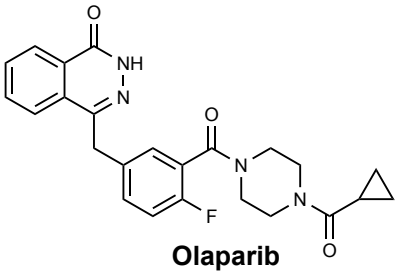
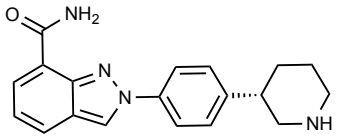
DRUG of the week

Pamiparib (BGB-290)

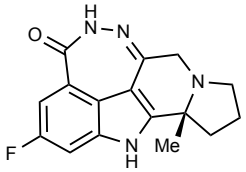
The SARLAH Group



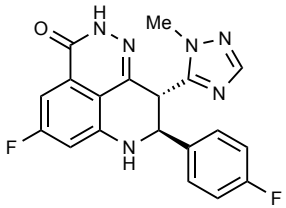
Olaparib



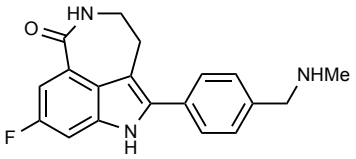
Niraparib



Pamiparib



Talazoparib

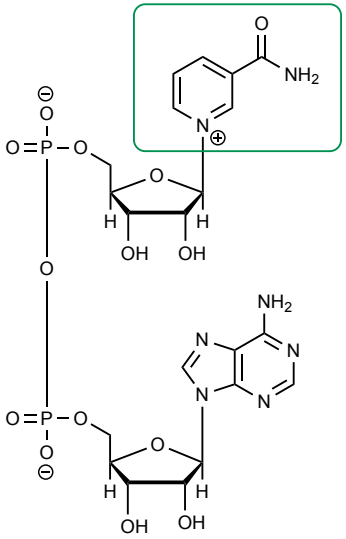


Rucaparib

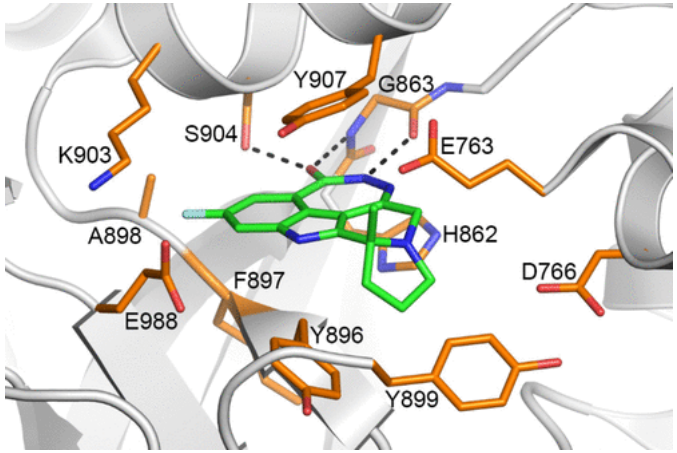
- Poly (ADP-Ribose) Polymerase (PARP) inhibitor
  - Currently in phase III clinical trials
- Prevents repair of single-strand DNA breaks
  - SSBs cause double-strand breaks if unrepaired
- Exceptional stability, and blood-brain permeability
  - Potential as a treatment for solid brain tumors
- 16-fold better activity than Olaparib

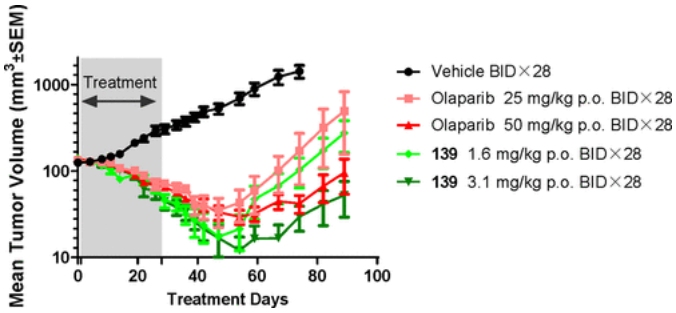
Key structural features:

- Dihydrodiazepinone locks hydrogen bonding moieties in active conformation
- Indole participates in π−π stacking in binding pocket
- Structure mimics NAD+, the normal substrate for PARP
  - Nicotinamide binds in enzymatic pocket



