Chapter

Phosphonates: Their Natural Occurrence and Physiological Role

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Abstract

The first natural compound containing carbon-to-phosphorus bond—ciliatine was discovered 60 years ago, and for four decades, phosphonates were considered simply as a biological curiosity. Finding the importance of these compounds in biogeochemical phosphorus cycling, their role in methane production, as well as discovery of numerous phosphonates and phosphonopeptides of promising antibacterial and antifungal activities has stimulated the development of studies on this class of compounds, especially on their metabolism and biochemistry. These studies are driven by the use of ^{31}P NMR and by a clever combination of genomics and innovative chemistry by using the method of selective labeling of metabolites. These studies revealed unusual and interesting chemistry of these compounds.

Keywords: C—P bond, phosphonates, ciliatine, phosphonopeptides, mimetics, antibiotics, ^{31}P NMR, genome mining

1. Introduction

Phosphonates are organophosphorus compounds characterized by a stable carbon-to-phosphorus (C—P) bond, which usually resists biochemical, thermal, and photochemical decomposition. The first phosphonate (compound **1**, **Figure 1**), being an analog of β-alanine and taurine, was isolated in 1959 from ciliated protozoa in the rumen of sheep [1]. That was the cause why its discoverers—M. Horiguchi

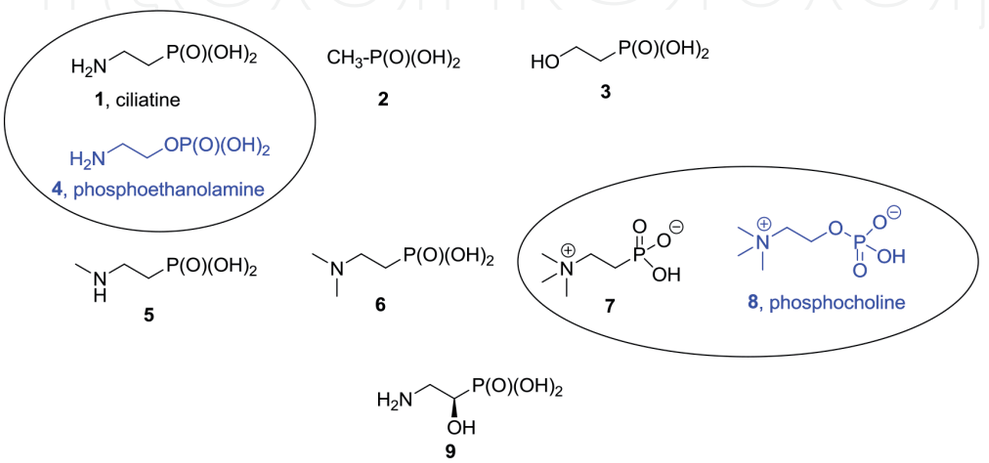

Figure 1.
Ciliatine (2-aminoethylphosphonic acids) and its derivatives found in lipids, glycans, glycoproteins, and bile acids.

and M. Kandatsu, named it ciliatine. This amino acid was then considered as a possible marker of the content of protozoa in sheep rumen, which appeared further to be misleading. For many years, natural compounds containing the C—P bond had been considered as curiosity being only scarcely studied. This is not the case in science currently because of their involvement in the global phosphorus cycle and in oceanic methane production. Some aspects of their occurrence, environmental role, biochemistry, and biological functions have been reviewed [2–5]. This chapter will concentrate on discussion of chemical diversity of the naturally occurring phosphonates and on the indication of open problems, which have not yet been solved.

2. Occurrence of carbon-to-phosphorus bond

The discovery of ciliatine stimulated intensive studies on the distribution of phosphonates in nature. Despite the fact that early studies were hampered by the lack of simple and sensitive methods for the identification of the presence of carbon-to-phosphorus bond in natural samples, it was found to exist in protozoa, bacteria, coelenterates, and mollusks [6–11]. Presumably, the unbreakable record is held by the snail *Helisoma* sp. freshly laid eggs, which contain over 95% of total phosphorus in phosphonate form [12]. Upon embryonic development, phosphonate is converted into phosphoric acid and subsequently incorporated into cellular constituents. It is believed that the physiological role of incorporation of phosphonates into the lipid fraction might function as a means to protect the eggs against predators, because they are presumably not able to disrupt and digest such membranes.

The advent of ^{31}P NMR for the analysis of tissue extracts, body fluids, and later—whole cells provided an effective tool for tracking the forms of phosphorus and its interchanges during organism development and growth. Quite paradoxically, the availability of ^{31}P NMR was accompanied with a significant decrease in the number of papers dealing with distribution of phosphonates in various species. Applications of this simple technique enabled the determination of the presence of C—P bond in bacteria and bacterial communities [13, 14], cyanobacteria [15], sponges [16], higher fungi [17, 18], or even human specimens [19]. However, these studies did not explain if phosphonates are synthesized *de novo* or are introduced to these organisms by cohabiting organisms or diet. On the other hand, phosphonate xenobiotics are quite massively released into environment [20], and various organisms might use them, or products of their decomposition, as building blocks of more complex structures.

