

Review

Phosphorus Compounds of Natural Origin: Prebiotic, Stereochemistry, Application

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Abstract: Organophosphorus compounds play a vital role as nucleic acids, nucleotide coenzymes, metabolic intermediates and are involved in many biochemical processes. They are part of DNA, RNA, ATP and a number of important biological elements of living organisms. Synthetic compounds of this class have found practical application as agrochemicals, pharmaceuticals, bioregulators, and others. In recent years, a large number of phosphorus compounds containing P-O, P-N, P-C bonds have been isolated from natural sources. Many of them have shown interesting biological properties and have become the objects of intensive scientific research. Most of these compounds contain asymmetric centers, the absolute configurations of which have a significant effect on the biological properties of the products of their transformations. This area of research on natural phosphorus compounds is still little-studied, that prompted us to analyze and discuss it in our review. Moreover natural organophosphorus compounds represent interesting models for the development of new biologically active compounds, and a number of promising drugs and agrochemicals have already been obtained on their basis. The review also discusses the history of the development of ideas about the role of organophosphorus compounds and stereochemistry in the origin of life on Earth, starting from the prebiotic period, that allows us in a new way to consider this most important problem of fundamental science.



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1. Introduction

Phosphorus compounds are essential for modern biological systems, and their diverse biological properties testify to their importance in the world of living organisms. They provide stable ligation necessary for fixing information in RNA and DNA, contribute to cellular structure in phospholipids, serve as the main source of biochemical energy (e.g., ATP, phosphoenolpyruvate, creatinephosphate), and are present in a large number of metabolites. Phosphates retain a central place in biological systems, which allows us to conclude that they played an important role in the emergence of life on Earth [1–4]. In recent years, a large number of natural phosphorus compounds have been isolated from living organisms and significant advances have been made in understanding the effects of phosphates on prebiotic chemistry. A number of natural phosphorus compounds have practical applications (Figure 1) [2].

Natural phosphorus compounds are invaluable sources for modeling and creating new biologically active substances on their basis. A number of organophosphorus compounds that are C-P analogs of natural compounds are used in the clinic as drugs for the treatment of various diseases. Among the natural phosphorus compounds, effective pharmaceuticals, antibiotics, herbicides, insecticides, and various bioregulators were found.

Research on such important for the vital functions of substances containing phosphorus as phosphagens, especially ATP or creatine phosphate, is of great importance for physiology. The study of polyphosphates in the structure of DNA and RNA allows a better

understanding of the functioning of these polymeric molecules, vital for life. The purpose of this review is to show the role of phosphorus in the processes occurring in nature and primarily in living organisms, starting from the early period of prebiotics and the emergence of life, as well as the role of stereochemistry in these processes. In addition, we want to show the high practical value of natural phosphorus compounds in pharmacology, agrochemistry, and various technological processes.

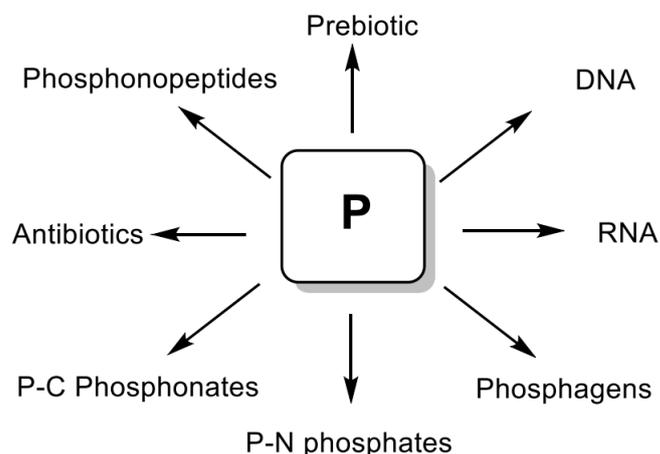


Figure 1. Natural organophosphorus compounds.

2. The Role of Phosphorus at the Origin and Evolution of Life

Phosphorus is one of the main elements of living organisms. Despite its low content in organisms, phosphorus plays an important role in biochemical reactions. In the human body, phosphorus is the main component of bones and teeth, and acts as a link between DNA and the RNA scaffold, in which the phosphorus content is 9%. Phospholipids are the main component of cell membranes, which are involved in the regulation of membrane permeability participate in the transport of fats, fatty acids and cholesterol. ATP acts as a form of energy conversion in living cells, while protein phosphorylation/dephosphorylation is a way of transmitting the life signal. There are reasons to assert that under the conditions of ancient Earth, phosphorus could contribute to the formation of amino acids, nucleosides/nucleotides, and basic groups and peptides. It is believed that phosphorus was the catalyst for the evolution of the ancient Earth. A series of experiments were reported, the authors of which concluded that phosphorus could have an effect on the prebiotic synthesis of small biomolecules (amino acids, nucleosides, and basic groups) and biomacromolecules (peptides and nucleotides) [5]. When considering the chemistry of natural organophosphorus compounds and their biological significance, it is important to discuss their formation during the prebiotic period. Phosphorus is undoubtedly the central element of living organisms, and along with carbon, nitrogen, oxygen, it undoubtedly played a decisive role in the origin of life [5]. Westheimer in his article “Why nature chose phosphorus” showed that phosphates are ionized at physiological pH due to the low first pK_a value ($pK_a = 2.2, 7.2, 12.3$ [1,6]). The advantage of tribasic phosphorus acid over organic tribasic acids, for example citric acid, can be inferred from a comparison of the ratios of successive ionization constants of these acids. The sequential ionization constants of phosphoric acid differ by more than 10^5 times, while the constants for citric acid differ by less than 50 times, even taking into account statistical factors.

The negative charges of phosphoric acid diesters in DNA help retain molecules within the cell membrane and give nucleic acid the stability necessary for genetic reproducibility. The ionic nature makes phosphates hydrophilic and promotes their retention in the cell membrane. It is important to note that in the case of RNA and DNA ligation, the ionic structure of phosphates allows the ligation of two nucleosides whilst retaining a negative charge

at the phosphodiester. The data of Table 1 is taken from [1,6] and <https://ru.wikipedia.org>, accessed on 2 January 2021.

Table 1. Ionization constants for orthophosphoric and citric acids

Acid	pKa(1)	pKa(2)	pKa(3)
Phosphoric	2.12	7.2	12.3
Citric	3.22	4.8	6.4

The charge carried by the bonds of phosphodiester between nucleotides provides an important solubilizing element and, importantly, protects the phosphodiester from hydrolysis. Unlike carboxylic acid anhydrides, phosphoric anhydrides are protected by their negative charges from the rapid impact of water and other nucleophiles, so they can persist in an aqueous environment, even if they are thermodynamically unstable, and thus, can control chemical processes (Figure 2) [7].

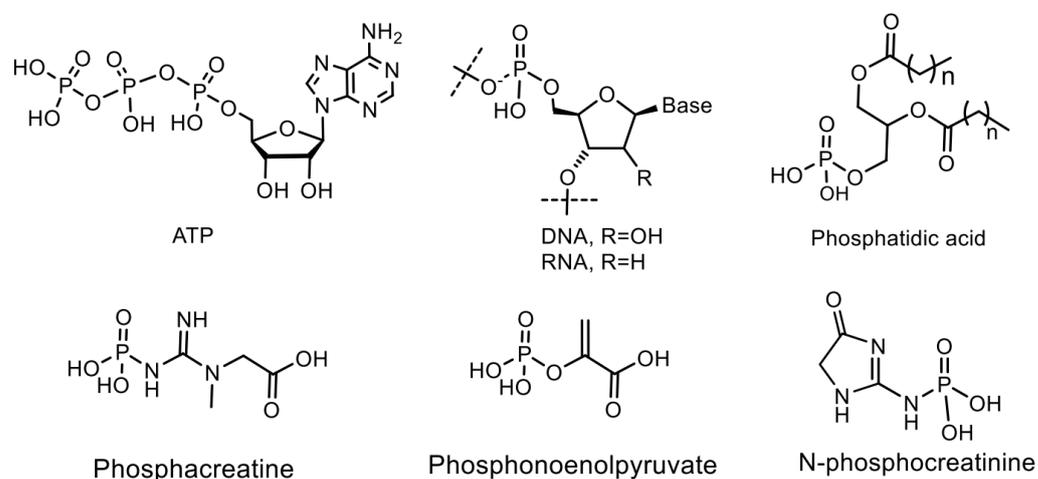


Figure 2. Biologically important phosphates.

Phosphorus plays an important role in genetics and in the energy systems of living cells, as well as in the cell membranes. An alternative hypothesis is that a protometabolism could have emerged prior to the incorporation of phosphates. It has been suggested that thioether-based metabolism could have pre-dated the incorporation of phosphates and an RNA-based genetic system [8].

Under the control of DNA ligase, covalent cross-linking of DNA strands in a duplex occurs during replication, repair and recombination. They form phosphodiester bridges between the 5'-phosphoryl and 3'-hydroxyl groups of adjacent deoxynucleotides at DNA breaks or between two DNA molecules. For the formation of these bridges, ligases use the energy of hydrolysis of the pyrophosphoryl bond of ATP, in particular, under the influence of DNA ligase of bacteriophage T4. Considering the influence of phosphates on the most important life processes, it is important to take into account the role of phosphate in the formation of primary organisms [8], lipids and genetics [9–11], considering phosphates as the main element in the energy system of nascent organisms. Therefore, the role of inorganic phosphates in the prebiotic period of the early Earth attracted considerable attention and was widely discussed. Various theories have been proposed explaining the role of phosphorus in the formation of primary organisms that led to the emergence of life on Earth. For example, the availability of phosphorus has been widely discussed, due to the fact that orthophosphate (PO_4^{3-}), a common form of phosphorus on Earth [12]. The mineral apatite, which is the significant source of phosphate on Earth, has long been thought to be problematical in this respect due to its low solubility and reactivity. The insolubility and thus, the insufficient availability of phosphate minerals has been

called the “phosphate problem” [13,14], for the phosphate to react and has been used in prebiotic chemistry. The use of phosphates requires an aqueous medium with a low content of dissolved calcium, which can precipitate orthophosphates, making it difficult their participation in the formation of prebiotic organisms [15–18]. Fernandez-Garcia et al. [1] described several prebiotic pathways for the synthesis of nucleotides, amino acids and basic metabolites, which are controlled by phosphate, which acts as an acid-base catalyst or chemical buffer. The mechanisms that use phosphates for organizing selective prebiotic chemistry, combined with the central and universal role of phosphates in biochemistry, provide an increasingly clear idea that phosphates were a key element in the origin of life on Earth.

The mineral schreibersite $(\text{Fe,Ni})_3\text{P}$ is a reactive source of phosphorus capable of forming phosphorylated molecules [16,18]. These molecules could be an important component of prebiotics. The authors suggest two ways of using phosphorus in the formation of living organisms in the prebiotic period: The first is the delivery of phosphides by meteorites, and the second is the reduction of phosphates to phosphides under conditions of high temperature and low redox potential. It is estimated that about 1–10% of all phosphorus in the earth’s crust was in schreibersite during Hadean eon, making this mineral likely to react with organic-rich water. Ultimately, such conditions could presumably contribute to the formation of life in the form in which we know it today [18]. The mechanisms of aqueous electrophilic and aqueous nucleophilic phosphorylation, as well as phosphorylation in the anhydrous state, which is carried out by dissociative phosphoryl transfer, were discussed. The mechanisms by which phosphate controls the reactivity of prebiotics through catalysis or buffering effects have been discussed, promoting selective conversions in neutral water. Several prebiotic pathways have been described for the synthesis of nucleotides, amino acids and basic metabolites, which are facilitated or controlled by phosphates, which act as a basic acid-base catalyst, pH buffer or chemical buffer. These mechanisms lead to the conclusion that understanding phosphate chemistry is a key element in elucidating the origin of life on Earth [12].

It has been suggested that most potential prebiotic phosphorylation reactions are based on phosphate anhydrides as sources of phosphorus. In addition, it is quite possible that the geochemistry of phosphorus on the early Earth was controlled by phosphorus compounds with a reduced oxidation state, such as hypophosphite (H_2PO_2^-), which are more soluble and reactive than orthophosphates. It was suggested that phosphorus with a reduced oxidation state was introduced from extraterrestrial space [15,16].

The most important criterion used to define a living organism is the ability to metabolism, constant renewal and reproduction, the ability to convert molecules that have absorbed solar energy into building blocks of their own structures. These functions, like many others, require an energy system in which energy can be stored, transported and released in a controlled and timely manner. The most common concept of the origin of nucleic acids and life is the hypothesis of the RNA world supported by many scientists. There are other concepts as well. For example, the progene hypothesis proposed by Altstein, which is a development of the chemical evolution hypothesis [7]. According to this hypothesis, the bimolecular genetic system does not arise from mononucleotides and monoamino acids, but from precursors, namely trinucleotides aminoacylated at the 3'-end with a non-random amino acid ($\text{NpNpNp}\sim\text{pX}\sim\text{Aa}$, where N—deoxyribo- or ribonucleoside, p—phosphate, X—a bifunctional agent, for example ribose, Aa—an amino acid, ~macroerge bond. Progenes are used as substrates for the interconnected synthesis of a polynucleotide and a polypeptide. The growth of the “polynucleotide-polypeptide” system is controlled by the enzymatic properties of the growing polypeptide. The mechanism of progen formation ($\text{NpNp} + \text{Np}\sim\text{pX}\sim\text{Aa}$) explains the emergence of the prebiotic physicochemical genetic code of the group, as well as the selection of organic compounds for the future genetic system from the racemic heterogeneous environment. The system is reproduced on a progenetic basis by means of replication-transcription-translation (the first molecular genetic process). The weak point of this theory is the impossibility of explaining how the

stereoselective selection of enantiomers from the racemic mixture is carried out, since in this case the process should occur with violation of chiral parity, which is unlikely.

The definition of life as a way of existence, evolution and transmission of information recorded on an organic matrix attracts attention. For example, it was proposed to consider life as “a highly stable state of matter, using information encoded by the states of individual molecules to develop conserving reactions”. That is the Life is a stable informational state capable of independent existence, development and self-reproduction. An elementary representative of such an information state is a living cell, which is essentially a biocomputer filled with a huge volume of information concentrated in DNA or RNA. DNA can carry out its activity only inside the cell with its full complex of vital processes. A cell without DNA cannot support the metabolic process and the work of the energy block, which is performed by phosphagens. Therefore, in order to be viable, all elements of the organism must be formed simultaneously and within a short time, which excludes the possibility of chemical evolution over billions of years. The elements of the body that support metabolism are very unstable, which is why the metabolic process can easily be disrupted. RNA, DNA, proteins are polymeric homochiral molecules consisting of thousands of chiral units that must be constantly renewed. It should be borne in mind that racemization of only one unit of chain will disrupt the configuration of the polymer molecule, as a result of which the double helix of DNA molecule will be impossible. For example, the half-life for ribose decomposition is 73 min at 100 °C and pH 7, and 44 years at 0 °C and pH 7. Other sugars are similarly unstable at 100 °C and pH 7. Examples are ribose 5-phosphate ($t_{1/2} = 9$ min), deoxyribose ($t_{1/2} = 225$ min) and ribose-2,4-diphosphate ($t_{1/2} = 31$ min) [19].

Geological research suggests that the first forms of life on Earth were microorganisms that appeared about 4 billion years ago. The process of the primary organism formation was short-lived. This conclusion is confirmed by biochemical studies. For example, Lazcano and Miller [3] came to the conclusion that Archean cells had a random rate of duplicons fixation and a rate of spontaneous gene duplications comparable with the present values of 10^{-5} – 10^{-3} gene duplications. Hence, it requires a relatively short time for the genome of a heterotrophic DNA/protein into 7000 genes of filamentous cyanobacteria. It is well-known that directed evolution experiments take only a few weeks to rapidly proliferate in bacterial populations under stressful conditions. The results on organophosphate and phosphonate hydrolysis of phosphotriesterase from *Pseudomonas diminuta* and other soil eubacteria suggest that this new enzyme, as a result of duplication, separated from its family and reached the diffusion limit in just 40 years. Therefore, the rate of duplication and fixation of new genes can be very high on the geological time scale [19]. There are additional mechanisms that can increase the rate of metabolic evolution, including modular assembly of new proteins, gene fusion, and horizontal gene transfer. Experimentally, it was shown that, after a few weeks, existing enzymes acquire new substrate features as a result of recombination within the gene. Perhaps the widespread belief that the origins and early evolution of life were slow processes that took billions of years stems from the classical Darwinian approach, according to which major changes occur slowly and in stages over long periods of time. Directed evolution experiments, conducted by Hall and Zuzel [20], showed that after a few weeks, existing enzymes acquire new specific substrates as a result of recombination within the gene. In accordance with the theory of Oparin-Haldane chemical evolution, for the formation of coacervates originating in the primary broth, chiral molecules of high chemical purity (homochiral molecules) are required. Modern life is homochiral, and this is reflected in macromolecules, DNA, RNA and proteins. So far remains an unsolved mystery how homochirality originally arose, and several physical and chemical processes of “symmetry breaking (Parity violation in chiral molecules)” have been proposed. However, even the event of a violation of chirality does not solve the problem of enantiomeric cross-inhibition. First of all, biopolymers, such as DNA, RNA and protein must be homochiral, in order to adopt well-defined secondary and tertiary structures oriented to the sequence that is a prerequisite for their biological function. Moreover, in the course of chemical polymerization of D-ribonucleotide-RNA

using a homochiral matrix, the building blocks of D-ribonucleotide phosphate effectively inhibit the formation of incorrect building blocks of L-ribonucleotide phosphate by chain termination. Homochirality of organic substances is inherent only in living organisms. Homochiral molecules of abiotic origin are absent in the nature of Earth. In turn, it can be noted that chiral molecules of high stereochemical purity are interconnected with a living organism, because in nature, only living organisms are capable of producing them. Consequently, the initial chiral substances that are necessary for the construction of DNA, RNA, and proteins should have been formed directly during the formation of a living organism. Therefore, summarizing the above data, it can be assumed that in nature there is a programmed process that, under certain conditions, leads to the formation of a primary Life. It is not entirely clear how this program works, but the origin and evolution of life is the subject of intense scientific research, the results of which, unfortunately, still cannot satisfy the discerning scientist [21]. Attempts to explain the emergence of chirality on Earth using chiral amino acid molecules brought by meteorites from space do not look convincing enough. Molecules of chemical compounds, including amino acids, that are delivered to Earth by meteorites, such as the Murchison meteorite, or formed under action of cosmic radiation, have very low enantiomeric excesses, while absolute chirality (homochirality) is required. In addition to meteorites, there is also the theory of panspermia, that is, the emergence of life in other worlds, in distant galaxies and the travel of living spores to Earth over tens and hundreds of light years. However, this theory also looks unconvincing. Although it has not been refuted, but equally it has not been proven. Geological studies have established that life on Earth appeared about 4 billion years ago, in time period between the Hadean and Archean eons, almost immediately as soon as the Earth cooled down to an acceptable temperature. At that time, there was no oxygen atmosphere on Earth yet, but the first anaerobic bacteria appeared, which formed many of the currently existing deposits of minerals: Sulfur, graphite, iron and nickel. The first living microorganisms could appear in limited quantities and therefore there was no deficiency in building material, including phosphorus. However, they later multiplied, changing the ecology of the Earth. Anaerobic bacteria obtain energy in the absence of oxygen through substrate-level phosphorylation, i.e., reaction that results in the production of ATP or GTP by the transfer of a phosphate group from a substrate directly to ADP or GDP. During the oxidation of organic compounds in living cells, inorganic phosphate is transferred to organic matter to form energy-rich molecules (Figure 3) [22].

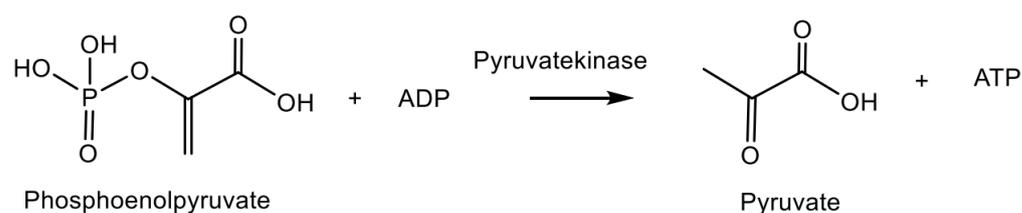


Figure 3. An example of the substrate-level phosphorylation.

It is not entirely clear whether anaerobic bacteria were the original organisms in the subsequent development of life on Earth. It is also unclear whether anaerobic bacteria evolved into subsequent species of living organisms, or these new organisms appeared independently of them, like other later forms of life, that is, the origin of life occurred repeatedly. To a certain extent, this is consistent with the theory of punctuated equilibrium in evolution [21]. Nevertheless, in any case, in all forms of life, the phosphorus played a primary role as an irreplaceable binding element of nucleotides, and also as a source of energy for maintaining vital functions of organisms.

Summing up this section, we can conclude that the emergence of life is an extremely complex, so far unresolved and at the same time important scientific problem [22]. This problem requires the close attention of many scientists in various fields of science. Its importance is determined by the fact that if we do not know the origins of life, then it is impossible to foresee what awaits life on Earth in the future. Additional information on the role and influence of naturally occurring phosphorus compounds on life processes will be presented in the following sections of review.

3. Stereochemistry of DNA and RNA

The most important and most amazing phosphorus-containing molecules is deoxyribonucleic acid (DNA)—a macromolecule (one of the three life-forming polymer molecules, along with RNA and proteins) that provides storage, transmission from generation to generation and the implementation of the genetic program for the development and functioning of living organisms [23,24]. A DNA molecule stores biological information in the form of a genetic code consisting of a sequence of nucleotides, conformations, and a convolution of a polymer molecule. DNA contains information about the structure of various types of RNA and proteins. DNA is made up of repeating blocks called nucleotides. Each nucleotide is composed of a nitrogenous base, deoxyribose, and a phosphate group. The connections between nucleotides in the DNA chain are formed by phosphodiester bonds (Figure 4) [24].

