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Enantiomer Separation of Chiral Drugs on HPLC Chiral Stationary Phases

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1. Chromatographic Enantiomer Separation of New Fluoroquinolones Including Gemifloxacin

Living organisms are chiral and, therefore, the chemical or biological activity of a compound often depends upon its stereochemistry in living organisms [1,2]. This gives consequences for chemical substances used as pharmaceuticals, agrochemicals and flavors due to different biological responses to enantiomers. Racemic gemifloxacin mesylate (formerly LB20304a), an investigational new fluoroquinolone with potent *in vitro* and *in vivo* antibacterial profile, has been developed as a chemotherapeutic agent for various infections (Fig. 1). The efficacy of gemifloxacin is better than that of ciprofloxacin and ofloxacin in terms of its good *in vitro* antibacterial activity as well as *in vivo* pharmacokinetic characteristics [3,4].

The enantiomers of gemifloxacin mesylate were resolved on a commercially available Crownpak CR chiral stationary phase (CSP) based on a chiral crown ether. All of fluoroquinolones including gemifloxacin were well enantioseparated on Crownpak CR column. The behavior of chromatographic parameters by the change of mobile phase additives for the resolution of gemifloxacin was investigated [5,6].

2. Development of HPLC Chiral Stationary Phase Derived From (+)-(18-Crown-6)-2,3,11,12-tetracarboxylic acid

Crown ethers, a class of the synthetic host molecules, have aroused considerable interest because they bind not only alkali cations, but also protonated amines with high selectivity and affinity. Many studies using crown ethers as chiral selectors have been effectively accomplished for resolution of racemic α-amino acids and primary amines by liquid-liquid extraction and high-performance liquid chromatography [7,8]. Among several chiral crown ether derivatives, (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid (18-C-6-TA) derived from L-tartaric acid has been employed in capillary electrophoresis to resolve the enantiomers of α-amino acids and primary amines [9].

We recently reported the synthesis and evaluation of a new chiral stationary phase (CSP) prepared by bonding 18-C-6-TA to aminopropyl silica gel (Fig. 1). This CSP was successfully utilized in resolving not only various α-amino acids, but also their ester and amide derivatives [10-14].It was also found to be capable of separating the enantiomers of primary amines including amino alcohols and quinolone antibacterials. More recently, we developed a dynamic CSP prepared by hydrophobically

bonding N-dodecyl diamide of 18-C-6-TA to octadecyl silica gel [15]. It was also successfully employed in resolving various racemic compounds containing a primary amino group as well as α-amino acids.

At present, the (+)- and (-)-18-C-6-TA covalently bonded chiral column is commercially available as ChiroSil® RCA(+) and SCA(-) from RS Tech corporation (Daejon, Korea, www.rstechcorp.com), respectively. In a quest for the origin of chiral recognition of α-amino acids in the presence of 18-C-6-TA as a chiral selector, we performed detailed NMR studies for each enantiomer of phenylglycine and phenylglycine methyl ester with 18-C-6-TA to investigate the chiral recognition mechanism of the diastereomeric complexes in solution state [16].

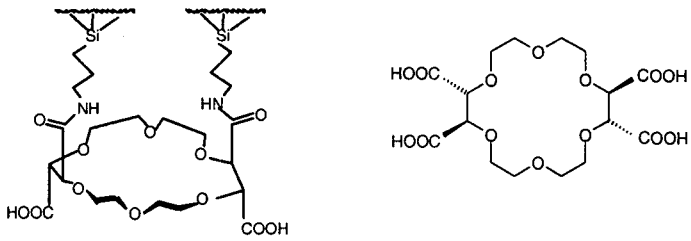

Fig. 1: Structure of CSP 1 and (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid

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