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PHOSPHONATES AND ACYCLIC NUCLEOSIDE PHOSPHONATES: A NEW FRONTIER IN OVERCOMING THE GLOBAL CRISIS OF ANTIMICROBIAL RESISTANCE

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ABSTRACT

Antimicrobial resistance is a serious problem worldwide. It becomes harder to treat infections. It requires new innova-tive strategies to combact resistant microbes. One of the approach is using phosphonates. These are organophosphate that contain phosphorus and carbon and are di*ff*erent from traditional antibiotics. Phosphonates that fall outside the category of conventional antibiotics constitute a broad group of organophosphorus compounds with notable antimicrobial potential. Their chemically stable carbon–phosphorus (C–P) bond enables interaction with microbial targets through mechanisms unlike those of standard antibiotics, such as the inhibition of key enzymes, disruption of nucleotide synthesis, and interference with membrane-related processes. There are large number of phosphonates available against bacteria, viruses, protozoans and fungi. This review focuses on diverse mechanisms by which non-antibiotic phosphonates interact with various pathogens. By knowing how these compounds specifically target microbial pathways, one can explore their therapeutic ability for medical treatment as well as their e*ff*ectiveness as potent herbicides.

KEYWORDS: Antiviral activity, Organophosphorus compound, Antibacterial activity, Antifungal activity, Nonantibiotic phosphonates.

1. INTRODUCTION

The increasing crisis of antimicrobial resistance (AMR) represents one of the most severe threat to global health in the 21st century.[1] It is often named as "silent pandemic," AMR occurs when microorganisms-like bacteria, viruses, fungi, and parasites-evolve mechanisms to withstand the medications originally designed to eliminate them. This evolutionary resistance significantly increases mortality rates, prolonged illness and economic burden on global healthcare systems.[2]

Statistical estimation highlight the severity of this threat. While 2014 approximation predicted that AMR could cause upto 10 million deaths annually by 2050, re-cent data suggests even more aggressive timeline.[3,4] Global deaths associated with resistant infection in-creases from 16.5 million in 1990 to 21.4 million in 2021. in 2019 alone was responsible for more than 1.2 million deaths worldwide. Currently, infectious dis-eases account for over 20% of all global mortality, situation worsened as it was increased by 36% between 2000 and 2010.[5]

The drivers of AMR are versatile, ranging from clinical misuse of drugs to systemic issues like poor sanitation. Incorrect prescriptions, overuse and the failure to complete treatment cycles permit microbes to mutate and survive. These microbes uses com-plex survival strategies like, target site modifications, deployment of e*ffl*ux pumps, formation of protective biofilms, and production of degradative enzymes.[6] The clinical strategies mainly focus on highpriority pathogens, including carbapenem-resistant *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and multidrug-drug resistant *Mycobacterium tuberculosis*.[7] The importance of this issue was further highlighted during COVID-19 pandemic, where antibiotic use increased even without confirmed bacterial infections-increasing rate of development of resistant phenotype.[8]

Faced the decline of traditional antibiotics, re-searchers are turning towards phosphonates and phosphinates(Pns). These compounds are distinguished by highly stable carbon-phosphorus bond, which is more resistant to breakdown then the oxygen-phosphorus bonds found in common phosphate esters.[9]

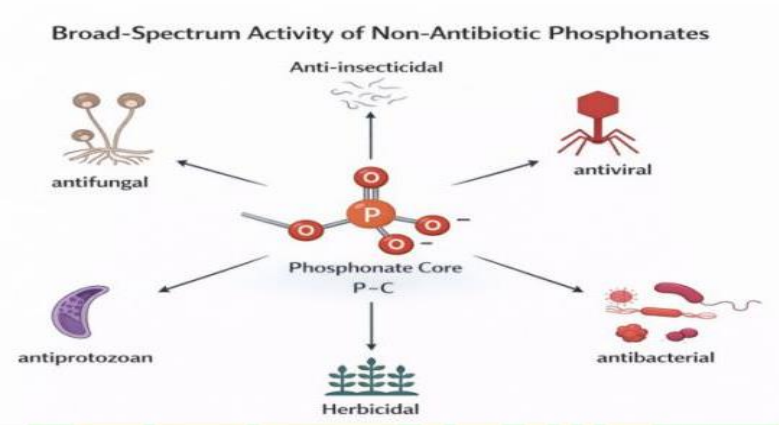

Figure 1: Figure 1 Broad-Spectrum Activity of Non-Antibiotic Phosphonates.

