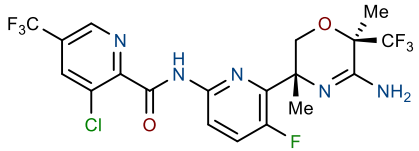
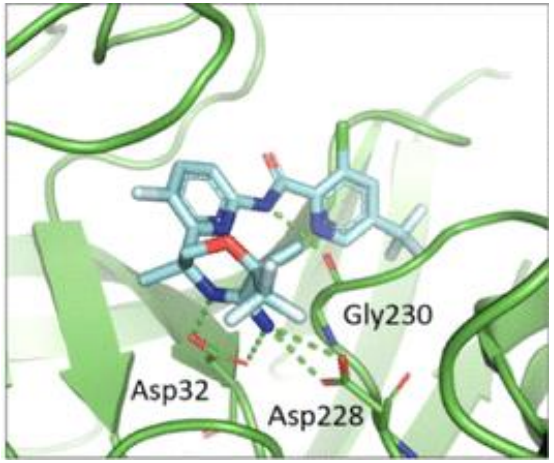
Umibecestat (CNP520)

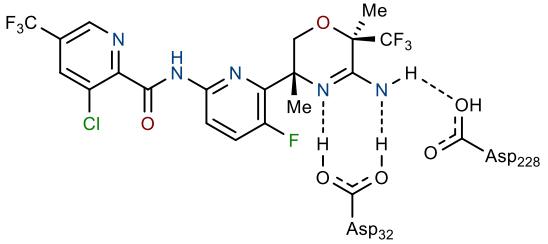


Umibecestat

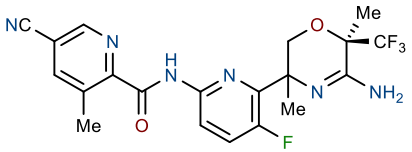
Background

- Alzheimer's Disease (AD) is the most prevalent neurodegenerative disease world
- Genetically linked to the amyloid precursor protein (APP) and its degradation amyloid-β (Aβ)
  - Membrane-bound aspartic protease BACE1 initiates the Aβ production pathway by cleaving the Met671-Asp672 peptide bond
- BACE1 inhibitors have been identified as potential AD therapeutics.
  - Umibecestat binds the Asp32 and Asp228 residues of BACE1



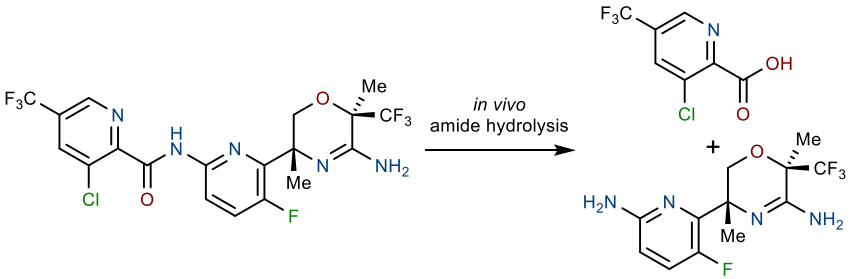


Potential Problems



NB-360

- Previously developed BACE1 inhibitors have been identified as possessing affinity for the BACE2 enzyme as well
- Off target inhibition of BACE2 leads to improper melanin distribution
  - Grey patches of fur in mice trials indicative of this off target inhibition
- "Unknown physiological consequences of the impaired melanin processing, beyond the effect on the hair color, were internally rated a significant development risk for an AD drug, in particular when chronic treatment over several years is expected."

