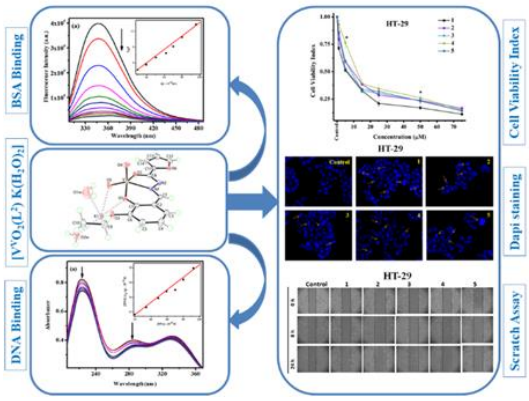
Aqueous dioxidovanadium(V)-aroylhydrazones: Role of biomolecular interactions, and hydrophobicity in anticancer potential

Gurunath Sahu[1], Sudhir Lima[1], and Rupam Dinda[1,*]
[1]e-mail: gurunathsahu@gmail.com, National Institute of Technology, Rourkela, India
* e-mail: rupamdinda@nitrkl.ac.in, National Institute of Technology, Rourkela, India

Vanadium(V) complexes with aroylhydrazones having bio-important heterocyclic moieties in the ligand backbone are very efficient for cytotoxicity studies.[1] Another important aspect for this class of compounds to be a good metallodrug is their solubility and stability in aqueous media which plays an important role in drug delivery to the targeted organ in its intact form. However, because of poor solubility many well-known therapeutic drugs found to be less effective with common side effects. Therefore, incorporating such moieties for synthesis of water soluble complexes could be fascinating for cytotoxicity studies.

In this presentation, we have explored the detailed study on the synthesis and biological activity[2,3] of some dioxidovanadium(V), $[\{V^{V}O_2L^{1-2}\}A(H_2O)_n]_\alpha$ (**1**−**5**), complexes with aroylhydrazone ligands having hetero cycles moiety incorporated with alkali metals (Na^+, and K^+) as counter cation.[1] To study the biological behaviour, complexes were tested for solution phase stability, hydrophobicity, and DNA/BSA binding propensity experiments. Finally, the cytotoxicity study of **1**−**5** was performed against several cancer cell lines such as HeLa, HT-29, MCF-7 and also for comparison a normal cell line NIH-3T3 was used. Remarkably, **1** with IC_{50} value = 5.42 ± 0.15 μM showed greater activity than cisplatin against HT-29 cell line. However, in this study, we have established a relation of hydrophobic behavior of compounds directly to their anticancer activities. In addition, we found that **1**−**5** were selectively effective against HT-29 cells in comparison with MCF-7 and HeLa cells.



Keywords: Cytotoxicity; DNA and protein interaction; Dioxidovanadium(V); Partition coefficient; Water-soluble

1. G. Sahu, A. Banerjee, R. Samanta, M. Mohanty, S. Lima, E. R. T. Tiekink, and R. Dinda, *Inorg. Chem.* **2021**, 60, 15291−15309
2. A. Banerjee, S.P. Dash, M. Mohanty, G. Sahu, G. Sciortino, E. Garribba, M.F.N.N. Carvalho, F. Marques, J. Costa Pessoa, W. Kaminsky, K. Brzezinski, R. Dinda, *Inorg. Chem.* **2020**, 59, 14042–14057
3. S. Roy, M. Böhme, S.P. Dash, M. Mohanty, A. Buchholz, W. Plass, S. Majumder, S. Kulanthaivel, I. Banerjee, H. Reuter, W. Kaminsky, R. Dinda, *Inorg. Chem.* **2018**, 57, 5767–5781

Aqueous dioxidovanadium(V)-aroylhydrazones: Role of biomolecular interactions, and hydrophobicity in anticancer potential

Gurunath Sahu, Sudhir Lima and Rupam Dinda*

Department of Chemistry, National Institute of Technology, Rourkela, Odisha-769008, India.

