Final Report on the project
Study of the structure-retention relationships in chiral separations applying potential pharmacons as model compounds (K108847)

The main objectives of the project were:

- obtaining information on the retention (selectivity)-molecular structure relationships
- to gain deeper knowledge of the separation mechanism
- to develop new separation methods for the resolution and identification of different chiral analytes

All the results obtained in this period were presented at several scientific conferences, and twenty eight scientific articles were published by the research group in the period 2014-2017 (2018) indicating the OTKA grant, with a cumulative impact factor ca. 90. In accordance with the project proposal we focused our research activity on the effects of bulk solvent composition of mobile phase and the nature and concentration of different modifiers. Experiments were performed in order to study the effect of temperature and thermodynamic parameters were calculated.

Results obtained in this project contribute to shed light on the enantiodiscrimination processes observed with different chiral selectors and serve valuable data for the enantioseparation of potential pharmacons with various structures.

Results obtained on structure-retention (selectivity) relationships

Exploring the structure-retention (selectivity) relationships played substantial role in our research work. Some of our findings are mentioned below.

Applying zwitterionic chiral stationary phases (CSPs) and β^2- and β^3-amino acids as model compounds the retention factor was found to depend strongly on the volume of the alkyl group: via steric effects, a bulkier substituent inhibited the overall interaction with the selector, and the retention decreased. However, a longer chain length and a bulkier molecular structure resulted in improved chiral recognition. The aromatic π-π interactions in most cases led to stronger binding to the selector, but in a non-selective way. The substituent of the aromatic ring (e.g. methoxy or hydroxyl group, halogen element) may lead to the formation of additional H bonds enhancing the retention. The configurational characteristics influence the chiral recognition in an essential way. The *trans* configuration in most cases favors the formation of interactions responsible for sufficient retention. For cyclic *β*-amino acids the *trans* configuration, while for bicyclic *β*-amino acids *exo-endo* and *diexo* configuration offer higher selectivity. A double bond may induce secondary interactions which play a role in the retention, but the enantiorecognition more strongly influenced by the molecular structure than by the presence or absence of a double bond.

Applying macrocyclic glycopeptide-based CSPs the effects of sugar units were explored. The steric hindrance effect of the sugar moieties was evidenced for the β^2-amino acids, while for the β^3-amino acids sugar units support the enantiorecognition. The importance of ionic interactions for the retention was justified with ampholytic model compounds. The *trans* isomers was found to interact more strongly with the teicoplanin-based selectors then the *cis* isomers, but this interaction was dominated by non-selective contributions. Aromatic substituents could enhance the chiral recognition through selective π-π interactions.

The results obtained applying polysaccharide-based CSPs and napthol analogs as model compounds reveal that the bulkier substituents inhibited the interaction with the selector leading

to lower retentions. Oppositely, with higher size descriptor significant enhancement was found in selectivity, indicating how the steric effects influence the retention and chiral discrimination of the 2-naphthol derivatives. The influence of the molecular size was also explored in case of *β*-lactams. Increasing number of carbon atoms attached to the *β*-lactam ring exerted a considerable influence on the retention (and chiral discrimination) demonstrating the high importance of steric effects for the polysaccharide-based CSPs.

Since all the results have been published (in peer-reviewed scientific journals) here only a short summary is presented on the basis of each article.

The separation of the enantiomers of phenylalanine amide and methyl derivatives as well as some aminoalcohols by CE using cyclodextrins (CDs) as chiral selectors in an acidic background electrolyte was studied [P1]. The native CDs displayed no or only low chiral recognition ability, while the application of sulfated *α*-, *β*- and *γ*-CDs resulted in enantioseparations of these compounds. The migration behavior could be attributed to the mobilities of the enantiomer-CD complexes adding another example to the CE-specific phenomenon of enantioseparations based primarily on complex mobilities.

Our research activity was focused on the enantioseparations achieved by HPLC applying macrocyclic glycopeptide- [P14, P23, P24], modified polysaccharide [P9, P18, P20] and ion exchanger-based [P2-P6, P8, P10-P11, P13-P17, P20-P24, P26-P28] CSPs. The majority of the scientific efforts were centered on the ion exchange-based CSPs because of their novelty.