Next, gene-based methods for assessing the abundance and identity of biological phosphonate producers were applied. This approach based on knowledge regarding C—P compound biosynthesis. Thus, with a single exception [21], all the known phosphonates are derived from phosphoenolpyruvate by isomerization to phosphonopyruvate in a reaction catalyzed by the phosphoenolpyruvate mutase, followed by its fast utilization because the reaction of formation of the C—P bond is thermodynamically unfavorable (see **Figure 3**). Most common, decarboxylation of phosphonopyruvate by phosphonopyruvate decarboxylase to produce phosphonoacetaldehyde is the next, irreversible step [3, 22–24]. Mining in genome databases for genes related to these two enzymes, as well as their homologs, enabled to determine that 10–15% of bacterial species are able to produce phosphonates [23–25].

Discovery that phosphonates form around 10% of dissolved and particulate phosphorus in the oceans [15, 25, 26] brought the increasing recognition of the importance of these compounds in biogeochemical phosphorus cycling and an awareness of the interdependence between the global phosphorus cycle and those of the other biologically significant elements [27, 28]. It is important because

phosphorus availability has been shown to be a key determinant of marine phytoplankton productivity [15]. Phosphonates are mostly concentrated in dissolved organic phosphorus (DOP), an integral and dynamic part of the marine organic matter pool. The composition of the DOP pool is complex and largely unknown, but phosphonates account for one third of its high molecular weight fraction. Thus, they seem to be an important resource of this element for aquatic organisms; however, the understanding of their utilization by eukaryotic phytoplankton is severely limited [29, 30]. They most likely occur in a form of polysaccharides esterified with methylphosphonate (compound **2**, **Figure 1**) and 2-hydroxyethylphosphonate (compound **3**, **Figure 1**). These compounds have been mainly found in *Nitrosopumilus maritimus*, one of the most abundant organisms on the planet and a resident of the oxygen-rich regions of the open oceans [31, 32].

Up to 4% of the methane on Earth comes from the oxygen-rich waters through the cleavage of the highly unreactive carbon-to-phosphorus bond in methyl phosphonate [32]. The production of methylphosphonic acid (MPn) by cyanobacteria or marine archaea related to *N. maritimus* and its subsequent decomposition by phosphate-starved bacterioplankton may partially explain the production of methane in oceanic and lake surfaces [33–35]. The concentration of methane in the upper ocean being above equilibrium with the atmosphere is known as the oceanic methane paradox [36, 38].

Some researchers believe that phosphonates are a form of relic of evolution. Being of slightly lower formal oxidation state, they might predominate in prebiotic reductive conditions [37]. This assumption, although debatable, finds some support by finding several phosphonic acids in Murchison meteorite [39].

3. Ciliatine (AEP, 2-aminoethylphosphonic acid)

Ciliatine (compound **1**) is the most ubiquitous phosphonate present in lower organisms and occurs in remarkably high amounts. It is either presented in a free, unbound form being a common intermediate in numerous phosphonate biosynthetic pathways or incorporated into lipids and glycans. It is not surprising if considering that ciliatine is a formal analog of common component of lipids—phosphoethanolamine (compound **4**). Most of the studies on natural occurrence of ciliatine and its lipids had been published in 1960–1990 and are comprehensively reviewed [2–5]. Only single paper was published after this period. As shown in **Figure 1,** its methylated forms, namely *N*-methyl, *N*,*N*-dimethyl-, and *N*,*N*,*N*-trimethylciliatine (compounds **5**, **6,** and **7**), were also found in lipid fractions of some organisms albeit in significantly smaller quantities. Compound **7** is an analog of the most common component of lipids—phosphocholine (compound **8**). The presence of an unusual aminophosphonate—(R)-2-amino-1-hydroxyethylphosphonic acid (compound **9**) and its acetyl derivative has been determined in lipid fractions of *Bacteriovorax stolpii* [40, 41]. Its configuration was elegantly determined by a combination of chemical synthesis and biochemical studies [42].

Lipids containing aminophosphonates are called phosphonolipids. There are two classes of these compounds—glycerophosphonolipids and sphingophosphonolipids (representative structures are shown in **Figure 2**). They have been isolated from numerous organisms including humans, mammals (sheep, goats, and rats), egg yolk, fish, insects, sea anemones, sponges, numerous species of freshwater and marine mollusks, seeds of plants, protozoa, and bacteria [3, 43–46]. Usually they are a small fraction of the total lipids present, and their isolation and exact identification/characterization are difficult and cumbersome.

The physiologic function of phosphonolipids is still unknown, and the suggested protecting role against predators resulting from their stability toward hydrolysis by lipases and phosphatases has not been proved so far. Moreover, the distribution and abundance of phosphonolipids among organisms vary with species, tissue, or cellular location. For example, vertebrates have sphingophosphonolipids as components of nervous tissue sphingomyelin, while invertebrates frequently contain high levels of these lipids as outer membrane components.

