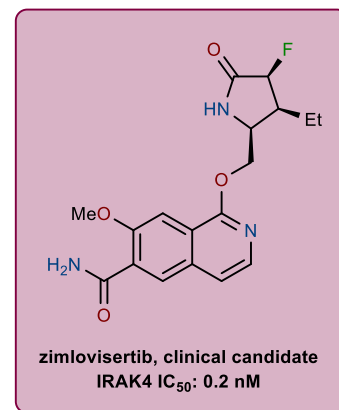
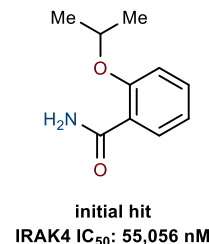


## Overview

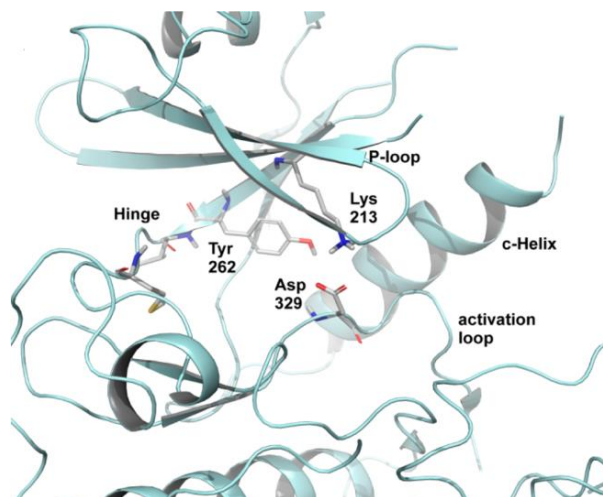
- Potent and selective inhibitor of IRAK4 (Interleukin-1 Receptor Associated Kinase 4)
- Currently in Phase I clinical trials for COVID-19 associated pneumonia and Phase II clinical trials for rheumatoid arthritis
- Zimlovisertib discovered through a fragment-based drug design strategy



Lee, K. L. *J. Med. Chem.* **2017**, *60*, 5521. <https://doi.org/10.1021/acs.jmedchem.7b00231>

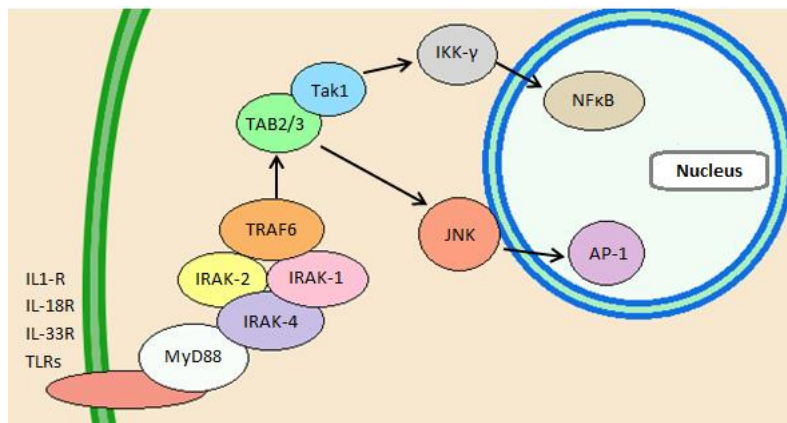
## IRAK4 Inhibition

- IRAK4 is an important node in innate inflammatory signaling pathways, responsible for the immediate immune response to pathogens
- Rheumatoid arthritis, lupus, and inflammatory bowel disease result from abnormal activation of the innate immune system



IRAK 4 active site

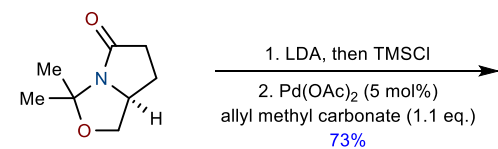
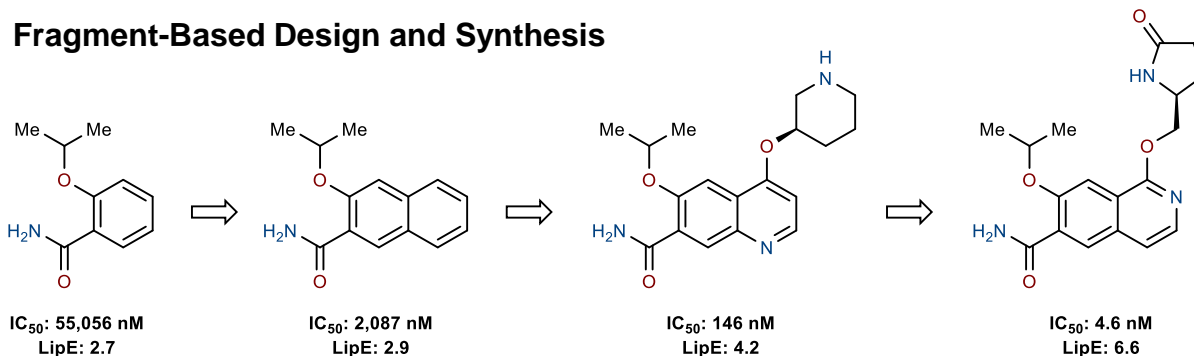
- Features a challenging and confined binding pocket, with "gatekeeper" residue Tyr262 to control ATP binding



