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BIOLOGICAL APPLICATIONS OF MOLYBDENUM INORGANIC COMPOUNDS

Arcadie FUIOR

Moldova State University
Université de Versailles Saint-Quentin-en-Yvelines

Molybdenum is an essential element for nature in both organic and inorganic environments. It is present in more than 50 enzymes that catalyze very important red-ox reactions for the majority of the living organisms and for the entire biogeochemical cycle of nitrogen. Biocompatibility of this metal within various chemical combinations motivated the investigation of eventual useful biological properties. In this review article, molybdenum compounds are explored in order to highlight their applications in biology and medicine as promising antitumor, antibacterial, antiviral and antioxidant agents.

Keywords: *molybdenum, biological properties, antitumor, antiviral, antibacterial, antioxidant.*

APLICAȚIILE BIOLOGICE ALE COMPUȘILOR ANORGANICI AI MOLIBDENULUI

Molibdenuul este un element esențial în natură – atât în mediul organic, cât și anorganic. Este prezent în mai mult de 50 de enzime care catalizează reacții red-ox foarte importante pentru majoritatea organismelor vii și pentru întregul ciclu biogeochimic al azotului. Biocompatibilitatea acestui metal sub formă de numeroase combinații chimice a motivat investigarea eventualelor proprietăți biologice utile. În acest articol review sunt explorați compușii molibdenului cu scopul de a evidenția aplicațiile lor în biologie și medicină în calitate de substanțe anticancer, antibacteriene, antivirale și antioxidante.

Cuvinte-cheie: *molibden, proprietăți biologice, anticancer, antiviral, antibacterian, antioxidant.*

1. Introduction

Molybdenum, the 42nd element in the periodic system, is a transition metal having the electronic configuration [Kr] $4d^5\ 5s^1$. Due to the typical wide range of manifested oxidation states (+2 to +6), molybdenum has a rich and diverse chemistry. One notable application is industrial catalysis. Undoubtedly, molybdenum disulfide MoS_2 in various forms (nanosheets, nanoparticles, quantum dots, composite materials etc.) is reported as the most famous and promising compound, both highly efficient and affordable (electro- and photo-) catalyst in hydrogen evolution reaction [1-7]. Molybdates and polyoxo(thio)molybdates are also known for good electrocatalytic properties [3,8-21].

In physiological medium, molybdenum is still redox-active and maintains its versatility, being able to switch between oxidation states that range from +6, +5 and +4 (and even +3 in molybdenum nitrogenase). This is one good reason for this heavy metal's presence in the active sites of more than 50 enzymes, as these metalloprotein systems can catalyze many oxidation-reduction reactions, essential for the metabolism of the majority of living organisms (from unicellular microbes and bacteria to higher plants, mammals and even humans). Moreover, the catalytic competence of molybdenum is justified also by its capacity to facilitate electron, proton and even oxo- transfer processes [22]. Molybdenum-containing enzymes are grouped in several families, based on the arrangements in the Mo coordination sphere of the ligands that are part of active site. The active site includes pyranopterin cofactor molecule(s) that can coordinate to Mo by the *cis*-dithiolene **(**–**S**–(R)C=C(R)–S–**)** group (see Figure 1.1), and it also includes oxygen and/or sulfur and/or selenium atoms.

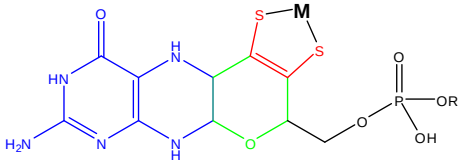

Fig.1.1. Schematic representation of the structure of the pyranopterin cofactor. The pyranopterin cofactor molecule is formed by pyrano(green)-pterin(blue)-dithiolene(red)-methylphosphate(black) moieties. M stands for metal (Mo in case of molybdoenzymes).

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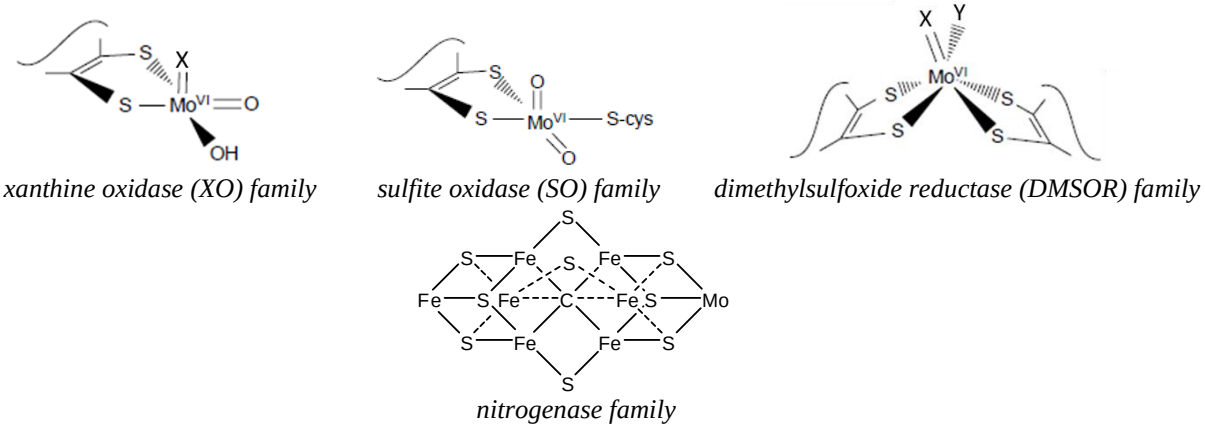
So there are three large families of mononuclear molybdoenzymes – the xanthine oxidase family, the sulfite oxidase family and the dimethylsulfoxide reductase family; and one more – nitrogenase family, with a complex heteropolynuclear active centre (see Figure 1.2.) [22-24].

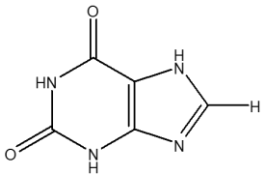


xanthine oxidase (XO) family *sulfite oxidase (SO) family* *dimethylsulfoxide reductase (DMSOR) family*

nitrogenase family

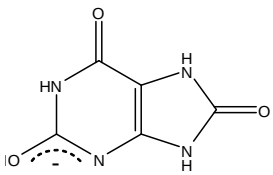
Fig.1.2. Schematic representation of the structures of the active site of molybdoenzymes. For simplicity, only the cis-dithiolene group of the pyranopterin cofactor is represented in XO, SO and DMSOR families.

