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Review article

Harvesting phosphorus-containing moieties for their antibacterial effects

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ABSTRACT

Clinically manifested resistance of bacteria to antibiotics has emerged as a global threat to society and there is an urgent need for the development of novel classes of antibacterial agents. Recently, the use of phosphorus in antibacterial agents has been explored in quite an unprecedent manner. In this comprehensive review, we summarize the use of phosphorus-containing moieties (phosphonates, phosphonamidates, phosphonopeptides, phosphates, phosphoramidates, phosphinates, phosphine oxides, and phosphoniums) in compounds with antibacterial effect, including their use as β-lactamase inhibitors and antibacterial disinfectants. We show that phosphorus-containing moieties can serve as novel pharmacophores, bioisosteres, and prodrugs to modify pharmacodynamic and pharmacokinetic properties. We further discuss the mechanisms of action, biological activities, clinical use and highlight possible future prospects.

1. Introduction

Microbial resistance to antibiotics is a naturally occurring phenomenon that became a primary concern globally in present times.[1] The emergence of multi-drug resistant bacteria is of high epidemiological relevance, associated with difficult and costly treatments, and resulting in high morbidity and mortality. In 2019, antibiotic resistance led to 1.27 million deaths globally, and this number is expected to be on the rise.[2] Pan drug-resistant bacteria have already been identified worldwide, with *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae classified as the critical priority pathogens by the World Health Organization in 2017.[3–4] Since then, international attention has been judiciously attracted to the topic, in order to reduce the accompanying health and economic burden. In particular, a massive demand for alternative approaches towards the treatment of bacterial infections has been registered.

Various strategies have been employed to combat microbial resistance. These include discovery of new targets,[5] leads,[6] structure-activity relationship (SAR) studies, *in silico* modeling,[7] and optimization of *in vitro* and *in vivo* models, all extensively reviewed.[8] Importantly, the isolation of novel natural products alongside mechanistic identification of resistance mechanisms led to the development of β-lactamase inhibitors which would ably restore efficacy of β-lactam antibiotics.[9] However, bacteria have been rapidly evolving, making even so-called last-resort antibiotics, e.g., aztreonam, in many cases ineffective and obsolete.[10] Currently, bacterial enzymes called metallo-β-lactamases (MBLs) are a major threat, with no existing inhibitor yet marketed.[11] Several drugs are thus becoming futile and sustained efforts are necessary to provide viable options to treat deadly pathogens.[12]

Both new and old molecular scaffolds are utilized and revisited in the search for novel antibacterial hits. Especially compounds with atypical structural features are highly valued since they might provide different mechanism of action (MoA) or other benefits in terms of their pharmacokinetic and/or pharmacodynamic properties. For instance, boronic acid moiety has been successfully applied in the design of β-lactamase inhibitors, with vaborbactam **1** (Fig. 1) clinically approved in 2017.[13] Boron-containing taniborbactam **2** (Fig. 1) has been discovered as the first broad-spectrum serine- and metallo-β-lactamase inhibitor, and just completed Phase 3 of clinical trials.[14] Advanced cephalosporin cefiderocol **3** (Fig. 1) harnessing a chlorocatechol moiety that acts also as a siderophore has been developed, targeting even carbapenem-resistant bacteria.[15–16] A novel fluorine-based fluorocycline eravacycline **4** (Fig. 1) with a broad spectrum of activity was granted fast track designation by the U.S. Food and Drug Administration (FDA) and is now available for the treatment of complicated intraabdominal and urinary tract infections.[17] Moreover, next-generation semisynthetic aminoglycoside plazomicin **5** (Fig. 1) has emerged as an entity used to treat infections by multidrug-resistant bacteria.[18] These significant advances in the quest for novel antibiotics and MoAs brought enrichment to the antibacterial pipeline and have been reviewed recently.[19–24] However, more thorough efforts are still necessary since bacteria have already been developing resistance, alarmingly even in the case of some of the

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recently-approved drugs.[25–26] For this reason, exploring alternative functional moieties and scaffolds is a useful and necessary way to extend the antimicrobial arsenal.[23]

Phosphorus is one of the most essential elements of life. Phosphorus-containing compounds are highly abundant in nature and are most frequently present in their oxidized forms as phosphates or phosphonates. They are found as building blocks in nucleotides, both in DNA and RNA,[27] and they are crucially important in biomembranes as a part of highly complex group of phospholipids where they play not only structural roles, but also exert functional properties.[28] Furthermore, reversible phosphorylation is one of the most important cellular regulatory mechanism and adenosine-5′-triphosphate (ATP) is the most known energy storage.[29–30] Notably, phosphorus-bound derivatives have their prominent place also in organic chemistry and biochemistry and they have been heavily used in agriculture and industry.[27]

Typically, relevant phosphorus species in medicinal chemistry are characterized by exhibiting oxidation states of +5.[27,31] Phosphorus-containing drugs have found their place as therapeutic agents and are quite widely applied in clinical practice. Phosphorus-containing moieties may either be a part of a pharmacophore exerting biological function, or they are used to improve drug's pharmacokinetics properties, including prodrug strategies. Notably, they are not just isolated entities and there are also main classes of marketed phosphorus-containing drugs. A key class of antivirals are the acyclic nucleoside phosphonates, which have been recently thoroughly reviewed by Krecmerova *et al.*[32–34] Another important class of phosphorus-based therapeutics are the bisphosphonates, which are commonly used in the treatment of osteoporosis, Paget's disease of bone, myeloma, and bone metastases.[35–36] Furthermore, derivatives based on alkylating scaffolds have been developed as anti-cancer and immunosuppressive agents.[37–38] The medicines portfolio thus ranges from antibacterial, antiviral, anti-cancer, chemoprotective, immunosuppressive to bone-modulatory drugs.

Herein, we describe the use of phosphorus-containing moieties in compounds with antibacterial effects. We provide thorough overview of phosphorus-containing compounds divided into respective groups by their chemical structures (Table 1). We discuss the biological activity, MoA, pathogen spectra, clinical use, to-date analogs, and other useful aspects that will serve as good starting points for further research.

2. Phosphonates and their analogs

Phosphonates are a class of organophosphorus compounds containing the C−PO(OR)$_2$ functional group. They are often used as isosteric replacements for phosphates, and can also serve as analogs of carboxylic acids, amino acids, and peptides.[39] The phosphonyl group is a useful mimetic of enzyme-binding transition-states, intermediates, and primary metabolites, allowing this class of compounds to act as enzyme inhibitors. The direct carbon-phosphorus bond provides chemical and metabolic stability, making this class of compounds particularly interesting for drug design.[40] Phosphonates have been shown to have a broad range of biological activities, including antiviral, antifungal, antibacterial, anti-cancer, and anti-inflammatory properties. Furthermore, bisphosphonates, a subclass of phosphonates, are commonly used for the treatment of bone diseases, such as osteoporosis.[41] Several phosphonate-based drugs have already been developed and are used for the treatment of various diseases, including antiviral drugs adefovir, cidofovir and foscarnet, antibiotic fosfomycin and anti-osteoporotic zoledronic acid.[34,41] Various prodrug strategies have been developed to overcome poor bioavailability of phosphonates due to their high charge at physiological pH.[42] In this section, three different subclasses of phosphonates with antibacterial properties are discussed: phosphonates, α-amino-phosphonates and bisphosphonates.

2.1. Antibacterial phosphonates

Fosfomycin **6** (Fig. 2) is a small-molecule drug that is so far the only phosphonate antibiotic used in the clinic. It was first isolated from *Streptomyces* spp. in 1969,[43] and remains one of the first-line antibiotics for the treatment of acute urinary tract infections. Its synthesis has been described in detail and published.[44–45] Fosfomycin is commercially available in oral formulations as fosfomycin trometamol and fosfomycin calcium, and in parental formulations as fosfomycin disodium.[46] Fosfomycin has bactericidal activity which results from the inactivation of bacterial cell wall synthesis. It enters bacteria through two different uptake pathways, the L-alpha-glycerophosphate and the hexose-6-phosphate transporter systems (GlpT and UhpT, respectively). After entering the cytoplasm, it irreversibly inhibits UDP-*N*-acetylglucosamine-3-enolpyruvyltransferase (MurA), a cytoplasmic enzyme involved in the first step of peptidoglycan biosynthesis.[46] As this inhibition happens at an earlier step than the action of β-lactams or glycopeptides, fosfomycin has a different MoA compared to other cell wall inhibitors as well as other classes of antibiotics, suggesting minimal chances of cross-resistance to other antibiotics.[46–47]

Fosfomycin has a broad spectrum of activity against several Gram-positive and Gram-negative bacteria, including *Enterococcus faecalis*, *Staphylococcus aureus, S. epidermidis, Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Salmonella* spp., *Shigella* spp., *Citrobacter* spp., *Serratia* spp., and *Proteus mirabilis*.[46] Importantly, fosfomycin has also shown activity against multidrug-resistant (MDR), extensively drug-resistant

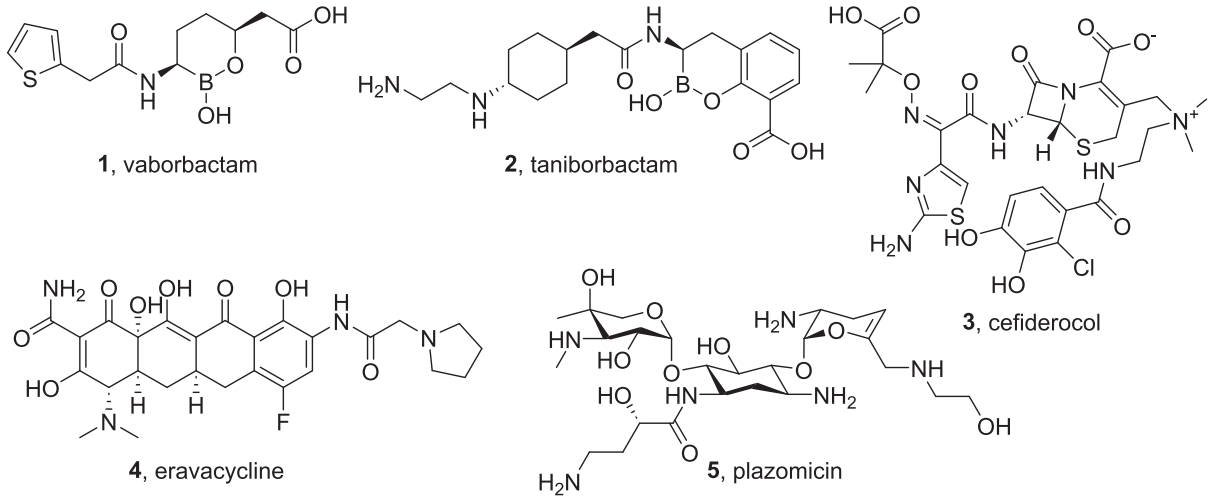
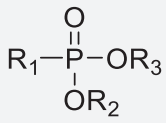
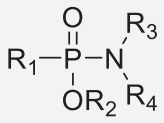
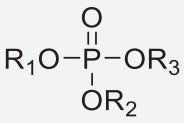
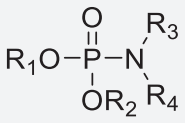
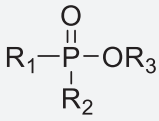
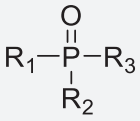
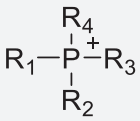


Fig. 1. Recent advances in antimicrobials: Chemical structures of novel antibiotics.

