Polyoxometalates in Medicine

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I. Introduction

This issue of *Chemical Reviews* is a testimonial to the diversity and richness of polyoxometalate chemistry. Polyoxometalates (henceforth POMs for convenience) are early transition metal oxygen anion clusters. More specifically, they are oligomeric aggregates of metal cations (usually the d^0 species V(V), Nb(V), Ta(V), Mo(VI), and W(VI)) bridged by oxide anions that form by self-assembly processes.[1−4] The number of POMs reported in the literature is still increasing with time, rendering a comprehensive review of all their physical, chemical and biological properties problematical. Most of the fundamental chemical and physical properties of POMs have been addressed in the other articles in this issue; this article addresses the interface of POM chemistry and medicine. While an on-line Boolean search of Chemical Abstracts (intersection of "polyoxo", "polyanion", and related terms with a large number of biological terms) produced 471 citations, a great majority of these publications were only peripherally relevant. Another group of papers, none of recent vintage, were omitted as they failed to provide definitive structural/electronic or biological information relevant to the title topic. In addition, the experimental sections in some of these papers do not unequivocally define the particular POM examined. It is likely in some cases that a mixture of POMs was submitted to biological evaluation.

There are two generic families of POMs, the isopoly compounds, (also called isopolyanions or isopolyoxometalates) that contain only the d^0 metal cations and oxide anions and the heteropoly compounds (also called heteropolyanions or heteropolyoxometalates) that contain one or more p-, d-, or f-block "heteroatoms" in addition the other ions.[1,2] The heteroatoms in the heteropoly compounds can reside in either buried (not solvent accessible) or surface (solvent accessible) positions in the POM structure. Over half of the elements in the periodic table are known to function as heteroatoms in heteropoly compounds. As heteropoly compounds are more numerous and their structural and electronic properties are easier to modify synthetically than those of the isopoly compounds, the former have dominated the medically oriented research on POMs to date. Representative structural families of POMs addressed in context with biological issues are illustrated in Figure 1.

Several general attributes of POMs render them attractive for applications in medicine, while one property renders them unattractive. The principal advantageous feature of POMs is that nearly every molecular property that impacts the recognition and reactivity of POMs with target biological macromolecules can be altered. These include polarity, redox potentials, surface charge distribution, shape, and acidity. Another attractive feature is that rational and reproducible synthetic methods are now available for the replacement of one or more of the skeletal d^0 early transition metal cations in POMs with d- or p-block ions and also for the covalent attachment of organic groups to POMs via linkages that are compatible with physiological conditions (long half-lives in H_2O or buffers at pH ~7). Both metal substitution and organic derivatization extend considerably the number of POMs that are potentially available. Pendent organic/biological groups could be used to

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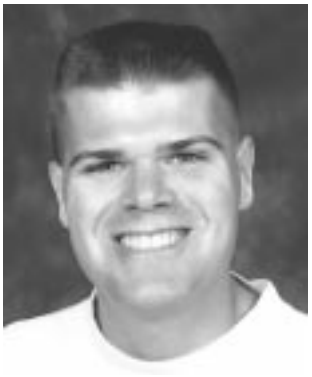

Jeffrey T. Rhule was born in 1974 in Southwestern Ohio. He graduated with a B.A. in Chemistry, *cum laude*, from Thomas More College, Crestview Hills, KY. As an undergraduate, Mr. Rhule participated in a NSF-REU at the University of Kentucky, Lexington, KY. While at UK, he studied radioanalytical chemistry under Professor J. D. Robertson. He is currently in his second year at Emory University, Atlanta, GA, studying under the tutelage of Professor Craig L. Hill. His area of research interest is the direct application of inorganic chemistry to address societal challenges and problems. Specifically, he is interested in the use of polyoxometalates in biology and medical applications.

Craig L. Hill was born in Pomona, CA, in 1949. He received his Ph.D. from M.I.T. in 1975 under the direction of George M. Whitesides. After a NSF postdoctoral fellowship at Stanford with Richard H. Holm and an Assistant Professorship at the University of California at Berkeley, he joined the faculty at Emory University where he is currently Goodrich C. White Professor. His research interests include the design of catalysts for challenging or environmentally benign processes, the design of catalytic systems that buffer themselves, repair damage, and catalyze more than one reaction ("intelligent" catalysts), and in general the chemistry of large multicomponent and multifunctional molecules such as polyoxometalates, the subject of this volume of *Chemical Reviews* edited by him. His recent awards include a Humboldt Senior Scientist Award (1995), the USDA National Award for Group Excellence in Research (shared with Drs. I. A. Weinstock, R. Atalla, and R. Reiner of the Forest Products Laboratory) (1996) for the development of a new pollution-free catalytic aerobic technology to convert trees (wood pulp) to paper, and the Albert E. Levy Award from Sigma Xi (1996). Currently or recently he has served several journals (editing or editorial boards) and national panels (NAS, NSF, and NIH). This article targets another interest he shares with collaborators, the design of multifunctional clusters as multiply interacting inhibitors of HIV protease and other targets in disease-causing entities. He enjoys time with his domestic and research families and yearly mountaineering and other adventures in the Americas and Eurasia.

modulate bioavailabilities, increase recognition (selective binding usually under kinetic control) of key substructures in target biomacromolecules, and enhance the facility of drug formulation. To date, there are only two or three papers involving the biological properties of POMs derivatized with organic groups so this is largely uncharted technical territory.

The principal disadvantage of POMs vis-à-vis medicine is that they are not organic species. Low molecular weight organic species dominate in the

Deborah A. Judd was born in Rochester, NY, in 1967 and received a B.S. from the SUNY at Geneseo in 1989, a M.S. from Rochester Institute of Technology (R.I.T.) in 1991 under the supervision of Ellis Bell, and a Ph.D. from Emory University under the supervision of Craig L. Hill. At R.I.T. her work included measuring the reactivity of Lys-126 in the active site of glutamate dehydrogenase (GDH) using enzyme kinetics and the enzymatic synthesis of a Se-$NADP^+$ analog for X-ray structure determination of GDH. Her work in Dr. Hill's group introduced her to polyoxometalate (POM) chemistry and the use of POMs as antiviral agents and as homogeneous redox catalysts. While working in Dr. Hill's group she synthesized and characterized novel POMs including niobium-containing derivatives and investigated their catalytic oxidation and antiviral properties. She has investigated POM inhibition of the HIV enzymes reverse transcriptase and protease and the interaction between CD4 and gp120. She is currently a Plant Support Chemist at Ciba Specialty Chemicals.

Dr. Schinazi is Professor of Pediatrics and Chemistry and Director of the Laboratory of Biochemical Pharmacology at Emory University. He serves as the Research Career Scientist and Scientific Director at the Georgia Research Center on AIDS and HIV Infections. Dr. Schinazi received his Ph.D. in Chemistry from the University of Bath in 1976. He secured a postdoctoral position in pharmacology at Yale University with Dr. W. H. Prusoff in 1976. From 1978 to 1980, Dr. Schinazi was a postdoctoral fellow in infectious disease and immunology at Emory University. Dr. Schinazi joined the Department of Pediatrics faculty at the Emory University School of Medicine in 1981. He has served on study sessions for the NIH and various other funding agencies and is currently on the editorial board of five journals dealing with anti-infective agents, including *Antimicrobial Agents and Chemotherapy*, *Antiviral Research*, *Antiviral Chemistry and Chemotherapy*, *Antiviral Therapy*, *International Antiviral News*. In 1996, Dr. Schinazi was nominated and served on the Presidential Commission on AIDS. He has focused his research on the discovery of novel antiviral agents and the development of combined modalities to combat drug resistance. He has been involved in the discovery and development of several anti-HIV and antihepatitis B virus compounds including 3TC, (–)-FTC, DXG, DAPD, D4T, CS-92, water-soluble buckyballs, porphyrins, and polyoxometalates. His group was the first to publish on the mutation at codon 184 of the HIV reverse transcriptase associated with oxathiolane L-nucleosides such as 3TC, and continues to be interested in drug resistance associated with antiviral agents effective against HIV, HBV, herpesviruses, and cytomegalovirus.

pharmaceutical industry (drug discovery, synthesis, and development). An intrinsic counterpoint here involves the vast third world markets and their attendant requirements for pharmaceuticals. Most of the recently developed and optimally efficacious

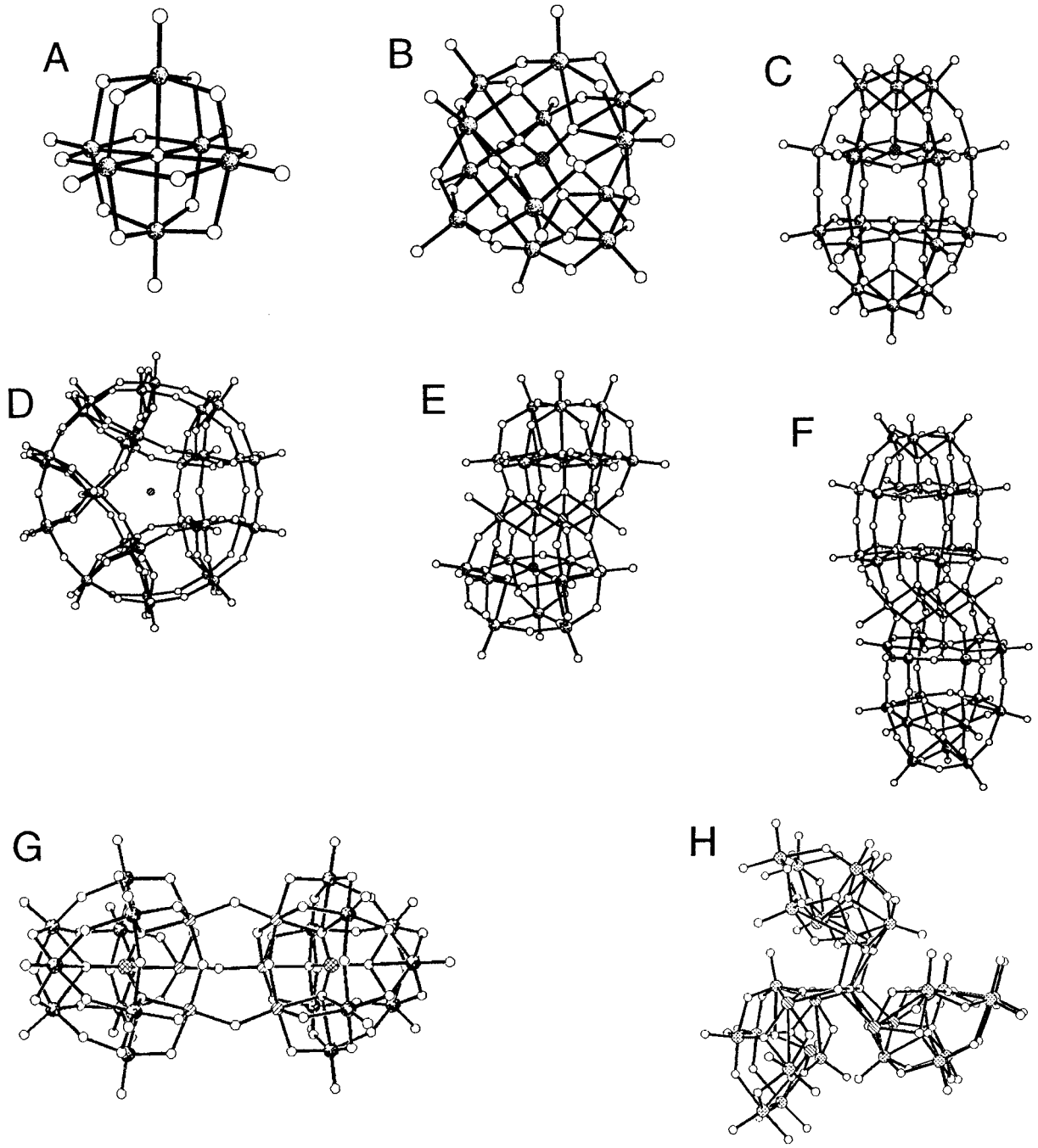

Figure 1. Atom notation ("ball-and-stick") drawings of 8 representative structural families of POMs: (A) the hexametalate structure, $[M_6O_{19}]^{x-}$ (the charge, *x*, depends on M); (B) common Keggin structure, $[XW_{12}O_{40}]^{x-}$ (the charge, *x*, depends on the heteroatom, X) (most antiviral POMs are of this structural class); (C) the Wells−Dawson structure, $[X_2W_{18}O_{62}]^{x-}$ (*x* depends on X); (D) the Pope−Jeannin−Preyssler (PJP) structure, $[MP_5W_{30}O_{110}]^{x-}$ (*x* depends on the central metal ion, M); (E) the trivacant Keggin-derived sandwich complex, $[(M^{II})_2(M^{II}L)_2(PW_9O_{34})_2]^{10-}$; (F) the trivacant Wells−Dawson-derived sandwich complex, $[(M^{II})_2(M^{II}L)_2(P_2W_{15}O_{56})_2]^{16-}$; (G) the double-Keggin structure, $[\{A\text{-}\alpha\text{-}SiO_4W_9O_{30}(OH)_3M_3\}_2(OH)_3]^{11-}$ (some of the most effective antiviral agents are of this class); and (H) HPA-23, $[NaSb_9W_{21}O_{86}]^{18-}$. Atom designations: O = open circle; W = dotted; heteroatoms = parallel lines or crossed hatched.

pharmaceuticals including anti-HIV agents are prohibitively expensive for such markets. As POM-based pharmaceuticals are much less expensive and more amenable to scale-up than the great majority of organic pharmaceuticals, their development might positively impact these large and growing markets in the emerging world.

Two general types of POM activity, antiviral and antitumoral, have dominated the medicinal chemistry of these compounds to date. A third area of POM activity has been demonstrated recently. When used in combination with β-lactam antibiotics, polyoxotungstates enhance the antibiotic effectiveness against otherwise resistant strains of bacteria.[5] While this new area is interesting and deems further examination, this review focuses on the antiviral and antitumoral research starting with the antiviral work which is older, more developed and better understood than the anticancer work. Research has also focused on the antiviral properties of POMs because they are

generally nontoxic to normal cells. Much of the information in this review is in the tables. Comments addressing technical concerns are provided for most of the investigations summarized in the tables. The subsequent two sections of the text provide material of value in reading the text and large tables. Section II provides a list of the abbreviations used in the review, and section III discusses the evidence as to whether POMs penetrate membranes and get into cells. The latter is a matter of direct relevance to the development of drugs that target biomolecules intracellularly including HIV-1 protease and reverse transcriptase inhibitors. Brief reviews of some of this material have recently appeared.[6−8]

II. Abbreviations

Various abbreviations are used throughout the text and tables.

5-FU	5-fluorouracil
AAG	α_1-acid glycoprotein
ACNU	nimustine; 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-3-nitrosourea
ADM	adriamycin, doxorubicin hydrochloride
ATP	adenosine 5′-triphosphate
AIDS	acquired immunodeficiency syndrome
AMV RT	avian myeloblastosis reverse transcriptase
AZT	3′-azido-3′-deoxythymidine (Zidovudine)
BT	borotungstate, $[BW_{12}O_{40}]^{5-}$
C3H/3T3	malignant C3H/3T3 mouse cells MO4
C3HBi	tumor-resistant mouse cell line
CD4	T-helper membrane molecule that recognizes class II MHC molecule
CER	chick embryo related
CMV	cytomegalovirus
DNA P	deoxyribonucleic acid polymerase
D*x*	time of injection abbreviation, where *x* is the number of days after infection (e.g., D0 is the day of infection, D−1 is 1 day prior to infection, etc.)
E_6SM	human embryonic skin-muscle fibroblasts
EBTr	bovine embryonic trachea cells
EBV	Epstein−Barr virus
EC_{50}	effective concentration; concentration which supresses virus by 50%
EMC	encephalomyocarditis
EPR	electron paramagnetic resonance
FLV	Friend leukemia virus
FluV-“x”	influenza virus, strain “x”
gp120	glycoprotein 120 (a 120 kDalton HIV protein)
HeLa	adenocarcinoma from cervix of 31 year-old black woman; epithelial morphology
HEp-2	human larynx epidermoid carcinoma cells
HIV	human immunodeficiency virus
HIV-1 RT	HIV type 1 reverse transcriptase
HIV-1 P	HIV type 1 protease
HMV-2	melanoma cell line
HPA-23	$(NH_4)_{17}Na[NaSb_9W_{21}O_{86}]$
HSV	herpes simplex virus
ic	intracerebrally
IC_{50}	inhibitory concentration; concentration where cellular toxicity is 50%
im	intramuscularly
ip	intraperitoneally
iv	intravenously
LD_{50}	dose resulting in 50% death
LDL	low-density lipoprotein
Ma 104	embryonic African green monkey kidney cells
MDCK	Madin−Darby canine kidney cells
MEF	mouse embryo fibroblast
MLSV	murine leukemia sarcoma virus
MLSV RT	MLSV reverse transcriptase
MMC	mitomycin C, mutamycin
MOLT-4	acute lymphoblastic leukemia, T-cell origin, human 19-year-old male; has high levels of terminal deoxynucleotidyl transferase (TdT)
MPSV	myeloproliferative sarcoma virus
mRNA	messenger RNA
MSW	mean spleen weight
MT2	human T-cell leukemia from cord blood, cocultured with cells from patients with adult T-cell leukemia, HTLV-1 transformed
MT-4	human T-cell leukemia isolated from patients with adult T-cell leukemia, HTLV-1 transformed
NADH	nicotinamide adenine dinucleotide (H)
PBMC	peripheral blood mononuclear cells
POM	polyoxometalate
PTMC	a combination of phosphotungstic acid, $H_3[PW_{12}O_{40}]$, phosphomolybdic acid, $H_3[PMo_{12}O_{40}]$, and caffeine
PV	plasma variant of Moloney murine sarcoma virus
RLV	Rauscher leukemia virus
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RT	reverse transcriptase
RV	rabies virus
sc	subcutaneously
SD_{50}	viral dosage required to result in leukamatic spleens for 50% of test population
SI	therapeutic (selectivity) index, usually IC_{50}/EC_{50}
SIV	simian immunodeficiency virus
ST	silicotungstate, $[SiW_{12}O_{40}]^{4-}$
SRC	subrenal capsule
TA	tungstoantimoniates, $[SbW_xO_y]^{z-}$
TAs	tungstoarsenates, $[AsW_xO_y]^{z-}$
TS	tungstosilicates, $[SiW_xO_y]^{z-}$
VSV	vesicular stomatitis virus
VZV	varicella-zoster virus
Vero	normal African green monkey kidney cells

III. Cellular Penetration of Polyoxometalates

The degree of cellular penetration and localization of a drug directly impacts its mechanism of viral inhibition and other biological attributes. As POMs have been reported to be active at both the cell surface and in the cytoplasm, we first summarize the evidence as to whether POMs penetrate cells. Certainly given their size and charge (3− to 20− or more) it would be surprising if they did penetrate the cellular membrane.

