

Review

Polyoxovanadates with emerging biomedical activities

Manuel Aureliano^{a,b,*}, Nadiia I. Gumerova^c, Giuseppe Sciortino^{d,e}, Eugenio Garribba^e, Annette Rompel^{c,*}, Debbie C. Crans^{f,*}

^a FCT, Universidade do Algarve, 8005-139 Faro, Portugal

^b CCMar, Universidade do Algarve, 8005-139 Faro, Portugal

^c Universität Wien, Fakultät für Chemie, Institut für Biophysikalische Chemie, 1090 Vienna, Austria, <http://www.bpc.univie.ac.at>

^d Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 43007 Tarragona, Spain

^e Dipartimento di Chimica e Farmacia, Università di Sassari, Via Vienna 2, I-07100 Sassari, Italy

^f Department of Chemistry and Cell and Molecular Biology Program Colorado State University, Fort Collins, CO 80523, USA



ARTICLE INFO

Article history:

Received 22 March 2021

Received in revised form 14 June 2021

Accepted 18 July 2021

Available online 19 August 2021

Keywords:

Polyoxovanadates

Polyoxometalates

Decavanadate

Vanadate

Metal-oxides speciation

Anticancer drug

Antimicrobial drug

Antiviral drug

ABSTRACT

Polyoxovanadates (POVs) are a subclass of a larger family of polyanionic group V and VI metal-oxo clusters that are known as polyoxometalates (POMs). POMs have been found to have antidiabetic, antibacterial, antiprotozoal, antiviral and anticancer activities, which have sparked interest in their use as bioinorganic drugs. Among POVs, decavanadate ($[V_{10}O_{28}]^{6-}$; V_{10}) is an isopolyoxovanadate recently described to have several medicinal applications. In the present review, recent insights into POVs with emergent anticancer, antimicrobial and antiviral applications are described. Additionally, POVs' stability and speciation under experimental biological conditions as well as POVs (in particular, V_{10}) *in vivo* and *ex vivo* effects are highlighted. Finally, we report the most important 21st century studies of POVs' effects and/or targets against cancer, bacteria and viruses including: apoptosis, cell cycle arrest, interference with ion transport system, inhibition of mRNA synthesis, cell morphology changes, changes in metabolic pathways, phosphorylase enzyme inhibition and cell signaling, formation of reactive oxygen species, lipid peroxidation, inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, penetration and interaction with virus protein cages.

© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Abbreviations: A549, human lung cancer cells; ADME, absorption, distribution, metabolism and excretion; AsPC-1, pancreatic cancer cells; ABC-transporters, ATPases, ATP binding-cassette ATPases; AMA, amavadin; BALB/c, albino, laboratory-bred strain of the house mouse; BMOV, bis-maltolato-oxovanadium(IV); CAT, catalase; Ca^{2+} -ATPase, calcium adenosine triphosphatase; CTS- $Ca_3V_{10}O_{28}$, chitosan- $Ca_3V_{10}O_{28}(NH_4)_6$; CT26WT, mouse colon carcinoma cell line; CHO, Chinese hamster ovaries; di-4-ANEPPDHQ, aminonaphthylethylpyridinium-based dye; DPPC, dipalmitoylphosphatidylcholine; DTNB, 5,5'-dithiobis-(2-nitrobenzoic acid); E-NTPDase, ecto-nucleotide triphosphate diphosphohydrolase; EC_{50} , half maximal effective concentration; en, ethylenediamine; EXAFS, extended X-ray absorption fine structure; FcεRI, type I Fcε receptors; Fluv, influenza virus; FIPV, feline infectious peritonitis virus; F-actin, filamentous polymerized actin; 5-FU, 5-fluorouracil; GI_{50} , half maximal growth inhibition concentration; G-actin, monomeric actin; GPCRs, G protein-coupled receptor; GPx, glutathione peroxidase; gp120, glycoprotein expressed by HIV; HCB, hepatitis B virus; hCG, human chorionic gonadotropin; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HDAC, histone deacetylase; HeLa, human cervical cancer cell line; HEK 293, human embryonic kidney cell line; HepG2, human liver cancer cell line; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HMTA, hexamethylenetetramine; IC_{50} , half maximal inhibitory concentration; IPOV, isopolyoxovanadate; L-02, human normal hepatocytes; LHR, luteinizing hormone receptor; MDA-MB-231, human breast adenocarcinoma cell line; MDCK, madin-darby canine kidney cells; MCF-7, human breast cancer cell line; Me, methyl; MIC, minimum inhibitory concentration; MRB, mitochondrial respiration buffer; MRSA, methicillin-resistant *Staphylococcus aureus*; MT-4, human Lymphocyte cells; NCI-H460, human non-small cell lung cell lines; P388, murine leukemia cells; RBL-2H3, rat basophilic leukemia; ROS, reactive oxygen species; SARS, severe acute respiratory syndrome; SF-268, human brain tumor cell line; SR, sarcoplasmic reticulum; S1, myosin subfragment 1; SMMC-7721, Cellosaurus cell line; SOD, superoxide dismutase; SKOV-3, human ovary cancer cell line; TBA, tetrabutylammonium; tmen, N,N,N',N'-tetramethylethylenediamine; U-87, human primary glioblastoma cell line; ^{51}V -NMR, vanadium-51 NMR; V_1 , monomeric vanadate, simplest oxovanadate; V_{10} , ($V_{10}O_{28}^{6-}$) decavanadate, decameric oxovanadate; V^V -dipic, 2,6-pyridinedicarboxylatodioxovanadium(V); Vero, kidney epithelial cells; VRSA, vancomycin-resistant *Staphylococcus aureus*; BSA, bovine serum albumin; HA, hemagglutinin A; HSA, human serum albumin.

* Corresponding authors at: FCT, Universidade do Algarve, 8005-139 Faro, Portugal (M. Aureliano); Universität Wien, Fakultät für Chemie, Institut für Biophysikalische Chemie, 1090 Vienna, Austria (A. Rompel); Department of Chemistry and Cell and Molecular Biology Program Colorado State University, Fort Collins, CO 80523, USA (D.C. Crans).

E-mail addresses: maalves@ualg.pt (M. Aureliano), annette.rompel@univie.ac.at (A. Rompel), debbie.crans@colostate.edu (D.C. Crans).

<https://doi.org/10.1016/j.ccr.2021.214143>

0010-8545/© 2021 The Authors. Published by Elsevier B.V.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1. Introduction	2
2. Polyoxovanadates' speciation and stability in biological media	3
3. POVs <i>in vivo</i> and <i>ex-vivo</i> studies	5
3.1. Effects of POVs on fundamental metabolic processes	5
3.2. Studies carried out probing the effects of POVs as antidiabetic agents	6
3.3. POVs as cellular activators	7
4. Mitochondria as a potential subcellular target for POVs	8
5. Recent insights into POVs' biomedical applications	8
5.1. Anticancer activities of POVs	8
5.2. Antibacterial activities of POVs	9
5.3. Antiviral activities of POVs	11
6. Conclusions and perspectives	12
Declaration of Competing Interest	13
Acknowledgments	13
References	13

1. Introduction

Polyoxometalates (POMs) are oxo-clusters of transition metal ions, such as Mo, W, V, Nb and Ta [1–3] forming a variety of structures within a wide range of applications, not only in chemistry but in many other fields, from environmental science to medicine [4–14]. The metal oxo-clusters consist in building blocks of metal-oxo components, generally octahedral, and can be classified in homo- or hetero-polyoxometalates containing only one or multiple metal ions, respectively. The ability to replace a small part of the cluster with a different metal-oxo component further diversifies the properties and supports a range of reactivities which, from the first synthesis by Berzelius two centuries ago, has fascinated scientists with their seemingly endless possibilities. As such POMs are divided up into specific families, such as polyoxotungstates (POTs), polyoxovanadates (POVs), polyoxomolybdates (POMos), and polyoxoniobates (PONbs), although heteropolyoxometalates may belong to more than one of these families.

A literature search since 1985 in Web of Science finds more than eleven thousand articles using the search word “Polyoxometalate” including pure inorganic, organic-hybrid, encapsulated, nanoparticle, or other POM-based composites (Fig. 1). In the last decade (2011–2020) the number of papers has more than tripled in comparison to the previous decade (2001–2010) (Fig. 1A). Also, several review papers on different aspects and applications of

POMs have been published covering chemical engineering [15], catalysis [16], environmental chemistry [17], material science [18], biochemistry, biology, pharmacology and medicine [4,8,11,19–21]. This testifies the growing and expanding interest in POMs, amenable to a variety of structural transformations, in several scientific areas from basic to applied sciences [1–19]. In this review we will describe the subclass of POVs either as iso- or hetero-polyoxometalates in which vanadium is part of a cluster in POTs and POMos families.

In the last 20 years, the number of medicinal applications is increasing with several studies describing POMs with anticancer, antibacterial and antiviral activities [4,7,8,12,22–30]. POMs were found to be insulin mimetic agents [31,32], inhibitors of amyloid β -peptides aggregation and known to be associated with Alzheimer's disease [33–35] as well as enzyme inhibitors [4,36–40]. About 200 papers in the Web of Science concern the potential application of POMs as anticancer, antibacterial and antiviral agents, with 57% of those focusing on cancer, 17% on bacterial and 26% on virus studies, with the latter growing particularly in 2020 (Fig. 1B).

The first reports of anticancer, antiviral and antibacterial activities of POMs, were in 1965 [41], 1971 [42] and 1993 [43], respectively (Fig. 2). Over the years, POMs were reported to have beneficial properties against cancer and even been licensed toward the chemotherapy of solid tumors (such as human gastric cancer

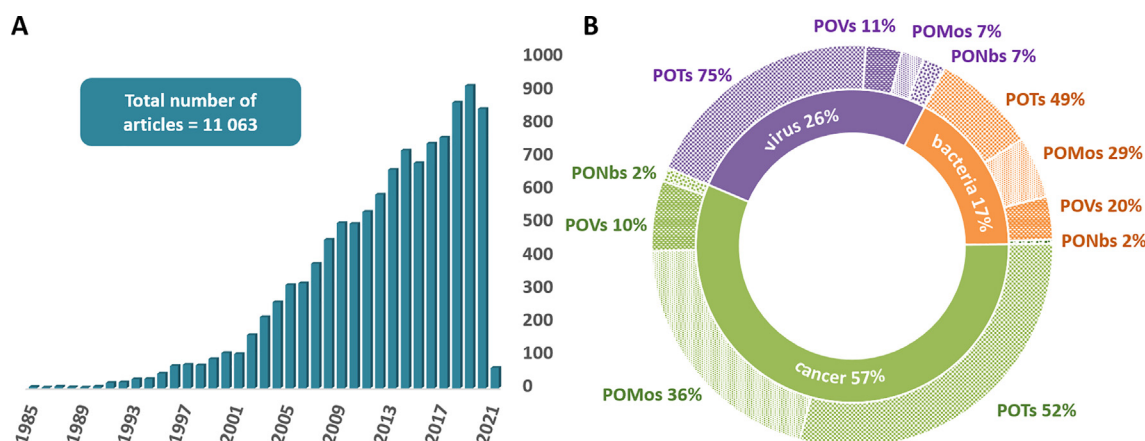


Fig. 1. Publication of studies involving POMs. A) Number of publications along the last 35 years (Web of Science); B) Relative contribution of POMs are divided up into specific families' of polyoxovanadates (POVs), polyoxomolybdates (POMos), polyoxoniobates (PONbs), and polyoxotungstates (POTs) and their application in anticancer, antibacterial and antiviral studies in each biomedical area.

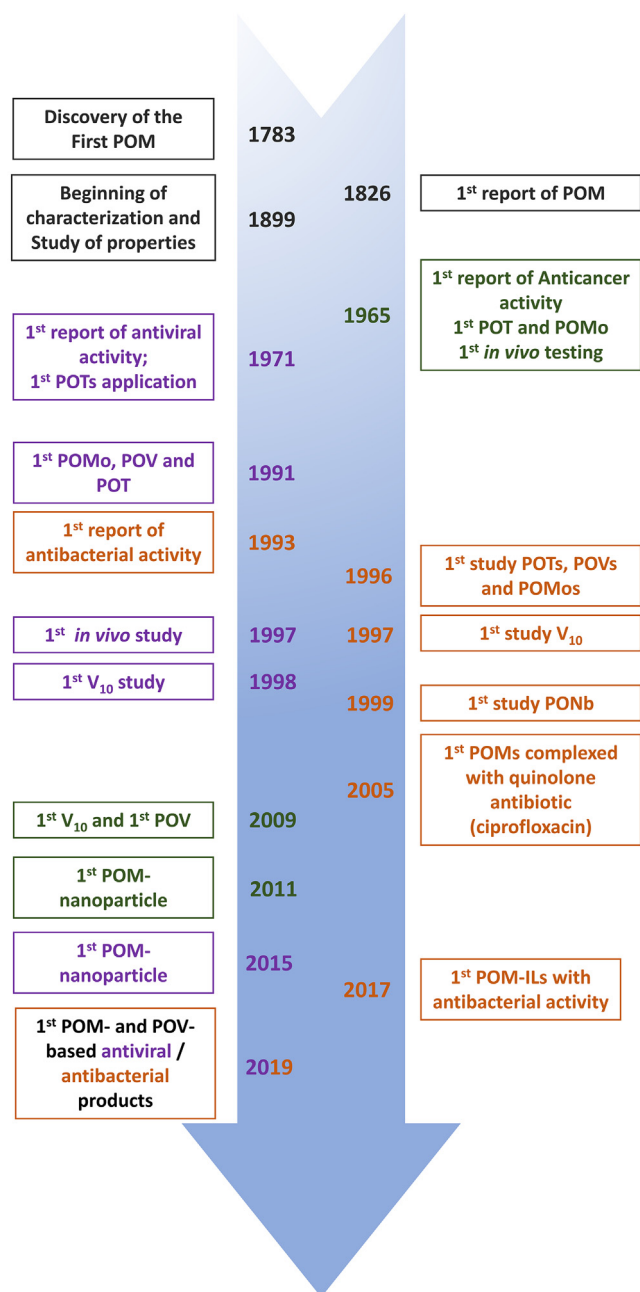


Fig. 2. Discovery (black) of the first biological studies described for polyoxotungstates (POTs), polyoxomolybdates (POMos), polyoxovanadates (POVs) and decavanadate (V₁₀), polyoxoniobates (PONbs) as well as for POM-nanoparticle and POM-Ionic liquids (ILs) anions in the treatment of cancer (green), viral (purple) and bacterial (orange) infections highlighting also *in vivo* animal studies.

and pancreatic cancer) [7,44,45], as well as against viruses (such as herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza, and severe acute respiratory syndrome (SARS)) [46], and drug-resistant bacteria (such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VISA)) [44]. Some milestones related to biomedical POMs' applications are listed chronologically in Fig. 2. After Hill's first review about medical application of POMs in 1998 [6], two fundamental papers pushing forward the understanding of POMs in medicine were published in 2005 [19,20]. In the case of vanadium, whose status as an essential element in humans is highly controversial, an extensive body of literature documented that simple vanadium salts had antidiabetic properties and extensive exploration of other

vanadium compounds has been carried out [47–49]. These studies include the effects of smaller oxovanadates [50] as well as the larger POVs such as V₁₀ [31,51]. Recent studies point to beneficial properties of POVs against drug-resistant bacteria and have recently been added to anti-virus and anti-bacterial products [52], which might be caused by the versatility of the vanadium coordination modes and oxidation states (V^{III}, V^{IV} and V^V) compared to other POMos and POTs. In this review, we combine the information on vanadium coordination complexes with the knowledge of the molecular and cellular processing and interactions of POMs in bacteria and in cancer cells [7,8] to describe the potential for the subclass of POVs.

For organic drugs, unless they are prodrugs, is known that they reach the target organs in an unaltered form. It is not the case for a metal-based drug because of its speciation chemistry. In fact, in biological fluids a metal-based drug can undergo many chemical changes, including ligand exchange, redox reactions at the metal ion and on proteins and metabolites, hydrolysis and several metabolic transformations once the metal ion binds to metabolites and proteins [53,54]. Although several metal-based compounds have been used for diagnostics and treatments of various pathologies, many aspects of the ADME (absorption, distribution, metabolism and excretion) remain to be further investigated and the speciation in aqueous solution and its redox reactions must be determined to identify the active POM species in body fluids and cells and finally understand POMs' mechanism of action [6,7,8,14,53–57]. In the present review the most important 21st century studies of POVs' effects and/or targets against cancer, bacteria and viruses are highlighted. Although POVs' mechanism of action against cancer cells remains unclear, as described throughout the review, the effects include among others, changes in the morphology of cells and activation of apoptosis pathways [20,58–61]. Similarly, the antibacterial mechanisms of action described for several POVs also comprise changes in the morphology of cells [20,62], besides the interference with ions' transport system, inhibition of mRNA synthesis, interference with metabolic pathways and signaling processes [8,63,64]. Finally, POVs' antiviral modes of action are based on the inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, inhibition of virus penetration and interaction with virus protein cages [65,66].