Table 1
Relevant phosphorus-bearing functional groups covered in this review. R = alkyl or aryl.

Phosphonates	Phosphonamidates	Phosphates	Phosphoramidates
			

Phosphinates	Phosphine oxides	Quaternary phosphonium salts
		

(XDR), and pandrug-resistant (PDR) bacteria, including methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and species associated with extended spectrum β-lactamases (ESBL) and MBLs.[46,48–49] Remarkably, fosfomycin seems to be one of the most effective agents for the therapy of PDR *E. coli* and has been proposed for the treatment of other Gram-negative infections, extending its use beyond urinary tract infections.[50]

While fosfomycin remains active against a significant number of Gram-positive and Gram-negative bacteria, several mechanisms responsible for resistance to fosfomycin have been described, including decreased fosfomycin penetration, mutation, or overproduction of the target MurA, and inactivation by fosfomycin-modifying enzymes.[51–52] Nevertheless, the current resistance to fosfomycin in clinical settings seems to be low-to-moderate and the antibacterial activity is more than satisfactory.[52] Furthermore, fosfomycin has shown synergistic effect in combination with other antibiotics, including β-lactams, fluoroquinolones, and aminoglycosides, against several clinically relevant bacteria.[46,53] Thus, there is a global interest to further investigate fosfomycin for the treatment of multidrug-resistant bacterial infections, either as a monotherapy or in combination with other antibiotics.

Fosmidomycin **7** and its acetyl analog FR900098 **8** (Fig. 2) are highly potent natural antibacterial and antiparasitic molecules based on the structure of phosphonohydroxamic acid. They act as inhibitors of 1-deoxy-D-xylulose-5-phosphate reductoisomerase (DXR), an essential enzyme in the methylerythritol phosphate (MEP) pathway of isoprenoid biosynthesis.[54] The MEP pathway is distinctive and natural to several pathogens, such as *Mycobacterium tuberculosis*, *E. coli*, *P. aeruginosa, Plasmodium falciparum* and *Toxoplasma gondii*, while absent in mammals, fungi, archaebacteria and most Gram-positive bacteria. Since the MEP pathway has no known ortholog in humans, the target-related toxicity is to be excluded and DXR inhibitors have excellent species selectivity.[55–56] Although fosmidomycin and FR900098 have activity against a broad spectrum of pathogens, they have not been marketed yet due to their insufficient membrane permeability and a short half-life, resulting in poor pharmacokinetic properties.[55] Recently, Courtens *et al.*[54] published a series of acyloxymethyl and alkoxycarbonyloxymethyl prodrugs of fosmidomycin surrogate, aiming to improve biological activities and pharmacokinetic properties. Compound **9** (Fig. 2) displayed potent antiplasmodial activity (IC_{50} = 50 nM) and several other prodrugs also showed significantly superior activity against *P. falciparum* compared to fosmidomycin. Furthermore, compound **9** showed sub-micromolar activity against *A. baumannii* (IC_{50} = 390 nM), a bacterium against which fosmidomycin is inactive.[54] A comprehensive review highlighting other synthesized fosmidomycin analogs as well as prospects for further development of DXR inhibitors has recently been published by Knak *et al.*[55]

In recent years, Brodzka *et al.*[57] prepared a series of diethyl benzylphosphonates with potent antibacterial activity particularly against K12 and R2 strains of *E. coli*. The tested compounds were found to affect the bacterial DNA and membranes, changing the spatial structure of the lipopolysaccharides in their cell membranes. Subramanyam *et al.*[58] reported a library of newly synthesized substituted arylphosphonates and phosphinates with moderate to good activity against *S. aureus*, *Bacillus subtilis*, *E. coli* and *Pseudomonas marginalis*, as well as good antifungal activity against *Aspergillus niger* and *Fusarium oxysporum*. Cressina *et al.*[59] designed a library of phosphorus-based transition state analogs as inhibitors of the MurM, a tRNA-dependent ligase involved in the peptidoglycan biosynthesis of *Streptococcus pneumoniae*. 2′-Deoxyadenosine 3′-phosphonate analog **10** (Fig. 2) showed the best inhibitory activity (IC_{50} = 100 μM), however, no antibacterial activity was observed against *S. pneumoniae* up to 1 mM, suggesting that **10** is not effectively transported through the bacterial membrane.[59] Nevertheless, there is a prospect for development of a selective transition state analogs for the MurM family of enzymes, providing sufficient transport across the cell membrane.

Phosphonates have been also found to inhibit the activity of β-lactamases. In earlier reports, Pratt *et al.*[60] investigated the activity of phosphonate monoanions against β-lactamases. Firstly, they identified *m*-carboxyphenyl phenylacetamidomethylphosphonate **11** (Fig. 2) to specifically inhibit the class C β-lactamase of *Enterobacter cloacae* P99 in a time-dependent manner. The authors suggested that phosphonylation of an active site functional group takes place. Compound **11** had no intrinsic activity against a variety of Gram-positive and Gram-negative strains.[60–61] Subsequently, the authors synthesized a library of analogs and demonstrated that the compounds phosphonylate the nucleophilic serine hydroxyl group of the β-lactamase active site with a concomitant displacement of a leaving group from phosphorus.[62–65] Better inhibitors had a good leaving group (e.g., *p*-nitrophenoxide) and an amino side chain (exemplary compound **12**, Fig. 2). The carboxylate substituent in the prototypic inhibitor was not essential, and monoaryl phosphonates have been found effective, while monoalkyl analogs were not active.[65] While these compounds were proposed mainly for studying the β-lactamase enzymes function, Yan *et al.*[66] focused on targeting clinically relevant MBLs. In 2023, they employed a strategy that utilized metal binding pharmacophore bound to another fragment by the azide-alkyne click reaction. Subsequent thorough structure-activity studies which

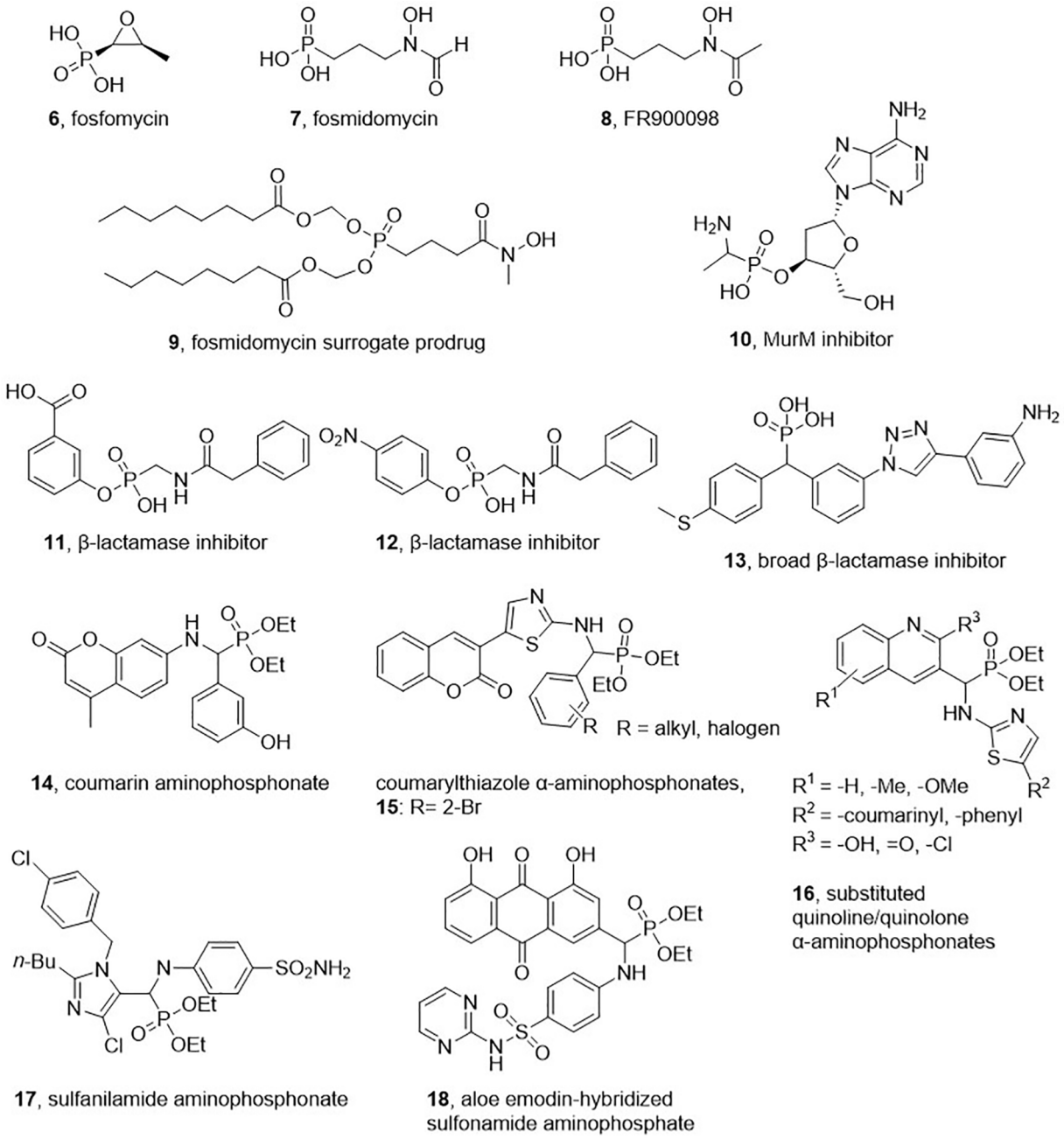


Fig. 2. Antibacterial phosphonates and aminophosphonates.

varied both sides of the molecule led to identification of several potent broad-spectrum MBL inhibitors based on the benzylphosphonic acid scaffold. In particular, compound **13** (Fig. 2) exhibited IC_{50} values ranging from 0.12 nM to 0.64 μM against multiple MBLs (NDM-1, IMP-1, VIM-1, VIM-2, VIM-5).[66]

2.2. α-Aminophosphonates

α-Aminophosphonates, or α-aminophosphonic acids, are analogs of amino acids, in which a carboxyl group is replaced by phosphonic acid or related group. Acting as analogs of amino acids, they can inhibit enzymes involved in amino acid metabolism and thus possess a broad range of biological activities. An extensive review highlighting the potential of α-aminophosphonates for drug development was published by Mucha *et al.* in 2011.[67] Aminophosphonates are commonly used also as building blocks of phosphonopeptides, which are reviewed separately in Section 4.

Yang *et al.*[68] prepared a series of multitargeting coumarin α-aminophosphonates as potential antibacterial agent. The most promising 3-hydroxyphenyl aminophosphonate **14** (Fig. 2) showed potent inhibitory activity against *S. aureus* (MIC = 0.5 μg/mL) as well as ability to eradicate *S. aureus* biofilms, low hemolytic activity, and low tendency to induce resistance development. MoA studies showed that compound **14** is able to destroy the integrity of the cell membrane, which resulted in the leakage of protein. Furthermore, **14** can interfere with the cellular redox homeostasis by inducing reactive oxygen and nitrogen species, causing oxidative damage, and restraining metabolism. Compound **14** could also intercalate into DNA and hinder normal biological function.[68]

A series of α-aminophosphonates bearing coumarylthiazole[69] or substituted quinoline/quinolone and thiazole moieties[70] was prepared by Litim *et al.* The synthesized coumarylthiazole α-aminophosphonates showed good antibacterial activities with MIC between 0.125 and 128

μg/mL against broad spectrum of microbes. Compound **15** (Fig. 2) showed the highest activities with MIC of 0.125 μg/mL against several tested pathogens, including *B. cereus*, *S. aureus*, *Candida albicans*, *E. coli*, *P. aeruginosa* and *A. baumannii*.[69] Similar antimicrobial activity was obtained also for several α-aminophosphonate derivatives containing quinoline/quinolone and thiazole moieties against several Gram-positive and Gram-negative bacteria (MIC = 0.25–128 μg/mL) and against fungi (MIC = 0.25–32 μg/mL), based on structure **16** (Fig. 2).[70] SAR analysis showed that the coumarylthiazole ring and hydroxyl group in the quinoline increased the inhibitory activity against the microbes.[70] These findings suggest that α-aminophosphonates with coumarin, thiazole and/or quinoline moieties could be potential candidates for antimicrobial drugs.