Phosphonates functions as important metabolic inhibitors by acting as mimics of carboxylate and phosphate groups. This structural similarity permit them to competitively inhibit enzymes essential for microbial survival like those involved in peptidoglycan and isoprenoid biosynthesis. Important clinical examples include fosmidomycin, targets malaria-causing protozoa, and fosfomycin, treatment for cystitis.[10]

Other than antibacterial applications, Acyclic Nucleoside Phosphates(ANPs) have emerged as revolutionary class of broad-spectrum antivirals. ANPs like adefovir, tenofovir, and cidofovir have transformed treatment of DNA viruses, including HIV and Hepatitis B. These compounds are converted into active diphosphate forms within host cells, where they compete with nucleotides to terminate viral DNA chain elongation.[11] New research in prodrug design, such as Brincidofovir(BCV) and Tenofovir Alafenamide(TAF), have fur-ther enhanced cellular uptake and reduced toxicity, making them e*ff*ective against wide range of pathogens like herpesviruses, human papillomavirus(HPV) and or-thopoxviruses like monkeypox.[12] This review fo-cusses to explore the diverse bioactivities of ANPs and non-antibiotic phosphonates. By studying their unique mechanisms metabolic stability, action and e*ff*ectiveness against resistant strains, we underscore their ability as a critical frontier in the fight against the global rise of antimicrobial resistance.[13]

Antiviral activity of non-antibiotic phosphonates

The global health care environment remains disturbed by viral pathogens a*ff*ecting diverse physio-logical systems, from respiratory to central nervous system. Despite the extreme socioeconomic impact of these infections-aggravated by global connectivity and urbanization-therapeutic options remain abnormally rare. Currently, direct acting

antivirals(DAAs) are FDA-approved for only nine of 200 known human viruses, with heavy concentration on influenza, hepatitis virus and HIV.[14]

A primary challenge in antiviral development is the rising of resistance, often controlled unfavourable phar-macokinetic profiles and low genetic barriers that limit bio availability. Potent drugs like tenofovir maintain high rate of success, many conventional therapies struggle against specific patient associated conditions or emerging variants. This has promoted a shift towards host-targeted therapies, which inhibit essential human factors essential for viral multiplication, such as the protein DDX3.[15] By aiming host mechanisms rather than virus itself, these strategies minimize the risk of resistance and provide broad-spectrum potential.

Advancing the frontiers, recent research has turned toward acyclic nucleoside phosphonates (ANPs), specifically xanthine based derivatives. These compounds represent a promising class of therapeutics designed to overcome limitations of traditional DAAs, o*ff*ering robust activity against clinically important viruses and providing a multifaceted framework for next-generation antiviral design.[16]

Table 1: Antiviral compounds and their mechanisms.

Compound	Target Enzyme/ Pathway	Mechanism	Active Against	Reference
Acyclic nucleo- side phosphonates (ANPs)	Viral DNA poly-merases / reverse transcriptases	Mimic natural nucleotides; incorporated into viral DNA leading to chain termination	Broad (DNA viruses, retroviruses)	[11]
Cidofovir (HPMPC)	Viral DNA poly-merase	Competes with dCTP and leads to DNA chain termination	Hepatitis B Virus (HBV)	[38]
Adefovir	Reverse transcriptase (HBV)	Incorporates into viral DNA and causes premature chain termination	Hepatitis B Virus (HBV)	[38]
Tenofovir (TDF)	Reverse transcriptase (HIV-1, HBV)	Competes with dATP and causes chain termination	HIV-1, HBV	[38]
ODE-Bn-PMEG	Viral DNA poly-merase	Potent nucleotide analog; in-duces chain termination	CMV, HSV, adenovirus	[39]
Brincidofovir (BCV)	Viral DNA poly-merase	Lipid-conjugated cidofovir enhances	CMV, adenoviruses, orthopoxviruses	[40]

		cellular uptake		
Cidofovir (CDV)	Viral DNA poly-merase	Nucleotide analog causing DNA chain termination	CMV, HPV (topical), adenoviruses	[38]