POMs structures have various sizes and shapes and may include other heteropolyoxido anions such as P^V and As^V. The anions consist of {VO₄} tetrahedral or {VO₆} octahedral components to generate small oligomers or compact larger POVs. Even though POVs in general contain vanadium in the oxidation state +5, recent reports have described POVs with both oxidation states, V(IV) and V(V). These multi-valence POVs can also contain metal ions in {VO₅} square-pyramidal units to generate structures that differ from the classical POMs and dramatically enrich POVs chemistry. Furthermore, in POMs structure one or more of the addenda metal oxoanions M = O (M = W^{VI}, Mo^{VI}, V^V, etc.) can be absent and/or substituted by transition metal ions (e. g. Co^{II}, Mn^{II}). Examples of pure inorganic and hybrid POVs structures described along this review are given in Fig. 3. However, the interested readers can find excellent reviews about POV structures elsewhere [1,2,5–8,14,19,21].

2. Polyoxovanadates' speciation and stability in biological media

The chemistry of POVs have been investigated using a range of different methods including potentiometry, ⁵¹V NMR, EPR spectroscopy, FT-IR spectroscopy, UV–Vis spectroscopy, X-ray crystallography, EXAFS and other spectroscopies [3,50,54]. Although some of the POVs are stable under physiological conditions others are not and it is important to establish the speciation of

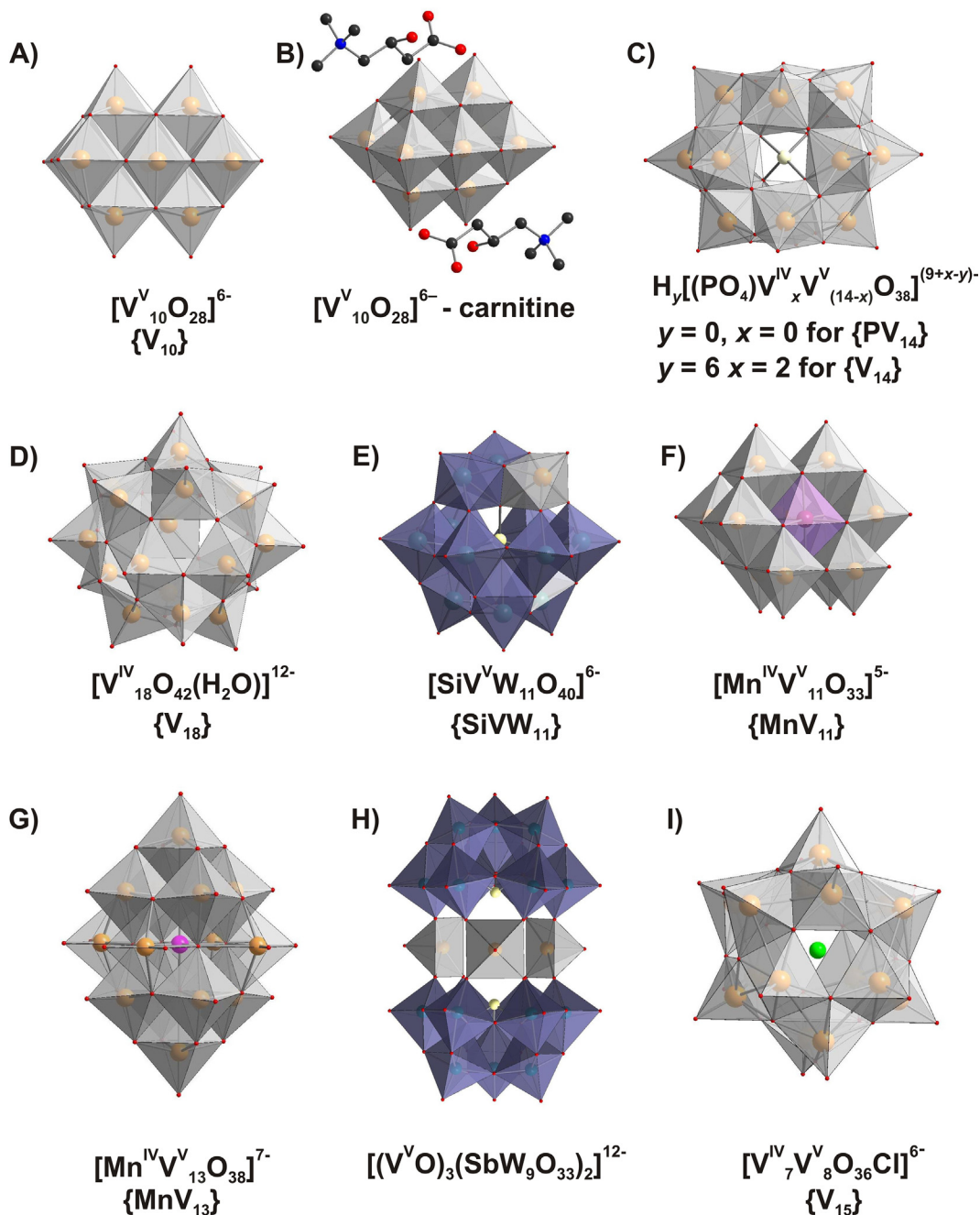


Fig. 3. POVs and mixed POV-POTs structures, which exhibit biological activity. In MnV_{13} (G) structure four equatorial V atoms have 75% occupancy [67] and so in total correspond to three V atoms with full occupancy in the sum formula. Color code: $\{\text{VO}_x\}$, grey; $\{\text{WO}_6\}$, violet; P or Sb, yellow; Mn, pink; Cl, green; O, red; C, black; N, blue.

compounds in order to properly attribute the species present causing biological activities. The studies investigating the effects of POVs should always take into consideration the stability of the POV under the given experimental conditions. Often, the lack of information about POVs' stability might contribute to misinterpretations about their effects for any biomedical or biological application. When POVs are incubated with proteins and/or exposed to cell cultures during long periods of time (up to 72 h) and physiological temperature (37 °C) in aqueous or semi-aqueous environments, their stability may be affected by the specific experimental conditions [4,54,68–73]. Therefore, without a clear demonstration that a POV species is stable under the given conditions, attributing the observed effects to the structure of the solid compound is a mere speculation.

The most commonly used speciation model (Fig. 4) was constructed about thirty five years ago as a result of rigorous ^{51}V NMR investigations in conjunction with potentiometric titration studies [74–81]. To testify the interest in such models, various computation methods were developed. In the 1980's speciation programs were based on calculations using the LAKE software [79], and since then more user friendly programs have been used. Recently, computational efforts point toward the automated search of POMs nucleation mechanism, providing speciation diagrams from first-principles [82].

The speciation model for vanadate solutions without heteroions postulates that, at pH higher than 6, polymers with one to five vanadium centers are formed, where many of these also undergo several individual protonation steps (Fig. 4). These oligomeric

Table 1

POVs in vivo and ex-vivo studies in the 21st century.

POV	Organ(s) tissue	Effects	Administration mode*	Year	Ref.
V ₁₀ (Fig. 3A)	Heart, Fish	Antioxidant enzymes	i.p.*	2002	[98]
V ₁₀ (Fig. 3A)	Heart, kidney, liver, Fish	Histological effects	i.p.	2003	[101]
V ₁₀ (Fig. 3A)	Liver	Vanadium accumulation/Antioxidant enzymes	i.v.*	2005	[93]
V ₁₀ (Fig. 3A)	Fish				
V ₁₀ (Fig. 3A)	Heart, blood, Fish	Vanadium accumulation	i.v.	2006	[99]
V ₁₀ (Fig. 3A)	Heart, Fish	Lipid peroxidation/Antioxidant enzymes	i.v.	2007	[100]
V ₁₀ (Fig. 3A)	Rat	Antidiabetic parameters	in vivo	2007	[51]
V ₂ O ₅ (Fig. 7A)	Male F344 Rat	Pulmonary Immunotoxicity/	Ad libitum		
Modelled by V ₁₀ (Fig. 3A)	Lungs	Pneumonia inducing <i>Listeria monocytogenes</i>	Airborne particles	2007	[102]
V ₁₀ (Fig. 3A)	Heart, Fish	Vanadium accumulation/Antioxidant enzymes	in vivo		
V ₁₀ (Fig. 3A)	Rat adipocytes	Antidiabetic parameters	ex-vivo	2008	[68]
V ₂ O ₅ (Fig. 7A)	Male F344 Rat	Pulmonary Immunotoxicity/	Airborne particles	2009	[31]
Modelled by V ₁₀ (Fig. 3A)	Lungs	Pneumonia inducing <i>Listeria monocytogenes</i>	in vivo	2010	[103]
V ₁₀ (Fig. 3A)	RBL-2H3 cells	Cell degranulation	ex-vivo	2013	[104]
Model for V ₂ O ₅	Leukemia cells	FcεRI signaling			
V ₁₀ (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	in vivo	2016	[96]
V ₁₀ (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	Ad libitum		
V ₁₀ (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	In vivo	2018	[97]
V ₁₀ (Fig. 3A), metformium complex	Rat	Antidiabetic parameters	Ad libitum		
PV ₁₄ (Fig. 3C)	Epithelia, Fish	Na ⁺ /K ⁺ -ATPase	In vivo	2019	[105]
V ₁₀ (Fig. 3A)	CHO cells	Signal Transduction	Ad libitum		
Na ₃ H ₃ V ₁₀ O ₂₈]		luteinizing hormone receptor (LHR)	ex-vivo	2019	[106]
K(NH ₄) ₄ [H ₆ V ₁₄ O ₃₈ (PO ₄)]	CHO cells	Signal Transduction	ex-vivo	2020	[107]
MVPV ₁₄ (Fig. 3C)		LHR			
[(CH ₃) ₄ N] ₆ [V ₁₅ O ₃₆ (Cl)]	CHO cells	Signal Transduction	ex-vivo	2020	[107]
MVV ₁₅ (Fig. 3I)		LHR			

* - i.p. is intraperitoneal; i.v. is intravenous administration.

tion of the V₁₀ species on the reported toxicological effects [90,93,99,100]. Several studies described intraperitoneal (i.p.) and intravenous (i.v.) administration of V₁₀ in two different fish models, *Halobatrachus didactylus* also known as the Lusitanian toadfish and *Sparus aurata* also known as the gilthead seabream [93,99,100]. The studies were carried out with both orthovanadate [VO₄]^{3−} (V₁) and V₁₀ (Fig. 3A) solutions (although V₁₀ solution pH was adjusted from 4 to near neutral, before administration, where vanadate exist as HVO₄^{2−} or H₂VO₄[−]) and the effects were analyzed in several organs and/or tissues such as cardiac, hepatic, renal and blood, Table 1 [90,93,99,100]. It was found that V₁₀ administration induces changes in sarcoplasmic reticulum Ca²⁺-pump, lipid peroxidation and antioxidant enzymes activities besides vanadium's subcellular accumulation and histological changes in heart and liver tissues (Table 1) [90,93,99,100]. It was proposed that oxidative stress responses, lipid peroxidation and vanadium subcellular distribution is dependent on V₁ or V₁₀ present in the administration fluid [68,72,73,90,93,98–101]. V₁₀ administration resulted in different effects not observed for monovanadate alone and, likewise, some effects observed for V₁ were not observed with V₁₀ (Table 1), findings which suggest that these species are not rapidly interconverting under biological conditions or that the processing of V₁₀ does not always result in V₁.

3.2. Studies carried out probing the effects of POVs as antidiabetic agents

Vanadium is well known to induce insulin-like or insulin-enhancing effects [47–51,108–111]. In 2021, it will be 100 years since insulin was discovered by Banting, Best and McLeod at the University of Toronto [112–114]. More than 350 million people are projected to suffer from diabetes mellitus in 2030 [115]. Diabetic patients are subject to other pathologies such as nephropa-

thy, arterial and neurodegenerative diseases. The usage of vanadium compounds with putative applications as insulin-mimetic agents was due to early discoveries that the simple inorganic salts generate an insulin-like effect [47–51,116]. At least part of the insulin enhancing effects was soon attributed to an increase of protein phosphorylation or inhibition of protein tyrosine phosphatases [117,118]. However, vanadium compounds also induce formation of reactive oxygen species (ROS), some of which could arise from Fenton-like reactions [119]. POVs have an effect on phosphatases, glucosidases, dehydrogenases, aldolases and other enzymes that are important for glucose processing [50].

A large number of different vanadium salts and complexes have been investigated reporting insulin-enhancing properties [48–50,111], among which several POVs, in particular, derivatives of V₁₀ [50,51]. V₁₀ with an ammonium counter-ion based on a molecule comparison increases about 6-fold the basal glucose uptake in rat adipocytes compared with other active vanadium compounds like bis(maltolato)oxovanadium(IV) (BMOV) or about 3-fold with respect to 2,6-pyridinedicarboxylatodioxovanadium(V) (V^V-dipic) (Fig. 6A, orange columns) [31]. However, only the incubation of adipocytes with decavanadate in the presence of insulin reaches an increase of the glucose uptake, of about 50% at decavanadate concentration of 1 mM (total vanadium, which is 100 μM decameric vanadate, Fig. 6A blue columns). Therefore, V₁₀ exerts *per se* insulin-like activity as well as is the unique V-based compound enhancing the glucose uptake also in presence of insulin (Fig. 6A blue columns).

Recent studies with different counterions showed that the effects of ammonium decavanadate (NH₄)₆[V₁₀O₂₈] can be improved and the use of benzylammonium C₇H₁₀N⁺ [51] or metforminium C₄H₁₂N₅⁺ [97,105] salts appear to exceed the insulin-enhancing effects of ammonium V₁₀ even more. However, in the latter case a different animal model system was used so that

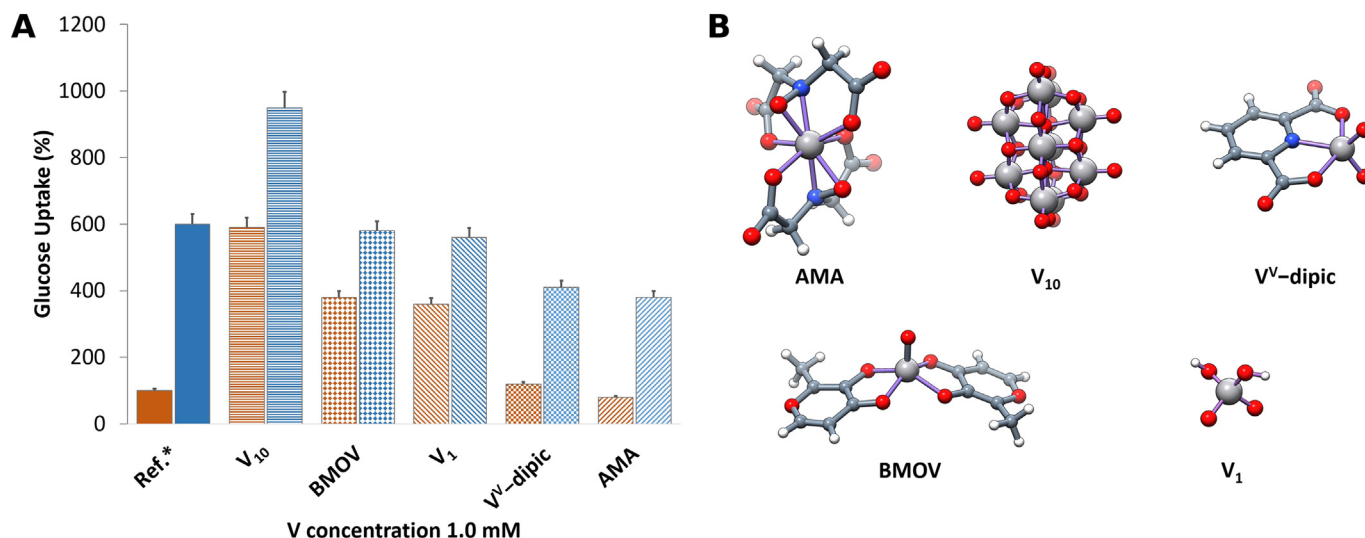


Fig. 6. A) Comparison of the [¹⁴C] glucose uptake (%) between five different vanadium compounds (total vanadium concentration of 1.0 mM) measured in primary rat adipocytes. The samples are incubated for 45 min with vanadium compounds in the absence (orange) or in the presence (blue) of 10 nM insulin for 30 min. B) Structures for V₁₀ (decavanadate); V₁ (orthovanadate, V₁); BMOV (Bis-maltolato-oxovanadium(IV)); VV-dipic (2,6-pyridinedicarboxylatodioxovanadium(V)); AMA (amavadin). Vanadate (V₁) is illustrated as monomeric vanadate for simplicity although vanadate solutions at physiological pH values contains also others vanadate oligomers such as V₂ and V₄. Modified from reference [31].

comparisons are non-trivial and studies showing a direct comparison of these V₁₀ salts would be desirable.

3.3. POVs as cellular activators

It has been suggested that V₁₀ structurally resembles the surface of V₂O₅ oxide [104], which has been identified as low molecular weight sensitizing agent associated with occupational asthma and compromised pulmonary immune competence, Fig. 7 [103]. As V₂O₅ is a polymeric material with sheets of oxides which alter speciation upon dissolution, studies probing the effects of this material are controversial, because dissolution of V₁₀ is observed. However, since V₂O₅ is an important heterogeneous catalyst, produced each year in high amount, there is significant interest in the biological effects of this material, which has been categorized as a toxic compound [120].

