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Oxovanadium(IV) Complexes with Cephradine: Synthesis, Semi-Empirical Study, Spectroscopy, Potentiometric Study and Antimicrobial Activity

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The reactions between cephradine and $VOSO_4.3H_2O$ in 1:1, 1:2 and 1:3 molar ratios in methanol were investigated at room temperature, 0 °C and -10 °C. In various pH conditions, the different complexes formulated as $VO(H_2O)_3L^{2-}$, $VO(H_2O)L_2^{2-}$ and VL_3^- were formed by titration of $VOSO_4.3H_2O$ and cephradine with NaOH. These complexes were characterized by elemental analysis and IR spectroscopy. IR spectra of all the complexes show the disappearance of ν(O-H) band of cephradine, which confirms complexation. Estimation of vanadium in the complexes was carried out by ICP-AES. The stability constants of each complex were calculated on the basis of which a general mechanism is hereby proposed with regard to the formation of these complexes. In complex (**1**) the cephradine ligand bind in bidentate [O,O] fashion together with a terminal oxo ligand and water molecules complete the metal coordination sphere. In complex (**2**) the cephradine ligands bind in bis-bidentate [O,O] fashion and the axial positions are occupied by the oxo ligand and a trans-water molecule. Biological screening tests show significant anti-bacterial and anti-fungal activities against various bacterial and fungal strains.

Keywords: Oxovanadium(IV) complexes, IR, Potentiometric study, PM6 calculations, Biological activities

INTRODUCTION

Vanadium is a ubiquitous element dispersed throughout the earth's crust, rivers, lakes and oceans [1]. Vanadium is a powerful alloying agent; a small amount adds strength, toughness and heat resistance. Vanadium-aluminum-titanium alloys are used in high-speed airframes and jet engines. The halides of vanadium generally react with different ligands to form complexes of the type $[ML_6]^{3+}X_3$, $[ML_4X_2]^+X^-$, $[ML_3X_3]$ and $[ML_2X_3]$ as well as several anionic types formed with unidentate ligands.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are pain-relievingmedications which also have the effect of reducing inflammation when used over a period of time. The major clinical application of NSAIDs is their action as anti-inflammatory agents in muscle skeletal diseases [2]. Mefenamic acid (2-[(2,3-dimethylphenyl)amino-]benzoic acid), ketoprofen (2-(3-benzoylphenyl)propionoic acid), flurbiprofen (2-(2-fluro-4-biphenyl)propanoic acid, Ibuprofen (2-(4-isobutylphenyl)propanoic acid), are only a few examples of non-steroidal anti-inflammatory drugs. Several transition metal complexes with NSAIDs have extensively been studied. Vanadium forms complexes with NSAIDs that are mainly

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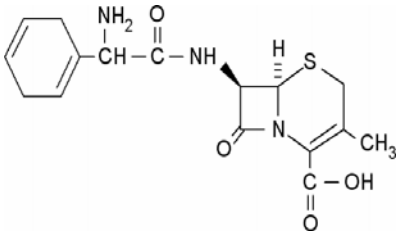

Fig. 1. Chemical structure of cephradine (**HL**).

effective in their biological activity as compared to their parent ligand [3]. Vanadium complexes potentially active as anti-tumors. They are also used as anti-diabetic and anti-carcinogenic agents. From among the complexes of vanadium in +4 oxidation state, mostly oxovanadium complexes with NSAIDs have been reported as being effective anti-diabetic agents. Moreover, these complexes are reported to possess certain other biological activities [4].

We are reporting here the oxovanadium(IV) complexes of cephradine, (6R-(6alpha,7))-((amino-,1,4-cyclohexadien-1-ylacetyl)amino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid (Fig. 1), a first generation cephalosporin antibiotics and their characterization by elemental analysis, IR spectroscopy, potentiometric and semi-empirical study. These complexes were duly screened against different bacterial and fungal strains to check their biological activity.

EXPERIMENTAL

Materials and Methods

All the reagents and solvents were commercially available in the highest grade and used without further purification. $VOSO_4.3H_2O$ was purchased from Aldrich. Melting points were determined in a capillary tube on an electrothermal melting point apparatus model Sanyo Gallen Kamp MPD-350 BM3.5 and were uncorrected.