Antibacterial activity of non-antibiotic phosphonates

The global expansion of multidrug-resistant(MDR) infections represents a serious threat to public health, with annual mortality rates estimated to reach 10 million by 2050 if current trends exist.[17] As traditional antibiotics fail due to mechanisms such as e*ffl*ux pumps and enzymatic degradation, the knowledge gap of the last half century -producing only six new antibiotic classes-has necessitated a fundamental transformation. Recent researches identifies non-antibiotic phosphonates (Pn) as a emerging field. Defined by stable C-P bonds that copy natural carboxylate or phosphate groups, these compounds o*ff*er unique bioisosteric advantages, allowing them to interfere with essential bacterial metabolic pathways that traditional drugs often miss.[18] One of the most demading applications of phosphonate chemistry involves nanocomposites and hybridization. For example, graphene oxide (GO) functionalized with phosphonate ionic liquids and (GO@PEI-PFIL-Ag/Ag/AgBr) has demonstrated broad-spectrum e*ff*ec-tiveness against both Gram-negative(P. aeruginosa) and Gram-positive (MRSA) pathogens. These combinations utilize a multidimensional attack: generating reactive oxygen species (ROS), damaging bacterial membrane and disrupting biofilms. Identically, quinoline-thiazole-aminophosphonates and coumarin-phosphonate hybrids have shown exceptional impact. Specifically, the compound 9g achieved Minimum Inhibitory Concentrations (MICs) as low as 0.25 µg/mL against resistant S. aureus, suggesting that the coordination between the phosphate group and the coumaryl-thiazole moiety significantly increases cellular penetration and tar-get a*ff*inity.[19] Beyond synthetic hybrids, metabolic and natural targeting remains foundation of phosphonate research. Compounds like alkyl acetylphospho-nates(alkyIAPs) and fosmidomycin disrupt the non-mevalonate(MEP) pathway, specifically targeting en-zymes like DXPS and DXR. These enzymes are im-portant for the synthesis of vitamins(B1 and B6) and isoprenoids in bacteria but are absent in humans, pro-viding a high degree of selective toxicity.[20] Additionally, phosphonopeptides such as phosphinothricin and alaphosphin act as trojan horses, entering cells via peptide transporters to inhibit essential enzymes glutamine synthetase and alanine racemose. This mecha-nism avoid certain resistance pathways, rendering even tough pathogens like *Enterobacter* cloacae and *Acinobacter baumannii* at risk.[21] The synthesis of cyclosulfamidophosphonates and sufamidophosphonates in-cluding quinolone rings has

yielded results superior to traditional sulfonamides, with MICs as low as 8 µg/mL against E. coli. The development of boronophosphonate versions of fosmidomycin represents development in medicinal chemistry, utilizing boronic acid to replace retrohydroxamate groups to maintain activity even in absence of specific transporters.[22] Some reused non-antibiotics such as alendronate and amitriptyline show tolerable antibacterial activity, the selected design of phosphonate derivatives o*ff*ers more robust solution. By merging phosphonate groups into diverse molecular platforms, researchers are making long lasting, stable and highly specific medium capable of overcoming predetermined resistance of modern era.[23]

Table 2: Antibacterial compounds and their mechanisms.

