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Vanadium complexes as potential anticancer agents

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Abstract

Metals are important for the structure and functioning of biomolecules. The main focus of research remains in designing and synthesis of novel metal-based complexes and metal ion binding substances in search of novel medicines. This paper summarizes the anticancer activity of vanadium with different ligands. Vanadium is a well-known transition metal and its complexes have received extensive studies for their pharmacological properties. The medicinal properties of vanadium complexes particularly their anticancer activity is a rapidly expanding research field. Vanadium complexes such as VO-salen (N,N' bis(salicylidene)ethylenediamine, Metvan, vanadocene dichloride, vanadium(III)-L-cysteine complexes, vanadium complexes with flavonoids and other polyphenols, semicarbazone derivatives and vanadium Schiff base complexes exhibited anticancer activity. Majority of the reported complexes contain vanadium in +4 and +5 oxidation states. In past it has been established that vanadium in different oxidation states exhibited well-defined geometry and coordination power making them thermodynamically stable. The literature was reviewed and collected from leading indexing database of last 10 years to find the potentiality of vanadium as anticancer agents. The biological potential of vanadium complexes with different ligands open new horizons for future interdisciplinary studies and investigation focussed on understanding the biochemistry of these complexes.

Introduction

➢Metals ions control a wide range of important biological processes with remarkable sensitivity and selectivity [1].

➢Metal ions and their ligands exhibit a wide range of physiochemical properties, redox states, coordination numbers, and geometries, resulting in a variety of reactivities which are important tools for research in this area [2].

➢Cisplatin (Fig. 1a) has been used successfully in medicine to treat several types of tumours [3] but it has several adverse effects [4].

➢New platinum based drugs like carboplatin and oxaliplatin helped to some extent to mitigate the drawback of cisplatin [5].

➢The recent advancements in medicine have established a wide variety of metal compounds with low toxicity and side effects for treating tumours [6-7].

Anticancer activity of vanadium complexes

- Vanadocene, a vanadium based drug exhibited anticancer activity which is a member of metallocene [8].
- The first vanadocene to exhibit important preclinical result was bis(cyclopentadienyl) dichloro-V(IV) (vanadocene dichloride) [VCp_2Cl_2] (Fig. 1) [9].
- Oxidovanadium (IV) complexes such as bis(4,7-dimethyl-1,10-phenanthroline)sulfatooxovanadium (IV) (Metvan) (Fig. 2) exhibited anticancer activity [10].

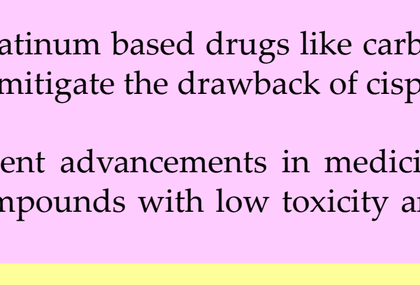

Fig. 1 Vanadocene dichloride

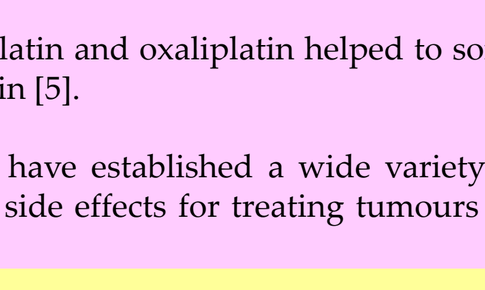

Fig. 2 Metvan

- Many flavonoids, like morin, quercetin, hesperidin, chrysin and silibinin as well as their oxidovanadium (IV) complexes have been investigated to reduce the proliferation of both normal (MC3T3E1) and malignant (UMR106) osteoblast cells.
- In human osteosarcoma cells MG-63, oxidovanadium(IV)-chrysin and silibinin have been well studied.
- VO-salen (N,N'bis(salicylidene)ethylenediamine) exhibit anticancer activity (Fig. 3).

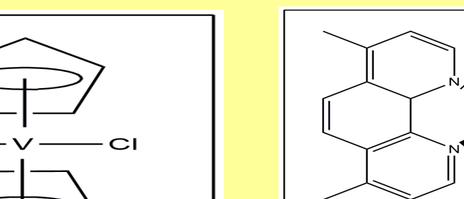

Fig. 3 VO-salen

- Some other known vanadium complexes which also exhibited anticancer activity are bis(triethylammonium)tris[1,1-bis(indol-3-yl)-1-(3,4-catecholate)methane]vanadate(IV), Vanadium N-(2-hydroxyacetophenone)glycinate, and Vanadium(V)pyridyl benzimidazole complex.

Mechanism of Action

❖ *The Warburg effect: Targeting tumour cell metabolism*

Oxidovanadium compounds have been reported to arrest G0/G1 phase cell cycle causing mitochondrial membrane depolarization in human hepatoma cell lines HUH-7, HepG2 and BEL-7402. In another investigation the metabolism of cancer cells can be modified by vanadium. Cancer cells as compared to normal cell metabolism, cancer cells upregulated glycolysis and glucose absorption, which causes an increase in the formation of glycolytic metabolites and pyruvate .

❖ *Vanadium compounds and Formation of ROS*

A potent anticancer treatment involves the redox balance because cancer cells are highly susceptible to redox susceptibility, including hypoxia It has been demonstrated that vanadium complexes produce ROS ($OH^{\cdot}$ And $O_2^{\cdot}$) both in the solvated ions and gas phase. The anticancer activity against thyroid papillary carcinoma has been demonstrated by vanadium complexes. At low concentration, orthovanadate induced tumour suppression which increased RET/PTC1 tyrosine 451 phosphorylation and activated Mtor/S6R member of the P13K/AKT signaling route via apoptosis, which include loss of mitochondrial membrane potential, ROS generation,DNA fragmentation and activation of caspase-3.

❖ *The Notch-1 Signalling Path*

Notch signalling route is a highly regulated cell signalling mechanism that regulates the development of embryo as well as disrupted many kinds of tumours, like breast or lung cancer. Recently, it has been demonstrated that complexes of vanadium inhibit the proliferation of MDA-MB-231 cell line, which is an example of malignant and triple-negative breast cancer that is resistant to therapy.

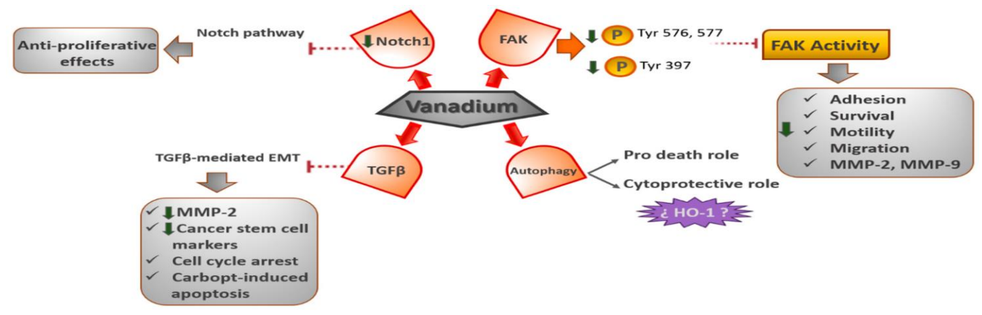

Fig. 4 Downregulation of proteins induced by vanadium complexes

Conclusion

➢It has been established that the vanadium in different oxidation states exhibited anticancer activity and has well defined geometry as well as coordination power making them thermodynamically stable.

➢Vanadium complexes with different ligands open new horizons for future interdisciplinary studies and investigation focused on understanding the biochemistry of these complexes.

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