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Spectral Studies and Antimicrobial Activities of Novel Synthesized Oxovanadium (IV) Complexes with Steroid Ligands

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Abstract: ***Two novel vanadyl complexes (ML) with steroid ligands (betamethasone and prednisolone) have been successfully synthesized at ambientconditionsusing suitable solvents, where M is VO^{IV} and L is betamethasone or prednisolone. The complexes were synthesized by reacting $VOSO_4$ and the corresponding ligands in 1:2 molar ratio. The synthesized compounds were structurally characterized by their melting point, UV-Vis, and FT-IR spectra. The spectral features of the new complexes $[VO^{IV}(Prd)_2]$ (1) and $[VO^{IV}(Beta)_2]$ (2) confirm the formation of the complexes. The synthesized complexes were further screened against microbial growth with different cultures which disclosed the potency of the new compounds. The complexes possess higher antimicrobial potencies against Proteus mirablis and Salmonellatyphithan betamethasone and prednisolone ligands even at concentrations lower than the MIC values.***

Keywords: Oxovanadium (IV), prednisolone, betamethasone, metal complex, FTIR, antimicrobial

1. Introduction

Vanadium compounds have been identified for significant roles in humans, especially in the regulation of metabolic processes. At low concentrations, vanadium is nontoxic but at higher intake, it will increase in body tissues such as bones, kidneys, and liver [1]. In pharmaceuticals, vanadium play vital roles as a biometal and in the development of drug compounds. Many vanadium compounds have shown antidiabetic, antihypertensive, and anticancer activity [2]. For diabetic conditions, inorganic vanadyl sulfate, vanadate, peroxidovanadates and organic vanadium compounds have proved beneficial in suffocating cellular glucose update and controlling free fatty acid level in a body system affected by either type 1 and type 2 diabetes [2].

Coordination chemistry has revealed the interaction between vanadium and a variety of ligands especially oxygen, nitrogen, and sulfur donor ligands [3]. Prednisolone and betamethasone belong to the family ofcorticosteroid drugs that can act as viable ligands for vanadium coordination because of their potential metal-binding sites which are capable of increasing and diversifying their biological effects.

Prednisolone is a medication used to treat conditions such as autoimmune disorder, allergies, asthma and arthritis [4], inflammatory conditions and cancer [4,5]. Prednisolone has also shown strong medical effects against eye inflammation, high blood calcium, and multiple sclerosis [5]. Prednisolone therapy has shown few side effects with short-term use which include nausea and tiredness [4] but long-term use gives rise to more severe effects including weight gain, rise in cholesterol, increase in blood pressure, and diabetes [6,7].

Betamethasone is a synthetic corticosteroid medication with immunosuppressive and anti-inflammatory properties [6]. It has shown strong effects in the treatment of various diseases including rheumatoid arthritis, allergies and cancer e.g. leukemia [9]. Betamethasone was one of the corticosteroid agents identified to be effective against COVID-19, among others like dexamethasone [10].Betamethasone can be administered via the mouth, applied to the skin as a cream and injected into the muscle [9]. Betamethasone is associated with serious side effects like allergic reactions, muscle weakness, and risk of infection [9]. All the same, betamethasone has been shown to possess antibacterial effects against some clinically relevant gram-positive and gram-negative bacteria [8]. In view of this, we explored the synthesis, UV-Visible, and FTIR spectroscopic characterization of vanadyl complexes of prednisolone and betamethasone and investigated their antimicrobial activity against two gram-negative bacteria: *Proteus mirablis and Salmonellatyphi*.

