Report on the results obtained accordingly the research proposal

1. Synthesis of novel monoterpene-based β-amino acid and their derivatives

1.1. Stereoselective synthesis of carane-based chiral β- and γ-amino acid derivatives via conjugate addition

Michael addition of dibenzylamine to (–)-*tert*-butyl isochaminate, prepared in three steps from (–)-perillaldehyde, furnished a carane-based β-amino acid derivative in a highly stereospecific reaction. The resulting amino ester was transformed to the corresponding bicyclic amino acid stereoselectively. The conjugate addition of nitromethane to α,β-unsaturated methyl ester likewise resulted in nitro esters in stereospecific reactions. Catalytic reduction of the nitro group yielded a γ-amino ester. Under acidic conditions, the hydrolysis of the methyl ester resulted in an unexpected aminolactone-type product through rearrangement of the bicyclic carane system, whereas an alternative synthetic pathway through α,β-unsaturated benzyl ester furnished the desired γ-amino acid. Our result was presented as conference poster and lecture, and was also published in *Tetrahedron* journal.

1.2. Stereoselective synthesis of perillaldehyde-based chiral β-amino acid derivatives

The Michael addition of dibenzylamine to (+)-*tert*-butyl perillate and to (+)-*tert*-butyl phellandrate, derived from (*S*)-(–)-perillaldehyde, furnished diastereomeric mixtures of β-amino esters in a moderately stereospecific reaction in a ratio of 76:17:6:1. After separation of the diastereoisomers, the major product *cis* isomer was quantitatively isomerized to the minor component *trans* amino ester. All four isomers were transformed to the corresponding β-amino acid in three steps. The steric effects of the isopropyl group at position 4 and of the α-methyl substituent of (*R*)-*N*-benzyl-*N*-α-methylbenzylamine on the reactivity were also studied and, on the application of a chiral amine, excellent stereoselectivity of the conjugate addition was observed. Amino ester obtained was a single product and transformed to the corresponding *cis*- and *trans*-amino acid in good yields on a gram scale. Our results were presented as conference poster and lecture, and were also published in *Beilstein J. Org. Chem.*

2. Conversion of monoterpene-based aldehydes to highly functionalized aminodiol-type building blocks.

2.1. Stereoselective synthesis of carane-based aminodiols as chiral ligands for the catalytic addition of diethylzinc to aldehydes

Reductive amination of (–)-2-carene-3-aldehyde served 2-carene-based allylamines. Boc or Cbz protection of the resulting amines, followed by stereoselective dihydroxylation in a highly stereospecific reaction with OsO_4, and deprotection resulted in *N*-benzylaminodiols, which were transformed to primary and tertiary aminodiols. In the reactions of *N*-benzyl- and *N*-(1-phenylethyl)-substituted derivatives with formaldehyde, highly regioselective ring closure was observed, where aminodiols gave carane-fused 1,3-oxazines. The aminodiols and their 1,3-oxazine derivatives were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde. The best (*R*)-enantioselectivity was observed in the case of the *N*-((*R*)-1-phenylethyl)-substituted aminodiol while the changing of the chiral direction was observed when 1,3-oxazines were applied. The phenomenon was interpreted by using molecular modeling at an *ab initio* level. The molecular modeling at RHF/LANL2DZ level of theory was successfully applied and optimised 1,3-oxazines were developed affording excellent stereoselectity (*ee*: 95% and 98%) for the examined transformation. The manuscript was published in *Chemistry a European Journal.*

2.2. Synthesis and pharmacological application monoterpene-based nucleoside analogues

Starting from monoterpene-based beta-hydroxy-epoxides a comparative syntheses were developed for pinane-based chiral carbocyclic nucleosides. Regioselective ring opening of the oxirane ring with nucleoside bases resulted in adenine-, cytosine- and uracil-based carbocyclic nucleosides in a single-step synthsesis. An alternative 6 step synthesis of purine derivatives was also achieved. The prepared compounds were examined as a novel NCX inhibitor, on the NCX, L-type calcium and main repolarizing potassium currents as well as action potential parameters were investigated. Our results were published in *Can. J. Physiol. Pharmacol.*

2.3. Stereoselective synthesis of limonene-based 1,3-aminoalcohols and aminodiols

An unexpected ring-closing reaction of an α,β-unsaturated carboxylic acid, derived from (*S*)-limonene, in the presence of trifluoroacetic anhydride resulted in bicyclic α-methylene ketones and their hydroxylated analogues in a stereoselective intramolecular acylation. The reaction was studied in detail and optimized for both compounds. Addition of secondary and primary amines to both keto alkenes followed by *in situ* reduction of formed aminoketones with sodium borohydride gave new bicyclic terpenoid secondary and tertiary 1,3-aminoalcohols and aminodiols with excellent diastereoselectivity. Regioisomeric aminodiols were prepared stereoselectively from the unsaturated 1,3-aminoalcohols via hydroboration reaction with Me_2S. BH_3/H_2O_2 system. The work was published in *Eur. J. Org. Chem.*