Recently, hybrid antibacterial agents containing aminophosphonate and sulfonamide group, two functional groups with known antibacterial properties, were designed. In 2021, Wang *et al.*[71] developed a class of novel sulfanilamide aminophosphonates *via* one-pot three-component reaction. Compound **17** (Fig. 2) exhibited strongest activity against *E. coli* (MIC = 2 μg/mL) and moderate activity against *E. faecalis*, *S. aureus*, *K. pneumoniae* and *P. aeruginosa* (MIC = 4–32 μg/mL). Furthermore, compound **17** showed low tendency to induce drug resistance in *E. coli* and no obvious toxicity against mammalian cells. MoA studies revealed that **17** can efficiently disrupt the bacterial membrane, induce reactive oxygen species, and intercalate into DNA.[71] A very similar MoA, yet stronger antibacterial activity was later found for a library of natural aloe emodin-hybridized sulfonamide aminophosphates synthesized by Deng *et al.* in 2022.[72] Compound **18** (Fig. 2) showed potent activity with MIC values between 0.25 and 8 μg/mL against *E. faecalis*, *S. aureus*, *E. coli*, *K. pneumoniae* and *P. aeruginosa*. Further investigation showed that compound **18** effectively disrupts biofilms, has low tendency to induce resistance development and only a weak hemolytic activity, making it worthy of further development.[72]

Finally, Sabry *et al.* synthesized a series of α-aminophosphonates bearing sulfisoxazole moiety; however, the reported compounds showed only moderate antibacterial activity.[73]

2.3. Bisphosphonates

Bisphosphonates (BisPs) are a class of drugs that are commonly used in the treatment of osteoporosis, as well as other conditions that exhibit bone fragility, such as Paget's disease and bone metastases. They are characterized by a chemical structure that includes two phosphonate groups linked by a carbon atom. Bisphosphonates mimic the structure of pyrophosphate and as such can adsorb to the hydroxyapatite and inhibit the function of osteoclasts, thus reducing the loss of bone density.[74]

Only a few studies have examined the direct antibacterial effect of BisPs. Ermer *et al.*[75] showed that three commonly used BisPs, i.e., pamidronic, ibandronic, and zoledronic acid, may have an inhibitory effect on selected bacterial species and might inhibit the growth of some relevant pathogens in osteonecrosis. A few new antibacterial BisPs targeting farnesyl diphosphate synthase and undecaprenyl diphosphate synthase, enzymes involved in isoprenoid biosynthesis, were designed by Malwal *et al.*[76] Several alkyl-substituted BisPs showed potent activity against *B. anthracis* (MIC = 0.4 μg/mL), *M. smegmatis* (MIC = 1.4 μg/mL), *B. subtilis* (MIC = 1 μg/mL), and *S. aureus* (MIC = 13 μg/mL).

A more common approach for the application of BisPs in antimicrobial chemotherapy is to exploit their affinity to bone for the treatment of bone infections. Treatment of osteomyelitis, mainly caused by *S. aureus*, is much more challenging and time-consuming than other bacterial infections due to the poor distribution of antibiotics to bone.[74,77] Early research by Herczegh and Buxton[78–79] found that ciprofloxacin-BisP conjugate **19** (Fig. 3) retained the *in vitro* antibacterial activity of the ciprofloxacin and demonstrated its effectiveness in preventing bacterial burden in an *in vivo* rat fracture model of osteomyelitis.

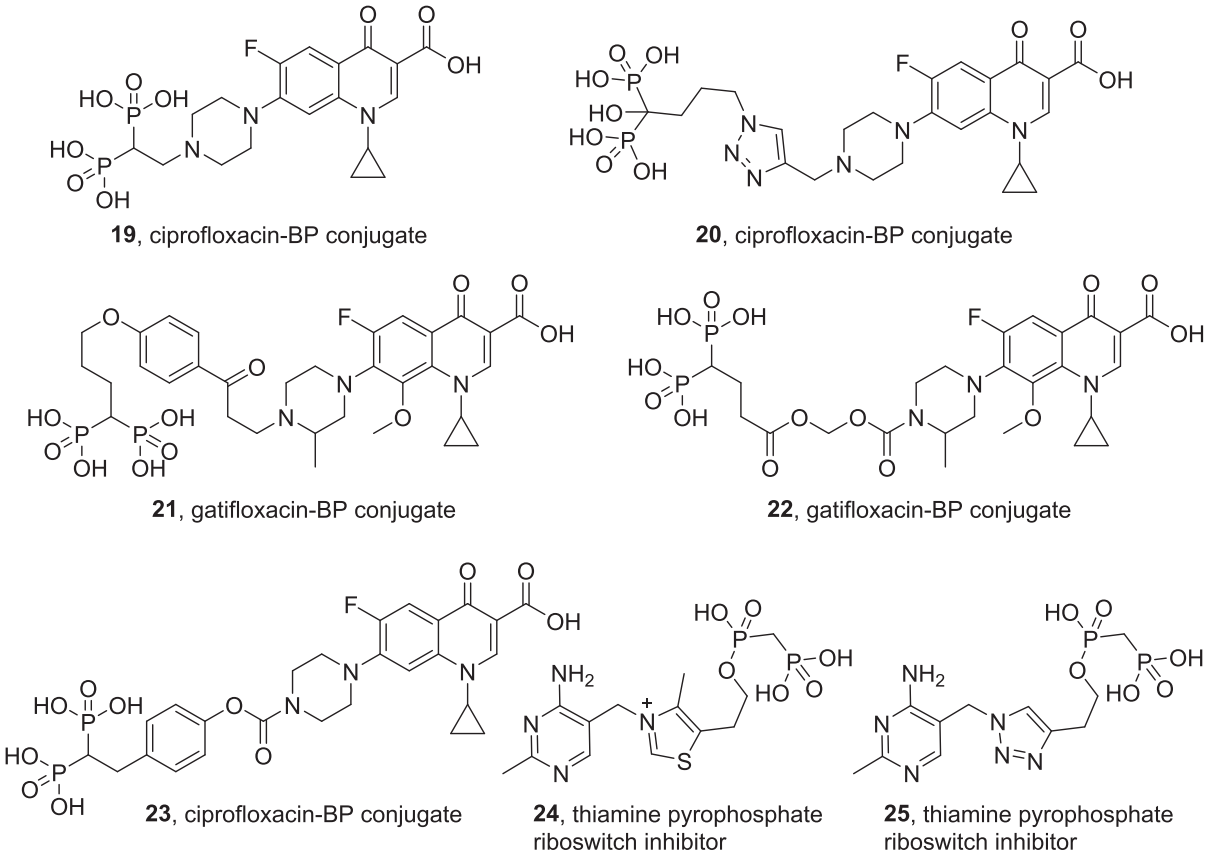


Fig. 3. Antibacterial bisphosphonates.

In a follow-up study, 1,2,3-triazole-linked hydroxybisphosphonate derivative of ciprofloxacin **20** (Fig. 3) showed improved antibacterial activity compared to **19**, as well as strong osteotropic properties.[80] Although the ciprofloxacin–BisP conjugates described above seemed to efficiently bind to bone, they are probably unable to release the ciprofloxacin, possibly limiting the potential of this agent for treatment of bone infections. It is predicted that bacteria are less likely to be inhibited by an antibiotic that is irreversibly bound to the bone. Such challenges were addressed by several authors by designing BisP-antibiotics conjugates with cleavable linkers. This "target and release" approach involves conjugation of antibiotic to BisPs, delivery of the conjugate to the hydroxyapatite in the bones, cleavage of antibiotic–BisP linker and release of the antibiotic at the bone surface.[77] Houghton *et al.* prepared 13 BisP prodrugs of fluoroquinolones, able to release the antibiotics once bound to bone.[81] Compounds **21** and **22** (Fig. 3), utilizing phenylpropanone and acyloxyalkyl carbamate linker, respectively, significantly prevented the establishment of infection in a rat model of osteomyelitis, while the parent drug gatifloxacin failed to do so. Furthermore, the study highlighted the value of the prodrug strategy, as the stable conjugates that irreversibly bound the drug to the bone were not useful in managing osteomyelitis.[81] In 2017, the work of Sedghizadeh *et al.*[82] resulted in a BisP–ciprofloxacin conjugate **23** (Fig. 3) with aryl carbamate linker, which showed significantly improved therapeutic index compared to ciprofloxacin for the treatment of osteomyelitis *in vivo*. Furthermore, conjugate **23** demonstrated great bactericidal activity in all *in vitro* and *in vivo* biofilm models, both for the treatment and prevention of biofilms.[82] Several other carbamate BisP-conjugated fluoroquinolones were also able to inhibit *S. aureus* biofilms in a dose-dependent manner.[83]

Bisphosphonates are also emerging as phosphorus-based ligands to riboswitches.[84] Riboswitches are non-coding regulatory RNAs almost exclusively located in the 5′ untranslated regions of mRNAs to control genes responsible for bacterial metabolism, virulence, and survival. Upon binding of a specific ligand, riboswitches change their conformation to affect downstream transcription or translation. A riboswitch-driven era of antibacterial compounds is now at its beginning, expected to contribute to the fight against drug resistance.[85–86] In a very recent report, compound **24** (Fig. 3) was identified based on a fragment-linking approach as a ligand for thiamine pyrophosphate (TPP) riboswitch, with K_d value of 20 nM.[87] Similarly, the analog with a simplified core **25** (Fig. 3) was a potent ligand with K_d of 9 nM. All known ligands to TPP riboswitch and their SAR have been reviewed in 2023 by Wakchaure *et al.*,[84] however, detailed antibacterial evaluations are yet lacking.

