1. Introduction and Motivation

Actin is a key protein building block of actin microfilaments, which are constructed and deconstructed in response to cellular signaling pathways to regulate cellular processes such as motility, division, and endocytosis. Arp2/3 Complex is a 7-subunit protein complex that is involved in cellular structure of branching actin networks, functioning by attaching to the side of a pre-existing actin filament and nucleating a daughter branch.

2. Mode of Inhibition

Arp2/3 inhibitor scaffolds were identified using high-throughput screening. The CK-669 inhibitor scaffold stabilizes the inactive conformation of the Arp2/3 complex while the CK-689 inhibitor scaffold destabilizes the active conformation.

3. CK-869 Inhibitor Scaffold and IC50 Results

Currently known inhibitors CK-669 and CK-689 must be used in undesirably high concentrations to achieve complete suppression of Arp2/3 complex in vitro. The key goals of this project are to intelligently design, synthesize, and test the potency of a library of derivatives of each inhibitor class. Computational docking between proposed inhibitors and a crystal structure of Arp2/3 complex guided synthesis efforts that produced the following derivatives of CK-669 and CK-666, which were then studied using an in vitro actin polymerization assay to determine their potency.

4. CK-666 Inhibitor Scaffold and IC50 Results

These molecules are thiazolidinones

- The most favorable modification to the A ring was found to be removal of one methoxy substituent
- The meta rather than para substituent on the B ring was favorable
- Bromine was generally the best substituent on the B ring

5. Bulk Polymerization Assay

There are Aspartic acid residues near the site where the CK-666 scaffold binds. We plan to alter the indole ring by adding a nitrogem at position 4 or 7 to increase the number of hydrogen bonds between the inhibitor and Arp2/3.

6. Future Directions

There is a Cysteine with a sulfur group near the site where the CK-669 scaffold binds. We plan to alter the R group to increase the binding strength between the inhibitor and Arp2/3.

7. Acknowledgements and Funding

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- Synthesis: Members of the Levent Cavas group at DEU

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**Section 1 References**


**Section 2 References**


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**Images**

A bulk actin polymerization assay is used as the key method to determine the potency of inhibitor candidates. Results of structure-activity relationships will be used to evaluate how actin inhibition may play a role in anticansexual applications and in general actin research.