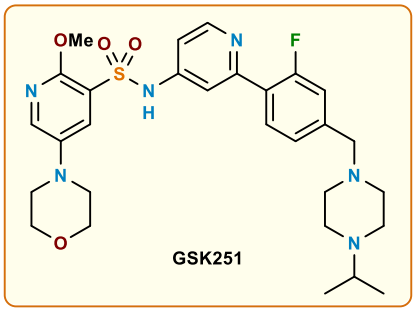
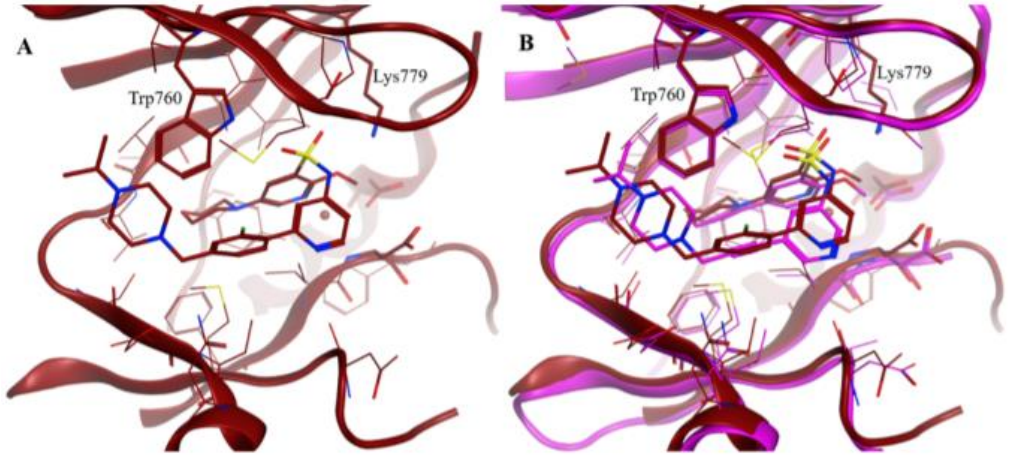
GSK251

