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Review

The Future Is Bright for Polyoxometalates

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Abstract: Polyoxometalates (POMs) are clusters of units of oxoanions of transition metals, such as Mo, W, V and Nb, that can be formed upon acidification of neutral solutions. Once formed, some POMs have shown to persist in solution, even in the neutral and basic pH range. These inorganic clusters, amenable of a variety of structures, have been studied in environmental, chemical, and industrial fields, having applications in catalysis and macromolecular crystallography, as well as applications in biomedicine, such as cancer, bacterial and viral infections, among others. Herein, we connect recent POMs environmental applications in the decomposition of emergent pollutants with POMs' biomedical activities and effects against cancer, bacteria, and viruses. With recent insights in POMs being pure, organic/inorganic hybrid materials, POM-based ionic liquid crystals and POM-ILs, and their applications in emergent pollutants degradation, including microplastics, are referred. It is perceived that the majority of the POMs studies against cancer, bacteria, and viruses were performed in the last ten years. POMs' biological effects include apoptosis, cell cycle arrest, interference with the ions transport system, inhibition of mRNA synthesis, cell morphology changes, formation of reaction oxygen species, inhibition of virus binding to the host cell, and interaction with virus protein cages, among others. We additionally refer to POMs' interactions with various proteins, including P-type ATPases, aquoporins, cinases, phosphatases, among others. Finally, POMs' stability and speciation at physiological conditions are addressed.

Keywords: polyoxometalates; decavanadate; emergent pollutants; cancer; bacterial resistance; virus infection

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1. Introduction

Polyoxometalates (POMs) represent a broad class of anionic inorganic clusters of oxoanions of transition metals, such as Mo, W, V, and Nb, with versatile structures resulting in a variety of chemical and physical properties (Figure 1). POM structures can also include other elements, such as P or As, or one of the major metal oxoanions missing and/or substituted by other metals, such as Co or Mn. These inorganic clusters have applications in environmental, chemical, and industrial fields, and are well-known, particularly in catalysis, prevention of corrosion, and macromolecular crystallography, among others [1–6]. The majority of the studies describing POMs' effects in bacteria, viruses, and tumor proliferation, as well as potential drugs for the treatment of several diseases, such as diabetes and Alzheimer's, have been published in the last ten years [1,2,7–18].

Prominent emerging pollutants (EPs) include, for example, antibiotics, antifungals, antidepressants, synthetic hormones, cosmetics, and plastics. Contamination of the environment with those, as well other EP residues, can develop bacteria resistance, itself also an emerging and growing phenomenon worldwide in the 21st century [19–21]. In fact, the resistance of bacteria to antibiotics agents, together with growing cancer incidence all around the world, represent health concerns with increasing relevance. Furthermore, the actual pandemic situation begs for new drugs in the fight against coronavirus, SARS-CoV-2 infection. POMs have been selected [22–24] and followed by an increasing number of researchers as alternative antivirus, antibacterial, and antitumor substances with promising

results [1,2,7–18]. In sum, the application of polyoxometalates in the environment and in biomedicine represents two branches of science with rapid growth. Herein, we summarize the reports on the environmental applications of POMs on the eradication of emergent pollutants, and highlight important 21st century studies of POMs' effects and/or targets against cancer, bacteria, and viruses.

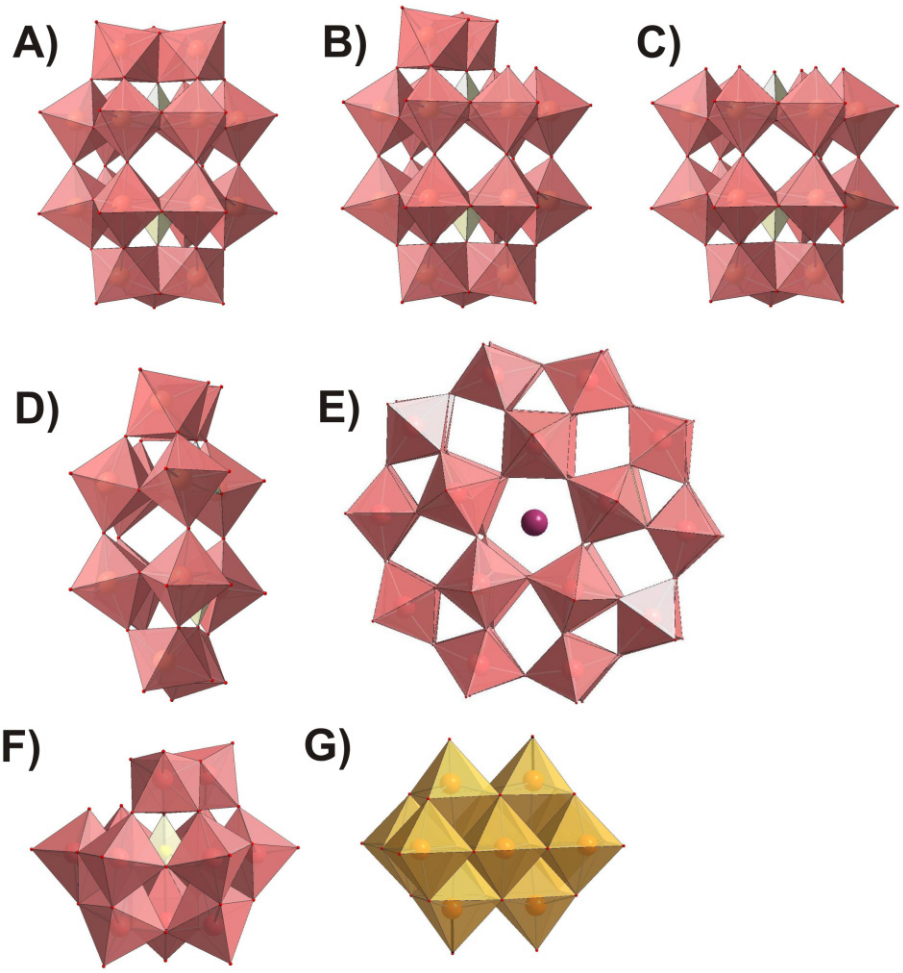

Figure 1. POM-type structures. (**A**) Wells–Dawson (P_2W_{18}); (**B**) mono-lacunary Wells–Dawson (P_2W_{17}); (**C**) tri-lacunary Wells–Dawson (P_2W_{15}); (**D**) hexa-lacunary Wells–Dawson (P_2W_{12}); (**E**) Preyssler (P_5W_{30}); (**F**) mono-lacunary Keggin (MnV_{11}); (**G**) isopolyoxometalate (V_{10}). Color code (**A**–**F**): {WO_6}, reddish; P, yellow; Na, red; (**F**) {VO_6}, reddish; Mn, light yellow; (**G**) {VO_6}, orange.

