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Synthesis of (S)-Naproxen Based Amide Bond Forming Chiral Reagent and Application for Liquid Chromatographic Resolution of (RS)-Salbutamol

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Abstract : This work describes a very efficient approach for synthesis of activated ester of (S)-naproxen which was characterized by UV, IR, ^{1}HNMR, elemental analysis and polarimetric studies. It was used as a C-N bond forming chiral derivatizing reagent for further synthesis of diastereomeric amides of (RS)-salbutamol (a β_2 agonist that belongs to the group β-adrenolytic and is marketed as racamate) under microwave irradiation. The diastereomeric pair was separated by achiral phase HPLC, using mobile phase in gradient mode containing methanol and aqueous triethylaminephosphate (TEAP); separation conditions were optimized with respect to pH, flow rate, and buffer concentration and the method of separation was validated as per International Council for Harmonisation (ICH) guidelines. The reagent proved to be very effective for on-line sensitive detection of the diastereomers with very low limit of detection (LOD) values of 0.69 and 0.57 ng mL^{-1} for diastereomeric derivatives of (S)- and (R)-salbutamol, respectively. The retention times were greatly reduced (2.7 min) with less consumption of organic solvents and large (α) as compared to literature reports. Besides, the diastereomeric derivatives were separated and isolated by preparative HPLC; these were characterized and were used as standard reference samples for recording ^{1}HNMR and IR spectra for determining absolute configuration and elution order; it ensured the success of diastereomeric synthesis and established the reliability of enantioseparation and eliminated the requirement of pure enantiomer of the analyte which is generally not available. The newly developed reagent can suitably be applied to several other amino group containing compounds either from organic syntheses or pharmaceutical industries because the presence of (S)-Npx as a strong chromophore would allow sensitive detection.This work is significant not only in the area of enantioseparation and determination of absolute configuration of diastereomeric derivatives but also in the area of developing new chiral derivatizing reagents (CDRs).

Keywords : chiral derivatizing reagent, naproxen, salbutamol, synthesis
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