Compound	Target	Mechanism	Active against	Reference
GO@PEI-PFL-Ag/Ae/AeBr	Bacterial cell envelope	Silver nanoparticles release Ag causing membrane damage, protein inactivation, ROS generation; graphene oxide enhances contact and killing	Nosocomial pathogens (Gram-positive & Gram-negative, e.g., Klebsiella)	[41]
Coumarin-phosphonate hybrids	DNA-related enzymes	Enzyme inhibition and DNA in-tercalation; coumarin core exhibits bacteriostatic and bactericidal ac-tivity	*S. aureus*, *E. coli*, *P. aeruginosa*	[42]
Dehydrophos, Alaphosphin	Broad bacterial metabolic enzymes	Prodrug conversion leads to en-zyme inhibition	Strong activity mainly against Gram-positive bacteria	[19]
Phosphinothricin	Glutamine synthetase and metabolic enzymes	Competitive enzyme inhibition; peptide-mimic uptake enhances spectrum	Multidrug-resistant *Klebsiella pneumoniae* and some isolates	[43]
Alkyl phosphonates (alkylAPs)	Serine hydrolases and dehydrolases	Enzyme inhibition; chain length/branching a*ff*ects mem-brane interaction and uptake	Antibacterial and an-tiparasitic (depends on alkyl chain)	[45]
γ-Borono phospho-nates	Bacterial enzymes and proteases	Boron/phosphonate motifs form re-versible covalent complexes with enzymes	*E. coli* and *Mycobac-terium smegmatis*	[45]
Amitriptyline	Multiple targets (mem-brane, e*ffl*ux pumps)	E*ffl*ux pump inhibition and mem-brane perturbation	Gram-negative bacteria	[45]

Antifungal Activity of Non-antibiotic Phosphonates

The global responsibility of fungal disease is accelerating, with over 1.5 million annual deaths and more than one billion people a*ff*ected by infections varying from surface skin conditions to life threatning inva-sive diseases such as mucormycosis and cryptococcal meningitis. This crisis is magnifying by the rise of antimicrobial resistance against conventional drugs like echinocandins and triazoles, especially among vulnerable immunocompromised populations. Hence, research has turned towards inventive chemical sca*ff*olds, with phosphonates emerging as a highly promising class of non-antibiotic antifungal agents.[24,25]

The current studies highlight aminophosphonates as prime candidates. These compounds, synthesized via cascade of reactions, demonstrate vigorous activity against pathogens such as *Scedosporium* and *Microsporum canis*. Their potential is often assigned to their unique structural features; for example, indole-ring derivatives have shown a high a*ffi*nity for binding with fungal tubulin.[26] Additionally, phosphonate containing antibiotics such as rhizocticins uses "Trojan horse" strategy to enter target cells. Once transferred into the fungus, it releases (Z)-L-2-amino-5-phosphono-3-pentenoic acid(APPA), which inhibits threonine synthase. Since humans lack this enzyme, these compound o*ff*er pathway to high-specificity treatments with least host toxicity.[27]

The nitrogenous bisphosphonate zoledronate has been shown to enhance the e*ff*ectiveness of fluconazole by blocking farnesyl pyrophosphate synthase, therefore disrupting ergosterol synthesis. This combination remains e*ff*ective even against resistant biofilms. Anthraquinone phosphonates illustrate chain-length-dependent activity against *Fusarium* species, while potassium phosphonates function as systemic resistance inducers in plants, stimulating rapid defense gene expression against pathogens like *Phytophthora infestations.*[28,29] Compound Target Mechanism Active Against Reference. Moreover, the discovery that certain fungi can enzymatically reconstruct heterophosphonates facilitates for creating chiral building blocks for future drug development.

As the acceptance of resistant fungal infections grows, the multi-model action and structural adaptability of phosphonates represent cutting edge in securing the next generation of anti fungal therapy.[30,31]