Each of these enzyme families are very useful for living beings. In animals and humans, xanthine oxidoreductase is involved in the oxidation of hypoxanthine and xanthine into urate (eqn 1.1), considerably important since xanthine excess in blood and urine leads to health problems. The mammalian aldehyde oxidases (AO, part of XO family) participate in the formation of retinol (vitamin A) which is important for growth and development. In plants, AO enzymes help to obtain two important phytohormones – abscisic and indole-3-acetic acids [25]. The SO family includes enzymes with a vital role for human body and almost all other forms of life, being able to oxidize sulfite into sulfate (eqn 1.2) and participate in the catabolism of sulfur-containing amino acids and other sulfurated compounds). Nitrate reductases that catalyze the reactions needed for nitrate assimilation (eqn 1.3) by plants are also part of the same SO family [26]. In the DMSOR family, the benchmark enzyme *Rhodobacter sphaeroides* DMSOR catalyzes the reduction of dimethylsulfoxide to dimethylsulfide (eqn 1.4). Other noteworthy enzymes included are prokaryotic NaR[i] and FDH[ii] enzymes for instance, that are involved in biochemical processes in cells and interact with physiological redox partners (cytoplasmatic and periplasmatic cytochromes, ferredoxins etc.) [22]. The Nitrogenase family gathers enzymes that catalyze the remarkable dinitrogen reduction reaction to ammonium, by the cleavage of the very stable triple bond N≡N (eqn 1.5). These enzymes were purified from *Azotobacter vinelandii, Klebsiella pneumonia and Clostridium pasteurianum* bacteria, and they are primordial for the biogeochemical cycle of nitrogen [22,27].



xanthine

$$+ H_2O \rightleftarrows$$



urate

$$(H^+) + 2\bar{e} + 2H^+ \quad (1.1)$$

$$SO_2^{2-} + H_2O \rightleftarrows OSO_2^{2-} + 2\bar{e} + 2H^+ \quad (1.2)$$

$$ONO_2^- + 2\bar{e} + 2H^+ \rightleftarrows NO_2^- + H_2O \quad (1.3)$$

$$(CH_3)_2S{=}O + 2\bar{e} + 2H^+ \rightleftarrows (CH_3)_2S + H_2O \quad (1.4)$$

$$N{\equiv}N + 8H^+ + 8\bar{e} + 16MgATP \rightleftarrows 2NH_3 + H_2 + 16MgADP + 16P_i \quad (1.5)$$

[i] NaR = nitrate reductase
[ii] FDH = formate dehydrogenase

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Mechanisms of action in enzymes are very complex and in many cases still not fully revealed. Scientists are trying to imitate structural organization and mimic the catalytic properties of enzymes by developing synthetic enzyme-inspired models. Examples of artificial models in hope for catalytic properties similar to natural enzymatic systems were reported mainly by D. Coucouvanis *et al.* starting in the early 90's. [28-35]. For instance, the $MoFe_3S_4$ synthetic cubanes exhibited good efficiency in reduction of hydrazine to ammonia, in analogy with the nitrogenase enzyme [28].

Mo has a small abundance (in comparison with other elements with biological importance) in different environments (Table 1.1), and is found in even smaller quantities in biological tissues. Yet the bioavailability of this trace element seems crucial for the existence and the evolution of life on Earth. Cells take up Mo from external medium in the form of molybdate oxyanion MoO_4^{2-}, since this is the predominant highly water-soluble form at pH > 4,2 [22,36,37].

Table 1.1

Abundance of Mo and other elements with biological importance

Location	Abundance (ppb by atoms)						
	Mo	W	Fe	H	C	N	O
Universe	0.1	0.003	20×10^3	930×10^6	500×10^3	90×10^3	800×10^3
Crustal rocks	230	120	23×10^6	31×10^6	3.1×10^3	29×10^3	600×10^6
Oceans	0.64	0.004	0.33	662×10^6	14.4×10^3	220	331×10^6
Human body	7	-	3.7×10^3	620×10^6	120×10^6	12×10^6	240×10^6

Generally, heavy metals are reported cytotoxic when found in excessive concentrations in plants, therefore they become dangerous for human health considering their entry into the food chain [38]. Nonetheless, a study on Mo absorption, excretion and retention in young men (published in 1995 by the American Society for Clinical Nutrition) showed that no clinical symptoms or toxicity were observed of insufficient and excessive intakes of dietary molybdenum, thus confirming its safety and non-toxicity [39]; additionally it was proved that this trace element has more other surprisingly important benefits for human body [40]. In a consequent deduction, Mo can be considered biocompatible if given appropriate ligands. This is the case of many new molybdenum inorganic compounds (Mo-based clusters, Mo complexes, polyoxomolybdates etc.), that show remarkable biological properties. In this review article, molybdenum compounds are explored in order to highlight their applications in biology and medicine.

2. SYNTHETIC MOLYBDENUM COMPOUNDS WITH BIOLOGICAL PROPERTIES

2.1 Antitumoral properties

One biological property for many molybdenum-based compounds that earned good reputation so far seems to be the *in vitro* cytotoxic effect on different types of cancer cells, as showed hereafter.

To start with simpler compounds, it should be mentioned that the simple molybdenum combination with sulfur in the form of MoS_2 sulfide is effective in *in vitro* photothermal therapy upon near infrared (NIR) irradiation of HeLa cervical cancer cells; also chitosan-incorporated MoS_2 dispersion gives good results on treatment of mice with pancreatic cancer and if combined with doxorubicin (DOXO, a chemotherapeutic drug) great anticancer ability is observed thanks to a synergistic effect [41]. Here we're talking about hypothermia-induced destruction of cancer cells by photo-excited MoS_2 particles, since layered MoS_2 (see figure 2.1.1) alone has low toxicity. Other studies have confirmed this antitumor effect of MoS_2, this time modified with polyglycidyl polymer, which demonstrated better efficiency [42], and its suitability for the development of an electrochemical biosensor based on gold nanoparticle-decorated MoS_2 nanosheet for early cancer diagnosis [43].

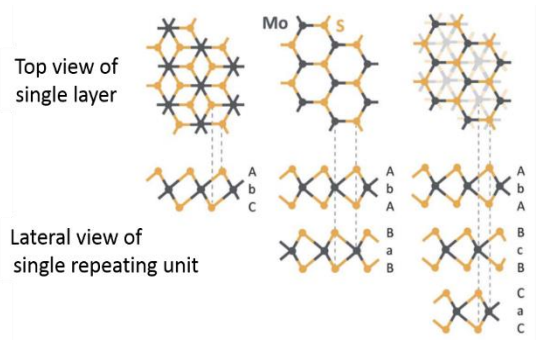

Fig.2.1.1. Structure of bulk MoS_2

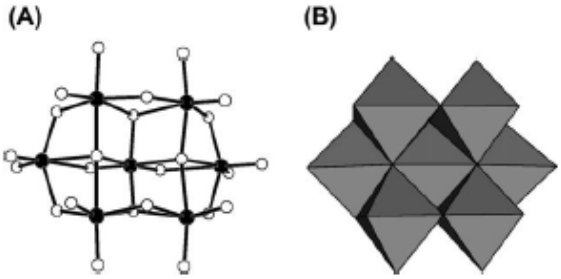

Fig.2.1.2. Structure of $[Mo_7O_{24}]^{6-}$. Large block circles represent Mo atoms and small open circles represent oxygen atoms (A); octahedral model (B).

