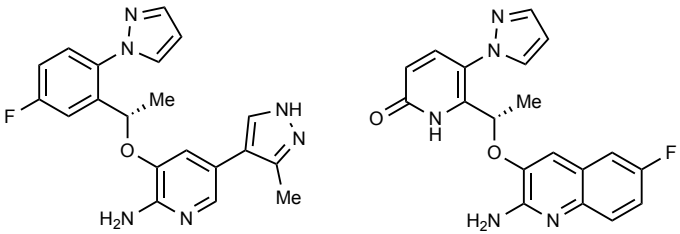
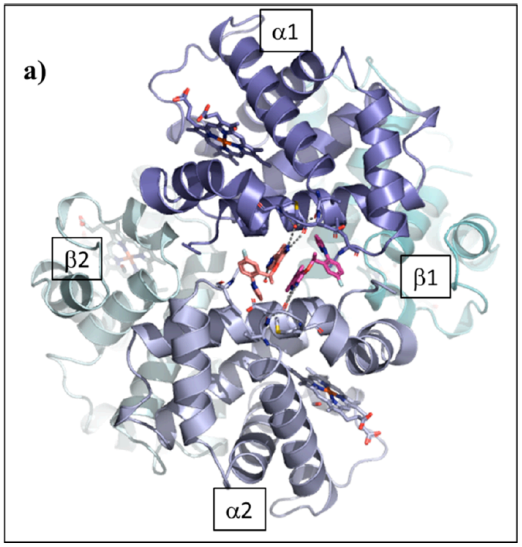
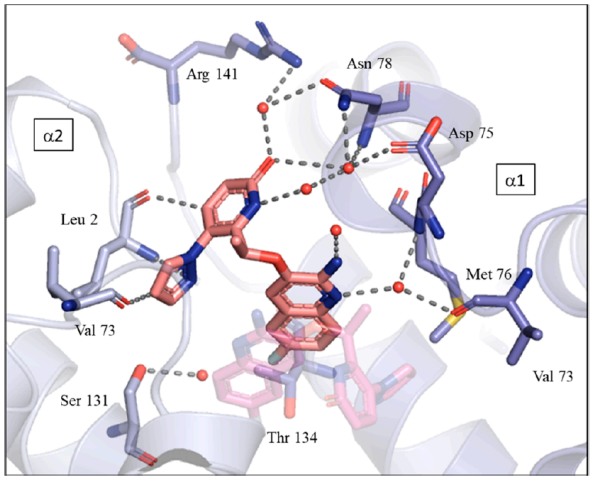
PF-07059013



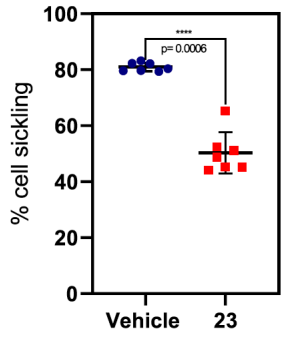
- Sickle Cell Disease (SCD) affects 15 million people
  - Causes anemia, stroke, vaso-occlusion
- SCD is caused by a single amino acid mutation
  - Glu6 -> Val in β chain of hemoglobin (Hb)

- Hb is a tetrameric protein consisting of 2α and 2β chains
  - Proteins arrange in $\alpha\beta$ dimers
- Upon deoxygenation, a hydrophobic pocket is revealed
  - Increased hydrophobicity in mutant Hb leads to polymerization of Hb
- Oxygenated Hb cannot polymerize
  - Treatment needs only slow polymerization until deoxygenated cells can reenter the lungs
- Complete prevention of polymerization not necessary
  - 25% decrease allows normal circulation
  - Common treatment requires regular transfusion

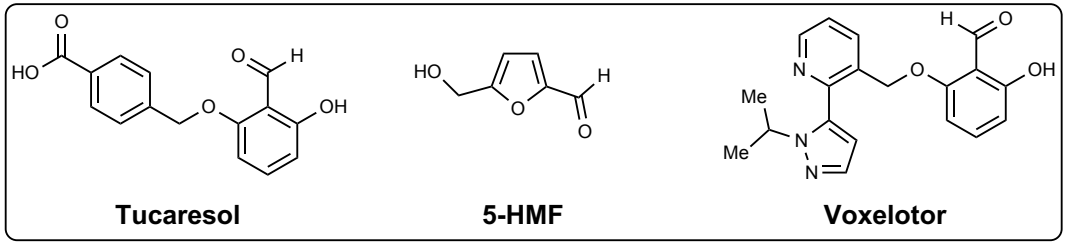




PF-07059013 bound in hemoglobin tetramer
Two drug molecules bind per hemoglobin molecule
Non-covalent binding mode in contrast to other known small molecule treatments for SCD
Aldehydes condense at N-terminus of α chains and prevent polymerization



PF-07059013 decreases sickling by ~40%!



J. Med. Chem. 2020, ASAP. https://doi.org/10.1021/acs.jmedchem.0c01518

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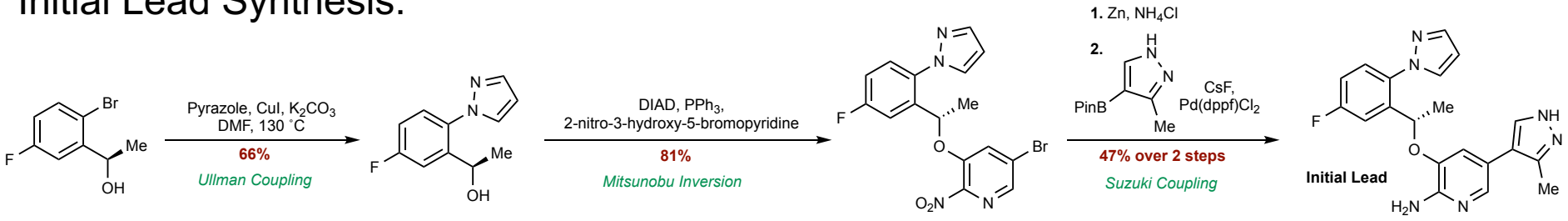
Initial Lead Synthesis:



Optimized Drug Synthesis