Several lines of evidence using different techniques and types of experiments indicate that POMs do, in fact, cross cell membranes. Raman laser spectroscopy was used by Cibert et al. to provide evidence for HPA-23 entering C3HBi fibroblast cells.[9] HPA-23 is a polytungstoantimoniate of formula $[NaSb_9W_{21}O_{86}]^{18-}$ (usually the $(NH_4)_{17}Na$ salt) that dominated much of the early antiviral research on POMs (vide infra). HPA is an acronym for “het-

eropoly acid" and 23 is the molecular weight of the Na ion in the center of the structure. The structure of HPA-23, reported by Weiss and co-workers in 1976, indicates it has C_{3h} molecular symmetry with 6 possible sites where additional metal ions could bind.[10−12] The HPA-23-treated cells showed a band at 947 cm^{-1} that was clearly attributable to a W−O−W stretching mode of HPA-23 (this stretching band for HPA-23 as a solution or a crystalline solid occurs at 937 cm^{-1}). Examination of the treated cells by photonic microscopy revealed hexagonal cellular precipitates in the cytoplasm that resembled HPA-23 crystals in morphology. In addition, X-ray fluorescence of these precipitates indicated the presence of tungsten.[9] Electron probe (electron microscopy) analysis was used by Berry and Galle to detect POMs in cells taken from rats treated with HPA-23.[13] These investigators found cytoplasmic precipitates with the same W/Sb ratio as HPA-23 concentrated in the intracytoplasmic lysosomes of various cell-proximal tubule cells of the kidney, thymus, bone marrow, and spleen, and localizing in the macrophages. On the basis of the elemental analyses (W/Sb ratio) Berry and Galle argued, reasonably, that HPA-23 remained intact, at least in the cellular precipitates. Electron probe analysis failed to show any HPA-23 in the nucleus.

Cholewa et al. used a scanning proton microprobe to confirm the presence of $[Co_4(H_2O)_2(PW_9O_{34})_2]$,[10−] a sandwich-type heteropolytungstate, inside the cellular membrane of human peripheral blood mononuclear cells (PBMC).[14] These investigators made two observations consistent with the POM remaining intact inside the cells: first, the W/Co ratio remained the same as that in the intact POM, and second, both elements were located in the same area of the cell. The activity of POMs against HIV-1 was determined to be lower in PBM cells than in MT2 cells. Initially, it was thought the lower activity in PBM cells was a result of either the failure of the POM to penetrate the cell or the instability of the POM once inside the cell. The authors ruled out both scenarios, however, when the intact POM was detected inside the PBM cell.

In a subsequent study, Cholewa et al. addressed the uptake and concentration of heteropolytungstates and non-POM chromium compounds into various cell lines again using a scanning proton microprobe.[15] Treated cells were freeze-dried and the concentration of the metals inside the cells was calculated on the basis of the assumptions that the diameter of the control and treated cells remained constant, the cellular density was 1 g/mL, and the POM remained intact once inside the cell. Cholewa et al. found initial uptake of heteropolytungstates into Vero cells was rapid, but then declined as it approached a saturation point after 2 h. The concentration of the heteropolytungstates within cells varied from 120 to 820 ng/mL, 1 order of magnitude lower than the drug concentration in the cell medium.

Fluorescence microscopy was used by Ni et al. to detect an increase in the number of vacuoles within POM-treated J774 cells, indicative of POM transport into the cell.[16] To determine whether macrophages were involved in the transport of POMs, Ni and her group used ^{125}I-labeled acetyl-LDL to show that POMs inhibited acetylated LDL uptake by half. Since macrophages generally facilitate the removal of polyanionic macromolecular ligands including acetylated LDL, Ni and co-workers suggested that POMs may bind to the scavenger receptor and be moved into the cell by endocytosis.[16] Electron-dense particles similar to those reported by Cibert and Jasmin[9] were detected by transmission electron microscopy. Energy dispersive spectroscopy X-ray microanalysis was unable to definitively confirm the presence of POMs in the cell membrane, although wavelength dispersive spectroscopy X-ray microanalysis did indicate that W was present within the cell. Scanning electron microscopy showed no difference in the ultrastructure of the treated and untreated cells.[16]

IV. In Vitro Antiviral Studies of Polyoxometalates

A. Early Studies

The antiviral activity of POMs was reported as early as 1971. Raynaud et al. noted that polytungstosilicate heteropoly compounds inhibited murine leukemia sarcoma virus in vitro.[17] Much of the early work focused on these polytungstosilicates and HPA-23.

Prior to 1990, in vitro studies conducted by various groups showed the efficacy of these POMs against several viruses: murine leukemia sarcoma (MLSV), vesicular stomatitis (VSV), polio, rubella, Rauscher leukemia (RLV), Rabies (RV), Rhabdovirus, and Epstein−Barr (EBV).[17−26] Polytungstosilicate heteropoly compounds showed significant promise against VSV, MLSV, rubella, RLV, and polioviruses. Most of these POMs showed good inhibitory activity with low cytotoxicity, in a variety of cell lines.[17−19,21,22] HPA-23 was shown to be an effective antiviral agent against MLSV, RV, rhabdovirus, and EBV at doses nontoxic to cells.[22−26] Because HPA-23 exhibited sufficiently promising results in vitro,[27] it was reasoned that it might be effective against human immunodeficiency virus, HIV, the causative agent of AIDS. The results of clinical trials were less than promising. When administered to four patients with AIDS, Rozenbaum et al. reported a reduction in the surrogate markers for HIV.[27] However, subsequent clinical trials with HPA-23 conducted by two different groups, Moskovitz et al. in the United States and Burgard et al. in France, failed to show significant reduction of HIV as measured by HIV p24 antigenemia. The low antiviral activity coupled with the marked toxicity of HPA-23 (hepatotoxicity, renal toxicity, and thromobocytopenia) rendered further trials of the drug unacceptable.[28,29] These results prompted several groups to develop less toxic POM antiviral agents that could be effective against HIV.

B. Cell Culture Studies, an Overview

Table 1 summarizes nearly all the published data on the antiviral activity and toxicity of POMs in cell culture. The table is arranged primarily by POM so

Table 1. In Vitro Antiviral Activities of Polyoxometalates

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[A\text{-}\alpha\text{-}SiNb_3W_9O_{40}]^{7-}$							
K_7[62]	RSV	Ma 104	0.5	>100			CPE inhibition assay
	RSV	Ma 104	0.7	80			neutral red assay
	RSV, strain A2	Ma 104	2	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	10	>100			neutral red assay
K_7[72]	FluV-A/Texas	MDCK	0.95	>100			mean IC_{50} and EC_{50} values were
	FluV-A/NWS	MDCK	17	>100			determined by NR dye uptake
	FluV-A/Beijing	MDCK	48	>100			
	FluV-A/ Port Chalmers	MDCK	26	>100			
	FluV-B/Panama	MDCK	6.8	>100			
	FluV-B/Hong Kong	MDCK	13	>100			
$[Me_3NH]_7$[47]						3.8	assayed using NENQUEST system
$[SiTaW_{11}O_{40}]^{5-}$							
$[Me_3NH]_5$[47]						21.5	assayed using NENQUEST system
$[SiNbW_{11}O_{40}]^{5-}$							
$[Me_3NH]_5$[47]						48.6	assayed using NENQUEST system
$[\alpha\text{-}GeW_{12}O_{40}]^{4-}$							
K_4[45]	FluV-A/Ishikawa	MDCK	4.5	>100			
$[(O_3POPO_3)_4W_{12}O_{36}]^{16-}$							
K_{16}[84]					4.3		HIV-1 RT
					3.5		MSLV RT
					63.0		AMV RT
Na_{16}[84]					5.2		HIV-1 RT
					6.2		MSLV RT
					>300		AMV RT
$[Eu(P_2W_{17}O_{61})_2]^{17-}$							
K_{17}[42]	$HIV\text{-}1_{IIIB}$	MT-4	11.6	42.0			
K_{17}[42]	$HIV\text{-}1_{SF-2H}$	MT-4	5.0	83.5			
$[V_4O_{12}]^{4-}$							
$(t\text{-}BuNH_3)_4$[42]	$HIV\text{-}1_{IIIB}$	MT-4		2.4			
$[W_7O_{24}]^{6-}$							
K_6[34]	$HIV\text{-}1_{IIIB}$	MT-4		>800			
$[W_{12}O_{42}]^{10-}$							
Na_{10}[42]	$HIV\text{-}1_{IIIB}$	MT-4		208			
$[H_2W_{12}O_{42}]^{10-}$							
K_{10}[32]	$HIV\text{-}1_{LAI}$	PBMC	2.5	>100			
$[H_2W_{12}O_{40}]^{6-}$							
Na_6[32,43]	$HIV\text{-}1_{LAI}$	PBMC	0.34	>100			
$[BW_{12}O_{40}]^{5-}$							
$(NH_4)_nH_{(5-n)}$[62]	RSV	Ma 104	6	40			CPE inhibition assay
	RSV	Ma 104	6	>50			neutral red assay
$(NH_4)_5$[62]	RSV	Ma 104	1.0	56			CPE inhibition assay
	RSV	Ma 104	0.7	63			neutral red assay
$(ArgH^+)_5$[62]	RSV	Ma 104	1	20			CPE inhibition assay
	RSV	Ma 104	<0.6	22			neutral red assay
K_5[34,41,42]	$HIV\text{-}1_{IIIB}$	MT-4	17.5	194			
					19*		*percent inhibition at 50 μg/mL
$\alpha,\beta\text{-}H_5$[32]	$HIV\text{-}1_{LAI}$	PBMC	0.46	126			
$(NH_4)_nH_{(5-n)}$[32]	$HIV\text{-}1_{LAI}$	PBMC	3.2	>100			
K_5[32]	$HIV\text{-}1_{LAI}$	PBMC	0.36	>100			
$(NH_4)_5$[32]	$HIV\text{-}1_{LAI}$	PBMC	6.69	>100			
Na_5[32]	$HIV\text{-}1_{LAI}$	PBMC	3.61	>100			
$(HisH^+)_nH_{(5-n)}$[32]	$HIV\text{-}1_{LAI}$	PBMC	>10	>100			
$(LysH^+)_nH_{(5-n)}$[32]	$HIV\text{-}1_{LAI}$	PBMC	3.0	>100			
$(ArgH^+)_nH_{(5-n)}$[32]	$HIV\text{-}1_{LAI}$	PBMC	0.58	328			
Na_5[94]	vaccinia	MEF	25**	>400			**EC_{100} value is reported
$(HisH^+)_nH_{(5-n)}$[47]						12.5	assayed using NENQUEST system
$(LysH^+)_nH_{(5-n)}$[47]						58.4	assayed using NENQUEST system
$(ArgH^+)_nH_{(5-n)}$[47]						26.1	assayed using NENQUEST system
K_5[36]	$HIV\text{-}1_{IIIB}$	MT-4	0.2	>80			
	$HIV\text{-}1_{RF}$	MT-4	2.6	>80			
	$HIV\text{-}1_{HE}$	MT-4	0.2	>80			
	$HIV\text{-}2_{ROD}$	MT-4	0.2	>80			
	$HIV\text{-}2_{EHO}$	MT-4	0.1	>80			
	SIV_{MAC251}	MT-4	0.003	>80			
	MLSV, cell transformation	C3H/3T3	4.6	>80			
	$HIV\text{-}1_{IIIB}$, giant cell formation	MOLT-4	13.2	>80			
	$HIV\text{-}2_{ROD}$, giant cell formation	MOLT-4	0.7	>80			

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[BW_{12}O_{40}]^{5-}$							
K_5[36]	Sindbis	Vero	6.6	>80			
	Semliki Forest	Vero	99	>80			
	measles	Vero	19.8	>80			
	RSV	HeLa	1.3	>80			
	ParaFluV	Vero	>132	>80			
	Junin	Vero	5.3	>80			
	Tacaribe	Vero	7.9	>80			
	VSV	HeLa	28.1	>80			
	polio-1	HeLa	>132	>80			
	reo-1	Vero	>132	>80			
	$HSV\text{-}1_{KOS}$	E_6SM	49.5	>90			
	$HSV\text{-}1_{B2006(TK^-)}$	E_6SM	23.1	>90			
	$HSV\text{-}1_{VMW1837(TK^-)}$	E_6SM	36.3	>90			
	HSV-2 (G)	E_6SM	23.1	>90			
	CMV_{AD-169}	HeLa	4.6	>90			
	CMV_{Davis}	HeLa	1.7	>90			
	vaccinia	MEF	>66	>90			
					0.58		p66 HIV-1 RT and virion derived
					1.85		$HIV\text{-}1_{IIIB}$ RT used
$[ZnW_{12}O_{40}]^{6-}$							
H_6[32,43]	$HIV\text{-}1_{LAI}$	PBMC	0.90	12			
H_6[94]	vaccinia	MEF		50			
$[PMo_{12}O_{40}]^{3-}$							
$[(DMA)_2H]_3$[32,43]	$HIV\text{-}1_{LAI}$	PBMC	>100	>100			
Na_3[34,41]	$HIV\text{-}1_{IIIB}$	MT-4		750			
					19*, 70#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[CoW_{11}O_{38}]^{7-}$							
K_7[42]	$HIV\text{-}1_{IIIB}$	MT-4		131			
$[BVW_{11}O_{40}]^{7-}$							
K_7[42]	$HIV\text{-}1_{IIIB}$	MT-4	9.9	102			
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4	4.4	310			
					5*, 41#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
K_7[71]	HIV-1	*	1.5				*cell line not given
	FLV	*	0.1				
$[BVW_{11}O_{40}]^{6-}$							
K_6[34]	$HIV\text{-}1_{IIIB}$	MT-4	7.0	140			
					3*, 26#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
K_6[71]	HIV-1	*	1.0				*cell line not given
	FLV	*	1				
$[H_2Co_2W_{11}O_{40}]^{8-}$							
$(NH_4)_8$[42]	$HIV\text{-}1_{IIIB}$	MT-4		63.8			
$[H_2Co^{II}Co^{III}W_{11}O_{40}]^{6-}$							
$(NH_4)_6$[94]	vaccinia	MEF	100*	200			*EC_{100} value is reported
$[Cr_2Mo_{12}O_{42}]^{6-}$							
$(NH_4)_6$[42]	$HIV\text{-}1_{IIIB}$	MT-4		368			
$(NH_4)_6$[41]	$HIV\text{-}1_{IIIB}$	MT-4		300			
$[Si_2Zr_3W_{18}O_{71}H_3]^{11-}$							
$(Me_3NH)_{10}(H)$[72]	FluV-A/Texas	MDCK	0.2	69			mean IC_{50} and EC_{50} values were determined by NR dye uptake
	FluV-A/NWS	MDCK	6.5	69			
	FluV-A/Beijing	MDCK	5.2	69			
	FluV-A/ Port Chalmers	MDCK	7.2	69			
	FluV-B/Panama	MDCK	0.25	69			
	FluV-B/Hong Kong	MDCK	6.6	69			
$[SbW_6O_{24}]^{7-}$							
$[K_{5.5}H_{1.5}]$[42]	$HIV\text{-}1_{IIIB}$	MT-4		209			
$[Mn^{II}P_2W_{17}O_{61})_2]^{8-}$							
K_8[44]	FluV-A	MDCK	3.8	50.0			
	RSV	HEp-2	1.6	6.2			
	MLSV	HMV-2	>80	8.0			
	$HIV\text{-}1_{LAI}$	PBMC	0.2	5.9			
$[NaSb_9W_{21}O_{86}]^{18-}$							
$[(NH_4)_{17}Na]$[41,42]	$HIV\text{-}1_{IIIB}$	MT-4		7.5			
	$HIV\text{-}1_{SF-2H}$	MT-4		14.6			
$[(NH_4)_{17}Na]$[32,37,43]	$HIV\text{-}1_{LAI}$	PBMC	0.4	35			
$[(NH_4)_{17}Na]$[44]	FluV-A	MDCK	1.8	50			
	RSV	HEp-2	1.9	1.9			
	MLSV	HMV-2	1.5	26.0			
	$HIV\text{-}1_{LAI}$	PBMC	0.4	44.8			

