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Synthesis, characterization, anticancer activity and biological activities of vanadium complexes of 2-mercapto-5-methyl-benzimidazole as sulphur donor ligand

Abstract

Vanadium complexes have been synthesized by the reaction of 2-mercapto-5-methyl-benzimidazole with carbon disulphide and then with different vanadium salts in different M/L ratio. The synthesized vanadium complexes have been characterized by elemental microanalysis (CHN), FT-IR spectroscopy and NMR (^{1}H, ^{13}C) spectroscopy. Elemental analysis data shows good agreement between found and calculated values. FT-IR spectroscopic data suggests the bidentate nature of the ligand. The results of multinuclear NMR revealed that coordination occurs through NCS_2 moiety. Antibacterial activity data showed that ligand and complexes showed moderate antibacterial and anti-biofilm activity. The cytotoxicity studies showed that vanadium complex (3) is less cytotoxic (2.27%) and complex (1) has maximum cytotoxicity (11.04%). *In vitro* oxidative DNA damage protection assay showed that synthesized vanadium complexes exhibited plasmid DNA protection by scavenging the oxidation products. Results of *in vitro* anticancer activity showed that oxoperoxo vanadium complex (2) exhibited significant anticancer activity (IC_{50}2.55µM) against H460 MX2 cell line.

Keywords: vanadium complexes, synthesis, characterization, anticancer activity, biological activities

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Introduction

The significance of metal ions is well established in the biological system. The most important feature of metal-coordinated system is the spatial arrangement of ligands around the central metal ion.[1–3] Among different transition metal ions which are used for various pharmacological activities, vanadium complexes are reported to exhibit various biological activities including antimicrobial, antitumor, anti hyperlipidemic, anti obesity, anti hypertension, insulin-enhancing effect, improvement of oxygen carrying efficiency of hemoglobin and myoglobin and so on.[4–6] Vanadium complexes are also used for lowering of blood glucose level,[7–10] natriuretic and diuretic effects. For the development of vanado drugs, much work has been done for vanadyl ion coordinated to various organic ligands which show insulin-mimetic effects.[11–13] Vanadium complexes exert preventive action against chemical carcinogenesis by the arrest of cell-cycle through the process of DNA fragmentation and cleavage.[14] Vanadium penetrates to the cells in the form of vanadate VO^{-3} which is then reduced to VO^{2+} (vanadyl)ion at physiological pH.[15–17] Such ions combine with different bio molecules such as nucleic acids, proteins, phospholipids, phosphates and alter the structural properties of these molecules.[18,19] The effect of vanadium complexes on pulmonary inflammation and chemokine mRNA expression have been investigated.[20] Vanadate ion induces the activation of a protein tyrosine kinase and also on the biological action of insulin. The inhibitory action of vanadyl ions on Na^- and K-ATPase activity has also been investigated.[16,21,22] Marine biofouling which is the colonization of marine microorganisms on ship's hulls is a problem that does not have any environmentally-compatible solution. Marine biofouling leads to more hydrodynamic drag that causes increased consumption of fuel and emissions of greenhouse gases.[23] Vanadium compounds inhibit the marine biofouling. These compounds exert significant antibacterial effect that prevents biofouling without being harmful to marine biota. Vanadium compounds can be used as an alternative to conventionally used antifouling agents.[24] In continuation of our previous research work,[25–29] here we report the synthesis of three new vanadium complexes which have been characterized by elemental microanalysis (CHN), NMR and FTIR spectroscopy. These complexes were also checked for various biological activities.

Materials and methods

All chemicals used for experimental work were of analytical grade and used without any further purification. Vanadyl sulphate trihydrate ($VOSO_4.3H_2O$), vanadium (III) chloride (VCl_3) and 2-mercapto-5-methyl-benzimidazole were purchased from Aldrich Chemical Company (USA). Ammonium-meta-vanadate (NH_4VO_3) was purchased from BDH (England). All organic solvents (methanol, ethanol, chloroform, acetone, DMSO etc.) were of analytical grade and purchased from Merck (Germany).

Melting points of all compounds were checked using electro thermal melting point apparatus, MP-D Mitamura Rieken Kogyo (Japan) and are found uncorrected. Elemental microanalysis was performed using CHNS-932 analyzer Leco (USA). FTIR spectra were recorded as KBr/CsBr pellets using a Perkin Elmer FT-IR-1000 spectrophotometer in the range 4000-250 cm^{-1}.