2. Materials and Methods

Materials

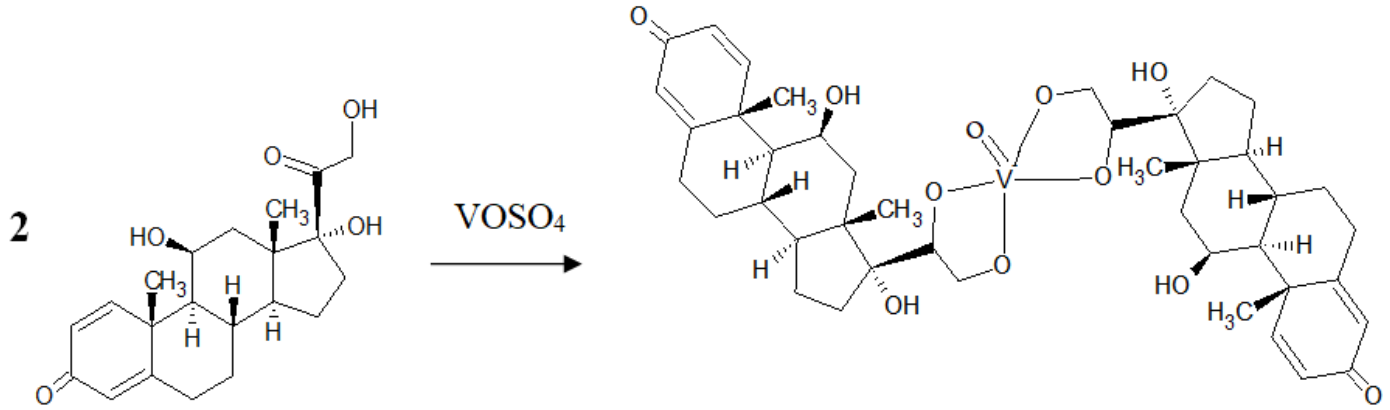
Prednisolone and betamethasone (99%) were gifts from Sidom Pharmaceuticals Industries,Enugu, Nigeria. Vanadium sulfate was from VWRinternational, England.Chloroformand analytical grade ethanol (98%) were from Merck Germany. All other reagents and chemicalsused were of analytical reagent grade andwere used as such without any furtherpurification. Double distilled water was usedwherever required. Electronic absorption spectra of the prepared complexes **1** and **2** were taken on JASCO V-730 Ultraviolet-Visible spectrophotometer and infrared spectra were recorded using Fourier transform infrared spectrophotometer Shimadzu 8400S as potassium bromide disc at the wavelength range of

4000-400 cm^{-1}. Melting points were collected on Stuart digital melting point apparatus.

Synthesis of Complexes

$[VO^{IV}(Prd)_2]$ (1): 0.72g (2mmol) of prednisolone was dissolved in 7 ml chloroform in a round bottom flask, and stirred for 1 hour. 7 ml methanolic solution of 0.163g (1mmol) $VOSO_4$ was then added and the resulting light blue solution was stirred for 5 hours and kept overnightin round bottom flask. The colour of the solution changed to green. The solution was filtered into a 250 ml beaker and the filtrate was allowed to evaporate slowly at ambient conditions; the green residue was kept in a desiccator to dry. After a few days, green precipitated crystals were formed from the filtrate. Weight of the product: 0.468g (60.7%). The synthetic route can be shown according to the following reaction equation and Scheme 1.

