 7.84 (d, 1H, $J = 3.8$ Hz, furanyl C_3-H), 7.99 (d, 1H, $J = 3.5$ Hz, furanyl C_4-H), 8.86 (s, 1H, C_6-H), and 12.11 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6, δ, ppm): δ 121.12 (C_3), 127.34 (C_4), 142.71 (C_2), 149.65 (C_5), 157.54 (C_6), 162.39 (C_8), and 166.49 (C_7); EIMS (70 eV) m/z (%): 222 ([M]$^+$, 100), 176 (71), 167 (8), 166 (7), 152 (20), 140 (60), 134 (45), 112 (21), 110 (10), 94 (9), 83 (85), 79 (37), and 68 (31); Anal. Calcd for $C_7H_6N_6O_3$ (222.16) (%): C, 37.84; H, 2.72; and N, 37.83; Found (%): C, 37.81; H, 2.71; and N, 37.80.

3.6. *Procedure for preparation of oxovanadium(IV) complexes*

To a hot magnetically stirred dioxane (50 mL) solution of N^3-[(E)-furan-2-methylidene]-1H-1,2,4-triazole-3,5-diamine (L^1) (0.35 g, 2 mmol), a methanol solution (20 mL) of vanadyl(IV) sulphate (0.163 g, 1 mmol) was added. The mixture was refluxed for 3 h and then cooled to room temperature. During reflux, precipitation took place. The precipitated product thus formed was filtered off, washed with methanol, then with diethyl ether, and dried under vacuum to obtain the required complex (**1**). Complexes **2–4** were prepared following the same method with the respective ligands (scheme 1).

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4. Results and discussion

4.1. *Chemistry*

Triazole-derived Schiff bases were formed by an equimolar reaction of 3,5-diamino-1,2,4-triazole with a variety of aldehydes such as methyl-, chloro-, and nitro-substituted furan-2-carboxaldehydes, respectively. All were stable to air and moisture and were soluble in dioxane, DMF and DMSO. The oxovanadium(IV) complexes were air- and water-stable and prepared by stoichiometric reaction of $VOSO_4$ with the respective triazole-derived ligands in a molar ratio (M : L) 1 : 2, $[M(L)_2]SO_4$, where $L = L^1$–L^5 and $M = V^{IV}O$ in a square-pyramidal geometry (scheme 1).

The oxovanadium(IV) complexes are green solids which decompose on heating instead of melting. All of them are soluble in DMF and DMSO but not in common organic solvents like ethanol, methanol, and chloroform. The elemental analysis, decomposition, and solubility data strongly suggest monomers. The structures of Schiff bases and their oxovanadium(IV) complexes have been established by physical (magnetic susceptibility and molar conductance), spectral (IR, ^{1}H-NMR, ^{13}C-NMR, mass, UV-Visible), and analytical data (tables 1 and 2).

4.2. *IR spectra*

Important IR bands of the triazole Schiff bases and their oxovanadium(IV) complexes are listed in section 2 and table 1. All Schiff bases display bands resulting from NH_2 at

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Table 1. Physical and micronalytical data of the oxovanadium(IV) complexes.

Compound	Structure	Yield (%) [color]	[MW] ($g\,mol^{-1}$) Formula	Decomposition (°C)	Elemental analyses Calculated (Found) (%)			
					C	H	N	V
1	$[VO(L^1)_2]SO_4$	74	[517.25]	247–249	32.50	2.70	27.06	9.85
		[green]	$C_{14}H_{14}N_{10}O_7SV$		32.48	2.67	27.03	9.83
2	$[VO(L^2)_2]SO_4$	79	[545.30]	234–236	35.26	3.30	25.67	9.34
		[green]	$C_{16}H_{18}N_{10}O_7SV$		35.22	3.28	25.63	9.32
3	$[VO(L^3)_2]SO_4$	67	[545.30]	242–245	35.26	3.30	25.67	9.34
		[green]	$C_{16}H_{18}N_{10}O_7SV$		35.23	3.28	25.64	9.32
4	$[VO(L^4)_2]SO_4$	69	[586.14]	256–259	28.69	2.04	23.89	8.70
		[green]	$C_{14}H_{12}Cl_2N_{10}O_7SV$		28.66	2.02	23.86	8.68
5	$[VO(L^5)_2]SO_4$	72	[607.24]	274–276	27.70	1.98	27.67	8.39
		[green]	$C_{14}H_{12}N_{12}O_{11}SV$		27.67	1.96	27.65	8.35

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Table 2. Conductivity, magnetic, and spectral data of complexes.