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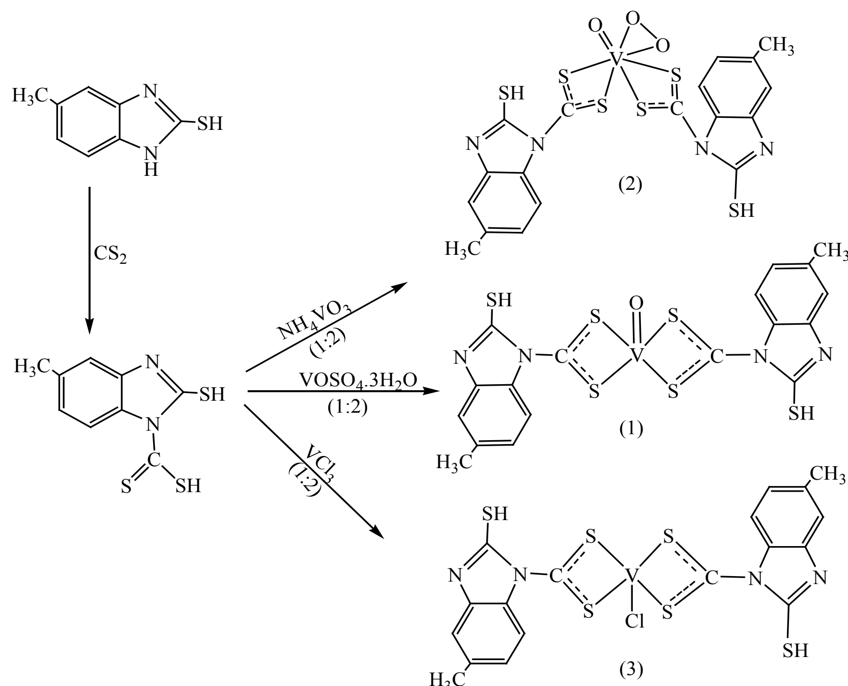
A. General procedure for the synthesis of vanadium complexes

Dissolved 2-mercapto-5-methyl-benzimidazole (1mmol) in 30mL of absolute methanol in a round bottom flask (250mL) with continuous stirring, then CS_2 (1mmol) was added drop wise in the above solution and reaction mixture was stirred at room temperature for about half an hour; then added methanolic solution of $VOSO_4.3H_2O$ (1) / NH_4VO_3 and H_2O_2 solution (2) / VCl_3 (3) in 1:2M/L ratio. The reaction mixture was stirred for about 6 h at room temperature. The solvent was evaporated through rotary evaporator and solid product obtained was dried in air (Scheme 1).



Scheme 1 Synthesis of vanadium complexes from 2-mercapto-5-methyl-benzimidazole.

B. Antibacterial activity

3,2-mercapto-5-methyl-benzimidazole and its vanadium complexes (1)-(3) were screened for *in vitro* antibacterial activity against two bacteria as *Bacillus subtilis* and *Escherichia coli* by disc diffusion method.[30] Cultures were grown by using nutrient agar as a medium in Petri plates and slants. For the preparation of inoculums 13g/L of nutrient broth was mixed well with distilled water and autoclaved. Added pure culture (10µL) of bacterial strain in growth medium stirred well and then kept in an orbital shaker at 37°C for about 24h. The inoculums were stored in a refrigerator at about 4°C temperature. The preserved inoculums ($1x10^8$spores/mL) were further used for analysis. Nutrient agar (28g/L) was mixed well in distilled water and homogenously distributed. Sterilized the growth medium by using an autoclave for about 15minutes at 121°C temperature; inoculums (100µL/100mL) were then shifted to growth medium and poured in sterilized petri plates. Discs of filter paper were made and laid flat on growth medium containing 100µL of tested sample; incubated the Petri plates at about 37°C temperature for 24hours in order to multiply bacteria. The compounds having good antibacterial activity stopped the growth of bacteria and clear zones are visualized. Zone reader is used to measure the inhibition zone.[31]