Infrared spectra were recorded in the range of 4000-400 cm^{-1} as KBr pellets on a Bio-Red Elmer 16 FPC FTIR Spectrophotometer. Distilled water was used for the preparation of 0.2 M NaOH solution. Methanol was used as a solvent for the preparation of 0.01 M solution of vanadyl sulphate trihydrate and 0.01 M solution of cephradine. pH meter was calibrated by using the buffer tablet of pH 4.

Quantum Chemical Methods

The structure of complexes (**1**) and (**2**) were modeled by MOPAC 2007 [5] program using PM6 method [6] parts of the molecule not containing the metal ion were preoptimized using molecular mechanics method before subjecting the whole molecule to geometry optimization. Molecular Mechanics correction was applied to the -CO-NH- barrier. Stability constants were calculated using the computer program BEST [7].

General Procedure

For potentiometric titrations, 1:1, 1:2 and 1:3 molar ratios were prepared by mixing 25 ml of 0.01 M $VOSO_4.3H_2O$ solutions with 25 ml, 50 ml and 75 ml of 0.01 M solution of cephradine in volumetric flask. The titrations were carried out at 20 °C, 0 °C and -10 °C with standard 0.2 M NaOH. The 20 °C was the room temperature, while 0 °C and -10 °C were maintained by keeping the titration flask in ice and ice-salt bath, respectively.

The reaction mixtures were stirred on a magnetic stirrer while the titrations were being carried out and pHs were measured after every 0.2 ml addition of NaOH solution. For all the three molar ratios, the first addition of NaOH solution caused color change of the solutions with turbidity, which meant that complexation had started. At the end of the reactions all solutions became clear and white precipitates of Na_2SO_4 were formed. These precipitates were filtered and solvents evaporated at room temperature. Green-colored solid products obtained were recrystallized in choroform:petroleum ether (1:1).

RESULTS AND DISCUSSION

The complexes (**1**)-(**3**) were obtained in good yield, stable at room temperature and showed good solubility in common organic solvents. Some physical parameters of the complexes are reported in Table 1.

Infrared Spectroscopy

The most important features of the infrared spectra of the complexes and corresponding free ligand are shown in Table 2.

Table 1. Physical Parameters of Oxovanadium(IV) Complexes of Cephradine

Compound	General formula	Mol. Wt.	Yield (%)	m.p. (^oC)	Molar ratios	Elemental analysis calcd. (found)		
						%C	%H	%N
(**1**)	$[VO(H_2O)_3L]^{2-}$	454	62	147	1:1	42.29 (42.32)	5.06 (5.02)	6.16 (6.20)
(**2**)	$[VO(H_2O)L_2]^{2-}$	751	69	123	1:2	51.13 (51.09)	4.79 (4.75)	7.45 (7.49)
(**3**)	$[VL_3]^-$	1002	80	112	1:3	57.48 (57.44)	5.08 (5.12)	8.38 (8.42)

Table 2. Infrared Spectral Data (cm^{-1}) for Oxovanadium(IV) Complexes of Cephradine

Compound	$\nu(H_2O)$	ν(COO)		$\triangle\nu$	ν(V-O)	ν(V=O)	ν(C=O)
		Asym.	Sym.				
NaL	-	1692	1382	308	-	-	1762
(**1**)	3432	1570	1410	160	560	911	1751
(**2**)	3445	1597	1452	145	572	908	1750
(**3**)	-	1553	1419	134	591	904	1752

The significant absorption frequencies were ν(O-H), ν(C=O), ν_{asym}(COO), ν_{sym}(COO), ν(V-O) and $\nu(H_2O)$. The values assigned to these bands were in accordance with the values reported in literature [8,9]. The complexation of vanadium(IV) with the ligand is confirmed by the disappearance of ν(O-H) band in complexes occurring at 2874 cm^{-1} which is a characteristic of carboxylic acid. The complexation of vanadium with oxygen donor ligand is also confirmed by the appearance of ν(V-O) band in the range 591-560 cm^{-1} and ν(V=O) band in the range of 911-904 cm^{-1}. The ν(COO) stretching vibrations are significant in predicting the bonding mode of ligand. The fall of ν_{asym}(COO) *vs*. the rise of ν_{sym}(COO) for carboxylate group show the bidentate nature of ligand in the complexes.