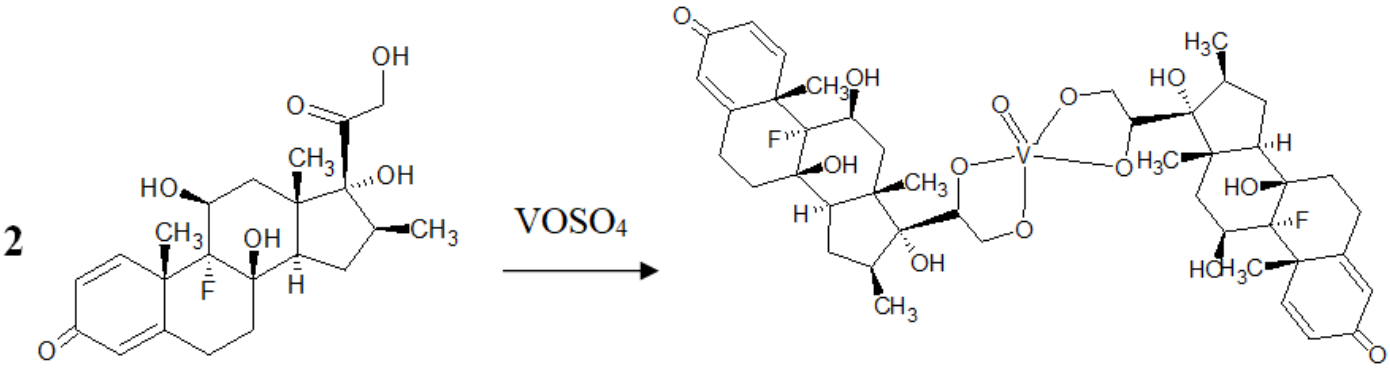
$$VOSO_4.5H_2O + 2(Prd\text{-}H) \longrightarrow [VO\text{-}(Prd)_2].5H_2O + H_2SO_4$$



Scheme 1: Schematic synthesis of $[VO^{IV}(Prd)_2]$ complex

$[VO^{IV}(Beta)_2]$(2): $VOSO_4$ 0.163g (1mmol) was dissolved in 12 ml methanol in a round bottom flask and stirred for one hour. Betamethasone 0.588g (1.5mmol) was added directly into the solution and stirring was continued for 6 hours. The solution was filtered into a 250 mLbeaker and was kept for slow evaporation at ambient conditions. (There was no precipitate formed and no residue during the filtration). After four days of slow evaporation of the solution, green crystalline compound was precipitated. Weight of the product: 0.546g (62.9%). Synthesis can be shown according to the following reaction equation and Scheme 2.

$$VOSO_4.5H_2O + 2(Beta\text{-}H) \longrightarrow [VO\text{-}(Beta\text{-}H)_2].5H_2O + H_2SO_4$$



Scheme 2: Schematic synthesis of $[VO^{IV}(Beta)_2]$ complex

Antimicrobial Susceptibility Test

The complexes were tested for their antimicrobial activity by agar well diffusion method. The pre-sterilized petri-dish containing 20 ml of nutrient agar was allowed to solidify. Then bacteria were introduced aseptically using striking plate method. A sterile cork borer was used to make wells in each of the plates. Suitable dilutions of the complexes were made with distilled sterile water and carefully placed in each well by micropipette. The plates were incubated at 37 °C for 24 hours. Antimicrobial activity was evaluated by measuring the inhibition zones. Inhibition zones were recorded as the diameter of no growth area.

3. Result and Discussion

Uv-Vis Absorption Spectra Studies

The absorption spectra of the ligands and complexes were recorded in the range of 200-1100 nm and were illustrated in Table 1. The absorption peaks at 227 nm, 340 nm, 380 nm, 251 nm, 309 nm, 372 nm, 249 nm and 382 nm were assigned to intra ligand transitions ($\pi \rightarrow \pi *$) of the ligands. The peaks at 800 nm and 781 nm were due to the d-d electronic transitions of the type $^2B_2g \rightarrow {}^2E_g$ ($d_{xy} \rightarrow d_{xz}$) of the VO(IV) complexes [11]. The UV-Visible spectra of both the ligands and complexes are shown in figures 1 and 2.

Table 1: Uv-Vis Absorption Spectra of ligands and VO(IV) complexes

Compounds	UV-Vis absorption peaks (nm)	Transition
Prednisolone	254 310	$\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$
Betamethasone	227 340 380	$\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$
	251 372 800	$\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$ d-delectronic transition ($^2B_2g \rightarrow {}^2E_g$)
[VO(IV) $(Beta)_2$]	249 382 781	$\pi \rightarrow \pi *$ $\pi \rightarrow \pi *$ d-delectronic transition ($^2B_2g \rightarrow {}^2E_g$)

