medical sciences forum

MDPI

Proceedings

Pharmacological, Antimicrobial and Toxicological Actions of Vanadium Compounds †

Citation: Fraqueza, G.; Aureliano, M,, Pharmacological, Antimicrobial and Toxicological Actions of Vanadium Compounds, *Med. Sci. Forum* **2022**, 2, x. https://doi.org/

Academic Editor: Firstname Lastname

Published: date

Gil Fraqueza[1,2,] and Manuel Aureliano[1,3] *

[1]Instituto Superior de Engenharia, Universidade do Algarve, 8005-139 Faro, Portugal;
[2]Faculdade de Ciências e Tecnologia (FCT), University of Algarve, 8005-139 Faro, Portugal; maalves@ualg.pt
[3]Centro de Ciências do Mar (CCMar), University of Algarve, 8005-139 Faro, Portugal; maalves@ualg.pt
†Presented at the Biosystems in Toxicology and Pharmacology – Current challenges (BTP-2022), 8-9 September, 2022.

Abstract: Studies of the pharmacological action of vanadium compounds have shown that vanadium has been arousing interest as a potential candidate for therapeutic applications. Some compounds/complexes of vanadium can be effective against various ailments, such as microbial diseases caused by viruses, bacteria, parasites, and protozoa, gastrointestinal disorders, typhoid fever, respiratory infections, tuberculosis, pneumonia, strep throat and skin diseases. Certain vanadium compounds/complexes may have potential in anti-cancer, anti-diabetic, and anti-hypercholesterolemic activity and can act as cardioprotective and neuroprotective agents. Thus, vanadium compounds have a great potential in the treatment of many types of diseases.

Keywords: Vanadate**,** polyoxovanadates; antibacterial agents; drug discovery; metal-based drugs.

1. Introduction

Vanadium (V) is an element with a wide range of effects on the mammalian organism [1,2]. The ability of this metal to form polyoxovanadates (POVs) and organometallic compounds contributed to the increase in the number of studies on the multidirectional biological activity in view of their application in medicine [3,4,5,6,7]. Vanadium compounds receives a great deal of attention from chemists, biologists, biochemists, toxicologists, and pharmacologists. The biological activity of compounds containing this element has many investigations of many organic vanadium complexes and its inorganic compounds in terms of their potential use in the treatment of certain diseases in humans. Studies carried out so far on vanadium compounds have shown that the bioactive complexes/compounds of this metal can be therapeutically active at low concentrations [1,3]. Structures of several vanadium complexes and compounds showing several biological and biomedical activities were described elsewhere [3,5,6,7,8].

2. Vanadium compounds – physiological aspects

The research on aspects of the biological activity of vanadium compounds has demonstrated an essential role of this element in the metabolism of carbohydrates showing effects at the level of glycolysis, glycogenolysis and gluconeogenesis pathways. On the other hand, lipid metabolism can be affected by stimulation of lipogenesis and inhibition

of lipolysis, phospholipids, and cholesterol. The action of vanadium is also known to influence bone mineralization, thyroid and erythrocyte metabolism, accumulation and transport of calcium in the cell [1,3,4].

Vanadium compounds, also regulate the activity of key enzymes involved in the phosphorylation and dephosphorylation of proteins, kinases, and phosphatases, taking part not only in carbohydrate and lipid metabolism but also in cell proliferation and differentiation [1,3,4,6,7].

3. Vanadium compounds – pharmacological aspects

Studies of the pharmacological action of vanadium compounds have shown that vanadium has been arousing interest of is potential candidate for therapeutic applications [6,7].

Many research studies have been shown its anti-bacterial, anti-fungal, anti-parasitic, anti-viral anti-cancer, anti-diabetic, and anti-hypercholesterolemic activity and cardioprotective, neuroprotective, and anti-obesity effects of vanadium compounds (Figure 1). It has reported that in human beings, affect cholesterol and triglyceride metabolism, influence the erythrocyte shape, stimulate hepatic glucose oxidation and glycogen synthesis at pharmacological amounts of vanadium, i.e. 10 to 100 times higher than the normal intake [2]. On the other hand, vanadium compounds have also been found to act as an antioxidant (Figure 1) [9-12].