C. Cytotoxicity by hemolytic activity

Cytotoxicity of the compounds was checked by hemolytic activity using the standard Powell's method,[32] freshly taken heparinized 3mL human blood was smoothly mixed and poured to a sterilized falcon tube (15mL) and centrifuged for 5minutes at 4,200rpm. The supernatant was poured off and formed viscous pellet was washed three times with chilled (4°C) (5mL) sterile isotonic PBS (phosphate-buffered saline) solution, adjusted the system to pH 7.4. Mix the solution for half hour at 25-30°C temperature; then suspended the washed cells in 20mL of chilled phosphate buffer saline. The blood cell suspension was maintained on wet ice and diluted with sterile PBS, the cell count should be 7.068×10^8 cells per mL for each test. The sample (20µL) in five different solvents was taken in 2mL eppendorf tubes. For each assay Triton X-100 (0.1%) was taken as control (positive) for 100% blood lysis and PBS was taken as a negative control (0% lysis). In each eppendorf tube that contained 20µL of sample, 180µL of blood cell suspension was added and mixed thoroughly with a pipette tip. The tubes were then incubated for 37°C for 35minutes and agitated for 10minutes after the incubation. The eppendorf tubes were placed on ice for about 5minutes and then centrifuged at 4,200rpm. About 100µL of supernatant was taken from supernatant and diluted with 900µL cold PBS. All tubes were maintained on wet ice after dilution. Then poured 200µL into 96 well plates and three replicates were taken which contain one positive control and one negative control. After this, absorbance at 576nm was taken at BioTek, µ CuantTM instrument (BioTek, Winooski, VT, USA). Triton X-100 (0.1%) was used as positive control (100% of blood lysis) and PBS buffer as negative control (0% of blood lysis). The experiment was done in triplicate. The % hemolysis values were obtained using the following formula:

$$\%\ Hemolysis = Hb_{ABS}\ /\ Hb_{100\%ABS} \times 100$$

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D. Biofilm inhibition assay

Those bacteria that possess good adhesion property to the surfaces can produce the biofilm. For determination of microbial adhesion to the surfaces in the presence of the vanadium complexes, the micro titre plates were prepared as previously described.[33] Briefly, a bacterial culture and yeast were grown overnight in the broth media. Then, the cultures were diluted upto 1:100 into fresh medium for biofilm inhibition assay. The diluted solution (200µL) was added to 96-well plate. After the growth phase, the medium was removed carefully with pipette, the wells present in micro titre plates were rinsed three times with 200µL of sterile PBS. After washing, wells were filled with 96% ethanol for 15minutes. The micro titre plates were dried in air and then, 200µL of 1% crystal violet were added for 5minutes. Then, the micro titre plates were washed with distilled water, and then dried. Finally, 200µL of 33% glacial acetic acid were added to the wells and absorbance was measured at 540nm with an ELISA reader. Data for biofilm formation of all strains were compared with the data obtained for the negative control. *S. aureus* PTCC 1431 was used as positive control and microbial medium without microorganisms was used as the negative control.

E. *In vitro* anticancer activity

The *in vitro* anticancer activity of the synthesized vanadium complexes against different cancer cell lines was performed by MTT assay according to Mosmann's method.[34] In MTT assay, the reduction of soluble 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) occurs into a blue-purple Formosan product that is mainly formed by the mitochondrial reductase activity within living cells. The cells used for this assay were cultured in RPMI 1640 medium which is supplemented with fetal calf serum (10%). Cells were suspended in growth medium (2×10^4 cells/mL) were poured in 96-well plates and incubated at about 37°C in a CO_2 (5%) incubator. After 12hours, 2mL of test sample was added to cells in 96-well plates and cultured at 37°C for 3 days. The cells were mixed with MTT solution (20µL) and then incubated for about 4h at 37°C. The supernatant was removed from each well and DMSO (100mL) was added to each well in order to dissolve the Formosan crystals that were formed by the reduction of MTT. After mixing with mechanical plate mixer, the absorbance of each well was measured by a micro plate reader using a test wavelength of 570nm. The results were expressed in IC_{50} values which is concentration of drugs inducing 50% inhibition of cell growth of treated cells when compared to the growth of control cells. Each experiment was performed in triplicate. There was a good reproducibility between replicate wells with standard errors below 10 %.

Results

The ligand and vanadium complexes are solids and stable at room temperature. Physical data is summarized in **Table 1.**

a. FTIR spectroscopy

FT-IR spectra were recorded as KBr/CsBr discs, in the range 4000-250cm^{-1} (Table 2). The vanadium complexes (1)-(3) showed complexation through sulphur atom of -NCS_2 moiety.

b. ^{1}H-NMR spectroscopy

The characteristic signals in the ^{1}H NMR spectra were recorded in duterated DMSO and data is given in Table 3 while NMR numbering scheme is given in Scheme 2.