Additionally, the $(NH_4)_2MoS_4$ thiomolybdate and possibly its hydrolysis products were mentioned to have anticancer potential through angiostatic action on tumor cells [44]. With a similar photothermal mechanism, nanoparticles of molybdenum dioxide MoO_2 displayed a significant inhibition by inducing cellular apoptosis of HeLa *in vitro;* and *in vivo* complete ablation of tumors in mice after 3 days with only 4 minutes NIR irradiation exposure, while not harming the healthy tissue [45]. Another molybdenum oxide – MoO_3 as nanoparticles displayed anticancer property on MCF-7 and HEP G2 cells, reducing the percentage of viability at 25 μL to 7,94 % for MCF-7 and 10,88 % for HEP G2 [46]. Polyoxomolybdates are anionic clusters of molybdenum oxides, part of the polyoxometallates (POMs) class, which are very versatile in terms of nuclearity, size, structure and properties. The biological properties of POMs were investigated by T.Yamase and his coworkers and they have found good antitumor effects against different cancer cell lines, in particular for the $(NH_3Pr^i)_6[Mo_7O_{24}]\cdot 3H_2O$. Their experiments showed that this heptamolybdate is active against human cancer xenografts (Co-4 colon cancer, MX-1 breast cancer, OAT lung cancer). At day 6 after tumor implantation in mice, a 200 mg/kg dose of $(NH_3Pr^i)_6[Mo_7O_{24}]\cdot 3H_2O$ reduced the tumor size of Co-4, MX-1 and OAT by 55.6%, 48.3% and 42.9% respectively [47]. Later in 2005 they reported the cytotoxic effect of the same compound on the proliferation of human pancreatic AsPC-1 cell culture and MKN-45 human gastric cancer. IC_{50} values for 24 and 48 hour treatments were 1.65 mg/mL and 500 μg/mL, respectively. To prove the induced apoptotic cell death one of the methods used was for example cell staining with Hoechst dye 33342 with following morphological analysis (see figure 2.1.3). They also demonstrated that the structure of $[Mo_7O_{24}]^{6-}$ (see figure 2.1.2) is apparently important for anticancer activity by showing that when the $[NH_3Pr^i]^+$ cation was replaced by $[NH_4]^+$ and K^+ and the $[Mo_7O_{24}]^{6-}$ anion was replaced by Cl^-, $(NH_4)_6[Mo_7O_{24}]\cdot 4H_2O$ and $K_6[Mo_7O_{24}]\cdot 4H_2O$ were effective, but $[NH_3Pr^i]Cl$ was ineffective against tumor growth [48-50]. In the next 3 years, they published papers on the proposed mechanism of action (eqn 2.1.1) for this polyoxomolybdate: repeated cycles of the redox transformation of $[Mo_7O_{24}]^{6-}$ core in the complex with flavin mononucleotide [51-53]; they showed enhancement of the NGF-induced neurite-outgrowth of PC12 cells by the representative $(NH_3Pr^i)_6[Mo_7O_{24}]\cdot 3H_2O$ [54] and the higher antitumor potency of photolysis product $[Me_3NH]_6[H_2Mo^V{}_{12}O_{28}(OH)_{12}(Mo^{VI}O_3)_4]\cdot 2H_2O$ (IC_{50} values against AsPC-1 cells and MKN45 cells were 175 and 40 $\mu g*mL^{-1}$, respectively) compared to the precursor $[Mo_7O_{24}]^{6-}$ [55,56].

$$[Mo_7O_{24}]^{6-} + \bar{e} + H^+ \leftrightarrow [Mo_7O_{23}(OH)]^{6-} \qquad (2.1.1)$$

There is another example where a polyoxomolybdate ($(PPh_4)_4Mo_8O_{26}$) is used as precursor to synthesize a new complex with 2,5-dihydroxybenzoate – $(PPh_4)_2[Mo_3O_6(\mu\text{-}O)_2(2,5\text{-}DHBA)_2]$ well qualified for treatment of human HL-60 and K562 leukemic cells [57]. Heteropolyoxomolybdates can also have antileukemic activity, as reported by Li *et al.*: the arsenomolybdate $K_2Na[AsMo_6O_{21}(O_2CCH_2NH_3)_3]\cdot 6H_2O$ has anti-proliferative effects on acute myeloid leukemia HL-60 and U937 cells (IC_{50} = 8,61 μM and 14,50 μM) and had low inhibitory effect on normal cells HUVEC at 24 h with IC_{50} value of 889.18 μM [58]. Another way to increase antitumor properties of POMs is to functionalize them. Illustrative examples are seen in A. Dolbecq's *et al*. work, where organic bisphosphonate (BP) ligands are covalently bonded to different POMs. The group in Versailles synthesized and characterized many POM-BP derivatives with different Mo valence and nuclearity. Their *in vitro* studies on anticancer activities of such hybrid POMs with grafted organic ligands against three human tumor cell lines (MCF-7 (breast cancer), NCI-H460 (lung cancer), and SF-268 (central nervous system cancer) show weak Mo^V–ale (figure 2.1.4) activity while the Mo^{VI} derivative $[(Mo_3O_8)_4(Hale^*)_2]^{6-}$

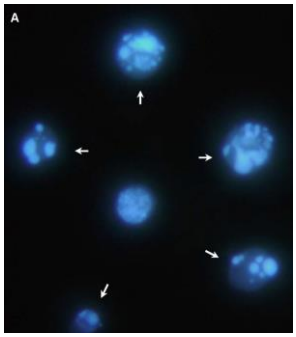

Fig.2.1.3. Formation of apoptotic small bodies in AsPC-1 visualized by fluorescence microscopy

(figure 2.1.5) has IC_{50} values of ~10 μM [59]. They explored even further new combinations with other bisphosphonates and reached better results for anticancer activities of compound $Mo_6(Zol)_2$ (see figure 2.1.6 for structures) with a mean IC_{50} equal to 5 μM (table 2.1.1) [60], and of heterometallic

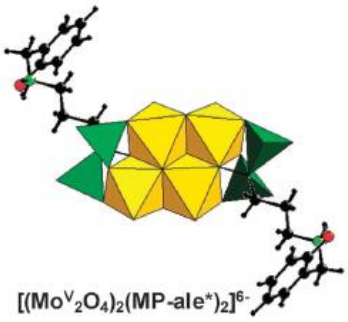

Fig.2.1.4. Polyhedral representation of antitumor-active Mo^V-BP derivative.Yellow octahedra: Mo^VO_6, green tetrahedra: PO_4, large black spheres: C, small black spheres: H, light green spheres: N, red spheres: O

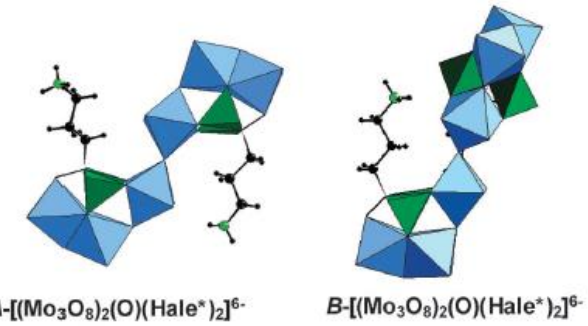

Fig.2.1.5. Polyhedral representation of antitumor-active Mo^{VI}-BP derivatives.Blue octahedra: $Mo^{VI}O_6$, green tetrahedra: PO_4, large black spheres: C, small black spheres: H, light green spheres: N, red spheres: O

POM-BD hybrid Mn^{III}-containing $Rb(NH_4)_4[(Mo_2O_6)_2(O_3PC(CH_2C_3H_4N_2)(O)PO_3)_2Mn]\cdot 14H_2O$ (abbreviated Mo_4Zol_2Mn) – being the most potent agent (IC_{50} = 1.3 ± 0.24 μM) against human breast adenocarcinoma cell line MCF-7 [61].