Due to this suggested structural analogy, the effects of V₁₀ on biological systems and its interactions with lipid interfaces and membranes are of particular interest. In this context, the biological effects of V₁₀ (Fig. 3A), used as model of V₂O₅, on plasma membrane lipid packing of leukemia cells (RBL-2H3) as well as on Langmuir monolayers were investigated [104]. Then, the possibility that V₁₀ as a model for V₂O₅ may be initiating plasma membrane

events associated with activation of Type I Fcε receptors (FcεRI) signal transduction using RBL-2H3 cells as a mast cell model was reported [28,104,123]. The exposure of RBL-2H3 cells to V₁₀ caused a concentration-dependent increase in degranulation of RBL-2H3. In addition, an increase in plasma membrane lipid packing was observed as measured by the fluorescent probe, aminonaphthylethenylpyridinium-based dye (di-4-ANEPPDHQ). V₁₀ also increases FcεRI accumulation in low-density membrane fragments, i.e., lipid rafts, which may facilitate FcεRI signaling. To determine whether V₁₀ affects the packing of plasma membrane lipid, both V₁ and V₁₀ were investigated. V₁₀ increased the surface area of DPPC Langmuir monolayers by 6%, while V₁ decreased the surface area by 4%. These results are consistent with V₁₀ interacting with this class of membrane lipids and altering dipalmitoylphosphatidylcholine (DPPC) packing and showed that V₁₀ and V₁ act differently [104,124].

The luteinizing hormone receptor (LHR), a G protein-coupled receptor (GPCRs), can initiate signaling in the presence of two mixed-valence POVs, K(NH₄)₄[H₆V₁₄O₃₈(PO₄)] (MVPV₁₄, Fig. 3C) and [(CH₃)₄N]₆[V₁₅O₃₆(Cl)] (MVV₁₅, Fig. 3I) or V₁₀ (Fig. 3A) and V₁ [107]. The ability of LHR expressed in Chinese hamster ovaries (CHO) cells to initiate signaling in the presence of highly charged, water-soluble and redox active POVs, MVPV₁₄ and MVV₁₅, is a result of the vanadium compound interactions with the membrane lipids and/or the cell membrane lipid interface [107]. Interactions of the vanadium compounds with CHO cells decreased the packing of membrane lipids, drove aggregation of LHR and increased signal transduction by LHR. For V₁₀, MVPV₁₄ and MVV₁₅, cell responses were greater than those observed for cells treated with human chorionic gonadotropin (hCG), a naturally-occurring LHR ligand produced in early pregnancy in humans. POV effects were observed for CHO cells where LHR was expressed at 10,000 or 32,000 LHR per cell but not when LHR was overexpressed with receptor numbers >100,000 LHR per cell. The speciation of V₁, V₁₀, MVPV₁₄ or MVV₁₅ in cell medium was monitored using ⁵¹V NMR and EPR spectroscopy. In the case of both V₁ and MVPV₁₄ the conversion to trace levels of V₁₀ and the smaller oligomers was observed after 3–10 h of incubation in the cell medium. All the POVs and V₁ initiated signaling, but V₁₀ (Fig. 3A), MVPV₁₄ (Fig. 3C) and MVV₁₅ (Fig. 3I) had the greatest effects on cell function, while V₁ was sig-

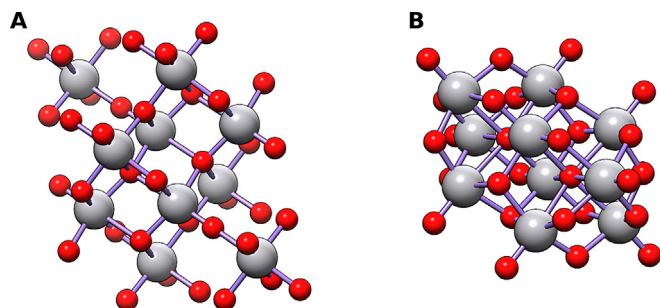


Fig. 7. Representation of: A) the partial structure (10 units) for V₂O₅ sheet [121]; and B) the structure for the discrete decavanadate anion (V₁₀) [122]. While V₂O₅ falls apart in solution; the discrete V₁₀ anion retains its structure upon dissolution. Adapted with permission from reference [104].

nificantly less active. The observed IC_{50} per each V compounds were 56.5, 3.2, 6.1 and 8.2 μM or expressed per V-atom 56.5, 32, 85 and 123 μM , respectively [107]. However, the chemistry of these mixed valence polyoxovanadates include oxidation of the POV and in the case of MVV_{15} ($[(\text{CH}_3)_4\text{N}]_6[\text{V}^{\text{V}}\text{V}^{\text{IV}}\text{O}_{36}(\text{Cl})]$, Fig. 31) the oxidized anion is formed in solution. Because of the complex nature of vanadium compounds speciation, it cannot be ruled out that some of the observed effects on cell function may be due to vanadium species formed in the cell medium over time. Still, the data clearly do show that the three POVs exhibit different effects of each other and of V_1 .

In summary, these results demonstrate that V_{10} , the major POV studied in these systems, shows effects different from those of V_1 in fundamental biochemical processes, including activating signal transduction. Furthermore, the data of the studies as an antidiabetic agent are rather promising and demonstrate that optimization of effects can be done by altering the nature of the counterion.

4. Mitochondria as a potential subcellular target for POVs

As referred above, POVs have distinct effects other than orthovanadate (V_1) or metavanadate (V_1 , V_2 , V_4) species in mitochondria. Studies with both vanadate and decavanadate (Fig. 3A) in two different fish models, *Halobatrachus didactylus* and *Sparus aurata*, following POVs administration, detected that more vanadium is accumulated in mitochondrial fractions than when treated with V_1 alone [98,100]. Moreover, *in vivo* administration of V_{10} resulted in specific effects in mitochondrial antioxidants enzyme activities [99,100].

In order to further explore the effects of V_{10} on mitochondria, studies were performed *in vitro*. In both hepatic and cardiac mitochondria V_{10} inhibits mitochondrial respiration and induces mitochondrial membrane depolarization [70]. For instance, V_{10} concentrations lower than 100 nM inhibit 50% of oxygen consumption in mitochondria, while a 100-fold higher concentration of V_1

(10 μM) (or 10-fold higher concentrations of V-atoms) is needed to induce the same effect. Moreover, V_{10} also induces mitochondrial depolarization (IC_{50} 0.5 μM) much more strongly than V_1 (IC_{50} 50 μM) [125]. Considering the concentrations and biodistribution of vanadium upon administration and the observation that nM concentration of decavanadate inhibits oxygen consumption and membrane depolarization, it could be argued that mitochondria are a potential cellular target organelle for V_{10} (Fig. 8) [70,100,124,125].

In summary, herein not only *in vitro*, but specially *in vivo* and *ex-vivo* effects for POVs, mainly decavanadate (V_{10}) are described and summarized in Fig. 8. Thus, regarding POVs *in vivo* studies many effects were reported in several organs and tissues such as heart, kidney, liver and blood in: 1) Ca^{2+} -ATPase activity; 2) lipid peroxidation; 3) antioxidants enzyme activity, in particular superoxide dismutase (SOD), involved in the elimination of superoxide radical anions, catalase (CAT) involved in the decomposition of hydrogen peroxide and glutathione peroxidase (GPx) involved in the recovery of glutathione (GSH); 4) reactive oxygen species (ROS) production; 5) vanadium accumulation; and 6) histological effects. In addition, recently *ex-vivo* studies effects were described for: 7) Na^+/K^+ -ATPase activity coupled with chloride secretion; 8) adipocytes glucose uptake; 9) signal transduction. Finally, effects of *in vitro* POVs studies were associated with: 10) signal transduction processes; 11) inhibition of mitochondrial respiration; and 12) mitochondrial membrane depolarization (summarized in Fig. 8).

5. Recent insights into POVs' biomedical applications

5.1. Anticancer activities of POVs

A search in Web of Science shows that the number of papers published on the subjects "POMs and cancer", increased 7-fold in the past 10 years, in comparison to the previous decade, from 14 to 93 publications, representing 57% of POM papers in the biomedical field, with only 3 papers published prior to year 2000. Polyoxotungstates (52%) and polyoxomolybdates (36%) represent the majority of studied POMs, whereas the number of papers on polyoxovanadates (10%) and other types of POMs, such as polyoxoniobates (2%) is much less. For POTs and POMos the first studies on anticancer activity were described in 1965 [41], whereas the first report for V_{10} and/or POVs was published in 2009 [126]. The anticancer activity of POM-nanoparticle composites, which are promising candidates for the drug delivery in cancer therapy, as their particle size can be fine-tuned to ensure appropriate accommodation of guest molecules, was actively investigated (Fig. 2) [7,127,128]. Table 2 summarizes the results published with V_{10} , V-containing POMs and others POVs in cancer studies for the last 15 years.

Two decavanadate compounds, $(\text{H}_2\text{tmen})_3[\text{V}_{10}\text{O}_{28}]$ (tmen = N,N,N',N'-tetramethylethylenediamine) and $(\text{H}_2\text{en})_3[\text{V}_{10}\text{O}_{28}]$ (en = ethylenediamine), were tested against human lung carcinoma cells (A549) and murine leukemia cells (P388) [26]. The IC_{50} values for A549 inhibition are 4.3 ± 0.3 and 1.5 ± 0.1 μM , for $(\text{H}_2\text{tmen})_3[\text{V}_{10}\text{O}_{28}]$ and $(\text{H}_2\text{en})_3[\text{V}_{10}\text{O}_{28}]$, respectively and for P388 inhibition 20.0 ± 1.5 and 59.0 ± 4.3 μM , respectively [26]. Considering that there are 10 V-atoms in one V_{10} anion, these values are 10-fold larger if focusing on concentrations of vanadium. Against human lung carcinoma cells, these POVs exhibited inhibition values 1.8–5.2 times lower than cisplatin (IC_{50} value: 7.8 ± 0.5 nM for A549 and 5.2 ± 0.3 nM for P388). The most lipophilic compound $(\text{H}_2\text{tmen})_3[\text{V}_{10}\text{O}_{28}]$ showed higher cytotoxicity presumably due to a better uptake through the lipid bilayer [26]. The cytotoxicity of both $\text{H}_2\text{tmen}^{2+}$ and H_2en^{2+} V_{10} salts was also measured on human normal hepatocytes (LO2) and resulted in IC_{50} of 6.5 ± 0.6 μM for

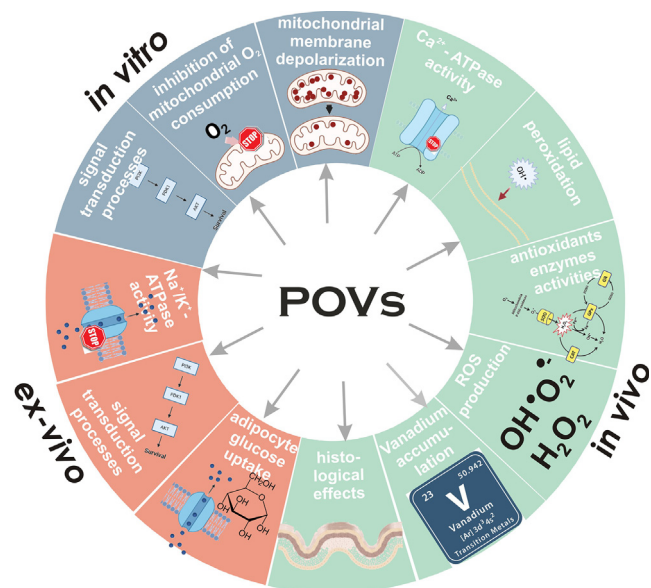


Fig. 8. Scheme of the described *in vitro*, *in vivo* and *ex-vivo* effects for POVs, mainly V_{10} . POVs *in vivo* effects in: 1) Ca^{2+} -ATPase activity; 2) lipid peroxidation; 3) antioxidants enzymes activities (SOD, CAT, GPx); 4) ROS production; 5) vanadium accumulation and 6) histological effects. POVs *ex-vivo* studies effects in: 7) Na^+/K^+ -ATPase activity coupled with chloride secretion; 8) adipocytes glucose uptake; 9) signal transduction and *in vitro* POVs studies; 10) signal transduction processes; 11) inhibition of mitochondrial respiration and 12) mitochondrial membrane depolarization.

Table 2Studies published during the past 15 years on the anticancer activity of V₁₀, V-containing POMs and others POVs.

POVs	Cell line	Effects	Year	Ref.
[NiV ₁₃ O ₃₈] ⁷⁻ and [V ₁₈ O ₄₂ (PO ₄)] ⁹⁻	Human melanoma	Antitumor parameters	2005	[129]
[NiV ₁₃ O ₃₈] ⁷⁻ and [V ₁₈ O ₄₂ (PO ₄)] ⁹⁻	Lung cancer cells	Antitumor parameters	2005	[130]
Na ₄ Co(H ₂ O) ₆ V ₁₀ O ₂₈ ·18H ₂ O (CoV ₁₀) (Fig. 3A)	SKOV-3	Growth reduction	2009	[126]
(H ₂ tmen) ₃ [V ₁₀ O ₂₈], tmen = N,N,N',N'-tetramethylethylenediammonium (Fig. 3A)	SMMC-7721			
POV-bisphosphonate complexes:	A549 and P388	Growth reduction	2010	[26]
V ₆ (Ale) ₄ , V ₃ (Zol) ₃ , V ₅ (Ale) ₂ , V ₅ (Zol) ₂ ,	NCI-H460, MCF-7, and SF-268	Growth reduction	2012	[131]
Ale = alendronate, Sul = (2-Hydroxy-2,2-bis-phosphono-ethyl)-dimethyl-sulfonium and Zol = zoledronate				
V ₁₀ -betaine complexes	MCF-7, A549	Growth reduction	2013	[132]
K ₂ [(MeNC ₃ H ₄ COOH) ₂][V ₁₀ O ₂₈ H ₂ ·2H ₂ O], [(H ₂ NMe ₂) ₄][V ₁₀ O ₂₈ H ₂][Me ₃ NCH ₂ COO] ₂ , [(Me ₃ NCH ₂ COOH) ₄][V ₁₀ O ₂₈ H ₂][Me ₃ NCH ₂ COO] ₂ ·2H ₂ O (anion Fig. 3A)				
Na ₅ [PMo ₁₀ V ₂ O ₄₀] (Keggin archetype Fig. 3E) encapsulated in starch or lipid nanoparticles	MCF-7 and HEK-293	Growth reduction	2015	[133]
{(Me ₃ N-CH ₂ -CH(OH)-CH ₂ -COOH) ₂ } {Na ₄ (H ₂ O) ₁₆ [V ₁₀ O ₂₈]}·MeOH	MDA-MB-231	Growth reduction	2016	[134]
V ₁₀ -carnitine (Fig. 3B)	A549			
Na ₁₀ [V ₁₁ V ₉ O ₄₄ (N ₃)]	Cervical cancer cells	Antitumor parameters	2016	[135]
K ₁₂ [V ₁₈ O ₄₂ (H ₂ O)]·6H ₂ O (V ₁₈ , Fig. 3D)	MCF-7	DNA, BSA and HSA binding Induced apoptosis. G2/M phase cell cycle arrest	2017	[58]
K ₁₂ [V ₁₈ O ₄₂ (H ₂ O)]·6H ₂ O (V ₁₈ , Fig. 3D)	MDA-MB-231	Growth reduction	2017	[58]
(TBA) ₄ H ₃ [GeW ₉ V ₃ O ₄₀], TBA - tetrabutylammonium (Keggin archetype Fig. 3E)	U-87	Growth reduction	2017	[127]
Na ₄ [(HOCH ₂ CH ₂) ₃ NH] ₂ [V ₁₀ O ₂₈]·6H ₂ O (Fig. 3A)	HeLa	Induced apoptosis	2018	[60]
V ₁ at pH 3–5 V ₁₀ (Fig. 3A)	HepG2			
{V ₅ O ₉ Cl(COO) ₄ } with TATB (VMOP-31)	MDA-MB-231	Tumor decrease	2018	[60]
	SMMC-7721	Cell cycle arrest, DNA damage, induced apoptosis	2019	[59]

(H₂tmen)₃[V₁₀O₂₈] and 7.2±0.7 μM for (H₂en)₃[V₁₀O₂₈]. In contrast, the V₁₀-carnitine complex (Fig. 3B) exhibits anti-tumor activity against various human cancer cells, whereas normal human cells were not affected even when it was applied at high concentrations [134]. V₁₀-carnitine had IC₅₀ values of 0.72 and 1.8 μM against a human lung adenocarcinoma cell line (A549) and a human breast adenocarcinoma cell line (MDA-MB-231), respectively. Compared to cisplatin's cytotoxicity, V₁₀-carnitine exhibited lower cytotoxicity values against A549 [134]. The IC₅₀ for the V₁₀-carnitine complex against MDA-MB-231 cells was 1.7 μM compared to 700 μM for cisplatin, showing that V₁₀-carnitine is 400 times more effective. Even when considering that V₁₀ has ten metal ions and cisplatin only one, the V₁₀-carnitine complex is still more effective in the comparison of the efficacy of the two compounds per metal ion [126].