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[NaSb_9W_{21}O_{86}]^{18-}$							
$[(NH_4)_{17}Na]$[36]	$HIV\text{-}1_{IIIB}$	MT-4	0.2	>80			
	$HIV\text{-}1_{RF}$	MT-4	0.1	>80			
	$HIV\text{-}1_{HE}$	MT-4	0.04	>80			
	$HIV\text{-}2_{ROD}$	MT-4	0.06	>80			
	$HIV\text{-}2_{EHO}$	MT-4	0.6	>80			
	SIV_{MAC251}	MT-4	0.008	>80			
	MLSV, cell transformation	C3H/3T3	2.9	>80			
	$HIV\text{-}1_{IIIB}$, giant cell formation	MOLT-4	2.8	>80			
	$HIV\text{-}2_{ROD}$, giant cell formation	MOLT-4		>80			
	Sindbis	Vero	2.8	>80			
	Semliki Forest	Vero	9.8	>80			
	measles	Vero	>28	>80			
	RSV	HeLa	7.2	>80			
	ParaFluV	Vero	>56	>80			
	Junin	Vero	1.4	>80			
	Tacaribe	Vero	1.7	>80			
	VSV	HeLa	2.8	>80			
	polio-1	HeLa	>5.6	>80			
	reo-1	Vero	>56	>80			
	$HSV\text{-}1_{KOS}$	E_6SM	2	>90			
	$HSV\text{-}1_{B2006(TK^-)}$	E_6SM	0.4	>90			
	$HSV\text{-}1_{VMW1837(TK^-)}$	E_6SM	1	>90			
	HSV-2 (G)	E_6SM	2.8	>90			
	CMV_{AD-169}	HeLa	0.4	>90			
	CMV_{Davis}	HeLa	0.4	>90			
	vaccinia	E_6SM	>28	>90			
					0.18		p66 HIV-1 RT and virion derived
					1.48		$HIV\text{-}1_{IIIB}$ RT used
$[(NH_4)_{17}Na]$[34]	$HIV\text{-}1_{IIIB}$	MT-4		5.7			*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL, **actual IC_{50} not reported, this value represents concentration where partial cell division was inhibited assayed using NENQUEST system
$[(NH_4)_{17}Na]$[24]	RV	CER	0.46	100**			
	VSC	CER	6.25	100**			
					4*, 77#		
$[(NH_4)_{17}Na]$[47]						1.2	
$[SiW_9O_{34}]^{10-}$							
Na_{10}[42]	$HIV\text{-}1_{IIIB}$	MT-4	53.3	179			
Na_{10}[42]	$HIV\text{-}1_{SF-2H}$	MT-4	0.22	339			
Na_9H[43]	$HIV\text{-}1_{LAI}$	PBMC	2.4	>100			
Na_{10}[34]	$HIV\text{-}1_{IIIB}$	MT-4	9.9	120			
					23*, 76#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
β-$[SiW_9O_{34}]^{10-}$							
Na_9H[32]	$HIV\text{-}1_{LAI}$	PBMC	2.4	>100			
$[SiW_9O_{34}H]^{9-}$							
Na_9[34]	$HIV\text{-}1_{IIIB}$	MT-4	28	120			
					12*		*percent inhibition at 50 μg/mL
$[SiW_9Nb_3O_{40}]^{7-}$	FluV-A	PBMC	5.0	100			
$(Me_3NH)_7$[44]	RSV	MDCK	4.5	>50			
	MLSV	HEp-2	>50	>50			
	$HIV\text{-}1_{LAI}$	HMV-2	0.6	>100			
$[SiW_9O_{33}(OH)]^{9-}$							
Na_9[42]	$HIV\text{-}1_{IIIB}$	MT-4	21.5	134			
Na_9[42]	$HIV\text{-}1_{SF-2H}$	MT-4	0.076	154			
$[PW_{12}O_{40}]^{3-}$	$HIV\text{-}1_{LAI}$	PBMC	14.0	>100			
H_3[32,43]	HIV-1	PBMC	>50	>100			
$[(NMP)_2H]_3$[32]	$HIV\text{-}1_{IIIB}$	MT-4		180			
Na_3[34]							
					32*		*percent inhibition at 50 μg/mL
$[SiW_{12}O_{40}]^{4-}$							
$(ArgH^+)_nH_{(4-n)}$[62]	RSV	Ma 104	1.3	>100			CPE inhibition assay
	RSV	Ma 104	1.1	72			neutral red assay
	RSV, strain A2	Ma 104	3.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	3.0	>100			neutral red assay
$(HisH^+)_nH_{(4-n)}$[62]	RSV	Ma 104	1.5	>100			CPE inhibition assay
	RSV	Ma 104	0.6	100			neutral red assay
	RSV, strain A2	Ma 104	3.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	8.0	75			neutral red assay
H_4[42]	$HIV\text{-}1_{IIIB}$	MT-4	5.9	134			
	$HIV\text{-}1_{SF-2H}$	MT-4	0.11	291			
H_4[32,43]	$HIV\text{-}1_{LAI}$	PBMC	0.12	>200			
$(NH_4)_nH_{(4-n)}$[32]	$HIV\text{-}1_{LAI}$	PBMC	2.4	>100			

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[SiW_{12}O_{40}]^{4-}$							
$(HisH^+)_nH_{(4-n)}$[32]	HIV-1_{LAI}	PBMC	0.22	182			
$(LysH^+)H_{(4-n)}$[32]	HIV-1_{LAI}	PBMC	1.61	>100			
$(ArgH^+)_nH_{(4-n)}$[32]	HIV-1_{LAI}	PBMC	1.03	>100			
β-$[SiW_{12}O_{40}]^{4-}$							
H_4[32]	HIV-1	PBMC	0.25	>100			
H_4[44]	FluV-A	MDCK	6.3	>100			
	RSV	HEp-2	>50	50.0			
	MLSV	HMV-2	>43	43.0			
	HIV-1_{LAI}	PBMC	0.3	>100			
H_4[47]						8.0	assayed using NENQUEST system
$[PMoW_{11}O_{39}]^{3-}$							
$(t\text{-}Bu_4N)_3$[32]	HIV-1_{LAI}	PBMC	3.4	>100			
$[SiFeW_{11}O_{39}(H_2O)]^{5-}$							
K_5[42]	HIV-1_{IIIB}	MT-4	6.0	115			
K_5[34]	HIV-1_{IIIB}	MT-4	5.0	140			
$[SiAlW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	4.0	140			
					37*, 51[#]		*percent inhibition at 50 μg/mL, [#]percent inhibition at 10 μg/mL
$[SiCoW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	3.4	77			*EC_{100} value is reported,
					15**, 26[#]		**percent inhibition at 50 μg/mL,
K_5[94]	vaccinia	MEF	50*	200			[#]percent inhibition at 10 μg/mL*
$[SiCrW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	8.3	90			
					9*, 9[#]		*percent inhibition at 50 μg/mL, [#]percent inhibition at 10 μg/mL
$[SiCuW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	8.2	130			
$[SiMgW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	8.2	110			
					15*		*percent inhibition at 50 μg/mL
$[SiMnW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	7.1	140			
$[SiNiW_{11}O_{39}(H_2O)]^{6-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	6.8	43			
					22*, 59[#]		*percent inhibition at 50 μg/mL, [#]percent inhibition at 10 μg/mL
$[PNiW_{11}O_{39}(H_2O)]^{5-}$							
K_5[94]	vaccinia	MEF	50*	200			*EC_{100} value is reported
$[SiSrW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	7.6	130			
					2*		*percent inhibition at 50 μg/mL
$[SiZnW_{11}O_{39}(H_2O)]^{5-}$							
K_5[34]	HIV-1_{IIIB}	MT-4	6.5	85			
					31*		*percent inhibition at 50 μg/mL
$[Si(TiCp)W_{11}O_{39}]^{5-}$							
K_5[36]	HIV-1_{IIIB}	MT-4	0.6	>80			Cp = cyclopentadienyl
	HIV-1_{RF}	MT-4	0.4	>80			
	HIV-1_{HE}	MT-4	0.002	>80			
	HIV-2_{ROD}	MT-4	0.2	>80			
	HIV-2_{EHO}	MT-4	0.5	>80			
	SIV_{MAC251}	MT-4	0.003	>80			
	MLSV, cell transformation	C3H/3T3	1.5	>80			
	HIV-1_{IIIB}, giant cell formation	MOLT-4	22.2	>80			
	HIV-2_{ROD}, giant cell formation	MOLT-4	0.3	>80			
	Sindbis	Vero	4.3	>80			
	Semliki Forest	Vero	46.5	>80			
	measles	Vero	31	>80			
	RSV	HeLa	4.3	>80			
	ParaFluV	Vero	>124	>80			
	Junin	Vero	13.3	>80			
	Tacaribe	Vero	15.5	>80			
	VSV	HeLa	6.2	>80			
	polio-1	HeLa	>124	>80			
	reo-1	Vero	>124	>80			
	HSV-1_{KOS}	E_6SM	21.7	>90			
	HSV-$1_{B2006(TK^-)}$	E_6SM	6.2	>90			
	HSV-$1_{VMW1837(TK^-)}$	E_6SM	12.4	>90			
	HSV-2 (G)	E_6SM	6.2	>90			
	CMV_{AD-169}	HeLa	1.2	>90			
	CMV_{Davis}	HeLa	0.9	>90			
	vaccinia	E_6SM	>62	>90			
					0.28		p66 HIV-1 RT and virion derived
					1.74		HIV-1_{IIIB} used

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[W_{10}O_{32}]^{4-}$							
$(Me_4N)_4$[62]	RSV	Ma 104	3	50			CPE inhibition assay
	RSV	Ma 104	1	83			neutral red assay
	RSV, strain A2	Ma 104	5	50			CPE inhibition assay
	RSV, strain A2	Ma 104	8	70			neutral red assay
$(NH_4)_4$[32,43]	HIV-1_{LAI}	PBMC	1.8	115			
$(Me_4N)_4$[32,43]	HIV-1_{LAI}	PBMC	3.1	>100			
$[Fe_4(H_2O)_2(P_2W_{15}O_{56})_2]^{16-}$							
Na_{16}[44]	FluV-A	MDCK	0.7	>100			
	RSV	HEp-2	1.4	>50			
	MLSV	HMV-2	0.2	>50			
	HIV-1_{LAI}	PBMC	0.4	20.8			
	FluV-A (Ishikawa)		0.59				
	FluV-B (Singapore)		35.5				
	RSV-A (Long)	MDCK	2.8	>200			
	RSV-A (FM-58-8)	HEp-2	5.0	88			
	RSV-B (SM61-48)	HMV-2	7.6	>200			
	MLSV (Edmonston)	Vero	0.3	50			
	MPSV (EXCH-3)		20.6				
	PFluV-2 (Greer)		1.8				
	PFluV-3 (C243)		28.0				
$[Ni_4(H_2O)_2(P_2W_{15}O_{56})_2]^{16-}$							
Na_{16}[44]	FluV-A	MDCK	0.9	100			
	RSV	HEp-2	>2.7	2.7			
	MLSV	HMV-2	>0.8	1.0			
	HIV-1_{LAI}	PBMC	0.1	39.2			
K_{16}[47]						<2.5	assayed using NENQUEST system
$[Mn_4(H_2O)_2(P_2W_{15}O_{56})_2]^{16-}$							
Na_{16}[44]	FluV-A	MDCK	1.1	100			
	RSV	HEp-2	1.4	>50			
	MLSV	HMV-2	>28.1	25.6			
	HIV-1_{LAI}	PBMC	0.3	4.5			
$[Zn_4(H_2O)_2(P_2W_{15}O_{56})_2]^{16-}$							
Na_{16}[47]						1.3	assayed using NENQUEST system
$[P_2W_{15}O_{56}]^{12-}$							
Na_{12}[44]	FluV-A	MDCK	2.7	>100			
	RSV	HEp-2	>8.6	8.6			
	MLSV	HMV-2	>16.2	20.4			
	HIV-1_{LAI}	PBMC	4.7	>100			
$[P_2CoW_{17}O_{62}]^{8-}$							
K_8[42]	HIV-1_{IIIB}	MT-4	7.1	51.4			
K_8[42]	HIV-1_{SF-2H}	MT-4	1.31	64.0			
$[P_2Co(H_2O)W_{17}O_{61}]^{8-}$							
K_8[34]					100*, 100#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/m
$[P_2Mn^{2+}W_{17}O_{61}(H_2O)]^{8-}$							
K_8[42]	HIV-1_{IIIB}	MT-4	9.0	49.4			
K_8[42]	HIV-1_{SF-2H}	MT-4	1.04	95.0			
$[Cu_4(H_2O)_2PW_9O_{34})_2]^{10-}$							
K_{10}[32,43]	HIV-1_{LAI}	PBMC	<4.4	>100			
$[Mn_4(H_2O)_2(PW_9O_{34})_2]^{10-}$							
K_{10}[62]	RSV	Ma 104	5.0	24			CPE inhibition assay
	RSV	Ma 104	2.0	59			neutral red assay
K_{10}[44]	FluV-A	MDCK	1.1	100			
	RSV	HEp-2	>50	>50			
	MLSV	HMV-2	20.6	31.8			
	HIV-1_{LAI}	PBMC	1.3	>100			
$[Ni_4(H_2O)_2(PW_9O_{34})_2]^{10-}$							
K_{10}[44]	FluV-A	MDCK	21.1	50			
	RSV	HEp-2	>22	22.0			
	MLSV	HMV-2	>1.6	1.8			
	HIV-1_{LAI}	PBMC	4.5	93.1			
K_{10}[47]						0.81	assayed using NENQUEST system
$[Zn_4(H_2O)_2(PW_9O_{34})_2]^{10-}$							
K_{10}[44]	FluV-A	MDCK	2.0	100			
	RSV	HEp-2	>26	26.0			
	MLSV	HMV-2	>16	22.0			
	HIV-1_{LAI}	PBMC	1.6	91.5			
K_{10}[47]						1.0	assayed using NENQUEST system

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[Co_4(H_2O)_2(PW_9O_{34})_2]^{10-}$							
K_{10}[32,43]	HIV-1_{LAI}	PBMC	0.8	>44			
$[Fe_4(H_2O)_2(PW_9O_{34})_2]^{10-}$							
K_{10}[62]	RSV, strain A2	Ma 104	<0.1				PE inhibition assay
	RSV, strain A2	Ma 104	<0.1				neutral red assay
K_{10}[44]	FluV-A (Ishikawa)		1.4				
	FluV-B (Singapore)		13.9				
	RSV-A (Long)	MDCK	5.6	>200			
	RSV-A (FM-58-8)	HEp-2	23.0	>200			
	RSV-B (SM61-48)	HMV-2	3.1	50			
	MLSV (Edmonston)	Vero	0.8	50			IC_{50} was determined
	MPSV (EXCH-3)		>50				by MTT method
	PFluV-2 (Greer)		0.43				
	PFluV-3 (C243)		>50				
	FluV-A	FluV-A	1.1	>100			
	RSV	RSV	3.8	>50			
	MLSV	MLSV	0.76	50.0			
	HIV-1_{LAI}	PBMC	1.7	>100			
β-$[HPW_9O_{34}]^{8-}$							
Na_8[32]	HIV-1_{LAI}	PBMC	11	>100			
$[Cu_3(NO_3)(PW_9O_{34})_2]^{13-}$							
K_{13}[42]	HIV-1_{IIIB}	MT-4		86.6			
$[PW_9Mo_2O_{39}]^{7-}$							
K_7[34]	HIV-1_{IIIB}	MT-4	89	170			
$[SiW_{11}O_{39}]^{8-}$							
K_8[37]	HIV-1_{LAI}	PBMC	1.2	79.5			
K_8[32,43]	HIV-1_{LAI}	PBMC	0.15	>100			
$[NbSiW_{11}O_{40}]^{5-}$							
$(Me_3NH)_5$[44]	FluV-A	MDCK	13.4	>100			
	RSV	HEp-2	7.8	50.0			
	MLSV	HMV-2	>50	50.0			
	HIV-1_{LAI}	PBMC	0.8	>100			
$[NbSiW_{11}O_{40}]^{5-}$							
$(Me_3NH)_5$[44]	FluV-A	MDCK	11.4	>100			
	RSV	HEp-2	7.3	>50			
	MLSV	HMV-2	29	37.6			
	HIV-1_{LAI}	PBMC	0.2	>100			
$[Si(TaO_2)W_{11}O_{39}]^{5-}$							
$(Me_3NH)_5$[44]	FluV-A	MDCK	4.0	100			
	RSV	HEp-2	5.1	>50			
	MLSV	HMV-2	>10	27.0			
	HIV-1_{LAI}	PBMC	1.4	>100			
$(Me_3NH)_5$[47]						23.7	assayed using NENQUEST system
$[Si(NbO_2)W_{11}O_{39}]^{5-}$							
K_5[37]	HIV-1_{LAI}	PBMC	1.6	>100			
					0.04/6.9		p66 HIV-1 RT used
$(Me_3NH)_5$[37]	HIV-1_{LAI}	PBMC	1.8	>100			
					0.06/5.0		
$(Me_3NH)_5$[44]	FluV-A	MDCK	2.5	85.6			
	RSV	HEp-2	9.2	47.1			
	MLSV	HMV-2	>50	50.0			
	HIV-1_{LAI}	PBMC	0.8	>100			
$(Me_3NH)_5$[47]						41.1	assayed using NENQUEST system
$[SiW_{11}O_{39}O(Si(CH_2)_5CH_3)_2]^{4-}$							
$[Me_4N]_4$[44]	FluV-A	MDCK	>35	35.2			
	RSV	HEp-2	>9.3	9.3			
	MLSV	HMV-2	23.6	31.0			
	HIV-1_{LAI}	PBMC	36.2	>100			
$[Me_4N]_4$[47]						27.1	assayed using NENQUEST system
$[(CH_2CH_2COOCH_3)SiW_{11}O_{39}]^{4-}$							
Cs_4[35]	HIV-1_{LAI}	PBMC	3.3	>100			
					13.2/17.8		p66 HIV-1 RT and *E. coli*
TMA_4[35]	HIV-1_{LAI}	PBMC	39.0	>100			DNA P were used
					1.1/65.2		
$[(CH_2CH_2CH_2CN)_2OSiW_{11}O_{39}]^{4-}$							
Cs_4[35]	HIV-1_{LAI}	PBMC	19.8	>100			p66 HIV-1 RT and *E. coli*
					0.91/65.2		DNA P were used
Cs_4[47]						1.7	assayed using NENQUEST system
$[(CH{=}CH_2)SiW_{11}O_{39}]^{4-}$							
Cs_4[35]	HIV-1_{LAI}	PBMC	35.3	>100			
					0.57/14.9		p66 HIV-1 RT and *E. Coli.* DNA P were used