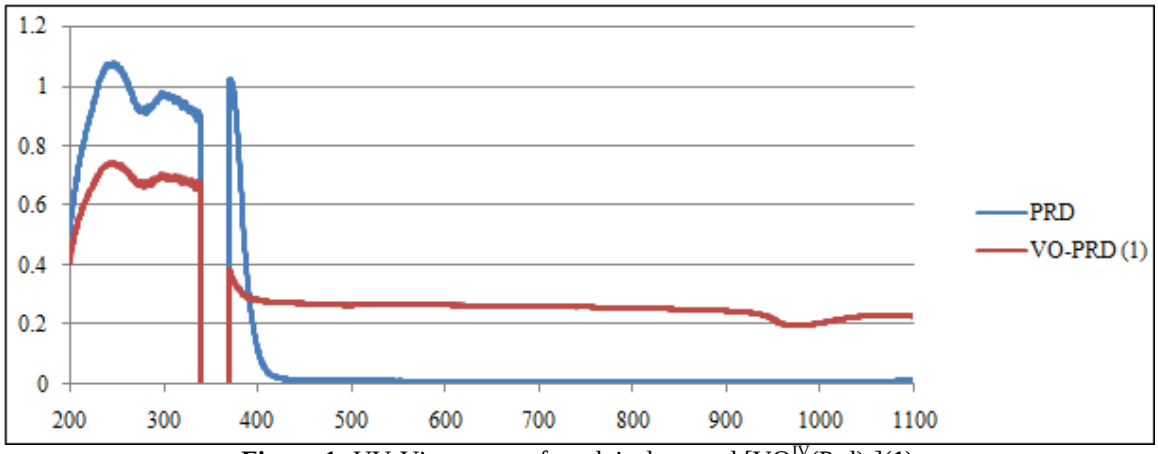


Figure 1: UV-Vis spectra of prednisolone and [$VO^{IV}(Prd)_2$](**1**)

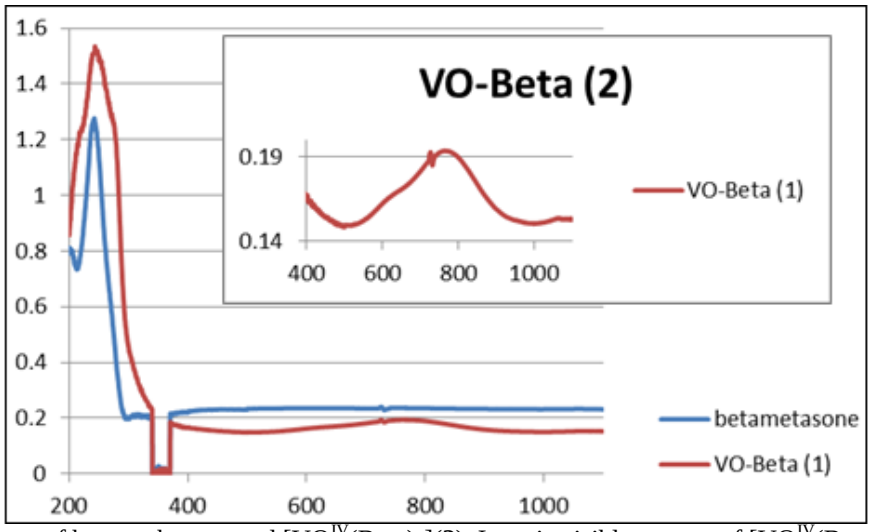


Figure 2: UV-Vis spectra of betamethasone and [$VO^{IV}(Beta)_2$](**2**). Inset is visible spectra of [$VO^{IV}(Beta)_2$] (**2**) from 400 -1100 nm.

