

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)

> Cell Length Change (µm)

-5

-10+

0.2

0.4

Time (sec)

0.6

0.8

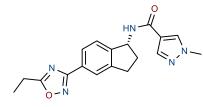
1.0

Background

Cardiac myosin inhibitor

Currently in Phase 3 clinical trials





Aficamten (CK-274)

## **Medicinal Chemistry**

## Initial hit from HTS Changing nitrogen position did not improve biological properties Aficamten (CK-274) Improved potency and better PK profile Cleared faster (problematic)

- 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

Morgan, B. P. J. Med. Chem. 2021, 64 (19), 14142–14152. https://doi.org/10.1021/acs.jmedchem.1c01290.

## Eric Pettipiece

Pre-dose

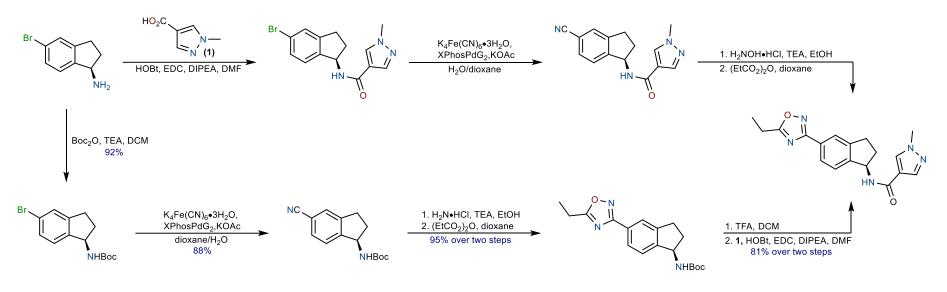
10 µM CK-2172010



Aficamten (CK-274)



## Synthesis



Synthesis of the Chiral Amine