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[Si(NbO_2)_3W_9O_{37}]^{7-}$							
Cs_7[37]	$HIV\text{-}1_{LAI}$	PBMC	1.0	>100			
					0.03/9.6		p66 HIV1 RT used
$(Me_3NH)_7$[37]	$HIV\text{-}1_{LAI}$	PBMC	2.4	>100			
					0.23/6.3		
$(Me_3NH)_7$[44]	FluV-A	MDCK	10.0	100			
	RSV	HEp-2	>50	>50			
	MLSV	HMV-2	>50	>50			
	$HIV\text{-}1_{LAI}$	PBMC	2.0	>100			
$(Me_3NH)_7$[47]						8.3	assayed using NENQUEST system
$[Eu(SiW_{11}O_{39})_2]^{13-}$							
K_{13}[42]	$HIV\text{-}1_{IIIB}$	MT-4	6.1	158			
K_{13}[42]	$HIV\text{-}1SF_{-2}H$	MT-4	0.23	346			
K_{13}[41,42]	$HIV\text{-}1_{IIIB}$	MT-4	3.4	54			
$[SiW_{11}O_{39}O(SiCH_2CH_2CH_2Cl)_2]^{4-}$							
Cs_4[62]	RSV	Ma 104	5.0	90			CPE inhibition assay
	RSV	Ma 104	3.0	82			neutral red assay
$[SiW_{11}O_{39}(t\text{-}C_4H_9Si)H_2O]^{4-}$							
$[(CH_3)_4N^+]_4$[62]	RSV	Ma 104	1.5	70			CPE inhibition assay
	RSV	Ma 104	1.2	74			neutral red assay
	RSV, strain A2	Ma 104	4.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	1.0	>100			neutral red assay
	RSV (Long)	HEp-2	5.0	>100			CPE inhibition assay
	RSV (Long)	HEp-2	5.0	>100			neutral red assay
	RSV (9320)	Ma 104	4.0	>100			CPE inhibition assay
	RSV (9320)	Ma 104	1.0	>100			neutral red assay
	RSV (18357)	Ma 104	4.0	>100			CPE inhibition assay
	RSV (18357)	Ma 104	0.4	>100			neutral red assay
	Bovine RSV	EBTr	10	>100			CPE inhibition assay
	Bovine RSV	EBTr	6.0	>100			neutral red assay
$[SiW_{11}O_{39}{\cdot}O(SiCH{=}CH_2)_2]^{4-}$							
$[(CH_3)_4N^+]_4$[62]	RSV	Ma 104	1.8	>100			CPE inhibition assay
	RSV	Ma 104	1.1	93			neutral red assay
	RSV, strain A2	Ma 104	4.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	1.0	>100			neutral red assay
	RSV (Long)	HEp-2	4.0	>100			CPE inhibition assay
	RSV (Long)	HEp-2	5.0	>100			neutral red assay
	RSV (9320)	Ma 104	5.0	>100			CPE inhibition assay
	RSV (9320)	Ma 104	<0.3	>100			neutral red assay
	RSV (18357)	Ma 104	5.0	>100			CPE inhibition assay
	RSV (18357)	Ma 104	1.0	>100			neutral red assay
	Bovine RSV	EBTr	10	>100			CPE inhibition assay
	Bovine RSV	EBTr	4.0	>100			neutral red assay
Cs_4[47]						2.4	assayed using NENQUEST system
$[Ce(SiW_{11}O_{39})_2]^{13-}$							
K_{13}[36]	$HIV\text{-}1_{IIIB}$	MT-4	0.03	>80			
	$HIV\text{-}1_{RF}$	MT-4	0.3	>80			
	$HIV\text{-}1_{HE}$	MT-4	0.08	>80			
	$HIV\text{-}2_{ROD}$	MT-4	0.06	>80			
	$HIV\text{-}2_{EHO}$	MT-4	1.3	>80			
	SIV_{MAC251}	MT-4	0.008	>80			
	MLSV, cell transformation	C3H/3T3	0.9	>80			
	$HIV\text{-}1_{IIIB}$, giant cell formation	MOLT-4	3.0	>80			
	$HIV\text{-}2_{ROD}$, giant cell formation	MOLT-4	0.3	>80			
	Sindbis	Vero	2.1	>80			
	Semliki Forest	Vero	22.5	>80			
	measles	Vero	>30	>80			
	RSV	HeLa	1.8	>80			
	ParaFluV	Vero	>60	>80			
	Junin	Vero	15	>80			
	Tacaribe	Vero	15	>80			
	VSV	HeLa	5.9	>80			
	polio-1	HeLa	>60	>80			
	reo-1	Vero	>60	>80			
	$HSV\text{-}1_{KOS}$	E_6SM	6.8	>90			
	$HSV\text{-}1_{B2006(TK^-)}$	E_6SM	0.6	>90			
	$HSV\text{-}1_{VMW1837(TK^-)}$	E_6SM	2.1	>90			
	HSV-2 (G)	E_6SM	6.8	>90			
	CMV_{AD-169}	HeLa	0.6	>90			
	CMV_{Davis}	HeLa	0.2	>90			
	vaccinia	E_6SM	>30	>90			
					0.04		p66 HIV-1 RT and virion derived
					1.25		$HIV\text{-}1_{IIIB}$ used

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[PW_{11}O_{39}]^{7-}$							
K_7[42]	HIV-1_{IIIB}	MT-4	16.7	144			
K_7[42]	HIV-1SF$_{-2}$H	MT-4	0.315	311			
Na_7[32,43]	HIV-1_{LAI}	PBMC	10.8	>100			
$(n\text{-}Bu_4N)_4H_3$[32]	HIV-1	PBMC	9.7	>100			
K_7[34]	HIV-1_{IIIB}	MT-4		180			
$[PW_{11}O_{39}O(SiCH_2CH_2COOCH_3)_2]^{3-}$							
$[Me_4N]_3$[44]	FluV-A	MDCK	11.2	71.7			
	RSV	HEp-2	>3.7	37.0			
	MLSV	HMV-2	>50	50.0			
	HIV-1_{LAI}	PBMC	51.5	>100			
$(Me_4N)_3$[47]						15.5	assayed using NENQUEST system
$[SiW_{11}O_{39}(SiMe_2)]^{6-}$							
K_6[62]	RSV	Ma 104	1.5	>100			CPE inhibition assay
	RSV	Ma 104	1.7	>100			neutral red assay
	RSV, strain A2	Ma 104	3.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	3.0	>100			neutral red assay
$[SiTiW_{11}O_{40}]^{6-}$							
K_6[71]	HIV-1		3.2				
	FLV		3.0				
$[PW_{10}O_{40}]^{5-}$							
Cs_5[71]	HIV-1		1.6				
	FLV		7.0				
$[W_{15}P_2O_{62}]^{12-}$							
Na_{12}[71]	HIV-1		2.6				
$[Ce_3W_{18}P_2O_{71}]^{12-}$							
K_{12}[71]	HIV-1		1.0				
	FLV		10				
$[Si_2Nb_6W_{18}O_{77}]^{8-}$							
$(Me_3NH)_8$[62]	RSV	Ma 104	0.8	>100			CPE inhibition assay
	RSV	Ma 104	0.3	75			neutral red assay
	RSV, strain A2	Ma 104	1.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	0.7	>100			neutral red assay
	RSV (Long)	HEp-2	1.0	>100			CPE inhibition assay
	RSV (Long)	HEp-2	0.4	>100			neutral red assay
	RSV (9320)	Ma 104	3.0	>100			CPE inhibition assay
	RSV (9320)	Ma 104	0.3	>100			neutral red assay
	RSV	Ma 104	0.6	>100			CPE inhibition assay
	RSV	Ma 104	0.3	59			neutral red assay
$(LysH^+)_7K$[62]	RSV (Long)	HEp-2	1.0	>100			CPE inhibition assay
	RSV (Long)	HEp-2	0.3	>100			neutral red assay
	RSV (9320)	Ma 104	5.0	>100			CPE inhibition assay
	RSV (9320)	Ma 104	0.5	>100			neutral red assay
	RSV (18357)	Ma 104	1.0	>100			CPE inhibition assay
	RSV (18357)	Ma 104	0.3	>100			neutral red assay
	Bovine RSV	EBTr	3.0	>100			CPE inhibition assay
	Bovine RSV	EBTr	2.0	>100			neutral red assay
$(Me_3NH)_8$[72]	FluV-A/Texas	MDCK	0.1	>96			mean IC_{50} and EC_{50} values were determined by NR dye uptake
	FluV-A/NWS	MDCK	5.2	>96			
	FluV-A/Beijing	MDCK	3.0	>96			
	FluV-A/ Port Chalmers	MDCK	8.6	>96			
	FluV-B/Panama	MDCK	2.6	>96			
	FluV-B/Hong Kong	MDCK	0.13	>96			
$(Me_3NH)_8$[44]	FluV-A	MDCK	3.6	100			
	RSV	HEp-2	>9.4	9.4			
	MLSV	HMV-2	>50	>50			
	HIV-1_{LAI}	PBMC	0.3	>100			
	FluV-A (Ishikawa)		2.8				
	FluV-B (Singapore)		45.7				
	RSV-A (Long)	MDCK	9.8	>200			
	RSV-A (FM-58-8)	HEp-2	10.0	>200			
	RSV-B (SM61-48)	HMV-2	4.5	20.7			
	MLSV (Edmonston)	Vero	>35.5	148			
	MPSV (EXCH-3)		>50				
	PFluV-2 (Greer)		7.8				
	PFluV-3 (C243)		>50				

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[Si_2Nb_6W_{18}O_{77}]^{8-}$							
$(Me_3NH)_8$[36]	HIV-1_{IIIB}	MT-4	0.6	>80			
	HIV-1_{RF}	MT-4	0.3	>80			
	HIV-1_{HE}	MT-4	0.002	>80			
	HIV-2_{ROD}	MT-4	0.5	>80			
	HIV-2_{EHO}	MT-4	0.3	>80			
	SIV_{MAC251}	MT-4	0.002	>80			
	MLSV, cell transformation	C3H/3T3	0.5	>80			
	HIV-1_{IIIB}, giant cell formation	MOLT-4	5.4	>80			
	HIV-2_{ROD}, giant cell formation	MOLT-4	0.2	>80			
	HSV-1_{KOS}	E_6SM	3.6	>90			
	HSV-$1_{B2006(TK^-)}$	E_6SM	0.5	>90			
	HSV-$1_{VMW1837(TK^-)}$	E_6SM	2.2	>90			
	HSV-2 (G)	E_6SM	2.5	>90			
	CMV_{AD-169}	HeLa	0.2	>90			
	CMV_{Davis}	HeLa	0.2	>90			
	vaccinia	E_6SM	>36	>90			
					0.23		p66 HIV-1 RT and virion derived
					1.06		HIV-1_{IIIB} RT used
$(Me_3NH)_8$[47]						1.3	assayed using NENQUEST system
[A-α-$Ge_2Nb_6W_{18}O_{77}$]$^{8-}$							
$K_7(H)$[62]	RSV	Ma 104	0.3	>100			CPE inhibition assay
	RSV	Ma 104	0.1	25			neutral red assay
	RSV, strain A2	Ma 104	3.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	2.0	>100			neutral red assay
	RSV (Long)	HEp-2	2.0	>100			CPE inhibition assay
	RSV (Long)	HEp-2	1.0	>100			neutral red assay
	RSV (18357)	Ma 104	2.0	>100			CPE inhibition assay
	RSV (18357)	Ma 104	1.0	>100			neutral red assay
$(Me_3NH)_8$[72]	FluV-A/Texas	MDCK	0.15	>100			mean IC_{50} and EC_{50} values were
	FluV-A/NWS	MDCK	5.6	>100			determined by NR dye uptake
	FluV-A/Beijing	MDCK	5.0	>100			
	FluV-A/ Port Chalmers	MDCK	13.5	>100			
	FluV-B/Panama	MDCK	0.4	>100			
	FluV-B/Hong Kong	MDCK	1.2	>100			
$K_7(H)$[72]	FluV-A/Texas	MDCK	0.15	92			mean IC_{50} and EC_{50} values were
	FluV-A/NWS	MDCK	6.6	92			determined by NR dye uptake
	FluV-A/Beijing	MDCK	5.6	92			
	FluV-A/ Port Chalmers	MDCK	25.5	92			
	FluV-B/Panama	MDCK	0.4	92			
	FluV-B/Hong Kong	MDCK	1.8	92			
[A-β-$Si_2Nb_6W_{18}O_{77}$]$^{8-}$							
K_8[62]	RSV	Ma 104	0.3	>100			CPE inhibition assay
	RSV	Ma 104	0.3	62			neutral red assay
	RSV, strain A2	Ma 104	3.0	55			CPE inhibition assay
	RSV, strain A2	Ma 104	1.0	100			neutral red assay
$(Me_3NH)_8$[62]	RSV	Ma 104	0.3	>100			CPE inhibition assay
	RSV	Ma 104	0.15	41			neutral red assay
K_8[72]	FluV-A/Texas	MDCK	0.2	71			mean IC_{50} and EC_{50} values were
	FluV-A/NWS	MDCK	6.2	71			determined by NR dye uptake
	FluV-A/Beijing	MDCK	11.5	71			
	FluV-A/ Port Chalmers	MDCK	36	71			
	FluV-B/Panama	MDCK	0.15	71			
	FluV-B/Hong Kong	MDCK	1.6	71			
[A-β-$Ge_2Nb_6W_{18}O_{78}$]$^{9-}$							
$(Me_3NH)_9$[62]	RSV	Ma 104	2.1	>100			CPE inhibition assay
	RSV	Ma 104	0.2	26			neutral red assay
	RSV, strain A2	Ma 104	2.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	1.0	>100			neutral red assay
[A-α-$HSi_2Nb_6W_{18}O_{78}$]$^{9-}$							
$(Me_3NH)_9$[42,62]	RSV	Ma 104	1.0	>100			CPE inhibition assay
	RSV	Ma 104	0.5	57			neutral red assay
	RSV, strain A2	Ma 104	2.0	55			CPE inhibition assay
	RSV, strain A2	Ma 104	0.2	55			neutral red assay
	RSV (18357)	Ma 104	1.0	>100			CPE inhibition assay
	RSV (18357)	Ma 104	0.6	>100			neutral red assay

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[P_2Zn_4(H_2O)_2W_{18}O_{68}]^{10-}$							
K_{10}[36]	HIV-1_{IIIB}	MT-4	0.2	>80			
	HIV-1_{RF}	MT-4	0.2	>80			
	HIV-1_{HE}	MT-4	0.05	>80			
	HIV-2_{ROD}	MT-4	0.2	>80			
	HIV-2_{EHO}	MT-4	0.1	>80			
	SIV_{MAC251}	MT-4	0.9	>80			
	MLSV, cell transformation	C3H/3T3	2.5	>80			
	HIV-1_{IIIB}, giant cell formation	MOLT-4	7.2	>80			
	HIV-2_{ROD}, giant cell formation	MOLT-4	3.6	>80			
	Sindbis	Vero	17.1	>80			
	Semliki Forest	Vero	12.6	>80			
	measles	Vero	>18	>80			
	RSV	HeLa	>18	>80			
	ParaFluV	Vero	>72	>80			
	Junin	Vero	>36	>80			
	Tacaribe	Vero	>36	>80			
	VSV	HeLa	12.6	>80			
	polio-1	HeLa	>36	>80			
	reo-1	Vero	>72	>80			
	HSV-1_{KOS}	E_6SM	7.2	>90			
	HSV-$1_{B2006(TK^-)}$	E_6SM	5.4	>90			
	HSV-$1_{VMW1837(TK^-)}$	E_6SM	4.3	>90			
	HSV-2 (G)	E_6SM	8.1	>90			
	CMV_{AD-169}	HeLa	0.4	>90			
	CMV_{Davis}	HeLa	0.5	>90			
	vaccinia	E_6SM	>36	>90			
					0.23		p66 HIV-1 RT and virion derived
					3.6		HIV-1_{IIIB} used
$[PZnMo_{11}O_{40}]^{7-}$							
$(NH_4)_6H$[42]	HIV-1_{IIIB}	MT-4		180			
$(NH_4)_6H$[34]	HIV-1_{IIIB}	MT-4		230			
$[P_2Mo_{18}O_{62}]^{6-}$							
K_6[62]	RSV	Ma 104	10	>100			CPE inhibition assay
	RSV	Ma 104	6.0	>100			neutral red assay
	RSV, strain A2	Ma 104	8.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	10	>100			neutral red assay
$[Si_2(ZrOH)_3W_{18}O_{68}]^{11-}$							
$(Me_3NH)_{10}(H)$[62]	RSV	Ma 104	0.1	80			CPE inhibition assay
	RSV	Ma 104	<0.1	14			neutral red assay
	RSV, strain A2	Ma 104	0.1	>55			CPE inhibition assay
	RSV, strain A2	Ma 104	0.1	>100			neutral red assay
$[P_2V_3W_{15}O_{62}]^{9-}$							
K_8H[36]	HIV-1_{IIIB}	MT-4	0.2	>80			
	HIV-1_{RF}	MT-4	0.1	>80			
	HIV-1_{HE}	MT-4	0.08	>80			
	HIV-2_{ROD}	MT-4	0.08	>80			
	HIV-2_{EHO}	MT-4	0.2	>80			
	SIV_{MAC251}	MT-4	1.1	>80			
	MLSV, cell transformation	C3H/3T3	1.8	>80			
	HIV-1_{IIIB}, giant cell formation	MOLT-4	2.0	>80			
	HIV-2_{ROD}, giant cell formation	MOLT-4	0.8	>80			
	Sindbis	Vero	0.2	>80			
	Semliki Forest	Vero	4.0	>80			
	measles	Vero	4.0	>80			
	RSV	HeLa	0.04	>80			
	ParaFluV	Vero	>80	>80			
	Junin	Vero	2.0	>80			
	Tacaribe	Vero	2.0	>80			
	VSV	HeLa	1.0	>80			
	polio-1	HeLa	>40	>80			
	reo-1	Vero	>80	>80			
					0.01		p66 HIV-1 RT and virion derived
					0.08		HIV-1_{IIIB} RT used

