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,3 and characterized by X-ray crystallography.4 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

Strategy one: Increase binding strength

4. Ester-Linked Inhibitor Strategy and Synthesis

Strategy two: Decrease SM-water interaction

5. New Synthesis Targets and Methods

6. Next Step: In Vitro Assays to Determine Potency

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.5

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