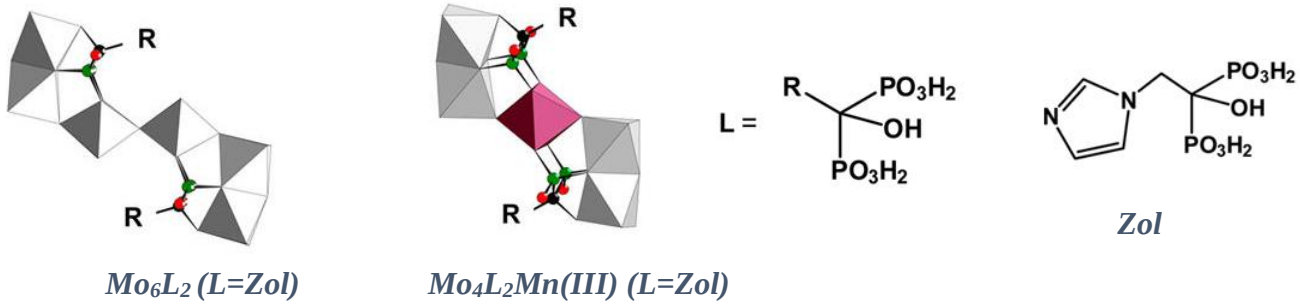

Fig.2.1.6. Abbreviation and formula of BP together with schematic structures of complexes. Gray polyhedra = MoO_6, purple polyhedron = MnO_6, green spheres =P, black spheres = C, red spheres = O.

Table 2.1.1.

Human tumor cell inhibition data

	NCI-H460 IC_{50} [μM]	MCF-7 IC_{50} [μM]	SF-268 IC_{50} [μM]	average IC_{50} [μM]	average/BP IC_{50} [μM]
$Mo_{12}(Ale)_4$	9.2 ± 5.0	5.6 ± 0.4	5.0 ± 0.1	6.6 ± 3.1	26 ± 12
$Mo_6(Ale)_2$	48 ± 38	56 ± 0.0	130 ± 16	78 ± 45	160 ± 89
$Mo_6(Sul)_2$	46 ± 0.3	35 ± 17	100 ± 11	61 ± 33	120 ± 66
$Mo_6(Zol)_2$	2.4 ± 0.2	2.2 ± 0.1	3.0 ± 1.0	2.5 ± 0.6	5.0 ± 1.2
$Mo(Ale)_2$	6.6 ± 2.2	9.4 ± 4.1	8.0 ± 0.8	8.0 ± 2.4	16 ± 4.9
Ale	200 ± 43	130 ± 2.2	140 ± 13	150 ± 42	150 ± 42
Zol	8.1 ± 1.7	7.7 ± 2.6	12.4 ± 1.4	9.4 ± 2.8	9.4 ± 2.8

The same heteropolyoxomolybdate-bisphosphonate hybrid Mo_4Zol_2Mn was tested *in vivo* and was found with pretty good performance, decreasing the tumor growth of SK-ES-1 sarcoma cells five times more efficiently than the zoledronate ligand alone (figure 2.1.7), having a IC_{50} value of 2.6 ± 0.3 μM) [62]. As most common for POMs, the metal centre (Mo in our case) adopts the octahedral geometry, having ligating atoms like O, S, and N in its first coordination sphere. Two more simple complexes with octahedral Mo (among 4 others non-octahedral but containing the common $[Mo_2O_2S_2]^{2+}$ core) have been reported to also have biological properties. This time it is about the convenient low cytotoxicity of the compounds,

considered useful for potential applications like the development of catalytic drugs. The structures of the six compounds are presented in figure 2.1.8 and their corresponding cytotoxicity on MCF-7 (breast cancer), PT45 (pancreatic cancer), HT29 (colon cancer) cell lines in comparison with the *cis*-platin is shown in table 2.1.2.

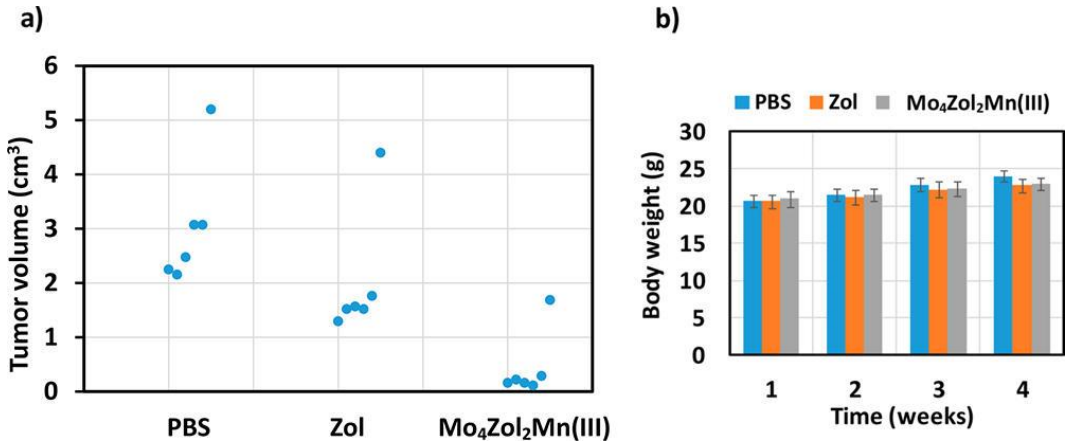

Fig.2.1.7. Effects of zoledronate and $Mo_4Zol_2Mn(III)$ on SK-ES-1 tumor volume in 6-week old athymic mice treated daily for 28 days with 5 μg compound or phosphate-buffer saline (PBS); 6 mice per group. a) Tumor volumes in each of the individual mouse after a 4 week treatment. b) Body weights as a function of time for different treatments.

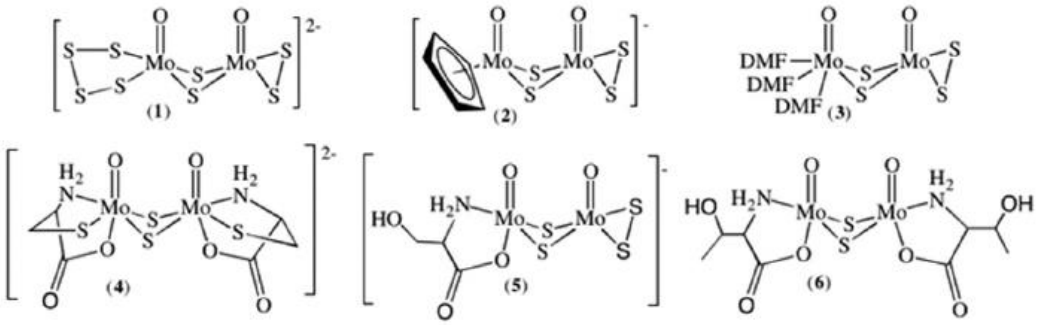

Fig.2.1.8. Structures of compounds $(Et_4N)_2$(**1**), Et4N(**2**), (**3**), Na_2(**4**), K(**5**), (**6**).

Table 2.1.2.

IC_{50} values (μM) obtained for complexes 1-6 and for cis-platin (7) in three different cell lines after treating the cells for 72 h and assayed with MTT method.

	Cell line, IC50 values[a]		
Compound no.	MCF-7	PT45	HT29
1	106 ± 32[a]	34 ± 7	50 ± 3
2	214 ± 35[b]	64 ± 7	780 ± 259
3	383 ± 45	118 ± 17	344 ± 10
4	868 ± 319	189 ± 34	–
5	882 ± 350	117 ± 15	635 ± 98
6	301 ± 126	95 ± 5	429 ± 219
7	19.2 ± 1.93	5.73 ± 1.03	10.6 ± 2.28

[a] Values for each measurement in the table are averages for four repeats.
[b] It was not possible to determine an end point for this compound in this cell line.