Compound	Ω_M ($\Omega^{-1}cm^2mol^{-1}$)	B.M. (μ_{eff})	λ_{max} (cm^{-1}) (nm)	IR (ν, cm^{-1})				
				(HC=N)	(SO_4)	(V=O)	(V–O)	(V–N)
1	82	1.77	13,322 (751), 18,795 (532), 27,689 (361)	1617	1087	980	492	453
2	86	1.73	13,309 (751), 18,810 (531), 27,936 (357)	1618	1085	978	487	459
3	85	1.74	13,282 (752), 18,843 (531), 27,889 (358)	1620	1085	985	489	457
4	87	1.70	13,390 (746), 18,887 (529), 28,018 (356)	1622	1083	984	493	462
5	92	1.76	13,422 (745), 18,912 (529), 28,053 (356)	1617	1085	979	484	463

3343–3349 cm^{-1}. The presence of a characteristic band at 1628–1633 cm^{-1} assigned to azomethine (HC=N) indicated that condensation between NH_2 of triazole and HC=O of aldehyde formed the Schiff base. However, all the ligands showed bands at 1130–1138 cm^{-1} due to (C–O) vibrations. In addition, NH, C=N and N–N bands of triazole were observed at 3182–3193, 1606–1613, and 1016–1024 cm^{-1}, respectively. IR frequencies of Cl and NO_2 substituents in the spectra of ligands, (L^4) and (L^5), were observed at 810 and 1355 cm^{-1}, respectively. The comparison of the IR spectra of the triazole Schiff bases with their oxovanadium(IV) complexes indicated that the triazole Schiff bases coordinate to oxovanadium(IV) bidentate. The vibrations of azomethine in spectra of oxovanadium(IV) complexes shifted to lower frequency (10–15 cm^{-1}) at 1617–1624 cm^{-1} [43], indicating coordination of azomethine. Coordination of triazole Schiff bases with the vanadium(IV) was confirmed by the appearance of weak low-frequency new bands at 487–497 and 415–465 cm^{-1} assigned to ν(V–O) and ν(V–N) [31], respectively. These new bands were only observed in spectra of the complexes, not present in spectra of the Schiff bases, supporting participation of O and N in coordination. Bands present in triazole Schiff bases at 3182–3193, 1606–1613, and 1016–1024 cm^{-1} due to NH, C=N, and N–N vibrations of triazole showed no change, indicating their non-participation with the oxovanadium(IV). All the vanadyl(IV) complexes possessed bands at 1083–1087 and 976–985 cm^{-1} assigned to SO_4 and ν(V=O) [44–46].

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4.3. *^{1}H-NMR spectra*

^{1}H-NMR spectra of the free ligands were recorded in DMSO-d_6. The ^{1}H-NMR spectral data with possible assignments are given in section 2. Protons due to heteroaromatic/aromatic groups were in their expected region [47]. The ^{1}H-NMR spectra of all the Schiff bases demonstrated characteristic amino (NH_2), azomethine, (CH=N) and NH protons of triazole at 5.98–6.08, 8.64–8.86, and 11.84–12.11, respectively, as singlets. The (CH_3) protons of L^2 and L^3 were at 2.26–2.36. In addition, the C_4–H, C_3–H, and C_5–H protons of furanyl ring found in L^1 were observed at 7.10 as a doublet of doublets, and 7.39 and 7.93 as a doublet, respectively. The C_3–H and C_4–H protons in L^2, L^4, and L^5, however, appeared as a doublet at 7.07–7.99. For L^3, C_5–H was observed at 7.74 as a doublet. Furthermore, the number of protons calculated from the integration curves [48] and those obtained from CHN analysis agreed well.