Results obtained on ion exchange-based CSPs

Quinine- or quinidine-based zwitterionic ion-exchanger as chiral selector was applied for the enantioseparation of 27 unusual cyclic secondary α-amino acids [P2]. The quinidine-based ZWIX(−) column appeared more suitable for the enantioseparation of the investigated unusual cyclic secondary amino acids.

Sixteen unusual *β*-amino acids were directly separated on CSPs containing quinine- or quinidine-based zwitterionic selectors [P3]. The mobile phases applied supported ionic interactions between the zwitterionic chiral selector and free, ampholytic amino acids. Aromatic π-π and nonspecific hydrophobic interactions were found to enhance the enantioselectivity to some extent.

Procedures for the direct HPLC enantiomer separation of four bicyclo[2.2.2]octane-based 3-amino-2-carboxylic acids were developed in polar-ionic mode [P4]. Separations carried out with MeOH and MeCN mobile phases containing different base and acid additives indicated that the quinidine-based ZWIX(−) column appeared more suitable for the enantioseparation of the investigated bicyclic *β*-amino acids.

The effects of temperature on the chiral recognition of cyclic *β*-amino acid enantiomers on zwitterionic CSPs were investigated [P5]. In some cases, unexpected temperature behavior was observed: the selectivity, and in special cases, the retention time increased with increasing temperature.

Stereoselective HPLC separations of five sterically constrained monoterpene-based 2-aminocarboxylic acid enantiomers were carried out by using newly developed zwitterionic CSPs [P6]. By variation of the chromatographic parameters, the separations of the stereoisomers were optimized; as a result, baseline resolution was achieved for all the investigated analytes.

The stereoisomers of 1,2,3,4-tetrahydroisoquinoline analogs were resolved for the first time by applying a polar ionic mobile phase on a quinine or a quinidine moiety fused with a chiral sulfonic acid-type chiral selector immobilized on silica support [P8]. Baseline resolution was

achieved in all cases, and the newly commercialized zwitterionic CSPs were found to behave as chiral cation exchangers.

Separation performances of Cinchona alkaloid-based zwitterionic CSPs were compared in the enantioseparation of β^2- and β^3-amino acids [P10]. A comparison of the zwitterionic CSPs revealed that the quinidine-based ZWIX(−) column exhibited much better selectivity for both β^2- and β^3-amino acids than the quinine-based ZWIX(+) column.

The enantiomers of four isoxazoline-fused 2-aminocyclopentanecarboxylic acids were directly separated on a quinine- or a quinidine-based zwitterionic ion-exchanger [P11]. The separations could be accomplished in polar ionic mode and the retention behavior proved to depend on the nature and concentration of the bulk solvent and the acid and base modifiers, the temperature and the nature and positions of the substituents.

Stereoselective HPLC separations of eight sterically constrained cyclic *ß*-amino acid enantiomer pairs were carried out using the newly developed Cinchona alkaloid-based zwitterionic CSPs [P13]. The elution sequence was determined in all cases and was found to be opposite on the ZWIX(+) and ZWIX(–) columns.

Polar-ionic and hydro-organic mobile phase mode of HPLC separations of 23 sterically constrained primary β^3-amino acid enantiomers containing, alkyl, aryl or heteroaryl sidechains were carried out by using Cinchona alkaloid-based zwitterionic chiral selectors [P15]. By variation of the chromatographic modes, the separations of the stereoisomers were optimized; as a result, baseline resolution was achieved for all the investigated analytes.

The enantiomers of *trans*-paroxetine were separated on four CSPs based on chiral zwitterionic Cinchona alkaloids fused with (*R,R*)- or (*S,S*)-*trans*-2-aminocyclohexanesulfonic acid [P16]. The elution sequences of the paroxetine enantiomers on the two pairs of pseudo-enantiomeric CSPs were investigated, and an attempt was made to explain the observed anomalies *in silico* in order to gain an insight into the underlying molecular recognition events between the four chiral selectors and the analyte enantiomers.

Cyclic *ß*-aminohydroxamic acid enantiomer pairs were stereoselectively separated by HPLC on Cinchona alkaloid-based four zwitterionic CSPs [P17]. The position (*diexo* or *diendo*) of the functional groups of the analytes exerted a significant effect on the enantiorecognition: higher enantioselectivity was observed for the *diexo* compounds. The elution sequence demonstrated that ZWIX(+) relative to ZWIX(–) and ZWIX(+A) relative to ZWIX(–A) behaved as pseudo-enantiomeric CSPs.