The sulfur-bridged cysteinato dimolybdenum complex $Na_2[Mo_2O_2S_2(cys)_2]4H_2O$ (**4**) has no toxicity at all on HT29 and is the least toxic on MCF-7 and PT45 (about 45 and respectively 35 times less toxic than *cis*-platin), therefore seems the most promising for therapeutic applications requiring non-toxic substances [63]. Interestingly, there are octahedral Mo clusters ($Na_2[Mo_6I_8(N_3)_6]$ and $Na_2[Mo_6I_8(NCS)_6]$) with well-defined luminescence properties, which would make them ideal as luminescent probes or singlet-oxygen sensitizers

in living cells, but unfortunately their hydrolytic species present acute *in vitro* toxicity for both HeLa (IC_{50} = 18 μM) and healthy HEK 293T (IC_{50} = 46 μM) cells [64].

2.2 Antiviral properties

Although initially many polyoxotungstates have been found with suppression efficiency against HIV antigen, the polyoxometallates with molybdenum could not distinguish themselves with such valuable characteristics. In 1991, Take *et al.* showed very low antiviral potential of two Keggin heteropolyoxomolybdates $K_4[PMo_{11}O_{39}Cr(H_2O)]$ and $K_3[PMo_{12}O_{40}]$: their 50% cytotoxic concentration (CC_{50}) was 420 μg/mL and 620 μg/mL respectively; and unavailable EC_{50} values (maximum antivirus protection of MT-4 cells being under 50%) [65]. Two years later, basically the same authors published their antiviral research – a screening of 26 (hetero)polyoxo-, molybdates (table 2.2.1) And they reported the most prominent compound $(NH_4)_{12}H_2(Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4)x13H_2O$ (see figure 2.2.1 for structure) with marked inhibition of the replication of human immunodeficiency virus type 1 (HIV-1) (see table 2.2.1 for values).

Table 2.2.1

Toxicity and anti-HIV-1 activity of polyoxomolybdates.

Compound	Chemical formula	CC_{50}, μg/ml	EC_{50}, μg/ml	TI_{50}[a]
Sodium molybdate	$Na_2MoO_4 \cdot 2H_2O$	>800	NA[b]	
Paramolybdate derivatives				
Ammonium heptamolybdate	$(NH_4)_6[Mo_7O_{24}] \cdot 4H_2O$	570	NA	
PM-8	$(iPrNH_3)_6[Mo_7O_{24}] \cdot 3H_2O$	260	NA	
PM-26	$(iPrNH_3)_5H[Mo_7O_{26}] \cdot 3H_2O$	280	NA	
PM-112	$(Me_4N)_2(NH_4)_8[Mo_{14}O_{46}] \cdot 8H_2O$	500	NA	
Keggin structure; 1:12[c], tetrahedral[d]				
PM-102	$Na_3[PMo_{12}O_{40}] \cdot nH_2O$	750	NA	
PM-66	$K_3[PMo_3W_9O_{40}] \cdot 25H_2O$[e]	150	83	1.8
PM-67	$K_3[PMo_9W_3O_{40}] \cdot 5H_2O$[e]	240	NA	
Lacunary Keggin structure; 1:11[c], tetrahedral[d]				
PM-62	$K_7[PMo_2W_9O_{39}] \cdot 19H_2O$[e]	160	82	2.0
Trivacant Keggin structure; 1:9[c], tetrahedral[d]				
PM-64	$Na_3H_6[PMo_9O_{34}] \cdot 13H_2O$	430	NA	
Anderson structure; 1:6[c], octahedral[d]				
PM-32	$Na_5[IMo_6O_{24}] \cdot 3H_2O$	68	NA	
PM-41	$(NH_4)_3H_6[CoMo_6O_{24}] \cdot 7H_2O$	49	NA	
PM-42	$Na_3H_6[CrMo_6O_{24}] \cdot 8H_2O$	430	NA	
Polyoxomolybdolanthanoates, tricapped trigonal prismatic[d]				
PM-104	$(NH_4)_{12}H_2[Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4] \cdot 13H_2O$	300	4.4	68
PM-113	$(NH_4)_{12}H_2[Nd_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4] \cdot nH_2O$	430	NA	
PM-114	$(NH_4)_{12}H_2[Pr_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4] \cdot nH_2O$	320	NA	
PM-115	$(NH_4)_{12}H_2[La_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4] \cdot nH_2O$	500	NA	
PM-116	$(NH_4)_{12}H_2[Ce_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4] \cdot nH_2O$	440	NA	
PM-119	$(NH_4)_{12}H_2[Sm_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4] \cdot nH_2O$	210	NA	
Miscellaneous tetrahedral[d]				
PM-15	$Na_6[Mo_6V_2O_{26}] \cdot nH_2O$	4.2	NA	
PM-117	$(iPrNH_3)_4[Se_2Mo_5O_{21}] \cdot nH_2O$	4.4	NA	
PM-118	$(iPrNH_3)_4[P_2Mo_5O_{23}] \cdot nH_2O$	460	NA	
Miscellaneous, octahedral[d]				
PM-5	$Na_6[NiMo_9O_{32}] \cdot nH_2O$[e]	14	NA	
PM-6	$Na_6[MnMo_9O_{32}] \cdot nH_2O$[e]	33	NA	
PM-13	$K_5NaH[Mo_9V_3O_{38}] \cdot 7H_2O$	4.4	NA	
PM-33	$(NH_4)_6[Cr_2Mo_{12}O_{42}] \cdot 20H_2O$	300	NA	

As seen in the three-dimensional structure, the anion consists of four europium atoms, one tetrahedral MoO_4^{2-} unit and four $Mo_7O_{24}^{6-}$ units. The $Mo_7O_{24}^{6-}$ unit is made up from seven MoO_6 octahedra in a structure identical to the anionic structures of ammonium heptamolybdate $(NH_4)_6(Mo_7O_{24})x4H_2O$. The virus inhibitory effect of $Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4)^{14-}$ is apparently due to its entire structure and the nature of peripheral metals and central heteroatoms since both MoO_4^{2-} and $Mo_7O_{24}^{6-}$ separately failed to exhibit anti-HIV-1 activity but $EuCl_3$ showed inhibition of HIV-1 cytopathic effect in MT-4 infected cells. Also this compound

was found good inhibitor of HIV's syncytium formation and herpes simplex viruses HSV-1 and HSV-2 [66]. Strangely, these good results weren't acclaimed in T.Yamase's 2005 article on anti-tumor, -viral, and –bacterial activities of polyoxometallates where he talked only about polyoxotungstates' potential for realizing an inorganic drug [49,50].