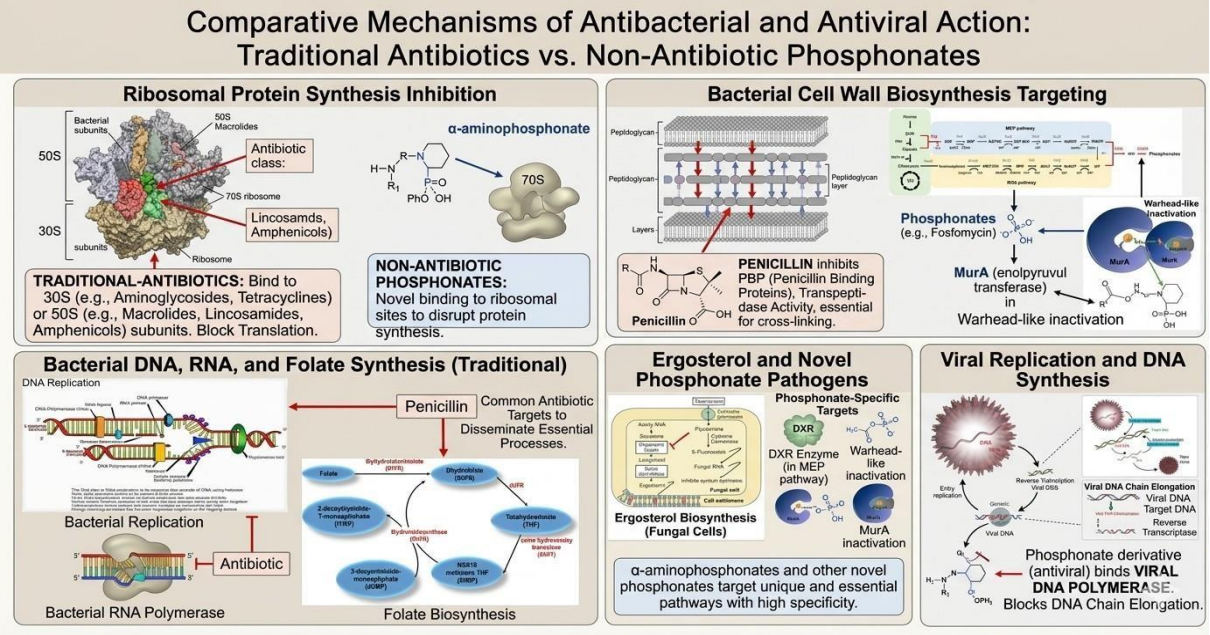

Figure 2: Comparative mechanisms of Antibacterial and Antiviral Action.

Table 3: Antifungal compounds and their mechanisms.

Compound	Target	Mechanism	Active Against	Reference
1. α-Aminophosphonates	Filamentous fungi and dermatophytes	Interfere with amino acid metabolism and inhibit fungal growth	*Microsporum canis*	[46]
2. Rhizocticins	Fungal protein synthesis	Act as amino acid analogues; dis-rupt peptide chain elongation	*Rhizoctonia solani*, yeasts	[47]
3. 1-amino-1-(3-hienyl)methyl phospho-nic acid and 1-amino-1-(4-imidazole)methyl phosphonic acid	Amino acid-metabolizing enzymes	Compete with natural substrates and impair enzymatic function	*Candida albicans* and other yeasts	[46]
4. Cerezin, Kitazin, Pyrazophos	Fungal respiration	ATP synthesis inhibition	*Fusarium, Phytophthora spp., Botrytis cinerea*	[48]
5. Zoledronate	Ergosterol biosynthesis	Inhibits farnesyl diphosphate syn-thase reducing ergosterol	*Candida albicans, Cryp-tococcus neoformans*	[49]
6. Ethyl-protected anthraquinone phospho-nates	Reactive oxygen species	Cause oxidative stress and disrupt fungal membranes	*Aspergillus niger, Can-dida albicans*	[48]
7. Potassium phosphite	Host defence and cell wall metabolism	Triggers host defense responses and suppresses fungal development	*Phytophthora infestans, Pythium spp.*	[50]

Antiprotozoal activity of non-antibiotic phosphontes

The global health issue of systemic and intestinal infections remains surprising, approximately 3.5 billion people infected annually. Traditional treatments are of-ten inhibited by toxicity and drug resistance, necessitating the exploration of novel non-antibiotic treatment methods. Recent research focused on transformative potential of bisphosphonates and phosphonates as mul-tipurpose structures for drug development. By stimulating natural phosphates but o*ff*ering higher water solubility and chemical stability, these compounds aim at essential metabolic pathways across a broad spectrum of parasites, like *Leishmania infantum, Trypanosoma cruzi and Plasmodium falciparum*.[32] One of the most important strategies involves the inhibition of farnesyl pyrophosphate synthase (FPPS). Lipophilic bisphosphonates and nitrogen-containing disrupt mitochondrial function and protein prenylation, in particular e*ffi*cacious against malaria and Leishmania. Lipophilic variants have demonstrated the capacity to fully safeguard the liver from malaria transmission, exhibiting a substantial therapeutic window.[33]

Table 4: Antiparasitic compounds and their mechanisms.