The sodium-cobalt(II) salt of V₁₀, Na₄Co(H₂O)₆[V₁₀O₂₈] (CoV₁₀), was tested against human liver (SMMC-7721) and ovary (SKOV-3) cancer cell lines [126]. CoV₁₀ inhibits cell proliferation by 95% and 90% of SMMC-7721 and SKOV-3, respectively, at 6.25 μg/mL with an IC₅₀ value estimated lower than 0.26 μg/mL, for both cancer cell lines. Similarly, the potency of CoV₁₀ as an antitumor drug was compared with the approved drug fluorouracil (5-FU) and verified to be 15 times more effective against SMMC-7721 [126]. Table 2 summarizes the results published for V₁₀ and others POVs in cancer studies in the last 15 years. Regarding the mode of POVs' action as antitumour agents, several potential mechanisms leading to apoptosis have been evoked [24,25,61,136,137]. For some POVs, such as K₁₂[V₁₈O₄₂(H₂O)] (V₁₈, Fig. 3D), the tumor inhibiting mechanism is identified and is based on the arrest of MCF-7 cells in the G2/M phase leading to the induction of apoptosis and necrosis [58].

In summary, these studies demonstrate that V₁₀, other V-containing POMs and POVs have desirable anticancer properties. Moreover, recent papers showed that their effects compete and exceed that of cisplatin and thus warrant consideration in the

future regardless of their charge and high polarity. In the last few years, in order to reduce the toxicity of POMs and improve their structural stability, the trend has shifted from testing inorganic POMs to testing POM-based nanohybrids. This resulted in a significant increase of the number of studies with hybrid POMs as potential agents in the fight against cancer [138–141]. Moreover, due to the functionalization and/or encapsulation with organic ligands, POVs with novel properties arise [142–147].

5.2. Antibacterial activities of POVs

Antibiotic resistance represents a real threat to the world public health since a high proportion of bacteria show significant resistance [148]. Combinations of different antibiotic agents are commonly adopted to combat infections caused by multi-resistant bacteria. Since 1996 a total of 75 POVs studies are available measuring antibacterial effects, with a clear increase (~40%) in the last decade [8]. POMs were recently suggested as putative future drugs fighting against pathogenic bacteria [8]. Historically, POMs as antibacterial agents started serendipitously. Thus, in 1993 an unknown compound named initially as “Factor T” was observed to enhance the antibacterial effect of β-lactams inhibiting methicillin-resistant *S. aureus* (MRSA) strains [149]. The aged mixture of tungstate and phosphate named “Factor T” was later identified as [PW₁₁O₃₉]⁷⁻, the first POT of many others following under investigation as antibacterial agents [43].

In an early study investigating the antibacterial activity of vanadates(V) and oxovanadium(IV) compounds *in vitro*, the minimum inhibitory concentration (MIC) values for V₁, V₁₀, and [V^{IV}O]²⁺ for *S. pneumoniae* are between 4 and 32 μg/mL. In 1996, the first antibacterial studies applying POMs and POVs were described, whereas the first paper investigating V₁₀' antibacterial power was reported in 1997 [8].

Table 3Studies published during the past 16 years on the antibacterial activity of V₁₀ and other POVs.

Sum formula of the solid decavanadate	Bacteria ^{a,b}	Quantitative characteristics	Year	Ref.
(C ₆ H ₁₄ N ₅ O) ₄ [H ₂ V ₁₀ O ₂₈]·9H ₂ O	<i>Staphylococcus aureus</i> , ^b <i>Staphylococcus epidermis</i> , ^b MRSA (methicillin-resistant <i>Staphylococcus aureus</i>), ^b MRSE (methicillin-resistant <i>Staphylococcus epidermis</i>) ^b	Growth inhibition	2004	[153]
(C ₆ H ₁₄ N ₅ O) ₆ [V ₁₀ O ₂₈]·4H ₂ O, C ₆ H ₁₄ N ₆ O – moroxydine chitosan–Ca ₃ V ₁₀ O ₂₈	<i>Escherichia coli</i> , ^a <i>Staphylococcus aureus</i> ^b	MIC = 12.5 μM against both strains	2005	[63]
[H ₂ V ₁₀ O ₂₈][4-picH] ₄ ·2H ₂ O, 4-pic = 4-picoline	<i>Pseudomonas aeruginosa</i> ^b , <i>Bacillus cirroflagellus</i> ^a	Growth inhibition	2014	[154]
[4-(CH ₃ O)C ₆ H ₄ CH ₂ NH ₃] ₆ V ₁₀ O ₂₈ ·2H ₂ O	<i>Enterococcus faecium</i> ^a	only qualitative determination	2015	[155]
K(NH ₄) ₄ [H ₆ V ₁₄ O ₃₈ (PO ₄)], MVPV ₁₄ (Fig. 3C)	<i>E. coli</i> ^a	Growth inhibition	2016	[156]
[(CH ₃) ₄ N] ₆ [V ₁₅ O ₃₆ (Cl)], MVV ₁₅	<i>E. coli</i> ^a	Protection against alkylating agents	2016	[156]
Na ₆ V ₁₀ O ₂₈ (Fig. 3A)	<i>Mycobacterium smegmatis</i> , ^{a,b} <i>Mycobacterium tuberculosis</i> ^{a,b}	EC ₅₀ (M. smeg) = 0.0037 mM; EC ₅₀ (M. tb) = 0.029 mM	2018	[151]
Na ₆ V ₁₀ O ₂₈ (Fig. 3A), (3-Hpca) ₄ [H ₂ V ₁₀ O ₂₈]·2H ₂ O·2(3-pca), 3-pca = 3-pyridinecarboxamide	<i>E. coli</i> ^a	GI ₅₀ (Na salt) = 0.1 mM; GI ₅₀ (3-Hpca salt) = 0.47 mM; GI ₅₀ (4-Hpca salt) = 0.67 mM	2018	[152]
(4-Hpca) ₄ [H ₂ V ₁₀ O ₂₈]·2(4-pca), 4-pca = 4-pyridinecarboxamide				
(NH ₄) ₄ (HMTA–H) ₂ V ₁₀ O ₂₈ ·4H ₂ O, HTMA – hexamethylenetetramine	<i>E. coli</i> ^a <i>Salmonella typhimurium</i> , ^a <i>Enterococcus faecium</i> , ^b <i>Streptococcus agalactiae</i> ^b	only qualitative determination	2019	[157]
(NH ₄) ₆ V ₁₀ O ₂₈ (Fig. 3A)	<i>E. coli</i> ^a	GI ₅₀ = 1.1 mM	2019	[158]
MnV ₁₁ (Fig. 3F), MnV ₁₃ (Fig. 3G) and V ₁₀ (Fig. 3A)	<i>E. coli</i> ^a	GI ₅₀ of 0.21, 0.27, and 0.58 mM	2019	[158]
Na ₅ PtV ₉ O ₂₈	<i>Mycobacteria smegmatus</i> ^{a,b}	EC ₅₀ (Na ₅ PtV ₉ O ₂₈) = 0.0048 mM; EC ₅₀ (Na ₅ MoV ₉ O ₂₈) = 0.0015 mM; EC ₅₀ (Na ₆ V ₁₀ O ₂₈) = 0.0036 mM	2021	[64]
Na ₅ MoV ₉ O ₂₈				
Na ₆ V ₁₀ O ₂₈				
(NH ₄) ₂ (Me ₄ N) ₅ [V ₁₂ V ₆ O ₄₂]·Me ₄ Ni·5H ₂ O (V ₁₈)	<i>E. coli</i> ^a	Protection against alkylating agents		[159]
[(K ₆ (OH) ₂) ₁₂ V ₁₁ V ₇ O ₄₁ (PO ₄)·4H ₂ O] _n (V ₁₈ P)				
V ₁₀ (Fig. 3A)				

^a Gram-negative bacteria.^b Gram-positive bacteria.

In 2012, the first study with a POM complexed with the quinolone antibiotic (ciprofloxacin) was published [150]. V₁₀ is the most common investigated POV also in antibacterial research, and Table 3 summarizes the antibacterial studies on V₁₀. Even when the starting compound is V₁, V₁₀ forms in the growth media, which usually has an acidic pH, e.g. 6. In a study of *Saccharomyces cerevisiae* (vide supra) V₁₀ was observed to be cell associated, which was interpreted as forming inside the cells in the acidic vacuoles through a proposed detoxification mechanism [94]. Willsky et al. was using ⁵¹V NMR for the detection of vanadium(V) and saw the V₁₀ signal forming as a function of time; they measured spectra of media and also consolidated cells (cell soup) and observed V₁₀ both in cells and in growth media [94]. These studies were carried out with EPR spectroscopy which allowed monitoring the reduction of vanadate as a function of time [94].

V₁₀ is more effective than V₁ and other rapidly converting smaller oxovanadates such as dimeric (V₂) and tetrameric vanadate (V₄), against Gram-positive bacteria, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Staphylococcus epidermis* [8]. Growth inhibition is also observed for Gram-negative bacteria such as *Escherichia coli* and *Salmonella typhimurium* [8]. V₁₀ also inhibits the growth of *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* more significantly than V₁ [151]. The higher efficacy of V₁₀ over V₁ is due not only to the large number of V centers, but also to the general properties of POM, such as total net charge, size, and redox activity. The association of V₁₀ with more complex cations such as (iso)nicotinamide (C₆H₈N₂O⁺) [152], Ca²⁺–chitosan [63] and other amine-based cations (Table 3) increases the toxicity

towards *Escherichia coli*, proving that V₁₀ also in a bacterial system can be fine-tuned by exchanging the counter-cation.

The symbiotic effect of chitosan together with V₁₀ was investigated against *E. coli* and *S. aureus* [63]. The chitosan–V₁₀ complex demonstrated the same antibacterial activity against both bacteria with a MIC value of 12.5 μM [63]. Chitosan is known for its antimicrobial activity as it inhibits the mRNA synthesis after penetration into the nuclei of microorganisms [160]. On the other hand, V₁₀ alone inhibits P-type ATPases, such as Ca²⁺–ATPase [73,161,162], leading to a disturbance in the molecular ion transport across the membrane and compromising the bacterial metabolism [63]. Thus, the mechanism of action of these combined POVs as antibacterial agents might include the inhibition of mRNA synthesis interfering with protein's production and the inhibition of P-type ATPases, destroying bacteria's metabolism and signaling. Several others possible mechanisms are discussed and reviewed in ref. [8].

Besides V₁₀, two manganese (Mn) containing polyoxovanadates, MnV₁₁ (Fig. 3F) and MnV₁₃ (Fig. 3G), were shown to inhibit the growth of *E. coli* [158]. MnV₁₁, MnV₁₃ and V₁₀ (pH of stock solution is 4) were all more effective inhibitors than simple V₁ (pH of stock solution is 10.5), with 50% maximal growth inhibition concentrations (GI₅₀) of 0.21, 0.27, and 0.58 mM, respectively, compared to 1.1 mM for simple vanadate. Strikingly, the V₁₀ isostructural species decaniobate (Nb₁₀) showed only residual effects on *E. coli* growth [158].

The mixed valence polyoxovanadates MVPV₁₄ (Fig. 3C) and MVV₁₅ (Fig. 3I) were evaluated for their chemoprotective activity

against the alkylating agent diethylsulphate in *Escherichia coli* DH5a cultures [156]. Their redox properties were examined as a potential protecting agent and compared to the effects of V_{10} and V_1 by monitoring the growth of *E. coli* treated with alkylating agent. MVPV₁₄ suffers rapid hydrolysis in both water and culture media, forming simple mononuclear complexes as well as larger aggregates such as $[H_4V_{14}O_{38}(PO_4)]^{5-}$ (Fig. 3C) or $[HV_{10}O_{28}]^{5-}$. This may explain the lack of chemoprotection by MVPV₁₄ and V_{10} , whereas MVPV₁₅ is effectively protecting the cells from alkylating agents. The observed chemoprotective effect is not only highly dependent on the solution stability of the polyoxometalates, but is also limited by the formation of decomposition products, such as V_{10} and V_1 species, which are not able to react and therefore do not deactivate the alkylating agent in the culture media of *E. coli*. In summary, the antibacterial effects of POVs vary based on speciation, although generally the POVs are more potent than V_1 .

Recently, the chemoprotective activity of three POVs, $(NH_4)_2(-Me_4N)_5[V_{12}V_6O_{42}I] \cdot Me_4NI \cdot 5H_2O$ ($V_{18}I$), $[K_6(OH_2)_{12}V_{11}V_7O_{41}(PO_4) \cdot 4H_2O]_n$ ($V_{18}P$), and V_{10} , towards the alkylating agent diethyl sulfate was assessed in *E. coli* cultures [159]. Comparing the results with previous findings described above for V_{14} and V_{15} [156], it was concluded that $V_{18}I$ is more stable than V_{15} , followed by $V_{18}P$ and V_{14} , and that the stability appears to originate from their interaction with cells and chemoprotective action against the deleterious effect of diethyl sulfate [159].

5.3. Antiviral activities of POVs

The number of studies testing metallodrugs which include POMs for treatment of viral infection has increased in 2020 due to the SARS-CoV2 pandemic [163–167]. Among the antiviral studies described so far for POMs, the investigations of POTs represent the largest contributions in this area (75%), followed by POVs (11%). The antiviral activity of POMs was initially studied and tested *in vivo* in France in 1973 by the Raynaud and Jasmin group [65]. They demonstrated that the POT $[NH_4]_{17}Na[Na(SbW_7O_{24})_3(-SbO_7)_2]$ inhibits the RNA-dependent DNA polymerases of retroviruses and hence prevents the virus from spreading [65]. This discovery initiated testing of other POMs for their activity against the human immunodeficiency virus (HIV). Thus, POTs have been successfully demonstrated to inhibit the binding of HIV particles to cells through blocking the binding of gp120 [6,168,169]. Studies with other Keggin and Dawson type POTs proved that their antiviral effect was caused by inhibiting the binding of the virus to the host cell membrane and/or its penetration [168–171]. It is known that HIV specially targets CD4 cells present in T-lymphocytes, monocytes and macrophage lineage. A glycoprotein, termed gp120, allows binding of the virus on the CD4 cells and, consequently, the injection of viral material into the host cell [172]. POMs are active also against the SARS virus with promising EC_{50} values [173,174].

One of the most cited paper on the subject of V_{10} in biology is a study about its interaction within the protein cages of virions [66]. Besides preventing the formation of virions, V_{10} is also able to inhibit viral activities by preventing the virus-cell host binding [66]. In 2005, Yamase group has demonstrated that tungstovanadate mixed Keggin derivatives exhibit a wide-range of anti-RNA virus activities against MDCK, Vero, Hep-2 and MT-4 cells [20]. All tungstovanadates showed toxicity at concentrations above 200 μM (except on MT-4 cells, which are between 46 and 100 μM) [20]. Another study on a Keggin-type tungstovanadate, $(K_5[SiW_{11}O_{40}])$, Fig. 3E) and two sandwich Keggin-type tungstovanadates, $K_{10}Na[(VO)_3(SbW_9O_{33})_2]$ (Fig. 3H) and

$K_{11}H[(VO)_3(SbW_9O_{33})_2]$ (Fig. 3H) showed inhibition against the dengue virus (DFV), influenza virus (FluV A), respiratory syncytial virus (RSV), parainfluenza virus (PfluV 2), distemper virus (CDV) and HIV [173]. All three tungstovanadates showed high toxicity, as their effective concentration (EC) values were lower than 1 μM , in comparison to other Keggin POTs used in the study ($EC_{50} > 10$ –60 μM). It was also demonstrated that $K_{10}Na[(VO)_3(SbW_9O_{33})_2]$ strongly inhibits the binding of the viral gp120 antibodies, in the step of syncytium formation between HIV-1-infected cells and uninfected cells [173].

It has been proposed that POMs have a dual mechanism of action in the inhibition of virus replication: firstly, POMs interaction with hemagglutinin A (HA), which is involved in viral attachment, impedes the fusion of viral particles into the cell [175]; secondly, inhibition of catalytic reactions promoted by sialyltransferases and sulfotransferases (neuraminidases) affect the carbohydrate chains in glycoproteins that play a major part in cell-viral recognition serving as a target for viral infections. Thus, by targeting virus membrane proteins, POMs affect the early stage of viral infection as illustrated schematically in Fig. 9.

The *Chlorella* virus was reported to be inhibited by V_{10} [176]. The *Paramecium bursaria Chlorella* virus is a large DNA virus that replicates in unicellular *Chlorella*-like algae [177]. The virus encodes an RNA triphosphatase which is involved in the synthesis of the RNA cap structure found at the 5' end of the viral mRNAs. The *Chlorella* virus RNA triphosphatase is the smallest member of the metal-dependent RNA triphosphatases. The ability of various vanadate oxoanions to inhibit the phosphohydrolase activity of the enzyme was investigated by first examining the binding of V_{10} to the enzyme using fluorescence and CD spectroscopy [176]. The enzyme assay shows that V_{10} is a potent non-competitive inhibitor of the phosphohydrolase activity, and mutagenesis studies indicate that the binding of V_{10} does not involve amino acids located in the active site of the enzyme [176].

Oncolytic viruses are an emerging class of anticancer biotherapeutics that induce antitumor immunity through selective replication in conventional drug resistant tumor cells. Vanadate was found to increase antitumor efficacy in combination with oncolytic viruses in several syngeneic tumor models *in vitro* and *ex-vivo*, leading to systemic and durable responses, even in models otherwise refractory to oncolytic viruses and drugs alone [178]. The ability of vanadate to simultaneously maximize viral oncolysis and systemic anticancer immunity offers new avenues for the development of improved immunotherapy strategies.