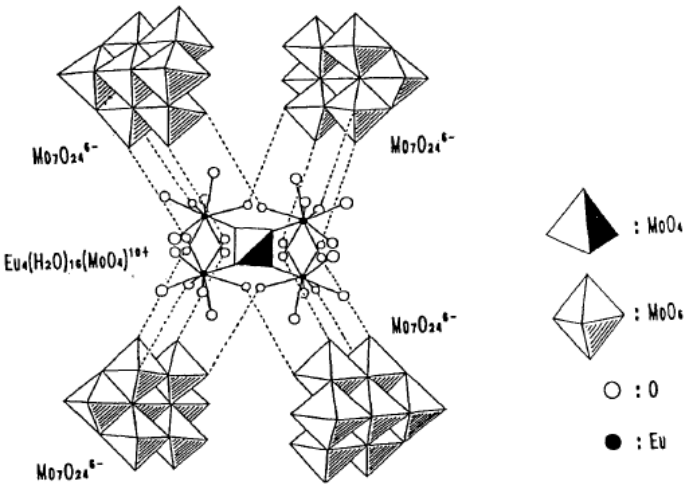

Fig.2.2.1. Structural features of the anion $(Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4)^{14-}$

2.3. Antibacterial properties

In a 2012 paper, C.Zollfrank *et al.* reported that different materials (polymers, metals) modified with MoO_3 presented antimicrobial surfaces. For example, Mo metal with oxidized surface had no microorganisms on it 12 h after being infected with *Staphyloccocus aureus* and *Pseudomonas aeruginosa*. MoO_2 loaded polymer exhibited noticeable antimicrobial activity as the surface of the sample was free of bacteria after 9 h. The activity drastically increased with the addition of MoO_3 particles to the polymer matrix. No infectious agents were detected after 3 h. The authors attribute this bacteria cell deterioration property to the formation of hydroxonium ions according to the reactions (2.3.1) and (2.3.2), suggesting the known fact that acidic surfaces slow down bacterial and fungal growth and effectively kill microorganisms at pH values of 3,5–4,0 [67].

$$MoO_3 + H_2O \rightleftharpoons H_2MoO_4 \quad (2.3.1)$$

$$H_2MoO_4 + 2H_2O \rightleftharpoons 2H_3O^+ + MoO_4^{2-} \quad (2.3.2)$$

Krishnamoorthy *et al.* also investigated MoO_3 and stated that it can be used as an effective antibacterial agent since the MoO_3 nanoplates that they synthesized had good minimum inhibitory concentration (MIC) against four bacterial species in comparison to the standard antibiotic *Kanamycin* (table 2.3.1).

Table 2.3.1.

MIC of MoO_3 nanoplates and kanamycin against Gram-negatice and Gram-positive bacterial strains. Experiments were performed in triplicate and the mean MIC value was reported.

Bacterial strains	MoO_3 nanoplates MIC (μg/mL)	Kanamycin MIC (μg/mL)
Gram-negative strains		
Escherichia coli	8	64
Salmonella typhimurium	8	64
Gram-positive strains		
Bacillus subtilis	8	128
Enterococcus faecalis	16	128

They demonstrated that this activity of MoO_3 nanoplates is due to the fact that it causes cell wall damage [68]. Later they showed the bacterial viability reduction property of surfaces coated with a MoO_3-based paint, and the MIC values against *E. coli*, *P. aeruginosa*, *S. aureus*, and *K. pneumoniae* were found to be 8, 8, 16, and 32 μgmL^{-1}, whereas the commercial antibiotic *Ciprofloxacin* exhibited a MIC of 16 (*E. coli*), 16 (*P. aeruginosa*), 128 (*S. aureus*), and 64 μgmL^{-1} (*K. pneumoniae*) respectively [69].

Table 2.3.2.

Zone of inhibition (mm) of MoO_3 nanoparticles against antibacterial pathogens

Organism	MoO_3 nanoparticles	Control
Antibacterial activity		
Escherichia coli	13.41 ± 0.41	4.21 ± 0.25
Bacillus subtilis	11.27 ± 0.37	3.15 ± 0.53

In a 2016 paper, A. Fakhri *et al.* reported high antibacterial activity of MoO_3 nanoparticles against Gram-negative and -positive bacteria (table 2.3.2) [46]. So molybdenum trioxide MoO_3 nanoparticles have recently been described to exhibit antimicrobial properties against pathogenic microbes, being activated under visible light. This motivated H.N. Nguyen *et al.* to design polymeric adhesives with MoO_3 nanoparticles deposited onto the surface, with the aim of producing useful antimicrobial coatings. According to them, coatings made of copolymer poly(DMA-co-MEA)* containing 50% MoO_3 particles manifested antimicrobial property, killing almost 100% of cells of *E. coli* and *B. subtilis* microbes (figure 2.3.1) by interfering with the cell's oxidation repair mechanisms. Moreover, such coating reduced biofilm formation from 13,7 $\mu m^3/\mu m^2$ to 0,1 $\mu m^3/\mu m^2$ when exposed to *E. coli*, *B. subtilis*, *P. aeruginosa* and *S. epidermidis* (figure 2.3.2). In addition, the aforementioned coatings seem biocompatible and absolutely nontoxic to human cells [70].

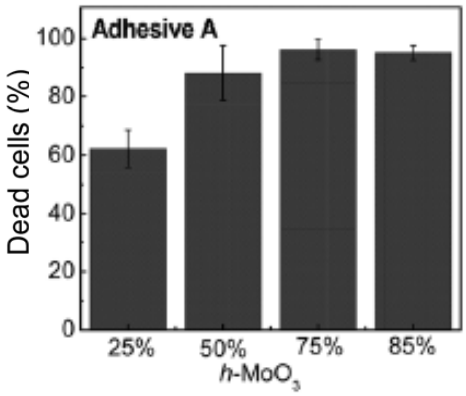

Fig.2.3.1. Selection of the best ratios of antimicrobials and their respective adhesive. The results using live and dead assays are expressed as the percentage of dead cells (2 h exposure).

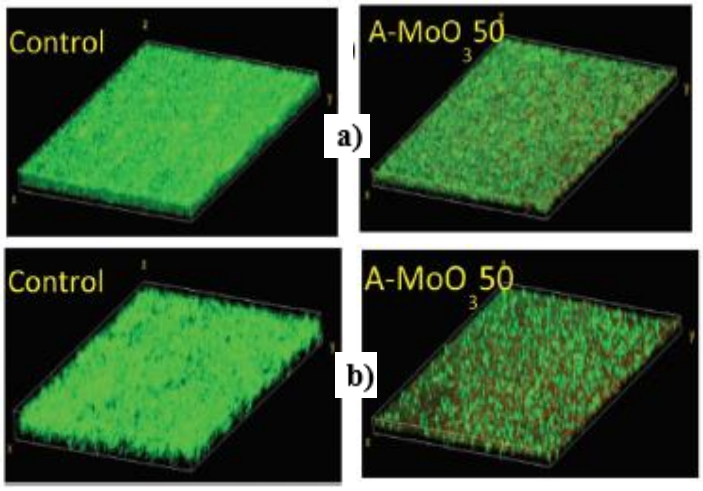

Fig.2.3.2. Images of biofilm thickness on the control and on adhesive A + 50% MoO_3 for E. coli (a) and B. subtilis (b).

