POLISH NATIONAL AGENCY FOR ACADEMIC EXCHANGE

STER PROGRAMME

name of the unit:

CHEMICAL BIOLOGY GROUP

Institute of Organic Chemistry, Lodz University of Technology

symbol:

I-32

http://www.chorg.p.lodz.pl

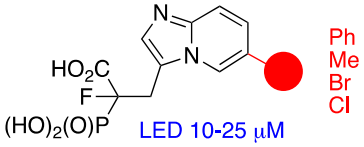
head of the unit:	potential promoters:	contact person:
Katarzyna Błażewska, Ph.D., D.Sc., TUL Prof	Katarzyna Błażewska, Ph.D., D.Sc., TUL Prof. Joanna Małolepsza, Ph.D (auxiliary promoter)	Katarzyna Błażewska, Ph.D., D.Sc., TUL Prof phone: 48-42-631-32-27 katarzyna.blazewska@p.lodz.pl

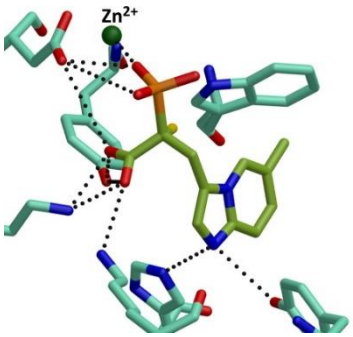
scope of activities:

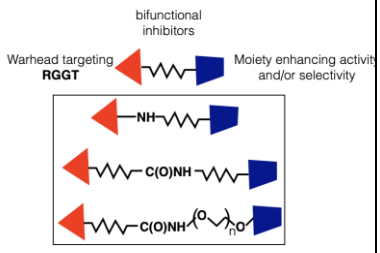
The main areas of interest and research directions:

- design and synthesis of new Rab geranylgeranyl transferase (RGGT) inhibitors derived from α-phosphonocarboxylates – structure-activity relationship studies;
- identification of the place of interaction of inhibitors with proteins in the cell - "affinity-based protein profiling";
- design and synthesis of inhibitors that induce proteolysis of desired protein – PROTAC;
- dual inhibitors of RGGT;

graphic material







present activities:

The main goal of our group is to develop new strategies towards controlling the potency of important class of enzymes, Rab GTPases (Rab proteins, Rabs), which are implicated in a number of human diseases, including cancer, neurodegenerative disorders and infections.

In order to be functional, Rab proteins are undergoing post-translational modification by introduction of lipophilic residues. This process is catalyzed by Rab geranylgeranyl transferase (RGGT). Its inhibition provides one of the ways to control the activity of Rab proteins. Thus, we are now interested in developing new inhibitors of RGGT with improved activity and selectivity. We also synthesize probes, in order to identify the place of interaction with RGGT and potential off-targets of phosphonocarboxylates.

Our recent interest is the development of bifunctional compounds that bear RGGT-targeting warhead combined with an inhibitor/ligand of a different protein. These two fragments are connected using appropriate linker. Such compounds can act as dual inhibitors and increase biological response.

Compounds designed and synthesized in our group are tested for their biological activity in the group of Prof. Edyta Gendaszewska-Darmach from Faculty of Biotechnology and Food Sciences, TUL).

Future activities:

Design and synthesis of peptide-based inhibitors of protein-protein interactions, which lead to selective regulation of Rabs.

Publications/ patents/ awards, grants:

Selected publications:

- D. Kusy, A. Marchwicka, J. Małolepsza, K. Justyna, E. Gendaszewska-Darmach, K.M Błażewska *Front. Chem.* **2021**, 8:596162;
- Kaźmierczak, D. Kusy, S. P. Niinivehmas, J. Gmach, Ł. Joachimiak, O. T. Pentikäinen, E. Gendaszewska-Darmach, K. M. Błażewska *J. Med. Chem.* **2017**, 60, 8781.
- E. Gendaszewska-Darmach, M.A. Garstka, K.M Błażewska *J. Med. Chem.* **2021**, 64, 9677-9710.

Grants: 1. NCN – Preludium Bis, 2021-2025: Application of PROTAC strategy for controlling Rab geranylgeranyl transferase and Rab proteins; 2. NCN – Sonata Bis, 2015-2021: Design and synthesis of probes for RabGGTase profiling and their application for identification of the site of phosphonocarboxylate inhibitors's interaction with the enzyme and potential off-targets; 3. NCN – Preludium, 2017-2020: Synthesis of 2-phosphonocarboxylates as potential covalent inhibitors of Rab geranylgeranyl transferase; 4.* NCN – Opus, 2019-2021: Unravelling the controversial role of palmitoleic acid in the dietary prophylaxis of carbohydrate and lipid homeostasis disorders *Prof. Błażewska group plays a role of investigator in this project.
Keywords: α-phosphonocarboxylates, α-phosphonocarboxylic acids, Rab GTPases, Rab geranylgeranyl transferase (RGGT), Parkinson's disease, inhibitors
List of internship proposal in this research team: Design and synthesis of linkers connecting two biologically active warheads. Synthesis of peptides as selective inhibitors of protein-protein interactions.
List of attachments:: none