The different $\triangle\nu$ of ν_{asym}(COO) and ν_{sym}(COO) stretching values for complexes (**1**)-(**3**) which fall in the range 160-134 cm^{-1} show that ligand acts as bidentate. The strong bands observed at 1750-1752 cm^{-1} can be assigned to ν(C=O) of other carboxylate groups in the ligand which remain practically unchanged after complexation. The overall infrared spectral evidence suggests that ligand acts as bidentate and coordinates through carboxylic oxygen atoms forming octahedral structure.

Table 3. Vanadium Content for Oxovanadium(IV) Complexes of Cephradine

Compound	%V
	calcd. (found)
(**1**)	11.23 (11.29)
(**2**)	6.79 (6.85)
(**3**)	5.08 (5.02)

ICP-AES

The oxovanadium samples were digested with the help of nitric acid and perchloric acid and diluted with double-distilled water. Linear calibration method was used to quantify the results. An inductively coupled argon plasma atomic emission spectrometer (ICP-AES) was used for the determination of vanadium. The data for the compounds (**1**)-(**3**) are given in Table 3.

Potentiometric Study

The potentiometric titration curves for M/L ratios of 1:1, 1:2 and 1:3, at different temperatures, are given in Fig. 2. These figures shows that titration curves of VO(IV) complexes at different temperatures have less depression but more twist indicating low stability constants values with more species present at a time. The logβ values (Table 4) show that the order of the stability would be 1:1 > 1:3 > 1:2 M/L molar ratio.

In case of 1:1 and 1:3, the degree of hydrolysis is the same which implies that entropy should be the same. This is because in both reactions only one H^+ is produced. According to equation (ii) and (iii), both types of mechanism are possible for 1:2 M/L ratio. Equation (ii) shows that entropy of 1:1 and 1:2 complexes should be the same but in case of second mechanism as given in equation (iii) entropy should be in negative value.

We can show the stability order as: 1:1 > 1:3 > 1:2

Stability of 1:3 is greater than that of 1:2 due to the removal of vanadyl oxygen during the formation of 6-coordinated complex with bidentate ligand. The pK value of the cephradine in the methanol/water solution is 8.79. The proposed structures of oxovanadium(IV) complexes in 1:1, 1:2 and 1:3 M/L ratios are given in Fig. 3.

Semi-Empirical Study

In complex (**1**) the cephradine ligands bind in bidentate [O,O] fashion. The terminal oxo ligand and additional water molecules complete the metal coordination sphere. In complex (**2**) the cephradine ligands bind in bis-bidentate [O,O] fashion and the axial positions are occupied by the oxo ligand and a trans-water molecule. Both the modeled structures (Figs. 4 and 5) show distorted octahedral geometry around vanadium. The apical vanadium oxygen distance of 1.548 Å in (**1**) and 1.551 Å in (**2**) are typical of V(IV)=O bond length. The V(IV)-O bond lengths for the coordinated water molecules in the equatorial plane in (**1**) are 2.149 Å and 2.240 Å, respectively. These values are close to the similar ranges of values in the literature [10]. The long V(IV)-O bond length in the axial position 2.56 Å in (**1**) and 2.65 Å in (**2**) may be due to the trans influence of the oxo group. The vanadium ion is 0.623 Å and 0.698 Å above the mean equatorial plane formed by the four oxygen atoms in (**1**) and (**2**), respectively. The bond lengths and bond angles for all non-hydrogen atoms are