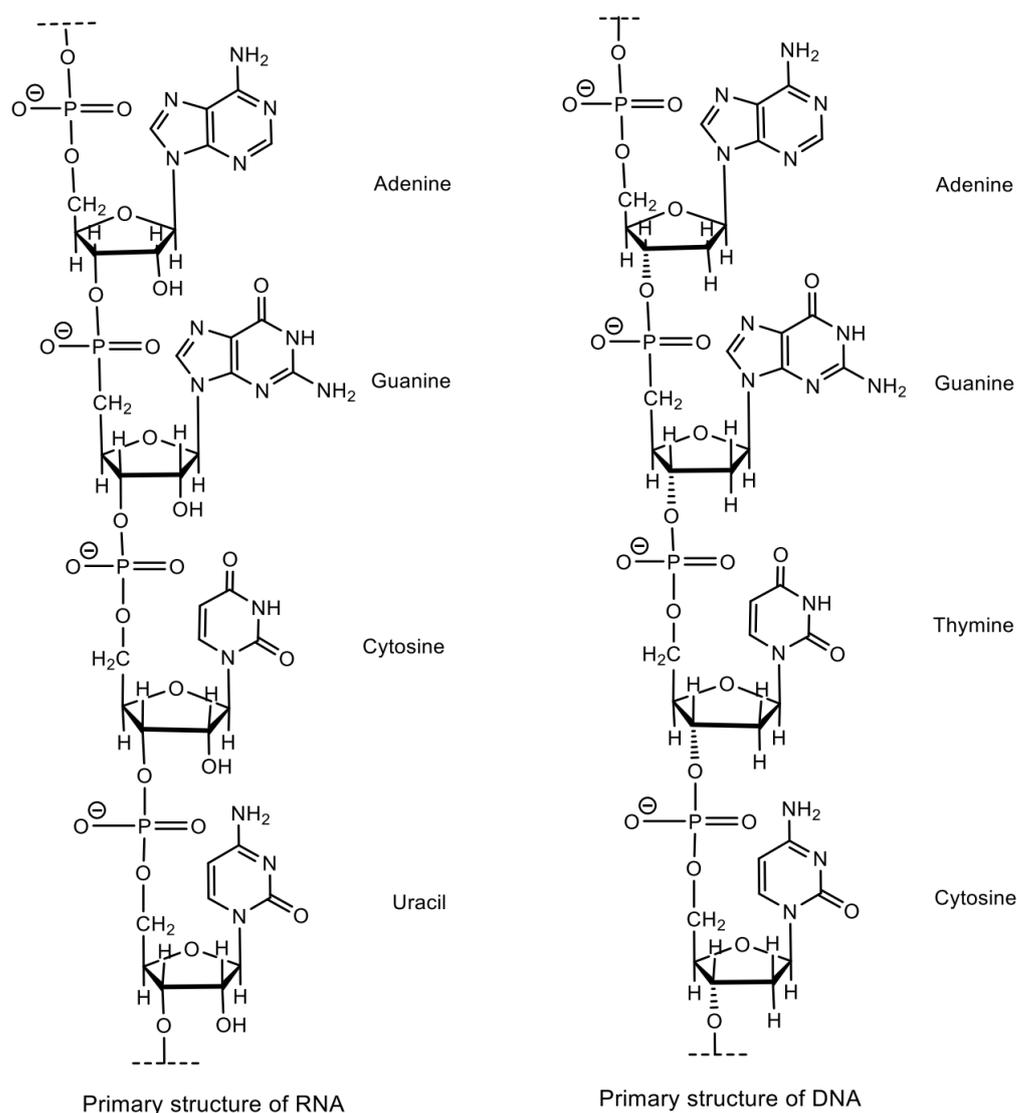


Figure 4. Structure of nucleic acids.

An example of a nucleotide is adenosine monophosphate, in which the base attached to phosphate and ribose is adenine. The most important energy molecule ATP (adenosine triphosphate) consists of an adenine base attached to sugar ribose and three phosphate groups. Depending on the structure of the pentose, ribonucleotides and deoxyribonucleotides are distinguished, which are monomers of biological polymers (polynucleotides)—RNA, or DNA, respectively. In nucleotides, the phosphate residue usually forms an ester bond with the 2'-, 3'- or 5'-hydroxyl groups of ribonucleosides, and in the case of 2'-deoxynucleosides, 3'- or 5'-hydroxyl groups are esterified

In the overwhelming majority of cases (except for some viruses containing single-stranded DNA), a DNA macromolecule consists of two chains oriented by nitrogenous bases to each other. This double-stranded molecule is twisted along a helical line, which can be right (A- and B-forms of DNA) or left (Z-form of DNA) (Figure 5) [25]. Phosphates have a significant effect on DNA conformation and twist. Phosphates in Z-DNA are not equivalent to each other and are located at different distances from the axis of the helix; for guanine nucleotides this distance is 0.62 nm, and for cytosine nucleotides it is 0.76 nm. At the same time, neighboring sugars “look” in opposite directions, and because of this, the line that sequentially connects phosphorus atoms in the chain becomes zigzag (hence the name—Z-DNA). B- and Z-forms are able to transform into each other. This occurs when the ionic strength of the solution or the concentration of cations that neutralize the negative charge of the phosphodiester framework changes. Deoxyribonucleic acid (DNA) is a biopolymer (polyanion), the monomer of which is a nucleotide.

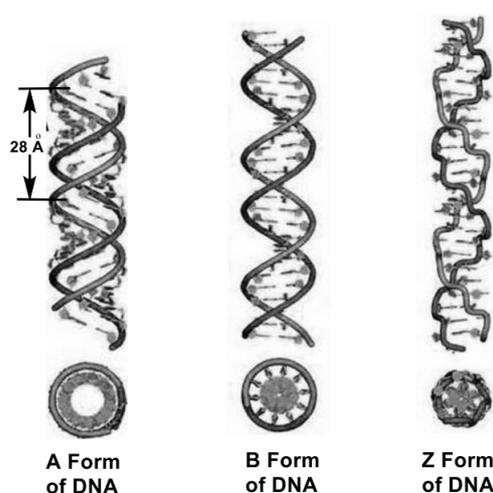


Figure 5. A-, B and Z-forms of DNA.

The incorporation of D- and/or L-amino acids into nucleopeptide molecules makes it possible to investigate the role of backbone stereochemistry in determining the formation of DNA and RNA hybrids. The characteristic helical structure and chiral environment of DNA was studied by measuring the spectra of induced CD and X-ray diffraction of both natural and synthetic DNA, which showed that it is a long polymer molecule consisting of nucleotides, bonds which form deoxyribose and a phosphate group (phosphodiester bonds). Circular dichroism (CD) studies have shown that the nucleopeptide forms stable hybrid complexes with RNA molecules, fully formed in the L-skeleton configuration. Molecular dynamics modeling suggests a potential structure of the complex resulting from the interaction between the L-nucleopeptide and the RNA chain. These studies have shown that both the backbone (ionic and H-bonds) and nucleotide bases (pairing and π -stacking) of the chiral nucleopeptide are involved in the hybrid complex formation, highlighting the key role of the backbone stereochemistry in the formation of the nucleopeptide/RNA complexes. (Figure 6) [25–27].

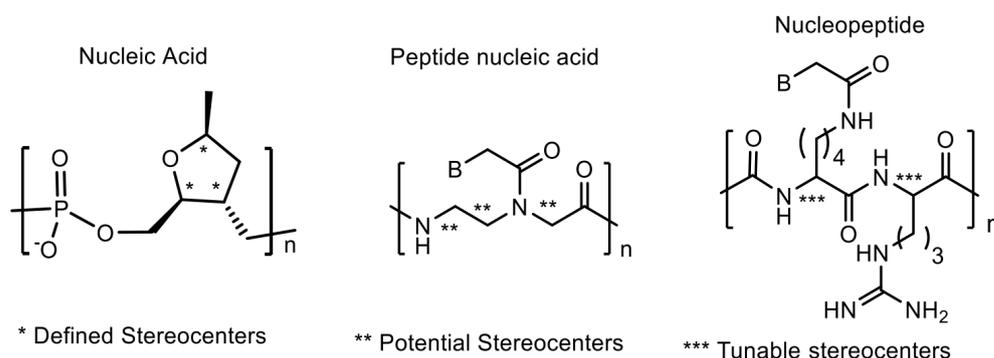


Figure 6. Nucleopeptides.

Helical junctions are important architectural elements in RNA, and three- and four-way DNA junctions are central intermediates in homologous genetic recombinations. The ideal (4H) junction is created by four double helices that are held together by interchange of strands (Figure 7a). Experimental confirmation of the existence of quadrilateral bonds of cruciform DNA molecules was obtained using electron microscopy, in which it is clearly observed in DNA molecules of X structures obtained from plasmid or bacteriophage DNA. The structure was confirmed by electrophoretic, chemical, and crystallographic studies (Figure 7b). The cruciform structure is formed by base pairing within a strand with an inverted repeating sequence, and their connections are recognized by enzymes that allow the connection. The cruciform shape is another form of quadrilateral bonds found in DNA derived from natural sources [28,29].

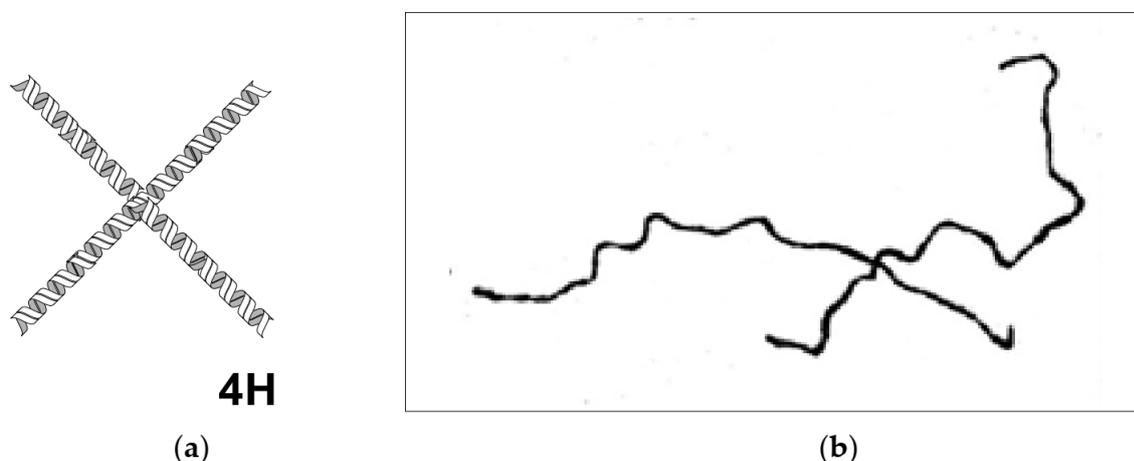


Figure 7. Cross-shaped structure of DNA: (a)—Schematic representation; (b)—Drawing from a photograph obtained using an electron micrograph of a four-way DNA junction (permission on reproduction of Cambridge University Press and Copyright Clearance Center, Order Number: 5065840479765 from 11 May 2021) [29].

The folded X-structure is formed by paired coaxial superposition of spirals forming a right-sided antiparallel cross. The formation of multilayer X-structure from an open square structure involves a decrease in symmetry from four to two times. Electrostatic forces are extremely important in the folding of the quadrilateral DNA junction, as indicated by the critical role of metal ions in the folding process. Formation of a multilayer X-structure requires either bivalent metal ions or very high concentrations of monovalent ions, and the conformer exchange rate strongly depends on the salt concentration [29,30]. A method was developed to track the stereochemical pathway of enzymatic DNA cleavage [25]. In accordance with this method, DNA with a phosphorothioate of known chirality is cleaved by the enzyme in $H_2^{18}O$ at a scissor bond. Cleavage results in a DNA molecule with a 5'-[^{16}O , ^{18}O , S]-thiophosphoryl group, the chirality of which depends on whether the cleavage reaction proceeds according to a one-step hydrolysis mechanism or a two-step

mechanism involving protein-DNA. To determine this chirality, the digested DNA was attached to the oligonucleotide using DNA ligase. Given the strict stereochemistry of the DNA ligase reaction, the initial chirality of the phosphorothioate can be retained or reversed in the product of ligation. In all cases, DNA cleavage occurred with inversion of the configuration, which indicates direct hydrolysis of the phosphodiester bond with water, in contrast to the reaction involving a covalent enzyme-DNA intermediate. Transcription of phosphorothioate-N-substituted RNA by T7 RNA polymerase has the same (RP)-configuration as *E. coli* RNA-polymerase. Thus, the reaction proceeds with configuration inversion for phosphorus [27]. In the cell, the binding of proteins to specific sequences of the DNA double helix is necessary to control the processes of protein synthesis (at the level of DNA transcription) and cell proliferation (at the level of DNA replication). In the laboratory, the sequence-specific DNA binding/cleaving properties of restriction endonuclease enzymes (secreted by microorganisms to protect them from foreign DNA molecules) have helped revolutionize molecular biology. DNA can take on several conformations, such as A-type, B-type, and others (for example, Z-type), depending on the DNA sequences and environmental conditions, for example, relative humidity, the ionic strength or polarity of the solvent and counterion. In contrast, RNA's are found in only two related conformations, A and A', which belong to type A double helical structures. The conformation of A-DNA structure is very similar to the structure of A-RNA. In the B-type double helix, stacking is largely limited by interactions between bases in the same polynucleotide chain. In the A-type double helix, stacking occurs both inside and between the overlapping strands, and bases belonging to two different chains participate in the stack.

In recent years, several successful attempts have been made to use DNA as chiral ligands in transition metal complexes in order to combine the catalytic capabilities of the transition metal with the chiral architecture of the biopolymer [31–40]. The hybrid catalyst comprises a synthetic catalyst, usually a transition metal complex, which is attached to a chiral biomolecular backbone. For example, salmon testes DNA (stDNA) and calf thymus DNA (ctDNA) are used as ligands. As a result, the catalyzed reaction takes place inside the DNA helix or very close to it, that allows DNA chirality, which is transferred into the reaction, leading to products having an excess one of enantiomers. Two general strategies can be distinguished, which are based either on supramolecular (non-covalent) or covalent attachment of the transition metal complex to DNA (Figure 4). The strategy of non-covalent or supramolecular anchoring is based on the tendency of DNA to bind small molecules using hydrophobic, π -stacking, electrostatic and/or hydrogen interactions leading to intercalation and/or binding of grooves. Supramolecular anchoring can be achieved by incorporating a DNA-binding moiety into a metal center ligand design. Covalent anchoring involves the binding of a transition metal complex through a ligand to DNA using a small spacer fragment. The attachment sites in this case can be modified nitrogenous bases or phosphate esters. The strategy of non-covalent or supramolecular anchoring includes the DNA-binding fragment in the ligand construct (Table 2). Rolfes and Feringa [39] presented a new concept of DNA catalysis, which realized the first DNA-catalyzed formation of symmetric C-C bonds in the Diels-Alder reaction. In the presence of a copper complex, asymmetric catalysis using DNA proceeded especially efficiently as a ligand for transition metal complexes that catalyze Michael addition, Friedel-Crafts alkylation, and others. G-Quadruplex, which induced reasonable levels of enantioselectivity in both Diels-Alder and Friedel-Crafts reactions, confirmed that the G-quadruplex DNA can also act as a suitable chiral template (Figure 8).

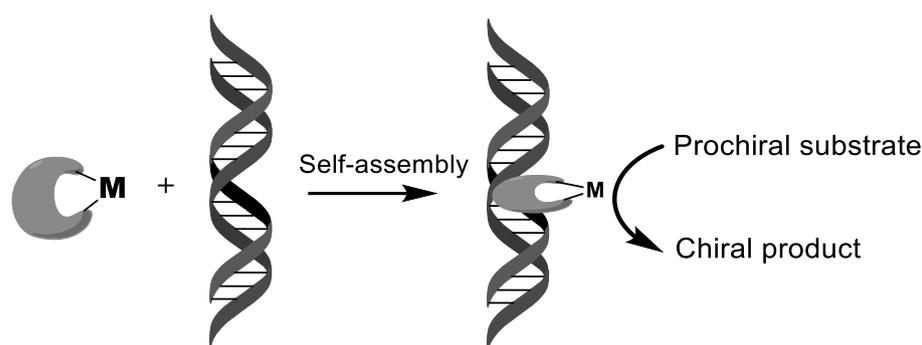


Figure 8. Schematic representation of DNA-based asymmetric catalysis using the supramolecular anchoring strategy.

The authors have successfully used L-DNA as an enantiomer with the opposite configuration than natural D-DNA. Indeed, L-DNA forms duplexes with identical physical properties in terms of the solubility and thermal duplex stability, resulting in levorotatory double-stranded helices (Table 2).

Erdmann and co-workers recently demonstrated the preferential stabilization of the natural D-configuration in versus the unnatural L-configuration in nucleic acids and have established using X-ray diffraction analysis of crystals grown under microgravity conditions that the D- and L-forms differ not only in their chirality, but also by way of interactions with divalent cations and water molecules (Figure 9) [32–38].

The chirality of the DNA double helix can be transferred directly to the reaction sites in reactions catalyzed by metal complexes. For example, a complex of DNA with copper catalyzed the Diels-Alder reaction. This was accomplished by placing a non-chiral or racemic catalyst in close contact with DNA and using the chiral information of the DNA double helix to obtain reaction products with an excess of one of the enantiomers. The Table 2 is constructed from different data extracted from article [31].

Table 2. The Friedel–Crafts addition with D- and L-DNA.

Entry	R ¹	R ²	R ³	ee [%] with D-DNA	ee [%] with L-DNA
1	MeO	H	Me	89	90
2	H	H	Me	76	76
3	H	Me	<i>o</i> -BrC ₆ H ₄	76	80
4	MeO	H	4-ClC ₆ H ₄	72	74

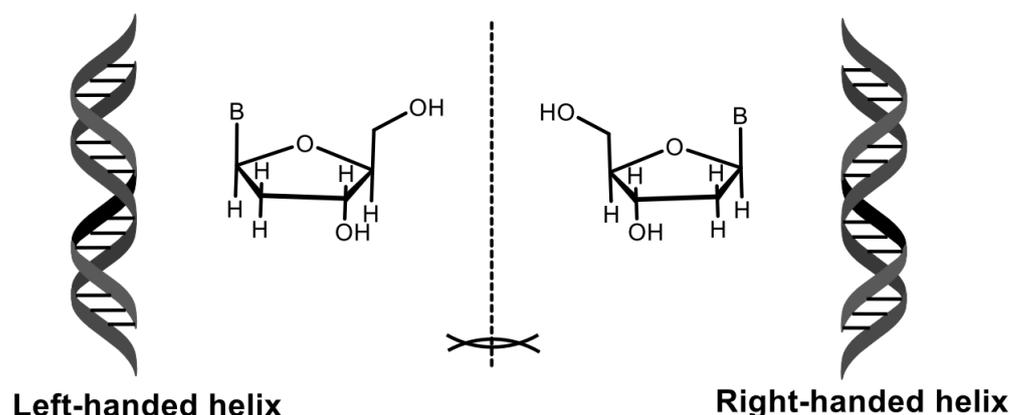


Figure 9. L- and D-Enantiomers of DNA: L-DNA (left) and natural D-DNA (right).

The catalyst is a complex formed in situ from copper(II) with a DNA ligand that contains three key structural features: A DNA intercalating moiety such as 9-aminoacridine, a spacer component, and a metal-binding group. The ligands were obtained in an efficient and simple way, starting from monoprotected diamines. The Diels-Alder reaction between cyclopentadiene and aza-chalcone was carried out in water in the presence of a copper (II) complex in the presence of salmon testes or calf thymus DNA, both of which are readily available. The reactions were brought to a conversion of >80%. Product of reaction was obtained as a mixture of *endo*- (major) and *exo* (minor) isomers, both with significant enantiomeric excess, depending on the ligand used [40]. Conversion of a centrally located phosphate group to an electrically neutral methylphosphonate in a quadrilateral DNA junction can have a large effect on its conformation (Figure 10) [33].

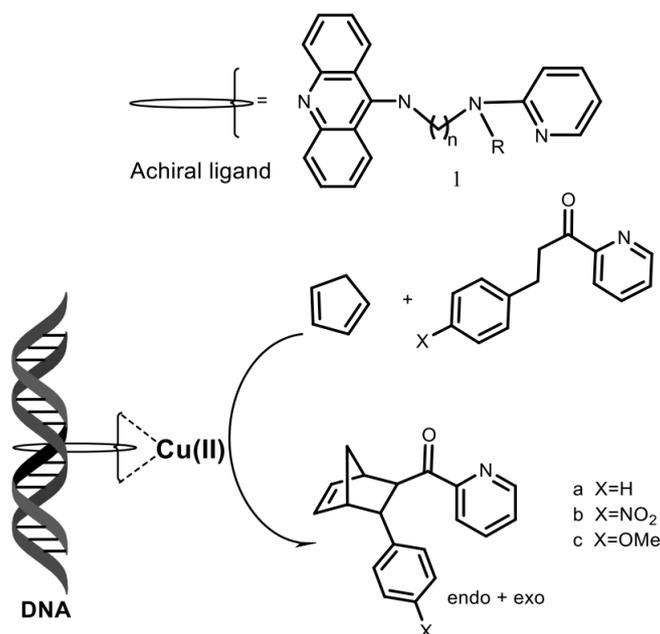


Figure 10. The asymmetric Michael addition reaction catalyzed by complexes formed between copper(II) ions and achiral ligands in the presence of DNA.

The methodology using DNA catalysts is now at the stage where it can be applied in the process of synthesis. Indeed, the first examples demonstrate that these reactions can be competitive with their “traditional” counterparts, both in terms of practicality and cost. DNA catalysts containing covalently linked catalytic moieties potentially provide greater control over catalyst geometry using a second coordination sphere [40]. Today, using DNA

catalysis, an impressive number of chiral compounds with high *ee* have been obtained, some of which are shown in Figure 11 [33–40].

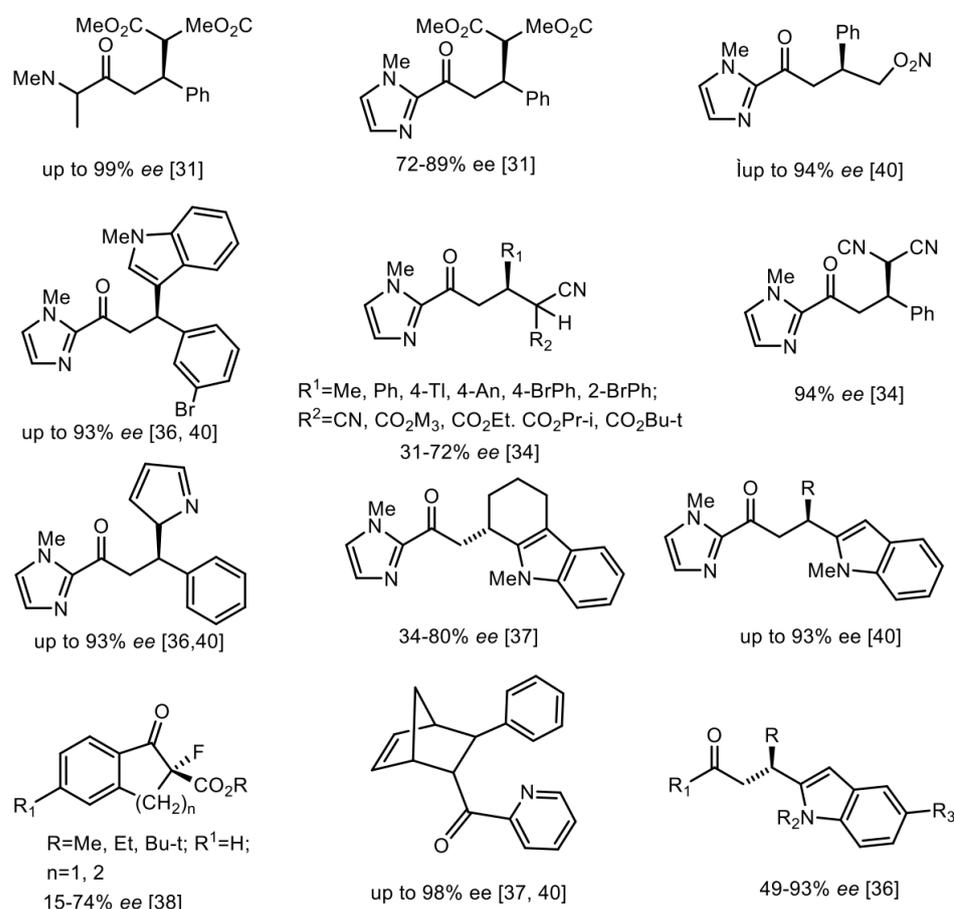


Figure 11. Some chiral compounds obtained by asymmetric DNA catalysis.

