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Organophosphorus Chemistry Has A Crucial Role In The Field Of Drug Research-A Review

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Abstract: The present paper submits a recent reviews and ongoing development in the usage of organophosphorus worldwide. The attempts have been made to highlight the advancement and the importance in drug formation.

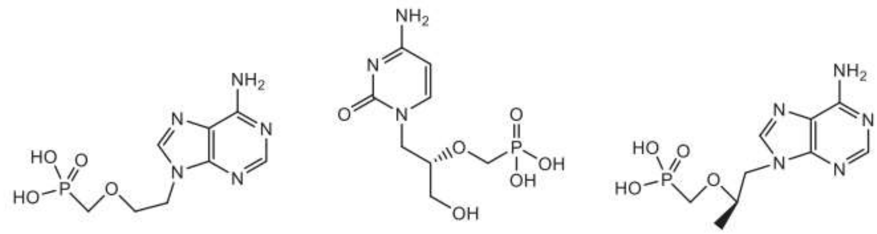
Keywords: Organophosphorus chemistry | Phosphocitrate (PC)|

INTRODUCTION

Organophosphorus chemistry has a crucial role in the field of drug research [1]. As generally well known, the Adenosine Triphosphate (ATP) plays a key role in the energy processes in all living cells of mammals. There are also natural phosphorus containing organic compound, Phosphocitrate (PC), found in mammalian mitochondria, likely produced by cytosolic phosphorylation of citrate, and which has important role in calcium metabolism, e.g. inhibiting hydroxyapatite precipitation in cells [2-4]. Phosphonates are analogs of natural phosphates, having characteristic C-P bond(s) and phosphonic acid moiety (R-PO3 H2). These compounds present as analogs of carboxylic acids, amino acids and peptides [5]. An interest related to these compounds has increased tremendously because of their potential as drugs (also pro-drugs). Phosphonate compounds were observed to have e.g. antibacterial, anticancer and antiparasitic activity [6]; they can be used in medical imaging and diagnostics, and they have phosphoantigen properties [7]. Several compounds containing phosphonate group are already in use as antiviral drugs, like for the treatment of hepatitis B virus (Adefovir or its pro-drug Adefovir dipivoxil), cytomegalovirus (Cidofovir) and HIV/AIDS (Tenofovir or its pro-drug Tenofovir disoproxil) (Figure 1) [6,8]. There is also at least one organophosphorus compound, Remdesivir, under investigation for the treatment of COVID-19 [9].

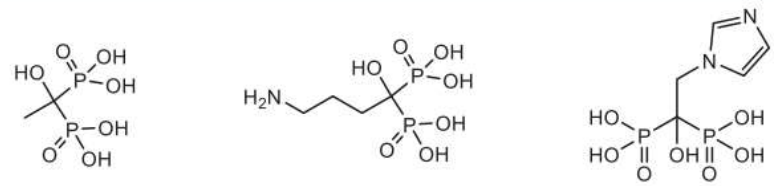
One very interesting group of organophosphorus compounds are, Bisphosphonates (BPs), which are analogs of natural pyrophosphate formed by hydrolysis of ATP and found in cells [10]. BPs are active drugs in many kinds of bone or calcium metabolism related diseases like osteoporosis and Paget´s disease [10,11]. They can also be used as bone targeting agents. BPs can be classified as non-nitrogen BPs (non-NBPs) and nitrogen containing BPs (NBPs); they are also categorized to different generations. In figure 2, structures of three different kind of BPs are presented: etidronic acid (1st generation, non-NBP), pralendronic acid (2nd generation, NBP) and zoledronic acid (3rd generation, NBP) [12]. BPs present rich chemistry and biology. Applications of BPs cover much more than just medicinal chemistry fi eld; and that is because of their very high affinity to almost any metal cations (alkali metal cations are exception because of their oxidation state +1); so they are potential compounds e.g. for removing/adsorbing metals from different kinds of water solutions [13-16]. Metal contaminated waters can be purified using BPs. As we know, pure water is crucial for all life on earth, and it is definitely health issue also.

When NBPs are used as drugs, they will induce to formation of ATP analogs ApppI and ApppD (Figure 3) in cells. Non-NBPs will be metabolized also in cells but little bit different way to form adenosine monophosphate (AMP) attached to non-NBP used (ATP analogs also) [17]. These ATP analogs have observed to inhibit cell signaling pathways [18]. Nowadays, ATP analogs can be chemically synthesized, so more options for further research are available [18-20].



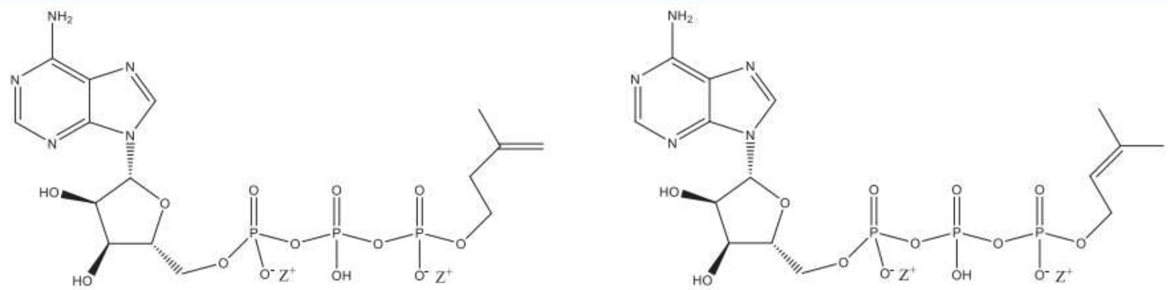
Adefovir Cidofovir Tenofovir

Figure 1 Examples of anti-viral phosphonate drugs in medicinal use.



