P-101 Dithiocarbazate based oxidomethoxidovanadium(V) and mixed-ligand oxidovanadium(IV) complexes: Study of solution behavior, DNA binding, and anticancer activity

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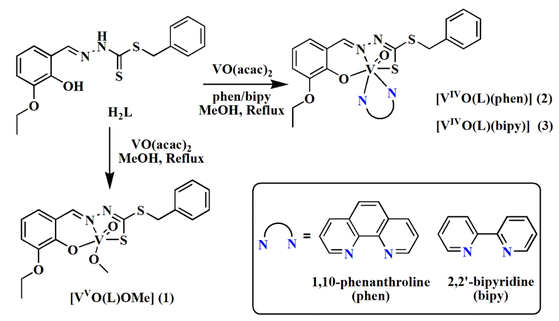
Introduction : In contrast to exogenous platinum group metals, vanadium is present as an important trace element in all living organisms and plays a crucial role in many enzymatic biotransformation reactions. After the report of vanadium complexes vanadocene dichloride ($Cp_2V^{IV}Cl_2$), Metvan, $[V^{IV}O(4,7\text{-}Me_2phen)_2(SO_4)]$ (4,7-Me_2phen = 4,7-dimethyl-1,10-phenanthroline), as promising anticancer drug against various cancer cell lines, there is a growing interest in the *in vitro* and *in vivo* studies of vanadium complexes towards the treatments of cancer. Moreover, vanadium also has the ability to control biological process such as cellular regulation and many physiological processes such as haloperoxidation, phosphorylation, vanadium nitrogenases, antifungal/antibacterial activities. Keeping these observations in mind, herein we have presented the synthesis of three dithiocarbazate based oxidovanadium (IV/V) complexes have been synthetized and characterized by elemental analytical tools.

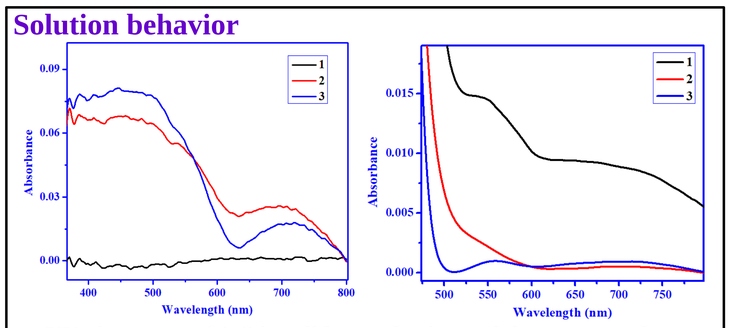
Objectives

- ❖ Synthesis of solvent coordinated dithiocarbazate-vanadium(V) (**1**) and mixed-ligand dithiocarbazate -vanadium(IV) with the diimine as co-ligands (**2** and **3**).
- ❖ All the compounds characterized by elemental analysis, FT-IR, UV−vis, NMR spectroscopy and HR-ESI-MS. Molecular structure of **1**−**3** has been solved by single crystal X-ray analysis.
- ❖ Stability studies of **1**–**3** performed in order to test the behavior of complexes in various solvents.
- ❖ Interaction of **1**−**3** with CT–DNA was investigated also, the anticancer potential against MCF-7, and NIH-3T3 cell lines. The efficacy of drugs on reproduction of cells with post treatment of the compounds tested by clonogenic assay. Further, cell cycle progression of complexes was investigated using flow cytometry analysis.