Whereas phosphate is a common modification of polysaccharides, there are only a few examples of polysaccharides containing phosphonate moieties. Their characterization/identification was made possible as well as substantially accelerated by the development of glycomics [47]. Ciliatine and compound **9** have been found to be bound to the sugar moieties of variable glycans (see **Figure 2** for schematic structures). Their occurrence was documented in fractions of glycocerebrosides (lipids) of many lower marine phyla [2, 12, 48], bacterial exopolysaccharides (secreted polysugars into the environment), and outer membrane components

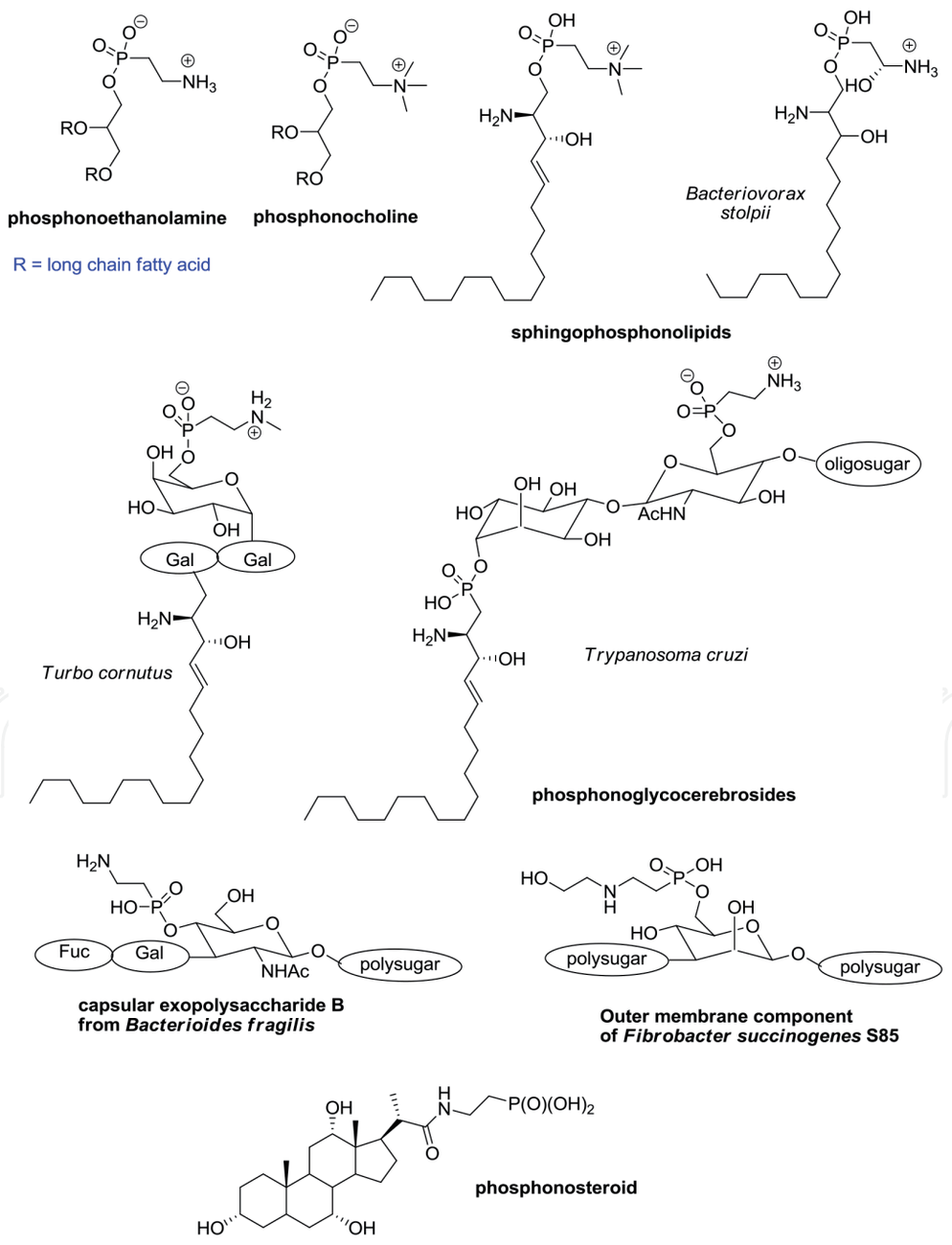

Figure 2.
Representative structures of phosphonolipids, phosphonoglycans, and phosphonosteroid.

[49–51] and glycoproteins deriving from marine snails, common jellyfish and locust [51–54]. Genome scanning led to the identification of methylphosphonic acid (compound **2**) in the exopolysaccharide of the marine archeon *N. maritimus*. Its function is not known, but it is ultimately a major source of methane production by the oceans [32].