In a systematic way enantioseparations of non-methylated and the corresponding *N*-monomethylated ampholytic cyclic β^3-amino acids were carried out on four zwitterionic chiral stationary phases [P21]. Via the consequent determination of the elution order of the resolved enantiomers, the effects of the absolute configuration of the chiral anionic and cationic subunits of the zwitterionic CSPs could be elucidated.

A sensitive HPLC protocol was developed for the identification and quantification of enantiomeric impurities of commercially available *N*-Fmoc-protected amino acids on quinine- and quinidine-based weak anion exchanger-type CSPs [P22]. The method developed permits detection of less than 0.01% enantiomeric impurity in the presence of the major enantiomer.

The eight stereoisomers of limonene-based carbocyclic *ß*-amino acids containing three chiral centers have been directly separated on CSPs containing Cinchona alkaloid-based zwitterionic selectors [P26]. The eight stereoisomers could be identified and separated in a traditional 1D chromatographic system in two runs by the application of the ZWIX(+) and ZWIX(–) columns.

The enantiomeric pairs of *cis* and *trans* stereoisomers of cyclic *ß*-aminohydroxamic acids and their related *cis* and *trans* cyclic *ß*-amino acids containing two chiral centers were directly

separated on four structurally related CSPs derived from quinine and quinidine modified with (*R*,*R*)- and (*S*,*S*)-aminocyclohexanesulfonic acids (ACHSA) [P27]. Evidence was provided for the decisive effect of the selectors subunits; both the quinine or qunidine moiety and the ACHSA subunit may take a determining role in the chiral recognition.

The effects of *N*-methylation and *N*-amidination of ampholytic cyclic *ß*-amino acids on their retention and enantioseparation characteristics on Cinchona alkaloid- and sulfonic acid-based zwitterionic chiral selectors were described [P28]. The retention behavior and resolution proved to be related to double ion-pairing interaction mechanism depending on both mobile phase compositions and temperature but also on structural features of the analytes.

Results obtained on macrocyclic glycopeptide-based CSPs

Separations of four bicyclo[2.2.2]octane based 2-amino-3-carboxylic acid enantiomers were developed on CSPs containing different macrocyclic glycopeptide antibiotic selectors [P7]. The values of thermodynamic parameters such as the changes in enthalpy, entropy, and Gibbs free energy were found depended on the structures of the analytes and on the chiral selectors used.

HPLC methods were developed for the separation of enantiomers of four unnatural paclitaxel precursor phenylisoserine analogs on CSPs containing macrocyclic glycopeptides and cyclofructans as chiral selectors [P12]. On Chirobiotic CSPs, *ß*-lactams and phenylisoserine were separable in the reversed phase and polar ionic mode, and the separation was found to be affected by the pH of the eluent and the MeOH content of the aqueous mobile phase.

Polar-ionic and reversed-phase HPLC separations of limonene-based cyclic *ß*-amino acid enantiomers were carried out applying Chirobiotic T, TAG and R columns [P25]. It was established that an ion-interactions mechanism is operative in chiral discrimination when teicoplanin aglycon exhibits a zwitterionic character.

Results obtained on polysaccharide-based CSPs

The stereoisomers of 1,2,3,4-tetrahydroisoquinoline amino alcohol analogues and derivatives thereof were separated in normal-phase mode on CSPs based on preprepared silica coated with cellulose carbamate derivatives [P9]. Baseline resolution was achieved in all cases; the polysaccharide-based CSPs were proved to have a complementary character which leads to successful resolution.

The stereoisomers of five fluorinated cyclic $ß^3$-amino acid derivatives and their nonfluorinated counterparts were separated on polysaccharide-based CSPs [P18]. Of the studied CSPs, cellulose *tris*-(3-chloro-4-methylphenyl carbamate) and amylose *tris*-(3,5-dimethylphenyl carbamate) appeared the best suitable for the direct enantioseparation of the studied derivatives.