2.4. Stereoselective synthesis of sabinol-based aminodiols, diols and triols

A library of bidentate diols as well as tridentate triols and aminodiols was synthesized from (+)-sabinol. Sabinol was transformed into allylic trichloroacetamide and after changing the protecting group to Boc, the enamine was subjected to stereospecific dihydroxylation with OsO_4/NMO resulting in the (1*R*,2*R*,3*R*,5*R*)-aminodiol diastereomer. The ring closure of the *N*-benzyl-substituted aminodiol with formaldehyde was investigated and regioselective formation of the spiro-oxazolidine ring was observed. Hydroboration or dihydroxylation of sabinol or its benzyl ether with OsO_4/NMO resulted in the formation of sabinane-based diols and triols following a highly stereospecific reaction. Our result was presented as conference poster, and was also published in *Molecules*.

2.5. Stereoselective synthesis of monoterpene-based 1,2,4- and 1,3,4-oxadiazoles

Stereoselective synthesis of monoterpene-based 1,2,4- and 1,3,4-oxadiazole derivatives was also accomplished starting from α,β-unsaturated carboxylic acids, obtained by the oxidation of (-)-2-carene-3-aldehyde and commercially available (-)-myrtenal. Our results were presented as conference poster and lecture, and were also published in *Int. J. Mol. Sci.*

3. Synthesis and application of potential chiral catalyst in divers stereoselective transformations

3.1. Stereoselective synthesis and transformations of pinane-based 1,3-diaminoalcohols

A library of pinane-based 1,3-diaminoalcohols and 5-aminomethyloxazolidin-2-ones was developed from commercially available (1*R*)-(-)-myrtenol which was transformed to *N*-trichloroacetyl protected allyl amine via Overmann rearrangement followed by stereoselective epoxidation with *m*CPBA resulting in key intermedier epoxy-amine. In order to obtain the diaminoalcohol moiety, aminolysis and azidolysis of the oxirane ring was performed. The cleavage of the oxirane ring proceeded regioselectively, affording *N*-trichloroacetyl protected 1,3-diaminoalcohols and oxazolidin-2-ones, which were obtained also via a thermal cyclisation. Since *N* deprotection of diaminoalcohols was unsuccessful under varied conditions, the protecting group was changed and Boc-protected analogues were synthesised. In this case, removal of the Boc protecting group was successful resulting in the planned diamino alcohols. The obtained potential catalysts were applied in the test reaction of benzaldehyde and diethylzinc with low to moderate enantioselectivities (up to 74% *ee*). Our results were published in *Tetrahedron* journal. Further, aminoalcohol- and aminodiol-based triphenylphisphine-type catalysts are under investigation.

3.2. Similarly to **3.1.**, aminoalcohols and aminodiols are prescribed in **chapter 1.** and **2.** have been successfully applied as chiral catalysts in enantioselective addition of dialkylzinc to aromatic aldehydes.

4. Synthesis of potential anti-cancer agent 1,3-heterocycles.

4.1. Stereoselective synthesis and cytoselective toxicity of monoterpene-fused 2-imino-1,3-thiazines

Starting from pinane-, apopinane- and carane-based 1,3-amino alcohols obtained from monoterpene-based β-amino acids, a library of monoterpene-fused 2-imino-1,3-thiazines as main products and 2-thioxo-1,3-oxazines as side-products were prepared via two- or three-step syntheses. When thiourea adducts prepared from 1,3-amino alcohols and aryl isothiocyanates were reacted with CDI under mild conditions, O-imidazolylcarbonyl intermediates were isolated which could be transformed to the desired 1,3-thiazines under microwave conditions. 1,3-Thiazines and side-product 2-thioxo-1,3-oxazines could also be prepared in one-step reactions through the application of CDI and microwave irradiation. The ring-closure process was extended to cycloalkane-based γ-hydroxythioureas. This method proved a new procedure for the preparation of 1,3-thiazines condensed with acid senzitive ring systems. The carane- and apopinane-based derivatives exhibited marked antiproliferative activity against a panel of human adherent cancer cell lines (HeLa, A2780, MCF7 and A431). Similar results were obtained when analogue 2-imino-1,3-oxazines were prepared from the above mentioned thiourea derivatves and examined. Our result was presented as conference poster and lecture, and was also published in *Molecules* and *Curr. Org. Synth.* journals.