2. Polyoxometalates against Emerging Health Pollutants

The behavior of humanity has a major impact on the release of organic and/or inorganic pollutants into the environment, and has a profound effect on our lives. In the 21st century, POMs have gained attention as efficient adsorbents and/or green catalysts, and have been used in the development of multifunctional POM materials that could, and can, solve environmental problems, such as water pollution [25–27]. Thus, POMs have been chosen as agents against emergent pollutants. In fact, about 10% (about 1100) of the total of the articles published within the word "polyoxometalate" (POM) (11,000) are studies associated with the environment. In a search on the Web of Science, about 850 articles about POM and degradation can be found, 650 for dyes, 202 for POM and pollutants, 135 for waste, 75 for industrial chemicals, and 70 for wastewater. A lower number of papers were found for POM and pesticides and antibiotics [28–36]. Herein, we describe examples of recent studies about POMs' ability for the degradation of mainly antibiotics, pesticides, and plastics.

Erythromycin and others antibiotics, such as ciprofloxacin, azithromycin, and cefalexin, were also found in effluents and surface waters [19,20]. Ciprofloxacin and erythromycin, together with the macrolide azithromycin, clarithromycin, and the penicillin-type amoxicillin, were included in the surface water watch list under the European Water Framework Directive [20]. More recently, this report was actualized, and the antibacterials sulfamethaxazole and trimethoprim; the anti-fungals clotrimazole, flucozanole, and miconazole; the antidepressant venlafaxine; and the synthetic hormone norethisterone were all added to the 3rd water watch list [21].

POMs were described as a good choice for antibiotic degradation, thus reducing the pharmaceutical environmental impact. In fact, C_3N_4 nanosheet composites loaded with POMs efficiently remove ciprofloxacin, tetracycline, as well as others pollutants, such as bisphenol A [28,29]. Polyoxotungstates (decatungstate, W_{10}) also showed the ability to decompose antibiotics, such as sulfasalazine (SSZ) and one of its human metabolites, sulfapyridine (SPD), with different specificities and rates [30]. W_{10} also has a role in the degradation of pesticides, for example, the ones used for plant growth, namely 2-(1-naphthyl)acetamide (NAD) [31]. A metal-organic frameworks (MOFs) composite of PW12@MFM was shown to display catalytic degradation of sulfamethazine [32]. Besides pharmaceutical drugs, POMs-incorporated frameworks were also found to have applications for the decontamination of dyes, phenolic compounds, and pesticides [33]. Polyoxometalate-based ionic liquid (POM-IL) was used also for the extraction of triazole pesticides, such as hexaconazole, triticonazole, and difenoconazole from aqueous samples [34]. Recent insights in these organic/inorganic hybrid materials, POM-based ionic liquid crystals (POM-ILCs), and their applications (namely on pollutant degradation, including microplastics) have been recently reviewed [35,36].

3. Antibacterial Activity of Polyoxometalates

As referred to above, antibiotic resistance represents a real threat to global public health. The high proportion of bacteria that are resistant to antibiotics is due, at least in part, to antibiotics, as well to other emergent pollutants and environmental contamination. Thus, it is of increasing relevance to pave the way for the exploration of new types of antibiotics for future antibacterial strategies [37]. It was serendipity that caused the first association of POMs with antibacterial activity to be discovered [38]. When comparing the date of the first POMs studies described against viruses and cancer, respectively, at 1971 and 1965 [39,40], the antibacterial activities can be considered recent (1993). However, insights in POMs as anti-microbial agents or adjuvants, as well as POM-ILs as antibacterial coatings, have been attracting interest by offering mechanisms of action different from other recent antibacterial therapies [41–50]. On the other hand, many POMs have poor antibacterial activity, but possess excellent redox activity, and their use as biosensors for bacterial detection has been described [51]. POMs studies reporting the antibacterial activity of POMs are mostly on polyoxotungstates (POTs) and polyoxomolybdates (POMos) (Figure 2). About 80% of these studies were performed in the last 10 years, making them emergent future drugs in the control against pathogenic bacteria [24,52–56]. For example, the POT Preyssler-type $[NaP_5W_{30}O_{110}]^{14-}$ (abbreviated P_5W_{30}) (Figure 1E) showed the highest activity against the Gram-negative human mucosal pathogen *Moraxella catarrhalis*, as well as against *S. aureus* and *E. faecalis* when compared with several others POTs [57]. For *H. pylori*, POMs exhibiting the highest activity were mostly Keggin-type POTs (Figure 1F); polyoxovanadotungstates; and large, highly negatively charged POMs [1].

POTs, such as $[KAs_4W_{40}O_{140}]^{27-}$, (abbreviated As_4W_{40}) and $[P_2W_{18}O_{62}]^{6-}$ (abbreviated P_2W_{18}), are active against H. pylori, as well as metronidazole-resistant H. pylori [58]. Synergetic effects were also found when the antibacterial effect of the β-lactam antibiotic, oxacillin, and the glycopeptide antibiotic, vancomycin, against MRSA and vancomycin-resistant *S. aureus* (VRSA), which is a gram-positive bacteria and one of the most resistant ones around the world, were analyzed in the presence of molybdenum- and tungsten-based POMs, such as the Wells–Dawson type P_2W_{18} (Figure 1A), besides $[SiMo_{12}O_{40}]^{4-}$

(abbreviated $SiMo_{12}$) and $[PTi_2W_{10}O_{40}]^{7-}$ (abbreviated $Pti_2W_{10)}$ [59]. Moreover, it was observed that P_2W_{18} and Pti_2W_{10} were able to change the β-lactam resistance to a β-lactam susceptible profile for the majority of the cases studied [59].