Methodology and Work plan

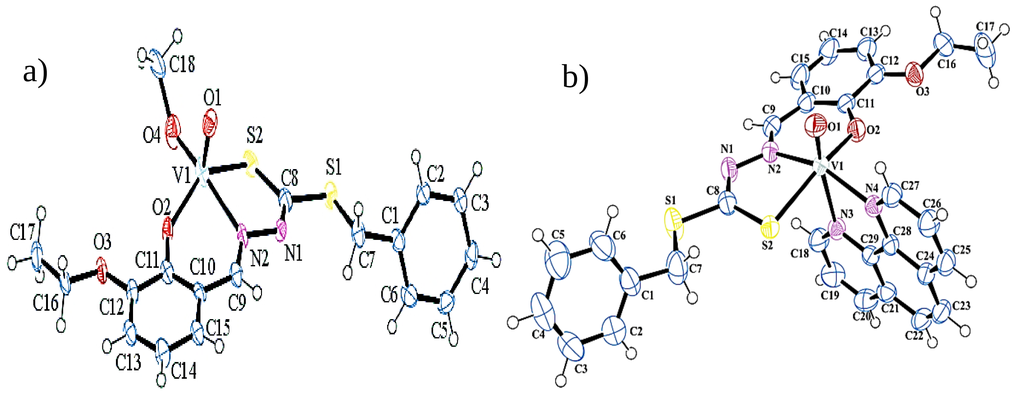


Solution behavior



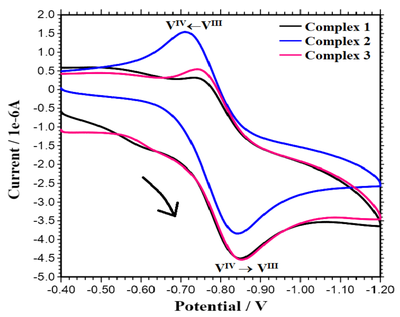
UV-vis spectra of 1–3 in solid state, barium sulphate was used as a non-absorbing reflectance (a); and in DMSO solution

Single crystal X-ray Diffraction Study



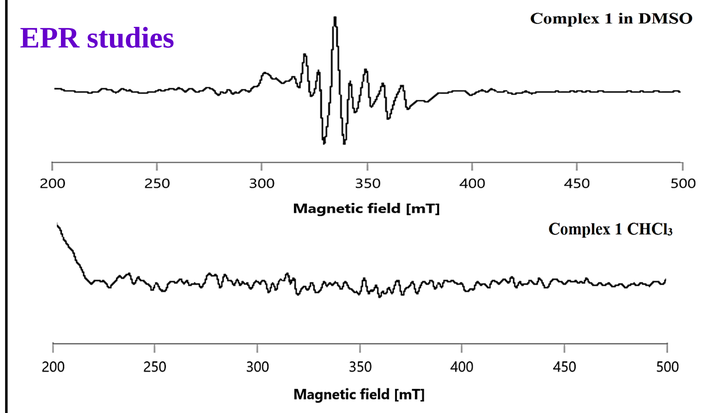
ORTEP diagrams of (a) $[V^{V}O(L)(OMe)]$ (1), (b) $[V^{IV}O(L)(phen)]$ (2) with thermal ellipsoids at the 50% probability level

Electrochemical studies



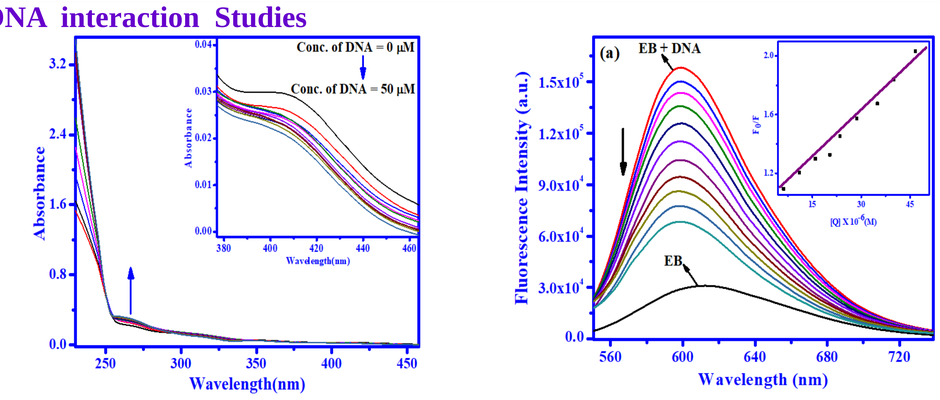
Cyclic voltammogram of 1–3 in DMSO (50 mVs^{-1})

EPR studies



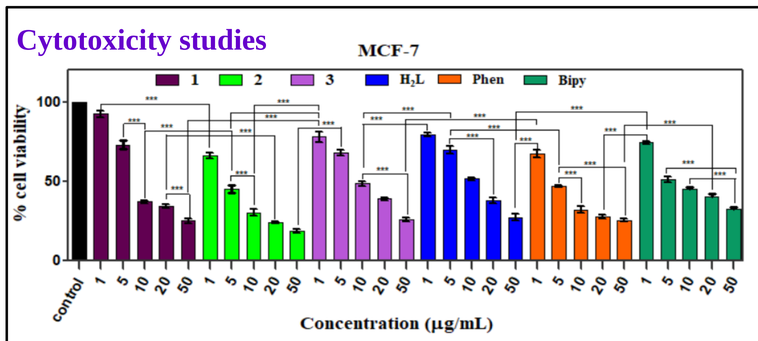
Frozen solution X-band EPR spectrum of 1 recorded in DMSO and $CHCl_3$