4. Phosphagens

The important natural compounds of phosphorus are phosphagens, which are energy sources for maintaining vital functions of organisms. Macroergic phosphagens are biological molecules that are capable of storing and transferring energy during a reaction. The hydrolysis of one bond in phosphagen gives usually more than 20 kJ/mol. About 15 representatives of phosphagens are known to support the vital activity of organisms. First of all, adenosine triphosphate (ATP), as well as about 15 phosphagens that contribute to the preservation and restoration of ATP reserves: N-phosphoguanidine, N-phosphocreatine, N-phosphoarginine, N-phosphocreatinine, 1,3-diphosphoglycerate, N-phosphotaurocyamine, 1,3-bisphosphoglycerate, phosphoglycocyanine, phosphoagmatine, N-phospholombricine, phosphoopheline, phosphotaurocyamine, phosphothalassemine phosphohypotaurocyamine, phospholombricine (Figure 8) Each phosphagen has its own corresponding phosphagen kinase: arginine kinase, thalassemine kinase, creatine kinase, glycocyanine kinase, taurocyamine kinase, hypotaurocyamine kinase, lombricine kinase and opheline kinase (Figure 12) [41].

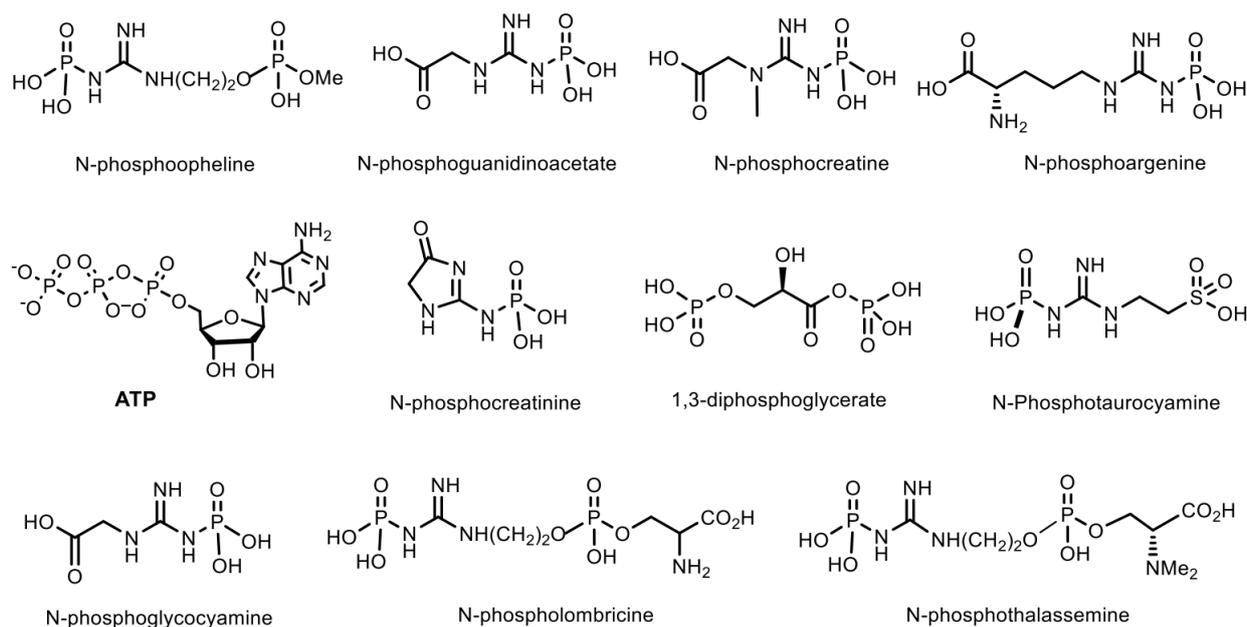


Figure 12. Some of the most important phosphagens.

Depending on the type of bond being broken, phosphagens release different amounts of energy. For example, during the hydrolysis of phosphoanhydride bond (nucleoside triphosphates and nucleoside diphosphates: ATP, HDF and their analogs), $\Delta G = 32$ kJ/mol is released. The thioether bond gives 42 kJ/mol; acyl phosphate bond (1,3-diphosphoglycerate, 1,3-diphosphoglycerate) $\Delta G = 46$ kJ/mol; and the enol phosphate bond (phosphoenolpyruvate) $\Delta G = 54$ kJ/mol. A universal source of energy in a cell (including muscle) is the free energy of the high-energy phosphate bond of adenosine triphosphate (ATP), released during the hydrolysis of ATP to adenosine di- and adenosine monophosphate (ADP and AMP) and an inorganic phosphorus compound [42,43]. However, the ATP contained in the muscles is sufficient to ensure work for a very short time, therefore, during muscle work, the energy of ATP is used, which is synthesized directly during work using the energy of other high-energy substances contained in the cell, including phosphates (phosphagens). Studying the mechanism of transfer of phosphoryl groups in natural phosphates is important for understanding the main metabolic pathways and for transmitting the cellular signal of fundamental processes in living systems. Monomolecular and bimolecular reactions of nucleophilic substitution at the phosphorus atom $S_N1(P)$ and $S_N2(P)$ are well known in the chemistry of phosphorus. $S_N1(P)$ reactions are involved in the processes of genetic inheritance through nucleic acids and in the generation of chemical energy, which makes it possible to stimulate thermodynamically unfavorable processes necessary for the construction of living cells. There are the following mechanisms of phosphoryl group transfer in substitution reactions at the phosphorus atom: (a) Dissociative mechanism of the S_N1 type, which includes the formation of a stable metaphosphate ion (PO_3^-), which interacts with the nucleophile at the stage of the rate-limiting reaction; (b) an associative, two-step attachment-elimination mechanism through the formation of an intermediate phosphorane (Figure 13) [42,44].

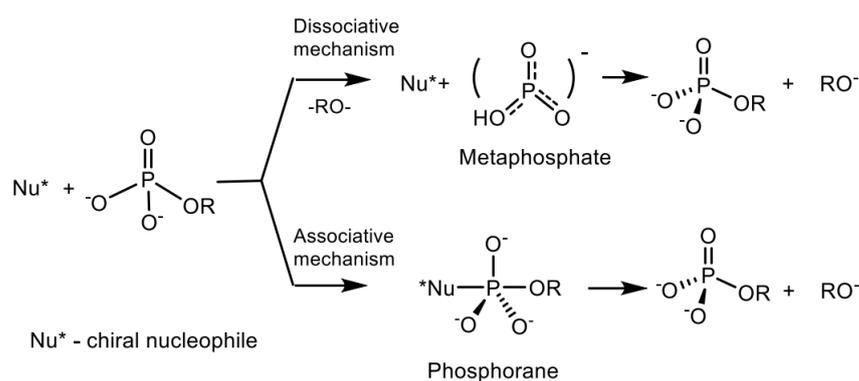


Figure 13. Mechanisms of phosphoryl group transfer in substitution reactions at phosphorus atom. (*) is a well-known designation for chirality, the absolute configuration of which is not defined.

The mechanism of the ATP hydrolysis reaction proceeding through the formation of an intermediate metaphosphate was described by Westheimer [45]. The dissociative method of breaking the P–O–C bond with the formation of an intermediate metaphosphonate is observed in the case of a sterically hindered phosphorus compound, most often in weakly nucleophilic solvents. The pentavalent tri-coordinated metaphosphate is very reactive in aqueous solutions. Consequently, it cannot be registered in aqueous solutions because of the insignificant lifetime under these conditions. However, metaphosphate can be detected in highly polar and weakly nucleophilic nonaqueous media [46–50]. In addition, the metaphosphate anion PO_3^- exists in a stable form in the gas phase and has been recorded by various physical methods. In the gas phase, metaphosphate has a relatively low reactivity. The enthalpy of deprotonation of HPO_3^- in the gas phase is only 314 kcal/mol. Metaphosphate anion was recorded in the mass spectra of various pesticides, in the products of ionization cleavage of phosphates, in the mass spectra of adenosine-50-monophosphate, in various phosphate triesters, etc. (Figure 14) [51–55].

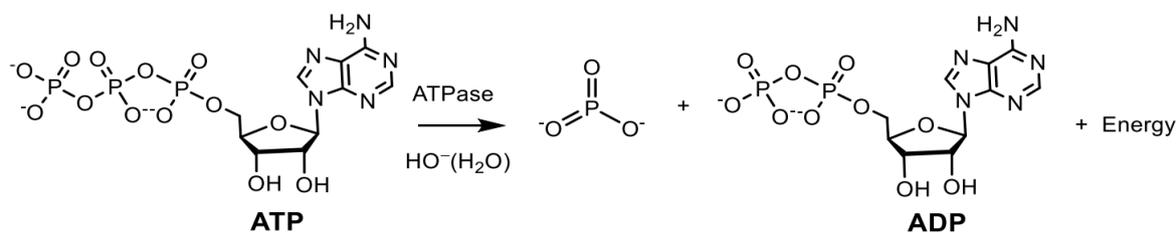


Figure 14. ATP hydrolysis by ATPase with formation of ADP.

The stereochemistry of the $\text{S}_{\text{N}}1(\text{P})$ reaction proceeding through the formation of an intermediate metaphosphate was studied using the example of phosphates carrying oxygen isotopes. The methanolysis of phenylphosphate monoanion and dinitrophenyl phosphate dianion using [(*R*)- ^{16}O , ^{17}O , ^{18}O]-phosphocreatine, proceeded with a complete inversion of the configuration was observed at the asymmetric phosphorus center. It was found that the intermediate metaphosphate in protic solvents does not leave the solvation cell in which it was formed, and then enters into a further reaction, which creates conditions for an asymmetric reaction [56–59]. The metaphosphate ion was detected by X-ray diffraction analysis in some biological molecules in the form of a particle stabilized by coordination bonds, for example, in fructose-1,6-bisphosphatase. The crystals of fructose-1,6-bisphosphatase were grown up in an equilibrium mixture of substratum and product in almost atomic resolution (1,3 Å) (Figure 15) [60].

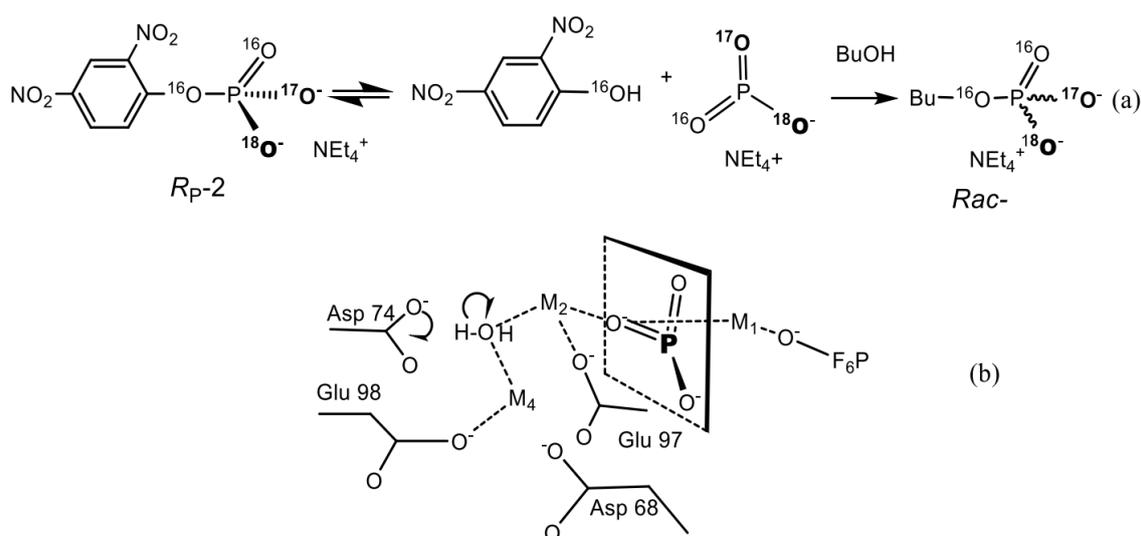


Figure 15. (a) Mechanism of solvolysis and racemization of dinitrophenyl phosphorous acid dianion; (b) The metaphosphate-anion in a crystal lattice of fructoso-1,6-bisphosphatase found by X-ray crystallographic analysis.

Phosphocreatine, as a source of energy for muscle contraction, plays a leading role in the work in the anaerobic alactate power zone, when its reserves in muscle cells limit the duration and intensity of physical activity. The phosphocreatine is a product of reversible metabolic N-phosphorylation of creatine, which, like ATP, is a high-energy compound. However, in unlike ATP, which is hydrolyzed at the pyrophosphate O-P bond, phosphocreatine is hydrolyzed at the phosphamide N-P bond to give a significantly greater energy effect of the reaction. The phosphocreatine is found mainly in muscle and nerve tissues and its biological function is to maintain a constant concentration of ATP due to a reversible rephosphorylation reaction: creatine phosphate + ADP \rightleftharpoons creatine + ATP. Thus, the phosphocreatine is an energy depot that provides a rapid synthesis of ATP (Figure 16) [61].

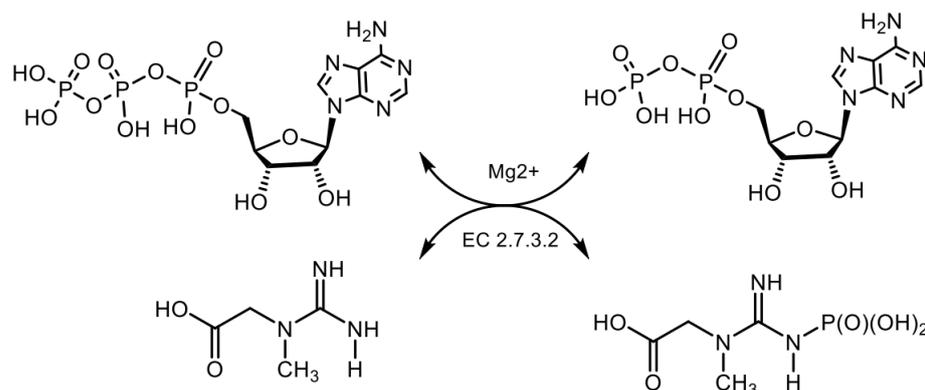


Figure 16. Interconversions of phosphocreatine/creatine kinase: the system of ATP + creatine is in equilibrium with ADP + phosphocreatine.

5. Natural Compounds with P-N Bonds

N-Phosphamides. A large number of various organophosphorus compounds with P-N bonds have been isolated from living organisms, which indicates the importance of these compounds in nature. For example, the N-phosphocreatine is one of natural P-N-amidophosphates, which have a significant impact on the formation and development of living organisms, starting from the prebiotic period [62,63]. Many amidophosphates have cytostatic, antitumor, chemotherapeutic properties to be alkylating-type drugs such as cyclophosphamide, diphosphamide, mafosfamide, trophosphamide, perphosphamide and others (Figure 17) [62–65]. Guanidine compounds containing PN-bonds play a central

role in the physiology and biochemistry. For example, up to 20–25% of N-phosphocreatine is converted in vivo, through the intermediate formation of N-phosphocreatinine to creatinine [62,63]. Natural phosphoramides such as N-phosphocreatine and phosphoramides shown in Figure 18 are formed by phosphorylation of histidine groups in histidine kinases.

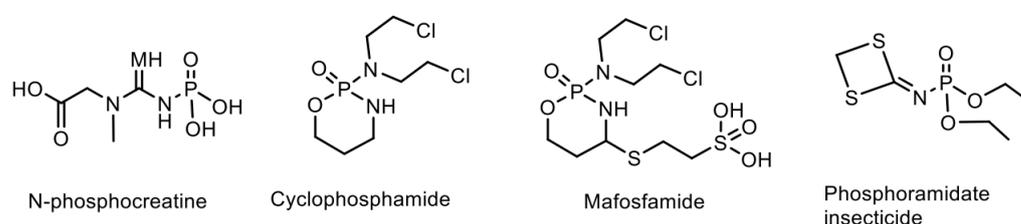


Figure 17. Examples of N-phosphamides.

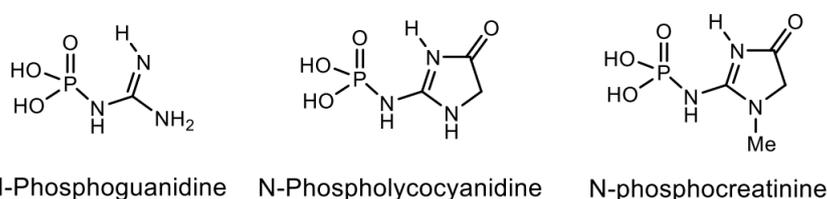


Figure 18. Examples of Phosphoguanidines.

An analog of N-phosphocreatinine, called dimethyl-N₂-creatinyl phosphate, was isolated from a sponge found in Bermuda [64]. Ulosantoin, which is a phosphorylated hydantoin, was isolated from extracts of the *Ulosa ruetzleri* sponge and exhibited marked insecticidal activity against tobacco hornworm larva and cockroaches. The structure of Ulosantoin was determined by X-ray structural analysis. A structurally related compound, dimethyl N₂-creatinyl phosphate, was also isolated from the sponge extracts, but was inactive in the insecticidal screens (Figure 19) [65].

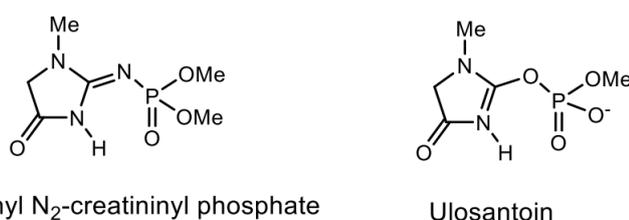


Figure 19. Analogs of N-phosphocreatinine.

Eschenmoser et al. [66] showed that glycolaldehyde is phosphorylated by AmTP₂ in the presence of divalent metals in water at room temperature and at neutral pH, with the formation of glycolaldehyde phosphate (GAP) in quantitative yields. A specific phosphorylation reagent in this process is amidotriphosphate, a compound known to be formed by the ammonolysis of cyclotriphosphate (“metatriphosphate”) in aqueous solution. It is noteworthy that cyclotriphosphate itself is not effective as a phosphorylation agent under the same conditions, its ammonolysis product phosphorylates glycolaldehyde in quantitative yield. The reason for this marked difference in reactivity is the specific ability of amidotriphosphate to reversibly form the addition product of carbonyl A with glycolaldehyde and to phosphorylate the α-hydroxyl group by intramolecular migration of the phosphate from A to intermediate B, which is then hydrolyzed to GAP (Figure 20) [66].

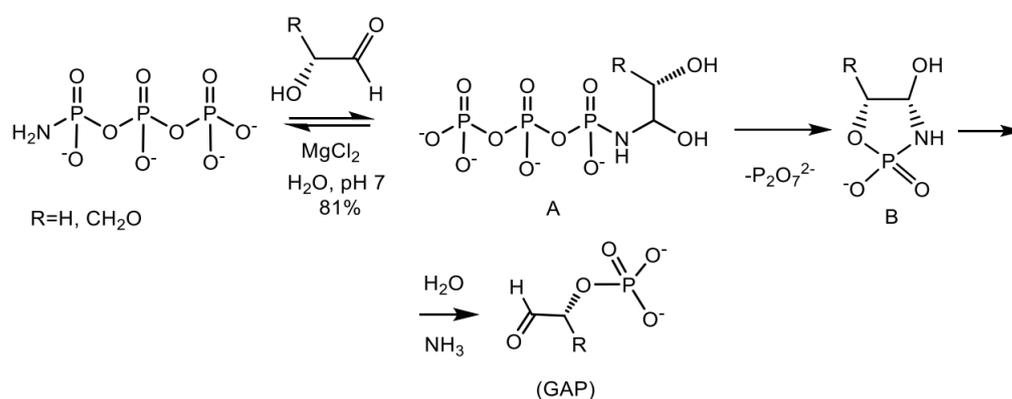


Figure 20. Regiospecific intramolecular phosphorylation of glycolaldehyde (R = H) and D-glyceraldehyde (R = CH₂OH) by amidotriphosphate.

The stereochemistry of P-N phosphates, isolated from natural sources, is relatively monotonous. Most natural P-N phosphates whose stereochemistry has been established by reliable methods are derivatives of L-amino acids and D-carbohydrates. Therefore, they contain asymmetric centers of the corresponding absolute configurations. For example the reaction shown in the Figure 21. Sutherland et al. [67] investigated the potentially prebiotic synthesis of nucleotides via arabinose-3-phosphate and its cyanamide derivative in an attempt to effect constitutional self-assembly of RNA via a simple pathway to RNA, including nucleotide polymerization. With this aim, the authors investigated several synthetic approaches, including phosphorylation, phosphate migration and 2,3-C-C bond building. In particular, they investigated the phosphorylation of arabinose by diamidophosphate (DAP). An aqueous solution of D-arabinose and DAP was stirred at room temperature for several days, taking aliquots for NMR spectroscopic analysis at regular intervals (Figure 21) [66,67].

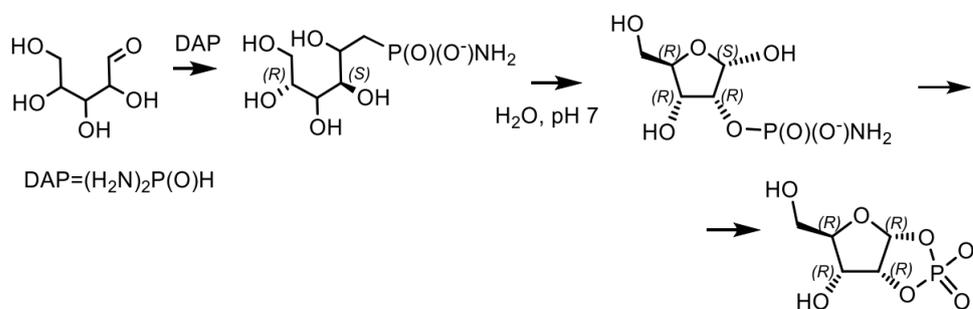


Figure 21. Intramolecular phosphorylation by transient tethering in the *arabino* series.

An example of a natural compound containing a P-N bond is adenosine-5'-phosphoramidate, which was isolated from *Chlorella pyrenoidosa* cells by high performance liquid chromatography; adenosine-5'-phosphoramidate was also synthesized from adenylyl 5'-phosphosulfate and ammonia by adenylyltransferase and SN-enzyme, which is found in various organisms, including bacteria, algae, fungi, and higher plants [68,69]. Therefore, adenosine-5'-phosphoramidate is a normal component of chlorella cells, as is the enzyme that forms it: adenylyl sulfate: ammonia adenylyltransferase. The enzyme that catalyses the formation of adenosine 5'-phosphoramidate from ammonia and adenosine 5'-phosphosulphate was purified to homogeneity from *Chlorella* by using (NH₄)₂SO₄ precipitation and DEAE-cellulose, Sephadex and Reactive Blue 2-agarose chromatography. In a non-enzymatic reaction, both adenosine-5'-phosphoramidate and AMP are formed. However in the presence of enzyme adenosine-5'-phosphoramidate, which selectively accelerates an already ongoing reaction, the Adenosine 5'-phosphoramidate is formed. *Auxenochlorella pyrenoidosa* has been identified in cell extracts of many other organisms, including *Chlorella pyrenoidosa*,

Euglena gracilis var. *bacillaris*, spinach, barley, *Dictyostelium discoideum* and *Escherichia coli* (Figure 22) [68,69].

