DRUG of the week

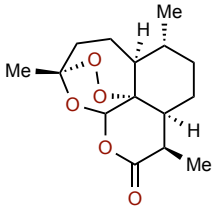
INE963 (Novartis)

The SARLAH Group

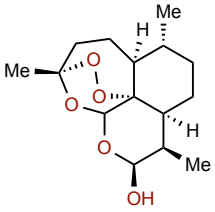
Background

- In 2019, there were 229 million cases of Malaria and 409,000 deaths – mostly in children under 5 years of age
- Artemisinin-based combination is the first-line treatment for malaria
  - Artemisinin derivatives are potent and fast acting, often only requiring a single dose
- Many reports of artemisinin resistance have been released alongside dual-therapy resistance
- Novartis is pursuing a novel chemotype to treat malaria through a new mechanism of action!
  - "Therefore, our goal at the Novartis Institute for Tropical Diseases (NITD) is to identify a fast-acting antimalarial compound from a novel chemotype with activity against known resistance mutations and which will also have the potential for single-dose cures."

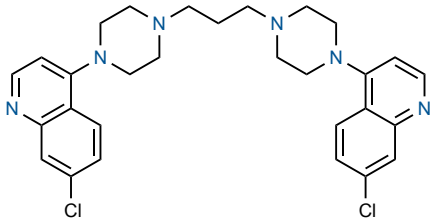
State-of-the-Art



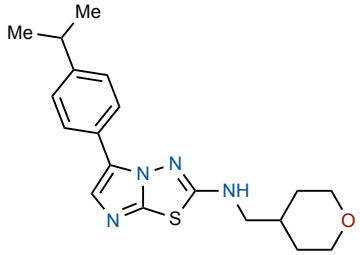
artemisinin



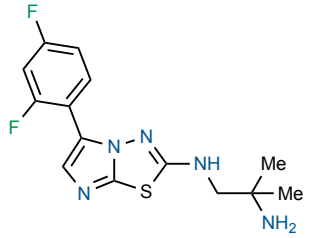
dihydroartemisinin



piperaquine



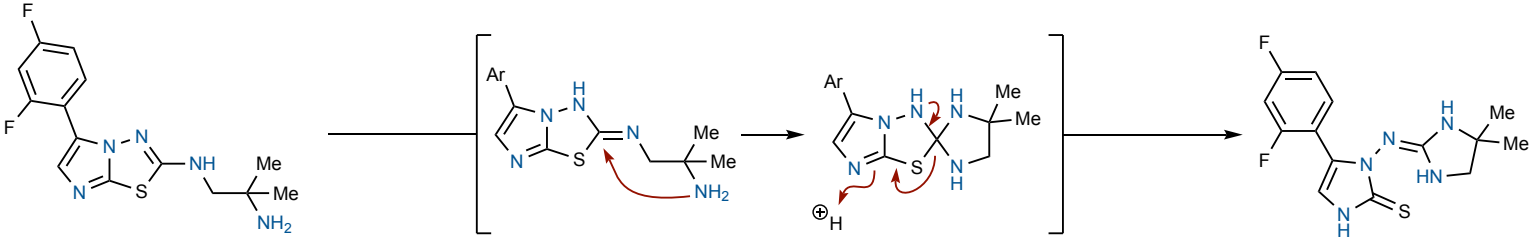
early lead



late lead

Imidazothiodiazoles show modest potency, but off-target activity and poor stability in solution

Origin of Instability



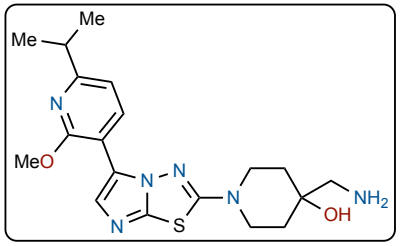
Structure optimization

Goals:

Reduce human kinase promiscuity

Improve chemical stability (2˚ amine to 3˚ amine)

Probe SAR



Outcome:

Pf 3D7 EC_{50} = 0.006 μM

10 out of 468 human kinases inhibited at 10 μM

$T_{1/2}$ = 60 hours in humans

"Artemisin-like kill kinetics"

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