DNA interaction Studies



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

Cytotoxicity studies

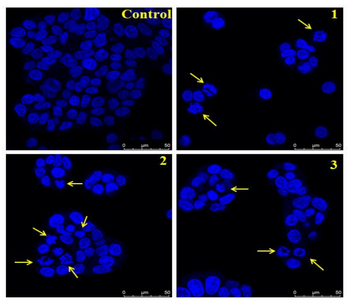


IC_{50} values for H_2L and 1−3

Complex	MCF-7 (μM)	NIH-3T3 (μM)
1	18.21 ± 0.01	37.09 ± 0.08
2	6.73 ± 0.36	23.48 ± 1.07
3	16.41 ± 0.26	33.99 ± 0.18
H_2L	30.50 ± 0.34	82.69 ± 0.15

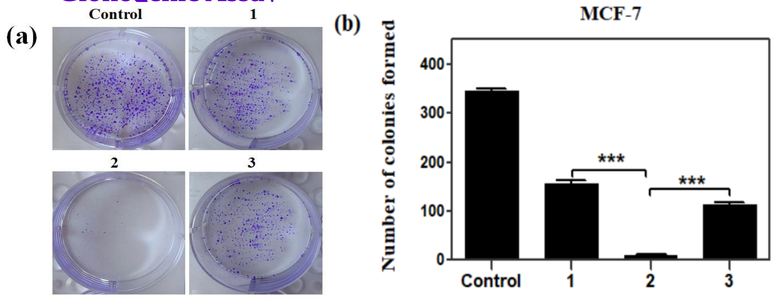
Cytotoxicity profiles of of MCF-7 and NIH-3T3 cells with H_2L ad 1−3

DAPI staining Assay



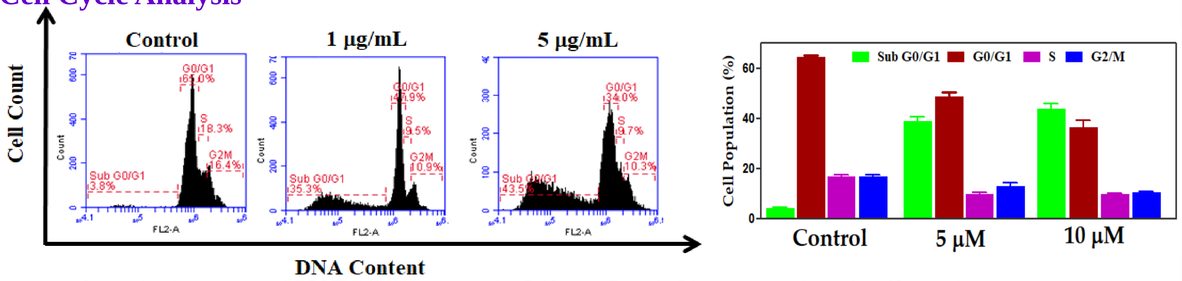
Morphologies of MCF-7 cells after treatment of 1–3

Clonogenic Assay



Representative images of colony formation (a) and quantification of colony number (b).

Cell Cycle Analysis



Analysis of cell cycle of MCF-7cells treated with 2 (1, and 5 mg/mL) concentrations for 48 h by flow cytometry.

Conclusion

- ❖ One monomeric oxidomethoxidovanadium (V) (**1**) and two mixed-ligand oxidovanadium(IV) complexes, (**2**−**3**) of dithiocarbazate based ligands are reported. **1**−**3** were characterized by various physicochemical techniques (FT-IR, UV-vis, NMR, and HR-ESI-MS, and SC-XRD analysis) and further tested for DNA binding and cytotoxicity activities.
- ❖ In this report, we were able to establish that the **1** completely and **2**−**3** partially decomposes and leads to the formation of penta-coordinated $[V^{IV}O(L)(DMSO/H_2O)]$ active species after the release of the methoxido group (**1**) or breaking of the diimine based co-ligands (**2** and **3**) in DMSO/aqueous solution through UV-vis, NMR, EPR, and HR-ESI-MS.
- ❖ The results of DNA binding and the cytotoxicity assay against MCF-7 and NIH-3T3 cell lines are explained along the lines of this transformation. The findings of all the studies confirm that the enhanced DNA interaction and cytotoxicity of **1**−**3** is due to the presence of different structural compositions of the respective complexes in solution medium.
- ❖ Clonogenic assay suggested **2** was the most significant in inhibiting the colony formation among the series. From the cell cycle analysis results, it is pointed out that the MCF-7 cells might be progressing towards apoptotic cell death on treatment of complex **2**. Overall, the results presented herein will contribute to the development of vanadium based anticancer agents.

References

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