

ENANTIOMER SEPARATION OF CHIRAL TETRAHYDROISOQUINOLINE ANALOGS BY SUPERCRITICAL FLUID CHROMATOGRAPHY AND HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

Attila Bajtai¹, Dániel Tanács¹, Tímea Orosz¹, Gyula Lajkó², István Szatmári², Ferenc Fülöp², Wolfgang Lindner³, István Ilisz¹, Antal Péter¹

¹*Institute of Pharmaceutical Analysis, University of Szeged, Somogyi utca 4, H-6720 Szeged, Hungary*

²*Institute of Pharmaceutical Chemistry, University of Szeged, Eötvös utca 6, H-6720 Szeged, Hungary*

³*Department of Analytical Chemistry, University of Vienna, Währinger Strasse 83, 1090 Vienna, Austria*

e-mail: bajtai@chem.u-szeged.hu

1,2,3,4-Tetrahydroisoquinoline and its analogs have received serious attention from synthetic and medicinal chemists lately. These compounds are core structural elements present in several peptide-based drugs and form an important part of various biologically active compounds. The optical purity of potential pharmacons has an immense importance during chiral drug development. Hence, there is a need for efficient separation methods of chiral 1,2,3,4-tetrahydroisoquinoline analogs. Selection of suitable chromatography technique is the first and the most difficult step in the method development. In our study we investigated the similarities and differences between liquid chromatography (LC) and supercritical fluid chromatography (SFC) methods on the bases of the separation of six 1,2,3,4-tetrahydroisoquinoline analogs and three structurally closely related enantiomer pairs.

Nine chiral stationary phases (CSPs) including quinidine- or quinine-based zwitterionic and polysaccharides based selectors were applied in HPLC and SFC mode to evaluate the chiral separation of the nine structurally related analogs. HPLC measurements were carried out in normal phase mode on seven polysaccharide-based CSPs and in polar ionic mode on the two zwitterionic CSPs. In normal phase LC mode, the effects of the composition of the bulk solvent and the natures of the alcohol and amine additives, while in SFC mode the effects of the content and natures of alcohol modifier, the counter-ion concentration and the structures of the analytes were investigated. The separations of the stereoisomers were optimized in both SFC and LC modes.

The effect of column temperature on the separation was also studied to gain deeper understanding of the complex thermodynamic processes taking part in the enantiorecognition. Thermodynamic parameters were calculated applying van't Hoff plots and the results showed that on the polysaccharide-based columns in both normal phase LC mode and in SFC mode mostly enthalpically-driven enantiomer separations were dominant. However, in some cases, entropically-driven separations were also observed.

The NP and SFC chromatographic mode exhibited different effectiveness in the separation of stereoisomers: separation was more efficient in SFC mode, however, sometimes very high resolutions were achieved in NP LC mode, which shows the different suitability of the SFC mode.