e-mail id: rupamdinda@nitrkl.ac.in (R. Dinda)

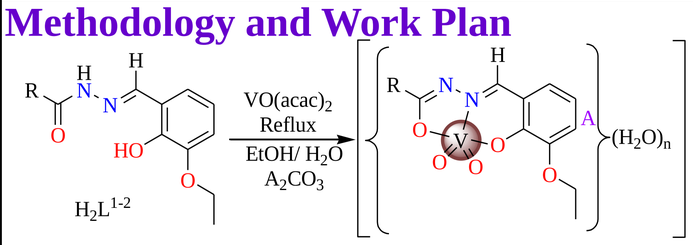
Inorg. Chem. 2021, 60, 15291−15309

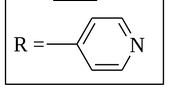
Introduction : Vanadium(V) complexes with aroylhydrazones having bio-important heterocyclic moieties in the ligand backbone are very efficient for cytotoxicity studies. Another important aspect for this class of compounds to be a good metallodrug is their solubility and stability in aqueous media which plays an important role in drug delivery to the targeted organ in its intact form. However, because of poor solubility many well-known therapeutic drugs found to be less effective with common side effects. Therefore, incorporating such moieties for synthesis of water soluble complexes could be fascinating for cytotoxicity studies.

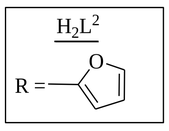
Objectives

- New anionic aqueous dioxidovanadium(V), $[\{VO_2L^{1-2}\}A(H_2O)_n]_\alpha$ (**1−5**), complexes with heterocyclic aroylhydrazone ligands were synthesized and characterised by UV_Vis, IR, NMR, ESI-MS and single crystal X-ray crystallography.
- The compounds were screened for DNA/BSA interactions, hydrophobicity, and cytotoxicity studies.
- Cytotoxicity was performed against three different HT-29, MCF-7, and HeLa cancer cell lines.
- Wound healing assays indicated anti-migration in case of HT-29 cells.

Methodology and Work Plan

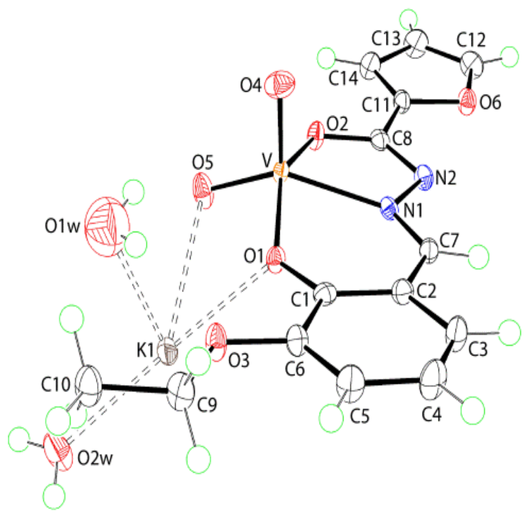


H_2L^1: R = 

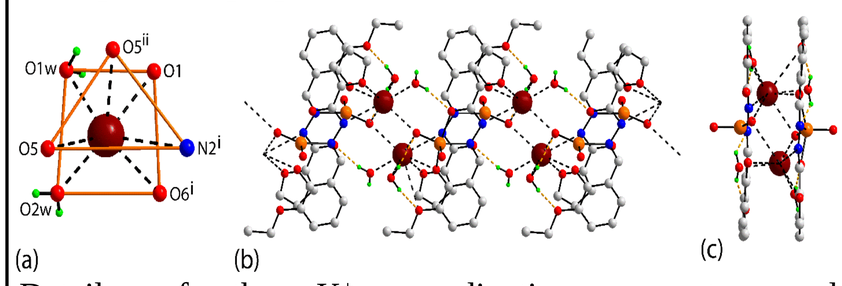
H_2L^2: R = 

Ligand	A	n	$[V^VO_2(L^{1-2})A(H_2O)_n]$ (**1-5**)
H_2L^1	Na^+	3	$[V^VO_2(L^1)Na(H_2O)_3]$ (**1**)
H_2L^2	K^+	2	$[V^VO_2(L^2)K(H_2O)_2]$ (**2**)
H_2L^1	K^+	2	$[V^VO_2(L^1)K(H_2O)_2]$ (**3**)
H_2L^2	Cs^+	0	$[V^VO_2(L^2)Cs]$ (**4**)
H_2L^1	Cs^+	2	$[V^VO_2(L^1)Cs(H_2O)_2]$ (**5**)