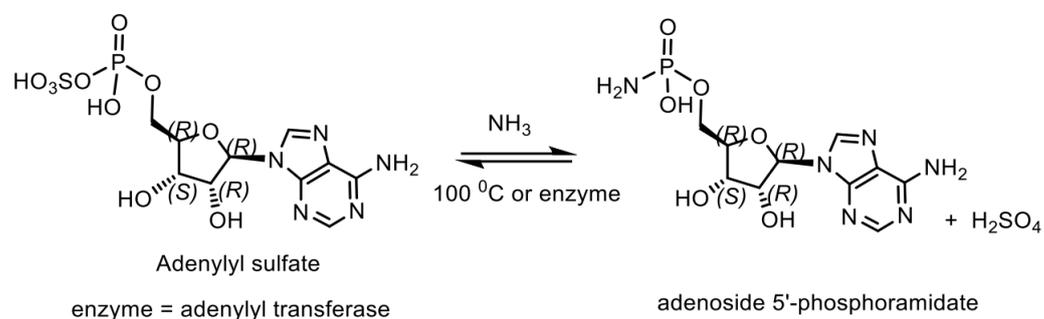


Figure 22. Formation of adenosine-5'-phosphoramidate from ammonia and adenosine-5'-phosphosulfate.

In addition to the identification of individual phosphoramidate nucleosides, N-adenylylated proteins were found in the membrane fraction of *Dictyostelium discoideum* [70–73]. Eukaryotic cells encode AMP-lysine (AMP-N-epsilon-(methyl N-alpha-acetyl lysinate)-5'-phosphoramidate) hydrolases related to the nucleotide binding protein 1 sequence of the rabbit histidine triad (Hint1) [74,75]. Adenosine 5'-phosphoramidate (NH₂-pA) is a rare naturally occurring nucleotide and its biochemistry and biological functions are poorly recognized (Figure 23).

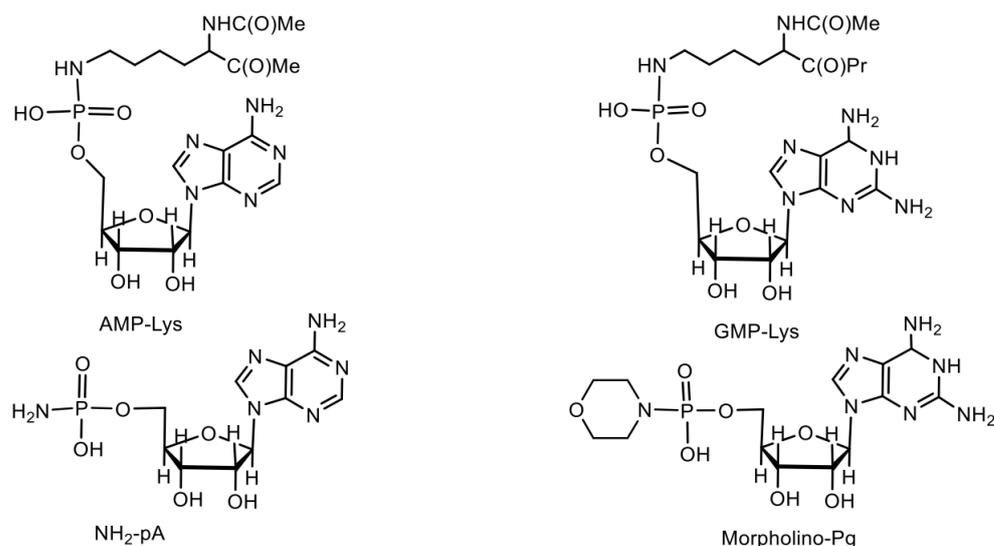


Figure 23. Structures of the nucleotidyl derivatives Hint 2.

All organisms have proteins that can be involved in NH₂-pA catabolism. They are members of the HIT family of proteins and catalyze the hydrolytic cleavage of NH₂-pA into 5'-AMP and ammonia. Hint1 (Histidine triad nucleotide binding protein 1) is a protein encoded by the gene of the same name, located in humans on the short arm of chromosome 5. It is involved in such biological processes as apoptosis, transcription, regulation of transcription. Hint proteins are present in almost all types of living organisms [70–77].

The histidine triad protein binding nucleotide is an enzyme that hydrolyzes lysine-bound AMP and in yeast functions as a positive regulator of the C-terminal domain kinase of RNA polymerase II, Kin28. Rossomando et al. [73,78] reported on protein release and characterization of phosphoramidates formed as a result of a membrane-bound adenylyltransferase reaction. The N-adenylyl-L-lysine derivatives are found, either as covalent enzyme substrate intermediates in DNA ligase EC 6.5.1.2 (i.e., enzyme catalyzing the ligation of DNA strands with 3'-hydroxyl and 5'-phosphate termini) in *Escherichia coli*

and RNA of wheat germ or as substrates of the evolutionarily conserved family of Hint phosphoramidate hydrolases AMP/GMP (Figure 24) [74].

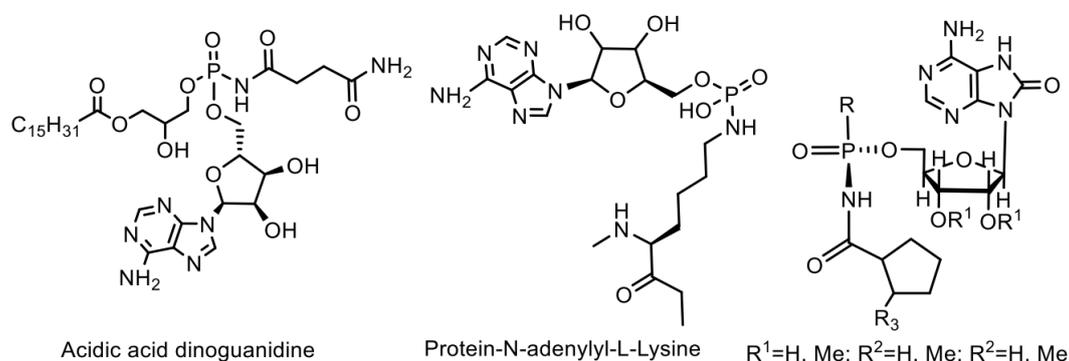


Figure 24. Nucleotides that bind protein of the histidine triad.

Among the nucleotides containing the P-N bond, nucleotide antibiotics, which are adenosine-containing phospholipids, attract attention. For example, stearic and palmitic acid dinogunellins and their structurally related dinogunellins A-D. A distinctive feature in dynogunellins is the presence of a phosphoramidate P-N bond common to many nucleotide antibiotics, for example, fosmidosines, antifungal nucleotide antibiotics from *Streptomyces durhameusiz* (Figure 25) [79–88]. The fosmidosine has a specific inhibitory activity against spores of *Botrytis cinerea*, a worldwide pathogenic fungus that causes gray rot disease in various fruits and vegetables [74,80].

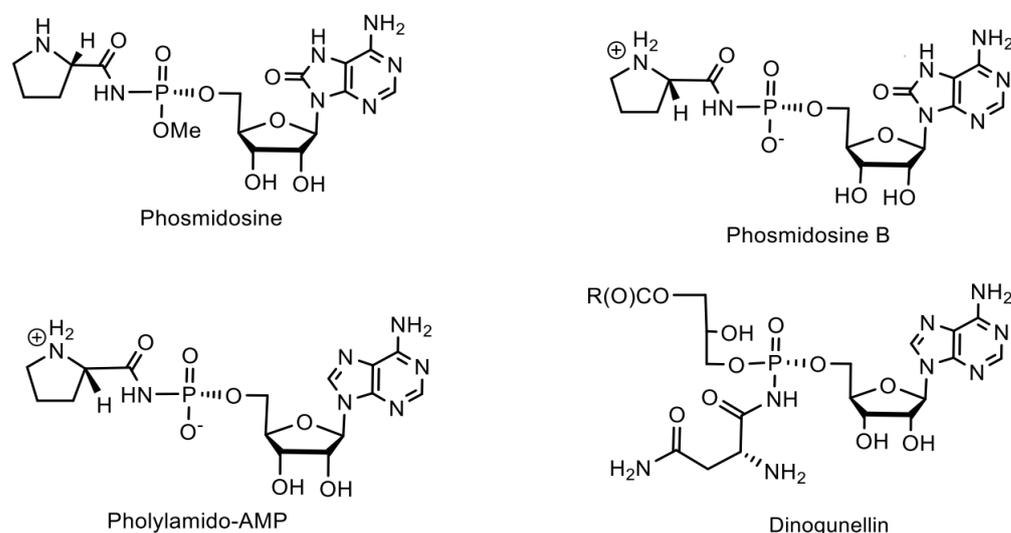


Figure 25. Natural products containing N-acylphosphoramidate bonds.

Fosmidosine has a powerful antitumor effect and is able to stop cell growth in the G1 phase of the cell cycle. Another example is Fosmidosine B, where 8-oxoadenosine is attached to proline through a similar phosphoramidate bond. This antifungal antibiotic, derived from *Streptomyces durhameusie*, also has anti-cancer activity. Both isolated diastereomers of fosmidosine have similar, but about 10 times higher, antitumor activity than fosmidosine B (Tables 3 and 4) [74]. The structure of fosmidosine was determined by various methods, including mass spectrometry and NMR spectroscopy [81]. Fosmidosine has a chiral center at the phosphorus atom of the N-acylphosphoramidate bond and therefore exists in the form of two diastereomers (Figure 26). Demethylated derivative of Fosmidosine, Fosmidosine B, has an achiral phosphorus atom, and thus, has no phosphorus chirality (Table 3). Fosmidosine was also successfully synthesized by use

of 5-(3,5-dinitrophenyl)-1H-tetrazole (DNPT) as the powerful activator of an N-prolyl phosphorodiamidite derivative that was condensed with an 8-oxoadenosine derivative.

Table 3. Structures of phosmidosine, phosmidosines B and C.

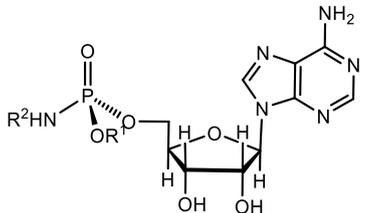
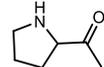
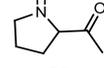
	R ¹	R ²	Name
	Me		Phosmidosine
	H		Phosmidosine B
	Me	H	Phosmidosine C

Table 4. The antitumor activities of phosmidosine and its stereoisomer.

Type of Tumor Cells	IC ₅₀ (μM)	
	Phosmidosine 1a	Phosmidosine 1b
KB	3.6	3.2
KATO-III	2.6	1.9
MKN-28	9.6	8.5
MKN-45	2.9	2.5

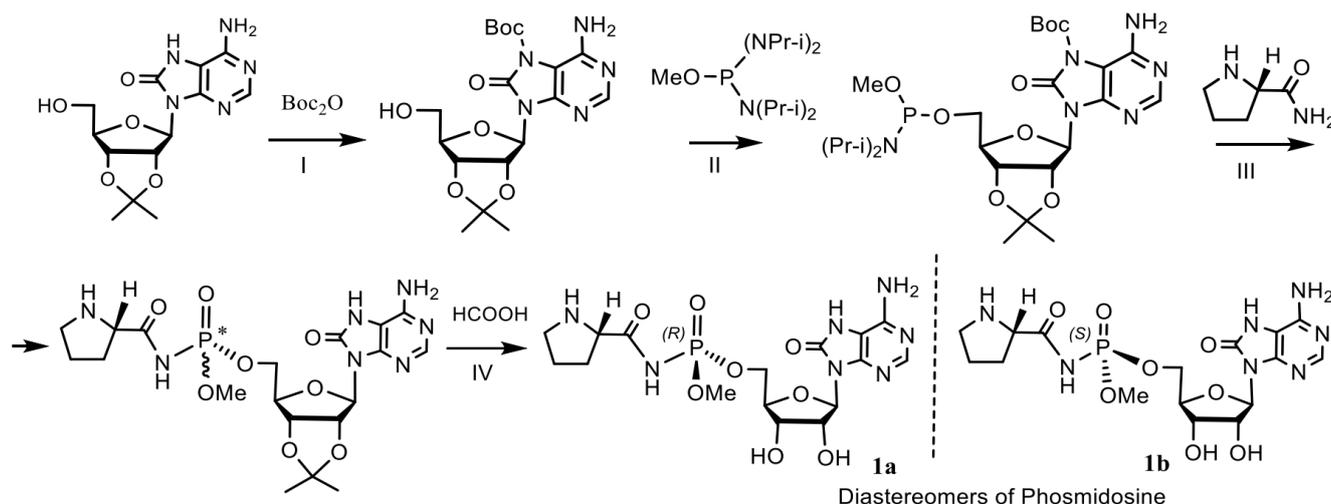


Figure 26. Synthesis of phosmidosine diastereomers. **Reagents and conditions:** (I) MeOH-Et₃N (9:1, v/v), rt, 1 h; (II) diisopropylammonium tetrazolide, CH₂Cl₂, rt, 1 h; (III) 17, 5-(3,5-dinitrophenyl)-1H-tetrazole, CH₂Cl₂-MeCN (1:1, v/v), rt, 10 min; tert-BuOOH, MeCN, rt, 5 min; I2, pyridine-H₂O (9:1, v/v), rt, 30 min; (IV) 80% HCOOH, rt, 12 h. (*) is a well-known designation for chirality, the absolute configuration of which is not defined.

The phosmidosine derivatives were found to exhibit significant antitumor activities. In connection with these studies, the synthesis and biological properties of aminoacylamido-AMP derivatives having N-P bonds as stable analogues of aminoacyl-AMP were also described (Table 4) [80,81].

The phosmidosine B was successfully synthesized by reaction of N-acetyl-8-oxoadenosine-5'-O-phosphoramidate derivative with N-protected prolinamide in the presence of 5-(3,5-dinitrophenyl)-1H-tetrazole. The synthesis of phosmidosine was achieved through the use of a tert-butoxycarbonyl (Boc) group, which is selectively introduced into the 7-NH-function of 8-oxoadenosine and serves as a pseudoprotective group so that the unmasked 6-amino group is not phosphorylated. The final reaction of coupling the 8-oxoadenosine-5'-phosphoramidite derivative with N-tritylprolinamide and subsequent complete deprotection gave a mixture of phosmidosine diastereoisomers. The ¹³C NMR

spectra of diastereomers suggest that the slowly eluted diastereomer is natural phosmidosine (Figure 27) [74].

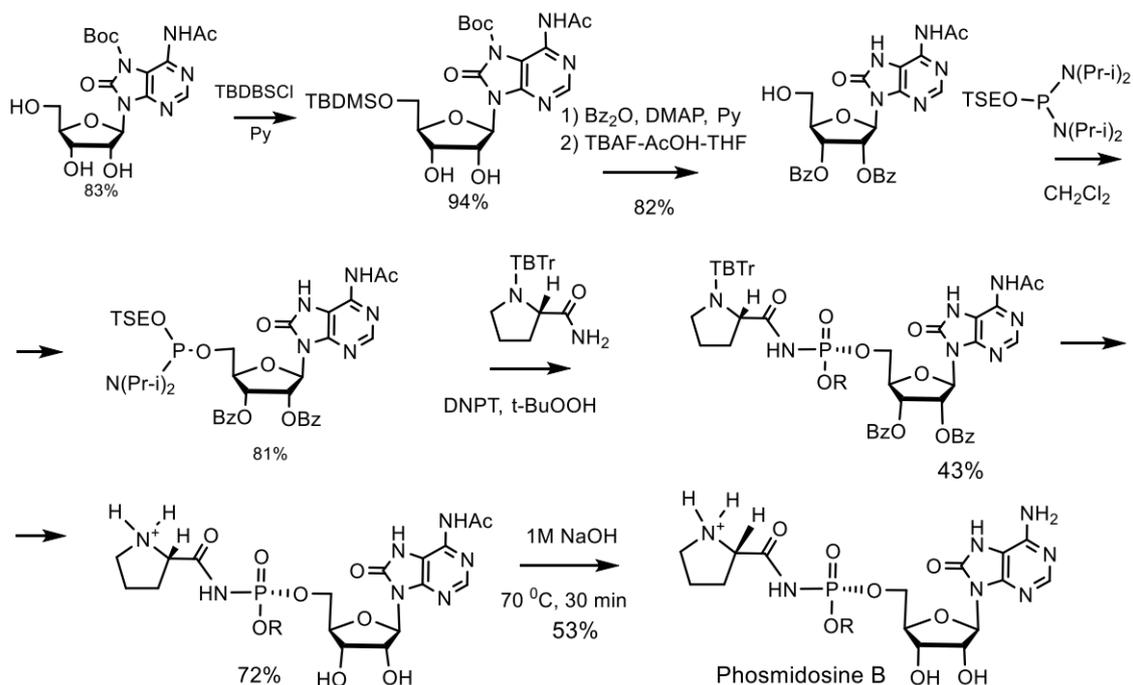


Figure 27. The synthesis of nucleotide antibiotic phosmidosine B.

A number of phosphoramidate nucleotide antibiotics, called phosmidosines, were isolated from the extract of *Streptomyces durhameusis* (fosmidosine, fosmidosine B and fosmidosine C), as well as two variants of N-methylphosmidosine. Fosmidosines appear to inhibit spore formation of *Botrytis cinerea* at a concentration of 0.25 µg/mL. *Botrytis cinerea* is a common pathogenic fungus responsible for gray mold disease in a variety of commercially important fruits and vegetables. Based on the conducted in vitro studies, it was proposed to use fosmidosines as potential anticancer agents. Phosmidosine analog, having an N-acylsulfamate linkage and possessing potent antitumor activities against cancer cells was synthesized by the sulfamylation of an 8-oxoadenosine derivative [89–91]. Sekine et al. reported the synthesis of a stable biotin–phosmidosine that is required for isolation of biomolecules that bind to phosmidosine (Figure 28) [91].

The selective antibiotic Agrocin 84, which is a member of the adenine nucleotide family, the first member of which is 6-N-AMP (R = H) [83], has attracted close attention. Agrocin 84, which is a 6-N-phosphoramidate, was isolated from *Agrobacterium radiobacter* K84 found in Australia [82–86]. Agrocin 84 is selectively active against several strains of phytopathogenic agrobacteria such as *Agrobacterium tumefaciens* and *Agrobacterium rhizogenes*. The toxic effect is achieved by inhibiting the pathogen tRNA synthetase [87,88]. The 1-phosphoglucufuranose sugar fragment at position N-6 is required for proper transport by susceptible bacteria, but it is not essential for the toxicity of agrocin 84. The complete synthesis of the nucleotide antibiotic Agrocin 84, which has two different types of unique phosphoramidate bonds, has been described in detail [80]. Agrocin 84 is an active factor in the biological control of coronal gall, a plant cancer caused by certain strains of *Agrobacterium*. Agrocin 84 neutralizes the pathogenic plant bacterium *Agrobacterium tumefaciens* (Figure 28).

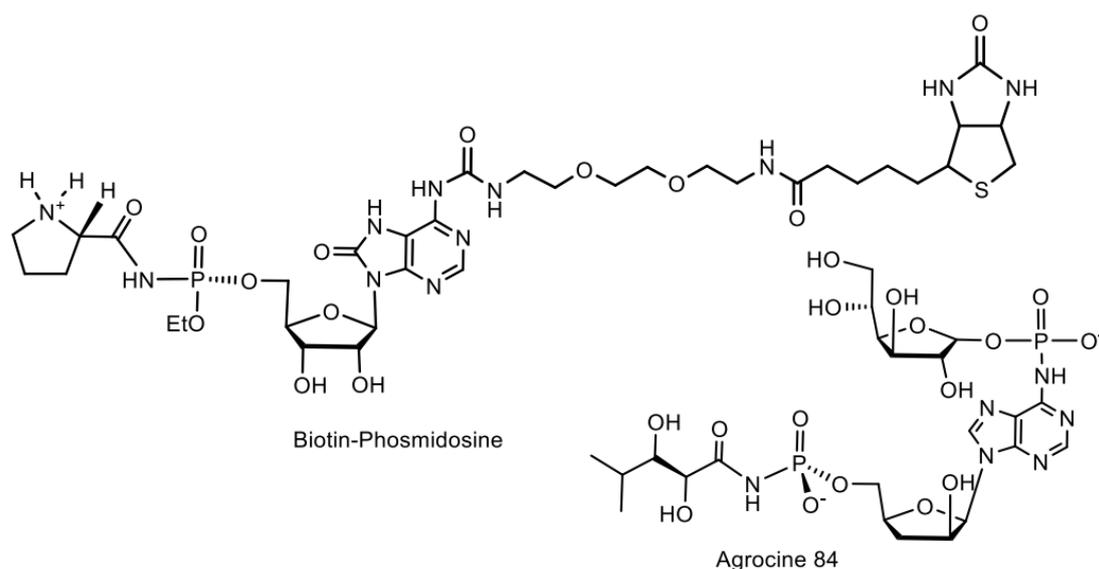


Figure 28. Agrocine 84 and Biotin-Phosmidosine.

The activity of agrocine 84 correlates with the pathogenicity and the presence of nopaline (N2-(1,3-dicarboxypropylarginine)) tumor-inducing plasmid. Structural analysis shows that the 5'-phosphoryl bond of the nucleoside core of 9-(3'-deoxy- β -D-threopentofuranosyl) adenine with the amide group of D-threo-2,3-dihydroxy-4-methylpentanamide is necessary for the manifestation of antibiotic activity, but the bactericidal specificity is due to the presence of the D-glucofuranosyloxyposphoryl substituent at the N6 adenine. Agrocine 84 acts as a molecular Trojan horse, mimicking a substrate derived from a plant tumor, and thus gaining access to the interior of the cell, where it is converted into a toxic moiety (TM84). TM84 is a potent inhibitor of leucyl-tRNA synthetase (LeuRS), an important enzyme that catalyzes the condensation of leucine with its related tRNA and is responsible for the correct translation of the genetic code. It was found that TM84 uses a unique tRNA-dependent mechanism to inhibit leucyl-tRNA synthetase (LeuRS), while the TM84 producer prevents self-poisoning by expressing resistant LeuRS and AgnB2 (Figure 29).

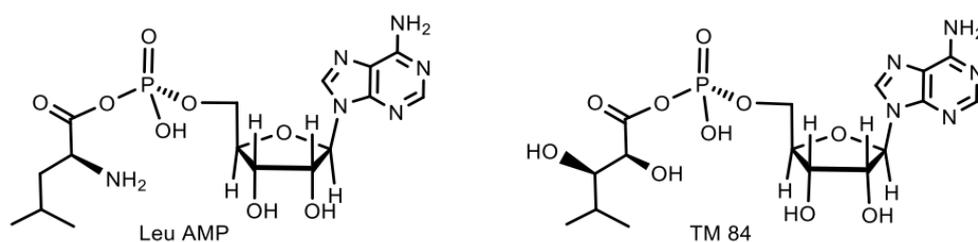


Figure 29. Metabolites of Agrocine 84.

Agrocine 84, when interacting with the pathogen, is cleaved into a toxic fragment of TM84 and a transport fragment. TM84 controls leucyl tRNA synthetase, thereby inhibiting the aminoacylation of tRNA^{Leu}. This subsequently leads to the cessation of protein synthesis in the pathogen and leads to cell death. Probably, the stable toxic component of Agrocine 84 can exert an antibiotic effect on bacteria by binding to the catalytic domain of the LeuRS genome-encoded *A. tumefaciens* as a Leu-AM mimetic (Figure 30) [86].

