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Macrocyclic Glycopeptide Chiral Selectors Bonded to Core-Shell Particles Enables Enantiopurity Analysis of the Entire Verubecestat Synthetic Route

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Highlights

- Macrocyclic glycopeptide chiral selectors bonded to core-shell particles for enantiopurity analysis of pharmaceutical drugs and synthetic intermediates
- A single poroshell chiral column (TeicoShell) chromatographically resolves all verubecestat intermediates
- Highly efficient chiral stationary phases in RPLC mode applied to the analysis of closely related compound classes
- EE determination of verubecestat is achieved using another fused-core column (NicoShell)
- TEAA: MeOH based eluent at different isocratic compositions allowed good enatioseparation of all species

ABSTRACT

Verubecestat is an inhibitor of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) being evaluated in clinical trials for the treatment of Alzheimer's disease. Synthetic route development involves diastereoselective transformations with a need for enantiomeric excess (ee) determination of each intermediate and final active pharmaceutical ingredient (API). The analytical technical package of validated methods relies on enantioselective SFC and RPLC separations using multiple 3 and 5 μm coated polysaccharide-based chiral stationary phases (CSPs) and mobile phases combinations. Evaluation of recently developed chiral columns revealed a single chiral selector (Teicoplanin) bonded to 2.7 μm core-shell particles using H_3PO_4 in H_2O/ACN and triethylammonium acetate: methanol based eluents at different isocratic compositions