3. Phosphonamidates

Phosphonamidates are a class of organophosphorus compounds known for the presence of a single covalent bond between the tetracoordinate P^V atom and N^{III} atom. They possess a stable phosphoryl bond (P═O), and phosphorus is linked to a carbon atom *via* a single bond. Phosphonamidates are a newer concept in the field of medicinal chemistry, with only one FDA-approved phosphonamidate drug, tenofovir alafenamide, marketed as an antiviral prodrug for the treatment of chronic hepatitis B.[88] Very recently, phosphonamidates have been explored as potential antiviral drugs, utilizing the phosphonamidate moiety as a prodrug motif.[89–91] When bacterial inhibition is concerned, β-lactamase inhibitors, inhibitors of β-class carbonic anhydrases, inhibitors of adenylate cyclases, and inhibitors of VanX have emerged among active compounds based on the phosphonamidate scaffold and

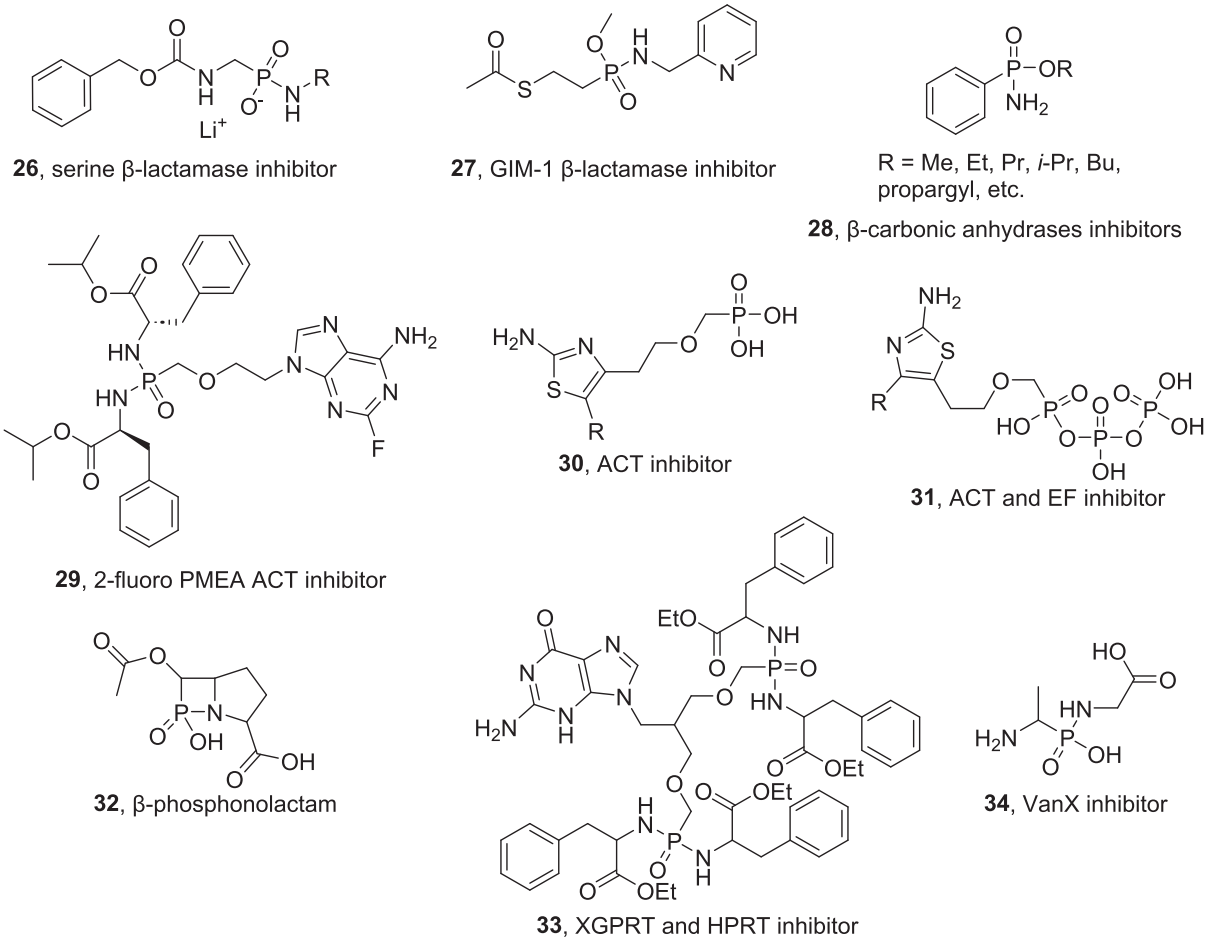


Fig. 4. Antibacterial phosphonamidates and other related active compounds.

are summarized below.

Payne *et al.*[92] prepared and characterized a series of phosphonamidate compounds and discovered inhibitory activities against serine-β-lactamase from *E. cloacae* P99. The compounds containing variable amino acid residues (R) **26** (Fig. 4) are irreversible inactivators, with decreasing potency as follows: β-phenyl-β-Ala > L-Phe > β-Ala > Gly > L-Phe > D-Pro > D-thiazolidine. The authors elucidated the MoA by electrospray ionization-mass spectrometry. Equimolar mixtures of the P99 enzyme with each phosphonamidate affected adduct formation resulting in 70–95% enzyme modified. Since all the primary amino acid derivatives gave a similar mass increment, authors suggested that a displacement of the variable part of the molecule occurs. Importantly, the compounds phosphonylate the active-site serine, the phosphonamidate bond being the scissile bond and amino acid being the leaving group.[92] Further research would be needed to determine e.g., the cytotoxicity and selectivity of said inhibitors.

Recently, Palica *et al.*[93] designed and developed an efficient synthetic procedure for novel MBL inhibitors inspired by the catalytic mechanism of β-lactamase enzyme NDM-1. The central phosphorus atom in the designed phosphonamidate monoester adopts a tetrahedral geometry which mimics the transition state of β-lactam hydrolysis. The authors performed backbone NMR assignment of the protein and studied the protein-ligand complex by a solution NMR spectroscopy. Non-cytotoxic high micromolar inhibitors of several β-lactamase enzymes, with the most active compound **27** (Fig. 4) having an IC_{50} of 86 μM against lactamase GIM-1, were discovered. Compound **27** bound to the hydrophobic substrate binding site of NDM-1, which has previously been proposed for antibiotics and other types of inhibitors, close to the catalytically important Zn^{2+} ions. The authors suggested that upon further optimization, phosphonamidates might become a new potent class of transition state mimicking MBL inhibitors.[93]

Alissa *et al.*[94] explored the inhibition of metalloenzymes β-carbonic anhydrases which are distinct from that of mammalian α-class isozymes. The inhibition of carbonic anhydrases in bacteria, fungi, and protozoa produces an impairment of the microorganism growth and virulence. Several of their simple phosphonamidates with variation of the ester alkyl chain (**28**,Fig. 4) showed inhibitory activity in sub-micromolar to low micromolar range (K_i = 0.02–64.9 μM) against most tested β-carbonic anhydrases. On the other hand, human isoforms were inhibited in a high micromolar range (32.8–961.2 μM). The obtained data thus propose phosphonamidates to be among the most selective carbonic anhydrase inhibitors for β-class over human isozymes known to date. Phosphonamidates were suggested to be interesting leads for the development of new anti-infective agents based on the carbonic anhydrase inhibition.[94]

The Janeba group focused on inhibition of adenylate cyclases (ACs) during the last decade.[95–100] ACs catalyze an intramolecular conversion of ATP to cyclic adenosine 3′,5′-monophosphate (cAMP), a universal second messenger involved in cell signaling. cAMP is involved in a wide range of cellular processes, from virulence mechanisms in various bacteria to regulation of metabolism and gene transcription in mammals.[101] The pioneering research of Tang *et al.* showed that the active metabolite of adefovir dipivoxil inhibits adenylate cyclase toxin (ACT), a key virulence factor of *Bordetella pertussis*.[100,102] *B. pertussis* is responsible for whooping cough, which is still a significant cause of childhood morbidity and mortality worldwide.[103] Furthermore, adefovir selectively inhibits anthrax edema factor (EF), which has calmodulin-activated adenylyl cyclase activity.[104] Smidkova and Cesnek *et al.* synthesized phosphonamidate prodrugs of adefovir, and later focused on the synthesis and biological evaluation of *C*2-modified analogs. 2-Substituted derivatives of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA, adefovir) were prepared in their bis(L-phenylalanine) prodrug form. Compounds bearing a small *C*2 substituent showed high potency against adenylate cyclase toxin with good selectivity over human adenylate cyclase isoforms AC1, AC2, and AC5. The most potent ACT inhibitor was found to be the noncytotoxic bisamidate prodrug of the 2-fluoro PMEA derivative **29** (Fig. 4) (IC_{50} = 0.145 μM).[99–100] Subsequently, inspired by the structure of MB05032 - a mimic of adenosine monophosphate, the researchers scaffold-hopped to the non-purine 5-subsituted 2-aminothiazole moiety. Interestingly, this led to the discovery of both ACT inhibitors (**30**,Fig. 4), and selective mammalian AC1 inhibitors, the latter of which were suggested to be potential leads in the development of neuropathic pain.[96] The research was followed by Cesnek *et al.* who reported yet unsurpassed activities of acyclic nucleoside phosphonates towards ACT, based on 2-amino-4-arylthiazoles.[95] The target compounds were prepared in their phosphonodiamidate prodrug form for cell-based assays and as their phosphono diphosphate form for enzymatic assays. Notably, several potent novel ACT inhibitors (IC_{50} = 9–18 nM), were discovered, with compound **31** (Fig. 4) being more potent EF inhibitor (IC_{50} = 12 nM), compared to adefovir diphosphate (PMEApp) with IC_{50} = 18 nM for ACT and IC_{50} = 36 nM for EF. The potency of the phosphonodiamidates to inhibit ACT activity in J774A.1 macrophage cells was, however, somewhat weaker. The most potent analog had IC_{50} = 490 nM compared to IC_{50} = 150 nM of the analogous adefovir phosphonodiamidate. The results suggested that optimization of the parent structure is still necessary. As one may expect, the phosphonamidate moiety serves here as a prodrug tool, modulating the pharmacokinetic properties. The authors suggested that more efficient type of prodrugs would be desirable to increase concentrations of the active species in the cells. This may lead to novel phosphorus-based functional moieties being discovered and optimized for this new highly valuable scaffold.

Within their research, Yang *et al.* synthesized several phosphonate and phosphinate analogs, together with small dipeptide mimics, which are summarized in the respective sections. Furthermore, they explored MBL inhibition by the synthesis of β-phospholactam as a carbapenem transition state analog.[105] The phosphonolactam 32 (Fig. 4) was shown to be a weak, time-dependent inhibitor of lactamases IMP-1 (70%), CcrA (70%), L1 (70%), NDM-1 (53%), and Bla2 (94%) at a concentration of 100 μM. Authors suggested that further modification to the phosphonolactam scaffolds may result in stronger binding and improving the binding affinities.[105]

Keough *et al.*[106] identified a new target of nucleoside phosphonates, two *E. coli* purine salvage enzymes xanthine-guanine phosphoribosyltransferase and hypoxanthine phosphoribosyltransferase. Nucleoside phosphonates, which are good inhibitors of both enzymes with K_i values as low as 10 nM, were therein used as phosphonamidate prodrugs to mask the negative charges of the phosphonate groups and thus to increase cell permeability. Once within the microbial cells, the authors propose that the prodrugs are hydrolyzed to their parent components. None of the parent compounds exhibited activity against *M. tuberculosis* at concentrations ≥ 250 μM. However, in their phoshonamidate form, as exemplified by compound **33** (Fig. 4), they were able to inhibit the growth of *M. tuberculosis* in cell culture, with IC_{50} values between 5 and 23 μM. Cytotoxicity data were as well determined, and the selectivity index was ≥ 17, demonstrating a potential therapeutic window. Furthermore, the scientists extended their research to other species, targeting parasites such as *P. falciparum* and *Trypanosoma brucei*, as reviewed by Cheviet *et al.* and Terán, respectively.[107–108]