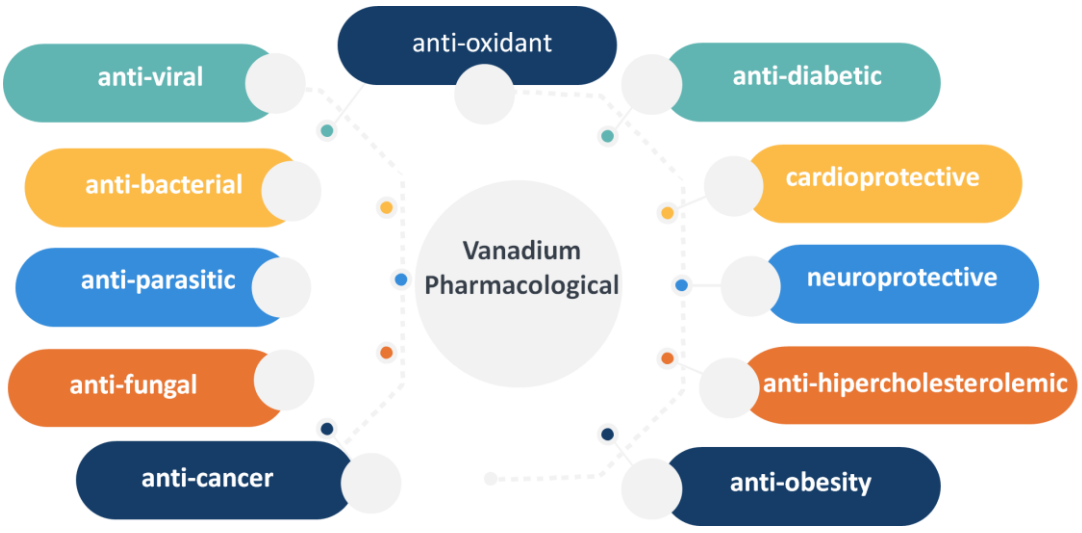

Figure 1. Pharmacological and/or biological activities of vanadium compounds.

4. Antimicrobial activities of vanadium compounds

In vitro and *in vivo* experimental models in several studies have demonstrated the pharmacological potential of vanadium compounds and has shown that some compounds/complexes of this element can be effective against many microbial diseases such as: (a) viruses, including dengue virus, influenza, HIV-1 virus and HIV-2

immunodeficiency virus and severe acute respiratory syndrome (SARS) virus (Figure 2) [13-15] responsible respectively for dengue fever, acute respiratory infection, acquired immune deficiency syndrome (AIDS) and SARS; (b) parasitic protozoan diseases caused of the genus *Trypanosoma* responsible for American trypanosomiasis and African trypanosomiasis known as Chagas disease and sleeping sickness, respectively; protozoan parasites of the genera *Leishmania* and *Entamoeba* (Figure 2) [14, 16-21] responsible for the development of leishmaniasis and amoebiasis, respectively; (c) mycotoxicosis caused from the genera *Candida*, *Aspergillus*, *Trichophyton*, and *Microscopus* (Figure 2) [22-26] and (d) bacterial diseases caused by Gram-negative and Gram-positive bacteria (Figure 2) [26-29] such as food poisoning, gastrointestinal, typhoid fever, respiratory infections, tuberculosis, pneumonia, strep throat and skin diseases. It was also shown that certain vanadium compounds/complexes may have potential in anti-cancer, anti-diabetic, and anti-hypercholesterolemic activity whereas it can act also as cardioprotective and neuroprotective agents.

Bacterial resistance to antibiotics has led researchers to find compounds with potential antibacterial action and/or with the ability to reverse antibiotic resistance. Polyoxovanadates (POVs) and polyoxotungstates are inorganic based clusters that may fulfill the need. In fact, it was report that polyoxometalates (POMs) showed the ability to disturb microorganisms, either susceptible or resistant to antibiotics [5,6,7,15,28]. Moreover, some POMs shows antiquorum sensing and anti-biofilm activities besides being a potent antibacterial agent against S. *aureu* and to exibit antiviral activities against enteric viruses [30].

