

FA-PROTACs - Design and Synthesis of Compounds Based on Folic Acid for Degradation of Enzyme Involved in Folate Metabolism: Exploring Novel Antitumor Pathways

Scientific goal of the project

Cancer diseases represent critical medical challenges. According to the recent estimates 2 001 140 new cancer cases and 611 720 cancer deaths are projected to occur in the United States in 2024 [1]. On the other hand, 2 740 000 new cancer cases (rose by 2.3 % compared to 2020) and 1 290 000 cancer-related deaths (rose by 2.4 % compared to 2020) were detected in European Union in 2022 [2]. In addition, the National Cancer Institute expects that the number of new cancer cases per year is expected to rise to 29.9 million and the number of cancer-related deaths to 15.3 million per year by 2040, worldwide [1]. This project may contribute to the creation of innovative therapeutic options to combat the global cancer challenge. Therefore in this project we decided to develop new classes of anticancer agents basing on the most recent and promising approaches to overcome resistance and to improve bioavailability and selectivity of anticancer agents. During this project we plan to obtain and biologically evaluate a series of novel PROteolysis-TArgeting Chimerics (PROTACs) targeting enzymes involved in the bioconversion of folic acid (dihydrofolate reductase (DHFR), methylenetetrahydrofolatereductase (MTHFR) and methionine synthase (MTR)). Such innovative agents may be a basis of innovative anticancer therapy in the future.

Due to the fact that the planned FA-PROTACs will be based on the derivatives of folic acid, we hope that we will be able to degrade enzymes involved in the bioconversion of folates, which action is crucial for the progression of cancer disease. Due to the fact that the higher folate uptake (e.g., via the folate receptor [FR] pathway) is observed in numerous types of cancers, we hope that the planned compounds based on the folic acid structure may allow to obtain anticancer agents characterized by greater bioavailability and selectivity toward cancer cells. Taking into account that the expression of FR grows with the tumor progression it is assumed that the newly synthesized compounds will be also effective in the treatment of advanced cancer disease. We believe that the implementation of this project will allow to develop a more effective potential therapy for many types of tumors using compounds that show limited side effects.

Research methodology

The project demonstrates highly interdisciplinary character combining efforts in different areas of science:

- The design process of chemical structure of compounds, which will be supported by computational studies,
- The organic synthesis of proposed FA-PROTACs as potential anticancer agents,
- The biological evaluation of anticancer activity and ability to induce the degradation of selected enzymes.

All mentioned above parts of the project will be performed at Gdańsk University of Technology using facilities of two departments (Department of Inorganic Chemistry and Department of Pharmaceutical Technology and Biochemistry).

The impact of the project results

PROTACs, which may be able to degrade enzymes of folate bioconversion have not been well known and none of them have been clinically applied until now. Therefore, all obtained during this project compounds will be novel and may be milestones in the development of innovative anticancer therapies. We hope that application of the folate unit will allow us to obtain very potent anticancer agents with improved selectivity and limited toxicity. Considering that compounds planned for synthesis during the project belong to prominent topics in drug design, we are planning to seek patents for our results as soon as we confirm the biological activity of the synthesized compounds. Subsequently, we will prepare manuscripts for publications in leading journals within the field of medicinal chemistry.

References

- [1] National Cancer Institute, <https://www.cancer.gov/about-cancer/understanding/statistics> (retrieved 10th October 2024).
- [2] European Commission; https://joint-research-centre.ec.europa.eu/jrc-news-and-updates/cancer-cases-and-deaths-rise-eu-2023-10-02_en, (retrieved 10th October 2024).