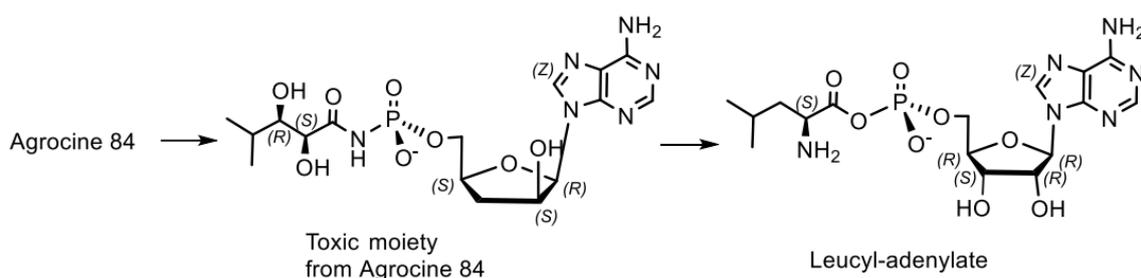


Figure 30. Conversion of agrocine 84 into a toxic fragment of TM84.

Microcin C (McC) is a member of the microcin family containing a heptapeptide covalently linked to 3-aminopropyl AMP via an acylphosphoramidate bond. McC is a «Trojan horse»-like inhibitor of aspartyl-tRNA synthetase, endowed with strong antibacterial properties, in which the heptapeptide fragment is responsible for the transport of the inhibitory metabolite into the bacterial cell [91,92]. The analogue of aspartyl AMP formed inside the cell carries a chemically more stable phosphoramidate bond in comparison with labile aspartyl adenylate and, in addition, is esterified with a 3-aminopropyl group. Biosynthesis and antibacterial activity mechanism [92,93] of McC are well-studied [94–101]. It has been found that some species of bacteria produce antibiotics containing peptide and nucleotide moieties for protection. *Escherichia coli*, for example, produces the antibiotic Microcin C7 [96]. The peptide moiety of this phosphoramidate mediates the transport of the antibiotic to the target bacterial cell, where processing leads to the breaking of the peptide bond between alanine and aspartic acid, releasing adenylyphosphoramidate aspartic acid, which acts as an inhibitor of protein synthesis in the target bacterium. A similar defense mechanism is used by the eggs of the Japanese fish *Stichaeus grigorjewi*, which produce the toxin dinogunelin (Figure 31).

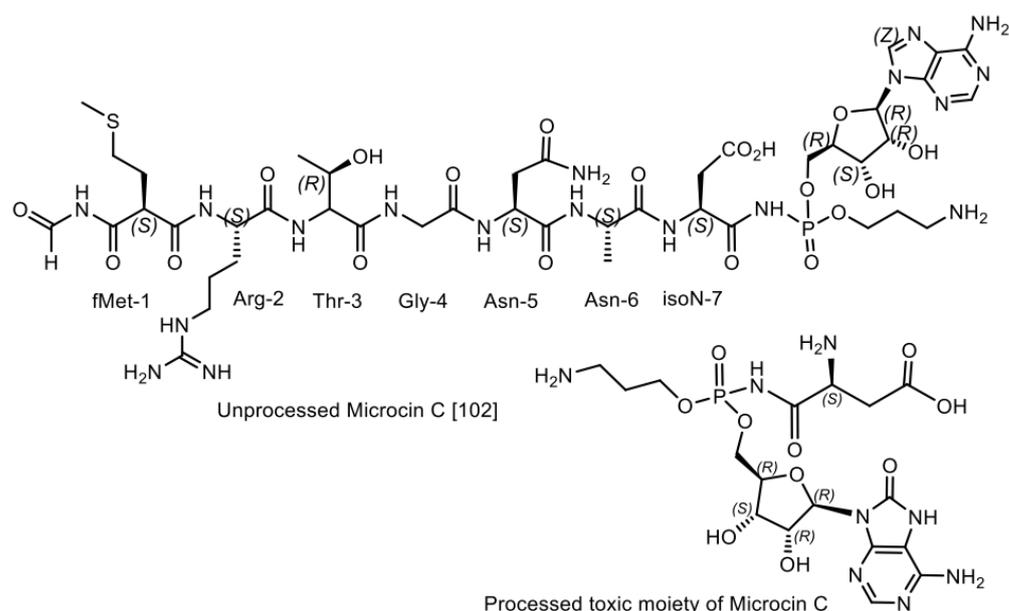


Figure 31. Antibiotics of the McC family.

Microcins C (McC) consists of a peptide with formylmethionine at the lateral nitrogen and C-terminal asparagine linked to nebularin-5'-monophosphate through a trimethylene bridge. MccC51 is produced by *E. coli* extract and inhibits the growth of a number of bacteria. The antibiotic is active against gram-negative bacteria of various taxonomic groups, as well as some gram-positive bacteria. As in most ribosomally-synthesized bacterial peptides, the N-terminus of the peptide moiety of McC bears a formyl cap.

Various McC derivatives were obtained, that lack either the formyl group (for example, the deformedylated McC, 4), the aminopropyl ester moiety (2), or both (3, Figure 31). McC derivatives lacking a formyl group (4, Figure 32) exhibit much lower activity than native McC (1), and a specific deformedylase is required to start McC processing. It was shown in vitro that deformedylation of the first methionine residue is the limiting step in McC processing [96,97,102]. Chemical structure of different McC derivatives shown in Figure 32: (1) Native McC; (2) obtained from cells harboring a plasmid with either disrupted *mccD* or double-disrupted *mccD* and *mccE*; (3) obtained from mutant cells lacking PepA, B, and N, and harboring a plasmid with disrupted *mccD*; and (4) deformedylated McC, obtained from mutant cells lacking Pep A, B, and N [97].

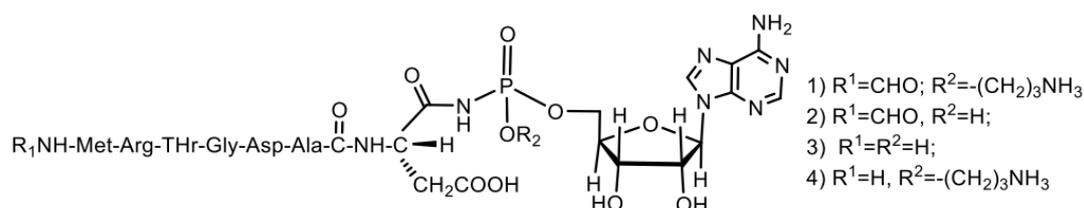


Figure 32. McC derivatives.

Microcins (Mc) are peptide antibiotics isolated from gram-negative bacteria that are similar to bacteriocins from various sources. They range from linear unmodified peptides to structures that undergo extensive post-translational modification, resulting in significant chemical diversity. Mc are produced by enterobacteria [97–101], and have potent antibacterial activity against closely related species. Typical gene clusters encoding a microcin precursor, are located either on plasmids or on the chromosome [102]. Unlike most antibiotics of microbial origin, which are synthesized by multimodular enzymes that represent peptide synthetases, Mc are synthesized by means of ribosomes and then undergo enzymatic modification. Mc form a class of potent antibacterial peptides. At the moment, fourteen microcins have been registered, of which seven have been isolated and characterized. Since aminoacyladenylates generally poorly penetrate into bacterial cells, natural compounds that mimic aminoacyl-adenylate intermediates often employ a “Trojan-horse” strategy, wherein the active component is conjugated with a specialized module that facilitates its active transport into bacterial cell. The transport module is subsequently removed, releasing the inhibitor inside the cell. The naturally occurring aminoacyladenylate-based antibiotics include, for example: Aspartyl-adenylate synthesized by aspartyl-tRNA synthetase (AspRS); Leucyl-adenylate synthesized by leucil-tRNA synthetase (LeuRS); Seryl-adenylate synthesized by seryl-tRNA synthetase (SerRS) (See Figure 33) [102].

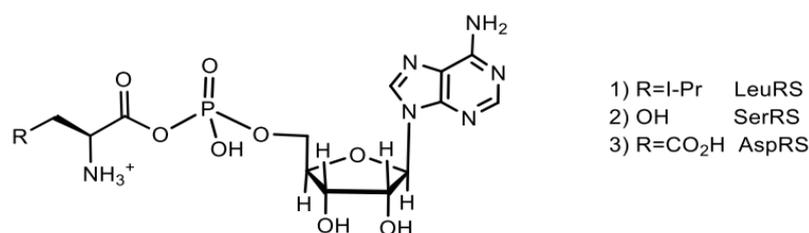


Figure 33. Examples of naturally occurring aminoacyladenylate-based antibiotics.

Antibiotics EM 2487 and 1100-50 were isolated from *Streptomyces sp.* Mer-2487 and *Streptomyces lavendulae* SANK 64297, respectively [103–108]. Amidophosphate 1100-50 was isolated from the culture of the SANK 64297 strain. The related compound EM 2487 also isolated from *Streptomyces lavendulae* has anti-HIV activity due to the inhibitory activity of Tat protein biosynthesis at the transcriptional level. This compound has an inhibitory effect on HIV-1 replication in chronically infected cells, as well as in acutely infected

cells [103–108]. The anti-nematode activity of compound 1100-50 may be due to inhibition of RNA synthesis. Antibiotics 1100-50 and EM2487 differ in their nucleoside substructural composition. EM2487 contains a uridine ring; while 1100-50 includes cytidine. In addition, EM2487 contains an N-methylated hydroxylamine group, while the hydroxylamine group (1100-50) is not N-methylated. Both EM2487 and 1000-50 were tested as potential agents against HIV and non-mitocide, respectively. The third known phosphoramidate pyrimidine nucleotide antibiotic HC 62 was isolated from *Bacillus sp.* HC-62 (Figure 34) [106].

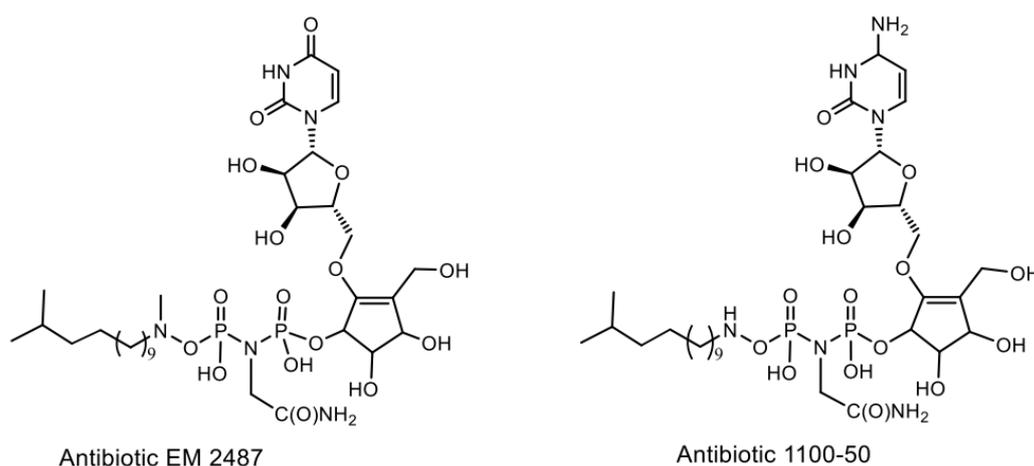


Figure 34. Phosphoramidate antibiotics.

N-phosphorylated proteins and peptides. “Reversible phosphorylation of protein side chains regulates almost all aspects of cell life” (Philip Cohen, 2002 [107]). Phosphorylation and dephosphorylation, catalyzed by protein kinases and protein phosphatases, can alter protein function in almost every possible way. For example, by increasing or decreasing its biological activity [108]. The simplicity, flexibility, and reversibility of phosphorylation, combined with the availability of ATP as a phosphoryl donor, explains its choice as the most general regulatory device adopted by eukaryotic cells. It is believed that 30% of the proteins encoded by the human genome contain covalently bound phosphate, and abnormal phosphorylation is currently recognized as a cause or consequence of many human diseases. Phosphorylation of amino acids is a widespread way for regulating the activity of key cell proteins, including enzymes and proteins of signaling pathways [108–111]. The protein phosphorylation is understood to mean the attachment of a phosphate group through a phosphoether bond (O-phosphorylation) to the hydroxyl group of the side chain of serine, threonine or tyrosine residue, with ATP being the phosphate donor. In the overwhelming majority of cases, phosphorylation occurs precisely at these three amino acid residues. The introduction of a phosphoric acid residue into a protein molecule, as a rule, changes its properties. This is due to the chemical nature of the phosphate group, which can form hydrogen bonds and electrostatic interactions with the components of the protein molecule. As a result, the spatial structure of the protein can change and, as a result, its activity and ability to bind with other molecules [109–111]. Phosphorylation of amino acid residues (Asp, Glu, forming an anhydride P-O bond) and basic (His, Arg, Lys, forming a P-N bond, namely N-phosphorylation) amino acid residues usually generates high-energy molecules that are intermediates for enzymatic catalysis [107]. Arginine is one of the main amino acid residues involving into the formation of protein-DNA interfaces (Figure 35).

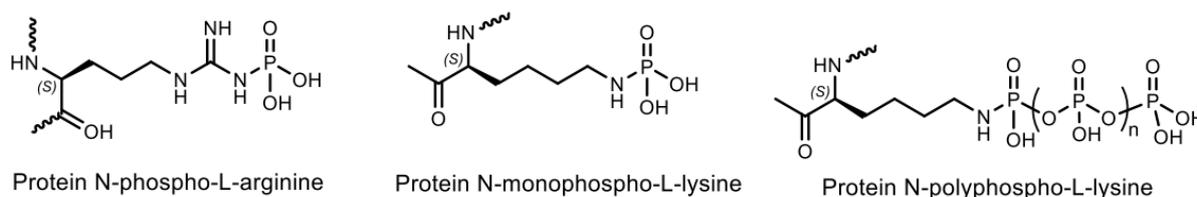


Figure 35. Protein-DNA intermediates.

N1-phosphohistidine (π -phosphohistidine) and N3-phosphohistidine (τ -phosphohistidine) have been found among prokaryotes, lower eukaryotes, and mammals [112]. Phosphohistidine has been identified as an enzyme intermediate in many biochemical reactions and plays a functional role in many regulatory pathways. In contrast to the phosphoester bond of its analogs—phosphoserine, phosphothreonine and phosphotyrosine, the phosphoramidate P-N bond of phosphohistidine is unstable in the presence of acids [113]. Several pathways of origin and co-evolution of nucleic acids and proteins, including amino acids phosphorylated at the N-terminus, have also been proposed as common prebiotic chemical building blocks for peptides and nucleic acids [114,115] (Figure 36).

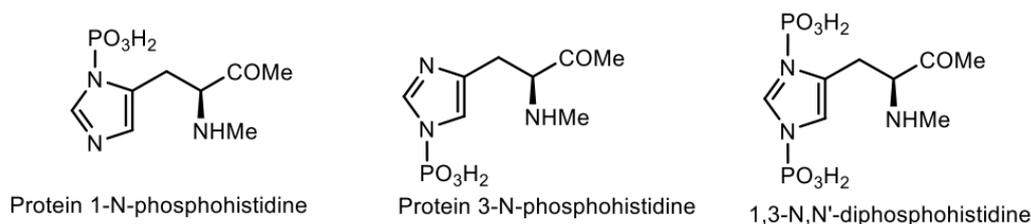


Figure 36. Examples of N-phosphohistidine.

Several natural phosphorus-sulfur bond-containing (thionophosphates and thiophosphates, respectively) are known, for example, S-phosphocysteine in several proteins and bacterial phosphorothioate modification of DNA. Phosphorus-containing phosphorothione hydrazone was isolated from the *Karenia brevis* dinoflagellate found off the coast of Florida and identified as an ichthyotoxin [116]. The second known small molecule of natural phosphorothione is a dimerized form of phosphorothione. This compound was isolated from the marine fungus *Lignincola laevis* and also exhibits cytotoxic properties (Figure 37) [117].

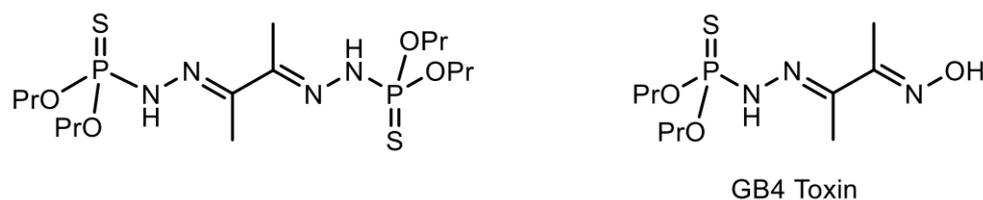


Figure 37. Natural phosphorus-sulfur bond containing phosphates.

Bacterial clusters of *dnd* genes have been found to incorporate sulfur into the DNA backbone as a stereospecific modification of phosphorothioate. Phosphorothioation occurs in phylogenetically diverse bacteria with different specific sequences and variable abundance in different bacterial genomes [118]. The *dnd* gene products have been found to incorporate sulfur into the DNA backbone. Since the initial observation of *Streptomyces lividans*, the presence of *dnd* genes has been established in dozens of different bacteria and archaea [119]. Synthetic phosphorothioate internucleotide bonds, in which non-bridging oxygen is replaced by a sulfur atom, have similar physical and chemical properties to phosphodiester, but give DNA/RNA increased resistance to nucleases. It was found that the modification of phosphorothioates occurs in nature in bacteria selectively in sequence

and specific for configuration (R_P). The widespread use of dnd systems is thought to be due to extensive horizontal gene transfer (Figure 38) [120–122].

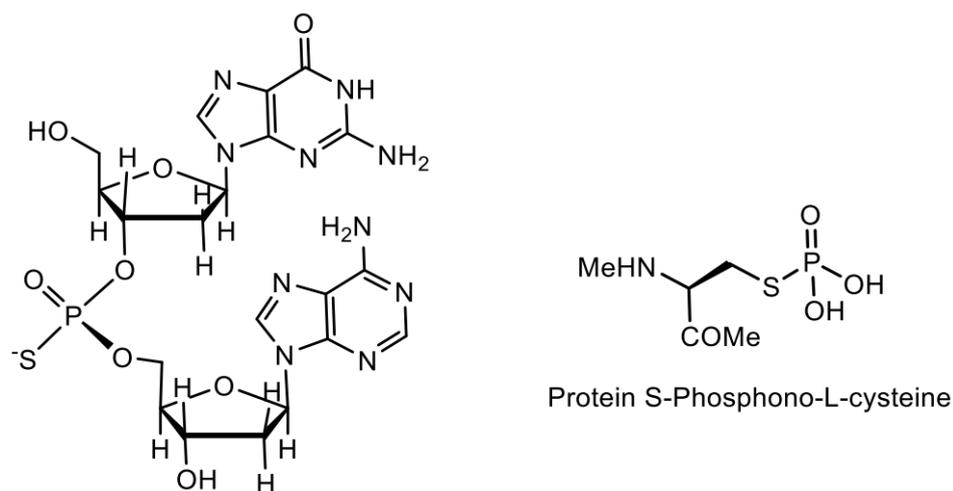


Figure 38. Phosphorothioate modified oligonucleotides.

6. Natural Organophosphorus Compounds with P-C Bond

Natural phosphonates are represented by low molecular weight metabolites and phosphorylated macromolecules, such as lipids, polysaccharides, and glycoproteins [123]. The widespread use of phosphonates is illustrated by the fact that in some organisms, PC compounds form the overwhelming majority of cellular phosphorus-containing molecules. For example, eggs from the freshwater snail *Helisoma* sp. contain 95% phosphonoglycans [123–125]. Aminophosphonic acids [126–129] and hydroxyphosphonic acids [130,131] are widely known, many of which have been studied in detail and found practical application [126]. These compounds are analogs of natural amino and hydroxycarboxylic acids, in which the planar carboxyl group is replaced by a tetrahedral phosphonic acid fragment. Due to the wide spectrum of biological activity, these classes of organophosphorus compounds have received considerable attention in recent decades. Some of them have found commercial applications in agriculture and medicine. For example, aminophosphonic acids and their conjugates with peptides have antibacterial, antitumor, antiviral and antifungal effects [126]. Some of their representatives have shown themselves as herbicides and plant growth regulators. The most well-known natural phosphonates are shown in Figure 39: fosfomycin (phosphonomycin) [132], bialaphos [SF-1293] [133], phosphinothricin tripeptide (PTT) [134], phosalacine [135], trialaphos [136], dehydrophos (A53868) [137], fosmidomycin [138], plumbemycins [139], SF-2312 [140] and fosfonochlorin [141,142]. The most part of compounds shown in Figure 23 were isolated from bacteria, the antibiotic phosphonochlorin was found in fungal strains isolated from soil: *Fusarium avenaceum*, *Fusarium oxysporum*, *Fusarium tricinctum*, and *Talaromyces flavus* [141]. It is moderately active against some species of gram-negative bacteria, and its synergistic effect with glucose-6-phosphate has been observed on *Staphylococcus aureus* and *Escherichia coli*. Cyanophos, which exhibits pesticide properties, was found in *Streptomyces regensis* [142].

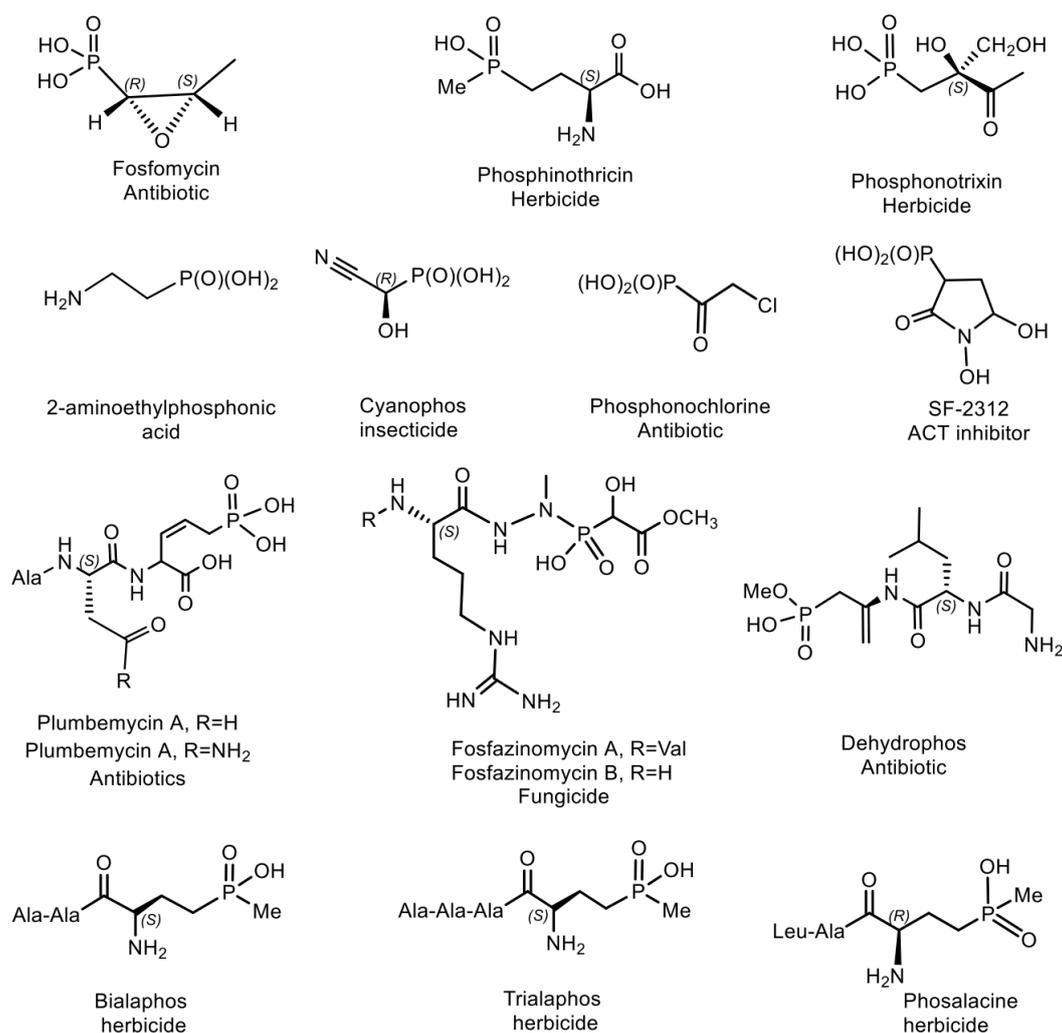


Figure 39. The most famous natural phosphonates.