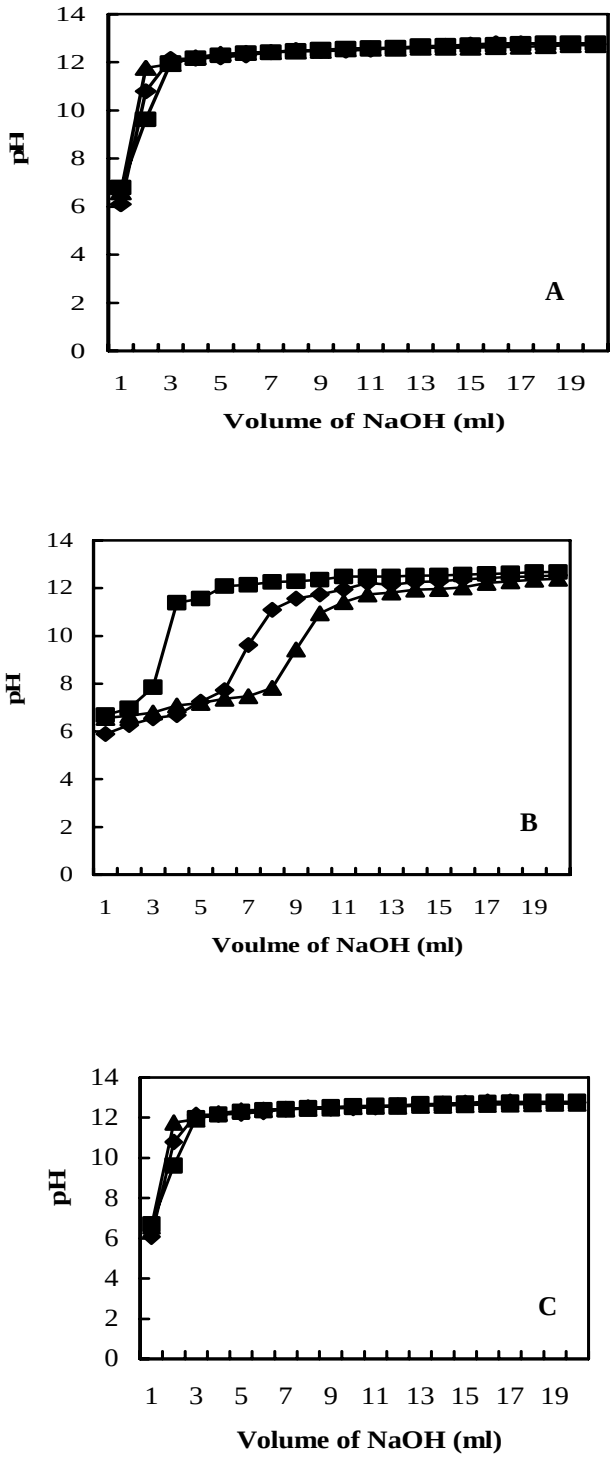

Fig. 2. Potentiometric titration curves for 1:1 (1), 1:2 (2) and 1:3 (3) at 20 °C (A), 0 °C (B) and -10 °C (C).

Table 4. Stability Constants for VO(IV)-Cephradine Complexes at Different Temperatures

Temperature (°C)	M/L Ratio	logβ	pqr[a]
20	1:1	3.32	1,6,1
	1:2	5.48	1,2,2
	1:3	7.67	1,0,3
0	1:1	3.21	1,6,1
	1:2	5.39	1,2,2
	1:3	7.50	1,0,3
-10	1:1	3.12	1,6,1
	1:2	5.29	1,2,2
	1:3	7.32	1,0,3

[b]p = number of metal, q = number of hydrogen, r = number of ligand in the complex.

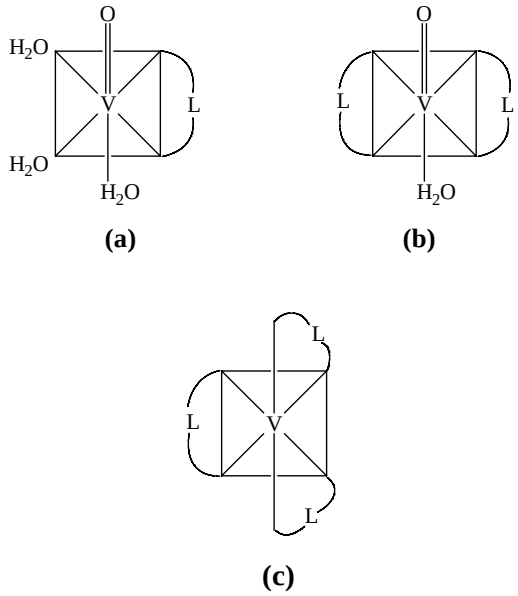

Fig. 3. Proposed structures of oxovanadium(IV) complexes in (a) 1:1, (b) 1:2 and (c) 1:3.

