Synthesis of 2-phosphonocarboxylates as potential covalent inhibitors of Rab geranylgeranyl transferase

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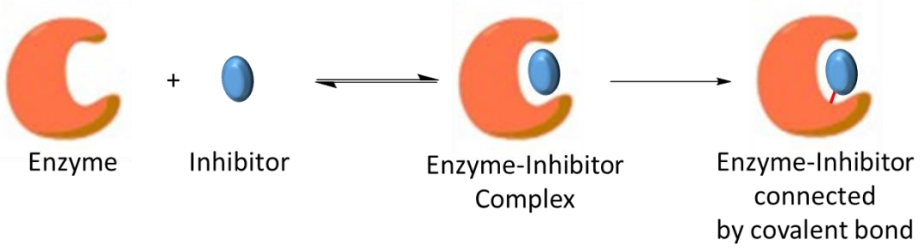
During the last decade a growing interest in drugs with covalent mechanism of action has been observed. The prominent examples of covalent inhibitors include aspirin, β-lactam antibiotics (avibactam), fosfomycin, proton pump inhibitors (omeprazole), antiplatelet drug (clopidogrel) and a number of anticancer drugs introduced in the past few years (e.g. carfilzomib - multiple myeloma, abiraterone - metastatic prostate cancer, afatinib - metastatic lung cancer). This interest also stems from such advantages as improved biochemical efficiency, prolonged duration of action, which can result in less-frequent drug dosing. The technological development, that allows more reliable methods for determination of the activity of covalent drugs and their potential side effects, also contributes to current increased interest in this class of compounds.



The aim of this proposal is the synthesis and biological evaluation of the new phosphonocarboxylates designed to be the first inhibitors of Rab geranylogeranyltransferase (RGGT) with covalent mechanism of action. RGGT is an enzyme responsible for the post-translational modification of Rab proteins, which malfunction has been found in such diseases as cancer, neurodegenerative disorders and infections. It has been shown that inhibition of enzyme RGGT can lead to cancer cells death.

The starting point of this project is one of the most active phosphonocarboxylate inhibitor of RGGT, which will be modified in order to facilitate the formation of a covalent bond with an amino acid residue located within the binding cavity of RGGT. The new compounds will be tested for cytotoxicity on the selected tumor cell lines. In addition, their reactivity will be determined in the model reaction using nuclear magnetic resonance.

The newly designed compounds may constitute the first covalent inhibitors of RGGT, enabling the control of pathological activity of Rab proteins and hopefully leading in the future to new therapeutics and/or tools for studying Rab proteins functions in cells.