

**P009** Oligoarginine-adenosine conjugates as efficient inhibitors of Rho kinase

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Aberrant regulation of protein kinases impairs normal cellular functioning and may lead to disease. Rho-kinase (ROCK) phosphorylates various substrates (e.g., MLC, myosin phosphatase), causing formation of actin fibers and tension inside cells. Hyperactivation of ROCK, for example, causes hypertension and cardiovascular disorders. Thus, design of highly specific protein kinase inhibitors is of highest importance. Up to date, majority of inhibitors mimic and compete with ATP, but a novel Rho-kinase inhibitor ARC (adenosine-oligoarginine conjugate), is designed to simultaneously interfere with the ATP site and the substrate binding pocket of the enzyme. ARC was able to pull down ROCK from cell lysates, showed no cytotoxicity and suppressed the assembly of the actin cytoskeleton (especially central actin bundles) as the result of interfering with the activity of ROCK. Combination of ARC with chloroquine yielded a stronger inhibitory effect and led to similar results with Y-27632, a commonly used ROCK inhibitor. However, ARC-treatment produced more actin fragments and yielded a longer lasting effect than Y-27632. We believe the bisubstrate strategy could be a useful lead for designing novel highly specific inhibitors for different protein kinases.