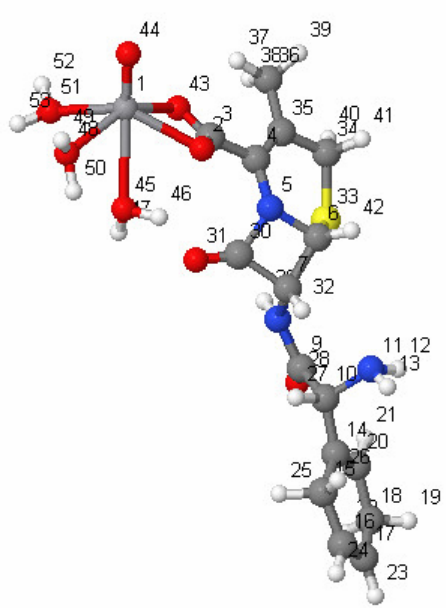

Fig. 4. Geometry Optimised Structure of V(IV)=O(H_2O)$_3$ (Cephradine) (**1**).

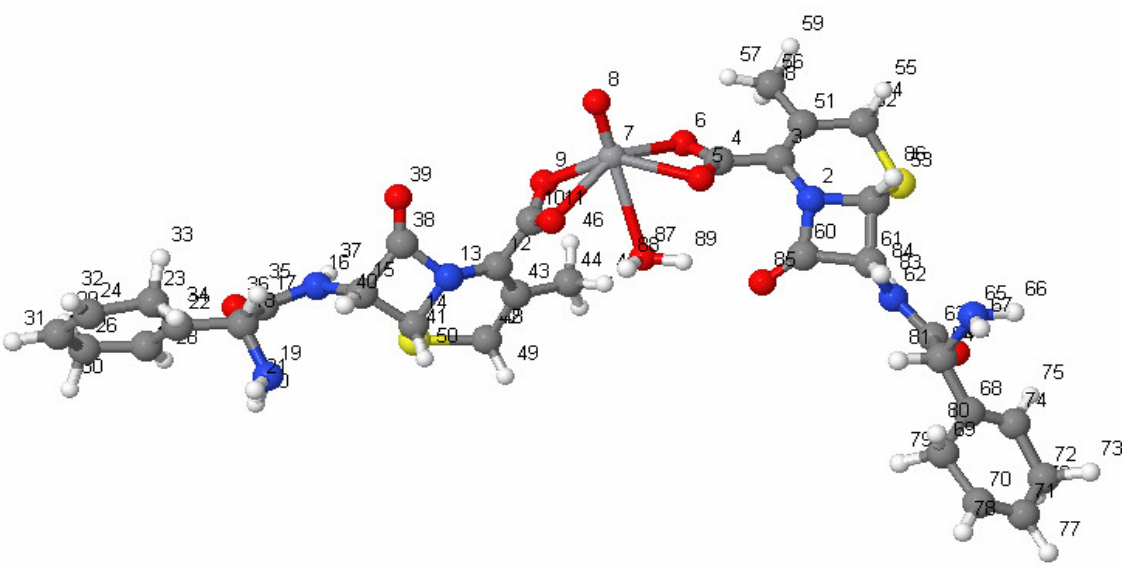

Fig. 5. Geometry Optimised Structure of V(IV)=O(H_2O) (Cephradine)$_2$ (**2**).

tabulated in Tables 5-8, respectively.

Anti-Bacterial Screening Tests

Anti-bacterial activity of compounds (**1**)-(**3**) was evaluated against six bacterial strains by agar well diffusion method [11]. All the tested complexes show significant anti-bacterial activity against the listed bacteria and the results are given in Table 9. Based on the results, all the tested compounds show significant activity especially against *Escherchia coli* and *Bacillus subtilis* and moderate activity against *Staphylococcus aureus* species.