Perspectives of the obtained results

The β-amino acid derivatives are prepared in 1-5 gramm scale, are available for commercial purpose and may serve as building blocks either for the synthesis of β-foldamers, or biologically active peptides. The 1,3-difunctional aminoalcohols, diamines, diols and the trifunctional aminodiols and diaminoalcohols can prove useful building blocks for the ynthesis of new, monoterpene-fused 1,3-heterocycle or peptide-like libraries with both pharmacological and catalytical purpose. Some of our monoterpene-based 1,3-heterocycles have been proved excellent catalysts in enantioselective transformations.

In this period an academic doctoral thesis was also written, submitted (and deffended) to the Hungarian Academy of Sciences entitle: „Monoterpénvázas β- és γ-aminosavszármazékok és 3-amino-1,2-diolok sztereoszelektív szintézise és alkalmazásai". The NKFI grant, providing the financial support, helped a lot to prepare it, undoubtedly.

Personal changes during the project:

Árpád Csőr and Timea Gonda finished their PhD studies, Timea Gonda has got her PhD degree, so they left the program int he second and third year, a new PhD Student Le Minh Tam has arrived for the last two years.

Similarly 1 technician, Katinka Horváth left the research group and a new technician Nóra Tóth arrived. Each case we applied and got permissions for changing.

Time-shifted supplies:

Because of the very slow administration process of the University, I could not supply the planned computer, printer and vacuum pump in the originaly planned period, but only in the last year (although the procedure started in time).

Scientific publications according to the grant topic with NKFI ID number in acknowledgement:

During the granted 4 year period, 16 articles, with summerized impact factor 46.175 were published. Most of them are Q1 and D1 article.

1. **Zsolt Szakonyi**, István Zupkó, Reijo Sillanpää, Ferenc Fülöp:
Stereoselective Synthesis and Cytoselective Toxicity of Monoterpene-Fused 2-Imino-1,3-thiazines
Molecules **19**, 15918–15937 (2014)
doi:10.3390/molecules191015918 I.f.: 2,416

2. **Zsolt Szakonyi**, Reijo Sillanpää, Ferenc Fülöp
Stereoselective synthesis of perillaldehyde-based chiral β-amino acid derivatives through conjugate addition of lithium amides
Beilstein J. Org. Chem. **10**, 2738–2742 (2014)
doi: 10.3762/bjoc.10.289 I.f.: 2,762

3. **Zsolt Szakonyi**, Árpád Csőr, Matti Haukka, Ferenc Fülöp:
Stereoselective synthesis of carane-based chiral β- and γ-amino acid derivatives via conjugate addition
Tetrahedron **71**, 4846–4852 (2015)
doi:10.1016/j.tet.2015.05.019 I.f.: 2,645

4. Gábor Olajos, Anasztázia Hetényi, Edit Wéber, Lukács J. Németh, **Zsolt Szakonyi**, Ferenc Fülöp, Tamás A. Martinek:
Induced Folding of Protein-Sized Foldameric β-Sandwich Models with Core β-Amino Acid Residues
Chem. Eur. J. **21**: 6173-6180 (2015)
DOI: 10.1002/chem.201405581 .f.: 5,771

5. Yolanda C. Rodriguez, Tayla M. Duarte, **Zsolt Szakonyi**, Enikő Forró, Ferenc Fülöp, Thomas J. Wenzel
Utilization of (18-Crown-6)-2,3,11,12-tetracarboxylic Acid as a Chiral NMR Solvating Agent for Diamines and -Amino Acids
Chirality **27**, 708–715 (2015)
DOI: 10.1002/chir.22491 I.f.: 2,025

6. **Zsolt Szakonyi**, Árpád Csőr, Antal Csámpai, Ferenc Fülöp

Stereoselective Synthesis and Modelling-Driven Optimisation of Carane-Based Aminodiols and 1,3-Oxazines as Catalysts for the Enantioselective Addition of Diethylzinc to Benzaldehyde.
Chem. Eur. J. **22**, 7163–7173 (2016)
DOI: 10.1002/chem.201600749 I.f.: 5,317

7. Szakonyi Zsolt
Monoterpénvázas 3-amino-1,2-diolok sztereoszelektív előállítása, átalakításai és alkalmazásai
Magyar Kémikusok Lapja **71**, 3-4 (2016)

8. Tímea Gonda**, Zsolt Szakonyi**, Antal Csámpai, Matti Haukka, Ferenc Fülöp
Stereoselective synthesis and application of tridentate aminodiols derived from (+)-pulegone
Tetrahedron: Asymmetry, **27**, 480–486 (2016)
DOI: 10.1016/j.tetasy.2016.04.009 I.f.: 2,126

