Report on the results obtained accordingly the research proposal

1. Transformations of electron rich aromatic rings to potentially bioactive compounds

Selective *N*-alkylations of tetrahydroisoquinolines, tetrahydrobenz[*d*]azepine, tetrahydro-benz[*c*]azepine and tetrahydrothieno[3,2-*c*]pyridine were achieved by using 1-naphthol and aromatic aldehydes under neat conditions. The reactions were extended to the synthesis of 1-aminoalkylated 2-naphthol derivatives by mixing 2-naphthol, aromatic aldehydes and the corresponding cyclic amines. It was assumed that a parallel *N*-alkylation and redox α-arylation take place during the reaction of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde at 65 °C. A simple synthesis of 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)indole and 3-(6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinolin-1-yl)indole has been developed, involving the reaction of 3,4-dihydroisoquinoline or 6,7-dimethoxy-3,4-dihydroisoquinoline and indole. The reaction was tested by starting from the latter cyclic imines and indole-2-carboxylic acid. The new γ-amino acids prepared in this way were obtained in good yields. The synthetic applicability of this aza-Friedel–Crafts reaction was extended to the preparation of 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole, 3-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-4-yl)indole, 3-(2,3,4,5-tetrahydro-1*H*-benz[*c*]azepin-1-yl)indole-2-carboxylic acid and 3-(4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-4-yl)indole-2-carboxylic acid from cyclic imines such as 4,6-dihydro-3*H*-benz[*c*]azepine and 6,7-dihydrothieno[2,3-*c*]pyridine. All the reactions could be accelerated dramatically by using microwave irradiation.

C1 couplings of 4,5-dihydro-3*H*-benz[*c*]azepine and 6,7-dihydrothieno[3,2-*c*]pyridine were achieved by reacting cyclic imines with 1- or 2-naphthol under neat conditions resulting in hydroxynaphthyl-benzazepines and hydroxynaphthyl-thienopyridines. *N*-Containing naphthol analogues such as 5-hydroxyisoquinoline and 6-hydroxyquinoline were also applied. Achieving the transformations under microwave irradiation at 80 °C, hydroxyisoquinolyl and hydroxyquinolyl derivatives were isolated as novel bifunctional compounds. Syntheses were then extended by the application of (4aS,8aS)-4a,5,6,7,8,8a-hexahydro-2-quinoxalinone as cyclic imine component in C1 coupling reactions. In these cases, conventional heating was preferred. The preparation of hydroxynaphthyl-quinoxalinones by the application of 2-naphthol found to be diastereoselective, while in the case of 1-naphthol, the formation of three diastereomers were observed that were then separated by column chromatography. Isolated bifunctional compounds underwent cyclizating reactions using a 35% aqueous solution of formaldehyde as cyclizing agent. Achieving the reactions at room temperature in

dichloromethane, the desired naphthoxazine-, oxazino-isoquinoline- and oxazino-quinoline-fused polyheterocycles were formed. A synthetic route to annelational analogue naphth[1,3]oxazino[2,3-*a*]benzazepines and -thienopyridines was developed. Starting from 4,5-dihydro-3*H*-benz[*c*]azepine or 6,7-dihydrothieno[3,2-*c*]pyridine and variously substituted primary aminonaphthols, the formation of desired polyheterocycles occurred. The diastereoselectivity of the reaction was found to depends on the steric effect of the aromatic ring at position 14 or 16 and on the position of annulation of the naphthalene ring. A systematic study was carried out to compare the reactivity and applicability of primary, secondary and tertiary aminonaphthols in the [4+2] cycloaddition reaction. Based on this study, tertiary aminonaphthols afforded the best results. Therefore, the synthesis of 16-naphth-2-yl-naphth[1,2-*e*][1,3]oxazino[2,3-*a*]benz[*c*]azepine, 14-naphth-1-yl-naphth[1,2-*e*]-[1,3]oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine and 14-naphth-2-yl-naphth[1,2-*e*][1,3]-oxazino[2,3-*a*]-6,7-dihydrothieno[3,2-*c*]pyridine was achieved starting from tertiary aminonaphthols. During the preparation of the initial bifunctional compounds, an unexpected transformation led to the formation of a diole derivative. The scope and limitations of its formation were investigated from the point of view of both amine and aldehyde scopes but no product with a structure similar to that of the diole could be isolated.