Anti-Fungal Screening Test

The antifungal tests were carried out by using agar tube dilution protocol method [11]. The antifungal results of the synthesized complexes are given in Table 10. All complexes showed significant antifungal activity against *Trichophyton longifusus, Candida albicans, Fusarium solani* and *Candida glaberata*. The complexes show moderate activity against *Microsporum canis*.

CONCLUSIONS

The elemental analyses showed a good agreement between the calculated and observed values for C, H and N. Pka values were determined for 1:1, 1:2 and 1:3 M/L ratio at different temperatures, which showed that end points of the titration were sharp. The order of the stability was 1:1 > 1:3 > 1:2 which is justified on the grounds of the proposed mechanism. IR data show that ciprofloxacine acts as bidentate ligand and 6-coordinated complexes are obtained for 1:1, 1:2 and 1:3 M/L ratios. In complex (**1**) the cephradine ligands bind in bidentate [O,O] fashion which, together with a terminal oxo ligand and water molecules, complete the metal coordination sphere, while in complex (**2**) the cephradine ligands bind in bis-bidentate [O,O] fashion and the axial positions are occupied by the oxo ligand and a trans-water molecule. Biological activity data show that all the complexes are biologically active as compared to free ligand and can be used as drugs.

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Table 5. Bond Lengths of V(IV)=O$(H_2O)_3$ (Cephradine) (**1**)

Atom1	Atom2	Bond length (ºA)
V1	O2	2.195
O2	C3	1.287
C4	C3	1.483
C4	N5	1.425
N5	C6	1.494
C7	C6	1.571
C7	N8	1.441
N8	C9	1.425
C10	C9	1.537
C10	N11	1.495
C14	C10	1.517
C14	C15	1.507
C15	C16	1.501
C16	C17	1.335
C17	C18	1.499
C20	C14	1.340
C18	C20	1.498
C9	O28	1.212
N5	C30	1.427
C30	C7	1.574
C30	O31	1.203
C6	S33	1.807
S33	C34	1.813
C34	C35	1.492
C35	C36	1.486
V1	O43	2.145
C3	O43	1.292
V1	O44	1.548
V1	O45	2.561
V1	O48	2.240
V1	O51	2.149

Table 6. Bond Angles of V(IV)=O$(H_2O)_3$ (Cephradine) (**1**)

Atom1	Atom2	Atom3	Bond angle (deg)
C14	C15	C16	113.49
C15	C16	C17	123.23
C17	C18	C20	113.77
C16	C17	C18	122.85
C18	C20	C14	123.17
C20	C14	C15	122.61
C14	C10	N11	112.68
C9	C10	N11	107.53
C9	C10	C14	112.76
N8	C9	O28	115.49
N8	C9	C10	118.37
C10	C9	O28	126.04
N8	C7	C30	112.95
C9	N8	C7	125.01
N8	C7	C6	118.51
C30	C7	C6	86.00
O31	C30	C7	138.39
O31	C30	N5	130.79
C30	N5	C6	94.46
N5	C6	C7	88.40
C7	C30	N5	90.69
S33	C6	C7	113.96
N5	C6	S33	109.73
C6	S33	C34	98.02
S33	C34	C35	113.63
C34	C35	C4	122.87
C35	C4	N5	123.32
C4	N5	C6	124.31
C36	C35	C4	122.63
C36	C35	C34	114.46
C35	C4	C3	123.49
C4	N5	C30	129.77
N5	C4	C3	113.18
C4	C3	O43	121.83
C4	C3	O2	123.03
O43	C3	O2	115.12
O43	V1	O2	60.20
O43	V1	O44	108.03
O44	V1	O51	106.03
O51	V1	O48	67.99
O48	V1	O45	60.05
O45	V1	O2	63.17
V1	O43	C3	93.22
V1	O2	C3	91.07

Table 7. Bond Length of V(IV)=O(H_2O)(Cephradine)$_2$ (**2**)