Phosphonic acids of natural origin. Fosfomycin is a structural analogue of phosphoenolpyruvate; it competes with the enzyme N-acetyl-D-glucosamino-3-o-enolpyruvyl transferase. The result is a specific, selective and irreversible inhibition of this enzyme, which ensures the absence of cross-resistance with other classes of antibiotics and the possibility of synergy with other antibiotics. Fosfomycin is used for the treatment of diseases of urinary tract and prostatitis; it is active as an antibiotic against gram-positive and gram-negative bacteria MDR and XDR. Fosmidomycin and FR-900098 have been suggested as drugs against *Plasmodium*, the causative agent of malaria [138]. The *Streptomyces* bacteria produces a tripeptide which was called bialaphos. It consists of two alanine residues and a unique amino acid “phosphinothricin”. The phosphinothricin (Glyphosate) was first synthesized as a racemate, which is used as an active ingredient in several commercial herbicidal formulations: L-Phosphinothricin is a broad-spectrum herbicide, which is an analogue of glutamate and works by inhibiting glutamine synthetase [134]. Aminoethylphosphonic acid (ciliatrin) is the most abundant phosphonate present in lower organisms. Ciliatrin and its derivatives have been studied in detail [143–145]. The phosphonopyruvate is a key substrate in the synthesis of many naturally occurring phosphonates: ciliatrin, phosphonoalanine, (R)-2-amino-1-hydroxyethylphosphonic acid, phosphonoacetaldehyde, phosphonomethylmalic acid and 2-keto-4-hydroxy-5-phosphonopentanoic acid [146,147]. After the discovery of natural C-P-phosphonates, such as ciliatrin, phosphonotricin, fosfomycin, etc., the mechanism of C-P-bond formation in biological systems aroused considerable interest, and a number of studies were devoted to this problem (Figure 40) [146–148].

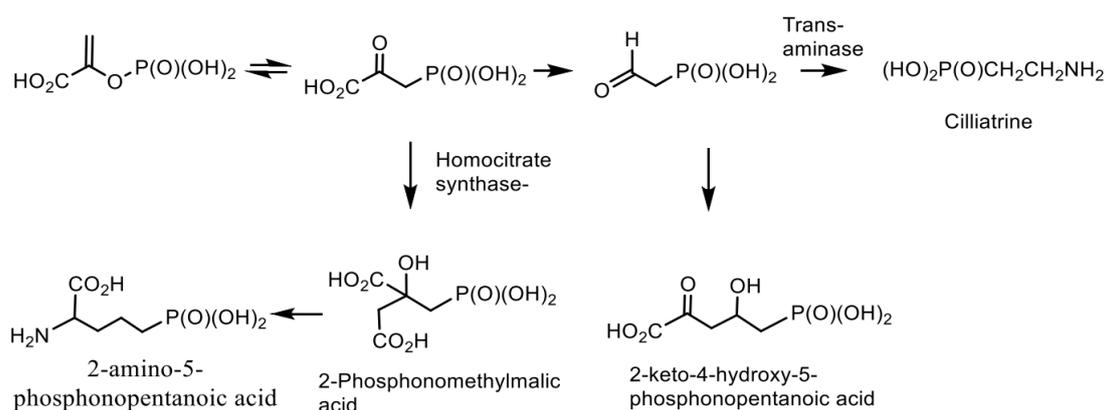


Figure 40. Overview of P-C phosphonate biosynthesis.

It was found that the main stage of the reaction resulting in the formation of phosphonate is the rearrangement of phosphoenolpyruvate (PEP) into phosphonopyruvate [148–150], catalyzed by the enzymes responsible for the formation of the P-C bond. The synthesis of phosphonate antibiotics starting from phosphoenolpyruvate is shown in the Figure 25 for the synthesis of phosphonomethylmalic acid and 2-keto-4-hydroxy-5-phosphonopentanoic acid. Following this figure, the fosfomicin is formed as a result of the biocatalytic rearrangement of phosphoenolpyruvate into phosphonopyruvate under the action of PEP-phosphomutase (EC 6.4.2.9), which was isolated from the *Tetrahymena pyriformis* and *Streptomyces hygroscopicus* [150]. As a result of intramolecular rearrangement of the acid PEPR then it is decarboxylated with the formation of phosphonoacetaldehyde and, through a series of successive steps, is converted to (1*R*, 2*S*)-phosphomycin [148,149]. Using ^{18}O labels, it was proved that the *Tetrahymena pyriformis* catalyzed transition of the phosphorus group from the oxygen atom to the carbon atom in enolpyruvate. The rearrangement represents an intramolecular process proceeding with the retention of absolute configuration at the phosphorus atom (Figure 41) [151,152].

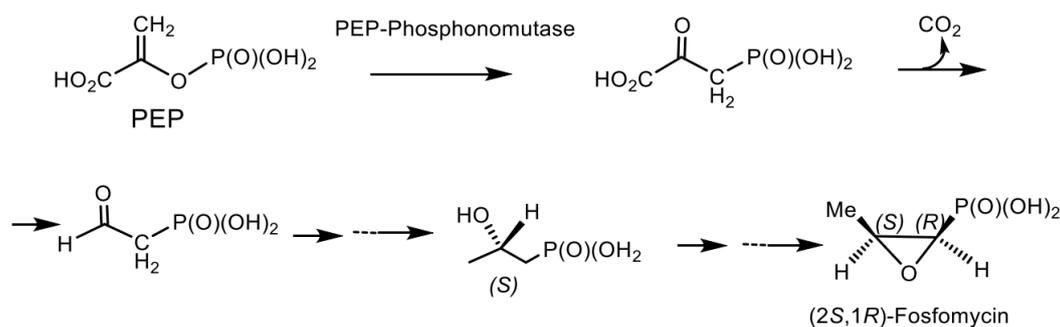


Figure 41. Synthesis of (2*S*,1*R*)-Fosfomicin starting from phosphoenolpyruvate.

The formation of the herbicide bialaphos, which is produced by *Streptomyces hygroscopicus* SF-1293, proceeds by a similar mechanism (Figure 26). Biocatalysis with the carboxyphosphoenolpyruvate phosphomutase isolated from *Tetrahymena piriformis* enzyme, initiated the condensation of phosphoenolpyruvate with phosphonoformate and the rearrangement of phosphoenolpyruvate into phosphonopyruvate with the formation of a P-C bond. The reaction catalyzed by carboxyphosphoenolpyruvate phosphomutase proceeded with retention of absolute configuration at the phosphorus atom [143] (Figure 42). The biosynthesis of (*R*)-2-amino-1-hydroxyethyl phosphinic acid was carried out by enantioselective hydroxylation of 2-aminoethylphosphinic acid by the *Acanthamoeba castellanii* enzyme (Figure 43) [148].

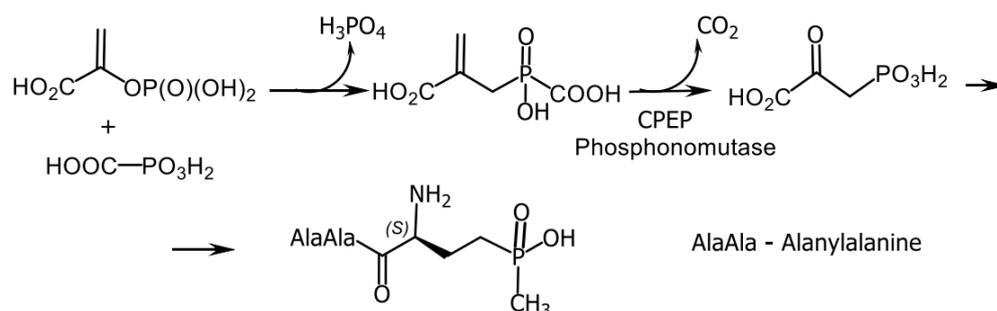


Figure 42. Formation of herbicide Bialaphos.

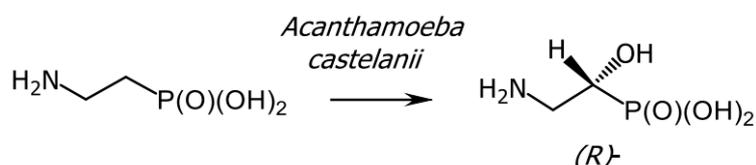


Figure 43. Biosynthesis of (2-amino-1-hydroxyethyl) phosphonic acid.

The biocatalytic epoxidation of (S)-2-hydroxyalkylphosphonic acids to epoxides, analogs of fosfomycin, in the presence of enzyme *Streptomyces fradiae* was investigated [152]. The replacement of the hydrogen atom at the carbon atom of deuterated 2-hydroxypropylphosphonic acid, catalyzed by *Streptomyces fradiae*, and the formation of epoxides proceeded stereospecifically [132,153–155]. The formation of cis-epoxides proceeded with the inversion of absolute configuration, while trans-epoxides were obtained with the retention of configuration. Deuterated (1S,2S)- and (1R,2S)-2-hydroxy-1-D-propylphosphonic acid were synthesized from (1S,2S)-2-benzyloxy-1-D-propanol, which in turn, was obtained by catalytic reduction of the corresponding aldehyde with horse liver alcohol dehydrogenase (Figure 44) [155,156].

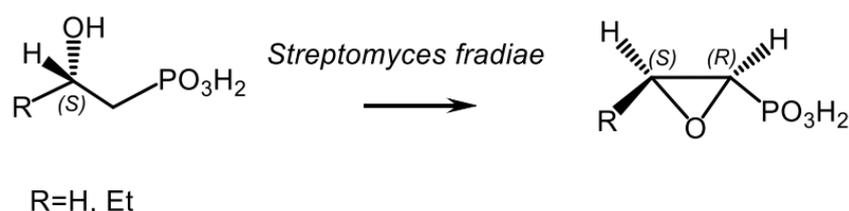


Figure 44. Biocatalytic epoxidation of (S)-2-hydroxyalkylphosphonic acids to epoxides.

A similar biocatalytic conversion of hydroxyphosphonate to fosfomycin in the presence of (S)-2-hydroxypropylphosphonic acid epoxidase (*Ps*-HppE) isolated from phytopathogenic bacteria *Pseudomonas syringae* was reported [157,158]. The *Ps*-HppE catalyzed the epoxidation of (S)-hydroxypropylphosphonic acid with formation of fosfomycin, while the oxidation of (R)-hydroxyphenylphosphonic acid under the same conditions gave 2-oxopropylphosphonic acid (Figure 45).

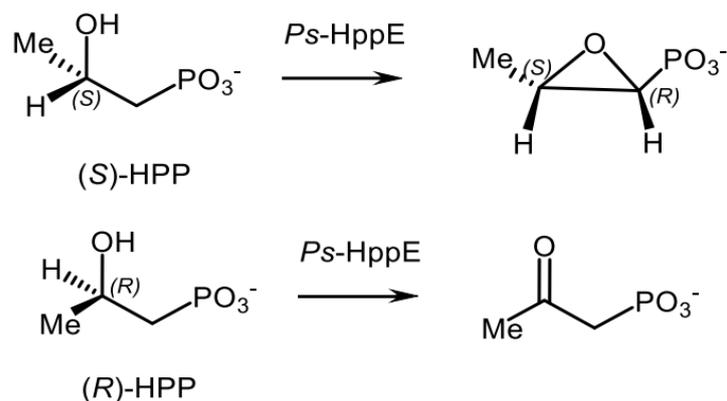


Figure 45. Biocatalytic conversion of hydroxyphosphonate to fosfomycin.

Biocatalytic acylation of (*S/R*)-hydroxyphosphonate with vinyl acetate was carried out in isopropyl ether in the presence of lipase from *Pseudomonas syringae*. The reaction was complete in 5 days at 30 °C. Chromatographic separation on silica gel, followed by deacetylation afforded optically active (*R*)-hydroxyphosphonate in yield 46%, which was then converted to a (*S,R*)-deuterated analogue of fosfomycin. The isotope label experiment showed that the epoxide oxygen atom of (*S,R*)-fosfomycin is derived from the hydroxyl group of hydroxyphosphonate (Figure 46) [157].

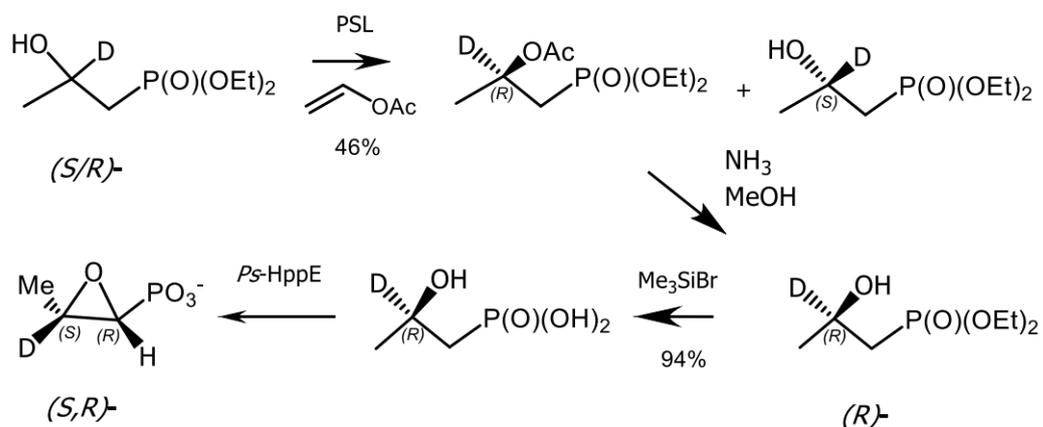


Figure 46. Synthesis of a deuterated analog of (*S,R*)-phosphomycin.

Important from the point of view of practical application are aminophosphonic antibiotics with an amino group at the gamma position relative to the phosphonic functional group, namely fosmidomycin, and its derivatives FR900098, FR-33289 and FR32863, isolated from *Streptomyces lavendulae*, as well as cyclic SF2312, isolated from *Micromonospora* sp. [159–161]. Glyphosate (Roundup) is a widely used herbicide that inhibits 5-enoylpyruvylshikimate-3-phosphate synthase as a phosphoenolpyruvate substrate mimic. Tenofivir is used as a drug for the treatment of HIV and hepatitis B. Zoledronate and phosphonofornate (Foscarnet) are analogs of pyrophosphate. They are used to treat osteoporosis and herpes. Zoledronate also has antitumor activity due to its ability to target human dimethylallylpyrophosphate farnesylpyrophosphate synthase (Figure 47).

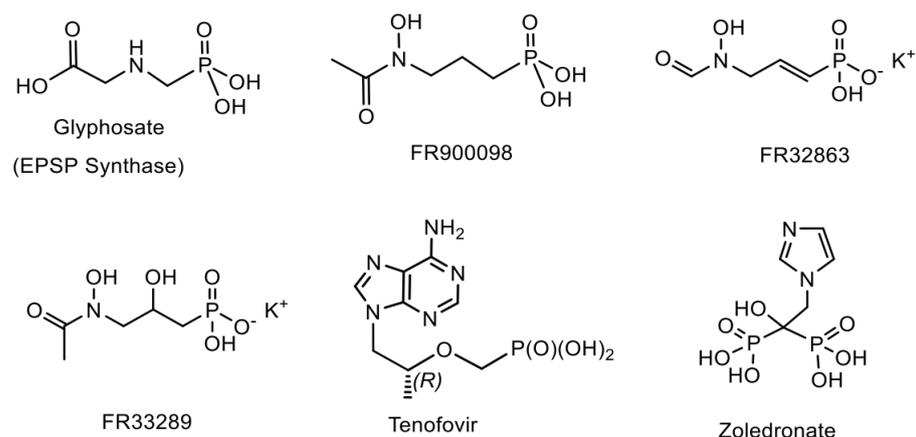


Figure 47. Biologically active phosphonates.

Fosmidomycin and its homologues are potent inhibitors of 1-deoxy-D-xylulose-5-phosphate reductoisomerase, an important enzyme in the nonmevalonate pathway of isoprenoid biosynthesis, active against a wide range of enterobacteria. 2-Acyloxyethylphosphonate, biosurfactant of a lipid nature, was isolated from the aquatic flowers of *Aphanizomenon flosaquae* [162]. Phosphinotricin is a non-protein amino acid that has been found as a component of the PT-Ala-Ala tripeptide (Bialaphos) in *Streptomyces viridochromogenes* DSM 40736 and *Streptomyces hygroscopicus* ATCC 21705 [163,164]. Phosphinothricin is an active inhibitor of glutamine synthetase [164–167]. The inhibition of the glutamine synthetase in plants determines its herbicidal activity as ammonium salt (ammonium glutamate). It has been reported that other glutamine synthetase inhibitors are promising for the treatment of tuberculosis and neurological diseases [165]. The D- and L-enantiomers of phosphinothricin (2-amino-4-hydroxymethylphosphinyl-butanoic acid) and its derivative were synthesized by bioenzymatic methods [168]. Acetylated D, L-3-aminopyrrolidin-2-one was converted to acyclic phosphinate by reaction with ethylmethylphosphinate. Sequential enzymatic hydrolysis with phosphodiesterase, acylase, and glutaminase through the formation of intermediates led to phosphinothricin, which after treatment with glutaminase, was converted into an ester of azaphospholidinocarboxylic acid, and then into cyclic phosphonic acid. The last stage also included the formation of an L-phosphinothricin derivative under the action of α -chymotrypsin (Figure 48).

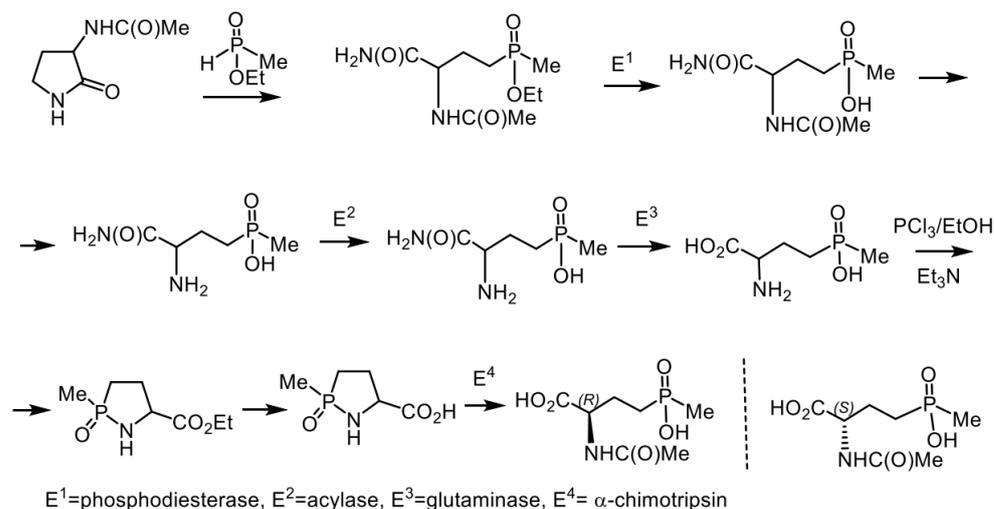


Figure 48. Enzymatic synthesis of D- and L-stereoisomers of phosphinotricin.

Phosphonotrixin was first isolated from the microorganism *Saccharotrix* sp. ST-888. This secondary metabolite has attracted interest primarily because of its antibiotic and herbicidal properties, as well as its unique structure containing a C–P bond on the isoprene group. As a result, several methods have been developed for the synthesis of this compound. The formation of phosphonotrixin by rearrangement of phosphoenolpyruvate (PEP) to phosphonopyruvate is shown in Figure 49. The biosynthesis of phosphonates begins with the rearrangement of phosphoenolpyruvate to phosphonopyruvate as a result of a reaction catalyzed by phosphoenolpyruvate mutase. In this equilibrium process, the formation of phosphoenolpyruvate is thermodynamically more favorable, at least 500 times. As a result, phosphonopyruvate is converted into metabolically preferred compounds. Therefore, it is a key substrate in the synthesis of phosphonotrixin [130,142].

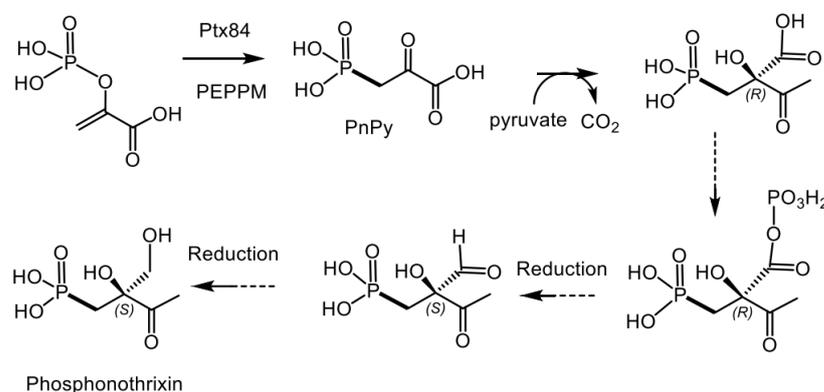


Figure 49. The enzymatic synthesis of Phosphonotrixin.

The total synthesis of phosphonotrixin (PTX) was developed on the basis of commercially available methyl 3-hydroxy-2-methylene butyrate, the reaction of which with diethyl chlorophosphite in the presence of triethylamine gave E-allyl phosphonate in 60% yield. Vicinal dihydroxylation of the diol, accompanied by the oxidation of secondary alcohol, led to the formation of protected phosphonotrixin in 80% yield. After removal of the protective groups, free RTX was obtained in a total 24% yield (Figure 50) [132,168,169].

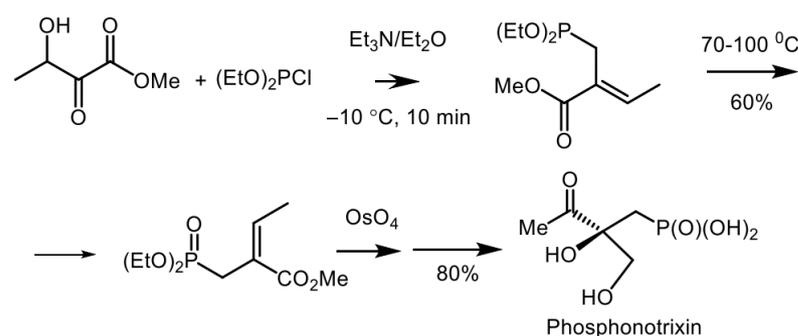


Figure 50. Synthesis of phosphonotrixin.

