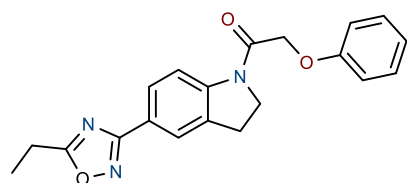


Aficamten (CK-274)

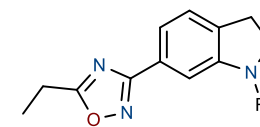
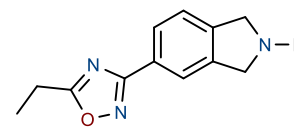
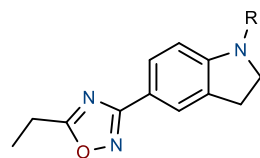
## Background

- Cardiac myosin inhibitor
- Used to treat hypertrophic cardiomyopathy (thickening of the left ventricular walls of the heart)
- Second generation of this drug class (following FDA approved mavacamten from BMS-MyoKardia)
- Currently in Phase 3 clinical trials

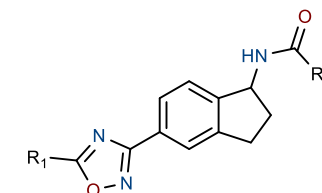
## Medicinal Chemistry



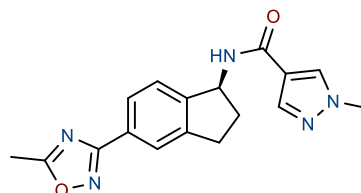
Initial hit from HTS



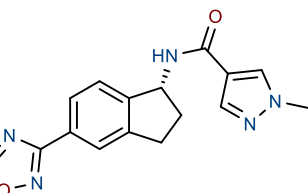
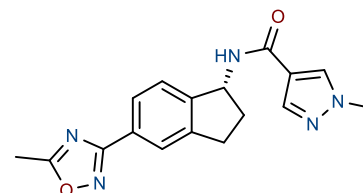
Changing nitrogen position did not improve biological properties



Improved potency and better PK profile



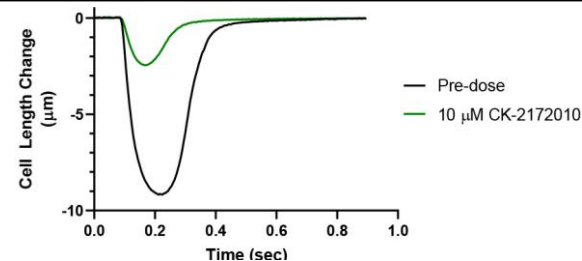
Cleared faster (problematic)



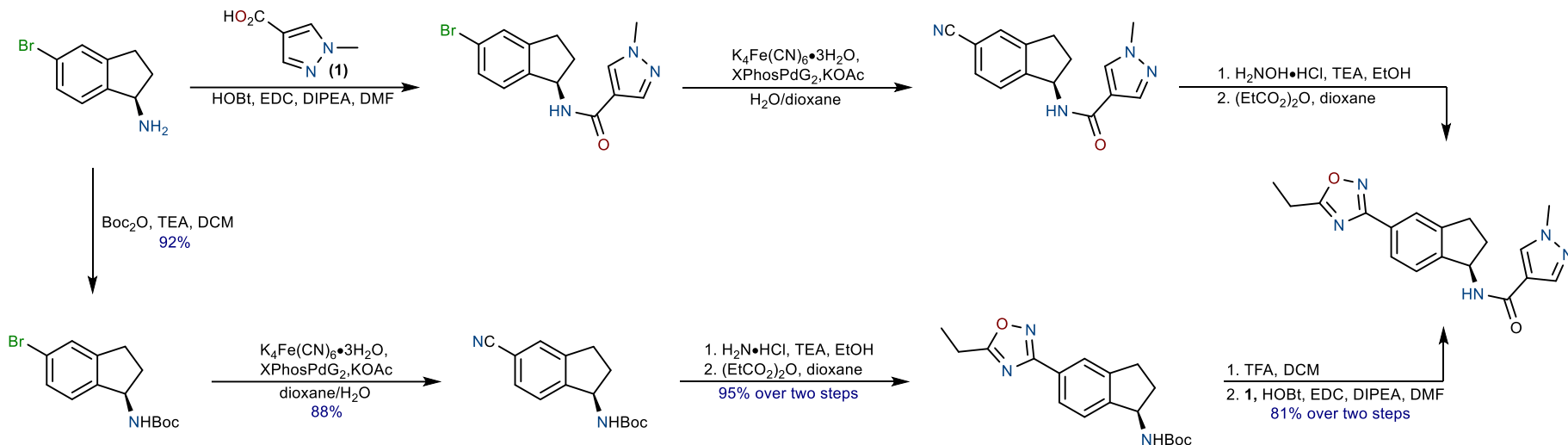
Aficamten (CK-274)

## Biology

- Reduces contractility of cardiac myofibrils
- Mechanism is not calcium channel related (binds myosin directly)
- Aficamten displays improved PK, therapeutic window, and reduced CYP induction compared to mavacamten



## Synthesis



## Synthesis of the Chiral Amine