Similarly as in the case of phosphonolipids, the physiological role of phosphonoglycans is not known and thus awaits determination. This might be important in the context that the glycans are essential molecules being well known to enable adaptive response to environmental changes [55]. The speculative roles of phosphonoglycans include cell-cell signaling or their action as phosphorus reservoirs in the environments of low phosphate concentration. The second assumption might be supported by the conservation of phosphonolipids at the expense of phosphodiesters in starved conditions by the oyster *Crassostrea virginica* [56]. Other possibility is demonstrated by the fact that *Bacteroides fragilis*, a part of the normal microbiota of the human colon, produces a capsular polysaccharide complex containing ciliatine, which is directly involved in abscess formation in animal models when bacteria are displaced into the bloodstream [57].

It is also important to mention that the phosphonic analog of taurocholic acid was found in the gall bladders of cows [58]; however, this finding may require additional confirmation.

4. Low-molecular phosphonates metabolically related to ciliatine

Biosynthesis of phosphonates starts from rearrangement of phosphoenolpyruvate (compound **10**) into phosphonopyruvate (compound **11**), a reaction catalyzed by phosphonoenolpyruvate mutase. In this equilibrium process, the thermodynamics favors phosphonoenolpyruvate by a factor of at least 500. Thus, phosphonopyruvate has to be rapidly converted into metabolically useful compounds, most favorably in the irreversible reactions. Consequently, it is a key substrate in the synthesis of ciliatine (compound **1**), phosphonoalalnine (compound **12**), 2-hydroxyethylphosphonic acid (compound **3**), phosphonoacetaldehyde (compound **13**), phosphonomethylmalic acid (compound **14**), and 2-keto-4-hydroxy-5-phosphonopentanoic acid (compound **15**). Most of the enzymes involved in the production of these compounds have been isolated and characterized and comprehensively reviewed [2, 59]. The metabolic relationships between these compounds and their precursor role in the synthesis of phosphonate antibiotics are shown in **Figure 3**.

Low-molecular antibiotics such as fosfomycin (compound **17**) [60], fosfonochlorin (compound **18** produced by several strains of *Fusarium* and *Talaromyces flavus*) [61], nitrilaphos and hydroxynitrilaphos (compounds **19** and **20** found in cultivating media of *Streptomyces*) [62], and herbicidal phosphonothrixin (compound **21**, produced by *Saccharothrix*) [63] might be also considered as low-molecular compounds related to ciliatine.

Only one of them—*fosfomycin* (also known as *Monuril*, *Monurol,* or *Monural*), produced by *Pseudomonas* and *Streptomyces,* has found limited use as therapeutic agent to cure urinary tract infections and diabetic foot [60]. It is an active site directed covalent inactivator of muramyl ligase A, the first enzyme of peptidoglycan synthesis, and causes disruption of bacterial cell wall. Unfortunately, bacteria adapted to be able to open the epoxy ring functionality of fosfomycin, thus resulting in the compound deactivation/degradation of this antibiotic and in the microorganism ability to readily develop drug resistance [64]. Quite interestingly, pathways for the biosynthesis of fosfomycin in *Streptomyces* and *Pseudomonas* are different

(see **Figure 3**). This shows that synthesis of natural phosphonates does not have to be normalized; many metabolic pathways are still yet to be discovered.

The separate class is aminophosphonate antibacterial antibiotics possessing an amino group in the gamma position in relation to the phosphonic functional group, namely fosmidomycin (compound **22**), and its derivatives denoted as FR900098 (compound **23**), FR-33289 (compound **24**), and FR32863 (compound **25**), originally isolated from culture broths of *Streptomyces* as well as cyclic SF2312 (compound **26**) isolated from *Micromonospora* sp. [65–67]. Their structures are shown in **Figure 4**.

Fosmidomycin and its homologs are potent inhibitors of 1-deoxy-d-xylulose-5-phosphate reductoisomerase, an essential enzyme of the non-mevalonate pathway of isoprenoid biosynthesis being active against a broad range of enterobacteria,