Atom1	Atom2	Bond length (ºA)
C1	N2	1.489
N2	C3	1.423
C4	C3	1.496
C4	O5	1.275
C4	O6	1.284
O5	V7	2.278
O6	V7	2.194
V7	O8	1.551
V7	O9	2.163
O9	C10	1.285
V7	O11	2.266
C10	O11	1.277
C12	C10	1.500
C12	N13	1.417
N13	C14	1.490
C15	C14	1.564
C15	N16	1.446
N16	C17	1.410
C18	C17	1.540
C18	N19	1.494
C22	C18	1.517
C27	C22	1.507
C26	C27	1.501
C25	C26	1.337
C24	C25	1.500
C22	C23	1.339
C17	O36	1.216
N13	C38	1.447
C15	C38	1.579
C38	O39	1.186
C14	S41	1.813
S41	C42	1.818
C43	C12	1.356
C42	C43	1.491
C1	S53	1.810
C52	S53	1.815
C51	C56	1.490
N2	C60	1.431
C1	C61	1.566
C61	N62	1.445
N62	C63	1.412
C63	C64	1.540
C64	N65	1.494
C63	O82	1.216
C60	O85	1.195
V7	O87	2.651

Table 8. Bond Angles of V(IV)=O(H_2O)(Cephradine)$_2$ (**2**)

Atom1	Atom2	Atom3	Bond angle
C26	C27	C22	123.15
C27	C22	C23	122.56
C27	C22	C18	122.91
C22	C18	N19	112.84
C18	C22	C23	114.51
N19	C18	C17	107.17
C18	C17	O36	124.89
O36	C17	N16	116.90
C18	C17	N16	118.12
C17	N16	C15	124.78
N16	C15	C14	118.07
C14	C15	C38	86.64
C15	C38	N13	89.59
C38	N13	C14	94.49
C15	C38	O39	137.64
O39	C38	N13	132.63
N13	C14	S41	110.95
C14	S41	C42	99.70
N13	C12	C10	114.66
C10	O11	V7	88.25
O9	C10	O11	117.56
O11	V7	O8	110.15
O8	V7	O5	106.82
O5	V7	O6	58.54
O6	V7	O87	85.45
O87	V7	O9	84.60
O9	V7	O11	59.22
O5	C4	O6	117.49
C4	C3	C51	123.56
N2	C60	O85	133.01
N2	C60	C61	89.99
C61	N62	C63	125.25
N62	C63	O82	116.51
C3	N2	C60	130.80
N2	C3	C4	113.19
C63	C64	C68	112.71
C68	C69	C70	113.48
C69	C70	C71	123.18
S53	C1	N2	109.93
S53	C1	C61	114.51
C3	C4	O6	120.56
V7	O9	C10	92.65
O11	C10	C12	122.19

Table 9. Anti-Bacterial Activity[a,b] Data for Vanadium(IV) Complexes of Cephradine

Name of bacteria	Zone of inhibition (mm)				
	HL	(**1**)	(**2**)	(**3**)	Standard drug
Escherichia coli	0	25	25	25	30
Bacillus subtilis	0	24	24	30	33
Shigella flexenari	0	24	24	25	27
Staphylococcus aureus	0	25	25	25	33
Pseudomonas aeruginosa	0	20	20	25	24
Salmonella typhi	0	20	20	25	25

[a]Standard drug; Imipenum = 10 μg $disc^{-1}$. [b]Concentration of sample = 3 mg ml^{-1} of DMSO.

Table 10. Anti-Fungal Activity[a-d] Data for Vanadium(IV) Complexes of Cephradine

Name of fungus	%Inhibition				Standard drug	Percent inhibition	MIC
	HL	(**1**)	(**2**)	(**3**)			(μg ml^{-1})
Trichophyton longifusus	0	40	40	45	Miconazole	100	70
Candida albicans	0	60	40	60	Miconazole	100	110.8
Aspergillus flavus	0	40	40	30	Amphotericum B	100	20
Microsporum canis	0	60	50	40	Miconazole	100	98.4
Fusarium solani	0	55	60	30	Miconazole	100	73.25
Candida glaberata	0	65	60	65	Miconazole	100	110.8

[a]concentration of sample 200 μg ml^{-1} of DMSO. [b]Incubation period 7days. [c]Incubation temp. 27 °C. [d]MIC = Minimum inhibitory concentration.

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