An attempt was made to describe in a comparative manner the enantioselectivity performance of six different polysaccharide- and two strong cation exchanger-type CSPs for the resolution of free and *N*-protected *ß*-carboline derivatives [P20]. Detailed thermodynamic investigations revealed that in all cases the enantioseparations observed were enthalpically driven.

Other research activities

Not planned in the project proposal, but strongly connected to the work plan, we carried out experiments applying SFC [P14, P23, P24]. On the basis of these results a useful comparison could be made between the liquid and subcritical fluid chromatographic enantioseparations.

Stereoselective SFC separations of the enantiomers of a large set of *N*-Fmoc proteinogenic amino acids were carried out on Chiralpak ZWIX(+) and ZWIX(−) columns with protic solvents as co-solvents [P14]. In the course of the optimization of the enantioseparations, the effects of MeOH as co-solvent in liquid CO_2 and several different additives (water, acid and base) were tested to improve the separation and peak shapes.

A comparative investigation for the enantioseparations of *N*-Fmoc proteinogenic amino acids on quinine-based zwitterionic and anion-exchanger type CSPs employing hydro-organic and polar-ionic liquid and SFC conditions [P23]. Elution sequence in all cases was determined, where a general rule could be observed, both in liquid and subcritical fluid chromatographic mode the D-enantiomers eluted before the L ones. In both modes, the principles of ion exchange chromatography could be justified.

Liquid and subcritical fluid chromatographic enantioseparation of *N*-Fmoc proteinogenic amino acids on quinidine-based zwitterionic and anion-exchanger type CSPs were compared [P24]. The comparison of the zwitterionic and anion exchanger-based CSPs revealed that generally much better performance could be observed with the single ionic anion exchange type CSP.

A review article on the analysis of natural and unnatural amino acid enantiomers by liquid chromatography was also published [P19].

It is important to note that besides the above mentioned scientific publications the research group has been paying continuous attention to the education of undergraduate students; project works (5), BSc (2) and MSc (5) degrees have been earned by chemists and environmental specialists who joined to the group. It is worth to mention that 1 PhD degree have also been earned, two 2 PhD students finished their research activity (in the near future they will defend their theses) and 2 PhD students started their research work during this period.

It is also worth mentioning that the principal investigator in January 2018 initiated the application process to be the doctor of the Hungarian Academy of Sciences. The results obtained in the period of OTKA grant served as a strong basis for the dissertation.

The financial support of the National Research, Development and Innovation Office which ensured possibilities to carry out research in the field of chiral separations is highly acknowledged.

Publications indicating the OTKA grant

P1. Aranyi A, Péter A, Ilisz I, Fülöp F, Scriba GKE
Cyclodextrin-mediated enantioseparation of phenylalanine amide derivatives and amino alcohols by capillary electrophoresis-Role of complexation constants and complex mobilities
Electrophoresis 35: (2014) 2848

P2. Ilisz I, Gecse Z, Pataj Z, Fulop F, Toth G, Lindner W, Peter A
Direct high-performance liquid chromatographic enantioseparation of secondary amino acids on Cinchona alkaloid-based chiral zwitterionic stationary phases. Unusual temperature behavior
Journal of Chromatography A 1363 (2014) 169

P3. Ilisz I, Grecsó N, Aranyi A, Suchotin P, Tymecka D, Wilenska B, Misicka A, Fülöp F, Lindner W, Péter A
Enantioseparation of β^2-amino acids on cinchona alkaloid-based zwitterionic chiral stationary phases. Structural and temperature effects
Journal of Chromatography A 1334 (2014) 44

P4. Ilisz I, Grecsó N, Palkó M, Fülöp F, Lindner W, Péter A
Structural and temperature effects on enantiomer separations of bicyclo[2.2.2]octane-based 3-amino-2-carboxylic acids on cinchona alkaloid-based zwitterionic chiral stationary phases
Journal of Pharmaceutical and Biomedical Analysis 98 (2014) 130

P5. Ilisz I, Pataj Z, Gecse Z, Szakonyi Z, Fulop F, Lindner W, Peter A
Unusual temperature-induced retention behavior of constrained *ß*-amino acid enantiomers on the zwitterionic chiral stationary phases ZWIX(+) and ZWIX(-)
Chirality 26: (2014) 385

