Isolation, enantioselective synthesis and structure elucidation of heterocycles with potential pharmacological activity
HETEROCYCLES

Goal of the project: The main goal of the joint project was to establish an interdisciplinary crossborder research network, which was going to pursue the following objectives.
1. HPLC-MS and HPLC-CD analysis and synthesis of the bioactive flavanolignan components of *Silybum marianum*.

2. Synthesis of optically active O- and O,Nheterocycles of potential pharmacological activity with kinetic resolution and organocatalysis.
3. Structureelucidationandcharacterization ofnewcompoundsbyMSandspectroscopic methods, determination of their absolute configuration by chiroptical methods.

Short description of the project: The essential role of optical activity and stereochemistry in pharmacological activities has been already recognized, and an increasingly larger portion of chiral drugs are used as a single enantiomer. In order to get a single enantiomer of pharmacological interest, one has to be proficient in a number of fields such as the isolation and synthesis of optically active compounds, enzymecatalyzed kinetic resolution, determination of stereochemistry and characterization by mass spectrometry (MS) and NMR spectroscopy.
The participating research groups merged their scientific experience and resources to achieve the main objectives of the project.

Project implemented by: The Department of Applied Chemistry and Engineering of Organic and Natural Compounds, in cooperationwiththeUniversityofDebrecen, Department of Organic Chemistry (leading partner of the project).

Implementation period:
01.04.2011 - 30.09.2012

Main activities:
1. Synthesis of 1,4-benzoxazepines and resolution of stereoisomers
2. Kinetic resolution of the sec-alcohol intermediates by enzymes
3. HPLC and GC analysis of synthetic and natural compounds

Hungary-Romania
Cross-Border Co-operation
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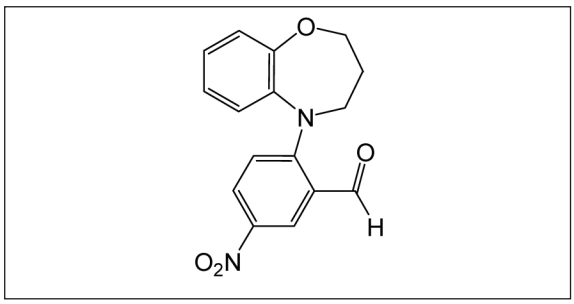
Results: Several substituted racemic tetrahydro-2-methyl-2,6-metano-2H-1-benzoxocin-4-on- and - 4-ol derivatives were synthesized in Domino reactions. The enantiomers were separated by chiral HPLC and the appropriate absolute configurations were allocated. 2,3,4,5-tetrahydro- 1,5-benzoxazepine synthesis has been investigated by several reaction pathways. The best method included three steps, synthesis of the 4- chromanone oxime, Beckmann transposition of this oxime, and reduction of the 2,3,4,5-tetrahydro-1,6-benzoxazepin-4-one intermediate. Condensation of 2,3,4,5-tetrahydro-1,4-benzoxazepine with 2-fluoro-5-nitrobenzaldehyde was initiated, with different catalytic systems. Among these catalytic possibilities, the Buchwald-Hartwig reaction yielded the highest product amount.

"The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom."

Isaac Asimov



Various lipases were immobilized by the sol-gel method and tested for optical resolution of model racemic secondary alcohols. Chiral GC and HPLC have been used for monitoring of the reactions. A combined method of sol-gel entrapment and adsorption on a porous material was also investigated, as well as utilization of ternary precursor systems. Various parameters influencing the immobilization yield and efficiency, as molar ratio of silane precursors, nature of catalyst and additives, enzyme/silane ratio, etc., were studied and optimized. Lipases from *Candida antarctica* and *Pseudomonas cepacia* showed the best results for optical resolution of heterocyclic compounds.

Important advantages of employing immobilized biocatalysts are less contamination of the reaction products with undesired protein, and possibility to increase the productivity of the process by reutilization of the enzyme in several reaction cycles.

Fields of interest:
The main fields of interest connected with the project applicability and implementation are organic chemistry and biotechnology. Synthesis of possible new bioactive components with pharmacological properties represents one of the most important topics in organic chemistry.

Enzyme-catalyzed kinetic resolution represents an innovative solution in the field of optically active compounds synthesis. Coupled MS techniques and chiroptical methods are innovative techniques for structure elucidation of natural and synthetic products.

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Research team:
UPT team: Prof. Dr. Eng. Francisc Peter (project manager assistant), Assist. Prof. Dr. Eng. VasileBercean, As. Dr. Eng. Cristina Paul, Eng. Ramona Croitoru, Eng. Anca Ursoiu.
University of Debrecen team: Assoc. Prof. Dr. Tibor Kurtán (project manager), Prof. Dr. Sándor Antus, Dr. Katalin Gulácsi, Dr. Attila Mándi

Research Centre for Organic, Macromolecular and Natural Compounds' Chemistry and Engineering

Applicability and transferability of the results:
All implemented original solutions and approaches were validated by publication in scientific journals and presentation at scientific conferences, consequently they are available for the scientific community. The biological activity of the synthesized compounds will be evaluated, for potential transfer to interested companies.

Contact information:
Prof. Dr. Eng. Francisc Peter
University „Politehnica" of Timişoara, Faculty of Industrial Chemistry and Environmental Engineering, C. Telbisz 6, 30001 Timişoara
Tel (0040) 256 404216
Fax (0040 256 403060
Email: francisc.peter@chim.upt.ro

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