Infrared Spectra Studies

FTIR spectra give basic information about the coordination mode of the ligands with the central metal and the structures of the complexes obtained from synthesis. The infrared spectra of the prepared complexes **1** and **2** were recorded as KBr disc on Shimadzu 8400S Fourier transform infrared spectrophotometer at the wavelength range of 4000-400 cm^{-1}. Spectra of the complexes show significant characteristic FTIR bands similar to the starting ligands. The obtained spectra of the complexes are listed in table 4. The spectrum of [VO-$(Prd)_2$] (**2**)showed a sharp band at 3412 cm^{-1}attributed to O-H stretching of water of crystallization, the band at 3254 cm^{-1} attributes to O-H stretching alcohol. The medium bands at 3014 cm^{-1} and 2847 cm^{-1}were assigned to the C-Hstretching of alkene and aliphatic moieties respectively. The weak band at 1624 $cm^{-1}$was assigned to stretching vibration of C=C aromatic alkene. The medium band at 1489 cm^{-1} is attributed to bending vibration of CH_2while the medium band at 1384 cm^{-1} is attributed to CH_3 bending. Similar spectra was obtained for [VO-$(Beta)_2$] (**2**).

The infrared spectrum of [VO-$(Beta)_2$] has strong broad band at 3404 cm^{-1} and weak broad bands 2945 cm^{-1} which were assigned to stretching vibrations of O-H of water of crystallization and C-H alkene respectively [9]. The medium broadband at 2875 cm^{-1} can be attributed to aliphatic C-H stretching. The strong band at 1724 $cm^{-1}$is attributed to the C=O stretching. Another weak band at 1660 cm^{-1} and a strong band at 1454 cm^{-1} were assigned to C=C alkene and CH_2 bending vibrationsrespectively. The strong absorption band that appeared at 1301 cm^{-1} can be attributed to the C-F stretching offluoro group. The strong broadband observed at 1143 and 1047 cm^{-1} can be assigned to C-O stretching vibration.