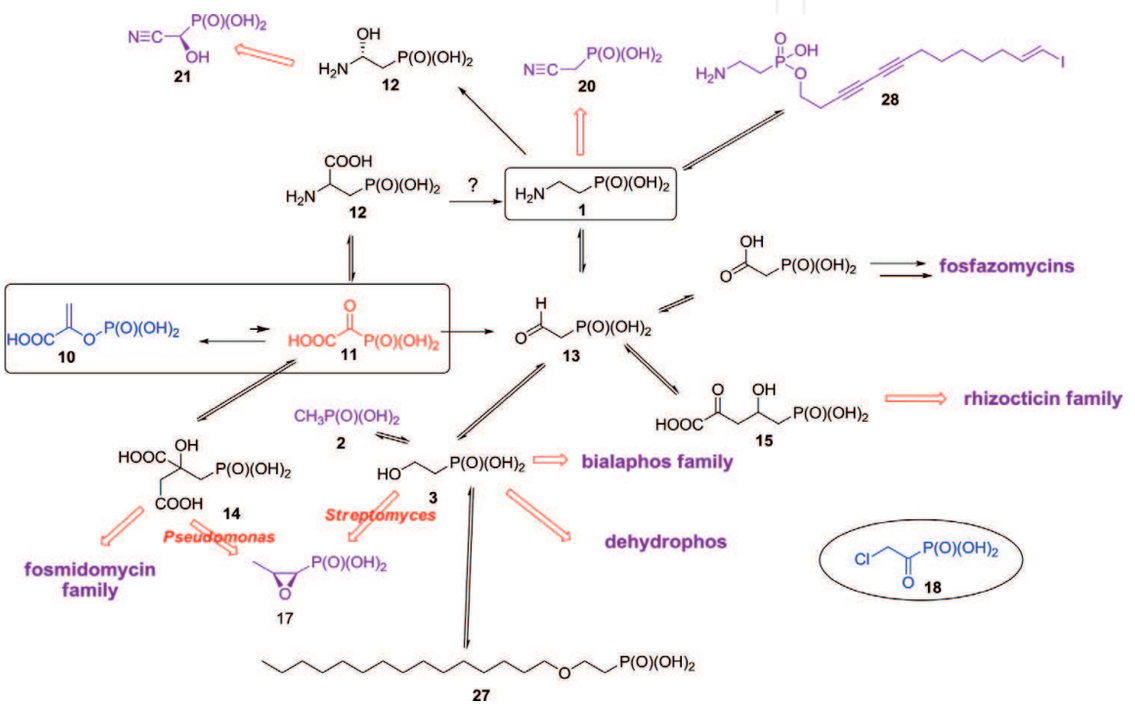

Figure 3.
Metabolic relationship between naturally occurring phosphonates.

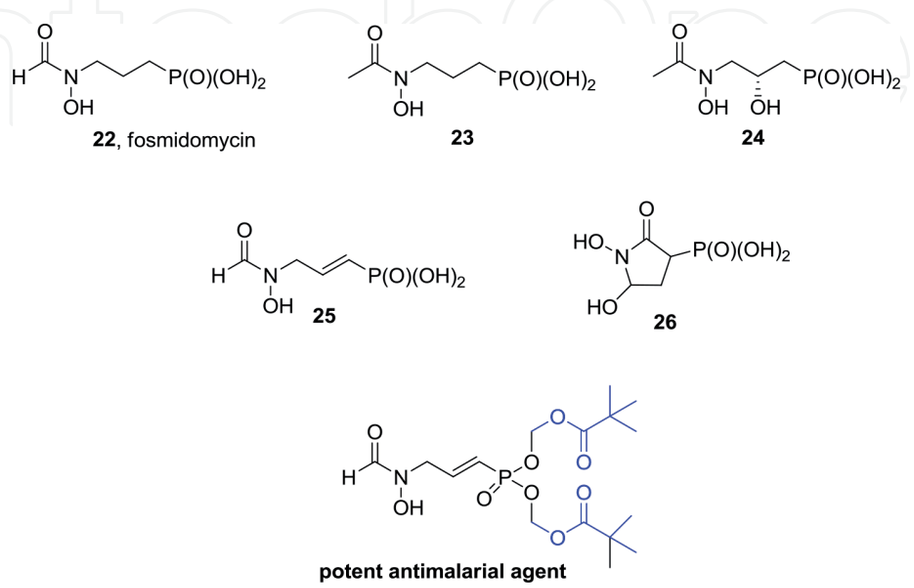

Figure 4.
Antibiotics structurally related to fosmidomycin.

but not against Gram-positive organisms or anaerobes. More importantly, they are blocking the development of isoprenoids in the parasite apicoplast, and thus, structurally modified fosmidomycin derivatives are considered as promising antimalarial agents (for representative structure, see **Figure 4**) [68].

Aphanizomenon flos-aquae is a cyanobacterium that grows in eutrophic Balgavies Loch in Scotland. From its water blooms, a novel biosurfactant of lipidic character—2-acyloxyethylphosphonate (compound **27**) was isolated; however, its ecological function remains to be evaluated [69].

Two unusual placotylene A esters [69] of ciliatine (phosphoiodyn A, compound **28**) and its phosphate congener—phosphoethanolamine (phosphoiodyn B) were isolated from a Korean marine sponge *Placospongia* sp. [70]. Phosphoiodyn A was found to exhibit a potent agonistic activity on human peroxisome proliferator-activated receptor delta (hPPARδ), which is thought to function as an integrator of transcriptional repression and nuclear receptor signaling [16, 71]. This compound, as well as its analogs, demonstrates significant neuroprotective activity in an *in vitro* cellular model indicating that such phosphonates may be an effective novel scaffold for the design of therapeutics for the treatment of neurodegenerative disorders [71].

5. Phosphonopeptide antibiotics

Half of the century after the discovery of ciliatine witnessed a slow progress in the isolation and identification of natural compounds containing the C—P bond with most of them being antibacterials. The majority of these compounds appeared to be peptides containing C-terminal phosphonic acids and mostly differ by their *N*-terminal peptide structure. They have drawn attention not only because of their bioactivity but also because of unusual and interesting chemistry associated with the biosynthesis and biodegradation of these molecules. Structures of antibiotic phosphonopeptides are shown in **Figure 5**.