Table 1 Physical data of vanadium complexes of 2-mercapto-5-methyl-benzimidazole

Comp No.	Mol formula	Mol.Wt	Melting point	Yield (%)	%C (found)	%H (found)	%N (found)
HL	$C_8H_8N_2S$	164.23	290-293	-	58.5(58.56)	4.91(4.95)	17.05(17.02)
1	$[VO(C_9H_7N_2S_3)_2]^{IV}$	545.65	202 Dec	65.43	39.62(39.58)	2.59(2.54)	10.26(10.3)
2	$[VO(O_2)(C_9H_7N_2S_3)_2]^{V}$	577.65	149 Dec	56.12	37.42(37.48)	2.44(2.48)	9.69(9.72)
3	$[VCl(C_9H_7N_2S_3)_2]^{IV}$	565.15	186 Dec	58.70	38.25(38.27)	2.50(2.48)	9.90(9.92)

Table 2 IR spectral data[a] (cm^{-1}) of vanadium complexes of 2-mercapto-5-methyl-benzimidazole

Comp No.	υ(V=O)	υ(V-S)	υ(CSS)	υ(V-Cl)	υ(C-N)
1	966s	439m	1182s	-	1368s
2	958s	504m	1170m	-	1371s
3	-	438w	1169m	400m	1370s

s-strong; m-medium; w-weak

Table 3 ^{1}H-NMR spectral data[a,b] (ppm) of ligand and its vanadium complexes

	Chemical Shift (ppm)			
Proton No.	(HL)	1	2	3
2	7.39-7.45d (6.3)	7.34-7.42d (6.4)	7.65-7.73d (6.3)	7.54-7.67d (6.3)
3	7.05-7.16d (6.4)	7.09-7.20d (6.5)	7.11-7.18d (6.3)	7.23-7.28d (6.4)

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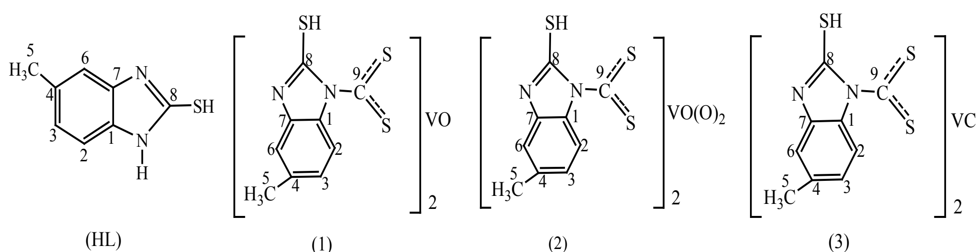
Table continue

Proton No.	Chemical Shift (ppm)			
	(HL)	1	2	3
4	-	-	-	-
5	2.32s	2.24s	2.36s	2.29s
6	7.48s	7.53s	7.48s	7.59s
-NH	5.07s	-	-	-

[a]Chemical shifts (δ) in ppm.

[b]Multiplicity is given as s-singlet, d-doublet, coupling values are given in parenthesis



Scheme 2 NMR numbering scheme.

c. ^{13}C-NMR spectroscopy

The characteristic resonance signals in the ^{13}C NMR spectra of synthesized vanadium complexes were recorded in duterated DMSO. The discrete ^{13}C signals for all the individual carbon atoms were identified and the data is given in Table 4.

Table 4 ^{13}C-NMR spectral data[a] (ppm) of vanadium complexes

Carbon No.	1	2	3
1	134.26	134.35	134.29
2	113.5	113.22	113.48
3	122.75	122.73	122.69
4	130.32	130.16	130.43
5	23.41	23.62	23.45
6	114.83	114.77	114.53
7	134.42	134.25	134.63
8	166.27	166.4	166.37
9	198.43	198.49	198.36

[a] Chemical shifts(δ) in ppm.

d. Antibacterial activity

The antibacterial activity was checked against two bacterial strains by using disc diffusion method (Table 5). Rifampicine was used as a standard drug.

e. Anti-biofilm activity

The *in vitro* anti biofilm activity was checked against *S. aureus*. Percentage biofilm inhibition of free ligand and its vanadium complexes is represented in Table 6.

Table 5 Antibacterial activity of ligand and vanadium complexes

Compound No.	Zone of inhibition (mm)	
	Escherichia coli	Bacillus subtilis
HL	10	10
1	13	14
2	11	12
3	11	11
*Standard drug	35	32

* Rifampicine

Table 6 Biofilm inhibition potential of ligand and vanadium complexes

Compound No.	Biofilm inhibition (%)
HL	3
1	18
2	16
3	14
*Rifamacin	87.43

*Standard drug

f. Cytotoxicity

The cytotoxicity was checked against human red blood cells by hemolytic method. The results were compared with standard drug Triton X-100 (positive control) and PBS (negative control). The % cytotoxicity is given in Table 7.

Table 7 Hemolytic activity of ligand and vanadium complexes

Compound No.	Hemolytic activity (%)
HL	0.311
1	11.04
2	3.54
3	2.27
PBS	0.64
Triton-X-100	100

g. *In vitro* anticancer activity

Anticancer activity of the vanadium complexes (1)-(3) was determined (IC_{50} values in μM) against two cancer cell lines as KBV200 and H460 MX2 by MTT assay. MTT is 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide. IC_{50} values for vanadium complexes are given in Table 8.

