

Summer Research Internship Project Proposal

Project Topic	Development of new chromatin modifying substances for anticancer therapy		
Name	Pavel Bobál	Field	Chemistry, Pharmacy
Department	Department of Chemical Drugs	Keywords	Organic synthesis, Medicinal chemistry

Description of the Project (overview, expected outcomes, reason for research, proposed outcomes for student(s))

Epigenetic alterations are involved in every step of carcinogenesis. The development of chromatin modifiers has provided the ability to fight tumors by reversing these changes. Six chromatin-modifying agents have recently been approved for the treatment of cancer: two DNA demethylating agents and four histone deacetylase inhibitors (HDACi). Many promising chromatin modifiers are currently being clinically evaluated in several types of tumors. Besides, already approved drugs from this group are still under clinical investigation to improve their efficacy and extend their use to various types of cancer. Combination therapy with chromatin modifiers is already considered a promising strategy to improve clinical effects and reduce side effects. The aim of the project will be the design and synthesis of new compounds capable of modifying chromatin with a potential effect on tumor growth. The work will build on the previous promising results of our group in the development of histone deacetylase inhibitors.

Preliminary aims

(1) Development of methodology for the preparation of substances capable of chelating zinc in HDAC enzyme (this also includes the design of suitable structures, design of their synthesis, synthesis itself, physicochemical characterization of prepared compounds, etc.) (2) Preliminary evaluation of their effect (cytotoxicity, inhibition of proliferation, etc.) to various strains of tumor cells in cooperation with the Department of Pharmacology and Toxicology, Faculty of Pharmacy MU. (3) Modification of structures regarding their preliminary evaluation and their synthesis. (4) Determination of the activity of selected most active substances on individual HDAC isoforms in cooperation with a foreign workplace.

The main outputs of the project are scientific publications. We expect the participation of student(s) on a scientific paper. Students will gain experience from experimental organic synthesis, medicinal chemistry, analytical chemistry and partially from computational methods.

Student Requirements (prerequisites, experience, acceptable fields of study, etc.)

- Student should have completed the subject organic chemistry including laboratory exercises,
- Student should have basic practical experiences in organic synthesis,
- Knowledge of working with instrumental analytical methods (NMR, HPLC, etc.) is beneficial,
- Practical experience with solving small research projects is beneficial,
- Active approach, initiative, and willingness to further professional growth,
- Acceptable fields of study: organic chemistry, pharmacy with interest in medicinal chemistry.

Proposed responsibilities of the student(s)

- Collaboration on the selection of prospective candidates for HDAC inhibition (*in silico*),
- Cooperation in synthesis proposal,
- Carrying out organic synthesis experiments,
- Spectral characterizations of prepared compounds (NMR, MS, IR, ...),
- Determination of structure-activity relationship from preliminary results of cytotoxicity and inhibition of proliferation.

Additional important information (max. number of students, additional staff/faculty involved, etc.)

- We can accept 2 students on this project,
- The student(s) will collaborate with regular PhD student in my group,