Taking all these data together, the present review describes the activities of POVs against cancer, bacterial resistance and antiviral infection, which are summarized in Fig. 10. Recently, the putative mechanisms of POMs as anticancer and antibacterial agents were reviewed [7,8]. Still, taken into account the studies described above regarding POVs' anticancer activity, several possible mechanisms leading to apoptosis (Fig. 10, 1 h) have been evoked [59,60,174]. However, for other POVs, both apoptosis and necrosis was observed [53], whereas cell cycle arrest was also described (Fig. 10, 12 to 3 h in the clock).

Examples of antibacterial effects described for several POVs, such as V_{10} , include the interference with ions transport system, inhibition of mRNA synthesis, cell morphology changes besides affecting metabolic pathways and signaling [8,63,64] (Fig. 10, 3–8 h in the clock). POVs' virus effects include the inhibition of viral mRNA polymerase, inhibition of virus binding to the host cell, inhibition of virus penetration and interaction with virus protein cages [65,66,175] (Fig. 10, 8–12 h in the clock).

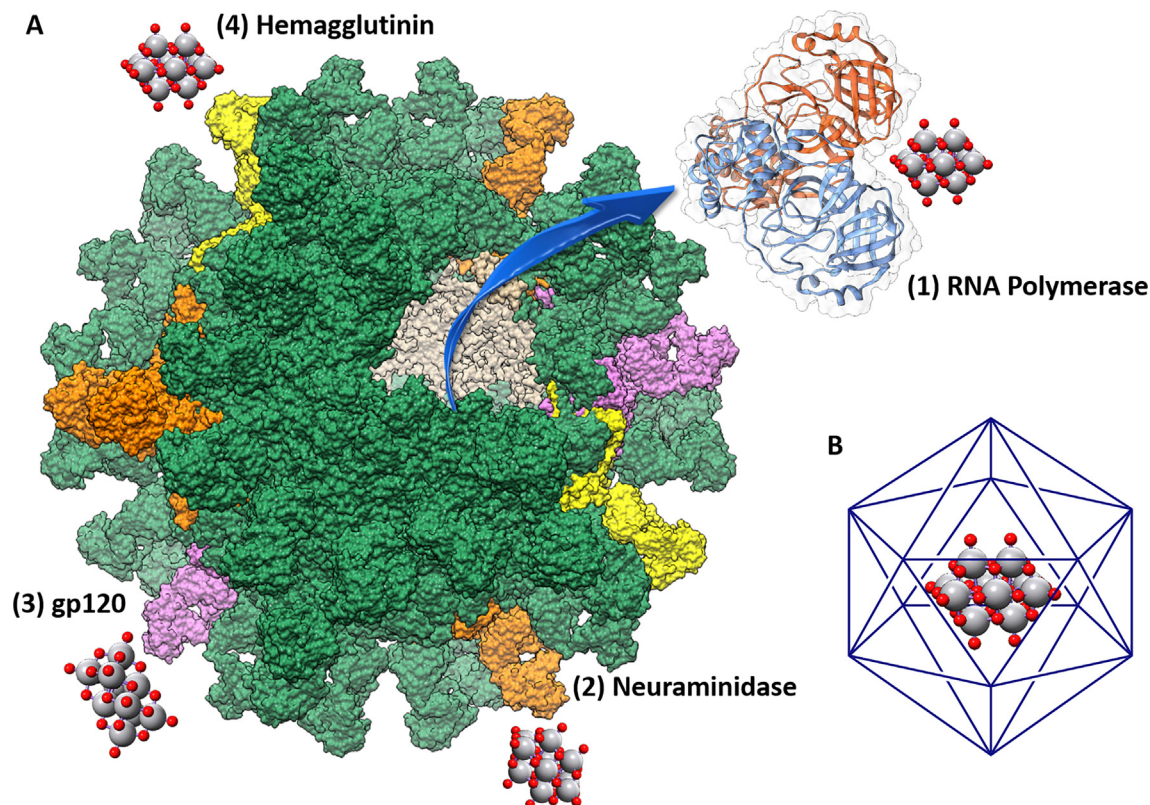


Fig. 9. A) POVs putative interactions with viral membrane proteins preventing an early stage of infection according to ref. [66]. In addition, the putative inhibition of neuraminidase prevents a later stage of infection. Color code: glycoprotein, dark pink; hemagglutinin, yellow; neuraminidase, orange. POM: vanadium, grey; oxygen, red. B) V_{10} interaction within the protein cages of HIV virions [66].

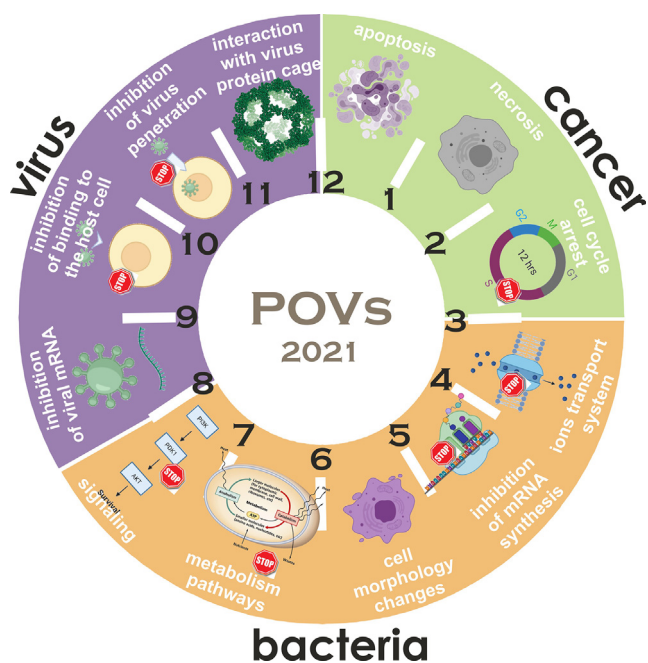


Fig. 10. POVs' clock in 2021 summarizing effects against cancer (green, Section 5.1), bacteria (orange, Section 5.2) and viruses (violet, Section 5.3). Some parts of this figure were created with BioRender.com.

6. Conclusions and perspectives

POVs, a subclass of POMs, are large anionic compounds that possess a rich diversity of structures and have shown biological

and biomedical effects that are of interest and potential applications. POVs' stability and speciation studies, although essential for understanding which POMs species are inducing the biological effects, remain scarce. At this time few POMs *in vivo* and *ex-vivo* studies have been completed using POVs, with V_{10} being the major target compound. The *in vitro* studies carried out showed that POVs inhibits mitochondrial respiration.

To be approved as a drug, a POM must show higher activity against its biological target and low toxicity toward normal cells in comparison to the approved drugs. In addition, the development of potential compounds for therapeutic treatment must be economically feasible and hence synthetically accessible at the concentration levels needed. Only a few clinical studies with some POMs, in particular POTs such as SiW_{12} have been undertaken. These studies demonstrate that potential applications of such large anionic POVs are possible and so far these include POTs containing selected vanadium atoms. The fact that only a few pre-clinical studies have been carried out with POVs, although much work has been done with other vanadium compounds, points towards POVs' applicability in medical treatment. POVs present promising future applications toward the chemotherapy of solid tumors, DNA and RNA viruses and drug-resistant bacteria. Future approaches, in order to reduce toxicity and improve efficacy, include a shift from application of pure POVs to investigate vanadium-containing POM-based nanohybrids. Until now, the majority of the studies have addressed the potential of POVs to control cancer, bacterial growth and virus infections. A few studies have explored the mechanism of action of these compounds and their speciation. However, several aspects of the virulence and community life of bacteria, were not yet explored. Additionally, in order for POVs treatment of cancer to be considered, further studies are needed, since different mechanisms of action might

be involved. New strategies are needed allowing to obtain the first evidences of such potential, anticipating early changes in cellular metabolism induced by POVs. However, such studies are demanding with regard to resources, require interdisciplinary teams of technical skilled people to adhere to the regulations when developing materials for human consumption [179] and much pre-clinical work is needed to select which POMs or POVs are most suited for further development against a particular disease or infection.

In the present decade, we expect that important questions will be answered, for instance that we will be able to: (i) observe POVs at different subcellular domains and possible their formation since we already know that V_{10} can form in acidic vacuoles; (ii) clarify the processing and ADME of POVs after administration; (iii) understand the speciation of POVs under biological conditions and, finally, (iv) apply clinically POVs in the treatment of cancer, bacterial resistance and viral infections. These and other questions will require continuous development of new POVs and exploration of these and known compounds in biology and medicine. However, the observed activities *in vitro* as antibacterial and antiviral agents document the potential of this group of compounds, encourage more research and stimulate the interest especially in the light of the widespread rise of antimicrobial resistance and the recent SARS-CoV2 pandemic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was funded by FCT – Foundation for Science and Technology through project UIDB/04326/2020 (M.A.); Regione Autonoma della Sardegna through the grant RASSR79857 (G.S. and E.G.); Spanish MICINN's Juan de la Cierva program, FJC2019-039135-I (G.S.); the Austrian Science Fund (FWF): P33927 (N.G.), P33089 (A.R.), the University of Vienna (N.G. and A.R.) and Colorado State University (D.C.C.).

References

- [1] M.T. Pope, *Heteropoly and Isopoly Oxometalates*, Springer-Verlag, New York, 1983.
- [2] M.T. Pope, A. Müller, Polyoxometalate chemistry: an old field with new dimensions in several disciplines, *Angew. Chem. Int. Ed.* 30 (1) (1991) 34–48, <https://doi.org/10.1002/anie.199100341>.
- [3] Y. Hayashi, Hetero and lacunary polyoxovanadate chemistry: synthesis, reactivity and structural aspects, *Coord. Chem. Rev.* 255 (19–20) (2011) 2270–2280, <https://doi.org/10.1016/j.ccr.2011.02.013>.
- [4] D.C. Crans, Enzyme interactions with labile oxovanadates and other polyoxometalates, *Comment. Inorg. Chem.* 16 (1–2) (1994) 35–76, <https://doi.org/10.1080/02603599408035851>.
- [5] C.L. Hill, Introduction: Polyoxometalates multicomponent molecular vehicles to probe fundamental issues and practical problems, *Chem. Rev.* 98 (1998) 1–2, <https://doi.org/10.1021/cr960395y>.
- [6] J.T. Rhule, C.L. Hill, D.A. Judd, R.F. Schinazi, Polyoxometalates in medicine, *Chem. Rev.* 98 (1) (1998) 327–358, <https://doi.org/10.1021/cr960396q>.
- [7] A. Bijelic, M. Aureliano, A. Rompel, Polyoxometalates as potential next-generation metallodrugs in the combat against cancer, *Angew. Chem., Int. Ed.* 58 (2019) 2980–2999, <https://doi.org/10.1002/ange.201803868> (*Angew. Chem.* 131 (2019) 3008–3029, <https://doi.org/10.1002/ange.201803868>).
- [8] A. Bijelic, M. Aureliano, A. Rompel, The antibacterial activity of polyoxometalates: structures, antibiotic effects and future perspectives, *Chem. Commun.* 54 (10) (2018) 1153–1169, <https://doi.org/10.1039/C7CC07549A>.
- [9] X. Chen, S. Yan, H. Wang, Z. Hu, X. Wang, M. Huo, Aerobic oxidation of starch catalyzed by isopolyoxovanadate $Na_4Co(H_2O)_6V_{10}O_{28}$, *Carbohydr. Polym.* 117 (2015) 673–680, <https://doi.org/10.1016/j.carbpol.2014.10.066>.
- [10] L. Mohapatra, K.M. Parida, Dramatic activities of vanadate intercalated bismuth doped LDH for solar light photocatalysis, *Phys. Chem. Chem. Phys.* 16 (32) (2014) 16985–16996, <https://doi.org/10.1039/C4CP01665C>.
- [11] A. Bijelic, A. Rompel, The use of polyoxometalates in protein crystallography – an attempt to widen a well-known bottleneck, *Coord. Chem. Rev.* 299 (2015) 22–38, <https://doi.org/10.1016/j.ccr.2015.03.018>.
- [12] Y. Fang, C. Xing, S. Zhan, M. Zhao, M. Li, H. Liu, A polyoxometalate-modified magnetic nanocomposite: a promising antibacterial material for water treatment, *J. Mater. Chem. B* 7 (11) (2019) 1933–1944, <https://doi.org/10.1039/C8TB03331E>.
- [13] J.M. Missina, L.B.P. Leme, K. Postal, F.S. Santana, D.L. Hughes, E.L. de Sá, R.R. Ribeiro, G.G. Nunes, Accessing decavanadate chemistry with tris (hydroxymethyl)aminomethane, and evaluation of methylene blue bleaching, *Polyhedron* 180 (2020) 114414, <https://doi.org/10.1016/j.poly.2020.114414>.
- [14] N.I. Gumerova, A. Rompel, Synthesis, structures and applications of electron-rich polyoxometalates, *Nat. Rev. Chem.* 2 (2018) 0112, <https://doi.org/10.1038/s41570-018-0112>.
- [15] S.-M. Wang, J. Hwang, E. Kim, Polyoxometalates as promising materials for electrochromic devices, *J. Mat. Chem. C* 7 (26) (2019) 7828–7850, <https://doi.org/10.1039/C9TC01722D>.
- [16] S.-S. Wang, G.-Y. Yang, Recent advances in polyoxometalate-catalyzed reactions, *Chem. Rev.* 115 (11) (2015) 4893–4962, <https://doi.org/10.1021/cr500390v>.
- [17] S.Y. Lai, K.H. Ng, C.K. Cheng, H. Nur, M. Nurhadi, M. Arumugam, Photocatalytic remediation of organic waste over Keggin-based polyoxometalate materials: a review, *Chemosphere* 263 (2021) 128244, <https://doi.org/10.1016/j.chemosphere.2020.128244>.
- [18] Y.-F. Song, R. Tsunashima, Recent advances on polyoxometalate-based molecular and composite materials, *Chem. Soc. Rev.* 41 (2012) 7384–7402, <https://doi.org/10.1039/C2CS35143A>.
- [19] B. Hasenknopf, Polyoxometalates: introduction to a class of inorganic compounds and their biomedical applications, *Front. Biosci.* 10 (2005) 275–287, <https://doi.org/10.2741/1527>.
- [20] T. Yamase, Anti-tumor, -viral, and -bacterial activities of polyoxometalates for realizing an inorganic drug, *J. Mater. Chem.* 15 (2005) 4773–4782, <https://doi.org/10.1039/B504585A>.
- [21] M.B. Čolović, M. Lacković, J. Lalatović, A.S. Mougharbel, U. Kortz, D.Z. Krstić, Polyoxometalates in biomedicine: Update and overview, *Curr. Med. Chem.* 27 (3) (2020) 362–379, <https://doi.org/10.2174/0929867326666190827153532>.
- [22] S. Mitsui, A. Ogata, H. Yanagie, H. Kasano, T. Hisa, T. Yamase, M. Eriguchi, Antitumor activity of polyoxomolybdate, $[NH_3Pri]_6Mo_7O_{24} \cdot 3H_2O$, against human gastric cancer model, *Biomed. Pharmacother.* 60 (2006) 353–358, <https://doi.org/10.1016/j.biopha.2006.02.009>.
- [23] A. Ogata, H. Yanagie, E. Ishikawa, Y. Morishita, S. Mitsui, A. Yamashita, K. Hasumi, S. Takamoto, T. Yamase, M. Eriguchi, Antitumor effect of polyoxomolybdates: induction of apoptotic cell death and autophagy in *in vitro* and *in vivo* models, *Br. J. Cancer* 98 (2) (2008) 399–409, <https://doi.org/10.1038/sj.bjc.6604133>.
- [24] W. Zhao, C. Wang, S. Dong, Y. Li, D. Zhang, L.W. Han, In vitro study on the antitumor activity of several new polyoxometalates, in: *Proceedings 2011 International Conference on Human Health and Biomedical Engineering*, 2011, pp. 594–597, <https://doi.org/10.1109/HBBE.2011.6028382>.
- [25] L. Wang, K. Yu, B.-B. Zhou, Z.-H. Su, S. Gao, L.-L. Chu, J.-R. Liu, L. Wang, The inhibitory effects of a new cobalt-based polyoxometalate on the growth of human cancer cells, *Dalton Trans.* 43 (2014) 6070–6078, <https://doi.org/10.1039/C3DT53030B>.
- [26] Y.-T. Li, C.-Y. Zhu, Z.-Y. Wu, M. Jiang, C.-W. Yan, Synthesis, crystal structures and anticancer activities of two decavanadate compounds, *Transit. Met. Chem.* 35 (5) (2010) 597–603, <https://doi.org/10.1007/s11243-010-9369-7>.
- [27] B. Zhang, J. Qiu, C. Wu, Y. Li, Z. Liu, Anti-tumor and immunomodulatory activity of iron hepta-tungsten phosphate oxygen clusters complex, *Int. Immunopharmacol.* 29 (2015) 293–301, <https://doi.org/10.1016/j.intimp.2015.11.003>.
- [28] S. Dianat, A.K. Bordbar, S. Tangestaninejad, B. Yadollahi, S.H. Zarkesh-Esfahani, P. Habibi, ctDNA binding affinity and *in vitro* antitumor activity of three Keggin type polyoxotungstates, *J. Photochem. Photobiol. B Biol.* 124 (2013) 27–33, <https://doi.org/10.1016/j.jphotobiol.2013.04.001>.
- [29] L. Fu, H. Gao, M. Yan, S. Li, X. Li, Z. Dai, S. Liu, Polyoxometalate-based organic-inorganic hybrids as antitumor drugs, *Small* 11 (24) (2015) 2938–2945, <https://doi.org/10.1002/sml.201500232>.
- [30] C. Pimpão, I.V. da Silva, A.F. Mósca, J.O. Pinho, M.M. Gaspar, N.I. Gumerova, A. Rompel, M. Aureliano, G. Soveral, The aquaporin-3-inhibiting potential of polyoxotungstates, *Int. J. Mol. Sci.* 21 (2020) 2467, <https://doi.org/10.3390/ijms21072467>.
- [31] M.J. Pereira, E. Carvalho, J.W. Eriksson, D.C. Crans, M. Aureliano, Effects of decavanadate and insulin enhancing vanadium compounds on glucose uptake in isolated rat adipocytes, *J. Inorg. Biochem.* 103 (2009) 1687–1692, <https://doi.org/10.1016/j.jinorgbio.2009.09.015>.
- [32] S. Bălici, S. Şuşman, D. Rusu, G.Z. Nicula, O. Soriţău, M. Rusu, A.S. Biris, H. Matei, Differentiation of stem cells into insulin-producing cells under the influence of nanostructural polyoxometalates, *J. Appl. Toxicol.* 36 (3) (2016) 373–384, <https://doi.org/10.1002/jat.3218>.
- [33] J. Zhao, K. Li, K. Wan, T. Sun, N. Zheng, F. Zhu, J. Ma, J. Jiao, T. Li, J. Ni, X. Shi, H. Wang, Q. Peng, J. Ai, W. Xu, S. Liu, Organoplatinum-substituted polyoxometalate inhibits β -amyloid aggregation for Alzheimer's therapy, *Angew. Chem. Int. Ed.* 58 (50) (2019) 18032–18039, <https://doi.org/10.1002/anie.201910521>.