Table 8 Anticancer activity of vanadium complexes against KBV200 and H460 MX2 cancer cell lines

	Anticancer activity IC50 (μM)	
Compound No.	KBV200	H460 MX2
1	41.78	12.84
2	39.59	2.55
3	>50	>50

Discussion

Elemental analysis (C, H and N) data of ligand and vanadium complexes (1)-(3) showed good agreement between found and calculated values. The characteristic IR peaks obtained for the ligand and vanadium complexes (1)-(3) were found in close agreement with the reported values given in the literature.[35] The NH band of ligand disappeared and new bands for υ(C-N), υ(V-S) and υ(CSS) were appeared in the range 1368-1371, 438-440 and 1169-1182cm^{-1}, respectively which confirms the complexation.[36,37] The SH group did not take part in complexation. For complexes (1) and (2), new bands for υ (V=O) were also observed in the range 958-966 cm^{-1}.

In the ^{1}H NMR spectra of studied complexes, all the protons present in the ligand and complexes have been identified in position and number with the protons calculated from incremental method.[38] ^{1}H NMR data of free ligand shows a singlet of –NH group at 5.07ppm. Signal of proton 2 appears as doublet in the range of 7.39-7.45ppm. The proton 3 shows a doublet in the range of 7.05-7.16ppm. The methyl protons appear as singlet at 2.32ppm. Proton 6 shows a singlet at 7.48ppm. Proton 2 appears as doublet in the range of 7.34-7.73ppm. The proton 3 also shows a doublet in the range of 7.09-7.28ppm. Proton 5 of methyl group gives singlet in the range of 2.24-2.36 ppm. Proton 6 shows a singlet in the range of 7.48-7.59ppm.

In the vanadium complexes (1)-(3), the important chemical shift of the carbon attached with sulphur atoms (CS_2) was observed in the range 198.36-198.49 ppm that indicates the attachment of vanadium at this site. The high value of thione carbon chemical shift could be explained by an increase of pi-bond order in the whole NCS_2 moiety.[39] The zone of inhibition for standard drug was found to be 35 and 32mm against *E. coli* and *B. subtilis*, respectively. Ligand (HL) and vanadium complexes (1)-(3) showed moderate antibacterial activity, while activity of complexes was found slightly greater than the ligand. Antibacterial activity for complex (1) was maximum than other complexes.

The ligand and vanadium complexes (1)-(3) showed moderate anti biofilm activity. Complex (1) showed highest value of biofilm inhibition activity (18%), while complex (3) showed lowest activity (14%). The activity of vanadium complexes was increased on complexation as reported earlier.[40] According to chelation theory, the lipophilic character of metal complexes is increased on complexation that favours their permeation through bacterial membrane and blocks the metal binding sites.[41]

Ligand showed negligible cytotoxicity (0.311%), while vanadium complexes (1)-(3) showed moderate values of hemolytic activity. Maximum cytotoxicity was found for complex (1) which was 11.04% while complex (3) showed minimum cytotoxicity. Vanadium complexes having IC_{50} values more than 50μM were considered inactive against anticancer activity. Vanadium complexes of 2-mercapto-5-methyl-benzimidazole ligand (HL) showed significant anticancer activity against H460 MX2 cell line. Complexes (1) and (2) were active against both cell lines but activity against H460 MX2 cells was greater and significant than KBV200. Complex (1) showed significant anticancer activity with IC_{50} value 12.84μM while complex (3) was found inactive against both cell lines. Complex (2) which is an oxo-peroxo-vanadium complex showed maximum activity (IC_{50} 2.55μM) against H460 MX2 cells and these results are also in accordance with the earlier reports.[42]

Conclusion

Vanadium complexes have been synthesized and characterized by different techniques. Elemental analysis data was found to be in good agreement with the calculated values. IR data suggested the bidentate nature of ligand. Multinuclear NMR data showed that complexation occurs through -NCSS moiety. The vanadium complexes and free ligand were checked for different biological activities such as antibacterial activity, cytotoxicity or hemolytic activity and *in vitro* anticancer activity. Ligand and synthesized vanadium complexes exhibited moderate antimicrobial and biofilm inhibition activity. The cytotoxicity study showed that % cytotoxicity of vanadium complexes is moderate but higher than free ligand. *In vitro* anticancer activity of synthesized vanadium complexes showed that complex (2) exhibited significant anticancer activity (IC_{50} 2.55μM) against H460 MX2 cell line.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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