Asymmetric epoxidation of alkene phosphonates was used in the synthesis of various hydroxyphosphonates of natural origin. For example, the synthesis of phosphonotrixin was developed starting from bromomethylallyl ketone, which was first converted into allyl phosphonate using the Michaelis-Becker reaction and then allylphosphonate via the *vic*-asymmetric dihydroxylation with osmium tetroxide according to Sharpless gave the dihydroxyphosphonate. The prepared dihydroxyphosphonate was converted into phosphonotrixine, as shown in the Figure 51 [168–171].

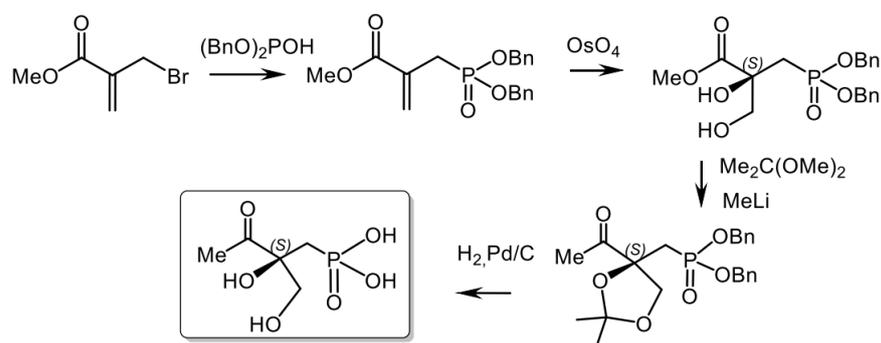
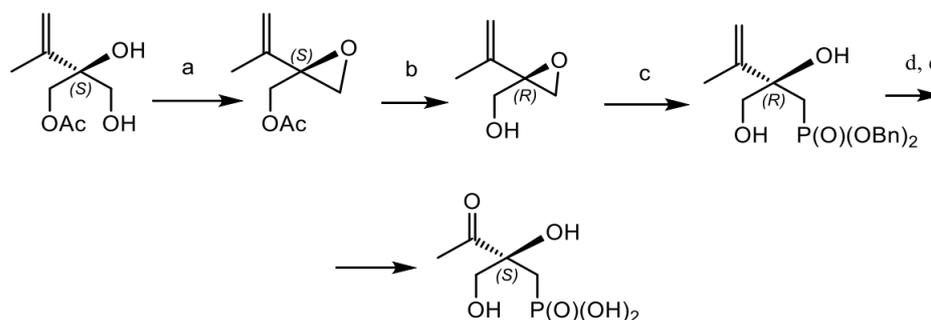


Figure 51. Asymmetric synthesis of phosphonothrixin.

The enantioselective synthesis of (*S*)-phosphonothrixin (*ee* 93%) in nine steps and 12% overall yield was developed starting from 1,3-dihydroxyacetone. The key reaction was the enzymatic desymmetrization of 2-isopropenylpropane-1,2,3-triol, which was resolved with vinyl acetate in the presence of porcine pancreatic lipase with formation of chiral (*S*)-monoester in good yield (88%) and with high enantiomeric excess 93%. Epoxy-alcohol was transformed into phosphonate, thus completing a formal synthesis of natural (*S*)-(–)-phosphothrixin. The chemical correlation confirmed the absolute configuration of dibenzyl ether phosphonate to be (*R*), which was converted into (*S*)-configuration at the newly created stereogenic centre (Figure 52) [170].



Reagents and conditions: (a) TsCl, Et₃N, DMAP, CH₂Cl₂, 71%; (b) *Candida antarctica* lipase, EtOH, Et₂O, 90%; (c) CIMg-PO(OBn)₂ (3.0 eq.) in Et₂O, -50–0 °C, 40%; (d) O₃ in CH₂Cl₂, -78 °C, 79%; (e) H₂-Pd(C) in MeOH-H₂O

Figure 52. Determination of (*S*)-phosphonothrixin configuration by chemical correlation.

Two unprecedented phosphorus-containing iodinated polyacetylenes, phosphoiodyns A and B (12), were isolated from a Korean marine sponge *Placospongia* sp.

Plakotilen A showing inhibitory activity against RANKL-induced differentiated osteoclasts at 10 μM was isolated from the marine sponge *Placospongia* sp. From the same sponge, *Placospongia* sp. phosphorus derivatives of *Plakotilen A* and B, phosphoiodynes A and B, containing iodinated polyacetylenes were isolated, [172]. Phosphoiodyne A was found to exhibit potent agonist activity at the peroxisome proliferator-activated delta receptor (hPPAR8), which is believed to function as an integrator of transcriptional repression and nuclear receptor signaling [164]. This compound, as well as its analogs, demonstrate significant neuroprotective activity in a cell model *in vitro*, indicating that such phosphonates may be an effective new basis for the development of therapeutic agents for the treatment of neurodegenerative disorders (Figure 53) [173].

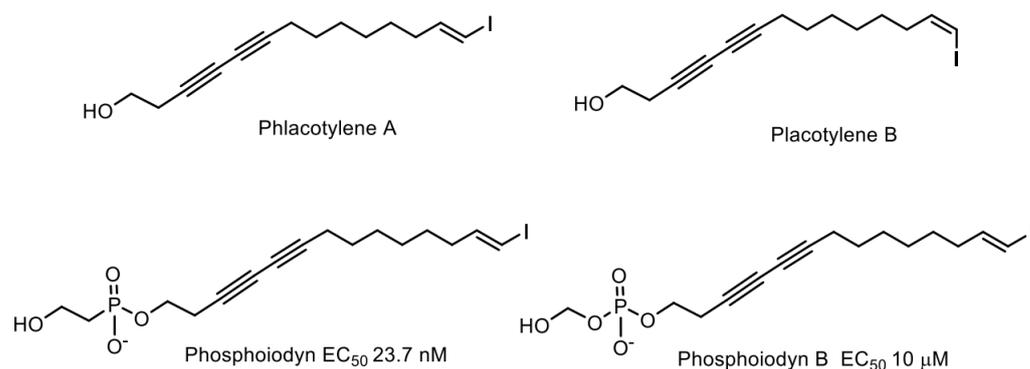
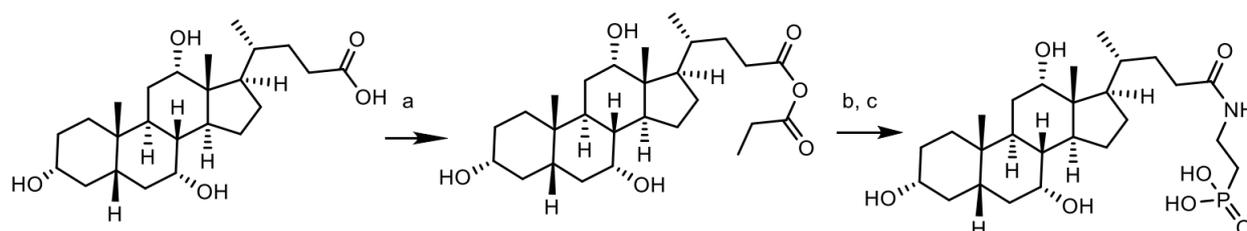


Figure 53. Phosphorus derivatives of Plakotilen A and B.

Ciliatocholic acid has been found in the bile of the gallbladder in cattle. The structure of ciliatocholic acid was confirmed by independent synthesis from choline and ciliatin [174]. Cholic acid was dissolved in a mixture of tributylamine and dioxane, then treated with chloroethyl formate and a solution of ciliatin in aqueous alkali. The product was recrystallized from ethanol-ethyl acetate. As a result, ciliatocholic acid was obtained in a satisfactory yield. This compound was further purified by preparative thin layer chromatography and confirmed to be ciliatocholic acid by phosphorus content and chromatographic performance. Thus, it was concluded that bovine gallbladder bile contains a small amount of ciliatocholic acid (Figure 54) [174].



a) $\text{Bu}_3\text{N}/\text{dioxane}$; EtOCOCI ; b) $\text{NaOH}/\text{H}_2\text{NCH}_2\text{CH}_2\text{P}(\text{O})(\text{OH})_2$; HCl ; c) Crystallization from ethanol/ethyl acetate

Figure 54. Reaction system for ciliatocholic acid synthesis.

Two nucleotide antibiotics, phosphadecin and phosphocytocin, were found in the extract of the *Pseudomonas viridiflava* PK-5 and *Pseudomonas fluorescens* PK-52 cultures, respectively. These antibiotics were purified by column chromatography using adsorption, gel filtration and ion exchange resins. These antibiotics were enzymatically and chemically hydrolyzed to form fosfomycin and a new antibiotic, phosphoxacin, which are also formed in culture filtrates. They showed antibacterial activity against gram-positive and gram-negative bacteria (Figure 55) [175].

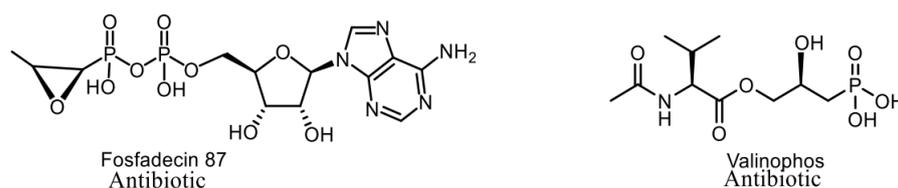


Figure 55. Nucleotide antibiotics—phosphadecin and phosphocytocin.

Phosphonolipids. Lipids containing aminophosphonates are called phosphonolipids [176]. There are three classes of these compounds—Glycerophosphonolipids and Sphingophosphonolipids and Sphingophosphoglycolipids (typical structures are shown in the Figure 56). Sphingolipids are a class of lipids related to aliphatic amino alcohol

derivatives. Glycerophospholipids or phosphoglycerides are glycerol-based phospholipids. Sphingophosphonoglycolipids, a subtype of glycolipids containing the amino alcohol sphingosine, are known and well-studied. The first evidence for the existence of phosphonolipids was obtained in 1963 by Rouser et al. [177] when analyzing the sea anemone *Anthropleura elegissima*. This new sphingolipid has previously been identified as acyl-sphingosyl-1-(2-aminoethyl) phosphonate (ceramide aminoethyl phosphonate, CAEPn). Subsequent studies have shown that CAEPn is widespread in many species of freshwater and marine bivalve molluscs, snails, cephalopods as well as in various crustaceans, plant seeds and bacteria. Phosphonolipids have been found in fractions of glycocerebrosides (lipids) of many lower marine organisms, bacterial exopolysaccharides. The amount of phosphonolipids in organisms varies depending on the species, tissue, or the location of the cell. For example, vertebrates have sphingophosphonolipids as components of sphingomyelin in neural tissue, whereas at invertebrates often contain high levels of these lipids as components of the outer membrane (Figure 56) [176–178].

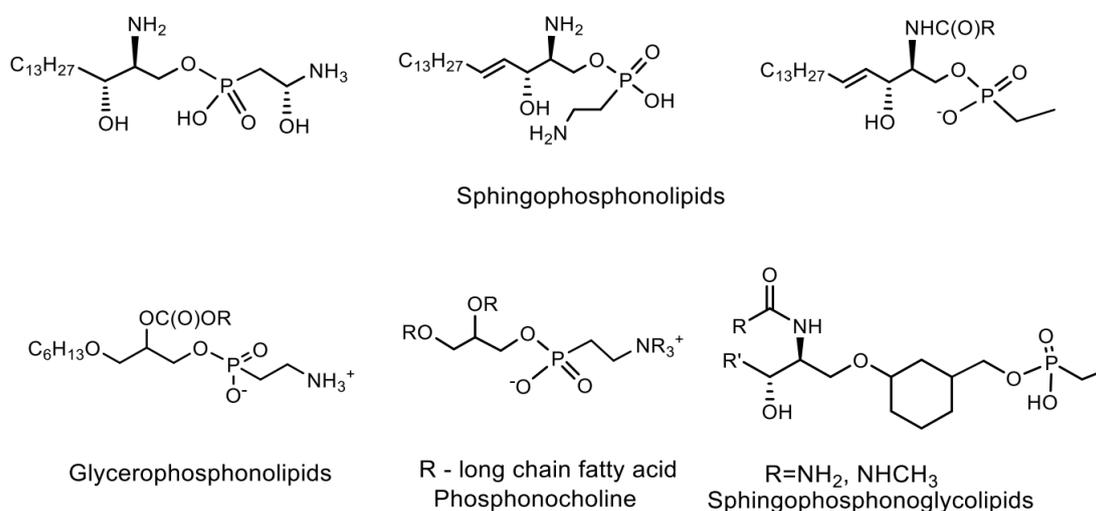


Figure 56. Representatives of phosphonolipids.

Phosphonopeptides of natural origin. Phosphonopeptides containing a P–C bond, like phosphopeptides, with a P–O–C bond, are relatively common substances in nature [179]. Currently, both phosphonopeptides isolated from natural sources and a significant amount of synthetic phosphonopeptides with a wide spectrum of biological activity are known. The peptides are thought to enhance cellular uptake through peptide permeases, masking the phosphonate antibiotic in the Trojan horse peptide, which is then hydrolyzed inside the cell by peptidases to release the phosphonate-active fragment. A typical representative is alaphosphin (or alafosfalin—a dipeptide consisting of alanine and 1-aminoethylphosphonic acid) (Figure 57).

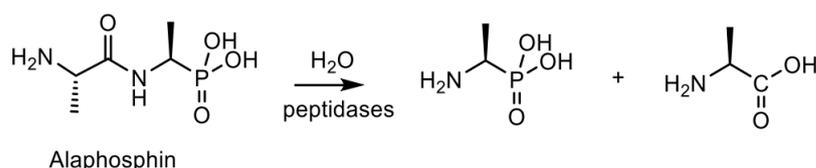


Figure 57. Hydrolytic treatment of alaphosphin peptides to obtain an alanine analog.

Dehydrophos is an antibiotic isolated from *Streptomyces luridus*, which is effective in vivo against Salmonella-infected chickens and has a broad spectrum of in vitro activity. Dehydrophos consists of a glycineleucin dipeptide bound to an O-methylated aminovinylphosphonate, its dehydrophosphorylation proceeds analogously to the similar in structure alaphosphine peptide and the Trojan horse peptide dehydrophosphine is

imported and cleaved by peptide permeases and peptidases, respectively, to release the alanine racemase inhibitor within the cell (Figure 58) [179,180].

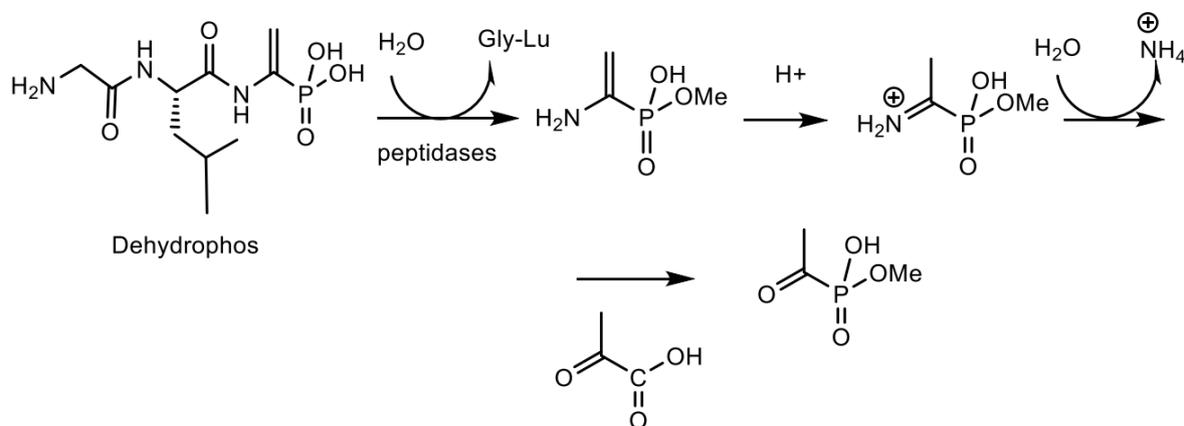


Figure 58. Hydrolytic treatment of dehydrophos peptides to release pyruvate analog.

In recent years, a number of P-C antibiotics, possessing antifungal activity: rhizocticins [139,180], phosphonocystoximic acid [181], plumbemycins [139,182], phosphacetamycin [183], have been isolated from *Bacillus subtilis* and *Streptomyces plumbeus*. They represent di- and tripeptides containing the C-terminal (Z)-L-2-amino-5-phosphono-3-pentenoic acid, a phosphonotreonine mimetic [184], reminiscent of dehydrophos as a broad-spectrum antibiotic that acts against infection of *Salmonella* [185]. Rhizocticin A, the main component of the antifungal, hydrophilic phosphono-oligopeptides *Bacillus subtilis* ATCC 6633, was used for sensitivity testing in experiments with the molecular mechanism of antibiotic action (Figure 59) [182].

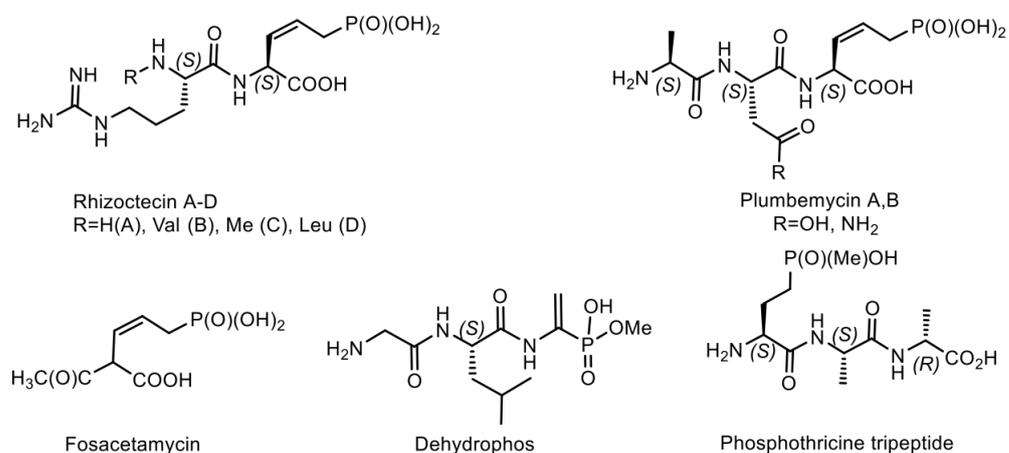


Figure 59. Antibiotic phosphonopeptides.

Rhizocticins and plumbemycins are natural phosphonate antibiotics produced by the bacterial strains *Bacillus subtilis* ATCC 6633 and *Streptomyces plumbeus*, respectively. The non-proteinogenic (S,Z)-2-amino-5-phosphonopent-3-enoic acid [(S,Z)-APPA] were used for the synthesis of Rhizocticin A and Plumbemycin A. The (S,Z)-APPA was synthesized via the Still–Gennari olefination starting from Garner’s aldehyde. The Michaelis–Arbuzov reaction was used to form a P-C bond. Oligopeptides were prepared using liquid phase peptide synthesis (LPPS) and were tested against selected bacteria and fungi [139]. Structurally, plumbemycins A and B, the new antimetabolites from *Streptomyces plumbeus* that antagonize L-threonine have been assigned to L-alanyl-L-aspartyl-D-2-amino-5-phosphono-3-cis-pentenoic acid and L-alanyl-L-asparaginyl-D-2-amino-5-phosphono-3-cis-pentenoic acid, respectively. Rhizocticins are phosphonate oligopeptide antibiotics containing a

C-terminal non-proteinogenic amino acid (APPA). Rhizoctin B was heterologously produced in the non-producing strain *Bacillus subtilis*. Rhizoctin biosynthesis proceeds on the basis of bioinformatic analysis of Rhi genes. One of the steps in APPA biosynthesis is the aldol reaction between phosphonoacetaldehyde and oxaloacetate, catalyzed by the aldolase homologue RhiG. Recombinant RhiG was obtained and the product of enzymatic transformation in vitro was characterized (Figure 60) [139,182–185].

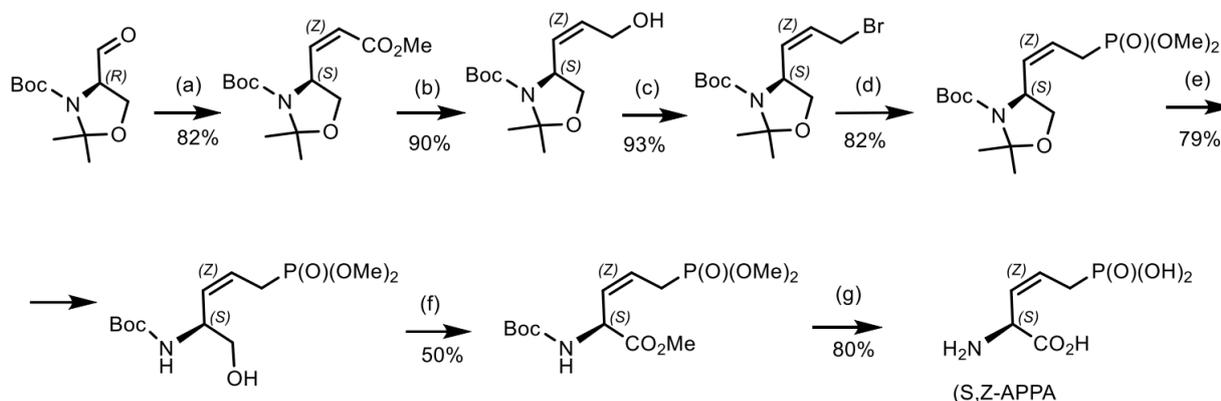


Figure 60. Seven step synthesis of (S,Z)-APPA starting from (R)-Garner's aldehyde. Reagents and conditions: (a) $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$, 18-Crown-6, NaH, THF, 78 °C; (b) DIBAL-H 1 M sol. in hexanes, toluene, 78 °C; (c) CBr_4 , PPh_3 , CH_2Cl_2 , 0 °C; (d) $\text{P}(\text{OMe})_3$, 80–100 °C; (e) Dowex 50WX4 H^+ , $\text{MeOH}/\text{H}_2\text{O}$:(9/1); (f) (i) $\text{H}_5\text{IO}_6/\text{CrO}_3$, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$:(99/1), 0 °C; (ii) CH_3I , K_2CO_3 , CH_3CN ; (g) (i) 10% $(\text{CH}_3)_3\text{SiBr}$ in CH_2Cl_2 , and then $\text{MeOH}/\text{H}_2\text{O}$:(9/1); (ii) 1 N LiOH, THF/ H_2O :(4/1).

One example of compounds isolated from natural sources are phosphazinomycins A and B, which were isolated from *Streptomyces lavendofoliae* and *Streptomyces unzenensis* [186–189]. They contain a hydrazide bond between the peptidylarginine carboxylic acid and phosphonic acid. Phosphonopeptides with an unusual structure include phosphazinomycin, which is a natural product containing a nitrogen-nitrogen (NN) bond, unlike other natural products in which the N–N bond is formed directly at the intermediate stage of biosynthesis during the biosynthesis of phosphazinomycin, kinamycin and related compounds. Phosphazinomycin and kinamycin are natural products that contain nitrogen-nitrogen (NN) bonds, but are otherwise structurally unrelated. Despite their significant structural differences, their biosynthetic gene clusters share a common set of genes that are thought to facilitate N–N bond formation (Figure 61) [189–191].

