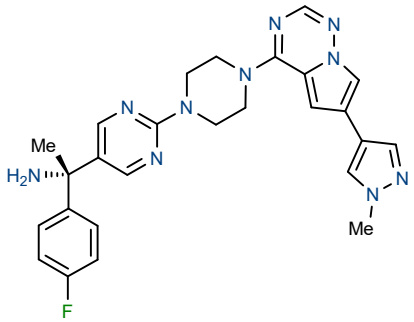
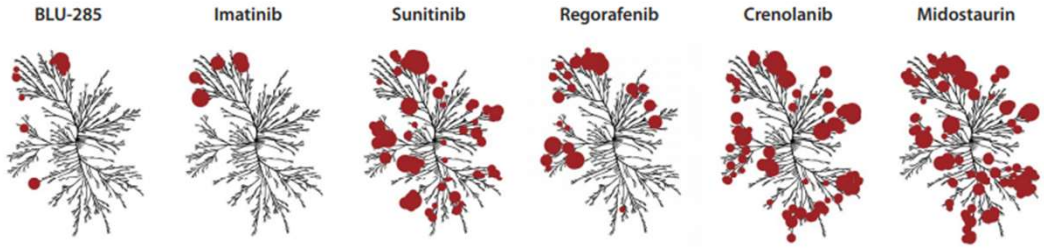
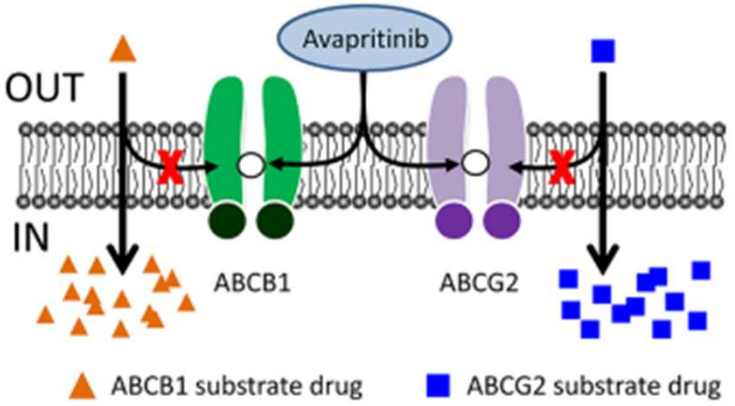
Avapritinib (Ayvakit)



- Approved in January 2020 for treatment of unresectable, metastatic gastrointestinal stromal tumors (GIST)
- Received Breakthrough Therapy, fast track and orphan drug designations
- Selective tyrosine kinase inhibitor of KIT and platelet derived growth factor receptor alpha (PDGFRA)
- One of the first medications available for treatment of MDR cancers
- First treatment approved for GIST patients with a PDGFRA exon 18 mutation
- Daily oral dose of 300 mg

- Imatinib is a tyrosine kinase inhibitor that transformed treatment of GIST
  - Achieves disease control in at 85% of cases
  - Limited response for metastatic GIST
  - Resistance occurs due to secondary mutations
- Secondary mutations in *KIT* or *PDGFRA* likely the most important event leading to TKI resistance
  - *KIT* exon 13 and 14 (ATP-binding pocket of receptor)
  - *KIT* exon 17 and 18 (kinase activation loop)
- Avapritinib (BLU-285) has limited potential for activity outside of KIT and PDGFRA
  - Activity against *KIT* exon 17 mutants, including D816V
  - Inhibits *PDGFRA* D842V
  - Type I inhibitor (binds active form)