P6. Pataj Z, Ilisz I, Gecse Z, Szakonyi Z, Fülöp F, Lindner W, Péter A
Effect of mobile phase composition on the liquid chromatographic enantioseparation of bulky monoterpene-based *ß*-amino acids by applying chiral stationary phases based on Cinchona alkaloid
Journal of Separation Sciences 37 (2014) 1075

P7. Zoltán Patai, István Ilisz, Nóra Grecsó, Márta Palkó, Ferenc Fülöp, Daniel W Armstrong, Antal Péter
Enantiomeric separation of bicyclo[2.2.2]octane-based 2-amino-3-carboxylic acids on macrocyclic glycopeptide chiral stationary phases
Chirality 26 (2014) 200

P8. István Ilisz, Nóra Grecsó, Ferenc Fülöp, Wolfgang Lindner, Antal Péter
High-performance liquid chromatographic enantioseparation of cationic 1,2,3,4-tetrahydroisoquinoline analogs on Cinchona alkaloid-based zwitterionic chiral stationary phases
Analytical and Bioanalytical Chemistry 407 (2015) 961

P9. Nóra Grecsó, István Ilisz, Zsanett Gecse, László Schönstein, Ferenc Fülöp, Antal Péter
High-performance liquid chromatographic enantioseparation of amino alcohol analogues possessing 1,2,3,4-tetrahydroisoquinoline skeleton on polysaccharide-based chiral stationary phases
Biomed Chromatography 29 (2015) 788

P10. István Ilisz, Nóra Grecsó, Aleksandra Misicka, Dagmara Tymecka, Lázár László, Wolfgang Lindner, Antal Péter
Comparison of separation performances of Cinchona alkaloid-based zwitterionic stationary phases in the enantioseparation of β^2- and β^3-amino acids
Molecules 20 (2015) 70

P11. István Ilisz, Zsanett Gecse, Gyula Lajkó, Melinda Nonn, Ferenc Fülöp, Wolfgang Lindner, Antal Péter
Investigation of the structure-selectivity relationships and van't Hoff analysis of chromatographic stereoisomer separations of unusual isoxazoline-fused 2-aminocyclopentanecarboxylic acids on *Cinchona* alkaloid-based chiral stationary phases
Journal of Chromatography A 1384 (2015) 67

P12. István Ilisz, Nóra Grecsó, Enikő Forró, Ferenc Fülöp, Daniel W. Armstrong, Antal Péter
High-performance liquid chromatographic separation of paclitaxel intermediate phenylisoserine derivatives on macrocyclic glycopeptide and cyclofructan-based chiral stationary phases
Journal of Pharmaceutical and Biomedical Analysis 114 (2015) 312

P13. István Ilisz, Zsanett Gecse, Gyula Lajkó, Enikő Forró, Ferenc Fülöp, Wolfgang Lindner, Antal Péter
High-performance liquid chromatographic enantioseparation of cyclic β-amino acids applying zwitterionic chiral stationary phases based on Cinchona alkaloids
Chirality 27 (2015) 563

P14. Gyula Lajkó, István Ilisz, Gábor Tóth, Ferenc Fülöp, Wolfgang Lindner, Antal Péter
Enantioseparation of N_α-protected proteinogenic amino acids by supercritical fluid chromatography on Cinchona alkaloid-based zwitterionic chiral stationary phases
Journal of Chromatography A 1415 (2015) 134

P15. István Ilisz, Nóra Grecsó, Roman Papoušek, Zoltán Pataj, Petr Barták, László Lázár, Ferenc Fülöp, Wolfgang Lindner, Antal Péter
High-performance liquid chromatographic separation of unusual β^3-amino acid enantiomers in different chromatographic modes on Cinchona alkaloid-based zwitterionic chiral stationary phases
Amino Acids 47 (2015) 2279

P16. Nóra Grecsó, Michal Kohout, Andrea Carotti, Roccaldo Sardella, Benedetto Natalini, Ferenc Fülöp, Wolfgang Lindner, Antal Péter, István Ilisz
Mechanistic considerations of enantiorecognition on novel Cinchona alkaloid-based zwitterionic chiral stationary phases from the aspect of the separation of trans-paroxetine enantiomers as model compounds
Journal of Pharmaceutical and Biomedical Analysis 124 (2016) 164