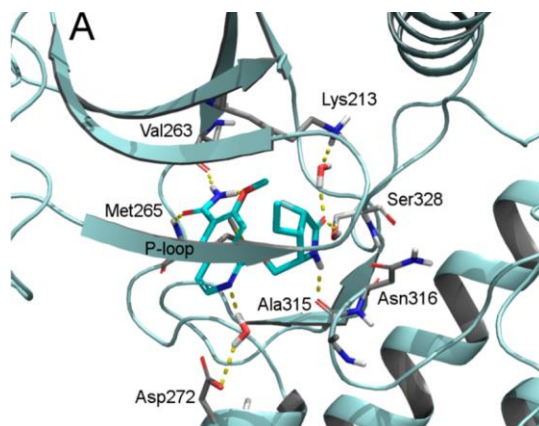
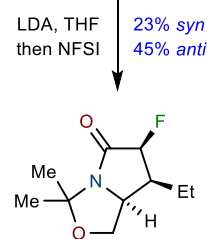
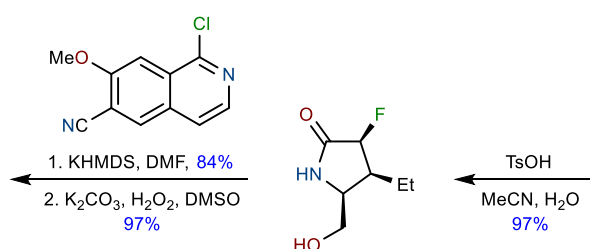
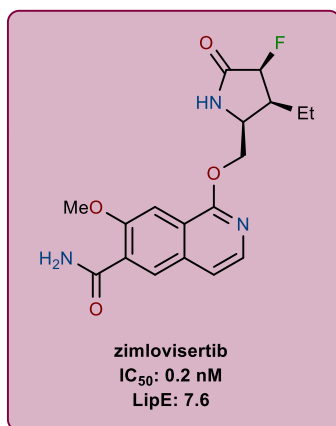
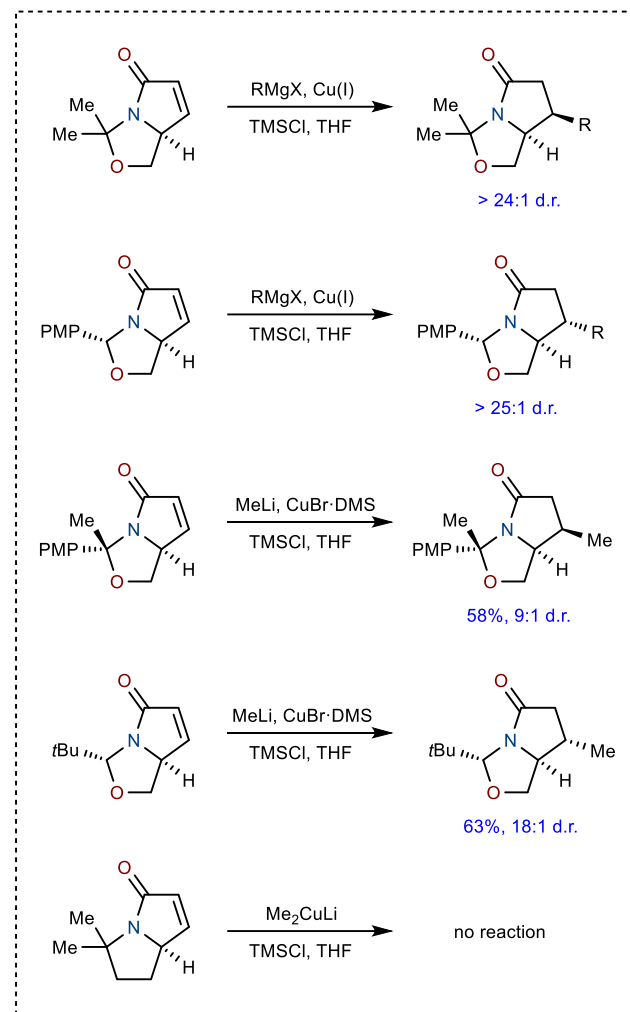
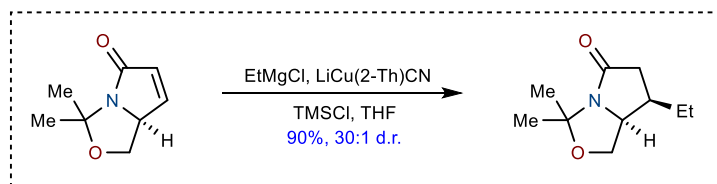
- IRAK4-deficient individuals have reduced inflammatory immune responses but don't display increased risk of infection in many cases, suggesting anti-inflammatory potential without overall broad immunosuppression
- In the past decade, IRAK4 has become a popular target for medicinal chemistry programs, with Pfizer, Merck, Amgen, Gilead, Bayer, and AstraZeneca all developing inhibitors

Bai, Y.-R. *Eur. J. Med. Chem.* **2023**, *258*, 115606. <https://doi.org/10.1016/j.ejmech.2023.115606>

## Fragment-Based Design and Synthesis



from (S)-pyroglutaminol



zimlovisertib  
cocrystallized  
in IRAK4

Lipophilic efficiency  
LipE = pIC<sub>50</sub> - LogP

Wright, S. W. *Org. Lett.* **2015**, *17*, 5204. <https://doi.org/10.1021/acs.orglett.5b02533>  
Lee, K. L. *J. Med. Chem.* **2017**, *60*, 5521. <https://doi.org/10.1021/acs.jmedchem.7b00231>