- [34] J. Iqbal, M. Barsukova-Stuckart, M. Ibrahim, S.U. Ali, A.A. Khan, U. Kortz, Polyoxometalates as potent inhibitors for acetyl and butyrylcholinesterases and as potential drugs for the treatment of Alzheimer's disease, *Med. Chem. Res.* 22 (3) (2013) 1224–1228, <https://doi.org/10.1007/s00044-012-0125-8>.
- [35] H. Chaudhary, I.A. Iashchishyn, N.V. Romanova, M.A. Rambaran, G. Musteikyte, V. Smirnovas, M. Holmboe, C.A. Ohlin, Ž.M. Svedružić, L.A. Morozova-Roche, Polyoxometalates as effective nano-inhibitors of amyloid aggregation of pro-inflammatory S100A9 protein involved in neurodegenerative diseases, *ACS Appl. Mater. Interfaces* 13 (23) (2021) 26721–26734, <https://doi.org/10.1021/acsami.1c04163>.
- [36] A.K. Saha, D.C. Crans, M.T. Pope, C.M. Simone, R.H. Glew, Inhibition of human seminal fluid and *Leishmania donovani* phosphatases by molybdate heteropolyanions, *J. Biol. Chem.* 266 (6) (1991) 3511–3517, [https://doi.org/10.1016/S0021-9258\(19\)67825-7](https://doi.org/10.1016/S0021-9258(19)67825-7).
- [37] H. Stephan, M. Kubeil, F. Emmerling, C.E. Müller, Polyoxometalates as versatile enzyme inhibitors, *Eur. J. Inorg. Chem.* (2013) 1585–1594, <https://doi.org/10.1002/ejic.201201224>.
- [38] 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>.
- [39] S.-Y. Lee, A. Fiene, W. Li, T. Hanck, K.A. Brylev, V.E. Fedorov, J. Lecka, A. Haider, H.-Jürgen. Pietzsch, H. Zimmermann, J. Sévigny, U. Kortz, H. Stephan, C.E. Müller, Polyoxometalates - potent and selective ecto-nucleotidase inhibitors, *Biochem. Pharmacol.* 93 (2) (2015) 171–181, <https://doi.org/10.1016/j.bcp.2014.11.002>.
- [40] S.H. Saeed, R. Al-Oweini, A. Haider, U. Kortz, J. Iqbal, Cytotoxicity and enzyme inhibition studies of polyoxometalates and their chitosan nanoassemblies, *Toxicol. Rep.* 1 (2014) 341–352, <https://doi.org/10.1016/j.toxrep.2014.06.001>.
- [41] H.N. Mukherjee, Treatment of cancer of the intestinal tract with a complex compound of phosphotungstic phosphomolybdic acids and caffeine, *J. Indian Med. Assoc.* 44 (1965) 477–479, <https://pubmed.ncbi.nlm.nih.gov/14299045/>.
- [42] M. Raynaud, J.C. Chermann, F. Plata, G. Mathé, Inhibitors of viruses of the leukemia and murine sarcoma group, *Biological inhibitor CJMR*, C. R. Acad. Hebd. Seances Acad. Sci. D. 272 (1971) 2038–2040.
- [43] Y. Tajima, Z. Nagasawa, I. Tanabe, K. Kusaba, J. Tadano, Anionic properties of β -lactam-enhancing factor on methicillin-resistant *Staphylococcus aureus*, *Res. Microbiol.* 147 (1996) 279–286, [https://doi.org/10.1016/0923-2508\(96\)81388-X](https://doi.org/10.1016/0923-2508(96)81388-X).
- [44] T. Yamase, Polyoxometalates active against tumors, viruses, and bacteria, *Biomed. Inorg. Polym.* 54 (2013) 65–116, https://doi.org/10.1007/978-3-642-41004-8_4.
- [45] L. Wu, J. Liang, Polyoxometalates and their complexes toward biological application, in: J. Li (Ed.), *Supramolecular Chemistry of Biomimetic Systems*, Springer Singapore, Singapore, 2017, pp. 311–354, https://doi.org/10.1007/978-981-10-6059-5_13.
- [46] D. Hu, C. Shao, W. Guan, Z. Su, J. Sun, Studies on the interactions of Ti-containing polyoxometalates (POMs) with SARS-CoV 3CL^{pro} by molecular modeling, *J. Inorg. Biochem.* 101 (1) (2007) 89–94, <https://doi.org/10.1016/j.jinorgbio.2006.08.013>.
- [47] C. Heyliger, A. Tahiliani, J. McNeill, Effect of vanadate on elevated blood glucose and depressed cardiac performance of diabetic rats, *Science* 227 (4693) (1985) 1474–1477, <https://doi.org/10.1126/science.3156405>.
- [48] K.H. Thompson, C. Orvig, Vanadium in diabetes: 100 years from Phase 0 to Phase I, *J. Inorg. Biochem.* 100 (12) (2006) 1925–1935, <https://doi.org/10.1016/j.jinorgbio.2006.08.016>.
- [49] D.C. Crans, L. Henry, G. Cardiff, G. Posner, Developing vanadium as an antidiabetic drug: a clinical and historical perspective, *Met. Ions Life Sci.* 19 (2019) 203–230, <https://doi.org/10.1515/9783110527872-014>.
- [50] D.C. Crans, Antidiabetic, chemical and physical properties of organic vanadates as presumed transition state inhibitors for phosphatases, *J. Org. Chem.* 80 (24) (2015) 11899–11915, <https://doi.org/10.1021/acs.joc.5b02229>.
- [51] S. García-Vicente, F. Yraola, L. Martí, E. González-Muñoz, M.J. García-Barrado, C. Cantó, A. Abella, S. Bour, R. Artuch, C. Sierra, N. Brandi, C. Carpié, J. Moratinos, M. Camps, M. Palacín, X. Testar, A. Gumà, F. Albericio, M. Royo, A. Mian, A. Zorzano, Oral insulin-mimetic compounds that act independently of insulin, *Diabetes* 56 (2) (2007) 486–493, <https://doi.org/10.2337/db06-0269>.
- [52] K. Dan, K. Fujinami, H. Sumitomo, Y. Ogiwara, S. Suhara, Y. Konno, M. Sawada, Y. Soga, A. Takada, K. Takanashi, K. Watanabe, T. Shinozuka, Application of antiviral polyoxometalates to living environments – antiviral moist hand towels and stationery items, *Appl. Sci.* 10 (2020) 8246, <https://doi.org/10.3390/app10228246>.
- [53] K.A. Doucette, K.N. Hassell, D.C. Crans, Selective speciation improves efficacy and lowers toxicity of platinum anticancer and vanadium antidiabetic drugs, *J. Inorg. Biochem.* 165 (2016) 56–70, <https://doi.org/10.1016/j.jinorgbio.2016.09.013>.
- [54] A. Levina, D.C. Crans, P.A. Lay, Speciation of metal drugs, supplements and toxins in media and bodily fluids controls *in vitro* activities, *Coord. Chem. Rev.* 352 (2017) 473–498, <https://doi.org/10.1016/j.ccr.2017.01.002>.
- [55] T. Jakusch, T. Kiss, *In vitro* study of the antidiabetic behavior of vanadium compounds, *Coord. Chem. Rev.* 351 (2017) 118–126, <https://doi.org/10.1016/j.ccr.2017.04.007>.
- [56] T. Kiss, É.A. Enyedy, T. Jakusch, O. Dömötör, Speciation of metal complexes of medicinal interest: relationship between solution equilibria and pharmaceutical properties, *Curr. Med. Chem.* 26 (4) (2019) 580–606, <https://doi.org/10.2174/0929867325666180307113435>.
- [57] N.I. Gumerova, A. Rompel, Polyoxometalates in solution: speciation under spotlight, *Chem. Soc. Rev.* 49 (21) (2020) 7568–7601, <https://doi.org/10.1039/D0CS00392A>.
- [58] W. Qi, B. Zhang, Y. Qi, S. Guo, R. Tian, J. Sun, M. Zhao, The anti-proliferation activity and mechanism of action of $K_{12}V_{18}O_{42}(H_2O)_4 \cdot 6H_2O$ on breast cancer cell lines, *Molecules* 22 (2017) 1535, <https://doi.org/10.3390/molecules22091535>.
- [59] Y. Zheng, H. Gan, Y. Zhao, W. Li, Y. Wu, X. Yan, Y. Wang, J. Li, J. Li, X. Wang, Self-assembly and antitumor activity of a polyoxovanadate-based coordination nanocage, *Chem. Eur. J.* 25 (67) (2019) 15326–15332, <https://doi.org/10.1002/chem.201903333>.
- [60] M. Cheng, N. Li, N. Wang, K. Hu, Z. Xiao, P. Wu, Y. Wei, Synthesis, structure and antitumor studies of a novel decavanadate complex with a wavelike two-dimensional network, *Polyhedron* 155 (2018) 313–319, <https://doi.org/10.1016/j.poly.2018.08.052>.
- [61] S. She, S. Bian, R. Huo, K. Chen, Z. Huang, J. Zhang, J. Hao, Y. Wei, Degradable organically-derivatized polyoxometalate with enhanced activity against glioblastoma cell line, *Sci. Rep.* 6 (2016) 33529, <https://doi.org/10.1038/srep33529>.
- [62] N. Fukuda, T. Yamase, *In vitro* antibacterial activity of vanadate and vanadyl compounds against *Streptococcus pneumoniae*, *Biol. Pharm. Bull.* 20 (8) (1997) 927–930, <https://doi.org/10.1248/bpb.20.927>.
- [63] S. Chen, G. Wu, D. Long, Y. Liu, Preparation, characterization and antibacterial activity of chitosan- $Ca_3V_{10}O_{28}$ complex membrane, *Carbohydr. Polym.* 64 (1) (2006) 92–97, <https://doi.org/10.1016/j.carbpol.2005.10.024>.
- [64] K. Kostenkova, Z. Arhouma, K. Postal, A. Rajan, U. Kortz, G.G. Nunes, D.C. Crick, D.C. Crans, PtIV- or MoVI-substituted decavanadates inhibit the growth of *Mycobacterium Smegmatis*, *J. Inorg. Biochem.* 217 (2021) 111356, <https://doi.org/10.1016/j.jinorgbio.2021.111356>.
- [65] D.K. Haapala, C. Jasmin, F. Sinoussi, J.C. Chermann, M. Raynaud, Inhibition of tumour virus RNA-dependent DNA polymerase by the heteropolyanion, silicotungstate, *Biomedicine* 19 (1973) 7–11, <https://pubmed.ncbi.nlm.nih.gov/4131535/>.
- [66] T. Douglas, M. Young, Host-guest encapsulation of materials by assembled virus protein cages, *Nature* 393 (6681) (1998) 152–155, <https://doi.org/10.1038/30211>.
- [67] K. Nagai, H. Ichida, Y. Sasaki, The structure of heptapotassium tridecavanadomanganate(IV) octadecahydrate, $K_7MnV_{13}O_{38} \cdot 18H_2O$, *Chem. Lett.* 15 (8) (1986) 1267–1270, <https://doi.org/10.1246/cl.1986.1267>.
- [68] D.C. Crans, Aqueous chemistry of labile oxovanadates: of relevance to biological studies, *Comm. Inorg. Chem.* 16 (1994) 1–33, <https://doi.org/10.1080/02603599408035850>.
- [69] S.S. Soares, F. Henao, M. Aureliano, C. Gutiérrez-Merino, Vanadate-induced necrotic death in neonatal rat cardiomyocytes through mitochondrial membrane depolarization, *Chem. Res. Toxicol.* 21 (2008) 607–618, <https://doi.org/10.1021/tx700204r>.
- [70] S.S. Soares, C. Gutiérrez-Merino, M. Aureliano, Decavanadate induces mitochondrial membrane depolarization and inhibits oxygen consumption, *J. Inorg. Biochem.* 101 (5) (2007) 789–796, <https://doi.org/10.1016/j.jinorgbio.2007.01.012>.
- [71] D.M. Tiago, V. Laizé, M.L. Cancela, M. Aureliano, Impairment of mineralization by metavanadate and decavanadate solutions in a fish bone-derived cell line, *Cell Biol. Toxicol.* 24 (3) (2008) 253–263, <https://doi.org/10.1007/s10565-007-9034-x>.
- [72] M. Aureliano, C.A. Ohlin, Decavanadate *in vitro* and *in vivo* effects: facts and opinions, *J. Inorg. Biochem.* 137 (2014) 123–130, <https://doi.org/10.1016/j.jinorgbio.2014.05.002>.
- [73] M. Aureliano, Decavanadate toxicology and pharmacological activities: V_{10} or V_1 , both or none?, *Oxid. Med. Cell. Longev.* 2016 (2016) 1–8, <https://doi.org/10.1155/2016/6103457>.
- [74] E. Heath, O.W. Howarth, Vanadium-51 and oxygen-17 nuclear magnetic resonance study of vanadate(V) equilibria and kinetics, *J. Chem. Soc., Dalton Trans.* (1981) 1105–1110, <https://doi.org/10.1039/DT9810001105>.
- [75] D.C. Crans, C.D. Rithner, L.A. Theisen, Application of time-resolved V-51 2D NMR for quantitation of kinetic exchange pathways between vanadate monomer, dimer, tetramer, and pentamer, *J. Am. Chem. Soc.* 112 (1990) 2901–2908, <https://doi.org/10.1021/ja00164a009>.
- [76] D.C. Crans, P.K. Shin, K.B. Armstrong, Application of NMR spectroscopy to studies of aqueous coordination chemistry of vanadium(V) complexes, *Adv. Chem.* 246 (1996) 303–328, <https://doi.org/10.1021/ba-1995-0246.ch011>.
- [77] A.S. Tracey, J.S. Jaswal, S.J. Angus-Dunne, Influences of pH and ionic strength on aqueous vanadate equilibria, *Inorg. Chem.* 34 (22) (1995) 5680–5685, <https://doi.org/10.1021/ic00126a043>.
- [78] K. Elvingsson, A. González Baró, L. Pettersson, Speciation in vanadium bioinorganic systems. 2. An NMR, ESR, and Potentiometric study of the aqueous H^+ -vanadate-maltol system, *Inorg. Chem.* 35 (11) (1996) 3388–3393, <https://doi.org/10.1021/ic951195s>.
- [79] N. Ingrid, I. Andersson, L. Pettersson, A. Yagasaki, L. Andersson, K. Holmström, LAKE - A program system for equilibrium analytical treatment of multimethod data, especially combined potentiometric and nuclear magnetic resonance data, *Acta Chem. Scand.* 50 (1996) 717–734, <https://doi.org/10.3891/acta.chem.scand.50-0717>.
- [80] L. Pettersson, I. Andersson, B. Hedman, Multicomponent polyanions, 37. A potentiometric and 51 V-NMR study of equilibria in the H^+ -HVO₄³⁻ system in