P17. Gyula Lajkó, Tímea Orosz, Nóra Grecsó, Márta Palkó, Ferenc Fülöp, Wolfgang Lindner, Antal Péter, István Ilisz
High-performance liquid chromatographic enantioseparation of cyclic β-amino hydroxamic acids on zwitterionic chiral stationary phases based on Cinchona alkaloids
Analytica Chimica Acta 921 (2016) 84

P18. Gyula Lajkó, Tímea Orosz, Lóránd Kiss, Ferenc Fülöp, Antal Péter, István Ilisz
High-performance liquid chromatographic enantioseparation of fluorinated cyclic β^3-amino acid analogs on polysaccharide-based chiral stationary phases. Comparison with non-fluorinated counterparts
Biomedical Chromatography 30 (2016) 1441

P19. István Ilisz, Antal Péter, Wolfgang Lindner
State-of-the-art enantioseparations of natural and unnatural amino acids by high-performance liquid chromatography
Trends in Analytical Chemistry 81 (2016) 11

P20. Gyula Lajkó, Nóra Grecsó, Rita Megyesi, Enikő Forró, Ferenc Fülöp, Denise Wolrab, Wolfgang Lindner, Antal Péter, István Ilisz
Enantioseparation of *β*-carboline derivatives on polysaccharide- and strong cation exchanger-based chiral stationary phases. A comparative study
Journal of Chromatography A 1467 (2016) 188

P21. Nóra Grecsó, Enikő Forró, Ferenc Fülöp, Antal Péter, István Ilisz, Wolfgang Lindner
Combinatorial effects of the configuration of the cationic and the anionic chiral subunits of four zwitterionic chiral stationary phases leading to reversal of elution order of cyclic β^3-amino acid enantiomers as ampholytic model compounds
Journal of Chromatography A 1467 (2016) 178

P22. Antal Péter, Nóra Grecsó, Gábor Tóth, Ferenc Fülöp, Wolfgang Lindner, István Ilisz
Ultratrace analysis of enantiomeric impurities in proteinogenic *N*-Fmoc-amino acid samples on Cinchona alkaloid-based chiral stationary phases
Israel Journal of Chemistry 56 (2016) 1042

P23. Gyula Lajkó, Nóra Grecsó, Gábor Tóth, Ferenc Fülöp, Wolfgang Lindner, Antal Péter, István Ilisz
A comparative study of enantioseparations of N_α-Fmoc proteinogenic amino acids on *quinine*-based zwitterionic and anion exchanger-type chiral stationary phases under hydro-organic liquid and subcritical fluid chromatographic conditions
Molecules 21 (2016) 1579

P24. Gyula Lajkó, Nóra Grecsó, Gábor Tóth, Ferenc Fülöp, Wolfgang Lindner, István Ilisz, Antal Péter
Liquid and subcritical fluid chromatographic enantioseparation of *N*-Fmoc proteinogenic amino acids on Quinidine-based zwitterionic and anion-exchanger type chiral stationary phases. A comparative study
Chirality 29 (2017) 225

P25. Tímea Orosz, Nóra Grecsó, Gyula Lajkó, Zsolt Szakonyi, Ferenc Fülöp, Daniel Armstrong, István Ilisz, Antal Péter
Liquid chromatographic enantioseparation of carbocyclic *β*-amino acids possessing limonene skeleton on macrocyclic glycopeptide-based chiral stationary phases
Journal of Pharmaceutical and Biomedical Analysis 145 (2017) 119

P26. 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
Journal of Separation Sciences 40 (2017) 3196

P27. Attila Bajtai, Beáta Fekete, Márta Palkó, Ferenc Fülöp, Wolfgang Lindner, István Ilisz, Antal Péter
A comparative study for the liquid chromatographic enantioseparation of cyclic *β*-amino acids and the related cyclic *β*-aminohydroxamic acids on Cinchona alkaloid-based zwitterionic chiral stationary phases
Journal of Separation Sciences (accepted for publication, jssc.201701190.R1)

P28. Tímea Orosz, Enikő Forró, Ferenc Fülöp, Wolfgang Lindner, István Ilisz, Antal Péter
Effect of *N*-substitution on chromatographic behavior of cyclic *ß*-amino acids on *Cinchona* alkaloid- and sulfonic acid-based chiral zwitterionic stationary phases
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