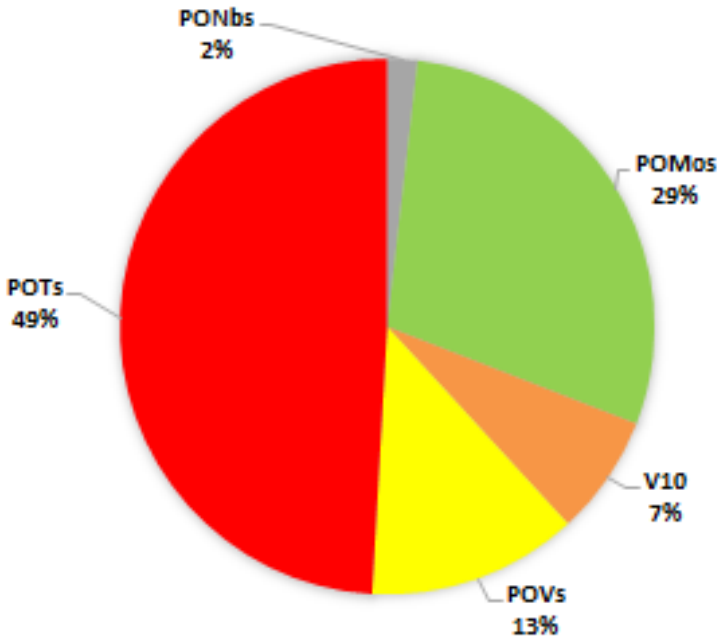

Figure 2. Studies for POMs tested against bacteria. Distribution, in percentage of the different POMs tested for antibacterial activity since 1996. POTs, polyoxotungstates; POMos, polyoxomolybdates; POVs, polyoxovanadates; PONbs, polyoxoniobates.

Besides POTs and POMos, polyoxovanadates (POVs), especially decavanadate (V_{10}), were pointed as the most potent against certain bacteria, such as *Streptococcus pneumoniae* [1]. Decavanadate, $[V_{10}O_{28}]^{6-}$ (abbreviated V_{10}), alone has also been described to inhibit the growth of *Mycobacterium smegmatis* and *Mycobacterium tuberculosis* [60]. Moreover, the association of V_{10} with (iso) nicotinamide compounds was described to increase the toxicity towards *Escherichia coli* [61]. Chitosan-V_{10} (CTS-V_{10}) complex were also active against *E. coli* and *S. aureus* [52]. Inhibition of *E. coli* growth was also verified for two manganesepolyoxovanadates, namely $K_5MnV_{11}O_{33}.10H_2O$ (abbreviated MnV_{11}) and $K_7MnV_{13}O_{38}\_18H_2O$ (abbreviated MnV_{13}) [62]. MnV_{11}, MnV_{13}, and V_{10} were all more potent than vanadate, with 50% maximal growth inhibition concentrations (GI_{50}) of 0.21, 0.27, 0.58, and 1.1 mm, respectively, whereas the decaniobate $[Nb_{10}O_{28}]^{6-}$ (abbreviated Nb_{10}) revealed only residual effects on *E. coli* growth [62].

POMs' antibacterial activity, and their comparison with antibiotic drugs are usually measured according to the minimum inhibitory concentration (MIC). Several POMs were tested against *Staphylococcus aureus*, and some showed significant antibacterial activity, exhibiting a MIC < 100 μg/mL, whereas antibiotic drugs have MIC values ranging from 0.001 to 10 μg/mL [1]. Moreover, POMs' MIC relationship with POM size and/or charge of POMs were found for several Gram-positive and Gram-negative bacteria [1]. When the structure-activity analysis was performed for *Streptococcus pneumoniae*, it was demonstrated that this bacterium is especially sensitive to POVs, with decavanadate exhibiting the highest antibacterial activity, whereas for *Heliobacter pylori*, most of the tested POMos were determined to be more active [1]. Table 1 summarizes the MIC values for some POTs, POMos, and POVs being pure, hybrids, and/or composites, which were tested on six bacterial strains, and three Gram-positive bacteria (*Staphylococcus aureus, Bacillus subtilis, Paenibacillus, and three Gram-negative (Escherichia coli, Vibrio, Pseudomona aeruginosa)*) [52,53,56,63–69].

Table 1. Antibacterial activity of POMs, POM-hybrids, and nanocomposites against a series of bacterial strains.

POM/POM-Hybrid	MIC(μg/mL)						
	S. aureus	***E. coli***	***B. subtilis***	***P. aeruginosa***	***Paenibacillus* sp**	***Vibrio* sp**	**Ref.**
Polyoxovanadates							
$[V_{10}O_{28}]^{6-}$	50	50	-	-	-	-	[52]
$[V_4O_{12}]^{4-}$	8000						[56]
Polyoxotungstates							
$[PW_{12}O_{40}]^{3-}$	3200						[53]
$[SiW_{12}O_{40}]^{4-}$	3200						
$[BW_{12}O_{40}]^{5-}$	800						[53]
$[PTi_2W_{10}O_{40}]^{7-}$	12,800						[53]
Polyoxomolybdates							[53]
$[P_2Mo_5O_{23}]^{6-}$	6400						[56]
$[MnMo_9O_{32}]^{6-}$	1600						[56]
$[Eu(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$	400						[56]
Organic-inorganic-POM:							
$[(PhSb^{III})\{Na(H_2O)\}As^{III}{}_2W_{19}O_{67}(H_2O)]^{11-}$	-	500	125	-	250	125	[64]
$[(PhSb^{III})_2As^{III}{}_2W_{19}O_{67}(H_2O)]^{10-}$	-	250	62.5	-	125	62.5	[64]
$[(PhSb^{III})_3(B\text{-}\alpha\text{-}As^{III}W_9O_{33})_2]^{12-}$	-	125	62.5	-	62.5	31.3	[64]
$[(PhSb^{III})_4(A\text{-}\alpha\text{-}As^{V}W_9O_{34})_2]^{10-}$	-	62.5	15.6	-	15.6	15.6	[65]
Quinolone-based drug-POM:							
$[Co^{II}(C_{19}FH_{22}N_3O_4)_3][C_{19}FH_{23}N_3O_4][HSiW_{12}O_{40}]$	2.52	2.42	-	-	-	-	[66]
Nanocomposite:							
Bamboo charcoal-POM:							
BC/POM	4	4	4	4	-	-	[67]
Polymer-POM:							
PVA/PEI-POM:							
PVA-PEI-$H_5PV_2Mo_{10}O_{40}$	0.02	2	0.2	0.02	-	-	[68]
Chitosan-POM:							
CTS-$Ca_3V_{10}O_{28}$	12.5	12.5	-	-	-	-	[52]
Polyoxometalate ionic liquids:							
$[N(C_6H_{13})_4]_8[\alpha\text{-}SiW_{11}O_{39}]$	10	1000	-	1000	-	-	[69]
$[N(C_7H_{15})_4]_8[\alpha\text{-}SiW_{11}O_{39}]$	2	25	-	100	-	-	[69]
$[N(C8H_{17})_4]_8[\alpha\text{-}SiW_{11}O_{39}]$	5	50	-	100	-	-	[69]