Noteworthy is also the earlier research of Yang *et al.*[109–111] who explored phosphonamidates as inhibitors of VanX. VanX is a Zn-dependent metalloenzyme responsible for vancomycin resistance in bacteria. Vancomycin is a tricyclic glycopeptide antibiotic that disrupts the formation of cell wall in Gram-positive bacteria. It does so by binding to the D-Ala-D-Ala subunit of peptidoglycan monomers that are necessary to form the bacterial peptidoglycan layer.[112] VanX hydrolyzes vancomycin-binding D-Ala-D-Ala dipeptides, thus yielding the antibiotic ineffective.[113] VanX is quite an underexplored drug target that could be valuable to combat vancomycin resistance in bacteria. Yang *et al.*[110] synthesized a small library of five phosphonamidates, with inhibitory activity against VanX with IC_{50} values of 0.39–4.13 mM. The most potent compound 34 (Fig. 4) also showed an antibacterial activity

against *S. aureus* with a MIC value of 0.25 μg/mL.[110]

4. Phosphonopeptides

Phosphonopeptides are peptide mimetics in which a carboxyl group or peptide bond is replaced by a phosphonic or related (phosphinic, phosphonous) group.[114] They can be divided into three main structural classes: i) phosphonate peptides, where phosphonic acid replaces C-terminal carboxyl group or mimics peptide bond, ii) phosphonamidic peptides, where a phosphonamidate bond replaces the amide bond and iii) phosphinic peptides, with phosphinic acid mimicking peptide bond.[115–116] Although phosphonic and carboxyl groups differ in shape, acidity, and steric bulk, they frequently show similar properties, with the phosphonic acid being recognized by enzymes or receptors as false substrates or inhibitors. Synthesis of phosphonopeptides and related compounds has been reviewed in detail.[116–118]

Phosphonopeptides have been widely explored as antibacterial agents in the late 20th century. The antibacterial MoA of phosphonopeptides is typical for all members of the class and differs from that of commonly used antibiotics. The peptidyl part of the compounds enables active transport through the bacterial membrane. Subsequently, upon peptidase-mediated hydrolysis, the bioactive phosphonate "warhead" is released to exert toxic effects by inhibiting vital enzymes. Phosphonopeptides were shown to have a broad spectrum of activity against Gram-positive and Gram-negative bacteria, as well as antifungal and herbicidal activity.[115]

The first and the best known antibacterial phosphonopeptide is alafosfalin **35** (Fig. 5), a phosphonic acid analog of alanine, which has been first reported by Allen *et al.*[119] in the late 1970s. Alafosfalin enters bacteria through L-L-dipeptide permeases and after hydrolysis, fosfalin is released. The latter binds to alanine racemase and prevents synthesis of D-alanine, an essential component for the biosynthesis of peptidoglycan.[120] Alafosfalin was shown to have a broad spectrum of activity against certain Gram-positive bacteria, such as *S. aureus* and *E. faecalis*, anaerobic bacteria (*Bacteroides* spp. and *Clostridium perfringens*) and many species of Enterobacterales (excluding *Pseudomonas* and *Acinetobacter*).[121] Alafosfalin has been extensively studied in animals and human volunteers, and it showed a low toxicity, good absorption, low protein binding, a bactericidal mode of action and a different target compared to other antibiotics.[121–124] However, despite several advantageous properties, alafosfalin has never been licensed, most likely due to the rapid development of bacterial resistance, a pH-dependent activity, a high inoculum effect, and its tendency to be hydrolyzed in body fluids and thus reduced bioavailability.[125]

In 2020, Marrs *et al.*[126] revisited the use of alafosfalin and related compounds as antibacterial compounds and reported the antibacterial activity of alafosfalin and its analog di-alanyl fosfalin **36** (Fig. 5) against 297 bacterial isolates, including MRSA and carbapenemase-producing Enterobacterales (CPE). Alafosfalin showed good activity against most isolates of Enterobacterales, with the minimal concentration of antimicrobial required to inhibit 90% of isolates (MIC_{90}) of 4 μg/mL against CPE. It showed strong activity against *E. coli* (MIC_{90} = 0.25 μg/mL) but was only moderately active against MRSA (MIC_{90} = 8 mg/L). On the other hand, di-alanyl fosfalin showed potent activity particularly against enterococci, with the MIC_{90} of 0.5 and 2 μg/mL against *E. faecalis* and *E. faecium*, respectively. This report shows that alafosfalin and related compounds may have a therapeutic role in the era of antimicrobial resistance.

Since the discovery of alafosfalin, several synthetic phosphonopeptides have been tested for their antibacterial activity[127] and several natural peptides have been isolated from bacteria and fungi. Bialaphos **37** and phosalacine **38** (Fig. 5) were isolated from *Streptomyces* spp. and *Kitasatosporia phosalacinea*, respectively, and they act as inhibitors of glutamine synthetase.[128–129] While they have shown antibacterial and antifungal activities, they have been mostly investigated as herbicides. Dehydrophos **39** (Fig. 5) was first isolated from *Streptomyces* spp. as a broad-spectrum antibiotic affective against both Gram-positive and Gram-negative bacteria.[130] It has a different MoA compared to other phosphonopeptides. After the peptide bond is cleaved, the phosphonic analog of dehydroalanine is converted to methyl acetylphosphonate, which is strongly antibacterial by acting as an antimetabolite of pyruvic acid.[131] Recently, dehydrophos has been used as a lead compound for

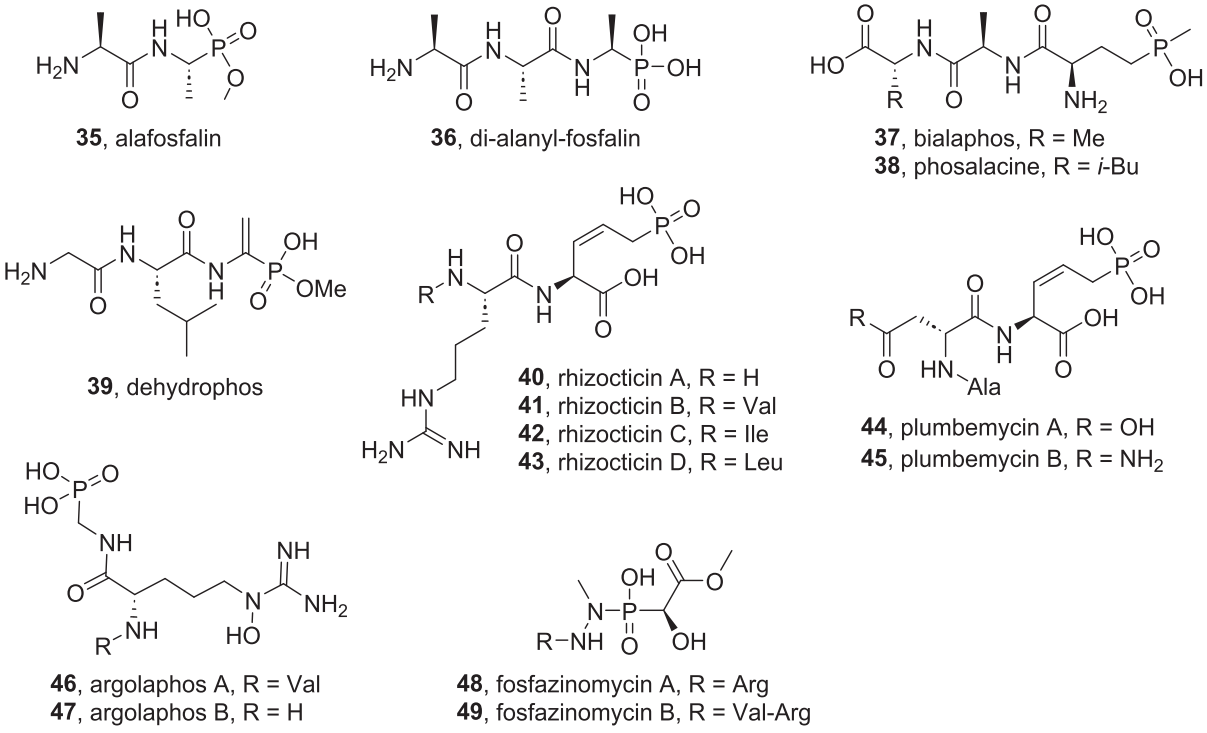


Fig. 5. Antibacterial phosphonopeptides.

the design of new antibacterial agents, as reported by Jiménez-Andreu *et al.*[132] and Bartee *et al.*[133]

Rhizocticins **40-43** and plumbemycins **44, 45** (Fig. 5), phosphonate antibiotics produced by the *B. subtilis* and *S. plumbeus*, act as inhibitors of threonine synthase,[134] and their antibacterial and antifungal activity have been described previously.[135–136] However, Gahungu *et al.* carried out validated experimental procedures and found no significant antimicrobial activities of rhizoctinins and plumbemycins against selected bacteria and fungi even with concentrations up to 1000 times of the MICs described.[134]

Other examples of phosphonopeptides with antibacterial properties include argolaphos A and B **46, 47** (Fig. 5), which have been discovered by a high-throughput genome mining of over 10,000 actinomycetes,[137] and fosfazinomycins **48, 49** (Fig. 5), which have been identified 30 years after their original isolation from *Streptomyces*.[138] Argolaphos is the first natural product to contain inhibitory nonproteinogenic amino acids aminomethylphosphonate (AMPn) and also N^{ϵ}-hydroxyarginine.[139] It has shown the highest activity against *Salmonella typhimurium*, *E. coli*, and *S. aureus*, and a weak inhibitory activity against *M. smegmatis*.[137] Recently, the complete biosynthetic pathway for the argolaphos phosphonopeptides has been reported. The authors suggested that wealth of potential AMPn and N^{ϵ}-hydroxyarginine containing natural products can be realized through genome mining. Therefore, this area of research is suspected to further grow in the future.[139]

5. Phosphates

Phosphates are derivatives of a phosphoric acid, bearing the functional group (RO)(R'O)(R"O)P=O. In drug development, this functional group is a useful moiety for enhancing the solubility of a parent drug. There are currently two marketed antibacterial drugs based on said principle, bearing the phosphate structural feature. Additionally, a few natural antibiotics belong into this group and are summarized herein.