4.4. *^{13}C-NMR spectra*

The ^{13}C-NMR spectral data with possible assignments are recorded in section 2. These studies present further support to the modes of bonding from IR and ^{1}H-NMR spectra. The ^{13}C-NMR spectra of the ligands showed azomethine carbon (C_6) at 155.72–157.54; carbons (C_2)–(C_5) of furanyl ring were observed at 119.86–149.65. Triazole carbons (C_7) and (C_8) appeared at 161.43–166.49, respectively. In L^2 and L^3, methyl carbons were at 11.32–16.78. Moreover, the number of carbons agrees with expected values.

Table 3. Antibacterial activities of compounds.

	Zone of inhibition (mm)					
	Gram-negative				Gram-positive	
Compound	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)
$\mathbf{L^1}$	15	17	14	16	12	16
$\mathbf{L^2}$	12	14	17	10	16	14
$\mathbf{L^3}$	16	18	14	15	08	13
$\mathbf{L^4}$	17	15	16	19	16	14
$\mathbf{L^5}$	19	18	19	21	17	18
1	19	14	18	23	13	17
2	15	18	22	13	17	16
3	18	24	17	19	12	16
4	24	19	20	25	21	18
5	26	25	24	26	26	28
Imipenum	29	31	30	29	26	28

Used concentration, 1 mg mL^{-1} of DMSO. (*a*), *E. coli*; (*b*), *S. flexenari*; (*c*), *P. aeruginosa;* (*d*), *S. typhi*; (*e*), *S. aureus*; (*f*), *B. subtilis*. <10 weak; >10 moderate; >16 and above significant.

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4.5. *Mass spectra*

The EIMS of the Schiff bases are reported in section 2. The fragmentation pattern of L^1 possessed a molecular ion peak at m/z 177 equivalent to its exact molecular weight and fragmented to $[C_7H_7N_5O]^+$. The mass fragmentation pattern of the ligands followed the breakage/cleavage of C=N (exocyclic as well as endocyclic), C–C, C=C, C–Cl, and C–NO_2 bonds. The mass spectral data and the most stable fragmentation pattern of the triazole ligands are depicted in "Supplementary material". All the ligands showed pronounced molecular ion peaks. The mass spectral data of the triazole Schiff bases confirmed the proposed structures and bonding.

4.6. *Electronic spectra, conductance, and magnetic susceptibility measurements of complexes*

Electronic spectra of the oxovanadium(IV) complexes were recorded in DMF solution at room temperature and exhibited three d–d transitions [49, 50]. These three distinct low intensity bands (labeled as $\nu 1$, $\nu 2$, and $\nu 3$) were assigned to 2B2 (d_{xy}) $\rightarrow$ 2E (d_{xz}, d_{yz}), 2B2 (d_{xy}) $\rightarrow$ 2B1 ($d_{x^2-y^2}$), and 2B2 (d_{xy}) $\rightarrow$ 2A1 (d_{z2}) transitions, respectively. The band at 13,282–13,422 cm^{-1} (745–751 nm) was assigned to 2B2 $\rightarrow$ 2E, the second at 18,795–18,912 cm^{-1} (529–532 nm) was attributed to 2B2 $\rightarrow$ 2B1, and the band at 27,689–28,053 cm^{-1} (356–361 nm) was due to LMCT. These observations are similar to square–pyramidal oxovanadium(IV) complexes [51, 52]. Details are given in table 2.

Conductance studies were carried out in DMF at room temperature. The molar conductance values (82–90 Ohm^{-1} cm^2 mol^{-1}) of oxovanadium(IV) complexes showed that the vanadyl(IV) complexes were electrolytic [51, 52]. The observed magnetic moment values (table 2) of the complexes at room temperature were 1.71–1.77 B.M., consistent with half-spin ($S = 1/2$) and close to the reported values [52, 53], showing square pyramidal geometry of the oxovanadium(IV) complexes.

Table 4. Antifungal activity of triazole Schiff bases and their oxovanadium(IV) complexes.