Bialaphos (compound **29**, [72]) was isolated from as the first such an antibiotic from the culture filtrates of *Streptomyces viridochromogenes* and *Streptomyces hygroscopicus* [72–74]. Further studies indicated that its antibacterial activity is a result of active transport of the peptide across bacterial membrane followed by hydrolysis of the peptide and release of terminal phosphonate—phosphinothricin, which inhibits glutamine synthetase. This enzyme converts glutamic acid and ammonia into glutamine; this reaction is an important step of the nitrogen metabolism in bacteria and plants [75]. That activity of phosphinothricin resulted in its introduction to agriculture as a popular herbicide, and it is sold as ammonium salt under the name glufosinate. Its application causes accumulation of ammonia in plants and consequently plant death [76]. It is worth to notice that bialaphos also exerts herbicidal activity and was applied in Japan [77]. Its activity relays on hydrolysis of bialaphos in plant tissues and release of herbicidal phosphinothricin. Further studies on bialaphos resulted in isolation of tetrapeptide trialaphos (compound **30**) [78] and phosalacine (compound **31**) [79] both of the same mechanism of action. Finally, studies on biosynthesis of this compound resulted in the identification of its desmethyl analog **32**, which is an intermediate in bialaphos metabolism.

The antibacterial activity of bialaphos is typical for all the phosphonopeptides. Peptide parts of these antibiotics usually function as a targeting unit. Thus, the peptides are efficiently transported through bacterial (or fungal) membranes and after hydrolysis release phosphonic acid, which exerts its toxic action by inhibiting parasite vital enzymes—in this case glutamine synthetase. This mechanism of action is shown schematically in **Figure 6**.

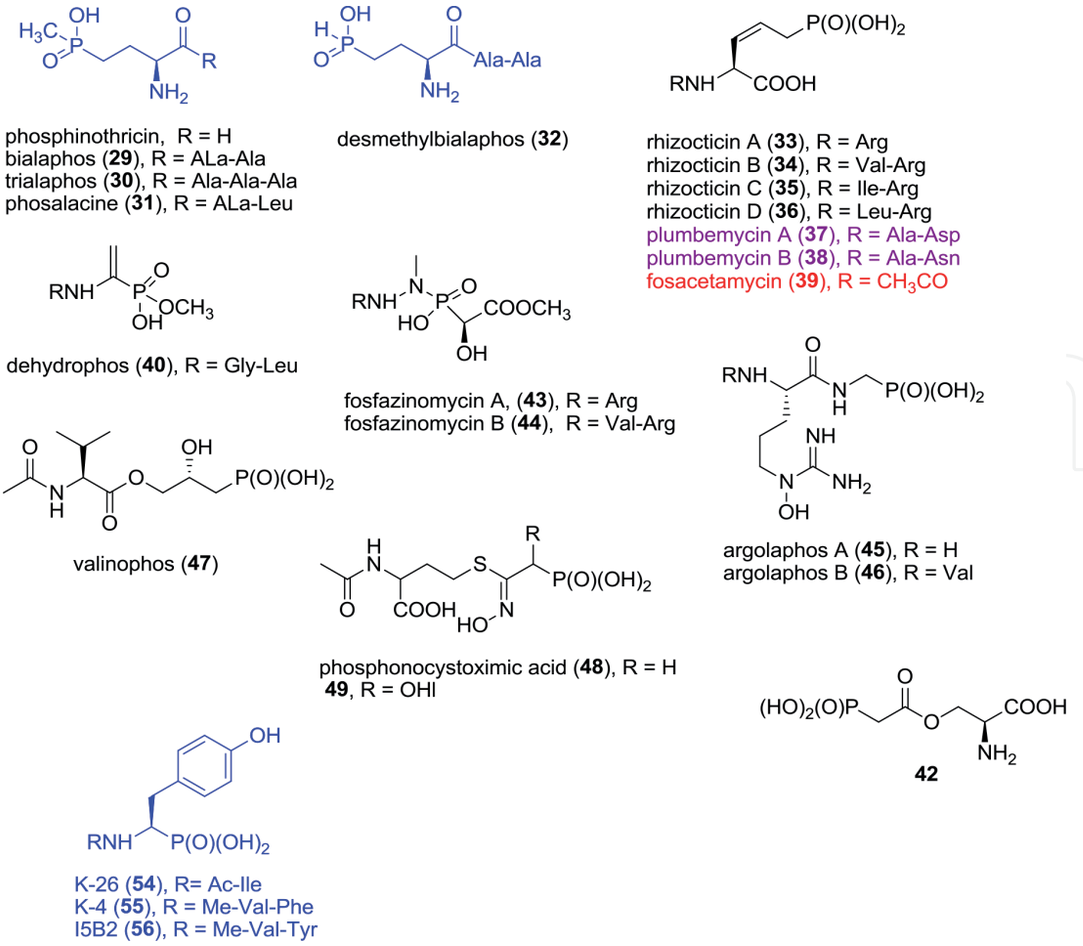

Figure 5.
Phosphonopeptide antibiotics.