Clindamycin **50** (Fig. 6) is a semi-synthetic inhibitor of protein synthesis from the group of lincosamides, specifically acting on the 50S ribosomal subunit, inhibiting early peptide chain elongation.[140] It is useful for the treatment of infections of the lungs and skin, as well as intra-abdominal and gynecological infections.[141] Clindamycin is widely used for the management of severe acne vulgaris with topical therapy. Fixed combinations, such as clindamycin-benzoyl peroxide 1.2%/3.75% and 1.2%/2.5% gels, and clindamycin phosphate 1.2%-tretinoin 0.025% were all found to be effective in severe acne.[142] Clindamycin phosphate as an aqueous-based gel minimizes skin irritation and thus optimizes adherence with therapy.[143] The phosphate ester is itself inactive against bacteria, but it is readily hydrolyzed to microbiologically active clindamycin.[144]

Tedizolid phosphate **51** (Fig. 6), previously known as TR-700, is a novel oxazolidinone-class antibiotic approved only in the last decade. It is used in the treatment of Gram-positive infections, including infections caused by staphylococci containing the *cfr* gene, which confers resistance to five classes of antibiotics. Tedizolid phosphate has several fold enhanced activities compared to its predecessor linezolid, achieved by novel structural features, including the addition of fourth ring to the structure.[145–146] It also has an improved pharmacokinetics, allowing for administration only once daily. The utilization of the phosphorylated prodrug has multiple advantages, including improved solubility in water and excellent oral bioavailability.[146] Furthermore, masking the C-5 hydroxymethyl group by phosphate prevents interactions with monoamine oxidase, which was previously problematic in this class of drugs.[147] Indeed, tedizolid phosphate is starting to play an important role especially in the treatment of complicated bacterial skin infections and has been proposed for a long-term treatment of nocardiosis in immunocompromised patients.[148–150] As the oxazolidine scaffold has been regarded as highly promising for the development of antibacterial drugs against resistant bacteria, research in this area is suspected to further grow.[151]

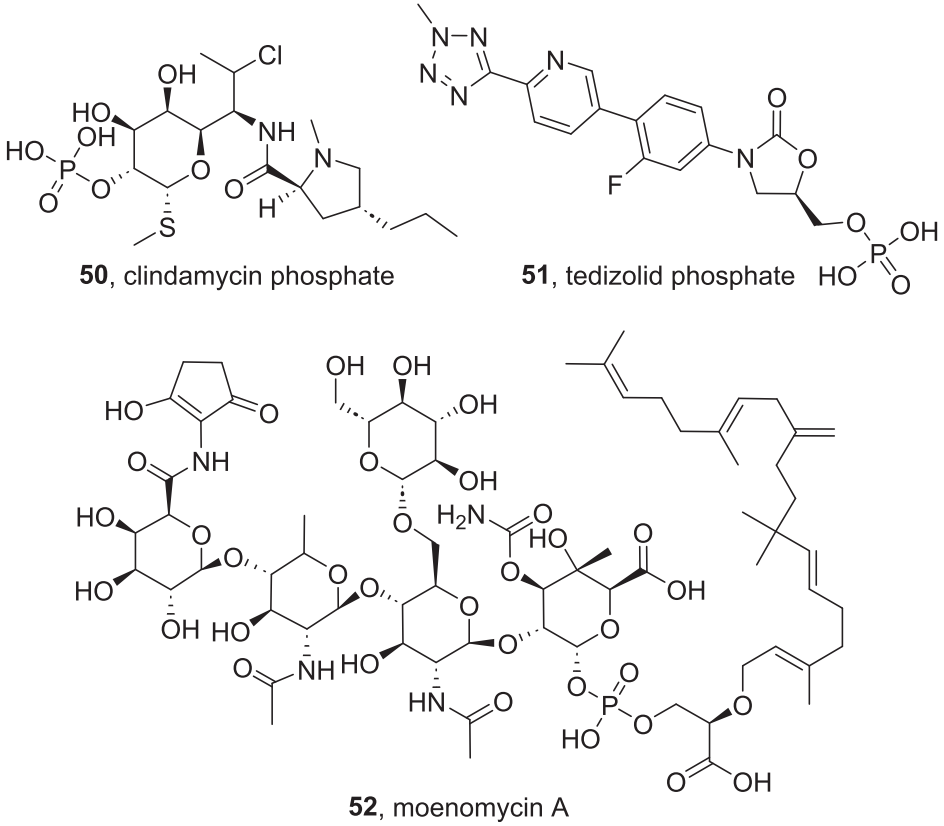


Fig. 6. Antibacterial phosphates.

Moenomycins, also called flavomycins, flavophospholipol or bambermycins, are a class of glycophospholipid antibiotics isolated in the 1960s from several strains of *Streptomyces*.[152] They contain an unusual isoprenoid chain with a phosphate group attached to the reducing end of a structurally complex pentasaccharide. They are the only known group of antibiotics that inhibit bacterial peptidoglycan glycosyltransferases in the penultimate step of bacterial cell wall biosynthesis. In contrast, β-lactam antibiotics target the transpeptidation reaction, responsible for cross-linking of two glycan chains *via* the peptide side chain. A member of the group, moenomycin A **52** (Fig. 6), has a potent antibiotic activity against various Gram-positive bacteria, being 10–1000-fold more active than vancomycin. However, its use as a therapeutical agent has been hindered by suboptimal pharmacokinetic properties, including poor oral bioavailability and a long serum half-life, that undermine its clinical value.[153–154] However, it has found its role as a feed additive growth promoter in cattle, pigs, chickens, and turkey.[155] Surprisingly, even after decades of animal feeding, almost no evolved resistance against moenomycin has been observed.[153,156] In addition, it was recently reported that moenomycin is effective against multidrug-resistant *Helicobacter pylori*, a microaerophilic Gram-negative bacterium responsible for gastritis and peptic ulcers, and a key risk factor of gastric cancer.[157] Specifically, combination of moenomycin A with clarithromycin or metronidazole provides almost 95% eradication of multidrug-resistant *H. pylori*.[158] Importantly, moenomycin was also identified as a potent antigonococcal agent in a screen of microbial natural products against drug-resistant *Neisseria gonorrheae*, demonstrating a potent activity (MIC = 0.004–0.03 μg/mL).[159] The research was followed by *in vitro* and *in vivo* murine studies by Yang *et al.*;[160] which upon promising results suggested that moenomycin be explored as an alternative therapy for the treatment of *N. gonorrhoeae* infections. Furthermore, moenomycin opened a new area of research consisting of targeting the bacterial transglycosylases.[161] According to some predictions, bacterial transglycosylases could be more promising target than transpeptidases for antibiotic development. Current challenges and future perspective related to moenomycin have been reviewed by Ostash *et al.*, Cochrane *et al.* and Chen *et al.*[162–164]

Prasinomycin is an antibiotic from the green spore *Streptomyces prasinus* belonging to the same family as moenomycins. Not much research has been devoted to prasinomycins to date, thus the full structure is not yet known. However, it is based on the diester of phosphoric acid. As for its antibacterial properties, it primarily inhibits the growth of Gram-positive microorganisms. In mice, it displayed a unique biological feature consisting of prolonged prophylactic action for as long as 2 months after administration of a single dose.[165–166]

6. Phosphoramidates

Phosphoramidates are a class of phosphorus compounds based on the substitution of OR for an NR_2. They are derivatives of phosphoramidic acids $O{=}P(OH)(NR_2)_2$ or $O{=}P(OH)_2(NR_2)$ and are linked to a carbon *via* an oxygen atom. The most known phosphoramidates are nucleoside phosphoramidates (so-called ProTides) that have been exploited as a prodrug technology, initially developed by McGuigan.[167] This prodrug approach was developed to overcome limitations of the parent acyclic nucleosides and even acyclic nucleoside phosphonates. In order to be biologically active, nucleoside analogs need to be converted into their phosphorylated counterparts. However, many analogs are not effectively phosphorylated in cells, which is the rate-limiting step. Furthermore, the native phosphate group is easily hydrolyzed by phosphatases and phosphodiesterases.[168] The ProTide technology thus overcomes these challenges and has been successfully applied to antiviral and cytostatic drugs. The efforts resulted in many patents and articles, as well as in two FDA-approved marketed drugs. Sofosbuvir, drug for the treatment of chronic hepatitis C infection, and remdesivir, the well-known antiviral medicine approved for the treatment of mild-to-moderate COVID-19.[169–171]

Munier *et al.*[172] reported the application of the ProTide strategy to antibacterial drug design. The authors synthesized aryl phosphoramidate prodrugs of fosfoxacin homologs, as exemplified by compound **53** (Fig. 7). No growth inhibition was observed for *M. smegmatis* or for *E. coli*. Apparently, no release of the active compounds occurred in the bacterial cells. The authors investigated the stability of the prodrugs in abiotic and biotic conditions to discover the prodrug approach to deliver non-nucleotide compounds is not obvious.[172] While Munier *et al.* concluded that the ProTide strategy may not be appropriated for antibacterial drug design, a successful phosphoramidate strategy was recently reported by Sivala *et al.*[173] The authors synthesized phosphoramidate derivatives of 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole **54** (Fig. 7) as a new class of potential antibacterial and antifungal agents. The compounds exhibited antibacterial activity against *S. aureus, B. subtilis, K. pneumoniae, S. typhi* and *P. mirabilis* and anti-fungal activity against *A. niger* and *A. flavus*. The study was supported by molecular docking studies to reveal high dock scores, as compared with standard drugs norfloxacin and nystatin. The authors evaluated their compounds as promising in the era of antibiotic resistance.[173]

Earlier reports by Cox *et al.*[174–175] and Adams *et al.*[174–175] focused on inhibition of aspartate-semialdehyde dehydrogenase (ASA-DH) by phosphonates and phosphoramidates. Said enzyme is the starting point of bacterial pathways leading to L-lysine and other amino acids, *via* diaminopimelic acid (DAP). DAP plays a crucial role in bacterial replication being responsible for cross-linking in the peptidoglycan layer of the cell wall of both Gram-positive and Gram-negative organisms. ASA-DH is also present in fungi but has no known ortholog in mammalian metabolism, rendering its inhibition highly selective.[176] The novel phosphoramidates **55** (Fig. 7) were designed based on the mechanistic rationale, adjusting the nucleophilicity of the analogs to provide better inhibition.

7. Phosphinates

Phosphinates are a class of phosphorus compounds based on the structure of hypophosphorous acid. Where relevant, some are described in the section phosphonopeptides in this review. We further provide a brief overview in this section to demonstrate the miscellaneous antibacterial activities of phosphinate derivatives. The synthetic methods, potential for drug discovery, and biological applications of phosphinic acid derivatives were reported on by Abdou *et al.*, with the most recent review in 2020.[177–179]

As briefly mentioned in the section of phosphopeptides, Wu and Walsh[180] explored phosphinate analogs of D-D-dipeptides as inhibitors of VanX, a D-Ala-D-Ala dipeptidase that is essential for vancomycin resistance in *E. faecium*. The inhibitors are analogs of the proposed tetrahedral intermediate for hydrolysis of D-Ala-D-Ala, with the compound **56** (Fig. 8) having K_i value of 90 nM.[180] Furthermore, Walsh *et al.*[181] discovered potent and selective inhibitor **57** (Fig. 8) of the *E. coli* bifunctional glutathionylspermidine synthetase/amidase. Glutathionespermidine conjugate is synthesized from tripeptide glutathione in *E. coli* and in trypanosomatid parasites by an ATP-cleaving Gsp synthetase activity. It is also a precursor to trypanothione, the major surveillance thiol involved in oxidant defense mechanism in trypanosomatid parasites. Because of that, targeting this unique defense system is an attractive method for the discovery of novel drugs.