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[H_2P_2W_{12}O_{48}]^{12-}$							
K_{12}[36]	RSV	Ma 104	0.3	50			neutral red assay
	$HIV\text{-}1_{IIIB}$	MT-4	0.1	>80			
	$HIV\text{-}1_{RF}$	MT-4	0.1	>80			
	$HIV\text{-}1_{HE}$	MT-4	0.03	>80			
	$HIV\text{-}2_{ROD}$	MT-4	0.1	>80			
	$HIV\text{-}2_{EHO}$	MT-4	0.2	>80			
	SIV_{MAC251}	MT-4	1.3	>80			
	MLSV, cell transformation	C3H/3T3	4.6	>80			
	$HIV\text{-}1_{IIIB}$, giant cell formation	MOLT-4	7.8	>80			
	$HIV\text{-}2_{ROD}$, giant cell formation	MOLT-4	0.8	>80			
	Sindbis	Vero	5.0	>80			
	Semliki Forest	Vero	37.5	>80			
	measles	Vero	>50	>80			
	RSV	HeLa	12.5	>80			
	ParaFluV	Vero	>100	>80			
	Junin	Vero	>50	>80			
	Tacaribe	Vero	>50	>80			
	VSV	HeLa	11.3	>80			
	polio-1	HeLa	>100	>80			
	reo-1	Vero	>100	>80			
	$HSV\text{-}1_{KOS}$	E_6SM	5.0	>90			
	$HSV\text{-}1_{B2006(TK^-)}$	E_6SM	0.8	>90			
	$HSV\text{-}1_{VMW1837(TK^-)}$	E_6SM	1.3	>90			
	HSV-2 (G)	E_6SM	5.0	>90			
	CMV_{AD-169}	HeLa	1.0	>90			
	vaccinia	E_6SM	>50	>90			
					0.16		p66 HIV-1 RT and virion derived
					0.9		$HIV\text{-}1_{IIIB}$ used
$[Nb_6O_{19}]^{8-}$							
K_7H[62]	RSV	Ma 104	1.9	>100			CPE inhibition assay
	RSV	Ma 104	0.3	>100			neutral red assay
K_7H[37]	$HIV\text{-}1_{LAI}$	PBMC	>100	>100			
$[Nb_2W_4O_{19}]^{6-}$							
$[Me_4N/Na/K]_6$[47]						7.1	assayed using NENQUEST system
$[Nb_3W_3O_{19}]^{5-}$							
$[Me_4N/Na/K]_5$[47]						55.2	assayed using NENQUEST system
$[W_6O_{19}]^{2-}$							
$(n\text{-}Bu_4N)_2$[32,43]	$HIV\text{-}1_{LAI}$	PBMC	107	>100			
$[IMo_6O_{24}]^{5-}$							
Na_5[41]	$HIV\text{-}1_{IIIB}$	MT-4		68			
$[CoMo_6O_{24}]^{9-}$							
$(NH_4)_3H_6$[41]	$HIV\text{-}1_{IIIB}$	MT-4		49			
$[CrMo_6O_{24}]^{9-}$							
Na_3H_6[41]	$HIV\text{-}1_{IIIB}$	MT-4		430			
$[Mo_6O_{19}]^{2-}$							
$(n\text{-}Bu_4N)_2$[32,43]	$HIV\text{-}1_{LAI}$	PBMC	>100	>100			
$[Mo_6V_2O_{26}]^{6-}$							
Na_6[41]	$HIV\text{-}1_{IIIB}$	MT-4		4.2			
$[Se_2Mo_5O_{21}]^{4-}$							
$(i\text{-}PrNH_3)_4$[41]	$HIV\text{-}1_{IIIB}$	MT-4		4.4			
$[P_2Mo_5O_{23}]^{4-}$							
$(i\text{-}PrNH_3)_4$[41]	$HIV\text{-}1_{IIIB}$	MT-4		460			
$[Nb_4W_2O_{19}]^{6-}$							
$[Na/K]_6$[36]	$HIV\text{-}1_{IIIB}$	MT-4	18.3	>80			
	$HIV\text{-}1_{RF}$	MT-4	14.0	>80			
	$HIV\text{-}1_{HE}$	MT-4	1.5	>80			
	$HIV\text{-}2_{ROD}$	MT-4	7.8	>80			
	$HIV\text{-}2_{EHO}$	MT-4	1.0	>80			
	SIV_{MAC251}	MT-4	2.8	>80			
	MLSV, cell transformation	C3H/3T3	>300	>80			
	$HIV\text{-}1_{IIIB}$, giant cell formation	MOLT-4	>60	>80			
	$HIV\text{-}2_{ROD}$, giant cell formation	MOLT-4	>60	>80			

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[Nb_4W_2O_{19}]^{6-}$							
$[Na/K]_6$[36]	Sindbis	Vero	>244	>80			
	Semliki Forest	Vero	>244	>80			
	measles	Vero	>122	>80			
	RSV	HeLa	>122	>80			
	ParaFluV	Vero	>244	>80			
	Junin	Vero	>122	>80			
	Tacaribe	Vero	>122	>80			
	VSV	HeLa	>244	>80			
	polio-1	HeLa	>244	>80			
	reo-1	Vero	>244	>80			
	$HSV\text{-}1_{KOS}$	E_6SM	>122	>90			
	$HSV\text{-}1_{B2006(TK^-)}$	E_6SM	>122	>90			
	$HSV\text{-}1_{VMW1837(TK^-)}$	E_6SM	>122	>90			
	HSV-2 (G)	E_6SM	>122	>90			
	CMV_{AD-169}	HeLa	12.2	>90			
	CMV_{Davis}	HeLa	9.2	>90			
	vaccinia	E_6SM	>122	>90			
					>12.2		
$[CH_3Sn(Nb_6O_{19})]^{5-}$							
Na_5[62]	RSV	Ma 104	0.7	>100			CPE inhibition assay
	RSV	Ma 104	0.3	95			neutral red assay
							p66 HIV-1 RT and virion derived $HIV\text{-}1_{IIIB}$ used
$[PTi_2W_{10}O_{40}]^{7-}$							
$(ArgH^+)_nNa_{(7-n)}$[62]	RSV	Ma 104	7.0	90			CPE inhibition assay
	RSV	Ma 104	6.0	>100			neutral red assay
	RSV, strain A2	Ma 104	46	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	40	>100			neutral red assay
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4	4.0	270			
					15*, 62#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$(Me_4N)_7$[34]	$HIV\text{-}1_{IIIB}$	MT-4	4.4	260			
					17*, 46#		
Ce_2H[95]	HIV-1	MT-4	5.5	270			
Pr_2H[95]	HIV-1	MT-4	4.2	288			
Nd_2H[95]	HIV-1	MT-4	6.2	262			
Gd_2H[95]	HIV-1	MT-4	7.3	241			
Tb_2H[95]	HIV-1	MT-4	10.5	220			
Yb_2H[95]	HIV-1	MT-4	9.0	209			
K_7[95]	HIV-1	MT-4	5.6	280			
K_7[71]	HIV-1	*	5.6				*cell line not given
	FLV	*	5.0				
$[PGe_2W_{10}O_{40}]^{7-}$							
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4	7.9	38			
					27*, 29#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[PSe_2W_{10}O_{40}]^{7-}$							
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4		280			
					5*, 93#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[PSi_2W_{10}O_{40}]^{7-}$							
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4	5.1	130			
					31*		*percent inhibition at 50 μg/mL
$[PTe_2W_{10}O_{40}]^{7-}$							
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4		<3.1			
					4*, 5#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[BTi_2W_{10}O_{40}]^{9-}$							
K_9[34]	$HIV\text{-}1_{IIIB}$	MT-4	71	260			
					95*, 100#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[SiTi_2W_{10}O_{40}]^{7-}$							
K_7[34]	$HIV\text{-}1_{IIIB}$	MT-4	13.5	300			
					100*, 100#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[PTiW_{11}O_{40}]^{5-}$							
$(i\text{-}Pr_2NH_2)_5$[42]	$HIV\text{-}1_{IIIB}$	MT-4	17.0	389			
$(i\text{-}Pr_2NH_2)_5$[42]	$HIV\text{-}1_{SF-2H}$	MT-4	0.319	476			
K_5[34]	$HIV\text{-}1_{IIIB}$	MT-4	30	>1600			
					99*, 100#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$[PTiW_{11}O_{39}(O_2)]^{5-}$							
$(i\text{-}Pr_2NH_2)_5$[42]	$HIV\text{-}1_{IIIB}$	MT-4	20.8	341			
$(i\text{-}Pr_2NH_2)_5$[42]	$HIV\text{-}1_{SF-2H}$	MT-4	0.343	469			

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[BGa(H_2O)W_{11}O_{39}]^{6-}$							
K_6[36]	HIV-1_{IIIB}	MT-4	0.1	>80			
	HIV-1_{RF}	MT-4	0.8	>80			
	HIV-1_{HE}	MT-4	0.2	>80			
	HIV-2_{ROD}	MT-4	0.2	>80			
	HIV-2_{EHO}	MT-4	1.1	>80			
	SIV_{MAC251}	MT-4	0.03	>80			
	MLSV, cell transformation	C3H/3T3	20.2	>80			
	HIV-1_{IIIB}, giant cell formation	MOLT-4	1.9	>80			
	HIV-2_{ROD}, giant cell formation	MOLT-4	0.6	>80			
	Sindbis	Vero	6.2	>80			
	Semliki Forest	Vero	93	>80			
	measles	Vero	>62	>80			
	RSV	HeLa	21.7	>80			
	ParaFluV	Vero	>124	>80			
	Junin	Vero	17.1	>80			
	Tacaribe	Vero	18.6	>80			
	VSV	HeLa	14	>80			
	polio-1	HeLa	>124	>80			
	reo-1	Vero	>124	>80			
					0.02		p66 HIV-1 RT and virion derived
					0.19		HIV-1_{IIIB} used
$[PrW_{10}O_{35}]^{7-}$							
Na_7[36]	HIV-1_{IIIB}	MT-4	1.3	>80			
	HIV-1_{RF}	MT-4	2.4	>80			
	HIV-1_{HE}	MT-4	0.3	>80			
	HIV-2_{ROD}	MT-4	1.1	>80			
	HIV-2_{EHO}	MT-4	0.2	>80			
	SIV_{MAC251}	MT-4	0.1	>80			
	MLSV, cell transformation	C3H/3T3	4.6	>80			
	HIV-1_{IIIB}, giant cell formation	MOLT-4	30.4	>80			
	HIV-2_{ROD}, giant cell formation	MOLT-4	>30	>80			
	Sindbis	Vero	>132	>80			
	Semliki Forest	Vero	>132	>80			
	measles	Vero	>66	>80			
	RSV	HeLa	>66	>80			
	ParaFluV	Vero	>132	>80			
	Junin	Vero	>66	>80			
	Tacaribe	Vero	>66	>80			
	VSV	HeLa	99	>80			
	polio-1	HeLa	>132	>80			
	reo-1	Vero	>132	>80			
	HSV-1_{KOS}	E_6SM	>66	>90			
	HSV-$1_{B2006(TK^-)}$	E_6SM	33	>90			
	HSV-$1_{VMW1837(TK^-)}$	E_6SM	>66	>90			
	HSV-2 (G)	E_6SM	44.6	>90			
	CMV_{AD-169}	HeLa	35	>90			
	CMV_{Davis}	HeLa	13.5	>90			
	vaccinia	E_6SM	>66	>90			
					>6.6		p66 HIV-1 RT and virion derived HIV-1_{IIIB} used
$[PTi_2W_{10}O_{40}]^{7-}$							
K_7[42]	HIV-1_{IIIB}	MT-4	3.9	138			
$(Me_4N)_7$[42]	HIV-1_{IIIB}	MT-4	4.4	262			
K_7[42]	HIV-1_{SF-2H}	MT-4	0.081	342			
$(Me_4N)_7$[42]	HIV-1_{SF-2H}	MT-4	0.066	328			
$[PTi_2W_{10}O_{38}(O_2)_2]^{7-}$							
$[(i\text{-}PrNH_3)_6H]$[45]	FluV-A/Ishikawa	MDCK	1.5	>100			
	FluV-A	MDCK	2.4				IC_{50} determined by
	FluV-B	MDCK	39.3	>400			MTT (stationary state)
	RSV	MDCK	3	201			TB exclusion (stationary state)
	PFluV-2	MDCK	2.7	213			MTT (growing state)
	measles	MDCK	11.0	43.3			TB exclusion (growing state)
$[(i\text{-}PrNH_3)_6H]$[42]	HIV-1_{IIIB}	MT-4	4.6	148			
Cs_7[42]	HIV-1_{IIIB}	MT-4	4.8	129			
$[(i\text{-}PrNH_3)_6H$[42]	HIV-1$SF_{-2}H$	MT-4	0.047	310			
$[A\text{-}\alpha\text{-}GeNb_3W_9O_{40}]^{7-}$							
K_7[62]	RSV	Ma 104	0.3	>100			CPE inhibition assay
	RSV	Ma 104	0.1	63			neutral red assay
	RSV, strain A2	Ma 104	1.0	>100			CPE inhibition assay
	RSV, strain A2	Ma 104	2.0	>100			neutral red assay

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[A\text{-}\alpha\text{-}GeNb_3W_9O_{40}]^{7-}$							
K_7[62]	RSV (Long)	HEp-2	1.0	>100			CPE inhibition assay
	RSV (Long)	HEp-2	1.0	>100			neutral red assay
	RSV (18357)	Ma 104	1.0	>100			CPE inhibition assay
	RSV (18357)	Ma 104	1.0	>100			neutral red assay
K_7[72]	FluV-A/Texas	MDCK	0.25	>100			
	FluV-A/NWS	MDCK	6.6	>100			mean IC_{50} and EC_{50} values were
	FluV-A/Beijing	MDCK	15.5	>100			determined by NR dye uptake
	FluV-A/ Port Chalmers	MDCK	5.2	>100			
	FluV-B/Panama	MDCK	5.0	>100			
	FluV-B/Hong Kong	MDCK	0.6	>100			
$[NbP_2W_{17}O_{62}]^{7-}$							
K_7[44]	FluV-A	MDCK	2.2	56.6			
	RSV	HEp-2	1.0	8.0			
	MLSV	HMV-2	>4.5	12.8			
	HIV-1_{LAI}	PBMC	0.2	49.7			
$[(NbO_2)_6P_2W_{12}O_{56}]^{12-}$							
K_{12}[44]	FluV-A	MDCK	2.1	100			
	RSV	HEp-2	11.6	11.6			
	MLSV	HMV-2	>50	>50			
	HIV-1_{LAI}	PBMC	0.1	58.4			
K_{12}[47]						0.55	assayed using NENQUEST system
$[Nb_6P_2W_{12}O_{62}]^{12-}$							
K_{12}[62]	RSV	Ma 104	0.2	2			CPE inhibition assay
	RSV	Ma 104	0.2	4			neutral red assay
	RSV, strain A2	Ma 104	<0.1	25			CPE inhibition assay
	RSV, strain A2	Ma 104	0.1	26			neutral red assay
K_{12}[44]	FluV-A		1.5				
	RSV	MDCK	>10	>100			
	MLSV	HEp-2	1.2	10.0			
	HIV-1_{LAI}	HMV-2	0.3	44.2			
	FluV-A (Ishikawa)	PBMC	2.8	75.0			
	FluV-B (Singapore)		36.5				
	RSV-A (Long)		14.2				
	RSV-A (FM-58-8)		8.5				
	RSV-B (SM61-48)		2.7				
	MLSV (Edmonston)	MDCK	1.4	164			
	MPSV (EXCH-3)	HEp-2	>50	82.7			
	PFluV-2 (Greer)	HMV-2	24.1	53.7			
	PFluV-3 (C243)	Vero	>50	>200			
K_{12}[47]						0.43	assayed using NENQUEST system
$[P_2W_{18}O_{62}]^{6-}$							
K_6[45]	FluV-A/Ishikawa	MDCK	1.6	74			
H_6[43]	HIV-1_{LAI}	PBMC	0.52	6.2			
$(NH_4)_6$[32,43]	HIV-1_{LAI}	PBMC	0.91	1.8			
$(NH_4)_6$[44]	FluV-A	MDCK	1.2	>100			
	RSV	HEp-2	0.9	12.4			
	MLSV	HMV-2	1.9	30.0			
	HIV-1_{LAI}	PBMC	0.9	1.8			
$(NH_4)_6$[47]						11.4	assayed using NENQUEST system
$[KSb_9W_{21}O_{86}]^{18-}$							
K_{18}[45]	FluV-A/Ishikawa	MDCK	1.7	49			EC_{50} and IC_{50} values are average of
K_{18}[34,42]	HIV-1IIIB	MT-4		27.7			two independent experiments
					24*		*percent inhibition at 50 μg/mL
$[(NH_4)_{17}Na]$[24]	RV	CER	6.3	100**			**actual IC_{50} not reported, this
	VSV	CER		100**			value represents concentration where partial cell division was inhibited
$[(NH_4)Sb_9W_{21}O_{86}]^{18-}$							
$(NH_4)_{18}$[42]	HIV-1_{IIIB}	MT-4		5.6			
					4*		*percent inhibition at 50 μg/mL
$[SrSb_9W_{21}O_{86}]^{17-}$							
$[(NH_4)_{17}Na]$[24]	RV	CER	6.3	>100			
	VSV	CER		>100			
$[\text{-}Sb_9W_{21}O_{86}]^{18-}$							
$[(NH_4)_{17}Na]$[24]	RV	CER	6.3	>100			
	VSV	CER		>100			
$[(NaSb_9W_{21}O_{84})Fe_2]^{17-}$							
$(NH_4)_{17}$[24]	RV	CER	6.3	>100			
	VSV	CER		>100			
$[(NaSb_8W_{21}O_{84})Co_2]^{17-}$							
$(NH_4)_{17}$[24]	RV	CER	6.3	>100			
	VSV	CER		>100			
$(NH_4)_9Na_9$[71]	HIV-1	*	1.6				*cell line not given
	FLV	*	2.0				

