

Research objective

In the course of drug design and development research, we obtained in our laboratory a series of simple polyfluorinated phosphonates (ZOTs) with a leading structure. They demonstrated high cytotoxic activity against cancer cells of solid tumours, especially glioblastoma multiforme cells. Preliminary results obtained *in silico* indicated that ZOTs meet the drug-likeness criteria, including: low molecular weight and high bioavailability, meeting the pharmacokinetic criteria for absorption, distribution, metabolism and excretion (ADME), not violating Lipinski's five rule (RO5) and not interfering with the PAINS (pan-assay interference complex) test. Combined with the predicted blood-brain barrier permeability, ZOTs are promising candidates for an anticancer drug against glioblastoma multiforme. Currently, our research group is interested in the exploration of the molecular mechanism of these compounds.

Aim of the project

The low efficiency of drug delivery across the blood-brain barrier is the main reason for the slow progress in the treatment of glioblastoma – currently survival extension of several months is achieved. From a clinical point of view, it is valuable to search for substances with the potential of chemotherapeutic agents which can penetrate the blood-brain barrier, in particular the compounds with a lead structure and unknown mechanism of action. **The aim of this project is to conduct preclinical studies of new compounds ZOT₅-1-Me and ZOT₅-1-Et as potential anticancer drugs against glioblastoma.**

Work plan

To achieve the above goal, we propose the following research tasks:

1. Selection of molecular targets for ZOTs and their *in vitro* evaluation in glioblastoma cells.
2. *In vitro* evaluation of the anticancer activity of ZOTs in glioblastoma cells at the molecular level.
3. *In vitro* evaluation of the anticancer activity of ZOTs in 2D and 3D models of primary cell lines derived from patients with glioblastoma multiforme.
4. *In vivo* evaluation of the anticancer activity of ZOTs using glioblastoma multiforme patient-derived xenografts mouse model.

Expected results

It is expected that the proposed project will broaden the knowledge of anticancer properties of new polyfluorinated phosphonates at the molecular, cellular, tissue and systemic levels. The implementation of the project will expand the knowledge in the field of cancer biology and drug design and development.