Compound	Organism [% Inhibition]						
	(*a*)	(*b*)	(*c*)	(*d*)	(*e*)	(*f*)	(SA)
L^1	43	57	00	45	48	49	20.33
L^2	58	50	41	00	55	39	21.21
L^3	49	46	55	42	38	60	8.16
L^4	58	46	25	41	55	37	12.16
L^5	56	59	63	54	43	49	7.16
1	54	65	18	58	56	59	16.91
2	65	57	55	11	71	41	21.56
3	44	60	68	43	49	15	18.23
4	73	62	39	58	67	55	11.71
5	60	71	78	66	57	75	8.16
SD	A	B	C	D	E	F	–

(*a*), *T. longifucus*; (*b*), *C. albicans*; (*c*), *A. flavus*; (*d*), *M. canis*; (*e*), *F. Solani*; (*f*), *C. glaberata*; SD, Standard Drugs MIC $\mu g\,mL^{-1}$; A, Miconazole ($70\,\mu g\,mL^{-1}$: 1.6822×10^{-7} mol L^{-1} mL^{-1}); B, Miconazole ($110.8\,\mu g\,mL^{-1}$: 2.6626×10^{-7} mol L^{-1} mL); C, Amphotericin B ($20\,\mu g\,mL^{-1}$: 2.1642×10^{-8} mol L^{-1} mL^{-1}); D, Miconazole ($98.4\,\mu g\,mL^{-1}$: 2.3647×10^{-7} mol L^{-1} mL^{-1}); E, Miconazole ($73.25\,\mu g\,mL^{-1}$: 1.7603×10^{-7} mol L^{-1} mL^{-1}); and F, Miconazole ($110.8\,\mu g\,mL^{-1}$: 2.66266×10^{-7} mol L^{-1} mL^{-1}). SA, Statistical analysis.

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Table 5. MIC (MIC in $\mu g\,mL^{-1}$) of **4** and **5** against selected bacteria.

Microorganisms	MIC ($\mu g\,mL^{-1}$)[a]	
	4	5
E. coli	45	0.02
S. flexenari	ND	42.0
P. aeruginosa	ND	0.09
S. typhi	32	23.0
S. aureus	0.08	0.04
B. subtilis	ND	15.0

ND is not determined at tested concentrations.
[a]Each compound was measured three times, with a standard deviation (SD) less than 10% in all the cases.

5. Pharmacology

The Schiff bases and oxovanadium(IV) complexes were screened for *in-vitro* antibacterial activity against *E. coli*, *S. flexenari*, *P. aeruginosa*, *S. typhi*, *S. aureus*, and *B. subtilis* bacterial strains, and for antifungal activity against *T. longifucus*, *C. albican*, *A. flavus*, *M. canis*, *F. solani*, and *C. glaberata*. The Schiff bases showed varied antibacterial and antifungal activities against one or more strains and their activities were generally enhanced upon coordination with vanadium(IV) (tables 3–5).

5.1. *Antibacterial activity (*in vitro*)*

In-vitro antibacterial results are reported in table 3 and figure 1. It is evident that coordination makes the ligands strong antibacterial agents and inhibits the growth of

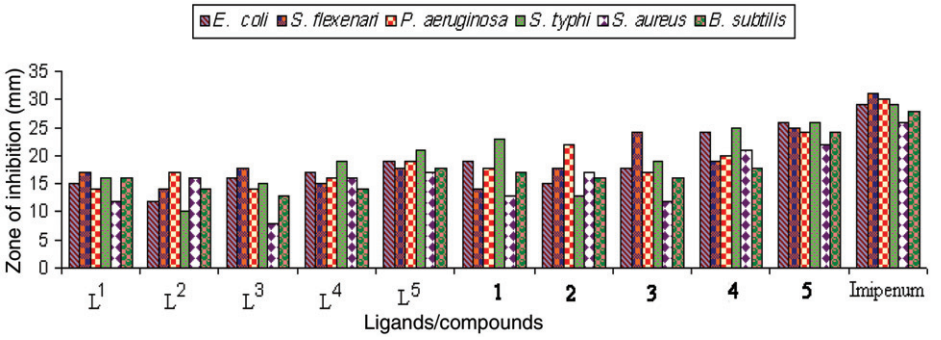

Figure 1. Comparison of antibacterial activities of triazole Schiff bases and their oxovanadium(IV) complexes.