A simple method was developed for the synthesis of naphth[1,3]oxazino[3,2-*a*]quinoxalinones. Starting from enantiomeric hexahydroquinoxalinone and 1-aminoalkyl-2-naphthols or 2-aminoalkyl-1-naphthols, successful transformations were accomplished at 80 °C under microwave irradiation. The formation of the possible diastereomers was confirmed by crude product NMR spectra and they were isolated by column chromatography.

2. Transformations of cyclic β-amino acids

During our work cyclohexane analogues of the antifungal icofungipen were selectively synthesized from unsaturated bicyclic lactams by transformation of the ring olefinic bond through three different regio- and stereocontrolled hydroxylation techniques, followed by hydroxy group oxidation and oxo-methylene interconversion. By a stereocontrolled approach to highly functionalized 3,4-disubstituted azetidin-2-ones and beta-2,3-amino acid derivatives was achieved. The syntheses involved 1,3-dipolar cycloaddition of chlorosulfonyl isocyanate, followed by ring-opening metathesis of the unsaturated bi- or tricyclic beta-lactams, and crossmetathesis of the resulting divinyl-substituted azetidinones. The substituted lactams were subsequently transformed by heteroring-opening into the corresponding functionalized acyclic

beta-2,3-amino acids. An overview of peptide and peptoid foldamers in medicinal chemistry was also published.

A convenient and robust synthetic method was developed for the preparation of fluoroalkyl-substituted β-amino acid derivatives containing piperidine and azepine skeleton. The method is based on the oxidation of the double bond-containing starting β-amino acids followed by reductive alkylation.

3. Enzymatic resolution with remote stereogenic centres

By using Candida antarctica lipase-B, the synthesis of 1-(*R*)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid was achieved. It was found that the enzyme catalysed selectively the hydrolysis of the ester via dynamic kinetic resolution. The selectivity of the reaction was found to be R, both by using buffer solation or by using organic solvents, and the selectivity of the reactions reached sometimes the value of 100% of ee.

The enantiomeric separation of *N*-Boc-protected 1-hydroxymethyl-, 1-hydroxymethyl-6-methoxy- and 1-hydroxymethyl-6-fluoro-1,2,3,4-tetrahydro-β-carboline derivatives were also performed by enzyme catalysed asymmetric acylation. The reactions were examined by using flow reactors and then were repeated/extended by applying "batch" conditions. As acylating agents acetic anhydride was used and toluene was found to be the optimal solvent.

We reported several efficient enzymatic resolutions for the preparation of new β-amino acid enantiomers. Both enantiomers of tetrahydro-β-carboline carboxylic acid have been prepared by dynamic kinetic resolution perotocols with high ee and high yield. The kinetic resolution of salsolidine and it β-carbolin analogue was also succesfully performed. Several review article were also published by us, in the field of cyclic β-amino acids, and the related heterocycles.

4. Synthesis of new heterocycles via retro-Diels Alder (rDA) reaction

From 2-aminonorbornene carboxylic acid enantiomers fused heterocycles were prepared. The domino ring-closure, follwed by retro Diels Alder protocols, the chirality of the desired products was transferred, from norbornene derivatives, with unique traceless chirality transfer.

A high-yielding synthetic route has been developed to constitute complicated heterocycles, applying domino, click and retro-Diels–Alder (RDA) reaction sequences. From 2-aminocarboxamides, a new set of isoindolo[2,1-a]quinazolinones was synthesized with

domino ring closure. A click reaction was performed to create the 1,2,3-triazole heterocyclic ring, followed by an RDA reaction resulting in dihydropyrimido[2,1-a]isoindole-2,6-diones. The synthesis of racemic and enantiopure tricyclic and tetracyclic pyrrolopyrimidinones, pyrimidoisoindoles, and spiropyrimidinones, as valuable new chemical entities (NCE), based on a highly controlled continuous-flow (CF) retro-Diels–Alder protocol were examined. This approach ensured enhanced safety, and gave the target pyrimidinone derivatives yields higher than those obtained in batch and microwave processes. These results were achieved through careful optimization of the reaction parameters. We also developed an alternative time-efficient route for the synthesis of intermediate quinazolinones involving a three-step domino ring-closure reaction followed by spirocyclization under continuousflow conditions, starting from -aminonorbornene carboxamides and γ-keto acids or cycloalkanones. Reactions of diastereochemically varied norbornene-condensed 2-thioxopyrimidin-4-ones with variously functionalized hydrazonoyl chlorides gave regioselectively angular norbornene-based [1,2,4]triazolo[4,3-a]pyrimidin-7(1H)-ones. Thermal retro Diels–Alder (RDA) reaction of the [1,2,4]triazolo[4,3-a]pyrimidin-7(1H)-ones resulted in the target heterocycles as single products. On the other hand, reactions of thiouracil and hydrozonoyl chlorides gave regioselectively [1,2,4]triazolo[4,3-a]pyrimidinone-5(1H)-ones. The opposite regioselectivity of thiouracil and norbornenecondensed 2-thioxopyrimidin-4-ones were attributed to electronic factors according to DFT calculations. The angular structure of norbornene based [1,2,4]triazolo[4,3-a]pyrimidin-7(1H)-ones was confirmed by single crystal X-ray crystallography.