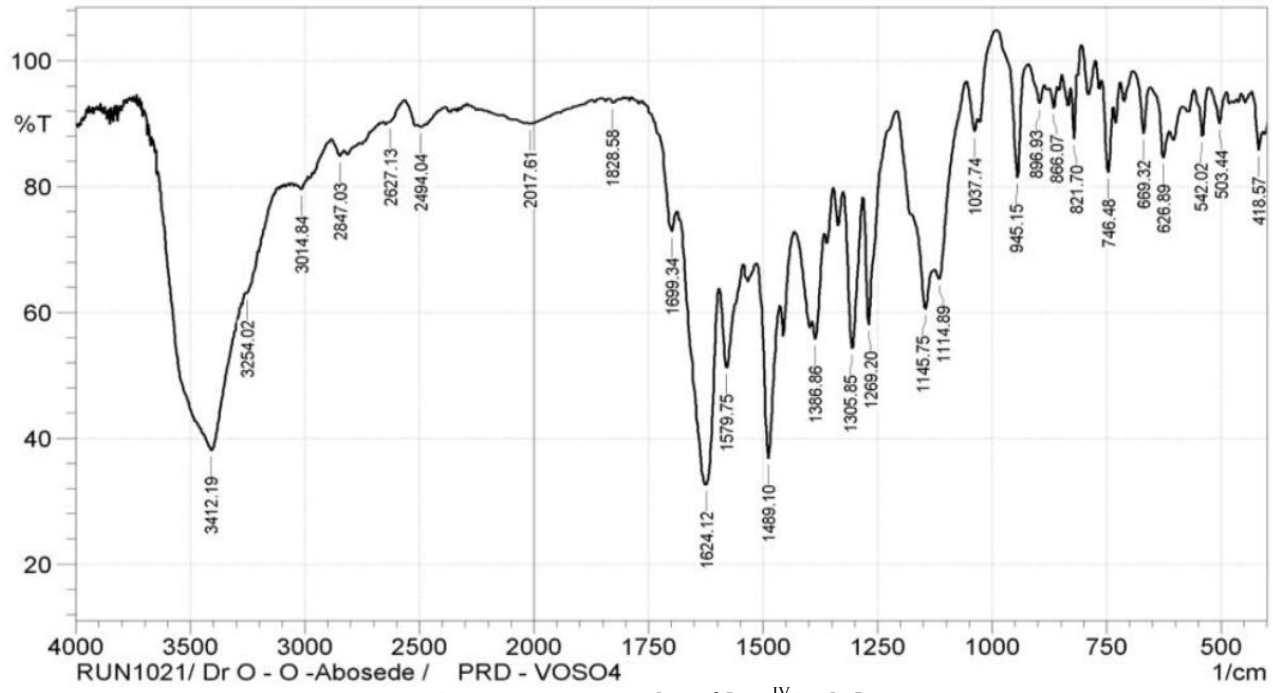


Figure 3: FTIR complex of [$VO^{IV}(Prd)_2$]

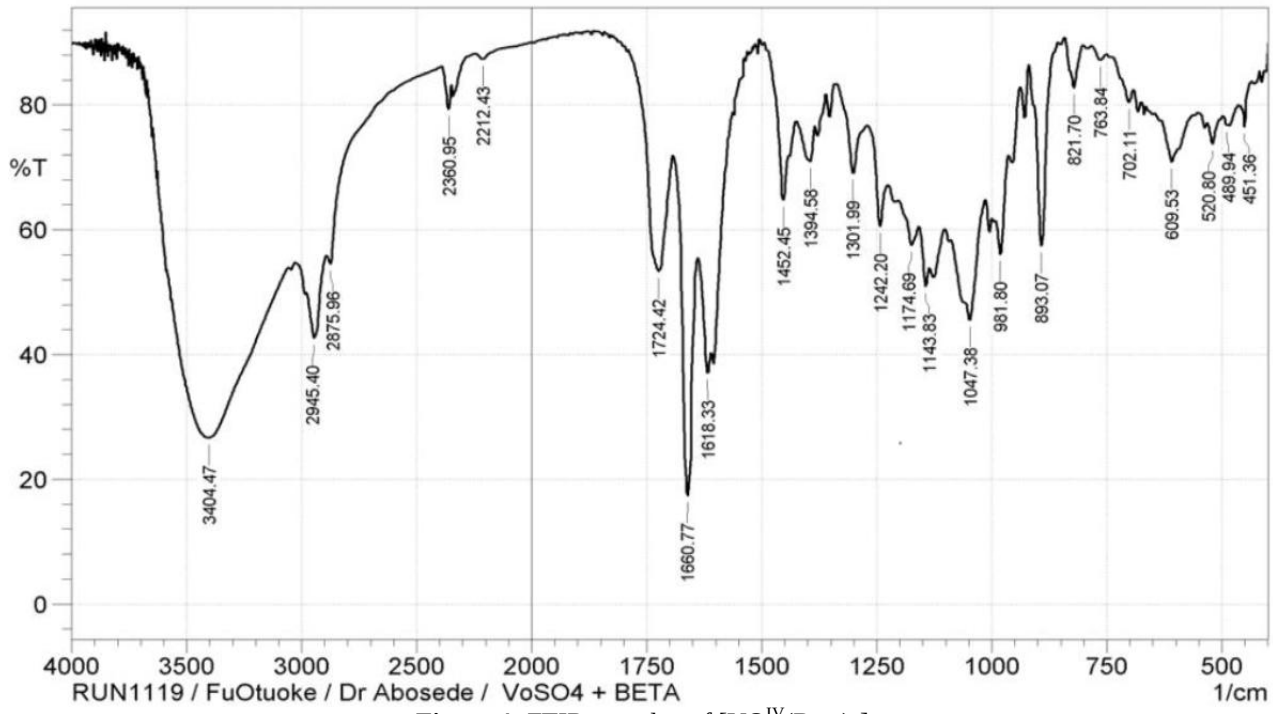


Figure 4: FTIR complex of $[VO^{IV}(Beta)_2]$

Table 2: Physical properties and absorption characteristic of ligands, metal salt, and complexes