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bacteria more than the parent ligand, tested according to literature protocol [38, 41]. The results were compared with those of the standard drug imipenum (figure 2). The activity was compared with the activity of the standard drug considering its activity as 100%. All ligands and their oxovanadium(IV) complexes possess varying degree of inhibitory effects: low (up to 33%), moderate (up to 53%), and significant (above 53%). L_1 exhibited a significant (55–57%) activity against bacterial strains (*b*), (*f*), and (*d*) and moderate (43–52%) activity against (*a*), (*c*), and (*e*). Also, L_2 showed significant (57–62%) activity against (*c*) and (*e*), moderate (41–50%) against (*a*), (*b*), and (*f*), and weaker (29%) against (*d*). However, L_3 possessed significant (55–58%) activity against (*a*) and (*b*), moderate (46–51%) activity against (*c*), (*d*), and (*f*), and weakest (31%) against (*e*). Similarly, L_4 exhibited significant (58–65%) activity against (*a*), (*c*), (*d*), and (*e*) except (*b*) and (*f*), which showed moderate (48–50%). Moreover, L_5 displayed overall significant (58–72%) activity against all bacterial strains (*a*)–(*e*). All complexes exhibited overall a significant (57–90%) activity against all bacterial strains except (*b*) and (*e*) of **1**, (*a*) and (*d*) of **2**, and (*e*) of **3** which showed moderate (44–50%) activity. The results of these studies indicated that antibacterial activity is overall enhanced upon chelation/complexation confirming our previous studies [54–56].

The antibacterial results of **4** and **5** were most (above 80%) active due to presence of chloro and nitro substituents, hence their MIC screening was carried out (table 5). MIC of **4** and **5** were in the range 0.02–48 $\mu g\,mL^{-1}$ of which, **5** was most active with maximum inhibition 0.02 $\mu g\,mL^{-1}$ against *E. coli*.

5.2. *Antifungal activity (in vitro)*

The antifungal screening of all compounds was carried out against *T. longifucus*, *C. albican*, *A. flavus*, *M. canis*, *F. solani*, and *C. glaberata* fungal strains (table 4), according to the literature protocol [38]. All triazole ligands and their complexes showed weak to significant antifungal activity against different fungal strains. The inhibition was compared with the results of standard drugs, miconazole and amphotericin B (figures 3 and 4).

L_1 possessed significant (57%) activity against fungal strain (*b*), moderate (37–49%) against (*a*), (*d*), (*e*), and (*f*) and showed no activity against (*c*). Also, L_2 showed

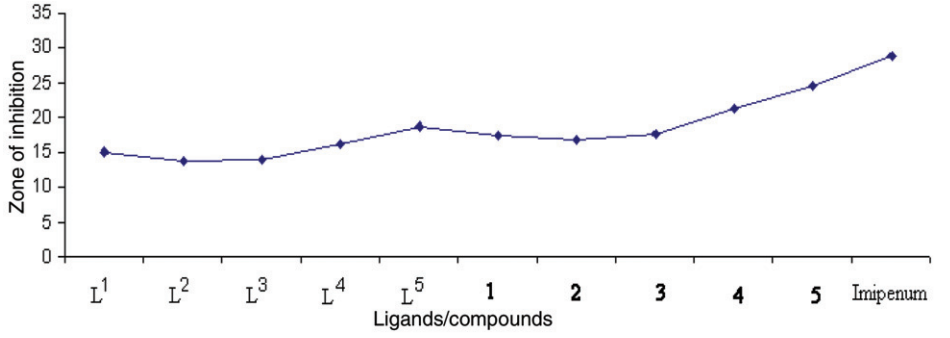

Figure 2. Average antibacterial activities of L^1–L^5 *vs.* **1**–**5**.