Single Crystal X-ray Diffraction Study



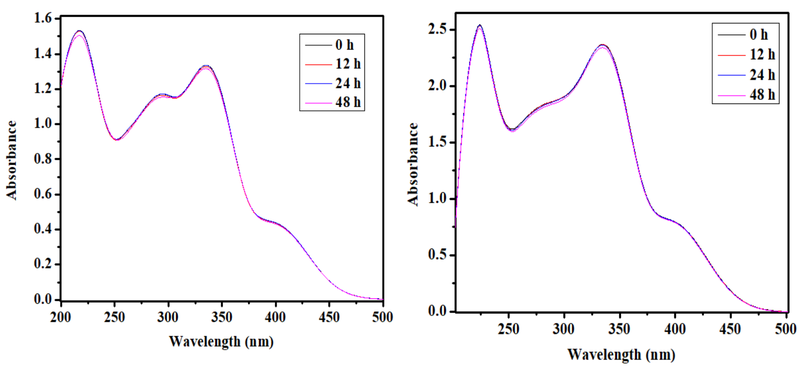
The molecular structures of the constituents of $[V^VO_2(L^2)K(H_2O)_2]$ (**2**)



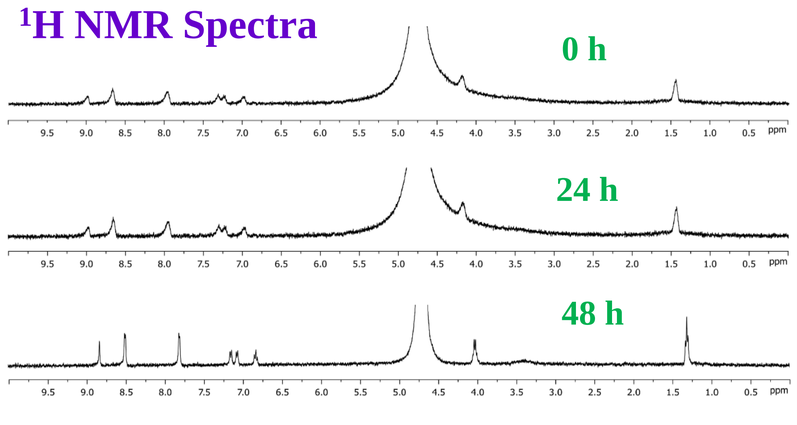
Details of the K^+ coordination geometry and supramolecular chains mediated by K···N/O interactions for $[V^VO_2(L^2)K(H_2O)_2]$ (**2**)

