

Title: From Milligrams to Kilograms - Manufacturing Route Development of Verubecestat

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Abstract: Verubecestat is an inhibitor of β -secretase being evaluated for the treatment of Alzheimer's disease. The first-generation route relies on an amide coupling with a functionalized aniline, the preparation of which introduces synthetic inefficiencies. Using high throughput experimentation technics, a second-generation route using a copper-catalyzed C-N coupling was developed, allowing for more direct access to the target. Other features of the new route include a diastereoselective Mannich-type addition into an Ellman sulfinyl ketimine and a late-stage guanidinylation. Several process chemistry type improvements were also developed, for example an optimized PMB deprotection or an innovative aqueous work-up for the removal of Ti side products. Finally, several publications related to this program will be presented, notably a direct C-H carbamoylation of heterocycles and a one-pot oxidation-cyanation of amines.