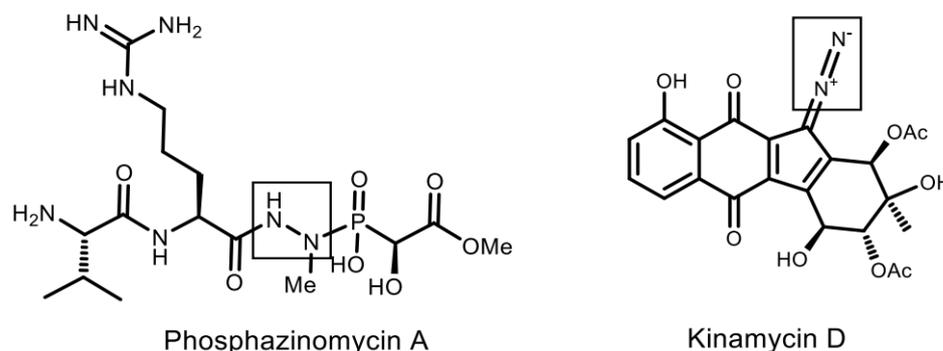


Figure 61. Phosphonopeptides containing a nitrogen-nitrogen (NN) bond.

Phosphazinomycins A and B, produced by *Streptomyces lavendofoliae*, have the same phosphonate fragment with one chiral center of unknown configuration, which was determined by synthesizing both enantiomers of 2-hydroxy-2-phosphonoacetic acid methyl ester. Chiral cyclic phosphite reacted with methylglyoxylate in the Pudovik reaction to form a pair of diastereomeric α -hydroxyphosphonates, which were separated by HPLC. The

configurations in C-2 were determined by X-ray diffraction analysis of a single crystal. The removal of protection from these diastereomers gives enantiomeric α -hydroxyphosphonic acids, the (–)-configuration of which has the same sign of optical rotation as the phosphonic acid fragment of two phosphazinomycines (Figure 62) [189–191].

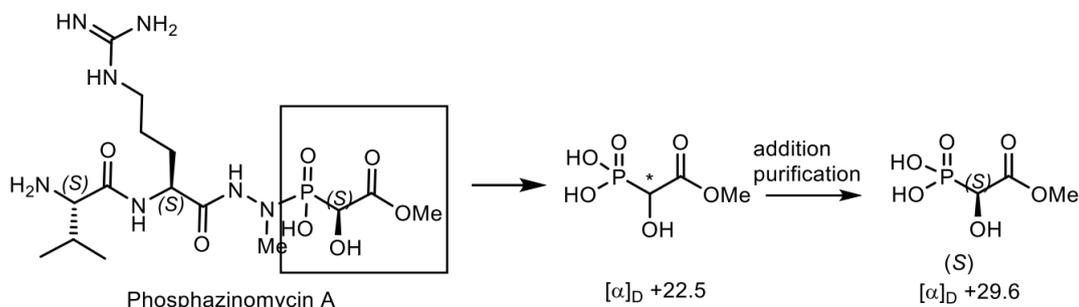


Figure 62. Determination of absolute configuration of phosphazinomycin by chemical correlation. (*)—center of chirality with an undefined absolute configuration.

Antibiotics, AC549, ATS 1287 (leptomycin) and AM630 (phosphazinomycin), depending on their activity, cause characteristic morphological changes in test organisms. Phosphonopeptides are of limited use in medicine, since they are easily hydrolyzed and release aminophosphonic acids, which are unable to overcome cell barriers and have an antibiotic effect. The genetic approach made it possible to isolate and characterize new peptidomimetics of *Streptomyces*, such as argolaphos A and B and valinophos [190]. A similar approach was used to isolate phosphonocystoximate and its hydroxylated derivatives: Among these, compounds are argolaphos A and B, a broad-spectrum antibacterial phosphonopeptide, rare amino acid N-(5)-hydroxyarginine; valinophos, N-acetyl-L-Val ester of 2,3-dihydroxypropylphosphonate [190]. Argolaphos has a broad spectrum of antibacterial activity, with the highest efficacy against *Salmonella typhimurium*, *Escherichia coli*, *Staphylococcus aureus*, it also inhibits *Mycobacterium smegmatis*. In addition valinophos, N-acetyl-L-Val ester of 2,3-dihydroxypropylphosphonate; and phosphonocystoximate, an unusual molecule containing sulfide group, representing a new chemotype of sulfur-containing phosphonate natural products. The absolute configuration of phosphonocystoximic acid was defined as (1*S*,6*S*)- (Figure 63) [181].

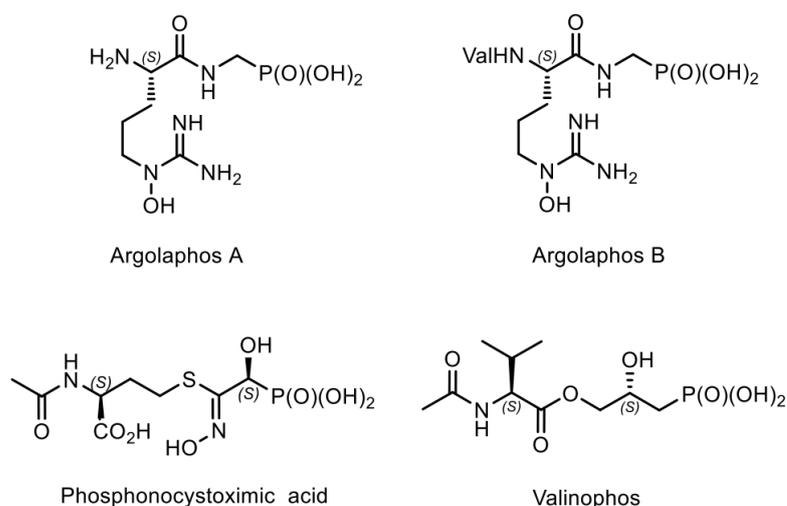


Figure 63. Some representatives of phosphonopeptides.

Antibiotic K-26 was isolated from the extract of the actinomycete K-26, which is a water-soluble acidic peptide composed of equal moles of L-isoleucine, L-tyrosine and (R)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid. The IC_{50} of K-26 for ACE inhibition

was 6.7 ng/mL when hippuril-L-histidyl-L-leucine was used as an ACE substrate. K-26 has hypotensive activity in vivo (Figure 64) [190,191].

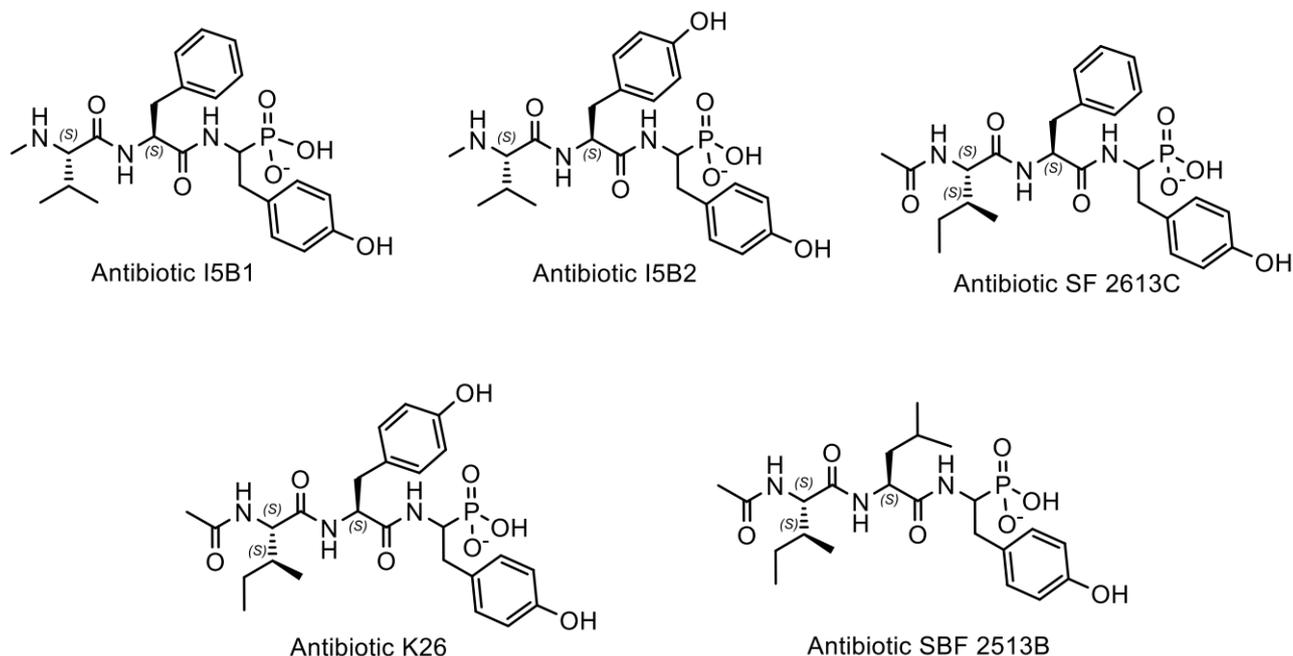


Figure 64. Representatives of peptide antibiotics.

The family of bacterial secondary metabolites of tripeptides K-26, K4, and I5B2 is a special group of phosphonic peptidomimetics [190]. They are produced by three different actinomycetes and act as potent inhibitors of the human angiotensin I, converting enzyme, selectively targeting the eukaryotic family of this enzyme. K-26 was isolated from the extract of the actinomycete K-26 [192,193]. The activity of the peptide in inhibiting ACE (angiotensin converting enzyme) in vitro is comparable to that of captopril. The absolute configuration of this connection has been determined. The conformation of the molecule is relatively rigid due to intramolecular restrictions, and the relative arrangement of heteroatoms necessary for its biological activity (Figure 20) [194–197]. Shibuya et al. [195] carried out a stereoscopic synthesis of hydroxyphosphonate tyrosine analogs by stereoselective reaction of 4-formyl-L-phenylalanine derivatives in the presence of a chiral heterobimetallic catalyst (Figure 65).

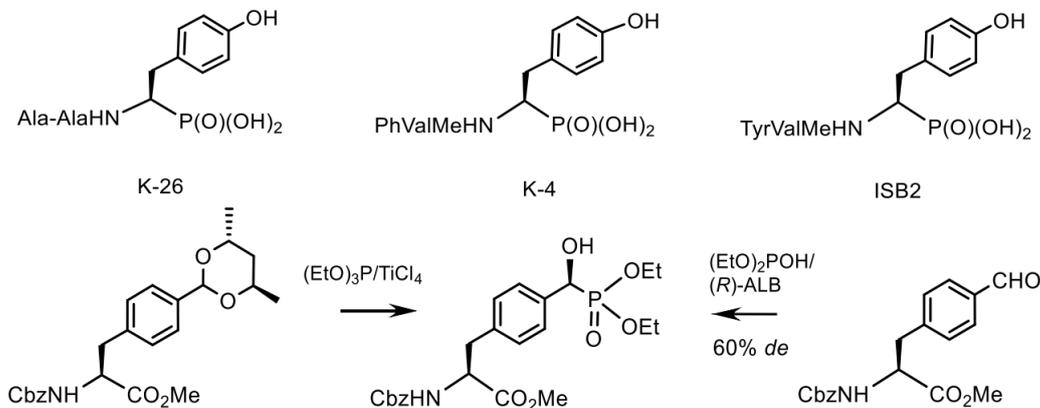


Figure 65. Stereocontrolled synthesis of the tyrosine hydroxyphosphonate analog.

The tripeptide of α -hydroxy-phosphonate, which is highly effective inhibitor of renin was prepared by stereoselective phosphadol reaction of dialkyl phosphites with chiral aldehyde [195]. The reaction with Titanium(IV) isopropoxide as a catalyst gave a mixture of diastereomers in a ratio of ~1:1, from which the (1*S*,2*S*)-diastereomer was isolated by column chromatography on silica gel (Figure 66) [198].

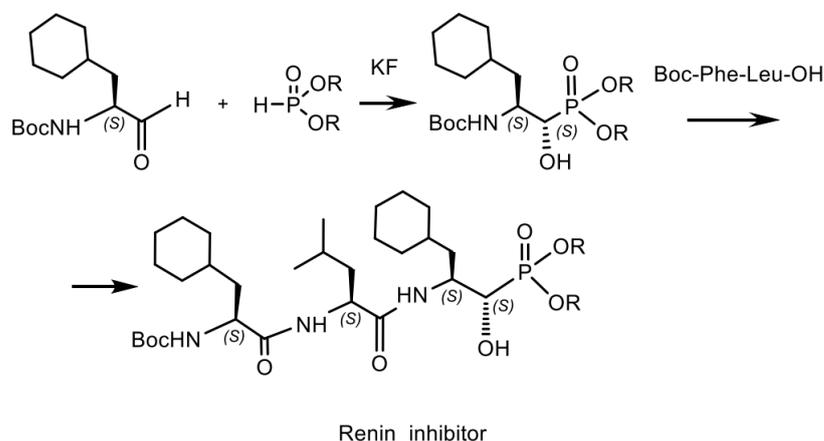


Figure 66. Stereoselective synthesis of tripeptide renin inhibitors.

The phosphonic tripeptides Bialaphos and Phosalacine, as well as the tetrapeptide Trialaphos, are biological herbicides isolated from soil actinomycetes that attracted close attention. The Bialaphos tripeptide was isolated from the filtrates of *Streptomyces viridochromogenes* and *Streptomyces hygrosopicus* [199–201]. The antibacterial activity of Bialaphos is a result of active transport of the peptide across the bacterial membrane, followed by hydrolysis of the peptide and the release of the terminal phosphonate, phosphinothricin, which inhibits glutamine synthetase. Further studies of Bialaphos led to the isolation of the tetrapeptide Trialaphos [136] and Phosalacine [135] from the *Streptomyces hygrosopicus* strain with a similar mechanism of action. Trialaphos (L-alanyl-L-alanyl-L-alanyl-phosphinothricin) is a naturally occurring tetrapeptide phosphinate composed of the combination of the three amino acids Alanine and Glufosinate (Figure 67).

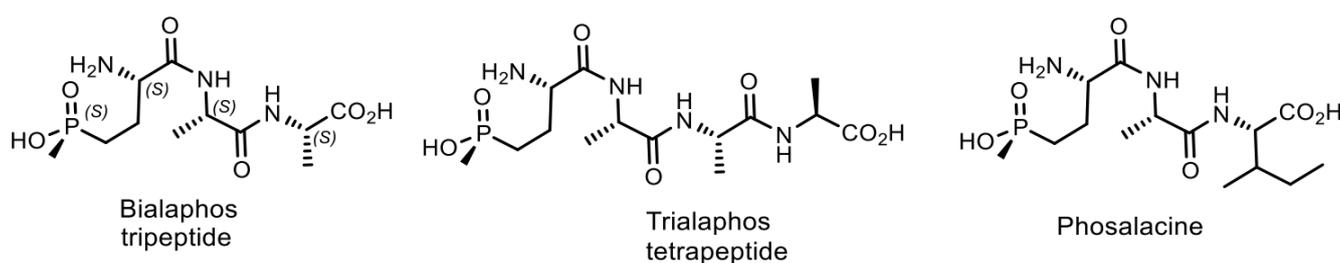


Figure 67. Phosphonic tripeptides and tetrapeptide.

Phosalacine was isolated from the fermentation broth of actinomycete strain KA-338 during the screening of antimetabolites competing with L-glutamine as structural analogs of the catalytic intermediate glutamine synthetase. Glufosinate actively inhibits this enzyme, but has low activity as a free amino acid, probably due to poor absorption. However, the “Trojan horse” peptides derived from glufosinate are readily imported into cells, where the peptidases release the active inhibitor [202,203]. Plant death due to inhibition of plant GS has made these substances successful herbicides, which are usually applied in the form of an ammonium salt. Phosalacin, a herbicidal antibiotic containing phosphinothricin, was isolated from a culture filtrate of *Kitasatosporia phosalacinea* KA-338 soil extract. Bialaphos and phosalacine, which are produced by soil actinomycetes, are tripeptides and contain phosphinothricin as the N-terminal amino acid. Phosphinothricin is released

from both Bialaphos and Phosalacine as an active substances by peptidases. The difference between the two peptides is due to the type of C-terminal amino acid, which is L-alanine for bialaphos and L-Leucine for Phosalacine. Bialaphos, Trialaphos and Phosalacine are pro-herbicides and are active only after their metabolic hydrolysis in the plant. Only the (S)-enantiomer of phosphinothricin exhibits herbicidal activity. The mechanism of action is shown in Figure 68.

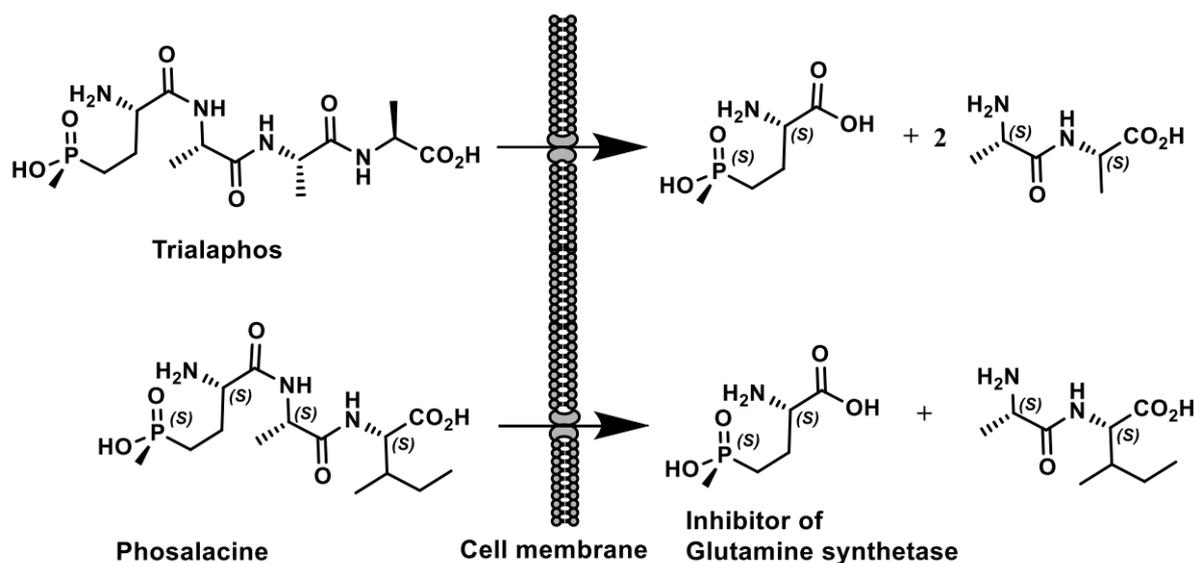


Figure 68. Mechanism of Trialaphos and Phosalacine transformation inside of cell.

It is assumed that phosalacin transported across cell membranes, incorporated into microbial or plant cells and, after hydrolysis decomposes with the formation of phosphinothricin, which exhibits antimicrobial and herbicidal effect by inhibiting vital parasite enzymes. 1-Phosphinothricin is a phosphinic acid that mimics (S)-glutamic acid, a natural substrate for glutamine synthetase. This target enzyme provides a reaction that incorporates inorganic nitrogen into organic forms (such as amino acids and nitrogenous bases) by releasing glutamine to detoxify ammonia. Inhibition of glutamine synthetase leads to the accumulation of ammonia in plant cells to toxic levels, and leads to the suppression of photorespiration due to a decrease in the level of amino acid donors [136,204–206].

7. Conclusions

This literature review has emphasized and described the importance of natural organophosphorus derivatives, which are a wide class of chemical compounds containing organic moieties usually bonded directly to phosphorus or bonded through a heteroatom, such as sulfur, oxygen or nitrogen. In recent years, significant advances have been made in understanding the influence of phosphates on the chemistry of prebiotics, among which two important aspects stand out. First, the phosphorylation reaction of prebiotics; second, the non-structural roles that phosphates may play in prebiotic chemistry. Several prebiotic pathways for the synthesis of nucleotides, amino acids and basic metabolites have been described, which are controlled by phosphates acting as acid-base catalysts, pH buffers or chemical buffers. These simple and subtle mechanisms of using phosphates to organize selective, robust prebiotic chemistry, combined with the central and universal role of phosphates in biochemistry, are increasingly making it clear that phosphate chemistry may be a key element in the origin of life on Earth. Phosphorous acid is adapted to play its role in nucleic acids because it can bind two nucleotides and be ionized. The resulting negative charge serves to both stabilize the diesters from hydrolysis and keep the molecules inside the lipid membrane. For the resulting material to remain inside the cell membrane, it must be charged, and therefore the binding element must have a third, ionizable group. The

bond is usually carried out by ester groups, but for the ester to be hydrolytically stable, this charge must be negative and must be physically close to the ester groups. Phosphoric acid meets all these conditions, and there is no alternative to it. The properties and role of phosphorus in maintaining life processes, combined with the conditions created by stereochemistry, homochirality, racemization and deracemization, open the way to solving one of the most important problems facing the science of the 21st century—to answer the question “How did Life on Earth arise?” In addition to the great problems of fundamental science, the study of the chemistry of natural phosphorus compounds is of great utilitarian importance [207]. Natural phosphonates can be considered as simple analogs of phosphoric acid esters and/or carboxylic acids. The stability of the C-P bond leads to the fact that phosphonates can act as inhibitors of enzymes and, therefore, can be considered as drugs or agrochemicals [208]. The development of modern physicochemical analysis and genomics, supplemented by biochemical research, has led to the development of new detection technologies that significantly accelerate the discovery of new natural phosphonates, the identification of their metabolic pathways, and their use as starting compounds for the creation of new promising drugs. Aminophosphonic and hydroxyphosphonic acids, phosphagens, phosphonopeptides, phosphonolipids, phosphorus antibiotics, agrochemicals, etc., confirm the importance of natural phosphorus compounds for science and economics [209].

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Conflicts of Interest: The author declares no conflict of interest.

Abbreviations

Ala—Alanine; AMP—Adenosine monophosphate, Arg—Arginine; ATF—Adenosyn triphosphate; Gly—Glycine; Asp—Asparagine; Boc—tert-Butoxycarbonyl; *de*—Diastereomeric excess; DIBAL-H—Diisobutylaluminum hydride; DMSO—Dimethylsulfoxide; DiPT—Diisopropyl tartrate; DiPE—Diisopropyl ether; *ee*—Enantiomeric excess; Gly—Glycine; GTP—Guanosine-5'-triphosphate; Hint—Histidine triad nucleotide binding protein; HppE—2-Hydroxypropylphosphonic acid epoxidase; *i*-Pr—iso-Propyl; Leu—Leucine; McC—Microcin C; Mes—Mesyl; Mnt—(1*R*,2*S*,5*R*)-Menthyl; Mops—3-Morpholinopropanesulfonic acid; MTBE—Methyl tert-butyl ether; PEP—Phosphoenolpyruvate; *rac*—Racemate; TBDMS—tert-Butyldimethylsilyl; THF—Tetrahydrofurane; TFA—Trifluoroacetic acid; TMS—Trimethylsilyl; Tol—Tolyl; Ts—toluenesulfonyl (tosyl); Val—Valine.

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