5. Synthesis and applications of chiral aminodiols, derived from natural (−)-β-pinene

A library of pinane-based chiral aminodiols, derived from natural (−)-β-pinene, were prepared and applied as chiral catalysts in the addition of diethylzinc to aldehydes. (−)-β-Pinene was reacted to provide 3-methylenenopinone, followed by a reduction of the carbonyl function to give a key allylic alcohol intermediate. Stereoselective epoxidation of the latter and subsequent ring opening of the resulting oxirane with primary and secondary amines afforded aminodiols. The regioselectivity of the ring closure of the *N*-substituted secondary aminodiols with formaldehyde was examined and exclusive formation of oxazolidines was observed. Treatment of the allylic alcohol with benzyl bromide provided the corresponding O-benzyl derivative, which was transformed into *O*-benzyl aminodiols by aminolysis. Ring closure of the *N*-isopropyl aminodiol derivative with formaldehyde resulted in

spirooxazolidine. The obtained potential catalysts were applied in the reaction of both aromatic and aliphatic aldehydes to diethylzinc providing moderate to good enantioselectivities (up to 87% ee). Through the use of molecular modeling at an ab initio level, this phenomenon was interpreted in terms of competing reaction pathways.

6. Application of continuous flow (CF) methodology for the synthesis new precursors

Using flow chemistry protocols several peptide syntheses, catalytic coulpling reactions was succesfully performed. For example valuable 1,4-disubstituted diynes and substituted aromatic azo-compounds were performed chemoselectively in excellent, yield, short process time even on preparative scale.

During our work a novel spherical activated carbon-supported palladium catalyst has been found to be useful for the catalytic deuterodehalogenation of haloarenes. After careful reaction parameter optimization, complete conversion was achieved for bromine- and chlorine-substituted haloarenes.

A flow chemistry-based approach is presented for the synthesis of 3,5-disubstituted pyrazoles via sequential copper-mediated alkyne homocoupling and Cope-type hydroamination of the intermediary 1,3-diynes in the presence of hydrazine as nucleophilic reaction partner. The proposed multistep methodology offers an easy and direct access to valuable pyrazoles from cheap and readily available starting materials.

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, aminonaphthols can prove useful building blocks for the synthesis of new, naphthalene-, quinoline- or monoterpene-fused 1,3-heterocycle or peptide-like libraries with both pharmacological and catalytical purpose.

In this period an academic doctoral thesis was also written, submitted (and defended) to the Hungarian Academy of Sciences entitle: „Elektrondús aromás vegyületek átalakításai a módosított Mannich, illetve *aza*-Friedel-Crafts reakció segítségével". The NKFI grant, providing the financial support, helped a lot to prepare it, undoubtedly.

Personal changes during the project:

Beáta Fekete, Ádám Georgiádes, Rita Megyesi and Alíz Szloszár finished their PhD studies, Beáta Fekete, Ádám Georgiádes and Rita Megyesi have got their PhD degree, so they left the program.
Similarly 3 researchers Dr. István Mándity, Dr. Sándor Balázs Ötvös and Dr. Ferenc Miklós left the research group. Because Prof. Ferenc Fülöp passed away in 2021, Dr. István Szatmári became the new principal investigator of the project.

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

During the granted 6 year period, **74** articles, with summarized impact factor of **246.096** were published. Most of them are Q1 and D1 article.

Szeged, 26/11/2021

(Prof. Dr. Ferenc Fülöp)
(former principal investigator)

Dr. István Szatmári
principal investigator