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Vanadium Complexes as Potential Anticancer Agents †

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Abstract: For the structure and functioning of bio-molecules metals are important. The main focus of research remains in the designing and synthesis of novel metal-complexes and metal ion binding substances in search of novel medicines. Studies have established well defined geometry, thermodynamically stability and excellent coordination power of vanadium in different oxidation states. This paper summarizes the biological activity of vanadium complexes particularly their anticancer activity. Future multidisciplinary research and analysis focused on comprehending the biochemistry of vanadium complexes with different ligands.

Keywords: vanadium; Schiff base; anticancer activity; metal-based complexes; biochemistry

1. Introduction

Metals ions control a wide range of important biological processes with remarkable sensitivity and selectivity. In the sixteenth century several metal ions have been implicated in the prevention and treatment of human cancer [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. Inorganic biochemistry provide interesting opportunities for the development of effective medicinal drugs [2,3]. It is important to mention that cisplatin (Figure 1a) has been used successfully in medicine to treat several types of tumours [4] but it has several adverse effects [5]. New platinum based drugs like carboplatin and oxaliplatin (Figure 1b,c) helped to some extent to mitigate the drawback of cisplatin [6,7]. The recent advancements in medicine have established a wide variety of metal compounds with low toxicity and side effects for treating tumours [8,9]. There have been several reports on the wide-ranging uses of vanadium complexes as potential therapeutic with low toxicity [10].

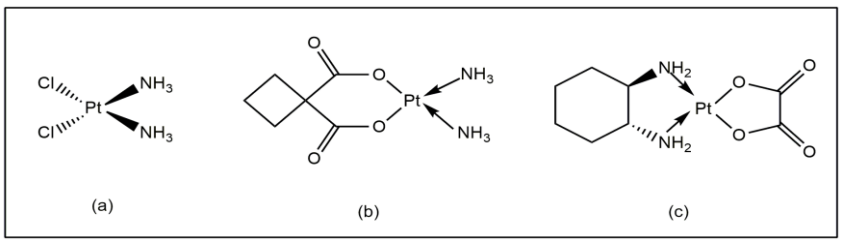

Figure 1. (**a**) Cisplatin, (**b**) Carboplatin, (**c**) Oxaliplatin.

2. Anticancer Activity of Vanadium Complexes

Vanadium exist in simple inorganic salts to more complicated coordination complexes with both organic and inorganic ligands [11,12]. Vanadocene, a vanadium based drug exhibited anticancer activity which is a member of metallocene [13]. The first

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vanadocene to exhibit important preclinical result was vanadocene dichloride (VCp_2Cl_2) (Figure 2) [14].

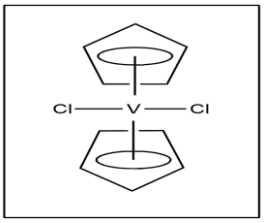

Figure 2. Vanadocene dichloride.

Recent research on speciation have demonstrated that [VCp_2Cl_2] changes into [$VCp_2(OH)_2$] at physiological pH and the two OH^- ions may be displaced by carbonate, oxalate, phosphate and lactate to form the adducts [$VCp_2(CO)_3$], [$VCp_2(ox)$], [$VCp_2(HPO_4)$] and [$VCp_2(lacH)^{(-1)}$] with these ligands [15]. The methyl and methoxy substituted vanadocene dichlorides exhibited anticancer activity against T-lymphocytic leukemia cells using MOLT-4 [16]. Oxidovanadium (IV) complexes such as Metvan [bis(4,7-dimethyl-1,10-phenanthroline)sulfatooxovanadium (IV)] (Figure 3) exhibited anticancer activity.

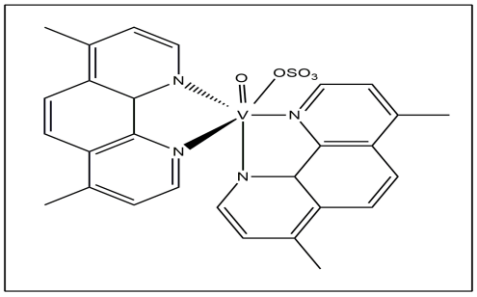

Figure 3. Metvan.