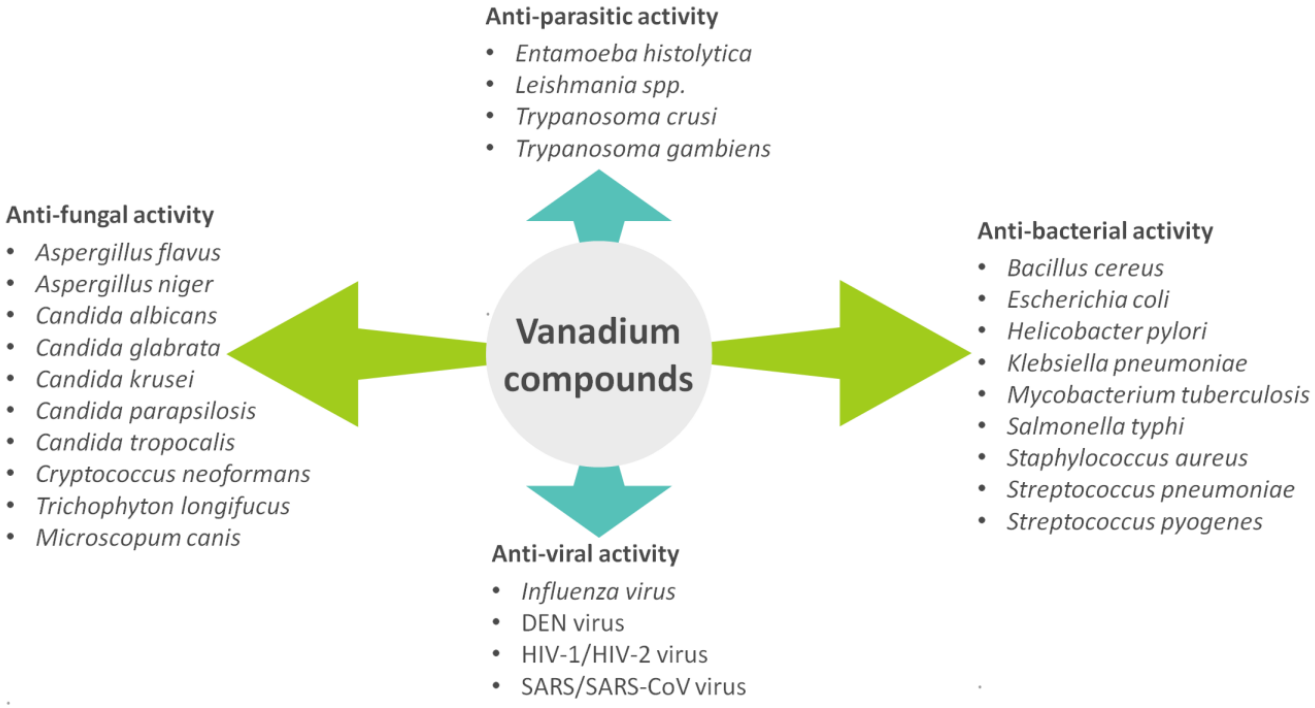

Figure 2 - Antimicrobial activities of vanadium compounds.

5. Vanadium compounds – toxicological aspects

Vanadium is essential in trace amounts (0.05 μM) and toxic in excess (> 10 μM) [1,2]. Vanadium at the highest oxidation state (+5) is the most toxic vanadium form and vanadium pentoxide (V_2O_5), is the most toxic form of this metal [1].

Toxicological and pharmacological aspects in animal models and humans are not understood completely. The redox properties of vanadium are determinant to its pharmacological effects because it can inhibit or stimulate enzymes. Many studies have revealed at the molecular level the interaction of vanadate, POVs and organometallic compounds containing vanadium with enzymes and revealed to have toxic activity on these enzymes in particular by inhibiting their activity. The enzymes most studied are phosphatases, PSPases and PTPases, kinases, glucose-6-phosphate dehydrogenase, triphosphate diphosphohydrolases, phosphodiesterases, phosphoglucomutases and ATPases [31].

The inhibitory effect of vanadium compounds, are observed in ion pumps such as Na^+/K^+ ATPase, H^+/K^+ ATPase and Ca^{2+}-ATPase and interestingly, decavanadate $[V_{10}O_{28}]^{6-}$ is a more potent Ca^{2+}-ATPase inhibitor than monomeric vanadate [32-34]. The recent study with several POVs namely $[V_{10}O_{28}]^{6-}$ (V_{10}), $[H_6V_{14}O_{38}(PO_4)]^{5-}$ (V_{14}), $[V_{15}O_{36}Cl]^{6-}$ (V_{15}) and $[V_{18}O_{42}I]^{7-}$ (V_{18}) demonstrated its inhibitory effect on three major multidrug resistance-linked ABC transporters: P-glycoprotein (P-gp), ABCG2 and MRP1, opening the door to a potential strategy to overcome multidrug resistance is the use of inhibitors of ABC drug transporters [35]. In fact, POVs have been referred as polyoxometalates with several biological activities [5,7,15], and a field rapidly growing [6]. Moreover, POVs were used in the degradation of emmerging pollutants, pointing out that the future is bright in environmental and biomedical research [7]. Examples of several POVs structures can be found elswehere [5,15]. The isopolyoxovanadate decavanadate (V_{10}), is perhaps the most studied in biology showing many important roles in fundamental processes [5,6,7,12,15,29,31,33].

