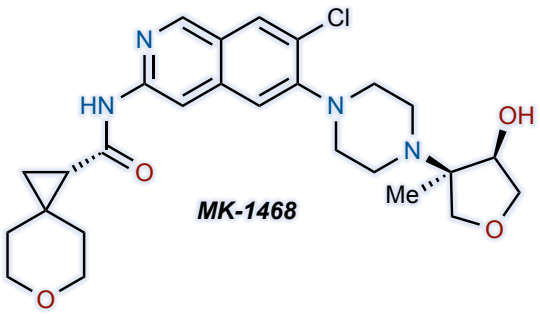
MK-1468

Background

- Parkinson's disease (PD) is a progressive, neurodegenerative disease affecting over 6 million people
- Involves loss of dopamine neurons and accumulation of α-synuclein rich protein deposits
- Approved therapies including dopamine agonists and monoamine oxidase-B inhibitors provide some relief of symptoms, but do not affect disease progression

MERCK



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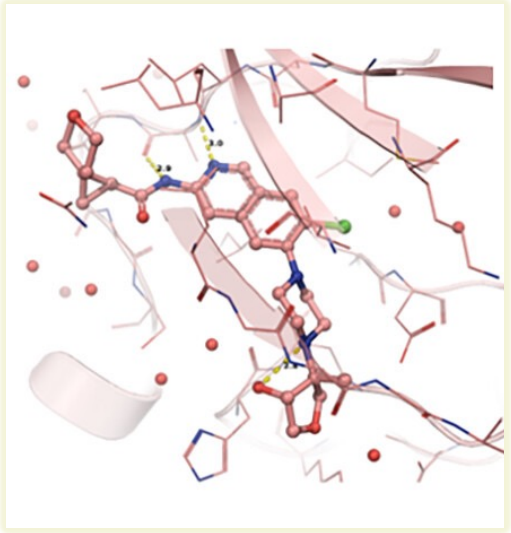
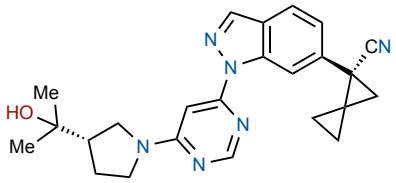
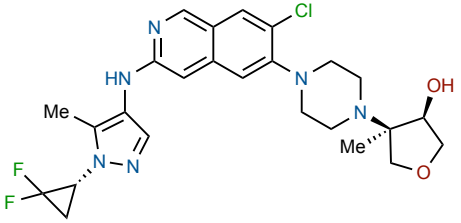


- Mutations in leucine-rice repeat kinase 2 (LRRK2) are the common cause of autosomal dominant Parkinson's disease
- Most common mutation is the glycine 2019 to serine mutation which causes 85% of LRRK2 Parkinson's cases
- Mutations result in a toxic 'gain of function' in kinase activity; increased kinase activity has also been observed in dopamine neurons in PD patient brain tissue
- Inhibition of LRRK2 could help patients with LRRK2 or idiopathic Parkinson's



Lead Compounds

Potent, selective, CNS penetrant LRRK2 inhibitors



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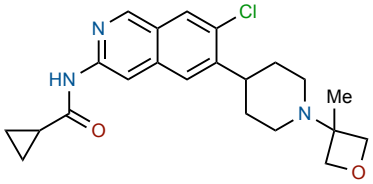
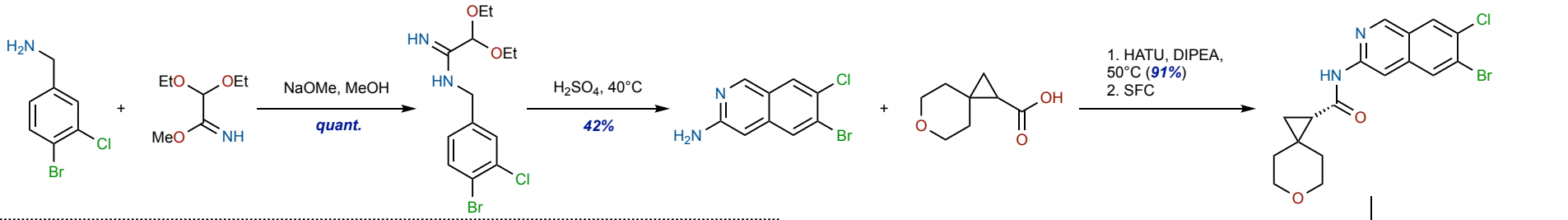
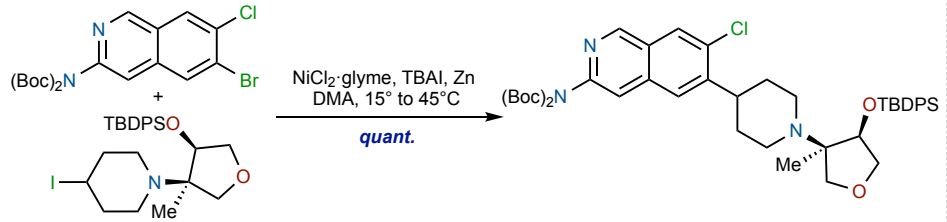
J. Med. Chem., **2022**, 65, 16801−16817 https://doi.org/10.1021/acs.jmedchem.2c01605

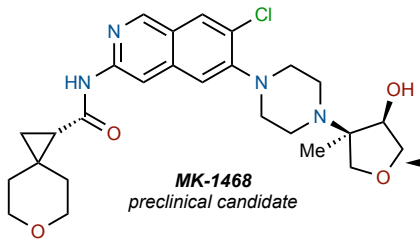


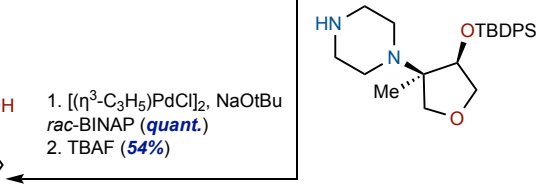
- *Favorable PK properties*
- *Low risk for CNS efflux*
- *Oxetane susceptible to oxidative metabolism*



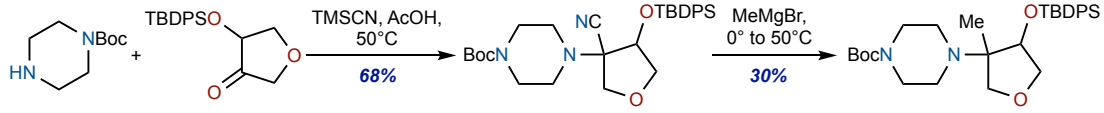
Reductive Coupling Approach to Piperidine Analogs:

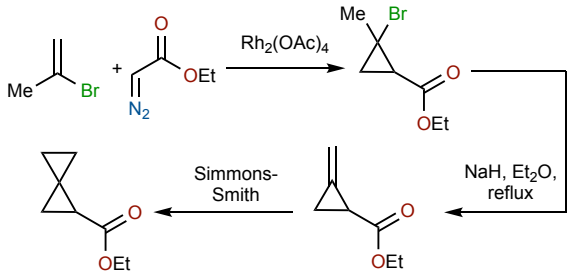






Piperazine Building Block





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