CHAPTER I: INTRODUCTION TO ORGANOPHOSPHORUS COMPOUNDS
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The heteroatom chemistry mimicking the chemistry of carbon had much explored since the early 1960’s. In such a consequence the organophosphorus chemistry gets popularized due to the diagonal analogy between the carbon and phosphorus, which is higher than with respect to Nitrogen, Silicon analogy having a period and group relation respectively.\textsuperscript{1,2} The element phosphorus was discovered in 1669 by Henning Brandt and since then, significant discoveries have been made regarding its biological function.\textsuperscript{3}

Phosphorus is an essential element in all fields of chemical and biological sciences and recognized as a key building block in all known forms of life.\textsuperscript{4} Phosphorus and carbon have diagonal relationship in the periodicity of elements and this carbon and phosphorus analogy determines the electronegativity of the element (C \textsubscript{2.5} Vs P \textsubscript{2.2}), which governs its ability to release or accept electrons. The tremendous structural and electronic diversity as well as the versatile chemical behaviour of organophosphorus compounds (OPC’s) make them to play a very important role in the pharmacology and synthetic organic chemistry. The rich chemistry and wide applications of OPC’s are receiving tremendous attraction by the scientists belonging to different scientific disciplines.\textsuperscript{5,6}

OPC’s are important in everyday applications ranging from agriculture, medicine and industry. They are used as flame retardants, metal extractants, and ancillary ligands for metals of agrochemicals and medicines. They are also useful as nutrients in plant growth. Furthermore they serve as key substrates, catalysts and reagents in the general organic synthesis.\textsuperscript{7}

So it is natural that this background of organophosphorus chemistry has made it a key thrust area. Its multifaceted and versatile applications motivated researchers all over the world for further research and development of new synthetic methods, by improving the already existing ones and in discovering new area of applications for the specially designed and synthesized compounds as such phosphorus chemistry gets recognized as one of the most important fields for the advancement of mankind.
Incorporation of a phosphorus atom within the structure of biomolecules is essential for life as DNA and RNA are present abundantly in the cells. This element plays a pivotal role within ATP, which is used by living organisms for storing and releasing energy (Figure 1.1). Phosphorus compounds also serve as cofactors of multiple enzyme systems and also act as essential buffering agents within the cellular milieu.\textsuperscript{3,8}

![Fragment of an RNA molecule](image)

Figure 1: Energy phenomenon in living organisms

The inherent properties of the element phosphorus include: (a) polarizability, (b) low to medium electronegativity and (c) low coordination number, thereby, allowing the synthesis of a diverse range of compounds. Biological and medicinal activities of organophosphorus compounds are modulated, in part, by the nature of the element bound to phosphorus and variations in its own oxidation state.

The Structure Activity Relationship (SAR) studies of OPC’s throws more light on their applications and paves the way for the discovery of better drugs as the critical structure-bioactivity analysis of previously reports points to the fact that the main pharmacophoric structural unit in them is a phosphoryl group (1). Slight variation in 1 can have very dramatic effects on the bioactive efficiency of OPC’s due to the fact that
the enzyme interaction is very sensitive to the size, shape and polarity of the OPC’s substrate molecules (Figure 1.2). This concept opened the design and synthesis of various OPC’s with the basic structural unit 1 and studies on their structure bioactivity relationship. These studies on their structure as a function of bioactivity showed the way for development of new drugs and also for improving the activity of the existing ones.

![Diagram](image1)

**Figure 2:** Basic pharmacophoric structure of organophosphorus compounds (OPC’s)

Research on Organophosphorus Chemistry made significant impact in the scientific community with its far reaching contributions in organic and medicinal chemistry in the form of phosphorus heterocycles. Recent advances involve the drug design, organic synthesis, quantitative structure-activity relationship, molecular modeling, prodrug synthesis, drug targeting, molecular aspects of drug metabolism, drug-receptor interactions, and pharmacological activities. The activity potency of these compounds depends on the nature of leaving group, stereochemistry and reactivity. This background served as a driving force for making significant contributions to the multifaceted research such as discovering the new chemistry, comparative studies on synthetic, mechanistic aspects, and structural features in wide areas like synthetic organic chemistry, bioorganic chemistry, biochemistry, natural products chemistry, pharmaceutical and medicinal chemistry, molecular modeling and structural biology.

In recent times phosphorus heterocycles have received considerable interest because of their unique biological activities as hydrolytic enzyme inhibitors and their anticancer effects, as well as of their wide ranging utilities as synthetic reagents in organic syntheses. Consequently, much attention has been bestowed as the synthesis of these compounds. Most of them are accompanied by the formation of five or six membered phosphorus heterocycles which in many cases demonstrate certain biological activity.