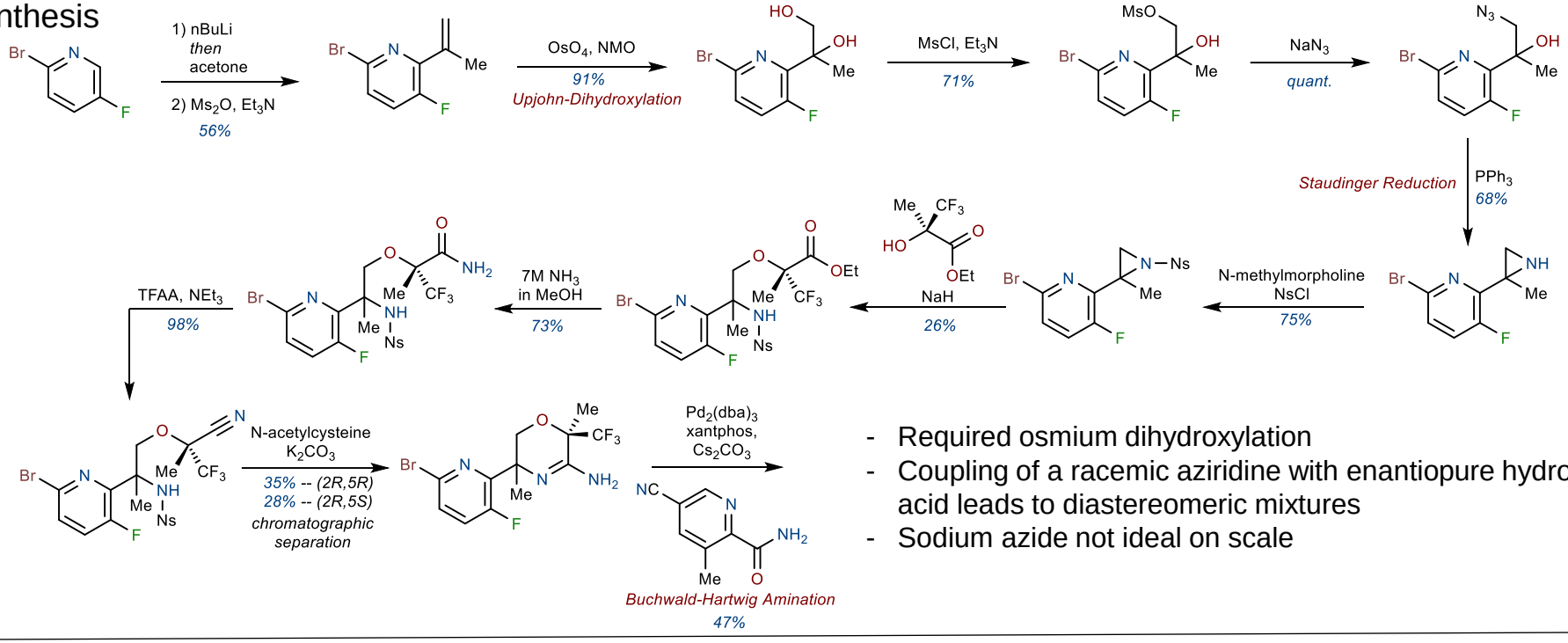


- Umibecestat was found to have higher metabolic stability than previous iterations
- Has 3-fold higher affinity for BACE1 over BACE2

J. Med. Chem. 2021 https://doi.org/10.1021/acs.jmedchem.1c01300

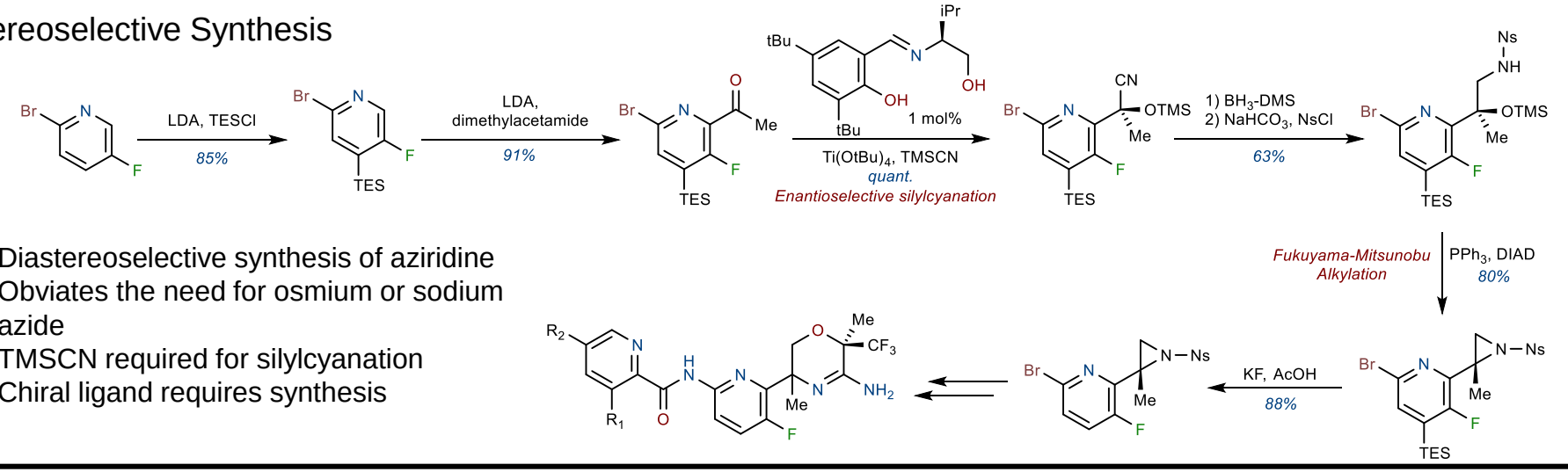
Umibecestat (CNP520)

Synthesis



- Required osmium dihydroxylation
- Coupling of a racemic aziridine with enantiopure hydroxy acid leads to diastereomeric mixtures
- Sodium azide not ideal on scale

Stereoselective Synthesis



- Diastereoselective synthesis of aziridine
- Obviates the need for osmium or sodium azide
- TMSCN required for silylcyanation
- Chiral ligand requires synthesis