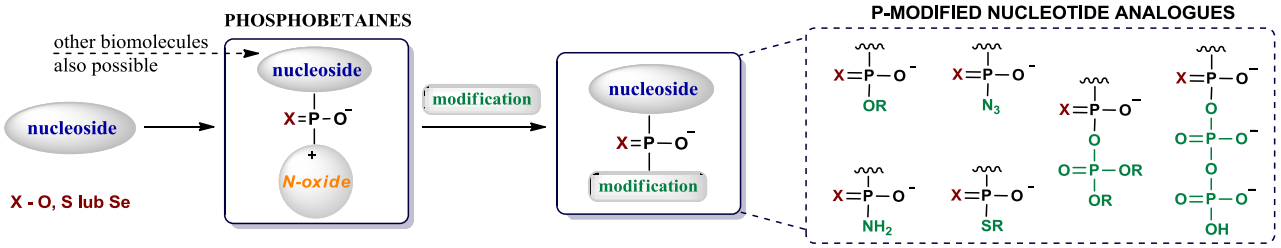
Description for the general public

Phosphorus is a crucial element of life, a component for the most fundamental biomolecules, *i.e.* DNA, RNA and phospholipids. Its functions in cells arise from their unique chemical properties that grant high structural diversity of phosphorus compounds. Phosphorylated biomolecules are not only the carriers of genetic information, but also can play a role of activators or substrates in biochemical processes, thereby becoming an interesting research objective in the field of chemistry, biochemistry and molecular biology.

Phosphorylation methods used nowadays struggle with challenges resulting from increasing demands for novel compounds with sophisticated structures and precisely defined properties. The vast number of scientific publications in this research area clearly underlines the importance of designing biologically active low molecular weight phosphorus compounds – P-modified phosphates and polyphosphates of natural compounds. Among them, chiral analogues of phosphates are of particular interest, which exist as stereoisomers that differ only in spatial arrangement of atoms around the phosphorus center. These structural implications require recognition of stereochemistry of the studied systems that is responsible for spatial aspects of reactions. Controlling the stereochemistry of phosphorus is a challenging but an attractive task and may provide new methods for preparation of potentially therapeutic compounds.

During our recent studies on phosphorylation using untypical reactivity of amine *N*-oxides towards P^{III} phosphorus compounds, we observed formation of previously unknown class of compounds – *N*-oxide phosphobetaines that have unique structural and chemical properties. The aim of the project is to investigate the potential of the aforementioned phosphobetaines in the synthesis of biologically active phosphorus-containing natural products and their analogues. Since modifications of the phosphate function in biomolecules is not an easy task, in our project we propose a novel solution based on *N*-oxides used as chemical activators in phosphobetaines, thereby playing a role of the universal "molecular tools" dedicated to introducing modified phosphate groups (*Scheme1*).



Scheme 1. *N-Oxide phosphobetaines in new synthetic strategies for modified biomolecules*

The first stage of the project is designed to elaborate various synthetic strategies for preparation of *N*-oxide phosphobetaines of nucleosides. Selected phosphobetaines, found to be the best precursors for nucleotides, will be used subsequently for synthesis of P-chiral analogues of nucleotides. The resulting nucleoside phosphates and polyphosphates will contain diverse modifications in bridging and non-bridging positions of phosphate functions (*Scheme1*). The proposed phosphorylation method will be tested for synthesis of nucleoside analogues with anticancer and antiviral activity as a matter of priority. Then, the results obtained in the first phase of the study will be exploited in development of a more general strategy for phosphorylation of natural compounds, *e.g.*, amino acids, carbohydrates, and lipids. In the project the analysis of stereochemical aspects of phosphorylation reactions is also included, with the use of chiral betaines, specially designed for this purpose. Synthetic studies will be accompanied with analysis of mechanisms for transformation of nucleoside phosphobetaines into nucleotides, supported additionally by computational methods.

The research topics presented in the project are perfectly adjusted to current studies on modern synthesis of natural compounds. The proposed concepts give a chance to elaborate novel strategies for phosphorylation of biomolecules with the use of amine *N*-oxides as unique "molecular tools" dedicated to the synthesis of phosphates and polyphosphates of nucleosides and other biomolecules. The postulated phosphorylation strategies will provide a method for preparation of phosphate derivatives of nucleoside analogues with potential anticancer and antiviral activity. It is very likely that the results obtained will expand the current knowledge in the field of chemistry, with particular emphasis on modern organic synthesis and natural product chemistry.