The research in this field led to the discovery of Cyclophosphamide (2), a chemotherapeutic drug used in the treatment of lymphomas, brain cancer and leukemia by
causing of the death of certain T cells. Its structural isomer, Ifosfamide (3) inhibits and minimizes the growth of cancer cells as potential antineoplastic agents. Recently, the DNA repair Inhibition is identified as a fundamental mechanism in anticancer treatment of tumor cells. Recently Thiotepa (4) and its major metabolite Tepa (5) were identified as trifunctional alkylating agents of DNA at Guanine. This is rationalized by the easy opening of aziridinium ring due to high strain and appears to be the suitable mechanism of DNA repair inhibition and thus they may be used in cancer therapy.15-16

Cystaphos (6) and Amifostine (7) are the cytoprotectors that can reduce toxicity and potentially improve the therapeutic ratio of radiotherapy compared to the alternative approaches in reducing radiation toxicity, an important problem that limits the treatment. Fludara (8) is an active compound on chronic lymphocytic leukemia (CLL) and low grade lymphomas. Fosinopril (9), a dialkyl substituted phosphonate is also identified as a potential organophosphorus anticancer drug.20

Recently, Gilead Sciences Inc. reported highly promising positive preclinical results against cancer with prodrug of 9-(2-phosphomethoxyethyl)guanine (10) and
dialkyl (2-(2-amino-6-(cyclopropylamino)-9H-purin-9-yl)ethoxy)methylphosphonate (11) and these appear to function as prodrugs against leukemia and non-Hodgkins lymphoma.\textsuperscript{21}

![Chemical structure 10]

![Chemical structure 11]

![Chemical structure 12]

![Chemical structure 13]

Recently, Jean-Luc Pirat group from Centre National de la Recherche Scientifique, Paris (FR) has developed some 1,2-oxaphosphinane-2-oxides (Phosha sugar analogues) with general structure 12 as anticancer compounds to be used in treating or preventing cancers.\textsuperscript{22} Similarly, OSI Pharmaceuticals, New York also developed some new phosphorylated amino pyrimidines with general structure 13 as as selective inhibitors of Focal Adhesion Kinase which plays a major role in the signal transduction of heterodimeric receptors in cancer cell adhesion.\textsuperscript{23}

Though many kinds of organophosphorus compounds are reported so far, the literature reports assures the phosphorine system (a six membered phosphorus ring) as an important pharmacological building block of matrix metalloproteinase inhibitors and alkylating anticancer drugs, which also exhibits pesticidal and antimicrobial activities.
The clear variation in the bio-activity susceptibility of the currently available oxazaphosphorine based drugs can be understood by the changes in their SAR studies and so new compounds have been developed and synthesized to improve selectivity and response with reduced toxicity.\textsuperscript{24}

![Diagram of potential anticancer drugs of oxazaphosphorinane ring system]

**Figure 3:** Potential anticancer drugs of oxazaphosphorinane ring system

Similarly some other organophosphorus compounds were also identified as antidiabetic like hyperglycemic and hypoglycemic agents. Matin and Siddiqui\textsuperscript{25} found increase in blood glucose and decrease in glycogen in various constituents of rat’s brain after treatment with Malathion (8). Glycogen levels were decreased in rat liver when treated with Dichlorovos (9).\textsuperscript{26} Hyperglycemia due to Parathion (10) and Dichlorovos has been reported.\textsuperscript{27,28} Diisopropyl phosphorofluoridate (11) has the ability to reduce glucose level in rats.\textsuperscript{29}
These oxazaphosphorine drugs including cyclophosphamide, ifosfamide, trofosfamide represent an important group of therapeutic agents due to their substantial antitumor and immune modulating activity (Figure 1.3). To circumvent the drawbacks of these drugs like substantial pharmacokinetic variability, resistance and severe host toxicity, new oxazaphosphorines derivatives have been designed, synthesized and evaluated with an attempt to improve the selectivity and response with reduced host toxicity. These include mafosfamide, glufosfamide, S-(-)-bromofosfamide, aldophosphamide perhydrothiazine and aldophosphamide thiazolidine. The synthesis and development of novel oxazaphosphorine analogs with favourable pharmacokinetic and pharmacodynamic properties still constitutes a great challenge for medicinal chemists and cancer pharmacologists.30

Figure 4: Classification of bio-potent phosphole ring systems

Similarly, the phospholes (five membered organophosphorus heterocycles) are the structural analogues of furanose derivatives and consist various family of compounds
like oxaphospholes, oxazaphospholes, thiazaphospholes, diazaphospholes and dioxaphospholes (Figure 1.4) which play an important role in organic chemistry due to diversity of their chemical transformations and broad spectrum of biological activities.\textsuperscript{31-32} But it is well noticed that the studies on their SAR studies and medicinal applications are inadequate when compared to phosphorine systems.\textsuperscript{33}

Based on this study and analysis we have accomplished the Synthesis of some new 1,3,2\textsuperscript{λ}5-Benzoxazaphosphonamides, 1,2-Thiapospholene-2-Sulfides, 3-Substituted Amino-1,2-Oxaphospholic Acids and 1,2,5-Oxazaphosphole-5-sulfides as target compounds and screened them for their anti-diabetic activity, anti-lung cancer activity, anti-pancreatic cancer activity and anti-breast cancer activity respectively and presented the work in this thesis.

References


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