# DETERMINATION OF ENANTIOMERIZATION ENERGY BARRIERS BY ENANTIOSELECTIVE STOPPED-FLOW HPLC

Giuseppe Cannazza[a], Claudia Carlucci[b] , Daniela Braghiroli[a], Carlo Parenti[a] and Luigino Troisi[b]

[a]Dipartimento di Scienze Farmaceutiche, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, 41100 Modena, Italy
[b]Dipartimento di Scienze e Tecnologie Biologiche ed Ambientali, Università di Lecce, Via Prov.le Lecce-Monteroni, 73100, Lecce, Italy

An on-column stopped-flow high-performance liquid chromatography (sfHPLC) procedure using a chiral stationary phase (CSP) has been developed for the determination of rate costants and free energy barriers of enantiomerization of 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide type compounds. After initial separation of the enantiomers in the first section of the column, the flow was stopped and the resolved species allowed to enantiomerize on-column. From this conversion, which could be determined from the enantiomeric ratios at different enantiomerization times, kinetic rate constants and free energy barriers of enantiomerization were calculated [1,2].

Several chiral 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide type compounds different substituted to the benzene ring and to C(3) chiral carbon atom were prepared and an enantioseparation HPLC method was developed in reversed phase mode employing cellulose tris (3,5-dimethylphenylcarbamate) as CSP (Chiralcel OD-R) [1]. It turned out that, during chromatography in aqueous solvents, a rapid enantiomer interconversion occurred resulting in pronounced peak coalescence phenomena.

The enantiomerization rate costants and the corresponding energy barriers were calculated by the sfHPLC procedure developed [2]. The results showed that substitution in C(3), C(6) and C(7) position of the benzothiadiazine ring exert a dramatic influence on free energy barriers of enatiomerization.

[1] Cannazza, G.; Braghiroli, D.; Baraldi, M.; Parenti, C. Chiral resolution of enantiomers of 7-chloro-3-methyl-3,4-diydro-2H-1,2,4-benzothiadiazine 1,1-dioxide using high-performance liquid chromatography on cellulose-based chiral stationary phases. *J. Pharm. Biomed. Anal.* 2000, 23, 117-125.
[2] Cannazza, G.; Braghiroli, D.; Tait, A.; Baraldi, M.; Parenti, C.; Lindner, W. Studies of enantiomerization of chiral 3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide type compounds. *Chirality* 2001, 13, 94-101.