# BIOCATALYST- CLICK CHEMISTRY DOWNSTREAMING TANDEM BASED INNOVATIVE KIT FOR OPTICALLY PURE FINE CHEMICALS SYNTHESIS

## Goal of the project:

Development of an innovative kit for efficient and cost-effective sequential continuous flow large-scale (multigram) preparation of optically pure chiral building blocks useful for synthesis of pharmaceutical compounds and agricultural chemicals, based on the tailor-made immobilized lipases mediated kinetic resolution of various racemic substrates and a subsequent click chemistry-type downstreaming of the reaction mixture.

## Short description of the project

A chemo-enzymatic process which integrates several innovative steps in both biocatalytic and down streaming parts was set up. The use of an immobilized biocatalysts-click chemistry tandem allowed to design easily scaled-up continuous flow procedures for industrial manufacturing of the target compounds.

## Project implemented by

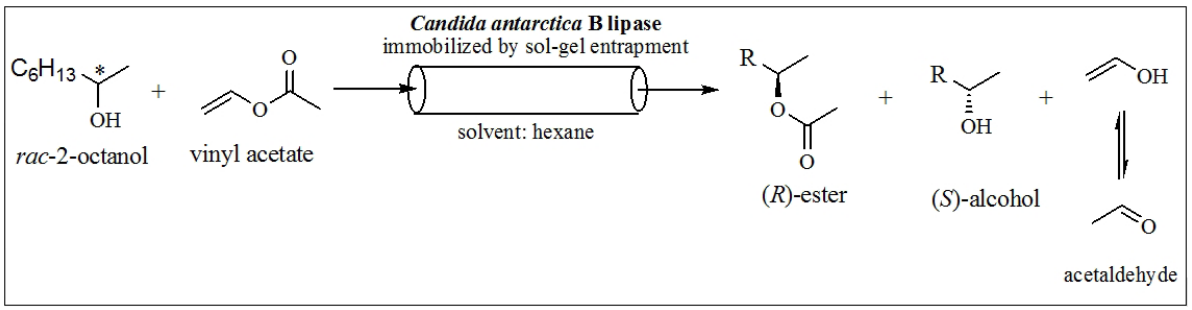
- University Politehnica Timişoara - Project leader
- University "Babes-Bolyai" Cluj Napoca - Project Partner 1
- Natural Ingredients R&D S.R.L - Project Partner 2

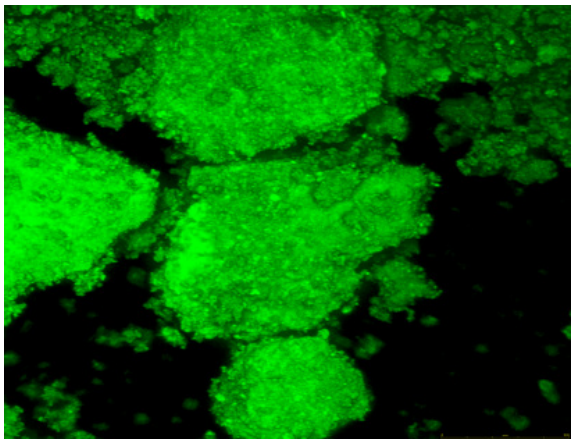
## Implementation period

01.07.2014 - 30.09.2017

## Main activities

1. Synthesis of various precursors: (hetero)aryl-ethanols, amines, hydroxy- and amino acids, as well as various propargylic esters as O- and N-acylating agents for enzymatic kinetic resolution (EKR).
2. Development of optimal EKR and click-chemistry type down streaming procedures.
3. Immobilization of lipases.
4. Development of the continuous flow procedure, on model substrates and newly synthesized substrates.



Fluorescence image of the sol-gel immobilized lipase

## Results

Racemic compounds holding a secondary OH group were subjected to lipase mediated kinetic resolution in the presence of an ester having a terminal ethynyl group. Click methodology was used to separate the enzymatic acylation reaction products, also at preparative scale, under the optimal reaction conditions identified on the analytical scale. Heteroaromatic compounds were synthesized with high optical purity (93-99%) and yields between 90-95%. The effectiveness of sol-gel immobilized enzyme preparations in enzymatic kinetic resolution reactions was tested in a continuous system for both aliphatic and aromatic substrates. The reactions were optimized by factorial experimental programs using the Box-Behnken method.

For the enzymatic kinetic resolution of rac-2-chloromandelic acid lipase from *Candida antarctica* A proved to be the most active, immobilized by entrapment in sol-gel matrices based on ternary mixture of silanes combined with adsorption on Celite.
Please visit also: http://chim.upt.ro/ro/cercetare/proiecte-de-cercetare/145-pn-ii-pt-pcca-2013-4-0734
Selected publications in the field of the project:
1. A. Todea, P. Borza, A. Cimporescu, C. Paul, F. Peter, *Catalysis Today,* 2017, https://doi.org/10.1016/j.cattod.2017.02.042.
2. M. E. Moisă, C. G. Spelmezan, C. Paul, H. J. Bartha-Vári, L. C. Bencze, F. D. Irimie, C. Paizs, F. Péter, M. I. Toşa, *RSC Advances*, 2017, 7, 52977-52987.
3. A. Cimporescu, A. Todea, V. Badea, C. Paul, F. Peter, *Process Biochemistry*, 2016, 51(12), 2076-2083.
4. D. Aparaschivei, A. Todea, I. Păuşescu, V. Badea, M. Medeleanu, E. Şişu, M. Puiu, A. Chiriță-Emandi, F. Peter, *Pure and Applied Chemistry*, 2016, 88 (12), 1191-1201.
5. C. Paul, P. Borza, A. Marcu, G. Rusu, M. Bîrdeanu, S. Marc Zarcula, F. Peter, *Nanomaterials and Nanotechnology*, 2016, 6:0, doi: 10.5772/62194.8.

## Applicability and transferability of the results

The application of tailor-made biocatalysts in industrial processes increases the economic benefits compared to the synthetic solutions. The productivity, stability, enantiomer selectivity and reusability of the enzymes increase by immobilization. The immobilized biocatalysts can be used in continuous bioreactors, under harsher conditions. The results will be scaled-up by the industrial partner, but they are available for all companies interested in fine synthesis of optically active compounds.

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## Research Center

Research Centre in Organic, Macromolecular and Natural Compounds Chemistry and Engineering

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