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[PVW_{11}O_{40}]^{5-}$							
K_5[42]	HIV-1_{IIIB}	MT-4	21.5	135			
K_5[42]	HIV-1_{SF-2H}	MT-4	2.93	310			
K_5[34]	HIV-1_{IIIB}	MT-4	29	270			
					19*, 98[#]		*percent inhibition at 50 μg/mL, [#]percent inhibition at 10 μg/mL
$[PV_2W_{10}O_{40}]^{5-}$							
K_5[34,42]	HIV-1_{IIIB}	MT-4	6.4	221			
K_5[42]	HIV-1_{SF-2H}	MT-4	0.067	83.4			
K_5[71]					61*		*percent inhibition at 50 μg/mL
	HIV-1	*	1.0				*cell line not given
	FLV	*	2.5				
$[PMo_2W_9O_{39}]^{7-}$							
K_7[42]	HIV-1_{IIIB}	MT-4		203			
K_7[42]	HIV-1_{SF-2H}	MT-4		305			
K_7[41]	HIV-1_{IIIB}	MT-4	82	160			
$[PMo_3W_9O_{40}]^{3-}$							
K_3[42]	HIV-1_{IIIB}	MT-4		298			
K_3[42]	HIV-1_{SF-2H}	MT-4		362			
K_3[41]	HIV-1_{IIIB}	MT-4	83	150			
$[NiMo_9O_{32}]^{6-}$							
Na_6[41,42]	HIV-1_{IIIB}	MT-4		14			
$[MnMo_9O_{32}]^{6-}$							
Na_6[41]	HIV-1_{IIIB}	MT-4		33			
$[PMo_9W_3O_{40}]^{3-}$							
K_3[42]	HIV-1_{IIIB}	MT-4		243			
K_3[42]	HIV-1_{SF-2H}	MT-4		331			
K_3[34,41]	HIV-1_{IIIB}	MT-4		240			
$[Mo_9V_3O_{38}]^{7-}$							
K_5NaH[41]	HIV-1_{IIIB}	MT-4		4.4			
$[PMo_9O_{34}]^{9-}$							
Na_3H_6[42]	HIV-1_{IIIB}	MT-4		344			
Na_3H_6[34,41]	HIV-1_{IIIB}	MT-4		430			
$[SiVW_{11}O_{40}]^{5-}$							
K_5[45]	FluV-A/Ishikawa	MDCK	4.4	>100			
K_5[42]	HIV-1_{IIIB}	MT-4	4.8	180			
K_5[42]	HIV-1_{SF-2H}	MT-4	0.241	299			
K_5[34]	HIV-1_{IIIB}	MT-4	6.1	220			
					7**, 37[#]		*percent inhibition at 50 μg/mL, [#]percent inhibition at 10 μg/mL
$[Ge_2Ti_6W_{18}O_{77}]^{14-}$							
K_9H_5[45]	FluV-A/Ishikawa	MDCK	0.9	>100			
	FluV-A	MDCK	1.3				IC_{50} determined by
	FluV-B	MDCK	68.3	>400			MTT (stationary state)
	RSV	MDCK	5.3	116			TB exclusion (stationary state)
	PFluV-2	MDCK	93.2	166			MTT (growing state)
	measles	MDCK	9.6	34			TB exclusion (growing state)
$[KAs_4W_{40}O_{140}]^{27-}$							
K_{27}[34,42]	HIV-1_{IIIB}	MT-4	13.5	73.1			
K_{27}[42]	HIV-1_{SF-2H}	MT-4	25	333			
					53*, 95[#]		*percent inhibition at 50 μg/mL, [#]percent inhibition at 10 μg/mL
$[NaP_5W_{30}O_{110}]^{14-}$							
$(NH_4)_{14}$[32,43]	HIV-1_{LAI}	PBMC	0.32	7.7			
$(NH_4)_{14}$[44]	FluV-A	MDCK	0.23	16.0			
	RSV	HEp-2	>1.1	1.1			
	MLSV	HMV-2	>3.7	3.9			
	HIV-1_{LAI}	PBMC	0.3	7.7			
$(NH_4)_{14}$[47]						0.86	assayed using NENQUEST system
$[Mo_7O_{24}]^{6-}$							
$(i\text{-}PrNH_3)_6$[42]	HIV-1_{IIIB}	MT-4		260			
$(i\text{-}PrNH_3)_6$[42]	HIV-1_{SF-2H}	MT-4		370			
$(NH_4)_6$[41]	HIV-1_{IIIB}	MT-4		570			
$(i\text{-}PrNH_3)_6$[41]	HIV-1_{IIIB}	MT-4		260			
$[W_4O_{10}(O_2)_6]^{4-}$							
K_4[32,43]	HIV-1_{LAI}	PBMC	>50	>100			
$[MoO_4]^{2-}$							
Na_2[41]	HIV-1_{IIIB}	MT-4		>800			
$[Mo_7O_{26}]^{6-}$							
$(i\text{-}PrNH_3)_5H$[41]	HIV-1_{IIIB}	MT-4		280			
$[Mo_{14}O_{46}]^{10-}$							
$(Me_4N)_2(NH_4)_8$[41]	HIV-1_{IIIB}	MT-4		500			
$[Mo_8O_{26}]^{4-}$							
$(n\text{-}Bu_4N)_4$[32,43]	HIV-1_{LAI}	PBMC	55.3	>100			

Table 1. Continued

POM counterion and reference	virus[a]	cell line[b]	antiviral activity EC_{50}, μM	toxicity IC_{50}, μM	HIV RT/ polymerase[c] IC_{50}, μM	gp120-CD4 IC_{50}, μM	comments
$[Nd_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$							
$(NH_4)_{12}H_2$[41]	HIV-1_{IIIB}	MT-4		430			
$[Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$							
$(NH_4)_{12}H_2$[34,41,42]	HIV-1_{IIIB}	MT-4	4.4	300			
					14*, 29#		*percent inhibition at 50 μg/mL, #percent inhibition at 10 μg/mL
$(NH_4)_{12}H_2$[96]	HIV-1_{IIIB}	MT-4	12.5**	200			**EC_{100} value reported
$[Pr_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$							
$(NH_4)_{12}H_2$[41]	HIV-1_{IIIB}	MT-4		320			
$[La_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$							
$(NH_4)_{12}H_2$[41]	HIV-1_{IIIB}	MT-4		500			
$[Ce_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$							
$(NH_4)_{12}H_2$[41]	HIV-1_{IIIB}	MT-4		440			
$[Sm_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4]^{14-}$							
$(NH_4)_{12}H_2$[41]	HIV-1_{IIIB}	MT-4		210			
$[Eu_3(H_2O)_3(W_5O_{18})_3(SbW_9O_{33})]^{18-}$							
$K_{15}H_3$[34,42]	HIV-1_{IIIB}	MT-4		150			
					4*		*percent inhibition at 50 μg/mL
$[V_{15}O_{36}(CO_3)]^{7-}$							
K_5H_2[41]	HIV-1_{IIIB}	MT-4		2.2			
$[MnV_{13}O_{38}]^{7-}$							
K_7[94]	vaccinia	MEF		<10			
$[NiV_{13}O_{38}]^{7-}$							
K_7[42]	HIV-1_{IIIB}	MT-4		0.5			
K_7[94]	vaccinia	MEF		<10			
AZT (Zidovudine)[32,41-44]	HIV-1_{LAI}	PBMC	0.004	>100			
phosphonoformate[35]	HIV-1_{LAI}	PBMC	21.0	>100			
					0.15		
ribavirin[62]	RSV	Ma 104	30	800			CPE inhibition assay
	RSV	Ma 104	20	400			neutral red assay
	RSV, strain A2	Ma 104	20	1310			CPE inhibition assay
	RSV, strain A2	Ma 104	40	520			neutral red assay
	RSV (Long)	HEp-2	10	740			CPE inhibition assay
	RSV (Long)	HEp-2	4.0	500			neutral red assay
	RSV (9320)	Ma 104	120	2825			CPE inhibition assay
	RSV (9320)	Ma 104	30	300			neutral red assay
	RSV (18357)	Ma 104	40	1400			CPE inhibition assay
	RSV (18357)	Ma 104	30	1530			neutral red assay
	Bovine RSV	EBTr	410	4100			CPE inhibition assay
	Bovine RSV	EBTr	120	4100			neutral red assay
ribavirin[72]	FluV-A/Texas	MDCK	8.6	620			mean IC_{50} and EC_{50} values were determined by NR dye uptake
	FluV-A/NWS	MDCK	19.2	620			
	FluV-A/Beijing	MDCK	7.6	620			
	FluV-A/ Port Chalmers	MDCK	79.9	620			
	FluV-B/Panama	MDCK	11.5	620			
	FluV-B/ Hong Kong	MDCK	5.8	620			
ribavirin[45]	FluV-A	MDCK	9.8				IC_{50} determined by
	FluV-B	MDCK	21.6	>400			MTT (stationary state)
	RSV	MDCK	8.6	>400			TB exclusion (stationary state)
	ParaFluV-2	MDCK	57.7	>400			MTT (growing state)
	measles	MDCK	59.0	160			TB exclusion (growing state)
ribavirin[44]	FluV-A	MDCK	8.7	>100			
	RSV	HEp-2	4.7	>50			
	MLSV	HMV-2	5.2	>100			
	HIV-1_{LAI}	PBMC					

[a] Abbreviations used for viruses: HIV, human immunodeficiency virus; RSV, respiratory syncytial virus; SIV, simian immunodeficiency virus; MLSV, murine leukemia sarcoma virus; VSV, vesicular stomatitis virus; HSV, herpes simplex virus; CMV, cytomegalovirus; FluV-"x", FluV virus, strain "x"; RV, rabies virus; MPSV, myeloproliferative sarcoma virus. [b] Abbreviations used for cell-lines: Ma 104, embryonic African green monkey kidney cells; MT-4, human T-cell leukemia isolated from patients with adult T-cell leukemia, HTLV-1 transformed; C3H/3T3, malignant C3H/3T3 mouse cells MO4; Vero, normal African green monkey kidney cells; HeLa, adenocarcinoma from cervix of a 31-year-old black woman, epithelial morphology; MOLT-4, acute lymphoblastic leukemia, T-cell origin; E_6SM, human embryonic skin-muscle fibroblast; MDCK, Madin–Darby canine kidney cells; CER, chick embryo related; HEp-2, human larynx epidermoid carcinoma cells; HMV-2, melanoma cell line; PBMC, peripheral blood mononuclear cells; EBTr, bovine embryonic trachea cells; MEF, mouse embryo fibroblast. [c] Abbreviations used for HIV RT/polymerases in comments column: HIV-1 RT, human immunodeficiency virus reverse transcriptase; MSLV RT, murine sarcoma leukemia virus reverse transcriptase; AMV RT, avian myeloblastosis virus reverse transcriptase; DNA P, DNA polymerase.

the reader may obtain the desired information quickly. The first column in Table 1 gives the POM with its counterion(s). Columns 2 and 3 list the virus strain and the cell line in which the studies were conducted, respectively. Column 4 lists the antiviral activity of the POM (effective concentration for 50% virus sup-

pression; EC_{50} value), and column 5 lists the toxicity of the POM (effective concentration for 50% inhibition of cell growth, IC_{50} value). Column 6 contains HIV-1 reverse transcriptase data in cell-free systems (see below), column 7 contains gp120-CD4 binding data, and column 8 provides comments pertinent to the studies. Evaluation of a promising antiviral agent in vitro should result in a low EC_{50}, a high IC_{50}, and a high therapeutic (selectivity) index, $SI = IC_{50}/EC_{50}$ (>5). Some currently used antiviral chemotherapeutic agents are listed at the end of the table for purposes of comparison. Much of this work was reviewed through 1992.[6,7]

POMs have been shown to selectively inhibit in vitro the replication of retro-, toga-, paramyxo-, flavi-, and several herpesviruses, including herpes simplex virus type 1 and 2 (HSV-1 and -2), and cytomegalovirus (CMV). Of significance was the finding that most POMs are highly effective against HIV-1, HIV-2, and simian immunodeficiency virus (SIV) in culture. Their activity is primarily antiviral and not virucidal (i.e., they do not interact directly with the virus in cell-free systems). The last 15 years has witnessed the development of new classes of POMs that have significantly better SI values than HPA-23 against HIV-1 and other viruses in cell culture and with significantly lower bone marrow toxicity.

The utility of POMs against flaviviruses has recently been reported by Bartholomeusz and coworkers in Australia.[30] The family Flaviviridae contain a plus-sense RNA genome and contains many human infectious agents, particularly yellow fever, Dengue, Japanese encephalitis virus, and hepatitis C virus. The high genetic similarity between these viruses suggests that some POMs could also interfere with their replication cycle. Clearly more work on the ability of POMs to selectively inhibit these viruses is warranted.

C. Mode of Antiviral Action

While the inhibition of viruses by POMs has been well documented, the primary mechanism for antiviral action has remained elusive. The data outlined below and the physical properties of POMs are consistent with multiple modes of action. The most likely of these are inhibition of viral enzymes (reverse transcriptase, RT, and/or protease in retroviruses) or surface viral proteins, such as gp120 for HIV.

In 1972, Raybaud et al. studied the effects of polytungstosilicates, polytungstoborates and polymolybdosilicates on VSV.[19] The group noted that these POMs may affect the cellular membrane. If cells were treated with POM immediately after infection, fewer cells became infected than in the control sample. However, if the cells were treated for 16 h before infection, the number of infections increased. Without proposing a possible mechanism, this group postulated that the POMs must act on viral replication.

Jasmin et al. also studied the effects on polytungstosilicates on different RNA viruses.[21] The primary mode of viral inhibition was speculated to be blockage of viral adsorption and penetration into the cell. Such blockage was reasoned to result from the polyanionic nature of POMs. Polyanionic species such as heparin and dextran sulfate have long been known to act at the cell surface.[31,32] By the same token, the Jasmin group believed that the polyanionic nature of the POM may alter the charge of the cell membrane interfering with viral adsorption. No definitive data addressing this point were given. These authors also noted the POM may exhibit other modes of action, notably interrupting the enzymes required for viral adsorption.

In 1975, Chermann et al. conducted tests on the effect of HPA-23 on MLV RNA dependent DNA polymerase.[22] Their results indicated that HPA-23 was acting directly on the enzyme, in the presence of the template. The inhibition was reversible and competitive between the POM and the enzyme, indicating that the POM binds to the enzyme active site with the template and not at the substrate. The authors cited unpublished work which detailed the selectivity of HPA-23 for particular polymerases. They contended that HPA-23 inhibits viruses on the basis of its selective action against the enzymatic polymerization step.

Hervé et al. suggested that inhibition of nonhuman retroviruses by certain POMs may occur by binding of the compounds to the RNA template, blocking reverse transcriptase (RT).[33] In *Escherichia coli*, HPA-23 was inferred to bind the RNA polymerase on the basis of kinetic analysis, implicating an irreversible inhibition of the enzyme. The polyanionic POM was proposed to bind to the polycationic polymerase template electrostatically. Consequently, the charge and size of the POM was postulated to be a factor in viral polymerase inhibition. In support of this, the study showed that the viral enzyme inhibition increased in the order of molecular charge (e.g., TS < TA < TAs, where TS are tungstosilicates, TA are tungstoantimoniates, and TAs are tungstoarsenates). However, other possibilities could not be ruled out.[33]

Another French group, Bussereau and Ermine, investigated the antiviral activity and mechanism of action of HPA-23 and its potassium analogue.[25] Two key points were noted: first, both mRNA and double-stranded RNA were inhibited by the POMs; second, POMs modified the rate of cellular protein synthesis, implying the POMs affected either the viability of the mRNA or the frequency of translation. These investigators hypothesized that the POM may be affecting the virus in two ways, inhibition of the transcriptase within the infectious virion and/or inhibition of viral development (budding). Bussereau and Ermine also noted the presence POMs within the cell in the form of "electron-dense granules" (see section III).

In 1992, Inouye et al. provided further support that POM antiviral activity may stem from inhibition of RT. However, this group noted that there was no correlation between RT inhibition and anti-HIV-1 activity.[34] Like Hervé et al., Inouye and co-workers surmised that POMs may also interfere with earlier stages of viral infection.

Weeks et al. studied the inhibition of RT using POMs with organic groups covalently attached through Si−O linkages.[35] These compounds were

targeted by the Hill group to increase their oral bioavailability. Most of the compounds evaluated were significantly more active against HIV-1 RT than against cellular DNA polymerase, demonstrating a preference for the HIV-1 RT. Also, the IC_{50} for HIV-1 RT was lower than the EC_{50} for HIV-1 activity in PBM cells for 3 of 4 of the compounds examined, suggesting that there must be some other contribution to viral inhibition. Like the Hervé and Inouye groups, Weeks et al. noted that other factors, such as fusion interruption, may be significant in viral inhibition (vide infra).[35]

Yamamoto et al. provided further support for this line of reasoning.[36] Enzymatic studies demonstrated that several structural classes of POMs inhibit HIV-1 RT in a concentration dependent manner. As indicated by the data of Weeks et al., however, the degree of RT inhibition was not comparable to the degree of HIV-1 inhibition in cells. The IC_{50} of HIV virion-derived RT was greater than that for recombinant RT. This was attributed to POM−virion protein binding at nonspecific sites.[36]

Similar results were obtained in subsequent additional work by the Hill/Schinazi group.[37] Kim et al. studied four mono- and trisubstituted peroxyniobium POMs and their biological activity. The niobium-containing POMs exhibited antiviral activity similar to that of their synthetic precursor, $[SiW_{11}O_{39}]$,$^{8-}$ yet were found to be less toxic. This study also noted that the inhibition of HIV-1 RT did not correlate with the inhibition of HIV-1, and that POMs exhibited greater potency against HIV-1 RT than DNA polymerase. Further, the IC_{50} values for RT inhibition were lower than the EC_{50} values for HIV-1 inhibition, again, suggesting some other mode of inhibition must be present. Subsequent work with a hexasubstituted peroxoniobium Wells−Dawson POM, $[P_2W_{12}(NbO_2)_6O_{56}]$,$^{12-}$ gave similar results.[38−40]

A shift in the focus of POM antiviral activity away from exclusive RT or polymerase inhibition and toward interference with viral absorption has taken place in recent years.[32] Strong interaction between a chemotherapeutic agent and viral surface proteins can lead to inhibition of virus−cell recognition and viral penetration into the cell (viral infectivity). In addition, since infected cells often express the same viral protein on their surfaces, drug−surface protein interactions can inhibit cell fusion (syncytium formation). Nearly all the early experimental work on POM antiviral activity addressed inhibition of RT. While the blockage of viral adsorption by POMs was postulated as early as 1973 by Jasmin and mentioned several times by other groups since then, experimental data establishing the frequency of this phenomenon has only been available recently.