- 3.0 M Na(ClO₄) medium covering the range $1 \leq -\lg [H^+] \leq 10$, Chem. Scr. 25 (1985) 309–317, <https://doi.org/10.3891/acta.chem.scand.45-0998>.
- [81] D.C. Crans, K.A. Woll, K. Prusinskas, M.D. Johnson, E. Norkus, Metal speciation in health and medicine represented by iron and vanadium, Inorg. Chem. 52 (21) (2013) 12262–12275, <https://doi.org/10.1021/ic4007873>.
- [82] E. Petrus, M. Segado, C. Bo, Nucleation mechanisms and speciation of metal oxide clusters, Chem. Sci. 11 (32) (2020) 8448–8456, <https://doi.org/10.1039/D0SC03530K>.
- [83] D.C. Crans, E.M. Willging, S.K. Butler, Vanadate tetramer as inhibiting species in enzyme reactions in vitro and in vivo, J. Am. Chem. Soc. 112 (1990) 427–432, <https://doi.org/10.1021/ja00157a063>.
- [84] D.C. Crans, G. Willsky, Oxovanadate and oxomolybdate cluster interactions with enzymes and whole cells, in: Adapted from the Proceedings the 25th Steenbock Symposium, University of Wisconsin-Madison, 1997, pp. 116–125.
- [85] N. McCann, M. Wagner, H. Hasse, A thermodynamic model for vanadate in aqueous solution – equilibria and reaction enthalpies, Dalton Trans. 42 (7) (2013) 2622–2628, <https://doi.org/10.1039/C2DT31993D>.
- [86] M.J. Gresser, A.S. Tracey, K.M. Parkinson, Vanadium(V) oxyanions: the interaction of vanadate with pyrophosphate, phosphate, and arsenate, J. Am. Chem. Soc. 108 (20) (1986) 6229–6234, <https://doi.org/10.1021/ja00280a020>.
- [87] D.C. Crans, R.L. Bunch, L.A. Theisen, Interaction of trace levels of vanadium (IV) and (V) in biological systems, J. Am. Chem. Soc. 111 (1989) 7597–7607, <https://doi.org/10.1021/ja00201a049>.
- [88] I. Andersson, A. Gorzsás, C. Kerezi, L. Tóth, L. Pettersson, Speciation in the aqueous $H^+/H_2VO_4/H_2O_2$ /phosphate system, Dalton Trans. (2005) 3658–3666, <https://doi.org/10.1039/B508273K>.
- [89] M. Aureliano, D.C. Crans, Decavanadate ($V_{10}O_{28}^{6-}$) and oxovanadates: Oxometalates with many biological activities, J. Inorg. Biochem. 103 (4) (2009) 536–546, <https://doi.org/10.1016/j.jinorgbio.2008.11.010>.
- [90] M. Aureliano, Decavanadate: a journey in a search of a role, Dalton Trans. (2009) 9093–9100, <https://doi.org/10.1039/B907581J>.
- [91] H.T. Evans, The molecular structure of the isopoly complex ion, decavanadate ($V_{10}O_{28}^{6-}$), Inorg. Chem. 5 (6) (1966) 967–977, <https://doi.org/10.1021/ic50040a004>.
- [92] S. Ramos, M. Manuel, T. Tiago, R.O. Duarte, J. Martins, C. Gutiérrez-Merino, J.J. G. Moura, M. Aureliano, Decavanadate interactions with actin inhibit G-actin polymerization and stabilize decameric vanadate species, J. Inorg. Biochem. 100 (2006) 1734–1743, <https://doi.org/10.1016/j.jinorgbio.2006.06.007>.
- [93] R.M.C. Gândara, S.S. Soares, H. Martins, C. Gutiérrez-Merino, M. Aureliano, Vanadate oligomers: in vivo effects in hepatic vanadium accumulation and stress markers, J. Inorg. Biochem. 99 (5) (2005) 1238–1244, <https://doi.org/10.1016/j.jinorgbio.2005.02.023>.
- [94] G.R. Willsky, D.A. White, B.C. McCabe, Metabolism of added orthovanadate to vanadyl and high-molecular-weight vanadates by *Saccharomyces cerevisiae*, J. Biol. Chem. 259 (21) (1984) 13273–13281, [https://doi.org/10.1016/S0021-9258\(18\)90689-7](https://doi.org/10.1016/S0021-9258(18)90689-7).
- [95] G.R. Willsky, A.B. Goldfine, P.J. Kostyniak, Pharmacology and toxicology of oxovanadium species: oxovanadium pharmacology ch. 22, in: Vanadium Compounds. Chemistry, Biochemistry, and Therapeutic Applications ACS Symp. Ser., 1998, pp. 278–296.
- [96] S. Treviño, D. Velázquez-Vázquez, E. Sánchez-Lara, A. Díaz-Fonseca, J.A. Flores-Hernández, A. Pérez-Benítez, E. Brambila-Colombres, E. González-Vergara, Metforminium decavanadate as a potential metallopharmaceutical drug for the treatment of Diabetes mellitus, Oxid. Med. Cell. Longev. 2016 (2016) 1–14, <https://doi.org/10.1155/2016/6058705>.
- [97] S. Treviño, E. González-Vergara, Metformin-decavanadate treatment ameliorates hyperglycemia and redox balance of the liver and muscle in a rat model of alloxan-induced diabetes, New J. Chem. 43 (45) (2019) 17850–17862, <https://doi.org/10.1039/C9NJ02460C>.
- [98] M. Aureliano, N. Joaquim, A. Sousa, H. Martins, J.M. Coucelo, Oxidative stress in toadfish (*Halobatrachus didactylus*) cardiac muscle: acute exposure to vanadate oligomers, J. Inorg. Biochem. 90 (2002) 159–165, [https://doi.org/10.1016/S0162-0134\(02\)00414-2](https://doi.org/10.1016/S0162-0134(02)00414-2).
- [99] S.S. Soares, H. Martins, M. Aureliano, Vanadium distribution following decavanadate administration, Arch. Environ. Contam. Toxicol. 50 (1) (2006) 60–64, <https://doi.org/10.1007/s00244-004-0246-2>.
- [100] S.S. Soares, H. Martins, R.O. Duarte, J.J.G. Moura, J. Coucelo, C. Gutiérrez-Merino, M. Aureliano, Vanadium distribution, lipid peroxidation and oxidative stress markers upon decavanadate in vivo administration, J. Inorg. Biochem. 101 (1) (2007) 80–88, <https://doi.org/10.1016/j.jinorgbio.2006.08.002>.
- [101] G. Borges, P. Mendonça, N. Joaquim, M. Aureliano, J. Coucelo, Acute effects of vanadate oligomers on heart, kidney, and liver histology in the Lusitanian toadfish (*Halobatrachus didactylus*), Arch. Environ. Contam. Toxicol. 45 (2003) 415–422, <https://doi.org/10.1007/s00244-003-2155-1>.
- [102] M.D. Cohen, M. Sisco, C. Prophete, L.-C. Chen, J.T. Zelikoff, A.J. Ghio, J.D. Stonehuerner, J.J. Smee, A.A. Holder, D.C. Crans, Pulmonary immunotoxic potentials of metals are governed by select physicochemical properties: vanadium agents, J. Immunotoxicol. 4 (1) (2007) 49–60, <https://doi.org/10.1080/15476910601119350>.
- [103] M.D. Cohen, M. Sisco, C. Prophete, K. Yoshida, L.-C. Chen, J.T. Zelikoff, J. Smee, A.A. Holder, J. Stonehuerner, D.C. Crans, A.J. Ghio, Effects of metal compounds with distinct physicochemical properties on iron homeostasis and antibacterial activity in the lungs: chromium and vanadium, Inhal. Toxicol. 22 (2) (2010) 169–178, <https://doi.org/10.3109/08958370903161232>.
- [104] A. Al-Qatati, F.L. Fontes, B.G. Barisas, D. Zhang, D.A. Roessa, D.C. Crans, Raft localization of Type I Fcε receptor and degranulation of RBL-2H3 cells exposed to decavanadate, a structural model for $V_{2}O_5$, Dalton Trans. 42 (2013) 11912–11920, <https://doi.org/10.1039/C3DT50398D>.
- [105] E. Sánchez-Lara, S. Treviño, B.L. Sánchez-Gaytán, E. Sánchez-Mora, M. Eugenia Castro, F.J. Meléndez-Bustamante, M.A. Méndez-Rojas, E. González-Vergara, Decavanadate salts of cytosine and metformin: A combined experimental-theoretical study of potential metallodrugs against diabetes and cancer, Front. Chem. 6 (2018), <https://doi.org/10.3389/fchem.2018.00402>.
- [106] G. Fraqueza, J. Fuentes, L. Krivosudský, S. Dutta, S.S. Mal, A. Roller, G. Giester, A. Rempel, M. Aureliano, Inhibition of Na^+/K^+ - and Ca^{2+} -ATPase activities by phosphotetradecavanadate, J. Inorg. Biochem. 197 (2019) 110700, <https://doi.org/10.1016/j.jinorgbio.2019.110700>.
- [107] D. Althumairy, K. Postal, B.G. Barisas, G.G. Nunes, D.A. Roess, D.C. Crans, Polyoxometalates function as indirect activators of a G protein-coupled receptor, Metallomics 12 (2020) 1044–1061, <https://doi.org/10.1039/D0MT00044B>.
- [108] D.C. Crans, J.J. Smee, E. Gaidamauskas, L. Yang, The chemistry and biochemistry of vanadium and the biological activities exerted by vanadium compounds, Chem. Rev. 104 (2) (2004) 849–902, <https://doi.org/10.1021/cr020607t>.
- [109] H. Sakurai, A new concept: the use of vanadium complexes in the treatment of diabetes mellitus, Chem. Rec. 2 (4) (2002) 237–248, <https://doi.org/10.1002/tcr.10029>.
- [110] M. Melchior, S.J. Rettig, B.D. Liboiron, K.H. Thompson, V.G. Yuen, J.H. McNeill, C. Orvig, Insulin-enhancing vanadium(III) complexes, Inorg. Chem. 40 (18) (2001) 4686–4690, <https://doi.org/10.1021/ic000984t>.
- [111] K.H. Thompson, J.H. McNeill, C. Orvig, Vanadium compounds as insulin mimics, Chem. Rev. 99 (9) (1999) 2561–2572, <https://doi.org/10.1021/cr980427c>.
- [112] F.G. Banting, C.H. Best, J.B. Collip, J.J.R. Macleod, E.C. Noble, The effect of pancreatic extract (insulin) on normal rabbits, Am. J. Phys. - Legacy Content 62 (1) (1922) 162–176, <https://doi.org/10.1152/ajplegacy.1922.62.1.162>.
- [113] I. Vecchio, C. Tornali, N.L. Bragazzi, M. Martini, The discovery of insulin: an important milestone in the history of medicine, Front. Endocrinol. 9 (2018) 613, <https://doi.org/10.3389/fendo.2018.00613>.
- [114] R.A. Hegele, G.M. Maltman, Insulin's centenary: the birth of an idea, Lancet Diabetes Endocrinol. 8 (12) (2020) 971–977, [https://doi.org/10.1016/S2213-8587\(20\)30337-5](https://doi.org/10.1016/S2213-8587(20)30337-5).
- [115] S. Wild, G. Roglic, R. Sicree, H. King, Global prevalence of diabetes, Diabetes Care 27 (2004) 1047–1053, <https://doi.org/10.2337/diacare.27.5.1047>.
- [116] J. Meyerovitch, Z. Farfel, J. Sack, Y. Shechter, Oral administration of vanadate normalizes blood glucose levels in streptozotocin-treated rats. Characterization and mode of action, J. Biol. Chem. 262 (14) (1987) 6658–6662, [https://doi.org/10.1016/S0021-9258\(18\)48292-0](https://doi.org/10.1016/S0021-9258(18)48292-0).
- [117] M.J. Gresser, A.S. Tracey, P.J. Stankiewicz, The interaction of vanadate with tyrosine kinases and phosphatases, Adv. Prot. Phosphatases 4 (1987) 35–57.
- [118] C.C. McLauchlan, B.J. Peters, G.R. Willsky, D.C. Crans, Vanadium-phosphatase complexes: Phosphatase inhibitors favor the trigonal bipyramidal transition state geometries, Coord. Chem. Rev. 301–302 (2015) 163–199, <https://doi.org/10.1016/j.ccr.2014.12.012>.
- [119] H. Sies, D.P. Jones, Reactive oxygen species (ROS) as pleiotropic physiological signalling agents, Nat. Rev. Mol. Cell Biol. 21 (2020) 363–383, <https://doi.org/10.1038/s41580-020-0230-3>.
- [120] A. Kulkarni, G.S. Kumar, J. Kaur, K. Tikoo, A comparative study of the toxicological aspects of vanadium pentoxide and vanadium oxide nanoparticles, Inhal. Toxicol. 26 (13) (2014) 772–788, <https://doi.org/10.3109/08958378.2014.960106>.
- [121] V.P. Filonenko, M. Sundberg, P.E. Werner, I.P. Zibrov, Structure of a high-pressure phase of vanadium pentoxide, β - V_2O_5 , Acta Cryst., Sect. B: Struct. Sci. 60 (2004) 375–381, <https://doi.org/10.1107/S0108768104012881>.
- [122] D.C. Crans, M. Mahroof-Tahir, O.P. Anderson, M.M. Miller, X-ray structure of $(NH_4)_6(Gly-Gly)_2V_{10}O_{28} \cdot 4H_2O$: Model studies for polyoxometalate-protein interactions, Inorg. Chem. 33 (1994) 5586–5590, <https://doi.org/10.1021/ic00102a036>.
- [123] N. Samart, J. Saeger, K.J. Haller, M. Aureliano, D.C. Crans, Interaction of decavanadate with interfaces and biological model membrane systems: characterization of soft oxometalate systems, J. Mol. Eng. Mat. 2 (2014) 1–21, <https://doi.org/10.1142/S2251237314500073>.
- [124] N. Samart, D. Althumairy, D. Zhang, D.A. Roess, D.C. Crans, Initiation of a novel mode of membrane signaling: Vanadium facilitated signal transduction, Coord. Chem. Rev. 416 (2020) 213286, <https://doi.org/10.1016/j.ccr.2020.213286>.
- [125] S.S. Soares, C. Gutiérrez-Merino, M. Aureliano, Mitochondria as a target for decavanadate toxicity in Sparus aurata heart, Aquat. Toxicol. 83 (1) (2007) 1–9, <https://doi.org/10.1016/j.aquatox.2007.03.005>.
- [126] F. Zhai, X. Wang, D. Li, H. Zhang, R. Li, L. Song, Synthesis and biological evaluation of decavanadate $Na_4Co(H_2O)_6V_{10}O_{28} \cdot 18H_2O$, Biomed. Pharmacother. 63 (1) (2009) 51–55, <https://doi.org/10.1016/j.biopha.2008.01.006>.
- [127] D. Karimian, B. Yadollahi, V. Mirkhani, Dual functional hybrid-polyoxometalate as a new approach for multidrug delivery, Microporous Mesoporous Mater. 247 (2017) 23–30, <https://doi.org/10.1016/j.micromeso.2017.03.048>.
- [128] Z. Dong, R. Tan, J. Cao, Y. Yang, C. Kong, J. Du, S. Zhu, Y. Zhang, J. Lu, B. Huang, S. Liu, Discovery of polyoxometalate-based HDAC inhibitors with profound

