Synthesis of Small Molecule Derivatives of CK-666 as Potential Inhibitors of the Arp2/3 Complex

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1. Introduction and Motivation

Actin related protein (Arp2/3) complex plays important roles in movement, endocytosis, and cell division. Constructing and deconstructing of actin mediates cellular motility.1 The Arp2/3 protein contributes to movement by creating branches. Arp2/3 can get disturbed by viral and bacterial pathogens, and metastasis of cancer cells is linked to Arp 2/3 activity.2 As a result, potent inhibitors that can block or prevent Arp2/3 to nucleate daughter strands of actin will be helpful as a basic research tool. Also they potentially can be used against cancers or diseases that use Arp 2/3 to survive.

2. Small Molecule Inhibitor CK-666

The known small molecule inhibitor (CK-666) has been identified through high throughput screening, and characterized by X-ray crystallography.3 It is highly desirable to develop more potent derivatives of this inhibitor class. Ideally our goal is to increase the potency towards Arp2/3 complex by three orders of magnitude.

3. Acyl Tryptamine Strategy and Synthesis

4. Ester-Linked Inhibitor Strategy and Synthesis

5. New Synthesis Targets and Methods

We study the potency of our inhibitor candidates by measuring the rate of polymerization of actin in the presence of Arp2/3 complex and inhibitors.13

6. Next Step: In Vitro Assays to Determine Potency

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References