9. Amir Geramipour, Zsófia Kohajda, Claudia Corici, János Prorok, **Zsolt Szakonyi**, Kinga Oravecz, Zoltán Márton, Norbert Nagy, András Tóth, Károly Acsai, László Virág, András Varró, Norbert Jost
The investigation of the cellular electrophysiological and antiarrhythmic effects of a novel selective sodium–calcium exchanger inhibitor, GYKB-6635, in canine and guinea-pig hearts
Can. J. Physiol. Pharmacol. **2016,** *94*, 1090–1101.
DOI: 10.1139/cjpp-2015-0566 I.f.: 1.822

10. **Zsolt Szakonyi**, István Zupkó, Ferenc Fülöp
Stereoselective Synthesis and Antiproliferative Activity of Monoterpene-Fused 2-Imino-1,3-oxazines
Current Organic Synthesis, **2017**, *14*, 612-619.
DOI: 10.2174/1570179414666161116110813 I.f.: 1.69

11. Tímea Gonda, Attila Balázs, Gábor Tóth, Ferenc Fülöp, **Zsolt Szakonyi**
Stereoselective synthesis and transformations of pinane-based 1,3-diaminoalcohols
Tetrahedron **2017**, *73*, 2638-2648.
DOI: 10.1016/j.tet.2017.03.050 I.f.: 2.377

12. Gyula Lajkó, Tímea Orosz, Imre Ugrai, **Zsolt Szakonyi**, Ferenc Fülöp, Wolfgang Lindner, Antal Péter, István Ilisz
Liquid chromatographic enantioseparation of limonene-based carbocyclic **β**-amino acids on zwitterionic Cinchona alkaloid-based chiral stationary phases
J. Sep. Sci. **2017**;*40*, 3196–3204.
DOI: 10.1002/jssc.201700450 I.f.: 2.415

13. Tam Minh Le, Ferenc Fülöp, **Zsolt Szakonyi**
Stereoselective Synthesis of Limonene-Based Chiral 1,3-Amino Alcohols and Aminodiols
Eur. J. Org. Chem **2017**, 6708-6713.
DOI: 10.1002/ejoc.201701299 I.f.: 2.882

14. Tímea Gonda, Péter Bérdi, István Zupkó, Ferenc Fülöp, Zsolt Szakonyi
Stereoselective Synthesis, Synthetic and Pharmacological Application of Monoterpene-Based 1,2,4- and 1,3,4-Oxadiazoles
Int. J. Mol. Sci., **2018**, *19*, 81.
DOI: 10.3390/ijms19010081 I.f.: 3.687

15. Yerbolat Tashenov, Mathias Daniels, Koen Robeyns, Luc Van Meervelt, Wim Dehaen, Yerlan M Suleimen, Zsolt Szakonyi
Stereoselective Syntheses and Application of Chiral Bi- and Tridentate Ligands Derived from (+)-Sabinol
Molecules, **2018**, *23*, 771. I.f.: 3.098

16. Tam Minh Le, Antal Csámpai, Ferenc Fülöp, Zsolt Szakonyi
Regio- and Stereoselective Synthesis of Bicyclic Limonene-Based Chiral Aminodiols and Spirooxazolidines
Chem. Eur. J. **2018**, *24*, 13607-13615. I.f.: 5.16

Lectures held in the last, 01.09.2017-31.08.2018. period:

1. Le Minh Tam, Ferenc Fülöp, **Zsolt Szakonyi**: ynthesis and transformation of isopulegol-based chiral trifunctional synthons. MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2018. június 6-8.

2. **Szakonyi Zsolt**: Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 17. Tudományos Előadói Ülése: Monoterpénvázas trifunkciós építőelemek sztereoszelektív előállítása, átalakításai és alkalmazásai (meghívott előadó)

3. Yerbolat Tashenov, Mathias Daniels, Koen Robeyns, Luc Van Meervelt, Wim Dehaen, Yerlan M. Suleimen, **Zsolt Szakonyi**: Stereoselective synthesis and application of chiral bi- and tridentate ligands derived from (+)-sabinol. 16th Belgian Organic Synthesis Symposium - July 8-13, 2018, Brussels, Belgium, PO-256

4. **Zsolt Szakonyi**, Ákos Bajtel, Matti Haukka, Ferenc Fülöp: Synthesis and application of monoterpene-based 2-amino-1,2-diols. XXII International Conference on Organic Synthesis – 22-ICOS, 16-21, szeptember, 2018, Firenze, Olaszország, P-238

Szeged, 26/09/2018

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