Several human cancer cell lines, including leukemia cells, solid tumours and multiple myeloma cells present in the ovary, breast, testis and prostrate are damaged by this complex through apoptosis [17–19]. Because of its positive pharmacodynamics properties and low toxicity, it has the potential to be the first vanadium complex used in place of the traditional platinum chemotherapy [20]. 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 [21–23]. In human osteosarcoma cells MG-63, oxidovanadium(IV)-silibinin (VOsil) and oxidovanadium(IV)-chrysin (VOchrys) have been well studied. VOchrys inhibited cell viability in a concentration dependent manner in human osteosarcoma cells. Additionally, VOchrys had a lower IC_{50} value 16 μM compared to vanadyl cation and chrysin > 100 μM, so it was the most potent anticancer agent in human osteosarcoma cells [24].

Moreover, VOsil reduced cell viability of the MG-63 cell line in a dose dependent manner more effectively than vanadyl cation and silibinin. The complex showed concentration effect in both cyto and genotoxic pathways [25]. Mixed ligands complexes of oxidovanadium(IV) with Schiff base and thiosemicarbazone showed antitumour activity towards several colonic cancer cell lines like HT-29, HTC-116 and Caco-2 along with non-malignant colon myofibroblasts (CCD18-Co) [26]. Some biologically active vanadium complexes and their anticancer activity with different ligands are illustrated in Table 1.

Table 1. Anticancer activity of vanadium complexes with different ligands.

S.No.	Complex	Ligand	Biological Activity	References
1.	bis(triethylammonium)tris [1,1-bis(indol-3-yl)-1-(3,4-catecholate)methane]vanadate(IV)	3,3′-diindolylmethane	Anticancer	[27]
2.	Vanadium N-(2-hydroxyacetophenone)glycinate	Potassium N-(-2-hydroxyacetophenone)glycinate	Anticancer	[28]
3.	Vanadium(V)pyridyl benzimidazole complex	2-(2-pyridyl)benzimidazole	Anticancer	[29]
4.	VO-salen complex	N,N'bis(salicylidene)ethylenediamine	Anticancer	[30]

3. Probable Mechanistic Action of Vanadium Complexes

3.1. The Warburg Effect: Targeting Tumour Cell Metabolism

Oxidovanadium compounds have been reported to arrest the G0/G1 phase cell cycle and lowered $\Delta\psi m$, causing mitochondrial membrane depolarization in human hepatoma cell lines HUH-7, HepG2 and BEL-7402 [31]. In another investigation the metabolism of cancer cells can be modified by vanadium [32]. Cancer cells as compared to normal cell metabolism, upregulated glycolysis and glucose absorption, which causes an increase in the formation of glycolytic metabolites and pyruvate. In cancer cells, glycolysis is uncoupled from the mitochondrial tricarboxylic acid (TCA) cycle and oxidative phosphorylation. As a result, numerous pyruvate produced during glycolysis is shifted towards lactate fermentation as compared to mitochondrial oxidative metabolism. These metabolic process known as "Warburg effect", was first discovered by Otto Warburg. Warburg phenotype is a typical tumour related trait. [33]

3.2. Vanadium Compounds and Formation of Reactive Oxygen Species

A potent anticancer treatment involves the redox balance because cancer cells are highly susceptible to redox susceptibility, including hypoxia [34]. Complexes of metals can influence cellular redox balance directly or indirectly by reducing/oxidizing metal or ligand centres as well as interactions with biomolecules in redox systems [35]. Only cancer cells are affected by redox activation of metal complexes thus reducing the adverse impacts. It has been demonstrated that vanadium complexes produce ROS (OH. And O_2.) both in the solvated ions and gas phase [36]. The anticancer activity against thyroid papillary carcinoma has been demonstrated by vanadium complexes [37]. 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 [38]. Vanadium complexes also induced ROS-mediated apoptosis in A549 lung adenocarcinoma and the MCF-7 human breast cancer cell line by reducing metalloproteinase-2(MMP-2) and H-ras activation [39].