Aqueous Stability Studies

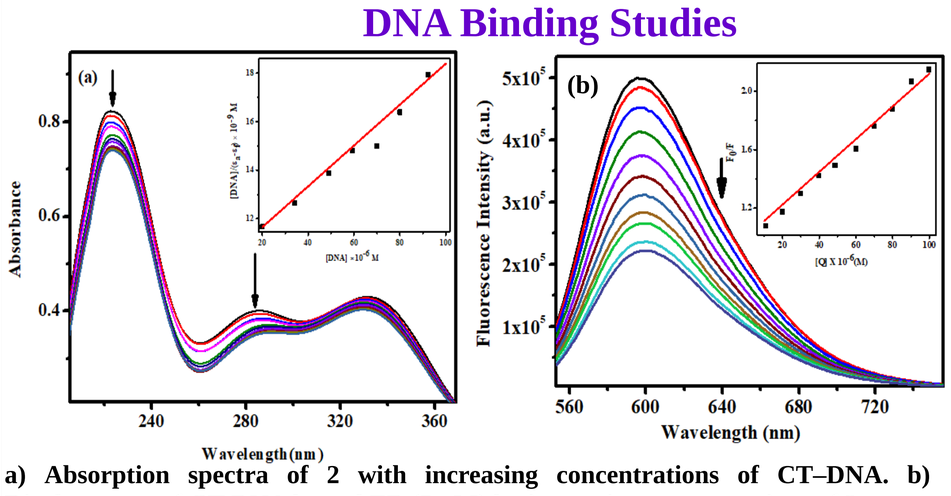
UV-visible Spectra



^{1}H NMR Spectra

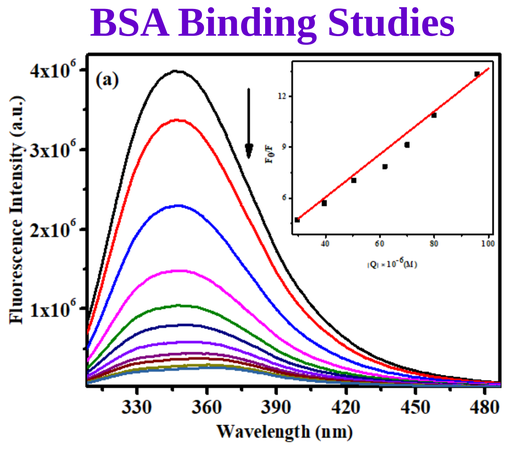


DNA Binding Studies



a) Absorption spectra of 2 with increasing concentrations of CT–DNA. b) Displacement of CT-DNA bound EB (5 μM) by increasing concentrations of 2

BSA Binding Studies



Fluorescence quenching of BSA (10 μM) by $[V^VO_2(L^2)K(H_2O)_2]$ (2) (0–100 μM)

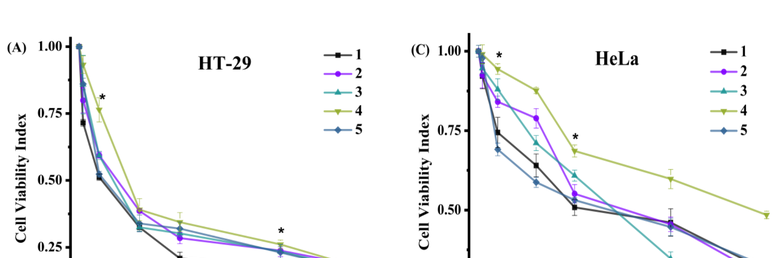
DNA and BSA Binding Parameters for 1–5

Complexes	DNA Binding	BSA Binding	
	Binding constant (K_b) (M^{-1})	Bimolecular rate constant K_q ($M^{-1}s^{-1}$)	Binding constant (K_b) (M^{-1})
1	1.27×10^4	5.3×10^{12}	4.5×10^6
2	6.43×10^4	2.0×10^{13}	7.7×10^8
3	1.95×10^4	9.0×10^{12}	1.7×10^8
4	1.25×10^4	3.1×10^{12}	2.1×10^9
5	1.90×10^4	5.9×10^{12}	4.0×10^6

Cytotoxicity Measurements:

