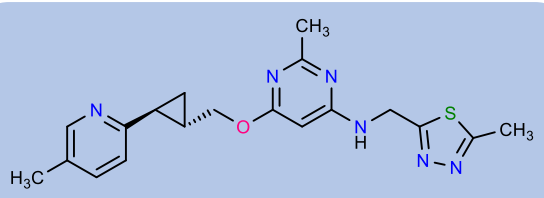
MK-8189 (Merck)

Background

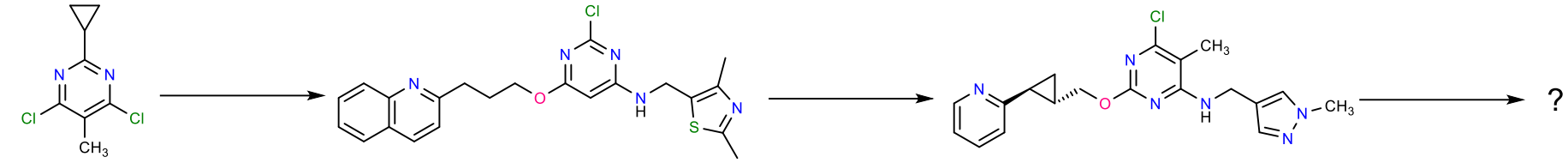
- Phase 2b clinical development for treatment of schizophrenia
- Potent and highly selective pyrimidine PDE (phosphodiesterases) 10A inhibitors
- PDE10A inhibition increases the striatal cAMP and cGMP signaling



MK-8189

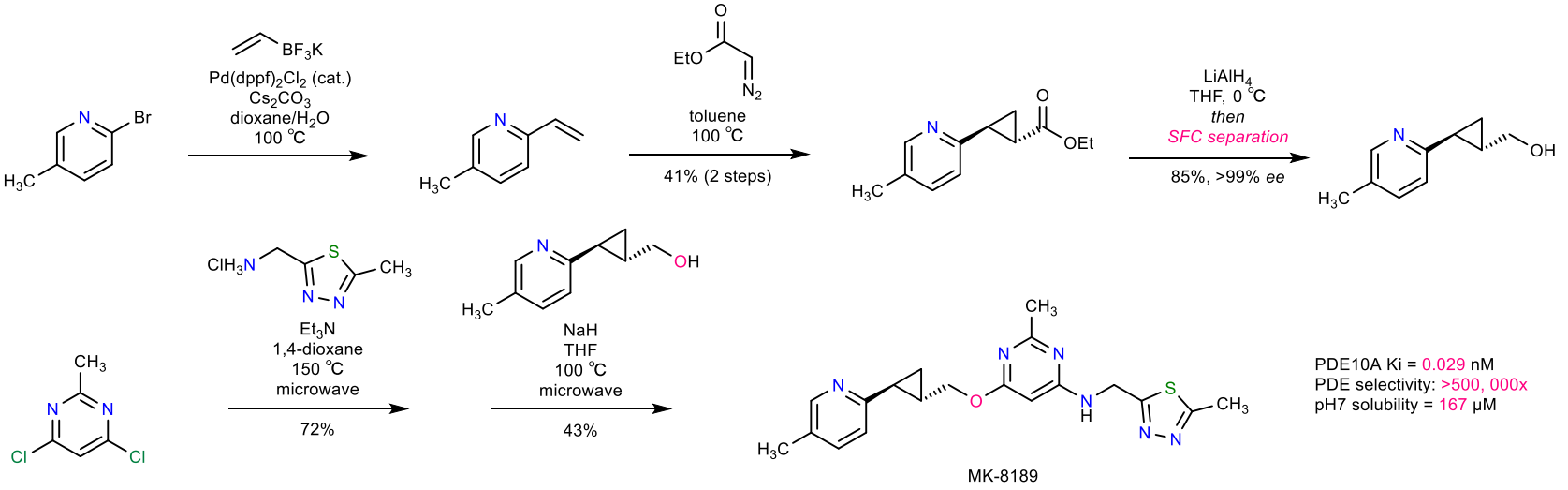
Layton, M. E. et al. *J. Med. Chem.* **2023**, *66*, 1157. https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c01521

Early Optimization Studies



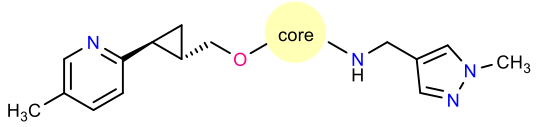
Shipe, W. D. et al. *J. Med. Chem.* **2015**, *58*, 7888. https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.5b00983

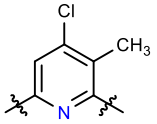
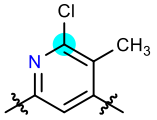
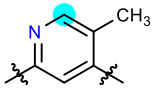
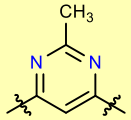
Component-Based Synthesis of MK-8189



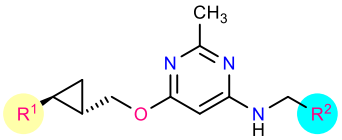
MK-8189 (Merck)

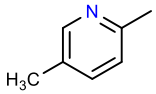
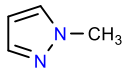
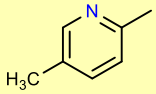
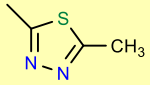
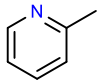
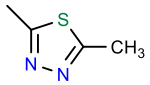
SAR Study of Core Heterocycle



	PDE10A K_i	pH7 solubility
	3.2 nM	N/D
	0.047 nM	86 μM
	7.8 nM	N/D
	0.60 nM	180 μM

SAR Study of Eastern and Western Fragments



R_1	R_2	PDE10A K_i
		0.061 nM
		0.029 nM
		0.33 nM

X-ray Crystal Structure

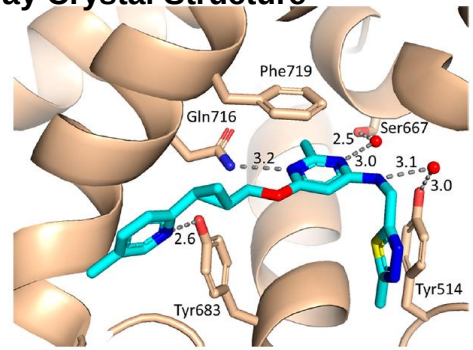


Figure 4. Crystal structure of PDE10A catalytic domain in complex with **18** (PDB ID: 8DI4).

- Western Fragment
  hydrogen bond with Tyr683
- Central Core
  hydrogen bonds with Gln716 and Ser 667
  π-π interaction with Phe719
- Eastern Fragment
  hydrogen bond with Tyr514
  π-π interaction with Tyr514

→ MK-8189 is a potent and selective PDE10A inhibitor!

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