3.3. Transforming Growth Factor-β (TGFβ) -Epithelial to Mesenchymal Transition (EMT) Signalling Path

Several studies indicated that, vanadium prevents tumour cells spread via lowering production of MMP-2 or induced ROS-dependent apoptosis [40]. Using human breast cancer MDA-MB-231 epithelial cell cultures and lung cancer A549 Petanidis et al. first documented the detrimental impact of vanadium on (TGF-β)-mediated EMT and subsequent down-modulation of tumour stem cell signaling. Additionally, they suggested that vanadium and carboplatin in combination arrest the G0/G1 cell cycle and and sensities tumour

cells to carboplatin-induced death. This information is used to target cancer stem cell-mediated metastatis and cancer cell metabolism in chemoresistant cells [41].

3.4. Focal Adhesion Kinase (FAK) Signalling Path

FAK is essential for cancer cells adhesion, angiogenesis, survival, metastatic growth, and motility [42]. Recently, it was shown that oxidovanadium(IV)-clioquinol ($VO(CQ)_2$) and VOchrys complexes inhibit FAK, and thus decrease the proliferation of human osteosarcoma cells [43,44]. Results indicated that VO(CQ)2 is situated in the kinase domain stimulation loop and interacts with proteins in the ATP site of binding. $VO(CQ)_2$ showed upmodulation of Tyr576 and Tyr577 sites at 2.5 μM and activation of Tyr576 and Tyr577 reduced 14-fold at 10 μM [45]. In a related study, researchers discovered that VOchrys upregulated the phosphorylation of Tyr577 site while down regulated Tyr397 [43]. The most active site for the autocatalytic action of FAK is the Tyr397 site, which is responsible for the phosphorylation of tyrosine [42]. These findings suggest that VOchrys targeting the Tyr397 site to inhibit the phosphorylation of FAK [46].

3.5. The Notch-1 Signalling Path

Notch-1 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 [47–49]. 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. $[VO(bpy)_2Cl]Cl$ compound (bpy = bipyridyl) increase caspase-3 levels including apoptosis cell death [50]. The researchers also discovered that the Notch-1 pathway was inhibited by reduction in the production of the Notch-1 gene [47]. Furthermore, Y-cell acute lymphoblastic leukemia in animal models and cultured cells has been shown to exhibit antiproliferative effects when Notch-1 signalling is inactivated [49] (Figure 4) [40] [open access].

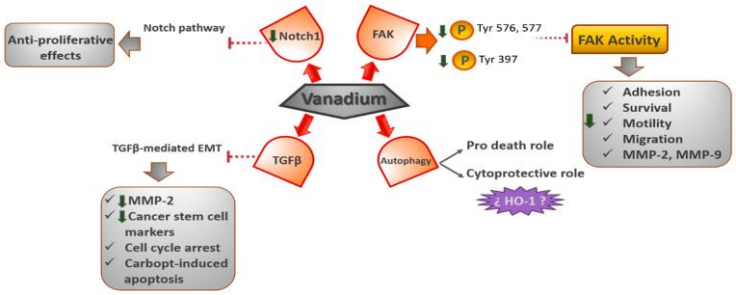

Figure 4. Downregulation of proteins induced by vanadium complexes for cell survival and death.

4. Conclusions

This paper summarized the anticancer activity of vanadium complexes with different ligands. Studies have established well defined geometry, thermodynamically stability and excellent coordination power of vanadium in different oxidation states. Multidisciplinary research focused on comprehending the biochemistry of vanadium complexes with different ligands as well as synthesizing novel complexes which have low toxicity, better solubility and bio-availability.

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