Mechanisms of Action of Polyoxometalates against Bacteria

The multiple mechanisms of POMs against bacteria and bacterial resistance are not fully understood. The antibacterial effects of POMs and, recently, of POVs, their modes of action, and future perspectives were reviewed [1]. Several possible mechanisms were anticipated, but further studies are required [1,52,56,58,59]. In this section, we resume some of the processes affected by the POMs. Some POVs and POTs are well-known for their interference with the transport system of ions and substrates by inhibiting P-type ATPases, such as Ca^{2+}-ATPase and Na^+/K^+-ATPase [70–73], leading to a disturbance in the molecular ion transport across the membrane, thus affecting bacteria growth [52]. Chitosan-V_{10} were described to induce the inhibition of mRNA synthesis, interfering with protein production, and destroying bacteria metabolism [52]. Suppression of *mecA*-induced mRNA expression, inhibition of the transcription process, and inhibition of the translational process were suggested for P_2W_{18}, $SiMo_{12}$, and PTi_2W_{10} [59]. POMs can also induce the production of reactive oxygen species (ROS), as described for phosphomolybdates and V_{10}-copper(II) tris derivatives, and can further disrupt bacterial cell integrity, showing promising antibacterial activities [74–76].

POMs have also been described to inhibit sialyl and sulfotransferases. Glycosyltransferase catalyzes the transfer of a sialic acid residue to the terminal position of an oligosaccharide chain of glycoproteins and glycolipids [77]. Sulfotransferase catalyzes the transfer reaction of a sulfate group to an acceptor sugar chain on the surface of cells [78]. These modifications of carbohydrate chains play a role in cell–cell recognition, serving as a target for bacterial and also viral infections. In a study with about twenty POMs, three tungstate-based POMs, $[H_2SiNiW_{11}O_{40}]^{6-}$ (abbreviated $SiNiW_{11}O_{40}$), $[Cu_3(PW_9O_{34})_2]^{12-}$ (abbreviated $Cu_3(PW_9O_{34})_2$), and $[SiVW_{11}O_{40}]^{5-}$ (abbreviated $SiVW_{11}O_{40}$), were shown to have a stronger inhibition activity, with IC_{50} values as low as 0.2 nM for the α-2,3-sialyltransferase (ST3Gal-I). Also, three vanadium-based POMs, $[KV_{13}O_{31}(MePO_3)_3]$, $[V_{18}O_{42}(H_2O)]^{12-}$ (abbreviated $V_{18}O_{42}$), and $[V_{18}O_{44}(N_3)]$, have shown to inhibit galactose-3-O-sulfotransferase (Gal3ST-2), with an IC_{50} value of 3 nM for the latter POVs [79].

POMs, such as $SiMo_{12}$ and P_2W_{18}, were suggested to affect the bacterial respiratory system, leading to inhibition of ATP synthesis, thus inducing bacterial death [59]. On the other hand, it was observed that *S. aureus* strains were able to reduce to blue color form POMs, such as P_2W_{18} and $SiMo_{12}$ [59]. Similar blue staining of *E. coli* cells was observed in the presence of vanadium (V) compounds, probably by reduced forms containing oxidovanadium (IV) [62]. Although the molecular mechanisms responsible for the reduction of these POMs by bacteria is not clear, it is reasonable to anticipate that it diverts electrons from cell redox systems, and hinders bacterial growth.

Though it is not clear if POMs can be accumulated by bacteria, there is evidence that some POTs were taken into the bacteria cells [58]. In bacterial cells treated with P_2W_{18}, it was observed that W atoms localized at the periphery of the cells [58]. Changes in cell morphology when *S. pneumoniae* was exposed to POVs [63] were also observed. Similarly, changes at *H. pylori* morphology from bacillary to coccoid upon exposition to several POTs, such as As_4W_{40}, $[KSb_9W_{21}O_{86}]^{18-}$ (abbreviated Sb_9W_{21}), and $[SiVW_{11}O_{40}]^{7-}$ (abbreviated $SiVW_{11}$) were also described [58].

4. Anticancer Activity of Polyoxometalates

As observed above regarding the bacterial studies, the number of studies about POMs with antitumor activities in the past 10 years also represents the majority of the POM anticancer studies: around 87% of all the papers in this field, since the first report by 1965 [40]. Similarly, POT and POMos studies together represent the majority (90%), whereas for POVs and PONbs, lower percentages can be found. In fact, more than 120 articles/papers have been published with POMos and polyoxotungstates POTs in antitumor studies [8,10–13,80–89]. POMs in cancer therapy and diagnostics, their modes of action, and future perspectives were reviewed [2,90–93]. Herein, we summarize examples of

POMs' anticancer effects and putative modes of action, particularly for POVs, for the last five years.

The decavanadate complex proved to exhibit anti-tumor activity against various cancer cell lines, including specific toxicity against human cancer cells, whereas normal human cells were not affected, even for high concentrations of the complex [84]. This complex presented IC_{50} values of 0.72 and 1.8 μM against the human lung adenocarcinoma cell line (A549) and human breast adenocarcinoma cell line (MDA-MB-231), respectively. When V_{10} complex was compared to the antitumor drug cisplatin for its cytotoxicity, it exhibited lower cytotoxicity against A549 than cisplatin, whereas its IC_{50} for MDA-MB-231 cells was 1.7 μM against 700 μM of cisplatin, meaning that it is 400 times more effective. On the other hand, decavanadate alone also showed anticancer activity against HeLa, Hep-2, HepG2, and MDA-MB-231, inducing apoptosis as the process of cell death [84]. The anti-proliferation activity of another POV, V_{18}, was observed to affect the cellular cycle, and to mediate the arrest of MCF-7 cells in the G2/M phase and induction of apoptosis, besides DNA-, BSA-, and HSA-binding [85]. POV studies were also performed with U-87 and human liver SMMC-7721 cancer cells, and cell cycle arrest, DNA damage, and apoptosis were observed [85,94].