Compound	Target	Mechanism	Active Against	Reference
1. Pentacyclic triter-penoids or PCTs (betulin, betulinic acid, oleanolic acid, ursolic acid)	Membranes and mito-chondrial pathways	Disintegrate membrane structure, induce apoptosis	Trypanosoma, Leishma-nia, some Plasmodium	[52]
2. Hexadecylphospho-choline (miltefosine)	Lipid metabolism	Acts on lipid rafts and induces pro-grammed cell death	Acanthamoeba	[53]
3. Dialkylphosphonato-colines	Membrane lipids, lipid signalling	Membrane modification, altered lipid metabolism	Acanthamoeba, Leish-mania	[53]
4. Acyclic immucillin phosphonates (AIPs)	HGXPRT	Acts on purine salvage pathway	Plasmodium falciparum	[54]
5. Bisphosphonates	Farnesyl synthase diphosphate	Inhibit FPPS, block isoprenoid biosynthesis and prenylation	Trypanosoma cruzi, Leishmania, Toxo-plasma	[54]
6. Enolase inhibitors (HEX)	Enolase in glycolysis	ATP depletion	Naegleria fowleri, ENO1-deleted cancers	[54]
7. Fosmidomycin	DXR and MEP pathways	Inhibits isoprenoid biosynthesis	Plasmodium falciparum	[55]
8. Lipophilic bispho-sphonates (BPH-715, BPH-942, BPH-943)	Isoprenoid synthases	Improved cell penetration	Plasmodium (liver stage), Leishmania	[56]
9. Nitrogen-containing bisphosphonates (rise-dronate, ibandronate, alendronate)	FPPS	Immunomodulatory activity	Leishmania, Plasmod-ium, Toxoplasma	[57]

Also, molecular changes, such as adding long chain alkyl groups or fluorine have been shown to greatly change how well drugs work. For example, fluorinated dialkylphosphonatocholines in particular are e*ff*ective against Acanthamoeba by damaging protozoal mem-branes, while sulfur-containing bisphosphonates have been e*ff*ective against T. cruzi.[34,35]

Following FPPS, acyclic immucillin phosphonates (AIPs) signify a sophisticated strategy for metabolic disruption by inhibiting the PfHGXPRT enzyme, thereby depriving *P. falciparum* of the purines essential for DNA synthesis. Enolase inhibitors like HEX also show promise for treating primary amoebic meningoencephalitis (PAM) they can cross the blood-brain barrier to target *Naegleria fowleri*. These advancements underscore a transition towards non-antibiotic therapies that exploit the distinctive biological vulnerabilities of parasites and to a certain degree, human hosts. The safety profiles of these phosphonate derivatives render them distinctive candidates for tackling neglected dis-eases in resource-constrained settings, establishing a dependable foundation for the advancement of future anti parasitic therapies.[36]

2. CONCLUSION

The increasing calamity of antimicrobial resistance(AMR) represents invisible pandemic that endanger to impair a century of medical progress, with annual mortality rates estimated to reach 10 million by 2050. While traditional antibiotics fail due to complex survival strategies like enzymatic degradation and active e*ffl*ux systems, phosphinates and phosphonates have emerged as a critical frontier in drug development. These compounds are esteemed by their highly stable carbon-phosphorus bonds, which are more metabolic resistance and stability compared to phosphate esters. Phosphonates inhibit important microbial enzymes involved in process like isoprenoid biosynthesis, nucleotide metabolism and peptidoglycan synthesis, by mimicking phosphates and carboxylates.

The adaptability of non-antibiotic phosphonates is illustrated across a broad spectrum pathogens. In virology, acyclic nucleoside phosphonates(ANPs) have altered the treatment of DNA viruses such as Hepatitis B and HIV. In antifungal and antibacterial appli-cations, hybrid nanocomposites have shown incredible e*ffi*ciency against high-priority resistant strains like *Acinebacter baumannii* and MRSA. Moreover, their ability to target pathways absent in humans like threonine synthase and MEP pathway ensures high toxicity and less side e*ff*ects. Eventually, the structural adaptibil-ity and multi-modal action of phosphonate derivatives o*ff*er stable and highly specific framework for securing the future generation of therapies against global rise of multi-drug resistant infections.[37]

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