The mechanisms of toxicity of vanadium compounds require further experimental work, as they have not been fully elucidated yet. Some of them have been reported to be implicated in the adverse effects and pharmacological activities of vanadium action. For example, the mechanisms by which vanadium compounds produce toxic effects include oxidative stress by formation of reactive oxygen species or reactive nitrogen species, lipoperoxidation, apoptosis, cell cycle arrest, interference with ions transport system, inhibition of mRNA synthesis, cell morphology changes, changes in metabolic pathways, phosphorylase enzyme inhibition and cell signaling, inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, penetration and interaction with virus protein cages, among others [5,6,8,15].

6. Conclusions

Vanadium compounds have been investigated as potential therapeutic agents for the treatment of various major health issues, including cancer, atherosclerosis, and diabetes. The translation of vanadium-based compounds into clinical trials and ultimately into disease treatments remains hampered by the absence of a basic pharmacological and metabolic comprehension of such compounds.

Most studies with vanadium compounds performed *in vitro* have contributed to elucidate potential sites of vanadium action. However, because the microenvironment does not provide all metabolic pathways, toxicology and detoxification between tissues, the effects observed *in vivo* are not necessarily the same.

From the biological perspective, we know that vanadium compounds have a great potential in the treatment of many types of diseases. However, we must first recognize the therapeutic targets and understand in detail the pharmacokinetics mechanisms and pharmacodynamics, for help to design better and more efficient vanadium-based drugs.

Author Contributions: Investigation, G.F. and M.A.; writing—original draft preparation, G.F. and M.A..; writing—review and editing, G.F. and M.A. The authors have read and agreed to the published version of the manuscript.

Funding: The authors' research received Portuguese national funds from FCT - Foundation for Science and Technology through projects UIDB/04326/2020 and LA/P/0101/2020.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare no conflict of interest.

References

[1] A. Ścibior, Ł. Pietrzyk, Z.Plewa, A. Skiba. Vanadium: Risks and possible benefits in the light of a comprehensive overview of its pharmacotoxicological mechanisms and multi-applications with a summary of further research trends. Journal of Trace Elements in Medicine and Biology. (2020). Vol.61. 126508.https://doi.org/10.1016/j.jtemb.2020.126508

[2] B.F. Harland, B.A. Harden-Williams, Is vanadium of human nutritional importance yet? J. Am. Diet. Assoc. 94 (1994) 891–894, https://doi.org/10.1016/0002. 8223(94)92371-X.

[3] J.C. Pessoa, E. Garribba, M.F.A. Santos, T. Santos-Silva, Vanadium and proteins: uptake, transport, structure, activity and function, Coord. Chem. Rev. 301-302 (2015) 49–86, https://doi.org/10.1016/j.ccr.2015.03.016.

[4] H. Zaporowska, A. Ścibior, Vanadium and its significance in animal cell metabolism, in: J.O. Nriagu (Ed.), Vanadium in the Environment. Part 2: Health Effects, 31 John Wiley and Sons, New York, Chichester, Weinheim, Brisbane, Singapore,Toronto, 1998, pp. 121–133.

[5] Aureliano, M.; Gumerova, N.I.; Sciortino, G.; Garribba, E.; McLauchlan, C.C.; Rompel, A.; Crans, D.C. Polyoxidovanadates' interactions with proteins: An overview. *Coord. Chem. Rev.* **2022**, *454*, 214344, doi:10.1016/j.ccr.2021.214344.

[6] Aureliano, M., Marques-da-Silva, D., Serrano, A., Martins, J., Faleiro, L., Fonseca, C., Fraqueza, G, Lagoa, R., (2022b) Chapter 7, Polyoxometalates with anticancer, antibacterial and antiviral activities, In: Polyoxometalates: Advances, Properties, and Applications. Edited by Leire Ruiz Rubio, Beñat Artetxe, Juan M. Gutiérrez-Zorrilla, José L. Vilas, 1st ed. Jenny Stanford Publishing; 2022, Singapore, eBook ISBN 9781003277446, ISBN 9789814968140.