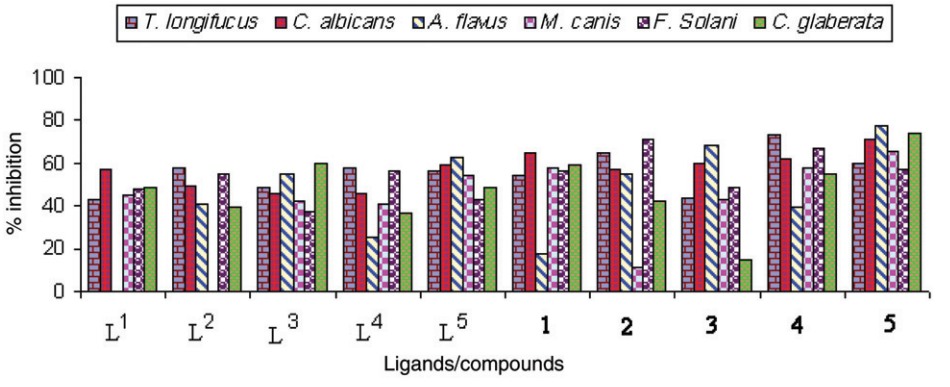

Figure 3. Comparison of antifungal activities.

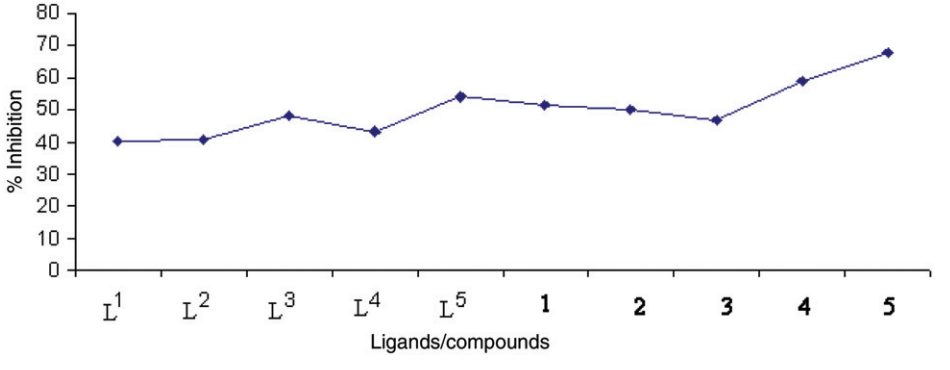

Figure 4. Average antifungal activities.

significant (55–58%) activity against (*a*) and (*e*), and moderate (39–50%) activity against (*b*), (*c*), and (*f*), but (*c*) was inactive. However, L_3 exhibited significant (55–60%) activity against (*c*) and (*f*) but showed moderate (38–49%) activity against (*a*), (*b*), (*d*), and (*e*). Similarly, L_4 possessed significant (55–58%) activity against (*a*) and (*e*),

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Table 6. Cytotoxicity against larvae of *Artemia salina*.

Ligands/complexes	LD50/10^{-3} (mol L^{-1} mL^{-1})[a]
L^1	$>3.456 \times 10^{-3}$
L^2	$>2.632 \times 10^{-3}$
L^3	$>4.116 \times 10^{-3}$
L^4	$>3.631 \times 10^{-3}$
L^5	$>3.356 \times 10^{-3}$
1	$>2.216 \times 10^{-3}$
2	$>1.364 \times 10^{-3}$
3	$>2.226 \times 10^{-3}$
4	2.154×10^{-4}
5	$>1.651 \times 10^{-3}$

Values with SD less than 10% in all the cases.
[a]Each compound was measured two times.

moderate (37–46%) against (*b*), (*d*), and (*f*), and weaker (25%) against (*c*). L_5 displayed significant (54–63%) activity against (*a*)–(*d*) and moderate (43–49%) against (*e*) and (*f*). Compound **1** showed significant (54–65%) activity against all fungal strains except strain (*c*) (18% activity). Similarly, **2** also possessed significant (55–71%) activity against (*a*), (*b*), (*c*), and (*e*), moderate (50%) against (*f*), and weaker (11%) against (*d*). Compound **3** displayed significant (60–68%) activity against (*b*)–(*c*), moderate (43–49%) against (*a*), (*d*), and (*e*) and weaker (15%) against (*f*), respectively. Compounds **4** and **5** possessed significant (55–74%) activity against all fungal strains except (*c*). The MICs (MIC in mol L^{-1} mL^{-1}) of **4** and **5** are given in table 5.