Inhibition of viral adsorption/fusion as a function of POM structure in a cell-based assay was first studied by Hill et al.[32] This work indicated that $[SiW_{12}O_{40}]^{4-}$, $[BW_{12}O_{40}]^{5-}$, and $[NaSb_9W_{21}O_{86}]^{18-}$ were able to completely inhibit cell fusion in HIV-infected lymphocytes at concentrations of 50 and 150 μM after 24 or 72 h of incubation. A limited correlation between POM size or charge density and antiviral activity was also reported. Smaller and/or less charged POMs were less effective inhibitors than the larger and/or more charged POMs.[32,41]

Time-of-addition studies by Yamamoto's group in HIV-infected MT-4 cells by a range of heteropolytungstates were consistent with interference of cellular adsorption of the virus by some POMs. They concluded that the majority of inhibitory action was linked to this interruption of viral adsorption and not inhibition of RT.[36]

Inouye et al. used a Eu-containing POM of formula $[(Eu_4(MoO_4)(H_2O)_{16}(Mo_7O_{24})_4)]^{14-}$ to further study the interruption of viral adsorption by POMs.[41] Time-of-addition studies were consistent with the inhibition of viral adsorption and/or penetration into the target cell by this POM. Competition studies involving $CD4^+$ in a co-culture of HIV-1 infected cells provided additional evidence that POMs inhibited syncytium formation. It was noted that inhibition of syncytium formation may be possible only with compounds that interfere with the binding of gp120 to CD4. This study also reported that the POMs of focus did inhibit HIV-1 RT, but there was no correlation between this and viral inhibition.[41]

In a subsequent investigation, Inouye et al. provided additional evidence for the interference of adsorption of $HIV\text{-}1_{SF-2H}$ and $HIV\text{-}1_{IIIB}$ by POMs.[42] They demonstrated using a syncytium formation inhibition assay that POMs were effective in blocking viral adsorption by interacting with the gp120 glycoprotein. As in the study by Hill et al.,[43] Inouye's group showed the ability of POMs to block the adsorption process may hinge on the structure, shape, or charge of the compound.

In 1995, Shigeta et al. provided data that showed some POMs blocked the fusion process for myxoviruses, while others did not.[44] By using a variety of viruses and POMs in time-of-addition studies, Shigeta et al. showed that adsorption was not interrupted in some cases (e.g., FluV-A in MDCK cells). However, after infection, the POM was effective in viral inhibition. Their data also indicated that RSV infection was prevented by some POMs, consistent with a role for POMs involving the inhibition of viral adsorption.[44] In a different study, the Shigeta and Schinazi groups provided additional evidence for selectivity with respect to fusion inhibition by POMs (some POMs active and others are inactive) by evaluating more POMs against different viruses.[45] Again, antibinding and fusion activities were found to be highly dependent on POM structure, cell line, and virus. For example, the Keggin sandwich compound $K_{10}Fe_4(H_2O)_2(PW_9O_{34})_2$ exhibited significant inhibitory activity against influenza A and B, RSV, measles virus, and parainfluenza virus 2, but no inhibitory activity against parainfluenza virus 3 or mumps virus. The most effective POMs against virus infection had Nb or Fe units incorporated into the POM structure. These reinforce the point that composition, charge, and size of POMs may all be interrelated in antiviral action.

In recent work, Kim et al. documented POM inhibition of the gp120-CD4 binding interaction using an immunosorbent assay. The data in this study

were consistent with POM inhibition of both RT and viral fusion to $CD4^+$ cells.[37]

Our group recently reported the selective anti-HIV-1 protease activity of a number of POMs at low micromolar concentrations.[39,46] The same compounds did not inhibit cellular aspartyl proteases such as pepsin even at 100 μM.

Upon collective consideration of all reports to date, it is likely that POM charge and charge density are an important consideration in the efficacy of binding inhibition. At the same time, the study of Judd et al. indicated that the correlation between charge density and inhibition of the gp120-CD4 interaction is marginal at best.[47]

D. Selectivity

While the early papers on the antiviral properties of POMs gave the impression that such activity is widespread (many POMs appeared to inhibit most of viruses evaluated), the compendium of data currently available clearly establishes that this is not the case. POM antiviral activity varies considerably not only with the structural class, composition, size, and charge of the POM, but also with the virus and viral strain and the cell line at parity of virus strain. Many of these data are cited in the previous section (IV.C) or in Table 1.

We note here three exemplary observations. First, a range of cell culture studies establish that antibinding and fusion activities by POMs are highly dependent on POM structure, cell line, and virus. Second, enzymic studies indicate that POMs exhibit selectivity, most notably a preference for HIV-1 RT over cellular DNA polymerase.[35−37] Third, some POMs (e.g., $[Ti_2PW_{10}O_{40}]^{7-}$) inhibit several members of one class of viruses (e.g., herpesviruses) but do not inhibit several other types (e.g., adenovirus, vaccinia virus, or varicella-zoster virus).

In addition to factors intrinsic to the polyanion unit in POMs itself (e.g., structure, size, charge, etc.), the countercations of the POM play a significant role in biological activity and selectivity. Unfortunately, ion pairing in POM salts (cation−POM anion interactions) in water as well as other solvents is highly complex and consequently difficult to investigate rigorously. There are a few informative studies of ion pairing in POMs. Specifically, X-ray crystallographic studies have established that the choice of cation in POM synthesis under conditions similar to those encountered in mammalian tissue can give rise to different POM structures,[48−53] while many structural studies (primarily X-ray and NMR) have implicated that the protons on heteropoly acids can be found either on the POM unit (usually on bridging oxygen atoms which are the most negatively charge and basic)[54] or associated with proximal solvent molecules.[55−58] A few papers characterize ion pairing in POMs by reactivity and spectroscopic methods.[3,59,60] The collective literature on ion pairing in POMs does yet provide a dependable and quantitative predictive paradigm as to where the cations on a particular POM will be or their role in the association processes that doubtless underlie drug transport, activity, and toxicity.

The data in Table 1 clearly indicate that varying the counterion affects the POM antiviral activity and cytotoxicity.[32,61−63] For example, $(NH_4)_5[BW_{12}O_{40}]$ exhibits an EC_{50} of 1.0 μM against RSV in Ma 104 cells, whereas the $(NH_4)_nH_{(5-n)}$ salt of this POM exhibits an EC_{50} value of 6 μM in the same evaluation.[62] Similarly, the IC_{50} for $(NH_4)_nH_{(5-n)}[BW_{12}O_{40}]^{5-}$ is 40 μM, however, when the counterion is changed to K_5, the IC_{50} value becomes 194 μM.[42,62] The SI values for most POMs compare favorably with those of commercial drugs. For example, the SI of ribavirin against RSV in the MDCK cell line is >11.5, whereas the SI of $Na_{16}[Ni_4(H_2O)_2(P_2W_{15}O_{56})]$ is 111, in the same evaluation.[44]

In addition to interactions between counterion and the polyanion moieties, interactions between organic functions and the polyanions are also likely to be quite significant in the molecular biology of POMs. In particular, the experimental delineation of interactions between POMs and the amino acid side group functions and peptides of the POM binding regions in POM-affected proteins would be of much intellectual and perhaps developmental interest. Unfortunately, such interactions are minimally characterized at present. There is one X-ray structural investigation of a POM in which the unit cell contains a peptide. In this study, Crans and co-workers, in conjunction with their studies of enzyme inhibition by vanadates,[64−67] crystallized $[V_{10}O_{28}]^{6-}$ in the presence of Gly-Gly·HCl. Crans, Anderson and co-workers reported the product was triclinic $(NH_4)_6(Gly\text{-}Gly)_2V_{10}O_{28}$ in which a zwitterionic Gly-Gly unit hydrogen bonds through both the carboxylate and ammonium termini to the doubly bridging oxygens of the polyanion moiety.[68]

POMs also exhibit selectivity toward hematopoietic cells. Sommadossi, Hill, Schinazi, and co-workers demonstrated the selectivity in a family of Keggin POMs, ($H_4[SiW_{12}O_{40}]$ (ST), $H_5[BW_{12}O_{40}]$ (BT) and their corresponding ammonium salts) with respect to toxicity toward human granulocyte-macrophage precursor cells.[32,61] The toxicity of the compounds to the cells was $(NH_4)_5BT$ (least toxic; no detectable toxicity) < H_5BT < $(NH_4)_4ST$ < H_4ST < HPA-23 (most toxic). $(NH_4)_5BT$ was found to be more than 2 orders of magnitude less toxic than HPA-23.

E. Polyoxometalate Stability

A key point in all biological/physiological studies of POMs is the issue of whether the POM stays intact during evaluation/treatment. Many POMs are thermodynamically and kinetically unstable in water at physiological pH and degrade into a mixture of inorganic products. Hill et al. has noted that in the absence of kinetic decomposition and thermodynamic speciation data on the POM under the conditions of evaluation, it is problematical to identify the truly active species.[43] There are a number of reports covered in this review where the POM under evaluation is not hydrolytically stable under the conditions of evaluation. Unfortunately there is very little

kinetics data available on POM degradation in solution. Our group is attempting to rectify this limitation. The effect of cation and buffer on this stability should be quantified and evidence for catalytic decomposition or transformation of the POMs by buffer-related species should be sought. In addition, for each set of conditions, it should be determined whether the hydrolytic products reconstitute the parent structure when neutral pH is restored.[69,70]

V. In Vivo Antiviral Studies of Polyoxometalates

A. Introduction

The logical progression in the development of candidate drugs involves in vivo evaluation after the successful demonstration of efficacy and selectivity in conjunction with in vitro evaluations. In vivo evaluations of a drug are necessary not only to ascertain how effective and nontoxic the compound is in mammals, but also as results from cell culture assays may not correlate in a satisfactory or reproducible way with results in animals. While the antiviral effectiveness of over 200 POMs has been documented in vitro, the efficacy of fewer than 20 POMs has been documented in vivo. Table 2 summarizes the anticancer and antiviral activity of POMs in vivo. Like Table 1, Table 2 is organized to allow efficient assimilation of the data. Column 1 lists the POM with its counterion used in the referenced study. Column 2 lists the tumor type or virus. Column 3 lists the animal in which the study was undertaken. Column 4 lists the in vivo efficacy. Column 5 gives comments pertinent to the study. For comparison, the last entries of the table list data for clinically approved agents. Some of the most encouraging results with POMs have come quite recently from the industrial and academic groups of Blasecki,[71] Huffman et al.,[72] Fujita et al.,[73] and Ikeda et al.[74] One study involving combination therapy in vivo has been reported. This effort by the DuPont Merck group shows significant synergy between AZT and $[BVW_{11}O_{40}]^{6-}$ in the treatment of FLV-induced splenomegaly.[71]

Table 2. In Vivo Activities of Polyoxometalates

POM counterion and reference	virus or tumor type[a]	animal	efficacy[c]	comments
		I. Antiviral Research		
$[KSb_9W_{21}O_{86}]^{18-}$				
K_{18}[97,98]	FLV	DBA/2 mice, male	++	efficacy determined by the mean spleen weight (MSW)
$(NH_4)_{17}Na$[98]	RV	OF_1 mice, male	++	recorded on D21, the minimum weight for scoring a leukamatic spleen was 250 mg
$[SbW_{11}O_{39}]^{7-}$				
Na_7[98]	RV	OF_1 mice, male	++	efficacy determined by the number of survivors/total number
$[PTi_2W_{10}O_{40}]^{7-}$				
K_7[74]	HSV-2_{UW}	ddY mice, female	++	efficacy determined by the number of survivors/total number effective only when given early
$[PTi_2W_{10}O_{40}]^{7-}$				
K_7[99]	HSV-2_{UW}	ddY mice, female	++	immunosuppresion via cyclophosphamide; efficacy determined by number of peritoneal cells ($\times 10^6$/mouse) or phagocytic activity of peritoneal macrophages or by comparing viral titers of nontreated mice with treated mice
$[NaSb_9W_{21}O_{86}]^{18-}$				
$(NH_4)_{17}Na$[100]	RV_{CVS}	Swiss OF_1 mice, female	++	efficacy determined by the number of survivors/total number
$(NH_4)_{17}Na$[100]	RV_{CVS}	adult foxes	++	
	RV		++	
$(NH_4)_{17}Na$[101]	$scrapie_{139A}$	CW mice, (Sinc), female	++	efficacy determined by change in effective titer (log_{10}/0.1 g of brain) or by change in number of incubation days
	$scrapie_{263K}$	golden hamsters	++	efficacy determined by change in number of incubation days
	$scrapie_{22A}$	IM mice, (Sinc), female	++	
	$scrapie_{ME7}$	CW mice, (Sinc), female	++/+++	efficacy determined by the change in incubation days
$(NH_4)_{17}Na$[102]	$scrapie_{ME7}$	IM mice, (Sinc), female	+/−	
Na_{18}[98]	RV	red foxes, both sexes	−	efficacy determined by the number of survivors/total number
$(NH_4)_{18}$[98]	RV	OF_1 mice, male	+/++	
$(NH_4)_{17}Na$[103]	RV	OF_1 mice, male	++	
$(NH_4)_{17}Na$[71]	$scrapie_{139A}$	CW mice, male	+	efficacy determined by change in effective brain titer
$(NH_4)_{17}Na$[104]	FLV	mice type *x*	+	(log_{10}/0.1 g of brain)
	EMC_{VR129}	CD-I mice, both sexes	+/++	efficacy determined by the number of survivors/total number
	EMC_{V77}	CD-I mice, both sexes	+/++	
	VSV	CD-I mice, both sexes	+	
	EMC_{VR129}	CD-I mice, both sexes	++	combined with interferon
$[Sb_2W_5O_{20}]^{4-}$				
$(NH_4)_4$[105]	FLV	DBA/2 mice, both sexes	+/++	efficacy determined by the mean spleen weight (MSW), the minimum weight for scoring a leukamatic spleen was 250 mg; MSW's were recorded on D21
	FLV	BALB/C mice, both sexes	+/++	
	PV	DBA/2 mice, both sexes	+/++	
$[SrSb_9W_{11}O_{86}]^{17-}$				
$(NH_4)_{17}$[98]	RV	OF_1 mice, male	+/++	efficacy determined by the number of survivors/total number
$[BVW_{11}O_{40}]^{6-}$				
K_6[71]	FLV induced splenomegaly	mice, type *x*	+	efficacy determined by reduction of splenomegaly
HPA-59*	RV	OF_1 mice, male	+/++	*the structure is not discernible from the article, note: W/P ratio = 14/4

Table 2 (Continued)

POM counterion and reference	virus or tumor type[a]	animal	efficacy	comments
		II. Antitumoral Research		
$[Mo_7O_{24}]^{6-}$				
$[NH_3Pr^i]_6$[106]	Meth A sarcoma	Balb/c mice, female	+/++	efficacy measured by tumor weight inhibition and increase in life span (ILS) = 100($t - c$)/c, where t is the mean survival of the treated group and c is the mean survival time of the control group
	MM-46 adeno-carcinoma	C3H/He mice, female	+/++	
$[NH_3Pr^i]_6$[91]	CO-4 human colon cancer	CR mice, female	+	efficacy measured by antitumor activity [(reduction of tumor size in treated group/tumor size in control group)100]
$[NH_3Pr^i]_6$[89]	CO-4 human colon cancer	cd-1 mice	+	
$[Mo_7O_{24}]^{6-}$				
$[NH_3Pr^i]_6$[89]	MX-1 human breast cancer	Balb/c mice	+	efficacy measured by antitumor activity [(reduction of tumor size in treated group/tumor size in control group)100]
	OAT human lung cancer		+/++	
	MX-1 human breast cancer		+/++	
	OAT human lung cancer		+	
$[H_xMo_7O_{24}]^{6-}$ (x = 1 or 2)				
$[NH_3Pr^i]_6$[106]	Meth A sarcoma	Balb/c mice, female	+/++	efficacy measured by tumor weight inhibition and increase in life span (ILS) = 100($t - c$)/c, where t is the mean survival of the treated group and c is the mean survival time of the control group
$[NH_3Pr^i]_6$[89]	CO-4 human colon cancer	cd-1 mice	+	efficacy measured by antitumor activity [(reduction of tumor size in treated group/tumor size in control group)100]
$[Mo_7O_{24}]^{6-}$				
$[NH_4]_6$[106]	Meth A sarcoma	Balb/c mice, female	+	efficacy measured by tumor weight inhibition and increase in life span (ILS) = 100($t - c$)/c, where t is the mean survival of the treated group and c is the mean survival time of the control group
K_6[106]			+	
$[IMo_6O_{24}]^{5-}$				
Na_5[91]	CO-4 human colon cancer	ICR mice, female	++	efficacy measured by antitumor activity [(reduction of tumor size in treated group/tumor size in control group)100]
Na_5[89]	CO-4 human colon cancer	cd-1 mice	−	
$[Mo_7O_{23}(OH)]^{6-}$			+	
$[NH_4]_6$[91]	CO-4 human colon cancer	ICR mice, female		
$[Mo_7O_{26}]^{6-}$				
$[NH_3Pr^i]_6$[89]	CO-4 human colon cancer	cd-1 mice	−	efficacy measured by antitumor activity [(reduction of tumor size in treated group/tumor size in control group)100]
5-FU[89]	CO-4 human colon cancer	cd-1 mice		
MMC[89]	CO-4 human colon cancer	cd-1 mice	+	
ACNU[89]	CO-4 human colon cancer	cd-1 mice	+	
ADM[89]	CO-4 human colon cancer	cd-1 mice	+	

[a] Abbreviations used for viruses: FLV, Friend leukemia virus; RV, rabies virus; HSV, herpes simplex virus; EMC, encephalomyocarditis; VSV, vesicular stomatitis virus; PV, plasma variant of Moloney murine sarcoma virus. [b] Abbrevations used for anticancer agents: 5-FU, 5-fluorouracil; ACNU, nimustine 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-3-nitrosourea; ADM, adriamycin, doxorubicin hydrochloride; MMC, mitomycin C, mutamycin. [c] Efficacy denoted by: −, not effective; +, somewhat effective; ++, effective; +++, very effective.