- anticancer activity *in vitro* and *in vivo*, *Eur. J. Med. Chem.* 46 (6) (2011) 2477–2484, <https://doi.org/10.1016/j.ejmech.2011.03.036>.
- [129] P.P. Fu, X.L. Wang, E.B. Wang, C. Qin, L. Xu, Synthesis, structure characterization and biological activity of a novel polyoxovanadate cluster: $[\text{NH}_3(\text{CH}_2)_2\text{NH}_2(\text{CH}_2)_2\text{NH}_3][\text{V}_6\text{V}_{10}\text{O}_{42}(\text{PO}_4)_4(\text{PO}_4)_2\cdot 2\text{H}_2\text{O}]$, *Chem. Res. Chin. Univ.* 21 (2005) 381–385.
- [130] Y. Liu, S. Tian, S. Liu, E. Wang, *In vitro* inhibitory effect of polyoxometalates on human tumor cells, *Transition Met. Chem.* 30 (1) (2005) 113–117, <https://doi.org/10.1007/s11243-004-3825-1>.
- [131] H. El Moll, W. Zhu, E. Oldfield, L.M. Rodriguez-Albelo, P. Mialane, Jérôme Marrot, N. Vila, I.M. Mbomekallé, E. Rivière, C. Duboc, A. Dolbecq, Polyoxometalates functionalized by bisphosphonate ligands: synthesis, structural, magnetic, and spectroscopic characterizations and activity on tumor cell lines, *Inorg. Chem.* 51 (14) (2012) 7921–7931, <https://doi.org/10.1021/jc3010079>.
- [132] E. Kioseoglou, C. Gabriel, S. Petanidis, V. Psycharis, C.P. Raptopoulou, A. Terzis, A. Salifoglou, Binary decavanadate-betaine composite materials of potential anticarcinogenic activity, *Z. Anorg. Allg. Chem.* 639 (8–9) (2013) 1407–1416, <https://doi.org/10.1002/zaac.201300144>.
- [133] S. Dianat, A.-K. Bordbar, S. Tangestaninejad, B. Yadollahi, R. Amiri, S.-H. Zarkesh-Esfahani, P. Habibi, *In vitro* antitumor activity of free and nano-encapsulated $\text{Na}_5\text{PMo}_{10}\text{V}_2\text{O}_{40}\cdot n\text{H}_2\text{O}$ and its binding properties with ctDNA by using combined spectroscopic methods, *J. Inorg. Biochem.* 152 (2015) 74–81, <https://doi.org/10.1016/j.jinorgbio.2015.08.015>.
- [134] A. Galani, V. Tsitsias, D. Stellias, V. Psycharis, C.P. Raptopoulou, A. Karaliota, Two novel compounds of vanadium and molybdenum with carnitine exhibiting potential pharmacological use, *J. Inorg. Biochem.* 142 (2015) 109–117, <https://doi.org/10.1016/j.jinorgbio.2014.10.004>.
- [135] L. Roubatis, N.C. Anastasiadis, C. Paratriantafyllou, E. Moushi, A.J. Tasiopoulos, S.C. Karkabounas, P.G. Veltsistas, S.P. Perlepes, A.M. Evangelou, A missing oxidation-state level in the family of polyoxo(azide) octadecavanadate(IV/V) clusters: Synthesis, structure and antitumoural properties of $[\text{V}_{11}\text{V}_9\text{O}_{44}(\text{N}_3)]^{10-}$ in a sodium containing-3D architecture, *Inorg. Chem. Commun.* 69 (2016) 85–88, <https://doi.org/10.1016/j.inoche.2016.04.019>.
- [136] A. Ogata, S. Mitsui, H. Yanagie, H. Kasano, T. Hisa, T. Yamase, M. Eriguchi, A novel anti-tumor agent, polyoxomolybdate induces apoptotic cell death in AsPC-1 human pancreatic cancer cells, *Biomed. Pharmacother.* 59 (5) (2005) 240–244, <https://doi.org/10.1016/j.biopha.2004.11.008>.
- [137] T. Yamase, H. Fujita, K. Fukushima, Medical chemistry of polyoxometalates. Part 1. Potent antitumor activity of polyoxomolybdates on animal transplantable tumors and human cancer xenograft, *Inorg. Chim. Acta* 151 (1) (1988) 15–18, [https://doi.org/10.1016/S0020-1693\(00\)83477-5](https://doi.org/10.1016/S0020-1693(00)83477-5).
- [138] F. Lu, M. Wang, N. Li, B. Tang, Polyoxometalate-based nanomaterials toward efficient cancer diagnosis and therapy, *Chem. Eur. J.* 27 (21) (2021) 6422–6434, <https://doi.org/10.1002/chem.202182164>.
- [139] M. Ramezani-Aliakbari, J. Varshosaz, H. Sadeghi-aliabadi, F. Hassanzadeh, M. Rostami, Biotin-targeted nanomicellar formulation of an anderson-type polyoxomolybdate: synthesis and *in vitro* cytotoxicity evaluations, *Langmuir* 37 (21) (2021) 6475–6489, <https://doi.org/10.1021/acs.langmuir.1c00623>.
- [140] L. Gong, W. Ding, Y. Chen, K. Yu, C. Guo, B. Zhou, Inhibition of mitochondrial ATP synthesis and regulation of oxidative stress based on $\text{SbW}_8\text{O}_{30}$ determined by single-cell proteomics analysis, *Angew. Chem. Int. Ed.* 60 (15) (2021) 8344–8351, <https://doi.org/10.1002/anie.202100297>.
- [141] A.G. Enderle, M. Bosso, R. Groß, M. Heiland, M. Bollini, M.J. Culzoni, J. Münch, C. Streb, Increased *in-vitro* Anti-HIV activity of caffeineium-functionalized polyoxometalates, *ChemMedChem* (2021), <https://doi.org/10.1002/cmdc.202100281>.
- [142] E. Sánchez-Lara, A. García-García, E. González-Vergara, J. Cepeda, A. Rodríguez-Diéguez, Magneto-structural correlations of cyclo-tetranavanadates functionalized with mixed-ligand copper(II) complexes, *New J. Chem.* 45 (2021) 5081–5092, <https://doi.org/10.1039/D0NJ06004F>.
- [143] L. Fernández-Navarro, A. Nunes-Collado, B. Artetxe, E. Ruiz-Bilbao, L. San Felices, S. Reinoso, A. San José Wéry, J.M. Gutiérrez-Zorrilla, Isolation of the elusive heptavanadate anion with trisalkoxide ligands, *Inorg. Chem.* 60 (8) (2021) 5442–5445, <https://doi.org/10.1021/acs.inorgchem.1c00448>.
- [144] K. Chen, Q. Yu, Y. Liu, P. Yin, Bacterial hyperpolarization modulated by polyoxometalates for solutions of antibiotic resistance, *J. Inorg. Biochem.* 220 (2021) 111463, <https://doi.org/10.1016/j.jinorgbio.2021.111463>.
- [145] H. Soria-Carrera, I. Franco-Castillo, P. Romero, S. Martín, J.M. Fuente, S.G. Mitchell, R. Martín-Rapún, On-POM ring-opening polymerisation of *n*-carboxyanhydrides, *Angew. Chem. Int. Ed.* 60 (7) (2021) 3449–3453, <https://doi.org/10.1002/anie.202013563>.
- [146] A.V. Anyushin, A. Kondinski, T.N. Parac-Vogt, Hybrid polyoxometalates as post-functionalization platforms: from fundamentals to emerging applications, *Chem. Soc. Rev.* 49 (2) (2020) 382–432, <https://doi.org/10.1039/C8CS00854J>.
- [147] S.F. Razavi, F.F. Bamoharram, T. Hashemi, K. Shahrokhadi, A. Davoodnia, Nanolipid-loaded Preyssler polyoxometalate: Synthesis, characterization and *in vitro* inhibitory effects on HepG2 tumor cells, *Toxicol. In Vitro* 68 (2020) 104917, <https://doi.org/10.1016/j.tiv.2020.104917>.
- [148] C. Nathan, Resisting antimicrobial resistance, *Nat. Rev. Microbiol.* 18 (5) (2020) 259–260, <https://doi.org/10.1038/s41579-020-0348-5>.
- [149] Y. Tajima, Z. Nagasawa, J. Tadano, A factor found in aged tungstate solution enhanced the antibacterial effect of β -lactams on methicillin-resistant *Staphylococcus aureus*, *Microbiol. Immunol.* 37 (9) (1993) 695–703, <https://doi.org/10.1111/j.1348-0421.1993.tb01694.x>.
- [150] J.-Q. Sha, L.-Y. Liang, P.-F. Yan, G.-M. Li, C. Wang, D.-Y. Ma, Study on ligation of copper complexes of the quinolone antibacterial drugs and octamolybdates POMs, *Polyhedron* 31 (1) (2012) 422–430, <https://doi.org/10.1016/j.poly.2011.09.029>.
- [151] 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) 519, <https://doi.org/10.3389/fchem.2018.00519>.
- [152] J.M. Missina, B. Gavinho, K. Postal, F.S. Santana, G. Valdameri, E.M. de Souza, D.L. Hughes, M.I. Ramirez, J.F. Soares, G.G. Nunes, Effects of decavanadate salts with organic and inorganic cations on *Escherichia coli*, *Giardia Intestinalis*, and vero cells, *Inorg. Chem.* 57 (19) (2018) 11930–11941, <https://doi.org/10.1021/acs.inorgchem.8b01298>.
- [153] S.-X. Liu, H. Di, J. Peng, D. Li, Z. Dai, E. Wang, N. Hu, H. Jia, Self-assembly synthesis, structure characterization and antibacterial activity of complexes $(\text{ABOB})_4\text{H}_2\text{V}_{10}\text{O}_{28}\cdot 9\text{H}_2\text{O}$ and $(\text{ABOB})_6\text{V}_{10}\text{O}_{28}\cdot 4\text{H}_2\text{O}$ ($\text{ABOB}=\text{Moroxidyne}$), *Chem. J. Chin. Univ. (Chin. Ed.)* 25 (2004) 997–1001.
- [154] M. Shahid, P.K. Sharma, Anjuli, S. Chibber, Z.A. Siddiqi, Isolation of a decavanadate cluster $[\text{H}_2\text{V}_{10}\text{O}_{28}[4\text{-picH}]]_4\cdot 2\text{H}_2\text{O}$ (4-pic = 4-picoline): crystal structure, electrochemical characterization, genotoxic and antimicrobial studies, *J. Clust. Sci.* 25 (2014) 1435–1447, <https://doi.org/10.1007/s10876-014-0721-5>.
- [155] S. Toumi, N. Ratel-Ramond, S. Akriche, Decavanadate cage-like cluster templated by organic counter cation: Synthesis, characterization and its antimicrobial effect against Gram positive *E. Faecium*, *J. Clust. Sci.* 26 (5) (2015) 1821–1831, <https://doi.org/10.1007/s10876-015-0881-y>.
- [156] K. Postal, D.F. Maluf, G. Valdameri, A.L. Rüdiger, D.L. Hughes, E.L. de Sá, R.R. Ribeiro, E.M. de Souza, J.F. Soares, G.G. Nunes, Chemoprotective activity of mixed valence polyoxovanadates against diethylsulphate in *E. coli* cultures: insights from solution speciation studies, *RSC Adv.* 6 (115) (2016) 114955–114968, <https://doi.org/10.1039/C6RA15826A>.
- [157] D. Jammazi, N. Ratel-Ramond, M. Rzaigui, S. Akriche, Trapped mixed $[(\text{water})_4\text{-(ammonium)}_4]^{4+}$ octamer in a 3D-binodal (4,8)-connected decavanadate core with hexamethylenetetramine: synthesis, structure, photophysical and antimicrobial properties, *Polyhedron* 168 (2019) 146–154, <https://doi.org/10.1016/j.poly.2019.04.042>.
- [158] D. Marques-da-Silva, G. Fraqueza, R. Lagoa, A.A. Vannathan, S.S. Mal, M. Aureliano, Polyoxovanadate inhibition of: *Escherichia coli* growth shows a reverse correlation with Ca^{2+} -ATPase inhibition, *New J. Chem.* 43 (45) (2019) 17577–17587, <https://doi.org/10.1039/C9NJ01208G>.
- [159] K. Postal, F.S. Santana, D.L. Hughes, A.L. Rüdiger, R.R. Ribeiro, E.L. Sá, E.M. de Souza, J.F. Soares, G.G. Nunes, Stability in solution and chemoprotection by octadecavanadates(IV/V) in *E. coli* cultures, *J. Inorg. Biochem.* 219 (2021) 111438, <https://doi.org/10.1016/j.jinorgbio.2021.111438>.
- [160] N.R. Sudarshan, D.G. Hoover, D. Knorr, Antibacterial action of chitosan, *Food Biotechnol.* 6 (3) (1992) 257–272, <https://doi.org/10.1080/08905439209549838>.
- [161] G. Fraqueza, C.A. Ohlin, W.H. Casey, M. Aureliano, Sarcoplasmic reticulum calcium ATPase interactions with decaniobate, decavanadate, vanadate, tungstate and molybdate, *J. Inorg. Biochem.* 107 (1) (2012) 82–89, <https://doi.org/10.1016/j.jinorgbio.2011.10.010>.
- [162] G. Fraqueza, L.A.E.B. de Carvalho, M.P.M. Marques, L. Maia, C.A. Ohlin, W.H. Casey, M. Aureliano, Decavanadate, decaniobate, tungstate and molybdate interactions with sarcoplasmic reticulum Ca^{2+} -ATPase: quercetin prevents cysteine oxidation by vanadate but does not reverse ATPase inhibition, *Dalton Trans.* 41 (2012) 12749–12758, <https://doi.org/10.1039/C2DT31688A>.
- [163] E.J. Anthony, E.M. Bolitho, H.E. Bridgewater, O.W.L. Carter, J.M. Donnelly, C. Imberti, E.C. Lant, F. Lermite, R.J. Needham, M. Palau, P.J. Sadler, H. Shi, F.-X. Wang, W.-Y. Zhang, Z. Zhang, Metallo drugs are unique: opportunities and challenges of discovery and development, *Chem. Sci.* 11 (48) (2020) 12888–12917, <https://doi.org/10.1039/D0SC04082G>.
- [164] R.E.F. de Paiva, A. Marçal Neto, I.A. Santos, A.C.G. Jardim, P.P. Corbi, F.R.G. Bergamini, What is holding back the development of antiviral metallo drugs? A literature overview and implications for SARS-CoV-2 therapeutics and future viral outbreaks, *Dalton Trans.* 49 (45) (2020) 16004–16033, <https://doi.org/10.1039/D0DT02478C>.
- [165] M.P. Lythgoe, P. Middleton, Ongoing clinical trials for the management of the COVID-19 pandemic, *Trends Pharmacol. Sci.* 41 (6) (2020) 363–382, <https://doi.org/10.1016/j.tips.2020.03.006>.
- [166] D. Cirri, A. Pratesi, T. Marzo, L. Messori, Metallo therapeutics for COVID-19. Exploiting metal-based compounds for the discovery of new antiviral drugs, *Expert Opin. Drug Deliv.* 16 (1) (2021) 39–46, <https://doi.org/10.1080/17460441.2020.1819236>.
- [167] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G.F. Gao, D. Phil, W. Tan, A novel coronavirus from patients with pneumonia in China, *N. Engl. J. Med.* 382 (2020) 727–733, <https://doi.org/10.1056/NEJMoa2001017>.
- [168] A. Flütsch, T. Schroeder, M.G. Grütter, G.R. Patzke, HIV-1 protease inhibition potential of functionalized polyoxometalates, *Bioorg. Med. Chem. Lett.* 21 (4) (2011) 1162–1166, <https://doi.org/10.1016/j.bmcl.2010.12.103>.
- [169] M. Witvrouw, H. Weigold, C. Pannecouque, D. Schols, E. De Clercq, G. Holan, Potent anti-HIV (type 1 and type 2) activity of polyoxometalates: structure-activity relationship and mechanism of action, *J. Med. Chem.* 43 (2000) 778–783, <https://doi.org/10.1021/jm980263s>.

- [170] R. Francese, A. Civra, M. Rittà, M. Donalisio, M. Argenziano, R. Cavalli, A. Mougharbel, U. Kortz, D. Lembo, Anti-zika virus activity of polyoxometalates, *Antiviral Res.* 163 (2019) 29–33, <https://doi.org/10.1016/j.antiviral.2019.01.005>.
- [171] Y. Qi, Y. Xiang, J. Wang, Y. Qi, J. Li, J. Niu, J. Zhong, Inhibition of hepatitis C virus infection by polyoxometalates, *Antiviral Res.* 100 (2) (2013) 392–398, <https://doi.org/10.1016/j.antiviral.2013.08.025>.
- [172] T.C. Chanh, G.R. Dreesman, R.C. Kennedy, Monoclonal anti-idiotypic antibody mimics the CD4 receptor and binds human immunodeficiency virus, *Proc. Natl. Acad. Sci.* 84 (11) (1987) 3891–3895, <https://doi.org/10.1073/pnas.84.11.3891>.
- [173] S. Shigeta, S. Mori, T. Yamase, N. Yamamoto, N. Yamamoto, Anti-RNA virus activity of polyoxometalates, *Biomed. Pharmacother.* 60 (2006) 211–219, <https://doi.org/10.1016/j.biopha.2006.03.009>.
- [174] Y.-f. Qi, H. Zhang, J. Wang, Y. Jiang, J. Li, Y. Yuan, S. Zhang, K. Xu, Y. Li, J. Li, J. Niu, E. Wang, *In vitro* anti-hepatitis B and SARS virus activities of a titanium-substituted-heteropolytungstate, *Antiviral Res.* 93 (1) (2012) 118–125, <https://doi.org/10.1016/j.antiviral.2011.11.003>.
- [175] S.M. Hosseini, E. Amini, M.T. Kheiri, P. Mehrbod, M. Shahidi, E. Zabihi, Anti-influenza activity of a novel polyoxometalate derivative (POM-4960), *Int. J. Mol. Cellular Med.* 1 (2012) 21–29, <http://ijmcmcd.org/article-1-33-en.html>.
- [176] I. Bougie, M. Bisaillon, Inhibition of a metal-dependent viral RNA triphosphatase by decavanadate, *Biochem. J.* 398 (2006) 557–567, <https://doi.org/10.1042/BJ20060198>.
- [177] Y. Kodama, M. Fujishima, Cycloheximide induces synchronous swelling of perialgal vacuoles enclosing symbiotic *Chlorella vulgaris* and digestion of the algae in the ciliate *Paramecium bursaria*, *Protist* 159 (3) (2008) 483–494, <https://doi.org/10.1016/j.protis.2008.02.005>.
- [178] M. Selman, C. Rouso, A. Bergeron, H.H. Son, R. Krishnan, N.A. El-Sayes, O. Varette, A. Chen, F. Le Boeuf, F. Tzelepis, J.C. Bell, D.C. Crans, J.-S. Diallo, Multi-modal potentiation of oncolytic virotherapy by vanadium compounds, *Mol. Ther.* 26 (1) (2018) 56–69, <https://doi.org/10.1016/j.ymthe.2017.10.014>.
- [179] N.I. Gumerova, A. Rompel, Interweaving disciplines to advance chemistry: applying polyoxometalates in biology, *Inorg. Chem.* 60 (9) (2021) 6109–6114, <https://doi.org/10.1021/acs.inorgchem.1c00125>.