Considering all the cancer POMs studies in recent years, only very few were performed in vivo [10,12,87,89,90]. In one of these studies, it was described that the degradability of an organic POMo, based in Mo_6O_{18}, is the key to inhibit human malignant glioma cells (U251), besides having the capacity to cross the blood brain barrier, pointing to a new type of anticancer agent [87]. Another recent study demonstrated the anti-tumor activity of an iron heptatungsten phosphate polyoxometalate complex, $Na_{12}H[Fe(HPW_7O_{28})_2]$ (IHTPO), against large cell lung cancer (NCi-H460), human hepatoma (HepG2), leukemia (K-562), and lung carcinoma (A549) *in vitro*, and against S180 sarcoma transplanted in mice in vivo [10]. Even the cytotoxic effects were only seen at higher concentrations, with IC_{50} values superior to 60 μM, and IHPTO proved to be more efficient against S180 sarcoma transplanted mice. It was concluded that even if this POT exhibited lower antitumor activity than the already approved chemotherapeutic drugs, such as cisplatin, the interesting part is that IHTPO activity might be correlated to an immunomodulatory activity [10].

In another in vivo study, Fu et al. synthesized an amphiphilic organic-inorganic hybrid POT, $[(C_{16}H_{33})_2NCONH(CH_2)_3SiNaP_5W_{29}O_{110}]$ (abbreviated Na-lipidP_5W_{29}), to improve biocompatibility, bioactivity, and biospecificity [12]. Basically, a long chain organoalkoxysilane lipid was grafted into a lacunary Preyssler-type, $[NaP_5W_{29}O_{107}]^{14-}$ (abbreviated P_5W_{29}) in order to produce the desired complex. The hybrid POT, Na-lipidP_5W_{29}, was tested for its antitumor activity against human colorectal cancer cells (HT29), and the results were compared to the parental POT, P_5W_{29}, and to 5-FU. For all concentrations tested, Na-lipidP_5W_{29} exhibited higher inhibitory rates than its parental POT and 5-FU. The cytotoxic effect of the studied POT was also tested against human umbilical vein endothelial cells (HUVECs). Finally, it was suggested that the higher antitumor effect of Na-lipidP_5W_{29} was due to its higher capacity to penetrate the cell, since it can spontaneously assemble into a vesicle [12]. In vivo studies with a Keggin-type POT, $[PW_{11}O_{39}]^{7-}$ (abbreviatedPW_{11}) were also performed against colorectal cancer [87]. To improve bioactivity, and decrease the toxicity effect of this POT, an organometallic derivative of PW_{11} was synthesized and encapsulated to form nanoparticles of Pt^{IV}-PW11-DSPE-PEG2000 (NPs). Results showed that these NPs were more efficient in inhibiting the growth of WT20 cancer cells, and treating human colorectal cancer in mice than cisplatin, pointing once again to a new strategy to fight against cancer [87].

Mechanisms of Action of Polyoxometalates against Cancer Cells

As described above regarding the effects of POMs on cancer cells, several effects were referred, such as cell cycle arrest, apoptosis cell death, and interactions with DNA, among other observations and/or suggestions. However, the multiple mechanisms of action of

polyoxometalates as antitumor agents are not yet fully understood. Recently, POMs as anticancer agents were reviewed [2]. In this section, we will resume some of them.

Research is looking for new non-competitive inhibitors of protein kinases, such as the human protein kinase CK2 inhibitors that have already been designated as promising drug targets in cancers [95,96]. POMs, such as P_2Mo_{18}, have been described as non-competitive and potent CK2 inhibitors (IC_{50} = 5 nM); although, due to its instability, it was not possible to know if this POM was responsible for the observed effects [96]. Nevertheless, POMs represent non-classical kinase inhibitors with increasing interest. Recently, aquaporins were also described to be potential protein membrane targets for POTs [97]. Aquaporins (AQPs) were found to be overexpressed in tumors, making their inhibitors of particular interest as anticancer drugs [98]. POTs strongly affect AQP3 activity, and induce inhibition of melanoma cancer cell migration and growth, unveiling their potential as anticancer drugs against tumors, opening a new window in this field of research [97]. P-type ATPases play a crucial role in cellular ion homeostasis, and have been described as potential molecular targets for several types of compounds used in the treatment of ulcers, cancer, heart ischemic failure, among other diseases. Among these compounds, several POMs have been described as PMCA (plasmatic membrane calcium ATPase) and SERCA (sarco(endo)plasmatic membrane calcium ATPase) inhibitors, and the effects compare with other inorganic compounds, as well as with therapeutic drugs [70–73,99,100].

Decavanadate species, and POMs in general, were described as strong inhibitors of phosphatases, such as alkaline phosphatase (ALP) [14,81]. Seven POTs were assessed for their inhibitory effect on alkaline phosphatases ALP, and as putative antitumor agents [14,81]. Abnormal levels of ALP in the serum are detected in cancer patients, since tumors are an abnormal cellular growth proliferating faster than normal cells, and thus, the inhibition of ALP will affect tumor cell metabolism and function. Three different POMs, P_5W_{30}, V_{10}, and the Anderson-Evans type $[TeW_6O_{24}]^{6-}$ (abbreviated TeW_6), with chitosan-encapsulated nanoassemblies were tested as anticancer agents on HeLa cells [15]. The maximum cytotoxicity against HeLa cells was observed for the compound chitosan-P_5W_{30}, which also has higher phosphatase inhibition. It was suggested, in both studies, that the POT with the largest number of tungsten and phosphorus atoms may provide the optimal interaction with the phosphatase [15,81]. Finally, disturbance of antioxidant systems is a plausible anticancer strategy once tumor cells have rapid growth and metastasis. It was found that PW_9Cu concentrations that induced osteosarcoma cells death in vitro also increased ROS, and decreased the reduced gluthatione/oxidized glutathione (GSH/GSSG) ratio in the cells [82]. Moreover, the cytotoxicity of the compound was prevented with the addition of GSH, suggesting that oxidative stress is a mechanism of POMs to induce cancer cell death [82].

5. Antiviral Activity of Polyoxometalates

The number of studies using POMs that address viral infection is comparatively lower than the ones found for cancer and bacteria. Nevertheless, and due to the SARS-CoV2 pandemic [101], the number of studies testing metallodrugs which include POMs for treatment of viral infection has increased in recent years [102–117]. Still, the studies performed so far in the past 10 years represent almost 50% of the total. Among the studies described, and since 1971 [39], the ones using POTs represent the major contribution in this field (75%). Herein, we summarized examples of POMs' antiviral effects and putative modes of action in recent years, highlighting, as above, the in vivo studies.