B. Pharmacokinetics

Detailed pharmacokinetics data are of central importance for in vivo studies and a fundamental requisite for clinical trials. The first published pharmacokinetics studies of POMs were conducted by Bountiff and reported in her 1982 doctoral thesis.[75] She used a scintillation counter to monitor the distribution of ^{185}W-labeled HPA-23 in extracts of tissues and fluids from Compton white mice. Bountiff found that 24 h postinjection, the HPA-23 levels had decreased in the blood, but had increased in the liver, kidney, spleen, and brain. Low levels of the HPA-23 were found in the urine consistent with partial excretion by renal clearance. While multiple doses of HPA-23 led to accumulation in the liver, kidney, spleen, and brain, once the dosages were stopped the POM cleared quickly from the liver and kidney, but not from the brain and spleen. Bountiff also probed the dosage dependence of HPA-23 pharmacokinetics. She found that intravenous (iv), intraperitoneal (ip), and subcutaneous (sc) administration led to the aforementioned accumulation in the liver, spleen, kidney, and brain. Interestingly, when HPA-23 was administered intragastrically, accumulation was not observed, even when "greater doses" were used (the exact doses were not given).

The most detailed published investigation of POM pharmacokinetics is that of Ni et al. (a collaboration between research groups at the University of Georgia, Emory University and Johnson Matthey Corpo-

ration). This paper examined the pharmacokinetics of three anti-HIV POMs ($K_{12}H_2[P_2W_{12}O_{48}]$, $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$, and $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$) following a single 50 mg/kg iv administration in rats.[76] The POMs were detected in urine, plasma, feces, and solubilized organ samples by atomic emission spectrometry. POM concentration was determined from the Nb and W concentrations present in the cell, while the consistency of the W/Nb ratio for $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$ provided strong evidence that this particular POM remained intact in vivo. These POMs were found to bind to serum proteins in a concentration-dependent manner, with more POM binding at lower concentrations. For example, the percentage of serum-bound $K_{12}H_2[P_2W_{12}O_{48}]$ decreased from >98% at 25 mg/mL, to 83% at 1500 mg/mL. This finding led Ni et al. to postulate the existence of two POM binding sites on the protein, one with a high affinity but low capacity and one with a lower affinity but higher capacity. The tissue concentration of all three compounds was determined one week after POM dosage. $K_{12}H_2[P_2W_{12}O_{48}]$ was found to concentrate in the liver and kidneys and to a lesser extent in the spleen, lungs, and heart. $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$ was found to concentrate in liver and kidneys, followed by the lungs, spleen, and heart. No POMs were found in the brain. The tissues retained 27.8, 8.7, and 34.0% of the initial dose of $K_{12}H_2[P_2W_{12}O_{48}]$, $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$, and $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$, respectively, one week after iv administration. These data suggest the POMs are redistributed slowly from the tissues back into the blood.

The systemic clearance of the compounds was also examined. On the basis of the pharmacokinetic models constructed, the systemic clearances of unbound $K_{12}H_2[P_2W_{12}O_{48}]$ and unbound $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$ were determined to be 20-fold higher than for unbound $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$. However, $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$ exhibited lower protein binding, so the total systemic clearance of the compounds was similar. $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$ was suggested to undergo renal tubular reabsorption since the renal clearance of the unbound POM was lower than the measured glomerular filtration rate. Tubular reabsorption may be attributed to $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$ binding to cell membranes or accumulation of the compound in renal tubules. $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$ also had the fastest rate of renal excretion, accumulating the least in the kidney. $K_{12}H_2[P_2W_{12}O_{48}]$ and $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$ exhibited greater renal clearance, suggesting these POM were secreted by renal tubules. One week after POM administration, total recovery from feces, urine, and solubilized tissues accounted for 45, 61, and 52% of the initial dose of $K_{12}H_2[P_2W_{12}O_{48}]$, $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$, and $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$, respectively. Since no POM was detected in the brain, distribution and accumulation of the compounds must take place in other tissues, i.e., skin, bone, and muscle. The investigators further concluded the POMs irreversibly distribute into cells because the systemic clearance was higher than the renal and biliary clearance.

In subsequent work, Ni and Boudinot further probed the pharmacokinetics of POMs by studying the renal and biliary clearances of $K_{12}H_2[P_2W_{12}O_{48}]$, $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$, and $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$ in rats.[77] They collected urine, fecal, and plasma samples from Sprague Dawley rats 168 h after dosage with POMs. The concentration of the POMs in the samples was assessed by atomic emission spectrometry. Ni and Boudinot used the previously cited work and compounds (vide supra) to construct pharmacokinetic models for renal and biliary clearance of POMs. They noted that urinary excretion rate data were not parallel to unbound plasma concentration versus time curves. Renal excretion of $K_{12}H_2[P_2W_{12}O_{48}]$ and $(Me_3NH)_8[Si_2Nb_6W_{18}O_{77}]$ was found to be a function of glomerular filtration, saturated active tubular secretion and active tubular absorption. Urinary excretion of $K_{10}[P_2W_{18}Zn_4(H_2O)_2O_{68}]$ was found to be a function of glomerular filtration, active tubular secretion and passive reabsorption. Biliary excretion of POMs was monitored by determining the amount present in feces. The biliary excretion rate versus time and unbound plasma concentration versus time curves were not similar, indicating nonlinear biliary clearance. The concentration dependent biliary elimination of POMs was further supported by the plots of biliary excretion rate versus unbound plasma POM concentration. Ni and Boudinot detected no POMs when administered orally.

It should be noted that the half-lives for the three POMs in the original study by Ni et al. were highly variable (a factor of 13.7-fold between just three POMs) with one of the three being 32 h.[76] No effort has been made to optimize pharmacokinetic properties thus far. Although the low clearance may be primarily due to effects of protein binding, we are confident that lead compounds with lower protein binding can be designed. Almost all the clinically viable HIV protease inhibitors bind to proteins or α-1 acid glycoprotein (AAG).[78] Ways to overcome this problem such as the use of competing nontoxic protein binders are being considered by our group.[79] Similarly, Weeks et al. and others have synthesized organosilyl POMs that may increase their oral bioavailability.[35]

VI. Experimental and Computational Investigations of POM-Enzyme/Protein Interactions

Investigations of POMs in the presence of viral enzymes (e.g., HIV-1 RT) and proteins (e.g., gp120 and CD4) have provided additional information into their mode of action. Table 1 also summarizes nearly all the available data of this type. The structural and electronic complexity of POMs interacting with biological macromolecules has limited the collective efforts to probe these interactions theoretically. While the structure (atomic coordinates) of many of the key biological targets including HIV-1 RT and HIV-1 P are readily available from Brookhaven National Protein Data Bank, and molecular modeling techniques of sufficient sophistication are also now available to investigate proteins, the situation is far less

straightforward for the POMs. The structures of many large or antivirally active POMs are now available[80−83] (see the article by Müller, Peters, Pope, and Gatteschi, in this issue). However, the effective parametrization of tungsten and polyoxotungstate fragments for meaningful molecular mechanics and dynamics calculations is not generally available. In addition, the size, structural complexity, and composition (many third-row transition metal centers) of POMs make high-level ab initio calculations of the electronic structure of these species very difficult. Fortunately this situation is rapidly improving as the requisite computer hardware and software become more sophisticated and powerful. To date only a few studies have attempted to computationally model the potent inhibition of enzymes by POMs. These investigations are limited to interactions between POMs and HIV-1 RT or HIV-1 P.

As previously mentioned, POMs selectively inhibit HIV-1 RT over DNA polymerase, usually by a significant factor. Sarafianos et al. reported that $[(O_3POPO_3)_4W_{12}O_{36}]^{16-}$ inhibits HIV-1 RT (IC_{50} values ranging from 2 to 10 μM).[84] Enzyme kinetic data were consistent with inhibition of HIV-1 RT via docking of this POM (Na and K salts) at the DNA binding region of the enzyme. Radiolabeled DNA template-primer was used to confirm competitive inhibition by the POM. With this evidence at hand, the steric and energetic feasibility of the POMs docking at the HIV-1 RT active site was modeled using SYBYL 6.1. While the complex did exhibit some unfavorable steric interactions (109 kJ/mol), the authors concluded that the favorable electrostatic interaction (the polyanionic POM-polycationic enzyme attraction, −1155 kJ/mol) was sufficient to make the overall interaction energetically favorable (−1046 kJ/mol).

Judd et al. investigated the inhibitory action of Nb-containing POMs of the Wells−Dawson structure (formula α_1(or α_2)-$K_7[P_2W_{17}(NbO_2)O_{61}]$ and α_1(or α_2)-$K_7[P_2W_{17}NbO_{62}]$) against HIV-1 P and used computer modeling to investigate the likelihood of this interaction.[39,40] These particular POMs inhibit HIV-1 P with IC_{50} values of 2.0 μM or lower. Initial high level calculations of the charge distributions for the POMs were conducted (Natural Population Analysis (NPA) following Restricted Hartree−Fock (RHF) calculations with the LANL2DZ basis set). These charges were input for subsequent computation using the Kollman All-Atom force field within SYBYL. The likelihood that these POMs bind to the active site in the normal mode—with the flaps over the active site in a closed position—is remote due to highly unfavorable steric interactions. Subsequent and more comprehensive modeling studies showed these POMs exhibit reasonable steric fits in the active site for the flaps-open form. However, the overall negative charges at the active site of HIV-1 P and on the POM make this electrostatically unattractive. The positively charged "hinge" regions located near the flaps on the enzymatic surface of HIV-1 P may be more likely sites for POM binding.[39,40]

Additional studies on virus-derived proteins and POMs involved binding to virion-derived gp120 from HIV-1.[47] Judd et al. further probed the relationship between the molecular size and charge density of POMs and their ability to inhibit the binding of HIV-1 gp120 to CD4. From this study, it was found that POMs with high molecular weights (above 3800 g/mol), completely inhibited the interaction between HIV gp120 and CD4.[47] Keggin POMs were generally more effective inhibitors of this interaction than organic derivatized POMs, Wells−Dawson POMs, or POMs of various other classes. The POMs containing covalently bound organic groups on their surfaces exhibited decreased levels of antibinding activity. This is a likely consequence of either reduced charge or steric congestion imparted by the organic groups.

Several biological attributes have been noted for a variety of POMs in addition to their antiviral and anticancer properties, and some of these deal specifically with their interactions with proteins. Nemetschek and co-workers investigated the interaction between collagen and $[PW_{12}O_{40}]^{3-}$ using synchrotron X-ray radiation. The data implicated stepwise binding of this POM to collagen.[85] $[PW_{12}O_{40}]^{3-}$ was also found to affect mitochondrial respiration and at high concentrations to solubilize mitochondrial protein.[86] Polytungstophosphates were shown to interact with NADPH oxidase and dehydrogenase, succinoxidase and influence phosphorus−ATP exchange activity in isolated mitochondria.[87]

Crans and co-workers have extensively investigated polyoxovanadate−enzyme interactions.[65−67] While this research may be peripherally pertinent to POMs in medicine, it should be noted here. Divanadate, tetravanadate, and decavanadate have been found to inhibit (and in some cases activate) a range of redox, hydrolytic, and other enzymes. This group has sought information on POM−peptide interactions by structural, spectroscopic, and other methods.[66,68]

Most recently, Holan and co-workers demonstrated that certain POMs inhibit phosphatases.[88] In contrast to vanadates which evoke a calcium-dependent contraction, POMs affect the contraction of guinea pig ileum smooth muscle in the absence of calcium. They speculated that POMs may affect different isoforms of phosphotyrosine phosphatase.

VII. In Vivo Antitumoral Studies of Polyoxometalates

A. Overview

Considering the number of POMs already synthesized and characterized chemically, there is limited information on their in vivo antitumoral activity. Table 2 summarizes these studies, all of which involve xenografted tumors. The antitumoral activity of POMs was found to compare favorably with that of commercial drugs. For example, the tumor growth inhibition exhibited by $[NH_3Pr^i]_6[Mo_7O_{24}]$ was 54.3% against CO-4 human colon cancer xenografted on CD-1 mice, whereas the tumor growth inhibition exhibited by 5-fluorouracil (5-FU) was 44.0% under the same conditions.[89] The first report of POM antitumoral activity in vivo was also the first and only report of POM antitumoral activity involving

humans. Mukherjee reported that a combination of phosphotungstic acid, $H_3[PW_{12}O_{40}]$, phosphomolybdic acid, $H_3[PMo_{12}O_{40}]$, and caffeine (referred to as PTMC) was used on patients suffering from carcinoma of the intestinal tract.[90] This investigator dissolved PTMC in an aqueous solution of sodium lactate or sodium bicarbonate (precise concentration not specified) and subjected the patient to daily intravenous or intramuscular injections for 6 days. Mukherjee selected four patients with uncomplicated (i.e., nonmetastatic) cases of carcinoma. After administration of PTMC for 2−4 weeks, the growths (adenocarcinomas) disappeared completely. In a single patient diagnosed with urinary bladder carcinoma as well intestinal tract carcinoma, PTMC shrunk the tumors completely. These are remarkable results that need to be confirmed in larger controlled clinical studies.

B. Mode of Anticancer Action

The only mechanism for the antitumoral activity of POMs, that proposed by Yamase, revolves around a single electron reduction/oxidation cycle in isopolymolybdates.[91] This group noted that the reduced form of heptamolybdate, $[Mo_7O_{23}(OH)]$,$^{6-}$ is highly toxic, whereas the oxidized form, $[Mo_7O_{24}]$,$^{6-}$ is not. They propose that some domains in tumor cells reduce heptamolybdate(VI) to heptamolybdate(V), eq 1, while other domains reoxidize $[Mo_7O_{23}(OH)]^{6-}$ back to $[Mo_7O_{24}]$.$^{6-}$ On the basis of the toxicity of the two

$$[Mo_7O_{24}]^{6-} + 1e^- + H^+ \rightleftharpoons [Mo_7O_{23}(OH)]^{6-} \quad (1)$$

forms, they argue it is the POM reoxidation and tumor cell reduction process that kills the cells. Yamase notes that a naturally occurring reductant, a reduced flavinmononucleotide, readily reduces $[Mo_7O_{24}]^{6-}$ by one electron.[91]

VIII. Conclusions

Despite the numerous POMs prepared and evaluated, the applications of POMs to medicine is in its infancy. It is unfortunate that the first POM put into humans, HPA-23, was one of the most toxic POMs examined to date, as this retarded investigation of all biological research on POMs. In the eight years since these clinical trials, at least two factors have lead to a continually increasing literature on the title subject. First, like the number of publications, the number of synthetically accessible and well-characterized POMs with diverse structural and electronic properties, has been increasing each year. Second, the toxicity problems exhibited by HPA-23 (renal toxicity, hepatotoxicity, and thromobocytopenia) are considerably less or nonexistent in second generation POM chemotherapeutic agents.

Perhaps the most significant general medical property of POMs is their antiviral activity—diverse but specific with efficacy in vivo not simply in vitro. The collective data available at present make a strong case that POMs can penetrate cell membranes and localize intracellularly. POMs effective against HIV-1 in vitro clearly exhibit at least three modes of action in vitro: some inhibit the binding of HIV gp120 to CD4 with the attendant consequences (interference with viral adsorption and fusion of infected lymphocytes with uninfected ones preventing syncytium formation); others inhibit HIV-1 RT, while still others inhibit HIV-1 P. More research will be required to determine the degree to which each of these three distinct activities is operable in mammals. Of significance is the potency of these compounds when used in combination with HIV nucleosides and/or protease inhibitors to prevent the development of resistant viruses.[92,93]

One cannot generalize from the biological behavior (activities, toxicities, etc.) of one POM antiviral agent to other. As for the well-developed nucleoside antiviral agents (e.g., AZT, DDC, DDI, D4T, 3TC, FTC, etc.), one must investigate each individual POM thoroughly with little prejudgment regarding behavior. A general goal at present is to obtain greater knowledge regarding the relationships between the physical and electronic structure of a POM and its behavior in vivo. Such defensible structure−activity information will facilitate the design of better drugs. This research needs to proceed through combined crystallographic, spectroscopic, and enzymatic studies with mutant as well as wild-type enzymes and appropriately engineered POMs.

The data on the anticancer properties of POMs are provocative. Clearly more data must be garnered in this area before its scope and promise can be defined. It is of interest to note that another inorganic complex, *cis*-platin, remains one of the most effective and biggest selling antitumoral agents.

The tempo of significant advancements in POM science including the development of POM therapeutic agents will likely increase with the advent of new technologies of particular value in characterizing these large and structurally complicated inorganic clusters. One of these is the X-ray diffractometer equipped with a charge-coupled device (CCD) detector that greatly increases the number of POMs viable for structural determination. Another is NMR methodology (pulse gradient capabilities, etc.) that facilitates acquisition of high signal-to-noise spectra for very weak samples. The low receptivity and/or natural abundance of key POM elements including ^{183}W and ^{17}O have negatively impacted progress in this field.

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