Other papers show bactericidal activity of molybdenum sulfide MoS_2 nanostructures along with advantageous very low cytotoxicity [41,71], with MIC values 300 and 1000 μg/mL against *B. subtilis* and *E. coli* respectively. Samples treated with MoS_2 showed shrinkage in depth of biofilm thickness by 12,5 μm compared to the control [72]. A recent study show weak (compared to *Azithromycin*) antibacterial activity of mono-, bi- and polynuclear Mo^{VI} complexes(see figures 2.3.3 and 2.3.4 for structures) based on ONO benzoylacetone derived enaminone ligands (table 2.3.3) [73]. Polyoxomolybdates again take credit for biological properties, possessing also antibacterial properties. T. Yamase observed an enhancement of antibacterial activity of β-lactam antibiotics against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *S. aureus* (VRSA) for $K_4[SiMo_{12}O_{40}]\cdot 3H_2O$ (figure 2.3.5) through a synergistic effect, considering this surprising since most of the polyoxomolybdates were not effective against MRSA. In contrast to $K_4[SiMo_{12}O_{40}]\cdot 3H_2O$, the same structural Keggin polyoxomolybdate $Na_3[PMo_{12}O_{40}]\cdot H_2O$ which is unstable at physiological pH did not exhibit synergistic activity, implying that the structural stability of polyoxometallates at the physiological pH level is another factor for the biological activity [49,74,75].

Still, polyoxomolybdates are weaker antibacterial agents than other polyoxometallates (with W, V, Nb) as shown also by the correlation with the amount of POM incorporated inside the cell membrane of MRSA strains MRS394-1: a) W – 1,05±0,18 mg/g of dry weight of cell; b) Mo – 0,05±0,02 mg/g of dry weight of cell [50]. Anyway, the Keggin heteropolyacid $H_3PMo_{12}O_{40}$ exhibited bacteriostatic activity on *Escherichia coli* (Gram-negative) and *Bacillus subtilis* (Gram-positive) bacteria under UV irradiation. The concentration of inactivated cells (*E. coli*), after 20 minutes of UV-irradiation, was three orders of magnitude higher in the presence of 0.05 mM of the POM than in the presence of 12.5 mM of the control TiO_2. In the context of the discovery that POM-loaded chitosan (CT) improves POM uptake into the target cells, there were reported Chitosan-Polyoxomolybdates nanocomposites to have antibacterial properties.

* DMA = Dopamine methacrylamide; MEA = 2-methoxyethyl acrylate

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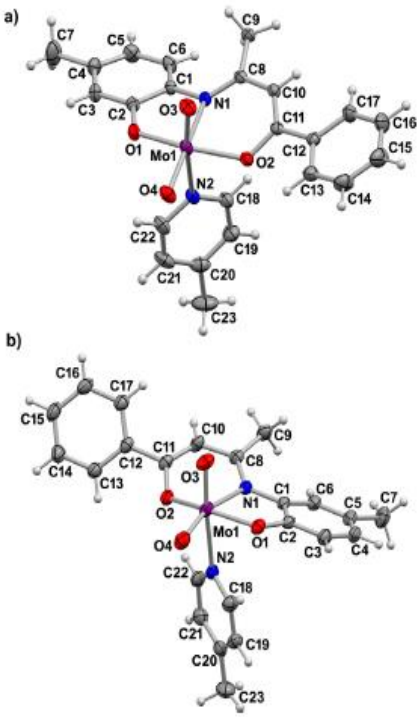

Fig.2.3.3. Mercury-POV-Ray rendered views of the asymmetric units of: (a) compound **1** and (b) compound **2** with the atom numbering scheme. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are presented as spheres of arbitrary radii.

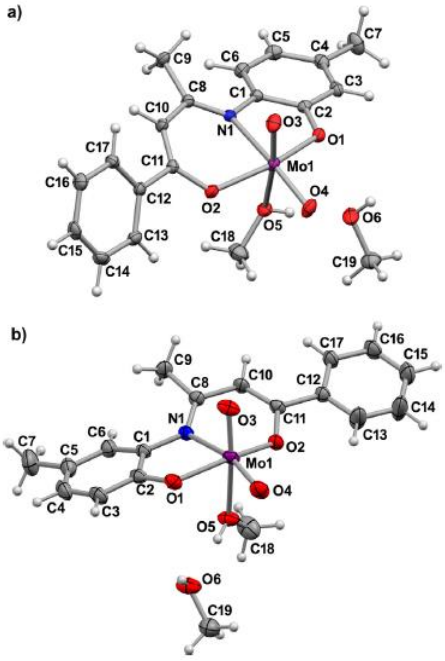

Fig.2.3.4. Mercury-POV-Ray rendered views, with the atom numbering scheme, of the molecular structures of: (a) compound **6** and (b) compound **7**. The two structures are shown as illustrative examples of the pyridine-based complexes. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are presented as spheres of arbitrary radii.

Table 2.3.3.

Antibacterial activity data for Mo(VI) complexes with enaminone ligands

Compound		MIC (μg/mL) on *M. catarrhalis* bacteria
1	$[MoO_2(L^i)(MeOH)]\cdot MeOH$	32
2	$[MoO_2(L^{ii})(MeOH)]\cdot MeOH$	32
3	$[MoO_2(L^{ii})(py)]$	32
4	$[MoO_2(L^i)(3\text{-Mepy})]$	32
5	$[MoO_2(L^{ii})(3\text{-Mepy})]$	64
6	$[MoO_2(L^i)(4\text{-Mepy})]$	64
7	$[MoO_2(L^{ii})(4\text{-Mepy})]$	64
8	$[\{MoO_2(L^i)\}_2(4,4'\text{-bpy})]$	64
9	$[\{MoO_2(L^{ii})\}_2(4,4'\text{-bpy})]$	64
10	$[MoO_2(L^i)]_n$	32
11	*Azithromycin*	0,06

For instance, CT-$H_3PMo_{12}O_{40}$ nanocomposite which is active against *E. coli*. An example where polyoxomolybdates are more efficient than polyoxotungstates in fighting bacteria is given by the same $[PMo_{12}O_{40}]^{3-}$ which was embodied in a hybrid CT-CTAB[iii] nanocapsule (figure 2.3.6) and this capsule was

H_2L^i = 3-(2-hydroxy-4-methylphenylamino)-1-phenylbut-2-en-1-one;
H_2L^{ii} = 3-(2-hydroxy-5-methylphenylamino)-1-phenylbut-2-en-1-one)
[iii] CTAB = cetyltrimethylammonium bromide

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considerably efficient against *E. coli*, (reducing cell viability by approximately 85% with 50 μg/mL of compound) while the analogue capsule with the polyoxotungstates was inactive. When this POM $[PMo_{12}O_{40}]^{3-}$ is used to functionalize the surface of Ag and Au nanoparticles, an enhancement in bactericidal activity is reached: + 49 % with silver and + 42 % with gold nanoparticles. If $[PMo_{12}O_{40}]^{3-}$ is integrated into an amino acid-/peptide-POM nanocomposite again an improve in antibacterial property is observed as $(HGly)_3[PMo_{12}O_{40}](Gly)_9$ (Gly = glycine), $(HLys)_9[PMo_{12}O_{40}](Lys)_4$ (Lys = lysine) and $(HHis)_3[PMo_{12}O_{40}](His)_3$ (His = histidine) produced *E. coli* inhibition zones of ~1,2-1,3 cm on solid growth agar plates. This extraordinary POM – $[PMo_{12}O_{40}]^{3-}$ amplifies its antibacterial activity when integrated into many composite systems like POM-PVA/PEI (poly(vinylalcohol)/polyethylenimine) membranes, POM-bamboo charcoal, POM-methylene blue multilayer films [75].