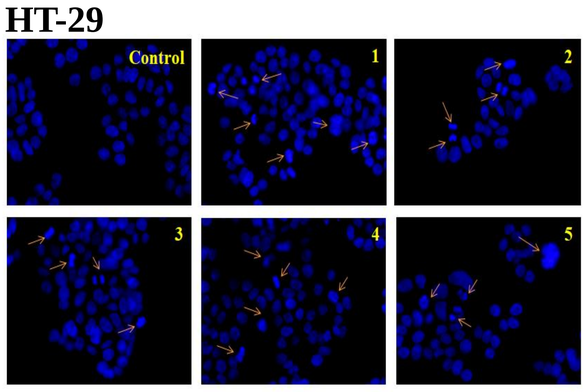
MTT Assay

Complexes	IC_{50} (μM)		
	HT-29	MCF-7	HeLa
1	5.42 ± 0.15	21.16 ± 1.05	29.24 ± 0.09
2	9.33 ± 0.42	35.01 ± 0.02	38.34 ± 0.51
3	8.51 ± 0.15	29.78 ± 1.43	35.31 ± 0.08
4	11.93 ± 0.1	37.96 ± 0.16	72.19 ± 0.12
5	6.13 ± 0.01	27.17 ± 1.91	33.91 ± 0.31

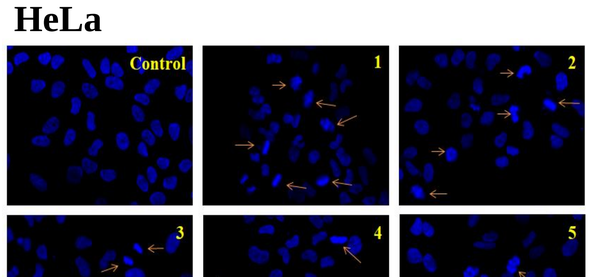


Nuclear Staining Assay

HT-29

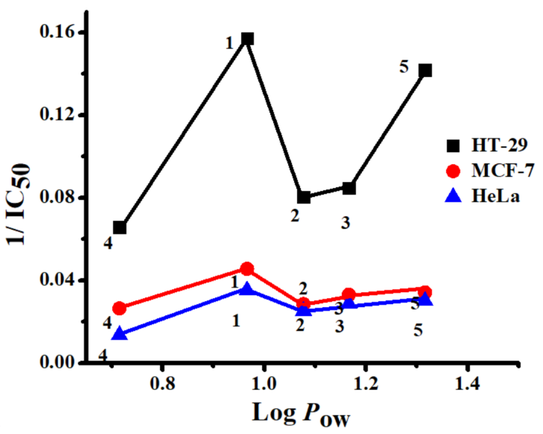


HeLa



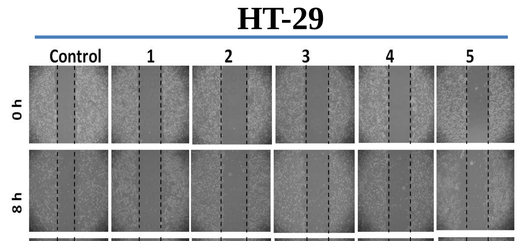
Hydrophobicity Vs Cytotoxicity

Complex	partition coefficient (log P_{ow})
1	0.966
2	1.077
3	1.166
4	0.715
5	1.316

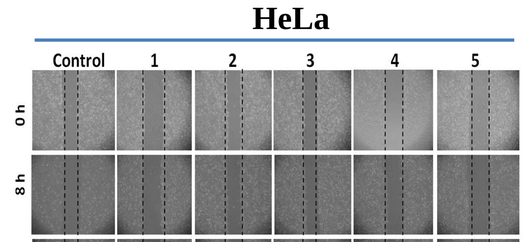


Wound Healing Assay

HT-29



HeLa



Conclusion

- The synthesized dioxidovanadium(V) complexes $[\{VO_2L^{1-2}\}A(H_2O)_n]_\alpha$ (**1−5**) were successfully characterized through several spectroscopic techniques.
- The study of structural, aqueous stability, hydrophobicity, interaction with bovine serum albumin (BSA) and CT-DNA and cytotoxicity against various cell lines are reported.
- Cell selective anticancer potential has been observed and correlated with wound healing assay.

References

- *Inorg. Chem.* **2021**, 60, 15291−15309
- *Inorg. Chem.* **2020**, 59, 14042–14057
- *Inorg. Chem.* **2018**, 57, 5767–5781

Acknowledgement

- Department of Chemistry, NIT Rourkela
- R. D thanks CSIR, Govt. of India [Grant No. 01(2963)/18/EMR-II] for funding this research.