[7] Aureliano, M. The Future Is Bright for Polyoxometalates. *BioChem* **2022**, *2*, 8–26. https://doi.org/10.3390/biochem2010002

[8] Amante C, De Sousa-Coelho AL, Aureliano M. Vanadium and Melanoma: A Systematic Review. Metals, 2021 18;11(5):828. https://doi.org/10.3390/met11050828

[9] N. Sekar, A. Kanthasamy, S. William, N. Balasubramaniyan, S. Govindasamy, Antioxidant effect of vanadate on experimental diabetic rats, Acta Diabetol. Lat. 27 (1990) 285–293, https://doi.org/10.1007/bf02580932.

[10] R. Yanardag, S. Bolkent, O Karabulut-Bulan, S. Tunali, Effects of vanadyl sulfate on kidney in experimental diabetes, Biol. Trace Elem. 95 (2003) 73–85, https://doi.org/10.1385/BTER:95:1:73.

[11] S. Tunali, R. Yanardag, Effect of vanadyl sulfate on the status of lipid parameters and on stomach and spleen tissues of streptozotocin-induced diabetic rats, Pharmacol. Res. 53 (2006) 271–277, https://doi.org/10.1016/j.phrs.2005.12.004.

[12] S.S. Soares, C. Gutierrez-Merino, M. Aureliano, Mitochondria as a target for decavanadate toxicity in *Sparus aurata* heart, Aquat. Toxicol. 83 (2007) 1–9, https://doi.org/10.1016/j.aquatox.2007.03.005.

[13] D. Rehder, Vanadium. Its role in humans, in: A. Sigel, H. Sigel, R.K. Sigel (Eds.), Interrelations between Essential Metal Ions and Human Diseases, Springer, Dordrecht, Heidelberg, New York, London, 2013, pp. 139–167.

[14] J.C. Pessoa, S. Etcheverry, D. Gambino, Vanadium compounds in medicine, Coord. Chem. Rev. 301-302 (2015) 24–48, https://doi.org/10.1016/j.ccr.2014.12.002.

[15] Manuel Aureliano, Nadiia I. Gumerova, Giuseppe Sciortino, Eugenio Garribba, Annette Rompel, Debbie C. Crans, Polyoxovanadates with emerging biomedical activities, Coordination Chemistry Reviews, Volume 447, 2021,214143, ISSN 0010-8545, https://doi.org/10.1016/j.ccr.2021.214143.

[16] D. Rehder, Vanadium in health issues, ChemTexts 4 (2018) 20, https://doi.org/10.1007/s40828-018-0074-z.

[17] J.C. Pessoa, Thirty years through vanadium chemistry, J. Inorg. Biochem. 147 (2015) 4–24, https://doi.org/10.1016/j.jinorgbio.2015.03.004.

[18] T.L. Turner, V.H. Nguyen, C.C. McLauchlan, Z. Dymon, B.M. Dorsey, J.D. Hooker, M.A. Jones, Inhibitory effects of decavanadate on several enzymes and *Leishmania tarentolae* in vitro, J. Inorg. Biochem. 108 (2012) 96–104, https://doi.org/10.1016/j.jinorgbio.2011.09.009.

[19] R.S. Mendez, B.M. Dorsey, C.C. McLauchlan, M. Beio, T.L. Turner, V.H. Nguyen, A. Su, W. Beynon, J.A. Friesen, M.A. Jones, Vanadium complexes are in vitro inhibitors of Leishmania secreted acid phosphatases, Int. J. Chem. 6 (2014) 35–49, https://doi.org/10.5539/ijc.v6n1p35

[20] I.O. Adriazola, A. Evangelista do Amaral, J.C. Amorim, B.L. Correia, C.L. Petkowicz, A.L. Merce, G.R. Noleto, Macrophage activation and leishmanicidal activity by galactomannan and its oxovanadium (IV/V) complex in vitro, J. Inorg. Biochem. 132 (2014) 45–51, https://doi.org/10.1016/j.jinorgbio.2013.09.017.

[21] Scalese G, Machado I, Salinas G, Pérez-Díaz L, Gambino D. Heteroleptic Oxidovanadium(V) Complexes with Activity against Infective and Non-Infective Stages of *Trypanosoma cruzi*. *Molecules*. 2021; 26(17):5375. https://doi.org/10.3390/molecules26175375

[22] Z.H. Chohan, S.H. Sumrra, M.H. Youssoufi, T.B. Hadda, Metal based biologically active compounds: design, synthesis, and antibacterial/antifungal/cytotoxic properties of triazole-derived Schiff bases and their oxovanadium(IV) complexes, Eur. J. Med. Chem. 45 (2010) 2739–2747, https://doi.org/10.1016/j.ejmech.2010.02.053.