Etidronic acid Alendronic acid Zoledronic acid

Figure 2 Examples of bisphosphonate drugs in medicinal use.



ApppI ApppD

Figure 3 ATP analogs ApppI and ApppD induced by NBPs.

Organophosphorus Conpounds in Medicine A source of C-P compounds of natural origin was first recognised in 1969.15 From the products in a fermentation broth of the bacterium Streptomyces fradiae a new phosphoric acid that had the properties of an antibacterial antibiotic was isolated. The compound was named Fosfomycin 16 (figure 4) and its discovery was an extremely important event in phosphorus chemistry. Phosphorus compounds had been largely ignored by medicinal chemists seeking new agents against infectious disease. Fosfomycin is active against both Gram-positive Gram-negative bacteria, and its effectiveness is comparable to that of the well-known antibiotics Tetracycline. 2c

High-level anticancer activity has been found in a large number of phosphorus compounds of quite different structural types, and there is much current research in this field. Probably the first organophosphorus compound to receive acclaim as a valuable chemotherapeutic agent is the anticancer drug cyclophosphamide 16 (figure 4). Its activity was discovered in 1958,[25] and remains in clinical use to this day.2c

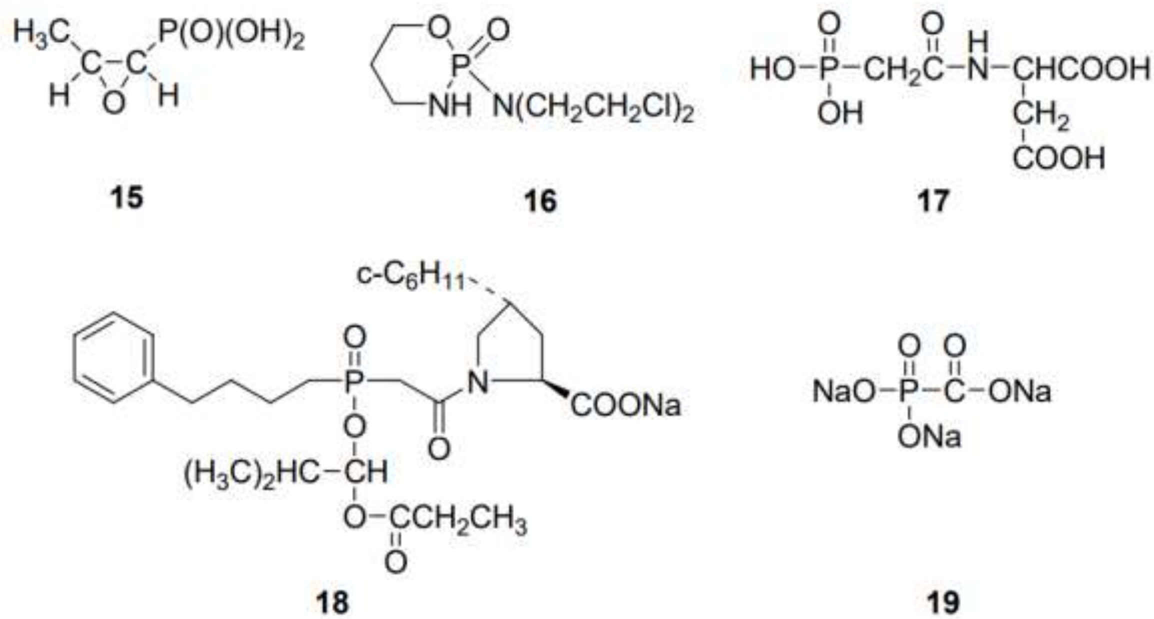


Figure 4. Organophosphorus compounds in medicine

In the design of anticancer drugs, rationales were done. An obvious one is that an exact phosphonate replica of a known biologically active phosphate could inhibit the process in which the phosphate is involved. The CH2 group attached to P has a very similar size and bond angle with an O atom of a phosphate. The high stability of P-C bond would block any important natural processes involving hydrolysis of a phosphate ester group. A second rationale is that a phosphonic acid designed to be similar to a naturally occurring carboxylic acid might inhibit the biochemical work of acid.12c Using those concepts a large amount of phosphonic acids has been synthesized and thus had useful chemotherapeutic properties. Some examples of the above rationalization are, the PALA (N-phosphonoacetyl-Laspartic acid (17) which is a potent anticancer drug and the Fosinopril (18) which has an antihypertensive activity.2c Phosphorus compounds can also have antiviral activity, the first active compound to be discovered had the very simple structure of trisodium phosphonoformiate. Its activity was discovered27 in 1978, and is still in clinical use under the name Foscarnet 19. It inhibits viral DNA polymerase, and it is a useful agent in the treatment of Herpes and is also active against HIV.