Considering all the POMs studies published on different types of viruses, it can be observed that influenza, HIV, herpes, and corona are the viruses most studied (Figure 3). Thus, the antiviral activity of POMs has been prevalent in respiratory tract viruses, mainly influenza viruses (Figure 3). A study with one Keggin-type POM, $[SiVW_{11}O_{40}]^{5-}$ (abbreviated $SiVW_{11}$), and two double Keggin-type POMs, ($K_{10}Na[(VO)_3(SbW_9O_{33})_2]$) and ($K_{11}H[(VO)_3(SbW_9O_{33})_2]$), showed activity against dengue virus (DFV), influenza virus

(FluV A), respiratory syncytial virus (RSV), parainfluenza virus (PfluV 2), distemper virus (CDV), and human immunodeficiency virus (HIV) [106]. It was further demonstrated that ($K_{10}Na[(VO)_3(SbW_9O_{33})_2]$) strongly inhibits the binding of the viral gp120 antibodies [106]. P_2W_{18} was also studied on influenza virus (FluV) in MDCK cell line [105]. It was suggested that P_2W_{18} could inhibit the role hemagglutinin A (HA), responsible for the first stage of viral attachment [105]. Thus, the Wells–Dawson-type POM P_2W_{18} is likely to have a dual mechanism of action in the inhibition of FluV replication: it reduces the binding of HA to the host cell membrane glycoprotein receptors, and impedes the fusion of viral particles into the cell [105].

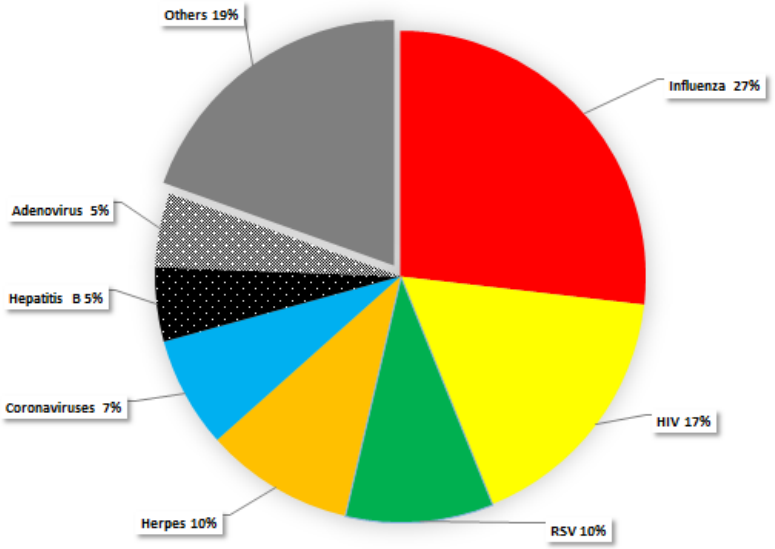

Figure 3. Studies published with all types of POMs on different types of viruses (influenza, HIV, corona, herpes).

It is known that HIV specially targets CD4 molecules present in T lymphocytes, monocytes, and macrophage lineage. It is also well-known that a glycoprotein, denominated gp120, allows it's binding on CD4 cells, and, consequently, the injection of viral material into the host cell [112]. The activity against the human immunodeficiency virus (HIV) was demonstrated for some POTs [102,104,113]. It was suggested that POMs exhibited their antiviral effect by inhibiting the binding of virus to the host cell and/or its penetration [58,59,102,104]. For example, the single Wells–Dawson structure of the compound (α_2-$[NMe_3H]_7[CH_3C_5H_4TiP_2W_{17}O_{61}]$), and the double Wells–Dawson of the structure compound ($Na_{16}[Mn_4(H_2O)_2(P_2W_{15}O_{56})_2]$) both inhibited the binding of HIV particles to CD4 cells by blocking the binding of gp120 to SUP-T1 cells [104]. Other studies reported that POMs could inhibit proteases in a non-competitive manner at low micro molar concentrations [14,102,104], thus affecting virus infection.

As referred before for the cancer studies, in vivo POMs antiviral studies remain scarce, and very few studies [114,115] have been performed (Table 2). In this table, we compared the effects of two POTs and two clinically approved drugs in a mouse, the animal model. The Keggin-type $POM[PW_{10}Ti_2O_{40}]^{7-}$ (abbreviated $PW_{10}Ti_2$) shows a survival rate (SR), indicating the percentage of mice that were still alive on day 14 after infection was 97%, for the treatment of HSV-2 virus infection when 25 mg/kg was administrated [114]. Higher survival rates of 90% were also observed upon a variant of influenza virus (FM1) infection for the POT $Ce_2H_3[BW_9{}^{VI}W_2{}^{V}Mn(H_2O)O_{39}]$ (abbreviated $BW_9{}^{VI}W_2{}^{V}Mn$). However, 10 times of the amount administrated was needed to obtain the same rate of survival upon oral administration (100 mg/kg) in comparison with the intraperitoneal mode (10 mg/kg). Lower rates of SR were observed using well-known clinically approved drugs, such as acyclovir (anti-HSV agent) and ribavirin (broad-spectrum antiviral agent) [114,115]. For acyclovir, a 33% survival rate was observed for a 50 mg/kg administration upon HSV-2

virus infection, whereas for ribavirin, a 70% survival rate was obtained after a 200 mg/kg administration for the FM1 influenza virus infection (Table 2). In sum, when comparing the same mode of oral administration upon the same influenza virus infection for the clinically approved drug, ribavirin, and the new antiviral compound, $BW_9{}^{VI}W_2{}^{V}Mn$, it clear that this POT has a higher SR (90% against 70%) for half of the dose administrated (100 mg/kg against 200 mg/kg).

Table 2. In vivo antiviral activity of POMs.

Polyoxotungstates	Virus	Animal	Survival Rate (SR)	Dose (Mode of Administration)	Ref.
$K_7[PW_{10}Ti_2O_{40}]$	HSV-2	mouse	97%	25.0 mg/kg	[114]
$Ce_2H_3[BW_9{}^{VI}W_2{}^{V}Mn(H_2O)O_{39}]$	FM1	mouse	90%	100 mg/kg (o.a.)	[115]
$Ce_2H_3[BW_9{}^{VI}W_2{}^{V}Mn(H_2O)O_{39}]$	FM1	mouse	90%	10 mg/kg (i.p.)	[115]
Clinically approved drugs					
Acyclovir	HSV-2	mouse	33%	50.0 mg/kg	[114]
Ribavirin	FM1	mouse	70%	200 mg/kg (o.a)	[115]

SR = survival rate, indicating the percentage of mice that were still alive on day 14 after infection; (o.a.) = oral administration; (i.p.) = intraperitoneal administration; FM1 = variant of influenza virus; HSV-2 = herpes simplex virus 2.