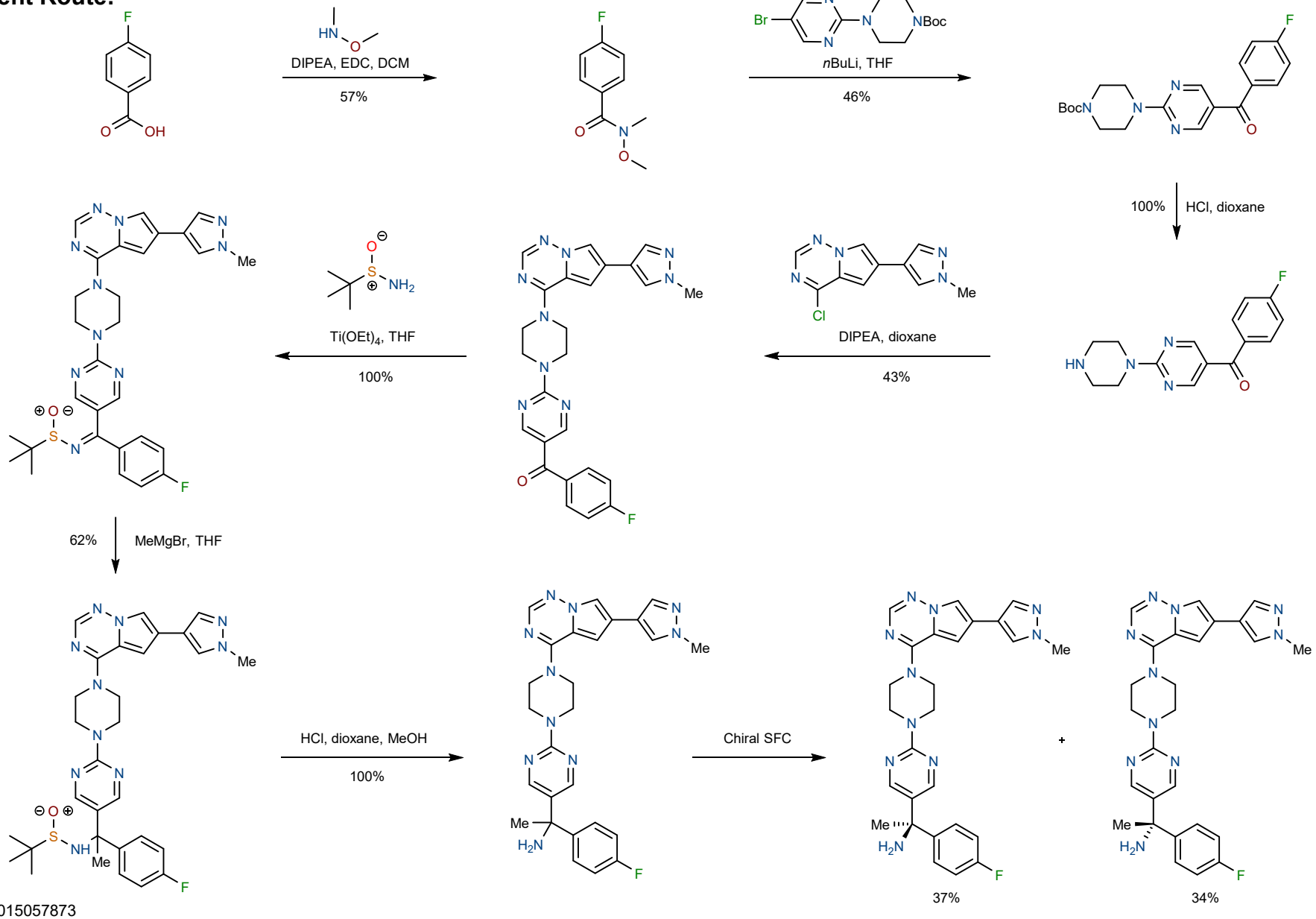


- Increases accumulation of ABCB1 and ABCG2 (ATP-binding cassette) substrates
- Reversed MDR mediated by ABCB1 or ABCG2 at nontoxic concentrations
- Has no effect on protein levels of ABCB1 or ABCG2
- Stimulates ATPase activity
- Docking studies show binding to the drug-binding pocket in transmembrane regions of transporters
- Overexpression of ABCB1 or ABCG2 doesn't alter chemosensitivity

Lengauer, C. *Sci. Transl. Med.* **2017**, *9*, 1690. DOI: 10.1126/scitranslmed.aao1690. Crews, C. *Mol. Pharmaceutics* **2019**, *16*, 3040. https://doi.org/10.1021/acs.molpharmaceut.9b00274.

Avapritinib (Ayvakit)

Patent Route:



WO2015057873