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α-Phosphonopropionic acids as Rab geranylgeranyl transferase inhibitors – the structure-activity relationship studies and the application of prodrug strategy to masking their ionic character

Rab geranylgeranyl transferase (RGGT) is an enzyme responsible for posttranslational modification of Rab proteins, resulting in their increased lipophilicity. Such modification enables proper localization and functioning of Rab proteins. Disruption of Rab proteins functions has been observed in several diseases, such as cancer and neurodegenerative disorders. As inhibition of RGGT leads to apoptosis of cancer cells, this enzyme may be considered a potential therapeutic target. Its selective inhibitors are also useful tools to study Rab-related disorders.

In the course of my PhD studies I was engaged in the design and synthesis of potential RGGT inhibitors derived from two known α-phosphonopropionic acids. Obtained compounds were utilised for determination of structure-activity relationship (SAR), which allowed identification of inhibitors with increased activity towards RGGT.

In the second part of my studies I elaborated a method of synthesis of prodrug analogs of the studied RGGT inhibitors. The ionic character of α-phosphonopropionic acids was masked in order to increase their bioavailability and thereby therapeutic potential. Elaborated methods were used in the synthesis of series of analogs bearing moieties that are labile under physiological conditions. These compounds were subject to preliminary stability studies in chemical and enzymatical environment using selected models. Products of decomposition were also identified.

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