Further research deals with the inhibitors of MurC, MurD, and MurE ligases, which catalyze the early steps of bacterial peptidoglycan biosynthesis and are yet underexploited targets for antibacterial drug design. They hold a great promise, as this biosynthetic pathway is absent in mammalian cells and is unique to eubacteria, providing selectivity in inhibition of the pathogens.[182] For example, Marmor *et al.*[183] synthesized the nanomolar *E. coli* MurC inhibitor **58** (Fig. 8) in the form of a transition state analog based on the phosphinate scaffold. The authors provided detailed binding analysis, suggesting that the inhibitor binds to several enzyme forms with varying, but significant, potencies. In

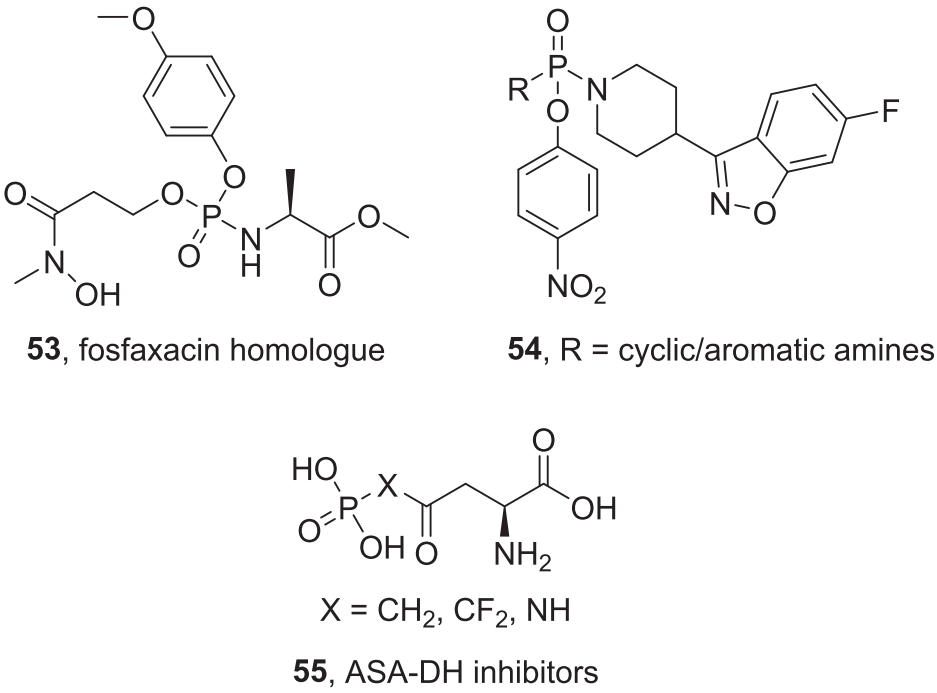


Fig. 7. Antibacterial phosphoramidates.

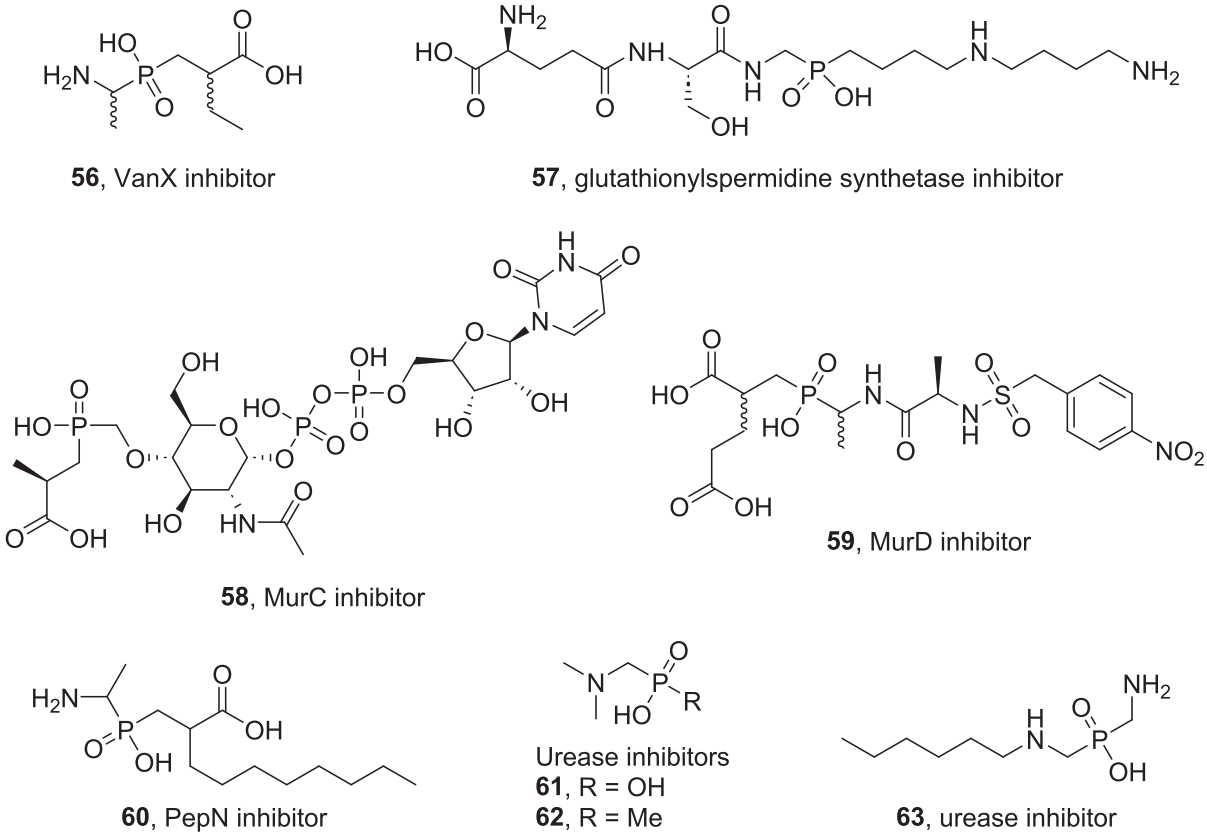


Fig. 8. Antibacterial phosphinates.

particular, the compound exhibits mixed-type inhibition with respect to all three enzyme substrates (ATP, UDP-*N*-acetylmuramic acid - UNAM, Ala).[183] Similarly, Strancar *et al.*[184] designed and synthesized inhibitors of MurD. In the starting series, two high micromolar inhibitors (IC_{50} values near 100 μM, e.g., **59,** (Fig. 8)) were discovered.[184] Furthermore, the series were extended both synthetically and target-wise, adding another target MurE to discover new inhibitors and a structure-activity relationship. The inhibitors were not transition-state

analogs, but rather analogs of the substrate UDP-MurNAc-dipeptide. The best inhibitor of MurD **59** (Fig. 8) was also one of the best inhibitors of MurE.[185]

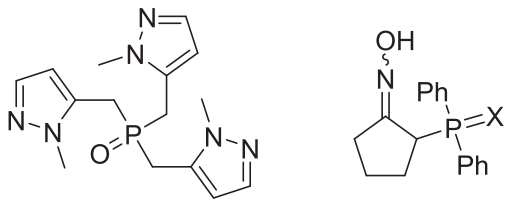
Yang *et al.*[186] prepared potential inhibitors of *E. coli* aminopeptidase N (PepN) based on a phosphinate, sulfonate and sulfonamide scaffold. Decylphosphinate 60 (Fig. 8) was shown to be a competitive inhibitor of PepN with a K_i of 1.1 μM. The inclusion of the hydrophobic substituent resulted in improved binding affinity. However, it was shown that the use of sulfonate/sulfonamide analogs to replace phosphinates is not a good strategy to improve the binding strength of the compounds.[186]

In more recent reports, Berlicki *et al.*[187–188] discovered nanomolar urease inhibitors based on the bis(aminomethyl)phosphinic acid scaffold. A rapid microbial decomposition of urea by urease produced by some bacteria releases ammonia and causes local increase in pH, which allows for survival in acidic conditions of the body, e.g., in the digestive tract. It is thus suggested that the inhibition of bacterial ureases might be promising in the treatment of *H. pylori* in the gastric tract, or *Proteus* species in the urinary tract.[189] Firstly, a structure-based inhibitor design approach was applied using available structures of bacterial ureases to discover *N*-substituted derivatives of aminomethylphosphonic and *P*-methyl-aminomethylphosphinic acid **61**, **62** (Fig. 8). The inhibitors were assayed against urease from *B. pasteurii* and enzyme from *Canavalia ensiformis* to show activities in the low micromolar range ($K_i = 13 \pm 0.8$ and 0.62 ± 0.09 μM, respectively), and high hydrolytic stability.[187–188] Subsequently, a series of analogs was prepared by a robust synthetic method, out of which the most potent phosphinate inhibitor aminomethyl(*N*-*n*-hexylaminomethyl)phosphinic acid **63** (Fig. 8), had a K_i = 108 nM. The compound exhibits both high stability and solubility in aqueous solutions.[189]

8. Phosphine oxides

Phosphine oxides are well-established structural motifs that are, however, still vastly underrepresented in medicinal chemistry. They are based on the structure O=PR_3, where R is alkyl or aryl. To date, there has been only one drug approved bearing this moiety, i.e., brigatinib, a small-molecule antineoplastic anaplastic lymphoma kinase inhibitor.[190] Phosphine oxides are known to be highly polar, able to decrease log*D*, enhance solubility and metabolic stability, but occasionally at the cost of reduced permeability. The design and synthesis of phosphorus-containing tool compounds, including phosphine oxides, for the use in medicinal chemistry has been recently reported by Finkbeiner *et al.*[191] These valuable polar structural elements deserve more attention, and their use is expected to be on rise.

In the field of antibacterial phosphine oxides, Malysheva *et al.*[192] synthesized a series of phosphorus-containing polyfunctional compounds bearing imidazole, pyrazole, or pyridine moieties, focusing mainly on the synthesis of tertiary phosphine oxides from affordable elemental phosphorus. Phosphine oxide with three methylpyrazole fragments **64** (Fig. 9) showed high to moderate antibacterial activity against four tested pathogens (MIC = 0.15–6.2 μg/mL). Alongside the antibacterial activity, toxicity towards human skin fibroblasts and human tumor cells A549 was evaluated. The authors proposed that the compound **64** represents a promising antibacterial compound for further preclinical trials.[192]



64 **65**, **66:** X = O, S

Fig. 9. Antibacterial phosphine oxides.

A series of unprecedented α-(diphenylphosphoryl)- and α-(diphenylphosphorothioyl)cycloalkanone oximes were prepared and evaluated for their *in vitro* antimicrobial activity against Gram-positive bacteria (*S. aureus* and *B. subtilis*), Gram-negative bacteria (*E. coli* and *S. typhimurium*) and fungal strains (*C. albicans* and *C. glabrata*).[193] Assessed oximes, isolated as a mixture of two inseparable isomers, exhibited very high antibacterial and antifungal activities at only 0.1–2.1 μg/mL, surpassing the standard drugs ciprofloxacin and fluconazole. Furthermore, a significant bactericidal activity (99.9%) was detected, with minimum bactericidal concentration (MBC) values ranging from 2.0 to 2.1 μg/mL for all studied compounds. Cyclopentane ring-bearing compounds **65** and **66** (Fig. 9) were evaluated to be the most potent agents, however, the increase in the size of the ring resulted nevertheless in a very slight decrease in activity.[193]

9. Quaternary phosphonium salts

Quaternary phosphonium compounds (QPCs) are compounds with a tetravalent phosphorus atom bearing a positive charge. Some of the pioneering works on QPCs against bacteria have emerged in the 1950s and 1980s.[194–195] Since then, slow progress was noted, up until very recently when novel antibacterial disinfectants have been required to combat resistant pathogens. Quaternary ammonium compounds (QACs) have, to date, been the first line of defense against resistant pathogens. However, QAC-resistant species already emerged due to a scarcity of innovation in this research area.[196] Next-generation compounds that offer improved activity over leading disinfectants have been discovered and described by numerous research groups in the last decade, with the last review on the advancements in the development of non-nitrogen-based amphiphilic antiseptics published in 2020.[197] At about the same time, an abrupt surge in QAC usage in the society due to SARS-CoV-2 was registered. For example, an increase in the mass load of QACs at a wastewater treatment plant by 331% compared to before the COVID-19 pandemic was noted.[198] Several reports highlighted the threat of impending resistances due to the increased use of antibacterial agents as cleaners and sanitizers.[197,199–200] Fortunately, the state of the field of phosphonium amphiphilic antiseptics has progressed further alongside and offers high promise in combating resistant species.