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5.3. *Cytotoxicity (*in-vitro*)*

The compounds were screened for cytotoxicity (brine shrimp bioassay) activity [39, 40]. Compounds **2**, **4**, and **5** exhibited potent cytotoxic activity against *Artemia salina*, while the others were inactive (table 6). Compound **2** possessed activity ($LD_{50} = 5.358 \times 10^{-3}$ mol L^{-1} mL^{-1}), **4** ($LD_{50} = 8.213 \times 10^{-4}$ mol L^{-1} mL^{-1}), and **5** ($LD_{50} = 6.819 \times 10^{-3}$ mol L^{-1} mL^{-1}) in the present series of compounds; only oxovanadium complexes showed potent cytotoxicity.

5.4. *Molecular property calculations*

5.4.1. Osiris calculations. Structure-based design is now fairly routine, but many potential drugs fail to reach clinical testing because of ADME-Tox liabilities [57]. One very important class of enzymes responsible for many ADMET problems is the cytochromes P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. An important program, Osiris, is available online. With our recent publication of the drug design combination of various pharmacophore sites by using spiro-heterocyclic structure, it is now possible to predict activity and/or inhibition with increasing success in bacteria and HIV [58]. This is done using a combined electronic/structure docking procedure, an example is given in table 7.

Table 7. Osiris calculations of ligands.

Ligands	Toxicity risks				Osiris calculations				
	Mutagenic	Tumorigenic	Irritant	Reproductive effective	MW[a] ($g\,mol^{-1}$)	CLP[a]	S[a]	DL[a]	DS[a]
L^1					177	0.11	−2.41	0.41	0.53
L^2					191	053	−2.78	1.80	0.56
L^3					191	0.43	−2.75	0.51	0.52
L^4					211	0.81	−2.91	1.95	0.69
L^5					222	0.46	−3.39	−1.62	0.42

[a]CLP, *c* log *P*; S, Solubility; DL, Drug-likeness; DS, Drug-Scor.

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The remarkably well-behaved mutagenicity of diverse synthetic molecules classified in data base of CELERON Company (Swiss) can be used to quantify the role played by various organic groups in promoting or interfering with the way a drug can associate with DNA. The OSIRIS Property Explorer is an integral part of Actelion's inhouse substance registration system drawing chemical structures and calculating on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red whereas a green color indicates drug conformation behavior.

5.4.2. Molinspiration calculations. *C* Log *P* (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors (table 8) [57]. The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA of L^1–L^5 is calculated based on the methodology published by Ertl *et al.* [42a] as a sum of fragment contributions.

6. Conclusions

The new class of triazole Schiff bases are bidentate ligands. The oxovanadium is coordinated through azomethine nitrogen and furanyl oxygen. The bonding of ligands to the oxovanadium(IV) ion was confirmed by their physical, analytical, and spectral data with the proposed structure depicted in scheme 1. Antibacterial and antifungal

Table 8. Molinspiration calculations of L^1–L^5.

	Molinspiration calculations						Drug-likeness			
Ligands	A	B	C	D	E	F	G	H	I	J
L^1	177	0.36	93	3	0	148	−1.34	−1.44	−1.62	−4.07
L^2	191	0.53	93	3	0	165	−1.28	−1.30	−1.56	−3.22
L^3	191	0.68	93	3	0	165	−1.24	−1.29	−1.40	−3.10
L^4	211	1.11	93	3	0	162	−1.16	−1.17	−1.23	−2.83
L^5	222	0.39	139	3	0	172	−1.73	−1.96	−1.10	−3.25

A, MW; B, *c* Log *P*; C, TPSA; D, OH–NH interaction; E, N violation; F, volume; G, GPCR ligand; H, ICM; I, KI; and J, NRL.

studies confirm that all triazole ligands are biologically active against one or more bacterial/fungal strains and their vanadyl(IV) complexes show enhanced activity against different strains upon coordination. The same behavior has been observed on the similar system containing oxovanadium(IV) [59]. Antibacterial and antifungal studies show similar triazole Schiff bases to be moderate to significantly active against one or more strains and their oxovanadium(IV) complexes to be more active against various strains on coordination.

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