

Targeting Compartmentalised cAMP-dependent Signalling Pathways with Small Molecules

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Small organic molecules for targeted disruption of protein-protein interactions are valuable tools to study cellular signalling processes. Of particular interest are direct protein-protein interactions mediated by scaffolding proteins, which position protein kinases, protein phosphatases, phosphodiesterases and other signalling proteins at defined sites within cells. This compartmentalisation facilitates temporally and spatially coordinated cellular signalling and thereby specific responses of cells to given external stimuli.

Compartmentalisation of protein kinase A (PKA) is achieved by direct interaction of its regulatory subunits (preferentially RII) with a class of scaffolding proteins termed A kinase anchoring proteins (AKAPs). AKAP-RII interactions are involved in various processes, including the regulation of cardiac myocyte contractility. Screening of a small molecule library (20,000 substances) led to the identification of a compound that modifies AKAP-RII interactions. Treatment of cardiac myocytes with the compound displaced RII subunits from AKAPs and influenced compartmentalised cAMP signalling at various stages, for example β -adrenoceptor-stimulated increases in L-type Ca^{2+} -channel currents, a process dependent on the interaction of AKAP18 α with RII subunits. The data suggest that AKAP-dependent protein-protein interactions are suitable targets for disruption with small molecules.