Mechanisms of Action of Polyoxometalates against Viral Infection

It was suggested that some POMs could inhibit the replication of HIV [102]. Certain POMs, such as $Cs_2K_4Na[SiW_9Nb_3O_{40}]$ (abbreviated $SiW_9Nb_3O_{40}$), can act directly on hepatitis C virus (HCV) virion particles, and destabilize the integrity of its structure [115]. It was further suggested that POMs could specifically inhibit HCV infection at an early stage of its life cycle [103]. Note that the most cited paper regarding decavanadate (V_{10}) in biology is the interaction of V_{10} in a spatially selective manner within the protein cages of virions [113]. Besides preventing the formation of virions, decavanadate is also able to inhibit viral activities by preventing the virus-cell host binding [113].

As mentioned before, the inhibition of catalytic reactions promoted by sialyltransferases and sulfotransferases would 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 would affect the early stage of viral infection. Moreover, some POMs are likely to have a dual mechanism of action in the inhibition of FluV replication: interacting with hemagglutinin A (HA), responsible for the first stage of viral attachment (Figure 4), and inhibiting the fusion of viral particles into the cell [110].

HIV is known to specially target CD4 molecules present in T lymphocytes, monocytes, and macrophage lineage. A glycoprotein, denominated gp120, which is located on the surface of the virus, is the principal weapon of HIV because it allows its binding on CD4 cells, and the injection of the viral material into the cell [112]. Other studies reported that POMs could inhibit proteases in a non-competitive manner at low micro molar concentrations [14,102,104]. The HIV-1 protease is important for the maturation of protein components of an infectious HIV virion; thus, its inhibition could be responsible for the anti-HIV effect of POMs. For SARS-CoV, it was referred that POMs interact with the $3CL^{pro}$ protein, affecting virus proliferation [116,117].

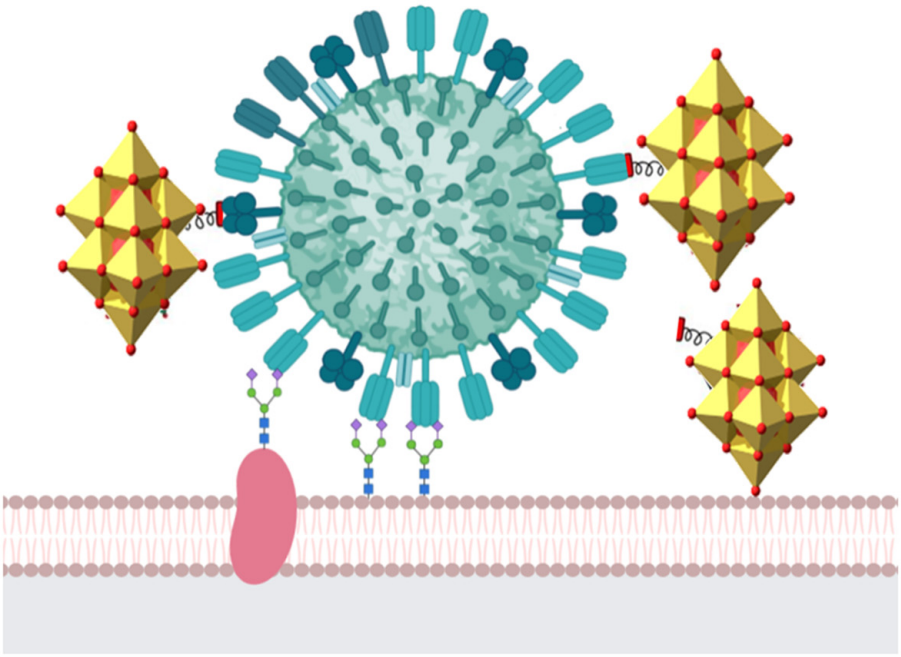

Figure 4. POM putative interactions with viral membrane proteins, such as hemagglutinin, preventing the early stage of infection. Moreover, interaction with neuraminidase would prevent a later stage of infection. Color code: glycoprotein, dark pink; hemagglutinin, dry green; neuraminidase, dark green; POM, yellow.

6. POMs Stability and Speciation in Solution

POMs are clusters of units of oxoanions of transition metals that can be formed upon acidification of neutral solutions of Mo, W, V, and Nb. Once formed, some POMs, such as POVs and PONbs, have shown to persist in solution, even in the neutral and basic pH range [118]. Speciation and/or stability studies are not usually taken into account when studies of the effects of POMs in biological systems are performed [91]. This speciation topic was recently reviewed and highlighted [119]. Nevertheless, it is well-known that some POMs are not stable in many of the experimental conditions, and references to POMs' stability are mentioned, even after it is realized that the POM added to the medium reaction is no longer there, or at least is partially decomposed 5 min, 30 min, or 24 h after incubation [91,118–124]. As mentioned above, in some studies with POTs and bacteria, a change at the color of the medium was detected, suggesting POT decomposition, whereas oxidation reduction reaction could be induced through bacterial metabolism [59,62]. That means that the biological effects observed could not, at least in part, be totally attributed to the POM that was added to the medium.

The isopolyoxovanadate decavanadate (V_{10}) is perhaps the most studied regarding its stability at biological conditions [118–124]. V_{10} demonstrates many important roles in fundamental biological processes [91,122,125–129]. It was suggested that the presence of proteins, such as actin and Ca^{2+}-ATPase, can significantly (5 and 3-fold) improve the stability of V_{10}, whereas no changes were observed for myosin and lipid structures namely liposomes [124]. In fact, it was observed that the half-life time of V_{10} decomposition increases from 5 to 27 h in the presence of G-actin, the monomeric form of actin (Figure 5). Further studies point out specific binding sites for V_{10} at G-actin, in the absence and in the presence of the natural ligand, ATP [130]. Thus, POMs' stability and speciation in the presence of biomolecules will be essential for understanding and deducing their fundamental roles in biology, and their applications in medicine.

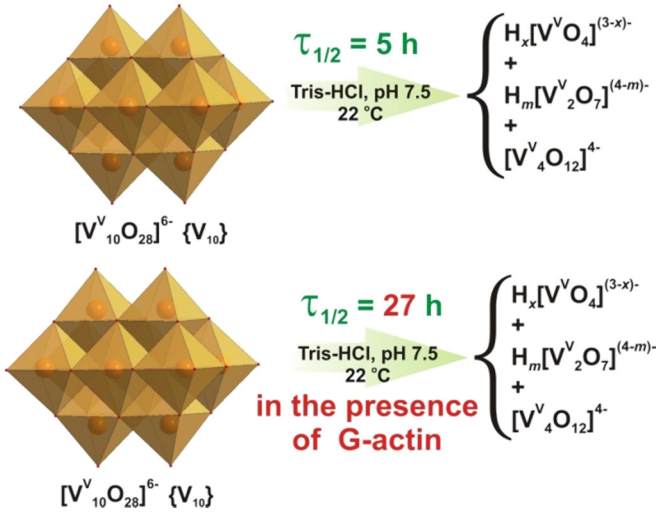

Figure 5. POM species in the presence of macromolecules. Decavanadate, an isopolyoxovanadate, was found to be stabilized upon interaction with G-actin and Ca^{2+}-ATPase [124].