In the earlier review, Carden *et al.*[197] noted that the most effective QPC was the structurally simple compound **67** (Fig. 10). It exhibited MIC of 0.78–3.13 ug/mL against *S. aureus* (incl. MRSA), *E. coli* and *E. aerogenes*. Notably, 67 was able to eradicate all *S. aureus* cells in only 30 min while analogous QACs have not killed any bacterial cells even upon extended exposure.[201]

Minbiole *et al.*[202] prepared analogs of common QACs as an extension of their earlier project;[203] taking advantage of simplicity, readiness in availability, and atom-economical approach. A library of 21 novel QPCs were prepared in robust high-yielding syntheses. The most potent bisQPC amphiphiles exhibited high activity in the single-digit micromolar region, comparable to that of analogous QACs, and outperforming the standard benzalkonium chloride. The highest antimicrobial activity was observed for compounds with alkyl chain lengths of 10–12 carbons (e.g., **68**,Fig. 10). Notably, the top-performing compounds maintained efficacy also against Gram-negative pathogens which bear known disinfectant resistance mechanism, such as the expression of multidrug efflux pumps.[202] Additionally, the focus has as well been on the preparation of so-called soft QPCs which degrade under environmental conditions. In high-yielding syntheses, amide moieties were introduced into the compounds' side chains to promote degradation in the environment. Indeed, the compounds maintain their stability in neutral solutions, while decompose under basic conditions to inactive, non-toxic phosphine oxide products. A low micromolar antimicrobial activity was accompanied by biofilm eradication ability, achieved by the most effective compound **69** (Fig. 10).[204] Together, the discovery of these

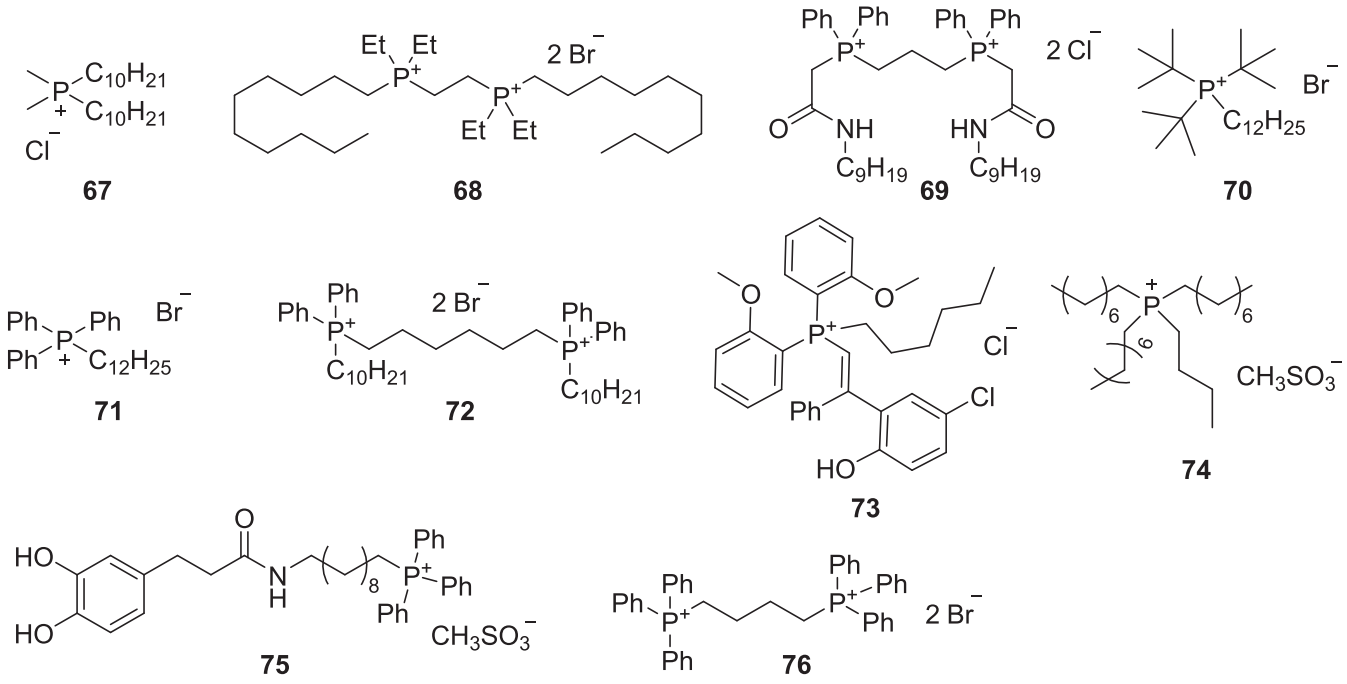


Fig. 10. Antibacterial quaternary phosphonium compounds.

potent compounds, such as **68** and **69** highlights the promise of QPCs as a structurally novel class that can evade the rapidly spreading QAC resistance.

Further advances were made by Ermolaev *et al.*[205] In recent years, they studied antimicrobial, hemolytic and cytotoxic activity of sterically hindered QPCs and discovered their SAR. The phosphonium compounds with 14–16 methylene fragments were the most effective in the inhibition of Gram-negative bacteria. Furthermore, QPCs containing longer 15–18 carbon atoms in the side chain demonstrated elevated activity against fungi, which could prove highly beneficial for disinfectants. The leading compound **70** (Fig. 10) exhibited low toxicity to the Chang liver cell line, showing high selectivity for pathogenic microorganisms. Surprisingly, mechanistic studies discovered that these QPCs have little influence on the cytoplasmic membranes of bacteria, as opposed to QACs. The authors speculated that the possible MoA might be the disruption of the balance of energy exchange inside bacterial cells. However, more detailed studies are needed to elucidate the precise MoA.[205]

In the next study conducted by Metelytsia *et al.*,[206] the focus was specifically on targeting multi-drug resistant *A. baumannii* with phosphonium-based ionic liquids (ILs). Especially newly identified *A. baumannii* strains are resistant to most known antibiotics and cause serious nosocomial infections, especially in intensive care units and in immunocompromised patients.[207] Metelytsia *et al.* developed model to predict antibacterial activity of ILs and they applied it in the assessment of novel phosphonium ILs, confirming their bioactivity also experimentally. Furthermore, they investigated the antioxidant activity by predictive *in silico* models using the OCHEM platform. The most active compounds were bearing ten- and twelve-carbon alkyl chains, with MIC values in the range of 6.25–12.5 μM, e.g., compound **71** (Fig. 10). The alkyl chains shorter than eight or longer than 12 carbon atoms resulted in the loss of activity. All tested ILs had similar antioxidant properties as the reference antioxidant ionol.[206] Other researchers that focused on *A. baumannii* were led by Wuest[196] to discover novel QACs and QPCs that were tested against a panel of 35 highly resistant *A. baumannii* clinical isolates, including QAC-resistant mutants. Under the treatment with novel compound **72** (Fig. 10), no cross-resistance was observed, as opposed to the treatment with analogous QACs. Significantly, **72** maintained efficacy against MRSN 17493, a clinical isolate pan-resistant to all tested antibiotics and both commercial and next-generation QACs, with an IC_{90} of 3 μM.[196]

Mironov *et al.*[208] extended their early work[209] by the synthesis of atypical QPCs based on the 2-(2-hydroxyaryl)alkenylphosphonium scaffold. The salts displayed pronounced activity (MIC < 1 μM) against Gram-positive bacteria, including MRSA strains, and some fungi. Interestingly, no loss of the cell wall integrity was observed by transmission electron microscopy. Rather, proteomic assays indicated that inhibition of protein synthesis and oxidative stress induction are behind the antibacterial activity. The most active compound **73** (Fig. 10) was also non-cytotoxic, with the selectivity index of 32.2. Furthermore, methylation of the phenolic hydroxyl in these types of compounds led to unexpected activity against Gram-negative bacteria, which is now under further investigation.[208]

Hassan *et al.*[210] provided a comparative evaluation of antibacterial activities of imidazolium-, pyridinium-, and phosphonium-based ILs with octyl side chains. The authors varied the corresponding cations to observe that a unique combination of cation and anion can influence the antibacterial activity. The ILs were tested against *S. pyogenes*, *E. coli*, *K. pneumoniae*, *E. aerogenes*, *P. vulgaris*, *P. aeruginosa*, and those based on imidazolium scaffold showed the best activities. The phosphorus-based ILs showed only weak activities against *E. coli* and *E. aerogenes*, with the highest inhibition zone value of 14 mm against *E. aerogenes* for compound **74** (Fig. 10).[210] A similar study of ILs as biocompatible antibacterial agents was recently published by Fernandes *et al.*, however with only limited discussion on the phosphorus-containing ILs.[211]

Chavarria *et al.*[212] discovered phytochemically-based triphenylphosphine conjugates and evaluated their antimicrobial activities against a panel of Gram-positive and Gram-negative bacteria, as well as fungi. The data were accompanied by cytotoxicity, haemolytic profile, and an assessment of membrane integrity and cytoplasmatic leakage, which lead to the establishment of comprehensive structure-activity-toxicity data. Compound **75** (Fig. 10) based on the dihydrocinnamic scaffold stood out as safe, potent and selective antibacterial agent against *S. aureus* with MIC below 0.25 μg/mL. The length of the alkyl linker correlated well with the antibacterial activity, where ten-carbon linkers were more potent than their eight-carbon counterparts.

Dihydrocinnamoyl moiety achieved better inhibition than cinnamoyl moiety, suggesting that low rigidity of the spacer between carboxamide group and the phenolic ring seems to be critical for effective antibacterial activity.[212]

Shi *et al.*[213] discovered quaternary phosphonium salts with hemocompatibility and nondetectable toxicity and proved their activity in a rat model of a superficial wound infected with MRSA. The salt **76** (Fig. 10) promoted wound healing and prevented the formation of bacterial biofilms. Wounds treated with **76** produced drastically fewer bacterial colonies than the control group and reduced abscesses in infected wounds.[213]

In summary, many effective QPCs have been prepared recently with excellent antibacterial activities and, in many cases, low reported cytotoxicities. These numerous advances in the field well underscore the promise of QPCs as next-generation disinfectant molecules.

10. Conclusion

Phosphorus-containing compounds play an important role in medicinal chemistry, as they display a wide range of pharmacological activities, including antibacterial. The interest in the use of phosphorus in drug development is increasing, and several phosphorus-containing drugs have found their place as therapeutic agents. By the inclusion of phosphorus atom into the structure, not only pharmacodynamics, but also pharmacokinetic properties can be modulated. Phosphorus-containing moieties can act as bioisosteres, resemble of biochemical entities as well as offer increased metabolic stability, polarity, and solubility.

In this review, we present a diverse array of phosphorus-based agents that exhibit potent antibacterial properties. A plethora of studies was systematically reviewed to highlight current advances and perspectives in the field of antibacterial drugs and active compounds based on phosphorus-containing scaffolds. Their versatile mechanisms of action, ability to target a broad spectrum of bacterial species, and potential for synergy with existing antibiotics make them valuable candidates for further exploration. Diverse prodrug types and drug delivery technologies spanning across the various functional groups are mentioned herein. Fosfomycin **6** has re-emerged as an active molecule of increasing importance in the times of bacterial resistance. Furthermore, the field of antibacterial phosphonium salts is highly prolific, with numerous recent publications stressing their potential as novel antiseptics. Overall, it can be expected that the field of phosphorus antibacterial compounds will continue to further grow in the near future, with hopes to produce an antibacterial arsenal to contribute to combating the antibiotic resistance.

Declaration of Competing Interest

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

Data availability

No data was used for the research described in the article.

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