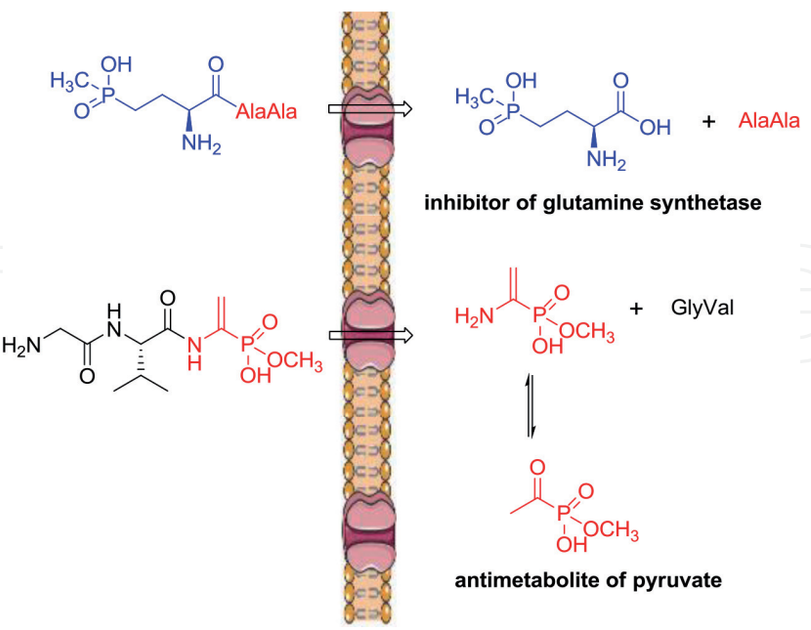

Figure 6.
Representative mechanism of action of phosphonopeptides.

The following years brought the discovery of a family of antibiotics called rhizocticins (compounds **33–36**) [80, 81], plumbemycins (compounds **37** and **38**) [81–83], and phosacetamycin (compound **39**) [84], first isolated as secondary metabolites of *Bacillus subtilis* on the basis of their antifungal activity and were

later found as products of *Streptomyces plumbeus*. They form a library of di- and tripeptides containing C-terminal (*Z*)-*L*-2-amino-5-phosphono-3-pentenoic acid, a mimetic of phosphonothreonine, which is the substrate for threonine synthetase. Thus, after the release from the peptide aminophosphonate acts as a potent inhibitor of this enzyme [85].

Dehydrophos (compound **40**) was first isolated from the broth of *Streptomyces luridus* as a broad-spectrum antibiotic affective in chicken model of *Salmonella* infection [86]. The history of determination of its structure is rather long and led to three propositions of which the last one appeared to be reasonable and compelling. It is a dehydrophosphonopeptide, which, after the cleavage of the peptide bond, provides an analog of dehydroalanine, which is then converted into methyl acetylphosphonate (compound **41**, an analog of pyruvic acid), which is strongly antibacterial by acting most likely as antimetabolite of pyruvate (**Figure 6**) [87]. Thus, it was considered as a lead compound for the design of novel antibacterial agents [88]. The non-typical and innovative is the application of its biosynthetic enzymes for obtaining new antibacterial phosphonopeptides [89]. Recently, the role of nonribosomal peptidyl transferase DhpH in the formation of peptide bond in dehydrophos was studied in detail using phosphonic analog of alanine and various amino acid-tRNAs as substrates [90].

Phosphonopeptides have very limited utility in human medicine because they are readily hydrolyzed in body fluids and released aminophosphonic acids that are not able to cross bacterial or fungal cell barriers and to exert antibiotic action. Additionally, they are being readily excreted through urine.

Published in 2015 work of Metcalf and van der Donk brought a significant breakthrough in studies on naturally occurring phosphonate antibiotics. By a clever combination of the mining of the genome of 10,000 of actinomycetes and selective labeling of phosphonate metabolites, they rediscovered a large number of old phosphonates and discovered 19 new compounds [24]. This opened a genetic approach in natural phosphonate chemistry and biochemistry, especially enabling the identification of metabolic pathways leading to this class of compounds. An important and instructive example here is an activation of gene cluster from *Streptomyces* sp. NRRL F-525 and its reengineering in *Streptomyces lividans*, which resulted in the isolation of *O*-phosphonoacetic acid serine (compound **42**) [91].

One of the examples of rediscovered compounds is fosfazinomycins A and B (compounds **43** and **44**), identified 30 years after their original isolation from *Streptomyces lavendofoliae* and *Streptomyces unzenensis* [92, 93]. They are a very specific since they contain an exotic structural feature, which is the hydrazide linkage between the carboxylic acid of peptidyl arginine and the phosphonic acid. Fosfazinomycin was also found further in one of 210 substances present in 42 actinomycetes associated with the Baltic sponge *Halichondria panacea* [94].

