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

Goal of the project:

The project main objective is to develop 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 like efficient downstreaming of the reaction mixture. Such an innovative approach of coupling kinetic resolution of a broad range of racemic substrates with click chemistry type downstreaming was not yet carried out.

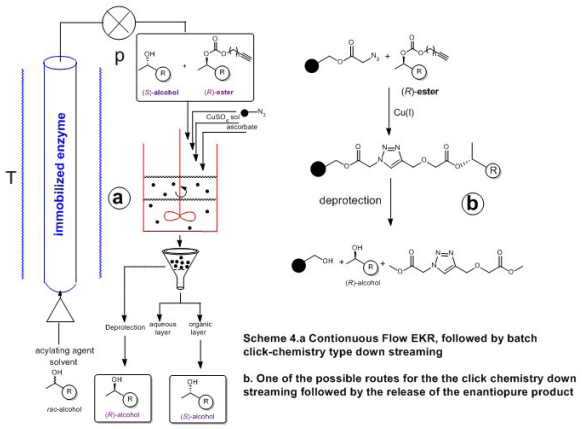
Short description of the project

Biocatalysis is an important tool to implement new, efficient, selective, cost effective and greener technologies, defining a new strategy in the industry of the future. For industrial applications, the stability and reusability of the biocatalysts are important requirements which can be achieved by immobilization, improving also their activity and selectivity. Optimization of the biocatalytic function, as well as the biocatalytic process design became essential topics in industrial biotechnology.

In this project a chemo-enzymatic process which integrates several innovative steps in both biocatalytic and down streaming parts will be set up. The utilization of tailor-made biocatalysts in industrial processes is an innovative approach, technically comparable to the synthetic solutions but with higher economic benefits. The use of immobilized biocatalysts-click chemistry tandem will permit to design easily scaled-up continuous flow procedures for industrial manufacturing of the target compounds, underlining the economic relevance of the proposal.

Project implemented by

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



Scheme 4.a Contionuous Flow EKR, followed by batch click-chemistry type down streaming

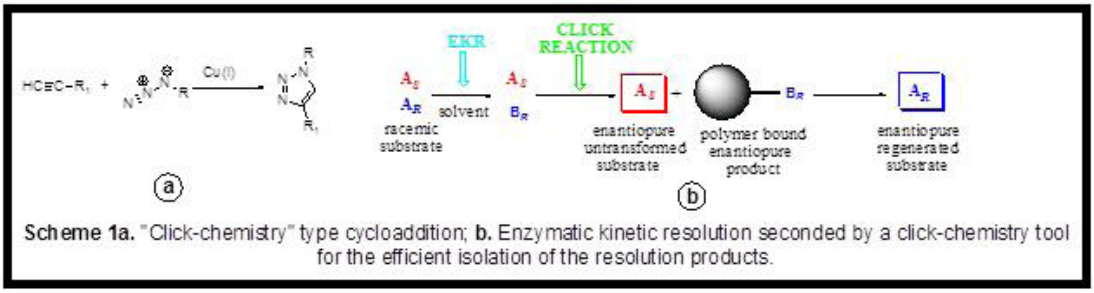
b. One of the possible routes for the the click chemistry down streaming followed by the release of the enantiopure product

Implementation period

01.07.2014-30.06.2016

Main activities

1. Preparation of various precursors: (hetero)aryl-ethanols, hydroxy- and amino acids and synthesis of various propargylic esters as O- and N-acylating agents used in 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



Scheme 1a. "Click-chemistry" type cycloaddition; **b.** Enzymatic kinetic resolution seconded by a click-chemistry tool for the efficient isolation of the resolution products.

Results

1. Multi-gram amounts of various racemic compounds and various propargylic esters as acyl donors for the EKR;
2. Enantiomeric separation protocol for previously synthesized racemates, chromatographic protocols for testing the enantioselectivity of the enzymatic reactions;
3. Scientific article submitted to an ISI quoted journal;
4. Scientific presentation, published in the abstract book of an international conference;
5. Experimental protocol of down streaming procedures;
6. Immobilization protocols and analysis procedures for tailor-made immobilized lipases;
7. Integrated EKR-click-chemistry type down streaming procedure;

Applicability and transferability of the results

The obtained kit, as well as the high-value products, will be marketable, but the process will be appropriate for further scaling-up, depending on the customer demands.

In the forthcoming period, a strong impact of industrial biotechnology can be expected in the fine chemicals sector. As lipases demonstrated the highest application capability among industrial enzymes, the efforts to improve their operational stability and catalytic efficiency led to a remarkable development of the immobilization methods. Certainly, the manufacturing of high value optically active compounds represents the main large-scale process where biocatalysis with lipases will replace the presently employed procedures.

Enzymatic kinetic resolution (EKR) of the racemic mixtures represents the most efficient way to obtain high optical purity compounds. However, in large scale EKR an important challenge remains the isolation and purification of the products, which generally involves expensive and laborious physical procedures, decreasing the global process yields and the optical purities of the isolated compounds.

To the best of our knowledge the use of click chemistry involving large carriers, as a tool for easy EKR product separation is still unknown and it could be a practical solution for the efficient large scale isolation and purification of the enzymatic resolution products. Performing the click reaction between a preactivated polymer and one of the appropriate functionalized reaction products in the enzyme free reaction mixture obtained by EKR, would circumvent the tedious isolation and purification procedures.

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