Compound	Colour	Melting point ^{O}C	Appearance	Yield
Prednisolone	White	235	Powder	---
Betamethasone	White	247	Powder	---
$VOSO_4$	Blue	105	Crystalline	---
$[VO(IV)(Prd)_2]$	Green	> 360	Crystalline	60.7
$[VO(IV)(Beta)_2]$	Green	> 360	Crystalline	62.9

Table 3: Solubility of ligands, metal salt, and complexes in different solvents

Compound	Distilled H_2O	IPA	Methanol	Ethanol	Chloroform	Acetone
Prednisolone	Slightly soluble	Insoluble	Soluble	Soluble	Slightly soluble	Slightly soluble
Betamethasone	Slightly soluble	Insoluble	Slightly soluble	Slightly soluble	Insoluble	Insoluble
$VOSO_4$	Soluble	Insoluble	Soluble	Insoluble	Insoluble	Insoluble
$[VO(IV)(Prd)_2]$	Soluble	Insoluble	Soluble	Slightly soluble	Slightly soluble	Insoluble
$[VO(IV)(Beta)_2]$	Insoluble	Insoluble	Slightly soluble	Insoluble	Insoluble	Insoluble

Table 4: Diagnostic FTIR bands of the complexes

Compound	υ(O-H) (water of crystallization)	υ(O-H)	υ(C-H)		υ(C=O)	υ(C=C)	υ(C-O)	υ(C-F)
			Ar	**Alip**				
$[VO\text{-}Prd)_2]$ (1)	3412	3245	3014	2847	1699	1624	1145, 1037	1305
$[VO\text{-}(Beta)_2]$ (2)	3404	---	2945	2875 1452	1724 1660	1618	1143, 1047	1301

Ar = aromatic, alip = aliphatic

Antimicrobial Studies against *Proteus mirablis* and *Salmonellatyphi*

Theligandsand their metal complexes were screened for their antimicrobial activities at different concentrations of 520, 260 and 130 mg/ml. The inhibition effects and minimum inhibitory concentrations of the ligands and their metal complexes on growth of *Proteus mirablis* and *Salmonella typhi* are summarized in Table 3. The growth of *Proteus mirablis* and *Salmonella typhi* is more inhibited by both complexes than the respective parent ligands (betamethasone has no inhibitory activity against both *Proteus mirablis* and *Salmonella typhi)*. $[VO(IV)(Prd)_2]$ has higher antibacterial activity against both *Proteus mirablis* and *Salmonella typhi* than $[VO^{IV}(Beta)_2]$. Both complexes have MIC value of 160 mg/ml against both *Proteus mirablis*and *Salmonella typhi*.

Table 5: Antimicrobial susceptibility of VO(II) complexes

	Zone diameter values (mm) at different concentrations						
Compound	*Proteusmirablis*			*Salmonellatyphi*			
(mg/ml)	520	260	130	520	260	130	MIC (mg/ml)
Prednisolone	-	-	-	22	16	-	520
$[VO(IV)(Prd)_2]$	42	40	32	36	24	20	160
Betamethasone	-	-	-	-	-	-	-
$[VO^{IV}(Beta)_2]$	20	20	-	20	16	-	160

4. Conclusion

Oxovanadium (IV) complexes of prednisolone and betamethasone were successfully synthesized at ambient conditions. The wavelength of absorption for d-d transition of 778 nm and 781 nm depicts square pyramidal geometry andFTIR spectra data obtained for the complexes substantiates the formation of the complexes and the complexes are stable. Vanadium ions are linked to oxygen (O) atoms of prednisolone and betamethasone in the complexes which crystallize with water of crystallization. The complexes possess higher antimicrobial potencies than the respective ligands. The complexes demonstrated antimicrobial potencies even at concentrations lower than the MIC values against *Proteus mirablis* and *Salmonellatyphi*. The outcome of this present research has further demonstrated the synergistic effect of biologically relevant metal ions and ligands leading to improved biological activities.

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