[23] E. Pahontu, F. Julea, T. Rosu, V. Purcarea, Y. Chumakov, P. Petrenco, A. Gulea, Antibacterial, antifungal and in vitro antileukaemia activity of metal complexes with thiosemicarbazones, J. Cell. Mol. Med. 19 (2015) 865–878, https://doi.org/10.1111/jcmm.12508.

[24] P. Jayaseelan, E. Akila, M.U. Rani, R. Rajavel, Synthesis, spectral characterization, electrochemical, anti-microbial, DNA binding and cleavage studies of new binuclear Schiff base metal(II) complexes derived from o-hydroxyacetophenone, J. Saudi Chem. Soc. 20 (2016) 625–634, https://doi.org/10.1016/j.jscs.2013.07.001.

[25] H. Li, H. Gong, Y. Qi, J. Li, X. Ji, J. Sun, R. Tian, H. Bao, X. Song, Q. Chen, G. Liu, *In vitro* and *in vivo* antifungal activities and mechanism of heteropolytungstates against *Candida* species, Sci. Rep. 7 (2017) 1–9, https://doi.org/10.1038/s41598- 017-17239-8.

[26] S. Guo, W. Yang, M. Zjao, R. Tian, B. Zhang, Y. Qi, In vitro anticandidal activity and mechanism of polyoxovanadate functionalized by Zn-fluconazole complexes, Molecules 23 (2018) 1–11, https://doi.org/10.3390/molecules23051122.

[27] J.C. Pessoa, Thirty years through vanadium chemistry, J. Inorg. Biochem. 147 (2015) 4–24, https://doi.org/10.1016/j.jinorgbio.2015.03.004.

[28] A. Bijelic, M. Aureliano, A. Rompel, The antibacterial activity of polyoxometalates: structures, antibiotic effects and future perspectives, Chem. Commun. 54 (2018) 1153–1169, https://doi.org/10.1039/C7CC07549A.

[29] N. Samart, Z. Arhouma, S. Kumar, H.A. Murakami, D.C. Crick, D.C. Crans**.** Decavanadate inhibits microbacterial growth more potently than other oxovanadates. Front. Chem., 6 (2018), p. 519, 10.3389/fchem.2018.00519

[30] Faleiro, L.; Marques, A.; Martins, J.; Jordão, L.; Nogueira, I.; Gumerova, N.I.; Rompel, A.; Aureliano, M. The Preyssler-Type Polyoxotungstate Exhibits Anti-Quorum Sensing, Antibiofilm,and Antiviral Activities. Biology **2022**,11, 994. https://doi.org/10.3390/biology11070994

[31] S. Trevino, A. Diaz, E. Sanchez-Lara, B.L. Sanchez-Gaytan, J.M. Perez-Aguilar, E. Gonzalez-Vergara, Vanadium in biological action: chemical, pharmacological aspects, and metabolic implications in diabetic mellitus, Biol. Trace Elem. Res. 188 (2019) 68–98, https://doi.org/10.1007/s12011-018-1540-6.

[32] Garrahan PJ, Rossi RC (2011) Rb(+) occlusion stabilized by vanadate in gastric H(+)/K(+)-ATPase at 25°C. Biochim Biophys Acta 1808(1):316–322. https://doi.org/10.1016/j.bbamem.2010.08.022

[33] Aureliano M (2016) Decavanadate toxicology and pharmacological activities: V10 or V1, both or none? Oxidative Med Cell Longev 2016:6103457. https://doi.org/10.1155/2016/6103457

[34] G. Fraqueza, J. Fuentes, L. Krivosudsky´, S. Dutta, S.S. Mal, A. Roller, G. Giester, A. Rompel, M. Aureliano, Inhibition of Na+/K+- and Ca2+-ATPase activities by phosphotetradecavanadate, J. Inorg. Biochem. 197 (2019) 110700, https://doi.org/10.1016/j.jinorgbio.2019.110700.

[35] Kita, D.H., de Andrade, G.A., Missina, J.M., Postal, K., Boell, V.K., Santana, F.S., Zattoni, I.F., Zanzarini, I.d.S., Moure, V.R., Rego, F.G.d.M., Picheth, G., de Souza, E.M., Mitchell, D.A., Ambudkar, S.V., Nunes, G.G. and Valdameri, G. (2022), Polyoxovanadates as new P-glycoprotein inhibitors: insights into the mechanism of inhibition. FEBS Lett. https://doi.org/10.1002/1873-3468.14265