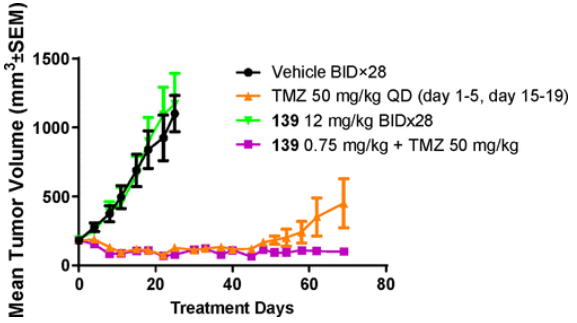
NAD$^+$





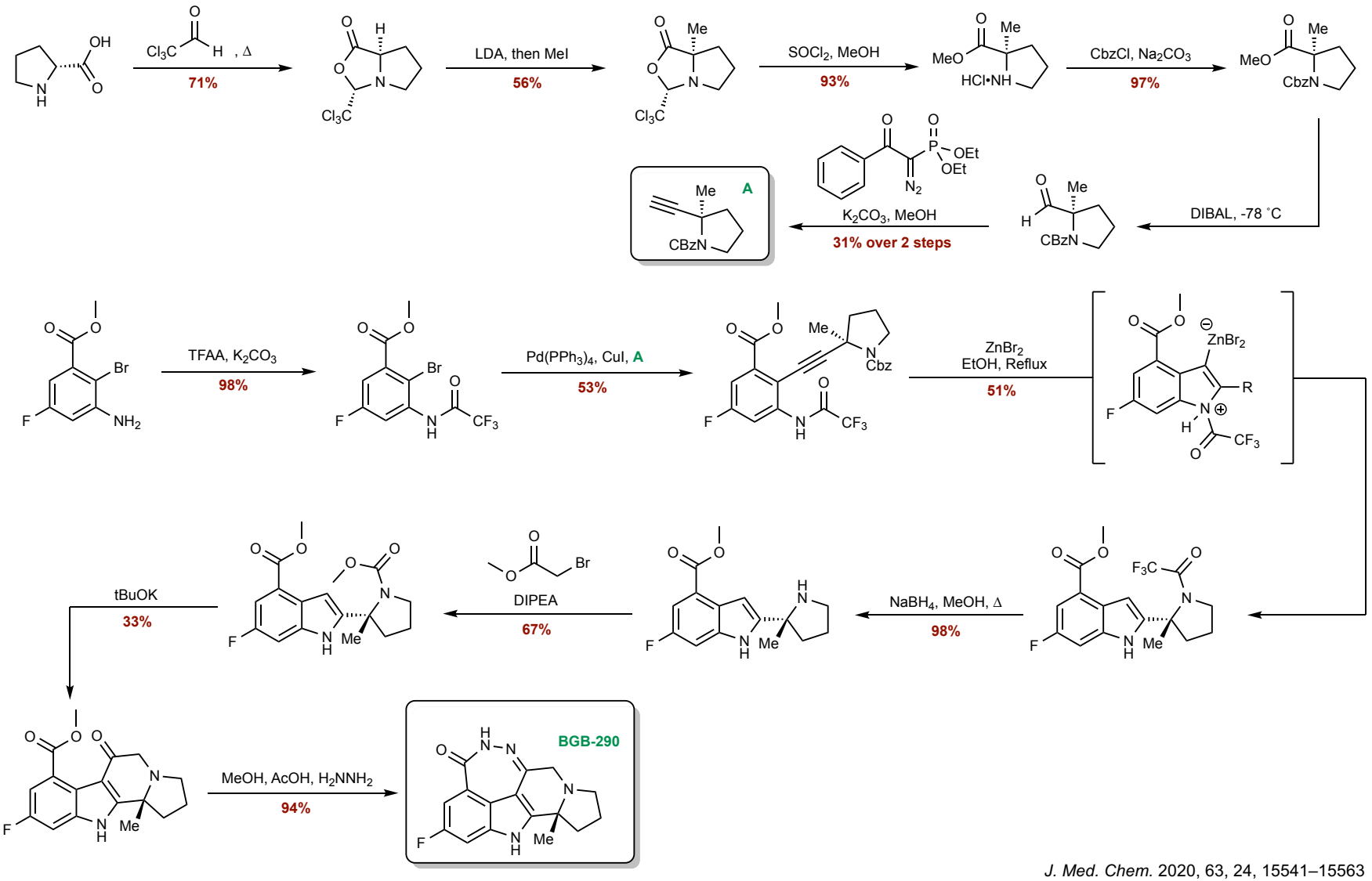
Left: treatment of *BRCA-1* mutant cells with Pamiparib

Right: Combination therapy with Pamiparib and TMZ (DNA Methylating agent)



Pamiparib (BGB-290)

Med-Chem Synthesis:



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