The genetic approach also enabled the isolation and characterization of novel of *Streptomyces* peptidomimetics such as argolaphos A and B (compounds **45** and **46**) and valinophos (compound **47**) [24]. Similar approach was used for the isolation of phosphonocystoximate and its hydroxylated derivative (compounds **48** and **49**) [24]. Detailed NMR studies on their biosynthesis, which starts from ciliatine and its analog—compound **9**, enabled to confirm the presence of intermediates such as mixtures of the (E)- and (Z)-isomers of corresponding oximes (compounds **50** and **51**), substrates for the synthesis of phosphonocystoximate and its hydroxylated derivative [95]. They are formed by the action of specific flavin-dependent, oxime-forming N-oxidases. These oxidases are also able to convert the oximes **50** and **51** into corresponding nitroethylphosphonates (compounds **52** and **53**) [96]. Structures of these intermediates and side products are depicted in **Figure 7**.

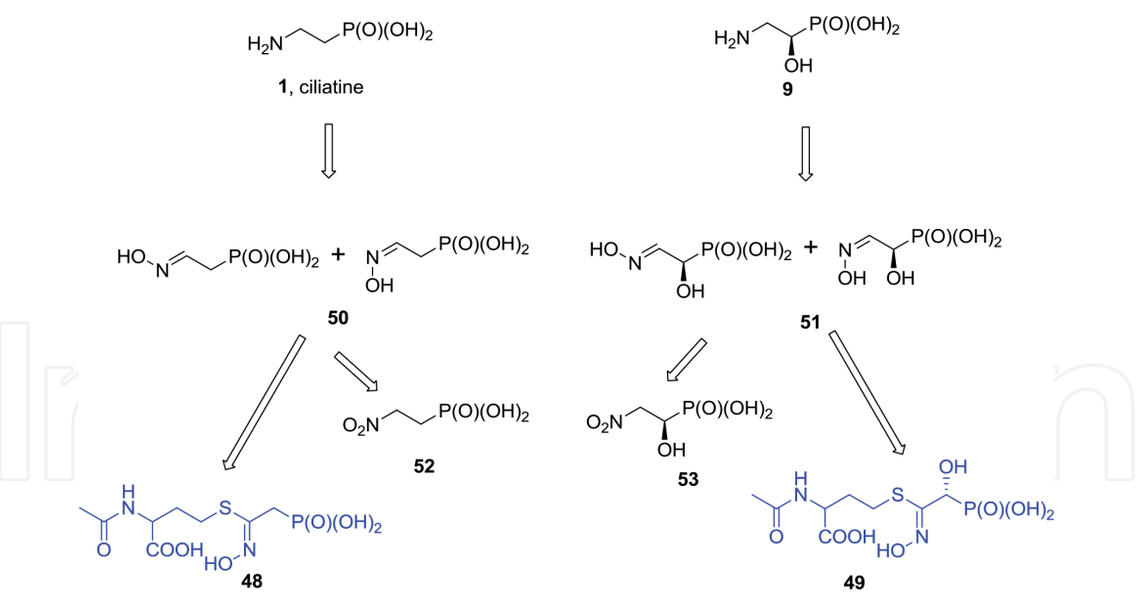

Figure 7.
Intermediates and side products in the synthesis of phosphonocystoximate.

A separate group of phosphonic peptidomimetics is compounds denoted as K-26, K4, and I5B2 (compounds **54**, **55,** and **56,** respectively) [21, 97–99], a small family of bacterial secondary metabolites, tripeptides terminated by an unusual phosphonate analog of tyrosine (see **Figure 6**). They are produced by three different actinomycetales and act as potent inhibitors of human angiotensin-I converting enzyme selectively targeting the eukaryotic family of the enzyme [100, 101]. These compounds derived from *L*-tyrosine, which suggests the existence of novel and not discovered yet reaction of carbon-to-phosphorus bond formation [21, 102].

6. Conclusions

Natural phosphonates might be considered as simple analogs of phosphate esters and/or carboxylic acids. The inherent stability of the C—P bond causes that they often display promising activities as enzyme inhibitors and therefore might be considered as drugs or agrochemicals. Moreover, the wide use of xenobiotics containing carbon-to-phosphorus bond has led to the spread of these compounds in the environment, which may result in their incorporation into variable metabolic pathways. All of this stimulate interest in these, still somewhat exotic, compounds. The development of ^{31}P NMR and genomics supplemented by biochemical studies resulted in the development of new detection technologies, which enormously speed out the discovery of novel naturally occurring phosphonates, identification of their metabolic pathways (both biosynthesis and degradation), and their use as lead compounds for the design of new promising medicines. With the exception of the identification of antibacterial and antifungal antibiotics, these studies are not accompanied, however, with the determination of physiologic importance of these compounds.

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Conflict of interest

I declare that there is no conflict of interest that might have any bearing on research reported in this work.

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