7. Conclusions

POMs are interesting compounds with a diversity of structures. POMs have been studied and applicated in a large variety of fields. POM applications in environmental and biomedical sciences are promising. Herein, we highlighted POMs' degradation of emergent health pollutants, and their anticancer, antibacterial, and antiviral effects, and mechanisms of action.

POMs, as organic/inorganic hybrid materials, seem to be a good choice for emergent health pollutant degradation, including microplastics. In fact, POMs efficiently induce antibiotics degradation, thus reducing the pharmaceutical environmental impact. Emergent pollutant antibiotics, such ciprofloxacin, tetracycline, sulfasalazine, among others, as well as others pollutants, such as bisphenol A, can be decomposed in the environment using POMs.

POMs showed antibacterial activity by inducing morphological changes through cytoskeleton interactions, interfering with the ionic transport systems, leading bacteria to death. Moreover, POMs have demonstrated activity against antibiotic-resistant bacteria. The majority of the studies have addressed the potential of POMs to control bacterial growth, and some explored the mechanism of action of these compounds; however, several aspects of the virulence and community life of bacteria were not yet explored. POMs showed their antiviral activity against influenza, HIV, and several other viruses. POMs are able to inhibit virus infection by preventing the virus-cell host binding at an early stage of the viral infection by targeting viral membrane proteins.

In general, POMs inhibit the growth of tumor cells through apoptosis. Generation of oxidative stress, inhibition of the kinases, ATPases, and/or aquaporin's function, among others, was proposed by some authors. For example, decavanadate and other POMs exhibited anti-tumor activities through the inhibition of ALP, kinases, and P-type ATPases, whereas, so far, no decavanadates were found to inhibit HDAC or ecto-ATPases. POMs' effects on different types of cancer cells were also found to be different.

In sum, several types of POMs have proved to be efficient against viruses, bacteria, and tumor cells, besides their applications in the decomposition of emergent health pollutants. POTs are among those POMs that have been the subject of the largest number of studies on anticancer, antiviral, and antibacterial activities. POM molecular targets are unveiling their potential as anticancer, antibacterial, and antiviral drugs of the future, thus opening new windows for future research in these fields. Further studies involving interdisciplinary teams must be conducted to understand which POM is better-tuned against a particular disease or infection. Thus, the future is bright for polyoxometalates.

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Conflicts of Interest: The author has no conflict of interest to declare.

Abbreviations

A549	Human lung cancer cells
ALP	Alkaline phosphatase
As_4W_{40}	$[KAs_4W_{40}O_{140}]^{27-}$
ATPase	Adenosine triphosphatase
BWCN	$(Himi)_2[Bi_2W_{20}O_{66}(OH)_4CO_2(H_2O)_6Na_4\ (H_2O)_{14}]\cdot 17H_2O$
BW9VIW2VMn	$Ce_2H_3[BW_9{}^{VI}W_2{}^{V}Mn(H_2O)O_{39}]$
Ca^{2+}-ATPase	Calcium adenosine triphosphatase
CTS-$Ca_3V_{10}O_{28}$	Chitosan-$Ca_3V_{10}O_{28}(NH_4)_6$
$Cu_3(PW_9O_{34})_2$	$[Cu_3(PW_9O_{34})_2]^{12-}$
gp120	Glycoprotein expressed by HIV
HCB	Hepatitis B virus
HCMV	Human cytomegalovirus
HCV	Hepatitis C virus
HDAC	Histone deacetylase
HeLa	Human cervical cancer cells
Hep-2	Human Larynx carcinoma cell line
HepG2	Human hepato-cellular carcinoma
HIV	Human immunodeficiency virus
HUVEC	Human umbilical vein endothelial cells
IC_{50}	Half inhibitory concentration
K-562	Human myelogenous leukemia
MCF-7	Human breast cancer cells
MDA-MB-231	Human breast adenocarcinoma cell line
MDCK	Madin–Darby canine kidney
mecA	Gene that codes for PBP2′
MnV_{11}	$K_5MnV_{11}O_{33}\cdot 10H_2O$
MnV_{13}	$K_7MnV_{13}O_{38}\cdot 18H_2O$
Na-lipidP_5W_{29}	$[(C_{16}H_{33})_2NCONH(CH_2)_3SiNaP_5W_{29}O_{110}]$
Nb_{10}	$[Nb_{10}O_{28}]^{6-}$
POMos	Polyoxomolybdates
POMs	Polyoxometalates
PONbs	Polyoxoniobates
POTs	Polyoxotungstates
POVs	Polyoxovanadates
PVA/PEI	poly(vinylalcohol)/polyethylenimine
PW_{11}	$[PW_{11}O_{39}]^{7-}$
P_2W_{18}	$K_6[P_2W_{18}O_{62}]\cdot 14H_2O$
P_5W_{29}	$[NaP_5W_{29}O_{107}]^{14-}$
P_5W_{30}	$[NaP_5W_{30}O_{110}]^{14-}$
$PW_{10}Ti_2$	$[PW_{10}Ti_2O_{40}]^{7-}$
S180	Murine sarcoma cells
SARS-V	Severe acute respiratory syndrome virus
SARS-CoV	Severe acute respiratory syndrome coronavirus
SERCA	Sarco(endo)plasmatic membrane calcium ATPase
$SiW_9Nb_3O_{40}$	$Cs_2K_4Na[SiW_9Nb_3O_{40}]$
$SiVW_{11}$	$[SiVW_{11}O_{40}]^{7-}$
Sb_9W_{21}	$[KSb_9W_{21}O_{86}]^{18-}$
SR	Survival rate
TeW_6	$[TeW_6O_{24}]^{6-}$

U-87	Human brain-like glioblastoma cells
U251	Human malignant glioma cells
VRSA	Vancomycin-resistant *Staphylococcus aureus*
V_{10}	$[V_{10}O_{28}]^{6-}$
$V_{18}O_{42}$	$[V_{18}O_{42}(H_2O)]^{12-}$

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