Phosphorus in Biological Compounds

Phosphorus is present in plants and animals. There is over 454 grams of phosphorus in the human body. It is a component of fundamental living compounds. It is found in complex organic compounds in the blood, muscles, and nerves, and in calcium phosphate, the principal material in bones and teeth. Phosphorus compounds are essential in the diet. Organic phosphates, ferric phosphate, and tricalcium phosphate are added to foods. Especially, phosphoric acid is essential in many biological derivatives such as nucleotides, nucleic acids, phospholipids and sugar phosphates.

Nucleotides are monomers consisting of a phosphate group, a five carbon sugar (either ribose or deoxyribose) and a one or two ring nitrogen containing base. Nucleotides are the monomers of nucleic acids, with three or more bonding together in order to form a nucleic acid. The genetic material (DNA) is a polymer of four different nucleotides. The genetic information is coded in the sequence of nucleotides in a DNA molecule. Nucleotides and related compounds are also important "energy carrying" compounds. Among the ones commonly encountered are ATP (20), and NADH (21) (Figure 1.2).26a adenosine triphosphate ATP 20 Nicotinamide adenine dinucleotide dehydrogenase NADH 21

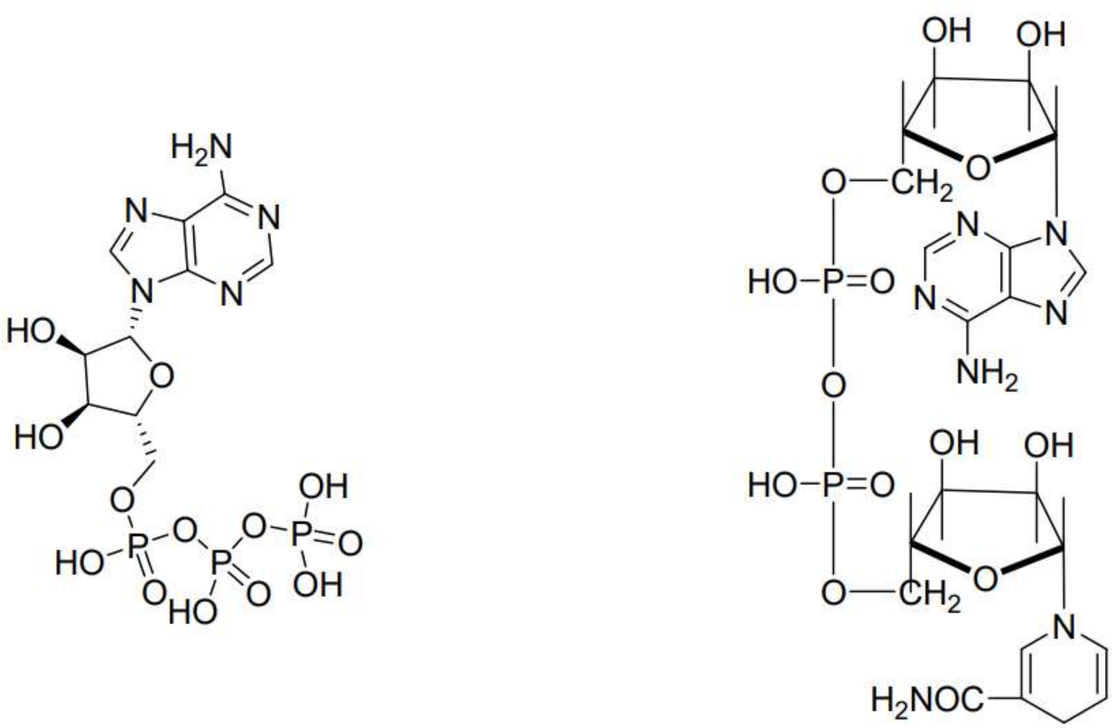


Figure 5. Structures of ATP and NADH.

Certain phosphoric acid derivatives play a major role in driving some processes by "energy release" that accompanies the cleavage of a phosphate group and transfer to a nucleophilic substrate. The best known of the "energy-rich" phosphates is adenosine triphosphates ATP (20, Figure 5), which can transfer the terminal phosphate group to a substrate with the release of significant energy.2c Actually the phosphoryl group transfer mechanism, in "energy-rich" phosphate substrates, is explained by intervention of penta-coordinated phosphorus in the transition state species. In particular the formation of cyclic penta-coordinated phosphorus species on the reactive phosphate group facilitate the attainment of the required transition state or intermediate allowing to obtain a fast and selective reaction.[25]

CONCLUSION

As a conclusion, it is more than clear that organophosphorus chemistry and compounds are very important in medicinal chemistry fi eld and they off er an extremely fascinating "world", which is constantly expanding. Organophosphorus compounds can be found in our bodies either as natural compounds (like ATP and PC) or induced by other compounds; and we really still do not know much of their biological functions and possibilities e.g. as drug LEADs.

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