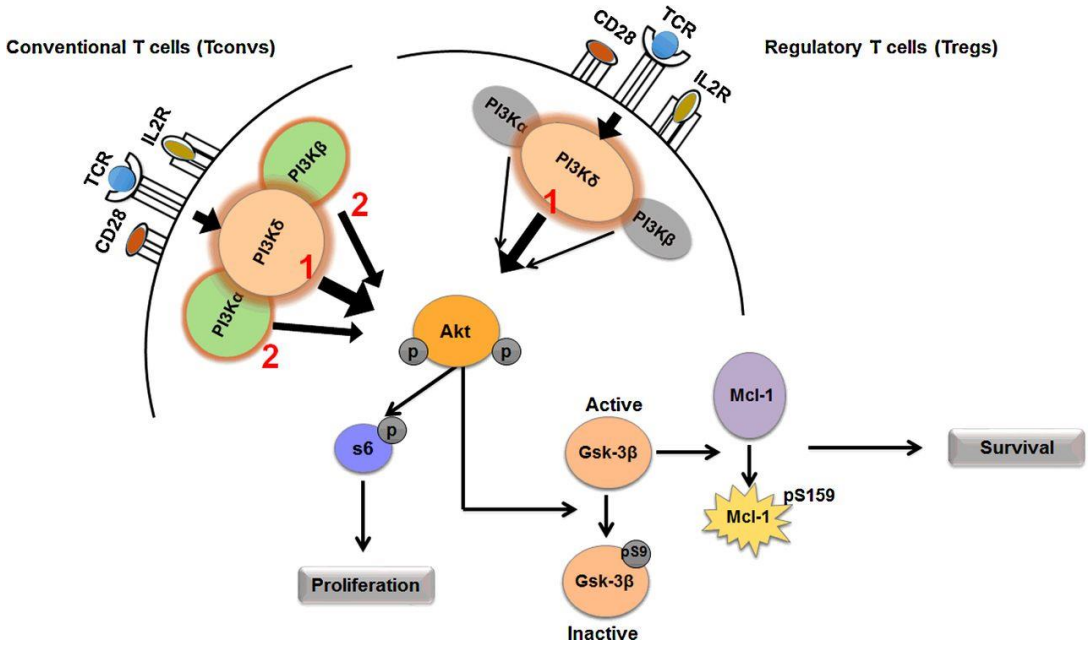


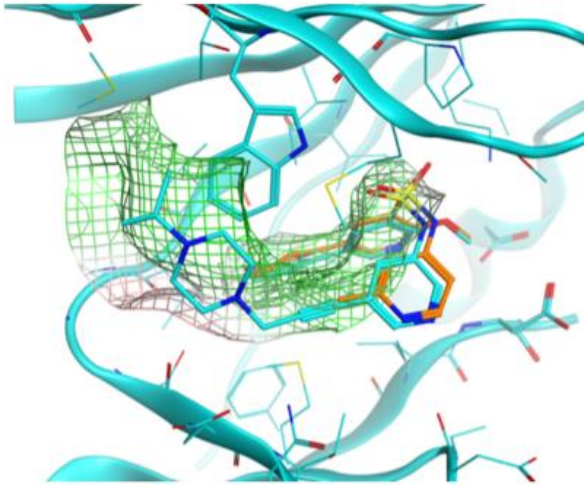
- Currently in preclinical toxicology studies for anti-inflammatory treatment
- > 10000-fold P13Kδ selective with pK_i 10.9
- hWB pIC_{50} 8.2 and 45 mg b.i.d. human dose predication



- Highly selective towards a P13Kδ via interaction with Trp760

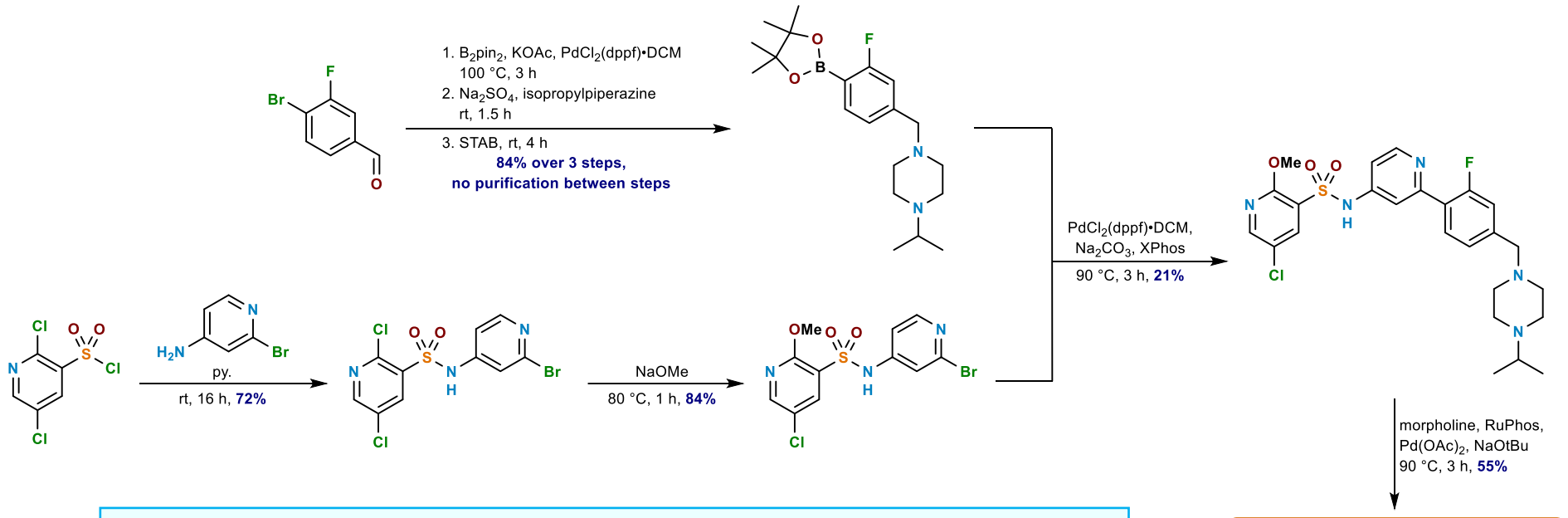
- As a P13Kδ inhibitor, GSK251 triggers downstream biological events affecting cell growth, chemotaxis, differentiation, proliferation, and survival





Down, K. *J. Med. Chem.* **2021**, DOI: 10.1021/acs.jmedchem.1c01102. https://doi.org/10.1021/acs.jmedchem.1c01102

GSK251



Key Biological Interactions:

- Oxygen of morpholine key hinge binding interaction with Val828
- Pyridine sulfonamide interacts with Trp760, Lys779, and through water to Asp787
- Isopropylpiperazine aligns alongside Trp760
- Fluorophenyl allows better alignment of isopropylpiperazine to Trp760

Biological Testing Statistics:

- High FaSSIF solubility 899 μg/mL
- Moderate MDCK permeability 23 nm/s
- Reasonable free fraction in rat blood 2.1% and human blood 13.2%
- Rat iv/po PK study doseed at 1 mg/kg demonstrates low clearance 3.8 mL/min/kg, low Vdss 0.5 L/kg, moderate half-life 2.6 h, good bioavailability 46%, and good exposure AUC 2023 ng/h/mL