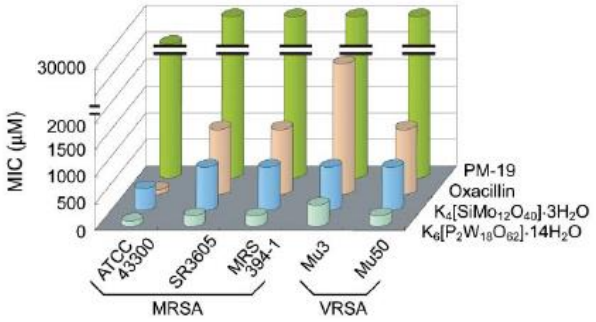

Fig.2.3.5. MIC values of three POMs and oxacillin for a variety of both MRSA and VRSA

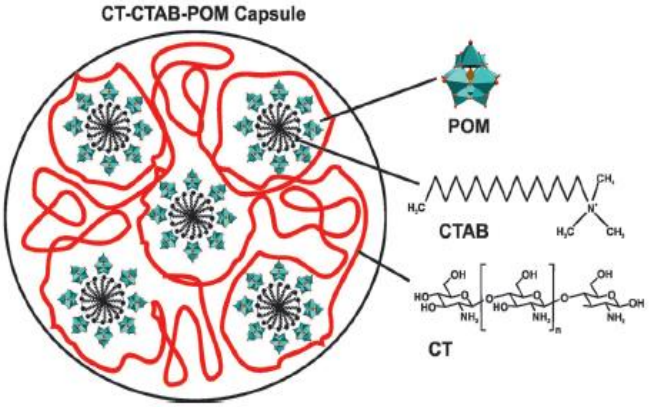

Fig.2.3.6. Scheme of the CT-CTAB-POM capsule. POM = $[PMo_{12}O_{40}]^{3-}$or $[PW_{12}O_{40}]^{3-}$.

2.4. Other properties

Molybdenum trioxide MoO_3, along with its other reported properties (antitumor, antimicrobial) seems to be also an excellent antioxidant. MoO_3 scavenged more $ABTS^{\bullet+}$ radical cation with the increase in concentration (in the diapason 0.125 – 1 mM), so that at 1 mM it reached maximum inhibition 82,54% (figure 2.4.1) [46]. Antioxidant activity was tested for some other Mo complexes of pyridoxal Schiff base derivatives: $[(MoO_2)(pysb^{i})(H_2O)]$ (**1**), $[MoO(pysb)]_n$ (**2**), [MoO(pysb)bpy] (**3**), and $[(MoO_2)(pytol^{ii})_2]$ (**4**). The DPPH radical scavenging activity of the complexes have been investigated and only compound (**4**) had a weak antioxidant activity: the obtained IC_{50} value was 80 μM compared to 52 μM for the standard antioxidant ascorbic acid (*Vitamin C)* [76].

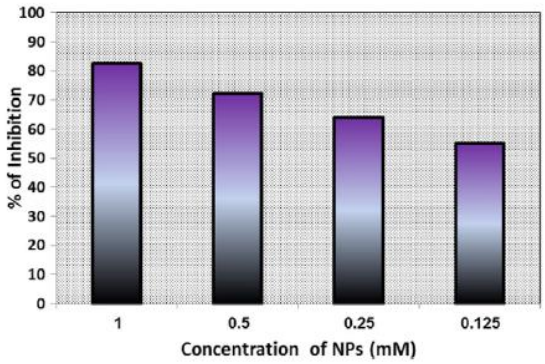

Fig.2.4.1. Percentage of inhibition MoO3 nanoparticles (NPs) for antioxidant activity.

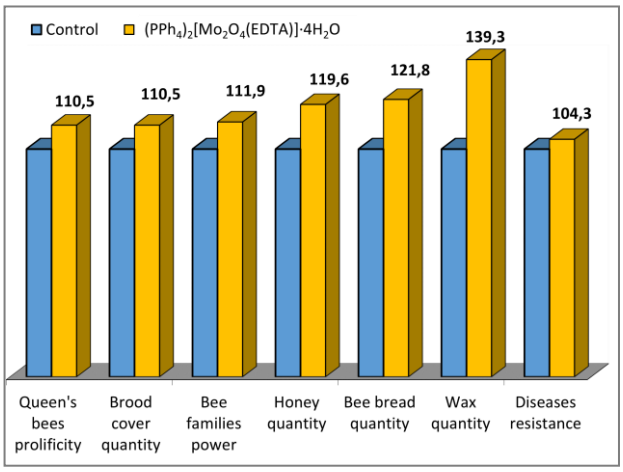

Fig..4.2. Increase (values in %) in morpho-productive parameters of Apis mellifera honey bees due to $(PPh_4)_2[Mo_2O_4(EDTA)]\cdot 4H_2O$ compared to control.

[i] H_2pysb = Pyridoxal-S-benylhydrazinodithicarbazate
[ii] Hpytol = Pyridoxal-p-toluidine

Some very impressive discoveries regarding biological applications of inorganic compounds with molybdenum come from a collaboration between Versailles Saint-Quentin-en-Yvelines University, Moldova State University and the Institute of Zoology from Moldova. An international team of chemists and biologists from the above-mentioned research institutions have recently found that the compound $(PPh_4)_2[Mo_2O_2S_2(IDA)_2]\cdot 2,8H_2O$ can increase the antioxidant activity of *Spirulina platensis* cyanobacteria by regulating its acidic and sulfated polysaccharides ratios. Thus, a cultivation media including 0,02 – 0,03 g/L of this coordination compound multiplies the composition of acidic polysaccharides by 1,38 – 1,43 times and sulfated polysaccharides by 1,76 – 2,0 times, compared to MoO_3 solution [77]. The second study of this team was about the action of another molybdenum compound, $(PPh_4)_2[Mo_2O_4(EDTA)]\cdot 4H_2O$, on *Apis mellifera* bee colonies and their results were remarkable. It appears that sugar syrup containing a very small quantity of $(PPh_4)_2[Mo_2O_4(EDTA)]\cdot 4H_2O$ (mixture of 1 mg% aqueous solution of compound with sugar syrup in a 2:100 ratio) given to bee families during the 3 weeks feeding period can boost their productivity in honey (+20%), wax (+39%) and bee bread (+22%). It is suggested that this bioactive molybdenum compound has a stimulating impact on queen bee's reproductive system and not only the colony gets bigger, but also their resistance to diseases becomes higher (figure 2.4.2) [78].

Conclusions

To conclude, it shall be said that molybdenum is definitely an element whose chemical combinations possess interesting red-ox properties. In nature, in spite of the trace amounts, molybdenum found its way into the living organisms and became a key element for essential biological processes and in the biogeochemical cycle of nitrogen. Scientists learned to explore and harness multiple biological properties (antitumor (**AT**), antiviral (**AV**), antibacterial (**AB**) and antioxidant (**AO**)) from various molybdenum compounds: molybdenum sulfide (**AT + AB)**, molybdenum oxides (**AT + AB + AO**), Mo-based (functionalized)POMs (**AT + AB + AV**), various molybdenum complexes (**AT + AB + AO**), molybdenum clusters and composites (**AT + AB**). These extraordinary results would encourage and inspire more scientists to find many more biological and biomedical applications for molybdenum.

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Data about author:
Arcadie FUIOR, PhD, Moldova State University and Université de Versailles Saint-Quentin-en-Yvelines.
E-mail: arcadiefuior@gmail.com

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